Consistent platelet inhibition with ticagrelor 60 mg twice-daily following myocardial infarction regardless of diabetes status

Thomas, Mark R; Angiolillo, Dominick J; Bonaca, Marc P; Ajjan, Ramzi A; Judge, Heather M; Rollini, Fabiana; Franchi, Francesco; Ahsan, Arif J; Bhatt, Deepak L; Kuder, Julia F; Steg, Philippe Gabriel; Cohen, Marc; Muthusamy, Rangasamy; Sabatine, Marc S; Storey, Robert F

DOI: 10.1160/TH16-09-0703

License: None: All rights reserved

Citation for published version (Harvard):

Link to publication on Research at Birmingham portal

Publisher Rights Statement:
Final Version of Record available at: http://dx.doi.org/10.1160/TH16-09-0703

Checked 17/5/2017

General rights
Unless a licence is specified above, all rights (including copyright and moral rights) in this document are retained by the authors and/or the copyright holders. The express permission of the copyright holder must be obtained for any use of this material other than for purposes permitted by law.

• Users may freely distribute the URL that is used to identify this publication.
• Users may download and/or print one copy of the publication from the University of Birmingham research portal for the purpose of private study or non-commercial research.
• Users may use extracts from the document in line with the concept of ‘fair dealing’ under the Copyright, Designs and Patents Act 1988 (?)
• Users may not further distribute the material nor use it for the purposes of commercial gain.

Where a licence is displayed above, please note the terms and conditions of the licence govern your use of this document.

When citing, please reference the published version.

Take down policy
While the University of Birmingham exercises care and attention in making items available there are rare occasions when an item has been uploaded in error or has been deemed to be commercially or otherwise sensitive.

If you believe that this is the case for this document, please contact UBIRA@lists.bham.ac.uk providing details and we will remove access to the work immediately and investigate.

Download date: 12. Sep. 2020
Consistent platelet inhibition with ticagrelor 60 mg twice-daily following myocardial infarction regardless of diabetes status

Mark R. Thomas1, Dominick J. Angiolillo2, Marc P. Bonaca3, Ramzi A. Ajjan4, Heather M. Judge1, Fabiana Rollini2, Francesco Franchi2, Arif J. Ahsan5, Deepak L. Bhatt3, Julia F. Kuder3, Philippe Gabriel Steg6, Marc Cohen7, Rangasamy Muthusamy8, Marc S. Sabatine3, Robert F. Storey1

1Cardiovascular Research Unit, Department of Infection Immunity and Cardiovascular Disease, University of Sheffield, Sheffield, United Kingdom
2Division of Cardiology, University of Florida College of Medicine, Jacksonville, Florida
3TIMI Study Group, Division of Cardiovascular Medicine, Brigham and Women's Hospital, Boston, Massachusetts
4Leeds Institute of Cardiovascular and Metabolic Medicine, University of Leeds, Leeds, United Kingdom
5Trent Cardiac Centre, Nottingham University Hospitals NHS Trust, Nottingham, United Kingdom
6INSERM-Unité 1148, Assistance Publique- Hôpitaux de Paris, Département Hospitalo-Universitaire FIRE, Hôpital Bichat, and Université Paris-Diderot, Sorbonne-Paris Cité, Paris, France
7Newark Beth Israel Medical Center, Rutgers–New Jersey Medical School, Newark, New Jersey
8Rotherham NHS Foundation Trust, Rotherham, United Kingdom

Running Title: Diabetes in the PEGASUS Platelet Function Substudy

Corresponding author:
Professor Robert F. Storey MD DM FESC
Department of Infection, Immunity and Cardiovascular Disease
University of Sheffield
Beech Hill Road, Sheffield, S10 2RX, UK

Keywords: Coronary artery disease, acute coronary syndromes, pharmacology, pharmacodynamics

Word count: 3,518

Figures: 2
Tables: 1

Funding sources

This study was supported by AstraZeneca, Accumetrics, University of Sheffield and National Institute for Health Research Sheffield Clinical Research Facility award.
Abstract

Objective
Diabetes increases cardiovascular risk and reduces pharmacodynamic response to some oral antiplatelet drugs. This study aimed to determine whether ticagrelor 60 mg twice daily (bid) provided potent and consistent platelet inhibition in patients with vs. without diabetes in the PEGASUS-TIMI 54 platelet function substudy.

Methods
Out of 180 patients studied, 58 patients were randomized to and had received at least 4 weeks of ticagrelor 60 mg bid, with 20 (34%) having diabetes, 58 patients received ticagrelor 90 mg bid, with 12 (21%) having diabetes, and 64 patients received placebo, with 18 (28%) having diabetes. Blood was sampled pre- and 2 hours post-maintenance dose.

Results
In patients treated with ticagrelor 60 mg bid, on-treatment platelet reactivity to ADP, as determined by light transmission aggregometry (LTA), VerifyNow and VASP, was similar in patients with vs. without diabetes (LTA post-dose, ADP 20 µM: 29 ± 14 vs. 34 ± 10%, respectively; P = 0.19). A consistent inhibitory effect of ticagrelor 60 mg bid was observed pre- and post-dose regardless of diabetes status, even in insulin-treated patients. Patients with diabetes did not have an increased incidence of high platelet reactivity in either ticagrelor group. Platelet reactivity was similar in patients with diabetes treated with ticagrelor 60 mg vs. 90 mg bid. Pharmacokinetics of ticagrelor were not affected by diabetes status.

Conclusions
Ticagrelor 60 mg bid is equally effective at reducing platelet reactivity in patients with and without diabetes, yielding a consistently high level of platelet inhibition regardless of diabetes status.

Trial registration number: NCT01225562
What is already known about this subject?

Patients with diabetes have both a reduced pharmacodynamic response to some antiplatelet medications and an increased risk of atherothrombotic events.

It has not previously been demonstrated whether the 60 mg twice-daily dose of ticagrelor is sufficient to achieve satisfactory platelet inhibition in patients with diabetes.

What does this study add?

A new 60 mg twice-daily dose of ticagrelor provides potent and consistent platelet inhibition in patients with diabetes, similar to the level seen in patients without diabetes.

These findings provide insight into the similar effect of ticagrelor 60 mg and 90 mg twice daily on clinical outcomes in patients with diabetes in the PEGASUS TIMI-54 study.
Introduction

Patients with diabetes are at increased risk of coronary artery disease and their prognosis following acute coronary syndromes (ACS) remains worse than patients without diabetes (1). Diabetes is associated with increased platelet turnover and other platelet abnormalities, which increases the risk of thrombosis and highlights the importance of optimizing antithrombotic therapy in patients with diabetes (2).

It is well established that dual antiplatelet therapy, consisting of aspirin and a platelet P2Y\textsubscript{12} inhibitor, reduces the risk of further adverse cardiovascular events in the year following ACS (3). More recently, long-term treatment with dual antiplatelet therapy, initiated or continued from 1-3 years after ACS, has also been shown to reduce the risk of further myocardial infarction, stent thrombosis and cardiovascular death compared to aspirin alone (4,5). However, more intensive antiplatelet therapy also increases major bleeding (4,5). Diabetes is characterized by an enhanced thrombotic environment and compromised response to some oral antiplatelet agents (6-12), suggesting this population requires more aggressive antiplatelet therapy to reduce atherothrombotic risk. The challenge, however, is to individualize therapy to maximise cardiovascular benefit whilst minimising bleeding risk. Dosing of antiplatelet therapy and selection of appropriate patients are critical considerations for achieving the optimal balance between preventing thrombosis and causing bleeding.

The PEGASUS TIMI-54 study tested both ticagrelor 90 mg bid (the standard maintenance dose used in patients presenting with ACS) and a new lower dose of ticagrelor 60 mg bid against placebo in low dose aspirin-treated patients 1-3 years after acute myocardial infarction (AMI) (4). Overall, the reduction in major adverse cardiovascular events prevented by ticagrelor 60 mg was similar to that observed with ticagrelor 90 mg. However, encouragingly, the rates of TIMI major bleeding were numerically lower in patients treated
with ticagrelor 60 mg compared with ticagrelor 90 mg. Interestingly, patients with diabetes showed higher absolute cardiovascular benefit from long-term dual antiplatelet therapy than patients without diabetes (13). Platelet function analysis demonstrated that ticagrelor 60 mg caused a similar level of platelet P2Y$_{12}$ inhibition compared with ticagrelor 90 mg in the overall population (14). However, it has not yet been demonstrated whether this lower dose of ticagrelor is sufficient to reach levels of platelet inhibition that are equivalent to the 90 mg dose in patients with diabetes mellitus. We therefore investigated, using a number of platelet function tests, whether ticagrelor 60 mg and ticagrelor 90 mg caused a similar level of platelet P2Y$_{12}$ inhibition in patients with and without diabetes. This was complemented by investigating the pharmacokinetic properties of ticagrelor in patients with and without diabetes.
Materials and Methods

Study Design

A total of 180 patients from the PEGASUS-TIMI 54 study took part in a platelet function substudy, which was conducted at 4 centers: 3 in the United Kingdom (Sheffield, Rotherham and Nottingham) and 1 in the United States (Jacksonville, Florida). Details of study design, methods and primary results have been published (4,14). The substudy was approved by the appropriate ethics committees and institutional review boards. Patient allocation was blinded and patients were randomized to receive placebo, ticagrelor 60 mg bid or ticagrelor 90 mg bid in a ratio of 1:1:1. All patients had received at least 4 weeks of study medication prior to assessment of platelet function. Patients took the last dose of their study medication the evening before their morning substudy visit. Venous blood was collected by venipuncture in the morning, before (pre) and 2 hours after study drug administration (post). Diabetes was defined as a known diagnosis at the baseline visit.

Light transmission aggregometry

Platelet aggregation was assessed in platelet rich plasma (PRP) using light transmission aggregometry (LTA) (14). A Chrono-log aggregometer (Haverton, Pennsylvania) was used to assess maximum platelet aggregation response to adenosine diphosphate (ADP) (5 and 20 µM) and arachidonic acid (1 mM). In order to minimise inter-centre variability, all assays were performed to an established standard operating procedure (SOP).

VerifyNow P2Y_{12} Assay

Citrate-anticoagulated blood was analysed using the VerifyNow P2Y_{12} assay (Accumetrics Inc., San Diego, California) according to the manufacturer’s instructions (15). P2Y_{12} reaction units (PRU) and percent inhibition (determined from the estimated baseline response derived
by stimulating with thrombin receptor-activation peptide) were recorded. In order to minimise inter-center variability, all assays were performed to an established SOP.

**Vasodilator-stimulated phosphoprotein (VASP) phosphorylation assay**
Whole blood was processed using a VASP phosphorylation kit and flow cytometry. Platelet reactivity index (PRI) was determined according to the manufacturer’s instructions (BioCytex, Marseille, France) (15).

**Serum thromboxane B₂**
Venous blood was collected into a serum separator tube (Becton Dickinson, Oxford, UK) and incubated at 37°C for 30 minutes, followed by centrifugation at 1,000 g for 15 minutes (14). Serum was then transferred to cryovials and stored at -80°C prior to analysis. An ELISA kit (Cayman Chemicals, Ann Arbor, Michigan) was used to measure thromboxane B₂ levels.

**Determination of high platelet reactivity**
High on-treatment platelet reactivity (HPR) was determined using thresholds for each assay that have previously been shown to be associated with increased ischaemic risk (16). These thresholds are as follows: maximum LTA response to 20 μM ADP > 59%; maximum LTA response to 5 μM ADP > 46%; VerifyNow P2Y₁₂ assay >208 PRU; VASP PRI > 50%; VerifyNow aspirin response units > 550; and maximum LTA response to arachidonic acid >20% (16-19).

**Pharmacokinetic studies**
Venous blood was collected into lithium heparin tubes and kept on ice before centrifugation at 1,500 g within 30 minutes. Plasma was immediately frozen at -20°C in a polypropylene tube prior to transfer to Covance Central Laboratories (Indianapolis, Indiana) for measurement of ticagrelor and AR-C124910XX levels (14).
Statistical analysis

Continuous data are expressed as mean ± standard deviation (SD) or medians (interquartile range), as appropriate. Categorical data are expressed as proportions (%). Patient characteristics were compared using Fisher’s exact test for categorical data and continuous baseline characteristic data were compared using the Mann-Whitney U test. Continuous data were compared between patients with or without diabetes in each of the treatment groups using 2-way ANOVA with correction for multiple comparisons as appropriate. For the purposes of this post-hoc exploratory analysis, a P value < 0.05 was considered nominally significant. Data were analysed using R version 3.2.4 (the R Project for Statistical Computing). Analyses included assessment by centre to exclude significant inter-centre variability (Figure S14).
Results

Study Population

Fifty of the 180 patients who took part in the PEGASUS platelet function substudy had a baseline history of diabetes mellitus (Figure S1). The prevalence of diabetes was 18/64 (28%), 20/58 (34%) and 12/58 (21%) in the placebo, ticagrelor 60 mg and ticagrelor 90 mg groups, respectively. Of patients with diabetes, 58% were treated with oral hypoglycemic therapy (but not insulin), 26% were treated with insulin and 16% were diet-controlled. Compared with patients without diabetes, patients with diabetes had significantly greater body mass index, higher prevalence of hypercholesterolaemia and hypertension, and a lower proportion of patients of Caucasian race (Table 1 and Table S2). The proportion of patients with a preceding non-ST-elevation MI, as opposed to an ST-elevation MI, was greater in patients with diabetes compared with those without diabetes (Table 1). The time interval between the last dose of study medication and measurement of the pre-dose sample was slightly greater in patients with diabetes (Table 1).

Platelet $\text{P2Y}_{12}$ Inhibition in Ticagrelor 60 mg-treated Patients with Diabetes

Ticagrelor 60 mg potently and consistently inhibited $\text{P2Y}_{12}$-mediated platelet reactivity both in patients with and without diabetes (Figures 1A-C). LTA maximum platelet aggregation responses to 20 µM ADP were similar in patients with and without diabetes, both pre-dose (34 ±14 vs. 41 ± 10 %; $P = 0.15$) and post-dose (29 ± 14 vs. 34 ± 10 %; $P = 0.19$) (Figure 1A). As measured by the VerifyNow $\text{P2Y}_{12}$ assay, PRU values were also similar in patients with vs. without diabetes, both pre-dose (60 ± 56 vs. 58 ± 68 PRU; $P > 0.9$) and post-dose (32 ± 42 vs. 27 ± 38 PRU; $P > 0.9$) (Figure 1B). In accordance with these findings, LTA maximum platelet aggregation responses to 5 µM ADP and VASP PRI values were also
similar in patients with vs. without diabetes (all \( P > 0.05 \)) (Supplementary Figure S3 and Figure 1C).

**Platelet P2Y\textsubscript{12} Inhibition in Ticagrelor 90 mg-treated Patients with Diabetes**

In patients treated with ticagrelor 90 mg, LTA maximum platelet aggregation responses to 20 \( \mu \text{M} \) ADP were similar in patients with and without diabetes, both pre-dose (35 ± 16 vs. 36 ± 13 %; \( P > 0.9 \)) and post-dose (29 ± 14 vs. 29 ± 11 %; \( P > 0.9 \)) (Figure 1A). In patients treated with ticagrelor 90 mg, VerifyNow pre-dose PRU values were higher in patients with vs. without diabetes (86 ± 57 vs. 37 ± 32 PRU; \( P = 0.01 \)) (Figure 1B), but there was no significant difference post-dose (32 ± 21 vs. 17 ± 17 PRU; \( P = 0.6 \)) (Figure 1B). Neither LTA maximum platelet aggregation responses to ADP (5 or 20 \( \mu \text{M} \)) nor VASP PRI levels demonstrated a difference between patients with and without diabetes treated with ticagrelor 90 mg (Figures 1A, Supplementary Figure S3 and Figure 1C), suggesting the difference in VerifyNow PRU values may have been due to chance.

**Platelet P2Y\textsubscript{12} Inhibition in Placebo-treated Patients with Diabetes**

LTA maximum platelet aggregation responses to 20 \( \mu \text{M} \) ADP were similar in patients with and without diabetes, both pre-dose (72 ± 13 vs. 74 ± 10 %; \( P > 0.9 \)) and post-dose (71 ± 10 vs. 73 ± 9 %; \( P > 0.9 \)) (Figure 1A). VerifyNow PRU values were also similar in patients with vs. without diabetes, both pre-dose (270 ± 46 vs. 263 ± 38 PRU; \( P > 0.9 \)) and post-dose (267 ± 50 vs. 267 ± 35; \( P > 0.9 \)) (Figure 1B). In addition, LTA maximum platelet aggregation responses to 5 \( \mu \text{M} \) ADP and VASP PRI values were similar in patients with vs. without diabetes (all \( P > 0.05 \)) (Supplementary Figure S3 and Figure 1C).

**High P2Y\textsubscript{12}-mediated Platelet Reactivity**

HPR, as determined by VerifyNow, VASP and LTA, was uncommon in patients treated with either ticagrelor 60 mg or ticagrelor 90 mg (Supplementary Table S2). Patients with diabetes
did not have a higher incidence of HPR than patients without diabetes in either the ticagrelor 60 mg or ticagrelor 90 mg groups (all \( P > 0.05 \); Supplementary Table S2).

**Platelet inhibition in Patients Treated with Ticagrelor 60 mg vs. Ticagrelor 90 mg**

Ticagrelor 60 mg twice daily and ticagrelor 90 mg twice daily had a similar inhibitory effect, in both patients with and without diabetes (Figures 1 and 2), which was similar to the findings of the main PEGASUS platelet function sub-study (14). In patients with and without diabetes, the effect of ticagrelor 60 mg was not significantly lower than the effect of ticagrelor 90 mg according to VerifyNow, VASP, LTA and serum thromboxane B\(_2\) levels (all \( P > 0.05 \)).

**Pharmacokinetics**

The pharmacokinetics of ticagrelor and its active metabolite AR-C124910XX were not affected by diabetes status (Supplementary Figure S4). Pre-dose and post-dose plasma ticagrelor levels were similar in those with and without diabetes in the ticagrelor 60 mg treatment group and there were also no differences in the ticagrelor 90 mg treatment group (Supplementary Figure S4). Similarly, plasma levels of AR-C124910XX were not affected by diabetes status (Supplementary Figure S4).

**Response to Aspirin**

Both LTA maximum aggregation response to arachidonic acid and serum thromboxane B\(_2\) levels showed high levels of cyclooxygenase (COX)-1 inhibition by aspirin in both diabetes and non-diabetes patients in all treatment groups both pre-dose and post-dose of study medication (Supplementary Figure S5 and Figure 2).

**Diabetes Subgroups**

Ticagrelor 60 mg bid and ticagrelor 90 mg bid both had a consistently potent antiplatelet effect in patients with diabetes, regardless of the pharmacological management of their
diabetes (Supplementary Figures S6-S10). LTA, VerifyNow and VASP PRI values were not significantly different in diabetes patients who were diet-controlled, on oral pharmacotherapy, or treated with insulin compared with the non-diabetes population (Supplementary Figures S6-10).

**Relationship Between Level of HbA1c and Platelet Reactivity**

HbA1c values were available for patients with diabetes, but not patients without diabetes. There was no significant correlation between HbA1c and the results of VerifyNow PRU, VASP PRI, LTA and levels of serum thromboxane B2 (Figures S11-S13; Pearson correlation co-efficient varied between -0.27 – 0.22, all P > 0.05). This was consistent regardless of treatment group (Figure S12) and diabetes treatment (Figure S13).

**Relationship Between Centre and Platelet Reactivity**

Analyses of results according to centre revealed no statistically significant differences between centres for any of the assays (Figure S14).
Discussion

Recent studies show a cardiovascular benefit of long-term administration of dual antiplatelet therapy in patients with MI 1-3 years previously (4). In the overall PEGASUS-TIMI 54 platelet function substudy population, the level of platelet inhibition and cardiovascular benefit provided by ticagrelor 60 mg bid was similar to ticagrelor 90 mg bid (14). However, it has previously been shown that patients with diabetes have a reduced pharmacodynamic response to some types of oral antiplatelet therapy, such as aspirin and clopidogrel (7-12). Multiple mechanisms may contribute to these findings, which underscore the need for more efficacious antiplatelet therapies in patients with diabetes. We therefore investigated whether the 60 mg dose of ticagrelor is sufficient to provide consistent, potent platelet inhibition even in patients with diabetes.

The main finding of this study was that ticagrelor 60 mg bid provides equally effective platelet inhibition in patients with diabetes as it does in patients without diabetes. For the first time, this study demonstrates that the 60 mg bid dose of ticagrelor is sufficient to provide consistent and potent P2Y12 inhibition in patients with diabetes. Indeed, platelet reactivity was similar in patients with diabetes treated with ticagrelor 60 mg and patients with diabetes treated with ticagrelor 90 mg. Patients with diabetes are at particularly high risk of subsequent adverse cardiovascular events and therefore gain more absolute benefit from potent P2Y12 inhibition (13). The finding that the 60 mg dose of ticagrelor is sufficient to potently inhibit platelet reactivity in diabetes patients is important, as this lower dose may provide a more favourable safety profile than the 90 mg dose (4). This is particularly significant for patients with diabetes, as they have an increased risk of bleeding following ACS (20) and our findings provide further insight into the similar effect of ticagrelor 60 mg and ticagrelor 90 mg on clinical outcomes in patients with diabetes in the PEGASUS-TIMI
54 study (13). Furthermore, these results provide reassurance for the change in dose of ticagrelor from 90 mg bid to 60 mg bid in the ongoing THEMIS study, which is investigating ticagrelor in patients with type 2 diabetes (ClinicalTrials.gov identifier NCT01991795). A recent study by Nardin et al. suggested a possible trend for higher platelet reactivity in diabetes patients treated with ticagrelor 90 mg (n=29) compared to patients without diabetes (21). However, a larger study by Alexopoulos et al. (22) did not show any effect of diabetes on the incidence of high platelet reactivity in ticagrelor 90 mg-treated patients, which is consistent with our findings. Although Nardin et al. demonstrated statistically significant correlation between the level of HbA1c and platelet reactivity in ticagrelor-treated patients, the degree of correlation was very weak and unlikely to be clinically meaningful (21). In patients treated with ticagrelor 90 mg bid, VerifyNow P2Y_{12} PRU pre-dose values were slightly higher in patients with diabetes than patients without diabetes. However, the PRU post-dose values and the LTA and VASP assays did not demonstrate higher platelet reactivity in this group of patients, suggesting that this difference in VerifyNow PRU values may have been due to chance, particularly since no difference was observed in the ticagrelor 60 mg group.

Administration of ticagrelor 60 mg bid resulted in similar plasma levels of both ticagrelor and its active metabolite in patients with or without diabetes. In contrast, in a previous study, administration of a clopidogrel loading dose resulted in approximately 40% lower levels of clopidogrel active metabolite in patients with diabetes compared with those without diabetes (9). Combined with our results, this therefore suggests that high platelet reactivity in clopidogrel-treated patients with diabetes may be related to impaired metabolism of clopidogrel, rather than upregulated P2Y_{12} signaling. It is, however, unknown why diabetes may impair the metabolism of clopidogrel. Interestingly, there is some evidence that sulfonylureas, which are commonly used in the treatment of diabetes, are associated with a
reduced response to clopidogrel (23). Further work is therefore needed to demonstrate whether medications used for diabetes may interfere with the metabolism of clopidogrel. It has recently been shown that the 90 mg twice daily dose of ticagrelor provides more potent P2Y₁₂ inhibition than prasugrel (24), although it remains to be established whether this is also true of the 60 mg dose.

It is well-recognized that diabetes is associated with an increased risk of adverse cardiovascular events in patients with ACS (1). Patients with diabetes have upregulated platelet turnover and other platelet abnormalities, which may confer an increased risk of thrombosis (2). In addition, as seen in our study and others, patients with diabetes have a higher prevalence of obesity, hypertension, and hypercholesterolemia than patients without diabetes. Obesity, in particular, has been shown to be associated with higher platelet reactivity in aspirin-treated patients (25). Furthermore, diabetes is characterized by chronic low-grade systemic inflammation and altered fibrin clot structure, which shifts the homeostatic balance towards thrombosis (26). Targeting novel pathways related to these mechanisms therefore also has potential for reducing thrombotic risk in patients with diabetes in addition to the benefits already provided by platelet P2Y₁₂ inhibition (27,28). Our study did not demonstrate a significant difference in levels of platelet reactivity to ADP in placebo-treated patients with diabetes compared to patients without diabetes. The reason for this is unclear, but may be due to the small sample size. Alternatively, this may suggest that higher levels of platelet reactivity in patients with diabetes are predominantly related to response to antiplatelet therapy rather than inherently increased platelet reactivity.

**Limitations**

This study demonstrates the effects of ticagrelor 60 mg bid in stable patients with diabetes who had a prior history of MI 1-3 years previously. It has not yet been demonstrated whether ticagrelor 60 mg bid is capable of equivalent potent P2Y₁₂ inhibition in other conditions, such
as during acute MI. Further studies are needed to investigate whether the 2 ticagrelor regimens also cause similar levels of adenosine uptake inhibition, as this may contribute to the effects of ticagrelor in vivo (29,30). Since we primarily intended to assess the impact of P2Y₁₂ inhibition on COX-1 activity, we did not assess platelet function pre-aspirin maintenance dose and so could not compare trough levels of COX-1 inhibition in patients with and without diabetes. Another limitation of this study is that the number of patients with diabetes was relatively small, with 20 or fewer patients with diabetes in each of the treatment groups.

**Conclusions**

In conclusion, ticagrelor 60 mg bid is equally effective at reducing platelet reactivity in patients with and without diabetes, yielding a consistently high level of platelet inhibition regardless of diabetes status.


**Acknowledgements**

**Disclosures of Potential Conflicts of Interest**

**Dr. Mark R. Thomas:** has no conflicts of interest to report.

**Dr. Dominick J. Angiolillo:** has received payment as an individual for: a) Consulting fee or honorarium from Amgen, Bayer, Pfizer, Sanofi, Eli Lilly, Daiichi-Sankyo, The Medicines Company, AstraZeneca, Merck, Abbott Vascular and PLx Pharma; b) Participation in review activities from Celona, Johnson & Johnson, and St. Jude Medical. Institutional payments for grants from Glaxo-Smith-Kline, Eli Lilly, Daiichi-Sankyo, The Medicines Company, AstraZeneca, Janssen Pharmaceuticals, Inc., Osprey Medical, Inc., Novartis, CSL Behring, and Gilead.

**Dr. Marc P. Bonaca:** reports grant support to Brigham and Women’s Hospital from AstraZeneca for the PEGASUS-TIMI 54 trial, consulting for AstraZeneca, Merck and Bayer.

**Dr. Ramzi Ajjan:** discloses research support from the National Institute for Health Research, British Heart Foundation, Sir Jules Thorn Trust, Roche, Abbott, Bayer, Eli Lilly, LifeScan, NovoNordisk and Takeda. He also received Advisory Board and speaker’s honoraria from Abbott, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Merck Sharpe & Dohme, NovoNordisk, Janssen and Takeda.

**Dr. Heather M. Judge:** has no conflicts of interest to report.

**Dr. Fabiana Rollini:** has no conflicts of interest to report.

**Dr. Francesco Franchi:** has no conflicts of interest to report.

**Dr. Ahrif J. Ahsan:** has no conflicts of interest to report.

**Dr. Deepak L. Bhatt:** discloses the following relationships - Advisory Board: Cardax, Elsevier Practice Update Cardiology, Medscape Cardiology, Regado Biosciences; Board of Directors: Boston VA Research Institute, Society of Cardiovascular Patient Care; Chair:
American Heart Association Quality Oversight Committee; Data Monitoring Committees: Duke Clinical Research Institute, Harvard Clinical Research Institute, Mayo Clinic, Population Health Research Institute; Honoraria: American College of Cardiology (Senior Associate Editor, Clinical Trials and News, ACC.org), Belvoir Publications (Editor in Chief, Harvard Heart Letter), Duke Clinical Research Institute (clinical trial steering committees), Harvard Clinical Research Institute (clinical trial steering committee), HMP Communications (Editor in Chief, Journal of Invasive Cardiology), Journal of the American College of Cardiology (Guest Editor; Associate Editor), Population Health Research Institute (clinical trial steering committee), Slack Publications (Chief Medical Editor, Cardiology Today’s Intervention), Society of Cardiovascular Patient Care (Secretary/Treasurer), WebMD (CME steering committees); Other: Clinical Cardiology (Deputy Editor), NCDR-ACTION Registry Steering Committee (Chair), VA CART Research and Publications Committee (Chair); Research Funding: Amarin, Amgen, AstraZeneca, Bristol-Myers Squibb, Eisai, Ethicon, Forest Laboratories, Ischemix, Lilly, Medtronic, Pfizer, Roche, Sanofi Aventis, The Medicines Company; Royalties: Elsevier (Editor, Cardiovascular Intervention: A Companion to Braunwald’s Heart Disease); Site Co-Investigator: Biotronik, Boston Scientific, St. Jude Medical; Trustee: American College of Cardiology; Unfunded Research: FlowCo, PLx Pharma, Takeda.

Ms. Julia F. Kuder: has no conflicts of interest to report.

Dr. Philippe Gabriel Steg: discloses research grants from Merck, Sanofi, Servier and speaking or consulting fees from Amarin, AstraZeneca, Bayer, Boehringer-Ingelheim, Bristol-Myers-Squibb, CSL-Behring, Daiichi-Sankyo, GlaxoSmithKline, Janssen, Lilly, Merck, Novartis, Pfizer, Regeneron, Roche, Sanofi, Servier and The Medicines Company.

Dr. Marc Cohen: discloses advisory board membership: AstraZeneca speakers bureau.
**Dr. Marc S. Sabatine:** discloses research grant support through Brigham and Women’s Hospital from: Abbott Laboratories, Amgen, AstraZeneca, Critical Diagnostics, Daiichi-Sankyo, Elsai, Gilead, GlaxoSmithKline, Intarcia, MedImmune, Merck, Novartis, Poxel, Roche Diagnostics, Sanofi Aventis and Takeda and disloses consultancy fees from Alnylam, AstraZeneca, CVS Caremark and Merck.

**Dr. Robert F. Storey:** reports institutional research grants, consultancy fees, honoraria and travel support from AstraZeneca; consultancy fees from Aspen, Correvio, PlaqueTec, ThermoFisher Scientific and The Medicines Company; honoraria from Medscape; and travel support from Medtronic.
References


### Tables

#### Table 1 Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>No Diabetes (n = 130)</th>
<th>Diabetes (n = 50)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (median, years)</td>
<td>65 (60 – 68)</td>
<td>63 (56 – 68)</td>
<td>0.20</td>
</tr>
<tr>
<td>Male sex (%)</td>
<td>111 (85)</td>
<td>40 (80)</td>
<td>0.37</td>
</tr>
<tr>
<td>Caucasian race (%)</td>
<td>126 (97)</td>
<td>42 (84)</td>
<td>0.004</td>
</tr>
<tr>
<td>Body Mass Index (median, kg/m²)</td>
<td>27.8 (25.2 – 30.8)</td>
<td>30.5 (27.8 – 35.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>85 ± 16</td>
<td>95 ± 23</td>
<td>0.003</td>
</tr>
<tr>
<td>Prior MI diagnosis:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NSTEMI (%)</td>
<td>51 (39)</td>
<td>32 (64)</td>
<td>0.004</td>
</tr>
<tr>
<td>STEMI (%)</td>
<td>79 (61)</td>
<td>17 (34)</td>
<td>0.002</td>
</tr>
<tr>
<td>Unknown (%)</td>
<td>0 (0)</td>
<td>1 (2)</td>
<td>0.28</td>
</tr>
<tr>
<td>Years since MI (median, years)</td>
<td>1.7 (1.3 – 2.2)</td>
<td>1.7 (1.2 – 2.1)</td>
<td>0.66</td>
</tr>
<tr>
<td>Hypercholesterolaemia (%)</td>
<td>70 (54)</td>
<td>41 (82)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>59 (45)</td>
<td>34 (68)</td>
<td>0.008</td>
</tr>
<tr>
<td>Current smoker (%)</td>
<td>19 (15)</td>
<td>9 (18)</td>
<td>0.65</td>
</tr>
<tr>
<td>Prior transient ischaemic attack (%)</td>
<td>1 (1)</td>
<td>1 (2)</td>
<td>0.48</td>
</tr>
<tr>
<td>Prior stroke (%)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>NA</td>
</tr>
<tr>
<td>Multivessel CAD (%)</td>
<td>80 (62)</td>
<td>30 (60)</td>
<td>0.87</td>
</tr>
<tr>
<td>Time since last dose of study medication, pre-dose (median, h)</td>
<td>11.8 (11.1 – 12.5)</td>
<td>12.0 (11.6 – 14.0)</td>
<td>0.01</td>
</tr>
<tr>
<td>Chronic kidney disease (%)</td>
<td>4 (3)</td>
<td>1 (2)</td>
<td>&gt;0.9</td>
</tr>
<tr>
<td>Aspirin use (%)</td>
<td>130 (100)</td>
<td>50 (100)</td>
<td>NA</td>
</tr>
<tr>
<td>Statin use (%)</td>
<td>125 (96)</td>
<td>47 (94)</td>
<td>0.69</td>
</tr>
<tr>
<td>Ace inhibitor use (%)</td>
<td>104 (80)</td>
<td>33 (66)</td>
<td>0.05</td>
</tr>
<tr>
<td>Beta blocker use (%)</td>
<td>118 (91)</td>
<td>42 (84)</td>
<td>0.20</td>
</tr>
<tr>
<td>Hypoglycemic therapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diet-controlled (%)</td>
<td>NA</td>
<td>8 (16)</td>
<td>NA</td>
</tr>
<tr>
<td>Oral (%)</td>
<td>NA</td>
<td>29 (58)</td>
<td>NA</td>
</tr>
<tr>
<td>Insulin (%)</td>
<td>NA</td>
<td>13 (26)</td>
<td>NA</td>
</tr>
</tbody>
</table>

Data are expressed as mean ± standard deviation or median (interquartile range).
Figures
Figure 1. Light transmission aggregometry (LTA) maximum platelet aggregation response to 20 µM ADP (A), VerifyNow P2Y_{12} Reaction Units (PRU) (B) and vasodilator-stimulated phosphoprotein (VASP) phosphorylation platelet reactivity index (PRI) (C). Pre and post maintenance dose of placebo, ticagrelor 60 mg bid or ticagrelor 90 mg bid. Data expressed as mean (circle) ± SD (lines). Patients with diabetes mellitus (DM) compared to patients without DM (No DM) in each treatment group using 2-way ANOVA with Bonferroni correction for multiple comparisons. Dotted line indicates threshold value for high platelet reactivity.
Figure 2. Serum thromboxane B\textsubscript{2} concentration (log transformed) pre and post maintenance dose of placebo, ticagrelor 60 mg bd or ticagrelor 90 mg bd. Data expressed as mean (circle) ± SD (lines). Patients with diabetes mellitus (DM) compared to patients without DM (No DM) in each treatment group using 2-way ANOVA with Bonferroni correction for multiple comparisons.