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

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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). 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: $p_{\text{interaction}}=0.767$; first versus later generation: $p_{\text{interaction}}=0.940$). 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 ■ antplatelet 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...
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 P2Y12 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 filtration rate >60 ml/min/1.73 m². All analyses were
smoker, stent type, statin use, and estimated glomeru-
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Statistical Analysis
Baseline patient characteristics are summarized by
coronary stent status and BMS versus DES at ran-
domization. Differences across groups were tested
using a chi-square test for categorical variables and
and a Wilcoxon test for continuous variables given that the
distributions were skewed positively. Rates of the pri-
mary and secondary efficacy and safety end points
were calculated using the Kaplan-Meier method in pa-
tients 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 com-
pared by randomized treatment arm among patients
with prior stents. Events were further analyzed by type
of stent and time elapsed since most recent stent im-
plantation. 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 re-
siduals. Baseline predictors of ST were examined in
the placebo arm using a multivariable logistic regres-
sion model that included age, sex, race, diabetes mel-
itus, 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 glomeru-
lar filtration rate >60 ml/min/1.73 m². All analyses were
performed by the TIMI Study Group using commer-
cially 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 stent-
ing. 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%) re-
cived 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 sta-
tus 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 qualify-
ing 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 re-
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 coro-
nary 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 possi-
ble (any) ST was 0.9% and the rate of definite ST
was 0.7%. Therefore, 91% of first MACE events in
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 DES 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, 0.75–0.96; 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
reported previously, ticagrelor significantly reduced the occurrence of MACE in patients with no prior coronary stenting, without significant interaction with prior stent status (pinteraction = 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; pinteraction = 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 (pinteraction = 0.725). The findings were similar for each separate ticagrelor dose (Table S4).
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, recent acute coronary syndrome, PCI for elective or urgent indications, and high-risk patients with diabetes mellitus and stable coronary artery disease, including those with prior PCI. 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\textsubscript{12} inhibition achieved with this lower dose. 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. The comparative efficacy and safety of P2Y\textsubscript{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. 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\textsubscript{12} inhibition to a background of aspirin therapy, reduces ischemic risk. Second, a strategy of deescalation to P2Y\textsubscript{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. How to reconcile these data is not straightforward, although it may be that aspirin adds relatively little on top of potent P2Y\textsubscript{12} inhibition. Regardless, the data in this study combined with the other published studies support the importance of long-term potent P2Y\textsubscript{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 (0.62–1.06)                        | 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)                        | 0.08     | 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.
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 P2Y12 inhibition.

**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.

**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\(^\text{34}\) and these patients were previously shown to derive even greater benefit from extended duration ticagrelor,\(^\text{35}\) as reflected in the European Medicines Agency label.\(^\text{36}\) 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),\(^\text{18}\) 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.\(^\text{19,20}\) 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.\(^\text{8}\)

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,\(^\text{37–40}\) 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.\(^\text{6}\) 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.\(^\text{41,42}\) 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.\(^\text{5}\)

**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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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 (85.6)                  | 14,665 (78.8)               |        |
| **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)                   |         |
| **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 (41.6%)                 | 9,552 (56.6)                | <0.0001 |
| **Aspirin (n, %)**     | 4,196 (99.9%)                 | 16,865 (99.9)               | 0.29    |
| **Statin (n, %)**      | 3,660 (87.1%)                 | 15,884 (94.0)               | <0.0001 |
| **Beta-blocker (n, %)**| 3,386 (80.6%)                 | 14,043 (83.1)               | 0.0001  |
| **ACE inhibitor or ARB (n, %)** | 3,373 (80.33%)             | 13,604 (80.5)               | 0.77    |
| **Region (n, %)**      |                               |                             |         |
| North America          | 352 (8.4)                     | 3,548 (21.0)                | <0.0001 |
| 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  | Ticagrelor 60 mg | P-Value (Ticagrelor 60 mg vs Placebo) | Ticagrelor 90 mg | P-Value (Ticagrelor 90 mg vs Placebo) |
|----------------------|----------|------------------|---------------------------------------|------------------|---------------------------------------|
|                      | N=5,621  | N=5,658          |                                       | N=5,612          |                                       |
| **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 (%) |     |                  |                                       |                  |                                       |
| 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**           |          |                  |                                       |                  |                                       |
| 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 |
| Category                              | Value 1 | Value 2 | p-value | Value 3 | p-value |
|---------------------------------------|---------|---------|---------|---------|---------|
| 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 |
|-----------------------------------------------|------------------------------|-----------------------|------------------------|---------|
| **Parameter**                                |                              |                       |                        |         |
| 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/1.73m²                        | 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.