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Acute coronary syndrome in older populations: integrating evidence into clinical practice

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Abstract

Acute coronary syndrome (ACS) disproportionately affects older populations. This is despite advancements in diagnosis and management over the past few decades leading to an overall improvement in clinical outcomes in patients with ACS. Patients aged ≥ 70 years account for more than one third of all patients admitted to hospital with ACS and are at the highest risk of complications including mortality. This article reviews ACS in older populations, including the epidemiology, changes in physiology contributing to increased risk, clinical manifestations, inadequacy of current diagnostic methods, and controversies around recommended management strategies.

Keywords: Myocardial infarction, aging, clinical manifestation, diagnosis, treatment, older

INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of death worldwide[1], with acute coronary syndrome (ACS) accounting for a significant socioeconomic burden, death, and disability[2]. Although there are many risk factors that predispose an individual to ACS, age is an independent and non-modifiable risk factor. The majority of patients with acute ACS are older than 70 years of age. There is a complex interplay of variables,

such as comorbidities, functional impairment, physiological changes, and increased vulnerability to polypharmacy, which complicate ACS management in the elderly. These factors are also likely to underlie the significant disparities in care experienced by older populations with CVD. Given the rapidly increasing aging population, the burden of ACS continues to rise, and improvements in prevention, diagnosis, and treatment are urgently needed[1,3,4].

EPIDEMIOLOGY

Age is an important non-modifiable CVD risk factor. The incidence of ACS increases with advancing age [Figure 1], with over half of all ACS occurring in people aged ≥ 65 years old and a third in people aged ≥ 75 years old[1]. Notably, the prevalence of ACS in individuals aged 65-74 years is seven-fold that of those aged 35-44 years, with the prevalence among people aged ≥ 85 years six times that of those aged 55-64 years[5,6]. Similarly, the incidence of ACS increases with age, such that there is a nearly three-fold increase in prevalence among people older than 80 years compared to those aged 65-69[7].

The prevalence of non-ST elevation ACS (NSTEACS) is higher in the elderly population compared to ST elevation ACS (STEACS)[8]. Older people are more likely to present with NSTEACSs than STEACSs, with 24.7% of STEACS and 31.6% of Non-ST elevation acute coronary syndrome (NSTEACS) patients aged 75 years old or older[9].

AGE-RELATED CHANGES IN PHYSIOLOGY

Age-related physiological changes in endothelial function, cardiac structure, and hemostasis both predispose to ACS and adversely influence post-ACS outcomes in the elderly [Figures 2 and 3].

Age-related changes in vascular endothelial function:

Age-related vascular endothelial dysfunction can increase the risk of cardiovascular disease[10,11]. A major contributor to vascular endothelial dysfunction is the reduced bioavailability of nitric oxide[12,13]. Nitric oxide induces vascular relaxation under mechanical forces such as hypertension-induced stress. With aging, there is an increase in the accumulation of free radicals and oxidative species. These cause the breakdown of nitric oxide, therefore reducing its bioavailability and impairing endothelium-mediated vasodilation[11,14]. This reduction in vasodilation increases arterial stiffness and facilitates the development of atherosclerosis[15].

Age-related changes in cardiac structure and function:

Aging leads to changes in valves, cardiomyocytes, and the conduction system. Previous studies have reported that aging leads to a loss of elasticity and fibrotic changes within the leaflets of both semilunar valves and atrioventricular valves, causing changes in valvular dimension and a decrease in extensibility of the leaflets[16,17]. There is also a shortening of tendon chords and papillary muscles, which prohibit the complete closure of valves[16,18]. Furthermore, aging can lead to a loss of the total number of cardiomyocytes, but with compensatory hypertrophy of the remaining cells[19]. There is also an association between increasing age and the decreasing function of cardiac pacemaker cells[20]. A variable degree of calcification can occur in the cardiac skeleton, which can alter electrical conduction, thus predisposing to cardiac arrhythmias[21]. These anatomical and physiological changes in cardiac structure and function can predispose to ACS and post-ACS complications.

Age-related changes in hemostasis, favoring thrombus formation:

There are age-related changes in the production of coagulation factors and platelet function which may account for a higher incidence of thrombotic cardiovascular disorders. Studies have shown that the aging process leads to enhanced production of coagulation factor IX and expression of the *hFIX* gene[22-24]. While

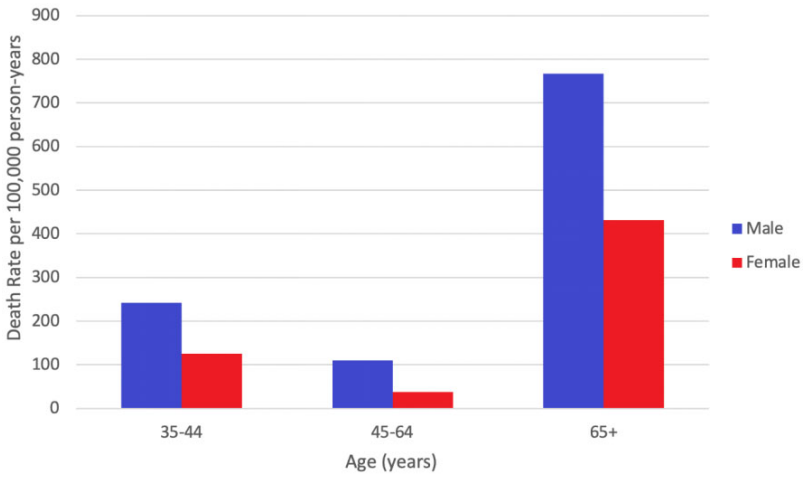

Figure 1. Mortality in the United States of America for acute coronary syndrome by age and gender, 2017-2019[131].

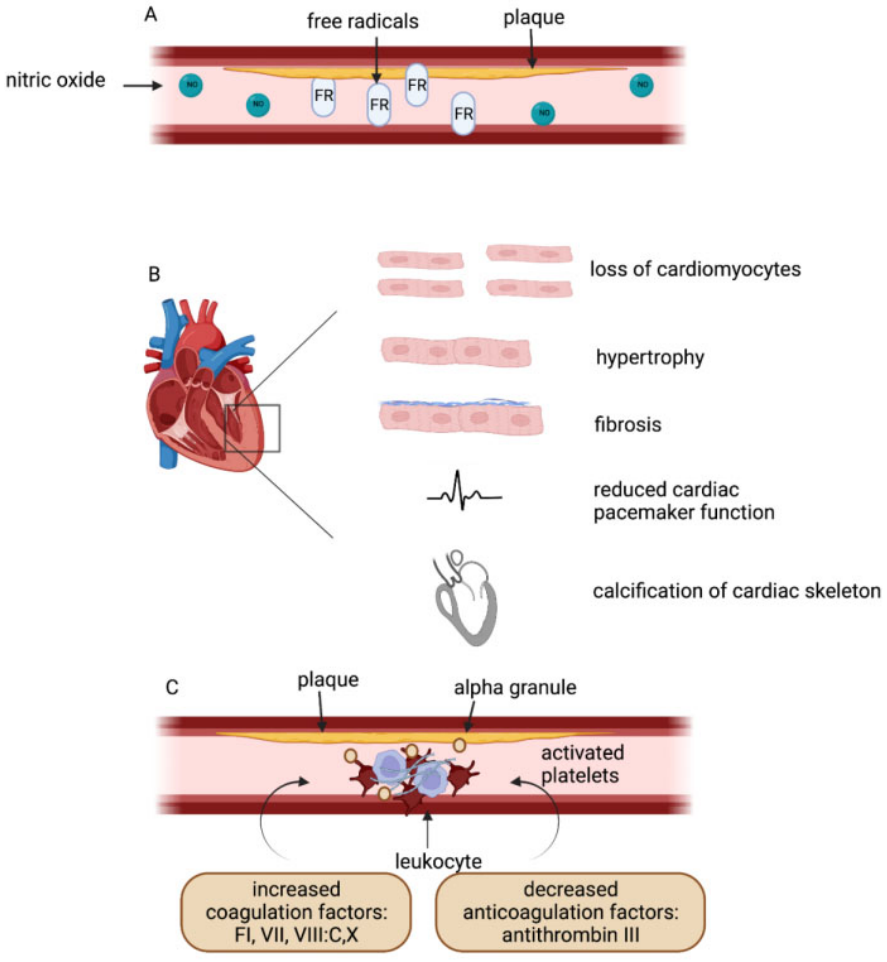

Figure 2. Age-related changes in pathophysiology in elderly patients. (A) Pathophysiological changes in blood vessels include reduced availability of nitric oxide, increased accumulation of free radicals, and increased arterial stiffness. (B) Aging leads to loss of the total number of cardiomyocytes, compensatory hypertrophy, and fibrotic changes. These changes together with calcification of the cardiac skeleton contribute to a loss of function of cardiac pacemaker cells. (C) Aging processes lead to increased release of coagulation factors and decreased release of anti-coagulation factors, which favor thrombus formation.

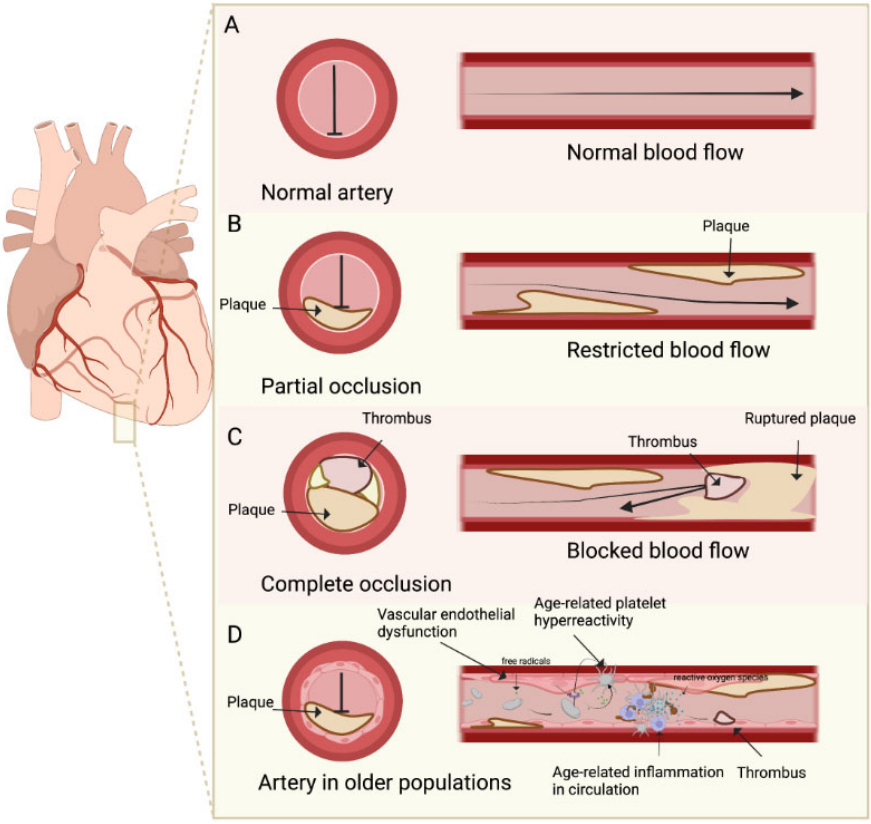

Figure 3. Coronary anatomy and blood flow in the normal artery and myocardial infarction: (A) normal arterial lumen with normal, non-restricted blood flow; (B) restricted blood flow from partially occluded vessel can result in NSTEACS or angina; (C) complete vessel occlusion from plaque rupture and local thrombus formation leading to STEACS; and (D) age-related physiological changes that increase susceptibility to ACS. Aging is associated with an increase in the production of reactive oxidative species and free radicals, which impair endothelium-mediated vasodilation, leading to vascular endothelial dysfunction. Endothelial dysfunction causes the phenotype of vessels to be more prone to atherogenesis. The aging process also leads to platelet hyperreactivity to activation and aggregation, and immune dysregulation leads to a chronic systemic inflammatory state. NSTEACS: Non-ST elevation acute coronary syndrome; STEACS: ST elevation acute coronary syndrome; ACS: acute coronary syndrome.

prothrombotic factors increase, there is reduced production of anti-coagulant factors[25,26]. This imbalance between pro-coagulation and anti-coagulation factors with aging favors thrombus formation.

Another significant change that occurs is age-related chronic inflammation. The literature reports the increased release of pro-inflammatory mediators and dysfunctional immune cells in elderly patients[27-30]. These pro-inflammatory mediators stimulate thrombus formation and predispose to ACS[31].

Furthermore, aging is associated with changes in platelet biology and function[32]. Although platelet counts decrease with age, platelet reactivity increases[32,33]. Thus, the hyperreactivity makes platelets more prone to activation, aggregation, and thrombus formation[32,34]. Studies have shown that the aging process leads to changes in the lipid profile of the platelet membrane, which results in decreased membrane lipid fluidity[35,36]. Although the exact mechanism remains unknown, reduced platelet membrane lipid fluidity has been shown to cause hypersensitivity to adenosine diphosphate-induced platelet activation via modifications in phosphoinositide signaling and metabolism[37-40]. Aging is also associated with an increase in the release of alpha granules upon platelet activation[40]. Enhanced secretion of alpha granules promotes platelet–leukocyte binding, circulating mixed aggregate formation, and thrombotic progression[39-41].

CLINICAL PRESENTATION IN OLDER PEOPLE WITH ACS

The diagnosis of ACS can be challenging in older patients due to atypical clinical presentation compared to younger populations. Studies have shown that only half of hospitalized patients with ACS aged ≥ 75 years experience chest pain[42,43]. The characteristics of the pain, including the character, location, and intensity, tend to be different compared to younger people[44-46]. Pain in the elderly often presents as upper abdominal pain, rather than classic parasternal or precordial pain[47,48]. As the level of pain perception is also significantly reduced in the elderly, there is an increased prevalence of silent/asymptomatic ACS[49,50].

Dyspnea is a common presentation of ACS in the elderly[51-54]. Older people with ACS present with dyspnea (49%), fatigue, nausea (24%), syncope (19%), decreased physical activity, or confusion as the most prominent symptoms[42,55,56]. Altered mental status is a key presenting feature in approximately 20% of patients aged ≥ 80 years[46,57]. Other symptoms, such as gastrointestinal symptoms, have also been reported, especially in the elderly female population[42,43,48].

Although the reasons behind age-related changes in the symptomatology of ACS remain largely unknown, such atypical presentations are likely to account for the delays in diagnosis, pre-hospital care, and in-hospital treatments experienced by older people compared to younger age groups.

DIAGNOSIS

Electrocardiogram

Diagnosis of ACS is based on a combination of clinical manifestations, electrocardiographic changes, and troponin elevation. However, as discussed above, elderly populations tend to demonstrate abnormal clinical manifestations. In addition, the electrocardiograms (ECG) of older patients with ACS are more likely to demonstrate non-typical patterns, which confound the ability to diagnose ACS[58]. This subsequently leads to a delay in providing treatment for the elderly. Specifically, the presence of ST elevation is less prevalent in the elderly compared to younger populations[59].

Additionally, older people are likely to have a higher rate of baseline pre-existing ECG abnormalities even in the absence of ACS including resting T-wave abnormalities and non-specific ST changes. ST-elevation caused by pre-existing non-ischemic events is commonly seen, which can make interpretation of a true acute ACS challenging[60].

Troponin elevation

Detection of a rise in serial troponin levels is critical for the diagnosis of ACS. Despite this, data suggest that older populations tend to have elevated baseline troponin levels due to age-related changes[61,62]. Troponin elevation due to non-ischemic causes, such as hypertensive cardiac disease, chronic renal failure, acute pulmonary embolism, and chronic obstructive pulmonary disease, is commonly reported in the elderly[63-67]. This can further impede the diagnosis of ACS as troponin elevation may be disregarded as being "normal" for the age group. Even though troponin levels can be elevated in the elderly, the combination of symptoms, ECG, and typical rise and fall in troponin levels remains highly specific.

Angiographic findings

Elderly patients are more likely to have multivessel disease, high-grade stenosis, and complex lesions on angiography. From 66% to 75% of patients aged over 80 years presenting with a NSTEACS have multivessel disease[68,69]. Octogenarians undergoing PCI have a higher prevalence of calcified lesions (46.2% *vs.* 20.7%), tortuous lesions (18.3% *vs.* 11.8%), ostial lesions (12.2% *vs.* 7.1%), and left main stenosis (8.7% *vs.* 2.8%) compared to those < 80 years old[70]. Reduced coronary arterial collateral circulation in the infarct zone has

also been observed in older populations[71]. The nature of the coronary disease thus poses challenges to successful revascularization in this age group.

TREATMENT

Older people have been underrepresented in ACS trials, which complicates the extrapolation of results[72]. There are very few randomized controlled trials (RCTs) assessing the management of ACS that are adequately powered to assess outcomes in older people. The majority of evidence derives from subgroup analyses of ACS trials and/or observational data. Additionally, older populations are less likely to receive guideline-based therapy for ACS, less likely to be admitted to a coronary care unit (CCU), and less likely to receive revascularization[9].

However, age alone should not be the sole criterion excluding older people from CCU admission. All patients who are being actively managed with a reasonable prognosis should be strongly considered for CCU. Given challenges with the management of elderly patients, clinicians should strive to integrate geriatric principles into the current standard of care in CCU to achieve optimal care for elderly patients[73], including assessment of prognosis and frailty. Frailty is a common geriatric syndrome and is well-recognized for its role as a predictor of the poor prognosis from cardiovascular disease[74]. Secondly, strategies should be implemented to ensure safe and effective medication use in CCU. Older patients often take many different prescribed medications at the time of CCU admission[75]. The existing medications in combination with the commencement of new therapies in CCU and age-related changes in physiology make elderly patients more susceptible to adverse effects from polypharmacy[76,77]. Discussion of end-of-life plans should also be introduced early in the disease trajectory[78].

The following section describes the evidence for current therapies in older people and the controversies surrounding their use.

Medical treatment

Anti-platelet agents

Anti-platelet therapy is the cornerstone of ACS management in older populations[79]. Since platelet activation and aggregation play important roles in the pathogenesis of ACS, a large part of ACS treatment and recurrent coronary event prevention involves platelet inhibition[80,81]. Aspirin is recommended for routine administration in older patients with ACS[79]. Aspirin inhibits cyclooxygenase enzymatic reaction, therefore blocking the generation of thromboxane A_2 production[82]. Decreased thromboxane A_2 leads to reduced platelet aggregation and prostaglandin-mediated vasoconstriction[82].

In the general population, there is clear evidence that aspirin reduces cardiovascular mortality post ACS. The Second International Study of Infarct Survival (ISIS2) demonstrated a significant reduction of cardiovascular mortality, non-fatal ACS, and stroke with aspirin alone or when used in conjunction with streptokinase at 15 months post ACS[83]. Similarly, the Multicenter Study of Myocardial Ischaemia demonstrated a mortality rate that was approximately five times higher in non-aspirin users (n = 185) than in aspirin users at 23 months post-ACS in the general population (n = 751) (P = 0.0028)[84]. While data from RCTs are limited in older people, an observational study conducted in older populations (n = 1410, mean age 81 ± 9 years) showed consistent effects, with a reduction in the incidence of new coronary events in those who take aspirin compared to no aspirin at three years post-ACS (event rate 50% *vs.* 72%, $P < 0.001$)[85].

Dual antiplatelet therapy (DAPT), including low-dose aspirin and a $P2Y_{12}$ inhibitor, is the cornerstone of therapy post-ACS to prevent recurrent major adverse events[79,86]. $P2Y_{12}$ inhibitors act upon the platelet ADP receptor to reduce platelet activation. There are benefits of clopidogrel and ticagrelor use post-ACS in older people, but the increased risk of bleeding in elderly patients must also be balanced. The Percutaneous Coronary Intervention Clopidogrel in Unstable angina to prevent Recurrent ischaemic Events (PCI-CURE) study demonstrated the benefit of clopidogrel taken with aspirin in reducing cardiovascular mortality and ACS compared to aspirin alone regardless of age[87]. However, compared with younger patients, the subgroup > 65 years of age had both smaller absolute (3.5% *vs.* 3.9%) and smaller relative (20.7% *vs.* 39.8%) reductions. Meanwhile, the superiority of ticagrelor over clopidogrel remains controversial. The prospective randomized PLATelet inhibition and patient Outcomes (PLATO) trial demonstrated that the superiority of ticagrelor in reducing cardiovascular mortality, ACS, or stroke compared to clopidogrel did not vary with age, specifically between older patients aged ≥ 75 years (n = 2878, adjusted hazard ratio (HR) 0.89, 95%CI: 0.74-1.08) and younger patients aged < 75 years (n = 15,744, HR 0.84, 95%CI: 0.75-0.93) (interaction P = 0.56)[88], but this was largely driven by benefit in older patients who did not undergo revascularization[89]. The sub-analysis of the PLATO trial in patients with NSTEACS who underwent revascularization within 10 days of randomization demonstrated a diminished benefit of ticagrelor on the primary outcome compared to clopidogrel in patients > 65 years of age who underwent PCI compared to younger patients (HR 1.17, 95%CI: 0.86-1.61, P value of interaction < 0.01)[89]. While the rate of major bleeding events also did not differ between older and younger patients when a combined endpoint of CABG- and non-CABG-related bleeding was assessed (≥ 75 years, HR 1.02, 95%CI: 0.82-1.27; < 75 years, 1.04, 95%CI: 0.94-1.15; interaction P = 0.89)[88], there was a ~30% increase in non-CABG-related bleeding in older people with ticagrelor. Similarly, real-world evidence in the SWEDEHEART registry demonstrated that the incidence of recurrent ACS was similar in both the ticagrelor group (n = 5571) and the clopidogrel group (n = 8434) in ACS patients aged > 80 years (HR 0.97, 95%CI: 0.88-1.06)[90], but ticagrelor was associated with a higher risk of bleeding (HR 1.48, 95%CI: 1.25-1.76)[90].

Another $P2Y_{12}$ inhibitor, cangrelor, is well-known for its reversibility as an antiplatelet agent and is therefore proposed to be a safer option for elderly patients[91]. There was no significant difference in moderate to severe bleeding between cangrelor and clopidogrel in older patients > 75 years old post-PCI (n = 10,942, 1.1% and 1.0%, OR 1.07, 95%CI: 1.02-4.93; P = 0.21)[92]. Cangrelor produced similar efficacy in reducing mortality post-PCI when compared with clopidogrel (5.4% *vs.* 7.4%; 95%CI: 0.50-2.01; P = 0.07)[92].

There is no clear benefit supporting the use of prasugrel in older people. The Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis in Myocardial Infarction (TRITON–TIMI) 38 trial showed no benefit of prasugrel in reducing cardiovascular events post-ACS in older patients aged > 75 years (HR 0.99, 95%CI: 0.81-1.21, P = 0.92), but an increased risk of major bleeding (P = 0.06)[93]. The Elderly ACE 2 trial also showed no benefit of prasugrel in reducing stent thrombosis rate in older patients aged > 74 years with ACS undergoing PCI (OR 0.36, 95%CI: 0.13-1.00, P = 0.06), but an increased risk of bleeding (OR 1.42, 95%CI: 0.85-3.16, P = 0.18)[94].

However, risks of recurrent CVD events may need to be balanced against those with high bleeding risks. Current guidelines recommend 12 months of DAPT post-ACS and/or coronary percutaneous revascularization regardless of age[79]. In patients who are at high risk of bleeding, the duration of therapy may need to be carefully considered, particularly as the risk of stent thrombus with modern drug-eluting stents is very low three months post-insertion.

The role of glycoprotein IIb/IIIa (GpIIb/IIIa) receptor antagonists in older people is unclear. GpIIb/IIIa receptor antagonists inhibit the binding of fibrinogen and vWF, thereby preventing platelet crosslinking and aggregation[95]. Compared to younger patients aged < 55 years, abciximab may not offer additional post-PCI clinical benefits to older patients aged > 75 years[96]. Composite major adverse cardiovascular events (MACE) (20.8 *vs.* 20.4%, $P = 0.74$) or angiographic restenosis also did not differ in older patients between the abciximab group and the non-abciximab group at one-year follow-up[96]. In addition, there were no significant differences in major hemorrhagic events in patients aged > 65 years who received abciximab ($n = 668$) compared to no abciximab ($n = 671$) (5.8% and 3.9%, respectively; $P = 0.22$)[96]. Findings from these trials suggest that there is no clear benefit that abciximab use improves outcomes in older populations undergoing PCI. However, the data are limited, and future research is required.

Anti-coagulation

Current guidelines recommend anticoagulation for all patients with ACS[79]. Intravenous unfractionated heparin has been the standard anti-coagulant to support primary PCI[79,97]. Despite the validation of heparin's efficacy in reducing post-PCI thrombotic complications in various studies, heparin-induced major hemorrhagic events are also observed across different age groups[98,99]. Studies have been conducted to explore the optimal dosing of heparin[100]. Interestingly, there is no significant difference in major hemorrhagic events between unfractionated and low molecular weight heparin dosing in the general population[101]. The FUTURA/OASIS-8 trial showed no difference in the rate of major hemorrhagic events at 30 days after PCI between the low-dose group ($n = 1024$) and the standard-dose group in patients aged > 65 years ($n = 1002$) (4.7% and 5.8%, respectively; odds ratio (OR), 0.80; 95%CI: 0.54-1.19; $P = 0.27$)[98].

Recent studies have focused on utilizing low molecular weight heparin with PCI in older patients[102]. Enoxaparin is low molecular weight heparin with a more predictable pharmacokinetic profile, increased bioavailability, and longer duration of action[100]. The ATOLL trial involving 165 patients aged > 75 with ACS reported a significant reduction in the risk of post-PCI major hemorrhagic events and a similar anti-thrombotic effect from enoxaparin use compared to unfractionated heparin[101]. Although the sample size was small, there were no significant differences in cardiovascular events between the enoxaparin group ($n = 85$) and the unfractionated heparin group ($n = 80$) in patients aged > 75 years (38% *vs.* 48%, respectively; relative risk (RR), 0.79; 95%CI: 0.55-1.13; $P = 0.66$)[101]. A significant reduction in post-PCI bleeding events in the enoxaparin group ($n = 85$) was noticed compared to unfractionated heparin group ($n = 80$) (11% *vs.* 25%, RR 0.59; 95%CI: 0.21-0.87)[101]. The FAST-MI registry also reported that the rate of major hemorrhage post-ACS was markedly reduced in the enoxaparin group ($n = 583$) compared to the heparin group ($n = 380$) in older patients aged > 75 years (2.4% *vs.* 6.1%, OR 0.41, 95%CI: 0.56-0.91, $P = 0.004$)[102]. Mortality at one year post-ACS was significantly reduced in the enoxaparin group ($n = 583$) compared to the heparin group ($n = 380$) in older patients (OR 0.66, 95%CI: 0.50-0.85, $P < 0.001$)[102]. Hence, enoxaparin appears to be superior to intravenous unfractionated heparin, especially in older patients with ACS and those undergoing PCI[101].

Lipid-lowering therapy

All older patients should commence statin therapy if tolerated post-ACS as optimal lipid management is an important part of the secondary prevention of ACS[103]. There is reasonable evidence supporting statin use for secondary prevention in those with ischemic heart disease (IHD). A meta-analysis by Afilalo *et al.* of patients aged ≥ 65 years in nine major secondary prevention studies ($n = 19,569$) demonstrated that statin use produced a five-year reduction in all-cause mortality (RR 0.78, 95%CI: 0.65-0.89), coronary heart disease (CHD) mortality (RR 0.70, 95%CI: 0.53-0.83), nonfatal ACS (RR 0.74, 95%CI: 0.60-0.89), revascularization (RR 0.70, 95%CI: 0.53-0.83), and stroke (RR 0.75, 95%CI: 0.56-0.94)[104,105]. Statin therapy in older patients

remains underused[106,107], resulting in failure to achieve lipid-lowering goals in a large proportion of patients[108]. Statins appear to be generally well tolerated in older people, with a similar adverse effect and tolerance profile between younger and older people[109].

Angiotensin-converting enzyme inhibitors

ACE inhibitors improve cardiovascular outcomes in older people, particularly in the presence of LV dysfunction. The GISSI-3 trial demonstrated that there was no significant early effect on mortality in patients aged ≥ 70 years with ACS, but lisinopril lowered the combined end point of death, heart failure, or severe left ventricular (LV) dysfunction at six months[110]. Similarly, the Survival And Ventricular Enlargement trial (SAVE) trial showed that captopril in elderly patients with LV dysfunction post-ACS resulted in a significant reduction in all-cause mortality, symptomatic heart failure, and heart failure-related hospitalizations[111].

Even though angiotensin-converting enzyme inhibitors (ACEI) are generally well-tolerated in older patients, an increased incidence of elevated serum creatinine levels has been observed in older patients compared to younger patients (0.2% and 0.1%, respectively; $P < 0.0001$)[112]. In the ramipril group, patients aged > 70 years were more likely to discontinue therapy due to hypotension compared to those < 70 years of age (2.6% and 1.6%, HR 1.65, 95%CI: 1.08-2.51, $P = 0.02$)[112]. While ACEI are of utility in older patients, these results suggest that renal function, electrolytes, and blood pressure should be closely monitored when commencing such therapies in older populations[112].

Beta-blockers

Current guidelines recommend that beta-blockers should be continued during and after hospitalization to reduce myocardial oxygen demand[79]. The short-term benefits of beta-blocker use in older patients are well established. The ISIS-1 study showed that intravenous followed by oral atenolol significantly reduced post-ACS mortality and risk of reinfarction in patients aged > 65 years ($n = 2644$)[113]. In the general population, early and immediate intravenous beta-blocker use ($n = 720$) in the treatment course of ACS reduced the risk of reinfarction compared to deferred treatment ($n = 714$) (2.7% *vs.* 5.1%, respectively; $P = 0.02$)[114-116]; however, studies in older population are lacking. There is some evidence that the use of beta-blockers markedly reduces adverse coronary events in older patients with silent ischemia[117]. The ASIST trial involving 104 patients with asymptomatic ischemia aged > 65 years found that the risk of major coronary events at one year after diagnosis is around two times higher in the placebo group ($n = 54$) compared to the atenolol group ($n = 50$) (25.3% *vs.* 11.2%, respectively; RR 0.44, 95%CI: 0.26-0.75, $P = 0.001$)[117]. Direct evidence of long-term beta-blocker use in older patients is lacking. Hence, further research is needed on the optimal duration and utilization of beta-blocker therapy in the elderly population post ACS.

Nitrates

Current guidelines recommend the administration of sublingual or intravenous nitrates as part of the initial symptomatic management of ACS[79,118]. Nitrates directly relax vascular smooth muscles, thus inducing vasodilation as well as increasing blood flow and oxygen supply to the heart[119]. In addition, nitrates also act as a vasodilator to reduce cardiac preload and further decrease myocardial wall stress[120]. Hence, nitrates efficiently restore the oxygen supply–demand equilibrium to maintain optimal function in the ischemic heart[119]. Although the role of nitrates in acting as rapid symptom relievers is well established, there is no evidence to show the independent effect of nitrates on post-ACS survival in older people[110,121]. GISSI-3 trial involving 18,895 patients with ACS aged > 70 years found no significant differences in mortality at six weeks post-ACS in the nitrate therapy group ($n = 9453$) compared to the control group ($n = 9442$) (15.9% *vs.* 16.7 respectively, OR, 0.94, 95%CI: 0.87-1.02; $P = 0.12$)[110]. A similar finding was seen in the ISIS-4 trial involving

15,254 patients aged > 70 years (7.3% *vs.* 7.5%, OR 0.3, 95%CI: -0.09 to 0.03, $P = 0.3$)[112]. Both studies observed that nitrate therapy was generally well-tolerated in older patients[110,122].

Invasive management versus conservative management

The 2015 European Society of Cardiology Guidelines made a Class IIa recommendation that older people be considered for invasive therapy and revascularization if appropriate after careful evaluation of the potential risks and benefits, patient preferences, estimated life expectancy, quality of life, comorbidities, and frailty[123].

Reperfusion is associated with increased STEACS survival in older adults[124]. PCI has been shown to reduce the 30-day composite endpoint of death, recurrence of MI and disabling stroke, and decreased need for subsequent target vessel revascularization compared to thrombolytic therapy in people ≤ 80 years old[125]. De Luca *et al.* analyzed data from five registries conducted between 2001 and 2014 and reported that the increase in primary PCI rates in elderly patients > 65 years of age with STEACS was associated with an overall decline in in-hospital mortality ($n = 7147$, $P < 0.0001$)[126].

In comparison, there has been much more debate about the conservative versus invasive treatment of those with NSTEACS. Invasive management options tend to be used less frequently in the frail geriatric population due to the balance and concerns between their safety and utility[127]. Only four RCTs have been conducted to compare the safety and efficacy of invasive and conservative therapy in elderly patients with NSTEACS[68,94,128,129] [Table 1]. Studies restricted to RCTs suggest that, when compared to conservative treatment, invasive therapy significantly reduces MI (OR 0.51, 95%CI: 0.40-0.66), revascularization (OR 0.27, 95%CI: 0.13-0.56), and a trend to reduced mortality (OR 0.84, 95%CI: 0.66-1.06) at the expense of major bleeding (OR 2.19, 95%CI: 1.12-4.28)[130]. However, when the studies were stratified by year of publication, the overall rate of bleeding and the differences between routine invasive and initially medically managed groups were reduced[130]. This may reflect the increased use of radial access rather than femoral access, which was the dominant access route in the Italian Elderly ACS and After Eighty trials (radial access 71% and 90%, respectively)[68,94]. Further research is needed with a larger and more representative randomized population to better represent the general elderly population. Furthermore, the refined use of post-PCI anti-coagulants should also be studied to decrease the risk of bleeding. Age alone should not be a factor to preclude elderly patients from receiving revascularization.

PROGNOSIS

The overall mortality rates following ACS increases exponentially with age, especially after the age of 65 years. Increasing age is strongly predictive of mortality after an ACS; each 10-year increment in age was associated with a 70% increase in mortality (HR 1.70, 95%CI: 1.52-1.82)[9]. The elderly also have an increased risk of cardiogenic shock, recurrent ACS, heart failure (1-12 months post-ACS: < 75 years. 6.3%; > 75 years. 15%), re-hospitalization, and prolonged hospitalization[9].

The CRUSADE trial showed that elderly patients who survived their initial cardiac insult remained at high risk of mortality. Even those who are alive one year post-ACS have a risk of mortality as high as almost 60% at eight-year follow-up[3]. The poor prognosis can be attributed to many risk factors, including but not limited to comorbidity, atypical symptomology, cognitive impairment, and difficulty in accessing healthcare in a timely fashion.

CONCLUSION

The development of ACS in the elderly involves a complex interplay of various cardiovascular risk factors and comorbidities, leading to atypical clinical manifestations, delayed presentation, and poor prognosis.

Table 1. RCTs conducted to compare ACS at follow-up between routine invasive therapy and conservative treatment

Author	Patient	Odds ratio	Follow up
Tegn *et al.*[68]	routine invasive therapy (*n* = 229) conservative (*n* = 228)	0.47 [0.30, 0.74]	1.5 years (median)
Savonitto *et al.*[132]	routine invasive therapy (*n* = 154) conservative (*n* = 159)	0.64 [0.29, 1.42]	1 year
Damman *et al.*[128]	routine invasive therapy (*n* = 437) conservative (*n* = 402)	0.56 [0.39, 0.79]	5 years
McCullough *et al.*[129]	routine invasive therapy (*n* = 139) conservative (*n* = 139)	0.28 [0.11, 0.74]	6 months

RCT: Randomized controlled trial; ACS: acute coronary syndrome.

Future research is urgently needed to refine the management of this high-risk heterogenous population, including improved strategies to diagnose and manage ACS.

DECLARATIONS

Authors contributions

Involve in the conception and writing of the manuscript: Li S, Gnanenthiran SR
Reviewed the manuscript: Chaudhri K, Michail P

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All authors declared that there are no conflicts of interest.

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