

Editorial

Prolonged double antiplatelet therapy vs association of antiplatelet and low dose of anticoagulant therapy: PEGASUS or COMPASS?

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Two recent trials will deeply affect the clinical management of patients with coronary artery disease (CAD), peripheral artery disease (PAD) and ischemic heart disease (IHD).

The Prevention of Cardiovascular Events in Patients With Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin-Thrombolysis in Myocardial Infarction 54 (PEGASUS-TIMI 54) trial, published in 2015, showed as 60 mg ticagrelor BID may significantly reduce the incidence of the primary composite endpoint of cardiovascular death, myocardial infarction, or stroke (hazard ratio 0.84; 95% CI, 0.74 to 0.95, $p < 0.01$) [1]. The study was the first to show a clinical benefit of prolonged dual anti-platelet therapy (DAPT), beyond the first year after an acute myocardial infarction, although with a reduced dose of second additional anti-platelet drug.

The Cardiovascular Outcomes for People Using Anticoagulation Strategies (COMPASS) Trial, instead, explored a novel alternative approach for the treatment of CAD and PAD, with a dual anti-thrombotic therapy (DATT, anti-platelet plus low dose anti-coagulant drug). The primary outcome cardiovascular death, stroke, or myocardial infarction occurred in fewer patients in the rivaroxaban 2.5 mg OD -plus-aspirin group than in the aspirin-alone group (hazard ratio, 0.76; 95% confidence interval 0.66 to 0.86, $p < 0.001$) [2].

With such compelling evidence supporting this couple of novel options for the treatment of stable CAD, the clinical scenario, and international guidelines, are likely to change in the near future. Studies on large clinical registries show 40% possible eligibility rates for both the PEGASUS and COMPASS profiles [3,4]. According to real-life clinical registries, however, the actual implementation of ticagrelor 60 mg based

DAPT is far from being acceptable; <12% of patient are treated with DAPT after the first year following an acute myocardial infarction (AMI) [3] and negligible rates of patients are treated with ticagrelor 60 mg BID in some countries [5].

The same eligibility studies revealed a 70% overlap in eligibility between PEGASUS and COMPASS criteria [4].

Facing therefore this duplicity of options, the raising question is: Who could benefit most from PEGASUS rather than from COMPASS approach among CAD patients? Or, again, which is the optimal PEGASUS rather than COMPASS profile among potential eligible CAD patients?

After a careful examination of both PEGASUS and COMPASS inclusion and exclusion criteria [6,7], excluding some overt contraindications (breastfeeding, poor life expectancy, very recent bleeding) the following flow-chart could be used for the identification for the optimal choice. The flowchart is not intended to identify those subjects that, once treated with either ticagrelor 60 mg BID or rivaroxaban 2.5 mg plus aspirin, would benefit more from the treatment, as shown in several sub-group analyses from randomized studies (multi-vessels coronary disease [8], more recent acute myocardial infarction [9], PAD in CAD [10]). The table is merely intended to be useful in helping the clinical management and a wise choice between either the PEGASUS or the COMPASS approach in patients eligible for both, exclusively according to inclusion and exclusion criteria.

We therefore found that, when subjects with CAD/PAD do not present with high bleeding risk, history of hemorrhagic stroke or intracranial bleeding, severe liver disease, dialysis, and none of the following points, both the PEGASUS and the COMPASS treatment can be used: PAD without CAD, AMI > 3 years earlier, central nervous system tumour, intracranial vascular abnormality, gastro-intestinal bleeding

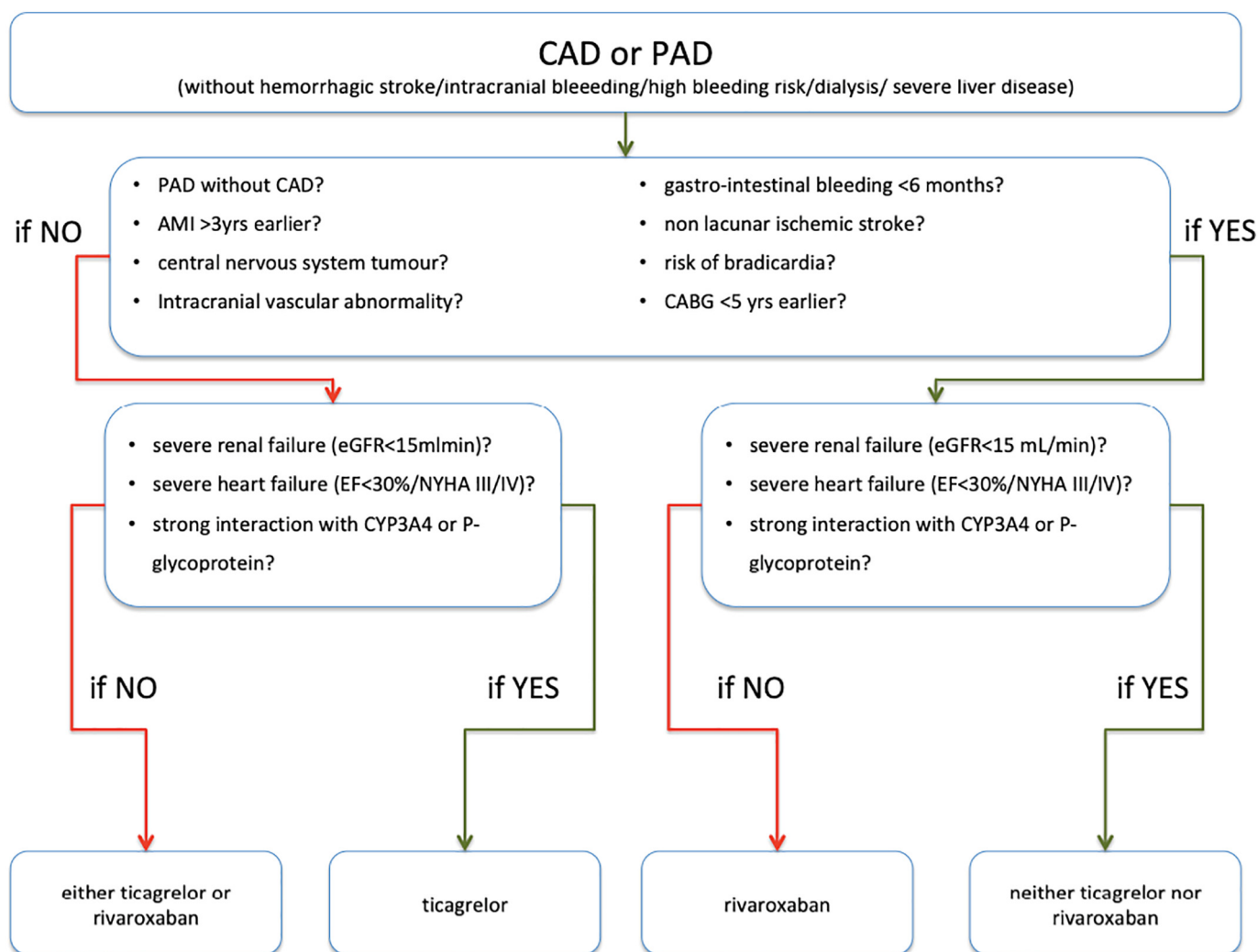


Fig. 1. Flowchart indicating ticagrelor, rivaroxaban, either or neither (green, yes-option; red, no-option). Patients with eGFR<15 mL/min not in dialysis could be potentially candidate for ticagrelor 60 mg bid. Legend. CAD, coronary artery disease; PAD, peripheral artery disease; AMI, acute myocardial infarction; CABG, coronary aortic bypass grafting; Renal failure, estimated glomerular filtration rate < 15 mL/min; Heart Failure, left ventricular ejection fraction < 30% or New York Heart Association class III or IV symptoms (as reported in the COMPASS trial).

< 6 months, non-lacunar ischemic stroke, risk of bradycardia, CABG < 5 years earlier (Fig. 1).

In this case, the choice between PEGASUS and COMPASS should be based on the presence of severe renal failure (estimated glomerular filtration rate < 15 mL/min), severe heart failure (known ejection fraction < 30% or New York Heart Association class III or IV symptoms) or strong interaction with CYP3A4 or P-glycoprotein, which indicate the PEGASUS approach. When instead the PEGASUS approach is excluded, the same points contraindicate any PEGASUS nor COMPASS approach. Alternatively, a COMPASS approach is indicated.

The hope is that, a little guidance in this Buridan's dilemma, would eventually improve the appropriateness of treatment in all potentially eligible PEGASUS and COMPASS patients. A direct comparison between the strategies should be probably tested in future clinical trial.

Declaration of Competing Interest

No conflict of interest to disclose.

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