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Breaking boundaries: Ticagrelor monotherapy in high-risk patients

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ABSTRACT

Atherosclerotic plaque formation is a leading cause of arterial thrombosis that significantly impacts global health by instigating major adverse cardiovascular events (MACE) like myocardial infarction (MI) and stroke. Platelets are central to this process, leading to the development of antiplatelet therapies, to mitigate MACE risks. The combination of aspirin with a potent $P2Y_{12}$ inhibitor known as dual antiplatelet therapy (DAPT) is the standard for post-percutaneous coronary intervention (PCI) aimed at reducing ischemic events. However, DAPT's associated bleeding risks, particularly in high bleeding risk (HBR) patients, require a balanced approach to optimize therapeutic outcomes. Recent advancements have led to the exploration of ticagrelor monotherapy as a promising strategy after short-term DAPT to reduce bleeding risks while preserving ischemic protection. This review manuscript focuses on ticagrelor monotherapy for HBR patients with discussion on optimal timing, patient selection, and treatment duration. It highlights ticagrelor's broad efficacy in diverse patient sub-groups and outlines its superiority over aspirin (ASA) and clopidogrel monotherapies. Trials such as TICO, TWILIGHT, GLOBAL LEADERS, and ULTIMATE-DAPT as well as literature *meta*-analyses validate ticagrelor monotherapy's role in lowering mortality and clinical adverse events versus conventional DAPT. The review endorses a personalized treatment regimen, beginning with DAPT before moving to ticagrelor monotherapy, as a balanced method for managing both bleeding and ischemic risks in post-PCI acute coronary syndrome (ACS) patients, especially those facing higher bleeding threats.

1. Introduction

Atherosclerotic plaque formation significantly increases the risk of arterial thrombosis, leading to vascular blockages and tissue ischemia or infarction. This process is a substantial contributor to premature morbidity and mortality globally, often resulting in MACE, such as cardiovascular death, MI, and stroke. In the coronary arteries, this can quickly evolve into ACS, including ST-elevation MI (STEMI) and non-ST-elevation ACS (NSTE-ACS) [1].

1.1. Role of platelets and antiplatelet therapy

Platelets play a pivotal role in the formation of atherosclerotic plaques, which has led to the development of antiplatelet agents aiming to mitigate the risk of MACE by inhibiting platelet functions [2]. DAPT, comprising aspirin and a $P2Y_{12}$ inhibitor, is the established regimen for ACS patients post-PCI to inhibit thromboxane A2 synthesis and ADP-induced platelet activation, effectively reducing ischemic incidents [3]. However, in HBR patients, the significant increase in bleeding

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associated with DAPT requires strategies to balance these risks while preserving ischemic benefits [4].

1.2. Ischemic and bleeding risks

The European Society of Cardiology (ESC) and European Association for Cardio-Thoracic Surgery (EACTS) guidelines recommend defining ischemic risk based on age ≥ 50 years, and having one additional high-risk criteria such as age ≥ 65 years, diabetes mellitus (DM) on medication, a second prior MI, multivessel coronary artery disease (CAD), or chronic renal dysfunction (estimated creatinine clearance < 60 ml/min). Furthermore, high ischemic risk (HIR) is considered either an acute clinical presentation or an anatomical/procedural feature which might increase the MI risk [5].

The 2017 ESC guidelines advised personalized adjustment of DAPT using risk assessments tools such as PRECISE-DAPT and DAPT scores, especially for HBR patients identified by specific criteria such as age, comorbidities, and prior bleeding events [6]. HBR is defined as a risk of experiencing a Bleeding Academic Research Consortium (BARC) type 3 or 5 bleeding event of ≥ 4 %, or a risk of intracranial hemorrhage (ICH) of ≥ 1 %, within 1 year. Academic Research Consortium for High Bleeding Risk (ARC-HBR) uses a major criterion of BARC 3 or 5 at ≥ 4 % or ICH ≥ 1 % at 1-year, with minor criteria of increasing bleeding risk to BARC 3 or 5 at < 4 % at 1-year. HBR patients meet at least one major or two minor criteria, impacting clinical decisions and trial analyses. Risk factors for post-PCI bleeding include advanced age (≥75 years), comorbidities, prior bleeding events, iatrogenic factors, anemia, and low platelet count [7]. Nearly 40 % of PCI patients fall into the HBR category, highlighting the need for tailored antiplatelet therapy to minimize bleeding while preserving efficacy [8]. The PEGASUS-TIMI 54 study identified two independent major risk predictors for HBR, including a history of spontaneous bleeding requiring hospitalization and low hemoglobin levels (<10 g/dL), and others with no such predictors of bleeding were categorized as low bleeding risk (LBR) [9].

Recent advancements in antiplatelet therapy, with DAPT as the standard, have greatly improved the outcomes for patients with post-ACS PCI. However, the challenge lies in managing bleeding risks, particularly in HBR patients. The shift towards ticagrelor monotherapy after DAPT presents a promising strategy, but further exploration is needed to determine the appropriate timing, selection, and duration of treatment. This review study aimed to evaluate the transition from DAPT to ticagrelor monotherapy in ACS patients post-PCI, focusing on HBR patients. It compares the efficacy of short-term DAPT followed by ticagrelor versus standard DAPT across various sub-groups, aiming to minimize bleeding risks while maintaining ischemic protection. This approach is supported by strong evidence from multiple randomized trials and *meta*-analyses.

2. Temporal dynamics of risks post-PCI

Immediately following PCI, patients face the highest risk of ischemic events, particularly within the first two weeks, which then tends to decrease over time [10,11]. However, the bleeding risk associated with continuous use of DAPT remains high and constant, suggesting that the benefit of DAPT may decline over time. This understanding has led to the exploration of DAPT de-escalation strategies in ACS management, focusing to balance the initial high ischemic risk and the subsequent consistent bleeding risk, promoting a customized antiplatelet therapy approach post-ACS [12].

2.1. Advanced $P2Y_{12}$ inhibitors in DAPT: Guidelines and recommendations

Extensive research has been dedicated to understanding the DAPT's (aspirin with a $P2Y_{12}$ inhibitor) effectiveness in reducing ischemic events versus aspirin alone. Initially, clopidogrel was the standard choice; however, newer $P2Y_{12}$ inhibitors such as prasugrel and ticagrelor have emerged, offering superior benefits. Consequently, current clinical guidelines issued by the American College of Cardiology (ACC), the American Heart Association (AHA), and ESC have endorsed the preferential use of these advanced $P2Y_{12}$ inhibitors in combination with aspirin [13]. Current ESC 2023 guidelines suggest revising the standard 12-month DAPT regimen for ACS to shorter periods (1 or 3–6 months) or transitioning from potent agents such as prasugrel/ticagrelor to clopidogrel based on individual risk profiles, with an emphasis on minimizing bleeding risks, especially in HBR patients. This approach includes abbreviated DAPT and de-escalation strategies, tailored to a patient's bleeding and ischemic risks, including choosing $P2Y_{12}$ inhibitors, DAPT duration, or switching to single antiplatelet therapy (SAPT) based on bleeding risk [14].

2.2. Strategies to minimize bleeding post-PCI

DAPT plays a vital role in preventing thrombotic events, especially in patients with HIR [15]. The ACC/AHA and ESC guidelines suggest a tailored DAPT duration of 6-months for chronic coronary syndrome and 12-months for post-ACS patients, with shorter periods considered for those with HBR [13]. To further minimize bleeding risks, current research mainly focuses on strategies including shortening DAPT (either by stopping the $P2Y_{12}$ inhibitor or aspirin) or adjusting DAPT (drug type and dose modulations) [16]. Fig. 1 outlines treatment options for ACS patients based on their risk profiles [17].

2.3. De-escalation strategies and clinical trial insights

Clinical trials such as TALOS-AMI [18], STOP DAPT-2 ACS [19], and SMART-DATE [20] have explored the feasibility of shortening DAPT, ranging from 1 to 6 months, with subsequent switch to monotherapy, often using either aspirin or clopidogrel. These studies aim to find an optimal balance between reducing bleeding risk and maintaining adequate protection against ischemic events; thus, underlining the necessity of personalized antiplatelet therapy tailored to each patient's risk profile [18–20].

3. Balancing bleeding and ischemic risks in ACS patients: Strategies for HBR patients

3.1. Short-term DAPT followed by ASA + decreased $P2Y_{12}$ inhibition: A 12-month strategy

In the TALOS-AMI trial involving 2,697 Korean AMI patients post-PCI, participants were randomized to switch to clopidogrel and ASA or continue with ticagrelor and ASA, without a clopidogrel loading dose. The primary endpoint was a composite of MACE, including cardiovascular death, nonfatal MI, and stroke, as well as clinically significant bleeding. After 12 months, the de-escalation group had a lower incidence of the primary endpoint (4.6 %) compared to the control group (8.2 %; $p = 0.0001$), with no significant difference in major cardiovascular events (2.1 % vs. 3.1 %; $p = 0.15$). However, the de-escalation group experienced significantly less major bleeding (3.0 % vs. 5.6 %; $p = 0.0012$). Despite these findings, limitations such as the study's open-label design, lack of genotyping, and undefined noninferiority threshold for ischemic outcomes limit definitive conclusions regarding ischemic safety and the impact of genetics on treatment strategy [21].

3.2. Short-term DAPT to ASA monotherapy: A 12-month transition

Recent studies on ACS patients, including SMART-DATE [22], DAPT-STEMI [23], and REDUCE ACS [24], have investigated ASA monotherapy following short-term DAPT.

The SMART-DATE study on 2,712 patients, compared the results of 6-months of DAPT followed by ≥ 12 months of ASA monotherapy with

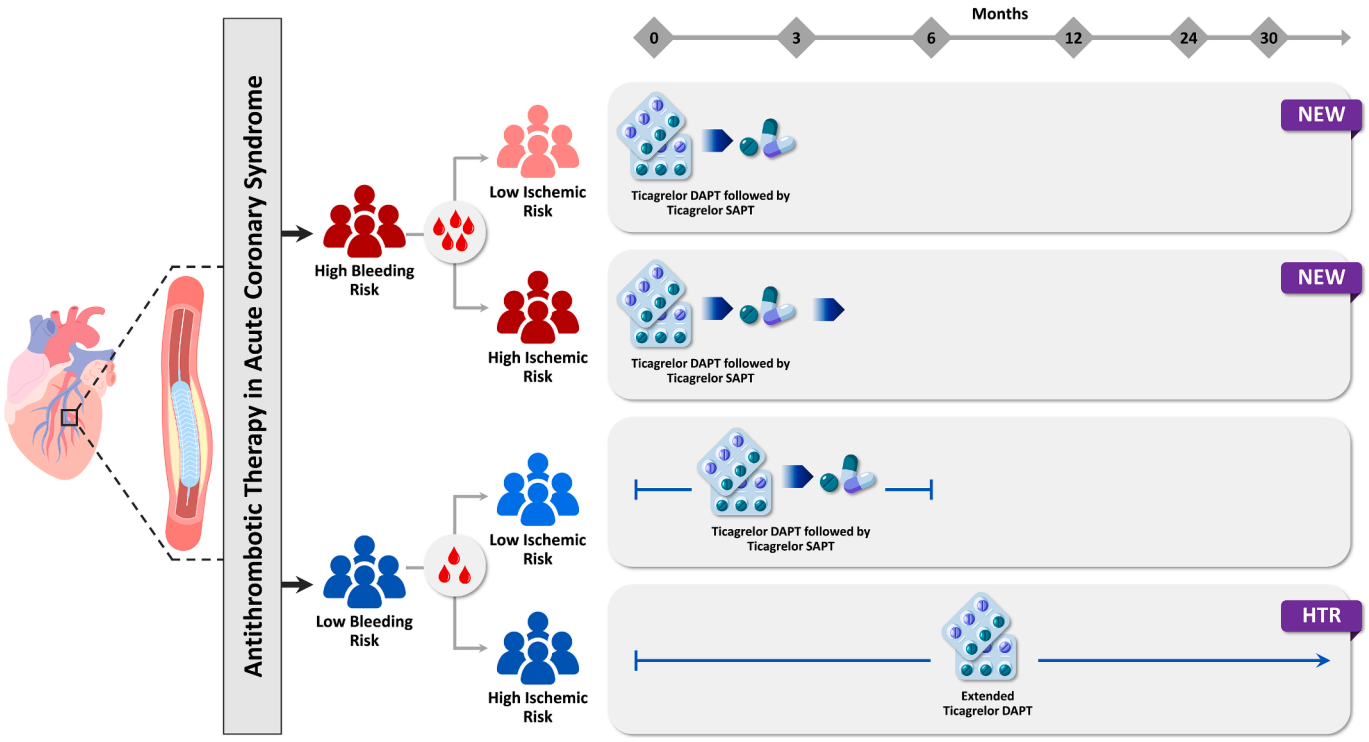

Fig. 1. Patient-tailored antithrombotic approaches for acute coronary syndrome patients. DAPT, dual antiplatelet therapy; HTR, high ticagrelor responders; SAPT, single antiplatelet therapy.

DAPT. At 18 months, the ASA group had reported slightly higher major adverse cardiovascular and cerebrovascular events (MACCE) (4.7 % vs. 4.2 %, non-inferior), and a higher incidence of MI (1.8 % vs. 0.8 %), but they experienced fewer bleeding events (2.7 % vs. 3.9 %) when compared to the extended DAPT group. These findings suggest that 6-month DAPT regimen may increase the MI risk in ACS patients with drug-eluting stent (DES) compared with ≥ 12-month DAPT. However, the limitations in study design, patient selection criteria, and biases, such as clopidogrel use, might affect the result validity and the ability to detect the rare events [22].

The DAPT-STEMI study on 870 patients with ST-Elevation Myocardial Infarction (STEMI), showed that 6-month of DAPT followed by ASA monotherapy was non-inferior to the 12-month DAPT, with lower net adverse clinical events (NACE, which includes death, MI, stroke, major bleeding, and revascularization) at 18 months (4.8 % vs. 6.6 %, non-inferior) and MI rates (1.8 %) remained consistent. Bleeding events were non-significant between the groups. The study that focused on second-generation DES post-PCI had limitations, including unclear composite endpoints, patient exclusion, and varied $P2Y_{12}$ inhibitor use, mainly applying to Resolute Integrity stents; thus, limiting generalizability [23].

The REDUCE ACS study on 1,496 patients compared 3-month DAPT followed by ASA with 12-month DAPT and showed similar 1-year NACE rates (8.2 % ASA vs. 8.4 % DAPT, non-inferiority). ASA monotherapy exhibited a slight increase in MACE risk at 12 months (4.1 % vs. 3.1 %) and a lower bleeding events compared to DAPT (2.5 % vs. 3.0 %). Despite concluding that 3-month DAPT is non-inferior in ACS patients with the COMBO stent, the study recommends 1-year DAPT due to slightly higher mortality and stent thrombosis rates in the 3-month cohort, advising shorter DAPT only when necessary [24].

3.3. Short-term DAPT to clopidogrel monotherapy: A 12-month transition

The STOP DAPT-2 ACS randomized controlled trial (RCT) involving 4,136 ACS patients post-PCI, found that clopidogrel monotherapy after 1–2 months of DAPT did not meet the non-inferiority criteria compared to 12 months of DAPT, with the short-duration group showing higher cardiovascular events (2.8 % vs. 1.9 %) but fewer bleeding incidents (0.5 % vs. 1.2 %). This suggests that early transition to clopidogrel monotherapy was less effective than 12-month DAPT, highlighting the need for further research on treatment optimization [25].

Moreover, clopidogrel's effectiveness is compromised in 5–44 % of patients globally, including India, primarily due to genetic variations such as those in the CYP2C19 gene and issues with drug interactions and absorption [26,27]. This resistance in high-risk groups like those with diabetes, renal problems, or transient ischemic attack (TIA) history emphasizes the need for personalized adjustments or stronger $P2Y_{12}$ inhibitors like prasugrel or ticagrelor [26]. The POPular Genetics trial advocates for a genotype-guided approach to tailor DAPT de-escalation, highlighting the importance of integrating genetic and clinical data to improve clopidogrel efficacy and outcomes in ACS management [28–30].

Considering the challenges with clopidogrel and ASA monotherapies post-DAPT, including higher MI rates with ASA (SMART DATE) [22] and clopidogrel's failure to demonstrate non-inferiority (STOP DAPT2-ACS) [25], ticagrelor monotherapy presents a promising alternative that highlights ticagrelor's preferable risk–benefit balance. However, studies such as SMART-DATE [22], DAPT-STEMI [23], and REDUCE ACS [24] have design limitations (open-label, non-inferiority designs) that might bias results, underlining the need for careful interpretation and an effective monotherapy option post-DAPT [22–24].

4. Shifting gears: Transition to ticagrelor monotherapy after short-term DAPT

Multiple studies have consistently shown that after a short period of DAPT, transitioning to ticagrelor monotherapy can reduce bleeding risks without increasing ischemic events in patients undergoing PCI.

The ULTIMATE-DAPT study found that ticagrelor monotherapy significantly lowered the risk of bleeding compared to a continued DAPT

regimen, while maintaining similar rates of ischemic events [31]. Similarly, the TWILIGHT trial showed that switching to ticagrelor monotherapy after 3 months of DAPT significantly reduced bleeding risk in high-risk PCI patients, without increasing ischemic events such as heart attack, stroke, or death [32]. This benefit was consistent across various patient subgroups. Notably, elderly patients aged ≥ 65 years experienced a substantial reduction in significant bleeding while maintaining ischemic safety, irrespective of age [33]. Patients with and without a prior heart attack [34], as well as those with diabetes [35], experienced reduced bleeding risks without an increase in ischemic complications [34,35]. These positive outcomes were consistent across different types of DES, with similar rates of target lesion failure (TLF) and a reduction in both bleeding and major cardiac events [36]. The benefits extended both to HBR and non-HBR patients [37], further reducing the occurrence of major bleeding across all DES types [38].

In both NSTE-ACS and stable patients, ticagrelor monotherapy effectively lowered bleeding rates while maintaining similar rates of death, heart attack, or stroke [39]. Overall, the trial highlights the potential of ticagrelor monotherapy in post-PCI management to significantly reduce bleeding risks without increasing ischemic events, across a wide range of patient subgroups and clinical scenarios [33–39] (Table 1).

The TICO trial, an open-label RCT, compared ticagrelor monotherapy post 3-month DAPT with a 12-month ticagrelor-based DAPT regimen in ACS patients post-PCI with new-generation Sirolimus-eluting stents. The study showed that switching to ticagrelor monotherapy after 3 months of DAPT in ACS patients post-PCI with new-generation Sirolimus-eluting stents resulted in a significant reduction in adverse events and major bleeding compared to continuing a 12-month DAPT regimen. The risk of ischemic events was similar between the two groups [40]. Subgroup analyses further supported these findings, with diabetic patients experiencing reduced bleeding risks without an increase in ischemic events after switching to ticagrelor monotherapy. In patients with STEMI, including those at high bleeding risk, both bleeding and ischemic event rates were comparable across different types of ACS [41,42]. This highlights the advantage of ticagrelor over prolonged DAPT in diverse patient groups (Table 1).

The T-PASS study showed that ACS patients with DES, who switched to ticagrelor monotherapy after a short course of DAPT (average 16 days) had a lower incidence of adverse events and major bleeding compared to those who continued with longer-term DAPT. These results suggest that ticagrelor monotherapy might be a safer and more effective option than prolonged aspirin use for ACS patients following DES implantation [43].

A sub-study of the GLOBAL LEADERS trial demonstrated that an aspirin-free approach (1 month of DAPT followed by 23 months of ticagrelor monotherapy) significantly reduced major bleeding in ACS patients compared to standard therapy (12 months of DAPT followed by 12 months of aspirin). This improvement was most evident in patients who had their procedures over 10 days after the initial PCI [44]. In another analysis of multivessel PCI patients within the GLOBAL LEADERS trial, the aspirin-free approach significantly lowered the risk of death or new heart attacks, without increasing the bleeding risks as compared to the standard regimen [45]. For patients with complex PCI, the ticagrelor monotherapy regimen also reduced the risk of death or heart attack and other composite endpoints, without increasing major bleeding. These findings emphasize the potential benefits of such approaches in managing a range of complex PCI cases [46].

The GLASSY sub-study demonstrated that ticagrelor monotherapy after 1 month of DAPT was equally effective as 12 months of DAPT in reducing ischemic events over two years. Moreover, major bleeding rates were similar between both groups. Ticagrelor significantly reduced the risk of heart attacks and stent thrombosis after one year, confirming it as a safe and effective option without increasing the major bleeding risk [47].

Overall, studies suggest that ticagrelor monotherapy after short DAPT can effectively reduce bleeding events and all-cause mortality in patients experiencing complex/staged PCI procedures, without increasing the risk of ischemic events. Sub-studies details are available in Table 1.

5. Ticagrelor monotherapy post-PCI: Insights from *meta*-analyses

A *meta*-analysis comparing short-term DAPT (1–3 months) followed by ticagrelor monotherapy with standard DAPT duration in PCI patients demonstrated significant advantages for the ticagrelor-based approach. It was associated with a 20 % reduction in all-cause mortality, an 18 % decrease in adverse events, and a 33 % lower risk of major bleeding. Importantly, there was no significant difference in major cardiovascular events between the two approaches. These results indicate that short-term DAPT followed by ticagrelor monotherapy could be a safer and more effective treatment strategy, particularly for patients with ACS, thus, possibly shaping future medical guidelines as an alternative to standard DAPT [57].

Another *meta*-analysis, SYDNEY, involving 14,628 patients compared ticagrelor monotherapy with DAPT following PCI in patients with DES. The study demonstrated that ticagrelor monotherapy significantly reduced major bleeding without increasing the risk of ischemic events. The incidence of all-cause death, heart attack, or stroke were comparable between both the treatment approaches, with ticagrelor further reducing all-cause and cardiovascular mortality. These findings suggest that ticagrelor monotherapy could be a safer and viable option to extended DAPT in post-PCI patients, providing an opportunity to better balance manage both in managing both bleeding and ischemic risks. These findings may result into potential shifts in clinical practice, leading to greater adoption of ticagrelor monotherapy treatment for specific group of patients [58].

A systematic *meta*-analysis assessed the efficacy and safety of ticagrelor monotherapy post-PCI by analysing studies from 2015 to 2020, where 1-month DAPT followed by 23 months of ticagrelor was compared with 12 months of DAPT followed by aspirin. The study findings showed no significant differences in the rates of MI, stroke, stent thrombosis, or new Q-wave events between the two treatment strategies. However, ticagrelor monotherapy was associated with significantly lower rates of all-cause death, cardiovascular death, and revascularization compared to the standard DAPT approach, which had higher rates of severe bleeding [59].

Overall, these analyses indicate that transitioning to ticagrelor monotherapy after a brief course of DAPT could lead to improved outcomes and lower mortality rates, in certain PCI patients, especially those at heightened risk of bleeding.

6. Beyond the year: Exploring the extended benefits of ticagrelor monotherapy

In the PANTHER trial, a *meta*-analysis of seven RCTs with 24,325 CAD participants, 12,178 received $P2Y_{12}$ inhibitors (62 % clopidogrel, 38 % ticagrelor) and 12,147 received aspirin monotherapy. The study demonstrated that long-term use of $P2Y_{12}$ inhibitors was more effective than aspirin monotherapy in reducing the risk of cardiovascular events, such as cardiovascular death, non-fatal heart attacks, and strokes. Moreover, $P2Y_{12}$ inhibitors were associated with a lower risk of stent thrombosis and certain bleeding events, including gastrointestinal bleeding and intracranial hemorrhage, without a significant increase in major bleeding or overall mortality rates. These findings indicate that extended $P2Y_{12}$ inhibitor monotherapy may be more effective than aspirin alone in preventing recurrent cardiovascular events in CAD patients, potentially shaping future guidelines to favor long-term $P2Y_{12}$ inhibitor use, especially in patients at high risk for stent thrombosis and bleeding [53].

Collectively, these *meta*-analyses support the use of ticagrelor

Table 1
Trials of $P2Y_{12}$ inhibitor monotherapy in patients undergoing PCI.

Study	Year	Number of patients	Design	Population	Intervention	Control	Main findings (intervention vs control)	Ref.
ULTIMATE-DAPT	2024	3,505	Double-blind	ACS Patients of age ≥ 18 years undergoing PCI with DES	Ticagrelor monotherapy after 1-month DAPT	DAPT	BARC 2, 3 or 5 bleeding at 12 months: 2.1 % vs. 4.6 %; HR 0.45, 95 % CI 0.30–0.66, P < 0.0001 MACCE at 12 months: 3.6 % vs. 3.7 %; HR 0.98, 95 % CI 0.69–1.39, P = 0.89 NACE at 12 months: 5.7 % vs. 8.2 %; HR 0.68, 95 % CI 0.53–0.88, P = 0.0066 BARC 3 or 5 bleeding at 12 months: 0.7 % vs. 1.7 %; HR 0.39, 95 % CI 0.19–0.79, P = 0.0087 TIMI major or minor bleeding at 12 months: 0.7 % vs. 1.6 %; HR 0.41, 95 % CI 0.20–0.82, P = 0.012	[31]
TWILIGHT – RCT study	2019	7,119	Double-blind	Elderly patients of age at least 65 years undergoing PCI with DES having troponin positive ACS	Ticagrelor monotherapy after 3 months of DAPT	DAPT	BARC 2, 3 or 5 bleeding at 12 months: 4.0 % vs. 7.1 %; HR 0.56, 95 % CI 0.45–0.68, P < 0.001 BARC 3 or 5 bleeding at 12 months: 1.0 % vs. 2.0 %; HR 0.49, 95 % CI 0.33–0.74 Death, MI or stroke at 12 months: 3.9 % vs. 3.9 %; HR 0.99, 95 % CI 0.78–1.25, $P_{non\text{-}inferiority}$ < 0.001	[32]
TWILIGHT sub study	2020	7,119	Double-blind	Elderly HBR patients (≥65 years, age) with DM undergoing PCI	Ticagrelor monotherapy after 3 months of DAPT	DAPT	BARC 2, 3 or 5 bleeding at12 months: 4.5 % vs. 6.7 %; HR 0.65, 95 % CI 0.47–0.91, P = 0.012 BARC 3 or 5 at 12 months: 1.1 % vs. 3.1 %; HR 0.34, 95 % CI 0.19–0.63, P = 0.001 Death, MI, or stroke at 12 months: 4.6 % vs. 5.9 %; HR 0.77, 95 % CI 0.55–1.09, P = 0.14	[35]
TWILIGHT-ACS	2020	7,119	Double-blind	Elderly HBR patients (≥65 years, age) with NSTE-ACS undergoing PCI with DES	Ticagrelor monotherapy after 3 months of DAPT	DAPT	BARC 2, 3 or 5 bleeding at 12 months: 3.6 % vs. 7.6 %; HR 0.47, 95 % CI 0.36–0.61, P < 0.001 Death, MI or stroke at 12 months: 4.3 % vs. 4.4 %; HR 0.97, 95 % CI 0.74–1.28, P = 0.84	[39]
TWILIGHT sub study	2020	7,119	Double-blind	Elderly HBR patients (≥65 years, age) undergoing complex PCI	Ticagrelor monotherapy after 3 months of DAPT	DAPT	BARC 2, 3 or 5 bleeding at 12 months: Complex PCI[n(%) = 32.8]: 4.2 % vs. 7.7 %; HR 0.54, 95 % CI 0.38–0.76 Noncomplex PCI[n(%) = 67.1]: 3.9 % vs. 6.8 %; HR 0.57, 95 % CI 0.44–0.73 $P_{interaction}$ = 0.79 BARC 3 or 5 bleeding at 12 months: Complex PCI[n(%) = 32.8]: 1.1 % vs. 2.6 %; HR 0.41, 95 % CI 0.21–0.80 Noncomplex PCI[n(%) = 67.1]: 0.9 % vs. 1.7 %; HR 0.56, 95 % CI 0.33–0.94 $P_{interaction}$ = 0.47 Death, MI or stroke at 12 months: Complex PCI[n(%) = 32.8]: 3.8 % vs. 4.9 %; HR 0.77, 95 %	[48]

(*continued on next page*)

Table 1 (*continued*)

Study	Year	Number of patients	Design	Population	Intervention	Control	Main findings (intervention vs control)	Ref.
							CI 0.52–1.15 Noncomplex PCI[n(%) = 67.1]: 3.9 % vs. 3.5 %; HR 1.13, 95 % CI 0.84–1.53 $P_{interaction} = 0.13$	
TWILIGHT-SYNERGY	2021	7,057	Open-label	Elderly HBR patients (≥65 years, age) with DES (SYNERGY BP-DES and DP-DES)	Ticagrelor monotherapy after 3 months of DAPT	DAPT	Cardiac death, MI, TLR, ST or stroke at 15 months: SYNERGY BP-DES [n(%) = 9.3]: 3.4 % vs. 3.3 %; HR 1.27, 95 % CI 0.47–3.44. DP-DES [n(%) = 90.7]: 3.9 % vs. 3.9 %; HR 0.99, 95 % CI 0.74–1.31. $P_{interaction} > 0.10$ BARC 2, 3 or 5 bleeding at 12 months: SYNERGY BP-DES [n(%) = 9.3]: 5.1 % vs. 8.2 %; HR 0.66, 95 % CI 0.32–1.37. DP-DES [n(%) = 90.7]: 4.1 % vs. 6.7 %; HR 0.60, 95 % CI 0.47–0.77. $P_{interaction} > 0.10$	[36]
TWILIGHT-HBR	2021	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: Non-HBR [n(%) = 82.8]: 3.5 % vs. 5.9 %; HR 0.59, 95 % CI 0.46–0.77 HBR [n(%) = 17.2]: 6.3 % vs. 11.4 %; HR 0.53, 95 % CI 0.35–0.82 $P_{interaction} = 0.67$ BARC 3 or 5 bleeding at 12 months: Non-HBR [n(%) = 82.8]: 0.8 % vs. 1.3 %; HR 0.62, 95 % CI 0.36–1.09 HBR [n(%) = 17.2]: 1.6 % vs. 5.0 %; HR 0.31, 95 % CI 0.14–0.67,P = 0.098 $P_{interaction} = 0.15$ ARD: −3.0 %, 95 % CI −5.2 % to −0.8 %; P = 0.008) Ischemic events: Non-HBR [n(%) = 82.8]: 3.6 % vs. 3.6 %; HR 1.01, 95 % CI 0.75–1.35, P = 0.949, ARD −0.0 % (95 % CI −1.0 % to 1.1 %) HBR [n(%) = 17.2]: 6.5 % vs. 5.6 %; HR 1.16, 95 % CI 0.71–1.90,P = 0.554, ARD 0.9 % (95 % CI −2.1 % to 3.8 %) $P_{interaction} = 0.637$	[37]
TWILIGHT sub study	2021	6,532	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: 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, $P_{interaction} = 0.77$	[33]
TWILIGHT sub study	2021	7,119	Open-label	Elderly HBR female patients (≥65 years, age) and elderly male patients (≥63 years, age) undergoing PCI	Ticagrelor monotherapy after 3 months of DAPT	DAPT	BARC 2, 3 or 5 bleeding at 12 months: Women[n(%) = 23.9]: 5.0 % vs. 8.6 %; AHR 0.62, 95 % CI 0.42–0.92, P = 0.02 Men [n(%) = 76.1]: 3.7 % vs. 6.6 %; AHR 0.57, 95 % CI 0.44–0.73, P < 0.001 $P_{interaction} = 0.69$ Death, MI or stroke at 12	[49]

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Table 1 (*continued*)

Study	Year	Number of patients	Design	Population	Intervention	Control	Main findings (intervention vs control)	Ref.
							months: Women[n(%) = 23.9]: 3.5 % vs. 3.5 %; AHR 1.04, 95 % CI 0.61–1.77,P = 0.88 Men [n(%) = 76.1]: 4.0 % vs. 4.1 %; AHR 1.06, 95 % CI 0.80–1.39,P = 0.69 $P_{interaction}$ = 0.95	
TWILIGHT-STENT	2021	7,119	Open-label	Elderly HBR patients (≥65 years, age) undergoing PCI stratified according to the different DES type	Ticagrelor monotherapy after 3 months of DAPT	DAPT	BARC 2, 3 or 5 bleeding at 12 months: DP-EES [n(%) = 52.2]: 3.8 % vs. 6.7 %; HR 0.56, 95 % CI 0.41–0.78 DP-ZES [n(%) = 23.4]: 4.6 % vs. 6.9 %; HR 0.66, 95 % CI 0.42–1.04 BP-DES [n(%) = 24.4]: 4.2 % vs. 7.9 %; HR 0.52, 95 % CI 0.33–0.81, $P_{interaction}$ = 0.76 Death, MI or stroke at 12 months: DP-EES [n(%) = 52.2]: 4.2 % vs. 4.3 %; HR 0.97, 95 % CI 0.68–1.37 DP-ZES [n(%) = 23.4]: 4.1 % vs. 3.1 %; HR 1.32, 95 % CI 0.75–2.33 BP-DES [n(%) = 24.4]: 3.9 % vs. 4.2 %; HR 0.92, 95 % CI 0.54–1.55, $P_{interaction}$ = 0.60	[38]
TWILIGHT-Sub study	2022	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 [n(%) = 29.7]: 3.4 % vs. 6.7 %; HR 0.50, 95 % CI 0.33–0.76. No prior MI [n(%) = 70.3]: 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 [n(%) = 29.7]: 6.0 % vs. 5.5 %; HR 1.09, 95 % CI 0.75–1.58. No prior MI [n(%) = 70.3]: 3.1 % vs. 3.3 %; HR 0.92, 95 % CI 0.67–1.28. $P_{interaction}$ = 0.52	[34]
TWILIGHT sub study	2022	7,038	Open-label	Elderly HBR patients (≥65 years, age) undergoing PCI categorized according to different BMI	Ticagrelor monotherapy after 3 months of DAPT	DAPT	BARC 2, 3 or 5 bleeding at 12 months: Normal weight [n(%) = 25.7]: HR 0.48, 95 % CI 0.32–0.73. Overweight [n(%) = 41.6]: HR 0.57, 95 % CI 0.41–0.78. Obese [n(%) = 32.7]: HR 0.63, 95 % CI 0.44–0.91. $P_{interaction}$ = 0.627 Death, MI, or stroke at 12 months: Normal weight[n(%) = 25.7]: HR 1.36, 95 % CI 0.84–2.19. Overweight [n(%) = 41.6]: HR 0.92, 95 % CI 0.63–1.35. Obese [n(%) = 32.7]: HR 0.84, 95 % CI 0.56–1.25. $P_{interaction}$ = 0.290	[50]
TWILIGHT sub study	2023	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,	[51]

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Table 1 (*continued*)

Study	Year	Number of patients	Design	Population	Intervention	Control	Main findings (intervention vs control)	Ref.
							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 %	
TICO – RCT study	2020	3,056	Open-label	ACS patients undergoing PCI with ultrathin bioresorbable polymer sirolimus-eluting stents	Ticagrelor monotherapy after 3 months of DAPT	DAPT	Death, MI, stroke, ST, TVR or major bleeding: 3.9 % vs. 5.9 %; HR 0.66, 95 % CI 0.48–0.92, P = 0.01 TIMI major bleeding: 1.7 % vs. 3.0 %; HR 0.56, 95 % CI 0.34–0.91, P = 0.02	[40]
TICO – sub study	2021	3,056	Open-label	South Korean patients with or without diabetes mellitus undergoing PCI	Ticagrelor monotherapy after 3 months of DAPT	DAPT	Any Ischemic events: Diabetes[n(%) = 27.3]: 4.5 % vs. 5.5 %; HR 0.83, 95 % CI 0.45–1.52, P = 0.540 No Diabetes[n(%) = 72.6]: 2.3 % vs. 3.4 %; HR 0.69, 95 % CI 0.42–1.13, P = 0.138 $P_{interaction} = 0.645$ BARC 3 or 5 bleeding: Diabetes[n(%) = 27.3]: 5.7 % vs. 7.0 %; HR 0.83, 95 % CI 0.48–1.43, P = 0.505 No Diabetes[n(%) = 72.6]: 0.6 % vs. 4.9 %; HR 0.54, 95 % CI 0.34–0.84, P = 0.007 $P_{interaction} = 0.219$ TIMI major bleeding: Diabetes[n(%) = 27.3]: 2.9 % vs. 4.3 %; HR 0.67, 95 % CI 0.32–1.39, P = 0.281 No Diabetes[n(%) = 72.6]: 1.2 % vs. 2.4 %; HR 0.48, 95 % CI 0.25–0.94, P = 0.031 $P_{interaction} = 0.513$	[41]
TICO – sub study	2021	3,056	Open-label	Patients undergoing PCI for ACS (STEMI, NSTEMI and unstable angina)	Ticagrelor monotherapy after 3 months of DAPT	DAPT	NACE at 1 year: STEMI[n(%) = 4.4]: 3.7 % vs. 5.0 %; HR 0.73, 95 % CI 0.41–1.29 NSTEMI[n(%) = 6.0]: 4.8 % vs. 7.4 %; HR 0.66, 95 % CI 0.40–1.09 Unstable angina[n(%) = 4.1]: 2.9 % vs. 5.2 %; HR 0.57, 95 % CI 0.29–1.12 $P_{interaction} = 0.64$ TIMI major bleeding: STEMI[n(%) = 4.4]: 0.9 % vs. 2.9 %; HR 0.32, 95 % CI 0.12–0.87 NSTEMI[n(%) = 6.0]: 2.4 % vs. 3.5 %; HR 0.69, 95 % CI 0.34–1.43 Unstable angina[n(%) = 4.1]: 1.6 % vs. 2.5 %; HR 0.64, 95 % CI 0.25–1.63 $P_{interaction} = 0.36$ TIMI major or minor bleeding: STEMI[n(%) = 4.4]: 3.1 % vs. 5.0 %; HR 0.62, 95 % CI 0.34–1.13 NSTEMI[n(%) = 6.0]: 3.3 % vs. 7.4 %; HR 0.45, 95 % CI 0.25–0.79 Unstable angina[n(%) = 4.1]: 4.1 % vs. 3.9 %; HR 1.05, 95 % CI 0.55–2.00 $P_{interaction} = 0.29$ Ischemic outcomes: MACCE at	[42]

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Table 1 (*continued*)

Study	Year	Number of patients	Design	Population	Intervention	Control	Main findings (intervention vs control)	Ref.
							1 year STEMI[n(%) = 4.4]: 2.7 % vs. 2.5 %; HR 1.10, 95 % CI 0.53–2.27 NSTEMI[n(%) = 6.0]: 2.6 % vs. 4.5 %; HR 0.58, 95 % CI 0.30–1.13 Unstable angina[n(%) = 4.1]: 4.1 % vs. 3.1 %; HR 0.44, 95 % CI 0.17–1.13 $P_{interaction} = 0.14$	
T-PASS	2020	2,850	Open-label	Patients undergoing DES implantation with biodegradable polymer sirolimus-eluting stent with ACS (MI and unstable angina)	Ticagrelor monotherapy after < 1-month DAPT	Ticagrelor based 12-month DAPT	All-death, MI, stroke, ST or major bleeding: 2.8 % vs. 5.2 %; HR 0.54, 95 % CI 0.37–0.80, $P_{noninferiority} < 0.001$ $P_{superiority} = 0.002$ Major bleeding (BARC 3 or 5): 1.2 % vs. 3.4 %; HR 0.35, 95 % CI 0.20–0.61, P < 0.001	[43]
GLOBAL LEADERS	2018	15,968	Open-label	Patients of age ≥ 18 years with CAS	Ticagrelor monotherapy (23 months) after 1 month of DAPT	DAPT	Death or Q- wave MI at 24 months: 3.81 % vs. 4.37 %; RR 0.87, 95 % CI 0.75–1.01, P = 0.073 BARC 3 or 5 bleeding at 24 months: 2.04 % vs. 2.12 %; RR 0.97, 95 % CI 0.78–1.20, P = 0.77	[52]
GLOBAL LEADERS-post-hoc study	2019	15,845	Open-label	Patients of age ≥ 18 years with CAS undergoing multivessel PCI	1-month DAPT followed by 23-month ticagrelor monotherapy	12-month DAPT followed by 12-month aspirin monotherapy	Death or Q- wave MI at 24 months: 3.06 % vs. 4.85 %; HR 0.62, 95 % CI 0.44–0.88, P = 0.006 BARC 3 or 5 bleeding at 24 months: 2.47 % vs. 2.68 %; HR 0.92, 95 % CI 0.61–1.39, P = 0.685	[45]
GLOBAL LEADERS-post-hoc study	2019	15,450	Open-label	Patients of age ≥ 18 years with CAS undergoing complex PCI	1-month DAPT followed by 23-month ticagrelor monotherapy	12-month DAPT followed by 12-month aspirin monotherapy	All-cause death or new Q- wave MI at 24 months: 4.47 % vs. 3.94 %; HR 1.14, 95 % CI 0.96–1.35, P = 0.124 BARC 3 or 5 bleeding at 24 months: 2.49 % vs. 1.96 %; HR 1.28, 95 % CI 1.02–1.61, P = 0.034	[46]
GLOBAL LEADERS-sub study	2020	15,968	Open-label	Patients of age ≥ 18 years with CAS undergoing staged PCI	1-month DAPT followed by 23-month ticagrelor monotherapy	12-month DAPT followed by 12-month aspirin monotherapy	Death or Q- wave MI at 24 months: 4.7 % vs. 4.7 %; HR 0.922, 95 % CI 0.586–1.450, P = 0.725 BARC 3 or 5 bleeding at 24 months: 2.4 % vs. 3.4 %; HR 0.7, 95 % CI 0.392–1.247, P = 0.226 Patients with ACS BARC 3 or 5 bleeding 1.8 % vs 4.5 %; HR 0.387; 95 % CI 0.179 to 0.836; p = 0.016	[44]
GLASSY	2019	7, 585	Open-label	Patients of age ≥ 18 years with CAS undergoing PCI for ACS	Ticagrelor monotherapy (23 months) after 1 month of DAPT	12-month DAPT followed by 12-month aspirin monotherapy	Death, MI, stroke or urgent TVR at 24 months: 7.1 % vs. 8.4 %; RR 0.85, 95 % CI 0.72–0.99, $P_{non\text{-}inferiority} < 0.001$ $P_{superiority} = 0.047$ BARC 3 or 5 bleeding at 24 months: 2.5 % vs. 2.5 %; RR 1.00, 95 % CI 0.75–1.33, P = 0.99	[47]
PANTHER	2022	24,325	Meta-analysis	Patients with CAD	$P2Y_{12}$ inhibitor (clopidogrel or prasugrel or ticagrelor) monotherapy	DAPT	CV death, MI or stroke: 5.5 % vs. 6.3 %; HR 0.88, 95 % CI 0.79–0.97, P = 0.014 Major bleeding: 1.2 % vs. 1.4 %; HR 0.87, 95 % CI 0.70–1.09, P = 0.23 NACE:	[53]

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Table 1 (*continued*)

Study	Year	Number of patients	Design	Population	Intervention	Control	Main findings (intervention vs control)	Ref.
TREAT	2019	3,799	Open label	ACS patients of age < 75 years with STEMI receiving fibrinolytic therapy	Ticagrelor group	Clopidogrel group	6.4 % vs. 7.2 %; HR 0.89, 95 % CI 0.81–0.98, P = 0.02 (Ticagrelor vs. Clopidogrel) Death from vascular causes, MI or stroke at 12 months: 6.7 % vs 7.3 %; HR 0.93; 95 % CI 0.73–1.18; P = 0.53 Death from vascular causes, MI, stroke, severe recurrent ischemia, TIA or other ATE at 12 months: 8.0 % vs. 9.1 %; HR 0.88, 95 % CI 0.71–1.09, P = 0.25 TIMI major bleeding at 12 months: 1.0 % vs. 1.2 %; HR 0.86, 95 % CI 0.47–1.56, P = 0.61 PLATO major bleeding at 12 months: 1.6 % vs. 2.1 %; HR 0.74, 95 % CI 0.46–1.18, P = 0.21 BARC 3 or 5 bleeding at 12 months:	[54]
Other study	2023	3,528	–	Patients with ACS treated with primary PCI	Ticagrelor group	Clopidogrel group	(1.6 % vs 2.0 %; HR 0.82; 95 % CI 0.51 to 0.1.33; p = 0.43) (Ticagrelor vs. Clopidogrel) MACE: 11.9 % vs 13.0 %; HR 0.6; 95 % CI 0.4–0.9; P = 0.021 BARC total bleeding: 3.3 % vs. 5.8 %; HR 0.5, 95 % CI 0.3–1.1, P = 0.085	[55]
Other study	2024	5,713	–	Patients with ACS	Ticagrelor group	Clopidogrel group	(Ticagrelor vs. Clopidogrel) All-cause death: 15.4 % vs 33.3 %; HR 0.69; 95 % CI 0.45–1.04; P = 0.061 BARC ≥ 2 bleeding: 6.4 % vs. 7.9 %; HR 0.92, 95 % CI 0.70–1.21, P = 0.549 BARC ≥ 3 bleeding: 3.0 % vs. 3.9 %; HR 0.76, 95 % CI 0.51–1.13, P = 0.178	[56]

monotherapy post-PCI showing reduced major bleeding, potential improvements in all-cause mortality, and preserved cardiovascular protection across diverse patient groups. However, further extensive research is required to confirm these results and assess cost-effectiveness. Overall, ticagrelor monotherapy emerges as a promising approach for HBR patients post-PCI.

7. Conclusion

The management of ACS with DAPT is increasingly shifting towards a more personalized approach. Initiation with DAPT for a shorter duration, followed by a transition to ticagrelor monotherapy, particularly in patients with HBR, has proven effective in managing both bleeding and ischemic risks. This mitigates bleeding risks particularly in patients with HBR while maintaining protection against ischemic events. Balancing these risks is crucial post-PCI in HBR patients. Initially after ACS, both risks are heightened, but while ischemic risk decreases over time, bleeding risk remains constant. Adjusting DAPT intensity or duration can reduce bleeding risks without compromising ischemic protection. Clinical evidence shows that shorter duration of DAPT followed by transition to ticagrelor monotherapy demonstrates benefits in reducing bleeding, mortality, rates of MI, stroke, and revascularization without increasing bleeding risks. While this approach has the potential to improve outcomes, more research is needed to confirm these findings and assess the cost-effectiveness of this approach. This review study lays the foundation for reconsidering how we manage post-PCI care to better meet the needs of individual patients.

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Declaration of competing interest

Shital Sarda is an employee of AstraZeneca Pharma India Ltd

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Declaration of competing interest

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