Dyspnea-Related Ticagrelor Discontinuation After Percutaneous Coronary Intervention

Short Title: Dyspnea in the TWILIGHT trial

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ABSTRACT

Objectives: To evaluate the incidence, predictors, and outcomes of dyspnea-related ticagrelor discontinuation after percutaneous coronary intervention (PCI).

Background: Nearly 20% of patients on ticagrelor experience dyspnea, which may lead to treatment discontinuation in up to one third of cases.

Methods: In the TWILIGHT (Ticagrelor With Aspirin or Alone in High-Risk Patients after Coronary Intervention) trial, after 3 months of ticagrelor plus aspirin, patients were maintained on ticagrelor and randomized to aspirin or placebo for 1 year. The occurrence of dyspnea associated with ticagrelor discontinuation was evaluated among all patients enrolled in the trial. A landmark analysis was performed at 3 months after PCI, i.e., the time of randomization. Predictors of dyspnea-related ticagrelor discontinuation were obtained from multivariable Cox regression with stepwise selection of candidate variables.

Results: The incidence of dyspnea-related ticagrelor discontinuation was 6.4% and 9.1% at 3 and 15 months after PCI, respectively. Independent predictors included Asian race (lower risk), smoking, prior PCI, hypercholesterolemia, prior coronary artery bypass, peripheral artery disease, obesity, and older age. Among 179 patients who discontinued ticagrelor because of dyspnea after randomization, ticagrelor monotherapy was not associated with a higher risk of subsequent ischemic events (composite of all-cause death, myocardial infarction, or stroke) compared with ticagrelor plus aspirin (5.0% vs. 7.1%, p-value=0.566).

Conclusions: In TWILIGHT, dyspnea-related ticagrelor discontinuation occurred in almost one in ten patients and tended to occur earlier rather than late after PCI. Several demographic and clinical conditions predicted its occurrence, and their assessment may help identify subjects at risk for therapy non-adherence.

Keywords: dyspnea; antiplatelet therapy discontinuation; ticagrelor monotherapy; aspirin; PCI

Condensed Abstract

Dyspnea is a common side effect of ticagrelor which may lead to treatment discontinuation. Among 9006 patients enrolled in the TWILIGHT (Ticagrelor with Aspirin or Alone in High-Risk Patients after Coronary Intervention) trial, the incidence of dyspnea-related ticagrelor discontinuation was 6.4% at 3 months and 9.1% at 15 months. Advanced age was the strongest predictor of dyspnea-related treatment discontinuation while Asian race was associated with lower risk. Among randomized patients who discontinued ticagrelor because of dyspnea, ticagrelor monotherapy was not associated with higher risk of all-cause death, myocardial infarction, or stroke compared with ticagrelor plus aspirin (5.0% vs.7.1%, p-value=0.566).

LIST OF ABBREVIATIONS

PCI: percutaneous coronary intervention

ACS: acute coronary syndrome

DAPT: dual antiplatelet therapy

CKD: chronic kidney disease

BARC: Bleeding Academic Research Consortium

MI: myocardial infarction

BMI: body mass index

CABG: coronary artery bypass graft

ENT1: equilibrative nucleoside transporter

INTRODUCTION

Antiplatelet therapy non-adherence is associated with an increased risk of cardiovascular events.[1,2] Ticagrelor is a potent $P2Y_{12}$ receptor inhibitor and is prescribed in combination with aspirin after percutaneous coronary intervention (PCI).[3–5] Compared with other $P2Y_{12}$ inhibitors, ticagrelor has been associated with higher rates of treatment discontinuation due to dyspnea, a side effect thought to be partly related to increased plasmatic levels of adenosine.[6] Dyspnea occurs in nearly 20% of patients taking ticagrelor 90 mg and result in treatment discontinuation in up to one third of cases, although lower drug dosages (60 mg) may mitigate this phenomenon and the rate may vary according to the clinical setting.[7–9]

In the PLATO study, the occurrence of dyspnea did not seem to have an impact on the benefit of ticagrelor over clopidogrel among acute coronary syndrome (ACS) patients who were on concomitant aspirin therapy, even though dyspnea was associated with higher discontinuation rates, especially in patients treated with ticagrelor.[9] The TWILIGHT trial demonstrated that compared with ticagrelor plus aspirin, ticagrelor monotherapy after 3 months of dual antiplatelet therapy (DAPT) significantly reduced bleeding without increasing ischemic events among high-risk patients undergoing PCI. However, dyspnea-related treatment discontinuation may be particularly problematic in the setting of ticagrelor monotherapy. Therefore, we conducted an exploratory analysis of the TWILIGHT trial to identify the incidence and predictors of dyspnea-related ticagrelor discontinuation among high-risk patients undergoing PCI, and to evaluate clinical outcomes associated with ticagrelor monotherapy in those who discontinued because of dyspnea.

METHODS

Trial design and population

TWILIGHT (NCT02270242) was a randomized, placebo-controlled trial conducted at 187 sites across 11 countries. The trial rationale, design, and principal results have been reported elsewhere.[10,11] The protocol was approved by national regulatory agencies and institutional review boards or ethics committees of participating sites.

The study population consisted of patients at high ischemic or bleeding risk who underwent successful PCI with implantation of a drug-eluting stent. The ischemic and bleeding risks were defined by having at least one clinical and one procedural high-risk criterion. High risk clinical criteria included age ≥65 years, female sex, troponin positive ACS, prior myocardial infarction, prior PCI, prior coronary artery bypass graft, peripheral arterial disease, diabetes mellitus requiring medication, and chronic kidney disease (CKD). High risk angiographic criteria included multivessel coronary artery disease, total stent length >30 mm, thrombotic target lesion, bifurcation lesion requiring 2 stents, obstructive left main or proximal left anterior descending lesion, and calcified target lesion requiring debulking devices. Key exclusion criteria included presentation with ST-segment elevation myocardial infarction, cardiogenic shock, prior stroke, or need for oral anticoagulation.

After enrollment at the time of the index PCI, patients were treated with open-label ticagrelor (90 mg twice daily) and enteric-coated aspirin (81-100 mg daily) for 3 months. Enrolled patients who had been event-free and compliant with treatment at 3 months were randomized in a 1:1 double-blinded fashion to aspirin or placebo for an additional 12 months on a background of open-label ticagrelor therapy.

Clinical endpoints

The primary endpoint of the trial was Bleeding Academic Research Consortium (BARC) type 2, 3, or 5 bleeding through 1 year after randomization.[12] The key secondary endpoint was a composite of all-cause death, myocardial infarction (MI), or stroke. Other secondary endpoints included a composite of all-cause death, MI, stroke, or revascularization, and its individual components. Net adverse clinical event was defined as a composite of BARC type 3 or 5 bleeding, death, MI, or stroke. MI was defined according to the third universal definition, and stent thrombosis was classified according to the Academic Research Consortium criteria.[13,14] An independent committee, blinded to treatment assignment, adjudicated all clinical events.

Dyspnea-related antiplatelet therapy discontinuation

In TWILIGHT, all sites were given a standardized algorithm to address ticagrelor-related shortness of breath in a uniform fashion (**Figure S1**). The algorithm emphasized a stepwise approach that included patient counseling, intake of concomitant caffeine, and a brief "drug-holiday" off ticagrelor switching to an alternative open label $P2Y_{12}$ agent (e.g., clopidogrel). The aim was to minimize ticagrelor non-adherence that would have prevented patients from undergoing randomization.

Study definitions of antiplatelet therapy discontinuation were based upon a modification of the PARIS criteria and categorized as protocol-guided discontinuation, brief interruption, or disruption (i.e., due to bleeding or non-compliance).[1] Details surrounding medication adherence were collected using site reported cessation forms at each follow-up visit and manual pill count at the 9- and 15-month in-person visits. For each medication, the reason

for discontinuation, including dyspnea, and information on medication restart were collected. All patients with a reported episode of dyspnea-related permanent ticagrelor discontinuation were included in this analysis irrespective of whether they switched to another oral $P2Y_{12}$ inhibitor.

Statistical analyses

Continuous variables are reported as mean (standard deviation) and compared with the Student t test or, if not normally distributed, as median (interquartile range) and compared with the Mann Whitney U test. Categorical variables are reported as number (%) and were compared with the $\chi 2$ test with Yates correction for continuity. The incidence of dyspnea-related ticagrelor discontinuation was estimated with the Kaplan-Meier method in all 9006 patients enrolled at the time of index PCI, including those who were not subsequently randomized. Survival analyses were based on the time to first dyspnea-related ticagrelor discontinuation event and patients were censored at the time of death, last known contact, or 450 days, whichever came first. A landmark analysis was performed at 3 months after PCI, i.e., the time of randomization to aspirin or placebo. Independent predictors of dyspnea were obtained from multivariable Cox regression, with stepwise selection of candidate variables ($p<0.10$ inclusion, $p>0.20$ for exclusion), for the overall study duration as well as early (before 3 months) versus late (after 3 months) dyspnea.

Additional exploratory analyses evaluated the risk of ischemic and bleeding events following treatment discontinuation in patients randomized to ticagrelor monotherapy vs. ticagrelor plus aspirin at 3 months post-PCI (n=7119). A two-sided p-value<0.05 was considered

statistically significant. All analyses were performed using Stata version 16.0 (College Station, Texas).

RESULTS

Incidence and predictors of dyspnea

Of 9006 patients enrolled in the trial, 794 had discontinued any antiplatelet agent because of dyspnea at 15-month follow-up: 781 (98.4%) discontinued ticagrelor and 13 (1.6%) discontinued aspirin or matching placebo (**Figure 1**). Among those who discontinued ticagrelor, 36 (4.6%) restarted ticagrelor and were not considered as permanent discontinuers, while 700 (89.6%) switched to another oral $P2Y_{12}$ inhibitor [599 (76.7%) to clopidogrel, 98 (12.5%) to prasugrel, and 3 (0.4%) to ticlopidine], and 45 (5.8%) did not restart any $P2Y_{12}$ inhibitor (**Figure S2**). Hence, a total 745 (9.1%) patients were included in the present analysis; of those 544 (6.4%) discontinued ticagrelor within the first 3 months after PCI, while in those randomized (n=7119) dyspnea-related ticagrelor discontinuation occurred in 201 subjects (2.8%) between 3 and 15 months post-PCI (**Figure 2**).

Baseline clinical, laboratory and procedural features of patients who discontinued ticagrelor because of dyspnea (dyspnea group) are compared with those who did not (no dyspnea group) in **Tables 1** and **2**. Patients with dyspnea were older, with a higher body mass index (BMI), and had more cardiovascular risk factors and comorbidities, including more frequent CKD, hypertension, hypercholesterolemia, peripheral artery disease, history of congestive heart failure, and prior coronary revascularization. Patients without acute MI presentation experienced a higher rate of dyspnea as compared to those with an acute MI.

With respect to angiographic and procedural features, patients who discontinued ticagrelor because of dyspnea were less likely to have undergone PCI via radial access, of left anterior descending artery, and thrombotic lesions as compared with non-dyspnea patients.

Independent predictors of dyspnea-related ticagrelor discontinuation included current smoking status, prior PCI, hypercholesterolemia, prior coronary artery bypass graft (CABG), peripheral artery disease, obesity (BMI ≥30 kg/m^2) and advanced age (**Figure 3**). Asian race was associated with a lower risk of dyspnea-related ticagrelor discontinuation (HR 0.25, 95% CI 0.18-0.38; p<0.001) whereas age was the strongest predictor (65-74 years: HR 1.70, 95% CI 1.43-2.03, p-value<0.001; ≥75 years: HR 2.25, 95% CI 1.81-2.78, p-value<0.001). Non-significant trends were observed for CKD (HR 1.19, 95% CI 1.00-1.42, p-value=0.053) and female sex (HR 1.17, 95% CI 0.99-1.40, p-value=0.061). Predictors stratified by timing of occurrence of dyspnea-related ticagrelor discontinuation (before vs. after 3 months post-PCI) are reported in **Table S1**.

Safety and efficacy of ticagrelor monotherapy

Ischemic and bleeding events between randomized treatment arms among patients who discontinued (or switched) ticagrelor because of dyspnea are reported in **Table 3**. Ticagrelor monotherapy was associated with a lower rate of BARC type 2, 3, or 5 bleeding compared with ticagrelor plus aspirin (3.8% vs. 12.1%, p-value=0.044). The occurrence of death, MI, or stroke was similar with ticagrelor monotherapy vs. ticagrelor plus aspirin (5.0% vs. 7.1%; p-value=0.566). Finally, net adverse clinical events (the composite of BARC type 2, 3, or 5 bleeding, death, MI, or stroke) were numerically lower with ticagrelor monotherapy (8.8% vs. 17.2%; p-value=0.100) among patients with dyspnea-related ticagrelor discontinuation.

DISCUSSION

The principal findings (**Central Illustration**) from this exploratory analysis of the TWILIGHT trial are:

1) Ticagrelor discontinuation due to dyspnea occurred in almost one out of ten (9.1%) patients and tended to occur earlier rather than late after treatment initiation (6.4% in the first 3 months and 2.8% thereafter).
2) Independent predictors of dyspnea-related ticagrelor discontinuation included both demographic and clinical parameters, with Asian race (lower risk) and advanced age (higher risk) being the most strongly associated.
3) Among high-risk PCI patients who discontinued ticagrelor because of dyspnea (with in most cases, switch to another $P2Y_{12}$ inhibitor), ticagrelor monotherapy was not associated with higher risk of subsequent ischemic events as compared with ticagrelor plus aspirin.

Dyspnea is a common side effect of ticagrelor, although most cases are transient and not severe in intensity. The mechanisms by which dyspnea occurs is patients treated with ticagrelor is poorly understood but have been partly related to increased half-life and plasma concentration of adenosine.[6] Experimental studies provide evidence that that ticagrelor inhibits the cellular uptake (and subsequent metabolism) of adenosine by inhibiting the sodium-independent equilibrative nucleoside transporter (ENT1).[15–17] However, dipyridamole, a stronger ENT1 inhibitor than ticagrelor, has not been reported to increase sensation of dyspnea while other reversible $P2Y_{12}$ inhibitors (i.e., cangrelor and elinogrel) not affecting adenosine

levels do. Hence, to what extent adenosine contributes to the sensation of dyspnea induced by ticagrelor remains matter of conjecture.[6,18]

Dyspnea usually occurs early after treatment initiation but some patients may experience recurrent or persistent symptoms over several weeks.[19,20] It is recommended to continue ticagrelor in case of mild episodes of dyspnea in order to maximize treatment adherence while spontaneous resolution usually occurs. However, if symptoms persist, switching ticagrelor to another $P2Y_{12}$ inhibitor should be considered.[21,22]

In the present study, dyspnea leading to discontinuation of antiplatelet therapy (98.4% ticagrelor) occurred mostly at the beginning of treatment. The majority of patients (76.7%) switched to clopidogrel after ticagrelor discontinuation. In prior studies, the rates of dyspnea resulting in ticagrelor discontinuation were somewhat lower than those observed in TWILIGHT, ranging from 0.9% to 6.5% through the available follow-up (up to 33 months).[7–9,23–28] There are several possible explanations. First, TWILIGHT is more recent and greater awareness of this ticagrelor side effect is expected among both patients and study investigators. Second, ticagrelor was provided with an open label formulation thus potentially increasing the risk of treatment discontinuation. Third, a specific form for dyspnea-related discontinuation was present in the case report form of the trial. Finally, the TWILIGHT trial specifically enrolled patients characterized by a high burden of comorbidities and high-risk features. This is noteworthy because patients may develop dyspnea after PCI due to clinical factors unrelated to ticagrelor such as heart failure, lung infection, adverse reaction to beta-blockers, recurrent ischemia, anemia, or worsening of pre-existing chronic obstructive pulmonary disease.[21] In the present study, dyspnea was associated with a worse clinical profile as shown by the higher

prevalence of features known to be associated with ischemic and bleeding events, which were also part of the trial inclusion criteria (e.g., age, troponin positive ACS, prior PCI, prior coronary artery bypass graft, peripheral arterial disease, and CKD).[29–32] The rates of dyspnea were 13.8% in the PLATO and 18.9% in the PEGASUS-TIMI 54 trials, the latter being more recent and enrolling stable patients enriched with high thrombotic risk features.[8,25] Dyspnea-related ticagrelor discontinuation was 6.5% in PEGASUS-TIMI 54 while only 0.9% in PLATO.[8,25] Our findings add to previous observations (**Table S1**) and underscores the challenges faced by clinicians in evaluating the causes of dyspnea in patients with multiple comorbidities and risk factors while on ticagrelor therapy.

The PLATO trial showed higher rates of dyspnea in patients receiving ticagrelor compared with clopidogrel and that dyspnea by itself was associated with a higher risk of ischemic outcomes irrespective of the $P2Y_{12}$ inhibitor used. Moreover, occurrence of dyspnea did not appear to reduce the benefit of ticagrelor over clopidogrel in an ACS setting.[9] Notably, in PLATO, $P2Y_{12}$ inhibitors were given on top of aspirin therapy and ticagrelor discontinuation because of dyspnea was only 0.9%. Hence, dyspnea-related non-adherence warrants further evaluation in patients on ticagrelor monotherapy.[4] Our data suggest that the occurrence of dyspnea did not impact on the safety and efficacy of this treatment strategy, even in a high-risk cohort such that of TWILIGHT. In a post-hoc analysis from the GLOBAL LEADERS trial, which evaluated a strategy of short DAPT followed by ticagrelor monotherapy vs. standard of care, the occurrence of dyspnea was not associated with a higher risk of adverse events.[33] Furthermore, despite a higher incidence of dyspnea in the experimental arm, safety outcomes did not seem to be affected.[33] Nevertheless, these findings should be interpreted in view of the pragmatic

design of the trial, which was open label and enrolled an all-comer cohort of PCI patients.[34] Moreover, in this sub-study, the impact of dyspnea leading to therapy discontinuation was not evaluated. Although explorative, our analysis seems to reassure about the safety of dropping aspirin and continuing with ticagrelor only, despite a tangible risk for dyspnea-related ticagrelor discontinuation.

Finally, we provided a prediction model to guide appropriate selection of those patients who might benefit from closer monitoring of treatment adherence during follow-up, especially in the early phase post-PCI. Elderly patients, those with CKD, prior PCI or CABG, or peripheral artery disease more often experienced sensation of dyspnea leading to ticagrelor discontinuation, which is of particular concern in such vulnerable subgroups. Timely identification of subjects at risk may prompt use alternative strategies including de-escalation from ticagrelor to clopidogrel to ensure adequate antithrombotic protection. [35] Such an approach might eventually mitigate medication non-adherence, which represents the first barrier to secondary prevention strategies.

Limitations

First, this is a post-hoc analysis on a subgroup of patients who experienced a side effect related to a study medication. Second, in TWILIGHT, both the experimental and control groups received ticagrelor; therefore, the association between dyspnea and the study drug was reported in the case report form as per the investigator clinical assessment. Third, the present study was likely underpowered to detect differences in clinical endpoints occurring after dyspnea. Hence, our findings must be considered explorative and hypothesis-generating.

Studies evaluating rare side effects of medications deal with the same limitations, yet they are needed to evaluate the safety and clinical applicability of new treatment strategies.

CONCLUSIONS

Dyspnea-related ticagrelor discontinuation occurred in 9.1% of patients enrolled in TWILIGHT and was associated with several demographic and clinical conditions that are worth careful assessment to prevent therapy non-adherence. Withdrawing aspirin and continuing with ticagrelor monotherapy 3 months after PCI seems a safe strategy despite this relatively common dyspnea side effect. Prospective confirmation in dedicated studies is warranted.

CLINICAL PERSPECTIVES

What's known? Dyspnea is a common side effect of ticagrelor and may lead to treatment discontinuation, which is of particular concern in the setting of ticagrelor monotherapy.

What's new? In the TWILIGHT trial, dyspnea-related antiplatelet therapy discontinuation (with switch to another $P2Y_{12}$ inhibitor in most cases) occurred in 9.1% of patients and was associated with demographic and comorbid conditions indicating a worse clinical profile. Among high-risk patients who discontinued, ticagrelor monotherapy was not associated with a higher risk of ischemic events as compared with ticagrelor plus aspirin.

What's next? Ticagrelor monotherapy remains a safe and effective bleeding-avoidance strategy after PCI, despite a significant risk of dyspnea-related treatment discontinuation. Future studies should investigate alternative strategies, such as $P2Y_{12}$ inhibitor de-escalation, to ensure medication adherence in patients at high risk of developing ticagrelor-related dyspnea.

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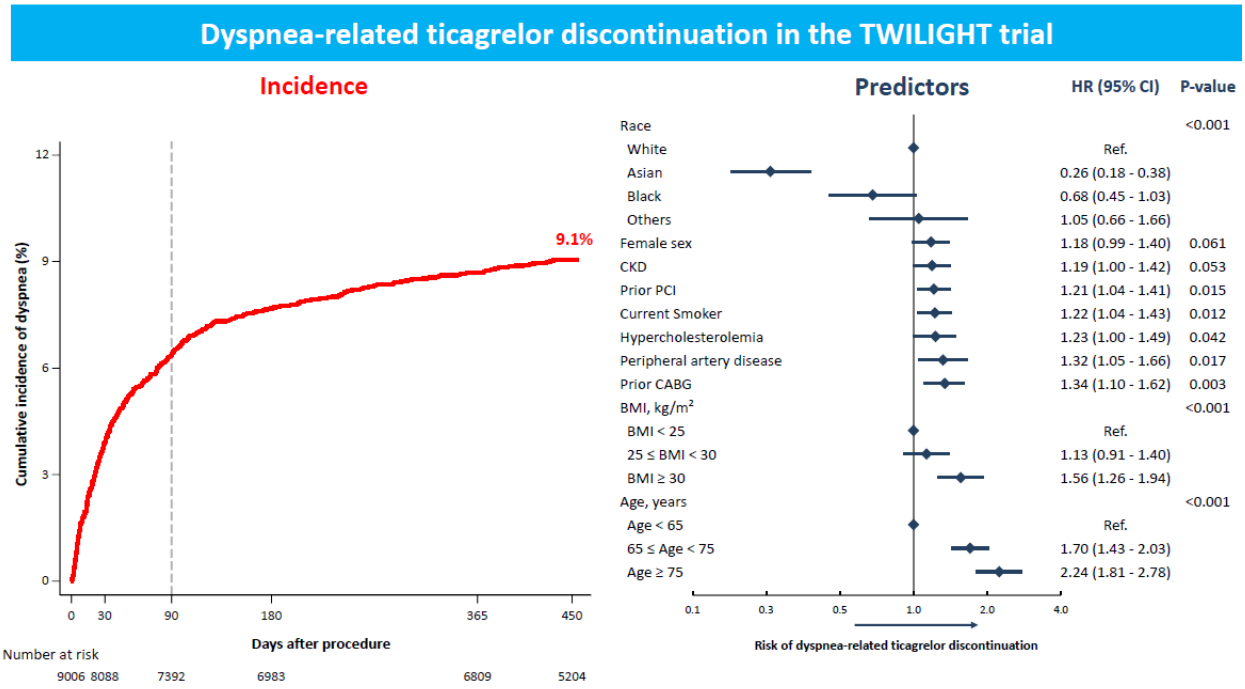
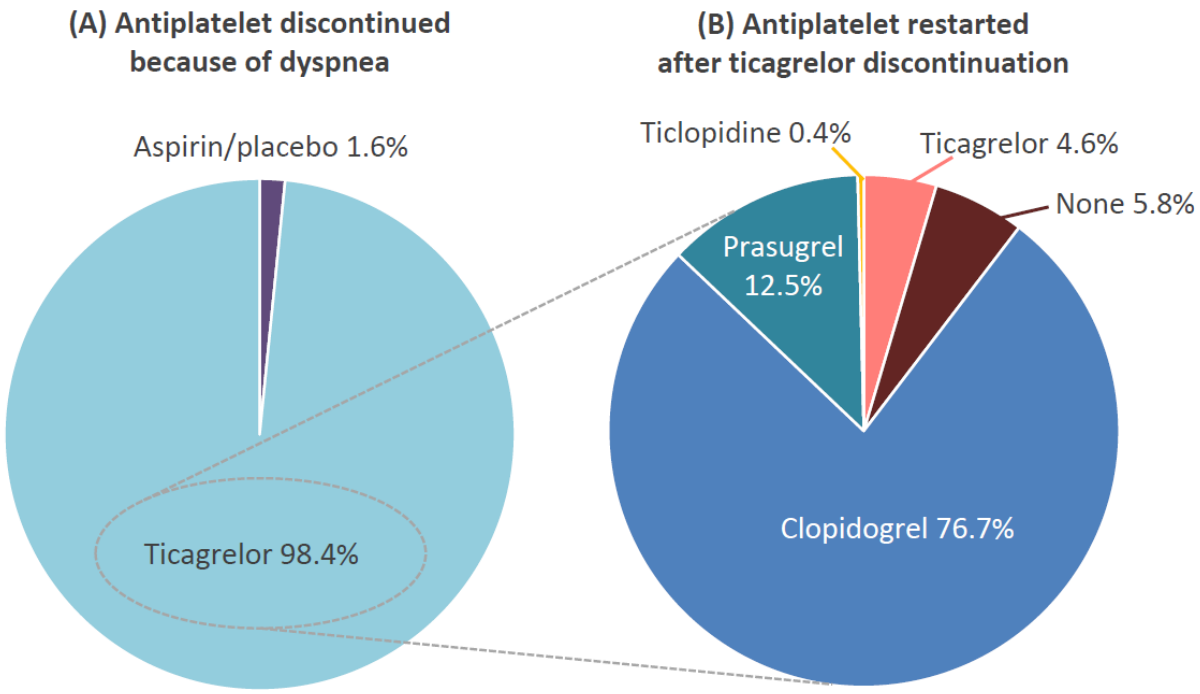
FIGURE LEGENDS

CENTRAL ILLUSTRATION. Incidence and predictors of dyspnea-related ticagrelor discontinuation in the TWILIGHT trial.



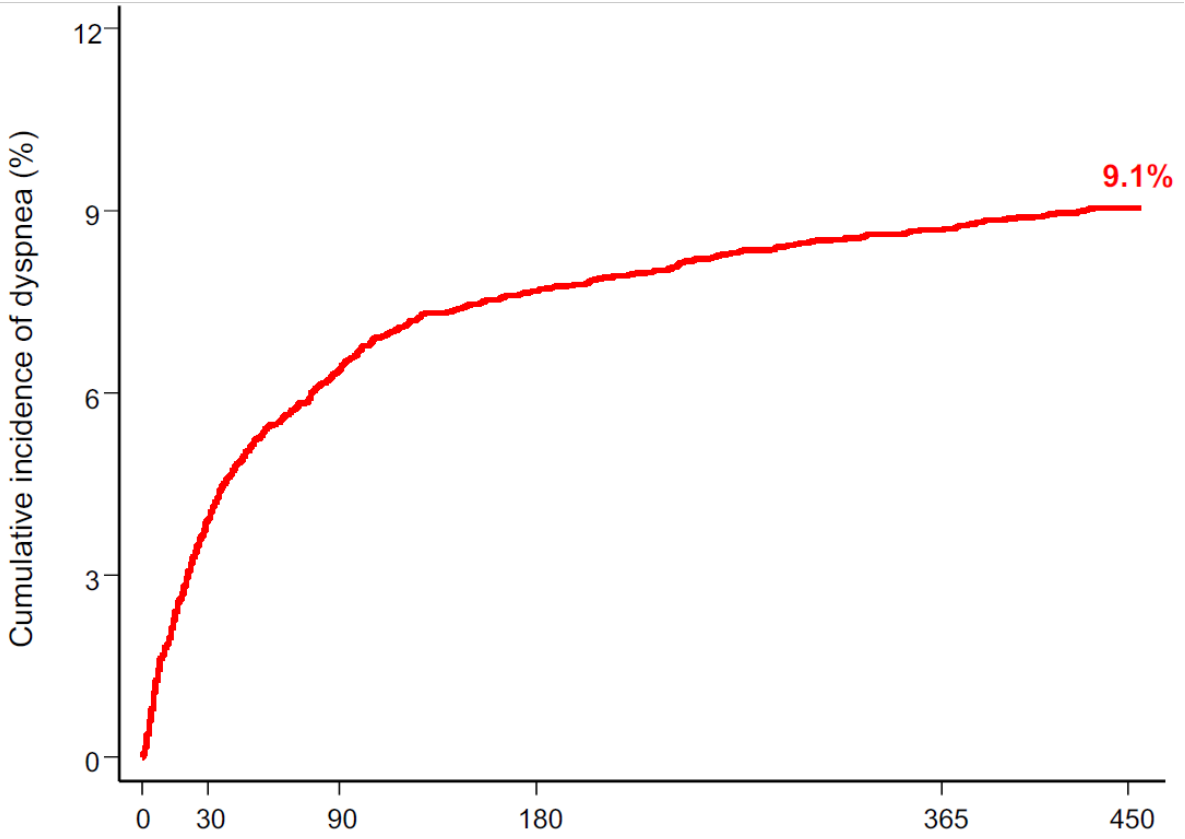
In the TWILIGHT trial, dyspnea-related ticagrelor discontinuation (with switch to another $P2Y_{12}$ inhibitor in most cases) occurred in 9.1% of patients and tended to occur earlier rather than late after PCI (6.4% in the first 3 months and 2.8% thereafter). Independent predictors of dyspnea-related ticagrelor discontinuation included several demographic and clinical parameters, with Asian race (lower risk) and advanced age (higher risk) being the most strongly associated.

Figure 1. Antiplatelet therapy discontinuation and restart.



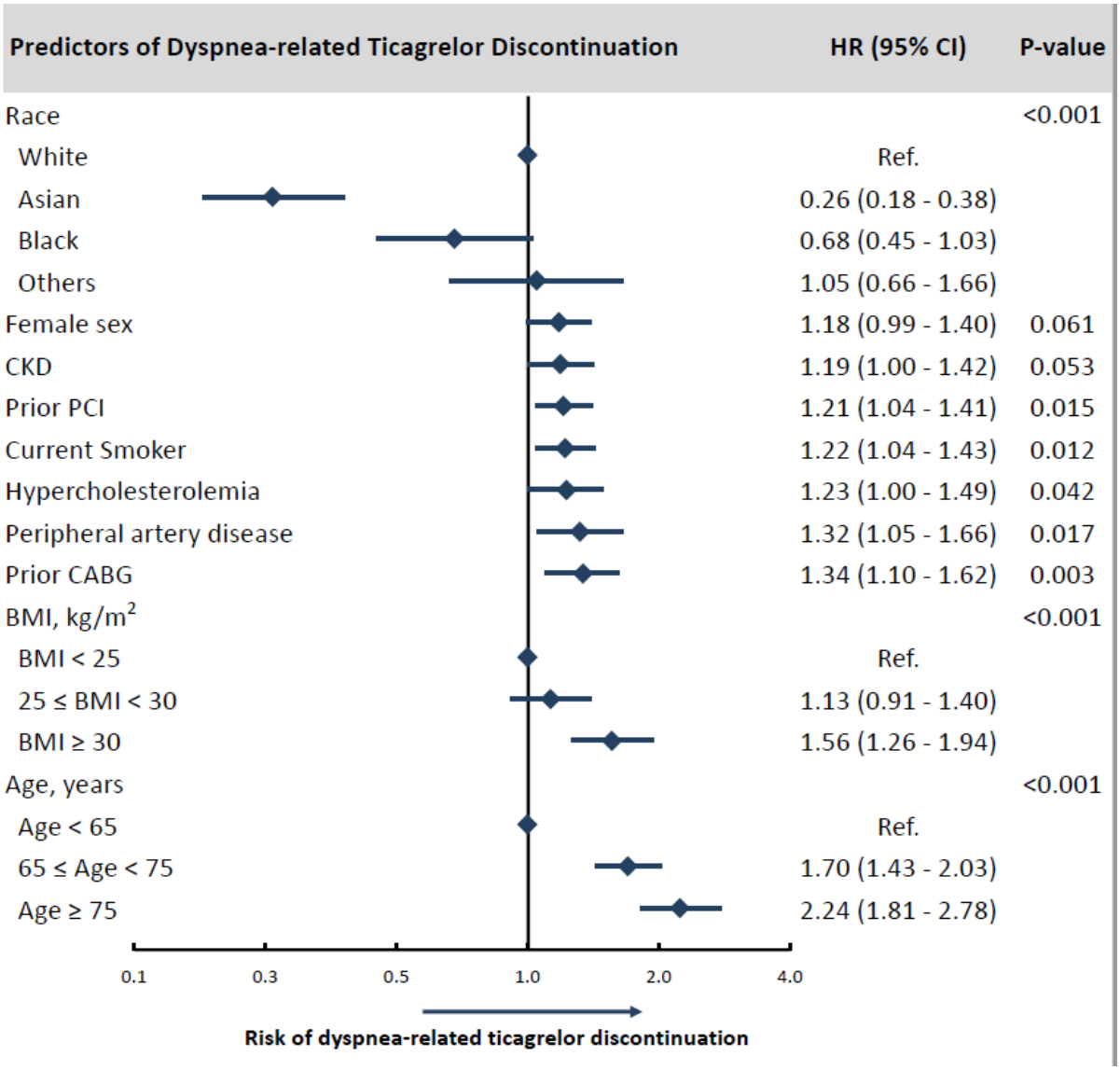
Pie-charts showing the antiplatelet drug discontinued because of dyspnea (panel A), and the antiplatelet drug restarted after ticagrelor was discontinued (panel B).

Figure 2. Incidence of dyspnea-related ticagrelor discontinuation.



Kaplan–Meier curves showing the cumulative incidence of dyspnea-related antiplatelet therapy discontinuation at 15 months (bottom), and landmark analysis at 3 months, i.e., time of randomization (top).

Figure 3. Predictors of dyspnea-related ticagrelor discontinuation.



Forest plots showing the predictors of dyspnea-related ticagrelor discontinuation. Candidate variables for selection: age (years), sex, race, body mass index (BMI, kg/m^2), smoking status, diabetes (no vs. non-insulin dependent vs. insulin dependent), estimated glomerular filtration rate (eGFR, mL/min/1.73m^2), hemoglobin (g/dL), hypertension, hypercholesterolemia, peripheral artery disease, congestive heart failure, prior percutaneous coronary intervention

(PCI), prior coronary artery bypass graft (CABG), indication for PCI, complex PCI. Harrell's C-statistic = 0.691.

HR: hazard ratio, CI: confidence interval.

TABLES

Table 1. Baseline clinical characteristics.

Clinical parameters	Overall N=9006	Dyspnea N=745 (8.3%)	No dyspnea N=8261 (91.7%)	p-value
Age, years	64.4±10.2	67.9±9.5	64.1±10.2	<.001
Female sex	2235 (24.8%)	194 (26.0%)	2041 (24.7%)	0.420
Race				<.001
White	6369 (70.7%)	660 (88.6%)	5709 (69.1%)	
Black	367 (4.1%)	25 (3.4%)	342 (4.1%)	
Asian	2059 (22.9%)	41 (5.5%)	2018 (24.4%)	
Others	211 (2.3%)	19 (2.6%)	192 (2.3%)	
BMI, kg/m^2	28.7±5.7	30.2±5.8	28.6±5.6	<.001
Enrolling region				<.001
North America	4092 (45.4%)	515 (69.1%)	3577 (43.3%)	
Europe	3048 (33.8%)	199 (26.7%)	2849 (34.5%)	
Asia	1866 (20.7%)	31 (4.2%)	1835 (22.2%)	
Diabetes	3395 (37.7%)	299 (40.1%)	3096 (37.5%)	0.152
Diabetes treated with insulin	978 (28.8%)	97 (32.4%)	881 (28.5%)	0.146
Chronic kidney disease	1551 (18.0%)	189 (27.0%)	1362 (17.2%)	<.001
Anemia	1779 (20.6%)	149 (21.3%)	1630 (20.5%)	0.657
Smoking status				<.001
Never	4848 (53.9%)	447 (60.0%)	4401 (53.3%)	
Hypercholesterolemia	5630 (62.5%)	583 (78.3%)	5047 (61.1%)	<.001
Hypertension	6607 (73.4%)	596 (80.0%)	6011 (72.8%)	<.001
Peripheral arterial disease	708 (7.9%)	91 (12.2%)	617 (7.5%)	<.001
Congestive heart failure	530 (5.9%)	57 (7.7%)	473 (5.7%)	0.032
Chronic lung disease	425 (4.7%)	37 (5.0%)	388 (4.7%)	0.740
Previous MI	2593 (28.8%)	218 (29.3%)	2375 (28.7%)	0.767
Previous PCI	3927 (43.6%)	398 (53.4%)	3529 (42.7%)	<.001

Clinical parameters	Overall N=9006	Dyspnea N=745 (8.3%)	No dyspnea N=8261 (91.7%)	p-value
Previous CABG	1019 (11.3%)	140 (18.8%)	879 (10.6%)	<.001
Previous major bleed	89 (1.0%)	10 (1.3%)	79 (1.0%)	0.308
Indication for PCI				<.001
No MI	6394 (71.0%)	615 (82.6%)	5779 (70.0%)	
MI	2607 (29.0%)	130 (17.4%)	2477 (30.0%)	
Laboratory				
Hemoglobin, g/dL	13.8±1.6	13.8±1.5	13.8±1.6	0.134
eGFR, mL/min/1.73m^2	78.9±19.4	72.5±18.6	79.4±19.4	<.001

BMI: body mass index, MI: myocardial infarction, PCI: percutaneous coronary intervention, CABG: coronary artery bypass graft, CAD: coronary artery disease, MI: myocardial infarction, eGFR: estimated glomerular filtration rate.

Table 2. Baseline procedural characteristics.

Procedural characteristics	Overall N=9006	Dyspnea N=745 (8.3%)	No dyspnea N=8261 (91.7%)	p-value
Radial artery access	6328 (70.3%)	408 (54.8%)	5920 (71.7%)	<.001
Multivessel CAD	5685 (63.1%)	474 (63.6%)	5211 (63.1%)	0.768
Target vessel				
Left Main	436 (4.8%)	34 (4.6%)	402 (4.9%)	0.713
LAD	5010 (55.6%)	382 (51.3%)	4628 (56.0%)	0.012
LCX	2927 (32.5%)	255 (34.2%)	2672 (32.3%)	0.293
RCA	3153 (35.0%)	257 (34.5%)	2896 (35.1%)	0.757
Number of vessels treated				
Mean±SD	1.3±0.5	1.2±0.5	1.3±0.5	0.065
Median [QR]	1 [1-1]	1 [1-1]	1 [1-2]	0.048
Number of lesions treated				
Mean (SD)	1.5±0.8	1.5±0.8	1.5±0.8	0.614
Median (IQR)	1 [1-2]	1 [1-2]	1 [1-2]	0.607
Lesion morphology†				
Moderate/severe calcification	1287 (14.3%)	118 (15.8%)	1169 (14.2%)	0.207
Bifurcation	1056 (11.7%)	72 (9.7%)	984 (11.9%)	0.068
Total occlusion	562 (6.2%)	34 (4.6%)	528 (6.4%)	0.048
Thrombotic	893 (9.9%)	44 (5.9%)	849 (10.3%)	<.001
Total stent length, mm‡	39.4±24.0	37.1±22.4	39.6±24.2	0.004
Minimum stent diameter, mm	2.8±0.5	2.8±0.5	2.8±0.5	0.862
Complex PCI§	2956 (32.8%)	244 (32.8%)	2712 (32.8%)	0.960

CAD: coronary artery disease, LAD: left anterior descending, LCX: left circumflex, RCA: right coronary artery, PCI: percutaneous coronary intervention.

†Lesion morphology assessed by operators.

‡Stent length calculated by operators.

§Complex PCI is defined as any of the following: 3 vessels treated, ≥ 3 lesions treated, total stent length > 60 mm, bifurcation with 2 stents implanted, atherectomy device use, left main PCI, surgical bypass graft or chronic total occlusion as target lesions.

Table 3. Safety and efficacy of ticagrelor monotherapy in patients with dyspnea-related ticagrelor discontinuation.

	Discontinuation due to dyspnea (N=179)		
	Ticagrelor+placebo	Ticagrelor+ASA	p-value
BARC 2, 3, or 5 bleeding	3 (3.8%)	12 (12.1%)	0.044
Death, MI, or stroke	4 (5.0%)	7 (7.1%)	0.566
Death, MI, stroke, or revascularization	11 (13.8%)	16 (16.2%)	0.654
MI or stroke	2 (2.5%)	6 (6.1%)	0.252
NACE	7 (8.8%)	17 (17.2%)	0.100

BARC: Bleeding Academic Research Consortium, MI: myocardial infarction, NACE: net adverse clinical events, including BARC type 2, 3 or 5 bleeding, all-cause death, MI, or stroke.