Antiplatelet therapy in very elderly and comorbid patients with acute coronary syndromes

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Abstract

With population ageing and rise of life expectancy, a progressively increasing proportion of patients presenting with an acute coronary syndrome (ACS) are older adults, including those at extreme chronological age. Increasing amounts of data, including randomized clinical trials, have shown that the benefits of an early revascularization are maintained also at very old age, resulting in improved outcome after an acute coronary event. On the contrary, the optimal antiplatelet therapy (APT) remains unclear in these patients, because of both safety and efficacy concerns. Indeed, age-related multiple organ dysfunction and high prevalence of comorbidities may on the one hand reduce the therapeutic effects of administered drugs; on the other hand, it leads to increased vulnerability to drug toxicity and side effects. Therefore, management of APT is particularly challenging in elderly patients because of higher risk of both ischemic and bleeding events. The aim of the present paper is to review the current evidence, gaps in knowledge and ongoing research regarding APT in the setting of an ACS in elderly and very elderly patients, and in those with significant comorbidities including chronic kidney disease, diabetes mellitus and frailty.

Keywords: Acute coronary syndrome; Antiplatelet therapy; The elderly

1 Introduction

Elderly patients represent an increasing proportion of patients presenting with an acute coronary syndrome (ACS), and older age has been identified as a major predictor of mortality and morbidity both in non-ST-elevation ACS (NSTE-ACS) and in ST-elevation ACS (STE-ACS). In the last decade, several data have shown that the benefits of an early revascularization, including primary percutaneous intervention (PCI) in STE-ACS and routine invasive approach in troponin-positive NSTE-ACS, are maintained also at very old age, resulting in improved outcome both in-hospital and at long-term follow-up despite higher risk of bleeding. On the contrary, the management of antiplatelet therapy (APT) following an ACS remains a major clinical challenge in elderly patients, because of high risk of both ischemic and bleeding events. In addition, scientific evidence regarding the optimal therapeutic regimen for elderly patients in this clinical setting has been very limited, since large randomized clinical trials forming the evidence basis for ACS clinical practice guidelines have often enrolled a very small proportion of older patients and excluded those with significant comorbidities. The aim of the present review is to summarize the current scientific evidence as well as gaps in knowledge and ongoing research about APT in older ACS patients and in those with significant comorbidities including chronic kidney disease, diabetes mellitus and frailty.

2 General considerations for antiplatelet therapy in elderly

There is no universally accepted definition of an “elderly” patient. The cutoff of ≥ 75 years is the most commonly used in current literature, since a significant worsening of outcome after an acute coronary event has been shown by this age. However, lower cutoffs (60 or 65 years, intended as median population age) have also been used. Similarly, although not bearing a universal definition, the “very elderly” patient is mostly identified by an age cutoff ranging from 80 to 85 years. These “oldest old” patients are characterized by a number of significantly comorbidities and high prevalence of frailty, and they show a significantly higher mortality rate compared with “younger elderly” patients. The gap between large trials and real world observed with regard to the overall elderly population appears to be still

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larger with regard to very elderly patients that represent up to 13% of patients admitted with an ACS in community registries (Figure 1), but only 2% of those enrolled in randomized controlled clinical studies.\textsuperscript{[7]}

APT is a milestone of ACS treatment. A dual antiplatelet therapy (DAPT) using aspirin and a platelet P2Y\textsubscript{12} receptor blocker (RB) has been clearly demonstrated to reduce the risk of ischemic events and improve net clinical outcome at follow-up, despite a higher risk of bleeding.\textsuperscript{[11]} In the treatment of elderly ACS patients, identifying the optimal balance between ischemic and bleeding risk may be challenging for the clinician who must consider the higher atherothrombotic milieu; it implies an increased rate of mortality and major adverse cardiovascular events, but also the increased risk of bleeding, which in turn significantly impacts on mortality.\textsuperscript{[12]} Indeed, several biological and pharmacological variables affect the safety and efficacy of APT in the elderly. Firstly, significant alterations occur with ageing in the haemostatic system, leading to a prothrombotic state. Secondly, enhanced blood viscosity, endothelial dysfunction, increased inflammation and oxidative stress occur with cardiovascular ageing, leading to accelerated atherothrombosis.\textsuperscript{[13,14]} Thirdly, physiological age-related organ changes (reduced kidney function, decreased activity of hepatic cytochromes, muscle wasting) determine changes in absorption and metabolism of antithrombotic drugs, with a higher interindividual variability of drug-response and increased risk of drug toxicity and side effects.\textsuperscript{[15]} Finally, a high rate of significant comorbidities is observed in the elderly and, even more, in the very elderly population; as a consequence, polypharmacy is very common, and a higher risk of adverse drug-to-drug interactions exists in these patients.

3 Current recommendations for antiplatelet therapy in elderly

As in younger patients, current practice guidelines recommend for elderly ACS patients to start DAPT using aspirin and a P2Y\textsubscript{12} RB at the time of index event and to continue this therapy for 12 months, irrespective of treatment strategy.\textsuperscript{[16,17]} Along the same line, therapy with aspirin should be started at the time of the acute event, and continued indefinitely.\textsuperscript{[16,17]} Among the P2Y\textsubscript{12} RBs, current guidelines recommend the use of the “3rd generation” drugs (either prasugrel or ticagrelor) in all patients with an ACS. Nevertheless, real world data have shown that clopidogrel still represents the most used P2Y\textsubscript{12} RB in elderly patients;\textsuperscript{[18,19]} indeed, this drug appears to be associated with a lower rate of bleeding events, thus showing a safer profile compared with the more potent agents prasugrel and ticagrelor.\textsuperscript{[20,21]} Due to delayed onset of action and large response variability, clopidogrel is associated with a not negligible proportion of patients with on-treatment high platelet reactivity.\textsuperscript{[22]} Noteworthy, elderly patients have been shown to have significantly higher rates of high on-clopidogrel platelet reactivity compared with younger patients,\textsuperscript{[23]} and high on-treatment platelet reactivity has been associated with poor outcome in elderly patients with NSTE-ACS.\textsuperscript{[24]} These differences are thought to be due both to impaired response to the drug and to a higher baseline level of platelet reactivity in the elderly.\textsuperscript{[23]} The 3rd generation P2Y\textsubscript{12} RBs prasugrel and ticagrelor have shown a more powerful and predictable ADP-receptor blocking effect compared to clopidogrel, and clinical trials have demonstrated superiority of these agents over clopidogrel as adjunct to aspirin across the ACS spectrum in preventing ischemic events.\textsuperscript{[20,21]} Nevertheless, as expected, a higher risk of bleeding has been observed with these more potent agents, with mixed effects on overall outcome especially in elderly patients. Indeed, prasugrel did not demonstrate a net clinical benefit in patients aged 75 years or older enrolled in the TRI-TON-TIMI 38 trial compared to clopidogrel, because of significantly increase in fatal and life-threatening bleedings;\textsuperscript{[21]} thus, in patients ≥ 75 years, prasugrel at standard dosing is not recommended by the European Medical Agency, whereas it has very limited indications in high-risk elderly patients according to United States Food and Drug Administration (FDA).\textsuperscript{[25]} On the contrary, the reversible P2Y\textsubscript{12} RB ticagrelor has been shown to reduce cardiovascular mortality as well as the composite end-point of cardio-
vascular death, myocardial infarction or stroke in the overall population of patients enrolled in the PLATO trial, including the older subgroup (patients aged ≥ 75 years); nevertheless, the reduction in ischemic endpoint was less compared with what observed in the overall population, and it was obtained at the expense of higher frequency of major bleedings.[26] Moreover, in a population comparable to the TRITON-TIMI 38 study, that is patients undergoing revascularization during index admission, a significant interaction with older age was observed with regard to treatment effect, with benefit in patients aged < 65 years (n = 3048, primary endpoint HR = 0.59, 95% CI: 0.41–0.85) and harm in those aged > 65 years (n = 2368, primary endpoint HR = 1.17, 95% CI: 0.85–1.61, P for interaction < 0.01).[27]

4 Optimizing the balance between ischemic benefit and bleeding risk of antiplatelet therapy in elderly ACS patients: which way to go?

4.1 Stage-adapted DAPT

Recent landmark analyses of large clinical trials investigating DAPT in patients with ACS[28,29] found a clear benefit in thrombotic risk reduction during the acute and subacute treatment period (up to 30 days after the index event), when both platelet reactivity and stent thrombosis risk are higher, whereas this benefit decreases during the chronic phase and it is counterbalanced by a higher bleeding risk.[28,30] Accordingly, the first month after an ACS would require a more powerful platelet inhibition, using a potent 3rd generation P2Y12 RB, whereas thereafter a less potent platelet inhibition using clopidogrel might achieve an optimal balance between ischemic and bleeding risk. Recently, three randomized clinical trials have investigated the clinical effect of a de-escalating DAPT (potent P2Y12 RB in the acute and subacute phase, followed by clopidogrel in the chronic phase) in patients with ACS. In detail: (1) the TOPIC study was a single centre randomized trial enrolling 646 all-comer ACS patients (mean age: 61 ± 10 years) treated with PCI. In all patients, a DAPT with aspirin and one of the novel P2Y12 inhibitors, prasugrel (57% of the patients) or ticagrelor (43% of the patients), was started at the time of the index event and continued for 1 month; thereafter, patients were randomized to the switched group (de-escalation to clopidogrel) or to standard group (unchanged DAPT regimen). At 12 months, no significant differences were reported in ischemic endpoints (although the study was not powered to discriminate individual endpoints), whereas BARC ≥ 2 bleeding events were significantly lower in the switch group, resulting in significantly better net clinical outcome.[31] (2) The ANTaRCTIC study was a multicentre randomized clinical trial designed to specifically address the effect of a de-escalating DAPT in 877 patients aged ≥ 75 years with ACS treated by PCI. In this trial, de-escalation was guided by on-treatment platelet reactivity measured by platelet function testing. Patients were randomly assigned to receive 12-month DAPT (aspirin plus prasugrel 5 mg daily) with (experimental group) or without (standard group) monitoring of on-treatment platelet function. In detail, patients in the monitoring group underwent platelet function testing 14 days after randomization and dose or drug adjustment was performed in case of inadequate response: in those with high platelet reactivity (4% of the monitoring group), the prasugrel dose was increased to 10 mg daily, whereas those with low platelet reactivity (39%) were switched to clopidogrel 75 mg daily; patients with adequate response (55%) carried on therapy with prasugrel 5 mg daily. In patients requiring dose or drug-adjustment, a subsequent check of platelet function was repeated after 14 days. The primary endpoint (a composite of cardiovascular death, MI, stroke, stent thrombosis, urgent revascularisation, and BARC-defined bleeding types 2, 3, or 5 at 12 months) did not differ significantly between the two groups; similarly, neither significant differences nor trends were observed in the rates of ischemic or bleeding events.[32]

and (3) the TROPICAL ACS study was a multicentre randomized clinical trial enrolling 2610 patients with biomarker-positive ACS successfully treated with PCI. Like in the ANTaRCTIC trial, a platelet function testing-guided approach was used to determine de-escalation therapy. In detail, enrolled patients were randomly assigned to either standard treatment with prasugrel for 12 months (control group) or a stepdown regimen (1-week prasugrel followed by 1-week clopidogrel and platelet function testing to guide maintenance therapy with clopidogrel or prasugrel from day 14 after hospital discharge: guided de-escalation group). In the guided de-escalation group, patients with high platelet reactivity were switched back to prasugrel (511 out of 1304 patients, 39% of the intention-to-treat population), while those without high platelet reactivity continued on clopidogrel. The primary endpoint (composite of cardiovascular death, myocardial infarction, stroke or bleeding grade ≥ 2 according to BARC criteria at 12 months) as well as the rate of ischemic or bleeding events did not differ between the two groups.[33] A pre-specified analysis of the trial confirmed these findings in the elderly (defined as patients aged 70 years or older).[34]

Overall, although not providing conclusive evidence about the potential benefit of a de-escalating DAPT, the results of these studies should at least discourage the use of platelet function testing for adapting APT to disease stage;
more extensive data investigating the effect of a routine de-escalation of APT after an ACS might be of interest both in the general and in the elderly population.

4.2 Tailored therapy with reduced-dose prasugrel

Conversely to what observed in the general population, no net clinical benefit was observed with prasugrel compared with clopidogrel in elderly patients with ACS, owing to increased risk of fatal and intracranial bleeding. Pharmacodynamic studies have shown overexposure to the active metabolite with a prasugrel daily dose of 10 mg in the elderly, suggesting that a reduced dose of 5 mg/day could achieve a more efficient platelet inhibition compared with clopidogrel without excessive increase in bleeding risk.[35,36]

On this basis, two multicenter randomized clinical trials have investigated the effect of reduced-dose prasugrel (5 mg daily) compared with standard dose clopidogrel (75 mg daily) in elderly patients with ACS, either medically managed (TRILOGY ACS elderly substudy) or invasively treated (Elderly ACS-2). In detail: (1) the elderly substudy of the TRILOGY ACS trial was conducted on the cohort of patients aged 75 years or older (n = 2083) with NSTE-ACS who had a final treatment strategy of medical management without revascularization. Up to 30-month follow-up, no significant differences in outcome were demonstrated between the two treatment groups, both in ischemic (composite of cardiovascular death, myocardial infarction or stroke) and bleeding (Thrombolysis in Myocardial Infarction-TIMI major bleeding unrelated to coronary artery bypass) events.[37]

Therefore, like in the general population, prasugrel is not recommended in elderly patients treated medically; and (2) the Elderly ACS-2 study was a multicenter, open-label, blinded-endpoint randomized trial comparing the effect of reduced-dose prasugrel with standard-dose clopidogrel in ACS patients aged ≥74 years treated with PCI during index admission.[38] After a pre-defined interim analysis of the first 1000 patients with completed 12-month follow-up, the trial was interrupted because of “futility” for efficacy and enrolled 1443 patients (mean age: 80 years). No significant difference was observed with regard to the primary endpoint (composite of mortality, myocardial infarction, disabling stroke and re-hospitalization for cardiovascular causes or bleeding) between prasugrel and clopidogrel treatment groups (HR = 1.007, 95% CI: 0.78–1.30, P = 0.955). In patients treated with prasugrel, opposite trends toward lower rate of stent thrombosis, but non-significant increase in BARC 2, 3 and 5 bleedings were observed. Indeed, the rate of ischemic adverse events (about 17% in both treatment group at 12 months) was overall lower compared to that observed in previous clinical trials, suggesting an overall improvement in the therapeutic management of elderly patients across the ACS spectrum.[39]

Most of the enrolled patients were treated with drug-eluting-stent (DES), implanted in about 75% of study population and received a guideline-recommended therapy at discharge (statin in 93%, angiotensin-converting enzyme inhibitors or angiotensin RB in 83%, beta-blockers in 78% of the population). The incidence of bleedings was lower than expected (4.1% in prasugrel group, 2.7% in clopidogrel group), probably thanks to the extensive use of proton-pump inhibitors (prescribed in 93% of patients) and to the prevalent use of a radial access for PCI (78% of patients).[38]

4.3 Shorter DAPT

The 12-month DAPT regimen currently recommended by ACS guidelines has been based on the results of a single trial, carried out more than 15 years ago, showing the superiority of a DAPT with aspirin and clopidogrel, given for up to 12 months, over aspirin alone in patients with NSTE-ACS.[41] Since that time, considerable advances have been made in ACS treatment. Firstly, ubiquitous use of guideline-recommended drug therapy, in particular high-dose statins, has contributed to plaque stabilization and improved outcome after an ACS episode. Secondly, PCI-operator expertise has increased, and intra-vascular techniques allowing anatomical and functional lesion characterization, as well as guidance in stent deployment and optimization have become widely available. Finally, stent technology is continuously improving, with the introduction of drug-eluting stents (DES), development of thin and more biocompatible polymers, resorbable polymers and polymer-free stents, as well as surface tissue engineering to promote re-endothelialization and vascular healing. These new-generation DES are becoming an increasingly attractive option for elderly patients undergoing PCI, with improved outcome and reduced risk of repeat revascularization, and also for their better performance in the setting of complex coronary lesions which are more common in the elderly as compared to younger patients.[40]

Considering this evolution, several recent large studies and metanalyses have challenging the concept of 12-month DAPT, some of them testing shorter duration, and some testing longer duration of therapy.[41] In detail: the SENIOR randomized clinical trial has demonstrated that among patients aged ≥75 years undergoing PCI (n = 1200, 45% ACS), implantation of a DES with short DAPT duration (1 month in patients with stable clinical presentation, 6 months in patients presenting with an ACS) is associated with better 1-year outcome in terms of ischemic events (all-cause mortality, myocardial infarction, stroke, ischaemia-driven re-
vascularization) compared with implantation of a bare-metal stent and a similar DAPT duration, with very low rates of bleeding (about 5%) in both groups. These findings suggest that concerns regarding the need of prolonged DAPT after DES implantation may be overcome and that a strategy combining DES-PCI with a short-DAPT regimen may preserve the benefit on ischemic outcome and minimize the risk of bleedings.[42]

Age is a predominant risk factor for bleeding in both the PRECISE-DAPT and the DAPT score.[43] In detail, using the PRECISE-DAPT score, where age is considered as a continuous variable, the bleeding risk increases continuously with age (for example, in case of no previous bleeding and normal value of haemoglobin, blood white cell count and creatinine clearance, a patient aged 85 years has a bleeding risk almost twofold higher than a patient aged 65 years and more than threefold higher than a patient aged 55 years in Figure 2). Accordingly, although scientific evidence about the optimal DAPT duration in elderly patients is very limited, subgroup analyses of trials investigating safety and efficacy of shorter or longer DAPT suggest that elderly patients are more prone to have a net clinical benefit from shorter DAPT compared with younger patients.[43] Recently, an individual participant data meta-analysis of randomized trials explored the effect on outcome of short (3-6 months) versus standard (12 months) DAPT in 11,473 patients undergoing PCI with DES implantation.[44] Age-stratification was made using a cut-off of ≥65 years, and identified 6152 (40% ACS) younger and 5319 (42% ACS) elderly patients. In the overall population, shorter DAPT was found to be as effective as, but safer than, the standard 12-month regimen (HR = 1.12, 95% CI: 0.88–1.43, P = 0.358 for ischemic outcome; HR = 0.50, 95% CI: 0.30–0.84, P = 0.0081 for major bleedings). When exploring age-subgroups, the authors observed that shorter DAPT, compared with longer DAPT, was non-inferior in terms of ischemic outcome (composite of myocardial infarction, stent thrombosis or stroke at 12 months), and reduced significantly major bleedings in elderly patients (HR = 0.84, 95% CI: 0.60–1.16, P = 0.286; and HR = 0.46, 95% CI: 0.24–0.88, P = 0.0196, respectively). These results were confirmed after adjustment for clinical presentation (stable/unstable). On the contrary, in younger patients, the shorter regimen was associated with higher risk of ischemic events (HR = 1.67, 95% CI: 1.14–2.44, P = 0.0082), whereas major bleedings were numerically lower but without statistically significant difference (HR = 0.59, 95% CI: 0.26–1.34, P = 0.2073).[44] Overall, these studies suggest that a short-term DAPT may be a promising strategy to minimize the risk of bleeding without increasing the ischemic risk in elderly patients.

Short DAPT duration (one to 3 months) after an ACS is recommended in patients with an indication for anticoagulant therapy, mostly because of coexisting atrial fibrillation.[45] Due to the fact that all trials comparing various treatment strategies with direct oral anticoagulants and APT were sized to investigate safety, rather than efficacy, these recommendations fall short of evidence with regard to efficacy. Nevertheless, since atrial fibrillation is a disease of older age, the mean age of patients enrolled in these studies exceeds 70 years,[46] and these conclusions may serve as a reasonable guide to clinical practice for ACS in elderly patients.

Figure 2. Increase in PRECISE-DAPT score according to patients’ age. (A): Example of use of PRECISE-DAPT score in patients aged 55, 65, 75 and 85 years with no prior bleeding and normal values of haemoglobin and white blood count (12 g/dL and 7 × 10⁹/L, respectively) and a creatinine clearance of 55 mL/min; and (B): the 12-months risk of major and minor bleedings significantly increases with ageing, even in the absence of previous bleedings and without significant alterations of the other parameters included in the score.

4.4 “Aspirin-free” antiplatelet approach

Recently, a stand-alone P2Y₁₂ inhibition strategy has been proposed to replace long-term DAPT regimens for secondary prevention. Indeed, both intracranial and extracranial (particularly, gastrointestinal) bleeding are increased during aspirin therapy,[47] even at very low dose, more likely in elderly patients and in those receiving long-term treatment. As expected, this effect is amplified in patients receiving combination of aspirin with other antiplatelet drugs,
as P2Y12 RB, or with anticoagulants. The current availability of drugs with potent and reliable antiplatelet effect efficacy has raised the question whether aspirin should remain the mainstay of APT when alternative antithrombotic agents are also used, hypothesizing that an “aspirin-free” antiplatelet approach, based on the use of newer and more potent P2Y12 RB, might lead to an increased net benefit for the patient by reducing bleeding risk without impairing antithrombotic efficacy.\[48\] Since these drugs have been tested mostly in addition to aspirin, data investigating use of monotherapy with a P2Y12 RB are limited, and no current evidence is available specifically in the elderly population. Recently, the results of the first trial investigating the effect of P2Y12 RB monotherapy in patients treated with PCI have been released.\[49\] The study compared 1-month DAPT followed by 23 months of full-dose ticagrelor compared with a conventional regimen of 12-month DAPT followed by 12-month aspirin-monotherapy in 16000 patients (17% aged ≥ 75 years) and it failed to show a superiority of this strategy both in terms of ameliorated ischemic outcome and lower risk of bleeding at 2-year follow-up. These results were consistent both in stable CAD (n = 8481) and in ACS (n = 7487) patients.\[40\] Results of on-going studies are warranted to establish whether an “aspirin-free” antiplatelet regimen may be safe and effective in patients treated with PCI, as well as to identify subgroups that could potentially take advantage from this novel therapeutic approach.

5 Patients with comorbidities

5.1 Chronic kidney disease

The prevalence of chronic kidney disease (CKD) increases with aging (from 4% at age 20–39 years to 47% at age > 70 years), due to physiological progressive decline in glomerular function as well as to higher prevalence of comorbidities associated with renal damage such as hypertension and diabetes mellitus.\[50\] CKD affects a substantial proportion of patients hospitalized with an ACS (20% to 40%) \[51\] and, as expected, its prevalence is still higher in elderly patients (Figure 3A). As shown by the serial analysis of the Italian ACS registries, the proportion of patients with CKD among ACS patients admitted to the Italian CCU network has increased from 8% in 2001 to 21% in 2010 (Figure 4).\[52\]

Renal dysfunction is associated with alterations of endothelial function, platelet adhesion and aggregation, coagulation cascade and mineral metabolism. It leads to accelerated and severe atherosclerosis, increases prothrombotic status and increased risk of both ischemic and bleedsing events.

\[Figure 3.\] Prevalence of chronic kidney disease in elderly ACS patients. (A): Prevalence of renal dysfunction according to eGFR classes in the Italian elderly ACS trials enrolling ACS patients aged > 75 years; and (B): prevalence of eGFR < 60 mL/min in the Italian elderly ACS trials and in guideline-generating trials. ACS: acute coronary syndrome; eGFR: estimated glomerular filtration rate; NSTE-ACS: non-ST-elevation acute coronary syndrome; STE-ACS: ST-elevation acute coronary syndrome.

\[Figure 4.\] Prevalence of CKD in ACS patients. Increase of the proportion of ACS patients with CKD among those admitted to Italian cardiac care units from 2001 to 2010.\[52\] ACS: acute coronary syndrome; CKD: chronic kidney dysfunction.

Moreover, alterations in pharmacodynamic and pharmacokinetic drug profiles increase the risk of side effects, particularly bleeding.\[51\] For these reasons, renal dysfunction is associated with a significantly worse short-term and long-term clinical outcome both in young and elderly patients with ACS.\[51,53\] CKD patients have been usually excluded or
represented only a small minority in major clinical trials of ACS (Figure 3B), and this is mostly true in elderly patients.\[54]\] Indeed, elderly patients with ACS and CKD, despite representing a very high-risk population, have been trapped in a “therapeutic nihilism”, mostly by not receiving evidence-based treatments and being deprived of the benefit of current therapeutic advances.\[55\] In the Italian ACS-CCU registries, CKD was an independent predictor of not undergoing coronary angiography during admission for NSTE-ACS (Adjusted OR = 0.50, 95% CI: 0.41–0.60, \(P < 0.0001\)).\[52\]

Since creatinine production decreases with age, serum creatinine levels do not accurately represent renal function in elderly patients; therefore, estimation of glomerular filtration rate (eGFR) is recommended. While most anticoagulants may need dose adjustment in renal insufficiency, this is not the case for oral antiplatelet agents.\[16,17\] Since aspirin may induce further deterioration in renal function by inhibiting the synthesis of renal prostaglandins, as a consequence, reducing volume of renal blood flow, low doses (< 100 mg/die) are recommended in CKD patients after the acute event.\[50\] Among the P2Y12 RB, clopidogrel has been largely used in CKD patients; nevertheless, pharmacodynamic studies have underlined that, despite similar active metabolite generation, on-treatment platelet reactivity is increased in CKD versus non-CKD patients.\[56\] These findings are supported by subgroup analyses of clinical trials showing reduced efficacy of clopidogrel compared with placebo in patients with CKD,\[57,58\] thus emphasizing the need for more efficient antiplatelet agents. The more potent P2Y12 RB ticagrelor has been suggested to be more effective and safe than clopidogrel in a subgroup analysis of the PLATO trial (both in invasively-treated and in medically managed patients),\[59\] and also in a large registry shows a significantly less ischemic events as compared to clopidogrel-treated patients, without a significant difference in bleeding.\[60\] However, no benefit on ischemic outcome has been observed with prasugrel in a large registry of ACS patients with CKD.\[21,61,62\] Whether these findings could be applied in patients with more advanced CKD and to which extent they could be extended to elderly and very elderly population needs to be addressed by dedicated studies.

### 5.2 Diabetes mellitus

Data from large community registries has shown that a large proportion (up to 30%) of elderly patients admitted with an ACS had established or newly diagnosed diabetes mellitus (DM).\[63\] DM represents a powerful independent predictor of adverse in-hospital and long-term outcome in the general ACS population. Elderly patients with DM also show higher rates of mortality and adverse events following an ACS compared with non-diabetic patients, but this association has been demonstrated to relate mostly to CKD and low left-ventricular ejection fraction, suggesting that pre-existing cardiac and renal damage, rather than diabetic status per se, are they the real predictors of worse outcome in the elderly population.\[6\]

Current ACS guidelines do not recommend specific antiplatelet regimens in patients with DM. However, some considerations may be derived from the current available scientific evidence and should be taken into account in clinical practice. Firstly, the platelets of patients with DM are characterized by dysregulation of several signaling pathways, including increased expression of surface receptors and abnormalities in intracellular downstream pathways, which leads to intensified platelet activation and aggregation.\[64\] Indeed, a higher platelet reactivity has been demonstrated in patients with DM.\[65\] Secondly, DM has been associated with significantly higher platelet reactivity (and worse outcome) also in patients on treatment with clopidogrel.\[66,67\] Therefore, use of 3rd generation P2Y12 RBs, prasugrel or ticagrelor, is particularly appealing in these patients, also in the elderly population. Indeed, in a prespecified subgroup analysis of the TRITON-TIMI 38 trial, a greater reduction in ischemic events was observed in patients with DM when compared to those without DM, there is also no significant difference in TIMI major bleeding;\[68\] thus enhancing the magnitude of the net clinical benefit with prasugrel compared with clopidogrel in patients with DM (14.6% vs. 19.2%, HR = 0.74, \(P = 0.001\)), as compared to those without DM (11.5% vs. 12.3%, HR = 0.92, \(P = 0.16\); HR for interaction = 0.05). Also in the subgroup of patients aged ≥ 75 years, there was a significant 36% risk reduction in the primary endpoint with prasugrel use.\[69\] On this basis, the United States Food and Drug Administration (but not the European Medical Agency) considers the cautious use of prasugrel at standard dosing in elderly (≥ 75 years old) ACS patients with diabetes, if they are at low-risk for bleeding.\[25\]

On the contrary, no benefit has been demonstrated in the elderly ACS patients with DM treated with reduced dosing of prasugrel compared with those treated with clopidogrel.\[60\] In the PLATO trial, the ischemic benefit achieved with ticagrelor compared with clopidogrel was consistent in patients with DM, and there was no heterogeneity in relation to diabetic status.\[69\] Notably, pharmacodynamic studies have shown that ticagrelor provides faster and more potent antiplatelet effects compared with clopidogrel in the overall population and in patients with DM. Although DM has been shown to be an independent predictor of adverse outcome in patients treated with PCI, studies investigating the effect of
short versus long-term DAPT did not demonstrate reduced risk of major adverse cardiovascular events with long-term DAPT in patients with DM after DES-PCI; moreover, higher rates of major and minor bleedings were observed in patients treated with long-term DAPT.[70]

5.3 Frailty

Beyond chronological age, functional status and cognitive abilities should be considered with regard to elderly ACS patients. A status of decreased physiological reserve and lower functional capacity identifies the so named “frailty”, a complex clinical syndrome leading to increased vulnerability to stressors.[71] Frailty is common among elderly patients admitted with an acute cardiovascular event and it might involve about a half of the patients aged ≥ 75 years hospitalized in the intensive coronary care unit.[72] Several scores have been developed and can be used to identify frail patients.[73] Despite its high prevalence among elderly patients with cardiovascular disease, frailty is currently not routinely assessed in clinical practice, and most clinical trials did not include specific frailty assessment. The limited available scientific evidence has demonstrated that frailty is strongly and independently associated with adverse outcome after an acute cardiovascular event, including a higher rate of acute and late mortality, in-hospital complications (especially bleeding and delirium), rehospitalisation, longer length of stay and poor quality of life.[73] However, the association with incidence of major bleedings is currently unclear, although frail patients tend to have decreased skeletal muscle mass and poor nutrition, factors that could predispose to increased risk of falls and bleeding.[74] In line with these considerations, a recent report from a Spanish registry including patients ≥ 80 years with NSTE-ACS (n = 531, 27% frail) showed better ischemic outcome (composite of cardiac death, reinfarction or new revascularization) of an invasive versus conservative therapy in non-frail patients, but not in those with frailty.[75] Specific evidence about the optimal APT in frail patients is lacking and no specific recommendation is mentioned in the current ACS guidelines. As a general rule, evidence-based therapies should not be denied to frail patients; however, after stabilization of the acute condition and relief of symptoms, decisions on how to manage the individual elderly frail patients should be based on estimated life-expectancy, ischaemic and bleeding risk assessment, estimated risks and benefit of revascularization, comorbidities, quality of life and patient preferences. Discussion with the patient and his/her family or caregivers is pivotal to increase compliance with medical therapy, and careful clinical judgment is required to weigh up the risk of medication-related side effects. In patients requiring DAPT, a shorter regimen may be recommended.

6 Conclusions

Management of APT is particularly challenging in elderly patients because of the higher risk of both ischemic and bleeding events. Although in the last decade major advances have been made in the management of elderly ACS patients, further studies are warranted, particularly in the older old (≥ 85 years), to support and guide the clinician to a tailored therapeutic approach. Moreover, studies should be developed specifically addressing the best therapeutic strategy in the not negligible, but still neglected, proportion of elderly patients with significant comorbidities as well as in frail patients.

References

1 Madhavan MV, Gersh BJ, Alexander KP, et al. Coronary artery disease in patients ≥ 80 years of age. J Am Coll Cardiol 2018; 71: 2015–2040.
2 Savonitto S, Cavallini C, Petronio AS, et al. Early aggressive versus initially conservative treatment in elderly patients with non-ST-segment elevation acute coronary syndrome: a randomized controlled trial. JACC Cardiovasc Interv 2012; 5: 906–916.
3 Tegn N, Abdelnoor M, Aaberge L, et al. Invasive versus conservative strategy in patients aged 80 years or older with non-ST-elevation myocardial infarction or unstable angina pectoris (After Eighty study): an open-label randomised controlled trial. Lancet 2016; 387: 1057–1065.
4 Bueno H, Betriu A, Heras M, et al. Primary angioplasty vs. fibrinolysis in very old patients with acute myocardial infarction: TRIANA (TRatamiento del Infarto Agudo de miocardio en Ancianos) randomized trial and pooled analysis with previous studies. Eur Heart J 2011; 32: 51–60.
5 Kvakkestad KM, Abdelnoor M, Claussen PA, et al. Long-term survival in octogenarians and older patients with ST-elevation myocardial infarction in the era of primary angioplasty: a prospective cohort study. Eur Heart J Acute Cardiovasc Care 2016; 5: 243–252.
6 De Luca L, Marini M, Gonzini L, et al. Contemporary trends and age-specific sex differences in management and outcome for patients with ST-segment elevation myocardial infarction. J Am Heart Assoc 2016; 5: e004202–e004202.
7 Alexander KP, Newby LK, Cannon CP, et al. Acute coronary care in the elderly, part I: non-ST-segment-elevation acute coronary syndromes: a scientific statement for healthcare professionals from the American Heart Association Council on Clinical Cardiology: in collaboration with the Society of Geriatric Cardiology. Circulation 2007; 115: 2549–2569.
8 Alexander KP, Newby LK, Armstrong PW, et al. Acute coronary care in the elderly, part II: ST-segment-elevation myocardial infarction: a scientific statement for healthcare professionals from the American Heart Association Council on Clinical Cardiology: in collaboration with the Society of Geriatric Cardiology. Circulation 2007; 115: 2570–2589.
clinical outcomes in the TRITON-TIMI 38 substudy. J Clin Pharmacol 2012; 52: 789–797.

36 Vivioiatt SD, Antman EM, Winters KJ, et al. Randomized comparison of prasugrel (CS-747, LY640315), a novel thienopyridine P2Y12 antagonist, with clopidogrel in percutaneous coronary intervention: results of the Joint Utilization of Medications to Block Platelets Optimally (JUMBO)-TIMI 26 trial. Circulation 2005; 111: 3366–3373.

37 Roe MT, Goodman SG, Ohman EM, et al. Elderly patients with acute coronary syndromes managed without revascularization: insights into the safety of long-term dual antiplatelet therapy with reduced-dose prasugrel versus standard-dose clopidogrel. Circulation 2013; 128: 823–833.

38 Savonitto S, Ferri LA, Piatti L, et al. Comparison of reduced-dose prasugrel and standard-dose clopidogrel in elderly patients with acute coronary syndromes undergoing early percutaneous revascularization. Circulation 2018; 137: 2435–2445.

39 Morici N, Savonitto S, Ferri LA, et al. for the Elderly ACS 2 Investigators. Outcomes of elderly patients with ST-elevation or non-ST-elevation acute coronary syndrome undergoing percutaneous coronary intervention. Am J Med 2019; 132: 209–216.

40 Palmerini T, Benedetto U, Biondi-Zoccai G, et al. Long-term safety of drug-eluting and bare-metal stents: evidence from a comprehensive network meta-analysis. J Am Coll Cardiol 2015; 65: 2496–2507.

41 Valgimigli M, Bueno H, Byrne RA, et al. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS: The Task Force for dual antiplatelet therapy in coronary artery disease of the European Society of Cardiology (ESC) and of the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J 2018; 39: 213–260.

42 Varenne O, Cook S, Sideris G, et al. Drug-eluting stents in elderly patients with coronary artery disease (SENIOR): a randomised single-blind trial. Lancet 2018; 391: 41–50.

43 Gargiulo G. To encourAGE individualized dual antiplatelet therapy duration after drug-eluting stent implantation: a new pAGE of an intriguing book. JACC Cardiovasc Interv 2018; 11: 444–447.

44 Lee SY, Hong MK, Palmerini T, et al. Short-term versus long-term dual antiplatelet therapy after drug-eluting stent implantation in elderly patients: a meta-analysis of individual participant data from 6 randomized trials. JACC Cardiovasc Interv 2018; 11: 435–443.

45 Lip GYH, Collet JP, Haude M, et al. Management of anti-thrombotic therapy in AF patients presenting with ACS and/or undergoing PCI: A Summary of the Joint Consensus Document of the European Heart Rhythm Association (EHRA), European Society of Cardiology Working Group on Thrombosis, European Association of Percutaneous Cardiovascular Interventions (EAPCI) and European Association of Acute Cardiac Care (ACCA) endorsed by the Heart Rhythm Society (HRS), Asia-Pacific Heart Rhythm Society (APHRS), Latin America Heart Rhythm Society (LAHRS), and Cardiac Arrhythmia Society of Southern Africa (CASSA). Eur Heart J 2018; 39: 2847–2850.

46 Golwala HB, Cannon CP, Steg PG, et al. Safety and efficacy of dual vs. triple antithrombotic therapy in patients with atrial fibrillation following percutaneous coronary intervention: a systematic review and meta-analysis of randomized clinical trials. Eur Heart J 2018; 39: 1726–1735.

47 Antithrombotic Trials’ (ATT) Collaboration, Bainton C, Blackwell L, et al. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. Lancet 2009; 373: 1849–1860.

48 Capodanno D, Mehran R, Valgimigli M, et al. Aspirin-free strategies in cardiovascular disease and cardioembolic stroke prevention. Nat Rev Cardiol 2018; 15: 480–496.

49 Vranckx P, Valgimigli M, Jüni P, et al. Ticagrelor plus aspirin for 1 month, followed by ticagrelor monotherapy for 23 months vs aspirin plus clopidogrel or ticagrelor for 12 months, followed by aspirin monotherapy for 12 months after implantation of a drug-eluting stent: a multicentre, open-label, randomised superiority trial. Lancet 2018; 392: 940–949.

50 Capodanno D, Angiolillo DJ. Antithrombotic therapy in patients with chronic kidney disease. Circulation 2012; 125: 2649–2661.

51 Bonello L, Angiolillo DJ, Aradi D, et al. P2Y12-ADP Receptor Blockade in Chronic Kidney Disease Patients With Acute Coronary Syndromes. Circulation 2018; 138: 1582–1596.

52 De Luca L, Olivari Z, Bolognese L, et al. A decade of changes in clinical characteristics and management of elderly patients with non-ST elevation myocardial infarction admitted in Italian cardiac care units. Open Heart 2014; 1: e000148–e000148.

53 Morici N, De Servi S, Toso A, et al. Renal dysfunction, coronary revascularization and mortality among elderly patients with non ST elevation acute coronary syndrome. Eur Heart J Acute Cardiovasc Care 2015; 4: 453–460.

54 Morici N, De Servi S, Toso A, et al. Renal function estimation and one-year mortality in elderly patients with non-ST-segment elevation acute coronary syndromes. Int J Cardiol 2014; 174: 127–128.

55 Laine M, Burtey S, Puynimat E, et al. Research and therapeutic nihilisms in chronic kidney disease. JACC Cardiovasc Interv 2017; 10: 2343–2344.

56 Baber U, Mehran R, Kirtane AJ, et al. Prevalence and impact of high platelet reactivity in chronic kidney disease: results from the Assessment of Dual Antiplatelet Therapy with Drug-Eluting Stents registry. Circ Cardiovasc Interv 2015; 8: e001683–e001683.

57 Best PJ, Steinleib SR, Berger PB, et al. The efficacy and safety of short- and long-term dual antiplatelet therapy in patients with mild or moderate chronic kidney disease: results from the Clopidogrel for the Reduction of Events During Observation (CREDO) trial. Am Heart J 2008; 155: 687–693.
De Rosa R, et al. Antiplatelet therapy in elderly and comorbid patients

58 Dasgupta A, Steinhubl SR, Bhatt DL, et al. Clinical outcomes of patients with diabetic nephropathy randomized to clopidogrel plus aspirin versus aspirin alone (a post hoc analysis of the clopidogrel for high atherothrombotic risk and ischemic stabilization, management, and avoidance [CHARISMA] trial). Am J Cardiol 2009; 103: 1359–1363.

59 James S, Budaj A, Aylward P, et al. Ticagrelor versus clopidogrel in acute coronary syndromes in relation to renal function: results from the Platelet Inhibition and Patient Outcomes (PLATO) trial. Circulation 2010; 122: 1056–1067.

60 Szummer K, Lundman P, Jacobson SH, et al. Influence of renal function on the effects of early revascularization in non-ST-elevation myocardial infarction: data from the Swedish Web-System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies (SWEDHEART). Circulation 2009; 120: 851–858.

61 Baber U, Chandrasekhar J, Sartori S, et al. Associations between chronic kidney disease and outcomes with use of prasugrel versus clopidogrel in patients with acute coronary syndrome undergoing percutaneous coronary intervention: a report from the PROMETHEUS study. JACC Cardiovasc Interv 2017; 10: 2017–2025.

62 Melloni C, Cornel JH, Hailey G, et al. Impact of chronic kidney disease on long-term ischemic and bleeding outcomes in medically managed patients with acute coronary syndromes: insights from the TRILOGY ACS trial. Eur Heart J Acute Cardiovasc Care 2016; 5: 443–454.

63 Rosengren A, Wallentin L, Simoons M, et al. Age, clinical presentation, and outcome of acute coronary syndromes in the Euroheart acute coronary syndrome survey. Eur Heart J 2006; 27: 789–795.

64 Vinik AI, Erbas T, Park TS, et al. Platelet dysfunction in type 2 diabetes. Diabetes Care 2001; 24: 1476–1485.

65 Ferreiro JL, Angiolillo DJ. Diabetes and antiplatelet therapy in acute coronary syndrome. Circulation 2011; 123: 798–813.

66 Angiolillo DJ, Jakubowski JA, Ferreiro JL, et al. Impaired responsiveness to the platelet P2Y12 receptor antagonist clopidogrel in patients with type 2 diabetes and coronary artery disease. J Am Coll Cardiol 2014; 64: 1005–1014.

67 De Servi S, Crimi G, Calabrò P, et al. Relationship between diabetes, platelet reactivity, and the SYNTAX score to one-year clinical outcome in patients with non-ST-segment elevation acute coronary syndrome undergoing percutaneous coronary intervention. EuroIntervention 2016; 12: 312–318.

68 Wiviott SD, Braunwald E, Angiolillo DJ, et al. Greater clinical benefit of more intensive oral antiplatelet therapy with prasugrel in patients with diabetes mellitus in the trial to assess improvement in therapeutic outcomes by optimizing platelet inhibition with prasugrel-Thrombolysis in Myocardial Infarction 38. Circulation 2008; 118: 1626–1636.

69 James S, Angiolillo DJ, Cornel JH, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes and diabetes: a substudy from the PLATE inhibition and patient Outcomes (PLATO) trial. Eur Heart J 2010; 31: 3006–3016.

70 Gargiulo G, Windecker S, da Costa BR, et al. Short term versus long term dual antiplatelet therapy after implantation of drug eluting stent in patients with or without diabetes: systematic review and meta-analysis of individual participant data from randomised trials. BMJ 2016; 355: i5483–i5483.

71 Afifalo J, Alexander KP, Mack MJ, et al. Frailty assessment in the cardiovascular care of older adults. J Am Coll Cardiol 2014; 63: 747–762.

72 Leonardi S, Bueno H, Ahrens I, et al. Optimised care of elderly patients with acute coronary syndromes. Eur Heart J Acute Cardiovasc Care 2018; 7: 287–295.

73 Rockwood K, Mitnitski A. Frailty defined by deficit accumulation and geriatric medicine defined by frailty. Clin Geriatr Med 2011; 27: 17–26.

74 Walker DM, Gale CP, Lip G, et al. Frailty and the management of patients with acute cardiovascular disease: A position paper from the Acute Cardiovascular Care Association. Eur Heart J Acute Cardiovasc Care 2018; 7: 176–193.

75 Lió I, Ariza-Solé A, Sanchis J, et al. Invasive strategy and frailty in very elderly patients with acute coronary syndromes. EuroIntervention 2018; 14: e336–e342.

76 Puymirat E, Aissaoui N, Simon T, et al. Acute myocardial infarction in the elderly. The FAST-MI registry. Presse Med 2013; 42: 1432–1441.

77 Zaman MJ, Stirling S, Shepstone L, et al. The association between older age and receipt of care and outcomes in patients with acute coronary syndromes: a cohort study of the Myocardial Ischaemia National Audit Project (MINAP). Eur Heart J 2014; 35: 1551–1558.

78 Avezu A, Makdissi M, Spencer F, et al. Impact of age on management and outcome of acute coronary syndrome: observations from the Global Registry of Acute Coronary Events (GRACE). Am Heart J 2005; 149: 67–73.

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