2014 NSTE-ACS Guideline Data Supplements

(Section numbers correspond to the full-text guideline.)

Data Supplement 1. Clinical Assessment and Initial Evaluation (Section 3.1) 3
Data Supplement 2. Risk Stratification (Section 3.3) 7
Data Supplement 3. Cardiac Injury Markers and the Universal Definition of AMI (Section 3.4) 8
Data Supplement 4. Cardiac Troponins (Section 3.4.3) 10
Data Supplement 5. CK-MB, MB Isoforms and Myoglobin, Compared With Troponins (Section 3.4.4) 12
Data Supplement 6. Bedside Testing for Cardiac Biomarkers (Section 3.4.4) 14
Data Supplement 7. Summary Comparison of Injury Markers (Section 3.4.4) 17
Data Supplement 8. Discharge from ED or Chest Pain Unit (Section 3.5.1) 20
Data Supplement 9. Nitrates (Section 4.1.2.1) 22
Data Supplement 10. Analgesic Therapy (Section 4.1.2.2) 25
Data Supplement 11. Beta-Adrenergic Blockers (Section 4.1.2.3) 26
Data Supplement 12. Calcium Channel Blockers (Section 4.1.2.4) 29
Data Supplement 13. Other Anti-Ischemic Inverventions (Ranolazine) (Section 4.1.2.5) 32
Data Supplement 14. Inhibitors of the Renin-Angiotensin-Aldosterone System (Section 4.2) 34
Data Supplement 15. Oral and Intravenous Antiplatelet Therapy in Patients With Likely or Definite NSTE-ACS Treated With Initial Invasive or Conservative Strategy (Section 4.3.1) 37
Data Supplement 16. Combined Oral Anticoagulant Therapy and Antiplatelet Therapy in Patients With Definite NSTE-ACS (Section 4.3.2) 52
Data Supplement 17. Parenteral Anticoagulant and Fibrinolytic Therapy (Section 4.3.3) 57
Data Supplement 18. Comparison of Early Invasive and Initial Conservative Strategy (Section 4.4.4) 74
Data Supplement 19. Comparison of Early Versus Delayed Angiography (Section 4.4.4.1) 80
Data Supplement 20. Risk Stratification Before Discharge for Patients With Conservatively Treated NSTE-ACS (Section 4.5) 81
Data Supplement 21. RCTs and Relevant Meta-Analyses of GP IIb/IIIa Inhibitors in Trials of Patients With NSTE-ACS Undergoing PCI (Section 5) 83
Data Supplement 22. Studies of Culprit Lesion Versus Multivessel (Culprit and Nonculprit) PCI in Patients with NSTE-ACS (Section 5) 83
Data Supplement 23. Risk Reduction Strategies for Secondary Prevention (Sections 6.3.) 84
Data Supplement 24. Older Patients (Section 7.1) 86
Data Supplement 25. Heart Failure (Section 7.2) 95
Data Supplement 26. Cardiogenic Shock (Section 7.2.2) 101
Data Supplement 27. Diabetes Mellitus (Section 7.3) 103
Data Supplement 28. Post-CABG (Section 7.4) 106
Data Supplement 29. Chronic Kidney Disease (Section 7.6) 110
Data Supplement 30. Women (Section 7.7) 113
Data Supplement 31. Anemia, Bleeding, and Transfusion-Relationship Between Transfusion and Mortality (Section 7.8) 120
Data Supplement 32. Anemia, Bleeding, and Transfusion Studies for Weight-Based and Renally-Adjusted Dosing of Anticoagulants (Section 7.8) 121
Data Supplement 33. Cocaine and Methamphetamine Users (Section 7.10) 122
Additional Data Supplement Tables 125
  Data Supplement A. Other (Newer) Biomarkers 125

Data Supplement B. Other Anticoagulants 127
Data Supplement C. Lipid Management 129
Data Supplement D. Blood Pressure Control 132
Data Supplement E. Diabetes Mellitus 133
Data Supplement F. Smoking Cessation 135
Data Supplement G. Weight Management 138
Data Supplement H. Cardiac Rehabilitation 140
References 141

Data Supplement 1. Clinical Assessment and Initial Evaluation (Section 3.1)

Title, Author, Year	Study Aim	Study Type/Size (N)	Patient Population		Endpoints		P Values, OR: HR: RR: & 95 CI:	Adverse Events	Study Limitations
			Inclusion Criteria	*Exclusion Criteria*	*Primary Endpoint & Results*	*Safety Endpoint & Results*			
Antman EM et al. 2000 10938172 (1)	Develop a simple scoring system to predict the risk of death and ischemic events for pts with UA/NSTEMI	Retrospective, observational study; TIMI 11B pts not receiving UFH group test cohort (N=1,957); TIMI 11B pts receiving enoxaprin (N=1,953) and ESSENCE trial pts (N=3,171) validation cohort	Inclusion in TIMI 11B trial or ESSENCE trial	Not included in these trials	Adverse events defined as new or recurrent MI, severe recurrent ischemia requiring urgent revasc, and death within 14 d of pt presentation; regression model selected the following 7 significant risk factors: ≥65 y, ≥3 coronary risk factors, documented prior stenosis ≥50%; ST-segment deviation on initial ECG, ≥2 anginal events in prior 24 h, use of ASA within 7 d of presentation, and elevated serum markers; presence of factor was given 1 point and absence of risk factor given 0 points; rates of adverse events for TIMI score as follows: 0/1: 4.7%; 2: 8.3%; 3:13.2%; 4: 19.9%; 5:26.2%; 6/7: 40.9%	N/A	Event rates <significantly as TIMI risk score <in test cohort in TIMI 11B (p=001 by ×2 for trend). Pattern of <event rates with <TIMI risk score confirmed in all 3 validation groups (p=001). Slope of <in event rates with <numbers of risk factors significantly lower in enoxaparin groups in both TIMI 11B (p=0.01) and ESSENCE (p=0.03) and there was significant interaction between TIMI risk score and treatment (p=0.02)	N/A	Regression model developed in pts with diagnosed ACS and was not designed to be applied indiscriminately to undifferentiated chest pain pts
Boersma E et al. 2000 10840005 (2)	Develop a model for predicting 30-d death and myocardial (re)infarction in pts without STE-ACS	Retrospective analysis of pts with NSTE-ACS enrolled in PURSUIT trial (N=9,461; 3.6% with 1° outcome)	Pts enrolled in PURSUIT trial	Pts not enrolled in PURSUIT trial; pts with STE on initial ECG	1° outcome: 30-d death; 2° outcome: composite of 30-d death and myocardial (re)infarction; More than 20 variables were found to be predictive of 1° and 2° outcomes	N/A	7 factors most predictive of death: age (adjusted $[X]^2$=95), heart rate ($[X]^2$=32), SBP ($[X]^2$=20), ST-segment depression ($[X]^2$=20), signs of HF ($[X]^2$=18), and cardiac markers ($[X]^2$=15); C-index for the mortality model was 0.814	N/A	Regression model developed in pts with diagnosed ACS and not designed to be applied indiscriminately to undifferentiated chest pain pts; difficult to calculate; original model requires preexisting programmed calculator; simplified version requires print-out of scoring system for each variable with corresponding figure to interpret data
Granger CB et al. 2003 14581255 (3)	Develop a regression model in pts with diagnosed ACS (including pts with	Retrospective observational study utilizing pts from GRACE (N=11,389; 509 deaths); validation set	Inclusion in GRACE or GUSTO-IIb trial	Not included in these trials	Adverse event defined as in-hospital mortality; Regression model identified following 8 independent risk factors: accounted age, Killip class, SBP,	N/A	The discrimination ability of the simplified model was excellent with C-statistics of 0.83 in the derived database, 0.84 in the confirmation	N/A	Regression model developed in pts with diagnosed ACS (including STEMI pts) and was not designed to be applied indiscriminately to

	STEMI) for in-hospital mortality	included a subsequent cohort of 3,972 pts enrolled in GRACES and 12,142 pts enrolled in GUSTO-IIb trial			ST-segment deviation, cardiac arrest during presentation, serum creatinine level, positive initial cardiac enzyme findings, and heart rate		GRACE data set, and 0.79 in the GUSTO-IIb database; OR for the 8 independent risk factors were: age (OR: 1.7 per 10 y), Killip class (OR: 2.0 per class), SBP (OR: 1.4 per 20 mmHg decrease), ST-segment deviation (OR: 2.4), cardiac arrest during presentation (OR: 4.3), serum creatinine level (OR: 1.2 per 1 mg/dL [88.4 µmol/L] increase), positive initial cardiac enzyme findings (OR: 1.6), and heart rate (OR: 1.3 per 30 beat/min increase)		undifferentiated chest pain pts; difficult to calculate; original model requires pre-existing programmed calculator; simplified version requires print-out of scoring system for each variable with corresponding nomogram
Chase M et al. 2006 16934646(4)	Validate TIMI score in ED chest pain pts	Prospective (N=1,354; 136 with 1° outcome)	Pts with chest pain who had an ECG obtained	Pts <30; cocaine use within 7 d	1° outcome composite of death, MI, PCI, CABG within 30 d of initial presentation	Increasing TIMI score associated with increased rates of adverse outcome	N/A	The incidence of 30-d death, AMI, and revasc according to TIMI score is as follows: TIMI 0, 1.7% (95% CI: 0.42–2.95); TIMI 1, 8.2% (95% CI: 5.27–11.04); TIMI 2, 8.6% (95% CI: 5.02–12.08); TIMI 3, 16.8% (95% CI: 10.91–22.62); TIMI 4, 24.6% (95% CI: 16.38–32.77); TIMI 5, 37.5% (95% CI: 21.25–53.75); and TIMI 6, 33.3% (95% CI: 0–100)	15% of pts did not have cardiac marker measurements; pts with STEMI included
Lyon R et al. 2007 17360096(5)	Compare GRACE and TIMI score in risk stratification of undifferentiated chest pain pts	Retrospective analysis of prospective database (N=760; 123 with 1° endpoint)	Pts with undifferentiated chest pain	Pts<20 y	Recurrent MI, PCI, or death within 30 d of pt presentation (note: pts with MI on initial presentation excluded from outcome)	GRACE score and TIMI score equivalent in risk stratification of undifferentiated ED chest pain pts	N/A	GRACE AUC-ROC 0.80 (95% CI: 0.75–0.85). TIMI AUC-ROC 0.79 (95% CI: 0.74–0.85)	Retrospective; 240 pts from initial database of 1,000 excluded; Did not count MI on presentation as adverse event
Hess EP et al. 2010 20370775(6)	Prospectively validate a modified TIMI risk	Prospective; 117 pts with 1° endpoint (N=1,017)	Pts presenting to ED with chest pain in whom a	Pts with STE-AMI, hemodynamic instability, cocaine	1° outcome defined as MI, PCI, CABG, or cardiac death within 30 d of initial presentation	Increasing sens of modified TIMI score seen with increasing	N/A	The modified TIMI risk score outperformed the original with regard	Only 72% of eligible pts enrolled; 4.6% of pts without 30-d follow-up

	score to risk stratify ED chest pain pts; The modification of TIMI score was assigning 5 points if pt had either elevated Tn or ischemic ECG findings		Tn value was obtained	use, terminal illness, or pregnancy		score; sens and spec at potential decision thresholds were: >0=sens 96.6%, spec 23.7%; >1=sens 91.5%, spec 54.2%; and >2=sens 80.3%, spec 73.4%; sens for 30-d ACS for a score of 0, 1, 2 was 1.8%, 2.1%, and 11.2%		to overall diagnostic accuracy (area under the ROC curve=0.83 vs. 0.79; p=0.030; absolute difference 0.037; 95% CI: 0.004-0.071)	
Lee B et al. 2011 21988945(7)	Compared GRACE, PURSUIT, and TIMI scores in risk stratification of chest pain pts	Prospective data collection for TIMI score; retrospective determination of PURSUIT and GRACE score (N=4,743; 319 pts with 1° outcome)	Chest pain pts>30 y who had ECG obtained and were enrolled in previous study utilizing TIMI score in risk stratification of chest pain pts	Pts in which scores were unable to be calculated due to incomplete data (e.g., no creatinine obtained)	1° outcome composite of death, MI, PCI, or CABG within 30 d of presentation	The TIMI and GRACE score outperformed the PURSUIT score in risk stratification of ED chest pain pts	N/A	The AUC for TIMI was 0.757 (95% CI: 0.728-0.785); GRACE, 0.728 (95% CI: 0.701-0.755); and PURSUIT, 0.691 (95% CI: 0.662-0.720)	Retrospective nature of comparison of TIMI score to GRACE and PURSUIT
Sanchis J et al. 2005 16053956(8)	Develop a risk score for ED pts with chest pain	Retrospective (N=646; 6.7% with 1° endpoint)	Chest pain pts presenting to ED undergoing evaluation for ACS who subsequently were admitted to chest pain unit	Significant STE or depression on initial ECG; abnormal Tn; not admitted to chest pain unit	N/A	1° endpoint: 1-y mortality or MI; point); 4 factors were found to be predictive of 1° endpoint and were assigned following score: chest pain score ≥10 points: 1 point, ≥2 pain episodes in last 24 h: 1 point; age≥67 y: 1 point; IDDM: 2 points, and prior PCI: 1 point; Pts were classified in 5 categories of risk (0, 1, 2, 3, 4, >4) with direct correlation of increasing rates of 1° outcome with risk score	N/A	Accuracy of score was greater than that of the TIMI risk score for the 1° (C-index of 0.78 vs. 0.66; p=0.0002) and 2° (C-index of 0.70 vs. 0.66; p=0.1) endpoints	Small study size; selection bias towards more healthy pts as study population limited to pts admitted to chest pain unit; chest pain component of score is not easily calculated

Christenson J et al. 2006 16387209(9)	Develop a scoring system for discharge of pts from the ED that would miss <2% of ACS	Prospective cohort with retrospective creation of decision rule (N=769; 165 with 1° outcome)	Pts presenting to ED with chest pain between 7 am-10 pm h	<25, traumatic or radiologically evident cause of CP, enrolled in study in previous 30 d, or had terminal noncardiac illness	1° outcome MI or definite UA	Prediction rule: if pt had normal initial ECG, no Hx CAD, age<40 y, and normal baseline CK-MB<3.0 ng/mL, or no increase in CK-MB or Tn at 2 h; 30-d ACS; prediction rule 98.8% sens and 32.5% spec	CI for prediction rule not supplied	N/A	Prediction rule developed retrospectively; not supplied, but exceed the threshold of allowed 2% miss rate; 2% miss rate not standard of care in United States
Backus BE et al. 2010 20802272(10)	Validation of the HEART Score which utilizes elements of patient History, ECG, Age, Risk factors, and Troponin to risk stratify ED chest pain pts	Retrospective analysis of prospective database (N=880; 158 with 1° outcome)	Pts admitted to "cardiology" ED	STE on initial ECG	1° outcome was a composite of AMI, PCI, CABG, and death within 6 wk of initial presentation	Rates of 1° outcome seen with increasing score: 0–3: 0.1%; 4–6: 11.6%; 7–10: 65.2%	N/A	Hx, ECG, and Tn were independent predictors of the combined endpoint (p<0.0001). Avg HEART score in the no endpoint group was 3.8±1.9; pts with at least 1 endpoint 7.2 ±1.7 (p±0.0001). C–stat 0.897	Retrospective; weighting of the elements of HEART Score arbitrarily assigned and not based on likelihood ratio analysis or regression analysis
Fesmire et al. 2012 22626816(11)	Improve upon the HEART score in risk stratification of chest pain pts by incorporating sex, serial ECG, and serial Tn; weighting of elements of scoring determined by likelihood ratio analysis	Retrospective analysis of prospective database (N=2,148; 315 with 1° outcome)	Pts presenting to ED with chest pain undergoing evaluation for ACS	STE on initial ECG; chest pain in the presence of TAAR, pts with pulmonary edema, pts with chest pain deemed not to require any cardiac workup (obvious nonischemic chest pain and absence of risk factors or pre-existing disease that would prompt screening workup)	1° outcome was 30-d ACS defined as MI, PCI, CABG, life-threatening cardiac complications, or death within 30 d of initial presentation	Increasing $HEARTS_3$ score was associated with increasing risk of 30-d ACS; likelihood ratio analysis revealed significant discrepancies in weight of the 5 individual elements shared by the HEART and $HEARTS_3$ score	N/A	$HEARTS_3$ score outperformed the HEART score as determined by comparison of areas under the receiver operating characteristic curve for 30-d ACS (0.901 vs. 0.813; 95% CI difference in areas, 0.064–0.110)	Retrospective; utilized older-generation Tn
Hess EP et al. 2012 21885156(12)	Develop a prediction rule for pts at low risk of 30-d adverse cardiac events	Retrospective analysis of prospective database (N=2,718 pts; 336 with adverse events)	Pts presenting to ED with chest pain in whom Tn value was obtained	Pts with STE-AMI, hemodynamic instability, cocaine use, terminal illness, or pregnancy	1° outcome defined as MI, PCI, CABG, or cardiac death within 30 d of initial presentation	Prediction rule consisted of the absence of 5 predictors: ischemic ECG changes, Hx of CAD, pain typical for ACS, initial or 6-h Tn	N/A	Rule was 100% sens (95% CI: 97.2%–100.0%) and 20.9% spec (95% CI: 16.9%–24.9%) for a cardiac event within 30 d	Rule developed retrospectively; only 82% of eligible pts enrolled

						level > 99th percentile, and age <50 y. Pts aged ≤40 y required only a single Tn evaluation			

1º indicates primary; ACS; acute coronary syndrome; AMI, acute myocardial infarction; ASA, aspirin; AUC, area under the curve; BP, blood pressure; CABG, coronary artery bypass graft; CAD, coronary artery disease; CK-MB, creatine kinase-MB; CP, chest pain; ECG, electrocardiograph; ED, emergency department; ESSENCE, Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q wave Coronary Events; GRACE, Global Registry of Acute Coronary Events; GUSTO, Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries trial; HEART, Healing and Early Afterload Reducing Therapy Trial; HF, heart failure; Hx, history; MI, myocardial infarction; N/A, not applicable; NSTE, non-ST-elevation; NSTE-ACS, non-ST-elevation acute coronary syndrome; NSTEMI, non–ST-elevation myocardial infarction; Pts, patients; PCI, percutaneous coronary intervention; revasc, revascularization; PURSUIT, Platelet Glycoprotein IIb/IIIa in Unstable Angina:Receptor Suppression Using Integrilin Therapy; ROC, receiver operator curve; SBP, systolic blood pressure; Sens, sensitivity/sensitivities; Spec, specificity/specificities; STE, ST-elevation; STE-AMI, ST-elevation acute myocardial infarction; STEMI, ST-elevation myocardial infarction; TAAR, tachyarrhythmia; TIMI, Thrombolysis In Myocardial Infarction; Tn, troponin; UA, unstable angina; and UFH, unfractionated heparin.

Data Supplement 2. Risk Stratification (Section 3.3)

Study Name, Author, Year	Study Aim	Study Type/Size (N)	Intervention vs. Comparator (n)	Patient Population		Study Intervention	Endpoints		*P Values OR: HR: RR: & 95 CI:*	*Study Limitations*
				Inclusion Criteria	*Exclusion Criteria*		*Primary Endpoint & Results*	*Secondary Endpoint & Results*		
Antman 2000 10938172(1)	Development of original score to risk stratify pts presenting with ACS	Multisite RCTs, TIMI-11 B and ESSENCE	N/A	Clinical ACS, ECG changes, and elevated biomarkers	Planned revasc, bleeding risks, and correctable cause for angina	N/A	All-cause mortality, new or recurrent MI, severe ischemia leading to revasc	N/A	p<2 selected for multivariate modeling, then variables scored	Biomarkers all elevated; 65 y pg age cutoff
Pollack 2006 16365321(13)	Validation in ED population with chest pain	Convenience sample N=3,326 without new STE	N/A	Chest Sx and ECG obtained	New STE	N/A	Death/MI/revasc over 30 d	In-hospital and 14-d events	Graded relationship between score and events	Used parts of score to define management
Go 2011 21691204(14)	Attempt to add creatinine to TIMI risk score	Single center N=798	N/A	Ischemic Sx within 48 h	STEMI	N/A	CV death, MI, urgent revasc or Sx, and elevated biomarkers	N/A	Renal dysfunction increased risk, but not enough to add variable to system	Small and only 9% with eGFR, 30
Huynh 2008 19960136(15)	Across all ACS spectrum	Multicenter RCT with N=1,491 from angiographic arm	N/A	NSTE-ACS and STEMI	N/A	N/A	6-mo death and MI	N/A	2 mm ST deviation increased risk and risk was less regardless of score with less	All high-risk pts
Boersma 2000 10840005(2)	N/A	Multicenter RCT-Pursuit	N/A	NSTE-ACS	STE	N/A	Death and MI	N/A	Similar risk prediction to TIMI over groups with many similar variables	No biomarkers
Eagle 2004 15187054(16)	Original GRACE validation	Registry N=17,141	N/A	All ACS	N/A	N/A	6-mo all-cause mortality	N/A	p<0.25 into multivariate model	Registry data, 200 pts without 6-mo follow-up

Granger 2003 14581255(3)	Validation in NSTE-ACS as training set and then test set in registry with validation in RCT	11,389 from registry and then testing in 3,872 from GRACE and 12,142 from GUSTO IIb	N/A	NSTE-ACS	N/A	N/A	All-cause mortality during hospitalization	N/A	p<0.25 into multivariate model	Only high-risk pts
Eggers 2010 20598977(17)	Incremental prognostic value of multiple biomarkers in NSTE-ACS	Single center trial of 453 chest pain pts	NT-proBNP, cystatin GDF-15	Possible ACS	N/A	Biomarkers at presentation	All-cause mortality at 6 mo	NT-pro BNP not additive, cystatin minimally and GDF-15 helpful	ROC analysis	Small, but 92 deaths
Abu-Assi 2010 21095268(18)	Does GRACE score still work with modern management	MASCARA national registry N=5,985	N/A	Confirmed ACS	N/A	LVEF included	In-hospital and 6-mo mortality	LVEF did not add to GRACE score	N/A	Registry data, but contemporary management
Meune 2011 21444339(19)	Question as to whether hs-cTn or NT-proBNP influence prediction	370 pts from APACE trial with 192 MIs	Hs-cTnT and NT-pro added to GRACE score	Non-STE-ACS	N/A	N/A	Hospital and 1-y mortality	No additive benefit	N/A	All pts likely had elevated hs-cTnT

ACS indicates acute coronary syndrome; APACE, Advantageous Predictors of Acute Coronary Syndromes Evaluation trial; BNP, B-type natriuretic peptide; CV, cardiocvascular; ECG, electrocardiograph; ED, emergency department; ESSENCE, Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q wave Coronary Events; eGFR, estimated glomerular filtration rate; GDF,growth and differentiation factors; GRACE, Global Registry of Acute Coronary Events; GUSTO, Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries trial; hs-cTn, high sensitivity cardiac troponin; hs-cTnT, high sensitivity cardiac troponin T; LVEF, left ventricular ejection fraction; MASCARA, Manejo del Síndrome Coronario Agudo. Registro Actualizado national registry; MI, myocardial infarction; N/A, not applicable; NSTE, non-ST-elevation; NSTE-ACS, non-ST-elevation acute coronary syndrome; Pts, patients; NT-pro, N-terminal pro; NT-proBNP, N-terminal pro-brain natriuretic peptide revasc, revascularization; RCT, randomized controlled trial; ROC, receiver operating characteristic; STE, ST-elevation; STEMI, ST-elevation myocardial infarction; Sx, symptom; and TIMI, Thrombolysis In Myocardial Infarction.

Data Supplement 3. Cardiac Injury Markers and the Universal Definition of AMI (Section 3.4)

Study Name, Author, Year	Study Aim	Study Type/Size (N)	Intervention vs. Comparator (n)	Patient Population		Study Intervention	Endpoints		P Values, OR: HR: RR: & 95 CI:	Study Limitations
				Inclusion Criteria	*Exclusion Criteria*		*Primary Endpoint & Results*	*Secondary Endpoint & Results*		
Thygesen 2012 22958960(20)	Definition of MI	Guideline	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Roger 2006 16908764(21)	Prospective Evaluation of new criteria for Dx of MI	Prospective community based epidemiologic study	Identification of MI using TrT vs. CK-MB and CK compared with WHO and ARIC criteria	County residents with TrT ≤0.03 ng/mL identifying MI	Lower TrT values	N/A	Identification of MI 538 MI with TrT; 327 with CK; 427 with CK-MB	Clinician Dx mentioned MI in only 42% of TrT-based criteria (diagnosing UA in many) vs. 74% using previous criteria p<0.001	74% increase TrT vs. CK (95% CI: 69%–79%) 41% inc TrT vs. CK-MB (95% CI: 37%–46%)	Participation rate of MIs was only 80% but similar to median of similar participation studies
Hamm 2000 10880424(22)	Classification of UA	Reclassification based on Tr levels	N/A	Angina at rest within 48-h Class IIIB into Tr+ and Tr-	N/A	N/A	30-d risk of death 20% in IIIB Tr+, <2% in IIIB Tr +	N/A	N/A	N/A

Kavsak 2006 16824840(23)	Impact of new classification of MI	Retrospective analysis using CK-MB vs. TnI analysis for MI defined by 258 pts with ACS	TrI vs. CK-MB Dx based on MONICA or AHA definition of MI	2 SPSS CK-MB, TrI ≥20% change using 99% TrT cutoff	N/A	2 specimens CK-MB, TrI drawn at least 6 h apart	AMI prevalence MONICA CK-MB 19.4% AHA 19.8%. TnI to 35.7%	TrI-vs. CK-MB p<0.001 for increase MI definition using TnI	cTnI 35.7% (30.1–41.7) Relative increase 84%	Exclusion of nonischemic diseases causing Tr elevation
Eggers 2009 19231317(24)	Effects of new UDMI on misdiagnosis with single evaluation of Tr	Retrospective evaluation of stable community sample (995) and post-AMI pts (1380) with TrI≥99th percentile	Evaluation of single Tr in stable population	Stable community population. Stable 3-mo post-MI pts	Evidence of clinical instability	1 cTnI	Community Sample; 0.6% MI by UDMI Stable post-MI; 6.7% MI by UDMI	N/A	N/A	N/A
Goodman 2006 16504627(25)	Diagnostic and prognostic impact of new UDMI	Multicenter observational prospective Registry (GRACE) 26,267 pts with ACS	Use of CK and Tn neg 16,797 vs. CK-MB and Tn 10,719 for hospital. fatality, 14,063 vs. 8,785 for 6-mo mortality	>18 y with possible ACS with ECG abnormal or CAD history. CK, CK-MB. Tn.	NS comorbity, trauma, surgery, lack of 1 biomarker	CK CK-MB Tn Follow up for 6 mo	Tn+ levels demonstrate higher in-hospital and 6-mo mortality rates than higher CK levels	In entire population, Tn+ status vs. CK status 6-mo. mortality:1.6 (1.4–1.9)	Hospital fatality rates higher with Tn+ vs. CK+: 2.2 (95% CI: 1.6–2.9) with Tn+/CK-MB-: 2.1 (95% CI: 1.4-3.2)	34% in GRACE registry excluded because of use of 1 biomarker only
Eggers 2011 20869357(26)	Clinical implications of relative change in cTnI levels with chest pain	Retrospective study of 454 pts with ACS within 24 h of admission with 5.8-y follow-up	UDMI with prespecified cTnI changes from ≥20%, 50%, 100%	N/A	cTnI <99th percentile	cTnI levels	Peak cTnI level ≥99th percentile positive change ≥20% in 160 pts. 25 pts had no AMI by ESC/ACC criteria	N/A	All 160 pts had significant raised mortality HR 2.5 (95% CI: 1.7–3.8) Higher TnI deltas were not associated with higher mortalities	Analysis of assay could not be validated by hs-Tr assay. No review of pts records for type I or 2 AMI No long-term risk assessment
Mills 2012 22422871(27)	Evaluation of ACS pts by using cTnI diagnostic threshold and ≤99th percentile on Dx and risk for future events	Retrospective cohort study with 1-y follow-up of 2,092 consecutive pts with suspected ACS	Study groups: cTnI <0.012, 0.012–0.049, and ≥0.50 (99th percentile) with C of V ≥20% vs. previous diagnostic criteria	cTnI ACS	Noncardiac chest pain, tachyarrhythmia, anemia. Severe Valve HD, HOCM, pericarditis, cocaine use	cTnI values	1-y outcomes based on cTnI subgroups: 0.012–0.049 had higher mortality and re-MI than <0.012 (13% vs. 3%) Increase in Dx of MI based on new criteria by 47%	Compared with ≥0.050, Tr 0.012–0.049 had a higher risk profile, but less likely to be investing for AMI	p<0.001 for 1-y outcome of 0,012–0.049 vs. <0.012	Not a prospective study. Tn levels of 0.012-0.049 were considered "normal" and not repeated. Possible myocardial ischemia due to noncardiac illness.
TRITON-TIMI 38 Bonaca 2012 22199016(28)	Association between new and recurrent MI using new UDMI classification system and risk of death	Prospective cohort analysis of 13,608 pts with ACS undergoing PCI TRITON-TIMI 38 study	Follow-up of recurrent MI vs. no follow-up MI and risk of death at 6 mo	Types 1, 2, 3, 4, 5 MI	Cardiogenic shock or any condition that was associated with decreased survival over 15 mo	Tn used preferentially for recurrent MI and CK-MB for peri-PCI MI	Risk of death at 6 mo after follow-up MI: MI at follow-up 6.5% vs. 1.3% and by subtypes	N/A	p<0.001 for death after recurrent MI vs. no recurrent MI p<0.001 for difference with each of 5 subtypes	Association of MI with death not necessarily related to causality. Confounders could explain relationship. Standard Cox regression may bias

										results

ACC indicates American College of Cardiology; ACS, acute coronary syndrome; AHA, American Heart Association; AMI, acute myocardial infarction; ARIC, Atherosclerosis Risk in Communities; CAD, coronary artery disease; C of V, coefficient of variation; CK, Creatine Kinase; CK-MB, Creatine kinase-MB; cTnI, Cardiac troponin I; Dx, diagnosis; ECG, electrocardiograph; Elev, elevation; ESC, European Society of Cardiology; GRACE, Global Registry of Acute Coronary Events; HD, heart disease; Hs-Tn, high-sensitivity Troponin; HOCM, Hypertrophic Obstructive Cardiomyopathy; MB, myocardial band; MI, myocardial infarction; MONICA, Multinational MONItoring of trends and determinants in CArdiovascular disease; N/A, not applicable; NSTEMI, non-ST segment elevation myocardial infarction; pt, patient; PCI, percutaneous coronary intervention; SPSS; STEMI, ST elevation MI; TIMI, thrombolysis in myocardial infarction; Tn, Troponin; Tn+, positive troponin, Tn-, negtative troponin; Tr, Troponin; TRITON, Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel; TrT, Troponin T; TrI, Troponin I; UA, Unstable angina; UDMI, Universal Definition of MI; and WHO, World Health Organization.

Data Supplement 4. Cardiac Troponins (Section 3.4.3)

Study Name, Author, Year	Study Aim	Study Type/Size (N)	Intervention vs. Comparator (n)	Patient Population		Study Intervention	Endpoints		P Values, OR: HR: RR: & 95 CI:	Study Limitations
				Inclusion Criteria	*Exclusion Criteria*		*Primary Endpoint & Results*	*Secondary Endpoint & Results*		
Apple 2009 19299542(29)	Dx, accuracy of cTnI for early detection of AMI and risk prediction for adverse events	Prospective cohort study 381 with possible ACS	VITROS TnI-ES assay 2× vs. clinical Dx of AMI	Sx suggestive of ACS in ED	No 2nd Tn level	Tn assay at admission and 6 h later for delta change	Sens and spec for MI from admission and delta change (see p values) Sens increased from admission to 6-h cTnI and ROC from 0.82–0.96 (p<0.001)	Risk stratification improved by 30^ Delta to initial cTnI >99th percentile. Risk of death/follow-up MI within 60 d	Sens admission cTnI for AMI 69% (95% CI: 55%–81%) Spec 78% (95% CI: 73%–82%) 6-h cTnI Sens 94% (95% CI: 84–99) Spec 81% (95% CI: 77%–85%) Deltas >30% Sens 75% (95% CI: 6%–86%) Spec 91% (95% CI: 87%–94%) Delta cTnI added to initial or follow-up cTnI improved risk stratification p<0.001	Difficulty in ascertaining time of initial Sx. Problems with getting 2nd sample at 6 h Question of false +cTnI Initial rather than discharge sampling may have biased evaluation of risk at 60 d
Bonaca 2010 20447535(30)	Px implication.of low-level inclusion in Hs-cTnI in possible ACS	Prospective multi study 4,513 with NST-ACS	+ or – hs-cTnI 99th percentile for death/MI in 30 d	NST-ACS	Shock ,ST-elevation, revasc before random	Baseline cTnI with cutpoint at 99th percentile	+cTnI higher risk of death/MI at 30 d than -cTnI 6.1% vs. 2.0% p<0.001	Pts with low-level increases 0.04-1.0 at <risk than cutpoint of 0.04 (5.0% vs. 2.0%); p=0.001	Risk of death 12 mo vs. <0.04 ug/L 6.4% vs. 2.4%; p=0.005	Does not address all pts with nontraumatic chest pain
Kontos 2010 21095267(31)	NSTEMI with +Tn but -CK-MB in treatment and outcomes	Post hoc data base analysis 16,064 with NSTEMI	Tr+ MB- vs. Tr+ MB+	Present within 24 h of Sx with NSTEMI	No STEMI	Biomarkers on admission, Tr and CK-MB	Treatment and in-hospital outcomes. In-hospital mortality lower in MB pts	MB- were older and had more comorbidities. p<0.01 and fewer intervals	In-hospital mortality: MB+ 4.9 vs. 3.8 MB− p<0.02	No central core lab in multi-institutional study

		Tr+ and MBCK -								
Lindahl 2010 20691825(32)	Hs-cTnT comparison with std cTnT for risk assessment	Prospective cohort 1,452	Effect of + by both assays vs. only 1 assay	Pts with ACS	No coronary angiography within 12 h	Both cTnT collected 48 h after randomization	+Hs-TnT same 1-y mortality. Whether + or - with St-TnT	For death or AMI at 30 d + only for Hs-TnT had interim risk	+Hs-TnT 1-y mortality 9,2% vs. 1.6%; p=0.001 For – by both assays	Pts with higher pretest risk than typical chest pain pts in ED
Giannitsis 2010 20167697(33)	Dx, performance of Hs-cTnT for detection of NSTEMI in ACS	Retrospective cohort analysis 57 with UA and evolving NSTEMI	Baseline concentrations and serial concentrations at 3 h and 6 h	UA or NSTEMI with initial –cTnT	Immediate PCI or kidney dysfunction	Hs-cTnT baseline, 3, 6 h delta change >20%,or ROC optimized value >117% 3 h, or 246% 6 h	Hs-cTnt Dx 61% at baseline to 100% at 6 h. Dx increase by 34% above std cTnT	Doubling of hs-TnT with initial 99% + positive predicted value 100% − predicted value 88%	Delta changes and ROC optimized values spec 100% with sens 69% and 76%	Admission to chest pain unit more selective than typical ED admissions
Giannitsis 2008 18206741(34)	Serial TnT measurements vs. MRI infarct mass	Retrospective cohort analysis 31 STEMI and 30 NSTEMI	AMI with TnT and MRI	STEMI and NSTEMI with MRI before discharge	Lack of biomarkers at any of 5× up to 96 h from admission	TnT at admission and daily to 96 h.	Except for admission values, all TnT at various times correlated with infarct size	Estimation of infarct mass on d 4 was lower for NSTEMI than STEMI r=0.75 STEMI r=0.36 NSTEMI	cTnT at d 4 showed highest correlation and performed as well as peak cTnT and AUC r=0.66 vs. r=0.65 vs. r=0.69	Possible poor timing of sampling with NSTEMI and visualization problems with MRI in NSTEMI vs. STEMI
Keller 2011 22203537(35)	Diagnostic performance of hs-cTnI with continued. cTnI for serial changes	Prospective multicenter analysis 1,818 with suspected ACS, 413 with AMI	Hs-TnI and St-TnI	Suspected ACS	Major surgery or trauma within 4 wk, pregnancy, drug abuse	Hs-TnI and St-TnI at baseline and 3 h serial changes	Both Hs-TnI and St-TnI at 99th percentile at admission and 3 h had similar sens and spec	3 h after admission. Sens 98.2% and –predicted value 99.4% for both assays.	Hs-TnI at admission sens 82.3%,−pred value 94.7% St TnI sens 79.4%	Final Dx of AMI by in house Tn, biasing biomarker assays toward Tn High proportion of MI vs. other studies
Younger 2007 17540686(36)	72-h TnI estimate with MRI for infarct size	Prospective cohort analysis 93 MI 19 NSTEMI	TnI correlation with MRI	STEMI, NSTEMI, LBBB 1st MI TnI CK MRI	Prior AMI contraindication to MRI previous revasc, PCI before MRI	Admission and 12-h TnI and CK MRI average 3.7 d from admission	72h Tn similar to CK for infarct size estimate and superior to 12-h TnI	Correlation of 12-h TnI with microvascular obstruction was NS p=0.16 Compared with peak CK r=0.44 72-h TnI r=0.46 p=0.0002	72 h TnI vs. MRI R=0.62 p<0.0001 12-h TNI R=0.56 p=0.0003 Peak CK R=0.75 p<0.0001	12 and 72-h TnI available only on 37 pts and 64 pts. Only 19 NSTEMI. Data larger than on previous studies of Tn MRI correlations.
Apple 2012 22465126(37)	Diagnostic accuracy and risk stratification of cTnI-ultra assay	Prospective cohort study 371	cTnI at admission and up to 24 h for optimum deltas using ROC analysis	Possible ACS with follow-up for 60 d	N/A	cTnI at 0-, 6-, 24-h for optimum % change, absolute % change, change, absolute value of change	Cardiac events and death in 60 d. Optimal value of change was absolute value of change delta	Sens and Specs: Absolute value: 89.8-93.7 Change: 67.5-99.0 Absolute value of % change: 75.5-85.7 % change: 71.4-89.7	AUC Diagnostic accuracy of absolute value of change 0.96 (0.94, 0.98). Change 0.76 Absolute value of % change 0.88 % change 0.77	Long period needed to evaluate deltas. Further studies need to determine whether 2–3-h changes can provide adequate Dx and prognostic information

Reichlin 2011 21709058(38)	Diagnostic accuracy of absolute value relative changes in cTn	Prospective multicenter 836 with ACS	Absolute value relative changes in cTn	Sx suggesting AMI	STEMI, terminal kidney failure	Hs-TnT and cTnI ultra at admission and 1 h and 2 h	ROC at 2-h higher for absolute than relative changes	ROC absolute cutoff 2 h 0.007 ug/L hs and 0.020 ug/L for ultra	ROC absolute change Hs-TnT 0.95 (95% CI: 0.92–0.98) vs. relative change 0.76 (95% CI: 0.70–0.83) p<0.001	Observation cannot quantify clinical benefit of results
Aldous 2012 22291171(39)	Early means of hs-TnT vs. conventional cTnT in NSTE-ACS	Prospective cohort 909, and 205 with AMI	NSTE-ACS with conventional and hs-TnT assays	NSTE-ACS	STEMI <18 y, unable to follow-up	Hs-TnT and conservative TnT at admission, 2 h and 6-12 h	Dx of MI on admission at 2 h Hs-sens 92.2% and spec of 79.7%	Mortality at 1 y Hs superior to conventional Death 5.4 (95% CI: 2.7–10.7) and HF 27.8 (95% CI: 6.6–116.4)	Hs TnT 95% CL for MI Dx at 2 h Sens (95% CI: 88.1%–95.0%) spec (95% CI: 78.6–80.5)	Blood samples not taken beyond 2 h. Used cTnI as gold standard for Dx of MI
Mueller 2012 22134520(40)	Kinetic changes on hs-cTnT in ACS and non-ACS	Prospective cohort 784 NSTEMI 165	Pts with ACS with hs TnT vs. non-ACS with hs-TnT above 99th percentile	ACS with 2nd blood draw within 6-h Non-ACS with 2 blood draws	STEMI or LBBB	Hs-TnT-ACS and non-ACS with elevated hs-TnT2 blood draw within 6 h	Absolute delta vs. relative delta ROC-optimized value 6.9 ng/L was sup to rel change ≥20%	+Predicted value of absolute change 82.8% -predicted 93.0%	ROC for absolute change added value for entire ACS cohort vs. relative change. p<0.0001	Relative changes confined to 6 h, not 24 h. Not all pts received angiography

ACS indicates acute coronary syndrome; AMI, acute myocardial infarction; ASA, aspirin; AUC, area under the curve; CK, Creatine Kinase; CKD, chronic kidney disease; CK-MB, creatine kinase-MB; cTnT, cardiac troponin T; cTn, cardiac troponin; cTnI, cardiac troponin I; Dx, diagnosis; ED, emergency department; Hs, high sensitivity; hs-cTnI, high-sensitivity cardiac troponin I; hs-cTnT, high-sensitivity cardiac troponin T; hs-TnT, high-sensitivity troponin T; LBBB, left bundle-branch block; MBCK, MB Isoenzyme of Creatine Kinase; MI, myocardial infarction; MRI, magnetic resonance imaging; N/A, not applicable; NST-ACS, non-ST acute coronary syndrome; NSTE, Non-ST-elevation; NSTEMI, Non-ST elevation myocardial infarction; PCI, percutaneous coronary intervention; Pts, patients; Px, prognosis; ROC, Receiver Operating Curves; Sens, sensitivity/sensitivities; Spec, specificity/specificities; Std TnI, standard troponin I; Std cTnT, standard cardiac troponin T; STEMI, ST-elevation myocardial infarction; Sx, symptom; Tn, troponin; TnT, troponin T; TnI, troponin I; and UA, unstable angina.

Data Supplement 5. CK-MB, MB Isoforms and Myoglobin, Compared With Troponins (Section 3.4.4)

Study Name, Author, Year	Study Aim	Study Type/Size (N)	Intervention vs. Comparator (n)	Patient Population		Study Intervention	Endpoints		P Values, OR: HR: RR: & 95 CI:	Study Limitations
				Inclusion Criteria	*Exclusion Criteria*		*Primary Endpoint & Results*	*Secondary Endpoint & Results*		
Apple 1999 9931041(41)	Use of triage panel of TrT, CK-MB, and myoglobin for AMI detection	Multicenter prospective study 192	Comparison of myoglobin, TnI and CK-MB for sens and spec	Pts in ED with ACS	N/A	Triage panel biomarkers to evaluate ROC for AMI pred	Concordance for detection or rule-out of MI TnI >89% CK-MB >81% Myoglobin >69%	Sens/Spec TnI: 98/100 CK-MB: 95/91 Myoglobin: 81/92	ROC values TnI: 0.97 CK-MB: 0.905 Myoglobin: 0.818 diff p<0.05	Does not address reinfarction or AMI presenting after 72 h
TACTICS-TIMI 18 Kleiman 2002 12354426(42)	CK-MB vs. TnT to predicted cardiac risk and benefit in AMI invasive strategy	Multicenter prospective study 2,220	CK-MB elevated in 826. With CK-MB-, TnT elevated in 361	1st 24 h of chest pain	N/A	Invasive or conservative strategy with CK-MB and TrT for 30-d and 180-d risk.	CV events 30 d/180 d Event rates 2× as high with CK-MB+ value −. benefit in invasive with Tr+, but CK-	No evidence of interaction between CK-MB elevation and strategy on 30-d and 180-d endpoints	OR benefit of invasive strategy CK-Tr+ 30 d: 0.13 (95% CI: 0.04–0.39) 180 d: 0.29 (95% CI: 0.16–0.52)	Small group analysis–hypothesis generating

Aviles 2002 12372578(43)	Long term Px in UA with elevated TnI and normal CK-MB and CK	Retrospective cohort 724	All CK-MB- and TnI+	Clinical UA including Class IIIa	N/A	Using TrI with normal CK and CK-MB for 2-y risk evaluation	2-y all-cause mortality 20% with Tn>0.5 ug/L, 8% with <0.5 ug/L	N/A	2-y mortality Tr >0.5 vs. <0.5 HR 2.59 (95% CI: 1.66–4.05); p<0.001	Study did not evaluate serial ECGs for dynamic changes
Sallach 2004 15464666(4)	Sens of myoglobin with normal TnI in AMI	Prospective multicenter 817	Myoglobin and TnI	Possible AMI with normal TrI (27)	Incomplete biomarker panel or noncardiac	Myoglobin Dx of MI with normal TnI	Increase myoglobin of 20 ng/mL from 0-90 min max diagnostic utility with –myoglobin and-TnI at admission	Combination sens change myoglobin+ TnI at 90 min 97.3%	Change Myoglobin >20 90 min Sens: 83.3%, 88.6% spec: 99.5% – Predicted value for AMI	Relatively small number of AMIs. Predetermined values of myoglobin not evaluated
Eggers 2004 15459585(44)	Value of adding myoglobin to TnI to exclude AMI	Prospective cohort 197	TnI and CK-MB	Chest pain >15 min in past 24 h	STE	TnI and Myoglobin for exclusion of MI	TnI highest sens of all markers at all-time pts.	TnI 0.07 ug/L cutoff sens: 30 min=93%, 2 h=98%, 3 h=100%	TnI sens 93% spec 81% at 2-h CK-MB 79% Myoglobin 67%	Relatively small group. Relatively long delay time from pain to admission
Storrow 2006 17112930(45)	Associated among discordant Tn, CK, and CK-MB chest pain evaluation	Multicenter prospective registry 1,614	Discordant CK-MB/Tn 113 includes MB with normal CK 239	Possible ACS	Transfer or ECG for routine purposes	CK-MB and Tr with evaluation of significance. of discordant values	OR for AMI vs. Tr-/CK-MB-both positive: 26.6 Tn+ 4.8 CK-MB+ 2.2	CK-MB+/CK- 5.7 (95% CI: 4.4–7.4) CKMN+/CK+ 4.36 (95% CI: 3.6–5.2) Ref: vs. CK-MB-	CK-MB/Tn+: 26.6 (95% CI: 18.0–39.3) Tn+/CK-MB-: 4.8 (95% CI: 3.4–6.8) Tn-/CK-MB+: 2.2 (95% CI: 1.7–2.8)	N/A
CRUSADE Newby 2006 16412853(46)	Frequency and implications of discordant CK-MB and Tn in ACS	Multicenter prospective 29,357	22,687 Tn+ 20,506 CK-MB+ 3,502 both – 2,988 only CK+ 5,349 only Tn +	High-risk NSTE-ACS	N/A	CK-MB and Tr during 1st 36 h of ACS to evaluate discordance	Adjusted OR for hospital mortality CK-MB+/Tn +: 1.53 CK-MB-/Tn+: 1.15 CK-MB+/Tn- 1.02	In-hospital mortality both−: 2.7% both+: 5.9% Only CK-MB+: 3.0% Only Tn: 4.5%	CK-MB+/Tn+: 1.53 (95% CI: 1.18–1.98) CK-MB-tn+: 1.15 (95% CI: 0.86–1.54) NS CK-MB+/Tn-: 1.02 (95% CI: 0.75–1.38) NS	Used individual labs for ULN. No account for timing of positive markers
Kavsak 2007 17306781(47)	Effect of Tn on myoglobin and CK-MB isoforms in ACS	Retrospective cohort 228	CK-MB isoforms, myoglobin and Accu TnI	Possible ACS	N/A	CK-MB , myoglobin and TrI to compare utility in R/O MI <6 h assays	Clinical sens for AMI: For both myoglobin and CK-MB Dec. in ESC/ACC MI def	N/A	WHO MI def: sen >90% ESC/ACC def: Both sen<70% Using TnI assay	Insufficient time elapse before remeasuring TnI
Jaffery 2008 19061710(9)	Myoglobin and TnI pred of long-term mortality in ACS	Retrospective cohort 951	TnI, myoglobin, and CK-MB	Possible ACS	N/A	TnI, Myoglobin, and CK-MB at presentation with ACS	+TnI and +Myoglobin, but not +CK-MB Pred. 5-y all-cause mortality	N/A	+TnI: 1.7 (95% CI: 1.3–2.3) +Myoglobin: 1.6 (95% CI: 1.2–2.1) +MB: NS	Single center. TnI assay no longer in use. No peak levels of markers recorded
Di Chiara 2010	Pred value of TnI vs.	Prospective	55 STEMI and 5	AMI + reperfusion	No pacemakers,	TnI and CK-MB at	Tn at 72 h most accurate	N/A	TnI:	Blood samples every

20588136(10)	CK-MB for infarct size with CMR	cohort 60	NSTEMI TnI, CK-MB	with CMR within 7 d	clips, peak markers on admission	admission and serially up to 96 h from Sx onset	estimate of predischarge infarct volume		0.84 (95% CI: 0.75–0.91) CK-MB: 0.42 (0.19–0.62) p<0.02	6 h could be too sparse. Could miss biomarker peak
ACTION-GWTG Registry Chin 2012 22434769(48)	Prognostic value of CK-MB vs. Tn in AMI	Retrospective registry 26,854	Peak CK-MB and TnI	AMI in data registry with biomarkers	Peak values below lab ULN	Peak CK-MB and TnI for in-hospital mortality	Both peak CK-MB and TnI are independently associated with hospital mortality CK-MB >TnI	N/A	Peak CK-MB C-statistic 0.831 Peak TnI C-statistic 0.824 p=0.001	Registry only collects in-hospital outcomes. Participation in registry voluntary
Ilva 2005 15667582(12)	Novel TnI in early risk stratification in ACS	Prospective cohort 531	Standard TnI novel TnI myoglobin	Biomarkers at 0 h, 1-12 h and 24 h after admission	Absence of 1 or more biomarkers	Comparison of 3 biomarkers at times indicated	Positivity of novel TnI assay for AMI in higher percent than other biomarkers	MI within 3 h of presentation: 50% by novel TnI and only 11.5% by reference TnI assay, (p<0.001) 44% by myoglobin (p=NS)	Novel TnI+ in 27.5%, standard TnI in 17.5%, (p<0.010) and myoglobin+ in 24.1% (p=0.067) ROC: novel TnI 0.937, ref TnI 0.775, myoglobin 0.762 (p<0.001)	Use a 1st generation TnI assay with low analytic limits
Volz 20012 21129891(13)	Can Tn alone be used for initial AMI screening with elimination of CK-MB	Retrospective cohort 11,092	TrT and CK-MB	All pts with TrT in ED with correspond CK-MB	Initial nonnegative Tn	CK-MB+ with TnT- to determine value on AMI screening	None with Tn- but CK-MB+ Judged to have AMI	N/A	Rate of true +CK MB with Tn- : 0% (95% CI: 0–0.04%)	No evaluation of CK-MB in pts with intermed or Tn+. No follow-up with -CK-MB or Tn.
Lim 2011 21292125(49)	CK-MB vs. Tn in Dx of AMI after PCI	Prospective cohort 32	TnI and CK-MB	PCI and CMR imaging baseline and 7 d	N/A	CK-MB and TnI after PCI to determine Dx of AMI	Only small min of +Tn had CMR abnormal CK-MB+ closely approximate CMR injury	Percent changes in inflamed markers corresponded with CK-MB, but not TnI levels for CRP and SAA	ROC for detection of new MI CK-MB: 0.97 TnI: 0.985 NS, but poor TnI specific 22% TnI 93% CK-MB	Small sample size. No evaluation of inflammed markers after 24 for TNF alpha

ACC indicates American College of Cardiology; ACS, acute coronary syndrome; AMI, acute myocardial infarction; CK, creatine kinase; CK-MB, creatine kinase MB; CK-Tr+, creatine kinase troponin positive; CMR, cardiovascular magnetic resonance; CRP, C-reactive protein; CV, cardiovascular; Dx, diagnosis; ECG, electrocardiograph; ED, emergency department; ESC, European Society of Cardiology; MI, myocardial infarction; Myo, myoglobin; N/A, not applicable; NSTE-ACS, Non-ST elevation acute coronary syndrome; NS, not significant; NSTEMI, non-ST segment myocardial infarction; OR, odds ratio; PCI, percutaneous coronary intervention; Pred, predicted; pts, patients; Px, prognosis; ROC, receiver operator curve; SAA, serum amyloid A protein; Sens, sensitivity/sensitivities; Spec, specificity/specificities; STEMI, ST segment elevation MI; Tn, troponin; Tn+, positive troponin, Tn-, negtative troponin; TNF, tumor necrosis factor; TnI, troponin I; TnT, troponin T; TrT, troponin T; UA, unstable angina; ULN, upper limit normal; and WHO, World Health Organization.

Data Supplement 6. Bedside Testing for Cardiac Biomarkers (Section 3.4.4)

Study Name, Author, Year	Study Aim	Study Type/ Size (N)	Intervention vs. Comparator (n)	Patient Population	Study Intervention	Endpoints	P Values, OR: HR: RR: & 95 CI:	Study Limitations

				Inclusion Criteria	*Exclusion Criteria*		*Primary Endpoint & Results*	*Safety Endpoint & Results*	*Secondary Endpoint & Results*		
Hamm 1997 9385123(50)	Bedside evaluation of TnT and TnI in acute chest pain	Prospective cohort 773	TnT vs. TnI for Dx of MI and 30-d events +TnT 123 +TnI 171	Acute chest pain <12 h without STE	STE or AMI within 2 wk	Bedside tests of TrT and TrI 2×, arrival and >4 h	AMI TrI sens: 100% TrT sens: 94%	N/A	Event rates for – tests: 1.1% TnT 0.3% TnI	30-d event TrT 26 (10–49) TrI 61 (15–512)	All pts with +TnT admitted so event rate may be lower than that with conventional decision making
Van Domburg 2000 10980212(51)	Long-term prognostic significance of bedside TnT	Prospective cohort 163	TnT, CK-MB, myoglobin 98 TnT + <12 h 48 + baseline 50 positive 3-12 h 2 positive 12-96 h	Suspected ACS	MI within previous wk	Blood specimen at 0 h, 3 h, 6 h, 12 h, 24 h, 48 h, 72 h, 96 h Bedside assay TROPT and quantitative assay sample up to 12-h effect on mortality prediction	29%+ on admission 60%+ in 12 h	N/A	Early myoglobin predict 3-y mortality 3.7 (95% CI: 1.0–12.0)	+TROPT risk for 3-y mortality: 4.3 (95% CI: 1.3–14.0) Quantitative assay 2.9 (95% CI: 1.0–8.6)	Detection limit of TnT higher than 2nd generation Tn
Amodio 2007 17429291(52)	POC TnI at 99th percentile cutoff for diagnostic accuracy of MI	Retrospective cohort 516	Higher vs. lower TnI cutoffs and Dx of AMI 70 TnI+	Suspected angina or AMI	STE-ACS or LBBB	Bedside TrI Stratus CS for AMI Dx using different cutoffs 0.03–0.07 ug/L	Best clinical cutoff at 99th percentile 0.03	N/A	Sens of myoglobin at 2 cutoffs 36.4% and 49%	Tn Sens at 99th percentile 77.3% (68.3–84.7) 0.03>0.07 p<0.005	No info on outcomes Long median delay time from pain onset to admission No consideration of muscle trauma or renal insufficiency
DISPO-ACS Ryan 2009 18691791(53)	POC length of stay in ED	Multi-institute prospective study 2,000	Bedside Tn testing + central lab Central lab only 1,000 in each arm	Suspected ACS with biomarkers	Tachyarrhythmia or ECG AMI	POC markers vs. lab markers	POC discharge Home 4.5 h Lab discharge Home 4.6 h	N/A	Transfer to inpt POC 5.4 h Lab 5.5 h	Turnaround at baseline POC 0.30 h Lab 1.07 h	Possible Hawthorne effect bias in testing areas. Different interinstitute sampling times.
CRUSADE Takakuwa 2009 19743496(54)	Use patterns of POC testing for Tn in NSTE-ACS	Retrospective multi-institutional 12,604	POC with Tn+ vs. Tn- 6,185 +POC result 6,419 negative POC result	POC Tn in NSTE-ACS	Death within 24 h Hospital with 30 pts. Infrequent percentage use of bedside Tn	Hospital and pt characteristics In-hospital events and care variables Hospital using POC testing >50% vs. <50% testing	Higher POC had shorter ED stay, less likely to use drug IV	N/A	ED length of stay (h) No POC 4.2 (2.9–6.5) High POC 3.9 (2.6–6.0) p<0.0001	+POC results associated with expedited and higher use of anti-ischemic therapy. p<0.0001	Sample size relatively limited. No record of type of bedside marker test. No std. for + or − test
Birkhahn 2011 20825823(55)	POC vs. core lab testing for time saving and cost/benefit	Prospective cohort 151	POC and core lab testing of TnT TnT+ in 12 pts	Suspected ACS with 2 TnT 6 h apart	STE, ECG, or lack of serial biomarkers	POC (TnT) CK-MB, myoglobin vs. central lab testing (TnI) baseline +2h vs. baseline +6 h	6.5 h saved using POC and relative sens of 100%. p<.00001	N/A	POC pathway had 32% false positives POC sens 100%, spec 65% Accuracy 68%	POC benefited 60% (95% CI: 52–68) of pts with cost of $7.40 (95% CI: $6.40–$8.70) per direct pt care h saved.	Time of 2nd blood test varied widely

Scharnhorst 2011 21350097(56)	Sens and spec of bedside Tn compared with CK-MB and myoglobin	Prospective cohort 137	POC evaluation Tn, CK-MB, myoglobin, for rapid detection of +test 37+ ACS: 7 UA 26 NSTEMI 4 STEMI	Suspected NSTEMI	STE on AD ambulance to hospital	POC Tn values T0–T12 h and sens/spec for MI at 99% cutoff	At T2 Sens: 87% Spec: 100% +PV: 100% −PV: 96%	N/A	Use of 30% Diff T2-T0 without absolute included above 99th percentile Sens: 100% Spec: 87%	2-h sens and spec of myoglobin and CK-MB lower than Tn Myoglobin: 50/92 CK-MB: 48/96	Low number of pts. No subgroup analysis. Broad 95% CI.
ASPECT Than 2011 21435709(57)	Validate safety of predefine 2 h protocol (ADP) for ACS	Multicenter prospective observation study 3,582	POC evaluation Tn, CK-MB, Myoglobin 3260 ADP+ 270 ADP– 3,582 30-d follow-up	Suspected ACS	STE ACS, Noncoronary chest pain	ADP use of POC Tn, CK-MB, and myoglobin with 30-d follow-up	Major CV events at 30 d ADP Sens 99.3%	ADP class. 9.8% low risk. Major adverse event in only 0.9%	For 30-d events TIMI + ECG Sens: 98.1% Spec: 14.6% -PV: 98.3%	For 30-d events ADP Sens: 99.3% (95% CI: 07.9–99.8) Spec: 11% (10–12.2) −PV: 99.1% (97.3–99.8)	Low specificity. Atypical Sx not included
GUSTO-IV Venge 2010 21095269 (58)	Comparison of POC vs. laboratory assays of Tn	Prospective cohort 1,069	2 POC vs. 2 central laboratory assays cTnI	All pts in ED with Tn assays	N/A	Tn assays with 99th percentile URL cutoffs	99th percentile cutoffs: central lab cutoffs identified more pts with high cTnI and predicted higher % deaths	N/A	Central lab identified more who died of CV disease up to 3 mo: 88% vs. 50% 1: 81% vs. 54% 2	99th percentile POC 1 vs. central lab 1: 20% vs. 39% POC 2 vs. central lab: 2:27% vs. 74% p<0.001 for each	No attempts to relate results to Dx of MI, only outcome predictions
[RATPAC] Bradburn 2012 21617159(10)	Variation in outcomes and costs in different hospitals using POC	Multicenter prospective analysis 2,243	POC vs. central lab assays at 6 hospitals	Suspected, but not proven AMI at 6 hospitals.	Proven MI by ECG, high-risk ACS, known CAD, serious noncoronary pathology, recurrent chest pain	POC or std care with CK-MB, myoglobin, and Tn biomarkers	Difference in proportion of pts successfully discharged. POC led to higher proportion in 4, lower in 1 and equivocal in 1.	N/A	The cost per pt varied from £214.49 <control group to £646.57 more expensive with weak evidence of heterogeneity among centers p=0.08	OR varied from 0.12 (95% CI: 0.01–1.03) to 11.07 (05% CI: 6.23–19.66) with significant heterogeneity between hospitals	1° outcome based upon 1° effectiveness outcome rather than economic measures. Response rate was only 70% so possible responder bias
[RATPAC] Fitzgerald 2011 21569168(59)	Cost effectiveness of POC biomaker assay	Multicenter prospective analysis 2,243	Std care 1,118 POC 1,125	Suspected, but not proven AMI at 6 hospitals	Proven MI by ECG, high-risk ACS, known CAD, serious noncoronary pathology, recurrent chest pain	POC or std care with CK-MB, myoglobin, and Tn biomarkers	POC associated with higher ED costs, coronary care costs, and cardiac intervention costs, but lower general pts costs	N/A	Probability of std care being dominant 0.888 POC dominant 0.004	Mean costs per pt $1,987.14 with POC vs. $1,568.64 with std care p=0.056	1° outcome based on 1° effectiveness outcome rather than economic measures. Response rate 70% so possible responder bias.

1º indicates primary; ACS, acute coronary syndrome; ADP, adenosine diphosphate; AMI, acute myocardial infarction; CAD, coronary artery disease; CK-MB, creatine kinase MB; cTnI, cardiac troponin I; CV, cardiovascular; Dx, diagnosis; ECG, electrocardiograph; ED, emergency department; IV, intravenous; Lab, laboratory; LBBB, left bundle-branch block; MI, myocardial infarction; Myo, myoglobin; NSTE ACS, non-ST elevation acute coronary syndrome; NSTEMI, Non-ST-elevation MI; POC, point of care; pts, patients; +PV, positive predictive value; -PV, negative predictive value; Sens, sensitivities; Spec, specificities; Std, standard; STE, ST-elevation; STE ACS, ST-elevation acute coronary syndrome; STEMI, ST-elevation MI; Sx, symptom; TIMI, thrombolysis in MI; TnI, Troponin I; TnT, troponin T; TrI, troponin I; TROPT, Troponin T rapid test; TrT, troponin T; and UA, unstable angina.

Data Supplement 7. Summary Comparison of Injury Markers (Section 3.4.4)

Study Name, Author, Year	Study Aim	Study Type / Size (N)	Intervention vs. Comparator (n)	Patient Population		Study Intervention	Endpoints		P Values, OR: HR: RR: & 95 CI:	Study Limitations
				Inclusion Criteria	*Exclusion Criteria*		*Primary Endpoint & Results*	*Secondary Endpoint & Results*		
FRISC Lindahl 2000 11036119(60)	Multiple biomarkers as long-term risk predictors for CV death	Multi-institution prospective 917	TnT CRP Fibrinogen	UA or possible MI within 72 h	Increased risk of bleeding (dalteparin trial)	Biomarker samples at 0 h, 12 h, 24 h	Cardiac death at 37 mo Multivariate analysis TnT and CRP independently predicted of mortality	Highest tertile of CRP significant for mortality. Lowest 2 tertiles NS difference p=0.001 3rd vs. 2nd tertile	Multivariate analysis: High TnT: 10.8 (95% CI: 2.6–44.6) High CRP 2.3 (95% CI: 1.3–4.0) Fibrinogen NS	No evaluation of LV function. Use of death certificates may misclassify.
TACTICS-TIMI18 Sabatine 2002 11956114(61)	Use of multiple biomarkers to predict MACE in NSTE-ACS	Multi-institution prospective 450 (OPUS-TIMI 16) 1,635 (TACTICS-18)	TnI, CRP, BNP in combination vs. each alone	Possible ACS within 72 h	Age <18 y pregnancy, significant comorbidities, bleeding tendency	3 biomarkers at enrollment	Death/MI/HF at 6 mo Number of elevated biomarkers include prediction of outcome	30-d mortality RR 0 Biomarker+: 1 1 Biomarker+: 1.8 2 Biomarker+: 3.5 3 Biomarker+: 6 p=0.014	1 Biomarker+:2.1 p=0.006 2 Biomarker+:3.1 p<0.001 3 Biomarker+: 3.7 p=0.001 (6 mo)	Using binary cutpoints of biomarkers rather than higher levels. Very insensitive cTn assay
HOPE Blankenberg 2006 16831981(62)	9 Biomarkers to evaluate improved CV risk in a 2nd d prevention population	Multicenter prospective 3,199	Evaluation of CRP fibrinogen, IL-6, TNF 1, 2, sIAM-1, s-IAM-1, BNP, IL-1 RA microalbuminuria, individually for MACE	Hx of CAD, stroke, PAD, diabetes	HF, low LVEF, nephropathy MI, or stroke 4 wk before enrollment	9 biomarkers on enrollment	Combined events 4.5 y Significant relations: BNP, sIAM, Microalbuminuria, s-IRA-1, fibriongen	Only inclusion of BNP provided info above that from traditional risk factors	HR: BNP 1.721<0.001 sIAM 1.46=0.0003 Microalbuminuria 1.55=0.0004 sIAM1.46=0.0003 Fibriogenen 1.31=0.02	Only baseline measurements; later analysis on frozen specimens; for our purposes, not an ACS study
McCann 2008 18682444(63)	Role of novel biomarkers in AMI Dx	Multicenter prospective 664	Multiple biomarker comparisons including cTnT, H-FABP, BNP, hs-CRP, D-dimer, MPO, MMP-9, PAPP-A, sCD40L	Chest pain <24 h to 2 CCUs	Transfer from other hospital thrombolytics or anticoagulant	Biomarkers on entry	Dx of AMI only H-FABP challenged cTnT and combined approach improved -PV	-PV H-FABP 75% cTnT–90% Either–97% (95% CI: 91%–99%)	Sens H-FABP: 73% Sens cTnT: 55% On admission p=0.043. Combined improved sens: 85%; p≤0.04 vs. individual values	Only single measure of biomarker.
FRISC Eggers 2009 (64) 1960803464)	Risk predicted by multiple biomarkers in NST-ACS	Multicenter retrospective analysis 877	Evaluated: cTnI, BNP, CRP, estimated GFR	NSTE-ACS	Bleeding risk, high creatinine, PCI in previous 6 mo, decision for PCI before randomization	Biomarkers at enrollment, 6 wk, and 6 mo	5-y follow-up BNP strongest predictor for mortality	BNP: 6 wk: 1.5 p<0.001 6 mo: 1.4 p=0.001	BNP 1.7 (95% CI: 1.3–2.1); p<0.00 1 5 y only 6 wk BNP showed significant increments to established risk factors C-statistic 0.69; p=0.03	Outcomes before more advanced 2º previous measures. Preselected population
ARCHIPELAGO	Multiple biomarkers	Multicenter	Evaluated 9	NSTE-ACS	STE-ACS,	Biomarkers at	Biomarkers for	IL-6 AUC significant	IL-6: 1.69 (95% CI: 1.2–2.3)	Post-hoc analysis;

Beygui 2010 20723640(65)	for risk in NSTE-ACS	prospective trial Post hoc analysis 440	biomarkers: CRP, IL-6, MPO, PL-22, MMP-9, IMA, sCD40L, BNP, aldosterone, cTnI		planned corresponding interval, CHF, hypotension, low creatinine Cl	randomization	Ischemia/HF at 2 mo IL-6 corresponding with Ischemia BNP, aldosterone MMP-9 for HF	improved model for ischemia, 3 biomarkers + for HF improved performance models for HF	BNP :3.2 (95% CI: 2.0–5.0) Aldo: 1.57 (95% CI: 1.1–2.6) MMP-9: 0.64 (95% CI: 0.46–0.88)	Only 2-mo follow-up Select group of pts. No indication of severity of HF.
Manhenke 2011 22197217 (66)	Elucidating complex interactions between circulated biomarkers following AMI	Multicenter prospective trial 236	37 biomarkers	AMI complicated by HF	Not Stated	Biomarkers median 3 d after AMI Dx	2 sets of biomarkers corresponded with risk for death and combined death/reinfarction	Natriuretic peptides among others provided significant contribution to risk assessment	Of 5 sets of biomarkers only 2 sets showed significant prediction	Limited number pts Relatively small number events. Blood Time frame 1 d–10 d post- MI
Bhardwaj 2011 21835288(67)	Assess role of 5 biomarkers in Dx in ACS	Prospective cohort 318	Evaluated: BNP, IMA, H-FABP, hs-TnI, FFAu vs. cTnT	Possible ACS	Multiple including ESRD, thrombolytic agents, noncardiac chest pain	Biomarkers at presentation	Compared with cTnT, diagnostic information increased with BNP, FFAu, hs-TnI, but not IMA and H-FABP	+PV cTnT: 65% hs-TnI: 50% FFAu: 40% BNP: 28% IMA: 17% H-FABP: 26%	Sens and –PV: BNP: 73%, 90% Hs-TnI: 57%, 89% FFAu: 75%, 92% (Highest) Increased C-statistic for cTnT : BNP 0.09 Hs-TnI 0.13 FFAu 0.15 All p≤0.001	Small sample size Incomplete biomarker Data. Dichotamous cutpoints rather than multiple cutpoints
MERLIN-TIMI Scirica 2011 21183500(68)	Incremental prognostic value of multiple biomarkers in NSTE-ACS	Multicenter prospective 4,352	cTI BNP CRP MPO	Possible ACS	STE-ACS ESRD CV Shock Short life expectancy	Biomarkers at presentation	Including all biomarkers only BNP and cTnI associated with 12-mo CV death Only TnI with reinfarction	Addition of biomarkers to reference for CV death/HF: cTnI: 0.776 BNP: 0.790Ref: 0.749	Addition of biomarkers to reference for CV Death: cTnI: 0.805 BNP: 0.809 p<0.001 Ref: 0.784	LV function incomplete. No serial evaluations of biomarkers, not generalizable to overall population.
CAPTURE Oemrawsingh 2011 21558475(69)	Predictive value of 7 Biomarkers in NSTE-ACS	Multicenter prospective 1,090	Hs-CRP MPO sCD40L IL-10 TnT PIGF PAPP-A	Possible NSTE-ACS	Ischemia >48 h from enrollment	Biomarkers after last episode of angina	4-y MI/death A multimarker model of TnT, IL-10, MPO, and PIGF predicted 4-y rates: 6.0% (all normal) 35.8% (3+ abnormal)	TnT: 1.8 (95% CI: 1.2–2.6) IL10: 1.7 (95% CI: 1.1–2.6) PIGF: 1.9 (95% CI: 1.3–2.8) CRP: 1.0 NS sCD40L: 1.2 NS MPO :1.5 (95% CI: 1.1–2.1) PAPP-A: 1.1 NS	Admission levels of +TnT: HR 1.8 +IL-10:HR: 1.7 +PIGF:HR: 1.9 +Myoglobin:HR: 1.5 Significant prediction for outcomes in multivariate analysis	Not adjudicated data for MI Dx No info on long-term medications
FAST II FASTER I Eggers 2011 22456003(70)	Predictive of MI with multiple biomarkers Combines with hs-TnT	Retrospective cohort 360	Hs-TnT + h-FABP copeptin	NSTEMI (retrospective Classification)	STEMI	Biomarkers at enrollment	Hs-TnT greater accuracy in Dx of AMI than H-FABP and copeptin	No increase in C-statistic for hs-TnT by combining with H-FABP 0.85 or copeptin 0.84	C-statistics Hs-Tnt: 0.84 H-FABP: 0.80 p=0.04	Retrospective, small sample, from 2 different studies. No serial biomarkers

									Copeptin: 0.62 p<0.001	
Meune 2012 22507551(71)	Multimarker evaluation in suspected AMI with undetectable cTn levels	Retrospective multi-institution 325 with undetectable cTnT	cTnT- 15 biomarkers Including CK-MB and MPO	ACS with undetectable cTnT at 0 h and 6 h.	Detectable cTnT	Biomarkers >6 h from enrollment ESRD	At mean follow-up 668 d for death/MI hs-TnT, MR-Pro ADM and PDF-15 showed increased risk	Sens/spec for death/MI (%) Hs-TnT: 43,86 MR-Pro ADM: 43,76 GDF-15: 95,55	ROC AUC for death/MI: Hs-TnT: 0.73 (95% CI: 0.6–0.8) MR-Pro ADM: 0.71 (95% CI: 0.6–0.8) GDF-15: 0.78 (95% CI: 0.71–0.86)	Subgroup analysis Relatively low cardiac events in follow-up
Schaub 2012 22057876(72)	Markers of plaque instability use in AMI Dx and risk	Prospective multicenter 398	Multimarkers: Hs-cTnT cTnT MPO PAPP-A CRP MRP 8/14	Possible ACS	ESRD	Biomarkers at presentation	Diagnostic accuracy for all non-TnT biomarkers was low using ROC AUC	AUC for combination with hs-TnT: MPO: 0.95 MRP-8/14: 0.95 PAPP-A: 0.95 CRP: 0.95 (NS change)	ROC (AUC): MPO: 0.63 MRP8/14: 0.65 PAPP-A: 0.62 CRP: 0.59 cTnT: 0.88 hs-TnT: 0.96	Biomarkers linked to factors related to morbidity: potentially confusing. No info on avoiding adverse outcomes
Weber 2008 18355657(73)	Prognosis. value of BNP with normal TnT in ACS	Retrospective multicenter 2,614 From 2 center registries 1,131 and 1,483	BNP vs. TnT	Cohorts different, 1 higher risk (1,131) and the other lower risk (1,483) analyzed separately	PCI within 6 mo, or C and for reperfusion cancer, autoimmune inflammatory disease	Biomarkers at entry	Among TnT-pts ROC analysis yielded an optimal cutoff of BNP that was able to discriminate pts at higher risk for death at 6 mo	Mortality rate TnT+ vs. TnT-: Registry 1: 8.2 vs. 3.8% p=0.009 Registry 2: 8.6 vs. 2.8% p=0.009	Kaplian-Meier analysis of risk for death by BNP: Registry 1: Log-rank: 19.01 p<0.001 Adjusted HR: 9.56 (95% CI: 2.42–37.7) p=0.001 Registry 2: Log rank: 23.16 p<0.001 HR: 5.02 (95% CI: 2.04–12.33) p<0.001	Retrospective study. No serial measurements
Wiviott 2004 14769678(74)	Gender and biomarkers in ACS	Multicenter prospective trial off 1,865 pts in TACTICS-TIMI 18, 34% were women	Multiple biomarker analysis Men vs. women	Women with ACS with criteria for PCI. Randomized to invasive vs. conservative strategies	No criteria for PCI	Biomarkers at entry: TnT TnI CK-MB CRP BNP	Women more likely had elevated CRP and BNP. Men more likely had elevated CK-MB and Tn	Women with +Tn were more likely to have recurrent 6-mo MI whether TnI or TnT	Women more likely to have elevated hs-CRP 1.49 (95% CI: 1.16-1.92) and elevated BNP 1.33 (95% CI: 1.02-1.75)	Cutpoints rather than continuum. N/A to atypical chest pain. Not designed to answer pathophysiological questions

ACS indicates acute coronary syndrome; AMI, acute myocardial infarction; AUC, area under the curve; BNP, B-type natriuretic peptide; CAD, coronary artery disease; CHF, congestive heart failure; CRP, C- reactive protein; cTn, cardiac troponin; cTnI, cardiac troponin I; cTnT, cardiac troponin T; CCU, cardiac care unit; CV, cardiovascular; Dx, diagnosis; ESRD, end stage renal disease; FFAu, unbound free fatty acids; GDF-15, growth differentiation factor-15; GP-BB, glycogen phosphorylase-BB; GRF, growth hormone releasing factor; H-FABP, heart type fatty acid binding protein; HF, heart failure; Hs, high sensitivity; Hs-CRP, high sensitivity C-reactive protein; Hs-TnI, high sensitivity troponin I; Hs-cTnt, high sensitivity cardiac troponin T; Hx, history; IL, interleukin; IL-1 RA, interleukin-1 receptor antagonist; IMA, ischemia-modified albumin; LV, left ventricle; LVEF, left ventricular ejection fraction; MACE, major adverse cardiac and cerebrovascular events; MI, myocardial infarction; MMP-9, matrix metalloproteinase- 9; MPO, myeloperoxidase; MRP 8/14, myeloid related protein 8/14; MR-pro-ADM, midregional pro-adrenomedullin; N/A, not applicable; NS, not significant; NST-ACS, non-ST- segment acute coronary syndrome; NSTE-ACS, Non-ST-Segment-Elevation Acute Coronary Syndrome; OPUS-TIMI, orbofiban in

patients with unstable coronary syndromes; PAD, Peripheral Artery Disease; PAPP-A, pregnancy- associated plasma protein-A; PCI, percutaneous coronary intervention; PIGF, placenta growth factor; PL-22, sectretory type II phospholipase-22; pts, patients; PV, predictive value; RA, rheumatoid arthritis; ROC, receiver operating curve; RR, relative risk; sCD40L, soluble CD40; Sens, sensitivities; sIAM, solube intercellular adhesion molecule-1; sIRA, soluble intercellular adhesion molecule- 1; Spec, specificities; STEMI, ST-elevation myocardial infarction; TACTICS, Thrombolysis and Counterpulsation to Improve Cardiogenic Shock Survival; TIMI, Thrombolysis In Myocardial Infarction; Tn, troponin; TnI, troponin I; TnT, troponin T; and UA, unstable angina.

Data Supplement 8. Discharge from ED or Chest Pain Unit (Section 3.5.1)

Study Name, Author, Year	Aim of study	Study Type	Study Size (N)	Study Intervention Group (n)	Study Comparator Group (n)	Patient Population		Study Intervention	Study Comparator	Endpoints			P Values, OR: HR: RR & 95% CI:	Study Limitations & Adverse Events
						Inclusion Criteria	*Exclusion Criteria*			*Primary Endpoint (efficacy) and Results*	*Safety Endpoint and Results*	*Secondary Endpoint and Results*		
CHEER, Farkouh,1998 9862943(75)	Evaluate utility of CPU management of low-risk pts with CP	Single-center, prospective RCT	424	212	212	Intermediate risk, UA	MI, instability marked ST changes	6-h CPU observation followed by pre-D/C ETT or Ex-MPI with early D/C if negative	Routine hospital admission	No significant diff in early (30 d) and late (6 mo) MI, death, CHF, CVA, card arrest in-hospital admission vs. CPU pts	Same as 1º endpoint	CPU pts: Fewer follow-up ED visits, cardiac tests (p<0.003). (Also, median LOS in CPU 9.2 h)	No significant diff in early 30-d/late 6-mo cardiac events. Fewer repeat ED visits, cardiac tests (p<0.003)	Relatively small single-center, tertiary care with extensive expertise/resources; Pts 95% white. No. ETT/Nuc pts not given. Study not blinded
ROMIO Gomez, 1996 8752791(76)	Test rapid R/O MI to ↓time/$	Single-center, prospective RCT	100	50	N/A	CP low-risk for MI (Goldman), stable, nonischemic ECG; injury marker data not required	<30 y, >7% MI prob (Goldman), ECG, ischemia, VT, AV Bl, new BBB, BP >220/120, unstable	Rapid rule-out MI protocol in ED: Serial ECGs and CK-MB q 3-h x 4. If negative, PD-ETT	Routine hospital adm	No diff in low 30-d cardiac events. ITT analysis: LOS shorter, $ less in ED rule-out pts with MI	No MI missed	Echo substudy: low incremental value in rapid rule-out patients with MI	Admission vs. rapid rule-out: LOS 14 h vs. 27 h; p<0.0001; Initial cost: $2,089 vs. $1,108; p>0.0001; 30-d cost: $2,253 vs. $1,237	Small single center study, not blinded, shorter follow-up, hospital charges, and costs not equivalent
Amsterdam, 2002 12106928(77)	Utility of immediate ETT in triage of ED CP pts	Observational, single-center	1,000	1,000	N/A	Nontraumatic CP, negative ECG, marker, no arrhythmia, stable, Hx CVD not excluded	Abnormal ECG, positive marker, clinically unstable	Immediate ETT, Max/Sx/Sign limited	N/A	Negative ETT in 64% pts enabled direct discharge from ED, 30-d follow-up: NPV 98.3%. Non-Dx: 23% pts, 7 revasc predischarge; positive: 13%, 4 NSTEMI at	No adverse effects of ETT. No deaths at 30 d.	No MACE at 6 mo in pts who did not have ACS at index visit. Approx 40 min total time for scan and interpret.	N/A	ETT performed by specially trained MDs (Noncardiologist), 7 d/12 h function. Limitation: Includes only pts able to do ETT

										30 d				
Udelson, 2002 12460092(78)	Does addition of rest MPI improve ED triage of low-risk CP pts to admission or D/C from ED	Prospective Multicenter (n=7) RCT	2,475	1,215	N/A	Suspected acute ischemia (CP or equivalent) present within ≤3 h, nonischemic ECG, ≥30 y	Hx of MI, non-Dx ECG	Rest SPECT Tc 99m sestamibi, results to ED for use in clinical decision-making	Usual ED strategy in each institution's ED	MPI: Admission rate <UC (RR: 0.87; 95% CI: 0.81-0.93; p<0.001)	No adverse effects of MPI except radiation and longer time to discharge from ED in negative scan pts.	MPI: ↓unnecessary admission rate to 42% (10% absolute ↓); RR: 0.84; 95% CI: 0.77–0.92; p<0.001. 30-d cardiac event rate was related to MPI data; p<0.001	See 1°/ 2° endpoint columns	May not be generalizable to small hospitals; performed during daytime. LOS MPI>UC (5.3 vs. 4.7 h; p<0.001)
Trippi, 1997 9283518(79)	Evaluate utility of DSE telemedicine triage of low-risk pts with CP in ED	Prospective, single-center, DSE by nurse and sonographer	173 screened, 139 eligible and received DSE (24 no DSE d/t LV wall motion abnormal)	139	N/A	ROMI, negative markers, NL ECG, No Hx CVD. Initially: pts obs'v'd 12 h; later. neg DSE: direct D/C from ED	No Hx CAD, screened for exclusions by nurse (not specified) (LV wall motion abnormal = exclusion)	DSE by nurse & sonographer Card present; later cardiol available by phone, ED MDs present. DSE telemetry to Card, Dx to ED. Follow-up confirm, ECG	N/A	3-mo follow-up: NPV for ACS 98.5%, PPV 51.5%. Agreement TeleEcho/convential Echo kappa 0.78; 95% CI: 0.65–0.90	54.7% Sx with DSE: test terminated for PVCs=6.3%; CP, nausea, SOB common Sx	72.0% pts D/C'd directly from ED in phase 4. DSE report to ED in 2.5 h from request. ED MDs adm some pts despite neg DSE.	See 1°/2° endpoints	No control group. Method not generalizable, highly developed/specialized personnel
Bholasingh, 2003 12598071(80)	Study prognostic value of DSE in low-risk CP pts	Prospective single-center, blinded. ED MDs blinded to DSE results.	377 of 557 eligible pts received DSE. No DSE: 119 ACS, 34 other serious Dis., 24 rest LV abn.	377	N/A	≥18 y, non-Dx ECG, present within 6 h of CP, neg cTt.	Arrhythmias, HF, severe HTN, serious noncard disease	DSE after 12-h observation, 6.9% (26/377) pts had Pos DSE	N/A	6-mo follow-up: 1° endpoints: Neg DSE 4% (1 death), Pos DSE 30.8% (1 death); OR 10.7; 95% CI: 4.0–28.8; p<0.0001)	All DSE completed within 24 h of admission; follow-up 100%; 19.9% protocol terminated d't ECG changes, CP, arrhythmia, severe HTN, hypotension.	Revasc: Pos DSE 3/26 pts, Neg DSE 7/351 pts ~5X greater in neg DSE	See 1°/2° endpoints Pts discharged	No control group. DSE not performed d/t poor window in 5.7% pts.
ROMICAT, Hoffman, 2009 19406338(81)	Utility of CCTA in acute CP pts	Observational cohort study	368	368	N/A	CP, neg initial Tn, nonischemic ECG	Hx CAD: stent or CABG, renal discharge	CCTA before admission, results not	N/A	Pts without CAD: NPV for ACS at 6	1 ACS in absence of + CCTA showing	No MACE at 6 mo in pts who did not have	See 1° endpoint column	Single center, wkd h, underrepresent of elderly d/t

		(blinded)						disclosed, sig stenosis: >50%		mo=98% (95% CI: 98%–100%; PPV=35% (95% CI: 24%–48%)	coronary plaque	ACS at index visit. ~40 min total time for scan & interpret		exclusion of CAD, renal dis. May not be generalizable to smaller hospitals, radiation
Litt, 2012 22449295(82)	CCTA vs UC to assess low-risk CP pts in ED	Prospective multictr (n=5) RT	1370, 2:1 ratio to CTA and traditional care	908	462	≥30 y, nonischemic ECG, TIMI 0-2	Noncard sx, NL angio within 1 y, contraind to CTA, CrCl <60	CTA was 1st test in CTA group. In traditional care pts clinicians decided 1st tests	Traditional care	No MI/death at 6 mo in pts with neg CTA (<50% stenosis): 0% (95% CI 0-0.57) (100%)	No MI or death at 60 d in the 640 pts with neg CTA	CTA: higher rate of D/C from ED: 50% vs. 23%, 95% CI 21-32; shorter LOS: 18 h vs. 25 h, p<0.001; higher ID of CAD: 9.0 % vs. 3.5%, 95% CI 0-11.	See 1°/2° endpoint columns	All exclusions to CCTA not noted, young study group (age 50 y), radiation
ROMICAT II, Hoffman, 2012 22830462(83)	CCTA vs UC to assess low-risk CP pts in ED	Prospective multictr (9) RCT	1000	501	499	CP, 40-74 y, NSR	CAD, ischemic ECG, +Tn, Cr >1.5, instability, allergy to contrast, BMI >40, asthma	CTA	Traditional care	LOS: CCTA 23 h vs. UC 31 h (p<0.001)	28-d follow-up: no missed ACS; no difference in MACE at 28 d	Direct D/C from ED: CTA 47% vs. 12%, p<0.001; no difference in downstream care	See 1° and 2° endpoint columns	Wkd, daytime, radiation. May not be generalizable to smaller hospitals

1°indicates primary; 2°, secondary; ACS, acute coronary syndrome; BBB, bundle branch block; BMI, body-mass index; BP, blood pressure; CAD, coronary artery disease; CABG, coronary artery bypass graft; CCTA, coronary computed tomographic angiography; CTA, computed tomographic angiography; CHF, congestive heart failure; CK, creatine kinase; CP, chest pain; CPU, chest pain unit; Cr, creatinine; CrCl, creatinine clearance; CTA, computed tomography angiography; CVA, cardiovascular accident; CVD, cardiovascular disease; D/C, discharge; diff, difference; DSE, dobutamine stress echocardiography; Dx, diagnosis; ECG, echocardiograph; ED, emergency department; pts, patients; ETT, exercise treadmill testing; HF, heart failure; HR, hazard ratio; HTN, hypertension; Hx, history; ITT, intention to treat; LOS, length of stay; MACE, major adverse cardiac events; MI, myocardial infarction; MPI, myocardial perfusion imaging; NPV, net present value; NSR, normal sinus rhythm; PPV, positive predictive value; PVC, premature ventricular contractions; R/O, rule out; RCT, randomized controlled trial; ROMI, rule out myocardial infarction; TIMI, Thrombolysis In Myocardial Infarction; and UA, unstable angina.

Data Supplement 9. Nitrates (Section 4.1.2.1)

Study Name, Author, Year	Aim of Study	Study Type	Study Size (N)	Study Intervention Group (n)	Study Comparator Group (n)	Patient Population		Study Intervention	Study Comparator	Endpoints			P Values, OR: HR: RR & 95% CI:	Study Limitations & Adverse Events
						Inclusion Criteria	*Exclusion Criteria*			*Primary Endpoint (efficacy) and Results*	*Safety Endpoint and Results*	*Secondary Endpoint and Results*		
Ambrosio G., 2010	Investigate whether	Multicenter registry	52,693	10,555 (20%) pts on	42,138 (80%) (nitrate-naïve	Clinical history of ACS,	Pts with non-CV causes for the	Chronic nitrates on	Nitrate-naïve	Chronic nitrate use was	N/A	Antecedent nitrate use was	Chronic nitrate use remained	Registry data– No data on dose

19903682 (84)	antecedent nitrate therapy affords protection toward acute ischemic events	(GRACE)		chronic nitrates on admission	pts)	accompanied by at least 1: ECG complete with ischemia, serial increases in cardiac markers, documented CAD	clinical presentation were excluded, as were pts in whom initial Dx of ACS was not confirmed at discharge	admission		associated with a shift away from STEMI in favor of NSTE-ACS. Chronic nitrate use remained independent predictor of NSTE-ACS: (OR: 1.36; 95% CI: 1.26–1.46; p<0.0001)		associated with significantly lower levels of peak CK-MB and Tn (p<0.0001 for all) (in both STEMI and NSTEMI)	independent predictor of NSTE-ACS: (OR: 1.36; 95% CI: 1.26–1.46; p<0.0001)	or duration of antecedent Rx
Mahmarian, 1998 9610531 (85)	Investigate the long-term (6 mo) efficacy of NTG patches on LV remodeling in pts surviving a AMI	Multicenter RCT	291	214	77	Pts surviving a A-QMI	Exclusion criteria: severe CHF, persistent hypotension, sustained VT, or high-degree AVB, UA, significant noncardiac illness, or either a requirement for or known intolerances	Intermittent NTG patch therapy initiated within 1 wk after AMI and continued for 6 mo (0.4, 0.8, and 1.6 mg/h)	PC	1º endpoint: Change in ESVI was significantly reduced with 0.4 mg/h NTG patches	Cardiac event rates were not significantly different between PC and active treatment groups	The beneficial effects seen primarily in pts with baseline LVEF ≤40% (delta ESVI, -31 mL/m^2; delta EDVI, -33 mL/m^2; both p<0.05) and only at the 0.4 mg/h dose	Both ESVI and EDVI were significantly reduced with 0.4 mg/h NTG patches (-11.4 mL/m^2 and -11.6 mL/m^2, p<0.03)	No associated clinical or survival advantage associated with the beneficial remodeling effects. Gated radionuclide angiography used to assess changes in LVEF and cardiac volumes –no TTE, and as such unable to address other aspects of LV remodeling. Higher NTG doses prevented LV remodeling to a lesser degree (NTG tolerance may be limiting efficacy at the higher doses).
ISIS-4, 1995 7661937 (86)	Examine the effect of oral controlled-release	RCT	58,050	29,018	28,539	Within 24 h of Sx onset of suspected AMI with no clear	Contraindications at the clinician's discretion (e.g., conditions	1 mo of oral controlled-release mononitrate	PC	NS difference in 5-wk mortality (mononitrate vs. PC):	Greater effect early after starting treatment	No effect on any subgroup studied (age, sex, previous MI, ECG on	5-wk mortality: (mononitrate vs. PC) 7.34% vs.	Hypotension 17.4% vs. 14.4%, p<0.0005 (mononitrate vs.

	mononitrate on early mortality (4 wk)					indications for, or contraindications to, any 1 of the study treatments	associated with a high risk of adverse effects, such as cardiogenic shock, persistent severe hypotension, evidence of severe fluid depletion, etc.) Or conditions associated with only a small likelihood of worthwhile benefit	(30 mg initial dose titrated up to 60 mg qd)		7.34% vs. 7.54%; p=NS	(deaths on d 0–1: 514 [1.77%] mononitrate vs. 628 [2.16%] PC; p<0.001).	presentation, HF at entry, early after Sx onset, etc) No difference in 12-mo mortality	7.54%, p=NS	PC) 50%-60% had open label nitrate therapy. Contraindications were specified not by the protocol, but by the responsible clinician
GISSI-3, 1994 7910229 (87)	Assess the effects of lisinopril and transdermal glyceryl trinitrate alone and their combination on 6-wk mortality and LVEF after AMI	Multicenter RCT	19,394	N/A	N/A	AMI pts within 24 h of Sx onset and no clear indications for or against the study treatments	N/A	Nitrates (IV for the 1st 24 h, then transdermal GTN 10 mg daily)	PC (open label)	No effect of nitrate on 6-wk mortality: OR: 0.94 (95% CI: 0.84–1.05) No effect of nitrates on the combined outcome measure of mortality and severe ventricular dysfunction.	Systematic combined administration of lisinopril and GTN produced significant reductions in overall mortality (OR: 0.83; 95% CI: 0.70–0.97) and in the combined endpoint (OR: 0.85; 95% CI: 0.76–0.94)	The trend toward reduction in cardiac events with nitrate therapy reached statistical significance among the elderly and women. Significant reductions in 6-wk mortality and combined outcome with lisinopril.	6-wk mortality: GTN vs. PC: OR: 0.94; 95% CI: 0.84–1.05 Combined outcome: GTN vs. PC: OR: 0.94; 95% CI: 0.87–1.02	No excess of unfavorable clinically-relevant events in the treated groups was reported. 2D echo data were available only for 14,209 pts (73%) 50%–60% had open label nitrate therapy.
Yusuf, 1988 2896919 (88)	Examine the effect of IV nitrates on mortality in AMI	Meta-analysis (10 RCTs)	2,000	N/A	N/A	AMI pts–inclusions of individual trials	Exclusions of individual trials	Nitrate	PC	35% reduction (SD 10) in the odds of death (2p<0.001; 95% CI of approximately 0.166-0.50)	The greatest reduction in mortality occurred predominantly during the 1st wk of follow-up	Both NTG and nitroprusside reduced mortality, the reduction being NS greater with NTG than with nitroprusside	NS reduction after the 1st wk of follow-up	Publication bias Baseline risk heterogeneity Different definitions of clinical endpoints across the various studies

1º indicates primary; 2D, two-dimensional; ACS, acute coronary syndrome; AMI, acute myocardial infarction; A-QMI, acute Q-myocardial infarction; AVB, auriculoventricular block; CAD, coronary artery disease; CHF, congestive heart failure; CK-MB, creatine kinase-MB; CV, cardiovascular; Dx, diagnosis; ECG, electrocardiogram; EDVI, end-diastolic volume index; ESVI, end-systolic volume index; GTN, glyceryl trinitrate; GRACE, Global Registry of Acute Coronary Events; HF, heart failure; IV, intravenous; LV, left ventricular;

LVEF, left ventricular ejection fraction; MI, myocardial infarction; NS, nonsignificant; NTG, intermittent transdermal nitroglycerin; NSTE-ACS, non-STE-elevation acute myocardial infarction; PC, placebo; pts, patients; qd, daily; RCT, randomized controlled trial; Rx, prescription; SD, standard deviation; STEMI, non-ST-elevation myocardial infarction; Sx, symptoms; Tn, troponin; TTE, transthoracic echocardiography; UA, unstable angina; and VT, ventricular tachycardia.

Data Supplement 10. Analgesic Therapy (Section 4.1.2.2)

Study Name, Author, Year	Aim of Study	Study Type	Study Size (N)	Study Intervention Group (n)	Study Comparator Group (n)	Patient Population		Study Intervention	Study Comparator	Endpoints			P Values, OR: HR: RR & 95% CI:	Study Limitations & Adverse Events
						Inclusion Criteria	*Exclusion Criteria*			*Primary Endpoint (Efficacy) and Results*	*Safety Endpoint and Results*	*Secondary Endpoint and Results*		
Iakobishvili, 2011 21627393 (89)	Determine the impact of IVM on outcomes of pts with ADHF with and without ACSs	Observational registry	2,336	218 (9.3%)	2,118 (90.7%)	Consecutive pts with ADHF participating in a national HF survey	N/A	IVM	No IVM	IM associated with higher unadjusted (11.5% vs. 5.0%) and adjusted in-hospital mortality using logistic regression adjustment	IVM increased in-hospital mortality	Using adjustment with propensity matched analysis, IVM was not associated with increased in-hospital death (OR: 1.2; 95% CI: 0.6–2.4; p=0.55)	IVM had higher adjusted OR for in-hospital death: 2.0; 95% CI: 1.1-3.5; p=0.02) using logistic regression analysis	Pts with IVM were more likely to have ACSs
Iakobishvili, 2010 20346305 (90)	Assess the 30-d outcomes stratified by IVNs use among pts enrolled in a national survey of pts with STEMI and NSTE-ACS	Multicenter retrospective analysis from the ACSIS 2008 database	993 pts with NSTE-ACS	97 (9.8%)	896 (90.2%)	Consecutive pts presenting with ACS to any of 26 CCU and cardiology wards in Israel	Pts transferred to another institution	IVM	No IVN	No diff in 30-d mortality with IVN use. Using propensity adjustment (95 matched NSTE-ACS pairs): 30-d death rate (2.2% for pts receiving IVNs vs. 6.3%; p=0.16)	N/A	Using propensity analysis, of 249 matched STEMI pairs, 30-d death was lower in pts receiving IVN; this trend persisted after logistic regression analysis (OR: 0.40; 95% CI: 0.14-1.14; p=0.09)	Using logistic regression analysis, there were no diff in 30-d mortality among NSTE-ACS (OR: 0.56; 95% CI: 0.14-2.33; p=0.43)	Retrospective On-site catheterization and bypass surgery facilities were available in 22 and 10 of the centers only. Relatively small cohort. No data regarding the exact timing of IVN use or the cumulative dose administered. Did not specify the types of IVN used.

														Only a minority of pts were treated with IVN
Meine, 2005 15976786 (91)	Compare outcomes in pts who received IVM vs. those who did not receive IVM	Observational registry, GRACE	57,039	17,003 (30%)	40,036 (70%)	Pts presenting with NSTE-ACS at 443 hospitals across the US from 01/2003–06/2003 Pts included in the CRUSADE initiative have ischemic Sx at rest within 24 h prior to presentation and high-risk features including ST-segment depression, transient ST-segment elevation, and/or positive cardiac markers.	Pts who were transferred out to another institution were excluded, because data could not be collected	Morphine within 24 h of presentation	No morphine at presentation	Higher adjusted risk of in-hospital death in pts treated with morphine compared with no morphine (OR: 1.48; 95% CI: 1.33-1.64)	Increased adjusted OR of in-hospital death in all subgroups (including pts with CHF, ST depression, <75 y, positive biomarkers, nonhypotensive pts) Also, increased adjusted OR of in-hospital adverse outcomes (death/MI; CHF; postadmission MI; cardiac shock)	Relative to those receiving NTG, pts treated with morphine had a higher adjusted OR of death: 1.50; 95% CI: 1.26-1.78	In-hospital death: morphine vs. no morphine: adjusted (OR: 1.48; 95% CI: 1.33-1.64) Using propensity score matching, morphine use was associated with increased in-hospital mortality (OR: 1.41; 95% CI: 1.26-1.57)	Nonrandomized, retrospective, observational data Only a minority of pts were treated with IVM

ACS indicates acute coronary syndrome; ADHF, acute decompensated heart failure; CCU, cardiac care unit; CHF, congestive heart failure; CRUSADE, Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the American College of Cardiology/American Heart Association Guidelines; diff, differences; GRACE, Global Registry of Acute Coronary Events; HF, heart failure; IVM, intravenous morphine; IVN, intravenous narcotics; MI, myocardial infarction; NSTE-ACS, non-ST-elevation acute coronary syndrome; NTG, intermittent transdermal nitroglycerin; pts, patients; STEMI, ST-elevation myocardial infarction; Sx, symptoms; and US, United States.

Data Supplement 11. Beta-Adrenergic Blockers (Section 4.1.2.3)

Study Name, Author, Year	Study Aim	Study Type/ Size (N)	Intervention vs. Comparator (n)	Patient Population		Study Intervention	Endpoints			P Values, OR: HR: RR: & 95 CI:	Adverse Events	Study Limitations
				Inclusion Criteria	*Exclusion Criteria*		*Primary Endpoint & Results*	*Safety Endpoint & Results*	*Secondary Endpoint & Results*			
TIMI-IIB Roberts,	Immediate vs. deferred BB	Prospective multicenter	Immediate IV group	AMI treated with invasive	Implanted pacemaker; resting	IV metoprolol as soon as rt-PA	Global LVEF at time of discharge using	No diff in mortality in both	Lower incidence of reinfarction	Resting EF: immediate 51.0% vs. 50.1%	NS diff in deaths at 6 wk or 1 y	Complexity of interventions other

1991 1671346 (92)	therapy	1,434	720 Deferred group 714	vs. conservative strategy. Susceptible to BB therapy.	HR <55; SBP <100 mm Hg; pulmonary edema; advanced 1st degree or higher heart block; asthma or COPD.	was started followed by oral metoprolol or oral metoprolol beginning on d 6	radionuclide ventriculography. LVEF 50.5% at discharge was virtually the same in both groups	groups. In low-risk group there were 7 deaths in 6 wk in deferred group vs. none in immediate group	(2.7% vs. 5.1%; p=0.02) at 6 d in the immediate group and less recurrent chest pain (18.8% vs. 24.2%; p<0.02)	delayed p=0.22 NS diff invasive or conservatives strategy in EF comparisons	with immediate vs. delayed BB treatment. More intracranial hemorrhage in the delayed group	than BB administration may have affected results.
Ryden, 1983 6828092 (93)	Occurrence of ventricular tachyarrhythmias in suspected AMI with BB.	Prospective multicenter 2,395	Metoprolol 698 PC 697	Sx suggestive of AMI	Contraindications for beta-blockade; need for beta-blockade's "administrative considerations."	Metoprolol IV than po or PC with admission to CCU	Significant ventricular tachyarrhythmias: More cases of VF in the PC group	No increase in significant heart block with BB	BB did not influence PVCs or short bursts of VT in 1st 24 h. 3-mo mortality lower in BB group (5.7% vs. 8.9%) p<0.03	VF: 6 in BB group, 17 in PC group (0.9% vs. 2.4%) p<0.01 Requirement for lidocaine less in BB group 16 vs. 38 p<0.01	NS adverse events with BB vs. PC	Use of a beta-1-blocker precludes assessment with other type BB. No indication of whether deferred BB would have affected results.
Al Reesi, 2008 19019272 (94)	Effect of BB use within 72 h of MI on 6-wk mortality vs. PC	Meta-analysis 18 studies 74 643 1966–2007	BB vs. PC or no control group Roughly 50% each	RCT of MI with BB vs. PC within 72 h of AMI	No information on 6-wk mortality. Treatment started after 72 h. Non-English speakers	Beta-1 or nonselective BB or PC within 72 h of MI. Follow-up for 6 wk	6-wk mortality: Adding a BB had no effect compared with control	N/A	Subgroup analysis that excluded high-risk pts showed mortality benefit of BB: 0.93 [0.88–0.99]	6-wk mortality Reduction BB vs. control: 0.95 (95% CI: 0.90–1.01) NS With high quality studies only: 0.96 (95% CI: 0.91–1.02) NS	N/A	Publication bias as with all meta-analyses. No evaluation of other outcomes or adverse events. Mixed beta-1 and nonselective BB.
Janosi, 2003 14564329 (95)	BB effects in post-MI with CHF	Multi-institute prospective trial 1,926	950 metoprolol 976 PC	MI >0.28 d before.	AMI or UA <28 d Contraindicated to BB.	Metoprolol or PC for 1 y.	BB reduced total mortality by 40%, combined MACE by 31%.	Withdrawal of BB vs. PC NS.	Reduced CV death, MI by 45%, SCD by 50%	Total mortality p=0.0004, MACE p<0.0001	Death from worsening HF educed 49% vs. PC	Only 68% of post-MI pts ideal candidates for BB
Hjalmarson 1997 9375948 (96)	Meta-analysis of early BB trials in MI	>55 RCT of over 73,000 pts	Over 38,000 BB Over 35,000 PC	AMI	Contraindicate to BB, sever HF, heart block.	BB vs. PC	Total deaths 13% reduction. Short-term SCD 34% reduction.	Lipophilic BBs prevent vs. fibrillation after MI	N/A	Total mortality p<0.0001 SCD reduction <0.0001	N/A	N/A
Emery, 2006 17161045 (97)	Use of early BBs in NSTEMI	Registry of 96 hospital pts admitted for ACS retrospective 7,106	5,422 early BB 1,684 None	NSTEMI	STEMI Ccontraindications to BB therapy Transfer pts with Hx of CHF Cardiac arrest on admission	Early BB therapy or none beginning <24 h	BB therapy showed lower hospital mortality 6-mo mortality also lower	N/A	Hospital Mortality Killip II/III 0.39 (95% CI: 0.23–0.68)	Hospital mortality 0.58 (95% CI: 0.42–0.81) 6-mo mortality 0.75 (95% CI: 0.56–0.997)	N/A	Observational No adjustment for confounders. No indication of dose or brand
Freemantle, 1999 10381708 (98)	BBs in short-term Rx in MI and in longer term	Meta - regression analysis of trials with	82 randomized trials Short-term: 29,260	BB in MI in PC or alternative Rx in controlled trials	N/A	BB/PC or alternative Rx begun at any stage of AMI	Short-term: small and NS reduction of risk for death Long-term:	N/A	N/A	Short-term risk for death 0.96 (95% CI: 0.85–0.98)	Usually bradycardia or hypotension	Multiple BB brands, varied follow-up, diff times of initiation

	secondary preview	acute or past AMI 54,234	Long-term: 24,974 pts				significant reduction			Long-term: 0.77 (95% CI: 0.69–0.85)		and withdrawal.
Dargie, 2001 11356434 (99)	Outcomes of carvedilol in AMI with LV dysfunction	Multicenter randomized PC controlled 1,959	Carvedilol 975 PC 984	AMI with LVEF≤40%, use of ACE inhibitors	<18 y, use of diuretics or inotropes	6.25 mg BB to 25 mg bid or PC followed until requisite number of endpoints	Death or hospital admission for CV problem no difference	N/A	All-cause mortality alone Lower in BB group 0.77 (0.60–0.98) p=0.03	1° endpoint 0.92 (95% CI: 0.80–1.07)	N/A	Insignificant power to detect a diff in all-cause mortality
Chen, 2005 16271643 (100)	Effect of adding BB to current std therapies in AMI	Multicenter randomized PC controlled 45,852	Metoprolol 22,929 PC 22,923	<24 h of ACS with STEMI, NSTEMI, or LBBB	Scheduled for PCI, hypotension, bradycardia, heart block, shock	IV then po, BB, or PC for up to 4 wk	Death/reinfarction/ cardiacarrest NS	11/1,000 more with BB having cardiac shock during d 0–1 of admission	Less vs. fibrillation with BB p=0.001 Less reinfarct p=0.001	MACE for BB: 0.96 (95% CI: 0.90–1.01); p=0.1 NS	More cardiac shock with BB (d 0–1)	Different population groups at centers
Ellis, 2003 14562669 (101)	BB therapy in ACS PCI ± abciximab	Pooled date from 5 RCTs 2,894	1,939 BB 955 No BB	MI or UA within 48 h	Pts presenting within 24 h with ECG change /UA	BB vs. control through hospital stay PCI	30-d, 6-mo MACE BB decreased death during both periods	N/A	NS diff recurrent MI Death or MI	Death 30-d BB vs. no BB 0.6% vs. 2.0% p=0.017 Death 6 mo 1.7% vs. 3.7% p=0.01	NA	1° comparison not randomized. Diff pt populations. No uniform definition of ACS
McMurray, 2005 15708698 (102)	Effect of BB in reducing arrhythmias added to ACEI	Multicenter PC controlled 1,959 Post hoc analysis of arrhythmias	975 carvedilol 984 PC	3–21 d after MI follow-up 1.3 y	Not stated	Carvedilol of PC for duration of study (average 1.3 y)	Arrhythmias over 2 y, atrial and ventricular arrhythmias lower in BB group	N/A	Malignant vs. arrhythmias: 0.9% BB 3.9% PC 0.24 (95% CI: 0.11–0.49) p<0.0001	Atrial arrhythmias: 0.41 (95% CI: 0.25–0.68); p=0.0003 vs. arrhythmias 0.34 (95% CI: 0.11–0.49); p<0.0001	AT, atrial flutter, atrial fibrillation, vs. tachm, vs. fibrillation	Not prespecified analysis. ECG confirmation not available
Miller, 2007 17679127 (103)	Impact of early use of BB in ACS	Multi-institutional retrospective analysis 72,054 at 509 hospitals	82.5% received acute BB vs. no BB	Acute ischemia <24 h, NSTE, contrary to BB	Hospital transfer, no +cardiac markers, no acute medications recorded	BB vs. no BB	Lower in-hospital mortality, reinfarction, shock with BB. No diff in CHF	N/A	Acute BB associated with more invasive procedures and other acute therapy	Hospital mortality: 0.66 (95% CI: 0.60–0.72) Reinfarction 0.80 (95% CI: 0.72–0.89) Shock 0.76 (95% CI: 0.67–0.87)	N/A	Undocumented contraindicated to BB use, hospital actively seeking to improve performance
Brandler, 2010 20078433 (104)	Literature review to determine BB effects on outcome in ACS	Meta-analysis of RCTs 72,249 18 articles	Early BB 36,173 pts with/without PC 36,076	18+ y, ACE within 24-h pain onset, BB within 8 h of presentation	Contraindications to BB	Early BB vs. no BB ± PC	No diff in in-hospital mortality	N/A	In largest study (45,852) higher cardio shock in BB 5.0% vs. control 3.9% p<0.0001	In-hospital mortality 0.95 (95% CI: 0.90–1.01)	N/A	Single outcome variable. No long-term evaluation. Heterogeneous pt population

Kontos, 2011 21570515 (105)	Registry of BB use in ACS	NCDR ACTION-GWTG registry 34,661 pts with NSTEMI 21 822	291 hospitals 2007–2008 21 822 BB	BB within 24 h of ACS	Contraindications to BB Missing data	BB only: early vs. late use	Very early BB use increased cardiogenic shock and death or shock	Evidence of increased cardiogenic shock with early use (<24 h) of BB	NS diff between early or late use in death alone	Early vs. late use cardiogenic shock: 1.54 (95% CI: 1.26–1.88); p<0.001 Death or shock: 1.23 (95 % CI: 1.08–1.40); p=0.0016	Cardiogenic shock with use of BB in ED	Oral or IV? No infomation on type of BB or dose. No information on arrhythmias.

1º indicates primary; ACS, acute coronary syndrome; ACE, angiotensin- converting enzyme; ACEI, angiotensin-converting enzyme inhibitor; ACTION, Acute Coronary Treatment and Intervention Outcomes Network Registry; AMI, acute myocardial infarction; AT, atrial tachycardia; BB, beta blocker; CCU, cardiac care unit; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; CV, cardiovascular; diff, difference; ECG, electrocardiograph; ED, emergency department; EF, ejection fraction; GWTG, Get With the Guidelines; HF, heart failure; Hx, history; IV, intravenous; LBBB, left bundle-branch block; LV, left ventricular; LVEF, left ventricular ejection fraction; MACE, major adverse cardiac and cerebrovascular events; MI, myocardial infarction; NCDR- National Cardiovascular Data Registry; NCDR ACTION-GWTG, National Cardiovascular Data Registry Acute Coronary Treatment and Intervention Outcomes Network Registry- Get With the Guidelines; NS, no/t significant; NSTE, non-ST-elevation; NSTEMI, non-ST-elevation MI; PC, PC; PCI, percutaneous coronary intervention; pt, patient; PVCs, premature ventricular contractions; RCT, randomized controlled trial; Rt-PA, recombinant tissue plasminogen activator; Rx, prescription; SBP, systolic blood pressure; SCD, sudden cardiac death; std, standard; STEMI, ST-elevation MI; UA, unstable angina; VF, ventricular fibrillation; and VT, ventricular tachycardia.

Data Supplement 12. Calcium Channel Blockers (Section 4.1.2.4)

Study Name, Author, Year	Aim of Study	Study Type	Study Size (N)	Study Intervention Group (n)	Study Comparator Group (n)	Patient Population		Study Interventio n	Study Comparator	Endpoints			P Values, OR: HR: RR & 95% CI:	Study Limitations & Adverse Events
						Inclusion Criteria	*Exclusion Criteria*			*Primary Endpoint (Efficacy) and Results*	*Safety Endpoint and Results*	*Secondary Endpoint and Results*		
Gibson, 1986 3526151 (106)	Effect of diltiazem on NQMI.	Multicenter double-blind randomized	576	Diltiazem 287	PC 289	NQMI >30 m Ischemic pain or ST changes	Q waves or conduction disturbances AV block Bradycardia Cardio shock	Diltiazem 24–72 h from admission Up to 14 d	PC	14-d reinfarction 9.3% in PC 5.2% in Diltiazem Reduced by diltiazem	No increased mortality with CCB Tolerated well with BB	Refractory angina reduced by diltiazem	Reinfarction: 51.2%(90% CI: 7%–67%); p=0.0297 Refractory angina 49.7% (90% CI: 6%–73%); p=0.0345	Only 4.8% withdrawn because of adverse effects. No diff vs. PC in LV failure, shock, AV block, severe bradycardia, or hypotension
Lubsen, 1987 2887097 (107)	Efficacy of BB and CCB in UA in a CCU	Multicenter PC control	338	Combination of nifedipine and metoprolol	PC	UA not previously on BB	AMI	Nifediipine, metoprolol, or combination	PC	Ischemia or progression to MI in 48 h. Only pretreatment with BB showed favorable effects with nifedipine.	No increased mortality with CCB.	Starting a BB plus nifedipine showed no benefit from BB initiation alone vs. PC.	Rate ratio for CCB: pretreated with BB: 0.68 (0.47, 0.97) Not on BB: 1.51 (0.87, 2.74) vs. PC	Equal numbers on BB alone or combination developed AMI or reversible ischemia.
Gibson, 1987 3303886	Px effect of dilriazem on recurrent	Multicenter double-blind	576	Diltiazem 287	PC 289	Confirmed NQMI	Q waves or conduction disturbances	Diltiazem 24-72 h from	PC	Incidence of early recurrent ischemia	N/A	N/A	CCB red of ischemia: 28% (95% CI:	N/A

(108)	ischemia						AV block Bradycardia Cardio shock	admission Up to 14 d		decreased by CCB 15.7% vs. 24.2%			9.3%–53.8%); p=0.0103	
Held, 1989 2513047 (109)	CCB effect on events	Meta-analysis of 28 trials	19,000	8,870 CCB	8,889 control	MI 22 trials UA 6 trials	CHF Hypotension AV block (most common)	CCB usually early in ACS	Control	Risk of death, infarct size, or reinfarction. No effect by CCB vs. PC in MI trials.	No increase in reinfarction or infarct size vs. PC by CCB	Results similar in UA trials	Mortality: CCB vs. PC 1.06 (95% CI: 0.96–1.18) in MI trials	Usual limitation of meta-analysis heterogeneity of populations and various agents. Adverse effects not addressed per se
Moss, 1991 1872266 (110)	Diltiazem and long-term outcome	Multicenter PC control	2,464	No HTN Diltiazem: 760 PC: 762	Hypertension Diltiazem: 471 PC: 471	MI treated with diltiazem with or without hypertension	CHF Hypotension AV block	Diltiazem at ACS for 12-52 mo	PC for same time period	1st recurrent cardiac event: CCB benefit only in hypertensives with no pulmonary congestion.	+pulmonary congestion; CCB increased Risk: Hypertension/ No hypertension 1.32 (95% CI: 0.83-2.10) 1.63 (0.99, 2.69) vs. PC	Significant reduction in BP and HR with CCB though small.	CCB benefit hyperension without pulmonary congestion 0.67 (95% CI: 0.47–0.96)	Retrospective analysis. Post-hoc analysis of HTN effect. Adverse effect of pulmonary congestion on diltiazem outcome
Furberg, 1995 7648682 (111)	Meta-analysis of nifedipine trials on outcome	Meta-analysis of 16 studies	8,350	Nifedipine 4,171	Control 4,183	Nifedipine 2° prevention trials with mortality data	No randomization	Nifedipine 12 AMI 3 UA 1 SA Short-acting	PC	Effect on mortality Nifedipine increased mortality by 16% Dose related	Increased sympathy stim and active of RAAS	Total mortality Low dose 1.06 (95% CI: 0.89-1.27) High dose 2.83 (95% CI: 1.35–5.93)	Total mortality 1.16 (95% CI: 1.01-1.33); p=0.01	Heterogeneity of clinical trial populations
Rengo, 1996 8602564 (112)	Effect of verapamil on mortality after AMI	Multicenter prospective trial	1,073	Verapamil 531	PC 542	Dx of AMI	Contraindication to verapamil Hx of severe HF	Long acting Verapamil 7-21 d after AMI 360 mg qd for 24 mo	PC For 24 mo	Total mortality and CV deaths. No diff between groups	No safety issues	Verapamil group had lower reinfarction rates (NS) 39 vs. 49 Significantly less angina OR: 0.8 (95% CI: 0.5-0.9)	Total mortality verapamil vs. PC 30 vs. 29 NS Cardiac deaths 21 vs. 22 NS	No diff in discontinuation of therapy due to adverse reactions. Death rate and number of pts recruited were lower than expected and pts were relatively young decreasing the power of study

Smith, 1998 9809940 (113)	Long-term outcome BB + CCB in UA	Retrospective cohort	247	Diltiazem 188	BB 59	At discharge with UA Dx	MI or stroke during hospitalization	Monotherapy CCB for 1-7 y	Monotherapy BB for 1-7 y	Deaths in 51 mo No diff between BB and CCB	N/A	Adjusted: for CCB NS increase in CAD rehospitalization/ death 1.4 (95% CI: 0.8–2.4)	Deaths: CCB vs. BB 1.1 (95% CI: 0.49-2.4)	Compliance issues. No infomation on follow-up treatment. Relatively small number of BB users
Pepine, 1998 9755379 (114)	Safety of CCB in CV disease	Meta-analysis 14 randomized parallel group studies	4,000 person y	Verapamil	PC	Randomized studies of verapamil and PC from AMI	No randomization or control group	Verapamil	PC	Outcomes with CCBs after MI: vs. PC No diff in deaths Decreased nonfatal MI Decreased death/reinfarction	Data too limited for pts with hypertension No evidence for increased harm with verapamil	No diff verapamil vs. PC in angina pts	Combined death/reinfarction: 0.82 (95% CI: 0.70–0.97); p=0.016 Death: 0.93 (95% CI: 0.78–1.1) Reinfarction: 0.79 (95% CI: 0.65–0.97); p=0.024	No evidence of harm with CCB in angina.
DAVIT Danish study, 1984 6383832 (115)	6 mo and 12 mo mortality after AMI with verapamil	Multicenter prospective study	3,498	Verapamil roughly 50%	PC roughly 50%	AMI	HF, AV block, severely disabling diseases, treatment with BB or CCB	Verapamil 120 tid for 6 mo	PC for 6 mo	NS diff in 6-mo or 12-mo mortality rate verapamil vs. PC	Higher number of AV block in verapamil group not associated with increased mortality. NS decreased in vs. fibrillation in verapamil group.	6-mo reinfarctions: verapamil 7% PC 8.3 % NS	6-mo mortality: 12.8% verapamil 13.9% PC NS 12-mo mortality: 15.2% verapamil 16/4% PC NS	Dosage of verapamil caused significantly increased AV block in 1st wk More HF in verapamil group p<0.005
DAVIT II Danish study, 1990 2220572 (116)	18 mo mortality rates and major CV events with verapamil after AMI	Multicenter prospective trial	1,775	Verapamil 878	PC 897	AMI	HF, AV block, severely disabling diseases, treatment with BB or CCB	Verapamil 360 mg qd from 2nd wk of AMI and up to 18 mo	PC for same period	Long-term treatment with verapamil decreased major CV events without significant effect on mortality	Significant diff in reasons for permanently stopping verapamil vs. PC: 2nd or 3rd degree AV block , sinus bradycardia,	In pts without HF in CCU 18-mo mortality: verapamil vs. PC 7.7% vs. 11.8% p=0.02 0.64 (95% CI: 0.44–0.94) Major CV event rates:	18-mo mortality: verapamil vs. PC: 11.1% vs. 13.8%; p=0.11 0.80 (95% CI: 0.61–1.05) Major CV events:	Minor discrepancies between resulting confidence limits and p values from the Tarone-Ware tests occurred because HR are based on proportional hazards

											abdominal pain, constipation	14.6% vs. 19.7%; p=0.01 0.70 (95% CI: 0.52–0.93) In HF, NS diff in mortality or major CV events	18.0% vs. 21.6%; p=0.03 0.80 (95% CI: 0.64–0.99)	assumption, not the case for the Tarone-Ware test

2º indicated secondary; ACS, acute coronary syndrome; AMI, acute myocardial infarction; AV, atrioventricular; BB, beta-blocker; BP, blood pressure; CAD, coronary artery disease; CCB, calcium channel blocker; CCU, cardiac care unit; CHF, congestive heart failure; CV, cardiovascular; diff, difference(s); Dx, diagnosis; HF, heart failure; Hx, history; HTN, hypertension; LV, left ventricular; MI, myocardial infarction; NQMI, Non-Q Wave myocardial infarction; NS, no/t significant; PC, placebo; pts, patients; Px, prognosis; qd, once daily; RAAS, Renin-Angiotensin-Aldosterone System; SA, stable angina; t.i.d., three times daily; and UA, unstable angina.

Data Supplement 13. Other Anti-Ischemic Inverventions (Ranolazine) (Section 4.1.2.5)

Study Name, Author, Year	Aim of Study	Study Type	Study Size (N)	Study Intervention Group (n)	Study Comparator Group (n)	Patient Population		Study Intervention	Study Comparator	Endpoints			P Values, OR: HR: RR & 95% CI:	Study Limitations & Adverse Events
						Inclusion Criteria	*Exclusion Criteria*			*Primary Endpoint (Efficacy) and Results*	*Safety Endpoint and Results*	*Secondary Endpoint and Results*		
Wilson SR, 2009 19389561 (117)	Evaluate the efficacy and safety of ranolazine in pts with prior chronic SA	Substudy from a multinational RCT	3,565	1,789	1,776	Pts with NSTE-ACS within 48 h of ischemic Sx (between Oct 2004–Feb 2007) Eligibility criteria: ≥18 y; Sx of myocardial ischemia; at least 1 moderate-high-risk indicator	Cardiogenic shock, persistent STE, successful revasc before randomization, clinically significant hepatic disease, ESRD requiring dialysis, treatment with agents known to prolong the QT interval, ECG abnormal levels interfering with Holter interpretation, life expectancy <12 mo	Ranolazine	PC	1º endpoint (CV death, MI, recurrent ischemia) was less frequent with ranolazine (HR: 0.86; 95% CI: 0.75–0.97; p=0.017) (Follow-up was a median of 350 d)	Symptomatic documented arrhythmias (2.9% vs. 2.9%; p=0.92) and total mortality (6.2% vs. 6.4%; p=0.96) were similar with ranolazine or PC. CV death or MI did not differ between treatment groups (HR: 0.97; 95% CI: 0.80–1.16; p=0.71)	Composite endpoint driven by significant reduction in recurrent ischemia (HR: 0.78; 95% CI: 0.67–0.91; p=0.002). Ranolazine reduced worsening angina (p=0.048) and intensification of antianginal therapy (p=0.005) Exercise duration at 8 mo greater with ranolazine (p=0.002)	1º endpoint: ranolazine vs. PC HR: 0.86; 95% CI: 0.75-0.97; p=0.017	Substudy of a RCT that did not meet its 1º endpoint (exploratory) Randomization was not stratified by Hx of prior angina, small diffs in clinical characteristics between those randomized to ranolazine or PC exist.
Scirica, 2007 17804441	Assess the potential	Sub-study from a	6,351	3,162	3,189	Pts with NSTE-ACS	Cardiogenic shock,	Ranolazine	PC	Ranolazine was associated	(numerically, but not statistically,	Lower incidence of pauses ≥3 s	VT ≥8 beats (5.3% vs. 8.3%;	Substudy of a RCT that did not

(118)	antiarrhythmic actions of ranolazine after ACS	multinational RCT				within 48 h of ischemic Sx (between Oct 2004–Feb 2007) Eligibility criteria: ≥18 y; Sx of myocardial ischemia; at least 1 moderate-high-risk indicator	persistent STE, successful revasc before randomization, clinically significant hepatic disease, ESRD requiring dialysis, treatment with agents known to prolong the QT interval, ECG abnormal levels interfering with Holter interpretation, life expectancy <12 mo			with fewer episodes of VT ≥8 beats (5.3% vs. 8.3%; p<0.001), SVT (44.7% vs. 55.0%; p<0.001), or new-onset AF (1.7% vs. 2.4%; p=0.08) (Continuous ECG [Holter] recording was performed for the 1st 7 d after randomization)	lower incidence of sudden cardiac death in pts treated with ranolazine over the entire study period)	with ranolazine (3.1% vs. 4.3%; p=0. 01)	p<0.001) SVT (44.7% vs. 55.0%; p<0.001), New-onset AF (1.7% vs. 2.4%; p=0.08)	meet its 1º endpoint (exploratory)
Morrow, 2007 17456819 (119)	Determine the efficacy and safety of ranolazine during long-term treatment of pts with NSTE-ACS	Multinational RCT	6,560	3,279	3,281	Pts with NSTE-ACS within 48 h of ischemic Sx (between Oct 2004 and Feb 2007) Eligibility criteria: ≥18 y; Sx of myocardial ischemia; at least 1 mod-high-risk indicator	Cardiogenic shock, persistent STE, successful revasc before randomization, clinically significant hepatic disease, ESRD requiring dialysis, treatment with agents known to prolong the QT interval, ECG abnls interfering with Holter interpretation, life expectancy <12 mo	Ranolazine (initiated IV followed by oral ranolazine extended-release 1000 mg 2× daily)	PC	1º efficacy endpoint (composite of CV death/MI/recurrent ischemia): 21.8% in the ranolazine group vs. 23.5%, p=0.11 Follow-up was a median of 350 d	No diff in total mortality with ranolazine vs. PC (HR: 0.99; 95% CI: 0.80–1.22) No diff in QTc prolongation requiring dose reduction: 0.9% in pts receiving ranolazine vs. 0.3% in PC, p NS No difference in symptomatic arrhythmias (ranolazine: 3.0% vs. PC: 3.1%; p=0.84)	No diff in the major 2º endpoint (CV death/MI/ severe recurrent ischemia), or in the composite of CV death/MI. Ranolazine was associated with reduced recurrent ischemia: 13.9% vs.16.1%; HR: 0.87; 95% CI: 0.76–0.99; p=0.03).	1º efficacy endpoint (ranolazine vs. PC): HR: 0.92; 95% CI: 0.83–1.02	Given the statistically NS result for the 1º endpoint, all additional efficacy analyses, although prespecified, should be considered as de facto exploratory 915 and 736 pts discontinued the study Rx in the ranolazine and PC arms, respectively.

1º indicates primary; 2º, secondary; ACS, acute coronary syndrome; AF, atrial fibrillation; CV, cardiovascular; diff, difference; ECG, electrocardiograph; ESRD, end-stage renal disease; Hx, history; IV, intravenous; MI, myocardial infarction; NS, no/t significant; NSTE, non-ST-elevation; NSTE-ACS, non-ST-elevation acute coronary syndrome; pts, patients; RCT, randomized controlled trial; revasc, revascularization; Rx, prescription; SA, stable angina; STE, ST-elevation; Sx, symptoms; SVT, sustained ventricular tachycardia; and VT, ventricular tachycardia.

Data Supplement 14. Inhibitors of the Renin-Angiotensin-Aldosterone System (Section 4.2)

Study Name, Author, Year	Aim of Study	Study Type	Study Size (N)	Study Intervention Group (n)	Study Comparator Group (n)	Patient Population		Study Intervention	Study Comparator	Endpoints			P Values, OR: HR: RR & 95% CI:	Study Limitations & Adverse Events
						Inclusion Criteria	*Exclusion Criteria*			*Primary Endpoint (Efficacy) and Results*	*Safety Endpoint and Results*	*Secondary Endpoint and Results*		
SAVE Pfeffer, 1992 1386652 (120)	Captopril on events in AMI with LV dysfunction	Multi-institute prospective	2,231	Captopril 1,115	PC 1,116	3 d after AMI LVEF≤4% 21–79 y.	Contraind. to ACEI Creatinine >2.5 mg/dL	Captopril for 42 mo	PC	All-cause mortality reduced in captopril group vs. PC (20% vs. 25%) Reduction of MACE by 21%	No prospective safety evaluators	Reduction of CV death by ACEI 37% Reduction of severe HF by 22% Reduction of recurrent MI by 25%	All-cause mortality reduction by ACEI 19% (95% CI: 3%–32%); p=0.019 MACE: 21% (95% CI: 5–35); p=0.014 CV deaths 37% (95% CI: 20–50); p<0.001 Recurrent MI: 25%:(95% CI: 5–40); p=0.015	Adverse: dizziness, dysgeusia, cough, diarrhea. Exclusion of pts with symptomatic HF
Ambrosioni, 1995 7990904 (121)	ACEI for short-term events	Multi-institute prospective	1,556	Zofenopril 772	PC 784	CCU with AMI	Contraindication to ACEI	ACEI for 6 wk	PC	6-wk death or severe HF reduced by 34% with ACEI	N/A	1-y death rate reduced by ACEI 29%; p=0.011	6-wk death reduction: 34% (95% CI: 8%–54%); p=0.018 MACE: 46% (95% CI: 11–71); p=0.018	Side effects: 6.8% PC, 8.6% ACEI No use of initial IV ACI to see beneficial or adverse effects.
CONSENSUS II Swedberg, 1992 1495520 (122)	Long-term reduction in mortality with ACEI	Multi-institute prospective	6,090	Enalapril 3,044	PC 3,046	<24 h after onset of chest pain with ECG/ enzyme changes	BP <100/60; need for vasopressors, severe heart block, valvular disease, contraindication to ACEI, TIA	Enalapril for 6 mo	PC	1- and 6-mo mortality unchanged with enalapril vs. PC 7.2% vs. 6.3% 1 mo 11.0% vs. 10.2% 6 mo	Death due to HF 4.3% ACEI 3.2% PC p=0.06	Change in therapy due to HF increased in PC group. p<0.006 NS diff in reinfarctions or rehospitalizatio n due to HF	Mortality; p=0.26	Early hypotension 12% ACEI and 3% PC p<0.001 Lack of ACEI benefit possibly due to low dose of ACEI
ACEI MI Coll. Group 1998 9631869 (123)	Use of ACEI in early AMI	Meta-analysis of 4 clinical trials	98,496	ACEI roughly 1/2	PC roughly 1/2	AMI-early short-term trials>1,000 pts	Smaller trials, no control group	ACEI from 28–42 d	PC	30-d mortality reduction 7% by ACEI	Hypotension less common in ACEI vs. controls 9.3 vs. 17.6%	Absolute benefit highest in Killip 2, 3 anterior MI	30-d mortality reduction 7% (95% CI: 2%–11%); p<0.004 HF reduction 14.6% vs. 15.2%	Significant increase in cardiac shock and renal dysfunction with ACEI Higher 2nd-3 d AV block.

													2p=0.01	
AIREX Hall, 1997 9167457 (124)	Cumulative Mortality 3 y after end of AIRE trial of MI with HF	Multi-institute prospective-	603 in initial AIRE trial of 15 mo	Ramipril 302	PC 301	AMI with evidence of HF	Clinical instability, contraindication to ACEI, HF of valvular or congenital HD, need for open label ACEI.	Ramipril beginning 2-9 d after admission and up to 15 mo with 3-y follow-up poststudy	PC for 15 mo, then 3-y follow-up	15-mo mortality reduced with ACEI and 3-y follow-up mortality also reduced	N/A	N/A	15-mo mortality: 16.9% ACEI 22.6% PC 27% (95% CI: 11–40); p=0.002 3-y post-AIRE mortality: 27.5% ACEI 38.9% PC 36% (95% CI: 15–52); p=0.002 Reduction with ACEI.	Mortality benefit only in 1st 24 mo after study ended. Possibly because more severally ill PC pts died before 24 mo leaving a relatively healthy post-PC population.
Squire, 2010 20478862 (125)	Benefit of BNP in use of ACEI in ACS	Observational cohort study retrospective	1,725	ACEI in all or ARB in some cases	Various levels of BNP	ACS in CCU 44% NSTE-ACS	Resident pts outside health authority area.	ACEI or ARB median 528 d follow-up.	NT-pro-BNP values by quartiles	MACE: only in top quartile of BNP was ACEI associated with reduction of MACE. NS benefit in other BNP quartiles	ACEI treatment. Had survival benefit only in pts without diabetes mellitus or hypertension.	Death or HF: reduced risk in top quartile of BNP: 0.498 (0.31, 0.80); p=0.004 NS reduction of death in top BNP quartile.	Decreased MACE in top quartile of BNP: HR: 0.613 (0.46,0.82); p=0.001	Observational only. Possible residual confounding of variables. Demographic diff in BNP. Single center, but 2 hospitals.
Pfeffer, 2003 14610160 (126)	Effect of ACEI and ARB combination in AMI with HF/LV Dysfunction	Multicenter prospective trial	14,703	Valsartan 4,909 Captopril 4,909 Both 4,885	3-way comparison	AMI 0.5–10 d HF and/or LVEF <0.35 by echo or <0.40 by RN	Low BP Creatinine >2.5	ACE, ARB or combination Median 24.7 mo	3-way comparison	Total mortality: NS diff among 3 groups	Valsartan: hypotension, renal abnormalities more common. Captopril: cough, rash, dysgeusia more common.	Noninferiority of valsartan vs. captopril for death	Total mortality: valsartan vs. captopril 1.00 (97.5% CI: 0.90–1.11) Combined vs. captopril 0.98 (97.5% CI: 0.89–1.09)	Significant adverse events: hypotension, renal causes, hyperkalemia, cough, rash, dysgeusia, angioedema. Significant greater adverse events with combination vs. valsartan alone. 9.0% vs. 5.8% for permanent discontinuation of drug.
Pitt, 2003 12668699 (127)	Effect of eplerenone in AMI with LV dysfunction	Multicenter prospective trial	6,632	Eplerenone 3,319	PC 3,313	3-14 d after AMI LVEF ≤0.40 CHF on ACEI, BB,	K+ sparing diuretics use; Creatinine >2.5 K+>5 meq/L	Eplerenone mean follow-up 16 mo	PC	Total and CV death Total deaths and CV deaths decreased by eplerenone vs.	BP increase less in eplerenone than PC increase in creatinine EP>PC;	Reduction in sudden death 0.79 (95% CI: 0.64–0.97); p=0.03	Total deaths: 0.85 (95% CI: 0.75–0.96); p=0.008 CV deaths: 0.83 (95% CI: 0.72–0.94); p=0.005	Low rate of D/C of EP for adverse events. No gynecomastia. However, increased incidence of serious hyperkalemia

						diuretics				PC	p<0.001 Increase in K+ greater in EP		CV Death or Hospital: 0.87 (95% CI: 0.79–0.95); p=0.02	5.5% vs. 3.9%; p=0.002
Gheorghiade, 2009 19699868 (128)	Effect of eplerenone on readmission hospital stay after MI with LV dysfunction	Retrospective analysis of prospective multicenter trial	6,632; 827 with subsequent hospital readmission	Eplerenone 3,319	PC 3,313	Rehospitalization for HF 827	No rehospitalization from original group 5,805	Eplerenone 16-mo follow-up	PC	Reduction of d of rehospitalization by eplerenone	In rehospitalization pts: K+>6.0 in 10.1% EP vs. 5.8% PC p=0.02	NS effect of geographic region on results	Total d in hospital for HF; (reduction) 3.6 (13.3–16.9) p=0.0006 vs. PC	In subset rehospitalized: No deaths from hyperkalemia, 2-fold reduction of hypokalemia, impotence was rare
Weir, 2009 19464421 (129)	MRI study to evaluate eplerenone effects on LV after MI	Prospective cohort study	100	Eplerenone 50	PC 50	AMI 1-14 d LVEF <040	Clinical HF, DM, preexisting, LV dysfunction, elevated creatinine, K+> mmol/L	Eplerenone 24 wk	PC	Change in LV systolic volume after covariate adjusted volume fell by 6.1± 2.7 mL/m^2 vs. PC	NS diff between eplerenone and PC in HR, BP changes 2/50 EP pts developed K+ bet, 5.6 and 5.9	Diastolic volume fell EP vs. PC 7.5±3.4 mL/m^2 p=0.031 Increased MMP -9 and decreased MMP-2	Systolic volume decreased with EP vs. PC: p=0.027	3 eplerenone pts died, vs. fibrillation, stroke, recurrent AMI, NS change in creatinine or eGFR. Need for covariate adjustment; LVEF changes between screening TTE and MRI.
Rossignol 2011, 22032706 (130)	Mechanism of eplerenone benefit in AMI	Retrospective analysis of multicenter study	6,080	Eplerenone 3,055	PC 3,025	3-14 d after overall AMI; LVEF ≤0.40 CHF on ACEI, BB, diuretics	K+ sparing diuretic Creatinne >2.5 K+>5 meq/L	Eplerenone 1-mo evaluation	PC	Interaction between diuretic effects and K+ sparing effects of eplerenone and benefit of CV outcome	Decreased rate of CV death due to K+ sparing effect of EP vs. PC	EP vs. PC Reduced weight <0.0001 Plasma volume p=0.047 Increased K+ p<0.0001	EP decreased total mortality, CV death/ hospitalization and hospitalization for HF independent of K+ and diuretic effects	Post-hoc analysis Short-term evaluation of K+ and diuretic effects only
Rossignol, 2012 22128223 (131)	Eplerenone effects on renal function after AMI	Retrospective analysis of multicenter study	5,792	Eplerenone 2,918	PC 2,874	3-14 d after AMI; LVEF ≤0.40 CHF, on ACEI, BB, diuretics	K+ sparing diuretic Creatinine>2.5 K+>5 meq/L	Eplerenone 24 mo follow-up	PC	Serial changes in eGFR EP had a decline in eGFR from 1st mo and persisted throughout study	Most salient: early decline in eGFR by EP vs. PC	Early decline in eGFR by>20% associated with worse CV outcomes independent of baseline eGFR and use of eplerenone	Decline >20% eGFR 1st mo: 16.9% EP vs. 14.7% PC OR: 1.15 (95% CI: 1.02–1.30); p=0.017	Post-hoc analysis and included nonprespecified subgroups Changes focused only on a 1-mo timepoint At this timepoint, deaths in eplerenone were already lower than PC
GISSI-3, 1994 7910229(87)	Effect of ACEI on mortality and LV function	Multicenter prospective trial	18,895	Lisinopril, 9,435	Open control 9,460	In CCU within 24 h of chest pain, ECG	Severe HF requiring study treatment, hemodynamic	Lisinopril 10 mg qd for 6 wk	PC	Deaths and combined deaths and LV dysfunction	Rates of hypotension and renal dysfunction	Rates of reinfarction, cardiogenic shock, and	Overall 6-wk mortality reduction: OR: 0.88 (95% CI: 0.79–0.99) Overall reduction in	Relatively low dosage of lisinopril, many elderly and women excluded

	after MI					changes and no contraindications to study med	deterioration, bilateral renal artery stenosis, other life threatening disorders			Lisinopril reduced mortality and combined outcome	higher with ACEI	stroke did not differ	death plus decreased. LV dysfunction: 0.90 (0.84-0.98)	Concern about slightly increased creatinine and hypotension with ACEI
ISIS-4, 1995 7661937(86)	Effect of ACEI on 5-wk mortality after AMI	Multicenter prospec trial	58,050	Captopril 29,028	PC 29,022	In CCU within 24 h of chest pain	Hypotension, cardiogenic shock, fluid depletion	Captopril 50 mg bid for 28 d	PC	5-wk mortality lower with ACE inhibitor	Rates of hypotension increased with ACEI, renal dysfunction No excess of deaths with lower BPs on ACEI	Somewhat fewer deaths 1st 2 d of treatment with ACEI vs. PC	5-wk mortality:7.19% ACI vs. 7.69% PC 2p=0.02	Possible contending effects of magnesium and nitrates in regard to results

ACS indicates acute coronary syndrome; ACEI, angiotensin-converting enzyme inhibitor; AIRE Trial, Acute Infarction Ramipril Efficacy Trial; AMI, acute myocardial infarction; ARB, angiotensin receptor blocker; AV,block, atrioventricular block; BB, beta blocker; bid, twice a day; BNP, B-type Natriuretic Peptide; BP, blood pressure; CCU, cardiac care unit; CHF, congestive heart failure; CV, cardiovascular; diff, diference(s); D/C, discharge; ECG, electrocardiograph; eGFR, estimated glomerular filtration rate; EP, eplerenone; HD, heart disease; HF, heart failure; IV, intravenous; LV, left ventricular; LVEF, left ventricular ejection fraction; MACE, major adverse cardiac events; MI, myocardial infarction; MMP-2, matrix metalloproteinase-2; MMP-9, matrix metalloproteinase-9; MRI, magnetic resonance imaging; NS, no(t) significance; NSTE, non-ST-elevation; NSTE-ACS, non-ST-elevation-acute coronary syndrome; NT-pro-BNP, N-terminal pro-brain natriuretic peptide; PC, placebo; pts, patients; RN, radionuclide; and TTE, transthoracic echocardiography.

Data Supplement 15. Oral and Intravenous Antiplatelet Therapy in Patients With Likely or Definite NSTE-ACS Treated With Initial Invasive or Conservative Strategy (Section 4.3.1)

Study Name, Author, Year	Study Aim	Study Type / Size (N)	Intervention vs. Comparator (n)	Patient Population		Study Intervention	Endpoints			P Values, OR: HR: RR: & 95 CI:	Adverse Events	Study Limitations
				Inclusion Criteria	*Exclusion Criteria*		*Primary Endpoint & Results*	*Safety Endpoint & Results*	*Secondary Endpoint & Results*			
Baigent 2009 19482214 (132)	Low-dose ASA is of definite and substantial net benefit for people who already have occlusive vascular disease. Assessed the benefits and risks in 1° prevention.	Meta-analysis N=95,000 pts at low avg risk	ASA vs. no ASA	1° or 2° prevention trials eligible only if they involved randomized comparison of ASA vs. no ASA (with no other antiplatelet drug in either group).	1° prevention trials excluded individuals with any Hx of occlusive disease at entry	ASA or no ASA	Serious vascular events (MI, stroke, or vascular death) 0.51% vs 0.57%	Major bleeds 0.10% vs. 0.07% per y; p<0.0001	2° prevention trials ASA allocation yielded greater absolute reduction in serious vascular events (6.7% vs. 8.2% per y; p<0.0001) with NS increase in haemorrhagic stroke but reductions of about a 1/5 in total stroke (2.08% vs. 2.54% per y;	p=0.0001	N/A	N/A

									p=0.002) and in coronary events (4.3% vs 5.3% per y; p<0.0001).			
CURE Yusuf 2001 11519503 (133)	Compare efficacy and safety of the early and long-term use of clopidogrel plus ASA with those of ASA alone in pts with ACS and no STE	Randomized, double-blind, PC trial N=12,562 pts	Clopidogrel vs. PC in addition to ASA	Pts were eligible for study if they had been hospitalized within 24 h after onset of Sx and no STE	Contraindications to antithrombotic or antiplatelet therapy, high risk for bleeding or severe HF, taking oral anticoagulants, had undergone coronary revasc in the previous 3 mo or received IV GP IIb/IIIa receptor inhibitors in the previous 3 d	Clopidogrel (300 mg immed followed by 75 mg od) vs. PC in addition to ASA	Death from CV causes, nonfatal MI, or stroke 9.3% vs 11.4%	Pts with major bleeding 3.7% vs. 2.7%; p=0.001 RR: 1.38	1st1° outcome or refractory ischemia 16.5% vs 18.8% RR: 0.86; CI: 0.79–0.94; p<0.001 Percentage of pts with in-hospital refractory or severe ischemia, HF, and revasc procedures were significantly lower with clopidogrel.	p<0.001 RR: 0.80 CI: 0.72–0.90	Clopidogrel was not associated with excess rate of any other type of adverse event that necessitated discontinuation of study drug	N/A
PLATO Mahaffey 2011 21709065 (134)	Prespecified subgroup analysis showed significant interaction between treatment and region (p=0.045), with less effect of ticagrelor in NA than in ROW. Exploratory analyses performed to identify potential explanations for observed region-by-treatment interaction.	Observed regional interaction driven by interaction of randomized treatment with 78% of NA pts in US compared with ROW pts (p=0.01 vs. p=0.045 for interaction using NA). Analyses focus on comparison of US and ROW, with Canadian pts included in ROW group.	Reasons for the interaction were explored independently by 2 statistical groups.	N/A	N/A	2 independently performed analyses identified statistical interaction with ASA maintenance dose as possible explanation for regional difference. Lowest risk of CV death, MI or stroke with ticagrelor compared with clopidogrel is associated with low-maintenance dose of concomitant ASA	Large number of subgroup analyses performed and result numerically favoring clopidogrel in at least 1 of the 4 prespecified regions could occur with 32% probability. More pts in US (53.6%) than in the rest of the world (1.7%) took median ASA dose ≥300 mg qd. Of 37 baseline and postrandomization factors explored, only ASA dose explained substantial fraction of the regional interaction.	N//A	Pts taking low-dose maintenance ASA, ticagrelor associated with better outcomes compared with clopidogrel, with statistical superiority in the rest of the world and similar outcomes in US cohort.	N/A	N/A	N/A
Gremmel 2010	Investigate age dependency of	Prospective observational	Clopidogrel and age	Pts on dual antiplatelet therapy	Known acetylsalicylic acid or	LD of 300 mg (n=116; 60.7%)	ADP-inducible platelet reactivity increased	N/A	N/A	p=0.003 for LTA and p<0.001 for	N/A	Lack of clinical outcome data,

19818001 (135)	clopidogrel mediated platelet inhibition	study N=191 pts		after angioplasty and stenting for CVD	clopidogrel intolerance (allergic reactions and gastrointestinal bleeding), therapy with VKA (warfarin, phenprocoumon and acenocoumarol), treatment with ticlopidine, dipyridamol or NSAID, a family or personal Hx of bleeding disorders, malignant paraproteinemias, myeloproliferative disorders or heparininduced thrombocytopenia, severe hepatic failure, known qualitative defects in thrombocyte function, a major surgical procedure within 1 wk before enrollment, a platelet count <100, 000 or >450, 000 IL-1 and hematocrit <30%.	or 600 mg (n=50; 26.2%) of clopidogrel prior intervention followed by 75 mg of clopidogrel od Pts received daily acetylsalicylic acid therapy (100 mg qd).	linearly with age after adjustment for CV risk factors, type of intervention, medication, CRP and renal function [using LTA 0.36% of maximal aggregation per y, 95% CI: 0.08–0.64%; p=0.013; using the VerifyNow $P2Y_{12}$ assay 3.2 $P2Y_{12}$ reaction units (PRU) per y, 95% CI: 1.98–4.41 PRU; p<0.001. ADP-inducible platelet reactivity significantly higher in pts 75 y or older compared with younger pts (p=0.003 for LTA and p<0.001 for VerifyNow $P2Y_{12}$ assay). High on-treatment residual ADP-inducible platelet reactivity significantly more common among pts 75 y or older (p=0.02 for LTA and p<0.001 for VerifyNow P2Y12 assay).			the VerifyNow $P2Y_{12}$ assay		the relatively small number of patients on chronic clopidogrel therapy and pts were not studied again under maintenance therapy with clopidogrel.
CAPRIE 1996 8918275 (136)	Assess potential benefit of clopidogrel compared with ASA in reducing risk of ischaemic stroke, MI, or vascular death in pts with	Randomized N=19,185 pts	N=9577 clopidogrel (75 mg od) plus PC n=9,566 ASA (325 mg od) plus PC	Ischaemic stroke (including retinal origin and lacunar infarction); MI; Atherosclerotic PAD	Severe cerebral deficit likely lead to pts being bedridden or demented; Carotid endarterectomy after qualifying stroke; Qualifying stroke induced by carotid endarterectomy or	Clopidogrel (75 mg od) ASA (325 mg od)	Pts treated with clopidogrel had annual 5.32% risk of ischaemic stroke, MI, or vascular death compared with 5.83% with ASA. Significant (p=0.043) relative-risk reduction of 8.7% in favor of clopidogrel (95% CI:	There were no major differences in terms of safety	N/A	p=0.043 RR reduction of 8.7% in favor of clopidogrel CI: 0.3–16.5	Reported adverse experiences in the clopidogrel and ASA groups judged to be severe included rash (0.26% vs. 0.10%), diarrhoea (0.23% vs. 0.11%), upper gastrointestinal	N/A

	recent ischaemic stroke, recent MI, or PAD.				angiography; Pts unlikely to be discharged after qualifying event; Severe comorbidity likely to limit pts life expectancy to less than 3 y, Uncontrolled hypertension, Scheduled for major surgery, Contraindications to study drugs; Women of childbearing age not using reliable contraception, Currently receiving investigation drug; Previously entered in other clopidogrel studies.		0.3-16.5). Corresponding on-treatment analysis yielded RR reduction of 9.4%.				discomfort (0.97% vs. 1.22%), intracranial haemorrhage (0.33% vs. 0.47%), and gastrointestinal haemorrhage (0.52% vs. 0.72%). 10 pts (0.10%) in clopidogrel group with significant reductions in neutrophils (<1.2 x 10(9)/L) and 16 (0.17%) in ASA group.	
Gollapudi 2004 15613671 (137)	Provide diagnostic strategy for evaluating and treating pts with ASA sensitivity, with additional consideration for issues specific to pts with CAD.	Literature review	N/A	N/A	N/A	N/A	Prevalence of ASA-exacerbated respiratory tract disease approximately 10% and for ASA-induced urticaria prevalence varies 0.07% to 0.2% of general population. ASA sensitivity most often manifested as rhinitis and asthma or urticaria/angioedema induced by cross-reacting NSAID that inhibit cyclooxygenase 1. 1° mechanism of sensitivity less often related to drug-specific IgE antibody production leading to	N/A	N/A	N/A	N/A	N/A

							urticaria/angioedema and rarely to anaphylaxis. Most pts with acetylsalicylic acid sensitivity are able to undergo desensitization therapy safely and successfully except in cases of chronic idiopathic urticaria. Experience with acetylsalicylic acid desensitization in pts with CAD very limited.					
TRITON – TIMI 38 Wiviott 2007 17982182 (138)	Compare regimens of prasugrel and clopidogrel	N=13,608 pts with ACS with scheduled PCI	Prasugrel n=6813 (60 mg LD and 10 mg qd maintenance dose) or Clopidogrel n=6795 (300 mg LD and 75 mg qd maintenance dose), for 6-15 mo	Pts with UA NSTEMI, TIMI risk score ≥3, either ST-segment deviation of 1 mm or more or elevated levels of a cardiac biomarker of necrosis. Pts with STEMI could be enrolled within 12 h after onset of Sx if 1° PCI was planned or within 14 d after receiving medical treatment for STEMI	Increased risk of bleeding, anemia, thrombocytopenia, a Hx of pathologic intracranial findings, or use of any thienopyridine within 5 d before enrollment.	Prasugrel or clopidogrel	Death from CV causes, nonfatal MI, or nonfatal stroke 12.1% clopidogrel vs 9.9% prasugrel rates of MI 9.7% clopidogrel vs. 7.4% prasugrel; p<0.001) urgent target-vessel revasc 3.7% vs. 2.5%; p<0.001 stent thrombosis 2.4% vs. 1.1%; p<0.001	Major bleeding- TIMI major bleeding not related to CABG, non-CABG related TIMI life threatening bleeding, and TIMI major or minor bleeding 2.4% prasugrel vs. 1.8% clopidogrel HR: 1.32; 95% CI: 1.03–1.68; p=0.03 rate of life-threatening bleeding 1.4% vs. 0.9%; p=0.01 including	Stent thrombosis and composite of death from CV causes, nonfatal MI, nonfatal stroke, or rehospitalization due to a cardiac ischemic event. Rate of MI with subsequent death from CV causes 0.7% vs. 0.4% HR: 0.58; CI:0.36 - 0.93; p=0.02	p<0.001 HR: 0.81 CI: 0.73 - 0.90	More pts treated with prasugrel 2.5% vs. 1.4% clopidogrel; p<0.001 discontinued the study drug owing to adverse events related to hemorrhage; rate of serious adverse events not related to hemorrhage was similar 22.5% vs 22.8% p=0.52	N/A

								nonfatal bleeding 1.1% vs. 0.9%; HR: 1.25; p=0.23 fatal bleeding 0.4% vs. 0.1%; p=0.002				
PLATO Wallentin 2009 19717846 (139)	Determine whether ticagrelor is superior to clopidogrel for the prevention of vascular events and death in broad population of pts presenting with ACS.	N=18,624 pts with ACS with or without STE	Ticagrelor n=9333 (180 mg LD, 90 mg bid thereafter) or clopidogrel (n=9291) (300-600 mg LD, 75 mg daily thereafter)	Hospitalized for ACS with or without STE; with an onset of Sx during the previous 24 h. Pts who had ACS NSTE at least 2 of the following 3 criteria had to be met: ST changes on ECG indicating ischemia; positive test of biomarker, indicating myocardial necrosis; one of several risk factors (age≥60 y; previous MI or CABG; CAD with stenosis of ≥50% in at least 2 vessels; previous ischemic stroke, TIA, carotid stenosis of at least 50% or cerebral revasc; DM; PAD; chronic renal dysfunction, defined as a creatinine clearance of <60 ml/min per 1.73 m2 of body surface area with STE the following 2 inclusion	Any contraindication against the use of clopidogrel, fibrinolytic therapy within 24 h before randomization, a need for oral anticoagulation therapy, an increased risk of bradycardia, and concomitant therapy with a strong cytochrome P-450 3A inhibitor or inducer	Ticagrelor or clopidogrel	Composite of death from vascular causes, MI, or stroke 9.8% of pts receiving ticagrelor vs 11.7% clopidogrel (HR: 0.84; 95% CI: 0.77–0.92; p<0.001).	Major bleeding 11.6% vs 11.2%, p=0.43 ticagrelor was associated with a higher rate of major bleeding not related to CABG 4.5% vs. 3.8%, p=0.03), including more instances of fatal intracranial bleeding and fewer of fatal bleeding of other types	MI alone 5.8% vs. 6.9%, p=0.005 Death from vascular causes 4.0% vs. 5.1%, p=0.001 Stroke alone 1.5% vs. 1.3%, p=0.22 The rate of death from any cause 4.5% vs. 5.9%, p<0.001	p<0.001 HR: 0.84 CI: 0.77-0.92	Discontinuation of the study drug due to adverse events 7.4% ticagrelor vs 6.0% clopidogrel p<0.001 Dyspnea 13.8% vs. 7.8%; Higher incidence of ventricular pauses in 1 wk but not at 30 d in ticagrelor group than clopidogrel group	Geographic differences between populations of pts or practice patterns influenced the effects of the randomized treatments

				criteria had to be met: persistent STE of at least 0.1 mV in at least 2 contiguous leads or a new left bundle-branch block, and the intention to perform 1º PCI.								
Mehta 2010 20818903 (140)	Clopidogrel and ASA are widely used for pts with ACS and those undergoing PCI. However, evidence-based guidelines for dosing have not been established for either agent.	N=25,086 pts	Pts randomly assigned to double-dose clopidogrel received 600 mg LD followed by 150 mg od d 2-7. Pts assigned to standard-dose clopidogrel received 300 mg LD before angiography followed by 75 mg od days 2-7. D 8-30 both double-dose and standard-dose groups received 75 mg of clopidogrel od. Pts randomly assigned to lower-dose ASA received 75-100 mg daily on d 2-30. Those	≥18 yand presented with a NSTE, ACS or STE MI. Either ECG changes compatible with ischemia or elevated levels of cardiac biomarkers; coronary angiographic assessment, with plan to perform PCI as early as possible but no later than 72 h after randomization	Increased risk of bleeding or active bleeding and known allergy to clopidogrel or ASA	2×2 factorial design. Pts were randomly assigned in double blind fashion to double-dose regimen of clopidogrel or standard-dose regimen. In the 2nd component of factorial design pts were randomly assigned in open label fashion to higher-dose ASA or lower-dose ASA.	Time to CV death, MI, or stroke whichever occurred 1st, up to 30 d. Primary outcome occurred in 4.2% of pts assigned to double-dose clopidogrel compared with 4.4% assigned to standard-dose clopidogrel HR: 0.94, 95% CI: 0.83-1.06 p=0.30 NS difference between higher-dose and lower-dose ASA respect to 1º outcome 4.2% vs. 4.4% HR: 0.97: 95% CI: 0.86-–1.09; p=0.61	Major bleeding occurred in 2.5% of pts in double-dose group and 2.0% in standard-dose group HR: 1.24; 95% CI: 1.05–1.46; p=0.01 NS difference between higher-dose and lower-dose ASA with respect to major bleeding (2.3% vs. 2.3%; HR: 0.99; 95% CI: 0.84-1.17; p=0.90).	Composite of death from CV causes, MI, stroke, or recurrent ischemia; the individual components of 1º outcome; death from any cause; Definite or probable stent thrombosis. Double-dose clopidogrel associated with significant reduction in 2º outcome of stent thrombosis among the 17,263 pts who underwent PCI (1.6% vs. 2.3%; HR: 0.68; 95% CI: 0.55–0.85; p=0.001).	p=0.30 HR=0.94 CI=0.83–1.06	N/A	Nominally significant reduction in 1º outcome was associated with use of higher-dose clopidogrel in subgroup of 17,263 study participants who underwent PCI after randomization (69%). Test for interaction between pts who underwent PCI and those who did not undergo PCI (p=0.03) did not meet prespecified threshold of p<0.01 for subgroup interactions. 13 prespecified subgroup analyses were performed for the clopidogrel dose comparison; this

			randomly assigned to higher-dose ASA received 300 to 325 mg daily d 2-30.									result could have been due to the play of chance.
Plato James 2011 21685437 (141)	Evaluate efficacy and safety outcomes in pts in PLATelet inhibition and pts outcomes (PLATO) trial who at randomization were planned for a non-invasive treatment strategy.	Randomized N=5216 pts	Ticagrelor n=2601 vs. clopidogrel n=2615	Admitted to hospital with STE ACS scheduled for PCI or NSTE-ACS, with onset of Sx during the previous 24 h. At least two of the following three criteria were required for NSTE-ACS: STE depression or transient elevation of at least 1 mm in ≥2 contiguous leads; a positive biomarker indicating myocardial necrosis; and 1 additional risk indicator, including age >60 y, previous MI or CABG, CAD, previous ischaemic stroke. TIA, carotid stenosis, cerebral revasc, DM, PAD, or chronic renal dysfunction	Contraindication to clopidogrel, fibrinolytic treatment within 24 h, need for oral anticoagulation treatment, need for dialysis, and clinically important anaemia or thrombocytopenia	ticagrelor or clopidogrel	CV death, MI, and stroke; their individual components; and PLATO defined major bleeding during 1 y 12.0% (n=295) ticagrelor vs. 14.3% (n=346) clopidogrel HR 0.85, 95% CI 0.73 to 1.00; p=0.04).	Incidence of total major bleeding 11.9% vs. 10.3%, HR: 1.17; 95% CI: 0.98–1.39; p=0.08 non-CABG related major bleeding 4.0% vs. 3.1%; HR: 1.30; 95% CI: 0.95–1.77; p=0.10	Overall mortality 6.1% vs. 8.2% HR: 0.75; 95% CI: 0.61–0.93; p=0.01	p=0.04 HR: 0.85 95% CI: 0.73–1.00	N/A	N/A
ISAR-REACT 2 Kastrati 16533938 (142)	Assess whether abciximab is associated with clinical benefit in high-risk pts with ACS undergoing PCI after	Randomized N=2,022 pts	Abciximab n=1012 vs PCn=1010	High-risk ACS pts undergoing PCI	STE-AMI	Abciximab (0.25 mg/kg bolus, followed by a 0.125-microg/kg/min max, 10 mcg/min) infusion for 12 h plus	Death, MI or UTVR at 30 d 8.9% vs. 11.9%	NS differences between 2 groups regarding risk of major and minor bleeding as	N/A	p=0.03 RR: 0.75 95% CI: 0.58–0.97	N/A	Cannot exclude possibility that greater benefit from abciximab might have been present had therapy been initiated

	pretreatment with 600 mg of clopidogrel					heparin, 70 U/kg or PC (PC bolus and infusion of 12 h, plus heparin bolus, 140 U/kg). All pts received clopidogrel 600 mg at least 2 h prior to procedure as well as 500 mg oral or IV ASA		well as need for transfusion.				earlier prior to the cath lab
PURSUIT Trial 2010 9705684 (143)	Inhibition of platelet aggregation with eptifibatide would have incremental benefit beyond that of heparin and ASA in reducing frequency of adverse outcomes in pts with ACS who did not have persistent STE.	Double blind N=10,948 pts	Bolus and infusion of eptifibatide or PC n=1487 low-dose eptifibatide group n=4722 high-dose eptifibatide group n=4739 PC group	Pts who had presented with ischemic chest pain within previous 24 h and who had either ECG changes indicative of ischemia (but not persistent STE) or high serum concentrations of CK-MB isoenzymes	Persistent STE of more than 1 mm, active bleeding or a Hx of bleeding diathesis, gastrointestinal or genitourinary bleeding within 30 d before enrollment, systolic blood pressure above 200 mmHg or diastolic blood pressure above 110 mmHg, a Hx of major surgery within the previous 6 wk, a Hx of nonhemorrhagic stroke within previous 30 d or any Hx of hemorrhagic stroke, renal failure, pregnancy, the planned administration of platelet GP IIb/IIIa receptor inhibitor or thrombolytic agent, or receipt of	Eptifibatide or PC bolus dose of 180 mcg/kg of body weight, followed by infusion of 1.3 mcg/kg/min or bolus dose of 180 mcg/kg followed by infusion of 2.0 mcg/kg/min or bolus and infusion of PC	Composite of death and nonfatal MI occurring up to 30 d after index event compared with PC group. Eptifibatide group had 1.5% absolute reduction in incidence of 1° endpoint (14.2% vs. 15.7% in PC group; p=0.04) Effect was consistent in most major subgroups except for women (odds ratios for death or nonfatal MI, 0.8 (95% CI: 0.7-0.9) in men and 1.1 (95% CI: 0.9-1.3) in women	Bleeding complications More red-cell transfusions among the pts treated with eptifibatide 11.6% vs. 9.2%; RR: 1.3; 95% CI: 1.1-1.4 Study would be stopped in lower-dose group after independent DSMB conducted interim review of safety data, provided the higher dose had acceptable safety profile. After 3,218 pts been	Mortality from all causes within 30 d after the index event, a 1st for recurrent MI within 30 d, composite endpoint (death or nonfatal MI) at 96 h and 7 d	p=0.04	Bleeding was more common in eptifibatide group, although there was no increase in the incidence of hemorrhagic stroke.	N/A

					thrombolytic therapy within previous 24 h			randomly assigned to treatment groups, committee recommended dropping to lower dose				
PRISM-PLUS 1998 9599103 (144)	Evaluate tirofiban, a specific inhibitor of platelet GP IIb/IIIa receptor, in treatment of UA and non–Q-wave MI	Double-blind N=1915 pts	Tirofiban, heparin, or tirofiban plus heparin	Prolonged anginal pain or repetitive episodes of angina at rest or during minimal exercise in previous 12 h and new transient or persistent ST-T ischemic changes on ECG, or elevation of plasma levels of CK and CK-MB fraction	STE lasting more than 20 min, thrombolysis in previous 48 h, coronary angioplasty within previous 6 m or bypass surgery within previous mo, angina caused by identifiable factors, a Hx of a platelet disorder or thrombocytopenia, active bleeding or a high risk of bleeding, and stroke within previous y. Pts who had serum creatinine values above 2.5 mg/dL (220 µmol/L) or a platelet count below 150,000/m^3	Tirofiban, heparin, or tirofiban plus heparin. Study drugs were infused for mean (±SD) of 71.3±20 h, during which time coronary angiography and angioplasty were performed when indicated after 48 h	Death, MI, or refractory ischemia within 7 d lower among pts who received tirofiban plus heparin than among those who received heparin alone (12.9% vs. 17.9%; RR: 0.68; 95% CI: 0.53–0.88; p=0.004).	Study was stopped prematurely for group receiving tirofiban alone because of excess mortality at 7 d (4.6%, compared with 1.1% for pts treated with heparin alone	Death, MI, or refractory ischemia within 48 h and 30 d after randomization, the three components of this end point as separate measures, and composite of death and MI.	Tirofiban plus heparin vs. heparin alone p=0.004 RR=0.68 CI=0.53–0.88	Major bleeding occurred in 3.0% of pts receiving heparin alone and 4.0% of pts receiving combination therapy p=0.34	N/A
EARLY ACS Giugliano 2009 19332455 (145)	Determine optimal timing for initiation of treatment with GP IIb/IIIa inhibitors in pts who have ACS without STE and undergoing invasive procedures	Randomized N=9492 pts	Early, routine administration of Eptifibatide n=4722 vs. delayed Eptifibatide n=4684	Pts ACS NSTEMI undergoing invasive strategy	N/A	Early, routine administration of Eptifibatide or delayed Eptifibatide after angiography but before the pts underwent PCI	Composite of death, MI, recurrent ischemia requiring urgent revasc or occurrence of thrombotic complication during PCI at 96 h 9.3% vs. 10.0%	Major bleeding Pts in early eptifibatide group had significantly higher rates of bleeding. There was NS difference between 2 groups in	Rate of death or MI at 30 d 11.2% vs. 12.3%; OR=0.89; 95% CI: 0.79–1.01; p=0.08	p=0.23 OR=0.92 95% CI=0.80–1.06	N/A	Convergence of use of eptifibatide during PCI in 2 study groups probably reduced the difference in efficacy. Could not assign pts to strict PC group since guidelines

								rates of severe bleeding or nonhemorrhagic serious adverse events.				at time of planning trial strongly endorsed use of GP IIb/IIIa inhibitors during PCI
ACUITY subgroup analysis Stone 2007 17368152 (146)	Assess anticoagulation with the direct thrombin inhibitor bivalirudin during PCI in individuals with moderate- and high-risk ACS	Randomized N=7789 pts	n=2561 heparin (unfractionated or enoxaparin) plus GP IIb/IIIa inhibitors n=2609 bivalirudin plus GP IIb/IIIa inhibitors n=2619 bivalirudin alone	Pts undergoing PCI after angiography, new ST-segment depression; raised TnI, TnT, or CK-MB isozyme; known CAD; or all 4 other UA risk criteria defined by TIMI study group	Included - STE AMI or shock; bleeding diathesis or major bleeding episode within 2 wk; thrombocytopenia; CrCl <30 mL/min	Heparin (unfractionated or enoxaparin) plus GP IIb/IIIa inhibitors, bivalirudin plus GP IIb/IIIa inhibitors, or bivalirudin alone	30-d endpoints of composite ischemia (death, MI, or unplanned revasc for ischemia), major bleeding, and net clinical outcomes (composite ischemia or major bleeding) Bivalirudin plus GP IIb/IIIa inhibitors vs. heparin plus GP IIb/IIIa inhibitors - composite ischemia 9% vs. 8%; major bleeding 8% vs. 7%; net clinical outcomes 15% vs. 13%	N/A	N/A	Composite ischemia p=0.16; major bleeding p=0.32; net clinical outcomes p=0.1	N/A	Randomization occurred before angiography, study drugs were administered at median of 4 h before PCI. PCI subgroup represents subset of 56% of all pts enrolled in ACUITY, and randomization was not stratified by treatment assignment
BRILINTA ™ (ticagrelor) tablets AstraZeneca LP (147)	BRILINTA is indicated to reduce rate of thrombotic CV events in pts with ACS, UA, NSTEMI or STEMI	N/A	N/A	N/A	N/A	N/A	N/A	Daily maintenance dose of ASA, coadministered with BRILINTA, should not exceed 100 mg Increased risk of bleeding Decreased efficacy with BRILINTA (ticagrelor) in	N/A	N/A	N/A	N/A

								combination with ASA doses exceeding 100 mg				
GUSTO IV-ACS Ottervanger 2003 12551868 (148)	Investigate long term effects of GP IIb/IIIa inhibitor abciximab in pts with ACS without STE who were not scheduled for coronary intervention	Randomized N=7800 pts	n=2590 abciximab for 24 h n=2612 abciximab for 48 h n=2598 PC	Pts with ACS without persistent STE including NSTEMI and UA. ≤ 21 y and should have had 1≥ episodes of angina lasting at least 5 min within 24 h before admission. Either abnormal cardiac TnT or TnI test or at least 0.5 mm of transient or persistent ST-segment depression.	N/A	Abciximab for 24-h (0.25 mg/kg bolus followed by 0.125 mcg/kg/min infusion up to max of 10 mcg/min for 24 h), followed by 24-h PC infusion; abciximab for 48 h (same bolus and infusion for total duration of 48 h); matching PC (bolus and 48-h infusion)	Death (of any cause) or MI within 30 d Follow-up data obtained up to 1 y for 7746 pts (99.3%). Overall 1-y mortality rate 8.3% (649 pts). 1-y mortality was 7.8% PC, 8.2% in the 24-h abciximab, and 9.0% in 48-h abciximab	N/A	N/A	24-hour abciximab HR: 1.1; 95% CI: 0.86–1.29), and 48-h abciximab HR: 1.2; 95% CI: 0.95–1.41	N/A	N/A
PCI-CURE Mehta 2001 11520521 (149)	Find out whether in addition to ASA pretreatment with clopidogrel followed by long-term therapy after PCI is superior to strategy of no pretreatment and short-term therapy for only 4 wk after PCI	Randomized N=2658 pts	clopidogrel (n=1313) or PC (n=1345)	N/A	N/A	Clopidogrel vs. PC	Composite of CV death, MI, or urgent target-vessel revasc within 30 d of PCI. 4.5% vs. 6.4% Long-term administration of clopidogrel after PCI associated with a lower rate of CV death, MI, or any revasc (p=0.03), and of CV death or MI (p=0.047). Overall (including events before and after PCI) there was 31% reduction CV death or MI (p=0.002). Less use of GP IIb/IIIa inhibitor in clopidogrel group (p=0.001)	At follow-up, there was NS difference in major bleeding between groups p=0.64	N/A	p=0.03 RR: 0.70 95% CI: 0.50–0.97	N/A	N/A

Petersen 2004 18056526 (150)	Systematically evaluate end points of all-cause death and nonfatal MI, transfusion, and major bleeding observed in the 6 randomized controlled trials comparing enoxaparin and UFH in treatment of ACS	Systematic overview N=21946 pts ESSENCE, A to Z, and SYNERGY, TIMI 11B, ACUTE II, and INTERACT Performed using a random-effects empirical Bayes model	N/A	All 6 RCTs comparing enoxaparin and UFH in NSTE ACS were selected for analysis	N/A	N/A	Enoxaparin is more effective than UFH in preventing combined endpoint of death or MI NS difference found in death at 30 d for enoxaparin vs UFH (3.0% vs. 3.0%; OR: 1.00; 95% CI: 0.85-1.17). Statistically significant reduction in combined endpoint of death or nonfatal MI at 30 d observed for enoxaparin vs. UFH in overall trial populations (10.1% vs 11.0%; OR: 0.91; 95% CI: 0.83-0.99). Statistically significant reduction in combined endpoint of death or MI at 30 d observed for enoxaparin in populations receiving no prerandomization antithrombin therapy (8.0% vs 9.4%; OR: 0.81; 95% CI: 0.70–0.94).	NS difference found in blood transfusion (OR: 1.01; 95% CI: 0.89-1.14) or major bleeding (OR: 1.04; 95% CI: 0.83–1.30) 7 d after randomization	N/A	10.1% vs 11.0% OR: 0.91 CI: 0.83–0.99	N/A	Systematic overviews do not replace RCTs but provide important insights through analyses of totality of data. Trial populations are not identical with respect to baseline characteristics, duration of study treatment, time to revasc, or use of concomitant medical therapies in management of UA/NSTEMI ACS. Imprecision exists in frequency of events as protocols for data collection and definitions of efficacy and safety events varied among studies. Not having the individual pt data from all trials precluded more sophisticated

												statistical analyses.
PRINCIPLE-TIMI 44 Wiviott 2007 18056526 (150)	Compare prasugrel with higher than currently approved 300-mg LD and 75-mg/d MD of clopidogrel	Randomized, double-blind, 2-phase crossover study N=201 subjects	Prasugrel compared with high-dose clopidogrel in pts	≥18 y and scheduled to undergo cardiac catheterization with planned PCI for angina and at least one of the following: coronary angiography within 14 d with at least 1 lesion amenable to PCI, a functional study within 8 wk with objective findings of ischemia, or prior PCI or CABG surgery	Planned PCI for immediate treatment of MI, any thienopyridine within 5 d, GP IIb/IIIa inhibitor within 7 d or planned use (bailout was permitted), high risk of bleeding, thrombocytopenia, or anemia.	Prasugrel compared with high-dose clopidogrel	1º endpoint of LD phase (prasugrel 60 mg vs. clopidogrel 600 mg) was IPA with 20 mumol/L ADP at 6 h IPA at 6 h significantly higher in subjects receiving prasugrel (mean±SD; 74.8±13.0%) compared with clopidogrel (31.8±21.1%; p<0.0001).	N/A	Pts with PCI entered the maintenance dose phase, a 28-d crossover comparison of prasugrel 10 mg/d vs. clopidogrel 150 mg qd with a 1º endpoint of IPA after 14 d of either drug. IPA with 20 mumol/L ADP was higher in subjects receiving prasugrel (61.3±17.8%) compared with clopidogrel (46.1±21.3%; p<0.0001). Results were consistent across all key 2º endpoints; significant differences emerged by 30 min and persisted across all time points	p<0.0001 CI: 38.0–48.4	N/A	LTA requires very precise sample conditions and processing. Significant proportion of samples did not meet prespecified conditions and were excluded from analyses. Absence of a washout period between MD treatments also could be considered limiting.
TRILOGY ACS Roe 2012 22920930 (151)	Evaluate whether ASA plus prasugrel is superior to ASA plus clopidogrel for long term therapy in pts with UA or MI without STE who were <75 y	Double-blind, randomized trial N=7243 pts <75 y N=2083 pts ≥75 y	ASA prasugrel (10 mg daily) vs. clopidogrel (75 mg qd). Low dose 5 mg of prasugrel versus 75 mg of clopidogrel	ACS consisting of UA or MI without STE. Pts were eligible if selected for final treatment strategy of medical management without revasc within 10 d after index event. Pts required to have at least one of four risk criteria: an age ≥60 y, presence of DM, previous MI, or previous revasc	Hx of TIA or stroke, PCI or CABG within the previous 30-d, renal failure requiring dialysis, and concomitant treatment with an oral anticoagulant	Prasugrel or clopidogrel. Prasugrel (10 mg daily) adjusted to (5 mg qd) pts ≥75 y. Clopidogrel (75 mg/d)	Death from CV causes, MI, or stroke among pts <75 y occurred in 13.9% of prasugrel group and 16.0% of the clopidogrel group (HR prasugrel group: 0.91; 95% CI: 0.79–1.05; p=0.21).	Rates of severe and intracranial bleeding similar in 2 groups in all age groups. NS between group differences in frequency of nonhemorrhagic serious adverse	Prespecified analysis of multiple recurrent ischemic events (all components of 1º endpoint) suggested lower risk for prasugrel among pts <75 y (HR: 0.85; 95% CI: 0.72–1.00; p=0.04).	P=0.21 Prasugrel group, HR: 0.91 95% CI: 0.79–1.05	Higher frequency of HF in clopidogrel group	N/A

				with either PCI or CABG.				events.				
PLATO Trial Becker 2011 22090660 (152)	Determine the rate, clinical impact, and predictors of major and fatal bleeding complications in the PLATO study	Randomized, double-blind, active control N=18,624 pts	Ticagrelor n=9235 or clopidogrel n=9186 in addition to ASA	Pts admitted to hospital with either STE or NSTE-ACS	N/A	Ticagrelor oral LD of 180 mg, followed by 90 mg bid Clopidogrel 300 mg oral LD followed by maintenance dose of 75 mg daily. All pts received ASA at dose of 75–100 mg daily	PLATO major bleeding (11.6 vs. 11.2%; p=0.43), TIMI major bleeding (7.9 vs. 7.7%, p=0.56) and GUSTO severe bleeding (2.9 vs. 3.1%, p=0.22)	Fatal bleeding and transfusion rates did not differ between groups	Procedure related bleeding rates were also similar. Non-CABG major bleeding (4.5 vs. 3.8%, p=0.02) and nonprocedure related major bleeding (3.1 vs. 2.3%, p=0.05) were more common in ticagrelor treated pts, primarily after 30 d on treatment.	PLATO major bleeding p=0.43 TIMI major bleeding p=0.56) GUSTO severe bleeding p=0.22	N/A	N//A
Valgimigli 2010 19755402 (153)	To perform a thorough and updated systematic review of randomized clinical trials comparing tirofiban vs. PC or vs. abciximab.	Meta analysis 31 studies involving 20,006 pts	12,874 comparing tirofiban vs. heparin plus PC or bivalirudin alone, and 7132 vs. abciximab	Pts undergoing treatment for various CAD conditions	N/A	N/A	Tirofiban associated at 30 d with significant reduction in mortality compared with PC (OR: 0.68; 95% CI: 0.54–0.86; p=0.001) and death or MI (OR: 0.69; 95% CI: 0.58–0.81; p<0.001) Compared with abciximab, mortality at 30 d did not differ (OR: 0.90; 95% CI: 0.53–1.54; p=0.70) In overall group tirofiban tended to increase the composite of death or MI (OR=1.18; 95% CI: 0.96–1.45; p=0.11)	N/A	N/A	N/A	N/A	Heterogenity in pt populations, different study drug regimens, and variable endpoint definitions across studies
ACUITY Stone 2007 17299194 (154)	To determine optimal strategy for use of GP IIb/IIIa inhibitors in pts with moderate and	Randomized N=9207 pts	Routine upstream (n=4605) deferred selective (n=4602) GP	Moderate- and high-risk ACS pts undergoing invasive-treatment strategy	Included STE AMI or shock; bleeding diathesis or major bleeding within 2 wk; thrombocytopenia; CrCl <30 mL/min	Routine upstream or deferred selective GP IIb/IIIa inhibitor administration	Composite ischemic events (death, MI, or unplanned revasc for ischemia) at 30 d 7.1% vs. 7.9%	N/A	Noninferiority or superiority of major bleeding and net clinical outcomes (composite ischemia or major bleeding).	p=0.044 for noninferiority; p=0.13 for superiority RR: 1.12 95% CI: 0.97–	N/A	Open label design of the trial, a result of the logistic complexities of the study

	high-risk ACS undergoing an early invasive treatment strategy		IIb/IIIa inhibitor administration						30-d rates of major bleeding 6.1% vs. 4.9% p<.001 for noninferiority; p=009 for superiority Net clinical outcomes (11.7% vs. 11.7%; p<.001 for noninferiority; p=0.93 for superiority).	1.29		design, introducing the potential for bias.

1º indicates primary; 2º, secondary; A to Z, AGGRASTAT to ZOCOR; ACS, acute coronary syndrome; ACUTEAcute Catheterization and Urgent Intervention Triage strategy; ADP, adenosine diphosphate; ASA, aspirin; bid, twice daily; CABG, coronary artery bypass graft; CAD, coronary artery disease; CI, confidence interval; CK, creatine kinase; CK-MB, creatine kinase-MB; CRP, C-reactive protein; ;DM, diabetes mellitus; DSMB, Data and Safety Monitoring Board; ECG, electrocardiography; ESSENCE, Efficacy and Safety of Subcutaneous Enoxaparin in Non–Q wave Coronary Events; GP, glycoprotein; GUSTO, Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries; HF, heart failure; HR, hazard ratio; Hx, history; IgE, Immunoglobin E; INTERACT, Intensive blood pressure reduction in acute cerebral haemorrhage trial; IPA; IV, intravenous; LD, loading dose; pts, patients; LTS, ;MI, myocardial infarction; OD, once daily; NA, North America; NS, no(t) significant; NSAID, nonsteroidal anti-inflammatory drugs; NSTE, non-ST elevation; NSTEMI, non-ST-elevation myocardial infarction; PAD, peripheral arterial disease; PC, placebo; PCI, percutaneous coronary intervention; PLATO, Platelet Inhibition and Patient Outcomes; qd, daily; Revasc, revascularization; ROW, rest of the world; RR, relative risk; STE, ST elevation; STEMI, ST-elevation myocardial infarction; SYNERGY, Superior Yield of the New Strategy of Enoxaparin, Revascularization and Glycoprotein IIb/IIIa Inhibitors; Sx, symptoms; TIA, transient ischemic attack; TIMI, thrombolysis in MI; TnI, troponin I; TnT, troponin T; UA, unstable angina; US, United States; UTVR, Urgent Target Vessel Revascularization; and VKA, vitamin K antagonist.

Data Supplement 16. Combined Oral Anticoagulant Therapy and Antiplatelet Therapy in Patients With Definite NSTE-ACS (Section 4.3.2)

Study Name, Author, Year	Study Aim	Study Type/ Size (n)	Intervention vs. Comparator (n)	Patient Population		Study Intervention	Endpoints			P Values, OR: HR: RR: & 95 CI:	Adverse Events	Study Limitations
				Inclusion Criteria	*Exclusion Criteria*		*Primary Endpoint & Results*	*Safety Endpoint & Results*	*Secondary Endpoint & Results*			
CURE Yusuf 2001 (133) 11519503	Compare the efficacy and safety of early and long-term use of clopidogrel plus ASA with those of ASA alone in pts with ACS and no STE	Randomized, double-blind, PC-controlled trial 12,562 pts	Clopidogrel vs. PC in addition to ASA	Pts were eligible for the study hospitalized within 24 h after the onset of Sx and did not have STE	Contraindications to antithrombotic or antiplatelet therapy, high risk for bleeding or severe HF, taking OACs, had undergone coronary revasc in the previous 3 mo or had received IV GP IIb/IIIa receptor inhibitors in the previous 3 d	Clopidogrel (300 mg immediately followed by 75 mg once daily) vs. PC in addition to ASA	Death from CV causes, nonfatal MI, or stroke 9.3% vs. 11.4%	Pts with major bleeding 3.7% vs. 2.7% p=0.001 RR: 1.38	1º outcome or refractory ischemia 16.5% vs. 18.8% RR: 0.86; 95% CI: 0.79–0.94; p<0.001 % of pts with in-hospital refractory or severe ischemia, HF, and revasc procedures were also significantly lower with clopidogrel	p<0.001 RR: 0.80 95% CI: 0.72 — 0.90	Clopidogrel not associated with excess rate of any other type of adverse event that necessitated discontinuation of study drug	N/A
ASPECT-2 van Es 2002	Investigate whether ASA or OACs is more	Randomized N=999 pts	LDASA n=336, Coumadin-high intensity OAC	Men or non-pregnant women admitted with	Established indications for treatment with OAC,	LDASA, high intensity OAC, or combined LDASA	1st occurrence of MI, stroke, or death 9% vs. 5% vs. 5%	Major bleeding 1% ASA, 1% on OAC	N/A	ASA vs. coumadin HR: 0.55; 95% CI:	N/A	N/A

(155) 12126819	effective in the long term after ACS, and whether the combination of ASA and OAC offers greater benefit than either of these agents alone, without excessive risk of bleeding		n=325, combined LDASA and coumadin-moderate intensity OAC n=332	AMIMI or UA within preceding 8 wk	contraindications for the study drug, planned revasc procedure, serious comorbidity, increased risk of bleeding, abnormal blood platelets or erythrocytes, anemia, Hx of stroke, and inability to adhere to the protocol	and moderate intensity OAC	ASA vs. coumadin HR: 0.55; 95% CI=0.30-1,00; p=0.0479 ASA vs. combined HR=: 0.50; CI: 0.27-0.92; p=0.03	(HR: 1·03; 95% CI: 0·21-5·08; p=1.0), and 2% on combination therapy HR: 2.35; 95% CI: 0.61-9.10; p=0.2		0.30-1.00; p=0.0479 ASA vs. combined HR: 0.50; 95% CI: 0.27-0.92; p=0.03		
Karjalainen 2008 (156) 18346963	Determine the safety and efficacy of various periprocedural antithromboticstrategies in pts on long-term OAC with warfarin undergoing PCI to assess the safety of the simplistic UAC strategy	Retrospective analysis n=523 pts	IAC group; UAC group	All consecutive pts on warfarin therapy referred for PCI in 4 centers with a main policy to IAC before PCI and in 3 centers with a long experience on UAC during PCI	N/A	IAC vs. UAC	Major bleeding, access-site complications, and MACE (death, MI, target vessel revasc, and stent thrombosis) Major bleeding 5.0% vs. 1.2%, p=0.02 and after adjusting for propensity score OR: 3.9; 95% CI: 1.0-15.3; p=0.05) Access-site complications 11.3% vs. 5.0%, p=0.01 After adjusting for propensity score OR: 2.8; 95% CI: 1.3-6.1; p=0.008	N/A	N/A	N/A	Major bleeding, stroke, access-site complications	Inherent limitations of a retrospective study including individual risk-based decision making in the treatment choices; outcome assessment was not blinded; sample size may not be sufficient to cover small, but clinically significant diff in bleeding and thrombotic complications
BAAS ten Berg 2001 (157) 11319192	Study the intensity and the duration of AC as predictors of thrombotic and bleeding events	N=530 pts	ASA plus coumarins	Pts who were prospectively randomized to the use of coumarins as part of the BAAS study	N/A	ASA (300 mg LD; then 100 mg qd) and coumarins (acenocoumarol or Sintrom at 6 mg on 1 d, 4 mg on 2 d, 2 mg on 3 d and after	Thrombotic events - death, MI, target lesion revasc, and thrombotic stroke 17 early thrombotic events (3.2%), 7 early bleeding	Bleeding complications - hemorrhagic stroke, major extracranial bleeding, and false aneurysm	N/A	N/A	N/A	N/A

						until intervention) started 1 wk before intervention Target INR 2.1-4.8 during angioplasty and 6 mo follow-up INR was measured on the morning before PTCA and daily thereafter until discharge	episodes (1.3%), and 10 false aneurysms (1.9%) 61 late thrombotic events occurred (11.6%) Optimal AC was an independent predictor of late thrombotic events (RR: 0.33; 95% CI: 0.19-0.57) and was associated with a 0.21 mm (95% CI: 0.17-0.42) larger vessel lumen 6 mo	Late bleeding episodes (1.4%) lowest in pts in the target range				
ACCF/ACG /AHA report Bhatt 2008 (158) 19017521	Not a study but a report with recommendations	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Ruiz-Nodar 2009 (159) 19246502	Evaluate the safety and efficacy of use of DES vs. BMS in a cohort of pts with AF	Retrospectiv e cohort study N=604 pts	DES (n=207) vs. BMS (n=207)	Pts with AF who had undergone PCI with stent	N/A	DES or BMS	All bleeding episodes, thromboembolism, and MACE; i.e. death, AMI, TVF. Incidence density of MACE as well as the incidence of all-cause mortality in both groups was similar. Higher incidence of major bleeding in DES group (2.26 vs. 1.19/10,000 d of exposure; p=0.03)	Major bleeding was higher in the DES group (2.26 vs. 1.19/10,000 d of exposure, p=0.03) Rate of definitive and probable thrombosis was similar in both DES and BMS groups (0.43 vs. 0.06/10,000 d of exposure, p=0.09)	N/A	N/A	N/A	Limited by its registry design and as well as being the experience of only 2 European centers; study may not be adequately powered enough to detect diff in clinical outcomes; the retrospective design of the study could explain an underreporting of minor

												bleeding; the exact length of triple treatment in BMS and DES groups
Lip 2010 (160) 20447945	Not a study but a summary report Full consensus document comprehensively reviews published evidence and presents consensus statement on 'best practice' antithrombotic therapy guideline for management of antithrombotic therapy in AF pts	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
WARSS Mohr 2001 (161) 11794192	Investigate whether warfarin, which is effective and superior to ASA in the prevention of cardiogenic embolism, would also prove superior in the prevention of recurrent ischemic stroke in pts with a prior noncardioembolic ischemic stroke	Multicenter, double-blind, randomized	Warfarin (dose adjusted INR of 1.4-2.8) n=1,103 vs. ASA (325 mg qd) n=1,103	Pts were 30-85 y, considered acceptable candidates for warfarin therapy, had ischemic stroke within previous 30 d, and had scores of ≥3 on GOS	Baseline INR above normal range (>1.4), stroke that was due to procedure or attributed to high-grade carotid stenosis which surgery was planned, or stroke associated with an inferred cardioembolic source	Warfarin (dose adjusted INR 1.4-2.8) vs. ASA (325 mg qd)	Combined recurrent ischemic stroke or death from any cause within 2 y Death or recurrent ischemic stroke 17.8% vs. 16.0% p=0.25; HR: 1.13; 95% CI: 0.92-1.38	Major hemorrhage 2.22 per 100 pt-y vs. 1.49 per 100 pt-y	N/A	p=0.25 HR:1.13 95% CI: 0.92-1.38	N/A	N/A
CARS Peverill 1997 (162) 15687136	N/A	Commentary	Fixed low-dose warfarin (1-3 mg) combined ASA (80 mg)	N/A	N/A	Fixed low-dose warfarin (1-3 mg) combined ASA (80 mg)	Reinfarction, stroke, or CV death. Provides no reduction in reinfarction beyond	N/A	N/A	N/A	N/A	N/A

							that achievable with 160 mg ASA					
Rossini 2008 (163) 19064015	Assess long-term outcomes associated with the use of triple-therapy in pts undergoing coronary stenting and evaluate how these may be affected by targeting INR values to the lower therapeutic range	N=102	Triple antiplatelet therapy ASA and clopidogrel and OAC n=102 Control group: dual antiplatelet therapy ASA and clopidogrel n=102	Pts undergoing coronary stenting treated with dual antiplatelet therapy also requiring OAC	Pts requiring OAC therapy because of mechanical valve prosthesis	Triple antiplatelet therapy ASA and clopidogrel and OAC or control group: dual antiplatelet therapy ASA and clopidogrel INR targeted to lower therapeutic range (2.0-2.5)	Bleeding 10.8% vs. 4.9%, p=0.1 INR values were higher in pts with bleeding (2.8+1.1 vs. 2.3+0.2, p=0.0001) INR values within target range risk of bleeding was lower compared with pts who did not (4.9 vs. 33%, p=0.00019) and in control group (4.9%)	N/A	MACE 5.8% vs. 4.9%, p=0.7	N/A	N/A	N/A
Sarafoff 2008 (164) 18624903	Investigate the efficacy and safety of 2 regimens of antithrombotic AC therapy in pts who present for DES implantation whilst on OAC	N=515 pts	n=306 pts continued OAC (triple therapy) and n=209 pts discontinued OAC (dual therapy) they received antiplatelet therapy with clopidogrel and ASA	Pts on chronic OAC who underwent DES implantation	N/A	Clopidogrel and ASA	Composite of death, MI, stent thrombosis or stroke During SRAT 13 pts in group with triple therapy vs. 15 pts in the group with dual therapy Kaplan–Meier estimates 4.2% and 7.2%, OR: 0.61, 95% CI: 0.29-1.28; p=0.19. 2 y follow-up, 35 pts triple therapy vs. 36 pts dual therapy (Kaplan–Meier estimates 14.1% and 18.0%, OR: 0.76, 95% CI: 0.48-1.21; p=0.25).	Major bleeding 2 y 1.4% (n=4, triple therapy) vs. 3.1% (n=6, dual therapy, p=0.34)	N/A	N/A	N/A	Lack of randomization; diff regarding indication for OAC amongst both groups; study may be underpowered

1º indicates primary; AC, anticoagulants; ACS, acute coronary syndrome; AF, atrial fibrillation; AMI, acute myocardial infarction; ASA, aspirin; BAAS, Balloon Angioplasty and Anticoagulation Study; BMS, bare metal stents; CV, cardiovascular; DES, drug-eluting stents; diff, difference(s); GOS, Glascow Outcome Scale; GP, glycoprotein; HF, heart failure; Hx, history; IAC, interrupted anticoagulation; INR, internationalized normalized ratio; IV, intravenous; LDASA, low-dose aspirin; MACE, major adverse cardiac events; MI, myocardial

infarction; N/A, not applicable; NSTE, non-ST-segment elevation; OAC, oral anticoagulant(s); OR, odds ratio; PC, placebo; PCI, percutaneous coronary intervention; PTCA, percutaneous coronary angioplasty; pt, patient; revasc, revascularization; RR, relative risk; STE, ST-segment elevation; SRAT, stent-related antithrombotic treatment; Sx, symptoms; TVF, target vessel failure; UA, unstable angina; and UAC, uninterrupted anticoagulation.

Data Supplement 17. Parenteral Anticoagulant and Fibrinolytic Therapy (Section 4.3.3)

Study Name, Author, Year	Study Aim	Study Type / Size (N)	Intervention vs. Comparator (n)	Patient Population		Study Intervention	Endpoints			P Values, OR: HR: RR: & 95 CI:	Adverse Events	Study Limitations
				Inclusion Criteria	*Exclusion Criteria*		*Primary Endpoint & Results*	*Safety Endpoint & Results*	*Secondary Endpoint & Results*			
PLATO Mahaffey 2011 (134) 21709065	Prespecified subgroup analysis showed significant interaction between treatment and region (p=0.045), with less effect of ticagrelor in North America than in rest of world. Additional exploratory analyses performed to identify potential explanations for observed region by treatment interaction.	Observed regional interaction driven by interaction of randomized treatment with 78% of North American pts in US compared with the ROW pts (p=0.01 vs. p=0.045 interaction using NA), analyses focus on comparison of US and rest of world with Canadian pts included in the rest of world group.	Reasons for interaction explored independently by 2 statistical groups.	N/A	N/A	Regional interaction could arise from chance alone. Results of 2 independently performed analyses identified underlying statistical interaction with ASA maintenance dose as possible explanation for regional difference. Lowest risk of CV death, MI, or stroke with ticagrelor compared with clopidogrel associated with low maintenance dose of concomitant ASA.	Cox regression analyses performed to quantify how much of regional interaction could be explained by pt characteristics and concomitant treatments, including ASA maintenance therapy. Landmark Cox regressions at 8 timepoints evaluated association of selected factors, including ASA dose, with outcomes by treatment. Systematic errors in trial conduct ruled out. Given large number of subgroup analyses performed and that result numerically favoring clopidogrel in at least 1 of 4 prespecified regions could occur with 32% probability, chance alone cannot be ruled out. More pts in US (53.6%) than rest of world (1.7%)	N/A	Both Cox regression with median maintenance dose and landmark techniques showed pts taking low-dose maintenance ASA, ticagrelor associated with better outcomes compared with clopidogrel with statistical superiority in ROW and similar outcomes in US cohort.	N/A	N/A	N/A

							took median ASA dose ≥300 mg qd. Only ASA dose explained substantial fraction of regional interaction in 37 baseline and postrandomization factors explored.					
PLATO Wallentin 2009 (139) 19717846	Determine whether ticagrelor is superior to clopidogrel for prevention of vascular events and death in broad population of pts presenting with ACS	N=18,624 Pts with ACS with or without STE	Ticagrelor (n=9333) (180-mg LD, 90 mg bid after) or clopidogrel (n=9291) (300-600 mg LD, 75 mg daily after)	Hospitalized for ACS, with or without STE, with onset of Sx during the previous 24 h. Pts who had ACS NSTE, at least two of following three criteria had to be met: ST changes on ECG indicating ischemia; positive test of biomarker indicating myocardial necrosis; or one of several risk factors (age ≥60 y; prev MI or CABG; CAD with stenosis of ≥50% at least 2 vessels; prev ischemic stroke, TIA, carotid stenosis ≥50%, or cerebral revasc; DM; PAD; chronic renal dysfunction, defined as CrCl of <60 mL/min per 1.73 m^2 of body surface area). With STE following two inclusion criteria had to be met: persistent STE ≥0.1 mV at least 2 contiguous leads or new LBBB, and intention to perform 1° PCI.	Contraindication against use of clopidogrel, fibrinolytic therapy within 24 h before randomization, need for oral anticoagulation therapy, increased risk of bradycardia, and concomitant therapy with strong cytochrome P-450 3A inhibitor or inducer	Ticagrelor or clopidogrel	Composite of death from vascular causes, MI, or stroke 9.8% pts receiving ticagrelor vs. 11.7% clopidogrel (HR: 0.84; 95% CI: 0.77–0.92; p<0.001).	Major bleeding 11.6% vs. 11.2%, p=0.43 Ticagrelor associated with higher rate of major bleeding not related to CABG 4.5% vs. 3.8%, p=0.03, including more instances of fatal intracranial bleeding and fewer fatal bleeding of other types	MI alone 5.8% vs. 6.9%, p=0.005 Death from vascularcauses 4.0% vs. 5.1%, p=0.001 Stroke alone 1.5% vs. 1.3%, p=0.22 Rate of death from any cause 4.5% vs. 5.9%, p<0.001	p<0.001 HR=0.84 95% CI=0.77-0.92	Discontinuation of study drug due to adverse events 7.4% ticagrelor vs. 6.0% clopidogrel p<0.001 Dyspnea was 13.8% vs. 7.8% Higher incidence of ventricular pauses in 1 wk but not at 30 d in ticagrelor group than in clopidogrel group	Geographic differences between populations of pts or practice patterns influenced effects of the randomized treatments

Mehta 2010 (140) 20818903	Clopidogrel and ASA widely used for pts with ACS and those undergoing PCI. Evidence-based guideline for dosing not been established for either agent.	25,086 pts	Pts randomly assigned to double-dose clopidogrel received LD of 600 mg 1 d followed by 150 mg od on 2-7 d. Pts assigned to standard-dose clopidogrel received 300 mg LD 1 d before angiography followed by 75 mg od 2-7 d. 8-30 d both double-dose and standard-dose groups received 75 mg of clopidogrel od. Pts randomly assigned to lower-dose ASA received 75 to 100 mg daily 2-7 d and those randomly assigned to higher-dose ASA received 300-325 mg daily on d 2-30.	≥18 y and presented with NSTE ACS or STEMI. ECG changes compatible with ischemia or elevated levels of cardiac biomarkers; coronary angiographic assessment, with plan to perform PCI early as possible but no later than 72 h after randomization	Increased risk of bleeding or active bleeding and known allergy to clopidogrel or ASA	2×2 factorial design pts randomly assigned in double-blind fashion to double-dose regimen of clopidogrel or to standard-dose regimen. 2nd component of factorial design, pts were randomly assigned in open label fashion to higher-dose ASA or lower-dose ASA.	Time to CV death, MI, or stroke, whichever occurred 1st, up to 30 d. Primary outcome occurred in 4.2% of pts assigned to double dose clopidogrel as compared with 4.4% assigned to standard-dose clopidogrel (HR: 0.94; 95% CI: 0.83–1.06; p=0.30). No significant difference between higher-dose and lower-dose ASA with respect to 1° outcome (4.2% vs. 4.4%; HR: 0.97; 95% CI: 0.86–1.09; p=0.61)	Major bleeding occurred in 2.5% of pts in double dose group and in 2.0% in standard-dose group (HR, 1.24; 95% CI: 1.05–1.46; p=0.01). No significant difference between higher-dose and lower-dose ASA with respect to major bleeding (2.3% vs. 2.3%; HR: 0.99; 95% CI: 0.84–1.17; p=0.90).	Composite of death from CV causes, MI, stroke, or recurrent ischemia; individual components of 1° outcome; death from any cause; Definite or probable stent thrombosis. Double-dose clopidogrel associated with significant reduction in 2° outcome of stent thrombosis among the 17,263 pts who underwent PCI (1.6% vs. 2.3%; HR: 0.68; 95% CI: 0.55–0.85; p=0.001).	p=0.30 HR: 0.94 CI: 0.83–1.06	N/A	Nominally significant reduction in 1° outcome associated with use of higher-dose clopidogrel in subgroup of 17,263 study participants who underwent PCI after randomization (69%). Test for interaction between pts who underwent PCI and those who did not undergo PCI (p=0.03) did not meet prespecified threshold of p≤0.01 for subgroup interactions since 13 prespecified subgroup analyses were performed for clopidogrel dose comparison, result could have been due to play of chance.
ACUITY subgroup analysis Stone 2007 (146) 17368152	Assess anticoagulation with direct thrombin inhibitor bivalirudin during PCI in	Randomized n=7789 pts	n=2561 Heparin (unfractionated or enoxaparin) plus GP IIb/IIIa inhibitors n=2609	Pts undergoing PCI after angiography, ST depression; raised TnI, TnT, or CK-MB isozyme; known CAD; or all 4 other UA risk criteria as defined by TIMI study	Included - STE AMI or shock; bleeding diathesis or major bleeding episode within 2 wk; thrombocytopenia; CrCl <30 mL/min	Heparin (unfractionated or enoxaparin) plus GP IIb/IIIa inhibitors, bivalirudin plus GP IIb/IIIa	30-d endpoints of composite ischemia (death, MI, or unplanned revasc for ischemia), major bleeding, and net clinical outcomes	N/A	N/A	Composite ischemia p=0.16; major bleeding p=0.32; net clinical outcomes p=0.1	N/A	Randomization occurred before angiography, study drugs were administered at median of 4 h before PCI. PCI

	individuals with moderate- and high-risk ACS.		Bivalirudin plus GP IIb/IIIa inhibitors, or n=2619 bivalirudin alone.	group		inhibitors, or bivalirudin alone	(composite ischemia or major bleeding) bivalirudin plus GP IIb/IIIa inhibitors vs. heparin plus GP IIb/IIIa inhibitors - composite ischemia 9% vs. 8%; major bleeding 8% vs. 7%; net clinical outcomes 15% vs. 13%					subgroup represents subset of 56% of all pts enrolled in ACUITY, randomization not stratifi ed by treatment assignment.
Petersen 2004 (165) 15238596	Systematically evaluate endpoints of all-cause death nonfatal MI, transfusion, and major bleeding observed in 6 RCT comparing enoxaparin and UFH in treatment of ACS	Systematic overview N=21946 pts ESSENCE, A to Z, and SYNERGY, TIMI 11B, ACUTE II, and INTERACT performed using random effects empirical Bayes model	N/A	All 6 RCT comparing enoxaparin and unfractionated heparin in NSTE ACS selected for analysis	N/A	N/A	Combined endpoint of death or MI enoxaparin more effective than UFH in preventing combined endpoint of death or MI. NS difference found in death at 30 d for enoxaparin vs UFH (3.0% vs 3.0%; OR: 1.00; 95% CI: 0.85–1.17). Statistically significant reduction in combined endpoint of death or nonfatal MI at 30 d observed for enoxaparin vs. UFH in overall trial populations (10.1% vs. 11.0%; OR, 0.91; 95% CI, 0.83-0.99). Statistically significant reduction in combined endpoint of death or MI at 30 d also observed for enoxaparin in populations receiving no prerandomization antithrombin therapy	NS difference was found in blood transfusion (OR: 1.01; 95% CI: 0.89–1.14) or major bleeding (OR, 1.04; 95% CI: 0.83–1.30) at 7 d after randomization	N/A	10.1% vs. 11.0% OR: 0.91 CI: 0.83-0.99	N/A	Systematic overviews do not replace RCT but provide important insights through analyses of totality of the data. Trial populations are not identical with respect to baseline characteristics, duration of study treatment, the time to revasc or the use of concomitant medical therapies in management of UA/NSTEMI ACS. Some imprecision exists in frequency of events as protocols for data collection and definitions of efficacy and safety events varied among

							(8.0% vs. 9.4%; OR: 0.81; 95% CI: 0.70–0.94)					studies. Not having individual pt data from trials precluded more sophisticated statistical analyses.
Hochman 1999 (166) 10426845	Evaluate regimens that reduced heparin dosage for low body weight on weight adjusted basis in prospective, nonrandomized cohort pts with UA and MI who did not receive thrombolytic agents	Nonrandomized N=80 pts	Heparin Group 1 n=23 Group 2 n=19 Group 3 n=38	Pts admitted with UA and NSTEMI	Exclusion criteria included Hx of bleeding, Coumadin or thrombolytic therapy, and failure to comply exactly with dosing regimen	Standard (group 1) non weight adjusted 5000-U IV bolus/1000 U/hr infusion. 2 weight adjusted heparin regimens group 2 70 U/kg IV bolus; 15 U/kg/h pts <70 kg and a fixed 5000-U IV bolus/1000 U/hr for pts who weighed ≥70 kg) (group 3) 60 U/kg IV bolus, 12 U/kg/hr infusion pts <70 kg and capped 4000-U IV bolus; 900 U/hr infusion pts ≥70 kg.	Proportion of pts achieving a target aPTT at 6 h. Pts treated with lower dose of weight adjusted heparin group 3 more often within the target range for aPTT at 6 h (34% vs. 5% vs. 0%) required fewer heparin infusion changes (1.0 ± 1.0 vs. 1.9 ± 1.0 vs. 2.0 ± 0.9) within 1st 24 h compared with other regimens. Pts in groups 1 and 2 above target range at 6 h (95% and 84% compared with 48% in group 3)	N/A	Proportion of pts achieving a target aPTT at 24 h and number of times heparin dose adjusted within 1st 24 h. 52% pts in group 1 within target range compared with 79% in group 2 and 74% in group 3 significantly fewer changes in infusion rate required over 24 h period in group 3 compared with other regimens (1.05 ± 1.0 for group 3 vs. 2 ± 0.9 for group 1 vs. 1.9 ± 1.0 in group 2; p<0.001).	Significantly higher proportion of pts above target range in groups 1 (95%) and 2 (84%) versus group 3 (47%) (p<0.0005)	No major complications in any group	Pts not randomly assigned, and the 2 weight adjusted regimens were not concurrently tested. At initiation of 2nd weight-adjusted nomogram the target aPTT changed to 45-70 s from 50-75 s
Garcia 2012 (167) 22315264	Pharmacology of approved parenteral anticoagulants including indirect anticoagulants, UFH, LMWH, fondaparinux, and danaparoid, and direct	Parenteral Anticoagulants Evidence-Based Clinical Practice Guidelines	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

	thrombin inhibitors hirudin, bivalirudin, and argatroban.											
TIMI 11B Antman 1999 (168) 10517729	Test benefits of strategy of extended course of uninterrupted antithrombotic therapy with enoxaparin compared with standard treatment with UFH for prevention of death and cardiac ischemic events in pts with UA/NQMI	Randomized N=3910 pts	UFH n=1957 vs. enoxaparin n=1953	Pts with UA/NQMI ischemic discomfort of >5 min duration at rest; Hx of CAD (abnormal coronary angiogram, prior MI, CABG surgery, or PTCA), ST deviation, or elevated serum cardiac markers	Planned revasc within 24 h, treatable cause of angina, evolving Q-wave MI, Hx of CABG surgery within 2 mo or PTCA within 6 mo, treatment with continuous infusion of UFH for >24 h before enrollment, Hx of heparin-associated thrombocytopenia with or without thrombosis, and contraindications to anticoagulation	UFH >3 d followed by subcutaneous PC injections or enoxaparin (30 mg IV bolus followed by injections of 1.0 mg/kg every 12 h) Outpatient phase (injections every 12 h of 40 mg pts <65 kg, 60 mg >65 kg)	Composite of all-cause mortality, recurrent MI, or urgent revasc at 8 d 14.5% vs. 12.4% OR: 0.83; 95% CI: 0.69–1.00; p=0.048 at 43 d 19.7% vs. 17.3% OR: 0.85; 95% CI: 0.72–1.00; p=0.048	Major hemorrhage, bleed in retroperitoneal, intracranial, or intraocular location; hemoglobin drop of >3 g/dL; requirement of transfusion of >2 U blood 72 h no difference	Individual elements of 1º endpoint and composite of death or nonfatal MI	8 d p=0.048 OR=0.83 95% CI: 0.69-1.00 at 43 d p=.048 OR= 0.85 95% CI= 0.72–1.00	Stroke (1.0% vs. 1.2%), TIA (0.3% vs. 0.3%), or thrombocytopenia (2.1% vs. 1.9%)	N/A
OASIS-5 trial Mehta 2007 (169) 17964037	Study reports prospectively planned analysis of pts with ACS who underwent early PCI in the OASIS-5 trial	Double-blind, randomized 20,078 pts	n=1,414 subcutaneous fondaparinux 2.5 mg od or n=1,420 subcutaneous enoxaparin 1 mg/kg bid	Pts with UA or NSTEMI; at least 2 of following criteria: age >60 y, positive cardiac biomarkers, or ECG changes compatible with ischemia.	Contraindication to low molecular weight heparin, hemorrhagic stroke within last 12 mo, indication for anticoagulation other than ACS, revasc procedure already performed for qualifying event, and severe renal insufficiency	Fondaparinux or enoxaparin total of 12,715 pts underwent heart catheterization during the initial hospitalization, and 6,238 pts underwent PCI.	Rates of major bleeding and efficacy by evaluating composite of death, MI, or stroke at 9, 30, 180 d Fondaparinux vs. enoxaparin reduced major bleeding by >0.5 (2.4% vs. 5.1%; HR: 0.46, p<0.00001) at 9 d with similar rates of ischemic events resulting in superior net clinical benefit (death, MI, stroke, major bleeding: 8.2% vs.	Catheter thrombus more common in pts receiving fondaparinux (0.9%) than enoxaparin alone (0.4%), but largely prevented by using UFH at the time of PCI without increase in bleeding	N/A	p<0.00001 HR: 0.46	N/A	Randomized treatments may have influenced which pts underwent PCI. Types of pts undergoing PCI and number and timing of PCI procedures similar in 2 randomized treatment groups. Number of pts who received open-label UFH before PCI in OASIS-5 trial

							10.4%; HR: 0.78, p=0.004). Fondaparinux reduced major bleeding 48 h after PCI irrespective of whether PCI was performed <6 h of the last enoxaparin dose (1.6% vs. 3.8%; HR: 0.42, p<0.0001) or >6 h when UFH was given (1.3% vs. 3.4%; HR: 0.39, p<0.0001).					modest.
OASIS-5 Yusuf (170) 16537663	Compare the efficacy and safety of fondaparinux and enoxaparin in high-risk pts with UA or NSTEMI	Randomized, double-blind, double-dummy trial N=20,078 pts	n=10,057 fondaparinux vs. n=10,021 enoxaparin	Pts with UA or NSTEMI; ≥60 y, elevated level of troponin or CK-MB isoenzyme, or ECG changes indicative of ischemia.	Contraindications to low molecular weight heparin, recent hemorrhagic stroke, indications for anticoagulation other than ACS or serum creatinine level of ≥3 mg/dL (265 µmol/L)	Fondaparinux (2.5 mg d) or enoxaparin (1 mg/kg od) for mean of 6 d	Death, MI, or refractory ischemia at 9 d 1º outcome events similar in 2 groups (5.8% (579 events) with fondaparinux vs. 5.7% (573 events) enoxaparin HR=1.01; 95% CI, 0.90-1.13); composite of 1º outcome and major bleeding at 9 d favored fondaparinux (737 events) 7.3% vs. (905 events) 9.0%; HR=0.81; p<0.001.	Rate of major bleeding at 9 d markedly lower with fondaparinux than with enoxaparin (217 events) 2.2% vs. 412 events 4.1%; HR: 0.52; p<0.001	Death, MI, or refractory ischemia; and individual components of composite outcomes at 30 d and at end of study NS trend toward lower value in fondaparinux group at 30 d (805 vs. 864, p=0.13) and at end of study (1222 vs. 1308, p=0.06). Fondaparinux associated with significantly reduced number of deaths at 30 d (295 vs. 352; p=0.02) and at 180 d (574 vs. 638; p=0.05).	HR: 1.01 CI: 0.90-1.13	N/A	N/A
FUTURA/ OASIS-8 Steg 2010 (171) 20805623	Compare safety of 2 UFH regimens during PCI in high-risk pts with NSTE	Double-blind randomized parallel group N=2,026 pts	Low-dose UFH n=1024 vs. standard-dose UFH n=1002	Pts undergoing PCI within 72 h Hx consistent with new or worsening ischemia, occurring at rest or with minimal activity;	<21 y; contraindications to UFH or fondaparinux; contraindications for angiography; pts	IV low-dose UFH, 50 U/kg , regardless of use of GpIIb-IIIa inhibitors or standard-dose	Composite of major bleeding, minor bleeding, or major vascular access-site complications up to 48 h after PCI	Major bleeding or minor bleeding Major bleeding no difference minor bleeding	Composite of major bleeding at 48 h 5.8% vs. 3.9%; OR: 1.51; 95% CI: 1.00–2.28; p=0.05 death, MI, or target	p=0.27 OR: 0.80 95% CI: 0.54-1.19	Catheter thrombus 0.5% vs. 0.1% p=0.15	FUTURA still underpowered to conclusively rule out moderate, but important, reductions in

	acss initially treated with fondaparinux			enrollment within 48 h of most recent Sx; planned coronary angiography, with PCI if indicated, within 72 h; at least 2 of following criteria: >60 y, TnT or TnI or CK-MB above upper limit of normal; ECG changes compatible with ischemia	requiring urgent coronary angiography due to refractory or recurrent angina associated with dynamic ST changes, HF, life-threatening arrhythmias, hemodynamic instability; treatment with other injectable anticoagulants hemorrhagic stroke within 12 mo; indication for anticoagulation other than acss; women pregnant, breastfeeding, or of childbearing potential not using contraception; life expectancy <6 mo; receiving experimental pharmacological agent; revasc procedure for qualifying event already performed; creatinine clearance < 20 mL/min.	UFH, 85 U/kg (60 U/kg with GpIIb-IIIa inhibitors), adjusted by blinded ACT	4.7% vs. 5.8% OR: 0.80; 95% CI: 0.54–1.19; p=0.27	0.7% vs. 1.7% ; OR: 0.40; 95% CI: 0.16–0.97; p=0.04)	vessel revasc within 30 d 4.5% vs. 2.9%; OR: 1.58; 95% CI: 0.98–2.53; p=0.06			bleeding from use of low-dose UFH. Based on observed 5.8% event rate of 1° endpoint, a sample size of 11, 542 pts needed to have 80% power to detect 20% RR reduction
Grosser 2013 (172) 23212718	Determine commonality of mechanistically consistent, stable, and specific phenotype of	N=400	Group 1 (n=40) received regular, immediate release ASA response was assessed 8 h after dosing. Group 2 (n=210)	Healthy, nonsmoking volunteers (aged 18–55 y)	N/A	Single oral dose of 325-mg immediate release ASA or enteric coated ASA	Pharmacological resistance to ASA is rare; study failed to identify single case of true drug resistance. Variable absorption caused high frequency of apparent	N/A	Pseudoresistance, reflecting delayed and reduced drug absorption, complicates enteric coated but not immediate release ASA	N/A	N/A	N/A

	true pharmacologic al resistance to ASA—such as might be explained by genetic causes		received enteric coated ASA response was measured 8 h after dosing. Group 3 (n=150) received enteric coated ASA, response was assessed at 4 h				resistance to single dose of 325 mg enteric coated ASA (up to 49%) but not to immediate release ASA (0%).					
FUTURA/ OASIS 8 Steg (173) 21146654	Evaluate safety of 2-dose regimens of adjunctive IV UFH during PCI in high-risk pts with NSTE-ACS initially treated with fondaparinux and referred for early coronary angiography.	International prospective cohort study N=4,000	4,000 high-risk pts treated with fondaparinux as initial medical therapy Within cohort, 2,000 pts undergoing PCI enrolled into double-blind international randomized parallel-group trial evaluating standard ACT guided doses of IV UFH versus a non-ACT-guided weight-adjusted low dose.	UA or NSTEMI; be enrolled within 48 h of the onset of most recent episode of Sx; planned coronary angiography with PCI if indicated within 72 h of enrolment; at least 2 of following: age ≥60 y, TnT or TnI or CK-MB above upper limit of normal; ECG changes compatible with ischemia.	Age <21 y; contraindication to UFH or fondaparinux; contraindication for angiography or PCI; subjects requiring urgent (<120 min) coronary angiography because of refractory or recurrent angina associated with dynamic ST changes, HF, life-threatening arrhythmias, and hemodynamic instability; subjects already receiving treatment with other injectable anticoagulants for treatment of qualifying event, unless the last dose was ≥8 h for LMWH, ≥60 min for bivalirudin, ≥90 min for UFH; hemorrhagic stroke	N/A	Composite of peri-PCI major bleeding, minor bleeding, or major vascular access site complications	Major and minor bleeding; major vascular access site complications	Composite of peri-PCI major bleeding with death, MI, or target vessel revasc at 30 d.	N/A	N/A	N/A

					within last 12 mo; indication for anticoagulation other than ACS; pregnancy, women who are breastfeeding or childbearing potential who are not using effective method of contraception; comorbid conditions with life expectancy <6 mo; currently receiving an experimental pharmacologic agent; revasc procedure for qualifying event already performed; and severe renal insufficiency							
ACUITY Stone 2006 (174) 17124018	Examine usefulness of bivalirudin as part of early invasive strategy with optimal antiplatelet therapy in pts with acss	Randomized N=13,819 pts	n=4603 UFH or enoxaparin plus a GP IIb/IIIa inhibitor n=4604 bivalirudin plus GP IIb/IIIa inhibitor n=4612 bivalirudin alone	Pts with Sx of UA lasting ≥10 min within preceding 24 h eligible for enrollment if one or more following criteria were met: new ST-segment depression or transient elevation of at least 1 mm; elevations in the TnI, TnT, CK-MB levels; known CAD; or all four other variables for predicting TIMI risk scores for UA.	MI associated with acute STE or shock; bleeding diathesis or major bleeding episode within 2 wk before episode of angina; thrombocytopenia; a calculated creatinine clearance rate of <30 mL/min; recent administration of abciximab, warfarin, fondapar inux, fibrinolytic agents, bivalirudin, ≥2 doses of LMWH; and allergy to any study	UFH or enoxaparin plus a GP IIb/IIIa inhibitor, bivalirudin plus a GP IIb/IIIa inhibitor, or bivalirudin alone	Composite ischemia endpoint (death, MI, or unplanned revasc for ischemia), major bleeding, and net clinical outcome, defined as combination of composite ischemia or major bleeding. Bivalirudin plus GP IIb/IIIa inhibitor, as compared with heparin plus GP IIb/IIIa inhibitor, associated with noninferior 30-d rates of composite ischemia	N/A	N/A	N/A	N/A	Logistic complexities of trial necessitated an open-label design, introduced potential for bias; 59% of study cohort presented with NSTEMI. Significant proportion of pts pretreated with either UFH or LMWH before randomization; 25% noninferiority margin used may

					drugs or to iodinated contrast medium that could not be controlled in advance with medication.		endpoint (7.7% and 7.3%, respectively), major bleeding (5.3% and 5.7%), and net clinical outcome endpoint (11.8% and 11.7%). Bivalirudin alone, compared with heparin plus GP IIb/IIIa inhibitor, associated with noninferior rate of composite ischemia endpoint (7.8% and 7.3%, respectively; p=0.32; RR=1.08; 95% CI=0.93-1.24) significantly reduced rates of major bleeding (3.0% vs. 5.7%; p<0.001; RR=0.53; 95% CI=0.43-0.65) net clinical outcome endpoint (10.1% vs. 11.7%; p=0.02; RR=0.86; 95% CI=0.77-0.97).					be considered wide
Fibrinolytic Therapy Trialists' (FTT) Collaborative Group 1994 (175) 7905143	Systematic overview of effects of treatment on mortality and on major morbidity in various pt categories in 9 trials designed to randomize >1000 pts with AMI between fibrinolytic	Collaborative overview	N=58600 pts	All trials of fibrinolytic therapy vs. control that randomized >1000 pts with suspected AMI GISSI-1, ISAM, AIMS, ISIS-2, ASSET, USIM, ISIS-3, EMERAS, LATE	N/A	Streptokinase, anistreplase, tPA, urokinase	Deaths during 1st 5 wk and major adverse events occurring during hospitalization 10.5% deaths 1.0% strokes 0.7% major non-cerebral bleeds Fibrinolytic therapy excess of deaths during 0-1 d (especially among pts presenting >12 h after Sx and in the elderly)	N/A	Benefit in 45,000 pts presenting with STE or BBB irrespective of age, sex, blood pressure, HR, or previous MI or D greater earlier treatment began Relation between benefit and delay from Sx onset indicated highly significant absolute	N/A	Fibrinolytic therapy associated with 4 extra strokes per 1000 during 0-1 d	N/A

	therapy and control – GISSI-1, ISAM, AIMS, ISIS-2, ASSET, USIM, ISIS-3, EMERAS, LATE						Much larger benefit during 2-35 d		mortality reductions – 30 per 1000 within 0-6 h; 20 per 1000 presenting 7-12 h; statistically uncertain benefit 10 per 1000 within 13-18 h			
TIMI IIIB 1994 (176) 8149520	TIMI III focused on UA and NQMI. Determine by coronary arteriography the incidence of coronary thrombi in these conditions and response of these thrombi to 0.8 mg/kg dose (max 80 mg) of TPA. Determine effects of thrombolytic therapy and early invasive strategy on clinical outcome (TIMI IIIB). Provide further understanding of natural Hx of UA and NQMI	Randomized using 2×2 factorial design N=1473 Pts	Compare TPA vs. PC as initial therapy and an early invasive strategy (early coronary arteriography followed by revasc when anatomy was suitable) vs. early conservative strategy (coronary arteriography followed by revasc if initial medical therapy failed).	Pts seen within 24 h of ischemic chest discomfort at rest, considered to represent UA or NQMI.	Treatable cause of UA, experienced MI within preceding 21 d, undergone coronary arteriography within 30 d, PTCA within 6 mo, CABG anytime, or if, at enrollment, were in pulmonary edema, had SBP >180 mm Hg or DBP >100mm Hg, contraindication to thrombolytic therapy or heparin, LBBB, a coexistent severe illness, woman of child-bearing potential, receiving oral anticoagulants.	TPA versus PC Early invasive strategy vs. early conservative strategy	TPA-PC comparison (death, MI, or failure of initial therapy at 6 wk) occurred in 54.2% of the TPA-treated pts and 55.5% of PC-treated pts (p=NS). Fatal and nonfatal MI after randomization (reinfarction in NQMI pts) occurred more frequently in TPA-treated pts (7.4%) than in PC-treated pts (4.9%, p=0.04, Kaplan-Meier estimate).	N/A	Endpoint for comparison of the two strategies (death, MI, or unsatisfactory Sx-limited exercise stress test at 6 wk) occurred in 18.1% of pts assigned to early conservative strategy and 16.2% of pts assigned to the early invasive strategy (p=NS).	p=NS	4 intracranial hemorrhages occurred in TPA-treated group vs. none in PC treated group (p=.06).	N/A
Eikelboom 2000 (147)	Systematic overview of randomized	Meta-analysis 12 trials, n=17,157 pts	UFH or LMWH or PC	Trials had to be randomized; include pts with UA or NQMI; and	Studies were excluded: Randomized	UFH or LMWH or PC	Composite of death or MI at 7 d (OR: 0.53 95% CI: 0.38–0.73;	1º safety outcome major bleeding	2º outcomes of interest were recurrent angina	N/A	N/A	Large numbers of pts randomized to receive short-

	trials to assess effect of UFH and LMWH on death, MI, and major bleeding.			include ASA-treated pts randomly assigned to UFH or LMWH or to PC or untreated control	comparison heparin vs. ASA, heparin plus ASA vs. combined antiplatelet therapy, or heparin vs. non-ASA control; nonrandomized comparison reported; dose-ranging uncontrolled study; pts alternately allocated to LMWH or UFH therapy; lack of clarity as to whether study was properly randomized.		p=0.0001) Short term LMWH vs UFH (OR: 0.88; 95% CI: 0.69–1.12; p=0·34). Long-term LMWH (up to 3 mo) vs PC or untreated control (OR: 0·98; 95% CI: 0.81–1.17; p=0·80	Long-term LMWH OR=2·26, 95% CI=1.63–3.14, p<0.0001	and need for revasc.			term therapy who did not continue therapy long term may have reduced power of studies to detect significant difference. Pts who did not receive long-term LMWH were those at highest risk for recurrent events.
ACCF/ ACG/ AHA report Bhatt 2008 (158) 19017521	ACCF/ACG/AHA 2008 Expert Consensus Document on Reducing the Gastrointestinal Risks of Antiplatelet Therapy and NSAID Use	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Karjalainen 2008 (156) 18346963	Determine safety and efficacy of various periprocedural antithrombotic strategies in pts on long-term OAC with warfarin undergoing PCI. Assess safety of	Retrospective analysis n=523 pts	IAC and UAC group	All consecutive pts on warfarin therapy referred for PCI in four centers with a main policy to IAC before PCI and in three centers with a long experience on UAC during PCI.	N/A	IAC vs. UAC	Major bleeding, access-site complications, and major adverse cardiac events (death, MI, target vessel revasc, and stent thrombosis) Major bleeding 5.0% vs. 1.2%, p=0.02 and after adjusting for propensity score (OR:3.9, 95% CI: 1.0–15.3, p=0.05)	N/A	N/A	N/A	Major bleeding, stroke, access-site complications	Inherent limitations of retrospective study including individual risk-based decision making in treatment choices; outcome assessment not blinded; sample size may not be sufficient to cover

	simplistic UAC strategy.						Access-site complications (11.3% vs. 5.0%, p=0.01) After adjusting for propensity score (OR=2.8, 95% CI: 1.3–6.1, p=0.008)					small but clinically significant differences in bleeding and thrombotic complications
BAAS ten Berg 2001 (157) 11319192	Study intensity and duration of anticoagulation as predictors of thrombotic and bleeding events	N=530 pts	ASA plus coumarins	Pts who were prospectively randomized to use of coumarins as part of BAAS study	N/A	ASA (LD, 300 mg; then 100 mg qd) and coumarins (acenocoumarol or Sintrom at 6 mg 1 d, 4 mg on 2 d, 2 mg on 3 d and after until intervention) started 1 wk before intervention Target INR was 2.1-4.8 during angioplasty and 6-mo follow-up INR measured on morning before PTCA and daily after until discharge	Thrombotic events - Death, MI, target lesion, revasc, and thrombotic stroke 17 early thrombotic events (3.2%), 7 early bleeding episodes (1.3%), and 10 false aneurysms (1.9%). 61 late thrombotic events occurred (11.6%). Optimal anticoagulation an independent predictor of late thrombotic events (RR: 0.33; 95% CI: 0.19-0.57) and associated with 0.21 mm (95% CI: 0.17-0.42) larger vessel lumen at 6 mo	Bleeding Complications, hemorrhagic stroke, major extracranial bleeding, and false aneurysm Late bleeding episodes (1.4%) lowest in pts in target range.	N/A	N/A	N/A	N/A
RE-DEEM Oldgren 2011 (177) 21551462	Evaluate the safety and indicators of efficacy of four dose regimens of dabigatran etexilate compared with PC when given in addition to dual antiplatelet	Double-blind, PC-controlled, dose-escalation trial N=1861 pts	Dabigatran vs. PC	Pts age ≥18 y, hospitalized with NSTEMI or STEMI within last 14 d, and receiving treatment with dual antiplatelet therapy (ASA and clopidogrel or another thienopyridine). ≥1 risk factor for subsequent CV complications: age ≥65 y, DM on treatment, previous MI, LBBB,	Ongoing or planned treatment with VKAs, severe disabling stroke within previous 6 mo or any stroke within previous 14 d, conditions associated with increased risk of bleeding such as major surgery (including bypass	Dabigatran initially one of two lower doses (50 mg bid n=369 and 75 mg bid) n=368 vs. PC n=371 N=406 110 mg dose in 2nd stage n=347 150 mg dosegroup in third stage	Composite of major or clinically relevant minor bleeding during 6 mo treatment period.Composite of major or clinically relevant minor bleeding events 3.5, 4.3, 7.9, and 7.8% in respective 50, 75, 110, and 150 mg dabigatran groups, compared with 2.2%	N/A	Indicators of efficacy such as reduction in D-dimer levels and incidences of CV ischaemic events. D-dimer concentrations reduced in all dabigatran dose groups by an average of 37 and 45% at wk 1 and 4,	p<0.001 for linear trend HR 1.77 (95% CI: 0.70–4.50) for 50 mg; HR=2.17 (95% CI: 0.88–5.31) for 75 mg; HR=3.92 (95% CI: 1.72–8.95) for 110 mg; and HR=4.27 (95% CI: 1.86–9.81)	14(3.8%) pts died, had a MI or stroke in PC group compared with 17 (4.6%) in 50 mg, 18 (4.9%) in 75 mg, 12 (3.0%) in 110 mg, and 12 (3.5%) in the 150 mg	N/A

	treatment in pts with recent STEMI or NSTEMI at high risk of new ischaemic CV events.			congestive HF requiring treatment or LVEF 40%, PAD, moderate renal insufficiency (CrCl ≥30–60 mL/min), or no revasc for the index event.	surgery) in previous mo, Hx of severe bleeding, gastrointestinal haemorrhage with in past y, gastroduodenal ulcer in previous 30 d, fibrinolytic agents within 48 h of study entry, uncontrolled hypertension, haemoglobin ,10 g/dL or platelet count ,100 × 109/L, normal coronary arteries at angiogram for index event, congestive HF New York Heart Association Class IV, and severe renal impairment (CrCl ,30 mL/min).		in the PC group, p<0.001 for linear trend. 96 1º outcome events, compared with PC a dose dependent increase with dabigatran, HR 1.77 (95% CI: 0.70–4.50) for 50 mg; HR=2.17 (95% CI: 0.88–5.31) for 75 mg; HR=3.92 (95% CI: 1.72–8.95) for 110 mg; and HR=4.27 (95% CI: 1.86–9.81) for 150 mg. Compared with PC, D-dimer concentrations reduced in all dabigatran dose groups by average of 37 and 45% at wk 1 and 4, respectively (p=0.001).		respectively (p<0.001).	for 150 mg.	dabigatran groups	
Uchino 2012 (178) 22231617	Systematically evaluated risk of MI or ACS with use of dabigatran.	Meta-analysis Seven trials were selected N=30,514	N/A	Searched PubMed, Scopus, and Web of Science for randomized controlled trials of dabigatran that reported on MI or ACS as 2º outcomes.	N/A	Fixed-effects M-H used to evaluate the effect of dabigatran on MI or ACS. Expressed associations as OR and 95% CIs.	Dabigatran was significantly associated with higher risk of MI or ACS than seen with agents used in control group (dabigatran, 237 of 20 000 [1.19%] vs. control, 83 of 10 514 [0.79%]; OR_{M-H}, 1.33; 95% CI: 1.03-1.71; p=.03).	N/A	N/A	p=.03 OR_{M-H}, 1.33 CI=1.03-1.71	N/A	Dominant effect of RE-LY trial on results of meta-analysis. Other 6 trials had cohort sizes of 515-3451 with durations of ≤6mo. In RE-LY, 18,113 participants monitored for median of 2 y. Owing to sample size and duration of study, RE-LY comprised 59% of the cohort and

												74% of the events.
Alexander 2011 (179) 21780946	Determine whether in high-risk pts with ACS benefit of apixaban in reducing ischemic events outweigh increased risk of bleeding.	Randomized, double-blind, PC-controlled N=7392	n=3705 apixaban, 5 mg bid vs. n=3687 PC	ACS (MI, NSTEMI, STEMI, or UA) within previous 7 d, Sx of MI lasting 10 mo or more with pt at rest plus either elevated levels of cardiac biomarkers or dynamic ST-segment depression or elevation of ≥0.1 mV. 2 or more of the following high-risk characteristics: age ≥65 y, DM, MI within previous 5 y, cerebrovascular disease, peripheral vascular disease, clinical HF or LVEF of <40% in association with index event, impaired renal function with calculated creatinine clearance <60 ml/min and no revasc after index event.	N/A	Apixaban 5 mg bid PC, in addition to standard antiplatelet therapy	CV death, MI, or ischemic stroke Median follow-up of 241 d 7.5% pts assigned to apixaban 7.9% assigned to PC HR=0.95; 95% CI: 0.80-1.11; p=0.51	Major bleeding according to TIMI definition occurred in 1.3% pts who received apixaban and in 0.5% pts who received PC HR=2.59; CI, 1.50-4.46; p=0.001. Greater number of intracranial and fatal bleeding events occurred with apixaban than PC.	N/A	P=0.51 HR=0.95 CI=0.80-1.11	N/A	N/A
Mega 2012 (180) 22077192	N/A	Double-blind, PC-controlled trial N=15,526 pts	bidbid doses of either 2.5 mg or 5 mg of rivaroxaban or PC	Within 7 d after hospital admission for ACS. Condition of pts needed to be stabilized before enrollment with initial management strategies (e.g., revasc) completed	N/A	bid doses of either 2.5 mg or 5 mg of rivaroxaban or PC	Composite of death from CV causes, MI, or stroke. Rivaroxaban compared with PC, 8.9% and 10.7% (HR in rivaroxaban group, 0.84; 95% CI: 0.74-0.96; p=0.008), significant improvement for both bid 2.5-mg dose (9.1% vs. 10.7%, p=0.02) and bid 5 mg dose (8.8% vs. 10.7%, p=0.03).	Compared with PC, rivaroxaban increased rates of major bleeding not related to CABG (2.1% vs. 0.6%, p<0.001) and intracranial hemorrhage (0.6% vs. 0.2%, p=0.009), without	bid 2.5-mg dose of rivaroxaban reduced rates of death from CV causes (2.7% vs. 4.1%, p=0.002) and from any cause (2.9% vs. 4.5%, p=0.002),	p=0.008 HR=0.84 CI=0.74-0.96	Rates of adverse events that were not related to bleeding similar in rivaroxaban and PC groups	N/A

								significant increase in fatal bleeding (0.3% vs. 0.2%, p=0.66) or other adverse events. bid 2.5-mg dose resulted in fewer fatal bleeding events than bid 5-mg dose (0.1% vs. 0.4%, p=0.04).				
Warkentin 2012 (181) 22383791	Report timeline of bleeding, hemostatic parameters, and dabigatran plasma levels (by HPLC) in response to emergency management with rFVIIa and hemodialysis.	Single patient case	N/A	N/A	N/A	N/A	Pts developed massive postoperative bleeding resulting from elective cardiac surgery performed with therapeutic dabigatran levels. This illustrates importance of adjusting the number of d off dabigatran before surgery according to current renal function.	N/A	N/A	N/A	N/A	N/A
Eerenberg 2011 (182) 21900088	Evaluated potential of PCC to reverse anticoagulant effect of rivaroxaban and dabigatran	Randomized, double-blind, PC-controlled N=12	Rivaroxaban 20 mg bid (n=6) or dabigatran 150 mg bid(n=6)	Twelve healthy male subjects	N/A	Rivaroxaban 20 mg bid (n=6) or dabigatran 150 mg bid. (n=6) for 2.5 d followed by either single bolus 50 IU/kg PCC or similar volume of saline. After washout period procedure	Rivaroxaban induced significant prolongation of prothrombin time (15.8±1.3 vs. 12.3±0.7 s at baseline; p<0.001) that was immediately and completely reversed by PCC (12.8±1.0;	N/A	N/A	N/A	No major or clinically relevant bleeding complications occurred during treatment, no serious adverse events.	Small size of study population accounting for variation in results of a few coagulation tests. No measurements performed between 6-24 h after infusion of

						repeated with other anticoagulant treatment.	p<0.001). Endogenous thrombin potential inhibited by rivaroxaban (51±22%; baseline, 92±22%; p<0.002) normalized with PCC (114±26%; p<0.001), saline had no effect. Dabigatran increased activated partial thromboplastin time, ECT, and thrombin time. Administration of PCC did not restore these coagulation tests.					PCC or PC. If PCC had any effect of reversal for dabigatran it may have been missed; any rebound effect on anticoagulant activity of rivaroxaban in that same period could not be observed.

1º indicates primary; 2º, secondary; ACCF, American College of Cardiology Foundation; ACS, acute coronary syndrome; ACT, activated clotting time; ACUITY, Acute Catheterization and Urgent Intervention Triage strategY; ACUTE II, Assessment of Cardioversion Using Transesophageal Echocardiography; ADP, adenosine diphosphate; AGC, ; AHA, American Heart Association; AIMS, APSAC Intervention Mortality Study; aPTT, Activated Partial Thromboplastin Time; ASA, aspirin; ASSET, Anglo-Scandinavian Study of Early Thrombolysis; BID, twice daily; CABG, coronary artery bypass graft; CAD, coronary artery disease; CI, confidence interval; CK, creatine kinase; CK-MB, creatine kinase-MB; CRP, C-reactive protein; DBP, diastolic blood pressure; DM, diabetes mellitus; ECG, electrocardiography; ECT, ecarin clotting time; EMERAS, Estudio Multicentrico Estreptoquinasa Republicas de America del Sur; ESSENCE, Efficacy and Safety of Subcutaneous Enoxaparin in Non–Q wave Coronary Events; FUTURA, The Fondaparinux Trial With Unfractionated Heparin During Revascularization in Acute Coronary Syndromes ; GISSI-1, Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico acuto-1; GP, glycoprotein; HF, heart failure; HR, hazard ratio; Hx, history; IAC, Interrupt anticoagulation; IgE, Immunoglobin E; ISAM, Intravenous Streptokinase in Acute Myocardial Infarction; ISIS, International Study of Infarct Survival; INTERACT, Intensive blood pressure reduction in acute cerebral haemorrhage trial; ISAM, Intravenous Streptokinase in Acute Myocardial Infarction; IV, intravenous; LATE, Late Assessment of Thrombolytic Efficacy Study; LBBB, left bundle-branch block; LD, loading dose; LMWH, low molecular weight heparins; LVEF, left ventricular ejection fraction; MH, Mantel-Haenszel test; MI, myocardial infarction; NQMI, non–Q-wave myocardial infarction; NS, not significant; NSAID, nonsteroidal anti-inflammatory drugs; NSTE, non-ST elevation; NSTEMI, non-ST-elevation myocardial infarction; OAC, Oral anticoagulation; OASIS, Organization for the Assessment of Strategies for Ischemic Syndromes; OD, once daily; OR, odds ratio; PAD, peripheral arterial disease; PC, placebo; PCC, prothrombin complex concentrate, PCI, percutaneous coronary intervention; PLATO, Platelet Inhibition and Patient Outcomes trial; pts, patients; RCT, randomized clinical trials; Revasc, revascularization; RE-LY, Randomized Evaluation of Long-Term Anticoagulant Therapy Trial; ROW, rest of the world; RR, relative risk; SBP, systolic blood pressure; STE, ST elevation; STEMI, ST-elevation myocardial infarction; Sx, symptoms; TIMI, thrombolysis in MI; TnI, troponin I; TnT, troponin T; TPA, ; UA, unstable angina; UAC, Uninterrupted anticoagulation; UFH, unfractionated heparin; US, United States; and USIM, Urochinasi per via Sistemica nell'Infarto Miocardico.

Data Supplement 18. Comparison of Early Invasive and Initial Conservative Strategy (Section 4.4.4)

Study Name, Author, Year	Study Aim	Study Type / Size (n)	Intervention vs. Comparator (n)	Patient Population		Study Intervention	Study Comparator	Endpoints			P Values, OR: HR: RR: & 95 CI:	Study Limitations & Adverse Events
				Inclusion Criteria	*Exclusion Criteria*			*Primary Endpoint & Results*	*Safety Endpoint & Results*	*Secondary Endpoint & Results*		
TIMI IIIB, 1994 8149520 (176)	To determine the effects of an early invasive strategy on clinical	RCT 1,473	Intervention: 740; Comparator: 733	Chest discomfort at rest caused by ischemia that lasted >5 min but <6 h. The discomfort must have occurred within	Pts were excluded if they had a treatable cause of UA, had experienced a MI within the preceding 21 d, had undergone	The protocol called for pts assigned to the early invasive strategy to have cardiac catheterization, LVA, and coronary	Pts randomized to the early conservative strategy were to have angiography	Death, postrandomization MI, or an unsatisfactory ETT performed at the time of the 6-	None	Analyses for differences and interactions in the results of invasive vs. conservative strategies for death	1º endpoint occurred in 16.2% of the pts randomized to the early invasive	Significant crossover with 64% in the conservative arm undergoing angiography by 42

	outcome			24 h of enrollment and accompanied by objective evidence of ischemic HD, i.e., either new or presumably new ECG evidence of ischemia in at least 2 contiguous leads or documented CAD	coronary arteriography within 30 d, PTCA within 6 mo, CABG at any time, or if, at enrollment, they were in pulmonary edema, had a systolic arterial pressure >180 mmHg or a diastolic pressure >100 mmHg, a contraindication to thrombolytic therapy or heparin. LBBB, a coexistent severe illness, were a woman of child-bearing potential, or were receiving OAC.	arteriography 18-48 h after randomization	carried out only after failure of initial therapy	wk visit		or MI were carried out on several prespecified subgroups	strategy vs. 18.1% of those assigned to the early conservative strategy (p=NS)	d
MATE, 1998 Mccullogh et al, (183) 9741499	To determine if early revasc favorably affects clinical outcomes in pts with suspected AMI	RCT 201	Intervention: 201; Comparator: 90	Pts 18 y and older who presented to the ED with an acute chest pain syndrome consistent with AMI	Exclusion criteria were Sx lasting for more than 24 h or an absolute indication or contraindication to cardiac catheterization	Subjects randomized to triage angiography were taken as soon as possible directly to the catheterization laboratory from the ED. All triage angiography pts underwent catheterization within 24 h of arrival to the hospital	Subjects randomized to the conservative arm were admitted to a monitored bed and received continued medical therapy and noninvasive evaluation encouraged by the protocol	Composite endpoint of all recurrent ischemic events or death	None	2º endpoints including LOS and hospital costs	The composite endpoint of all recurrent ischemic events or death occurred in 14 (13%) and 31 (34%), yielding a 45% risk reduction (95% CI 27-59%, p=0.0002)	High crossover rate (60%). No long-term benefit in cardiac outcomes compared with conservative medical therapy with revasc prompted by recurrent ischemia
VANQWISH, Boden et al 1998 (184) 9632444	To compare an invasive with a conservative strategy in pts with acute NQMI	RCT 920	Intervention: 462; Comparator: 458	Eligible pts had to have evolving AMI, a level of (CK-MB isoenzymes that was more than 1.5× the ULN for the hospital, and no new abnormal Q waves	Pts were excluded if they had serious coexisting conditions, ischemic complications that placed them at very high risk while in the CCU (persistent or	Pts assigned to the early invasive strategy underwent coronary angiography as the initial diagnostic test soon after randomization. Thereafter, the	Pts assigned to the early conservative strategy underwent RNV to assess LV function as the initial noninvasive	Death or nonfatal MI	Major procedural complications after coronary angiography or myocardial revasc	Overall mortality	A total of 152 1º endpoint events occurred in the invasive-strategy group, as did 139 cardiac events in the	The trial was conducted before coronary stents or platelet GP IIb/IIIa receptor antagonists were widely available

				(or R waves) on serial electrocardiograms	recurrent ischemia at rest despite intensive medical therapy or severe HF that persisted despite treatment with IV diuretics, vasodilators, or both	management guidelines of the TIMI IIIB for revasc were followed	test; this was followed before discharge by a Sx-limited treadmill exercise test with thallium scintigraphy				conservative-strategy group (p=0.35) during an average of 23 mo of follow-up	
FRISC II, 1999 (185) 10475181	To compare an early invasive with a non-invasive treatment strategy in UCAD	Prospective, randomized, multicenter trial 2,457	Intervention: 1,222; Comparator: 1,235	Pts were eligible for inclusion if they had Sx of ischaemia that were increasing or occurring at rest, or that warranted the suspicion of AMI, with the last episode within 48 h	Exclusion criteria were raised risk of bleeding episodes, anaemia, or indication for or treatment in the past 24 h with thrombolysis, angioplasty in the past 6 mo, being on a waiting list for coronary revasc, other acute or severe CD, renal or hepatic insufficiency, known clinically relevant osteoporosis, other severe illness, hypersensitivity to randomized drugs, anticipated difficulties with cooperation or participation in this or another clinical trial	The direct invasive treatments were coronary angiography within a few d of enrollment, aiming for revasc within 7 d of the start of open-label treatment	Non-invasive treatment included coronary pts with refractory or recurrent Sx, despite max medical treatment, or severe ischaemia on a Sx-limited exercise test before discharge	Composite endpoint of death and MI after 6 mo	Bleeding	Total death, MI, Sx of angina, need for late coronary angiography and revasc, bleeding episodes, and stroke	There was a significant 22.0% relative and 2.7% absolute decrease in death and MI in the invasive compared with the non-invasive group after 6-mo RR: 0.78 (95% CI: 0.62–0.98), p=0.031	Revasc window of 7 d longer than actual contemporary practice
TACTICS - TIMI 18, Cannon et al 2001 (186) 11419424	To compare an early invasive strategy to a more conservative approach	Prospective, randomized, multicenter trial 2,220	Intervention: 1,114 vs. Comparator: 1,106	Pts ≥18 y if they had had an episode of angina (with an accelerating pattern or prolonged [>20 min] or recurrent episodes at rest or	Persistent STE, 2º angina, a Hx of PCI or CAB grafting within the preceding 6 mo, factors associated with an increased risk of	Pts assigned to the early invasive strategy were to undergo coronary angiography between 4 h and 48 h after randomization and revasc when	Pts assigned to the early conservative strategy were treated medically and, if their condition was	Combined incidence of death, nonfatal MI, and rehospitalization for an ACS at 6 mo	Bleeding	Death, death or MI, fatal or nonfatal MI, reshospitaliztion for MI	At 6 mo, the rate of the 1º endpoint was 15.9% with use of the early invasive strategy and	Study excluded pts with severe comorbid conditions or other serious systemic illness

				with minimal effort) within the preceding 24 h, were candidates for coronary revasc, and had at least 1 of the following: a new finding of ST-segment depression of at least 0.05 mV, transient (<20 min) STE of at least 0.1 mV, or T-wave inversion of at least 0.3 mV in at least 2 leads; elevated levels of cardiac markers; or coronary disease, as documented by a Hx of catheterization, revasc, or M	bleeding, LBBB or paced rhythm, severe CHF or cardiogenic shock, serious systemic disease, a serum creatinine level of <2.5 mg/dL (221 µmol/L), or current participation in another study of an investigational drug or device	appropriate on the basis of coronary anatomical findings	stable, underwent an exercise-tolerance test (83% of such tests included nuclear perfusion imaging or echocardiography performed according to the protocol of the institution) before being discharged				19.4% with use of the conservative strategy (OR: 0.78; 95% CI: 0.62–0.97; p=0.025).	
VINO, Spacek et al 2002 (120) 11792138	To compare 1st d angiography/ angioplasty vs. early conservative therapy of evolving MI without persistent STE	RCT 131	Intervention: 64 vs. Comparator: 67	Rest ischaemic chest pain, lasting <20 min, within the last 24 h before randomization; ECG evidence of AMI without STE (ST-segment depressions minimally 0.1 mm in at least 2 contiguous leads and/or negative T waves or documented old LBBB/RBBB; CK-MB higher than 1.5× X ULN and/or positive TnI assay	Unstable post-infarction angina pectoris resistant to maximal pharmacotherapy; cardiogenic shock; acute LBBB or RBBB or STE 2 mm in 2 leads; QMI or IV thrombolysis >1 mo; coronary angioplasty or bypass surgery >6 mo; any concomitant disease which may have possible influence on 1-y Px; lack of pt cooperation	1st d angiography/angioplasty treatment strategy guidelines were characterized by a coronary angiogram as soon as possible after randomization followed by immediate coronary angioplasty of the culprit coronary lesion + stent implantation whenever suitable	Conservative treatment strategy guidelines were characterized by initial medical treatment with coronary angiography and subsequent revasc only in the presence of recurrent myocardial ischaemia	Composite of death or nonfatal RMI 6 mo after the randomization	None	Length of the initial hospitalization and the number of subsequent hospitalizations for UAP	The primary endpoint (death/ reinfarction) at 6 mo occurred in 6.2% vs. 22.3% (p<0.001). 6 mo mortality in the 1st d angiography/ angioplasty group was 3.1% vs. 13.4% in the conservative group (p<0·03).	Small sample size, interventions were done in only one high volume tertiary center
RITA -2, Fox et al, 2002	To compare interventional	RCT 1,810	Intervention: 895 vs.	Pts were eligible for inclusion if they had	All those with probable evolving	Pts assigned to the interventional treatment	Pts assigned to the conservative	The coprimary trial endpoints	Bleeding	Death, MI, refractory angina	At 4 mo, 86 (9.6%) of 895	Primary endpoint driven by reduction

(187) 12241831	strategy and conservative strategy in pts with unstable CAD		Comparator: 915	suspected cardiac chest pain at rest and had documented evidence of CAD with at least 1 of the following: evidence of ischaemia on ECG (ST-segment depression, transient STE, LBBB [documented previously], or T-wave inversion); pathological Q waves suggesting previous MI; or arteriographically proven CAD on a previous arteriogram	MI, including those for whom reperfusion therapy was indicated, were ineligible. Those in whom new pathological Q waves developed, or those with CK or CK-MB concentrations 2× the ULN before randomization, were excluded. Also excluded were those with MI within the previous mo, PCI in the preceding 12 mo, or CABG at any time.	strategy were managed with optimum antianginal and antiplatelet treatment (as for the conservative group), and enoxaparin 1 mg/kg subcutaneously 2× for 2-8 d. The protocol specified that coronary arteriography should be done as soon as possible after randomization and ideally within 72 h	strategy were managed with antianginal and antithrombotic medication	were: a combined rate of death, nonfatal MI, or refractory angina at 4 mo; and a combined rate of death or nonfatal MI at 1 y		as individual endpoints	pts in the intervention group had died or had a MI or refractory angina, compared with 133 (14.5%) of 915 pts in the conservative group (RR: 0.66; 95% CI: 0.51–0.85; p=0.001).	of refractory angina with no difference in hard clinical endpoints
ICTUS, de Winter et al, 2005 (188) 16162880	To compare an early invasive strategy to a selectively invasive strategy for pts who have ACS without STE and with an elevated cTnT level	RCT 1,200	Intervention: 604 vs. Comparator: 596	Eligible pts had to have all 3 of the following: Sx of ischemia that were increasing or occurred at rest, with the last episode occurring no more than 24 h before randomization; an elevated cTnT level (≥0.03 μg/L); and either ischemic changes as assessed by ECG (defined as ST-segment depression or transient STE exceeding 0.05 mV, or T-wave inversion of ≥0.2 mV in 2 contiguous leads) or	Exclusion criteria were an age >18 y or <80 y, STEMI in the past 48 h, an indication for primary PCI or fibrinolytic therapy, hemodynamic instability or overt CHF, the use of oral anticoagulant drugs in the past 7 d, fibrinolytic treatment within the past 96 h, PCI within the past 14 d, a contraindication to treatment with PCI or GP IIb/IIIa inhibitors, recent trauma or risk of bleeding, hypertension despite	Pts assigned to the early invasive strategy were scheduled to undergo angiography within 24-48 h after randomization and PCI when appropriate on the basis of the coronary anatomy	Pts assigned to the selectively invasive strategy were treated medically. These pts were scheduled to undergo angiography and subsequent revasconly if they had refractory angina despite optimal medical treatment, hemodynamic or rhythmic instability, or clinically significant ischemia on the predischarge	The primary endpoint was a composite of death, RMI, or rehospitalization for angina within 1 y after randomization	Bleeding	Percentage of pts free from anginal Sx	The estimated cumulative rate of the primary endpoint was 22.7% in the group assigned to early invasive management and 21.2% in the group assigned to selectively invasive management (RR: 1.07; 95% CI: 0.87-1.33; p=0.33).	Revasc rates were high in the 2 groups in our study (76% in the early-invasive-strategy group and 40% in the selectively-invasive-strategy group during the initial hospitalization, and 79% and 54%, respectively, within 1 y after randomization

				a documented Hx of CAD as evidenced by previous MI, findings on previous coronary angiography, or a positive exercise test	treatment (i.e., systolic pressure >180 mmHg or diastolic pressure >100 mmHg), weight <120 kg, or inability to give informed consent		exercise test.					
Italian Trial J Am Coll Cardiol Intv 2012;5:906-16) (189) 22995877	To determine the risk vs. bebefut ratio of an EA approach in elderly pts with NSTE-ACS	RCT 313	Intervention: 154 vs. Comparator : 159	Eligible were pts with NSTE-ACS and an age of ≥75 y, with cardiac ischemic Sx at rest within 48 h before randomization, together with ischemic ECG changes and/or elevated levels of either Tn or CK-MB	Excluded were pts with 2º causes of myocardial ischemia, ongoing myocardial ischemia or HF despite optimized therapy, PCI or CABG within 30 d before randomization, serum creatinine >2.5 mg/dL, a cerebrovascular accident within the previous mo, recent transfusions, gastrointestinal or genitourinary bleeding within 6 wk before randomization, platelet count 90,000 cells/ l, ongoing oral anticoagulation, severe obstructive lung disease, malignancy, or neurological deficit limiting follow-up	Pts enrolled in the trial were randomly assigned to either: 1) an EA strategy of coronary angiography within 72 h and, when indicated, coronary revasc by either PCI or CABG according to coronary anatomy, pt preference, and local skills; or 2) IC therapy	IC therapy, in which case pts had to be managed with medical therapy, and coronary angiography during index hospital stay was allowed in the case of refractory ischemia, myocardial (re)infarction, HR of ischemic origin, or malignant ventricular arrhythmias	The primary endpoint was the composite of death, MI, disabling stroke, and repeat hospital stay for CV causes or severe bleeding within 1 y	Bleeding	Individual components of the primary endpoint	The 1outcome occurred in 43 pts (27.9%) in the EA group and 55 (34.6%) in the IC group (HR: 0.80; 95% CI: 0.5– 1.19; p=0.26)	The main limitation of this study is its relative lack of power, because our original sample size was amended due to slow enrollment

1º indicates primary; 2º, secondary; ACS, acute coronary syndrome; AMI, acute myocardial infarction; CAB, coronary artery bypass; CABG, coronary artery bypass graft; CAD, coronary artery disease; CCU, cardiac care unit; CD, cardiac disease; CHF, congestive heart failure; CK, creatine kinase; CK-MB, creatine kinase-MB; cTnT, cardiac troponin T; CV, cardiovascular; EA, early invasive; ECG, electrocardiograph; ETT; exercise treadmill test; GP, glycoprotein; HD, heart disease; HF, heart failure; Hx, history; IC, initially conservative; IV, intravenous; LBBB, left bundle branch block; LOS, length of stay; LV, left ventricular; LVA, left ventricular angiography; MI, myocardial infarction; NQMI, Non Q-wave myocardial infarction; NS, no(t) significant; OAC, oral anticoagulants; PCI, percutaneous coronary intervention; PTCA, percutaneous transluminal coronary angioplasty; pts, patients; Px, prognosis; QMI, Q-wave myocardial infarction; RBBB, right bundle branch block; RCT, randomized controlled trial; revasc, revascularization; RMI; recurrent MI;RNV, radionuclide ventriculogram; STE, ST-segment elevation; Sx, symptom(s); TIMI, thrombolysis in MI; TnI, troponin I; UA, unstable angina; UAP, unstable angina pectoris; UCAD, unstable coronary artery disease; and ULN, upper limits of normal.

Data Supplement 19. Comparison of Early Versus Delayed Angiography (Section 4.4.4.1)

Study Name, Author, Year	Study Aim	Study Type/ Size (N)	Intervention vs. Comparator (n)	Patient Population		Study Intervention	Study Comparator	Endpoints			P Values, OR: HR: RR: & 95 CI:	Study Limitations & Adverse Events
				Inclusion Criteria	*Exclusion Criteria*			*Primary Endpoint & Results*	*Safety Endpoint & Results*	*Secondary Endpoint & Results*		
ISAR-COOL, Neumann et al 2003 14506118 (190)	To test the hypothesis that prolonged antithrombotic pretreatment improves the outcome of catheter intervention in pts with acute unstable coronary syndromes compared with early intervention	RCT 410	Intervention: 207 vs. Comparator: 203	Pts with AP at rest or with minimal exertion, with the last episode occurring ≥24 h before study entry	Pts with evidence of large MI, including STE of at least 1 mV in 2 or more contiguous leads or elevation of the catalytic activity of creatine kinase and its MB isoenzyme to ≤3× the ULN; those with hemodynamic instability; those with contraindications to study medication; or those unable to provide written informed consent for participation	With the early intervention strategy investigators performed coronary angiography as soon as possible, at least within 6 h, during which time antithrombotic pretreatment was instituted	With the prolonged antithrombotic pretreatment strategy, investigators continued pretreatment for at least 3 d, to a max of 5 d, after which all pts underwent coronary angiography	Composite 30-d incidence of large nonfatal MI or death from any cause	Bleeding, thrombocytopenia	Death, nonfatal MI	1° endpoint was reached in 11.6% (3 deaths, 21 infarctions) of the group receiving prolonged antithrombotic pretreatment and in 5.9% (no deaths, 12 infarctions) of the group receiving early intervention (RR: 1.96; 95% CI: 1.01–3.82; p=0.04)	Small sample size
TIMACS, Mehta et al, 2009 (191) 19458363	To study efficacy of an early invasive strategy (within 24 h of presentation) compared with delayed invasive strategy (anytime 36 h after presentation)	RCT 3,031	Intervention: 1,593 vs. Comparator: 1,438	Presentation to a hospital with UA or MI without STE within 24 h after onset of Sx and if 2 of the following 3 criteria for increased risk are present: age ≥60 y, cardiac biomarkers above ULN, or results on ECG compatible with ischemia (i.e., ST-segment depression ≥1 mm or transient	Pt who is not a suitable candidate for revasc	Among pts who were randomly assigned to the early-intervention group, coronary angiography was to be performed as rapidly as possible and within 24 h after randomization	Pts who were assigned to the delayed-intervention group underwent coronary angiography after a min delay of 36 h after randomization	Composite of death, MI, or stroke at 6 mo	Bleeding	1st occurrence of the composite of death, MI, or refractory ischemia and the composite of death, MI, stroke, refractory ischemia, or repeat intervention at 6 mo	At 6 mo, 1° outcome (death, new MI, or stroke) occurred in 9.6% of pts in the early-intervention group, as compared with 11.3% in the delayed-intervention group (HR: 0.85; 95% CI: 0.68-1.06; p=0.15)	The trial may have been relatively underpowered. Heterogeneity was observed in the 1° endpoint, with pts in the highest tertile experiencing a sizeable risk reduction and suggesting a potential advantage of

				STE or T-wave inversion >3 mm)								early revasc in this high-risk subgroup
ABOARD, Montalescot et al (192) 19724041	To determine if immediate intervention on admission can result in reduction of MI vs. delayed intervention	RCT 352	Intervention: 175 vs. Comparator: 177	Presence of at least 2 of the following: ischemic Sx, ECG abnormalities in at least 2 contiguous leads, or positive Tn, TIMI risk score 3	Hemodynamic or arrhythmic instability requiring urgent catheterization, chronic oral anticoagulation, or thrombolytic therapy in the preceding 24 h	An immediate invasive strategy	An invasive strategy scheduled on the next working d	Primary endpoint was peak Tn value during hospitalization	Bleeding	2º endpoints were composite of death, MI, or urgent revasc at 1-mo follow-up	The primary endpoint did not differ between the 2 strategies (median [IQR] TnI value, 2.1 [0.3-7.1] ng/mL vs. 1.7 [0.3-7.2] ng/mL in the immediate and delayed intervention groups, respectively; p=0.70)	Immediate (at a median of 70 min) vs. delayed (at a median of 21 h) angiography and revasc in UA/ NSTEMI pts conferred no advantage with regard to the primary endpoint

1º indicates primary; 2º, secondary AP, angina pectoris; ECG, electrocardiograph; IQR, interquartile range; MB, myocardial band; MI, myocardial infarction; non-ST-elevation myocardial infarction; pts, patients; RCT, randomized controlled trial; revasc, revascularization; RR, relative risk; STE, ST- segment elevation; Sx, symptom(s); TIMI; thrombolysis in myocardial infarction; Tn, troponin; TnI, troponin I; UA, unstable angina; and UA/NSTEMI, unstable angina/ non-ST-elevation MI.

Data Supplement 20. Risk Stratification Before Discharge for Patients With Conservatively Treated NSTE-ACS (Section 4.5)

Study Name, Author, Year	**Study Aim**	**Study Type/ Size (n)**	**Intervention vs. Comparator (n)**	**Patient Population**		**Study Intervention**	**Study Comparator**	**Endpoints**			**P Values, OR: HR: RR: & 95 CI:**	**Study Limitations & Adverse Events**
				Inclusion Criteria	***Exclusion Criteria***			***Primary Endpoint & Results***	***Safety Endpoint & Results***	***Secondary Endpoint & Results***		
DANAMI, Valeur et al 2004 (193) 15618067	To test the prognostic importance of predischarge maximal Sx-limited ET following AMI in the era of aggressive reperfusion	Post hoc subgroup analysis of a RCT 1,164	N/A	In the DANAMI-2 study, pts with STEMI were randomized to 1º angioplasty (PCI) or fibrinolysis	N/A	N/A	N/A	1º endpoint was a composite of death and re-infarction	N/A	N/A	ST-depression was predictive of the clinical outcome (RR: 1.57 [1.00- 2.48]; p<0.05) in multivariable analysis, there was a significant association between ST-depression and outcome in the fibrinolysis group (RR: 1.95 [1.11- 3.44]; p<0.05), but not in the 1º PCI group (RR: 1.06 [0.47-2.36]; p=NS). However, the p-value for interaction was 0.15.	Post hoc analysis. Exercise capacity was a strong prognostic predictor of death and re-infarction irrespective of treatment strategy, whereas the prognostic significance of ST-depression seems to be strongest in the fibrinolysis-treated pts.
INSPIRE, Mahmarian et al 2006	To test whether gated ADSPECT could accurately	Cohort study 728 pts	N/A	The study cohort consisted of 728 stabilized pts 18 y of	N/A	Event rates were assessed within prospectively	Pt risk and subsequent therapeutic	Composite of death, MI, or stroke at 6 mo	N/A	N/A	Total cardiac events/death and reinfarction significantly increased within each INSPIRE	Investigators did not track the percentage of eligible pts who were

(194) 17174181	define risk and thereby guide therapeutic decision making in stable survivors of AMI			age who had either QAMI or NQAMI and were prospectively enrolled		defined INSPIRE risk groups based on the adenosine-induced LV perfusion defect size, extent of ischemia, and EF	decision making were prospectively defined by specific ADSPECT variables. Pts with a small (<20%) ischemic PDS were classified as low risk and most had a LVEF of 35% (96%) and an ischemic PDS of <10% (97%).				risk group from low (5.4%, 1.8%), to intermediate (14%, 9.2%), to high (18.6%, 11.6%) ($p<0.01$). Event rates at 1 y were lowest in pts with the smallest perfusion defects but progressively increased when defect size exceeded 20% ($p<0.0001$).	enrolled in the INSPIRE trial so there may be selection bias. The perfusion results significantly improved risk stratification beyond that provided by clinical and EF variables. The low-risk INSPIRE group, comprising 1/3 all enrolled pts, had a shorter hospital stay with lower associated costs compared with the higher-risk groups ($p<0.001$).
COSTAMI -II, Decidari et al (195) 15657220	To compare in a prospective, randomized, multicenter trial the relative merits of predischarge exercise ECG and early pharmacological stress echocardiography concerning risk stratification and costs of treating pts with uncomplicated AMI	RCT 262	Intervention: 132; Comparator: 130	262 pts from 6 participating centers with a recent uncomplicated MI were randomly assigned to early (d 3-5) pharmacological stress echocardiography (n=132) or conventional predischarge (d 7-9) maximum Sx limited exercise ECG (n =130)	Exclusion criteria were age >75 y, serious arrhythmias (VF, SVT, or fixed 2nd or 3rd degree AV blocks), LBBB, pericarditis, insufficient acoustic window, and poor short-term Px because of concomitant disease	Pharmacological stress echocardiography	Maximum Sx limited exercise ECG	1º endpoint was cost effectiveness of the diagnostic strategies. The 2º endpoint was quality of life evaluation. Pts were seen at 1 and 6 mo and 1 y after discharge. Cardiac events, use of resources, costing, and quality of life were recorded.	N/A	2º endpoints were composite of death, MI, or urgent revasc at 1-mo follow-up	No complication occurred during either stress echocardiography or exercise ECG. At 1-y follow-up there were 26 events (1 death, 5 nonfatal reinfarctions, 20 pts with UA requiring hospitalization) in pts randomly assigned to early stress echocardiography and 18 events (2 reinfarctions, 16 UA requiring hospitalization) in the group randomly assigned to exercise ECG (NS). The negative predictive value was 92% for stress echocardiography and 88% for exercise ECG (NS). Total costs of the two strategies were similar (NS).	Early pharmacological stress echocardiography and conventional predischarge Sx limited exercise ECG have similar clinical outcome and costs after uncomplicated infarction. Early stress echocardiography may be considered a valid alternative even for pts with interpretable baseline ECG who can exercise.

1º indicates primary; 2º, secondary; ADSPECT, adenosine Tc-99m sestamibi single-photon emission computed tomography; AMI, acute myocardial infarction; AV, atrioventricular; DANAMI-2, Danish Multicenter Study of Acute Myocardial Infarction 2; ECG, electrocardiograph; EF, ejection fraction; ET, exercise test; INSPIRE, Investigating New Standards for Prophylaxis in Reduction of Exacerbations; LBBB, left bundle branch block; LV, left ventricular; LVEF, left ventricular ejection fraction; NS, non/t significant; NQAMI, non-Q-wave myocardial infarction; PCI, percutaneous coronary intervention; PDS, perfusion defect size; pts, patients; Px, prognosis; QAMI, Q-wave myocardial infarction; RCT, randomized controlled trial; revasc, revascularization; STEMI, ST-elevation myocardial infarction; SVT, sustained ventricular tachycardia; Sx, symptom (s); UA, unstable angina; and VF, ventricular fibrillation.

Data Supplement 21. RCTs and Relevant Meta-Analyses of GP IIb/IIIa Inhibitors in Trials of Patients With NSTE-ACS Undergoing PCI (Section 5)

Trial	Study Drug / Comparator	Population	Primary Endpoint	Results	Statistics	Comments
Elective (stable) and urgent (ACS) patients enrolled (without routine clopidogrel pretreatment)						
EPILOG (196) 9182212	Abciximab vs. PC	2,792 pts with stable ischemia or UA	Death, MI or UTVR at 30 d	5.2% vs. 11.7% HR: 0.43	95% CI: (0.30-0.60); p<0.001	N/A
ACS/high risk (without routine clopidogrel pretreatment)						
CAPTURE (197) 10341274	Abciximab (administered for 18-24 h before PCI) vs. PC	1,265 pts with "refractory UA" undergoing PCI 18-24 h after diagnostic catheterization	Death, MI or UTVR at 30 d	11.3% vs. 15.9%	p=0.012	Significant reduction in MI rate both before and during PCI with abciximab therapy. No diff in 6-mo composite endpoint
EPIC (198) 8121459	Abciximab vs. PC	Pts at high risk for abrupt vessel closure	Death, MI, UTVR, IABP, or unplanned stent placement at 30 d	Bolus only: 11.4% Bolus + infusion: 8.3% PC: 12.8%	p=0.009 overall; p=0.008 for bolus + infusion vs. PC	N/A
RESTORE (199) 9315530	Tirofiban (std dose) vs. PC	2,139 pts with ACS undergoing PTCA or DCA	Death, NFMI, UTVR, or stent placement at 30 d	10.3% vs. 12.2%	p=0.160	Composite endpoint was statistically lower at 2 and 7 d follow-up (but not at the 30-d 1º endpoint)
ACS/high risk or mixed study population (with routine clopidogrel pretreatment)						
ISAR-REACT 2 (142) 16533938	Abciximab vs. PC	2,022 "high-risk" ACS pts undergoing PCI	Death, MI or UTVR at 30 d	8.9% vs. 11.9% RR: 0.75	p=0.03 95% CI: 0.58–0.97	RR: 0.71 in +Tn pts; RR: 0.99 in -Tn pts
ADVANCE (200) 15234398	Tirofiban (high-dose) vs. PC	202 pts undergoing elective or urgent PCI (1/3 with stable angina; 1/2 with ACS)	Death, NFMI, UTVR or bailout GPI therapy at median of 185 d	20% vs. 35% HR: 0.51	p=0.01 95% CI: 0.29–0.88	Pts pretreated with either ticlopidine or clopidogrel Death/MI/TVR at 6-mo lower (HR: 0.57; 95% CI: 0.99-0.33; p=0.48)
Pannu Meta-analysis (201) 18458661	GP IIb/IIIa vs. PC	5,303 pts undergoing PCI	Death, MI or TVR	OR: 0.84	95% CI: 0.58–1.22; p=0.35	N/A

1º indicates primary; ACS, acute coronary syndrome; DCA, directional coronary atherectomy; diff, difference; GP, glycoprotein; GPI, glycoprotein IIb/IIIa inhibitors; IABP, intraaortic balloon pump; MI, myocardial infarction; NFMI, nonfatal myocardial infarction; PC, placebo; PCI, percutaneous coronary intervention; PTCA, percutaneous transluminal coronary angioplasty; pts, patients; RR, relative risk; std, standard; Tn, troponin; +Tn, positive troponin; -Tn, negative troponin; TVR, target vessel revascularization; UA, unstable angina; and UTVR, urgent target vessel revascularization.

Data Supplement 22. Studies of Culprit Lesion Versus Multivessel (Culprit and Nonculprit) PCI in Patients with NSTE-ACS (Section 5)

Study	Aim of Study	Type of Study	Study Size	Patient Population	Primary Endpoint	Outcome
Brener SJ, 2008 (202) 18082505	To compare outcomes of culprit only PCI to multivessel PCI in NSTE-ACS pts	Post hoc database analysis	105,866 pts	NCDR database	Multiple endpoints analyzed	Procedural success: 91% culprit PCI vs. 88% multivessel PCI (p<0.001) In-hospital mortality: 1.3% culprit PCI vs. 1.2% multivessel PCI (p=0.09; adjusted OR: 1.11; 95% CI: 0.97–1.27)
Shishehbor MH, 2007 (203)	Examination of the safety and efficacy of nonculprit multivessel	Post hoc database analysis	1,240 pts	NSTE-ACS pts in institutional	Death, MI or TVR Median follow-up 2.3 y	Multivessel PCI associated with lower death/MI/TVR rate; adjusted HR: 0.80 (95% CI: 0.64–0.99; p=0.04); propensity matched analysis HR: 0.67 (95% CI: 0.51–0.88; p=0.004)

17320742	PCI with culprit-only PCI in pts with NSTE-ACS			database		Lower revasc rate with multivessel PCI drove endpoint differences
Zapata GO, 2009 (204) 19515083	To investigate MACE at 1-y follow-up in pts with NSTE-ACS and multivessel CAD who underwent either culprit vessel PCI or multivessel PCI	Post hoc database analysis	609 pts	NSTE-ACS pts in institutional database	MACE at 1 y	MACE lower with multivessel PCI than culprit vessel PCI (9.45% vs.16.34%; p=0.02; no OR given) Revasc lower with multivessel PCI than culprit vessel PCI (7.46 vs. 13.86%; p=0.04; no OR given) No diff in death or death/MI between groups
Palmer ND, 2004 (205) 15152143	Compare short and medium-term outcomes of complete revasc PCI vs. culprit revasc in NSTE-ACS pts	Retrospective database review with additional pt follow-up	151 pts	NSTE-ACS pts treated at a tertiary care institute	Multiple endpoints analyzed	Compared to multivessel PCI, culprit lesion only PCI resulted in: More pts with residual angina (22.8% vs. 9.9%; p=0.041; no OR given) More pts required further PCI (17.5% vs. 7.0%; p=0.045; no OR given) Trend towards more readmissions for UA Greater use of long-term antianginal medications (52.6% vs. 38.0%; p=0.043; no OR given)
Brener, 2002 (206) 12231091	To compare 30-d and 6-m outcome in NSTE-ACS pts undergoing PCI with (1) 1 VD and culprit PCI; (2) multivessel disease and culprit PCI; and (3) multivessel disease and multivessel PCI	Post hoc trial analysis	427 pts	NSTE-ACS pts in TACTICS-TIMI 18	In-hospital and 6-mo MACE	NS diff between the 3 groups at either 30-d or 6-mo follow-up for any of the endpoints: death; MI; and MACE

ACS indicates acute coronary syndrome; CAD, coronary artery disease; diff, difference(s); MACE, major adverse coronary events; MI, myocardial infarction; NCDR, National Cardiovascular Data Registry; NS, no(t) significance; NSTE, non-ST-elevation; NSTE-ACS, non-ST-elevation acute coronary syndrome; PCI, percutaneous coronary intervention; pts, patients; revasc, revascularization; TACTICS, Treat Angina with Tirofiban and Determine Cost of Therapy with an Invasive or Conservative Strategy; TACTICS-TIMI, Treat Angina with Tirofiban and Determine Cost of Therapy with an Invasive or Conservative Strategy-Thrombolysis In Myocardial Infarction; TIMI, Thrombolysis In Myocardial Infarction; UA, unstable angina; VD, vascular disease; and TVR, target vessel revascularization.

Data Supplement 23. Risk Reduction Strategies for Secondary Prevention (Sections 6.3.)

Study Name, Author, Year	Aim of study	Study Type	Study Size (n)	Study Intervention Group (n)	Study Comparator Group (n)	Patient Population		Study Intervention	Study Comparator	Endpoints			P Values, OR: HR: RR & 95% CI:	Study Limitations & Adverse Events
						Inclusion Criteria	*Exclusion Criteria*			*Primary Endpoint (efficacy) and Results*	*Safety Endpoint and Results*	*Secondary Endpoint and Results*		
6.3.1 Physical activity														
Munk, 2009 (207) 19853690	To evaluate high intensity interval training on in-stent restenosis following PCI for stable or UA	RCT	40	20	20	Had PCI with implantation of a stent	History of MI or CABG, significant valvular heart disease, >80 y, inability to give informed consent, inability to participate in	High-intensity interval training program	Usual care, no exercise intervention	Restenosis was smaller in the treatment group (0.10 mm) compared to the control group (0.39) p-value (0.01)	N/A	Peak oxygen uptake increased by 16.8% (T) and 7.8% (C) (p<0.01). Flowmediated dilation improved by 5.2% (T) and -0.1% (C) (p=0.01).	Unknown	Limitations: small sample size and large interquartile ranges; heterogeneity of stents implanted. There were no serious training-related adverse events.

							regular training, any known chronic inflammatory disease other than atherosclerosis, or planned surgery in next 6 mo.					Levels of high-sens C-reactive protein decreased by -0.4 mg/L (T) and increased by 0.1 mg/L (C) (p=0.03 for trend)		
Depression and other psychological conditions														
Tisminetzky 2011 (208) 22409097	To ID Sx profiles of depression and anxiety in pts with ACS and examine changes over time	Randomized trial	79	45	34	Age 35+, hospitalized with ACS, mild/medium anxiety and/or depression	Mental healthcare in prior 3 mo, psychoactive drug use in past y, Dx substance abuse in past y	4-6 30 min cognitive behavioral therapy sessions	Booklet on coping with cardiac illness, and told to contact PCP if depressed	26% of treatment Sx improved vs. 10% in control group	N/A	N/A	N/A	Limitations: findings do not apply to high-risk individuals because they were excluded from study, short duration of follow-up and small sample size.
6.3.4 Nonsteroidal anti-inflammatory drugs														
Lee, 2007 (209) 17051359	To compare the use of celecoxib and rofecoxib on CV risk	Adjusted indirect comparison of 2 published RCTs (APPROVe and APC trials)	APPROVe=2,586 APC=2,035	APPROVe=1287 APC=685 (200 mg group) 671 (400 mg group)	APPROVe=1299 APC=679	History of colorectal neoplasia/ adenomas	None mentioned	APPROVe: 25 mg rofecoxib for 3 y APC: Either 200mg or 400mg of celecoxib for 3 y	PC	N/A	There were NS differences in CV events	N/A	RR (95% CI) p-value Celecoxib vs. 200mg rofecoxib 0.74-1.38 (0.96) Celecoxib vs. 400mg rofecoxib 1.09 0.81 — 1.45 (0.57)	Limitations: interpretation of adjusted indirect comparison should be done with caution
6.3.6 Antioxidant vitamins and folic acid														
Galan, 2010 (210) 21115589	To determine if vitamin B & omega 3 fatty acids can prevent CV events in pts with Hx of heart disease or stroke.	Double blind RCT	2,501	G1=622 (Vitamin B + PC) G2 = 633 (omega 3 + PC) G3 = 620 (vitamin B + omega 3)	626	Personal Hx of MI, UA, or ischaemic stroke	<45 or >80 y; ill defined Dx of CV disease; inability or unwillingness to comply with study treatment	Vitamin B: 560 mg 5 methyltetrahydrofolate, 3 g B-6, 20 mcg B-12 Omega 3: 600 mg of eicosapentanoic acid and docosahexaenoic acid at a ratio of 2:1	Double PC	1st major CV event, NS for Vitamin B or Omega 3	N/A	Significant 2º endpoints: Vitamin B use associated with fewer strokes (HR: 0.57; 95% CI: 0.33-0.97; p=0.04); and a higher risk of death from any cause (HR: 1.55; 95% CI: 1.07–2.25; p=0.02)	Vitamin B: HR: 0.9 95% CI: 0.66-1.23 (0.5) Omega 3: HR: 1.08 95% CI: 0.79-1.47 (0.6)	Limitations: number of participants, short duration (4.7 y) to provide statistical power to detect effects on major vascular events.

Imasa, 2009 (211) 19515873	To determine the effect of folic acid supplementation on prevention of ACS	RCT	240	116	124	UA or NSTEMI in previous 2 wk	Hemodynamic instability, liver disease, renal disease, <18 y, pregnant, Hemoglobin <10 g/dL, high-output failure, inability to provide adequate self-care, malignancy or any terminal illness, and geographic location	1 mg folic acid, 400mcg B12, 10 mg B6 daily	PC	Re-hospitalization and composite of death, nonfatal ACS, and re-hospitalization were significantly increased in the treatment group	N/A	N/A	RR (95% CI), p value all-cause mortality 1.18 (0.68- 2.04), 0.54 Nonfatal ACS 1.28 (0.64-2.54), 0.5 Re-hospitalization 5.11 (1.14-23.0), 0.016 Composite endpoint 1.20 (1.00-1.44), 0.04	Limitations: small sample size; compliance rate=60%; adverse events in treatment group: skin irritation, dyspnea, dizziness

ACS indicates acute coronary syndrome; APC, Adenoma Prevention with Celecoxib trial; APPROVe, Adenomatous Polyp Prevention on Vioxx trial; CABG, coronary artery bypass graft; CV, cardiovascular; Dx, diagnosis; ID, identification; MI, myocardial infarction; N/A, not applicable; NSTEMI, non-ST-elevation myocardial infarction; PCI, percutaneous coronary intervention; PCP, primary care physician; Pts, patients; RCT, randomized controlled trials; and UA, unstable angina.

Data Supplement 24. Older Patients (Section 7.1)

Study Name, Author, Year	Aim of study	Study Type	Study Size (N)	Study Intervention Group (n)	Study Comparator Group (n)	Patient Population		Study Intervention	Study Comparator	Endpoints			P Values, OR: HR: RR & 95% CI:	Study Limitations & Adverse Events
						Inclusion Criteria	*Exclusion Criteria*			*Primary Endpoint (efficacy) and Results*	*Safety Endpoint and Results*	*Secondary Endpoint and Results*		
Alexander 2007 (212) 17502590	Summarize evidence on pt heterogeneity, clinical presentation, and treatment of NSTE-ACS in relation to age (65-74, 75-84, and 85 y)	Summary or 5 pooled NSTE-ACS clinical trials and 3 large NSTE-ACS registries to assess and grade evidence and provide descriptive finding and compare pts in clinical trials vs those not	Clinical Trials n=34266 (18.1% ≥75 y); Registries n=114572 7 (38.3% ≥75 y)	N/A	N/A	Clinical trial and registry specific- pooled (VIGOUR) included GUSTO IIb, PARAGON A and B, PURSUIT, GUSTO IV-ACS Registries=NR MI 2-4, CRUSADE, GRACE	Clinical trial and registry specific	Clinical trial specific	Clinical trial specific	Too numerous to list	Serum creatinine inadequately assesses age-related renal function decline- CrCl should be calculated in all older NSTE-ACS pts. Excess bleeding related to excess AP/AT dose	Summarizes available evidence of presentation, treatment and outcomes of OA in RCTs and registries.	Too numerous to list	Not a trial but an important paper on understanding mgt of older pts. Older NSTE-ACS are underrepresented in clinical trials and are younger and have less comorbidities vs. older pts in registries (and likely 'real world') warranting cautious extrapolation of results.

		included												
Gale 2012 (213) 22009446	Assess difference in risk factors, presentation, management and outcomes across age groups and trends over 7 y in MI pts in United Kingdom	Mixed-effects regression analysis using data from MINAP registry in United Kingdom. Comparison across older age groups and over 7 y	N=616 011 ACS pts: age <55 y=23%;55-64y=20%; 65-74 y=40%; 75-84 y=39%; ≥85 y=29%	N/A	N/A	ACS pts in National Audit registry with outcomes linked to national database. Pts included if met ACS definition on admission (diagnosis was adjudicated but did not exclude pt if not ACS).	Missing data or follow-up	N/A	N/A	Compared to younger NSTE-ACS pts, older pts had sig higher in-pt mortality rates, longer rates of stay and were prescribed less GDMT (med and procedures) despite same or better efficacy vs. young. These age discrepancies have decreased over time.	N/A	Too numerous to list include effect of age on presenting symptoms, comorbidities, use of GDMT, PCI, outcome, and trends over time.	Inpatient mortality from 2003-2010 across all age groups including pts ≥85 y age: OR, 95% CI: 2004: 0.94, 0.88–1.01; 2010: 0.52, 0.44–0.61; 75–84 y age: 2004: 0.98, 0.93–1.03; 2010: 0.52, 0.45–0.60, and pts ,55 y age: 2004: 0.94, 0.79–1.13; 2010: 0.64, 0.44–0.93	Diverse sample of hospital in United Kingdom but less in Wales- not all pts entered into MINAP. Approx. 4% missing data.
Devlin 2008 (214) 18387940	Determine whether increasing age impacts in-hosp and 6-mo outcome of revasc therapy in high-risk NSTE-ACS pts	Retrospective multiple logistic regression analyses on NSTE-ACS pts in GRACE registry by age groups	N=18466 NSTE-ACS pts (27% 70-80 y 'elderly';16% >80 y very elderly')	Data assessed by use of GDMT and early invasive treatment (cath with approp revasc) by 3 age groups	In-hospital and 6-mo outcomes compared for age group and by intervention	GRACE registry pts meeting criteria for NSTE-ACS who had data during hospitalization and 6 mo after discharge. (STEMI data also reported but omitted here)	Pts with non-CV causes for the clinical presentation such as trauma, surgery, or aortic aneurism, were excluded.	Pts who underwent revasc during initial hospitalization classified under revasc included high-risk pts with dynamic ECG changes or recurrent ischemia-regardless of timing of revasc strategy	Medical therapy types were specifically recorded for comparison. Age and intervention strategy were compared.	In NSTE-ACS pts, revasc vs. medical therapy sig lowered 6-mo MACE (stroke, death, MI) and 6-mo mortality. Older NSTE-ACS pts were sig less likely to undergo revasc (and GDMT) than younger pts.	N/A	Elderly and very elderly pts less likely than younger pts to receive GDMT	Revasc vs. no revasc 6-mo MACE <70 yo OR=0.69, 95% CI 0.56–0.86; 70-80 y OR=0.60, 95% CI 0.47–0.76; >80 y OR=0.72,95 % CI,0.54–0.95 Revasc vs. no revasc 6-mo mortality: <70 y OR=0.52,	Although study reports benefit of early invasive therapy, pts who underwent PCI/CABG during admission were included including those who underwent revasc >24 h after admission and high-risk pts were also included (including dynamic ST changes, recurrent ischemia)

													95% CI 0.37–0.72; 70-80 OR=0.38,95 %CI 0.26–0.54; >80 y OR=0.68,9% CI 0.49–0.95	
Damman 2012 (215) 21930723	To assess the impact of early invasive vs. early conservative stragety on long term outcomes (5 y) in older NSTE-ACS pts	Meta-analyses of FRISC II, ICTUS and RITA-3 studies	N=5467 NSTE-ACS pts (51.3% <65 y, 33.3% 65-74 y, 15.3% ≥75 y)	Early Invasive: <65 y=1383 65-75 y=901 ≥75 y=437	Selective invasive (EC): <65 y =1424 65-75 y=920 ≥75 y=402	Pts enrolled in FRISC II, ICTUS and RITA-3 with follow-up data were included.	Those with missing data for specific analyses	Routine invasive strategy defined as card cath within 24-48 h in ICTUS trial, within 72 h in RITA-3 trial and within 7 d with subsequent revasc when appropriate.	Initial medical treatment with card angio and revasc only if refractory angina despite OMT, hemodynamic instability or positive stress (ICTUS and FRISC II)	Routine invasive strategy sig reduced 5-y MACE (death/MI) in 65-74 and ≥75 y but not in those <65 y.	In-hosp bleeding rates sig higher in older pts: <65 y=1.7%; 65-74 y=2.2%; ≥75 y=6.1% (p<0.001 for trend). Bleeding rates higher in each age group with Routine invasive vs. Selective Invasive strategy but all p>0.1	The benefits were smaller for women than for men but sample size small (esp ≥75) underpowered for gender and age analyses	Routine Invasive vs. Selective Invasive on 5-y death/MI: <65 y (HR 1.11, 95% CI 0.90 to 1.38), 65-74 y (HR 0.72, 95% CI 0.58-0.90); ≥75 y (HR 0.71, 95% CI 0.55-0.91)	Trials had different time windows for routine invasive strategy (up to 7 d in FRISC II) and other between trial heterogeneity exists
Bach 2004 (216) 15289215	To assess impact of age and early invasive vs. initial conservative strategy on outcomes in NSTE-ACS pts	Prespecified subgroup analyses by age strata of TACTICS TIMI 18, a RCT evaluating Early Invasive vs. Initial Conservative strategy in NSTE-ACS pts	N=2220 NSTE-ACS pts: <65 y=1258 ≥65 y=962	Early Invasive: <65 y=623 ≥65 y=491	Early Conservative: <65 y=635 ≥65 y=471	Pts with NSTE-ACS eligible for card cath/revasc	Persistent STE; 2º angina; PCI or CABG within previous 6 mo; contain to AP and GP meds. Stroke/TIA; LBBB or paced rhythm, CHF or cardiogenic shock; clinically important systemic disease; SCr >2.5 mg/dL)	Coronary angiography 4-48 h after randomization and have revasc when appropriate All pts received ASA 325 mg, UFH and tirofiban.	Pt received ASA 325 mg, UFH and tirofiban, treated medically and, if stable, underwent ETT before discharge. Card angio in pts w failure of OMT or stress-induced ischemia	Among pts ≥75 y, Early Invasive vs. Initial Conservative strategy conferred an absolute reduction (10.8% vs. 21.6%; p=0.016) and relative reduction of 56% in death or MI at 6 mo. RR=0.61 in death/MI at 6 mo for Early	Major bleeding rates higher with Early Invasive vs. Initial Conservative strategy in pts ≥75y (16.6% vs. 6.5%; p=0.009); Sig higher minor bleeding rates and trasfusions w Early Invasive vs. Initial Conservative	Sig reduction in 30-d outcomes of MI, death/MI, ACS Rehosp and MACE for NSTE-ACS pts ≥75 y (none were sig for pts <65 y)	NSTE-ACS pts ≥75 y Early Invasive vs. Initial Conservative 6-mo outcomes: Death/MI: RR=0.61 (0.41–0.92) MI: 0.49 (0.29–0.81) Death: RR=0.88 (0.51–1.53) ACS Rehosp: RR=0.75	TACTICS-TIMI 18 excluded pts with multiple co-morbidities and marked renal dysfunction (included older pts with mild renal dysfunction by CrCl). Underpowered for many comparisons in older pts. Additional age group beyond single 65-y stratification were not prespecified and done post hoc

										Invasive vs. Initial Conservative in NSTE-ACS pts ≥65 y but no sig diff in 6-mo outcome seen in pts <65 y	in ≥75 y		(0.50–1.11) MACE RR=0.75 (0.54–1.03) None of 6 mo outcomes sig in NSTE-ACS pt <65 y	
Yourman (217) 22235089	Assess quality and limitations of prognostic indices for mortality in older adults through systematic review.	Extensive literature review of prognostic indices for mortality (6 m-5 y) in pts age ≥60 y	N=21,593 titles reviewer	N/A	N/A	Prognostic indiex studies included if they validated and predicted absolute risk of mortality in pts whose average age ≥60 y	Studies were excluded if prognostic index estimated intensive care unit, disease-specific, or in-hospital mortality.	N/A	N/A	16 prognostic indices identified predicting overall mortality (6 m-5 y) in diff pt groups/ settings including community, nursing home and hospital. 2 were validated.	N/A	Reports potential sources of bias for each measure	Identified mortality predictors for older adults need additional external validation but may be useful in comparing efficacy of treatment/intervention recommendation (time to benefit) vs. life expectancy in older pts.	N/A
Fenning 2012 (218) 22530044	Compare utility of palliative care prognostic tool GSF and GRACE score, to help identify patients approaching EoL	Single site study of consecutive pts admitted with NSTE-ACS pts-compared 12-mo outcome vs. prog tool estimate of EoL care.	N=172 NSTE-ACS pts, of these compared n=40 pts identified by GSF with n=32 by GRACE score	N/A	N/A	172 consecutive, unselected pts admitted for NSTE-ACS to urban hosp over 8 wk	Pts admitted with ACS who died in hospital were excluded from analysis.	N/A	N/A	GSF identified 40 pts (23%) meeting criteria for approaching EoL (GSF+ older, more comorb vs. GSF-). 1-y mortality: GSF+ vs. GSF- (20% vs. 7%, p=0.03). GRACE identified 32 (19%) pts with ≥10% risk of	N/A	GSF and GRACE positive score both independently associated with increased number of comorbidities, readmissions, older age.	GRACE score 12-mo mortality prediction (C-statistic 0.75) + prev hosp adm and stroke (C-statistic 0.88). GRACE (upper tertile)+GSF Sens=78%, Spec=89%, NPV= 97%,	Single-center study, additional validation studies needed.

										death within 6 mo. GRACE score at discharge highly predictive of 12-mo mortality and associated with readmission during subseq y. Improved by adding prev hosp adm and prev stroke hx.			PPV=44%	
Tinetti 2004 (219) 15625341	This is a very relevant expert/consensus opinion paper, but is not a study which can be put into a data supplement table.													
Corsonello 2010 (220) 20015034	This reference is an extensive review and summary of major PD/PK changes with aging and their relevance to CV drugs. However, it is not amenable to list in data supplement format.													
Trifiro 2011 (221) 21495972	This reference is an extensive review and summary of major PD/PK changes with aging and their relevance to CV drugs. However, it is not amenable to list in data supplement format.													
Alexander 2005 (222) 16380591	Investigation of relationship between UFH, LMWH and GPI excess dosing and major outcomes	Retrospective exploratory analysis of CRUSADE registry	N=30,136 NSTE-ACS pts who received AT agents	N/A	N/A	NSTE-ACS pts in CRUSADE registry who had received AT agents	Pts with missing weight (n=826) or missing creatinine clearance (n=1120) data excluded from dosing calculations that required these variables. Pt who were transferred or underwent CABG excluded from bleeding anal.	N/A	N/A	42% of NSTE-ACS pts received ≥1 initial dose of AT agent outside rec range. Excess doses per agent: UFH+32.8%, LMWH=13.8% and GPI=26.8%. Excess dose assoc with older age, female, low body wt, DM and CHF. Pt who received excess AT dose had higher	15% of major bleeding in NSTE-ACS pts attributable to excess AT dosing	Higher adjust mortality in those receiving excess vs. recomm dose of GPI (OR=1.50, 95% CI 1.01-2.17). LOS sig longer in pts given excess vs. rec doses of UFH, LMWH and GPI.	Adjusted OR for major bleeding with excess dosing (vs. no excess dosing): UFH: OR: 1.08 (0.94-1.26) LMWH: OR: 1.39 (1.11-1.74) GPI: OR: 1.36 (1.10-1.68)	Dosing categories based on weight and renal function dosing (dependent on recorded data) studied population may vary from those with missing data in addition to limited generalizability to general NSTE-ACS pts in real world, esp older.

										bleeding rate, mortality and length of stay vs. those given rec dose.				
Lincoff 2003 (223) 12588269	Determine efficacy of bivalrudin +GPI vs. GPI+UFH for PCI on periproc ischemia and bleeding	RCT, double-blind trial in pt undergoing urgent or elective PCI-prespecified for non-inferiority	N=6010	Bival+GPI-2999	UFH+GPI=3011	Pts ≥21 y undergo PCI with approved device	PCI performed as reperfusion therapy for AMI, poorly controlled Htn, unprotected LM, PCI w/l past mo., risk for bleeding, serum Cr >4 mg/dL, prior heparin tx.	Bivalrudin 0.75 mg/kg bolus + 1.75 mg/kg/hr inf during PCI with provisional GPI Pts received ASA and thienopyridine for ≥ 30 d post PCI	UFH 65 U/kg bolus+ GPI (abciximab or eptifibitide) Pts received ASA and thienopyridine for ≥ 30 d post PCI	Provisional GPI given to 7.2% Bil pts. Noninferiority statistically achieved in 30 d endpoint: MI/death/ revasc/ in-hosp major bleeding between BiV+GPI vs. UFH+GPI	In Hosp major bleeding rates sig lower in Biv+GPI vs. UFH+GPI (2.4% v 4.1%, p<0.001)	30 d death/MI/revasc: no diff in MACE BiV+GPI vs. UFH+GPI (OR=0.90, p=0.4)	30 d death/MI/revasc/in-hosp major bleeding:no diff in MACE in BiV+GPI v UFH+GPI (OR=0.92, p=0.32).	Included elective PCI – NSTE-ACS pts approx. 42% each arm + 30% positive stress test; 13% ≥75 y
Lopes RD, 2009 (224) 19298914	Evaluate impact of age on antithrombotic strategy and outcomes in moderate and high-risk NSTE-ACS pts	Pre-specified analysis of 30-d and 1-y outcomes in 4 age groups, overall and among those undergoing PCI	Of 13,819 ACUITY pts, 3,655 (26.4%) were <55 y, 3,940 (28.5%) were 55-64 y, 3,783 (27.4%) were 65-74 y, and 2,441 (17.7%) were ≥75 y.	Of the pts in each age group (prev column), 1/3 were randomized to receive bival alone	Of the pts in each age group (4th column), 1/3 were randomized to receive Hep+GPI	NSTE-ACS pts at moderate or high risk for adverse clinical outcomes at 30 d. All pts underwent cath w/l 72 h of admission	Pts excluded for any of following: STEMI, recent bleeding, CrCl <30 mg/mL, thrombocytopenia, shock, recent use of abciximab, warfarin, fondaparinux, bival, LMWH, fibrinolytics	Bivalrudin alone All pts- ASA+ mtn Clopidogrel post PCI × 1 y Clopidogrel load per invest	Bivalrudin+ GPI-randomized (2×2 factorial) to upstream or cath lab GPI admin Heparin +GPI randomized (2×2 factorial) to upstream or cath lab GPI admin All pts- ASA+ mtn Clopidogrelpost PCI × 1-y Clopidogrel load per invest	Mortality and composite ischemic outcomes at 30 d and 1 y were not statistically different in pts randomized to bivalirudin alone or randomized to heparin with GP IIb/IIIa inhibitors across all age categories.	Major bleeding increased in each age group regardless. Major bleeding rates were higher in PCI pts in the age groups: 3.4%, 5.1%, 5.5%, and 11.8%, for ages <55, 55-64, 65-74, and ≥75 y, respectively. Rates were signif lower in those treated w Bivalrudin alone in each age group	Older pts had more comorb, were more often female, weighed less, and had more hypertension, prior cerebral vascular disease, renal insufficiency (creatinine clearance ≤50 mL/min), and prior CABG	Number needed to treat with bivalirudin alone to avoid 1 major bleeding event was lower in pts ≥75 y (23 overall and 16 for PCI-treated pts) than in any other age group.	N/A

Lemesle G,. 2009 (225) 19360860	Analyze impact of replacing heparin with bivalirudin in octogenarians undergoing PCI on post-procedure hemorrhage and 6-mo mortality.	Single center retrospective observational analyses of consecutive pts ≥80 y who underwent PCI	N=2766	N=1,207 (43.6%) received bivalrudin	N=1,559 (56.4%).received UFH	Consecutive pts ≥80 y at single center who underwent PCI/stent from 2000-2007	None	Bivalrudin (dose not reported) at operator's discretion. GPI given at operator's discretion. ACT target >250 s All pts received ASA 325 mg, clopidogrel ≥300 mg load then 75 mg qd mtn advised for 1 y	UFH (dose not reported) at operator's discretion. GPI given at operator's discretion. ACT target >250 s All pts received ASA 325 mg, clopidogrel ≥300 mg load then 75 mg qd mtn advised for 1 y	Overall in-hospital bleeding and 6-mo mortality rates were 4.6% and 11.8%, respectively. Bival vs. UFH reduced 6 mo mort (8.8% vs. 13.4%, p=0.003). Bival was assoc with sig less in-hosp bleeding rate (2.2% vs. 6.8%, p< 0.001).)	After propensity score matching, bival sign reduced periproc bleeding vs. UFH (HR=0.38, 95% CI=0.22–0.65, p=0.001). Bival vs. hep reduced 6 mo MACE (10.1% vs. 20.2%, p<0.001)	In-hospital major bleeding assoc with 6-mo mortality HR=2.5, 95%CI=1.6–3.9, p<0.001)	Bival vs. UFH reduced 6-m mortality HR=0.6, 95% CI=0.4–0.9, p=0.01) In-hosp bleeding Bival vs. UFH: HR= 0.41, (95% CI=0.23–0.73, p=0.003) by MRL anal. and by multivar COX (HR=0.6, 95% CI= 0.4–0.9, p=0.01)	Non-randomized observational study. Doses not reported. Differences in baseline characteristics-propensity analyses used.
Summaria F, 2012 (226) 22476002	To explorefeasibility and safety of PCI via transradial approach and intraprocedural bivalirudin in >70 y MI pts	Retrospective analyses of data from consecutive ACS pts >70 y with Early Invasive strategy via transradial approach with bivalrudin as AT.	N=84 pts (22 male; 52 pts >80 y) STEMI=53, NSTEMI=31	All pts were treated with bivalrudin and via tranradial approach	N/A	Consecutive pt >70 y with ACS treated with EI strategy using tranradial approach and bivalrudin as AT regimen.	None	Bivalrudin bolus dose of 0.75 mg/kg immediately followed by continuous infusion of 1.75 mg/kg/h. All pts received ASA 300 mg, clopidogrel 600 mg, UFH bolus and infusion in emer dept – stopped 6 h prior to PCI	N/A	Transradial approach successful in 100%, manual thrombus aspir in 52% of NSTEMI pts. Transfusions=0, sign bleeding events=1 (GI bleed), in-pt mort=0,30 d MACE=5 (6%, 1 death, 2 MI, 2 TLR)	N/A	N/A	N/A	Pilot feasibility study in very elderly cohort. Single center, no comparison group.
McKellar SH, 2008 (227) 18825133	To assess pt characteristics, procedural success,	Systematic review and meta-analyses of 66 studies of	N=66 studies (65,376 pts, 56% male)	35 CABG studies	32 PCI studies	Studies which included baseline characteristic and outcomes	Studies that reported combined CABG and valve operations or	CABG without additional procedure (i.e. valve	PCI with last enrollment 1997	30-d mort CABG vs. PCI (7.2% v 5.4%). 1-y survival: CABG=86%	3 y survival CABG 78% (74%−82%) v PCI 78% (68%−87%), 5	Greater number of reinterventions post PCI vs. CABG.	Univariate analysis showed that CABG, male gender,	Clinical trials comparing PCI vs. CABG enrolled younger pts of lower risk with less

	complications and outcomes of ≥80 y who undergo PCI vs. CABG	coronary revasc in ≥80 y (subgroup anal by revasc type)				in ≥80 y undergoing revascularizton (PCI vs. CABG) with 30-d survival (English lang)	studies where baseline clinical data or outcomes were not reported separately were excluded.	replacement), last enrolled 1996		(83%−88%) vs. PCI 87% (84%−91%)	y survival CABG 68% (62%−73%) v PCI 62% (46%−77%),		multivessel disease, and abnormal LVEF predicted 30-d mortality. Being treated more recently, having nonelective status, and having DM were protective. The only univariate predictor of decreased survival at 1 y was CABG (p=0.005); a more recent date of enrollment (p=0.003) and diabetes (p<0.001) were protective factors.	comorbidities, 65 of 66 studies observational, Older studies w/o DES
Kimura T, 2008 (228) 18824755	Assess long-term outcomes between PCI vs. CABG in younger and older pts (≥75 y)	Retrospecitve analyses of multicenter registry (CREDO-Kyoto) of consecutive pts undergoing 1st PCI or	N=9,877 enrolled, 5420 (PCI: 3712, CABG: 1708) had multivessel disease without left main	CABG=1,708 ≥75 y, (21%) ≥80 y (6%)	PCI=3,712 ≥75 y (27%) ≥80 y (12%)	Consecutive pts undergoing 1st PCI or CABG and excluding those pts with AMI within wk before index procedure.	Pts undergoing concomitant valvular, left ventricular, or major vascular operation were excluded from the current analysis. Pts with disease of the left main	N/A	N/A	≥75 y of age: 3-y survival adjusted for baseline char favored CABG (HR for death PCI vs. CABG HR=1.23 (0.99-1.53, p=0.06), but not for younger pts	Stroke rate higher in 4 y follow-up in CABG vs PCI	≥75 y: Adj HR for death PCI vs. CABG prespecifieds ubgroups: DM HR= 1.85 (1.1–3.12) p=0.02 All-cause death cum	75 y of age: 3-y survival adjusted for baseline char favored CABG HR for death PCI vs. CABG HR=1.23 [0.99-1.53, p=0.06], but	Nonrandomized observational study. Meta-analyses performed in BMS era, non-urgent cases only

		CABG-stratified by age <75 vs. ≥75 y	involvement.				coronary artery and with single-vessel disease were excluded.			(HR=1.09, p=0.55); 3VCAD Cox survival favors CABG vs. PCI (p=0.004)		incidence: 1 y: PCI 9% vs. CABG 8.8% 2 y: PC 15.4% vs. CABG 12.2% 3 y: PCI 20.7% vs. CAGB 13.3% 4y: PCI 22.7% vs. 15.5%	not for younger pts (HR=1.09, p=0.55)	
Dacey LJ, 2007 (229) 18036905	Compare long-term survival after PCI vs. CABG in ≥80 y	Retrospective observational analyses of regional (New England) registries of consecutive 80-89 y pts (1992-2001) who underwent PCI or CABG but eligible for both	N=1693 (57% 2V CAD, 42.3% 3V CAD without LM disease.	CABG=991 (2VCAD=443, 3VCAD=548) 80-84 y=83% 85-89=17%	PCI=702 (2VCAD=532, 3VCAD=170) 80-84 y=72% 85-89=27%	Pts included were 80-89 y with 2 or 3 VCAD (>70% stenosis), eligible for 1st PCI or CABG. (BARI criteria)	Pts undergoing emergent procedure or <24 h of MI, those with left main disease, or sig valve disease.	N/A	BMS era	In-hospital mortality: PCI=3.0% vs. CABG= 5.9% (p=0.005). 6-mo survival: CABG vs. PCI (HR,1.32; p=0.135). 6-mo to 8-y survival- all pts: CABG vs. PCI (HR, 0.72; p=0.005) and for pts with 2VCAD (HR, 0.68; p=0.016). 3VCAD (HR=0.75, p=0.17)	N/A	CABG pts were more freq male, had more PVD and CHF and less renal failure and prior MI.	In-hospital mortality: PCI=3.0% vs. CABG= 5.9% (p=0.005). 6-mo to 8-y survival- all pts: CABG vs. PCI (HR, 0.72; p=0.005)	Nonrandomized observational study. Analyses performed in BMS era. Regional data. Limited data in older half of cohort and those with 3VCAD.Various revasc indications.

2º indicates secondary; 2VCAD, double-vessel coronary artery disease ; 3VCAD, triple-vessel coronary artery disease; ACC-NCDR indicates American College of Cardiology National Cardiovascular Data Registry; ACE, angiotensin-converting enzyme; ACS, acute coronary syndromes; ACUITY, Acute Catheterization and Urgent Intervention Triage Strategy; AMI, acute myocardial infarction; AP, antiplatelet; ASA, aspirin; AT, antithrombins; BARI, Bypass Angioplasty Revascularization Investigation; BEIR, Biological Effects of Ionizing Radiation; BMS, bare metal stent; CHF, congestive heart failure; CABG, coronary artery bypass graft; CAD, coronary artery disease; CANRACE, Canadian Registry of Acute Coronary Events; cath, catheterization; CHF, congestive heart failure; CR, creatinine; CrCl, creatinine clearance; CREDO-Kyoto, Coronary Revascularization Demonstrating Outcome Study in Kyoto; CRUSADE, Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the American College of Cardiology/American Heart Association Guidelines; CT, computed tomography; CTCA, Cancer Treatment Centers of America; DES, drug-eluting stent; DM, diabetes mellitus; EoL, end of life; EPR, electronic patient record; EPS, electrophisiology study; ETT, Exercise tolerance testing; FRISC, Framingham and Fast Revascularization During Instability in Coronary Artery Disease; GDMT, guideline-directed medical therapy; GI, gastrointestinal; GP, glycoprotein; GPI, glycoprotein IIb/IIIa inhibitors; GRACE; Global Registry of Acute Coronary Events; GSF, Gold Standards Framework; GUSTO, Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries; HF, heart failure; HTN, hypertension; Hx, history; ICTUS, Invasive versus Conservative Treatment in Unstable Coronary Syndromes; LAR, life attributable risk; LBBB, left bundle branch block; LOS; length of stay; LVEF, left ventricular ejection fraction; MACE, major adverse cardiac event; MI, myocardial infarction; MINAP, Myocardial Ischaemia National Audit Project; MPI, myocardial perfusion imaging; MUGA, Multigated Wall Motion Study; N/A, not applicable; NPV, negative predictive value; NS, not significant; NRMI, National Registry of Myocardial Infarction; NSTE-ACS, non-ST-elevation acute coronary syndrome; NSTEMI, non-

ST-elevation myocardial infarction; OA, osteoarthritis; OMT, optimal medical therapy; PCI, percutaneous coronary intervention; PET, positron emission tomography; PPV, positive predictive value; pts, patients; PVD, peripheral vascular disease; RITA, Randomized Trial of a Conservative Treatment Strategy Versus an Interventional Treatment Strategy in Patients with Unstable Angina; RBC, red blood count; revasc, revascularization; RR, relative risk; Rx, prescription; SCr, serum creatinine; Sx, symptom(s); TACTICS, Treat Angina With Tirofiban and Determine Cost of Therapy With an Invasive or Conservative Strategy; TIA, transient ischemic attack, TIMI, Thrombolysis In Myocardial Infarction; UFH, unfractionated heparin; U.S., United States; and VIGOUR, Virtual Coordinating Center for Global Collaborative Cardiovascular Research.

Data Supplement 25. Heart Failure (Section 7.2)

Study Name, Author, Year	Aim of study	Study Type	Study Size (n)	Study Intervention Group (n)	Study Comparator Group (n)	Patient Population		Study Intervention	Study Comparator	Endpoints			P Values, OR: HR: RR & 95% CI:	Study Limitations & Adverse Events
						Inclusion Criteria	*Exclusion Criteria*			*Primary Endpoint (efficacy) and Results*	*Safety Endpoint and Results*	*Secondary Endpoint and Results*		
Boersma 2000 (2) 10840005	Develop a model for predicting 30-d death and myocardial (re)infarction in pts without STE-ACS	Retrospective analysis of pts with NSTE-ACS enrolled in PURSUIT trial (n=9,461; 3.6% with 1° outcome)	N/A	Pts enrolled in PURSUIT trial	Pts not enrolled in PURSUIT trial; pts with STE on initial ECG	N/A	1° outcome: 30-d death; 2° outcome: composite of 30-d death and myocardial (re)infarction; More than 20 variables were found to be predictive of 1° and 2° outcomes	N/A	N/A	There were 7 factors most predictive of death: age (adjusted $[X]^2$=95), heart rate ($[X]^2$=32), SBP ($[X]^2$=20), ST-segment depression ($[X]^2$=20), signs of HF ($[X]^2$=18), and cardiac markers ($[X]^2$=15); The C-index for the mortality model was 0.814	N/A	Regression model developed in pts with diagnosed ACS and not designed to be applied indiscriminately to undifferentiated chest pain pts; difficult to calculate; original model requires preexisting programmed calculator; simplified version requires print-out of scoring system for each variable with corresponding figure to interpret data	Develop a model for predicting 30-d death and myocardial (re)infarction in pts without STE-ACS	Retrospective analysis of pts with NSTE-ACS enrolled in PURSUIT trial (n=9,461; 3.6% with 1° outcome)
Granger 2003 (3)	Develop a regression	Retrospective	N/A	Inclusion in GRACE or	Not included in these trials	N/A	Adverse event defined as in-	N/A	N/A	The discrimination ability of the	N/A	Regression model	Develop a regression model	Retrospective observational study

14581255	model in pts with diagnosed ACS (including pts with STEMI) for in-hospital mortality	observational study utilizing pts from GRACE (n=11,389; 509 deaths); validation set included a subsequent cohort of 3,972 pts enrolled in GRACES and 12,142 pts enrolled in GUSTO-IIb trial		GUSTO-IIb trial			hospital mortality; Regression model identified the following 8 independent risk factors:accounted age, Killip class, SBP, ST-segment deviation, cardiac arrest during presentation, serum creatinine level, positive initial cardiac enzyme findings, and heart rate			simplified model was excellent with C-statistics of 0.83 in the derived database, 0.84 in the confirmation GRACE data set, and 0.79 in the GUSTO-IIb database; OR for the 8 independent risk factors were: age (OR: 1.7 per 10 y), Killip class (OR: 2.0 per class), SBP (OR: 1.4 per 20 mmHg decrease), ST-segment deviation (OR: 2.4), cardiac arrest during presentation (OR: 4.3), serum creatinine level (OR: 1.2 per 1 mg/dL [88.4 µmol/L] increase), positive initial cardiac enzyme findings (OR: 1.6), and heart rate (OR: 1.3 per 30 beat/min increase)		developed in patients with diagnosed ACS (including STEMI pts) and was not designed to be applied indiscriminately to undifferentiated chest pain pts; difficult to calculate; original model requires pre-existing programmed calculator; simplified version requires print-out of scoring system for each variable with corresponding nomogram	in pts with diagnosed ACS (including pts with STEMI) for in-hospital mortality	utilizing pts from GRACE (n=11,389; 509 deaths); validation set included a subsequent cohort of 3,972 pts enrolled in GRACES and 12,142 pts enrolled in GUSTO-IIb trial
Pollack 2006 (13) 16365321	Validation in an ED population with chest pain	Convenience sample N=3,326 without new STE	N/A	Chest Sx and ECG obtained	New STE	N/A	Death/MI/revasc over 30 d	N/A	In-hospital and 14-d events	Graded relationship between score and events	N/A	Used parts of score to define management	Validation in an ED population with chest pain	Convenience sample N=3,326 without new STE
Go 2011 (14) 21691204	Attempt to add creatinine to TIMI risk score	Single center N=798	N/A	Ischemic Sx within 48 h	STEMI	N/A	CV death, MI, urgent revasc or Sx and elevated biomarkers	N/A	N/A	Renal dysfunction increased risk but not enough to add variable to system	N/A	Small and only 9% with eGFR, 30	Attempt to add creatinine to TIMI risk score	Single center N=798
Huynh 2009 (15) 19960136	Across all ACS spectrum	Multicenter RCT with N=1,491	N/A	NSTE, ACS and STEMI	N/A	N/A	6-mo death and MI	N/A	N/A	2 mm ST deviation increased risk and risk was less	N/A	All high-risk pts	Across all ACS spectrum	Multicenter RCT with N=1,491 from angiographic arm

		from angiographic arm								regardless of score with less				
Eagle 2004 (16) 15187054	Original GRACE validation	Registry N=17,141	N/A	All ACS	N/A	N/A	6-mo all-cause mortality	N/A	N/A	p<0.25 into multivariate model	N/A	Registry data, 200 pts without 6 mo follow-up	Original GRACE validation	Registry N=17,141
Eggers 2010 (17) 20598977	Incremental prognostic value of multiple biomarkers in NSTE-ACS	Single center trial of 453 chest pain pts	NT-proBNP, cystatin GDF-15	Possible ACS	N/A	Biomarkers at presentation	All-cause mortality at 6 mo	N/A	NT-proBNP not additive, cystatin minimally and GDF-15 helpful	ROC analysis	N/A	Small but 92 deaths.	Incremental prognostic value of multiple biomarkers in NSTE-ACS	Single center trial of 453 chest pain pts
Cannon 2001 (186) 11419424	To compare an early invasive strategy to a more conservative approach	Prospective, randomized, multicenter trial 2,220	Intervention: 1,114 vs. Comparator: 1,106	Pts ≥18 y if they had episode of angina (with accelerating pattern or prolonged [>20 min] or recurrent episodes at rest or with minimal effort) within preceding 24 h, candidates for coronary revasc, and at least 1 of the following: new finding of ST-segment depression of at least 0.05 mV, transient (<20 min) STE of at least 0.1 mV, or T-wave inversion of	Persistent STE, 2º angina, Hx of PCI or CAB grafting within preceding 6 mo, factors associated with increased risk of bleeding, LBBB or paced rhythm, severe CHF or cardiogenic shock, serious systemic disease, a serum creatinine level of <2.5 mg/dL (221 µmol/L), or current participation in another study of an investigational drug or device	Pts assigned to early invasive strategy were to undergo coronary angiography between 4 h and 48 h after randomization and revasc when appropriate on the basis of coronary anatomical findings	Pts assigned to early conservative strategy were treated medically and, if their condition was stable, underwent an exercise-tolerance test (83% of such tests included nuclear perfusion imaging or echocardiography performed according to the protocol of the institution) before being discharged	Combined incidence of death, nonfatal MI, and rehospitalization for an ACS at 6 mo	Bleeding	Death, death or MI, fatal or nonfatal MI, rehospitalization for MI	At 6 mo, the rate of the 1º endpoint was 15.9% with use of the early invasive strategy and 19.4% with use of the conservative strategy (OR: 0.78; 95% CI: 0.62-0.97; p=0.025).	Study excluded pts with severe comorbid conditions or other serious systemic illness	To compare an early invasive strategy to a more conservative approach	Prospective, randomized, multicenter trial 2,220

				at least 0.3 mV in at least 2 leads; elevated levels of cardiac markers; or coronary disease, as documented by Hx of cath, revasc, or M										
de Winter 2005 (188) 16162880	To compare an early invasive strategy to a selectively invasive strategy for pts who have ACS without STE and with an elevated cTnT level	RCT 1,200	Interventi on: 604 vs. Compara tor: 596	Eligible pts have all 3 of the following: Sx of ischemia that were increasing or occurred at rest, with the last episode occurring no more than 24 h before randomizatio n; elevated cTnT level (≥0.03 µg/L); and either ischemic changes as assessed by ECG (defined as ST-segment depression or transient STE exceeding 0.05 mV, or T-wave inversion of	Exclusion criteria were an age >18 y or <80 y, STEMI in past 48 h, indication for 1° PCI or fibrinolytic therapy, hemodynamic instability or overt CHF, the use of oral anticoagulant drugs in past 7 d, fibrinolytic treatment within past 96 h, PCI within the past 14 d, contraindicatio n to treatment with PCI or GP IIb/IIIa inhibitors, recent trauma or risk of bleeding, hypertension	Pts assigned to early invasive strategy were scheduled to undergo angiography within 24-48 h after randomizatio n and PCI when appropriate on the basis of the coronary anatomy	Pts assigned to the selectively invasive strategy were treated medically. Pts were scheduled to undergo angiography and subsequent revasc only if they had refractory angina despite optimal medical treatment, hemodynamic or rhythmic instability, or clinically significant ischemia on the predischarge exercise test.	1° endpoint was composite of death, RMI, or rehospitali zation for angina within 1 y after randomizat ion	Bleeding	Percentage of pts free from anginal Sx	Estimated cumulative rate of 1° endpoint was 22.7% in the group assigned to early invasive manageme nt and 21.2% in the group assigned to selectively invasive manageme nt (RR: 1.07; [0.87-1.33]; p=0.33).	Revasc rates were high in the 2 groups in our study (76% in the early-invasive-strategy group and 40% in the selectively-invasive-strategy group during the initial hospitalization, and 79% and 54%, respectively, within 1 y after randomization	To compare an early invasive strategy to a selectively invasive strategy for pts who have ACS without STE and with an elevated cTnT level	RCT 1,200

				≥0.2 mV in 2 contiguous leads) or documented Hx of CAD as evidenced by previous MI, findings on previous coronary angiography, or a positive exercise test	despite treatment (i.e., systolic pressure >180 mmHg or diastolic pressure >100 mmHg), weight <120 kg, or inability to give informed consent									
Fox KA 2002. (187) 12241831	To compare interventional strategy and conservative strategy in pts with unstable CAD	RCT 1,810	Intervention: 895 vs. Comparator: 915	Pts eligible for inclusion if they had suspected cardiac chest pain at rest and had documented evidence of CAD with at least 1 of the following: evidence of ischaemia on ECG (ST-segment depression, transient STE, LBBB [documented previously], or T-wave inversion); pathological Q waves suggesting previous MI; or arteriographic	All those with probable evolving MI, including those for whom reperfusion therapy was indicated, were ineligible. Those in whom new pathological Q waves developed, or those with CK or CK-MB concentrations 2× the ULN before randomization, were excluded. Also excluded were those with MI within the previous mo, PCI in the	Pts assigned to interventional treatment strategy were managed with optimum antianginal and antiplatelet treatment (as for the conservative group), and enoxaparin 1 mg/kg subcutaneously 2× for 2-8 d. Protocol specified that coronary arteriography should be done as soon as possible after randomization and ideally within 72 h	Pts assigned to the conservative strategy were managed with antianginal and antithrombotic medication	Coprimary endpoints were: a combined rate of death, nonfatal MI, or refractory angina at 4 mo; and a combined rate of death or nonfatal MI at 1 y	Bleeding	Death, MI, refractory angina as individual endpoints	At 4 mo, 86 (9.6%) of 895 pts in intervention group had died or had a MI or refractory angina, compared with 133 (14.5%) of 915 pts in the conservative group (RR: 0.66, [0.51-0.85], p=0.001).	1º endpoint driven by reduction of refractory angina with no difference in hard clinical endpoints	To compare interventional strategy and conservative strategy in pts with unstable CAD	RCT 1,810

				ally proven CAD on a previous arteriogram	preceding 12 mo, or CABG at any time.									
Spacek 2002 (120) 11792138	To compare 1-d angiography /angioplasty vs. early conservative therapy of evolving MI without persistent STE	RCT 131	Interventi on: 64 vs. Compara tor: 67	Rest ischaemic chest pain, lasting <20 min, within last 24 h before randomizatio n; ECG evidence of AMI without STE (ST-segment depressions minimally 0.1 mm in at least 2 contiguous leads and/or negative T waves or documented old LBBB/ RBBB; CK-MB higher than 1.5× X ULN and/or positive TnI assay	Unstable post-infarction angina pectoris resistant to maximal pharmacother apy; cardiogenic shock; acute LBBB or RBBB or STE 2 mm in 2 leads; QMI or IV thrombolysis >1 mo; coronary angioplasty or bypass surgery >6 mo; any concomitant disease which may have possible influence on 1 y Px; lack of pt cooperation	1-d angiography /angioplasty treatment strategy guidelines characterized by coronary angiogram as soon as possible after randomizatio n followed by immediate coronary angioplasty of the culprit coronary lesion + stent implantation whenever suitable	Conservative treatment strategy guidelines were characterized by initial medical treatment with coronary angiography and subsequent revasc only in the presence of recurrent myocardial ischaemia	Composite of death or nonfatal RMI 6 mo after the randomizat ion	None	Length of the initial hospitalization and the number of subsequent hospitalizations for UAP	1º endpoint (death/ reinfarction) at 6 mo occurred in 6.2% vs. 22.3% (p<0.001). 6-mo mortality in 1-d angiograph y/ angioplasty group was 3.1% vs. 13.4% in the conservativ e group (p<0.03).	Small sample size, interventions were done in only one high volume tertiary center	To compare 1-d angiography/ angioplasty vs. early conservative therapy of evolving MI without persistent STE	RCT 131
Hochman 1999 (230) 10460813	Evaluate early revascularizat ion in pts with cardiogenic shock	Multicenter RCT	302 pts	152 pts randomized to emergency revasc	150 pt-initial medical stabilization	STEMI, new LBBB, posterior infarction with anterior ST segment depression and cardiogenic	N/A	N/A	N/A	Mortality from all causes at 30 d At 30-d mortality p=0.11 Revasc 46.7% Medical therapy 56.0%	N/A	6-mo survival 6-mo mortality p=0.027 Revasc 50.3% Medical therapy 63.1%	N/A	Emergency revasc did not significantly reduce overall mortality at 30 d. However, at 6 mo significant survival benefit

						shock 2º to LV dysfunction								
Bhatt 2004 (231) 15523070	Determine use and predictors of early invasive management strategies in high-risk pts with NSTEMI	Registry-observational study trial	17,926 with NSTEMI 8,037 (44.8%) underwent early cardiac cath <48 h	8,037 (44%) underwent early cardiac cath <48 h	N/A	NSTEMI pts presenting to 248 US hospitals with cardiac cath facilities and PCI or CABG availability	N/A	N/A	N/A	Use of early invasive management within 48 h of presentation Predictors of early invasive management In-hospital mortality	N/A	N/A	N/A	Predictors of early invasive management: lower-risk pts with lack of prior or current CHF, renal insufficiency, positive biomarkers Pts treated with early invasive strategy had lower in-hospital mortality 2.5% vs 3.7%, p<0.001

1º indicates primary; 2º indicates primary; ACS, acute coronary syndromes; AMI, acute myocardial infarction; BNP, B-type natriuretic peptide; CHF, congestive heart failure; CAB, coronary artery bypass; CABG, coronary artery bypass graft; CAD, coronary artery disease; CI, confidence interval; CK-MB, creatine kinase MB; cTnT, cardiac troponin T; CV, cardiovascular; ECG, electrocardiography; ED, emergency department; eGFR, estimated glomerular filtration rate; GDF, growth differentiation factor; GP, glycoprotein; GRACE; Global Registry of Acute Coronary Events; GUSTO, Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries trial; HF, heart failure; Hx, history; LBBB, left bundle-branch block; MI, myocardial infarction; NSTE-ACS, non–ST-elevation acute coronary syndrome; NSTE, non–ST-elevation; NSTEMI, non–ST-elevation myocardial infarction; NT-pro, N-terminal pro; PCI, percutaneous coronary intervention; PURSUIT, Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy; Pt, patient; Px, prognosis; QMI, q-wave myocardial infarction; RBBB, right bundle-branch block; RCT, randomized clinical trial; RMI, recognized myocardial infarction; ROC, receiver operating characteristic; RR, relative risk; SBP, systolic blood pressure; STEMI, ST-elevation myocardial infarction; Sx, symptom; TIMI, Thrombolysis In Myocardial Infarction trial; TnI, troponin I; ULN, upper limit normal; US, United States.

Data Supplement 26. Cardiogenic Shock (Section 7.2.2)

Study Name, Author, Year	Aim of study	Study Type	Study Size (N)	Study Intervention Group (n)	Study Comparator Group (n)	Patient Population		Study group	Comparator group	Endpoints		Conclusions	Study Limitations & Adverse Events
						Inclusion Criteria	***Exclusion Criteria***			***Major Study Findings***	***Additional Findings***		

Jacobs A. et al, 2000 (232) 10985710	Determine the outcomes of pts with cardiogenic shock complicating NSTEMI	Registry Sub-study of the SHOCK trial	881	152 pts with NSTEMI and cardiogenic shock	729 pts with STEMI and cardiogenic shock	Cardiogenic shock due to LV failure	Excluded pts with missing ECG + cardiogenic shock due to mechanical complications, tamponade, cardiac catheter laboratory complication, isolated RV dysfunction, severe valvular heart disease	NSTEMI + cardiogenic shock	STEMI + cardiogenic shock	In-hospital mortality similar in the 2 groups (62.5% for NSTEMI vs. 60.4% STEMI). After adjustment, STEMI did not independently predict in-hospital mortality (OR: 1.30; 95% CI: 0.83-2.02; p=0.252)	Compared with shock pts who had STEMI, pts with NSTEMI were older and more likely to have comorbid disease, prior infarctions and MVD Left circumflex artery was the culprit vessel in 34.6% of non-ST-elevation vs. 13.4% of ST-elevation MI pts (p<5 0.001) Similar LVEF in-hospital, and similar revascularization	Pts with cardiogenic shock and NSTEMI have a higher-risk profile than shock pts with ST-segment elevation, but similar in-hospital mortality.	No hemodynamic or LV function data Registry data – subject to confounding
Holmes DR et al., 1999 (233) 10562262	Assess the incidence and outcomes of cardiogenic shock developing among pts with and without ST-segment elevation	Pre-specified sub-study from the GUSTO-IIb trial	12, 084 (of those 4,092 or 34% had NSTEMI)	200 pts developed cardiogenic shock (out of 7,986 NSTEMI pts) 2.5%	173 pts developed cardiogenic shock (out of 4,087 STEMI pts) 4.2%	Pts who developed shock after enrollment in GUSTO GUSTO eligibility criteria: chest pain of myocardial ischemia within 12 h + STE or ST-depression, or persistent T-wave inversion	Pts who had shock on presentation (n=58) + 11 pts with missing data Also excluded pts with STEMI who were not candidates for thrombolytic therapy	NSTEMI (incidence/ outcome of cardiogenic shock)	STEMI (incidence/ outcome of cardiogenic shock)	Lower OR of developing cardiogenic shock in NSTEMI compared with STEMI Incidence: 4.2% vs. 2.5% (OR: 0.58; 95% CI: 0.47-0.72; p<0.001) High 30-d mortality in both: 63% among pts with STEMI with shock vs. 73% in NSTEMI with shock (p NS)	Pts without ST-segment elevation were older, more frequently had DM and 3-vessel disease, but had less TIMI grade 0 flow at angiography Shock developed significantly later among pts without ST-segment elevation No STE was significant predictor of 30-d mortality (p=0.048)	Pts without STE developed shock much later than those with STEMI suggesting a window of opportunity to prevent shock Shock pts without STE had more high-risk clinical characteristics, more extensive CAD, and more frequent recurrent ischemia and MI before the development of shock Regardless of the initial ECG findings, Shock was associated with a marked increase in mortality.	GUSTO-IIb is a thrombolytic trial (excluded pts ineligible for thrombolytics) Subgroup analysis Different baseline risk

1º indicates primary; CAD, coronary artery disease; DM, diabetes mellitus; ECG, electrocardiogram; GUSTO, Global Use of Strategies To Open Occluded Coronary Arteries; LV, left ventricular; LVEF; left ventricular ejection fraction; MVD, multi-vessel disease; NS, nonsignificant; NSTEMI, non-ST-elevation myocardial infarction; OR, odds ratio; Pts, patients; RV, right ventricular; SHOCK, Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock; STE, ST-elevation; STEMI, ST-elevation myocardial infarction; and TIMI, Thrombolysis In Myocardial Infarction.

Data Supplement 27. Diabetes Mellitus (Section 7.3)

Study Name, Author, Year	Aim of study	Study Type	Study Size (N)	Study Intervention Group (n)	Study Comparator Group (n)	Patient Population		Study Intervention	Study Comparator	Endpoints			P Values, OR: HR: RR & 95% CI:	Study Limitations & Adverse Events
						Inclusion Criteria	*Exclusion Criteria*			*Primary Endpoint (efficacy) and Results*	*Safety Endpoint and Results*	*Secondary Endpoint and Results*		
Cannon 2001 (186) 11419424	To compare an early invasive strategy to a more conservative approach	Prospective, randomized, multicenter trial 2,220	Intervention: 1,114 vs. Comparator: 1,106	Pts ≥18 y if they had had an episode of angina (with an accelerating pattern or prolonged [>20 min] or recurrent episodes at rest or with minimal effort) within the preceding 24 h, were candidates for coronary revasc, and had at least 1 of the following: a new finding of ST-segment depression of at least 0.05 mV, transient (<20 min) STE of at least 0.1 mV, or T-wave inversion of at least 0.3 mV in at least 2 leads; elevated levels of cardiac markers; or coronary disease, as documented by a Hx of catheterization, revasc, or M	Persistent STE, 2º angina, a Hx of PCI or CABG within the preceding 6 mo, factors associated with an increased risk of bleeding, LBBB or paced rhythm, severe CHF or cardiogenic shock, serious systemic disease, a serum creatinine level of <2.5 mg/dL (221 µmol/L), or current participation in another study of an investigational drug or device	Pts assigned to the early invasive strategy were to undergo coronary angiography between 4 h and 48 h after randomization and revasc when appropriate on the basis of coronary anatomical findings	Pts assigned to the early conservative strategy were treated medically and, if their condition was stable, underwent an exercise-tolerance test (83% of such tests included nuclear perfusion imaging or echo performed according to the protocol of the institution) before being discharged	Combined incidence of death, nonfatal MI, and rehospitalization for an ACS at 6 mo	Bleeding	Death, death or MI, fatal or nonfatal MI, reshospitaliztion for MI	At 6 mo, the rate of the 1º endpoint was 15.9% with use of the early invasive strategy and 19.4% with use of the conservative strategy (OR: 0.78; 95% CI: 0.62-0.97; p=0.025).	Study excluded pts with severe comorbid conditions or other serious systemic illness	To compare an early invasive strategy to a more conservative approach	Prospective, randomized, multicenter trial 2,220

FRISC II (185) 10475181	Compare early invasive with a noninvasive treatment strategy in unstable CAD	Multicenter RCT of 2,457 pts	2,457 pts, 21.4% diabetic	Early invasive strategy N=1,222	Study comparator group: noninvasive strategy n=1,235	Inclusion: UA, NSTEMI Pts with DM– 21.4% of total but not analyzed separately	N/A	N/A	N/A	6-mo composite of death or MI 9.4% in invasive vs. 12.1% in noninvasive group (RR: 0.78, 95% CI: 0.62–0.98, p=0.031) Decrease in MI alone 7.8% in invasive vs. 10.1% in conservative group (RR: 0.77 95% CI: 0.60–0.99; p=0.045) Nonsignificant decrease in death 1.9% vs. 2.5% (HR: 0.65, 95% CI: 0.39–1.09; p=0.10)	N/A	Angina at 6 mo In pts with DM invasive strategy improved anginal Sx – 24% for invasive vs. 41% for noninvasive RR: 0.59 (0.41–0.84)	N/A	Early invasive strategy preferred in most pts with unstable CAD who have signs of ischemia or have NSTEMI Benefit is greatest in pts at higher risk at entry
Norhammar 2004 (234) 14975468	Evaluate influence of DM in outcome of unstable CAD	Randomized clinical trial	299 pts with diabetes mellitus and 2,158 without Randomization to early invasive or a noninvasive strategy	299 pts with DM	2,158 patients without DM	UA, NSTEMI Pts with DM defined as treated with diet, oral agents, or insulin Pts with DM were at higher baseline risk – more prior MI, CHF, PAD, HBP, more 3VD	N/A	N/A	N/A	1º composite of death or MI. ITT. DM remained a strong independent predictor of death and MI in multivariable analyses Invasive strategy reduced composite of death or MI in pts with DM from 29.9% to 20.6% (OR 0.61; CI 0.36–1.04, p=0.066) Invasive strategy	N/A	N/A	N/A	An invasive strategy improved outcomes for both patients with and without DM with unstable CAD DM is an independent risk factor for dearth and MI in both invasive and noninvasive groups

										reduced composite of death or MI in nondiabpatients without DM from 12.0% to 8.9% (OR 0.72; CI 0.54–0.95 p=0.019)				
Farkouh 2012 (235) 23121323	Compare strategy of aggressive medical therapy and DES vs. CABG for pts with DM and multivessel CAD	Multicenter randomized clinical trial	1,900 pts	Aggressive medical therapy plus DES, n=953	CABG, n=947	Pts with DM with angiographically confirmed MVD of ≥2 major epicardial vessels	LMCA lesions excluded Minimum follow-up 2 y	N/A	N/A	Composite of death from any cause, nonfatal MI or nonfatal stroke Composite 5-y rate 26.6% in PCI vs. 18.7% in CABG; p=0.005 5-y rate death from any cause 16.3% vs. 10.9%; p=0.049 PCI vs. CABG 5-y rate MI 13.0 vs. 6.0%;p<0.001 PCI vs. CABG Rate stroke increased with CABG 5.2% - CABG vs. 2.4% PCI; p=0.03 No subgroup analysis of pts with ACS	N/A	MACE at 30 d and 12 mo	N/A	For pts with DM and severe CAD undergoing revascularization, CABG was associated with significant reduction in death and MI, but with a significant increase in stroke compared with PCI Limitations: Trial not blinded Some prespecified subgroups had very low prevalence

1º indicates primary; 2º, secondary; 3VD, three-vessel disease; ACS indicates acute coronary syndrome; CABG, coronary artery bypass graft; CAD, coronary artery disease; CHF, congestive heart failure; DES, drug-eluting stents; DM, diabetes mellitus; HBP, high blood pressure; Hx, history; ITT, intention to treat; LBBB, left bundle-branch block; LMCA, left main coronary artery disease; MACE, major adverse cardiac events; MI, myocardial infarction; MVD, multi-vessel disease; N/A, not applicable; NSTEMI, non-ST-elevation myocardial infarction; PAD, peripheral arterial disease; PCI, percutaneous coronary intervention; Pts, patients; RCT, randomized controlled trial; RR, relative risk; Sx, symptom(s); UA, unstable angina.

Data Supplement 28. Post-CABG (Section 7.4)

Study Name, Author, Year	Aim of study	Study Type	Study Size (N)	Study Intervention Group (n)	Study Comparator Group (n)	Patient Population		Study Intervention	Study Comparator	Endpoints			P Values, OR: HR: RR & 95% CI:	Study Limitations & Adverse Events
						Inclusion Criteria	*Exclusion Criteria*			*Primary Endpoint (efficacy) and Results*	*Safety Endpoint and Results*	*Secondary Endpoint and Results*		
Kavsak 2006 16824840 (23)	Impact of new classification of MI	Retrospective analysis using CK-MB vs. TrI analysis for MI def. 258 pts with ACS	TrI vs. CK-MB Dx based on MONICA or AHA def of MI	2 SPSS CK-MB, TrI ≥20% change using 99% TrT cutoff	N/A	2 specimens CK-MB, TrI drawn at least 6 h apart	AMI prevalence" MONICA CK-MB 19.4% AHA 19.8%. TnI increase. to 35.7%	N/A	TrI vs. CK-MB p<0.001 for increase MI def using TnI	cTnI 35.7% (30.1-41.7) Relative inc 84%	N/A	Exclusion of nonischemic diseases causing Tr elevation	Impact of new classification of MI	Retrospective analysis using CK-MB vs. TrI analysis for MI def. 258 pts with ACS
Goodman 2006 16504627 (25)	Diagnostic and prognostic impact of new UDMI	Multicenter observational prospective Registry (GRACE) 26,267 ACS pts	Use of CK and -Tn 16,797 vs. CK-MB and Tn 10,719 for hospital. fatality, 14,063 vs. 8,785 for 6-mo mortality	>18 y with possible ACS with ECG abnormal or CAD history. CK, CK-MB. Tn	NS comorbity, trauma, surgery, lack of 1 biomarker	CK CK-MB Tn Follow-up for 6 mo	Tn+ levels demonstrated higher in hospital and 6-mo mortality rates than higher CK levels	N/A	In entire population, Tn+ status vs. CK status 6-mo mortality:1.6 (1.4-1.9)	Hospital fatality rates higher with Tn+ vs. CK+: 2.2 (1.6-2.9) with Tn+/CK-MB-: 2.1 (1.4-3.2)	N/A	34% in GRACE registry excluded because of use of 1 biomarker only	Diagnostic and prognostic impact of new UDMI	Multicenter observational prospective Registry (GRACE) 26,267 ACS pts
Eggers 2011 20869357 (26)	Clinical implications of relative change in cTnI levels with chest pain	Retrospective study of 454 ACS pts within 24 h of admission with 5.8 y follow-up	UDMI with presp cTnI changes from ≥20%, 50%, 100%	N/A	cTnI <99th percentile	cTnI levels	Peak cTnI level ≥99th percentile + change ≥20% in 160. 25 had no AMI by ESC/ACC criteria	N/A	N/A	All 160 had significant raised mortality HR: 2.5 (1.7-3.8) Higher TnI deltas were not associated with higher mortalities	NA	Analysis of assay could not be validated by hs Tr assay. No review of pts records for type I or 2 AMI No long-term risk assessment	Clinical implications of relative change in cTnI levels with chest pain	Retrospective study of 454 ACS pts within 24 h of admission with 5.8 y follow-up
Giannitsis 2010 (33) 20167697	Dx, perf. of hs-cTnT for detection. of NSTEMI in ACS	Retrospective cohort analysis 57 with UA	Baseline vs. and serial conc. at 3 h and 6 h	UA or NSTEMI with initial -cTnT	Immed PCI or kidney dysfunction	Hs-cTnT baseline,3,6 h delta change	Hs –cTnt Dx 61% at baseline to 100% at 6 h.	N/A	Doubling of hs-Tnt with initial 99% + pos	Delta changes and ROC opt. values spec 100% with	N/A	Admission to chest pain unit more selective than typical ED	Dx, perf. of hs-cTnT for detection. of NSTEMI in ACS	Retrospective cohort analysis 57 with UA and evolving NSTEMI

		and evolving NSTEMI				>20%,or ROC optimized value >117% 3 h, or 246% 6 h	Dx inc by 34% above std cTnT		predicted value 100% neg predicted value 88%	sens 69% and 76%		admissions		
Ie 2004 (236) 15528943	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Lindahl 2010 (32) 20691825	Hs-cTnT comparison with std cTnT for risk assessment	Prospective cohort 1,452	Effect of pos. by both assays vs. only 1 assay	ACS pts	No coronary angiography within 12 h	Both cTnT collected 48 h after randomization	+hs-TnT same 1-y mortality. Whether + or – with st-TnT	N/A	For death or AMI at 30 d + only for hs-TnT had interim risk	+hs-TnT 1-y mortality 9,2% vs. 1.6% p=0.001 For – by both assays	N/A	Pts with higher pretest risk than typical chest pain pts in ED	Hs-cTnT comparison with std cTnT for risk assessment	Prospective cohort 1,452
Cannon 2001 (186) 11419424	To compare an early invasive strategy to a more conservative approach	Prospective, randomized, multicenter trial 2,220	Intervention: 1,114 vs. Comparator: 1,106	Pts ≥18 y if they had had an episode of angina (with an accelerating pattern or prolonged [>20 min] or recurrent episodes at rest or with minimal effort) within the preceding 24 h, were candidates for coronary revasc, and had at least 1 of the following: a new finding of ST-segment depression of at least 0.05	Persistent STE, 2º angina, a Hx of PCI or CABG within the preceding 6 mo, factors associated with an increased risk of bleeding, LBBB or paced rhythm, severe CHF or cardiogenic shock, serious systemic disease, a serum creatinine level of <2.5 mg/dL (221	Pts assigned to the early invasive strategy were to undergo coronary angiography between 4 h and 48 h after randomization and revasc when appropriate on the basis of coronary anatomical findings	Pts assigned to the early conservative strategy were treated medically and, if their condition was stable, underwent an exercise-tolerance test (83% of such tests included nuclear perfusion imaging or echocardiography performed according to the protocol of the institution) before being discharged	Combined incidence of death, nonfatal MI, and rehospitalization for ACS at 6 mo	Bleeding	Death, death or MI, fatal or nonfatal MI, rehospitalization for MI	At 6 mo, the rate of the 1º endpoint was 15.9% with use of the early invasive strategy and 19.4% with use of the conservative strategy (OR: 0.78; 95% CI: 0.62-0.97; p=0.025).	Study excluded pts with severe comorbid conditions or other serious systemic illness	To compare an early invasive strategy to a more conservative approach	Prospective, randomized, multicenter trial 2,220

				mV, transient (<20 min) STE of at least 0.1 mV, or T-wave inversion of at least 0.3 mV in at least 2 leads; elevated levels of cardiac markers; or coronary disease, as documented by a Hx of catheterization, revasc, or M	µmol/L), or current participation in another study of an investigational drug or device									
Fox 2002 (187) 12241831	To compare interventional strategy and conservative strategy in pts with unstable CAD	RCT 1,810	Intervention: 895 vs. Comparator: 915	Pts were eligible for inclusion if they had suspected cardiac chest pain at rest and had documented evidence of CAD with at least 1 of the following: evidence of ischaemia on ECG (ST-segment depression, transient STE, LBBB [documented previously],	All those with probable evolving MI, including those for whom reperfusion therapy was indicated, were ineligible. Those in whom new pathological Q waves developed, or those with CK or CK-MB concentrations 2× the ULN before	Pts assigned to the interventional treatment strategy were managed with optimum antianginal and antiplatelet treatment (as for the conservative group), and enoxaparin 1 mg/kg subcutaneously 2× for 2-8 d. The protocol specified that coronary	Pts assigned to the conservative strategy were managed with antianginal and antithrombotic medication	The coprimary trial endpoints were: a combined rate of death, nonfatal MI, or refractory angina at 4 mo; and a combined rate of death or nonfatal MI at 1 y	Bleeding	Death, MI, refractory angina as individual endpoints	At 4 mo, 86 (9.6%) of 895 pts in the intervention group had died or had a MI or refractory angina, compared with 133 (14.5%) of 915 pts in the conservative group (RR: 0.66, [0.51-0.85], p=0.001).	1° endpoint driven by reduction of refractory angina with no difference in hard clinical endpoints	To compare interventional strategy and conservative strategy in pts with unstable CAD	RCT 1,810

				or T-wave inversion); pathological Q waves suggesting previous MI; or arteriographically proven CAD on a previous arteriogram	randomization, were excluded. Also excluded were those with MI within the previous mo, PCI in the preceding 12 mo, or CABG at any time.	arteriography should be done as soon as possible after randomization and ideally within 72 h								
Spacek 2002 (120) 11792138	To compare 1st d angiography/ angioplasty vs. early conservative therapy of evolving MI without persistent STE	RCT 131	Intervention: 64 vs. Comparator: 67	Rest ischaemic chest pain, lasting <20 min, within the last 24 h before randomization; ECG evidence of AMI without STE (ST-segment depressions minimally 0.1 mm in at least 2 contiguous leads and/or negative T waves or documented old LBBB/ RBBB; CK-MB higher than 1.5 × X ULN and/or positive TnI assay	Unstable post-infarction angina pectoris resistant to maximal pharmacotherapy; cardiogenic shock; acute LBBB or RBBB or STE 2 mm in 2 leads; QMI or IV thrombolysis >1 mo; coronary angioplasty or bypass surgery >6 mo; any concomitant disease which may have possible influence on	1st d angiography/ angioplasty treatment strategy guidelines were characterized by a coronary angiogram as soon as possible after randomization followed by immediate coronary angioplasty of the culprit coronary lesion + stent implantation whenever suitable	Conservative treatment strategy guidelines were characterized by initial medical treatment with coronary angiography and subsequent revasc only in the presence of recurrent myocardial ischaemia	Composite of death or nonfatal RMI 6 mo after the randomization	None	Length of the initial hospitalization and the number of subsequent hospitalizations for UAP	1° endpoint (death/ reinfarction) at 6 mo occurred in 6.2% vs. 22.3% (p<0.001). 6 mo mortality in the 1st d angiography/ angioplasty group was 3.1% vs. 13.4% in the conservative group (p<0·03).	Small sample size, interventions were done in only one high volume tertiary center	To compare 1st d angiography/ angioplasty vs. early conservative therapy of evolving MI without persistent STE	RCT 131

					1-y Px; lack of pt cooperation									

1º indicates primary; 2º, secondary; 3VD, three-vessel disease; ACS indicates acute coronary syndrome; AMI acute myocadial infarction; CABG, coronary artery bypass graft; CAD, coronary artery disease; CHF, congestive heart failure; CK, creatine kinase;; CK-MB, creatine kinase MB; Dx, diagnosis; ECG, electrocardiograph; ESC, European Society of Cardiology; GRACE, Global Registry of Acute Coronary Events; HBP, high blood pressure; Hs-cTnT, high-sensitivity cardiac troponin I; Hx, history; IV, intravenous; LBBB, left bundle-branch block; MI, myocardial infarction; MONICA, Multinational MONItoring of trends and determinants in CArdiovascular disease; NS, no(n) significance; PCI, percutaneous coronary intervention; Pt, patient; Px, prognosis; QMI, Q-wave myocardial infarction; RBBB, right bundle-branch block; RCT, randomized controlled trials; revasc, revascularization; ROC, receiver operating characteristic;RMI; RR, relative risk; cTnT, cardiac troponin T; SSPS; STE, ST-elevation; Tn, troponin; TnI, troponin I; UAP; UDMI, Universal Definition of Myocardial Infarction; and ULN, upper limit of normal.

Data Supplement 29. Chronic Kidney Disease (Section 7.6)

Study Name, Author, Year	Aim of study	Study Type	Study Size (N)	Study Intervention Group (n)	Study Comparator Group (n)	Patient Population		Endpoints			P Values, OR: HR: RR & 95% CI:	Study Limitations & Adverse Events
						Inclusion Criteria	*Exclusion Criteria*	*Primary Endpoint (efficacy) and Results*	*Safety Endpoint and Results*	*Secondary Endpoint and Results*		
Wright 2002 12353943 (237)	Compare outcomes after AMI in pts with varying degrees of renal function	Retrospective cohort study	4,426	n=3,106 with: endstage renal disease, severe renal insufficiency CrCl <35 mL/min, moderate renal insufficiency CrCl ≥35, ≤50 mL/min, mild renal insufficiency CrCl > 50 mL/min	n=1,320 with normal renal function	Consecutive pts with acute infarction between 1988 and 2000. Renal function estimated according to the Cockcroft-Gault.	N/A	Short- and long-term survival compared after pts were stratified by CrCl. In-hospital mortality : 2% in pts with normal renal function, 6% in pts with mild renal failure, 14% in pts with moderate renal failure, 21% in pts with severe renal failure, and 30% in pts with endstage renal disease; p<0.001 Post-discharge mortality in abnormal renal function vs. normal renal function Mild renal failure HR: 2.4 (CI 1.7–3.3; p<0.001) Moderate renal failure HR: 2.2 (CI: 1.5–3.3; p<0.001)	Pts with renal failure received reperfusion therapy less frequently than pts with normal renal function; p<0.001. Post-discharge death less likely in pts who received acute reperfusion therapy. OR: 0.7 (CI: 0.6–0.9) ASA OR: 0.7 (CI: 0.5–0.8) BB OR: 0.7 (CI: 0.6–0.9)	N/A	N/A	Retrospective Analysis Potential referral bias Single center study

								Severe renal failure HR: 1.9 (CI: 1.2–3.0; p=0.006) End-stage renal disease HR: 5.4 (CI: 3.0–9.7; p<0.001)			
Shlipak 2002 12353942 (238)	Determine how pts with renal insufficiency are treated during MI Determine association of renal insufficiency on survival after MI	All nongovernmental U.S. hospitals cohort study	130,099 older pts with MI 1994-1995	Mild renal insufficiency: Cr: 1.5-2.4 mg/dL n=36,756 Moderate renal insufficency: Cr: 2.5-3.9 mg/dL n=10,888	No renal insufficiency: Cr <1.5 mg/dL n=82,455	All older (age ≥65 y) Medicare beneficiaries with AMI 1994-1995	6,790 pts with severe renal insuffieciency Cr ≥4.0 mgm/dL 10,570 pts with no information on estimating CrCl	Primary: pts with moderate renal insufficiency less likely to receive aspirin, BB, thrombolytic therapy, angiography or PCI	N/A	1 y-mortality 24% with no renal insufficiency 46% with mild renal insufficiency 66% with moderate renal insuffieciency Secondary: after adjustment for pt and treatment characteristics, renal insufficiency was associated with elevated risk of death after MI Mild renal insufficiency: HR: 1.68 (95% CI: 1.68–1.73) Moderate renal insufficiency: HR: 2.35 (95% CI: 2.26–2.45)	N/A	No measurement of true GFR Size of data collected from 1994-1995 Focus on patients ≥65 y

Solomon 1994 7969280 (239)	Evaluate effect of saline, mannitol on renal function in pts undergoing coronary angiography	RCT	78	n=28, 45% saline alone for 12 h before and 12 h after	n=25 1) 45% saline plus mannitol n=25 2) 45% saline plus furosemide	78 pts with chronic renal insufficiency undergoing coronary angiography Serum Cr measure prior to and 48 h after angiography	N/A	An increase in baseline serum Cr of ≥0.5 mgm/dL within 48 h of angiography 11% with saline 28% with saline + mannitol 40% with saline + furosemide p=0.05	N/A	N/A	N/A	Hydration with 0.45% saline provides better protection against CIN than hydration plus either mannitol or furosemide Limitations: Small sample size
Charytan 2009 19423566 (240)	Evaluate effectiveness of an early invasive strategy or conservative strategy in pts with CKD admitted with UA/NSTEMI	Collaborative meta-analysis of RCT	5 randomized studies of 1,453 pts with CKD	Early invasive strategy of routine coronary angiography	Conservative strategy of selective coronary angiography	Total 1,453 pts with CKD in 5 RCT stages 3a, 3b, and 4-5 GFR calculated using modification of diet in renal disease Serum Cr measure prior to and 48 h after angiography	N/A	1-y mortality Invasive strategy associated with: Nonsignificant reduction in all-cause mortality RR: 0.76; 95% CI: 0.49–1.17; p=0.21 Nonfatal MI RR: 0.78; 95% CI: 0.52–1.16; p=0.22 Death or nonfatal MI RR: 0.79; 95% CI: 0.53–1.18; p=0.24 Significant reduction in rehospitalization RR: 0.76; 95% CI: 0.66–0.87; p<0.0001	N/A	In-hospital death, MI, death/MI, 1-y MI, rehospitalization, combined death/MI	N/A	Routine coronary angiography should be considered for pts with CKD who are admitted with NSTEMI Limitations: Publication bias Small number trials Small number of stage 4-5 CKD
Szummer 2009 19704097 (241)	Evaluate influence of renal function on effects of early revascularization in NSTEMI	Nationwide registry	23,262 consecutive NSTEMI pts ≤80 y old treated from 2003-2006	Pts revascularized within 14 d of admission, N=12,030	Patients not revascularized within 14 d of admission, n=11,232	23,262 consecutive pts ≤80 y with NSTEMI Subdivision in 5 groups eGFR ≥90 n=6,064 eGFR 60-89 n=11,509 eGFR 30-59 n=4,839 eGFR 15-29 n=572 eGFR <15/dialysis N=278	N/A	After adjustment overall 1-y mortality was 36% lower (HR: 0.64; 95% CI: 0.56–0.73; p<0.001) with invasive strategy Magnitude of survival difference similar in normal to moderate renal function groups Lower mortality observed with invasive therapy declined with lower renal function No difference in mortality in pts with	N/A	N/A	N/A	Early invasive therapy is associated with greater 1-y survival in pts with NSTEMI and mild-moderate renal insufficiency. Benefit declines with lower renal function. Limitations: Registry study Selection bias Arbitrary cut point 14 d Pts ≤80 y

						Cox regression model with adjustment for propensity score and discharge medication to assess association between early revascularization and 1-y mortality		kidney failure or in those dialysis p=0.15, HR: 1.61; 95% CI: 0.84–3.09				

AMI indicates acute myocardial infarction; BB, beta blocker; CKD, chronic kidney disease; CIN, contrast induced nephropathy; Cr, creatinine; CrCl, creatinine clearance; eGFR, estimated glomerular filtration rate; GFR, glomerular filtration rate; MI, myocardial infarction; N/A, nonapplicable; NSTEMI, Non–ST-elevation myocardial infarction; PCI, percutaneous coronary intervention; pts, patients; RCT, randomized controlled trial; RR, relative risk; UA, unstable angina; and U.S., United States.

Data Supplement 30. Women (Section 7.7)

Study Name, Author, Year	Aim of study	Study Type	Study Size (N)	Study Intervention Group (n)	Study Comparator Group (n)	Patient Population		Study Intervention	Study Comparator	Endpoints			P Values, OR: HR: RR & 95% CI:	Study Limitations & Adverse Events
						Inclusion Criteria	*Exclusion Criteria*			*Primary Endpoint (efficacy) and Results*	*Safety Endpoint and Results*	*Secondary Endpoint and Results*		
Hutchinson-Jaffe AB, Goodman SG, Yan RT, et al. Comparison of baseline characteristics, management and outcome of patients with non-ST-segment elevation acute coronary syndrome in versus not in clinical trials. Am J Cardiol. 2010;106:1389-96.	Characterize differences in clinical characteristics and clinical management between pts with NSTE-ACS in clinical trials and not in clinical trials	Retrospective case-control of several large NSTE-ACS registries	N=13,556 pts with NSTE-ACS (8.3% in clinical trials)	None	None	Pts with NSTE-ACS in 4 large prospectively collected registries: Canadian ACS I (1999 to 2001), ACS II (2002-2003), GRACE (2004-2007), and CANRACE (2008) over 10 y, ≥18 y age, within 24 h of NSTE-ACS presentation	Pts with NSTE-ACS with ACS precipitated or accompanied by a serious concurrent illness, such as trauma or GI bleeding	N/A	N/A	Pts enrolled in clinical trials were younger, more likely to be men, and had fewer comorbidities. Clinical trial pts were more likely to be on several GDMT, undergo invasive procedures (all p<0.001). Unadjusted in-hospital mortality nonclinical vs. clinical trials (2.1% vs. 0.7%, p<0.001) and 1-y (8.9% vs. 6.3%, p=0.037) In	N/A	N/A	Results too numerous to list	N/A

21059426 (242)										multivariable analysis, pts who were older, women, had Hx of CHF failure, and increased CrCr levels on presentation were less likely to be enrolled in clinical trials.				
Akhter N, Milford-Beland S, Roe MT, et al. Gender differences among patients with acute coronary syndromes undergoing percutaneous coronary intervention in the American College of Cardiology-National Cardiovascular Data Registry (ACC-NCDR). Am Heart J. 2009;157:141-8. 19081410 (243)	To assess clinical and angiographic characteristics, procedural and treatment patterns, and in-hospital outcomes between men and women	Retrospective case-control of registry data	N=199,690 pts, 55,691 women presented with NSTE-UA vs. 101,961 men	All pts underwent PCI (index)	None	Men and women with NSTE-ACS who underwent PCI in ACC-NCDR Registry 1/104-3/30/06; index PCI only	Not fitting predefined NSTE-ACS definition or not undergoing PCI	N/A	N/A	Women presented more often with NSTE-ACS than men (82% vs. 77% of men, <0.0001). Women with NSTE-ACS had more comorbidities, but fewer high-risk angiographic features than men. Women were less likely to receive ASA, GPI, and less often discharged on ASA or statin. In-hospital mortality, was similar for women and men (OR: 0.97, p=0.5). Women had higher rates of cardiogenic shock, CHF, any bleeding (7.6 vs. 3.6%, p<0.01), and any vascular complications, but subacute stent	N/A	Too numerous to list	Too numerous to list	Limited extrapolation – all subjects are registry NSTE-ACS pts

										thrombosis rates were less in women compared to men (0.43% vs. 0.57%, p=0003).				
Blomkalns AL, Chen AY, Hochman JS, et al. Gender disparities in the Dx and treatment of non-ST-segment elevation acute coronary syndromes: large-scale observations from the CRUSADE National Quality Improvement Initiative. J Am Coll Cardiol. 2005;45:832-7. 15766815 (244)	To examine differences of gender in treatment and outcomes among pts with NSTE ACS	Retrospecti ve case-control of registry data	N=35,875 pts (41% women)	None	None	35,875 pts with NSTE-ACS (14,552 women) at 391 U.S. hospitals participating in the CRUSADE initiative between March 31, 2000, and December 31, 2002	Pts excluded from this analysis included those who were transferred to another hospital, (3,210 men and 1,827 women), and pts with missing gender status (n=66)	N/A	N/a	Women were older (median age 73 vs. 65 y) and more often had DM and HTN. Women were less likely to receive acute heparin, ACE-I, and GPI and ASA, ACE-I, and statins at discharge. Men underwent more angiography/ revere then women, but among pts with significant CAD, PCI was performed similarly in men and women. NS gender difference was seen in adjusted rates of in-hospital death, reinfarction, HF, and stroke. RBC transfusion rates were higher in women (OR: 1.17; CI: 1.09-1.25)	N/A	Too numerous to list	Too numerous to list	Limited generalizability from registry data
Lansky AJ, Mehran R, Cristea E, et al. Impact of gender and	To examine gender impact on antithrombotic therapy for	Retrospecti ve analysis of ACUITY trial (prespecifie	4,157 women with NSTE-ACS (31% of total	Overall women =4, 157 GPI + heparin	Overall men =9,662 GPI + heparin (UFH or	Men and women enrolled in ACUITY trial, randomized to open-label AT	Missing data/follow-up	AT Strategy: GPI + heparin Bivalirudin + GPI	1) Men vs. women ± PCI – bleeding, net	No gender difference in 30 d composite ischemia; women significantly	In women: bivalirudin alone significantly less	Same as 1° endpoint findings at 1 y and ± PCI	30-d composite ischemia: women=7%, men=8% p=NS; 30-d bleeding:	Although prespecificed gender analysis, study was underpowered to detect difference so

antithrombin strategy on early and late clinical outcomes in patients with non-ST-elevation acute coronary syndromes (from the ACUITY trial). Am J Cardiol. 2009;103:1196-203. 19406258 (245)	ischemia vs. bleeding in pts with NSTE-ACS in ACUITY trial	d but not powered)	enrolled)	(UFH or enoxaparin) n=1,354 women vs. bivalirudin + GPI=1,386 women vs. bivalirudin =1,417 women PCI=1,190 women No PCI =2,967 women	enoxaparin) vs. bivalirudin + GPI vs. bivalirudin PCI=3,838 men No PCI=5,824 men	treatment		Bivalirudin Intervention: PCI Non-PCI	ischemia, and overall clinical benefit at 30-d 2) AT strategy on outcome in women ± PCI at 30 d	higher 30-d bleeding; net clinical outcome 30 d worse in women due to bleeding	bleeding than GPI + heparin (5% vs. 10%, p<0.0001) with no difference in composite ischemia (7% vs. 6%); no difference in bivalirudin + GPI and GPI + herparin		women=8% vs. men=3%; p<0.0001; 30-d net clinical outcome women=13% vs. men=10%; p<0.0001	regression analysis performed to account for baseline difference
Alexander KP, Chen AY, Newby LK, et al. Sex differences in major bleeding with glycoprotein IIb/IIIa inhibitors: results from the CRUSADE initiative. Circulation. 2006;114:1380-7. 16982940 (246)	To examine gender impact on GPI use, dose, bleeding in pts with NSTE-ACS in CRUSADE	Retrospective analysis of CRUSADE registry	N=32,601 total; GPI Rx=18,436 (6,084 women, 12,352 men)	Use of GPI-dose was evaluated based on pts' CrCl	Rate of dosing, excessive dosing, bleeding and outcome were compared by gender	All enrolled CRUSADE pts Jan.-Dec. 2004	Contraindicated to GPI; those without complete data including GPI dose, CrCl, follow-up	Those treated with GPI vs. not; women vs. men	Those treated with GPI vs. not; women vs. men	For GPI Rx: Rate of bleeding significantly higher in women vs. men (15.7% vs. 7.3%; p<0.0001); For those NOT GPI Rx'd: women had significantly higher bleeding rates than men (8.5 vs. 5.4%; p<0.0001)	Despite NS difference in serum Cr, women had mean CrCl significantly lower (20 mg/min) vs. men; excess GPI dose given to women significantly more than men (46.4 vs. 17.2%; p<0.0001)	Excess GPI dose associated with increased bleeding. Women (OR: 1.72; 95% CI: 1.30-2.28) Men (OR: 1.27; 95% CI: 0.97-1.66) GPI bleeding attributed risk=25% women, 4.4% men; Excess GPI dose for women vs.	N/A	N/A

												men=3.81 (95% CI: 3.39-4.27)		
Bhatt DL, Roe MT, Peterson ED, et al. Utilization of early invasive management strategies for high-risk patients with non-ST-segment elevation acute coronary syndromes: results from the CRUSADE Quality Improvement Initiative. JAMA. 2004;292:2096-104. 15523070 (231)	Determine use and predictors of early invasive management strategies in high-risk pts with NSTEMI	Registry-observational study trial	17,926 with NSTEMI in CRUSADE (women =7,353) 8,037 (44.8%) underwent early cardiac cath <48 h (women =2,842)	8,037 (44%) underwent early cardiac cath <48 h	N/A	Pts with NSTEMI presenting to 248 UShospitals with cardiac cath facilities and PCI or CABG availability	N/A	N/A	N/A	Use of early invasive management within 48 h of presentation; predictors of early invasive management; in-hospital mortality Propensity matched analyses revealed OR: 0.8 significantly favors early invasive over selective invasive in women	N/A	Female sex as predictor of early invasive OR: 0.86 (95% CI: 0.80-0.92);	Registry data estimating "real world" practice' with usual limitations of generalizability	Predictors of early invasive management: lower-risk pts with lack of prior or current CHF, renal insufficiency, positive biomarkers Pts treated with early invasive strategy had lower in-hospital mortality 2.5% vs. 3.7%; p<0.001
O'Donoghue M, Boden WE, Braunwald E, et al. Early invasive vs conservative treatment strategies in women and men with unstable angina and non-ST-	To compare the effects of an invasive vs. conservative strategy in women and men with NSTE ACS	Meta-analysis of RCTs (1970-4/2008) with gender-specific analyses	Data combined from8 trials (3,075 women and 7,075 men).	Women: Early invasive =1,571 Initial conservative =1,581	Men: Early invasive: 3,641 Initial conservative : 3,619	Pts with NSTE-ACS in 8 RCTs evaluate early invasive vs. selective invasive (if recurrent Sx) or positive stress test after initial pharmacological test	Pts with missing biomarker data excluded from high-risk analyses	N/A	N/A	Women had lower MACE with early invasive vs. initial conservative as did men without significant gender interaction. Biomarker-positive women. Early invasive vs. initial conservative for death/MI/ACS (OR: 0.67; 95%	N/A	In men: early invasive vs. initial conservative for MACE. Biomarker positive: OR: 0.56) (95% CI: 0.46-0.67) Biomarker	MACE early invasive vs. initial conservative: Women: OR: 0.81 (95% CI: 0.65-1.01) Men: OR: 0.73 (95% CI: 0.550.98)	Results persisted for 12-m follow-up. Heterogeneity between trials; trials not individually powered for sex-specific analyses

segment elevation myocardial infarction: a meta-analysis. JAMA. 2008;300:71-80. 18594042 (247)										CI: 0.50-0.88), but not in biomarker negative women and 35% higher risk of death/MI (OR: 1.35; 95% CI: 0.78-2.35)		Negative OR: 0.72 (95% CI: 0.51-1.01)		
Dolor RJ, Melloni C, Chatterjee R, et al. Treatment Strategies for Women With Coronary Artery Disease [Internet].2012 23016160 (248)	To determine efficacy and safety of early invasive vs. initial conservative strategy in women with NSTE-ACS	Meta-analyses of RCTs and systematic reviews of observational studies	7 studies early invasive vs. initial conservative for women with NSTE-ACSMI N=17,930 pts, of which 6,084 (34%) were women	Analyses run separately for different time points (6 mg, 1 y, 5 y); n=4,030 (36% women) for risk modifier studies; n=2,220 (34% women) for safety studies	N/A	Pts with NSTE-ACS in RCT of early invasive vs. initial conservative studies including FRISC-II, TACTICS-TIM-18, GUSTO-IV-ACS, ICTUS, RITA-3, TIMI-IIIB	Those with missing data	Early invasive vs. initial conservative	N/A	Women showed trend toward benefit from early invasive vs. initial conservative at 6 mo and 1 y (death/MI) OR: 0.78; OR: 0.77, respectively), but at 5 y the trend favored initial conservative (1.05; CI: 0.81-1.35); Troponin-positive women benefit from early invasive vs. initial conservative (OR: 0.56; CI: 0.32-0.97)	Increased bleeding in women vs. men in NSTE-ACS pts undergoing PCI (adjusted OR: 3.6; 95% CI: 1.6-8.3)	Early invasive showed benefit (death/MI) over initial conservative in men at 6 m (OR: 0.65; CI: 0.52-0.82; p=0.0002). Results for these at 1y (OR: 0.88; CI: 0.64-1.20); 5 y (OR: 0.91; CI: 0.53-1.56)	N/A	N/A
Glaser R, Herrmann HC, Murphy SA, et al. Benefit of an early invasive management strategy in women with acute coronary syndromes.	To determine sex differences in baseline characteristics and outcome in ACS and if women benefit from early invasive strategy	Analyses of data from TACTIC TIMI-18 by gender (multivariable logistic regression of sex as predictor of outcome– prospective	N=2,220 (women =757)	Early invasive =1,114 – Angiography 4-48 h after randomization with PCI/revasc as indicated	Initial conservative =1,106 – medical therapy – angiography/ PCI if recurrent Sx or positive stress test	Pts with NSTE-ACS without contraindications to angiography; pt received ASA (325 mg), UFH, tirofiban	Missing data, lack of follow-up (6 mo and 1 y)	Early invasive =angiography 4-48 h after randomization with PCI/revasc as indicated	Initial conservative =medical therapy – angiography/PCI if recurrent Sx or positive stress test	Women were older, had more HTN, less Hx CAD, and less positive biomarkers, no difference in TIMI risk score. Women had less severe CAD. Women benefit from early	Women who underwent PCI had higher bleeding rate vs. men (8.3% vs. 2.9%, OR: 3.6, 1.6-8.3). Rates of	For women with NSTE-ACS troponin negative OR: 1.46 (CI: 0.78, 2.72); TIMI Risk 0-2 OR: 1.59 (CI: 0.69-3.67), no	Early invasive vs. initial conservative for MACE Women: OR: 0.45 (95% CI: 0.24-0.88) adjusted for baseline difference Men: OR: 0.6 (95% CI: 0.47- 0.88) (p=0.6 for gender interaction)	This subanalysis may not be adequately powered to detect differenced among women.

JAMA. 2002;288(24): 3124-9. 12495392 (249)		RCT of early invasive vs. initial conservative strategy)								invasive vs. initial conservative in MACE (OR: 0.72; 95% CI: 0.47-1.11) overall but OR: 0.47 (95% CI: 0.26-0.83) for elevated troponin	bleeding and stroke showed in women undergoing CABG no different from men	ST segment changes OR: 1.00 (CI: 0.61-1.65)		
Chen J, Einstein AJ, Fazel R, et al. Cumulative exposure to ionizing radiation from diagnostic and therapeutic cardiac imaging procedures: a population-based analysis. J Am Coll Cardiol. 2010;56:702-11. 20619569 (250)	To determine the cumulative dose of ionizing radiation exposure of cardiac imaging over 3 y	Retrospective, observational. Administrative claims used to identify insured adults undergoing cardiac imaging	N=952,420 enrollees, n=90,121 ≥1 cardiac imaging procedure	Determine cumulative dose-cardiac procedure= myocardial perfusion imaging (CT or PET), cardiac CT, diagnostic cath/PCI, cardiac PET, MUGA, EPS/ ablation 2005-7 vs. background radiation level	3 categories were 3 mSv/y background level of naturally absorbed radiation in the U.S; 3-20 mSv/y, and 20 mSv/y (upper annual limit for occupational exposure for at-risk workers/ 5 y)	Insured adults (18-65) with 3 y data – member 1 of 5 health care markets having ≥1 cardiac imaging procedure	N/A	N/A	N/A	9.5% underwent having ≥1 cardiac imaging procedure within 3 y. Mean cumulative dose=23.1 mSv (range 1.5 mSv-544 mSv). MPI accounted for 74%; 80/100 rec >3-20 mSv; 3.3/1,000 rec >20 mSv	Myocardial imaging studies account for most of radiation-identifies potential to reduce radiation with alternate imaging	Radiation levels for comparable procedure higher in doctors' office vs. hospital. Higher in men and increasing exposure with age.	N/A	Radiation estimates, insured younger adult population studied, not specific to those with NSTE-ACS
Einstein AJ, Weiner SD, Bernheim A, et al. Multiple testing, cumulative radiation dose, and clinical indications in patients undergoing myocardial perfusion imaging.	To characterize procedure counts, cumulative estimated effective radiation doses, and clinical indications for pts undergoing MPI	Retrospective cohort study of consecutive pts undergoing MPI –single center-index exam linked to all radiation studies pre (18 y)/post (2 y) follow-	N=1,097 pts with index exam in 2006; (51.5% women)	MPI	N/A	Consecutive inpts and outpts in single center undergoing single-photon emission CT MPI (index procedure) in 2006- EPR linked records 1988-2008	Radiotherapy procedures excluded	N/A	N/A	Median procedures=15 (IQR 6-32), 4 were high-dose ionizing radiation; 31% received cumulative dose >100 mSv. Multiple MPIs performed on 39% pts, MPI accounted for majority of radiation	N/A	Women underwent more ionizing radiation procedures than men, even excluding mammogram, but cumulative effective-dose higher	Multiple outcomes-doses/types of testing. Multiple MPI performed on individual pats with highest radiation dose associated	Likely underestimation of longitudinal radiation exposure if scans could not be assess (other institutions, not known); changes in technology over time, some date imputed, single center experience.

JAMA. 2010;304:2137-44. 21078807 (251)		up								exposure.		in men. More procedure/dose in White>Blacks and Hispanics		
Einstein AJ, Henzlova MJ, Rajagopalan S. Estimating risk of cancer associated with radiation exposure from 64-slice computed tomography coronary angiography. JAMA. 2007 Jul 18;298(3):317-23. 17635892 (252)	To determine the LAR of cancer incidence associated with 64-slice CTCA radiation exposure and determine influence of age, sex, and scan protocol	Monte Carlo simulation estimation of organ doses from 64 slice CTCA- age and sex-specific LAR of cancer using BEIR VII	N/A	N/A	N/A	N/A	N/A	N/A	N/A	Doses of 8 CTCA protocols given for organs; younger women had a significantly higher LAR of cancer, especially breast and lung, from single CTCA	N/A	N/A	RR of attributable cancer vs. 80 y Male: 20 y Female RR: 23, 40 y Female OR: 11.5, 60 y Female OR: 7.0 for heart scan (slightly higher for heart/aorta scan)	Models for single CTCA scans without shielding

ACC-NCDR indicates American College of Cardiology National Cardiovascular Data Registry; ACE, angiotensin-converting enzyme; ACS, acute coronary syndromes; ACUITY, Acute Catheterization and Urgent Intervention Triage Strategy trial; ASA, aspirin; AT, antithrombins; BEIR, Biological Effects of Ionizing Radiation VII; CHF, congestive heart failure; CABG, coronary artery bypass graft; CAD, coronary artery disease; CANRACE, Canadian Registry of Acute Coronary Events; cath, catheterization; Cr, creatinine; CrCl, creatinine clearance; CRUSADE, Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the American College of Cardiology/American Heart Association Guidelines; CT, computed tomography; CTCA, Cancer Treatment Centers of America; DM, diabetes mellitus; EPR, electronic patient record; EPS, electrophisiology study; FRISC, Framingham and Fast Revascularization During Instability in Coronary Artery Disease trial; GDMT, guideline-directed medical therapy; GI, gastrointestinal; GPI, glycoprotein IIb/IIIa inhibitors; GRACE; Global Registry of Acute Coronary Events; GUSTO-IV-ACS, Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries –IV-acute coronary syndrome trial; HF, heart failure; HTN, hypertension; Hx, history; ICTUS, Invasive Versus Conservative Treatment in Unstable Coronary Syndromes trial ; IQR, interquartile range; LAR, life attributable risk; MACE, major adverse cardiac event; MI, myocardial infarction; MPI, myocardial perfusion imagin; MUGA, Multigated Wall Motion Study; N/A, not applicable; NS, not significant; NSTE-ACS, non–ST-elevation acute coronary syndrome; NSTEMI, non–ST-elevation myocardial infarction; PCI, percutaneous coronary intervention; PET, positron emission tomography; pts, patients; RCTs, randomized controlled trials; RITA, Randomized Trial of a Conservative Treatment Strategy Versus an Interventional Treatment Strategy in Patients with Unstable Angina-3 trial; RBC, red blood count; revasc, revascularization; RR, relative risk; Rx, prescription; Sx, symptom(s); TACTICS, Treat Angina With Tirofiban and Determine Cost of Therapy With an Invasive or Conservative Strategy; TIMI, Thrombolysis In Myocardial Infarction; UFH, unfractionated heparin; and U.S., United States.

Data Supplement 31. Anemia, Bleeding, and Transfusion-Relationship Between Transfusion and Mortality (Section 7.8)

Study	Aim of Study	Type of Study	Study Size	Patient Population	Primary Endpoint	Outcome	Comments
Alexander KP 2008 18513518 (253)	To describe the association between transfusion nadir HCT and outcome	Post hoc registry analysis	44,242	CRUSADE registry of NSTE-ACS pts	Numerous endpoints. Most relevant: adjusted OR for mortality with transfusion for	Adjusted OR: •HCT ≤24%: 0.67 (0.45-1.02) •HCT 24.1%-27%: 1.01 (0.79-1.30)	Transfusion only beneficial at HCT ≤24%

					HCT range	•HCT 27.1%-30%: 1.18 (0.92-1.50) •HCT >30%: 3.47 (2.30-5.23)	
Yang 2007 17711710 (254)	To assess transfusion patterns and in-hospital outcomes in pts receiving transfusions	Post hoc registry analysis	74,271	CRUSADE registry of NSTE-ACS pts	Relevant endpoints: Death and death or MI	Adjusted OR: •Death: 1.67 (1.48-1.88) •Death or MI: 1.44 (1.30-1.60)	N/A
Rao 2004 15467057 (255)	To determine the association between blood transfusion and mortality in pts with ACS	Post hoc analysis of data from 3 randomized trials	24,112	GUSTO-IIb, PURSUIT, and PARAGON pts with ACS	30-d mortality rates in transfused and nontransfused pts	Adjusted HR: •3.94 (3.26- 4.75)	Transfusion associated with increased mortality for Hct >25%
Carson 2012 22751760 (256)	Clinical guideline from the AABB on RBC transfusion	Analysis of all randomized trials of restrictive vs. liberal transfusion strategies	19 trials; 30-d mortality available in 11 trials	Published randomized trials; various pt populations	Numerous endpoints assessed. Most relevant: 30-d mortality	•Restrictive transfusion strategy: 6.9% •Liberal transfusion strategy: 8.0% •RR: 0.85 (0.7- 1.03)	N/A
Carson 2012 22513904 (257)	Cochrane Database Systematic Review	Analysis of randomized trials of restrictive vs. liberal transfusion strategies	19 trials	Various trials in context of surgery, acute blood loss/trauma, coronary care unit pts, or leukemia pts	Numerous endpoints assessed. Restrictive transfusion strategy compared to liberal transfusion strategy	•Hospital mortality OR: 0.77 (0.62- 0.95) •30-d mortality OR: 0.85 (0.70- 1.03) •MI OR: 0.88 (0.38-2.04)	N/A

AABB indicates American Association of Blood Banks; ACS, coronary artery syndrome; CRUSADE, Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the ACC/AHA Guidelines Registry; GUSTO IIb, GUSTO, Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries trial; HCT, hematocrit; MI, myocardial infarction; N/A, nonapplicable; NSTE-ACS, non-ST-elevation-acute coronary syndrome; PARAGON, Platelet IIb/IIIa Antagonism for the Reduction of Acute Coronary Syndrome Events in a Global Organization Network trial; Pts, patients; PURSUIT, Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy; and RBC, red blood cell.

Data Supplement 32. Anemia, Bleeding, and Transfusion Studies for Weight-Based and Renally-Adjusted Dosing of Anticoagulants (Section 7.8)

Study	Aim of Study	Type of Study	Study Size	Patient Population	Primary Endpoint	Outcome
Alexander 2005 16380591 (258)	Investigation of relationship between UFH, LMWH and GPI excess dosing and major outcomes	Exploratory registry analysis	3,354	NSTE-ACS pts in CRUSADE registry	Major clinical outcomes and bleeding	Adjusted OR for major bleeding with excess dosing (vs. no excess dosing): •UFH: OR: 1.08 (0.94 — 1.26) •LMWH: OR: 1.39 (1.11 — 1.74) •GPI: OR: 1.36 (1.10 — 1.68)
Melloni 2008 18657648 (259)	Exploratory analysis of CRUSADE registry examining relation between UFH dosing and bleeding	Post hoc analysis of registry	31,445	NSTE-ACS pts in CRUSADE registry	Excess dosing percent; factors associated with excess dosing; major bleeding	•Dosing of UFH above recommended weight-based dosing associated with increased major bleeding •Excess bolus OR: 1.03 (1.00 — 1.06) •Excess infusion dosing OR: 1.16 (1.05 — 1.28)
LaPointe 2007 17646609 (260)	Exploratory analysis of CRUSADE registry examining relation between enoxaparin dosing and bleeding	Post hoc analysis of registry	10,687	NSTE-ACS pts in CRUSADE registry	Inappropriate dosing percent; major bleeding and death	Excess dosing associated significantly associated with increased risk of major bleeding (adjusted OR: 1.43; CI: 1.18 — 1.75)
Taylor LA 2012 22170973 (261)	Chart review assessing incidence of bleeding in CKD pts with incorrectly dosed bivalirudin or GPI	Chart review	199	Pts undergoing PCI	Incidence and extent of bleeding (TIMI or GUSTO)	Eptifibatide: •Incorrectly dosed in 64% •Incorrectly dosed pts experienced more overall bleeding (64% vs. 35%; p=0.04), numerically more TIMI major bleeding (19% vs. 5%; no p value given), and a greater extent of bleeding (p=0.03 for TIMI bleeding and p=0.009 for GUSTO bleeding)

						Bivalirudin: •Incorrectly dosed in 28% •Bleeding rates (incorrect vs. correct) 37% vs. 21% (p=0.055) •Extent of bleeding greater with incorrect bleeding (p=0.013 for GUSTO bleeding; p=0.058 for TIMI bleeding)
Becker 2002 12040334 (262)	Pharmacokinetic/dynamic study of enoxaparin and anti-Xa activity and factors that affect anti-Xa levels	Pharmacokinetic/pharmacodynamic substudy		TIMI 11A study of ACS pts	Relationship of pt factors and anti-Xa levels	Pts with creatinine clearance <40 mL/min had sig higher trough and peak anti-Xa levels (numerous statistically significant p values for multiple comparisons)

ACS indicates acute coronary syndrome; CKD, chronic kidney disease; CRUSADE, Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes with Early Implementation of the ACC/AHA Guidelines Registry; GPI, glycoprotein; GUSTO, Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries; LMWH, low molecular weight heparin; N/A, not applicable; NSTE-ACS, non-ST-elevation-acute coronary syndrome; PCI, percutaneous coronary intervention; Pts, patients; TIMI, Thrombolysis In Myocardial Infarction; and UFH, unfractionated heparin.

Data Supplement 33. Cocaine and Methamphetamine Users (Section 7.10)

Study Name, Author, Year	Study Aim	Study Type/ Size (N)	Intervention vs. Comparator (n)	Patient Population		Study Intervention	Endpoints			P Values, OR: HR: RR: & 95 CI:	Adverse Events	Study Limitations
				Inclusion Criteria	*Exclusion Criteria*		*Primary Endpoint & Results*	*Safety Endpoint & Results*	*Secondary Endpoint & Results*			
Potentiation of cocaine-induced vasoconstriction by beta-blockade Lange RA et al. 1990 1971166 (263)	To determine whether beta-blockade augments cocaine-induced coronary vasoconstriction	Prospective; N=30	Intracoronary propranolol (n=15) vs. saline (n=15)	Pts referred for coronary arteriogram for chest pain	HTN, recent MI	Quantitative angiography performed before and 15 min after intranasal saline or cocaine; repeat measurements obtained following intracoronary propranolol	Heart rate, arterial BP, coronary sinus blood flow, epicardial left coronary arterial dimensions; Intracoronary propranolol caused no change in BP or heart rate, but decreased coronary sinus blood flow and increased coronary vascular resistance	N/A	None	Decrease in coronary blood flow ($p<0.05$); increase in coronary vascular resistance ($p<0.05$)	N/A	Small n; not randomized; intranasal cocaine during catheterization does not apply to real world pts presenting with cocaine induced chest pain; intracoronary propranolol does not pertain to intravenous BB
BB associated with reduced risk of MI after cocaine use Dattilo PB et al. 2008 17583376 (264)	Determine if rates of MI increased with BB treatment after recent cocaine use	Retrospective N=348 (60 with recent cocaine use)	BB treatment vs. no BB treatment	Admitted pts with positive urine drug screen for cocaine who received BB	Cardiac markers not obtained; pt on oral BB	N/A	In-hospital MI after BB use; lower incidence of MI after administration of BB	N/A	In-hospital mortality; trend for lower mortality in pts receiving BB	Incidence MI in BB vs. no BB 6.1% vs. 26.0% (95% CI: 10.3% — 30.0%); Mortality 1.7% vs.4.5% (95% CI: -	N/A	Included pts without ACS Sx (56% with chest pain); retrospective; did not take into consideration time of cocaine use;

				during current hospitalization						1.2% — 6.7%		did not check serum cocaine levels; urine drug screen only detects pts with cocaine use within 48-72 h. Selection bias as pts receiving BB were older, more frequent Hx of HBP and CHF, higher SBP, and higher glucose levels; mortality mainly due to non-ACS causes
BB for chest pain associated with recent cocaine use Rangel C et al 2010 20498415 (265)	Determine if rates of adverse advents associated with BB treatment in chest pain pts with recent cocaine use	Retrospective 331 (151 received BB)	BB treatment vs. no BB treatment	Chest pain pts with urine drug screen positive for cocaine	No chest pain; urine drug screen not performed or urine drug screen negative for cocaine	N/A	Death on long-term follow-up of National Death Registry (median 972 d)	N/A	ED BP; Peak Tn levels, ventricular fibrillation/tachycardia, intubation, or vasopressor agents Pts receiving BB had larger decrease in SBP in ED even after adjusting for other anti-HTN agents administered; there were no differences in any of the secondary outcome measures	BB use associated with 70% reduction in risk of CV death (HR: 0.29; 95% CI: 0.09 — 0.98)	N/A	Retrospective; unknown how recent was time of cocaine use; patients treated with BB more likely to be given nitrates in ED which may have ameliorated any cocaine induces spasm; unknown what factors may have influenced clinican to treat or not treat with BB (note: clinicians most commonly were treating pt without knowledge of cocaine use as results of drug screen pending)
Benzodiazepines and Nitroglycerine in treatment of cocaine chest pain Honderick T et al 2003 12563578 (266)	To compare the use of lorazepam and nitroglycerine in treatment of cocaine chest pain	Prospective, randomized, single-blinded controlled trial; N=27	NTG (n=15) vs. NTG + lorazepam (n=12)	Chest pain and self-reported cocaine use in the preceding 72 h	Age >45 y, chest pain duration >72 h, documented CAD, pretreatment with NTG	NTG vs. NTG + lorazepam	Chest pain relief as assessed on a 0- 10 ordinal scale was greatest in the pts treated with the combination of NTG and lorazepam.	N/A	N/A	Kruskal-Wallis testing showed a sig difference in pain relief between the 2 study groups (p=0.003) with greater pain relief noted at 5 and 10 min in the NTG + lorazepam group	None	Small n; none of the pts diagnosed with MI; lorazepam only subgroup not investigated

										(p=0.02 and 0.005 respectively)		
Diazepam, Nitroglycerin, or both for treatment of cocaine ACS Baumann BM et al 2010 10958127 (267)	To compare diazepam, nitroglycerin, or both in treatment of pts with potential cocaine-associated ACS	Randomized double-blinded trial; N=40.	Diazepam (n=12) vs. NTG (n=13) vs. both (n=15)	Chest pain and cocaine use within the preceding 24 h	<18 y age; >60 y age	Diazepam vs. NTG vs. both	Chest pain resolution as measured by a visual analog scale	Chest pain resolution equivalent in all 3 groups	Changes in BP, pulse rate, cardiac output, cardiac index, stroke volume, and stroke index	Hemodynamic parameters equivalent in all subgroups. Outcomes: though not statistically sig, changes in mean arterial pressure for diazepam, diazepam + NTG, and NTG respectively were 2.1, -12.1, and -8.4 mm Hg respectively (p=0.08)	None	Small n; only 3 pts had MI and 5 pts Dx of UA
ACS in chest pain pts after amphetamine use 2003 Turnipseed SD et al. 12745036 (268)	Determine frequency of ACS in pts presenting with methamphetamine induced chest pain	Retrospective N=36 visits in 33 pts (3 with CV events)	N/A	Nontraumatic chest pain, positive amphetamine on urine drug screen	Not admitted for MI rule out; abnormal CXR	N/A	ACS defined as MI, ischemia on cardiac stress testing, or ≥70% stenosis on cardiac cath	N/A	Cardiac arrhythmias (V-tach, V-fib, SVT)	ACS diagnosed in 9 pt visits (25%; 95% CI: 11%- 48%) 3 pt visits with arrhythmias (8%; 95% CI: 2%- 24%)	N/A	Retrospective; small n; only investigated results in admitted pts and thus ACS rate over-estimated; urine drug testing in admitted pts not done routinely

ACS indicates acute coronary syndrome; BB, beta blocker(s); BP, blood pressure; CAD, coronary artery disease; CHF, congestive heart failure; CV, cardiovascular; CXR, chest x-ray; Dx, diagnosis; ED, emergency department; HBP, high blood pressure; HTN, hypertension; Hx, history; MI, myocardial infarction; N/A, not applicable; NTG, nitroglycerin; pt(s), patient(s); SBP, systolic blood pressure; SVT, supraventricular tachycardia; Sx, symptoms; Tn, troponin; UA, unstable angina; V-fib, ventricular fibrillation;and V-tach, ventricular tachycardia.

Additional Data Supplement Tables

(These tables were created during the evidence review process but do not support a specific section of recommendations in the guideline. They are provided for transparency and completeness.)

Data Supplement A. Other (Newer) Biomarkers

Study Name, Author, Year	Study Aim	Study Type/Size (N)	Intervention vs. Comparator (n)	Patient Population		Study Intervention	Endpoints		P Values, OR: HR: RR: & 95 CI:	Study Limitations
				Inclusion Criteria	Exclusion Criteria		Primary Endpoint & Results	Secondary Endpoint & Results		
FRISC-II Wollert 2007 (269) 17848615	Effect of PGF-15 on ACS outcomes in invasive vs. conservative strategy	Multicenter prospective study (FRISC –II) 2,079	PGF-15 in intervention vs. conservative treatment outcomes	ACS with criteria for PCI or conservative strategy with PGF-15 levels	Previous heart surgery, PCI within 6 mo, bleeding tendency, high creatinine	PGF-15 with PCI or conservative strategy	2-y MACE. PGF independently predicted outcomes in conservative strategy only	Occurrence of MACE reduced with PCI with highest PGF-15 levels: 0.49 (0.33-0.73) p=0.001	2-y MACE prediction with PGF-15 levels p=0.016	PGF-15 not independently related to ST depression or Tn levels
C-NET Viswanathan 2010 (270) 20513600	Px value of H-FABP in low-int. risk ACS pts	Prospective observational cohort 955	H-FABP vs. Tn	Chest pain	Non-cardiac Chest pain. Age <18 y	H-FABP/Tn 12-24 h from Sx onset	Death/MI 12 mo H-FABP predicted outcome after multivariate adjustment	Among Tr-pts, (79% of cohort) high FH-FA bp identify pts at high risk	HR:2.62 (1.30- 5.28) p=0.0007 H-FABP for adverse events ROC 0.79 (0.74- 0.84) ROC TnI 0.77 (0.72- 0.82)	Only 53% of eligible pts enrolled because of timing. Statistical modeling/ adjustment
Charpentier 2010 (271) 20078436	Detection of AMI by H-FABP and IMA	Prospective. observational cohort 677	H-FABP vs. IMA	Chest pain and suspected NSTEMI	Age <18 y Skeletal muscle injury, trauma, renal impairment.	H-FABP and IMA on admission	Dx NSTEMI IMA not predictor of ACS Dx H-FABP predictor	H-FABP did not add info to std predicted model	IMA OR 1.23 (0.87-1.81) H-GFABP OR 4.65 (2.39-9.04) Sens 96.8% Spec 98.1%	Relatively low enrollment. Some lack of agreement on Dx by 2 physicians. Possible misclassification of UA pts. No serial testing.
Haaf 2011 (272) 21531234	BNP in Dx and risk in chest pain pts	Prospective multicenter 1,075	BNP vs. TnT	Possible ACS	ESRD with dialysis	BNP and TnT at admission and 1 h, 2 h, 3 h, 6 h	Dx accuracy of BNP for MI lower than Tn	BNP predicted 24 mo outcome more accurate than TnT AUC 0.81 vs. 0.76 p<0.001	BnP Dx: AUC: 0.74 (0.70-0.78) TnT: 0.88 (0.84-0.92) p<0.001	Clinical benefit of risk stratification BNP levels linked to factors related to outcome confusing.
Keller 2010 (273) 20447532	Copeptin in Dx of AMI	Prospective multicenter 1,386	Copeptin vs. TnI	Possible ACS	Trauma, major surgery, IV drug abuse, anemia	Copeptin and TnT on admission	TnT vs. combined C-statistic vs. TnT alone: 0.93 vs.0.84	C-statistic within 3 h chest pain combined 0.90 T alone 0.77	Combination of copeptin and TnT superior to all single or other marker detm.	Using Tn for Dx might favor tested Tr compared with copeptin

								p<0.001	(myocardial, CK-MB, BNP)	
Peacock 2011 (274) 22093206	MPO for Dx of AMI	Prospective multicenter 1,018	MPO vs. TnI	Possible ACS <8 h Sx	<18-y non-cardiac chest pain	MPO and TnT on admission	Using 90% spec. cutpoint MPO had insufficient accuracy	MPO C-statistic: ACS vs. NCCP 0.623 AMI vs. NCCP 0.666	MPO sens 18% -PV 69%, +PV 0.47 to diff ACS from non-cardiac chest pain.	Spectrum bias Physician Dx bias Differing local Tn platforms
Iversen 2009 (275) 19932776	PAPP-A as risk marker in ACS	Prospective cohort 123 NSTEMI	PAPP-A vs. std Dx (TnT)	Possible ACS NSTE	STE-ACS (evaluated separately)	PAPP-A on admission and every 6 h to 8 h	Risk for MI and death 2.66 y to 3.47 y PAPP-A related to risk for both in NSTEMI	N/A	PAPP-A risk MI p =0.02 Death p=0.03 Multivariable: combined risk 2.65 (1.40-5.03) in NSTEMI	Long time between sample collection (6 h to 8 h)
RISCA Bogaty 2008 (276) 18549920	CRP in pred 1-y outcome in ACS	Prospective cohort 1,210	CRP No comparator	Dx of UA or AMI	Transfer from other hospital	CRP on admission discharge and 1 mo later	MACE at 1-y multivariate analysis: NS predictability	NS pred of UA, MI, or death individually	Adjusted OR for MACE admission:1.04 (0.91-1.14) Discharge: 0.90 (0.77-1.06) 1 m. 1.12 (0.93-1.34)	Not stated
Kuch 2008 (277) 18940277 MONICA/KORA	CRP and TnT in short term Px in NSTEMI	Prospective cohort 697 NSTEMI (612 with STEMI)	CRP vs. Tn in 28-d mortality event	Dx of NSTEMI	STEMI separately evaluated	CRP and TnT on admission	Multivariate analysis Both CRP+ and TnT+ showed pred of 28 d mortality	In NSTEMI CRP+ but not Tr+ pred mortality: 4.59 (1.68 — 12.5) vs. 1.75 (0.55 — 5.54)	Tr+ OR 1.99 (1.15-3.44) CRP+ OR 2.05 (1.09-3.84) For 28-d mortality prediction	Possible CRP influenced by larger myocardial necrosis or longer prehospital delay
Schaub 2012 (278) 22205695	GDF-15 in early Dx and risk in AMI	Prospective multicenter 646	GDF-15 vs. TnT and BNP	ACS Sx	ESRD	Assays on admission to ED	ROC for MIAUC GDF-15 0.69 Hs-TnT 0.96 BNP 0.74	GDF-15 pred 26-mo mortality >TnT and BNP	26-mo mortality AUC GDF-15: 0.85 TnT: 0.77 p=0.002 BNP: 0.75 p=0.007	Clinical benefit of imp. risk strategy
Mega 2008 (279) 18565400	Px of TpP in ACS	Prospective multicenter 2,349 with ACS	TpP+ vs. TpP– in predicted. Compared with Tn	NSTEMI UA	STEMI evaluated separately	Assay at median 40 h from presentation	10-mo MACE TpP significant pred risk for comparative events as well as death or MI	Weak correlation of TpP with TnI, BNP, and Hs-CRP R<0.15 for each	HR for MACE: 1.45 (1.20-1.95)<0.001 adjusted for Cl. characteristic and other biomarkers: 1.51 (1.19-1.91) <0.001	TpP not measured at presentation Possible that study median inflated TpP levels
Saraf 2010 (280) 20447533	Px significant of ETA in ACS	Prospective cohort 300 with ACS on dual	Use of GTT	ACS	Sepsis, malignancy blood, Dyscrasia, anticoagulant	Assay time not stated Evaluation OT and LT	12-mo death, MI, or stroke by LT pred MACE and CV death	No correlation between OT and MACE	LT predicted MACE: 2.52 (1.34-4.71)=0.004	Antiplatelet effects of ASA and Clopidogrel. Heparin effects.

		antiplatelet therapy							CV Death: 4.2 (1.13-15.62)=0.033	Diurnal variation of TpP
Body 2010 (281) 21167826	Effect of P-selectin on Dx of AMI and risk	Prospective cohort 713	P-selectin vs. TnT with 5 other novel biomarkers	Suspected ACS	Chest trauma, ESRD, pregnancy, prisoners	Assay time at present. for P-selectin	Only P-selectin and PAPP-A Dx AMI	30-d MACE prediction: only P-selectin 1.84 (1.1-3.1) <0.001	C-statistic for MI P-selectin: 0.68 (0.63-0.73) PAPP: 0.57 (0.51-0.63)	No serial evaluation
Wang 2007 (282) 16887214	Presence of PMAs and other novel biomarkers in ACS	Prospective cohort 132 74 ACS 58 SAP	PMAs and other novel biomarkers	ACS SAP	Renal, hepatic, hematologic, immunologic disorders	Assay at presentation included IL-6, IL-8, MCP-1, sCD40L	Pts with ACS have higher levels of PMAs compared with SA	PMA, CRP, IL-6 Each confer risk for ACS	Regression analysis ACS and biomarkers PMA 1.33 (1.05-1.68) CRP 2.64 (1.01-6.89) IL-6 1.03 (1.001- 1.06)	Small observational study

ACS indicates acute coronary syndrome; ACS NSTE, acute coronary syndrome non-ST elevation; AMI, acute myocardial infarction; ASA, aspirin; AUC, area under the curve; BNP, B-type natriuretic peptide; BP, blood pressure: CK-MB, creatine kinase- MB; CRP, C-reactive protein; CV, cardiovascular; Dx, diagnosis; ED, emergency department; ESRD, end stage renal disease; ETA, End Thrombosis Act; FRISC, Fragmin During Instability in Coronary Artery Disease; GDF- 15, growth differentiation factor- 15; GTT, global thrombosis test; H-FABP, heart fatty acid- binding protein; hs-CRP, high sensitivity C-reactive protein; hs-TnT, high-sensitivity troponin T; IL, interleukin; IMA, ischemia-modified albumin; IV, intravenous; LT, lysis time; MACE, major adverse cardiac events; MCP, monocyte chemaatractive protein; MI, myocardial infarction; MPO, myeloperoxidase; N/A, not applicable; NS, not significant; NSTEMI, non-ST elevation MI; NCCP, non-cardiac chest pain; OT, occluded time; PAPP-A, pregnancy-associated plasma protein A; PCI, percutaneous coronary intervention; PMA, platelet-monocyte aggregates; Pts, patients; Px, prognosis; ROC, receiver operator curve; SA, stable angina; SAP, stable agina pectoris; sCD40L, soluble CD40 ligand; Sens, sensitivities; Spec, specificities; Std, standard; STE-ACS, ST-elevation acute coronary syndrome; Sx, symptoms; Tn, troponin; TnI, troponin I; TnT, troponin T; TpP, thrombus precursor protein; and UA, unstable angina.

Data Supplement B. Other Anticoagulants

Study Name, Author, Year	Aim of study	Study Type	Study Size (N)	Study Intervention Group (n)	Study Comparator Group (n)	Patient Population		Study Intervention	Study Comparator	Endpoints			P Values, OR: HR: RR & 95% CI:	Study Limitations & Adverse Events
						Inclusion Criteria	Exclusion Criteria			Primary Endpoint (efficacy) and Results	Safety Endpoint and Results	Secondary Endpoint and Results		
Oldgren 2011 (283) 21551462 RE-DEEM	Safety and efficacy of dabigatr in ACS	Multictr Prosp. Dose Escalation trial	1,861 on dual platelet therapy	Dabigatran bid. 50 mg 369 75 368 110 406 150 347	PC 371 Both groups ASA and clopidogrel	AMI <14 d Dual antiplatelet therapy at least 1 risk factor for CV complications	Severe stroke Bleeding diathesis Recent GI ulcer Uncontrolled HTN Anemia Recent fibrinolytic agents	4 doses of dabigatran for 6 mo	PC	6-mo bleeding Dose dependent Increase with Dabigatran Sig with 110 mg and 150 mg dose	3.8% PC pts had stroke, MI, or death vs., 3.0%-4.9% Dabigatran (not dose related)	Dabigatran reduced D-dimer in all dose groups	Bleeding Dabigatran vs. Warfarin Significant: Dabigatran 110 m: 3.92 (1.71,8.95) Dabigatran 150 mg 4.27 (1.86,9.81)	Dose-dependent increase in bleeding significant at 110 and 150 mg qd Dabigatran.
Uchino 2012 (178) 22231617	AMI risk with dabigatrn	Meta-analysis of 7 trials	30,514	Dabigatran 20,001	Warfarin 7,357 Enoxaparin	RCTs including stroke, AFIB,	Not stated	Dabigatran 6-10 d 28- 35 d	Warfarin, enoxaparin,or PC	Risk of ACS with Dabigatran higher than control	Not analyzed	Dabigatran risk with exclusion of	Dabigatran risk : 1.33 (1.03,1.71) p=0.03	Dominant effect of RE-LY trial on results of

					2,851 Or PC 371	ACS, DVT, acute embolus		12 wk 6 mo		group. Risk similar when eliminating short-term trials.		short-term trials: 1.33 (1.03 — 1.72) p=0.03		meta-analysis. MI events few and infrequent in other studies.
APPRAISE 2009 (284) 19470889	Safety and efficacy of apixaban in ACS	Multcenter prospective trial	1,715	Apixaban 2.5 bid 317 10 qd 318 10 bid248 20 qd 221 (611 total)	PC 611	MI within 7 d with at least 1 additional risk factor for recurrent events	Planned PCI ASA allergy Significant. HTN Bleeding diathesis Recent stroke Pericardial effusion	1 of 4 doses of apixaban 26-wk follow-up on ASA	PC On ASA	Clinically relevant bleeding: Apixaban increased bleeding at 10 mg qd	Similar liver enzyme elevations Apixaban and PC	Apixaban 2.5 mg bid and 10 mg qd trend toward decreased ischemic events	Bleeding with 10 mg 2.45 (1.31 — 4.61) p=0.005 Reduced ischemia 0.61 (0.35 — 1.04) p=0.07	One intracranial hemorrhage with apixaban. 2 higher-dose Apixaban arms discontinued because of excess bleeding.
Alexander 2011 (179) 21780946	Risk of events with Apixaban in ACS	Multicenter prospective trial	7,392	Apixaban 3705	PC 3687	Median 6 d after ACS with significant risk factors: prior MI, DM, HF	Planned PCI, ASA allergy, Significant HTN Bleeding diathesis Recent stroke Pericardial effusion	Apixaban 5 mg bid Median follow-up 241 d ASA	PC ASA	MACE: NS difference between apixaban and PC	Trial stopped because of major bleeding with apixaban	Bleeding Apixaban vs. PC 1.3% vs. 0.5% 2.59 (1.5,4.46) p=0.001	MACE: Apixaban vs. PC. 0.95 (0.80- 1.11) p=0.051	Only high-risk pts. No pts undergoing revascularization.
RUBY-1 Steg 2011 (285) 21878434	Safety and tolerability of darexaban	Multicenter prospective trial	1,258	Darexaban Multiregimen 939 5 mg bid 10 mg qd 15 mg bid 30 mg qd 30 mg bid 60 mg qd	PC 319	ACS <7 d from event	Bleeding diathesis Planned PCI Recent stroke Renal or hepatic Insufficiency Allergy to study drug	One of 6 regimens Darexaban 26-wk follow-up	PC 26 wk	Bleeding numerically higher in all darexaban arms than PC. Dose response effect	Safety was primary outcome	Sl Increase in efficacy outcomes Darexaban 5.6% PC 4.4%	Pooled bleeding rate for darexaban: 2.275 (1.13- 4.60) p=0.022 Dose response: 6.2,6.2,9.3% Sig for 30 bid p=0.002	Limited power for efficacy. Only relevant with dual platelet treatment
ATLAS ACS-2 TIMI-51Mega 2012 (180) 22077192	CV outcomes with Rivaroxaban in ACS	Multicenter prospective trial	15,526	Rivaroxaban 2.5 mg bid (5,174) Rivaroxaban 5 mg bid (5,176)	PC (5,176)	ACS <7 d from event	Low platelet count Low hematocrit Renal dysfunction Recent GI bleed Hx of intracranial bleed	1 of 2 rivaroxaban regimens Mean 13 mo follow-up	PC Mean 13mo follow-up	MACE Rivaroxaban lower than PC	Increased major bleeding 2.1% vs, 0.6% p<0.01	Decreased total mortality 9.2% vs. 11.0% HR:0.84 (0.74-0.95)p=0.006	Primary endpoint 8.9% vs. 10.7% 0.84 (0.74, 0.96) 9=0.008 2.5 mg dose CV death 2.7% vs. 4.1% p=0.002 Total mortality:	Increased major bleeding unrelated to CABG Large missing data

							Stroke/TIA with antiplatelets					Reduced stent-throm 0.69 (0.51, 0.93) p-0.002	2.9% vs. 4.5% p=0.002	
Meta-analysis 2012 (7)	Bleeding, outcomes in ACS	Meta-anlysis	31,286	Apixaban Dabigatran Darexaban Rivaroxaban Ximelagatran	PC or warfarin	ACS (4-71%) <6 to <14 d from event	Trials of parental AC, VKA	OAC with antiplatelet 6-31 mo	Antiplatelet with PC or warfarin	Increase major bleeding: Decrease stent thrombosis, ischemic events, no difference in overall death, net clinical benefit	Major Bleeding 3.03 (2.20-4.16) <0.01	Net clinical benefit 0.98 (0.90-1.06) Ischemic events 0.73 (0.63-0.84)<0.001 Mortality 0.90 (0.76-1.06) Stent thrombosis 0.73 (0.54-0.98)	Mixed clinical conditions Only 58% (avg) ACS <pst;y PC but also warafarin control Ximelagatran no longer active Newer antiplatelet drugs not adjuncts	

ACS indicates acute coronary syndrome; AMI, acute myocardial infarction; ASA, aspirin; AFIB, atrial fibrillation; bid, twice daily; CABG, coronary artery bypass graft; CV, cardiovascular; DM, diabetes mellitus; DVT, deep vein thrombosis; GI, gastrointestinal; HF, heart failure; HTN, hypertension; Hx, history; MACE, major adverse cardiovascular events; MI, myocardial infarction; NS, nonsignificant; OAC, oral anticoagulant; PC, placebo; PCI, percutaneous coronary intervention; Pts, patients; qd, daily; RE-LY, Randomized Evaluation of Long-Term Anticoagulant Therapy; RCT, randomized controlled trial; TIA, transient ischemic attack; and VKA, vitamin K antagonist.

Data Supplement C. Lipid Management

Study Name, Author, Year	Aim of study	Study Type	Study Size (N)	Study Intervention Group (n)	Study Comparator Group (n)	Patient Population		Study Intervention	Study Comparator	Endpoints			P Values, OR: HR: RR & 95% CI:	Study Limitations & Adverse Events
						Inclusion Criteria	*Exclusion Criteria*			*Primary Endpoint (efficacy) and Results*	*Safety Endpoint and Results*	*Secondary Endpoint and Results*		
Cannon 2006 (286) 15687136	Efficacy of high dose vs. standard dosing for CV	Meta-analysis 4 trials	27,548	High-dose statin 13,798	Standard-dose statin 13,750	Stable CAD or ACS Intensive vs. standard statin >1000 pts each	Not stated	High-dose statin	Standard-dose statin	High dose produced a significant 16% reduction in coronary death or MI Significant 16% reduction in	High-dose: Rhabdomyolysis 0.13% A to Z trial CK>10× ULN 0.15% PROVE-IT AST or ALT	Trend toward decreased CV mortality with high dose p=0.054	Coronary death or MI 0.84 (0.77- 0.91) p<0.00001 Coronary death or CV events 0.84 (0.80- 0.89) p<0.0000001	Underpowered for CV death and total death. Different duration and treatments. No individual pt data. No evaluation of benefit from statin or LDL–C level.

	outcome									coronary death or any CV event	3× ULN: 3.3% PROVE-IT			
Spencer 2007 (287) 17826369 GRACE	Use of statin at hospital discharge with ACS	Registry Retrospective analysis	8,492	Statin use with LDL-C <100 mg/dL or ≥100 mg/dL at discharge 5,710	No statin at discharge 2,782	ACS	ACS not precipitated by non-CV comorbidities	Statin use with LDL-C<100 or ≥100 mg/dL	Control	LDL levels <100 55% receiving statin at discharge LDL levels >100 72% receiving statin at discharge	N/A	Statin at time of discharge associated with MACE reduction 0.76 (0.63,0.93)	Statin at time of discharge associated with 6-mo total mortality 0.66 (0.51- 0.85)	6-mo statin use by pt self-report No info on statin types or dosages
Robinson 2009 (288) 19161879	Non-HDL–C reduction and CV risk	Meta-analysis 30 trials	11,254 1	Non-HDL–C change 14 statin 100,827 7 fibrate 21,667 6 niacin 4,445 3 others 5,102	Change in risk	Randomized PC or active control trials	<2-y trial No serious non-CV disease	Change in lipid level	Change in risk	Statins: each 1% Decrease in non-HDL-C decreased 4.5-y RR by 1% (0.98-1.00)	N/A	Fibrate and niacin models also had a 1:1 relation between non-HDL–C reduction and risk reduction	Fibrate trials vs. statin trials no different results Bayes factor K=0.49 Moderate different effect on non-HDL–C niacin vs. statin Bayes factor K=7.43	Lack of access to pt data Unknown method of endpoint adjudication. No info on fibrates=statins.
Hulten 2008 (289) 17000936	Effect of statin therapy in ACS	Meta-analysis 13 trials	17,963	Early statin in ACS Approximately 50%	No statin, PC or usual care Approximately 50%	Statin<14 d of hospitalization for ACS	Standard attain dose	Intensive statin	PC or standard statin	2-y rate of death and CV events reduced with intensive statin therapy	Comparable tolerability for intensive statins and control. Only 3 cases of rhabdomyolysis. PROVE-IT: 3.3% hepatitis in high-dose GP.	Pooled 2-y HR For intensive statin therapy MI 0.89 (0.60,1.33) Ischemia 0.68 (0.50-0.92) CV death 0.76 (0.66=0.87)	Rate of death and CV events reduction: 0.81 (0.77 — 0.87) p<0.001	Sig. statistical heterogeneity. Limited trials available. Not a pooled analysis. Adverse effects under safety box.
Sattar 2007 (290) 20167359	Risk of DM with statins	Meta-analysis 13 statin trials	4,278	Statin use 2,226	No statin 2,052	Statin Trials with >1 y follow-up in both treatment groups	Mean follow-up ≤1 y	Statin	No statin	Statin therapy was associated with a 9% increased risk of incident DM with little	Aside from DM risk, not available	Lipophilic Statins risk: 1.10 (0.99=1.22) Hydrophilic Statins risk:	DM risk: 1.09 (1.02 — 1.17) PC controlled trials: 1.10 (1.01 —	Varied methods of dx of DM. HRs not available in all trials.In 2 trials Dx based on physician reporting rather than biochemical analysis.

										heterogeneity (11%) between trials		1.08 (0.98-1.20)	1.20)	Nonstandard criteria for Dx of DM in some studies.
Javed 2010 (291) 21146668 GWTG	Discharge intensive LLT in ACS	Retrospective data base analysis	65,396	Intensive LLT regimen likely to cause >50% LDL reduction 25,036	Less intensive LLT regimen 40,360	ACS related hospitalization with LLT	Left against medical advice discontinued care Discharged to nonparticipating facility	Intensive LLT regimen	Less intensive LLT regimen	Mostly AMI pts at discharge 38% received intensive LLT and 62% less intensive LLT	N/A	Factors associated with lack of LLT Female sex Increased age Dialysis (Multivariate 95% CI<1.00)	Factors associated with intensive LLT: LLT prior to admission PCI with stent Known CAD on admission PVD Prior MI (Mltivariate 95% CI>1.00)	Discharge LLT dosing data not available on 50% of pts. Performance feedback in GWTH hospitals may influence pt care giving higher rates of LLT than general hospitals. Change in LLT dosing after not available.
Baigent 2010 (292) 21067804 CTT	Efficacy and safety of intensive LDL–C decrease	Meta-analysis 26 trials	165,138	More intensive 19,829 5 trials Statin 64,744 21 trials	Less intensive 19,783 Control 64,782	Main effect of trial to lower LDL–C 1000+ pts >2 y follow-up treatment	Lack of trial eligibility criteria	Intensive LLT regimen	Less intensive LLT regimen	MACE reduction in 4.8 y by intensive LLT 15%	No further adverse effects from lowering cholesterol including cancer risk	Reduction in revasc 19% (15-24) p<0.0001 Ischemic stroke 16% (5-26] p=0.005	MACE reduction by intensive LLT 15% (11-18) <0.0001 Major vascular events 13% 97-19) <0.0001 Total mortality 10%/1 mmol/L LDL–C Reduction 0.90 (0.87 — 0.93)	Nonsignificant excess of hemorrhagic stroke with lowering cholesterol p=0.2
Boekholdt 2012 (293) 22453571	RRs of lipid values in statin treatment	Meta-analysis 8 trials	38,153	Statin therapy	Risk with 1 SD increase in LDL–C non--HDL–C apoB	Trials with serial evaluation of TC, LDL–C, HDL–C, TG >2 y followup 1000+ participants	Lack of trial eligibility criteria	LDL–C HDL–C Apo B during statin Rx	RRs for values	Adjusted HR for major CV events Per 1-SD increase 1.16 non-HDL–C 1.14 apoB 1.13 LDL–C	N/A	HRs higher for non-HDL–C than LDL–C p=0.002 and apo B p=0.02	Adjusted HR per I-SD increase non-HDL–C :1.16 (1.12,1.19) apo B 1.14 (1.11 — 1.18) LDL–C 1.13 (1.10 — 1.17)	Fatal CV events occurring in the 1st y of therapy not accounted for. Participating trials had different inclusion criteria.
Mora 2012 (294) 22461416	CV risk in statin treated pts	Retrospective evaluation of a multice	9251	High-dose statin 80 mg Atorvastatin Approximatel	Low-dose statin 10 mg Atorvastatin Approximately	CAD	TG>600 mg/dL Unstable CAD	High-dose atorvastatin	Low-dose atorvastatin	Multivariable detection of increased residual risk Older age	Decreased residual risk: High-dose statin Aspirin use	Known baseline variables performed moderately	Residual increased risk: HTN 1.38 (1.17,1.63) DM 1.33	Excluded patients >130 mg/dL on Atorvastatin 10 mg, study was observational, novel risk factor data not available for

		nter trial		y 50%	50%					Increased BMI Male sex HTN DM Apo B BUN	Apo A1	well in discriminating future cases Harrell c index=0.679	(1.11,1.60) Male 1.33 (1.07,1.65) Age 1.13 (1.04,1.23) Apo B 1.19 (1.11,1.28) BUN 1.10 (1.03,1.17) BMI 1.09 (1.02,1.17)	the entire study group

A to Z indicates Aggrastat to Zocor; ACS, acute coronary syndrome; ALT, alanine aminotransferase; AMI, acute myocardial infarction; Apo A, Apolipoprotein A; Apo B, Apolipoprotein B; AST, aspartate aminotransferase; BMI, body mass index; BUN, blood urea nitrogen test; CAD, coronary artery disease; CV, cardiovascular; DM, diabetes mellitus; Dx, diagnosis; GP, glycoprotein; GWTG, Get With the Guidelines; HDL–C, high density lipoprotein cholesterol; HR, hazard ratio; HTN, hypertension; LDL–C, low-density lipoprotein cholesterol; LLT, lipid lowering therapy; MACE, major adverse cardiovascular events; N/A, not available; PC, placebo; PCI, percutaneous coronary intervention; PROVE-IT, Pravastatin or Atorvastatin Evaluation and Infection Therapy; Pts, patients; PVD, peripheral vascular disease; Revasc, revascularization; Rx, prescription; Sig, significant; TC, total cholesterol; TG, triglyceride; and ULN, upper limit of normal.

Data Supplement D. Blood Pressure Control

Study Name, Author, Year	Aim of study	Study Type	Study Size (N)	Study Intervention Group (n)	Study Comparator Group (n)	Patient Population		Study Intervention	Study Comparator	Endpoints			P Values, OR: HR: RR & 95% CI:	Study Limitations & Adverse Events
						Inclusion Criteria	*Exclusion Criteria*			*Primary Endpoint (efficacy) and Results*	*Safety Endpoint and Results*	*Secondary Endpoint and Results*		
Nissen 2004 (295) 15536108 CAMELOT	Antihypertensive agents on CV events in CAD and normal BP	Multicenter prospective study	1991 274 IVUS	Amlodipine 663 Enalapril 673 IVUS substudy: Amlodipine 91 Enalapril 86	PC 655 IVUS substdy: 95	Angiog.Doc. CAD Age 30- 79 DBP<100 BB, a1 blockers, Diuretics permitted	Left main CAD LVEF<40% Moderate or severe CHF >79 y	Amlodipine 10 mg or Enalapril 20 mg + IVUS Substudy 24-mo follow-up	PC	CV events in 24 mo/CV events in fewer Amlodipine vs. PC Substdy: No athero. Px in amlodipine Trend toward Px in Enalapril, progression in PC p<0.001	BP baseline 129/78 Decreased by 4.8/2.5 mm in Amlodipine, 4.9'2.4 in Enalapril increased in PC p<0.001 vs. Amlodipine and Enalapril	Individual components of primary and 2º endpoints showed trend toward fewer events with enalapril	CV events: Amlodipine: 16.6% 0.69 (0.54 — 0.88)=.003 Enalapril:20.2% 0.85 (0.67 — 1.07)=.16 NS diff between Enalapril and Amlodipine 0.81 (0.63 — 1.04)=.10	Amlodipine D/ced for edema in 5.0%. Enalapril D/C for cough in 3.9% HTN in 3.2% PC, 2.2% amlodipine, 9.5% enalapril. Limitations: extended composite endpoint, modest sample size, CIs around point estimates relatively large.

Messerli 2006 (296) 16785477	Low BP with adverse events in CAD	Multictr Ad hoc analysis	22576	BP reduction Sustained Rel. verapamil or atenolol	Outcome	Stable pts with CAD and hypertension	MI within 3 mo and Class IV or V CHF	Verapamil Purpose was to evaluate BP with outcomes, not compare agents	Atenolol	All-cause death and total MI 2.7 y/pts J-shaped curve Nadir at 119/84	Lowest outcome 120-140 systolic 70-90 diastolic	DBP Nadir for MI: 70-90 mmHg Nadir for stroke 70-90 mmHg	Primary outcome 18% vs. 9% SBP 110 vs. 120-130 32% vs. 8% DBP 60 vs. 80-90 No p values provided	2º analysis, limited to hypertensive pts with stable CAD.
PROVE-IT TIMI 22 Bangalore 2010 (297) 21060068	BP control and adverse events in ACS	Multicenter prospective study Ad hoc analysis	4162	BP level reached	Outcome MACE	ACS within 10 d Randomly assigned to Pravastatin or atorvastatin	Not stated	Pravastatin 40 mg Purpose was to evaluate BP with outcome, not to compare agents	Atorvastatin 80 mg	Composite MACE SBP followed a J- or U-shaped curve Risk Nadir: 136 mmHg systolic 85 mmHg diastolic HR 49% vs. 13% SBP<100 vs. 130-140 HR 46% vs. 15% DBP<60 vs. 80-90	Significant increased risk for outcomes As SBP decrease below 110 systol. or 70 diastolic	CAD death,nonfatal MI or revasc Similar J- or U-shaped curve. For SBP/DBP X^2=37,<0.0001 X^2=47,<0.0001 respectively	Risk for 1º outcome increased 4.9 fold with SBP<100 vs. 130-140 mmHg 136 mmHg had lowest event rate by Cox model on a continuous scale X^2 =49, p<0.0001	Ad hoc analysis limited to pts studies for lipid evaluation. Not adjusted for many confounders nor dosages of antihypertensive agents received. Cannot determine whether SBP, DBP, or mean BP is main risk
Cooper-DeHoff 2010 (298) 20606150 INVEST	Effect of tight BP control in CAD and diabetes	Observational substudy of multicenter clinical trial	6400	Tight BP control BP 130/85	Usual BP control	Stable CAD and hypertension with diabetes	Not stated	Tight BP control Verapami/trandolapril 16,893 patient/y of follow-up	Usual BP control	Composite MACE Usual control vs. uncontrolled 12.8% vs. 19.8% Tight vs. usual Control : NS diff. 12.6% vs. 12.7%	Extended analysis follow-up indicated increased risk with tight BP control	Mortality: 11.0% vs. 10.2% Tight vs. Usual 1.20 (0.99-1.45) p=0.06 Extended follow-up 1.15 (1.01-1.32) p=0.04	Tight vs. usual control MACE Usual control: 1.11(0.93-1.32)= 24	Post hoc analysis. No randomization for different BP groups. Data only applied to CAD pts with diabetes.

1º indicated primary; 2º, secondary; ACS, acute coronary syndrome; BP, blood pressure; CAD, coronary artery disease; CHF, congestive heart failure; CV, cardiovascular; DBP, diastolic blood pressure; IVUS, intravascular ultrasound; LVEF, left ventricular ejection fraction; MACE, major adverse cardiovascular events; PC, placebo; Pts, patients; Px, prognosis; and SBP, systolic blood pressure.

Data Supplement E. Diabetes Mellitus

Study Name, Author, Year	Aim of study	Study Type	Study Size (N)	Study Intervention Group (n)	Study Comparator Group (n)	Patient Population	Study Intervention	Study Comparator	Endpoints	P Values, OR: HR: RR & 95% CI:	Study Limitations & Adverse Events

						Inclusion Criteria	*Exclusion Criteria*			*Primary Endpoint (efficacy) and Results*	*Safety Endpoint and Results*	*Secondary Endpoint and Results*		
DIGAMI Malmberg 1999 (299) 10338454	Glyco-metabolic state in DM in ACS and mortality risk	Multicenter prospective study	620	Intensive Insulin 306	314 Routine diabetic therapy	DM with AMI <24 h	Not stated	Intensive insulin-glucose infusion, then sc insulin 3.4-y follow-up	Regular DM coverage	Mortality 33% died in intensive group, 44% in regular group	Admission body weight, HbA1c, pulmonary rates, heart rate were all independently linked to hyperglycemia p<0.001-0.001	Admission blood glucose HbA1c were independent predictors of mortality	Long-term mortality reduction Intensive vs. regular 28% (8-45%)p=0.011 No prior insulin and low CV risk: reduction 51%(19-70)=0.004	No indication whether increased use of insulin or decreased use of sulfonylureas decreased risk.
Diabetes Prevention Program Research Group Knowler 2002 (300) 11832527	Effects of treating elevated glucose on development of DM	Multicenter prospective study	3234	Metformin 1,073 Or lifestyle modification 1,079	PC 1,082	25 y or older BMI ≥24 FBS 95-125 Or 140-199 2-h global thrombosis test	Glucose tolerance affects medications Short life expentancy	Metformin 850 mg bid Or lifestyle Int. to reduce weight and inc exercise	PC or lack of lifestyle intervention	Incidence of DM 2.8-y follow-up Cases/100 pat-y PC 11.0 Metformin 7.8 Lifestyle 4.8	Hospitalizations and deaths NS different among groups GI sx p<0.0167 metformin vs. PC	Average weight loss PC 0.1 kg Metformin 2.1 kg Life 5.6 kg p<0.001 v. Metformin and PC	Reduced incidence vs. PC Lifestyle: 58% (48 — 66) Metformin 31 (17 — 43) Lifestyle vs. metformin 39%[24-51%]	GI Sx highest in metformin group and musculoskeletal highest in lifestyle GP Incidence of DM in PC group higher than anticipated
Suleiman 2005 (301) 15699267	Fasting glucose and 30-d mortality in AMI	Prospective cohort observational study	735	Fasting glucose	Admission glucose	Non-DM AMI <24 h	>24 h from Sx onset, inflammatory disease, surgery or trauma preceding mo	Fasting blood glucose	Admission blood glucose	30-d mortality compared with FBG <110, adjusted 30 d-mortality increased with increasing tertile of FBG	30-d death and heart failure vs. normal FBG: Impaired FBS: 2.6 (1.3-5.0)=0.004 FBS ≥126: 5.8 (2.2 — 10.3) <0.0001	30 d-mortality compared with normal AG and FG Elevated FG and AG: 9.6 Elevated AG and Normal FG 3.4	30-d mortality by tertile vs. normal FBS 1st: 4.6 (1.7 — 12.7) P=0.003 2nd: 6.4 (2.5 — 16.6) P<0.0001 3rd: 11.5 (4.7 — 20.0) P<0.0001	Did not attempt to evaluate for undiagnosed DM Significant overlap in HbA1c levels in AMI in known or newly diagnosed DM and no DM
Sinnaeve 2009 (302) 19237725 GRACE	Elevated FBS in ACS and	Multicenter retrospective	13,526	Range of FBS	In-hospital and 6-mo mortality	ACS	Noncardiac chest pain	Admission and FBS 6-mo follow-up	Mortality in-hospital 6 mo	Higher FBS associated with graded in-hospital and 6-mo	Major bleeding complications increased with	6-mo death: FBS <100 vs. 100- 125	6 mo-mortality: FBS 126 — 199 mg/dL 1.71 (1.25 —	Retrospective analysis, unmeasured variables not accounted for, hospital glucose levels may not

	mortality	study								mortality. 6 mo sig higher with FBS above 125 mg/dL vs. <100 mg/sL	higher FBS. Stroke level unrelated to glucose level.	NSTEMI: 4.66 vs. 7.14I% UA: 2.56 vs.2.28	2.34) FBS≥300: 2.93 (1.33 — 6.33) But not 200 — 299: 1.08 (0.60 — 1.95)	reflect "true" glucose levels. Because of glucose infusions, some FBS levels might not have been truly fasting levels.

ACS indicates acute coronary syndrome; AG, admission glucose; AMI, acute myocardial infarction; bid, twice daily; CV, cardiovascular; DM, diabetes mellitus; FBG, fasting blood glucose; FBS, fasting blood sugar; FG, fasting glucose; GI, gastrointestinal; GP, glycoprotein; HbA1c, Hemoglobin A1c; NS, nonsignificant; NSTEMI, non-ST-elevation myocardial infarction; PC, placebo; Sig, significant; Sx, symptom; and UA, unstable angina.

Data Supplement F. Smoking Cessation

Study Name, Author, Year	Aim of study	Study Type	Study Size (N)	Study Intervention Group (n)	Study Comparator Group (n)	Patient Population		Study Intervention	Study Comparator	Endpoints			P Values, OR: HR: RR & 95% CI:	Study Limitations & Adverse Events
						Inclusion Criteria	*Exclusion Criteria*			*Primary Endpoint (efficacy) and Results*	*Safety Endpoint and Results*	*Secondary Endpoint and Results*		
Daly 1983 (303) 6409291	Persistence of smoking cessation after ACS	Prospective cohort study	498	Smoking cessation 217 Nonsmokers at entry and follow-up 147	Continued smoking 157	Survived 1st attack of ACS by at least 28 d	Nonsmokers at entry who started to smoke died within 2 y of entry.	Follow up by life tables for 13 y beyond 2 y survival stopped smoking	Continued smoking	Mortality 13-y life tables beyond 1st 2 y from ACS Stopped smoking vs. continued smoking was 2.8× lower	Vascular causes of death: 68% 24% MI 35% sudden death NS diff among 3 groups	Mortality of previous nonsmoker 62.1% n=124 Average annual RR of death: 2.4× for smokers vs. stopped p<0.01	Mortality 2-15 y beyond ACS: stopped vs. continued 36.9% vs. 82.1% p<0.01	Average annual mortality: stopped vs. continued smoking Initial ACS St Cont RR UA 1.9 10.0 5.4; p<0.01 MI uncomp 3.9 8.6 2.2 p<0.05 MI comp 4.7 12.4 2.7 p<0.01
Jorenby 2006 (304) 16820547	Efficacy and safety of varencline	Multicenter Prospective Study	1,027	Varencline 344 Bupropion 342	PC 341	18-75 y. 10+ cigarettes/d during previous y No abstinence longer than 3 mo	Previous use of bupropion. Contraindications to medications. Sig CV disease; HTN; pulmonary disease; depression	Varencline 1 mg bid Bupropion SR 150 mg bid 12 wk + brief counseling 12 wk with 40-wk follow-	PC+brief smoking cessation counseling	Continuous abstinence: wk 9-12 Varecline vs. PC: 43.9% vs. 17.6% Bupropion vs. PC: 29.8% vs. 17.6%	>10% side effects: Bupropion Insomnia 21% Varencline Nausea 29% Abnormal dreams 13.1%	Wk 9-52 Abstinence Varecline vs. PC 23% vs. 10.3% 2.66 (1.72,4.11) p<0.001	Abstinence 9-12 vs. PC 3.85 (2.69,5.50) p<0.001 9-12 Bupropion vs. PC: 1.90 (1.38- 2.62) p<0.001	Volunteers. Minimal counseling may confound results. Exclusion of depression. 35% did not complete follow-up period. Dropout rate for adverse events higher in PC group.

								up			Headache 12.8%	Bupropion vs. PC 1.77 (1.19,2.63) p=0.004		
Tonstad 2006 (305) 16820548	Effect of varenicline on smoking cessation	Multicenter Prospective Study	1,210	Varencline 603	PC 607	18-75 y. 10 cigarettes/d + smoking cessation Ation after 12 wk of varenicline	Unstable disease, depression, COPD, CV disease within 6 mo, uncontrolled HTN, smoking cessation aid	12-wk open label vs. if stopped smoking Randomized for 40 wk	PC	Continued abstinence Wk 13-24 Varenicline vs. PC 70.5% vs. 49.6% Wk 13- 52 43.6% vs. 36.9%	Major adverse Effects: Varenclin Nasopharyngitis 4.8% Headache 2.8% Psych disorders 6.4%	N/A	Abstinence vs. PC Wk 13-24 2.48 (1.95-3.16)<0.001 Wk 13-52 1.34 (1.06,1.69)=0.02	Generally healthy group. No depression. CO may not evaluate complete check on self-report of nonsmoking. Those lost to follow-up differed between groups.
Rigoitti 2006 (306) 17145253	Bupropion in smokers with ACS	Multicenter Prospective Study	248	Bupropion 124	PC 124	Smoked >1 Cigarette in previous mo CAD admissions	Not willing to stop Smoking. Risk of seizure, sig. HTN, heavy alcohol use, depression, liver or renal disease, illegal drug use	Smoking counseling to 12-wk postdischarge Bupropion SR 1-y follow-up	Same smoking counseling PC	Abstinence and CV events 3 m and 1 y Borderline Sig abstinence at 3 mo only. NS diff in outcome events	Noncardiac serious adverse events: NS 3 mo: 1.31 (0.62,2.77) 1 y: 1.34 (0.64,2.84)	CV mortality 1 y Bupropion vs. PC 0% vs. 2% CV events 1 y: 26% vs. 18% 1.56 (0.91,2.69) NS	Abstinence vs. PC 3 mo: 37.1% vs. 26.8% 1.61 (0.94,2.76)=0.08 1 y: 25.0% vs. 21.3% 1.23 (0.68,2.23) NS	1/3 lost at 1 y. Study not powered to detect less than a 1.8-fold increase in cessation rates with bupropion. Many eligible declined to enroll. Reluctance to be randomized to PC.
PREMIER Registry Dawood 2008 (307) 18852396	Predictors of smoking cessation after AMI	Retrospective from registry	639	342 smokers at 6 m	297 Nonsmokers at 6 mo	AMI Smoker >18 y age	Transfer to hospital >24 h from AMI Did not speak English or Spanish. Could not consent	Smoking behavior by self-report During hospital and 6 mo in pt smoking cessation program Continued smoking	Same but stopped smoking at 6 mo	6-mo post MI: 46% had stopped Odds greater for those receiving discharge recommendations for cardiac rehab or smoking cessation facility	Not evaluated	Hospital smoking cessation counseling did not predict cessation: 0.80 (0.51,1.25) Depressive pts during MI less likely to quit:	Smoking cessation with rehab: 1.80 (1.17-2.75) Treated at smoking cessation facility: 1.71 (1.03=2,83)	Limited insights on smoking cessation programs available at different hospitals. Loss to follow-up. Self-reporting assessment without biochemical evaluation. Unmeasured confounding.

												0.57 (0.36-0.90) p<0.05		
Mohuiddin 2007 (308) 17296646	Intensive smoking cessation intervention in acute CV disease	Prospective randomized cohort	209	Intensive intervention 109 2 y follow-up	Usual care 100 2-y follow-up	30-75 y Daily smokers >5 y in CCU with AMI or heart failure	Alcohol or illicit drug use Unfamiliar with English	30-min counseling before discharge. Intensive counseling for 3 mo + pharmacotherapy in 75%	Same counseling before discharge only.	At each follow-up interval, point prevalence and continued abstinence greater in the intensive treatment group	Over 2-y period more in UC group Hospitalized RR reduction:44% (16,63)=0.007	2-y all-cause mortality: 2.8% intensive vs. 12.0% UC RR reduction: 77% (27, 93%) p=0.014	2-y abstinence: 33% intensive vs. 9% UC p<0.0001	Small sample size-lacking multivariate analysis to adjust for other factors on outcome. Pharmacotherapy at no cost. Question of whether results would have been achieved if smokers purchased their own medications.
Smith 2009 (309) 19546455	Hospital smoking cessation in CAD with long-term effects	Multi-institute Prospective Study	275	Intensive smoking cessation intervention 136	Minimal intervention 139	18 or older Smoked in previous mo AMI or CABG admission	Pregnant Medically unstable Lived in an institution No English Psychiatric disorder Substance abuse	Minimal intervention + 45-60 min bedside counseling 7 telephone counseling sessions after discharge	Minimal intervention 2 pamphlets No smoking message by physician	1-y abstinence self-reported 62% intensive GP vs. 46% minimal GP Confirmed: 54% intensive GP vs. 35% minimal group	Not evaluated	Abstinence lower in those using pharmacotherapy p<0.01 Abstinence higher in CABG vs. MI pts p<0.05	1-y abstinence self-reported: 2.0 (95% CI: 1.2-3.1) Confirmed: 2.0 (CI: 1.3-3.6)	Pharmacotherapy used by 34% of pts in both groups. Slightly less than ½ smokers did not want to quit or refused to participate. Exclusion of pts with substance abuse or psychiatric comorbidities, many of whom are smokers, limits generalizability of results.
Rigotti 2008 (310) 18852395	Hospital smoking cessation intervention with 6-mo follow-up	Meta-analysis of 33 trials	6,252 (using numbers in Figure 1 and 2)	Intensive intervention counseling 2,673 Pharmacotherapy 332	Usual care or control counseling 2,935 No pharmacotherapy 312	Hospitalized and current smokers	Trials not recruiting on basis of smoking, Hx, Hospitalization with psychiatric disorder, or substance abuse	Intensive intervention with or without pharmacotherapy	Usual care with minimal smoking counseling	Smoking cessation rates 6-12 mo decreased with smoking counseling. No benefit with less postdischarge contact.	Not evaluated	Adding NRT produced a trend toward efficacy vs. counseling alone: 1.47 (CI: 0.92- 2.35)	Smoking cessation 6-12 mo with counseling: 1.65 (CI: 1.44-1.90)	Benefit of adding bupropion limited to 1 study. Counseling intervention not delivered by staff responsible for patient care. Only 1/2studies used sustained abstinence to assess outcome, the rest point prevalence
Colivicchi 2011 (311) 21741609	Smoking relapse rate after quitting following ACS	Prospective cohort study	813	12-mo relapse 813 (of 1,294 not relapsing)	Predictors of relapse	Previous smokers who stopped after ACS following hospital	Major concurrent illness, depression, alcohol and drug abuse,	Several in-hospital counseling sessions. 12-mo follow-up	Predictors of relapse	Age and female sex were predictors of relapse. Pts in cardiac rehab and pts	Resumption of smoking predicted 1-y mortality: 3.1 (CI: 1.3-5.7) p=0.004	Age and resumption: 1.034 (1.03,1.04) p=0.001 Female:	Cardiac rehab and abstinence: 0.74 (CI: 0.51-0.91)=0.02 DM and abstinence:	Sig diff in age and CV risk factors in cohort. Questions about sens of troponin assay for Dx of AMI

						discharge	renal, lung, liver disease, stroke, malignancy			with DM more likely to remain abstinent		1.23 (1.09,1.42)	0.79 (CI: 0.68-0.94)=0.03	
Planer 2011 (303) 21403011	Efficacy of bupropion in smoking cessation after AMI	2 center prospective study	149	Bupropion 74	PC 75	Smokers hospitalized for ACS Smoking >10 cigarettes/d Intention to quit smoking	Prior use of bupropion in past y or NRT in past 6 mo Prior head trauma, depression, bulimia liver or kidney disease, pregnancy	Bupropion 150 mg bid for 2 mo 1-y abstinence evaluation	PC Same abstinence evaluation	Abstinence rates at 3 mo, 6 mo and 1 y were not increased by bupropion	Bupropion safe. NS diff vs. PC in: death, any hospitalizations, MI, ACS, Chest pain	Adverse effects attributed to treatment was a negative predictor of smoking cessation: 0.23 (95% CI: 0.07-0.78)	3-mo abstinence: Bupropion vs. PC: 45% b 44% p=0.99 6 mo. Abstinence: Bupopion vs. PC: 37% vs. 42% p=0.61 1-y abstinence: 31% vs. 33% p=0.86	Recruitment stopped early after interim analysis limiting sample size. Self-reports of quitting, no biochemical confirmation. High self-reports of quitting in PC group. Dizziness more common than PC 14% vs. 1.4% p=0.005

ACS indicates acute coronary syndrome; AMI, acute myocardial infarction; bid, twice daily; CAD, coronary artery disease; CABG, coronary artery bypass graft; CCU, coronary care unit; CO, COPD, chronic obstructive pulmonary disease; CV, cardiovascular; Diff, difference(s); DM, diabetes mellitus; GP, glycoprotein; HTN, hypertension; Hx, history; MI, myocardial infarction; N/A, not available; NRT, nicotine replacement therapy; NS, nonsignificant; PC, placebo; Pt, patient; RR, relative risk; Sens, sensitivity; Sig, significance; SR, sustained release; UA, unstable angina; and UC, usual care.

Data Supplement G. Weight Management

Study Name, Author, Year	Aim of study	Study Type	Study Size (N)	Study Intervention Group (n)	Study Comparator Group (n)	Patient Population		Study Intervention	Study Comparator	Endpoints			P Values, OR: HR: RR & 95% CI:	Study Limitations & Adverse Events
						Inclusion Criteria	Exclusion Criteria			Primary Endpoint (efficacy) and Results	Safety Endpoint and Results	Secondary Endpoint and Results		
Nordmann 2006 (312) 16476868	Low-carb vs. low-fat diets on weight loss and CV risk	Meta-analysis	447 5 trials	Low carb 222	Low fat 225	Randomized controlled low carb vs. low fat, BMI≥25, Follow-up 6 mo + Age 16+	Trials with cross-over or sequential design	Low-carb weight loss at 6 and 12 mo	Low fat same	Weight loss to 6 and 12 mo. 6 mo: low carb>weight loss. 12 mo: NS difference	Trend toward lower BP in low carb group at 6 mo only. TG and HDL changed more favorably in high-carb diets, LDL-C in low-fat diets	In diabetics, HbA1cdec. In low carb gp. vs. low fat: 12 mo -0.7% vs.-0.1% p=0.02	Weighted mean difference 6 mo Low carb vs. low fat -3.3 kg (-5.3,-1,4) 12 mo. -1.0 kg (-3.5,1.5)	Substantial losses to follow-up. No blinded outcome assessment. Had to use ITT analysis because of dropouts. Heterogeneity concerning main outcome.

Chow 2010 (313) 20124123	Adherence to behavioral recommendation in CV risk	Multicenter Observational substudy	18,809	Adherence to diet, exercise, smoking cessation	Nonadherence to individual components	UA, NSTEMI Age 60+ y	Contraindication to LMW heparib, recent hemorrhagic stroke AC for other than ACS, high creatinine	Survey at 30, 90, 180 d on 3 lifestyle values adherence	No diet, exercise, No smoking cessation	CV events at 6 mo decreased with exercise onlyand diet + exercise and ex-smoker vs. persistent smoker	Side effects not addressed	Decreased independent risk of stroke/MI/death All 3 with diet/exercise Death with ex-smoker vs. continued smoker	Risk of CV events Exercise vs. no 0.69 (0.54,0.89)]=.0037 Exercise/diet vs. no 0.46 (0.38- 0.57) <0001 Ex-smoker vs. smoker 0.68 (0.51- .90).0067	No active study intervention program. Self-report of outcomes. No details of actual diet and exercise quantification. Adherers/nonadherers categorized only at 30-d follow-up.
Gadde 2011 (314) 21481449	Efficacy and safety of Qnexa	Multicenter prospective trial Phase 3	2,448	Phenteramine/Topiramate 7.5mg/46mg 488 P/T 15/92mg 981	PC 979	Age: 18-70 BMI: 27-45 Or diabetes 2 or more CV risk factors	BP >160/100 FBS >13.32 mmol/L TG >4.52 mmol/L Type 1 diabetes or Type 2 managed with antidiabetic drugs except for metformin	Phenteramine/ Topiramate 1 of 2 dosages for 56 wk	PC for same period	Proportion of pts achieving at least 5% weight loss: Low-dose Qnexa: 62% High-dose Qnexa:70% PC: 21%	Adverse effects vs. PC 10% or more with sig dif: Dry mouth 21% Paresthesia 21% Constipation 17% Dysgeusia 10% Headache 10% Cognitive (sig Attention dist 4%	>10% weight loss Low-dose Qnexa 37% p<0.0001 High-dose Qnexa 48% p<0.0001 PC 7%	5% weight loss: Low-dose Qnexa OR: 6.3 (4.9-8.0) p<0.0001 High-dose Qnexa OR: 9.0 (7.3-11.1) p<0.0001	Endpoint assessment not available for 31% of sample. Restriction of upper limit to BMI: 45. Lack of ethnic diversity (86% white), few men (30%). No active comparator group such as orlistat or lorcaserin
Garvey 2012 (315) 22158731	Long-term efficacy and safety of Qnexa	Multicenter prospective trial Extension of previous trial (4)	676 Out of original 2,448	Phenteramine/Topiramate 7.5mg/46mg 173 P/T15/92mg 295	PC 227	See above agreed to extension	See above	See above 52-wk extension	PC for same period	Percentages achieving >5%, >10%, >15% and >20% weight loss in 108-wk period, in all 4 categories, Qnexa low and high dose >PC	Change in percentages Adverse effects were 0-56 vs. 56-108 High-dose Q constipation 21% to 4% Paresthesia 21% to 2.4% Dry mouth	Percentage changes in BP, lipid, DM meds: High-dose Q BP: -9.8% Lipid: +4.7% DM: 0% Low-dose Q BP: -3.9%	>5% weight loss Low dose: 79.3% High dose: 75.2% PC: 30.0% p<0.0001 >10% weight loss Low dose: 53.9 High dose: 50.3% PC: 11.5% p<0.0001 >15% weight loss Low dose: 31.9%	Discontinuation rates similar to 1st 56-wk period above. Higher rate lost to follow-up in the 15/92 arm. Impact of Rx of dyslipidemia and HTN on secondary cardiometabolic variables. Type of adverse events similar to 1st 56-wk period but incidence rates lower.

											20% to 1.4% upper respitory infection 18.6% to 15.3% Nasopharyngitis 13.2% to 8.8% Depression NS From PC	Lipid:+5.2% DM: +1.9% PC BP: +3.5% Lipid:+17.2% DM: +7.1%	High dose: 24.2% PC: 6.6% p<0.0001 >20% weight loss Low dose 9.2% High dose: 15.3% PC: 2.2% p=.0072 for low dose <0.0001 for high dose.	

AC indicates anticoagulant; ACS, acute coronary syndrome; BMI, body mass index; BP, blood pressure; CV, cardiovascular; DM, diabetes mellitus; FBS, fasting blood sugar (glucose); HbA1c, Hemoglobin A1C; HDL–C, high-density lipoprotein cholesterol; HF, heart failure; HTN, hypertension; ITT, intention-to-treat; LDL-C, low-density lipoprotein cholesterol; LMW, low molecular weight; MI, myocardial infarction; NS, no(n) significance; NSTEMI, non-ST-elevation myocardial infarction; PC, placebo; Pt, patient; Rx, prescription; TG, triglycerides; and UA, unstable agina.

Data Supplement H. Cardiac Rehabilitation

Study Name, Author, Year	Study Aim	Study Type/ Size (N)	Intervention vs. Comparator (n)	Patient Population		Study Intervention	Endpoints			P Values, OR: HR: RR: & 95 CI:	Adverse Events	Study Limitations
				Inclusion Criteria	*Exclusion Criteria*		*Primary Endpoint & Results*	*Safety Endpoint & Results*	*Secondary Endpoint & Results*			
Goel, K et al Circulation. 2011; 123: 2344-2352 (316) 21576654	Assess CR participation and impact on mortality	2,395	CR (1431) vs. non-CR (964) participants	PCI registry, Olmstead County	No prior pt authorization	At least 1 CR outpatient session	All-cause mortality HR	Subsequent MI, PCI-NS	Death, PCI, MI, CABG p=0.28	HR 0.54 (0.41-0.71) p<0.001	Events in CR=83; in non-CR=139	Observational, Cohort
Hammil, Circulation. 2010;121:63-70 (317) 20026778	Characterize dose-response for # CR sessions	30,161 (6,181 with AMI as qualifying reason for CR)	Internal: cumulative comparison with # of CR sessions ("dose")	Medicare 5% sample 2001-2005	None identified	At least 1 CR outpatient session billed to Medicare	Death	Subsequent hospitalization	MI	Death HR 0.86 (0.76-0.97) for those attending >6 sessions	Subsequent hospitalization	Observational, sample of Medicare claims

AMI indicates acute myocardial infarction; CABG, coronary artery bypass graft; CR, cardiac rehabilitation; HR, hazard ratio; MI, myocardial infarction; NS, not significant; PCI, percutaneous coronary intervention; Pt, patient; and RR, relative risk.

References

1. Antman EM, Cohen M, Bernink PJ, et al. The TIMI risk score for unstable angina/non-ST elevation MI: A method for prognostication and therapeutic decision making. JAMA. 2000;284:835-42.
2. Boersma E, Pieper KS, Steyerberg EW, et al. Predictors of outcome in patients with acute coronary syndromes without persistent ST-segment elevation. Results from an international trial of 9461 patients. The PURSUIT Investigators. Circulation. 2000;101:2557-67.
3. Granger CB, Goldberg RJ, Dabbous O, et al. Predictors of hospital mortality in the global registry of acute coronary events. Arch Intern Med. 2003;163:2345-53.
4. Chase M, Robey JL, Zogby KE, et al. Prospective validation of the Thrombolysis in Myocardial Infarction Risk Score in the emergency department chest pain population. Ann Emerg Med. 2006;48:252-9.
5. Lyon R, Morris AC, Caesar D, et al. Chest pain presenting to the Emergency Department--to stratify risk with GRACE or TIMI? Resuscitation. 2007;74:90-3.
6. Hess EP, Perry JJ, Calder LA, et al. Prospective validation of a modified thrombolysis in myocardial infarction risk score in emergency department patients with chest pain and possible acute coronary syndrome. Acad Emerg Med. 2010;17:368-75.
7. Lee B, Chang AM, Matsuura AC, et al. Comparison of cardiac risk scores in ED patients with potential acute coronary syndrome. Crit Pathw Cardiol. 2011;10:64-8.
8. Sanchis J, Bodi V, Nunez J, et al. New risk score for patients with acute chest pain, non-ST-segment deviation, and normal troponin concentrations: a comparison with the TIMI risk score. J Am Coll Cardiol. 2005;46:443-9.
9. Christenson J, Innes G, McKnight D, et al. A clinical prediction rule for early discharge of patients with chest pain. Ann Emerg Med. 2006;47:1-10.
10. Backus BE, Six AJ, Kelder JC, et al. Chest pain in the emergency room: a multicenter validation of the HEART Score. Crit Pathw Cardiol. 2010;9:164-9.
11. Fesmire FM, Martin EJ, Cao Y, et al. Improving risk stratification in patients with chest pain: the Erlanger HEARTS(3) score. Am J Emerg Med. 2012.
12. Hess EP, Brison RJ, Perry JJ, et al. Development of a clinical prediction rule for 30-day cardiac events in emergency department patients with chest pain and possible acute coronary syndrome. Ann Emerg Med. 2012;59:115-25.
13. Pollack CV, Jr., Sites FD, Shofer FS, et al. Application of the TIMI risk score for unstable angina and non-ST elevation acute coronary syndrome to an unselected emergency department chest pain population. Acad Emerg Med. 2006;13:13-8.
14. Go J, Narmi A, Sype J, et al. Impact of renal dysfunction on the prognostic value of the TIMI risk score in patients with non-ST elevation acute coronary syndrome. Coron Artery Dis. 2011;22:411-5.
15. Huynh T, Nasmith J, Luong TM, et al. Complementary prognostic values of ST segment deviation and Thrombolysis In Myocardial Infarction (TIMI) risk score in non-ST elevation acute coronary syndromes: Insights from the Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms (PRISM-PLUS) study. Can J Cardiol. 2009;25:e417-21.
16. Eagle KA, Lim MJ, Dabbous OH, et al. A validated prediction model for all forms of acute coronary syndrome: estimating the risk of 6-month postdischarge death in an international registry. JAMA. 2004;291:2727-33.
17. Eggers KM, Kempf T, Venge P, et al. Improving long-term risk prediction in patients with acute chest pain: the Global Registry of Acute Coronary Events (GRACE) risk score is enhanced by selected nonnecrosis biomarkers. Am Heart J. 2010;160:88-94.
18. Abu-Assi E, Ferreira-Gonzalez I, Ribera A, et al. "Do GRACE (Global Registry of Acute Coronary events) risk scores still maintain their performance for predicting mortality in the era of contemporary management of acute coronary syndromes?". Am Heart J. 2010;160:826-34.
19. Meune C, Drexler B, Haaf P, et al. The GRACE score's performance in predicting in-hospital and 1-year outcome in the era of high-sensitivity cardiac troponin assays and B-type natriuretic peptide. Heart. 2011;97:1479-83.
20. Thygesen K, Alpert JS, Jaffe AS, et al. Third universal definition of myocardial infarction. J Am Coll Cardiol. 2012;60:1581-98.
21. Roger VL, Killian JM, Weston SA, et al. Redefinition of myocardial infarction: prospective evaluation in the community. Circulation. 2006;114:790-7.
22. Hamm CW, Braunwald E. A classification of unstable angina revisited. Circulation. 2000;102:118-22.
23. Kavsak PA, MacRae AR, Lustig V, et al. The impact of the ESC/ACC redefinition of myocardial infarction and new sensitive troponin assays on the frequency of acute myocardial infarction. Am Heart J. 2006;152:118-25.
24. Eggers KM, Lind L, Venge P, et al. Will the universal definition of myocardial infarction criteria result in an overdiagnosis of myocardial infarction? Am J Cardiol. 2009;103:588-91.
25. Goodman SG, Steg PG, Eagle KA, et al. The diagnostic and prognostic impact of the redefinition of acute myocardial infarction: lessons from the Global Registry of Acute Coronary Events (GRACE). Am Heart J. 2006;151:654-60.
26. Eggers KM, Jaffe AS, Venge P, et al. Clinical implications of the change of cardiac troponin I levels in patients with acute chest pain - an evaluation with respect to the Universal Definition of Myocardial Infarction. Clin Chim Acta. 2011;412:91-7.
27. Mills NL, Lee KK, McAllister DA, et al. Implications of lowering threshold of plasma troponin concentration in diagnosis of myocardial infarction: cohort study. BMJ. 2012;344:e1533.
28. Bonaca MP, Wiviott SD, Braunwald E, et al. American College of Cardiology/American Heart Association/European Society of Cardiology/World Heart Federation universal definition of myocardial infarction classification system and the risk of cardiovascular death: observations from the TRITON-TIMI 38 trial (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel-Thrombolysis in Myocardial Infarction 38). Circulation. 2012;125:577-83.
29. Apple FS, Pearce LA, Smith SW, et al. Role of monitoring changes in sensitive cardiac troponin I assay results for early diagnosis of myocardial infarction and prediction of risk of adverse events. Clin Chem. 2009;55:930-7.
30. Bonaca M, Scirica B, Sabatine M, et al. Prospective evaluation of the prognostic implications of improved assay performance with a sensitive assay for cardiac troponin I. J Am Coll Cardiol. 2010;55:2118-24.
31. Kontos MC, de Lemos JA, Ou FS, et al. Troponin-positive, MB-negative patients with non-ST-elevation myocardial infarction: An undertreated but high-risk patient group: Results from the National Cardiovascular Data Registry Acute Coronary Treatment and Intervention Outcomes Network-Get With The Guidelines (NCDR ACTION-GWTG) Registry. Am Heart J. 2010;160:819-25.
32. Lindahl B, Venge P, James S. The new high-sensitivity cardiac troponin T assay improves risk assessment in acute coronary syndromes. Am Heart J. 2010;160:224-9.
33. Giannitsis E, Becker M, Kurz K, et al. High-sensitivity cardiac troponin T for early prediction of evolving non-ST-segment elevation myocardial infarction in patients with suspected acute coronary syndrome and negative troponin results on admission. Clin Chem. 2010;56:642-50.

34. Giannitsis E, Steen H, Kurz K, et al. Cardiac magnetic resonance imaging study for quantification of infarct size comparing directly serial versus single time-point measurements of cardiac troponin T. J Am Coll Cardiol. 2008;51:307-14.
35. Keller T, Zeller T, Peetz D, et al. Sensitive troponin I assay in early diagnosis of acute myocardial infarction. N Engl J Med. 2009;361:868-77.
36. Younger JF, Plein S, Barth J, et al. Troponin-I concentration 72 h after myocardial infarction correlates with infarct size and presence of microvascular obstruction. Heart. 2007;93:1547-51.
37. Apple FS, Smith SW, Pearce LA, et al. Delta changes for optimizing clinical specificity and 60-day risk of adverse events in patients presenting with symptoms suggestive of acute coronary syndrome utilizing the ADVIA Centaur TnI-Ultra assay. Clin Biochem. 2012;45:711-3.
38. Reichlin T, Irfan A, Twerenbold R, et al. Utility of absolute and relative changes in cardiac troponin concentrations in the early diagnosis of acute myocardial infarction. Circulation. 2011;124:136-45.
39. Aldous SJ, Richards M, Cullen L, et al. Diagnostic and prognostic utility of early measurement with high-sensitivity troponin T assay in patients presenting with chest pain. CMAJ. 2012;184:E260-E268.
40. Mueller M, Biener M, Vafaie M, et al. Absolute and relative kinetic changes of high-sensitivity cardiac troponin T in acute coronary syndrome and in patients with increased troponin in the absence of acute coronary syndrome. Clin Chem. 2012;58:209-18.
41. Apple FS, Christenson RH, Valdes R, Jr., et al. Simultaneous rapid measurement of whole blood myoglobin, creatine kinase MB, and cardiac troponin I by the triage cardiac panel for detection of myocardial infarction. Clin Chem. 1999;45:199-205.
42. Kleiman NS, Lakkis N, Cannon CP, et al. Prospective analysis of creatine kinase muscle-brain fraction and comparison with troponin T to predict cardiac risk and benefit of an invasive strategy in patients with non-ST-elevation acute coronary syndromes. J Am Coll Cardiol. 2002;40:1044-50.
43. Aviles RJ, Wright RS, Aviles JM, et al. Long-term prognosis of patients with clinical unstable angina pectoris without elevation of creatine kinase but with elevation of cardiac troponin i levels. Am J Cardiol. 2002;90:875-8.
44. Eggers KM, Oldgren J, Nordenskjold A, et al. Diagnostic value of serial measurement of cardiac markers in patients with chest pain: limited value of adding myoglobin to troponin I for exclusion of myocardial infarction. Am Heart J. 2004;148:574-81.
45. Storrow AB, Lindsell CJ, Han JH, et al. Discordant cardiac biomarkers: frequency and outcomes in emergency department patients with chest pain. Ann Emerg Med. 2006;48:660-5.
46. Newby LK, Roe MT, Chen AY, et al. Frequency and clinical implications of discordant creatine kinase-MB and troponin measurements in acute coronary syndromes. J Am Coll Cardiol. 2006;47:312-8.
47. Kavsak PA, MacRae AR, Newman AM, et al. Effects of contemporary troponin assay sensitivity on the utility of the early markers myoglobin and CKMB isoforms in evaluating patients with possible acute myocardial infarction. Clin Chim Acta. 2007;380:213-6.
48. Chin CT, Wang TY, Li S, et al. Comparison of the prognostic value of peak creatine kinase-MB and troponin levels among patients with acute myocardial infarction: a report from the Acute Coronary Treatment and Intervention Outcomes Network Registry-get with the guidelines. Clin Cardiol. 2012;35:424-9.
49. Lim CC, van Gaal WJ, Testa L, et al. With the "universal definition," measurement of creatine kinase-myocardial band rather than troponin allows more accurate diagnosis of periprocedural necrosis and infarction after coronary intervention. J Am Coll Cardiol. 2011;57:653-61.
50. Hamm CW, Goldmann BU, Heeschen C, et al. Emergency room triage of patients with acute chest pain by means of rapid testing for cardiac troponin T or troponin I. N Engl J Med. 1997;337:1648-53.
51. van Domburg RT, Cobbaert C, Kimman GJ, et al. Long-term prognostic value of serial troponin T bedside tests in patients with acute coronary syndromes. Am J Cardiol. 2000;86:623-7.
52. Amodio G, Antonelli G, Varraso L, et al. Clinical impact of the troponin 99th percentile cut-off and clinical utility of myoglobin measurement in the early management of chest pain patients admitted to the Emergency Cardiology Department. Coron Artery Dis. 2007;18:181-6.
53. Ryan RJ, Lindsell CJ, Hollander JE, et al. A multicenter randomized controlled trial comparing central laboratory and point-of-care cardiac marker testing strategies: the Disposition Impacted by Serial Point of Care Markers in Acute Coronary Syndromes (DISPO-ACS) trial. Ann Emerg Med. 2009;53:321-8.
54. Takakuwa KM, Ou FS, Peterson ED, et al. The usage patterns of cardiac bedside markers employing point-of-care testing for troponin in non-ST-segment elevation acute coronary syndrome: results from CRUSADE. Clin Cardiol. 2009;32:498-505.
55. Birkhahn RH, Haines E, Wen W, et al. Estimating the clinical impact of bringing a multimarker cardiac panel to the bedside in the ED. Am J Emerg Med. 2011;29:304-8.
56. Scharnhorst V, Krasznai K, van't Veer M, et al. Rapid detection of myocardial infarction with a sensitive troponin test. Am J Clin Pathol. 2011;135:424-8.
57. Than M, Cullen L, Reid CM, et al. A 2-h diagnostic protocol to assess patients with chest pain symptoms in the Asia-Pacific region (ASPECT): a prospective observational validation study. Lancet. 2011;377:1077-84.
58. Venge P, Ohberg C, Flodin M, et al. Early and late outcome prediction of death in the emergency room setting by point-of-care and laboratory assays of cardiac troponin I. Am Heart J. 2010;160:835-41.
59. Fitzgerald P, Goodacre SW, Cross E, et al. Cost-effectiveness of point-of-care biomarker assessment for suspected myocardial infarction: the randomized assessment of treatment using panel Assay of cardiac markers (RATPAC) trial. Acad Emerg Med. 2011;18:488-95.
60. Lindahl B, Toss H, Siegbahn A, et al. Markers of myocardial damage and inflammation in relation to long-term mortality in unstable coronary artery disease. FRISC Study Group. Fragmin during Instability in Coronary Artery Disease. N Engl J Med. 2000;343:1139-47.
61. Sabatine MS, Morrow DA, de Lemos JA, et al. Multimarker approach to risk stratification in non-ST elevation acute coronary syndromes: simultaneous assessment of troponin I, C-reactive protein, and B-type natriuretic peptide. Circulation. 2002;105:1760-3.
62. Blankenberg S, McQueen MJ, Smieja M, et al. Comparative impact of multiple biomarkers and N-Terminal pro-brain natriuretic peptide in the context of conventional risk factors for the prediction of recurrent cardiovascular events in the Heart Outcomes Prevention Evaluation (HOPE) Study. Circulation. 2006;114:201-8.
63. McCann CJ, Glover BM, Menown IB, et al. Novel biomarkers in early diagnosis of acute myocardial infarction compared with cardiac troponin T. Eur Heart J. 2008;29:2843-50.
64. Eggers KM, Lagerqvist B, Venge P, et al. Prognostic value of biomarkers during and after non-ST-segment elevation acute coronary syndrome. J Am Coll Cardiol. 2009;54:357-64.
65. Beygui F, Silvain J, Pena A, et al. Usefulness of biomarker strategy to improve GRACE score's prediction performance in patients with non-ST-segment elevation acute coronary syndrome and low event rates. Am J Cardiol. 2010;106:650-8.

66. Manhenke C, Orn S, von HS, et al. Clustering of 37 circulating biomarkers by exploratory factor analysis in patients following complicated acute myocardial infarction. Int J Cardiol. 2011.
67. Bhardwaj A, Truong QA, Peacock WF, et al. A multicenter comparison of established and emerging cardiac biomarkers for the diagnostic evaluation of chest pain in the emergency department. Am Heart J. 2011;162:276-82.
68. Scirica BM, Sabatine MS, Jarolim P, et al. Assessment of multiple cardiac biomarkers in non-ST-segment elevation acute coronary syndromes: observations from the MERLIN-TIMI 36 trial. Eur Heart J. 2011;32:697-705.
69. Oemrawsingh RM, Lenderink T, Akkerhuis KM, et al. Multimarker risk model containing troponin-T, interleukin 10, myeloperoxidase and placental growth factor predicts long-term cardiovascular risk after non-ST-segment elevation acute coronary syndrome. Heart. 2011;97:1061-6.
70. Eggers KM, Venge P, Lindahl B. High-sensitive cardiac troponin T outperforms novel diagnostic biomarkers in patients with acute chest pain. Clin Chim Acta. 2012;413:1135-40.
71. Meune C, Balmelli C, Twerenbold R, et al. Utility of 14 novel biomarkers in patients with acute chest pain and undetectable levels of conventional cardiac troponin. Int J Cardiol. 2012.
72. Schaub N, Reichlin T, Meune C, et al. Markers of plaque instability in the early diagnosis and risk stratification of acute myocardial infarction. Clin Chem. 2012;58:246-56.
73. Weber M, Bazzino O, Navarro Estrada JL, et al. N-terminal B-type natriuretic peptide assessment provides incremental prognostic information in patients with acute coronary syndromes and normal troponin T values upon admission. J Am Coll Cardiol. 2008;51:1188-95.
74. Wiviott SD, Cannon CP, Morrow DA, et al. Differential expression of cardiac biomarkers by gender in patients with unstable angina/non-ST-elevation myocardial infarction: a TACTICS-TIMI 18 (Treat Angina with Aggrastat and determine Cost of Therapy with an Invasive or Conservative Strategy-Thrombolysis In Myocardial Infarction 18) substudy. Circulation. 2004;109:580-6.
75. Farkouh ME, Smars PA, Reeder GS, et al. A clinical trial of a chest-pain observation unit for patients with unstable angina. Chest Pain Evaluation in the Emergency Room (CHEER) Investigators. N Engl J Med. 1998;339:1882-8.
76. Gomez MA, Anderson JL, Karagounis LA, et al. An emergency department-based protocol for rapidly ruling out myocardial ischemia reduces hospital time and expense: results of a randomized study (ROMIO). J Am Coll Cardiol. 1996;28:25-33.
77. Amsterdam EA, Kirk JD, Diercks DB, et al. Immediate exercise testing to evaluate low-risk patients presenting to the emergency department with chest pain. J Am Coll Cardiol. 2002;40:251-6.
78. Udelson JE, Beshansky JR, Ballin DS, et al. Myocardial perfusion imaging for evaluation and triage of patients with suspected acute cardiac ischemia: a randomized controlled trial. JAMA. 2002;288:2693-700.
79. Trippi JA, Lee KS, Kopp G, et al. Dobutamine stress tele-echocardiography for evaluation of emergency department patients with chest pain. J Am Coll Cardiol. 1997;30:627-32.
80. Bholasingh R, Cornel JH, Kamp O, et al. Prognostic value of predischarge dobutamine stress echocardiography in chest pain patients with a negative cardiac troponin T. J Am Coll Cardiol. 2003;41:596-602.
81. Hoffmann U, Bamberg F, Chae CU, et al. Coronary computed tomography angiography for early triage of patients with acute chest pain: the ROMICAT (Rule Out Myocardial Infarction using Computer Assisted Tomography) trial. J Am Coll Cardiol. 2009;53:1642-50.
82. Litt HI, Gatsonis C, Snyder B, et al. CT angiography for safe discharge of patients with possible acute coronary syndromes. N Engl J Med. 2012;366:1393-403.
83. Hoffmann U, Truong QA, Schoenfeld DA, et al. Coronary CT angiography versus standard evaluation in acute chest pain. N Engl J Med. 2012;367:299-308.
84. Ambrosio G, Del PM, Tritto I, et al. Chronic nitrate therapy is associated with different presentation and evolution of acute coronary syndromes: insights from 52,693 patients in the Global Registry of Acute Coronary Events. Eur Heart J. 2010;31:430-8.
85. Mahmarian JJ, Moye LA, Chinoy DA, et al. Transdermal nitroglycerin patch therapy improves left ventricular function and prevents remodeling after acute myocardial infarction: results of a multicenter prospective randomized, double-blind, placebo-controlled trial. Circulation. 1998;97:2017-24.
86. ISIS-4: a randomised factorial trial assessing early oral captopril, oral mononitrate, and intravenous magnesium sulphate in 58,050 patients with suspected acute myocardial infarction. ISIS-4 (Fourth International Study of Infarct Survival) Collaborative Group. Lancet. 1995;345:669-85.
87. GISSI-3: effects of lisinopril and transdermal glyceryl trinitrate singly and together on 6-week mortality and ventricular function after acute myocardial infarction. Gruppo Italiano per lo Studio della Sopravvivenza nell'infarto Miocardico. Lancet. 1994;343:1115-22.
88. Yusuf S, Collins R, MacMahon S, et al. Effect of intravenous nitrates on mortality in acute myocardial infarction: an overview of the randomised trials. Lancet. 1988;1:1088-92.
89. Iakobishvili Z, Cohen E, Garty M, et al. Use of intravenous morphine for acute decompensated heart failure in patients with and without acute coronary syndromes. Acute Card Care. 2011;13:76-80.
90. Iakobishvili Z, Porter A, Battler A, et al. Effect of narcotic treatment on outcomes of acute coronary syndromes. Am J Cardiol. 2010;105:912-6.
91. Meine TJ, Roe MT, Chen AY, et al. Association of intravenous morphine use and outcomes in acute coronary syndromes: results from the CRUSADE Quality Improvement Initiative. Am Heart J. 2005;149:1043-9.
92. Roberts R, Rogers WJ, Mueller HS, et al. Immediate versus deferred beta-blockade following thrombolytic therapy in patients with acute myocardial infarction. Results of the Thrombolysis in Myocardial Infarction (TIMI) II-B Study. Circulation. 1991;83:422-37.
93. Ryden L, Ariniego R, Arnman K, et al. A double-blind trial of metoprolol in acute myocardial infarction. Effects on ventricular tachyarrhythmias. N Engl J Med. 1983;308:614-8.
94. Al-Reesi A, Al-Zadjali N, Perry J, et al. Do beta-blockers reduce short-term mortality following acute myocardial infarction? A systematic review and meta-analysis. CJEM. 2008;10:215-23.
95. Janosi A, Ghali JK, Herlitz J, et al. Metoprolol CR/XL in postmyocardial infarction patients with chronic heart failure: experiences from MERIT-HF. Am Heart J. 2003;146:721-8.
96. Hjalmarson A. Effects of beta blockade on sudden cardiac death during acute myocardial infarction and the postinfarction period. Am J Cardiol. 1997;80:35J-9J.
97. Emery M, Lopez-Sendon J, Steg PG, et al. Patterns of use and potential impact of early beta-blocker therapy in non-ST-elevation myocardial infarction with and without heart failure: the Global Registry of Acute Coronary Events. Am Heart J. 2006;152:1015-21.
98. Freemantle N, Cleland J, Young P, et al. beta Blockade after myocardial infarction: systematic review and meta regression analysis. BMJ. 1999;318:1730-7.

99. Dargie HJ. Effect of carvedilol on outcome after myocardial infarction in patients with left-ventricular dysfunction: the CAPRICORN randomised trial. Lancet. 2001;357:1385-90.
100. Chen ZM, Pan HC, Chen YP, et al. Early intravenous then oral metoprolol in 45,852 patients with acute myocardial infarction: randomised placebo-controlled trial. Lancet. 2005;366:1622-32.
101. Ellis K, Tcheng JE, Sapp S, et al. Mortality benefit of beta blockade in patients with acute coronary syndromes undergoing coronary intervention: pooled results from the Epic, Epilog, Epistent, Capture and Rapport Trials. J Interv Cardiol. 2003;16:299-305.
102. McMurray J, Kober L, Robertson M, et al. Antiarrhythmic effect of carvedilol after acute myocardial infarction: results of the Carvedilol Post-Infarct Survival Control in Left Ventricular Dysfunction (CAPRICORN) trial. J Am Coll Cardiol. 2005;45:525-30.
103. Miller CD, Roe MT, Mulgund J, et al. Impact of acute beta-blocker therapy for patients with non-ST-segment elevation myocardial infarction. Am J Med. 2007;120:685-92.
104. Brandler E, Paladino L, Sinert R. Does the early administration of beta-blockers improve the in-hospital mortality rate of patients admitted with acute coronary syndrome? Acad Emerg Med. 2010;17:1-10.
105. Kontos MC, Diercks DB, Ho PM, et al. Treatment and outcomes in patients with myocardial infarction treated with acute beta-blocker therapy: results from the American College of Cardiology's NCDR((R)). Am Heart J. 2011;161:864-70.
106. Gibson RS, Boden WE, Theroux P, et al. Diltiazem and reinfarction in patients with non-Q-wave myocardial infarction. Results of a double-blind, randomized, multicenter trial. N Engl J Med. 1986;315:423-9.
107. Lubsen J, Tijssen JG. Efficacy of nifedipine and metoprolol in the early treatment of unstable angina in the coronary care unit: findings from the Holland Interuniversity Nifedipine/metoprolol Trial (HINT). Am J Cardiol. 1987;60:18A-25A.
108. Gibson RS, Young PM, Boden WE, et al. Prognostic significance and beneficial effect of diltiazem on the incidence of early recurrent ischemia after non-Q-wave myocardial infarction: results from the Multicenter Diltiazem Reinfarction Study. Am J Cardiol. 1987;60:203-9.
109. Held PH, Yusuf S, Furberg CD. Calcium channel blockers in acute myocardial infarction and unstable angina: an overview. BMJ. 1989;299:1187-92.
110. Moss AJ, Oakes D, Rubison M, et al. Effects of diltiazem on long-term outcome after acute myocardial infarction in patients with and without a history of systemic hypertension. The Multicenter Diltiazem Postinfarction Trial Research Group. Am J Cardiol. 1991;68:429-33.
111. Furberg CD, Psaty BM, Meyer JV. Nifedipine. Dose-related increase in mortality in patients with coronary heart disease. Circulation. 1995;92:1326-31.
112. Rengo F, Carbonin P, Pahor M, et al. A controlled trial of verapamil in patients after acute myocardial infarction: results of the calcium antagonist reinfarction Italian study (CRIS). Am J Cardiol. 1996;77:365-9.
113. Smith NL, Reiber GE, Psaty BM, et al. Health outcomes associated with beta-blocker and diltiazem treatment of unstable angina. J Am Coll Cardiol. 1998;32:1305-11.
114. Pepine CJ, Faich G, Makuch R. Verapamil use in patients with cardiovascular disease: an overview of randomized trials. Clin Cardiol. 1998;21:633-41.
115. Verapamil in acute myocardial infarction. The Danish Study Group on Verapamil in Myocardial Infarction. Eur Heart J. 1984;5:516-28.
116. Effect of verapamil on mortality and major events after acute myocardial infarction (the Danish Verapamil Infarction Trial II--DAVIT II). Am J Cardiol. 1990;66:779-85.
117. Wilson SR, Scirica BM, Braunwald E, et al. Efficacy of ranolazine in patients with chronic angina observations from the randomized, double-blind, placebo-controlled MERLIN-TIMI (Metabolic Efficiency With Ranolazine for Less Ischemia in Non-ST-Segment Elevation Acute Coronary Syndromes) 36 Trial. J Am Coll Cardiol. 2009;53:1510-6.
118. Scirica BM, Morrow DA, Hod H, et al. Effect of ranolazine, an antianginal agent with novel electrophysiological properties, on the incidence of arrhythmias in patients with non ST-segment elevation acute coronary syndrome: results from the Metabolic Efficiency With Ranolazine for Less Ischemia in Non ST-Elevation Acute Coronary Syndrome Thrombolysis in Myocardial Infarction 36 (MERLIN-TIMI 36) randomized controlled trial. Circulation. 2007;116:1647-52.
119. Morrow DA, Scirica BM, Karwatowska-Prokopczuk E, et al. Effects of ranolazine on recurrent cardiovascular events in patients with non-ST-elevation acute coronary syndromes: the MERLIN-TIMI 36 randomized trial. JAMA. 2007;297:1775-83.
120. Spacek R, Widimsky P, Straka Z, et al. Value of first day angiography/angioplasty in evolving Non-ST segment elevation myocardial infarction: an open multicenter randomized trial. The VINO Study. Eur Heart J. 2002;23:230-8.
121. Ambrosioni E, Borghi C, Magnani B. The effect of the angiotensin-converting-enzyme inhibitor zofenopril on mortality and morbidity after anterior myocardial infarction. The Survival of Myocardial Infarction Long-Term Evaluation (SMILE) Study Investigators. N Engl J Med. 1995;332:80-5.
122. Swedberg K, Held P, Kjekshus J, et al. Effects of the early administration of enalapril on mortality in patients with acute myocardial infarction. Results of the Cooperative New Scandinavian Enalapril Survival Study II (CONSENSUS II). N Engl J Med. 1992;327:678-84.
123. Indications for ACE inhibitors in the early treatment of acute myocardial infarction: systematic overview of individual data from 100,000 patients in randomized trials. ACE Inhibitor Myocardial Infarction Collaborative Group. Circulation. 1998;97:2202-12.
124. Hall AS, Murray GD, Ball SG. Follow-up study of patients randomly allocated ramipril or placebo for heart failure after acute myocardial infarction: AIRE Extension (AIREX) Study. Acute Infarction Ramipril Efficacy. Lancet. 1997;349:1493-7.
125. Squire I, Quinn P, Narayan H, et al. Identification of potential outcome benefit from ACE inhibition after acute coronary syndrome: a biomarker approach using N-terminal proBNP. Heart. 2010;96:831-7.
126. Pfeffer MA, McMurray JJ, Velazquez EJ, et al. Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both. N Engl J Med. 2003;349:1893-906.
127. Pitt B, Remme W, Zannad F, et al. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. N Engl J Med. 2003;348:1309-21.
128. Gheorghiade M, Khan S, Blair JE, et al. The effects of eplerenone on length of stay and total days of heart failure hospitalization after myocardial infarction in patients with left ventricular systolic dysfunction. Am Heart J. 2009;158:437-43.
129. Weir RA, Mark PB, Petrie CJ, et al. Left ventricular remodeling after acute myocardial infarction: does eplerenone have an effect? Am Heart J. 2009;157:1088-96.
130. Rossignol P, Menard J, Fay R, et al. Eplerenone survival benefits in heart failure patients post-myocardial infarction are independent from its diuretic and potassium-sparing effects. Insights from an EPHESUS (Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study) substudy. J Am Coll Cardiol. 2011;58:1958-66.

131. Rossignol P, Cleland JG, Bhandari S, et al. Determinants and consequences of renal function variations with aldosterone blocker therapy in heart failure patients after myocardial infarction: insights from the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study. Circulation. 2012;125:271-9.
132. Baigent C, Blackwell L, Collins R, et al. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. Lancet. 2009;373:1849-60.
133. Yusuf S, Zhao F, Mehta SR, et al. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. N Engl J Med. 2001;345:494-502.
134. Mahaffey KW, Wojdyla DM, Carroll K, et al. Ticagrelor compared with clopidogrel by geographic region in the Platelet Inhibition and Patient Outcomes (PLATO) trial. Circulation. 2011;124:544-54.
135. Gremmel T, Steiner S, Seidinger D, et al. Adenosine diphosphate-inducible platelet reactivity shows a pronounced age dependency in the initial phase of antiplatelet therapy with clopidogrel. J Thromb Haemost. 2010;8:37-42.
136. CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). Lancet. 1996;348:1329-39.
137. Gollapudi RR, Teirstein PS, Stevenson DD, et al. Aspirin sensitivity: implications for patients with coronary artery disease. JAMA. 2004;292:3017-23.
138. Wiviott SD, Braunwald E, McCabe CH, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. N Engl J Med. 2007;357:2001-15.
139. Wallentin L, Becker RC, Budaj A, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. N Engl J Med. 2009;361:1045-57.
140. Mehta SR, Bassand JP, Chrolavicius S, et al. Dose comparisons of clopidogrel and aspirin in acute coronary syndromes. N Engl J Med. 2010;363:930-42.
141. James SK, Roe MT, Cannon CP, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes intended for non-invasive management: substudy from prospective randomised PLATelet inhibition and patient Outcomes (PLATO) trial. BMJ. 2011;342:d3527.
142. Kastrati A, Mehilli J, Neumann FJ, et al. Abciximab in patients with acute coronary syndromes undergoing percutaneous coronary intervention after clopidogrel pretreatment: the ISAR-REACT 2 randomized trial. JAMA. 2006;295:1531-8.
143. PURSUIT Trial Investigators. Inhibition of platelet glycoprotein IIb/IIIa with eptifibatide in patients with acute coronary syndromes. The PURSUIT Trial Investigators. Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy. N Engl J Med. 1998;339:436-43.
144. PRISM-PLUS Study Investigators. Inhibition of the platelet glycoprotein IIb/IIIa receptor with tirofiban in unstable angina and non-Q-wave myocardial infarction. Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms (PRISM-PLUS) Study Investigators. N Engl J Med. 1998;338:1488-97.
145. Giugliano RP, White JA, Bode C, et al. Early versus delayed, provisional eptifibatide in acute coronary syndromes. N Engl J Med. 2009;360:2176-90.
146. Stone GW, White HD, Ohman EM, et al. Bivalirudin in patients with acute coronary syndromes undergoing percutaneous coronary intervention: a subgroup analysis from the Acute Catheterization and Urgent Intervention Triage strategy (ACUITY) trial. Lancet. 2007;369:907-19.
147. AstraZeneca. Brilinta REMS Document. NDA 22-433. 2011;
148. Ottervanger JP, Armstrong P, Barnathan ES, et al. Long-term results after the glycoprotein IIb/IIIa inhibitor abciximab in unstable angina: one-year survival in the GUSTO IV-ACS (Global Use of Strategies To Open Occluded Coronary Arteries IV--Acute Coronary Syndrome) Trial. Circulation. 2003;107:437-42.
149. Mehta SR, Yusuf S, Peters RJ, et al. Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study. Lancet. 2001;358:527-33.
150. Wiviott SD, Trenk D, Frelinger AL, et al. Prasugrel compared with high loading- and maintenance-dose clopidogrel in patients with planned percutaneous coronary intervention: the Prasugrel in Comparison to Clopidogrel for Inhibition of Platelet Activation and Aggregation-Thrombolysis in Myocardial Infarction 44 trial. Circulation. 2007;116:2923-32.
151. Roe MT, Armstrong PW, Fox KA, et al. Prasugrel versus clopidogrel for acute coronary syndromes without revascularization. N Engl J Med. 2012;367:1297-309.
152. Becker RC, Bassand JP, Budaj A, et al. Bleeding complications with the P2Y12 receptor antagonists clopidogrel and ticagrelor in the PLATelet inhibition and patient Outcomes (PLATO) trial. Eur Heart J. 2011;32:2933-44.
153. Valgimigli M, Biondi-Zoccai G, Tebaldi M, et al. Tirofiban as adjunctive therapy for acute coronary syndromes and percutaneous coronary intervention: a meta-analysis of randomized trials. Eur Heart J. 2010;31:35-49.
154. Stone GW, Bertrand ME, Moses JW, et al. Routine upstream initiation vs deferred selective use of glycoprotein IIb/IIIa inhibitors in acute coronary syndromes: the ACUITY Timing trial. JAMA. 2007;297:591-602.
155. van Es RF, Jonker JJ, Verheugt FW, et al. Aspirin and coumadin after acute coronary syndromes (the ASPECT-2 study): a randomised controlled trial. Lancet. 2002;360:109-13.
156. Karjalainen PP, Vikman S, Niemela M, et al. Safety of percutaneous coronary intervention during uninterrupted oral anticoagulant treatment. Eur Heart J. 2008;29:1001-10.
157. ten Berg JM, Hutten BA, Kelder JC, et al. Oral anticoagulant therapy during and after coronary angioplasty the intensity and duration of anticoagulation are essential to reduce thrombotic complications. Circulation. 2001;103:2042-7.
158. Bhatt DL, Scheiman J, Abraham NS, et al. ACCF/ACG/AHA 2008 expert consensus document on reducing the gastrointestinal risks of antiplatelet therapy and NSAID use: a report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents. J Am Coll Cardiol. 2008;52:1502-17.
159. Ruiz-Nodar JM, Marin F, Sanchez-Paya J, et al. Efficacy and safety of drug-eluting stent use in patients with atrial fibrillation. Eur Heart J. 2009;30:932-9.
160. Lip GY, Huber K, Andreotti F, et al. Antithrombotic management of atrial fibrillation patients presenting with acute coronary syndrome and/or undergoing coronary stenting: executive summary--a Consensus Document of the European Society of Cardiology Working Group on Thrombosis, endorsed by the European Heart Rhythm Association (EHRA) and the European Association of Percutaneous Cardiovascular Interventions (EAPCI). Eur Heart J. 2010;31:1311-8.
161. Mohr JP, Thompson JL, Lazar RM, et al. A comparison of warfarin and aspirin for the prevention of recurrent ischemic stroke. N Engl J Med. 2001;345:1444-51.
162. Peverill RE, Harper RW, Smolich JJ. CARS trial: warfarin and thrombin generation. Coumadin Aspirin Reinfarction Study. Lancet. 1997;350:1177-8.
163. Rossini R, Musumeci G, Lettieri C, et al. Long-term outcomes in patients undergoing coronary stenting on dual oral antiplatelet treatment requiring oral anticoagulant therapy. Am J Cardiol. 2008;102:1618-23.
164. Sarafoff N, Ndrepepa G, Mehilli J, et al. Aspirin and clopidogrel with or without phenprocoumon after drug eluting coronary stent placement in patients on chronic oral anticoagulation. J Intern Med. 2008;264:472-80.

165. Petersen JL, Mahaffey KW, Hasselblad V, et al. Efficacy and bleeding complications among patients randomized to enoxaparin or unfractionated heparin for antithrombin therapy in non-ST-Segment elevation acute coronary syndromes: a systematic overview. JAMA. 2004;292:89-96.
166. Hochman JS, Wali AU, Gavrila D, et al. A new regimen for heparin use in acute coronary syndromes. Am Heart J. 1999;138:313-8.
167. Garcia DA, Baglin TP, Weitz JI, et al. Parenteral anticoagulants: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141:e24S-e43S.
168. Antman EM, McCabe CH, Gurfinkel EP, et al. Enoxaparin prevents death and cardiac ischemic events in unstable angina/non-Q-wave myocardial infarction. Results of the thrombolysis in myocardial infarction (TIMI) 11B trial. Circulation. 1999;100:1593-601.
169. Mehta SR, Granger CB, Eikelboom JW, et al. Efficacy and safety of fondaparinux versus enoxaparin in patients with acute coronary syndromes undergoing percutaneous coronary intervention: results from the OASIS-5 trial. J Am Coll Cardiol. 2007;50:1742-51.
170. Yusuf S, Mehta SR, Chrolavicius S, et al. Comparison of fondaparinux and enoxaparin in acute coronary syndromes. N Engl J Med. 2006;354:1464-76.
171. Steg PG, Jolly SS, Mehta SR, et al. Low-dose vs standard-dose unfractionated heparin for percutaneous coronary intervention in acute coronary syndromes treated with fondaparinux: the FUTURA/OASIS-8 randomized trial. JAMA. 2010;304:1339-49.
172. Grosser T, Fries S, Lawson JA, et al. Drug Resistance and Pseudoresistance: An Unintended Consequence of Enteric Coating Aspirin. Circulation. 2012.
173. Steg PG, Mehta S, Jolly S, et al. Fondaparinux with UnfracTionated heparin dUring Revascularization in Acute coronary syndromes (FUTURA/OASIS 8): a randomized trial of intravenous unfractionated heparin during percutaneous coronary intervention in patients with non-ST-segment elevation acute coronary syndromes initially treated with fondaparinux. Am Heart J. 2010;160:1029-34.
174. Stone GW, McLaurin BT, Cox DA, et al. Bivalirudin for patients with acute coronary syndromes. N Engl J Med. 2006;355:2203-16.
175. Indications for fibrinolytic therapy in suspected acute myocardial infarction: collaborative overview of early mortality and major morbidity results from all randomised trials of more than 1000 patients. Fibrinolytic Therapy Trialists' (FTT) Collaborative Group. Lancet. 1994;343:311-22.
176. Effects of tissue plasminogen activator and a comparison of early invasive and conservative strategies in unstable angina and non-Q-wave myocardial infarction. Results of the TIMI IIIB Trial. Thrombolysis in Myocardial Ischemia. Circulation. 1994;89:1545-56.
177. Oldgren J, Budaj A, Granger CB, et al. Dabigatran vs. placebo in patients with acute coronary syndromes on dual antiplatelet therapy: a randomized, double-blind, phase II trial. Eur Heart J. 2011;32:2781-9.
178. Uchino K, Hernandez AV. Dabigatran association with higher risk of acute coronary events: meta-analysis of noninferiority randomized controlled trials. Arch Intern Med. 2012;172:397-402.
179. Alexander JH, Lopes RD, James S, et al. Apixaban with antiplatelet therapy after acute coronary syndrome. N Engl J Med. 2011;365:699-708.
180. Mega JL, Braunwald E, Wiviott SD, et al. Rivaroxaban in patients with a recent acute coronary syndrome. N Engl J Med. 2012;366:9-19.
181. Warkentin TE, Margetts P, Connolly SJ, et al. Recombinant factor VIIa (rFVIIa) and hemodialysis to manage massive dabigatran-associated postcardiac surgery bleeding. Blood. 2012;119:2172-4.
182. Eerenberg ES, Kamphuisen PW, Sijpkens MK, et al. Reversal of rivaroxaban and dabigatran by prothrombin complex concentrate: a randomized, placebo-controlled, crossover study in healthy subjects. Circulation. 2011;124:1573-9.
183. McCullough PA, O'Neill WW, Graham M, et al. A prospective randomized trial of triage angiography in acute coronary syndromes ineligible for thrombolytic therapy. Results of the medicine versus angiography in thrombolytic exclusion (MATE) trial. J Am Coll Cardiol. 1998;32:596-605.
184. Boden WE, O'Rourke RA, Crawford MH, et al. Outcomes in patients with acute non-Q-wave myocardial infarction randomly assigned to an invasive as compared with a conservative management strategy. Veterans Affairs Non-Q-Wave Infarction Strategies in Hospital (VANQWISH) Trial Investigators. N Engl J Med. 1998;338:1785-92.
185. Invasive compared with non-invasive treatment in unstable coronary-artery disease: FRISC II prospective randomised multicentre study. FRagmin and Fast Revascularisation during InStability in Coronary artery disease Investigators. Lancet. 1999;354:708-15.
186. Cannon CP, Weintraub WS, Demopoulos LA, et al. Comparison of early invasive and conservative strategies in patients with unstable coronary syndromes treated with the glycoprotein IIb/IIIa inhibitor tirofiban. N Engl J Med. 2001;344:1879-87.
187. Fox KA, Poole-Wilson PA, Henderson RA, et al. Interventional versus conservative treatment for patients with unstable angina or non-ST-elevation myocardial infarction: the British Heart Foundation RITA 3 randomised trial. Randomized Intervention Trial of unstable Angina. Lancet. 2002;360:743-51.
188. de Winter RJ, Windhausen F, Cornel JH, et al. Early invasive versus selectively invasive management for acute coronary syndromes. N Engl J Med. 2005;353:1095-104.
189. Savonitto S, Cavallini C, Petronio AS, et al. Early aggressive versus initially conservative treatment in elderly patients with non-ST-segment elevation acute coronary syndrome: a randomized controlled trial. JACC Cardiovasc Interv. 2012;5:906-16.
190. Neumann FJ, Kastrati A, Pogatsa-Murray G, et al. Evaluation of prolonged antithrombotic pretreatment ("cooling-off" strategy) before intervention in patients with unstable coronary syndromes: a randomized controlled trial. JAMA. 2003;290:1593-9.
191. Mehta SR, Granger CB, Boden WE, et al. Early versus delayed invasive intervention in acute coronary syndromes. N Engl J Med. 2009;360:2165-75.
192. Montalescot G, Cayla G, Collet JP, et al. Immediate vs delayed intervention for acute coronary syndromes: a randomized clinical trial. JAMA. 2009;302:947-54.
193. Valeur N, Clemmensen P, Saunamaki K, et al. The prognostic value of pre-discharge exercise testing after myocardial infarction treated with either primary PCI or fibrinolysis: a DANAMI-2 sub-study. Eur Heart J. 2005;26:119-27.
194. Mahmarian JJ, Shaw LJ, Filipchuk NG, et al. A multinational study to establish the value of early adenosine technetium-99m sestamibi myocardial perfusion imaging in identifying a low-risk group for early hospital discharge after acute myocardial infarction. J Am Coll Cardiol. 2006;48:2448-57.
195. Desideri A, Fioretti PM, Cortigiani L, et al. Pre-discharge stress echocardiography and exercise ECG for risk stratification after uncomplicated acute myocardial infarction: results of the COSTAMI-II (cost of strategies after myocardial infarction) trial. Heart. 2005;91:146-51.
196. Platelet glycoprotein IIb/IIIa receptor blockade and low-dose heparin during percutaneous coronary revascularization. The EPILOG Investigators. N Engl J Med. 1997;336:1689-96.

197. Hamm CW, Heeschen C, Goldmann B, et al. Benefit of abciximab in patients with refractory unstable angina in relation to serum troponin T levels. c7E3 Fab Antiplatelet Therapy in Unstable Refractory Angina (CAPTURE) Study Investigators. N Engl J Med. 1999;340:1623-9.
198. Use of a monoclonal antibody directed against the platelet glycoprotein IIb/IIIa receptor in high-risk coronary angioplasty. The EPIC Investigation. N Engl J Med. 1994;330:956-61.
199. Effects of platelet glycoprotein IIb/IIIa blockade with tirofiban on adverse cardiac events in patients with unstable angina or acute myocardial infarction undergoing coronary angioplasty. The RESTORE Investigators. Randomized Efficacy Study of Tirofiban for Outcomes and REstenosis. Circulation. 1997;96:1445-53.
200. Valgimigli M, Percoco G, Barbieri D, et al. The additive value of tirofiban administered with the high-dose bolus in the prevention of ischemic complications during high-risk coronary angioplasty: the ADVANCE Trial. J Am Coll Cardiol. 2004;44:14-9.
201. Pannu R, Andraws R. Effects of glycoprotein IIb/IIIa inhibitors in patients undergoing percutaneous coronary intervention after pretreatment with clopidogrel: a meta-analysis of randomized trials. Crit Pathw Cardiol. 2008;7:5-10.
202. Brener SJ, Milford-Beland S, Roe MT, et al. Culprit-only or multivessel revascularization in patients with acute coronary syndromes: an American College of Cardiology National Cardiovascular Database Registry report. Am Heart J. 2008;155:140-6.
203. Shishehbor MH, Lauer MS, Singh IM, et al. In unstable angina or non-ST-segment acute coronary syndrome, should patients with multivessel coronary artery disease undergo multivessel or culprit-only stenting? J Am Coll Cardiol. 2007;49:849-54.
204. Zapata GO, Lasave LI, Kozak F, et al. Culprit-only or multivessel percutaneous coronary stenting in patients with non-ST-segment elevation acute coronary syndromes: one-year follow-up. J Interv Cardiol. 2009;22:329-35.
205. Palmer ND, Causer JP, Ramsdale DR, et al. Effect of completeness of revascularization on clinical outcome in patients with multivessel disease presenting with unstable angina who undergo percutaneous coronary intervention. J Invasive Cardiol. 2004;16:185-8.
206. Brener SJ, Murphy SA, Gibson CM, et al. Efficacy and safety of multivessel percutaneous revascularization and tirofiban therapy in patients with acute coronary syndromes. Am J Cardiol. 2002;90:631-3.
207. Munk PS, Staal EM, Butt N, et al. High-intensity interval training may reduce in-stent restenosis following percutaneous coronary intervention with stent implantation A randomized controlled trial evaluating the relationship to endothelial function and inflammation. Am Heart J. 2009;158:734-41.
208. Tisminetzky M, Bray BC, Miozzo R, et al. Identifying symptom profiles of depression and anxiety in patients with an acute coronary syndrome using latent class and latent transition analysis. Int J Psychiatry Med. 2011;42:195-210.
209. Lee YH, Ji JD, Song GG. Adjusted indirect comparison of celecoxib versus rofecoxib on cardiovascular risk. Rheumatol Int. 2007;27:477-82.
210. Galan P, Kesse-Guyot E, Czernichow S, et al. Effects of B vitamins and omega 3 fatty acids on cardiovascular diseases: a randomised placebo controlled trial. BMJ. 2010;341:c6273.
211. Imasa MS, Gomez NT, Nevado JB, Jr. Folic acid-based intervention in non-ST elevation acute coronary syndromes. Asian Cardiovasc Thorac Ann. 2009;17:13-21.
212. Alexander KP, Newby LK, Cannon CP, et al. Acute coronary care in the elderly, part I: Non-ST-segment-elevation acute coronary syndromes: a scientific statement for healthcare professionals from the American Heart Association Council on Clinical Cardiology: in collaboration with the Society of Geriatric Cardiology. Circulation. 2007;115:2549-69.
213. Gale CP, Cattle BA, Woolston A, et al. Resolving inequalities in care? Reduced mortality in the elderly after acute coronary syndromes. The Myocardial Ischaemia National Audit Project 2003-2010. Eur Heart J. 2012;33:630-9.
214. Devlin G, Gore JM, Elliott J, et al. Management and 6-month outcomes in elderly and very elderly patients with high-risk non-ST-elevation acute coronary syndromes: The Global Registry of Acute Coronary Events. Eur Heart J. 2008;29:1275-82.
215. Damman P, Clayton T, Wallentin L, et al. Effects of age on long-term outcomes after a routine invasive or selective invasive strategy in patients presenting with non-ST segment elevation acute coronary syndromes: a collaborative analysis of individual data from the FRISC II - IC. Heart. 2012;98:207-13.
216. Bach RG, Cannon CP, Weintraub WS, et al. The effect of routine, early invasive management on outcome for elderly patients with non-ST-segment elevation acute coronary syndromes. Ann Intern Med. 2004;141:186-95.
217. Yourman LC, Lee SJ, Schonberg MA, et al. Prognostic indices for older adults: a systematic review. JAMA. 2012;307:182-92.
218. Fenning S, Woolcock R, Haga K, et al. Identifying acute coronary syndrome patients approaching end-of-life. PLoS One. 2012;7:e35536.
219. Tinetti ME, Bogardus ST, Jr., Agostini JV. Potential pitfalls of disease-specific guidelines for patients with multiple conditions. N Engl J Med. 2004;351:2870-4.
220. Corsonello A, Pedone C, Incalzi RA. Age-related pharmacokinetic and pharmacodynamic changes and related risk of adverse drug reactions. Curr Med Chem. 2010;17:571-84.
221. Trifiro G, Spina E. Age-related changes in pharmacodynamics: focus on drugs acting on central nervous and cardiovascular systems. Curr Drug Metab. 2011;12:611-20.
222. Alexander KP, Chen AY, Roe MT, et al. Excess dosing of antiplatelet and antithrombin agents in the treatment of non-ST-segment elevation acute coronary syndromes. JAMA. 2005;294:3108-16.
223. Lincoff AM, Bittl JA, Harrington RA, et al. Bivalirudin and provisional glycoprotein IIb/IIIa blockade compared with heparin and planned glycoprotein IIb/IIIa blockade during percutaneous coronary intervention: REPLACE-2 randomized trial. JAMA. 2003;289:853-63.
224. Lopes RD, Alexander KP, Manoukian SV, et al. Advanced age, antithrombotic strategy, and bleeding in non-ST-segment elevation acute coronary syndromes: results from the ACUITY (Acute Catheterization and Urgent Intervention Triage Strategy) trial. J Am Coll Cardiol. 2009;53:1021-30.
225. Lemesle G, De LA, Bonello L, et al. Impact of bivalirudin on in-hospital bleeding and six-month outcomes in octogenarians undergoing percutaneous coronary intervention. Catheter Cardiovasc Interv. 2009;74:428-35.
226. Summaria F, Romagnoli E, De Luca L., et al. Feasibility and safety of transradial approach and bivalirudin treatment in elderly patients undergoing early invasive strategy for ACS: 'The OLDER Research Project' preliminary study. J Cardiovasc Med (Hagerstown). 2012;13:351-2.
227. McKellar SH, Brown ML, Frye RL, et al. Comparison of coronary revascularization procedures in octogenarians: a systematic review and meta-analysis. Nat Clin Pract Cardiovasc Med. 2008;5:738-46.
228. Kimura T, Morimoto T, Furukawa Y, et al. Long-term outcomes of coronary-artery bypass graft surgery versus percutaneous coronary intervention for multivessel coronary artery disease in the bare-metal stent era. Circulation. 2008;118:S199-S209.
229. Dacey LJ, Likosky DS, Ryan TJ, Jr., et al. Long-term survival after surgery versus percutaneous intervention in octogenarians with multivessel coronary disease. Ann Thorac Surg. 2007;84:1904-11.

230. Hochman JS, Sleeper LA, Webb JG, et al. Early revascularization in acute myocardial infarction complicated by cardiogenic shock. SHOCK Investigators. Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock. N Engl J Med. 1999;341:625-34.
231. Bhatt DL, Roe MT, Peterson ED, et al. Utilization of early invasive management strategies for high-risk patients with non-ST-segment elevation acute coronary syndromes: results from the CRUSADE Quality Improvement Initiative. JAMA. 2004;292:2096-104.
232. Jacobs AK, French JK, Col J, et al. Cardiogenic shock with non-ST-segment elevation myocardial infarction: a report from the SHOCK Trial Registry. SHould we emergently revascularize Occluded coronaries for Cardiogenic shocK? J Am Coll Cardiol. 2000;36:1091-6.
233. Holmes DR, Jr., Berger PB, Hochman JS, et al. Cardiogenic shock in patients with acute ischemic syndromes with and without ST-segment elevation. Circulation. 1999;100:2067-73.
234. Norhammar A, Malmberg K, Diderholm E, et al. Diabetes mellitus: the major risk factor in unstable coronary artery disease even after consideration of the extent of coronary artery disease and benefits of revascularization. J Am Coll Cardiol. 2004;43:585-91.
235. Farkouh ME, Domanski M, Sleeper LA, et al. Strategies for Multivessel Revascularization in Patients with Diabetes. N Engl J Med. 2012.
236. Ie EH, Klootwijk PJ, Weimar W, et al. Significance of acute versus chronic troponin T elevation in dialysis patients. Nephron Clin Pract. 2004;98:c87-c92.
237. Wright RS, Reeder GS, Herzog CA, et al. Acute myocardial infarction and renal dysfunction: a high-risk combination. Ann Intern Med. 2002;137:563-70.
238. Shlipak MG, Heidenreich PA, Noguchi H, et al. Association of renal insufficiency with treatment and outcomes after myocardial infarction in elderly patients. Ann Intern Med. 2002;137:555-62.
239. Solomon R, Werner C, Mann D, et al. Effects of saline, mannitol, and furosemide to prevent acute decreases in renal function induced by radiocontrast agents. N Engl J Med. 1994;331:1416-20.
240. Charytan DM, Wallentin L, Lagerqvist B, et al. Early angiography in patients with chronic kidney disease: a collaborative systematic review. Clin J Am Soc Nephrol. 2009;4:1032-43.
241. Szummer K, Lundman P, Jacobson SH, et al. Influence of renal function on the effects of early revascularization in non-ST-elevation myocardial infarction: data from the Swedish Web-System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies (SWEDEHEART). Circulation. 2009;120:851-8.
242. Hutchinson-Jaffe AB, Goodman SG, Yan RT, et al. Comparison of baseline characteristics, management and outcome of patients with non-ST-segment elevation acute coronary syndrome in versus not in clinical trials. Am J Cardiol. 2010;106:1389-96.
243. Akhter N, Milford-Beland S, Roe MT, et al. Gender differences among patients with acute coronary syndromes undergoing percutaneous coronary intervention in the American College of Cardiology-National Cardiovascular Data Registry (ACC-NCDR). Am Heart J. 2009;157:141-8.
244. Blomkalns AL, Chen AY, Hochman JS, et al. Gender disparities in the diagnosis and treatment of non-ST-segment elevation acute coronary syndromes: large-scale observations from the CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the American College of Cardiology/American Heart Association Guidelines) National Quality Improvement Initiative. J Am Coll Cardiol. 2005;45:832-7.
245. Lansky AJ, Mehran R, Cristea E, et al. Impact of gender and antithrombin strategy on early and late clinical outcomes in patients with non-ST-elevation acute coronary syndromes (from the ACUITY trial). Am J Cardiol. 2009;103:1196-203.
246. Alexander KP, Chen AY, Newby LK, et al. Sex differences in major bleeding with glycoprotein IIb/IIIa inhibitors: results from the CRUSADE (Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA guidelines) initiative. Circulation. 2006;114:1380-7.
247. O'Donoghue M, Boden WE, Braunwald E, et al. Early invasive vs conservative treatment strategies in women and men with unstable angina and non-ST-segment elevation myocardial infarction: a meta-analysis. JAMA. 2008;300:71-80.
248. Dolor RJ, Melloni C, Chatterjee R, et al. Treatment Strategies for Women With Coronary Artery Disease [Internet]. AJRQ. 2012.
249. Glaser R, Herrmann HC, Murphy SA, et al. Benefit of an early invasive management strategy in women with acute coronary syndromes. JAMA. 2002;288:3124-9.
250. Chen J, Einstein AJ, Fazel R, et al. Cumulative exposure to ionizing radiation from diagnostic and therapeutic cardiac imaging procedures: a population-based analysis. J Am Coll Cardiol. 2010;56:702-11.
251. Einstein AJ, Weiner SD, Bernheim A, et al. Multiple testing, cumulative radiation dose, and clinical indications in patients undergoing myocardial perfusion imaging. JAMA. 2010;304:2137-44.
252. Einstein AJ, Henzlova MJ, Rajagopalan S. Estimating risk of cancer associated with radiation exposure from 64-slice computed tomography coronary angiography. JAMA. 2007;298:317-23.
253. Alexander KP, Chen AY, Wang TY, et al. Transfusion practice and outcomes in non-ST-segment elevation acute coronary syndromes. Am Heart J. 2008;155:1047-53.
254. Yang XC, Zhang DP, Wang LF, et al. [Effects of intracoronary or intravenous tirofiban administration in patients with acute ST-elevation myocardial infarction undergoing primary percutaneous coronary intervention]. Zhonghua Xin Xue Guan Bing Za Zhi. 2007;35:517-22.
255. Rao SV, Jollis JG, Harrington RA, et al. Relationship of blood transfusion and clinical outcomes in patients with acute coronary syndromes. JAMA. 2004;292:1555-62.
256. Carson JL, Grossman BJ, Kleinman S, et al. Red Blood Cell Transfusion: A Clinical Practice Guideline From the AABB. Ann Intern Med. 2012.
257. Carson JL, Carless PA, Hebert PC. Transfusion thresholds and other strategies for guiding allogeneic red blood cell transfusion. Cochrane Database Syst Rev. 2012;4:CD002042.
258. Alexander KP, Chen AY, Roe MT, et al. Excess dosing of antiplatelet and antithrombin agents in the treatment of non-ST-segment elevation acute coronary syndromes. JAMA. 2005;294:3108-16.
259. Melloni C, Alexander KP, Chen AY, et al. Unfractionated heparin dosing and risk of major bleeding in non-ST-segment elevation acute coronary syndromes. Am Heart J. 2008;156:209-15.
260. LaPointe NM, Chen AY, Alexander KP, et al. Enoxaparin dosing and associated risk of in-hospital bleeding and death in patients with non ST-segment elevation acute coronary syndromes. Arch Intern Med. 2007;167:1539-44.
261. Taylor LA, Mauro VF. Incidence of bleeding in renally impaired patients receiving incorrectly dosed eptifibatide or bivalirudin while undergoing percutaneous coronary intervention. Ann Pharmacother. 2012;46:35-41.
262. Becker RC, Spencer FA, Gibson M, et al. Influence of patient characteristics and renal function on factor Xa inhibition pharmacokinetics and pharmacodynamics after enoxaparin administration in non-ST-segment elevation acute coronary syndromes. Am Heart J. 2002;143:753-9.

263. Lange RA, Cigarroa RG, Flores ED, et al. Potentiation of cocaine-induced coronary vasoconstriction by beta-adrenergic blockade. Ann Intern Med. 1990;112:897-903.
264. Dattilo PB, Hailpern SM, Fearon K, et al. Beta-blockers are associated with reduced risk of myocardial infarction after cocaine use. Ann Emerg Med. 2008;51:117-25.
265. Rangel C, Shu RG, Lazar LD, et al. Beta-blockers for chest pain associated with recent cocaine use. Arch Intern Med. 2010;170:874-9.
266. Honderick T, Williams D, Seaberg D, et al. A prospective, randomized, controlled trial of benzodiazepines and nitroglycerine or nitroglycerine alone in the treatment of cocaine-associated acute coronary syndromes. Am J Emerg Med. 2003;21:39-42.
267. Baumann BM, Perrone J, Hornig SE, et al. Randomized, double-blind, placebo-controlled trial of diazepam, nitroglycerin, or both for treatment of patients with potential cocaine-associated acute coronary syndromes. Acad Emerg Med. 2000;7:878-85.
268. Turnipseed SD, Richards JR, Kirk JD, et al. Frequency of acute coronary syndrome in patients presenting to the emergency department with chest pain after methamphetamine use. J Emerg Med. 2003;24:369-73.
269. Wollert KC, Kempf T, Lagerqvist B, et al. Growth differentiation factor 15 for risk stratification and selection of an invasive treatment strategy in non ST-elevation acute coronary syndrome. Circulation. 2007;116:1540-8.
270. Viswanathan K, Kilcullen N, Morrell C, et al. Heart-type fatty acid-binding protein predicts long-term mortality and re-infarction in consecutive patients with suspected acute coronary syndrome who are troponin-negative. J Am Coll Cardiol. 2010;55:2590-8.
271. Charpentier S, Ducasse JL, Cournot M, et al. Clinical assessment of ischemia-modified albumin and heart fatty acid-binding protein in the early diagnosis of non-ST-elevation acute coronary syndrome in the emergency department. Acad Emerg Med. 2010;17:27-35.
272. Haaf P, Reichlin T, Corson N, et al. B-type natriuretic peptide in the early diagnosis and risk stratification of acute chest pain. Am J Med. 2011;124:444-52.
273. Keller T, Tzikas S, Zeller T, et al. Copeptin improves early diagnosis of acute myocardial infarction. J Am Coll Cardiol. 2010;55:2096-106.
274. Peacock WF, Nagurney J, Birkhahn R, et al. Myeloperoxidase in the diagnosis of acute coronary syndromes: the importance of spectrum. Am Heart J. 2011;162:893-9.
275. Iversen KK, Dalsgaard M, Teisner AS, et al. Usefulness of pregnancy-associated plasma protein A in patients with acute coronary syndrome. Am J Cardiol. 2009;104:1465-71.
276. Bogaty P, Boyer L, Simard S, et al. Clinical utility of C-reactive protein measured at admission, hospital discharge, and 1 month later to predict outcome in patients with acute coronary disease. The RISCA (recurrence and inflammation in the acute coronary syndromes) study. J Am Coll Cardiol. 2008;51:2339-46.
277. Kuch B, von SW, Kling B, et al. Differential impact of admission C-reactive protein levels on 28-day mortality risk in patients with ST-elevation versus non-ST-elevation myocardial infarction (from the Monitoring Trends and Determinants on Cardiovascular Diseases [MONICA]/Cooperative Health Research in the Region of Augsburg [KORA] Augsburg Myocardial Infarction Registry). Am J Cardiol. 2008;102:1125-30.
278. Schaub N, Reichlin T, Twerenbold R, et al. Growth differentiation factor-15 in the early diagnosis and risk stratification of patients with acute chest pain. Clin Chem. 2012;58:441-9.
279. Mega JL, Morrow DA, de Lemos JA, et al. Thrombus precursor protein and clinical outcomes in patients with acute coronary syndromes. J Am Coll Cardiol. 2008;51:2422-9.
280. Saraf S, Christopoulos C, Salha IB, et al. Impaired endogenous thrombolysis in acute coronary syndrome patients predicts cardiovascular death and nonfatal myocardial infarction. J Am Coll Cardiol. 2010;55:2107-15.
281. Body R, Pemberton P, Ali F, et al. Low soluble P-selectin may facilitate early exclusion of acute myocardial infarction. Clin Chim Acta. 2011;412:614-8.
282. Wang J, Zhang S, Jin Y, et al. Elevated levels of platelet-monocyte aggregates and related circulating biomarkers in patients with acute coronary syndrome. Int J Cardiol. 2007;115:361-5.
283. Oldgren J, Budaj A, Granger CB, et al. Dabigatran vs. placebo in patients with acute coronary syndromes on dual antiplatelet therapy: a randomized, double-blind, phase II trial. Eur Heart J. 2011;32:2781-9.
284. Alexander JH, Becker RC, Bhatt DL, et al. Apixaban, an oral, direct, selective factor Xa inhibitor, in combination with antiplatelet therapy after acute coronary syndrome: results of the Apixaban for Prevention of Acute Ischemic and Safety Events (APPRAISE) trial. Circulation. 2009;119:2877-85.
285. Steg PG, Mehta SR, Jukema JW, et al. RUBY-1: a randomized, double-blind, placebo-controlled trial of the safety and tolerability of the novel oral factor Xa inhibitor darexaban (YM150) following acute coronary syndrome. Eur Heart J. 2011;32:2541-54.
286. Cannon CP, Steinberg BA, Murphy SA, et al. Meta-analysis of cardiovascular outcomes trials comparing intensive versus moderate statin therapy. J Am Coll Cardiol. 2006;48:438-45.
287. Spencer FA, Goldberg RJ, Gore JM, et al. Comparison of utilization of statin therapy at hospital discharge and six-month outcomes in patients with an acute coronary syndrome and serum low-density lipoprotein>or=100 mg/dl versus<100 mg/dl. Am J Cardiol. 2007;100:913-8.
288. Robinson JG, Wang S, Smith BJ, et al. Meta-analysis of the relationship between non-high-density lipoprotein cholesterol reduction and coronary heart disease risk. J Am Coll Cardiol. 2009;53:316-22.
289. Hulten E, Jackson JL, Douglas K, et al. The effect of early, intensive statin therapy on acute coronary syndrome: a meta-analysis of randomized controlled trials. Arch Intern Med. 2006;166:1814-21.
290. Sattar N, Preiss D, Murray HM, et al. Statins and risk of incident diabetes: a collaborative meta-analysis of randomised statin trials. Lancet. 2010;375:735-42.
291. Javed U, Deedwania PC, Bhatt DL, et al. Use of intensive lipid-lowering therapy in patients hospitalized with acute coronary syndrome: an analysis of 65,396 hospitalizations from 344 hospitals participating in Get With The Guidelines (GWTG). Am Heart J. 2010;160:1130-6, 1136.
292. Baigent C, Blackwell L, Emberson J, et al. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. Lancet. 2010;376:1670-81.
293. Boekholdt SM, Arsenault BJ, Mora S, et al. Association of LDL cholesterol, non-HDL cholesterol, and apolipoprotein B levels with risk of cardiovascular events among patients treated with statins: a meta-analysis. JAMA. 2012;307:1302-9.
294. Mora S, Wenger NK, Demicco DA, et al. Determinants of residual risk in secondary prevention patients treated with high- versus low-dose statin therapy: the Treating to New Targets (TNT) study. Circulation. 2012;125:1979-87.
295. Nissen SE, Tuzcu EM, Libby P, et al. Effect of antihypertensive agents on cardiovascular events in patients with coronary disease and normal blood pressure: the CAMELOT study: a randomized controlled trial. JAMA. 2004;292:2217-25.
296. Messerli FH, Mancia G, Conti CR, et al. Dogma disputed: can aggressively lowering blood pressure in hypertensive patients with coronary artery disease be dangerous? Ann Intern Med. 2006;144:884-93.

297. Bangalore S, Qin J, Sloan S, et al. What is the optimal blood pressure in patients after acute coronary syndromes?: Relationship of blood pressure and cardiovascular events in the PRavastatin OR atorVastatin Evaluation and Infection Therapy-Thrombolysis In Myocardial Infarction (PROVE IT-TIMI) 22 trial. Circulation. 2010;122:2142-51.
298. Cooper-DeHoff RM, Gong Y, Handberg EM, et al. Tight blood pressure control and cardiovascular outcomes among hypertensive patients with diabetes and coronary artery disease. JAMA. 2010;304:61-8.
299. Malmberg K, Norhammar A, Wedel H, et al. Glycometabolic state at admission: important risk marker of mortality in conventionally treated patients with diabetes mellitus and acute myocardial infarction: long-term results from the Diabetes and Insulin-Glucose Infusion in Acute Myocardial Infarction (DIGAMI) study. Circulation. 1999;99:2626-32.
300. Knowler WC, Barrett-Connor E, Fowler SE, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med. 2002;346:393-403.
301. Suleiman M, Hammerman H, Boulos M, et al. Fasting glucose is an important independent risk factor for 30-day mortality in patients with acute myocardial infarction: a prospective study. Circulation. 2005;111:754-60.
302. Sinnaeve PR, Steg PG, Fox KA, et al. Association of elevated fasting glucose with increased short-term and 6-month mortality in ST-segment elevation and non-ST-segment elevation acute coronary syndromes: the Global Registry of Acute Coronary Events. Arch Intern Med. 2009;169:402-9.
303. Planer D, Lev I, Elitzur Y, et al. Bupropion for smoking cessation in patients with acute coronary syndrome. Arch Intern Med. 2011;171:1055-60.
304. Jorenby DE, Hays JT, Rigotti NA, et al. Efficacy of varenicline, an alpha4beta2 nicotinic acetylcholine receptor partial agonist, vs placebo or sustained-release bupropion for smoking cessation: a randomized controlled trial. JAMA. 2006;296:56-63.
305. Tonstad S, Tonnesen P, Hajek P, et al. Effect of maintenance therapy with varenicline on smoking cessation: a randomized controlled trial. JAMA. 2006;296:64-71.
306. Rigotti NA, Thorndike AN, Regan S, et al. Bupropion for smokers hospitalized with acute cardiovascular disease. Am J Med. 2006;119:1080-7.
307. Dawood N, Vaccarino V, Reid KJ, et al. Predictors of smoking cessation after a myocardial infarction: the role of institutional smoking cessation programs in improving success. Arch Intern Med. 2008;168:1961-7.
308. Mohiuddin SM, Mooss AN, Hunter CB, et al. Intensive smoking cessation intervention reduces mortality in high-risk smokers with cardiovascular disease. Chest. 2007;131:446-52.
309. Smith PM, Burgess E. Smoking cessation initiated during hospital stay for patients with coronary artery disease: a randomized controlled trial. CMAJ. 2009;180:1297-303.
310. Rigotti NA, Munafo MR, Stead LF. Smoking cessation interventions for hospitalized smokers: a systematic review. Arch Intern Med. 2008;168:1950-60.
311. Colivicchi F, Mocini D, Tubaro M, et al. Effect of smoking relapse on outcome after acute coronary syndromes. Am J Cardiol. 2011;108:804-8.
312. Nordmann AJ, Nordmann A, Briel M, et al. Effects of low-carbohydrate vs low-fat diets on weight loss and cardiovascular risk factors: a meta-analysis of randomized controlled trials. Arch Intern Med. 2006;166:285-93.
313. Chow CK, Jolly S, Rao-Melacini P, et al. Association of diet, exercise, and smoking modification with risk of early cardiovascular events after acute coronary syndromes. Circulation. 2010;121:750-8.
314. Gadde KM, Allison DB, Ryan DH, et al. Effects of low-dose, controlled-release, phentermine plus topiramate combination on weight and associated comorbidities in overweight and obese adults (CONQUER): a randomised, placebo-controlled, phase 3 trial. Lancet. 2011;377:1341-52.
315. Garvey WT, Ryan DH, Look M, et al. Two-year sustained weight loss and metabolic benefits with controlled-release phentermine/topiramate in obese and overweight adults (SEQUEL): a randomized, placebo-controlled, phase 3 extension study. Am J Clin Nutr. 2012;95:297-308.
316. Goel K, Lennon RJ, Tilbury RT, et al. Impact of cardiac rehabilitation on mortality and cardiovascular events after percutaneous coronary intervention in the community. Circulation. 2011;123:2344-52.
317. Hammill BG, Curtis LH, Schulman KA, et al. Relationship between cardiac rehabilitation and long-term risks of death and myocardial infarction among elderly Medicare beneficiaries. Circulation. 2010;121:63-70.