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ORIGINAL RESEARCH

Long-Term Ticagrelor in Patients With Prior Coronary Stenting in the PEGASUS-TIMI 54 Trial

Brian A. Bergmark, MD; Deepak L. Bhatt, MD, MPH; P. Gabriel Steg, MD; Andrzej Budaj, MD, PhD; Robert F. Storey, MD; Yared Gurmu, PhD; Julia F. Kuder, MA; KyungAh Im, PhD; Giulia Magnani, MD, PhD; Ton Oude Ophuis, MD, PhD, LLB, LLM; Christian Hamm, MD; Jindřich Špinar, MD; Robert G. Kiss, MD, PhD; Frans J. Van de Werf, MD, PhD; Gilles Montalescot, MD, PhD; Per Johanson, MD; Eugene Braunwald, MD; Marc S. Sabatine, MD, MPH; Marc P. Bonaca, MD, MPH

BACKGROUND: Coronary stent type and risk of stent thrombosis remain important factors affecting recommended duration of dual antiplatelet therapy. We investigated the efficacy and safety of long-term ticagrelor in patients with prior coronary stenting enrolled in the 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) trial.

METHODS AND RESULTS: Patients in PEGASUS-TIMI 54 had a myocardial infarction 1 to 3 year prior and were randomized 1:1:1 to ticagrelor 60 or 90 mg BID or placebo. The primary end point was a composite of cardiovascular death, myocardial infarction, or stroke (major adverse cardiovascular events). Stent thrombosis was prospectively adjudicated (Academic Research Consortium definition). Baseline characteristics were compared by most recent stent type (bare metal versus drug-eluting stent and first- versus later-generation drug-eluting stent). Treatment arms were compared using Cox proportional hazards models. Of 21 162 patients randomized, 80% (n=16 891) had prior coronary stenting. Following randomization, myocardial infarction was the most frequent ischemic event in patients with prior stenting in the placebo arm, occurring in 5.2% of patients (Type 1: 4.1%), followed by cardiovascular death (2.3%), stroke (1.7%), and stent thrombosis (0.9%). Ticagrelor$_{pooled}$ reduced major adverse cardiovascular events (7.0% versus 8.0%; hazard ratio [HR], 0.85; 95% CI, 0.75–96) regardless of stent type (bare metal stent versus drug-eluting stent: $p_{interaction}$=0.767; first versus later generation: $p_{interaction}$=0.940). The rate of any stent thrombosis was numerically lower with ticagrelor$_{pooled}$ (0.7% versus 0.9%; HR, 0.73; 95% CI, 0.50–1.05) and Thrombolysis in Myocardial Infarction major bleeding was increased (HR, 2.65; 95% CI, 1.90–3.68).

CONCLUSIONS: Long-term ticagrelor reduces major adverse cardiovascular events in patients with prior myocardial infarction and coronary stenting regardless of stent type, with the benefit driven predominantly by reduction in de novo events. Nonfatal major bleeding is increased with ticagrelor.

REGISTRATION INFORMATION: clinicaltrials.gov. Identifier: NCT01225562.

Key Words: acute coronary syndrome ■ antiplatelet therapy ■ P2Y$_{12}$ inhibitor ■ PCI

Strategies for long-term secondary prevention of ischemic events in patients with cardiovascular disease are evolving rapidly.[1,2] Recent trial data have supported extended-duration P2Y$_{12}$ inhibition as well as low-dose anticoagulant treatment.[3–8] Patients with prior percutaneous coronary intervention (PCI) are a population of particular interest, as the underlying disease substrate and coronary intervention

Correspondence to: Brian A. Bergmark, MD, TIMI Study Group, Cardiovascular Division, Brigham and Women's Hospital, Harvard Medical School, 60 Fenwood Rd., Suite 7022, Boston, MA 02115. E-mail: bbergmark@bwh.harvard.edu

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CLINICAL PERSPECTIVE

What Is New?

- Long-term ticagrelor reduces major adverse cardiovascular events in patients with prior myocardial infarction and coronary stenting with the benefit driven predominantly by reduction in de novo events.

What Are the Clinical Implications?

- Patients with prior coronary stenting enrolled 1 to 3 years following a myocardial infarction remain at elevated risk for cardiovascular death, myocardial infarction, or stroke and derive benefit from long-term therapy with ticagrelor regardless of prior stent type.

Nonstandard Abbreviations and Acronyms

BMS	bare metal stent
DES	drug-eluting stent
MACE	major adverse cardiovascular events
PEGASUS	Prevention of Cardiovascular Events in Patients With Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin
PES	paclitaxel-eluting stent
ST	stent thrombosis
TIMI	Thrombolysis in Myocardial Infarction

provide overlapping but separate potential indications for antithrombotic therapy. Indeed, there are conflicting data concerning the appropriate duration of intensive antithrombotic therapy following an acute coronary syndrome versus elective PCI, with antithrombotic therapy largely intended for secondary prevention in the former scenario and focused primarily on stent protection in the latter.[9]

The 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) trial compared ticagrelor (60 or 90 mg twice a day) with placebo in high-risk patients with prior myocardial infarction (MI) on a background of low-dose aspirin.[6,10] Ticagrelor reduced the risk of ischemic events but increased nonfatal major bleeding.[6] In this prespecified subgroup of patients with prior coronary stenting enrolled in the PEGASUS-TIMI 54 trial, we investigated rates of stent thrombosis (ST) relative to spontaneous atherothrombotic events, the effects of ticagrelor on ST and de novo cardiovascular events, and the interaction between ticagrelor effect and prior stent type.

METHODS

Study Design and Participants

The data supporting the findings of this study are not available to be shared, but individuals interested in collaboration are encouraged to contact the corresponding author. The design, rationale, and primary results of the PEGASUS-TIMI 54 (NCT01225562) trial have been reported previously.[6,10] PEGASUS-TIMI 54 enrolled patients at least 50 years of age with a spontaneous MI in the preceding 1 to 3 years who additionally had at least 1 further risk factor (age ≥65 years, diabetes mellitus requiring treatment, more than 1 prior MI, multivessel coronary artery disease, or chronic kidney disease [estimated creatinine clearance <60 mL/min]). Patients with anticipated use of a $P2Y_{12}$ inhibitor, cilostazol, dipyridamole, or an anticoagulant during the course of the trial, prior ischemic stroke, prior intracranial bleeding, central nervous system tumor or vascular malformation, gastrointestinal bleeding, or recent major surgery (<30 days) were excluded. Patients were randomized in a 1:1:1 fashion to ticagrelor 60 mg twice a day, ticagrelor 90 mg twice a day, or placebo on a background of low-dose aspirin therapy. 21 162 patients were randomized from October 2010 through May 2013 and followed for a median duration of 33 months. All participants provided written informed consent. The study protocol was approved by all relevant institutional review boards.

End Points

The primary efficacy end point for the trial and for this analysis was the composite of cardiovascular death, MI, or stroke. The primary safety end point was TIMI major bleeding. Secondary efficacy end points included the individual components of the primary end point and ST. Safety end points included fatal bleeding and intracranial hemorrhage as well as all-cause mortality. All outcomes were adjudicated by a blinded clinical end point committee. ST was formally adjudicated by blinded board-certified cardiologists using angiograms and were categorized as definite, probable, or possible according to the Academic Research Consortium definition.[11]

Prior Coronary Stenting

The type and date of the most recent coronary stent were to be reported at baseline. Patients within the prior stent subgroup were further categorized by type of stent received most recently. Patients who received

bare metal stents (BMS) only were categorized as "BMS" and patients who received at least 1 drug-eluting stent (DES) were categorized as "DES." DES were further categorized where data were available as first-generation (sirolimus-eluting stent or paclitaxel-eluting stent [PES]) or later-generation DES. If an implanted stent was not a first-generation sirolimus-eluting stent or PES, it was categorized as a "later-generation" DES without further subcategorizations within this group.

Statistical Analysis

Baseline patient characteristics are summarized by coronary stent status and BMS versus DES at randomization. Differences across groups were tested using a chi-square test for categorical variables and a Wilcoxon test for continuous variables given that the distributions were skewed positively. Rates of the primary and secondary efficacy and safety end points were calculated using the Kaplan-Meier method in patients with and without prior stenting in the placebo arm and compared using the log-rank test. Kaplan-Meier rates of the same end points were also compared by randomized treatment arm among patients with prior stents. Events were further analyzed by type of stent and time elapsed since most recent stent implantation. The risk of major adverse cardiovascular events major adverse cardiovascular events (MACE) and its components, ST (any, definite or probable, and definite), and TIMI major bleeding were calculated by randomized treatment arm and prior stent status using Cox proportional hazard models. The proportional hazards assumption was tested using Martingale residuals. Baseline predictors of ST were examined in the placebo arm using a multivariable logistic regression model that included age, sex, race, diabetes mellitus, peripheral artery disease, prior coronary artery bypass graft, time from qualifying MI to randomization, time from most recent PCI to randomization, time from last adenosine diphosphate-receptor antagonist use to randomization, qualifying MI type (non–ST-segment–elevation MI or ST-segment–elevation MI), current smoker, stent type, statin use, and estimated glomerular filtration rate >60 ml/min/1.73 m^2. All analyses were performed by the TIMI Study Group using commercially available statistical software (SAS version 9.4, SAS institute, Cary, NC). A 2-sided *P* value of 0.05 was considered significant for all tests.

RESULTS

Of the 21 162 patients randomized in the PEGASUS-TIMI 54 trial, 80% (n=16 891) had prior coronary stenting. The median time from most recent stent placement to trial enrollment was 1.6 (interquartile range 1.2–2.3) years. Five percent (n=786) of patients in the prior coronary stent group received a stent within 1 year preceding trial enrollment. Comparing the most recent stent implanted before randomization for each patient, 49% (n=8294) had DES and 51% (n=8597) had BMS. Among patients who received DES, 2289 (27.6%) received a first-generation DES, 4539 (54.7%) received a later-generation DES, and 1466 (17.7%) received an unspecified DES. Among patients treated with a first-generation DES, 1119 (49%) received a PES and 1170 (51%) received a DES without paclitaxel.

Baseline patient characteristics by prior stent status are shown in Table S1. Patients with prior coronary stenting had higher rates of multivessel coronary artery disease and ST-segment–elevation MI as the qualifying event, less frequently had diabetes mellitus and renal dysfunction, and had a shorter time from index MI to enrollment as compared with patients with no prior coronary stenting. There was regional variation in prior stent status, with greater proportions of patients having prior stenting in Western Europe (88%), North America (91%), and Asia/Pacific (84%) as compared with Eastern Europe (68%) and South America (69%) (*P*<0.001).

Among patients with prior stenting, those in Western Europe, North America, and Asia/Pacific were more likely than patients in Eastern Europe and South America to have received a DES as compared with BMS (*P*<0.001) (Table 1). There was additionally regional variation in stent generation among those treated with DES, with first-generation DES predominating in all regions other than Western Europe (*P*<0.001) (Table 1). Patients receiving later-generation DES more commonly had non–ST-segment–elevation MI as the index event as compared with patients treated most recently with first-generation DES and were more likely to have diabetes mellitus or >1 prior MI. There were no major differences in baseline characteristics across randomized treatment arms in patients with prior coronary stenting (Table S2).

MACE in Patients With Prior Coronary Stenting Randomized to Placebo

The median duration of follow-up for patients with prior stenting was 32 (interquartile range 27–37) months. Among the 5621 patients with prior stenting randomized to placebo, a total of 479 MACE events occurred in 409 patients. MI was the most frequent ischemic event, occurring in 5.2% of patients, with a rate of 4.1% for Type I MI (Table 2 and Figure 1). Rates of cardiovascular death and stroke were 2.3% and 1.7%, respectively. The rate of Academic Research Consortium definite, probable, or possible (any) ST was 0.9% and the rate of definite ST was 0.7%. Therefore, 91% of first MACE events in

Table 1. Baseline Patient Characteristics by Stent Type

	Prior DES* N=8294	Prior BMS[1] N=8597	*P* value	First-Generation DES N=2289	Later-Generation DES N=4539	*P* value
Demographics						
Age, y, median (IQR)	65 (58–71)	65 (59–71)	0.022	65 (58–71)	65 (58–71)	0.324
Body mass index, kg/m^2, median (IQR)	27.7 (25.1–31.0)	28.0 (25.4–31.2)	0.002	27.6 (24.8–30.9)	27.8 (25.1–31.1)	0.045
Female sex (%)	1668 (20.1)	1935 (22.5)	<0.001	460 (20.1)	875 (19.3)	0.440
Clinical characteristics						
Hypertension (%)	6208 (74.9)	6614 (76.9)	0.002	1742 (76.1)	3353 (73.9)	0.049
Hyperlipidemia (%)	6530 (78.7)	6725 (78.2)	0.451	1781 (77.8)	3662 (80.7)	0.006
Current smoking (%)	1425 (17.2)	1515 (17.6)	0.466	408 (17.8)	762 (16.8)	0.293
Diabetes mellitus (%)	2685 (32.4)	2501 (29.1)	<0.001	793 (34.6)	1403 (30.9)	0.002
Multivessel coronary artery disease (%)	5883 (70.9)	5419 (63.0)	<0.001	1670 (73.0)	3260 (71.8)	0.337
History of > 1 prior MI (%)	1383 (16.7)	1229 (14.3)	<0.001	433 (18.9)	660 (14.5)	<0.001
Last dose of $P2Y_{12} \leqq 30$ d (%)	3803 (47.5)	2628 (32.4)	<0.001	1043 (47.6)	2203 (49.8)	0.097
Months from most recent percutaneous coronary intervention, median (IQR)	19.5 (14.5–27.0)	21.1 (14.8–29.1)	<0.001	22.4 (16.0–28.7)	18.3 (14.1–25.4)	<0.001
Estimated glomerular filtration rate at baseline <60 mL/min (%)	1778 (21.7)	1812 (21.3)	0.578	480 (21.22)	971 (21.68)	0.688
Region						
Western Europe (%)	3078 (37.1)	2319 (27.0)	<0.001	587 (25.6)	1786 (39.4)	<0.001
Eastern Europe (%)	1163 (14.0)	3099 (36.1)		282 (12.3)	532 (11.7)	
North America (%)	2340 (28.2)	1208 (14.1)		775 (33.9)	1385 (30.5)	
South America (%)	327 (3.9)	1371 (16.0)		102 (4.5)	71 (1.6)	
Asia/Pacific (%)	1386 (16.7)	600 (7.0)		543 (23.7)	765 (16.9)	
Qualifying event						
Months from MI, median (IQR)	20.1 (14.7–27.4)	20.8 (14.8–28.5)	<0.001	23.0 (16.5–29.8)	18.9 (14.2–26.0)	<0.001
ST-segment–elevation MI (%)	4206 (50.8)	5346 (62.2)	<0.001	1185 (51.8)	2270 (50.1)	0.199
Non–ST-segment–elevation MI (%)	3714 (44.9)	2895 (33.7)	<0.001	973 (42.5)	2123 (46.9)	0.001
MI type unknown (%)	361 (4.4)	351 (4.1)	0.397	130 (5.7)	137 (3.0)	<0.001

Categorical variables were compared using the chi-square test and continuous variables using the Wilcoxon test.
BMS indicates bare metal stent; DES, drug-eluting stent; IQR, interquartile range; and MI, myocardial infarction.
*Patients who received BMS only were categorized as "BMS" and patients who received at least 1 DES were categorized as DES.

the placebo group were due to de novo events unrelated to ST. As the majority of most recent coronary stents were placed greater than 1 year before randomization, 89% of ST events were classified as very late (>1 year), 6% were late (30 days–1 year), and 5% were acute or subacute (within 30 days) (includes stents placed during the trial). Rates of ST in the placebo arm were higher in patients with peripheral artery disease (HR_{adj}, 2.89; 95% CI, 1.17–7.16; *P*=0.022) and lower with increased age (HR_{adj} per year, 0.95; 95% CI, 0.91–1.00; *P*=0.030) (Table S3). Among patients previously treated with a first-generation DES (n=2289), prior PES treatment (n=1119; 49%) was not associated with subsequent mortality. The rate of all-cause mortality was 4.68% in the patients receiving a first-generation PES and 4.70% in the patients receiving a non-paclitaxel-eluting first-generation DES (HR, 1.04; 95% CI, 0.70–1.56; *P*=0.830).

Efficacy of Ticagrelor in Patients With Prior Coronary Stenting

Both doses of ticagrelor reduced the primary end point (PEP) relative to placebo in patients with prior coronary stenting (ticagrelor 60 mg versus placebo: 6.8% versus 8.0%; HR, 0.84; 95% CI, 0.73–0.97; ticagrelor 90 mg versus placebo: 7.1% versus 8.0%; HR, 0.86; 95% CI, 0.75–0.99; ticagrelor pooled versus placebo: 7.0% versus 8.0%; HR, 0.85; 95% CI, 0.75–96; absolute risk reduction, 1.02%; Figure 2 and Table 2). These reductions translate into a number needed to treat of 118 for the 90 mg dose and 85 for the 60 mg dose over this time frame. The benefit of ticagrelor in patients with prior coronary stents was consistent across all components of the primary end point including cardiovascular death, MI, and stroke (Table 2), including a 20% reduction in Type 1 MI for pooled ticagrelor (3.4 versus 4.1%; HR, 0.80; 95% CI, 0.68–0.96) (Figure 1). As has been

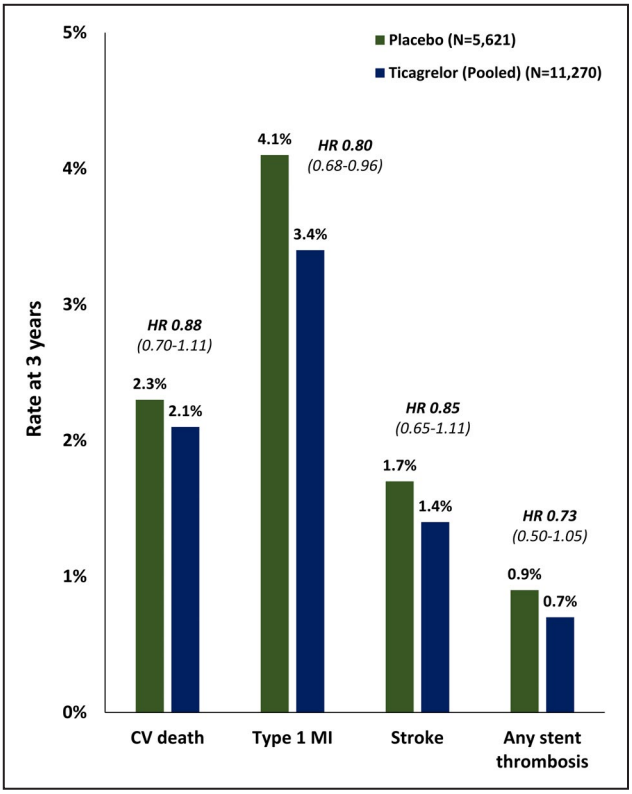

Figure 1. Ischemic events at 3 years among patients with prior coronary stenting.
Spontaneous (Type 1) MI was the most frequent event type. CV indicates cardiovascular; HR, hazard ratio; and MI, myocardial infarction.

reported previously, ticagrelor significantly reduced the occurrence of MACE in patients with no prior coronary stenting, without significant interaction with prior stent status ($p_{interaction}$=0.76).[12]

The rate of any ST was low overall and was reduced with ticagrelor 90 mg (0.6% versus 0.9%; HR, 0.63; 95% CI, 0.40–0.99; absolute risk reduction, 0.28%; 95% CI, −0.08 to 0.65%) with directional consistency for ticagrelor 60 mg (0.7% versus 0.9%; HR, 0.83; 95% CI, 0.54–1.26; absolute risk reduction, 0.18%; 95% CI, −0.18 to 0.55; $p_{interaction}$=0.81). Ticagrelor (doses pooled) numerically reduced any ST in the intention-to-treat cohort with a greater apparent effect in the on-treatment cohort (Figure 3). Similar trends were seen for definite or probable ST and definite ST (Figure 3 and Table 2).

Stent Type

The rate of any ST in the placebo arm was similar across stent types (first-generation DES: 1.3%; later-generation DES: 1.0%; BMS; 0.7%; *P*=0.071). Ticagrelor was equally efficacious in patients with DES compared with BMS and in those with later-generation versus first-generation DES as the most recent stent type received (Figure 4).

Time from Most Recent Coronary Stent

The median time from the most recent coronary stent implantation was slightly shorter than the time from the qualifying MI (19.0 [14.0–27.0] versus 20.4 [14.8–27.9] months). As would be expected, the time from most recent stenting was shorter for patients receiving DES (19.0 [14.0–26.0] months) compared with BMS (20.0 [14.0–28.0] months) and for later-generation (18.0 [13.0–25.0] months) rather than first-generation (22.0 [15.0–29.0] months) DES. The efficacy of ticagrelor was consistent irrespective of elapsed time from the most recent stent implantation. The 3-year Kaplan-Meier rate of MACE for pooled ticagrelor was 7.2% compared with 7.0% for placebo (HR, 0.93; 95% CI, 0.53–1.63) for patients with stenting within the preceding 1 year, 6.9% versus 8.2% (HR, 0.82; 95% CI, 0.70–0.96) for patients with stenting 1 to 2 years before randomization, and 7.1% versus 7.7% (HR, 0.90; 95% CI, 0.74–1.10) for patients with stenting >2 years before randomization ($p_{interaction}$=0.725). The findings were similar for each separate ticagrelor dose (Table S4).

Safety

Ticagrelor increased TIMI major bleeding with a numerically greater excess with the 90 mg dose versus placebo relative to the 60 mg dose versus placebo in patients with prior coronary stenting (Table 2). There was no significant excess in intracranial hemorrhage or fatal bleeding with either dose relative to placebo (Figure S1).

DISCUSSIONS

Patients with prior MI are at elevated risk of recurrent ischemic events across all vascular territories.[13,14] Increased atherothrombotic risk following MI is multifactorial with contributions from the inflammatory response to the index event, alterations in intrinsic prothrombotic factors, PCI and stent-related characteristics, and other patient and environmental characteristics.[13,15,16] In this prespecified analysis from the PEGASUS-TIMI 54 trial, we have shown that patients with prior coronary stenting enrolled 1 to 3 years following an MI remain at elevated risk for cardiovascular death, MI, or stroke and that the risk of ST is relatively low. This subgroup derived benefit from long-term therapy with ticagrelor despite low rates of ST, underscoring that the benefit of ticagrelor is largely driven by reduction of de novo atherothrombotic events.

Patients with prior PCI present an important and growing population for focused secondary prevention, with prior observations in patients undergoing PCI for acute coronary syndrome showing approximately one half of future adverse cardiovascular events being related to nonculprit lesions.[14] A principal finding of the

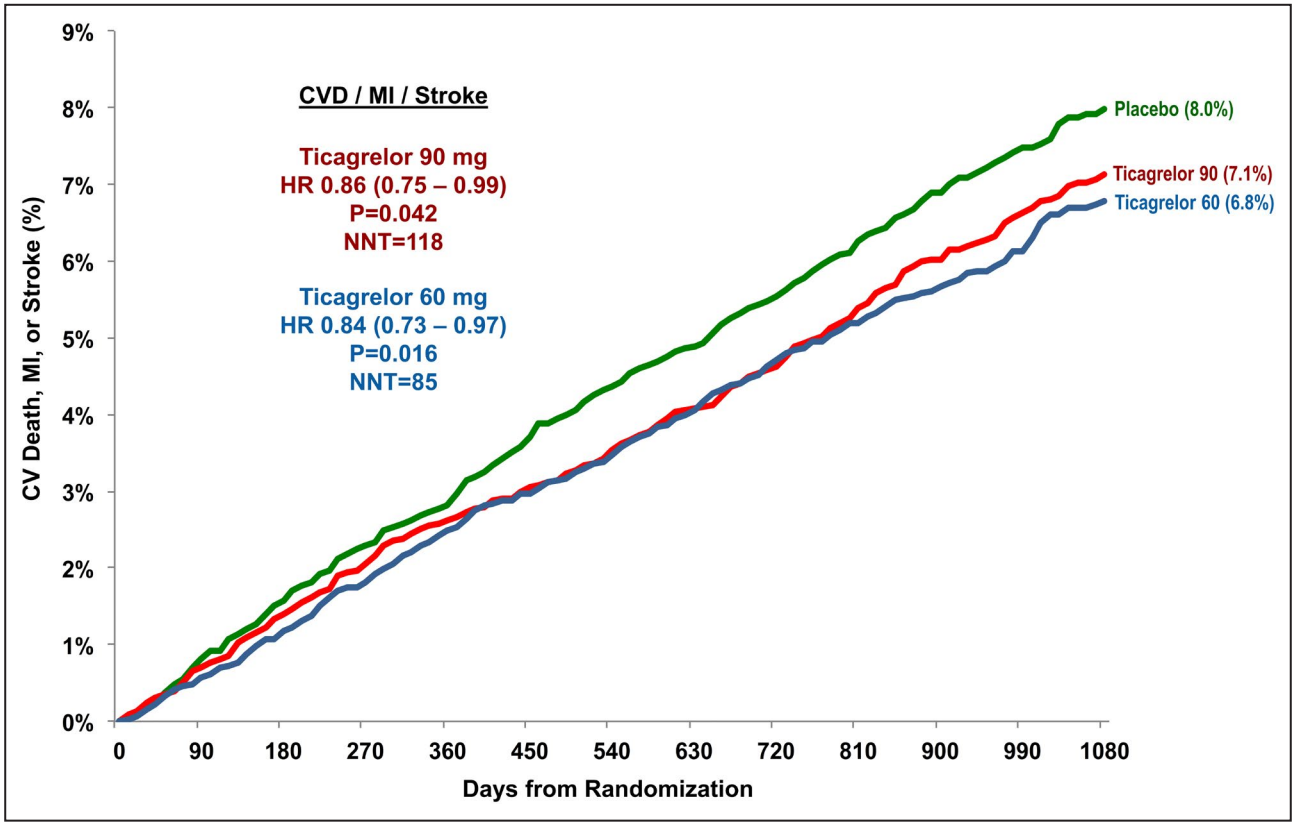

Figure 2. Kaplan-Meier rates of MACE by randomized treatment arm in patients with prior coronary stenting.
CV indicates cardiovascular; CVD, cardiovascular death; MACE, major adverse cardiovascular event; HR, hazard ratio; MI, myocardial infarction; and NNT, number needed to treat.

present analyses, that patients with prior MI and PCI remain at elevated risk for further ischemic events, aligns with the findings of other contemporary trials showing reduction in ischemic events with increased antithrombotic duration and/or intensity. These trials have been performed in several populations, including patients with prior MI,[3,17] recent acute coronary syndrome,[7] PCI for elective or urgent indications,[5] and high-risk patients with diabetes mellitus and stable coronary artery disease,[18] including those with prior PCI.[19,20] Here we show benefit with extended-duration ticagrelor specifically in patients with prior MI and prior coronary stenting. The similar efficacy of the lower dose of ticagrelor (60 mg twice daily) compared with 90 mg twice daily may be explained by the similarly high and consistent levels of platelet $P2Y_{12}$ inhibition achieved with this lower dose.[21] Some studies have indicated further pleiotropic effects of ticagrelor on the inflammatory cascade and endothelial function, though the clinical relevance of these potential actions remains under investigation.[22,23] The comparative efficacy and safety of $P2Y_{12}$ inhibitors and low-dose direct oral anticoagulants for long-term ischemic risk reduction remain unknown in the absence of head-to-head data, particularly with respect to high-risk subgroups such as patients with prior MI and prior PCI.

Although not the focus of the analyses presented here, it is important to interpret these findings in the context of recent trials exploring early discontinuation of aspirin following PCI.[24–30] The data are complex, but there do appear to be 2 consistent findings. First, in appropriately selected patients, more potent antithrombotic therapy, specifically, adding long-term $P2Y_{12}$ inhibition to a background of aspirin therapy, reduces ischemic risk. Second, a strategy of deescalation to $P2Y_{12}$ monotherapy 1 to 3 months after PCI leads to fewer bleeding events without apparent excess ischemic risk in carefully selected patients, albeit with relatively little follow-up beyond 1 year currently available.[30] How to reconcile these data is not straightforward, although it may be that aspirin adds relatively little on top of potent $P2Y_{12}$ inhibition. Regardless, the data in this study combined with the other published studies support the importance of long-term potent $P2Y_{12}$ inhibition.

Stent type

Despite the evidence base supporting the use of DES over BMS, BMS continue to be used in a substantial portion of PCIs, particularly in the setting of ST-segment–elevation MI, renal insufficiency, or vein graft

Table 2. Efficacy and Safety of Ticagrelor in Patients With Prior Percutaneous Coronary Intervention

	Ticagrelor 90 mg KM (%)	Ticagrelor 60 mg KM (%)	Ticagrelor pooled KM (%)	Placebo KM (%)	Ticagrelor 90 mg vs placebo HR (95% CI)	*P* value	Ticagrelor 60 mg vs placebo HR (95% CI)	*P* value	Ticagrelor pooled vs placebo HR (95% CI)	*P* value
Efficacy										
Cardiovascular death/MI/stroke	7.13	6.80	6.96	7.98	0.86 (0.75–0.99)	0.042	0.84 (0.73–0.97)	0.016	0.85 (0.75–0.96)	0.009
Cardiovascular death	2.19	1.90	2.05	2.28	0.94 (0.72–1.23)	0.656	0.82 (0.62–1.08)	0.154	0.88 (0.70–1.11)	0.277
MI	4.33	4.47	4.40	5.18	0.79 (0.66–0.95)	0.012	0.84 (0.70–1.00)	0.046	0.81 (0.70–0.95)	0.008
Type 1 MI	3.38	3.36	3.37	4.08	0.81 (0.66–0.99)	0.041	0.80 (0.65–0.98)	0.032	0.80 (0.68–0.96)	0.014
Stroke	1.45	1.30	1.37	1.65	0.88 (0.65–1.21)	0.440	0.81 (0.59–1.12)	0.206	0.85 (0.65–1.11)	0.234
Coronary heart death	1.14	0.97	1.05	1.57	0.73 (0.52–1.03)	0.075	0.64 (0.45–0.91)	0.013	0.68 (0.51–0.92)	0.011
Stent thrombosis										
Any ST	0.65	0.75	0.70	0.93	0.63 (0.40–0.99)	0.045	0.83 (0.54–1.26)	0.380	0.73 (0.50–1.05)	0.091
Definite/probable ST	0.57	0.69	0.63	0.74	0.65 (0.40–1.07)	0.09	0.92 (0.59–1.44)	0.712	0.79 (0.53–1.17)	0.235
Definite ST	0.50	0.64	0.57	0.71	0.60 (0.35–1.01)	0.055	0.94 (0.59–1.49)	0.793	0.77 (0.51–1.16)	0.214
Safety										
TIMI Major	2.70	2.46	2.58	1.05	2.86 (2.01–4.08)	<0.001	2.45 (1.71–3.50)	<0.001	2.65 (1.90–3.68)	<0.001
TIMI minor	1.29	1.15	1.22	0.23	5.42 (2.83–10.39)	<0.001	4.11 (2.12–7.98)	<0.001	4.74 (2.54–8.86)	<0.001
Fatal bleeding or intracranial hemorrhage	0.62	0.76	0.69	0.57	1.37 (0.78–2.43)	0.272	1.38 (0.79–2.41)	0.258	1.38 (0.84–2.26)	0.205
Fatal bleeding	0.08	0.29	0.19	0.23	0.59 (0.18–1.95)	0.383	1.36 (0.54–3.44)	0.518	0.99 (0.41–2.35)	0.976

Comparisons across treatment groups were made using a Cox proportional hazards model. HR, hazard ratio; KM, Kaplan-Meier; MI, myocardial infarction; TIMI, thrombolysis in myocardial infarction; and ST, stent thrombosis.

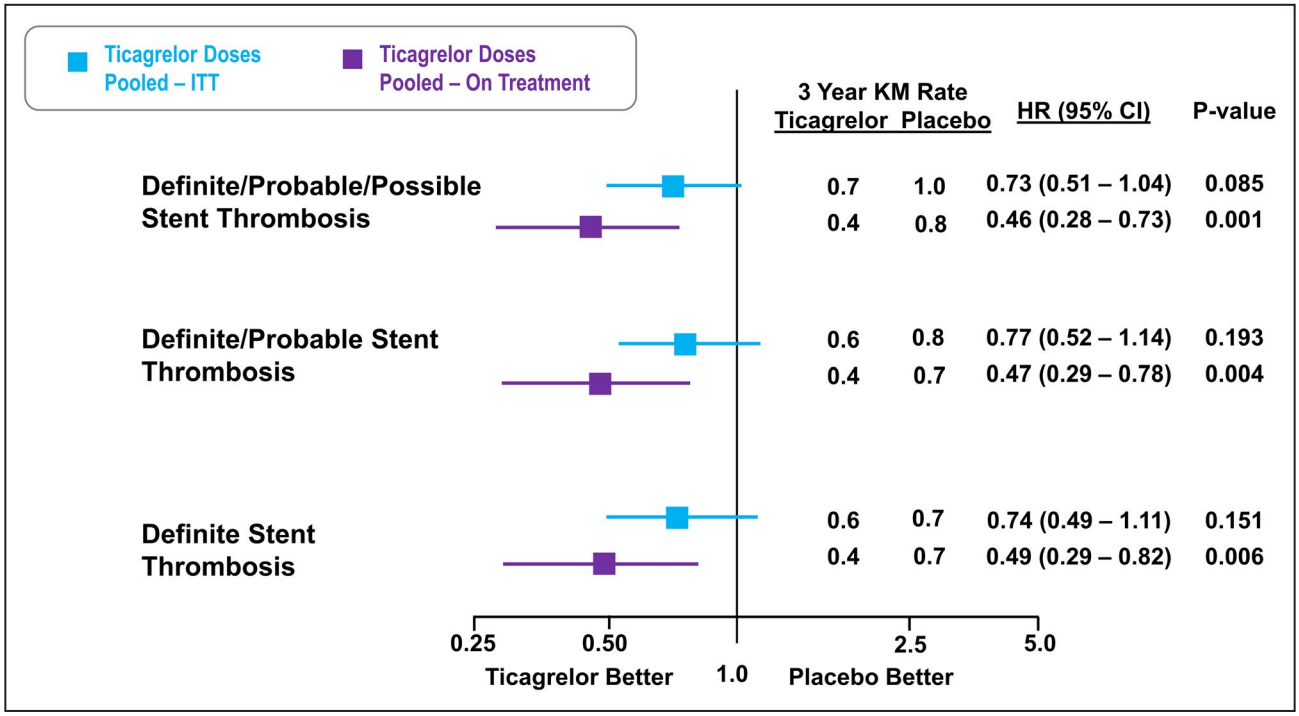

Figure 3. Stent thrombosis with ticagrelor in ITT and on-treatment cohorts.
The on-treatment cohort was defined as patients who received at least 1 dose of study drug with events included through 7 days from their last dose or the common study end date. CV indicates cardiovascular; HR, hazard ratio; ITT, intention to treat; and KM, Kaplan-Meier

interventions.[31–33] We observed no significant interaction between ticagrelor efficacy and prior stent type, supporting the notion that prior MI and prior PCI are important risk markers for atherothrombotic events, but overall patient risk, rather than stent type, drives the potential benefit from extended-duration $P2Y_{12}$ inhibition.

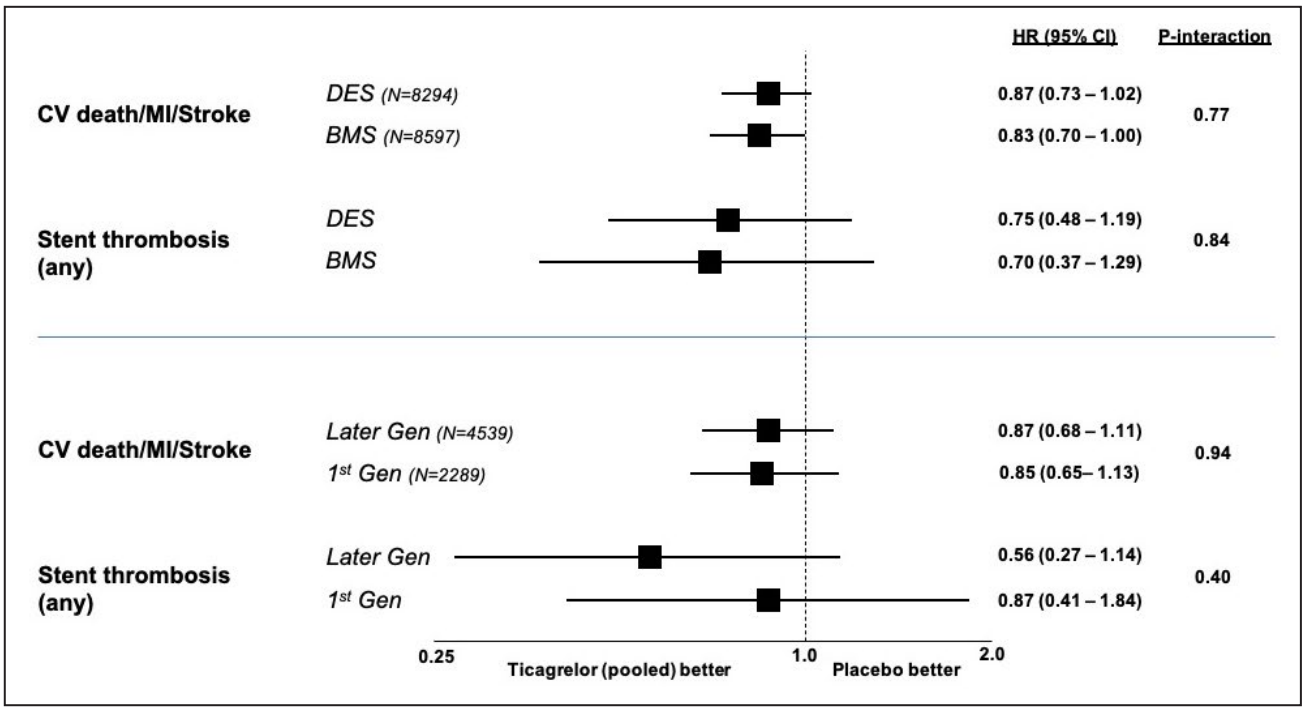

Figure 4. Ticagrelor efficacy in patients with DES vs BMS and later generation DES vs first-generation DES.
A consistent effect of ticagrelor is observed across stent types. BMS indicates bare metal stent; CV, cardiovascular; DES, drug eluting stent; Gen, generation; HR, hazard ratio; and MI, myocardial infarction.

This observation is additionally supported by the consistent efficacy of ticagrelor irrespective of time from most recent coronary stent. Because some patients received stents for non-MI indications subsequent to the most recent MI, the time from PCI and time from MI were distinct. As has been previously reported, patients with more recent MI are at heightened cardiovascular risk[34] and these patients were previously shown to derive even greater benefit from extended duration ticagrelor,[35] as reflected in the European Medicines Agency label.[36] Conversely, timing from stent placement per se does not appear to reflect this same degree of heightened risk with potential additional benefit from extended antithrombotic therapy in this cohort. A similar finding was observed in THEMIS (The Effect of Ticagrelor on Health Outcomes in Diabetes Mellitus Patients Intervention Study),[18] in which the net clinical benefit of ticagrelor added to aspirin in patients with diabetes mellitus and stable coronary artery disease was accentuated in those with prior PCI, but this benefit did not vary based on time from most recent PCI.[19,20] There was similarly no interaction between low-dose rivaroxaban efficacy and time from most recent PCI in the COMPASS (Cardiovascular Outcomes for People using Anticoagulation Strategies) trial.[8]

We observed significant regional variation in the type of most recent stent, both in terms of BMS versus DES as well as in generation of DES. Patients in Western Europe, North America, and Asia/Pacific were more likely to have received a DES, whereas only 19% of patients in South America were treated with a DES. These differences are notable, though it is important to acknowledge that these findings indicate stent use patterns before enrollment in this trial and may not reflect contemporary practice. Although treatment with DES, and in particular later-generation DES, has established benefits,[37–40] stent-related events were infrequent in this cohort of stable patients removed an average of 1.6 years from stent placement and no regional variation was observed in the overall trial results.[6] The rates of ST were numerically but not statistically highest in patients with a first-generation DES. However, any observed differences need to be viewed in the context that patients were not randomized to different stent types and we do not have detailed lesion or procedural characteristics.

Regarding safety, there is recent uncertainty around a long-term association between paclitaxel exposure in the peripheral artery beds and all-cause mortality.[41,42] In the cohort presented here of over 2000 patients with first-generation coronary DES followed until an average of approximately 5 years post-stent implantation, there was no significant signal of excess mortality in those patients previously treated with PES. Importantly, there was very infrequent loss to follow-up or missing vital status information in the PEGASUS-TIMI 54 trial.[6]

LIMITATIONS

Although this analysis benefits from a large, well-characterized patient cohort with prospectively collected and adjudicated outcomes, there are several limitations. First, patients received PCI in a nonrandomized manner before study enrollment and treatment decisions regarding revascularization were presumably influenced by perceived patient risk, likelihood of benefit, and numerous other relevant factors. Only limited data are available from these procedures which predated trial enrollment, including no coronary anatomical detail. Further, although the prior coronary stenting subgroup was prespecified, the trial was not designed to accommodate statistical power for this subgroup. Additionally, no adjustment was performed for multiple testing in this hypothesis-generating subgroup analysis. Finally, the proportion of BMS relative to DES was greater than that seen in current clinical practice.

CONCLUSIONS

In this prespecified analysis from the PEGASUS-TIMI 54 trial, we have shown that patients with prior coronary stenting enrolled 1 to 3 years following an MI remain at elevated risk for cardiovascular death, MI, or stroke and derive benefit from long-term therapy with ticagrelor regardless of prior stent type. The ischemic risk reduction is driven largely by fewer de novo atherothrombotic events, though ST is also reduced with long-term $P2Y_{12}$ inhibition.

ARTICLE INFORMATION

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Affiliations

TIMI Study Group, Cardiovascular Medicine, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA (B.A.B., D.L.B., Y.G., J.F.K., K.I., E.B., M.S.S., M.P.B.); French Alliance for Cardiovascular Trials, AP-HP, Hôpital Bichat, Université de Paris, Institut National de la Santé et de la Recherche Médicale U-1148, Paris, France (P.G.S.); National Heart and Lung Institute, Royal Brompton Hospital, Imperial College London, London, UK (P.G.S.); Centre of Postgraduate Medical Education, Grochowski Hospital, Warsaw, Poland (A.B.); University of Sheffield, Sheffield, UK (R.F.S.); University Hospital of Parma, Parma, Italy (G.M.); Canisius-Wilhelmina Hospital, Nijmegen, the Netherlands (T.O.O.); Kerckhoff Heart Center, Bad Nauheim, University of Giessen, Giessen, Germany (C.H.); University hospital St. Ann, Pekarska and Medical faculty, Brno, Czech Republic (J.Š.); Department of Cardiology, Military Hospital, Budapest, Hungary (R.G.K.); University of Leuven, Leuven, Belgium (F.J.V.d.); Sorbonne Université, Paris 6, ACTION Study Group, INSERM-UMRS 1166, Institut de Cardiologie, Pitié-Salpêtrière Hospital (AP-HP), Paris, France (G.M.); AstraZeneca, Mölndal, Sweden (P.J.); and Colorado Prevention Center (CPC) Clinical Research, the Department of Medicine, Division of Cardiovascular Medicine, University of Colorado Anschutz Medical Campus, Aurora, CO (M.P.B.).

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Supplementary Material

Tables S1-S4
Figure S1

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Supplemental Table S1. Baseline patient characteristics by prior coronary stenting status.[1]

	No prior stenting (n = 4,199)	Prior stenting (n = 16,891)	P-value
Age (Median, IQR)	67.0 (60.0,73.0)	65.0 (58.0,71.0)	< 0.0001
Female sex (n, %)	1,441 (34.3)	3,603 (21.3)	<0.0001
White race (n, %)	3,595 (85.62)	14,665 (86.8)	0.04
Weight in kg (Median, IQR)	78.0 (68.5, 89.0)	81.0 (71.0,92.0)	<0.0001
Hypertension (n, %)	3,533 (84.1)	12,822 (75.9)	<0.0001
Hypercholesterolemia (n, %)	2,936 (69.9)	13,255 (78.5)	<0.0001
Current smoker (n, %)	581 (13.8)	2,940 (17.4)	<0.0001
Diabetes mellitus (n, %)	1,591 (37.9)	5,186 (30.7)	<0.0001
Multivessel CAD (n, %)	1,219 (29.1)	11,302 (66.9)	<0.0001
Prior CABG (n, %)	292 (7.0)	679 (4.0)	<0.0001
Prior PCI* (n, %)	608 (14.5)	16,891 (100.0)	<0.0001
> 1 prior MI (n, %)	872 (20.8)	2,612 (15.5)	<0.0001
PAD (n, %)	270 (6.4)	863 (5.1)	<0.0001
eGFR < 60 ml/min/1.73m2 (n, %)	1,241 (29.9)	3,590 (21.5)	<0.0001
Years since qualifying MI Median (IQR)	1.8 (1.3,2.4)	1.7 (1.2,2.3)	<0.0001
STEMI (n, %)	1,744 (41.62%)	9,552 (56.6)	<0.0001
Aspirin (n, %)	4,196 (99.93%)	16,865 (99.9)	0.29
Statin (n, %)	3,660 (87.16%)	15,884 (94.0)	<0.0001
Beta-blocker (n, %)	3,386 (80.64%)	14,043 (83.1)	0.0001
ACE inhibitor or ARB (n, %)	3,373 (80.33%)	13,604 (80.5)	0.77
Region (n, %)			<0.0001
North America	352 (8.4)	3,548 (21.0)	
South America	746 (17.8)	1,698 (10.1)	
Western Europe	715 (17.0)	5,397 (32.0)	
Eastern Europe	2,005 (47.8)	4,262 (25.2)	
Asia/Pacific	381 (9.1)	1,986 (11.8)	

Categorical variables were compared using the Chi square test and continuous variables using the Wilcoxon test.

Note: Prior stenting status was missing for 72 patients; * for non-stented subgroup, this means balloon angioplasty only without deployment of stents; ACE = angiotensin converting enzyme; ARB = angiotensin receptor blocker; CAD = coronary artery disease; eGFR = estimated glomerular filtration rate; IQR = interquartile range; PAD = peripheral artery disease; STEMI = ST-elevation myocardial infarction

[1] Furtado RHM, Nicolau JC, Magnani G, et al. Long-term ticagrelor for secondary prevention in patients with prior myocardial infarction and no history of coronary stenting: insights from PEGASUS-TIMI 54. *Eur Heart J.* 2019.

Supplemental Table S2. Baseline patient characteristics by randomized treatment arm among patients with prior coronary stenting.

	Placebo N=5,621	Ticagrelor 60 mg N=5,658	P-Value (Ticagrelor 60 mg vs Placebo)	Ticagrelor 90 mg N=5,612	P-Value (Ticagrelor 90 mg vs Placebo)
Demographics					
Age, median (IQR)	65.0 (59.0, 71.0)	65.0 (58.0, 71.0)	0.029	65.0 (59.0, 71.0)	0.728
BMI, median (IQR)	27.8 (25.1, 31.0)	27.9 (25.2, 31.2)	0.109	27.9 (25.2, 31.2)	0.180
Female (%)	1226 (21.8)	1190 (21.0)	0.325	1187 (21.2)	0.407
Clinical Characteristics					
Hypertension (%)	4289 (76.3)	4292 (75.9)	0.594	4241 (75.6)	0.375
Hyperlipidemia (%)	4431 (78.8)	4429 (78.3)	0.490	4395 (78.3)	0.509
Current smoking (%)	941 (16.8)	1029 (18.2)	0.048	970 (17.3)	0.469
Diabetes mellitus (%)	1722 (30.6)	1782 (31.5)	0.334	1682 (30.0)	0.456
Multivessel CAD (%)	3768 (67.0)	3791 (67.0)	0.987	3743 (66.7)	0.719
History of > 1 prior MI (%)	880 (15.7)	887 (15.7)	0.996	845 (15.1)	0.393
Last dose of P2Y12 <= 30 days (%)	2131 (39.9)	2150 (39.8)	0.939	2150 (39.9)	0.974
Months from most recent PCI, median (IQR)	19.0 (14.0, 27.0)	20.0 (14.0, 27.0)	0.397	19.0 (14.0, 27.0)	0.893
eGFR at baseline <60 ml/min (%)	1225 (22.0)	1165 (20.9)	0.137	1200 (21.7)	0.652
Region			0.989		0.821
Western Europe (%)	1787 (31.8)	1801 (31.8)		1809 (32.2)	
Eastern Europe (%)	1426 (25.4)	1443 (25.5)		1393 (24.8)	
North America (%)	1178 (21.0)	1172 (20.7)		1198 (21.3)	
South America (%)	570 (10.1)	587 (10.4)		541 (9.6)	
Asia/Pacific (%)	660 (11.7)	655 (11.6)		671 (12.0)	
Qualifying Event					
Months from MI, median (IQR)	20.6 (14.8, 27.9)	20.4 (14.8, 28.1)	0.769	20.3 (14.7, 27.9)	0.641

STEMI (%)	3213 (57.2)	3198 (56.6)	0.505	3141 (56.0)	0.198
NSTEMI (%)	2145 (38.2)	2202 (39.0)	0.419	2262 (40.3)	0.022
MI type unknown (%)	256 (4.6)	251 (4.4)	0.797	205 (3.7)	0.018

Categorical variables were compared using the Chi square test and continuous variables using the Wilcoxon test.

Supplemental Table S3. Baseline predictors of stent thrombosis (any) in the placebo arm

Parameter	Frequency (%) or Median (IQR)	Adjusted Hazard Ratio	95% Confidence Limits		P Value
			Lower	Upper	
Age (per 5-year increase)	65 (59-71)	0.78	0.62	0.98	0.030
Female sex	1031 (21)	0.78	0.32	1.89	0.576
Non-White race	623 (13)	2.80	0.66	11.89	0.163
Diabetes	1458 (30)	0.80	0.39	1.66	0.551
PAD	283 (6)	2.89	1.17	7.16	0.022
Prior CABG	183 (4)	2.48	0.83	7.38	0.104
Time from qualifying MI (per 1-month increase)	21 (15-28)	0.98	0.93	1.04	0.514
Time from last ADP-receptor antagonist ≤ 30 days	1932 (40)	1.87	0.94	3.71	0.076
Qualifying MI type - NSTEMI	1826 (38)	1.61	0.21	12.22	0.644
Qualifying MI type - STEMI	2805 (58)	1.40	0.18	10.71	0.749
Current smoker	812 (17)	0.59	0.22	1.55	0.284
Stent type (1st-generation DES vs BMS)	737 (15)	2.30	0.98	5.36	0.055
Stent type (Later-generation DES vs BMS)	1427 (30)	1.68	0.79	3.60	0.180
eGFR <60 mL/min/1.73m^2	1055 (22)	0.86	0.37	1.99	0.726
Statin use at baseline	4533 (94)	1.90	0.26	13.99	0.530

Comparisons were made using a multivariable Cox proportional hazards model among patients with prior stenting in the placebo arm who have non-missing data for all variables in the model (N=4800).
ADP – Adenosine diphosphate; BMS – Bare metal stent; CABG – Coronary artery bypass graft surgery; DES – Drug-eluting stent; NSTEMI – Non-ST segment elevation myocardial infarction; STEMI – ST segment elevation myocardial infarction; PAD – Peripheral artery disease

For categorical variables, the referent group comprises subjects not in the indicated category.

Supplemental Table S4. Efficacy of ticagrelor 90 mg and 60 mg based on time from most recent coronary stent.

	Ticagrelor 3-yr KM rate MACE	Placebo 3-yr KM rate for MACE	HR (95% CI)	P-value	Interaction P-value
Ticagrelor 90 mg					
PCI <1yr	8.57%	7.04%	1.07 (0.57, 2.03)	0.826	0.669
PCI 1-2yrs	6.96%	8.20%	0.82 (0.68, 1.00)	0.044	
PCI >2yrs	7.16%	7.71%	0.90 (0.71, 1.13)	0.357	
Ticagrelor 60 mg					
PCI <1yr	5.71%	7.04%	0.78 (0.39, 1.55)	0.474	0.755
PCI 1-2yrs	6.76%	8.20%	0.81 (0.67, 0.97)	0.0262	
PCI >2yrs	6.98%	7.71%	0.90 (0.71, 1.14)	0.3821	

Comparisons were made using a Cox proportional hazards model.

Supplemental Figure S1. Safety of ticagrelor in patients with prior coronary stent. ICH – intracranial hemorrhage; TIMI – Thrombolysis in Myocardial Infarction.