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INVITED EDITORIAL

Antiplatelet treatment for older patients with ACS — a challenging issue

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Patients with ≥ 75 years of age represent a large and significant proportion of those admitted for acute coronary syndromes (ACS) in our hospitals [1]. Older patients frequently present with peculiar features and comorbidities (complex coronary lesions, anaemia, chronic kidney dysfunction, peripheral vascular disease) associated with geriatric syndromes (frailty, disability, cognitive impairment) that are relevant determinants of patients health and outcomes [2]. Older adults have frequently low-grade inflammation ("inflammaging") which has been associated with the occurrence of frailty and with the development of the atherosclerotic process [2]. The prevalence of frailty increases as age advances and is more frequent among elderly women: it is present in more than 20% of patients with 80 to 84 years of age [2, 3]. Cognitive impairment is not infrequent among frail older patients and may deteriorate at the time of ACS presentation, due to the stress of the acute event, the unfamiliar environment and side effects of medications [2]. Because older patients are underrepresented in clinical trials, evidence for more precise treatments is still limited and the cardiologist has to rely on his own clinical judgement to select the most appropriate treatment strategies [1, 2].

It is important to emphasize that therapeutic management of older patients should be more individualized younger ones, because the clinicians have to take into consideration comorbid medical and geriatric conditions that are not included in traditional ACS risk scores (Fig. 1). Patients presenting with persistent ST-segment elevation myocardial infarction (STEMI) are currently treated with mechanical reperfusion by percutaneous coronary intervention (PCI). The European Society of Cardiology (ESC) STEMI guidelines recommend "no upper age limit with respect to reperfusion, especially with primary PCI" [4], despite relatively few data concerning outcomes of older patients undergoing primary PCI. Although more information is available from

randomized trials specifically focused on elderly patients with non-ST-segment elevation ACS (NSTE-ACS) than in STEMI in favour of an invasive approach [5, 6], the different presentation at admittance (patients with STEMI have ongoing ischemia while NSTE-ACS may be asymptomatic) may favour the clinical choice of an initially conservative strategy. Coronary angiography and PCI are seldom performed in frail patients who are thought to be at higher risk if treated invasively. In this regard, observational registries provided conflicting data: no benefit was observed in the Spanish LONGEVO registry, whereas a better outcome was associated with PCI in the ISACS-TC registry [1].

Antiplatelet therapy in older patients with ACS

Since older patients are more liable to bleeding complications than younger ones due to the presence of clinical comorbidities that increase bleeding risk [1, 2], the choice of an appropriate antiplatelet strategy is difficult to pursue. Moreover, the large pivotal trials on dual antiplatelet therapy (DAPT) comparing potent P2Y12 inhibitors with clopidogrel (TRITON-TIMI 38 and PLATO) enrolled few aged patients [7, 8]. Because prasugrel at 10 mg significantly increased bleeding, its use in older patients was not recommended by Food and Drug Administration (FDA) whereas a 5 mg/day maintenance dose was indicated by the European Medicines Agency [9]. In PLATO the superiority of a DAPT regimen with ticagrelor over a DAPT with clopidogrel (including a reduction in cardiovascular mortality) was confirmed in older patients enrolled in that trial [10].

Yet, recent trials specifically undertaken in elderly patients did not support the findings of that PLATO sub-analysis. The POPular AGE study showed that a DAPT including clopidogrel significantly decreased bleeding rates (including fatal bleeding) compared with a DAPT with ticagrelor, without any increase in thrombotic complications [11]. Patients taking clopidogrel and prasugrel 5 mg maintenance dose had similar rates of bleeding and thrombotic events in the randomized ELDERLY ACS 2 trial [12]. In the 5 mg prasugrel arm, thrombotic events were lower during the first month of treatment, whereas bleeding events were higher than in the clopidogrel arm in the late phase of the trial (31–365 days) [13]. Despite the large response variability observed after clopidogrel administration and subsequent high on-treatment platelet reactivity in a not negligible proportion of patients [14], the refined technology of new drug-eluting stents and improved operator expertise may have made unnecessary the requirement of potent antiplatelet agents [15].

DAPT composition and duration should be tailored on individual patients according to the thrombotic and bleeding risk. Current guidelines recommend the use of scores, especially for the assessment of bleeding [16]. For that purpose, the PRECISE DAPT score and the Academic Research Consortium – High Bleeding Risk (ARC-HBR) criteria are helpful tools for the clinician [16] to estimate the bleeding risk and establish tailored treatments. Advanced age is a well-known risk factor for bleeding events. However, the large majority of older patients with ACS carry both high bleeding and thrombotic risk: in the ELDERLY-ACS 2 trial more than two thirds of patients (68%) satisfied the criteria for the definition of high thrombotic risk according to the ARC-HBR trade-off model [17] that reported the predictors of thrombotic complications in patients undergoing

stent implantation who met the ARC-HBR definition.

Based on available evidence, we believe that a short DAPT should be the preferred strategy in elderly patients with isolated HBR. One-month DAPT, followed by antiplatelet monotherapy, was non-inferior to standard DAPT for net and major adverse clinical events and significantly reduced bleeding in the MASTER DAPT trial [18] that randomized only HBR patients undergoing PCI (with more than two thirds aged ≥ 75 years). However, one-month DAPT seems a too short DAPT treatment in ACS, since these patients may incur in an excess of cardiovascular events (particularly MI) as shown by the One-month DAPT trial [19]. Clopidogrel seems preferable to ticagrelor [11] for the initial DAPT period for a better safety profile and comparable efficacy; clopidogrel may also be preferred to aspirin as long-term monotherapy, due to a lower discontinuation rate for gastrointestinal discomfort or bleeding, frequently associated with aspirin use in older patients.
A de-escalation strategy appears suitable for patients in whom HBR is associated with a high thrombotic risk [20]. In a post-hoc analysis of the Elderly ACS-2 trial, low-dose prasugrel reduced thrombotic complications in the subacute (first month after index event) and chronic phases (from second month to 1 year) compared with clopidogrel, whereas bleeding was lower with clopidogrel in the late phase [13]. In these patients, an initial DAPT including with low-dose prasugrel followed after 2–3 months by a DAPT with clopidogrel up to 12 months appears an appropriate strategy. However, these considerations are speculative and need to be confirmed by randomized trials conducted in elderly ACS populations.

In conclusion, although the appropriate use of antiplatelet agents in older ACS patients is challenging, the evidence is in favour of a cautious approach, avoiding potent P2Y12 inhibitors like full-dose prasugrel and ticagrelor and relying on clopidogrel for initial DAPT and subsequent monotherapy. Short DAPT or de-escalation appear also suitable strategies, whose choice should be based on the assessment of the bleeding and the thrombotic risk.

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Figure 1. Key factors contributing to the geriatric syndrome including cognitive decline, disability, delirium, frailty, polypharmacy and multimorbidity