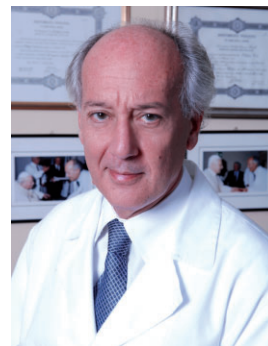


Percutaneous coronary interventions: more complex than fixing stenoses

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For over 20 years, a combination of aspirin and a P2Y₁₂ inhibitor has been the mainstay antithrombotic strategy in patients undergoing percutaneous coronary intervention (PCI).^{1,2} This drug combination, referred to as dual antiplatelet therapy (DAPT), has been proven superior to aspirin alone in preventing cardiovascular events after stent implantation, although at the expense of increased bleeding. Contemporary advances in device technologies and pharmacological strategies have allowed PCI to be extended to older and more vulnerable cohorts. As such, an increasing number of patients undergoing PCI have high bleeding risk (HBR) conditions, which make a standard DAPT regimen clinically undesirable. The TWILIGHT trial recently demonstrated that ticagrelor monotherapy after a short course of DAPT is an effective and safe bleeding avoidance strategy among high-risk patients undergoing PCI.^{3–5} This Focus Issue on Interventional Cardiology contains the Fast Track contribution ‘**Ticagrelor monotherapy in patients at high bleeding risk undergoing percutaneous coronary intervention: TWILIGHT-HBR**’ by Javier Escanero from the Complutense University of Madrid in Spain, and colleagues.⁶ This pre-specified analysis of the TWILIGHT trial evaluated the treatment effects of early aspirin withdrawal followed by ticagrelor monotherapy in HBR patients undergoing PCI with drug-eluting stents. After 3 months of ticagrelor plus aspirin, event-free patients were randomized to 12 months of aspirin or placebo in addition to ticagrelor. A total of 1064 patients (17%) met the Academic Research Consortium definition for HBR.^{7,8} Ticagrelor monotherapy reduced the incidence of the primary endpoint of Bleeding Academic Research Consortium (BARC) 2, 3, or 5 bleeding compared with ticagrelor plus aspirin in HBR [6.3% vs. 11.4%; hazard ratio (HR) 0.53] and non-HBR patients (3.5% vs. 5.9%; HR 0.59) with similar relative risk reduction (*P* for interaction = 0.67) but a trend towards greater absolute risk

reduction in the former [–5.1% vs. –2.3%; difference in absolute risk differences (ARDs) –2.8, *P* = 0.130]. A similar pattern was observed for more severe BARC 3 or 5 bleeding with a larger absolute risk reduction in HBR patients (–3.5% vs. –0.5%; difference in ARDs –3.0%, *P* = 0.008). There was no significant difference in the key secondary endpoint of death, myocardial infarction (MI), or stroke between treatment arms, irrespective of HBR status (Figure 1).

The authors conclude that among HBR patients undergoing PCI who completed 3-month DAPT without experiencing major adverse events, aspirin discontinuation followed by ticagrelor monotherapy significantly reduced bleeding without increasing ischaemic events, compared with ticagrelor plus aspirin. The absolute risk reduction in major bleeding was larger in HBR than in non-HBR patients. The contribution is accompanied by an **Editorial** by Zuzana Motovska from the Charles University and University Hospital Kralovske Vinohrady in Prague, Czech Republic, and colleagues.⁹ The authors note that the TWILIGHT-HBR analysis raises new questions in the field of antithrombotic therapy management. How should we deal with long-term (>15 months) antiplatelet treatment after PCI? Should we continue with ticagrelor monotherapy, or rather switch to clopidogrel or aspirin? Or even aspirin plus rivaroxaban? Before deciding, it is essential that the patients’ risk profile is re-evaluated. It should also be emphasized that carefully considering the patient’s preference, whose compliance with treatment fundamentally affects its benefits, is crucial when deciding on the long-term treatment plan.

The value of elective coronary revascularization plus medical therapy over medical therapy alone in managing stable patients with coronary artery disease is debated.^{10–12} In another Fast Track Clinical Research article entitled ‘**Cardiac mortality in patients randomized to elective coronary revascularization plus medical therapy or medical therapy alone: a systematic review and meta-analysis**’, Eliano Navarese from the University of Alberta in Canada, and colleagues reviewed all trials comparing the two strategies in this population.¹³ From inception through

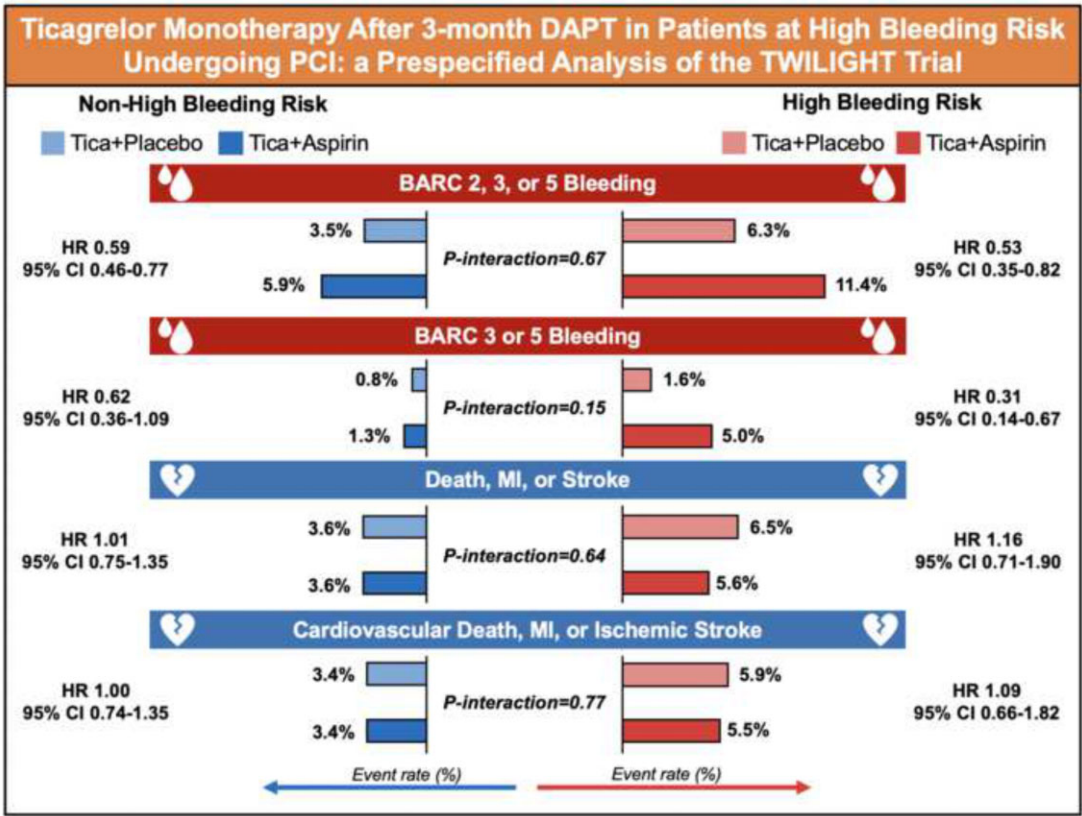


Figure 1 Effects of ticagrelor plus placebo vs. ticagrelor plus aspirin on bleeding and ischaemic events among HBR and non-HBR patients who tolerated 3 months of DAPT after PCI with a drug-eluting stent. HBR, high bleeding risk; PCI, percutaneous coronary intervention; DAPT, dual antiplatelet therapy; tica, ticagrelor; HR, hazard ratio; CI, confidence interval; BARC, Bleeding Academic Research Consortium; MI, myocardial infarction. (from Escaned J, Cao D, Baber U, Nicolas J, Sartori S, Zhang Z, Dangas G, Angiolillo DJ, Briguori C, Cohen DJ, Collier T, Dudek D, Gibson M, Gil R, Huber K, Kaul U, Kornowski R, Krucoff MW, Kunadian V, Mehta S, Moliterno DJ, Ohman EM, Oldroyd KG, Sardella G, Sharma SK, Shlofmitz R, Weisz G, Witzenbichler B, Pocock S, Mehran R. Ticagrelor monotherapy in patients at high bleeding risk undergoing percutaneous coronary intervention: TWILIGHT-HBR. See pages 4624–4634)

November 2020, MEDLINE, EMBASE, Google Scholar, and other databases were searched for randomized trials comparing revascularization against medical therapy alone in clinically stable coronary artery disease patients. Treatment effects were measured by rate ratios (RRs) with 95% confidence intervals, using random-effects models. Cardiac mortality was the pre-specified primary endpoint. Spontaneous MI was a secondary endpoint. The longest follow-up data were abstracted. Twenty-five trials involving 19 806 patients (10 023 randomized to revascularization plus medical therapy and 9783 to medical therapy alone) were included. Compared with medical therapy alone, revascularization yielded a lower risk of cardiac death (RR 0.79, $P < 0.01$) and spontaneous MI (RR 0.74, $P < 0.01$), while all-cause mortality (0.94, $P = 0.11$) and any MI ($P = 0.14$) did not differ significantly between strategies.

The authors conclude that in stable coronary artery disease patients, randomization to elective coronary revascularization plus medical therapy leads to reduced cardiac mortality compared with medical therapy alone. The cardiac survival benefit after revascularization improves with longer follow-up times and is associated with fewer spontaneous MIs. The article is accompanied by an **Editorial**

by William Boden from the Boston University School of Medicine and David Brown from the Washington University School of Medicine in the USA.¹⁴ Boden and Brown highlight that trial-level meta-analysis of agnostically selected studies with minimal clinical and statistical heterogeneity that assess relevant, patient-centric endpoints can provide accurate, objective, and clinically meaningful estimates of the effect size of one therapy vs. another. The authors hope readers of this paper will be both circumspect and wise in interpreting the totality of evidence that should inform our beliefs and decision-making in the guideline-endorsed management of chronic coronary syndrome (CCS) patients—namely, an ‘optimal medical therapy (OMT) first’ approach to reduce symptoms and events and one which considers revascularization only for improvement of quality of life in those whose symptoms are either unresponsive or refractory to OMT.

Fractional flow reserve (FFR)-guided revascularization, as compared with angiography-guided PCI, improves the outcome.¹⁵ The utility of measuring FFR after PCI is less certain, but post-PCI FFR values are reported to be inversely associated with adverse cardiac events. In a third Fast Track Clinical Research article entitled ‘Post-

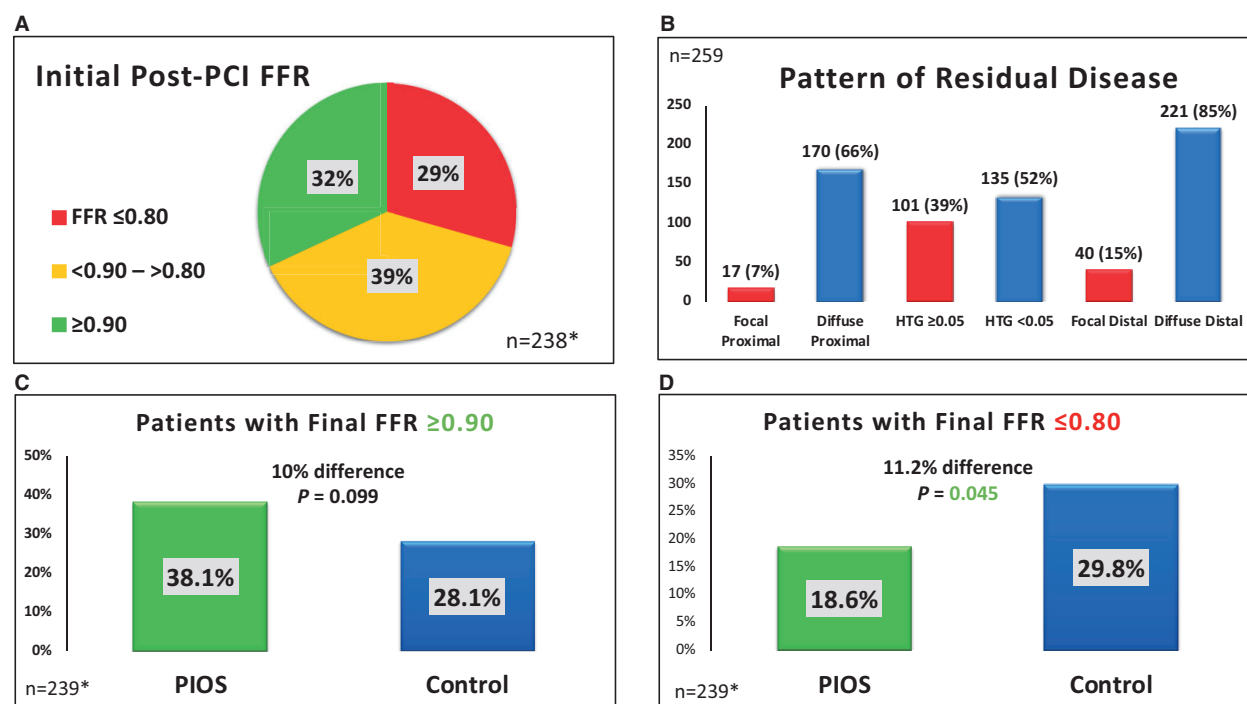


Figure 2 Key findings of the TARGET-FFR randomized trial, (from Collison D, Didagelos M, Aetesam-Ur-Rahman M, Copt S, McDade R, McCartney P, Ford TJ, McClure J, Lindsay M, Shaukat A, Rocchiccioli P, Brogan R, Watkins S, McEntegart M, Good R, Robertson K, O'Boyle P, Davie A, Khan A, Hood S, Eteiba H, Berry C, Oldroyd KG. Post-stenting fractional flow reserve vs. coronary angiography for optimization of percutaneous coronary intervention: TARGET-FFR trial. See pages 4656–4668).

stenting fractional flow reserve vs. coronary angiography for optimization of percutaneous coronary intervention (TARGET-FFR), Damien Collison from the University of Glasgow in the UK, and colleagues note that TARGET-FFR is an investigator-initiated, single-centre, randomized controlled trial to determine the feasibility and efficacy of a post-PCI FFR-guided optimization strategy vs. standard coronary angiography in achieving final post-PCI FFR values ≥ 0.90 .¹⁶ After angiographically guided PCI, patients were randomized 1:1 to receive a physiology-guided incremental optimization strategy (PIOS) or a blinded coronary physiology assessment (control group). The primary outcome was the proportion of patients with a final post-PCI FFR ≥ 0.90 . Final FFR ≤ 0.80 was a prioritized secondary outcome. A total of 260 patients were randomized. In the PIOS group, 30.5% underwent further intervention (stent post-dilation and/or additional stenting). There was no significant difference in the primary endpoint of the proportion of patients with final post-PCI FFR ≥ 0.90 between groups ($P = 0.099$). The proportion of patients with a final FFR ≤ 0.80 was significantly reduced when compared with the angiography-guided control group (-11.2% , $P = 0.045$).

The authors conclude that over two-thirds of patients had a physiologically suboptimal result after angiography-guided PCI. An FFR-guided optimization strategy does not significantly increase the proportion of patients with a final FFR ≥ 0.90 but it does reduce the proportion of patients with a final FFR ≤ 0.80 (Figure 2).

The article is accompanied by an **Editorial** by David Erlinge and Matthias Götberg from Lund University in Sweden.¹⁷ The two

conclude that Collison *et al.* should be congratulated for completing a well-performed randomized trial on the important question of post-PCI physiology. Interventionalists should be encouraged to make physiological measurements including pullback to identify patterns of disease not only before PCI but also after stenting to understand the physiological effect of their procedure, and to optimize the results. Whether this will result in an improvement in clinical outcome remains to be demonstrated by larger randomized trials.

Evidence suggests that in some patient categories, such as those with diabetes mellitus (DM) and/or acute coronary syndromes (ACS), decision-making on revascularization based on FFR is associated with an excess of cardiovascular events, compared with patients without such clinical features. It has been proposed that atherosclerosis progression and destabilization of angiographically intermediate medically treated lesions is considerable, particularly in DM patients, and responsible for the majority of the adverse events during the follow-up.^{18–20} In a Clinical Research article entitled '**Thin-cap fibroatheroma predicts clinical events in diabetic patients with normal fractional flow reserve: the COMBINE OCT-FFR trial**', Elvin Kedhi from the Medical University of Silesia in Poland, and colleagues sought to understand the impact of optical coherence tomography (OCT)-detected thin-cap fibroatheroma (TCFA) on clinical outcomes of DM patients with fractional FFR-negative lesions.²¹ The COMBINE OCT-FFR study was a prospective, double-blind, international, natural history study. After FFR assessment, and revascularization of FFR-positive lesions, patients with ≥ 1 FFR-

negative lesions (target lesions) were classified in two groups based on the presence or absence of ≥ 1 TCFA lesion. The primary endpoint compared FFR-negative TCFA-positive patients with FFR-negative TCFA-negative patients for a composite of cardiac mortality, target vessel MI, clinically driven target lesion revascularization, or unstable angina requiring hospitalization at 18 months. Among 550 patients enrolled, 81% patients had ≥ 1 FFR-negative lesions. Among FFR-negative patients, 25% were TCFA positive and 75% were TCFA negative. The incidence of the primary endpoint was 13.3% and 3.1% in TCFA-positive vs. TCFA-negative groups, respectively ($P < 0.001$). The Cox regression multivariable analysis identified TCFA as the strongest predictor of MACE (major adverse clinical events) (HR 5.12; $P < 0.001$).

The authors conclude that among DM patients with ≥ 1 FFR-negative lesions, TCFA-positive patients represent 25% of this population and are associated with a five-fold higher rate of MACE despite the absence of ischaemia. This discrepancy between the impact of vulnerable plaque and ischaemia on future adverse events may represent a paradigm shift for coronary artery disease risk stratification in DM patients. This manuscript is accompanied by an **Editorial** by Rasha Al-Lamee from Imperial College London and Gary Mintz from the Cardiovascular Research Foundation in New York.²² The authors conclude that we may need to move away from the concept that ischaemia is the major driver of events and consider that it is only a surrogate for the burden of atherosclerosis. The contribution of plaque morphology to future events needs to be considered. More study is needed to direct its detection, and effective treatment strategies need to be developed.

In a Clinical Research article entitled '**Ticagrelor monotherapy in patients with chronic kidney disease undergoing percutaneous coronary intervention: TWILIGHT-CKD**' Giulio Stefanini from the Humanitas University in Milan, Italy, and colleagues sought to assess the impact of chronic kidney disease (CKD) on the safety and efficacy of ticagrelor monotherapy among patients undergoing PCI.³ In this pre-specified subanalysis of the TWILIGHT trial, the authors evaluated the treatment effects of ticagrelor with or without aspirin according to renal function. A total of 1111 patients (16.3%) had CKD (estimated glomerular filtration rate < 60 mL/min/1.73 m²). Ticagrelor plus placebo reduced the primary endpoint of BARC type 2, 3, or 5 bleeding as compared with ticagrelor plus aspirin in both patients with (4.6% vs. 9.0%; HR 0.50) and without (4.0% vs. 6.7%; HR 0.59; P for interaction = 0.508) CKD, but the absolute risk reduction was greater in the former group. Rates of death, MI, or stroke were not significantly different between the two randomized groups irrespective of the presence or absence of CKD.

Stefanini and colleagues conclude that among CKD patients undergoing PCI, ticagrelor monotherapy reduces the risk of bleeding without a significant increase in ischaemic events as compared with ticagrelor plus aspirin. The contribution is accompanied by an **Editorial** by Robert Storey and William Parker from the University of Sheffield in the UK.²³ The authors conclude that further insights may be gained from the ongoing Duration of Dual Anti-Platelet Therapy (DUAL-ACS, NCT03252249) trial that is planning to randomize ~19 000 patients with ACS to 3 or 12 months of DAPT,

albeit in an open-label fashion. In the meantime, current ESC Guidelines recommend, except in those with contraindications or excessive bleeding risk, DAPT for ≥ 6 months after PCI for CCS and ≥ 12 months for ACS, including in those with CKD.

The issue is also complemented by two Discussion Forum contributions. In a commentary entitled '**Cardiac death should be the primary endpoint for revascularization trials and meta-analyses**', Harvey D. White from the Auckland City Hospital in New Zealand and colleagues comment on the article published in this issue entitled '**Cardiac mortality in patients randomized to elective coronary revascularization plus medical therapy or medical therapy alone: a systematic review and meta-analysis**' by Eliano Navarese from the University of Alberta in Canada.^{13,24} Navarese et al. respond in a separate comment.²⁵

The editors hope that this issue of the *European Heart Journal* will be of interest to its readers.

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