Jurnal Farmasi dan Ilmu Kefarmasian Indonesia
Pharmacy and Pharmaceutical Sciences Journal
Published by Faculty of Pharmacy Universitas Airlangga
OPEN ACCESS
E-ISSN 2580-8303
P-ISSN 2406-9388

Jurnal Farmasi dan Ilmu Kefarmasian Indonesia Vol. 12 No. 2 August 2025, 173-193
DOI: 10.20473/jfiki.v12i22025.173-193
Available online at https://e-journal.unair.ac.id/JFIKI/

Efficacy of Ticagrelor Monotherapy in Patients at High Bleeding Risk Undergoing Percutaneous Coronary Intervention: a Systematic Review

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Submitted: 9 March 2025
Revised: 3 June 2025
Accepted : 11 July 2025

Abstract

Background*: Dual antiplatelet therapy (DAPT) after percutaneous coronary intervention (PCI) prevents ischemic events. However, prolonged therapy increases the risk of bleeding. In this context, an antithrombotic strategy is applied to post-PCI patients by discontinuing aspirin and maintaining P2Y12 receptor monotherapy. Currently, patients with ACS treated with the single antiplatelet agent ticagrelor prefer to apply DAPT for 1 to a few months to open blocked arteries.* ***Objectives:*** *This systematic review aimed to evaluate the clinical efficacy of transitioning high-bleeding-risk patients to ticagrelor monotherapy following a three-month course of DAPT.* ***Methods:*** *A systematic literature review based on the PRISMA statement was conducted to review articles on DAPT, PCI, ticagrelor monotherapy, and high bleeding risk (HBR). The article search was conducted using Internet search databases, including PubMed and ScienceDirect, published between January 2014 and December 2024.* ***Results:*** *Six studies met the inclusion criteria and were included in the analysis. Clinical outcomes were assessed over a follow-up period of up to one year, including endpoints such as all-cause mortality, myocardial infarction, stent thrombosis, stroke, and target vessel revascularization. The secondary endpoints included major adverse cardiovascular and cerebrovascular events (MACCE), significant bleeding defined by Bleeding Academic Research Consortium (BARC) types 2, 3, or 5, and net adverse clinical events (NACE).* ***Conclusion:*** *the use of ticagrelor monotherapy after 3 months of dual antiplatelet therapy is expected to assist healthcare professionals in considering the risk-benefit of single therapy for patients after percutaneous coronary intervention.*

Keywords: *high bleeding risk, monotherapy, percutaneous coronary intervention, ticagrelor*

How to cite this article:
Arifana, E. N. & Zulkarnain, B. S. (2025). Efficacy of Ticagrelor Monotherapy in Patients at High Bleeding Risk Undergoing Percutaneous Coronary Intervention: a Systematic Review. *Jurnal Farmasi dan Ilmu Kefarmasian Indonesia*, 12(2), 173-193. http://doi.org/10.20473/jfiki.v12i22025.173-193

P-ISSN: 2406-9388
E-ISSN: 2580-8303

INTRODUCTION

Aspirin is commonly administered with P2Y12 inhibitors, such as clopidogrel, prasugrel, or ticagrelor, to patients with acute coronary syndrome (ACS) who undergo percutaneous coronary intervention (PCI). Thrombotic events and platelet inhibition are reduced because patients with ACS need to preserve dual antiplatelet therapy (DAPT) for a complete 12 months after PCI. DAPT reduces stent thrombosis and different ischemic events (Levine et al., 2016; Valgimigli et al., 2018) to improve platelet blockading (Mourikis & Polzin, 2023).

Prolonged DAPT increases bleeding, which may jeopardize the patient's existence, fitness, and economic responsibilities (Valgimigli et al., 2017). Previous research has suggested that the use of aspirin after DAPT could reduce the risk of bleeding without increasing the risk of thromboembolic events (Navarese et al., 2015). Even though aspirin is commonly applied to decrease the chance of cardiovascular troubles, the drug may increase the chance of myocardial infarction in patients at expanded threat stricken by acute coronary syndrome (ACS) (Costa et al., 2019). Different studies have also investigated the role of the P2Y12 receptor in clotting and bleeding events caused by aspirin (Li et al., 2017). Mehran et al. (2019) encouraged treatment with a P2Y12 receptor inhibitor and prohibited the use of aspirin (Gargiulo et al., 2016).

Recent research using subsequent-era drug-eluting stents (DES) has reported a decreased threat of stent thrombosis. In this context, DAPT treatment may be reduced to six months without increasing the risk of thrombosis (Windecker et al., 2020; Valgimigli et al., 2021). This threshold has been decreased through step-by-step methods in research on the use of randomized trials. Currently, patients with ACS treated with the single antiplatelet agent ticagrelor prefer to apply DAPT for 1 to a few months to open blocked arteries (B. K. Kim et al., 2020). Based on the description above, this systematic overview aimed to report the potency level of ticagrelor after three months of DAPT in patients at a high risk of bleeding to open blocked coronary arteries.

MATERIALS AND METHODS

Search strategy

This systematic review was reported according to the PRISMA 2020 standard (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) (Page et al., 2021). PubMed and ScienceDirect were used to retrieve articles, and keyword selection was guided by the PICOT framework, which includes population/problem, intervention, comparison, outcome, and time. Additionally, relevant medical subject terms were identified using the Medical Subject Headings (MeSH) database. Keywords appropriate for the systematic review were used to identify journals, making the search more targeted and comprehensive. For example, literature searches used Boolean operators (AND/OR) to combine terms into search strings such as “dual antiplatelet” OR “DAPT” AND “percutaneous coronary intervention” OR “ticagrelor” OR “monotherapy” AND “HBR,” ensuring that all relevant articles were captured.

Criteria for selection

The selected articles were expected to meet the necessities for the primary research query, which was approximately the potency level of ticagrelor in lowering the hazard of bleeding in patients with ACS undergoing PCI. Articles published from January 2015 to 2025 were used in the systematic overview. This research must meet the following requirements: (1) randomized controlled trials (RCTs); (2) inclusion of ACS patients with high bleeding risk (HBR) who had PCI and published in English; (4) the whole textual content should be available and the effectiveness of ticagrelor monotherapy must be examined; (6) 10-year period guaranteed; and (7) the outcomes of negative cardiovascular activities, all-reason dying, stent thrombosis, or bleeding occasions must be reported. However, the research was limited by a lack of access to full-text content and the inclusion of patients with ACS subjected to PCI without HBR.

For a full search, the method did not use observation groups or clinical effect standards within the first database searches (PubMed and ScienceDirect). In this context, the titles and descriptions were checked before conducting full-text content searches to locate related gadgets. The reference lists of the applicable articles were searched manually to discover more research. Subsequently, resources with greater facts were selected over those without substantial statistics. The selection was checked for every sponsored search to prevent bias. Screening and qualification checks were based on the set parameters. Obtaining the proper articles led to discarding the copies and deciding on the right key phrases and outlines. A content evaluation of important information answered the question concerning the proper use of ticagrelor in patients with ACS subjected to PCI and an excessive chance of bleeding (Table 1).

The quality of the articles was assessed using the JBI Critical Appraisal Checklist for Randomized Controlled Trials to evaluate the validity of the research. The key elements included allocation concealment

P-ISSN: 2406-9388
E-ISSN: 2580-8303

(blinding), group comparison, identical treatment, follow-up, analysis, outcome measurement, statistical analysis, research design, research quality assessment, result evaluation, and decision guidance (Table 2).

Data extraction

The selected articles were obtained from two sources: after removing 14 comparable entries, the titles and summaries of 156 articles were analyzed. Therefore, 126 articles were removed, leaving 30 full-text articles for analysis. A total of 24 were removed because the requirements for the admission standards were not met. In this context, only six articles were left for the closing thorough assessment, as indicated by the PRISMA waft chart in Figure 1.

RESULTS AND DISCUSSION

A search of databases such as PubMed and ScienceDirect yielded 170 articles. However, only six were selected based on their appearance, as shown in Table 1. The primary goal of this study was to determine the effects of ticagrelor on patients with a high risk of bleeding after 3 months of DAPT.

Characteristics of the research

The six reviewed articles evaluated the efficacy of ticagrelor monotherapy in patients with a high chance of bleeding after 3 months of DAPT. Over the past decade, PCI has been performed in a broader and more complex patient population with comorbidities that increase bleeding during the procedure (Neumann et al., 2019). There may be a connection between the duration and severity of antithrombotic therapy and bleeding events after PCI. Therefore, shorter periods and unmarried antiplatelet regimens are becoming readily available for patients with a high risk of bleeding (Levine et al., 2016; Valgimigli et al., 2018). Patients in DAPT clinical research with a high threat of bleeding also have a higher risk of cardiac events, which increases the difficulty of determining unmarried remedies (Cao et al., 2020; Ueki et al., 2020; Singh et al., 2024).

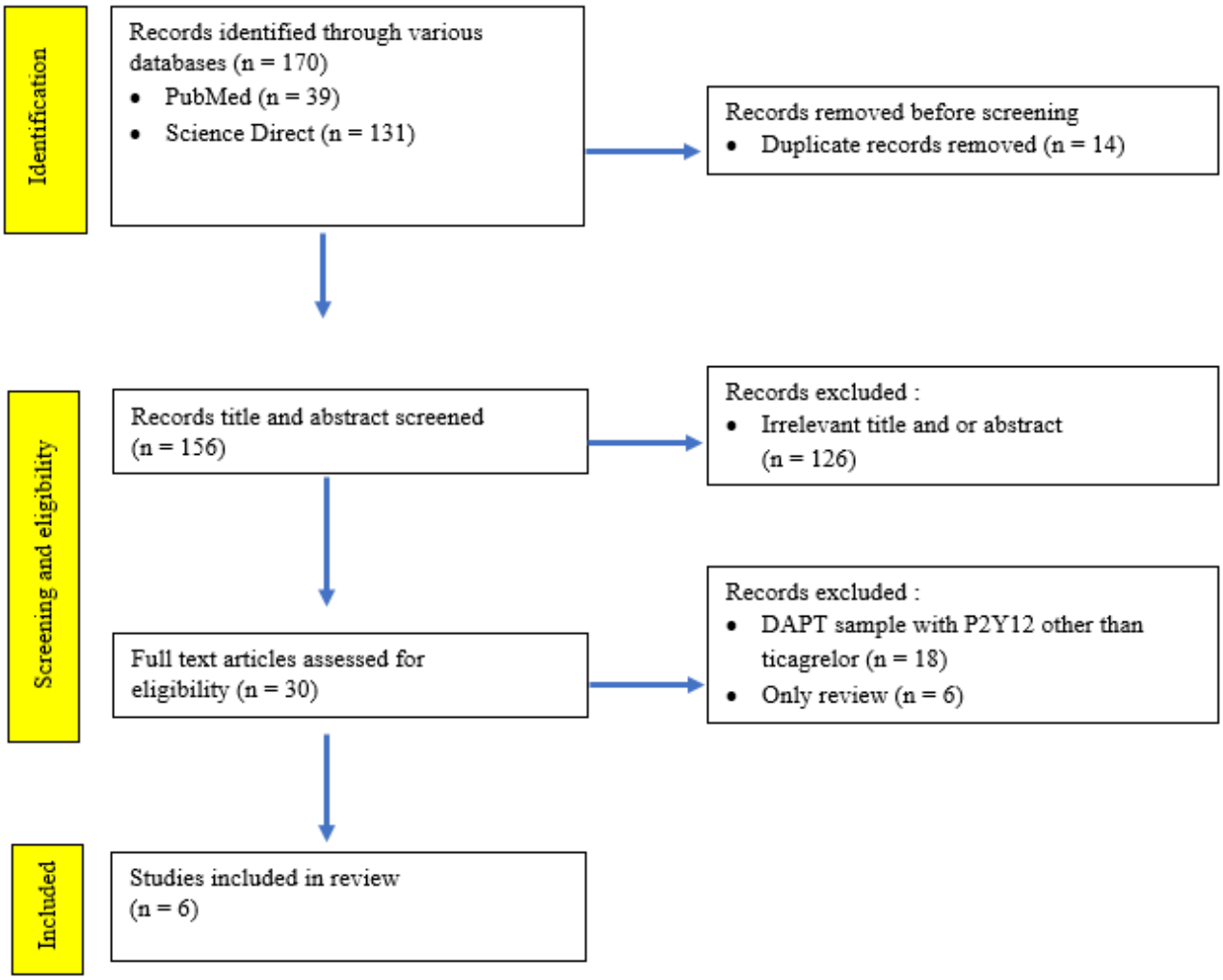

Figure 1. PRISMA

P-ISSN: 2406-9388
E-ISSN: 2580-8303

Table 1. Studies on ticagrelor monotherapy after 3 months of DAPT with ticagrelor 12 months of DAPT

Study Year	Country	Number of patients	Design	Population	Intervention	Control	Main findings (intervention vs control)	Outcome
TWILIGHT HBR (Escaned et al., 2021)	Canada, USA, Italy, UK, Poland, Spain, Austria, Germany, India, Israel.	7,119	Double blind	Elderly HBR patients (≥65 years, age) undergoing PCI	Ticagrelor monotherapy after 3 months of DAPT	DAPT	**BARC 2, 3 or 5 bleeding at 12 months:** HBR: 6.3% vs. 11.4%; HR 0.53, 95% CI 0.35–0.82, Non-HBR: 3.5% vs. 5.9%; HR 0.59, 95% CI 0.46–0.77 with no evidence of heterogeneity (P interaction = 0.673). **BARC 3 or 5 bleeding at 12 months:** HBR: 1.6% vs. 5.0%; HR 0.31, 95% CI 0.14–0.67, Non-HBR: 0.8% vs. 1.3%; HR 0.62, 95% CI 0.36–1.09, P = 0.098, P interaction = 0.48 **Ischemic events:** HBR: 6.5% vs. 5.6%; HR 1.16, 95% CI 0.71–1.90, P = 0.554, Non-HBR: 3.6 % vs. 3.6 %; HR 1.01, 95 % CI 0.75–1.35, P = 0.949, P interaction = 0.637	Patients with excessive bleeding risk (HBR) after PCI have strong records of the efficacy and protection of ticagrelor monotherapy from the TWILIGHT-HBR trial and sub-analyses. These patients also experienced hemorrhages and ischemia. The risk was increased by the satisfaction of extra ARC-HBR standards. After three months of DAPT, the frequency of clinically significant bleeding episodes of type 2, 3, or 5 was considerably reduced when ticagrelor was used compared with aspirin. This was genuine, irrespective of the presence or absence of HBR. Less severe bleeding occurred in patients with HBR than in those with NON-HBR. All ARC-HBR chance classes were favored by ticagrelor monotherapy in reducing bleeding and stroke occurrence. Escaned et al. (2021) discovered that the use of ticagrelor was supported by a selected population of high-risk patients, lending credence to its use in a selection of high-risk patients.
TWILIGHT sub study (Angiolillo et al., 2021)	Canada, USA, Italy, UK, Poland, Spain, Austria, India, Israel.	6,532	Double blind	Elderly HBR patients (≥65 years, age) undergoing DAPT PCI	Ticagrelor monotherapy after 3 months of DAPT	DAPT	**BARC 2, 3 or 5 bleeding at 12 months:** 4.5% vs. 8.2%; HR 0.53, 95% CI 0.40–0.71, P interaction = 0.62 **Death, MI or stroke at 12 months:** 4.2% vs. 4.4%; HR 0.96, 95% CI 0.68–1.35, P interaction = 0.77	The results showed that (i) the frequency of BARC 2, 3, or 5 hemorrhages increased appreciably after the age of 65 years. Meanwhile, the frequency of mortality, myocardial attack, or stroke improved after 70 years of age. In patients aged ≥ 65 years, the risk of BARC bleeding was approximately 50% lower when ticagrelor was used as monotherapy than when it was combined with aspirin. Loss of life, myocardial infarction, and stroke were not significantly associated. Regardless of age,

P-ISSN: 2406-9388
E-ISSN: 2580-8303

								ticagrelor was safe and effective in lowering bleeding without increasing the risk of ischemic events. Reducing the threat of bleeding while preserving ischemia protection in older patients presents a challenge in PCI. In this context, high-risk bleeding patients can transition from DAPT to ticagrelor monotherapy after a short duration.
TWILIGHT Sub study (Chiarito et al., 2022)	Canada, USA, Italy.	7,119	Double blind	Elderly HBR patients (≥65 years, age) undergoing PCI with prior MI	Ticagrelor monotherapy after 3 months of DAPT	DAPT	**BARC 2, 3 or 5 bleeding at 12 months:** Prior MI: 3.4% vs. 6.7%; HR 0.50, 95% CI 0.33–0.76. No prior MI: 4.2% vs. 7.0%; HR 0.58, 95% CI 0.45–0.76. P interaction = 0.54 **Death, MI, or stroke at 12 months:** Prior MI: 6.0% vs. 5.5%; HR 1.09, 95 % CI 0.75–1.58. No prior MI: 3.1% vs. 3.3%; HR 0.92, 95 % CI 0.67–1.28. P interaction = 0.52	Patients at high risk of myocardial infarction (MI) were analyzed in the TWILIGHT study. According to Chiarito et al. (2022), patients with a history of myocardial infarction and PCI have a higher risk of ischemic events. Regardless of the event, ticagrelor monotherapy reduced the risk of clinically critical and dangerous bleeding. Patients receiving ticagrelor as monotherapy or in combination with aspirin did not show significantly higher rates of mortality, myocardial infarction, or stroke. After meeting the PEGASUS-TIMI 54 criteria, treatment with ticagrelor monotherapy showed a lower risk of clinically significant and severe bleeding. Furthermore, there were no substantial differences in the ischemic outcomes between the treatment groups.
TWILIGHT sub study (Mendieta et al., 2023)	Canada, USA, Italy, UK, Poland, Spain, Austria.	7,119	Double blind	Elderly HBR patients (≥65 years, age) undergoing successful DES implantation	Ticagrelor monotherapy after 3 months of DAPT	DAPT	**BARC 2, 3 or 5 bleeding at 12 months:** LBR: 3.1% vs. 5.7%; RR 1.85, 95% CI 1.40–2.46 HBR: 6.0% vs. 9.7%; RR 1.61, 95% CI 1.21–2.14 P interaction = 0.54 LIR: 3.5% vs. 7.0%; RR 2.01, 95% CI 1.55–2.60 HIR: 5.1% vs. 7.3%; RR 1.43, 95% CI 1.04–1.96 P interaction = 0.11 **MACCE at 12 months:** LBR: 3.4% vs. 3.2% HBR: 4.0% vs. 4.7% LIR: 1.9% vs. 2.2% HIR: 7.0% vs. 6.8%	The TWILIGHT sub-study aimed to assess bleeding events (BARC types 2, 3, or 5) and major adverse cardiac and cerebrovascular events (MACCE) at 12 months after a three-month ticagrelor-based DAPT. Patients with high and low bleeding risks experienced significantly fewer events when aspirin was discontinued, with ticagrelor continued as monotherapy. The reduction in bleeding was not associated with an increase in

P-ISSN: 2406-9388
E-ISSN: 2580-8303

								MACCE or ischemic events across various risk profiles. Therefore, this study provides personalized risk estimates that balance the bleeding reduction benefits of ticagrelor monotherapy against potential ischemic risks.
TICO – sub study (S. J. Lee et al., 2021)	South Korea	3,056	Open label	Patients undergoing PCI for ACS (STEMI, NSTEMI and unstable angina)	Ticagrelor monotherapy after 3 months of DAPT	DAPT	**NACE at 12 months:** STEMI: 3.7% vs. 5.0%; HR 0.73, 95% CI 0.41–1.29 NSTEMI: 4.8% vs. 7.4%; HR 0.66, 95% CI 0.40–1.09, Unstable angina: 2.9% vs. 5.2%; HR 0.57, 95% CI 0.29–1.12 P interaction = 0.64 **TIMI major bleeding at 12 months:** STEMI: 0.9% vs. 2.9%; HR 0.32, 95% CI 0.12–0.87 NSTEMI: 2.4% vs. 3.5%; HR 0.69, 95% CI 0.34–1.43 Unstable angina: 1.6% vs. 2.5%; HR 0.64, 95% CI 0.25–1.63 Pinteraction = 0.36 **TIMI major or minor bleeding at 12 months** STEMI: 3.1% vs. 5.0%; HR 0.62, 95% CI 0.34–1.13 NSTEMI: 3.3% vs. 7.4%; HR 0.45, 95% CI 0.25–0.79 Unstable angina: 4.1% vs. 3.9%; HR 1.05, 95% CI 0.55–2.00 P interaction = 0.29 **Ischemic outcomes:** **MACCE at 12 months:** STEMI: 2.7% vs. 2.5%; HR 1.10, 95% CI 0.53–2.27 NSTEMI: 2.6% vs. 4.5%; HR 0.58, 95% CI 0.30–1.13 Unstable angina: 4.1% vs. 3.1%; HR 0.44, 95% CI 0.17–1.13 P interaction = 0.14	Ticagrelor monotherapy following a short course of DAPT was safe and feasible. The key results were as follows: (i) the rates of MACCE in patients with STEMI were comparable to those in patients with non-STEMI or unstable angina; (ii) there was no significant interaction between treatment strategy and clinical presentation, as ticagrelor monotherapy after three months of DAPT was consistently effective; and (iii) ticagrelor monotherapy reduced major bleeding across all clinical presentations without increasing the risk of MACCE. These results support the discontinuation of aspirin after three months of DAPT, with continued ticagrelor monotherapy, as a strategy for reducing bleeding risk without ischemic events across a broad range of patients.
TICO – sub analysis from the TICO Trial (Y. J. Lee et al., 2022)	Korea	3,056	Open label	Patients undergoing PCI for ACS (unstable angina, non-ST-elevation	Ticagrelor monotherapy after 3 months of DAPT	DAPT	**ARC-HBR** **NACE**, HBR vs. non-HBR : (5.4% vs. 1.9%; HR, 2.87; 95% CI, 1.76–4.69; p<0.001).	The research examined the impact of ticagrelor monotherapy initiated after three months of DAPT in patients with ACS treated with a new-generation sirolimus-eluting stent. The primary outcome was the incidence of adverse clinical events, while

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E-ISSN: 2580-8303

				myocardial infarction [MI], or ST-elevation MI)			**Major bleeding**, HBR vs. non-HBR (2.7% vs. 0.6%; HR, 4.91; 95% CI, 2.27–10.61; p<0.001) **MACCE**, HBR vs. non-HBR (3.2% vs. 1.4%; HR, 2.34; 95% CI, 1.26–4.36, p=0.006) **PRECISE-DAPT** **NACE**, HBR vs. non-HBR (5.5% vs. 1.9%; HR, 3.09; 95% CI, 1.92–4.98; p<0.001). **Major Bleeding**, HBR vs. non-HBR (2.9% vs. 0.5%; HR, 5.96; 95% CI, 2.76– 12.88; p<0.001) **MACCE,** HBR vs. non- HBR (3.1% vs. 1.4%; HR, 2.31; 95% CI, 1.25–4.25; p=0.006).	the secondary outcomes included all-cause mortality, myocardial infarction, stent thrombosis, stroke, major bleeding, target vessel revascularization, and MACCE. The results reported the following: (i) patients with ACS treated with DES and identified as HBR had a higher incidence of primary outcomes, including bleeding and ischemic events. (ii) Regardless of HBR status, switching to ticagrelor monotherapy after three months of DAPT significantly reduced major bleeding and primary outcomes compared to continuing ticagrelor-based DAPT for 12 months. No significant interaction was observed between the treatment strategy and bleeding risk. (iii) These results were consistent whether HBR status was defined using the PRECISE-DAPT score or the ARC-HBR criteria**.**
TWILIGHT HBR (Escaned et al., 2021)	Canada, the USA, Italy, the UK, Poland, Spain, Austria, Germany, India, Israel.	7,119	Double blind	Elderly HBR patients (≥65 years) undergoing PCI	Ticagrelor monotherapy after 3 months of DAPT	DAPT	**BARC 2, 3 or 5 bleeding at 12 months:** HBR: 6.3% vs. 11.4%; HR 0.53, 95% CI 0.35–0.82; P=0,004, Non-HBR: 3.5% vs. 5.9%; HR 0.59, 95% CI 0.46–0.77; P<0,001 with no evidence of heterogeneity (P interaction = 0.673). **BARC 3 or 5 bleeding at 12 months:** HBR: 1.6% vs. 5.0%; HR 0.31, 95% CI 0.14–0.67; P= 0,003, Non-HBR: 0.8% vs. 1.3%; HR 0.62, 95% CI 0.36–1.09, P=0.098, P interaction = 0.148. **Ischemic events:** HBR: 6.5% vs. 5.6%; HR 1.16, 95% CI 0.71–1.90, P=0.554, Non-HBR: 3.6 % vs. 3.6 %; HR 1.01, 95% CI 0.75–1.35, P=0.949, P interaction = 0.637.	Patients with excessive bleeding risk (HBR) after PCI have strong records of the efficacy and protection of ticagrelor monotherapy from the TWILIGHT-HBR trial and sub-analyses. These patients also experienced hemorrhages and ischemia. The risk was increased by the satisfaction of extra ARC-HBR standards. After three months of DAPT, the frequency of clinically significant bleeding episodes of type 2, 3, or 5 was considerably reduced when ticagrelor was used compared with aspirin. This was genuine, irrespective of the presence or absence of HBR. Less severe bleeding occurred in patients with HBR than in those with NON-HBR. All ARC-HBR chance classes were favored by ticagrelor monotherapy in reducing bleeding and stroke occurrence. Escaned et al. (2021) discovered that the use of

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E-ISSN: 2580-8303

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TWILIGHT Sub study (Chiarito et al., 2022)	Canada, the USA, Italy.	7,119	Double blind	Elderly HBR patients (≥65 years) undergoing PCI with prior MI	Ticagrelor monotherapy after 3 months of DAPT	DAPT	**BARC 2, 3 or 5 bleeding at 12 months:** Prior MI: 3.4% vs. 6.7%; HR 0.50, 95% CI 0.33–0.76. No prior MI: 4.2% vs. 7.0%; HR 0.58, 95% CI 0.45–0.76. P interaction = 0.54 **Death, MI, or stroke at 12 months:** Prior MI: 6.0% vs. 5.5%; HR 1.09, 95 % CI 0.75–1.58. No prior MI: 3.1% vs. 3.3%; HR 0.92, 95 % CI 0.67–1.28. P interaction = 0.52	Patients at high risk of myocardial infarction (MI) were analyzed in the TWILIGHT study. According to Chiarito et al. (2022), patients with a history of myocardial infarction and PCI have a higher risk of ischemic events. Regardless of the event, ticagrelor monotherapy reduced the risk of clinically critical and dangerous bleeding. Patients receiving ticagrelor as monotherapy or in combination with aspirin did not show significantly higher rates of mortality, myocardial infarction, or stroke. After meeting the PEGASUS-TIMI 54 criteria, treatment with ticagrelor monotherapy

P-ISSN: 2406-9388
E-ISSN: 2580-8303

								showed a lower risk of clinically significant and severe bleeding. Furthermore, there were no substantial differences in the ischemic outcomes between the treatment groups.
TWILIGHT sub study (Mendieta et al., 2023)	Canada, the USA, Italy, the UK, Poland, Spain, Austria.	7,119	Double blind	Elderly HBR patients (≥65 years) undergoing successful DES implantation	Ticagrelor monotherapy after 3 months of DAPT	DAPT	**BARC 2, 3 or 5 bleeding at 12 months:** LBR: 3.1% vs. 5.7%; RR 1.85, 95% CI 1.40–2.46 HBR: 6.0% vs. 9.7%; RR 1.61, 95% CI 1.21–2.14 P interaction = 0.54 LIR: 3.5% vs. 7.0%; RR 2.01, 95% CI 1.55–2.60 HIR: 5.1% vs. 7.3%; RR 1.43, 95% CI 1.04–1.96 P interaction = 0.11 **MACCE at 12 months:** LBR: 3.4% vs. 3.2% HBR: 4.0% vs. 4.7% LIR: 1.9% vs. 2.2% HIR: 7.0% vs. 6.8%	The TWILIGHT sub-study aimed to assess bleeding events (BARC types 2, 3, or 5) and major adverse cardiac and cerebrovascular events (MACCE) at 12 months after a three-month ticagrelor-based DAPT. Patients with high and low bleeding risks experienced significantly fewer events when aspirin was discontinued, with ticagrelor continued as monotherapy. The reduction in bleeding was not associated with an increase in MACCE or ischemic events across various risk profiles. Therefore, this study provides personalized risk estimates that balance the bleeding reduction benefits of ticagrelor monotherapy against potential ischemic risks.
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E-ISSN: 2580-8303

							4.1% vs. 3.9%; HR 1.05, 95% CI 0.55–2.00 P interaction = 0.29 **Ischemic outcomes:** **MACCE at 12 months:** STEMI: 2.7% vs. 2.5%; HR 1.10, 95% CI 0.53–2.27 NSTEMI: 2.6% vs. 4.5%; HR 0.58, 95% CI 0.30–1.13 Unstable angina: 1.4% vs. 3.1%; HR 0.44, 95% CI 0.17–1.13 P interaction = 0.14	bleeding risk without ischemic events across a broad range of patients.
TICO – sub analysis from the TICO Trial (Y. J. Lee et al., 2022)	Korea	3,056	Open label	Patients undergoing PCI for ACS (STEMI, NSTEMI and unstable angina)	Ticagrelor monotherapy after 3 months of DAPT	DAPT	**ARC-HBR** **NACE**, HBR vs. non-HBR : (5.4% vs. 1.9%; HR, 2.87; 95% CI, 1.76–4.69; p<0.001). **Bleeding events**, HBR vs. non-HBR (2.7% vs. 0.6%; HR, 4.91; 95% CI, 2.27–10.61; p<0.001) **MACCE**, HBR vs. non-HBR (3.2% vs. 1.4%; HR, 2.34; 95% CI, 1.26–4.36, p=0.006) **PRECISE-DAPT** **NACE**, HBR vs. non-HBR (5.5% vs. 1.9%; HR, 3.09; 95% CI, 1.92–4.98; p<0.001). **Bleeding events**, HBR vs. non-HBR (2.9% vs. 0.5%; HR, 5.96; 95% CI, 2.76– 12.88; p<0.001) **MACCE,** HBR vs. non- HBR (3.1% vs. 1.4%; HR, 2.31; 95% CI, 1.25–4.25; p=0.006).	The research examined the impact of ticagrelor monotherapy initiated after three months of DAPT in patients with ACS treated with a new-generation sirolimus-eluting stent. The primary outcome was the incidence of adverse clinical events, while the secondary outcomes included all-cause mortality, myocardial infarction, stent thrombosis, stroke, bleeding events, target vessel revascularization, and MACCE. The results reported the following: (i) patients with ACS treated with DES and identified as HBR had a higher incidence of primary outcomes, including bleeding and ischemic events. (ii) Regardless of HBR status, switching to ticagrelor monotherapy after three months of DAPT significantly reduced bleeding events and primary outcomes compared to continuing ticagrelor-based DAPT for 12 months. No significant interaction was observed between the treatment strategy and bleeding risk. (iii) These results were consistent whether HBR status was defined using the PRECISE-DAPT score or the ARC-HBR criteria**.**

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Table 2. JBI critical appraisal

No.	JBI Critical Appraisal	TWILIGHT HBR (Escaned et al., 2021)	TWILIGHT sub study (Angiolillo et al., 2021)	TWILIGHT Sub study (Chiarito et al., 2022)	TWILIGHT sub study (Mendieta et al., 2023)	TICO – sub study (S. J. Lee et al., 2021)	TICO – sub analysis from the TICO Trial (Y. J. Lee et al., 2022)
1.	Was true randomization used for assignment of participants to treatment groups?	√	√	√	√	√	√
2.	Was allocation to treatment groups concealed?	√	√	√	√	X	X
3.	Were treatment groups similar at the baseline?	√	√	√	√	X	X
4.	Were participants blind to treatment assignment?	√	√	√	√	X	X
5.	Were those delivering treatment blind to treatment assignment?	√	√	√	√	X	X
6.	Were outcomes assessors blind to treatment assignment?	X	X	X	X	X	X
7.	Were treatment groups treated identically other than the intervention of interest?	√	√	√	√	X	X
8.	Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analyzed?	√	√	√	√	√	X
9.	Were participants analyzed in the groups to which they were randomized?	√	√	√	√	√	√
10.	Were outcomes measured in the same way for treatment groups?	√	√	√	√	√	√
11.	Were outcomes measured in a reliable way?	√	√	√	√	√	√
12.	Was appropriate statistical analysis used?	√	√	√	√	√	√
13.	Was the trial design appropriate, and any deviations from the standard RCT design (individual randomization, parallel groups) accounted for in the conduct and analysis of the trial?	√	√	√	√	√	√

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The RCTs listed in Table 1 analyzed the effects of discontinuing aspirin and administering ticagrelor monotherapy (a P2Y12 inhibitor) instead of DAPT. In the TWILIGHT-HBR study conducted by Escaned et al. (2021), primary and secondary targets were identified. The final result examined was the occurrence of bleeding of types 2, 3, or 5 in one year, as determined with the aid of the Bleeding Academic Research Consortium (BARC). Secondary bleeding results were reported by (Costa et al. (2017) and Ueki et al. (2019), Urban et al. (2019) and Corpataux et al. (2020). Subsequent secondary ischemic events, such as death from any cause, myocardial infarction, stroke, cardiovascular death, non-fatal myocardial infarction, ischemic stroke, and stent thrombosis, were protected. Patients with excessive bleeding risk (HBR) after PCI have strong records of the efficacy and protection of ticagrelor monotherapy from the TWILIGHT-HBR trial and sub-analyses. The TWILIGHT HBR study in 2021 included 7.119 patients from Canada, the USA, Italy, the UK, Poland, Spain, Austria, Germany, India, and Israel. These patients also experienced hemorrhages and ischemia. The risk was increased by the satisfaction of extra ARC-HBR standards. After three months of DAPT, the frequency of clinically significant bleeding episodes of type 2, 3, or 5 was considerably reduced when ticagrelor was used compared with aspirin. This was genuine, irrespective of the presence or absence of HBR. Less severe bleeding occurred in patients with HBR than in those with NON-HBR. All ARC-HBR chance classes were favored by ticagrelor monotherapy in reducing bleeding and stroke occurrence. Escaned et al. (2021) discovered that the use of ticagrelor was supported by a selected population of high-risk patients, lending credence to its use in a selection of high-risk patients.

The analysis of the TWILIGHT subtitle in 2021 included 6.532 patients from Canada, the USA, Italy, the UK, Poland, Spain, Austria, India, and Israel. Angiolillo et al. (2021) examined the connection between age and detrimental activities. The results showed that (i) the frequency of BARC 2, 3, or 5 hemorrhages increased appreciably after the age of 65 years. Meanwhile, the frequency of mortality, myocardial attack, or stroke improved after 70 years of age. In patients aged ≥ 65 years, the risk of BARC bleeding was approximately 50% lower when ticagrelor was used as monotherapy than when it was combined with aspirin. Loss of life, myocardial infarction, and stroke were not significantly associated. Regardless of age, ticagrelor was safe and effective in lowering bleeding without increasing the risk of ischemic events. Reducing the threat of bleeding while preserving ischemia protection in older patients presents a challenge in PCI. In this context, high-risk bleeding patients can transition from DAPT to ticagrelor monotherapy after a short duration.

Meanwhile, the TWILIGHT sub-study in 2022 included 7.119 patients from Canada, the USA, and Italy. Patients at high risk of myocardial infarction (MI) were analyzed in the TWILIGHT study. According to Chiarito et al. (2022), patients with a history of myocardial infarction and PCI have a higher risk of ischemic events. Regardless of the event, ticagrelor monotherapy reduced the risk of clinically critical and dangerous bleeding. Patients receiving ticagrelor as monotherapy or in combination with aspirin did not show significantly higher rates of mortality, myocardial infarction, or stroke. After meeting the PEGASUS-TIMI 54 criteria, treatment with ticagrelor monotherapy showed a lower risk of clinically significant and severe bleeding. Furthermore, there were no substantial differences in the ischemic outcomes between the treatment groups.

Additionally, the TWILIGHT sub-study in 2023 included 7.119 in Canada, the USA, Italy, the UK, Poland, Spain, and Austria. This information shows that ticagrelor significantly lowers the threat of bleeding without increasing the risk of ischemic activities. This is particularly appropriate for patients at high risk of myocardial infarction. Extraordinary predictive models have been developed through interventions (Mendieta et al., 2023). The TWILIGHT sub-study aimed to assess bleeding events (BARC types 2, 3, or 5) and major adverse cardiac and cerebrovascular events (MACCE) at 12 months after a three-month ticagrelor-based DAPT. Patients with high and low bleeding risks experienced significantly fewer events when aspirin was discontinued, with ticagrelor continued as monotherapy. The reduction in bleeding was not associated with an increase in MACCE or ischemic events across various risk profiles. Therefore, this study provides personalized risk estimates that balance the bleeding reduction benefits of ticagrelor monotherapy against potential ischemic risks.

In another trial, the TICO sub-study in 2021 included 3.056 in South Korea. S. J. Lee et al., 2021 investigated patients with ST-segment elevation myocardial infarction (STEMI) treated with DES. In this context, ticagrelor monotherapy following a short course of DAPT was safe and feasible. The key results were as follows: (i) the rates of MACCE in patients with STEMI were comparable to those in patients with non-

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E-ISSN: 2580-8303

STEMI or unstable angina; (ii) there was no significant interaction between treatment strategy and clinical presentation, as ticagrelor monotherapy after three months of DAPT was consistently effective; and (iii) ticagrelor monotherapy reduced bleeding events across all clinical presentations without increasing the risk of MACCE. These results support the discontinuation of aspirin after three months of DAPT, with continued ticagrelor monotherapy, as a strategy for reducing bleeding risk without ischemic events across a broad range of patients.

The TICO trial in 2022 included 3.056 patients in Korea. Y. J. Lee et al., 2022 reported the primary and secondary clinical outcomes of post-hoc analysis of the TICO-HBR trial. The research examined the impact of ticagrelor monotherapy initiated after three months of DAPT in patients with ACS treated with a new-generation sirolimus-eluting stent. The primary outcome was the incidence of adverse clinical events, and the secondary outcomes included all-cause mortality, myocardial infarction, stent thrombosis, stroke, bleeding events, target vessel revascularization, and MACCE. The results reported the following: (i) patients with ACS treated with DES and identified as HBR had a higher incidence of primary outcomes, including bleeding and ischemic events. (ii) Regardless of HBR status, switching to ticagrelor monotherapy after three months of DAPT significantly reduced bleeding events and primary outcomes compared to continuing ticagrelor-based DAPT for 12 months. No significant interaction was observed between the treatment strategy and bleeding risk. (iii) These results were consistent whether HBR status was defined using the PRECISE-DAPT score or the ARC-HBR criteria**.**

HBR stratification assessment

Patients were classified as having HBR according to the standardized definition developed by the ARC, which requires the presence of a major criterion or two minor criteria. HBR is defined by the ARC as a risk of 4% for BARC type 3 or 5 bleeding or 1% for intracranial hemorrhage (ICH) within one year (Urban et al., 2019).

ARC-HBR criteria were used for HBR categorization in the TWILIGHT-HBR experiment performed by Escaned et al., 2021. Several criteria for HBR include advanced or end-stage chronic kidney disease (CKD) with an estimated glomerular filtration rate (eGFR) of less than 30 mL/min/1.73 m² or patients subjected to dialysis, hemoglobin levels below 11 g/dL, moderate to severe thrombocytopenia with a platelet count below 100×10^9cells/L, a history of significant bleeding, and liver disease. The minor criteria include age ≥ 75 years, moderate CKD (eGFR 30–59 mL/min/1.73 m²), hemoglobin levels between 11 and 13 g/dL and 11–12 g/dL in men and women, respectively, and the use of non-steroidal anti-inflammatory drugs (NSAIDs). The eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (Corpataux et al., 2020).

Patients were categorized into HBR and non-HBR in the TICO-HBR trial by Y. J. Lee et al., 2022 throughuseduse of precise DAPT rating and ARC-HBR criteria (Urban et al., 2019; Costa et al., 2017). The correct DAPT score was based on five characteristics taken from massive randomized clinical research. The ARC-HBR was composed of 20 evidence-based medical criteria labeled as essential and minor categories. According to PCI registries, both tools are highly predictive of patients at risk for bleeding or ischemic complications following PCI (Costa et al., 2017; Natsuaki et al., 2019; Ueki et al., 2019; Urban et al., 2019; Ueki et al., 2020). In TICO-HBR, patients with HBR had an increased hazard of net adverse clinical events (NACE), including extreme bleeding and MACCE, compared to those without HBR.

Previous trials

The duration of the twin antiplatelet medicinal drugs and their association with the expanded bleeding threat have been the subject of several investigations. Costa et al. stated that patients with HBR with a prolonged DAPT period (12-24 months) experienced greater bleeding (Costa et al., 2017). Longer DAPT duration may also decrease the risk of ischemia in 20.8% of patients undergoing hard PCI. However, extended durations of DAPT appear to reduce ischemic events in patients without HBR subjected to complex or standard PCI. The decisions regarding the duration of DAPT following PCI should be primarily guided by bleeding risk, since the benefit has not been reported in HBR patients (Costa et al., 2019). An opportunity for ordinary DAPT has been proposed, which includes the prevention of aspirin use and the use of P2Y12 inhibitor monotherapy (Capodanno et al., 2018).

The GLOBAL LEADERS trial was the first large-scale randomized study to evaluate antiplatelet therapy strategies. In the general population, ticagrelor monotherapy for 23 months following only one month of DAPT did not lead to superior outcomes compared with the standard 12-month DAPT. Generally, 16% of the participants were classified as having HBR, defined by a PRECISE-DAPT score of 25 or higher (Vranckx et al., 2018 ; Gragnano et al., 2022). In contrast, the TWILIGHT trial focused on patients at an elevated risk

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of bleeding or ischemic events. Transitioning from DAPT to ticagrelor monotherapy after three months significantly reduced bleeding events without compromising antithrombotic efficacy compared to the continued use of ticagrelor in combination with aspirin (Baber et al., 2016; Mehran et al., 2019). The TICO trial showed that ticagrelor monotherapy following three months of DAPT led to fewer NACE events than ticagrelor-based DAPT continued for the full 12 months (B. K. Kim et al., 2020).

Net adverse clinical events (NACE)

NACE is a composite outcome of bleeding events and MACCE, comprising all-cause mortality, myocardial infarction, stent thrombosis, cerebrovascular accident, and target vessel revascularization (C. Kim et al., 2019). Ticagrelor monotherapy after three months of DAPT was associated with a lower incidence of bleeding. Furthermore, the PRECISE-DAPT score showed no significant interaction between the treatment strategy and bleeding risk. B. K. Kim et al., (2020) reported that switching to ticagrelor monotherapy after three months of DAPT reduced NACE compared to the standard 12-month ticagrelor-based DAPT. Among patients with ACS treated with DES, ticagrelor monotherapy was associated with a lower risk of NACE and bleeding events, regardless of bleeding risk status. The treatment showed consistent efficacy across the HBR and non-HBR groups.

Major adverse cardiac or cerebrovascular events (MACCE)

MACCE describes deaths, myocardial infarctions, and crashes resulting from the brain and coronary heart. This measure is used to assess the mortality risk and severity of ischemic outcomes. In the TWILIGHT-HBR subanalysis, patients were selected based on a broad spectrum of clinical and angiographic factors not related to HBR or ischemic risk classification criteria. Patients who were on long-term oral anticoagulants, had a history of stroke, were scheduled for surgery within 90 days, and had conditions associated with an increased risk of bleeding events were excluded from the trial. Although patients with thrombocytopenia (platelet count $<100\times10^9$/L), liver disease, or those on dialysis were excluded, some were included in the population. According to the ARC criteria, only 17.2% of patients were classified as HBR, which is lower than the proportions reported in previous large-scale community registries. This reflects the study design, which limited enrollment to patients suitable for long-term ticagrelor-based DAPT. In the TWILIGHT trial, two-thirds of the patients were subjected to PCI for non-ST-elevation acute coronary syndrome (NSTE-ACS), one-third had complex PCI procedures, and 37% had diabetes (Angiolillo et al., 2020; Baber et al., 2020; Dangas et al., 2020).

The use of ticagrelor after 3 months of DAPT lowers the risk of bleeding in patients with HBR and a higher risk of ischemia. This is mainly true when doctors recall a robust P2Y12 inhibitor. Additionally, the widespread distribution of critical and small threat factors is related to ARC-HBR validation (Cao et al., 2020; Ueki et al., 2020). Aspirin and strong P2Y12 inhibitors effectively increase antiplatelet motion, supporting the treatment benefits of ticagrelor (Baber et al., 2020; Armstrong et al., 2011).

Death/myocardial infarction and stent thrombosis

According to (Levine et al. (2016) and Valgimigli et al. (2018), patients who receive DES for ACS are typically prescribed 12 months of DAPT, including newer and more effective antiplatelet agents. In the TWILIGHT-HBR study, patients who received ticagrelor plus placebo showed similar rates of all-cause mortality, myocardial infarction, and stroke compared to those receiving the drug in combination with aspirin.

The TICO trial exclusively used an ultrathin bioresorbable polymer sirolimus-eluting stent (Orsiro; Biotronik AG, Bülach, Switzerland). This stent has been reported to have superior clinical outcomes owing to its ability to reduce thrombus formation, inflammation, and neointimal proliferation (Kandzari et al., 2017; Roguin et al., 2018; C. Kim et al., 2019; B. K. Kim et al., 2020). Similarly, DAPT with P2Y12 receptor inhibitors (ticagrelor) is better at reducing ischemic events than clopidogrel alone. In this context, a longer duration of DAPT is needed to forestall ischemic events with other DES and P2Y12 receptor blockers.

Y. J. Lee et al., 2022 reported that the most significant reduction in bleeding occurred among HBR patients who were not receiving anticoagulation therapy. This reduction was not accompanied by an increase in MACE in patients expected to receive anticoagulation therapy. Evidence from research, including HBR patients treated with DAPT for 1 to 3 months, shows that shorter DAPT durations do not significantly increase MACE or all-cause mortality. Stent thrombosis rates remained below 0.5% in the short- and standard-duration DAPT groups with extended follow-up. Previous research has reported that the risk increases within the first 30 days post-implantation and declines sharply thereafter. Therefore, short-term DAPT was sufficient to provide protection during the critical period. Consistently low rates of stent

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E-ISSN: 2580-8303

thrombosis were largely attributed to the use of modern DES, such as biodegradable polymer and second-generation DES, used in the TICO and TWILIGHT trials. Additional research supports the safety of shorter DAPT durations in patients subjected to complex PCI (Valgimigli et al., 2022).

Bleeding

European guidelines for the management of NSTE-ACS recommend ticagrelor monotherapy following three months of DAPT in selected low-risk patients. This recommendation is based on the TWILIGHT trial, which reported a relatively low incidence of adverse events within the first year of follow-up (Collet et al., 2021). The safety and efficacy of discontinuing aspirin and continuing ticagrelor monotherapy were evaluated during the initial phase of dual antiplatelet therapy (DAPT). Patients with HBR experienced more than three times the incidence of severe BARC type 3 or 5 compared to without those HBR. These individuals had approximately twice the rate of bleeding events (BARC types 2, 3, and 5). The research design contributed to an underestimation of the overall bleeding rates, but the risk of BARC type 3 or 5 bleeding in high-risk patients receiving ticagrelor monotherapy was significantly reduced from 5.0% to 1.6% (Koo et al., 2021).

Direct comparisons of clopidogrel and aspirin monotherapies for secondary prevention show that early discontinuation of aspirin may reduce the risk of bleeding beyond the first year after percutaneous coronary intervention (PCI). In patients with HBR, shortening the duration of DAPT to 1–3 months led to a statistically significant and clinically meaningful reduction in bleeding events. However, this benefit is less pronounced in non-HBR patients (Yin et al., 2019; Khan et al., 2020; Benenati et al., 2021; Benenati et al., 2022; Bainey et al., 2023).

Heterogeneity in patient populations

In the TWILIGHT HBR study, there was no evidence of heterogeneity (Escaned et al., 2021). In the TICO trials short (3-6 months) and long (12-24 months) duration DAPT was heterogeneous, with aspirin continuation after DAPT in previous studies; the definition was strictly limited to 3 months of DAPT with P2Y12 receptor inhibitor continuation versus 12 months of DAPT (Y. J. Lee et al., 2022). However, the TICO pre-specified subgroup analysis did not reveal heterogeneity in the effect of ticagrelor monotherapy after 3 months of DAPT, compared with 12 months of DAPT, on the primary outcomes, bleeding events, and MACCE across clinical presentations, including STEMI (S. J. Lee et al., 2021)

Intervention protocols

The risk of ischemic events is highest within the first two weeks and gradually declines. In contrast, the bleeding risk associated with prolonged DAPT is consistently elevated. This divergence supports the rationale for de-escalation strategies that tailor both the duration and selection of antiplatelet agents based on individual patient risk profiles to minimize bleeding without compromising ischemic protection in patients with ACS. Current clinical guidelines recommend the use of potent P2Y12 inhibitors, such as prasugrel or ticagrelor, in combination with aspirin. This is followed by a reduced DAPT duration (1–6 months) or a transition to clopidogrel in patients with HBR. Evidence from large-scale clinical trials, including TALOS-AMI and STOPDAPT-2 ACS, showed that short-term DAPT followed by monotherapy provided a favorable balance between ischemic protection and bleeding risk, reinforcing the value of individualized antiplatelet therapy (Singh et al., 2024).

Switching to ticagrelor monotherapy after a brief course of DAPT

Transitioning to ticagrelor monotherapy after a brief period of DAPT significantly reduced the bleeding risk without increasing the risk of ischemic events in post-PCI patients. Studies such as ULTIMATE-DAPT and TWILIGHT have shown that ticagrelor monotherapy leads to a marked reduction in bleeding complications compared to continued DAPT, while maintaining comparable rates of ischemic events. These benefits are consistent across diverse patient subgroups experiencing reduced bleeding risk without an increase in ischemic complications. Similar outcomes have been observed across various types of DES, as well as in high- and low-bleeding-risk populations.

Ticagrelor monotherapy effectively lowers bleeding rates without adversely affecting the risks of death, myocardial infarction, or stroke in patients with NSTE-ACS and stable coronary artery disease (CAD). The TICO trial reported that switching to ticagrelor monotherapy after 3 months of DAPT in patients with ACS treated with new-generation sirolimus-eluting stents reduced adverse and bleeding events compared with 12-month DAPT, with no significant difference in ischemic risk. Furthermore, comparable results have been reported in patients with STEMI and other subgroups (Angiolillo et al., 2021; Escaned et al., 2021; S. J. Lee et al., 2021; Y. J. Lee et al., 2022; Chiarito et al., 2022; Mendieta et al., 2023)

According to T-PASS research, patients with ACS who received DES and transitioned to ticagrelor

P-ISSN: 2406-9388
E-ISSN: 2580-8303

monotherapy after a short course of DAPT experienced fewer adverse and bleeding events. Collectively, these results suggest that ticagrelor monotherapy following short-term DAPT is a safer and more effective strategy than prolonged DAPT across a broad spectrum of post-PCI patient populations (Singh et al., 2024).

Follow-up durations

In the TWILIGHT-HBR study, follow-up occurred 1 month after randomization via telephone and in-person at 6 and 12 months after randomization (Escaned et al., 2021). Meanwhile, for the TICO trial, patient follow-up was 365 days for the primary outcome (net adverse clinical events) (S. J. Lee et al., 2021).

Clinical implications and research limitations

The TWILIGHT study suggests that ticagrelor monotherapy following a short course of DAPT provides greater benefits to patients with HBR than to those at a lower risk. Patients with HBR experienced a high reduction in bleeding events, leading to an overall lower net clinical risk. Therefore, this systematic review evaluated the safety of bleeding-reduction strategies and the potential for further shortening of the duration of DAPT, as well as optimizing outcomes through antiplatelet regimens (Voudris & Feldman, 2023). However, this study had several limitations, as the TICO-HBR subgroup analysis was not prespecified in the original trial design. The TWILIGHT-HBR study was restricted to data available within the trial. The ARC-HBR and PRECISE-DAPT criteria used to identify HBR were not available at the time of the trials, leading to retrospective application for hypothesis generation and post-hoc analysis. This highlights the need for future prospective and randomized studies. Most of the included evidence stemmed from subgroup analyses of HBR patients in larger randomized controlled trials. Additionally, not all ARC-HBR criteria could be assessed because of the relatively small number of HBR patients compared to non-HBR patients. This study lacked sufficient statistical power to detect clinically meaningful differences in ischemic events, and the results were limited to ticagrelor, with no applicability to other P2Y12 inhibitors.

Different studies have been conducted in South Korea, India, the United States, and certain parts of Europe. This highlights the importance of gathering data from diverse populations in countries such as Indonesia. Therefore, further investigation is needed to evaluate ticagrelor monotherapy following three months of DAPT in HBR patients. The HBR subgroup sample reported the need for more comprehensive research, including larger patient cohorts. Despite these limitations, clinicians consider ticagrelor monotherapy after a short DAPT course a valuable method for enabling more personalized treatment strategies and potentially offering better therapeutic options.

CONCLUSION

The prevention of aspirin and administration of ticagrelor monotherapy after 3 months of DAPT lowered the risk of the most important or clinically significant bleeding in high-risk patients undergoing PCI and DES. This could increase the risk of ischemic events, such as myocardial infarction and stroke. Treatment lasting for 3 months was more effective than the usual 12-month ticagrelor-based DAPT in lowering the incidence of NACE and bleeding events in HBR and non-HBR patients. The results showed that ticagrelor was used to lower bleeding after PCI in patients experiencing bleeding.

AUTHOR CONTRIBUTIONS

Conceptualization, B.S.Z.; Methodology, E.N.A.; Software, B.S.Z.; Validation, B.S.Z.; Formal Analysis, E.N.A.; Investigation, B.S.Z.; Resources, B.S.Z.; Data Curation, B.S.Z., E.N.A.; Writing - Original Draft, B.S.Z., E.N.A.; Writing - Review & Editing, B.S.Z., E.N.A.; Visualization, B.S.Z., E.N.A.; Supervision, B.S.Z.; Project Administration, B.S.Z., E.N.A.; Funding Acquisition, E.N.A.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

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