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THE PRESENT AND FUTURE

JACC REVIEW TOPIC OF THE WEEK

Premature Ticagrelor Discontinuation in Secondary Prevention of Atherosclerotic CVD

JACC Review Topic of the Week

Sameer Arora, MD,[a,*] Kamal Shemisa, MD,[b,*] Muthiah Vaduganathan, MD, MPH,[c] Arman Qamar, MD,[c] Ankur Gupta, MD, PhD,[b] Sushil K. Garg, MD,[d] Dharam J. Kumbhani, MD, SM,[b] Helen Mayo, MLS,[e] Houman Khalili, MD,[f] Ambarish Pandey, MD, MSCS,[b] Sandeep R. Das, MD, MPH, MBA[f]

ABSTRACT

Ticagrelor is a cornerstone of modern antithrombotic therapy alongside aspirin in patients with acute coronary syndrome and after percutaneous coronary intervention. Adverse effects such as bleeding and dyspnea have been associated with premature ticagrelor discontinuation, which may limit any potential advantage of ticagrelor over clopidogrel. The randomized trials of ticagrelor captured adverse events, offering the opportunity to more precisely quantify these effects across studies. Therefore, a meta-analysis of 4 randomized clinical trials of ticagrelor conducted between January 2007 and June 2017 was performed to quantify the incidence and causes of premature ticagrelor discontinuation. Among 66,870 patients followed for a median 18 months, premature ticagrelor discontinuation was seen in 25%; bleeding was the most common cause of discontinuation followed by dyspnea. Versus the comparators, the relative risk of dyspnea-related discontinuation during follow-up was 6.4-fold higher, the relative risk of bleeding was 3.2-fold higher, and the relative risk of discontinuation due to any adverse event was 59% higher for patients receiving ticagrelor. Understanding these potential barriers to adherence to ticagrelor is crucial for informed patient-physician decision making and can inform future efforts to improve ticagrelor adherence. This review discusses the incidence, causes, and biological mechanisms of ticagrelor-related adverse effects and offers strategies to improve adherence to ticagrelor.
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Acute coronary syndromes (ACS) continue to be associated with significant morbidity and mortality. More than 780,000 people in the United States will experience ACS annually (1). After experiencing an event, dual antiplatelet therapy (DAPT) and risk factor modification remain essential in secondary prevention. While prescription of DAPT is an essential first step to optimal secondary

From the [a]Division of Cardiology, University of North Carolina School of Medicine, Chapel Hill, North Carolina; [b]Division of Cardiology, University of Texas Southwestern School of Medicine, Dallas, Texas; [c]Heart & Vascular Center, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts; [d]Division of Gastroenterology, Mayo Clinic, Rochester, Minnesota; [e]Health Sciences Digital Library and Learning Center, University of Texas Southwestern School of Medicine, Dallas, Texas; and the [f]Department of Medicine, Florida Atlantic University, Boca Raton, Florida. *Drs. Arora and Shemisa contributed equally to this work. Dr. Shemisa has served on the Speakers Bureau for Boehringer Ingelheim. Dr. Vaduganathan is supported by the KL2/Catalyst Medical Research Investigator Training award from Harvard Catalyst (National Institutes of Health/National Center for Advancing Translational Sciences Award UL 1TR002541); has served on advisory boards for Amgen, AstraZeneca, Bayer AG, and Baxter Healthcare; and has participated in clinical endpoint committees for studies sponsored by Novartis and the National Institutes of Health. Dr. Qamar is supported by the NHLBI T32 postdoctoral training grant (T32HL007604) and the American Heart Association Strategically Focused Research Network in Vascular Disease grant (18SFRN3390085 & 18SFRN33960262); has received grant support through Brigham and Women's Hospital from Daiichi-Sankyo; and has received fees for educational activities from the American College of Cardiology, Society for Cardiovascular Angiography and Interventions, Pfizer, Medscape, and Clinical Exercise Physiology Association. Dr. Kumbhani has received honoraria from the American College of Cardiology. Dr. Pandey is funded by the Texas Health Resources Clinical Scholarship. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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HIGHLIGHTS

- Ticagrelor is a cornerstone of antithrombotic therapy after ACS, but its effectiveness is limited by nonadherence.
- Premature ticagrelor discontinuation occurs in 25% of patients and is related to adverse events.
- The most frequent adverse events of ticagrelor are bleeding and dyspnea.
- Appropriate patient selection, early follow-up, patient education, and appropriate bleeding prophylaxis can mitigate ticagrelor nonadherence.

ABBREVIATIONS AND ACRONYMS

ACS = acute coronary syndrome

DAPT = dual antiplatelet therapy

RR = relative risk

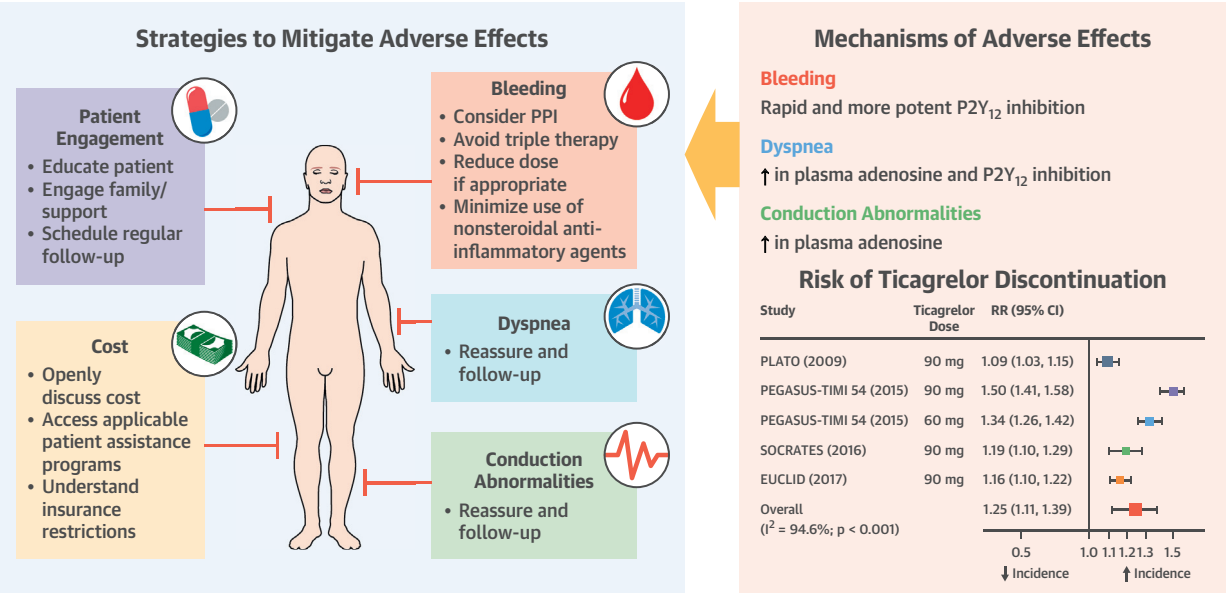
prevention medical therapy, the rates of long-term adherence have been estimated to be <50% (2). Premature discontinuation of DAPT in the first year of prescription has been associated with increased morbidity and mortality (3). Patient adherence to DAPT is therefore a crucial and frequently encountered issue in clinical practice. There are many barriers to DAPT adherence after hospital discharge; however, a major driver of discontinuation may be drug-related adverse effects. Ticagrelor has emerged as first-line therapy in patients with ACS in European guidelines (Class I) and as co-first line (along with clopidogrel) in U.S. guidelines (Class IIa) (4–6). Conversely, ticagrelor has important potential drug-related adverse effects versus clopidogrel: higher bleeding due to a more potent antiplatelet effect, and a known side effect of dyspnea (7–10). This contributes to higher observed rates of nonadherence to ticagrelor following percutaneous coronary interventions when compared with clopidogrel (11). This in-depth review more precisely quantifies incidence and causes of ticagrelor discontinuation and offers strategies to improve adherence to long-term ticagrelor therapy (**Central Illustration**).

DATA FROM RANDOMIZED CLINICAL TRIALS

From 316 screened citations, we reviewed 229 full-text papers and identified 28 eligible studies of which 4 randomized clinical trials were included in the primary analysis (**Figure 1**). Relevant patient characteristics, comorbidities, and medication history were recorded from each of the trials (**Table 1**). In the PLATO (Study of Platelet Inhibition and Patient Outcomes) and EUCLID (Examining Use of Ticagrelor in Peripheral Artery Disease) trials, ticagrelor was compared with clopidogrel, whereas in PEGASUS-TIMI 54 (Prevention of Cardiovascular Events in Patients with Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin-Thrombolysis In Myocardial Infarction 54) and SOCRATES (Acute Stroke or Transient Ischemic Attack Treated with Aspirin or Ticagrelor and Patient Outcomes) trials, the comparator was aspirin (7–10). The discontinuation rates (premature, dyspnea, and any adverse events) attributed to ticagrelor were higher versus the comparator (clopidogrel or aspirin) and were statistically significant across studies (**Table 2**). Discontinuation attributed to bleeding was significantly higher with ticagrelor in 3 of the 4 studies. On meta-analysis, a total of 66,870 patients were followed for a median of 18 months and the relative risk of premature discontinuation during follow-up was 25% higher for patients receiving ticagrelor compared with those receiving the comparator (relative risk [RR]: 1.25; 95% confidence interval [CI]: 1.11 to 1.39; $I^2 = 94.6\%$; $p < 0.001$). The RR of dyspnea-related discontinuation during follow-up was 6.4-fold higher for patients receiving ticagrelor than for those receiving comparator (RR: 6.40; 95% CI: 5.39 to 7.41; $I^2 = 95\%$; $p < 0.001$) (**Figure 2**). The RR of bleeding-related discontinuation during follow-up was 3.2-fold higher for patients receiving ticagrelor than for those receiving comparator (RR: 3.22; 95% CI: 1.56 to 4.87; $I^2 = 94.4\%$; $p < 0.001$) (**Figure 3**). Finally, the RR of discontinuation due to any adverse event was 59% higher for patients receiving ticagrelor than for those receiving comparator (RR: 1.59; 95% CI: 1.29 to 1.89; $I^2 = 95\%$; $p < 0.001$) (**Figure 4**).

Based on available randomized clinical trial data, we confirmed that ticagrelor therapy was associated with a higher risk of premature discontinuation and discontinuation attributed to dyspnea, bleeding, or any adverse event as compared with clopidogrel or aspirin. Our findings are consistent with a patient-level analysis of early discontinuation of ticagrelor in the PEGASUS-TIMI 54 trial. In this secondary analysis, bleeding was the most frequent adverse event (7.8% vs. 6.2% vs. 1.5%; $p < 0.001$) followed by dyspnea (6.5% vs. 4.6% vs. 0.8%; $p < 0.001$) in those receiving ticagrelor 90 mg versus ticagrelor 60 mg versus comparator, respectively. Furthermore, the discontinuation rate for patients receiving the 90 mg dose was 2-fold higher (hazard ratio: 2.00; 95% CI: 1.84 to 2.16) and for patients taking the 60 mg dose was 59% higher (hazard ratio: 1.59; 95% CI: 1.46 to 1.73) than comparator in the first year (11). Adherence rates by treatment groups also differed; ticagrelor had lower rates of adherence as compared with comparator (83% vs. 86%;

CENTRAL ILLUSTRATION **Ticagrelor's Adverse Effects and the Risk of Premature Ticagrelor Discontinuation**



Arora, S. et al. J Am Coll Cardiol. 2019;73(19):2454–64.

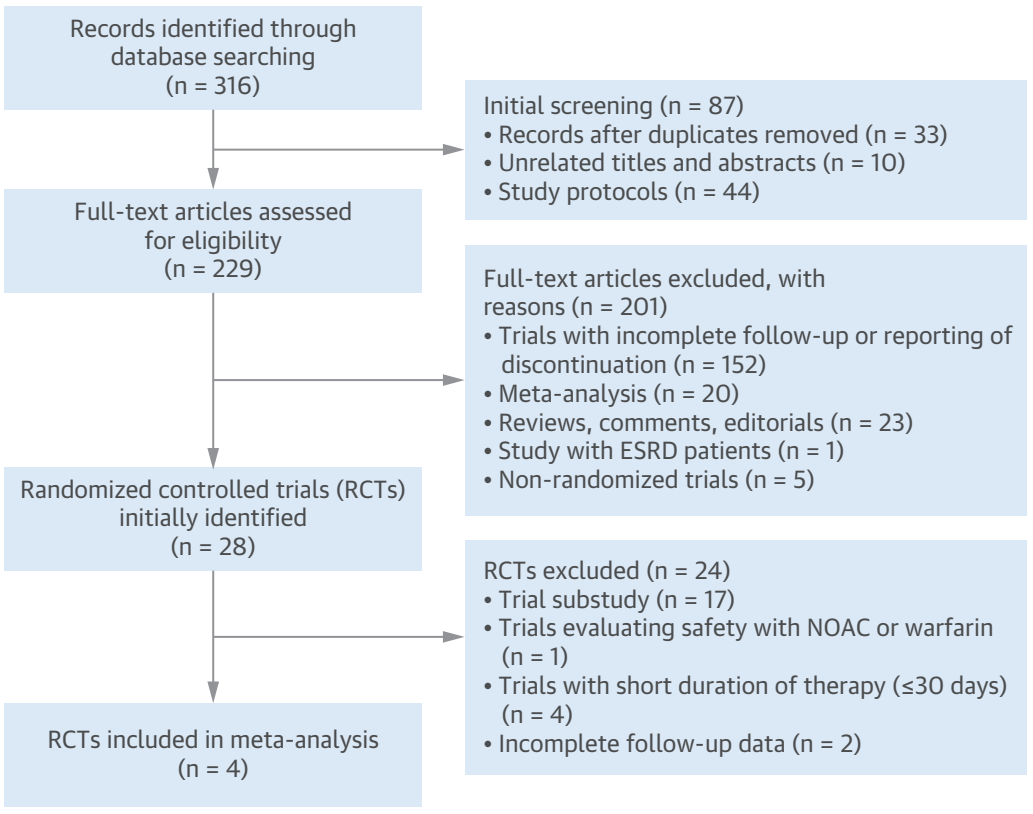
Forest plot demonstrating a 25% higher relative risk of premature discontinuation during follow-up for patients receiving ticagrelor versus comparator across included trials, along with an illustration of the mechanisms of the most commonly reported ticagrelor adverse effects across trials (bleeding, dyspnea, and conduction abnormalities), as well as strategies to mitigate ticagrelor's adverse effects in clinical practice. CI = confidence interval; EUCLID = Examining Use of Ticagrelor in Peripheral Artery Disease; PEGASUS-TIMI 54 = Prevention of Cardiovascular Events in Patients with Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin-Thrombolysis In Myocardial Infarction 54; PLATO = Study of Platelet Inhibition and Patient Outcomes; PPI = proton pump inhibitor; RR = relative risk; SOCRATES = Acute Stroke or Transient Ischemic Attack Treated with Aspirin or Ticagrelor and Patient Outcomes.

$p < 0.001$). The lack of patient-level data and inability to account for trial- and disease-specific factors were limitations to this analysis. Timing of the outcome assessment varied among the studies, the shortest being 3 months (SOCRATES) and the longest 3 years (PEGASUS-TIMI 54). If discontinuation rates are time varying, pooling data from studies with different lengths of follow-up may introduce bias. These limitations may have contributed to statistical heterogeneity observed in our quantitative analysis.

TICAGRELOR DISCONTINUATION IN OBSERVATIONAL EXPERIENCES

Premature discontinuation of DAPT due to early adverse effects has also been recognized in observational settings. In a large retrospective cohort study using administrative claims from United Healthcare between 2008 and 2016, the rates of discontinuation of $P2Y_{12}$ inhibitors increased with increasing use of prasugrel and ticagrelor (12). Bleeding and dyspnea were the most frequent adverse events leading to discontinuation of ticagrelor in a secondary analysis of PEGASUS-TIMI 54 (11). In a large prospective study embedded within the Veterans Affairs health care system, 7.6% of patients were found to discontinue clopidogrel prematurely. Risk of ACS and event-free survival were worse in this group (13). In a Dutch registry study (n = 354) evaluating the incidence and causes for early ticagrelor discontinuation over 330 days, the rate of discontinuation was 24.3%; the most frequency cited reasons for discontinuation were dyspnea (11.6%), bleeding (3.7%), and planned surgery (2.7%) (14). A similar rate of premature discontinuation was observed in a Saskatchewan Registry (n = 227), where premature discontinuation was 20.7% (15). In a study of 614 patients from the German Arbeitsgemeinschaft Leitende Kardiologische Krankenhausärzte registry, among patients surviving 12 months after discharge, 21.7% discontinued ticagrelor prematurely and age >75 years, atrial fibrillation, and prior stroke were identified as predictors of early discontinuation (16).

FIGURE 1 PRISMA Flowchart



Search strategy for selection and inclusion of eligible studies. ESRD = end-stage renal disease; NOAC = non-vitamin K antagonist oral anticoagulants; PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCT = randomized controlled trials.

MECHANISMS OF COMMON ADVERSE EFFECTS OF TICAGRELOR

BLEEDING. Ticagrelor is a potent and reversible oral $P2Y_{12}$ inhibitor (17). Ticagrelor reversibly binds to the platelet $P2Y_{12}$ receptor without requiring metabolic activation, is rapidly absorbed, and has a half-life of 7 to 12 h. This contrasts with the mode of action of the thienopyridine $P2Y_{12}$ receptor antagonists clopidogrel and prasugrel, which must be metabolically activated. When compared with clopidogrel, ticagrelor inhibits the platelet $P2Y_{12}$ receptor more rapidly and is known to achieve a markedly higher degree of adenosine diphosphate-mediated inhibition of platelet aggregation (18,19). The rapid onset of action and more potent platelet inhibition are speculated to be responsible for higher rates of bleeding with ticagrelor than seen with clopidogrel. The degree of platelet inhibition achieved by ticagrelor matches that of prasugrel (20). However, the relatively lower rate of fatal bleeding complications with ticagrelor as compared with prasugrel has been attributed to the reversible nature of ticagrelor $P2Y_{12}$ inhibition at a nonadenosine diphosphate-binding site. In contrast, prasugrel causes an irreversible inhibition of the $P2Y_{12}$ receptor, which has been linked to a higher rate of fatal bleeds (21).

DYSPNEA. Approximately 1 in 20 patients treated with ticagrelor suffers from dyspnea (6,8). The mechanism by which ticagrelor induces dyspnea has been debated. By inhibiting the sodium-independent nucleoside transporter-1, ticagrelor increases plasma adenosine levels (22). Adenosine can elicit dyspnea by activating vagal C fibers through its action on adenosine A1 and possibly on A2 receptors on the bronchial wall (23). However, despite being a more potent adenosine uptake inhibitor than ticagrelor, dyspnea has never been reported in multiple clinical trials where dipyridamole was orally administered to patients at risk for coronary or cerebrovascular events (24). Moreover, only 2.6% of patients undergoing intravenous dipyridamole-perfusion imaging for the

TABLE 1 Patient Characteristics, Comorbidities, and Medication History as Recorded From Each of the Trials

	PLATO	PEGASUS-TIMI 54 (Ticagrelor 90 mg)	PEGASUS-TIMI 54 (Ticagrelor 60 mg)	SOCRATES	EUCLID
Total participants, n	18,624	21,162	21,162	13,199	13,885
Ticagrelor recipient, n	9,333	7,050	7,045	6,589	6,930
Ticagrelor dose, mg	90.0	90.0	60.0	90.0	90.0
Comparator drug, mg	Clopidogrel 75	Aspirin 75-150	Aspirin 75-150	Aspirin 100	Clopidogrel 75
Median follow-up period, months	9.0	33.0	33.0	4.0	30.0
Age, yrs	62.0	65.0	65.0	66.0	66.0
Female, %	28.0	24.0	24.0	41.6	28.0
Weight, kg	80.0	82.0	82.0	NA	76.5
Hypertension, %	65.4	77.5	77.5	73.7	78.1
Hypercholesterolemia, %	46.7	76.7	76.4	38.1	75.4
Current smoker, %	35.8	16.7	17.1	NA	31.0
Diabetes mellitus, %	25.0	32.2	32.8	24.4	38.5
Coronary artery disease, %	19.3	83.0	84.0	8.6	29.0
Acute myocardial infarction, %	100.0	0.0	0.0	0.0	0.0
Prior myocardial infarction, %	20.6	100.0	100.0	4.2	18.2
Prior TIA or ischemic stroke, %	3.9	NA	NA	19.0	8.3
Peripheral vascular disease, %	6.1	5.5	5.2	NA	100.0
Beta-blocker use, %	89.5	82.8	82.3	NA	NA
Statin use, %	89.5	92.7	92.2	NA	73.5
ACE inhibitors/ARB use, %	12.1	80.6	79.9	NA	65.7

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blockers; EUCLID = Examining Use of Ticagrelor in Peripheral Artery Disease; PEGASUS-TIMI 54 = Prevention of Cardiovascular Events in Patients with Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin–Thrombolysis In Myocardial Infarction 54; PLATO = Study of Platelet Inhibition and Patient Outcomes; SOCRATES = Acute Stroke or Transient Ischemic Attack Treated with Aspirin or Ticagrelor and Patient Outcomes; TIA = transient ischemic attack.

evaluation of ischemia developed dyspnea (25). In a recent study, Ortega-Paz et al. (26) conducted simultaneous measurements of plasma concentrations of adenosine and ticagrelor in patients stratified by presence or absence of dyspnea and failed to find a correlation between adenosine levels and timing of ticagrelor administration in patients with or without dyspnea. Therefore, it is unlikely that adenosine-mediated dyspnea fully explains the dyspnea observed in patients receiving ticagrelor. Nevertheless, TROCADERO (A TRial Of Caffeine to Alleviate DyspnEa Related to ticagrelor) (NCT02311088) was designed to investigate the effect of caffeine, a xanthine derivative with nonselective adenosine receptor antagonist properties, on ticagrelor-related dyspnea; however, it was terminated early due to low enrollment (27).

The concern that dyspnea may indicate an adverse impact of ticagrelor on pulmonary or cardiac function was refuted by findings from the ONSET/OFFSET and PLATO studies (19,28). The potential of ticagrelor to cause dyspnea via $P2Y_{12}$ inhibition has gained attention (22). This is supported by the fact that the $P2Y_{12}$ receptors are expressed in many cell lines, including smooth muscle cells, neurons, and glial cells; patients with ticagrelor-related dyspnea were identified to have a pattern of periodic breathing associated with increased chemosensitivity to hypercapnia, likely mediated by its neuronal effects (26,29). Additionally, it is known that 30% of patients treated with clopidogrel experience inadequate inhibition of $P2Y_{12}$, which may explain the lower incidence of clopidogrel-associated dyspnea compared with ticagrelor (27,30). However, the relationship between $P2Y_{12}$ inhibitory potency to the degree of dyspnea is challenged by the fact that prasugrel, which is an equally potent inhibitor of $P2Y_{12}$ as ticagrelor, is only associated with a 1.1-fold higher frequency of dyspnea as compared with clopidogrel in TRITON-TIMI 38 (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis In Myocardial Infarction 38) (31). Therefore, the mechanistic underpinnings of dyspnea with ticagrelor warrant further investigation.

ARRHYTHMIAS. The association of arrhythmias, mainly ventricular pauses, with ticagrelor was first noted in phase 2, and higher incidence was later seen in the PLATO trial, which performed serial electrocardiographic monitoring (32,33). Bradyarrhythmias were the third most common cause of study drug discontinuation in the PEGASUS-TIMI 54 trial (11). The most frequently speculated mechanism of bradyarrhythmia with ticagrelor is an increase in adenosine levels, independent of antiplatelet effects.

Adenosine suppresses the automaticity of cardiac pacemakers and inhibits atrioventricular nodal conduction, thus producing a negative dromotropic effect (34). This mechanism was speculated to cause bradycardic events observed in prior trials (32,33). In animal models, ticagrelor simulates dipyridamole by augmenting cardiac blood flow (35). In a fibrinolytic-treated canine infarct model comparing ticagrelor and clopidogrel at similar levels of platelet inhibition, ticagrelor led to improved perfusion times, lower re-occlusion levels, and faster restoration of myocardial tissue perfusion, mediated by increased adenosine levels (36,37). The increased adenosine levels during acute ischemia can induce bradyarrhythmias due to their effect on the sinoatrial and atrioventricular nodes, which also supports this theory (33,34).

TOLERABILITY OF TICAGRELOR AND ADDRESSING NONADHERENCE IN CLINICAL PRACTICE. The adherence to $P2Y_{12}$ inhibitors has significantly declined in the last decade and has been attributed to the emergence of newer $P2Y_{12}$ inhibitors such as ticagrelor (12). This is despite a reported rate of prescribing of $P2Y_{12}$ inhibitors from NCDR (National Cardiovascular Disease Registry) data after stenting at discharge as high as 99% (38). As reported in the meta-analysis, the higher rates of adverse effects with ticagrelor, albeit nonserious, may have affected these observed adherence patterns (11). Other potential reasons are higher out-of-pocket costs with ticagrelor and the 2× daily regimen, compared with a once daily regimen with clopidogrel (12). The fact that the patient feels no immediate effect when these antiplatelet treatments are taken makes nonadherence a more difficult problem to overcome (39). Therefore, it is crucial to focus on measures to improve both tolerability and adherence to ticagrelor to optimize treatment-related benefits. Treatment nonadherence may be related to failure at multiple junctions along the care system (40). Patient and clinician education, patient reminders, and patient tools to organize medications are important measures with proven effectiveness in improving adherence after ACS (19,41,42). For improving tolerability, comprehensive counselling regarding the most frequent adverse effects of treatment and approaches to manage these given both at the time of discharge and at follow-up visits are essential. Involvement of social workers early for patients who are at risk of nonadherence due to cost reasons and taking additional measures, such as provision of vouchers, may reduce the risk of ticagrelor discontinuation. In a large clinical trial enrolling 11,000 patients, the provision of a voucher to offset copayments resulted in a 3.3% absolute increase in persistence with $P2Y_{12}$ inhibitors, as reported by the patient, without a significant difference in major adverse cardiac events (43).

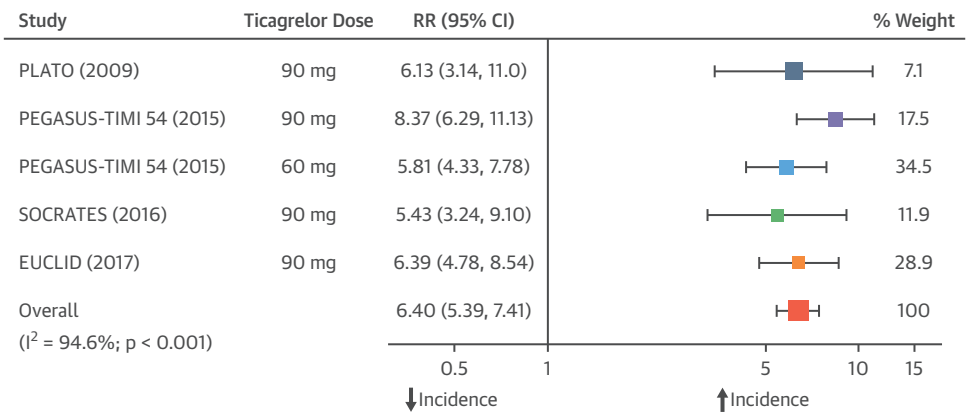
TABLE 2 Comparison of Discontinuation Rates Attributed to Ticagrelor Versus Comparator

Absolute Event Rates	Ticagrelor (%)	Comparator* (%)	p Value
PLATO: ticagrelor dose: 90 mg BID			
Premature discontinuation	23.4	21.5	0.002
Bleeding discontinuation	2.4	1.0	<0.001
Dyspnea discontinuation	0.9	0.1	<0.001
Any adverse event discontinuation	7.4	6.0	<0.002
PEGASUS-TIMI 54: ticagrelor dose: 90 mg BID			
Premature discontinuation	32.0	21.4	<0.001
Bleeding discontinuation	7.8	1.5	<0.001
Dyspnea discontinuation	6.5	0.8	<0.001
Any adverse event discontinuation	19.0	8.9	<0.001
PEGASUS-TIMI 54: ticagrelor dose: 60 mg BID			
Premature discontinuation	28.7	21.4	<0.001
Bleeding discontinuation	6.2	1.5	<0.001
Dyspnea discontinuation	4.6	0.8	<0.001
Any adverse event discontinuation	16.4	8.9	<0.001
SOCRATES: ticagrelor dose: 90 mg PO BID			
Premature discontinuation	17.5	14.7	<0.001
Bleeding discontinuation	1.3	0.6	<0.001
Dyspnea discontinuation	1.4	0.3	<0.001
Any adverse event discontinuation	9.7	7.1	<0.001
EUCLID: ticagrelor dose: 90 mg PO BID			
Premature discontinuation	30.1	25.9	<0.001
Bleeding discontinuation	2.4	0.8	<0.001
Dyspnea discontinuation	4.8	0.8	<0.001
Any adverse event discontinuation	15.4	11.1	<0.001

*Comparator: clopidogrel or aspirin.
BID = twice daily; other abbreviations as in Table 1.

MANAGEMENT OF BLEEDING. In the PLATO trial, rates of nonprocedural bleeding were higher with ticagrelor than clopidogrel (19). Ticagrelor has exhibited efficacy in preventing cardiovascular events in those with prior myocardial infarction and in those with multivessel disease at a cost of a higher rates of bleeding overall, but not higher rates of intracranial or fatal bleeding (9,44). Most bleeding was nonfatal; however, bleeding was the most common cause of medication discontinuation across trials (11). Therefore, it is important to reduce bleeding events and devise strategies to promptly address them when they occur. Identifying patients with higher risk of bleeding before drug administration represents the first step to bleeding risk reduction. A recent multicenter, retrospective, cohort study including patients from the RENAMI (REgistry of New Antiplatelet therapy in patients with acute Myocardial Infarction) found that among patients receiving ticagrelor or prasugrel for ACS, patients age >75 years

FIGURE 2 Dyspnea-Related Discontinuation Risk for Ticagrelor Versus Comparator

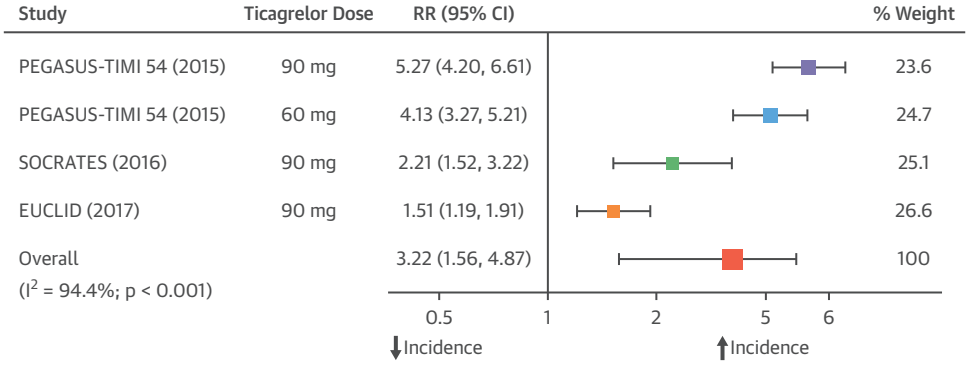


Forest plot showing a 6-fold higher relative risk of dyspnea-related discontinuation during follow-up for ticagrelor versus comparator across included trials. CI = confidence interval; EUCLID = Examining Use of Ticagrelor in Peripheral Artery Disease; PEGASUS-TIMI 54 = Prevention of Cardiovascular Events in Patients with Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin-Thrombolysis In Myocardial Infarction 54; PLATO = Study of Platelet Inhibition and Patient Outcomes; RR = relative risk; SOCRATES = Acute Stroke or Transient Ischemic Attack Treated with Aspirin or Ticagrelor and Patient Outcomes.

and women experienced higher rates of bleeding (45). An important strategy that should be emphasized is dose reduction of ticagrelor after the acute post-MI phase, as the 60-mg dose has been found to have similar efficacy, but significantly lower nonadherence rates, mostly attributed to less bleeding and dyspnea compared with the 90 mg dose (PEGASUS-TIMI 54). Additionally, the use of ticagrelor in patients on oral anticoagulants has not been thoroughly investigated and therefore, ticagrelor should be used with caution in combination antithrombotic regimens. The concomitant use of nonsteroidal anti-inflammatory agents (NSAIDs) and antithrombotic agents after MI continues to be a common practice and should be minimized. In a large Danish study of patients age >30 years, post-first-time MI, 34% of the 61,971 included patients filled at least 1 prescription of NSAIDs (46). The investigators concluded that NSAIDs levy a significant higher risk of bleeding and adverse cardiovascular events.

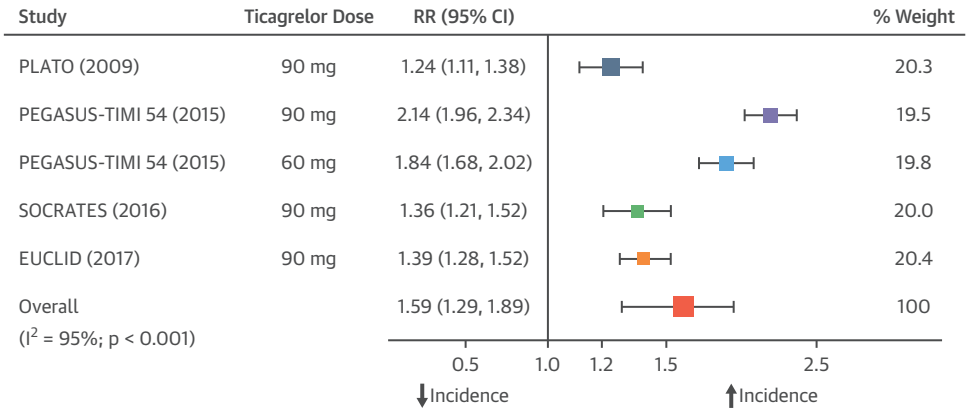
The most common site of bleeding in the PLATO trial was gastrointestinal; despite low rates of intracranial bleeding, incidence was still higher for ticagrelor versus clopidogrel (19). Therefore, cautious use of ticagrelor in patients who are at higher risk of bleeding, such as those with recent history of peptic

FIGURE 3 Bleeding-Related Discontinuation Risk for Ticagrelor Versus Comparator



Forest plot showing a 3-fold higher relative risk of bleeding-related discontinuation during follow-up for ticagrelor versus comparator across included trials. Abbreviations as in Figure 2.

FIGURE 4 Discontinuation Risk Due to Any Adverse Event for Ticagrelor Versus Comparator



Forest plot showing a 59% higher relative risk of discontinuation due to any adverse event during follow-up for ticagrelor versus comparator across included trials. Abbreviations as in Figure 2.

ulcer, other gastrointestinal hemorrhage, or prior history of intracranial hemorrhage, may help reduce bleeding rates (19). Clinical efficacy of omeprazole in addressing gastrointestinal bleeding risk with clopidogrel was investigated in COGENT (Clopidogrel and the Optimization of Gastrointestinal Events Trial) (47). A total of 3,761 patients were included in the analysis, out of which 51 experienced bleeding events. The event rate was 1.1% in the omeprazole arm and 2.9% in the placebo arm at 180 days, but the trial follow-up was terminated early due to loss of sponsor funding. A similar trial for ticagrelor is currently lacking, but use of proton pump inhibitors is reasonable in patients who are at elevated gastrointestinal bleeding risks treated with DAPT. Once bleeding occurs, standard protocols such as maintenance of hemodynamic stability, endoscopy within 24 h to achieve hemostasis, and administration of proton pump inhibitors for gastrointestinal bleeding are recommended.

ADDRESSING TICAGRELOR-RELATED DYSPNEA. Although the prevalence of ticagrelor-induced dyspnea is widely agreed upon, whether this leads to significant discontinuation rates continues to be investigated (48,49). The pattern of dyspnea with ticagrelor varies from brief episodes starting early in the first week of treatment to intermittent or persistent episodes occurring over several weeks (45). Fortunately, the severity of most episodes is reported as mild (50). To ensure an accurate diagnosis and to prevent missing an alternate diagnosis such as heart failure or asthma, a thorough clinical evaluation is important (51). An accurate history, including questions regarding the timing of dyspnea onset relative to ticagrelor initiation, is necessary to making the correct diagnosis. If dyspnea is attributed to ticagrelor, especially if symptoms are mild, clinicians should allow time for spontaneous resolution of these symptoms (51). If symptoms persist but are easily tolerated, continuation of ticagrelor is reasonable to allow for maximization of outcome benefits from the drug (51). Patients should be counseled and reassured that ticagrelor-induced dyspnea is not associated with any compromise of cardiac or pulmonary function (18). If symptoms persist or are intolerable, discontinuation of the drug and switching to either prasugrel or clopidogrel can be considered (52); a loading dose of clopidogrel should be given if that switch is made for nonhemorrhagic adverse effects of ticagrelor (53).

CONDUCTION ABNORMALITIES WITH TICAGRELOR. Conduction disturbances/arrhythmias were the third most common cause of drug discontinuation among patients in the PEGASUS-TIMI 54 trial (11). Awareness of this adverse effect is important, as ticagrelor use is currently not recommended in patients with advanced conduction defects. Multiple reports have raised concerns about the potential of ticagrelor to worsen conduction deficits in those with no or mild baseline disease (54–56). The PLATO investigators recently studied the safety profile of ticagrelor (compared with clopidogrel) in patients with ACS and mild conduction disease (right or left bundle branch block, left anterior or posterior fascicular block, bradycardia, or first-degree atrioventricular block)

and did not find an increase in arrhythmic events with ticagrelor (57). Therefore, there is no contraindication to the use of ticagrelor in those with mild conduction abnormalities.

LIMITING FINANCIAL TOXICITY RELATED TO ANTIPLATELET REGIMENS

Atherosclerotic cardiovascular disease is not only the leading cause of morbidity and mortality in the United States, it also represents the disease with the highest health care costs (58). Therefore, therapies such as ticagrelor need to be scrutinized not only for their efficacy and safety, but also for their incremental health benefits versus the social costs. The use of ticagrelor on daily basis is significantly more expensive for patients than clopidogrel in direct medication costs (58). However, economic analysis from PLATO suggested that 1 year of ticagrelor therapy, when compared with clopidogrel, cost an estimated $29,665 per quality-adjusted-life-year gained, which was well within the accepted cost standards (59). Similarly, ticagrelor + low dose aspirin therapy appeared to provide greater value for high-risk subgroups in a cost-effectiveness analysis from the PEGASUS-TIMI 54 trial (59). Nevertheless, the significance of medication affordability cannot be underestimated. A retrospective claims study from a large U.S. private insurer found a correlation between lower rates of mean drug possession and higher daily copayment rates when comparing clopidogrel and newer $P2Y_{12}$ inhibitors (12). Furthermore, these discontinuation rates were worse in areas with the lowest socioeconomic status. A large-scale study suggested that 1 of 4 low-income families with a member with atherosclerotic cardiovascular disease, including those with insurance coverage, experience a significant financial burden and one-tenth experience a catastrophic financial burden due to out-of-pocket expenses that accumulate over time (60). Therefore, prescribing providers should account for these patient-related factors when deciding upon the appropriate choice of antiplatelet therapy post-ACS.

CONCLUSIONS AND FUTURE PERSPECTIVES

Premature discontinuation of ticagrelor occurs in about one-quarter of patients at follow-up. Certain adverse events of ticagrelor, including bleeding, dyspnea, and conduction abnormalities, may contribute to treatment nonadherence. Improved adherence may be facilitated by appropriate patient selection, patient counseling and adequate provision of information, and prophylactic strategies, such as proton pump inhibitors. In case they do occur, these side effects are not typically serious and ongoing therapy can be facilitated in many cases with appropriate follow-up and conservative management. Therefore, routine follow-up in the early months on this therapy is important and should include in-depth counseling. Providers should also be aware of the potential of financial toxicity levied by the higher out-of-pocket costs of ticagrelor. Patients who are at high risk of nonadherence due to unaffordability should be identified early, and measures such as vouchers to offset the effect of high copayments should be provided or considerations should be given to switch to clopidogrel. Nonadherence to antiplatelet therapy represents a prevalent and potentially preventable barrier to optimal secondary prevention of cardiovascular events.

ADDRESS FOR CORRESPONDENCE: Dr. Sandeep Das, University of Texas Southwestern Medical Center, Cardiology Division, 5323 Harry Hines Boulevard, MC 8830, Dallas, Texas 73590-8830. E-mail: Sandeep.Das@UTSouthwestern.edu. Twitter: @sandeepdasmd, @UTSWNews.

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