The largest emerging epidemic in CV medicine: Major perioperative events around the time of noncardiac surgery

P.J. Devereaux, MD, PhD
McMaster University
Hamilton, Ontario, Canada

Disclosure

- A research group, I am a member of,
  - has policy of not accepting honorariums or other payments from industry for own personal financial gain
- We accept honorariums or other payments from industry to support
  - research endeavors and reimbursement of costs to participate in meetings (e.g., scientific or advisory)
- Based on study questions I originated and grants I wrote
  - I have received grants from AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Stryker, and Roche Diag
- I have participated in
  - advisory boarding meeting GlaxoSmithKline
  - expert panel meeting AstraZeneca

Goals of presentation

- Perioperative vascular complications
  - magnitude of the problem
  - risk of missing event
  - monitoring and prevention strategies

Prior observational studies

- Range of event rates
  - patients with, or at risk of, CAD
    - 4% for major vascular event
  - unselected patients
    - 1.5% for major vascular event
- Limitations
  - old data, single centre studies, small sample sizes, CK-MB

VISION Study design

- Prospective cohort study
- Sample size – 40,000 patients
- Participating countries
  - Brazil, Canada, China, Colombia, India, Italy, Malaysia, South Africa, Spain, US
- Eligibility criteria
  - all patients $\geq$ 45 undergoing noncardiac surgery requiring overnight hospital admission
- F/U
  - Troponin T post op and days 1, 2, 3 after surgery
  - patients followed for 1 year after surgery

Status of Study

- Over 20 sub-studies
- Over 40 funding sources
- Currently recruiting in 9 countries
- Have recruited > 15,000 patients
- Interim analysis at 10,000 patients
  - primary outcome – 6.5%
    - > 3 fold higher than expected

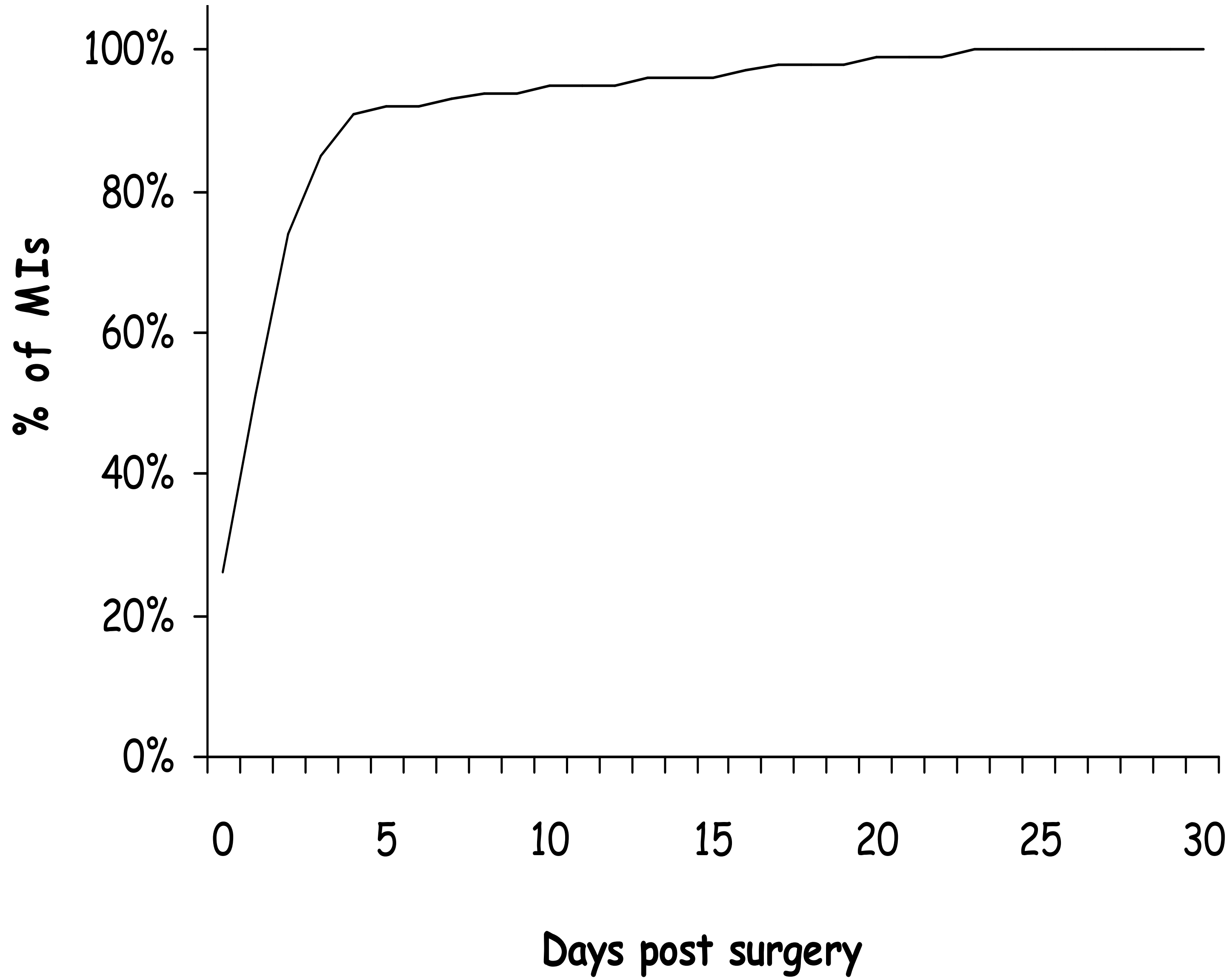
Largest emerging CV epidemic

- During last few decades
  - substantial advances in noncardiac surgery
    - improved disease treatment and patients' QOL
- Globally 200 million adults annually undergo major noncardiac surgery
  - > 5 million suffer major perioperative vascular complication
    - range of global annual incidence of patients acquiring HIV

POISE Perioperative MIs: Insights from POISE-1 cohort

- Randomized 8351 patients
  - 190 centres in 23 countries
- Eligibility criteria
  - age ≥ 45 yrs, undergoing noncardiac surgery, and have or risk of atherosclerotic disease
- Monitoring
  - Troponin post op and days 1, 2, and 3 after Sx
- Follow-up
  - 30 days after randomization
    - 415 patients had MI
      - 2/3rds were asymptomatic

Timing of MI

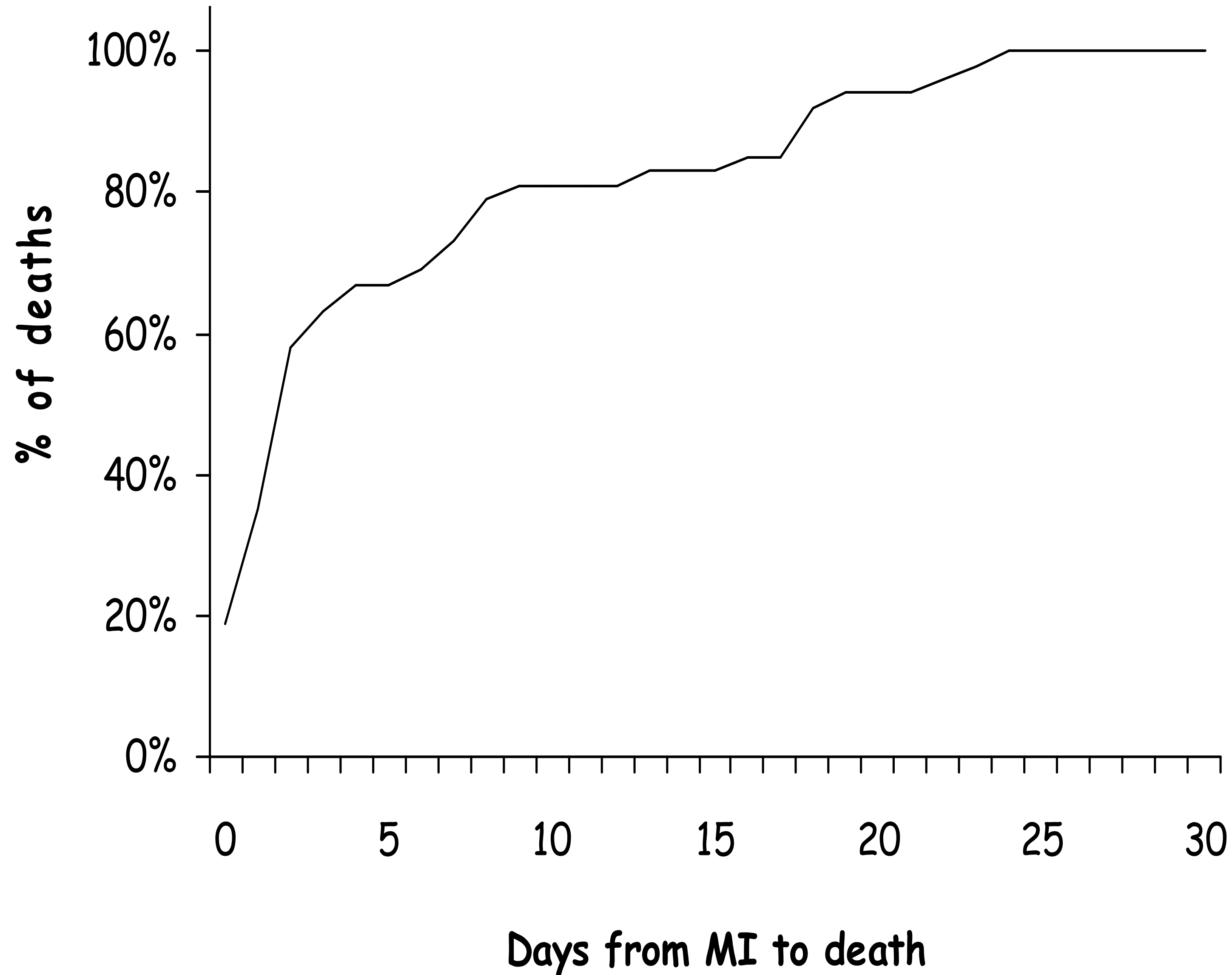


Impact of MI on mortality

- 30-day mortality rate
  - 2.2% (178 of 7936 patients) among patients who did not suffer periop MI
  - 11.6% (48 of 415 patients) among patients who suffered periop MI
    - $P<0.0001$
- Independent predictors of death at 30 days

Predictor	HR	95% CI
symptomatic MI	3.31	1.78-6.15
asymptomatic MI	3.45	2.20-5.41

Timing of death after periop MI



Monitoring and prevention strategies

- Measuring troponin values on the first few days after surgery
- Initiating medical services focusing on perioperative CV risk

POISE-1

- Primary objective – does metoprolol CR reduce 30 day risk of major CV events after noncardiac surgery
- Design – blinded RCT
- Intervention – metoprolol CR or placebo started 2-4 hrs preoperatively, continued for 30 days
- Main outcome measure – 30 day composite of
  - CV death, nonfatal MI, and nonfatal cardiac arrest

Final Recruitment
8351 pts from 190 sites in 23 countries

3548

1506

406

2005

886

POISE

Preoperative characteristics

Characteristics	Metoprolol (N=4174)	Placebo (N=4177)
HR (mean)	77.6	78.1
BP (mean)	138.7/78.3	138.7/78.5
Current smoker	19.3%	19.0%

POISE

Outcomes

Outcome	Metoprolol (N=4174)	Placebo (N=4177)	HR (95% CI)	P
	no.			
Primary outcome (CV death, nonfatal MI, nonfatal CA)	244 (5.8%)	290 (6.9%)	0.84 (0.70-0.99)	0.0399
nonfatal MI	152 (3.6%)	215 (5.1%)	0.70 (0.57-0.86)	0.0008

POISE

Secondary Outcomes

Outcome	Metoprolol (N=4174)	Placebo (N=4177)	HR (95% CI)	P
		no.		
total mortality	129 (3.1%)	97 (2.3%)	1.33 (1.03-1.74)	0.0317
stroke	41 (1.0%)	19 (0.5%)	2.17 (1.26-3.74)	0.0053

Insights from POISE-1 regarding negative outcomes

Outcome	Metoprolol (N=4174)	Placebo (N=4177)	HR (95% CI)	P
		no.		
significant hypotension	625 (15.0%)	404 (9.7%)	1.55 (1.38-1.74)	<0.0001

	HR (95% CI)	PAR
Predictor of death		
hypotension	4.97 (3.62-6.81)	37.3
Predictor of stroke		
hypotension	2.13 (1.15-3.96)	14.7

Perioperative period results in

- High physiological stress marked by
  - rise in sympathetic output, inflammation, shivering
    - clonidine reduces these effects
- Platelet activation
  - ASA can inhibit platelet aggregation

Need for perioperative clonidine and ASA trial

- Perioperative RCTs suggest low-dose clonidine ($\leq$ 0.3 mg/day)
  - prevents myocardial ischemia
  - may not increase clinically important hypotension
- Perioperative clonidine is used infrequently
- Perioperative RCTs suggest ASA
  - prevents vascular deaths
  - effect on MI is unclear
  - increased risk of bleeding is imprecise
- Perioperative ASA administration is highly variable
- This evidence establishes rationale and identifies need for large RCT to determine effects of periop low-dose clonidine and low-dose ASA

POISE-2

- Primary objective
  - determine the effect of perioperative low-dose clonidine and low-dose ASA
- Design – blinded factorial RCT
- Sample size – 10,000 patients
- Setting – 150 centres in 20 countries
- Planned 1st patient recruited
  - June 2010

Summary

- Noncardiac surgery is common
- Major perioperative vascular complications represent the largest emerging epidemic in cardiology
- Monitoring troponins after surgery can help avoid missing important MIs
- Perioperative beta-blockers prevent MIs but at a cost of excess strokes and likely deaths
- POISE-2 will inform periop effect of clonidine and ASA
- Need programs to tackle periop smoking and hypotension