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Study of Two Dose Regimens of Ticagrelor Compared with Clopidogrel in Patients Undergoing Percutaneous Coronary Intervention for Stable Coronary Artery Disease (STEEL-PCI)

Running Title: Orme et al.; Ticagrelor in Elective PCI

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Abstract

**Background**—Ticagrelor has superior efficacy to clopidogrel in the management of acute coronary syndromes but has not been assessed in patients undergoing percutaneous coronary intervention (PCI) for stable coronary artery disease (CAD). We compared the pharmacodynamic effects of ticagrelor and clopidogrel in this stable population.

**Methods**—180 aspirin-treated stable CAD patients, who were planned to undergo elective PCI in a single center, were randomized 1:1:1 to either a standard clopidogrel regimen or one of two regimens of ticagrelor, either 90mg (T90) or 60mg twice-daily (T60), both with 180mg loading dose. Cellular adenosine uptake was assessed, at the time of the procedure and pre- and post-dose at 1 month, by adding adenosine 1 μmol/L to aliquots of anticoagulated whole blood and mixing with a stop solution at 0, 15, 30 and 60 seconds then measuring residual plasma adenosine concentration by high-performance liquid chromatography. Systemic plasma adenosine concentration and platelet reactivity were assessed at the same timepoints. High-sensitivity troponin T (hsTnT) was measured pre- and 18-24 hours post-PCI.

**Results**—174 patients underwent an invasive procedure, of which 162 patients received PCI (mean age 65 years, 18% female, 21% with diabetes mellitus). No effect on in vitro adenosine uptake was seen post-dose at 1 month for either ticagrelor dose compared with clopidogrel (residual adenosine at 15s, mean ± SD: clopidogrel 0.274 ± 0.101 μmol/L; T90 0.278 ± 0.134 μmol/L; T60 0.288 ± 0.149 μmol/L; P = 0.37). Similarly no effect of ticagrelor on in vitro adenosine uptake was seen at other timepoints, nor was plasma adenosine concentration affected (all P > 0.1). Both maintenance doses of ticagrelor achieved more potent and consistent platelet inhibition than clopidogrel (VerifyNow PRU, 1 month, mean ± SD: pre-dose, T60: 62 ± 47, T90: 40 ± 38, clopidogrel 181 ± 44; post-dose, T60: 34 ± 30, T90: 24 ± 21, clopidogrel 159 ± 57; all P < 0.0001 for ticagrelor vs clopidogrel). High platelet reactivity was markedly less with both T60 and T90 compared with clopidogrel (VerifyNow PRU>208, 1-month post-dose: 0%, 0% and 21%, respectively). Median (IQR) hsTnT increase was 16.9 (6.5-46.9) ng/l for clopidogrel, 22.4 (5.5-53.8) ng/L for T60 and 17.7 (8.1-43.5) ng/L for T90 (P = 0.95). There was a trend towards less dyspnea with T60 versus T90 (7.1% vs 19.0%; P = 0.09).

**Conclusions**—Maintenance therapy with T60 or T90 had no detectable effect on cellular adenosine uptake at 1 month, nor was there any effect on systemic plasma adenosine levels. Both regimens of ticagrelor achieved greater and more consistent platelet inhibition than clopidogrel but did not appear to affect troponin release following PCI.

**Clinical Trial Registration**—URL: [https://clinicaltrials.gov](https://clinicaltrials.gov) Unique Identifier: NCT02327624

**Key Words:** ticagrelor; clopidogrel; adenosine; platelets; percutaneous coronary intervention
Clinical Perspective

What is new?

- Ticagrelor does not significantly impair adenosine uptake or increase circulating adenosine levels in patients with stable coronary artery disease (CAD)
- Ticagrelor 60mg or 90mg twice-daily provide greater and more consistent platelet inhibition than clopidogrel in stable CAD patients undergoing elective percutaneous coronary intervention (PCI)
- More potent platelet P2Y12 inhibition did not modify troponin release related to PCI

What are the clinical implications?

- Further studies of ticagrelor 60mg twice-daily are warranted in stable CAD patients undergoing PCI
- Asymptomatic troponin release may be not be a suitable endpoint for assessing the impact of greater platelet inhibition in stable CAD patients undergoing PCI
Introduction

Dual antiplatelet therapy (DAPT) with aspirin and an oral platelet P2Y\textsubscript{12} receptor antagonist is the standard therapy for patients undergoing percutaneous coronary intervention (PCI). Three oral platelet P2Y\textsubscript{12} receptor antagonists are currently available, the thienopyridines clopidogrel and prasugrel and the non-thienopyridine, reversibly-binding drug ticagrelor.\textsuperscript{1-4} In the absence of contraindications or concurrent oral anticoagulant therapy, ticagrelor is recommended in preference to clopidogrel for patients with acute coronary syndromes, including those managed with PCI, but has not been assessed in patients undergoing PCI for stable coronary artery disease (CAD).\textsuperscript{1-3} Similarly, prasugrel is recommended in preference to clopidogrel for ACS patients managed with PCI but is not licensed for use in stable CAD.\textsuperscript{1-3} Consequently, aspirin and clopidogrel remain the predominant DAPT strategy in stable CAD patients undergoing PCI.

Thienopyridines, such as clopidogrel, are pro-drugs that require hepatic metabolism to generate active metabolites that bind irreversibly to the platelet P2Y\textsubscript{12} receptor, blocking the binding of adenosine diphosphate (ADP) to this receptor.\textsuperscript{5} The efficacy of clopidogrel is limited in some individuals due to poor efficiency of active metabolite formation and poor pharmacodynamic response has been associated with increased risk of stent thrombosis in clopidogrel-treated patients.\textsuperscript{6,7}

Ticagrelor is not a pro-drug but does have an active metabolite, AR-C124910XX, that is equipotent to ticagrelor and contributes approximately 30% of the total inhibitory effect.\textsuperscript{5,8,9} Ticagrelor achieves a consistent and high level of platelet P2Y\textsubscript{12} inhibition following a loading dose (although onset of action can be delayed in patients with ST-elevation myocardial infarction\textsuperscript{10,11}), as well as during maintenance therapy with either 90 mg or 60 mg twice-daily (bid) in patients with prior myocardial infarction.\textsuperscript{9} Ticagrelor and AR-C124910XX also have weak inhibitory effects on cellular adenosine uptake via equilibrative
nucleoside transporter 1 (ENT-1) although the clinical significance of this effect remains uncertain.\textsuperscript{12-14} The effects of ticagrelor 60 mg bid on adenosine metabolism have not been previously reported. In the Study of Two dosEs of ticagrELor in PCI (STEEL-PCI; NCT02327624), we assessed and compared the effects of ticagrelor and clopidogrel on cellular adenosine uptake as well as platelet reactivity in stable CAD patients undergoing PCI.

**Methods**

The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure.

**Study design**

One-hundred and eighty patients with stable CAD provided written informed consent and were enrolled into the STEEL-PCI study, conducted at a single center (Northern General Hospital, Sheffield, United Kingdom). All patients had had previous coronary angiography and were planned to undergo PCI. Other inclusion as well as exclusion criteria are shown in the online Supplement. The study was performed according to a protocol approved by the National Research Ethics Service and regulatory authorities. Aspirin-treated patients who provided informed consent were randomized in a 1:1:1 fashion to receive open-label treatment with a 180mg loading dose of ticagrelor at 2 hours pre-PCI followed by either 60mg bid or 90mg bid for one month or a standard loading regimen of clopidogrel (600mg at least 4 hours prior to procedure or maintenance therapy with 75mg for at least 5 days) followed by 75mg qd for one month (Figure 1). Blood samples were collected at the time of PCI, either from a large antecubital vein using a 21G needle and syringe with minimum use of tourniquet or from the arterial sheath, before the administration of heparin. Patients attended the morning after PCI for collection of venous blood samples by venipuncture. At
one-month post-PCI, patients attended before the morning maintenance dose of study medication for further collection of venous blood samples. The maintenance dose was then administered and a further blood sample obtained 2 hours later. Patients were instructed to return unused study medication at their 1-month visit and compliance was assessed by pill-counting. When indicated, patients were switched to open-label clopidogrel at the 1-month visit by administration of a loading dose 24 hours after the last dose of ticagrelor, as recommended.\textsuperscript{15,16} Staff of the Clinical Research Office of Sheffield Teaching Hospitals NHS Foundation Trust monitored the study and a Data Monitoring Committee periodically reviewed the conduct of the study and clinical outcomes.

**Adenosine uptake and plasma adenosine level**

For adenosine reuptake measurements, blood was collected into a standard EDTA tube and then aliquots pipetted into tubes containing adenosine (final concentration 1 μmol/L). Uptake of adenosine was halted by the addition of a cold pharmacological stop solution (2-parts blood:1-part stop solution) at 0, 15, 30 or 60 seconds after mixing blood with the adenosine. The stop solution was composed of dipyridamole 40 μmol/L, disodium ethylenediaminetetraacetic acid 13.2 mmol/L, erythro-9-(2-hydroxy-3-nonyl)adenine 50 μmol/L, α,β-methylene adenosine 5'-diphosphate 200 μmol/L, iodotubercidin 50 μmol/L and p-nitrobenzylthioinosine 40 μmol/L in 0.9% w/v sodium chloride. Adenosine concentration was measured using high-performance liquid chromatography (HPLC)(see Supplement).

Samples for plasma adenosine concentration measurement were collected into S-Monovette tubes containing the stop solution and immediately placed on ice before centrifugation at 1500g. Adenosine concentration was then measured as described above.

**VerifyNow P2Y\textsubscript{12} assay**

Whole blood was collected into 2ml Greiner Bio-One citrate tubes and gently mixed before analysis after 20 minutes using the VerifyNow P2Y\textsubscript{12} assay (Accumetrics Inc.,
SanDiego, USA). P2Y<sub>12</sub> reaction units (PRU) and VerifyNow percentage inhibition (estimated using the Base channel result as 100% response) were recorded.

**Light transmittance aggregometry**

Light transmission aggregometry (LTA) was performed using a PAP8 aggregometer (Biodata, Horsham, PA, USA) with ADP 20 μmol/L as the agonist. Maximum percentage LTA responses were recorded.

**High-sensitivity troponin (hsTnT)**

hsTnT was determined in serum samples (Elecsys assay, Roche, on Cobas E602 analyser) before PCI and the morning after PCI.

**Pharmacokinetic analysis**

Plasma derived from blood anticoagulated with lithium heparin was stored at -80°C prior to analysis. Plasma concentrations of ticagrelor and AR-C124910XX were determined using liquid chromatography with tandem mass spectrometry by York Bioanalytical Solutions (Upper Poppleton, York, United Kingdom).<sup>17</sup>

**Genetic analysis**

DNA was extracted from whole blood and analyzed for relevant genetic variants of CYP2C19, CY3A43, UGT2B7 and SLC01B1 (see Supplement).

**Sample size and statistical analysis**

The primary endpoint of the study was in vitro adenosine uptake post-maintenance dose at 1 month, measured as residual adenosine concentration at 15 seconds after ex-vivo addition of adenosine. The sample size was based on (1) our preliminary in-vitro studies of adenosine uptake indicating 15 seconds as the optimal time for assessing residual adenosine concentration and previous data indicating an estimated residual adenosine concentration at 15 seconds post-mixing in the adenosine uptake assay of 0.80 ± 0.051 μmol/L for the ticagrelor 90 mg group and 0.45 ± 0.068 μmol/L for clopidogrel<sup>18</sup> and (2) the assumption that
the effects of ticagrelor 60mg would yield levels between those with ticagrelor 90mg and clopidogrel: data on forty-two patients per group were required in each group to provide >90% power to detect a 0.05 μmol/L higher mean residual adenosine level in the ticagrelor 60mg group compared with the clopidogrel group, with a significance threshold of 0.05 and assuming a common SD of 0.06 μmol/L, and >99% power to detect a similar difference between the ticagrelor 90mg and clopidogrel groups to that previously reported. 60 patients were, therefore, required in each group to allow for 30% drop-out or sample failure at 1 month. Secondary endpoints were plasma adenosine concentration, platelet function measurements and the PCI-induced troponin release (determined as increase from pre-PCI to post-PCI). Based on our previous work,8,9 the proposed sample size provided >90% power to detect expected differences in platelet aggregation, assessed by either VerifyNow P2Y12 assay or LTA, between ticagrelor and clopidogrel, with a significance threshold of 0.01 (to allow for multiple testing), allowing for 30% drop-out or sample failure at 1 month.

Data were analyzed using SAS version 9.3 (SAS Institute, Cary, North Carolina) and expressed as mean and SD for normally-distributed data or median and interquartile range for non-parametric data. Continuous data were compared using Kruskal-Wallis test, where appropriate using Mann-Whitney test for pairwise comparisons, as indicated in Results. Categorical variables were compared using Chi-square test or Fisher’s exact test, as indicated in Results. High platelet reactivity was defined as VerifyNow PRU > 208 or LTA response > 59%.9 Myocardial infarction was defined according to the 3rd Universal Definition.19 Bleeding events were defined according to the PLATO study criteria.20

Results

Study population
One hundred and eighty patients were recruited to the study (Figure 2). Sixty patients in the clopidogrel group, 56 in the ticagrelor 60mg bid group and 58 in the ticagrelor 90mg bid group underwent an invasive procedure. Some patients did not proceed to PCI for several reasons including significant disease progression requiring surgical management or non-flow-limiting coronary stenoses on updated angiography. One hundred and fifty-five patients completed the study period of maintenance therapy with either clopidogrel 75mg qd (n=53), ticagrelor 60mg bid (n=54) or ticagrelor 90mg bid (n=48). One patient in the ticagrelor 60mg bid group was subsequently found to have been taking an excluded medication (a strong CYP3A inducer) and was excluded from the main analysis but their results are included in the Supplement. The demographic characteristics, cardiovascular risk factors and concomitant medications were well matched between the groups at randomization and subsequent timepoints, as were the procedural characteristics for those proceeding with PCI (Table 1 and Supplementary Tables 1 and 2). At the time of their procedure, 100% patients were receiving aspirin 75 mg daily and continued on this for the duration of the study.

**Adenosine uptake and plasma adenosine level**

No effect on in vitro adenosine uptake was seen with a ticagrelor loading dose or the 90 mg or 60 mg bid maintenance doses compared to clopidogrel at the time of PCI or at 1 month (Figure 3 and Supplementary Figure 1). Similarly, there was no impact of ticagrelor at any time point on plasma adenosine level (Figure 4).

**VerifyNow P2Y\(_{12}\) assay and light transmittance aggregometry**

Ticagrelor 180mg loading dose achieved greater and more consistent platelet inhibition than clopidogrel at the time of PCI when assessed by the VerifyNow P2Y\(_{12}\) assay (Figure 5A and B). Both maintenance doses of ticagrelor achieved greater and more consistent platelet inhibition than clopidogrel 75mg daily at 1 month (Figure 5C and D): The mean pre-dose PRU values were 62±47 versus 40±38 (p<0.01) for the 60mg versus 90mg ticagrelor doses.
and post-dose values were 34±30 versus 24±21 (p=0.09), respectively; corresponding PRU values for clopidogrel-treated patients were 181±44 pre-dose and 159±57 post-dose (all P < 0.0001 vs both ticagrelor groups). The mean LTA responses were also significantly lower in the ticagrelor groups compared with the clopidogrel group, both at the time of PCI and at one month (Figure 6).

High platelet reactivity, as assessed by the VerifyNow P2Y₁₂ assay, was seen infrequently in the ticagrelor group (n=1) at the time of PCI (Table 2). This patient also had high platelet reactivity when assessed by LTA. No patients in the ticagrelor 90mg bid group had high platelet reactivity (PRU>208) at one month compared to one patient in the ticagrelor 60mg bid group. This patient had PRU value of 232 at one-month pre-dose and 39 post-dose with PRU of 1 at the time of PCI; their drug compliance at one month was calculated at 100%. High platelet reactivity was more common in the clopidogrel group at all the timepoints compared to both ticagrelor groups (Table 2).

There were a small number of patients with high platelet reactivity in the ticagrelor groups (<15%) according to LTA responses compared to greater proportions in the clopidogrel group (>30%) at each timepoint (Figure 6B and Table 2).

**Efficacy, safety and tolerability**

There were no myocardial infarctions, strokes or cardiac deaths in any of the groups at 30 days. There was only one death, which occurred as a result of sepsis following mesenteric infarction that did not appear to be related to the PCI procedure. There was no effect of the higher levels of platelet inhibition with ticagrelor on PCI-induced increase in hsTnT: median (IQR) increases the morning after PCI were 16.9 (6.5-46.9) ng/L for the clopidogrel group, 22.4 (5.5-53.8) ng/L for the ticagrelor 60mg group and 17.7 (8.1-43.5) ng/L for the ticagrelor 90mg group (P = 0.95, Kruskal-Wallis test).
The tolerability of the ticagrelor 60mg bid dose appeared slightly better than the 90mg bid dose due to less frequent dyspnea events in the 60mg group (7.1% vs 19.0%; P = 0.09) (Supplementary Table 3). Two patients (3.6%) in the ticagrelor 60mg group and 3 patients (5.2%) in the ticagrelor 90mg group stopped study medication prematurely due to adverse effects. There was no reported dyspnea in the clopidogrel group and no patients stopped clopidogrel prematurely due to adverse effects. There were no PLATO-defined major or minor bleeds and no MACE or stent thrombosis events in any of the treatment groups.

Pharmacokinetics

The mean plasma levels of ticagrelor and AR-C124910XX following ticagrelor 180mg loading dose were 1109±549 and 223±121 ng/mL, respectively (Supplementary Figure 2A). After 1-month maintenance therapy with either ticagrelor 60mg or ticagrelor 90mg bid, pre-dose mean levels of ticagrelor were 278±217 and 365±189 ng/mL, respectively, and pre-dose mean levels of AR-C124910XX were 97±55 and 127±73 ng/mL, respectively. Post-dose mean levels of ticagrelor were 510±281 and 776±347 ng/mL and mean levels of AR-C124910XX were 135±69 and 199±96 ng/mL, respectively (Supplementary Figure 2B).

Genetic analysis

The ticagrelor loading dose and both ticagrelor maintenance doses achieved greater platelet inhibition than clopidogrel in those who either did or did not carry CYP2C19 loss-of-function alleles (Supplementary Tables 4 and 5). The other genetic variants studied did not significantly influence the pharmacodynamic and pharmacokinetic results (Supplementary Tables 6 to 11).

Discussion

In this study, we compared the pharmacodynamic effects of ticagrelor and clopidogrel, obtaining data on the 60mg bid dose of ticagrelor for the first time in stable CAD patients.
undergoing PCI and collecting preliminary efficacy, safety and tolerability data on the two doses of ticagrelor in this setting. Consistent with previous comparisons of ticagrelor 180-mg loading dose and 90-mg twice-daily maintenance dose with standard regimens of clopidogrel in other clinical settings, we confirmed that the ticagrelor loading dose and maintenance doses achieved greater and more consistent levels of platelet inhibition compared to standard regimens of clopidogrel in stable CAD patients at the time of, and 1 month after, PCI. Of note, we show that ticagrelor 60-mg twice-daily maintenance dose provides much more consistent platelet inhibition than clopidogrel, even in those with normal CYP2C19 activity as predicted by CYP2C19 genotyping. Our data are broadly consistent with previously-reported data on ticagrelor 90-mg and 60-mg twice-daily in patients with prior myocardial infarction.9,21 Our finding of significant difference in pre-dose platelet reactivity during maintenance therapy in the two ticagrelor groups in contrast to lack of significance of this comparison in the PEGASUS-TIMI 54 platelet function substudy9 likely reflects small sample sizes in both studies limiting the power to detect such a difference. Dyspnea was more frequent in the ticagrelor groups and this is a well-characterized adverse effect of ticagrelor that is usually mild or moderate in severity, as confirmed here.22-24 The lower rates of dyspnea in the ticagrelor 60-mg group, combined with the reliable P2Y\textsubscript{12} inhibition, as also previously demonstrated in the PEGASUS-TIMI 54 study,9,24 favor this dose for further exploration in clinical outcomes studies.

Contrary to some previous published studies,18,25 we found no evidence of any effect of the ticagrelor regimens on cellular adenosine uptake or plasma adenosine concentration. The reasons for this are unclear since our data show clearly that the assay assessed adenosine uptake over 1 minute in whole blood samples, with the expected baseline levels of adenosine after in vitro addition of 1 \(\mu\)mol/L (indicating efficacy of the stop solution in preventing further adenosine uptake) and almost complete adenosine uptake at 1 minute (indicating
efficacy of the stop solution in preventing adenosine generation). Our stop solution for adenosine metabolism included additional inhibitors to those used by Bonello et al, including p-nitrobenzylthioinosine as an additional inhibitor of adenosine uptake and iodotubercidin as a potent adenosine kinase inhibitor, and so might have been more effective. In agreement with our findings, a recent study in healthy volunteers found no impact of ticagrelor on plasma adenosine level.\textsuperscript{26} Furthermore, using the same methodology, we found no impact of ticagrelor on plasma adenosine concentration in ACS patients awaiting coronary artery bypass graft surgery suggesting that the nature of the patient population in our current study was not a determinant of the findings.\textsuperscript{27} In vitro studies predict little effect of ticagrelor on adenosine uptake at therapeutic concentrations due to high levels of plasma protein binding that limit the free ticagrelor available to bind to ENT-1.\textsuperscript{14,28} On the other hand, an effect of ticagrelor on adenosine uptake is more clearly seen at approximately therapeutic concentration in the absence of plasma proteins.\textsuperscript{29} Since ticagrelor has been shown to induce a leftward shift in the dose-response curves for intravenous adenosine in studies of coronary blood flow responses and dyspnea severity, it remains likely that ticagrelor has an impact on the kinetics of adenosine uptake in vivo at the tissue level, such as in myocardium, that is not detected by the currently available blood assays and more work is required to assess this.\textsuperscript{13,30} There were substantial numbers of patients with asymptomatic rises in troponin after PCI but no evidence that ticagrelor was more effective than clopidogrel in attenuating troponin release, suggesting that the extent of myocardial injury induced by PCI is not usually sensitive to levels of platelet P2Y\textsubscript{12} inhibition in a low-risk population. This observation is consistent with a previously-reported, small elective PCI study\textsuperscript{31} but contrasts with another small study that demonstrated a reduced rate of MI with ticagrelor compared to clopidogrel.\textsuperscript{32} Larger clinical outcomes studies are in progress that will provide more definitive data on this comparison (NCT02617290 and NCT02548611).
This study was limited by a small sample size for assessing efficacy, safety and tolerability and a larger study is required to establish the benefits and risks of ticagrelor in stable CAD patients undergoing PCI. Our study simply provides pilot data for planning such a study. Only the impacts of ticagrelor on adenosine uptake in whole blood and circulating adenosine levels were assessed, not the impact of ticagrelor on tissue-level adenosine metabolism. The study was also not well powered for comparing the pharmacodynamic effects of the two maintenance doses of ticagrelor although some significance was seen in pre-dose levels of platelet reactivity suggesting that the 90mg bid dose may have slightly greater consistency of effect than the 60mg bid dose.

In conclusion, ticagrelor 60mg and 90mg bid regimens both achieved greater and more consistent platelet inhibition than standard clopidogrel therapy but had no detectable impact on cellular adenosine uptake or circulating plasma adenosine concentration in stable CAD patients undergoing PCI. Further work is warranted to characterize the efficacy and safety of ticagrelor in this clinical setting.

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### Table 1. Demographic and procedural characteristics and medications for patients proceeding with percutaneous coronary intervention

|                       | Clopidogrel | Ticagrelor 60mg | Ticagrelor 90mg |
|-----------------------|-------------|-----------------|-----------------|
| n=57                  | n=54        | n=51            |
| **Age, years, mean (SD)** | 64.6 (8.5)  | 66.9 (8.6)      | 66.0 (7.73)     |
| **Male sex, n (%)**   | 44 (77%)    | 46 (85%)        | 42 (82%)        |
| **Body weight, kgs, median (IQR)** | 85.5 (77-102) | 88.0 (73-97)   | 85.0 (80-98)    |
| **Body mass index, mean (SD)** | 30.3 (5.7)  | 28.8 (3.7)      | 30.0 (4.6)      |
| **Race, n (%)**       |             |                 |                 |
| White                 | 56 (98%)    | 53 (98%)        | 49 (96%)        |
| Black                 | 1 (2%)      | 0 (0%)          | 1 (2%)          |
| Asian                 | 0 (0%)      | 1 (2%)          | 1 (12%)         |
| **Cardiovascular risk factors, n (%)** |             |                 |                 |
| Current smoker        | 7 (12%)     | 6 (11%)         | 6 (12%)         |
| Hypertension          | 39 (68%)    | 37 (69%)        | 34 (67%)        |
| Dyslipidemia          | 51 (90%)    | 47 (87%)        | 49 (96%)        |
| Diabetes mellitus     | 12 (21%)    | 11 (20%)        | 12 (24%)        |
| **Medical history, n (%)** |             |                 |                 |
| Myocardial infarction | 9 (16%)     | 9 (17%)         | 4 (8%)          |
| PCI                   | 5 (9%)      | 5 (9%)          | 7 (14%)         |
| Coronary artery bypass graft | 3 (5%)   | 3 (6%)          | 1 (2%)          |
| Cardiac failure       | 5 (9%)      | 5 (9%)          | 2 (4%)          |
| Transient ischemic attack | 3 (5.3%) | 3 (5.6%)        | 2 (4%)          |
| Non-hemorrhagic stroke| 1 (1.8%)    | 1 (1.9%)        | 2 (4%)          |
| Peripheral arterial disease | 6 (11%) | 5 (9%)          | 3 (6%)          |
| COPD                  | 5 (9%)      | 5 (9%)          | 3 (6%)          |
| **Concomitant medication, n (%)** |             |                 |                 |
| Aspirin 75mg daily    | 57 (100%)   | 54 (100%)       | 51 (100%)       |
| Beta-blocker          | 50 (88%)    | 40 (74%)        | 33 (65%)        |
| ACE inhibitor         | 15 (26%)    | 18 (33%)        | 13 (26%)        |
| Statin                | 51 (90%)    | 48 (89%)        | 44 (86%)        |
| CYP2C19 LOF carrier   | 18 (32%)    | 20 (37%)        | 12 (24%)        |
| **Procedural characteristics** |             |                 |                 |
| Number of vessels treated, mean (SD) | 1.2 (0.5) | 1.2 (0.4)       | 1.1 (0.6)       |
| Number of lesions treated, mean (SD) | 1.5 (0.8) | 1.5 (0.7)       | 1.4 (0.7)       |
| Total stent length, mm, mean (SD) | 39 (27) | 39 (23)         | 37 (24)         |
| Minimum stent diameter, mm, mean (SD) | 3.0 (0.6) | 3.0 (0.5)       | 3.0 (0.5)       |
| Bifurcation treated, n (%) | 1 (2%)    | 4 (7%)          | 2 (4%)          |
| Left main stem treated, n (%) | 1 (2%)    | 3 (6%)          | 2 (4%)          |
| **Arterial Access, n (%)** |             |                 |                 |
| Radial                | 45 (79%)    | 41 (76%)        | 38 (75%)        |
| Femoral               | 10 (18%)    | 13 (24%)        | 12 (24%)        |
| Radial-to-femoral     | 2 (4%)      | 0 (0%)          | 0 (0%)          |
| Brachial              | 0 (0%)      | 0 (0%)          | 1 (2%)          |

SD: standard deviation. COPD: chronic obstructive pulmonary disease. ACE: angiotensin-converting enzyme. CYP2C19 LOF: loss-of-function allele carrier for cytochrome P450 2C19.

Groups were compared using Kruskal-Wallis or Chi-square tests, as appropriate: all P values > 0.1 except for beta-blockers (p = 0.02)
### Table 2. Proportions of patients with high platelet reactivity according to predefined threshold values

| Threshold of high platelet reactivity | Clopidogrel | Ticagrelor 60mg | P | Clopidogrel vs. Ticagrelor 90mg | P | Clopidogrel vs. Ticagrelor 90mg |
|-------------------------------------|-------------|----------------|---|--------------------------------|---|--------------------------------|
| VerifyNow PRU > 208                 |             |                |   |                                |   |                                 |
| Post-loading dose                   | 59          | 18 (31)        | 53 | 1 (2)                         | <0.0001 | 57 | 0 (0)                         | <0.0001 |
| 1 month, pre-dose                   | 50          | 14 (28)        | 51 | 1 (2)                         | <0.0001 | 45 | 0 (0)                         | <0.0001 |
| 1 month, post-dose                  | 52          | 11 (21)        | 52 | 0 (0)                         | <0.0001 | 48 | 0 (0)                         | <0.0001 |
| LTA 20μM ADP > 59%                  |             |                |   |                                |   |                                 |
| Post-loading dose                   | 59          | 18 (31)        | 54 | 4 (7)                         | 0.002 | 56 | 1 (2)                         | <0.0001 |
| 1 month, pre-dose                   | 50          | 30 (60)        | 51 | 6 (12)                        | <0.0001 | 45 | 2 (4)                         | <0.0001 |
| 1 month, post-dose                  | 53          | 22 (42)        | 52 | 2 (4)                         | <0.0001 | 48 | 1 (2)                         | <0.0001 |

LTA: light transmittance aggregometry. n = number of patients with available data in each treatment group, N = number of patients with values above the given threshold value. % = (N/n) x 100.

Clopidogrel and each ticagrelor group are compared using Fisher’s exact test. All comparisons between the ticagrelor groups: P > 0.1.
Figure Legends

Figure 1. Study design
R: randomization; LD: loading dose; LTA (ADP): light transmittance aggregometry with adenosine diphosphate; hs: high-sensitivity; qd: once daily; bid: twice daily.

Figure 2. Study CONSORT flow diagram
Number of patients in each of the three treatment groups (clopidogrel, ticagrelor 60mg bid and ticagrelor 90mg bid) at each stage of the study.

Figure 3. Whole blood in vitro adenosine uptake
Residual adenosine levels at 15 seconds after mixing adenosine 1 μmol/L with blood samples obtained (A) at the time of PCI following a standard loading regimen of clopidogrel (n=54) or 180-mg loading dose of ticagrelor (n=50 and 54 for 60mg and 90mg groups, respectively), (B) after one month of treatment, pre-maintenance dose and post-maintenance dose for each of the three treatment groups (clopidogrel 75mg qd: n=45; ticagrelor 60mg bid: n=46; and ticagrelor 90mg bid; n=43 & 45). Horizontal bars indicate mean ± SD. P values determined using 3-group comparison with Kruskal-Wallis test.

Figure 4. Plasma adenosine concentration
Plasma adenosine levels (A) at the time of PCI following a standard loading regimen of clopidogrel (n=56) or 180-mg loading dose of ticagrelor (n=50 and 54 for 60mg and 90mg groups, respectively) and (B) after one month of treatment, pre-maintenance dose and post-maintenance dose for each of the three treatment groups (clopidogrel 75mg qd: n=45;
ticagrelor 60mg bid: n=46; and ticagrelor 90mg bid: n=43). Horizontal bars show mean ± SD. P values determined using 3-group comparison with Kruskal-Wallis test.

**Figure 5. VerifyNow P2Y12 Assay Results**

Individual VerifyNow P2Y12 assay results expressed as (A,C) P2Y$_{12}$ reaction units (PRU) and (B,D) VerifyNow percentage inhibition, (A,B) at the time of PCI following a standard loading regimen of clopidogrel (n=59) or 180mg loading dose of ticagrelor (n=54 and 58 for 60mg and 90mg groups, respectively) and (C,D) after one month of treatment, pre-maintenance dose and post-maintenance dose for each of the three treatment groups (clopidogrel 75mg qd, n=52; ticagrelor 60mg bid: n=52; and ticagrelor 90mg bid: n=48). The dashed lines indicate a level of 208 PRU as a threshold for high platelet reactivity. Horizontal bars indicate mean ± SD. P values determined using 3-group comparison with Kruskal-Wallis test with pairwise comparisons using Mann-Whitney test; * P < 0.01; *** P < 0.0001.

**Figure 6. ADP-induced platelet aggregation determined by LTA**

Individual results for the platelet aggregation measured by light transmittance aggregometry in response to ADP 20 μmol/L (A) at the time of PCI following a standard loading regimen of clopidogrel (n=59) or 180-mg loading dose of ticagrelor (n=54 and 55 for 60mg and 90mg groups, respectively) and (B) after one month, pre-maintenance dose and post-maintenance dose for each of the three treatment groups (clopidogrel 75mg qd: n=50 & 51; ticagrelor 60mg bid: n=51 & 52; and ticagrelor 90mg bid: n=45 & 48). The dashed lines indicate a level of 59% as a threshold value for high platelet reactivity. Horizontal bars indicate mean ± SD. P values determined using 3-group comparison with Kruskal-Wallis test with pairwise comparisons using Mann-Whitney test; *** P < 0.0001.
B

Adenosine concentration at 15s (μmol/L)

P = 0.12

P = 0.37

Clopidogrel

Ticagrelor 60mg

Ticagrelor 90mg

Clopidogrel

Ticagrelor 60mg

Ticagrelor 90mg

Pre-dose

Post-dose
A

$p2Y_{12}$ Reaction Units (PRU)

| Treatment           | PRU 208 |
|---------------------|---------|
| Clopidogrel         |         |
| Ticagrelor 60mg     |         |
| Ticagrelor 90mg     |         |

$p=0.55$

***
A

% Platelet aggregation (max response)

Clopidogrel Ticagrelor 60mg Ticagrelor 90mg

p = 0.43

59%

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