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REVIEW

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

Rutao Wang[1,2,3†], Sijing Wu[2,4,5†], Amr Gamal[2,6,7], Chao Gao[1,2,3], Hironori Hara[2,5], Hideyuki Kawashima[2,5], Masafumi Ono[2,5], Robert-Jan van Geuns[3], Pascal Vranckx[8,9], Stephan Windecker[10], Yoshinobu Onuma[2], Patrick W. Serruys[2,11*], and Scot Garg[12]

[1]Department of Cardiology, Xijing Hospital, Changle West Road 127, Xi'an 710032, China; [2]Department of Cardiology, National University of Ireland, Galway (NUIG), University Road, Galway H91 TK33, Ireland; [3]Department of Cardiology, Radboud University Medical Center, Geert Grooteplein Zuid 8, 6525 GA Nijmegen, The Netherlands; [4]Department of Cardiology, Beijing Anzhen Hospital, Anzhen road No.2, Beijing 100029, China; [5]Department of Cardiology, Academic Medical Center, University of Amsterdam, Meibergdreef 9, 1105 AZ Amsterdam, The Netherlands; [6]Department of Cardiology, North Cumbria University Hospitals NHS Trust, Newtown Road, Cumbria CA2 7HY, UK; [7]Department of Cardiology, Zagazig University, Zagazig, Sharkia, 44519, Egypt; [8]Department of Cardiology and Critical Care Medicine, Hartcentrum Hasselt, Jessa Ziekenhuis, Stadsomvaart 11, 3500 Hasselt, Belgium; [9]Faculty of Medicine and Life Sciences, University of Hasselt, Martelarenlaan 42, 3500 Hasselt, Belgium; [10]Department of Cardiology, Bern University Hospital, Freiburgstrasse 4, 3010 Bern, Switzerland; [11]Department of Cardiology, Imperial College London, Exhibition Rd, London SW7 2BX, UK; and [12]Department of Cardiology, East Lancashire Hospitals NHS Trust, Haslingden Rd, Blackburn BB2 3HH, Lancashire, UK

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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 $P2Y_{12}$ 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 • P2Y12 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 $P2Y_{12}$ inhibitor firmly established dual antiplatelet therapy (DAPT) as mandatory treatment following percutaneous coronary intervention (PCI).[1] 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.[2–6] Furthermore, increasing use of more potent $P2Y_{12}$ 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.[7] Over the last decade, this strategy has been assessed in several randomized controlled trials with the GLOBAL LEADERS (GL) trial being the largest.[8–14] Notably, whilst randomized trials have consistently demonstrated the safety and efficacy of $P2Y_{12}$ inhibitor monotherapy compared to DAPT, it has been unclear

* Corresponding author. Tel: +353 91 524411, Email: patrick.w.j.c.serruys@gmail.com
†The first two authors contributed equally to the study.

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).[15] 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.[8]

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,[9,16–23] whilst the Supplementary material online summarizes the *post hoc* analyses[24–49] (*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.[9] 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

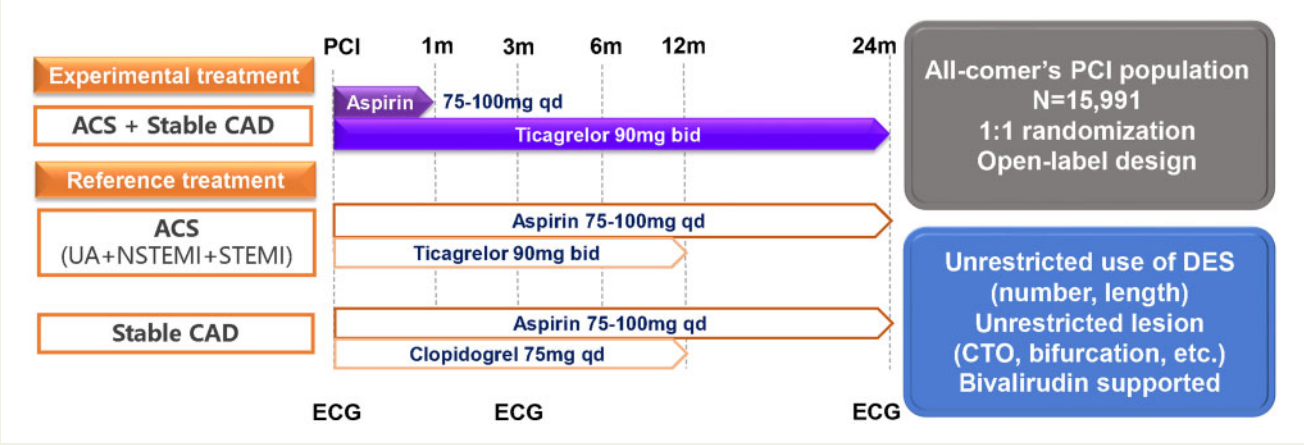

Figure 1 GLOBAL LEADERS trial design.

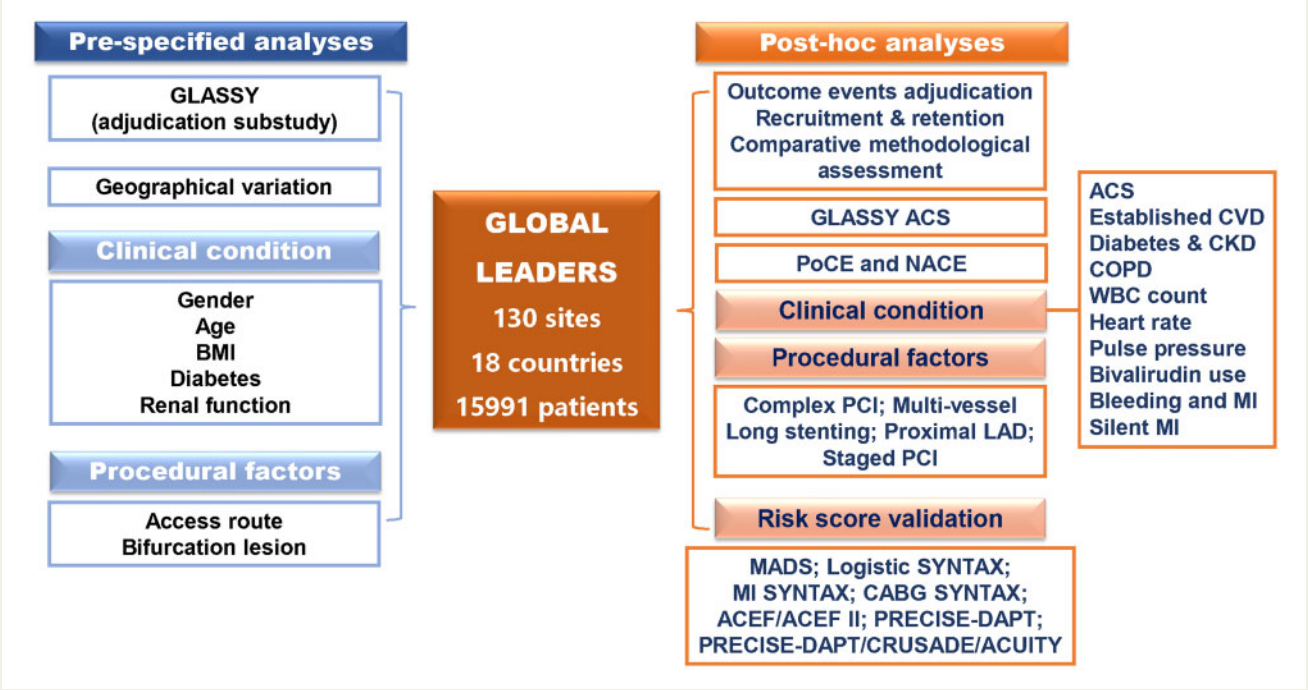

Figure 2 Central illustration for sub-studies in GLOBAL LEADERS trial.

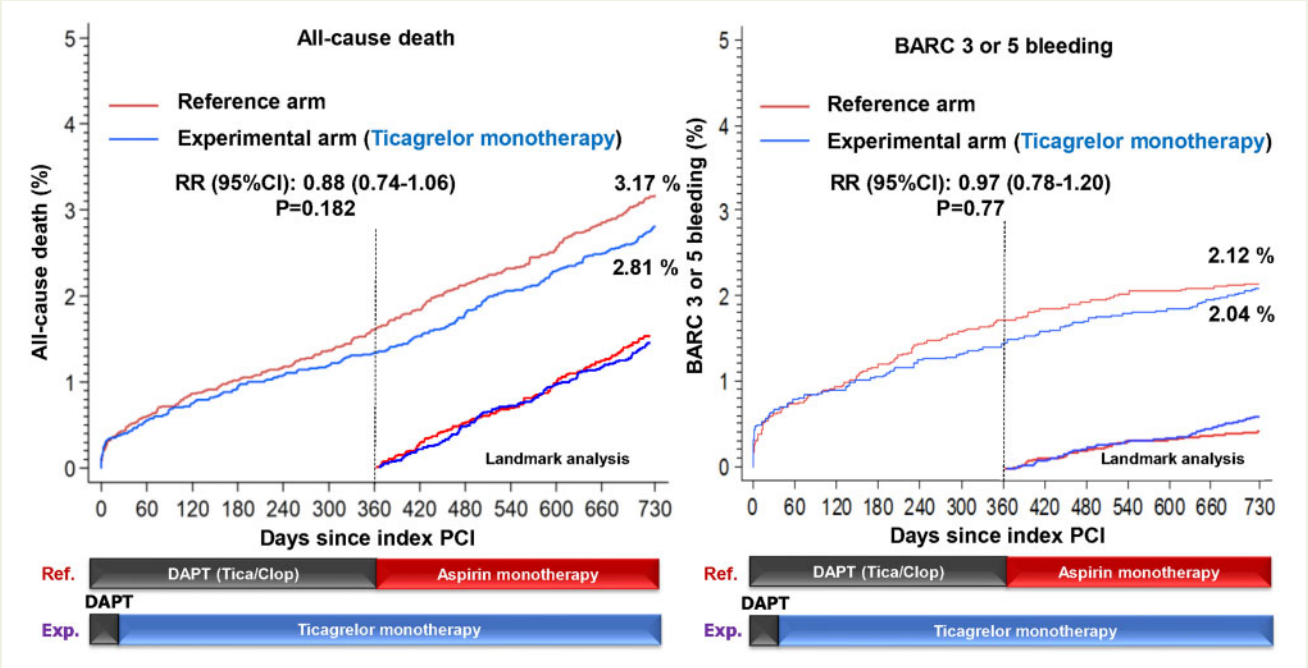

Figure 3 Kaplan–Meier estimate of mortality and safety outcome at 2 years of GLOBAL LEADERS trial.

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

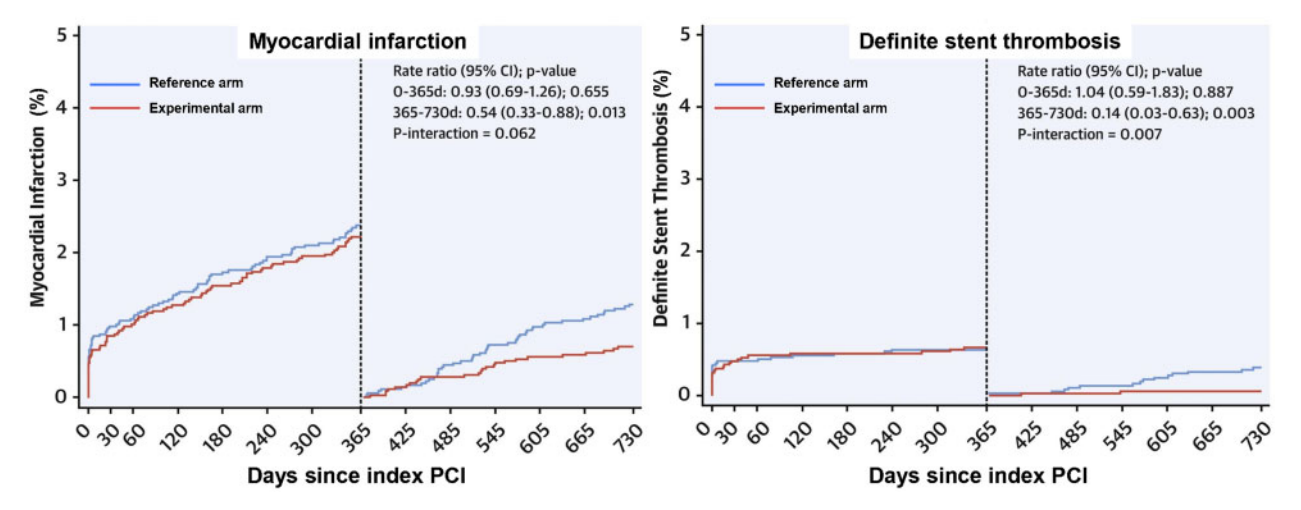

Figure 4 Kaplan–Meier graphs by landmark analysis for MI and definite ST in GLASSY study.

(RR: 0.54, 95% CI: 0.33–0.88, $P_{interaction}$ = 0.062) and definite ST (RR: 0.14, 95% CI: 0.03–0.63, $P_{interaction}$ = 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 ($P_{interaction}$ = 0.027). Amongst measurable factors, differences in the rate of complex PCI were seen as the major contributor to this geographical variation.[16]

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.[17] At 1 year, ticagrelor monotherapy lowered the risk of bleeding in men but not women when compared with standard DAPT ($P_{interaction}$ = 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.[18] 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, $P_{interaction}$ = 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).[19] There was no treatment effect on the primary endpoint in patients with low (<27 kg/m^2) or high (≥27 kg/m^2) BMI. In patients with ACS, however, the primary endpoint was significantly reduced with the experimental strategy in patients with a BMI <27 kg/m^2, which was not observed in those with a BMI ≥27 kg/m^2. 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.[20] 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^2, 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.[21] 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, $P_{interaction}$ = 0.343).[22] In patients having PCI for a bifurcation lesion the experimental treatment was associated with less definite/probable ST ($P_{interaction}$ = 0.027) and more stroke ($P_{interaction}$ = 0.021) compared to standard treatment.

Impact of access route

Gao *et al.*[23] 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 $P2Y_{12}$ 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[12] 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[11] compared the safety and efficacy of 3-month DAPT followed by $P2Y_{12}$ 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%, $P_{non\text{-}inferiority}$ = 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[10] 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,[50] diabetes,[51] and those undergoing complex PCI[52] (*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[53] are being challenged by the results from the ACS sub-groups from the aforementioned studies, together with new dedicated ACS trials such as TICO,[13] 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[14] 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

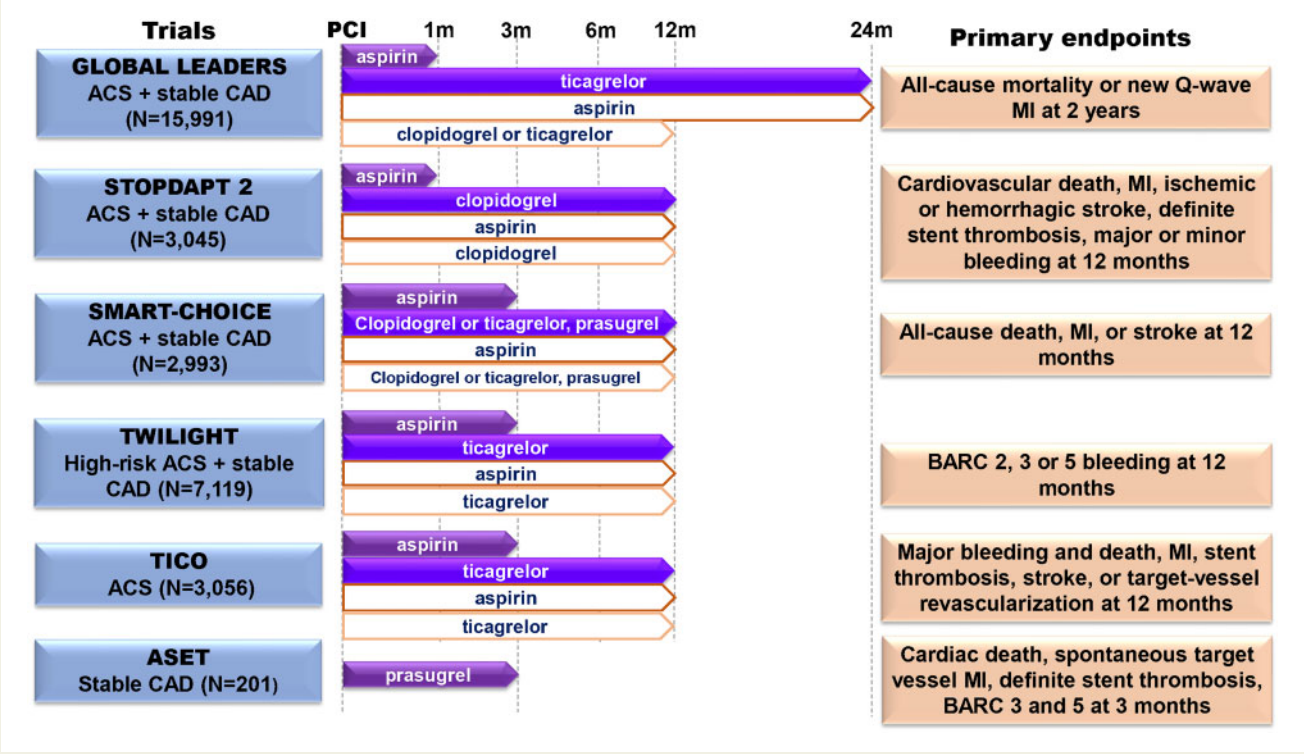

Figure 5 Trials of aspirin-free antiplatelet therapies.

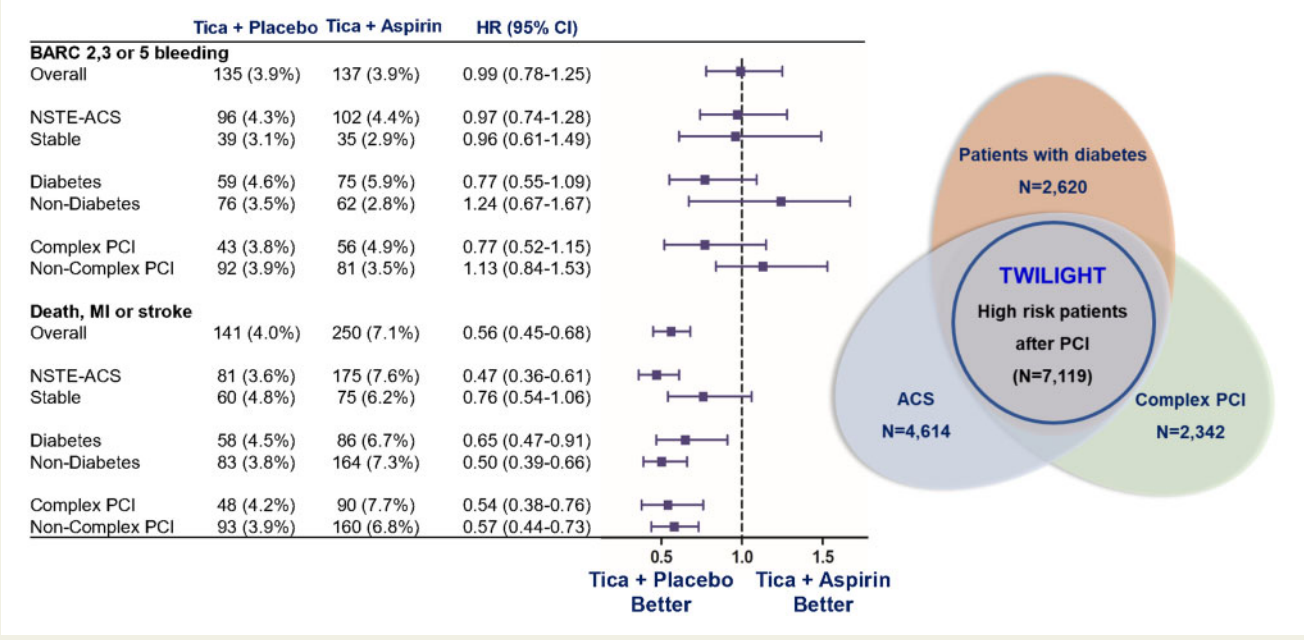

Figure 6 The main findings and subgroup analyses from TWILIGHT trial.

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-constraint DAPT followed by $P2Y_{12}$ inhibitor monotherapy from 1 to 3 months post-PCI to standard DAPT.[54–57] McClure *et al.*[54] and O'Donoghue *et al.*[55] separately pooled results from over 32,000 patients enrolled in the same five randomized studies and showed that $P2Y_{12}$ 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.[54,55] Similarly, a meta-analysis by Hong *et al.*,[56] 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, $P = 0.01$, $I_2 = 65\%$, number needed to treat for benefit (NNTB) = 156], and all-cause mortality (RR: 0.80, 95% CI: 0.65–0.98, $P = 0.03$, $I_2 = 0\%$, NNTB = 320). There appeared to be no evidence of benefit with prolonged DAPT. More recently, Giacoppo *et al.*[57] performed a systematic review and meta-analysis of short DAPT followed by $P2Y_{12}$ 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 $P2Y_{12}$ 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 ($P2Y_{12}$ 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.[57]

These results support a strategy of discontinuing aspirin from 3 months post-PCI and continuing with 'aspirin-free' $P2Y_{12}$ 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 $P2Y_{12}$ 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 $P2Y_{12}$ 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 $P2Y_{12}$ inhibitor.

Supplementary material

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

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