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Population Health Research Institute
HEALTH THROUGH KNOWLEDGE

Hamilton Health Sciences

McMaster University
HEALTH SCIENCES

POISE-3

PeriOperative ISchemic Evaluation-3 Trial

Background and Rationale

Perioperative bleeding

- Perioperative bleeding is frequent and impacts prognosis
- Strongly associated with 30-day CV complications and mortality
  - VISION – patients with Bleeding Impacting Mortality after noncardiac Surgery (17%): 6% vs 1% death at 30 days
  - POISE – bleeding was independent predictor of MI (aOR 3.62; 95% CI 2.07-6.36)
  - Kamel *et al.* (651,775 noncardiac surgeries) – bleeding was a predictor of stroke (aOR, 2.5; 95% CI 1.9-3.3)

Tranexamic acid (TXA)

- TXA - antifibrinolytic agent with potential to reduce perioperative bleeding, but efficacy and safety in noncardiac surgery not established yet
  - several small RCTs in orthopedics suggesting efficacy versus placebo on blood loss and transfusion
  - very few RCTs in other noncardiac surgeries
  - RCTs in other settings demonstrated efficacy on major and fatal bleeding (ATACAS, CRASH-2, WOMAN trials)
- Potential for TXA to cause thrombotic events; however, may prevent some CV events by preventing bleeding
  - noncardiac surgery = prothrombotic state

Perioperative hypotension

- Perioperative hypotension is frequent and impacts prognosis
  - VISION - clinically important hypotension: intraop 28%, postop 19%
  - Preoperative hypotension:
    - Every 1 mm Hg decrease in preop SBP below 130 mm Hg associated with significant increase in 30-day mortality and CV complications (VISION)
  - Intraoperative hypotension:
    - An intraop TWA-MAP change from 80 to 50 mm Hg, risk of mortality tripled (Cleveland Clinic studies)
    - MAP <55 mm Hg associated with MINS and AKI (*dose-effect* relationship)
  - Postoperative hypotension:
    - Clinically important hypotension (10% of placebo patients) had PAR for death at 30 days 37%, PAR for stroke 15% (POISE)
    - Clinically important hypotension associated with risk of MI (POISE-2)

Perioperative hypertension

- Data suggest association between perioperative hypertension and complications

- Routine practice commonly reflects “hypertension-avoidance” strategy

  - >70% VISION pts continue all antihypertensive meds 24 h before surgery

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Trial Design and Outcomes

Primary objectives

- In patients at high CV risk undergoing noncardiac surgery determine effect of
  - TXA versus placebo
    - on life-threatening, major, and critical organ bleeding (*superiority*)
    - on major arterial and venous thrombosis (*non-inferiority*)
  - Hypotension-avoidance versus Hypertension-avoidance strategy
    - on major CV events (*superiority*)

Trial design

- Investigator initiated trial
- 10,000 patients randomized to TXA or placebo
  - patients, health care providers, data collectors, outcome adjudicators, and investigators blinded
  - sample size based upon non-inferiority safety outcome
- Partial 2x2 factorial design
  - randomized to hypotension-avoidance or hypertension avoidance-strategy

Primary outcomes – TXA

- Co-primary *efficacy* outcome: composite of life-threatening bleeding, major bleeding, and critical organ bleeding at 30 days after randomization

- Co-primary *safety* outcome: composite of MI, non-hemorrhagic stroke, peripheral arterial thrombosis, and symptomatic proximal VTE at 30 days after randomization

Primary outcomes – BP management

- Composite of vascular death, and non-fatal MI, stroke, and cardiac arrest at 30 days after randomization

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Eligibility Criteria

Inclusion criteria

- Patients undergoing noncardiac surgery,
- ≥45 yrs of age,
- expected ≥1 night admission, and
- at risk of major bleeding and CV events

Inclusion criteria (details)

- Patients undergoing noncardiac surgery; ≥45 yrs of age; expected ≥1 night admission; and ≥1 of following (A-F)

  A. NT-proBNP ≥200 ng/L

  B. history of coronary artery disease

  C. history of peripheral vascular disease

  D. history of stroke

  E. undergoing major vascular surgery; OR

  F. any 3 of 9 risk criteria

     i. undergoing major surgery

     ii. history of congestive heart failure

     iii. history of a transient ischemic attack

     iv. diabetes and currently taking an oral hypoglycemic agent or insulin

     v. age ≥70 yrs

     vi. history of hypertension

     vii. serum creatinine >175 µmol/L (>2.0 mg/dl)

     viii. history of smoking within 2 years of surgery

     ix. undergoing emergent/urgent surgery

Exclusion criteria

- Patients undergoing cardiac surgery
- Patients undergoing cranial neurosurgery
- Planned use of systemic TXA during surgery
- Low-risk surgical procedure (based on individual physician's judgment)
- Hypersensitivity or known allergy to TXA
- Creatinine clearance <30 mL/min (Cockcroft-Gault equation) or on chronic dialysis
- History of seizure disorder
- Patients with recent stroke, myocardial infarction, acute arterial thrombosis or venous thromboembolism (<3 month)
- Patients with fibrinolytic conditions following consumption coagulopathy
- Patients with subarachnoid hemorrhage within the past 30 days
- Women of childbearing potential who are not taking effective contraception, pregnant or breast-feeding
- Previously enrolled in POISE-3 Trial

Eligibility criteria – BP management factorial

- Inclusion criteria
  - –treated chronically (at least 30 days in the 6 weeks preceding randomization) with ≥1 antihypertensive medication (any class)

Eligibility criteria – BP management factorial

- Exclusion criteria
  - advanced CHF (NYHA class III or IV or left ventricular EF ≤30%)
  - unsecured brain aneurysm
  - history of hypertension-related cerebral hemorrhage
  - pheochromocytoma
  - hemodynamically unstable requiring vasopressor or inotropic support before surgery
  - thyrotoxicosis

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Intervention and Follow-up

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TXA intervention

- TXA (1 g) or placebo (normal saline) given by IV bolus (or 10 min infusion)
  - 1st dose: within 20 mins preceding anticipated skin incision
  - 2nd dose: at end of surgery (at wound closure)
- Study drug sourced by local pharmacies
- Study drug prepared by local pharmacies or designated unblinded study personnel

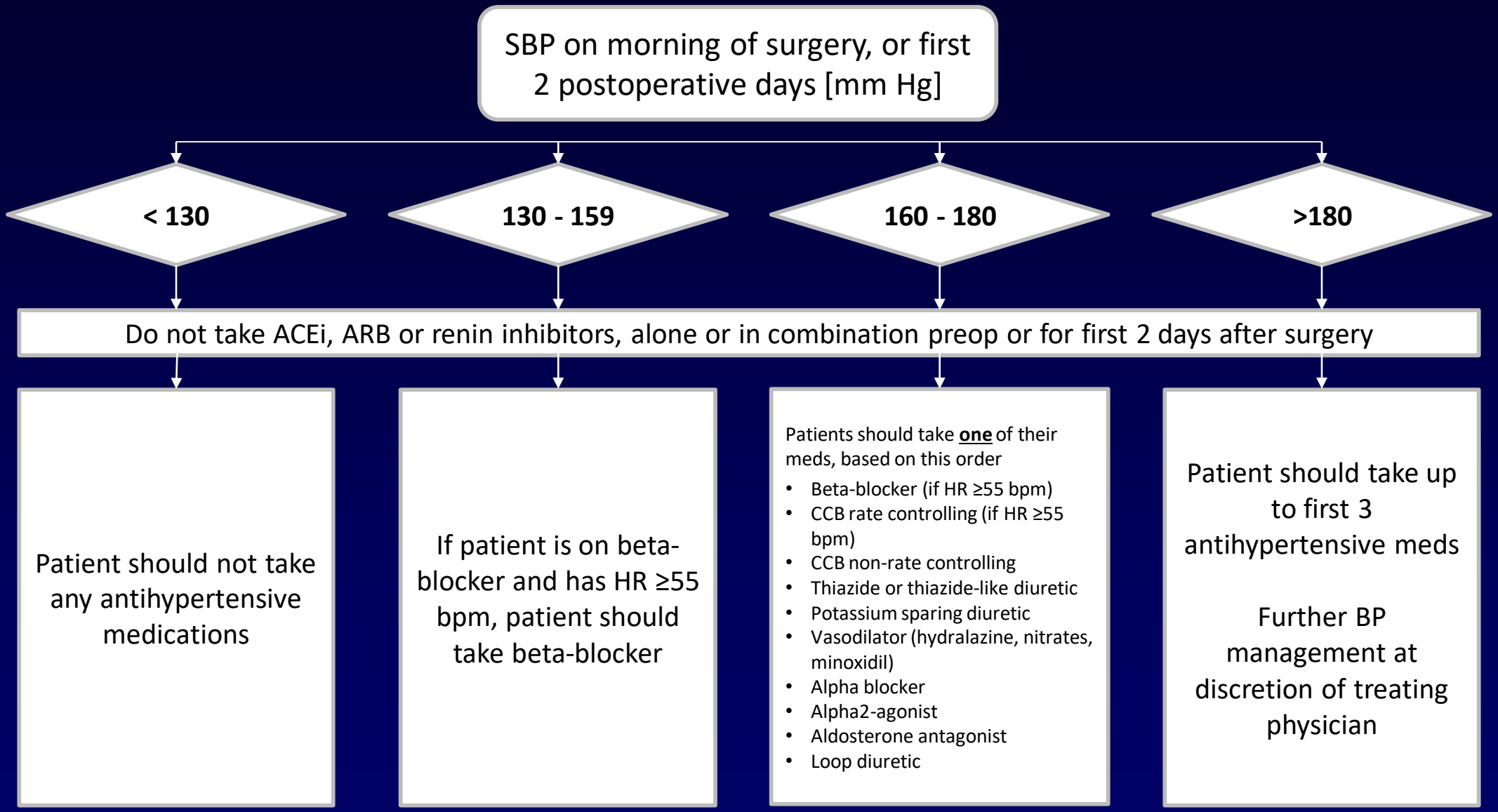
BP management strategy intervention

- All patients advised not to take their antihypertensive medications night before and morning of surgery but bring medications to preop holding area
- **Intervention: Hypotension-avoidance strategy**
  - **Preop**: antihypertensive meds management based on algorithm
  - **Intraop**: target MAP ≥80 mm Hg from time of anesthetic induction until end of surgery
  - **Postop day 1-2**: antihypertensive meds management based on algorithm

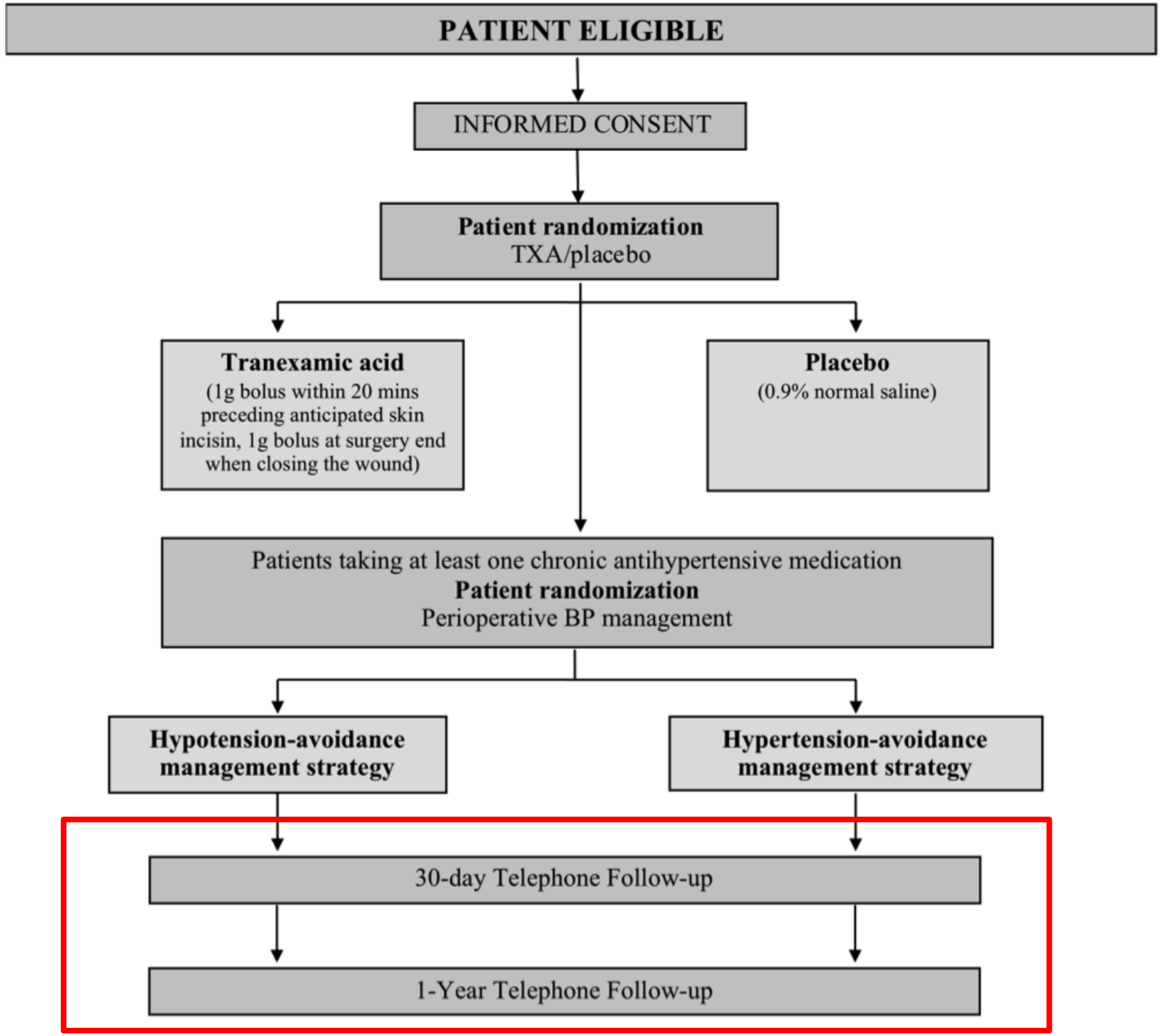
BP management strategy intervention

- **Control: Hypertension-avoidance strategy**
  - **Preop**: patient given normal antihypertensive meds in preop holding area
  - **Intraop**: target MAP ≥60 mm Hg from time of anesthetic induction until end of surgery
  - **Postop**: immediately after Sx restart antihypertensive meds

Preop and Postop Hypotension-avoidance strategy algorithm



If on drug combination and meds cannot be given separately (e.g. preop), patient can take it only if : i) SBP > 180 mm Hg; and ii) combination does not contain ACEi/ARB/renin inhibitors. The combination will count for as many meds as number of active drugs it contains


PATIENT ELIGIBLE
INFORMED CONSENT
Patient randomization
TXA/placebo
Tranexamic acid
(1g bolus within 20 mins preceding anticipated skin incisin, 1g bolus at surgery end when closing the wound)
Placebo
(0.9% normal saline)
Patients taking at least one chronic antihypertensive medication
Patient randomization
Perioperative BP management
Hypotension-avoidance management strategy
Hypertension-avoidance management strategy
30-day Telephone Follow-up
1-Year Telephone Follow-up