Optimal dual antiplatelet therapy strategy in elderly patients with acute coronary syndrome

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ABSTRACT One out of three hospitalizations for acute coronary syndrome (ACS) involve nowadays elderly patients, carrying together a significant burden of comorbidities and a higher risk of complications. In particular, both ischemic and haemorrhagic risk are markedly enhanced in advanced age, and strictly interconnected, challenging the management of dual antiplatelet therapy (DAPT) in these patients. The recent development of several therapeutic options in terms of duration and combination of antiplatelet agents have offered a wider spectrum of opportunities for a more individualized approach in the management of DAPT after an ACS, although the criteria for the selection of the most appropriate strategy in each patient still lack validation. In particular, dose-adjustment, early aspirin discontinuation, laboratory-driven tailoring and shorter or extended DAPT have been addressed with promising safety and efficacy results. The present review provides an updated overview on the emerging evidence from randomized clinical trials and subanalyses dedicated to the management of DAPT in elderly patients presenting with ACS.

Elderly patients, considered as subjects above 75 years of age, currently account for over one third of the population being treated for acute coronary syndrome (ACS), and certainly the most challenging ones.\(^1\)

In fact, age represents per se a major determinant of cardiovascular risk, being furthermore associated to a higher prevalence of other established risk factors, more complex anatomy and clinical condition, with increased comorbidities and frailty, accounting for the poor outcome results achieved in this particular subset of ACS patients.\(^2\)\(^-\)\(^7\)

Despite medical management is still preferred in a large proportion of elderly patients, for the fear of periprocedural complications or the potential restraints to the use of dual antiplatelet therapy in patients undergoing percutaneous revascularization, several studies have demonstrated the prognostic advantages of an invasive approach and ad-hoc percutaneous coronary intervention (PCI) even in extremely advanced age.\(^8\)\(^-\)\(^10\)

Moreover, the pivotal role of dual antiplatelet therapy in the management of ACS has been documented even in medically managed patients, thus further reinforcing the need to identify appropriate criteria for optimizing antiplatelet strategies, tailored according to patients’ characteristics and risk profile.

DETERMINANTS OF PLATELET REACTIVITY IN ADVANCED AGE

Advanced age represents a condition where both thrombotic and haemorrhagic risk are markedly increased, as a direct consequence of aging and the coexistence of several factors, such as diabetes, hypertension and renal failure, that significantly condition the coagulative balance.

Firstly, vascular damage and endothelial dysfunction are more common in advanced age, favouring the creation of a pro-thrombotic ambience, inducing platelet adhesion and aggregation. In addition, oxidative stress is generally prevalent in advanced age, due to metabolic dysregulation and depletion of anti-oxidant substances, further enhancing the thrombotic risk.\(^11,12\)

On the other side, platelets of elderly patients have been described more frequently as dysfunctional, being potentially less reactive.\(^13\) Indeed, lower platelet turnover, with the permanence in the bloodstream of older platelets, containing a lower quantity of granules, nucleic acids and proteins, has been described with ageing,\(^11,14\) being associated...
with a lower aggregating potential. Alterations in the thrombopoiesis, in effect, could favour also the release from the bone marrow of immature forms of platelets,\(^{15-17}\) displaying an impaired activity and thus, being associated oppositely with an increased haemorrhagic risk.

**FACTORS AFFECTING ANTIPLATELET THERAPY IN ELDERLY PATIENTS**

Pharmacokinetics and dosing of the different antiplatelet drugs play certainly a more relevant role in advanced age.

In fact, low body weight is more common in very elderly and frail patients, potentially resulting in overdosing with the standard antiplatelet regimens.\(^{18}\) This issue has emerged in particular for prasugrel, while no dose adjustment has been recommended for other antiplatelet drugs. In fact, the use of the conventional dose of prasugrel of 10 mg daily has been associated with an excess of bleeding complications, in the TRITON-TIMI 38 trial, while a dose reduction to 5 mg daily has recently emerged as a safer option in elderly patients undergoing PCI.\(^{19}\)

In fact, the ELDERLY 2-ACS trial demonstrated among 1,443 patients aged > 74 years with ST-elevation (STE)- or non-ST-elevation (NSTE)-ACS treated with PCI during index admission that a reduced-dose of prasugrel offered similar results as compared to clopidogrel.\(^{20}\)

However, in this trial and other studies dedicated to patients in advanced age, mean values of body mass index were surprisingly high, with a large proportion of overweight patients, where the lowering of the dose could have resulted paradoxically in a suboptimal dosing of the drugs, thus potentially explaining the negative findings of the study.

In addition, a reduction of renal function is common in advanced age and could result in impaired excretion of antiplatelet drugs with prevalent urinary excretion. However, the renal elimination of unmetabolized antiplatelet drugs has been shown to be 1.5% with acetylsalicylic acid (ASA),\(^{21}\) and lower with clopidogrel (0%), prasugrel (0%) and ticagrelor (0.05%).\(^{22}\) Thus, no dose-adjustment is generally indicated among patients with renal failure for any of the oral antiplatelet drugs, although their use in haemodialysis patients is poorly validated.

On the other side, hepatic metabolism leading to activation and inactivation of the antiplatelet drugs, which is particularly relevant for thienopyridines, can either be affected by age.\(^{22}\) In fact, an impairment in the efficiency of the metabolic processes has been described with aging and furthermore, polypharmacy is common in the elderly, paving the risk of drug-drug interaction.\(^{23}\) Finally, atrophy of the intestinal mucosa and gastrointestinal comorbidities have been pointed as translating into reduced drug absorption and the achievement of insufficient therapeutic doses of drugs.

**DAPT IN ELDERLY PATIENTS: FROM RANDOMIZED TRIALS TO REAL LIFE**

Even though in daily practice elderly patients represent a relevant proportion of the ACS population, patients in advanced age have been seldom enrolled in randomized clinical trials, in consequence of the poorer outcomes of these patients (Figure 1), therefore resulting into an insufficient evidence when applying the standard antiplatelet regimens to this population.

Larger data for the use of DAPT in advanced age have recently emerged from large scale registries, where patients above 75 years of age accounted for over 25% of the total population.\(^{24}\)

In the Myocardial Ischaemia National Audit Project (MINAP) registry,\(^{25}\) more aggressive revascularization and pharmacological strategies were associated to a significant prognostic advantage,

![Figure 1](http://www.jgc301.com; jgc@jgc301.com)
even in advanced age. Similar conclusions were reached in the Global Registry of Acute Coronary Events (GRACE), enclosing the largest cohort of ACS patients worldwide, although patients over 65 years displayed a 2–3 fold increased risk of bleeding complications, that were independent from interventional procedures but were associated with worse outcome.[26]

In the SWEDEHEART registry,[27] more than 14,000 patients with myocardial infarction aged over 80 were discharged on DAPT with ASA and clopidogrel or ticagrelor. Ticagrelor use was associated with a higher risk of bleeding and death compared with clopidogrel.

However, in the sub-analysis of the 2878 patients over 75 years enrolled in the PLATO trial, the significant clinical benefits and overall safety of ticagrelor compared with clopidogrel were not found to depend on age.[28]

A similar increase in bleedings has also been demonstrated with prasugrel: in the TRITON-TIMI 38 trial prasugrel increased fatal and life-threatening bleedings over 75 years of age,[19] thus not being recommended in this subset of patients.

On the contrary, in the TRILOGY trial,[29] that was focused on a more fragile subset of 2083 ACS patients managed medically, the low-dose 5 mg prasugrel provided no anti-ischemic benefit but also analogous bleeding risk compared to clopidogrel.

Similar results were also achieved in the ELDERLY-2 ACS trial,[20] including, instead, only patients undergoing PCI, as displayed in Figure 2.

The recent POPular Age trial randomized 1002 patients with ACS aged > 70 years to clopidogrel (n = 500) or ticagrelor or prasugrel (n = 502, 95% treated with ticagrelor).[30] They showed that clopidogrel had fewer bleeding events without an increase in the combined endpoint of all-cause death, myocardial infarction, stroke, and bleeding, re-uprising the use of a “less aggressive” antiplatelet strategy, with either reduced dose P2Y12 or clopidogrel advanced age.

Nevertheless, suboptimal response to antiplatelet medications or residual high-on treatment platelet reactivity (HRPR) has been demonstrated more frequently in advanced age. Gremmel, et al.[31] evaluated a population of 191 patients undergoing PCI and receiving a clopidogrel loading dose of 300 mg.

![](http://www.jgc301.com/jgc@jgc301.com)

Figure 2  Clopidogrel vs. new ADP antagonists in elderly patients. PLATO: composite of cardiovascular death, myocardial infarction, or stroke; Elderly ACS2: composite of mortality, myocardial infarction, disabling stroke and re-hospitalization for cardiovascular causes or bleeding within one year; POPular Age: mortality, myocardial infarction, stroke, rehospitalisation for cardiovascular causes, or bleeding; SWEDEHEART: Stroke, MI, death, readmission for bleeding. ADP: adenosin-diphosphate; MI: myocardial ischaemia.

They demonstrated a higher rate of high on-treatment residual platelet reactivity among the 49 patients aged ≥ 75 years, confirmed by different aggregation tests.

In the SENIOR-PLATELET trial,[32] including 1331 coronary patients chronically treated with aspirin and a thienopyridines, the 148 elderly patients treated with clopidogrel 75 mg were more likely to have HPR than younger patients (adjusted OR: 1.83, 95% CI: 1.16–2.87; P = 0.009), with clopidogrel dose increase or new thienopyridines therapy, only blunting, but not eliminating the difference in antiplatelet response observed according to age.

Similar data were reported by Verdoia, et al. among ACS patients treated with DAPT,[33] showing that ADP-mediated platelet aggregation increased with decades of age, with reduced effectiveness of ADP-antagonists being more common in patients aged > 70 years, both in clopidogrel treated patients (38.5% vs. 27.9%, P = 0.09, adjusted OR [95% CI] = 2.85 [1.42–5.7], P = 0.003) and in the patients receiving ticagrelor (19.1% vs. 8.1%, P = 0.03, adjusted OR [95% CI] = 2.93 [1.01–9.45], P = 0.049), whereas no age-related difference was observed for ASA.
However, opposite findings were reported in other studies and meta-analyses,[34] documenting that age was inversely associated with the risk of low-platelet reactivity in patients treated with a ticagrelor maintenance dose.

Thus, the contrasting conclusions achieved in currently available data further reinforce the concept that elderly patients probably represent a heterogeneous population, with certain patients being more prone to a pro-thrombotic phenotype and other ones to an enhanced haemorrhagic risk, thus further reinforcing the need on additional tools for better defining such risk and individualize the antiplatelet strategy.

EMERGING DAPT STRATEGIES FOR ADVANCED AGE

The increasing need of identifying alternative antiplatelet strategies allowing to cope with both ischemic and bleeding risk, especially among more complex subsets of ACS patients, as the elderly,[35] has led to the development of different therapeutic options, that have been recently assessed in dedicated studies, including a shortening of DAPT duration,[36,37] the de-escalation either clinically or laboratory driven, and ASA free strategies. Table 1 displays the potential options assessed in the available studies.

The newer generations of drug-eluting stents (DES), being associated with thinner struts, no-polymer or biocompatible polymer, faster re-endothelization and neglectable rates of thrombosis have allowed to consider a progressive shortening of the optimal duration of DAPT, from the traditional 12 months to 1–6 months in the majority of the patients.

| Antiplatelet strategy | Study reference | Elderly population | Outcome results |
|-----------------------|-----------------|--------------------|-----------------|
| **Experimental strategy** | **Control** | Ischemic events = | Bleeding events = |
| **Dose adjustment** | | | |
| Prasugrel 5 mg | Clopidogrel | TRILOGY | 22.3% | Ischemic events = |
| | | | | Bleeding events = |
| Prasugrel 5 mg | Clopidogrel | ELDERLY-2 ACS | 100% | Ischemic events = |
| | | | | Bleeding events = |
| **Shorter duration** | | | |
| DAPT 1 month+DES | DAPT 1 month + BMS | LEADERS-FREE | 33.7% > 80 yrs | Ischemic events: lower |
| DAPT 1-6 months+DES | DAPT 1-6 months + BMS | SENIOR | 100% | Ischemic events: lower |
| **De-escalation** | | Ischemic events = | Bleeding events = |
| Prasugrel/ticagrelor 1 month then clopidogrel + ASA | ASA + ticagrelor/prasugrel for12 months | TOPIC | NR | Ischemic events = |
| | | | | Bleeding events: lower |
| PFT-based optimization | Standard therapy | TROPICAL-ACS | ≥ 80 yrs excluded | NACE = |
| PFT-based optimization | Prasugrel 5 mg | ANTARCTIC | 100% | Ischemic events = |
| | | | | Bleeding events = |
| CYP2C19 genotype-guided strategy | Standard therapy | POPULAR Genetics | NR | Ischemic events = |
| | | | | Bleeding events: lower |
| **ASA-free** | | Ischemic events = | Bleeding events = |
| ASA + ticagrelor 3 months then ticagrelor | ASA + ticagrelor 12 months | TWILIGHT | About 50% > 65 yrs | Ischemic events = |
| | | | | Bleeding events: lower |
| ASA + ticagrelor 1 month then ticagrelor | ASA + clopidogrel 12 months | GLOBAL LEADERS | 21.5% | Ischemic events: lower |
| | | | | only in elderly |

ASA: acetylsalicylic acid; DAPT: dual antiplatelet therapy; DES: drug-eluting stents; NR: not reported.
tion even among the 659 ACS patients.

Focusing on elderly patients, the DES in elderly patients with coronary artery disease (SENIOR) trial reported that any DES and a short duration of DAPT (one month for patients with stable presentation and six months for ACS) were better than BMS and a similar duration of DAPT with respect to the occurrence of all-cause mortality, thrombotic and haemorrhagic complications.\[39\]

De-escalation of DAPT has been proposed as another potential option, considering that the thrombotic risk is especially enhanced in the first period after the acute event and PCI, whilst the bleeding risk is prevailing at long term.\[40\] Therefore, a reduction in the intensity of platelet inhibition after the first months has been proposed in different studies.

The Timing Of Plaletet Inhibition after acute Coronary syndrome (TOPIC) study was the first to investigate the switch from prasugrel or ticagrelor to clopidogrel one month after PCI for ACS. They showed a significant reduction in minor bleeding complications with a systematic de-escalation strategy, with no difference in major bleedings.\[41\]

In the TROPICAL-ACS trial, a guided de-escalation of antiplatelet treatment from prasugrel to clopidogrel after 14 days, according to platelet function testing, was non-inferior to standard treatment with prasugrel at one year after PCI in terms of net clinical benefit.\[42\] Positive results were also observed in the POPULAR Genetics by CYP2C19-directed genotyping for the assessment of poor clopidogrel metabolisers.\[43\]

More specific to the elderly, the ANTARCTIC trial, randomly assigned elderly ACS patients to prasugrel 5 mg daily with dose or drug adjustment in case of inadequate response (including up-titration to 10 mg or down-grade to clopidogrel according to platelet function test) or oral prasugrel 5 mg daily with no monitoring. They showed comparable results with the two strategies.\[44\]

Based on these data, current guidelines consider a de-escalation of the P2Y12 regimen, either clinically driven or based on laboratory tests in class IIb recommendation, a strategy that could be even more promising among the elderly, also in view of the positive results observed with clopidogrel in the recent POPular Age trial.\[30\]

Indeed, among patients with high-bleeding risk, gastrointestinal bleedings have clearly emerged as the most frequent complication.\[45\] and ASA has been certainly claimed as a major determinant of such complications. Thus, an early discontinuation of ASA, with the maintenance of a single antiplatelet regimen with only the P2Y12 at long-term has been proposed for the management of HBR patients.

Among the over 9,000 patients enrolled in the TWILIGHT trial,\[46\] ticagrelor monotherapy (after 3 months DAPT) was associated with a lower incidence of clinically relevant bleeding than ticagrelor plus aspirin, with no higher risk of death, myocardial infarction, or stroke. The results were confirmed when restricted to older patients (Figure 3).

Similar conclusions were also reached in other studies (Figure 3), such as in the GLOBAL LEADERS trial,\[47\] TICO\[48\] and STOPDAPT-2,\[49\] and in recent trials conducted among patients with atrial fibrillation requiring oral anticoagulation, where a single antiplatelet therapy, generally with clopidogrel, was used after even one week from PCI, although the rate of patients with ACS, in these studies, was low.\[50,51\]
DISCUSSION AND CONCLUSIONS

Despite the increased awareness of the challenge represented by the elderly patients presenting with ACS and the efforts accomplished in order to overcome their prognostic gap, the optimal management of DAPT in these patients is still debated.\[32\]

Indeed, elderly patients enclose a very heterogeneous population, comprising patients with ACS as the only event or those elderly fragile patients with several comorbidities, since anagraphical age does not always reflect biological age.

So far, however, the only promising tools for the classification of the patients and the definition of their bleeding risk on DAPT are represented by risk scores.\[53\] Both the PRECISE-DAPT and ARC-HBR scores are proposed in guidelines for guiding the duration and optimization of antiplatelet therapies, whose major criteria are summarized in Table 2.

However, despite the PRECISE-DAPT represents the only one to have received a validation in randomized clinical trials, its applicability in elderly patients is still debated. In fact, Guerrero, et al\[54\] reported in a recent study that the vast majority of elderly patients have PRECISE-DAPT values above the recommended cut-off point for bleeding risk, suggesting that the identification of different cut-off points could be appropriated in advanced age.

Therefore, individualization of the therapy certainly represents the safer and most effective strategy in advanced age, although the criteria for

| Table 2  | Criteria for the definition of bleeding risk scores (ARC-HBR and PRECISE-DAPT) on dual antiplatelet therapy. |
|-----------------|-----------------------------------------------------------------------------------------|
| **ARC-HBR criteria** | **PRECISE-DAPT score** |
| **Major criteria** |                                    |
| Long-term oral anticoagulation | Haemoglobin |
| Severe or end-stage CKD (estimated Haemoglobin < 11 g/dL rate eGFR < 30 mL/min) | White blood cells |
| Haemoglobin < 11 g/dL | Age |
| Spontaneous bleeding requiring hospitalization and transfusion in the past 6 months | Creatinine |
| Moderate to severe baseline thrombocytopenia (platelet count < 100 × 10^9/L) | Prior bleeding |
| Chronic bleeding diathesis |                                    |
| Liver cirrhosis with portal hypertension |                                    |
| Active cancer in the past 12 months |                                    |
| Previous spontaneous ICH (at any time) |                                    |
| Previous traumatic ICH within the past 12 months |                                    |
| Presence of known brain arteriovenous malformations |                                    |
| Moderate to severe ischemic stroke within the past 6 months |                                    |
| Nondeferrable major surgery on dual antiplatelet therapy |                                    |
| Recent major surgery or trauma within 30 days before PCI |                                    |
| **Minor criteria** |                                    |
| Age > 75 yrs |                                    |
| Moderate CKD (eGFR 30-59 mL/min) |                                    |
| Haemoglobin 11–12.9 g/dL for men and 11–11.9 g/dL for women |                                    |
| Spontaneous bleeding requiring hospitalization or transfusion within the past 12 months not meeting major criterion |                                    |
| Long-term use of oral nonsteroidal anti-inflammatory drugs or steroids |                                    |
| Any ischemic stroke at any time not meeting major criterion |                                    |

CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; ICH: intracranial hemorrhage; PCI: percutaneous coronary interventions.
risk stratification and decision making still need further elucidation.

Indeed, ongoing studies dedicated to the elderly population, as the British Heart Foundation SENIOR-RITA trial or the MASTER DAPT will certainly help to elucidate the criteria for the optimization and management of DAPT in this complex subset of patients, where both ischemic and bleeding risk are markedly enhanced.

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