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Cardiovascular and Bleeding Events of Ticagrelor Monotherapy after Short-term Dual Antiplatelet Therapy (DAPT) in Diabetics and Non-Diabetics Patients Undergoing Percutaneous Coronary Intervention: A Systematic Review and Meta-Analysis

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Original Article

Abstract

INTRODUCTION: Ticagrelor monotherapy after short-term (1-3 months) dual antiplatelet therapy (DAPT) with aspirin and ticagrelor can reduce bleeding without increasing ischemic events after percutaneous coronary intervention (PCI). However, its effect in diabetic and non-diabetic individuals has not been evaluated as a meta-analysis so far.

METHOD: This systematic review and meta-analysis were conducted covering PubMed, ISI Web of Science, and Scopus without date restrictions for English published clinical trials. The authors searched the mentioned databases, wherein the screening led to 151 studies, of which 40 were assessed for eligibility, and finally, three studies were included. These trials compared ticagrelor monotherapy after a short duration of aspirin plus ticagrelor with conventional 12 months DAPT.

RESULTS: The results showed that the risk of major bleeding (based on Bleeding Academic Research Consortium (BARC) type 3 or 5) for ticagrelor monotherapy subjects was lower in both diabetics and non-diabetics. It was especially significant in non-diabetic patients (HR 95%CI: 0.79(0.64, 0.98); p=0.029). In cardiovascular events assessment, the pooled estimate on cardiac deaths was significantly lower in diabetic subjects treated by ticagrelor monotherapy (HR 95%CI: 0.71(0.51, 1); p=0.05), while this reduction was not significant for non-diabetics (p=0.843) in comparison to patients treated by 12 months DAPT. However, there was no significant decrease or rise in myocardial infarction (MI) and ischemic stroke in patients treated by short-term DAPT strategy.

CONCLUSION: In conclusion, discontinuing aspirin after short-duration DAPT could minimize the incidence of cardiac death and BARC type 3 or 5 bleeding in diabetic and non-diabetic patients who underwent PCI, with no increase in MI and ischemic stroke.

Keywords: Ticagrelor, Dual Antiplatelet Therapy, Cardiac Death, Diabetics, Bleeding, Percutaneous Coronary Intervention

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Introduction

Aspirin is the cornerstone of treatment for coronary heart disease [1]. However, despite treatment with aspirin, high recurrent ischemic events led to the discovery of adjuvant antithrombotic drugs, especially in high-risk patients. The need for oral P2Y12 inhibitors has been demonstrated in patients with acute coronary syndrome (ACS) undergoing Percutaneous Coronary Intervention (PCI) and stent implantation. Thus, combination therapy of aspirin with P2Y12 receptor inhibitors was used as a gold standard to treat patients undergoing coronary stent treatment, referred to as Dual Anti Platelet Therapy (DAPT) [2, 3]. Due to the increased risk of bleeding in these treatments, various strategies have been proposed to reduce these complications while maintaining effective efficacy [4]. Aspirin discontinuation was investigated for this purpose. The hypothesis is that a strong blockade of P2Y12 receptors in the platelet activity pathway would suggest that aspirin would be minimally involved while reducing bleeding complications [5, 6].

Clopidogrel is commonly used as an inhibitor of P2Y12, and despite evidence of its efficacy, some studies have shown inadequate antiplatelet activity and an increased risk of stent thrombosis [4, 6]. This has led to the development of P2Y12 inhibitors such as ticagrelor, which is clearly more potent and has more reliable antiplatelet effects. In fact, compared to clopidogrel, ticagrelor significantly reduces recurrent ischemic events in ACS patients, including stent thrombosis [2]. The use of aspirin-free strategies following PCI was tried in patients with atrial fibrillation (AF) who underwent PCI and needed anticoagulant therapy, and these studies showed that aspirin should be discontinued as soon as possible and continued with dual antithrombotic therapy [2, 7, 8]. Dual antithrombotic therapy (mostly with clopidogrel and oral anticoagulants) significantly reduces bleeding without reducing effectiveness, and it is an approved treatment strategy in AF patients that underwent PCI [8-10].

Aspirin has been shown to have limited pharmacodynamics effects in-vitro on the effective blockade of the P2Y12 receptor [5]. The clear link between aspirin and bleeding (especially gastrointestinal) suggests that gradual discontinuation of aspirin after the high-risk thrombotic phase (1-3 months after PCI) may reduce the risk of bleeding complications without reducing its effectiveness [11]. Diabetes was found to be an independent predictor of major adverse cardiac events, cardiac death, and myocardial infarction (MI) after PCI in pooled randomized trials [12]. Diabetic patients with ACS had a higher bleeding risk compared to non-diabetic in both the ticagrelor and clopidogrel groups in the Platelet Inhibition and Patient Outcomes (PLATO) study [13]. To date, no meta-analysis has been performed on the effect of monotherapy with ticagrelor after a brief period of dual antiplatelet therapy treatment in terms of side effects and efficacy in diabetic cardiovascular patients and its comparison with non-diabetic undergoing PCI. To the best of the authors' knowledge, this study is the first in this regard.

Materials and Methods

Search and study design

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (PRISMA) was used to design this systematic search. The search was conducted using the PubMed, ISI Web of Science, and Scopus databases with no date restrictions. The search was carried out with the help of related keywords and MeSH terms including [("ticagrelor" OR "DAPT" OR "short duration DAPT") AND ("cardiovascular disease" OR ("cardiovascular diseases" OR "percutaneous coronary intervention" OR "PCI"))]. To combine different concepts and similar concepts, the authors used the "AND" and "OR" Boolean Operators respectively. Only English studies were considered. Figure 1 shows the study selection process for this study.

PICO

The PICO was: diabetic and non-diabetic individuals with cardiovascular disease as intervention and control groups respectively un-

derwent Percutaneous Cardiac Intervention (PCI)/monotherapy with ticagrelor after a brief period of dual antiplatelet therapy (aspirin and ticagrelor)/comparison between diabetic and non-diabetic participants/Bleeding Academic Research Consortium (BARC) type 3 or 5 bleeding, cardiovascular related death, myocardial infraction (MI) and ischemic stroke incidence.

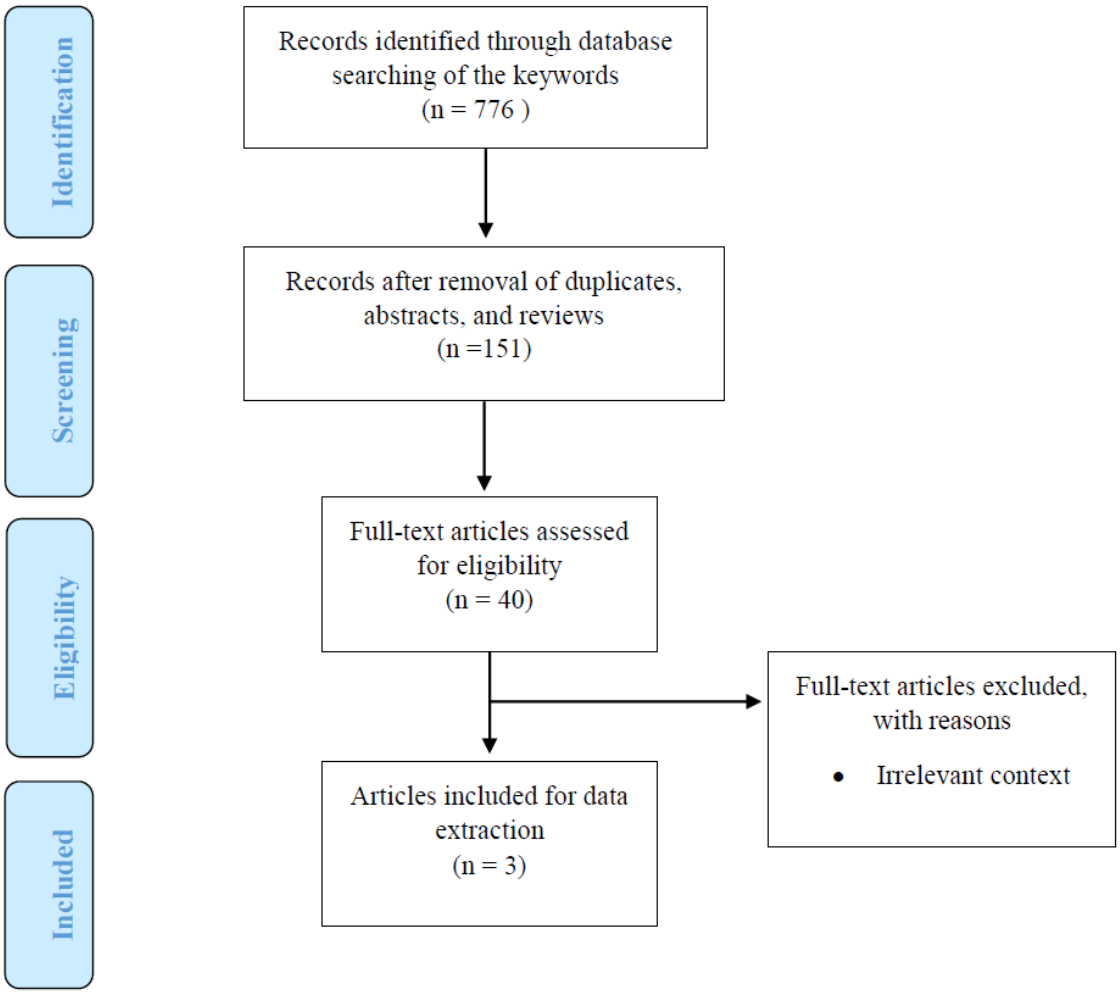

Figure 1. Flowchart of study selection

Inclusion and Exclusion Criteria

Eligible studies for this meta-analysis fulfilled the following criteria: 1) the study design was a randomized clinical trial (RCT), 2) the study of interest was the effect of monotherapy with ticagrelor after a brief period of dual antiplatelet therapy in diabetic and non-diabetic patients who underwent PCI, 3) BARC type 3 or 5 bleeding, cardiovascular related death, myocardial infraction (MI), and ischemic stroke incidence as results, and 4) the relative risk (RR) with corresponding 95% confidence interval (CI, or data to calculate them) were reported. The increased risk of bleeding associated with prior hemorrhagic stroke, traumatic brain injury, or brain surgery within the previous 6 months, internal bleeding within the previous 6 weeks, need for oral anticoagulation therapy, and anemia were key exclusion criteria in the included studies.

Study selection

All references were entered into the reference

management software EndNote and then analyzed for duplication, screening, and data extraction. The full text of the articles was made available, and each article was read in its entirety. The list of articles did not include reviews, case studies, conferences, or abstracts. Two reviewers (MKA & AA) worked independently on the search, data extraction, and quality assessment. Any disagreements between the two reviewers were settled through discussion until a consensus was reached.

Statistical methods

To report the pooled result of the studies, the random effect model was used in the case of heterogeneity between studies; otherwise, the fixed effect model was applied [14, 15]. Heterogeneity between studies was investigated using two statistics, I2 and chi-square (Q) test. Publication bias was assessed using the Egger's regression test [16] and the 'trim and fill' method was used if any publication bias was significant [15-17]. All statistical analyses were performed in Stata version 14.

Results

The final search resulted in three studies [18-20]. Characteristics and details of the included studies have been listed in Table 1. All three studies reported HR and 95% confidence interval for each outcome based on diabetics and non-diabetics. The results of the meta-analysis on bleeding events showed that the risk of BARC type 3 or 5 bleeding in patients with ticagrelor monotherapy approaches in both diabetic and non-diabetic patients was lower than conventional 12-months DAPT. This reduction was significant in non-diabetics (HR 95%CI: 0.79 (0.64, 0.98); p=0.029); while it was not significant for diabetic individuals (p=0.079) (Figure 2).

Table 1. Outcomes for diabetics and non-diabetics PCI-patients after ticagrelor mono therapy compared to conventional dual antiplatelet therapy

Author/Ref	Year	Original study name	Duration of treatment	Outcomes
Yun et al. (19)	2021	New Generation Sirolimus Eluting Stent for Acute Coronary Syndrome (TICO) trial	Ticagrelor monotherapy therapy after 3-months DAPT	In diabetic patients, ticagrelor monotherapy showed a lower incidence of bleeding complications after 3-months DAPT period, without increasing ischemic complications, compared with ticagrelor-based 12-months DAPT
Angiolillo et al. (18)	2020	Ticagrelor with Aspirin or Alone in High-Risk Patients after Coronary Intervention (TWILIGHT) trial	Ticagrelor monotherapy therapy after 3-months DAPT	Compared with ticagrelor plus aspirin, the effect of ticagrelor monotherapy in reducing the risk of clinically relevant bleeding without any increase in ischemic events was consistent among patients with or without diabetes undergoing PCI
Chichareon et al. (20)	2020	GLOBAL LEADERS study	Ticagrelor monotherapy therapy after 1-month DAPT	Diabetic patients had higher risk of ischemic events after PCI than non-diabetic patients, whilst bleeding risk was comparable. The outcomes of diabetic patients following PCI were not affected by the two different antiplatelet strategies.

DAPT: Dual Antiplatelet Therapy, PCI: Percutaneous Coronary Intervention

The pooled estimate on cardiac deaths was significantly lower in diabetics (HR 95%CI: 0.71 (0.51, 1); p=0.05) and not significantly lower for non-diabetics in patients treated by ticagrelor monotherapy strategy in comparison to conventional DAPT (p=0.843) (Figure 3). Regarding MI and ischemic stroke events, the decrease and rise results were not signifi-

cant for both diabetes and non-diabetes individuals (Figs. 4 and 5). The result of the Egger test to examine the publication bias, except for MI, was not significant for other variables. The Trim and Fill methods were used, but the result did not change. The summary of the results is listed in Table 2.

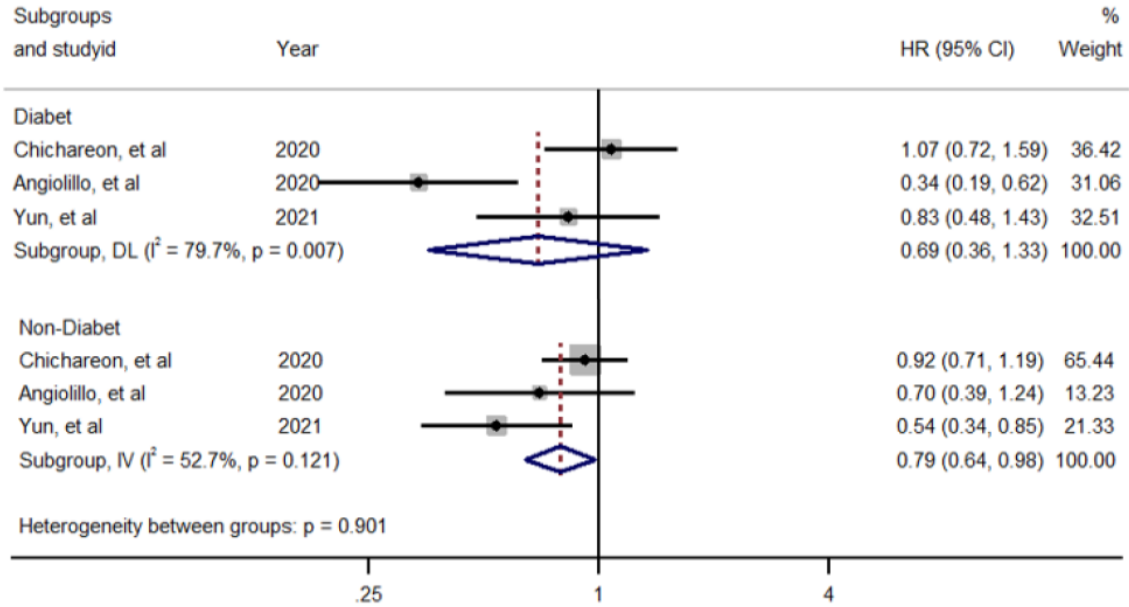

Figure 2. Forrest plot of BARC type 3 or 5 bleeding of diabetic and non-diabetic patients treated with ticagrelor monotherapy after a brief period of dual antiplatelet therapy (aspirin and ticagrelor)

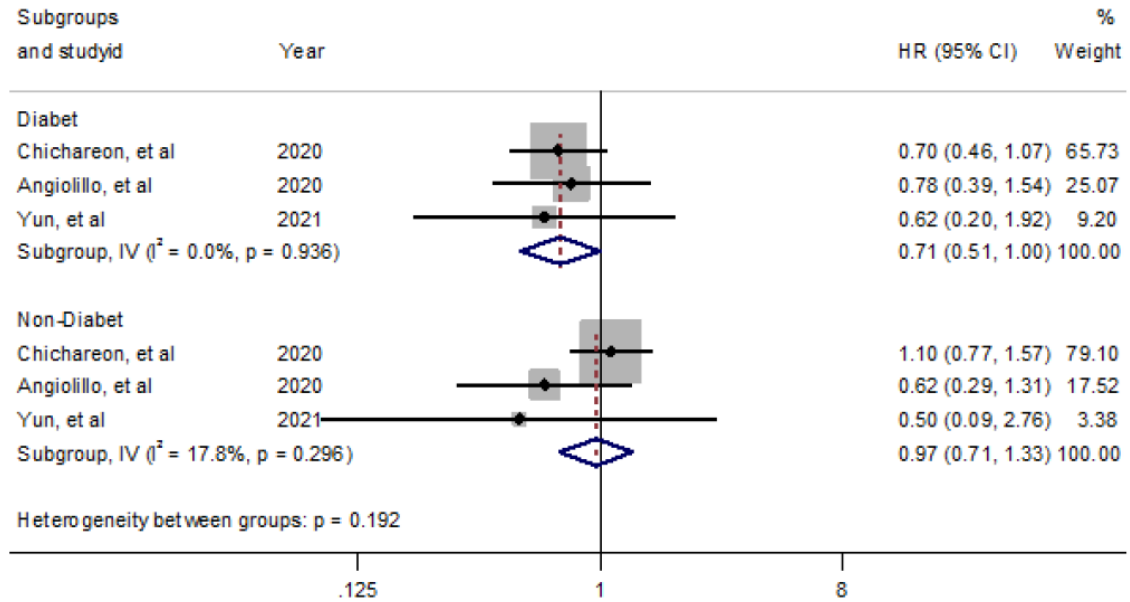

Figure 3. Forrest plot of cardiac death of diabetic and non-diabetic patients treated with ticagrelor monotherapy after a brief period of dual antiplatelet therapy (aspirin and ticagrelor)

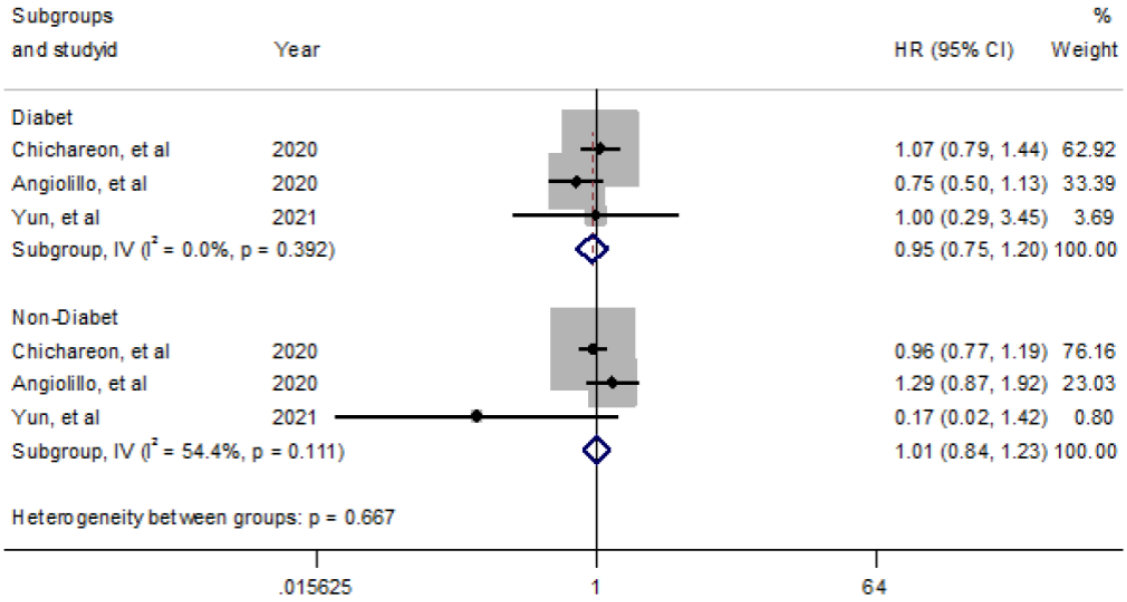

Figure 4. Forrest plot of MI in diabetic and non-diabetic patients treated with ticagrelor monotherapy after a brief period of dual antiplatelet therapy (aspirin and ticagrelor)

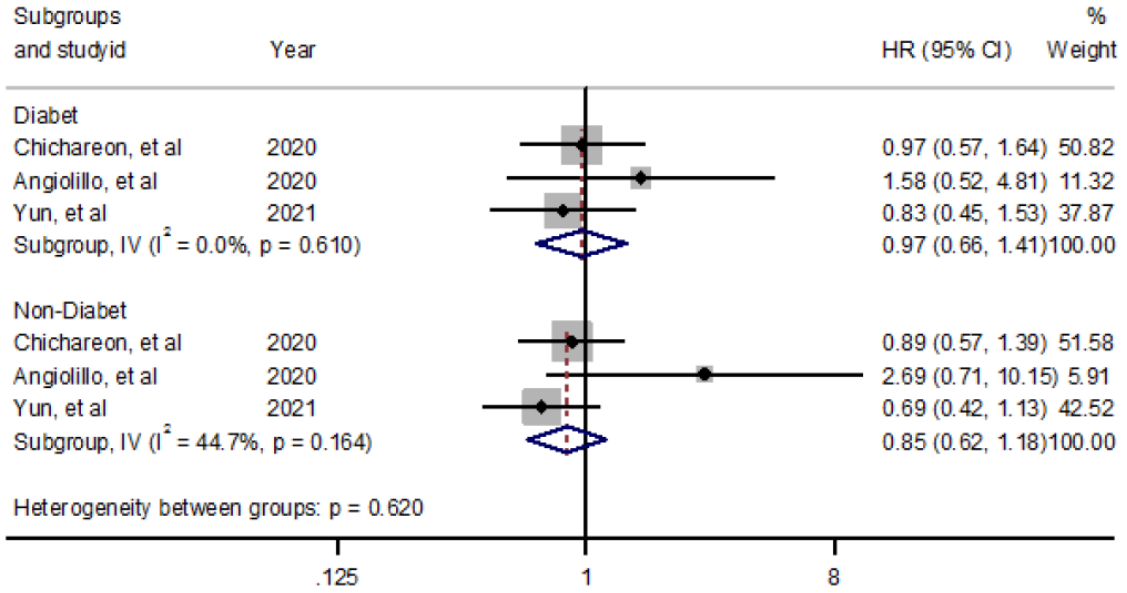

Figure 5. Forrest plot of ischmeic stroke in diabetic and non-diabetic patients treated with ticagrelor monotherapy after a brief period of dual antiplatelet therapy (aspirin and ticagrelor)

The evaluation of the quality of the studies by the risk of bias table is shown in Figure 6. The authors evaluated the quality of the studies in some important areas such as selection bias, performance bias, etc. In all three studies, there was no mention of blindness, so all of them have bias only in this area. This table and figure were designed according to Review Manager 5.3 (Figure 6).

Table 2. Summery of results

Variables	HR (95% CI)	P-value *	P-value **
BARC 3 or 5			
Diabetics	0.69 (0.36,1.33)	0.076	0.172
Non-diabetics	0.79 (0.64,0.98)	0.029	
Cardiac death			
Diabetics	0.71 (0.51,1)	0.05	0.150
Non-diabetics	0.97 (0.71,1.33)	0.843	
Ischemic stroke			
Diabetics	0.97 (0.66,1.41)	0.858	0.031
Non-diabetics	0.85 (0.62,1.18)	0.333	
MI			
Diabetics	0.95 (0.75,1.20)	0.660	0.415
Non-diabetics	1.01 (0.84,1.23)	0.890	

*for test (HR=1); **for publication bias.
BARC: Bleeding Academic Research Consortium, MI: Myocardial Infarction

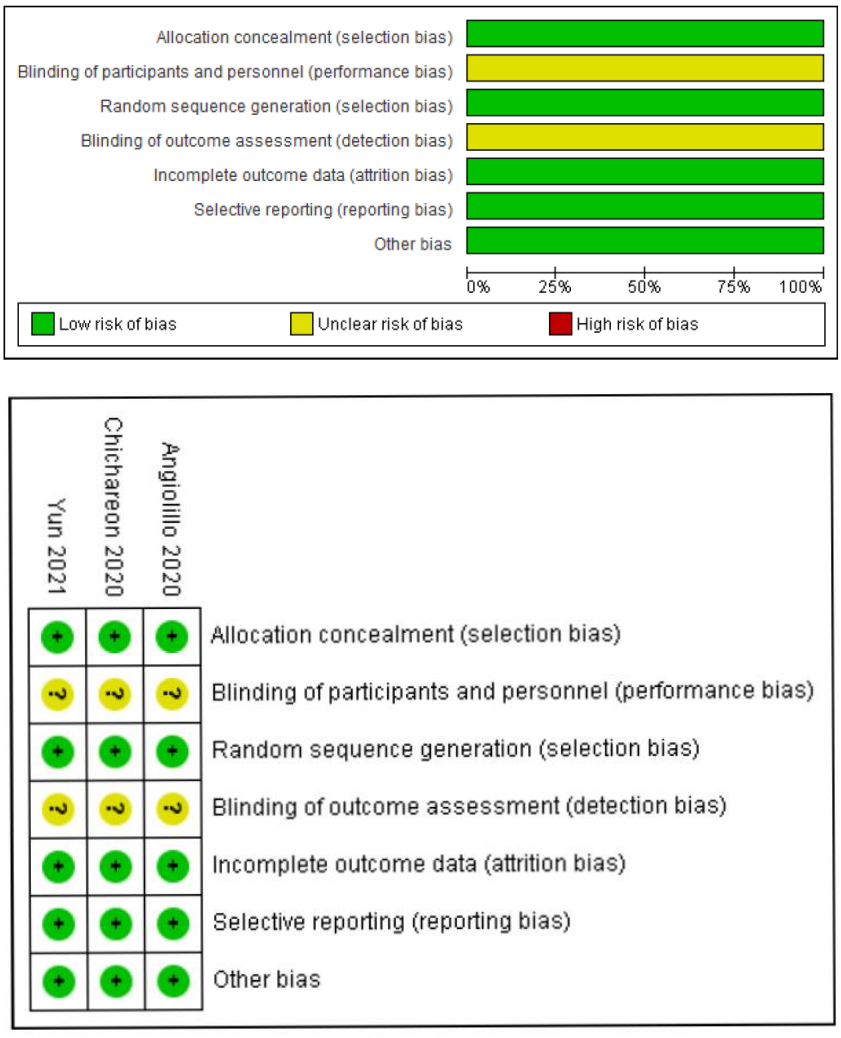

Figure 6. Summary of the risk of bias in all included RCTs (A). The judgement of the review authors about each risk of bias item presented individually for all included RCTs (B).

Discussion

This meta-analysis demonstrated that compared to conventional 12-months DAPT, short-term (1-3 months) DAPT treatment consisting of ticagrelor and aspirin, followed by ticagrelor monotherapy in diabetic (patients treated with activated insulin, an oral antidiabetic drug, or administered through diet) and non-diabetic patients undergoing PCI, the rate of BARC type 3 or 5 bleeding and cardiac death decreased in both groups. However, the reduction in the rate of BARC type 3 or 5 bleeding was only significant for non-diabetics, and in terms of cardiac-related death, the results were opposite, with the reduction being significant in diabetic patients. Regarding MI and ischemic stroke, no significant decrease or increase was observed in the ticagrelor monotherapy approach, and as a result, it did not have an adverse effect on cardiovascular events. Therefore, the present meta-analysis showed that ticagrelor monotherapy or short DAPT strategy did not increase the incidence of cardiovascular events/death or bleeding events in diabetic patients and even significantly decreased cardiac death.

In diabetic individuals, CVDs, particularly coronary artery disease (CAD) caused by accelerated atherosclerosis, is the leading cause of morbidity and mortality [21]. Diabetes has been associated with an increased risk of post-PCI diabetes in terms of both bleeding and ischemic complications [22, 23]. Dysfunction in insulin action and secretion leads to chronic hyperglycemia and some comorbidity affecting the cardiovascular systems [24]. The deregulation of numerous signaling pathways in diabetic patients' platelets, including both receptor (e.g., elevated expression) and intracellular downstream signaling problems, leads to increased platelet reactivity [25, 26]. This could explain why diabetic patients have a higher chance of developing ACS and have worse outcomes than non-diabetic patients, as well as why a higher proportion of diabetic patients have an inadequate response to antiplatelet medications [27-29]. Diabetic patients also have a higher turnover rate and amount of reticulated platelets, resulting in enhanced endothelial cell adhesion [30]. This may also play a role in the poor results seen in diabetic individuals despite adherence to antiplatelet therapy regimens. However, recent investigations have found no change in the risk of MI between non-diabetics and diabetics patients [12, 31, 32].

Ticagrelor monotherapy has been studied in three randomized trials so far, namely the TICO trial, GLOBAL LEADERS trial, and TWILIGHT trial [33-35]. The TICO trial, which focused on patients treated with a new generation of sirolimus-eluting stents for acute coronary syndrome, found that ticagrelor monotherapy after short-duration DAPT resulted in a 34% reduction in net adverse consequences compared to 12-months DAPT with aspirin and ticagrelor, primarily a reduction in bleeding events [34, 36].

Due to the significance of diabetes in cardiovascular disease outcomes, a subgroup analysis of the TICO trial was performed by Yun et al. [19] on diabetic subjects. This analysis showed that after three months of DAPT, ticagrelor monotherapy reduced the incidence of any bleeding (TIMI and BARC type 3 or 5) by 80% in diabetic patients.

According to the TICO study, when compared to ticagrelor-based 12-months DAPT, ticagrelor monotherapy after three months of DAPT significantly lowered composite outcomes and the risk of major bleeding, while not increasing the risk of major adverse cardio-cerebrovascular events [34, 36]. They found that regardless of the presence or absence of diabetes mellitus, ticagrelor monotherapy reduced the incidence of bleeding complications without increasing the incidence of ischemic complications over 3–12 months. This finding aligns with the results of the present study meta-analysis.

The findings from the pre-specified analysis of clinical outcomes in diabetic patients in the TWILIGHT trial after 3 months of adherence to DAPT post-PCI showed no severe bleeding or ischemic events [18]. The sub-analysis of the TWILIGHT trial demonstrated that ticagrelor monotherapy resulted in a 66% decrease in BARC 3 or 5 bleeding without an increased risk of ischemic events. Despite the differences in study designs and endpoints in the TICO

trial and the TWILIGHT trial, these two trials found that the ticagrelor monotherapy group after DAPT in diabetic patients reduced the risk of major cardiovascular events.

The goal of the GLOBAL LEADERS study was to determine the risk of diabetic patients with CAD undergoing current PCI treatment, as well as the impact of diabetes and antiplatelet treatments on PCI results [20]. They found that patients with diabetes, whether managed with insulin or not, had a considerably increased risk of ischemic events after contemporary PCI. Non-diabetics, insulin-treated diabetics, and non-insulin-treated diabetics all had the same risk of stent thrombosis and significant hemorrhage. They found no significant association between diabetes and antiplatelet strategies on any outcomes, including cardiac death and bleeding.

They mentioned that the outcomes and selection of the best platelet treatment may be influenced not only by the diabetes state but also by the intricacy of the CAD or other comorbidities. According to their data and a pooled analysis of randomized studies involving 18,441 participants, the incidence of repeat revascularization in diabetic patients was found to be dependent on the intricacy of the coronary lesion [12].

Limitations

Since this is a very new topic, only 3 RCTs were found and the number of studies entered was small and limited.

Conclusion

In comparison with 12-months conventional DAPT, discontinuing aspirin after short-duration DAPT (1 to 3 months) and monotherapy with ticagrelor could minimize the incidence of cardiac death and BARC type 3 or 5 bleeding in diabetic and non-diabetic patients who underwent PCI with no increase in MI and ischemic stroke.

Authors' Contribution

1. Conception and design: All authors
2. Search and interpretation of data: MS, MKA, AA, MS
3. Drafting of the manuscript and revising it: MS, MKA, AA
4. Final approval: All authors

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

Ethics approval

Not applicable.

Data Availability

All analysed research papers are presented in the Table 1. Other data underlying this analysis and study will be shared on reasonable request to the corresponding author.

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