Journal of the American Heart Association

CONTEMPORARY REVIEW

Frailty and Cardiovascular Health

Kirstyn James, MD; Yasser Jamil, MD; Manish Kumar, MD; Min J. Kwak, MD, MS, DrPH; Michael G. Nanna, MD; Saadia Qazi, MD, MPH; Aaron L. Troy, MD, MPH; Jawad H. Butt, MD; Abdulla A. Damluji, MD, PhD; Daniel E. Forman, MD; Ariela R. Orkaby, MD, MPH

ABSTRACT: The incidence of frailty and cardiovascular disease (CVD) increases as the population ages. There is a bidirectional relationship between frailty and CVD, and both conditions share several risk factors and underlying biological mechanisms. Frailty has been established as an independent prognostic marker in patients with CVD. Moreover, its presence significantly influences both primary and secondary prevention strategies for adults with CVD while also posing a barrier to the inclusion of these patients in pivotal clinical trials and advanced cardiac interventions. This review discusses the current knowledge base on the relationship between frailty and CVD, how managing CVD risk factors can modify frailty, the influence of frailty on CVD management, and future directions for frailty detection and modification in patients with CVD.

Key Words: aging ■ cardiovascular diseases ■ cardiovascular interventions ■ frailty ■ geriatric syndromes ■ primary prevention ■ secondary prevention

The number of older adults is steadily increasing. In 2034, a significant change is predicted to occur in the US population: for the first time, the number of adults 65 years and older will outnumber children younger than 18 years.[1] Age is the strongest single risk factor for the development of cardiovascular disease (CVD). As a result of changing demographics, a parallel increase in the incidence and prevalence of CVD is expected, posing a significant societal burden in terms of morbidity and mortality, resources, and cost. Aging is also a risk factor for geriatric syndromes such as frailty, sarcopenia, functional disability, and cognitive impairment. Frailty is a state of vulnerability caused by dysregulation among various physiological systems, with multifactorial causes, leading to impaired resilience and subsequent failure of hemostatic mechanisms to cope with internal and external stressors.[2] Sarcopenia is a loss of muscle mass and reduced muscle function and is often present in patients with frailty.[3]

These geriatric syndromes complicate and adversely impact management and outcomes in older adults with CVD.[4] Herein, we review the relationship between CVD and frailty, the appropriate management of CVD risk factors to modify frailty, the influence of frailty on CVD management, and future directions for frailty detection and modification in patients with CVD.

FRAILTY AND CVD HAVE A BIDIRECTIONAL RELATIONSHIP

Frailty increases vulnerability to disease, particularly CVD, and physiological derangements such as sarcopenia, inflammation, and autonomic changes that predispose to disease and disability.[2,5]

There are 2 leading conceptual frameworks for defining frailty: the physical frailty phenotype, developed by Fried and colleagues, and the frailty deficit accumulation index, developed by Rockwood and colleagues.[2,5] The physical phenotype identifies the presence of ≥3 of 5 components: weight loss (>5% in past year), exhaustion (positive response to the question regarding effort required for activity), weakness (decreased grip strength), slowness (>6–7 seconds to walk 15 feet),

Correspondence to: Ariela R. Orkaby, MD, MPH, Division of Aging, Brigham and Women's Hospital, Harvard Medical School, 150 South Huntington Street, GRECC, Boston, MA 02130. Email: aorkaby@bwh.harvard.edu

K. James and Y. Jamil are co-first authors.

This article was sent to Tiffany M. Powell-Wiley, MD, MPH, Associate Editor, for review by expert referees, editorial decision, and final disposition.

For Sources of Funding and Disclosures, see page 15.

JAHA is available at: www.ahajournals.org/journal/jaha

Nonstandard Abbreviations and Acronyms

ACC	American College of Cardiology
ADA	American Diabetes Association
AHA	American Heart Association
ASPREE	Aspirin in Reducing Events in the Elderly
DAPA-HF	Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure
DAPT	Dual Antiplatelet Therapy
DELIVER	Dapagliflozin Evaluation to Improve the Lives of Patients With Preserved Ejection Fraction Heart Failure
DPPOS	Diabetes Prevention Program Outcomes Study
EAST-AFNET 4	Early Treatment of Atrial Fibrillation for Stroke Prevention Trial
EFT	Essential Frailty Toolset
ELDERCARE-AF	Edoxaban Low-Dose for Elder Care Atrial Fibrillation Patients
ELSA	English Longitudinal Study of Aging
FI	Frailty Index
FRAIL-AF	Frail Atrial Fibrillation
HOPE-3	Heart Outcomes Prevention Evaluation-3
HYVET	Hypertension in the Very Elderly Trial
JUPITER	Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin
LE8	Life's Essential 8
Look AHEAD	Action for Health in Diabetes
LS7	Life's Simple 7
MACE	major adverse cardiovascular events
PARAGON-HF	Prospective Comparison of ARNI with ARB Global Outcomes in HF With Preserved Ejection Fraction
PREVENTABLE	Pragmatic Evaluation of Events and Benefits of Lipid Lowering in Older Adults
Pro. V.A.	Progetto Veneto Anziani
RACE II	Rate Control Efficacy in Permanent Atrial Fibrillation: a Comparison Between Lenient Versus Strict Rate Control II
SAGE	Study on Global Aging and Adult Health
SCD-HeFT	Sudden Cardiac Death in Heart Failure Trial
SENIOR-RITA	British Heart Foundation Older Patients With Non-ST Segment Elevation Myocardial Infarction Randomized Interventional Treatment Trial
SHARE	Study on Health, Aging, and Retirement in Europe
SPRINT	Systolic Blood Pressure Intervention Trial
STAREE	Statins in Reducing Events in the Elderly
TOPCAT	Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist
VHD	valvular heart disease

and low physical activity (kilocalorie spent per week: <383 kcal for men and <270 kcal for women).[5] The frailty deficit accumulation index quantifies the total burden of age-related acquired health deficits among multiple domains, including cognitive, functional, morbidity, social, and psychological aspects, informed by comprehensive geriatric assessment.[2]

More than 60 validated tools have been developed to measure frailty, with tools available for different clinical scenarios (Table 1).[6] While there is no single "best tool," any validated measure is better than not measuring frailty at all. For example, in a busy outpatient clinic, assessment of gait speed over a short distance (4 to 5 meters) is a rapid way to assess frailty, while, in an acute or inpatient setting, the Clinical Frailty Scale, which assesses how an older adult has been managing in the past 2 weeks, can be readily implemented.

The prevalence of frailty in older adults with established CVD is higher than the general population, impacting up to 30% of those with coronary artery disease, 80% of those with heart failure (HF), and 74% of those with aortic stenosis.[7] Frailty has a bidirectional relationship with CVD; individuals with established CVD are predisposed to developing frailty, and the presence of frailty increases the risk for faster onset of CVD.[8] Furthermore, frailty adds complexity to the management of CVD and increases the incidence of major adverse cardiovascular events (MACE) and mortality, even in patients with less severe CVD.[7,8]

Table 1. Common Frailty Measure Scales Utilized in Individuals With Cardiovascular Diseases

Select frailty measures[6]	Description
Physical phenotype (Fried criteria)	Unintentional weight loss (≥10 lb in the past year) Exhaustion (positive response to questions regarding effort required for activity) Weakness (decreased grip strength) Slowness (>6–7 s to walk 15 ft) Low physical activity (kcal spent per week: <383 kcal for men and <270 kcal for women)
Deficit accumulation index (Frailty Index)[6]	Deficit of symptoms/signs Comorbidities Deficits of activities of daily living Deficits of social interaction and social support
Clinical Frailty Scale	1. Very fit: robust, active, energetic, and motivated. Regular exercise. They are among the fittest for their age. 2. Well: no severe disease symptoms but are less fit than category 1. They exercise or are very active occasionally, eg, seasonally. 3. Managing well: well-controlled medical problems but are not regularly active beyond routine walking. 4. Living with very mild frailty: previously named "vulnerable," while not dependent on others for daily help, symptoms often limit activities. A common complaint is being "slowed up" and being tired during the day. 5. Living with mild frailty: more evident slowing and need help in higher-order instrumental activities of daily living such as finance, transportation, heavy housework, and medication management. Typically, mild frailty progressively impairs shopping and walking outside alone, meal preparation, and housekeeping. 6. Living with moderate frailty: need help with all outside activities and housekeeping. Inside often have problems with stairs, need help with bathing, and may need minimal assistance with dressing. 7. Living with severe frailty: completely dependent for cognitive and physical personal care. However, they seem stable and not at high risk of dying (within 6 mo). 8. Living with very severe frailty: completely dependent for personal care and approaching end of life. Typically, they could not recover even from minor illnesses. 9. Terminally ill: approaching the end of life. This category applies to people with a life expectancy of <6 months who are not otherwise living with severe frailty. (Many terminally ill people can still exercise until very close to death.)
FRAIL scale	Fatigue ("Have you felt fatigued? Most or all of the time over the past month?"): yes = 1, no = 0 Resistance ("Do you have difficulty climbing a flight of stairs?"): yes = 1, no = 0 Ambulation ("Do you have difficulty walking one block?"): yes = 1, no = 0 Illnesses ("Do you have any of these illnesses: hypertension, diabetes, cancer (other than a minor skin cancer), chronic lung disease, heart attack, congestive heart failure, angina, asthma, arthritis, stroke, and kidney disease?"): ≥5 = 1, <5 = 0 Loss of weight ("Have you lost more than 5% of your weight in the past year?"): yes = 1, no = 0 Score interpretation: prefrail: 1–2, frail: 3–5
Essential frailty toolset	Anemia (<13 g/dL in men and 12 g/dL and women) Hypoalbuminemia (<3.5 g/dL) Lower-extremity muscle weakness defined as a time of ≥15 s or inability to complete 5 sit-to-stand repetitions without using arms Cognitive impairment defined as a score of <24 on the Mini-Mental State Examination (which is highly unlikely if the patient is able to correctly recall 3 of 3 words after a distractive task and may obviate the need for further cognitive testing) Score interpretation: scored 0 (least frail) to 5 (most frail)
Four- or 5-m gait speed	Patient asked to walk a distance of 4 to 5 m at comfortable pace Slow: <0.83 m/s (>6 s)
Handgrip strength	Squeeze a dynamometer as hard as possible (repeated 3 times, once with each hand and then with strongest hand), with the strongest value recorded (men <30 kg, women <20 kg)
Short physical performance battery	• Standing balance test • Gait-speed (4-m walk) test • Strength test (as assessed by the time needed to rise from a chair 5 times) Scored 0 to 12, lower scores (<9) indicating frailty

FRAILTY AND CVD SHARE UNDERLYING BIOLOGICAL MECHANISMS

López-Otín et al[9] described 12 hallmarks of aging: genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, disabled macroautophagy, deregulated nutrient-sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, altered intercellular communication, chronic inflammation, and dysbiosis. A few of these biological alterations have been associated with frailty and CVD, with several underlying mechanisms highlighted in Figure 1. However, this area remains underdeveloped, and further research is needed to determine the triggers for pathological changes. Highlighted below are key selected areas of ongoing investigation (Table 2).

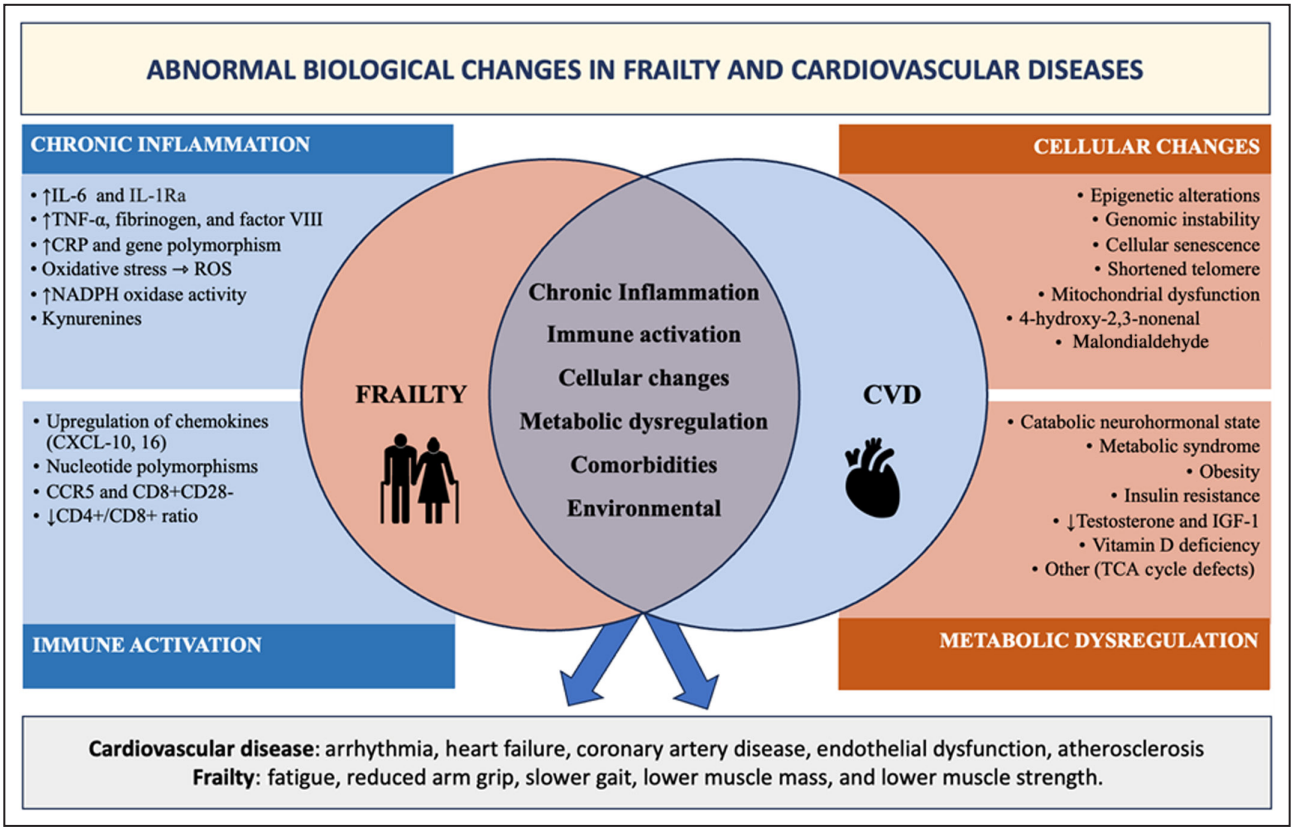

Figure 1. Biological mechanisms common to frailty and cardiovascular disease.
CCR indicates CC chemokine receptor; CD, clusters of differentiation; CRP, C-reactive protein; CXCL, chemokine (C-X-C motif) ligand; IGF-1, insulin-like growth factor 1; IL, interleukin; NADPH, nicotinamide adenine dinucleotide phosphate; ROS, reactive oxygen species; TNF-α, tumor necrosis factor α; and TCA cycle, tricarboxylic acid cycle.

Chronic inflammation and immune activation are marked by an imbalance between inflammatory and anti-inflammatory pathways, contributing to "inflammageing" and frailty. Elevated inflammatory markers, including interleukin (IL) 6, tumor necrosis factor α (TNF-α), C-reactive protein, and chemokine ligand 10,16, are associated with frailty (reduced hand grip strength, functional decline, lower muscle mass/strength).[10,16] Other inflammatory markers, such as IL-6, have also been associated with CVD.[11] For example, a 1-SD increase in IL-6 independently predicts coronary artery disease (relative risk [RR], 1.27) and HF events (RR, 1.72). In addition, a 1-SD higher $\log_e$ C-reactive protein concentration is linked to an RR of 1.63 for coronary artery disease in adults without a history of CVD.[12] Notably, associations of elevated inflammatory markers may be confounded, as most cited studies are observational or part of a treatment clinical trial, potentially reflecting downstream consequences rather than activation sites.[17]

Cellular changes encompass mitochondrial dysfunction, characterized by reduced mitochondrial DNA and increased oxidative stress. It is marked by elevated markers such as lipoprotein phospholipase A2, isoprostanes, malondialdehyde, 8-hydroxy-20-deoxyguanosine, and a derivative of reactive oxygen metabolites. These factors are implicated in pathological aging, disability, cardiac remodeling, plaque formation, neurohormonal overactivity, decreased nitric oxide availability, endothelial dysfunction, and the onset of arrhythmias and HF.[18] For example, reduced skeletal muscle mitochondrial function is correlated with an increased risk for incident CVD.[13] Other cellular changes, including epigenetic alterations and genomic instability, including accumulated DNA damage, loss of repair mechanisms, DNA methylation, and histone modification, play a role in the development of CVD (vascular calcification, hypertension, HF, and coronary artery disease). Some of these alterations are markers of disease progression and represent potential treatment targets.[19]

Metabolic dysregulation can result in altered hormone levels, such as low testosterone, vitamin D deficiency, insulin resistance, and metabolic syndrome, which are prevalent in both frailty and CVD. A systematic review revealed a significant association between metabolic syndrome and frailty (odds ratio [OR], 1.82) in 12 640 adults.[14] Importantly, complications within these disorders independently elevate the incidence of

Table 2. Select Studies Highlighting the Shared Biology Between Frailty and CVD

Author, y	Design	No.	Marker	Outcomes
Shared biologic markers associated with cardiovascular diseases and frailty				
Xu et al. (2022)[10]	Systematic review and meta-analysis	53 cross-sectional studies (5720 adults with frailty)	Biomarker leukocyte, lymphocytes, CRP, IL-6, IL-10, and TNF-α	The mean difference of CRP among the group with frailty was higher than the group with prefrailty (SMD, 1.104 [95% CI, 0.394–1.813], $P=0.002$) and robust group (SMD, 1.837 [95% CI, 0.599–3.075], $P=0.004$) The levels of IL-6 were significantly higher in patients with frailty (SMD, 0.882 [95% CI, 0.569–1.195], $P=0.000$) Groups with prefrailty (SMD, 0.517 [95% CI, 0.313–0.722], $P=0.000$) than in the control group The level of TNF-α in the group with frailty was significantly higher than in the group with prefrailty (SMD, 0.549 [95% CI, 0.075–1.023], $P=0.023$) and robust group (SMD, 0.561 [95% CI, 0.046–1.076], $P=0.033$) No significant differences in the levels of leukocytes and IL-10
Cesari et al (2003)[11]	Observational	2225 (70–79 y) without CVD	IL-6, TNF-α, and CRP	IL-6 was significantly associated with: CHD events, per IL-6 SD increase: RR, 1.27 (95% CI, 1.10–1.48) CHF events, per IL-6 SD increase: RR, 1.72 (95% CI, 1.40–2.12) TNF-α showed significant associations with: CHD, per TNF-α SD increase: RR, 1.22 (95% CI, 1.04–1.43) CHF, per TNF-α SD increase: RR, 1.59 (95% CI, 1.30–1.95) CRP was significantly associated with CHF events, per CRP SD increase: RR, 1.48 (95% CI, 1.23–1.78)
The Emerging Risk Factors Collaboration, (2010)[12]	Individual participant meta-analysis	160 309 people without a history of vascular disease	Log_e CRP concentration	RRs per 1-SD higher log_e CRP concentration (3-fold higher) when adjusted further for conventional risk factors CHD: 1.37 (95% CI, 1.27–1.48) Ischemic stroke: 1.27 (95% CI, 1.15–1.40) Vascular mortality: 1.55 (95% CI, 1.37–1.76)
Ashar et al (2017)[13]	Prospective, population-based cohort analysis	21 870 participants (20 163 free from CVD at baseline) from the CHS, ARIC, and MESA trials	mtDNA-CN	HRs for incident associated with a 1-SD decrease in mtDNA-CN CHD: 1.29 (95% CI, 1.24–1.33) Stroke: 1.11 (95% CI, 1.06–1.16) CVD: 1.23 (95% CI, 1.19–1.26)
Jiang et al (2022)[14]	Systematic review and meta-analysis	One prospective cohort study and 10 cross-sectional studies with 12 640 participants	Metabolic syndrome	Association of metabolic syndrome Frailty (OR, 1.82 [95% CI, 1.46–2.27]) Weakness (OR, 1.35 [95% CI, 1.15–1.58]) Slow gait speed (OR, 1.80 [95% CI, 1.51–2.14]) Weight loss (OR, 1.77 [95% CI, 1.36–2.29]) Decreased physical activity (OR, 1.87 [95% CI, 1.49–2.35])
Shakya et al (2022)[15]	Systematic review	12 studies	Cardiometabolic risk factors among older adults (60 y and older)	Associated risk factors with increased risk of frailty: Abdominal obesity (sex-specified raised waist circumference) Hyperglycemia (elevated fasting blood glucose or glycated hemoglobin) Multiple cardiometabolic risk factors (cardiometabolic syndrome and Framingham cardiovascular risk score) Inconsistency seen among dyslipidemia and elevated BP

ARIC indicates Atherosclerosis Risk in Communities; BP, blood pressure; CHD, coronary heart disease; CHF, congestive heart failure; CHS, Cardiovascular Health Study; CRP, C-reactive protein; CVD, cardiovascular disease; HR, hazard ratio; IL-6, interleukin 6; MESA, Multi-Ethnic Study of Atherosclerosis; mtDNA-CN, mitochondrial DNA copy number; OR, odds ratio; RR, relative risk; SMD, standardized mean difference; and TNF, tumor necrosis factor.

Table 3. Frailty as a Risk Factor for CVD

Author, y	Number	Design	Frailty tool	Outcomes
Damluji et al (2021)[8]	4656 participants	Prospective cohort study	Fried frailty phenotype	HRs of CVD among patients with frailty MACE: 1.77 (95% CI, 1.53–2.06) AMI: 1.95 (95% CI, 1.31–2.90) Stroke: 1.71 (95% CI, 1.34–2.17) PVD: 1.80 (95% CI, 1.44–2.27) CAD: 1.35 (95% CI, 1.11–1.65)
Liu et al (2022)[20]	5015 aged 55 y and older, free of CVD	Prospective cohort study	Modified Fried criteria	Prefrailty and frailty were associated, respectively, with 1.6-fold and 2.6-fold increased risk of fatal CVD in the fully adjusted model
Sergi et al (2015)[21]	1567 participants aged 65–96 y	Population-based prospective cohort study	Modified Fried criteria	One or 2 modified Fried criterion had a significantly higher risk of CVD Low energy expenditure, exhaustion, and slow gait speed were significantly associated with the onset of CVD
Veronese et al (2017)[22]	18 cohorts with a total of 31 343 participants	Meta-analysis/systematic review	Modified Fried criteria	HRs for any type of CVD in the group with frailty (1.70 [95% CI, 1.18–2.45]) Prefrailty (1.23 [95% CI, 1.07–1.36])
Shrauner et al (2022)[23]	3 068 439 US veterans aged 65 y and older	Observational	Frailty Index	The presence of frailty was associated with an increased risk of cardiovascular mortality at every stage of frailty (severity dependent), in addition to MI and stroke

AMI indicates acute myocardial infarction; CAD, coronary artery disease; CVD, cardiovascular disease; HR, hazard ratio; MACE, major adverse cardiovascular event; MI, myocardial infarction; and PVD, peripheral vascular disease.

frailty and CVD. For instance, diabetes is associated with vascular dysfunction, loss of subcutaneous fat, increased visceral fat, reduced energy consumption, and altered sex hormone secretion, ultimately contributing to frailty and CVD.[15]

FRAILTY AS A RISK FACTOR FOR CVD

Frailty in Patients Without CVD

Frailty has been linked to a higher incidence of future cardiovascular events, even after accounting for traditional CVD risk factors. Several studies have highlighted the bidirectional relationship between CVD and frailty, leading to a vicious cycle. However, given shared pathophysiology, determining the chronological order of frailty and CVD remains challenging.

In a cohort study of 5015 adults 55 years and older with no known CVD at baseline, over 10 years of follow-up, frailty or its components (eg, abnormal knee extension strength) significantly increased the incidence of developing CVD by almost 1.5 times.[20] Damluji et al, in a prospective study, demonstrated that patients with physical frailty were more likely to develop MACE.[8] Similarly, the Pro. V.A. (Progetto Veneto Anziani) study, which followed 1567 participants 65 years and older with nonfrailty, noted that components of frailty (low energy expenditure and exhaustion), were significantly associated with the onset of CVD, such as HF.[21] These findings were replicated in different patient populations, including individuals with prefrailty[22,23] (Table 3).

Frailty, Subclinical CVD, and Multimorbidity

Although studies have demonstrated an association between frailty and the incidence of CVD independent of the traditional risk factors, both frailty and prefrailty are also associated with multimorbidity, cognitive dysfunction, metabolic dysregulation, and other atherosclerotic risk factors.[8,21] Older adults with frailty are often burdened by multimorbidity (≥2 chronic conditions), with rates as high as 72%. Conversely, the presence of multimorbidity doubles the risk of frailty compared with those without multimorbidity.[24]

Furthermore, frailty is associated with subclinical cardiovascular abnormalities. These include carotid stenosis >75%, major ECG, and echocardiographic parameters such as left atrial volume, lower stroke volume, diastolic function, pulmonary artery pressure, and autonomic dysfunction. These findings were present in patients without established CVD and may explain the subclinical progression of the cardiovascular process contributing to both frailty and clinical CVD.[8,21] These processes offer valuable

insights into disease progression and potential opportunities for CVD and frailty prevention and management (Table 3).

LIFESTYLE, BEHAVIOR, AND SOCIAL INTERVENTIONS MAY REDUCE FRAILTY

A key strategy for reducing the incidence of both frailty and CVD is the management of known risk factors. As described, there is an overlap between risk factors for frailty and CVD, and modification of CVD may offer an additional benefit of reducing the risk of frailty. An example of how optimal cardiovascular health can prevent frailty is the impact of the American Heart Association (AHA's) Life's Simple 7 (LS7), which has recently been updated to include sleep as Life's Essential 8 (LE8).[25] LS7 included 4 lifestyle interventions (physical activity, weight management, diet, and smoking cessation) along with glucose, lipids, and blood pressure (BP) management, resulting in 7 metrics contributing to the LS7 score. In addition to lowering CVD risk, optimization of LS7 has been associated with reduced risk of frailty among age groups.[26] Data for LE8 are not yet available but are expected to show similar associations. A 2016 cohort study of older adults found that participants with ≥3 LS7 optimal metrics had a lower incidence of frailty (hazard ratio [HR], 0.63 [95% CI, 0.39–0.99]).[27] In addition, studies suggest that optimal LS7 scores in midlife could lower the risk of frailty in later life.[26]

Physical Activity

Regular exercise and physical activity improve cardiovascular outcomes, and structured physical activity programs are associated with preserving mobility.[28] In overweight/obese adults aged 45 to 76 years with diabetes who were randomized to reduced caloric intake and increased physical activity (>175 min/week) to induce weight loss, a decrease in CVD events was observed, with the greatest benefit among those with lower frailty levels. Furthermore, CVD incidence was inversely related to baseline Frailty Index (FI), with relative benefit for individuals in the first FI tertile and no benefit among those in the third FI tertile.[29] Although physical activity remains the only proven strategy for preventing and reversing frailty. Early intervention might be key to optimal outcomes (reduced progression of frailty and CVD).[2,29]

Diet and Obesity

Diet and obesity are modifiable risk factors for CVD and also offer the potential to modify frailty risk. An abnormal body mass index and suboptimal nutrition are associated with a higher risk of frailty.[2] On the other hand, despite heterogeneity, a meta-analysis of 9 observational studies in certain countries showed that healthy dietary patterns (high in fruits, vegetables, and whole grains) were associated with lower odds of frailty.[30] Furthermore, an inverse dose–response relationship of diet quality with prefrailty and frailty, as seen in 9861 initially healthy men (60 years and older).[31] Another study demonstrated that adherence to the Mediterranean diet was associated with a 0.004 to 0.005 unit per year slower progression of frailty.[32]

A key challenge in frailty prevention is the maintenance of both a healthy weight and the prevention of sarcopenia. A sole focus on weight loss to reduce CVD could worsen frailty through loss of muscle mass.[33] Therefore, strategies should focus on lowering adiposity while increasing muscle strength.

Substance Use

Substance use can increase the risk of frailty through several mechanisms. Substances such as alcohol and cocaine can result in direct brain toxicity. Substance use disorders are associated with suboptimal nutrition, poverty, reduced access to health care, and social isolation, which are associated with the development of frailty.[34] Chronic use of substances such as opioids and amphetamines is associated with cognitive impairments on neuropsychological testing, which may be related to oxidative stress.[35] Furthermore, smoking is also a risk factor for the progression of frailty. Hence, providing assistance and implementing substance cessation programs could present an avenue to mitigate frailty and reduce the risk of CVD.

Mental Health

Anxiety, depression, and chronic mental health conditions share a bidirectional relationship with frailty. The UK Biobank recruited 500 000 adults aged 37 to 73 years, followed for 12.2 years, and found that those experiencing mental disorders such as anxiety, bipolar disorders, and depression showed a propensity for elevated frailty scores.[36] In addition, ELSA (English Longitudinal Study of Aging) found that social isolation is associated with both incident CVD and frailty.[37] The contribution of mental health to both frailty and CVD risk in older adults is an ongoing area of investigation.

Socioeconomic Status

Lower socioeconomic status is associated with poorer health outcomes and accelerated aging. A systematic review of studies that included populations from high-income countries found an overall weighted prevalence

of frailty of 10.7% (95% CI, 10.5–10.9).[38] SHARE (Study on Health, Aging, and Retirement in Europe) and the World Health Organization's (WHO) SAGE (Study on Global Aging and Adult Health) both found that lower educational attainment and socioeconomic status were associated with increased prevalence of frailty.[39]

Another study investigating the incidence of frailty following myocardial infarction (MI) found that participants from lower socioeconomic groups were at a higher risk of developing frailty (OR, 2.29 [95% CI, 1.41–3.73]).[40]

INFLUENCE OF FRAILTY ON CVD PREVENTION AND TREATMENT

Many of the evidence-based CVD prevention tools and treatments for primary and secondary prevention are underutilized in older adults because of a paucity of data regarding their benefits and safety in this medically complex population. Moreover, major risk calculators such as the Framingham Risk Score, Reynold Risk, and QRISK-3 have maximum age cutoffs of 79 years, 80 years, and 84 years, respectively.

Incorporating the impact of frailty in CVD prevention may address the challenges of both aging physiology and competing risks when assessing CVD risk in older adults who may be the most likely to benefit from preventive strategies (Figure 2).

Lipid Reduction

Hyperlipidemia is associated with frailty, and observational data have shown an association between higher serum remnant cholesterol and higher FI scores.[41] Guideline recommendations for secondary prevention in older adults are generally similar to those for younger adults. However, there are considerable gaps in guidelines for lipid-lowering therapies in primary prevention, particularly in those older than 75 years, leaving management strategies largely to individualized, patient-specific considerations.[42] While large observational studies have shown that lipid-lowering therapy benefits older adults, the current body of randomized controlled trials (RCTs) is limited.[43] A meta-analysis from the Cholesterol Treatment Trialists' Collaboration, comprising 28 major statin trials and nearly 186 000 participants, found that statin therapy reduced vascular events and mortality, with attenuation of the benefit of statins for primary prevention in adults 75 years and older due to limited enrollment in this age group.[44] A meta-analysis of JUPITER (Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin) and the HOPE-3 (Heart Outcomes Prevention Evaluation-3) trial demonstrated that rosuvastatin was superior to placebo for patients 70 years and older for preventing atherosclerotic CVD.[45] Furthermore, despite the few published studies for the role of lipid-lowering therapies in older adults with frailty, at least one observational study suggests similar or greater benefits of statins for mortality and MACE prevention in those with frailty.[46]

Limitations in current data to guide statin use have partly been attributed to the heterogeneity of patient ages and geriatric complexities such as multimorbidity, frailty, cognitive decline, polypharmacy, and falls. Thus far, statin therapy has not been shown to have adverse impacts on physical function and frailty in this population. However, 2 ongoing RCTs, STAREE (Statins in Reducing Events in the Elderly) and the PREVENTABLE (Pragmatic Evaluation of Events and Benefits of Lipid Lowering in Older Adults) trials, seek to fill the gaps in CVD prevention in older adults.[25]

Glucose Control

Diabetes increases the risk of physical disability and loss of functional independence.[47] The presence of both diabetes and frailty increases mortality and risk of CVD. A recent study of participants from the UK Biobank found that the presence of prediabetes and frailty increased the risk of developing diabetes (HR, 1.73 [95% CI, 1.55–1.92]) and mortality (HR, 1.81 [95% CI, 1.51–2.16]).[48] Evidence suggests that tight glycemic control in older adults with frailty is associated with increased CVD events, frailty, cognitive impairment, mortality, and functional impairment through complications such as falls and hip fractures.[49] In addition, established diabetes interventions for improving CVD outcomes may not produce the same effects in older adults with frailty. In this context, the American Diabetes Association (ADA) recommends a glycated hemoglobin of <7.5% in older adults who are functionally intact and are without multimorbidity or life-limiting illness and avoidance of pharmacologic agents that cause significant hypoglycemia older adults.[50] The ADA also recommends the evaluation of geriatric syndromes that may impair self-management of diabetes and quality of life.

The advent of new pharmacologic agents such as sodium-glucose cotransporter 2 inhibitors and glucagon-like peptide-1 receptor agonists in diabetes management is promising for promoting cardiovascular health and healthy vascular aging.[25,51] Furthermore, sodium-glucose cotransporter 2 inhibitors and metformin have antiaging properties that may offer supplementary benefits to simply glycemic control in older adults.[25] The DPPOS (Diabetes Prevention Program Outcomes Study) found that intensive lifestyle modification reduced 10-year frailty risk.[52] A subanalysis of the Look AHEAD (Action for Health in Diabetes) study found that metformin therapy was associated with slower progression of frailty.[53] While these emerging

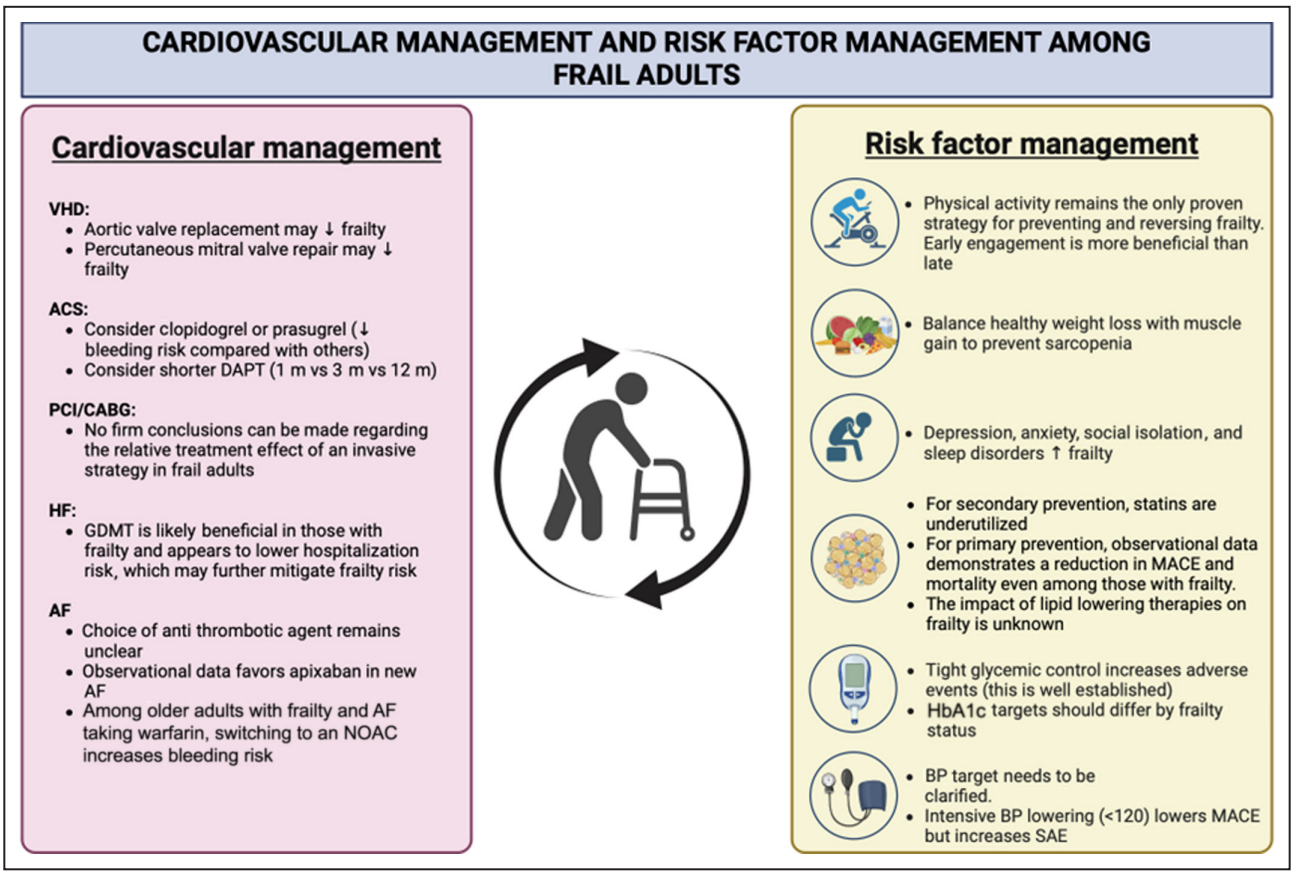

Figure 2. Interplay between cardiovascular risk factor management and frailty: mutual influences on health outcomes.
ACS indicates acute coronary syndrome; AF, atrial fibrillation; CABG, coronary artery bypass graft; DAPT, dual antiplatelet therapy; GDMT, guideline-directed medical therapy; HF, heart failure; HbA1c, glycated hemoglobin; MACE, major adverse cardiovascular events; NOAC, non–vitamin K oral anticoagulant; PCI, percutaneous coronary intervention; SAE, serious adverse event; and VHD, valvular heart disease.

data are intriguing, the impact of diabetes treatments on frailty and aging remains inconclusive.

BP Reduction

Hypertension is one of the most common chronic diseases, prevalent in up to 80% of older adults, particularly among those with frailty.[54] Elevated BP leads to arterial stiffness and risk of developing chronic conditions such as chronic kidney disease, CVD, and dementia, all of which increase the risk of frailty. Age-related vascular changes leading to arterial stiffness are the major underlying causes of elevated systolic BP and lower diastolic BP, leading to the progression of wider pulse pressure over time. Age-related alterations in BP have been shown to significantly increase the risk of major CVD events and all-cause mortality.[55] The 2017 American College of Cardiology (ACC) guidelines recommend a target systolic BP of <130/80 mm Hg for most adults 65 years and older.[56] Meanwhile, the European Society of Cardiology and the European Society of Hypertension guidelines recommend systolic BP and diastolic BP targets between 130 to 139 mm Hg and 70 to 79 mm Hg, respectively.[57]

Multiple RCTs have demonstrated that improved BP control, even to a systolic BP ≤120 mm Hg, in older adults has benefits for mitigating CVD risk and cognitive impairment.[25] However, prospective RCTs such as SPRINT (Systolic Blood Pressure Intervention Trial), HYVET (Hypertension in the Very Elderly Trial), and the more recent STEP (Strategy of Blood Pressure Intervention in the Elderly Hypertensive Patients) trial have not adequately accounted for older adults with frailty, cognitive impairment, and multiple comorbidities.[58] A post hoc analysis of SPRINT in which the SPRINT 36-item FI was applied, participants with frailty (n=2560; mean age, 69 years) had a higher prevalence of prior CVD at baseline. The study found no significant differences in adverse outcomes between intensive or standard BP control among participants with frailty.[59] Another post hoc analysis from SPRINT used mediation analysis to explore the effect of incident nonfatal MACE or serious adverse events on the relationship between BP treatment intensity and mortality

outcomes. Key findings included a higher frequency of serious adverse events than the incidence of MACE and higher noncardiovascular mortality, mostly pronounced in those 80 years and older.[60] This analysis adds to a limited collection of literature on the impact of frailty on BP management in older adults and the importance of focusing on important occurrences after the event. Yet, it is worth noting that individuals with frailty have typically been excluded from clinical trials and, when included, may not represent patients with the most frailty, such as those living in nursing homes. Therefore, a definitive BP target for patients with CVD and frailty is undecided.

Cardiovascular Management

The ACC/AHA guidelines recommend that low-dose aspirin not be administered on a routine basis for the primary prevention of CVD in adults 70 years and older due to the risk of bleeding outweighing the benefit.[61]

Given the importance of frailty as a consideration in pharmacotherapy for CVD prevention, a subgroup analysis of patients stratified by frailty status using the adapted Fried FI was also conducted in the ASPREE (Aspirin in Reducing Events in the Elderly) trial. Among participants characterized as not having frailty, prefrailty, and frailty, there was a trend toward aspirin improving disability-free survival in individuals with prefrailty; however, this was statistically inconclusive.[62] Aspirin for the prevention of frailty has also been evaluated in observational studies showing an independent inverse association between regular long-term aspirin use and frailty.[63] A more recent post hoc analysis of the ASPREE trial found no difference in incident frailty among participants randomized to aspirin versus placebo.[64] These findings suggest that more work needs to be done in evaluating the potential antiaging effects of aspirin.

Antiplatelet therapy remains the cornerstone of secondary prevention, providing absolute risk reduction in cardiovascular events in older adults who have experienced a prior CVD event. Despite this, there remains concern regarding increased risk of disabling or fatal bleeding, which might be more pronounced in adults with frailty. Furthermore, the choice of agent, duration, and combination of antiplatelet agents in older adults can be challenging due to lack of consensus, especially in individuals with frailty. Despite that, clopidogrel and prasugrel seem to be associated with favorable clinical outcomes among older adults (older than 75 years) with coronary syndromes.[65]

The duration of antiplatelet therapy has also been an important consideration in older adults. Overall, the landmark DAPT (Dual Antiplatelet Therapy) trial resulted in fewer ischemic events with a higher rate of bleeding in patients randomized to 30 months of DAPT versus aspirin only after 12 months of DAPT. Bleeding events increased by age in stratified analyses, which factors considerably into the DAPT score for assessing the utility of prolonged DAPT.[66] Adding to the argument for shorter-duration DAPT, a meta-analysis of nearly 6000 participants showed that shorter DAPT (3–6 months versus 12 months) may not increase the risk of ischemic events but does result in favorable bleeding outcomes in adults 65 years and older.[67] Furthermore, in a post hoc analysis of outcomes in the DAPT trial among participants with frailty, there was an overall higher number of ischemic events, and frailty was associated with a higher bleeding risk among those receiving extended-duration DAPT. However, these findings were limited due to limited sample size. In light of these data, there has been greater emphasis on the effects of de-escalating DAPT by both potency and duration for secondary prevention in older adults. The approach to antiplatelet therapy for secondary prevention in older adults requires individualization as the literature remains limited on the efficacy of different agents in the context of aging physiology, leading to variations in platelet reactivity, bleeding risk, functional status, and frailty.[68]

FRAILTY INFLUENCES OUTCOMES FROM CVD INTERVENTIONS AND TREATMENTS

Just as frailty influences cardiovascular risk factors, it can also affect the management and outcomes of CVDs. In the following sections, we examine the impact of frailty on therapeutic (pharmacological and interventional) outcomes among common CVDs.

Valvular Heart Disease

The prevalence of valvular heart disease (VHD) rises proportionately with age. Specifically, VHD is diagnosed in 0.7% of individuals younger than 45 years and escalates to 13.3% in those older than 75 years.[69] VHD leads to significant hemodynamic changes, affecting both longevity and the occurrence of MACE, even among those with moderate or moderate to severe VHD.[70] For example, severe symptomatic aortic stenosis is most common among the very old and is a strong predictor of mortality risk in this population. Moreover, the presence of moderate or severe mitral regurgitation in older patients with geriatric syndromes is also associated with worse intermediate and long-term mortality.[71]

Frailty is prevalent in older adults with VHD, with estimates as high as 68% of older adults.[70] In addition to this high prevalence, the cumulative impact of frailty

on VHD is compounded by its association with other adverse clinical outcomes, including higher rates of medication intolerance, complications of transcatheter or surgical aortic valve replacement, and in-hospital mortality, as well as progression of cognitive decline, disability, falls, and loss of independence.[70]

While frailty results in worse outcomes in patients with VHD disease, VHD can also influence the burden of frailty and other geriatric risks over time. The presence of multiple chronic conditions, a frequent finding in patients with VHD, leads to the introduction of several concurrent medications, which has long been associated with an increased risk of frailty, falls, and worsening cognitive impairment, further complicating risks.[72] To address these complexities, individualized care informed by geriatric principles may reduce the risk of frailty when managing patients with VHD. Due to the recognition that various therapeutic interventions in patients with frailty living with VHD can result in adverse effects (eg, direct oral anticoagulants increasing the risk of bleeding in patients with frailty), frailty should be incorporated into the assessment of patients with VHD. Frailty can worsen VHD outcomes, and efforts to address and prevent frailty syndrome in the setting remain critical.

In a study investigating the effects of percutaneous mitral valve repair in patients with HF, frailty was assessed using Fried criteria (weight loss, weakness, exhaustion, slowness, and low activity). Among the initially identified participants with frailty, comprising 45.7% with a mean age of 78 ± 9 years, it was observed that after undergoing percutaneous mitral valve repair, the prevalence of frailty significantly decreased to 28.7% during follow-up. This reduction encompassed improvements in frailty domains such as slowness, exhaustion, and inactivity.[73] Similarly, in patients undergoing transcatheter aortic valve replacement, frailty is strongly associated with time in hospital and mortality, as seen in Danish patients who underwent transcatheter aortic valve replacement.[74] On the other hand, aortic valve replacement either surgically or percutaneously demonstrated improvement in patient-reported quality of life, depression, angina, and frailty following repair.[75] Therefore, evaluating frailty is a reasonable step during preprocedural assessments and consideration for intervention. Exploring whether lowering the threshold for valve repair in the prefrailty stage, rather than waiting until frailty fully develops, is also a crucial aspect that warrants exploration in future trials.

Revascularization

Frailty status can impact access to invasive care, short-term risk related to revascularization procedures such as percutaneous coronary intervention (PCI) and coronary artery bypass graft (CABG) surgery, and subsequent clinical and quality-of-life outcomes.

Percutaneous Coronary Intervention

Frailty is common among patients 75 years and older admitted with acute MI (AMI), with estimates ranging from 19% to 66%.[76] Patients with frailty who have AMI are less likely to undergo PCI and CABG than patients without frailty, and frailty is associated with increased mortality, major bleeding, and stroke in this population.[76] Even among older adults undergoing PCI for stable ischemic heart disease, the presence of frailty predicts adverse outcomes. Given these risks, older patients with frailty consistently have lower revascularization rates than their counterparts without frailty.[76] This is despite the fact that patients with frailty who have AMI still appear to glean an immediate in-hospital survival benefit from revascularization in observational studies.[76] RCTs in older adults with non–ST-segment–elevation MI have suffered from slow recruitment and demonstrated conflicting results, though the totality of evidence appears to lean in favor of an invasive strategy in many older adult patients without a clear increase in bleeding risk compared with a conservative strategy.[77] A more recent trial, specifically in older patients with frailty who have non–ST-segment–elevation MI, failed to demonstrate an increase in the number of days alive out of hospital with a routine invasive strategy, though the trial had a limited sample size and several limitations.[78] For example, 40% of patients in the invasive arm did not undergo revascularization, only 32% received complete revascularization, and 10% of patients in the conservative arm ultimately crossed over to undergo revascularization. Thus, no firm conclusions can be made regarding the relative treatment effect of an invasive strategy in older adults with frailty to date. The SENIOR-RITA (British Heart Foundation Older Patients With Non-ST Segment Elevation Myocardial Infarction Randomized Interventional Treatment Trial; NCT03052036) is currently enrolling 2300 patients 75 years and older with non–ST-segment–elevation MI and randomizing participants to an invasive or noninvasive strategy and will hopefully shed further light on this important clinical question.

Coronary Artery Bypass Graft

Patients with frailty undergoing CABG will have a longer hospital stay, leading to a higher risk of developing disability, subsequent hospitalization, and mortality.[79] In a registry of 500 older individuals (mean age, 71 years) undergoing urgent CABG for AMI, 60% qualified as having prefrailty and 14% as having frailty based on the Essential Frailty Toolset (EFT), and those who had frailty had a 3-fold increase in all-cause mortality.[80] In a study of 13 554 US veterans who underwent CABG from 2016 to 2020, frailty identified an increased risk of mortality even among those younger than 60 years.[81]

This study raises the issue of what age should trigger a frailty assessment, as frailty, while more common in older adults, is independent of age. Finally, while frailty is frequently cited as an exclusion criterion for CABG surgery, it remains unknown whether opting for a less-invasive treatment strategy in populations with frailty, such as PCI, improves the poor short- and long-term outcomes observed in those undergoing surgery.

Heart Failure

Clinical guidelines for the management of HF do not provide specific recommendations for the use of medical therapy in the frail. This is due to the lack of RCTs designed to evaluate the efficacy and safety of pharmacological therapies in individuals with frailty. However, post hoc and prespecified subgroup analyses from key clinical trials of HF have provided data on the effects of pharmacological interventions in these individuals. However, the data must be interpreted in the context of the inclusion and exclusion criteria applied in the trials (ie, patients with HF enrolled in clinical trials are typically younger and healthier than individuals with HF in the general population). These findings collectively challenge the common reluctance of clinicians to introduce new pharmacological therapies to patients who are perceived to have frailty because of doubts about the benefit of treatments and concerns about treatment intolerance and adverse events.[82]

In PARAGON-HF (Prospective Comparison of ARNI with ARB Global Outcomes in HF With Preserved Ejection Fraction), sacubitril-valsartan, compared with valsartan, did not significantly reduce the risk of the primary outcome, which was a composite of total HF hospitalizations and cardiovascular death. Interestingly, there seemed to be a greater reduction in the primary outcome and HF hospitalizations with sacubitril/valsartan with increasing frailty, with no increased adverse events, irrespective of frailty class.[83] Similarly, in the DAPA-HF (Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure) and DELIVER (Dapagliflozin Evaluation to Improve the Lives of Patients With Preserved Ejection Fraction Heart Failure) trials, dapagliflozin, compared with placebo, substantially reduced the risk of worsening HF events, cardiovascular death, all-cause death, improved symptoms, physical function, and quality of life, regardless of frailty status in patients with reduced and preserved ejection fraction.[84] Importantly, among all frailty classes, there was an absolute reduction in clinical events and improvements, with a favorable safety profile.[84] Finally, in the TOPCAT (Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist) study, spironolactone showed beneficial clinical outcomes, including the composite of cardiovascular death, HF hospitalization, and aborted cardiac arrest, that were not modified by frailty status.[85]

Primary prophylactic implantable cardioverter–defibrillator (ICD) reduces the risk of sudden cardiac death in patients with HF with reduced ejection fraction. However, whether the benefit remains evident in patients with frailty remains interesting. This was examined in a post hoc analysis of SCD-HeFT (Sudden Cardiac Death in Heart Failure Trial). It was found that baseline frailty modified the efficacy of ICD therapy, such that a significant mortality benefit was observed among participants with a low frailty burden. However, older patients with higher frailty burden experienced no reduction in the risk of all-cause mortality with ICD, which might be related to the advanced HF status and comorbidity burden, to which the risk of mortality might not be reduced through ICD.[86] According to the 2022 AHA/ACC/Heart Failure Society of America guideline, "for patients whose comorbidities or frailty limit survival with good functional capacity to <1 year, ICD is not indicated." However, there is a lack of recommendations for patients with a survival of >1 year but with varying frailty status.[87]

Atrial Fibrillation

Frailty is highly prevalent among older adults with atrial fibrillation (AF) and is associated with increased rates of mortality, stroke, and persistent or permanent AF.[88] Despite this, the 2014 AHA/ACC/Heart Rhythm Society guidelines and their 2019 update do not explicitly address frailty.[89] The 2020 ESC guidelines briefly address patients with older age and frailty, emphasizing that these patients benefit from oral anticoagulants and rate or rhythm control options offered to younger or more robust patients.[90] In the years since these guidelines were published, a robust body of practice-guiding research has grown about anticoagulation for patients with AF and frailty, while fewer studies have investigated rhythm and rate control in this population.

Anticoagulation

The decision for anticoagulation is challenging in adults with frailty due to increased risk of both stroke and bleeding. Studies have demonstrated that the net benefit of oral anticoagulants remains similar among frailty and fall-risk statuses, with stroke-protective benefits improving mortality and outweighing the risk of hemorrhage.[91] Compared with warfarin, rivaroxaban, and dabigatran, apixaban has the most favorable outcomes, specifically in terms of reduced bleeding risk.[92] Moreover, in certain patients not deemed suitable for full-dose oral anticoagulation, the ELDERCARE-AF (Edoxaban Low-Dose for Elder Care Atrial Fibrillation Patients) RCT compared low-dose edoxaban (15 mg daily) with placebo in

Japanese patients with nonvalvular AF and age older than 80 years. Among these patients, 40.9% were frail, and the use of edoxaban showed a significant reduction in thromboembolic events without a significantly increased incidence of major bleeding.[93]

However, in patients already established on warfarin, switching to a direct oral anticoagulant was associated with increased adverse events, including a higher bleeding risk (HR, 1.69 [95% CI, 1.23–2.32]), as demonstrated in the FRAIL-AF (Frail Atrial Fibrillation) RCT.[94] Therefore, while direct oral anticoagulants may be preferred for patients with AF and frailty who are anticoagulant-naïve, switching patients already taking stable therapeutic doses of warfarin may do more harm than good.

Despite this evidence, patients with frailty remain less likely to be prescribed oral anticoagulants among health care settings, with frailty and falls cited as the most common reasons for anticoagulant nonprescription.[95] In summary, based on the evidence and the 2023 Beer list recommendation, and in the context of shared decision-making, clinicians should avoid prescribing warfarin and rivaroxaban. Instead, they should consider apixaban or a low dose in anticoagulant-naïve patients with frailty.

Rate and Rhythm Control

In recent years, in part driven by EAST-AFNET 4 (Early Treatment of Atrial Fibrillation for Stroke Prevention Trial) (which did not measure frailty), early rhythm control has gained favor over rhythm control alone.[96] While few have investigated rate and rhythm control in patients with AF and frailty, current evidence suggests that rate and rhythm control strategies are underutilized in this population.[97]

Current evidence to support rhythm control in patients with AF and frailty is mixed, and patients with frailty are more likely to have persistent or permanent AF.[98] A large retrospective study using Korean data found that early rhythm control is associated with improved outcomes across frailty levels without increased risk of complications, but the degree of benefit attenuates with increasing frailty.[99] In the same data set, ablation was not associated with clinical benefit in patients with frailty and age 75 years and older but was associated with reduced risk of death and a composite of death, HF admission, stroke, and cardiac arrest among patients without frailty in the same age group.[100] Similarly, cardioversion was less effective in maintaining sinus rhythm at 6 months for patients with frailty compared with patients without frailty in a 2017 prospective cohort study at a Polish academic medical center.[101]

While these data suggest patients with frailty may be less likely to benefit from procedural rhythm control strategies, there is little evidence to guide medical antiarrhythmic therapy in those with AF and frailty. Amiodarone is a common choice given frequent contraindications to other agents in this population; however, due to severe long-term toxicities, the 2023 Beers Criteria recommends avoiding amiodarone as first-line therapy for patients without HF or substantial left ventricular hypertrophy and for patients with permanent AF or severe or recently decompensated HF.[102]

Despite the mixed evidence, an attempt at early rhythm control should be considered for patients with frailty and new AF, given the potential adverse effects of long-term rate control therapy. Patients with frailty are more susceptible to bradycardia and atrioventricular block from β-blockers and calcium channel blockers.[103] Moreover, Beers Criteria specifically recommends avoiding digoxin as the first line for rate control of AF and avoiding dosages >0.125 mg/d.[102] Given these limitations, a lenient heart rate goal (eg, <110 beats per minute) should be considered over a strict target (eg, <80 beats per minute), despite the relatively young population and lack of frailty measurement in the RACE II (Rate Control Efficacy in Permanent Atrial Fibrillation: a Comparison Between Lenient Versus Strict Rate Control II) trial.[104] The impact of frailty on benefits, risks, selection, and dosage of rate control agents in older patients with AF is understudied and remains a key area for future research.

FUTURE DIRECTIONS

Frailty has become an additional vital sign in caring for and studying older patients with CVD. However, significant challenges in studying frailty remain due to a lack of consensus on the definition and numerous instruments used in practice, resulting in inconsistency and irreproducibility of some of these studies. An effective frailty assessment tool should be reliable, consistent, reproducible, and universally accepted, much like the gold-standard instruments to measure other chronic conditions in practice (eg, diabetes). The EFT shows premise in this aspect, but its application has been mostly restricted to clinical trials in patients with VHD.[70] Studies incorporating frailty may rely on simpler tools that capture a single aspect of physical frailty, such as walking speed and grip strength, though more comprehensive assessments may be needed in practice. Future research should emphasize the holistic approach to studying the broader risks of frailty syndrome and, in parallel, studying frailty as an outcome measure in patients with CVD that is potentially modifiable.

There is a pressing need to explore whether frailty is reversible in patients with CVD. While some data hint at the possibility of reversing frailty,[6,105] their implications on CVD progression remain unknown.[6] To better

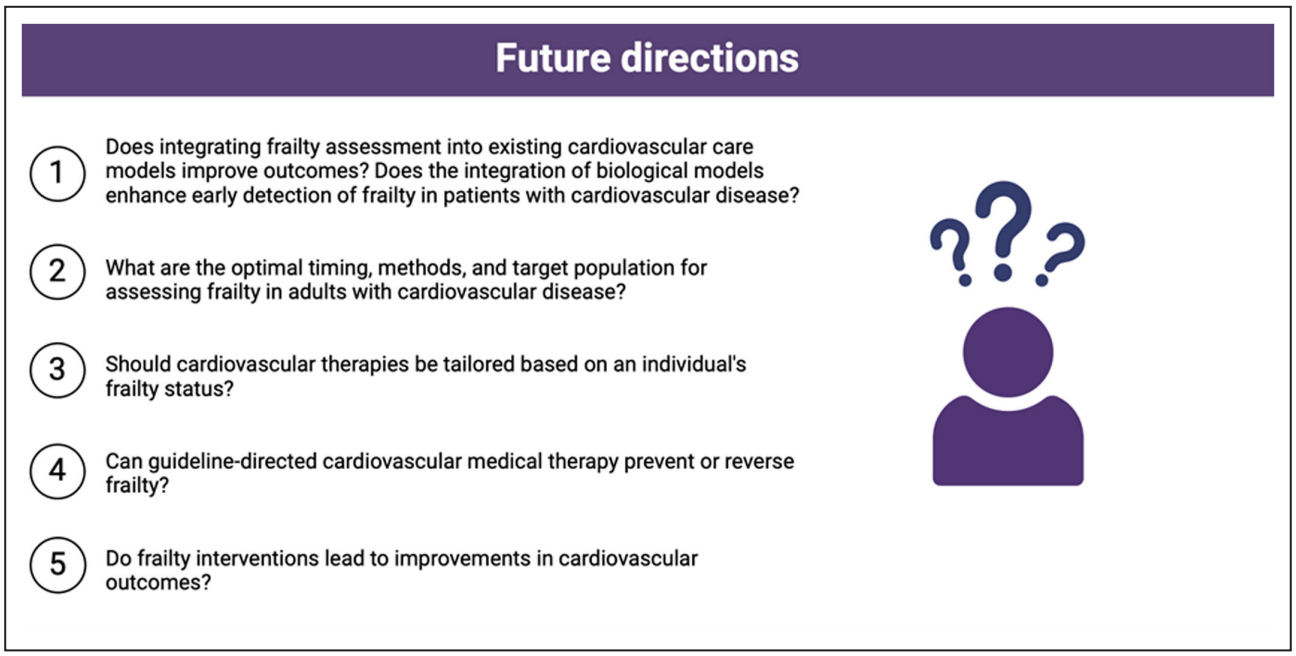

Figure 3. Unanswered questions in managing frailty and cardiovascular disease.

understand the interaction of frailty with CVD risk, future trials in older adults should use a well-defined frailty assessment tool that can be used universally in other domains of cardiovascular illness.[106] Although frailty and CVD are closely interlinked, the direct causal relationships need further study. It is important to consider that frailty could just be a phenotypic expression of pathologic aging due to higher underlying oxidative stress that also influences the development of CVD. Nevertheless, recent research points to mechanistic causes of frailty, such as inflammation, metabolic imbalance, and coagulation disorders, observed in patients with CVD onset. The roles of biomarkers, imaging, and pharmacotherapeutics will be the next frontiers in the study of older patients with frailty to uniquely address mechanistic pathways that concomitantly influence the development and progression of CVD.

Not surprisingly, the inclusion of frailty in the risk assessment of older adults undergoing cardiovascular procedures improves the predictive performance of existing risk stratification tools. The most recent version of the CathPCI Registry model for predicting in-hospital mortality risk following PCI included frailty as one of the strongest predictors of risk in the final full model.[107] Similarly, functional mobility as a proxy for frailty status was the strongest predictor in models predicting 30-day readmission risk and 6-month mortality among older adults (75 years and older) admitted with AMI.[108] In response to the predictive value of frailty status and other geriatric syndromes, a recent expert panel proposed their inclusion as a key pillar of risk in older adults being considered for cardiovascular intervention.[109] The authors propose a comprehensive geriatric risk assessment in patients being considered for invasive cardiovascular procedures that includes an assessment of frailty using one of the many validated measurement tools before synthesizing the information gleaned from that assessment with the Geriatric Heart Team to arrive at a shared person-centered decision.[110] A key future area of investigation will center around the impact of routine implementation of frailty assessments and interventions to modify frailty in patients with ischemic heart disease.

Finally, an ounce of prevention is worth a pound of cure. In this context, there is a need to study patients with prefrailty in midlife to see whether interventions that can improve physical function and reduce frailty can delay or prevent the development of frailty in later life when the risk of CVD is highest[6] (Figure 3).

ARTICLE INFORMATION

Affiliations

Department of Geriatric Medicine, Cork University Hospital, Cork, Ireland (K.J.); Department of Internal Medicine, Yale University School of Medicine, New Haven, CT (Y.J., M.G.N.); University of Connecticut, Hartford, CT (M.K.); University of Texas Health Science Center at Houston, TX (M.J.K.); VA Boston Healthcare System, Boston, MA (S.Q., A.R.O.); Department of Medicine, Beth Israel Deaconess Medical Center, Boston, MA (A.L.T.); British Heart Foundation Cardiovascular Research Centre, University of Glasgow, UK (J.H.B.); Department of Cardiology, Rigshospitalet Copenhagen University Hospital, Copenhagen, Denmark (J.H.B.); Department of Cardiology, Zealand University Hospital, Roskilde, Denmark (J.H.B.); Johns Hopkins University School of Medicine, Baltimore, MD (A.A.D.); The Inova Center

of Outcomes Research, Inova Heart and Vascular Institute, Baltimore, MD (A.A.D.); Department of Medicine (Geriatrics and Cardiology), University of Pittsburgh, PA (D.E.F.); Pittsburgh GRECC (Geriatrics Research, Education and Clinical Center), VA Pittsburgh Healthcare System, Pittsburgh, PA (D.E.F.); and Division of Aging, Brigham and Women's Hospital, Harvard Medical School, Boston, MA (A.R.O.).

Sources of Funding

Dr Nanna reports current research support from the ACC Foundation supported by the George F. and Ann Harris Bellows Foundation, the Patient-Centered Outcomes Research Institute (PCORI), the Yale Claude D. Pepper Older Americans Independence Center (P30AG021342), and the National Institute on Aging/National Institutes of Health from R03AG074067 (GEMSSTAR award), and consulting fees from HeartFlow Inc. Dr Forman receives research funding support from NIAAG058883, R01AG060499, U19AG065188, R01 AG073633, R01AG077179, and P30AG024827; VA RR&D 1I21RX004409 and HSR&D I01 HX003518; and PCORI IHS-2021C3-24 147. Dr Damluji receives research funding from the Pepper Scholars Program of the Johns Hopkins University Claude D. Pepper Older Americans Independence Center (OAIC) funded by the NIA P30-AG021334, and receives mentored patient-oriented research career development award from the National Heart, Lung, and Blood Institute K23-HL153771-01. He also reports a grant from Medtronic unrelated to this work. Dr Butt reports advisory board honoraria from AstraZeneca and Bayer; consultant honoraria from Novartis and AstraZeneca; and travel grants from AstraZeneca unrelated to this work. Dr Orkaby receives research funding support from NIA R01AG071807, U19AG065188, R01AG071807, and the Boston Older Americans Independence Center Pepper Center, NIA P30-AG031679.

Disclosures

None.

REFERENCES

1. Vespa J, Armstrong DM, Medina L. *Demographic Turning Points for the United States: Population Projections for 2020 to 2060*. Suitland: U.S. Census Bureau; 2020. Report Number P25-1144
2. Clegg A, Young J, Iliffe S, Rikkert MO, Rockwood K. Frailty in elderly people. *Lancet*. 2013;381:752–762. doi: 10.1016/S0140-6736(12)62167-9
3. Rosenberg IH. Sarcopenia: origins and clinical relevance. *J Nutr*. 1997;127:990S–991S. doi: 10.1093/jn/127.5.990S
4. Aidoud A, Gana W, Poitau F, Debacq C, Leroy V, Nkodo JA, Poupin P, Angoulvant D, Fougere B. High prevalence of geriatric conditions among older adults with cardiovascular disease. *J Am Heart Assoc*. 2023;12:e026850. doi: 10.1161/JAHA.122.026850
5. Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, Seeman T, Tracy R, Kop WJ, Burke G, et al. Frailty in older adults: evidence for a phenotype. *J Gerontol A Biol Sci Med Sci*. 2001;56:M146–M156. doi: 10.1093/gerona/56.3.M146
6. Ijaz N, Buta B, Xue QL, Mohess DT, Bushan A, Tran H, Batchelor W, de Filippi CR, Walston JD, Bandeen-Roche K. Interventions for frailty among older adults with cardiovascular disease: JACC state-of-the-art review. *J Am Coll Cardiol*. 2022;79:482–503. doi: 10.1016/j.jacc.2021.11.029
7. Marinus N, Vigorito C, Giallauria F, Haenen L, Jansegers T, Dendale P, Feys P, Meesen R, Timmermans A, Spildooren J, et al. Frailty is highly prevalent in specific cardiovascular diseases and females, but significantly worsens prognosis in all affected patients: a systematic review. *Ageing Res Rev*. 2021;66:101233. doi: 10.1016/j.arr.2020.101233
8. Damluji AA, Chung SE, Xue QL, Hasan RK, Moscucci M, Forman DE, Bandeen-Roche K, Batchelor W, Walston JD, Resar JR, et al. Frailty and cardiovascular outcomes in the National Health and Aging Trends Study. *Eur Heart J*. 2021;42:3856–3865. doi: 10.1093/eurheartj/ehab468
9. López-Otín C, Blasco MA, Partridge L, Serrano M, Kroemer G. Hallmarks of aging: an expanding universe. *Cell*. 2023;186:243–278. doi: 10.1016/j.cell.2022.11.001
10. Xu Y, Wang M, Chen D, Jiang X, Xiong Z. Inflammatory biomarkers in older adults with frailty: a systematic review and meta-analysis of cross-sectional studies. *Aging Clin Exp Res*. 2022;34:971–987. doi: 10.1007/s40520-021-02022-7
11. Cesari M, Penninx BW, Newman AB, Kritchevsky SB, Nicklas BJ, Sutton-Tyrrell K, Rubin SM, Ding J, Simonsick EM, Harris TB, et al. Inflammatory markers and onset of cardiovascular events: results from the health abc study. *Circulation*. 2003;108:2317–2322. doi: 10.1161/01.CIR.0000097109.90783.FC
12. Kaptoge S, Di Angelantonio E, Lowe G, Pepys MB, Thompson SG, Collins R, Danesh J. C-reactive protein concentration and risk of coronary heart disease, stroke, and mortality: an individual participant meta-analysis. *Lancet*. 2010;375:132–140. doi: 10.1016/S0140-6736(09)61717-7
13. Ashar FN, Zhang Y, Longchamps RJ, Lane J, Moes A, Grove ML, Mychaleckyj JC, Taylor KD, Coresh J, Rotter JI, et al. Association of mitochondrial DNA copy number with cardiovascular disease. *JAMA Cardiol*. 2017;2:1247–1255. doi: 10.1001/jamacardio.2017.3683
14. Jiang X, Xu X, Ding L, Lu J, Zhu H, Zhao K, Zhu S, Xu Q. The association between metabolic syndrome and presence of frailty: a systematic review and meta-analysis. *Eur Geriat Med*. 2022;13:1047–1056. doi: 10.1007/s41999-022-00688-4
15. Shakya S, Bajracharya R, Ledbetter L, Cary MP Jr. The association between cardiometabolic risk factors and frailty in older adults: a systematic review. *Innov Aging*. 2022;6:igac032. doi: 10.1093/geroni/igac032
16. Qu T, Yang H, Walston JD, Fedarko NS, Leng SX. Upregulated monocytic expression of CXC chemokine ligand 10 (CXCL-10) and its relationship with serum interleukin-6 levels in the syndrome of frailty. *Cytokine*. 2009;46:319–324. doi: 10.1016/j.cyto.2009.02.015
17. Liu C, Li C. C-reactive protein and cardiovascular diseases: a synthesis of studies based on different designs. *Eur J Prev Cardiol*. 2023;30:1593–1596. doi: 10.1093/eurjpc/zwad116
18. Münzel T, Camici GG, Maack C, Bonetti NR, Fuster V, Kovacic JC. Impact of oxidative stress on the heart and vasculature: part 2 of a 3-part series. *J Am Coll Cardiol*. 2017;70:212–229. doi: 10.1016/j.jacc.2017.05.035
19. Shi Y, Zhang H, Huang S, Yin L, Wang F, Luo P, Huang H. Epigenetic regulation in cardiovascular disease: mechanisms and advances in clinical trials. *Signal Transduct Target Ther*. 2022;7:200. doi: 10.1038/s41392-022-01055-2
20. Liu X, Tou NX, Gao Q, Gwee X, Wee SL, Ng TP. Frailty and risk of cardiovascular disease and mortality. *PLoS One*. 2022;17:e0272527. doi: 10.1371/journal.pone.0272527
21. Sergi G, Veronese N, Fontana L, de Rui M, Bolzetta F, Zambon S, Corti MC, Baggio G, Toffanello ED, Crepaldi G, et al. Pre-frailty and risk of cardiovascular disease in elderly men and women: the Pro.V.A. Study. *J Am Coll Cardiol*. 2015;65:976–983. doi: 10.1016/j.jacc.2014.12.040
22. Veronese N, Cereda E, Stubbs B, Solmi M, Luchini C, Manzato E, Sergi G, Manu P, Harris T, Fontana L, et al. Risk of cardiovascular disease morbidity and mortality in frail and pre-frail older adults: results from a meta-analysis and exploratory meta-regression analysis. *Ageing Res Rev*. 2017;35:63–73. doi: 10.1016/j.arr.2017.01.003
23. Shrauner W, Lord EM, Nguyen XT, Song RJ, Galloway A, Gagnon DR, Driver JA, Gaziano JM, Wilson PW, Djousse L, et al. Frailty and cardiovascular mortality in more than 3 million us veterans. *Eur Heart J*. 2022;43:818–826. doi: 10.1093/eurheartj/ehab850
24. Vetrano DL, Palmer K, Marengoni A, Marzetti E, Lattanzio F, Roller-Wirnsberger R, Lopez Samaniego L, Rodríguez-Mañas L, Bernabei R, Onder G. Frailty and multimorbidity: a systematic review and meta-analysis. *J Gerontol A Biol Sci Med Sci*. 2019;74:659–666. doi: 10.1093/gerona/gly110
25. Kumar M, Orkaby A, Tighe C, Villareal DT, Billingsley H, Nanna MG, Kwak MJ, Rohant N, Patel S, Goyal P, et al. Life's essential 8: optimizing health in older adults. *JACC Adv*. 2023;2:100560. doi: 10.1016/j.jacadv.2023.100560
26. Wang Q, Zhou C, Dong C, Zhang J, Xie Z, Sun H, Fu C, Hao W, Zhu D. Midlife life's simple 7, psychosocial health, and physical frailty, hospital frailty, and comprehensive frailty 10years later. *Nutrients*. 2023;15:2412. doi: 10.3390/nu15102412
27. Graciani A, García-Esquinas E, López-García E, Banegas JR, Rodríguez-Artalejo F. Ideal cardiovascular health and risk of frailty in older adults. *Circ Cardiovasc Qual Outcomes*. 2016;9:239–245. doi: 10.1161/CIRCOUTCOMES.115.002294
28. Pahor M, Guralnik JM, Ambrosius WT, Blair S, Bonds DE, Church TS, Espeland MA, Fielding RA, Gill TM, Groessl EJ, et al. Effect of structured physical activity on prevention of major mobility disability in older adults: the life study randomized clinical trial. *JAMA*. 2014;311:2387–2396. doi: 10.1001/jama.2014.5616
29. Simpson FR, Pajewski NM, Beavers KM, Kritchevsky S, McCaffery J, Nicklas BJ, Wing RR, Bertoni A, Ingram F, Ojeranti D, et al. Does

the impact of intensive lifestyle intervention on cardiovascular disease risk vary according to frailty as measured via deficit accumulation? *J Gerontol A Biol Sci Med Sci*. 2021;76:339–345. doi: 10.1093/gerona/glaa153
30. Rashidi Pour Fard N, Amirabdollahian F, Haghighatdoost F. Dietary patterns and frailty: a systematic review and meta-analysis. *Nutr Rev*. 2019;77:498–513.
31. Ward RE, Orkaby AR, Chen J, Hshieh TT, Driver JA, Gaziano JM, Djousse L. Association between diet quality and frailty prevalence in the physicians' health study. *J Am Geriatr Soc*. 2019;68:770–776. doi: 10.1111/jgs.16286
32. Tanaka T, Talegawkar SA, Jin Y, Bandinelli S, Ferrucci L. Association of adherence to the mediterranean-style diet with lower frailty index in older adults. *Nutrients*. 2021;13:1129. doi: 10.3390/nu13041129
33. Coker RH, Wolfe RR. Weight loss strategies in the elderly: a clinical conundrum. *Obesity (Silver Spring)*. 2018;26:22–28. doi: 10.1002/oby.21961
34. Bachi K, Sierra S, Volkow ND, Goldstein RZ, Alia-Klein N. Is biological aging accelerated in drug addiction? *Curr Opin Behav Sci*. 2017;13:34–39. doi: 10.1016/j.cobeha.2016.09.007
35. Ersche KD, Clark L, London M, Robbins TW, Sahakian BJ. Profile of executive and memory function associated with amphetamine and opiate dependence. *Neuropsychopharmacology*. 2006;31:1036–1047. doi: 10.1038/sj.npp.1300889
36. Mutz J, Choudhury U, Zhao J, Dregan A. Frailty in individuals with depression, bipolar disorder and anxiety disorders: longitudinal analyses of all-cause mortality. *BMC Med*. 2022;20:274. doi: 10.1186/s12916-022-02474-2
37. Davies K, Maharani A, Chandola T, Todd C, Pendleton N. The longitudinal relationship between loneliness, social isolation, and frailty in older adults in England: a prospective analysis. *Lancet Healthy Longev*. 2021;2:e70–e77. doi: 10.1016/S2666-7568(20)30038-6
38. Collard RM, Boter H, Schoevers RA, Oude Voshaar RC. Prevalence of frailty in community-dwelling older persons: a systematic review. *J Am Geriatr Soc*. 2012;60:1487–1492. doi: 10.1111/j.1532-5415.2012.04054.x
39. Harttgen K, Kowal P, Strulik H, Chatterji S, Vollmer S. Patterns of frailty in older adults: comparing results from higher and lower income countries using the Survey of Health, Ageing and Retirement in Europe (SHARE) and the Study on Global AGEing and Adult Health (SAGE). *PLoS One*. 2013;8:e75847. doi: 10.1371/journal.pone.0075847
40. Myers V, Drory Y, Goldbourt U, Gerber Y. Multilevel socioeconomic status and incidence of frailty post myocardial infarction. *Int J Cardiol*. 2014;170:338–343. doi: 10.1016/j.ijcard.2013.11.009
41. Hu Y, Wang X, Lin L, Huan J, Li Y, Zhang L. Association of remnant cholesterol with frailty: findings from observational and Mendelian randomization analyses. *Lipids Health Dis*. 2023;22:115. doi: 10.1186/s12944-023-01882-4
42. Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, Braun LT, de Ferranti S, Faiella-Tommasino J, Forman DE, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APHA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: executive summary: a report of the american college of cardiology/american heart association task force on clinical practice guidelines. *Circulation*. 2019;139:e1082–e1143. doi: 10.1161/CIR.0000000000000625
43. Orkaby AR, Driver JA, Ho YL, Lu B, Costa L, Honerlaw J, Galloway A, Vassy JL, Forman DE, Gaziano JM, et al. Association of statin use with all-cause and cardiovascular mortality in us veterans 75 years and older. *JAMA*. 2020;324:68–78. doi: 10.1001/jama.2020.7848
44. Armitage J, Baigent C, Barnes E, Betteridge DJ, Blackwell L, Blazing M, Bowman L, Braunwald E, Byington R, Cannon C, et al. Efficacy and safety of statin therapy in older people: a meta-analysis of individual participant data from 28 randomised controlled trials. *Lancet*. 2019;393:407–415. doi: 10.1016/S0140-6736(18)31942-1
45. Ridker PM, Lonn E, Paynter NP, Glynn R, Yusuf S. Primary prevention with statin therapy in the elderly: new meta-analyses from the contemporary jupiter and hope-3 randomized trials. *Circulation*. 2017;135:1979–1981. doi: 10.1161/CIRCULATIONAHA.117.028271
46. Orkaby AR, Lu B, Ho YL, Treu T, Galloway A, Wilson PW, Cho K, Gaziano JM, Alexander KP, Gagnon DR, et al. New statin use, mortality and first cardiovascular events in older us veterans by frailty status. *J Am Geriatr Soc*. 2024;72:410–422. doi: 10.1111/jgs.18700
47. Wong E, Backholer K, Gearon E, Harding J, Freak-Poli R, Stevenson C, Peeters A. Diabetes and risk of physical disability in adults: a systematic review and meta-analysis. *Lancet Diabetes Endocrinol*. 2013;1:106–114. doi: 10.1016/S2213-8587(13)70046-9
48. Cao X, Li X, Zhang J, Sun X, Yang G, Zhao Y, Li S, Hoogendijk EO, Wang X, Zhu Y, et al. Associations between frailty and the increased risk of adverse outcomes among 38,950 UK biobank participants with prediabetes: prospective cohort study. *JMIR Public Health Surveill*. 2023;9:e45502. doi: 10.2196/45502
49. Sinclair AJ, Abdelhafiz AH. Multimorbidity, frailty and diabetes in older people-identifying interrelationships and outcomes. *J Pers Med*. 2022;12:1911. doi: 10.3390/jpm12111911
50. ElSayed NA, Aleppo G, Aroda VR, Bannuru RR, Brown FM, Bruemmer D, Collins BS, Hilliard ME, Isaacs D, Johnson EL, et al. 13. Older adults: standards of care in diabetes—2023. *Diabetes Care*. 2022;46:S216–S229. doi: 10.2337/dc23-S013
51. Giugliano D, Scappaticcio L, Longo M, Bellastella G, Esposito K. Glp-1 receptor agonists vs. Sglt-2 inhibitors: the gap seems to be leveling off. *Cardiovasc Diabetol*. 2021;20:205. doi: 10.1186/s12933-021-01400-9
52. Hazuda HP, Pan Q, Florez H, Luchsinger JA, Crandall JP, Venditti EM, Golden SH, Kriska AM, Bray GA. Association of intensive lifestyle and metformin interventions with frailty in the diabetes prevention program outcomes study. *J Gerontol A Biol Sci Med Sci*. 2021;76:929–936. doi: 10.1093/gerona/glaa295
53. Simpson FR, Justice JN, Pilla SJ, Kritchevsky SB, Boyko EJ, Munshi MN, Ferris CK, Espeland MA; Group LAR. An examination of whether diabetes control and treatments are associated with change in frailty index across 8 years: an ancillary exploratory study from the action for health in diabetes (look ahead) trial. *Diabetes Care*. 2023;46:519–525. doi: 10.2337/dc22-1728
54. Vetrano DL, Palmer KM, Galluzzo L, Giampaoli S, Marengoni A, Bernabei R, Onder G; Group JAAW. Hypertension and frailty: a systematic review and meta-analysis. *BMJ Open*. 2018;8:e024406. doi: 10.1136/bmjopen-2018-024406
55. Benetos A, Petrovic M, Strandberg T. Hypertension management in older and frail older patients. *Circ Res*. 2019;124:1045–1060. doi: 10.1161/CIRCRESAHA.118.313236
56. Whelton PK, Carey RM, Aronow WS, Casey DE Jr, Collins KJ, Dennison Himmelfarb C, DePalma SM, Gidding S, Jamerson KA, Jones DW, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APHA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Hypertension*. 2018;71:1269–1324. doi: 10.1161/HYP.0000000000000066
57. Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M, Clement DL, Coca A, de Simone G, Dominiczak A, et al. ESC/ESH Guidelines for the management of arterial hypertension: the Task Force for the management of arterial hypertension of the European Society of Cardiology (ESC) and the European Society of Hypertension (ESH). *J Hypertens*. 2018;36:1953–2041. doi: 10.1093/eurheartj/ehy339
58. Odden MC, Anderson TS. How low should you go in the presence of frailty? *Hypertension*. 2022;79:33–35. doi: 10.1161/HYPERTENSIONAHA.121.18373
59. Wang Z, Du X, Hua C, Li W, Zhang H, Liu X, Wang Y, Jiang C, Guo J, Lv Q, et al. The effect of frailty on the efficacy and safety of intensive blood pressure control: a post hoc analysis of the sprint trial. *Circulation*. 2023;148:565–574. doi: 10.1161/CIRCULATIONAHA.123.064003
60. Krishnaswami A, Rich MW, Kwak MJ, Goyal P, Forman DE, Damluji AA, Solomon M, Rana JS, Kado DM, Odden MC. The association of intensive blood pressure treatment and non-fatal cardiovascular or serious adverse events in older adults with mortality: mediation analysis in sprint. *Eur J Prev Cardiol*. 2023;30:996–1004. doi: 10.1093/eurjpc/zwad132
61. Arnett DK, Blumenthal RS, Albert MA, Buroker AB, Goldberger ZD, Hahn EJ, Himmelfarb CD, Khera A, Lloyd-Jones D, McEvoy JW, et al. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: A report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation*. 2019;140:e596–e646. doi: 10.1161/CIR.0000000000000678
62. McNeil JJ, Nelson MR, Woods RL, Lockery JE, Wolfe R, Reid CM, Kirpach B, Shah RC, Ives DG, Storey E, et al. Effect of aspirin on all-cause mortality in the healthy elderly. *N Engl J Med*. 2018;379:1519–1528. doi: 10.1056/NEJMoa1803955
63. Orkaby AR, Yang L, Dufour AB, Travison TG, Sesso HD, Driver JA, Djousse L, Gaziano JM. Association between long-term aspirin use

and frailty in men: the physicians' health study. *J Gerontol A Biol Sci Med Sci*. 2021;76:1077–1083. doi: 10.1093/gerona/glaa233
64. Espinoza SE, Woods RL, Ekram A, Ernst ME, Polekhina G, Wolfe R, Shah RC, Ward SA, Storey E, Nelson MR, et al. The effect of low-dose aspirin on frailty phenotype and frailty index in community-dwelling older adults in the aspirin in reducing events in the elderly study. *J Gerontol A Biol Sci Med Sci*. 2022;77:2007–2014. doi: 10.1093/gerona/glab340
65. Andreotti F, Geisler T, Collet J-P, Gigante B, Gorog DA, Halvorsen S, Lip GY, Morais J, Navarese EP, Patrono C, et al. Acute, periprocedural and longterm antithrombotic therapy in older adults: 2022 update by the ESC Working Group on Thrombosis. *Eur Heart J*. 2022;44:262–279. doi: 10.1093/eurheartj/ehac515
66. Mauri L, Kereiakes DJ, Yeh RW, Driscoll-Shempp P, Cutlip DE, Steg PG, Normand SL, Braunwald E, Wiviott SD, Cohen DJ, et al. Twelve or 30 months of dual antiplatelet therapy after drug-eluting stents. *N Engl J Med*. 2014;371:2155–2166. doi: 10.1056/NEJMoa1409312
67. Khan SU, Singh M, Valavoor S, Khan MU, Lone AN, Khan MZ, Khan MS, Mani P, Kapadia SR, Michos ED, et al. Dual antiplatelet therapy after percutaneous coronary intervention and drug-eluting stents: a systematic review and network meta-analysis. *Circulation*. 2020;142:1425–1436. doi: 10.1161/CIRCULATIONAHA.120.046308
68. Capranzano P, Angiolillo DJ. Antithrombotic management of elderly patients with coronary artery disease. *JACC Cardiovasc Interv*. 2021;14:723–738. doi: 10.1016/j.jcin.2021.01.040
69. Nkomo VT, Gardin JM, Skelton TN, Gottdiener JS, Scott CG, Enriquez-Sarano M. Burden of valvular heart diseases: a population-based study. *Lancet*. 2006;368:1005–1011. doi: 10.1016/S0140-6736(06)69208-8
70. Afilalo J, Lauck S, Kim DH, Lefèvre T, Piazza N, Lachapelle K, Martucci G, Lamy A, Labinaz M, Peterson MD, et al. Frailty in older adults undergoing aortic valve replacement: the FRAILTY-AVR study. *J Am Coll Cardiol*. 2017;70:689–700. doi: 10.1016/j.jacc.2017.06.024
71. Huang H, Liu J, Bao K, Huang X, Huang D, Wei H, Remutula N, Tuersun T, Lai W, Li Q, et al. Prevalence and mortality of moderate or severe mitral regurgitation among patients undergoing percutaneous coronary intervention with or without heart failure: results from CIN study with 28,358 patients. *Front Cardiovasc Med*. 2022;9:796447. doi: 10.3389/fcvm.2022.796447
72. O'Neill DE, Forman DE. Cardiovascular care of older adults. *BMJ*. 2021;374:n1593. doi: 10.1136/bmj.n1593
73. Metze C, Iliadis C, Körber MI, Stein JV, Halbach M, Baldus S, Pfister R. Disentangling heart failure and physical frailty. *JACC Heart Fail*. 2023;11:972–982. doi: 10.1016/j.jchf.2023.04.011
74. Strange JE, Christensen DM, Sindet-Pedersen C, Schou M, Falkentoft AC, Østergaard L, Butt JH, Graversen PL, Køber L, Gislason G, et al. Frailty and recurrent hospitalization after transcatheter aortic valve replacement. *J Am Heart Assoc*. 2023;12:e029264. doi: 10.1161/JAHA.122.029264
75. Surman TL, Abrahams JM, Kim J, Surman HE, Roberts-Thomson R, Montarello JM, Edwards J, Worthington M, Beltrame J. Quality of life and frailty outcomes following surgical and transcatheter aortic valve replacement. *J Cardiothorac Surg*. 2022;17:113. doi: 10.1186/s13019-022-01876-w
76. Damluji AA, Huang J, Bandeen-Roche K, Forman DE, Gerstenblith G, Moscucci M, Resar JR, Varadhan R, Walston JD, Segal JB. Frailty among older adults with acute myocardial infarction and outcomes from percutaneous coronary interventions. *J Am Heart Assoc*. 2019;8:e013686. doi: 10.1161/JAHA.119.013686
77. Sanchis J, Nunez E, Barrabes JA, Marin F, Consuegra-Sanchez L, Ventura S, Valero E, Roque M, Bayes-Genis A, Del Blanco BG, et al. Randomized comparison between the invasive and conservative strategies in comorbid elderly patients with non-st elevation myocardial infarction. *Eur J Intern Med*. 2016;35:89–94. doi: 10.1016/j.ejim.2016.07.003
78. Sanchis J, Bueno H, Miñana G, Guerrero C, Martí D, Martínez-Sellés M, Domínguez-Pérez L, Díez-Villanueva P, Barrabés JA, Marín F, et al. Effect of routine invasive vs conservative strategy in older adults with frailty and non–st-segment elevation acute myocardial infarction: a randomized clinical trial. *JAMA Intern Med*. 2023;183:407–415. doi: 10.1001/jamainternmed.2023.0047
79. Lee JA, Yanagawa B, An KR, Arora RC, Verma S, Friedrich JO. Frailty and pre-frailty in cardiac surgery: a systematic review and meta-analysis of 66,448 patients. *J Cardiothorac Surg*. 2021;16:184. doi: 10.1186/s13019-021-01541-8
80. Solomon J, Moss E, Morin JF, Langlois Y, Cecere R, de Varennes B, Lachapelle K, Piazza N, Martucci G, Bendayan M, et al. The essential frailty toolset in older adults undergoing coronary artery bypass surgery. *J Am Heart Assoc*. 2021;10:e020219. doi: 10.1161/JAHA.120.020219
81. Kochar A, Deo SV, Charest B, Peterman-Rocha F, Elgudin Y, Chu D, Yeh RW, Rao SV, Kim DH, Driver JA, et al. Preoperative frailty and adverse outcomes following coronary artery bypass grafting surgery in us veterans. *J Am Geriatr Soc*. 2023;71:2736–2747. doi: 10.1111/jgs.18390
82. Smetana GW, Ho JE, Orkaby AR, Reynolds EE. How would you manage this patient with heart failure with preserved ejection fraction?: Grand rounds discussion from beth Israel deaconess medical center. *Ann Intern Med*. 2023;176:1656–1665. doi: 10.7326/M23-2384
83. Butt JH, Dewan P, Jhund PS, Anand IS, Atar D, Ge J, Desai AS, Echeverria LE, Køber L, Lam CSP, et al. Sacubitril/valsartan and frailty in patients with heart failure and preserved ejection fraction. *J Am Coll Cardiol*. 2022;80:1130–1143. doi: 10.1016/j.jacc.2022.06.037
84. Butt JH, Dewan P, Merkely B, Belohlávek J, Drożdż J, Kitakaze M, Inzucchi SE, Kosiborod MN, Martinez FA, Tereshchenko S, et al. Efficacy and safety of dapagliflozin according to frailty in heart failure with reduced ejection fraction: a post hoc analysis of the DAPA-HF trial. *Ann Intern Med*. 2022;175:820–830. doi: 10.7326/M21-4776
85. Sanders NA, Supiano MA, Lewis EF, Liu J, Claggett B, Pfeffer MA, Desai AS, Sweitzer NK, Solomon SD, Fang JC. The frailty syndrome and outcomes in the topcat trial. *Eur J Heart Fail*. 2018;20:1570–1577. doi: 10.1002/ejhf.1308
86. Segar MW, Keshvani N, Singh S, Patel L, Parsa S, Betts T, Reeves GR, Mentz RJ, Forman DE, Razavi M, et al. Frailty status modifies the efficacy of icd therapy for primary prevention among patients with HF. *JACC Heart Fail*. 2024;12:757–767. doi: 10.1016/j.jchf.2023.06.009
87. Heidenreich PA, Bozkurt B, Aguilar D, Allen LA, Byun JJ, Colvin MM, Deswal A, Drazner MH, Dunlay SM, Evers LR, et al. 2022 AHA/ACC/HFSA Guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation*. 2022;145:e895–e1032. doi: 10.1161/CIR.0000000000001073
88. Guo Q, Du X, Ma CS. Atrial fibrillation and frailty. *J Geriatr Cardiol*. 2020;17:105–109.
89. January CT, Wann LS, Calkins H, Chen LY, Cigarroa JE, Cleveland JC Jr, Ellinor PT, Ezekowitz MD, Field ME, Furie KL, et al. 2019 AHA/ACC/HRS focused update of the 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society in collaboration with the Society of Thoracic Surgeons. *Circulation*. 2019;140:e125–e151. doi: 10.1161/CIR.0000000000000665
90. Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomström-Lundqvist C, Boriani G, Castella M, Dan GA, Dilaveris PE, et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS) The Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. *Eur Heart J*. 2021;42:373–498.
91. Oqab Z, Pournazari P, Sheldon RS. What is the impact of frailty on prescription of anticoagulation in elderly patients with atrial fibrillation? A systematic review and meta-analysis. *J Atr Fibrillation*. 2018;10:1870. doi: 10.4022/jafib.1870
92. Kim D, Yang PS, Sung JH, Jang E, Yu HT, Kim TH, Uhm JS, Kim JY, Pak HN, Lee MH, et al. Effectiveness and safety of anticoagulation therapy in frail patients with atrial fibrillation. *Stroke*. 2022;53:1873–1882. doi: 10.1161/STROKEAHA.121.036757
93. Akashi S, Oguri M, Ikeno E, Manita M, Taura J, Watanabe S, Hayashi T, Akao M, Okumura K, Akishita M, et al. Outcomes and safety of very-low-dose edoxaban in frail patients with atrial fibrillation in the ELDERCARE-AF randomized clinical trial. *JAMA Netw Open*. 2022;5:e2228500. doi: 10.1001/jamanetworkopen.2022.28500
94. Joosten LP, van Doorn S, van de Ven PM, Köhlen BT, Nierman MC, Koek HL, Hemels ME, Huisman MV, Kruip M, Faber LM, et al. Safety of switching from a vitamin k antagonist to a non-vitamin k antagonist oral anticoagulant in frail older patients with atrial fibrillation: results of the FRAIL-AF randomized controlled trial. *Circulation*. 2024;149:279–289. doi: 10.1161/CIRCULATIONAHA.123.066485

95. Troy AL, Herzig SJ, Trivedi S, Anderson TS. Initiation of oral anticoagulation in us older adults newly diagnosed with atrial fibrillation during hospitalization. *J Am Geriatr Soc*. 2023;71:2748–2758. doi: 10.1111/jgs.18375
96. Kirchhof P, Camm AJ, Goette A, Brandes A, Eckardt L, Elvan A, Fetsch T, van Gelder IC, Haase D, Haegeli LM, et al. Early rhythm-control therapy in patients with atrial fibrillation. *N Engl J Med*. 2020;383:1305–1316. doi: 10.1056/NEJMoa2019422
97. Nguyen TN, Cumming RG, Hilmer SN. Atrial fibrillation in older inpatients: are there any differences in clinical characteristics and pharmacological treatment between the frail and the non-frail? *Intern Med J*. 2016;46:86–95. doi: 10.1111/imj.12912
98. Madhavan M, Holmes DN, Piccini JP, Ansell JE, Fonarow GC, Hylek EM, Kowey PR, Mahaffey KW, Thomas L, Peterson ED, et al. Association of frailty and cognitive impairment with benefits of oral anticoagulation in patients with atrial fibrillation. *Am Heart J*. 2019;211:77–89. doi: 10.1016/j.ahj.2019.01.005
99. Yu GI, Kim D, Sung JH, Jang E, Yu HT, Kim TH, Pak HN, Lee MH, Lip GY, Yang PS, et al. Impact of frailty on early rhythm control outcomes in older adults with atrial fibrillation: a nationwide cohort study. *Front Cardiovasc Med*. 2022;9:1050744. doi: 10.3389/fcvm.2022.1050744
100. Yang PS, Sung JH, Kim D, Jang E, Yu HT, Kim TH, Uhm JS, Kim JY, Pak HN, Lee MH, et al. Frailty and the effect of catheter ablation in the elderly population with atrial fibrillation—a real-world analysis. *Circ J*. 2021;85:1305–1313. doi: 10.1253/circj.CJ-20-1062
101. Mlynarska A, Mlynarski R, Marcisz C, Golba KS. Modified frailty as a novel factor in predicting the maintenance of the sinus rhythm after electrical cardioversion of atrial fibrillation in the elderly population. *Clin Interv Aging*. 2020;15:1193–1199. doi: 10.2147/CIA.S255853
102. 2023 American Geriatrics Society Beers Criteria® Update Expert Panel. American Geriatrics Society 2023 updated AGS Beers Criteria® for potentially inappropriate medication use in older adults. *J Am Geriatr Soc*. 2023;71:2052–2081. doi: 10.1111/jgs.18372
103. Savelieva I, Fumagalli S, Kenny RA, Anker S, Benetos A, Boriani G, Bunch J, Dagres N, Dubner S, Fauchier L, et al. EHRA expert consensus document on the management of arrhythmias in frailty syndrome, endorsed by the heart rhythm society (HRS), Asia Pacific Heart Rhythm Society (APHRS), Latin America Heart Rhythm Society (LAHRS), and Cardiac Arrhythmia Society of Southern Africa (CASSA). *Europace*. 2023;25:1249–1276. doi: 10.1093/europace/euac123
104. van Gelder IC, Groenveld HF, Crijns HJ, Tuininga YS, Tijssen JG, Alings AM, Hillege HL, Bergsma-Kadijk JA, Cornel JH, Kamp O, et al. Lenient versus strict rate control in patients with atrial fibrillation. *N Engl J Med*. 2010;362:1363–1373. doi: 10.1056/NEJMoa1001337
105. Damluji AA, Ijaz N, Chung SE, Xue QL, Hasan RK, Batchelor WB, Orkaby AR, Kochar A, Nanna MG, Roth DL, et al. Hierarchical development of physical frailty and cognitive impairment and their association with incident cardiovascular disease. *JACC Adv*. 2023;2:100318. doi: 10.1016/j.jacadv.2023.100318
106. Damluji AA, Cohen MG. The influence of frailty on cardiovascular disease: the time for a "Frailty Academic Research Consortium" is now! *Circ Cardiovasc Interv*. 2022;15:e011669. doi: 10.1161/CIRCINTERVENTIONS.121.011669
107. Castro-Dominguez YS, Wang Y, Minges KE, McNamara RL, Spertus JA, Dehmer GJ, Messenger JC, Lavin K, Anderson C, Blankinship K, et al. Predicting in-hospital mortality in patients undergoing percutaneous coronary intervention. *J Am Coll Cardiol*. 2021;78:216–229. doi: 10.1016/j.jacc.2021.04.067
108. Dodson JA, Hajduk AM, Geda M, Krumholz HM, Murphy TE, Tsang S, Tinetti ME, Nanna MG, McNamara R, Gill TM, et al. Predicting 6-month mortality for older adults hospitalized with acute myocardial infarction: a cohort study. *Ann Intern Med*. 2020;172:12–21. doi: 10.7326/M19-0974
109. Nanna MG, Sutton NR, Kochar A, Rymer JA, Lowenstern AM, Gackenbach G, Hummel SL, Goyal P, Rich MW, Kirkpatrick JN, et al. Assessment and management of older adults undergoing PCI, part 1: a JACC: advances expert panel. *JACC Adv*. 2023;2:100389. doi: 10.1016/j.jacadv.2023.100389
110. Nanna MG, Sutton NR, Kochar A, Rymer JA, Lowenstern AM, Gackenbach G, Hummel SL, Goyal P, Rich MW, Kirkpatrick JN, et al. A geriatric approach to percutaneous coronary interventions in older adults, part II: A JACC: advances expert panel. *JACC Adv*. 2023;2:100421. doi: 10.1016/j.jacadv.2023.100421