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THE PRESENT AND FUTURE

JACC COUNCIL PERSPECTIVES

Cardiovascular Biomarkers and Imaging in Older Adults

JACC Council Perspectives

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ABSTRACT

Whereas the burgeoning population of older adults is intrinsically vulnerable to cardiovascular disease, the utility of many management precepts that were validated in younger adults is often unclear. Whereas biomarker- and imaging-based tests are a major part of cardiovascular disease care, basic assumptions about their use and efficacy cannot be simply extrapolated to many older adults. Biology, physiology, and body composition change with aging, with important influences on cardiovascular disease testing procedures and their interpretation. Furthermore, clinical priorities of older adults are more heterogeneous, potentially undercutting the utility of testing data that are collected. The American College of Cardiology and the National Institutes on Aging, in collaboration with the American Geriatrics Society, convened, at the American College of Cardiology Heart House, a 2-day multidisciplinary workshop, "Diagnostic Testing in Older Adults with Cardiovascular Disease," to address these issues. This review summarizes key concepts, clinical limitations, and important opportunities for research. (J Am Coll Cardiol 2020;76:1577–94) © 2020 the American College of Cardiology Foundation. Published by Elsevier. All rights reserved.

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ABBREVIATIONS AND ACRONYMS

BNP = B-type natriuretic peptide

CAC = coronary artery calcium

CAD = coronary artery disease

CI = confidence interval

CKD = chronic kidney disease

CMR = cardiac magnetic resonance

CTA = computed tomography angiography

cTnI = cardiac troponin I

cTnT = cardiac troponin T

CVD = cardiovascular disease

E/A = early diastolic E to late A wave (ratio)

ECG = electrocardiogram

HF = heart failure

HR = hazard ratio

hs = high-sensitivity

MI = myocardial infarction

NP = natriuretic peptides

NPV = negative predictive value

NT-proBNP = N-terminal pro-B-type natriuretic peptide

PPV = positive predictive value

TTE = transthoracic echocardiography

UDMI = universal definition of myocardial infarction

Biomarker- and imaging-based testing has become a major part of cardiovascular disease (CVD) care for diagnosis, prognosis, and surveillance. Advancing age is a dominant risk factor for CVD, and the vast armamentarium of biomarker and imaging assessments are logical considerations for the rapidly growing population of older adults. However, advanced age is also associated with greater prevalence of comorbid diseases and geriatric syndromes (e.g., frailty, disability, cognitive decline, and sarcopenia) that commonly confound interpretation of traditional CVD assessments (1). Moreover, the ranges of "normal" for biomarkers and imaging metrics are often broader in older populations such that they overlap with the abnormal range of younger adults, further reducing specificity.

Given the many uncertainties associated with cardiovascular diagnostic testing in older populations, experts from the American College of Cardiology and the National Institute on Aging, in collaboration with the American Geriatrics Society, convened at the American College of Cardiology Heart House for a 2-day workshop titled "Diagnostic Testing in Older Adults with Cardiovascular Disease." Attendees included cardiologists, geriatricians, anesthesiologists, nurses, pharmacists, patients, and stakeholders from the Centers for Medicare and Medicaid Services; U.S. Food and Drug Administration; National Heart, Lung, and Blood Institute; Agency for Healthcare Research and Quality; and industry. The primary goal of the workshop was to identify knowledge gaps and formulate research strategies to advance the utility and value of cardiovascular testing for older adults.

HIGHLIGHTS

- Age-related biological changes and shifting patient priorities warrant adjustment of strategies for evaluation and management of CVD.
- The sensitivity, specificity, and clinical value of biomarker and imaging tests for CVD change as patients age.
- Research is needed to better align diagnostic testing for CVD with the needs and priorities of an aging population.

AGING ENTAILS MORE THAN A NUMBER OF YEARS

Longevity has increased in the United States and much of the world, with more people now living into their 80s and beyond, a life phase when biological changes intrinsically predispose to the development and progression of CVD (2,3). Age-related biological changes provide a substrate for the development and progression of CVD. Often multiple CVDs as well as non-CVDs and geriatric syndromes arise from the same biologically activated vulnerability (4). Multimorbid stresses often overwhelm diminished cardiovascular reserves (e.g., type 2 myocardial infarction [MI]). In such situations, the prototypical approach to CVD as a discrete problem with specific evidence-based guidelines is often misaligned with patients' priorities amid many diseases, wide-ranging symptoms, and concurrent social and cognitive changes. For many older adults, the foremost clinical priority becomes optimized physical function (5); correspondingly, the value of common medications such as beta-blockers and statins (6,7) may be less clear. Hence, whereas testing has the potential to illuminate critical findings that could guide care (e.g., 3-vessel coronary artery disease [CAD] (8) or low ejection fraction), it cannot be presumed that testing leads to interventions and outcomes that all older patients perceive as beneficial in relation to their overarching life concerns.

BIOMARKERS FOR DIAGNOSIS AND PROGNOSIS IN OLDER ADULTS

AGING EFFECTS ON TROPONINS AND NATRIURETIC PEPTIDES. Biomarkers have proliferated as one of the most important tools to distinguish normal and abnormal physiology and for diagnostic, prognostic, and monitoring assessments. However, aging alters fundamental characteristics of biomarkers and often reduces their clinical utility.

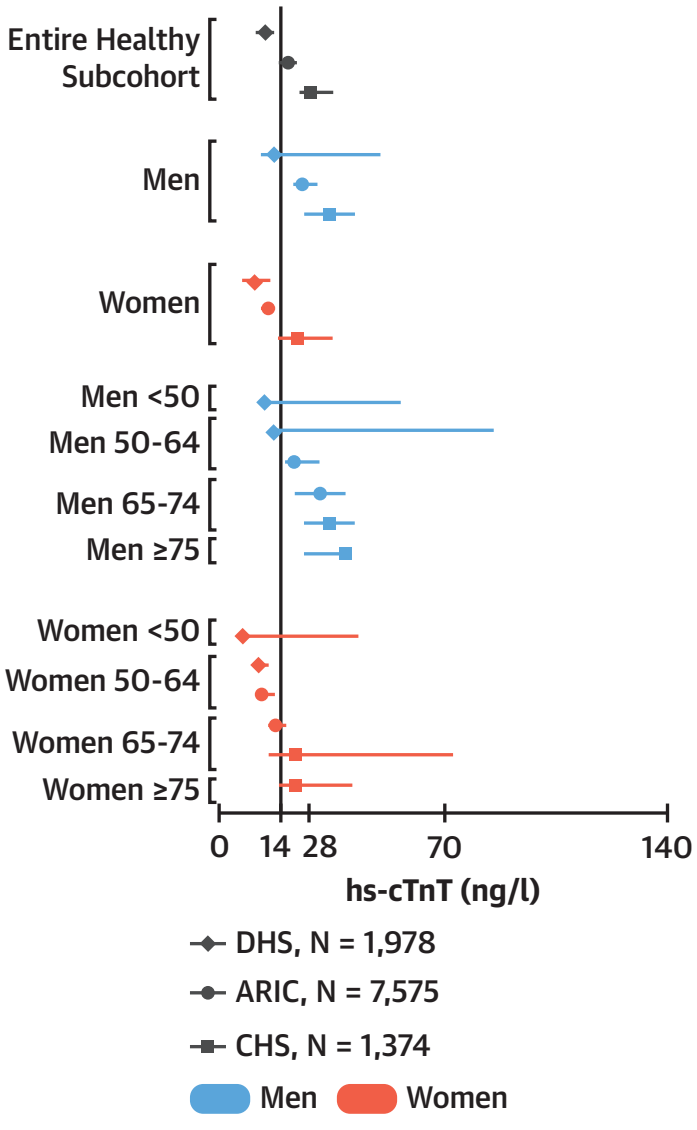
The most commonly used biomarkers in cardiovascular diagnosis are cardiac troponin T (cTnT) and cardiac troponin I (cTnI) for diagnosis of MI and the natriuretic peptides (NPs) B-type natriuretic peptide (BNP), and N-terminal pro-B-type natriuretic peptide (NT-proBNP) for the diagnosis of heart failure (HF). Circulating plasma levels of these biomarkers change across the life span. Factors that influence levels of these biomarkers in relation to age include the presence and severity of clinical or subclinical disease, declining renal function, changes in body composition, and hormonal changes, particularly in postmenopausal women (9–14).

TROPONINS TO DIAGNOSE MI. Among asymptomatic individuals, circulating cTn levels reflect the degree of ongoing, subclinical cardiomyocyte injury, with higher levels in men than women, and in older versus younger adults (13,15,16). These age-and sex-based differences are especially relevant in contemporary management as high-sensitivity (hs)-cTnT and hs-cTnI are replacing older assays. Age-related factors associated with higher hs-cTn among asymptomatic adults without apparent CVD include diabetes and hypertension, declining renal function, and subclinical abnormalities in cardiac structure (e.g., left ventricular hypertrophy, pathological remodeling, and the degree of myocardial fibrosis) (13,17).

The universal definition of myocardial infarction (UDMI) subclassifies MI into subtypes, including type 1 MI, which is caused by acute atherothrombosis, and type 2 MI, which results from acute supply-demand mismatch without atherothrombosis. Both subtypes of MI require evidence of acute myocardial injury associated with myocardial ischemia (18). Acute myocardial injury requires a troponin level above a threshold value defined at the 99th percentile from a healthy reference population, with levels that rise or fall over serial measurement. The current consensus UDMI, therefore, is contingent on an accurate determination of the threshold 99th percentile value. The age-related increases in hs-cTn levels described have important implications for determining and applying the 99th percentile value. In an analysis of individuals without clinical or subclinical CVD from the Dallas Heart Study, compared with younger individuals, asymptomatic adults >60 years had more than a 5-fold greater likelihood of having an hs-cTnT value above the manufacturer's recommended MI diagnostic threshold (13). Similar findings were observed in the ARIC (Atherosclerosis Risk In Communities) study and CHS (Cardiovascular Health Study) (15,16).

Figure 1 shows an age-stratified analysis performed across these 3 cohorts, demonstrating that the 99th percentile value varied markedly by age and sex, with the manufacturer's recommended cutpoint (14 ng/l) being higher than the observed 99th percentile in women <50 years, but lower than the observed 99th percentile for men and women 65 to 74 years of age and particularly those ≥75 years (19). Thus, using a uniform threshold to define "normal range" could potentially lead to false-positive MI diagnoses in older adults and men and false-negative diagnoses in younger women. On the other hand, as the "pre-test" probability of CAD increases with age and is higher in men, the net effect on the positive predictive value (PPV) and negative predictive value (NPV) is less clear.

FIGURE 1 Age and Sex Differences in hs-cTnT to Diagnose MI



In an age-stratified analysis of the DHS (Dallas Heart Study), ARIC (Atherosclerosis Risk In Communities) study, and CHS (Cardiovascular Health Study), the 99th percentile value for high-sensitivity cardiac troponin T (hs-cTnT) varied markedly by age and sex, with the manufacturer's reported cutpoint (14 ng/l) being higher than the observed 99th percentile value in younger women <50 years of age, but lower than the observed 99th percentile value for men and women 65 to 74 and particularly those >75 years of age (19). Data for men are shown in **blue** and women in **red**. MI = myocardial infarction.

Only limited data are available on age-adjustment of the 99th percentile threshold value. In an analysis of the TRAPID-AMI (High Sensitivity Cardiac Troponin T Assay for Rapid Rule-out of Acute Myocardial Infarction) study, retrospective application of age-specific cutpoints resulted in a decrease of acute MI diagnosis from 29.8% to 18.3% and improved

classification of short-term mortality risk (14.2% net reclassification improvement; $p < 0.001$) (20). In a second study, age-specific cutpoints also offered improved risk classification, but the effects on clinical management were more modest (21). Likewise, application of sex-specific cutpoints appears to have only a modest impact on MI classification (20,22,23). The UDMI recognizes age and sex effects on the 99th percentile value, but it does not recommend using age- and sex-specific cutpoints for MI diagnosis (18). The additional UDMI requirement for a rise and/or fall in troponin levels may mitigate to some extent the lower specificity and PPV for troponin values ≥99th percentile in older patients. Moreover, it should be emphasized that troponin values ≥99th percentile are associated with higher short- and long-term cardiac events, even when MI is not present (24,25).

A potential solution to ambiguity around the 99th percentile cTn value in older adults is to design MI diagnostic protocols that de-emphasize such arbitrary thresholds. Innovative protocols have been developed and implemented that capitalize on the higher sensitivity and precision of the hs-cTn versus standard cTn assays to exclude MI using very low levels of hs-cTn at the time of presentation and/or the absence of small changes over serial measurements in short time frames (e.g., no significant change in hs-cTn in 1 h) (26–29). These protocols allow exclusion of MI in >50% of individuals and outperform algorithms based solely on the 99th percentile value (30,31). However, these protocols are much more effective for ruling-out than for ruling-in MI (28), and low specificity and PPV are limitations, particularly when troponin is measured indiscriminately in patients with low probability of MI, as is common in U.S. emergency departments.

A recent study evaluated performance of the European Society of Cardiology rapid 0/1 h rule-out algorithm across age strata (**Figure 2**) (32). Overall accuracy for MI diagnosis for hs-cTnT and hs-cTnI decreased modestly across age categories. Exclusion of MI with the algorithm was "safe" as defined by a high NPV across all age ranges. However, the proportion of patients who met rule-out criteria by 1 h was markedly lower in older patients. Although specificity decreased modestly across age ranges, PPV for rule-in was similar in the older group due to a higher prevalence of MI (32). In an exploratory analysis (32), the investigators evaluated modestly higher thresholds for both absolute and change values and found that this increased the proportion of older patients who were ruled out without compromising safety. More study is needed to determine whether age-specific hs-cTn thresholds and change criteria should be adopted for older adults with suspected MI.

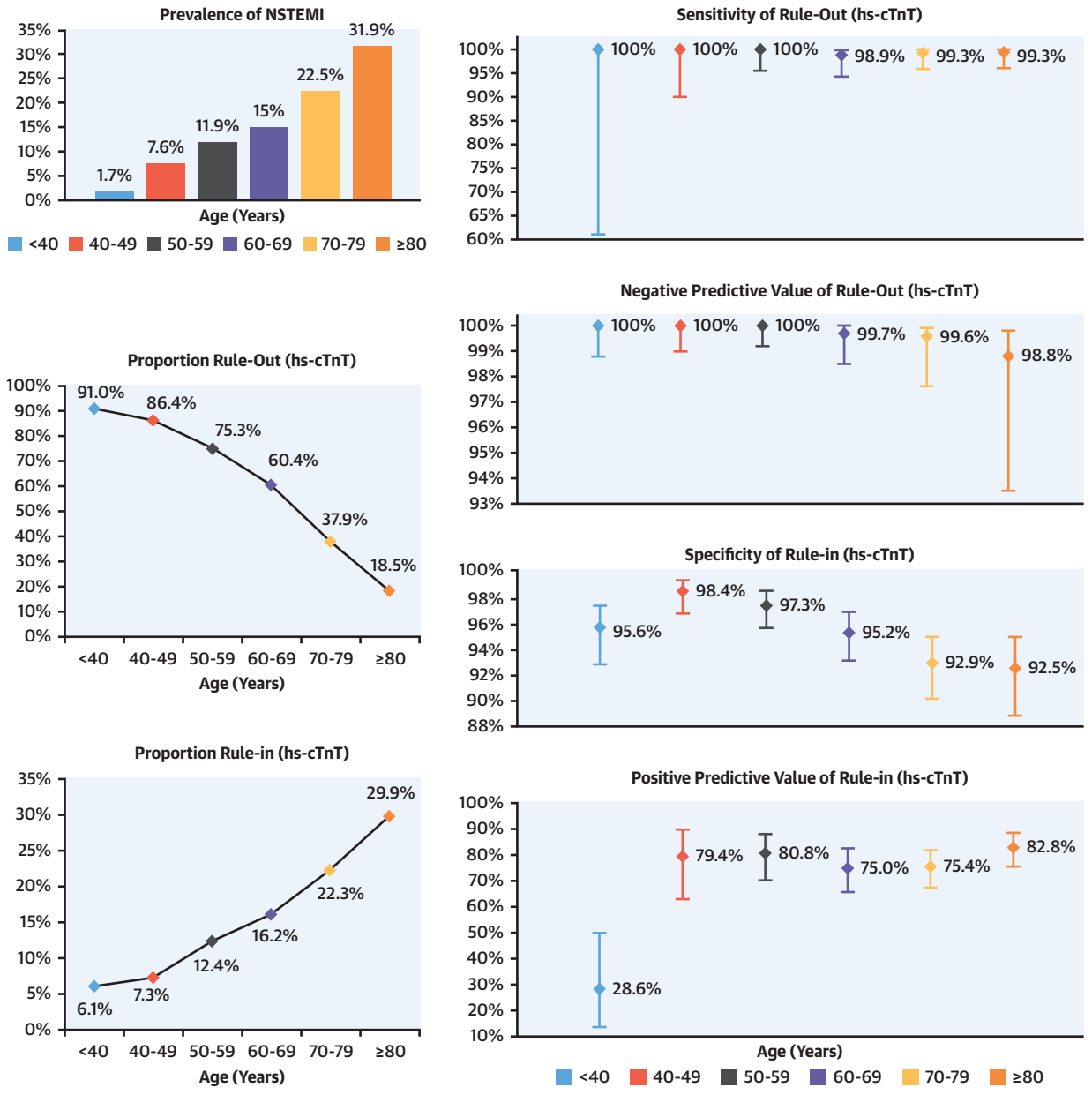
NPs TO DIAGNOSE HF. BNP and NT-proBNP are released from cardiomyocytes in response to increases in left ventricular wall stress, and function in a counter-regulatory role to promote natriuresis, vasodilation, lusitropy, and antiproliferative effects (33). BNP and NT-proBNP levels tend to be higher in older versus younger asymptomatic individuals without CVD for several reasons. Asymptomatic left ventricular hypertrophy and left ventricular systolic dysfunction, and to a lesser extent coronary atherosclerosis, are associated with higher levels of these neurohormones (34,35). Similarly other cardiovascular conditions such as valvular heart disease, infiltrative cardiomyopathy, and pulmonary hypertension may lead to elevated NP levels and are more common in older adults (36–38). In addition, a robust log-linear association is seen with renal dysfunction, with the association stronger for NT-proBNP than BNP (9). Lower lean body mass, common among older adults, is associated with higher levels of NPs, an effect that is likely mediated via changes in androgens across the life span (12,14). Atrial fibrillation, which is highly prevalent in older adults, contributes independently to higher levels of BNP and NT-proBNP (39).

In contrast to hs-cTn, levels of BNP and NT-proBNP are higher in healthy women than men due to greater androgen suppression of BNP synthesis in men (40,41). Among individuals with HF, BNP and NT-proBNP levels are usually much higher than in healthy individuals, and sex-related differences are not clinically relevant at these ranges.

While the sensitivity and NPV of BNP and NT-proBNP are high, the specificity and PPV are modest (42,43) due to the many other conditions that can lead to elevation of these neurohormones. As comorbid conditions associated with NP elevation are more common among older individuals, diagnostic performance of BNP and NT-proBNP to rule in or rule out HF diminishes. For example, in a recent prospective study, the area under the diagnostic receiver-operating characteristic curve was 0.97 for patients <50, 0.89 for those 50 to 75, and 0.84 for patients >75 years of age (44). Application of a uniform diagnostic threshold for HF diagnosis across age ranges is therefore problematic.

To maximize PPV without compromising NPV, strategies have emerged that maintain a low threshold for rule-out, but which incorporate a higher threshold for rule-in, with an indeterminate "gray" zone between (45). The low rule-out threshold works well regardless of age, but the threshold for rule-in

FIGURE 2 Diagnostic Performance of the ESC hs-cTnT 0/1 h Algorithm According to Age



Specificity of high-sensitivity cardiac troponin T (hs-cTnT) decreases modestly across age ranges, but the positive predictive value for rule-in was similar in the older group due to a higher prevalence of myocardial infarction (32). NSTEMI = non-ST-segment elevation myocardial infarction.

must increase with age to maintain specificity and PPV. With NT-proBNP, for example, a uniform age-independent rule-out threshold of 300 pg/ml resulted in a sensitivity of 99% and NPV of 99% in a derivation study, and 94% and 98% in a validation study (44,45). Using higher rule-in thresholds across increasing age ranges (450 pg/ml for patients <50, 900 pg/ml for those 50 to 75, and 1,800 pg/ml for patients >75 years of age), the PPV was maintained at a similar or higher level among older versus younger individuals in both the derivation and validation studies (44,45). However, this approach results in a large expansion of the indeterminate gray zone in older patients.

Thus, BNP and NT-proBNP are useful for diagnosing HF in older adults when levels are either low or very high, but indeterminate values are common and difficult to interpret. Comparison with a previously measured BNP or NT-proBNP may be helpful to determine whether the value represents a clinically meaningful change. However, due to much higher biological variability with NPs than with cTns, interpreting changes is more difficult. Large relative changes are required with NPs to exceed the range of biological variation. Thus, clinicians should be cautious when interpreting small changes in NPs over time.

BIOMARKERS TO SCREEN FOR CVD IN OLDER ADULTS WITHOUT KNOWN DISEASE. Age is the foremost risk for CVD. However, risk stratification for incident CVD among older adults remains poorly demarcated (46), and biomarkers are increasingly considered as a means to discriminate risk in wide-ranging populations. The association of traditional risk factors with atherosclerotic CVD events typically attenuates at older ages (47,48). The pooled cohort equations, which are standardized risk factor models recommended to guide allocation of primary prevention lipid and blood pressure lowering therapies, are not recommended in adults >79 years of age (46,49). Current risk models focus on a time window (10 years) that is often irrelevant for older adults who may be more interested in shorter-term risk (3 to 5 years) due to limited life expectancy and personal end-of-life goals. Furthermore, these models omit important CVD endpoints that are particularly common among older adults (e.g., HF and atrial fibrillation), as well as quality of life and preservation of physical function.

Newer approaches to risk stratification among asymptomatic individuals without CVD focus on global CVD events (i.e., atherosclerotic CVD plus HF with or without atrial fibrillation) and consider multiple subclinical CVD biomarkers in addition to atherosclerotic CVD risk factors. These subclinical CVD markers include hs-cTnT, NT-proBNP, high-sensitivity C-reactive protein (hs-CRP), coronary calcium by computed tomography, and electrocardiogram (ECG) evidence of left ventricular hypertrophy. Compared with traditional risk factors, models including these biomarkers improve performance, particularly for HF and global CVD risk prediction (50,51). Among older adults without prior CVD (n = 4,760, mean age 75.4 years, 63% female) in ARIC (48), NT-proBNP and hs-cTnT outperformed traditional risk factors and were the most powerful predictors of short-term global CVD events (**Figure 3**). Hs-CRP also correlated with subsequent risk but the magnitude of association was lower than for NT-proBNP and hs-cTnT. These findings suggest that age-related changes in NT-proBNP and hs-cTnT (discussed previously) may reflect "unhealthy aging" and that monitoring levels of these biomarkers may provide insights into near-term risk of CVD. Notably, recent evidence demonstrates the prognostic role of biomarkers (NPs and hs-TnT) in cardiac amyloid, highlighting novel applications to identify and manage disease (52). It is important to recognize that screening with these tests is not currently recommended, and additional study is needed to determine whether these tests can help guide personalized or precision-medicine approaches to global CVD prevention in older populations.

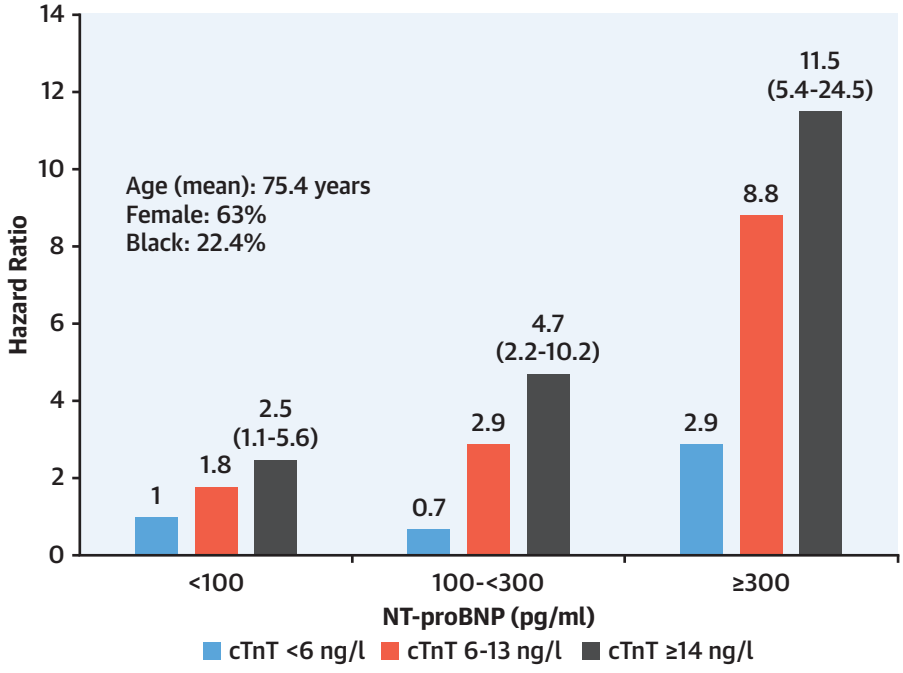
IMAGING IN OLDER ADULTS

AGE-RELATED CHALLENGES RELATED TO TECHNIQUE AND SAFETY. Cardiovascular imaging is frequently used for diagnosis and management of older adults (**Table 1**), but aging also predisposes to many impediments to imaging. Changes in body habitus can lead to nondiagnostic results, repeat testing, and diminished confidence in results. Kyphoscoliosis, chronic lung disease, and Parkinsonian tremor are common confounders. Similarly, arthritis in the hips, shoulders, knees, and neck frequently interfere with patient positioning for obtaining optimal images. Cognitive impairment may limit the patient's ability to follow basic instructions or even to provide informed consent. More fundamentally, age-related alterations in cardiovascular structure, physiology, function, and response to stimuli commonly limit testing interpretations.

Whereas imaging modalities for CVD generally have excellent safety profiles, older adults are vulnerable to risks related to age. Contrast-induced nephropathy (53) and bleeding complications (54,55) are more likely to occur. Chronic kidney disease (CKD) may preclude the use of gadolinium or iodinated contrast. Esophageal disorders, including dysmotility, may compromise the safety and feasibility of transesophageal echocardiography. Dobutamine is more likely to induce arrhythmias, whereas dipyridamole and regadenoson are more likely to cause hypotension or bradycardia when administered to older versus younger patients.

Radiation exposure potentially contributes to a modest increase in the risk for cancer, but this is a late effect and is commonly dismissed as a lesser concern in populations with shorter life expectancies (56). Nonetheless the burden of cumulative lifetime radiation exposure raises concern for those who have

FIGURE 3 Utility of NT-proBNP and cTnT to Predict Short-Term Risk for CVD Events in Older Adults Without Known CVD



N-terminal pro-B-type natriuretic peptide (NT-proBNP) was used to predict short-term risk for cardiovascular disease (CVD) events in conjunction with cTnT in a cohort of older adults without known CVD at baseline. Over 4 years, higher NT-proBNP and hs-cTnT predicted relatively more CVD events in models adjusted for traditional CVD risk factors in the pooled cohort equation (48). Abbreviations as in **Figures 1 and 2**.

received significant diagnostic and/or therapeutic radiation earlier in their lives, especially in younger subgroups of older adults who may have decades of life ahead of them.

INTERPRETATION. There are scant data on diagnostic accuracy and risk stratification specific to patients of advanced age (57). In the absence of such information, test accuracy is often extrapolated from higher risk younger patient cohorts. However, data regarding test performance in these cohorts is of uncertain applicability to older individuals (58). Studies are needed to better clarify the diagnostic accuracy of all imaging modalities in older adults.

ECHOCARDIOGRAPHY. Transthoracic echocardiography (TTE) is performed for a wide variety of CVD conditions and has important advantages, including widespread availability and the ability to provide detailed, reliable, and multidimensional assessments of cardiac morphology, wall motion, flow dynamics, and hemodynamics. Costs are moderate and data acquisition time is relatively rapid. Echocardiography is also portable (e.g., accessible to the intensive care unit as well as to nursing facilities). It is suited to evaluating many common cardiovascular conditions as an initial procedure.

Many standard echocardiographic and Doppler measurements have sex-specific normal values, but there are limited data across age groups (59). **Table 2** depicts common age-related TTE changes, and **Figure 4** presents 95% confidence intervals for normal left ventricular end-diastolic and end-systolic dimensions relative to age (60). An important challenge is the distinction between structural and functional changes that are "normal for age" versus outside the range of what might be expected due to age alone. For example, left ventricular volume decreases with age to a greater degree than left ventricular mass does, resulting in age-related concentric remodeling (61). Yet the threshold beyond which these changes are pathologic has not been defined. Similarly, diastolic function changes with normal aging, resulting in decrease in the early diastolic E to late A wave (E/A) ratio and a pattern of impaired relaxation in mitral valve inflow velocities assessed by Doppler echo. Data from the CHS

TABLE 1 Noninvasive Testing for IHD in Older Adults

Testing Modality	Intended Use and Value	Age-Related Limitations
Exercise stress test	Can assess cardiorespiratory fitness and ventilatory efficiency, particularly with cardiopulmonary exercise testing Corroborates or clarifies patients' accounts of their functional capacity Hemodynamic and chronotropic responses to exercise Arrhythmia Prognostic assessment based on functional capacity and exercise arrhythmia Value: comprehensive assessment for a population with at least intermediate pre-test ischemic risk based on age	Deconditioning and reduced exercise capacity Reduced diagnostic and prognostic value for cardiac endpoints Often confounded by physical and comorbid limitations (frailty, PAD, COPD, orthopedic limitations, dementia) Greater prevalence of subtle executive cognitive changes increases difficulty of following directions Age-related chronotropic changes reduce ability to reach ischemic threshold, especially patients taking beta-blockers Compared with assessments in younger adults, more thoughtful exercise testing procedures are required, with careful choices in protocols, and greater attention to safety and support
Exercise echocardiography	Provides all the utility of exercise testing (as listed) Imaging assesses left ventricular size and systolic function Imaging assesses infarct and ischemia No radiation exposure Prognostic assessments based on the LVEF, the extent of ischemia, as well as the functional capacity and exercise arrhythmia	Age-related limitations to exercise testing as noted Limitation in positioning affects echocardiographic acoustic windows High prevalence of baseline wall motion abnormalities diminishes diagnostic sensitivity of echocardiographic assessments More difficulty reaching target heart rate and obtaining images at peak heart rate
Exercise MPI	Provides all the utility of exercise testing (as listed) MPI assesses left ventricular size and systolic function MPI assesses extent of infarct and ischemia Prognostic assessments based on LVEF, extent of ischemia, as well as the functional capacity and exercise arrhythmia	Age-related limitations to exercise testing as noted Increased prevalence of cognitive changes (especially subtle executive cognitive changes) and movement limitations in older patients increases difficulty of maneuvering, following directions, and lying flat for image acquisition Mounting effects of ionizing radiation over a lifetime
Pharmacological stress imaging	In patients who are unable to exercise or have abnormal ECG (LBBB, paced rhythm, ventricular pre-excitation	Forgoes opportunities for exercise assessments for patients who are often could exercise, but are reflexively referred for pharmacological stress due to age
Dobutamine	Imaging assesses left ventricular size and systolic function Imaging assesses infarct and ischemia No radiation exposure Prognostic assessments based on the LVEF and the extent of ischemia	Greater vulnerability to atrial and ventricular arrhythmias in older patients Greater vulnerability to severe hemodynamics fluctuations (hyper- and hypotension) in older patients Sigmoid septum increases vulnerability to ventricular outflow obstruction especially in combination with low-volume status
Vasodilator (adenosine, dipyridamole, regadenoson)	MPI assesses left ventricular size and systolic function MPI assesses extent of infarct and ischemia Prognostic assessments based on LVEF, extent of ischemia	Greater vulnerability to severe hemodynamics fluctuations (hyper- and hypotension) in older patients Greater vulnerability to conduction abnormalities in older patients (bradycardia, sinus node disease, second- and third-degree heart block) Greater risk of confusion among older patients administered atropine after vasodilator therapy Greater prevalence of cognitive changes (especially subtle executive cognitive changes) and movement limitations in older patients increases difficulty of maneuvering, following directions, and lying still on the table Increased risks of bronchospasm in older patients administered vasodilators Increased risk of seizure disorder in patients administered vasodilators
Stress CMR	Functional assessment for IHD Assesses left ventricular size and function, extent of ischemia Assesses presence of scar and infiltrative process (amyloid) No ionizing radiation	Limited use in patients with implanted devices (PPM/ICD), which tends to be more common in older age patients Gadolinium contraindicated in stage 4 to 5 CKD Physical and cognitive limitations in older patients limit their capacities to maneuver comfortably, follow directions, and lie still on the table, particularly in an enclosed environment; can provoke anxiety; difficult to sedate
CTA	Anatomic assessment for IHD Assessment of left ventricular size and function Detection of nonobstructive CAD	Reduced impact on outcomes compared to functionally based (physical and cardiac) diagnostic assessments in older adults Reduced accuracy due to overestimation degree of stenosis with a higher prevalence of calcifications in older adults Mounting effects of ionizing radiation exposure over a lifetime Allergy to contrast agents Higher prevalence of CKD and risk for CIN confound options for contrast with in older patients Physical and cognitive limitations in older patients limit their capacities to maneuver comfortably, follow directions, and lie still on the table
Coronary calcium score	Risk assessment in asymptomatic individuals	Mounting effects of ionizing radiation exposure over a lifetime High prevalence of coronary calcification in older patients reduces specificity

CAD = coronary artery disease; CIN = contrast-induced nephropathy; CKD = chronic kidney disease; CMR = cardiac magnetic resonance; COPD = chronic obstructive pulmonary disease; CTA = computed tomographic angiography; ECG = electrocardiogram; ICD = implantable cardioverter-defibrillator; IHD = ischemic heart disease; LBBB = left bundle brunch block; LVEF = left ventricular ejection fraction; PAD = peripheral artery disease; PPM = permanent pacemaker.

TABLE 2 Age-Related Echocardiographic Changes in Older Adults

	Parameters	Clinical Considerations and/or Manifestations
LV size	LV volume decreases; LV wall mass increases; LV wall thickness increases (113)	Concentric remodeling Basal septal hypertrophy, "sigmoid septum," more common in older patients with hypertension and MAC (114); can result in symptomatic LV outflow gradient
LV systolic function	Ejection fraction does not change; LV stroke volume decreases; global longitudinal strain decreases modestly (113,115)	Impaired longitudinal systolic function with preserved ejection fraction
Diastolic function	E/A decreases; e′ decreases; E/e′ increases (113)	Grade I diastolic dysfunction Abnormalities in diastolic indices are more prominent in women Severe MAC can affect diastolic indices
Atrium	LA volume increases (113)	Important to index LA volume to body surface area, especially in small older patients; LAVI can underestimate LA volume in obese patients LA volume is a component of diastolic function assessment
Right ventricle	RV volume decreases; RV ejection fraction increases; TAPSE and RV S′ decrease (116)	Impaired longitudinal RV function with preserved ejection fraction
Pulmonary pressure	Estimated PASP slightly increases with age (38)	PASP is a component of diastolic function assessment
Valvular assessment	Mitral annular calcifications Degenerative aortic valve sclerosis Lambl's excrescences	MAC more common in female patients and those with advanced renal insufficiency

e′ = early wave of the mitral annulus by tissue Doppler imaging; E/A = ratio of mitral inflow velocities of early filling (E) and mitral inflow peak of late diastolic filling (A); LA = left atrium/left atrial; LAVI = left atrial volume index; LV = left ventricle; MAC = mitral annular calcification; PASP = pulmonary artery systolic pressure; RV = right ventricle; S′ = systolic velocity of the tricuspid annulus by tissue Doppler imaging; TAPSE = tricuspid annular plane systolic excursion.

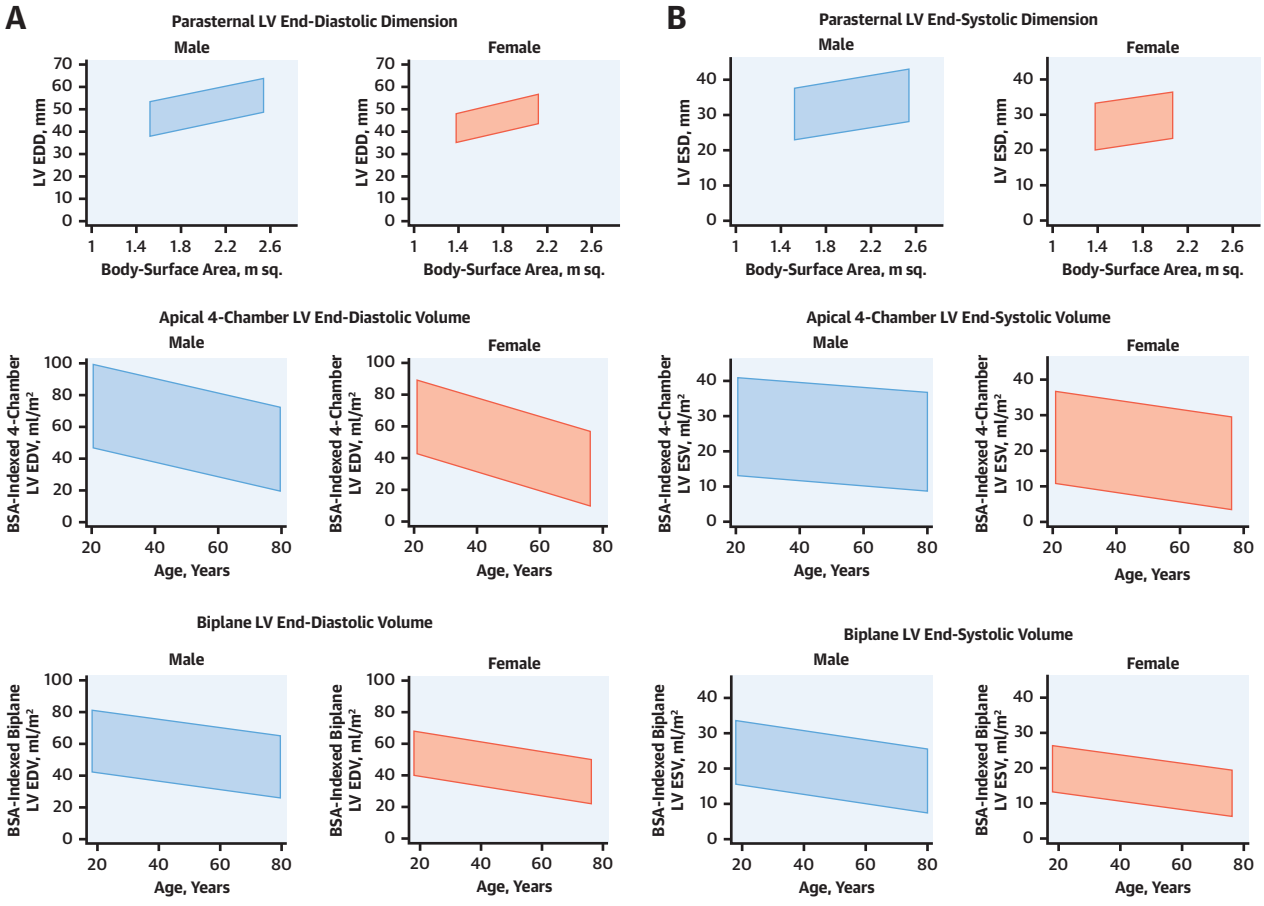
demonstrate a U-shaped relationship between the E/A ratio and incident HF in community-dwelling older adults, such that those with E/A ratios of 0.7 to 1.5 had the lowest risk for incident HF (62). This implies that this might be considered the normal range in this population, but these findings have not been integrated into echo guidelines. Assessment of diastolic function can also be confounded in older adults due to high prevalence of mitral annular calcification, especially in women and in those with advanced renal dysfunction (63). Cardiac amyloidosis remains an under-recognized contributor to diastolic dysfunction in older adults, in part due to lack of disease awareness and relatively low sensitivity of TTE for diagnosing early stage cardiac amyloidosis, although strain imaging improves recognition of this condition (64). With the emergence of effective therapies for transthyretin cardiac amyloidosis, there is a need to refine criteria for echo diagnosis of this condition and indications for multimodality imaging, including radionuclide imaging with bone-avid tracers or cardiac magnetic resonance (CMR) imaging (52).

Whereas TTE image quality is often more challenging in older adults, echocardiographic contrast agents can often be used to compensate. Echocardiography contrast has an excellent safety profile, with no increased risks in older adults (65). Nevertheless, the reliability of stress echocardiography to diagnose ischemia in older adults may still be confounded by resting wall motion abnormalities that challenge interpretability of segmental wall motion changes.

NUCLEAR IMAGING. Myocardial perfusion imaging is a widely used modality for diagnostic and prognostic assessment of CAD in older adults. However, image acquisition requires patients to lie flat on the imaging table without movement for 20 to 40 min for both rest and stress images, which can be challenging for many older adults. Compared with single-photon emission computed tomography, positron emission tomography has the advantages of shorter image acquisition time and substantially lower radiation exposure. Overall diagnostic accuracy is preserved in older patients, but with higher prevalence of CAD, PPV of myocardial perfusion imaging increases and NPV decreases (66). In a study of 13,254 patients, of whom 517 were ≥80 years old, diagnostic and prognostic accuracy of myocardial perfusion imaging were similar or higher in octogenarians than in younger patients (67).

Viability assessment with single-photon emission computed tomography and positron emission tomography enable identification of patients with viable but dysfunctional myocardium that has potential for recovery with revascularization. These techniques are particularly attractive in older patients with stage 4 to 5 CKD, when CMR with gadolinium is not recommended, and in those with cardiac arrhythmia, for whom dobutamine stress echocardiography may be associated with arrhythmia exacerbation.

FIGURE 4 Changes in LVED Measurements With Age in Men and Women



For men **(left)** and women **(right)**, the 95% confidence intervals for the following measurements are presented: **(A)** on graphs to the **left**: left ventricular end-diastolic dimension (LVEDD) measured from a parasternal long-axis window on the basis of body surface area (BSA) **(top)**, BSA-indexed left ventricular end-diastolic volume (LVEDV) measured from an apical 4-chamber view on the basis of age **(middle)**, and BSA-indexed biplane LVEDV on the basis of age **(bottom)**; **(B)** on the graphs to the **right**: LV end-systolic dimension (LVESD) measured from a parasternal long-axis window on the basis of BSA **(top)**, BSA-indexed LV end-systolic volume (LVESV) measured from an apical 4-chamber view on the basis of age **(middle)**, and BSA-indexed biplane LVESV based on age **(bottom)** (60). LVESV = left ventricular end-systolic volume.

Myocardial scintigraphy with bone avid tracers (technetium Tc 99m pyrophosphate and others) has a central role in diagnosing transthyretin cardiac amyloidosis, which is the predominant form of cardiac amyloid in older adults (52). Prevalence of transthyretin amyloidosis increases in older adults, with significant impact on HF with preserved ejection fraction, aortic stenosis (68,69), and other age-related CVD, as well hopes for new clinical benefits as treatments for transthyretin amyloidosis emerge (70). Myocardial scintigraphy is widely available at relatively low cost and has high sensitivity and moderate specificity (particularly in patients without elevated serum paraprotein levels), which has reduced the need for invasive endomyocardial biopsy in some patients (52). Notably, this technique can identify transthyretin cardiac amyloidosis prior to increased wall thickness or decreased ECG voltage.

CMR IMAGING. CMR produces high-quality images of cardiovascular structures in older adults without distortions caused by age-related changes in body composition. CMR with late gadolinium enhancement can detect prior MIs, including those that have been previously unrecognized (71). CMR with late gadolinium enhancement is also useful for diagnosing cardiac amyloidosis, other infiltrative cardiomyopathies (e.g., sarcoid), and identifying scar tissue that

might predispose to life-threatening ventricular arrhythmias. The principal limitations of CMR in older adults are that prolonged scanning times may compromise image quality due to motion artifact (especially in those with cognitive impairment), implanted cardiac devices may preclude use of CMR (although less of an issue with some newer devices), and stage 4 to 5 CKD when gadolinium is not recommended.

Several randomized clinical trials have established the utility of stress CMR perfusion imaging, usually using adenosine, to identify territories of myocardial ischemia, and to guide management of patients with stable chest pain (72,73). In a large multicenter registry, an abnormal stress CMR was associated with a nearly 2-fold increase in all-cause mortality (74). Median age in this study of 9,151 patients was 63 years, and 25% were age 70 or older. Subgroup analysis revealed similar findings by age group (<50, 50 to 64, ≥65 years), as well as by sex. Limitations of stress CMR are similar to those for CMR in general, and very limited data are available on test performance among patients ≥75 years of age or in those with multiple comorbidities (75).

CORONARY CTA. Noninvasive coronary CTA (computed tomography angiography) is able to detect CAD without the challenges associated with exercise or pharmacological stress (76,77). Image acquisition time is faster and the cost is often lower than with other imaging modalities. Coronary CTA also enables detection of prevalent, nonobstructive atherosclerosis that surpasses perfusion imaging (78). In younger individuals, detection of nonobstructive plaque with coronary CTA has been endorsed as an effective strategy to guide more intensive preventive therapies, including lipid lowering (79).

Nevertheless, nearly three-fourths of women and 92% of men ≥70 years of age have atherosclerotic plaque (80). Given the high prevalence of nonobstructive plaque, coronary CTA may have less value in guiding primary prevention decisions in older individuals. Age-related compositional changes in atherosclerotic plaque (i.e., increased density of calcified plaque) as compared with a larger burden of noncalcified plaque in younger patients may have implications for interpretation and clinical significance of coronary CTA findings (81). Heavily calcified arteries are difficult to assess accurately with coronary CTA, and the degree of stenosis may be overestimated in calcified segments due to blooming artifact. Recent evidence suggests that very dense calcified plaque is associated with a reduced incidence of acute coronary syndromes and may represent more stable plaque (82). However, the clinical implications of age-related differences in plaque burden and composition have not been well studied.

Coronary CTA requires intravenous contrast, which often limits use in older adults with impaired renal function. Furthermore, atrial fibrillation or other tachyarrhythmia may preclude acquisition of high-quality images. An additional limitation is that coronary CTA fails to provide insight into functional capacity or the degree of stress required to induce ischemia. The dimension of functional assessment is particularly helpful in discriminating risk in sedentary patients who may have accommodated their daily activities to avoid inducible symptoms.

Clinical trial evidence has not revealed a clear advantage of coronary CTA versus stress testing (usually with nuclear imaging) for ambulatory, older patients with chest pain. The PROMISE (Prospective Multicenter Imaging Study for Evaluation of Chest Pain) trial showed that 2-year event rates (death, acute coronary syndrome, or procedural complications) were similar among patients ≥65 years referred for coronary CTA versus functional testing and were comparable to those in adults <65 years of age (83). The low rates of adverse events in both arms of PROMISE raise questions about whether any testing is needed for many patients with chest pain. A watchful waiting strategy may be appropriate for some patients and may be concordant with many older adults' preferences.

A recent secondary analysis from the PROMISE trial also highlighted the relative utility of functional testing in comparison to coronary CTA in adults who were older (84). Functional testing (including exercise ECG, stress echocardiography, and stress nuclear) that was positive for ischemia among patients <65 years of age was not associated with an elevated risk of cardiovascular death or MI (hazard ratio [HR]: 1.09; 95% confidence interval [CI]: 0.43 to 2.82), but risk was significantly elevated among enrollees ages 65 to 74 (HR: 3.18; 95% CI: 1.44 to 7.01) and ≥75 years (HR: 6.55; 95% CI: 1.46 to 29.35). These data imply that diagnostic assessments incorporating physical and cardiac functional domains are particularly important in older adults, with clinical value that surpasses assessments based exclusively on CTA images. Similarly, an elevated coronary artery calcium (CAC) score (HR: 2.73; 95% CI: 1.31 to 5.69) or obstructive CAD on coronary CTA (HR: 3.04; 95% CI: 1.46 to 6.34) were associated with increased risk for cardiovascular death or MI among patients <65 years of age but not in the 65 to 74- and ≥75-year age groups.

IMPLICATIONS OF THE ISCHEMIA TRIAL FOR CARDIOVASCULAR TESTING IN OLDER ADULTS. The ISCHEMIA (International Study of Comparative Health Effectiveness With Medical and Invasive Approaches) trial is not directly about imaging and only 25% of study participants were ≥70 years of age, but it is pertinent as it demonstrates limitations of CAD management that relies primarily on testing as a guide for revascularization. In ISCHEMIA, there was no benefit of an invasive strategy (angiography and coronary intervention in addition to medical therapy vs. an initial strategy of medical therapy alone) on MI or death in patients with diagnostic criteria for CAD (85). However, ISCHEMIA also showed that revascularization was associated with improvements in health status, including symptoms, function, and quality of life (85,86). The health status benefits were not defined by the magnitude of ischemia, but by whether participants had angina prior to randomization. Overall, ISCHEMIA highlights the importance of modifiable symptoms as a particularly important consideration before initiating diagnostic testing. The ISCHEMIA investigators suggest the utility of tools such as the Seattle Angina Questionnaire (87) to enhance symptom discrimination. Nonetheless, the ambiguity of symptoms in older populations remains a difficult challenge that may diminish sensitivity of any symptom assessment tool.

HOLISTIC CONTEXT. In addition to symptoms, broader holistic context bears on the utility of diagnostic testing. In a study of CAD, event rates in patients with multivessel abnormalities were increased more than 3-fold when associated with (vs. without) extensive comorbidities (88). In another study of CAD detected by positron emission tomography in adults ≥85 years, there were no differences in event rates in those with normal versus moderate-severe perfusion abnormalities (89). These findings underscore the need for more research regarding comorbidities and broad clinical context when assessing for ischemia. In addition to comorbidities, testing is likely to be improved by metrics of more fundamental biology (e.g., biomarkers [90] or sarcopenia [91]).

ROLE OF IMAGING SCREENING TESTS FOR PRIMARY PREVENTION OF CAD. At present there are no Class I guideline-based recommendations for routine imaging for detection of CVD in asymptomatic individuals, with the exception of abdominal ultrasound to evaluate for aortic aneurysm in older men who smoked (92). Recently, use of computed tomography–based CAC scoring has been endorsed to help inform decisions on the use of statins in adults age 75 to 80 years (Class IIb, Level of Evidence: B [46]), based on data such as that from the MESA (Multi-Ethnic Study of Atherosclerosis) (93,94). Utility after age 80 is unproven and likely not useful given the high prevalence of CAC in this age group. In one report (80), 60% of women and 89% of men age 65 years and older had detectable CAC; by age 80, nearly 100% of women and men had detectable CAC.

STRESS TESTING

STRESS TESTING: A LOGICAL OPTION FOR OLDER ADULTS? YES AND NO. Common indications for stress testing include an evaluation of chest pain or dyspnea (or other suspected ischemic symptoms) or for serial evaluation of the patient with an established CAD diagnosis. For patients with ambiguous symptoms, exercise testing can help induce and characterize angina as well as other types of CVD (e.g., arrhythmia, hemodynamic lability, and pulmonary hypertension). This can be particularly useful for older patients who often obscure symptoms and signs by decreasing their activity. Nevertheless, diagnostic testing in older adults can still be confounded by atypical symptoms, limited physical functioning, baseline ECG abnormalities, baseline wall motion abnormalities, and/or reduced image quality.

The accuracy of diagnostic stress testing for CAD in younger versus older patients has not been clearly delineated. As with imaging, high pre-test risk estimates drive PPV of diagnostic stress tests in older patients (95). Knuuti et al. (96) reported the accuracy of diagnostic tests, showing that most stress imaging procedures in older adults (i.e., high risk due to age) were accurate for ruling in CAD (i.e., high PPV). Conversely, a negative test was also associated with a higher event rate in older adults (i.e. reduced NPV), likely due to the presence of occult CAD and comorbidity.

Current clinical practice guidelines (97) and appropriate use criteria (98) do not support stress testing for diagnosis of CAD in the absence of symptoms in younger or older adults and recommend a symptom-guided approach to avoid unnecessary procedures and reduce the economic burden of diagnostic testing in the United States. It has been estimated that up to one-third of testing for CAD could be avoided if it was limited to appropriate patient subgroups (99–101). Furthermore, even a symptomatic patient on medical therapy with an established CAD diagnosis and worsening symptoms does not necessarily need stress testing and may be better managed with intensified medical therapy.

TABLE 3 Selected Examples of Choosing Wisely Recommendations for Diagnostic Testing

Organization	Recommendation
American College of Cardiology	Avoid performing stress cardiac imaging or advanced noninvasive imaging in the initial evaluation of patients without cardiac symptoms unless high-risk markers are present.
American Society of Anesthesiologists	Do not obtain baseline diagnostic cardiac testing (TTE/TEE) or cardiac stress testing in asymptomatic stable patients with known cardiac disease (e.g., CAD, valvular disease) undergoing low- or moderate-risk noncardiac surgery.
American Society for Clinical Pathology	Do not routinely order expanded lipid panels (particle sizing, nuclear magnetic resonance) as screening tests for CVD.
American Society of Echocardiography	Avoid using stress echocardiograms on asymptomatic patients who meet low-risk scoring criteria for coronary disease.
American Society of Nuclear Cardiology	Do not perform radionuclide imaging as part of routine follow-up in asymptomatic patients.
Society for Cardiovascular Angiography and Interventions	Avoid performing routine stress testing after PCI without specific clinical indications.
Society of Cardiovascular Computed Tomography	Do not order CAC scoring for pre-operative evaluation for any surgery, irrespective of patient risk.
Society of Nuclear Medicine and Molecular Imaging	Do not perform routine annual stress testing after coronary artery revascularization.

CAC = coronary artery calcium; CAD = coronary artery disease; CVD = cardiovascular disease; PCI = percutaneous coronary intervention; TEE = transesophageal echocardiography; TTE = transthoracic echocardiography.

Nonetheless, apart from the application of exercise to provoke ischemia, exercise testing is useful as a means to gauge prognosis. In this respect, exercise testing might be relatively underutilized. Zafrir et al. (102) showed that older adults who failed to exercise beyond 3 metabolic equivalents were at highest risk for CAD events. Older adults with poor exercise capacity and/or those who must rely on nonexercise stress stimuli for diagnostic testing are at inherently greater prognostic risk. Notably, in a lower-risk group of women who were assessed using exercise echocardiography, a normal study was associated with a 5-year CAD death rate of ~0.5% (88). In contrast, among women incapable of exercise who were referred for dobutamine stress echocardiography, a normal study was associated with a 10-fold increase in CAD death compared with those deemed normal with exercise provocation, even after adjusting for age and other factors (88).

Given the challenges of limited exercise capacity in many older patients, many clinicians reflexively opt for pharmacological testing to assess for CVD (97). Whereas pharmacological stress testing has strong diagnostic and prognostic validation for CAD, the exercise stress provocation is still likely to provide broader clinical insights (103,104). However, to achieve the conceptual benefits of exercise testing in older adults, specialized approaches are often required. Ideally, exercise testing protocols should be aligned with each patient's physical capacities: starting at lower metabolic equivalent levels and progressing with smaller incremental increases in workload (e.g., Balke or Naughton) when appropriate (105).

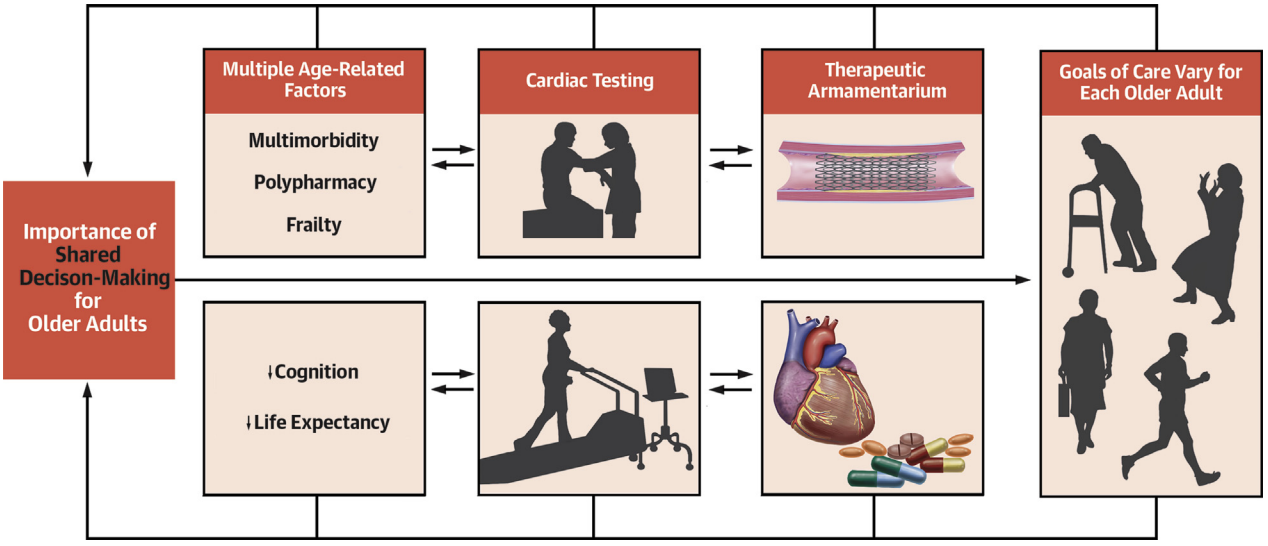
STRATEGIES TO IMPROVE APPROPRIATE USE OF CARDIAC TESTING

In addition to the American College of Cardiology's appropriate use criteria, the Choosing Wisely initiative, which began in 2012, of the American Board of Internal Medicine aims to promote conversations between clinicians and patients regarding medical interventions and to identify areas of potential procedural overuse. As of April 2019, 51 cardiology-related Choosing Wisely recommendations were published, many of which focus on diagnostic testing (**Table 3**). Specific recommendations pertain to blood tests for acute MI; echocardiography, radionuclide imaging, CTA, and CMR; coronary angiography; carotid and renal artery imaging; stress testing; lipid panels; ECG screening; pre-operative testing; and telemetry monitoring. Related reports describe the utility of these recommendations, for example, 75.1% of primary care physicians reported that they agreed or somewhat agreed that the Choosing Wisely initiative empowered them to reduce the use of unnecessary tests and procedures (106).

SHARED DECISION MAKING

Amid the inherent complexity pertaining to diagnostic testing in older adults, decision making regarding testing is neither simple nor suited to an algorithmic approach. Therefore, a more individualized process for shared decision making is an important priority. Whereas diagnostic testing has been widely accepted by patients as a part of routine care, even to the point where it is often regarded as a

CENTRAL ILLUSTRATION The Increased Importance of Shared Decision Making When Considering Testing for Older Adults With or at Risk for Cardiovascular Disease



Forman, D.E. et al. J Am Coll Cardiol. 2020;76(13):1577–94.

Whereas diagnostic, prognostic, and surveillance testing is often perceived as relatively straightforward and fundamental in the care of younger adults with or at risk for cardiovascular disease (CVD), testing strategies and cardiovascular therapies in older adults tend to become less clearly aligned with what many older adults describe as their goals of care. Shared decision making is especially important when considering diagnostic testing as the value of each test is more likely to be shaped by each older adult's preferences, particularly amid the confounding effects of multimorbidity, frailty, polypharmacy, cognitive decline, and reduced life expectancy. Age-related differences in the burden a patient may associate with testing as well as in the interpretability of results may also have an impact on the perceived value of testing to older adults as well as to their clinicians.

marker of quality, the escalation in the number of tests, the ambiguities of interpretation, the potentially burdensome clinical implications, and the associated costs are all reasons to engage patients in a more active decision process. Shared decision making implies that the concept of choice is integrated into standard care and that patient preferences (i.e., what matters most to each patient) are gauged and incorporated into an actionable process to achieve outcomes that are meaningful to the patient (**Central Illustration**). It also presumes that patients are informed and can participate fully in this activity.

Shared decision making has been advancing within mainstream cardiology, with utility that is particularly germane for older adults. Decisions regarding implantable cardioverter-defibrillators (107), left atrial appendage occlusion devices (108), statin therapy (46), anticoagulation (109), and even chest x-rays (110) are now linked to recommendations for structured decision making that aim to align care choices with each patient's personal goals of care (111). Research in this area focuses on pertinent elements of behavior and values and is sensitive to limits imposed by literacy, cognition, sensory, and other deficits, as well as considerations regarding timing and implementation (112). Shared decision making is evolving as a new benchmark of quality care, catalyzing new decision tools and skill sets. Creation of evidence-based shared decision-making tools for diagnostic testing, based on outcomes data for older adults, would be an important step forward.

FUTURE RESEARCH

To better define the role and optimal utilization of testing in older adults with or at risk for CVD, much additional research is needed. Key priorities are to ensure adequate representation of diverse older adults in studies of testing strategies and modalities (including imaging and biomarkers); creation of shared decision-making tools that can transparently estimate the outcomes of one testing strategy versus another based on patients' age and comorbidities; integrating patients' goals and preferences into decision making; and assessing "value" of each test based on patient factors (cardiovascular risk factors, function, frailty, cognition), relevant outcomes (quality of life, patient-defined goals), and geriatrics

TABLE 4 Top 15 Research Priorities for Diagnostic Testing in Older Adults

1. Ensure adequate representation of heterogeneous older adults in studies of diagnostic testing strategies and modalities (including imaging and biomarkers) and incorporate pre-specified subgroup analyses by age into study design.
2. Develop better tools for assessing prognosis, integrating CV and geriatric factors (comorbidity, geriatric syndromes, function).
3. Develop standardized data collection templates for assessing health status, quality of life, function, cognition, and frailty suitable for use in large population-based studies, as well as clinical trials.
4. Develop and test methodologies for more effectively incorporating patient preferences and goals of care into a shared-decision making process for diagnostic testing.
5. Delineate normal values and/or ranges for test results across age, sex, racial, and/or ethnic groups, including patients ≥85 yrs of age.
6. Develop better models for assessing pre-test probability prior to stress or anatomical testing in older adults.
7. Conduct observational studies and randomized trials to examine the utility of screening tests (versus not screening) with respect to meaningful outcomes, including analysis of factors (e.g., frailty, cognitive impairment) that determine downstream resource utilization and clinical outcomes.
8. Determine the utility of age- and sex-specific biomarker thresholds for cardiac troponins in the diagnosis of acute MI and natriuretic peptides in the diagnosis of heart failure.
9. Evaluate the role of biomarkers in older adults with no or uncharacterized CV disease to inform further evaluation, including impact on relevant outcomes.
10. Develop better approaches to point-of-care risk-benefit assessment in older adults to aid in shared decision making for diagnostic testing.
11. Integrate data from emerging sources (e.g., wearables, tablets, cell phone apps, and telemonitoring) into the EHR and the decision-making process.
12. Use artificial intelligence and/or machine learning methods to integrate CV factors, biomarkers, imaging, frailty, cognition, and other factors into a model to improve decision making for diagnostic testing.
13. Clarify the value and cost-effectiveness of pre-operative cardiac testing prior to noncardiac surgery as a function of aging phenotype, pre-operative risk, and patient preferences, as well as with respect to peri-operative and long-term clinical and patient-centered outcomes.
14. Develop better methods for clinician-patient communication regarding potential benefits and harms of testing in the context of patient preferences and health care goals.
15. Determine the impact of alternative reimbursement models (e.g., value-based contracting) that shift incentives for diagnostic testing away from financial and toward patient-centeredness.

CV = cardiovascular; EHR = electronic health record; MI = myocardial infarction.

perspectives (time to benefit and time to harm). **Table 4** and Supplemental Table 1 delineate specific research needs in multiple domains, including test selection and interpretation; screening and surveillance; biomarkers; integration and interpretation; pre-operative testing; shared decision making, communication, and ethical issues; and public policy.

SUMMARY AND CONCLUSIONS

CVD is endemic in the burgeoning population of older adults, which is rapidly becoming the dominant population with CVD in the United States and throughout the world. Whereas diagnostic testing is an elemental aspect of CVD care, the use and interpretation of biomarker, imaging, and exercise metrics are fundamentally altered when applied to older individuals. Just as aging is conducive to physiological changes that predispose to CVD, it is also accompanied by physiological and social dimensions that confound many aspects of testing itself, testing interpretation, and traditional CVD management goals. Among the key limitations, diagnostic testing in older adults lacks age-based normative ranges from which to best gauge disease, and there is relatively little integration of testing metrics with patient-reported outcomes (in contrast with extensive data linking testing metrics with disease outcomes). Additional interdisciplinary research is essential to better inform test selection and interpretation for older adults who routinely develop CVD in a context of clinical complexity and who are now, de facto, "typical" CVD patients.

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KEY WORDS aging, biomarkers, cardiovascular testing, imaging, shared decision making, stress testing

APPENDIX For a supplemental table, please see the online version of this paper.