TC4

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Ticagrelor compared to clopidogrel in acute coronary syndromes - the TC4 comparative effectiveness study

TC4 Research Protocol

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Hypothesis to be tested

We are proposing a novel randomized clinical trial (RCT) to investigate which dual antiplatelet therapy (DAPT) strategy is superior following an acute coronary syndrome (ACS). The trial acronym, a necessity for all good trials (!), is TC4 (Ticagrelor compared to clopidogrel in ACS).

Our null hypothesis is that there will be no clinical differences in CV outcomes between patients randomized to ticagrelor or clopidogrel.

Specific goals to be investigated are as follows;

1. The primary objective will compare the composite outcome of total mortality, myocardial infarction (MI), or stroke at 12 months in the two treatment arms (primary hypothesis).

2. A secondary objective will compare the individual outcomes of total mortality, acute MI stroke, major bleeding requiring hospitalization, recurrent coronary revascularizations, patient drug compliance and drug side effects at 12 months in the two treatment arms (secondary hypothesis).

3. A secondary objective will compare the primary outcome according to gender at 12 months in the two treatment arms (secondary hypothesis).

4. A tertiary objective will compare the composite outcome of total mortality and rehospitalization for acute MI at 36 months in the two treatment arms (tertiary hypothesis not to be funded with this grant proposal).

5. Another tertiary objective will be to perform a quality of life and cost-effectiveness of the competing interventions (tertiary hypothesis not to be funded with this grant proposal).

Knowledge to date

1) Role of dual antiplatelet therapy in ACS ACS is most often caused by an erosion or rupture of an atherosclerotic plaque associated with inflammation, thrombus formation, vasoconstriction, and microembolisation. In unremitting circumstances, thrombosis at the site of plaque rupture or erosion leads to complete compromise of coronary blood flow and ultimately myocardial infarction (MI). Platelet adhesion, activation and aggregation therefore play key roles in the transformation of a stable atherosclerotic plaque to an unstable lesion. Platelet aggregation can proceed by several different mechanisms but the most important mediators appear to be thromboxane A2 and adenosine diphosphate (ADP). Aspirin permanently

acetylates platelet cyclooxygenase 1, thereby blocking the synthesis of thromboxane A2 and inhibiting platelet aggregation. Thienopyridine derivatives, of which clopidogrel was one of the first commercial entities, bind to the platelet P2Y12 receptor thereby blocking the ADP dependent mechanisms of platelet activation.
Against this pathophysiological background, it is not surprising that antiplatelet drugs have become a mainstay in the prevention of recurrent cardiovascular events. The Antithrombotic Trialists' Collaboration Group[1] reviewed 16 studies of aspirin (total of approximately 20,000 patients) following MI and found a greater than 25% reduction in vascular outcomes with aspirin. In 4 RCTs[2-5] of more than 63,000 ACS patients, clopidogrel has been shown to improve CV outcomes beyond aspirin by 10-20%. Based on the consistency and strength of this evidence, clopidogrel and aspirin, combined known as dual antiplatelet therapy (DAPT), with or without percutaneous coronary intervention (PCI) revascularization, has become a pillar of the contemporary ACS treatment and is recommended by all professional society guidelines[6-8].

However, a large multicenter RCT (PLATO)[9] showed a statistically significant decrease in composite CV outcomes with the newer ticagrelor compared to clopidogrel. This has prompted both European[6] and Canadian[8] guideline writers to endorse ticagrelor / aspirin as the DAPT of choice. However residual uncertainties regarding the choice of DAPT are highlighted by the PLATO subgroup analysis[9] that showed an increased risk with ticagrelor in North America (NA) patients. This led to delayed FDA approval, dissenting FDA reviews[10] and an unwillingness of US guidelines [7] to recommend the ticagrelor DAPT regime over others.

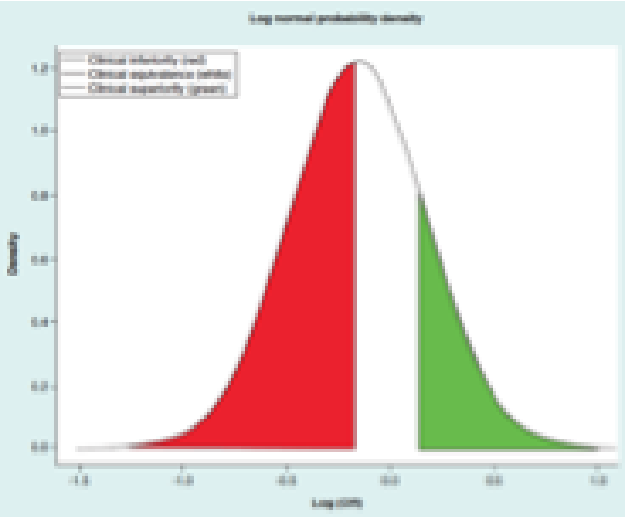
2) The specific need for another DAPT RCT Do we really need a replication study after an 18,000 patient RCT showed a statistically significant decrease in composite CV outcomes? Unfortunately, as I have demonstrated in two peer review publications, the answer is an unequivocal yes[11, 12]. While the integrity of the PLATO data has been questioned by some [13-15], the main area of uncertainty, at least from a NA perspective, hinges on the small number of NA patients randomized in this trial and their increased risk with ticagrelor (n=1814, HR 1.25; 95% CI 0.93 - 1.67). The risk in NA patients was statistical significantly different from the benefit seen in the other subgroups (p=0.04) and the crux of the debate is then whether to believe the subgroup analysis or the combined study results (n=18624, HR, 0.84; 95% CI 0.77 to 0.92). The complete study provides maximal information but perhaps at a cost of being less representative of what to expect in NA practice. Conventional statistical paradigms would say that given the pre-specified nature of the geographic subgroup analysis and given the statistically significant interaction observed, one should concentrate on the subgroup results and not the combined results.

However, the FDA by approving the drug ultimately did not share that view. Unfortunately, the FDA did not provide any qualitative logic or guidance on how they integrated these apparently disparate results and arrived at their regulatory decision. The conventional statistical model used in the PLATO analysis subsumes that every patient, regardless of differences in recruitment characteristics or ancillary treatment strategies received in the different regions, is completely identical in their response to the studied intervention. It seems highly unlikely that patients from the 43 PLATO enrolling countries are truly identical in their drug response given recruitment, genetic and background treatment variations. For example, while not reported in the original NEJM article[9], the FDA review shows a statistically significant negative interaction between ticagrelor and early PCI (HR 1.32, 95% CI 1.02 – 1.73). In other words, patients undergoing early PCI has worse outcomes when randomized to ticagrelor. As early PCI is the norm in NA patients, this raises the distinct possibility that the overall superiority results with ticagrelor in PLATO study may not be applicable to NA patients. While this or any other subgroup analysis does not prove that interactions between the interventions and the health care system exist, it does support the notion that such potential interactions merit at least serious reflection and thoughtful consideration. The question then becomes how to weight the relative strengths of a consolidated single analysis of all the data (an underparameterized model) with a separate analysis that considers each group to be completely independent (an overparameterized model)?

A method to sort out this conundrum is hierarchical analysis. This method by considering the subgroups not to be identical but rather exchangeable avoids being restricted to the extreme interpretability positions of considering all regions to be identical or totally distinct. Hierarchical analysis defaults to the identity model when there is no between group variability. As the between group variability increases so does the weight given to each separate subgroup. This borrowing of information tends to move the extreme NA subgroup

more towards the study mean [11] but by acknowledging between group variations, the uncertainty around the overall population mean result increases. Thus simply changing the statistical model to the more reasonable hierarchical (random effects model) while using the same PLATO data results in a similar combined point estimate of 0.86 but with 95% CI 0.49 to 1.60. It is worth taking a moment to fully understand what these intervals from the 2 different models are actually providing and recognizing the important differences. For the original NEJM analysis, the point estimate and confidence interval have assumed no between region variation and the result thus provides the best estimate of a common treatment effect, and the confidence interval depicts the uncertainty around this estimate. For the hierarchical model, the point estimate and confidence interval have acknowledged the between region variation and the result provides an estimate of the average treatment effect, and the confidence interval depicts the uncertainty around this estimate. Ignoring heterogeneity, such as possible regional variation, may lead to a false sense of certainty with an overly precise summary result (that is, the confidence interval is too narrow) and may incorrectly imply that a common treatment effect exists when actually there are meaningful differences in treatment effectiveness across regions. Finally, as has been cogently argued by others[16] with hierarchical models it appropriate to consider not only the average result but also the prediction interval which gives the range of possible values of the next study. The prediction interval for the next ticagrelor / clopidogrel study is very wide (0.86, 95%CI 0.24 – 3.34) providing additional justification for this proposal.

The use of Bayesian hierarchical modeling also allows the formulation of probability statements.



The Figure (white area represents clinical equivalence (+/- 15%), red & green areas are ticagrelor & clopidogrel superiority), plots the average hierarchical treatment interval as a probability density function, providing further justification for this proposal as it shows that the probability of clopidogrel non-inferiority (measured as white & green area under the curve) is 52% [11, 12]. Regardless of which statistical model one believes, the DAPT evidence base in favor of ticagrelor is obviously not robust when a simple change in the analytical model leads to extreme variability in conclusions. This project will resolve these uncertainties and address the crucial clinical question of which DAPT regime is best after an ACS? The financial stakes are also high with a potential increase by switching to ticagrelor in Quebec and Canadian drug costs of $25 and $100 million annually respectively with at present great uncertainty about any clinical benefits. This proposal will double the currently available evidence with a novel research design using inexpensive, electronic data and will provide a feasible answer to this important clinical question. Our approach using a valid, inclusive, generalizable study design will enable an accurate population assessment of drug side effects and long term patient compliance which are notoriously under reported in conventional industry sponsored trials[17].

Methods t

Regulatory agencies evaluate and approve drugs based on individually clinical randomized parallel two-arm trial (RCT) evidence due to their superior validity compared to non-experimental designs. Given that standard RCTs require major financial resources, the majority of large scale trials are industry sponsored

and replication, a former cornerstone of the scientific method, has now been largely superseded by single large multinational studies. This lack of replication[18] as well as concerns of possible interactions between studies drug intervention and different healthcare systems can result in residual uncertainties even following "positive" results from large, single, comparative RCT evaluations[11, 12]. Conventional RCTs also have important limitations including inclusion/exclusion intricacies with recruitment difficulties, complexities in implementation, incomplete follow-up (especially for side effects) and high cost[17]. These limitations often reduce the feasibility of performing RCTs in everyday practice with a consequence that many routine practices are never fully evaluated or confirmed. While non-experimental methodologies can provide information in a more cost-efficient manner, the associated uncertainties, often principally but by no means limited to confounding by indication bias, is such that the gold standard design for drug assessment remains randomization. The "trick" to increasing RCTs is to employ both novel RCT designs and analytical elements to address these barriers and make trials more clinically and economically feasible.

As individual randomization may be difficult in situations where there are many clinicians involved in patient care and when rapid access to care is a priority, we have elected to use the novel pragmatic RCT cluster randomization (CR) design. This design resolves these issues and enhances practicality, efficacy, and bias reduction. A variation of the parallel group CR design is the cluster randomized crossover (CRXO) design which will control any temporal trends which might occur, for example with the rapidly evolving PCI technology. We are therefore proposing a CRXO design whereby a single center will perform 6-10 cluster periods each of 2 months duration during which all patients will receive one of the two allotted treatments regimes.

The CRXO design will simplify trial conduct, enhance overall recruitment, and generalizability while maintaining study integrity. The merits of the CRXO design have been increasingly appreciated with recent publications in several high impact journals[19, 20]. RCTs with individual randomization is logistically difficult in situations where there are many acute caregivers and where patients may be recruited in a 24X7 emergency environment as with ACS. CR, by simplifying the mechanics of randomization, avoids these problems as well as the potential bias of cross contamination while maintaining the integrity of randomization. Given that the division of cardiology (Chief of Cardiology support letter in the Appendix) has agreed that equipoise exists regarding these competing interventions, all patients who are candidates for DAPT will be eligible for the study. Also CRXO importantly portends that individual informed consent for an ACS trial can be obtained in a less urgent setting, permitting more detailed information sharing and a more thorough and meaningful researcher / patient dialogue to occur.

A CR trial usually requires a larger sample size to achieve the same power as a standard RCT due to possible correlated measures with the clusters, measured by the intracluster correlation coefficient (ICC). In our trial, the marked increased recruitment possibilities will more than compensate for this minimally decreased power. The CRXO design increases efficiency over standard CR studies. and importantly controls for any secular trends in concomitant therapies. CR trials do have diminishing returns in power and precision as cluster size increases but this may be mitigated by increasing the number of clusters as with a CRXO design[21]. The CRXO design can achieve up to 50% better power than the standard CR design[22]. Analyses must also account for the clustering to avoid the bias of overly precise estimates of the treatment effect.

A major driver of standard RCT costs is the expense of securing long term follow-up. To overcome this barrier and the vexing potential bias of lost to follow-up, we will use the novel "randomized registry" design. An early example of this design involved a non-industry sponsored, multicenter, prospective, randomized, controlled, open-label clinical trial of manual thrombus aspiration in 7244 Swedish STEMI patients undergoing PCI[23]. In this remarkable trial, over 80% of all eligible patients were recruited and the trial took only 1 year to complete. The data were monitored and adjudicated as part of a regular registry validation. A NEJM editorial[24] called this the next disruptive technology in clinical research by allowing high quality trials to be successfully and rapidly completed at a small fraction of the usual cost.

Our study will employ baseline CRXO randomization (to avoid indication bias) with follow-up using the administrative database environment of the hospital electronic medical records and the universal Quebec healthcare system, which provides validated long-term follow-up of meaningful health outcomes of all patients[25-27] at minimal costs and with which the PI has a vast experience[28-31]. Moreover, these

databases will permit the acquisition of long term outcomes (beyond 12 months) which have been previously lacking in virtually all ACS trials. More specific details on patient side effects will be obtained via the hospital's electronic medical record and data warehouse which has been built using a CFI grant.

This novel RCT design will help reinvigorate investigator / patient initiated RCTs. Scientific feasibility and replication will be enhanced as the onerous costs and difficulties of standard RCTs, current drivers of a regulatory drug approval process often now based on single studies, are addressed. There are empirical and theoretical reasons why the uncritical belief that single "positive" large scale multicenter RCTs provides a definitive window to the "truth" is suspect[12, 32-34]. For example, Drotrecogin alfa, approved without replication for severe sepsis, based on a single large multicenter trial[35] with an absolute 6% mortality benefit (!) was withdrawn in 2011 after a decade with billions of sales, when replicate studies were finally performed showing that the risks outweighed any benefits. Replication of RCTs, has historically been, and should continue to be, the cornerstone of the scientific method. The proposed novel methods will make this process more clinically feasible in our economically challenging research environment.

The recruiting hospital

This study will involve the main McGill University teaching / research hospital in Montreal, the McGill University Health Centre. This hospital has a distinguished pedigree in clinical research and is a high volume referral hub for PCI with an annual caseload of exceeding 2000-2500, which should assure recruitment within 18 months. The institution's referral patient population is approximately 1.5 million people, including 7-8 community hospitals who refer all their ACS patients. As such, the patient population is reflective of clinical practice across Quebec hospitals. Recruitment of additional centers across Quebec and Canada would add significantly to the trial complexity and cost, surpassing the funding opportunity of this competition. Moreover, there is no published evidence of any difference in ACS patients and their outcomes between Quebec and Canadian institutions. To be noted, even this single site study should more than double the current evidence base of NA patients addressing this clinical question and will ultimately allow better informed decisions to be made.

Study population

All patients hospitalized for an ACS, with or without ST-segment elevation, will be eligible to participate. For STEMI and NSTEMI positive biomarkers and appropriate ECG changes will be required. NSTEMI patients with negative biomarkers are generally considered as unstable angina and will also be eligible for study inclusion if their treating physician has determined that DAPT is appropriate. It is important to note that the entrance criteria of this study are well aligned with those of PLATO allowing synthesis of the totality of the evidence (see analysis section below).

The intervention

Patients will be randomly assigned to receive standard doses of ticagrelor or clopidogrel. Ticagrelor will be given according to PLATO dose[9] of a 180 mg loading dose followed by 90 mg BID. Clopidogrel patients will receive a 300-mg loading dose followed by 75 mg daily. All patients will receive aspirin loading dose of 325 mg followed by 81 mg daily. Patients will be encouraged to take their DAPT medication for 12 months. Patient compliance will be monitored electronically via the provincial drug formulary. This will allow for the assessment for any specific DAPT interactions, particularly with anticoagulants. This is of clinical importance since bleeding is the main adverse outcome associated with DAPT.

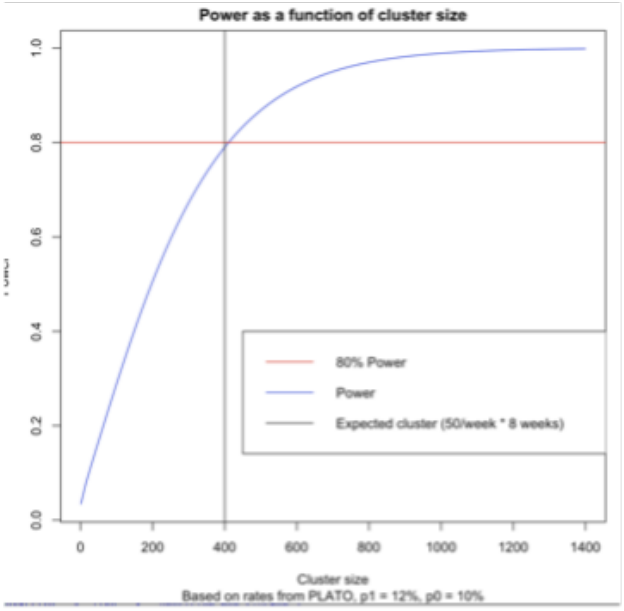
Study outcomes

The main outcome will be a composite of total mortality, myocardial infarction (MI), or stroke at 12 months (PLATO primary outcome). Secondary outcomes will be cardiovascular mortality, stroke, major bleeding requiring hospitalization, recurrent coronary revascularizations, patient compliance and drug side effects. Clinical events will be independently assessed from hospital and provincial electronic health records which have been previously validated for these outcomes[25-27]. Data extraction will be by blinded observers so the initial unblinding of treatment assignment should not result in bias. At the time of consent, patients

will also be consented to consult their electronic health records at 1 and 3 years post randomization. The ability to measure long term outcomes at 3 years, via electronic databases, is another distinctive aspect of the study and will offer a unique opportunity to assess the long term consequences of different DAPT strategies following an ACS. While the main objective of this project is the evaluation of clinical effectiveness and safety outcomes, the expertise of the team will permit future ancillary investigations into quality of life and economic sub-studies. The project will also provide unique training and research opportunities for graduate students.

Sample size calculations

As there is some similarity between individuals within the same cluster, both within the same time period and across different time periods, CR trials require an increased sample size compared to a standard individual parallel group RCT. This loss of efficiency is more than offset by a more comprehensive patient recruitment. In addition to effect size and variation, CRXO sample size calculation depends upon the number of clusters, the size of the clusters, the number of time periods, and the similarity between individuals (both within and between clusters) as measured by the ICC. Assuming the event rates recorded in PLATO (12% vs. 10%), type 1 and type 2 errors of 5% and 20% respectively, power calculations for a standard individual randomized trial approach would suggest the need for 1,500 patients in each arm. For a CR trial, calculations using R (library(CRTsize) suggests that we need 6 clusters of 400 patients for each arm (total 4800, larger sample size due to ICC). However CRXO design has been shown to increase the statistical efficiency over the standard CR design[22]. The Figure below shows that 5 clusters for each arm (total sample size 4000) will provide greater than 80% power[21], suggesting that our 18-month recruitment period will be sufficient Given our current annual angiogram / PCI volume and with the expected additional 10% of potential recruited ACS patients coming from the hospital CCU without an angiogram, we should have the capacity to meet our power calculations within an 18 month recruitment period based on the excellent (>90%) recruitment rates observed in other pragmatic comparative effectiveness trials[36].



In addition to a standalone analysis, our main Bayesian analysis will incorporate the 1800 PLATO NA patients as our prior distribution, essentially providing a > 50% safety margin for our sample size calculations (see next section).

Statistical analysis

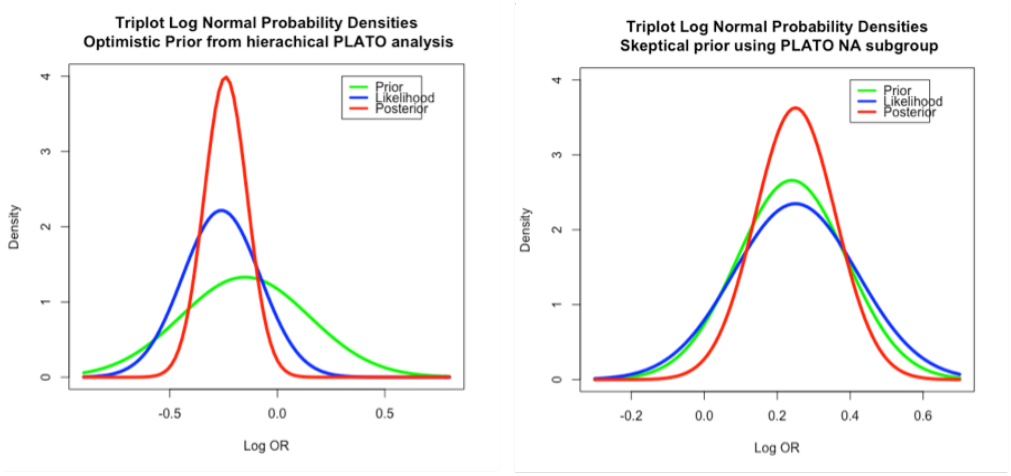
The trial data will be analyzed following the intention to treat principal. Clustered data require appropriate advanced statistical techniques that accounts for the likeness of cluster members, otherwise analysis can lead to overly precise estimates and potentially incorrect inferences about the effectiveness of the intervention.

Appropriate analysis will involve generalized estimating equations and hierarchical models. Bayesian analyses will be performed using JAGS [37] version 3.4.0 and R [38]. All Markov Chain Monte Carlo simulations will be run on two chains with 10 000 iterations discarding the first 1000. Convergence will be monitored using CODA [39] and checked by observing the traces of posterior samples, and by inspecting the Gelman-Rubin R statistic [40] and the Raftery-Louis diagnostics.[41]

Our primary analysis will involve a Bayesian approach that synthesizes all the pertinent evidence concerning these DAPT regimes by incorporating our prior information (PLATO data) with the likelihood of the current data. The advantages of this approach include a mathematically rigorous and exact combination of the totality of the data allowing direct probability statements about the relative strengths of the two regimes (statements that are desired by clinicians and decision-makers but which are technically impossible with the usual frequentist (p value) approach). The strength of this approach is displayed graphically and is described more fully in the next section. We will also perform a "standalone" Bayesian analysis by using a non-informative prior so that results driven uniquely by the data from this proposal may be appreciated.

Anticipated results and conclusions

Concretely the question remains which PLATO data shall we use for the prior data, the whole dataset or that limited to the NA subgroup. Our Bayesian approach will examine the robustness of the data by considering both! First, consider in the Figure (top) what might be called the "enthusiastic" prior which uses all the data and shows the overall benefit with ticagrelor.



Remember due to the between region variability this result (green curve) is not as definitive as implied in the original PLATO result as reported in the NEJM[9]. Next suppose that we are able only to recruit only 1500 (blue curve), not the expected 4000, patients but that the results are concordant with the overall PLATO results (green curve). The combined results will provide definitive results for the superiority of ticagrelor over clopidogrel with almost 100% probability as virtually all the area under the red curve is to the left of 0 line. In this circumstance, there is at least 80% probability that this superiority is clinically significant (defined as $> 15\%$ improvement, area under the red curve to the left of a vertical line at -0.15). Conversely suppose we also use the "skeptical" prior of PLATO's NA subgroup and that our data again concords, a scenario shown graphically in the Figure (right). In this case, the contribution of our data removes all uncertainty about DAPT in NA patients and we become virtually certain that clopidogrel is superior to ticagrelor (99% of the area under the red curve to the right of 0). It must be emphasized that these definitive conclusions are available using $< 50\%$ of our projected data and hence should allow definitive conclusions for all other combinations of prior and new data.

Study timeline

We project that patient recruitment will be 18-20 months. The primary outcome for this project will be safety and effectiveness outcomes at 12 month follow-up. The securing of outcome data from provincial databases

will take approximately 3 months. Allowing 3 months for analyses and manuscript preparation will lead to the project being completed within a 36 month schedule. We will apply to other sources for the minimal funding required to obtain the data base outcomes for 36 months of follow-up and for the proposed long term effectiveness, genomic, economic and quality of life analyses. ### Ethics Although both treatment arms represent accepted therapeutic options for which in routine practice informed consent is not required, we will appropriately, in the name of complete transparency, inform all patients of the existence of this research project and explicitly request their consent to participate. At the time of consent, patients will be approached for permission to have access to their ongoing electronic medical records (see Appendix for draft of informed consent). As both intervention arms represent standards of care there is minimal risk and we anticipate little patient resistance to participation. Given the objective clinical equipoise in the cardiology community we have already secured divisional participation (see Appendix).

Possible problems - Risk evaluation and mitigation strategies

The main risk or limitation to this study is whether a single center is able to produce compelling, practice altering research. Here the trade-off is between maximizing generalizability by performing a multicenter trial and respecting economic realities and feasibility. It must also be recognized that evidence from this study will not be considered in isolation but in combination with pre-existing evidence. As previously discussed, this study will provide as much, and likely at least 50% more, evidence for NA patients than presently exists. Importantly, this single center is representative of most Quebec hospitals. Also, there is objective evidence of a single center performing a practice altering pragmatic RCT. The pragmatic HEAT trial[36], comparing antithrombotic therapy with bivalirudin or unfractionated heparin for PCI, recruited 1917 patients (97% of possible total) from a single center in 20 months and showed an increased risk (RR 1.52, 95% CI 1.09–2.13, p=0.01) in the primary efficacy outcome (a composite of all-cause mortality, cerebrovascular accident, reinfarction, or unplanned target lesion revascularization) with the much more expensive bivalirudin. This trial has been pivotal not only in the clarifying the role, or lack thereof, of bivalirudin but also in furthering the debate about matching ethical concerns of informed consent in pragmatic RCTs with the degree of risk involved[42]. Another risk or limitation is our dependency on administrative databases for evidence of ongoing drug exposure and outcome data. This dependency on electronic databases is an innovative use of data science to render feasible clinical experimentation. Critics may fear that these measures are not as reliable as direct measures obtained during scheduled research mandated clinical encounters. However ample research into the use of the Quebec administrative databases has repeatedly confirmed their reliability for drug exposure[43] and hard outcomes, particularly for cardiovascular outcomes[25, 27]. Typically, conventional RCTs do not measure drug exposure, other than occasional isolated pill counts, and so monthly evidence of drug purchases, while not perfect, should give an as good as, or likely better, proxy to compliance. Also RCTs often have trouble recording side effects but the systematic nature of these databases should assure that all clinically meaningful adverse accounts are captured. Of course any baseline differences between the 2 intervention arms should be balanced by the randomization process. Another limitation is our inability to simultaneously address other pertinent and related ACS questions. For example, prasugrel is another antiplatelet agent but we didn't have the power for a 3 way comparison and the additional complexity was seen as a barrier to obtaining a definitive answer. Therefore, we selected to investigate what are arguably the 2 principal competing DAPT interventions. The preferred aspirin DAPT dose also remains unknown and while a 2nd randomization to low or high dose aspirin might address that, it was felt that the additional complexity and limited power to answer this type of interaction would again distract from our principal research question.

Team experience

The main applicant (JB) has experience as a local PI in numerous multicenter trials and as an investigator initiated trialist[44]. His experience in manipulating large datasets and drawing meaningful inferences from a Bayesian perspective were recently demonstrated again with a BMJ paper[45] examining the safety of non-steroidal anti-inflammatory drugs in 446,763 individuals including 61,460 with MI (paper downloaded 110,000 in the first 4 months following publication). JB has also served on numerous DSMB boards for trials funded by CIHR and mandated by the FDA[46]. Nandini Dendukuri is an expert in Bayesian statistics and has a strong interest in the translation of clinical research into practice through the performance of health

technology assessments. Clinical expertise and patient recruitment will be facilitated by Dr. Sonny Dandonna (SD), an interventional cardiologist and MUHC director of the coronary care unit (CCU), who is an assistant professor at McGill. Michèle de Guise (MD) who in addition to being a trained cardiologist is Scientific Director Quebec Institut National d'Excellence en Santé et en Services Sociaux (INESSS) who can facilitate future knowledge translation. Brenda Macgibbon (BM) a patient representative on several hospital boards, and a professional biostatistician and former university professor will assist in prioritizing patient orientated outcomes.

Conclusion

Our proposed pragmatic, randomized – registry, cluster crossover randomized clinical trial is a novel design well suited to evaluating DAPT comparative effectiveness and addressing a pertinent patient orientated research question. The design can be seamlessly integrated into routine practice with minimal costs or ethical barriers, logistical feasibility, increased generalizability and enhanced capture of effectiveness and safety parameters. The proposed novel design and analysis of this trial will allow a timely answer to an important clinical question to obtained in a very efficient manner at a small fraction (<1/100) of the cost of a standard RCT and a small fraction of the projected annual ticagrelor cost (<1/1000). While the main objective of this project is the evaluation of clinical effectiveness and safety outcomes, the structure of the project and the expertise of the team members will provide the data sources to permit later ancillary investigations into long term outcomes, quality of life, genomic and economic substudies. The project will also provide the first opportunity to look at long term comparative outcomes and will offer unique training opportunities.

Data analysis Amendment Oct 29 2019 While we obtain baseline patient information at the time of recruitment, follow-up data is obtained from the RAMQ provincial electronic records (patients sign consent at recruitment) as there are no follow-up direct patient visits with the research team. Historically we would apply to RAMQ and they would send us the follow-up data for consented patients. I was informed last week that this process has now been modified. Data will only be released to Centre d'accès aux données de recherche de l'Institut de la statistique du Québec (CADRISQ) and all analyses must be performed on their physical site. Therefore we must take our MUHC baseline data to CADRISQ, merge and then analyse the data at their site. Consequently I require an amendment to the protocol and a letter of authorization from the REB that I can submit to CADRISQ.

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