Update on pharmacological treatment of acute coronary syndrome without persistent ST segment elevation myocardial infarction in the elderly

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Abstract

The increase in cardiovascular disease prevalence with ageing has been attributed to several age-related changes such as changes in the vascular wall elasticity, the coagulation and haemostatic system and endothelial dysfunction, among other causes. There is a 50% increased mortality risk per 10-year increase in age starting at 65 years old. Here, we aimed to discuss pharmacological treatment in acute coronary syndrome (ACS) without persistent ST segment elevation myocardial infarction in the elderly. The main aim of ACS treatment in elderly people is to prevent ischemia, myocardial damage and complications. A meta-analysis suggests that invasive revascularization therapy is probably most useful in older patients. Dual antiplatelet therapy is currently the standard of care post-ACS. Platelet P2Y12 inhibitors are among the most commonly used medications worldwide, due to their established benefits in the treatment and prevention of arterial thrombosis. The main recommendation is to tailor antithrombotic treatment, considering body weight, renal function (Class I, level C) and careful evaluation of life expectancy, comorbidities, risk/benefit profile, quality of life and frailty when invasive strategies are considered (Class IIa, level A) on top of the different recommendations given for a general non ST elevation ACS population. It is obvious that potent P2Y12 inhibitors will continue to play an important role in pharmacological treatment for elderly ACS patients in the future.

Keywords: Acute coronary syndrome; Pharmacological interactions; The elderly; Treatment

1 Introduction

According to the WHO estimates, ischemic heart disease is the global leading cause of death (13.2% of total deaths). Moreover, epidemiological studies have indicated that elderly populations are a growing cohort with over 85 year olds expected to triple by the next two decades.[1–3] Importantly, ischemic heart disease affects mainly males and females aged > 70 years worldwide.[4] The prevalence in the general US population aged > 80 of ischaemic heart disease is about 35% in males and 19% in females[5] with a clear-cut gender-related difference in incidence, mortality and clinical recognition capacity.[5,6,7] It was demonstrated that elderly patients over 75 years old represent 27%–34% of the whole acute coronary syndrome (ACS) population in the European countries.[8,9] Unstable angina and non-ST segment elevation myocardial infarction are often continuous and clinically indistinguishable, collectively referred as non-ST elevation ACS (NSTE-ACS).[10] The risk for cardiovascular atherothrombotic disease starts in the second decade of life and progresses over the years.[11] In the GRACE registry, when comparing the youngest (< 45 years) with the oldest (≥ 85 years) age groups, cardiogenic shock was nearly six times more common, and the rate of major bleeding was nearly tripled.[12] Analysis of the percutaneous coronary intervention (PCI ) Registry of the Euro Heart Survey Programme demonstrated that patients > 75 years were more likely to suffer a non-fatal stroke, major bleeding or renal failure requiring dialysis following PCI for ACS.[13] It is demonstrated that evidence based therapies has significantly decreased mortality and morbidities of ACS.[5,14,15] However, these improvements in ACS management have not equally improved outcomes for older adults.[10] Because of there are not enough clinical trials about this subject, efficacy and safety of some treatments in elderly patient were not well documented. Mortality is at least three fold higher in patients older than 85 years compared with the younger than 65 years of age group.[11,5,6] A few years ago, patients over 75 years of age were frequently excluded from randomised trials.[17–21]

Ageing brings in a series of physiological changes, which narrow therapeutic ranges for several drugs, and changes the
benefit-risk ratio for several therapies and interventions, making elderly patients prone to secondary effects and less predictable effectiveness.\cite{18,22} The increase in cardiovascular disease prevalence with ageing has been attributed to several age-related changes such as changes in the vascular wall elasticity, the coagulation and haemostatic system, and endothelial dysfunction.\cite{9,22–24} Briefly, the cardiovascular system functions change with ageing. Age related decline organ function increases cardiovascular diseases. Moreover, age related changes in pharmacokinetic and pharmacodynamic parameters may result in unpredictable clinical outcomes. Also another important problem is side effects of polypharmacy use in elderly. For instance, polypharmacy itself has been shown to increase bleeding risk in elderly patients with venous thromboembolism.\cite{25} So there is a clear need to perform clinical trials designed for elderly population. Here, we aimed at discussing pharmacological treatment in especially elderly patient with NSTE-ACS.

2 Invasive therapy

The main aim of the ACS treatment in the elderly is at preventing ischemia, myocardial damage and complications. Although the use of an invasive strategy offers the greatest relative benefit to younger patients, it offers the greatest absolute benefit to those over 75 years; within each age group, the 1-year mortality rate was lower in those who underwent PCI compared with those who did not (≤ 65 years: 1.6% vs. 4.9%; 65–74 years: 4.9% vs. 10.5%; ≥ 75 years: 11.6% vs. 21.8%; P < 0.001).\cite{26} European based guidelines recommended that invasive revascularization therapy is useful in high risk elderly ACS patients. Angiography and PCI are generally safe and highly successful but increased risks of stroke and bleeding are important complications of this strategy.\cite{27–31} Especially in patients > 75 years of age post-PCI bleeding is an important prognostic factor.\cite{32} Despite being a high-risk group, data from multiple global registries have consistently shown that older patients are much less likely to undergo invasive revascularization following ACS.\cite{18–21} In the reality, the clinical trials showed that the invasive revascularization therapy in patient over 75 years old was less performed.\cite{33,34} FRISC II study was the first to show a clinical benefit of an invasive strategy in patients with NSTE-ACS (incidence of death or myocardial infarction at 6 months: 9.4% vs. 12.1%; risk ratio 0.78). In this trial, patients older than 75 years of age were excluded. However, the subgroup analysis by age indicated that all the benefit was concentrated in the patients aged 65 years or older, with a RR 0.66 (95% CI: 0.50–0.89), with no benefit seen in younger patients.\cite{35,36} TACTICS trial found a greater absolute benefit in reducing the incidence of the primary end point-death, nonfatal MI, or rehospitalization for an ACS at 6 months in patients aged over 65 years (17.1% vs. 21.7%) compared with the younger patients (14.9% vs. 17.8%).\cite{39} In the meta-analysis, the short and long term studies suggest that the age group in which invasive revascularization therapy is probably more useful is that of the oldest patient. In contrast, in the Italian elderly ACS trial, 313 patients aged over 75 years with NSTE-ACS were randomized to an early invasive strategy or to an initial conservative therapy. It was found that primary endpoint of death, myocardial infarction, bleeding and hospitalization was not significantly different between invasive and conservative therapies.\cite{38} De Luca, et al.,\cite{39} analyzed data from five consecutive Italian nationwide registries of patients with non-ST segment elevation myocardial infarction, conducted between 2001 and 2010. In their analysis, an invasive approach increased from 26.6% in 2001 to 68.4% in 2010 and revascularization rates increased from 9.9% to 51.7%. Overall, 30-day observed mortality decreased from 14.6% to 9.5%.\cite{39} In the study by Bach, et al.,\cite{27} among patients aged ≥ 65 years, the early invasive strategy compared with the conservative strategy yielded a 4.8% absolute reduction in death or myocardial infarction at six month (8.8% vs. 13.6%). Among patients older than 75 years, there was 10.8% reduction in death or myocardial infarction at six month in the early invasive strategy (10.8% vs. 21.6%) with an increase of major bleeding rates (16.6% vs. 6.5%).\cite{27} In a recent Norwegian trial of 457 patients over 80 years and presenting with NSTE-ACS, the primary composite end point of death, myocardial infarction, need for urgent revascularization and stroke was markedly reduced by an initial invasive strategy versus conservative strategy (41% vs. 61%).\cite{40}

3 Noninvasive therapy

Dual anti-platelet therapy (DAT) is currently the standard of care post-ACS, irrespective of age.\cite{41} Independently of the underlying disorder, all anti-platelet drugs variously amplify age-related major bleeding risk, and older (especially ≥ 75 years) patients are poorly represented in randomized trials.\cite{5,29–31,42–46} Thus, the benefit/risk balance of single or combined anti-platelet treatment in elderly patients with ACS comes from subgroup analyses, post-hoc or meta-analyses or registries, with intrinsic methodological limitations.\cite{18}

It is acceptable that age-related slowed megakaryopoiesis, reduced platelet mass and modified transcriptome might all contribute to higher bleeding diathesis as well as to sensitiv-
ity to anti-platelet drugs. Poor responsiveness to prasugrel has been recently associated with a high fraction of circulating immature platelets in patients with ST elevation myocardial infarction.\(^4\) High mean platelet volume, a feature of youngest platelets, has been correlated with poor response to clopidogrel.\(^5\,6\) High platelet turnover reduces the capacity of standard, low-dose aspirin to inhibit circulating platelets over the 24-h dosing interval.\(^7\) In patients at high cardiovascular risk on secondary cardiovascular prevention with aspirin, as in ACS, age is an independent risk factor of bleeding.\(^8\) Thus, it is conceivable that elderly subjects might be more sensitive to aspirin, likely depending on age-related changes in megakaryopoiesis and platelets.

Anti-platelet treatment is the most important step in ACS. Platelet P2Y12 inhibitors are some of the most commonly used medications worldwide, due to their established benefit in the treatment and prevention of arterial thrombosis.\(^9\) The first-generation thienopyridine ticlopidine was the first P2Y12 inhibitor to be used in clinical practice, although its use was limited by adverse effects including neutropenia.\(^10\) The second-generation thienopyridine clopidogrel had a superior safety profile and therefore replaced ticlopidine.\(^11\) Clopidogrel is a thienopyridine approved in DAT for up to one year after ACS on the basis of the CURE trial.\(^12\) However, it has demonstrated that clopidogrel does not satisfactorily inhibit the platelets of approximately one-third of patients due to its metabolism in liver.\(^13\) However, more potent P2Y12 receptor inhibitors are now available in clinical use for patient with acute myocardial infarction after PCI such as ticagrelor and prasugrel. According to recent guidelines, clopidogrel is not the first choice in DAT for NSTE-ACS, because of the demonstrated superiority of ticagrelor and prasugrel.\(^14\)

The third-generation thienopyridine prasugrel is less dependent on CYP enzymes and therefore causes a more potent and consistent decrease in platelet reactivity.\(^15\) In the TRITON-TIMI 38 trial, prasugrel reduced the rate of cardiovascular death, myocardial infarction or stroke compared with clopidogrel (HR: 0.81, 95% CI: 0.73–0.90, \(P < 0.001\)).\(^16\) In this study, it was also demonstrated that prasugrel doses need to be reduced by half (from 10 to 5 mg daily) in the elderly patients (over 75 years old) with ACS due to increased major bleeding risk.\(^17\) TRILOGY trial tested the efficacy and safety of prasugrel compared with clopidogrel during 30 months in medically managed patients with NSTE-ACS. Among the 2083 patients 75 years old or older, no benefit with 5 mg of prasugrel daily was observed while major bleeding risk remained similar to that seen in younger patients with conventional doses (4.1% vs. 3.4%, \(6.7%\) vs. 1.5%, \(+0.6\%\)).\(^18\)

Ticagrelor is the first reversibly binding oral P2Y12 receptor antagonist evaluated for the prevention of clinical thrombotic events in patients with ACS.\(^19\) PLATO trial found a significant reduction in ischemic events and total mortality with ticagrelor versus clopidogrel in patients with ACS.\(^20\) It was found that no more advantages were observed in the elderly patient with ticagrelor. But the rate of major bleeding was increased.\(^21\) The efficacy/safety balance of DAT including ticagrelor 90 mg, administered twice daily, versus DAT with clopidogrel for 6–12 months post-ACS appears maintained above or below 75 years in the PLATO trial.\(^22\) In the PEGASUS trial, patients with myocardial infarction that occurred 1–3 years before enrolment were randomized to ticagrelor 90 mg bid, 60 mg bd or placebo on top of aspirin, with a median follow-up of 33 months. A subgroup analysis showed that older patients had approximately a doubled incidence of major bleeding in all treatment groups (placebo: 0.96% vs. 1.68%; 90 mg: 2.3% vs. 4.81%; 60 mg: 2.05% vs. 4.11%, below and above 75 years, respectively).\(^23\)

Recent study in China was designed to investigate the efficacy and safety outcomes of ticagrelor in comparison with clopidogrel on a background of aspirin in elderly ACS. It was a double-blinded, randomized controlled study and 200 patients older than 65 years with the diagnosis of ACS were assigned 1: 1 to take ticagrelor or clopidogrel for one year. The study demonstrated that ticagrelor reduced the primary efficacy end point at no expense of increased bleeding risk compared with clopidogrel, suggesting that ticagrelor is a suitable alternative for use in elderly Chinese patients with ACS.\(^24\) It should be noted that ticagrelor specific antidot is under clinical development. It might offer a great therapeutic advantage, especially in elderly patients.

The intravenous P2Y12 inhibitor cangrelor can achieve almost immediate potent P2Y12 inhibition.\(^25\) In another clinical trial with cangrelor, it was found that the benefit was more significant among patient aged 75 years or older. In the EPICOR trial, the reduction of death, myocardial infarction and urgent revascularization seemed lower in patients aged \(\geq 65\) years versus younger ones (age \(< 65\) years: 13.6% vs. 5.1% in placebo versus abciximab and standard heparin; age \(\geq 65\) years: 8.3% vs. 5.8% in placebo vs. abciximab and standard heparin).\(^26\) However, the recent studies showed that glycoprotein IIb/IIIa receptor inhibitors should be avoided due to bleeding risk in the elderly patient with ACS.\(^27\)

The use of anticoagulant therapy during primary PCI is a class I indication according to all major international guidelines.\(^28\) Bivalirudin and unfractionated heparin are the two adjunctive antithrombotic therapies most commonly
used during primary PCI.\[69\] Bivalirudin may provide benefit in reducing bleeding in comparison to unfractionated heparin plus glycoprotein IIb/IIIa inhibitor to support revascularization. The combination of glycoprotein IIb/IIIa inhibitors and full dose fibrinolytic medications is associated with high rates of bleeding and intracranial hemorrhage in older people.\[10\]

Vorapaxar, formerly known as SCH 530348, is an oral protease activated receptor-1 antagonist with high bioavailability. The drug prevents thrombin induced platelet aggregation by competitively inhibiting the protease activated receptor-1 platelet receptor. Vorapaxar has a long half-life. The terminal elimination half-life is 7–11 days while the effective half-life based on accumulation at steady state is between three and four days.\[70\] Vorapaxar 2 mg has recently gained approval in the EU and US as aspirin add-on treatment, with or without clopidogrel, in patients with a history of myocardial infarction, based on a pre-specified subgroup analysis of the TRA2P-TIMI 50.\[71\] TRA2P was a large (26449-patient), international, multicenter, randomized, double-blind, parallel group, cardiovascular outcomes trial in patients with a history of myocardial infarction, cerebrovascular disease, or peripheral arterial disease. Vorapaxar dosing was 2.5 mg per day, and the median duration of treatment was 823 days with follow-up to four years. TRA2P was successful on its primary endpoint of cardiovascular death, myocardial infarction, stroke, or urgent coronary revascularization. Moderate to severe bleeding occurred in 4.2% of patients who received vorapaxar and 2.5% of individuals who received placebo (HR: 1.66; 95% CI: 1.43–1.93; P < 0.001).\[72\]

The TRACER trial randomized 12,944 patients with NSTE-ACS in 37 countries throughout the world to receive vorapaxar or placebo on top of standard care with clopidogrel and aspirin. A composite of death from cardiovascular causes, myocardial infarction, or stroke occurred in 822 patients in the vorapaxar group versus 910 in the placebo group (14.7% and 16.4%, respectively; HR: 0.89; 95% CI: 0.81–0.98; P = 0.02). Vorapaxar significantly increased all types of bleeding including major an intracranial hemorrhage.\[73\] It should be mentioned that especially in older patients vorapaxar and prasugrel and ticagrelor concomitant use should be avoided.

There is another important point that pharmacological interaction is the concomitant use of DAT and selective serotonin reuptake inhibitors because of increased bleeding.\[74\] Therefore, especially in elderly patients on the long term DAT the underlying risk of bleeding should be carefully considered when choosing antidepressants.\[75\]

Rivaroxaban and apixaban, both direct inhibitors of activated factor Xa, have been tested in phase III clinical trials as add-on therapy to DAT combining aspirin and clopidogrel in ACS. The 2.5-mg bid dosage has been approved for ACS patients with elevated cardiac biomarkers, and caution is recommended in patients aged ≥ 75 years due to the low number of patients enrolled in the phase III trial and to the known age-related hemorrhagic risk.\[76\] There is no study about concomitant use of rivaroxaban with prasugrel and ticagrelor in ACS. This combination could lead to severe bleeding in elderly patient.

### 4 Important points for clinical use

Thienopyridines, such as clopidogrel and prasugrel, are produgs that require conversion into their active metabolites by hepatic cytochrome P450 enzymes in vivo to reduce platelet reactivity. Ticagrelor is directly acting and therefore does not require conversion into an active metabolite to reduce platelet reactivity, thereby resulting in a predictable pharmacokinetic profile.\[77\] However, ticagrelor is metabolized by CYP3A enzymes so prescribers should pay attention to drug-drug interactions with CYP3A inhibitors.\[78\]

The active metabolites of clopidogrel and prasugrel covalently bind to P2Y12 receptors, causing irreversible inhibition that lasts for the lifespan of the platelet, which is approximately 10 days.\[79\] In contrast, ticagrelor is a reversibly-binding P2Y12 inhibitor, which results in a more rapid offset of platelet inhibition, within approximately 72 h.\[80\] Also it was demonstrated that crushed tablets of ticagrelor achieved a significantly greater reduction in platelet reactivity than ordinary tablets.\[81\] The availability of cangrelor offers the opportunity to circumvent the problem of delayed absorption of oral P2Y12 inhibitors in opioid-treated patients undergoing emergency coronary stenting.\[82\] The most important adverse effect of antiplatelet drugs is bleeding. But other adverse effects are observed clinically. For example ticagrelor may cause dyspnoea due to increased plasma levels of adenosine and ticlopidine caused neutropaenia.\[52\]

Another important point, life style modification (weight control, smoking cessation, etc) and additional pharmacological treatment (blood pressure and serum glucose control, etc) management is important in elderly patient with ACS. Also exercises training improves long-term survival and well-being on ACS in elderly patient.

### 5 Conclusions

Post ACS, elderly patients have a high risk of re-hospitalization and death both from cardiovascular and non-cardiovascular causes. There is a 50% increased mortality risk

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per 10-year increase in age starting from 65 years of age.\textsuperscript{[83]}

The recently issued NSTE-ACS guidelines from the European Society of Cardiology have specific recommendations for elderly patients within the special population section.\textsuperscript{[46]}

The main recommendation is to tailor antithrombotic treatment, considering body weight, renal function (Class I, level C) and careful evaluation of life expectancy, comorbidities, risk/benefit profile, quality of life and frailty when invasive strategies are considered (Class IIa, levelA) on top of the different recommendations given for a general NSTE-ACS population.

It is obvious that potent P2Y12 inhibitors will continue to play an important role in pharmacological treatment for ACS elderly patients in the future. Pretreatment with P2Y12 inhibitors prior to coronary angiography is likely to continue, unless future studies indicate a more favorable alternative, such as initial use of an intravenous P2Y12 inhibitor.

**Acknowledgements**

This study was supported by Scientific Research Project Coordination Unit of Akdeniz University. The authors report no relationships that could be construed as a conflict of interest.

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