Investigating the effectiveness and safety of dual-antiplatelet therapies in acute coronary syndrome patients

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Abstract
BACKGROUND:

Cardiovascular diseases are the second leading cause of mortality in Canada. Many cardiovascular-related morbidities and deaths are the consequence of ischemic cardiac episodes called acute coronary syndromes (ACS). In recent decades, advancements in medical procedures and medications have substantially reduced the morbidity and mortality following an ACS event. Patients are surviving an ACS at higher rates but are at an increased risk of a recurrent ischemic event, which is a leading cause of re-hospitalizations. Antiplatelet medications have a long history of improving ACS survival and for the prevention of a secondary cardiac event. Based on the consistency and strength of multiple randomized controlled trials (RCTs), the dual antiplatelet therapy (DAPT), clopidogrel and aspirin, following an ACS event, had long been considered the gold standard in the leading clinical guidelines.

More recently, a new DAPT regimen, ticagrelor and aspirin, was approved following a single multinational, multicenter RCT (PLATO) that found a reduction in major acute coronary events (MACE) in comparison to clopidogrel and aspirin (n=18,624, hazard ratio [HR] 0.84; 95% confidence interval [CI], 0.77, 0.92) with no significant increase in bleeding outcomes (HR, 1.04; 95% CI: 0.95–1.13). The results were convincing to most clinicians and the major clinical guidelines were quickly updated to recommend ticagrelor as a replacement for clopidogrel.

However, the outcomes for the efficacy endpoint, MACE, presented in PLATO were ultimately not evenly distributed across the study regions. For, example, the pre-specified North American subgroup showed a non-significant increased risk with ticagrelor (n=1,814, HR 1.25; 95% CI 0.93, 1.67). A re-evaluation of this heterogeneity using a hierarchical analysis, accounting for the regional variability of the sub-regional estimates, resulted in the NULL effect being included in the updated 95% confidence limits (HR, 0.87; 95% credible interval [CrI]: 0.70, 1.15). While there is no

universal agreement on the preferred selection between the two models (fixed versus random effects) regarding their underlying assumptions, in the least these discordant results highlight the uncertainty around the robustness of the PLATO evidence when the conclusions are appreciably dependent upon statistical modeling assumptions.

Given the frequency of ACS events in the Canadian population and the prevailing uncertainty concerning the superiority of ticagrelor over clopidogrel DAPT, further research is necessary, especially in a North American context. The accumulation of this new evidence can be achieved through, 1) a synthesis of all existing RCTs; 2) the execution of a well designed non-randomized study; and, 3) the addition of a new RCT. Below, this thesis will describe how these applied research designs can further our understanding and knowledge around the effectiveness and safety of DAPT in ACS patients.

METHODS AND RESULTS

MANUSCRIPT 1:

The objective of the first manuscript was to systematically search, review, and synthesize the literature for RCTs investigating the efficacy or safety of the newer DAPTs ticagrelor and prasugrel, compared to the clopidogrel standard in ACS patients. A total of 29 RCTs, each with a minimum of 6 months of follow-up, were identified from an initial search query of 15,232 articles. From these, 17 studies (n=57,814) were identified as being a "low" risk of bias and were included in a Bayesian network meta-analysis. The evidence on the primary efficacy endpoint, major acute coronary events (MACE), and primary safety endpoint, major bleeding outcomes, were summarized using a logit transformed generalized linear model with a log-transformed 'time' variable to account for varying lengths of study follow-up. Overall, prasugrel was associated with a moderate reduction in MACE endpoints by a median of 13% ($HR_{Pvs.C}$, 0.87; 95% CrI: 0.74, 1.06) and a moderate increase in major bleeding ($HR_{Pvs.C}$, 1.23; 95% CrI: 1.04, 1.40) when compared to clopidogrel. Ticagrelor was

associated with a mild reduction in MACE events by a median of 5% ($HR_{Tvs.C}$, 0.95; 95% CrI: 0.81, 1.14) and a mild increase in bleeding episodes ($HR_{Tvs.C}$, 1.07; 95% CrI: 0.99, 1.17). After summarizing the existing RCT evidence, this study suggested that the possible clinical benefits of prasugrel are likely outweighed by an increased risk of bleeding, while ticagrelor has a similar efficacy profile and the potential for a mild increase in bleeding outcomes, when compared to clopidogrel DAPT. We were also unable to identify any ancillary RCTs from our systematic search specifically examining DAPTs in a North American population.

MANUSCRIPT 2:

The objective of the second manuscript was to determine if new ticagrelor DAPT users were at a decreased risk of MACE endpoints and similar risk of major bleeding events that required hospitalization, when compared to new clopidogrel DAPT users in a North American (Québec) context. This was achieved through a non-randomized population-based cohort study between April 1, 2010, and March 31, 2018. Following the target trial framework, the Québec, Canada, medico-administrative health and insurance databases were used to identify ACS patients undergoing a percutaneous coronary intervention (PCI). Average treatment effect (ATE) weights were calculated using inverse probability of treatment weights of the propensity score to generate a pseudo-population where treatment assignment was independent from the observed confounders. The weights were used to up- and downweigh individual subjects to create a balanced set of baseline characteristics. These weights were included in Cox proportional hazard models to calculate the intention-to-treat HRs and 95% CI's. During the study period, we identified 6,959 new users of ticagrelor and 15,777 new users of clopidogrel. After ATE weighting and also adjusting for age, "other" heart diseases, atrial fibrillation, and the Charlson Index, ticagrelor initiation was associated with non-significant reductions in both MACE (adjusted HR [aHR], 0.91; 95% CI: 0.81, 1.01) and bleeding outcomes (aHR, 0.97; 95% CI: 0.75, 1.24), when compared to patients' who initiated

clopidogrel. This study showed that, when compared with clopidogrel, the initiation of ticagrelor was not associated with a significant decreased risk in MACE or hospitalized bleeding outcomes, in the Québec population.

MANUSCRIPT 3:

The objective of the third manuscript was to conduct a prospective, open-label, pragmatic, cluster, randomized registry trial comparing ticagrelor and clopidogrel in a clinical-based population of ACS patients undergoing a planned PCI in Montréal, Canada. This novel RCT design randomized subjects to ticagrelor or clopidogrel using 2-month alternating time clusters from October 1, 2018, to March 31, 2021, and was analysed within a prespecified Bayesian framework. During the 12 months of patient follow-up, the primary effectiveness (MACE) and safety outcomes (hemorrhagic stroke or gastrointestinal bleeding requiring hospitalization) were acquired through the Québec medico-administrative health databases using validated ICD-10 codes. We randomized 450 patients to ticagrelor and 555 patients to clopidogrel across thirteen 2-month cluster periods and one 4-month cluster period (due to the COVID-19 pandemic). Bayesian Cox proportional hazard models were used to estimate HR's and their 95% CrI's, as well as, the probability that the posterior distribution that lies above (HR > 1.11), below (HR < 0.9) the minimum clinically important difference (MID) thresholds, and within (HR = [0.9, 1.11]) the region of practical equivalence (ROPE). The trial data was incorporated with a range of priors (vague, enthusiastic, skeptical, and summary) to capture a comprehensive range of prior beliefs. Using a vague prior, in other words relying only on the trial data, ticagrelor was estimated to reduce the hazard for MACE endpoints by a median of 3% (HR, 0.97; 95% CrI: 0.67, 1.40) along with a median reduction in hospitalized bleeding by 12% (HR, 0.88; 95% CrI: 0.49, 1.50). A total of 40% of the posterior distribution for MACE, and 25% for bleeding events, fell within the ROPE, with 35% and 53% falling below the MID threshold for each respective outcome. The MACE results, when the trial data was combined

with the enthusiastic (HR, 0.89; 95% CrI: 0.71, 1.11), skeptical (HR, 1.13; 95% CrI: 0.90, 1.42), and summary (HR, 0.95; 95% CrI: 0.81, 1.12) informative priors, estimated that 42%, 38%, and 72% of the respective posteriors fell within the ROPE. While 55% of the posteriors for the enthusiastic, 2% of the skeptical, and 24% of the summary evidence integrations fell below the 10% MID threshold. This trial was able to contribute over 50% more ACS patients to the existing DAPT evidence base from North America. The findings from our trial did not find an overall effectiveness or safety benefit associated with ticagrelor, when compared to those assigned to clopidogrel DAPT, nor did it find consistent evidence that exceeded a clinically meaningful benefit threshold.

CONCLUSIONS:

The overall findings from this thesis added important information regarding the effectiveness and safety of DAPTs, especially in the North American context. Specifically, using three independent research designs, our results were unable to support the superiority of ticagrelor over clopidogrel in the prevention of secondary events in ACS patients undergoing a PCI. Although further research may enhance the precision of these estimates, our findings provide good evidence that any differences between ticagrelor and clopidogrel likely does not exceed the 10% threshold of a clinically meaningful effect. Lastly, these findings do not fully align with the current Canadian guidelines that recommend ticagrelor and prasugrel over clopidogrel DAPT in ACS management and should be revised.

Résumé
CONTEXTE:

Les maladies cardiovasculaires sont la deuxième cause de mortalité au Canada. Un grand nombre de morbidités et de décès liés aux maladies cardiovasculaires sont la conséquence d'épisodes cardiaques ischémiques appelés syndromes coronariens aigus (SCA). Au cours des dernières décennies, les progrès des procédures médicales et des médicaments ont considérablement réduit la morbidité et la mortalité à la suite d'un SCA. Les patients survivent plus souvent à un SCA, mais ils courent un risque accru de récidive d'un événement ischémique, qui est l'une des principales causes de réhospitalisation. Les médicaments antiplaquettaires améliorent depuis longtemps la survie après un SCA et la prévention d'un événement cardiaque secondaire. Sur la base de la cohérence et de la solidité de multiples essais contrôlés randomisés (ECR), la double thérapie antiplaquettaire (DAPT), clopidogrel et aspirine, à la suite d'un SCA, a longtemps été considérée comme l'étalon-or dans les principales directives cliniques.

Plus récemment, un nouveau traitement DAPT, le ticagrelor et l'aspirine, a été approuvé à la suite d'un seul essai clinique randomisé multinational et multicentrique qui a révélé une réduction des événements coronariens aigus majeurs (MACE) par rapport au clopidogrel et à l'aspirine (n=18 624, rapport de risque [HR] 0,84 ; intervalle de confiance à 95 % [IC], 0,77, 0,92) sans augmentation significative des saignements (HR, 1,04 ; IC à 95 % : 0,95-1,13). Les résultats ont été convaincants pour la plupart des cliniciens et les principales directives cliniques ont été rapidement mises à jour pour recommander le ticagrelor en remplacement du clopidogrel.

Cependant, les résultats pour le critère d'efficacité, MACE, présentés dans PLATO n'ont finalement pas été distribués de manière égale dans les régions étudiées. Par exemple, le sous-groupe nord-américain pré-spécifié a montré un risque accru non significatif avec le ticagrelor (n=1 814, HR 1,25 ; 95% CI 0,93, 1,67). Une réévaluation de cette hétérogénéité à l'aide d'une analyse hiérarchique,

tenant compte de la variabilité régionale des estimations sous-régionales, a permis d'inclure l'effet nul dans les limites de confiance actualisées à 95 % (HR, 0,87 ; intervalle crédible à 95 % [CrI] : 0,70, 1,15). Bien qu'il n'y ait pas d'accord universel sur le choix préféré entre les deux modèles (effets fixes ou aléatoires) concernant leurs hypothèses sous-jacentes, ces résultats discordants soulignent au moins l'incertitude concernant la robustesse des preuves de l'étude PLATO lorsque les conclusions sont grandement dépendantes des hypothèses de modélisation statistique.

Compte tenu de la fréquence des événements liés au SCA dans la population canadienne et de l'incertitude qui prévaut quant à la supériorité du ticagrelor par rapport au clopidogrel DAPT, il est nécessaire de poursuivre les recherches, en particulier dans un contexte nord-américain. L'accumulation de ces nouvelles preuves peut être réalisée par 1) une synthèse de tous les ECR existants ; 2) l'exécution d'une étude non randomisée bien conçue ; et 3) l'ajout d'un nouvel ECR. Ci-dessous, cette thèse décrira comment ces modèles de recherche appliquée peuvent améliorer notre compréhension et notre connaissance de l'efficacité et de la sécurité du DAPT chez les patients atteints de SCA.

MÉTHODES ET RÉSULTATS

MANUSCRIT 1:

L'objectif du premier manuscrit était de rechercher, d'examiner et de synthétiser de façon systématique la littérature sur les ECR portant sur l'efficacité ou la sécurité des nouveaux DAPT, le ticagrelor et le prasugrel, par rapport au clopidogrel standard chez les patients atteints d'un SCA. Un total de 29 ECR, chacun avec un minimum de 6 mois de suivi, a été identifié à partir d'une recherche initiale de 15 232 articles. Parmi ceux-ci, 17 études (n=57 814) ont été identifiées comme présentant un risque de biais "faible" et ont été incluses dans une méta-analyse en réseau bayésienne. Les données relatives au critère principal d'efficacité, les événements coronariens aigus majeurs (MACE), et au critère principal de sécurité, les hémorragies majeures, ont été résumées à l'aide d'un modèle

linéaire généralisé transformé en logit avec une variable "temps" transformée en logarithme afin de tenir compte des différentes durées de suivi de l'étude. Globalement, le prasugrel a été associé à une réduction modérée des critères d'évaluation MACE d'une médiane de 13 % (HR_{PC}, 0,87 ; IC à 95 % : 0,74, 1,06) et à une augmentation modérée des hémorragies majeures (HR_{PC}, 1,23 ; IC à 95 % : 1,04, 1,40) par rapport au clopidogrel. Le ticagrelor a été associé à une légère réduction des événements MACE d'une médiane de 5 % (HR_{TC}, 0,95 ; 95 % CrI : 0,81, 1,14) et à une légère augmentation des épisodes hémorragiques (HR_{TC}, 1,07 ; 95 % CrI : 0,99, 1,17). Après avoir résumé les résultats des ECR existants, cette étude suggère que les avantages cliniques possibles du prasugrel sont probablement contrebalancés par un risque accru de saignement, tandis que le ticagrelor présente un profil d'efficacité similaire et un léger potentiel d'augmentation des épisodes de saignement, par rapport au DAPT clopidogrel. Nous n'avons pas non plus été en mesure d'identifier des ECR auxiliaires à partir de notre recherche systématique portant spécifiquement sur les DAPT dans une population nord-américaine.

MANUSCRIT 2:

L'objectif du deuxième manuscrit était de déterminer si les nouveaux utilisateurs de DAPT ticagrelor présentaient un risque réduit de critères d'évaluation MACE et un risque similaire d'événements hémorragiques majeurs ayant nécessité une hospitalisation, par rapport aux nouveaux utilisateurs de DAPT clopidogrel dans un contexte nord-américain (Québec). Cet objectif a été atteint grâce à une étude de cohorte non randomisée basée sur la population entre le 1er avril 2010 et le 31 mars 2018. Conformément au cadre de l'essai cible, les bases de données médico-administratives de santé et d'assurance du Québec (Canada) ont été utilisées pour identifier les patients atteints d'un SCA ayant subi une intervention coronarienne percutanée (ICP). Les pondérations de l'effet moyen du traitement (EMTT) ont été calculées en utilisant les pondérations de la probabilité inverse de traitement du score de propension pour générer une pseudo-population

où l'assignation du traitement était indépendante des facteurs de confusion observés. Les pondérations ont été utilisées pour augmenter ou diminuer le poids des sujets individuels afin de créer un ensemble équilibré de caractéristiques de base. Ces pondérations ont été incluses dans les modèles de risques proportionnels de Cox pour calculer les HR en intention de traiter et les IC à 95 %. Au cours de la période d'étude, nous avons identifié 6 959 nouveaux utilisateurs de ticagrelor et 15 777 nouveaux utilisateurs de clopidogrel. Après pondération des EMTT et ajustement pour l'âge, les "autres" maladies cardiaques, la fibrillation auriculaire et l'indice de Charlson, l'instauration du ticagrelor a été associée à des réductions non significatives des MACE (HR ajusté [aHR], 0,91 ; 95% CI : 0,81, 1,01) et des hémorragies (aHR, 0,97 ; 95% CI : 0,75, 1,24), par rapport aux patients qui ont commencé à prendre du clopidogrel. Cette étude a montré que, par rapport au clopidogrel, l'instauration du ticagrelor n'était pas associée à une diminution du risque de MACE ou de saignement en milieu hospitalier, dans une population québécoise.

MANUSCRIT 3:

L'objectif du troisième manuscrit était de mener un essai clinique prospectif, ouvert, pragmatique, en grappes et randomisé comparant le ticagrelor et le clopidogrel dans une population clinique de patients atteints de SCA subissant une ICP planifiée à Montréal, au Canada. Cet ECR novateur a randomisé les sujets entre le ticagrelor et le clopidogrel en utilisant des grappes temporelles alternées de 2 mois, du 1er octobre 2018 au 31 mars 2021, et a été analysé dans un cadre bayésien préspécifié. Au cours des 12 mois de suivi des patients, les résultats primaires d'efficacité (MACE) et de sécurité (AVC hémorragique ou saignement gastro-intestinal nécessitant une hospitalisation) ont été acquis par le biais des bases de données médico-administratives de santé du Québec en utilisant des codes CIM-10 validés. Nous avons randomisé 450 patients pour le ticagrelor et 555 patients pour le clopidogrel sur treize périodes de deux mois et une période de quatre mois (en raison de la pandémie de COVID-19). Des modèles bayésiens de risques proportionnels de Cox

ont été utilisés pour estimer les HR et leurs ICR à 95 %, ainsi que la proportion de la distribution postérieure qui se situe au-dessus (HR > 1,11), au-dessous (HR < 0,9) des seuils de différence minimale cliniquement importante (DMCI), et dans (HR = [0,9, 1,11]) la région d'équivalence pratique (ROPE). Les données de l'essai ont été incorporées avec une série d'antécédents (vagues, enthousiastes, sceptiques et sommaires) afin d'obtenir une gamme complète de croyances pronostics préalables. En utilisant un a priori vague, c'est-à-dire en se basant uniquement sur les données de l'essai, on a estimé que le ticagrelor réduisait le HR pour les critères d'évaluation MACE d'une médiane de 3 % (HR, 0,97 ; 95% CrI : 0,67, 1,40) ainsi qu'une réduction médiane des hémorragies chez les hospitalisés de 12 % (HR, 0,88 ; 95% CrI : 0,49, 1,50). Au total, 40 % de la distribution postérieure pour la MACE et 25 % pour les événements hémorragiques se situent dans la ROPE, 35 % et 53 % se situant sous le seuil de la DMCI pour chaque résultat respectif. Les résultats de la MACE, lorsque les données de l'essai ont été combinées aux a priori informatifs enthousiastes (HR, 0,89 ; 95% CrI : 0,71, 1,11), sceptiques (HR, 1,13 ; 95% CrI : 0,90, 1,42) et sommaires (HR, 0,95 ; 95% CrI : 0,81, 1,12), ont estimé que 42%, 38% et 72% des postérités respectives tombaient dans la ROPE. En revanche, 55 % des postérieurs des intégrations enthousiastes, 2 % des intégrations sceptiques et 24 % des intégrations de données sommaires se situaient en dessous du seuil de 10 % de la DMCI. Cet essai a permis d'ajouter plus de 50 % de patients atteints de SCA à la base de données probantes existante sur le DAPT en Amérique du Nord. Les résultats de notre essai n'ont pas mis en évidence de bénéfice global en termes d'efficacité ou de sécurité associé au ticagrelor, par rapport aux patients assignés au DAPT clopidogrel, et n'ont pas non plus mis en évidence de preuves cohérentes dépassant un seuil de bénéfice cliniquement significatif.

CONCLUSIONS:

Les résultats globaux de cette thèse ont apporté des informations importantes sur l'efficacité et la sécurité des DAPT, en particulier dans le contexte nord-américain. Plus précisément, en

utilisant trois modèles de recherche indépendants, nos résultats n'ont pas pu soutenir la supériorité du ticagrelor sur le clopidogrel dans la prévention des événements secondaires chez les patients atteints de SCA subissant une ICP. Bien que des recherches supplémentaires puissent améliorer la précision de ces estimations, nos résultats fournissent de bonnes preuves que toute différence entre le ticagrelor et le clopidogrel ne dépasse probablement pas le seuil de 10 % d'un effet cliniquement significatif. Enfin, ces résultats ne sont pas totalement en accord avec les lignes directrices canadiennes actuelles qui recommandent le ticagrelor et le prasugrel plutôt que le clopidogrel DAPT dans la prise en charge du SCA et devraient être révisées.

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Where do I even begin? Countless people have contributed to my growth, not only in my understanding and application of Epidemiological concepts, but also towards my development as an individual. I feel fortunate to have had the opportunities and experiences, starting in my youth, through adolescence, and into my young academic career, to end up in this once obscure field (at least to myself). Here I will briefly express my sincerest gratitude to a collection of individuals and groups.

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consenting patients in an urgent health setting. This requires not only skill but also compassion. You provided the necessary legwork required to see this project to the end.

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Thank you to the faculty in the department of Epidemiology, Biostatistics, and Occupational Health (EBOH) who challenged and changed my way of thinking throughout my doctoral training. A special mention goes out to Dr. Jay Kaufman, Dr. Lawrence Joseph, Dr. Gilles Paradis, and Dr. Maida Sewitch. To the EBOH student body, especially those of you who regularly participated in all of the student-led activities. You made my experience here unforgettable, sometimes distracting me a bit too much from my doctoral research. Couscous! Thank you to the "second best Ph.D. cohort" who made the learning environment both rigorous but welcoming. Special thanks to my pals, Jean-Paul Soucy, Emily MacLean, and Devin Abrahami for… everything. Love y'all. And a big thank you to both Leah Flatman and Emmalin Buajitti for always saying "yes" to my foolish ideas.

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Finally, to my now wife, Emily Bell. Here it is. The culmination of your leap of faith after you followed me to Montréal so I could pursue my graduate studies in Epidemiology. I don't think

either of us really knew what we were getting into. Nonetheless, you were my number one supporter from day one until day <insert large number>. I will never be able to thank you enough. I look forward to having more time to spend with you and Warren. I love you.

I dedicate this thesis to my late grandmother, Ria Kutcher-Gyra, and late aunt, Kathryn Dingwell (Martinson). You both were in my thoughts throughout this entire process encouraging me during the pursuit of my goals. You will forever be remembered.

Contribution to Original Knowledge

The research outlined in this thesis represents original contributions that advances the knowledge about the effectiveness and safety of dual-antiplatelet (DAPT) medications in patients with an acute coronary syndrome (ACS) event. Despite the passing of two decades since the completion of large, multicenter randomized controlled trials (RCTs) gaps still exist surrounding the superiority of ticagrelor and prasugrel over clopidogrel DAPT, especially in the North American population. This thesis attempts to address these limitations by using three different data sources and methodological approaches in the evaluation of the main DAPT's association with efficacy and safety outcomes in ACS patients. Manuscript 1 provides a systematic overview of the current available RCT evidence comparing the three DAPT's, improving on previous efforts through random effect modelling and incorporating clinically meaningful estimates. This study also highlights the continued absence of additional RCT studies in North American subjects. Manuscript 2 was a non-randomized observational study that leveraged the electronic healthcare databases from the province of Québec, Canada. Average treatment effect (ATE) weights, estimated from propensity scores, were used in a time-to-event Cox Proportional Hazards model to evaluate the effectiveness and safety of DAPT in a large ACS population, undergoing revascularization. Last, Manuscript 3 is the product of a pragmatic, time-clustered randomized controlled trial conducted in a hospital in Montreal, Canada. It similarly compares the efficacy and safety of DAPT's in ACS patients recruited from the Cardiac catheterization laboratory, in which patients are follow for clinical outcomes via the electronic healthcare databases in Québec, Canada. Overall, this thesis summarizes the existing state of evidence surrounding DAPT's and contributes original evidence regarding DAPT's in North American patients.

I declare that the works presented in this thesis dissertation are my own and that my supervisor and advisory committee provided guidance on the substantive and methodological aspects.

Contributions of Authors

MANUSCRIPT 1: Kutcher, S.A., Flatman, L.K., Haber, R., Dendukuri, N., Dandona, S., & Brophy, J.M. [*Prepared for journal submission*]. The efficacy and safety of the prasugrel, ticagrelor, and clopidogrel dual antiplatelet therapies following an acute coronary syndrome: A systematic review and Bayesian network meta-analysis.

Under the guidance of Dr. James Brophy, I conceptualized this project and developed the study research question. I created the study protocol and data collection tools, and then performed the data collection and quality assessment of the included RCTs. I developed the statistical analysis plan (SAP), performed the analyses, interpreted the results, and drafted the manuscript. L.K.F and R.H. contributed to the quality assessment, and N.B. and J.B contributed to study design and data interpretations All authors contributed manuscript revisions.

MANUSCRIPT 2: Kutcher, S.A., Dendukuri, N., Dandona, S., Nadeau, L., & Brophy, J.M. [*Prepared for journal submission*]. A real-world comparative effectiveness of clopidogrel and ticagrelor for acute coronary syndromes in Québec, Canada. [*Prepared for journal submission*]

Under the guidance of Dr. James Brophy, I conceptualized this project and developed the study research question. I formed the study cohort and defined the outcome/exposure definitions. I prepared the SAP performed the analyses, interpreted the results, and drafted the manuscript. L.N. assisted with cohort formation and data cleaning. N.D. and J.B. contributed to study design and data interpretations All authors contributed manuscript revisions.

MANUSCRIPT 3: Kutcher, S.A., Dendukuri, N., Dandona, S., Nadeau, L., & Brophy, J.M. [*Prepared for journal submission*]. Ticagrelor Compared to Clopidogrel in aCute Coronary syndromes – the TC4 pragmatic cluster randomized controlled trial. [*Prepared for journal submission*]

Under the guidance of Dr. James Brophy, I conceptualized this project and developed the study research question. I created the informed consent forms and data collection tool. I was responsible for the overall trial management, in coordination with our research nurse, Nina Mamishi, R.N., MSc. I prepared the SAP, performed the analyses, interpreted the results, and drafted the manuscript. L.N. assisted with data cleaning. N.D. and J.B. contributed to study design and data interpretations All authors contributed manuscript revisions.

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List of Abbreviations

ACS	acute coronary syndrome
ADP	adenine diphosphate
AHA	American Heart Association
ASA	acetylsalicylic acid
ATE	average treatment effect
BNMA	Bayesian network meta-analysis
CABG	coronary a rtery bypass graft
CI	confidence interval
cloglog	complementary log-log model
CoxPH	Cox proportional hazards model
CrI	credible interval
CV	cardiovascular
CVD	cardiovascular disease
CYP450	cytochrome P450 enzyme
DAG	direct acyclic graph
DAPT	dual antiplatelet therapy
DIC	deviance information criterion
DIN	drug identification number
EBAL	entropy balancing
FDA	Food and Drug Administration
FE	fixed effect
HMC	Hamiltonian Monte Carlo
aHR	adjusted hazard ratio
HR	hazard ratio
ICD-10	international classification of diseases, version 10
INSPQ	Institut national de santé publique du Québec
IPTW	inverse probability of treatment weights
LOO	leave-one-out cross-validation
MA	meta-analysis
MACE	major acute cardiovascular events
MCMC	Markov Chain Monte Carlo
MED-ÉCHO	maintenance et exploitation des données pour l'étude de la clientèle hospitalière
MeSH	medical subject headings
MI	myocardial infarction
MID	minimum important difference
MSSS	Ministère de la Santé et des Services sociaux
MUHC	McGill University Health Centre
NMA	network meta-analysis
NSTEMI	non-ST-elevation myocardial infarction
NUTS	No-U-Turn Sampler
aOR	adjusted odds ratio
OR	odds ratio
$P2Y_{12}$	blood platelet cell receptor
PCI	Percutaneous coronary intervention

PLATO	the PLATelet inhibition and patient Outcomes trial
PRIMSA	preferred reporting items for systematic reviews and meta-analyses
PS	propensity score
RAMQ	Régie de l'assurance maladie du Québec
RCT	randomized controlled trial
RE	random effects
RoB 2.0	revised Cochrane risk of bias tool for randomized trials
ROPE	region of practical equivalence
RR	risk ratio
sd	standard deviation
STEMI	ST-elevated myocardial infarction
TCRX	time-cluster randomization
TIMI	Thrombolysis In Myocardial Infarction
TRITON-TIMI	the TRial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet InhibitioN with Prasugrel Thrombolysis In Myocardial Infarction 38
TTP	thrombotic thrombocytopenic purpura
UA	unstable angina

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Chapter One. Introduction

1.1 Overview

Cardiovascular-related diseases (CVD) are the 2nd leading cause of mortality in Canada.[1] Québec alone has reported 17,014 cardiovascular-related deaths in 2022, with approximately 45 percent being directly attributed to ischemic heart diseases.[2] These ischemic cardiac events are largely the consequence of plaque rupture with thrombosis resulting in the sudden reduction or complete loss of blood flow through the coronary arteries to cardiac myocytes. This is clinically known as acute coronary syndromes (ACS) and comprises ST elevated myocardial infarction (STEMI) and non-ST elevated myocardial infarction (NSTEMI) along with unstable angina (UA).[3,4] Modern medical and public health advancements have dramatically reduced CVD-related mortality over the past several decades but those surviving an ACS event remain at a high risk of a recurring ischemic event and are a leading cause of hospitalizations.[5,6] Medications and revascularization procedures are important adjunct interventions to improve ACS outcomes.[5–8]

Based on the strength of two phase III trials – the PLATelet inhibition and patient Outcomes (PLATO)[9] and the TRial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet InhibitioN with Prasugrel Thrombolysis In Myocardial Infarction 38 (TRITON-TIMI)[10] – the Canadian,[11] American,[12] and European[13,14] agencies have updated their guidelines to recommend ticagrelor or prasugrel, in addition to aspirin, over clopidogrel as the dual antiplatelet therapy (DAPT) of choice following an ACS requiring revascularization. The TRITON-TIMI study found that prasugrel was associated with fewer major cardiac events (hazard ratio [HR], 0.81; 95% confidence interval [CI]: 0.73, 0.90) but an increase in bleeding outcomes (HR, 1.31; 95%CI: 1.11, 1.56). Meanwhile, PLATO reported a reduction in secondary composite cardiovascular events (HR, 0.84; 95% CI: 0.77, 0.92) with no associated increase in major bleeding (HR, 1.04; 95%CI: 0.95, 1.13). In the minds of most clinicians and guideline producers, the evidence from these large,

multinational randomized controlled trials (RCTs) established ticagrelor and prasugrel as superior to clopidogrel in reducing recurrent cardiac events and death, with an increase in bleeding associated with prasugrel.

With a closer look at the details of the PLATO analyses these conclusions of ticagrelor superiority over clopidogrel may not be as persuasive. The PLATO trial was analyzed using a fixed effects approach that assumed a single true effect measure across all study regions. Or rather, that each study location was measuring the same treatment effect of ticagrelor on cardiovascular outcomes, independently of any interactions with local health care systems or practices. This estimated a simple weighted average of the measured effect across all the pre-specified regions, essentially pooling the results from across the study regions. However, it seems reasonable to assume an existence of variations in recruitment, population genetics, and healthcare treatment/systems across those 43 enrolled countries and the over 800 study centres. Consequently, the fixed effects analysis approach may have underestimated the variance of the PLATO trial. For example, the North American sub-group showed a non-significant increased risk of ticagrelor when compared to clopidogrel (HR=1.25; 95% CI: 0.93, 1.67).[15] Are we comfortable assuming the North American risk of 1.25 is homogenous to that of the study's overall pooled risk of 0.84 when comparing ticagrelor to clopidogrel? Do we accept this observed variation is due to random error? Although there may be no clear answer to these questions, it may be more appropriate to implement a random-effects model that assumes that regional effect estimates rather come from an overall distribution of effect measures, which assumes its own mean and variance. In fact, when a hierarchical (random effects) model was applied to the PLATO data, allowing for those between-regional effect variations across the study regions, it estimated a HR of 0.87 (95% credible interval [Cr]): 0.70, 1.15)[16] . The point estimate is quite similar to that of the original trial (HR, 0.84)[9] but, due to the accounting for the between region variations, the width of 95% interval from the hierarchical

model was substantially wider (95% CrI: 0.70, 1.15) crossing the NULL threshold of 1.0. Drawing classic frequentist inferences from this random effects model would result in a failure to reject the NULL hypothesis of no difference between the two drugs. In other words, insufficient evidence to claim the superiority of ticagrelor over clopidogrel. The choice of the data generating statistical model remains challenging, and the application of a random effects model to the PLATO data may not be convincing to all audiences. Nonetheless, this *should* highlight the uncertainty surrounding the robustness of the PLATO evidence, when the conclusions can be appreciably changed with a simple adjustment of a modelling decision.

Given the frequency of ACS events in the Canadian population, prevailing uncertainty surrounding the superiority of ticagrelor over prasugrel and clopidogrel, lack of high quality North American evidence, and the increased costs attached to the newer DAPTs, further studies are required to address existing gaps in our knowledge base.

1.2 Research Objectives

1.2.1 Objective 1

To systematically search, review, and synthesize the literature for randomized controlled trials evaluating the use of the dual antiplatelet medications clopidogrel, ticagrelor, and prasugrel, in combination with aspirin, and their associations with mortality, major adverse cardiovascular and major bleeding events following an acute coronary syndrome event.

1.2.2 Objective 2

To perform a real world, contemporary, local, non-randomized cohort analysis comparing the dual antiplatelet medications clopidogrel and ticagrelor, in combination with aspirin, and their associations with major adverse cardiovascular and major bleeding outcomes following an acute

coronary syndrome event using retrospective healthcare data from the province of Québec between 2010-18.

1.2.3 Objective 3

To conduct a prospective pragmatic registry clustered randomized controlled trial comparing the dual antiplatelet medications of clopidogrel and ticagrelor, in combination with aspirin, and their associations with all-cause mortality, cardiovascular morbidity, and major bleeding events in patients with an acute coronary syndrome event at the McGill University Health Centre. The trial will be analyzed using Bayesian statistical methods which will incorporate historical (prior) information with the current data (likelihood) to better inform the final (posterior) parameter distributions.

1.3 Structure

This manuscript-based thesis is organized around three research papers, containing a total of eight chapters. Chapter 1 provides a brief overview of the rationale for this thesis, as well as the three main thesis objectives and its structure. Chapter 2 involves a detailed background on acute coronary syndromes (ACS), the existing options for dual-antiplatelet therapies (DAPT), and the current gaps in the research. Chapter 3 describes the data sources and a more detailed description of the methodologies for each research objective found in the three subsequent chapters (Chapters 4 through 6), representing the individual manuscripts. Chapter 4 is a Bayesian network meta-analysis that synthesizes both efficacy and safety estimates across clopidogrel, ticagrelor, and prasugrel, from published randomized controlled trials. Chapter 5 is a non-randomized cohort of acute coronary patients from Québec, between April 2010 and March 2018, that uses an average treatment effect, inverse-probability of treatment weighted survival analysis to estimate the effectiveness and safety of ticagrelor versus clopidogrel. Chapter 6 is a pragmatic, time-cluster randomized controlled trial comparing effectiveness and safety of ticagrelor compared to clopidogrel, in a cohort of acute coronary syndrome patients recruited from the McGill University Health Center between October

2018 and March 2021. Chapter 7 presents and overall summary of the findings, research implications, the strengths and limitations of our findings, and future directions. The final chapter, Chapter 8, lists the references used in the general portions of this thesis. Each individual manuscript, Chapters 4 through 6, identifies their corresponding references at the end of their respective section.

Chapter Two. Literature Review

2.1 Acute coronary syndrome

Cardiovascular-related diseases (CVD) are the number one cause of death Worldwide,[3] including the U.S.[17] and Europe.[18] Meanwhile CVD's are the 2nd leading cause of mortality in Canada.[1] Québec alone has reported 17,014 cardiovascular-related deaths in 2022, with approximately 45 percent being directly attributed to ischemic heart diseases.[2] These ischemic cardiac events are largely the consequence of the sudden loss of blood flow through the coronary arteries to cardiac myocytes, collectively known as acute coronary syndromes (ACS). This loss of flow is commonly due to an erosion or rupture of a plaque, deposits of underlying cholesterol and fats, resulting in thrombosis formation and leading to an occlusion of the coronary artery. ACS are comprised of three syndromes; ST- (STEMI) and non-ST elevated myocardial infarctions (NSTEMI), as well as unstable angina (UA).[3,4] STEMI can be generally defined as a thrombosis causing total occlusion of a vessel paired with both elevated troponin levels and the ST-segments of an echocardiogram (ECG). While NSTEMI and UA are typically the result a partial or intermittent vessel occlusion that lack ST-wave elevation on an ECG, with NSTEMI's also presenting with elevated troponin levels.[4]

Modern medical and public health advancements have dramatically reduced CVD-related mortality over the past several decades. Québec has seen a drop in the CVD-related death rate from over 800 and 550 cases per 100,000 persons, for men and women respectively in 1975, to 200 and 100 cases per 100,000 persons in 2017.[19] These advances have resulted in an increased prevalence of those living with CVD, plateauing at around 8 percent of the total Québec population starting in 2006-07 (10.1 % in men and 6.2% in women).[20] These surviving ACS patients remain at a high risk of a recurring ischemic event which are a leading cause of re-hospitalizations.[5,6] Medications and revascularization procedures are important adjunct interventions with a long history of successfully treating these ACS conditions.[5–7]

2.2 Pharmaceutical therapies

2.2.1 Acetylsalicylic acid

Pharmacological agents targeting blood platelet adhesion, activation, and aggregation play key roles in the prevention of secondary ischemic events and death following an ACS episode. Acetylsalicylic acid (ASA), more commonly known by the brand name aspirin, is a non-steroidal anti-inflammatory drug that irreversibly blocks platelet activation through its cyclooxygenase-1 antagonist activity. ASA supresses the production of Thromboxane 2, a potent vasoconstrictor and platelet agonist, from the inflammatory agent Prostaglandin H, through the acetylation of the hydroxyl group on the prostaglandin G/H synthase I.[7,21] In short, aspirin limits the 'stickiness' of platelet cells while also reducing the ability of blood vessels to constrict, diminishing the chances of blood clot formation and the probability of occlusions in cardiac arteries due to platelet aggregation. The irreversible nature of platelet inactivation due to ASA inhibition cannot be repaired and the antiplatelet aggregation effects can only be recovered through platelet cell regeneration, a process that takes between seven to ten days.

Initial research found that ASA, when compared to a placebo, was associated with a one-sixth reduction in cardiovascular-related deaths and a one-third reduction in non-fatal strokes and MI's in patients with unstable angina.[22] The continuation of this research demonstrated that ASA reduced (ASA, 10.7% versus placebo, 13.2%) 'serious vascular' outcomes – non-fatal myocardial infarction, non-fatal stroke, or death from a vascular cause – following an initial acute MI or stoke, when compared to a control, based on a meta-analysis of 195 randomized controlled trials (RCT), which included over 135,000 patients.[23] As such, ASA remains the foundation of ACS treatment and continues to be an anti-thrombotic component of the current ACS therapeutic guidelines.[11–13]

2.2.2 Ticlopidine

The thienopyridine molecular family inhibits the $P2Y_{12}$ platelet cell receptor thereby reducing the aggregation capabilities of the platelet cells via a different molecular pathway than ASA.[5,7] Although the mechanism of action has not been well described, thienopyridines irreversibly attach to the $P2Y_{12}$ receptor preventing the binding of adenine diphosphate (ADP), depressing downstream platelet aggregation.

Several RCTs[24–27] demonstrated the benefits of ticlopidine in the prevention of cardiovascular-related outcomes relative to oral anticoagulants (e.g., warfarin) and/or ASA in clinical populations undergoing stenting procedures. The STAR trial (n=1,965)[24] reported frequencies of the primary efficacy end point – composite of death, revascularization, thrombosis, or MI within 30 days – of three (0.5%) in the ticlopidine plus ASA treatment group, 15 (2.7%) in patients assigned to warfarin and ASA, and 20 events (3.6%) in those on ASA monotherapy. The combination of a thienopyridine along with ASA proved to be more beneficial in reducing cardiovascular events relative to both the combination anticoagulation therapy (risk ratio [RR], 0.20; 95% CI: 0.07, 0.61) and, as well, versus Aspirin alone (RR, 0.15; 95% CI: 0.05, 0.43). However, the concomitant therapies (ticlopidine, 30 [5.5%]; warfarin, 34 [6.2%]) reported more hemorrhagic complications than ASA only (10 [1.8%]). The MATTIS,[25] FANTASTIC,[26] and ISAR[27] trials, which compared the combinations of ticlopidine and ASA to the use of anticoagulants and ASA, further supported the use of dual antiplatelet therapy over the anticoagulation combination. Each respective trial found substantial reductions in both cardiovascular (RR, 0.52, 95% CI: 0.25, 1.07;[25] odds ratio [OR], 0.60, 95% CI: 0.36,0.98;[26] OR, 0.25, 95% CI: 0.06, 0.77[27]) and bleeding outcomes when compared to combinations with oral anticoagulants.

The clinical benefits of ticlopidine, however, were overshadowed by other safety concerns besides excessive bleeding. The most serious was the development of thrombotic thrombocytopenic

purpura (TTP), a condition described as microangiography platelet aggregation, or the formation of small blood clots throughout the body.[28,29] The incidence rate of TTP in patients treated with ticlopidine was estimated to occur between once per 1,600 to 5,000 treated. This is substantially more frequent than the estimated base population rate of one case per 3.7 million people.[30] During this time, the continued investigation into ticlopidine analogs identified a potentially more suitable molecule with a better safety profile, clopidogrel.[29]

2.2.3 Clopidogrel

Clopidogrel, also a thienopyridine, structurally differs from ticlopidine by a single carboxymethyl group.[21,31] Yet, while also requiring hepatic activity to achieve its antiplatelet properties *in vivo*, clopidogrel's active metabolites are structurally distinct of those from ticlopidine.[30] Although the mechanisms have again not been well described, clopidogrel has been lauded for providing a better safety profile than that of ticlopidine, without sacrificing the beneficial reductions in cardiovascular endpoints.[32,33] For example, following 2 years of active surveillance it was estimated that the rate of TTP in patients treated with clopidogrel (3.7 per million; 95% CI: 1.5, 5.8 per million)[28] was comparable to that estimated in the general population.[30]

With clopidogrel providing a more favorable safety profile than ticlopidine,[32,33] research continued into its effects across a range of ACS clinical presentations. The Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) trial, randomized 12,562 NSTEMI patients to clopidogrel (75 mg) and aspirin or a placebo and aspirin.[34] Clopidogrel was associated with a reduction in the composite of death, non-fatal MI, or stroke (9.3% vs. 11.4%; RR, 0.80; 95% CI: 0.72, 0.90) and a slight increase in bleeding events requiring 2 or more blood transfusions (3.7% vs. 2.7%; RR, 1.38; P-value, 0.001). The Clopidogrel for the Reduction of Events During Observation (CREDO) trial,[35] was a placebo-controlled RCT that evaluated clopidogrel in 2,116 subjects undergoing a PCI. After 12 months, it was reported that clopidogrel was associated with a 26.9%

relative risk reduction (95% CI: 3.9, 44.4%; P-value, 0.02) in the composite outcome of death, non-fatal MI, or stroke (8.5% vs. 11.5%). However serious bleeding, defined as intercranial or bleeding associated with a decrease in hemoglobin of more than 5 g/dL, was increased with clopidogrel.

The ClOpidogrel and Metoprolol in Myocardial Infarction Trial (COMMIT) randomized 45,852 STEMI patients without a planned PCI[36] to clopidogrel (75 mg) and aspirin (162 mg) had fewer events of combined deaths, reinfarction, or stroke (9.2% vs. 10.1%; OR, 0.91; 95%CI: 0.86, 0.97) relative to a placebo and aspirin. No increase in cerebral and non-cerebral major bleeding outcomes (0.58% vs. 0.55%) were observed after the 28-day follow-up period. An additional 3,491 STEMI patients were randomized to clopidogrel or a placebo, dual-antiplatelet therapy in the Clopidogrel as Adjunctive Reperfusion Therapy (CLARITY)–Thrombolysis in Myocardial Infarction (TIMI) 28 trial.[37] At 30 days, clopidogrel was associated with a reduction (15% vs. 21.7%; OR, 0.64; 95% CI: 0.53, 0.76) in death or reinfarction events, and no difference in TIMI-defined major bleeding outcomes (7.5% vs. 7.2%; P-value, 1.00).

Based on the consistency and strength of these RCT's it is not surprising that clopidogrel and ASA, known as dual antiplatelet therapy (DAPT), became the pillar of contemporary ACS treatment and were recommended by major professional society guidelines at the time.[38,39]

Notwithstanding the above, clopidogrel is a prodrug that requires a 2-step enzymatic process to be metabolized into its potent metabolites, its active antiplatelet form. This hepatic conversion engages the CYP450 enzymatic family, with some limited evidence suggesting a reduced activity within sub-portions of the population. It has been estimated that between five and 44% of patients do not respond well to clopidogrel.[7,40] This theoretical potential for heterogeneity of the enzymatic proficiency of converting ticlopidine and clopidogrel into active compounds across different populations led to the further development of a third generation thienopyridine, prasugrel.

2.2.4 Prasugrel

The thienopyridine prasugrel is similar to ticlopidine and clopidogrel, in that it is also an irreversible $P2Y_{12}$ platelet cell receptor antagonist and a prodrug that relies upon CYP450 metabolism. Where prasugrel differs from ticlopidine and clopidogrel is that it only engages the enzymes in a 1-step hepatic conversion process to reach its active form.[5,7,40,41] Intestinal hydroxyesterases, which can convert clopidogrel into inactive metabolites, instead converts prasugrel into thiolactone, an inactive intermediate. The thiolactone then gets metabolized into its active form via the single step process when interacting with the CYP450 enzymatic family upon reaching the liver. Prasugrel is considered to have both an advantage of a shorter therapeutic onset, in as little as 15 minutes, and a more potent antiplatelet ability relative to both ticlopidine and clopidogrel.[40]

Several large phase-III RCTs evaluated prasugrel against the standard DAPT regimen of clopidogrel. The Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis in Myocardial Infarction (TRITON–TIMI) 38[10] enrolled 13,608 ACS patients – 10,074 UA/NSTEMI and 3,534 STEMI – scheduled for a PCI. The subjects were randomized to 10 mg of prasugrel or 75 mg of clopidogrel in combination with between 75 and 162 mg of ASA. After a median of 14.5 months the study reported fewer (9.9% vs. 12.1%) efficacy outcomes – composite of death from vascular cause, non-fatal MI or stroke – in those assigned to prasugrel relative to clopidogrel (HR, 0.81; 95% CI: 0.73, 0.90). Conversely, those assigned to prasugrel were also observed to have more (2.4% vs. 1.8%) major serious bleeding events (HR, 1.32; 95% CI: 1.03, 1.68). Further, the researchers noted that a net clinical benefit, the balance between its positive antithrombotic and negative bleeding effects, of prasugrel was not apparent in several patient subgroups. Those patients over the age of 75 years, weighing less than 60 kg, and with a history of stroke or transient ischemic attack were susceptible to an increased risk / benefit ratio.[10,40]

Subsequently, the Targeted Platelet Inhibition to Clarify the Optimal Strategy to Medically Manage Acute Coronary Syndromes (TRILOGY ACS) trial recruited a total of 9,326 UA (32.2%) and NSTEMI (67.8%) ACS patients planned for DAPT management without revascularization.[42] Based on the previous subgroup experiences in TRITON-TIMI, those that were over the age of 75 years and less than 60 kg and were randomized to prasugrel therapy received a 5 mg maintenance dose in lieu of the standard 10 mg. The 75 mg daily clopidogrel dose was assigned to the comparison group, with both groups being recommended a 100 mg dose of ASA or less per day. After a 30-month follow-up period, slightly fewer events were observed in the group assigned to prasugrel (13.3% vs. 13.9%), which resulted in a statistically non-significant decrease (HR, 0.96; 95% CI: 0.86, 1.07) in major cardiovascular endpoints compared to clopidogrel subjects. Major bleeding was observed at a lower frequency in the clopidogrel group (1.0% vs. 1.3%), reflecting a non-significant increased risk of bleeding for patients on prasugrel (HR, 1.23; 95% CI: 0.84, 1.81). The PRASugrel compared with clopidogrel For Japanese patIenTs with ACS undergoing PCI (PRASFIT-ACS) trial[43] also failed to identify a statistically significant benefit of prasugrel (HR, 0.77; 95% CI: 0.56, 1.07) in 1,363 Japanese ACS patients who underwent a planned PCI.[43] These trials highlight the inconsistent evidence regarding the superiority of prasugrel over clopidogrel for important clinical endpoints.

2.1.5 Ticagrelor

Due to the delayed onset of the thienopyridines – ticlopidine, clopidogrel, and prasugrel – the potential for population variations of CYP450 liver enzyme activity, along with the irreversible nature of these antiplatelet therapies a new antiplatelet medication, ticagrelor, was developed. Ticagrelor is suspected of preventing ADP-induced signalling cascades involved in platelet aggregation, through allosteric modulation[5,8] from reversible binding to a different region of the $P2Y_{12}$ receptor than the thienopyridines.[3,5–8] Ticagrelor is also a direct acting $P2Y_{12}$ receptor inhibitor, meaning it does not require hepatic conversion into its active antiplatelet metabolic form.

This direct-acting and reversible binding nature of ticagrelor was postulated to provide meaningful clinical benefits. First, it would allow for a shorter therapeutic onset of the beneficial antiplatelet properties for the prevention of future ischemic events, than ticlopidine and clopidogrel. Although ticagrelor has a similar timing to the onset of prasugrel.[5] Second, since ticagrelor does not require CYP450 hepatic activation, it is not susceptible to the suspected heterogeneity of the pharmacodynamic response in some patient subgroups. Lastly, the reversible feature of the drug, again in theory, would make ticagrelor preferred for ACS patients who may require a quick reversal of antiplatelet properties for procedures, such as coronary by-pass grafting (CABG) surgeries.

A multicenter trial (PLATO)[9] on 18,624 ACS patients reported an improvement in composite cardiovascular (CV) outcomes in subjects who were randomized to the newer, ticagrelor dual antiplatelet regimen, when compared to dual clopidogrel / aspirin therapy. The PLATO trial reported a hazard ratio of 0.84 (95% CI: 0.77, 0.92), a significant reduction in major acute cardiovascular events (MACE) – a composite of CV-related deaths, recurrent myocardial infarctions, and ischemic strokes – for patients assigned to ticagrelor relative to clopidogrel. Ticagrelor was also not found to have any significant differences in the reported safety outcomes, PLATO-defined bleeding (ticagrelor, 11.6%; clopidogrel, 11.2%; HR, 1.04; 95% CI: 0.95, 1.13). This was an interesting and unexpected finding as it marked the first time in the history of antithrombotic research that a more potent antithrombotic drug also reported less bleeding. Thus, when compared to the clopidogrel DAPT, the ACS patients randomized to ticagrelor demonstrated a reduction in ischemic events without being associated with increased risk of bleeding episodes.

In light of this evidence, the European[14] and Canadian[11] agencies updated their ACS guidelines to recommend ticagrelor over other antiplatelet medications. Clopidogrel was only recommended in ACS patients who were scored a higher risk of bleeding, or when DAPT treatment extended beyond one year of the index hospitalization. The American Heart Association (AHA),[12]

meanwhile, added ticagrelor to their guidelines without any explicit superiority endorsement of the different DAPT regimes. The AHA recognized the need for replication and further research, a tenant of scientific discovery, which was noted in the call by the FDA for more research in their report approving ticagrelor.[15] As such, several large (n > 1,000) RCTs have explored ticagrelor in the subsequent decade following the publication of PLATO but none explicitly focused on the North American context.

The TicagRElor in pAtients with ST-elevation myocardial infarction treated with pharmacological Thrombolysis (TREAT) trial,[44] was an academically led, multinational, open-label RCT that investigated the efficacy and the safety of ticagrelor relative to clopidogrel in STEMI patients between 18 and 75 years of age. Of the 3,799 patients recruited from across 10 countries, 1,913 were randomized to ticagrelor and 1,886 to clopidogrel. After 12 months of follow-up, the ticagrelor arm reported 129 (6.7%) efficacy endpoints, a composite of death from vascular causes, myocardial infarction, or stroke, compared to 137 (7.3%) in the clopidogrel arm (HR, 0.93; 95% CI: 0.73, 1.18). The two treatment arms of the trial also reported similar rates (ticagrelor, 1.0%; clopidogrel,1.2%) of major bleeding episodes (HR, 0.86; 95% CI: 0.47, 1.56).

The POPular AGE trial[45] was another RCT that instead included NSTEMI patients from the Netherlands, over the age of 70 years. This open-label trial randomized 1,002 patients to clopidogrel (n = 500) and either ticagrelor (n = 475) or prasugrel (n = 27). Meaning ticagrelor and prasugrel formed one combined trial arm (n = 502) – which will be referred to as the ticagrelor group as it represents the majority (95%) of this treatment arm. This underpowered study reported that the MACE efficacy outcomes were similar in those assigned either to clopidogrel (11%) or ticagrelor (12%), resulting in an indeterminate effect (HR, 1.09; 95% CI: 0.75, 1.56) in favor of clopidogrel. Ticagrelor, however, was associated with a significant increase in TIMI defined major bleeding (HR,

2.38; 95% CI: 1.08, 5.26) and a non-significant increase in PLATO defined major bleeding (HR, 1.41; 95% CI: 0.93, 2.13), relative to clopidogrel.

Neither of these moderately large, follow-up RCT's were able to replicate the efficacy benefit of ticagrelor over clopidogrel, seen in PLATO. Though, it is possible these moderately sized trials may have been insufficiently powered[46] for the observed event rates in their respective studies. A further issue, the abovementioned RCTs may not include participants that represent the effect of DAPTs within a clinically relevant population.[46,47] In light of these underpowered studies and limitations in RCT transportability, the evaluation of the effects of ticagrelor in a larger, more clinically representative populations would be valuable to health practitioners and decision makers.

2.3 Other dual-antiplatelet research

2.3.1 Cohort studies

The RCT is often presented as the "gold standard" for efficacy research in clinical settings due to its strong internal validity.[48] However, often designed with strict inclusion/exclusion criteria, highly standardized treatment regimens and limited power (often due to the high financial costs), RCTs can be accompanied by concerns that the recruited study population and their adherence to their assigned treatment may not always reflect typical clinical conditions.[46,49–51] Performing an RCT can also be resource intensive. Challenged with patient recruitment, successful randomization, blinding practices, and the need for complete meticulous follow-up procedures can make RCTs more complex and costly than alternative designs.[52]

In the non-experimental domain, there have also been advancements in causal methodologies at the level of both the design phase, for instance directed acyclic graphs (DAG)[53,54] and the target trial framework,[55,56] and statistical stage, such as propensity scores, inverse probability of treatment weighting and G-methods.[57,58] Also improvements in the collection and widespread availability of quality electronic health records for research, has enhanced the practicality of

population-based cohorts for research.[47,48] The use of more readily available electronic health data to investigate the effectiveness of DAPTs in clinically relevant ACS populations has been explored in several recent non-randomized cohort studies that have often applied these more advanced causal inference techniques.

The SWEDEHEART study,[59] was a non-randomized cohort identified from the Swedish national MI registry, from which a total of 34,722 ACS patients who underwent a PCI between 2010 and 2013 were included. To assist in the identification of important covariates, a DAG was developed to establish the confounders needed to obtain conditional independence from regression adjustments. The confounders identified from the DAG were fit into random effects Cox proportional hazard (CoxPH) models to estimate the conditional association of the 11,221 ticagrelor and 23,501 clopidogrel subjects across both MACE and bleeding outcomes. After 1-year ticagrelor was associated with a significant decrease in MACE (adjusted HR [aHR], 0.83; 95% CI: 0.73, 0.95) and a non-significant increase in bleeding outcomes (aHR, 1.10; 95% CI: 0.89, 1.30). Findings that were similar to that of the original PLATO study.

Meanwhile, a North American cohort study,[60] relied upon a Coronary Heart Disease registry from Alberta, Canada, to identify ACS subjects discharged from hospital following a PCI. This large (n=11,185), non-randomized study, however, failed to replicate the overall PLATO findings after using multivariable CoxPH models to adjust for confounding. Though ticagrelor had fewer (10.3%) crude MACE outcomes, compared with clopidogrel (11.6%) after 1-year, the fully adjusted CoxPH model did not find a significant benefit in those who filled a ticagrelor prescription (aHR, 0.97; 95% CI: 0.85, 1.10), compared with clopidogrel. Furthermore, those ticagrelor subjects were also associated (ticagrelor, 6.8%; clopidogrel, 6.3%) with an increase in hospitalized bleeding, which remained significant even after adjustment (aHR, 1.51; 95%CI: 1.29, 1.78). Therefore, in this

clinically representative North American population, relative to clopidogrel, ticagrelor was associated with a higher risk of bleeding without the ischemic benefits that were observed in PLATO.

Similar to the TREAT and POPular AGE trial findings, the results from these non-randomized studies were not always consistent with those from the original PLATO trial. While these cohorts certainly improved on power and generalizability, relative to the moderately sized RCTs contentious debate related to whether the effect estimates from non-randomized studies are biased compared with RCTs, remains.[61–64] Nonetheless, this existing heterogeneity would benefit from further evaluation.

2.3.4 Meta-analyses

Meta-analyses are a method for synthesizing evidence from multiple study sources. The synthesis of multiple RCTs, identified through a systematic search, is commonly accepted as the highest quality of causal evidence, and well-executed meta-analysis are often placed atop the hierarchy of evidence pyramid.

An extension of the meta-analysis (MA), the network meta-analysis, is a method that allows for the comparison of multiple (>2) treatments.[65] Several publications have summarized some of the existing RCT evidence that examined antiplatelet therapeutics in the secondary prevention of clinical outcomes, following an ACS. One example, is a Bayesian network MA that identified a total of 37 studies,[66] a mix of RCTs and non-randomized designs, that compared either prasugrel, ticagrelor, or clopidogrel in STEMI patients undergoing a PCI. A fixed effect summary was performed on a sub-group of RCT study designs ($n_{studies}$= 10). After 1-year follow-up, they found prasugrel to be associated with a reduction in MACE, relative to both ticagrelor (OR, 0.78; 95% CI: 0.61, 0.96) and clopidogrel (OR, 0.68; 95% CI: 0.56, 0.81), without a significant difference in major bleeding outcomes. No direct head-to-head comparison between ticagrelor and clopidogrel was reported.

Another, network MA[67] identified 47 RCTS that investigated antithrombotic agents in patients presenting with an MI or ACS, that were followed between 1 and 41 months. In contrast to the previous network MA, the random effects generalized linear model found that neither ticagrelor (OR, 0.88; 95% CI: 0.76, 1.00) nor prasugrel (OR, 0.94; 95% CI: 0.82, 1.08) were significantly associated with a reduction in all-cause mortality, relative to clopidogrel. Also, ticagrelor had a non-significant risk of major bleeding relative to clopidogrel (OR, 1.11; 95% CI: 0.97, 1.26), while prasugrel was shown to have a significant increase (OR, 1.35; 95% CI: 1.05, 1.72) in bleeding outcomes.

A further network MA[68] identified a total of 12 RCTs that assessed ACS outcomes between ticagrelor, prasugrel, and clopidogrel with more than 30 days follow-up, post-hospital discharge. The 12 trials comprised of a total of 52,816 ACS subjects and were all evaluated to be of "low" risk of bias. Fixed or random effects analyses were performed depending on the level of heterogeneity between the included study estimates, as determined by the I^2 value. It was reported that fixed effect analyses for ticagrelor found significant reductions in all-cause (HR, 0.83; 95% CI: 0.75, 0.92) and cardiovascular-related mortality (HR, 0.82; 95% CI, 0.72, 0.92), compared to clopidogrel, while a random effect model found a non-significant reduction of MI outcomes (HR, 0.97; 95% CI: 0.78, 1.22). Prasugrel, however, was shown to be not significantly associated with a reduction in all-cause (HR, 0.92; 95% CI: 0.84, 1.02) and cardiovascular-related (HR, 0.90; 95% CI, 0.84, 1.01) outcomes in the fixed effect models, but it was associated with a significant reduction in MI (HR, 0.81; 95% CI: 0.67, 0.98) in the random effects model versus clopidogrel. Meanwhile, both ticagrelor (HR, 1.27; 95% CI: 1.04, 1.55) and prasugrel (HR, 1.26; 95% CI: 1.01, 1.56) had significantly more major bleeding events than patients randomized to clopidogrel.

In the same year, another network MA reported on 16 RCTs, evaluating ticagrelor, prasugrel or clopidogrel, that included a minimum of 100 ACS subjects.[69] Random effects modelling, on the

77,896 included ACS patients, found that relative to clopidogrel, ticagrelor was not associated with a significant decrease in MACE (OR, 0.89; 95% CI: 0.75, 1.05) nor a significant association with major bleeding outcomes (OR, 1.07; 95% CI: 0.97, 1.19). Prasugrel, in contrast, was associated with both a significant decrease in MACE (OR, 0.80; 95% CI: 0.69, 0.94) and significant increase in major bleeding (OR, 1.24; 95% CI: 1.05, 1.48) when compared with clopidogrel.

Evidently, the network MA's that have summarized the existing RCT evidence are quite heterogeneous. This was somewhat unsurprising, given the range of inclusions and exclusions, varying outcomes that were reported, and the inconsistent choice of analytical methods (fixed versus random effects). It led to a wide range of the total number of included RCTs (from 10 to 47 trials). In theory, a network MA of RCTs bolsters the overall sample size and should improve on the power limitations seen in the smaller trials, while maintaining the internal validity of the trials design. However, substantial underlying variabilities in the characteristics of populations recruited across the many RCTs clearly impacted the consistency of effects of DAPTs observed in trials involving ACS patients.

2.4 Research gap

At first glance, the aforementioned multinational TRITON-TIMI and PLATO study results are convincing. These large trials from across 30 and 43 countries, respectively, found a significant efficacy benefit of prasugrel and ticagrelor over clopidogrel – though, ticagrelor came without a significant increased risk of bleeding – and three major clinical guidelines[11,12,14] were quickly updated to reflect these findings. However, a closer look at the PLATO[9] subgroup analyses and then the subsequently published DAPT studies, reveal that the results are not totally consistent nor as persuasive. An article reporting on the pre-specified PLATO regional estimates and a Food and Drug Administration (FDA) found no ticagrelor benefit for MACE in the 1,413 subjects from the United States (HR_{US}: 1.27, 95%CI: 0.92 to 1.75)[70] nor the 1,814 North American subgroup (HR_{NA}:

1.25, 95%CI: 0.93 to 1.67).[15] The North American efficacy estimates deviated from the original overall PLATO estimate (HR, 0.84), and in fact suggest a possible increased risk in MACE.

This change in risk estimate found in the North American population relative to the overall results reported in PLATO highlights the challenges that can come with statistical modelling. The PLATO trial outcomes were pooled and analyzed using a fixed effects approach. This modelling choice assumed a single "true" treatment effect from ticagrelor across all study regions, and that the events observed in the North American patients were due to random chance. It resulted in a simple weighted average of the measured effect of ticagrelor across all the pre-specified PLATO regions. In contrast to the fully pooled version above, one could adopt a separate view in which each region is considered completely independently. The results from each region would be reported and interpreted individually. Another alternative view is that the observed HR discrepancies come from fundamental and meaningful differences in population characteristics and healthcare practices across the many included countries from which the patients were recruited. Under this perspective, it seems reasonable to assume the estimates from large, multinational RCTs come from a distribution of effects (random effects). This extra regional variability is an added uncertainty that should be properly accounted for in the statistical analyses.[71] A re-evaluation of the PLATO data,[16] using a Bayesian hierarchical (random effects) model to account for the observed regional differences, updated to a pooled HR of 0.87 and 95% credible interval between 0.70 and 1.15 to describe the effect of ticagrelor on MACE. The confidence in the superiority of ticagrelor was diminished, as the width of the 95% confidence limits became wider and included the NULL (HR, 1.0). The inferences drawn from the original PLATO results are not robust to a simple change from a fixed to a random effects model, as seen in the updated hierarchical estimate. Reviewers from the FDA did not dismiss this North American signal, as multiple calls for further evidence were made prior to the drug's approval.[15]

The potential for variability in the observed effects were not isolated to PLATO. TRITON-TIMI also enrolled patients (n=13,608) from 30 different countries. The effect of prasugrel on the reduction of ischemic endpoint varied from a HR of 0.76 to 0.87 across the five pre-specified study regions.[72] Though they reported no regional interaction (P-value > 0.1) for the primary efficacy endpoint, they did highlight significant heterogeneity in stent thrombosis (P-value = 0.033) and bleeding (P-value = 0.045) between countries defined as "high" or "low" on the Human Developmental Index. Since these RCTs are likely underpowered to detect an interaction effect, the results of these exploratory interaction analyses should be interpreted with caution on their own merits. Rather, these regional analyses simply highlight the potential for these large, multicenter RCTs to underestimate uncertainty and should re-emphasize the scientific importance of reproducibility and replication of research.[71]

This heterogeneity observed in PLATO and TRITON-TIMI was evidently not restricted to these two RCTs. In fact, as mentioned in preceding sections, the POPular AGE trial[45] noted a possible increased risk in TIMI-defined bleeding, which contrasts the findings from the initial RCT evidence – which could be explained by differing trial-level outcome definitions or important population differences. The observational studies, that included patients from different geographic regions, also came to different conclusions about the efficacy benefits and safety risks of ticagrelor relative to clopidogrel. Even the network MA's, which summarized the existing trial evidence reporting on DAPTs in ACS patients was widely inconsistent. Yet, the ACS guidelines[11–13] currently recommend prasugrel and ticagrelor over clopidogrel, though, the AHA is a bit more restrained in their language saying only that "it is reasonable to use ticagrelor in preference to clopidogrel".[12] The impediment becomes whether we can rely upon evidence from a single, albeit large, multicentre RCT from an analysis that did not consider regional variations but rather considered all participants, from different regions, to be identical. Though, Western ACS treatment guidelines remain

supportive of ticagrelor and prasugrel over clopidogrel the uncertainties regarding these benefits and the risks of the newer DAPTs are recognizable. Consequently, need for a further replication study is obvious, especially in the North American context.

2.5 Summary

Ischemic heart disease maintains a leading cause of mortality and morbidity in Canada, resulting in high healthcare utilization. DAPTs are a key element used in the prevention of secondary clinical outcomes. The ACS guidelines[11–13] are currently in favour of prasugrel and ticagrelor DAPT, though, the AHA is more restrained in their language.[12] However, following the hierarchical re-analysis of PLATO, subsequent DAPT RCTs, non-randomized registry studies, and several network MA's, the heterogeneity of the evidence has obscured much of the obvious clinical superiority of ticagrelor over clopidogrel that was derived from PLATO. Given the frequency of ACS events in Canada and the prevailing uncertainty of the superiority of ticagrelor, its potential increase in bleeding, its potentially negative effect of compliance due to twice daily dosing and its significant increase in cost mandates further research. This thesis aims to address this gap in knowledge using three separate study designs and datasets to answer the clinically relevant question of the effectiveness and safety of the ticagrelor, prasugrel, and clopidogrel DAPTs, especially in North America.

Chapter Three. Methodology

The epidemiological and statistical designs for each study included in this thesis are described in detail within each corresponding manuscript (Chapters 4 through 6). This current section provides additional information of some of the methodological aspects, including data sources and the weighted analytical designs.

3.1 Data sources

3.1.1 Bayesian network meta-analysis

The first manuscript (Chapter 4) in this thesis is a Bayesian network meta-analysis (BNMA) of RCTs evaluating DAPTs ticagrelor, prasugrel or clopidogrel on MACE and major bleeding outcomes. The data utilized in the BNMA was extracted from RCTs that were identified from two biomedical research databases, EMBASE and MEDLINE, of published literature as well as two repositories, the Cochrane controlled register of trials (CENTRAL) and clinicaltrials.gov, for pre-registration of RCTs. A Google Forms document was created and tested on several relevant RCTs for the data extraction process. The information that described the publishing aspects of the RCTs (authorship, the medical journal title, year of publication, the study's source of funding, registration number) and the details of the study population and design aspects (the average age of participants, the proportion of included males, the type of ACS patient recruited, number of treatment arms and the antiplatelet dosages, the length of study follow-up, the number of clinical centers and countries enrolling patients) was extracted for a qualitative assessment of the heterogeneity of participants included from the 29 identified RCTs. Importantly, the reported events of the components for the primary outcomes of interest were extracted individually across all RCTs in order to produce a homogeneous effect estimate for the primary efficacy outcome, MACE, which was a composite of all-cause mortality, non-fatal MI, or stroke. The purpose for this was two-fold, first, because published RCTs could report a composite efficacy endpoint that included different individual

components from our pre-specified MACE definition. Second, the published RCTs could report only on individual, non-composite outcomes. Thus, we selected all-cause mortality, MI, and stroke events as our composite since they are commonly defined trial endpoints reported in cardiovascular research. The extraction of the data from the RCTs was completed by S.K., while quality assessment of each RCT was completed by authors S.K., L.H., or R.H. in pairs. Each RCT identified in the systematic search was assessed across five categories in the Cochrane revised tool to assess risk of bias in randomized trials (RoB 2.0).[73]

The five RoB 2.0 assessment categories evaluate potential biases that can arise from (1) the randomization process, (2) deviations from treatment protocols, (3) missing data, (4) measurement, and (5) the choice of outcomes reported. The RoB 2.0 tool is a set of signalling questions with a set of response options – yes, probably yes, probably no, no and no information – that corresponds to a "level" of bias, ranging from "low", "some concerns", to "high", following a decision tree within each of the five bias assessment categories. This means that each of the five individual categories from the Rob 2.0 tool receives one of the three a bias score levels. To be included in the final overall outcome summary estimates of the BNMA (Chapter 4) the study must achieve a "low" risk of bias score across all five assessment categories. Any disagreements between the reviewers of the quality assessment of RCTs was resolved through discussion.

3.1.2 Non-randomized cohort study

The second manuscript (Chapter 5) relied upon the linkage of several Québec medico-administrative health and insurance databases to identify and follow ACS patients for important clinical outcomes within the province. The Régie de l'assurance maladie du Québec (RAMQ) provides the publicly funding pharmacare for residents of Québec above the age of 65 years, as well as for those younger and on social assistance. The pharmacare insurance claims database contains information on the type of drug dispensed, the dosage, and the duration of dosage for all those

covered by the provincial insurance program. RAMQ further contains another database of all medical services distributed within the publicly funded healthcare system. This database includes important information on healthcare billing codes, including procedures physicians record performing and their type of clinical specialty, which can measure important health utilization measures such as the number of physician visits. The RAMQ also anonymously links their information with the Ministère de la Santé et des Services sociaux (MSSS), and l'Institut national de santé publique du Québec (INSPQ) databases. The maintenance et exploitation des données pour l'étude de la clientèle hospitalière (MED-ÉCHO) data source, from a subset from the MSSS, contains the international classification of diseases, tenth revision (ICD-10) diagnostic coding for all hospitalizations within the province of Québec. Included is the principal diagnostic code and up to 15 secondary codes that may be used to assess comorbidities and potential confounders.

3.1.2.1 Cohort

The datasets, anonymously linked by RAMQ, were used to identify the study cohort for the second objective (Chapter 5). All ACS patients undergoing a PCI between April 1st, 2010 and March 31st, 2018 were ascertained by ICD-10 codes for an ACS hospitalization (ICD-10 codes: I20.x, I21.x, I22.x et I24.x) and a PCI procedure billing codes within 7 days of that index ACS code. To be included in the cohort patients needed to be discharged alive from hospital following their index ACS event and be over the age of 65 years. Restricting the study cohort to those over 65 years ensured a more representative sample of those at risk in the Québec population. Patients must also have filled at least one clopidogrel or ticagrelor DAPT medication in the 365 days after the index ACS hospitalization. Subjects were also excluded if they filled a DAPT prescription in the 365 days prior to the index ACS hospitalization.

3.1.2.2 Exposure

The DAPT exposure was defined by a filled prescription in the RAMQ drug insurance plan database via drug identification numbers (DIN). The first prescription, following hospital discharge, was set as time zero, the beginning of patient follow-up, to minimize prevalence and immortal time biases.[74] Similar to the commonly reported RCT analytical approach, we applied a intention-to-treat (ITT) definition where we based a subjects' exposure status on their first DAPT prescription and carried it through for the duration of their follow-up. With ASA being available over the counter, all patients were assumed to have received it in addition to their initial P2Y12 inhibiter.

3.1.3 The TC4 trial

In the third manuscript (Chapter 6), the Ticagrelor Compared to Clopidogrel in aCute Coronary syndromes (TC4) trial was a single center, open-label, active control, parallel-arm, RCT that enrolled patients undergoing a planned revascularization procedure at the McGill University Health Centre (MUHC). Patients were recruited through the cardiac catheterization laboratory, by our clinical nurse coordinator, Nina Mamishi, RN, MScN, MSc, who obtained informed consent for permission to follow participants using their health insurance information. All baseline patient characteristics were collected using the Research Electronic Data Capture (REDCap) software, hosted at the research institute of the MUHC.[75,76]

This pragmatic trial was designed to curtail barriers to RCTs in several ways. One was through the novel approach to randomization that was a time-cluster randomized (TCRX) design.[77] The TCRX process functioned in a way that ACS patients who arrived at the MUCH following an ACS episode, were randomized to ticagrelor or clopidogrel in alternating 2-month cluster periods. The first DAPT exposure period (October/November 2018) was set using a random number generating sequence algorithm. Then, the ACS patients who arrived to the MUHC, during the specific 2-month cluster, received the DAPT scheduled for that particular time period (see Figure

3.1.3.). The ACS patients that arrived in the subsequent 2-month period (December 2018/January 2019) then received the alternative DAPT, and so forth. The TCRX enhanced the practicality and efficiency for situations involving multiple clinicians and when rapid access to care and multiple physicians are involved in the acute care process, where individual randomization would be difficult.

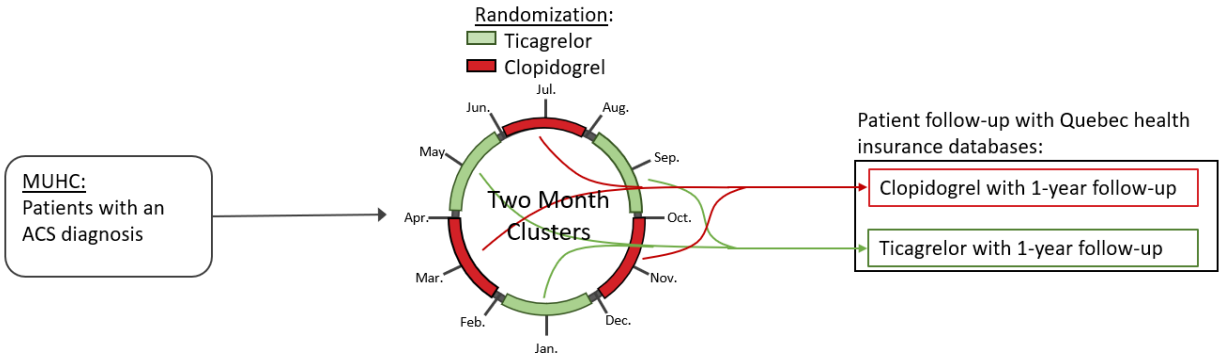

Figure 3.1.3. A visualization of patient's allocation to the dual-antiplatelet therapy ticagrelor or clopidogrel using two-month time cluster randomization

3.1.4 Outcome ascertainment

The outcomes ascertained during the one year of patient follow-up for the second and third objectives (Chapters 5 and 6) was accomplished through the linking of the Québec health administrative databases described in the section 3.1.2. above. The components of the primary effectiveness (mortality, MI, and ischemic stroke) and safety (gastrointestinal hemorrhage and hemorrhagic stroke) outcomes were identified using their ICD-10 codes (Table 3.1.4).

Table 3.1.4. The ICD-10 codes used to identify clinical outcomes within the electronic healthcare databases

Outcome	**ICD-10 code**
Myocardial infarction	I21.X, I22.X, I23.X, I25.2
Stroke (ischemic)	H34.1, I63.X, I64.X, I67.X
Stroke (hemorrhagic)	I60.X, I61.X, I62.X
Gastrointestinal Bleeding	K92.X

3.1.5 Data validity

The data used in the cohort formation for the second manuscript (Chapter 5) and the ascertainment of clinical outcomes for the second and third manuscripts (Chapters 5 and 6) relied on RAMQ prescription claims and MED-ÉCHO data sources that have been previously validated.[78–80] The prescriptions claims data accuracy was examined in a sample of 723 prescriptions filled from 306 patients who attended a internal medicine clinic, over a 12-week period.[78] They found that 83% of the prescriptions were filled by patients within 1-month, with 89% having accurately matched both the prescribing physician and medication type. The remaining 11% were reported to have the correct medication type but incorrect prescribing physician detail. This suggested that up to 100% of the 599 prescriptions prescribed to patients, from a single clinic, correctly matched the type of medication that was dispensed by the pharmacist. The prescribed duration of the prescribed medication also correctly matched to the RAMQ database in 72.1% of the dispensed prescriptions.

Important medical diagnoses, clinical endpoints, and comorbidities used to identify the ACS cohort, comorbidities, and clinical outcomes are captured by the MED-ÉCHO medico-administrative health database. Validation of this data reported good positive predictive values (PPV) and specificities (Sp) for cardiovascular patients.[79,80] For example, the medical charts of a 10% random sample of subjects enrolled in the MOXXI trial, were screened for 26 health indicators by trained health professionals. Of the components that comprise the Charlson comorbidity index, they all produced high specificities, above 90%, except for chronic obstructive pulmonary disease (Sp, 88%).[79] In another random sample of acute MI, PCI, and coronary artery bypass patients (CABG) sampled from 13 primary, secondary, and tertiary hospitals across Québec, there were good PPVs, sensitivity, and specificity values reported. In in the 1,989 sampled charts, it was found that acute MI had a PPV of 98% (95% CI: 97, 99), and revascularization procedures (PCI/CABG) had a PPV of 98% (95% CI: 96, 100) and sensitivity of 93% (95% CI: 89, 96) across all hospital centers. The PPVs

for important comorbidities ranged from 67% (cerebrovascular disease) to as high as 100% (Rheumatic disease, dementia, and acute renal disease), with most PPVs being measured in the 86% to 95% range.[80] Overall, these Québec health administrative and insurance databases provide high quality cardiovascular-related and prescription claims data to support the clinical research aspects of this doctoral thesis.

3.2 Statistical analyses

3.2.1 Bayesian network meta-analysis

For the first objective (Chapter 4) we used a network meta-analyses (NMA), which is a technique that allows for the synthesis of multiple treatment strategies from independent research studies, to synthesize existing DAPT evidence using both direct (head-to-head) and indirect (common node/comparator) comparisons.[81,82] Indirect effects come from comparing the non-head-to-head RCT treatment arms by using the information borrowed from across the studies that have a common node, or comparator.

There is a strong likelihood for variations in the outcome and length of follow-up reported across identified RCTs from the systematic review. Thus, we chose a Bayesian random effect generalized linear model with a logit outcome transformation, and a complementary log-log (cloglog) link function to account for the differing lengths of reported follow-up time.[65] The cloglog model estimates log-hazard ratios and assumes that hazards are constant over the duration of follow-up and is homogenous across each trial.[65]

Both fixed and random effects binomial likelihood models with the cloglog link function were applied to the data using Bayesian sampling from the Markov Chain Monte Carlo (MCMC). The models were estimated using a minimum of 50,000 iterations with a 10,000 burn-in period run on 3 chains. Model diagnostics were verified by examining traceplots (via monitoring of MCMC sampling). Non-informative priors were used for all model parameters since all available informative

evidence will contribute to the likelihood of the model. The random effects (RE) model was selected as our primary analysis as the fixed effect (FE) assumption of a homogeneous population-level effect across multiple study populations seems improbable.

The use of a Bayesian analytical approach allows for direct probability statements for the interpretation of the summarized evidence for the efficacy and safety endpoints. It eliminates the need for NULL hypothesis significance testing and the commonly misunderstood P-value.[83] Instead, probability statements, about the likely benefit or harm of the antiplatelet strategy relative to the reference, clopidogrel, will be presented. In addition, probability statements will be provided for a net "clinical" benefit or harm, which has been arbitrarily set at a 10% decrease (HR=0.9) or an equivalent increase (HR=1.11) in the effect estimate. The proportion of the posterior distribution that falls within the region of practical equivalence (ROPE), between HR = [0.9, 1.11], will also be reported.[84] In short, we are presenting readers the proportion of the HR posterior distribution that lies above, below, and between what we selected as "important" clinical thresholds.[85]

3.2.2 Non-randomized cohort

In the second objective (Chapter 5), inverse probability of treatment weighting (IPTW) methods were used to balance baseline measures between the ticagrelor and clopidogrel treatment arms. First, propensity scores were calculated using a maximum likelihood algorithm with a logistic regression, which calculated the predicted probabilities of being assigned to either ticagrelor or clopidogrel, based on measured baseline covariates. These propensity scores were then weighted, using the IPTW method that assigned *average treatment effect* (ATE) weights to individual study participants. The ATE is the causal contrast that mimics an RCT, where we are interested in estimating the causal effect in the whole study population. Meaning, that we are creating a pseudo-population that is balanced across the two treatment arms using the totality of the study population, and we would not be at risk of losing patients from matching procedures.[58,86] One potential

drawback is that this process can produce extreme weights. We decided to trim the weights at a maximum value of 5 to limit the potential impact from large ATE generated weights.[86–88] As a sensitivity analysis, we also used an entropy balancing (EBAL) algorithm to estimate ATE weights of the propensity score. This removes the risk of inter-user variability from the iterative process of manually identifying the propensity score model. Instead of individually exploring and repetitively comparing models with different covariate patterns (e.g., using a cubic spline for a non-linear covariates) the EBAL procedure does this automatically. The EBAL algorithm runs through an iterative process of estimating propensity score weights, through an iterative process that optimizes the balance of covariates in the weighting function.[89,90] These two methods should produce DAPT treatment arms that are conditionally exchangeable on the observed covariates identified in the Québec health administrative databases. These ATE weights are then simply added to the Cox proportional hazards (CoxPH) model[91] to estimate hazard ratios and their 95% confidence limits. Any covariates included in the propensity score models that remain unbalanced, which was set at a standardized mean difference of greater than 0.5, can be included in the CoxPH regression.[90]

3.2.3 The TC4 trial

For the third objective (Chapter 6), all analyses used Cox proportional hazards models to estimate hazard ratios (HR)[91] of ticagrelor compared with clopidogrel DAPT. We examined the time to the first occurrence of an outcome (see Table 3.1.4.), 1-year post-index ACS hospitalization, or a loss-to-follow-up. A full Bayesian statistical inference was performed using the No-U-Turn Sampler (NUTS), an extension of the Hamiltonian Monte Carlo (HMC) sampling,[92] to estimate the posterior of the HR and 95% credible intervals (95% CrI). The NUTS algorithm is considered to be more efficient than other Gibbs samplers.[92] Three HMC chains, each a minimum of 10,000 iterations with a 5,000 burn-in period were used to produce a total of 15,000 posterior samples. For each model, the three chains were observed to determine if they had converged.

For each outcome (see Table 3.1.4.), we fit both a fixed effect (assumes the same treatment effect within each cluster) and a hierarchical CoxPH model (assumes the treatment effect within each cluster comes from a distribution). Model comparison was done using the leave-one-out cross-validation (LOO), to evaluate model fit.[93] Since we used a full Bayesian analysis, we placed prior distributions on model parameters. For nuisance parameters we used the non-informative priors: a Student-t prior, with 3 degrees of freedom (student_t(3, 0, 2.5) for the standard deviation (*sd*) and a Lewandowski-Kurowicka-Joe (LKJ) uniform distribution (η=1) for the correlation structure of the cluster-levels in the random effects model. We also supplied priors for the population level-effect of the treatment on the primary outcomes.

It is recommended to present the totality of clinical possibilities as clinical beliefs may vary,[94,95] thus we included a range of treatment priors (see Table 3.2.3.). A Student-t distribution around the NULL effect (HR=1.0), with 3 degrees of freedom and a *sd* of 5 was used as a vague (i.e., non-informative) prior for both the MACE and bleeding outcomes. The "skeptical", "enthusiastic", and "summary" informative priors[94,95] were extracted from the literature. The North American, PLATO estimates (HR_{MACE} = 1.25, 95% CI: 0.93, 1.67; HR_{Bleed} = 1.05, 95% CI: 0.76, 1.45) and the results from a Bayesian Network Meta-analysis (BNMA) of all previous RCTs[96] (HR_{MACE} = 0.95, 95% CrI: 0.81, 1.14; HR_{Bleed} = 1.07, 95% CrI: 0.99, 1.17) formed the *skeptical* and *summary* priors, respectively. Finally, the *enthusiastic* prior was formed by combining the point estimate from the pooled PLATO results (HR_{MACE} = 0.84; HR_{Bleed} = 1.04) with the *sd* from the North American subgroup from PLATO (sd_{MACE}=0.17 & sd_{bleed}=0.16).

The minimum important difference (MID)[85] of each DAPT comparison were also presented as probability statements, which was set at a greater than 10% change. A 10% decrease in the HR is represented as 0.9, the lower MID threshold and the inverse (HR>1.11) as the upper threshold. The range of practical equivalence (ROPE) is the region between those two thresholds. Meaning, when

the posterior of the HR falls between 0.9 and 1.11. We reported on the proportion of the posterior distribution that lies above, below, and between our, admittedly somewhat arbitrary, clinical thresholds. The analyses for this third objective followed the Bayesian Analysis Reporting Guidelines.[84]

Table 3.2.3: Distributions representing a range of Bayesian clinical priors for MACE and bleeding outcomes.

Type of prior	**Distribution†**	
	MACE	**Bleeding**
Vague	student_t(3, 1, 5)	student_t(3, 1, 5)
Skeptical (PLATO[NA])	N(1.25, 0.15)	N(1.05, 0.17)
Enthusiastic (PLATO)	N(0.84, 0.15)	N(1.04, 0.17)
Summary (BNMA)	N(0.95, 0.09)	N(1.07, 0.05)

Distributions: student_t(degrees of freedom, mean, standard deviation); N(mean, standard deviation)
Abbreviations: MACE, major acute coronary syndrome; NA, North American; BNMA, Bayesian network meta-analysis.
†For Bayesian model specification, prior distributions are log-transformed for inclusion into the 'brms' R package

3.3 Ethics

The first objective (Chapter 4) did not require ethics approval as all clinical information was in aggregate form and extracted from public facing documents. The second and third manuscripts (Chapters 5 and 6) received approval from the McGill University Health Centre's Research Ethics Board (MUHC REB). The MUCH REB protocol numbers are "DAPT / 2019-4993" and "TC4 / 2019-4530", respectively for objectives two and three and the correspondence is provided in appendices of the corresponding manuscript.

Chapter Four. The efficacy and safety of the prasugrel, ticagrelor, and clopidogrel dual antiplatelet therapies following an acute coronary syndrome: A systematic review and Bayesian network meta-analysis

4.1 Preface

Acute coronary syndromes (ACS) remain a leading cause of mortality and morbidity.[1,2] Dual-antiplatelet therapies (DAPT) are routinely prescribed for the prevention of secondary ischemic events following an index ACS. While ticagrelor and prasugrel have been reported as superior to clopidogrel, based on evidence from two large multinational randomized controlled trials (RCTs),[9,10] there remains some uncertainty in the benefits of ticagrelor in North American patients. Relative to clopidogrel, ticagrelor was associated with a non-significant increased risk of major acute coronary events, in this regional subset.[15] The first objective of this thesis is to systematically search and summarize the literature for RCTs that compare the efficacy and safety of the DAPTs of prasugrel, ticagrelor, or clopidogrel, with a special focus on studies conducted in North America.

4.2 Title page

The efficacy and safety of the prasugrel, ticagrelor, and clopidogrel dual antiplatelet therapies following an acute coronary syndrome: A systematic review and Bayesian network meta-analysis

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4.3 Abstract

Background: The dual-antiplatelet therapies (DAPT) of clopidogrel, prasugrel, or ticagrelor in concomitant use with acetylsalicylic acid are the contemporary treatment regimens for acute coronary syndromes (ACS). Systematic comparative effectiveness and safety analyses currently lack clinically meaningful interpretations of the summarized evidence.

Methods: We systematically searched (August 1st, 2022) MEDLINE, EMBASE, CENTRAL, and clinicaltrials.gov for randomized controlled trials (RCTs) that reported on either the efficacy or safety between clopidogrel, prasugrel, or ticagrelor DAPTs in ACS patients. The primary efficacy endpoint was a composite of all-cause mortality, a recurrent non-fatal myocardial infarction, or non-fatal stroke. The primary safety endpoint was study-reported major bleeding events. A Bayesian network meta-analysis was performed using a generalized linear model logit transformation with a log-transformation of 'time' for varying lengths of study follow-up. Studies published in either English or French with a minimum of 6 months of follow-up and a "low" rating from the Cochrane risk of bias assessment tool were included in the main analyses. Fixed and random effects models fit was assessed by the deviance information criterion (DIC) and node-splitting methods were used to assess the consistency of direct and indirect network evidence. An HR <0.9 and >1.11 were set as our clinically important thresholds, with the range of practical equivalence (ROPE) as a HR between 0.9 and 1.11.

Results: From a total of 15,232 articles identified, 138 were selected for full-text review. From a total of 29 identified RCT's, 17 trials, representing 57,814 subjects, were identified as a "low" risk of bias and were included in the final Bayesian network meta-analysis. Compared to clopidogrel, prasugrel and ticagrelor reduced major acute coronary events (MACE) endpoints by a median of 13% (Hazard ratio $[HR]_{PC}$, 0.87; 95% credible interval [95% CrI]: 0.74, 1.06) and 5% (HR_{TC}, 0.95; 95% CrI: 0.81, 1.14), respectively. The HR posterior distributions estimated that prasugrel had a 67.5% chance of producing a clinically meaningful – greater than 10% (HR<0.9) – decrease in the risk of MACE outcomes, while ticagrelor only had a 22.4% chance of exceeding the clinically important threshold. The primary safety outcome found prasugrel (HR_{PC}, 1.23; 95% CrI: 1.04, 1.40) and ticagrelor (HR_{TC}, 1.07; 95% CrI: 0.99, 1.17) DAPTs to be associated with a median increase in events relative to clopidogrel. This translates to a probability of a clinically meaningful increase (HR>1.11) in major bleeding of 83.7% for prasugrel and 67.7% for ticagrelor, when compared to clopidogrel.

Conclusion: When compared with ACS patients assigned to clopidogrel, prasugrel and ticagrelor were associated with moderate and modest probabilities in clinically meaningful MACE reductions, respectfully. Prasugrel and ticagrelor had high and modest probabilities of clinically meaningful increases in bleeding. Despite guideline recommendations, the net clinical benefit for these drugs compared to clopidogrel appears uncertain.

4.4 Introduction

Dual antiplatelet therapy (DAPT), consisting of the concomitant use of acetylsalicylic acid (ASA) and clopidogrel, is standard secondary prevention following an acute coronary syndrome (ACS) hospitalization. The most recent American,[1] Canadian,[2] and European[3] ACS guidelines suggest the use of ticagrelor and prasugrel DAPT over clopidogrel for the treatment of ACS, unless patients are at high-risk of bleeding. These ACS guidelines largely rely on evidence from two large multinational randomized controlled trials, PLATO[4] and TRITON-TIMI-38,[5] that reported a clinical efficacy benefit of ticagrelor (hazard ration[HR]: 0.84, 95% confidence interval [CI]: 0.77 to 0.92; P<0.001) and prasugrel (HR: 0.81, 95%CI: 0.73 to 0.90; P<0.001), respectively, when compared to clopidogrel.

However, if one desires to personalize DAPT choice, for example by considering the geographic region where the patient is treated the situation becomes less clear. Two publications report on the pre-specified PLATO regional analysis. One study includes the 1,413 patients from the United States (HR_{US}: 1.27, 95%CI: 0.92 to 1.75)[6] and another by the Food and Drug Administration (FDA) on the whole 1,814 North American subjects (HR_{NA}: 1.25, 95%CI: 0.93 to 1.67),[7] find no benefit for the efficacy outcome, major acute coronary events (MACE), from ticagrelor over clopidogrel. In fact, the sub-analyses suggest the potential for an increase in MACE outcomes with reported HRs greater than one. These North American sub-population estimates deviate substantially from the overall pooled effect reported for the entire study population (HR_{PLATO}: 0.84).

It may be argued that there is *one* overall "true" treatment effect (a fixed effect) and that the results within North American patients are simply due to random chance. Alternatively, it can be viewed that the observed HR discrepancies are due to inherent and meaningful population differences and healthcare practices across the study regions; patients were recruited from a total of

43 and 21 countries in PLATO and TRITON-TIMI-38, respectively. It is plausible that the effect estimates from these large RCTs rather come from a distribution of effects (a random effect) and the added uncertainty from regional variability should be accounted for in the analyses.[8] A recent discussion[9] describing the utility of Bayesian analytical methodologies, re-analyzed the PLATO data applying a hierarchical (random effects) approach accounting for the regional differences. They reported a pooled HR of 0.87 with a 95% credible interval (CrI) from 0.70 to 1.15. The superiority of ticagrelor over clopidogrel became less confident using the hierarchical model, as the interpretation of the effect estimate was not robust – the 95%CrI crosses the NULL (HR=1.0) – to a simple change in a modelling assumption (fixed versus random effects). This signal was not dismissed in the FDA report,[7] as multiple reviewers made calls for further evidence prior to the drug's approval.

The purpose of this paper is to systematically search the literature for RCTs comparing clopidogrel, ticagrelor, or prasugrel in ACS patients that include MACE and/or major bleeding outcomes with a minimum of 6 months follow-up. A Bayesian network meta-analysis will be performed to compare the direct and indirect evidence on the efficacy and safety across the three DAPTs, with a particular focus on identifying RCT evidence from North American study populations.

4.5 Methods

Following the PRISMA extension for network meta-analyses[10] we performed a systematic search of EMBASE, MEDLINE, the Cochrane controlled register of trials (CENTRAL), and clinicaltrials.gov, last updated on August 1st, 2022. The PRISMA checklist can be found in the appendix. The complete search strategy is also described in the appendix but briefly, we searched for RCTs using the terms "acute coronary syndrome" or "myocardial ischemia" or "unstable angina" or "ST segment elevation myocardial infarction" or "non-ST segment elevation myocardial infarction" or "unstable angina" and related keywords. Additionally, we searched for "dual antiplatelet therapy" or "DAPT" or a combination of "prasugrel" and "clopidogrel" and "ticagrelor". A hand-search of the references from relevant articles was further performed. Article inclusion criteria were: (1) patients diagnosed with ACS with or without percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) surgeries; (2) patients assigned to two of the following DAPT treatment regimens: clopidogrel, ticagrelor, or prasugrel – with a minimum of 6-month planned treatment duration and follow-up; (3) randomized controlled trials of human subjects; (4) reporting at on the main composite outcome of MACE (defined as mortality, recurrent MI, or stroke); and, (5) studies published in either English or French.

Due to likely variations in reporting definitions of major acute coronary events (MACE), we adopted a "hard" MACE definition for the primary efficacy outcome, a composite measure of reported all-cause mortality, non-fatal MI, or stroke. Secondary efficacy endpoints include the individual MACE outcomes, all-cause mortality, non-fatal MI, or non-fatal stroke, as well as cardiovascular-caused mortality, if available. The primary safety endpoint of interest was major bleeding as defined by the trial. Our expectation was that most studies will report Thrombolysis In Myocardial Infarction (TIMI) major bleeding, PLATO-defined major bleeding, and Bleeding Academic Research Consortium (BARC) types 3-5, but we accepted the bleeding definition

provided by the included study (Table 1). The secondary safety endpoint included minor bleeding as defined by TIMI, PLATO, and BARC (types 1 and 2), or other reported minor bleeding definitions.

Data extraction was performed by S.K. and quality assessment of eligible studies was carried out simultaneously by S.K., L.F., and R.H. Information on the year of publication, sample size, the loading and maintenance dosages of treatment regimens, length of planned treatment duration, the mean age, body mass index (BMI), proportion of males, and those who underwent PCI or CABG, as well as the description of the study population and country of origin were collected. The Cochrane revised tool to assess risk of bias in randomized trials (RoB 2.0)[11] was used to assess allocation concealment, blinding of participants and trial personnel, reporting on completeness and selection of outcomes, and other biases. The scoring system for each component of the RoB 2.0 includes a "low", "some concerns" or "high" risk of bias. Studies with a score of "low" across all five categories were considered low risk of bias and included in the analyses. A funnel plot was used to visually assess publication bias.

STATISTICAL ANALYSES

Mixed treatment, or network meta-analyses (NMA), is a technique that allows for the synthesis of multiple treatment strategies from independent research studies, using direct and indirect comparisons.[12,13] Direct effects come from the head-to-head comparisons of the treatments. Indirect effects come from comparing the non-head-to-head comparisons by using the information from across the studies that have a common node, or comparator.

Due to the potential for variations in reporting practices of the outcomes of interest, we chose a Bayesian random effect generalized linear model with a logit outcome transformation.[14] The further potential for trials reporting differing lengths of follow-up, a complementary log-log (cloglog) link function was included to the model, by adding a log(follow-up time) variable, to

account for these variations in follow-up times. The cloglog model estimates log-hazard ratios and assumes that hazards are constant over the duration of follow-up and is homogenous across each trial.[14]

Both fixed and random effects binomial likelihood models with a cloglog link function were applied to the data using the "*gemtc*" R package[15] with Bayesian posterior distribution sampling from the Markov Chain Monte Carlo (MCMC) which was estimated via the Just Another Gibbs Sampler (JAGS) using the "*rjags*" R package.[16] The models were estimated using a minimum of 50,000 iterations with a 10,000 burn-in period run on 3 chains. Model diagnostics were verified by examining traceplots (via monitoring of MCMC sampling), posterior distributions and a multivariate potential scale reduction factor (mpsrf) above 1.1.[17,18] In the case of model inconsistencies, the burn-in and number of iterations were increased. The *gemtc* default non-informative priors were used for all model parameters. Statistical analyses were performed using R version 4.0.2 from the R Project for Statistical Computing.[19]

The random effects (RE) model was selected as our primary analysis as the fixed effect (FE) assumption of a homogeneous population-level effect across multiple study populations seems improbable. Nonetheless, the assessment of model fit was performed using the lowest deviance information criterion (DIC) – the sum of the models' residual deviance and its' leverage – which penalizes models with more parameters. Some have suggested that when a FE and a RE model are within five DIC units,[14] the model with fewer parameters (FE) should be favoured. To be comprehensive, we also reported the FE estimates for comparative purposes. Further, the network consistency – the agreement between the direct, indirect and total network evidence across the pair-wise comparisons – was visually assessed using the node splitting methods.[12]

The use of a Bayesian analytical approach allows for direct probability statements for the interpretation of the summarized evidence for the efficacy and safety endpoints. It eliminates the need for NULL hypothesis significance testing and the commonly misunderstood P-value.[20] Instead, probability statements, about the likely benefit or harm of the antiplatelet strategy relative to the reference, clopidogrel, will be presented. In addition, probability statements will be provided for a net "clinical" benefit or harm, which has been arbitrarily set at a 10% decrease (HR=0.9) or an equivalent increase (HR=1.11) in the effect estimate. The proportion of the posterior distribution that falls within the region of practical equivalence (ROPE), between HR = [0.9, 1.11], will also be reported.[21] In short, we are presenting readers the proportion of the HR posterior distribution that lies above, below, and between the "important" clinical thresholds. [22]

4.6 Results

A total of 9,196 titles and abstracts were screened following the removal of duplicates and research abstracts from the 15,232 records identified from the systematic search. This resulted in a full-text assessment of 138 articles from which 29 trials,[4,5,23–49] for a total of 60,278 study participants, met the inclusion criteria for the primary efficacy or safety endpoint. A flowchart (Figure 1) presents a summary of the screening process, and a description of the included studies are presented in Table 1. Seventeen[4,5,23–37] of the 29 articles were assessed a "low" risk of bias score, across all five RoB 2.0 assessment categories, and included in the Bayesian network meta-analysis.

For this triangular NMA a total of nine (52.9%),[4,23–30] of the included RCTs compared the DAPTs' clopidogrel with ticagrelor, while five (29.4%)[5,31–34] trials compared clopidogrel to prasugrel and three (17.6%)[35–37] contrasted ticagrelor with prasugrel (Figure 2). The majority of the included RCTs built-in 12 months of follow-up time, with two[24,27] studies following patients for 6 months, and another two trials[5,31] following subjects for up to 15 and 30 months, respectively. The average or median age of the included study populations ranged from 47.9 years [28] to 80 years.[33] In the majority (76.5%) of included trials, the median age was between 60 to 69 years. Twelve (70.6%) of the study populations had planned invasive ACS management and reported that greater than 80% of patients underwent a PCI. All but one RCT (5.9%)[27] reported studying a majority (>60%) of male patients.

PRIMARY OUTCOMES

Major acute coronary events

The seventeen included studies, with a total of 57,814 subjects, reported a total of 6,897 (11.9%) "hard" MACE outcomes. The RE model (DIC_{RE}=56.60) was considered a better overall fit relative to the FE model (DIC_{FE}=65.29). Visual inspection of the node-splitting models favoured the

RE model, with more concordance between the direct, indirect, and network evidence (Figure 3E-F), suggesting heterogeneity of the efficacy estimates across the included pairwise RCTs.

The ticagrelor to clopidogrel HR estimand for MACE outcomes was 0.95 (95% CrI: 0.81, 1.14) (Table 2; Figure 5). This translated to 22.4% of the posterior distribution being below the 10%, clinically important reduction threshold (HR<0.9) (Table 2; Figure 3C). The majority of the HR_{TC} distribution (73.2%) for MACE outcomes fell within the ROPE (HR = [0.9 to 1.11]).

The prasugrel to clopidogrel HR estimand for MACE outcomes was, 0.87 (95% CrI: 0.74, 1.06) (Table 2; Figure 5). This extrapolated to 67.5% of the posterior distribution of the HR falling beyond the meaningful clinical threshold (HR<0.9) for a reduction in MACE outcomes, with 31.4% of the distribution captured within the ROPE (Table 2; Figure 3C).

Major bleeding

The primary safety outcome, reported major bleeding (Table 1), was available in the 17 (57,110 patients) trials for a total of 2,858 (5.0%) recorded events. The RE model (DIC_{RE}=52.82) was considered a similar fit overall relative to the FE model (DIC_{FE}=54.40). Visual inspection of the node-splitting models found superior concordance between estimates from the direct, indirect, and network in the RE model (Figure 4 E-F), across all 3 pairwise comparisons.

In comparison to clopidogrel, the ticagrelor HR estimand for major bleeding, as defined within the included trial, was 1.16 (95% CrI: 0.98, 1.48) (Table 2; Figure 5). This translated to 67.7% of the posterior surpassing a clinically meaningful increase in major bleeding events in those exposed to clopidogrel, relative to ticagrelor, while 31.9% of the posterior fell within the ROPE (Table 2; Figure 4C).

The prasugrel to clopidogrel HR estimand for major bleeding events was 1.23 (95% CrI: 0.99, 1.57) (Table 2; Figure 5). This extrapolated to 83.7% of the posterior surpassing the clinically important threshold for an increase in bleeding, with 15.7% found within the ROPE (Table 2; Figure 4E).

SECONDARY OUTCOMES

All-cause mortality

The 17 RCTs reported a total of 2,688 (4.6%) mortality outcomes. The FE (DIC=51.38) and RE (DIC=51.60) models had comparable fits, though, node-splitting models identified some potential inconsistency (disagreement) between the indirect, direct, and network model estimates. The HR estimand for all-cause mortality, comparing ticagrelor to clopidogrel, was 0.87 (95% CrI: 0.75, 1.07), where 64.2% of the posterior fell below the clinically important reduction threshold (HR<0.9). Meanwhile, the HR estimand, for prasugrel relative to clopidogrel, was 0.94 (95% CrI: 0.79, 1.14), with 30.5% of the posterior found below the clinically meaningful threshold (Supplemental Table 2).

Cardiovascular-related mortality

Fifteen trials (57,438 patients) reported 2,182 (3.80%) cardiovascular-related deaths (CV-deaths). In comparison to clopidogrel, the HR estimand of CV-related mortality for ticagrelor was 0.85 (95% CrI: 0.73, 1.04). It was estimated that 75.3% of the posterior was below the clinically meaningful threshold. Meanwhile, the HR estimand comparing prasugrel to clopidogrel was 0.90 (95% CrI: 0.76, 1.07), where 51.6% of the posterior distribution was below the threshold of clinical importance (Supplemental Table 2).

Myocardial infarction

The 17 RCTs (57,148 patients) reported a total of 3,539 (6.1%) non-fatal MIs. The RE model (DIC=52.09) was borderline a statistical improvement (<5 DIC units), relative to the FE model (DIC=57.00). However, moderate qualitative inconsistency from the node-splitting method reinforced the RE model assumptions. When compared to clopidogrel, the HR for MI outcomes for ticagrelor was found to be 0.94 (95% CrI: 0.76, 1.17), with 32.8% of the posterior being represented below a clinically meaningful threshold and 61.2% within the ROPE. The HR estimand, comparing prasugrel to clopidogrel, was estimated as 0.81 (95% CrI: 0.65, 1.00) (Supplemental Table 2). A total of 87.4% of the prasugrel posterior was beyond the threshold of a clinical important reduction in MI's.

Stroke

A total of 12 studies (56,521 patients) reported on 670 (1.2%) stroke outcomes. Node-splitting models suggested the network to be unstable with inconsistent direct, indirect, and network estimates across all three (C-T, C-P, and T-P) pair-wise comparisons. The posterior distributions for ticagrelor (HR, 1.02; 95% CrI: 0.72, 1.33) and prasugrel (HR, 0.88; 95% CrI: 0.64, 1.18), when compared with clopidogrel are presented (Supplemental Table 2).

Minor bleeding

Twelve (49,677 patients) RCTs reported a total of 1,352 (2.7%) minor bleeding events. Node-splitting models, under both FE and RE assumptions, suggested the network to be somewhat unstable regarding the inconsistent direct, indirect, and network estimates across all three (C-T, C-P, and T-P) pair-wise comparisons. The RE posterior distributions for minor bleeding outcomes for

ticagrelor (HR, 1.35; 95% CrI: 1.08, 1.71) and prasugrel (HR, 1.42; 95% CrI: 1.08, 1.94), when compared with clopidogrel are provided (Supplemental Table 2).

The FE results for both the primary and secondary, efficacy and safety outcomes were reported in the appendix (Supplemental Tables 1 & 3).

4.7 Discussion

The main efficacy findings from this large (n=57,814) Bayesian network meta-analysis of DAPT strategies following an ACS hospitalization are: (1) ticagrelor is associated with a small decrease in MACE outcomes but that is unlikely to provide a meaningfully clinically important (>10%) reduction in endpoints; (2) prasugrel, when compared with clopidogrel, is associated with a larger (13%) reduction in MACE but only a moderate probability (67.5%) of providing a clinically relevant reduction. The primary safety findings from the NMA include: (3) that ticagrelor compared to clopidogrel is associated with an increase in major bleeding events, but only a small probability (21.3%) that this exceeds a clinically meaningful increase. And (4) prasugrel, when compared with clopidogrel, is also associated increased in major bleeding with a moderate to high probability (85.3%) that this exceeds a clinically meaningful threshold.

The results from our Bayesian NMA do not fully align with the recommendations of the published North American guidelines[1,2] and other previous NMAs.[50,51] While the summary estimates for prasugrel and ticagrelor show a reduction in MACE outcomes, they do not demonstrate the same degree of certainty as the PLATO and TRITION-TIMI trials or NMAs, on which the guidelines rely. Using classic confidence limits of 95%, neither prasugrel (95%CrI: 0.74, 1.06) nor ticagrelor (95%CrI: 0.81, 1.14) establish superiority over clopidogrel. Further, our results estimate that there is a 32.5% and 77.6% chance that prasugrel and ticagrelor, respectively, do not provide a clinically meaningful reduction in MACE endpoints when compared with clopidogrel. There is some

concordance in the guidelines with respect to the primary safety outcome, major bleeding, and exercising caution when using these more potent platelet inhibitors – prasugrel (95% CrI: 0.99, 1.17) and ticagrelor (95% CrI: 1.04, 1.40) – in subjects with a higher risk of bleeding. It remains a balance of weighing the benefits and harms of the treatments and secondary patient outcomes.

The strength of our findings are built upon the mixed-treatment models of the BNMA, which optimizes evidence synthesis, under certain assumptions, by permitting the use of both direct and indirect evidence across the three guidelines approved DAPTs – clopidogrel, ticagrelor, and prasugrel – in ACS patients. The inclusion of only low-risk RCTs bolsters the internal validity of the current findings, which is supported by a large ACS patient population (n=57,814). The Bayesian approach in this study allows for direct probability statements to be made for the interpretation of the treatment effect estimates, thus avoiding the often-misinterpreted P-value. This BNMA goes beyond others[50,51] by also providing probability statements regarding the chances of observing a clinically meaningful change (>10%) in the benefits or harms, an important factor for clinical decision-makers.

As with all research, our study comes with limitations. Our findings *do not* account for the potential challenges previously identified internal modelling decisions (RE vs FE) found in the large multinational RCTs[4,5,23,31] included in this BNMA. This study assumed that the within study variance was properly specified in the individual RCTs when the between-study and between-study-arm variance were modelled. Meaning, we likely underestimated the size of the credible intervals of the posterior estimates. Further, our BNMA models included only those studies that received a "low" risk of bias score across the five RoB 2.0 bias assessment tool. Twelve studies (2,464 patients)[38–41,43–49] received at minimum a "some concerns" reviewer score in at least one RoB 2.0 assessment category. Of note, all twelve excluded studies recruited 200 or fewer patients, and only two[38,49] of the

excluded RCTs (16.7%) reported a RCT registration number versus all seventeen (100%) of the included trials. Conditioning the analyses on those RCTs with a "low" risk of bias score could also impact funnel plot symmetry for bias assessment. Although our analyses did not elucidate any concerns regarding the distribution of effect sizes (Supplemental Figure 1), it has been suggested that this is difficult to assess with fewer than 10 studies[52] – T vs. C (n=9); P vs. C (n=5); and, P vs. T (n=3). Transitivity (between network arms) and homogeneity (between study arms) can be assessed qualitatively by comparing the similarity of study populations and treatments. There were some minor differences across some of the study populations, such as age, percent PCI, percent male characteristics, and outcome definitions, which could represent some between study heterogeneity of which could impact the transitivity and consistency assumptions. Overall, the populations represented patients with acute cardiac symptoms (STEMI, NSTEMI, and/or UA) and received well defined medications. Reporting differences for the efficacy outcome was minimized through adopting a "hard" MACE outcome, to include the more objective clinical outcomes of death, MI, or stroke.

In conclusion, ticagrelor was estimated to have a 22.4% chance of decreasing MACE and a probability of 21.3% of increased major bleeding, while prasugrel was associated with a 67.5% probability in reducing MACE and an 85.3% increased chance of major bleeding outcomes, when compared with ACS patients assigned to clopidogrel. The results of this BNMA do not provide robust evidence regarding the superiority of ticagrelor and prasugrel, over clopidogrel, as the 95% credible intervals include the NULL and are substantially captured within the ROPE region. We were also unable to identify a recent RCT on North American subjects. Further research is required to better understand the heterogeneity in the effects of DAPTs within diverse ACS populations, especially with limited North American evidence.

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4.9 Tables

Table 4.9.1 The descriptive characteristics of the twenty-nine studies identified from the systematic review. The first seventeen studies were identified as having a "low" risk of bias and included in the meta-analysis.

Study; First author (year)	Registry	N.Cnts	Sample Size	DAPT, dose (mg)	F-up (mths)	Age (years)	PCI (n, %)	Men (n, %)	ACS population	MACE definition	Major Bleeding definition	RoB 2.0 score
TREAT; Berwanger, O. (2019)	NCT 02298088	10	1886	Clopidogrel, 75	12	58.8	1064, 56.4	1449, 76.8	STEMI, <75yrs, w/ fibrinolytic therapy	death from vascular causes, myocardial infarction, or stroke	TIMI major, PLATO major	low
			1913	Ticagrelor, 90	12	59	1095, 57.2	1480, 77.4				
Gasecka, A. (2020)	NCT 02931045	1	28	Clopidogrel, 75	6	63	28, 100.0	21, 75	STEMI, NSTEMI; PCI	N/A	N/R	low
			27	Ticagrelor, 90	6	66	27, 100.0	19, 70				
POPular AGE; Gimbel, M. (2020)	NCT 02317198	1	500	Clopidogrel, 75	12	77	232, 46.4	313, 63	NSTEMI, >70yrs	death from any cause, nonfatal MI, nonfatal stroke, and PLATO major and minor bleeding	TIMI major	low
			502	Ticagrelor, 90	12	77	242, 48.2	325, 65				
PHILO; Goto, S. (2015)	NCT 01294462	3	400	Clopidogrel, 75	12	66	338, 84.5	307, 76.8	NSTEMI, STEMI	CV-related death, MI, and stroke	PLATO major	low
			401	Ticagrelor, 90	12	67	340, 84.8	306, 76.3				
He, P. (2021)	ChiCTR 1800015104	1	133	Clopidogrel, 75	6	64	133, 100.0	47, 35.3	PCI diabetic	nonfatal MI, target vessel revascularization, rehospitalization, stroke, and death from any cause	BARC types 1 - 5	low
			133	Ticagrelor, 90	6	64	133, 100.0	39, 29.3				
Mohareb, M.W. (2020)	NCT 03613857	1	472	Clopidogrel, 75	12	47.91	472, 100.0	302, 64.0	PCI	recurrent ACS, namely, acute stent thrombosis, nonacute stent thrombosis, nonfatal MI, cardiovascular death, and nonfatal stroke	major bleeding events	low
			471	Ticagrelor, 90	12	49.84	471, 100.0	318, 67.5				
TICAKOREA; Park, D-W. (2019)	NCT 02094963	1	400	Clopidogrel, 75	12	62.3	342, 85.5	302, 75.5	STEMI, NSTEMI, UA, planned invasive management	death from cardiovascular causes, nonfatal MI, or nonfatal stroke	PLATO major	low
			400	Ticagrelor, 90	12	62.5	326, 81.5	297, 74.2				
PLATO; Wallentin, L. (2009)	NCT 00391872	43	9291	Clopidogrel, 75	12	62	5676, 61.1	6658, 71.7	STEMI, NSTEMI	death from vascular causes, myocardial infarction, or stroke	PLATO major	low
			9333	Ticagrelor, 90	12	62	5687, 60.9	6678, 71.6				
Wu, X. (2021)	NCT 02140801	1	174	Clopidogrel, 75	12	64.1	174, 100.0	124, 70.9	ischemic symptoms, PCI	CV death, MI, revascularization	PLATO major	low
			176	Ticagrelor, 90	12	64.5	176, 100.0	134, 75.7				
TRILOGY ACS; Roe, M.T. (2012)	NCT 00699998	52	4663	Clopidogrel, 75	30	66	0, 0.0	2840, 60.9	UA, NSTEMI	death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke	TIMI major	low
			4663	Prasugrel, 10-5	30	66	0, 0.0	2835, 60.8				
PRASFIT-ACS; Saito, S. (2014)	JapicCTI-101339	1	678	Clopidogrel, 75	12	65.1	637, 94.0	558, 82.3	scheduled PCI, >20yrs	cardiovascular death, nonfatal myocardial infarction (MI), and nonfatal ischemic stroke	TIMI major	low
			685	Prasugrel, 3.75	12	65.4	651, 95.0	536, 78.2				
Elderly ACS II; Savonitto, S. (2018)	NCT 01777503	1	730	Clopidogrel, 75	12	80	726, 99.5	448, 61	STEMI, NSTEMI, PCI	all-cause mortality, MI, disabling stroke, and rehospitalization for cardiovascular causes or bleeding	BARC type 2 or 3	low
			713	Prasugrel, 5	12	80	707, 99.0	419, 59				
TRITON-TIMI 38; Wiviott, S.D. (2007)	NCT 00097591	30	6795	Clopidogrel, 75	15	61	N/A, 99.0	N/A, 73	scheduled PCI	cardiovascular death, MI, or stroke	GUSTO and TIMI	low
			6813	Prasugrel, 10	15	61	NA, 99.0	N/A, 75				
Yabe T. (2022)	000044193	1	39	Clopidogrel, 75	12	63.1	39, 100.0	30, 76.9	PCI	cardiac death, nonfatal MI, hospitalization due to heart failure, or TVR	TIMI major	low
			37	Prasugrel, 3.75	12	62.5	37, 100.0	33, 89.1				
PRAGUE-18; Motovska, Z. (2018)	NCT 02808767	1	596	Ticagrelor, 90	12	61.8	591, 99.2	439, 73.7	ACS, PCI	cardiovascular death, nonfatal MI, or stroke	TIMI major	low
			634	Prasugrel, 10-5	12	61.8	629, 99.2	489, 77.1				
ISAR-REACT 5; Schupke, S (2019)	NCT 01944800	2	2012	Ticagrelor, 90	12	64.5	1676, 83.3	1534, 76.2	planned invasive evaluation	composite of death, myocardial infarction, or stroke	BARC type 3 - 5	low
			2006	Prasugrel, 10	12	64.6	1701, 84.8	1528, 76.2				
REDUCE-MVI Trial; van der Hoeven, N.W.	NCT 02422888	2	56	Ticagrelor, 90	12	60.2	N/R	49, 87.5	STEMI	death and recurrent myocardial infarction	BARC type > 2	low
			54	Prasugrel, 10	12	61	N/R	45, 83.3				

(2020)												
HOPE-TAILOR; Jin, C-D (2021)	NCT 02944123	1	41 40 39	Clopidogrel, 75 Ticagrelor, 90-45 Prasugrel, 10-5	9 9 9	63 61 57	41, 100.0 40, 100.0 39, 100.0	38, 92.7 34, 85.0 37, 94.9	PCI	cardiac death, myocardial infarction, target vessel revascularization (TVR) and stroke	BARC type > 2	high
Li, D-T. (2019)		1	100 100	Clopidogrel, 75 Ticagrelor, 90	6	79.1 70.8	100, 100.0 100, 100.0	61, 61.0 55, 55.0	STEMI, diabetes	recurrent myocardial infarction, recurrent angina, and heart failure	hemorrhage	high
Lu, Y. (2016)		1	108 95	Clopidogrel, 75 Ticagrelor, 90	12	59.6 59.3	108, 100.0 95, 100.0	60, 55.6 52, 54.7	PCI	N/A	Hemorrhage	some concerns
Tang, X. (2016)		1	200 200	Clopidogrel, 75 Ticagrelor, 90	6 6	64.2 64.4	200, 100.0 200, 100.0	146, 73 142, 71	STEMI, PCI	death, myocardial infarction (MI), unplanned revascularization, and stroke.	TIMI major	some concerns
Wang, H. (2016)		1	100 100	Clopidogrel, 75 Ticagrelor, 90	12 12	80 79	71, 71.0 75, 75.0	66, 66.0 69, 69.0		myocardial infarction (MI), stroke, or CV death	PLATO major	some concerns
Wang, X. (2019)		1	148 150	Clopidogrel, 75 Ticagrelor, 90	6 6	59.7 60.9	148, 100.0 150, 100.0	121, 81.8 115, 76.7	STEMI, PCI	death, nonfatal myocardial infarction (MI), and target vessel revascularization were recorded	"major bleeding"	some concerns
Wu, H-B. (2018)		1	120 124	Clopidogrel, 75 Ticagrelor, 90	12 12	61.1 59	120, 100.0 124, 100.0	94, 78.3 98, 79.0	PCI	recurrent angina, recurrent myocardial infarction, stroke, heart failure, in-stent thrombosis, other thromboembolic events and cardiovascular death	"no massive hemorrhage event occurred"	some concerns
Yang, B. (2018)		1	60 60	Clopidogrel, 75 Ticagrelor, 90	6 6	58.7 59.6	60, 100.0 60, 100.0	38, 63.3 35, 58.3	AMI, PCI	target vascular remodeling, recurrence of myocardial infarction, heart failure, re-hospitalization and sudden cardiac death	none	some concerns
Yao, Z. (2017)		1	60 60	Clopidogrel, 75 Ticagrelor, 90	6 6	59.8 60.4	60, 100.0 60, 100.0	36, 60.0 38, 63.3	AMI, undergoing PCI	contained restenosis of target vessel and non-target vessel, thrombosis, recurrent angina, second myocardial infarction, all-cause death and so forth.	BARC >=3	some concerns
PATROL; You, J. (2020)		1	195 105	Clopidogrel, 75 Ticagrelor, 90	12 12	68.62 66.29	195, 100.0 105, 100.0	118, 60.5 77, 73.3	STEMI, PCI	all-cause death, cardiac death, recurrence of myocardial infarction (MI), target vessel revascularization (TVR), and ischemic stroke	BARC >=3	high
Zhang, Y. (2016)		1	90 91	Clopidogrel, 150(7d)-75(6m) Ticagrelor, 90	6 6	71.7 68.8	90, 100.0 91, 100.0	49, 54.4 42, 46.2	PCI (CYP2C19*2 or *3 carriers)	death, stroke, recurrent MI, and stent thrombosis	PLATO major	some concerns
PACS Study; Kitano, D. (2020)	UMIN 000015192	1	39 39	Clopidogrel, 75 Prasugrel, 3.75	12 12	64 65.6	39, 100.0 39, 100.0	33, 84.6 31, 79.5	UA, NSTEMI, STEMI	all-cause death, revascularization, stroke, and bleeding were defined as adverse cardiac events	N/R	some concerns

Abbreviations: N.Cnts, number of countries; DAPT, dual-antiplatelet therapy; mg, milligram; F-up, follow-up; mnths, months PCI, pucutaneous coronary intervention; n, number of patients; %, percentage; ACS, acute coronary syndrome; MACE, major acute coronary syndrome; RoB 2.0, risk of bias assessment tool.

Table 4.9.2. The results of the random effects Bayesian network meta-analyses for the primary outcomes of MACE and major bleeding.

					Posterior distribution		
Outcome	**DAPT**	**events**	**n**	**HR (95% CrI)**	**Pr $_{HR<0.9}$**	**Pr $_{HR[0.9, 1.11]}$**	**Pr $_{HR>1.11}$**
MACE	C	3,402	26,189	1.0 (ref.)	-	-	-
N=17	T	1,614	16,020	0.95 (0.81, 1.14)	0.224	0.732	0.044
n=57,814	P	1,811	15,605	0.87 (0.74, 1.06)	0.675	0.314	0.011
Maj. Bleeding	C	1,224	25,959	1.0 (ref)	-	-	-
N=17	T	1,251	15,894	1.16 (0.98, 1.48)	0.004	0.319	0.677
n=57,110	P	383	15,257	1.23 (0.99, 1.57)	0.006	0.157	0.837

Abbreviations: dapt, dual-antiplatelet therapy; N, number of studies; n, number of patients; HR, hazard ratio; CrI, credible interval; Pr, probability; MACE, major acute coronary event (composite of death, non-fatal myocardial infarction, and non-fatal stroke); C, clopidogrel; T, ticagrelor; P, prasugrel; ref., reference group; Maj., major.

4.10 Figures

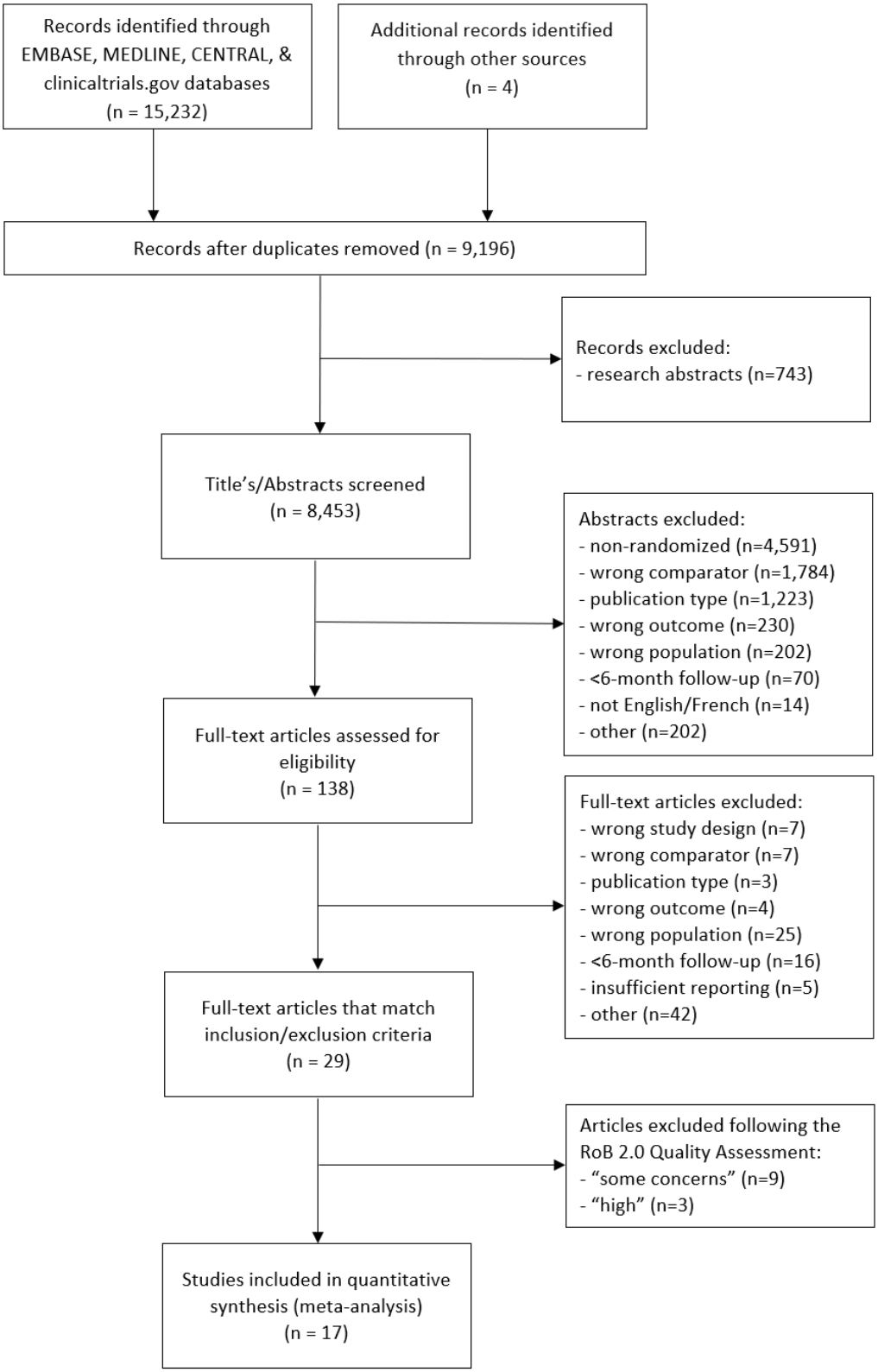


Figure 4.10.1. A flowchart describing the systematic screening results.

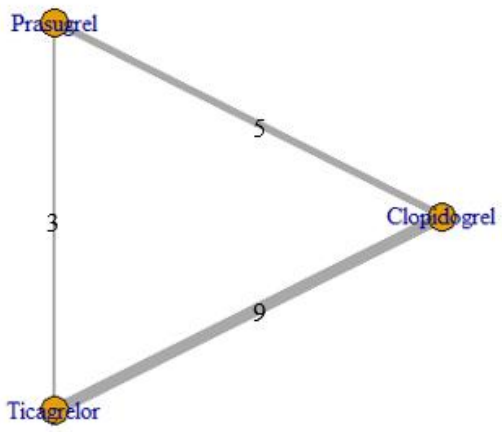


Figure 4.10.2. The network structure of the Bayesian meta-analysis for the 17 trials identified from the systematic review.

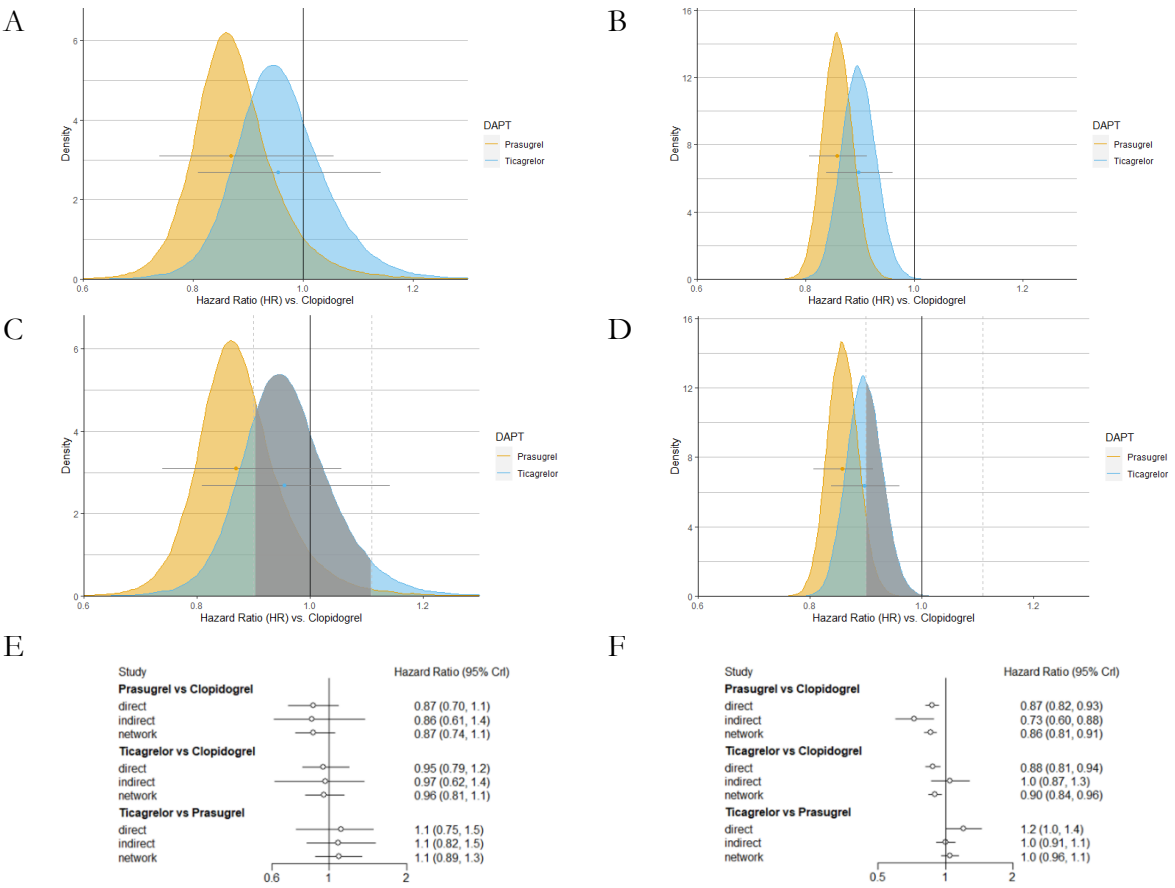


Figure 4.10.3. The posterior distributions for major acute coronary events (MACE) comparing clopidogrel (reference) to ticagrelor (blue) and prasugrel (yellow) using a [A] random effects (RE) and [B] fixed effects models. The range of practical equivalence (ROPE) is highlighted in grey across the RE [C] and FE [D] models. The node splitting results for MACE in the RE [E] and FE [F] models. *Abbreviations: DAPT, dual anti-platelet therapy; CrI, credible interval.*

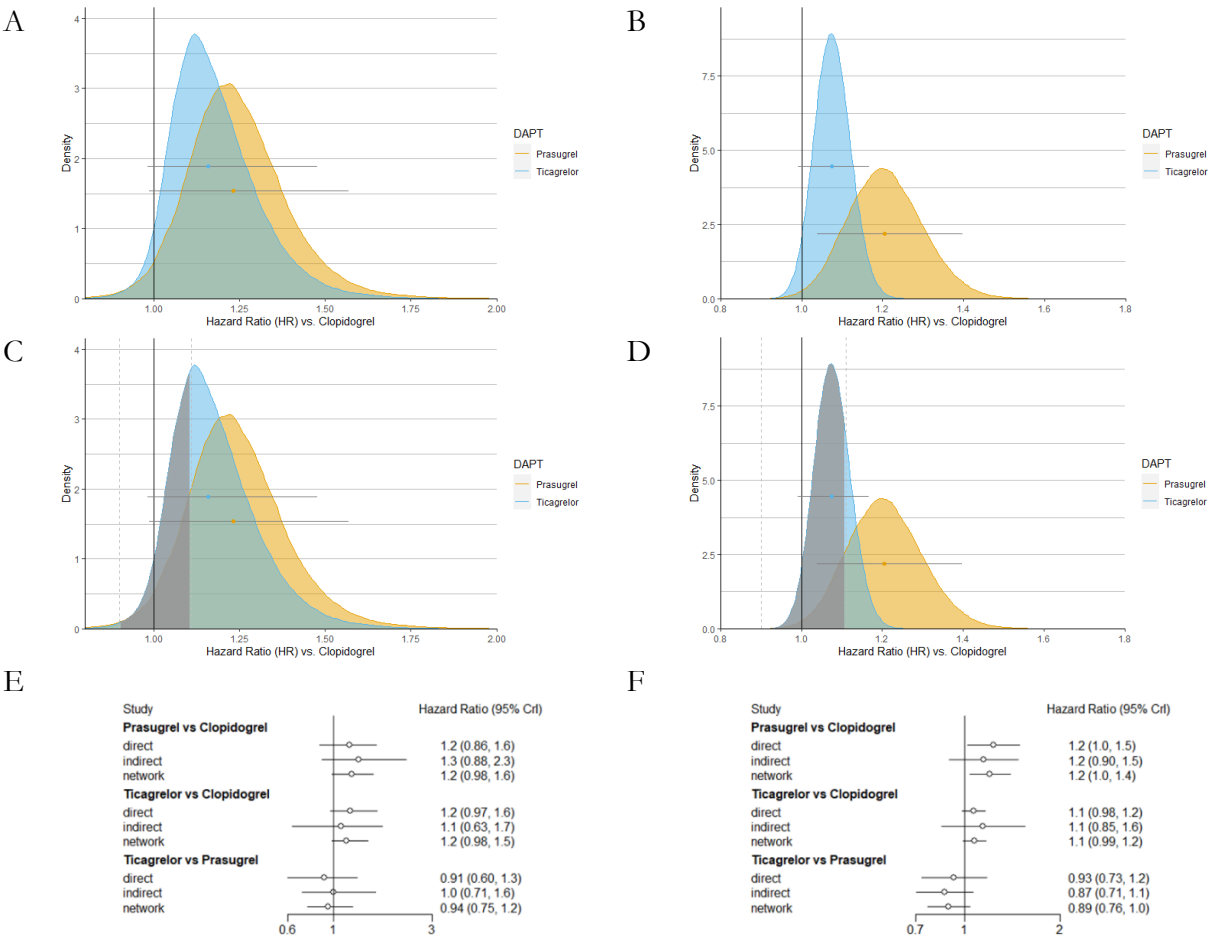


Figure 4.10.4. The posterior distributions for major bleeding events comparing clopidogrel (reference) to ticagrelor (blue) and prasugrel (yellow) using a [A] random effects (RE) and [B] fixed effects models. The range of practical equivalence (ROPE) is highlighted in grey across the RE [C] and FE [D] models. The node splitting results for major bleeding in the RE [E] and FE [F] models. *Abbreviations: DAPT, dual anti-platelet therapy; CrI, credible interval.*

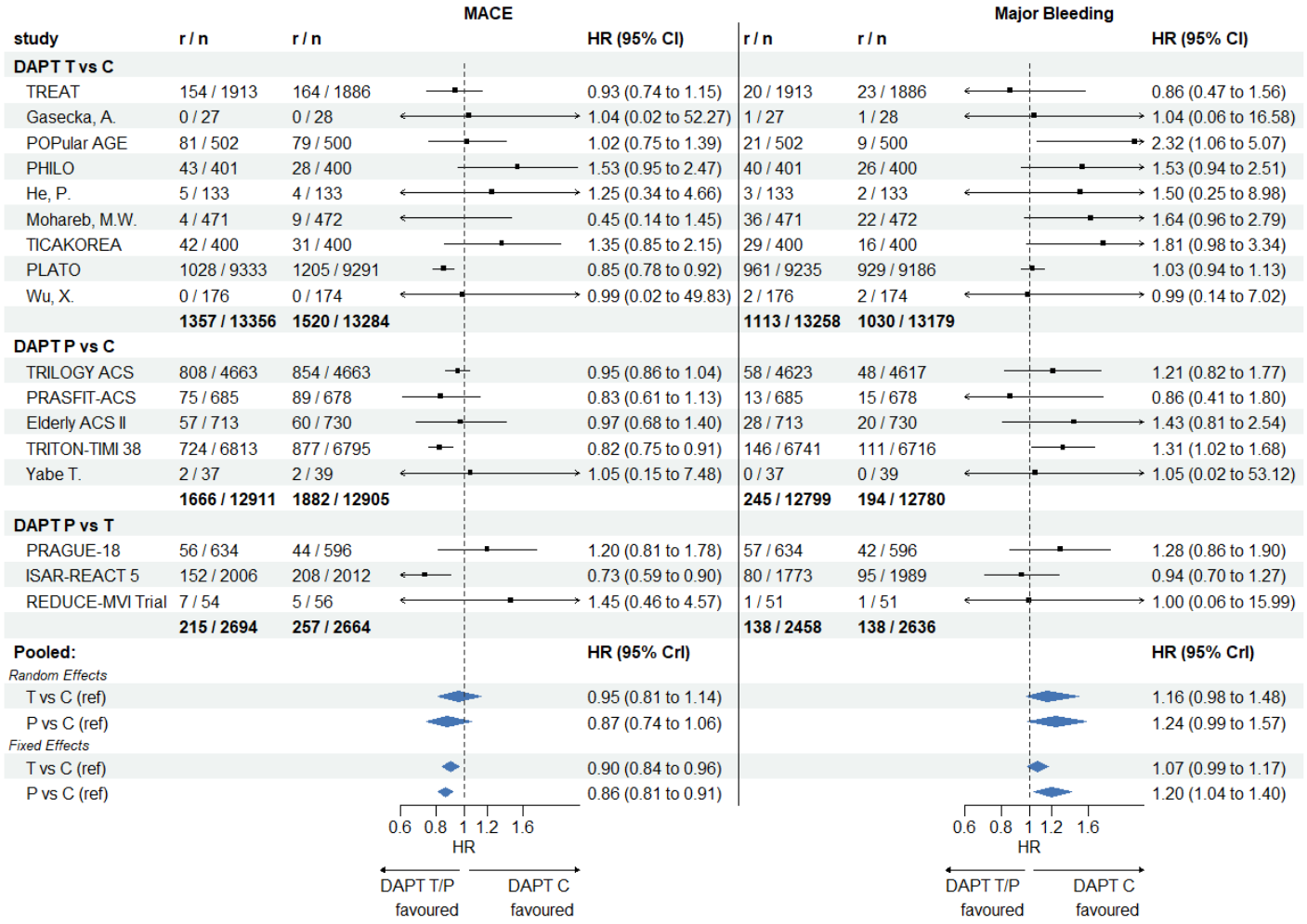


Figure 4.10.5. Forest plot of summary of the Bayesian network meta-analyses for MACE and major bleeding events in patients taking clopidogrel compared to ticagrelor and clopidogrel. *Abbreviations: MACE, major acute coronary events; r, number of events; n, number of subjects per study arm; HR, hazard ratio; CI, confidence interval; CrI, Bayesian credible interval; DAPT, dual-antiplatelet therapy; C, clopidogrel; T, ticagrelor; P, prasugrel; ref, reference group.*

4.11 Appendix

4.11.1 Supplemental Tables

Supplemental Table 4.11.1.1. The results of the fixed effects Bayesian network meta-analyses for the primary outcomes of MACE and major bleeding.

					Posterior distribution		
Outcome	**DAPT**	**events**	**n**	**HR (95% CrI)**	**Pr $_{HR<0.9}$**	**Pr $_{HR[0.9, 1.11]}$**	**Pr $_{HR>1.11}$**
MACE	C	3,402	26,189	1.0 (ref)	-	-	-
N=17	T	1,614	16,020	0.90 (0.84, 0.96)	0.534	0.466	0.00
n=57,814	P	1,811	15,605	0.86 (0.81, 0.91)	0.932	0.068	0.00
Maj. Bleeding	C	1,224	25,959	1.0 (ref)	-	-	-
N=17	T	1,251	15,894	1.08 (0.99, 1.17)	0.00	0.787	0.213
n=57,110	P	383	15,257	1.20 (1.04, 1.40)	0.00	0.147	0.853

Abbreviations: dapt, dual-antiplatelet therapy; N, number of studies; n, number of patients; HR, hazard ratio; CrI, credible interval; Pr, probability; MACE, major acute coronary event (composite of death, non-fatal myocardial infarction, and non-fatal stroke); C, clopidogrel; T, ticagrelor; P, prasugrel; ref., reference group; Maj., major.

Supplemental Table 4.11.1.2. The random effect results of secondary outcomes from the Bayesian network meta-analyses.

					Posterior distribution		
Outcome	**DAPT**	**events**	**n**	**HR (95% CrI)**	**Pr $_{HR<0.9}$**	**Pr $_{HR[0.9, 1.11]}$**	**Pr $_{HR>1.11}$**
Mortality	C	1,299	26,189	1.0 (ref)	-	-	-
N=17	T	661	16,020	0.87 (0.75, 1.07)	0.642	0.344	0.014
n=57,814	P	728	15,605	0.94 (0.79, 1.14)	0.305	0.658	0.037
CV Mortality	C	1,076	26,056	1.0 (ref)	-	-	-
N=15	T	547	15,831	0.85 (0.73, 1.04)	0.753	0.239	0.008
n=57,438	P	559	15,551	0.90 (0.76, 1.07)	0.516	0.473	0.011
MI	C	1,798	26,189	1.0 (ref)	-	-	-
N=17	T	750	16,020	0.94 (0.76, 1.17)	0.328	0.612	0.060
n=57,814	P	991	15,605	0.81 (0.65, 1.00)	0.874	0.121	0.005
Stroke	C	305	25,543	1.0 (ref)	-	-	-
N=15	T	203	15,373	1.02 (0.72, 1.33)	0.199	0.552	0.249
n=56,521	P	162	15,605	0.88 (0.64, 1.18)	0.551	0.388	0.061
Min. Bleeding	C	548	24,729	1.0 (ref)	-	-	-
N=12	T	550	12,811	1.35 (1.08, 1.71)	0.002	0.034	0.964
n=49,677	P	254	12,137	1.42 (1.08, 1.94)	0.003	0.031	0.966

Abbreviations: dapt, dual-antiplatelet therapy; N, number of studies; n, number of patients; HR, hazard ratio; CrI, credible interval; Pr, probability; CV, cardiovascular; MI, non-fatal myocardial infarction, and non-fatal stroke); C, clopidogrel; T, ticagrelor; P, prasugrel; ref., reference group; Min., minor.

Supplemental Table 4.11.1.3. The fixed effect results of secondary outcomes from the Bayesian network meta-analyses.

					Posterior distribution		
Outcome	**DAPT**	**events**	**n**	**HR (95% CrI)**	**Pr $_{HR<0.9}$**	**Pr $_{HR[0.9, 1.11]}$**	**Pr $_{HR>1.11}$**
Mortality	C	1,299	26,189	1.0 (ref)	-	-	-
N=17	T	661	16,020	0.84 (0.76, 0.94)	0.890	0.110	0.00
n=57,814	P	728	15,605	0.93 (0.83, 1.03)	0.305	0.695	0.00
CV Mortality	C	1,076	26,056	1.0 (ref)	-	-	-
N=15	T	547	15,831	0.83 (0.74, 0.93)	0.918	0.082	0.00
n=57,438	P	559	15,551	0.90 (0.80, 1.01)	0.517	0.483	0.00
MI	C	1,798	26,189	1.0 (ref)	-	-	-
N=17	T	750	16,020	0.90 (0.81, 0.99)	0.531	0.469	0.00
n=57,814	P	991	15,605	0.81 (0.74, 0.88)	0.992	0.008	0.00
Stroke	C	305	25,543	1.0 (ref)	-	-	-
N=15	T	203	15,373	1.06 (0.86, 1.29)	0.059	0.632	0.309
n=56,521	P	162	15,605	0.91 (0.73, 1.12)	0.471	0.498	0.031
Min. Bleeding	C	548	24,729	1.0 (ref)	-	-	-
N=12	T	550	12,811	1.34 (1.18, 1.52)	0.00	0.002	0.998
n=49,677	P	254	12,137	1.39 (1.15, 1.68)	0.00	0.009	0.991

Abbreviations: dapt, dual-antiplatelet therapy; N, number of studies; n, number of patients; HR, hazard ratio; CrI, credible interval; Pr, probability; CV, cardiovascular; MI, non-fatal myocardial infarction, and non-fatal stroke); C, clopidogrel; T, ticagrelor; P, prasugrel; ref., reference group; Min., minor.

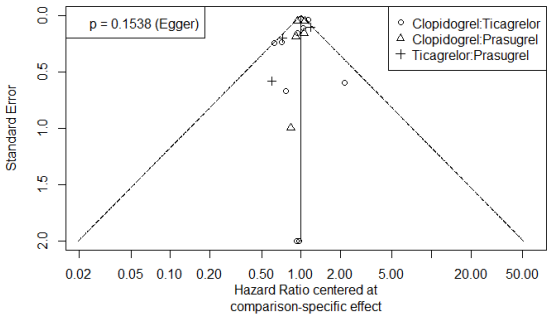
Supplemental Table 4.11.1.4. Quality assessment of the identified randomized trials using the risk of bias (RoB 2.0) tool.

Study; First author (year)	Rob 2.0 Section 1	Rob 2.0 Section 2	Rob 2.0 Section 3	Rob 2.0 Section 4	Rob 2.0 Section 5	Overall
TREAT; Berwanger, O. (2019)	Low	Low	Low	Low	Low	Low
Gasecka, A. (2020)	Low	Low	Low	Low	Low	Low
POPular AGE; Gimbel, M. (2020)	Low	Low	Low	Low	Low	Low
PHILO; Goto, S. (2015)	Low	Low	Low	Low	Low	Low
He, P. (2021)	Low	Low	Low	Low	Low	Low
Mohareb, M.W. (2020)	Low	Low	Low	Low	Low	Low
TICAKOREA; Park, D-W. (2019)	Low	Low	Low	Low	Low	Low
PLATO; Wallentin, L. (2009)	Low	Low	Low	Low	Low	Low
Wu, X. (2021)	Low	Low	Low	Low	Low	Low
TRILOGY ACS; Roe, M.T. (2012)	Low	Low	Low	Low	Low	Low
PRASFIT-ACS; Saito, S. (2014)	Low	Low	Low	Low	Low	Low
Elderly ACS II; Savonitto, S. (2018)	Low	Low	Low	Low	Low	Low
TRITON-TIMI 38; Wiviott, S.D. (2007)	Low	Low	Low	Low	Low	Low
Yabe T. (2022)	Low	Low	Low	Low	Low	Low
PRAGUE-18; Motovska, Z. (2018)	Low	Low	Low	Low	Low	Low
ISAR-REACT 5; Schupke, S (2019)	Low	Low	Low	Low	Low	Low
REDUCE-MVI Trial; van der Hoeven, N.W. (2020)	Low	Low	Low	Low	Low	Low
HOPE-TAILOR; Jin, C-D (2021)	Some concerns	Low	Low	Low	Low	Some concerns
Li, D-T. (2019)	High	High	Some concerns	Low	Low	High
Lu, Y. (2016)	Some concerns	Some concerns	Low	Low	Low	Some concerns
Tang, X. (2016)	Some concerns	Low	Low	Some concerns	Low	Some concerns

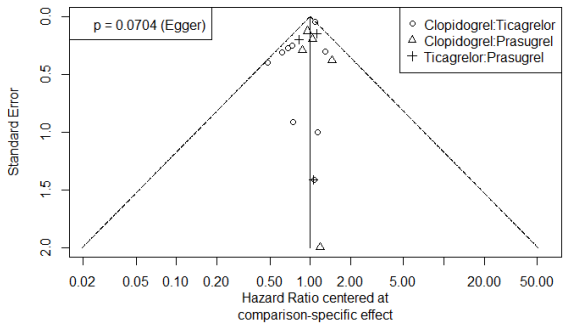
Wang, H. (2016)	Some concerns	Low	Low	Low	Low	Some concerns
Wang, X. (2019)	Some concerns	Low	Some concerns	Low	low	Some concerns
Wu, H-B. (2018)	Some concerns	Low	Low	Low	Low	Some concerns
Yang, B. (2018)	Some concerns	Some concerns	Low	Low	Low	Some concerns
Yao, Z. (2017)	Some concerns	Some concerns	Low	Low	Low	Some concerns
PATROL; You, J. (2020)	High	Some concerns	Low	Low	Low	High
Zhang, Y. (2016)	Some concerns	Low	Low	Low	Low	Some concerns
PACS Study; Kitano, D. (2020)	Some concerns	Low	Low	Low	Low	Some concerns

4.11.2 Supplemental Figures

A



B



Supplemental Figure 4.11.2.1. Publication bias funnel plots for major acute coronary events and major bleeding outcomes

$$logit(p_{ik}) = \log(time_i) + \mu_i + \delta_{i,bk}$$
$$\delta_{i,bk} = N(d_{bk}, \sigma_{bk})$$

Supplemental Figure 4.11.2.2. The Bayesian network meta-analysis complementary log-log hierarchical generalized linear model

4.11.3 Search strategies

MEDLINE

1. ((randomized controlled trial or controlled clinical trial).pt. or randomized.ab. or randomised.ab. or placebo.ab. or drug therapy.fs. or randomly.ab. or trial.ab. or groups.ab.) not (exp animals/ not humans.sh.)
2. acute coronary syndrome*.mp. or Acute Coronary Syndrome/ or ((myocardial or heart) adj infarction*).mp. or acute mi.mp. or exp Myocardial Infarction/ or ((myocardial or heart muscle) adj isch?emi*).mp. or Myocardial Ischemia/ or unstable angina*.mp. or Angina, Unstable/ or STEMI.mp. or NSTEMI.mp.
3. (((percutaneous coronary or heart muscle) adj (intervention* or revasculari#ation*)) or pci).mp. or Percutaneous Coronary Intervention/
4. stent*.mp. or Stents/
5. coronary artery bypass*.mp. or Coronary Artery Bypass/
6. 2 or 3 or 4 or 5
7. (clopidogrel and ticagrelor).mp.
8. (clopidogrel and prasugrel).mp.
9. (prasugrel and ticagrelor).mp.
10. (dual antiplatelet* or dual anti platelet* or DAPT).mp.
11. 7 or 8 or 9 or 10
12. 1 and 6 and 11

EMBASE

1. crossover-procedure/ or double-blind procedure/ or randomized controlled trial/ or single-blind procedure/ or (random* or factorial* or crossover* or cross over* or placebo* or (doubl* adj blind*) or (singl* adj blind*) or assign* or allocat* or volunteer*).tw.
2. acute coronary syndrome*.mp. or acute coronary syndrome/
3. ((myocardial or heart) adj infarction*).mp. or heart infarction/
4. acute mi.mp.
5. myocardial isch?emi*.mp. or heart muscle ischemia/
6. unstable angina*.mp. or unstable angina pectoris/
7. non ST segment elevation myocardial infarction/
8. ST segment elevation myocardial infarction/
9. percutaneous coronary intervention.mp. or percutaneous coronary intervention/
10. heart muscle revascularization/ or ((percutaneous coronary or heart muscle) adj revasculari#ation*).mp.
11. percutaneous coronary revasculari#ation*.mp.
12. stent*.mp. or stent/
13. coronary artery bypass*.mp. or coronary artery bypass graft/
14. 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13
15. (clopidogrel and prasugrel).mp.
16. (clopidogrel and ticagrelor).mp.
17. (prasugrel and ticagrelor).mp.
18. (dual antiplatelet* or dual anti platelet* or DAPT).mp.
19. 15 or 16 or 17 or 18
20. 1 and 14 and 19

CENTRAL

ID	Search	Hits
#1	MeSH descriptor: [Acute Coronary Syndrome] this term only	1544
#2	(acute coronary syndrome*):ti,ab,kw	5194
#3	MeSH descriptor: [Myocardial Infarction] this term only	9758
#4	((myocardial or heart) NEAR/1 infarction*):ti,ab,kw	25161
#5	((myocardial or "heart muscle") NEAR/1 isch*emi*):ti,ab,kw	5803
#6	(acute MI):ti,ab,kw	2007
#7	MeSH descriptor: [Angina, Unstable] this term only	975
#8	(unstable angina*):ti,ab,kw	2910
#9	MeSH descriptor: [ST Elevation Myocardial Infarction] this term only	226
#10	(STEMI):ti,ab,kw	2364
#11	MeSH descriptor: [Non-ST Elevated Myocardial Infarction] this term only	47
#12	(NSTEMI):ti,ab,kw	339
#13	MeSH descriptor: [Percutaneous Coronary Intervention] this term only	1541
#14	(("percutaneous coronary" or "heart muscle") NEAR/1 (intervention* or revasculari?ation*)):ti,ab,kw	7932
#15	(PCI):ti,ab,kw	5681
#16	MeSH descriptor: [Stents] this term only	2807
#17	(stent*):ti,ab,kw	11274
#18	MeSH descriptor: [Coronary Artery Bypass] this term only	4919
#19	(coronary artery bypass*):ti,ab,kw	9676
#20	(prasugrel AND clopidogrel):ti,ab,kw	682
#21	(prasugrel AND ticagrelor):ti,ab,kw	343
#22	(clopidogrel AND ticagrelor):ti,ab,kw	743
#23	(dual anti platelet therap*):ti,ab,kw	150
#24	(dual antiplatelet therap*):ti,ab,kw	1279
#25	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19	46911
#26	#20 or #21 or #22 or #23 or #24	2256
#27	#25 AND #261880	

clinicaltrials.gov

Conditions or disease:

((Acute Coronary Syndrome*) OR (myocardial infarction*) OR (myocardial ischemia*) OR (unstable angina*) OR (stemi) OR (nstemi) OR (percutaneous coronary) OR (stent*) OR (coronary artery bypass*))

Other terms:

((clopidogrel AND ticagrelor) OR (prasugrel AND ticagrelor) OR (clopidogrel AND ticagrelor) OR (dual antiplatelet*) OR (dual anti platelet*) OR (DAPT))

4.11.4 PRISMA NMA Checklist of Items to Include When Reporting A Systematic Review Involving a Network Meta-Analysis

Section/Topic	Item #	Checklist Item	Reported on Page #
TITLE			
Title	1	Identify the report as a systematic review *incorporating a network meta-analysis (or related form of meta-analysis).*	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: **Background:** main objectives **Methods:** data sources; study eligibility criteria, participants, and interventions; study appraisal; and *synthesis methods, such as network meta-analysis.* **Results:** number of studies and participants identified; summary estimates with corresponding confidence/credible intervals; *treatment rankings may also be discussed. Authors may choose to summarize pairwise comparisons against a chosen treatment included in their analyses for brevity.* **Discussion/Conclusions:** limitations; conclusions and implications of findings. **Other:** primary source of funding; systematic review registration number with registry name.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known*, including mention of why a network meta- analysis has been conducted*	4-5
Objectives	4	Provide an explicit statement of questions being addressed, with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists and if and where it can be accessed (e.g., Web address); and, if available, provide registration information, including registration number.	Not Published

Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. *Clearly describe eligible treatments included in the treatment network, and note whether any have been clustered or merged into the same node (with justification).*	5-6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5, Appendix
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6
Geometry of the network	**S1**	Describe methods used to explore the geometry of the treatment network under study and potential biases related to it. This should include how the evidence base has been graphically summarized for presentation, and what characteristics were compiled and used to describe the evidence base to readers.	7, Figure 2
Risk of bias within individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means). *Also describe the use of additional summary measures assessed, such as treatment rankings and surface under the cumulative ranking curve (SUCRA) values, as well as modified approaches used to present summary findings from meta-analyses.*	7
Planned methods of analysis	14	Describe the methods of handling data and combining results of studies for each network meta-analysis. This should include, but not be limited to:	7

		• *Handling of multi-arm trials;* • *Selection of variance structure* • *Selection of prior distributions in Bayesian analyses; and* • *Assessment of model fit.*	
Assessment of inconsistency	**S2**	Describe the statistical methods used to evaluate the agreement of direct and indirect evidence in the treatment network(s) studied. Describe efforts taken to address its presence when found.	7
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	5, Figure 6
Additional analyses	16	Describe methods of additional analyses if done, indicating which were pre-specified. This may include, but not be limited to, the following: • Sensitivity or subgroup analyses; • Meta-regression analyses; • *Alternative formulations of the treatment network; and* • *Use of alternative prior distributions for Bayesian analyses (if applicable).*	5-6
RESULTS†			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	7, Figure 1
Presentation of network structure	**S3**	Provide a network graph of the included studies to enable visualization of the geometry of the treatment network.	Figure 2
Summary of network geometry	**S4**	Provide a brief overview of characteristics of the treatment network. This may include commentary on the abundance of trials and randomized patients for the different interventions and pairwise comparisons in the network, gaps of evidence in the treatment network, and potential biases reflected by the network structure.	7
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	7, Table 1

Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment.	Table 1
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: 1) simple summary data for each intervention group, and 2) effect estimates and confidence intervals. *Modified approaches may be needed to deal with information from larger networks.*	8-10, Tables 2-3
Synthesis of results	21	Present results of each meta-analysis done, including confidence/credible intervals. *In larger networks, authors may focus on comparisons versus a particular comparator (e.g. placebo or standard care), with full findings presented in an appendix. League tables and forest plots may be considered to summarize pairwise comparisons.* If additional summary measures were explored (such as treatment rankings), these should also be presented.	8-10, Figure 4
Exploration for inconsistency	**S5**	Describe results from investigations of inconsistency. This may include such information as measures of model fit to compare consistency and inconsistency models, P values from statistical tests, or summary of inconsistency estimates from different parts of the treatment network.	Figures 3-4
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies for the evidence base being studied.	Table 1
Results of additional analyses	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression analyses*, alternative network geometries studied, alternative choice of prior distributions for Bayesian analyses,* and so forth).	Not Applicable
DISCUSSION			
Summary of evidence	24	Summarize the main findings, including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy- makers).	11-12
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias). *Comment on the validity of the assumptions, such as transitivity and consistency. Comment on any concerns regarding network geometry (e.g., avoidance of*	12-13

		certain comparisons).	
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	13
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. This should also include information regarding whether funding has been received from manufacturers of treatments in the network and/or whether some of the authors are content experts with professional conflicts of interest that could affect use of treatments in the network.	None

PICOS = population, intervention, comparators, outcomes, study design.
* Text in italics Indicates wording specific to reporting of network meta-analyses that has been added to guidance from the PRISMA statement.
† Authors may wish to plan for use of appendices to present all relevant information in full detail for items in this section

Chapter Five. A real-world comparative effectiveness of clopidogrel and ticagrelor for acute coronary syndromes in Québec, Canada

5.1 Preface

In Chapter four, from the 15,232 articles matching our search criterion we identified 17 "low" risk of bias RCTs that examined either prasugrel, ticagrelor, or clopidogrel DAPTs in ACS patients. Bayesian hierarchical summary analyses found that prasugrel was associated with a moderate reduction of major cardiac events (hazard ratio [HR]$_{Pvs.C}$, 0.87; 95% credible interval [95% CrI]: 0.74, 1.06), relative to clopidogrel, but also a moderate increase in bleeding episodes ($HR_{Pvs.C}$, 1.23; 95% CrI: 1.04, 1.40). Ticagrelor, meanwhile, was associated with a mild decrease in major cardiac events ($HR_{Tvs.C}$, 0.95; 95% CrI: 0.81, 1.14) and mild increase in bleeding events, ($HR_{Tvs.C}$, 1.07; 95% CrI: 0.99, 1.17), in comparison to clopidogrel. This study showed that there is limited evidence supporting a superior DAPT regimen. Further, we were unable to address the concerns of an increased risk associated with ticagrelor in PLATO, as we did not detect an RCT reporting results in a North American population. The second objective aims to address this limited knowledge through a non-randomized cohort analysis to determine if ticagrelor is associated with a decreased risk of cardiac events, compared with clopidogrel DAPT, in ACS patients undergoing a PCI in Québec, Canada.

5.2 Title page

A real-world comparative effectiveness of clopidogrel and ticagrelor for acute coronary syndromes in Québec, Canada

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Lyne Nadeau MSc[2], James M. Brophy MD PhD[1,2,3]

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Email: stephen.kutcher@mail.mcgill.ca

Abstract: 402 words

Word count: 2765 words

5.3 Abstract

Background: Ticagrelor has usurped clopidogrel in major clinical guidelines for acute coronary syndrome (ACS) as the choice complement to aspirin in dual-antiplatelet therapy for the secondary prevention of ischemic events. Though, concerns of regional heterogeneity of the effects within the North American patients from the pivotal PLATO trial remain. With limited subsequent North American antiplatelet research and generalizability challenges from randomized trials we examined the associations between ticagrelor and clopidogrel with major coronary and bleeding outcomes in ACS subjects identified from electronic health records in Québec, Canada.

Methods: Healthcare billing and ICD-10 codes were used to identify ACS patients who underwent a percutaneous coronary intervention (PCI) between April 2010 and March 2018. Following hospital discharge, prescription claims data was used to determine the antiplatelet exposure of clopidogrel or ticagrelor in subjects above the age of 65 years on the Québec pharmacare plan. Follow-up began after the date of the first prescription after hospital discharge. Average treatment effect (ATE) weights were calculated using inverse probability of treatment weights of the propensity score. The ATE weighted Cox proportional hazard models compared the event rates of the primary effectiveness and bleeding outcomes between ACS patients prescribed to either clopidogrel or ticagrelor after 12 months. The primary effectiveness outcome was major acute coronary events (MACE), a composite of mortality, non-fatal myocardial infarction, and ischemic stroke. The primary safety endpoint was intercranial and gastrointestinal bleeding requiring hospitalization.

Results: A total of 100,251 ACS patients who underwent a PCI were identified during the study period. Of these, 22,736 met our inclusion criteria and filled at least one ticagrelor (n=6,959) or clopidogrel (n=15,777) prescription within 12 months of the index ACS hospitalization. The primary efficacy endpoint occurred in 490 (7.0%) patients who initiated ticagrelor and 1,733 (11.0%) of those on clopidogrel (crude hazard ratio[cHR], 0.66; 95% confidence interval [CI]: 0.59, 0.73). After ATE weighting from the propensity score, there was a non-significant reduction in MACE events in patients who initiated ticagrelor (adjusted HR [aHR], 0.91; 95% CI: 0.81, 1.01). Bleeding requiring hospitalization was observed in 84 (1.2%) of the ACS subjects who initiated ticagrelor and in 235 (1.5%) on clopidogrel (cHR, 0.97; 95% CI: 0.75, 1.24). The estimate did not change after ATE weighted adjustment (aHR, 0.97; 95% CI: 0.75, 1.24).

Conclusions: After ATE weighting using propensity scores in ACS patients who underwent a PCI, ticagrelor was not significantly associated with a decrease in ischemic events nor bleeding outcomes.

5.4 Introduction

A $P2Y_{12}$ receptor inhibitor paired with acetylsalicylic acid (ASA) form dual-antiplatelet therapy (DAPT) which is the foundational treatment for reducing secondary ischemic events in acute coronary syndrome (ACS) patients. Universally, current ACS guidelines[1–3] now recommend the $P2Y_{12}$ inhibitor ticagrelor over clopidogrel. The evidence, from which the guidelines are based, came from a single randomized clinical trial (RCT), the Platelet Inhibition and Patient Outcomes (PLATO) study.[4] In PLATO, when compared to clopidogrel, ticagrelor was associated with a reduction (hazard ration[HR]: 0.84; 95% confidence interval [CI]: 0.77, 0.92; P<0.001) in major adverse coronary events (MACE) without a significant increase in major bleeding (HR:1.04; 95% CI: 0.95, 1.13; P=0.43) seen in other $P2Y_{12}$ receptor inhibitors. However, some residual uncertainly persists due to the heterogeneity of the effects observed across the PLATO study sub-regions.[5]

The Food and Drug Administration (FDA) deliberated the results from the pre-specified PLATO regional sub-analysis, where an efficacy benefit for MACE outcomes (HR_{NA}: 1.25, 95% CI: 0.93 to 1.67) was not observed in the 1,814 North American subjects, concluding with a need for more research.[6] The original estimate (HR: 0.84) was the result from pooling the PLATO outcomes, which makes the assumption that the events from across the 43 countries come from one "true" or "fixed" treatment effect. A reanalysis of the data[7] utilizing a hierarchical (random effects) model, allowing for flexibility in which the effect size can vary in each region due to meaningful population and practice differences, resulted in a wider confidence limit (HR: 0.87, 95% credible interval [CrI]: 0.70 to 1.15), no longer reaching conventional statistical significance. When the choice of the underlying statistical model can alter a trial's interpretation, its robustness is clearly called into question and further research should be recommended.

The RCT is often considered the "gold standard" for efficacy research in the clinical setting due to strong internal validity. However, the strict inclusion/exclusion criteria and highly

standardized treatment regimens are often associated with concerns that the population in an efficacy RCT and their adherence to treatment do not reflect a typical clinical population.[8,9] With the lack of North American populations in follow-up RCTs[10] along with a recent Canadian observational study reporting no cardiovascular benefit (adjusted hazard ratio [aHR], 0.97; 95%CI: 0.85, 1.10) and an increase in major bleeding outcomes (aHR, 1.51; 95%CI: 1.29, 1.78) warrants further investigation.

The main objective of this study is to investigate the association of ticagrelor, prasugrel, and clopidogrel DAPTs with MACE – composite of death, MI, stroke – and major bleeding events in Québec cohort of ACS patients who underwent a percutaneous coronary intervention (PCI) between 2011 and 2018.

5.5 Methods

This study's explicit goal is to estimate causal associations from data collected through existing public healthcare infrastructure in Québec, Canada. The "target trial" framework[11] guided the current study's design in terms of patient eligibility, exposure as well as outcome definitions, and analytical decisions.

Data sources

The patient, demographic, and clinical information, as well as healthcare utilization, prescription claims, and patient outcomes were retrieved from deidentified and individually linked Québec provincial healthcare administrative databases.

Cohort Definition

Study cohort entry was defined by an ACS hospitalization (ICD-10 codes: I20.x, I21.x, I22.x et I24.x) between April 1st, 2010, to March 31st, 2018, along with a revascularization billing code within 7 days of the index ACS hospitalization. Patients had to be discharged alive from hospital and over the age of 65 years. The province of Québec provides essential medical care and drug insurance coverage-to all registrants over the age of 65 years as well as to younger individuals without access to a private plan through an employer or who are on financial assistance. Restricting the study cohort to those over 65 years ensured a more representative sample of those at risk in the Québec population. Patients must also have filled at least one clopidogrel or ticagrelor DAPT medication in the 365 days after the index ACS hospitalization. Subjects were excluded if they died prior to hospital discharge or filled a DAPT prescription in the 365 days prior to the index ACS hospitalization.

Exposure

The DAPT exposure was defined by a filled prescription in the RAMQ drug insurance plan database via drug identification numbers (DIN). The first prescription following hospital discharge

was set as time zero, the beginning of patient follow-up, to minimize prevalence and immortal time biases.[12] Similar to the commonly reported RCT analytical approach, we applied a intention-to-treat (ITT) definition where we based a subjects' exposure status on their first DAPT prescription and carried it through for the duration of their follow-up. With ASA being available over the counter, all patients were assumed to have received it in addition to their initial P2Y12 inhibiter.

Outcomes

The primary effectiveness outcome was the first incident of all-cause mortality, non-fatal MI, or ischemic stroke (MACE) within 12 months of the index ACS hospitalization. The primary safety outcome was a composite of hospitalizations caused by gastrointestinal bleeding or a hemorrhagic stroke. Secondary outcomes of interest included the evaluation of the individual components of the MACE outcome – all-cause mortality, non-fatal MI, or ischemic stroke – along with sex-stratified analyses of the primary effectiveness and safety outcomes. All of the outcomes of interest were identified using previously validated[13–16] ICD-10 codes (suppl. Table 1) and death certificates from hospital and provincial electronic health records.

Statistical Analyses

Baseline characteristics of the study cohort will be summarized as means and standard deviations for continuous variables and proportions for categorical variables. This observational study did not employ randomization to allocate treatment, since we utilized passively collected electronic healthcare administrative data to identify the ACS patients and the prescription claims information for their exposure status. To estimate causal effects, we used the inverse probability of treatment weighting (IPTW) of the propensity score (PS) to produce exchangeable treatment populations conditional on their observed covariates.[17–20]

Propensity scores were estimated via a maximum likelihood algorithm with a logistic regression, setting the DAPT exposure status (clopidogrel and ticagrelor) as the dependent variable

against multiple covariates. The covariates included in the PS model can be found as the baseline characteristics presented in Table 1. The PS's were leveraged to create average treatment effect (ATE) weights in two ways. First, for the primary analysis, we directly used the inverse probability of PS weights. These generated weights are then used to upweight or downweigh individual ACS patients to create a pseudo-population with a balanced set of baseline characteristics.[18] Since this process of manually specifying PS's until a desired model is identified can be an iterative procedure, it can be prone to variability due to the inputs from different users. This manual process also makes the weights susceptible to poor covariate balance after modelling. As a sensitivity analysis, we also applied a second method to estimate ATE weights using the PS's via an entropy balancing (EBAL) algorithm. The EBAL procedure iteratively runs through the PS weighting models to optimize the balance of covariates across the study population.[21,22] The algorithm incorporates the covariate balance into the weighting function as it repeatedly searches for the set of weights to satisfy those balancing constraints. In the end, the ATE weights produced from either model, assuming they were properly specified, should have generated pseudo-populations where the treatment assignment was independent from the observed confounders.[18,23] The ATE was considered the appropriate causal estimand since the entire ACS cohort was eligible for both DAPTs.[17,18]

The ATE weights from the IPTW and EBAL methods were calculated using the "WeightIt" R package[24] and were trimmed at the size of 5 to minimize the impact of extreme weights. Covariate balance was assessed by the standardized mean difference, with a difference greater than 0.5 considered "unbalanced". Hazard ratios (HR) and 95% confidence intervals (95% CI) were estimated using Cox proportional hazards models.[25] Crude, unadjusted HR's were calculated along with fully adjusted HR's using the ATE weights calculated from both methodologies.

Power calculation

Canadian guidelines have long recommended dual antiplatelet treatment following a coronary intervention,[26] which should result in excellent DAPT coverage. In Québec, from 2015 to 2018, it was reported that over 51,000 PCI procedures were performed,[16] with an estimated average age of 66 years.[27] Due to our study inclusion criteria of greater than 65 years, we assumed that approximately 8,500 PCI's would be performed in Québec each year, in those subscribed to the public health insurance plan. We further assumed that approximately half would satisfy our "new user" definition – no DAPT prescription in the previous 12 months – resulting in 4,250 PCI procedures per year who are DAPT naïve. Over the eight years – 2010-2018 – of the study database, we estimated that between 30 and 35 thousand ACS subjects underwent a PCI. With an assumed 2:1 clopidogrel to ticagrelor, prescribing pattern, this would give us approximately a total of 22,000 clopidogrel and 11,000 ticagrelor exposed subjects. With an assumed 10% event rate (similar to PLATO[4]) and a 5% false-positive (type 1) error rate, it would result in an 83% power to detect a 10% reduction in MACE outcomes within 1 year.

5.6 Results

Between April 1, 2010 and March 31, 2018 a total of 100,251 ACS patients were identified as undergoing a PCI in Québec, Canada. Of these, a total of 22,736 patients met our inclusion criteria (Figure 1) and filled a least one prescription for Ticagrelor or Clopidogrel. Clopidogrel was the more commonly prescribed DAPT (n=15,777) with a relatively stable number of exposures over time. In comparison, Ticagrelor prescriptions (n=6,959) steadily increased over time, from 203 to over 1600 prescriptions filled per year (Table 1).

As displayed in Table 1, patients exposed to clopidogrel were systematically sicker and at higher cardiovascular risk than ticagrelor subjects. For example, The subjects who filled a clopidogrel prescription were on average 2.5 years older (75.9 vs. 73.4 years), more likely to be male (39.9% vs. 36.5%), have a previous MI (12.1% vs. 7.5%), congestive heart failure (13.2% vs. 7.9%), atrial fibrillation (15.4% vs. 3.3%), chronic obstructive pulmonary disease (16.0% vs. 13.7%), a history of renal disease (13.1% vs. 8.6%), cancer (4.3% vs. 2.9%) when compared with those with a filled ticagrelor prescription.. Clopidogrel patients spent an average of 0.71 more days in hospital, in the previous year, with 9.8% having a Charlson index score greater than 2, versus 5.3% relative to their Ticagrelor counterparts.

After applying the ATE trimmed weights, generated through traditional PS IPTW methods, only the covariates of age, other heart disease (HD), atrial fibrillation, and the Charlson Index remained unbalanced at the 0.5 standardized mean difference (SMD) threshold (Figure 2A). These variables were then included as independent regressors in the first PS weighted CoxPH model. In the second PS weighted model, which leveraged the entropy balancing algorithm to produce ATE trimmed weights, all of the included covariates were balanced across the treatment groups at the 0.5 SMD threshold (Figure 2B).

Major Acute Coronary events

Overall, there were fewer unadjusted MACE events in the ticagrelor subjects (7.0%) than those exposed to clopidogrel (11.0%) during the 12 months of follow-up. The crude CoxPH model (Table 2) found ticagrelor to be associated with a lower risk of MACE than clopidogrel (HR, 0.66; 95% CI: 0.59, 0.73). After ATE propensity score (from standard maximum likelihood approach) and conditionally adjusting for age, other HD, atrial fibrillation, and the Charlson Index – ticagrelor was associated with a non-significant reduction in MACE outcomes (HR, 0.91; 95% CI: 0.81, 1.01). Meanwhile, adjustments using ATE weights derived from the entropy balancing algorithm found a borderline significant reduction in MACE outcomes (HR, 0.88; 95% CI: 0.79, 0.99) when compared to ACS patients exposed to clopidogrel.

Major bleeding

The crude primary safety outcome, major bleeding requiring hospitalization, occurred at similar rates in both treatment groups (ticagrelor, 1.2%; clopidogrel, 1.5%). Ticagrelor was not associated with an increase in bleeding in the unadjusted (HR, 0.97; 95%CI: 0.75, 1.24), IPTW-PS-weighted model (HR, 0.97; 95%CI: 0.75, 1.24), or the EBAL-PS-weighted models (HR, 0.88; 95%CI: 0.64, 1.19) (Table 2).

Secondary outcomes

In the evaluation of the individual MACE components, there were fewer deaths (ticagrelor, 2.0%; clopidogrel, 4.0%), MI's (ticagrelor, 4.6%; clopidogrel, 5.9%), and ischemic strokes (ticagrelor, 0.5%; clopidogrel, 1.1%) in those exposed to ticagrelor than clopidogrel. After PS adjustment, ticagrelor remained associated with a significant reduction (HR, 0.80; 95%CI: 0.66, 0.97) in death outcomes, though no significant reductions in MI's (HR, 0.99; 95%CI: 0.86, 1.13) or ischemic strokes (HR, 0.79; 95%CI: 0.53, 1.17) were observed (Table 2).

Exploring the primary outcomes stratified by sex (suppl. Tables 2-3), saw MACE and major bleeding outcomes at lower unadjusted rates in the ticagrelor treated populations across both

males and females. There was a significant reduction in MACE outcomes in males after PS adjustment (HR, 0.83; 95%CI: 0.72, 0.96), along with a non-significant reduction in bleeding outcomes (HR,0.76; 95%CI: 0.55, 1.06). In females, MACE outcomes were not significantly associated with either treatment (HR 1.02; 95%CI: 0.87, 1.20), while bleeding events were of higher risk in those prescribed ticagrelor (HR, 1.47; 95%CI: 1.01, 2.13).

5.7 Discussion

The present study is a large population-based cohort from Québec, where we observed a statistically non-significant reduction in MACE outcomes (HR, 0.91; 95% CI: 0.81, 1.01) as well as no statistically significant associations with major bleeding outcomes (HR, 0.97; 95%CI: 0.75, 1.24) 1-year after a PCI procedure following an ACS event. The results were relatively stable across both the ATE PS weighted methodologies, although the MACE estimates reached borderline statistical significance in the sensitivity EBAL-PS analysis. These differences appeared driven by the higher unadjusted mortality rates in those higher risk patients who filled a clopidogrel prescription (4.0%) versus ticagrelor (2.0%).

The results from our study are within the range of effectiveness findings from other non-randomized, propensity score adjusted observational studies, with MACE HR estimates ranging from 0.85 to 1.15.[28–30] However, our bleeding estimate, HR=0.97, was below their estimates that ranged from 1.20 to 2.88. Ticagrelor has been described[31–33] as the possible superior P2Y12-recptor inhibitor due to it's reversible-binding and direct-acting properties, as was demonstrated in PLATO.[4] The evidence from real-world clinical populations, however, continues to supply mixed evidence in support.

This study had several strengths. It was the second study,[29] to our knowledge, that investigated DAPT in ACS patients from North America, contributing 200% more patients towards the evidence base. We restricted to patients undergoing a PCI, to gather a more homogenous clinical population who had a higher likelihood of receiving a DAPT prescription. We excluded subjects with a DAPT script in the year prior to their current index ACS event to get a "new user" cohort, which minimized prevalent user biases. We also applied leading causal inference methodologies, leveraging propensity score weighting algorithms, to achieve a balance in the baseline covariates. Given the large number (>2,000) of primary outcomes, this study was sufficiently powered to assess

the effectiveness of DAPT use in patients undergoing PCI, though it was likely insufficiently powered to convincingly assess the primary safety and secondary endpoints.

This current study differed from PLATO in a variety of ways, which may have contributed to the incongruent observed results. The population from PLATO is younger (median 62 years) than the current study's recruited population (average 75 years), had a smaller proportion of females (28% vs. 40%), and had a lower rate of revascularization (PCI, 64.1%) compared to the Québec patients who exclusively underwent a PCI. The MACE rate for ticagrelor in PLATO was also noticeably higher (9.8%) than those observed in Québec (7.0%). It is plausible that treating physicians were actively prescribing the longer studied, clopidogrel, to their higher-risk patients. Although we designed our ITT analysis to mimic an RCT[11,34,35] an unmonitored clinical population may be impacted by more non-compliance or adherence to medication issues due increased administration, from twice-daily pills, from adverse events (dyspnea), and a more variable population from those who volunteer for a controlled study. The ultimate difference between PLATO and the current study is the non-randomized design. Although we applied PS weighting methods to create exchangeable pseudo-populations, conditioned on observed characteristics, the study is still susceptible to residual confounding Importantly, we acknowledge that there are other confounders (height, weight, family history, smoking, frailty, etc.) that could influence the relationship between the DAPTs and the study outcomes, which remain unmeasured. This missing covariate structure potentially influenced physician prescribing patterns and contributed to the disparate treatment populations with risk profiles that favoured ticagrelor. An issue no amount of advanced analytical techniques would reliably solve.

In conclusion, this non-randomized study, of ACS patients treated with a PCI, did not find ticagrelor to be superior to clopidogrel in either MACE or major bleeding endpoints. Further

confirmatory randomized studies to determine if ticagrelor is indeed more effective than clopidogrel in a North American population is necessary.

5.8 References

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5.9 Tables

Table 5.9.1. The baseline characteristics of the unweighted ACS study population by initial DAPT prescription.

	Clopidogrel	Ticagrelor
n	15,777	6,959
Age (mean (SD))	76 (7)	73 (6)
Sex (Female), n (%)	6294 (39.9)	2541 (36.5)
Year, n (%)		
2011	2230 (14.1)	2 (0.0)
2012	2826 (17.9)	203 (2.9)
2013	2159 (13.7)	780 (11.2)
2014	2070 (13.1)	1132 (16.3)
2015	1937 (12.3)	1270 (18.2)
2016	2039 (12.9)	1558 (22.4)
2017	2054 (13.0)	1618 (23.3)
2018	462 (2.9)	396 (5.7)
Previous MI, n (%)	1905 (12.1)	525 (7.5)
History of Angina, n (%)	1089 (6.9)	214 (3.1)
CVD, n (%)	468 (3.0)	111 (1.6)
CHF, n (%)	2082 (13.2)	552 (7.9)
Ischemic HD, n (%)	10512 (66.6)	4257 (61.2)
Pulmonary HD, n (%)	402 (2.5)	56 (0.8)
Rheumatic HD, n (%)	655 (4.2)	175 (2.5)
Other HD, n (%)	6162 (39.1)	1721 (24.7)
Atrial fibrillation, n (%)	2435 (15.4)	227 (3.3)
Cerebrovascular disease, n (%)	468 (3.0)	111 (1.6)
Arteries disease, n (%)	288 (1.8)	59 (0.8)
PVD, n (%)	1704 (10.8)	559 (8.0)
Hypertension, n (%)	10679 (67.7)	4312 (62.0)
Hypercholesterolemia, n (%)	9297 (58.9)	4230 (60.8)
Dementia, n (%)	295 (1.9)	76 (1.1)
COPD, n (%)	2521 (16.0)	952 (13.7)
Rheumatologic disease, n (%)	420 (2.7)	192 (2.8)
Digestive ulcer, n (%)	137 (0.9)	34 (0.5)
Liver disease, n (%)		
Mild	355 (2.3)	130 (1.9)
Moderate/Severe	37 (0.2)	6 (0.1)
Diabetes, n (%)	3737 (23.7)	1530 (22.0)
Complications, n (%)	348 (2.2)	112 (1.6)
Renal disease, n (%)	2063 (13.1)	599 (8.6)
Cancer, n (%)	681 (4.3)	205 (2.9)
Metastatic, n (%)	169 (1.1)	39 (0.6)
HIV, n (%)	6 (0.0)	2 (0.0)
Plegia, n (%)	82 (0.5)	18 (0.3)
Charlson index, n (%)		
0	6144 (38.9)	3325 (47.8)

1	4327 (27.4)	1998 (28.7)
2	2353 (14.9)	839 (12.1)
3+	1546 (9.8)	369 (5.3)
Previous year		
Hosp. visits, (mean (SD))	0.3 (0.7)	0.2 (0.7)
Days in hosp., (mean (SD))	1.70 (7.7)	1.00 (5.30)

Abbreviations: n, count; SD, standard deviation; %, percentage; MI, myocardial infarction; CVD, cardiovascular disease; CHF, congestive heart failure; HD, heart disease; PVD, peripheral vascular disease; COPD, Chronic obstructive pulmonary disease; HIV, human immunodeficiency virus; Hosp., hospital.

Table 5.9.2. The clinical outcomes and results of the propensity score ATE weighted Cox proportional hazards models.

	Ticagrelor *N=6,959*	Clopidogrel *N=15,777*	HR (95% CI) *unadjusted*	*ATE weighted + adjusted***	*ATE weighted (EBAL)*
MACE	490 (7.0%)	1733 (11.0%)	0.66 (0.59, 0.73)	0.91 (0.81, 1.01)	0.88 (0.79, 0.99)
All-cause mortality	137 (2.0%)	628 (4.0%)	0.51 (0.43, 0.62)	0.80 (0.66, 0.97)	0.76 (0.61, 0.94)
MI	317 (4.6%)	937 (5.9%)	0.78 (0.69, 0.89)	0.99 (0.86, 1.13)	0.96 (0.84, 1.12)
Stroke	36 (0.5%)	168 (1.1%)	0.50 (0.35, 0.72)	0.79 (0.53, 1.17)	0.82 (0.53, 1.25)
Bleeding	84 (1.2%)	235 (1.5%)	0.97 (0.75, 1.24)	0.97 (0.75, 1.24)	0.88 (0.64, 1.19)

Abbreviations: HR, hazard ratio; CI, confidence interval; N, number of patients; MACE, major acute coronary events; MI, myocardial infarction.
***Propensity score ATE weighted and regression adjustment for the covariates: age, other heart disease, atrial fibrillation, and the Charlson Index*

5.10 Figures

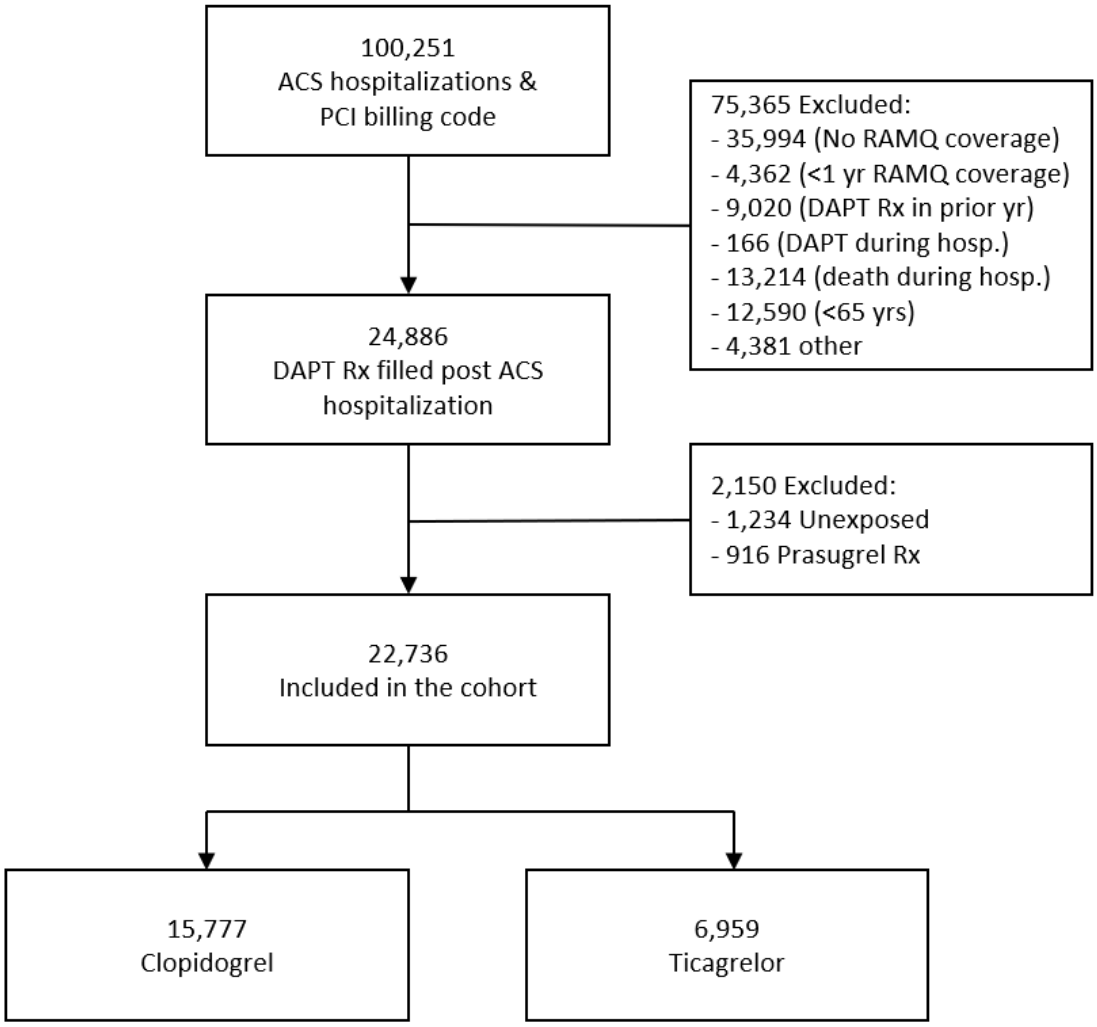
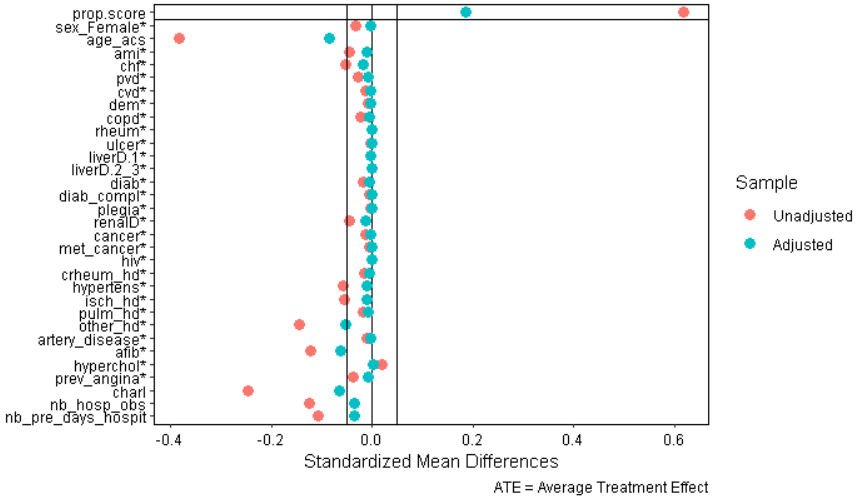


Figure 5.10.1. Flow chart describing the formation of the study cohort.

A



B

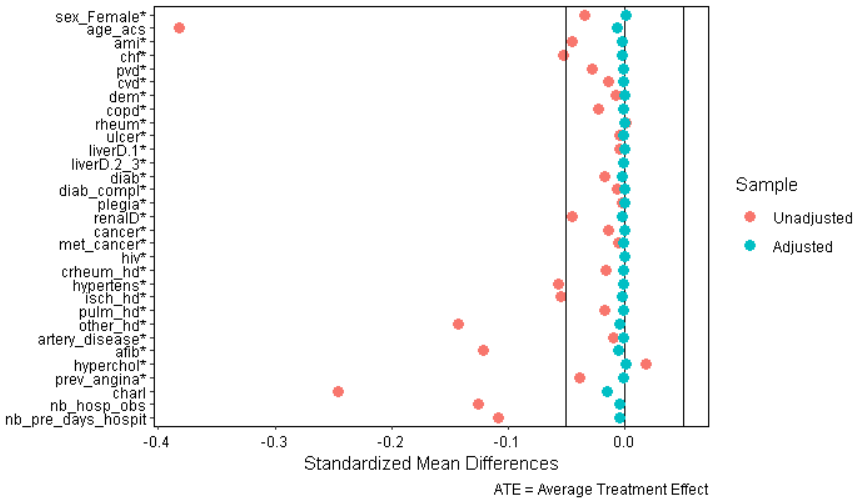


Figure 5.10.2. Love plot visualizations of covariate balance using the standardized mean differences in models using (A) ATE weights calculated from a classic PS model, and (B) ATE weights calculated from an entropy balancing algorithm. All ATE weights were trimmed at 5.

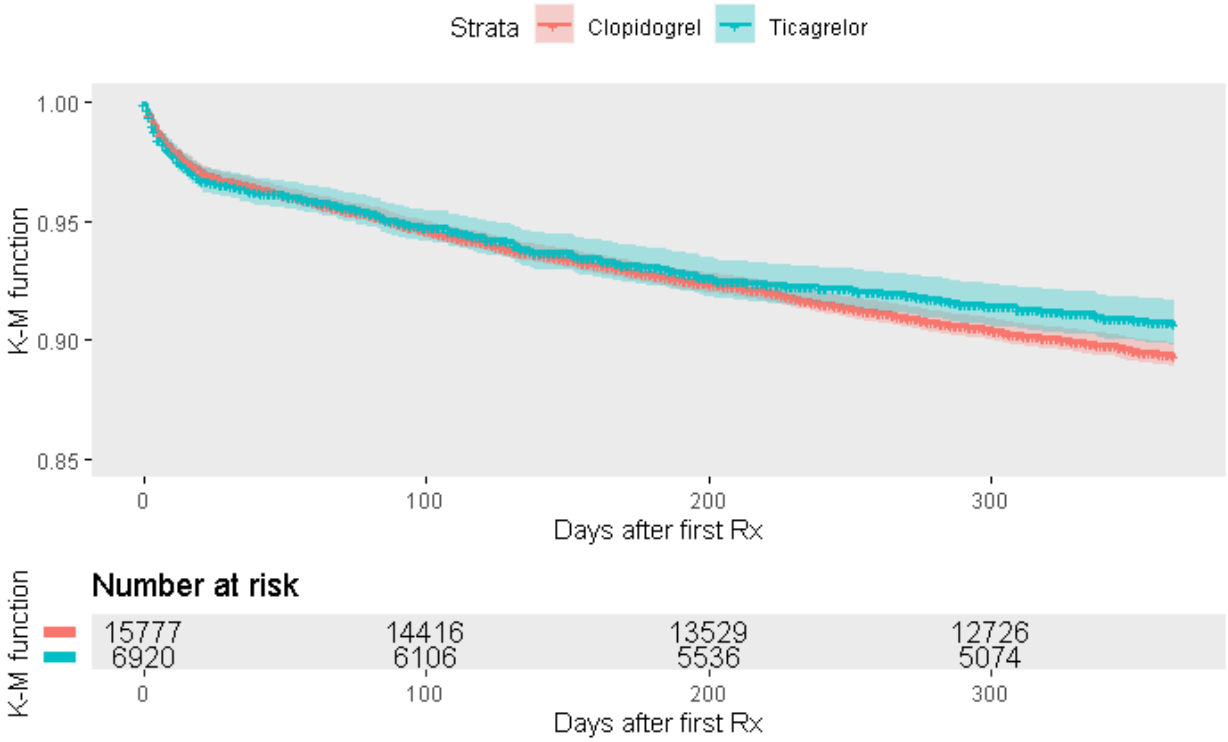


Figure 5.10.3. The Kaplan-Meier survival curve for MACE outcomes in ACS patients treated with ticagrelor or clopidogrel between April 1, 2010 and March 31, 2018 in Québec, Canada.

5.11 Appendix

5.11.1 Supplemental Tables

Supplemental Table 5.11.1.1. The ICD-10 codes used to identify clinical outcomes within the electronic healthcare databases.

Outcome	**ICD-10 code**
Myocardial infarction	I21.X, I22.X, I23.X
Stroke (ischemic)	H34.1, I63.X, I64.X, I67.X
Stroke (hemorrhagic)	I60.X, I61.X, I62.X
Gastrointestinal Bleeding	K92.X
Comorbidities	
Transient ischemic attack	H34.0, G45.X except G45.4
Heart Failure	I50.X
Angina	I20.X
Coronary atherosclerosis	I25.10, I25.81X
Other ischemic heart disease	I25.5 I25.8 I25.9
Atherosclerosis diagnostic	I71.3, I71.4
Diabetes	E10, E11, E13, E14

Supplemental Table 5.11.1.2. The clinical outcomes and results of the propensity score ATE weighted Cox proportional hazards models in male ACS patients.

	Ticagrelor N=4,418	Clopidogrel N=9,483	HR (95% CI) *unadjusted*	*ATE weighted + adjusted***	*ATE weighted (EBAL)*
MACE	271 (6.1%)	995 (10.5%)	0.60 (0.52, 0.68)	0.83 (0.72, 0.96)	0.80 (0.69, 0.94)
All-cause mortality	83 (1.9%)	380 (4.0%)	0.48 (0.38, 0.61)	0.75 (0.58, 0.96)	0.74 (0.56, 0.97)
MI	167 (3.8%)	529 (5.6%)	0.69 (0.58, 0.82)	0.88 (0.73, 1.05)	0.83 (0.69, 1.01)
Stroke	21 (0.5%)	86 (0.9%)	0.54 (0.34, 0.87)	0.86 (0.51, 1.45)	0.92 (0.52, 1.65)
Bleeding	49 (1.1%)	134 (1.4%)	0.82 (0.59, 1.14)	0.76 (0.55, 1.06)	0.66 (0.44, 1.00)

Abbreviations: HR, hazard ratio; CI, confidence interval; MACE, major acute coronary events; MI, myocardial infarction;
***PS ATE weighted and adjusted for: age, other HD, Afib, and Charlson Index*

Supplemental Table 5.11.1.3. The clinical outcomes and results of the propensity score ATE weighted Cox proportional hazards models in female ACS patients.

	Ticagrelor N=2,541	Clopidogrel N=6,294	HR (95% CI) *unadjusted*	*ATE weighted + adjusted***	*ATE weighted (EBAL)*
MACE	219 (8.6%)	738(11.8%)	0.76 (0.65, 0.88)	1.02 (0.87, 1.20)	0.99 (0.87, 1.17)
All-cause mortality	54 (2.1%)	248 (3.9%)	0.56 (0.42, 0.76)	0.90 (0.66, 1.23)	0.81 (0.58, 1.12)
MI	150 (5.9%)	408 (6.5%)	0.94 (0.78, 1.13)	1.16 (0.95, 1.41)	1.14 (0.93, 1.41)
Stroke	15 (0.5%)	82 (1.3%)	0.47 (0.27, 0.82)	0.71 (0.39, 1.29)	0.73 (0.39, 1.39)
Bleeding	35 (1.4%)	101 (1.6%)	1.23 (0.84, 1.82)	1.47 (1.01, 2.13)	1.39 (0.96, 2.02)

Abbreviations: HR, hazard ratio; CI, confidence interval; MACE, major acute coronary events; MI, myocardial infarction;
***PS ATE weighted and adjusted for: age, other HD, Afib, and Charlson Index*

5.12. Ethics

Centre universitaire de santé McGill | McGill University Health Centre

2018-10-03

Dr. James Brophy
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RE: Final REB Approval of a New Research Project
A pharmacoepidemiology study of Dual Antiplatelet Therapy (DAPT)
(DAPT / 2019-4993)

MUHC REB Co-Chair for the CTGQ panel: Me Marie Hirtle

Dear Dr. Brophy,

Thank you for submitting your responses and corrections for the research project indicated above, as requested by the McGill University Health Centre (MUHC) Research Ethics Board (REB).

The MUHC REB, more precisely its Cells, Tissues, Genetics & Qualitative (CTGQ) research panel provided conditional approval for the research project after a delegated review provided by its member(s).

On 2018-10-03, a delegated review of your responses and corrections was provided by member(s) of the MUHC REB. The research project was found to meet scientific and ethical standards for conduct at the MUHC.

The following documents were approved or acknowledged by the MUHC REB:

- Initial Submission Form (F11NIR - 36035)
- REB Conditions & PI Responses Form(s) (F20 - 36671)
- Research protocol
  - (protocol_MUHC_oct3_references_REBApproved.docx) [Date: 2018-10-03, Version: 1.1]

This will be reported to the MUHC REB and will be entered accordingly into the minutes of the next CTGQ meeting. Please be advised that you may only initiate the study after all required reviews and decisions are received and documented and you have received the MUHC authorization letter.

The approval of the research project is valid until 2019-10-03.

All research involving human subjects requires review at recurring intervals. To comply with the regulation for continuing review of at least once per year, it is the responsibility of the

Chapter Six. Ticagrelor Compared to Clopidogrel in aCute Coronary syndromes – the TC4 pragmatic cluster randomized controlled trial

6.1 Preface

In Chapter 5, we identified 100,251 ACS patients who underwent a PCI between April 2010 and March 2018. We found a total of 6,959 new ticagrelor and 15,777 new clopidogrel DAPT users, with a minimum of 1 year of RAMQ database history to assess DAPT exposure history and patient characterises. The average treatment effect (ATE) weights were calculated using inverse probability of treatment weight of the propensity score, from which a weighted cox model illustrated that ticagrelor initiators were not significantly associated with major cardiac events (adjusted HR [aHR], 0.91; 95% CI: 0.81, 1.01), nor major bleedings causing hospitalization (aHR, 0.97; 95% CI: 0.75, 1.24), relative to clopidogrel DAPT initiators. Though we were unable to find an association in this ACS cohort from a clinical health registry, some may be concerned with residual confounding from unobserved population characteristics not captured in electronic health data. Thus, the third objective of this thesis was a pragmatic time-cluster randomized trial to determine if ticagrelor is associated with a decreased risk of major cardiac events, compared with clopidogrel DAPT, in a clinical ACS population from Montréal, Canada.

6.2 Title page

Ticagrelor Compared to Clopidogrel in aCute Coronary syndromes – the TC4 pragmatic cluster randomized controlled trial

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Abstract: 365 words

Word count: 3,396 words

6.3 Abstract

Background: The dual-antiplatelet therapy (DAPT) ticagrelor, in combination with aspirin, is the recommended strategy for acute coronary syndrome (ACS) patients undergoing a percutaneous coronary intervention (PCI). Residual uncertainty remains in the superiority of ticagrelor over clopidogrel due to heterogeneity in the North American subgroup from the landmark PLATO trial. This along with limitations in the generalizability of large multinational trials motivated this investigation into the effectiveness and safety between ticagrelor and clopidogrel in a clinical ACS population from the McGill University Health Centre, in Montreal, Canada.

Methods: Between October 2018 and March 2021, we recruited ACS patients with a planned PCI into a pragmatic, open-label, time clustered, randomized trial of either ticagrelor or clopidogrel, in combination with aspirin. The primary effectiveness endpoint was a composite of all-cause mortality, non-fatal myocardial infarction, or ischemic stroke (MACE). The primary safety endpoint was hemorrhagic stroke or gastrointestinal bleeding requiring hospitalization. Outcomes were ascertained within the 12 months after the index ACS hospitalization using ICD-10 codes in the electronical health databases from Québec, Canada. Bayesian Cox proportional hazard models were used to evaluate all outcomes. The primary analysis included a vague prior for the population effect estimate. We also evaluated "skeptical", "enthusiastic", and "summary" informative priors. The results were presented as direct probability statements with the range of practical equivalence (ROPE, Hazard ratio [HR] = [0.9, 1.11]).

Results: A total of 1,005 ACS patients were randomized to ticagrelor (n = 450) or clopidogrel (n = 555) across thirteen 2-month cluster periods and one 4-month cluster period (due to COVID-19). MACE was observed in 11.1% of patients assigned to ticagrelor and 11.5% to clopidogrel. Using a vague prior, ticagrelor was attributed to a 3% median reduction in MACE endpoints (HR, 0.97; 95% credible interval [95% CrI]: 0.67, 1.40). The posterior distribution estimated that ticagrelor had only a 35% chance of producing a clinically important decrease in the risk of MACE outcomes. For the primary safety endpoint HR was 0.88 (95% CrI: 0.49, 1.50) in favor of ticagrelor.

Conclusions: The TC4 trial was the first RCT to assess ticagrelor DAPT in a North American population since PLATO. The stand-alone TC4 trial data did not support the superiority of ticagrelor over clopidogrel.

6.4 Introduction

The overall efficacy presented in the PLATelet inhibition and patient Outcomes (PLATO) trial, with a total of 862 study centers included in the trial from across 43 countries, was ultimately not distributed evenly across the study regions. The 1,814 North American patients showed a non-significant increase in major adverse cardiovascular events (MACE, HR_{NA}: 1.25, 95% CI: 0.93 to 1.67),[5] a considerable deviation from the PLATO pooled estimate (HR, 0.84; 95%CI: 0.77, 0.92). When a hierarchical (random effects) model, accounting for that regional variability, was applied using the PLATO sub-regional estimates the 95% confidence limits then included the NULL effect (HR=0.87; 95% credible interval (CrI): 0.70, 1.15).[6] Readers may arrive with different prior beliefs about how the data generating mechanism is structured, however, it should be evident that after reasonable modelling changes, the PLATO estimate cannot be considered robust, at least in its applicability to a North American context.

In the absence of a subsequent RCT investigating DAPTs in a North American population and the limitations from the fixed effect modelling decisions there is a need for a follow-up RCT in a North American population. As concerns regarding the potential generalizability issues from large multinational RCT's, we believe this would be best achieved using a pragmatic RCT design.

The current study, the **T**icagrelor **C**ompared to **C**lopidogrel in a**C**ute coronary syndromes – the TC4 trial (NCT04057300) – is a pragmatic, cluster RCT designed to assess the effectiveness and safety of DAPTs in a ACS population undergoing a percutaneous coronary intervention (PCI) in a single tertiary academic center in Montreal, Canada, between October 2018 and March 2021. The primary outcome is the association of ticagrelor with a composite of all-cause mortality, secondary myocardial infarctions (MI), or ischemic strokes in comparison to clopidogrel. The primary safety outcome is the association of the composite of hemorrhagic strokes and gastrointestinal bleeding – major bleeding requiring hospitalization – of ticagrelor versus clopidogrel.

6.5 Methods

Study design

The TC4 trial was a single center, open-label, active control, parallel-arm, RCT. This pragmatic trial used a novel approach to randomization using a time-cluster randomized (TCRX) design.[7] In summary, ACS patients were randomized to ticagrelor or clopidogrel in alternating 2-month cluster periods. The first exposure period (October/November 2018) was set using a random number generating sequence algorithm through the R software program.[8] ACS patients arriving to the McGill University Health Center (MUHC) during the 2-month cluster would receive the scheduled DAPT for that period. ACS patients arriving in the subsequent 2-month period (December 2018/January 2019) would receive the alternative DAPT, and so forth. Patients follow up was monitored electronically via Québec medico-administrative hospital databases.

Cohort

All newly admitted ACS patients treated at the MUHC emergency department, cardiology or intensive care unit between October 1, 2018, and March 31, 2021, were eligible to participate. Patients were approached by a research nurse coordinator to obtain informed consent following confirmation from the treating physician that DAPT was the appropriate treatment.

Exposure

Patients were randomized to receive ticagrelor or clopidogrel depending on the date of their ACS hospitalization visit. In accordance with PLATO, attending physicians were advised to prescribe a 180 mg loading dose followed by a 90 mg bid dose of ticagrelor or a 300 mg loading dose followed by a daily dose of 75 mg of clopidogrel to their patients. Both therapies were to be accompanied by a 325 mg loading dose and 81 mg daily dose of Aspirin, with patients encouraged to take their medications for 12 months following hospital discharge.

Outcome

The primary effectiveness outcome was major acute coronary events (MACE) – a composite of all-cause mortality, non-fatal MI, or ischemic stroke – within 12 months of the index ACS hospitalization. The primary safety outcome was a composite of bleeding events that required hospitalization – gastrointestinal bleeding or a hemorrhagic stroke. The secondary outcomes of interest were the individual MACE outcomes of all-cause mortality, non-fatal MI, or ischemic stroke as well as the primary composite endpoints – MACE and hospitalized bleeding – stratified by sex. The outcomes were independently assessed using ICD-10 codes (suppl. Table 1) and death certificates from hospital and provincial electronic health records, which have been previously validated for these outcomes.[9–12] Data extraction was by observers blinded to treatment assignment.

Statistical analyses

The baseline characteristics of study participants were summarized using means, standard deviations, for continuous variables and proportions for categorical groups. All analyses examined the time to the first occurrence of an outcome, 1-year post-index ACS hospitalization, or a loss-to-follow-up. Cox proportional hazards models were used to estimate hazard ratios (HR).[13] We used the *brms* R package[14] for a full Bayesian statistical inference using the No-U-Turn Sampler (NUTS), an extension of the Hamiltonian Monte Carlo (HMC) sampling,[15] to estimate posterior distributions of the HR and 95% credible intervals (95% CrI). The NUTS algorithm is considered to be more efficient than other Gibbs samplers.[15] Three HMC chains, each a minimum of 10000 iterations with a 5000 burn-in period were used to produce a total of 15000 posterior samples. For each model, the three chains were observed to determine if they had converged.

For each outcome, we fit both a fixed effect (assumes the same treatment effect within each cluster) and a hierarchical CoxPH model (assumes the treatment effect within each cluster comes from a distribution). Model comparison was done using the leave-one-out cross-validation (LOO),

to evaluate model fit.[16] Since we used a full Bayesian analysis, we placed prior distributions on model parameters. For nuisance parameters we used the default *brms* R package settings of non-informative priors: a Student-t prior, with 3 degrees of freedom (student_t(3, 0, 2.5) for the standard deviation (*sd*) and a Lewandowski-Kurowicka-Joe (LKJ) uniform distribution (η=1) for the correlation structure of the cluster-levels. We also supplied priors for the population level-effect of the treatment on the primary outcomes as described in the subsequent paragraph.

It has been recommended to acknowledge the possibility that clinical beliefs may vary,[17,18] thus we included a range of treatment priors (suppl. Table 2). A Student-t distribution around the NULL effect (HR=1.0), with 3 degrees of freedom and a *sd* of 5 was used as a vague (i.e., non-informative) prior for both the MACE and bleeding outcomes. The "skeptical", "enthusiastic", and "summary" informative priors[17,18] were extracted from the literature. The North American, PLATO estimates (HR_{MACE} = 1.25, 95% CI: 0.93, 1.67; HR_{Bleed} = 1.05, 95% CI: 0.76, 1.45) and the results from a Bayesian Network Meta-analysis (BNMA) of all previous RCTs (HR_{MACE} = 0.95, 95% CrI: 0.81, 1.14; HR_{Bleed} = 1.07, 95% CrI: 0.99, 1.17)[19] formed the *skeptical* and *summary* priors, respectively. Finally, the *enthusiastic* prior was formed by combining the point estimate from the pooled PLATO results (HR_{MACE} = 0.84; HR_{Bleed} = 1.04) with the *sd* from the North American subgroup from PLATO (sd_{MACE}=0.17 & sd_{bleed}=0.16).

The minimum important difference (MID)[20] was set at 10% and were presented as probability statements. A 10% change, which represents the lower and upper thresholds of the MID, were set at a 10% decrease (HR<0.9) and the inverse (HR>1.11) in the effect estimate. While a range of practical equivalence (ROPE) is the range between those two thresholds, where the posterior of the HR falls between 0.9 and 1.11. Meaning we estimated the proportion of the posterior distribution that lies above, below, and between our, admittedly somewhat arbitrary, clinical thresholds. These analyses have followed the Bayesian Analysis Reporting Guidelines [21]

Sample size calculation

The classic frequentist approach to sample size estimation, which assumes a NULL hypothesis and long-term Type I and Type II error rates, fails to address the goal of estimating the probability of any difference between the two treatments. A Bayesian hierarchical reanalysis of the PLATO trial estimated the North American HR as 1.13 (95% CI: 0.75 to 1.47) but still left considerable uncertainty with a 59% probability that ticagrelor increased MACE events by >2/100 patients. When this estimate is combined with a future hypothetical TC4 trial that assumes event rates similar to the overall PLATO trial (clopidogrel, 12%; ticagrelor, 9.8%) using conjugate Bayesian estimation, based on normal approximations for the prior and future hypothetical TC4 trial, the posterior probability that ticagrelor increases MACE outcomes by >2/100 patients falls from 59% to less than 3%, with the addition of 500 patients to each treatment arm. In short, adding a projected 1,000 subjects to the existing 1,800 North American data is a justifiable and clinically meaningful addition to the evidence base.

6.6 Results

We recruited 1,005 ACS patients, from thirteen 2-month and one 4-month cluster periods as the COVID-19 pandemic interrupted recruitment efforts from March through May 2020, disrupting a ticagrelor recruitment period cluster. As a result, we added an extra 2-month period to the end of our final recruitment cluster. Follow-up, using the provincial electronic healthcare databases, ended in April 2022. The clopidogrel (N=555) and ticagrelor (N=450) DAPT groups were generally well balanced across their baseline characteristics (Table 1).

Major acute coronary events

VAGUE PRIOR

The primary effectiveness outcomes occurred at similar rates in both exposure groups (clopidogrel, 11.5%: ticagrelor, 11.1%). The LOO cross-validation evaluation suggested the pooled model, when using a vague prior, had a better overall fit to the data than the hierarchical model. Consequently, unless otherwise specified results refer to the pooled model (Table 2). The results from the hierarchical models are available in the supplement (suppl. Table 4).

When using the vague prior, the equivalent of examining the TC4 data on its own, there was an estimated 3% median reduction (Table 2) for MACE outcomes in those assigned to ticagrelor when compared to clopidogrel (HR, 0.97; 95% CrI: 0.67, 1.40). This translated to a 35% probability that ticagrelor was responsible for a clinically meaningful reduction (HR<0.9), a 25% chance of a clinically meaningful increase (HR>1.11), and a 40% likelihood being within the ROPE, for comparing MACE outcomes when compared to clopidogrel (Table 2).

INFORMATIVE PRIORS

Table 2 also summarizes the posterior distributions of the likelihood from the TC4 trial data incorporated with the range of pre-specified priors. The *skeptical* prior, using only the North American, PLATO subgroup data, resulted in a posterior median for the HR of 1.13 (95% CrI: 0.90,

1.42), while the *enthusiastic* prior gave a median HR of 0.89 (95% CrI: 0.71, 1.11), and the *summary* prior a 5% decrease (HR, 0.95; 95% CrI: 0.81, 1.12) in MACE outcomes for ticagrelor patients, relative to clopidogrel. The MID summaries of these posterior distributions translated to a 2%, 55%, and 24% estimated meaningful reduction in MACE endpoints for ticagrelor, respectively for the *skeptical*, *enthusiastic*, and *summary* priors. The ROPE, for these same priors, were estimated to be 38%, 42%, and 72%, respectively. The *skeptical* prior estimated a 60% chance that ticagrelor was related to meaningful increased risk of MACE outcomes, while the *skeptical* and *summary* priors translated to 3% and 4% probabilities of a clinically relevant risks.

Major bleeding

VAGUE PRIOR

The major bleeding events that required hospitalization did not substantially differ across the TC4 treatment groups (clopidogrel, 5.0%; ticagrelor, 4.4%; HR, 0.88; 95% CrI: 0.49, 1.50) assuming a pooled model with vague prior. The TC4 data alone thereby translated to a 53% chance of a clinically meaningful reduction (HR<0.9), a 25% probability of clinical equivalence (ROPE), and a 22% chance for a relevant increase (HR>1.11) in ticagrelor bleeding events, in relation to clopidogrel (Table 2).

INFORMATIVE PRIORS

Summarizing the integration of the TC4 trial with the other major bleeding priors (Table 2), there was almost 0% probability of a clinically meaningful reduction in bleeding (HR < 0.9), a 77% likelihood of clinical equivalence, and a 23% probability of increased bleeding with ticagrelor per the incorporation with the *summary* prior. The *skeptical* and *enthusiastic* priors, when integrated with the TC4 data, estimated respective 22% and 67% decreases, 51% and 31% equivalences (ROPE), along with 27% and 2% probabilities of an increase in major bleeding events with ticagrelor.

Secondary outcomes

For the components of the primary effectiveness outcome, MACE, there were fewer deaths from all-cause mortality identified in the ticagrelor group (1.6% vs. 2.7%) than the clopidogrel arm (HR, 0.57; 95% CrI: 0.22, 1.35). A similar proportion of MI events in the ticagrelor patients (8.4% vs. 8.3%) in comparison to clopidogrel (HR, 1.02; 95% CrI: 0.67, 1.55). Lastly, a similar number of ischemic stroke outcomes between the two groups (clopidogrel, N≤5 vs. ticagrelor, N≤5) was observed (Table 2).

The exploratory sex stratified analyses found that MACE and bleeding outcomes occurred more frequently in females (MACE, 14.6%; Bleeding, 5.7%) than their male counterparts (MACE, 10.3%; Bleeding, 4.7%). In females, ticagrelor was associated with fewer MACE events (13.4% vs. 15.6%: HR, 0.86; 95% CrI: 0.44, 1.65) and slightly more bleeding events (6.3% vs. 5.2%: HR, 1.21; 95% CrI: 0.41, 3.47) relative to those treated with clopidogrel. While in the males, ticagrelor had similar MACE events (10.4% vs. 10.2%; HR, 1.01; 95% CrI: 0.64, 1.59) and fewer bleeding events (3.8% vs. 5.0%; HR, 0.76; 95% CrI: 0.37, 1.50) than patients on clopidogrel (Table 2).

6.7 Discussion

This cluster trial that compared DAPTs for ACS patients with planned PCI, randomized 1,005 patients to ticagrelor or clopidogrel, however, it was not powered to detect meaningful outcome differences solely on its own merits. Indeed, the observed TC4 trial HR, using a vague prior (HR, 0.97; 95% CrI: 0.67, 1.40), was consistent with substantial residual probabilities of a clinically important benefit (35%), equivalence (40%), and risk (25%) with ticagrelor compared to clopidogrel. However, by augmenting by more than 50% the existing evidence base for these differing strategies in our target North America population, the uncertainty regarding the relative efficacy of these two strategies in this specific context was reduced considerably. Specifically, when our prior knowledge (HR, 1.25; 95% CrI: 0.93, 1.67) from previously randomized North American patients from PLATO (to our knowledge, the only previous trial comparing ticagrelor to clopidogrel that included North American patients) was updated with TC4 data, there was only a 2% probability of a clinically meaningful benefit in MACE outcomes with ticagrelor compared to clopidogrel. As well, there was a 38% probability of clinical equivalency, and a 60% chance of clinically worse MACE outcomes in North American patients assigned to ticagrelor relative to clopidogrel.

To account for other potential pre-trial beliefs, beyond the North American PLATO evidence, the TC4 results were also combined with an *enthusiastic* (the main PLATO effect estimate using the *sd* from the North American estimate; HR, 0.84; 95% CrI: 0.51, 1.17) and *summary* priors (from a BNMA; HR, 0.95; 95% CrI: 0.81, 1.12). The distribution of the posteriors for the MACE outcome (suppl. Figure 1), when the *enthusiastic* and *summary* priors were combined with the TC4 trial data, varied when compared with the posterior estimates reported above, which were generated from the *vague* and *skeptical* priors. Incorporating the *enthusiastic* and *summary* prior beliefs with the current TC4 data resulted in posterior probabilities of clinically meaningful MACE reductions (HR < 0.9) of only 55% and 24%. Therefore, when the TC4 trial was incorporated with these more

heterogeneous, largely non-North American, population estimates, it was clear that the probability for ticagrelor's clinical superiority remained moderate, at best.

Unsurprisingly, the TC4 trial results for the primary safety outcome were also underpowered to identify clinically meaningful harms from major bleeding events that required hospitalizations. Again, substantial portions of the primary safety outcomes' posterior distribution, when relying on the TC4 trial data alone (using a vague prior), fell within the regions of clinical benefit (53%), equivalence (25%), and risk (22%) for ticagrelor when compared with clopidogrel. When the TC4 data was bolstered with the existing North American RCT evidence, the posterior moved towards a DAPT clinical equivalence (51%), with similar probabilities found for a clinically important reduction (22%) and risk (27%) of major bleeding events with ticagrelor. Coinciding with the primary effectiveness outcome, the posterior distributions shifted when integrated with the more heterogeneous *enthusiastic* and *summary* priors. The posterior probabilities, when the TC4 data was combined with the *enthusiastic* and *summary* priors, for a clinically meaningful reduction in major bleeding were 67% and 0%, respectively. The posterior distributions from the incorporation of the TC4 data with these largely non-North American population priors, extends little confidence for the superiority of ticagrelor with regards to major bleeding events.

Ultimately, our TC4 trial findings, either when taken alone or integrated with a wide spectrum of prior beliefs do not align with North American ACS guidelines,[1,2] which recommend ticagrelor as the superior DAPT to clopidogrel. PLATO, a multinational study dominated by Western and Eastern European centres, reported a clinically significant reduction in MACE outcomes (HR: 0.84; 95% CI [CI]: 0.77, 0.92) and no clinically significant association with bleeding (HR:1.04; 95% CI: 0.95, 1.13) when comparing ticagrelor to clopidogrel. The TC4 trial efficacy results fall between the overall PLATO and the PLATO North American subgroup results and are compatible with the BNMA efficacy summary of low risk of bias DAPT RCTs (HR: 0.95, 95% CrI:

0.81, 1.14). Considerable uncertainty remains concerning any increase or decrease in bleeding with ticagrelor when TC4 is analysed alone or with the inclusion of the multiple priors investigated (Table 2). Further refinement of the residual uncertainty regarding the precision of any efficacy or safety differences between the two treatments will require more experimentation.

The major strength of the TC4 trial is that it is the first RCT, to our knowledge, to be performed in North America since the publication of PLATO. We were able to recruit a large (N=1,005) sample of ACS patients undergoing a planned PCI and achieved excellent baseline covariate balance across the DAPT treatment arms. The pragmatic nature of this trial, by limiting the exclusion criteria for patient participation, allowed for the investigation of the effectiveness of ticagrelor versus clopidogrel in a more clinically representative population than a typical RCT. Lastly, by leveraging the provincial electronic healthcare databases, and focusing on clinically validated outcomes, we were able to minimize the loss of patients during the 1-year follow-up period for identifying clinical outcomes. The Bayesian analytical approach eliminated the need for NULL hypothesis significance testing and P-values.[22] Instead, it allowed for the incorporation of a wide-range of prior beliefs and provided direct probability statements regarding the interpretation of the effectiveness and safety evidence, with respect to clinically meaningful effect sizes. Finally, it is well known that large RCTs can typically cost over $100 million or approximately $10,000 per patient randomized.[23] This unique and innovative research design cost approximately $300 per patient randomized.

The aim of the TC4 trial was not to reproduce the overall PLATO findings, but rather to contribute more evidence to the estimation of the relative efficacy of ticagrelor versus clopidogrel in North American patients. As such, these two RCTs differed in some important ways. As mentioned, the pragmatic aspect of TC4 trial minimized the exclusion criteria and recruited all patients eligible for treatment with a DAPT, which should be a more clinically representative population than most

RCTs, including PLATO. This may explain why the TC4 patients were older, on average (~66 years vs. ~62 years) than the PLATO study participants. The TC4 also recruited only those ACS subjects undergoing a PCI (PLATO, 64%) from a single hospital center in Montreal, Canada (PLATO, 862 study centers), and relied upon the healthcare system to adjudicate clinical outcomes instead of dedicated research team. A further limitation of the TC4 trial includes only a reported ITT analytical approach of HRs, which may fall short of patient preferences for per protocol outputs.[24] Unfortunately, the per-protocol and as-treated analyses were unachievable due to structural restrictions of the TC4 databases whereby universal prescription follow-up data was only available for those subjects greater than 65 years of age.

In conclusion, the TC4 pragmatic RCT added a substantial amount of North American evidence to the DAPT literature. The stand-alone results did not find any convincing evidence for the superiority of ticagrelor over clopidogrel for either the primary effectiveness or safety outcomes. Even after the incorporation of a range of clinically relevant priors, selected from the literature, the results did not overwhelmingly support either DAPT treatment. Given the increased costs of ticagrelor, the inconvenience of its twice daily dosing, and the absence of anything more than a small to modest, in the order of a coin toss, probability of a clinically meaningful efficacy benefit, it is difficult to recommend ticagrelor over clopidogrel. These findings conflict with the current clinical ACS guidelines, highlighting a need for continued research and a comprehensive update of the available evidence surrounding the care of ACS patients.

6.8 References

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6.9 Tables

Table 6.9.1. The baseline characteristics of the TC4 study population by DAPT treatment assignment.

	Clopidogrel	Ticagrelor
n	555	450
Age (mean (SD))	68 (11)	65 (11)
Sex (male), n (%)	420 (75.7)	338 (75.1)
Height, cm (mean (SD))	170.60 (9.47)	171.04 (9.30)
Weight, kg (mean (SD))	83.05 (21.99)	83.31 (17.78)
Smoking status, n (%)		
Never	192 (34.7)	179 (40.0)
Experimental	0 (0.0)	2 (0.4)
Former, occasional	21 (3.8)	14 (3.1)
Former, daily	205 (37.0)	143 (31.9)
Current, occasional	16 (2.9)	7 (1.6)
Current, daily	120 (21.7)	103 (23.0)
Race, n (%)		
Caucasian	453 (81.6)	376 (83.6)
Other	102 (18.4)	74 (16.4)
Previous DAPT, n (%)		
None	409 (74.1)	341 (76.3)
Clopidogrel	137 (24.8)	88 (19.7)
Ticagrelor	6 (1.1)	17 (3.8)
Prasugrel	0 (0.0)	1 (0.2)
ACS diagnosis, n (%)		
STEMI	116 (20.9)	94 (20.9)
NSTEMI	210 (37.9)	207 (46.1)
Unstable Angina	89 (16.1)	69 (15.4)
Stable Angina	83 (15.0)	53 (11.8)
Other	56 (10.1)	26 (5.8)
Hypertension, n (%)	387 (69.9)	300 (67.0)
SBP (mean (SD))	140.62 (22.23)	140.02 (22.62)
DBP (mean (SD))	79.72 (13.69)	80.43 (14.99)
Heart rate (mean (SD))	72.94 (15.43)	72.39 (15.11)
Dyslipidemia, n (%)	376 (68.0)	301 (67.2)
Diabetic, n (%)	185 (33.5)	139 (31.0)
Type II, n (%)	168 (90.8)	130 (93.5)
Previous MI, n (%)	159 (28.6)	120 (26.9)
Previous PCI, n (%)	144 (25.9)	114 (25.4)
CHF, n (%)	32 (5.8)	15 (3.3)
Previous CABG, n (%)	77 (13.9)	32 (7.1)
Previous stroke, n (%)	27 (4.9)	14 (3.1)
History of PAD, n (%)	5 (0.9)	2 (0.4)
creatinine (median [IQR])	83.00 [71.00, 97.00]	83.00 [71.00, 97.00]
COPD, n (%)	97 (17.5)	64 (14.3)
Troponin, n (%)		

None	144 (26.5)	85 (19.1)
Standard troponin	21 (3.9)	14 (3.1)
Standard troponin I	130 (23.9)	115 (25.8)
HS troponin T	249 (45.8)	231 (51.9)
Troponin (median [IQR])	205.15 [15.95, 2440.78]	416.90 [25.75, 2521.93]

Abbreviations: n, number; SD, standard deviation; %, percentage; cm, centimeter; kg, kilogram; DAPT, dual-antiplatelet therapy; ACS, acute coronary syndrome; STEMI, ST-elevated myocardial infarction;, NSTEMI, non-ST-elevated myocardial infarction; SBP, systolic blood pressure; DBP, diastolic blood pressure; MI, myocardial infarction; PCI, percutaneous coronary intervention; CHF, congestive heart failure; CABG, coronary artery bypass graft; PAD, peripheral artery disease; IQQR, interquartile range; COPD, chronic obstructive pulmonary disease; HS, high-sensitivity.

Table 6.9.2. The clinical outcomes and effect measures for the pooled, non-clustered analyses.

	Clopidogrel N=555	**Ticagrelor** N=450	**Prior**	**HR (95% CrI)** *Pooled*	**Posterior distribution** $Pr_{HR<0.9}$	$Pr_{HR[0.9, 1.11]}$	$Pr_{HR>1.11}$
MACE	64 (11.5%)	50 (11.1%)	Vague	0.97 (0.67, 1.40)	0.35	0.40	0.25
			skeptical	1.13 (0.90, 1.42)	0.02	0.38	0.60
			enthusiastic	0.89 (0.71, 1.11)	0.55	0.42	0.03
			summary	0.95 (0.81, 1.12)	0.24	0.72	0.04
All-cause mortality	15 (2.7%)	7 (1.6%)	Vague	0.57 (0.22, 1.35)	0.84	0.08	0.07
MI	46 (8.3%)	38 (8.4%)	Vague	1.02 (0.67, 1.55)	0.27	0.37	0.36
Stroke	≤5 (≤0.9%)	≤5 (≤1.1%)	Vague	-	-	-	-
Bleeding	28 (5.0%)	20 (4.4%)	Vague	0.88 (0.49, 1.50)	0.53	0.25	0.22
			skeptical	1.01 (0.76, 1.34)	0.22	0.51	0.27
			enthusiastic	0.85 (0.66, 1.10)	0.67	0.31	0.02
			summary	1.06 (0.97, 1.16)	0.00	0.77	0.23

Abbreviations: HR, hazard ratio; CrI, credible interval; N, total number; MACE, major acute coronary events; MI, myocardial infarction; Isch, ischemic; BNMA, Bayesian network meta-analysis.

Population-level priors:

MACE: Vague, student_t(3, 0, 5); skeptical (PLATO NA), N(1.25, 0.15); enthusiastic (overall PLATO), N(0.84, 0.15); Summary (BNMA), N(0.95, 0.09).

Bleeding: Vague, student_t(3, 0, 5); skeptical (PLATO NA), N(1.05, 0.17); enthusiastic (overall PLATO), N(1.04, 0.17); Summary (BNMA), N(1.07, 0.05).

6.10 Figures

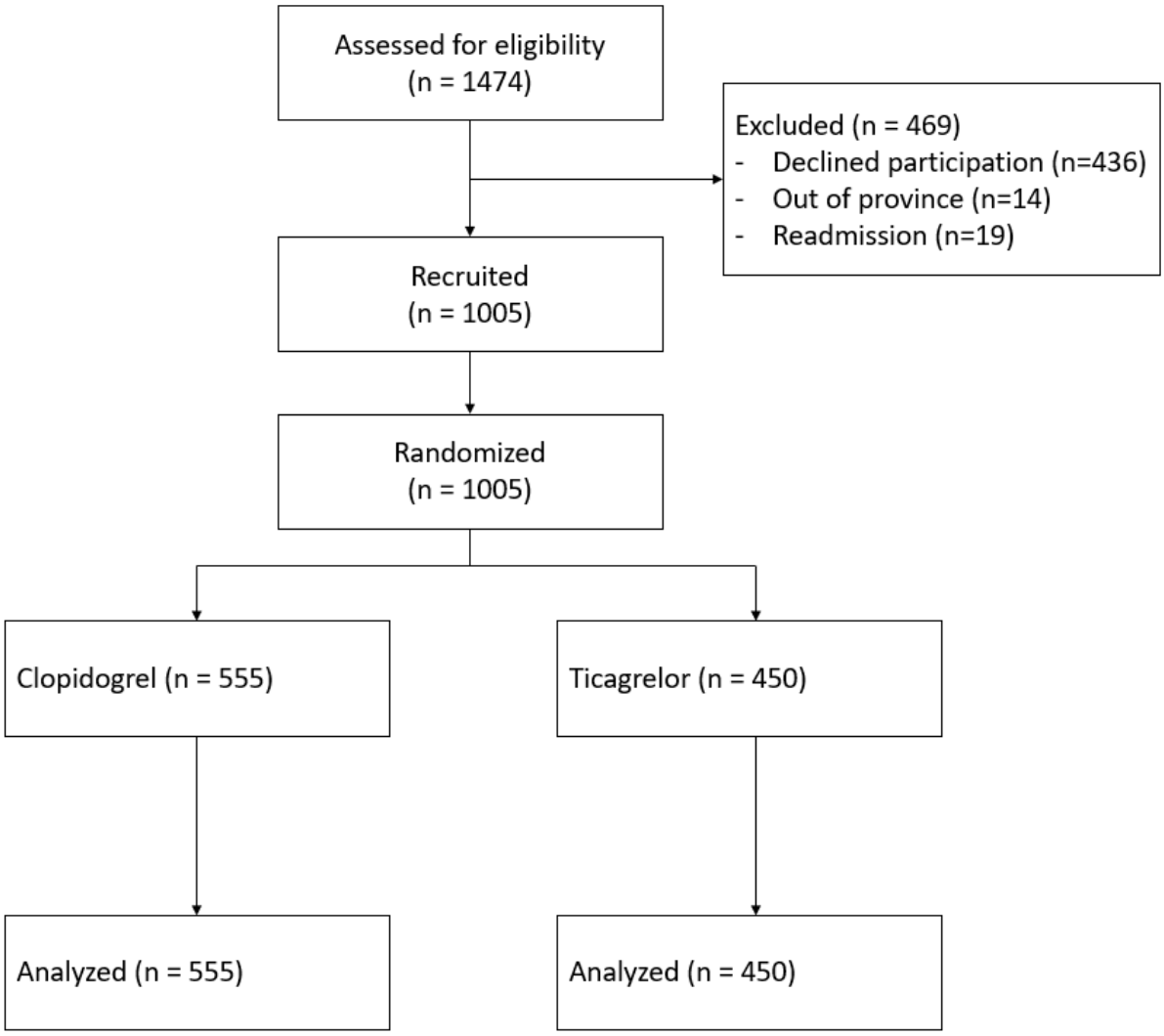


Figure 6.10.1. Flow chart of the TC4 study subjects.

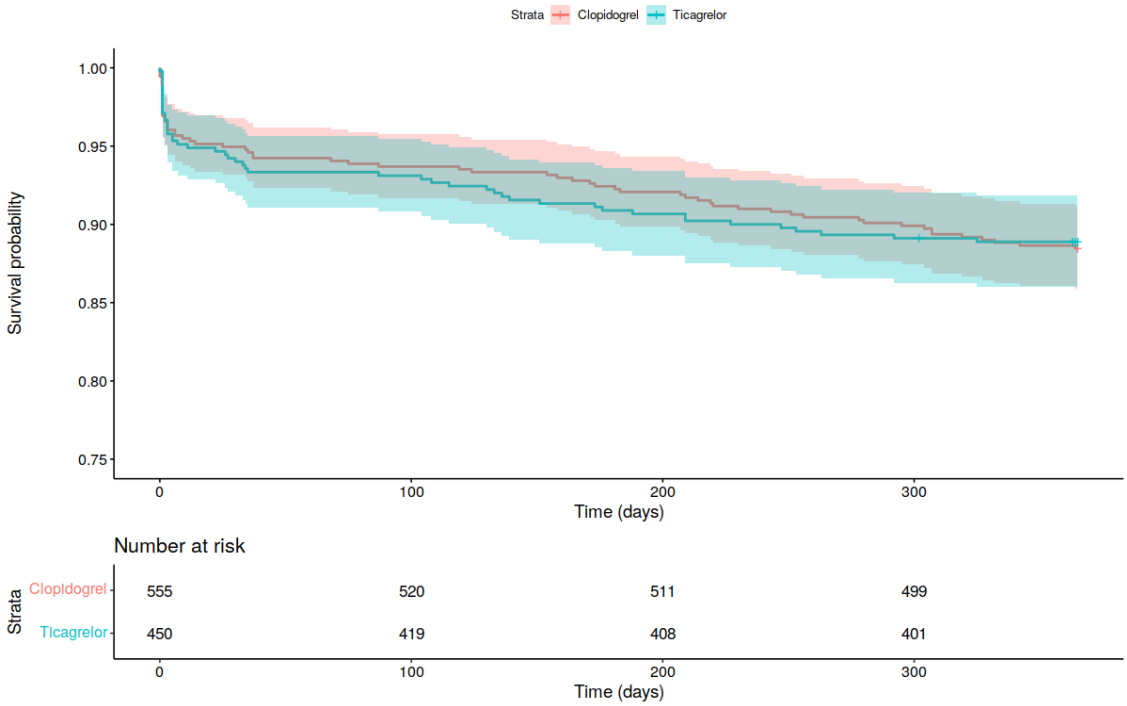


Figure 6.10.2. The Kaplan-Meier curve describing the MACE events in 1,005 ACS patients randomized to ticagrelor or clopidogrel.

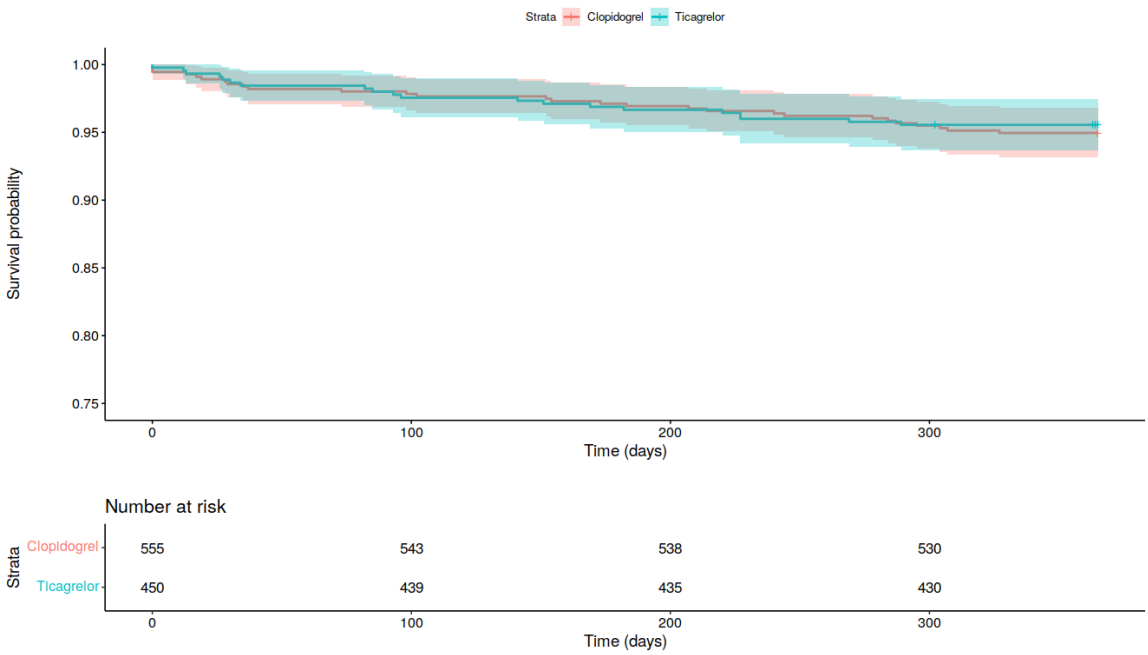


Figure 6.10.3. The Kaplan-Meier curve describing major bleeding events in 1,005 ACS patients randomized to ticagrelor or clopidogrel.

6.11 Appendix

6.11.1 Supplemental Tables

Supplemental Table 6.11.1.1. The ICD-10 codes used to identify clinical outcomes within the electronic healthcare databases.

Outcome	**ICD-10 code**
Myocardial infarction	I21.X, I22.X, I23.X, I25.2
Stroke (ischemic)	H34.1, I63.X, I64.X, I67.X
Stroke (hemorrhagic)	I60.X, I61.X, I62.X
Gastrointestinal Bleeding	K92.X

Supplemental Table 6.11.1.2. Distributions representing a range of Bayesian clinical priors for MACE and bleeding outcomes.

Type of prior	**Distribution**[†]	
	MACE	**Bleeding**
Vague	student_t(3, 1, 5)	student_t(3, 1, 5)
Skeptical (PLATO[NA])	N(1.25, 0.15)	N(1.05, 0.17)
Enthusiastic (PLATO)	N(0.84, 0.15)	N(1.04, 0.17)
Summary (BNMA)	N(0.95, 0.09)	N(1.07, 0.05)

Distributions: student_t(degrees of freedom, mean, standard deviation); N(mean, standard deviation)
Abbreviations: MACE, major acute coronary syndrome; NA, North American; BNMA, Bayesian network meta-analysis.
[†]*For Bayesian model specification, prior distributions are log-transformed for inclusion into the 'brms' R package*

Supplemental Table 6.11.1.3. Model comparison using leave-one-out cross-validation (LOO).

Model	elpd_diff	se_diff
MACE		
Pooled (FE)	0.0	0.0
Hierarchical (RE)	-1.0	1.7
Major Bleeding		
Pooled (FE)	0.0	0.0
Hierarchical (RE)	-1.5	1.3

FE, fixed effect equivalent; RE, random effects equivalent.

Supplemental Table 6.11.1.4. The clinical outcomes and effect measures for the hierarchical, clustered analyses.

	Clopidogrel N=555	**Ticagrelor** N=450	**Prior**	**HR (95% CrI)** *Hierarchical*	**Posterior distribution** $\Pr_{HR<0.9}$	$\Pr_{HR[0.9, 1.11]}$	$\Pr_{HR>1.11}$
MACE	64 (11.5%)	50 (11.1%)	Vague	0.88 (0.43, 1.51)	0.49	0.28	0.23
			skeptical	1.13 (0.90, 1.44)	0.03	0.33	0.65
			enthusiastic	0.86 (0.67, 1.10)	0.63	0.34	0.03
			summary	0.95 (0.81, 1.12)	0.28	0.68	0.04
All-cause mortality	15 (2.7%)	7 (1.6%)	Vague	0.37 (0.04, 1.84)	0.85	0.05	0.10
MI	46 (8.3%)	38 (8.4%)	Vague	0.96 (0.50, 1.72)	0.39	0.27	0.34
Stroke	≤5 (≤0.9%)	≤5 (≤1.1%)	Vague	-	-	-	-
Bleeding	28 (5.0%)	20 (4.4%)	Vague	0.81 (0.33, 1.79)	0.60	0.18	0.22
			skeptical	1.01 (0.76, 1.36)	0.22	0.47	0.29
			enthusiastic	0.84 (0.64, 1.09)	0.69	0.29	0.02
			summary	1.07 (0.98, 1.16)	0.00	0.76	0.24

Abbreviations: HR, hazard ratio; CrI, credible interval; N, total number; MACE, major acute coronary events; MI, myocardial infarction; Isch, ischemic; BNMA, Bayesian network meta-analysis.

Population-level priors:

MACE: Vague, student_t(3, 0, 5); skeptical (PLATO NA), N(1.25, 0.15); enthusiastic (overall PLATO), N(0.84, 0.15); Summary (BNMA), N(0.95, 0.09).

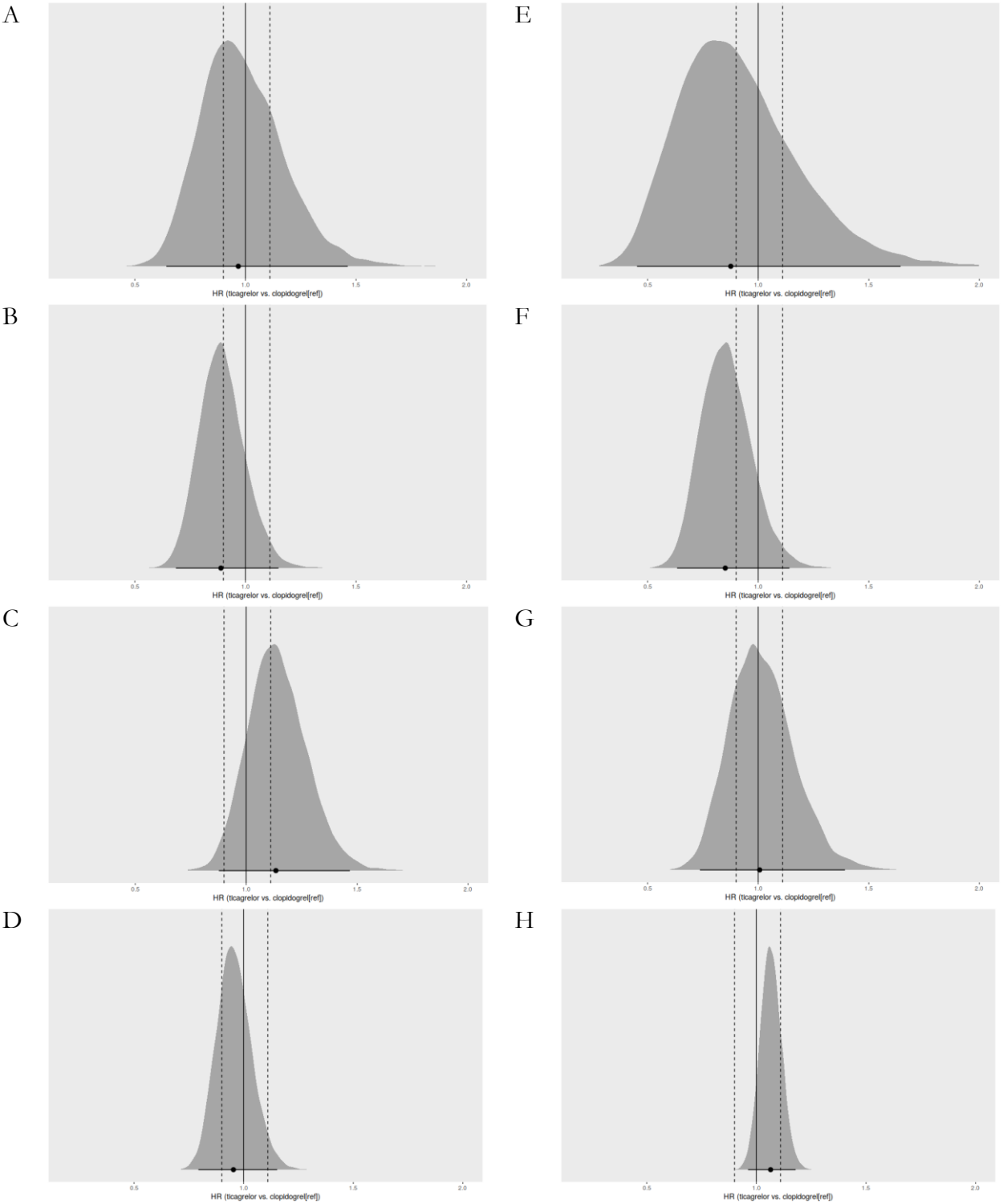
Bleeding: Vague, student_t(3, 0, 5); skeptical (PLATO NA), N(1.05, 0.17); enthusiastic (overall PLATO), N(1.04, 0.17); Summary (BNMA), N(1.07, 0.05).

Supplemental Table 6.11.1.5. The primary clinical outcomes and effect measures for both the non-clustered and clustered analyses stratified by sex.

	Clopidogrel N=420, 135	**Ticagrelor** N=338, 112	**Prior**	**HR (95% CrI)** *Pooled*	**HR (95% CrI)** *Hierarchical*
MACE					
Males	43 (10.2%)	35 (10.4%)	Vague	1.01 (0.64, 1.59)	0.93 (0.44, 1.81)
Females	21 (15.6%)	15 (13.4%)	Vague	0.86 (0.44, 1.65)	0.80 (0.27, 2.02)
Bleeding					
Males	21 (5.0%)	20 (3.8%)	Vague	0.76 (0.37, 1.50)	0.70 (0.24, 1.81)
Females	7 (5.2%)	7 (6.3%)	Vague	1.21 (0.41, 3.47)	1.12 (0.24, 4.71)

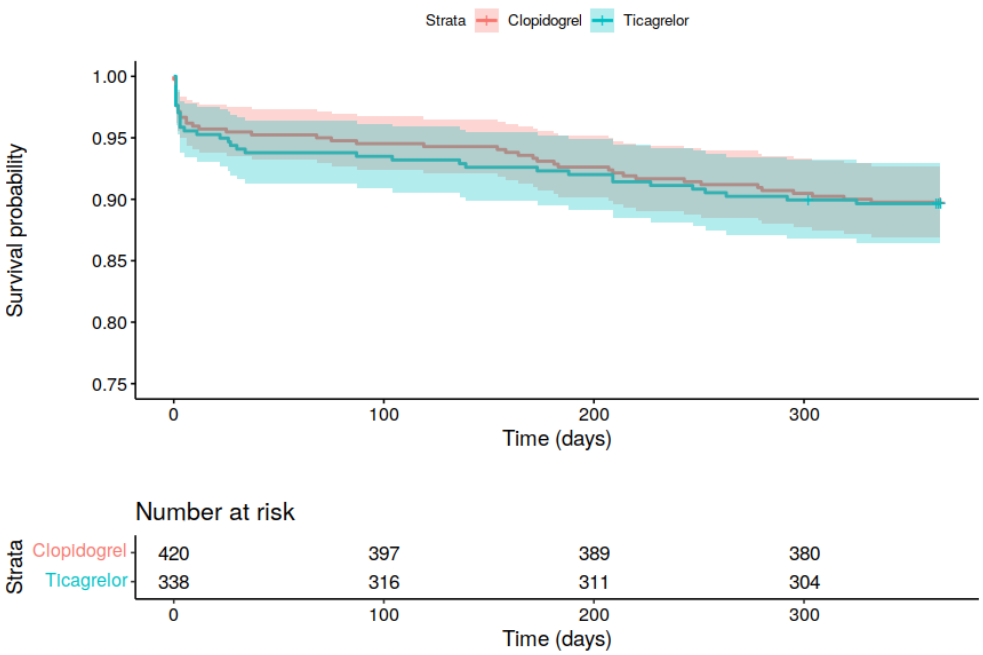
Abbreviations: HR, hazard ratio; CrI, credible interval; N, total number; MACE, major acute coronary events; Population-level prior: Vague, student_t(3, 0, 5).

6.11.2 Supplemental Figures



Supplemental Figure 6.11.2.1. The posterior distributions for the primary efficacy (MACE) and safety (bleeding) outcomes by a range of differing prior distributions. [A] MACE with a vague prior; [B] MACE with the PLATO prior; [C] MACE with the NA prior from PLATO; [D] MACE with the BNMA prior; [E] Bleeding with a vague prior; [F] Bleeding with the PLATO prior; [G] Bleeding with the NA prior from PLATO; [H] Bleeding with the BNMA prior.

A



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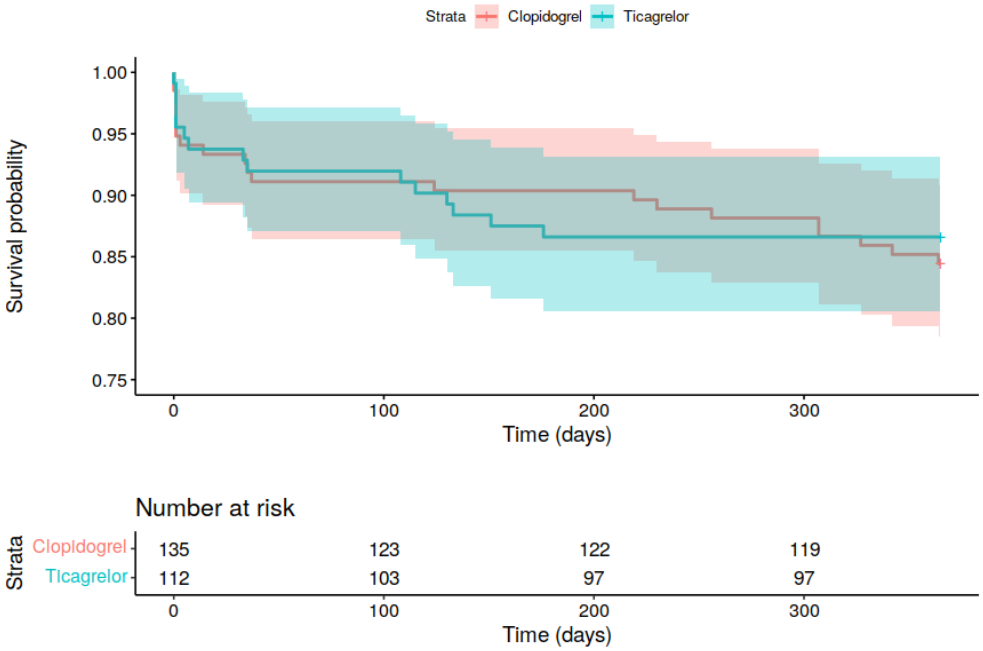
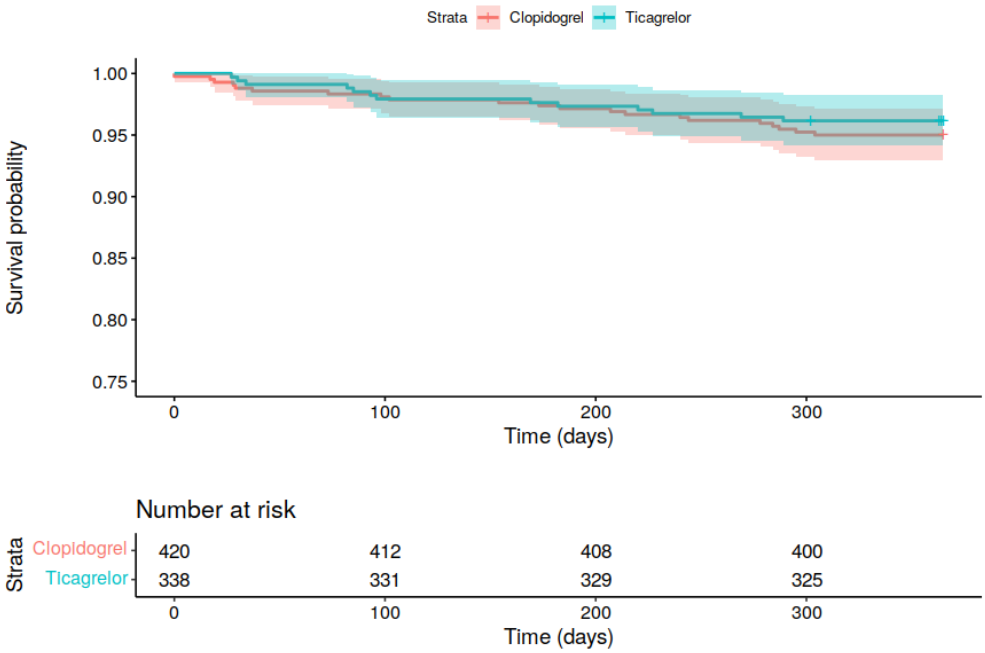
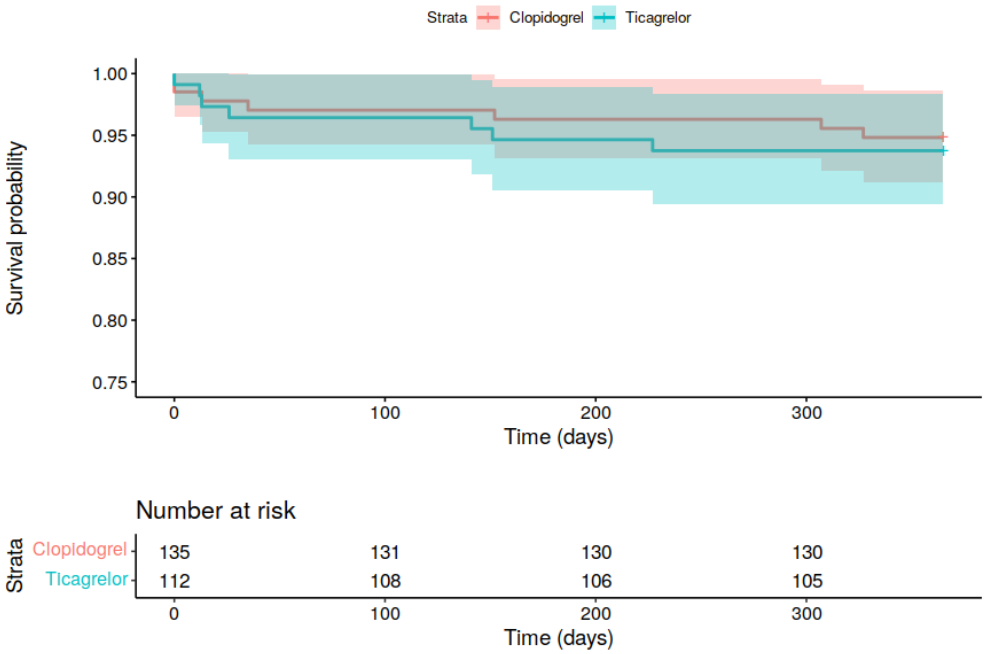


Supplemental Figure 6.11.2.2. The Kaplan-Meier curve for MACE outcomes stratified by sex. [A] Males; [B] Females.

A



B



Supplemental Figure 6.11.2.3. The Kaplan-Meier curve for major bleeding events stratified by sex. [A] Males; [B] Females.

$$h(t_i) = \mathrm{h}(t_0) \times e^{(w_j + \beta x_{ij})}$$
$$w_j = N(\mu_j, \tau_j)$$

Supplemental Figure 6.11.2.4. The Bayesian hierarchical Cox proportional hazards model which allows for the treatment effect (β) to vary across the time-cluster study periods (wj).

6.11.3. CONSORT checklist extension of items for reporting pragmatic trials

Section	Item	Standard CONSORT description	Extension for pragmatic trials	Pages
Title and abstract	1	How participants were allocated to interventions (eg, "random allocation," "randomised," or "randomly assigned")		1-2
Introduction				
Background	2	Scientific background and explanation of rationale	Describe the health or health service problem that the intervention is intended to address and other interventions that may commonly be aimed at this problem	2-3
Methods				
Participants	3	Eligibility criteria for participants; settings and locations where the data were collected	Eligibility criteria should be explicitly framed to show the degree to which they include typical participants and/or, where applicable, typical providers (eg, nurses), institutions (eg, hospitals), communities (or localities eg, towns) and settings of care (eg, different healthcare financing systems)	5

Interventions	4	Precise details of the interventions intended for each group and how and when they were actually administered	Describe extra resources added to (or resources removed from) usual settings in order to implement intervention. Indicate if efforts were made to standardise the intervention or if the intervention and its delivery were allowed to vary between participants, practitioners, or study sites	5
			Describe the comparator in similar detail to the intervention	5
Objectives	5	Specific objectives and hypotheses		
Outcomes	6	Clearly defined primary and secondary outcome measures and, when applicable, any methods used to enhance the quality of measurements (eg, multiple observations, training of assessors)	Explain why the chosen outcomes and, when relevant, the length of follow-up are considered important to those who will use the results of the trial	4
Sample size	7	How sample size was determined; explanation of any interim analyses and stopping rules when applicable	If calculated using the smallest difference considered important by the target decision maker audience (the minimally important difference) then report where this difference was obtained	6-8
Randomisation—sequence generation	8	Method used to generate the random allocation sequence, including details of any restriction (eg, blocking, stratification)		4
Randomisation—allocation concealment	9	Method used to implement the random allocation sequence (eg, numbered containers or central telephone), clarifying whether		N/A

		the sequence was concealed until interventions were assigned		
Randomisation—implementation	10	Who generated the allocation sequence, who enrolled participants, and who assigned participants to their groups		4
Blinding (masking)	11	Whether participants, those administering the interventions, and those assessing the outcomes were blinded to group assignment	If blinding was not done, or was not possible, explain why	
Statistical methods	12	Statistical methods used to compare groups for primary outcomes; methods for additional analyses, such as subgroup analyses and adjusted analyses		6-7
Results				
Participant flow	13	Flow of participants through each stage (a diagram is strongly recommended)—specifically, for each group, report the numbers of participants randomly assigned, receiving intended treatment, completing the study protocol, and analysed for the primary outcome; describe deviations from planned study protocol, together with reasons	The number of participants or units approached to take part in the trial, the number which were eligible, and reasons for non-participation should be reported	4-6
Recruitment	14	Dates defining the periods of recruitment and follow-up		5
Baseline data	15	Baseline demographic and clinical characteristics of each group		8, 18
Numbers analysed	16	Number of participants (denominator) in each group included in each analysis and whether analysis was by "intention-to-treat"; state the results in absolute numbers when feasible (eg, 10/20, not 50%)		8, 18

Outcomes and estimation	17	For each primary and secondary outcome, a summary of results for each group and the estimated effect size and its precision (eg, 95% CI)		8-10, 20
Ancillary analyses	18	Address multiplicity by reporting any other analyses performed, including subgroup analyses and adjusted analyses, indicating which are prespecified and which are exploratory		N/A
Adverse events	19	All important adverse events or side effects in each intervention group		8-10, 20
Discussion				
Interpretation	20	Interpretation of the results, taking into account study hypotheses, sources of potential bias or imprecision, and the dangers associated with multiplicity of analyses and outcomes		11
Generalisability	21	Generalisability (external validity) of the trial findings	Describe key aspects of the setting which determined the trial results. Discuss possible differences in other settings where clinical traditions, health service organisation, staffing, or resources may vary from those of the trial	12-14
Overall evidence	22	General interpretation of the results in the context of current evidence		14

6.12. Ethics

Centre universitaire de santé McGill | McGill University Health Centre

2018-09-12

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Re: Final REB Approval of a New Research Project (TC4 / 2019-4530)

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

MUHC REB Co-Chair for the Clinical Trials 2 (CT2) Panel: Dr. Bertrand Lebouche

Dear Dr. Brophy,

Thank you for submitting your responses and corrections for the research project indicated above, as requested by the McGill University Health Centre (MUHC) Research Ethics Board (REB).

The MUHC REB, more precisely its CT2 Panel provided conditional approval for the research project at its full board meeting of 2018-05-16.

On 2018-09-12, a delegated review of your responses and corrections was provided by a member of the MUHC REB. The research project was found to meet scientific and ethical standards for conduct at the MUHC.

The following documents were approved or acknowledged by the MUHC REB:

- Initial Submission Form (F11-29884)
- REB Conditions & PI Responses Form(s) (F20-32042, F20-35692)
- Letters of collaboration/support Giannetti.(2017-08-04)
- Letters of collaboration/support De Guise. (2017-08-23)
- Research Protocol (Version 1.0 2017-09-15)
- Information & Consent Form (2018-09-12) in French and English
- CIHR Scientific Officer's Notes. (2018-01-22)
- CIHR Notice of Decision(2018-01-22)
- Department Head Approval (2018-04-27)

This will be reported to the MUHC REB and will be entered accordingly into the minutes of the next CT2 Panel meeting. Please be advised that you may only initiate the study after all required reviews and decisions are received and document and you have received the MUHC authorization letter.

Chapter Seven. General Discussion

7.1 Summary of findings

Antiplatelet therapies are a crucial component in the prevention of secondary clinical outcomes in ACS patients, which are a leading cause of death and re-hospitalization.[5–8] The goal of this doctoral thesis was to investigate the effectiveness and safety of contemporary dual-antiplatelet therapies in a clinically representative population that experienced an ACS event with a specific focus on the Canadian perspective. Though, the current ACS guidelines[11,12,14] recommend ticagrelor and prasugrel DAPT's over clopidogrel, the selection of a fixed effect analytical approach in the initial large, multinational RCT likely underestimated the overall variance of the estimates, as was identified in the North American subgroup from PLATO.[15,70] This thesis aimed to address this regional heterogeneity by performing a hierarchical Bayesian meta-analysis and to improve the precision of the effect of DAPT in the North American population through the addition of evidence using both a population-based cohort and a pragmatic RCT design.

The first manuscript in this thesis (Chapter 4) compared the efficacy (MACE) and safety (reported major bleeding outcomes) of the DAPTs ticagrelor, prasugrel, and clopidogrel using a Bayesian network meta-analysis of RCTs identified from a systematic search of the literature. This study found that from the 17 included RCTs, screened as having a "low" risk of bias score, prasugrel had a 67.5% probability of providing a clinically meaningful reduction in MACE, relative to clopidogrel, but also an 83.7% chance of a clinically meaningful increase in major bleeding episodes. For ticagrelor, the random effects summary of RCTs estimated only a 22.4% probability of a clinically important decrease in MACE and a 67.7% chance of observing more clinically meaningful major bleeding events, compared with patients assigned clopidogrel DAPT. Our results signify that the possible clinical benefits in MACE seen with prasugrel, might be outweighed by an increased risk in major bleeding events. Further, there was limited evidence supporting ticagrelor superiority,

in comparison with clopidogrel, for MACE or bleeding outcomes. Further, no supplementary RCT reporting on the comparison of ticagrelor and clopidogrel DAPTs in a North American population was identified from our systematic review.

The second manuscript (Chapter 5) was initially designed to assess whether the DAPTs ticagrelor or prasugrel were associated with a decreased risk of MACE, compared with the DAPT clopidogrel, in a population-based cohort from Québec health administrative databases. However, prasugrel was not prescribed at the same frequency as the clopidogrel or ticagrelor DAPTs during the 2010 to 2018 study period. This unfortunately led to too few new users of prasugrel (~900) to adequately compare clinical outcomes with the new users of either ticagrelor (~7,000) or clopidogrel (~16,000). Ultimately, our study ended up settling on a comparison of ticagrelor to clopidogrel. From the 100,251 ACS patients who underwent a PCI between April 2010 and March 2018, we identified 22,736 new DAPT users. After ATE propensity score weighting the 6,959 ticagrelor and 15,777 clopidogrel DAPT users, and including age, "other" heart diseases, atrial fibrillation, and the Charlson Index in the CoxPH model, ticagrelor was associated with a 9% reduction in MACE (aHR, 0.91; 95% CI: 0.81, 1.01) and a 3% reduction in bleeding episodes (aHR, 0.97; 95% CI: 0.75, 1.24), when compared to patients' who initiated clopidogrel after 1-year. These findings suggest that, following an ACS with PCI, there is limited evidence that ticagrelor is clinically superior to clopidogrel in new DAPT users from Québec, Canada.

Lastly, the third manuscript in this thesis (Chapter 6) was designed to determine whether ticagrelor was associated with a reduced risk of MACE in an ACS population enrolled in a pragmatic time-cluster randomized trial at the McGill University Health Centre. To account for a comprehensive range of prior beliefs, a Bayesian analysis of the trial allowed for the incorporation of the study data with a range of prior data. When relying solely on the data from the 1,005 subjects recruited between October 2018 and March 2021, using a vague prior, it was estimated that

ticagrelor has median risk reduction of 3% in MACE (HR, 0.97; 95% CrI: 0.67, 1.40) and a median reduction of 12% in major bleeding outcomes (HR, 0.88; 95% CrI: 0.49, 1.50), compared to patients assigned to clopidogrel. The trial evidence, on its own, suggested that ticagrelor has a 35% chance of a clinically meaningful reduction (HR<0.9) in MACE but had a relatively similar chance (25%) of observing a clinically important increase (HR>1.11). When the trial data is incorporated with the existing North American evidence ($HR_{NA\ PLATO}$, 1.25; 95% CI 0.93, 1.67) from the PLATO trial, ticagrelor was associated with a 13% increased risk of MACE (HR, 1.13; 95% CrI: 0.90, 1.42) and a 1% heightened risk of major bleeding episodes (HR, 1.01; 95% CrI: 0.76, 1.34). Thus, going from the TC4 data alone, to the combined TC4 and North American PLATO subset, the probability of ticagrelor having a clinically meaningful decrease in clinical events (HR<0.9), went from 35% to 2% for MACE and 53% to 22% for hospitalized bleeding. Meaning, that when the TC4 data was incorporated with the existing North American data, from PLATO, the chance of ticagrelor having a clinically beneficial profile dropped for both the primary effectiveness and safety outcomes.

7.2 Clinical implications

The importance of DAPTs in the prevention of ischemic clinical outcomes while balancing the risk of bleeding following an ACS has been long established.[5–7,41] The purported superiority of ticagrelor and prasugrel DAPTs, over clopidogrel DAPT in the general ACS population, relied heavily on several large, multinational RCTs.[9,10] This thesis contributes important new North American data on the effectiveness of ticagrelor relative to clopidogrel DAPT, using clinically relevant patient populations. As was observed in several non-randomized,[60,97] randomized,[42,44,45] and network meta-analyses,[69] our findings from across all three doctoral thesis objectives were unable to attribute a clear clinical benefit to ticagrelor DAPT over clopidogrel. While, in an ideal setting, a comparison with prasugrel in the second and third objectives would have been completed. However, for manuscript 2, a lack of data on prasugrel limited our ability to produce balanced baseline

populations using IPTW across the three treatment groups. Meanwhile, adding a third treatment arm to the TC4 trial, in the third objective, would have substantially limited our power from our recruited study sample of ~1,000 subjects. Ultimately, we moved forward comparing the two more commonly prescribed DAPTS, ticagrelor and clopidogrel.

Our estimates from the non-randomized cohort in manuscript two (Chapter 5), aligned with the one other existing North American cohort study.[60] Meanwhile, to our knowledge, the TC4 trial was the first RCT to report on DAPT evidence in a North American population since PLATOs publication in 2009. Again, our findings were not able to demonstrate strong evidence in support of ticagrelor superiority. Although it may be argued that ticagrelor is suitable DAPT in a European context as 13,074 (70%) of PLATO subjects were recruited in Europe with 64.6% (n=1,214) of the clinical events. Evidence to support the benefits of ticagrelor DAPT relative to clopidogrel.[16,70] Unfortunately, these European PLATO results have not been replicated in the North American setting. It seems sensible that the clinical ACS guidelines for North American health professionals be updated to summarize the existing evidence of the benefit and risk profiles of DAPTs from the North American context.

7.3 Strengths and limitations

The totality of this thesis had many strengths. Overall, it used multiple, different research designs and datasets to evaluate a common, population-level issue. The results from each manuscript included in this thesis came to similar conclusions about the limited evidence regarding the superiority of ticagrelor over clopidogrel DAPT in the secondary prevention of ischemic events following an ACS event and PCI. Indeed, each study design had their own individual strengths and limitations, but the robust findings across all three investigations is an assuring resolution. Further, each individual research objective was built on strong theoretical foundations – a summary of existing RCTs, an ATE weighted cohort, and a stand alone RCT – for the causal evaluation of

DAPTs in effectiveness and safety clinical outcomes. The Bayesian statistical approach applied in the first and third manuscripts (Chapter 4 and 6) provide a more intuitive interpretation of the evidence for clinicians and decision makers. It allowed for the use of direct probability statements to present median estimates and also the proportion of the data that was within clinically important thresholds (e.g., ROPE). This also avoided the oftentimes misinterpreted NULL hypothesis significance testing used in the frequentist paradigm. But additionally, Bayesian analyses structurally allowed for the formal integration of the collected data from the TC4 trial with existing prior information. A Bayesian approach can provide researchers and clinicians with timely updates of the existing evidence base (prior information) with the totality of the current data (likelihood) into an integrated posterior distribution. Lastly, the second and third manuscripts evaluated the effectiveness of DAPT in a more clinically representative population than efficacy focused RCTs.[98] Both the non-randomized cohort study (Chapter 5) and pragmatic TC4 trial (Chapter 6), included patients directly from a broad clinical setting. These findings should provide North American health practitioners important evidence from a population that is more likely to reflect their clinical patients, in comparison to the existing large multinational, Eurocentric RCT.

This doctoral thesis also had some limitations. In simple terms, all study designs each come with their own constraints. For example, the first manuscript was limited by the availability of only aggregate level data. Having individual-level patient data would provide more flexibility to assess the variability within each of the included study populations, which we could not fully explored in the hierarchical Bayesian network meta-analysis. The availability of more granular data would have allowed for a more nuanced evaluation of characteristics that may be associated with the existing heterogeneity observed across the many existing RCTs. This also limited our potential to identify possible important sub-groups where ticagrelor could provide important clinical benefits, such as surgical patients. In the second manuscript (Chapter 5), although we identified important measured

confounders, residual lifestyle confounders, such as smoking habits and exercise, and other measures of increased risk of poor clinical outcomes in cardiovascular patients, such as frailty,[99] are not fully captured in Québec health administrative databases. Habitual smoking, for instance, has been shown to be associated with a greater risk of ischemic outcomes, in comparison to non or ex-smokers.[100] Although, advanced propensity score weighting methods can demonstrate excellent balance of measured confounders. Ultimately, the impact of these important unmeasured variables on the estimates are unknown, as their underlying distributions remain unobserved. Another consideration was the use of the intention-to-treat (ITT) analytical approach in the second and third objectives (Chapter 5 and 6) to mimic existing RCT analyses. To "preserve" randomization, the ITT method does not examine the adherence to the DAPT during the duration of follow-up and could lead to some exposure misclassification. A per-protocol analysis, which can make adjustments for treatment switching and cessation, may be valuable for aiding clinicians and patients in their individual decision-making process.[101] Lastly, we were unable to provide adequately powered sex-stratified analyses that assessed the impact of DAPT on cardiac outcomes in female ACS subjects. It is known that the presentation of ischemic heart disease in females is often distinct to their male counterparts, often occurring at a later life stage.[102,103] Yet, older populations and thus females, often remain underrepresented in RCTs.[104] Ultimately, we were also unable to reasonably assess the effects of DAPT in female ACS patients.

7.4 Future directions

The contents of this thesis have contributed to our understanding of the benefit and risk profiles of the commonly prescribed DAPTs, following an index ACS event. We first identified that limited DAPT research was available for North American populations (Chapter 4) and added data to this knowledge base through a non-randomized cohort study (Chapter 5) and a pragmatic randomized trial (Chapter 6). Even though our findings provide limited evidence of superiority

across any of the contemporary DAPTs, we do not believe this should deter continued research into DAPT usage in important subgroups. Here we describe several remaining gaps in the literature and important future directions in pragmatic causal research.

First, we suggest the results from our TC4 trial should become the informative prior to subsequent North American research. Even though we added 1,005 data points of North American evidence, it remains understudied with fewer than 3,000 ACS patients having been randomized to either ticagrelor or clopidogrel DAPTs. Second, as we discussed briefly in our limitations above (Chapter 7.3), our studies failed to address several important research gaps, which can be the focus of future research project. We identified a need for investigating the effectiveness of DAPTs in meaningful ACS sub-populations, such as females, geographic regions, and patients that represent everyday clinical practice. Also, addressing the impact of long-term adherence to 12-month long DAPT schedules, through a per-protocol analysis would help inform clinicians and their patients over the more commonly reported ITT analyses. Finally, future cost-effectiveness research studies are needed to evaluate the price of the existing DAPTs in the relation to the estimated clinical benefits, given the Canadian context of this thesis and the potential for added costs to our publicly funded healthcare system.

From a research perspective, we believe this thesis provides an important proof of concept for the use of pragmatic designs and approaches in clinical research. The randomized trial is widely regarded as the most rigorous design for causal inference, though some practical and substantive limitations for the clinical context has been discussed.[46,49–52] During the patient recruitment, for example, RCTs often set rigorous inclusion and exclusion criteria to minimize patient heterogeneity and maximize internal validity. This potentially comes at the cost of including a study population that might not represent patients seen in everyday clinical practice. More so, patients and clinicians participating in a closely monitored RCT may be more diligent in their patient examinations and

adherence to medications due to strict study protocols. These intrinsically strict trial protocols, randomization procedures, blinding practices, and the necessary patient follow-up for study outcomes requires substantial resources to effectively complete. In fact, it has been reported that cardiovascular trials, for example, can cost upwards of $10,000 USD per recruited patient.[105] The execution of successful randomization and trial protocols is complex and requires a team of highly invested and skilled health professionals and supportive staff. These challenges are especially true in an urgent care setting, like a cardiac revascularization hospital unit. However, these abovementioned challenges associated with RCTs can be mitigated through creative and conscientious epidemiological research.

Due to the rise in the quality of health administrative data,[47] the target trial framework[55,56] has been proposed as a passive method to causally assess exposure-outcome associations using the data captured during routine clinical practice. The target trial approaches the clinical research question similar to an RCT. It applies well-defined patient eligibility criterion (inclusion/exclusion), treatment definitions with a clearly defined time zero (to minimize immortal time bias[74]), specific follow-up time periods, a detailed list of pre-specified outcomes, a stated causal contrast of interest (e.g. ITT), and a statistical analysis plan.[55] All components necessary for RCT publication. In fact, the pre-registration of research protocols for non-randomized cohort designs has been proposed.[106] Obviously, this type of observational design lacks randomization. To achieve exchangeability across treatment arms, there are a range of design and analytical techniques – directed acyclic graphs (DAG),[53,54] propensity scores, inverse probability of treatment weighting, and G-methods,[57,58] to name a few – that help obtain conditional independence between the exposure and outcome of interest. While this framework may be suitable for researchers with access to high quality administrative and health insurance claims data, the range of eligible research questions may be limited by the breadth and quality of the collected health data.

In theory, the target trial framework addresses some of the limitation from the classic RCT. It is considered more generalizable since the study population is identified directly from a clinical dataset. Logistically, it is less complex, though it will require knowledge of more advanced statistical methods and skills in database management. But it is discernably less cost intensive. However, residual confounding remains possible as exposure independence is conditional on the observed, available covariates in the health database. As such, the pragmatic RCT is another option. We demonstrated a version of a pragmatic trial in the third manuscript (Chapter 6). A clinically relevant population was recruited by opening study enrolment to all patients that visited the cardiac revascularization unit at the MUHC. A time-clustered randomized design[77] was used to simplify patient recruitment and treatment allocation in an urgent clinical care setting, where randomizing individual patients would be disruptive. Lastly, patient's follow-up was completed using the Québec provincial health administrative databases to identify study outcomes. This substantially reduced patient recruitment costs, closer to $300 CAD per enrolled patient, which is a substantial reduction compared to previously reported studies.[105] This thesis not only contributed evidence for DAPT use in ACS patients, but we also demonstrated the feasibility of pragmatic research designs. These novel approaches come with cost inputs that are much more attainable for the general clinical research population. It comes with the potential to broaden the scope of credible, large causal research projects beyond the industry sponsored RCT.

7.5 Conclusions

Overall, this thesis presents evidence on the efficacy, effectiveness, and safety of DAPTs from three different data sources and study designs. The findings illustrate that the efficacy superiority of prasugrel is likely offset by inferior safety profile, while the body of evidence suggests the effectiveness and safety benefits of ticagrelor are likely clinically indiscernible relative to clopidogrel in the general ACS population, particularly in a North American setting. This new

information may be of interest to both practicing physicians and guideline writers when performing the next update. Though no robust clinical evidence was found to support a single DAPT over another, this thesis did provide a strong basis for the utilization of pragmatic research designs to address pressing clinical questions using existing healthcare infrastructures. The target trial framework or the pragmatic approach to RCTs provide novel, accessible approaches for researchers interested in investigating causal relationships in a clinical setting.

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