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Title

P2Y$_{12}$ inhibitors with Oral Anticoagulation for Percutaneous Coronary Intervention with Atrial Fibrillation:

A Systematic Review and Meta-Analysis

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Acutus, Inc., toSense, Inc., and Perminova, Inc.

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:

Lupercio F, Romero J, Peltzer B, et al. Efficacy and Safety Outcomes of Direct Oral Anticoagulants and Amiodarone in Patients with Atrial Fibrillation. The American Journal of Medicine 2018;131:573.e1-573.e8.

Word Count: 2,966

3

1 **ABSTRACT**

2 **Objective**

3 This study aimed to compare the safety and efficacy of third generation $P2Y_{12}$

4 inhibitors versus clopidogrel in combination with oral anticoagulation (OAC)

5 with or without aspirin in patients with atrial fibrillation (AF) undergoing

6 percutaneous coronary intervention (PCI).

7 **Methods**

8 We performed a systematic review including both prospective and

9 retrospective studies that compared dual and triple antithrombotic regimens

10 for bleeding and major adverse cardiac events (MACE) in patients with AF

11 undergoing PCI. We analyzed rates of bleeding and MACE by $P2Y_{12}$ inhibitor

12 choice. Risk ratio (RR) 95% confidence intervals were measured using the

13 Mantel-Haenszel method. Where study heterogeneity was low ($I^2 < 25\%$) we

14 used the fixed effects model, otherwise the random effects model was used.

15 **Results**

16 A total of 22,014 patients were analyzed from the 7 studies included. Among

17 patients treated with both OAC and $P2Y_{12}$ inhibitor with or without aspirin,

18 90% (n=9,708) were treated with clopidogrel, 8% (n=830) with ticagrelor,

19 and 2% (n=191) with prasugrel. When compared to clopidogrel, use of

20 ticagrelor [RR 1.36; 95% CI, 1.18-1.57] and prasugrel [RR 2.11; 95% CI, 1.34-

21 3.30] were associated with increased rates of bleeding. Compared to

22 clopidogrel, there were no significant differences in rates of MACE with

5

1 ticagrelor [RR 1.03; 95% CI, 0.65-1.62] or prasugrel [RR 1.49; 95% CI, 0.69-

2 3.24].

3 **Conclusion**

4 Based on this meta-analysis, the use of clopidogrel is associated with a lower

5 rate of bleeding compared to ticagrelor or prasugrel in patients with AF on

6 OAC undergoing PCI.

7

8 **Key Words:**

9 Antiplatelet, Atrial fibrillation, Oral anticoagulation, P2Y$_{12}$ inhibitor,

10 Percutaneous Coronary Intervention

11

12

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.

1 **Abbreviations and Acronyms**

2 ACS= acute coronary syndrome

3 AF= atrial fibrillation

4 CAD= coronary artery disease

5 CABG= coronary artery bypass graft

6 CV= cardiovascular

7 DAPT= dual antiplatelet therapy

8 DOAC= direct oral anticoagulant

9 MACE= major adverse cardiac events

10 MI= myocardial infarction

11 OAC= oral anticoagulation

12 PCI= percutaneous coronary intervention

13 VKA= vitamin K antagonist

1 **INTRODUCTION**

2 Up to 30% of patients with atrial fibrillation (AF) also have coronary artery

3 disease (CAD), 15% of whom will undergo percutaneous coronary

4 intervention (PCI).[1] Choosing an antithrombotic therapy regimen for these

5 patients can be challenging. Inhibition of platelet activation is a priority for

6 the treatment of acute coronary syndrome (ACS), and dual antiplatelet

7 therapy (DAPT) consisting of aspirin and a $P2Y_{12}$ inhibitor is optimal for

8 prevention against recurrent myocardial infarction (MI) and stent thrombosis

9 following PCI.[2] In patients with AF and CHA_2DS_2-VASc score ≥2,

10 antithrombotic agents are used to reduce the formation of platelet-rich

11 thrombi in the left atria. Oral anticoagulation (OAC) with either a direct oral

12 anticoagulant (DOAC) or vitamin K antagonist (VKA) is superior to single or

13 dual antiplatelet therapy for the prevention of stroke and systemic embolism

14 in AF.[3] Triple antithrombotic therapy, the combination of DAPT and OAC

15 increases the risk of bleeding 2- to 3-fold and thus can lead to a higher net

16 adverse cardiovascular event rate (combination of MACE and bleeding).[4] To

17 optimize bleeding and ischemic risk, varying combinations of antiplatelet and

18 OAC regimens have been evaluated.

19

20 Contemporary studies have shown that dual antithrombotic therapy,

21 combining OAC and a single $P2Y_{12}$ inhibitor, leads to less bleeding with

22 comparable major adverse cardiac events (MACE) when compared to triple

23 antithrombotic therapy.[5-8] In addition, increasing evidence suggests that in

9

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

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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.

11

1

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).

12

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

13

1   is provided in the supplement (Supplemental Table 1). We included seven

2   studies with a total of 22,014 patients in the analysis. In the 3 randomized

3   controlled trials all patients had AF. Three of the observational studies

4   included patients with either AF or other indications for systemic

5   anticoagulation such as venous thromboembolic disease, left ventricular

6   thrombus or mechanical heart valve. All seven studies included patients

7   undergoing PCI, with the most common indication being acute coronary

8   syndrome. $P2Y_{12}$ inhibitor selection in all studies was at the discretion of

9   treating physicians. Of patients prescribed both OAC and $P2Y_{12}$, 90%

10   (n=9,708) were treated with clopidogrel, 8% (n=830) with ticagrelor, and 2%

11   (n=191) with prasugrel. The rate of concurrent aspirin use in the prasugrel

12   group was higher than that of the clopidogrel group (83% versus 61%). The

13   rate of concurrent aspirin use in the ticagrelor group was lower than that of

14   the corresponding clopidogrel group (38% versus 52%) (Supplemental Data

15   Tables 2a-b.). The maximum time on triple antithrombotic therapy varied

16   between the randomized controlled trials included, ranging from three to

17   fourteen days (Table 1). Patients may have been randomized to dual

18   antithrombotic therapy prior to this. Two different doses of rivaroxaban,

19   dabigatran, and apixaban were used in the PIONEER-AF, RE-DUAL PCI, and

20   AUGUSTUS studies, respectively.

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14

1 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, 2x2 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 + 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

			VKA + P2Y$_{12}$ + 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
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	Presence of bioprosthetic or mechanical heart valves, severe renal insufficiency, use of	History of stroke or TIA, clinically significant GI bleeding with 12 months, creatinine	N/A	N/A	N/A	N/A

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	hemorrhage, recent or planned CABG, coagulopathy, ongoing bleeding, contraindication to OAC, P2Y$_{12}$ agents, aspirin	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	clearance <30cc/min, anemia with Hgb <10g/dl, coagulopathy				

1   N/A signifies category is not applicable to study.

2   NR signifies data was not reported in study.
3
4   ACS= acute coronary syndrome; AF= atrial fibrillation; ASA= acetylsalicylic acid; BID= twice daily; BMS= bare metal stent; CABG= coronary
5   artery bypass graft; CAD=coronary artery disease; CV=cardiovascular; DES=drug eluting stent; GI= gastrointestinal; MACE= major adverse
6   cardiac event; MI=myocardial infarction; OAC=oral anticoagulant; PCI=percutaneous coronary intervention; QD=daily; TIA= transient
7   ischemic attack; VKA=vitamin K antagonist
8
9   * 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,
10   creatinine of greater than 1.5mg per deciliter
11
12   † ISTH=International Society on Thrombosis and Haemostasis: Major bleeding defined as bleeding that resulted in death, in a critical organ, or
13   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.
14   Clinically relevant nonmajor bleeding defined as bleeding that resulted in hospitalization, medical or surgical intervention, an unscheduled
15   clinic visit, or a change in physician-directed antithrombotic therapy.
16
17   ‡ TIMI=Thrombolysis in Myocardial Infarction: Major bleeding defined as any symptomatic intracranial hemorrhage or clinically overt signs of
18   hemorrhage associated with a drop in hemoglobin of more than 5g per deciliter or an absolute drop in hematocrit of ≥ 15%. Minor bleeding
19   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
20   9 to <15%. Bleeding events requiring medical attention defined as one that requires medical treatment, surgical treatment, or a laboratory
21   evaluation and does not meet criteria for a major or minor event.
22
23   § BARC=Bleeding Academic Research Consortium: Type 5 bleeding defined as probable or definite fatal bleeding. Type 3 defined as overt
24   bleeding with hemoglobin drop of 3 to <5 grams per deciliter, requiring transfusion, causing cardiac tamponade, requiring surgical
25   intervention, requiring IV vasoactive agents or intracranial hemorrhage. Type 2 defined as overt bleeding requiring diagnostic studies,
26   hospitalization, or treatment by a health care professional.
27

17

1   ? HAS-BLED major bleeding defined as that with intracranial bleed, hospitalization, drop in hemoglobin of >2 grams per deciliter, or requiring
2   transfusion.
3   # To avoid risk of overestimation, only bleeding requiring hospitalization was used in this analysis. Patient reported bleeding data was

4   excluded

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18

1 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							

19

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

1

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

1 Supplemental Data Table 1. Antiplatelet and anticoagulant use by study

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)	total
Patients on both OAC + antiplatelet		4614	2725	2124	152	266	617	377	10875
N clopidogrel (% of total)		4165 (90%)	2398 (88%)	1981 (93%)	125 (82%)	157 (59%)	526 (85%)	356 (94%)	9708 (90%)
	N (%) on DAPT	2075 (50%)	890 (37%)	1333 (67%)	125 (100%)	157 (100%)	526 (100%)	356 (100%)	5462 (56%)
	N (%) without ASA	2090 (50%)	1508 (63%)	648 (33%)	0	0	0	0	4261 (44%)
	N (%) on DOAC	2105 (50%)	1508 (63%)	1310 (66%)	0	0	NR*	0	-
	N (%) on VKA	2060 (50%)	890 (37%)	671 (34%)	125 (100%)	157 (100%)	NR*	356 (100%)	-
N ticagrelor (% of total)		280 (6%)	327 (12%)	90 (4%)	27 (18%)	106 (40%)	-	-	830 (8%)
	N (%) on DAPT	147 (53%)	91 (28%)	54 (60%)	27 (100%)	0	-	-	319 (38%)
	N (%) without ASA	133 (48%)	236 (72%)	36 (40%)	0	106 (100%)	-	-	511 (62%)
	N (%) on DOAC	121 (44%)	236 (72%	69 (77%)	0	0	-	-	426 (51%)
	N (%) on VKA	159 (57%)	91 (28%)	21 (23%)	27 (100%)	106 (100%)	-	-	404 (49%)
N prasugrel (% of total)		51 (1%)	-	28 (1%)	-	-	91 (15%)	21 (6%)	191 (2%)
Prasugr	**N (%) on DAPT**	31 (61%)	-	16 (57%)	-	-	91(100%)	21 (100%)	159 (83%)
	N (%) witho	20 (39%)	-	12 (43%)	-	-	0	0	32 (17%)

21

e l	ut ASA								
	N (%) on DOAC	27 (53%)	-	23 (82%)	-	-	NR*	0	-
	N (%) on VKA	24 (47%)	-	5 (18%)	-	-	NR*	21	-

1   *Patients treated with oral anticoagulation in Jackson et al. (2015) may have been on any of: warfarin,
2   dabigatran or rivaroxaban. Individual ratios were not provided. ASA= aspirin; DAPT= dual antiplatelet
3   therapy; DOAC= direct oral anticoagulant; OAC= oral anticoagulation; VKA= vitamin K antagonist

1 Supplemental Data Tables 2a-b. Concurrent aspirin prescription with $P2Y_{12}$

2 inhibitor

Antiplatelet combination		N (%)
Ticagrelor (total)		830
Ticagrelor + aspirin		319 (38%)
Clopidogrel		8826
Clopidogrel + aspirin		4580 (52%)

3

Antiplatelet combination		N (%)
Prasugrel (total)		191
Prasugrel + aspirin		159 (83%)
Clopidogrel		7028
Clopidogrel + aspirin		4290 (61%)

4

23

1 **Quality Assessment**

2 Based on the Newcastle-Ottawa Scale 3 of the 7 studies were of high quality

3 and 4 of the 7 were of satisfactory quality. None were of unsatisfactory

4 quality (Table 3).

5

1 Table 3. Summary of appraisal of included studies using Newcastle-Ottawa
2 Scale for assessing quality of studies
3

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

4 *=Maximum 3 stars
5 †=maximum 2 stars
6 ‡=maximum 2 stars

25

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.

26

1

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.

27

1 Previous studies comparing the third generation $P2Y_{12}$ inhibitors versus

2 clopidogrel in patients with ACS have shown clinical benefits with regards to

3 MACE with a tradeoff of increased bleeding. These studies importantly

4 excluded patients on OAC, thus the safety and efficacy of $P2Y_{12}$ inhibitors

5 have not been previously compared in combination with OAC. In the original

6 Platelet Inhibition and Patient Outcomes (PLATO) study, the use of ticagrelor

7 when compared to clopidogrel led to reductions in a composite endpoint of

8 cardiovascular (CV) death, MI, and stroke.[10] Investigators did not find

9 differences in rates of all-cause major bleeding, although non-CABG related

10 major bleeding was higher with ticagrelor. In the Therapeutic Outcomes by

11 Optimizing Platelet Inhibition with Prasugrel-Thrombolysis in Myocardial

12 Infarction (TRITON-TIMI 38) study, the use of prasugrel was associated with

13 reductions in a composite endpoint of CV death, MI, and stroke, but

14 increases in major bleeding when compared to clopidogrel.[9] While these

15 studies excluded patients on OAC, the PIONEER-AF, RE-DUAL PCI, and

16 AUGUSTUS randomized controlled trials included in our analysis are focused

17 on AF patients on systemic OAC for stroke prevention. Our study results are

18 consistent with findings of increased bleeding risk with third generation $P2Y_{12}$

19 inhibitors, although diverge from PLATO and TRITON-TIMI 38 with respect to

20 MACE outcomes where we found no difference between antiplatelet agent.

21 The lack of improvement of MACE outcomes with third generation $P2Y_{12}$

22 inhibitors suggests that in the setting of background OAC, a less potent $P2Y_{12}$

28

1   inhibitor such as clopidogrel (with or without aspirin) protects against MACE

2   without inducing undue increased bleeding risk.

3

4   To disrupt platelet function the thienopyridines (clopidogrel and prasugrel), and

5   the pyrimidine derivative ticagrelor act on the $P2Y_{12}$ receptor to inhibit the

6   downstream adenosine diphosphate receptor.[2] Both ticagrelor and prasugrel lead

7   to faster and more potent platelet inhibition when compared to clopidogrel in

8   pharmacodynamic studies.[20-22] Prasugrel, a prodrug that is metabolized to an

9   active form, yielded greater inhibition of platelet aggregation (IPA) than clopidogrel

10   (58.2% compared to 15.7%) 24 hours after a loading dose.[21] Ticagrelor, which does

11   not require metabolism for activity, yielded greater IPA versus clopidogrel after 4

12   weeks (88% IPA compared to 68%).[23] When used in combination with OAC, it is

13   possible that third generation $P2Y_{12}$ inhibitors may further increase risk of bleeding

14   compared to clopidogrel, due to additive or synergistic effects and drug-drug

15   interactions. Ticagrelor is known to be a CYP3A4 and P-gp inhibitor, although

16   prasugrel has not been shown to significantly interfere with CYP450-mediated

17   metabolism of other drugs.[20,22] All DOACs on the US market are P-gp transporter

18   substrates and the factor Xa inhibitors (rivaroxaban, apixaban, and edoxaban) are

19   also CYP3A4 substrates.[24] Warfarin is also a partial CYP3A4 substrate. When in

20   combination, ticagrelor may lead to altered plasma concentration and excretion of

21   certain DOACs and warfarin and thus further increase bleeding.[25] In addition to

22   potent anti-platelet activity, these pharmacologic properties may help to explain

23   the increased tendency for bleeding with ticagrelor, as demonstrated in our

29

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

30

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,

31

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

1   in preference to prasugrel."[33] The two references cited to support this

2   recommendation are prospective observational studies which are also

3   included in our analysis.[17,18] Randomized controlled trial comparing third

4   generation $P2Y_{12}$ inhibitors versus clopidogrel in combination with OAC in

5   patients with AF undergoing PCI is needed, but may never be done. In the

6   absence of such a randomized trial, our current study provides strong

7   evidence against the use of third generation $P2Y_{12}$ agents with a DOAC or

8   VKA, from which further evidence-based recommendations can be made.

9

10   **LIMITATIONS**

11   This systematic review and meta-analysis has several important limitations

12   that should be acknowledged. First, the studies included in the meta-analysis

13   enrolled heterogenous populations with different study protocols and defined

14   endpoints. Both safety (bleeding) and efficacy (MACE) definitions varied

15   slightly between studies. Second, the studies in our analysis had low overall

16   ischemic event rates and were thus underpowered to detect significant

17   differences in individual thrombotic events such as stent thrombosis. Due to

18   small sample sizes of prasugrel and ticagrelor, wide confidence intervals are

19   seen which could lead to a type II error of no difference in MACE. Given this,

20   our study may remain underpowered to detect a benefit in MACE from third

21   generation $P2Y_{12}$ inhibitors. Third, $P2Y_{12}$ inhibitor selection in all studies was

22   at the discretion of treating physicians. In the prospective studies included in

23   this analysis patients were randomized to DOAC or VKA in combination with

33

1 antiplatelet agents, but not randomized to $P2Y_{12}$ inhibitor treatment groups.

2 Because of this we cannot exclude the possibility of selection bias and

3 additional confounding factors influencing our results. In addition, the use of

4 aspirin was not randomized between $P2Y_{12}$ inhibitor groups, leading to

5 unequal co-prescription and variance in duration of aspirin which may have

6 influenced bleeding rates. We were unable to exclude patients on aspirin

7 given we did not have access to the raw data to do this. As such, there were

8 both measured and unmeasured confounders that are likely to influence the

9 results and these have not been adjusted for.

10

11 **CONCLUSION**

12 According to the results of this meta-analysis, the use of clopidogrel may be

13 favored over ticagrelor or prasugrel in patients with AF on OAC undergoing

14 PCI due to increased bleeding risk without improved MACE in patients

15 prescribed ticagrelor or prasugrel. These findings are important given the

16 high prevalence of coronary artery disease and PCI in patients with AF.

17

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FIGURES

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

Supplemental Figure I. Funnel plot for the comparative risk of bleeding with ticagrelor versus clopidogrel in combination with oral anticoagulation

Supplemental Figure II. Funnel plot for the comparative risk of bleeding with prasugrel versus clopidogrel in combination with oral anticoagulation

Supplemental Figure III. Funnel plot for the comparative risk of composite major adverse cardiac events with ticagrelor versus clopidogrel in combination with oral anticoagulation

Supplemental Figure IV. Funnel plot for the comparative risk of composite major adverse cardiac events with prasugrel versus clopidogrel in combination with oral anticoagulation

Supplemental Figure V a-b. Forest plot and funnel plot for the comparative risk of bleeding with ticagrelor versus prasugrel in combination with oral anticoagulation

Supplemental Figure VI a-b. Forest plot and funnel plot for the comparative risk of composite major adverse cardiac events with ticagrelor versus prasugrel in combination with oral anticoagulation

39

TABLES

Table 1. Baseline trial characteristics for the studies included in analysis

Table 2. Baseline demographic characteristics for the studies included in analysis

Table 3. Summary of appraisal of included studies using Newcastle-Ottawa Scale for assessing quality of studies

Supplemental Data Table 1. Antiplatelet and anticoagulant use by study

Supplemental Data Tables 2a-b. Concurrent aspirin prescription with P2Y$_{12}$ inhibitor

40

1 **FIGURES**
2
3 Figure 1. Selection of studies

267 records indentified through database search

234 records after duplicates removed

234 records screened

223 of records excluded on the basis of title and or abstract

21 full–text articles assessed for eligibility

14 of full–text articles excluded:

4 no comparison group

5 did not specify P2Y12 inhibitor

5 did not stratify outcome by P2Y12 inhibitor group

7 studies included

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6

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1 Figure 2. Forest plot for the comparative risk of bleeding with ticagrelor
2 versus clopidogrel in combination with oral anticoagulation
3

Study or Subgroup	Ticagrelor Events	Total	Clopidogrel Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
4.1.1 RCTs						
AUGUSTUS (2019)	52	277	499	4106	27.8%	1.54 [1.19, 2.00]
PIONEER AF-PCI (2016)	22	90	360	1981	13.8%	1.35 [0.92, 1.96]
RE-DUAL PCI (2017)	86	327	483	2398	51.1%	1.31 [1.07, 1.59]
Subtotal (95% CI)		694		8485	92.6%	**1.38 [1.20, 1.60]**
Total events	160		1342			
Heterogeneity: Chi² = 1.05, df = 2 (P = 0.59); I² = 0%						
Test for overall effect: Z = 4.39 (P < 0.0001)						
4.1.2 Non-randomized observational						
Braun et al. (2015)	8	106	11	157	3.9%	1.08 [0.45, 2.59]
Fu et al. (2016)	5	27	22	125	3.4%	1.05 [0.44, 2.53]
Subtotal (95% CI)		133		282	7.4%	**1.07 [0.57, 1.98]**
Total events	13		33			
Heterogeneity: Chi² = 0.00, df = 1 (P = 0.97); I² = 0%						
Test for overall effect: Z = 0.20 (P = 0.84)						
Total (95% CI)		827		8767	100.0%	**1.36 [1.18, 1.57]**
Total events	173		1375			
Heterogeneity: Chi² = 1.70, df = 4 (P = 0.79); I² = 0%						
Test for overall effect: Z = 4.26 (P < 0.0001)						
Test for subgroup differences: Chi² = 0.64, df = 1 (P = 0.42), I² = 0%						

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1 Figure 3. Forest plot for the comparative risk of bleeding with prasugrel
2 versus clopidogrel in combination with oral anticoagulation
3

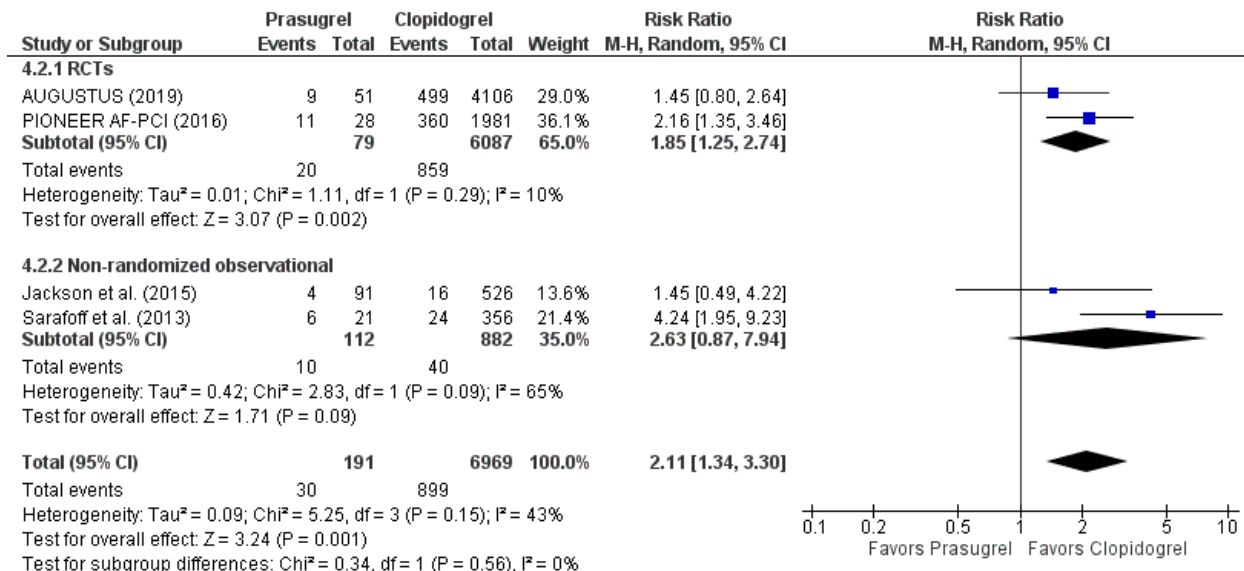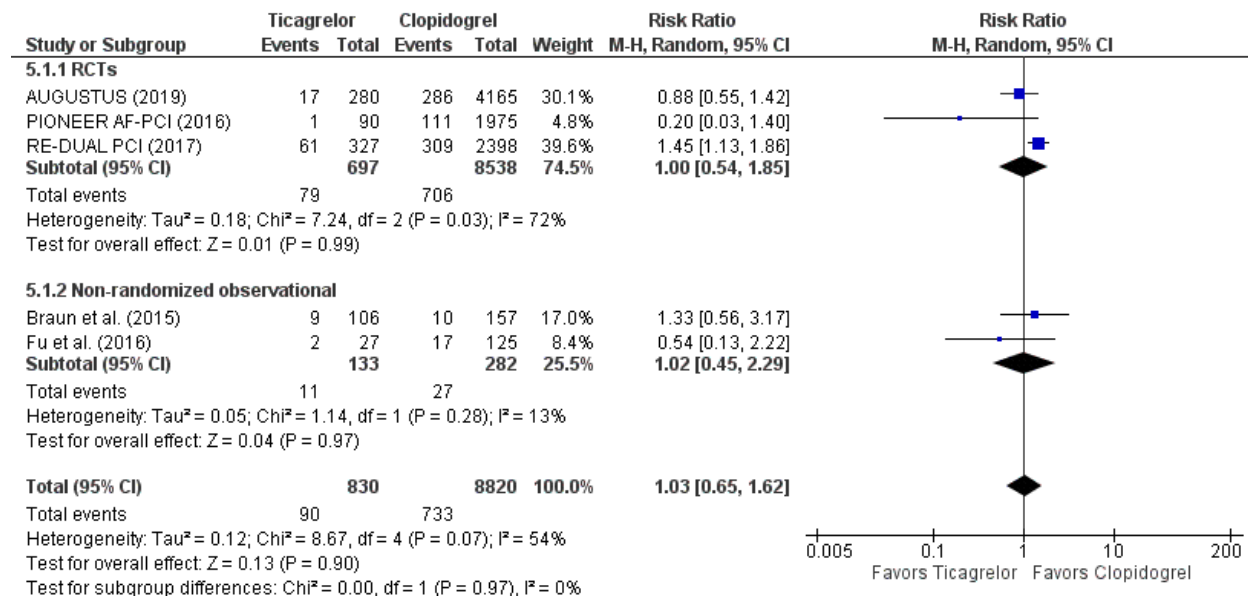| Study or Subgroup	Prasugrel Events	Prasugrel Total	Clopidogrel Events	Clopidogrel Total	Weight	Risk Ratio M-H, Random, 95% CI
4.2.1 RCTs						
AUGUSTUS (2019)	9	51	499	4106	29.0%	1.45 [0.80, 2.64]
PIONEER AF-PCI (2016)	11	28	360	1981	36.1%	2.16 [1.35, 3.46]
Subtotal (95% CI)		79		6087	65.0%	**1.85 [1.25, 2.74]**
Total events	20		859			
Heterogeneity: Tau² = 0.01; Chi² = 1.11, df = 1 (P = 0.29); I² = 10%						
Test for overall effect: Z = 3.07 (P = 0.002)						
4.2.2 Non-randomized observational						
Jackson et al. (2015)	4	91	16	526	13.6%	1.45 [0.49, 4.22]
Sarafoff et al. (2013)	6	21	24	356	21.4%	4.24 [1.95, 9.23]
Subtotal (95% CI)		112		882	35.0%	**2.63 [0.87, 7.94]**
Total events	10		40			
Heterogeneity: Tau² = 0.42; Chi² = 2.83, df = 1 (P = 0.09); I² = 65%						
Test for overall effect: Z = 1.71 (P = 0.09)						
Total (95% CI)		191		6969	100.0%	**2.11 [1.34, 3.30]**
Total events	30		899			
Heterogeneity: Tau² = 0.09; Chi² = 5.25, df = 3 (P = 0.15); I² = 43%						
Test for overall effect: Z = 3.24 (P = 0.001)						
Test for subgroup differences: Chi² = 0.34, df = 1 (P = 0.56), I² = 0%						

Favors Prasugrel   Favors Clopidogrel

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1

2 Figure 4. Forest plot for the comparative risk of composite major adverse
3 cardiac events with ticagrelor versus clopidogrel in combination with oral
4 anticoagulation
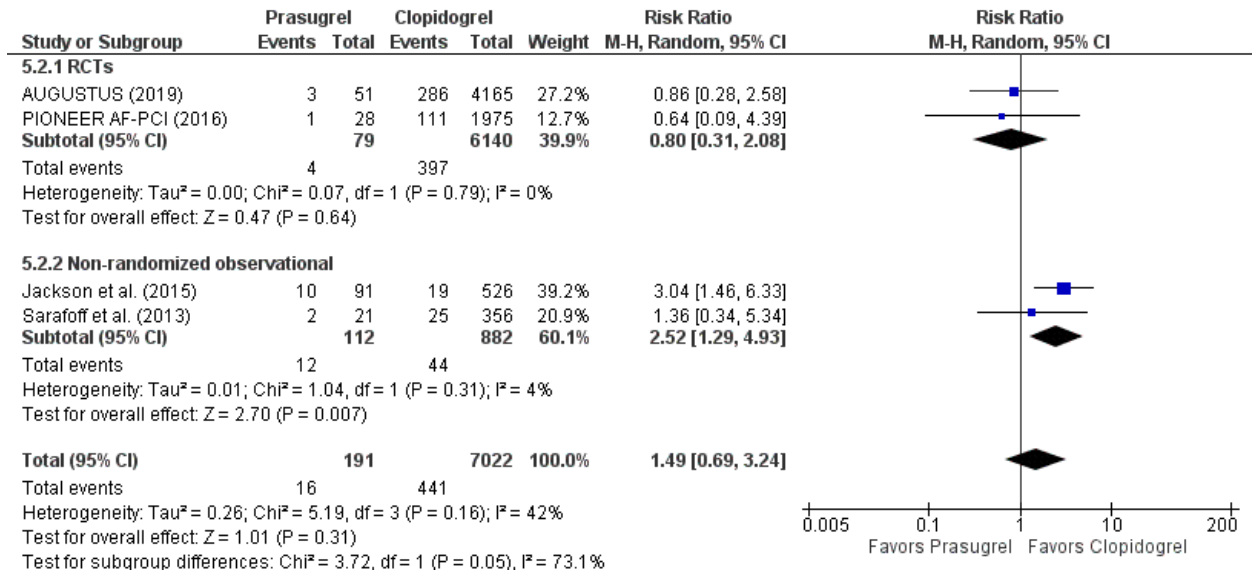5

6

1 Figure 5. Forest plot for the comparative risk of composite major adverse
2 cardiac events with prasugrel versus clopidogrel in combination with oral
3 anticoagulation
4

Study or Subgroup	Prasugrel Events	Total	Clopidogrel Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
5.2.1 RCTs						
AUGUSTUS (2019)	3	51	286	4165	27.2%	0.86 [0.28, 2.58]
PIONEER AF-PCI (2016)	1	28	111	1975	12.7%	0.64 [0.09, 4.39]
Subtotal (95% CI)		**79**		**6140**	**39.9%**	**0.80 [0.31, 2.08]**
Total events	4		397			

Heterogeneity: Tau² = 0.00; Chi² = 0.07, df = 1 (P = 0.79); I² = 0%
Test for overall effect: Z = 0.47 (P = 0.64)

5.2.2 Non-randomized observational						
Jackson et al. (2015)	10	91	19	526	39.2%	3.04 [1.46, 6.33]
Sarafoff et al. (2013)	2	21	25	356	20.9%	1.36 [0.34, 5.34]
Subtotal (95% CI)		**112**		**882**	**60.1%**	**2.52 [1.29, 4.93]**
Total events	12		44			

Heterogeneity: Tau² = 0.01; Chi² = 1.04, df = 1 (P = 0.31); I² = 4%
Test for overall effect: Z = 2.70 (P = 0.007)

Total (95% CI)		**191**		**7022**	**100.0%**	**1.49 [0.69, 3.24]**
Total events	16		441			

Heterogeneity: Tau² = 0.26; Chi² = 5.19, df = 3 (P = 0.16); I² = 42%
Test for overall effect: Z = 1.01 (P = 0.31)
5 Test for subgroup differences: Chi² = 3.72, df = 1 (P = 0.05), I² = 73.1%
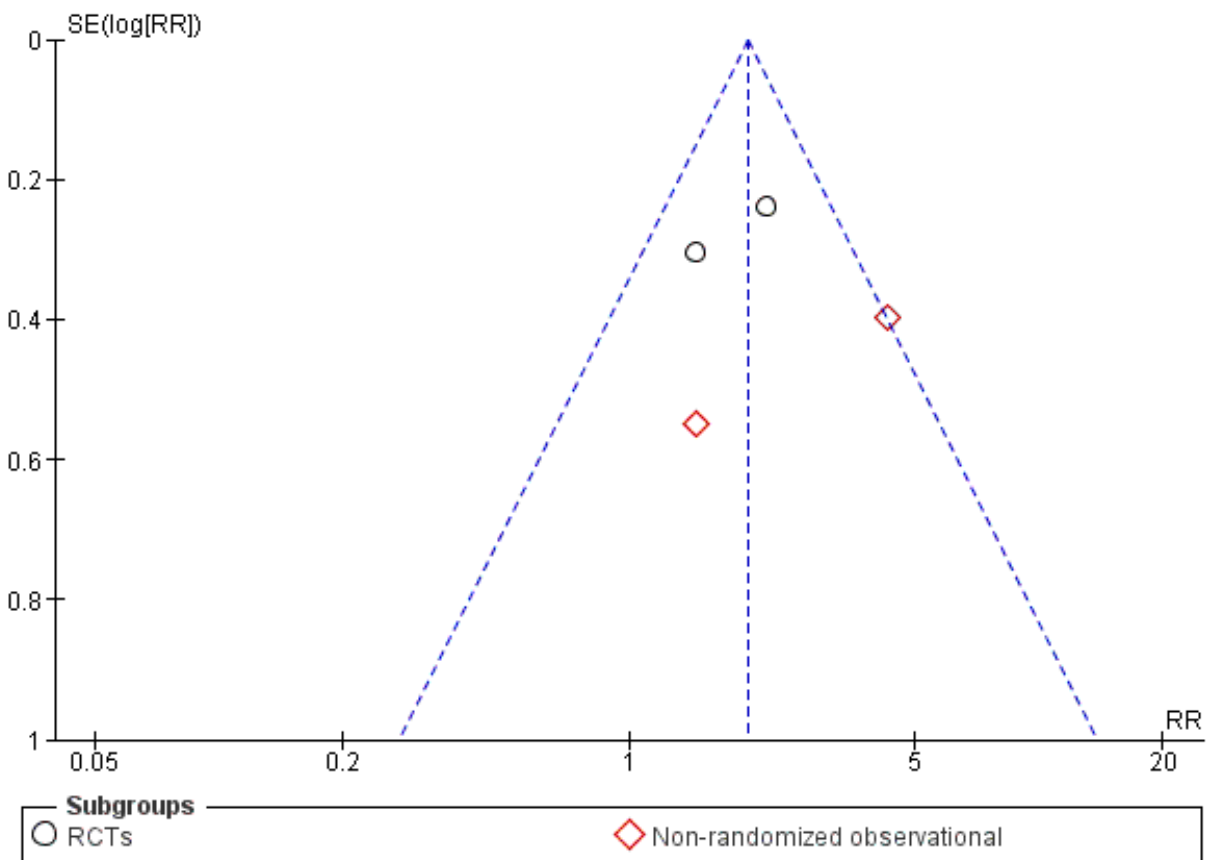
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1   Supplemental Figure I. Funnel plot for the comparative risk of bleeding with
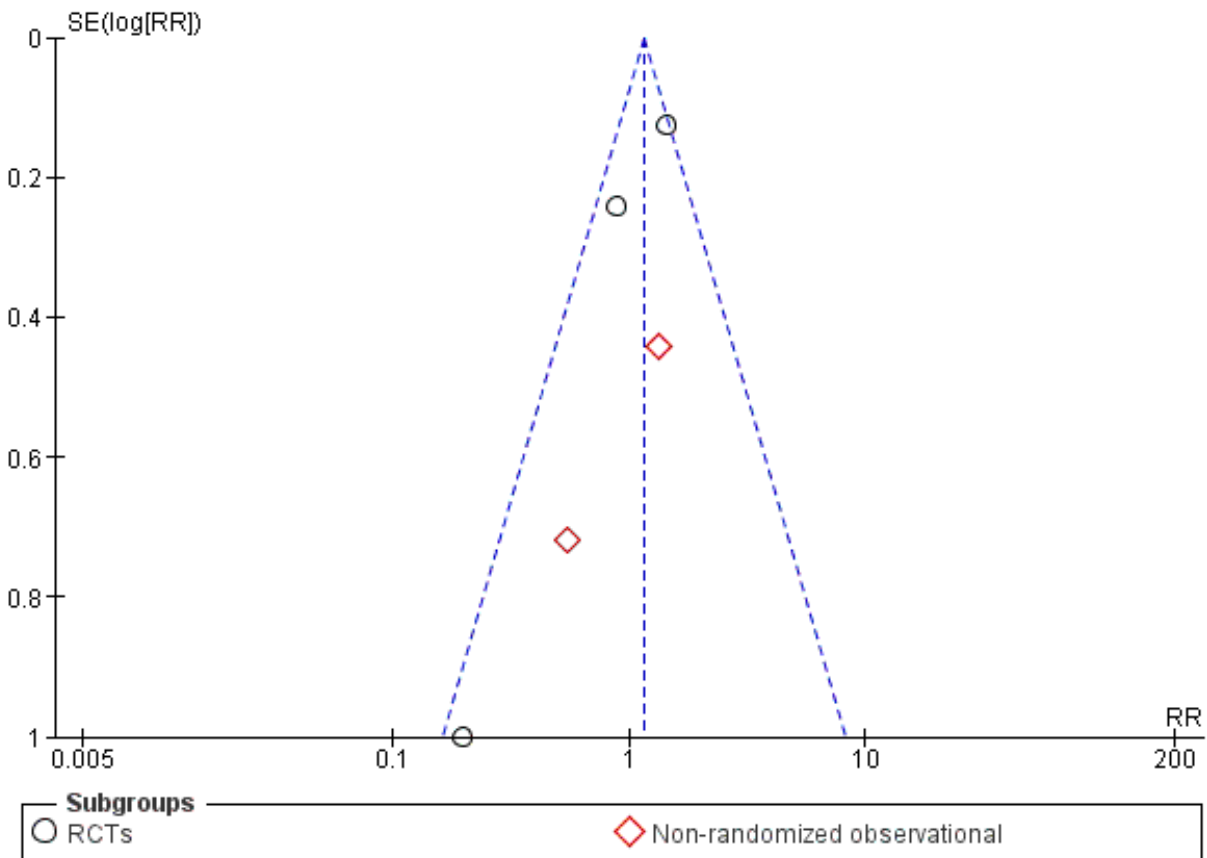2   ticagrelor versus clopidogrel in combination with oral anticoagulation
3

4
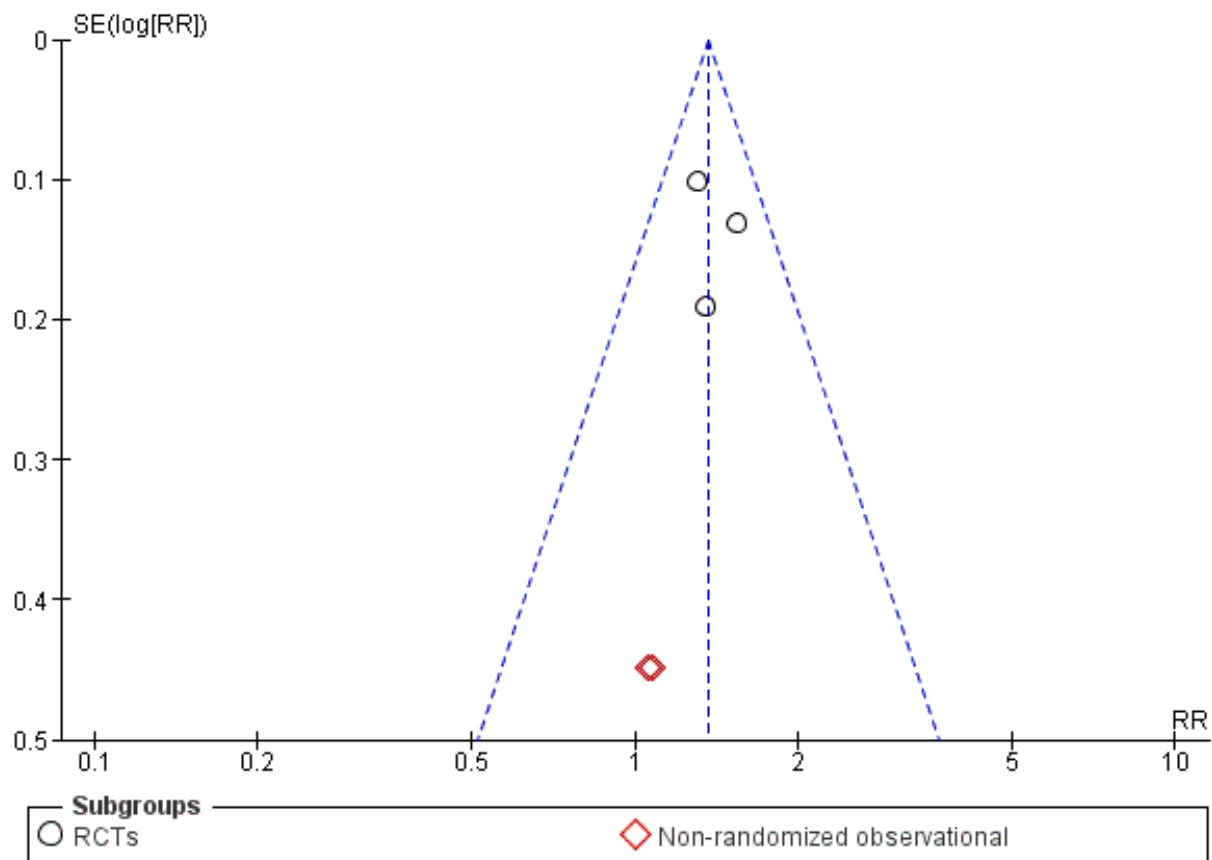
1   Supplemental Figure II. Funnel plot for the comparative risk of bleeding with
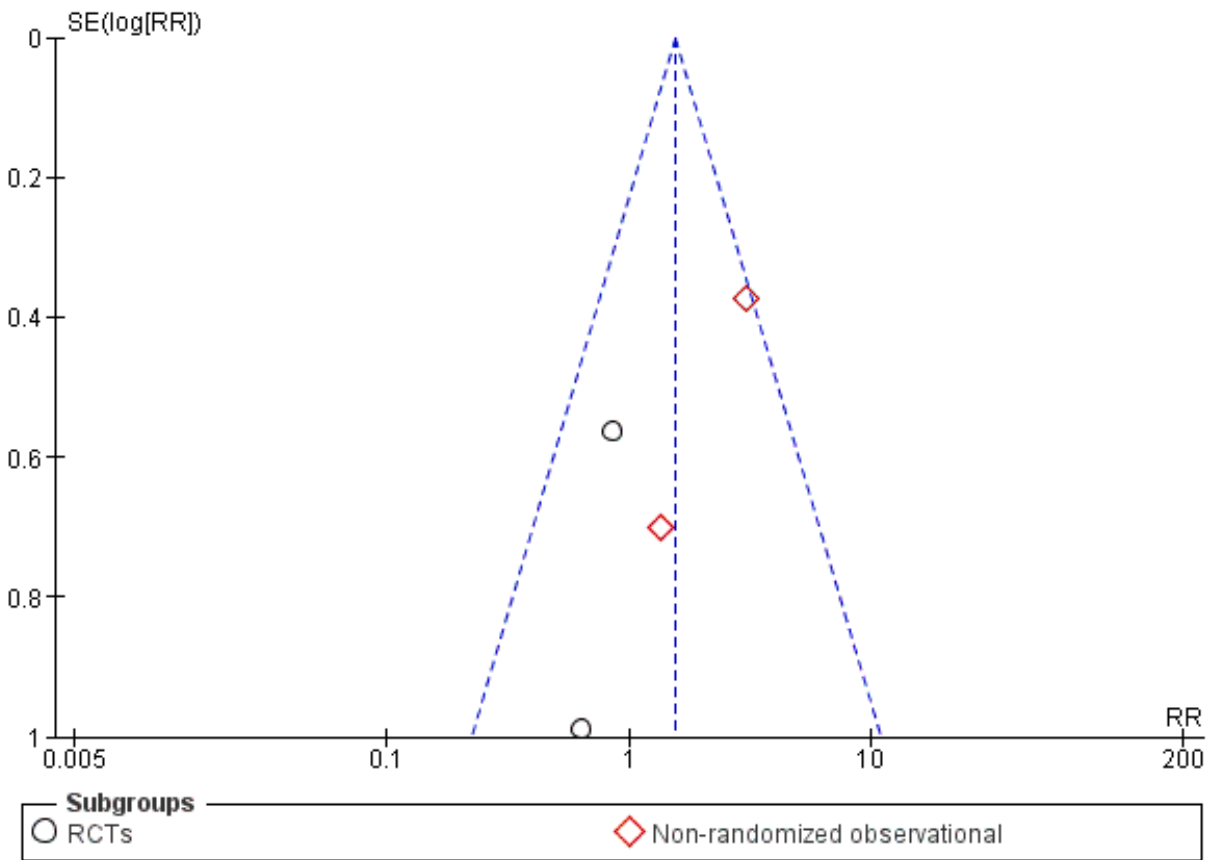2   prasugrel versus clopidogrel in combination with oral anticoagulation
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1 Supplemental Figure III. Funnel plot for the comparative risk of composite
2 major adverse cardiac events with ticagrelor versus clopidogrel in
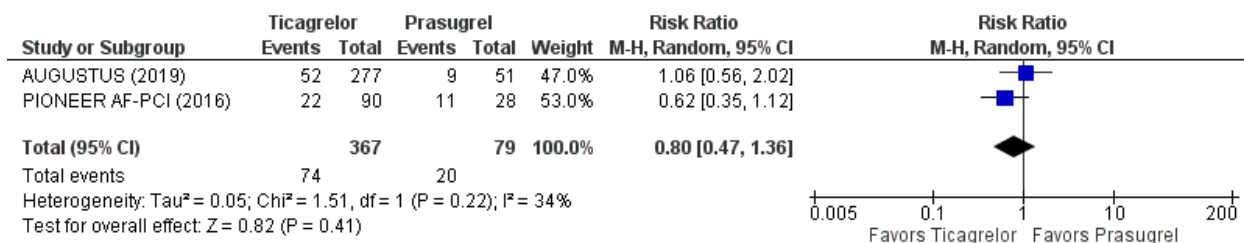3 combination with oral anticoagulation
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1   Supplemental Figure IV. Funnel plot for the comparative risk of composite
2   major adverse cardiac events with prasugrel versus clopidogrel in
3   combination with oral anticoagulation
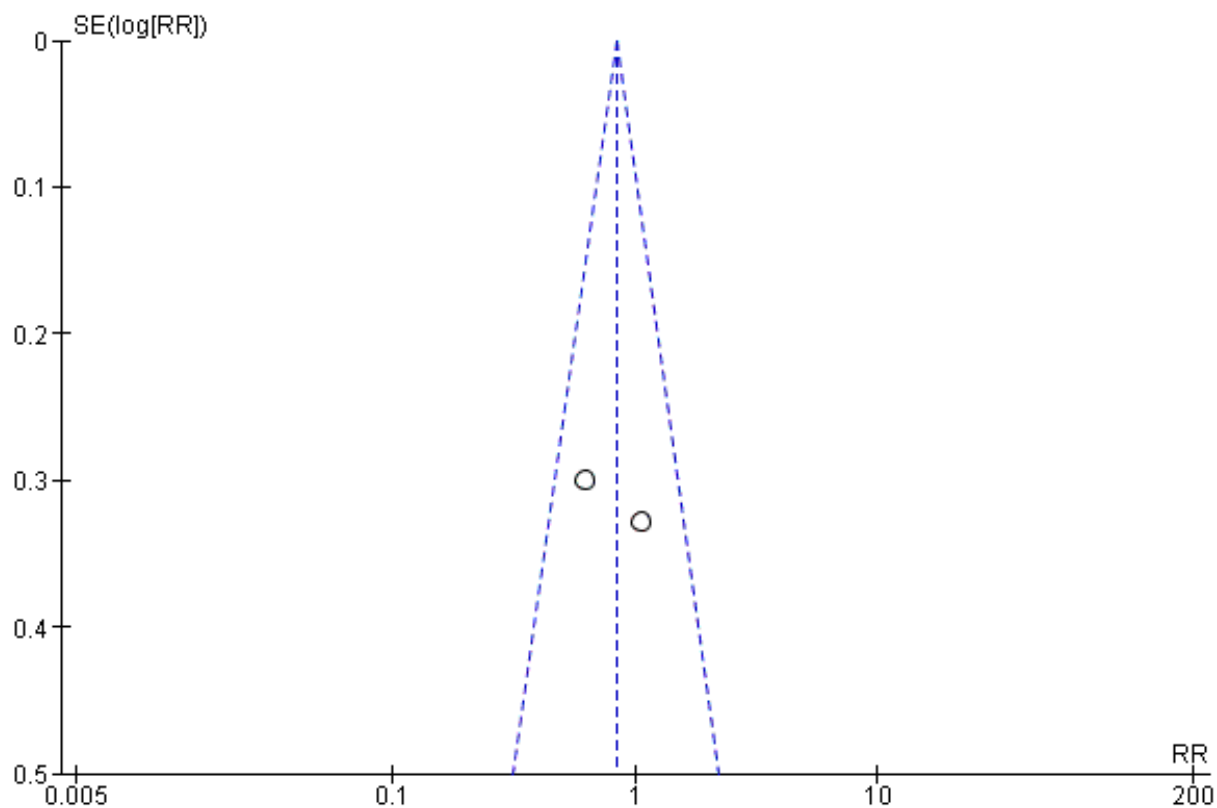4

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1   Supplemental Figure V a-b. Forest plot and funnel plot for the comparative
2   risk of bleeding with ticagrelor versus prasugrel in combination with oral
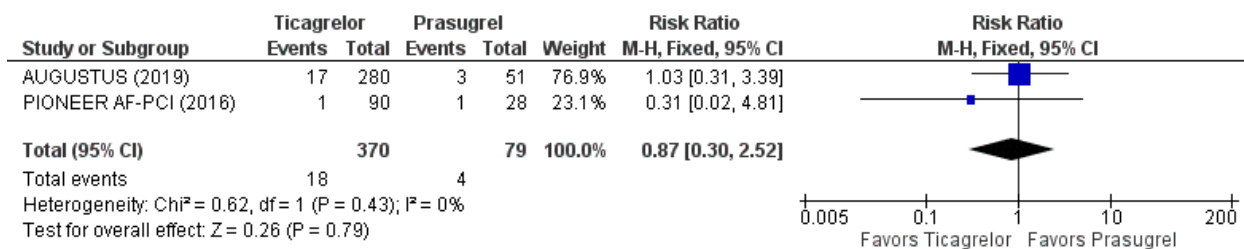3   anticoagulation
4

Study or Subgroup	Ticagrelor Events	Total	Prasugrel Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
AUGUSTUS (2019)	52	277	9	51	47.0%	1.06 [0.56, 2.02]
PIONEER AF-PCI (2016)	22	90	11	28	53.0%	0.62 [0.35, 1.12]
Total (95% CI)		367		79	100.0%	0.80 [0.47, 1.36]
Total events	74		20			

Heterogeneity: Tau² = 0.05; Chi² = 1.51, df = 1 (P = 0.22); I² = 34%
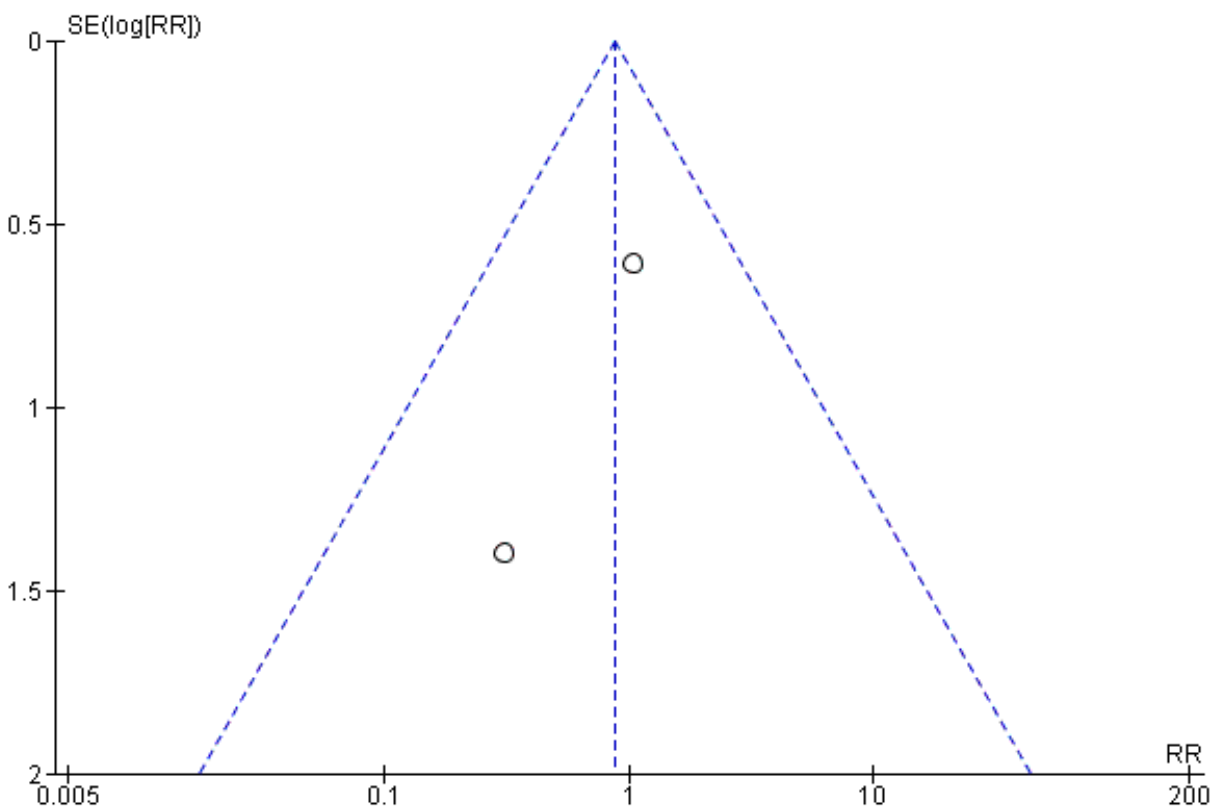Test for overall effect: Z = 0.82 (P = 0.41)

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1 Supplemental Figure VI a-b. Forest plot and funnel plot for the comparative
2 risk of composite major adverse cardiac events with ticagrelor versus
3 prasugrel in combination with oral anticoagulation
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