Antiplatelet for Older Patients with Acute Coronary Syndromes

Subjects: Cardiac & Cardiovascular Systems

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Patients ≥ 75 years of age account for about one third of hospitalizations for acute coronary syndromes (ACS). Since the European Society of Cardiology guidelines recommend that older ACS patients use the same diagnostic and interventional strategies used by the younger ones, most elderly patients are currently treated invasively. Therefore, an appropriate dual antiplatelet therapy (DAPT) is indicated as part of the secondary prevention strategy to be implemented in such patients. The choice of the composition and duration of DAPT should be tailored on an individual basis, after careful assessment of the thrombotic and bleeding risk of each patient. Advanced age is a main risk factor for bleeding. Data show that in patients of high bleeding risk short DAPT (1 to 3 months) is associated with decreased bleeding complications and similar thrombotic events, as compared to standard 12-month DAPT. Clopidogrel seems the preferable P2Y12 inhibitor, due to a better safety profile than ticagrelor. When the bleeding risk is associated with a high thrombotic risk (a circumstance present in about two thirds of older ACS patients) it is important to tailor the treatment by taking into account the fact that the thrombotic risk is high during the first months after the index event and then wanes gradually over time, whereas the bleeding risk remains constant.

Keywords: elderly patients ; acute coronary syndrome ; anti-platelet therapy

1. Introduction

Despite the improvements in revascularization techniques [1][2], antithrombotic therapies [3][4][5] and other measures of secondary prevention including lifestyle modifications and pharmacological treatments, coronary artery disease still represents the leading cause of mortality in developed countries [6] and several efforts have been made to identify new risk factors [7][8][9][10] in order to promote and improve primary and secondary prevention. Patients ≥ 75 years of age account for about one-third of hospitalizations of patients with acute coronary syndromes (ACS) [11]. However, these data consider only older patients admitted to Coronary Care Units or Cardiology wards and underestimate the true number of those hospitalized for ACS. In a prospective, multicentre study using principles of clinical governance [12], aiming to verify and quantify consecutive inclusion of hospitalized ACS patients, it was found that only 69.5% of patients admitted with a diagnosis of ACS were included, due to the prevalent enrolment by participating centres of patients admitted to cardiac wards. Since the greater number of ACS patients admitted to non-cardiac wards are older patients with multiple comorbidities and/or geriatric syndromes, these data show that current epidemiological data underestimate the true incidence of patients with advanced age in ACS series. Moreover, the mortality rates are greatly affected by the characteristics of the population samples included in randomized trials or in observational registries. In the elderly-ACS trial of non-ST-elevation ACS [13], the 1-year mortality rate in randomized patients was 13%, whereas it was 23% in those included in the concurrent registry and not randomized [14]. Patients enrolled in randomized trials, even in those designed for elderly patients, are the fittest ones and do not reflect the wide spectrum of clinical conditions associated with advanced age. It is likely that mortality rates are even higher than those reported in observational studies, due to the exclusion of “neglected” older patients admitted with ACS in medical wards.

Age itself does not accurately mirror the patient’s status, as other features such as comorbidities and geriatric syndromes (frailty, disability, cognitive impairment) are the factors determining patient health and outcomes [15][16][17][18]. Frailty represents a clinical condition associated with increased vulnerability to endogenous or exogenous stressors [16]. It is present in 25–50% of older adults >85 years admitted with ACS, although these figures depend on the definition applied [17]. Cognitive impairment is frequently found in frail, older patients with myocardial infarction (MI) [18], a condition frequently associated with the presence of diabetes, smoking, and the metabolic syndrome, all established risk factors for coronary artery disease and worse long-term outcomes [19][20].

2. Invasive versus Conservative Strategy

Although the European Society of Cardiology (ESC) STEMI guidelines state that “there is no upper age limit with respect to reperfusion, especially with primary PCI” [21], there is relatively little information regarding the outcomes of elderly patients undergoing primary PCI, due to the low representation of elderly patients in clinical trials assessing the effects of mechanical reperfusion for STEMI. A pooled analysis [22] including 834 patients enrolled in three randomized trials (Zwolle [23], SENIOR PAMI [24], and TRIANA [22]) showed that the overall risk of death, re-infarction, or disabling stroke was substantially lower for patients allocated to primary PCI compared with those treated with fibrinolysis (14.9% vs. 21.5%; odds ratio [OR], 0.64; 95% confidence interval [CI] 0.45–0.91; $p = 0.013$), and s only a trend toward reduction of death was found (10.7% versus 13.8%, hazard ratio [HR] 0.74, 95% CI 0.49–1.13), although the effect size was superimposable to that of the largest metanalysis comparing fibrinolysis and primary PCI in younger patients. Septuagenarians and octogenarians undergoing primary PCI show higher mortality rates, both at short-term and mid-term follow-up than younger patients.

In dedicated randomized trials in NSTE-ACS patients, the Italian Elderly ACS trial [13][25], which enrolled 313 patients with NSTE-ACS aged ≥75 years; the After Eighty trial [26], which randomized 557 patients with NSTE-ACS aged ≥80 years; and the RINCAL trial [27] that included 251 patients, the results went in the same direction: older patients allocated to the routine invasive strategy had a lower risk of death and MI, as shown by a meta-analysis (OR 0.65, 95% CI 0.51–0.83; $p < 0.001$) at a median follow-up of 36 months. This result was mostly driven by a statistically significant reduction in MI with a trend towards a lower mortality rate, without heterogeneity among the studies [28]. A significant reduction in mortality was, however, found in the observational SENIOR NSTEMI cohort study that included patients aged >80 years: applying a propensity-score model, the study showed that at 5 years the adjusted risk of dying was 44% lower with early invasive treatment, with the difference emerging from 1 year onwards [29]. The ongoing SENIOR-RITA trial is randomizing a large series of NSTEMI patients aged ≥75 years to determine the impact of a routine invasive strategy on cardiovascular death and non-fatal MI, compared with a conservative treatment strategy [30].

3. Dual Antiplatelet Therapy in Elderly ACS Patients: Comparative Efficacy and Safety among Different $P2Y_{12}$ Inhibitors

Data on optimal platelet inhibition in older adults is limited [31], because elderly patients were underrepresented in the pivotal trials: they accounted for only 13% of patients in the TRITON-TIMI 38 trial (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel—Thrombolysis in Myocardial Infarction study) [32] and for 15% in the PLATO (The Study of Platelet Inhibition and Patient Outcomes) trial [33]. Dual antiplatelet therapy (DAPT) with prasugrel at 10 mg daily dose associated with aspirin significantly increased bleeding in the TRITON-TIMI 38 trial as compared to DAPT with clopidogrel [32], so that its use in elderly patients was not recommended by the Food and Drug Administration, whereas the European Medicines Agency indicated a 5 mg/day maintenance dose [34]. On the contrary, an analysis of the PLATO trial showed that the superiority of DAPT with ticagrelor over DAPT with clopidogrel (including a reduction in cardiovascular mortality) was confirmed also in the elderly population [35]. These indications were issued despite the fact that the differences in the primary endpoint of death, MI and stroke between clopidogrel and prasugrel in the TRITON-TIMI 38 trial (18.3% vs. 17.2%) [32] and those between clopidogrel and ticagrelor in the PLATO trial (18.3% vs. 17.2%) [35] were exactly the same.

Specific trials have been conducted in older ACS patients, comparing different P2Y12 inhibitors in association with aspirin. The ELDERLY ACS 2 trial randomized 1443 ACS patients aged ≥75 years who underwent PCI and showed similar combined thrombotic and bleeding events in patients assigned to 12-month DAPT with a prasugrel 5 mg maintenance dose and in those assigned to 12-month DAPT with clopidogrel 75mg [36]. In a post hoc analysis, DAPT with prasugrel 5 mg, as compared to DAPT with clopidogrel, reduced thrombotic events in the first month after the index event, but increased late bleeding (31–365 days) [37]. DAPT with low-dose prasugrel and clopidogrel also had similar efficacy and safety in medically treated elderly patients enrolled in the TRILOGY ACS (Targeted Platelet Inhibition to Clarify the Optimal Strategy to Medically Manage Acute Coronary Syndromes) study [38].

At odds with the results of the post hoc analysis of the PLATO trial, the POPular AGE (Ticagrelor or Prasugrel Versus Clopidogrel in Elderly Patients With an Acute Coronary Syndrome and a High Bleeding Risk: Optimization of Antiplatelet Treatment in High-Risk Elderly) trial showed that DAPT with clopidogrel had significantly lower bleeding rates (including fatal bleeding) compared with DAPT with ticagrelor (17.6% vs. 23.1%; OR 0.74; 95% CI 0.56–0.97), without any difference in thrombotic events (12.8% vs. 12.5%; OR 1.02, 95% CI 0.72–1.45) [39]. Notably, ticagrelor was prematurely discontinued in about half of the patients randomly allocated to that drug, a finding that could have hampered its potential benefits, but that also indicates that side effects induced by that drug affect a large part of older adults.

4. Bleeding and Thrombotic Risk in Elderly ACS Patients

The goal of the antiplatelet therapy after ACS is to reduce the risk of recurrence of ischemic events, likewise attenuating the bleeding risk [40]. The choice of the composition and optimal duration of DAPT [41][42] should be made on an individual basis, and its effects repeatedly verified throughout the follow-up period. Therefore, cardiologists should assess the thrombotic and bleeding risk of each patient by considering clinical, anatomical, procedural and laboratory data. To this purpose, risk scores, especially for the measurement of the bleeding risk such as the PRECISE DAPT score [43] and the Academic Research Consortium High Bleeding Risk (ARC-HBR) criteria [44][45], may be helpful, and are recommended by guidelines [46].

Although almost all elderly patients satisfy the criteria for the definition of HBR, high thrombotic risk is also concomitant in many patients. This issue is well outlined in the ARC-HBR trade-off model proposed by Urban et al., who reported the results of 1-year clinical outcome of 6641 patients (26% with STEMI or NSTEMI) who underwent PCI with stent implantation and were categorized as HBR according to ARC criteria [47]. Prior MI, the presence of diabetes, STEMI presentation and bare-metal-stent implantation were predictors of MI and stent thrombosis in this HBR population. At the 1-year follow-up, slightly less than half of the patients (44.1%) had a greater risk of thrombotic events than major bleeding, and one third of patients faced a comparable risk of either type of adverse events. Of the 1.445 patients included in the ELDERLY-ACS 2 trial, more than two thirds (68%) had prior MI, diabetes or STEMI presentation, thus carrying a high thrombotic risk according to the ARC-HBR trade-off model [48]. These data show how HBR and high thrombotic risk coexist in a large number of elderly patients with ACS.

5. Antiplatelet Strategies in Elderly ACS Patients

In a recent review on antiplatelet therapy in ACS [49], scholars propose different DAPT strategies according to the presence or absence of HBR and high thrombotic risk. As discussed above, in elderly patients only two conditions are to be considered: (1) isolated HBR, and (2) HBR associated with high thrombotic risk.

For patients with isolated HBR, short DAPT is likely to be the best strategy. In the MASTER DAPT trial [50] that selectively randomized HBR patients (69% aged ≥75 years, 48% with ACS) to 1-month DAPT versus standard DAPT (median 157 days) followed by single antiplatelet agent (mostly clopidogrel in both groups), the abbreviated DAPT strategy was non-inferior to standard therapy for net adverse clinical events (NACE) and for ischemic events, but significantly reduced for major or clinically relevant non-major bleeding. This trial, however, also included patients taking anticoagulants (39%), for whom guidelines recommend an early DAPT cessation (1 week). The 1-month DAPT trial showed similar data [51]; that is, non-inferiority of short DAPT versus standard (6- to 12-month) DAPT followed by aspirin monotherapy for the 1-year composite of cardiovascular events or major bleeding in patients undergoing PCI for non-complex lesions [51]. However, in that trial a significant interaction was observed between treatment strategy and clinical presentation: ACS patients randomized to 1-month DAPT, contrary to stable ones, showed a numerical increase in cardiovascular events with no difference in bleeding as compared to standard-DAPT patients. These data caution against very short (1-month) DAPT periods followed by aspirin monotherapy in ACS patients [52].

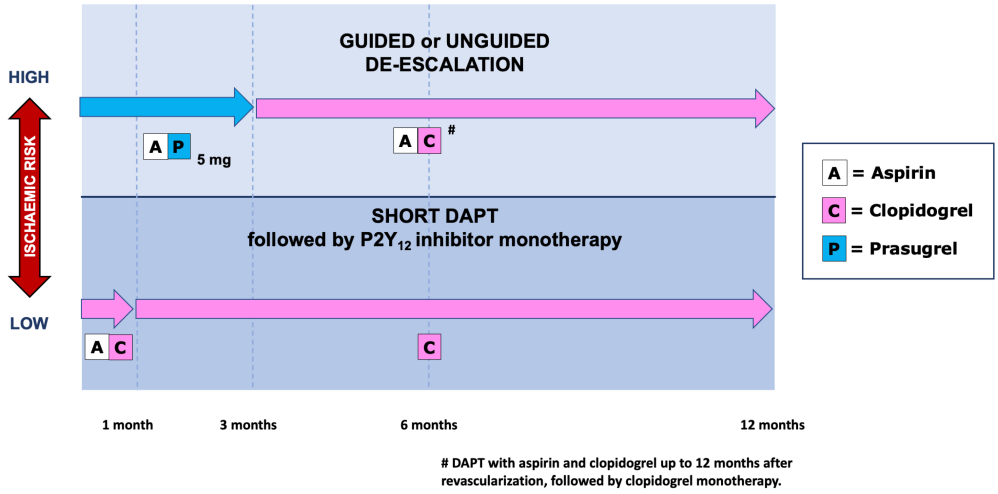

Figure 1. Algorithm for antithrombotic treatment strategies in elderly patients with acute coronary syndrome stratified by ischaemic risk. Abbreviations: DAPT, dual antiplatelet therapy.

Clopidogrel seems the most suitable P2Y12 inhibitor in older patients with HBR, due to a better safety profile than ticagrelor [39][53] and to an efficacy similar to ticagrelor [39][54] or low-dose prasugrel [55]. After DAPT cessation, clopidogrel may be preferred to aspirin as an antiplatelet monotherapy [56].

The higher risk of gastrointestinal discomfort or bleeding associated with aspirin is particularly evident in older patients [57]. This effect may result in a higher medication-discontinuation rate, a condition independently associated with increased mortality [58]. A higher adherence to clopidogrel than to aspirin was observed in the HOST EXAM trial, in which clopidogrel monotherapy was found to be superior to aspirin monotherapy as a chronic maintenance therapy among patients who had successfully completed the required duration of DAPT therapy after PCI [59]. Lower rates of both thrombotic and bleeding outcomes with clopidogrel as compared to aspirin were confirmed in an extended follow-up of over 5 years, after randomization [60]. Moreover, clopidogrel has an off-target anti-inflammatory action that may act as a modulator of the atherothrombotic risk [61][62]; this effect may be particularly beneficial in older patients, in whom frailty is frequently associated with a chronic low-grade inflammation (“inflammaging”), based on immunosenescence [18][63].

In patients with HBR associated with a high thrombotic risk (according to the variables included in the ARC-HBR trade-off model) [47] de-escalation appears as the most appropriate strategy. In a recent meta-analysis [64], de-escalation was superior to short DAPT for protecting against recurrent MI, and significantly reduced bleeding as compared to standard DAPT; a Bayesian meta-analysis showed that short DAPT ranked first in decreasing major bleeding, while de-escalation was first for NACE reduction, indicating that this strategy offers a balanced protection when both high thrombotic and high bleeding risks coexist [49].

Advanced age is a main risk factor for bleeding. It is included in the PRECISE DAPT score that consists of five variables (age, haemoglobin, creatinine clearance, white blood cell count, history of bleeding) and was developed to predict a 12-month bleeding risk, selecting patients suitable for a short DAPT strategy (those with a score value =>25) [43][46]. Older age is an important determinant of the score: consider a patient 80 years old without anaemia (haemoglobin 13 g/dL) no bleeding history, with a creatinine clearance of 60 mL/min and normal white blood cell count (7000 × 10^9/L). His calculated score is 26, which denotes a high bleeding risk. Moreover, almost all elderly patients admitted for ACS exceed the proposed cut-off for HBR of the PRECISE DAPT score, due to the very frequent concomitant presence of variables also related to bleeding [65].

6. Conclusions

The combination and duration of antiplatelet therapy in elderly patients with ACS is still a challenging issue, since most of these patients have both high bleeding and a high thrombotic risk. The evidence so far accumulated in the few studies involving this population favours a cautious approach, avoiding the use of powerful antiplatelet drugs such as full-dose prasugrel or ticagrelor. The suggestions expressed above and summarized in **Figure 1** are mostly speculative, based on post hoc analyses from dedicated studies or from studies performed in general ACS populations. Randomized trials addressing the effects of therapeutic schemes based on the individual risk of elderly patients are needed, to clarify this issue.

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