The PeriOperative ISchemic Evaluation-2 (POISE-2) Trial

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Perioperative period results in

• High physiological stress marked by
  - rise in sympathetic output
  - increased HR, BP, and hence myocardial $O_2$ demand
    • clonidine can reduce adrenergic output

• Platelet activation
  - ASA can inhibit platelet aggregation
Need for trial

• Perioperative RCTs suggest low-dose clonidine (≤ 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 impact of periop low-dose clonidine and separately low-dose ASA on composite of death and nonfatal MI at 30 days

• Design – blinded factorial RCT
  - ASA/clonidine
  - ASA/clonidine placebo
  - ASA placebo/clonidine
  - ASA placebo/clonidine placebo

• Sample size – 10,000 patients
Current status

• Funding
  - $3 Million from BI
  - study drug from BI and Bayer
  - CIHR bridge funding
  - national grant in Spain
  - grants submitted to CIHR, EU, NHMRC
    • evaluating NIH grant submission

• Recruitment set to start in June 2010
POISE-2 Summary

• This trial will answer two crucial management questions for patients undergoing noncardiac surgery and
  - influence future perioperative practices around the world
Eligibility criteria

• Inclusion criteria
  - age ≥ 45 yrs, undergoing noncardiac surgery, and have or be at risk of atherosclerotic disease

• Exclusion criteria
  - ASA within 72 hrs prior to surgery; hypersensitivity or allergy to ASA or clonidine; SBP < 105 mm Hg; HR < 55 bpm; 2nd or 3rd degree heart block without pacemaker; active PUD; drug-eluting stent in yr prior to randomization; bare-metal stent in 6 weeks prior to randomization; taking alpha-2 agonist, alpha methyldopa, reserpine, clopidogrel, or ticlopidine; undergoing intracranial surgery, CEA, or retinal surgery
Recruitment and F/U

• Centres
  - approximately 150 centres in 16 countries

• Research personnel will
  - screen all potential patients (elective, urgent/emerg)
  - randomize patients 2-4 hrs prior to surgery

• F/U
  - troponin post op and days 1, 2, 3 after surgery
  - throughout hospital course and contact at 30 days and 1 year after Sx
Clonidine intervention

- Prior to surgery (goal 2-4 hours) patients will take
  - 0.2 mg of oral clonidine or matching placebo and
  - will have a transdermal clonidine (0.2 mg/day) or placebo patch applied
    - patch will be removed at 72 hours after surgery
ASA intervention

- We will enroll patients in 1 of 2 ASA strata
  - ASA Continuation Stratum - patients taking ASA chronically
    - randomize to continue ASA or withdraw ASA and take placebo
  - ASA Starting Stratum - patients not taking ASA chronically
    - randomize to start ASA or placebo

- Patients in both strata will receive same study ASA intervention (i.e., either ASA 81 mg or placebo)

- 1st dose prior to Sx (goal 2-4 hrs) - 2 tablets

- After 1st dose
  - 1 tablet daily for 30 days in Starting Stratum and
  - 7 days in Continuation Stratum, after which they resume their regular ASA