2014 ACC/AHA Guideline on Perioperative Cardiovascular Evaluation and Management of Patients Undergoing Noncardiac Surgery

Data Supplement

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

Data Supplement 1. Coronary Artery Disease (Section 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*		
Wijeysundera DN, et al., 2012 (1) 22893606	To evaluate the outcomes of pts who underwent elective intermediate- to high-risk noncardiac surgery after stent implantation	Cohort study, secondary analysis of prospective clinical registry (2003–2009)	8,116 stent pts, who had stents within 10 y prior to noncardiac surgery	N/A	N/A	Surgeries included: AAA repair, carotid endarterectomy, peripheral bypass, total hip or knee replacement, large bowel resection, partial liver resection, Whipple, pneumonectomy, pulmonary lobectomy, gastrectomy, esophagectomy, total abdominal hysterectomy, radical prostatectomy, nephrectomy, and cystectomy	N/A	N/A	Stent pts <2 y after stent compared to those pts >2 y after stent at time of noncardiac surgery	Overall mortality for pts who previously had stent was 1.2% (n=100) at 30 d and 5.2% (n=419) at 1 y	N/A	The overall risk of MACE at 30 d was 2.1% (n=170) and at 1 y was 9.8% (n=798). MACE was highest when major elective noncardiac surgery was performed within 45 d after coronary stent.	N/A	Event rates are low, limiting statistical power. Administrative databases may not adequately capture all in-hospital complications.
Mashour GA, et al., 2011 (2) 21478735	Assess the incidence and predicators of periop stroke and its role in mortality in noncardiac, non-neurosurgical surgery	Secondary analysis of ACS NSQIP	523,059 pt data sets (deidentified from NSQIP database)	NSQIP participants from 250 participating U.S. medical centers for 4 y (2005–2008)	N/A	General surgery, orthopedic, urology, otolaryngology, plastics, thoracic, minor vascular, and gynecology cases	Cardiac, major vascular, and neurosurgical cases	N/A	N/A	The incidence of periop stroke was 0.1%	N/A	1. Multivariate analyses indicated MI within 6 mo of surgery and was an independent risk factor for periop stroke. 2. Multivariate analyses indicated HTN (requiring medication) and was an	MI within 6 mo of surgery was an independent risk factor for periop stroke (OR: 13.2; CI: 8.9–19.7; p<0.001). HTN was an independent risk factor for periop stroke (OR: 3.8; CI:	Observational study does not allow for additional data collection for pts exhibiting primary outcome. In addition, the data definitions are clinically relevant, but could not be modified for purposes of

												independent risk factor for periop stroke.	3.1–4.7; p<0.001).	this study.
Healy KO, et al., 2010 (3) 20412467	To evaluate the impact of LVEF on periop outcomes and long-term mortality in pts with HF undergoing intermediate- to high-risk surgery	Retrospective chart review	174 pts	Pts diagnosed with HF who underwent intermediate- or high-risk noncardiac surgery from 2001–2004	N/A	Diagnosis with HF; intermediate- or high-risk noncardiac surgery (including PVD surgery, aortic repair, carotid endarterectomy, head & neck, intraperitoneal, noncardiac intrathoracic, orthopedic or prostate surgery)	N/A	N/A	Pts with HF compared by LVEF (>50% normal; 40%–50% mildly reduced; 30%≥40% moderately reduced; <30% severely reduced)	1. 30.5% (n=53) had ≥1 periop events: death (n=14, 8.1%); MI (n=26, 14.9%); HF exacerbation (n=44, 25.3%) 2. Severely reduced LVEF (<30%) independently associated with adverse events.	N/A	N/A	1. Multivariate analyses for LVEF was an independent predictor of periop events including mortality (OR: 4.88; CI: 1.78–14.40).	Small, retrospective chart review from single institution.
Ferket BS, et al., 2011 (4) 21474039	To critically appraise guidelines on imaging of asymptomatic CAD	Systematic review	14 guidelines included in the review (published between 2003–2010)	N/A	N/A	1. Used IOM definition of clinical practice guidelines. 2. Contained recommendations on imaging of asymptomatic CAD aimed to prevent first coronary event. 3. Involved healthy persons (adults). 4. Produced on behalf of national or international medical specialty society.	N/A	N/A	N/A	1. 8 of 14 studies recommended against or concluded that there was insufficient evidence to recommend testing of asymptomatic CAD. 2. In 6 of the guidelines testing was indicated for pts with a priori elevated risk level based on absolute CAD risk or multiple risk factors (e.g., Framingham risk score).	N/A	1. 1 guideline recommended CT calcium scoring solely in an intermediate CAD risk population. 2. Guidelines unanimously did not advocate CT calcium scoring for low or high CAD risk pts.	N/A	Only guidelines developed by national or international medical specialty organizations were reviewed
Wijeysundera	To determine	Cohort study	Adult pts	Pts who had	Pts who did	Adults >40 y of	N/A	N/A	N/A	1. Hospital	1. Preop	Effects of	Mortality:	1. Did not

DN, et al., 2010 (5) 20110306	the association of noninvasive cardiac stress testing before elective intermediate-to high-risk noncardiac surgery with survival and hospital stay		from acute care hospitals in Ontario, Canada	noninvasive stress testing before surgical procedure (n=23,060)	not undergo stress testing before surgical procedure (n=247,090)	age, who had elective surgery from 1994–2004. Surgical procedures that had intermediate-to high-risk for periop cardiac complications.				mortality reduced among pts who had stress testing. 2. Hospital LOS reduced for pts who had stress testing prior to surgery.	stress testing was associated with harm in low-risk pts (RCRI: 0 points; HR: 1.35; 95% CI: 1.05–1.74). 2. Improved survival in intermediate-risk pts (RCRI: 1–2 points; HR: 0.92; 95% CI: 0.85–0.99) and high-risk pts (RCRI: 3–6 points; HR: 0.80; 95% CI: 0.67–0.97).	testing on mortality varied with RCRI class (p=0.005).	RR: 0.85; 95% CI: 0.73–0.98; p<0.03. Hospital LOS: difference of -0.24 d; 95% CI: 0.07–0.43; p<0.001.	compare outcomes form different stress tests (e.g., exercise treadmill, nuclear perfusion). 2. Observational design demonstrates association between preop testing and survival cannot determine causation.

AAA indicates abdominal aortic aneurysm; ACS, American College of Surgeons; CAD, coronary artery disease; CI: confidence interval; CT, computed tomography; HF, heart failure; HR, hazard ratio; HTN, hypertension; IOM, Institute of Medicine; LOS, length of stay; LVEF, left ventricular ejection fraction; MACE, major adverse cardiac event; MI, myocardial infarction; n, subgroup from N; N/A, not applicable; NSQIP, National Surgical Quality Improvement Program; OR: odds ratio; periop, perioperative; preop, preoperative; pt, patient; pts, patients; PVD, peripheral vascular disease; RCRI, Revised Cardiac Risk Index; and RR, relative risk.

Data Supplement 2. Influence of Age and Sex (Section 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*		
Bateman BT, et al., 2009 (6) 19194149	To conduct an analysis of AIS to determine incidence, risk factors, and effect of outcome on periop AIS in	Secondary analysis of NIS database	n=131,067 hemicolectomy surgical pts; n=201,235 total hip replacement surgical pts; n=39,339	N/A	N/A	Common noncardiac surgeries: hemicolectomy, total hip replacements, and segmental/ lobar lung	N/A	N/A	N/A	AIS incidence: hemicolectomy 935 cases—0.7% (95% CI: 0.7%–0.8%); total hip replacement 420 cases—	N/A	1. Higher incidence of AIS among pts ≥65 y of age. 2. Higher incidence of AIS among	1. Among pts >65 y of age, AIS incidence: hemicolectomy 1.0% (95% CI: 0.9%–1.0%); total hip replacement	Limited by range of variables that could be explored as risk factors for AIS. Use of database may

	noncardiac surgical pts		pulmonary lobectomy/ segment resection surgical pts			resection				0.2% (95% CI: 0.2%–0.2%); lobectomy/ segmental lung resection 242 cases—0.6% (95% CI: 0.7%–0.9%)		female pts and female sex was an independent risk factor for AIS.	0.3% (95% CI: 0.3%–0.3%); lobectomy/ segmental lung resection 0.8% (95% CI: 0.7%–0.9); 2. Female sex independent risk factor (OR: 1.21; CI: 1.07–1.36; p<0.001).	underestimate morbidity and mortality.
Mashour GA, et al., 2011 (2) 21478735	Assess the incidence and predicators of periop stroke and its role in mortality in noncardiac, non-neurosurgical surgery	Secondary analysis of ACS NSQIP	523,059 pt data sets (deidentified from NSQIP database)	NSQIP participants from 250 participating U.S. medical center for 4 y (2005–2008)	N/A	General surgery, orthopedic, urology, otolaryngology, plastics, thoracic, minor vascular, and gynecology cases	Cardiac, major vascular, and neurosurgical cases	N/A	Age dichotomized into 62 y of age and ≥62 y of age	The incidence of periop stroke was 0.1%	N/A	1. Multivariate analyses indicated age ≥62 y of age was an independent risk factor for periop stroke. 2. Multivariate analyses indicated male sex was an independent risk factor for periop stroke.	1. Older age was an independent risk factor for periop stroke (OR: 6.6; CI: 5.4–8.2; p<0.001). 2. Male sex was an independent risk factor for periop stroke (OR: 1.2; CI: 1.0–1.5; p=0.02).	Observational study does not allow for additional data collection for pts exhibiting primary outcome. In addition the data definitions are clinically relevant, but could not be modified for purposes of this study.
Rogers SO, et al., 2007 (7) 17544079	To develop and test a risk model for venous thromboembolic events. To develop and validate a risk index for VTE.	Secondary analysis of the PSS	183,069 pt records	Records from 128 VA and 14 private sector academic medical centers in general and peripheral vascular surgery subspecialties from 2002–	None	VTE defined as either PE or DVT	N/A	N/A	N/A	VTE occurred in 1,162 pts	N/A	Female sex was 1 of 15 independent factors associated with an increased risk of VTE compared to males	Female sex as independent risk factor for VTE (OR: 1.370; CI: 1.118–1.680).	Models limited by variables that are not part of NSQIP database that might impact the rates of VTE

				2004										
Dasgupta M, et al., 2009 (8) 18068828	To examine if frailty is associated with an increased risk of postop complications	Exploratory, prospective, descriptive	125	N/A	N/A	≥70 y of age, undergoing elective noncardiac surgery	Day surgery procedures, active cancer	N/A	N/A	Occurrence of an in-hospital, postop complication (unrelated to surgical technique). Adverse events occurred in 31/125 pts (25%). Both age (p<0.0074) and EFS scores (p<0.00042), indicators of frailty, were independently associated with being discharge to an institution and having a prolonged LOS.	N/A	N/A	OR was 1.14 for age (95% CI: 1.05–1.24) and 1.22 for EFS score (95% CI: 1.02–1.6)	Method of outcome identification using chart review. Single center study. Limited sample size.
Healy KO, et al., 2010 (3) 20412467	To evaluate the impact of LVEF on periop outcomes and long-term mortality in pts with HF undergoing intermediate- to high-risk noncardiac surgery	Retrospective chart review	174 pts	Pts diagnosed with HF who underwent intermediate- or high-risk noncardiac surgery from 2001–2004	N/A	Diagnosis with HF; intermediate- or high-risk noncardiac surgery (including PVD surgery, aortic repair, carotid endarterectomy, head & neck, intraperitoneal, noncardiac intrathoracic, orthopedic or prostate surgery)	N/A	N/A	Pts with HF compared by LVEF (>50% normal, 40%–50% mildly reduced, 30%–40% moderately reduced, <30% severely reduced)	N/A	≥80 y of age independently associated with adverse events	N/A	Multivariate analyses for older age as an independent predictor of periop events (OR: 3.84; CI: 1.70–8.17)	Small, retrospective chart review from single institution

ACS indicates American College of Surgeons; AIS, acute ischemic stroke; CI, confidence interval; DVT, deep vein thrombosis; EFS, Edmonton Frail Scale; HF, heart failure; HR, hazard ratio; LOS, length of stay; LVEF, left ventricular ejection fraction; n, subgroup from N; N/A, not applicable; NIS, Nationwide Inpatient Sample; NSQIP, National Surgical Quality Improvement Program; OR, odds ratio; PE, pulmonary embolism; periop, perioperative; postop, postoperative; PSS, protein secondary structure; pts, patients; PVD, peripheral vascular disease; RR, relative risk; VA, Veterans Affairs; and VTE, venous thromboembolism.

Data Supplement 3. HF and Cardiomyopathy (Sections 2.2 and 2.3)

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:
						Inclusion Criteria	*Exclusion Criteria*			*Primary Endpoint (Efficacy) and Results*	*Safety Endpoint and Results*	*Secondary Endpoint and Results*	
Impact of HF on Periop and Postop Outcomes													
Hammill BG, et al., 2008 (9) 18362586	To determine operative mortality and 30-d all-cause readmission among pts with HF, CAD, or neither who underwent major noncardiac surgery	Retrospective	159,327 procedures	N/A	N/A	Pts >65 y of age with Medicare FFS coverage, and underwent major noncardiac procedures from 2000–2004	Pts with end-stage renal disease and pts who did not have at least 1 y of Medicare FFS eligibility before surgery	N/A	Pts with HF or CAD against neither	Operative mortality and 30-d all-cause readmission	N/A	Pts with HF were at significantly higher risk for both outcomes compared with pts with CAD	Adjusted HR of mortality and readmission for pts with HF, compared with pts with neither HF nor CAD, were 1.63 (95% CI: 1.52–1.74) and 1.51 (95% CI: 1.45–1.58), respectively
Hernandez AF, et al., 2004 (10) 15464326	To evaluate mortality and readmission rates of pts with HF after major noncardiac surgery	Retrospective	1,532 pts with HF and 1,757 pts with CAD who underwent major noncardiac surgery. 44,512 pts in control group with major noncardiac surgery.	N/A	N/A	>65 y of age; 1997–1998 5% sample of Medicare beneficiaries, pts with HF who underwent major noncardiac surgery	?	N/A	Pts with HF or CAD against neither	Operative mortality (death before discharge or within 30 d of surgery)	?	Risk-adjusted 30-d readmission rate 0	The risk-adjusted operative mortality (death before discharge or within 30 d of surgery) for HF 11.7%, CAD 6.6%, and control 6.2% (HF vs. CAD, p<0.001; CAD vs. control; p=0.518). The risk-adjusted 30-d readmission rate for was HF 20.0%, CAD 14.2%, and control 11.0% (p<0.001).
van Diepen S, et al., 2011 (11) 21709059	To compare the postop mortality of pts with HF, AF, or CAD undergoing major and minor noncardiac	Retrospective	Nonischemic HF (n=7,700), ischemic HF (n=12,249), CAD (n=13,786), or AF (n=4,312)	N/A	N/A	Pts who underwent noncardiac surgery between April 1, 1999–September 31, 2006, in Alberta, Canada	?	N/A	?	The main outcome was 30-d postop mortality.	?	Among pts undergoing minor surgical procedures, the 30-d postop mortality was 8.5% in NIHF, 8.1% in IHF, 2.3% in CAD,	Unadjusted 30-d postop mortality was 9.3% in NIHF, 9.2% in IHF, 2.9% in CAD, and 6.4% in AF (each vs. CAD, p<0.0001). After multivariable

	surgery											and 5.7% in AF (p<0.0001)	adjustment, postop mortality remained higher in pts with NIHF, IHF, and AF than in those with CAD (NIHF vs. CAD, OR: 2.92; 95% CI: 2.44–3.48; IHF vs. CAD, OR: 1.98; 95% CI: 1.70–2.31; AF vs. CAD, OR: 1.69; 95% CI: 1.34–2.14).
Xu-Cai YO, et al., 2008 (12) 18315993	To evaluate modern surgical outcomes in pts with stable HF undergoing elective major noncardiac surgery and to compare the experience of pts with HF who have reduced vs. preserved LVEF	Retrospective	557 pts with HF (192 LVEF ≤40% and 365 LVEF>40%) and 10,583 controls	N/A	N/A	Pts who underwent systematic evaluation by hospitalists in a preop clinic before having major elective noncardiac surgery between January 1, 2003–March 31, 2006	?	N/A	Mortality in HF with reduced EF or preserved EF vs. control pts	1-mo postop mortality and1-y mortality	?	Unadjusted differences in mean hospital LOS among pts with HF vs. controls (5.7 vs. 4.3 d; p<0.001) and 1-mo readmission (17.8% vs. 8.5%; p<0.001) were also markedly attenuated in propensity-matched groups	Unadjusted 1-mo postop mortality in pts with both types of HF vs. controls was 1.3% vs. 0.4% (p=0.009), but NS in propensity-matched groups (p=0.09). Crude 1-y HR (p<0.01) for mortality were 1.71 (95% CI: 1.5–2.0) for both types of HF, 2.1 (95% CI: 1.7–2.6) in pts with HF who had LVEF ≤40%, and 1.4 (95% CI: 1.2–1.8) in those who had LVEF >40%; however, the differences were NS in propensity-matched groups (p=0.43).
Impact of LVEF on Periop and Postop Outcomes													
Meta-analysis Global Group in Chronic Heart Failure (MAGGIC), 2012 (13)	To determine whether survival in pts with HF-PEF is similar to those pts with HF-REF	Meta-analysis using individual pt data	41,972 pts (10,347 with HF-PEF and 31,625 with HF-REF)	N/A	N/A	31 studies including pts with HF	?	N/A	Deaths per 1,000-pt y	Mortality in HF-PEF vs. HF-REF	?	The risk of death did not increase notably until EF fell below 40%.	Pts with HF-PEF had lower mortality than those with HF-REF (adjusted for age, sex, etiology, and Hx of HTN, diabetes mellitus, and AF; HR: 0.68; 95% CI: 0.64–0.71)

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Kazmers A., et al., 1988 (14) 3047443	To determine periop (30-d) and subsequent outcome after major vascular surgery in those with severe cardiac dysfunction, defined by LVEF ≤35%	Retrospective	35 pts who required 47 major vascular procedures	N/A	N/A	From August 1, 1984–January 1, 1988, pts with LVEF ≤35% who required vascular surgery	?	N/A	Mortality according to LVEF	Cumulative mortality	?	?	Survival for those with an LVEF ≤29% was significantly worse than for those with an LVEF >29% (p<0.012). The cumulative mortality rate was 59% LVEF ≤29% and 18% in those with LVEF >29% (p<0.029)
Kazmers A., et al., 1988 (15) 3348731	To determine periop and long-term mortality according to LVEF in pts undergoing carotid endarterectomy	Retrospective	73 pts before 82 carotid operations	N/A	N/A	Pts who had radionuclide ventrioculography before carotid endarterectomy	?	N/A	Periop and long-term mortality in pts with LVEF <35% vs. LVEF >35%	Periop and cumulative1-y mortality	Periop cardiac complications were more frequent with LVEF ≤35% , occurring in 43% vs.9% in pts with LVEF >35%	?	There was no statistical difference in periop mortality, but cumulative mortality differed, being 57% (4/7) in those with EF of ≤35% vs. 11% (7/66) in pts with LVEF >35%
McCann RL, Wolfe WG, 1989 2778886	To evaluate the influence of LVEF on both periop and long-term morbidity and mortality	Retrospective	104	N/A	N/A	Preop LVEF measured in 104 of 208 pts undergoing elective AAA	?	N/A	19 pts with LVEF <35% was compared to 85 pts with LVEF >35%	Periop and cumulative mortality	?	?	The periop mortality was not significantly different (low EF, 5%; high EF, 2%). The cumulative life-table survival of the 2 groups was not statistically different. 4-y actuarial survival 0.74 in low EF compared to 0.63 (p=NS) in the high EF group
Healy KO, et al., 2010 (3) 20412467	To determine impact of LVEF on outcome in pts with HF undergoing noncardiac surgery	Retrospective	174	?	?	174 subjects who underwent intermediate- or high-risk noncardiac surgery	?	?	?	30-d and long-term mortality	Adverse periop events occurred in 53 (30.5%) of subjects, including 14 (8.1%) deaths within 30 d, 26 (14.9%) MI, and 44 (25.3%) HF exacerbations	Among the factors associated with adverse periop outcomes in the first 30-d were advanced age (e.g., >80 y), diabetes mellitus, and a severely decreased EF (e.g., <30%)	Long-term mortality was high and Cox proportional hazards analysis demonstrated that EF was an independent risk factor for long term mortality

Role of HF in CV Risk Indices													
Goldman L, et al., 1977 (15, 16) 904659	To determine which preop factors affect the development of cardiac complications after major noncardiac operations	Prospective cohort	1,001 pts	N/A	N/A	?	?	?	?	Postop fatality and life-threatening complication	?	36 of the 39 pts manifesting ≥1 life-threatening cardiac complications had pulmonary edema. 9 independent significant correlates of life-threatening and fatal cardiac complications: preop S3 or JVD; MI in the preceding 6 mo; >5 PVC/min; rhythm other than sinus or presence of PACs on preop ECG; >70 y of age; intraperitoneal, intrathoracic or aortic operation; emergency operation; important valvular AS; and poor general medical condition.	Clinical signs of HF including an S3 gallop or JVD were the most significant predictors of postop life-threatening or fatal cardiac complications. In the final analysis, signs of HF carried the highest weight in the original CRI. 10 of the 19 postop cardiac fatalities occurred in the 18 pts at highest risk.
Detsky AS, et al., 1986 (15, 17) 3772593	To validate a previously derived multifactorial index in their clinical setting and to test a modified version of the index	Prospective cohort	455	?	?	455 consecutive pts referred to the general medical consultation service for cardiac risk assessment prior to noncardiac surgery	?	?	?	Major cardiac complications	?		The interobserver agreement for S3 and JVD was poor (κ statistic, 0.42 and 0.50, respectively). Therefore, to make the diagnosis of HF more objective and reproducible preoperatively, grouped HF into 2 categories as the presence of alveolar pulmonary edema within 1 wk or ever. Definition was stricter; HF still had a major role in predicting events and being a

													major outcome. Of the 43 serious events, there were 10 new or worsened episodes of HF without alveolar pulmonary edema, and 5 episodes of alveolar pulmonary edema.
Lee TH, et al., 1999 (15, 18) 10477528	To develop and validate an index for risk of cardiac complications	Prospective cohort	4,315	N/A	N/A	4,315 pts ≥50 y of age undergoing elective major noncardiac procedures in a tertiary-care teaching hospital	?	?	?	The main outcome measures were major cardiac complications	?	?	HF was both an important predictor and a key complication. Outcome required a formal reading of pulmonary edema on the chest x-ray. In the validation set, it provided the highest OR (4.3) for major cardiac complications. 6 independent predictors of complications were identified in RCRI: high-risk type of surgery, Hx of ischemic heart disease, Hx of CHF, Hx of cerebrovascular disease, preop treatment with insulin, and preop serum creatinine >2.0 mg/dL.

AAA indicates abdominal aortic aneurysm; AF, atrial fibrillation; AS, aortic stenosis; CAD, coronary artery disease; CHF, congestive heart failure; CI, confidence interval; CRI, Cardiac Risk Index; CV, cardiovascular; ECG, electrocardiogram; EF, ejection fraction; FFS, fee-for-service; HF, heart failure; HF-PEF, heart failure with preserved ejection fraction; HF-REF, heart failure with reduced ejection fraction; HR, hazard ratio; HTN, hypertension; Hx, history; IHF, ischemic heart failure; JVD, jugular venous distention; LOS, length of stay; LVEF, left ventricular ejection fraction; MI, myocardial infarction; n, subgroup of N; N/A, not applicable; NIHF, nonischemic heart failure; NS, nonsignificant; OR, odds ratio; PAC, pulmonary artery catheterization; periop, perioperative; postop, postoperative; pts, patients; PVC, premature ventricular contraction; preop, preoperative; RCRI, Revised Cardiac Risk Index; RR, relative risk; and S3, third heart sound.

Data Supplement 4. Valvular Heart Disease (Section 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 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*	*Primary Endpoint*	
Agarwal S, et al., 2013 (19) 23481524	Postop outcomes after nonemergent noncardiac surgery in pts with moderate or severe AS	Retrospective cohort; age, sex, and propensity score matched control	3,170	634	2,536	Moderate AS (AVA=1.0–1.5 cm^2) or severe AS (AVA<1.0 cm^2)	Emergent surgery	N/A	Pts without AS	Composite of 30-d mortality and postop MI	N/A	30-d mortality, long-term mortality, postop MI, HF, stroke, and LOS	Moderate AS 4.4% vs. control 1.7% (OR: 2.6; p=0.002); Severe AS 5.7% vs. control 2.7% (OR: 2.1; p=0.02)	Retrospective, single center
Calleja AM, et al., 2010 (20) 20381670	Postop outcomes after noncardiac surgery in pts with asymptomatic, severe AS	Retrospective; age- and sex-matched control	90	30	60	Severe AS (AVA<1.0 cm^2)	Symptomatic AS, moderate or severe AR	N/A	Pts with mild-to-moderate AS	Composite of in-hospital death, MI, HF, ventricular arrhythmias, and intraoperative hypotension requiring vasopressor	N/A	Intraoperative hypotension requiring vasopressor	AS 33% vs. control 23% (OR: 1.4; p=0.06)	Retrospective, single center, small sample size
Leibowitz D, et al., 2009 (21) 19287130	Postop outcomes after hip fracture surgery in pts with severe AS	Retrospective; age-matched control	120	32	88	Severe AS (AVA<1.0 cm^2)	N/A	N/A	Pts without AS	30-d mortality	N/A	Composite of 30-d mortality, ACS, and pulmonary edema	AS 6.2% vs. control 6.8% (OR: 0.9; p=NS)	Retrospective, single center, small sample size
Zahid M, et al., 2005 (22) 16054477	Postop outcomes after noncardiac surgery in pts with AS from NHDS database	Retrospective; age and surgical risk-matched control	15,433	5,149	10,284	AS	N/A	N/A	Pts without AS	Composite of in-hospital mortality and MI	N/A	In-hospital MI	AS 8.3% vs. control 7.2%, (OR: 1.2; p=0.01)	Retrospective, claims database
Torsher LC, et al., 1998 (23) 9485135	Postop outcomes after noncardiac surgery in pts with severe AS	Retrospective; no control	19	19	N/A	Severe AS (mean gradient >50 mm Hg)	N/A	N/A	N/A	In-hospital mortality	N/A	N/A	AS 10.5%	Retrospective, no control group, single center, small sample size
Lai HC, et al., 2010	Postop outcomes after noncardiac	Retrospective; age, sex, and	334	167	167	Moderate-to-severe AR or	Pt is already intubated,	N/A	Pts without AR	In-hospital mortality	NA	Postop MI, stroke,	AR 9.0% vs. control 1.8%	Retrospective, single center,

(24) 19930243	surgery in pts with moderate-severe or severe chronic AR	surgical risk-matched control				severe AR	surgery performed with local anesthesia					pulmonary edema, intubation >24 h, and major arrhythmia	(OR: 5.0; p=0.008)	small sample size
Bajaj NS, et al., 2013 (25) 23587300	Postop outcomes after nonemergent noncardiac surgery in pts with moderate-to-severe or severe MR	Retrospective; age, sex, and propensity score matched control	1,470	298	1,172	Moderate-to-severe MR or severe MR	Emergent surgery	N/A	Pts without MR	Composite of 30-d mortality and postop MI, HF, and stroke	N/A	30-d mortality, postop MI, HF, stroke, and AF	MR 22.2% vs. control 16.4% (OR: 1.4; p=0.02)	Retrospective, single center
Lai HC, et al., 2007 (26) 17576968	Postop outcomes after noncardiac surgery in pts with moderate-to-severe or severe MR	Retrospective; no control	84	84	N/A	Moderate-to-severe MR or severe MR	Pt is already intubated, surgery performed with local anesthesia	N/A	N/A	In-hospital mortality	N/A	Postop MI, stroke, pulmonary edema, intubation >24 h, and major arrhythmia	MR 11.9%	Retrospective, no control group, single center, small sample size

ACS, acute coronary syndrome; AF, atrial fibrillation; AR, aortic regurgitation; AS, aortic stenosis; AVA, aortic valve area; CI, confidence interval; HF, heart failure; HR, hazard ratio; LOS, length of stay; MI, myocardial infarction; MR, mitral regurgitation; NHDS, National Hospital Discharge Survey; N/A, not applicable; NS, nonsignificant; OR, odds ratio; pts, patients; postop, postoperative, and RR, relative risk.

Data Supplement 5. Arrhythmias and Conduction Disorders (Section 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*		
Biteker M, et al., 2012 (27) 22057953	To determine ECG predictors of periop cardiac events in pts undergoing noncardiac/ nonvascular surgery	Prospective observational cohort	660	660	N/A	660 pts scheduled for elective noncardiac nonvascular surgery expected to stay ≥2 d	Cardiac or vascular surgery, day surgery, emergent surgery, ASA=5	None	None	Abnormal ECG (p=0.019) and AF (p<0.001) predicted PCE on univariate analysis but not multivariate	N/A	Pts with PCEs had longer QTc (437 ms) that those without (413 ms) (OR: 1.043/ms; CI: 1.028/ms–1.058/ms)	N/A	N/A
Goldman L, et al., 1977	To develop risk score for cardiac events	Prospective observational cohort	1,001	N/A	N/A	All pts >40 y of age undergoing general,	Cardiac or thoracic surgery, no consent	None	None	Rhythm other than sinus (MDFC 0.283)	N/A	N/A	p<0.001	N/A

(16) 904659	after noncardiac surgery					orthopedic, or urologic surgery at MGH over a 7 mo period				and PVCs >5/min (MDFC 0.279) both predictive of risk of MACE				
Lee TH, et al., 1999 (18) 10477528	To develop revised risk score for cardiac events after noncardiac surgery	Prospective observational cohort	4,315	2,893 derivation	1,422 validation	All pts >50 y of age undergoing noncardiac surgery at 1 center over 5 y	Cardiac surgery, no consent	None	None	Abnormal rhythm not predictive of risk	N/A	N/A	RR 0.8; CI: 0.3–2.6; p=NS	No validation cohort
Mahla E, et al., 1998 (28) 9428844	To evaluate whether frequency of periop ventricular dysrhythmia independently predicts risk of noncardiac surgery	Prospective observational cohort	70	70	N/A	70 pts scheduled for noncardiac surgery with ventricular couplets or NSVT	10 pts excluded for poor Holter quality	None	None	Frequency of VPBs not predictive of outcome	N/A	AF did predict worse outcome (p=0.05)	p=NS	N/A
Mangano DT, et al., 1992 (29) 1608143	To determine predictors of long-term adverse cardiac events after noncardiac surgery	Prospective observational cohort	444	444	N/A	Consecutive pts at high-risk for CAD undergoing noncardiac surgery at SFVAMC who survived initial hospitalization	Cardiac surgery	None	None	Preop dysrhythmia did not predict adverse outcome	N/A	Preop NSVT did not predict risk	Dysrhythmia RR:1.4 (p=0.08); NSVT HR: 0.7 (CI: 0.2–1.9; p=0.40)	Small study, no control group
O'Kelly B, et al., 1992 (30) 1608140	To determine incidence and clinical predictors of periop ventricular arrhythmias during noncardiac surgery	Prospective observational cohort	230	230	N/A	Consecutive males with CAD or high risk for CAD undergoing noncardiac surgery at SFVAMC	N/A	None	None	Preop ventricular arrhythmia predicted periop and postop VA, but not MACE	N/A	N/A	Periop ventricular arrhythmias OR: 7.3 (95% CI: 3.3–16.0); postop ventricular arrhythmias OR: 6.4 (95% CI: 2.7–15.0), nonfatal MI/cardiac death OR :1.6 (95% CI: 0.4–	No validation cohort

													6.2)	

AF indicates atrial fibrillation; ASA, aspirin; CAD, coronary artery disease; ECG, electrocardiogram; MACE, major adverse cardiac event; MGH, Massachusetts General Hospital; MI, myocardial infarction; N/A, not applicable; NS, nonsignificant; NSVT, non-sustained ventricular tachycardia; PCE, perioperative cardiovascular events; periop, perioperative; preop, preoperative; pts; patients; PVC, premature ventricular contraction; QTc, corrected QT interval; RR, relative risk; SFVAMC, San Francisco Veterans Affairs Medical Center; VA, ventricular arrhythmia; and VPB, ventricular premature beat.

Data Supplement 6. Pulmonary Vascular Disease (Section 2.6)

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*		
Ramakrishna G, et al., 2005 (31) 15893189	Determine predictors of poor outcome after noncardiac surgery in pts with PH	Retrospective review, single center	145 (all with PH)	None	None	Adults with Group 1, 3, or 4 PH; general anesthesia (100%); intermediate-/high-risk surgery (79%)	Cardiac, obstetric surgery	None	1) pts who died and 2) pts who had morbid event (HF, cardiac ischemia, stroke, respiratory failure, hepatic dysfunction, renal failure, sepsis, dysrhythmia) vs. those who did not	Death in 7% associated with 1) Hx of PE, 2) RAD on ECG, 3) RVH or RV dysfunction on echo, 4) RVSP/systolic BP ratio, 5) vasopressor use intraoperatively, 6) absence of iNO use intraoperatively	N/A	Morbidity in 42% associated with 1) functional class, 2) prior PE, 3) obstructive sleep apnea, 4) 5) vasopressor use intraoperatively	Independent multivariate predictors of postop morbidity: Hx of PE (OR: 7.3; CI: 1.9–38.3; p=0.01); PH symptoms (OR: 2.9; CI: 1.2–7.7; p=0.02); intermediate/high-risk vs. low-risk surgery (OR: 3.03; CI: 1.1–9.4; p=0.04); anesthesia duration >3 h (OR: 2.9; CI: 1.03–4.6; p=0.04)	Retrospective, single center, no comparison group
Minai OA, et al., 2006 (32) 16768070	Determine frequency of poor outcome after noncardiac surgery in pts with PH	Retrospective review, single center	28 (all with PH)	None	None	Adults with Group 1 PH; general anesthesia (79%); intermediate-/high-risk surgery (86%)	Cardiac, obstetric surgery	None	1) pts who died and 2) pts who had morbid event vs. those who did not	Death in 18%	N/A	Morbidity in 19%	N/A	Retrospective, single center, no comparison group
Lai HC, et al.,	Determine	Retrospective	124 (62	None	Controls	Adults with	Cardiac,	None	1) pts who	Death in 10% vs.	N/A	Morbidity in	Independent	Retrospective,

2007 (26) 17576968	predictors of poor outcome after noncardiac surgery in pts with PH	case control study, single center	PH and 62 non–PH controls)		matched for age, sex, anesthesia, LVEF, surgical risk, and urgency	Group 1, 2, 3, or 4 PH; general anesthesia (58%); intermediate-/high-risk surgery (65%)	obstetric surgery		died and 2) pts who had morbid event vs. those who did not	0% in controls		24% vs. 3% in controls	multivariate predictors of postop mortality: emergency surgery (OR: 45; CI: 1.5–1,315; p=0.03); CAD (OR: 9.9; CI: 1.1–91; p=0.04); PASP (OR: 1.1; CI: 1.0–1.2; p=0.03). Independent multivariate predictors of postop morbidity: Cardiac risk level (OR: 6.8; CI: 1.2–39; p=0.03); CAD (OR: 6.5; CI: 1.4–30; p=0.02).	single center
Kaw R, et al., 2011 (32, 33) 21195595	Determine association of PH with periop outcomes	Retrospective cohort study, single center	173 (96 PH and 77 non–PH controls)	None	Controls who underwent RHC but had normal PA pressures, otherwise unmatched	Adults with Group 1,2,3, or 4 PH; general anesthesia (100%); intermediate-/high-risk surgery (100%); RHC	Minor procedures, cardiac, obstetric surgery	None	1) pts who died and 2) pts who had morbid event vs. those who did not	Morbidity/mortality (HF, respiratory failure, sepsis, MI) in 26% vs. 3% in controls	N/A	N/A	Mortality/morbidity OR: 13.1 (p<0.0001). Independent multivariate predictors of postop morbidity: PH (OR: 15.2; p=0.001); CKD (OR: 3.2; p=0.03); age (OR: 1.04; p=0.09); ASA Class >2 (OR: 4.2; p=0.02); surgical risk class	Retrospective, single center
Price LC, et al., 2010 (34) 19897552	Discuss the anesthetic management and follow-up of well-characterized pts with PAH presenting for noncardiothoracic nonobstetric	N/A	28 (all with PH)	None	None	Adults with Group 1 or 4 PH; general anesthesia (50%); intermediate-/high-risk surgery (75%)	Cardiac, obstetric surgery	None	1) pts who died and 2) pts who had morbid event vs. those who did not	Death in 7%	N/A	Morbidity (HF, respiratory failure) in 29%	Periop complications more likely in FC 3–4 (p=0.14) and with lower 6-min walk distance (p=0.06)	Retrospective, single center, no comparison group

	surgery													
Meyer S, et al., 2013 (35) 23143546	Assess periop outcomes in pts with PAH undergoing noncardiac surgery	Prospective, multicenter registry	114 (all with PH)	None	None	Adults with Group 1 PH; general anesthesia (82%)	Minor, cardiac or obstetric surgery	None	1) pts who died and 2) pts who had morbid event vs. those who did not	Death in 3.5%	N/A	Morbidity in 6.1%	Predictors of postop events: emergency surgery (OR: 2.4; 95% CI: 1.4–3.6; p=0.01); use of vasopressors (OR: 1.5; 95% CI: 1.2–2.7; p=0.03); surgery performed in PH center (OR: 0.2; CI: 0.05–1.0; p=0.06); mRA pressure (OR: 1.1; 95% CI: 1.0–1.3; p=0.01)	No comparison group

ASA indicates American Society of Anesthesiologists; BP, blood pressure; CAD, coronary artery disease; CI, confidence interval; CKD, chronic kidney disease; ECG, electrocardiogram; FC, functional class; HF, heart failure; HR, hazard ratio; Hx, history; iNO, inhaled nitric oxide; LVEF, left ventricular ejection fraction; MI, myocardial infarction; N/A, not applicable; mRA, mean right atrial; OR, odds ratio; PA, pulmonary artery; PAH, pulmonary arterial hypertension; PASP, pulmonary artery systolic pressure; PE, pulmonary embolism; periop, perioperative; PH, pulmonary hypertension; postop, postoperative; pts, patients; RAD, right-axis deviation; RHC, right heart catheterization; RR, relative risk; RVH, right ventricular hypertrophy; and RVSP, right ventricular systolic pressure.

Data Supplement 7. Multivariate Risk Indices (Section 3.1)

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*		
McFalls EO, et al., 2004 (36) 15625331	Compare rates of morbidity and mortality with/without coronary artery revascularization before cardiovascular operations	RCT, multicenter	510	258	252	Elective vascular procedure, increased risk of cardiac complications, ≥1 major coronary arteries with >70% stenosis	Urgent or emergent vascular procedure, severe coexisting illness, prior revascularization without evidence of recurrent ischemia	CABG or coronary angioplasty	No coronary revascularization	Long-term mortality	N/A	Periop MI: 7.1% in intervention group vs. 5.0% in control group	NS	Only looked at rate of periop MI in vascular surgery pts
Davenport	Compare	Retrospective	427	99	328	ACS NSQIP	Pts who died	EVAR	Open AAA repair	Mortality: 22.2%	None	Cardiac	p=0.003	Retrospective

DL, et al., 2010 (37) 19939609	outcomes of open vs. endovascular repair of ruptured AAA	cohort study using prospectively collected national database NSQIP				database from 2005–2007 at 173 hospitals. Pts were selected who had ruptured AAA	before having operation			EVAR vs. 37.2% open		arrest or infarction: 4.0% in EVAR vs. 8.2% in open	for mortality; p=0.159 for cardiac arrest or infarction	and not randomized.
Jordan SW, et al., 2013 (38) 23249982	Comparing outcomes of plastic surgery operations with and without resident involvement	Retrospective cohort study using prospectively collected national database NSQIP	10,356	4,453	5,903	ACS NSQIP database from 2006–2010 with "plastics" listed as primary service to include pts with reconstructive procedures	Cosmetic procedures	Resident involvement	No resident involvement	Overall complication, wound infection, graft/prosthesis/flap failure, mortality rates	N/A	Cardiac arrest: 0.13% with resident; 0.14% no resident: MI: 0.11% with resident; 0.08% no resident	NS	Retrospective and not randomized.

AAA indicates abdominal aortic aneurysm; ACS NSQIP, American College of Surgeons National Surgical Quality Improvement Program; CI, confidence interval; EVAR, endovascular aneurysm repair; CABG, coronary artery bypass graft; HR, hazard ratio; MI, myocardial infarction; N/A, not applicable; NS, nonsignificant; OR, odds ratio; periop, perioperative; pts, patients; RCT, randomized controlled trial, and RR, relative risk.

Data Supplement 8. Exercise Capacity and Functional Capacity (Section 4.1)

Study Name, Author, Year	Aim of Study	Study Type	Study Size (N)	Patient Population		Study Intervention	Endpoints	P Values, OR: HR: RR & 95% CI:	Study Limitations & Adverse Events
				Inclusion Criteria	*Exclusion Criteria*		*Primary Endpoint (Efficacy) and Results*		
Leung JM, et al., 2001 (39) 11555070	To determine prevalence and predictors of adverse postop outcomes in older surgical pts undergoing noncardiac surgery	Prospective cohort	544	Pts ≥70 y of age undergoing noncardiac surgery at an academic medical center	Local anesthesia or MAC	N/A	3.7% of pts died and 21% experienced postop complications. Decreased functional status preop was an important predictor of adverse neurological outcomes (OR: 3)	OR: 3 (95% CI: 1.4–6.4) for adverse neurological outcome	N/A
Reilly DF, et al., 1999 (40) 10527296	To determine the relationship between self-reported exercise tolerance and serious periop complications	Cohort	600	Consecutive outpts referred to a medical consultation clinic at a tertiary care medical center	N/A	Pts were asked to estimate the number of blocks they could walk and stairs they could climb without symptoms	All pts were monitored for 26 serious periop complications. Pts with poor exercise tolerance (<4 blocks or <2 flights) had more complications (20.4% vs. 10.4%).	Likelihood of serious complications was inversely related to the number of blocks that could be walked (p=0.006) or flights of stairs climbed (p=0.01).	N/A
Older P, et al., 1999 (41) 10453862	To develop an integrated strategy for the identification and subsequent management	Cohort	548	>60 y of age (or younger with known cardiopulmonary disease) scheduled for	N/A	All pts underwent cardiopulmonary exercise testing. Anaerobic threshold results and hemic ECG	Mortality was 3.9%. There were no deaths in those assigned to a ward strategy based on their cardiopulmonary parameters.	N/A	N/A

	of high-risk pts in order to reduce both morbidity and mortality			major intra-abdominal surgery		changes with exercise were used to triage to ICU, HCU, and ward.			
Wiklund RA, et al., 2001 (42) 11393264	To evaluate METs as a predictor of cardiac complications following elective noncardiac surgery	Retrospective cohort	5,939	Pts undergoing preanesthetic assessment within 2 mo of elective noncardiac surgery	N/A	N/A	94 pts (1.6%) had cardiac complications, 38% occurred after vascular surgery. Age and ASA Physical Status Class were independent predictors of complications but METs were not once ASA Physical Status Class was included.	N/A	ASA Physical Status Class and METs were colinear
Crawford RS, et al., 2010 (43) 20141958	To relate preop functional status to periop morbidity and mortality	Cohort	5,639	Vascular surgery pts undergoing infrainguinal surgical bypass	N/A	N/A	Dependent pts (18.4%) were older and had more diabetes mellitus, COPD ESRD on dialysis, and critical limb ischemia. Dependent pts had higher mortality (6.1% vs. 1.5%) and complication rates (30.3% vs. 14.2%). Dependent status was an independent predictor of death and major complications.	Serious complications OR: 2 (95% CI: 1.7–2.4) and death OR: 2.3 (95% CI: 1.6–3.4)	N/A
Goswami S, et al., 2012 (44) 23042223	To determine incidence and risk factors for intraoperative cardiac arrest	Cohort	362, 767	Noncardiac surgeries in the ACS NSQIP database	N/A	N/A	Incidence of intraoperative CA was 7.22 per 10,000. Predictors included being functionally dependent (OR: 2.3) as well as emergency surgery and the amount of transfusions needed.	Adjusted OR:2.33 (95% CI: 1.69–3.22) for being functionally dependent	Definition of dependent in NSQIP database based on need for assistance with ADLs rather than METs values.
Tsiouris A, et al., 2012 (45) 22484381	To assess the effect of functional status on morbidity or mortality	Cohort	6,373	Thoracic surgery pts in 2005-2009 NSQIP database	N/A	N/A	812 pts had dependent functional status preoperatively. Mortality was 7.7 times higher in them than in those with nondependent functional status. Complications were also increased.	OR: 7.7 for mortality in dependent pts preop as compared with nondependent pts ($p<0.001$). OR: 9.3 for prolonged ventilation and OR: 3.1 for reintubation.	N/A

ACS indicates American College of Surgeons; ADLs, activities of daily living; ASA, American Society of Anesthesiologists; CA, cardiac arrest; CI, confidence interval; COPD, chronic obstructive pulmonary disease; ECG, electrocardiogram; ESRD, end-stage renal disease; HCU, high care unit; HR, hazard ratio; ICU, intensive care unit; MAC, monitored anesthesia care; METs, metabolic equivalent; N/A, nonapplicable; NSQIP; National Surgical Quality Improvement Program; OR, odds ratio; periop, perioperative; postop, postoperative, preop, preoperative; pts, patients; and RR, relative risk.

Data Supplement 9. The 12-Lead ECG (Section 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*	*Secondary Endpoint and Results*		
Biteker M, et al., 2012 (27) 22057953	To examine the association of preop ECG abnormalities and periop cardiovascular outcomes in pts undergoing noncardiac, nonvascular surgery	Prospective observational single-center cohort	660	N/A	N/A	Pts >18 y of age undergoing nonday case open surgery	Emergent cases and day-case surgery, ASA5	None	None	PCE 12.1%—Only QTc predicted periop CV events on MVA	Other ECG abnormalities did not predict CV events	N/A	Small sample size
Carliner NH, et al., 1986 (46) 3719447	To determine which ECG abnormalities were most predictive of high-risk surgical pts	Prospective observational single-center cohort	198	N/A	N/A	Pts >40 y of age undergoing elective thoracic, abdominal, or vascular surgery under GA	Recent MI, UA, CHF, AS, high-grade VE, uncontrolled HTN	None	None	Death/MI (3%)—Not reported due to small number of endpoints	All cardiac events including ischemia (17%)—Only abnormal ECG predicted	Sensitivity 85%, specificity 41%, PPV 22%; p<0.01	Small sample size, few primary hard endpoints. Individual ECG abnormalities did not predict events.
Gold BS, et al., 1992 (47) 1739358	To determine the value of preop ECG in an ambulatory surgical population	Retrospective single-center cohort	751	N/A	N/A	All ambulatory surgical pts with preop ECG undergoing surgery	Local anesthesia only	None	None	Any adverse CV event (1.6%)—no ECG abnormality predictive	N/A	No ECG abnormality predicted adverse CV events	Small sample size, few CV events (12/751= 1.6%)
Goldman L, et al., 1977 (16) 904659	To develop multifactorial risk score for cardiac events after noncardiac surgery	Prospective observational single-center cohort	1,001	N/A	N/A	All pts >40 y of age undergoing general, orthopedic, or urologic surgery at MGH over 7-mo period	Cardiac or thoracic surgery, local anesthesia only, endoscopy, TURP, no consent	None	None	Cardiac death (1.9%) or MACE (MI, pulmonary edema, VT–3.9%)-Rhythm other than sinus or PACs predicted cardiac death	N/A	Death—OR: 9 (p<0.001); nonfatal MACE—OR: 3.3 (p<0.001)	No validation cohort, older study, ECGs abnormalities not well-classified

										and MACE			
Jeger RV, et al., 2006 (48) 16442922	To determine whether preop ECG abnormalities predict death/MACE 2 y postop in pts with CAD or high CAD risk	Prospective observational single-center cohort	172	N/A	N/A	Clinically stable adult pts with documented or suspected CAD undergoing noncardiac surgery	None stated	None	None	Death (23%) or MACE (18%) at 2 y-ST depressions and faster HR predicted mortality	N/A	ST depression—OR: 4.5 (95% CI: 1.9–10.5); faster heart rate–OR: 1.6 (95% CI: 1.1–2.4)	Small sample size
Landesberg G, et al.,1997 (49) 9357456	To examine the association between preop ECG abnormalities, periop MI, and postop cardiac complications	Prospective observational 2-center cohort	405	N/A	N/A	Adult pts undergoing vascular surgery under GA or epidural	LBBB, LVH with strain	None	None	Cardiac death (0.5%) or MI (4.2%)—Only LVH and ST depression >0.5 mm predicted endpoint	N/A	OR: 5.8 (p=0.004)	Small sample size, limited to vascular surgery
Lee TH, et al., 1999 (15, 18) 10477528	To derive and validate a simple index for the prediction of the risk of cardiac complications in major elective noncardiac surgery	Prospective observational single-center cohort	4,315	N/A	N/A	Pts ≥50 undergoing nonemergent noncardiac procedures with expected LOS ≥2 d	Pt unwilling to consent to full study protocol	None	None	Major cardiac complications-MI, pulmonary edema, VF/SCA, complete AV block (2%)—Pathologic Q-waves (present in 17%) predictive in derivation set, but not ST-T changes	N/A	Pathologic Q-waves: RR: 2.4 (CI: 1.3–4.2; p<0.05)	Pt consent required, and pts who did not give consent had much higher event rate (4.8% vs. 1.7%)
Liu LL., et al., 2002 (50) 12133011	To determine whether abnormalities on preop ECGs were predictive of postop cardiac complications	Prospective observational single-center cohort	513	N/A	N/A	Pts ≥70 undergoing noncardiac surgery	Local anesthesia or MAC	None	None	Death (3.7%) and combined cardiac complications (MI, ischemia, arrhythmia, CHF: 10.1%)–No association between ECG abnormalities and postop cardiac	Other noncardiac adverse events	OR: 0.63 (95% CI: 0.28–1.40; p=0.26)	Small sample size, only age ≥70

										complications			
Payne CJ, et al., 2011 (51) 21989644	To assess the predictive value of a preop 12-lead ECG in pts undergoing major surgery in a population with a high prevalence of cardiovascular disease	Prospective observational single-center cohort	345	N/A	N/A	Consecutive adult pts undergoing major vascular surgery or laparotomy	None stated	None	None	MACE (MI and cardiac death:13.3%) and all-cause mortality (7.8%) within 6 wk—LV strain and prolonged QTc predictive of MACE on MVA	N/A	LV strain—HR: 3.93 (CI: 2.14–7.20; p<0.001); Prolonged QTc—HR: 2.38 (CI: 1.32–4.31; p=0.004)	Small sample size; other ECG abnormalities not predictive on MVA
Schein OD, et al., 2000 (52) 10639542	To determine whether routine testing helps reduce the incidence of intraop and postop medical complications	Prospective randomized multicenter controlled trial	18,189	9,411	9,408	Pts ≥50 scheduled to undergo cataract surgery	General anesthesia, MI within 3 mo, any preop testing within 28 d	Routine preop testing=12-lead ECG, CBC, SMA-7	No preop testing	Adverse medical events (3.1%)—No difference between groups	Individual cardiac endpoints	RR: 1.00 (CI: 0.9–1.2)	Limited to single type of low-risk surgery, cardiac events not specifically studied, unable to exclude testing done >28 d
Seymour DG, et al., 1983 (53) 6869118	To examine the role of the routine preop ECG in the elderly surgical pt	Prospective observational single-center cohort	222	N/A	N/A	Pts ≥65 undergoing general surgery	None stated	None	None	MI or CHF (12.2%–9.6% in men and 16.1% in women)—Major ECG abnormalities (LVH, Q-waves, ST depression, T-wave abnormalities) predicted events in women but not men	N/A	Women: X^2=4.0 (p<0.05); Men: X^2=0.17 (p=NS)	Small sample size, unusual statistical analysis, included emergency cases (24.3%)
Turnbull JM, et al., 1987 (54) 3592875	To investigate the value of traditionally accepted preop investigations in otherwise healthy pts admitted to hospital for open	Retrospective 2-center cohort	1,010	N/A	N/A	Adult pts admitted for cholecystectomy and no major medical conditions	Active or ongoing disease on admission, morbid obesity	None	None	Any adverse medical event—ECG not predictive	N/A	PPV=0.040 (p=NS)	Retrospective, ECG criteria not well-defined, statistical comparisons not rigorous

	cholecystectomy												
Van Klei WA, et al., 2007 (55) 17667491	To estimate the value of a preop ECG in addition to pt Hx in the prediction of MI and death during postop stay	Retrospective analysis of a prospective 2-center cohort study	2,967	N/A	N/A	Pts ≥50 undergoing noncardiac surgery with expected length of stay >24 h	Lung or liver transplant operation	None	None	Postop MI (2.3%) or death (2.5%)—RBBB predictive of postop MI, LBBB predictive of postop MI and death, other ECG abnormalities not predictive	N/A	RBBB/postop MI—OR: 2.1 (CI: 1.0–4.5; p=0.06); LBBB/postop MI—OR: 3.1 (CI: 1.0–9.9; p=0.05); LBBB/death—OR: 3.5 (CI: 1.3–10; p=0.02)	Retrospective, 20% did not get ECG. In ROC analysis, BBB not additive to risk prediction

AS indicates aortic stenosis; ASA, American Society of Anesthesiologists; AV, atrioventricular; BBB, bundle branch block; CAD, coronary artery disease; CBC, complete blood count; CHF, congestive heart failure; CI, confidence interval; CV, cardiovascular; ECG, electrocardiogram; GA, general anesthesia; HR, hazard ratio; HTN, hypertension; LBBB, left bundle-branch block; LOS, length of stay; LV, left ventricular; LVH, left ventricular hypertrophy; MACE, major adverse cardiac event; MGH, Massachusetts General Hospital; MI, myocardial infarction; MAC, monitored anesthesia care; MVA, multivariable analysis; N/A, not applicable; NS, nonsignificant; OR, odds ratio; PAC, pulmonary artery catheterization; PCE, perioperative cardiovascular event; periop, perioperative; postop, postoperative; PPV, positive predictive value; preop, preoperative; pts, patients; QTc, corrected QT interval; ROC, receiver operating characteristic; RBBB, right bundle-branch block; RR, relative risk; SCA, sudden cardiac arrest; SMA, sequential multiple analysis; TURP, transurethral resection of the prostate; UA, unstable angina; VE, ventricular ectopy; VF, ventricular fibrillation; and VT, ventricular tachycardia.

Data Supplement 10. Assessment of LV Function (Section 5.2)

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*		
Baron JF, et al., 1994 (56) 8107716	Ability of LVEF (and ischemia by dipyridamole thallium stress) by MUGA to predict periop MACE	Prospective	457	None	N/A	LVEF by MUGA undergoing elective abdominal aortic surgery	N/A	None	Pts with reduced LVEF vs. preserved LVEF	An LVEF <50% predicted cardiac complications (OR 2.1; 95% CI: 1.2–3.7)	N/A	EF<50% associated with postop HF (OR 4.6; 95% CI: 1.8–11.8) but not death (OR 1.3; 95% CI: 0.4–4.1), MI (OR 1.5; 95% CI: 0.5–4.4).Sensitivity of low EF to detech HF 25%; specificity 86%	N/A	N/A
Kontos MC, et al., 1996	Ability of LVEF by TTE to predict	Prospective	96 procedures in 87 pts	None	N/A	LVEF by TTE undergoing moderate- or	N/A	None	Pts with reduced LVEF (or	Major cardiac complications (MI, HF, arrhythmia) occurred	N/A	N/A	Sensitivity of low LVEF by ECG to predict MACE	N/A

(57) 8800025	periop MACE and compare to dypramidole thallium stress		(56 vascular, 40 general)			high-risk noncardiac surgery			ischemia on thallium stress) vs. preserved LVEF	in 10 pts. Reduced LVEF preoperatively present in 29%.			86% (95% CI: 60%–96%) and specificity 81% (95% CI: 70%–88%). LVEF by echo more specific than dipyridamole thallium stress for prediction of events.	
Halm EA, et al., 1996 (58) 8779454	Ability of LVEF by TTE to predict periop MACE	Prospective	339	N/A	N/A	Known or suspected CAD, major noncardiac surgery	N/A	N/A	N/A	Postop IEs (cardiac-related death, nonfatal MI, and UA), CHF, and VT. 10 pts (3%) had IEs; 26 (8%) had CHF; and 29 (8%) had VT. In univariate analyses, an EF<40% was associated with all cardiac outcomes combined (OR: 3.5; 95% CI: 1.8–6.7), CHF (OR: 3.0; CI: 1.2–7.4), and VT (OR: 2.6; CI: 1.1–6.2). In multivariable analyses that adjusted for known clinical risk factors, an EF<40% was a significant predictor of all outcomes combined (OR: 2.5; CI: 1.2–5.0) but not CHF (OR: 2.1; CI: 0.7–6.0) or VT [corrected] (OR: 1.8; CI: 0.7–4.7).	N/A	An EF <40% had a sensitivity of 28%-31% and a specificity of 87%-89% for all categories of adverse outcomes.	N/A	N/A
Rohde LE, et al., 2001 (59) 11230829	Ability of LVEF by TTE to predict periop MACE	Prospective	570	None	N/A	LVEF by TTE undergoing major noncardiac surgery	N/A	None	Pts with reduced LVEF vs. preserved LVEF	Preop systolic dysfunction was associated with postop MI, cardiogenic pulmonary edema (and major cardiac	N/A	ECG data added significant information for pts at increased risk for cardiac complications by clinical criteria,	With low LVEF: MI (OR: 2.8; 95% CI: 1.1–7.0), cardiogenic pulmonary edema (OR: 3.2; 95% CI: 1.4–7.0),	N/A

										complications		but not in otherwise low-risk pts	and major cardiac complications (OR: 2.4; 95% CI: 1.3–4.5).	
Healy KO, et al., 2010 (3) 20412467	Determine the impact of LVEF on outcome in pts with HF undergoing noncardiac surgery	Retrospective	174	N/A	N/A	LVEF assessment in pts with HF undergoing intermediate or high risk noncardiac surgery.	N/A	N/A	N/A	Mortality	MACE in 53 (31%), including 14 (8%) deaths within 30 d, 26 (14.9%) MI, and 44 (25.3%) HF exacerbations	Among the factors associated with adverse periop outcomes in the first 30 d were advanced age (e.g., >80 y), diabetes and a severely decreased EF (e.g., <30%)	Long-term mortality was high and Cox proportional hazards analysis demonstrated that EF was an independent risk factor for long term mortality	N/A

CAD indicates coronary artery disease; CHF, congestive heart failure; CI, confidence interval; ECG, echocardiogram; EF, ejection fraction; HF, heart failure; HR, hazard ratio; IE, ischemic event; LV, left ventricular; LVEF, left ventricular ejection fraction; MACE, major adverse cardiac event; MI, myocardial infarction; MUGA, Multigated Acquisition Scan; N/A, not applicable; NS, nonsignificant; OR, odds ratio; periop, perioperative; postop, postoperative; preop, preoperative; pts; patients; RR, relative risk; TTE, transthoracic echocardiogram; UA, unstable angina; and VT, ventricular tachycardia.

Data Supplement 11. Exercise Stress Testing for Myocardial Ischemia and Functional Capacity (Section 5.3)

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*		
Cutler BS, et al., 1981 (60) 7223937	Report of continuing experience with the electrocardiographically monitored arterial stress test in pts with peripheral vascular disease	Observational	130	N/A	N/A	Pts undergoing peripheral vascular reconstructive surgery	N/A	N/A	N/A	Lowest risk group was pts who achieved 75% maximum predicted heart rate without MI and no cardiac complications. Highest risk group was 26 pts who had an ischemic response at <75% maximum predicted heart	None	None	N/A	No stats. Event rates we don't see today.

										rate, 10 cardiac complications including 7 MIs (5 of which were fatal).				
Gerson MC, et al., 1985 (61) 4062085	To test whether objective assessment of rest and exercise LV function before elective noncardiac surgery is a more sensitive predictor of periop cardiac complications than data from pt Hx, physical exam, X-ray, lab ECG, and stress-rest radionuclide ventriculography	Consecutive series	Preliminary study: 100 (50 men and 50 women); prospective study: 54 pts (25 men and 29 women)	N/A	N/A	Pts aged ≥65 y scheduled for major elective abdominal or noncardiac thoracic surgery	N/A	N/A	N/A	Preliminary study: 13 pts (of 100) had a total of 22 major periop complications (cardiac death, VT or VF, MI, CHF) including 6 deaths. When radionuclide variables and clinical variables were entered into multivariate analysis that included preop Hx, physical examination, and x-ray, ECG, and chemical laboratory variables, individually and in combination, only resting radionuclide LV regional wall motion abnormality (p=0.002) and inability to exercise for 2 min to raise the heart rate above 99 bpm (p=0.006) were independent predictors of periop cardiac risk.	None	None	Preliminary study: Pts unable to bicycle at least 2 min to a heart rate >99 bpm had an 11-fold increase in the risk of developing a periop cardiac complication. Prospective study: 10 pts (out of 54) had a total of 12 periop complications including 2 deaths. The inability to bicycle 2 min to a heart rate >99 bpm was the only significant predictor of a periop cardiac complication ($p<0.05$). Inability to exercise had a sensitivity of 80% and specificity of 53% for prediction of periop cardiac complications.	Small sample size.
Arous EJ, et al., 1984 (62)	To determine the safest treatment option for the pt with	Retrospective analysis	Out of 808 pts with AAA or peripheral occlusive	135 pts with ischemia on stress test: Group 1 (56	37 pts with no Hx of MI or symptoms of CAD with	Pts with AAA or peripheral occlusive disease of the	None mentioned	Treadmill exercise (Bruce protocol) to	Pts with no Hx of MI or symptoms of CAD with	Positive exercise test (135): Group 1 (56) standard operation: MI in 15	None	None	In the positive stress test group, the total incidence of MI,	High rate of events compared with today's

6610402	combined coronary and PVD through a retrospective analysis of the postop course of pts with an ischemic response to treadmill exercise		disease of the lower extremities who underwent ECG monitored stress tests, this study concerns 135 with an ischemic response to exercise and 37 pts with no Hx of MI or symptoms of CAD with normal ECGs at rest	pts) standard operation, Group 2 (23 pts) extra-anatomic bypass, Group 3 (10 pts) CABG and standard operation, and Group 4 (46 pts) no operation	normal ECGs at rest: Group 1 (21), Group 2 (2), Group 3 (4), and Group 4 (10)	lower extremities		at least 75% max predicted heart rate; arm ergometer for those whose claudication precluded adequate treadmill exercise. Ischemia defined as new or additional ST segment depression of at least 1 mm.	normal ECGs at rest	(27%), fatal in 11; Group 2 (23) extra-anatomic bypass: 4 MI (17%), 3 fatal; Group 3 (10) CABG and standard operation: 0 MI; and Group 4 (46) no operation: 10 (22%) late fatal MI (1–5 y). No known CAD: Group 1 (21) 5 MI (24%), 4 fatal; Group 2 (2) 1 nonfatal MI (50%); Group 3 (4) 0 MI; and Group 4 (10) 1 late fatal MI (10%)			including both the postop and follow-up periods, was significantly reduced when Group 3 was compared with Group 1 (p=0.05).	standards. Decision on type of surgery influenced by stress test results. Arm ergometry used for some pts, but how many is unclear. Not really a study of ischemia vs. no ischemia on stress test.
Carliner NH, et al., 1985 (63) 4014040	To determine if preop exercise testing would be useful for predicting risk in pts undergoing a wide variety of major surgical procedures01078	Prospective	200	N/A	N/A	Pts over 40 y of age scheduled to undergo elective major noncardiac surgery under general anesthesia.	Documented MI within 6 mo, UA, decompensated HF, hemodynamically significant AS, low-grade 4A and 4B ventricular arrhythmias at rest, uncontrolled HTN, physical disability and mental incompetence	Treadmill (134), bicycle (21), arm ergometer (43). Treadmill was modified Balke or modified Bruce protocol.	N/A	2 pts with markedly positive stress tests were excluded from further analysis. 6 pts (3%) had a primary endpoint (death or MI). Only 1 of these 6 pts had a positive ST segment response to exercise, 5 of the 6 pts had a maximal exercise capacity of <5 METs.	None	On multivariate analysis, the preop ECG was the only factor that was a statistically significant predictor of postop outcome. A pt with an abnormal ECG was 3.2 times more likely to die postoperatively or MI or suspected myocardial ischemia/injury than was a pt with a normal ECG.	Postop death, MI, and suspected myocardial ischemia/injury occurred more frequently in pts who had an abnormal electrocardiographic response to exercise and/or an exercise capacity of <5 METs than in pts with neither of these findings; however, none of the exercise variables was statistically significant as an independent	Small number of primary events limits analysis. Mix of treadmill (67.7%), bike (10.6%), and arm (21.7%) exercise.

													predictor of risk.	
Leppo J, et al., 1987 (64) 3805515	It was hypothesized that the presence of thallium redistribution would be of prime importance in detecting those pts having coronary disease who have potentially jeopardized myocardium	Prospective	100 underwent dipyridamole thallium scintigraphy; 69 underwent exercise testing (56, Bruce protocol), 13 arm ergometry). 27 didn't undergo exercise because of physical limitations and 4 because of scheduling conflicts.	N/A	N/A	Consecutive pts admitted for elective aortic or limb vascular surgery.	New or medically UA, recent (4-6 mo) MI.	N/A	N/A	Of the 89 pts who underwent vascular surgery without cardiac catheterization, 15 had a periop MI (1 fatal and 10 non-Q wave infarctions). Only the presence of either an abnormal scan (p=0.001) or thallium redistribution (p=0.001) demonstrated a significant difference.	None	Although pts with ST depression and shorter total exercise time tended to have more events, these differences were not statistically significant. No events occurred in the 12 pts who were able to perform >9 min of exercise.	From the regression analysis, the predicted probability of a cardiac event in pts not having redistribution was 2±2% (1 of 47), but in pts with redistribution it was 33±7% (14 of 42) .In the second regression analysis which included the 60 pts having both exercise and scan studies, only the presence of thallium redistribution was significant at step 0.	Relatively small number of patients undergoing exercise (69, and 13 of these were arm ergometry). High event rates not seen today.
McPhail N, et al., 1988 (65) 3336127	To report on their experience with the use of exercise testing in an effort to predict cardiac complications in pts requiring arterial repair	Observational	110, 9 excluded. Treadmill exercise in 61 pts (Bruce protocol) and arm ergometry in 40 pts.	N/A	N/A	Consecutive pts requiring arterial surgery who had clinical evidence of significant CAD were referred for cardiac evaluation	9 pts with recent MI (<6 mo), UA, or CHF were excluded	N/A	N/A	Contingency table analysis showed that maximum heart rate achieved during exercise was a significant predictor of complications (MI, CHF, malignant ventricular arrhythmias and cardiac death). Of 70 pts who achieved <85% of their predicted maximum heart	None	Of 21 pts with a positive stress test (≥1 mm ST depression) who attained <85% of their predicted maximum heart rate, 7 (33.3%) developed cardiac complications. In contrast, no complications occurred among 9 pts	The logistic regression analysis indicates that pts who achieved a high maximal heart rate during exercise had a low probability of developing cardiac complications (p=0.040). A similar result was observed when high METs	Unclear selection of pts ("clinical evidence of significant CAD"). Relatively small number underwent treadmill exercise. High event rates not seen today.

										rate, 17 (24.3%) developed complications. Only 2 (6.6%) of 30 pts who achieved >85% maximum predicted heart rate had complications (p=0.0396). The degree of ST segment depression that occurred with exercise was NS in predicting cardiac complications.		with ST depression of ≥1 mm who were able to achieve 85% of their predicted maximum heart rate.	was present (p=0.033). Note: 4 METs ~25% event rate.	
Sgura FA, et al., 2000 (66) 11014727	To determine the value of preop exercise testing with a supine bicycle in predicting periop cardiovascular events and long-term outcomes in pts scheduled for vascular surgery	Consecutive series	149	N/A	N/A	Underwent supine exercise testing and vascular surgery	Underwent vascular surgery or coronary revascularization before exercise testing	N/A	N/A	Cardiovascular events within 30 d of surgery: death, MI, cardiac arrest; 7% had periop cardiovascular events	None	No significant association between exercise-induced ST depression, radionuclide angiographic factors, or any clinical variable (other than age) and periop cardiovascular events or long-term mortality	The level of peak exercise achieved was associated with periop CV events with 12% occurring in low-capacity pts (<4 METs), 3% occurring in intermediate-capacity pts (4–7 METs), and none in the high capacity pts (>7 METs) (p=0.03). Long-term survival rates were substantially less in the low-workload group than in intermediate- and high-workload groups (p=0.007).	Pts were selected who were felt to be capable of exercising. Selected group of pts for whom exercise radionuclide angiography was ordered.

AAA indicates abdominal aortic aneurysm; CABG, coronary artery bypass graft; CAD, coronary artery disease; CHF, congestive heart failure; CV, cardiovascular; ECG, echocardiogram; HR, hazard ratio; Hx, history; LV, left ventricular; MET; MI, myocardial infarction, N/A, not applicable; NS, nonsignificant; periop, perioperative; preop, preoperative; pts, patients; PVD, peripheral vascular disease; UA, unstable angina; VF, ventricular fibrillation; and VT, ventricular tachycardia.

Data Supplement 12. Cardiopulmonary Exercise Testing (Section 5.4)

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*		
Hartley RA, et al., 2012 (67) 23001820	To evaluate whether preop CPET is useful in the prediction of 30- and 90-d mortality in pts undergoing elective open AAA repair and EVAR	Prospective cohort	415	N/A	N/A	Pts undergoing AAA repair and CPET	None given	N/A	N/A	On multivariable analysis, open repair, AT <10.2 mL/kg/min, anemia and inducible cardiac ischemia were associated with 30-d mortality. Anemia, inducible cardiac ischemia and peak VO2 <15 mL/kg/min were associated with 90-d mortality on multivariable analysis. Pts with ≥2 subthreshold CPET values were at increased risk of both 30- and 90-d mortality.	None	None	On multivariable analysis, open repair (OR: 4.92; 95 % CI: 1.55–17.00; p=0.008), AT below 10.2 mL/kg/min (OR: 6.35; 95 % CI: 1.84–29.80; p=0.007), anemia (OR: 3.27; 95 % CI: 1.04–10.50; p=0.041) and inducible cardiac ischemia (OR: 6.16; 95 % CI: 1.48–23.07; p=0.008) were associated with 30-d mortality. Anemia, inducible cardiac ischemia and peak VO2 <15 mL/kg/min (OR: 8.59; 95 % CI: 2.33–55.75;	Observational study, relatively small number of deaths (6 in EVAR group and 8 with open AAA repair at 30 d and 11 EVAR/8 open repair at 90 d), mix of EVAR and open repair

													p=0.005) were associated with 90-d mortality on multivariable analysis. Pts with ≥2 subthreshold CPET values were at increased risk of both 30- and 90-d mortality.	
Thompson AR, et al., 2011 (68) 21929919	To assess the usefulness of CPET and the Detsky score to predict midterm mortality in AAA pts assessed for open repair. Secondary aim to compare ability of CPET and other scores to predict 30-d periop mortality.	Prospective cohort	102	66 (deemed "fit" by CPET variables, comorbidities, and size of AAA)	36 (deemed "unfit" by CPET variables, comorbidities, and size of AAA)	Consecutive pts undergoing AAA repair	None given	N/A	N/A	Midterm (30-mo) survival was predicted by the anaerobic threshold (p=0.02).	None	None of the scoring tools were able to predict 30-d major morbidity or mortality as defined by periop complications (p>0.05)	Midterm (30-mo) survival was predicted by the anaerobic threshold (p=0.02)	Lack of detail on cause of death, relatively small numbers total, and deaths (1 30-day death), not clear what "cardiac events" were
Prentis JM, et al., 2012 (69) 22858436	To assess the use of CPET to predict morbidity in unselected pts scheduled for elective EVAR or open AAA repair	Observational	185 pts (101 EVAR and 84 open repair)	N/A	N/A	"Unselected" pts undergoing EVAR or open AAA repair at a single center	AT not confidently determined from CPET data	N/A	N/A	Open repair: AT was a significant independent predictor of postop complications and hospital LOS. EVAR: No independent variables were significantly predictive of major postop complications on univariate analysis. No multivariate	None	Open repair: The in-hospital mortality rate was 5 of 84 (5.9%). 3 of 27 pts (11.1%) were in the unfit group (AT<10) compared with 2 of 58 (3.4%) in the fit group (AT>10), both of whom had an AT <12 mL/min/kg. Open repair: Cardiac complications (MI, LV failure, major arrhythmias) 18.5% unfit vs. 3.5% fit, p=0.03.	Open repair: ROC curve analysis showed that 10.0 mL/min/kg was the optimal AT level to predict those at risk for increased rates of postop complications. This was sensitive (70%) and specific (86%), with good accuracy (area under the curve, 0.75; 95% CI: 0.63–	Single center. Not consecutive pts although "unselected." No mortality data.

										analysis was performed.			0.83; p=0.001).	
Carlisle J, et al., 2007 (70) 17440956	To review whether preop fitness, measured by CPET, correlated with survival following elective open AAA repair	Observational	130 (37 pts did not undergo CPET and weren't analyzed)	N/A	N/A	Pts undergoing AAA repair	Did not undergo CPET	N/A	N/A	Multivariable analyses indicated that survival, to both 30 d and for the total observation period, correlated best with VE/VCO2. The risk of death was greater with higher values of VE/VCO2. The RCRI was significantly associated with midterm survival, as was the AT, but to a lesser degree.	None	Unfit pts had an RCRI >1 and a VE/VCO2 of >42. Fit pts had an RCRI of 1 (and any VE/VCO2), or an RCRI >1 but a VE/VCO2 lower than 43. There were 30 unfit pts and 100 fit pts.	Multivariable analysis of midterm (median 35 mo) survival: VE/VCO2 HR: 1.13 (CI: 1.07–1.19; p<0.001); RCRI HR: 1.76 (CI: 1.07–1.19; p=0.006); AT HR: 0.84 (CI: 0.72–0.98; p=0.033). The 2-y survival rate was 55% for unfit pts and 97% for fit pts; the absolute difference was 42% (95% CI: 18%–65%; p<0·001).	Single center, observational, unclear selection of CPET variable cutoffs
Older P, et al., 1993 (71) 8365279	To compare the extent of cardiac failure classified by AT and postop mortality	Prospective cohort	187	N/A	N/A	Pts >60 y of age scheduled for major abdominal surgery ("likely to cause a significant increase in oxygen demand, e.g., AAA resection, anterior resection of the rectum")	Could not complete CPET (4 of 191 pts)	N/A	N/A	10 CV deaths in 55 pts (18%) with AT <11 mL/kg/min vs. 1 CV death in 132 pts (0.8%) with AT of ≥11 mL/kg/min (p<0.001)	None	42% mortality in the 19 pts with an AT of <11 mL/min/kg and preop ischemia (h/o MI, angina or ischemia on CPET) vs. 4% mortality in the 25 pts with AT >11 and ischemia (p<0.01).	10 CV deaths in 55 pts (18%) with AT <11 mL/kg/min vs. 1 CV death in 132 pts (0.8%) with AT of ≥11 mL/kg/min (p<0.001)	Single center, not blinded to results (all pts with ischemic tests admitted to ICU regardless of AT)
Snowden CP, et al., 2010 (72) 20134313	To test the null hypothesis that CPET does not improve preop assessment of pt risk of postop	Prospective, single center cohort study	171 (123 went on for operation and 48 did not; 7	N/A	N/A	Pts planned to undergo major elective surgery (AAA repairs, aortobifem grafts, liver	Emergency and elective colorectal, urological, or orthopedic operations	N/A	N/A	POMS on postop d 7	None	Cardiovascular complication rate was 25% in pts with AT <10.1 mL/kg/min and 3% in those with AT	Receiver operator curve analysis showed an optimal AT threshold level of 10.1	Size and selected nature of the chosen pt cohort. 48 pts did not undergo planned

	complications when compared to a questionnaire-based assessment method		pts did not achieve AT leaving 116 for analysis)			resections, pancreatic and large retroperitoneal intra-abdominal sarcoma surgery) and low subjective functional capacity based on clinical Hx					>10.1 mL/kg/min (p=0.0005). Note POMS definition of CV complication: Diagnostic tests or therapy within the last 24 h for any of the following: new MI or ischemia, hypotension (requiring fluid therapy >200 mL/h or pharmacological therapy), atrial or ventricular arrhythmias, pulmonary edema, thrombotic event (requiring anticoagulation).	mL/kg/min to predict those at risk for increased rates of postop complications. This was highly sensitive (88%) and specific (79%) with high degree of accuracy (area under the curve 0.85; 95% CI: 0.78–0.91; p=0.001).	procedure. No comment on mortality.
Snowden CP, et al., 2013 (73) 23665968	To assess the relationship between cardiopulmonary fitness and age upon mortality and LOS in an unselected group of pts undergoing major hepatobiliary surgery	Single center prospective cohort study	389	N/A	N/A	All pts being considered for major hepatobiliary surgery (liver resection, Whipple, retroperitoneal intra-abdominal sarcoma excision)	Major surgery not performed because of extensive malignancy, laparoscopic rather than open procedure performed, or pts did not exercise enough to reach AT	N/A	N/A	Hospital mortality	None	Critical care and hospital LOS	Multivariate regression identified anaerobic threshold as the most significant independent predictor for postop mortality from the exercise variables in this population of major surgical pts (OR: 0.52; p=0.003; beta=−0.657). ROC analysis demonstrated an optimal anaerobic threshold level of 10 mL/min/kg with good	Limited to hepatobiliary surgery. Single center.

													accuracy (area under curve =0.75; 95% CI: 0.65–0.85; p=0.0001).	
Wilson RJT, et al., 2010 (74) 20573634	To evaluate whether CPET variables and clinical data from Lee's cardiac risk index are useful predictors of all cause hospital and 90-d mortality in pts undergoing nonvascular intra-abdominal surgery	Retrospective analysis of anonymized data	847	N/A	N/A	All pts aged >55 y being considered for colorectal surgery, bladder, or kidney cancer excision who performed or attempted a CPET as part of their routine preop evaluation at the Preassessment Clinic	Pts who did not proceed to planned surgery were excluded from analysis	N/A	N/A	An AT of ≤10.9 mL/kg/min, a VE/VCO2 of ≥34, and a Hx of ischemic heart disease were all associated with an increased relative risk for all-cause hospital mortality. The overall presence of any ≥1 of the Lee's cardiac risk factors was not significantly associated with an increased risk of mortality.	None	None	Nonsurvival: For AT of ≤10.9, RR: 6.8 (95% CI: 1.6–29.5); for VE/VCO2 of ≥34, RR: 4.6 (95% CI: 1.4–14.8). Survival at 90 d was significantly greater in pts with an AT of ≥11 (p=0.034), in pts with VE/VCO2 <34 (p=0.021), and in pts without IHD (p=0.02).	Low incidence of all-cause mortality (2.1% in hospital and 4.1% at 90 d)
Older P, et al., 1999 (41) 10453862	To test a strategy of postop triage based on CPET results	Prospective consecutive series	548 pts	153 to ICU	Pts sent to HDU (115) or ward (280)	Pts over 60 y of age scheduled for major surgery or <60 but had previous diagnosis of myocardial ischemia or cardiac failure	Pts undergoing thoracic surgery	AT <11 to ICU (28% of pts)	Pts with AT >11 with inducible ischemia or VE/VO2 >35 (21%) admitted to HDU; all others (51%) admitted to general ward	4.6% mortality in pts with AT <11	0.5% mortality in pts with AT >11	None	None given	Confounding of CPET results and postop care, but should have improved outcomes in higher risk pts. Lack of stats.
Junejo MA, et al., 2012 (75) 22696424	To evaluate the role of CPET in periop risk assessment in pts undergoing	Single center prospective cohort study	94 with CPET and surgery; 2 could not	94 in CPET group	23 pts deemed low risk	Pts over 65 y, younger pts with comorbidity and those likely to require complex	None given	N/A	N/A	Death within 30 d of operation	None	In-hospital deaths, LOS in ICU and high dependency unit, overall hospital stay and	AT was the only preop marker associated with postop in-hospital	AT cutoff derived from high-risk group; small number of in-hospital

	hepatic resection		attain AT leaving 92 for analysis			resection underwent CPET						longer-term survival (up to 4 y)	mortality (OR: 0.48; 95% CI: 0.25–0.94; p=0.032). ROC curve analysis identified a cut-off at 9.9 mLl/kg/min that provided 100% sensitivity and 76% specificity, with a PPV of 19% (95% CI: 9%–38%) and a NPV of 100% (95% CI: 94–100). Pts with an AT ≥9.9 mL/kg/min had improved long-term survival (median duration 1,067 d) compared with pts with a lower value (p=0.038), but worse survival than those low-risk pts who did not undergo CPET (p=0.038).	deaths (4.2% in whole group); CPET data available to managing clinicians; heterogeneous group in terms of type of resection and tumor histopathology

AAA indicates abdominal aortic aneurysm; AT, anaerobic threshold; CI, confidence interval; CPET, cardiopulmonary exercise stress test; EVAR, endovascular aneurysm repair; HR, hazard ratio; ICU, intensive care unit; LOS, length of stay; LV, left ventricular; MI, myocardial infarction; N/A, not applicable; NPV, net predictive value; OR, odds raio; periop, perioperative; POMS, postoperative morbidity survey; postop, postoperative; PPV, positive predictive value; preop, preoperative; RCRI, Revised Cardiac Risk Index; ROC, receiver operating characteristic; and VE/VO2, ventilatory equivalent of oxygen.

Data Supplement 13. Pharmacological Stress Testing (Section 5.5)

Study Name, Author, Year	Aim of Study	Study Type	Study Size (N)	Study Intervention 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*		
Beattie WS, et al., 2006 (76) 16368798	Compare SE vs. MPI in preop evaluation prior to noncardiac surgery	Meta-analysis of 68 studies	10,049	N/A	Preop noncardiac surgery	N/A	N/A	MI and/or death	MI and/or death	LR for SE more indicative of postop cardiac event vs. TI (LR: 4.09; 95% CI: 3.21–6.56 vs. LR: 1.83; 1.59–2.10; p<0.001). This difference was attributable to fewer false negative SEs. No difference in ROC curves (SE: 0.80; 95% CI: 0.76–0.84 vs. TI: 0.75; 95% CI: 0.70–0.81).	A moderate-to-large defect, seen in 14% of pts by either method predicts a postop cardiac event (LR: 8.35; 95% CI: 5.6–12.45)	N/A	N/A

CI indicates confidence interval; LR, likelihood ratio; MI, myocardial infarction; MPI, myocardial perfusion imaging; N/A, not applicable; postop, postoperative; preop, preoperative; ROC, receiver operating characteristic; SE, stress echocardiography; and TI, thallium imaging.

Data Supplement 14. Radionuclide MPI (Section 5.5.2)

Study Name, Author, Year	Aim of Study	Study Type	Study Size (N)	Patient Population		Ischemia	Endpoints			P Values, OR: HR: RR & 95% CI:
				Inclusion Criteria	*Exclusion Criteria*		*Primary Endpoint (Efficacy) and Results*	*Safety Endpoint and Results*	*Secondary Endpoint and Results*	
Eagle KA, et al.,1989 (77) 8653858	Periop risk assessment by MPI	Single center, retrospective	200	Vascular surgery	N/A	41%	Periop events: PPV: 16%; NPV: 98%	N/A	N/A	N/A
Younis LT, et al., 1990 (78) 2353615	Periop risk assessment by MPI	Single center, retrospective	111	Peripheral vascular disease	N/A	36%	Periop events: PPV: 15%; NPV: 100%	N/A	N/A	N/A
Hendel RC, et al., 1992 (79) 1442573	Periop risk assessment by MPI	Single center, retrospective	327	N/A	N/A	51%	Periop events: PPV: 14%; NPV: 99%	N/A	N/A	N/A
Lette J, et al., 1992 (80) 1598869	Periop risk assessment by MPI	Single center, retrospective	355	N/A	N/A	45%	Periop events: PPV: 17%; NPV: 99%	N/A	N/A	N/A

Brown KA, et al., 1993 (81) 8425993	Periop risk assessment by MPI	Single center, retrospective	231	N/A	N/A	33%	Periop events: PPV: 13%; NPV: 99%	N/A	N/A	N/A
Bry JD, et al., 1994 (82) 8301724	Periop risk assessment by MPI	Single center, retrospective	237	N/A	N/A	46%	Periop events: PPV: 11%; NPV: 100%	N/A	N/A	N/A
Marshall ES, et al., 1995 (83) 7572662	Periop risk assessment by MPI	Single center, retrospective	117	N/A	N/A	47%	Periop events: PPV: 16%; NPV: 97%	N/A	N/A	N/A
Stratman HG, et al., 1996 (84) 8615311	Periop risk assessment by MPI	Single center, retrospective	229	Nonvascvular surgery	N/A	29%	Periop events: PPV: 6%; NPV: 99%	N/A	N/A	N/A
Cohen MC, et al., 2003 (85) 14569239	Periop risk assessment by MPI	Single center, retrospective	153	N/A	N/A	31%	Periop events: PPV: 4%; NPV: 100%	N/A	N/A	N/A
Harafuji K, et al., 2005 (86) 15849442	Periop risk assessment by MPI	Single center, retrospective	302	N/A	N/A	30%	Periop events: PPV: 2%; NPV: 100%	N/A	N/A	N/A
Beattie WS, et al., 2006 (76) 16368798	Compare SE vs. MPI in preop evaluation prior to noncardiac surgery	Meta-analysis of 68 studies	10,049	Preop noncardiac surgery	N/A	N/A	Outcomes: MI and/or death	There were no differences in ROC curves between SE and TI (SE: 0.80; 95% CI: 0.76–0.84 vs. TI: 0.75; 95% CI: 0.70–0.81)	A moderate-to-large defect, seen in 14% of pts, by either method predicts a postop cardiac event (LR: 8.35; 95% CI: 5.6–12.45).	LR for SE more indicative of postop cardiac event vs. TI (LR: 4.09; 95% CI: 3.21–6.56 vs. TI: 1.83; 95% CI: 1.59–2.10; p<0.001); this difference was attributable to fewer false negative SEs

CI indicates confidence interval; LR, likelihood ratio; MPI, myocardial perfusion imaging; N/A, not available; NPV, net present value; periop, perioperative; postop, postoperative; PPV, positive predictive value; ROC, receiver operating characteristic; SE, stress echocardiography; and TI, thallium imaging.

Data Supplement 15. Dobutamine Stress Echocardiography (Section 5.5.3)

Study Name, Author, Year	Aim of Study	Study Type	Study Size (N)	Patient Population	Events (MI/death)	Ischemia, %	Endpoints		P Values, OR: HR: RR & 95% CI:	Study Limitations & Adverse Events
				Inclusion Criteria			*Primary Endpoint (Efficacy) and Results*	*Secondary Endpoint and Results*		
Lane RT, et al.,1991 (87) 1927965	Periop risk assessment by DSE	Single center, retrospective	38	Vascular and general surgery	8%	50%	PPV 16%, NPV 100%	N/A	N/A	N/A
Lalka SG. et al., 1992 (88) 1578539	Periop risk assessment by DSE	Single center, retrospective	60	Abdominal aortic surgery	15%	50%	PPV 23%, NPV 93%	N/A	Event rate 29% vs. 4.6%, p=0.025	N/A

Eichelberger JP, et al., 1993 (89) 8362778	Periop risk assessment by DSE	Single center, prospective	75	Major vascular surgery	3%	36%	PPV 7%, NPV 100%	N/A	N/A	N/A
Langan EM, et al., 1993 (90) 8264046	Periop risk assessment by DSE	Single center, retrospective	74	Aortic surgery	4%	24%	PPV 17%, NPV 100%	N/A	N/A	Surgery deferred in 4 highly positive DSE who proceeded with CABG
Davila-Roman V, et al., 1993 (91) 8450165	Periop risk assessment by DSE	Single center, prospective	88	Aortic and LE PVD surgery	2%	23%	PPV 10%, NPV 100%	Abnormal DSE associated with increased long-term event rate also (15% vs. 3%; p=0.038)	N/A	N/A
Shafritz R, et al., 1997 (92) 9293826	Periop risk assessment by DSE, comparison to historical cohort without preop DSE	Single center, retrospective	42	Aortic surgery	2%	0%	NPV 100%	No difference in overall mortality (2.3% vs. 4.4%) or cardiac mortality (0% vs. 2.9%) in those who had preop DSE testing vs. those who did not	N/A	N/A
Bossone, 1999 (93) 10469973	Periop risk assessment by DSE	Single center, prospective	46	Lung-volume reduction surgery	2%	9%	PPV 25%, NPV 100%	N/A	N/A	N/A
Ballal RS, et al., 1999 (94) 10047628	Periop risk assessment by DSE	Single center, prospective	233	Major vascular surgery	3%	17%	PPV 0%, NPV 96%	N/A	N/A	Surgery deferred in 8 highly positive DSE who proceeded with PCI
Das MK, et al., 2000 (95) 10807472	Periop risk assessment by DSE	Single center, prospective	530	Nonvascular surgery	6%	40%	PPV 15%, NPV 100%	High risk study (defined as ischemia before 60% of age-predicted heart rate threshold) associated event rate of 43%. Incremental risk prediction over clinical characteristics	N/A	N/A
Morgan PB, et al., 2002 (96) 12198027	Periop risk assessment by DSE	Single center, retrospective	78	Vascular and general surgery	0%	5%	PPV 0, NPV 100%	N/A	N/A	All 4 pts with ischemia underwent preop coronary angiography +/- PCI.
Torres MR et al., 2002 (97) 12127610	Periop risk assessment by DSE	Single center, prospective	105	Predominantly vascular surgery	10%	47%	PPV 18%, NPV 98%	N/A	N/A	Beta-blocker therapy given on basis of DSE, 4 pts had surgery deferred for PCI/CABG
Labib SB, et al., 2004 (98) 15234412	Periop risk assessment by DSE, comparison of maximal vs. submaximal achieved peak heart rate	Single center, prospective	429	1/3 vascular surgery	2%	7%	PPV 9%, NPV 98%	High NPV even when peak heart rate not achieved	N/A	N/A
Raux M, et al., 2006 (99)	Periop risk assessment by a	Single center, retrospective	143	Abdominal aortic surgery	N/A	N/A	NPV 93% events predominantly were	N/A	N/A	All with abnormal DSE underwent coronary

16973646	negative DSE and incidence of elevated troponin						nonclinical elevated troponin measures			angiogram +/- PCI prior to surgery
Umphrey LG, et al., 2008 (100) 18508373	Periop risk assessment by DSE	Single center, retrospective	157	Orthotropic liver transplantation	3.80%	0%	NPV	Inability during DSE to achieve >80% of targeted heart rate associated with increased cardiac events (22% vs. 6%; p=0.01)	N/A	N/A
Lerakis S, et al., 2007 (101) 18219774	Periop risk assessment by DSE	Single center, retrospective	539	Bariatric surgery	0.05% (all noncardiac death)	1.20%	N/A	N/A	N/A	All with abnormal DSE underwent coronary angiogram +/- PCI prior to surgery
Nguyen P, et al., 2013 23974907	Periop risk assessment by DSE	Pooled analysis of 7 studies	580	Orthotropic liver transplantation	N/A	N/A	PPV 37%, NPV 75%	N/A	N/A	N/A

CABG indicates coronary artery bypass graft; DSE, dobutamine stress echocardiography; N/A, not available; NPV, net predictive value; PCI, percutaneous coronary intervention; periop, perioperative; PPV positive predictive value; preop, preoperative; and PVD, peripheral valvular disease.

Data Supplement 16. Preoperative Coronary Angiography (Section 5.7)

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*	*Secondary Endpoint and Results*		
Monaco et al., 2009 (102) 19729114	RCT	208	105	103	Vascular surgery, CRI ≥2	N/A	Routine angiography	Selective angiography	L/T MACE (58±17 mo): p=0.01	MACE by 30 d preop: 11.7% selective vs. 4.8% routine	L/T MACE p=0.003; 30 d MACE p=0.1	Small sample size, unblinded; recruit/random methods unclear

CABG indicates coronary artery bypass graft; CRI, cardiac risk index; DSE, dobutamine stress echocardiography; MACE, major adverse cardiac event; NCS, noncardiac surgery; NPV, net predictive value; PCI, percutaneous coronary intervention; PPV, positive predictive value; preop, preoperative; and RCT, randomized controlled trial.

Data Supplement 17. Coronary Revascularization Prior to Noncardiac Surgery (Section 6.1)

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:
						Inclusion Criteria	*Exclusion Criteria*			*Primary Endpoint (Efficacy) and Results*	*Secondary Endpoint and Results*	
McFalls EO, et al., 2004 (36) 15625331	Revascularization vs. medical therapy before elective major vascular surgery	RCT	510	258	252	Vascular surgery	Urgent/emergency: UA; LM; EF<20%; AS	Revascularization (CABG or PCI)	Medical therapy	Death (30 d) 3.1% (revascularization) vs. 3.4% (medical therapy)	Lost to follow up: death 2.7 y	Primary endpoint p=0.87; secondary endpoint p=0.92 (RR: 0.98; 95% CI: 0.7–1.37)

AS indicates aortic stenosis; CABG, coronary artery bypass graft; CI, confidence interval; EF, ejection fraction; PCI, percutaneous coronary intervention; RCT, randomized controlled trial; RR, relative risk; and UA, unstable angina.

Data Supplement 18. Timing of Elective Noncardiac Surgery in Patients With Previous PCI (Section 6.1.1)

Table 1. Risk of NCS Following PCI With BMS and Risk of NCS Following PCI With DES

Author, Year	Study Type	Study Size (n)	Type of Surgery (%)					PCI to NCS (d)	MACE		APT in Perioperative Period (%)			Major Bleeding		Study Limitations	Risk of NCS in Stented Pt
			Low	*Intermediate*	*High*	*Cardiac*	*Unknown*		*Endpoints*	*(%)*	*ASA*	*$P2Y_{12}$ Inhibitor*	*DAPT*	*Endpoints*	*(%)*		
Risk of NCS following PCI With BMS																	
Kaluza, 2000 (103) 10758971	Retrospective	40	N/A	33	65	2	N/A	13	Death, MI	20, 17.5	5	12.5	2.5	Tx or reoperation	27	SC, small sample size, retrospective, APT status not well described	All MACE <2 wk after PCI, emphasizing high-risk early period
Wilson, 2003 (104) 12875757	Retrospective	207	N/A	36	58	N/A	6	1–60	Death, MI, ST or revascularization	4	51	14	26	"Excessive" surgical site bleed, Tx	2, 33	Retrospective, SC	All events occurred within first 6 wk
Sharma AK, et al., 2004 (105) 15390248	Retrospective	47	N/A	68	30	N/A	2	<21 (n=27); 21–90 (n=20)	Death or MI	25 (<21 d), 15 (21–90 d)	N/A	74 (<21 d), 70 (21–90 d)	N/A	Tx, reoperation	29 (<21 d), 0 (21–90 d)	Small sample size, retrospective, APT status not well described, SC, 6/7 deaths in first 21 d considered probable ST	Study confined to early phase NCS pt. 6/7 IE in pts who discontinued DAPT. This study suggests importance of continuation of DAPT during early period.
Reddy, 2005	Retrospective	56	10	60	20	N/A	10	<42	MI or CVD	14	79*	32*	N/A	Reoperation, Tx >2 PRBC, Hb drop >2 g/dL	5	Small sample size, retrospective, APT status not well described, SC.	All IE occurred within 42 d of PCI, emphasizing

(106) 15757604														or IC, IO or RP bleed		All 3 bleeding episodes were in pts receiving P2Y12 inhibitor.	high risk early period
Brichon, 2006 (107) 16996274	Retrospective	32	N/A	100	N/A	N/A	N/A	<90	ST	9	66	0	0	Hemothorax or RP bleed	10	Small sample size, retrospective. 30% of pts received only heparin	ST rather higher (9%) within 3 mo of stenting and lung surgery
Nuttal, 2008 (108) 18813036	Retrospective	889	21	46	33	N/A	N/A	64	Death, MI, ST, or TLR	Overall 5.2; <30 d 10.5; 30-90 d 3.8; 90-365 d 2.8	64.5†			Need for non–PRBC tx	5	Retrospective, APT status not well described, SC	This study emphasizes that risk is highest very early after PCI
Risk of NCS Following PCI With DES																	
Compton, 2006 (109) 17056330	Retrospective	38	31	35	15	N/A	19	260	MI	0	83	40	*†	Postop Tx	3	Small sample size, retrospective, APT status not well described, SC	MACE is low with NCS performed late after PCI
Brotman, 2007 (110) 18081175	Retrospective	114	52	42	6	N/A	N/A	236	MI, ST, or death	1.8	1.8	0	21	Reoperation, IC or RP bleed	0.9	Retrospective, SC	MACE is low with NCS performed late after PCI
Conroy, 2007 (111) 18084986	Retrospective	24 (42)	N/A	N/A	N/A	N/A	N/A	N/A	Ischemia on ECG, troponin elevation, or ST	7	N/A	50	N/A	Surgical site bleed or reoperation	2.4	Small sample size, retrospective, APT status not well described, SC. MACE and bleeding EP not well defined	IE: 3/14 pts who discontinued DAPT to ASA alone had ST. 4/4 with alternate anticoagulant or IV APT had no ST, suggesting value of DAPT to prevent IE.
Rhee, 2008 (112) 18475013	Retrospective	141	N/A	96	N/A	N/A	N/A	228	ST	5	5	0	0	N/A	N/A	Retrospective, SC, bleeding endpoint not well defined	IE: >7 d of $P2Y_{12}$ inhibitor discontinuation and use of Taxus stent was associated with ST
Godet, 2008 (113) 18310674	Retrospective	96	N/A	26	74	N/A	N/A	425	Troponin elevation, ST	12, 2	70	38	N/A	N/A	N/A	Small sample size, APT status and bleeding endpoints not well described, SC	The risk of a serious complication, i.e., ST, was relatively low (2%)
Rabbitts, 2008 (114) 18813037	Retrospective	520 (400 <1 y, 120 >1 y)	18	56	25	N/A	N/A	204	Death, MI, ST or revascularization	5.4 (6 <1 y, 3.3 >1 y)	70	33	*†	Surgical site, excessive bleed'	1	Retrospective, SC, APT not well described	IE: Trend to lower IE rate if NCS >1 y after PCI
Chia, 2010 (115) 20609638	Retrospective	710	N/A	N/A	N/A	N/A	N/A	348	MI or ST	1.5	14	9	18	N/A	N/A	Retrospective, bleeding endpoint not well defined, questionnaire-based	IE: The low IE rate may have been due to late NCS plus questionnaire method, i.e.,

																	underreporting
Anwaruddin, 2009 (116) 19539259	Retrospective	481 (606)	5.6	55.6	20	22	N/A	390	Primary ST (definite and moderate probability); secondary death, nonfatal MI, ST	2; 9	15	1	21	N/A	N/A	Retrospective, bleeding endpoint not well defined, SC	Risk of MACE higher if NCS <30 d after PCI but some level persisted for 2-3 y after PCI
Assali, 2009 (117) 19626693	Retrospective	78	N/A	81	19	N/A	N/A	414	MI, ST, or death	7.7	18	42	21	Hb drop >2 g/dL	16.7	Small sample size, retrospective, SC	Most MACE occurred <1 wk after NCS and there was no difference in MACE between 6–12 mo vs. >12 mo
Berger, 2010 (118) 20850090	Prospective registry, retrospective	206	N/A	76	20	N/A	4	179	Death, MI, or ST	1.9	N/A	N/A	N/A	N/A	N/A	APT status and bleeding endpoint not well described	Most IEs occur within 1st wk after NCS
Gandhi, 2011 (119) 20824750	Retrospective	135 (191)	23	62	15	N/A	N/A	547	Death, ST, or MI	0.5; 2	54	30	N/A	Bleeding with hypotension, blood loss >500cc, or >2 Tx	6	Retrospective, SC, APT status not well defined	Low risk of IE when NCS performed relatively late after PCI
Brilaki, 2011 (120) 21315220	Retrospective	164	100	N/A	N/A	N/A	N/A	<365	Death, MI or ST	0.6	N/A	N/A	N/A	N/A	N/A	Retrospective, APT status and bleeding endpoint not well defined	Low risk of events in low risk NCS

*All studies were retrospective analyses.
†Rates of individual or dual APT not provided.
APT indicates antiplatelet therapy; ASA, aspirin; BMS, bare-metal stent; CVD, cardiovascular disease; DAPT, dual antiplatelet therapy; ECG, echocardiogram; Hb, hemoglobin; IC, intracranial; IE, ischemic events; IO, intraocular; IV, intravenous; MACE, major adverse coronary event; MI, myocardial infarction; N/A, not applicable; NCS, noncardiac surgery; PCI, percutaneous coronary intervention; postop, postoperative; PRBC, packed red blood cell; pt, patient; RP, retroperitoneal; rx, therapy; SC, single center; and ST, stent thrombosis; and Tx, transfusion.

Table 2. Risk of Noncardiac Surgery Following BMS or DES

Author, Year	Study Type	Study Size (n)		Type of Surgery (%)				PCI to NCS (d)	MACE			APT in Periop Period (%)			Major bleeding		Study Limitations	Risk of NCS in Stented Pt
		BMS	*DES*	*Low*	*Intermediate*	*High*	*Unknown*		*Endpoint*	*BMS (%)*	*DES (%)*	*ASA*	*$P2Y_{12}$ Inhibitor*	*DAPT*	*EP*	*(%)*		
Kim, 2008 (121) 17346821	Retrospective	101	138	N/A	N/A	N/A	N/A	N/A	Death, ST, or MI	0	2.2	N/A	N/A	N/A	N/A	N/A	Retrospective, SC, APT status and bleeding definition not well described	Limited study but showed low rate of IE for both BMS and DES
Schouten, 2007 (122)	Retrospective	93	99	12	60	23	5	<730	MI or death	2	3	53 (either single or dual APT)			N/A	N/A	Small SC, retrospective, APT	IE: APT interruption was associated with higher

17207733																use, IE, and bleeding not well defined	MACE (5.5% vs. 0.0%; p=0.023). No difference in MACE between BMS and DES
Van Kuijk, 2009 (123) 19840567	Retrospective	174	376	33; 31	51; 47	15; 22	N/A	BMS 1314; DES 511	D, MI, ST, or revascularization	6	13	91*; 70*		9†; 30‡	Severe; moderate	10; 8	Retrospective, APT status not well described	Early NCS (<30 d) in either group was associated with increased MACE (overall p<0.001). Bleeding complications significantly higher with DAPT in both groups.
Cruden, 2010 (124) 20442357	Retrospective	1,383	570	19	71	10	N/A	BMS 503; DES 371	Primary in-hospital death + IE; secondary in-hospital death + MI	Primary 13.3; secondary 1.3	Primary 14.6; secondary 1.9	N/A	N/A	N/A	N/A	N/A	Retrospective, APT status and bleeding endpoint not well described	No significant difference in MACE risk in BMS vs. DES. MACE higher if NCS <6 wk
Albaladejo, 2011 (125) 21791513	Prospective registry; retrospective analysis	623	367	20	40	26	14	>80% were after 6 mo	MI, ST, HF, CS, SA, or stroke	10.9†		N/A	N/A	N/A	Major	9.5	APT status not well described	IE and bleeding relatively high despite relatively long time between PCI and NCS
Brancati, 2011 (126) 21297198	Retrospective	70	31	26	65	9	0	288	Death, MI, ST, or revascularization	6		39 (either ASA or $P2Y_{12}$)		49	Need for Tx or surgical hemostasis	BMS 14%, DES 6%	Retrospective, SC	Similar IE and bleeding for both groups
Tokushige, 2012 (127) 22396582	Prospective registry; retrospective analysis	1,103	1295	N/A	N/A	N/A	N/A	<42d BMS 4.4% DES 1.9%	Death, MI, ST 30 d with 2 groups:<42 after PCI; >42 d after PCI	3.5	2.9	17.8	0.6	27	Moderate, severe (GUSTO)	BMS 3.2%, DES 2.1%	Retrospective	IE and bleed risk low for both BMS and DES. >95% in each group had NCS >42 d after stent.
Wijeysundera, 2012 (1) 22893606	Retrospective	1820‡ (<2 y)	905 (<2 y)	0§	85.9	14.1	0	Range: 1–3,650	Death, ACS, revascularization by 30 d after surgery	6.7(<45 d), 2.6 (45–180 d), 2.9 (181–365 d), 1.7 (366–730 d), 0 (731–3,650 d)	20 (<45 d), 3.8 (45–180 d), 1.1 (181–365 d),1.6 (366–730 d), 1.5 (731–3,650 d)	N/A	N/A	N/A	N/A	N/A	Retrospective, administrative data base	First 45 d high-risk period; DES risk low and equal to intermediate risk surgery by 180 d

Small study defined as <100 patients

*Percentage of patients taking both ASA and $P2Y_{12}$ inhibitor not provided.

†Rates of individual or dual APT not provided.

‡Total number of patients in Wijeysundera study was 8116; 2725 patients underwent stenting <2 y.

§Total procedures=7,998; 2,725 <2 y after stent implantation.

ASA indicates aspirin; APT, anti-platelet therapy; BMS, bare-metal stent; DAPT, dual anti-platelet therapy; DES, drug-eluting stent; GUSTO, Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries; IE, ischemic events; MACE, major adverse cardiac events; MI, myocardial infarction; n, subgroup; N/A, not available; NCS, noncardiac surgery; PCI, percutaneous coronary intervention; periop, perioperative; postop, postoperative; pt, patient; SC, single center; ST, stent thrombosis; TLR, target lesion revascularization; TVR, target vessel revascularization; and Tx, transfusion.

Data Supplement 19. Perioperative Beta-Blocker Therapy (Section 6.2.1)

Please see the complete Evidence Review Committee's Systematic Review Report for more information (128). The following few tables/figures are provided for ease of use and may contain data from Poldermans studies which were included in the scope of the systematic review.

Table 1. Summary of Included Studies

Study (Year)	N	Inclusion Criteria	Exclusion Criteria	Types of Surgery	Long-Term Preoperative Beta-Blocker Therapy	Participant Characteristics
Randomized Controlled Trials						
Mangano et al. (1996) (129) 8929262	200	Known CAD or ≥2 risk factors (≥65 y of age, hypertension, current smoker, elevated cholesterol level, diabetes mellitus)	Pacemaker dependency, resting ECG abnormalities (left bundle-branch block, marked ST-T abnormalities)	Elective vascular (41%), intra-abdominal (21%), orthopedic (14%), neurosurgical (9%), or other (16%) procedures	13%	Mean age 67.5 y, 39% with known CAD
Jakobsen et al. (1997) (130) 9327317	100	Pts undergoing thoracotomy for lung resection with no known current or previous cardiovascular disease	NR	Intrathoracic (100%) procedures	NR	66% males, mean age 60.4 y
Bayliff et al. (1999) (131) 10086546	99	Pts >18 y of age undergoing major thoracic operation	Prior beta-blocker use, asthma, HF, heart block, supraventricular tachyarrhythmias, prior specific drug use (digoxin, quinidine, procainamide, amiodarone, diltiazem, verapamil)	Intrathoracic (100%) procedures	0%	62% males, mean age 62.5 y, 6% with prior MI, 5% with current angina
DECREASE-I (1999) (132) 10588963	112	Pts with ≥1 cardiac risk factor (>70 y of age, angina; prior MI, HF, diabetes mellitus, limited exercise capacity, ventricular arrhythmias) and positive result on dobutamine stress echocardiography.	Prior beta-blocker use, asthma, very high-risk dobutamine stress echocardiography result (extensive wall-motion abnormalities, strong evidence of left main or severe 3-vessel CAD)	Major vascular (100%) procedures	0%	87% males, mean age 67.5 y, 100% with known CAD, 52% with prior MI, 32% with current angina
Raby et al. (1999) (133) 10071990	26	Pts with preoperative myocardial ischemia detected by 24-h ECG monitoring performed within 1–12 d before surgery	Baseline ST-T abnormalities on ECG that preclude accurate interpretation of ECG monitoring for ischemia	Major vascular (100%) procedures	35%	46% males, mean age 68.1 y, 38% with prior MI or current angina
Zaugg et al. (1999)* (134) 10598610	43	Pts ≥65 y of age	Prior beta-blocker use, other prior drugs (beta-adrenergic agonists, glucocorticoids, anticonvulsants), heart block, rhythm other than sinus on ECG, HF, bronchospasm, systemic infection, neurological disorders	Intra-abdominal (81%), orthopedic (7%), and other (12%) procedures	0%	40% males, mean age 74.6 y, 37% with known CAD
Urban et al.	107	Pts 50 to 80 y of age undergoing elective	Specific ECG abnormalities (heart block,	Orthopedic (100%) procedures	28%	Mean age 69.5 y, 17% with prior MI, 31% with

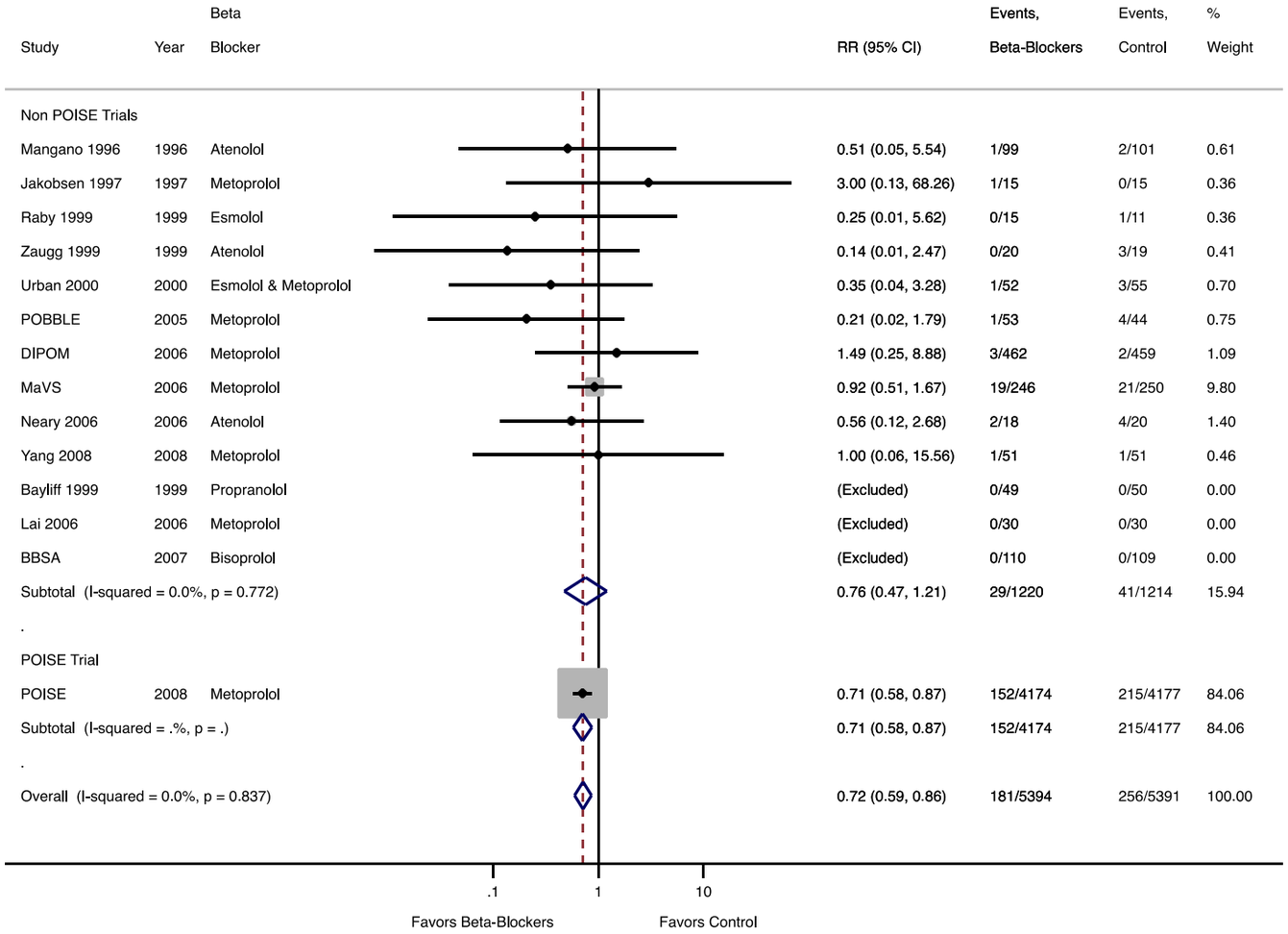
(2000) (135) 10825304		total knee arthroplasty with known CAD or ≥1 risk factor (≥65 y of age, hypertension, current smoker, elevated cholesterol level, diabetes mellitus)	bundle-branch block, atrial arrhythmias, LV hypertrophy with repolarization abnormalities), LVEF <30%, symptomatic mitral or aortic valvular disease, bronchospasm			current angina
POBBLE (2005) (136) 15874923	103	Pts undergoing major elective infrarenal vascular surgery under general anesthesia	Prior MI in past 2 y, unstable angina, positive dobutamine stress test, prior beta-blocker use, asthma, aortic stenosis, heart rate ≤45 beats/min, systolic BP <100 mm Hg	Major vascular procedures (100%)	0%	78% males, median age 73 y
DIPOM (2006) (137) 16793810	921	Pts with diabetes mellitus >39 y of age undergoing noncardiac surgery with expected duration >1 h	Long-term beta-blocker use, conditions indicating beta blocker treatment, severe HF, heart block	Orthopedic (33%), intra-abdominal (28%), neurosurgical (8%), vascular (7%), gynecological (5%), and other (19%) procedures	0%	59% males, mean age 64.9 y, 8% with prior MI, 11% with current angina
Lai et al. (2006) (138) 16687084	60	Pts ≥65 y of age undergoing esophagectomy for esophageal cancer with no known prior CAD	Prior beta-blocker use, heart rate ≤55 beats/min, systolic BP ≤100 mm Hg, heart block	Intrathoracic (100%) procedures	0%	82% males, median ages 66 (beta blocker arm) and 67 (control arm),
MaVS (2006) (139) 17070177	496	Pts (ASA-PS Class ≤3) undergoing major vascular (abdominal aortic repair, infra-inguinal, or axillo-femoral bypass) surgery	Long-term beta-blocker use, current amiodarone use, reactive airways disease, HF, heart block	Major vascular (100%) procedures	0%	76% males, mean age 66.1 y, 14% with prior MI, 9% with current angina
Neary et al. (2006) (140) 16764198	38	Pts undergoing emergency surgery with ≥1 of the following criteria: CAD, cerebrovascular disease (prior stroke or TIA), ≥2 minor risk criteria (≥65 y of age, hypertension, smoker, diabetes mellitus, hypercholesterolemia)	Prior beta-blocker use, heart rate <55 beats/min, heart block, chronic obstructive airway disease, asthma, cardiovascular collapse, uncorrected hypovolemia	Intra-abdominal (29%), amputation (24%), major vascular (21%), orthopedic (16%), and other (10%) procedures	0%	NR
BBSA (2007) (141) 17585213	219	Pts undergoing surgery with spinal anesthesia with known CAD or ≥2 risk factors (≥65 y of age, hypertension, current smoker, elevated cholesterol level, diabetes mellitus)	Prior beta-blocker use, significant HF, heart block, severe asthma, left bundle-branch block	Orthopedic (67%), urologic (25%), and other (8%) procedures	0%	55% males, mean age 70.0 y, 8% with prior MI, 6% with current angina
POISE-1 (2008) (142) 18479744	8,351	Pts ≥45 y of age and ≥1 of the following criteria: CAD, PVD, stroke, hospitalization for HF within past 3 y, major vascular surgery, or ≥3 minor risk factors (HF, TIA, diabetes mellitus, renal insufficiency, age >70 y, nonelective surgery, intrathoracic surgery, or intraperitoneal surgery)	Prior beta-blocker use, verapamil use, heart rate <50 beats/min, heart block, asthma, CABG surgery in previous 5 y with no subsequent ischemia, low-risk surgery	Vascular (41%), intraperitoneal (22%), orthopedic (21%), and other (16%) procedures	0%	63% males, mean age 69.0 y, 43% with known CAD
Yang et al. (2008) (143) 18953854	102	Pts ≥45 y of age with ≥1 of the following criteria: CAD, PVD, stroke, hospitalization for HF in prior 3 y, or ≥3 minor risk factors (HF, diabetes mellitus, ≥65 y of age, hypertension, hypercholesterolemia,	Prior beta-blocker use, heart rate <50 beats/min, cardiac pacemaker, heart block, asthma, chronic obstructive pulmonary disease	Intra-abdominal and intrathoracic procedures	0%	59% males, mean age 71.0 y

		smoker, intrathoracic surgery, or intraperitoneal surgery)				
DECREASE-IV (2009) (144) 19474688	1,066	Pts ≥40 y of age undergoing elective noncardiovascular surgery with an estimated 1%–6% perioperative cardiovascular risk	Current use, or contraindication to use, of beta blockers or statins	General surgical (39%), urologic (19%), orthopedic (16%), ear-nose-throat (12%), and other surgical (14%) procedures	0%	60% males, mean age 65.4 y, 6% with current angina, 5% with previous MI
Cohort Studies						
Matyal et al. (2008)† (145) 18503921	348	Pts undergoing supra- and infrainguinal vascular surgery	NR	Major vascular (100%) procedures	0%†	60% males

*Information on 2 of the study arms (preoperative/postoperative atenolol *versus* no beta-blocker therapy). The third study arm (intraoperative atenolol) did not meet the review definition for eligible perioperative beta-blockade.
†Only data on the subgroup of 348 pts who were not previously receiving preoperative long-term beta-blocker therapy.

ASA-PS indicates American Society of Anesthesiologists Physical Status; BBSA, Beta Blocker in Spinal Anesthesia; BP, blood pressure; CABG, coronary artery bypass graft; CAD, coronary artery disease; DECREASE, Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography; DIPOM, Diabetic Postoperative Mortality and Morbidity; ECG, electrocardiogram; HF, heart failure; LV, left ventricular; LVEF, left ventricular ejection fraction; MaVS, Metoprolol After Vascular Surgery; MI, myocardial infarction; NR, not reported; pts, patients; POBBLE, Perioperative Beta Blockage; POISE, Perioperative Ischemic Study Evaluation; PVD, peripheral vascular disease; and TIA, transient ischemic attack.

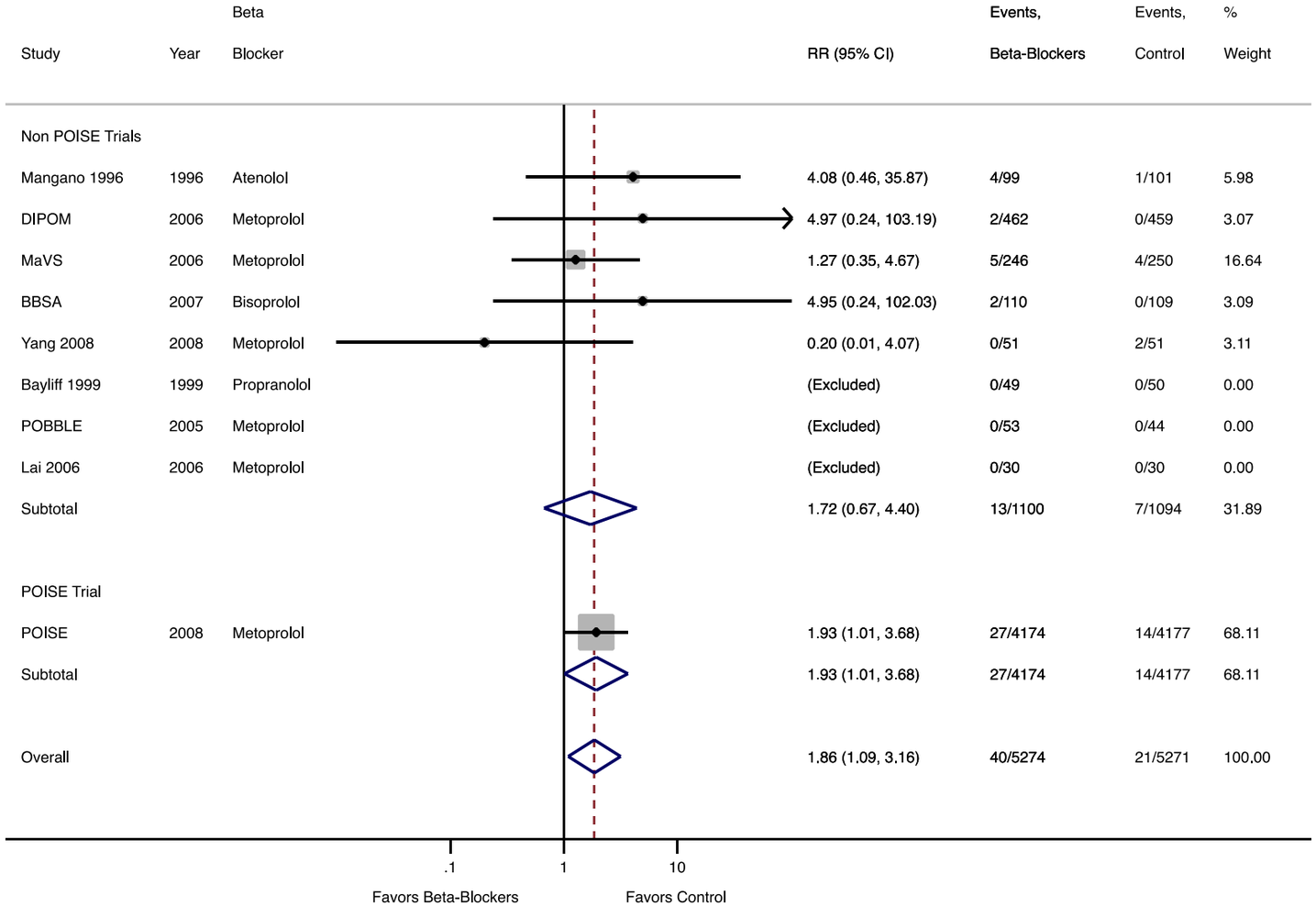
Figure 1. Effect of Perioperative Beta Blockade on In-Hospital or 30-Day Nonfatal MI in RCTs, With Members of the DECREASE Family of Trials Excluded



Effect of perioperative beta blockade on in-hospital or 30-day nonfatal MI, within subgroups defined by the POISE-1 trial versus other trials. The pooled effect is expressed as a pooled RR with associated 95% CI. The solid black diamonds represent point estimates in individual RCTs. The area of each gray square correlates with its contribution toward the pooled summary estimates. Horizontal lines denote 95% CIs. Estimates to the left of the line of unity (i.e., RR: 1) indicate superior clinical outcomes (i.e., fewer nonfatal MIs) with beta blockade ("*Favors Beta-Blockers*"), whereas estimates to the right of the line of unity indicate superior clinical outcomes with control ("*Favors Control*"). The blue diamonds represent the pooled estimates for all studies (RR: 0.72; 95% CI: 0.59–0.86), as well as the POISE-1 trial (RR: 0.70; 95% CI: 0.57–0.86) and the subgroup of other trials (RR: 0.76; 95% CI: 0.47–1.21). Statistical heterogeneity, as measured by the I^2 statistic, was 0% for the overall analysis.

BBSA indicates Beta Blocker in Spinal Anesthesia; CI, confidence interval; DECREASE, Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography; DIPOM, Diabetic Postoperative Mortality and Morbidity; MaVS, Metoprolol After Vascular Surgery; MI, myocardial infarction; POBBLE, Perioperative Beta Blockade; POISE, Perioperative Ischemic Evaluation Study; RCT, randomized controlled trial; and RR, relative risk.

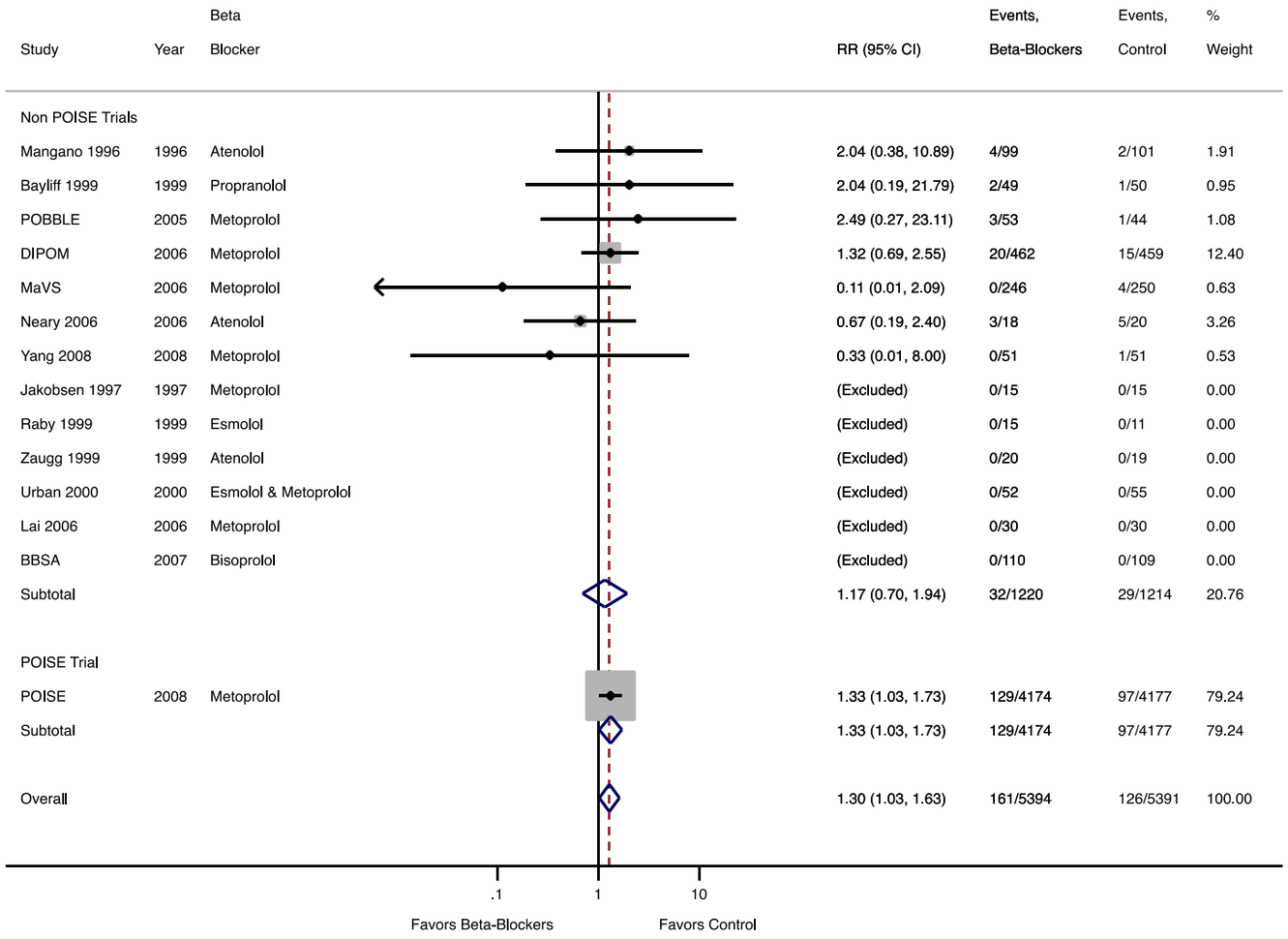
Figure 2. Effect of Perioperative Beta Blockade on In-Hospital or 30-Day Nonfatal Stroke in RCTs, With Members of the DECREASE Family of Trials Excluded



Effect of perioperative beta blockade on in-hospital or 30-day nonfatal stroke, within subgroups defined by the POISE-1 trial versus other trials. The pooled effect is expressed as a pooled RR with associated 95% CI. The solid black diamonds represent point estimates in individual RCTs. The area of each gray square correlates with its contribution toward the pooled summary estimates. Horizontal lines denote 95% CIs. Estimates to the left of the line of unity (i.e., RR: 1) indicate superior clinical outcomes (i.e., fewer nonfatal strokes) with beta blockade ("*Favors Beta-Blockers*"), whereas estimates to the right of the line of unity indicate superior clinical outcomes with control ("*Favors Control*"). The blue diamonds represent the pooled estimates for all studies (RR: 1.86; 95% CI: 1.09–3.16), as well as the POISE-1 trial (RR: 1.93; 95% CI: 1.01–3.68) and the subgroup of other trials (RR: 1.72; 95% CI: 0.67–4.40). Statistical heterogeneity, as measured by the I^2 statistic, was 0% for the overall analysis.

BBSA indicates Beta Blocker in Spinal Anesthesia; CI, confidence interval; DECREASE, Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography; DIPOM, Diabetic Postoperative Mortality and Morbidity; MaVS, Metoprolol After Vascular Surgery; POBBLE, Perioperative Beta Blockade; POISE, Perioperative Ischemic Evaluation Study; RCT, randomized controlled trial; and RR, relative risk.

Figure 3. Effect of Perioperative Beta Blockade on In-Hospital or 30-Day Mortality in RCTs, With Members of the DECREASE Family of Trials Excluded



Effect of perioperative beta blockade on in-hospital or 30-day mortality rate, within subgroups defined by POISE-1 trial versus other trials. The pooled effect is expressed as a pooled RR with associated 95% CI. The solid black diamonds represent point estimates in individual RCTs. The area of each gray square correlates with its contribution toward the pooled summary estimates. Horizontal lines denote 95% CIs. Estimates to the left of the line of unity (i.e., RR: 1) indicate superior clinical outcomes (i.e., fewer deaths) with beta blockade ("*Favors Beta-Blockers*"), whereas estimates to the right of the line of unity indicate superior clinical outcomes with control ("*Favors Control*"). The blue diamonds represent the pooled estimates for all studies (RR: 1.30; 95% CI: 1.03–1.63), as well as the POISE-1 trial (RR: 1.33; 95% CI: 1.03–1.73) and the subgroup of other trials (RR: 1.17; 95% CI: 0.70–1.94). Statistical heterogeneity, as measured by the I^2 statistic, was 0% for the overall analysis.

BBSA indicates Beta Blocker in Spinal Anesthesia; CI, confidence interval; DECREASE, Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography; DIPOM, Diabetic Postoperative Mortality and Morbidity; MaVS, Metoprolol After Vascular Surgery; POBBLE, Perioperative Beta Blockade; POISE, Perioperative Ischemic Evaluation Study; RCT, randomized controlled trial; and RR, relative risk.

Data Supplement 20. Perioperative Statin Therapy (Section 6.2.2)

Study Name, Author, Year	Aim of Study	Study Type	Study Intervention (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*		
Sanders RD, et al., 2013 (146) 23824754	Meta-analysis	Meta-analysis	Meta-analysis	Meta-analysis	Meta-analysis	Meta-analysis	Meta-analysis	Meta-analysis	Meta-analysis	Meta-analysis	Meta-analysis
Raju MG, et al., 2013 (147) 23670940	Impact of statin therapy on 0-d all-cause mortality, AF, and nonfatal MI	Retrospective cohort of pts undergoing intermediate-risk noncardiac, nonvascular surgery	Statin use	No statin use	All pts undergoing ACC/AHA intermediate-risk noncardiovascular surgeries during the study period	N/A	Decreased composite endpoint of 30-d all-cause mortality, AF, and nonfatal MI after adjusting for baseline characteristics	N/A	All-cause mortality reduced	OR: 0.54; 95% CI: 0.30–0.97; p=0.039. All-cause mortality p=0.0002.	Retrospective cohort
Lau WC, et al., 2013 (148) 23535525	Evaluated the benefits of adding ASA to beta blocker and statin (ABBS), with/without ACEI on postop outcome in high-risk pts undergoing major vascular surgery	Retrospective review	Statin, beta blocker and ASA use	No recorded use of combination therapy	Consecutive pts undergoing elective vascular surgery	Pts with emergent and traumatic vascular procedures, peripheral digit or distal limb amputation, or venous procedures	30-d and 12-mo mortality and survival status, MI was 3-fold lower in ABBS±ACEI (n=513) as compared with non–ABBS±ACEI (n=306). The 12-mo mortality was 8-fold lower in ABBS±ACEI as compared non–ABBS±ACEI (5.9% vs. 37.5%)	N/A	N/A	MI OR 0.31(95% CI: 0.15–0.61; p=0.001) in ABBS±ACEI (n=513) vs. non-ABBS±ACEI (n=306). 12-mo mortality HR: 0.13 (95% CI: 0.08–0.20; p<0.0001) in ABBS±ACEI vs. non-ABBS±ACEI	Retrospective , but reviews a real world pattern
Durazzo AE, et al., 2004 (149) 15111846	To analyze the effect of atorvastatin compared with placebo on the occurrence of a 6-mo composite of cardiovascular events after vascular surgery	RCT	20 mg by mouth atorvastatin for 45 d (55 pts)	Placebo (50 pts)	Pts scheduled to undergo elective noncardiac arterial vascular surgery, defined as aortic, femoropopliteal and carotid procedures	Severe hepatic or renal disease, pregnancy or breast-feeding; current or previous use of drugs to treat dyslipidemia; recent cardiovascular event, such as stroke, MI, or UA; serious infectious disease, malignancy	Less death from cardiac cause, nonfatal MI, UA, and stroke with active treatment	None	None	0.03	Small size

ACC indicates American College of Cardiology; ACEI, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; AHA, American Heart Association; ASA, aspirin; BB, beta-blocker; and MI, myocardial infarction; N/A, not available; postop, postoperative; pt, patient; RCT, randomized controlled trial; and UA, unstable angina.

Data Supplement 21. Alpha-2 Agonists (Section 6.2.3)

Study Name, Author, Year	Aim of Study	Study Type	Study Intervention (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*		
Oliver MF, et al., 1999 (150) 10519497	To evaluate the impact of the alpha-2 adrenergic agonist, mivazerol, on rates of MI or cardiac death in pts with known CHD undergoing noncardiac surgery	A double-blind randomized placebo-controlled trial was conducted in 61 European centers	Mivazerol, 4.0 mcg/kg, was given during the first 10 min followed by a constant rate infusion. Infusion was started 20 min before the induction of anesthesia and continued for 72 h postoperatively	0.9% saline solution started 20 min before the induction of anesthesia	Pts with known CHD and those at high risk for CHD were eligible for the trial. All were scheduled to have noncardiac surgery estimated to last for at least 1 h and to have postsurgical hospitalization of at least 4 d.	UA, MI in the past 14 d, uninterpretable ECG Q-waves, cardiogenic shock, prescribed alpha agonist, severe hepatic disorders, emergency surgery, pregnant or nursing women or women aged <45 y without adequate contraception	N/A	N/A	Results presented relate to the 1,897 pts with known previous CHD. Preplanned subgroup analysis based on tests of heterogeneity. Primary endpoint was the incidence of acute MI or death during the intra- and postop hospitalization period (up to 30 d after surgery). 10.4% decrease in the primary endpoint (MI or death) and a 37% reduction in all-cause death. Secondary endpoints relate to the period of 30 d (follow-up visit) included HF, life-threatening arrhythmias, and UA	Hypotension was defined as a decrease in systolic BP of ≥20% below the baseline figure. In 10.5% (150) of mivazerol group pts and 9.4% (134) of placebo group pts, the infusion had to be stopped prematurely: of these, 62% were because of adverse events, such as hypotension, brady- or tachycardia, cardiac arrest, or organ failure; 19% (of the 62%) had to be withdrawn from the trial	NS	Cardiac deaths: MI endpoint 95% CI: 0.25–0.96 (p=0.037); for all surgeries 95% CI: 0.67–1.18 (p=NS); for vascular surgery 95% CI: 0.45–0.98 (p=0.03)	Overall study negative, positive results presented from CHD pts (not those pts with only risk factors)
Stuhmeier KD, et al., 1996 (151) 8873539	To evaluate the effects clonidine (n=145) or placebo (n=152) on the incidence of periop myocardial ischemic episodes, MI,	Randomized double-blind study design	2 mcg/kg-1 oral clonidine (145 pts)	Oral placebo (15 pts)	Pts undergoing nonemergent vascular surgery who were not taking clonidine	Chronic myocardial ischemia, preop digitalis or chronic clonidine medication, AF, left or right BBB, and second-degree or greater atrioventricular-nodal block in the preop ECG	N/A	N/A	Myocardial IEs reduced, no change in MI and cardiac death	More fluid given to clonidine group to treat hypotension	N/A	Reduced the incidence of periop myocardial IEs from 39% (59 of 152) to 24% (35 of 145) (p<0.01)	Size

	and cardiac death												
Wallace AW, et al., 2004 (152) 15277909	To test the hypothesis that prophylactic clonidine reduces the incidence of periop myocardial ischemia and postop death in pts undergoing noncardiac surgery	Prospective, double-blinded, clinical trial	125 pts with CAD or risk factors	65 pts with CAD or risk factors	Definite CAD, peripheral arterial disease, and previous vascular surgery or 2 cardiac risk factors	UA, uninterpretable ECG, preop alpha blocker use, symptomatic AS; systolic BP <100 mmHg; and refusal or inability to give informed consent	0.2 mg oral tablet of clonidine 1 h before surgery and a 7.0 cm^2 transdermal patch of clonidine	Placebo pill and patch	30-d mortality reduced, 2-y mortality reduced, decreased IEs	N/A	N/A	p=0.035 for 30-d mortality, p=0.048 for 2-y mortality, p=0.01 for IEs	Size

AF indicates atrial fibrillation; AS, aortic stenosis; BBB, bundle branch block; BP, blood pressure; CAD, coronary artery disease; CHD indicates coronary heart disease; ECG, electrocardiogram; IE, ischemic episode; MI, myocardial infarction; N/A, not available; NS, nonsignificant; periop, perioperative; postop, postoperative; preop, preoperative; and UA, unstable angina.

Data Supplement 22. Perioperative Calcium Channel Blockers (Section 6.2.4)

Study Name, Author, Year	Aim of Study	Study Type	Study Intervention	Study Comparator Group	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*		
Wijeysundera DN, et al., 2003 (153) 12933374	To evaluate the impact of CCBs on death, MI, supraventricular tachycardia, and major morbid events	Meta-analysis RCT evaluating CCBs during noncardiac surgery	CCB, 11 studies with 1,107 pts	Placebo	Published RCTs that evaluated CCBs (administered immediately preoperatively, intraoperatively, or postoperatively within 48 h) during noncardiac surgery, and reported any of the following outcomes: death, MI, ischemia, or supraventricular tachycardia	Studies exclusively recruited prior organ transplant recipients, individuals younger than 18 y of age, pts who had already developed supraventricular tachycardia, or pts undergoing surgery for subarachnoid hemorrhage	Mortality not decreased, ischemia and supraventricular tachycardia reduced	Trend toward hypotension	Combined endpoint of MI and death	RR: 0.49 (95% CI: 0.3–0.8) for ischemia; RR: 0.52 (95% CI: 0.37–0.72) for supraventricular tachycardia; RR: 0.35 (95% CI 0.15–0.86)	Meta-analysis, different types of CCBs
Kashimoto S, et al., 2007 (154) 17321926	To assess whether nicorandil reduces the likelihood of cardiac events during and after intermediate risk surgery	Multicenter randomized trial	Nicoradil intraoperatively during surgery	Standard therapy, 237 pts	Intermediate cardiac risk pts having intermediate cardiac risk surgery	N/A	N/A	p=0.02; 95% CI: 0.03–0.76	N/A	95% CI: 0.03–0.76	Size, limited report

CCB indicates calcium channel blocker; MI, myocardial infarction; N/A, not available; pts, patients; RCT, randomized controlled trial; and RR, relative risk.

Data Supplement 23. Angiotensin-Converting Enzyme Inhibitors (Section 6.2.5)

Study Name, Author, Year	Aim of Study	Study Type	Study Intervention	Study Comparator Group	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*		
Turan A, et al., 2012 (155) 22253266	To evaluate the association of ACEI therapy with periop respiratory morbidity in adult noncardiac surgical pts, 30-d mortality secondary endpoint	Retrospective, controlled	ACEI	No ACEI	79,228 adult general surgical pts treated at the Cleveland Clinic main campus hospital between 2005 and 2009. Pts who received only general anesthesia were included.	30-d follow up data unavailable	The observed incidence of experiencing ≥1 intraoperative respiratory morbidity was 3.6% (n=360) for pts who took ACEI and 2.7% (n=1814) for pts who did not. The observed incidence of the collapsed postop respiratory morbidity was 4.2% (n=412) and 3.1% (n=2053) in pts who did and did not take ACEIs.	N/A	No significant association was found between ACEI use and any of the secondary outcomes, including 30-d mortality and the composite of in-hospital morbidity and mortality	Secondary endpoint: 30-d mortality (OR: 0.93; 95% CI: 0.73–1.19), ACEI vs. non–ACEI p=0.56; composite of in-hospital morbidity and mortality (OR: 1.06; 95% CI: 0.97–1.15)	Retrospective chart review to obtain data

ACEI indicates angiotensin-converting enzyme inhibitors; N/A, not available; periop, perioperative; and pt, patient.

Data Supplement 24. Antiplatelet Agents (Section 6.2.6)

Table 1. Risk of Bleeding on Single or Dual Antiplatelet Therapy With Noncardiac Surgery

Study Name, Author, Year	Patients on DAPT at Time of NCS	DAPT Patients With Bleeding	DAPT Patients With Bleeding (%)	Patients on Single APT at Time of NCS	Single APT Patients With Bleeding	Single APT Patients With Bleeding (%)	Study Limitations
Kaluza GL, et al., 2000 (103) 10758971	1	1	100	N/A	N/A	N/A	Small*, retrospective, SC, APT status not described
Wilson SH, et al., 2003 (104) 12875757	54	1	1.85	134	1	0.7	Retrospective, SC

Brotman DJ, et al., 2007 (110) 18081175	24	1	4	2	0	0	Retrospective, SC
Assali A, et al., 2009 (117) 19626693	17	3	17.6	47	7	15	Small, retrospective, SC
Van Kuijk JP, et al., 2009 (123) 19840567	128	27	21	421	17	4	Retrospective, APT status not described
Total	224	33	14.7	604	25	4.1	N/A

*Small= <100 patients

APT indicates antiplatelet therapy; DAPT, dual antiplatelet therapy; N/A, not applicable; NCS, noncardiac surgery; pt, patient; and SC, single center.

Table 2. Value of APT during NCS with BMS*

Author, Year	Study Size	Type of Surgery (%)				PCI to NCS (d)	MACE		APT in Periop Period (%)			Major Bleeding		Study Limitations	Value/Risk of APT
		Low	*Intermediate*	*High*	*Unknown*		*Endpoint*	*(%)*	*ASA*	*$P2Y_{12}$ Inhibitor*	*DAPT*	*Endpoint*	*(%)*		
Wilson, 2003 (12) 12875757	207	0	36	58	6	1-60	Death, MI, ST, or revascularization	4	51	14	26	"Excessive" surgical site bleed Tx	2 33 No APT: 38.5% ASA: 31.7% DAPT: 42.6%	Retrospective, SC	IE: unclear Bleeding: no excessive bleeding with ASA or DAPT
Sharma, 2004 (13) 15390248	47	0	68	30	2	<21 (n=27) 21-90 (n=20)	Death or MI	25 (<21 d) Death: ASA 5%, DAPT 85.7% 15 (21-90 d)	N/A	74 70	N/A	Tx Reoperation <21 d after PCI: ASA 43.8%, DAPT 25.0%	29 0	Small, retrospective, SC	IE: Suggestive of need for DAPT <21 d after PCI Bleeding: No excess with DAPT vs. ASA alone
Reddy, 2005 (14) 15757604	56	10	60	20	10	<42	MI or CVD ST	14 8.9 (3/5 on DAPT)	79*	32*	N/A	Reoperation, Tx >2 PRBC, Hb drop >2 g/dL or IC, IO or RP bleed	3 (2 DAPT, 1 $P2Y_{12}$ inhibitor only)	Small, retrospective	IE: unclear Bleeding: unclear
Nuttal,	899	21	46	33	0	64	Death, MI, ST or	Overall 5.2; <30 d	64.5†			Need for	5	SC, retrospective, APT status	IE: APT may be better than no APT,

2008 (16) 18813036							TLR	10.5; 30–90 d 3.8; 90–365 d 2.8 MACE: no APT after PCI 20 (4/20); ASA 3.8 (3/79); $P2Y_{12}$ 2.9 (1/35); DAPT 3.7 (28/752)		nonPRBC tx		not well defined at NCS	but SAPT vs. DAPT no difference Bleeding: unclear

*All studies were retrospective analyses.
†Rates of individual or dual APT not provided.
APT indicates antiplatelet therapy; ASA, aspirin; BMS, bare-metal stent; CVD, cardiovascular disease; DAPT, dual antiplatelet therapy; Hb, hemoglobin; IC, intracranial; IE, ischemic event; IO, intraocular; MACE, major adverse cardiac event; MI, myocardial infarction; N/A, not available; NCS, noncardiac surgery; PCI, percutaneous coronary intervention; periop, perioperative; PRBC, packed red blood cells; RP, retroperitoneal; SAPT, single antiplatelet therapy; SC, single center; ST, stent thrombosis; TLR, target lesion revascularization; and Tx, transfusion.

Table 3. Value of APT during NCS With DES*

Study, Author	Study Size (n)	Type of Surgery (%)				PCI to NCS (d)	MACE		APT in Periop Period (%)			Major Bleeding		Study Limitations	Value/Risk of APT
		Low	*Intermediate*	*High*	*Cardiac*		*Endpoint*	*(%)*	*ASA*	*P2Y12 inhibitor*	*DAPT*	*Endpoint*	*(%)*		
Brotman, 2007 (18) 18081175	114	52	42	6		236	MI, ST, or death	1.8	1.8	0	21	Reoperation or IC or RP bleed	0.9	Retrospective, SC	IE: In low- and intermediate-risk NCS late after PCI, lack of APT does not adversely impact IE
Rhee, 2008 (20) 18475013	141	N/A	96	N/A	4	228	ST	5 for >7 d of $P2Y_{12}$ discontinuation (OR: 12.8; p=0.027)	5	0	0	N/A	N/A	Retrospective, SC, bleeding endpoint not well defined	IE: Suggests value of DAPT or SAPT to prevent IE
Godet, 2008 (21) 18310674	96	N/A	26	74	N/A	425	Troponin elevation ST	12 2	70	38	N/A	N/A 26% of pts received LMWH in periop period	N/A	Retrospective, APT not well described, SC, bleeding not well defined	IE: IE uncommon late after PCI
Rabbitts, 2008 (22) 18813037	520 <1 y=400 >1 y=120	18	56	25	N/A	204	Death, MI, ST, or revascularization	5.4 (<1 y =6, >1 y =3.3)	70	33	*	Surgical site ‘excessive bleed’	1	Retrospective, APT not well defined, SC	IE: Continued $P2Y_{12}$ associated with MACE in univariate but not multivariate analysis; time after PCI most important factor
Anwaruddin, 2009 (25) 19539259	481 (606)	5.6	55.6	20	22	390	Primary: ST (definite + moderate probability)	2	15	1	21	N/A	N/A	Retrospective, SC, bleeding endpoint not well defined	IE: At a mean of slightly >1 y use or nonuse of ASA or clopidogrel was not related to MACE

							Secondary: death, non-fatal MI, ST	9							
Assali, 2009 (26) 19626693	78	N/A	81	19	N/A	414	MI, ST, or cardiac death	7.7 MACE according to APT use: no APT 10 (2/20); ASA or clopidogrel 3.9 (2/51); DAPT 11.8 (2/17)	18	42	21	Hb drop > 2g/dL	16.7	Retrospective, small, SC	Suggestion that one APT is better than none, but DAPT not better than SAPT

*All studies were retrospective analyses.
APT, antiplatelet therapy; ASA, aspirin; DAPT, dual antiplatelet therapy; DES, drug-eluting stent; Hb, hemoglobin; IC, intracranial; IE, ischemic events; MI, myocardial infarction; LMWH, low-molecular-weight heparin; MACE, major adverse cardiac events; n, subgroup of N; N/A, not available; NCS, noncardiac surgery; OR, odds ratio; PCI, percutaneous coronary intervention; periop, perioperative; RP, retroperitoneal; SAPT, single antiplatelet therapy; SC, single center; and ST, stent thrombosis.

Table 4. Value of APT During NCS With BMS or DES*

Author	Study Size		Type of Surgery (%)				PCI to NCS (d)	MACE			APT in Periop Period (%)			Major Bleeding		Study Limitations	Value/Risk of APT
	BMS	*DES*	*Low*	*Intermediate*	*High*	*Cardiac*		*Endpoint*	*BMS (%)*	*DES (%)*	*ASA*	*P2Y12 inhibitor*	*DAPT*	*Endpoint*	*(%)*		
Van Kuijk, 2009 (31) 19840567	174	376	BMS 33; DES 31	BMS 51; DES 47	BMS 15; DES 22	N/A	BMS: 1,314; DES: 511	Death, MI, ST, or revascularization	6	13	BMS 91*; DES 70*		BMS 9†; DES 30†	Severe: death, IC, reoperation, or Tx of >4 units Moderate : Tx of 1–3 units	Severe 10; moderate 8	Retrospective, APT not well described	Bleeding complications significantly higher with DAPT in both groups
Cruden, 2010 (5) 20442357	1,383	570	19	71	10	N/A	BMS: 503; DES: 371	Primary: in-hospital death or IE; secondary: in-hospital death or MI	Primary: 13.3; Secondary: 1.3	Primary: 14.6; Secondary 1.9	N/A	N/A	N/A	N/A	N/A	Retrospective, APT not well described, bleeding endpoint not well defined	IE: No difference between SAPT and DAPT for pts with MACE; SAPT 45% and DAPT 55% Bleeding: significantly worse (p<0.001) with DAPT (21%) than

																	SAPT (4%)
Albaladejo, 2011 (32) 21791513	623	367	20	40	26	14	??	MI, ST, HF, CS, SA, or stroke	10.9†		N/A	N/A	N/A	Major	9.5‡	Retrospective, APT not well defined	IE: By multivariate analysis, discontinuation of all APT increased MACE risk (OR: 2.11; CI: 1.04–6.55; p=0.04). Bleeding: no difference between APT and no APT during NCS; SAPT vs. DAPT not described.
Tokushige, 2012 (127) 22396582	1,103	1,295	N/A	N/A	N/A	N/A1	N/A	Death, MI, or ST 30 d after NCS	3.5	2.9	N/A	N/A	N/A	N/A	BMS: 3.2%; DES: 2.1%	Retrospective, use of APT based on hospital charts	IE (p=0.0005): No APT 2.3% (26/1088); SAPT: 1.1% (5/416); DAPT: 4.9% (28/534) Bleeding (p=0.047): no APT 2.4% (27/104); SAPT: 1.6% (7/403); DAPT: 4.0% 22/490)
Hawn, 2013 (156) 24101118	21,986	20,003	37.5	29.5	33	N/A	730 (52.2% <1 y)	Death, MI, revascularization	5.1	4.3	N/A	N/A	N/A	N/A	N/A	Retrospective, use of administrative database, APT analysis very small (n=369); APT cessation analysis limited to NCS >6 wk after stenting	MACE w/ APT cessation OR: 0.86 (95%CI: 0.6–1.29)

*All studies were retrospective analyses. The Tokushige study used data from a prospective registry. In the Hawn study, surgical risk was classified as “low” for operations of the eye, ear, skin, and other, “intermediate” for genitourinary and musculoskeletal, and “high” for digestive, respiratory, vascular, and nervous system.

†Rates of individual or dual APT not provided.

APT indicates antiplatelet therapy; ASA, aspirin; BMS, bare-metal stent; CABG, coronary artery bypass graft; CI, confidence interval; DES, drug-eluting stent; HF, heart failure; IC, intracranial; IE, ischemic event; MACE, major adverse cardiac event; MI, myocardial infarction; N/A, not available; NCS, noncardiac surgery; OR, odds ratio; PCI, percutaneous coronary intervention; periop, perioperative; pt, patient; SAPT, single antiplatelet therapy; ST, stent thrombosis; and Tx, transfusion.

Data Supplement 25. Management of Postoperative Arrhythmias and Conduction Disorders (Section 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*	*Secondary Endpoint and Results*		
Polanczyk CA, et al., 1998 (157) 9729180	To determine the incidence, clinical correlates, and effect on LOS of periop SVA in pts having major noncardiac surgery	Prospective SC cohort	4,181	4,181	N/A	Pts ≥50 y of age who had major, nonemergency, noncardiac procedures and were in sinus rhythm at the preop evaluation	N/A	N/A	N/A	Periop SVA occurred in 7.6% of pts (2.0% during surgery)	Male sex (OR: 1.3; 95% CI: 1.0–1.7); age >70 (OR: 1.3; CI: 1.0–1.7), valve disease (OR: 2.1; CI: 1.2–3.6), hx of SVA (OR: 3.4; CI: 2.4–4.8), asthma (OR: 2.0; CI: 1.3–3.1), CHF (OR: 1.7; CI: 1.1–2.7), PACs (OR: 2.1; CI: 1.3–3.4), intrathoracic procedure (OR: 9.2; CI: 6.7–13) were independent predictors of risk of SVA	N/A	Did not separate AF from other SVA, nor break out intrathoracic procedures
Amar D, et al., 2002 (158) 12198031	To determine incidence and outcomes of ventricular arrhythmia after lung resection	Prospective SC cohort	412	412	N/A	Pts undergoing lung resection at a single center 1994-1999	Rhythm other than sinus, receiving AADs, high grade AV block, hemodynamically unstable after	N/A	N/A	NSVT occurred in 15% of pts, no sustained VT or cancer. Postop AF predictive of NSVT (OR: 2.6; CI: 1.4–4.8; p=0.002)	Periop NSVT had no impact on outcome	N/A	Only included lung resection pts

							surgery						
Bayliff CD, et al., 1999 (131) 10086546	To determine whether propranolol decreases risk of postop arrhythmia in noncardiac thoracic surgery pts	Prospective randomized double blind placebo controlled trial	99	49	50	Pts undergoing major noncardiac thoracic surgery	Hx of CHF or asthma	Propranolol 10 mg every 6 h for 5 d	Placebo	Treated arrhythmia occurred in 6% of propranolol treated pts and 20% of placebo pts	N/A	p=0.07	Small size, mixed arrhythmias and included sinus tachycardia in outcome
Roselli EE, et al., 2005 (159) 16077410	To determine incidence and predictors of AF after lung cancer resection	Retrospective observational cohort	604	604	N/A	Consecutive pts undergoing lung cancer resection at CCF 1998–2002	Persistent AF, lung transplant, prior lung resection	N/A	N/A	Postop AF in 19% peaking d 2	Male sex (p=0.009), older age (p<0.0001), Hx PAF (p=0.0004), CHF (p=0.006), and right pneumonectomy predicted postop AF	N/A	Retrospective, outcomes not assessed
Amar D, et al., 2002 (2) (160) 11818768	To determine incidence and predictors of AF after major noncardiac thoracic surgery	Prospective observational SC cohort	527	527	N/A	All pts undergoing major thoracic surgery 1990–1999 in sinus rhythm	AF or on AADs	N/A	N/A	Postop AF occurred in 15%; age, preop heart rate, and postop pneumonia or respiratory failure predicted AF	N/A	Age OR: 2.5 (CI: 1.7–3.4; p<0.0001); heart rate >74, OR: 2.3 (95% CI: 1.4–3.8; p<0.0007); pneumonia OR: 3.2 (95% CI: 1.5–6.7; p<0.0021)	Limited to noncardiac thoracic surgery
Amar D, et al., 2005 (161) 16304294	To determine whether statin use is associated with lower risk of postop AF after noncardiac thoracic surgery	Prospective observational SC cohort	131	131	N/A	Pts undergoing major lung or esophageal surgery age ≥60	AF or taking AADs or steroids	N/A	N/A	Postop AF in 29%, peak at 70 h; statin use associated with lower risk of AF, but unrelated to CRP or IL-6	N/A	Statin use OR: 0.38 (p=0.025)	Small size, limited to noncardiac thoracic surgery
Amar D, et al., 2012 (162) 22841166	To determine whether BNP levels are associated with POAF after noncardiac thoracic surgery	Prospective observational SC cohort	415	415	N/A	Pts undergoing major lung or esophageal surgery age ≥60	AF or taking AADs or steroids	N/A	N/A	POAF in 16%; age, male sex, BNP>30 predicted POAF	N/A	Age OR: 1.28 per 5 y (95% CI: 1.01–1.61; p=0.04); male OR: 2.16 (95% CI: 1.12–4.17; p=0.02); BNP>30	Small size, limited to noncardiac thoracic surgery

												pg/mL OR: 4.52 (95% CI: 2.19–9.32; p<0.0001)	
Balser JR, et al., 1998 (163) 9821992	To compare outcome of post –SVA pts treated with beta blocker vs. CCB	Prospective RCT	63	Esmolol -28	Diltiazem -27	Pts in ICU with postop SVA	Shock, preop permanent SVA	Esmolol IV	Diltiazem IV	Conversion to sinus: Esmolol 59% vs. Diltiazem 33%	N/A	p<0.05	Small sample size, limited to surgical pts in the ICU
Bhave PD, et al., 2012 (1) (164) 23194493	To define the incidence of POAF and its impact on outcomes after major noncardiac surgery	Retrospective review of administrative data from 375 hospitals over 1 y period	370,447	370,447	N/A	Pts >18 y of age undergoing noncardiac surgery in 1 of 375 hospitals in database in 2008	N/A	N/A	N/A	POAF in 3%. Older age and CHF predictive. Black race, statin. ACE-I/ARB use protective. Mortality, LOS, and cost higher for POAF group	N/A	Mortality adjusted OR: 1.68 (95% CI: 1.52–1.86; p<0.001); LOS +37% (95% CI: 34%–41%; p<0.001); cost +5,900 (95% CI: 5,400–6,400; p<0.001)	Administrative data
Bhave PD, et al., 2012 (165) 21907173	To examine association of statin use with POAF after noncardiac surgery	Retrospective cohort	370,447	79,871 (statin)	290,576 (no statin)	Pts >18 y of age undergoing noncardiac surgery in 1 of 375 hospitals in database in 2008	N/A	Periop statin used	No periop statin	POAF 2.6% in statin users vs. 3.0% in nonstatin users	N/A	Adjusted OR: 0.74 (CI: 0.57–0.95; p=0.021)	Administrative data, retrospective nonrandomized design
Borgeat A, et al., 1991 (166) 1903918	To compare use of IV flecainide vs. IV digoxin to prevent POAF	RCT	30	15	15	Pts undergoing noncardiac thoracic surgery	N/A	IV flecainide periop	IV digoxin periop	POAF 7% (flecainide) vs. 47% (digoxin)	N/A	p<0.05	Very small study, IV use only, digoxin is poor comparator, not blinded
Brathwaite D, et al., 1998 (167) 9726731	To evaluate incidence and outcomes of POAF after noncardiac nonthoracic surgery	Prospective observational SC cohort	462	462	N/A	Consecutive pts admitted to surgical ICU after noncardiac-nonthoracic surgery	Thoracic surgery or chest tube insertion	N/A	N/A	POAF in 10.2%. Mortality with POAF 23% vs. 4% without POAF; LOS 8 d vs. 2 d	N/A	p<0.05 for both	Limited to surgical ICU pts, clustered analysis of atrial arrhythmias
Cardinale D, et al., 1999 (168) 10585066	To evaluate incidence and outcomes of POAF after lung cancer surgery	Prospective observational SC cohort	233	233	N/A	Consecutive pts undergoing surgery for lung cancer	Preop AF or AAD use	N/A	N/A	POAF in 12%. No difference in mortality or LOS	N/A	p=NS	SC, single type of thoracic surgery
Christians KK,	To estimate	Retrospective	13,696	13,696	N/A	All pts	Preop AF,	N/A	N/A	POAF in 0.37%. 30-	N/A	N/A	Retrospective

et al., 2001 (169) 11839344	incidence of POAF in large cohort of pts undergoing noncardiac nonthoracic surgery	SC cohort				undergoing any noncardiac nonthoracic surgery over 2 y period in SC	thoracic surgery, PE			d mortality 12% in POAF Group.			design, use of ICD-9 code for diagnosis of POAF, limited statistical analysis
Ojima T, et al., 2013 (170) 23674202	To evaluate incidence and outcomes of POAF after esophageal surgery	N/A	207	207	N/A	Consecutive pts undergoing transthoracic esophagectomy over 6 y by single surgeon	Preop AF, concomitant lung/laryngeal surgery, palliative surgery	N/A	N/A	POAF in 9.2% associated with use of ileocolon conduit and postop heart rate >100	N/A	Ileocolon use adjusted OR: 13.6 (p=0.0023); heart rate >100 beats/min adjusted OR: 18.4 (p=0.0004)	SC, single surgeon, single type of surgery
Oniatis M, et al., 2010 (171) 20667313	To determine risk factors for POAF in pts undergoing lung cancer surgery	Interrogation of STS database	13,906	13,906	N/A	Consecutive pts entered into STS database 2002–2008 for lung cancer surgery	N/A	N/A	N/A	POAF in 12.6%; predictors include pneumonectomy, older age, bilobectomy, male sex, higher cancer stage; black race protective	30-d mortality higher in POAF (5.6% vs. 1.6%, p<0.0001); LOS longer in POAF (8 d vs. 5 d; p<0.0001)	Pneumonectomy OR: 2.04 (CI: 1.58–2.64; p<0.0001); age OR: 1.81 per 10 y (CI: 1.69–1.93; p<0.0001); bilobectomy OR: 1.67 (CI: 1.30–2.14; p<0.0001); male sex OR: 1.60 (CI: 1.40–1.83; p<0.0001), clinical stage II+ OR: 1.28 (CI: 1.07–1.52; p=0.006), black race OR: 0.62 (CI: 0.45–0.85; p=0.003)	N/A
Polanczyk CA, et al., 1998 (157) 9729180	To determine incidence and predictors of SVA after noncardiac surgery	Prospective SC cohort	4,181	4,181	N/A	Pts ≥50 undergoing nonemergent noncardiac surgery	Rhythm other than sinus	N/A	N/A	SVA in 7.6%	Older age, male sex, valvular disease, CHF, type of surgery were predictors	N/A	N/A
Riber LP, et al., 2012 (172) 22516832	To determine whether periop amiodarone reduces POAF	RCT	254	122	120	Pts >18 y of age undergoing lobectomy for lung cancer	Preop AF, heart rate <40 beats/min, LQT, hypotension	Amio 300 mg IV then 600 mg by mouth twice	Placebo	Time to AF (9% vs. 32)	Time to symptomatic AF (3% vs. 10%)	p=0.001 × 2	N/A

	after lung cancer surgery							daily for 5 d					
Tisdale JE, et al., 2009 (173) 19699916	To determine whether periop amiodarone reduces POAF after pulmonary resection	RCT	130	65	65	Adult pts undergoing lung resection	Preop AF, heart rate <50 beats/min, on AAD, LQT, hypotension	Amio IV load 24 h then 400 mg twice daily for 6 d	Usual care	POAF requiring treatment (13.8% vs. 32.3%)	LOS	p=0.02	No placebo control, not blinded
Tisdale JE, et al., 2010 (174) 20381077	To determine whether periop amiodarone reduces risk of POAF after esophagectomy	RCT	80	40	40	Adult pts undergoing esophagectomy	Preop AF, heart rate <50 beats/min, on AAD, LQT, hypotension	Amio IV for 96 h	Usual care	POAF requiring treatment (15% vs. 40%)	LOS	p=0.02	No placebo control, not blinded
Vaporciyan AA, et al., 2004 (173, 175) 15001907	To determine risk factors for POAF in pts undergoing thoracic surgery	Prospective SC observational cohort	2,588	2,588	N/A	Adult pts undergoing resection of lung, esophagus, chest wall, or mediastinal mass >5-y period at MD Anderson	N/A	N/A	N/A	POAF in 12.3%	Male sex, older age, more extensive resection were significant predictors	N/A	N/A

AAD indicates antiarrhythmic drug; ACE-I/ARB, Angiotensin-converting enzyme/ angiotensin receptor blockers; AF, atrial fibrillation; AV, atrioventricular; BNP, B-type natriuretic peptide; CCB, calcium channel blocker; CCF, congestive cardiac failure; CHF, congestive heart failure; CI, confidence interval; CRP, c-reactive protein; HR, hazard ratio; Hx, history; ICD-9, international classification of diseases ninth revision; ICU, intensive care unit; IL, interleukin; IV, intravenous; LOS, length of stay; LQT, Long QT Syndrome; n, subgroup of N; N/A, not applicable; NS, not significant; NSVT, nonsustained ventricular tachycardia; OR, odds raio; PAC, premature atrial contraction; PAF, paroxysmal atrial fibrillation; PE, pulmonary embolism; STS, Society of Thoracic Surgeons; SVA, supraventricular arrhythmia; SVT, supraventricular tachycardia; periop, perioperative; POAF, post-operative atrial fibrillation; postop, postoperative; preop, preoperative; pts, patients; and PE, pulmonary embolism; RCT, randomized controlled trial; SC, single center; and VT, ventricular tachycardia.

Data Supplement 26. Perioperative Management of Patients With CIEDs (Section 6.4)

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*		
Cheng A, et al., 2008 (176) 18307631	To determine the frequency of PPM or ICD malfunction	Prospective observational single-center cohort	92	92	N/A	Adult pts with PPM or ICD >1 mo undergoing	Unwilling to give informed consent	All pts' CIEDs programmed to detect tachyarrhythmia	None	EMI seen in 5 PPMs and no ICDs; no permanent	No major device malfunctions; 1 pacemaker near ERI reset; no	N/A	N/A	Small sample size, observational only

	from periprocedural electrocautery					noncardiac surgery or endoscopy with electrocautery or ultrasound		and interrogated before and after surgery		damage to any device	complications related to CIED			
Fiek M, et al., 2004 (177) 15009852	Evaluate prevalence of EMI in pts with ICD undergoing noncardiac surgery	Prospective observational single-center cohort	33	N/A	N/A	Pts undergoing surgery with ICD	None	None	None	No EMI detected	No adverse effects on ICD	N/A	N/A	Retrospective observational design
Hauser RG, et al., 2004 (178) 15851191	To review reports of deaths to FDA associated with ICD failure to determine cause	Retrospective observational	212	N/A	N/A	Deaths associated with ICD failure reported to FDA database 1996–2003	N/A	N/A	N/A	11 deaths occurred in pts with tachytherapies turned off —3 documented to have been inactivated prior to elective surgery	N/A	N/A	N/A	Study relies upon voluntary reporting of events to FDA, so likely underestimates incidence
Mahlow WJ, et al., 2013 (179) 23252749	To determine whether an institutional protocol for periop CIED management would be associated with a reduction in the amount of device reprogramming without increase in complications	Retrospective single-center cohort	379	197	179	Consecutive pts undergoing surgery requiring anesthesia before and after new PACED-OP protocol	None stated	PACED-OP institutional protocol, which standardized recommendations for periop CIED management	CIED pts undergoing surgery before protocol started	Percent of pts needing preop reprograming—decreased from 42%–16%	No major adverse events in either group. 3% preintervention vs. 2.2% postinterventions required adjusting sensing or output	N/A	OR 0.26 [0.15–0.44]; p<0.001 (efficacy) HR/OR 0.55–1.1; p>0.1 (safety)	No randomization, not performed prospectively
Matzke TJ, et al., 2006 (180) 16970697	Evaluate effect of electrocautery during dermatological surgery on	Retrospective single-center cohort	186	N/A	N/A	Consecutive pts with CIEDs undergoing dermatologic surgery with	None	None	None	No CIED malfunction	No adverse effects related to CIED	N/A	N/A	Retrospective observtional design

	CIEDs					electrocautery 2001–2004								
Pili-Fluory, et al., 2008 (181) 18272014	To evaluate the periop outcome of pacemaker pts undergoing noncardiac surgery	Prospective observational single-center cohort	65	N/A	N/A	All adult pacemaker pts undergoing noncardiac surgery or procedures under general or regional anesthesia	Age <18 y, unwilling to consent	None	None	No EMI described, no adverse events related to PPM	No pacemaker malfunction	11% of pts had some pre-op problem with pacemaker requiring reprogramming	N/A	Small sample size, observational only, not all devices interrogated, not programmed to detect EMI

CIED indicates cardiac implantable electronic device; EMI, Electromagnetic interference; ERI, elective replacement interval; FDA, Food and Drug Administration; ICD, implantable cardioverter-defibrillator; N/A, not available; OR, odds ratio; PACED-OP, Program for All-Inclusive Care of the Elderly-Outpatient; periop, perioperative; PPM, permanent pacemaker; and pts, patients.

Data Supplement 27. Choice of Anesthetic Technique and Agent (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*		
Barbosa FT, et al., 2013 (182) 23897485	Effect of epidural /spinal anesthesia for lower limb revascularization compared with other types of anesthesia (general anesthesia)	Meta-analysis of RCTs (Cochrane review)	696	417	279	Adults (≥18 y) undergoing lower limb revascularization with neuraxial anesthesia (spinal or epidural)	N/A	Neuraxial anesthesia	General anesthesia	No definitive difference mortality, stroke, MI, nerve dysfunction, lower limb amputation	N/A	Reduction in pneumonia. Otherwise no difference in-hospital stay, postop cognitive dysfunction, postop wound infection, postop anesthesia recovery room issues (nausea/vomiting/ tremor/supplemental oxygen dependence/ hypotension/HTN/ dysrhythmia), pt satisfaction, pain	OR: 0.37 favoring decrease in pneumonia in pts receiving neuraxial anesthesia (95% CI: 0.15–0.89)	Risk of pneumonia was only analyzed in 2 studies

												score, transfusions, urinary retention, claudication distance, postop rest pain in limb.		
Park WY, et al., 2001 (183) 11573049	Test whether epidural anesthesia and postop epidural analgesia decrease morbidity and mortality after intra-abdominal surgical procedures	Randomized, controlled	984	489	495	≥21 y old and undergoing abdominal aortic surgery, gastric surgery, biliary surgery, or colon surgery	<21 y old, female, ASA Class I/II/V, confused, emergency, MI within past 6 mo, abdominal procedure within past 3 mo, any prior abdominal aortic surgery, receiving chemotherapy or immunosuppressives other than steroids, tracheostomy, preop intubation, hypersensitivity to drugs, contraindication to epidural, surgeon/ anesthesiologist preference for one anesthetic	Epidural and general anesthesia plus postop epidural morphine	General anesthesia plus postop systemic opioids	Death, MI, CHF, persistent VT, complete AV block, severe hypotension, cardiac arrest, PE, respiratory failure, cerebral event, renal failure; Decrease incidence of MI, respiratory failure and stroke in subgroup of pts who underwent abdominal aortic procedures with epidural. Otherwise no difference in primary or secondary endpoints in combined group of abdominal surgery pts.	N/A	Pneumonia, sepsis, GI bleed, new angina, epidural hematoma, respiratory depression, respiratory arrest, reoperation for complications. For results see primary endpoint heading.	p 0.03 for MI favoring aortic surgery pts with epidural	Gender-specific study
Norris EJ, et al.,	Determine effect of epidural	Randomized, controlled	168	Neuraxial intraop +	GA+ PCA postop =37	Pts undergoing abdominal aortic	Procedure requiring aortic	See aforemention	GA + PCA	No difference in	N/A	No difference in medical costs,	N/A	Underpowered study; study

2001 (184) 11684971	anesthesia+ general anesthesia vs. general anesthesia + intravenous opioid			PCA postop =39; Neuraxial + GA+ epidural postop =46, GA + epidural postop =38		reconstructive surgery	cross clamp, contraindicatio n to epidural anesthesia, previous surgery or severe deformity of thoracolumbar spine, opioid dependence, major surgery within 14 d prior, pt refusal, neurologic disease affecting thorax or lower	ed groups		LOS		hospital mortality, major cardiac morbidity		halted due to ethical concerns; monitoring committee terminated pt recruitment
Guarracin o F, et al., 2006 (185) 16884976	Determine if volatile anesthetics were associated with a decrease in myocardial damage	Multicenter, randomized, controlled	112	57 who received desflurane (volatile anesthetic)	55 pts who received propofol (total IV anesthetic)	Off-pump coronary artery bypass pts	MI within 6 wk of surgery, valvular insufficiency, acute CHF, additional surgeries during hospitalization, illicit drug use within 1 mo of surgery, unusual response to an anesthetic	Volatile anesthetic administration	Propofol anesthetic administration	Myocardial damage as measured by postop cTnI. Volatile anesthetic was associated with a significant reduction in median peak cTnI ($p<0.001$)	N/A	Prolonged hospitalization increased in total intravenous anesthesia group ($p=0.005$)	$p<0.001$ favoring volatile anesthetics for lower postop cTnI as a surrogate for decreased myocardial damage; $p=0.005$ favoring volatile anesthetics for reduced hospitalizati on	Used biomarker release as an indicator for myocardial injury; other data such as incidence of postop AF not collected
Zangrillo A, et al., 2011 (186) 21872490	Compare the effects of total intravenous anesthesia to sevoflurane on postop cTnI after noncardiac	Single center, randomized, controlled. Blinded to all study personnel other than	88	44 pts receiving sevoflurane	44 pts received propofol (TIVA)	Pts undergoing elective lung surgery pts or peripheral revascularization	Unusual prior anesthetic response; current use of sulfonylurea theophylline, or allopurinol	Volatile anesthetic (sevoflurane) administration	TIVA (propofol)	Myocardial damage as measured postop cTnI; no statistical difference between	N/A	N/A	$p=0.6$	Pt hx was not extensively taken, so may not have looked at a highly "at risk" group for myocardial

	surgery	anesthesiologists who did not participate in the analysis								volatile anesthetic group and TIVA group				ischemia, thus diminishing the potential to detect a difference if it did exist. No pt in the study had a periop MI or ischemia. Small sample of pts. Underpowered.
Landoni G, et al., 2009 (187) 23439516	To evaluate the effects of volatile anesthetics in myocardial protection in noncardiac surgery	Meta-analysis of randomized trials	79 trials, 6,219 pts	3,451 pts receiving either desflurane or sevoflurane (volatile anesthetics)	2,768 pts receiving TIVA	Pts undergoing noncardiac surgery	N/A	Volatile anesthetic (sevoflurane or desflurane) administration	TIVA (propofol)	Periop MI and death; no primary endpoint was observed in any of the studies	N/A	N/A	No infarctions or deaths reported in any of the studies examined in either the volatile anesthetic pts or the TIVA pts	No author reported any postop MI or death in their study populations. No report of any significant cardiac event in any study. Authors of the meta-analysis reported difficulty conducting meta-analysis because no author reported pt outcome. Poor quality studies. All studies were single center design.
Conzen PF, et al., 2003 (188) 14508313	To evaluate the myocardial protective effects of sevoflurane in pts undergoing OFF PUMP CABG	Randomized, controlled	20	10 pts undergoing OPCAB ≤=2 vessel) receiving sevoflurane	10 pts undergoing OPCAB (≤2 vessel) receiving propofol	Pts with unusual anesthetic response, experimental drug use, severe comorbid disease, prior coronary surgery, EF<30%, sulfonylurea use	N/A	Volatile anesthetic (sevoflurane) administration	TIVA (propofol)	cTNI; significantly lower in pts receiving volatile anesthetics vs. TIVA	N/A	N/A	Significantly higher troponin I levels in TIVA pts (p=0.009)	No deaths, no transmural MI in either group; underpowered to detect clinical cardiac events

Landoni G, et al., 2007 (189) 17678775	To evaluate whether or not the cardioprotective effects of volatile anesthetics translate into decreased morbidity and mortality in cardiac surgery pts	Meta-analysis of RCTs	1,922 pts	979 pts with CAB receiving volatile anesthetic (desflurane or sevoflurane)	874 pts with CAB receiving TIVA	N/A	N/A	Volatile anesthetic (sevoflurane or desflurane) administration	TIVA (propofol)	In-hospital MI, in-hospital mortality. Volatile anesthetics were associated with significant reductions in MI (2.4% vs. 5.1%), all-cause mortality (0.4% vs. 1.6%)	N/A	Peak cardiac troponin release, inotrope use, time on mechanical ventilation, ICU LOS, hospital LOS. Volatile anesthetics associated with significant decreased peak troponin release (p=0.001), ICU stay (p=0.001), time to hospital discharge (p=0.005)	Volatile anesthetic reduction in MI p=0.008; volatile anesthetic reduction in mortality p=0.02	Definition of MI as per author; suboptimal RCTs included in the study
Bignami, et al., 2013 (190) 22819469	Investigate the cardioprotective properties of isoflurane vs. any comparator in terms of MI and all-cause mortality	Meta-analysis of 37 RCTs	3,539 pts (both cardiac and noncardiac surgery)	N/A	N/A	N/A	N/A	N/A	N/A	Isoflurane reduced mortality in high-quality studies and showed a trend toward reduction in mortality when compared with propofol. Rates of overall mortality and MI were the same when all studies (high quality and otherwise) were considered.	N/A	N/A	p=0.4 for a reduction in mortality p=0.05 for reduction in mortality for isoflurane when propofol was the control group	Important study to demonstrate isoflurane is comparable to other anesthetic drugs with better pharmacokinetic profiles but higher cost and lower potency in terms of incidence of periop MI and death. The studies included had small sample sizes, marked heterogeneity regarding surgery/MI/ length of follow-up. Only 10 of 37 studies had a low risk of bias.

ASA indicates American Society of Anesthesiologists; AV, atrioventricular; CAB, coronary artery bypass; CHF, congestive heart failure; CI, confidence interval; cTnI, cardiac troponin I; EF, ejection fraction; GA, general anesthesia; GI, gastrointestinal; HTN, hypertension; Hx, history; ICU, intensive care unit; LOS, length of stay; MI, myocardial infarction; OPCAB, off-pump coronary artery bypass; N/A, not applicable; OR, odds ratio; PCA, patient-controlled analgesia; PE, pulmonary embolism; postop, postoperative; preop, preoperative; pt, patient; pts, patients; RCT, randomized controlled trial; TIVA, total intravenous anesthesia; and VT, ventricular tachycardia.

Data Supplement 28. Perioperative Pain Management (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*		
Nishimori M, et al., 2012 (191) 22786494	Assess benefits and harms of epidural analgesia compared with opioid-based analgesia for adult pts undergoing elective abdominal aortic surgery	Meta-analysis of RCTs	15 eligible trials out of 53 trials; 1297 pts	633 pts with epidurals	664 pts receiving systemic opioids	RCTs comparing postop epidural analgesia and postop sysemic opioid based analgesia for electiveabdominal aortic surgery	N/A	N/A	N/A	All cause death, cardiac death, MI, angina, ischemia, arrhythmia, CHF, severe hypotension; respiratory, GI, cerebrovascular, renal, DVT/PE	N/A	Extubation time, pain scores, bowel motility, functionality, ICU stay length, hospital stay length	Event rate of MI was reduced by epidural analgesia (RR; 0.52, CI: 0.29–0.93); no difference in angina, ischemia, CHF, arrhythmia, heart block)	N/A
Wu CL, et al., 2003 (192) 12945019	Assess effects of postop epidural analgesia compared with no postop epidural	Retrospective review of random sample of Medicare beneficiaries who underwent total hip arthroplasty	23,136	2,591 with postop epidural	20,545 without epidural	Medicare pts undergoing total hip arthroplasty	N/A	Postop epidural	No postop epidural	No difference between groups regarding mortality and morbidity: Acute MI, angina, dysrhythmias, HF, pneumonia, PE, DVT, sepsis, acute renal failure, acute cerebrovascular events, paralytic ileus.	N/A	N/A	N/A	Database designed for billing and administration, not clinical outcomes research
Matot I, et al., 2003	Assess risk of preop cardiac	Randomized controlled,	68	34	34	≥60 y old with traumatic hip	Pts with contraindication to	Preop epidural	Standard pain relief	Increased preiop cardiac events:	N/A	Postop cardiac	Preop cardiac	Unblinded study; only 1

(193) 12502992	events in pts with hip fracture who receive preop epidural (local anesthetic + opioid) vs. conventional (opioid) treatment	unblinded				fracture, known or high risk CAD	epidural, allergy to study drugs, LBBB, ?10 h from time of injury to presentation to ED; acute coronary syndrome at presentation		with opioids	combined cardiac death, MI, UA, CHF, new onset AF (20 events vs. 0 events in epidural group)		events are higher in the standard care group. No difference in postop PE, pneumonia	events p=0.01	dose of meperidine; used IM opioid instead of PCA (IV administration)
Park WY, et al., 2001 (183) 11573049	Test whether epidural anesthesia and postop epidural analgesia decrease morbidity and mortality after intra-abdominal surgical procedures	Randomized, controlled	984	489	495	≥21 y old and undergoing abdominal aortic surgery, gastric surgery, biliary surgery, or colon surgery	<21 y old, female, ASA Class I/II/V, confused, emergency, MI within past 6 mo, abdominal procedure within past 3 mo, any prior abdominal aortic surgery, receiving chemotherapy or immunosuppresses other than steroids, tracheostomy, preop intubation, hypersensitivity to drugs, contraindication to epidural, surgeon/anesthesiologist preference for 1 anesthetic	Epidural and general anesthesia plus postop epidural morphine	General anesthesia plus postop systemic opioids	Death, MI, CHF, persistent Vtach, complete AV block, severe hypotension, cardiac arrest, PE, respiratory failure, cerebral event, renal failure; Decrease incidence of MI, respiratory failure and stroke in subgroup of pts who underwent abdominal aortic procedures with epidural. Otherwise no difference in primary or secondary endpoints in combined group of abdominal surgery pts.	N/A	Pneumonia, sepsis, GI bleed, new angina, epidural hematoma, respiratory depression, respiratory arrest, reoperation for complications. For results see primary endpoint heading.	p0.03 for MI favoring aortic surgery pts with epidural	Gender-specific study
Liu LL, et al., 2012 (50) 12133011	Determine if there is an association between NSAID use and postop MI	Retrospective EMR from large orthopedic hospital (Hospital for Special	10,873	9,831 (NSAIDs)	1,042 (no NSAIDs)	Pts undergoing total hip arthroplasty at a single center	N/A	NSAID administration	No NSAID administration	No increase in postop MI with NSAID use	N/A	N/A	RR: 0.95, 95% CI: 0.5–1.8	Single center, healthy population? (mortality 0%)

		Surgery, NY) Propensity-matched controls												

AF indicates atrial fibrillation; CAD, coronary artery disease; CHF, congestive heart failure; CI, confidence interval; DVT, deep vein thrombosis; ED, emergency department; EMR, electronic medical records; GI, gastrointestinal; HF, heart failure; ICU, intensive care unit; IV, intravenous; LBBB, left bundle-branch block; MI; myocardial infarction; N/A, not applicable; NSAID, nonsteroidal anti-inflammatory drugs; PCA, patient-controlled analgesia; PE, pulmonary embolism; postop, postoperative; pt, patient; pts, patients; preop, preoperative; RCT, randomized controlled trial; RR, relative risk; and UA, unstable angina.

Data Supplement 29. Prophylactic Intraoperative Nitroglycerin (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*		
Dodds TM, et al., 1993 (194) 8466005	To determine the effect of prophylactic NTG on the incidence of myocardial ischemia in pts with either documented CAD or a high likelihood of clinically silent CAD who undergo noncardiac surgery	Randomized, placebo-controlled; unnblinded to anesthesiologists, blinded to cardiologist reading the Holter monitor	45	23	22	Hx of MI, angina, >70% narrowing of an epicardial artery, those undergoing vascular surgery for atherosclerotic disease	LBBB, WPW, nonsinus rhythm, pre-existing ST depression ≥1mm	NTG 0.9 mcg/kg/min titrated to maintain heart rate and systolic BP within 20% baseline; continued until 30 min following surgery	Placebo infusion	Myocardial ischemia as detected by Holter monitor	N/A	N/A	No difference in ischemia between pts receiving IV NTG or placebo, p=0.93; 7/23 controls, 7/22 NTG pts	Only 1 dosage of NTG; anesthesiologists were unblinded
Fusciardi J, et al., 1986 (195) 3085552	To determine if NTG infusion during airway instrumentation decreased the incidence of myocardial ischemia in pts with chronic	Randomized	46	20	26	Angina	LBBB, MI within prior 6 mo	NTG 0.9 mcg/kg/min	Fentanyl infusion alone	Myocardial ischemia as detected by 1mm ST depression on ECG lead V;	N/A	N/A	Reduced ischemia in pts receiving NTG (p<0.05)	Unblinded, no placebo control; small study; rudimentary analysis

	stable angina									PCWP>18				
Thomson IR, et al., 1984 (196) 6435481	To determine the effect of prophylactic NTG on the incidence of intraoperative myocardial ischemia in pts with CAD undergoing CABG	Randomized, placebo controlled	20	9	11	Elective CABG	Abnormal leads II and V5 at baseline	NTG 0.5 mcg/kg/min	Placebo	Myocardial ischemia as detected by 1mm ST segment depression	N/A	N/A	No significant difference in incidence of ischemia between the two groups	Randomized study population was not balanced with regard to treatment arms: Nitroglycerin group received significantly more bypass grafts, suggesting a higher burden of CAD which may increase the incidence of ischemia; beta blocker withheld the night before surgery in both groups

BP indicates blood pressure; CABG, coronary artery bypass graft; CAD, coronary artery disease; ECG, electrocardiogram; HR, hazard ratio; hx, history; IV, intravenous; LBBB, left bundle-branch block; MI, myocardial infarction; N/A, not applicable; NTG, nitroglycerin; PCWP, pulmonary capillary wedge pressure; pts, patients; ST, stent thrombosis; and WPW, Wolff–Parkinson–White.

Data Supplement 30. Maintenance of Body Temperature (Section 7.5)

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				Study Limitations & Adverse Events
						Inclusion Criteria	*Exclusion Criteria*			*Primary Endpoint (efficacy) and Results*	*Safety Endpoint and Results*	*Secondary Endpoint and Results*	P Values, OR: HR: RR & 95% CI:	
Sumer BD, et al., 2009 (197) 19620590	To determine if intraoperative hypothermia correlates with periop complications	Retrospective medical record chart review	136	None	None	Any pt undergoing head and neck surgery for tumors that required a free flap	None	None	Pts with temp ≤35 degrees Celsius vs. pts with temp >35 Celsius as measured by urinary catheter	Correlation of intraoperative hypothermia with postop complications (within 3 wk of surgery): Pneumonia, wound infections, other infections; flap loss, hematoma, fistula, wound breakdown, CSF leak, cardiac	N/A	Correlation of other study variables with postop complications	OR: 5.12; 95% CI: 1.317–19.917; p=0.002. Examining only local wound complications and infectious complications yielded same results (OR: 5.075; CI: 1.363–18.896).	Retrospective review from single institution; no documentation of periop antibiotic administration, smoking Hx, vasopressor use or preop radiation to the head and neck

										complications, donor site breakdown, DVT, death; This study showed that hypothermia was independently associated with a significant increase in postop complications in pts undergoing head and neck cancer surgery				
Kurz A, et al., 1996 (198) 8606715	To determine if intraoperative hypothermia increases the susceptibility to surgical wound infection and increases hospitalization	Randomized, double-blind	400	96	104	18–80 y of age undergoing elective colorectal resection for cancer or inflammatory bowel disease	Corticosteroid or immunosuppressive therapy within 4 wk of surgery; recent fever or infection; bowel obstruction; malnutrition (albumin <3.3 g/dL, wbc<2500 cell/mL; >20% weight loss)	Fluid warmer activation; forced-air cover at 40 degrees Celsius to maintain core temp near 36.5 degrees Celsius (tympanic membrane temp)	No fluid warming; forced air warmer at ambient temperature to 34.5 degrees Celsius	Postop wound infections increased in hypothermia group (6/104 in normothermia group vs. 18/96 in hypothermia group); d of hospitalization increased in hypothermia group (12 d in normothermia group vs. 14.7 in hypothermia group	N/A	Collagen deposition increased, d to first solid food decreased, d to suture removal decreased in normothermia group	p value for infection =0.009; OR: 4.9 (1.7–14.5)	Pts with hypothermia required more blood transfusion which may have confounded the results; smokers had a very high rate of complications, but were evenly distributed between the 2 groups
Frank SM, et al.,1997 (199) 9087467	To assess he relationship between body temperature and cardiac morbidity during the periop period	Randomized; cardiac outcomes double-blind	300	142	158	≥60 y of age undergoing peripheral vascular, abdominal, or thoracic surgery AND admitted to the ICU and had CAD or high risk of CAD	LBBB, LVH with strain, digitalis effect paced, preop hyper/ hypothermia, Raynaud, thyroid disorders	Upper or lower body forced air warmer full body warmer first 2 h postop adjusted to maintain temp at or near 37 degrees Celsius	No forced air warmer	Cardiac events (MI, UA, ischemia, arrest within 24 h postop); Significant increase in ECG event and morbid cardiac event (ischemia/UA, arrest, infarction) in hypothermic group	N/A	No difference in intraoperative cardiac events	Major cardiac event p=0.02;ECG event p=0.02; no significant difference in postop ischemia	Low overall incidence in postop ischemia (7%)

Nguyen HP, et al., 2010 (200) 20571361	To determine if periop hypothermia increased SAH-related cardiac abnormalities	Randomized; cardiac outcomes double-blind	1,000	499	501	Pts with subarachnoid hemorrhage who undergo cerebral aneurysm surgery	Intubated at the time of enrollment	Hypothermia (esophageal temp 33 degrees Celsius)	Normothermia 36.5 degrees Celsius	No increased incidence of any single or composite cardiovascular event as defined intraoperatively and postoperatively: hypo/HTN unintended, vasopressor use, ischemia or infarction, cardiogenic shock, CHEF, pulmonary edema, VF, VT, CPR, pacemaker placement, angioplasty and stenting. Hypothermia does not increase the incidence of cardiovascular events, at least in pts with a low preop risk of CAD	N/A	N/A	Any cardiovascular event p=0.11, OR: 1.24 (CI: 0.96–1.61)	Post hoc study; low incidence of many of the cardiovascular events

CAD, coronary artery disease; CPR, cardio-pulmonary resuscitation; CHEF, contour-clamped homogeneous electric field gel; CI, confidence interval; CSF, cerebrospinal fluid; DVT, deep vein thrombosis; ECG, electrocardiogram; hx, history; HTN, hypertension; ICU, intensive care unit; LBBB, left bundle-branch block; LVH, left ventricular hypertrophy; MI, myocardial infarction; periop, perioperative; postop, postoperative; preop, preoperative; pt, patient; pts, patients; UA, unstable angina; VF, ventricular fibrillation; and VT, ventricular tachycardia.

Data Supplement 31. Perioperative Use of Pulmonary Artery Catheters (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*		
Sandham JD, et al., 2003 (201) 12510037	RCT of PAC use in high-risk surgical pts	Prospective	1,994	997	997	ASA Class III/IV risk, ≥60 y old, scheduled for urgent or elective abdominal, thoracic, vascular or hip fracture surgery	N/A	PAC use	No PAC use, although a central venous catheter was permitted	In-hospital mortality	N/A	6 mo mortality, 12 mo mortality, and in-hospital morbidity	In-hospital mortality (p=0.93)	Increased incidence of pulmonary embolism in the PA catheter arm, 8 vs. 0, p=0.004
Valentine RJ, et al., 1998 (202) 9510275	RCT of PAC in aortic surgery	Prospective	120	120	60	Pts undergoing elective abdominal aortic reconstruction	MI w/in 3 mo, CABG within 6 wk, severe aortic/mitral valve disease, overt CHF	PAC use and presurgery hemodynamic optimization	No PAC and hydration	MI, arrhythmias, CHF, acute renal failure, CVA, graft thrombosis, pulmonary insufficiency, death	N/A	Duration of ventilation, ICU stay length, hospital stay length	All p=NS for MI, pulmonary insufficiency, CVA, death	Underpowered
Bender JS, et al., 1997 (203) 9339929	RCT of PAC in major elective vascular surgery (infra-renal aortic reconstruction or lower limb revasc)	Prospective	104	51	53	Major elective vascular surgery	Suprarenal cross-clamp, MI w/in 3 mo or UA, overt CHF, CABG within 6 wk, symptomatic aortic or mitral valve disease	PAC use	Radial artery catheter	Not defined (a lot of morbidity outcomes)	N/A	N/A	Postop complications no different between groups	Underpowered

ASA indicates American Society of Anesthesiologists; CABG, coronary artery bypass graft; CHF, congestive heart failure; CVA, cerebrovascular accident; ICU, intensive care unit; MI, myocardial infarction; N/A, not applicable; NS, nonsignificant; PAC, pulmonary-artery catheter; pts, patients; postop, postoperative; RCT, randomized controlled trial; revasc, revascularization; and UA, unstable angina.

Data Supplement 32. Surveillance and Management for Perioperative MI (Section 8.1)

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*		
Garcia S, et al., 2013 (204) 22975335	ECG and TnI postop prognosis	Retrospective	337	N/A	N/A	Pts undergoing vascular surgery	Incomplete data, amputations, low-risk procedures	N/A	ECG & TnI	HR for mortality with abnormal ECG/TnI	N/A	N/A	ECG & TnI NS for 30-d mortality	Retrospective
Van Waes JA, et al., 2013 (205) 23667270	TnT and postop prognosis	Prospective	2,232	TnT drawn on POD 1,2,3	N/A	Intermediate= and high-risk surgery pts (hospital stay >24 h)	Lost to follow up within 30 d	N/A	TnT	HR for mortality with TnI elevation	N/A	Mortality 3% MI (universal definition) 0.6%	HR: 2.4 TnI: 0.07 -0.59 ug/L, p<0.01 and 4.2 for TnI ≥0.6; p<0.01	N/A
Shroff GR, et al., 2012 (206) 22286592	TnI and postop prognosis	Retrospective	376	TnI drawn q8 h × 3 after arriving from OR	N/A	Renal and renal/pancreas transplant pts	None	N/A	TnI	HR for mortality with TnI elevation	N/A	25% abnormal TnI, 8 in-hospital cardiac events	HR: 4.6 TnI >1 ng/mL (95% CI: 2.04–14.6)	Retrospective
Devereaux PJ, et al., 2012 (207) 22706835	TnT and postop prognosis	Prospective	15,133	TnT 6–12 h postop and POD 1,2,3	N/A	Noncardiac surgery >44 y old, and had an overnight stay	Outpt surgery or declined consent	N/A	TnT	In-hospital mortality	N/A	Mortality 1.9% MI	N/A	N/A
Beattie WS, et al., 2012 (208) 22961610	Compare TnI ordered on a clinical basis vs. regularly scheduled post-op	Retrospective	51,791	TnI	N/A	Moderate to high-risk noncardiac surgery pts	Same day surgery, cardiac surgery, transplantation, eye surgery, and duplicate procedures	N/A	N/A	In-hospital mortality	N/A	2.1% 30-d mortality, 11.1% TnI elevated >0.7 mc/L	HR: 6.5 (5.4 7.9) for mortality with TnI >0.7	N/A
Redfern G, et	Troponin	Meta-	2,195	TnI drawn	N/A	Pts	N/A	N/A	N/A	30-d mortality	N/A	N/A	OR: 5.0;	N/A

al., 2011 (209) 21564046	and 30-d and 180-d outcomes in pts undergoing vascular surgery	analysis				undergoing vascular surgery						95% CI: 2.9–8.8. 30 d mortality with elevated TnI	
Nagele P, et al., 2011 (210) 20886662	TnI and Postop MI and death	Retrospective	378	TnI elevated	N/A	Head and neck cancer surgery and had TnI measured	No TnI measured	N/A	N/A	30-d mortality	N/A	57 pts (15%) had elevated TnI, 10 pts (2.6%) had MI	OR: 5.8 (0.8 42) 30-d mortality	N/A
Levy M, et al., 2011 (211) 21336095	TnI and postop death	Meta-analysis	3,318	Troponin elevated	N/A	Troponin measured	Poor studies	N/A	N/A	OR: 3.4 (95% CI: 2.2–5.2) 30-d mortality	N/A	5% had periop MI. 30-d mortality 11.6% with periop MI and 2.2% without MI	N/A	Significant heterogeneity in group (I2=56%)
Devereaux PJ, et al., 2011 (212) 21502650	TnI and postop events	Prospective	8,351	Troponin elevated	N/A	Noncardiac surgery >44 y old, and had an overnight stay and at-risk for cardiovascular disease	N/A	N/A	N/A	1.7% had symptomatic MI, 3.3% had asymptomatic MI, and 8.3% had isolated troponin rise	N/A	HR: for death 4.76 with symptomatic MI and 4.0 for asymptomatic MI	N/A	N/A
McFalls EO, et al., 2008 (213) 18245121	TnI and events	Prospective	377	TNI ≥0.1 ug/L	N/A	CARP Trial and samples stored	N/A	N/A	N/A	30-d mortality 9 (p=NS), 1 y mortality significantly higher 20% vs. 4.7%)	N/A	N/A	N/A	N/A

CARP indicates Coronary Artery Revascularization Prophylaxis; CI, confidence interval; DVT, deep vein thrombosis; ECG, electrocardiogram; HR, hazard ratio; MI; myocardial infarction; N/A, not applicable; NS, nonsignificant; POD, postoperative day; pts, patients; TnI, troponin I; TnT, troponin T I.

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