Data Supplement. 2012 UA/NSTEMI Focused Update Summary Table

Study	Aim of Study	Study Size	Patient Population Inclusion and Exclusion Criteria	Endpoints	Statistical Analysis Reported	P (95% CI)	OR/ HR/ RR	Conclusion
PLATO Ticagrelor vs. Clopidogrel in Patients with Acute Coronary Syndromes, Wallentin L, 2009. (1)	To compare ticagrelor (180 mg LD, 90 mg bid thereafter) and clopidogrel (300-600 mg LD, 75 mg daily thereafter) in the prevention of cardiovascular events among ACS pts.	18,624 patients (of whom 11,598 pts had UA/NSTEMI)	*Inclusion:* ACS w/out ST-segment elevation during previous 24 h and at least 2 of 3 criteria: ST-segment changes on ECG, positive biomarker, or 1of several risk factors (age ≥60 y, previous MI or CABG; CAD ≥50% in at 2 v; previous ischemic stroke, TIA, carotid stenosis at least 50%, or cerebral revascularization; DM,; PAD; or chronic renal dysfunction (CrCl <60 ml per min. per 1.73 m^2 of BSA). ACS with ST-segment elevation during previous 24 h, 2 criteria needed: persistent ST-segment elevation of at least 0.1 mV in at least 2 contiguous leads or a new LBBB, and, primary PCI. *Exclusion:* Contraindication against clopidogrel use, fibrinolytic therapy w/in 24 h prior to randomization, need for oral anticoagulation Rx, increased risk of	Primary efficacy endpoint: 12 mo composite of death from vascular causes, MI*, or stroke. Primary safety endpoint: any major bleeding event at 12 mo†.	Primary efficacy endpoint: 9.8% ticagrelor vs. 11.7% clopidogrel Secondary endpoints: Death from any cause, MI*, or stroke=10.2% ticagrelor vs. 12.3% clopidogrel Death from vascular causes, MI, stroke, severe recurrent ischemia, recurrent ischemia, TIA, or other arterial thrombotic event =14.6% ticagrelor vs. 16.7% clopidogrel Death from any cause (4.5% ticagrelor vs. 5.9% clopidogrel Subgroups (primary efficacy endpoint): NSTEMI: (n=7,955 pts; 11.4% ticagrelor vs. 13.9% clopidogrel UA: (n=3,112 pts; 8.6% ticagrelor vs. 9.1% clopidogrel	<0.001 (0.77 to 0.92) <0.001 (0.77 to 0.92 <0.001 (0.81 to 0.95) <0.001 (0.69 to 0.89 Not stated (0.73 to 0.94 Not stated (0.75 to	HR: 0.84 HR: 0.84 HR: 0.88 HR: 0.78 HR: 0.83 HR: 0.96	Ticagrelor Reduced primary and secondary endpoints in pts taking ticagrelor compared to clopidogrel. Ticagrelor was associated with an increase in the rate of non–procedure-related bleeding, but no increase in the rate of overall major bleeding compared to clopidogrel.

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			bradycardia, concomitant therapy w/ strong cytochrome P-450 3A inhibitor or inducer and clinically important anaemia or thrombocytopenia, and dialysis requirement (per PLATO study paper. James S, Akerblom A, Cannon CP, et al. Am Heart J. 2009;157:599-605.	Primary safety end point: any major bleeding event at 12 mo. Secondary safety end point	Primary safety endpoint (rates of major bleeding): 11.6% ticagrelor vs. 11.2% clopidogrel Non-CABG related major bleeding (4.5% ticagrelor vs. 3.8% clopidogrel	1.22) 0.43 (0.95 to 1.13) 0.03 (1.02 to 1.38)	HR: 1.04 HR: 1.19	
Ticagrelor Compared With Clopidogrel by Geographic Region in the Platelet Inhibition and Patient Outcomes (PLATO) Trial, Mahaffey KW, 2011. (2)	To investigate potential explanations for the observed region-by-treatment interaction in the PLATO study using Cox regression analyses.	U.S.=1413; rest of world =17,211	Less adherence to randomized treatment drug were seen in U.S. vs. rest of world pts. More US pts were treated with high-dose ASA after day 2 vs. rest of world pts (61% vs. 4%). Comprehensive statistical analyses of treatment interactions with baseline and post-randomization factors that including Cox analysis and landmark analyses, ASA was independently identified as a potential factor in the treatment-by-region interaction observed. Despite the number of analyses supporting the potential role of ASA maintenance dose to	Prespecified variables=31; post-randomization variables=6	CV death/MI*/stroke in U.S. =11.9% ticagrelor vs. 9.5% clopidogrel CV death / MI*/stroke in rest of the world = 9% ticagrelor vs. 11% clopidogrel CV death in U.S. = 3.4% vs. 2.7% clopidogrel CV death in rest of the world = 3.8% ticagrelor vs. 4.9% clopidogrel MI (excluding silent) in U.S. = 9.1% ticagrelor vs. 6.7% clopidogrel	0.1459 (0.92 to 1.75) <0.0001 (0.74 to 0.90) 0.4468 (0.69 to 2.31 0.0005 (0.67 to 0.89) 0.0956	HR: 1.27 HR: 0.81 HR: 1.26 HR: 0.77 HR: 1.38	Using an ASA dose >100 mg is a possible explanation for the outcome differences between the U.S. and the rest of the world. Higher doses of ASA were used at landmark points. More U.S. pts were treated with a high-dose ASA after day 2 compared with the rest of the world pts (61% vs. 4%). However, play of

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			explain the treatment-by-region interaction, statistical evaluations indicate the observed regional interaction and pattern of results seen across regions and countries were consistent with what might be expected by chance alone in a large, multiregional clinical trial with multiple exploratory analyses.		MI (excluding silent) in rest of the world = 5.1% ticagrelor vs. 6.4% clopidogrel Stroke in U.S. = 1.0% ticagrelor vs. 0.6% clopidogrel Stroke in rest of the world = 1.49% ticagrelor vs. 1.2% clopidogrel U.S. ASA dose ≥300 mg: ticagrelor 40 events vs. clopidogrel 27 events U.S. ASA dose >100 to <300 mg: ticagrelor 2 events vs. clopidogrel 2 events (HR: not calculated) U.S. ASA dose ≤100 mg: ticagrelor 19 events vs. clopidogrel 24 events Non-U.S. ASA dose ≥300 mg: ticagrelor 28 events vs. clopidogrel 23 events Non-U.S. ASA dose	(0.95 to 2.01) 0.0004 (0.70 to 0.90) 0.3730 (0.51 to 5.97) 0.2964 (0.88 to 1.50) Not stated (0.99 to 2.64) Not stated (not stated) Not stated (0.40 to 1.33) Not stated (0.71 to 2.14)	HR: 0.80 HR: 1.75 HR: 1.15 HR: 1.62 Not stated HR: 0.73 HR: 1.23	chance could not be excluded. This analysis indicated that $P2Y_{12}$ inhibition with ticagrelor in pts with ACS should be complemented with a low dose ASA maintenance regimen (75-100 mg), as this was associated with the most favorable cardiovascular outcomes.

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					>100 to <300 mg: ticagrelor 62 events vs. clopidogrel 63 events Non-U.S. ASA dose ≤100 mg: ticagrelor 546 events vs. clopidogrel 699 events	Not stated (0.71 to 1.42) Not stated (0.69 to 0.87)	HR: 1.00 HR: 0.78	
Ticagrelor vs. clopidogrel in patients with acute coronary syndromes intended for noninvasive management: substudy from prospective randomized PLATelet inhibition and patient Outcomes (PLATO) trial, James SK, 2011. (3)	To evaluate efficacy and safety outcomes in pts in PLATO (treating physician designated pts as planned for initial invasive management or initial conservatory management).	5216 pts specified for planned non-invasive management (n=2601 ticagrelor; n=2615 clopidogrel) (28% of 18,624 PLATO participants)	See main PLATO study (1)	Primary composite end point of cardiovascular death, MI, and stroke; their individual components; PLATO defined major bleeding at 1 yr.	Primary endpoint of CV death, MI*, stroke: 12% ticagrelor vs. 14.3% clopidogrel Secondary endpoints: MI*: 7.2% ticagrelor vs. 7.8% clopidogrel CV death: 5.5% ticagrelor vs. 7.2% clopidogrel All cause death: 6.1% ticagrelor vs. 8.2% clopidogrel CV death, MI, stroke, composite ischaemic events, other arterial thrombotic events: 18.6% ticagrelor vs. 20.3% clopidogrel Primary safety objective: total major bleeding:	0.04 (0.73 to 1.00) 0.555 (0.77 to 1.15) 0.019 (0.61 to 0.96) 0.010 (0.61 to 0.93) 0.309 (0.82 to 1.06) 0.08 (0.98 to 1.39)	HR: 0.85 HR: 0.94 HR: 0.76 HR: 0.75 HR: 0.94 HR: 1.17	PLATO pts with ACS managed w/ planned noninvasive strategy treated with ticagrelor compared to clopidogrel had a reduction in ischaemic events and mortality, without increasing major bleeding.

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					11.9% ticagrelor vs. 10.3% clopidogrel			
CURRENT-OASIS 7 Dose comparisons of clopidogrel and aspirin in acute coronary syndromes, Mehta SR, 2010. (4)	To evaluate whether doubling the dose of loading and initial maintenance doses of clopidogrel is superior to the standard-dose clopidogrel regimen and to investigate if higher-dose ASA is superior to lower-dose ASA. Pts were assigned in a 2 × 2 factorial design to 600 mg clopidogrel loading on Day 1, followed by 150 mg/d for 6 d, then 75 mg thereafter vs. 300 mg clopidogrel loading on Day 1, followed by 75 mg/d thereafter and either ASA 300-325 mg/d vs. lower-dose ASA	25,086	Inclusion criteria: Age ≥18 y with non–ST-segment ACS or STEMI. Requirements included ECG changes compatible with ischemia or elevated cardiac biomarkers and coronary angiographic assessment, with plan to perform PCI as early as possible, but no later than 72 h after randomization. Exclusion criteria: Increased risk of or known bleeding and allergy to clopidogrel or ASA.	Primary outcome was CV death, MI, or stroke, whichever occurred first, at 30 d. Prespecified secondary endpoint was definite or probable stent thrombosis (by ARC definition) in pts who underwent PCI. Main safety outcome was major bleeding according to trial criteria‡.	Primary outcome for clopidogrel dose comparison: 4.2% in double-dose clopidogrel group vs. 4.4% in standard-dose clopidogrel group.	0.30 (0.83 to 1.06)	HR: 0.94	This analysis of the overall trial in 25,086 pts failed to demonstrate a significant difference in the primary endpoint of CV death, MI, or stroke at 30 d between the double-dose clopidogrel for 7 d vs. standard-dose clopidogrel and between the higher-dose vs. lower-dose aspirin subgroups. The secondary endpoint of definite stent thrombosis in those undergoing PCI was reduced in the clopidogrel higher-dose group for both DES vs. non-DES subtypes, but this benefit was offset by increased major bleeding in the higher-dose clopidogrel group.
					Major bleeding for clopidogrel dose comparison: 2.5% in double-dose clopidogrel group vs. 2.0% in standard-dose clopidogrel group.	0.01 (1.05 to 1.46)	HR: 1.24	
					Primary outcome for ASA dose comparison: 4.2% in higher-dose ASA group vs. 4.4% in lower-dose ASA group.	0.47 (0.86 to 1.09)	HR: 0.97	
					Major bleeding for ASA comparison: 2.3% in higher-dose ASA group vs. 2.3% in lower-dose ASA group.	0.90 (0.84 to 1.17)	HR: 0.99	
					Clopidogrel and ASA dose interaction—primary outcome for pts on higher-dose ASA: 3.8% in double-dose clopidogrel vs.	0.03 (0.69 to 0.98)	HR: 0.82	

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	75-100 mg/d.				4.6% in standard-dose clopidogrel.			
					Clopidogrel and ASA dose interaction—primary outcome for pts on lower-dose ASA: 4.5% in double-dose clopidogrel vs. 4.2% in standard-dose clopidogrel	0.46 (0.90 to 1.26)	HR: 1.07	
					Stent thrombosis in pts who underwent PCI: 1.6% with double-dose clopidogrel vs. 2.3% with standard-dose clopidogrel.	0.001 (0.55 to 0.85)	HR: 0.68	
CURRENT-OASIS 7 Double-dose vs. standard-dose clopidogrel and high-dose vs. low-dose aspirin in individuals	The goal of this prespecified subgroup analysis of CURRENT-OASIS 7(4) was to examine efficacy and safety outcomes	17,263	Inclusion criteria: Pts with ACS (with or without ST-segment elevation) and either ECG evidence of ischemia or elevated biomarkers. Pts were required to have coronary angioplasty with intent to undergo PCI as	Primary outcome was composite of CV death, MI, or stroke from randomization to Day 30. Secondary outcomes included primary outcome plus recurrent ischemia, individual components	Primary outcome in clopidogrel dose comparison reduced with double-dose clopidogrel: 3.9% in double-dose clopidogrel group vs. 4.5% in standard-dose clopidogrel group.	0.039 (0.74 to 0.99)	Adjusted HR: 0.86	This sub-study of CURRENT-OASIS-7 analyzed the 69% of pts (n=17,263) who underwent PCI, a prespecified analysis in a postrandomization

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undergoing percutaneous coronary intervention for acute coronary syndromes (CURRENT-OASIS 7): a randomised factorial trial, Mehta SR, 2010. (5)	in pts who underwent PCI.		early as possible, but not later than 72 h after randomization. Exclusion criteria: Increased risk of bleeding or active bleeding. Additional information on study eligibility criteria in study Web appendix.	of composite outcomes, and stent thrombosis per ARC criteria.	Secondary outcome (CV death, MI, stroke, or recurrent ischemia) in clopidogrel dose comparison was reduced with double-dose clopidogrel: 4.2% in double-dose clopidogrel vs. 5.0% in standard-dose clopidogrel.	0.025 (0.74 to 0.98)	HR: 0.85	subset. In this PCI subgroup, the primary outcome of CV death, MI, or stroke at 30 d was reduced in those randomized to higher dose clopidogrel, and this was largely driven by a reduction in myocardial (re)infarction. Definite stent thrombosis also was reduced in the higher clopidogrel dose group with consistent results across DES vs. non-DES subtypes. Outcomes were not significantly different by ASA dose. Major bleeding was more common with higher-dose clopidogrel but not with higher-dose ASA.
					Rates of definite stent thrombosis were lower with double-dose clopidogrel (0.7%) vs. standard-dose clopidogrel (1.3%).	0.0001 (0.39 to 0.74)	HR: 0.54	
					CURRENT-defined major bleed was more common with double-dose (0.1%) than standard-dose clopidogrel (0.04%); however, no difference in TIMI-defined severe or major bleeding.	0.16 (0.71 to 7.49)	HR: 2.31	
TIMACS Early vs. delayed invasive intervention in acute coronary syndromes, Mehta	To study efficacy of an early invasive strategy (within 24 h of presentation) compared with	3031	Inclusion criteria: Presentation to a hospital with UA or MI without ST-segment elevation within 24 h after onset of symptoms and if 2 of the following 3 criteria for	Composite of death, MI, or stroke at 6 mo.	At 6 mo the primary outcome occurred in 9.6% of pts in early-intervention group vs. 11.3% of delayed-intervention group.	0.15 (0.68 to 1.06)	HR: 0.85	TIMACS initially targeted enrollment of 4000 pts but terminated enrollment at 3,031 pts due to recruitment

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SR, 2009. (6)	delayed invasive strategy (any time >36 h after presentation).		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 ST-segment elevation or T-wave inversion >3 mm). Exclusion criteria: Patient who is not a suitable candidate for revascularization.		28% risk reduction in secondary outcome of death, MI, or refractory ischemia in early-intervention group (9.5%) vs. delayed-intervention group (12.9%).	0.003 (0.58 to 0.89)	HR: 0.72	challenges, limiting its power. For the overall trial population, there was only a non-significant trend to a reduction in the primary ischemic endpoint in the early compared to delayed intervention groups. The prospectively-defined secondary endpoint of death, MI, or refractory ischemia was reduced by early intervention, mainly because of a reduction in refractory ischemia. Heterogeneity was observed in the primary ischemic endpoint by a pre-specified estimate of baseline risk according to the GRACE score, with pts in the highest tertile experiencing a sizeable risk reduction and suggesting a potential advantage
					Prespecified analyses indicated early intervention improved the primary outcome in the third of pts at highest risk.	0.006 (0.48 to 0.89)	HR: 0.65	
					Prespecified analyses did not show that early intervention improved primary outcome in the two thirds at low to intermediate risk.	0.48 (0.81 to 1.56)	HR: 1.12	

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								of early revascularization in this high risk subgroup.
CARE Cardiac Angiography in Renally Impaired Patients (CARE) study: a randomized double-blind trial of contrast-induced nephropathy in patients with chronic kidney disease, Solomon RJ, 2007. (7)	To compare iopamidol and iodixanol in pts with CKD (eGFR 20-59 mL/min) who underwent cardiac angiography or PCI.	482	Inclusion criteria: Men and women (≥18 y) with moderate to severe CKD scheduled for diagnostic cardiac angiography or PCI. Exclusion criteria: Pregnancy, lactation, administration of any investigational drug within the previous 30 d, intra-arterial or IV administration of iodinated CM from 7 d before to 72 h after administration of the study agents, medical conditions or circumstances that would have substantially decreased chance to obtain reliable data (NYHA class IV CHF, hypersensitivity to iodine-containing compounds, hyperthyroidism or thyroid malignancies, uncontrolled DM, unstable renal drug dependence, psychiatric	Primary endpoint was postdose SCr increase of 0.5 mg/dL (44.2 mol/L) over baseline. Secondary outcome was postdose SCr increase ≥25%, a postdose estimated GFR decrease ≥25%, and mean peak change in SCr.	In 414 pts, contrast volume, presence of DM, use of N-acetylcysteine, mean baseline SCr, and eGFR were comparable in the 2 groups. SCr increases of ≥0.5 mg/dL occurred in 4.4% (9 of 204 pts) after use of iopamidol and 6.7% (14 of 210 pts) after iodixanol.	0.39 (–6.7 to 2.1)	Not stated	In this randomized trial of moderate size, the rate of CIN in higher-risk pts with moderate CKD was not significantly different between the low-osmolar contrast medium iopamidol and the iso-osmolar contrast medium iodixanol.
					Rates of SCr increases ≥25% were 9.8% with iopamidol and 12.4% with iodixanol.	0.44 (–8.6 to 3.5)	Not stated	
					In pts with DM, SCr increases to ≥0.5 mg/dL were 5.1% (4 of 78 pts) with iopamidol and 13% (12 of 92 pts) with iodixanol.	0.11	Not stated	
					In pts with DM, SCr increases ≥25% were 10.3% with iopamidol and 15.2% with iodixanol.	0.37	Not stated	

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			disorders, dementia), administration of any medication to prevent CIN other than N-acetylcysteine, or intake of nephrotoxic medications from 24 h before to 24 h after administration of the study agent.		Mean post-SCr increases were significantly less with iopamidol (all pts: 0.07 mg/dL with iopamidol vs. 0.12 mg/dL with iodixanol).	0.03	Not stated	
					In pts with DM, SCr change from baseline was 0.07 mg/dL with iopamidol vs. 0.16 mg/dL with iodixanol.	0.013	Not stated	
					Decreases in eGFR ≥25% were recorded in 5.9% (12 pts) with iopamidol and 10% (21 pts) with iodixanol.	0.15 (–9.3 to 1.1)	Not stated	
The relative renal safety of iodixanol compared with low-osmolar contrast media: a meta-analysis of randomized controlled trials, Reed M, 2009. (8)	Meta-analysis to compare nephrotoxicity of the iso-osmolar contrast medium iodixanol with LOCM.	16 trials (2,763 subjects)	Pts enrolled in RCTs that compared incidence of CI-AKI with either iodixanol or LOCM.	Primary endpoint was incidence of CI-AKI. Secondary endpoints were need for renal replacement therapy and mortality.	No significant difference in incidence of CI-AKI in iodixanol group than in LOCM group (overall summary).	0.19 (0.56 to 1.12)	Summary RR 0.79	In this updated meta-analysis of 16 CIN trials, data supporting a reduction in CIN favoring the iso-osmolar medium iodixanol compared to LOCM were no longer significant. Sub-analyses suggested potential variations in relative renal safety by specific LOCM with reductions in CIN for iodixanol
					CI-AKI was reduced when iodixanol was compared with ioxaglate	0.022 (0.37 to 0.92)	RR 0.58	
					and when iodixanol was compared with iohexol,	(0.07 to 0.56)	RR 0.19	
					but no difference was noted when iodixanol was compared with iopamidol,	0.55 (0.66 to 2.18)	RR 1.20	

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					iodixanol was compared with iopromide,	0.84 (0.47 to 1.85)	RR 0.93	compared with the ionic LOCM ioxaglate and with iohexol, a nonionic LOCM, but not with 4 other LOCM.
					or iodixanol compared with ioversol.	0.68 (0.60 to 1.39)	RR 0.92	
					No significant difference between iodixanol and LOCM noted in rates of postprocedure hemodialysis.	0.20 (0.08 to 1.68)	RR 0.37	
					No significant difference between iodixanol and LOCM in rates of death.	0.663 (0.33 to 5.79)	RR 1.38	
Nephrotoxicity of iso-osmolar iodixanol compared with nonionic low-osmolar contrast media: meta-analysis of randomized controlled trials, Heinrich MC, 2009. (9)	Meta-analysis of RCTs to compare nephrotoxicity of iso-osmolar iodixanol with nonionic LOCM.	25 trials (3270 subjects)	Inclusion criteria: RCTs analyzing SCr levels before and after intravascular application of iodixanol or LOCM.	Incidence of CIN and change in SCr levels.	Iodixanol did not significantly reduce risk of CIN (or risk of SCr increase) compared with LOCM overall. However, risk of intra-arterial iohexol was greater than that of iodixanol.	0.10 (0.61 to 1.04)	RR 0.80	In this contemporary meta-analysis of 25 trials, the incidence of CIN was similar for a pooled comparison of all nonionic LOCM other than iohexol and for the iso-osmolar medium iodixanol, indicating equivalent safety for these 2 classes of CM.
					No significant risk reduction after IV administration of CM.	0.79 (0.62 to 1.89)	RR 1.08	
					In pts with intra-arterial administration and renal insufficiency, risk of CIN was greater for iohexol than for iodixanol.	<0.01 (0.21 to 0.68)	RR 0.38	

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					No difference between iodixanol and the other (noniohexol) LOCM.	0.86 (0.50 to 1.78)	RR 0.95	
EARLY-ACS Early vs. delayed, provisional eptifibatide in acute coronary syndromes, Giugliano RP, 2009. (10)	To evaluate upstream use of GP IIb/IIIa inhibitor eptifibatide vs. provisional eptifibatide administration in the catheterization lab in high-risk pts with NSTE ACS.	9492	Inclusion criteria: Pts at least 18 y of age were randomized within 8-12 h after presentation and assigned to an invasive treatment strategy no sooner than the next calendar day. To qualify as having a high-risk UA/NSTEMI, pts were required to have at least 2 of the following: ST-segment depression or transient ST elevation, elevated biomarker levels (CK-MB or troponin), and age ≥60 y. The study protocol was later amended to permit enrollment of pts age 50-59 y with elevated cardiac biomarker levels and documented vascular disease and clarified the timing of angiography as ≥12 h after randomization. Exclusion criteria: Increased risk of bleeding, allergy to heparin or eptifibatide, pregnancy, renal dialysis within previous 30 d, intention of investigator	The primary efficacy composite endpoint was death from any cause, MI, recurrent ischemia requiring urgent revascularization, or thrombotic bailout at 96 h. The secondary efficacy endpoint was composite of death from any cause or MI within the first 30 d. Safety endpoints included rates of hemorrhage, transfusion, surgical reexploration, stroke, thrombocytopenia, and serious adverse events at 120 h after randomization.	The primary endpoint was less in the early-eptifibatide group (9.3%) vs. the delayed-eptifibatide group (10%), but not significant.	0.23 (0.80 to 1.06)	OR 0.92	In the setting of frequent early (precatheterization) use of clopidogrel, the administration of early, routine eptifibatide (double-bolus and infusion) did not achieve statistically significant reductions in ischemic events at 96 h (i.e., 8%, primary endpoint) and 30 d (i.e., 11%, secondary endpoint) compared to provisional administration of eptifibatide, given after angiography but before PCI. Early, routine eptifibatide was associated with a greater risk of bleeding. No significant interactions were noted between efficacy endpoints
					At 30 d the rate of death or MI was 11.2% in the early-eptifibatide group vs. 12.3% in the delayed-eptifibatide group.	0.08 (0.79 to 1.01)	OR 0.89	
					Pts in the early-eptifibatide group experienced higher TIMI major hemorrhage compared with the delayed-eptifibatide group (2.6% vs. 1.8%, respectively), higher rates of moderate GUSTO bleeding (6.8% in the early-eptifibatide group vs. 4.3% in the delayed-eptifibatide group; p<0.001), similar severe GUSTO bleeding (0.8% early-eptifibatide group vs. 0.9% in delayed-eptifibatide group;	0.02 (1.07 to 1.89)	OR 1.42	

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			to use a nonheparin anticoagulant, recent use of a GP IIb/IIIa inhibitor, and any other condition that posed increased risk.		p=0.97), and need for red-cell transfusion was increased in the early-eptifibatide group compared with the delayed-eptifibatide group (8.6% vs. 6.7%, respectively; p=0.001).			and prespecified baseline characteristics.
ABOARD Immediate vs delayed intervention for acute coronary syndromes: a randomized clinical trial, Montalescot G, 2009. (11)	To determine if immediate intervention on admission can result in reduction of MI vs. delayed intervention.	252	Inclusion criteria: Presence of at least 2 of the following: ischemic symptoms, ECG abnormalities in at least 2 contiguous leads, or positive troponin, TIMI risk score ≥3. Exclusion criteria: Hemodynamic or arrhythmic instability requiring urgent catheterization, chronic oral anticoagulation, or thrombolytic therapy in the preceding 24 h.	Primary endpoint was peak troponin value during hospitalization. Secondary endpoints were composite of death, MI, or urgent revascularization at 1-mo follow-up.	No difference was found in peak troponin-I between groups (median 2.1 ng/dL [0.3 to 7.1 ng/mL] vs. 1.7 mg/mL [0.3 to 7.2 ng/mL] in immediate- and delayed-intervention groups, respectively).	0.70 (Not stated)	Not stated	Immediate (at a median of 70 min) vs. delayed (at a median of 21 h) angiography and revascularization in UA/NSTEMI pts conferred no advantage with regard to the primary endpoint (myocardial necrosis by TnI), nor did it result in even a trend toward improved outcome in the clinical secondary endpoint of death, MI, or urgent revascularization by 1 month.
					Secondary endpoint was seen in 13.7% (95% CI: 8.6% to 18.8%) of immediate-intervention group vs. 10.2% (95% CI: 5.7% to 14.6%) of delayed-intervention group. The other endpoints did not differ between the 2 strategies.	0.31	Not stated	
TRITON-TIMI 38 Prasugrel vs. clopidogrel in patients with acute coronary	To evaluate treatment with prasugrel compared with clopidogrel among pts undergoing	13,608	Inclusion criteria: Scheduled PCI for ACS. For UA/NSTEMI pts, ischemic symptoms ≥10 min within 72 h of randomization, TIMI risk score ≥3, and either ST-	Primary endpoints were death from CV causes, nonfatal MI, or nonfatal stroke. Key safety endpoint was major bleeding§.	Primary endpoint was significantly lower in prasugrel group compared with clopidogrel group (9.9% vs. 12.1%, respectively).	<0.001 (0.73 to 0.90)	HR: 0.81	TRITON-TIMI-38 compared the new thienopyridine prasugrel to clopidogrel in 13,608 moderate-to-high risk

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Study	Aim of Study	Study Size	Patient Population Inclusion and Exclusion Criteria	Endpoints	Statistical Analysis Reported	P (95% CI)	OR/ HR/ RR	Conclusion
syndromes, Wiviott SD, 2007. (12)	planned PCI for ACS.		segment deviation ≥1 mm or elevated cardiac biomarker of necrosis. For STEMI pts, symptom onset within 12 h of randomization if primary PCI was scheduled or within 14 d if medically treated for STEMI. Exclusion criteria: Included increased bleeding risk, anemia, thrombocytopenia, intracranial pathology, or use of any thienopyridine within 5 d.		Primary endpoint was consistent in UA/NSTEMI cohort (9.9% with prasugrel vs. 12.1% with clopidogrel; 18% RR).	0.002 (0.73 to 0.93)	HR: 0.82	STEMI and NSTEMI pts scheduled to undergo PCI. Prasugrel was associated with a reduction in the composite ischemic event rate over 15 mo of follow-up, including stent thrombosis, but it was associated with a significantly increased rate of bleeding. In subgroup analyses, those with prior stroke/TIA fared worse on prasugrel, and no advantage was seen in those age ≥75 y or <60 kg in weight.
					Primary endpoint in STEMI cohort (10% in prasugrel vs. 12.4% in clopidogrel; 21% RR).	0.02 (0.65 to 0.97)	HR: 0.79	
					Efficacy benefit evident by 3 d (4.7% in prasugrel group vs. 5.6% in clopidogrel group).	0.01 (0.71 to 0.96)	HR: 0.82	
					Efficacy benefit evident from Day 3 to end of follow-up (5.6% in pts receiving prasugrel vs. 6.9% of pts receiving clopidogrel).	0.003 (0.70 to 0.93)	HR: 0.80	
					Definite or probable stent thrombosis occurred less frequently in prasugrel group than in clopidogrel group (1.1% vs. 2.4%, respectively).	<0.001 (0.36 to 0.64)	HR: 0.48	
					Safety endpoint of TIMI major non-CABG bleeding was higher with prasugrel compared with clopidogrel (2.4% vs. 1.8%, respectively).	0.03 (1.03 to 1.68)	HR: 1.32	

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					Increase in bleeding consistent for different categories of TIMI major bleeding, including life-threatening bleeding (1.4% in prasugrel vs. 0.9% in clopidogrel.	0.01 (1.08 to 2.13)	HR: 1.52	
					Fatal bleeding (0.4% in prasugrel vs. 0.1% in clopidogrel.	0.002 (1.58 to 11.11)	HR: 4.19	
					And nonfatal bleeding (1.1% in prasugrel vs. 0.9% in clopidogrel.	0.23 (0.87 to 1.81)	HR: 1.25	
					CABG-related TIMI major bleeding increased with prasugrel compared with clopidogrel (13.4% vs. 3.2%, respectively).	<0.001 (1.90 to 11.82)	HR: 4.73	
					No difference in mortality (death from any cause) between groups (3.0% in prasugrel group vs. 3.2% in clopidogrel group).	0.64 (0.78 to 1.16)	HR: 0.95	
					Net clinical benefit endpoint (composite of death, MI, stroke or TIMI major bleeding) favored prasugrel over clopidogrel (12.2% vs. 13.9%, respectively).	0.004 (0.79 to 0.95)	HR: 0.87	

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Study	Aim of Study	Study Size	Patient Population Inclusion and Exclusion Criteria	Endpoints	Statistical Analysis Reported	P (95% CI)	OR/ HR/ RR	Conclusion
SWEDEHEART 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), Szummer K, 2009. (13)	To describe distribution of CKD and use of early revascularization, as well as to determine if an invasive approach is associated with lower mortality at every level of renal function.	23, 262	Inclusion criteria: NSTEMI pts ≤80 y of age from nationwide CCU register (2003 and 2006).	Description of 1-y survival according to renal function stage.	Pts treated with early revascularization had overall improved survival rate at 1 y.	<0.001 (0.56 to 0.73)	HR: 0.64	A contemporary nationwide Swedish registry, evaluated the use of early revascularization after NSTEMI across all stages of CKD, and stratified outcomes by stage of CKD. Early revascularization was associated with improved adjusted 1-y survival in UA/NSTEMI pts with mild-to-moderate CKD, but no association was observed in those with severe and end-stage disease. SWEDEHEART is limited by its observational nature, but by capturing unselected pts, it may be quite reflective of real-world experience.
					1-y mortality for pts with eGFR ≥90: 1.9% for invasive treatment vs. 10% for medical treatment	0.001 (0.42 to 0.80)	HR: 0.58	
					1-y mortality for pts with eGFR 60 to 89: 2.4% for invasive treatment vs. 10% for medical treatment.	<0.001 (0.52 to 0.80)	HR: 0.64	
					1-y mortality for pts with eGFR 30 to 59: 7% for invasive treatment vs. 22% for medical treatment.	0.001 (0.54 to 0.81)	HR: 0.68	
					1-y mortality for pts with eGFR 15 to 29: 22% for invasive treatment vs. 41% for medical treatment.	0.740 (0.51 to 1.61)	HR: 0.91	
					1-y mortality for pts with eGFR <15/dialysis: 44% for invasive treatment vs. 53% for medical treatment.	0.150 (0.84 to 3.09)	HR: 1.61	

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Study	Aim of Study	Study Size	Patient Population Inclusion and Exclusion Criteria	Endpoints	Statistical Analysis Reported	P (95% CI)	OR/ HR/ RR	Conclusion
COGENT Clopidogrel with or without Omeprazole in Coronary Artery Disease, Bhatt DL, 2010. (14)	To investigate efficacy and safety of concomitant clopidogrel and PPI administration in pts with CAD receiving clopidogrel and ASA.	3761	Inclusion criteria: Age ≥21 y, clopidogrel therapy with concomitant ASA anticipated for at least next 12 mo, including pts with ACS or coronary stent placement. Exclusion criteria: Hospitalized pts for whom discharge not anticipated within 48 h of randomization; need for current/long-term use of PPI, H2-receptor antagonist, sucralfate, or misoprostol; erosive esophagitis or esophageal or gastric variceal disease or previous nonendoscopic gastric surgery; clopidogrel or other thienopyridine >21 d before randomization; receipt of oral anticoagulant unable to be discontinued safely; recent fibrinolytic therapy.	Primary GI safety endpoint: composite of GI overt or occult bleeding, symptomatic gastroduodenal ulcers or erosions, obstructions, or perforation. Primary CV safety endpoint: composite of death from CV causes, nonfatal MI, coronary revascularization, or ischemic stroke.	Total GI event rate: 1.1% with omeprazole vs. 2.9% with placebo	<0.001 (0.18 to 0.63)	HR: 0.34	In this randomized, placebo controlled comparison in 3,873 pts with an indication for dual-antiplatelet therapy, no difference was found in the primary composite CV endpoint between clopidogrel plus omeprazole and clopidogrel plus placebo at 180 d. The rate of GI bleeding and associated complications were reduced with omeprazole. Study limitations include premature termination of planned enrollment, limited follow-up and power to discern small to moderate differences between therapies, inadequate ascertainment of all end points, and the use of a single-pill formulation, which might differ in release kinetics
					Overt upper GI bleeding rate: 0.1% with omeprazole vs. 0.6% with placebo	0.001 (0.03 to 0.56)	HR: 0.13	
					Total CV event rate: 4.9% with omeprazole vs. 5.7% with placebo	0.96 (0.68 to 1.44)	HR: 0.99	

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Study	Aim of Study	Study Size	Patient Population Inclusion and Exclusion Criteria	Endpoints	Statistical Analysis Reported	P (95% CI)	OR/ HR/ RR	Conclusion
								for its two components.

*These events excluded silent MI (which accounted for 0.1% in each treatment group in PLATO).

†PLATO major bleeding was defined as major life-threatening bleeding (fatal bleeding, intracranial bleeding, intrapericardial bleeding with cardiac tamponade, hypovolemic shock or severe hypotension due to bleeding and requiring pressors or surgery, a decline in the hemoglobin level of ≥5 g/dL, or the need for transfusion of ≥4 units of red cells) or other major bleeding (e.g., bleeding that led to clinically-significant disability (e.g., intraocular bleeding with permanent vision loss) or bleeding either associated with a drop in the hemoglobin level of ≥3 g/dL but <5/dL or requiring transfusion of 2-3 units of red cells.

‡The primary safety outcome is major bleeding (i.e., severe bleeding plus other major bleeding). Severe bleeding was defined as: Fatal or leading to a drop in hemoglobin of ≥5 g/dL, or significant hypotension with the need for inotropes, or requiring surgery (other than vascular site repair), or symptomatic intracranial hemorrhage, or requiring transfusion of ≥4 units of red blood cells or equivalent whole blood. Other major bleeding was defined as: significantly disabling, intraocular bleeding leading to significant loss of vision or bleeding requiring transfusion of 2 or 3 units of red blood cells or equivalent whole blood.

§Key safety endpoint was non–CABG-related TIMI major bleeding (Intracranial hemorrhage ≥5 g/dL decrease in the hemoglobin concentration, ≥15% absolute decrease in hematocrit.

ACS indicates acute coronary syndrome; ARC, academic research consortium; ASA, aspirin; CABG, coronary artery bypass graft; CAD, coronary artery disease; CCU, coronary care unit; CHF, congestive heart failure; CI-AKI, contrast-induced acute kidney injury; CI, confidence interval; CIN, contrast-induced nephropathy; CKD, chronic kidney disease; CK-MB, creatine kinase-MB; CM, contrast media; CURRENT, Clopidogrel optimal loading dose Usage to Reduce Recurrent EveNTs; CV, cardiovascular; DES, drug-eluting stent; DM, diabetes mellitus; ECG, electrocardiograph; eGFR, estimated glomerular filtration rate; GI, gastrointestinal; GP, glycoprotein; GRACE, Global Registry of Acute Coronary Events; GUSTO, Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries trial; HR, hazard ratio; IV, intravenous; LD, loading dose; LOCM, low-osmolar contrast media; MACCE, major adverse cardiac and cerebrovascular events; MI, myocardial infarction; NSTE, non-ST-elevation; NSTEMI, non–ST-elevation myocardial infarction; NYHA, New York Heart Association; OR, odds ratio; patients, pts; PCI, percutaneous coronary intervention; PPI, proton pump inhibitor; RCT, randomized controlled trial; RR, relative risk; SCr, serum creatinine; STEMI, ST-elevation myocardial infarction; TIA, transient ischemic attack; TIMI, Thrombolysis in Myocardial Infarction; TnI, troponin I; UA, unstable angina; and ULN, upper limit of normal

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