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Dabigatran for the Prevention of Myocardial Injury after Orthopedic Surgery (DMINS-PRE). A Study Protocol For A Randomized, Active-Controlled, Phase II Trial.

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Abstract:

Background and Aims: Myocardial Injury after Noncardiac Surgery (MINS) is a broader term that includes not only perioperative myocardial infarction but also other prognostically significant myocardial injuries due to ischemia, within 30 days after noncardiac surgery. Annually, around 1 million patients who undergo noncardiac surgery worldwide die during the first 30 days following surgery. The incidence of MINS is around 5-8%, with the majority occurring in the first two days after surgery. A recent study showed a potential positive effect of Dabigatran to prevent major vascular complications among patients with MINS. However, there is no evidence whether any drug may reduce the incidence of MINS after orthopedic surgeries. Our study aims to assess the efficacy of dabigatran to prevent MINS in a high cardiovascular risk population

Methods: This study will be a single-center randomized, two-arm (1:1 ratio), active-controlled and double-dummy, phase II trial. We will study 264 adults in total, age in range of 45 to 75 years and high cardiovascular risk associated with Framingham risk score higher than 20% and scheduled to undergo elective orthopedic surgery which requires a hospitalization for more than 24 hours. Patients which troponin measurement keeps negative after surgery will be randomly assigned (1:1) to receive dabigatran 150mg twice daily or enoxaparin daily, 6 hours after surgery for seven days. The primary outcome will be the incidence of MINS as ascertained by the difference in troponin (troponin delta) greater than 14ng/L in the perioperative period, after randomization. Secondary outcomes will be 30-day mortality, major thromboembolic complications, and severe bleeding complications

Discussion: This clinical trial will be the first to assess the efficacy and the safety of dabigatran to prevent MINS. Given MINS is estimated to affect every year about 8 million patients worldwide and is associated with cardiovascular complications and death after surgery, we believe this trial will provide relevant data to clinical practice and future research directions.

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INTRODUCTION

Background and rationale

In patients of age ≥ 45 years who undergo noncardiac surgery, there is at least a 5-8% risk of cardiac death, myocardial infarction (MI), heart failure or severe

dysrhythmia, such as ventricular tachycardia. However, there is an additional group of noncardiac surgery patients who have a rise in postoperative high-sensitive cardiac troponin T (troponin) due to ischemia, but without signs and symptoms of cardiac ischemia. As such, these two groups have been combined into the larger clinical entity of myocardial injury after noncardiac

surgery (MINS), which includes both symptomatic and asymptomatic elevations in troponin levels due to ischemia only, within 30-days after surgery, as previously established by the Vascular Events in Noncardiac Surgery Patients Cohort Evaluation (VISION) study (Botto et al., 2014). Prevention from MINS is important as all-cause perioperative mortality is the third most common cause of death in the United States (Douketis et al., 2015, Schulman et al., 2015, Pollack et al., 2015) with an expected increase in cardiovascular complications associated with increasing life expectancy of the population (Devereaux et al., 2017). In the past decade, clinical trials have been unsuccessful in demonstrating effective perioperative therapeutic approaches aimed to reduce MINS including statins, beta-blockers, and clonidine, among others population (Devereaux et al., 2017). Recently, the (Myocardial Injury after Noncardiac Surgery) MANAGE trial had reported that the use of dabigatran (110 mg twice daily) was safe and efficacious compared with placebo in reducing major vascular events among patients that had already developed MINS (Devereaux et al., 2018). Dabigatran is an oral, reversible thrombin inhibitor that specifically inhibits both free and clot bound thrombin and thrombin induced platelet activation (Kanuri & Kreutz, 2019, Oldgren et al., 2011). Dabigatran is primarily used to reduce the risk of stroke in non-valvular atrial fibrillation, prevent from deep vein thrombosis and pulmonary thromboembolism (Kanuri & Kreutz, 2019) and preferred for patients with high stroke and thromboembolism risk and low bleeding risk (Kanuri & Kreutz, 2019). High-sensitive cardiac TnT (hs-TnT) detects cTnT levels and more regularly used in the diagnosis of myocardial infarction, prognostic discrimination and risk stratification for cardiovascular events and mortality in both patients with stable coronary artery disease and the general population (Haider et al., 2017). However, to the best of our knowledge, evidence related to whether any effective drug may prevent the occurrence of MINS in the postoperative setting is still lacking. Therefore, we propose a randomized, single-center, two-arm (1:1 ratio), active-controlled, double-dummy, phase II trial of dabigatran for MINS prevention in a high cardiovascular risk population. Active-controlled double-dummy design allows to reduce observer's bias and placebo effect with the concealment of obvious difference in oral administration of dabigatran and enoxaparin injection.

Objectives

The main objective is to determine whether administration of dabigatran 150 mg bid starting six hours following surgery for a one-week period will

significantly reduce the occurrence of MINS compared to VTE prophylaxis with enoxaparin among patients at high cardiovascular risk who undergo elective orthopedic surgeries (knee and hip replacement).

Study design

This phase II trial will be an investigator-initiated, single-center, randomized, parallel, two-arm (1:1 ratio), active-controlled and double-blinded with double-dummy where active group will receive dabigatran/placebo-powder vs control group will receive VTE prophylaxis/placebo-injection. Active-controlled (enoxaparin) superiority trial design was chosen because of 1). our objective to study the efficacy and safety of dabigatran for a prevention from MINS in the context of no prior evidence of any known drug to reduce the incidence of MINS after orthopedic surgeries, to the best of our knowledge and 2). the use of placebo is unethical when standard-of-care (enoxaparin) exists for a VTE prophylaxis.

METHODS

Study setting

The study population will be sampled by tertiary care hospitals, in patients who will undergo elective orthopedic surgery. The hospital to conduct this trial must have a specialized orthopedic surgery department with adequate resources of expertise: at least one nurse per 5-patients, one cardiologist and internal medicine clinician per 10 patients at a time in addition to surgery-performing anesthesiologists and surgeons. For the analysis of data, a team of 5-8 biostatisticians will be required.

Eligibility

The inclusion criteria are, patients both gender, age ranging from 45 to 75 years, with a high cardiovascular risk (> 20% Framingham risk) and be scheduled to undergo elective orthopedic surgery which would require hospitalization for more than 24 hours. The creatinine clearance level is the part of eligibility criteria to protect the patients with renal insufficiency and ensure the validity of the trial results. Because around 80% of bioavailable dabigatran in serum is excreted through kidneys (Oldgren et al., 2011), renal insufficiency potentially leads to a drug bioaccumulation, thus, increase a bleeding risk and exacerbate pre-existing renal conditions (Sciascia et al., 2017). The exclusion criteria are: absolute contraindications to anticoagulation, existing indication of anticoagulation, creatinine

clearance (CrCl) < 50mL/min/m², dual antiplatelet therapy (DAPT) including the combination of aspirin (COX-1 inhibitor) with P2Y₁₂ antagonist (i.e., clopidogrel) or PDE inhibitor (i.e., dipyridamole) or GPIIb/IIIa inhibitor (i.e., eptifibatid) or PAR-1 antagonist (i.e., vorapaxar) (Oldgren et al., 2011, Wilson et al., 2017) elevated preoperative troponin and immediate postoperative troponin elevation prior to randomization, mechanical prosthetic heart valve (Eikelboom et al., 2013), severe infection, uncontrolled hypertension, known hypersensitivity to dabigatran or participating in another trial in the last 30 days.

Strategies to enhance adherence

Adherence support interventions will target both patients and health care providers (Osterberg & Blaschke, 2005). Patients will be provided with: 1). education sessions for patient and their care takers; 2). provision of medications by trained nurses for a direct monitoring and mental support. Additional measures to improve adherence in the follow-up period will include: 1). assistance in clinic scheduling and provision of free transportation, and assisted parking for all clinical appointments; 2). short wait period and extended hours of admissions. Health care providers will receive 1). education sessions of adherence objectives and interventions; 2). capacity building sessions to enhance the communications between health care providers and patients. In addition, the adherence to study protocol and drug intake will be actively monitored using a mandatory daily medication chart detailing the time, date, barriers in timely medications, and potential adverse effects. Patients who are prematurely discharged from the hospital before the trial end will be asked to complete the same medication chart completed by the patients who stayed hospitalized through a complete seven-day period. This chart will be used to assess the adherence to a medication of the trial

Intervention and timeline

The patients who have no MINS will be allocated to one of the arms (dabigatran or VTE prophylaxis with enoxaparin). All patients will receive proton pump inhibitors to reduce the risk of major gastrointestinal bleeding in both arms. In the patients with orthopedic surgery conducted under neuraxial anesthesia, the dabigatran/placebo intervention will start four hours after removal of the catheter to avoid neuraxial hemorrhagic complications (Majeed et al., 2013). The intervention will continue for seven days and the treatment group will receive dabigatran 150mg bid and placebo injection to for enoxaparin injection while the

control group receives enoxaparin and placebo pill for dabigatran. During this seven-day intervention period, troponin levels will be measured daily and afterward weekly until the end of the 30-day follow-up period. For monitoring purposes, creatinine clearance (CrCl) and activated partial thromboplastin time (aPTT) will be measured before surgery, and during the 4th and 15th day after surgery.

Outcomes

The primary outcome will be the incidence of MINS. The secondary outcomes will be 30-day mortality, major thromboembolic complications, and severe bleeding complications.

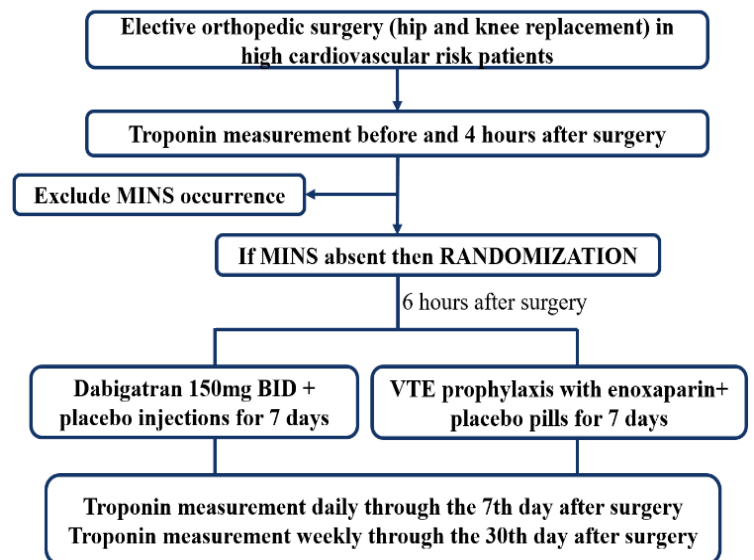


Fig. 1. Randomization and follow-up.

Sample size

According to George et al., the incidence of MINS in patients with high cardiovascular risk, such as coronary artery disease, has been estimated to be up to 29%, and specifically in orthopedic interventions, where it can be up to 19% (George et al., 2018). VISION cohort identified that cardiovascular disease is an independent predictor of MINS and adjusted Hazard Ratio that ranges from 1.34 for diabetes to 1.92 for peripheral vascular disease (Botto et al., 2014). Taking 19% times the expected increase in incidence derived from the averaged hazard ration of 1.64, we expect 31.16% event rate in our target population. The trial compared 150mg BID dabigatran to enoxaparin reported effect size of up to 17.4 for venous thromboembolism and 18.3 for deep venous thrombosis (Eriksson et al., 2005). Taking conservative approach for an effect-size and considering minimum clinically significant difference, we expect 16% difference between two groups. This means 250 patients in total is required

to obtain 80% power at 5% statistical significance level. After allowing 10% potential dropout, our trial needs 264 participants where 132 patients allocated each arm.

Sampling and Recruitment

Cardiologists, internal medicine clinicians, anesthesiologists, and surgeons will refer potential participants. All patients will receive informed consent. Those patients who meet the trial's eligibility criteria will be recommended for a preoperative troponin screening. Eligible patients who had no elevation in preoperative and immediate postoperative troponin level will be randomized to either treatment or control groups. Eligible patients who had no elevation in preoperative and immediate postoperative troponin level will be randomized to either treatment or control groups. The trial will aim to recruit in total of 264 patients in both arms in approximately 6 months.

Randomization and allocation concealment

All potential participants who consent for the trial will be screened for troponin levels before and four hours after the surgery to rule out the presence of MINS prior to randomization (see Figure 1). Patients whose postoperative troponin delta ≥ 14 ng/L levels will be excluded from the trial. Eligible patients (without MINS) will be randomized to receive either dabigatran 150mg BID or standard-of-care (enoxaparin) using 1:1 allocation ratio. Randomization will be performed by a centralized, computer-generated allocation sequence. Allocation concealment will be ensured by the computerized randomization internet system. To ensure equal distribution of the patients by the level of cardiovascular risk between the trial groups, blocked randomization will be used. The trial-group assignments will be concealed from the patients, clinicians, investigators, trial statisticians, and the members of the data and safety monitoring committee.

Blinding

Investigators and patients will be masked to treatments in a double-dummy fashion, whereby subjects randomized to receive dabigatran were given dabigatran and enoxaparin placebo injection, and subjects randomized to receive enoxaparin were given enoxaparin injection and dabigatran placebo.

Statistical analysis

Categorical variables will be described as frequency or percentages, while continuous variables will be described as means/standard deviations or medians/interquartile

ranges, according to the sample distribution. The primary outcome, the incidence of MINS in the groups, will be analyzed by Fisher exact test or Chi-square test. For the secondary outcomes 30-day mortality, major thromboembolic complications and severe bleeding, all categorical and binary, Fisher exact test or Chi-square test will also be used. The levels of troponin in the groups, also a secondary outcome will be analyzed with the Mann-Whitney test, as a right-skewed distribution is expected. A logistic regression model will be constructed with an incidence of MINS as a response variable and age, sex, prior cardiovascular events or stroke, surgery duration, smoking and diabetes mellitus for predictor variables. For the regression analysis, forced entry will be used, associated with the Wald statistics with significance level at 0.05. Adjusted ORs for the model will be reported. All the tests will be two-tailed, and a $p \leq 0.05$ to decide statistical significance.

The data will be analyzed on per protocol and intention-to-treat principles with description of dropout reasons as occurred. Sensitivity analysis will be performed if loss in follow-up is more than 10% to evaluate the extent of its impact on the validity of the final results. Interim-analysis will not be conducted due to 7-day short-term intervention period.

Monitoring and management plan of potential problems and adverse effects

The data and safety monitoring committee will oversee the conduct of the trial. The trial center will be provided with a general guideline for the monitoring and management of adverse events and encouraged to modify to the local contexts. The guideline shall specify the name of attending physicians to call for the management of adverse events in an emergency, instruction for unblinding and access dabigatran antidote (idarucizumab-Praxbind®), standard emergency assistance for the patients who received active control (enoxaparin). The trial physician will assess the attributability of adverse events either to the intervention (unrelated, unlikely, possible, probable and definite related) or other factors unrelated to the intervention and status code (whether adverse events worsened or improved from the baseline). Based on the Common Terminology Criteria for Adverse Events (CTCAE) attribution standards, subjects who develop suspected unexpected serious adverse reactions (SUSARs) will be unblinded to treatment and so will study staff.

I. Bleeding during the intervention period

A major and directly attributable adverse effect of dabigatran, as with other anticoagulants, is

gastrointestinal, cranial and stromal bleeding. In RE-LY trial (Connolly et al., 2009) and its sub-study trial (Douketis et al., 2015), the 30-day incidence of major bleeding among patients treated with dabigatran 150 mg twice daily vs dabigatran 150 mg once daily was reported 3.8% vs 1.8% respectively. However, major bleeding risk has been anticipated to be lower in our trial due to the shorter duration of intervention (7-day).

A major bleeding episode in this trial will be defined and identified according to the International Society on Thrombosis and Haemostasis (ISTH) criteria (Majeed et al., 2013, Connolly et al., 2009) as a reduction in the hemoglobin level of at least 20 g per liter, transfusion of at least two units of blood, or symptomatic bleeding in a critical organ. Extra caution will be exercised in the monitoring of older patients (Miller et al., 2012) and those who underwent neuraxial anesthesia and spinal punctures, due to an increased risk of hemorrhage (Schulman et al., 2015).

Given the short half-life of 12–14h of dabigatran, hemostasis is adequately restored in 1-2 days after the withhold of dabigatran in mild to moderate bleeding. However, in the event of major bleeding (also commensurate with CTCAE's grade 3 or 4), dabigatran/placebo will be held while emergency unblinding is facilitated. Intravenous administration of idarucizumab (antidote of dabigatran) will be recommended to the dabigatran arm patients, by two consecutive 2.5-g infusions (Pollack et al., 2015) to reverse the major bleeding in an emergency.

II. Renal impairment/failure during the intervention period
The Cockcroft-Gault formula will be used to calculate the estimated creatinine clearance. Subjects whose creatinine clearance are < 50 mL/min at any measurement point, will not be eligible to receive dabigatran treatment, thus, excluded from the trial. Patients identified with renal impairment will receive therapeutic measures at the discretion of the local medical team.

III. Additional surgery during the follow-up period
Time to complete hemostasis restoration is proportionate to the state of renal function (Majeed et al., 2013). Therefore, the timing and decision for stopping dabigatran/placebo study drug for those patients who need additional elective surgery during the intervention will be decided based on renal function and the elective surgery-related risk of bleeding, as recommended by Schulman et al., 2015 (Schulman et al., 2015). Dabigatran/placebo will be held if a patient requires urgent surgery during the intervention period. For patients who require therapeutic anticoagulation after the intervention period of the trial, the chosen

anticoagulant is recommended to start at least 12 hours after the last dose of dabigatran/placebo or when aPTT is <1.5 times the upper limit of normal (Sunkara et al., 2016).

DISCUSSION

Potential limitations

Difficult recruitment due to bleeding risk: in this trial, we will use full-dose anticoagulation with dabigatran 150mg twice daily. Safety of dabigatran has been evaluated in a dose-finding trial (Eriksson et al., 2004), and safety and efficacy for deep vein thrombosis in orthopedic surgeries population (Devereaux et al., 2017, Eriksson et al., 2005, Eriksson et al., 2007). Long-term clinical trials reported increased minor bleeding and clinically non-significant lower gastrointestinal bleeding during the two-year administration of dabigatran population (Devereaux et al., 2017, Connolly et al., 2009). Also, 33-day intervention trial to reduce VTE after orthopedic surgeries reported a statistically insignificant increase in major bleeding events in the dabigatran group compared with the enoxaparin group (Eriksson et al., 2007). However, benefit from reduced MINS and VTE which attributes to a significant portion of morbidity and mortality following orthopedic surgeries (Eriksson et al., 2005, Cionac Florescu et al., 2013) is provided with anticoagulation treatment. In cases of severe bleeding, dabigatran treatment will be immediately discontinued, and patients will receive 5g of intravenous idarucizumab, an approved monoclonal antibody fragment, developed to reverse the anticoagulant effect of dabigatran. The responsible site personnel will be adequately trained to correctly address this topic when discussing with the patient prior to informed consent and to act efficiently and in a timely manner in case the bleeding occurs. Combination of 1). short-period intervention; 2). use of anticoagulant antidote; 3). capacity building of trial staff in prevention and management of bleeding will reduce bleeding risk and the extent of its complications. In addition, proton pump inhibitors will be used among both arms for prevention from bleeding.

Uncertainty in the causal linkage of MINS and the observed mortality: according to the POISE trial (n=8,351), 11.6% of mortality cases were attributable to MINS alone population (Devereaux et al., 2017, Mauermann, Puelacher, & Lurati Buse, 2016). Patients who developed MINS have an increased rate of 30-day and 1-year mortality. Myocardial infarction due to MINS doubles the 30-day mortality risk compared with non-operative myocardial infarctions in the emergency room. However, the causal relationship between MINS and

mortality is still unclear. Nevertheless, MINS had been known to be reversible with appropriate and timely interventions in contrast with myocardial infarction due to non-operative causes. Therefore, an urgent solution is needed given that MINS is often undetected due to a lack of clinical manifestations unless systematic screening is conducted.

High sensitivity troponin assays, low-detection limit, and variability: it is recommended that all investigators participating in the clinical trial use the same assay in order to reduce the inter-assay variability. To decrease the variability, a central laboratory using the same assay for all measurements will be in place.

Strengths and future perspective

The incidence of MINS was reported to be 5-8%, making it a frequent complication (Botto et al., 2014, Coetzee et al., 2018) in the post-operative scenario, associated with a 4-time increase in mortality population (Devereaux et al., 2017). Due to this clinical significance, proper treatment and prophylaxis for MINS are necessary. Dabigatran is an oral anti-thrombin anticoagulant that has proved to be efficacious in decreasing the incidence of major cardiovascular events in patients who had already developed MINS (Devereaux et al., 2018). However, there is no evidence that prophylactic anticoagulation with dabigatran could benefit this population. The DMINS-PRE trial is the first to propose the use of dabigatran to prevent myocardial injury in patients undergoing non-cardiac surgery. The proposed short-term intervention favors recruitment and feasibility of ensuring time-cost efficiency. In the past few years, thrombin has shown to be generated within the atherosclerotic plaque and has been associated with upregulation of endothelial adhesion molecules, lipid peroxidation, and the production of reactive oxygen species (Kremers). However, the post-operative myocardial injury may not be completely avoided by thrombin inhibition. A broad intervention considering the multiple pathways involved in its pathophysiology is probably the optimal approach. Should this trial present with positive results, a phase III trial is mandatory to confirm its findings. Also, although the incidence of MINS is higher in the first postoperative days, a longer follow-up should be taken to assess long-term morbidity and mortality in these patients.

CONCLUSION

The DMINS-PRE trial is a randomized, active-controlled, phase II study that aims to assess the efficacy and safety of dabigatran as a new therapeutic target for post-operative myocardial injury. Up to this time, perioperative cardiovascular mortality is one of the

leading causes of death in the United States and a prophylactic approach to this significantly increasing population is still an unmet need

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Conflict of interest and financial disclosure

The authors followed the International Committee or Journal of Medical Journals Editors (ICMJE) form for disclosure of potential conflicts of interest. All the listed authors approved the contents of the manuscript. The authors have no financial or personal conflicts of interest to declare.

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