STUDY SYNOPSIS

Title	PericaRdiotomy IN Cardiac surgEry (PRINCE) trial
Principal Investigators	Drs. Richard Whitlock, Emilie Belley-Côté, Mario Gaudino, Sigrid Sandner, Björn Redfors
Sponsor	Hamilton Health Sciences, Through its Population Health Research Institute
Project Office	PRINCE Project Office, Population Health Research Institute, 237 Barton Street East, Hamilton, Ontario, Canada L8L 2X2 PRINCE@phri.ca
Study Design	An international multicentre randomized controlled trial of posterior pericardiotomy in 1400 patients without a history of atrial fibrillation or flutter undergoing cardiac surgery.
Study Population	**Inclusion Criteria** 1) Patients ≥18 years of age 2) Requiring surgical intervention on the proximal aorta, cardiac valves, and/or coronary arteries 3) Able to provide informed consent **Exclusion Criteria** 1) History of atrial fibrillation or flutter 2) Cardiac surgery procedures not included in the inclusion criteria (planned ventricular assistance device, planned aortic arch, transplantation surgery) 3) Prior cardiac surgery requiring opening of the pericardium 4) Previous surgical instrumentation of the left pleural cavity 5) Patient undergoing minimally invasive cardiac surgery.
Sample size	This study will enrol 1400 patients.
Study Intervention	The intervention under investigation is left posterior pericardiotomy which is compared to no posterior pericardiotomy during cardiac surgery.
Objectives	PRINCE has two objectives: 1) To evaluate whether left posterior pericardiotomy reduces the incidence of in-hospital postoperative atrial fibrillation (POAF) in the first 5 postoperative days. 2) To evaluate whether left posterior pericardiotomy decreases the risk of the hierarchical composite of all-cause death, stroke, systemic arterial embolism, unplanned hospital visit/readmission for cardiac reasons, or atrial fibrillation after index hospital discharge over the duration of follow-up.
Outcomes	The early co-primary outcome is in-hospital POAF within 5 days after index cardiac surgery. The late co-primary outcome is the hierarchical composite of time to all-cause death, time to ischemic stroke, time to systemic arterial embolism, time to unplanned hospital visit/readmission for cardiac reasons, and time to atrial

	fibrillation after index hospital discharge, evaluated using the win ratio (thereby accounting for the difference in importance of these outcomes) over the duration of follow-up. Secondary outcomes are POAF during the entire index hospital stay, length of postoperative in-hospital stay, pericardial effusion without tamponade within 30 days of index surgery, death within 30 days of index surgery, ischemic stroke or systemic arterial embolism within 30 days of index surgery, hospital visit/readmission within 30 days of index surgery, functional abilities and quality of life over duration of follow-up. Safety outcomes (all assessed within 30 days of index surgery unless otherwise noted) are phrenic nerve injury, left pleural interventions, esophageal injury, re-operation for bleeding within 48 hours of index surgery, and cardiac tamponade.
Statistical Considerations	The early co-primary outcome will be evaluated using multi-variable logistic regression, adjusting for CHA_2DS_2-VASc score and type of surgery. The late co-primary outcome will be evaluated using the win ratio. The early and late co-primary outcomes will be tested after multiple imputation of missing data (including missing outcomes data) using the fully conditional specification and 10 imputed datasets. Sensitivity analyses will use complete case data. Additional analyses will compare the results of the imputed data models to the ones with the missing data included. For the late co-primary outcome, patients who are lost to follow-up will be censored at their latest follow-up (time of last known status). Patients who cross-over from one treatment arm to another will be analyzed according to randomized treatment (intention to treat).
Duration of Study Period (per patient)	Follow-up will be performed in person or by telephone 1 and 6 months post-randomization (+7 days), and then every 6 months (+30 days) until a mean follow-up of 5 years for the study participants (estimated to be 4 years after completion of enrolment).