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Review Article

Predictors of major adverse cardiac events in elderly cardiac patients with coronary artery disease

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Abstract

Background: Elderly patients with coronary artery disease (CAD) carry a disproportionate burden of major adverse cardiac events (MACE), yet risk scores derived largely from younger cohorts often fail to capture the geriatric-specific determinants of outcome.

Objective: This review synthesizes published evidence on predictors of MACE in elderly CAD patients, spanning traditional risk factors, frailty and geriatric syndromes, biomarkers, comorbidity burden, and revascularization strategy.

Methods: We synthesized cohort studies, registry analyses, and trial substudies addressing risk stratification in patients aged 65 years and older with stable or acute CAD.

Findings: Age-adjusted risk scores such as GRACE and TIMI retain value but underweight frailty, multimorbidity, renal dysfunction, and anemia, each of which independently predicts MACE and, alongside natriuretic peptide and troponin measurement, improves discrimination beyond traditional models; anatomical complexity and revascularization completeness further modify risk.

Conclusions: Reliable MACE prediction in elderly CAD patients requires integrating traditional risk factors with frailty assessment, comorbidity indices, and biomarkers, with future models prospectively validated in geriatric cohorts rather than extrapolated from younger populations.

Keywords: coronary artery disease; major adverse cardiac events; elderly; frailty; risk prediction

1. Introduction

Coronary artery disease (CAD) remains the leading cause of morbidity and mortality among older adults, and the proportion of patients with stable or acute CAD aged 75 years or older continues to rise worldwide. Elderly patients experience major adverse cardiac events (MACE) — the composite of cardiovascular death, myocardial infarction, urgent revascularization, and stroke — at rates two- to fourfold higher than middle-aged patients with comparable angiographic disease, yet this population has historically been underrepresented in the trials that generated the risk tools used in routine practice. Registries such as the Global Registry of Acute Coronary Events (GRACE) enrolled a broader age spectrum than preceding trials and confirmed that age is among the strongest independent predictors of mortality after acute coronary syndrome, helping establish age-inclusive risk scores as a clinical standard [1,2]. The Thrombolysis in Myocardial Infarction (TIMI) risk score, derived in a somewhat younger population, likewise assigns incremental risk to age above 65 years, underscoring that age carries prognostic weight even before comorbidity or frailty are considered [3].

What distinguishes elderly CAD patients is not simply a higher prevalence of traditional risk factors but the emergence of geriatric-specific determinants of outcome that traditional risk scores were never designed to capture: frailty, sarcopenia, multimorbidity, renal dysfunction, and anemia. Each independently predicts MACE in elderly cohorts, and several interact in ways only beginning to be incorporated into risk models. This review synthesizes evidence across five domains — traditional risk factors, frailty and geriatric syndromes, circulating biomarkers, comorbidity burden, and coronary anatomical/revascularization factors — before considering how they might be integrated into geriatric-specific risk prediction.

2. Traditional risk factors and their age-specific

behavior

Table 1: Established risk scores used in elderly coronary artery disease populations and their principal limitations in geriatric risk stratification [1,2,3,5].			
Risk score	Key variables	Derivation population	Principal limitation in elderly patients
GRACE risk score	Age, heart rate, systolic BP, creatinine, cardiac arrest, ST deviation, elevated markers	Multinational ACS registry, broad age range	Age weighted heavily but frailty and comorbidity not captured
TIMI risk score (UA/NSTEMI)	Age >=65, risk factors, known CAD, aspirin use, angina severity, ST deviation, elevated markers	Unstable angina/NSTEMI trial cohorts	Few very elderly patients in derivation; age treated as single binary variable
SYNTAX score	Number of lesions, complexity, location, bifurcation/left main involvement	Multivessel/left main revascularization trial	Purely anatomical; excludes frailty, renal function, comorbidity
CRUSADE bleeding score	Age, sex, diabetes, prior vascular disease, heart rate, BP, hematocrit, creatinine clearance	NSTEMI registry cohort	Predicts bleeding, not ischemic MACE; used alongside ischemic risk scores

Hypertension, diabetes, dyslipidemia, smoking history, and prior infarction remain independently associated with MACE in elderly CAD cohorts, but their relative contribution shifts with advancing age. In the GRACE registry, Avezum and colleagues found that while traditional risk factors retained significance across all age strata, their discriminative contribution to mortality prediction diminished above age 75, at which point age itself, hemodynamic presentation, and renal function became dominant, a pattern not fully reproduced by equations calibrated on younger cohorts [4]. Granger and colleagues, analyzing predictors of in-hospital mortality across the GRACE cohort, confirmed that age contributed more to total risk than any single traditional factor, with each decade beyond 60 years adding a disproportionately

large mortality increment relative to diabetes or prior infarction [2].

The TIMI risk score treats age above 65 as one of seven equally weighted variables, an approach that performs reasonably well for stratification but was never intended to differentiate risk gradients within the elderly population, since few of its derivation cohort were octogenarians [3]. Alexander and colleagues, in an American Heart Association statement on acute coronary care in older adults, argued that this is clinically consequential: elderly patients are simultaneously at the highest absolute risk of MACE and the population in whom standard tools are least well calibrated [5]. Diabetes deserves particular mention, since its adverse prognostic effect after infarction, demonstrated in the DIGAMI trial population, appears at least as strong in elderly as in younger patients, and intensive peri-infarction glycemic management was associated with improved long-term survival across the age range studied [6].

3. Frailty and geriatric syndromes as independent predictors

Frailty has emerged as one of the most consistent independent predictors of MACE in elderly CAD patients, operating largely independently of the risk factors captured by GRACE or TIMI. Fried and colleagues' phenotype definition — unintentional weight loss, exhaustion, low activity, slow gait speed, and weak grip strength — provided the foundation for subsequent cardiovascular frailty research by establishing frailty as a measurable clinical syndrome [7]. Afilalo and colleagues, in a comprehensive review, catalogued evidence that frailty independently predicts mortality, MACE, and functional decline after percutaneous and surgical revascularization, adding incremental prognostic information beyond the Society of Thoracic Surgeons and EuroSCORE models [8]. In a prospective study, Afilalo and colleagues showed that a simple five-meter gait speed test independently predicted mortality and major morbidity

after cardiac surgery, roughly doubling risk even after adjustment for standard surgical scores [9].

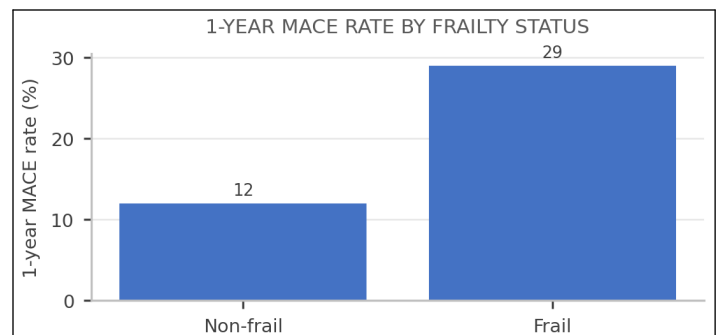


Figure 1: One-year MACE rate after percutaneous coronary intervention or non-ST-elevation myocardial infarction by frailty status, showing a substantially higher event rate among frail compared with non-frail elderly patients independent of angiographic disease severity [10,11].

This contribution extends into percutaneous coronary intervention (PCI) and acute coronary syndrome management. Singh and colleagues found that frail patients undergoing PCI experienced substantially higher death and morbidity rates than non-frail patients with comparable angiographic disease despite similar procedural success, indicating that frailty predicts vulnerability to physiological stress rather than technical failure [10]. Ekerstad and colleagues, studying elderly non-ST-elevation myocardial infarction patients, found frailty independently associated with death, reinfarction, stroke, and severe bleeding after adjustment for the GRACE score [11]. Sanchis and colleagues showed that a composite geriatric assessment incorporating frailty, cognitive impairment, and disability improved risk stratification beyond GRACE alone [12], and Bagnall and colleagues' review of preoperative frailty instruments reached a similar conclusion [13].

Sarcopenia, a component and consequence of frailty, has independently been linked to worse outcomes; a recent American Heart Association statement concluded that sarcopenia predicts MACE, disability, and mortality through reduced physiological reserve, impaired mobility, and shared inflammatory pathways with atherosclerosis [14]. Multimorbidity compounds this risk: Forman and

colleagues documented that coexisting chronic conditions independently predict adverse outcomes and complicate guideline-directed therapy, since most trials exclude patients with significant comorbidity burden [15], and Rich and colleagues identified the frailty-multimorbidity-risk-prediction interaction as among the most consequential unresolved questions in geriatric cardiology [16].

4. Circulating biomarkers of risk in elderly CAD

Natriuretic peptides and cardiac troponin are central to acute coronary syndrome risk stratification, and their prognostic value appears preserved, and in some analyses amplified, in elderly patients. De Lemos and colleagues established that B-type natriuretic peptide at presentation independently predicted mortality regardless of troponin status, marking it as a risk marker distinct from ischemic injury itself [17]. Omland's review argued that elevated natriuretic peptide in this setting reflects a broader state of neurohormonal activation disproportionately common in elderly patients with reduced physiological reserve [18].

High-sensitivity troponin assays have improved diagnostic sensitivity for myocardial infarction in older adults, but at an interpretive cost. Eggers and colleagues showed that troponin elevation without a specific ischemic diagnosis is common and itself prognostically important, particularly with structural heart disease or renal impairment, so a positive result requires careful clinical correlation [19]. Ridker and colleagues demonstrated that C-reactive protein predicted first cardiovascular events with discriminative power comparable to, and additive to, low-density lipoprotein cholesterol [20].

Anemia is among the most consistently reported hematologic predictors of MACE in this population. Sabatine and colleagues found a graded, independent relationship between admission hemoglobin and outcomes across the acute coronary syndrome spectrum, a U-shaped relationship attributable in the anemic range

to reduced myocardial oxygen delivery during ischemia [21]. Batty and colleagues extended this by showing that iron deficiency, with or without anemia, was independently associated with worse outcome [22].

Table 2: Circulating biomarkers associated with MACE in elderly coronary artery disease patients and the principal interpretive caveat specific to older age groups [17,19,21,22].		
Biomarker	Association with MACE	Interpretive caveat in elderly patients
B-type natriuretic peptide	Independent predictor of mortality across ACS spectrum	Elevated by age-related diastolic dysfunction independent of ischemia
High-sensitivity troponin	Improves sensitivity for myocardial infarction detection	High background prevalence of chronic elevation reduces specificity
Hemoglobin / anemia	U-shaped relationship with mortality; anemia increases risk	Anemia prevalence rises sharply with age and comorbidity
Iron deficiency	Independently associated with adverse outcome regardless of anemia	Often unmeasured in routine elderly ACS work-up

5. Comorbidity burden: renal function, diabetes, and multimorbidity

Renal dysfunction is among the strongest, most consistently replicated predictors of MACE across elderly CAD cohorts. Anavekar and colleagues demonstrated a graded, independent relationship between reduced estimated glomerular filtration rate and the composite of death, reinfarction, stroke, and heart failure after myocardial infarction, with risk rising sharply below 60 mL/min/1.73m, a threshold crossed disproportionately often in elderly patients [23]. Wright and colleagues reached a concordant conclusion, reporting that even moderate renal insufficiency at presentation was associated with substantially higher mortality after adjustment for age and traditional risk factors [24]. Because renal function correlates strongly with age and renally impaired patients are often excluded from trials, the combination of advanced age and reduced renal function represents a population in whom both risk and

evidentiary uncertainty are highest.

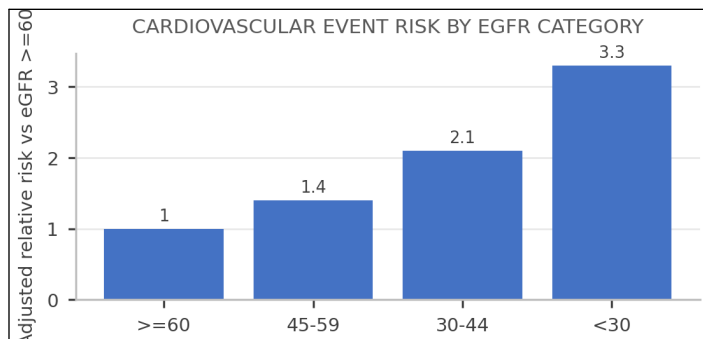


Figure 2: Gradient of cardiovascular death, reinfarction, stroke, and heart failure risk after myocardial infarction across categories of estimated glomerular filtration rate, illustrating the sharp rise in risk below 60 mL/min/1.73m² that disproportionately affects elderly patients [23].

Malmberg and colleagues' DIGAMI trial demonstrated that intensive insulin-glucose management around acute infarction reduced long-term mortality in diabetic patients across the enrolled age range, supporting glycemic management as a modifiable contributor to MACE risk in older patients [6]. Multimorbidity compounds these individual comorbidities: Forman and colleagues found that elderly CAD patients frequently carry three or more chronic conditions simultaneously, and that cumulative burden, rather than any single condition, drives both MACE risk and the complexity of treatment prioritization [15].

6. Coronary anatomy, revascularization strategy, and bleeding risk

Anatomical complexity, quantified using the SYNTAX score, independently predicts MACE after revascularization and interacts meaningfully with age in determining treatment strategy. Sianos and colleagues developed the SYNTAX score as a systematic angiographic tool grading lesion complexity, vessel involvement, and left main/bifurcation disease, providing a reproducible framework subsequently validated as prognostic across revascularization trials [25]. Serruys and colleagues, comparing percutaneous intervention with bypass grafting in left main/three-vessel disease, found higher SYNTAX scores associated with higher MACE after

percutaneous intervention relative to surgery, a differential with direct implications for elderly patients, in whom surgical risk is elevated but incomplete percutaneous revascularization of complex anatomy carries its own hazard [26].

Bach and colleagues found that a routine invasive strategy improved outcomes in elderly patients with non-ST-elevation acute coronary syndrome, though absolute benefit was attenuated relative to younger patients and accompanied by more procedural complications [27]. Steg and colleagues' analysis of the REACH registry found that one-year MACE rose progressively with the number of vascular beds affected and with age, reinforcing that systemic atherosclerotic burden, not coronary anatomy alone, shapes long-term risk [28].

Bleeding risk assessment is inseparable from MACE prediction in elderly revascularization patients. Subherwal and colleagues developed the CRUSADE bleeding score, finding advanced age among the strongest contributors to major bleeding risk [29]. Mehran and colleagues developed an analogous score for the PCI setting, again identifying age as an independent predictor, and showed that bleeding events were themselves strongly associated with subsequent mortality, closing the loop between bleeding risk and MACE prediction [30].

7. Toward integrated, geriatric-specific risk prediction

Statin and antiplatelet pharmacotherapy remain foundational to secondary prevention, though net benefit must be weighed against competing risks in this population. Savarese and colleagues' meta-analysis of statin therapy in elderly patients found a significant reduction in coronary events, though the benefit for all-cause mortality was more modest than in younger cohorts, consistent with competing non-cardiovascular mortality risk that becomes increasingly relevant with advancing age and comorbidity [31].

The cumulative evidence supports several practical conclusions. Traditional risk scores such as GRACE and TIMI remain useful starting points but systematically underweight frailty, multimorbidity, and geriatric syndromes [1,3,8]. Biomarkers including natriuretic peptides, high-sensitivity troponin, and hemoglobin or iron status add incremental discrimination but require age-specific interpretation [17,19,21]. Renal function and diabetes contribute substantially to risk in ways most standard equations do not explicitly model [23,6], and coronary anatomical complexity and revascularization completeness modify risk in a manner that must be balanced against elevated procedural and bleeding risk [26,29,30]. Prospective validation of composite risk models that formally integrate frailty and geriatric assessment alongside conventional variables, in cohorts enriched for patients aged 75 years and older, represents the most pressing unmet need in this field.

8. Conclusion

Predicting MACE in elderly cardiac patients with coronary artery disease requires moving beyond risk tools derived predominantly from middle-aged trial populations. Traditional scores such as GRACE and TIMI retain prognostic value, but frailty, sarcopenia, multimorbidity, renal dysfunction, anemia, and natriuretic peptide or troponin elevation each independently contribute to risk in ways these tools do not fully capture, while anatomical complexity and the bleeding-ischemia trade-off inherent to revascularization decisions further modify outcome. A multidimensional approach that integrates conventional risk assessment with structured frailty and comorbidity evaluation, interpreted alongside age-appropriate biomarker data, offers the most promising path toward risk prediction genuinely calibrated to elderly patients rather than extrapolated from younger ones.

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