Table 1. Results at Day 30

Outcome n (%)	Clonidine n=5009	Placebo n=5001	HR (95% CI)	p Value
Primary (death or MI)	367 (7.3)	339 (6.8)	1.08 (0.93–1.26)	0.29
Secondary (death, MI, or stroke)	380 (7.6)	352 (7.0)	1.08 (0.93–1.25)	0.30

MI=myocardial infarction.

Throughout the 30-day follow-up period, the composite of death or MI was greater, but not statistically significant, with clonidine versus placebo (HR, 1.08; 95% CI, 0.93 to 1.26; p=0.29). Of the assessed tertiary outcomes, nonfatal cardiac arrest was significantly more frequent in those given clonidine (n=16, 0.3%) versus placebo (n=5, 0.1%; HR, 3.20; 95% CI 1.17 to 8.73; p=0.02). Clinically important hypotension and bradycardia, but not stroke, were statistically more frequent in patients given clonidine (Table 2).

Table 2. Safety Outcomes

Outcome n (%)	Clonidine n=5009	Placebo n=5001	HR (95% CI)	p Value
Clinically important hypotension	2385 (48)	1854 (37)	1.32 (1.24–1.40)	<0.001
Clinically important bradycardia	600 (12)	403 (8)	1.49 (1.32–1.69)	<0.001
Stroke	18 (0.4)	17 (0.3)	1.06 (0.54–2.05)	0.87

Hypotension was an independent predictor of MI (adjusted HR, 1.37; 95% CI, 1.16 to 1.62; p<0.001). Hypotension was always more prevalent in patients given clonidine than placebo, especially during surgery and recovery, and decreasing over the next 3 days (Table 3). The duration of hypotension was markedly shorter during surgery and recovery, compared with the following 3 days (Table 3).

Table 3. Risk and Duration of Hypotension

Period	Prevalence of Hypotension			Duration of Hypotension		
	Clonidine (%)	Placebo (%)	p Value	Placebo, minutes	Clonidine, minutes	p Value
Surgery	39	32	<0.001	15	15	0.12
Post-anesthesia care unit	8	4	<0.001	30	30	0.30
Postop Day 1	8	5	<0.001	150	180	0.13
Postop Day 2	3	2	<0.001	110	160	0.03
Postop Day 3	1.1	0.6	0.004	109	214	0.07

The ineffectiveness of clonidine in reducing postoperative MI or death combined with the increase in frequency and duration of hypotension means that low-dose clonidine should not be given to patients having noncardiac surgery in an effort to lessen perioperative mortality or MI.

Consistent with the results of POISE-1 (β-blockers in noncardiac surgery), starting drugs that may have potent hemodynamic effects (eg, antihypertensive, sympatholytic) within 24 hours of major noncardiac surgery is not effective in a broad population of patients undergoing noncardiac surgery.

Methylprednisolone Not Beneficial in High-Risk Cardiac Surgery Patients (SIRS)

Written by Brian Hoyle

Findings of the Steroids in Cardiac Surgery Trial [SIRS Trial; NCT00427388] were presented by Richard Whitlock, MD, PhD, Hamilton Health Services/McMaster University, Hamilton, Ontario, Canada.

Inflammation triggered by cardiopulmonary bypass can be diminished using prophylactic steroids, which may produce clinical benefits. The SIRS trial assessed the hypothesis of whether methylprednisolone would reduce perioperative adverse events in high-risk patients undergoing cardiac surgery involving cardiopulmonary bypass.

A total of 7507 patients were randomized to intraoperative methylprednisolone (500 mg intravenously) (n=3755) or placebo (n=3752). The coprimary outcomes were total mortality within 30 days following surgery, and a composite of all-cause mortality, myocardial infarction (MI), stroke, renal failure, or respiratory failure over the same time. Secondary efficacy and safety outcomes were also evaluated.

The steroid and placebo groups were well-matched in terms of age (67.5±13.6 vs 67.3±13.8 years), male percentage (60.1% vs 60.8%), previous MI (26.2% vs 24.7%) or stroke (8.1% vs 8.4%), congestive heart failure (26.8% vs 27.2%), prevalence of diabetes (26.2% vs 26.4%), and EuroSCORE (both 7.1±2.0). The similarities between groups extended to any prior valve procedure (n=2646, 70.4% vs n=2723, 72.6%), prior coronary artery bypass graft (CABG; n=1838, 48.4% vs n=1796, 47.9%), isolated valve procedure (n=1206, 32.1% vs n=1228, 32.7%), and isolated CABG (n=826, 22.0% vs n=762, 20.3%)

Overall there was no difference in the rate of the coprimary outcomes between patients receiving steroids compared with those receiving placebo at 30 days (Table 1). Analysis of the individual components of the composite outcome revealed a significantly higher rate of MI in patients randomized to methylprednisolone (Table 1). In subanalyses, the results were consistent when stratified by gender, diabetes, age, EuroSCORE, type of surgery, and duration of cardiopulmonary bypass.

Table 1. Coprimary Outcomes

30-Day Outcome n (%)	Steroid n=3755	Placebo n=3752	Relative Risk (95% CI)	p Value
Death	155 (4.1)	176 (4.7)	0.88 (0.71–1.09)	0.23
Composite of death, MI, stroke, new renal failure, respiratory failure	908 (24.2)	869 (23.2)	1.04 (0.96–1.13)	0.30
Components of Composite				
MI	500 (13.3)	408 (10.9)	1.22 (1.08–1.38)	0.001
Stroke	72 (1.9)	80 (2.1)	0.90 (0.66–1.23)	0.51
New renal failure	105 (2.8)	114 (3.0)	0.92 (0.71–1.20)	0.53
Respiratory failure	343 (9.1)	375 (10.0)	0.91 (0.79–1.05)	0.21

MI=myocardial infarction.

Of the secondary outcomes, the prevalence of death or MI, and the postoperative level of insulin were significantly greater in the steroid group (Table 2).

Table 2. Secondary Outcomes of Efficacy and Safety

30-Day Outcome n (%)	Steroid n=3755	Placebo n=3752	Relative Risk (95% CI)	p Value
Efficacy				
Death or MI (%)	620 (16.5)	536 (14.3)	1.16 (1.04–1.29)	0.008
New atrial fibrillation (%)	821 (21.9)	846 (22.5)	0.97 (0.89–1.06)	0.53
Any transfusion (%)	1932 (48.8)	1865 (49.7)	0.98 (0.94–1.03)	0.43
Length of intensive care unit stay (hours)	46.0 (23.0–90.0)	47.0 (24.0–91.0)		0.05
Length of hospital stay (days)	9.0 (7.0–13.0)	9.0 (7.0–13.0)		0.06
Safety				
Infection (%)	464 (12.4)	494 (13.2)	0.94 (0.83–1.06)	0.29
Delirium (%)	295 (8.4)	290 (8.3)	1.01 (0.87–1.19)	0.84
Surgical site infection (%)	150 (4.0)	150 (4.0)	1.00 (0.80–1.25)	0.99
Gastrointestinal perforation or hemorrhage (%)	55 (1.5)	46 (1.2)	1.19 (0.81–1.76)	0.37
Peak blood glucose (mmol/L)	12.7±7.2	12.1±18.7		0.04
Postoperative insul1in (u)	50.3±66.3	32.6±52.9		<0.00001

MI=myocardial infarction.

The investigators concluded that the trial demonstrated that routine use of methylprednisolone in high-risk patients undergoing cardiac surgery with the use of cardiopulmonary bypass was ineffective in reducing death or major morbidity at 30 days and appeared to increase the risk of early postoperative MI.

Metformin Doses Not Reduce Heart Failure After STEMI in Patients Without Diabetes (GIPS-III)

Written by Brian Hoyle

Results of a double-blind, randomized, placebo-controlled, parallel-group trial do not support the routine use of metformin in nondiabetic patients after ST-segment elevation myocardial infarction (STEMI) for the purpose of preserving myocardial function. Findings of the Metformin to Reduce Heart Failure After Myocardial Infarction trial [GIPS-III; Lexis CPH et al. *JAMA* 2014] were presented by Chris P. H. Lexis, MD, University Medical Center, Groningen, Groningen, The Netherlands.

MI diminishes left ventricular function (LVF) in up to 50% of subjects and leads to clinical heart failure in up to 40% [Steg PG et al. *Eur Heart J* 2012]. Animal experiments and observational suggest metformin may have protective effects on the myocardium in the setting of ischemia-reperfusion; the mechanism of action being independent of the drug's glucose-lowering effect. The GIPS-III trial tested whether 4 months of metformin treatment started after successful percutaneous coronary intervention (PCI) for MI could preserve left ventricular ejection fraction (LVEF) in patients without diabetes at 4 months.

Acute STEMI patients, post-PCI with stenting, and with TIMI post-PCI flow Grade ≥2 were eligible for the trial. Key exclusion criteria were diabetes, prior MI, prior CABG, need for cardiothoracic surgery, contraindication for magnetic resonance imaging (MRI), and severe renal impairment. Three-hundred and eighty patients were randomized 1:1 to receive metformin 500 mg BID (n=191) or placebo BID (n=189) beginning immediately after PCI and continuing for 4 months. The primary endpoint was the LVEF measured in a blinded fashion at 4 months using a 3.0 Tesla MRI. The principal secondary endpoint was N-terminal brain natriuretic peptide (NT-proBNP) at 4 months. cardiovascular outcomes, adverse events, and markers of glycometabolic state were also collected.

Time from onset of symptoms to first coronary intervention was 161 minutes (IQR, 109-250). Time to administration of first dose of study drug after first coronary intervention was approximately 100 minutes in each arm. The two arms were similar at baseline for demographic and physiologic characteristics including specific angiographic parameters. Angiographic markers of successful reperfusion were less successful for patients receiving metformin versus placebo (TIMI post-PCI flow Grade <3, 12.6% vs 5.3%; myocardial blush Grade ≤1: 13.8% vs 5.9%).

In both arms, over 25% of subjects did not undergo MRI; 55 and 50 patients in the metformin and placebo