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Frailty and Cardiovascular Mortality: A Narrative Review

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Abstract

Purpose of review: The goal of the narrative review is to provide an overview of the epidemiology of frailty in cardiovascular disease and cardiovascular mortality and discuss applications of frailty in cardiovascular care of older adults.

Recent findings: Frailty is highly prevalent in older adults with cardiovascular disease and is a robust, independent predictor of cardiovascular death. There is a growing interest in using frailty to inform management of cardiovascular disease either through pre- or post-treatment prognostication or by delineating treatment heterogeneity in which frailty serves to distinguish patients with differential harms or benefits from a given therapy.

Summary: Frailty can enable more individualized treatment in older adults with cardiovascular disease. Future studies are needed to standardize frailty assessment across cardiovascular trials and enable implementation of frailty assessment in cardiovascular clinical practice.

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Declarations

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Human and Animal Rights and Informed Consent

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Keywords

frailty cardiovascular disease; mortality

Introduction

Over 54 millions of Americans are aged 65 years or older, and this number is projected to reach 81 million in 2040.[1] Cardiovascular (CV) disease affects at least 75% of adults aged 60–79 years and up to 90% of octogenarians,[2] and cardiovascular disease (CVD) remains the leading cause of death in older adults, making prevention and management of CVD of paramount importance for successful and healthy aging. However, many evidence-based CV prevention tools and treatments for primary and secondary prevention are underutilized in older adults because of a paucity of data regarding their benefit and safety in a medically complex, real-world older population. This has, perhaps inadvertently, led to the lower use of preventive medications in older adults out of fear of causing harm, although older adults, particularly those who are frail, may be the most likely to benefit.[3, 4] Subgroup analyses of pivotal trials that include older adults are often conducted using an arbitrary age cutoff of ≥65 or ≥75 years. These cutoffs however do not capture the wide heterogeneity in physiologic reserve and functional capacity that is present in the older adult population.

Frailty, a multisystem syndrome characterized by lack of physiologic reserve to maintain homeostasis in the face of a stress and increased vulnerability to adverse health outcomes,[5, 6] has emerged as a critical marker of biological aging. When exposed to stressors (*e.g.,* exacerbation of a chronic illness, acute illness, or invasive procedures), frail older adults are at a disproportionately higher risk of disability, hospitalization, and mortality.[6, 7] Initially described by geriatricians, frailty entered the vernacular of cardiologists a decade ago when there was an increasing interest in risk stratification of elderly patients for invasive procedures such as surgical or transcatheter aortic valve replacement (TAVR).[8–10] Since then, frailty has emerged as a an important predictor of adverse outcomes in a wide range of CVD.[11, 12]

The objectives of this review are to: 1) review the concept of frailty and how it is measured; 2) summarize the epidemiology of frailty in CVD and the association between frailty and CV mortality; and 3) review potential applications of frailty in CV care of older adults to lower the risk of CVD mortality in this high risk population.

How is frailty defined and how can it be measured?

Although there are dozens of tools with which to measure frailty, two leading theories of frailty have emerged: the physical phenotype and the cumulative deficit approach (Figure 1). The physical phenotype was developed by Fried and colleagues in 2001 from data in the Cardiovascular Health Study,[6] and measures five interrelated characteristics: slow walking speed, weakness, weight loss, low physical activity, and low energy. This approach requires measuring time to walk 12–15 feet, measuring grip strength using a dynamometer, and estimating weekly energy expenditure based on patient's activity report. The presence of three or more of these physical deficits comprise the diagnosis of frailty. Phenotypic

frailty has been previously shown to be associated with a marked increase in the risk of all-cause and CVD mortality.[6, 13, 14] Despite its utility for assessing frailty in prospective studies, the physical phenotype approach may pose a challenge for implementation in high-volume clinical practices. Additionally, while the theory intentionally distinguishes frailty from disability and multimorbidity,[15] it is agnostic to the contribution of mental health, cognitive dysfunction, and social determinants of health to the frailty syndrome.[5]

Rockwood and colleagues developed the cumulative deficit approach of frailty in the late 1990s, based on the comprehensive geriatric assessment from the prospective Canadian Study of Health in Aging. This theory of frailty posits that health-related deficits are accumulated over a lifetime across many body systems. These deficits cover a broad range of systems, including comorbidities, physical function, cognitive function, nutritional status, mental health and others and can be counted to generate an index of frailty.[16, 17] A Rockwood frailty index (FI) is generally calculated by reviewing a minimum of 30 deficits, with indices including over 90 potential items. A higher FI has been consistently shown to be associated with CVD and all-cause mortality.[18],[19] While manually calculating a comprehensive geriatric assessment based frailty index may seem daunting in a busy clinical setting, there have been efforts to develop automated, electronic health record or claims-based frailty indices in United States- and United kingdom-based health systems that abstract commonly collected electronic health record data for inclusion in the frailty index.[19–22] Because the FI can be calculated from routinely collected health care data, it has become a versatile tool that can be applied to existing clinical and research data, including clinical trials.[23–30] However, the cumulative deficit approach has been criticized as too inclusive and challenging to disentangle from multimorbidity and disability.

Other common tools to define frailty include the Clinical Frailty Scale (CFS), the Edmonton Frail Scale, the FRAIL scale, and single items such 4 meter gait speed. CFS is a semi-quantitative tool that generates a score from 1 (very fit) to 9 (terminally ill) based on clinical assessment in the following domains: mobility, ability to perform activities of daily living and instrumental activities of daily living, physical activity level, energy level, and disease-specific symptoms.[31] It has been extensively studied in TAVR populations.[32] The Edmonton Frail Scale can be easily administered by non-geriatricians and assesses the following 9 domains: cognition, general health status, functional independence, social support, medication use, nutrition status, mood, continence, and functional performance.[33, 34] The FRAIL scale is another simple tool that quickly ascertains a patient's level of frailty as part of the clinical history. The FRAIL scale that asks five questions regarding fatigue, resistance, ambulation, chronic illnesses, and loss of weight as part of the patient's evaluation making it advantageous as a quick screening tool in settings where direct measurements are not readily available.[35, 36] While it is entirely based on self-report, the FRAIL scale has been is predictive of six-month all-cause mortality in patients aged 80 years or older with acute myocardial infarction, demonstrating its utility in the acute clinical setting.[37] While these frailty scales offer critical information in a multifaceted format, single measurements such as the 4-meter gait speed assessments are also feasible as a quick frailty screen.[36] Slow gait is a known predictor of CVD risk and mortality that also serves as a key marker of functional capacity.[38, 39] Each tool provides a framework in which to best manage patients based on their level of vulnerability.

Prevalence of Frailty

The prevalence of frailty varies across studies and populations based on which definition of frailty is used and populations with specific disease states.[14] It has been estimated to range widely between 4–59% depending on the population studied.[13, 40] Population studies have demonstrated some general trends such a two-fold higher prevalence among women, after adjusting for age, compared to men.[6, 41] More recent data has described frailty prevalence among Medicare beneficiaries at 9–10%[18] and up to 45% among Veterans aged 65 years and older.[42]

Frailty is more common in patients with CVD compared to the general population. In studies of older adults with coronary artery disease undergoing percutaneous coronary intervention, phenotypic frailty and a claims-based frailty index were present in 21% and 27% of the study populations, respectively.[43, 44] In a randomized controlled trial of functionally independent older adults hospitalized with decompensated heart failure (HF) irrespective of left ventricular ejection fraction, the prevalence of phenotypic frailty was 55%.[45] In a multicenter prospective cohort of patients with severe aortic stenosis, 25% of the patients undergoing surgical aortic valve replacement and 49% of those undergoing TAVR were estimated to have phenotypic frailty.[46] Among older adults with atrial fibrillation the prevalence is estimated at 14%. [47]

Bidirectional Association between Frailty and Cardiovascular Disease

CVD as a risk factor for frailty[19, 22, 48] is intuitive to clinical cardiologists – patients who are hospitalized with myocardial infarction, HF, and stroke can become deconditioned and debilitated. Frailty has also been associated with an increased incidence of CVD independent of traditional atherosclerotic cardiovascular disease risk factors.[49] In the National Health and Aging Trends Study, a prospective cohort of a national representative of Medicare beneficiaries aged ≥65 years, phenotypic frailty was associated with increased risk of newly diagnosed coronary artery disease (hazard ratio [HR] 1.35, 95% confidence interval [CI] 1.11–1.65), myocardial infarction (HR 1.95, 95% CI 1.31–2.90), stroke (HR 1.71, 95% CI 1.34–2.17), and peripheral artery disease (HR 1.80, 95% CI 1.44–2.27) after multivariable adjustment.[26] Similarly, in a prospective international cohort study of older adults aged 65–74 years, phenotypic frailty was associated with increased risk of incident CVD (HR 1.35; 95% CI 1.05–1.74).[50] These findings have been attributed to the overlapping mechanisms that underlie both frailty and CVD, including inflammation, insulin resistance, and cellular senescence.[11] Systemic inflammation is a shared pathophysiologic mechanism leading to frailty, changes in muscle physiology with aging, and subclinical CVD impacting multiple organ systems.[11] This leads to a cyclical relationship of worsening mobility leading to progression of CVD risk factors such as adiposity, metabolic syndrome, and chronic low grade inflammation. [11, 48]

Frailty and Cardiovascular Mortality

Frailty is a robust predictor of CV mortality, and the association is comparable across different frailty measurements (Table 1). In a prospective cohort study of community-

dwelling ambulatory adults aged ≥65 years in France, individuals in the lowest third of gait speed were at higher risk of CV mortality compared to those in the highest third of gait speed after multivariable adjustment (HR 1.44, 95% CI 1.03–1.99).[51] Individuals with coronary artery disease were excluded from the analysis. The risk was higher after excluding individuals who were independent in ≥1 instrumental activity of daily living (HR 3.13, 95% CI 1.64–5.99).[51] Causes of death were adjudicated by an independent committee. CV death was defined as death where coronary heart disease, stroke peripheral vascular disease, other CV disease, or sudden death was listed as the cause. In a prospective cohort of community-dwelling older men in the US, phenotypic frailty was associated with a 2-fold increase in CV mortality in a competing risk model adjusting for non-CV death (subdistribution HR 1.98, 95% CI 1.45 – 2.71).[13] Cause of death was adjudicated by two independent investigators using death certificates and medical records.

There are several studies investigating association between the FI and CV mortality. Among 512,723 Chinese adults from the general population aged 30–79, frailty according to the FI was independently associated with cause-specific mortality.[52] There was an incremental increase in mortality related to ischemic heart disease (HR 1.89; 95% CI 1.79–1.89) and cerebrovascular diseases (HR 1.84; 95% CI 1.79–1.89) with increasing FI (per 0.1 increment). Similarly, in a community-based prospective cohort study of adults aged ≥65 years in Italy, FI was associated with an increased risk of CV mortality by a 5% per 0.1 increment increase at 3-years and 4% increase at 6 years ($p < 0.001$).[14] In a study of United States Veterans aged ≥65 years, higher Veterans Administration Frailty Index (VA-FI)[19] was associated risk of increased CV mortality among patients with and without CVD at the time of frailty measurement.[42] However, consistent with the national trend, [53] there was an overall decrease in CV mortality across all frailty statuses among Veterans from 2002–2014. CVD death in this observation study was defined as death where CVD was listed as the cause of death in the National Death Index.

In a meta-analysis of patients with prevalent CVD or at high risk of CVD enrolled in 14 randomized clinical trials, Farooqi et al show a cumulative deficit frailty index >0.21 was associated with increased risk of CV mortality after adjusting for baseline comorbidities (HR 2.06, 95% CI 1.76–2.42).[54] The frailty index was developed using 26 deficits and CV risk factors were excluded. In the trials included in the meta-analysis, CV death included death without clear non-CV causes, death within 7 days after myocardial infarction or stroke, death from congestive heart failure, malignant arrhythmia or aortic aneurysm. Veronese et al found a similar relationship between frailty and CV mortality in a meta-analysis of 18 cohorts with a nearly 4-fold increase in risk of CV mortality among those participants identified as frail (HR 3.89; 95% CI 2.40–6.34).[55]

Applications of Frailty in CVD Management

However defined, frailty may inform CVD management either through pre- or post-treatment prognostication or risk stratification, or more directly by delineating treatment heterogeneity in which frailty serves to distinguish patients with differential harms or benefits from a given therapy.[56] It is important to note that 1) frail patients have short life expectancy and competing non-CV health events, which may reduce the likelihood

of benefit from a CV treatment; 2) frail patients are at higher risk of CV events and CV mortality, and therefore they may derive a larger benefit from a CV treatment; or 3) frail patients may benefit from a CV treatment as much as non-frail patients. Having this knowledge can help individualize CV management of older adults, by reducing the under-treatment and over-treatment. Identifying patients at high risk (for example, for mortality or readmission) does not necessarily translate into futile care or fewer benefits from specific treatments. However, in selected settings where frailty identifies patients at very high risk for short-term mortality or treatment complications in particular, futility or at least diminished opportunity to benefit may be appropriately incorporated into shared decision-making.

Prognostication for TAVR

Frailty is a key predictor for functional decline after TAVR.[46, 57] The 2021 European Society of Cardiology guidelines recommend assessing for frailty using an objective measure to avoid TAVR in "high-risk patients in whom futility should be avoided."[58] The guideline does not specify what frailty measure should be used and how to define "futility" after AVR. Medically managed severe aortic stenosis (AS) carries 1-year mortality of 50%.[59] In a prospective, multicenter TAVR registry in Japan, 4% of the patients had CFS ≥7 (*i.e.,* completely dependent on activities of daily living), and this group had 1-year mortality of 44%.[32] In a prospective, single-center registry of adults aged ≥70 years undergoing TAVR (n=143) during 2014–2017, 23% had poor (low baseline functional status to moderate decline) or very poor (low baseline functional status to large decline) functional status trajectory during 1-year of follow-up post-TAVR with 1-year mortality rates of 25% and 69%, respectively.[57] These two studies suggest that there are patients, albeit small, in whom TAVR may be considered futile because of their exceedingly high mortality. In these high-risk patients, a shared-decision making is critical to reach a decision that reflects the wishes and values of the patient and caregivers.[60]

Frailty and Management of HF

Frailty is highly prevalent in patients with HF, ranging from 45% to 65% in patients with chronic stable HF with reduced ejection fraction (HFrEF) despite their relatively young age.[25, 61] In the pooled analyses of the patients with HFrEF in the Prospective Comparison of ARNI [Angiotensin Receptor–Neprilysin Inhibitor] with ACEI [Angiotensin-Converting–Enzyme Inhibitor] to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) and Aliskiren Trial of Minimizing Outcomes in Patients With Heart Failure (ATMOSPHERE) trials, FI was associated with CV mortality in a dose-dependent manner, with the frailest patients demonstrating an adjusted sub-distribution HR 1.75 (95% CI 1.55–1.96) compared to the least frail patients.[61] There was no interaction between sacubitril/valsartan and frailty indicating that those with frailty benefited as much as those without frailty.[61] Similarly, in the *post hoc* analysis of Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure (DAPA-HF) trial, FI ≥0.31 was associated with increased risk of the primary outcome, the composite of worsening HF or CV death.[62] There was no interaction between dapagliflozin and frailty, but the absolute risk reduction was greatest in patients with frailty index ≥0.31.[62]

Supervised aerobic exercise training (ET) and cardiac rehabilitation are approved for patients with chronic HFrEF by the Centers for Medicare and Medicaid services and are recommended by the professional guidelines to improve functional status, exercise capacity, and quality of life.[63, 64] Frail patients may derive more benefit from supervised aerobic ET compared to non-frail patients. In Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training (HF-ACTION) trial, supervised aerobic ET did not reduce the risk of primary composite end point of all-cause mortality and all-cause hospitalization compared to usual care.[65] In the post hoc analysis of the same trial, aerobic ET was associated with lower risk of primary composite end point in frail patients (frailty index ≥0.21) (HR 0.83, 95% CI 0.72–0.95) but not in non-frail patients (HR 1.04, 95% CI 0.87–1.25).[25] The association was driven by lower risk of all-cause hospitalization in frail patients (HR 0.84, 95% CI 0.72–0.99). Aerobic ET did not reduce the risk of all-cause mortality, CV mortality or CV hospitalization, and CV mortality or HF hospitalization. In Rehabilitation Therapy in Older Acute Heart Failure Patients (REHAB-HF) trial, physical rehabilitation program improved physical function in older adults (mean age 73 years, 55% with the Fried frailty phenotype) at 3 months following a hospitalization for acute decompensated HF.[45] The intervention was associated with greater benefit in frail patients compared to pre-frail patients. These findings suggest that ET may reduce the risk of frailty-related adverse outcome in HF through a non-CV mechanism.

Frailty and Stroke Prophylaxis in Atrial Fibrillation

Although the professional guidelines continue to recommend dabigatran, rivaroxaban, and apixaban on an equal footing,[66] apixaban is currently the most prescribed oral anticoagulant in the US.[67] The most important difference among the direct oral anticoagulants lies in their safety profile. Dabigatran and rivaroxaban increase the risk of gastrointestinal bleeding and do not reduce the risk of major bleeding compared to warfarin[68, 69] whereas apixaban does not increase the risk of gastrointestinal bleeding and reduces the risk of major bleeding compared to warfarin.[70] Additionally, only apixaban was tested against aspirin and was shown to have a comparable bleeding risk.[71] Multiple observational studies of older adults have shown results that are similar to the pivotal trials.[72–75] The favorable safety profile of apixaban is especially preferred in frail older adults who are at highest risk of bleeding. In a study of beneficiaries of Medicare Fee-for-Service aged ≥65 years, compared to warfarin, rivaroxaban was associated with increased risk whereas apixaban was associated with reduced risk of gastrointestinal bleeding across all frailty levels.[74]

Left atrial appendage occlusion (LAAO) is a second line treatment for patients at elevated stroke risk and who are deemed unsuitable for long-term anticoagulation.[66, 76] Medicare beneficiaries constitute 86% of the LAAO recipients,[77] and nearly half of them are considered frail.[78] Frailty is an important predictor of hospital stay >10 days (OR 3.15, 95% CI 2.25–4.41) and 30-day mortality (OR 2.96, 95% CI 1.82–4.82) after LAAO.[78] We do not yet have any data on the treatment effect of LAAO in routine care population compared to existing therapies and heterogeneous treatment effect of LAAO by frailty status.

Future Directions

There is a need to generate evidence to guide CVD management in the growing population of older adults with frailty. The best quality evidence would be generated from clinical trials adequately powered to study treatment effect in older adults with frailty, but there are significant challenges to conducting clinical trials focused on frail older adults. They are less likely to participate in clinical trials, more likely to experience treatment-related adverse events, and more likely to be lost to follow-up. Subgroup or post-hoc analyses of clinical trials to determine heterogeneity in treatment effect by frailty status are almost invariably underpowered to study this question. Analysis of real-world data (*e.g.,* electronic health records, administrative claims data) using robust pharmacoepidemiologic methods may generate evidence that can guide clinical decision making in frail older adults.

Systematic implementation of frailty assessment in CV clinical practice remains a challenge. The clinical need for frailty assessment in terms of CVD prevention and treatment needs to be clearly defined to improve its acceptability and adoption among cardiologists. Given the presence of various frailty assessment tools, they must be validated in the target population. Importantly, there is a need to standardize frailty assessment across CV trials because frailty index composed of different items can give different frailty levels and to develop a cross-walk that correlates similar risk populations across different frailty measures.

Conclusion

Frailty is a multisystem syndrome that is highly prevalent in older adults with CVD and increases the risk of poor outcomes and CV mortality. Despite the variations in the definition of frailty, the currently body of literature demonstrates that CV mortality risk is significantly increased with frailty. Additional studies are needed to gain better mechanistic insights into the role of frailty in CVD in order to guide treatment decisions. Moreover, data for primary and secondary prevention with medical management are urgently needed as most current evidence for CVD prevention is derived from younger, healthier populations, leaving those at highest risk of CVD and CVD mortality without clear evidence to guide management.

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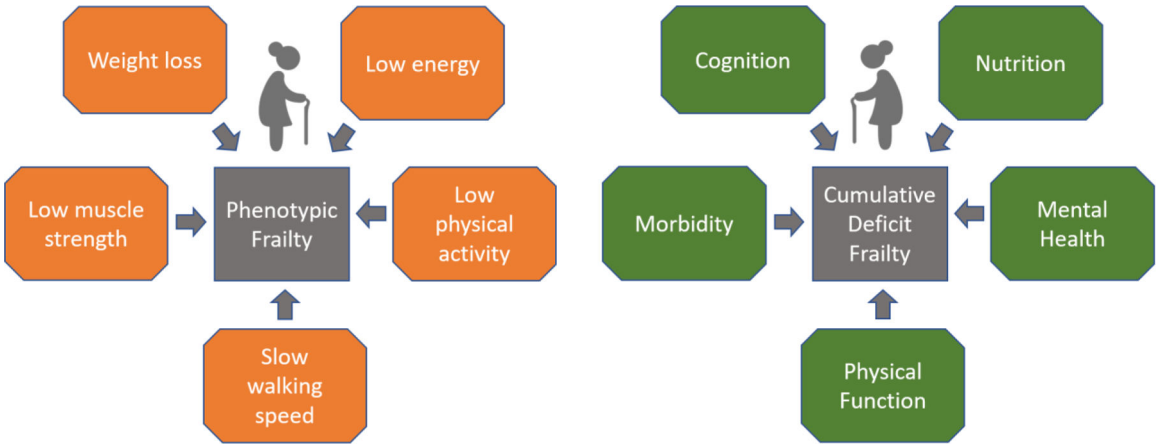

Figure 1. Two Approaches to Identifying Frailty.

In this figure we describe two leading theories of frailty: the physical phenotype or phenotypic frailty and the cumulative deficit frailty. The phenotypic frailty uses five direct measurements of physical characteristic: weight loss, energy level, physical activity, walking speed, and muscle strength. The cumulative deficit approach measures health-related deficits in a broad range of systems including morbidity, physical function, nutrition, cognition, mental health, and geriatric syndromes.

Table.

Summary of studies on the association between frailty and cardiovascular mortality

Study (author, year)	Country, dataset	Study type	Sample size	Population characteristics	Frailty definition	CVD Mortality definition	Outcome
Dumurgier et al 2009 [51]	France, Dijon centre (Three-City study)	Prospective cohort study	3,208	65% women, mean age 73	Gait speed	Trained adjudicators	Lower third walking pace vs upper third: HR 2.92 (1.46–5.84)
Sanchis et al 2014 [52]	Spain, patients hospitalized after ACS in Spain	Prospective cohort study	342	Age ≥65 after ACS	Fried and Green scores	Trained adjudicators	Compared to nonfrail, all-cause death after MI HR 1.19 (1.02–1.39) CV mortality reported as HR 4.80 in separate manuscript (Veronese, et al 2017)
Sergi et al 2015 [53]	Italy, Progretto Veneto Anziani Pro V.A. study	Prospective cohort study (Pro Veneti Anziani [VA])	1,567	Age 65–86, community-dwelling individuals, pre-frail patients (frail patients were excluded)	Fried (pre-frailty; 1 or 2 positive modified Fried criteria)	ICD-9 codes (390–459)	Compared to nonfrail, +2 Fried criteria = HR 1.79 (1.27–2.52) of CVD (composite of CAD, HF, stroke, PAD, or CV mortality). CV mortality reported as HR 3.41 in separate manuscript (Veronese, et al 2017)
Veronese et al 2017 [54]	Multi-national	Meta-analysis of 18 studies	31,343	Mean age ≥65	Variable	Variable: adjudicated, self-report, medical records	Pooled HR for frail vs robust: 3.89 (2.40–6.34)
Adabag et al 2018 [13]	United States, Outcomes of Sleep Disorders in Older Men (MrOS) study	Prospective cohort study	3,135	100% men, 90% white, 35% prior CVD	Fried	Trained adjudicators	Frail vs non-frail Cox model HR 2.73 (2.03–3.68); subdistribution model HR 1.98 (1.45–2.71)
Farooqi et al 2020 [55]	Multi-national	Meta-analysis of 14 multicenter clinical CVD trials	154,696	37% women; mean age, 70.8 years; 70% white with CVD or at risk for CVD	Frailty Index	Trained adjudicators	Per 0.1 unit increase in FI HR 1.44 (1.40–1.46); Frail vs non-frail HR 2.86 (2.64–3.10)
Dewan et al 2020 [56]	Multi-National	Pooled analysis of PARADIGM-HF and ATMOSPHERE trial data	13,625	HF patients enrolled in either trial; 22% female, mean age 63, with or without CVD	Frailty Index	Trained adjudicators	Frail vs non-frail HR 1.75 (1.56–1.96)
Hoogendjik et al 2020 [14]	Italy Aging in the Chianti area; InCHIANTI study	Prospective cohort study	1,129	Mean age 75, 57% women	Frailty Index	Vital status, ICD-9	HR range per 0.01 FI increase = 1.03–1.07, all $p < 0.001$
Fan 2020 [57]	China	Prospective cohort study	512,723	Adults age 30–79	Frailty index (28 baseline variables)	Mortality caused by IHD, cerebrovascular diseases (ICD-10 codes)	Compared to nonfrail pts, dose-dependent response: • IHD mortality; HR per 0.1 frailty incremement 1.89 (1.83–1.94) • Cerebrovascular mortality; HR per 0.1 frailty increment 1.84 (1.79–1.89)
Shrauner et al 2022 [42]	United States, Veterans Health Administration	Retrospective cohort study	3,068,439	US Veterans, 98% male; mean age 75, 90% white with or at risk for CVD	Frailty Index	National Death Index, ICD-9	Compared to nonfrail, HR for mild frail 2.7 (2.1–3.3)

Study (author, year)	Country, dataset	Study type	Sample size	Population characteristics	Frailty definition	CVD Mortality definition	Outcome
							Moderate frail 4.3 (3.3–5.6) Severe frail 7.9 (6.2–10.3)