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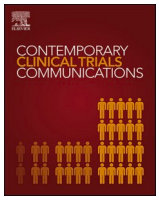

Anticoagulation in type 2 myocardial infarctions: Lessons learned from the rivaroxaban in type 2 myocardial infarctions feasibility trial

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ABSTRACT

Background: Type 2 myocardial infarction (T2MI) occurs when myocardial oxygen demand exceeds myocardial oxygen supply. T2MIs occur more frequently and have worse outcomes compared to Type 1 myocardial infarction caused by an acute plaque rupture. No clinical trial evidence is available to guide pharmacological therapies in this high-risk population.

Methods: The Rivaroxaban in Type 2 Myocardial Infarction (R2MI) trial (NCT04838808) was a trainee-led, pragmatic, pilot study that randomised patients with a T2MI to either rivaroxaban 2.5 mg twice daily or placebo. The trial was stopped early due to low recruitment. Investigators explored the challenges of conducting the trial in this population. This was supplemented by a retrospective chart review of 10,000 consecutive troponin assays undertaken during the study period.

Results: Over a 1-year period, 276 patients with T2MI were screened for inclusion of which only 7 (2.5%) were randomised in the trial. Study investigators identified trial design and participant population factors that limited recruitment. These included: heterogeneity of patient presentation, poor clinical prognosis, and lack of dedicated non-trainee study personnel. The major limitation to recruitment was the frequency of identified exclusion criterion. The retrospective chart review identified 1715 patients with an elevated high-sensitivity troponin level, of which 916 (53%) were adjudicated to be related to T2MI. Of these, 94.5% possessed an exclusion criterion for the trial.

Conclusion: Patients with a T2MI are challenging to recruit into clinical trials involving oral anticoagulation. Future studies should account for only ~1 in every 20 screened individuals being a candidate for study recruitment.

1. Background

Type 2 myocardial infarctions (T2MI) occur when myocardial oxygen demand exceeds myocardial oxygen supply, frequently described as demand ischemia [1]. This can occur in a variety of settings, such as overwhelming infection, tachyarrhythmia, hypertension and hypotension, severe hypoxia, and anemia. High sensitivity troponin assays have increased our ability to detect myocardial ischemia. Studies using these highly sensitive assays suggest that the incidence of T2MI is higher than Type 1 myocardial infarctions, accounting for ~35% of troponin elevations, compared to 26% for Type 1 myocardial infarction (an additional 38% of troponin elevations were assigned to multifactorial causes) [2]. T2MIs demonstrate rates of adverse cardiovascular outcomes that are equivalent or worse than Type 1 myocardial infarctions [2–4]. However, there are no robust clinical trials to guide management in this population.

Direct oral anticoagulants, at a range of doses, have been studies in a variety of cardiovascular populations, with the hypothesis that

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atherothrombotic events occur due to both platelet and activation of the coagulation cascade. As such, treatment regimens that utilise both an antiplatelet and antithrombotic may be more effective at reducing subsequent atherosclerotic complications. In the Management of Myocardial Injury After Noncardiac Surgery (MANAGE) trial demonstrated that anticoagulation with 110 mg of dabigatran twice daily in patients with myocardial injury after non-cardiac surgery reduced the risk of major vascular complications, without significant increase in bleeding [5]. Approximately half of all MANAGE trial participants were concomitantly on aspirin. In the Cardiovascular Outcomes for People using Anticoagulation Strategies (COMPASS) trial demonstrated that, in patients with atherosclerotic vascular disease, anticoagulation with rivaroxaban 2.5 mg twice daily combined with acetylsalicylic acid (ASA), compared to ASA alone, reduced the risk of major adverse cardiovascular outcomes, though there was an associated increase in major bleeding [6]. From these two trials, two key points can be taken away. 1 – In patients with myocardial injury after non-cardiac surgery, a potential etiology for a T2MI, moderate dose anticoagulation ± aspirin was effective at lowering cardiovascular complications. 2 – In patients with known coronary artery disease, low-dose anticoagulation with aspirin was effective at reducing adverse cardiovascular outcomes.

We extended the premise that dual pathway inhibition and hypothesize that the addition of antithrombotic may be effective in patients with a T2MI, who are known to have a high burden of underlying coronary artery disease.

We designed a feasibility clinical trial to explore the feasibility of the use of low-dose anticoagulation as a secondary prevention therapy in patients with a T2MI. This trial failed to meet its recruitment targets. In this article, we explore the feasibility of recruiting adults with T2MI for therapeutic trials, based on the results of our study and a subsequent chart review of patients with elevated troponins.

2. Methods

The Rivaroxaban in Type 2 Myocardial Infarction (R2MI) was a trainee-led, feasibility trial at a single tertiary care hospital in Canada (NCT04838808). All aspects of the trial including design, regulatory, screening and recruitment were conducted by internal medicine and cardiology trainees, with support from academic faculty. Participants were included if they had a rise in troponin above the 99% percentile, that was deemed by their attending or consulting care providers to be T2MI. Additional inclusion criteria included age >65 years or >45 years with additional cardiovascular risk factors (current smoking, diabetes, hypertension, dyslipidemia, established atherosclerotic disease). These additional inclusion criterions were utilized to select a patient population that was at higher risk of atherosclerotic events. Exclusion criteria included: Use of anticoagulation or dual antiplatelet therapy, severe kidney disease (eGFR <15 ml/min/1.73 m^2), any previous hemorrhagic stroke, embolic stroke within the past year, previous life-threatening bleeding, life expectancy less than one year, or surgery in the previous 30 days. Participants were randomised using a variable block randomization system to rivaroxaban 2.5 mg twice daily or placebo for 90 days starting on hospital discharge. All other therapies, including ASA use, were at the discretion of the care team. Participants were followed-up at 90 days. The primary outcome was time to recruitment of 100 patients and secondary exploratory outcomes included a composite of death, stroke, myocardial infarction and major bleeding. Outcomes assessors and statisticians were blinded to treatment arms. The trial was approved by the University of Alberta Research Ethics Board (Pro 00105055).

The trial was stopped early after one year due to low recruitment. To explore feasibility of future trials in this population, the study team discussed and highlighted challenges that faced this trial. This was undertaken by in-person and online discussions with all study members, both informally and during scheduled study investigator meetings. A summary of these conversation is provided in a narrative format. This was supplemented by a retrospective chart review of a convenience sample of 10,000 consecutive troponin results (Beckman Coulter Access high sensitivity troponin I assay, manufacturer suggested 99th percentile upper reference limit (URL) is 18 ng/L) from June 2021–June 2022, to identify the incidence of trial exclusion criterion. This chart review was undertaken electronically at the same institution as the trial.

3. Results

3.1. Brief trial results

Between March 2021 and April 2022, 276 participants were screened for enrollment of which 52 (18.9%) declined to participate, 199 (72.1%) had an exclusion criterion and 18 (6.5%) were excluded at the investigators' discretion. Examples of these non-protocolized exclusions included: planned upcoming outpatient surgery, known cerebrovascular malformations, history of non-compliance or of no fixed abode, ongoing intravenous substance misuse. Ultimately, 7 participants (2.5%) were recruited into the clinical trial of which three participants were randomised to the rivaroxaban group and four to placebo. No adverse cardiovascular or bleeding events occurred during 90-day follow-up.

3.2. Retrospective chart review

Of the 10,000 troponin results screened, we identified 1715 unique patients with a troponin level above the 99% of normal (Fig. 1). After adjudication, 799 (47%) did not have a T2MI. These included: patients with myocardial injury (without infarction) – 273; Type 1 MI – 268; non-MI etiology of troponin elevation such as myocarditis or stress-induced cardiomyopathy −174; pediatric – 45; unclear etiology of MI – 39). Of the remaining 916 (53%) patients adjudicated to have a T2MI, the most responsible etiology was: hypoxia (n = 253); hypotension (n = 112); stroke (n = 104); sepsis (n = 104); anemia (n = 96); tachycardia (n = 96); heart failure (n = 93); post-operative stress without another clear precipitant (n = 79); hypertension (n = 39); bradycardia (n = 11). Of these T2MI patients, 50 (5.5%) met all inclusion criteria and none of the exclusion criteria, with 534 (58.3%) having one exclusion criteria, 250 (27.3%) having two and 82 (9.0%) having three or more. The most common exclusion criteria were current use/indication for anticoagulation (38.6%), in-hospital death (20%) and recent major surgery (17.2%) (Fig. 1).

4. Discussion

T2MIs are the most common etiology of an elevated troponin result in the adult population, representing more than half of all positive troponins. In our retrospective chart review, we have corroborated this with T2MI representing the most common etiology (53%) of a troponin elevation. No randomised trials have identified therapies to be effective in this population. While low-dose anticoagulation is a biologically plausible effective treatment in this population, a large-scale, collaborative trial would be required to assess this.

Through both formal and informal discussions with study team members a number of challenges and barriers to this trial were identified. Identified challenges fell into several categories including trial design factors and patient population factors. With regards to trial design factors, the major limitation was the lack of ability to systematically screen for patients with T2MI in a pragmatic fashion. We explored the feasibility of screening all positive troponins at our institution (tertiary care centre), which identified 640 patients with an elevated troponin >99% over the span of one week. Given this volume of troponin assays, screening this proportion of patients was felt to be infeasible without a dedicated research coordinator. Our trial aimed to use trainee recruiters to identify and consent participants. While trainee recruiters demonstrated significant skill and knowledge to undertake this task, they lacked a consistent schedule (due to constantly changing clinical rotations) and dedicated time. Partial support from a dedicated

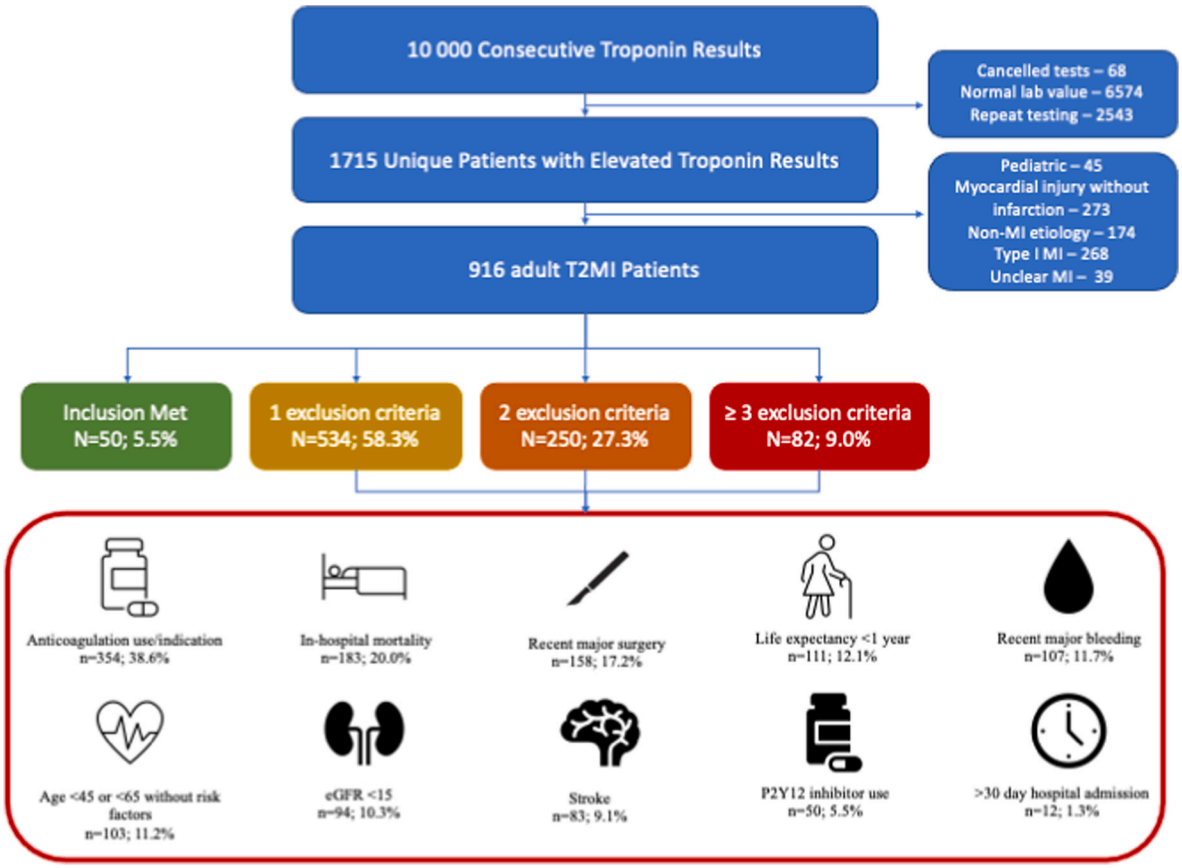

Fig. 1. Retrospective chart review of troponin elevation.

trial coordinator may improve this for trainee-led trials.

With regards to the patient population, a major challenge was the heterogenous presentations of patients with T2MI. Concomitantly, with the increasing use of high sensitivity troponins we are seeing the challenges of interpreting positive troponin levels, that are inappropriately ordered. In the era of high sensitivity troponins, inappropriate ordering is estimated to range from 30 to 45% [7,8]. There is evidence that there are Patients with a T2MI are seen in all hospital areas, including the emergency department, the intensive care unit, medicine wards and surgical wards. In the emergency department, patients with a positive troponin were not yet differentiated – the etiology of the troponin rise was often unclear. In the intensive care unit, patients with a T2MI were frequently critically ill, high-risk for bleeding and had an unclear prognosis. In both of these settings, trainee investigator still attempted to capture these patients for later follow-up in hospital, but patients were sometimes lost to follow-up (due to transfer to other acute care facilities, long-term care facilities, etc.). Patients admitted to the surgical ward were frequently observed to have a T2MI due to their presenting etiology (hypotension, tachycardia, sepsis), prior to a planned surgical procedure. However, as they were expected to undergo surgical intervention, they were excluded from our study. Most of our patients were recruited from medicine wards under the care of internal medicine specialists and hospitalists. This setting had unique challenges, not all of which are captured by our exclusion criterion. Many patients cited an already high medication burden, limiting their willingness to participate. There were also a higher proportion than expected of patients with a T2MI with cognitive impairment, were of no fixed residence or who were admitted with substance misuse. However, the largest limitation was felt to be that the vast majority of patients with T2MIs screened had an exclusion criterion.

Successful trials in this challenging population will require several characteristics. 1 – Multi-site recruitment: Depending on the intervention of interest and associated risks, a large sample size with necessitate multiple high-volume sites to achieve an acceptable recruitment rate. 2 – Multidisciplinary planning committee – our experience demonstrated that patients with T2MI are cared for in multiple hospital settings. As such recruitment strategies should be developed in consultation with a wide range of health care providers from various specialties including: family medicine, internal medicine, geriatrics, cardiology, surgery, intensive care and emergency medicine. 3 – Appropriate screening strategy – There is a delicate balance in choosing an appropriate screening population. A strategy of screening all troponins is very labour intensive but would capture all patients. On the other end of the spectrum screening only patients in which the cardiology service has been consulted, would lead failure to capture a large proportion of patients. An appropriate strategy may be balance between these two, screening all troponin values on general medicine wards. This may vary in different jurisdiction and will require local investigator input. Additionally, T2MI has recently been added to the newest iteration of International Classification of Diseases (ICD-10 code I21. A1). This may provide a novel recruitment strategy through electronic medical records. 4 – Distinction of type two myocardial injury versus infarction – Myocardial infarction versus injury is distinguished by the presence of clinical evidence of ischemia by history, imaging or electrocardiographically. Both populations of type two myocardial injury or myocardial infarction demonstrate similarly elevated risk of subsequent cardiovascular complications [9], however it is unclear if both would demonstrate similar treatment effects for any proposed future therapies. Optimising this definition has direct implications on the generalisability of future trial results and ease of recruitment.

In addition, while trainee participation in clinical trials should be encouraged, it is necessary that sufficient infrastructure and personnel support are available when taking into consideration the complexity of the trial. Future trials should account for the fact that for every 20 T2MI

patients screened, only one (~5%) may be a candidate for an anti-coagulation trial.

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: All authors declare no conflict of interest. This work was funded from a competitive research grant competition – the CCS-Bayer Cardiovascular Research Award which was awarded to Pishoy Gouda. The sponsor had no input in the design or conduct of the study.

Data availability

Data will be made available on request.

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