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$P2Y_{12}$ inhibitors with Oral Anticoagulation for Percutaneous Coronary Intervention with Atrial Fibrillation: A Systematic Review and Meta-Analysis

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Abstract

Objective—This study aimed to compare the safety and efficacy of third generation $P2Y_{12}$ inhibitors versus clopidogrel in combination with oral anticoagulation (OAC) with or without aspirin in patients with atrial fibrillation (AF) undergoing percutaneous coronary intervention (PCI).

Methods—We performed a systematic review including both prospective and retrospective studies that compared dual and triple antithrombotic regimens for bleeding and major adverse

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Conflict of Interest
Dr. Hsu has received honoraria from Medtronic, Abbott, Boston Scientific, Biotronik, Janssen Pharmaceutical, Bristol-Myers Squibb, and Bio-sense-Webster and has received research grants from Biosense-Webster and Biotronik.
Dr. Feld, as CCEP Fellowship Training Program Director, receives fellowship training program stipends from Medtronic, Biotronik, Biosense Webster, St. Jude/Abbott, Boston Scientific, Inc, and has stock options or co-ownership in Acutus, Inc., toSense, Inc., and Perminova, Inc.
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Dr. Lupercio has nothing to disclose.
Dr. Giancaterino has nothing to disclose.

Other Disclosures:
An abstract of this study was presented as a poster at the 2019 Transcatheter Cardiovascular Therapeutics Symposium on September 28th, 2019 in San Francisco, CA. This abstract was published in a special issue of the Journal of the American College of Cardiology: Giancaterino S, Lupercio F, Villablanca P, et al. TCT-412 Comparative Safety and Efficacy of Second-Generation P2Y12 Inhibitors Versus Clopidogrel in Combination With Oral Anticoagulation in Atrial Fibrillation Patients Undergoing Percutaneous Coronary Intervention: A Systematic Review and Meta-Analysis. Journal of the American College of Cardiology 2019;74:B408.
Dr. Lupercio has previously published a manuscript on a different topic that we were asked to cite and disclose:
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cardiac events (MACE) in patients with AF undergoing PCI. We analyzed rates of bleeding and MACE by $P2Y_{12}$ inhibitor choice. Risk ratio (RR) 95% confidence intervals were measured using the Mantel-Haenszel method. Where study heterogeneity was low (I^2<25%) we used the fixed effects model, otherwise the random effects model was used.

Results—A total of 22,014 patients were analyzed from the 7 studies included. Among patients treated with both OAC and $P2Y_{12}$ inhibitor with or without aspirin, 90% (n=9,708) were treated with clopidogrel, 8% (n=830) with ticagrelor, and 2% (n=191) with prasugrel. When compared to clopidogrel, use of ticagrelor [RR 1.36; 95% CI, 1.18–1.57] and prasugrel [RR 2.11; 95% CI, 1.34–3.30] were associated with increased rates of bleeding. Compared to clopidogrel, there were no significant differences in rates of MACE with ticagrelor [RR 1.03; 95% CI, 0.65–1.62] or prasugrel [RR 1.49; 95% CI, 0.69–3.24].

Conclusion—Based on this meta-analysis, the use of clopidogrel is associated with a lower rate of bleeding compared to ticagrelor or prasugrel in patients with AF on OAC undergoing PCI.

Keywords

Antiplatelet; Atrial fibrillation; Oral anticoagulation; $P2Y_{12}$ inhibitor; Percutaneous Coronary Intervention

INTRODUCTION

Up to 30% of patients with atrial fibrillation (AF) also have coronary artery disease (CAD), 15% of whom will undergo percutaneous coronary intervention (PCI).[1] Choosing an antithrombotic therapy regimen for these patients can be challenging. Inhibition of platelet activation is a priority for the treatment of acute coronary syndrome (ACS), and dual antiplatelet therapy (DAPT) consisting of aspirin and a $P2Y_{12}$ inhibitor is optimal for prevention against recurrent myocardial infarction (MI) and stent thrombosis following PCI.[2] In patients with AF and CHA_2DS_2-VASc score ≥2, antithrombotic agents are used to reduce the formation of platelet-rich thrombi in the left atria. Oral anticoagulation (OAC) with either a direct oral anticoagulant (DOAC) or vitamin K antagonist (VKA) is superior to single or dual antiplatelet therapy for the prevention of stroke and systemic embolism in AF.[3] Triple antithrombotic therapy, the combination of DAPT and OAC increases the risk of bleeding 2- to 3-fold and thus can lead to a higher net adverse cardiovascular event rate (combination of MACE and bleeding).[4] To optimize bleeding and ischemic risk, varying combinations of antiplatelet and OAC regimens have been evaluated.

Contemporary studies have shown that dual antithrombotic therapy, combining OAC and a single $P2Y_{12}$ inhibitor, leads to less bleeding with comparable major adverse cardiac events (MACE) when compared to triple antithrombotic therapy.[5–8] In addition, increasing evidence suggests that in combination with antiplatelet agents, DOACs lead to less bleeding than VKAs.[6–8] However, there is limited data to guide the choice of the ideal $P2Y_{12}$ inhibitor in combination with OAC, since the majority of the data currently used for clinical decision-making has been extrapolated from trials of patients with ACS not on OAC.[9,10] We aimed to compare the safety and efficacy of third generation $P2Y_{12}$ receptor inhibitors

(ticagrelor or prasugrel) versus the second generation thienopyridine clopidogrel in combination with OAC in patients with AF undergoing PCI.

METHODS

Search strategy

We searched PubMed, Embase, and the Cochrane Central Register of Clinical Trials up to April 1, 2019. Our search was limited to human subjects in peer-reviewed journals. No language restriction was applied. References of identified articles were also reviewed. Search terms included *atrial fibrillation AND (percutaneous coronary intervention or PCI) AND (oral anticoagulation OR direct oral anticoagulation OR DOAC OR vitamin K antagonist OR VKA OR warfarin) AND (antiplatelet therapy OR P2Y$_{12}$) AND (triple antithrombotic therapy OR triple therapy OR dual therapy)*.

Selection Criteria

The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement for reporting systematic reviews and meta-analyses was applied to the methods for this study.[11] Studies had to fulfill the following criteria to be included in this analysis: 1) any prospective or retrospective studies that included patients with AF undergoing PCI and assigned to receive any combination of OAC with P2Y$_{12}$ inhibitor or triple antithrombotic therapy regimens 2) studies had to include safety and efficacy outcomes as part of their analysis 3) studies had to include patients on both third generation P2Y$_{12}$ agents and clopidogrel for comparison 4) studies had to specify the use of P2Y$_{12}$ inhibitor among the trial cohort and its influence on the analyzed outcomes.

Study Endpoints

We compared the safety (clinically significant bleeding) and efficacy (composite of MACE) in patients assigned to take ticagrelor or prasugrel versus clopidogrel in combination with any oral anticoagulation, with or without aspirin.

Data Extraction

Two authors (FL and SG) searched the studies and extracted the data independently and in duplicate. Information about the outcomes was extracted from the original manuscript and supplementary data. Information was gathered using standardized protocol and reporting forms. Disagreements were resolved by consensus involving a third author (JCH). Both authors (FL and SG) reviewed and independently assessed the quality items and discrepancies were resolved by consensus.

Individual Study Quality Appraisal

Two authors (FL and SG) independently assessed the quality and reporting of the studies by the Newcastle-Ottawa Scale.[12] Three categories were included in the analysis. Studies were then classified into one of three categories: a) High Quality (6–7 points), b) Satisfactory Quality (3–5 points), c) Unsatisfactory Quality (0–2 points).

Statistical Analysis

Data were summarized across treatment arms using the Mantel-Haenszel risk ratio (RR). We evaluated heterogeneity of effects using the Higgins I^2 statistic.[13] For analyses with low heterogeneity (defined as I^2 <25%) we used fixed effect models, otherwise random effects models of DerSimonian and Laird were used.[14] We performed funnel plot analyses to address publication bias.[15] A separate sensitivity analysis of safety and efficacy outcomes was performed including only randomized controlled clinical trials. In addition, we performed a separate sensitivity analysis of safety and efficacy outcomes comparing ticagrelor to prasugrel. Descriptive statistics are presented as means and standard deviations for continuous variables or number of cases, and percentages for categorical variables. Statistical analysis was performed by Review Manager (RevMan), version 5.3 (2014; The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen).

Patient and Public Involvement Statement

This research was done without patient involvement. Patients were not invited to comment on the study design and were not consulted to develop patient relevant outcomes or interpret the results. Patients were not invited to contribute to the writing or editing of this document for readability or accuracy.

RESULTS

Study Selection

Study selection is outlined in Figure 1. We identified 267 abstracts, of which 234 abstracts were retrieved and reviewed for possible inclusion. Twenty-one full-text manuscripts were assessed for eligibility; from which 14 were excluded due to not meeting inclusion criteria. Seven studies, including 3 randomized controlled trials were included in our final analysis.[6–8,16–19] Randomized controlled trials included: Prevention of Bleeding in Patients with Atrial Fibrillation Undergoing PCI (PIONEER-AF),[6] Dual Antithrombotic Therapy with Dabigatran after PCI in Atrial Fibrillation (RE-DUAL PCI),[7] and Antithrombotic Therapy after Acute Coronary Syndrome or PCI in Atrial Fibrillation (AUGUSTUS).[8]

Baseline Characteristics Data Analysis

Study characteristics and baseline demographics are described in Tables 1 and 2. Additional data on anticoagulant and antithrombotic use in each study is provided in the supplement (Supplemental Table 1). We included seven studies with a total of 22,014 patients in the analysis. In the 3 randomized controlled trials all patients had AF. Three of the observational studies included patients with either AF or other indications for systemic anticoagulation such as venous thromboembolic disease, left ventricular thrombus or mechanical heart valve. All seven studies included patients undergoing PCI, with the most common indication being acute coronary syndrome. $P2Y_{12}$ inhibitor selection in all studies was at the discretion of treating physicians. Of patients prescribed both OAC and $P2Y_{12}$, 90% (n=9,708) were treated with clopidogrel, 8% (n=830) with ticagrelor, and 2% (n=191) with prasugrel. The rate of concurrent aspirin use in the prasugrel group was higher than that of the clopidogrel group (83% versus 61%). The rate of concurrent aspirin use in the ticagrelor group was

lower than that of the corresponding clopidogrel group (38% versus 52%) (Supplemental Data Tables 2a–b.). The maximum time on triple antithrombotic therapy varied between the randomized controlled trials included, ranging from three to fourteen days (Table 1). Patients may have been randomized to dual antithrombotic therapy prior to this. Two different doses of rivaroxaban, dabigatran, and apixaban were used in the PIONEER-AF, RE-DUAL PCI, and AUGUSTUS studies, respectively.

Quality Assessment

Based on the Newcastle-Ottawa Scale 3 of the 7 studies were of high quality and 4 of the 7 were of satisfactory quality. None were of unsatisfactory quality (Table 3).

Study Endpoints

When compared to clopidogrel, use of ticagrelor [RR 1.36; 95% CI, 1.18–1.57] and prasugrel [RR 2.11; 95% CI, 1.34–3.30] were associated with increased rates of bleeding (Figures 2 and 3). Compared to clopidogrel, there were no significant differences in rates of MACE between ticagrelor [RR 1.03; 95% CI, 0.65–1.62] or prasugrel [RR 1.49; 95% CI, 0.69–3.24] (Figures 4 and 5).

Sensitivity Analyses

Separate sensitivity analysis of safety and efficacy outcomes using only randomized controlled clinical trials demonstrated results consistent with our overall analysis. When compared to clopidogrel, use of ticagrelor [RR 1.38; 95% CI, 1.20–1.60] and prasugrel [RR 1.85; 95% CI, 1.25–2.74] were associated with increased rates of bleeding. There were no significant differences in rates of MACE between ticagrelor [RR 1.00; 95% CI, 0.54–1.85] or prasugrel [RR 0.80; 95% CI, 0.31–2.08] compared to clopidogrel (Included in Figures 2–5). Sensitivity analysis of safety and efficacy outcomes comparing ticagrelor to prasugrel in combination with OAC demonstrated no significant differences in bleeding [RR 0.80; 95% CI, 0.47–1.36] or MACE [RR 0.85; 95% CI, 0.29–2.54] (Supplemental Figures V and VI). A separate sensitivity analysis excluding patients receiving aspirin was considered, however not felt to be feasible as this raw data was not available for analysis. In addition, the sample size of patients after exclusion of the aspirin groups might have been too small to adequately power our analysis.

Publication Bias

Funnel plot analyses did not demonstrate asymmetry suggestive of publication bias for efficacy and safety outcomes analyses (Supplemental Figures I–VI).

DISCUSSION

The main findings of our study can be summarized as follows: 1) the use of either of the third generation $P2Y_{12}$ inhibitors ticagrelor or prasugrel, in combination with oral anticoagulation in patients with AF undergoing PCI were associated with higher rates of bleeding when compared to clopidogrel; 2) When compared to clopidogrel, use of third generation $P2Y_{12}$ inhibitors did not demonstrate a significant difference in MACE. To our knowledge this is the first meta-analysis to compare the safety and efficacy of all three major

$P2Y_{12}$ inhibitors in combination with OAC in patients with AF undergoing PCI. Our analysis, which is focused on those patients with AF, includes data from large randomized controlled trials as well as patients in observational studies. Our findings are significant given the high prevalence of CAD and PCI in patients on AF on OAC, the high baseline risk of bleeding in this population, and the limited evidence to support decision-making in this scenario.

Previous studies comparing the third generation $P2Y_{12}$ inhibitors versus clopidogrel in patients with ACS have shown clinical benefits with regards to MACE with a tradeoff of increased bleeding. These studies importantly excluded patients on OAC, thus the safety and efficacy of $P2Y_{12}$ inhibitors have not been previously compared in combination with OAC. In the original Platelet Inhibition and Patient Outcomes (PLATO) study, the use of ticagrelor when compared to clopidogrel led to reductions in a composite endpoint of cardiovascular (CV) death, MI, and stroke.[10] Investigators did not find differences in rates of all-cause major bleeding, although non-CABG related major bleeding was higher with ticagrelor. In the Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis in Myocardial Infarction (TRITON-TIMI 38) study, the use of prasugrel was associated with reductions in a composite endpoint of CV death, MI, and stroke, but increases in major bleeding when compared to clopidogrel.[9] While these studies excluded patients on OAC, the PIONEER-AF, RE-DUAL PCI, and AUGUSTUS randomized controlled trials included in our analysis are focused on AF patients on systemic OAC for stroke prevention. Our study results are consistent with findings of increased bleeding risk with third generation $P2Y_{12}$ inhibitors, although diverge from PLATO and TRITON-TIMI 38 with respect to MACE outcomes where we found no difference between antiplatelet agent. The lack of improvement of MACE outcomes with third generation $P2Y_{12}$ inhibitors suggests that in the setting of background OAC, a less potent $P2Y_{12}$ inhibitor such as clopidogrel (with or without aspirin) protects against MACE without inducing undue increased bleeding risk.

To disrupt platelet function the thienopyridines (clopidogrel and prasugrel), and the pyrimidine derivative ticagrelor act on the $P2Y_{12}$ receptor to inhibit the downstream adenosine diphosphate receptor.[2] Both ticagrelor and prasugrel lead to faster and more potent platelet inhibition when compared to clopidogrel in pharmacodynamic studies.[20–22] Prasugrel, a prodrug that is metabolized to an active form, yielded greater inhibition of platelet aggregation (IPA) than clopidogrel (58.2% compared to 15.7%) 24 hours after a loading dose.[21] Ticagrelor, which does not require metabolism for activity, yielded greater IPA versus clopidogrel after 4 weeks (88% IPA compared to 68%).[23] When used in combination with OAC, it is possible that third generation $P2Y_{12}$ inhibitors may further increase risk of bleeding compared to clopidogrel, due to additive or synergistic effects and drug-drug interactions. Ticagrelor is known to be a CYP3A4 and P-gp inhibitor, although prasugrel has not been shown to significantly interfere with CYP450-mediated metabolism of other drugs.[20,22] All DOACs on the US market are P-gp transporter substrates and the factor Xa inhibitors (rivaroxaban, apixaban, and edoxaban) are also CYP3A4 substrates.[24] Warfarin is also a partial CYP3A4 substrate. When in combination, ticagrelor may lead to altered plasma concentration and excretion of certain DOACs and warfarin and thus further increase bleeding.[25] In addition to potent anti-platelet activity, these pharmacologic properties may help to explain the increased tendency for bleeding with ticagrelor, as

demonstrated in our results. It should also be mentioned that more aspirin co-prescription with prasugrel relative to clopidogrel (83% versus 61%), and less co-prescription with ticagrelor relative to clopidogrel (38% versus 52%) might have influenced differences in bleeding rates. In our sensitivity analysis comparing ticagrelor to prasugrel we found no difference in bleeding or MACE between the groups. These findings differ from the recent Ticagrelor or Prasugrel in Patients with Acute Coronary Syndromes (ISAR REACT 5) randomized controlled trial, which found that prasugrel, when compared to ticagrelor, lead to lower incidence of MACE and no difference in bleeding.[26] One explanation for this difference may be the small sample size of patients on ticagrelor, and particularly prasugrel, in our analysis, leading to wide confidence intervals and limiting the strength of comparison between them. Given results from our study, PLATO, and TRITON-TIMI 38 we conclude that with or without OAC, the third generation $P2Y_{12}$ agents appear to raise bleeding risk. Our study may suggest a magnified bleeding risk of these agents with background OAC therapy.

Perhaps more surprising is that we found no difference in MACE between the $P2Y_{12}$ inhibitors in combination with OAC. A possible explanation for the difference between our study compared to previous data from PLATO and TRITON-TIMI 38 is the balance of additional antithrombotic effect from oral anticoagulants. It has been hypothesized that excess thrombin generation is a driver of recurrent thrombotic events following ACS.[27] By inhibiting synthesis of coagulation factors, or inhibiting activity of factor Xa or thrombin directly, VKAs and DOACs inhibit the final common pathway of the coagulation cascade, and thus indirectly inhibit platelet activation.[2] The antiplatelet effects of OAC are thought to be responsible for improved CV outcomes after ACS in clinical trials, however this remains a point of contention.[28,29] The Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects with Acute Coronary Syndrome-Thrombolysis in Myocardial Infarction 51 (ATLAS ACS 2-TIMI 51) randomized controlled trial demonstrated a modest reduction in composite MACE from low-dose rivaroxaban in addition to DAPT in patients with recent ACS.[28] The subsequent Cardiovascular Outcomes for People Using Anticoagulation Strategies (COMPASS) study demonstrated a similar small reduction in MACE from low-dose rivaroxaban plus aspirin compared to aspirin alone in patients with stable CAD.[29] In contrast, the Apixaban Plus Mono Versus Dual Antiplatelet Therapy in Acute Coronary Syndromes (APPRAISE-2) Trial found no difference in MACE, but increased rates of bleeding when apixaban was added to antiplatelet therapy in patients with ACS.[30] Another explanation of our results could be that our study was not adequately powered to detect a difference in MACE between clopidogrel and third generation $P2Y_{12}$ inhibitors. Compared to clopidogrel, the sample sizes of ticagrelor and prasugrel are small, leading to wide confidence intervals and the possibility of a type II error of no difference in MACE. Lastly, the differences in aspirin co-prescription with prasugrel relative to clopidogrel, and ticagrelor relative to clopidogrel, might have influenced differences in rates of MACE. In summary, we suggest that the indirect antiplatelet effect of OAC may balance the relative reduction in antiplatelet potency of clopidogrel compared to a third generation $P2Y_{12}$ inhibitors. This may explain the lack of difference in MACE between the third generation $P2Y_{12}$ inhibitors in our analysis.

Contemporary guidelines are in favor of clopidogrel over third generation $P2Y_{12}$ inhibitors when in combination with triple antithrombotic therapy, despite a lack of strong primary evidence to support their recommendation. The 2016 American Heart Association/American College of Cardiology guideline focused update on dual antiplatelet therapy suggests "clopidogrel is the $P2Y_{12}$ inhibitor of choice" in patients on triple antithrombotic therapy, citing only expert consensus and review articles.[31] The 2018 European Society of Cardiology guidelines on myocardial revascularization offer a class III, C recommendation against the use of ticagrelor or prasugrel as part of triple antithrombotic therapy without primary literature to support this.[32] The most recent guidelines from the 2019 American Heart Association/American College of Cardiology/Heart rhythm Society focused update on the management of patients with atrial fibrillation make a class IIa, B-NR recommendation supporting the choice of clopidogrel, as follows: "If triple therapy (oral anticoagulant, aspirin, and $P2Y_{12}$ inhibitor) is prescribed for patients with AF at increased risk of stroke (based on CHA2DS2-VASc risk score of 2 or greater) who have undergone percutaneous coronary intervention (PCI) with stenting for ACS, it is reasonable to choose clopidogrel in preference to prasugrel."[33] The two references cited to support this recommendation are prospective observational studies which are also included in our analysis.[17,18] Randomized controlled trial comparing third generation $P2Y_{12}$ inhibitors versus clopidogrel in combination with OAC in patients with AF undergoing PCI is needed, but may never be done. In the absence of such a randomized trial, our current study provides strong evidence against the use of third generation $P2Y_{12}$ agents with a DOAC or VKA, from which further evidence-based recommendations can be made.

LIMITATIONS

This systematic review and meta-analysis has several important limitations that should be acknowledged. First, the studies included in the meta-analysis enrolled heterogenous populations with different study protocols and defined endpoints. Both safety (bleeding) and efficacy (MACE) definitions varied slightly between studies. Second, the studies in our analysis had low overall ischemic event rates and were thus underpowered to detect significant differences in individual thrombotic events such as stent thrombosis. Due to small sample sizes of prasugrel and ticagrelor, wide confidence intervals are seen which could lead to a type II error of no difference in MACE. Given this, our study may remain underpowered to detect a benefit in MACE from third generation $P2Y_{12}$ inhibitors. Third, $P2Y_{12}$ inhibitor selection in all studies was at the discretion of treating physicians. In the prospective studies included in this analysis patients were randomized to DOAC or VKA in combination with antiplatelet agents, but not randomized to $P2Y_{12}$ inhibitor treatment groups. Because of this we cannot exclude the possibility of selection bias and additional confounding factors influencing our results. In addition, the use of aspirin was not randomized between $P2Y_{12}$ inhibitor groups, leading to unequal co-prescription and variance in duration of aspirin which may have influenced bleeding rates. We were unable to exclude patients on aspirin given we did not have access to the raw data to do this. As such, there were both measured and unmeasured confounders that are likely to influence the results and these have not been adjusted for.

CONCLUSION

According to the results of this meta-analysis, the use of clopidogrel may be favored over ticagrelor or prasugrel in patients with AF on OAC undergoing PCI due to increased bleeding risk without improved MACE in patients prescribed ticagrelor or prasugrel. These findings are important given the high prevalence of coronary artery disease and PCI in patients with AF.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Abbreviations and Acronyms

ACS	acute coronary syndrome
AF	atrial fibrillation
CAD	coronary artery disease
CABG	coronary artery bypass graft
CV	cardiovascular
DAPT	dual antiplatelet therapy
DOAC	direct oral anticoagulant
MACE	major adverse cardiac events
MI	myocardial infarction
OAC	oral anticoagulation
PCI	percutaneous coronary intervention
VKA	vitamin K antagonist

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Key Questions:

What is already known about this subject?

- Dual antithrombotic therapy, combining a direct oral anticoagulant and a single $P2Y_{12}$ inhibitor, leads to less bleeding with comparable major adverse cardiac events when compared to triple antithrombotic therapy. The optimal $P2Y_{12}$ inhibitor in this clinical scenario remains in question.

What does this study add?

- This meta-analysis of 7 studies involving 22,014 patients demonstrated that the use of ticagrelor or prasugrel (in combination with oral anticoagulation) were associated with increased rates of bleeding and no significant difference in rates of major adverse cardiac events when compared to clopidogrel.

How might this impact on clinical practice?

- The use of clopidogrel may be associated with less bleeding compared to third generation $P2Y_{12}$ inhibitors when in combination with oral anticoagulation in atrial fibrillation patients undergoing percutaneous coronary intervention.

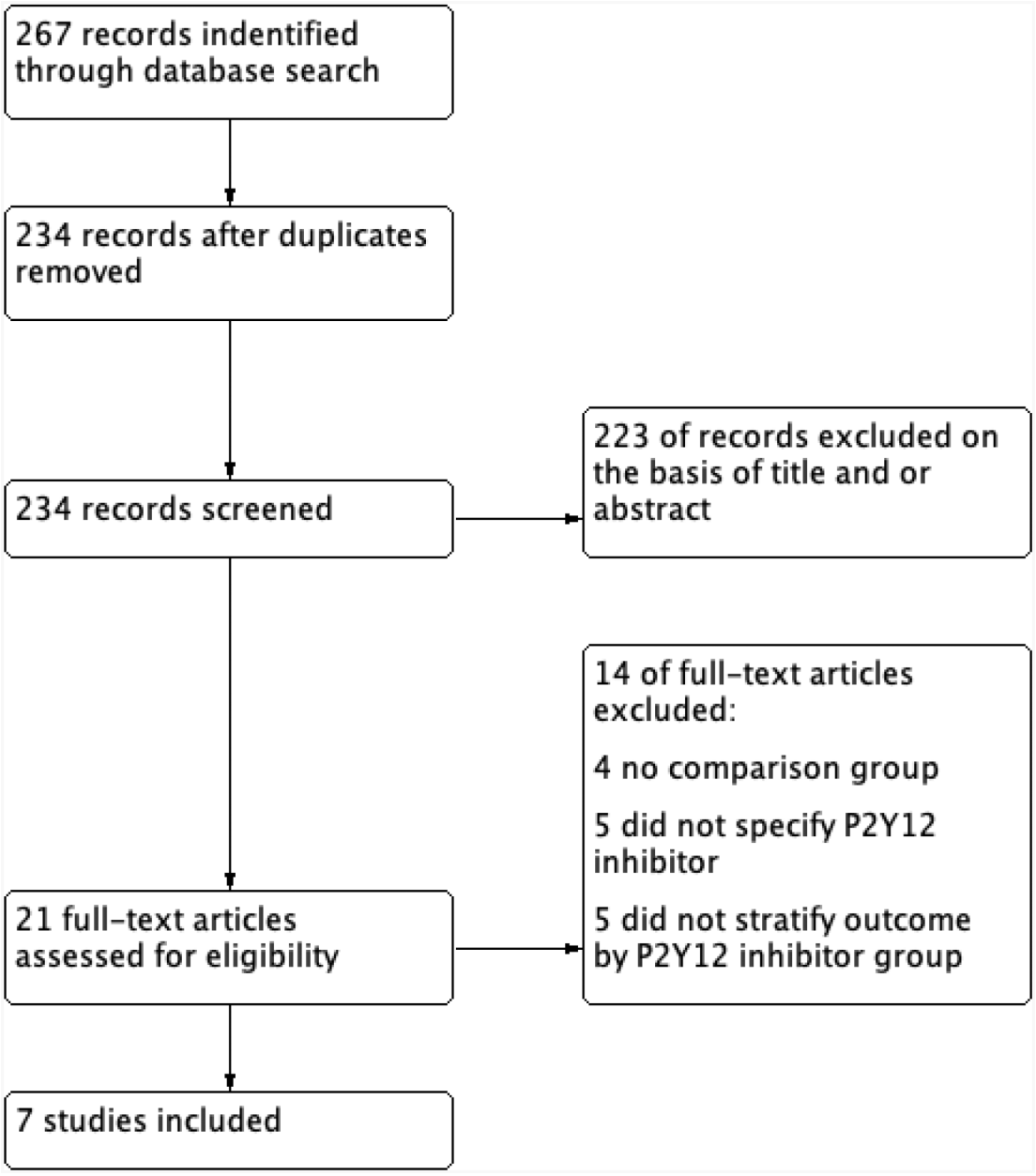

Figure 1.
Selection of studies

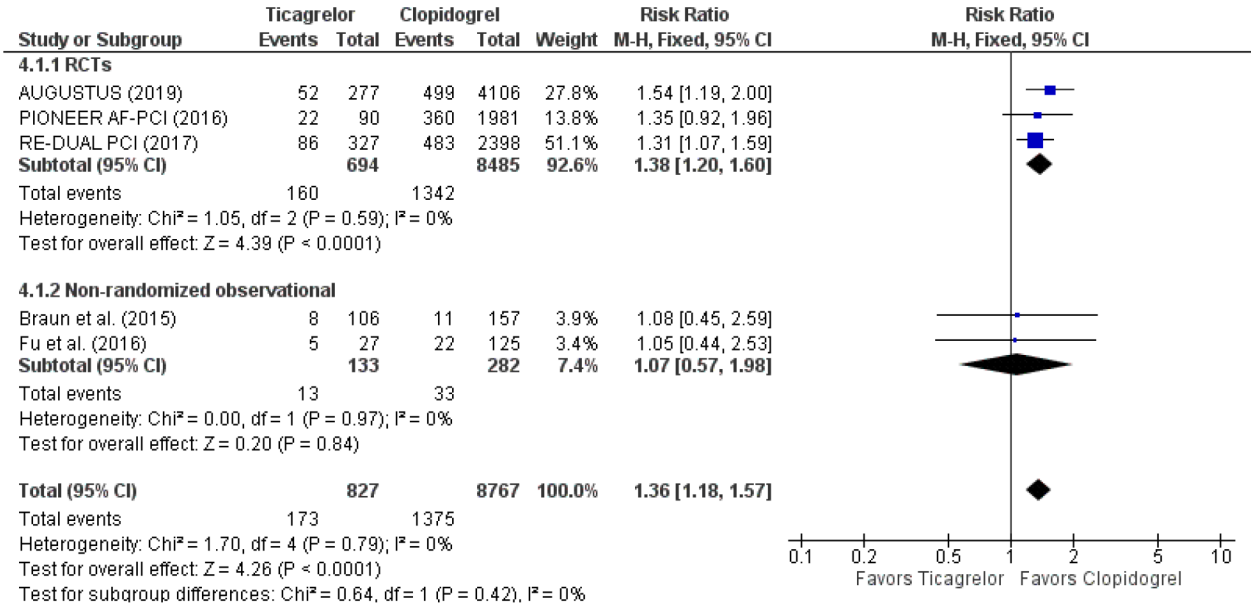

Figure 2.

Forest plot for the comparative risk of bleeding with ticagrelor versus clopidogrel in combination with oral anticoagulation

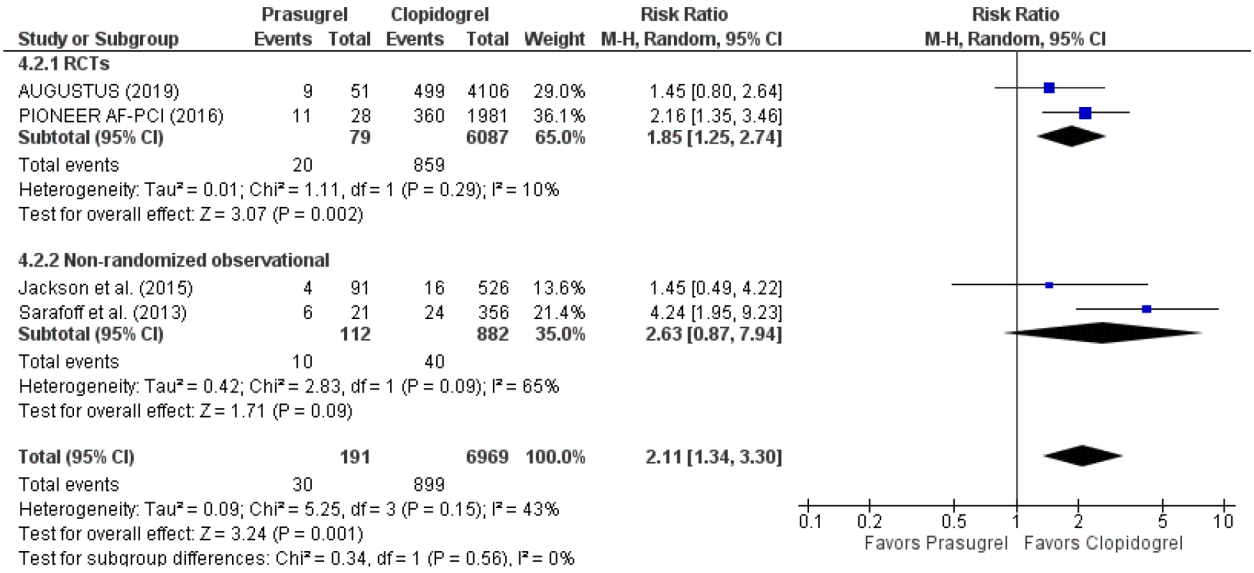

Figure 3.

Forest plot for the comparative risk of bleeding with prasugrel versus clopidogrel in combination with oral anticoagulation

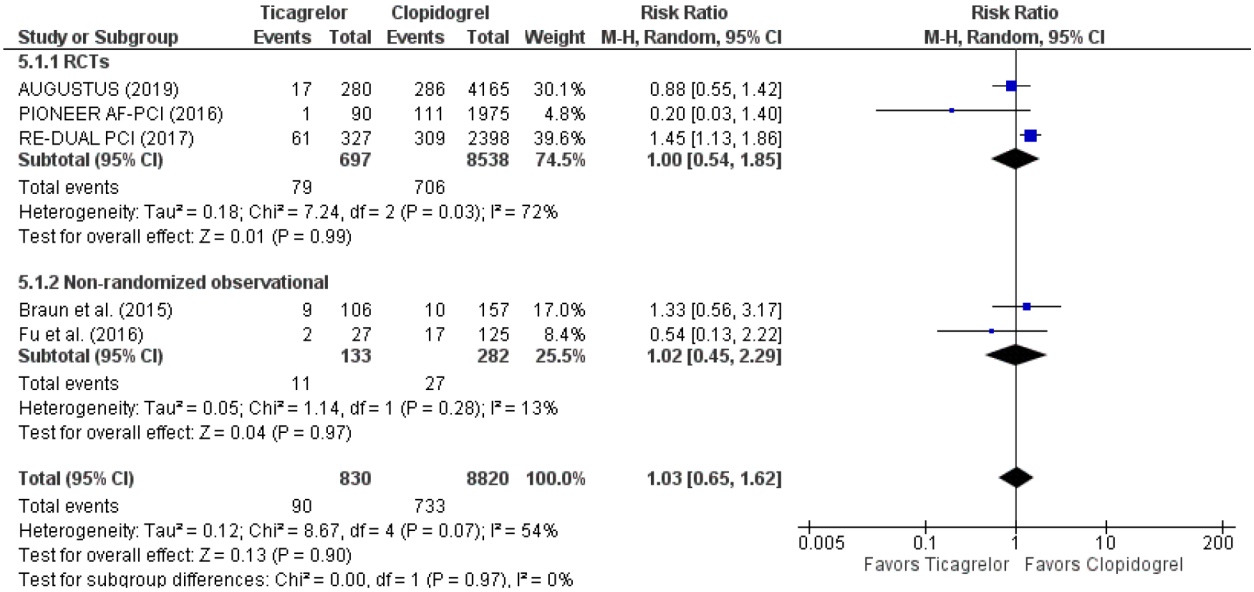

Figure 4.

Forest plot for the comparative risk of composite major adverse cardiac events with ticagrelor versus clopidogrel in combination with oral anticoagulation

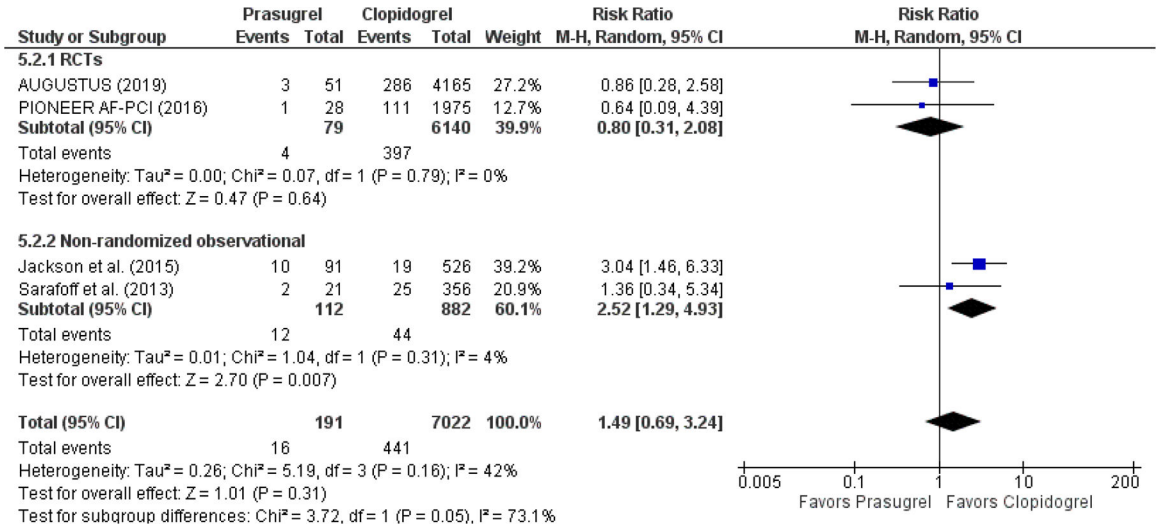

Figure 5.

Forest plot for the comparative risk of composite major adverse cardiac events with prasugrel versus clopidogrel in combination with oral anticoagulation

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Table 1.

Baseline trial characteristics for the studies included in analysis

Study	AUGUSTUS (2019)	RE-DUAL PCI (2017)	PIONEER AF-PCI (2016)	Fu et al. (2016)	Braun et al. (2015)	Jackson et al. (2015)	Sarafoff et al. (2013)
Design	Randomized, 2×2 factorial design: -Apixaban vs VKA open-label -Aspirin vs placebo double-blind	Randomized, open label	Randomized, open label	Prospective observational	Retrospective cohort	Prospective observational	Prospective observational
OAC regimens	Apixaban 5mg BID or 2.5 BID [*] VKA	Dabigatran 110mg BID Dabigatran 150mg BID VKA	Rivaroxaban 15mg daily Rivaroxaban 2.5mg BID VKA	VKA only	VKA only	Dabigatran (dose NR) Rivaroxaban (dose NR) VKA (93%)	VKA only
$P2Y_{12}$ regimens	Clopidogrel Prasugrel Ticagrelor	Clopidogrel Ticagrelor	Clopidogrel Prasugrel Ticagrelor	Clopidogrel Ticagrelor	Clopidogrel Ticagrelor	Clopidogrel Prasugrel	Clopidogrel Prasugrel
Maximum duration of triple antithrombotic therapy before combination of OAC with $P2Y_{12}$ inhibitor, if applicable	14 days	120 hours	72 hours	N/A	NR	N/A	N/A
Comparison	Apixaban + $P2Y_{12}$ +/− ASA Versus VKA + $P2Y_{12}$ +/− ASA	Dabigatran + $P2Y_{12}$ versus VKA + $P2Y_{12}$ + ASA	Rivaroxaban 15mg QD + $P2Y_{12}$ versus Rivaroxaban 2.5mg BID + $P2Y_{12}$ + ASA versus VKA + $P2Y_{12}$ + ASA	VKA + ticagrelor+ ASA versus VKA + clopidogrel + ASA	VKA + Ticagrelor versus VKA + clopidogrel + ASA	OAC + prasugrel + ASA versus OAC + clopidogrel + ASA	VKA + prasugrel + ASA versus VKA + clopidogrel + ASA
Safety endpoint/ Bleeding definition	Major bleeding + clinically-relevant nonmajor bleeding (ISTH) [†]	Major bleeding + clinically-relevant nonmajor bleeding (ISTH) [†]	Major bleeding + minor bleeding + bleeding requiring medical attention (TIMI) [‡]	BARC types 2, 3, and 5 bleeding [§]	Major bleeding (HAS-BLED) [?]	BARC types 2, 3, and 5 bleeding [§] and only that involving rehospitalization [#]	Major and minor bleeding (TIMI) [‡]
Efficacy endpoint/ “MACE” definition	Composite of all-cause mortality, stroke, MI, ischemic stent thrombosis, urgent revascularization	Composite of all-cause mortality, stroke, MI, systemic embolism, or unplanned revascularization (PCI or CABG)	Composite of CV death, MI, stroke	Composite of CV death, MI, or stroke	Composite of all-cause mortality, stroke, TIA, ACS, or peripheral arterial embolism	Composite of all-cause mortality, MI, stroke, or unplanned revascularization	Composite of all-cause mortality, MI, ischemic stroke, stent thrombosis

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Study	AUGUSTUS (2019)	RE-DUAL PCI (2017)	PIONEER AF-PCI (2016)	Fu et al. (2016)	Braun et al. (2015)	Jackson et al. (2015)	Sarafoff et al. (2013)
Inclusion criteria	AF and planned use of OAC, recent ACS or PCI and planned use of $P2Y_{12}$	Nonvalvular AF and successful PCI with DES or BMS for ACS or stable CAD within previous 120 hours, planned use of OAC and $P2Y_{12}$ agents	Nonvalvular AF and successful PCI with stent placement	N/A	N/A	N/A	N/A
Exclusion criteria	OAC for indications other than AF, severe renal insufficiency, history of intracranial hemorrhage, recent or planned CABG, coagulopathy, ongoing bleeding, contraindication to OAC, $P2Y_{12}$ agents, aspirin	Presence of bioprosthetic or mechanical heart valves, severe renal insufficiency, use of fibrinolytic agents with 24 hours, stroke within 1 month prior, GI hemorrhage within 1 month, major bleeding episode within 1 month, contraindication to OAC, $P2Y_{12}$ agents, or aspirin	History of stroke or TIA, clinically significant GI bleeding with 12 months, creatinine clearance <30cc/min, anemia with Hgb <10g/dl, coagulopathy	N/A	N/A	N/A	N/A

N/A signifies category is not applicable to study.

NR signifies data was not reported in study.

ACS= acute coronary syndrome; AF= atrial fibrillation; ASA= acetylsalicylic acid; BID= twice daily; BMS= bare metal stent; CABG= coronary artery bypass graft; CAD=coronary artery disease; CV=cardiovascular; DES=drug eluting stent; GI= gastrointestinal; MACE= major adverse cardiac event; MI=myocardial infarction; OAC=oral anticoagulant; PCI=percutaneous coronary intervention; QD=daily; TIA= transient ischemic attack; VKA=vitamin K antagonist

*2.5mg dose give if patients met two or more of the following dose-reduction criteria: at least 80 years of age, weight of less than 60kg, creatinine of greater than 1.5mg per deciliter

†ISTH=International Society on Thrombosis and Haemostasis: Major bleeding defined as bleeding that resulted in death, in a critical organ, or was associated with either a decrease in hemoglobin level of at least 2g per deciliter or a transfusion of at least 2 units of packed red cells. Clinically relevant nonmajor bleeding defined as bleeding that resulted in hospitalization, medical or surgical intervention, an unscheduled clinic visit, or a change in physician-directed antithrombotic therapy.

‡TIMI=Thrombolysis in Myocardial Infarction: Major bleeding defined as any symptomatic intracranial hemorrhage or clinically overt signs of hemorrhage associated with a drop in hemoglobin of more than 5g per deciliter or an absolute drop in hematocrit of ≥ 15%. Minor bleeding defined as any clinically overt sign of hemorrhage associated with a drop in hemoglobin of 3 to <5 grams per deciliter or drop in hematocrit of 9 to <15%. Bleeding events requiring medical attention defined as one that requires medical treatment, surgical treatment, or a laboratory evaluation and does not meet criteria for a major or minor event.

§BARC=Bleeding Academic Research Consortium: Type 5 bleeding defined as probable or definite fatal bleeding. Type 3 defined as overt bleeding with hemoglobin drop of 3 to <5 grams per deciliter, requiring transfusion, causing cardiac tamponade, requiring surgical intervention, requiring IV vasoactive agents or intracranial hemorrhage. Type 2 defined as overt bleeding requiring diagnostic studies, hospitalization, or treatment by a health care professional.

?HAS-BLED major bleeding defined as that with intracranial bleed, hospitalization, drop in hemoglobin of >2 grams per deciliter, or requiring transfusion.

#To avoid risk of overestimation, only bleeding requiring hospitalization was used in this analysis. Patient reported bleeding data was excluded

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Table 2.

Baseline demographic characteristics for the studies included in analysis

Demographic characteristics		AUGUSTUS (2019)	RE-DUAL PCI (2017)	PIONEER AF-PCI (2016)	Fu et al. (2016)	Braun et al. (2015)	Jackson et al. (2015)	Sarafoff et al. (2013)
Patients included		4614	2725	2124	152	266	11,576	377
Mean follow up (months)		6 months	14 months	12 months	12 months	3 months	6 months	6 months
Age (years)		70.7 (median)	70.8 (mean)	70.1 (mean)	67	69.8	64.7	71.1
Male (%)		3277 (71%)	2070 (76%)	1581 (74%)	109 (72%)	205 (78%)	469 (76%)	302 (80%)
AF (%)		100%	100%	100%	64 (42%)	263 (100%)	172 (28%)	292 (77%)
Type of AF								
	Paroxysmal	NR	1351 (50%)	938 (44%)	NR	NR	NR	NR
	Persistent	NR	484 (18%)	441(21%)	NR	NR	NR	NR
	Permanent	NR	888 (32%)	481 (35%)	NR	NR	NR	NR
CHA_2DS_2-Vasc score		4 (median), IQR 2–3	3.6 (mean)	3.6 (mean)	NR	NR	NR	NR
Other indication for OAC		N/A	N/A	N/A	88 (58%)	0	445 (72%)	85 (23%)
Acute coronary syndrome (%)		2811 (61%)	1744 (51%)	1096 (55%)	119 (78%)	266 (100%)	617 (100%)	139 (37%)
Type of stent								
	Drug eluting	NR	2251 (83%)	1403 (66%)	80 (53%)	NR	NR	NR
	Bare metal	NR	404 (15%)	675 (32%)	65 (43%)	NR	NR	NR
	Both	NR	41 (2%)	40 (2%)	4 (3%)	NR	NR	NR

Values are number (percentage) or mean ± standard deviation

NR signifies data was not reported in study.

AF= atrial fibrillation; IQR= interquartile range; OAC=oral anticoagulant

Table 3.

Summary of appraisal of included studies using Newcastle-Ottawa Scale for assessing quality of studies

Study	Selection*	Comparability†	Outcome‡
AUGUSTUS	3	2	2
RE-DUAL PCI	3	2	2
PIONEER AF PCI	3	2	2
Fu et al. (2016)	2	2	1
Braun et al. (2015)	2	2	1
Jackson et al. (2015)	2	2	1
Sarafoff et al. (2013)	2	2	1

*=Maximum 3 stars

†=maximum 2 stars

‡=maximum 2 stars