

Risk of bleeding with ticagrelor in elderly patients over 75 years old

A systematic review and meta-analysis

Shalan Alaamri, MD^a, Sultan Al Dalbhi, MD^{b,*} 

Abstract

Background: Bleeding is an untoward outcome in the management of elderly patients with acute coronary syndrome (ACS). Although the potent oral P2Y₁₂ inhibitor, ticagrelor is clinically beneficial, its association with bleeding events in elderly ACS patients (≥75 years) is poorly understood.

Methods: We conducted a systematic search of 7 databases up to May 20, 2020 to identify studies which examined the risk of bleeding (defined according to each study) among elderly ACS patients (≥75 years) receiving ticagrelor compared to clopidogrel. Summary risk ratios (RR) were estimated using the random effects model.

Results: Eight studies consisting of 5 observational studies and 3 randomized controlled trials involving 7032 elderly patients met the eligibility criteria. The mean age of the patients was 77.8 years, and the mean follow-up duration was 12 months. Overall, the pooled RRs showed higher risk of a bleeding event with ticagrelor compared to clopidogrel (RR 1.20, 95% confidence interval [95% CI] 1.03–1.40; $P = .017$). No statistically significant heterogeneity was observed among the studies ($Q = 6.93$; $P = .44$; $I^2 = 0$). Also, pooled RRs did not show a higher risk of major bleeding (RR 1.32, 95% CI 0.91–1.92; $P = .15$) or minor bleeding (RR 1.09, 95% CI 0.76–1.58; $P = .64$) when comparing the ticagrelor to the clopidogrel group.

Conclusions: There is a 20% increased risk of a bleeding event in elderly ACS patients treated with ticagrelor compared to clopidogrel; for such patients, clopidogrel may be considered as an alternative agent to ticagrelor due to its lower risk of bleeding.

Abbreviations: 95% CI = 95% confidence interval, ACC = American College of Cardiology, ACS = acute coronary syndrome, DAPT = dual anti-platelet therapy, HR = hazard ratio, OR = odds ratio, PCI = percutaneous coronary intervention, PLATO = Platelet Inhibition and Patient Outcomes, RCTs = randomized controlled trials, RR = rate ratio/risk ratio, STEMI = ST elevation myocardial infarction.

Keywords: acute coronary syndrome, bleeding, clopidogrel, dual anti-platelet therapy, elderly, ticagrelor

1. Introduction

Acute coronary syndrome (ACS) is a syndrome characterized by a reduction in blood flow in the coronary arteries.^[1] ACS is commonly classified into 3 clinical groups according to the

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pattern of their electrocardiogram: ST elevation myocardial infarction (STEMI), non-ST elevation myocardial infarction, or unstable angina.^[1] The pathophysiology of ACS is occlusion of the coronary arteries mediated by platelet aggregation. Thus, over the past 20 years, standard treatment for ACS involves oral dual anti-platelet therapy (DAPT) consisting of aspirin and a P2Y₁₂ receptor inhibitor irrespective of past management given or percutaneous coronary intervention (PCI).^[1–2] For individuals having ACS undertaking a PCI, early administration of a loading dose of DAPT is recommended as soon as possible or at the point of initiating the PCI.^[2–5]

The important clinical benefits of DAPT was first demonstrated in 2001 where it was shown that the administration of clopidogrel with aspirin was beneficial in preventing mortality and major adverse cardiovascular or cerebrovascular events in individuals with ACS.^[2] More recently, newer P2Y₁₂ inhibitors such as ticagrelor and prasugrel were shown to demonstrate superiority to clopidogrel in their clinical effects of preventing deaths and major adverse cardiovascular or cerebrovascular events in individuals with ACS.^[6–7] Recent guidelines by the European Society of Cardiology recommend DAPT involving ticagrelor or prasugrel with aspirin if there are no contraindications for patients with STEMI or non-ST elevation myocardial infarction.^[3–4] Similarly, the American College of Cardiology (ACC) have also replaced clopidogrel with ticagrelor or prasugrel in their guidelines of DAPT for the management of patients with STEMI.^[5] However, in the ACC guidelines,

prasugrel is contraindicated in individuals with ACS who have previous cerebrovascular events like stroke or transient ischemic attack. Both the guidelines of the European Society of Cardiology and ACC recommend the use of the P2Y12 blockers (ticagrelor and prasugrel) as Class 1 recommendation.^[3–5]

In the management of elderly patients (≥ 75 years), all the guidelines do not recommend the new-generation P2Y12 inhibitor prasugrel in place of clopidogrel because net clinical benefit could not be demonstrated for individuals belonging to this age group.^[7–8] Also, complications like bleeding events were higher in the prasugrel group.^[7] Ticagrelor, however, has been shown to be effective as part of DAPT regardless of age.^[9] In the sub-group analysis of the Platelet Inhibition and Patient Outcomes (PLATO) trial, the net clinical benefit of ticagrelor remained irrespective of age.^[9] This led to the current expert position for the management of elderly patients having ACS with ticagrelor.^[10] Elderly individuals (≥ 75 years) constitute a substantial percentage of patients with ACS.^[11] Also, risk scores analysis for the recurrence of ischemic events is 3 times higher for ACS patients who are over 80 years old compared to those who are 60 years old, and the risk of deaths or major bleeding events rises with age in patients with ACS.^[11–14] However, previous randomized controlled trials (RCTs) on the efficacy and safety of ticagrelor and prasugrel had marked underrepresentation of the elderly (≥ 75 years) – with these patients constituting less than 15% of the study population.^[11]

Although current expert position recommended that ticagrelor should be used as part of the DAPT for the management of elderly (≥ 75 years) ACS patients,^[9,11] the risk of bleeding in this group of patients following treatment with ticagrelor is poorly understood. A previous systematic review and meta-analysis on the safety of potent platelet P2Y12 receptor inhibitors in elderly versus non-elderly patients with ACS found only 1 study where ticagrelor was administered to elderly patients ≥ 75 years old.^[15] With recent literature published in this area, this systematic review and meta-analysis set out to summarize the state of the evidence on the risk of bleeding with ticagrelor in elderly patients 75 years old or over.

2. Methods

The development of this review followed the Preferred Reporting Items for Systematic reviews and Meta-Analyses statement, and the Meta-analysis Of Observational Studies in Epidemiology guidelines.^[16–17]

2.1. Search strategy

A systematic electronic search of the following databases was carried out independently by 2 reviewers (SA and SA) up to May 20, 2020 using EMBASE, PubMed/MEDLINE, SCOPUS, The Cochrane Library, ProQuest, Google Scholar databases, and AJOL. The following broad search terms were used alone and in combination: (“ticagrelor” OR “AZD6140”) AND (“acute coronary syndrome” OR “myocardial infarction” OR “non-ST-elevation myocardial infarction” OR “unstable angina” OR “non-ST-elevation acute coronary syndrome”) AND (elderly OR age). Medical Subject Heading terms were also utilized during the search. The bibliography of relevant studies and published reviews were further searched for potentially relevant articles.

2.2. Eligibility criteria

Both observational studies or RCTs were eligible for inclusion. The inclusion criteria include: the study population included elderly ACS patients with age or mean age (≥ 75 years); the study compared ticagrelor versus clopidogrel or reported on ticagrelor alone; and the study reported data on bleeding as safety endpoint and this was available as binary data and/or hazard ratio (HR). No language restrictions were applied.

2.3. Quality

The quality of the included studies was assessed by 2 of the investigators (SA and SA). Quality assessment for observational studies was performed using the Newcastle-Ottawa Quality Assessment Scale,^[18] while quality assessment for RCTs was performed using the Jadad scale.^[19]

2.4. Data extraction

Data extraction from the selected study was conducted independently by 2 investigators using a standardized form. Any discrepancies between the 2 investigators was resolved by review and consensus. The following data were retrieved from the studies: first author, publication year, country of study, study period, study design, total number of patients, indications, medication dose, follow-up duration, and bleeding events (defined according to each study).

2.5. Statistical analysis

Summary data for bleeding events were estimated using adjusted or estimated effect measures (odds ratio [OR] or HR) reported in each study and their 95% confidence interval (95% CI). To summarize the overall treatment effect, HRs and ORs were assumed to approximate the same measure of risk ratios (RR).^[20] All RR were reported as the risk associated with ticagrelor compared to clopidogrel. Cochrane Q and I^2 statistics were utilized to assess the heterogeneity of the studies, heterogeneity of the data was significant if $P < .1$ for the Q statistic or if $I^2 > 50\%$.^[26] All meta-analyses were performed using the random-effects model.

Publication bias was assessed through visual inspection of the funnel plot, Duval and Tweedie trim and fill and Egger regression test. Where possible, outcomes were stratified according to study type in order to lower the risk of bias, with separate analyses for RCTs and observational studies. The chi-squared test was used to assess differences between subgroups. A P value less than .05 was considered to meet statistical significance. Comprehensive Meta-Analysis (version 3.0; Biostat, NJ) was used for the meta-analysis.

3. Results

The electronic search identified 918 studies which reduced to 567 after duplicates were excluded. Following systematic screening of the titles of the publications, 53 studies were selected for full-text evaluation. Eight studies consisting of 7032 elderly patients (≥ 75 years) met the eligibility criteria.^[9,22–28] The Preferred Reporting Items for Systematic reviews and Meta-Analyses flow diagram of the study selection for the meta-analysis is shown in Figure 1. The included studies consist of 5 observational studies and 3 RCTs. All the patients had ACS. The mean age of the patients was 77.8 years, and the mean follow-up duration indicated in the studies

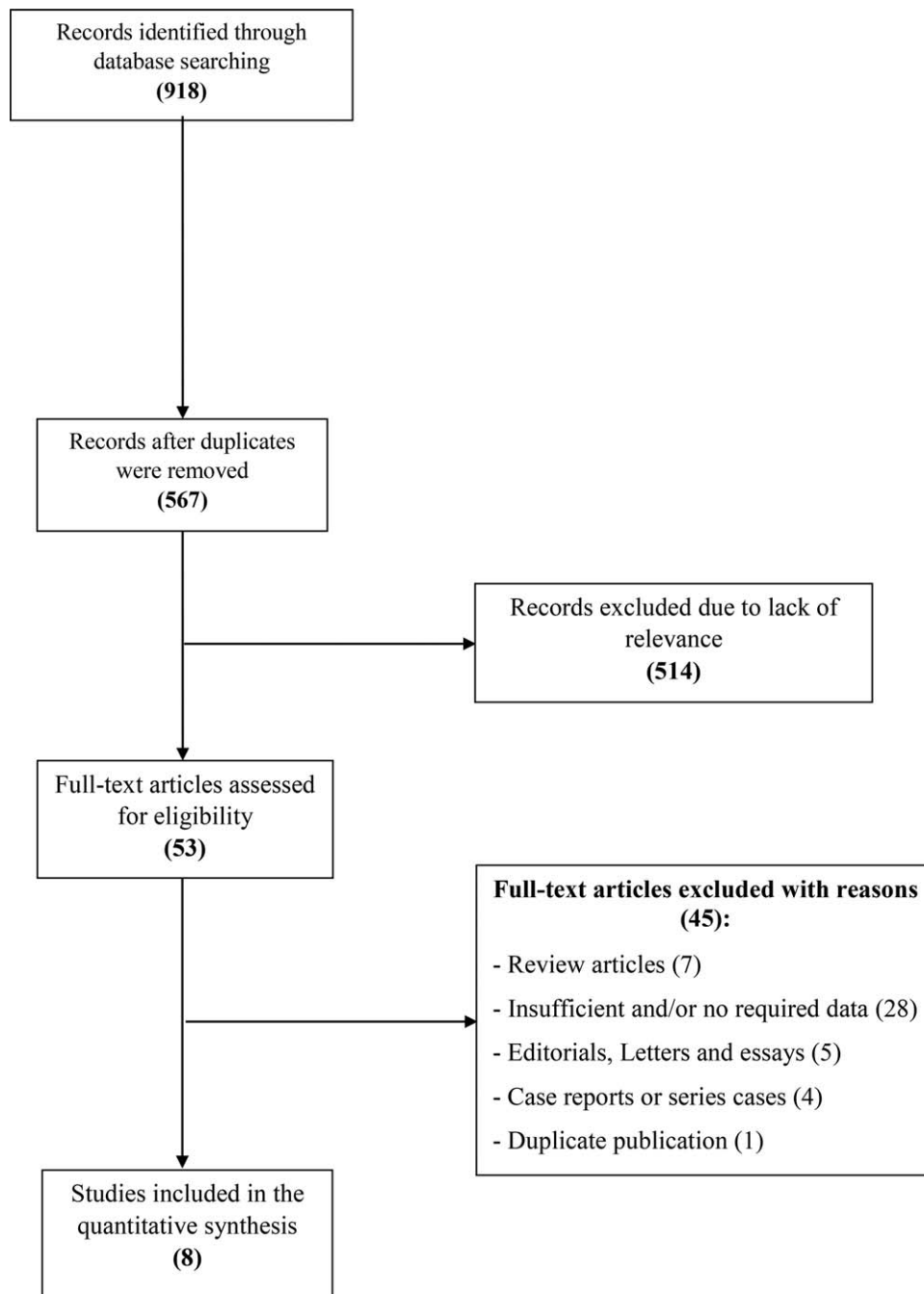


Figure 1. PRIMA flow diagram of study selection for the meta-analysis.

was 12 months. All the observational studies had moderate to high quality with a Newcastle-Ottawa Quality Assessment Scale score of 5 to 9; while all the RCTs are of high quality. The summary characteristics of the studies included in the review are as shown in Table 1.

3.1. Risk of any bleeding with ticagrelor

Figure 2 summarizes the meta-analysis on the risk of any bleeding events in elderly patients administered with ticagrelor compared to clopidogrel. Overall, the pooled RRs showed higher risk of a

bleeding event when comparing ticagrelor to the clopidogrel group (RR 1.20, 95% CI 1.03–1.40; $P=.017$). No statistically significant heterogeneity was observed among the studies ($Q=6.93$; $P=.44$; $I^2=0$). However, when the data were disaggregated according to study design (Table 2), there was no statistically significant difference in the risk of a bleeding event in the ticagrelor compared to clopidogrel group; RCTs (RR 1.17, 95% CI 0.98–1.41; $P=.08$) and observational studies (RR 1.38, 95% CI 0.96–1.98; $P=.09$), with no significant interaction ($P_{int}=.56$). Similarly, when the data were disaggregated according to region, there was no statistically significant difference in the risk of a

Table 1
Studies included in the systematic review and meta-analysis.

Name/author (year)	Country	Study design	N	Age grp Mean/median*	Indications	Ticagrelor, LD/MD (mg)	Clopidogrel, LD/MD (mg)	Follow-up (months)	Bleeding definition
Gimbel (2020)	Netherlands	RCT	1002	77*	NSTE-ACS	180/90	300 or 600/75	12	PLATO
Zocca (2018)	Netherlands	Obs	547	75.8	ACS	N/A	N/A	12	TIMI, BARC, CABG
Zhao (2020)	China	Obs	771	≥75	ACS-STEMI	/90	/75	N/A	Not stated
Wang (2016)	China	RCT	200	79*	ACS	180/90	300/75	12	PLATO
Schmucker (2019)	Germany	Obs	1087	81	STEMI	N/A	N/A	12	TIMI
Husted (2012)	Multicenter	RCT	2878	≥75	ACS	180/90	300/75	12	PLATO, TIMI, GUSTO
Liu (2019)	China	Obs	246	84.6	ACS	180/90	N/A	12	N/A
Fan (2017)	UK	Obs	301	≥75	ACS	N/A	N/A	12	Crusade score

ACS = acute coronary syndrome, BARC = Bleeding Academic Research Consortium, CABG = coronary artery bypass graft, GUSTO = Global Utilization of Streptokinase and Tpa For Occluded Arteries, LD = loading dose, MD = maintenance dose, NSTE-ACS = non-ST elevation acute coronary syndrome, Obs = observational study, PLATO = Platelet Inhibition and Patient Outcomes, RCT = randomized controlled trial, STEMI = ST-elevation myocardial infarction, TIMI = Thrombolysis in Myocardial Infarction, UK = United Kingdom.

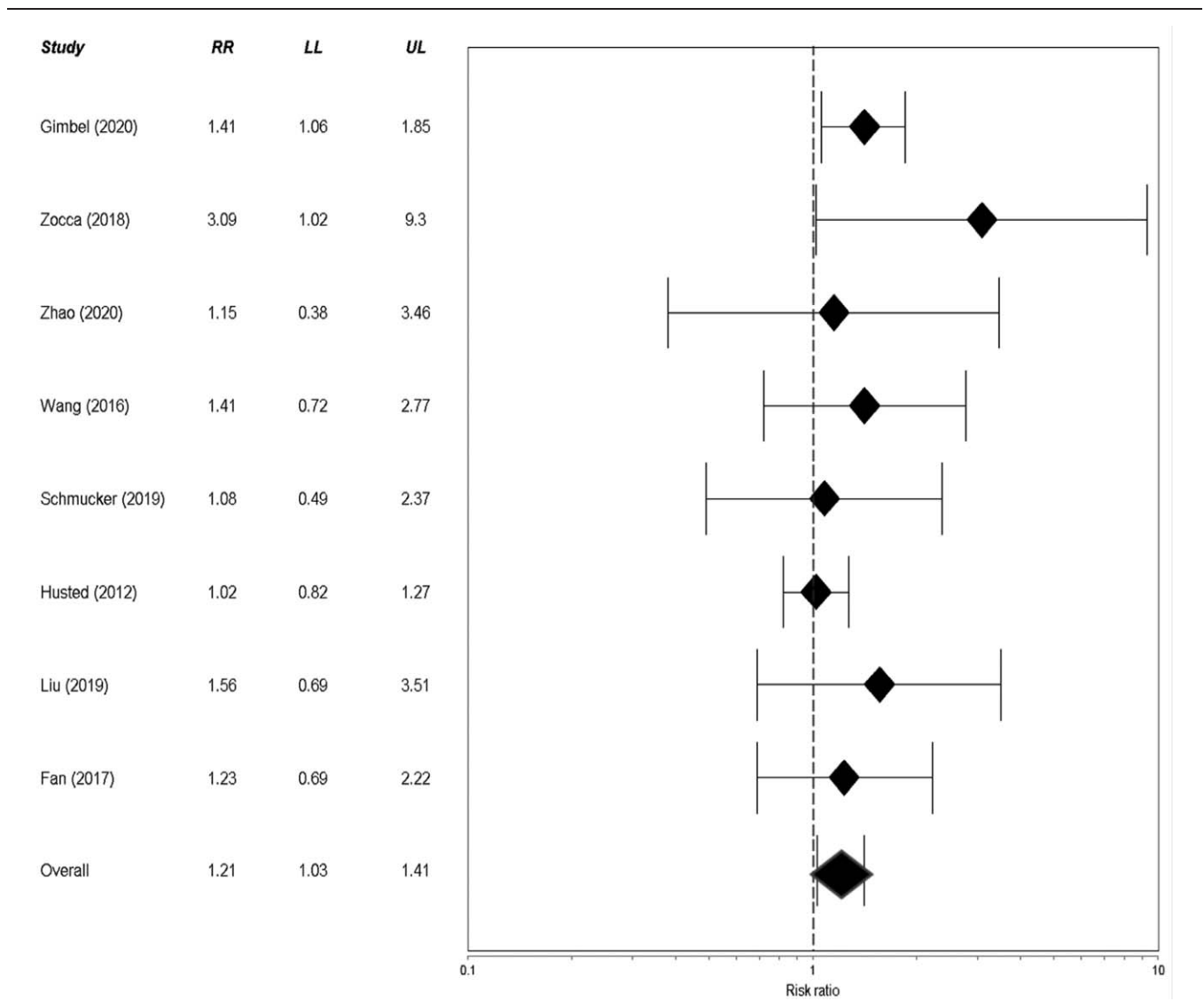


Figure 2. Forest plot of the meta-analysis on the risk of any bleeding event in elderly patients administered with ticagrelor compared to clopidogrel.

Table 2

Pooled risk ratios of bleeding in patients exposed to ticagrelor.

Variable	RR (95% CI)	P value	Number of studies	Heterogeneity (I ²) P value
Any bleeding		.56		
Observational	1.38 (0.96–1.98)	.09	5	(0) .60
RCT	1.17 (0.98–1.41)	.08	3	(43.5%) .17
Region		.53		
Asia	1.41 (0.87–2.26)	.16	3	(0) .91
Europe	1.20 (0.99–1.43)	.05	5	(36.1%) .18
Major bleeding		.21		
Observational	1.74 (0.99–3.05)	.05	4	(35.0%) .20
RCT	1.16 (0.85–1.58)	.36	3	(0) .39
Minor bleeding	1.09 (0.76–1.58)	.64	5	(35.4%) .19

95% CI=95% confidence interval, RCT = randomized controlled trial, RR=risk ratio.

bleeding event in the ticagrelor compared to clopidogrel group; Asia (RR 1.41, 95% CI 0.87–2.26; *P* = .16) and Europe (RR 1.20, 95% CI 0.99–1.43; *P* = .05), with no significant interaction (*P*_{int} = .53).

3.2. Risk of major and minor bleeding with ticagrelor

Figure 3 summarizes the meta-analysis on the risk of major bleeding in elderly patients administered with ticagrelor compared to clopidogrel. Overall, the pooled RRs did not show

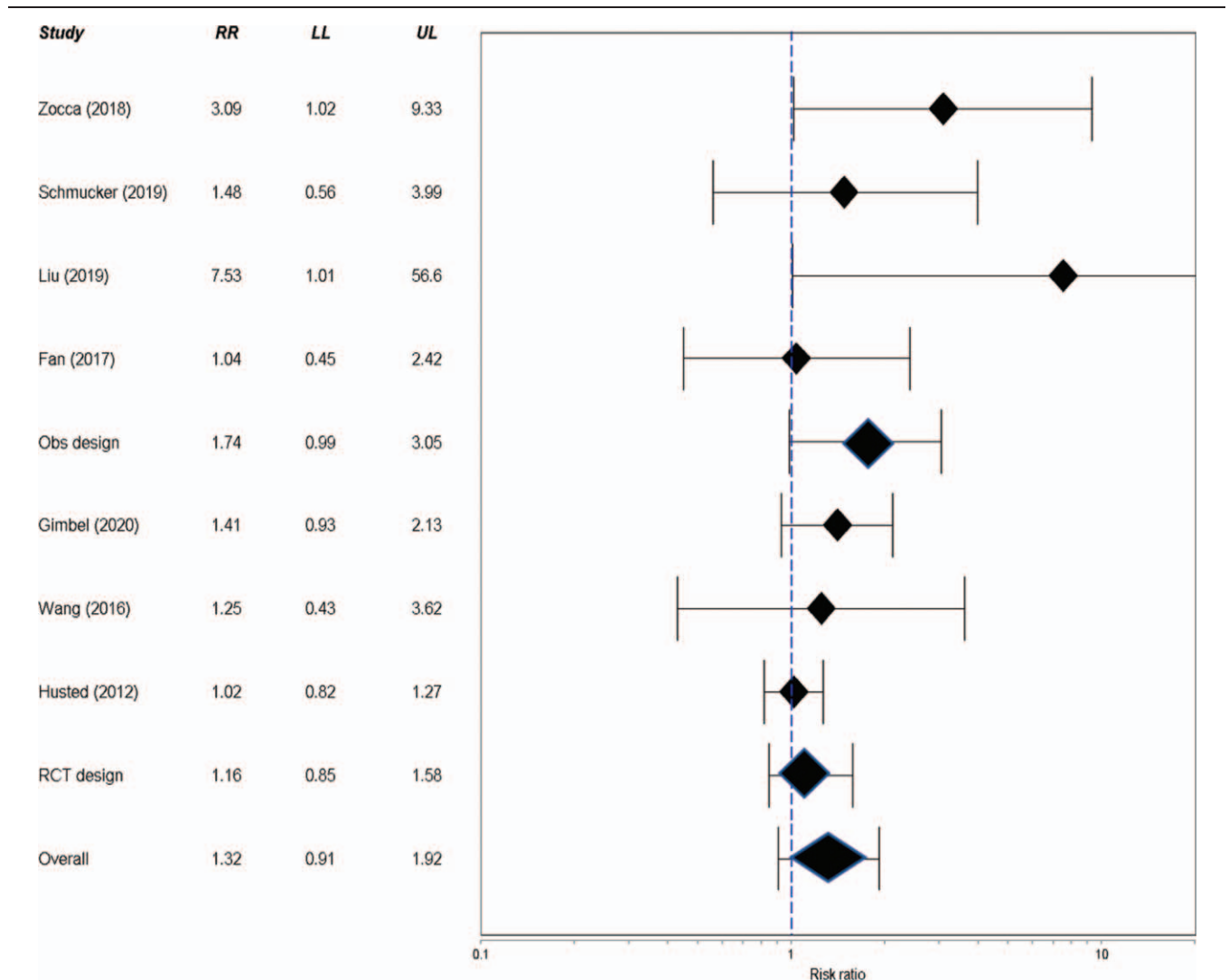


Figure 3. Forest plot of the meta-analysis on the risk of major bleeding in elderly patients (≥75 years) administered with ticagrelor compared to clopidogrel.

a higher risk of major bleeding when comparing ticagrelor to the clopidogrel group (RR 1.32, 95% CI 0.91–1.92; $P=.15$). No statistically significant heterogeneity was observed among the studies ($Q=8.82$; $P=.18$; $I^2=32.0\%$). Also, when the data were disaggregated according to study design (Table 2), there was no statistically significant difference in the risk of major bleeding in the ticagrelor compared to clopidogrel group; RCTs (RR 1.16, 95% CI 0.85–1.58; $P=.36$) and observational studies (RR 1.74, 95% CI 0.99–3.05; $P=.054$), with no significant interaction ($P_{\text{int}}=.21$). Furthermore, pooled RRs did not show a statistically significant difference in the risk of minor bleeding when comparing ticagrelor to the clopidogrel group (RR 1.09, 95% CI 0.76–1.58; $P=.64$).

3.3. Publication bias

Visual inspection of the funnel plot of studies examining the risk of any bleeding event in elderly patients receiving ticagrelor showed asymmetry between the observed and expected number of studies indicating that there may be publication bias (Fig. 4). Duval and Tweedie trim and fill showed that there may be 3 missing studies to the left of the mean of the funnel plot. Egger regression test showed an (Egger test $P=.04$).

4. Discussion

This is the largest meta-analysis currently available that assessed the effect of ticagrelor compared to clopidogrel in elderly patients (≥ 75 years old) with ACS. The analysis found that overall there was a 20% increase in the risk of a bleeding event with ticagrelor. However, the study found no significant differences in the risk of

a bleeding event in individuals treated with ticagrelor compared to clopidogrel according to their study design. Also, the occurrence of a bleeding events in patients exposed to ticagrelor did not significantly differ according to their region. Third, the meta-analysis found no statistically significant difference in the risk of a major bleeding in patients exposed to ticagrelor compared to clopidogrel. Similarly, no significant differences existed in the risk of minor bleeding in the patients exposed to these medications.

DAPT involving clopidogrel and aspirin was an important measure for the prevention of recurrent thrombotic events in patients with ACS over 2 decades ago.^[29] In the last decade, newer P2Y12 inhibitors such as ticagrelor and prasugrel are being recommended to replace clopidogrel unless in situations where there is an excessive risk of bleeding.^[29] With increasing age in the very elderly, there is increased risk of recurrent thrombotic events and bleeding tendencies compared with younger patients, making it difficult to consider the stronger P2Y12 inhibitors such as ticagrelor and prasugrel as optimal anti-thrombotic agents.^[11–14] Although the PLATO trial found that the effectiveness of ticagrelor was not age dependent, DAPT containing ticagrelor for ACS patients reportedly had higher risk of bleeding including fatal bleeding across all age groups.^[9] In this meta-analysis, we found that compared to clopidogrel, ticagrelor was associated with a 20% higher risk of a bleeding event in the elderly who are 75 years old or over. This suggest that in older patients (≥ 75 years) with ACS the need for a stronger anti-thrombotic effect using ticagrelor may need to be balanced by significant risk of the occurrence of a bleeding event. This is because previous studies have shown that such bleeding events (even if minimal nuisance bleeds) may lead to the stoppage of the

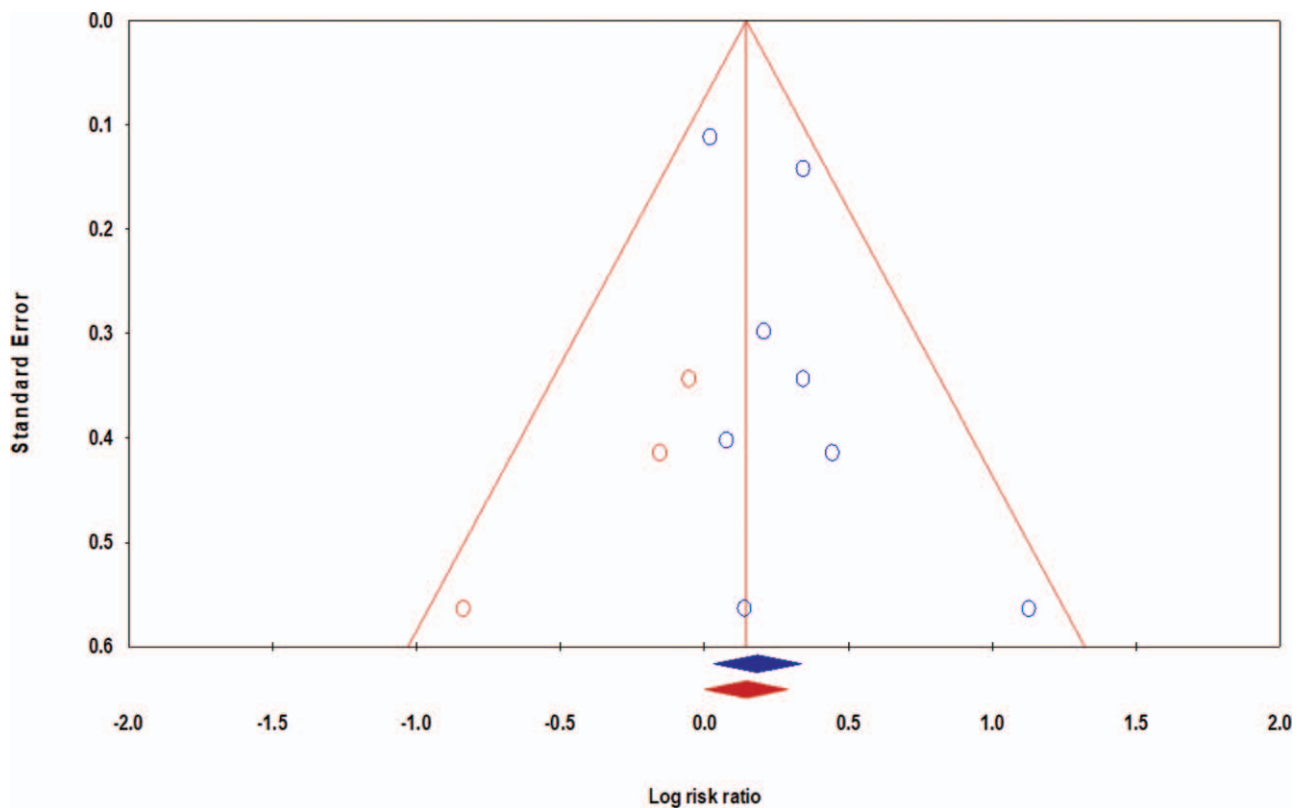


Figure 4. Funnel plot analysis of the meta-analysis on the risk of any bleeding event in elderly patients administered with ticagrelor compared to clopidogrel.

anti-platelet agent, which further increases the likelihood of thrombotic events and mortality in the patients.^[30–32]

Furthermore, our analysis found no significant differences in bleeding events in the ticagrelor group according to study design. Also, although the pooled RRs according to each study design for bleeding events did not reach statistical significance, it probably indicates the inadequacy of the number of studies from each design included in the meta-analysis. Similarly, we found no significant differences in bleeding events among elderly ACS patients in the ticagrelor compared to the clopidogrel in patients from Europe compared to Asia (China). A previous meta-analysis has found that ticagrelor was significantly associated with a 73% increased risk each of major and minor bleeding in younger Asian patients with ACS.^[33] Also, another meta-analysis showed that in young East Asian patients with ACS, ticagrelor was associated with a 52% higher risk of PLATO-defined major bleeding compared to clopidogrel.^[34] The differences in the response to ticagrelor between Asian and non-Asians have been proposed to be due to differences in body mass index, genetic polymorphisms, variations in the pattern of ACS as well as comorbidities.^[35] There is a need for future studies to delineate whether these racial differences between ticagrelor and clopidogrel exists in the elderly.

In this study, we found no statistically significant difference in the risk of a major or minor bleeding in patients exposed to ticagrelor compared to clopidogrel. This was consistent with the findings of a previous meta-analysis in younger patients which showed that major and minor bleeding events did not differ with either ticagrelor or clopidogrel.^[36] However, this finding needs to be interpreted with caution. All the various studies included in this review had varying definitions for major and minor bleeding. Our analysis agrees with the findings of the PLATO trial, and the recently published POPular AGE study that found no significant difference between ticagrelor and clopidogrel for PLATO major bleeding ($P=.11$) and PLATO minor bleeding ($P=.09$).^[6,9,22] However, using other methods for classifying bleeding like Thrombolysis in Myocardial Infarction score and Bleeding Academic Research Consortium in the POPular AGE study, some of the bleeding classes differed significantly between the ticagrelor and clopidogrel group.^[22] These findings further highlight the challenges in properly classifying clinically relevant bleeding in patients with ACS. Future studies should consider exploring elderly patients who had non-coronary artery bypass graft-related bleeding to see if this group could better help in classifying clinically-relevant bleeding in elderly patients with ACS receiving anti-platelet therapy.^[37]

This study has some limitations. Both observational studies and RCTs included in this meta-analysis differed somewhat according to their design, eligibility and exclusion criteria, and some of their study endpoints. However, our analysis did not find substantial heterogeneity between the studies for the endpoint assessed. Second, the dosage and drug type varied potentially causing heterogeneity in the studies. Third, some studies reported effect measures as HRs while others as ORs; as previously recommended,^[30] we assumed these ratios to approximate the RR – potentially introducing some imprecision. Fourth, our analysis had evidence of publication bias, our findings therefore need to be cautiously interpreted. Despite these limitations, the results of this meta-analysis are very crucial for clinical care and policy.

In conclusion, this meta-analysis suggests that there is a 20% increased risk of a bleeding event in elderly ACS patients treated

with ticagrelor compared to clopidogrel; and the analysis found no statistically significant difference in the risk of major or minor bleeding in elderly ACS patients exposed to ticagrelor compared to clopidogrel. This finding is reassuring considering the increasing use of stronger P2Y12 inhibitors like ticagrelor for elderly patients with ACS. Our data imply that for older patients (≥ 75 years) with ACS the need for a stronger anti-platelet effect with ticagrelor need to be balanced against the risk of encountering a bleeding event. In such cases, clopidogrel may be considered as an alternative agent to ticagrelor due to its lower risk of bleeding.

Author contributions

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Supervision: Sultan Al Dalbhi.

Validation: Sultan Al Dalbhi.

Visualization: Sultan Al Dalbhi.

Writing – original draft: Shalan Alaamri.

Writing – review & editing: Shalan Alaamri.

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