

Optimal Antithrombotic Strategy in NSTEMACS: Is Age Just a Number?

Estrategia antitrombótica óptima en SCASEST: ¿es la edad sólo un número?

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*Age is an issue of mind over matter.
If you don't mind, it doesn't matter.*

MARK TWAIN

Twenty years after the publication of the first randomized clinical trial (RCT) (1) reporting the ischemic benefits of the combination of clopidogrel plus aspirin versus aspirin alone, at the cost of increased bleeding, dual antiplatelet therapy (DAPT) still represents the cornerstone for the management of acute coronary syndrome (ACS). Furthermore, two pivotal RCTs demonstrated that the use of more potent P2Y₁₂ inhibitors (prasugrel or ticagrelor) was associated with a further reduction of ischemic events compared with clopidogrel, counterbalanced by an excess of major bleeding, which was particularly evident with prasugrel in the subgroup of elderly patients (2,3). Focusing on their comparative effectiveness, recent major meta-analyses reported similar clinical efficacy and safety of prasugrel and ticagrelor in patients with ACS (4,5). Moreover, further research underlined that extended DAPT beyond one-year provided marginal ischemic reduction counterbalanced by an increased rate of major bleedings, especially in frail patients, obviously including elderly individuals (6,7).

Today, cardiologists have many alternatives in terms of antithrombotic strategies, including choice of P2Y₁₂ inhibitor, and DAPT duration (Figure 1) (8). Despite the fact that 2020 European Society of Cardiology (ESC) guidelines on non-ST-elevation acute coronary syndromes (NSTEMACS) provided useful recommendations to individualize antithrombotic regimens and guide DAPT duration on the basis of bleeding and ischemic risk, the prediction of recurrent ischemic events and occurrence of bleeding events remains challenging (9). Therefore, further antithrombotic strategies have been developed with the aim of improving safety without any trade-off in ischemic events.

Among many publications in this field, the POPular AGE study advocated that a clopidogrel-based DAPT should be preferred over a ticagrelor-based DAPT for patients over 70 years old, as the former strategy was associated with less bleeding events without an increased risk of major adverse cardiovascular events (MACE). (10)

Nevertheless, the conclusion of the authors may be challenged.

Indeed, in addition to the well documented methodological limitations of an open-label study, a high number of patients that discontinued the investigated P2Y₁₂ inhibitor should be highlighted, with a premature discontinuation of the study drug in 47% of the ticagrelor group and in 22% of 500 patients randomly assigned to clopidogrel.

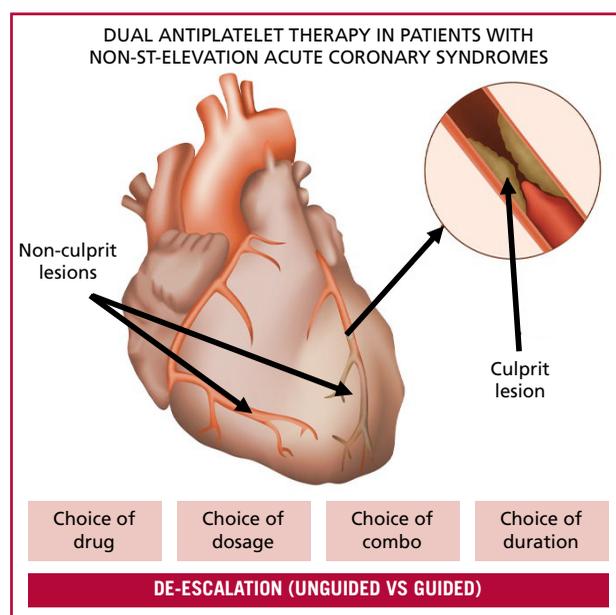


Fig. 1. Modern approach to dual antiplatelet therapy for non-ST-elevation acute coronary syndromes.

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This study was focused on bleeding for the primary outcome, which was significantly lower in the clopidogrel group [88 (18%) of 500 patients than in the ticagrelor group, 118 (24%) of 502; hazard ratio 0.71, 95% CI 0.54 to 0.94; $p=0.02$ for superiority]; and the choice of criteria for the co-primary endpoint with a mix of bleeding and ischemic events can be discussed, with a non-inferior net clinical benefit outcome for clopidogrel: [139 (28%) versus ticagrelor 161 (32%); absolute risk difference -4% , 95% to 1.4% ; $p=0.03$ for non-inferiority], which may not lead to definitive conclusions.

In view of the mentioned study limitations of the POPular AGE study, the prospective BUENOS AIRES I registry aimed to confirm the findings of POPular AGE in a large prospective multicenter registry (11).

This issue of the Journal provides further insights into this debated topic, by reporting the results of the prospective BUENOS AIRES I registry, with the purpose of ratifying the conclusions of the of POPular AGE study. (10). Actually, the authors reported similar Bleeding Academic Research Consortium (BARC) ≥ 2 type bleeding rates at 15-month follow up in NSTEMI patients aged above 70 years old, with more MACE in the clopidogrel group compared with the ticagrelor/prasugrel arm (36.3% vs. 18.6%; $p=0.023$). Of note, there was an imbalance in baseline characteristics between groups in terms of ischemic and bleeding risks, as supported by the higher percentage of smokers and men in the ticagrelor/prasugrel group and the increased CRUSADE score and higher rate of patients with concomitant atrial fibrillation in those receiving clopidogrel. As the analysis was not adjusted for these baseline characteristics, which may explain the contrasting findings as compared with those of the POPular AGE, this study, despite its informativeness, does not allow to draw definitive conclusions but leaves the debate open (9).

Indeed, despite the usual methodological limitations inherent to every registry, the authors report that ticagrelor or prasugrel may represent a valid strategy with a favorable risk-benefit balance in elderly NSTEMI patients, after accurate selection is implemented (and documented in the patient file). Further data are mandatory though, as it will also be of major interest to provide real life data focusing on de-escalation DAPT strategies, in light of the recent RCTs and meta-analyses which have reported lower major bleeding without an increase of ischemic events with this strategy (11-16).

Accordingly, further data remain crucial in order to optimize the management of elderly patients, which remains highly challenging. The results of the prospective BUENOS AIRES I registry emphasizes that one size definitely does not fit all, with the need of an individualized approach during the acute phase and adaptive during the first year, taking into account clinical characteristics, coronary anatomy, comorbidities, ischemic and/or bleeding risk scores and occur-

rence of events during follow-up.

In conclusion, we must bear in mind Henry Louis Mencken's "to every complex problem there is an answer that is clear, simple and wrong". Ongoing research focused on careful personalization of DAPT, ranging from duration to the choice of agent, but especially focusing on de-escalation (either guided or unguided) of DAPT, will be crucial in our quest to optimize current strategies and eventually settle ongoing controversy in this field.

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Conflict of interest

Giuseppe Biondi-Zoccai has consulted for Cardionovum, CrannMedical, Innovheart, Meditrial, Opsens Medical, Replycare, and Terumo. All other authors have no competing interest.

Authors' contributions

PS wrote the first draft, all three authors contributed to the development of this manuscript.

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