The COMBO stent: real-world patients *vs.* objective performance criteria

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Editorial

Drug-eluting stents (DES) are broadly used in percutaneous coronary interventions (PCI) because they have shown to reduce stent restenosis and improve cardiovascular outcomes compared with bare metal stents (BMS) [1,2]. The improvement in stent design and materials has come at the cost of needing longer dual antiplatelet therapy (DAPT) post-PCI [3]. To overcome the increased risk of bleeding complications, the COMBO dual therapy stent (OrbusNeich Medical, Hong Kong) has emerged as an alternative to the initial DES technology. The COMBO stent combines the antiproliferative drug sirolimus with an anti-CD34+ antibody which aims to attract circulating endothelial progenitor cells and therefore promote a fast re-endothelization. The efficacy and safety of the COMBO stent has been previously tested in randomized clinical trials (RCTs) and real-life registries, with inconsistent results [4].

In this issue of the journal, Nardin *et al.* [4] report the findings of the Mega COMBO Collaboration, a systematic review of the literature including 5 RCTs and 2 registries that evaluated the COMBO stent. They collected individual-level data from 6753 patients who underwent a PCI with at least one COMBO stent. The study population of this collaborative work was comparable to contemporary studies (only 23% were women) [5,6] whereas 62,8% had an acute coronary syndromes (ACS) [2]. At study design level, the most relevant feature is the lack of a comparator (i.e., control group), and the use of objective performance criteria. This means that the COMBO stent was not tested against a control group (such a different type of stent). Alternatively, both primary and secondary endpoints were compared with established performance goals, provided by an expert consensus paper of the European Association of Percutaneous Coronary Intervention (EAPCI) [1].

Despite a high rate of complex PCI cases (~45%), the COMBO stent showed an apparent acceptable performance. At 1-year follow-up post-PCI, the primary endpoint target lesion failure (composite of cardiovascular death, target vessel-myocardial infarction or clinically driven target

lesion revascularization) occurred in 4.6% patients. Secondary endpoints included the individual components of the composite: 1-year cardiovascular death (1.3%), target-vessel myocardial infarction (1.8%), and clinically driven target-lesion revascularization (2.5%). There were also other secondary endpoints meeting the performance standards suggested by the EAPCI [1].

The main strength of this study is emphasized by the effort to pool the largest cohort of patients exclusively treated with at least one COMBO stent. The main limitation is the lack of an active comparator. Although comparisons against standards of care (in this case, expected outcomes) defined by expert consensus papers has been conducted in other cardiovascular fields [7], the reality is that such comparisons are a step below the formal comparison against an active comparator provided by adequately powered RCTs.

In the light of the nature of the comparator group in this study (i.e., standards defined by a Task Force), several issues should be discussed. First, whether the upper interquartile range of the outcome reference value is enough to prove efficacy is a matter of debate. According to the systematic review of the expert consensus paper, the estimated rate of all-cause death was 1.92% (IQR 1.05–2.54%), hence the upper interquartile boundary (2.54%) was below the 2.44% reported in the Mega COMBO Collaboration. But most importantly, the EAPCI document did not provide an objective performance criterion for the primary endpoint of the Mega COMBO Collaboration (target lesion failure), raising the question about whether solid conclusions about efficacy can be made from this large cohort of pooled patients. Second, whether clinical practice and outcomes have changed between 2002-2013 (when the systematic review of RCTs supporting the evidence provided by EAPCI document was performed), and 2022 are also open to debate. Third, there is the issue of representativeness. The performance goals obtained from EAPCI were derived from 158 RCTs on DES. Whether RCT participants might be representative of real-world patients is another long-lasting discussion [8]. Although event rates in registry patients are usually higher, it should be acknowledged that the Mega COMBO collaboration

included ~50% of patients from registries. Therefore, the comparison might be actually biased towards the null hypothesis (i.e., favouring the lack of treatment effect), hence reinforcing the hypothesis-generating findings suggesting a potential treatment effect against the objective performance criteria. Finally, the evaluation of DAPT (reported in supplementary material) was suboptimal because the heterogeneity of data sources: SORT OUT X trial [9] did not collect data on DAPT, and the REDUCE trial [10] randomized DAPT duration to 3 *vs.* 12 months. Subsequent studies should elucidate the impact of different DAPT strategies on the treatment effect of the COMBO stent, since this topic is probably one of the most relevant innovations that the COMBO stent could bring to clinical practice.

In conclusion, the Mega COMBO Collaboration shows that the COMBO stent might be a reasonable alternative to new generation DES when compared with performance goals. Nevertheless, the efficacy of this stent technology should be confirmed in adequately powered RCTs aimed to provide evidence in head-to-head comparisons between different types of stents.

Declaration of Competing Interest

The authors report no relationships that could be construed as a conflict of interest.

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