

# Aspirin-free antiplatelet regimens after PCI: insights from the GLOBAL LEADERS trial and beyond

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Historically, aspirin has been the primary treatment for the prevention of ischaemic events in patients with coronary artery disease. For patients undergoing percutaneous coronary intervention (PCI) standard treatment has been 12 months of dual antiplatelet therapy (DAPT) with aspirin and clopidogrel, followed by aspirin monotherapy; however, DAPT is undeniably associated with an increased risk of bleeding. For over a decade novel P2Y<sub>12</sub> inhibitors, which have increased specificity, potency, and efficacy have been available, prompting studies which have tested whether these newer agents can be used in aspirin-free antiplatelet regimens to augment clinical benefits in patients post-PCI. Among these studies, the GLOBAL LEADERS trial is the largest by cohort size, and so far has provided a wealth of evidence in a variety of clinical settings and patient groups. This article summarizes the state-of-the-art evidence obtained from the GLOBAL LEADERS and other trials of aspirin-free strategies.

**Keywords** Aspirin-free therapy • P2Y<sub>12</sub> inhibitor • GLOBAL LEADERS • Randomized clinical trials • Percutaneous coronary intervention

## Introduction

The reduced risk of stent thrombosis (ST) with the combined use of aspirin and a P2Y<sub>12</sub> inhibitor firmly established dual antiplatelet therapy (DAPT) as mandatory treatment following percutaneous coronary intervention (PCI).<sup>1</sup> However, the duration and make-up of DAPT is now being questioned as ST rates have fallen significantly with contemporary PCI techniques and usage of current generation drug-eluting stents (DESs), whereas bleeding events whilst taking DAPT, continue to be an important predictor of adverse clinical

outcomes.<sup>2–6</sup> Furthermore, increasing use of more potent P2Y<sub>12</sub> inhibitors has challenged the dominant position of aspirin in antiplatelet regimens.

Shortening DAPT post-PCI through early cessation of aspirin has been proposed to mitigate the risk of bleeding without increasing ischaemic events.<sup>7</sup> Over the last decade, this strategy has been assessed in several randomized controlled trials with the GLOBAL LEADERS (GL) trial being the largest.<sup>8–14</sup> Notably, whilst randomized trials have consistently demonstrated the safety and efficacy of P2Y<sub>12</sub> inhibitor monotherapy compared to DAPT, it has been unclear

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which patients or lesion types benefit the most. Herein, we summarize the extensive wealth of evidence established from GL in a variety of clinical settings and patient groups, and highlight recent findings from other aspirin-free randomized trials.

## Section 1: The design and main findings of the GLOBAL LEADERS trial

Ticagrelor, a potent and selective antiplatelet drug, has been proposed as being superior to DAPT regimens using aspirin post-PCI, and/or aspirin monotherapy for the prevention of ischaemic events. Consequently, the GL investigators hypothesized that ticagrelor, in combination with aspirin for 1 month, followed by ticagrelor alone, would improve outcomes after PCI compared with standard 12-month DAPT followed by 12-month aspirin monotherapy. This all-comer's trial was therefore designed to answer: (i) Can ticagrelor monotherapy avoid the higher risk of bleeding potentially associated with adding aspirin? (ii) Can ticagrelor monotherapy maintain the clinical benefits of platelet inhibition after PCI, beyond the crucial initial 30 days when the risk of ST is highest? In the experimental group, patients received 1-month aspirin plus ticagrelor 90 mg b.i.d. followed by 23 months of ticagrelor 90 mg b.i.d. monotherapy. Patients in the control group were treated with standard 12-month DAPT [aspirin plus clopidogrel in chronic coronary syndrome (CCS), aspirin plus ticagrelor in acute coronary syndrome (ACS)] followed by 12-month aspirin monotherapy (Figure 1). The primary endpoint was a composite of all-cause mortality or non-fatal centrally adjudicated new Q-wave myocardial infarction (MI) at 2 years. The key secondary safety endpoint was site-reported bleeding assessed according to the Bleeding Academic Research Consortium (BARC) criteria grade 3 or 5 (BARC 3/5).<sup>15</sup> Sub-studies were planned and executed to enhance understanding of the treatment effects (Figure 2).

A total of 15 968 participants were randomly assigned to the experimental ( $n = 7980$ ) and control group ( $n = 7988$ ). At 2 years, the primary endpoint occurred in 304 (3.81%) patients in the

experimental group and 349 (4.37%) in the control group [rate ratio (RR): 0.87, 95% confidence interval (CI): 0.75–1.01,  $P = 0.073$ ]. The bleeding risk was comparable, with 163 and 169 BARC 3/5 bleeding events in the experimental and control group, respectively (2.04% vs. 2.12%; RR: 0.97, 95% CI: 0.78–1.20,  $P = 0.77$ ) (Figure 3). The study concluded that ticagrelor monotherapy following 1 month combination with aspirin was not superior to standard DAPT.<sup>8</sup>

## Section 2: Pre-specified and exploratory analyses from GLOBAL LEADERS

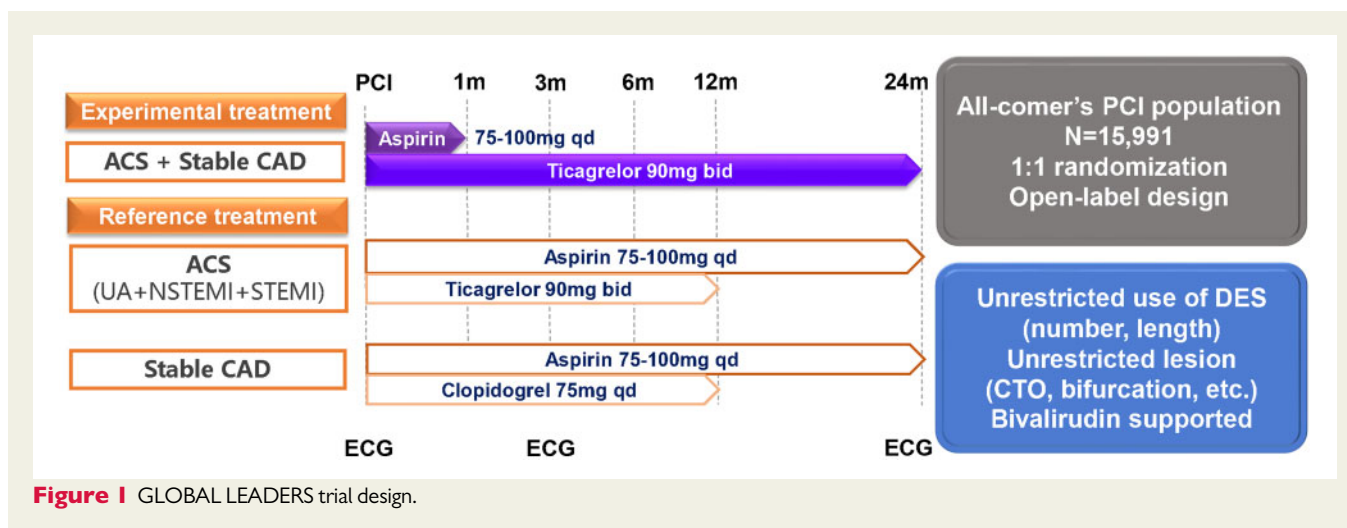
In the light of the size of the study and its all-comer's design, with minimal exclusion, the cohort offers amply opportunity, despite the negative results of the primary analysis, to try and identify a population who have most to gain from the experimental antiplatelet strategy tested in the study. Below is a summary of the results from pre-specified analyses from GL,<sup>9,16–23</sup> whilst the [Supplementary material online](#) summarizes the *post hoc* analyses<sup>24–49</sup> (Figure 2).

### Pre-specified analyses

Two of the nine pre-specified analyses investigated outcomes without differentiating between clinical or procedural characteristics.

#### GLOBAL LEADERS adjudication sub-study (GLASSY)

GLASSY was conducted prospectively at the 20 highest recruiting GL sites, and assessed whether the experimental therapy was non-inferior to standard therapy for the co-primary efficacy composite endpoint of all-cause death, non-fatal MI, non-fatal stroke, or urgent revascularization, and superior for the co-primary safety endpoint of preventing BARC 3/5 bleeding at 2 years.<sup>9</sup> For financial reasons, all events in GL were investigator reported, whilst in GLASSY, a blinded independent adjudication process was used for reported and unreported potential endpoints, using standardized clinical event committee procedures. The 2 years co-primary efficacy endpoint occurred



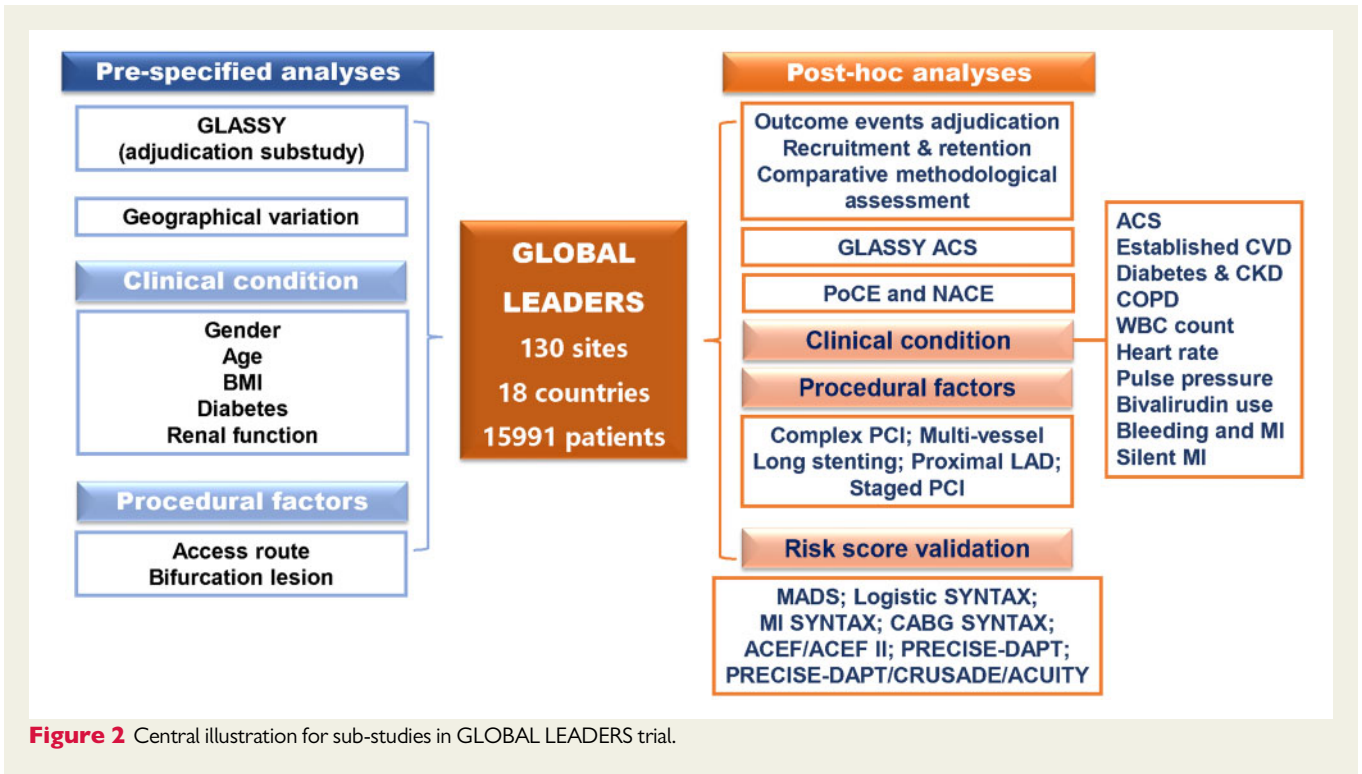


Figure 2 Central illustration for sub-studies in GLOBAL LEADERS trial.

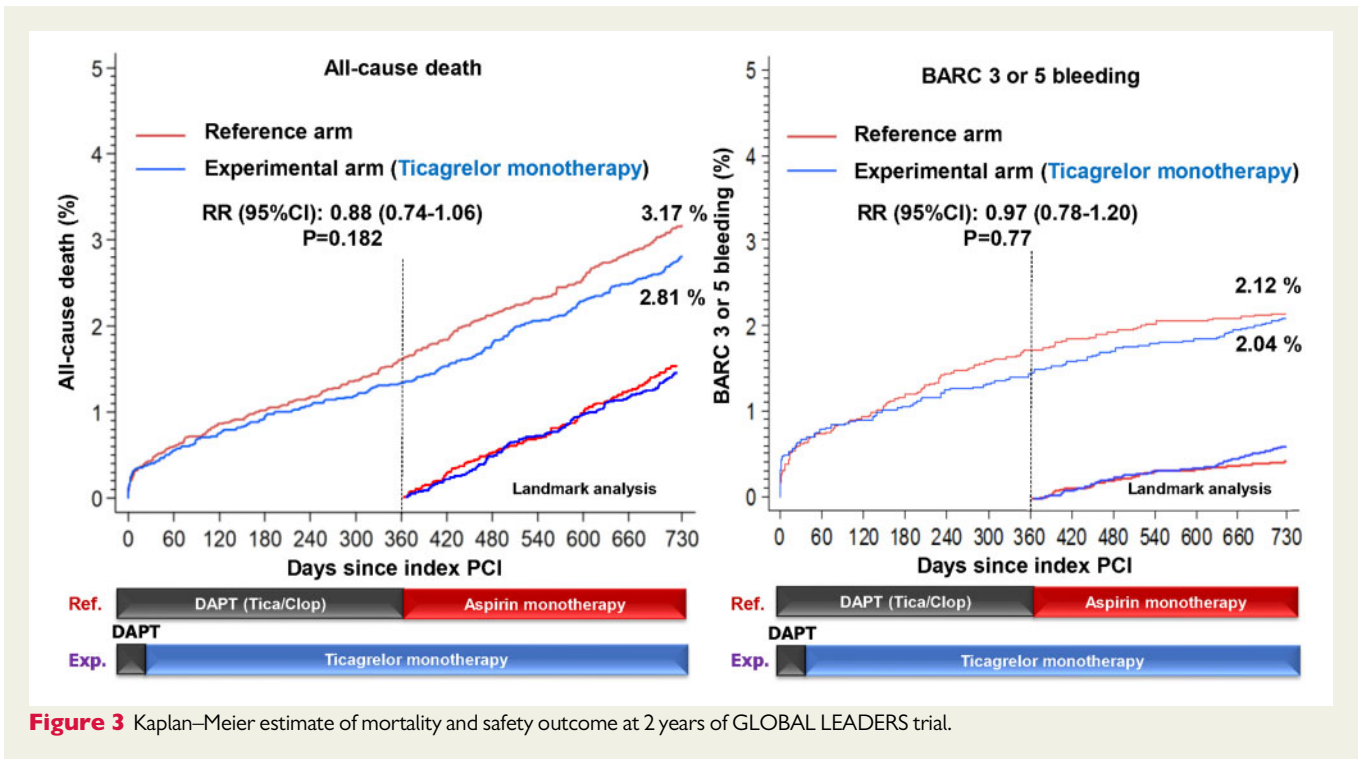
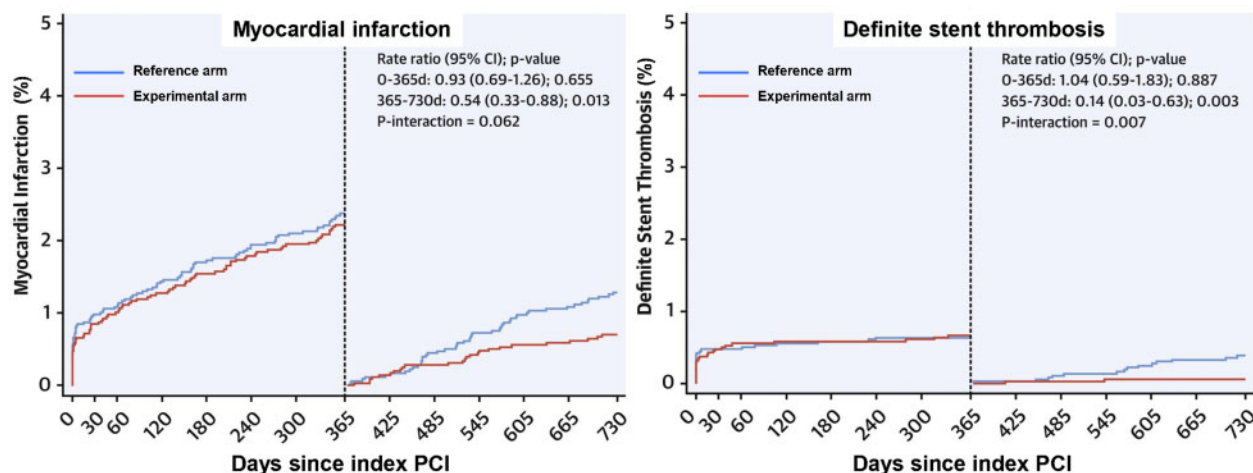


Figure 3 Kaplan-Meier estimate of mortality and safety outcome at 2 years of GLOBAL LEADERS trial.

in 271 (7.14%) and 319 (8.41%) patients in the experimental and conventional groups, respectively (RR: 0.85, 95% CI: 0.72–0.99), meeting the pre-specified criteria for non-inferiority ( $P_{\text{non-inferiority}} < 0.001$ ),

but not superiority ( $P_{\text{superiority}} = 0.0465$ ). The rates of BARC 3/5 bleeding did not differ (RR: 1.00, 95% CI: 0.75–1.33,  $P = 0.986$ ). At 1-year landmark, the experimental treatment lowered the risk of MI



**Figure 4** Kaplan–Meier graphs by landmark analysis for MI and definite ST in GLASSY study.

(RR: 0.54, 95% CI: 0.33–0.88,  $P_{\text{interaction}} = 0.062$ ) and definite ST (RR: 0.14, 95% CI: 0.03–0.63,  $P_{\text{interaction}} = 0.007$ ) (Figure 4).

### Impact of geography

Study recruitment took place across 5 continents and 18 countries, and analysis confirmed that the primary endpoint varied significantly according to country ( $P_{\text{interaction}} = 0.027$ ). Amongst measurable factors, differences in the rate of complex PCI were seen as the major contributor to this geographical variation.<sup>16</sup>

## Clinical conditions

Five pre-specified analyses were performed on the basis of patient's clinical characteristics.

### Gender

At 2 years post-PCI, gender had no impact on the risk of all-cause mortality or new Q-wave MI; however, rates of BARC 3/5 bleeding and haemorrhagic stroke were higher in women.<sup>17</sup> At 1 year, ticagrelor monotherapy lowered the risk of bleeding in men but not women when compared with standard DAPT ( $P_{\text{interaction}} = 0.045$ ); however, at 2 years, there was no between-sex difference in efficacy or safety with either antiplatelet strategy.

### Age

Similarly, no differential treatment effect on the primary endpoint was observed among 2565 elderly patients, defined as those aged >75.<sup>18</sup> Compared with standard DAPT, ticagrelor monotherapy resulted in lower rates of definite or probable ST amongst the elderly patients, however, tempered with this, were the higher rates of BARC 3/5 bleeding seen with elderly patients receiving ticagrelor monotherapy for CCS [hazard ratio (HR): 2.05, 95% CI: 1.18–3.55,  $P_{\text{interaction}} = 0.02$ ].

### Body mass index

In line with previous studies, the 'obesity paradox' was again observed with a reverse J-shape association between mortality risk and body mass index (BMI).<sup>19</sup> There was no treatment effect on the primary endpoint in patients with low (<27 kg/m<sup>2</sup>) or high (≥27 kg/m<sup>2</sup>) BMI. In patients with ACS, however, the primary endpoint was significantly reduced with the experimental strategy in patients with a BMI <27 kg/m<sup>2</sup>, which was not observed in those with a BMI ≥27 kg/m<sup>2</sup>. In patients with CCS, there was no risk difference between the two antiplatelet strategies in either BMI group.

### Diabetes mellitus

Approximately a quarter of the study cohort were diabetic (4038/15 957), and at 2 years, compared to non-diabetics, they had a significantly higher risk of the primary endpoint, which was mainly driven by a significantly higher risk of all-cause mortality, with comparable rates of BARC 3/5 bleeding.<sup>20</sup> There was no significant treatment effect on the 2-year primary efficacy or secondary safety endpoint, among patients with or without diabetes.

### Impaired renal function

The 2171 patients with impaired renal function (IRF), defined as an estimated glomerular filtration rate <60 mL/min/1.73 m<sup>2</sup>, had significantly higher rates of the primary endpoint, all-cause death, site-reported MI, all revascularization, and BARC 3/5 bleeding, compared to those patients without IRF.<sup>21</sup> In the IRF cohort, rates of the primary efficacy endpoint and secondary safety endpoint were, however, similar for both treatment strategies.

## Procedural factors

Two pre-specified analyses were performed on the basis of procedural characteristics.



### Bifurcation lesion

In 2498 patients PCI was performed for at least one bifurcation lesion. The experimental therapy had no significant effect on the primary endpoint in patients irrespective of whether PCI was performed for a bifurcation lesion or not (bifurcation: HR: 0.74, 95% CI: 0.51–1.07; non-bifurcation: HR: 0.90, 95% CI: 0.76–1.07,  $P_{\text{interaction}} = 0.343$ ).<sup>22</sup> In patients having PCI for a bifurcation lesion the experimental treatment was associated with less definite/probable ST ( $P_{\text{interaction}} = 0.027$ ) and more stroke ( $P_{\text{interaction}} = 0.021$ ) compared to standard treatment.

### Impact of access route

Gao *et al.*<sup>23</sup> analysed 30-day outcomes according to arterial access site and reported no difference in the primary endpoint between radial and femoral artery access (HR: 0.70, 95% CI: 0.42–1.15), however radial access resulted in significantly less BARC 3/5 bleeding (HR: 0.55, 95% CI: 0.36–0.84). In-depth analysis of the risk of bleeding stratified by the PRECISE-DAPT score showed that the primary efficacy endpoint and secondary safety endpoint were not significantly different between radial and femoral access in patients at low risk of bleeding (PRECISE-DAPT score < 16), however, they strongly favoured radial access in patients at high bleeding risk (PRECISE-DAPT score > 16).

In summary, no pre-specified subgroup analysis identified any patient or procedural characteristic where the experimental strategy led to any significant treatment benefit, or patient harm.

### Post hoc analyses

A summary of the results of numerous *post hoc* studies is contained in the [Supplementary material online](#).

## Section 3: Evidence from aspirin-free strategy trials

Although there have been several studies of short DAPT with aspirin discontinuation, GL remains the largest antiplatelet therapy study to date, and the first to test the strategy of P2Y<sub>12</sub> inhibitor monotherapy after stopping aspirin. Notably, the STOPDAPT-2, SMART-CHOICE, TWILIGHT, TICO, and ASET studies were all conducted after GL (Figure 5).

The STOPDAPT-2 trial<sup>12</sup> evaluated 1 month of DAPT followed by clopidogrel monotherapy ( $n = 1523$ ) vs. 12 months of DAPT with aspirin and clopidogrel ( $n = 1522$ ) among patients undergoing PCI. The results showed significantly lower rates of the composite of cardiovascular death, MI, ischaemic or haemorrhagic stroke, definite ST, or major or minor bleeding with 1-month DAPT (2.4% vs. 3.7%, HR: 0.64, 95% CI: 0.42–0.98), which met the criteria for both non-inferiority and superiority. Notably, whilst the reduction in secondary cardiovascular (2.0% vs. 2.5%, HR: 0.79, 95% CI: 0.49–1.29) and bleeding endpoints (0.4% vs. 1.5%, HR: 0.26, 95% CI: 0.11–0.64) with 1-month DAPT were both non-inferior to 12-month DAPT, only the bleeding reduction met the criteria for superiority.

The SMART-CHOICE trial<sup>11</sup> compared the safety and efficacy of 3-month DAPT followed by P2Y<sub>12</sub> inhibitor monotherapy, to

12-month DAPT among 2993 unselected patients undergoing PCI with a DES. The study concluded that 3 months of DAPT was non-inferior to prolonged DAPT for the primary endpoint of major adverse cardiovascular and cerebrovascular events (2.9% vs. 2.5%,  $P_{\text{non-inferiority}} = 0.007$ ). Whilst efficacy outcomes were comparable, rates of bleeding were significantly lower in the short DAPT group (2.0% vs. 3.4%, HR: 0.58, 95% CI: 0.36–0.92,  $P = 0.02$ ).

Despite their minimal exclusion criteria, GL, STOPDAPT-2, and SMART-CHOICE enrolled mainly low-risk patients. In contrast, the placebo-controlled, randomized, double-blind TWILIGHT study<sup>10</sup> enrolled 9006 patients undergoing PCI with at least one high-risk feature for ischaemia or bleeding, with the aim to compare the safety and efficacy of 3-month DAPT with aspirin and ticagrelor followed by 12 months of placebo and ticagrelor monotherapy, to 15-month DAPT with aspirin and ticagrelor, among patients who were at high risk for bleeding or an ischaemic event, and had undergone successful PCI without any major bleeding or ischaemic events at 3 months. Between randomization and 1 year, the use of ticagrelor monotherapy was associated with a significantly lower incidence of clinically relevant bleeding (BARC 2, 3, or 5) compared to DAPT with ticagrelor and aspirin (4.0% vs. 7.1%, HR: 0.56, 95% CI: 0.45–0.68,  $P < 0.001$ ), with no increased risk of death, MI, or stroke. These findings were maintained among sub-groups of patients presenting with ACS,<sup>50</sup> diabetes,<sup>51</sup> and those undergoing complex PCI<sup>52</sup> (Figure 6). These intriguing findings should help enhance our understanding of the optimal duration and type of antiplatelet agent to use post-PCI.

The current guideline recommendations of 12-month DAPT post-PCI for ACS<sup>53</sup> are being challenged by the results from the ACS sub-groups from the aforementioned studies, together with new dedicated ACS trials such as TICO,<sup>13</sup> which is the first randomized study to compare standard of care ticagrelor-based DAPT against ticagrelor monotherapy specifically in ACS patients. Similar to the design of TWILIGHT, the trial compared outcomes amongst 3056 patients with ACS treated with PCI who were randomized to receive either 3 months of ticagrelor based DAPT followed by ticagrelor monotherapy or 12 months of ticagrelor based DAPT. The trial showed that ticagrelor monotherapy after 3 months of DAPT, resulted in a modest but statistically significant reduction in the composite outcome of major bleeding and cardiovascular events at 1 year (3.9% vs. 5.9%, HR: 0.66, 95% CI: 0.48–0.92,  $P = 0.01$ ). In the TICO-STEMI study, rates of net adverse clinical events at 12 months in the intention-to-treat population were comparable between groups receiving ticagrelor monotherapy, and 12 months ticagrelor-based DAPT, with rates of 3.7% and 5.0%, respectively (HR: 0.73, 95% CI: 0.41–1.29,  $P = 0.27$ ). TIMI bleeding event rates at 12 months were significantly lower with ticagrelor monotherapy (0.9% vs. 2.9%, HR: 0.32, 95% CI: 0.12–0.87,  $P = 0.02$ ).

The ASET trial<sup>14</sup> was a proof-of-concept trial that introduced the concept of 'no DAPT'. Patients were included if they had CCS, a SYNTAX score < 23 and had undergone successful PCI with implantation of an everolimus-eluting stent. All participants were on standard DAPT at the time of the index PCI, however aspirin was discontinued on the day of the index PCI, whilst prasugrel was administered immediately afterwards, and prasugrel monotherapy was continued for 3 months. The study showed that aspirin-free prasugrel

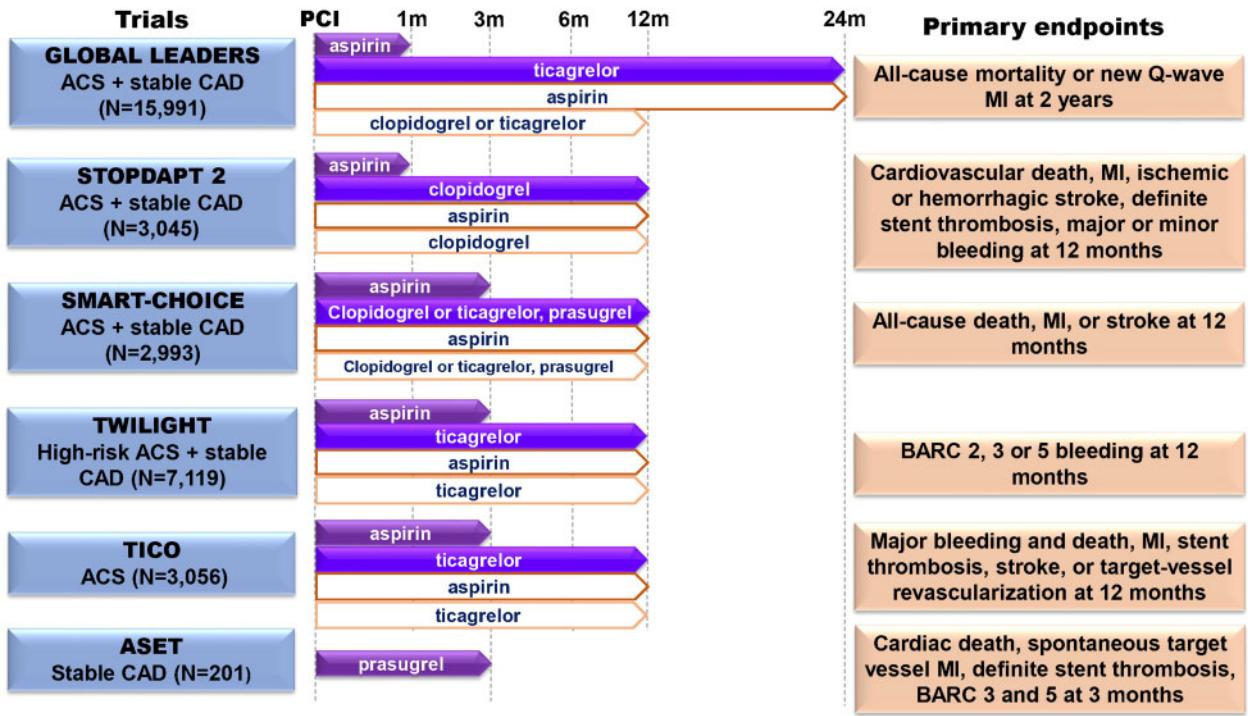


Figure 5 Trials of aspirin-free antiplatelet therapies.

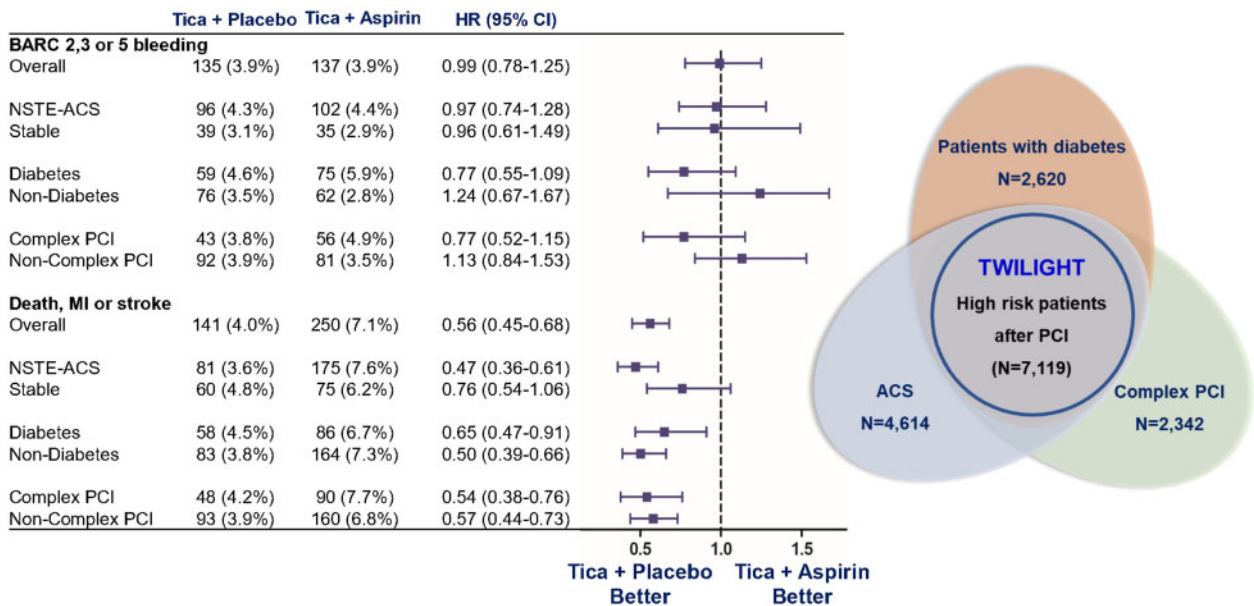


Figure 6 The main findings and subgroup analyses from TWILIGHT trial.

monotherapy was feasible and safe, with no ST, in selected low-risk patients with CCS.

## Section 4: Perspectives

Outcomes from PCI have improved significantly over the last two decades and consequently the mandate for 12-month DAPT after PCI is rightly being challenged. Despite the overall neutral results of GL, results from several hypothesis generating *post hoc* subgroup analyses have suggested that patients with ACS, and those undergoing complex PCI and/or multivessel PCI have more favourable outcomes with ticagrelor monotherapy compared to standard treatment. However, additional adequately powered studies in these sub-groups are required before any formal conclusions or recommendations can be made. Further support to a change in recommendation comes from pooled analyses of clinical trials comparing time-constrained DAPT followed by P2Y<sub>12</sub> inhibitor monotherapy from 1 to 3 months post-PCI to standard DAPT.<sup>54–57</sup> McClure *et al.*<sup>54</sup> and O'Donoghue *et al.*<sup>55</sup> separately pooled results from over 32,000 patients enrolled in the same five randomized studies and showed that P2Y<sub>12</sub> inhibitor monotherapy led to significant reductions in the risk of bleeding (HR: 0.60), with the greatest benefit seen in ACS patients (HR: 0.50), who made up more than half of the population. Reassuringly, this was associated with favourable benefits on major adverse cardiac event, all-cause mortality and MI.<sup>54,55</sup> Similarly, a meta-analysis by Hong *et al.*,<sup>56</sup> which pooled results from the 26 143 patients enrolled in GL, TWILIGHT and TICO, showed that compared to conventional therapy, ticagrelor monotherapy lead to significantly lower BARC 3/5 bleeding [RR: 0.67, 95% CI: 0.49–0.92, *P* = 0.01, *I*<sub>2</sub> = 65%, number needed to treat for benefit (NNTB) = 156], and all-cause mortality (RR: 0.80, 95% CI: 0.65–0.98, *P* = 0.03, *I*<sub>2</sub> = 0%, NNTB = 320). There appeared to be no evidence of benefit with prolonged DAPT. More recently, Giacoppo *et al.*<sup>57</sup> performed a systematic review and meta-analysis of short DAPT followed by P2Y<sub>12</sub> inhibitor monotherapy vs. prolonged DAPT after PCI with second-generation DES. No significant between-group differences were observed in terms of ST and the secondary endpoints of all-cause death, MI, and stroke. A sensitivity analysis comparing trials using P2Y<sub>12</sub> inhibitors or aspirin as the single antiplatelet agent following short DAPT therapy was also performed and showed similar results. Regardless of the type of single antiplatelet used after DAPT (P2Y<sub>12</sub> inhibitor or aspirin), short DAPT was associated with significantly lower major bleeding (random-effects model: HR: 0.63, 95% CI: 0.48–0.83) compared with standard DAPT, without any meaningful differences in ST, all-cause death, MI, or stroke.<sup>57</sup>

These results support a strategy of discontinuing aspirin from 3 months post-PCI and continuing with 'aspirin-free' P2Y<sub>12</sub> inhibitor monotherapy in intermediate- to high-risk patients. However, this strategy has not been fully assessed in patients with left main disease, chronic total occlusions, cardiogenic shock, and ST-elevation MI and therefore additional randomized studies in these dedicated populations are warranted. Moreover, whether aspirin or P2Y<sub>12</sub> inhibitors

should be continued long-term following the period of DAPT, needs further investigation.

## Conclusions

Increasing evidence demonstrates that 1–3 months of DAPT followed by P2Y<sub>12</sub> inhibitor monotherapy is associated with a lower risk of major bleeding, and no increased risk of ischaemic events compared with standard 12-month DAPT. Ceasing aspirin earlier after contemporary PCI should be considered in patients with high bleeding risk. Future studies should aim to establish the optimal time for the discontinuation of DAPT, and also whether monotherapy post-DAPT should be with aspirin or a P2Y<sub>12</sub> inhibitor.

## Supplementary material

Supplementary material is available at *European Heart Journal – Cardiovascular Pharmacotherapy* online.

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## References

1. Leon MB, Baim DS, Popma JJ, Gordon PC, Cutlip DE, Ho KKL, Giambartolomei A, Diver DJ, Lasorda DM, Williams DO, Pocock SJ, Kuntz RE. A clinical trial comparing three antithrombotic-drug regimens after coronary-artery stenting. *Stent*



- Anticoagulation Restenosis Study Investigators. *N Engl J Med* 1998;**339**: 1665–1671.
2. Escaned J, Collet C, Ryan N, De Maria GL, Walsh S, Sabate M, Davies J, Lesiak M, Moreno R, Cruz-Gonzalez I, Hoole SP, Ej West N, Piek JJ, Zaman A, Fath-Ordoubadi F, Stables RH, Appleby C, van Mieghem N, van Geuns RJ, Uren N, Zueco J, Buszman P, Iñiguez A, Goicolea J, Hildick-Smith D, Ochala A, Dudek D, Hanratty C, Cavalcanti R, Kappetein AP, Taggart DP, van Es GA, Morel MA, de Vries T, Onuma Y, Farooq V, Serruys PW, Banning AP. Clinical outcomes of state-of-the-art percutaneous coronary revascularization in patients with de novo three vessel disease: 1-year results of the SYNTAX II study. *Eur Heart J* 2017;**38**:3124–3134.
  3. Palmerini T, Benedetto U, Biondi-Zoccai G, Della Riva D, Bacchi-Reggiani L, Smits PC, Vlachojannis GJ, Jensen LO, Christiansen EH, Berencsi K, Valgimigli M, Orlandi C, Petrou M, Rapezzi C, Stone GW. Long-term safety of drug-eluting and bare-metal stents: evidence from a comprehensive network meta-analysis. *J Am Coll Cardiol* 2015;**65**:2496–2507.
  4. Ueki Y, Bär S, Losdat S, Otsuka T, Zanchin C, Zanchin T, Gragnano F, Gargiulo G, Siontis GCM, Praz F, Lanz J, Hunziker L, Stortecky S, Pilgrim T, Heg D, Valgimigli M, Windecker S, Räber L. Validation of the Academic Research Consortium for High Bleeding Risk (ARC-HBR) criteria in patients undergoing percutaneous coronary intervention and comparison with contemporary bleeding risk scores. *EuroIntervention* 2020;**16**:371–379.
  5. Corpataux N, Spirito A, Gragnano F, Vainora L, Galea R, Svab S, Gargiulo G, Zanchin T, Zanchin C, Siontis GCM, Praz F, Lanz J, Hunziker L, Stortecky S, Pilgrim T, Räber L, Capodanno D, Urban P, Pocock S, Heg D, Windecker S, Valgimigli M. Validation of high bleeding risk criteria and definition as proposed by the academic research consortium for high bleeding risk. *Eur Heart J* 2020;**41**: 3743–3749.
  6. Valgimigli M, Costa F, Likhnygina Y, Clare RM, Wallentin L, Moliterno DJ, Armstrong PW, White HD, Held C, Aylward PE, de Werf FV, Harrington RA, Mahaffey KW, Tricoci P. Trade-off of myocardial infarction vs. bleeding types on mortality after acute coronary syndrome: lessons from the Thrombin Receptor Antagonist for Clinical Event Reduction in Acute Coronary Syndrome (TRACER) randomized trial. *Eur Heart J* 2017;**38**:804–810.
  7. Capodanno D, Mehran R, Valgimigli M, Baber U, Windecker S, Vranckx P, Dangas G, Rollini F, Kimura T, Collet JP, Gibson CM, Steg PG, Lopes RD, Gwon HC, Storey RF, Franchi F, Bhatt DL, Serruys PW, Angiolillo DJ. Aspirin-free strategies in cardiovascular disease and cardioembolic stroke prevention. *Nat Rev Cardiol* 2018;**15**:480–496.
  8. Vranckx P, Valgimigli M, Juni P, Hamm C, Steg PG, Heg D, van Es GA, McFadden EP, Onuma Y, van Meijeren C, Chichareon P, Benit E, Mollmann H, Janssens L, Ferrario M, Moschovitis A, Zurakowski A, Dominici M, Van Geuns RJ, Huber K, Slagboom T, Serruys PW, Windecker S, for the GLOBAL LEADERS Investigators. Ticagrelor plus aspirin for 1 month, followed by ticagrelor monotherapy for 23 months vs aspirin plus clopidogrel or ticagrelor for 12 months, followed by aspirin monotherapy for 12 months after implantation of a drug-eluting stent: a multicentre, open-label, randomised superiority trial. *Lancet* 2018; **392**:940–949.
  9. Franzone A, McFadden E, Leonardi S, Piccolo R, Vranckx P, Serruys PW, Benit E, Liebetrau C, Janssens L, Ferrario M, Zurakowski A, Diletti R, Dominici M, Huber K, Slagboom T, Buszman P, Bolognese L, Tumscitz C, Bryniarski K, Aminian A, Vrolix M, Petrov I, Garg S, Naber C, Prokopcuk J, Hamm C, Steg PG, Heg D, Juni P, Windecker S, Valgimigli M. Ticagrelor alone versus dual antiplatelet therapy from 1 month after drug-eluting coronary stenting. *J Am Coll Cardiol* 2019;**74**: 2223–2234.
  10. Mehran R, Baber U, Sharma SK, Cohen DJ, Angiolillo DJ, Briguori C, Cha JY, Collier T, Dangas G, Dudek D, Dzavik V, Escaned J, Gil R, Gurbel P, Hamm CW, Henry T, Huber K, Kastrati A, Kaul U, Kornowski R, Krucoff M, Kunadian V, Marx SO, Mehta SR, Moliterno D, Ohman EM, Oldroyd K, Sardella G, Sartori S, Shlofmitz R, Steg PG, Weisz G, Witzencbichler B, Han Y-L, Pocock S, Gibson CM. Ticagrelor with or without aspirin in high-risk patients after PCI. *N Engl J Med* 2019;**381**:2032–2042.
  11. Hahn JY, Song YB, Oh JH, Chun WJ, Park YH, Jang WJ, Im ES, Jeong JO, Cho BR, Oh SK, Yun KH, Cho DK, Lee JY, Koh YY, Bae JW, Choi JW, Lee WS, Yoon HJ, Lee SU, Cho JH, Choi WG, Rha SW, Lee JM, Park TK, Yang JH, Choi JH, Choi SH, Lee SH, Gwon HC, for the SMART-CHOICE Investigators. Effect of P2Y12 inhibitor monotherapy vs dual antiplatelet therapy on cardiovascular events in patients undergoing percutaneous coronary intervention: the SMART-CHOICE randomized clinical trial. *JAMA* 2019;**321**:2428–2437.
  12. Watanabe H, Domei T, Morimoto T, Natsuaki M, Shiomi H, Toyota T, Ohya M, Suwa S, Takagi K, Nanasato M, Hata Y, Yagi M, Suematsu N, Yokomatsu T, Takamisawa I, Doi M, Noda T, Okayama H, Seino Y, Tada T, Sakamoto H, Hibi K, Abe M, Kawai K, Nakao K, Ando K, Tanabe K, Ikari Y, Hanaoka KI, Morino Y, Kozuma K, Kadota K, Furukawa Y, Nakagawa Y, Kimura T; for the STOPDAPT-2 Investigators. Effect of 1-month dual antiplatelet therapy followed by clopidogrel vs 12-month dual antiplatelet therapy on cardiovascular and bleeding events in patients receiving PCI: the STOPDAPT-2 Randomized Clinical Trial. *JAMA* 2019; **321**:2414–2427.
  13. Kim BK, Hong SJ, Cho YH, Yun KH, Kim YH, Suh Y, Cho JY, Her AY, Cho S, Jeon DW, Yoo SY, Cho DK, Hong BK, Kwon H, Ahn CM, Shin DH, Nam CM, Kim JS, Ko YG, Choi D, Hong MK, Jang Y, for the TICO Investigators. Effect of ticagrelor monotherapy vs ticagrelor with aspirin on major bleeding and cardiovascular events in patients with acute coronary syndrome: the TICO Randomized Clinical Trial. *JAMA* 2020;**323**:2407–2416.
  14. Kogame N, Guimarães PO, Modolo R, De Martino F, Tinoco J, Ribeiro EE, Kawashima H, Ono M, Hara H, Wang R, Cavalcanti R, Moulin B, Falcão BA, Leite RS, de Almeida Sampaio FB, Morais GR, Meireles GC, Campos CM, Onuma Y, Serruys PW, Lemos PA. Aspirin-free prasugrel monotherapy following coronary artery stenting in patients with stable CAD: the ASET Pilot Study. *JACC Cardiovasc Interv* 2020;**13**:2251–2262.
  15. Vranckx P, Valgimigli M, Windecker S, Steg PG, Hamm C, Juni P, Garcia-Garcia HM, van Es GA, Serruys PW. Long-term ticagrelor monotherapy versus standard dual antiplatelet therapy followed by aspirin monotherapy in patients undergoing biolimus-eluting stent implantation: rationale and design of the GLOBAL LEADERS trial. *EuroIntervention* 2016;**12**:1239–1245.
  16. Gao C, Takahashi K, Garg S, Hara H, Wang R, Kawashima H, Ono M, Montalescot G, Haude M, Slagboom T, Vranckx P, Valgimigli M, Windecker S, Hamm C, Steg PG, Storey R, van Geuns RJ, Tao L, Onuma Y, Serruys PW. Regional variation in patients and outcomes in the GLOBAL LEADERS trial. *Int J Cardiol* 2021;**324**:30–37.
  17. Chichareon P, Modolo R, Kerkmeijer L, Tomaniak M, Kogame N, Takahashi K, Chang CC, Komiyama H, Moccetti T, Talwar S, Colombo A, Maillard L, Barlis P, Wykrzykowska J, Piek JJ, Garg S, Hamm C, Steg PG, Juni P, Valgimigli M, Windecker S, Onuma Y, Mehran R, Serruys PW. Association of sex with outcomes in patients undergoing percutaneous coronary intervention: a subgroup analysis of the GLOBAL LEADERS randomized clinical trial. *JAMA Cardiol* 2020;**5**: 21–29.
  18. Tomaniak M, Chichareon P, Modolo R, Takahashi K, Chang CC, Kogame N, Spitzer E, Buszman PE, van Geuns RM, Valkov V, Steinwender C, Geisler T, Prokopcuk J, Sabate M, Zmudka K, Rademaker-Havinga T, Tijssen JGP, Juni P, Hamm C, Steg PG, Onuma Y, Vranckx P, Valgimigli M, Windecker S, Baber U, Anderson R, Dominici M, Serruys PW. Ticagrelor monotherapy beyond one month after PCI in ACS or stable CAD in elderly patients: a pre-specified analysis of the GLOBAL LEADERS trial. *EuroIntervention* 2020;**15**:e1605–e1614.
  19. Ono M, Chichareon P, Tomaniak M, Kawashima H, Takahashi K, Kogame N, Modolo R, Hara H, Gao C, Wang R, Walsh S, Suryapranata H, da Silva PC, Cotton J, Koning R, Akin I, Rensing BJWM, Garg S, Wykrzykowska J, Piek JJ, Juni P, Hamm C, Steg PG, Valgimigli M, Windecker S, Storey RF, Onuma Y, Vranckx P, Serruys PW. The association of body mass index with long-term clinical outcomes after ticagrelor monotherapy following abbreviated dual antiplatelet therapy in patients undergoing percutaneous coronary intervention: a prespecified sub-analysis of the GLOBAL LEADERS Trial. *Clin Res Cardiol* 2020;**109**: 1125–1139.
  20. Chichareon P, Modolo R, Kogame N, Takahashi K, Chang CC, Tomaniak M, Botelho R, Eeckhout E, Hofma S, Trendafilova-Lazarova D, Koszegi Z, Iñiguez A, Wykrzykowska J, Piek JJ, Garg S, Hamm C, Steg PG, Juni P, Vranckx P, Valgimigli M, Windecker S, Onuma Y, Serruys PW. Association of diabetes with outcomes in patients undergoing contemporary percutaneous coronary intervention: pre-specified subgroup analysis from the randomized GLOBAL LEADERS study. *Atherosclerosis* 2020;**295**:45–53.
  21. Tomaniak M, Chichareon P, Klimczak-Tomaniak D, Takahashi K, Kogame N, Modolo R, Wang R, Ono M, Hara H, Gao C, Kawashima H, Rademaker-Havinga T, Garg S, Curzen N, Haude M, Kochman J, Gori T, Montalescot G, Angiolillo DJ, Capodanno D, Storey RF, Hamm C, Vranckx P, Valgimigli M, Windecker S, Onuma Y, Serruys PW, Anderson R. Impact of renal function on clinical outcomes after PCI in ACS and stable CAD patients treated with ticagrelor: a pre-specified analysis of the GLOBAL LEADERS randomized clinical trial. *Clin Res Cardiol* 2020;**109**:930–943.
  22. Kogame N, Chichareon P, De Wilder K, Takahashi K, Modolo R, Chang CC, Tomaniak M, Komiyama H, Chieffo A, Colombo A, Garg S, Louvard Y, Juni P, P GS, Hamm C, Vranckx P, Valgimigli M, Windecker S, Stoll HP, Onuma Y, Janssens L, Serruys PW. Clinical relevance of ticagrelor monotherapy following 1-month dual antiplatelet therapy after bifurcation percutaneous coronary intervention: insight from GLOBAL LEADERS trial. *Catheter Cardiovasc Interv* 2020;**96**: 100–111.
  23. Gao C, Buszman P, Buszman P, Chichareon P, Modolo R, Garg S, Takahashi K, Kawashima H, Wang R, Chang CC, Kogame N, Tomaniak M, Ono M, Hara H, Slagboom T, Aminian A, Naber CK, Carrie D, Hamm C, Steg PG, Onuma Y, Geuns RV, Serruys PW, Zurakowski A. Influence of bleeding risk on outcomes of radial and femoral access for percutaneous coronary intervention: an analysis from the GLOBAL LEADERS trial. *Can J Cardiol* 2021;**37**:122–130.



24. Leonardi S, Branca M, Franzone A, McFadden E, Piccolo R, Jüni P, Vranckx P, Steg PG, Serruys PW, Benit E, Liebetrau C, Janssens L, Ferrario M, Zurakowski A, Diletti R, Dominici M, Huber K, Slagboom T, Buszman P, Bolognese L, Tumscitz C, Bryniarski K, Aminian A, Vrolix M, Petrov I, Garg S, Naber C, Prokopcuk J, Hamm C, Heg D, Windecker S, Valgimigli M. Comparison of investigator-reported and clinical event committee-adjudicated outcome events in GLASSY. *Circ Cardiovasc Qual Outcomes* 2021;**14**:e006581.
25. Serruys PW, Tomaniak M, Chichareon P, Modolo R, Kogame N, Takahashi K, Chang CC, Spitzer E, Walsh SJ, Adlam D, Hildick-Smith D, Edes I, van de Harst P, Krackhardt F, Tijssen JGP, Rademaker-Havinga T, Garg S, Steg PG, Hamm C, Juni P, Vranckx P, Onuma Y, Verheugt FWA. Patient-oriented composite endpoints and net adverse clinical events with ticagrelor monotherapy following percutaneous coronary intervention: insights from the randomized GLOBAL LEADERS trial. *EuroIntervention* 2019;**15**:e1090–e1098.
26. Hara H, van Klaveren D, Takahashi K, Kogame N, Chichareon P, Modolo R, Tomaniak M, Ono M, Kawashima H, Wang R, Gao C, Niethammer M, Fontos G, Angioi M, Ribeiro VG, Barbato E, Leandro S, Hamm C, Valgimigli M, Windecker S, Juni P, Steg PG, Verbeeck R, Tijssen JGP, Sharif F, Onuma Y, Serruys PW, for the GLOBAL LEADERS Investigators. Comparative methodological assessment of the randomized GLOBAL LEADERS trial using total ischemic and bleeding events. *Circ Cardiovasc Qual Outcomes* 2020;**13**:e006660.
27. Franzone A, McFadden EP, Leonardi S, Piccolo R, Vranckx P, Serruys PW, Hamm C, Steg PG, Heg D, Branca M, Juni P, Windecker S, Valgimigli M, Collaborators. Ticagrelor alone or conventional dual antiplatelet therapy in patients with stable or acute coronary syndromes. *EuroIntervention* 2020;**16**:627–633.
28. Tomaniak M, Chichareon P, Onuma Y, Deliangyris EN, Takahashi K, Kogame N, Modolo R, Chang CC, Rademaker-Havinga T, Storey RF, Dangas GD, Bhatt DL, Angiolillo DJ, Hamm C, Valgimigli M, Windecker S, Steg PG, Vranckx P, Serruys PW, for the GLOBAL LEADERS Investigators. Benefit and risks of aspirin in addition to ticagrelor in acute coronary syndromes: a post hoc analysis of the randomized GLOBAL LEADERS trial. *JAMA Cardiol* 2019;**4**:1092–1101.
29. Serruys PW, Takahashi K, Chichareon P, Kogame N, Tomaniak M, Modolo R, Chang CC, Komiyama H, Soliman O, Wykrzykowska JJ, de Winter RJ, Ferrario M, Dominici M, Buszman P, Bolognese L, Tumscitz C, Benit E, Stoll HP, Hamm C, Steg PG, Onuma Y, Juni P, Windecker S, Vranckx P, Colombo A, Valgimigli M. Impact of long-term ticagrelor monotherapy following 1-month dual antiplatelet therapy in patients who underwent complex percutaneous coronary intervention: insights from the Global Leaders trial. *Eur Heart J* 2019;**40**:2595–2604.
30. Takahashi K, Serruys PW, Chichareon P, Chang CC, Tomaniak M, Modolo R, Kogame N, Magro M, Chowdhary S, Eitel I, Zweiker R, Ong P, Ottesen MM, Tijssen JGP, Wykrzykowska JJ, de Winter RJ, Garg S, Stoll HP, Hamm C, Steg PG, Onuma Y, Valgimigli M, Vranckx P, Carrie D, Windecker S. Efficacy and safety of ticagrelor monotherapy in patients undergoing multivessel PCI. *J Am Coll Cardiol* 2019;**74**:2015–2027.
31. Takahashi K, Chichareon P, Modolo R, Kogame N, Chang CC, Tomaniak M, Moschovitis A, Curzen N, Haude M, Jung W, Holmvang L, Garg S, Tijssen JGP, Wykrzykowska JJ, de Winter RJ, Hamm C, Steg PG, Stoll HP, Onuma Y, Valgimigli M, Vranckx P, Windecker S, Serruys PW. Impact of ticagrelor monotherapy on two-year clinical outcomes in patients with long stenting: a post hoc analysis of the global leaders trial. *EuroIntervention* 2019.
32. Takahashi K, Wang R, Kawashima H, Tomaniak M, Gao C, Ono M, Hara H, Wykrzykowska JJ, de Winter RJ, Werner N, Teiger E, Almeida M, Barraud P, Lantelme P, Barlis P, Garg S, Hamm C, Steg PG, Onuma Y, Vranckx P, Windecker S, Valgimigli M, Serruys PW. Efficacy and safety of one-month DAPT followed by 23-month ticagrelor monotherapy in patients undergoing proximal LAD stenting: insights from the GLOBAL LEADERS trial. *Int J Cardiol* 2020;**320**:27–34.
33. Kawashima H, Tomaniak M, Ono M, Wang R, Hara H, Gao C, Takahashi K, Sharif F, Thury A, Suryapranata H, Walsh S, Cotton J, Carrie D, Sabate M, Steinwender C, Leibundgut G, Wykrzykowska J, de Winter RJ, Garg S, Hamm C, Steg PG, Jüni P, Vranckx P, Valgimigli M, Windecker S, Onuma Y, Serruys PW. Safety and efficacy of 1-month dual antiplatelet therapy (ticagrelor + aspirin) followed by 23-month ticagrelor monotherapy in patients undergoing staged percutaneous coronary intervention (a sub-study from GLOBAL LEADERS). *Am J Cardiol* 2021;**138**:1–10.
34. Garg S, Chichareon P, Kogame N, Takahashi K, Modolo R, Chang C-C, Tomaniak M, Fath-Ordoubadi F, Anderson R, Oldroyd KG, Stables RH, Kukreja N, Chowdhary S, Galasko G, Hoole S, Zaman A, Hamm CW, Steg PG, Jüni P, Valgimigli M, Windecker S, Onuma Y, Serruys PW. Impact of established cardiovascular disease on outcomes in the randomized global leaders trial. *Catheter Cardiovasc Interv* 2020;**96**:1369–1378.
35. Gao C, Tomaniak M, Takahashi K, Kawashima H, Wang R, Hara H, Ono M, Montalescot G, Garg S, Haude M, Slagboom T, Vranckx P, Valgimigli M, Windecker S, van Geuns R-J, Hamm C, Steg PG, Onuma Y, Angiolillo DJ, Serruys PW. Ticagrelor monotherapy in patients with concomitant diabetes mellitus and chronic kidney disease: a post hoc analysis of the GLOBAL LEADERS trial. *Cardiovasc Diabetol* 2020;**19**:179.
36. Tomaniak M, Chichareon P, Takahashi K, Kogame N, Modolo R, Chang CC, Spitzer E, Neumann FJ, Plante S, Hernandez Antolin R, Jambrik Z, Gelev V, Brunel P, Konteva M, Beygui F, Morelle JF, Filipiak KJ, van Geuns RJ, Soliman O, Tijssen J, Rademaker-Havinga T, Storey RF, Hamm C, Steg PG, Windecker S, Onuma Y, Valgimigli M, Serruys PW, for the GLOBAL LEADERS Investigators. Impact of chronic obstructive pulmonary disease and dyspnoea on clinical outcomes in ticagrelor treated patients undergoing percutaneous coronary intervention in the randomized GLOBAL LEADERS trial. *Eur Heart J Cardiovasc Pharmacother* 2020;**6**:222–230.
37. Ono M, Tomaniak M, Koenig W, Khamis R, de Silva R, Chichareon P, Kawashima H, Hara H, Gao C, Wang R, Huber K, Vrolix M, Jasonowicz P, Wykrzykowska JJ, Piek JJ, Juni P, Hamm C, Steg PG, Windecker S, Onuma Y, Storey RF, Serruys PW, for the GLOBAL LEADERS Investigators. Impact of white blood cell count on clinical outcomes in patients treated with aspirin-free ticagrelor monotherapy after percutaneous coronary intervention: insights from the GLOBAL LEADERS Trial. *Eur Heart J Cardiovasc Pharmacother* 2020;pvaa110.doi: 10.1093/ehjcvp/pvaa110. Online ahead of print.
38. Wang R, Takahashi K, Chichareon P, Gao C, Kogame N, Modolo R, Tomaniak M, Kawashima H, Ono M, Hara H, Schächinger V, Tonev G, Ungi I, Botelho R, Eekhout E, Hamm C, Jüni P, Vranckx P, Windecker S, Garg S, Van Geuns RJ, Onuma Y, Serruys PW. The impact of pre-procedure heart rate on adverse clinical outcomes in patients undergoing percutaneous coronary intervention: results from a 2-year follow-up of the GLOBAL LEADERS trial. *Atherosclerosis* 2020;**303**:1–7.
39. de Faria AP, Modolo R, Chichareon P, Chang C-C, Kogame N, Tomaniak M, Takahashi K, Rademaker-Havinga T, Wykrzykowska J, de Winter RJ, Ferreira RC, Sousa A, Lemos PA, Garg S, Hamm C, Juni P, Vranckx P, Valgimigli M, Windecker S, Onuma Y, Steg PG, Serruys PW. Association of pulse pressure with clinical outcomes in patients under different antiplatelet strategies after percutaneous coronary intervention: analysis of GLOBAL LEADERS. *Can J Cardiol* 2020;**36**:747–755.
40. Chang CC, Chichareon P, Modolo R, Takahashi K, Kogame N, Tomaniak M, Gao C, Royards KJ, Cequier A, Oldroyd K, Steg PG, Hamm C, Juni P, Valgimigli M, Windecker S, Onuma Y, Stables RH, Jan van Geuns R, Serruys PW. Association between post-percutaneous coronary intervention bivalirudin infusion and net adverse clinical events: a post hoc analysis of the GLOBAL LEADERS study. *Eur Heart J Cardiovasc Pharmacother* 2020;**6**:22–30.
41. Hara H, Takahashi K, Kogame N, Tomaniak M, Kerkmeijer LSM, Ono M, Kawashima H, Wang R, Gao C, Wykrzykowska JJ, de Winter RJ, Neumann FJ, Plante S, Lemos Neto PA, Garg S, Juni P, Vranckx P, Windecker S, Valgimigli M, Hamm C, Steg PG, Onuma Y, Serruys PW. Impact of bleeding and myocardial infarction on mortality in all-comer patients undergoing percutaneous coronary intervention. *Circ Cardiovasc Interv* 2020;**13**:e009177.
42. Louvard Y, Thomas M, Dzavik V, Hildick-Smith D, Galassi AR, Pan M, Burzotta F, Zelisko M, Dudek D, Ludman P, Sheiban I, Lassen JF, Darremont O, Kastrati A, Ludwig J, Iakovou I, Brunel P, Lansky A, Meerkin D, Legrand V, Medina A, Lefevre T. Classification of coronary artery bifurcation lesions and treatments: time for a consensus! *Catheter Cardiovasc Interv* 2008;**71**:175–183.
43. Katsikis A, Chichareon P, Cavalcante R, Collet C, Modolo R, Onuma Y, Stankovic G, Louvard Y, Vranckx P, Valgimigli M, Windecker S, Serruys PW. Application of the MADS classification system in a “mega mammoth” stent trial: feasibility and preliminary clinical implications. *Catheter Cardiovasc Interv* 2019;**93**:57–63.
44. Chichareon P, Onuma Y, van Klaveren D, Modolo R, Kogame N, Takahashi K, Chang CC, Tomaniak M, Asano T, Katagiri Y, van Geuns R-JM, Bolognese L, Tumscitz C, Vrolix M, Petrov I, Garg S, Naber CK, Sabaté M, Iqbal J, Wykrzykowska JJ, Piek JJ, Spitzer E, Jüni P, Hamm C, Steg PG, Valgimigli M, Vranckx P, Windecker S, Serruys PW. Validation of the updated logistic clinical SYNTAX score for all-cause mortality in the GLOBAL LEADERS trial. *EuroIntervention* 2019;**15**:e539–e546.
45. Kawashima H, Hara H, Wang R, Ono M, Gao C, Takahashi K, Suryapranata H, Walsh S, Cotton J, Carrie D, Sabate M, Steinwender C, Leibundgut G, Wykrzykowska J, Hamm C, Juni P, Vranckx P, Valgimigli M, Windecker S, de Winter RJ, Sharif F, Onuma Y, Serruys PW. Usefulness of updated logistic clinical SYNTAX score based on MI-SYNTAX score in patients with ST-elevation myocardial infarction. *Catheter Cardiovasc Interv* 2020;doi: 10.1002/ccd.29383. Online ahead of print.
46. Hara H, Kogame N, Takahashi K, Modolo R, Chichareon P, Tomaniak M, Ono M, Kawashima H, Gao C, Wang R, Valkov VD, Vom Dahl J, Steinwender C, Geisler T, Lemos Neto PA, Macaya Miguel C, Garg S, Jüni P, Hamm C, Steg PG, Valgimigli M, Vranckx P, Windecker S, Farooq V, Onuma Y, Serruys PW; for the GLOBAL LEADERS Trial Investigators. Usefulness of the updated logistic clinical SYNTAX score after percutaneous coronary intervention in patients with prior

- coronary artery bypass graft surgery: insights from the GLOBAL LEADERS trial. *Catheter Cardiovasc Interv* 2020;**96**:E516–e26.
47. Chichareon P, Modolo R, van Klaveren D, Takahashi K, Kogame N, Chang CC, Katagiri Y, Tomaniak M, Asano T, Spitzer E, Buszman P, Prokopczuk J, Fath-Ordoubadi F, Buysschaert I, Anderson R, Oldroyd KG, Merkely B, Garg S, Wykrzykowska JJ, Piek JJ, Juni P, Hamm C, Steg PG, Valgimigli M, Vranckx P, Windecker S, Onuma Y, Serruys PW. Predictive ability of ACEF and ACEF II score in patients undergoing percutaneous coronary intervention in the GLOBAL LEADERS study. *Int J Cardiol* 2019;**286**:43–50.
  48. Kawashima H, Gao C, Takahashi K, Tomaniak M, Ono M, Hara H, Wang R, Chichareon P, Suryapranata H, Walsh S, Cotton J, Koning R, Rensing B, Wykrzykowska J, de Winter RJ, Garg S, Anderson R, Hamm C, Steg PG, Onuma Y, Serruys PW. Comparative assessment of predictive performance of PRECISE-DAPT, CRUSADE, and ACUITY scores in risk stratifying 30-day bleeding events. *Thromb Haemost* 2020;**120**:1087–1095.
  49. Gragnano F, Heg D, Franzone A, McFadden EP, Leonardi S, Piccolo R, Vranckx P, Branca M, Serruys PW, Benit E, Liebetrau C, Janssens L, Ferrario M, Zurawski A, Diletti R, Dominici M, Huber K, Slagboom T, Buszman P, Bolognese L, Tumscitz C, Bryniarski K, Aminian A, Vrolix M, Petrov I, Garg S, Naber C, Prokopczuk J, Hamm C, Steg PG, Juni P, Windecker S, Valgimigli M, for the GLASSY Investigators. PRECISE-DAPT score for bleeding risk prediction in patients on dual or single antiplatelet regimens: insights from the GLOBAL LEADERS and GLASSY. *Eur Heart J Cardiovasc Pharmacother* 2020;pvaa106.doi: 10.1093/ehjcvp/pvaa106. Online ahead of print.
  50. Baber U, Dangas G, Angiolillo DJ, Cohen DJ, Sharma SK, Nicolas J, Briguori C, Cha JY, Collier T, Dudek D, Dzavik V, Escaned J, Gil R, Gurbel P, Hamm CW, Henry T, Huber K, Kastrati A, Kaul U, Kornowski R, Krucoff M, Kunadian V, Marx SO, Mehta S, Moliterno D, Ohman EM, Oldroyd K, Sardella G, Sartori S, Shlofmitz R, Steg PG, Weisz G, Witzencichler B, Han Y-L, Pocock S, Gibson CM, Mehran R. Ticagrelor alone vs. ticagrelor plus aspirin following percutaneous coronary intervention in patients with non-ST-segment elevation acute coronary syndromes: TWILIGHT-ACS. *Eur Heart J* 2020;**41**:3533–3545.
  51. Angiolillo DJ, Baber U, Sartori S, Briguori C, Dangas G, Cohen DJ, Mehta SR, Gibson CM, Chandiramani R, Huber K, Kornowski R, Weisz G, Kunadian V, Oldroyd KG, Ya-Ling H, Kaul U, Witzencichler B, Dudek D, Sardella G, Escaned J, Sharma S, Shlofmitz RA, Collier T, Pocock S, Mehran R. Ticagrelor with or without aspirin in high-risk patients with diabetes mellitus undergoing percutaneous coronary intervention. *J Am Coll Cardiol* 2020;**75**:2403–2413.
  52. Dangas G, Baber U, Sharma S, Giustino G, Mehta S, Cohen DJ, Angiolillo DJ, Sartori S, Chandiramani R, Briguori C, Dudek D, Escaned J, Huber K, Collier T, Kornowski R, Kunadian V, Kaul U, Oldroyd K, Sardella G, Shlofmitz R, Witzencichler B, Ya-Ling H, Pocock S, Gibson CM, Mehran R. Ticagrelor with or without aspirin after complex PCI. *J Am Coll Cardiol* 2020;**75**:2414–2424.
  53. Valgimigli M, Bueno H, Byrne RA, Collet JP, Costa F, Jpeppsson A, Juni P, Kastrati A, Kolh P, Mauri L, Montalescot G, Neumann FJ, Petricevic M, Roffi M, Steg PG, Windecker S, Zamorano JL, Levine GN, Group ESCSD, Guidelines ESCCIP, Societies ESCNC. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS: The Task Force for dual antiplatelet therapy in coronary artery disease of the European Society of Cardiology (ESC) and of the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J* 2018;**39**:213–260.
  54. McClure JD, Ramsay JC, Berry C. Pooled analysis of bleeding, major adverse cardiovascular events, and all-cause mortality in clinical trials of time-constrained dual-antiplatelet therapy after percutaneous coronary intervention. *J Am Heart Assoc* 2020;**9**:e017109.
  55. O'Donoghue ML, Murphy SA, Sabatine MS. The safety and efficacy of aspirin discontinuation on a background of a P2Y(12) inhibitor in patients after percutaneous coronary intervention: a systematic review and meta-analysis. *Circulation* 2020;**142**:538–545.
  56. Hong SJ, Ahn CM, Kim JS, Kim BK, Ko YG, Choi D, Jang Y, Hong MK. Effect of ticagrelor monotherapy on mortality after PCI: a systematic review and meta-analysis of randomized trials including 26143 patients. *Eur Heart J Cardiovasc Pharmacother* 2020;pvaa119. doi: 10.1093/ehjcvp/pvaa119. Online ahead of print.
  57. Giacoppo D, Matsuda Y, Fovino LN, D'Amico G, Gargiulo G, Byrne RA, Capodanno D, Valgimigli M, Mehran R, Tarantini G. Short dual antiplatelet therapy followed by P2Y12 inhibitor monotherapy vs. prolonged dual antiplatelet therapy after percutaneous coronary intervention with second-generation drug-eluting stents: a systematic review and meta-analysis of randomized clinical trials. *Eur Heart J* 2021;**42**:308–319.