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Management of Acute Coronary Syndrome in the Older Adult Population: A Scientific Statement from the American Heart Association

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Abstract

Diagnostic and therapeutic advances over the last decades have substantially improved health outcomes for patients with acute coronary syndrome (ACS). Both age-related physiologic changes and accumulated cardiovascular risk factors increase the susceptibility to ACS over a lifetime. Compared with younger patients, outcomes for ACS in the large and growing demographic of older adults are relatively worse. Increased atherosclerotic plaque burden and complexity of anatomic disease, compounded by age-related cardiovascular and non-cardiovascular comorbid conditions, contribute to the worse prognosis observed in older individuals. Geriatric syndromes including frailty, multimorbidity, impaired cognitive and physical function, polypharmacy and other complexities of care can undermine therapeutic efficacy of guidelines-based treatments as well as the resiliency of older adults to survive and recover.

In this American Heart Association (AHA) Scientific Statement, we: (1) review age-related physiologic changes that predispose to ACS and management complexity; (2) describe the influence of commonly encountered geriatric syndromes on cardiovascular disease (CVD) outcomes; and (3) recommend age-appropriate and guideline-concordant revascularization and ACS management strategies, including transitions of care, the use of cardiac rehabilitation,

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palliative care services, and holistic approaches. The primacy of individualized risk assessment and patient-centered care decision-making is highlighted throughout.

Keywords

Myocardial Infarction, Acute; Acute Coronary Syndrome; Older Adults; Aging; Geriatric Syndromes; Patient-cntered care

INTRODUCTION

Approximately 720,000 Americans suffer an acute myocardial infarction (MI)- or coronary artery disease (CAD)-related death per year, and more than 335,000 Americans suffer recurrent events annually.[1] The older adult population is disproportionately affected. Adults ≥75 years of age constitute approximately 30-40% of all hospitalized ACS patients and the majority of ACS-related mortality is observed in this segment of the population.[2-4] These patients often present with heavy atherosclerotic plaque burden, anatomic complexities, calcifications, vessel tortuosity, ostial lesions, multivessel disease, and left main stenosis. In addition to such disease-specific therapeutic challenges, older adults are also more likely to present with concomitant geriatric syndromes that compound aggregate prognostic risk.[5] Frailty, multimorbidity, cognitive impairment, functional decline, nutritional deficiencies, and polypharmacy are among a long list of geriatric domains that are endemic in the large and growing older population.[6] Consideration of these geriatric complexities is crucial for optimal management of ACS amidst contemporary healthcare trends.[5]

Clinical trials that are considered standards regarding the efficacy and safety of ACS therapeutics predominantly enrolled patients <75 years of age, and most did not include candidates with geriatric complexities. However, in contemporary clinical practice, cardiovascular (CV) as well as geriatric risks are entwined, and both are relevant in regard to determining therapeutics that minimize adverse outcomes and achieve health states that are most likely to be valued by older patients.[7] Timely differentiation between the different types of MI, especially MI with nonobstructive coronary arteries, is essential with related goals to avoid superfluous diagnostic tests, heterogeneity in clinical decisions, and underuse of treatments that are vital. These gaps highlight the need for updated recommendations for ACS management in older adults, with a synthesis of the information that has proliferated since the publication of the first American Heart Association (AHA) Scientific Statements on ACS in older adults.[8, 9] The 2007 AHA statement established the need for clinical studies enrolling older adult populations.[10] This document is primarily concerned with adults ≥75 years of age because most of the gaps in knowledge exist in this age group.[11]

In this AHA Scientific Statement, we review age-related physiologic changes in the heart and vascular systems that predispose to cardiovascular disease (CVD) and management complexities. We review commonly encountered “geriatric syndromes” and their influence on CVD outcomes. Guidelines-based revascularization and adjunctive strategies are emphasized, with relevant considerations regarding transitions of care, cardiac rehabilitation (CR), palliative care services, futility, and a holistic approach to care. Broader considerations regarding risk assessment and decision-making are highlighted.

CARDIOVASCULAR AGING

Cardiovascular Physiology

Normal aging is associated with multiple changes in CV structure and function that predispose older adults to CAD, myocardial ischemia, and ACS (Table 1).[12] A hallmark of aging is increased stiffness of the aorta and large central arteries primarily due to increased collagen deposition and cross-linking in conjunction with degradation of elastin fibers. These changes lead to increased impedance to the left ventricular (LV) ejection and a widening of central aortic pulse pressure reflected in an age-related increase in systolic blood pressure and a decline in diastolic blood pressure, especially after age 75.[13] To compensate for increased aortic impedance and central systolic blood pressure, aging myocytes tend to hypertrophy, provoking both increased apoptosis as well as left ventricular hypertrophy. In turn, the increased impedance to ejection and higher systolic blood pressure give rise to increased myocardial work and myocardial oxygen demand, whereas the lower diastolic pressure is associated with decreased coronary perfusion pressure. Thus, aging increases susceptibility to an imbalance between myocardial oxygen demand and supply.

Aging is also associated with increased collagen deposition in the myocardial interstitium as well as deposition of lipofuscin and other moieties. These factors and others lead to an increase in myocardial stiffness and impedance to LV filling with alteration in the diastolic filling pattern and increased force of left atrial contraction to maintain LV end diastolic volume.[12] Slowing of LV relaxation also contributes to age-related diastolic dysfunction. The net effect is an increase in LV diastolic pressure that further lowers coronary perfusion pressure, which is defined as the difference between aortic diastolic pressure and LV diastolic pressure.

Aging is also associated with impaired coronary endothelial function mediated primarily by a decline in nitric oxide synthase activity.[14] As a result, aged coronary arteries have less capacity to upregulate coronary blood flow in response to increased myocardial oxygen demands, which predisposes older adults to type II MI and non-ST-elevation MI (NSTEMI). In addition, endothelial dysfunction, along with inflammation, is a fundamental driver of atherosclerosis, thereby contributing to the increasing prevalence of both subclinical and overt CAD with advancing age. Further, while chronic inflammation is not inherent to normal aging, it is a common accompaniment to many age-associated diseases and conditions, including diabetes mellitus, arthritis, and frailty.[15] The combination of endothelial dysfunction and chronic inflammation provides a fertile milieu for the development and progression of CAD in older adults.

Additional age-related CV changes include diminished responsiveness to beta-adrenergic stimulation and a nearly linear decline in maximum attainable heart rate (i.e., maximum heart rate ~ 220-age), both of which contribute to an age-associated decline in peak cardiac output in response to physiologic or pathologic stress.[16] Although this decline in CV reserve with increasing age does not directly lead to ischemia under normal circumstances, it increases the risk for the development of acute and chronic heart failure in older patients with CAD.[17] Apart from the effects on the CV system, aging is associated with a shift in the intrinsic balance between thrombosis and fibrinolysis in favor of thrombosis.[18] As a result, older adults are more likely to develop venous thromboembolic disease, as well as arterial clots, including coronary thrombosis, the hallmark of type I MI, as well as left atrial appendage thrombus in patients with atrial fibrillation.[17]

Renal Aging

While the physiology of aging has broad impact on the CV system, kidney function is particularly pertinent to ACS as it exacerbates morbidity and mortality, and also diminishes accuracy of diagnosis and difficulty of therapeutic decision-making. Aging kidneys undergo macro- and microanatomical changes such as kidney cysts, focal inflammation, decreased cortical volume, nephrosclerosis (age-related histologic changes), and renal artery atherosclerosis. Other pathophysiologic changes in the kidney include loss of glomeruli and tubules and increased interstitial fibrosis, which need to be differentiated from other disease syndromes, such as those associated with diabetes mellitus and hypertension. The aging kidney is also characterized by tubular dysfunction, decreased sodium reabsorption, potassium excretion and urine concentrating ability, leading to volume depletion and risk of drug toxicity, all of which may predispose to acute kidney injury (AKI). Chronic kidney disease (CKD) is also more likely to develop in older patients due to the longitudinal loss of kidney function associated with aging.[19] CKD is associated with increased coronary calcium, which has significant implications on revascularization strategies and outcomes.

Kidney disease evaluation includes assessment of kidney function by estimated glomerular filtration rate (eGFR). The National Kidney Foundation and the American Society of Nephrology have recently recommended race-neutral equations or use of the CKD-EPI equation with cystatin C.[20] Additional indices for kidney function include urine test for albuminuria, serum electrolytes to evaluate for disorders of sodium, potassium, calcium and phosphate, as well as for volume assessment. Serum creatinine in older adults is less reliable than in younger adults as it may be spuriously low in the context of low muscle mass.

Implication of Kidney Disease on ACS

Cardiorenal syndrome (CRS) is defined as a *bidirectional* pathophysiologic disorder of both the heart and kidneys, which was initially classified into 5 different categories by Ronco.[21] These 5 subtypes of CRS are categorized based on acuity and sequential organ involvement, which is discussed in detail in a prior AHA Scientific Statement and summarized in Supplemental Table 1.[22] CRS type 1 is defined as an acute cardiac disease leading to acute kidney injury (AKI), typically caused by ACS, acute heart failure or cardiac surgery. Based on a systemic review and meta-analysis, Vandenberghe[23] found that the prevalence of AKI in patients with ACS is 12.7%. A greater severity of AKI was associated with worse outcomes, including mortality (risk ratio 3.53, 95% adjusted hazard ratio (aHR) 2.04-6.10), length of stay in the intensive care unit (ICU), and rehospitalizations. AKI in older patients typically presents with multiple comorbidities, including diabetes mellitus, hypertension, heart failure, and peripheral arterial disease.

Key Points for Clinical Practice

1. The CV aging process is characterized by increased stiffness of the aorta and large central arteries, concentric LV hypertrophy, elevated LV end diastolic

pressure, collagen deposition in the myocardial interstitium and impaired myocardial relaxation, impairment in the endothelial function of coronary arteries, diminished responsiveness to beta-adrenergic stimulation, and an imbalance between thrombosis and fibrinolysis.

2. The aging kidney is characterized by tubular dysfunction, decreased sodium reabsorption, potassium excretion and urine concentrating ability, predisposing to volume depletion and risk of drug toxicity, all of which increased risk for contrast induced AKI in the context of ACS.

3. Understanding of these pathophysiological changes is critical when evaluating guideline-directed medical therapy for ACS and for managing age-related risks in order to prevent physical, cognitive, or functional decline in older individuals.

GERIATRIC SYNDROMES

Geriatric syndromes are multifactorial conditions that are increasingly prevalent at older age. Whereas they are clinical syndromes, most stem from the same age-related physiologic vulnerabilities that underlie CVD.[15] Examples include multimorbidity, frailty, functional decline (cognitive and physical), delirium, sensory decline (hearing, vision, and pain), falls, and polypharmacy.[17] Notably, the incidence and prevalence of geriatric syndromes largely parallels the CV risk profile, such that older adults with low CV risk profiles are also at lower risk for the development of geriatric syndromes (Table 2).[24] Conversely, older adults presenting with ACS are more likely to have a spectrum of diminished functional (physical and cognitive) reserves ranging from mild impairment to more significant decline. In addition, the presence of one or more geriatric syndromes may substantially impact clinical presentation, clinical course and prognosis, therapeutic decision-making, and response to treatment for ACS. It is therefore fundamental that clinicians caring for older patients with ACS be alert to the presence of geriatric syndromes and to be able to integrate them into the care plan when appropriate (Figure 1).

Multimorbidity and polypharmacy.

Multimorbidity, defined as two or more chronic conditions, is ubiquitous in older adults with CV disease.[17] In Medicare fee-for-service beneficiaries with ischemic heart disease, 48% have 5 or more comorbid conditions, 32% have 3-4 co-existing conditions, 17.5% have 1-2 other conditions, and only about 2.5% have isolated ischemic heart disease.[25] Thus, ACS in older patients almost always occurs in the context of multiple comorbidities, many of which may intersect with the approach to treatment. In addition, high comorbidity burden is often associated with *polypharmacy* (usually defined as chronic use of 5 or more medications) and *hyperpolypharmacy* (usally defined as chronic use of 10 or more medications), which greatly increases the risk of adverse drug interactions and hospitalization.[26, 27] It has been estimated, for example, that patients taking 10 or more medications have >90% likelihood of having at least one clinically important drug-drug interaction. To mitigate the impact of multimorbidity and polypharmacy, it becomes important to consider treatment for ACS in the context of these competing risks and engage in a shared decision-making process with the patient and family to ensure that the approach to management is patient-centered and aligned with the patient's goals of care. A pharmacist with expertise in geriatric drug prescribing can provide guidance for discontinuing (i.e., deprescribing) non-essential prescription and over-the counter medications, as well as nutraceuticals, with goals to minimize the potential for drug-drug and drug-disease interactions and related susceptibilities to falls, confusion, and other age-related risks.[28]

Frailty.

Frailty, characterized by physiological decline across multiple organ systems resulting in increased vulnerability to stressors, is associated with an increased risk for adverse health outcomes, including functional decline, institutionalization, and death.[29, 30] As noted above, older adults often have chronic low grade inflammation ("inflammaging"), which represents a shared risk factor for frailty and CV disease (Figure 1).[15, 31, 32]

In community-dwelling older adults, the prevalence of frailty increases from 16% at ages 65-69 years to about 22.2% at ages 80-84.[29] The prevalence of frailty is higher in women than in men.[33] Commonly used tools to assess frailty include the Fried Frailty Index[34], Rockwood Clinical Frailty Score[35], and the Frail Scale.[36] In addition, slow gait speed (<0.8 m/sec), as assessed by a 4-6 meter walk, has been shown to be a reliable surrogate for frailty in ambulatory older adults. While there is still no consensus on the optimal method to assess frailty in ACS, there is consensus that this dimension of health status merits assessment as a criterion for clinical decisions in a manner that is at least standardized within each institution.[6] Notably, it is often not feasible to assess frailty by gait speed or other performance metrics in the context of ACS management; alternative approaches are provided in the percutaneous coronary intervention (PCI) and surgical sections below.

Because frailty heightens risk for adverse outcomes in patients undergoing procedures, a less aggressive approach may yield superior outcomes. Given that frail patients are at high risk for functional decline during and after hospitalization[37], physical therapy and CR with progressive mobilization are also particularly important to consider early in the course of treatment (*See* Cardiac Rehabilitation). Likewise, outpatient CR and nutrition are key components of long-term ACS care. Future clinical trials and observational studies evaluating patients admitted with ACS must include older patients living with geriatric syndromes including frailty.

Cognitive impairment.

In the United States, the prevalence of mild cognitive impairment (MCI), a condition associated with increased risk for subsequent dementia, is about 10% in people 70-79 years of age and about 25% in those 80 years of age or older.[38] The prevalence of Alzheimer's Disease, which accounts for 60-80% of dementia, increases from 5.3% at ages 65-74, to 13.8% at ages 75-84, and 34.6% after age 85.[39] Vascular cognitive impairment and dementia (VCID) is also present in 5-10% of older adults and often coexists with other dementia types. Women are about 50% more likely to develop dementia than men, and women account for nearly two-thirds of dementia cases in the U.S. In addition, the prevalence of dementia is 2-fold higher in older African Americans and 1.5-fold higher in older Hispanic-Americans compared to whites. While formal testing is required to establish a diagnosis of dementia, the Mini-Mental State Exam[40], Mini-Cog[41], and Montreal Cognitive Assessment[42] are commonly used screening tools to identify individuals who may benefit from further evaluation.

In the setting of ACS, patients with MCI or dementia may experience deterioration in cognitive function relative to their baseline due to the stress of the acute event, the unfamiliar environment, or medication side effects. The medical history may be unreliable and decision-making capacity may be impaired. When feasible, relevant history and goals of care, including resuscitation status, should be reviewed with a surrogate historian. It is also important to clarify if the patient has an advance directive and durable power of attorney for healthcare.

Delirium.

Delirium is an acute state of confusion characterized by a fluctuating course with alterations in attention, orientation, awareness of environment, cognition and behavior. The incidence of delirium in hospitalized patients over age 65 is about 20% and increases to over 70% among those requiring intensive care. Delirium is associated with increased risk for complications, longer length of stay, and higher likelihood of discharge to a post-acute care facility.[43] Risk factors for delirium include older age, pre-existing dementia, and certain psychoactive medications (especially benzodiazepines), which should therefore be avoided.[44] Several screening tools are available but the Confusion Assessment Method[45] is the most widely used. Patients at increased risk for delirium should be identified (including all older patients admitted to intensive care), as up to 40% of incident delirium cases can be prevented by implementing a series of specific interventions. Management of delirium requires attention to all potential causes, non-pharmacologic interventions, and judicious use of medications if necessary.[44]

Holistic approach to care—Given the complexity of disease management in older adults with ACS, optimal approaches to management usually entail care that is more individualized and patient-centered than among younger adults, as each patient’s unique set of circumstances has bearing on their sense of optimal outcomes. Comorbid medical and geriatric conditions, medications, pre-existing functional status, patient preferences and goals of care are among the issues that shape treatment decisions and extend beyond the parameters utilized in traditional disease-based ACS risk scores. In critically ill patients for whom an urgent therapeutic decision is required (e.g., emergency PCI or surgery vs. medical management), there may not be sufficient time to explore all relevant aspects of the patient’s situation, in which case clinicians must use assessments incorporating retrospective perspectives and best clinical judgement based on the information at hand, including discussions with the patient, health care proxy and family.[46, 47] In other cases requiring less urgent decision making, a more considered approach, including a determination of what matters most to the patient as a means to inform goals of care and therapeutic direction, coupled with shared decision-making, will likely yield outcomes that are most satisfying to the patient, health care proxy, family and clinical care team. It is optimal to have an advance directive or a durable power of attorney for older patients prior to hospitalization for acute ACS event.

Key Points for Clinical Practice

1. Geriatric syndromes are age-related physiologic vulnerabilities that include multimorbidity, polypharmacy, frailty, functional decline (cognitive and physical), delirium, sensory decline (hearing, vision, and pain), and falls.
2. Geriatric syndromes influence health outcomes for older patients with ACS, but ACS can also worsen the burden of preexisting geriatric syndromes.
3. A holistic approach to ACS care is commensurate with the relatively more complex issues pertaining to ACS in older adults, and includes an individualized and patient-centric approach to care, taking into consideration coexisting and overlapping healthcare domains.

DIAGOSTIC AND DISEASE-BASED CLASSIFICATION OF ACS IN OLDER ADULTS

Clinical History and Exam

The first step in the evaluation of patients presenting with possible ACS, either in the emergency or office setting, is classification of symptoms.[48] A comprehensive history captures the characteristics of chest pain or associated types of symptoms, including the nature, onset and duration, location, radiation, and precipitating or relieving factors. Nonetheless, in older adults, accounts of symptoms are more likely to be affected by multimorbidity, altered sensory capacities, and cognitive impairment, such that their diagnostic specificity and sensitivity are diminished. In a nationwide study of emergency department (ED) patients ≥80 years of age with chest pain, more than half were ultimately found to have a non-cardiac cause of chest pain, 5.7% had decompensated heart failure, 7.8% had CAD without MI, and only 3.7% had an ACS.[49] Thus, the vast majority of chest pain presentations do not represent ACS. ACS in older adults is also more likely to manifest with symptomology that is considered “non-ischemic” in younger populations, including shortness of breath, syncope, or sudden confusion.[50] In the prospective SILVER-AMI study of more than 3,000 patients ≥75 years of age hospitalized with AMI, 44% of patients did not report chest pain as their primary symptom, including 40% of patients presenting with STEMI. Women presenting with NSTEMI were less likely than men to report chest pain as a primary symptom (50.0% versus 58.6%, $P<0.001$).[51] In another analysis from the SILVER-AMI cohort, cognitive impairment was present in 17% of participants.[52] Women had a higher prevalence of cognitive impairment compared with men (NSTEMI: 20.6% versus 14.3%, $P<0.001$) – posing challenges for timely presentation to the ED and the description and recall of symptoms.[51] Heart failure, symptoms other than chest pain, and being African- or Hispanic-American were also associated with delayed arrival to the hospital.[53]

The electrocardiogram (ECG) is a key step in initial evaluation for ACS. The majority of older adults (~70%) in clinic and hospital settings have some form of baseline ECG abnormality. These include left ventricular hypertrophy (~20%), conduction system disease (10% right bundle branch block and ~5% left bundle branch block), paced rhythm (~5%) or atrial fibrillation (~12%).[54] Such high prevalence of pre-existing ECG abnormalities often complicates interpretation of the presenting ECG in older patients with suspected

ACS, and comparison with prior ECGs, when available, is essential. For older patients with non-diagnostic ECG presentations (e.g., LBBB or paced QRS), a high level of suspicion for ACS diagnosis is needed, especially if older patients present with cardiac symptoms, unstable hemodynamics, or the typical rise and fall pattern of cardiac biomarkers. The physical examination for older adults with ACS may be informative of conditions that alter myocardial oxygen supply and demand, including hypoxia, tachycardia (e.g., atrial fibrillation), hypotension, uncontrolled hypertension, or acute stressors such as an injurious fall – all contributors to type 2 MI. Aortic stenosis can be readily detected by physical examination and is a common confounder among patients with angina.

Due to the inherent complexities in older patients presenting with suspected ACS, the initial history, physical examination, and ECG alone often do not confirm or exclude the diagnosis. However, the initial evaluation can stratify those with possible ACS presentations into low, intermediate, or high risk to better inform the initial approach to care and interpretation of biomarker testing (Figure 2).[55] While the 4th Universal Definition of MI is widely used, it is often not ideal for guiding risk stratification in older patients with chest pain or ACS. There is need for refinements to estimate overall prognosis that incorporate concomitant (and biologically related) aging phenomena that exacerbate risk (reduced longevity as well as greater disability) when present (frailty, sarcopenia, multimorbidity, etc.). Older patients living with geriatric syndromes and presenting with NSTEMI are at increased risk for hospital associated complications. Characteristics that predict higher risks of complications requiring ICU admission in older patients include heart failure, initial heart rate, systolic blood pressure, initial troponin, initial serum creatinine, prior revascularization, chronic lung disease, ST-segment depression, and age.[56] The ACTION ICU risk score can be a helpful guide for older patient disposition into the CICU vs. intermediate care units.[56] The ACTION ICU risk score included patients ≥ 65 years old in the ACTION registry with a median [IQR] age of 77 [71-84] years.

Sex-related Differences in ACS

While men constitute the majority of ACS encounters, the proportion of women in the ACS population increases with age from 20-25% among patients <50 years of age to approximately 50% among older adults >80 years of age.[57, 58] These patients tend to be described in practice as "older and sicker" highlighting the sex-related differences among men and women.[59] The burden of CV risk factors among older women is higher than men including hypertension, diabetes mellitus, and older women may be more likely to have a prior heart failure or heart failure with preserved ejection fraction, but not heart failure with reduced ejection fraction.[59] In the Italian Elderly ACS collaboration, older women had a higher prevalence of cardiovascular risk factors, including diabetes, and non-cardiovascular comorbidities including kidney dysfunction.[60] While older men had longer duration of coronary disease, history of MI, revascularization, and more complex anatomic disease.[60] Symptoms like nausea or abdominal pain are more common among women, and pain in the jaw, neck, or back are also frequently observed. Weakness, dyspnea, or total lack of pain ("silent" ischemia) may affect interpretation of symptoms and result in delays in presentation. These issues can result in poor outcomes due to delays in implementation of reperfusion therapies. In the LADIES ACS study, the Gensini score, a surrogate for coronary artery disease severity, was higher in men than women at all ages.[61] In the CURE trial, high-risk women with ACS underwent less coronary angiography, CABG surgery and had higher incidence of MACE outcomes including recurrent MI, stroke, and refractory angina.[62] These sex-related differences should trigger improvement in quality care for older women presenting with ACS.

Biomarkers (hs-cTn and NT pro BNP)

The addition of high sensitivity troponin (hs-Tn) provides important diagnostic sensitivity for the presence of ACS in older adults, but that comes at the expense of reduced specificity, particularly among older adults with underlying kidney disease.[63,64] hs-cTn assays are the standard of care for identifying myocardial injury, although questions remain about whether minimal elevations, which carry prognostic value, are actionable in a manner that improves outcomes.[65] If the hs-cTn continue to rise, the biomarker is helpful in identifying the underlying cause of the injury and indicating myocardial ischemia. Chronic elevations of hs-Tn levels are associated with replacement fibrosis and progressive changes in left ventricular structure that are common in the older population.[66] Fluctuations in the levels of hs-Tn are also associated with age-related decline in kidney function (especially in the context of ACS), hormonal changes (menopause in women), and age-related changes in body composition.[65, 67] For this reason, evaluating patterns of rise and fall of hs-Tn is essential.[67] Independent determinants of higher levels of troponin in asymptomatic populations include older age, male sex, diabetes mellitus, lower eGFR, left ventricular mass, black race, hypertension, sarcopenia, and history of heart failure. Therefore, many asymptomatic older adults live with biomarkers that fluctuate or are persistently above the diagnostic thresholds for MI. Population studies such as Dallas Heart Study, Atherosclerosis Risk in Communities, and Cardiovascular Health Study demonstrate that the proportion of hs-Tn above the 99% URL is upwards of 19-28 ng/L (depending on vender) in asymptomatic individuals over the age of 75.

Classification of Myocardial Injury

Myocardial infarction is defined as myocardial cell death attributable to a prolonged period of inadequate oxygen supply to the myocardium. All four types of myocardial injury are more common in older adults. The taxonomies for myocardial injury include acute non-ischemic myocardial injury identified by a rise and fall of hs-Tn without a primary ischemic cause and chronic myocardial injury identified by persistent elevations of hs-Tn above the 99th URL over time. Type 1 MI is caused by atherothrombotic CAD, usually the result of plaque rupture. Type 2 MI is caused by a mismatch between oxygen supply and demand and indicates myocardial stress related to another condition (i.e. not due to plaque rupture). Older adults are predisposed to type 2 MI in part because of an age-related decline in endothelium-mediated coronary vasodilation and resultant impaired ability to increase coronary blood flow in response to increased myocardial oxygen demand.[17] Type 2 MI is particularly common in older adults admitted with comorbid conditions such as hypotension (e.g. due to sepsis), uncontrolled hypertension, chronic obstructive pulmonary disease, pneumonia, acute anemia, heart failure exacerbations, or chronic kidney disease.[68] Among patients with type 2 MI, the incidence of recurrent type 2 MI at five-year follow-up was 9.7%, compared to 1.7% five-year incidence of type I MI.[68] The survival prognosis among patients with type 2 MI is also determined by the underlying cause for the supply-demand mismatch, with arrhythmia having a more favorable prognosis than hypotension, anemia, or hypoxia. Adjusted long-term mortality after type 2 MI is markedly higher than after type 1 MI (52% vs. 31% at 5 years), driven by early non-cardiovascular death.[68] Patients with myocardial injury are also at increased risk for future cardiovascular events irrespective of pathogenesis.

Coronary CT Angiogram (CCTA) for Risk Stratification

Whereas coronary angiography has traditionally been regarded as the most definitive means to assess for CAD, it is associated with relatively greater risks in older adults. After MI has been ruled out by troponin, CCTA is a less invasive way than coronary angiography to exclude obstructive CAD in patients with intermediate or undetermined risk. CCTA can visualize the extent and severity of non-obstructive and obstructive CAD, as well as atherosclerotic plaque composition and high-risk features (e.g., positive remodeling, low attenuation plaque). Calculation of fractional flow reserve with CT (FFR-CT) may provide an estimation of lesion-specific ischemia. Clinicians may be able to use CCTA for triaging patients with suspected ACS by looking for features of high-risk plaque, but the reliability of the test is somewhat diminished particularly in very old patients.[69] High-risk plaque characteristics on CCTA may assist in identifying culprit lesions of ACS.[70] When evaluating older adults for CCTA, the use of contrast (typically 50-100 ml) must be considered, especially given the age-related vulnerabilities of acute and chronic kidney disease. The heart rhythm must be regular (i.e. not atrial fibrillation or atrial arrhythmia) with rate preferably less than 70 beat per minute. Heavily calcified coronary arteries in older patients may render interpretation of lesion severity difficult, and motion artifact (e.g. if patient is delirious) can obscure interpretation. Downstream testing is also a relevant consideration as CCTA may lead to additional testing that diverges from a patient’s goals and preferences.

Key Points for Clinical Practice

1. ACS represents a minority of all chest pain presentations in younger and older adults. ACS presentations without chest pain, such as shortness of breath, syncope, or sudden confusion, are more likely to occur in older adults.
2. hs-cTn assays are standard of care for identifying acute and chronic myocardial injury. Many older adults have persistent elevations due to myocardial fibrosis and CKD that lessen the positive predictive value. For this reason, evaluating patterns of rise and fall is essential.
3. Myocardial injury can be classified in 4 subtypes: Acute non-ischemic injury, chronic myocardial injury, myocardial infarction (type 1) and myocardial infarction (type 2). All types are more common in older than younger adults.

GUIDELINE-DIRECTED MEDICAL THERAPY FOR ACS IN OLDER ADULTS

Pharmacodynamics and Pharmacokinetics

With aging, multiple physiological changes affect both the pharmacokinetics and pharmacodynamics of many medications used for ACS. Older adults can exhibit reductions in kidney function, hepatic blood flow, and muscle mass with an increase in body fat that in turn impact the absorption, distribution, metabolism, and elimination of certain guideline-directed medical therapies (Figure 3).[71] These physiologic changes greatly affect the pharmacokinetics of orally administered medications that must undergo dissolution in order to be absorbed by the gut, then undergo first pass hepatic metabolism before entering the systemic circulation, and then potentially be renally eliminated. For intravenously administered medications, first pass metabolism is bypassed, but protein binding and elimination can be altered.[6] With a reduction in p-glycoprotein and cytochrome P450 isoenzymes, the potential exists for elevated serum concentrations anticoagulants (warfarin, apixaban, dabigatran, and rivaroxaban), β-adrenergic blockers (carvedilol), and statins (atorvastatin, simvastatin). Anticoagulants (bivalirudin, eptifibatide, tirofiban, enoxaparin, fondaparinux), as well as all the oral direct anticoagulants are eliminated renally and doses must be adjusted according to the patient’s glomerular filtration rate.[72, 73] As older adults may exhibit altered plasma protein concentrations, primarily due to underlying comorbid conditions, medications that are highly protein bound (e.g., > 90%) such as warfarin, heparin, amiodarone, lidocaine, furosemide, bumetanide, nicardipine, and all stains except pravastatin can exhibit higher free concentrations with the potential for greater distribution, which may accentuate the risk for toxicity.[6, 74]

Low body weight and lean mass are common in many older adults with ACS, which can impact medication dosing in order to avoid adverse events. Based on US package labeling, in patients <60 Kg, a lower maintenance dose of prasugrel (5mg/daily) should be considered in order to reduce the risk of bleeding.[75] In the case of apixaban, dosing adjustment is warranted if a patient meets two of the following: age ≥ 80 years of age, body weight ≤ 60 kg, or a serum creatinine ≥ 1.5 mg/dl.[73] For dabigatran, observational studies suggest increased dabigatran-induced bleeding at low body mass indexes (<23.9 kg/m2), and while no conclusive consensus exists regarding rivaroxaban dosing in patients weighing <60 kg, increased systemic exposure in cachectic patients has been suggested.[73] Finally, body weight is critical when dosing many intravenous antiplatelet medications such as the glycoprotein IIb/IIIa inhibitors (eptifbatide and tirofiban), prasugrel, and cangrelor, as well as unfractionated heparin, low molecular weight heparins (enoxaparin and dalteparin), and the factor Xa inhibitor fondaparinux.[72]

From a pharmacodynamic perspective, adaptive and structural vascular and myocardial changes due to aging can lead to exaggerated response to certain medications.[12] Diminished carotid sinus baroreceptor sensitivity as well as a slowing of both sinus node activity and atrioventricular conduction can increase the risk of bradycardia with β-adrenergic blockers, non-dihydropyridine calcium channel blockers, and amiodarone. With an increase in arterial and ventricular stiffness, older adults may become preload sensitive, leading to a greater risk of hemodynamic lability from vasodilator therapies and diuretics.[6, 76]

Pharmacotherapy for ACS in Older Adults

Medical therapy for ACS in the older adult is generally similar to that in younger patients but needs to take into consideration the increased atherothrombotic risk, higher bleeding risk compared with younger patients in the context of the physiologic changes described above, and prevalent geriatric syndroms. As such, risk versus benefit assessments, tailored to each individual, guide the use and dosing of ACS therapies. Therapies initiated in the hospital should be evaluated on a recurring basis during outpatient follow-up with escalation of treatment as needed to reduce overall CV risk, but also de-escalation or deprescribing as needed to relieve or prevent side effects in the context of patients' goals and preferences.[28]

While both clopidogrel and ticagrelor are recommended for older patients with ACS in the recent revascularization guidelines[77], clopidogrel may be the preferred P2Y12 inhibitor in older patients because it carries a lower bleeding risk profile when compared to ticagrelor. In the Elderly ACS 2 trial, prasugrel did not show superiority over clopidogrel in the primary endpoints of mortality, MI, disability stroke, rehospitalization, or bleeding among older patients.[78] However, the bleeding rate was numerically higher in the prasugrel group.[78] In the POPular AGE Trial that enrolled older patients with NSTE-ACS, clopidogrel had a similar efficacy to ticagrelor in reducing MACE events and had fewer bleeding events.[79] In the recent SWEDEHEART (Swedish Web-System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies) study, patients ≥80 years with MI who were discharged alive with aspirin combined with either clopidogrel or ticagrelor were evaluated. Older patients treated with ticagrelor did not have lower risk for the combined outcomes of death, MI, or stroke, but these patients had a 32% higher risk of bleeding.[80] A network metanalysis (n=14,485) comparing clopidogrel, prasugrel and ticagrelor in older adults with ACS has been recently published and showed that clopidogrel has the most favorable profile for reducing bleeding events.[81] While the benefit of ticagrelor over clopidogrel was consistent across age groups, there was a significantly higher risk of major bleeding in ticagrelor-treated older patients.[82] Further, there is a black box warning on the use of full dose prasugrel of 10mg/day in patients more than 75 years of age due to increased risk of serious bleeding. Limited evidence exists for $P2Y_{12}$ inhibitor switching. In older patients at high risk of both thrombosis and long-term bleeding, higher potency $P2Y_{12}$ inhibitors, such as ticagrelor or reduced dose (5mg) prasugrel, may be superior in the first month after PCI for ACS, then transitioning to clopidogrel for long-term bleeding risk reduction.[83] If more potent DAPT are used in older patients, DAPT de-escalation by switching from more potent drugs (e.g., ticagrelor or lower dose prasugrel) to clopidogrel can be considered 30 days after initial ACS event or guided by platelet function testing because a switch within the first 30 days after index admission may increase risk of ischemic events.[84-86]

Beta-blockers may be of particular benefit due to their anti-ischemic effects and influence on the burden of arrhythmia in the setting of acute myocardial ischemic injury. However, cautious dosing is warranted along with vigilance for bradycardia and incident heart failure in the acute setting, as well as chronotropic incompetence and fatigue during chronic management. In patients with severe asymptomatic bradycardia (heart rate <40 beats per minute), reduction or cessation of beta-blockade and other nodal agents is preferred to see if pacemaker implantation can be avoided. In a large observational study of patients over age 65 who were more than 3 years post-MI, no association between beta-blocker use and long-term cardiovascular outcomes was observed, suggesting that de-prescribing may be considered at that time.[87]

A recent meta-analysis confirmed that low density lipoprotein (LDL) cholesterol lowering had similar efficacy in reducing the risk of cardiovascular death, ACS, stroke, or coronary revascularization in patients over and under 75 years of age; the results were also consistent across trials of statins, ezetimibe, and PCSK9 inhibitors. While post-market reports have raised concern for cognitive impairment, particularly in the aging population, most recent data have shown that there is no impact of statins or PCSK9 inhibitors on patient reported cognition even with very low LDL levels.[88] Furthermore, randomized trials of statins[89], ezetimibe[90], and PCSK9 inhibitors[91] have not observed between-group differences in cognitive function. Studies with longer term follow-up of PCSK9 inhibitor treatment are needed. Moderate- or high-intensity statin therapy is recommended for patients older than 75 years with clinical atherosclerotic cardiovascular disease.[92] Myalgias can be dose dependent in older adults and influence mobility and quality of life, particularly among patients from Asian descent. Careful attention to statin dosing, dietary intake, and drug-drug interactions will allow older adults to benefit from secondary prevention lipid lowering effectively and safely.

Drugs targeting the renin-angiotensin-aldosterone (RAAS) system, namely angiotensin-converting enzyme inhibitors (ACEi), angiotensin II receptor blockers (ARB), and aldosterone antagonists, have been associated with mortality benefit in ACS patients with large infarcts and left ventricular dysfunction.[93] Of note, in patients with heart failure with reduced ejection fraction, low dose compared to higher doses of lisinopril, losartan, and sacubitril valsartan showed no difference in mortality, thus suggesting lower doses of these agents may be beneficial, particularly in patients with renal and hemodynamic vulnerabilities.[94-96] These are often under-utilized in older ACS patients due to clinician concerns regarding expected benefit in the face of shorter life expectancy, and potential complications (e.g., syncope, hyperkalemia, or worsening kidney function) of treatment. When possible, shared decision making is important, and kidney function, blood pressure, and potassium levels are best monitored within the first 12 weeks of initiation, with each dose increase, and on a yearly basis thereafter. Dose reduction or drug discontinuation may be needed for severe or symptomatic hypotension, hyperkalemia, or persistent >30% creatinine increases.[97] Recent data suggest that ACEi/ARBs that cross the blood brain barrier (ACEi: captopril, fosinopril, lisinopril, perindopril, ramipril, and trandolapril; ARB: telmisartan and candesartan) were associated with better memory recall at 3 years than those that did not.[98] The use of angiotensin receptor-neprilysin inhibitor (ARNI) vs ACEi to reduce MACE events following MI was investigated in the PARADISE-MI trial.[99] In that study, more than one-third of the patients were older than 70 years but only 24% were women. The primary outcome of death, first HF hospitalization or outpatient HF was not different between the ARNI vs. ACEi (11.9 vs. 13.2, p=0.17).[100]

Pharmacologic Management of Atrial Fibrillation in Context of ACS

Older adults are at higher risk for recurrent thrombotic events, and they may derive the most benefit from appropriately dosed anticoagulation therapy. The prevalence of atrial fibrillation increases with age and concomitant anticoagulation therapy increases bleeding risk. Among older adults in sinus rhythm treated with PCI for ACS, 1-4 weeks of triple anticoagulation therapy (aspirin, clopidogrel, and a direct oral anticoagulant [DOAC]) is recommended, followed by up to 1 year of clopidogrel and DOAC, after which DOAC monotherapy is continued.[101] For patients with chronic atrial fibrillation undergoing PCI for ACS, double antithrombotic therapy is superior to a strategy of triple therapy. This is achieved using a DOAC and a $P2Y_{12}$ inhibitor preferably clopidogrel without aspirin.[102] In older patients at increased thrombotic risk with acceptable bleeding risk, it is reasonable to continue triple therapy including aspirin for one month post PCI.[103] Double therapy is continued for 6 to 12 months, after which discontinuation of antiplatelet therapy is achieced and treatment with oral anticoagulation therapy alone is maintained thereafter.[103]

Enhanced communication between the hospital cardiology team and outpatient cardiology team (e.g., cardiologist, nurse practitioner, or physician assistant) caring for the older patient is critical to coordinate the medication regimen and to provide the rationale for longterm care. With this alignment between clinicians, older adults, particularly those with mobility or cognitive difficulties, may benefit from more simplified medication and dosing regimens than one that checks all the guideline indication boxes. Once daily medications are often more conducive to adherence but require careful assessment of potential interactions when multiple drugs are taken together. While within class medication switches or dosing changes can occur after discharge from an ACS hospitalization, 90-day prescriptions are often feasible and have been shown to improve post-ACS medication adherence.[104] Facilitating medication supplies in other ways, such as using mail order pharmacies[105], can make a big difference in long-term evidence-based medication persistence of older adults after ACS.

Key Points for Clinical Practice

1. In the older ACS patient, clopidogrel is the preferred $P2Y_{12}$ inhibitor because of significantly lower bleeding profile than ticagrelor or prasugrel, but for patients with STEMI or complex anatomy, the use of ticagrelor is reasonable.
2. In patients with chronic atrial fibrillation undergoing PCI for ACS, the duration of triple therapy should be minimized, with discontinuation of ASA and transition to dual antithrombotic therapy with clopidogrel and a NOAC, ideally within 4 weeks of PCI.
3. Therapies initiated in the hospital are best evaluated on a recurring basis during outpatient follow-up with escalation of treatment as needed to reduce CV risk, but also de-escalation or deprescribing to relieve or prevent side effects.
4. Older adults, particularly those with mobility or cognitive difficulties, may benefit from relatively simpler medication and dosing regimens than those commonly indicated by existing guidelines. Comorbidities, geriatric syndromes, and personal healthcare goals and preferences are also relevant factors to integrate within tailored regimens of care.

PERCUTANEOUS REVASCULARIZATION IN OLDER ADULTS

The management for STEMI in older adults follows the same general principles as for younger patients. The indication for primary PCI in older adults presenting with STEMI should consider STEMI-related variables including delay in presentation, extent of ECG changes, and left ventricular dysfunction, and patient-related variables, including severe comorbidity, severe cognitive impairment and limited life expectancy. Barring these end stage disease processes, primary PCI is safe and effective even among patients with very advanced age, as long as this is aligned with their preferences of care.[106, 107] For older patients with NSTEMI, cardiovascular and non-cardiovascular risk evaluation prior to revascularization are critical elements to achieve optimal outcomes, both in respect to cardiovascular (e.g. symptom control and low bleeding risk)[108] and non-cardiovascular (e.g., function, independence, quality of life, and overall well-being).

Cardiovascular Risk Evaluation for PCI

TIMI/Grace Risk Score: The ACC/AHA guideline recommends risk stratification of patients with suspected NSTEMI to determine the choice of management, e.g. through use of risk assessment scores such as Thrombolysis In Myocardial Infarction (TIMI) risk score and GRACE risk score.[77] The GRACE score is heavily age-weighted[109, 110] leading to older adults with NSTEMI being classified as high-risk warranting consideration of early invasive therapy. Type 2 MI is frequently observed in older adults[111] and the GRACE risk score provides only moderate discrimination of mortality risk for those with type 2 MI.[112] The baseline risk of bleeding during NSTEMI care among older adults is increased when compared to younger patients, and the CRUSADE bleeding score has the best discriminative function for in-hospital major bleeding across all postadmission treatments.[113] Importantly, these risk scores do not take into account characteristics that are especially prevalent in older adults, such as frailty, multimorbidity, polypharmacy, and cognitive dysfunction. The relationship between frailty and risk of adverse outcome following STEMI and NSTEMI has been demonstrated in many studies using different frailty assessment tools.[114-116]

Among NSTEMI patients, the composite outcome of MI, need for urgent repeat revascularization, stroke, significant bleeding, and all-cause mortality at one year occurred in more frail patients than in robust patients (39% vs. 18%, HR: 2.79; 95% CI: 1.28-6.08).[117] In a systematic review and meta-analysis, frailty was associated with a several-fold increase in the adjusted risk of mortality for patients with STEMI (HR: 6.51; 95% CI: 2.01–21.10) and NSTEMI (HR: 2.63; 95%CI: 1.51–4.60).[118] Multimorbidity is increasingly prevalent in the older population, particularly in those presenting with ACS. Comorbidity burden, as measured by the Charlson Comorbidity Index (CCI), predicts in-hospital and 1-year mortality in patients with ACS and is independently associated with adverse short-, medium- and long-term outcomes after PCI.[119, 120] In another study, older adults with NSTE-ACS referred for coronary angiography, the presence of multi-morbidity was associated with an increased risk of long-term adverse cardiovascular events, driven by a higher risk of all-cause mortality. On average, each additional CCI co-morbidity was associated with a 31% increased adjusted risk of all-cause mortality at five-years.[121]

Undiagnosed cognitive impairment is common in older patients with NSTEMI receiving coronary angiography, and these patients are more likely to experience adverse events at 1 year.[122] While the optimal risk indices for older adults with ACS remain undefined, considerations of frailty, cognition and comorbity are critical perspectives to foster in respect to guiding optimal care, particularly for prognostic stratification, and identifying those who are most as well as least likely to benefit from early invasive therapy. There is a need for refinements of standard risk scores to estimate ischemic and bleeding risks for older patients with ACS.

Geriatric and Patient-Centric Outcomes for the Older ACS Populations

While the older adult population is rapidly expanding, these patients do not represent a homogeneous group. They differ based on the presence or absence of frailty, comorbidities, physical or functional limitations, and social status when presenting with ACS.[123] Older patients living with a greater burden of geriatric syndromes are more likely to develop disability, loss of independence, and impairment in quality of like and ability to selfcare after an ACS event. When managing older patients presenting with ACS, the goals of care should extend beyond traditional cardiovascular outcomes including MI, need for urgent and repeat revascularization, stroke, significant bleeding, and all-cause mortality. Assessment of patient-centeric goals and outcomes remains necessarily with a focus on quality of life outcomes.[124] Other key outcomes for older patients are the ability to live independently and to return to their previous life environment/style. . For older patients with high burden of geriatric syndromes or with terminal cardiovascular illness, goals like “days at home” and other personal preferences that maximize quality of life should be prioritized as important outcomes for guiding ACS management.[124] With these considerations in mind, the most recent clinical trial designs in older frail patients with ACS included secondary outcomes like functional capacity, instrumental activities, cognitive capacity, and quality of life during follow-up when compared to baseline.[125] It should be noted that issues of senescence, inflammation, and other hallmarks of aging are variable from person to person, thus adding to the heterogeneity of older adults.

Key Points:

1. When managing older patients presenting with ACS, the goals of care should extend beyond traditional cardiovascular outcomes to include patient-aligned goals and preferences that maximize quality of life outcomes.

2. For older ACS patients at end of life, goals like “days spent at home in the last 6 months of life” and relief of pain/discomfort are important metrics for quality care.

Correlation between Frailty and Coronary Anatomical Complexity

Frail adults presenting with NSTEMI have more procedurally challenging angiographic findings independent of age (i.e., severe culprit lesion calcification, high SYNTAX scores, high risk lesions). In one study, frail patients had more than a five-fold increase in odds of severe culprit lesion calcification when compared to robust patients (unadjusted OR 5.40, 95% CI 1.75–16.8, p=0.03).[126] Frail patients also had a greater prevalence of high-risk lesions on intravascular ultrasound imaging, with a 2.81 increased adjusted odds (95% CI 1.06–7.48, P=0.039) of presence of thin-cap fibroatheroma.[127] During follow-up, frail older adults who underwent angiography for NSTEMI is associated were at increased risk of all-cause mortality, unplanned revascularization, myocardial infarction, stroke, and bleeding.[128]

Timing of Invasive Strategy

The current revascularization guidelines describe high-risk groups that may benefit from early invasive approach, which results in lower rate of death, myocardial infarction, or refractory angina during follow-up. Older patients with ACS are disproportionately affected with high-risk features favouring and early invasive approach to management. The GRACE score has been used to estimate the risk of death attributed to ischemic burden in patients with ACS. A GRACE score >140 indicates a high-risk patient group that benefits from revascularization within the 24 hours, resulting in lower incidence of recurrent ischemia, need for revascularization, and shorter hospital length of stay.[129] For patients ≥ 75 years of age, ST-segment deviation on ECG coupled with elevated hs-Tn levels yields a GRACE score >140, categorizing them as high-risk. When more precarious conditions coexist, the risk of mortality and major adverse cardiac events increases significantly. These conditions include the presence of cardiogenic shock, refractory angina, and hemodynamic or electrical instability, which require an immediate invasive assessment (preferably within 2 hours) to provide information on the extent and severity of coronary disease, hemodynamics, left ventricular function, and suitability for revascularization.[129] However, other factors, including patient's preferences and burden of geriatric syndromes that may affect life expectancy, must be taken into account when considering immediate revascularization strategies in older patients.

Key Points:

1. Older patients with ACS are often high risk (Grace Score >140) and should be considered for an early invasive approach to reduce the incidence of recurrent ischemia, need for revascularization, and shorten hospital length of stay
2. When cardiogenic shock, refractory angina, and hemodynamic or electrical instability are present immediate invasive approach may be associated with improved outcomes.
3. Patient preferences and geriatric syndromes affecting life expectancy must be considered when deciding on an invasive vs. conservative approach to ACS management.

Timing of DAPT Therapy

The use of DAPT is critical in the medical management of ACS because of its role in reducing ischemic and thrombotic complications. For older patients being considered for immediate or early invasive therapy, a loading dose of non-enteric coated aspirin 325mg, followed by a daily dose of 81mg is recommended prior to invasive assessment to reduce ischemic risks. Available P2Y12 inhibitors include clopidogrel, ticagrelor, and prasugrel. Of these, clopidogrel and ticagrelor are most commonly used in older patients with ACS because prasugrel is associated with adverse outcomes including major bleeding in the older adult populations. The timing of the loading dose of P2Y12 inhibitors remains an area of debate, but a strategy of introducing the loading dose after the anatomy is known was recently endorsed by the ACC/AHA/SCAI revascularization guidelines. This should be followed by daily dose to reduce ischemic events.[129] This strategy seems most reasonable because of the need to discuss approach to revascularization with the *Heart Team* and whether surgical evaluation is needed.

Key Points:

1. A loading dose of aspirin 325mg followed by a daily dose of 81mg should be given prior to invasive approach to management to reduce ischemic events.
2. A loading dose of a P2Y12 inhibitor should be given after the anatomy is known in patients proceeding to PCI. A P2Y12 inhibitor should be withheld in patients for whom cardiac surgery is being contemplated.

Efficacy of Percutaneous Revascularization in Older Adults

NSTEMI: To date, of the five randomized clinical trials (RCTs) specifically investigating an invasive strategy in older patients with NSTEMI, four have found no benefit of invasive treatment on the primary endpoint compared to conservative management,[130-133] whilst the other showed that an invasive strategy reduced recurrent MI and urgent repeat revascularization (Table 3).[134, 135] The Italian Elderly ACS trial randomized patients ≥75 years of age with NSTEACS to early invasive vs. initially conservative strategy. The trial did not report geriatric syndromes including frailty and multimorbidity.[136] Patients randomized to the initially conservative strategy had higher rates of ischemic events during index hospitalization, which prompted urgent angiography. While there was 20% reduction in the rate of death, reinfarction, disability stroke, or rehospitalization, this reduction was not statistically significant because the trial was powered to detect a 40% difference in event rates. Patients with elevated troponins who were randomized to the early invasive group showed a significant 57% reduction in the primary endpoint on subgroup analysis.[136] The After Eighty trial (2016) randomized patients aged 80 years or older with NSTEMI or unstable angina to an invasive vs. conservative strategy.[134] Similar to the Italian Elderly ACS study, frailty or other geriatric syndromes were not explicitly reported. During a median follow-up of 18 months, the invasive strategy was found to be superior to the conservative strategy in reducing MI, urgent revascularization, and stroke (41% vs. 61%; OR 0.48, 95% CI 0.37-0.63), p<0.001).[134] The MOSCA trial randomized patients ≥70 years of age with higher comorbidity burden to invasive vs. conservative strategy for NSTEMI. While there were numerically fewer primary endpoint events (death, reinfarction, or cardiac readmission) in the invasive arm, the difference did not reach statistical significance.[131] This study was followed by the MOSCA-Frail trial, which is currently ongoing (Table 3). Other smaller trials also did not show benefit of an early invasive strategy but were underpowered to detect clinically meaningful differences.[137, 138] The larger British Heart Foundation SENIOR-RITA Trial is currently randomizing patients ≥75 years of age with type 1 NSTEMI to either invasive or conservative treatment strategy. With an anticipated enrollment of 1,668 older participants, this trial is poised to inform practice in older NSTEMI patients living with geriatric syndromes (ClinicalTrials.gov/Identifier: NCT03052036). Using both observational and randomized data, systematic reviews and meta-analyses have shown a likely reduction in MI and recurrent revascularization associated with an invasive strategy, but no survival benefit and a higher risk of bleeding relative to a conservative strategy.[139, 140] More recently non-randomized data from the

SENIOR-NSTEMI study showed a survival advantage associated with invasive strategy among patients older than 80 years of age.[141] Thus, the value of an invasive strategy in the management of patients ≥75 years of age remains uncertain, and additional studies are needed.

STEMI: In the context of STEMI, a pooled analysis of the TRIANA, SENIOR-PAMI and Zwolle trials showed a significant reduction in the risk of a composite outcome of death, reinfarction or disabling stroke (OR 0.64; 95% CI 0.45-0.91, p=0.013) with primary PCI compared to fibrinolysis.[142] In a meta-analysis, patients aged 70-80 years who were randomized to primary PCI had reduced all-cause mortality (OR 0.55; 95% CI 0.39-0.76), reinfarction (OR 0.37; 95% CI 0.23-0.62), stroke (OR 0.36; 95% CI 0.20-0.68) and a composite of all three endpoints (OR 0.45; 95% CI 0.34-0.59).[143] The superiority of primary PCI over fibrinolysis appears to extend to older patients, although trials have been small, affected by slow recruitment, and findings are limited in the 'very old' cohort, with no evaluation of frailty or comorbidity included. However, the results also suggest that fibrinolysis may be safe and effective, providing rationale for fibrinolytic therapy in situations where prompt PCI is not readily available or the risk of invasive intervention is considered to be prohibitive. In patients over age 75, fibrin selective agents, such as recombinant tPA, appear to be more effective in reperfusing the occluded artery but with the tradeoff of increased risk for intracranial hemorrhage.[144] In the context of cardiogenic shock and cardiac arrest, age is an independent predictor of mortality following PCI.[145, 146] In addition, the value of mechanical circulatory support in these cases, e.g. with intraaortic balloon counterpulsation or an Impella left ventricular assist device, is uncertain. Therefore careful selection of patients most likely to benefit from PCI is required. In the CULPRIT-SHOCK trial, in which the mean age of the study population was 70 years and 31% were >75 years-old, no age x treatment interaction was observed with regard to the benefit in favor of culprit vessel PCI only, as compared to multivessel PCI during the index procedure.[147]

Adverse Outcomes of PCI in Older Adults: Management to Minimize Risks

While an invasive approach appears to reduce reinfarction and the need for further revascularization, a meta-analysis shows increased bleeding among patients undergoing invasive management (OR 2.19; 95% CI 1.12-4.28; P=0.02; I^2 = 0%) compared to those treated conservatively.[139] In contemporary practice, bleeding risk is reduced by the use of radial access, even among patients presenting with cardiogenic shock.[148, 149] Bleeding risk is further reduced with the use of latest generation drug eluting stents and shorter duration of dual antiplatelet therapy (DAPT).[150, 151] The SENIOR trial showed that in older adults with high bleeding risk, patients treated with drug-eluting stents and short duration DAPT had lower incidence of the composite endpoint of all cause-mortality, MI, stroke, or urgent revascularization compared to patients treated with bare-metal stents and short duration DAPT with no difference in risk of bleeding.[151] Additional approaches to reducing bleeding include age, weight and kidney function adjusted dosing of antithrombotic agents, shortening the duration of DAPT, and using double rather than triple antithrombotic therapy in patients who require anticoagulation.

As the population ages, the significant advancements in interventional strategies and technologies is often applied as rationale to prioritize this option of care for the increasing number of older adults with ACS. Nonetheless, robust RCT evidence in older patients with ACS is lacking, and geriatric domains (e.g., frailty, multimorbidity, polypharmacy, cognitive function, and healthcare goals), which often impact outcomes, have not been incorporated into most studies. The multidisciplinary heart team, integrating geriatrics experts with cardiologists and surgeons, providess an important opportunity to enhance decision-making and clinical process.

Key Points for Clinical Practice

1. Until a more specific risk score for older adults with ACS becomes available, the ACC/AHA chest pain and revasccularization guidelines recommend risk stratification for patients with suspected NSTEMI using the TIMI and GRACE risk scores, with added emphasis placed on high sensitivity troponins. Geriatric syndromes are acknowledged as relevant, but they are not formally integrated into risk assessment.
2. Immediate myocardial reperfusion by primary PCI is beneficial in older patients with STEMI, and it may also reduce recurrent MI and repeat revascularization in patients with NSTEMI, but for patients with cardiogenic shock and cardiac arrest, careful selection of older patients undergoing PCI is warranted given their high inherent risk for adverse outcomes and futility.
3. Strategies to mitigate the risk of major bleeding include the use of radial access; age, weight, and kidney function adjusted dosing of anticoagulant and antithrombotic therapy, and shorter duration of DAPT with clopidogrel, particularly among older adults at high bleeding risk.
4. Ideally, the multidisciplinary team that cares for older patients with ACS includes cardiologists, surgeons, geriatricians, primary care clinicians, nutritionist, cardiac rehabilitation professionals, social workers, nurses, family members, and pharmacists, but centers should tailor their team according to available resources and patient needs.
5. Among older patients advanced DNR directives, careful discussion with the patients, family, or their power of attorney must occur before invasive management and utilization of primary PCI. If the patient undergoes invasive treatment or primary PCI, the advanced DNR directive should be suspended for the duration of the invasive procedure.

SURGICAL REVASCULARIZATION IN OLDER ADULTS

Surgical Risk Evaluation and Patient Selection

Currently, the predicted risk of operative mortality is less than 0.5% for an 82 year old man with no major comorbidities undergoing coronary bypass surgery and defined as death within 30-days of surgery or during the index admission.[152, 153] Over the last two decades risk adjusted operative mortality associated with surgical revascularization in older patients has steadily decreased, which has been attributed to incremental improvements in case selection and perioperative management.[154-156] During this time the number of older patients undergoing surgical revascularization annually in the US hardly changed, while the prevalence of risk factors and comorbidities including diabetes, pre-operative dialysis, chronic obstructive airways disease, heart failure, cerebrovascular disease and prior stroke, prior percutaneous intervention, left main stem disease and urgent presentation, have all significantly increased.[154, 155]

Like other risk stratification systems, most surgical risk scores do not include a formal assessment of frailty or other geriatric domains that are important determinants of outcomes after cardiac surgery in older patients.[156] Frailty stands out as a particularly relevant risk. Both clinical and administrative data-based approaches to defining frailty may increase the accuracy of standard risk-prediction systems in older patients. For example, in an analysis of over two million patients undergoing coronary artery bypass graft surgery (CABG) between 2005 and 2016 identified using a national administrative claims database, 4.0% were considered frail according to the Johns Hopkins Adjusted Clinical Groups frailty indicator, a binary frailty variable derived from a diagnostic code cluster.[157] In this analysis, frailty (i.e. the presence of any one of those diagnoses) was an independent predictor of major complications and costs and associated with a more than two-fold increase in the odds of operative mortality (aOR 2.49, 95% CI 2.3-2.7). The same frailty indicator has also been reported to be associated with significantly reduced long-term survival after coronary artery bypass surgery: in an analysis of 40,083 patients operated on between 2008 and 2015 in Ontario, Canada in which 22% were defined as frail, adjusted mortality at 4 years was significantly higher in frail patients (adjusted hazard ratio 1.2, 95% CI 1.12-1.28).[158] Gait speed has also been reported to predict long-term survival after cardiac surgery.[159]

Efficacy of surgical revascularization in older patients with ACS

Medical literature has indicated that surgical revascularization is associated with an event-free survival benefit compared to PCI in select cohorts of older patients with left main or complex disease. Three overlapping meta-analyses of pivotal randomized trials of percutaneous versus surgical revascularization of multi-vessel and left main disease have evaluated mid-term outcomes in older patients, reporting that coronary bypass was associated with superior freedom from major adverse cardiac events compared to drug eluting stents.[160-162] In the EXCEL trial, patients aged over 75 years had an all-cause mortality of 16.6% in the PCI arm versus 8.4% in the CABG arm (OR: 1.96, 95% CI 1.00-3.83), and meta-regression analysis showed increasing mortality with advanced age with PCI.[161] It should be noted that approximately 60% of the EXCEL trial cohort had either stable angina or silent ischemia, while those who presented with recent ACS events (within 7 days of randomization) are approximately 40% of the cohort. Thus, the generalizability of the results to all older patients with ACS is limited. However, caution should be exercised when interpreting data from the EXCEL trial because the study population mostly consisted of stable angina patients rather than those with ACS and complex geriatric syndromes (stable angina ~ 53%; recent MI within 7 days of randomization ~ 15%; unstable angina with negative biomarkers ~ 24%). The event-free survival benefit observed in patients who received coronary bypass was primarily driven by lower risk of repeat revascularization and MI.[160-162] Lesion complexity appears to be highly relevant: in a meta-analysis of 4,686 patients with unprotected left main stem disease randomized in six trials, PCI was associated with lower mortality than coronary bypass in patients with SYNTAX score ≤22, but higher mortality in patients with SYNTAX scores ≥33.[160] In these meta-analyses the risk of early stroke was higher in surgical patients; however a recent analysis of 1,680 patients who underwent either PCI or CABG while participating in a prospective study of 23,860 adults undergoing two per year memory tests as part of a national longitudinal study on aging showed no significant differences between PCI and CABG in memory score or dementia up to 10 years after revascularization.[163]

Adverse Events of Surgical Revascularization in Older Adults: Management to Minimize Risk

Less invasive surgical approaches such as off-pump and hybrid revascularization are aimed at reducing post-operative morbidity particularly in older patients. However, the German Off-Pump Coronary Artery Bypass Grafting in Elderly Patients (GOBCABE) trial, in which 2,539 patients aged over 75 years were randomized to on-pump or off-pump surgery, suggests that off-pump techniques have no impact on stroke or new dialysis, and the most important surgical determinant of event-free survival after coronary bypass surgery in older patients is completeness of revascularization.[164, 165] In this landmark trial, the rate of death at five years was similar in patients who underwent off-pump (361, 31%) versus on-pump (352, 30%) surgery, as was the composite outcome of death, MI and repeat revascularization (33% versus 34%, respectively).[164] Incomplete revascularization, which was more common in off-pump compared to on-pump coronary bypass surgery, was associated with significantly worse survival at five years (HR 1.2, 95% CI 1.01-1.39). In this trial, there was no significant difference at 30-days in the incidence of stroke between on- and off-pump surgery, or between the incidence of stroke in off-pump patients stratified according to aortic clamping versus no-touch techniques.[165] Stroke rates may be minimized by individualized operative techniques and peri-operative management including aggressive prevention and treatment of atrial fibrillation and tailored pre-and intra-operative imaging of aortic and cerebrovascular disease.[166] Post operative delirium remains an important adverse outcome during index MI hospitalization, and proactive efforts to identify and prevent delirium postoperatively are warranted.[71] Rate of memory decline has been reported to be worse after off-pump compared to on-pump coronary bypass surgery, which may predominantly reflect patient selection but serves as a caution against pursuing less-invasive surgical revascularization strategies such as hybrid procedures in older patients with multi-vessel disease who may derive greatest long-term benefit from complete and durable revascularization.[163]

Prevention of AKI in Older Patients undergoing Revascularization—More than half a million percutaneous or surgical revascularization procedures are performed annually in the US.[167] Older patients are more likely to develop adverse outcomes such as contrast-induced acute kidney injury (CI-AKI) than younger patients due to underlying comorbid conditions such as CKD, DM, hypertension, and volume depletion. CI-AKI is defined as ≥ 0.5 mg/dL or 25% increase of serum creatinine from the baseline value at 48 h after contrast media administration.[168] The risk of AKI among patients undergoing revascularization varies with the volume of contrast and the patient's baseline risk.[169]

Several measures can be implemented to prevent CI-AKI following coronary interventions. Radial artery PCI is a potential method for decreasing AKI by prevention of bleeding or by reduction and avoidance of direct embolization into the renal circulation. The AKI-MATRIX trial show that radial artery PCI compared with femoral artery PCI resulted in a 13% reduction in AKI (aHR=0.87, 95% CI 0.77-0.98), defined as either an absolute (0.5mg/dL) or relative (>25%) increase in serum creatinine from baseline. In subgroup analyses, radial compared to femoral access was associated with 20% less AKI in patients age ≥ 75yrs. Overall, age >75 years (OR = 1.99, 1.75-2.27), DM (OR=1.33, 1.16-1.52), anemia (OR=1.20, 1.04-1.39), and contrast media volume per 100ml (OR=1.34, 1.26-1.72) were independent risk factors for AKI.[170] Evaluation of data from the National Cardiovascular Data Registry showed that a patient-centered approach to contrast use can attenuate the risk of AKI.[171] Using the formula 3 x estimated glomerular filtration rate (eGFR) to define contrast volume threshold, the authors found an AKI rate of 14.5% when the contrast volume threshold was exceeded vs. 9.8% if the volume was below the threshold. Meaningful reductions in CI-AKI risk can be attained by decreasing contrast volume among patients undergoing PCI. Best kidney practices for older adults with ACS are summarized in Table 4.[172-174]

Key Points for Clinical Practice

1. Among selected older adults with left main or multi-vessel coronary disease, CABG has been associated with improved survival and lower risk of repeat revascularization and myocardial infarction compared to PCI, but for older patients a Heart Team approach to revascularization strategy is suggested, including geriatrics expertise to assess frailty, multimorbidity, cognition, and other pertinent age-related elements of care.

2. STS PROM score quantifies the risk of early mortality after CABG at all ages; however, important additional considerations that may reduce the feasibility of safe and effective surgical revascularization or affect the goals of care are commonly encountered in older patients, including severe cognitive impairment, frailty, cerebrovascular disease and aortic calcification.

3. Among older adults with left main or multi-vessel coronary disease, CABG surgery with goal of complete revascularization has shown survival benefits, but shared decision making with patient and family is critical particularly among very old adults. The utilization of percutaneous revascularization with medical therapy or medical therapy alone are also reasonable options if symptom control is a primary patient-centered goal.

4. Stroke risk can be minimized by tailoring operative techniques and peri-operative management to include pre-and intra-operative imaging of aortic and cerebrovascular disease, and aggressive prevention and treatment of atrial fibrillation.

FUTILITY

Futility has been defined as (1) "as a lack of medical efficacy, particularly when the therapy is unlikely to produce its intended clinical result, as judged by the physician; or lack of a meaningful survival, as judged by the personal values of the patient"[175]; (2) "advanced life-prolonging treatments that would almost certainly result in a quality of life that the patient has previously stated that he/she would not want"; or (3) "when there is no reasonable expectation that the patient will improve sufficiently to survive outside the acute care setting".[176] It is frequently challenging to predict or recognize futility or gain consensus from the patient and caregivers, particularly after percutaneous or surgical revascularization when concerns around publicly reported outcomes may influence the decision to pursue aggressive care in the end-of-life setting. Establishing goals of care in older patients from the outset may help avoid unwanted or futile intervention.[6] Mechanical circulatory support for surgical revascularization is generally futile in older patients with advanced geriatric syndromes (such as delirium and cognitive impairment, frailty, multimorbidity, and polypharmacy), very poor baseline functional status, or prohibitive surgical risk (defined as STS PROM >20%).

The confirmation of futility often remains ambiguous and even misinterpreted within contemporary management. Those who are not candidates for procedures due to perceived futility often benefit significantly from palliative care, such that the concept of futility does not imply withdrawal of care.

Key Points:

1. Futility is a lack of medical efficacy when the therapy is unlikely to produce its intended clinical result or meaningful survival as judged the Heart Team.

2. Determining a priori goals of care in older patients may help avoid unwanted or futile intervention.

3. For older patients at a high-risk for mortality and adverse outcomes, a major challenge is to identify futility before rather than after revascularization but establishing goals of care in older patients from the outset may help avoid unwanted or futile intervention.

TRANSITIONS, CARDIAC REHABILITATION, AND FOLLOW-UP

Transitions of Care in Older Adults

ACS is associated with significant morbidity and mortality and older adults are at highest risk.[177] The 30-day readmission rate following ACS ranged from 11-14% in a meta-analysis of 14 studies.[178] Mortality rates vary among populations and range from 7-18% in the first year following STEMI.[179] These adverse outcomes suggest that transitions in care from hospital to home and to primary care are important and are a target for improvement. Continuity in care is particularly critical for aging adults who are more likely to experience frailty, multimorbidity, depression, cognitive decline, diminished functional status, and a higher symptom burden.[180] For example, depression is three times more common in patients following MI and complicates adherence to guideline-directed therapies, self-care, and clinic visits.[180] In addition, coronary disease predominantly affects older adults so multimorbidity is expected and contributes to MACE following ACS, making coordinated care during transitions critical.

Based on a Get with the Guidelines approach, Goldman et al.[177] recommended that the post-ACS discharge plan address 6 elements including: (1) medications, (2) lifestyle modification/cardiac rehabilitation, (3) management of comorbidities, (4) psychosocial support, (5) socioeconomic factors, and (6) patient/family education to include teaching and preparation of patients for their own self-care. (Figure 4). Polypharmacy is a frequent issue for older adults and transitions in care should include consideration of deprescribing potentially inappropriate medications and medications that are no longer needed.[181] To achieve optimal care coordination, the multidisciplinary team benefits from inclusion of the cardiologist and surgeon (when relevant), as well as the primary care clinician, geriatrician, nurses, social worker, patient, and the patient's family or significant other(s), with ready access to pharmacists, dieticians, psychologists, occupational therapists, and case managers as needed. The older adult's general health status is often a key patient-centered outcome that must be considered in addition to improving survival.[180] The American Heart Association recommends prioritizing three components of the patient's health status, including symptom burden, functional status, and quality of life.[182-184] Monitoring these domains during post-discharge follow-up can provide insight into how the patient is progressing relative to their goals of care and where there is potential for improvement.

The complexity of care required for many older adults following hospital discharge can lead to gaps in care, and multidisciplinary coordination is essential to ensure that all aspects of care are integrated into a cohesive plan. High-quality transitional care and case management can reduce the risk of recurring adverse events and improve patient-centered outcomes such as functional status and symptom control.

Key Points for Clinical Practice

1. Transitions of care are high risk times for older adults following ACS coordination of surgeons (when relevant), cardiologists, geriatricians, nurses, pharmacists, and primary care clinician is integral to successful discharge/ transitional care plan for older patients with ACS. Goals to better harmonize diverse clinicians involved with the care of older patients with ACS remains a challenging goal of care.

2. A detailed medication review and reconciliation is essential, ideally in collaboration with a pharmacist, to ensure that once at home, the patient has access to and is taking the medications prescribed at discharge and that they are integrated with any additional pharmaceuticals acquired over-the-counter and from other clinicians.

Palliative and End of Life Care in Older Adults

ACS is a sentinel event that can lead to deterioration in cognitive function, increasing frailty, loss of overall function, independence, and self-confidence among older patients. This presents a challenge to patients, their caregivers, and clinicians providing primary and specialty care, particularly when evaluating decision making. Palliative care is an important step in providing optimal treatment and support to patients and caregivers. The World Health Organization estimates that those with CVD have the greatest need for palliative care. Warraich et al. note that aggressive symptom management should be the cornerstone of management of CVD at the end of life rather than persistent life-prolonging therapies.[185]

Palliative care is defined as an interdisciplinary approach to improving quality of life and reducing suffering among patients with serious illness. Core domains include: (1) treating physical symptoms, (2) psychosocial care, 3) identifying the patient's priorities for care, and (4) patient and caregiver support for decision-making. The National Coalition for Hospice and Palliative Care published the *Clinical Practice Guidelines for Quality Palliative Care* and included eight domains: (1) structure and processes of care, (2) physical aspects of care, (3) psychological and psychiatric aspects, (4) social aspects of care, (5) spiritual, religious, and existential aspects of care, (6) cultural aspects of care, (7) care of the patient nearing the end of life, and 8) ethical and legal aspects of care. It is especially important to assess patient-reported symptoms and quality of life since symptoms and well-being do not necessarily correlate with objective measures of disease severity. Palliative care differs from hospice care in that hospice requires an estimated life expectancy of 6 months or less. Further, palliative care does not preclude hospitalization or life-prolonging interventions, whereas hospice care generally promotes comfort measures only.

While there are few studies that focused on ACS alone, for patients with ACS complicated by severe heart failure, home and team-based palliative interventions improved patient-centered outcomes, health related quality of life, documentation of preferences, and healthcare utilization. The burden of CVD is increasing and evidence in support of various palliative care delivery methods is growing. This provides an opportunity to adopt and integrate palliative care measures into the standards of cardiovascular care. Aggressive management of patients' symptoms is critical to improving their quality of life. Rigorous studies are needed to better define optimal timing, utilization and implementation of palliative care into practice for older patients with ACS.

Key Points for Clinical Practice

1. End of life management should be made available to all patients with progressive CVD to treat symptoms and improve quality of life.
2. Research is needed to better determine the utility and timing of palliative care interventions in older patients with ACS and how to best integrate palliative care precepts into standard post ACS-care.
3. Patient-reported outcome measures (PROMS) should encompass measure of function and health-related quality of life, symptoms and symptom burden, and health behavior.

Cardiac Rehabilitation in Older Adults

Cardiac Rehabilitation (CR) is a comprehensive secondary prevention CVD management program that utilizes exercise training, behavioral modification, education, and psychosocial counseling to improve outcomes in patients with ACS and other conditions. CR has been demonstrated to reduce recurrent CVD events, mortality, and rehospitalizations, as well as improve cardiorespiratory fitness, physical function, self-efficacy, and quality of life. It is an important component of ACS care for older adults with benefits applying across the clinical spectrum from those who are vigorous, robust, and confident to those who are weak, sedentary, and fearful.[186] CR has particular value for older adults as it provides opportunity to develop personalized approaches to CV health in the context each patient's aggregate healthcare challenges.[186]

Key components of CR include an initial medical assessment to determine a patient's CVD status as well as the comorbidities that may affect symptoms, signs, and cumulative medication effects.[187] Carefully prescribed exercise training regimens are also fundamental, with the goal to assess baseline capacity and to design tailored approaches that improve physical function over time.[183, 184] Medical assessments provide opportunity for medication review and reconciliation, and referral to clinicians who can address relevant medical issues (CVD and non-CVD).[183, 184] Risk reduction and psychosocial support can also be implemented, as well as steps to align overall care with each patient's personal goals of care. Most CR programs incorporate significant care partners (spouses, partners, adult children) to reinforce learning and support structures for the patient, and also to advance the premise of healthfulness that benefits the whole family.[183, 184]

Despite age-related benefits of CR, participation declines with increasing patient age, and only 25% of older patients eligible for CR actually participate.[188] Women also tend to participate less often than men across all ages, but since women outlive men, these gaps tend to worsen among older adults.[189] Common barriers include a lack of understanding among patients and clinicians of CR's value, prohibitive logistics particularly as many older adults cannot drive, unaffordable co-payments for CR for patients on fixed incomes, and inflexibility in format to achieve personalized therapeutic approaches in CR that are tailored to the wide range of needs and circumstances among older adults. While many contemporary initiatives now aim to improve CR participation using remote-based formats, often incorporating smartphones and wearable devices to facilitate and inform this care, the usability and safety of these novel methods for older adults who are frail, cognitively limited, and medically complex is still largely uncertain.

Benefits of CR in Older ACS patients

CR addresses heterogeneity of older adults: Principles of ACS disease management are potentially transformed by each patient's health circumstances. An older adult who is relatively robust is likely to have benefitted from revascularization and well-tolerated adjunctive therapies. Such a patient derives valuable benefit from CR through exercise and activity regimens that aim to increase cardiorespiratory fitness in combination with guidance to mitigate risks of over-exertion and injury. Likewise, CR provides a robust patient, i.e., those without physical frailty or pre-frailty, the opportunities to better understand ACS pathophysiology and treatment precepts, insights that correlate to improved adherence and diminished anxiety. Robust patients also benefit from improved understanding of symptoms, sleep hygiene, diet, and other aspects of care.

CR also benefits patients who are frail and sedentary. In this case, CR fosters safe and effective exercise strategies that promote physical function and confidence. Initial emphasis on strength and balance training in CR is often essential to provide a foundation before aerobic training is feasible. The effects of comorbidity, medications, nutrition, sleep, cognition, and fear are also factored into therapeutic goals and strategies. Patients who are the most functionally impaired often benefit the most from CR in terms of their relative improvements in function and quality of life.[190]

CR targets improved functional capacity: Whereas CVD research is typically predicated primarily on endpoints of Major Adverse Cardiovascular Events (MACE), CR benefits include enhanced physical function.[191] For many older adults, this is their primary goal of care, as it is associated with self-efficacy, independence, and improved quality of life. CR fosters opportunity for patients to maintain or regain vigor despite disease by targeting progressive strength, endurance, and cardiorespiratory fitness, with the associated aims of increased daily activity and long-term health.[192]

While a definitive therapy for frailty is still not known, exercise training and nutrition show promise.[193, 194] CR provides critical supervision for patients who are easily fatigued and highly susceptible to falls and injury. Multiple studies demonstrate the utility of CR to restore physical function and improve outcomes.[190, 195] While a cardiac hospitalization has the potential to trigger a cascade of progressive weakening and disablements for older adults who are frail, CR can potentially restore sufficient function for independence to be preserved. The concept of prehabilitation extends from CR as a complementary strategy to mitigate frailty risks even before surgical revascularization is undertaken.[196]

Whereas older patients with severe frailty are often excluded from cardiac surgery, patients who are treated with PCI or medical management may be relatively more functionally impaired. Ironically, the rate of referral of surgical patients to CR exceeds that for PCI and medical management, with the implication that many older PCI and medically managed ACS patients do not get the much-needed benefits of CR.[197] A secondary goal of a CR program is to identify older patient at a low socioeconomic status with of lack of social support, and at a high risk for chronic stress, anxiety, and depression. The CR program can thus provide a tailored interventions to enhance psychosocial support and care for older patients after ACS admission.[197]

Key Points for Clinical Practice

1. CR targets functional enhancement as a key outcome benefit. For many older adults this is a vital clinical priority that is not fostered by other aspects of treatment, thereby reinforcing the distinctive value of CR.
2. CR is best utilized with a tailored approach that addresses each patient’s distinctive circumstances and goals of care.
3. Frailty is biologically linked to CAD and plays a key role in ACS management. CR provides opportunity for strength training, nutritional emphasis and other strategies to mitigate frailty effects and improve patient-centered outcomes.

Whereas many clinicians avoid CR for patients who are frail, in fact patients who are frail often benefit the most.

CONCLUSION

The management of ACS in the older adult population is more complex than in younger patients owing to their anatomic complexity, physiologic vulnerability, age-related risks (including prevalent geriatric syndromes), and heterogeneity in life expectancy and goals of care. In this document, we propose a framework to integrate geriatric risks into the management of ACS, including the diagnostic approach, pharmacotherapy, revascularization strategies, prevention of adverse events, and transition care planning. Post MI care should include CR tailored to address each patient's aggregate circumstances and personal goals of care.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ABBREVIATIONS

ACS	Acute Coronary Syndrome
AKI	Acute Kidney Injury
CAD	Coronary Artery Disease
CKD	Chronic Kidney Disease
CR	Cardiac Rehabilitation
CRS	Cardiorenal Syndrome
CV	Cardiovascular
CVD	Cardiovascular Disease
eGFR	estimated Glomerular Filtration Rate
ED	Emergency Department
HRQoL	Health-related Quality of Life
LV	Left Ventricular
MI	Myocardial Infarction
MINOCA	Myocardial Infarction with No Obstructive Coronary Artery
NSTEMI	Non-ST elevation myocardial infarction
PCI	Percutaneous Coronary Intervention
STEMI	ST-Elevation Myocardial Infarction

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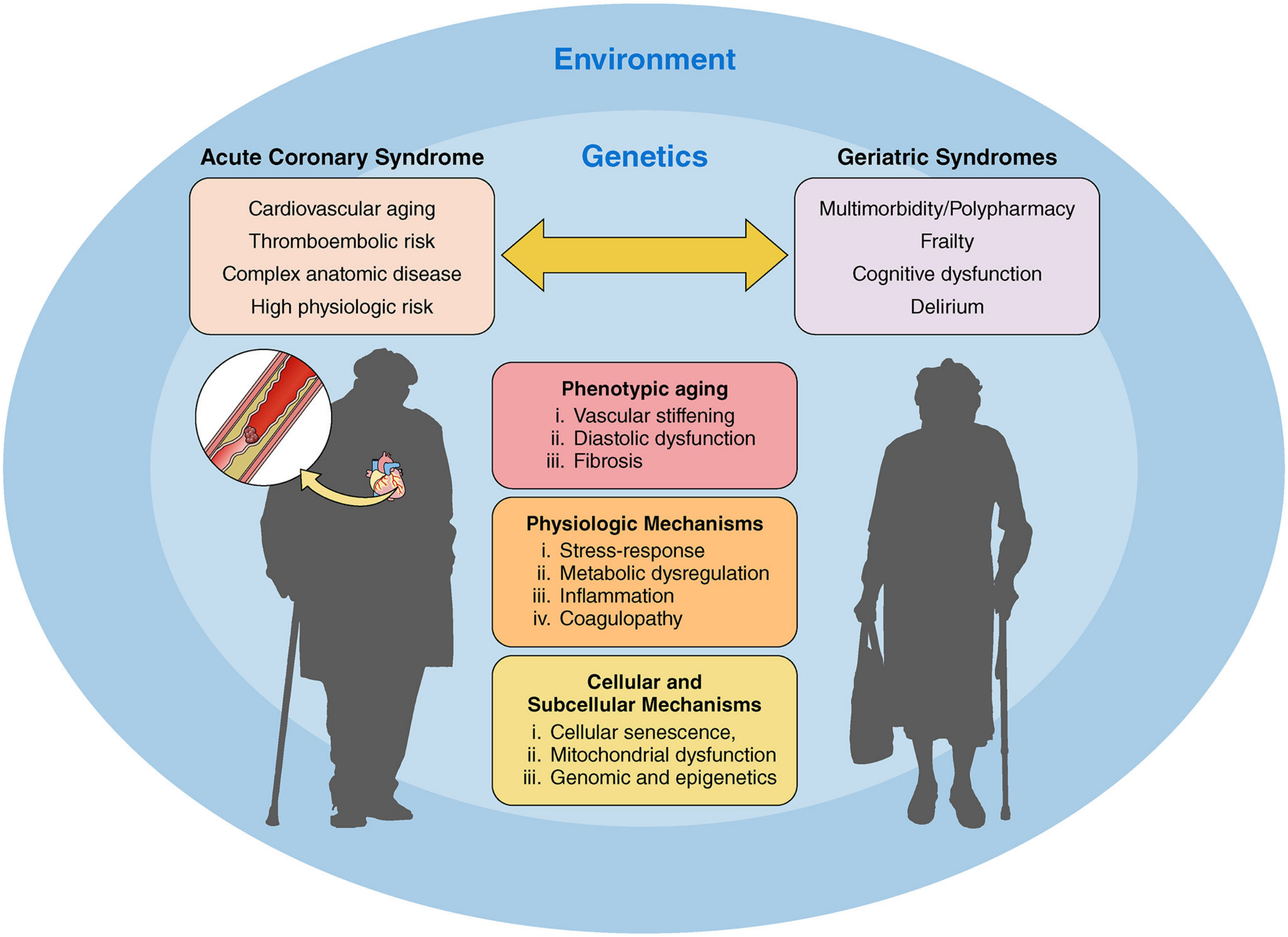

Figure 1.

The bidirectional association between acute coronary syndrome and geriatric syndromes. Several factors influence this bidirectional association including phenotypic aging, physiologic mechanisms, cellular and subcellular mechanisms, genetics, and the environment.

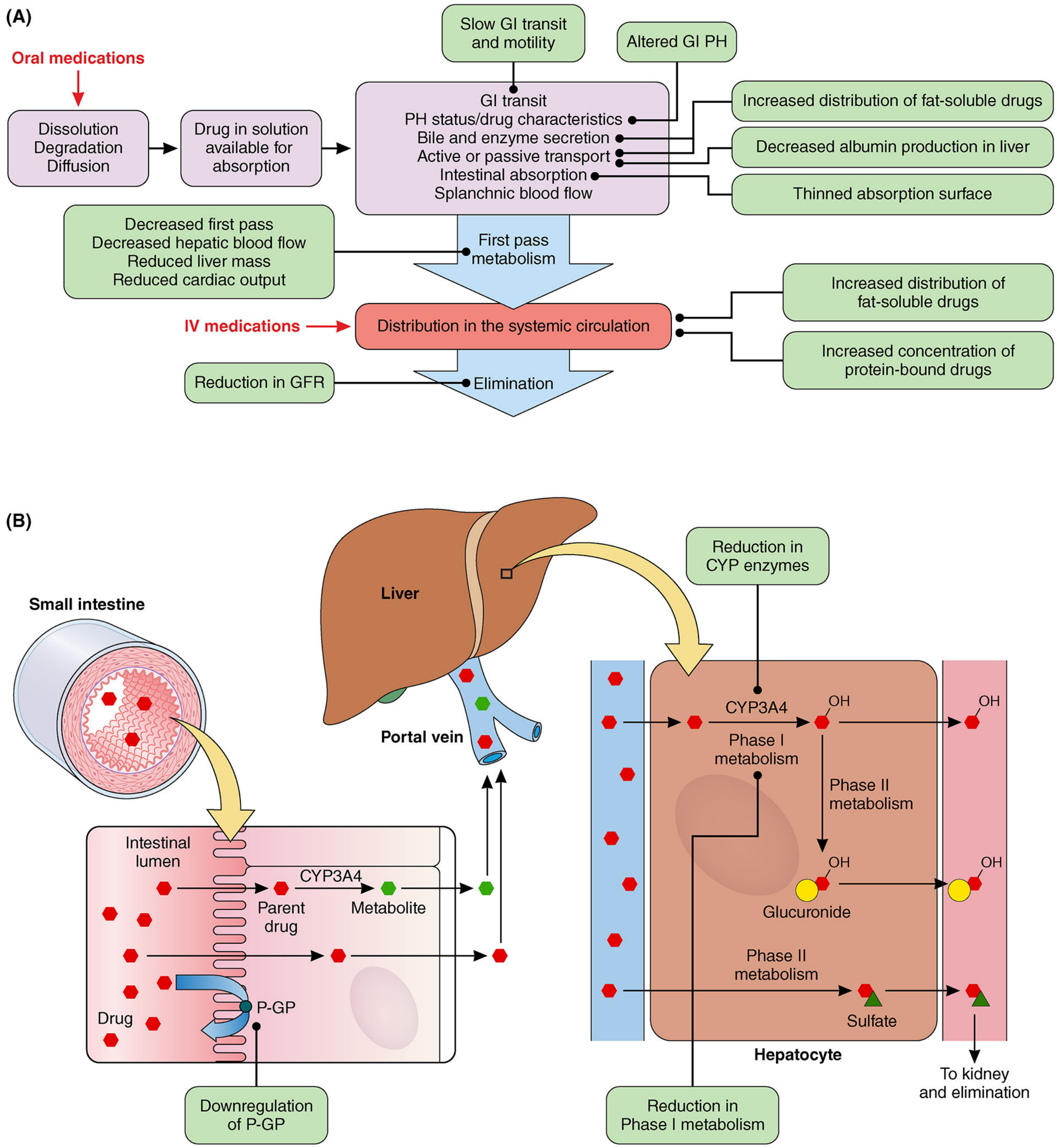

Figure 2.

A. Classification system for acute and chronic myocardial injury. **B.** The number of patients with each universal definition of myocardial infarction (UDMI). Modified with permission from Morrow et al.[55]

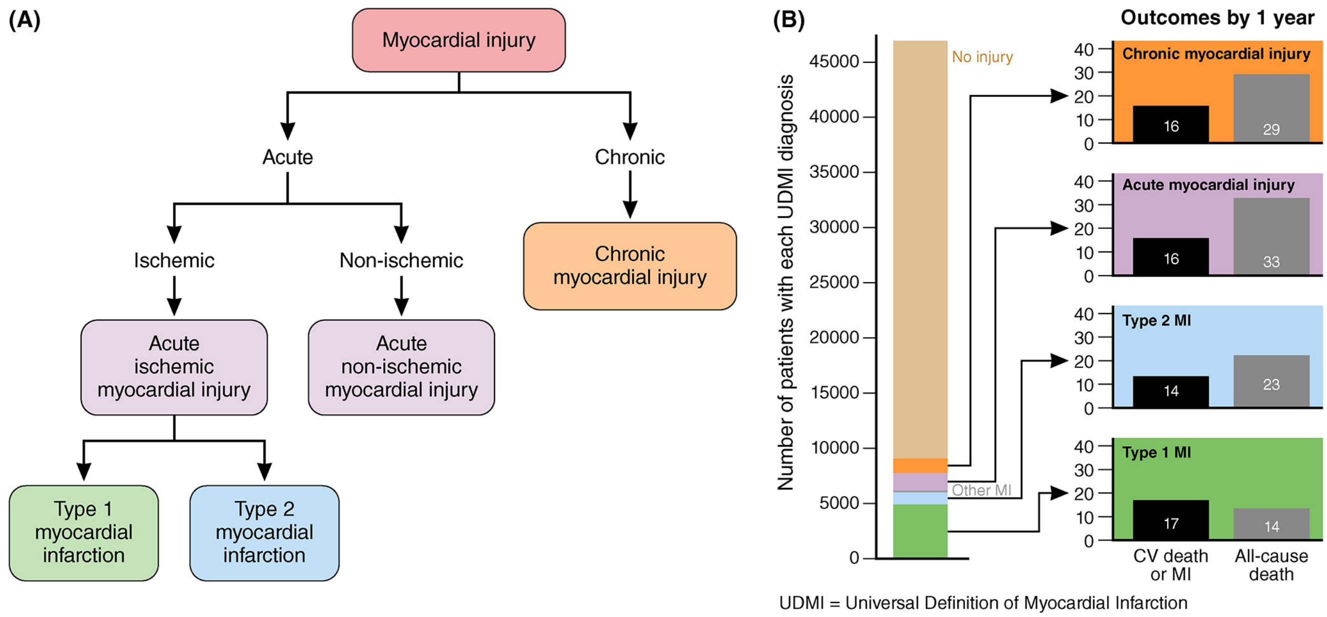

Figure 3.

A. Absorption, metabolism, distribution, and elimination of guideline directed medical therapy in older adults with acute coronary syndromes. **B.** Changes in small intestine and liver that influence drug metabolism in older adults with acute coronary syndrome.

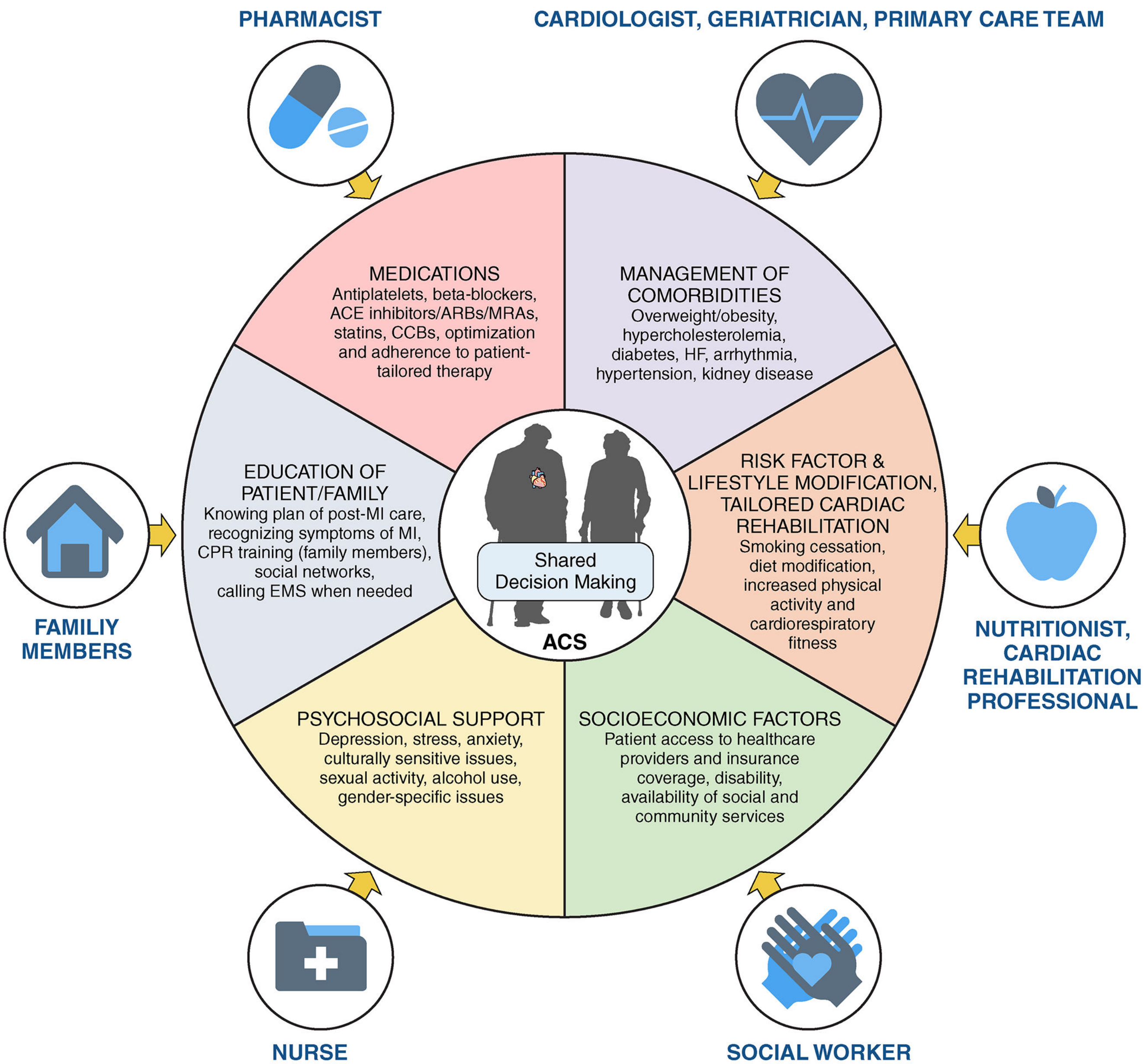

Figure 4.

Post discharge plan with shared decision making for older adults with acute coronary syndrome focusing on (1) medications, (2) lifestyle modification/cardiac rehabilitation, (3) management of comorbidities, (4) psychosocial support, (5) socioeconomic factors, and (6) patient/family education. Family and patient education is a collaborative effort performed by the primary medical team, and corroborated by cardiologist, geriatrician and social worker to improve overall comprehensive and health literacy.

Table 1.

Normal cardiovascular aging and risk for acute coronary syndromes.

Age-related Change	Implications for ACS
Increased central aortic stiffness due to increased collagen crosslinking and elastin fiber degeneration	Increased impedance to LV ejection, increased SBP and pulse pressure, increased myocardial work and O_2 demand, decreased coronary perfusion pressure
Altered LV diastolic relaxation and increased myocardial stiffness	Increased resistance to coronary perfusion; predisposition to atrial fibrillation and HFpEF
Decreased responsiveness to β-adrenergic stimulation	Decreased maximum HR and contractility, decreased peak cardiac output, decreased peripheral vasodilation
Impaired endothelium-mediated vasodilation	Decreased peak coronary blood flow and coronary flow reserve; increased atherogenesis; increase in vascular impedance as a result of impaired endothelium mediated vasodilatation.
Altered balance between intrinsic thrombosis and fibrinolysis	Increased risk for venous and arterial thromboembolism
Chronic low-grade inflammation (inflammaging[†])	Increased atherogenesis and geriatric syndromes, including frailty

[†]Not a normal age-related change but prevalent at advanced age.

Abbreviations: ACS: acute coronary syndrome; HFpEF: heart failure with preserved ejection fraction; HR: heart rate; LV: left ventricular; SBP: systolic blood pressure.

Table 2:

Geriatric Syndromes and Clinical Implications

Geriatric Syndrome	Diagnosis/Prevalence	Prognosis	Disease Management
Multimorbidity	2 or more chronic conditions (cardiac and non-cardiac) that are active simultaneously Prevalence: 63% of adults 65-74 years, 77% of adults 75-84 years, and 83% of adults ≥85 years.	↑Short and long-term prognostic risks due to CVD as well as uncontrolled CVD and non-CVD risk factors.	Confounds customary CVD symptoms and signs Multiple diseases and providers often result in desynchronized or even contradictory aspects of care ↑ likelihood that patients will experience high therapeutic burden
Frailty	State of vulnerability relating to diminished physiological reserves across multiple physiologic systems. • Definition controversial: some define frailty as a phenotype, while others define frailty as an index of cumulative clinical deficits Prevalence: 10%-60% of older adults depending on the CVD burden, as well as the tool and cutoff chosen to define frailty.	↑Risk from CVD as well as medical, device, percutaneous catheter, and surgical therapies used to treat CVD. ↑Risks, disability, falls, rehospitalization, poor quality of life, mortality	Guidelines-based therapy and procedures commonly overlook the impact of frailty on recommendations. Intensive care, bedrest and functional decrements associated with many conventional therapies can exacerbate frailty and functional decline. Nutrition and exercise may help mitigate frailty and risks of frailty
Cognitive decline	Mild cognitive impairment (MCI)→↓ cognitive function without loss of function; • Prevalence estimates vary with the population and methods, but it rises with age, generally in the range of 2-5% in those 60-65 to >20-40% in those ≥90 years. Dementia→ severe memory loss, loss of executive function, and other cognitive abilities that interferes with daily life and loss of functional independence • Prevalence increases with age, from ~5.0% of those aged 71–79 years to 35-40% of those aged 90 and older.	↓Independence ↓Adherence ↓Shared decision making ↓QOL ↑Hospitalization ↑Mortality	Often confounds assessments of symptoms Often confounds accounts of present illness and PMHx Often confounds adherence Does not negate the potential value of therapeutic intervention, but it impacts the decision and implementation process.
Delirium	Disturbance in cognition, attention, and consciousness or perception with fluctuating course • Can manifest as agitated state or quiet and withdrawn High prevalence in older adults who are hospitalized, i.e. ~30 to 60%.	↑LOS ↑Rehospitalization ↑Functional Decline ↑Falls ↑Long-term Care ↑Mortality	Prevention of delirium should take priority by optimizing the environment to increase orientation, avoid sedation, reduce meds, reduce pain. Predisposing risks include cognitive deficit, sensory limitations, and disorienting medications. Treat by optimizing environment to increase orientation, avoid sedation, reduce meds, reduce pain
Polypharmacy	• Polypharmacy refers to multiple medications usually 5 or more chronic and concomitant use. • May have unintended interactive effects (not required for definition). • 40% of older adults take ≥5 medications.	↑Adverse Events (errors and drug interactions) ↑Rehospitalizations ↑Mortality	↑Medication errors ↑Drug-drug and drug-body interactions ↓Adherence is common Under- and Over-treatment both commonly occur Consider deprescribing
Disability	The inability to care for oneself or to manage one's own home	↑Risk progressive functional and cognitive declines ↓Self-reliance and self-efficacy	Conventional care for CVD often contributes to a cycle of progressive disability, which highlights rationale for shared decision making for each aspect of therapy.

Geriatric Syndrome	Diagnosis/Prevalence	Prognosis	Disease Management
		↑Long-term care ↑Mortality	Conventional care for ACS (including pharmacotherapy, procedural care, and bedrest) can result in temporary immobility, delirium, disturbance in sleep pattern, and increase the risk of loss of independence. Suboptimal transitions are common contributors to disability, (e.g., hospital to home, and even hospital to post-acute care or hospital to home if support is inadequate or patient education has been deficient)
Sensory Loss	Vision and hearing deficits are common	↑Risk progressive functional and cognitive declines ↓Self-reliance and self-efficacy ↑Long-term care ↑Mortality	Same as disability

Modified with permission from O’Neil DE and Forman DE. *BMJ* 2021; 374 :n1593 doi:10.1136/bmj.n1593.

Abbreviations: ACS = Acute Coronary Syndrome; CVD = Cardiovascular Disease.

Table 3.

Randomized control trials comparing early or routine invasive strategies with conservative approaches in older patients with non-ST-elevation acute coronary syndromes

Study	Population	Primary Outcome	Frailty	Comorbidity
Savonitto et al. Italian Elderly ACS (2012)	n = 313 NSTEACS ≥ 75 years old	No difference in death, reinfarction, disabling stroke, repeat hospital stay for cardiovascular causes and severe bleeding at 1 year • Early invasive vs. initially conservative; 27.9% vs. 34.6%, HR 0.80, 95% CI 0.53-1.19, *p*=0.26	No frailty assessment	No assessment of comorbidity burden or severity
Tegn et al. After Eighty (2016)	n = 457 NSTEACS ≥ 80 years old	Reduction in death, reinfarction, need for urgent revascularization and stroke at 18 months, driven by lower rates of reinfarction and urgent repeat revascularization • Early invasive vs. conservative; 41% vs. 61%, HR 0.53, 95% CI 0.41-0.69, P=0.0001	No frailty assessment	No assessment of comorbidity burden or severity
Sanchis et al. MOSCA (2016)	n = 106 NSTEMI ≥ 70 years old	No difference in death, reinfarction or readmission for cardiac causes at 2.5 years • Invasive vs. conservative; HR 0.77, 95% CI 0.48-1.24, P=0.285	No frailty assessment	Participants had at least two comorbidities Comorbidity burden or severity assessed with CCI Findings not stratified by CCI score or comorbidities
MOSCA-Frail (2019)	n = 313 NSTEMI ≥ 70 years old	• Primary endpoint: number of days Alive out of hospital during first year. • Co-Primary endpoint: Time to first occurrence of CV death, MI, or post-discharge revascularization. • Secondary endpoints: functional capacity, instrumental activities, cognitive capacity, quality of life at 6 months. • Terminated recently (unpublished data) • No benefit of invasive strategy on primary or co-primary endpoints • Increased non-cardiac death and bleeding requiring hospitalization”	Clinical Frailty Scale ≥ 4	Comorbidity burden and total number of drugs used (polypharmacy)
Hirlekar et al. (2020)	n = 186 NSTEACS ≥ 80 years old	No difference in all-cause mortality, reinfarction, stroke, urgent revascularization or rehospitalization for cardiac causes at 1 year • Invasive vs. conservative; 34.3% vs. 37.7%, HR 0.90, 95% CI 0.55-1.46, P=0.66	Frailty assessed with the CSHA Clinical Frailty Scale Low prevalence of frailty Findings not stratified by frailty status	No assessment of comorbidity burden or severity
De Belder et al. RINCAL (2021)	n = 251 NSTEMI ≥ 80 years old	No difference in all-cause mortality or reinfarction at 1 year • Routine invasive vs. selective invasive; 18.5% vs. 22.2%, HR 0.79, 95% CI 0.45-1.35, P=0.39	No frailty assessment	No assessment of comorbidity burden or severity

Abbreviations: ACS = acute coronary syndromes; PCI = percutaneous coronary intervention; NSTEACS = non-ST elevation acute coronary syndrome; HR = hazards ratio; CI = confidence interval; NSTEMI = non-ST elevation myocardial infarction; CCI = Charlson comorbidity index; CSHA = Canadian Study of Health and Aging.

Table 4.

Best Kidney Practices for Older Adults with acute coronary syndrome.

Best Kidney Practices
Pre-procedure identification of older patients at risk for CI-AKI with the aim to stabilize renal function prior to coronary intervention in the context of ACS. Risk factors include preexisting kidney disease, DM, hemodynamic instability, and those on nephrotoxic medications.
If patients are not at risk for acute pulmonary edema associated with reduced LV function, assess volume status and consider gentle pre-procedure volume resuscitation and/or holding of diuretics to protect against CI-AKI.
Avoid hyperosmolar CM and minimize dose of isoosmolar or low-osmolar CM to avoid CA-AKI. A recommended dose of CM to avoid AKI: 3 X eGFR.
The use of transradial PCI to lower risk of AKI, bleeding, and death is important and avoidance of renal toxins, NSAIDS, diuretics, and aminoglycosides), adjustment of medication doses for reduced eGFR, and reduction of polypharmacy in the older patients are critical.
Avoid hypotensive episodes to protect renal function particularly among patients with left ventricular impairment.
Rule out other causes of AKI prior to procedures (obstruction, volume depletion, sepsis).
In case of multi-vessel PCIs, procedures can be staged to allow renal recovery.
Among patients already on dialysis, coordination of PCI procedures and dialysis with the renal team.
Short duration (1-3 months) of DAPT with DES in CKD patients reduces bleeding events post PCI.

Abbreviations: ACS = acute coronary syndrome; CI-AKI = contrast induced kidney injury; CM = contrast media; DAPT = dual antiplatelet therapy; DES = drug-eluting stent; DM = diabetes mellitus; eGFR = estimated glomerular filtration rate; LV = left ventricular; NSAIDS = nonsteroidal anti-inflammatory drugs; PCI = percutaneous coronary intervention.