

Frailty as a Risk Factor for Cardiovascular Versus Noncardiovascular Mortality in Older Men: Results From the MrOS Sleep (Outcomes of Sleep Disorders in Older Men) Study

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Background—Frailty is associated with greater mortality; however, whether frail patients primarily die of cardiovascular disease (CVD) or non-CVD causes is unknown.

Methods and Results—We assessed the cause of death in relation to frailty status, measured at baseline, among 3135 community-dwelling older men in the MrOS Sleep (Outcomes of Sleep Disorders in Older Men) study. Absolute probability and risk of CVD mortality associated with frailty status were estimated with traditional methods that used censoring and newer methods that considered non-CVD mortality as a competing risk. Of the 3135 men (mean age: 76.4 ± 5.6 years), 475 (15.2%) were frail. During an average follow-up of 9.2 years, 1275 (40.7%) men died, including 445 (34.9%) from CVD and 828 (64.9%) from non-CVD causes (2 deaths unadjudicated). Both CVD and non-CVD mortality risk increased with frailty. Cumulative absolute probability of CVD death at 10 years among frail men was 23.8% (20.2–27.6%) using the competing risk method versus 32.5% (27.3–37.8%) using the traditional Kaplan–Meier method (41.5% [95% confidence interval, 36.9–45.9%] and 48.6% [95% confidence interval, 43.6–53.4%], respectively, for non-CVD mortality). The multivariable-adjusted risk of CVD death among frail versus robust men was 1.38 (95% confidence interval, 0.99–1.92) using the competing risk method versus 1.84 (95% confidence interval, 1.35–2.51) using the traditional Cox proportional hazards method.

Conclusions—Among community-dwelling older men, $\approx 35\%$ of the deaths were due to CVD. Frail men were at increased risk of CVD death, but ignoring the competing risk of non-CVD mortality overestimated their long-term probability and relative risk of CVD death. (*J Am Heart Assoc.* 2018;7:e008974. DOI: 10.1161/JAHA.118.008974.)

Key Words: cardiovascular disease • cardiovascular disease risk factors • functional capacity impairment • mortality

With the rapid expansion of the number of elderly patients seeking cardiovascular care, frailty status has been suggested as an important factor to consider in clinical decision-making.^{1,2} Frailty, defined as a biological syndrome that reflects a state of decreased physical reserve and increased vulnerability to stressors, is associated with prevalent cardiovascular disease (CVD). Prospective studies of older adults have reported independent associations of frailty with higher risks of comorbidity, disability, all-cause mortality, and hospitalization.^{1,3–9} Frailty has also been

associated with worse outcomes after acute CVD events and a higher likelihood of adverse consequences after CVD interventions.^{1,10–13}

Emergence of new interventions, such as transcatheter aortic valve replacement, and improvement of existing interventions have increased the feasibility of treating CVD in later stages of life.^{14–16} Devices such as implantable cardioverter–defibrillators are being used prophylactically to prevent sudden cardiac death in patients of all ages, including older adults.^{17–20} Shown to prolong life in younger, more

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An accompanying Table S1 is available at <http://jaha.ahajournals.org/content/7/10/e008974/DC1/embed/inline-supplementary-material-1.pdf>

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Received March 3, 2018; accepted March 29, 2018.

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Clinical Perspective

What Is New?

- Among community-dwelling older men, frailty is associated with increases in both cardiovascular disease (CVD) and non-CVD mortality.
- Among these patients, ≈35% of the deaths were due to CVD and 65% were due to non-CVD causes.
- Ignoring the competing risk of non-CVD mortality overestimates the long-term probability and relative risk of CVD death.

What Are the Clinical Implications?

- Frailty status and the competing risk of non-CVD mortality need to be taken into account when assessing the benefit of CVD interventions regarding mortality.
- Studies assessing the association of frailty or its individual components with risk of CVD death should account for the competing risk of non-CVD death.

robust patients who have participated in randomized clinical trials, these CVD interventions are applied to older, more frail patients for whom the competing risk of non-CVD death is higher.^{21,22} However, because of more advanced disease, greater burden of comorbidity, and higher incidence of adverse consequences, frail patients may accrue less survival benefit from CVD therapies than younger, more robust patients. To assess the likelihood of an improvement in survival associated with a CVD intervention among frail patients, it is necessary to estimate the probability of cause-specific (CVD versus non-CVD) mortality first.

The primary objective of this study was to estimate the probability of CVD mortality by frailty status, with and without consideration of non-CVD mortality as a competing risk. We hypothesized that frailty would be associated with non-CVD mortality and that traditional analyses that did not consider the competing risk of non-CVD death would result in overestimation of the risk of CVD death among frail older men.

Methods

MrOS (Osteoporotic Fractures in Men) data, analytic methods, and study materials have been made available to other researchers for purposes of reproducing the results or replicating the procedure.²³

Participants

The MrOS study (n=5994) enrolled community-dwelling men aged 65 years and older between 2000 and 2002, from 6

geographic regions in the United States: Birmingham, Alabama; Minneapolis, Minnesota; Palo Alto, California; the Monongahela Valley near Pittsburgh, Pennsylvania; Portland, Oregon; and San Diego, California.^{24,25} Men with a history of bilateral hip replacement or those who were unable to walk without the assistance of another person were not eligible for the study. A subset of MrOS participants (n=3135) were enrolled in the MrOS Sleep (Outcomes of Sleep Disorders in Older Men) ancillary study between 2003 and 2005. These men had both a clinic examination with assessment of frailty and adjudication of vital status, including cause of death, and are included in the present analysis. The research protocols were approved by the institutional review board at each participating institution, and all participants gave written informed consent.

Frailty Assessment

Frailty status was defined at the initial MrOS Sleep examination using criteria similar to those proposed by Fried et al,²⁶ using data collected in the Cardiovascular Health Study:

1. Shrinking, identified by unintentional weight loss of $\geq 5\%$ between the MrOS baseline and sleep examination (mean \pm SD years between examinations: 3.38 \pm 0.48);
2. Weakness, identified by grip strength at the sleep examination in the lowest quintile stratified by body mass index (quartiles);
3. Poor energy, identified by an answer of “no” to the question, “Do you feel full of energy?” from the Geriatric Depression Scale,²⁷ administered at the sleep examination;
4. Slowness, identified by a walk speed at the sleep examination in the lowest quintile stratified by standing height (median); and
5. Low physical activity level at the sleep examination, identified by a Physical Activity Scale for the Elderly²⁸ score in the lowest quintile.

Men with none of these components were categorized as *robust*, those with 1 or 2 components were categorized as *intermediate stage*, and those with ≥ 3 components were categorized as *frail*.

Adjudication of Mortality

Men were contacted every 4 months by postcard and/or phone to ascertain vital status. A total of 135 individuals terminated study participation before the end of follow-up. Among the remaining 3000 participants, the follow-up for vital status was 99% complete. Deaths were centrally adjudicated as being due to CVD versus a non-CVD cause by 2 experts at the MrOS Coordinating Center using death certificates,

medical records, and a validated, prespecified adjudication protocol. Cause of death was categorized according to the *International Classification of Diseases, Ninth Revision (ICD-9)* codes for underlying disease as CVD (394.9, 396.9–442, 443.9, 459.7, 459.9, 785.51, and 966.71).²⁹ The follow-up for mortality in this analysis ended in February 2016. Mean duration of follow-up after the sleep examination for mortality was 9.2 ± 3.0 years.

Definition of CVD and Other Measurements

Prevalent CVD was defined as having a history of coronary heart disease (including myocardial infarction, coronary artery bypass grafting, percutaneous coronary intervention, or angina), peripheral vascular disease, valvular heart disease, or congestive heart failure.

At the sleep examination, participants completed a questionnaire and were interviewed regarding smoking status and history of physician-diagnosed selected medical conditions including stroke, diabetes mellitus, hypertension, coronary heart disease, peripheral vascular disease, valvular heart disease, congestive heart failure, and chronic obstructive pulmonary disease.

Statistical Analysis

Characteristics of the 3135 participants in the MrOS Sleep examination were compared across the 3 categories of frailty status using ANOVA (or nonparametric equivalent Kruskal–Wallis) tests for continuous variables and χ^2 tests for categorical variables. Among men who died during follow-up, we compared baseline characteristics, including frailty status, for those who experienced a CVD death versus a non-CVD death.

To estimate the absolute probability of CVD mortality during follow-up by frailty status category, we used 2 approaches: (1) a traditional Kaplan–Meier survival method that treats non-CVD death as a censored observation and (2) a cumulative incidence function that considers non-CVD mortality as a competing risk.³⁰ Similarly, we used 2 approaches (with and without accounting for the competing risk of non-CVD death) to determine adjusted associations of frailty status category with risk of CVD mortality. Men whose cause of death was uncertain were censored in both analyses. Taking robust individuals as the referent group, we used conventional Cox proportional hazards regression models that treat non-CVD mortality as an uninformative censoring event and subdistribution hazards models proposed by Fine and Gray^{21,31} that consider non-CVD death as a competing risk. In subdistribution models, men who died of non-CVD mortality are treated as an informative event and remain in the risk set until the end of study follow-up.³⁰ This permits estimation of

the hazard ratio of CVD mortality, which takes competing events into consideration. If the incidence rate of the competing risk is moderate to high, subdistribution hazards ratios tend to be smaller in magnitude than those from traditional Cox proportional hazards regression because those with the competing event are usually more similar to those with the outcome of interest than those who are event-free.

In multivariable analysis the associations were first adjusted for age, race, and site (base models). Multivariable models were further adjusted for selected risk factors for CVD death including smoking status, stroke, diabetes mellitus, hypertension, coronary heart disease, peripheral vascular disease, valvular heart disease, congestive heart failure, and chronic obstructive lung disease.

In secondary analyses, we repeated the above analyses among the subgroup of men with prevalent CVD at baseline. Among the overall cohort, we also estimated the absolute probability and adjusted risk of non-CVD mortality according to frailty status in men, using statistical approaches with and without consideration of CVD mortality as a competing risk. All statistical analyses were performed using SAS version 9.4 (SAS Institute).

Results

The mean age of the men who participated in the study was 76.4 ± 5.6 years. Of the 3135 men, 475 (15.2%) were categorized as frail, 1717 (54.8%) were intermediate stage, and 943 (30.1%) were robust (Table 1). Greater frailty status was associated with older age and higher prevalence of comorbid medical conditions (Table 1). Among the subset of men with prevalent CVD at baseline ($n=1103$, 35.2% of the entire cohort), 22.1% were frail and 20.1% were robust.

During an average follow-up of 9.2 ± 3.0 years, 1275 (40.7%) men died (445 [34.9%] CVD deaths, 828 [64.9%] non-CVD deaths and 2 [0.2%] unadjudicated). The distribution of the frailty status was not significantly different between men who died of CVD versus non-CVD causes (27.4% and 23.9%, respectively, were frail; 18.2% and 19.1%, respectively, were robust). Men with CVD death compared with those with non-CVD death had a higher prevalence of hypertension, coronary heart disease, and congestive heart failure (Table S1).

Incidence and Risk of CVD Mortality by Traditional and Competing-Risk Methods

The cumulative incidence of CVD mortality increased with greater frailty status using the traditional Kaplan–Meier method and the competing-risk method (Table 2). However, estimates were lower using the competing-risk method compared with the traditional approach, and the magnitude

Table 1. Characteristics of 3135 Men at MrOS Baseline Sleep Visit According to Frailty Status

Characteristic	Frail (n=475)	Intermediate Stage (n=1717)	Robust (n=943)	P Value
Age, y, mean (SD)	80.1 (5.9)	76.5 (5.4)	74.5 (4.7)	<0.001
White race, n (%)	425 (89.5)	1545 (90.0)	846 (89.7)	0.94
Smoking status				0.28
Never	168 (35.4)	676 (39.4)	391 (41.5)	
Former	295 (62.2)	1005 (58.5)	534 (56.7)	
Current	11 (2.3)	36 (2.1)	17 (1.8)	
Selected medical conditions, n (%)				
Stroke	37 (7.8)	63 (3.7)	17 (1.8)	<0.001
Diabetes mellitus	106 (22.4)	228 (13.3)	83 (8.8)	<0.001
Hypertension	345 (72.8)	1054 (61.4)	448 (47.5)	<0.001
Coronary heart disease	199 (41.9)	544 (31.7)	180 (19.1)	<0.001
Peripheral vascular disease	74 (15.6)	132 (7.7)	46 (4.9)	<0.001
Valvular heart disease	18 (3.8)	42 (2.4)	7 (0.7)	<0.001
Congestive heart failure	60 (12.7)	102 (5.9)	31 (3.3)	<0.001
COPD	38 (8.0)	95 (5.5)	31 (3.3)	0.001
Cancer	147 (30.9)	506 (29.5)	222 (23.5)	0.001
CKD*	220 (48.8)	490 (29.3)	165 (17.9)	<0.0001

CKD indicates chronic kidney disease (estimated glomerular filtration rate <60 mL/min); COPD, chronic obstructive pulmonary disease; MrOS, Osteoporotic Fractures in Men. *Number missing: 101.

of the difference in probabilities estimated by the 2 methods was greater with increasing duration of follow-up (Figure 1). Cumulative absolute probability of CVD mortality among frail men, for example, was 13.2% (95% confidence interval [CI], 10.9–15.7%) at 5 years and 32.5% (95% CI, 27.3–37.8%) at 10 years using the traditional Kaplan–Meier method versus 11.7% (95% CI, 9.8–13.9%) at 5 years and 23.8% (95% CI,

20.2–27.6%) at 10 years using the competing-risk method (Table 2).

Those who were frail or intermediate stage had a higher risk of CVD mortality than those who were robust, using both the traditional Cox proportional hazards model and the subdistribution (competing-risk) model, but point estimates of the association were lower using the competing-risk

Table 2. Cumulative Incidence of CVD and Non-CVD Mortality in Relation to Frailty Status Using Kaplan–Meier versus Competing-Risk Method

Frailty Status	Cumulative Incidence, % (95% CI)			
	Kaplan–Meier Method		Competing Risk Method	
	5 y	10 y	5 y	10 y
CVD Mortality				
Robust	2.4 (2.2–2.6)	8.0 (7.0–9.0)	2.3 (2.1–2.6)	7.4 (6.6–8.4)
Intermediate	5.3 (4.9–5.8)	15.3 (13.9–16.8)	5.0 (4.6–5.5)	13.1 (12.0–14.3)
Frail	13.2 (10.9–15.7)	32.5 (27.3–37.8)	11.7 (9.8–13.9)	23.8 (20.2–27.6)
Non-CVD mortality				
Robust	4.6 (4.1–5.2)	15.7 (13.8–17.6)	4.6 (4.1–5.1)	15.0 (13.3–16.8)
Intermediate	9.9 (9.0–10.8)	27.4 (25.3–29.6)	9.6 (8.8–10.5)	25.4 (23.5–27.4)
Frail	22.9 (19.4–26.7)	48.6 (43.6–53.4)	21.4 (18.1–24.8)	41.5 (36.9–45.9)

CI indicates confidence interval; CVD, cardiovascular disease.

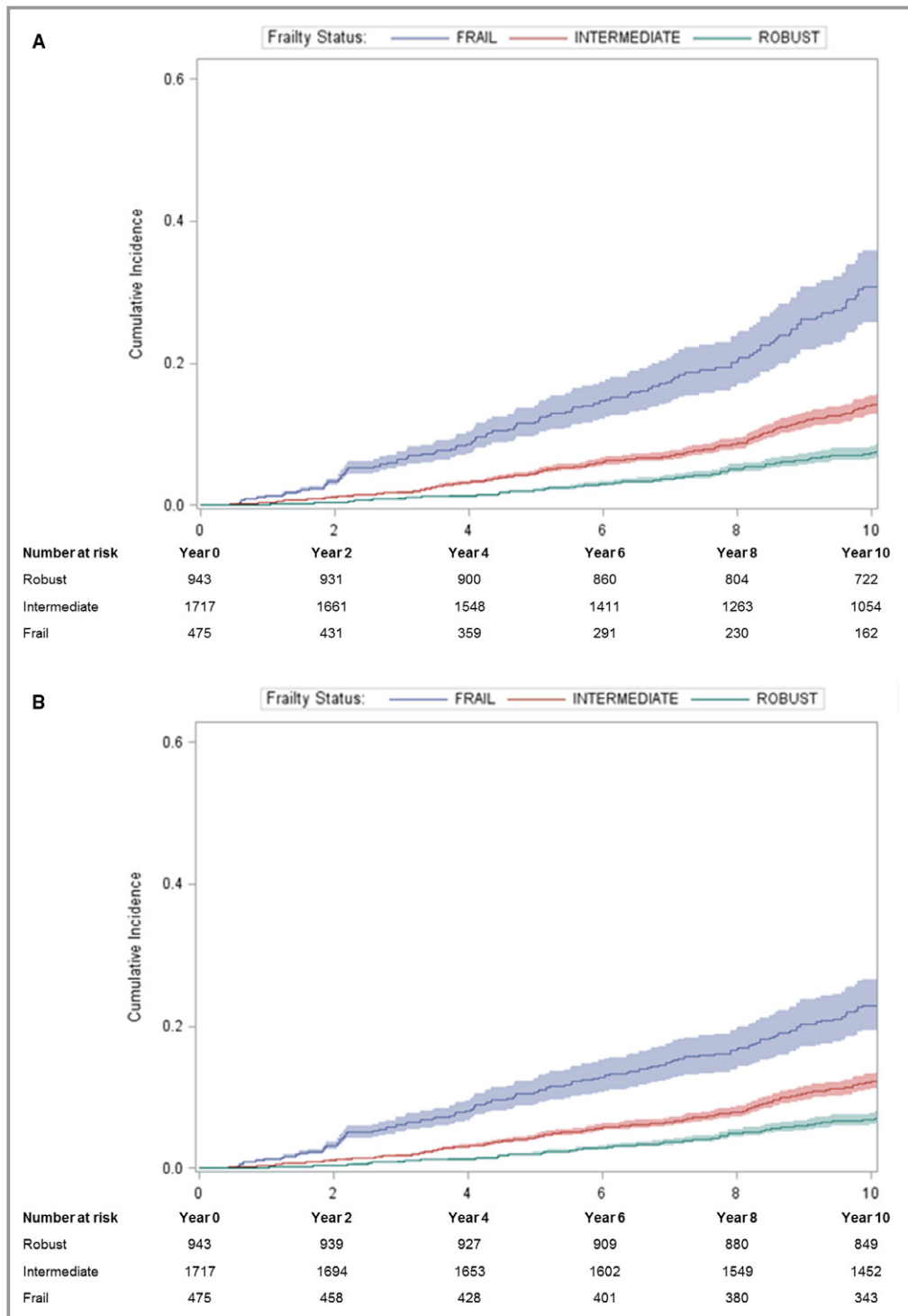


Figure 1. Cumulative absolute probabilities of CVD mortality in relation to frailty status using (A) the Kaplan–Meier method and (B) the competing risk method. CVD indicates cardiovascular disease.

approach (Table 3). Compared with robust men, the age- and race-adjusted risk of CVD mortality among frail men was 2.73-fold higher (95% CI, 2.03–3.68) using the traditional Cox model versus 1.98-fold higher (95% CI, 1.45–2.71) using the competing-risk model (Table 3). After further adjustment for

smoking and comorbid medical conditions (stroke, diabetes mellitus, hypertension, coronary heart disease, peripheral vascular disease, valvular heart disease, congestive heart failure, and chronic obstructive lung disease), the adjusted risk of CVD mortality among frail men was 1.84-fold higher

Table 3. Traditional Cox Proportional Hazards Models and Subdistribution Competing-Risk Models for Association of Frailty Status With CVD and Non-CVD Mortality

Frailty Status	Hazard Ratio (95% CI)*					
	CVD Mortality			Non-CVD Mortality		
	Events, n	Cox Proportional Hazards Model	Subdistribution Model	Events, n	Cox Proportional Hazards Model	Subdistribution Model
Robust	81	1.00 (referent)	1.00 (referent)	158	1.00 (referent)	1.00 (referent)
Intermediate stage	242	1.55 (1.20–1.99)	1.38 (1.07–1.78)	472	1.62 (1.35–1.94)	1.56 (1.30–1.87)
Frail	122	2.73 (2.03–3.68)	1.98 (1.45–2.71)	198	2.57 (2.06–3.21)	2.16 (1.73–2.70)

CI indicates confidence interval; CVD, cardiovascular disease.

*Adjusted for site, age, and race.

(95% CI, 1.35–2.51) using the traditional Cox model versus 1.38-fold higher (95% CI, 0.99–1.92) using the competing-risk model.

Among the subgroup of 1103 men with prevalent CVD, the cumulative incidence of CVD mortality was higher than the whole cohort, but the association of frailty status with CVD mortality and the attenuation of estimates with competing-risk analyses were similar to those among the overall cohort (results not shown).

Incidence and Risk of Non-CVD Mortality by Traditional and Competing-Risk Methods

The cumulative incidence of non-CVD mortality among frail men, although higher than CVD mortality, also increased with greater frailty status. Estimates of the absolute probability of non-CVD death were lower using the competing-risk method compared with the traditional approach (Figure 2). However, the attenuation in estimates of absolute probabilities of non-CVD mortality using the competing-risk versus traditional approach was smaller in magnitude than that observed for the outcome of CVD death: 22.9% (95% CI, 19.4–26.7%) at 5 years and 48.6% (95% CI, 43.6–53.4%) at 10 years using the traditional Kaplan–Meier method versus 21.4% (95% CI, 18.1–24.8%) at 5 years and 41.5% (95% CI, 36.9–45.9%) at 10 years using the competing-risk method (Table 2). Similarly, age- and race-adjusted risk of non-CVD mortality among frail men was 2.57-fold higher (95% CI, 2.06–3.21) using the traditional Cox model versus 2.16-fold higher (95% CI, 1.73–2.70) using the competing-risk model (Table 3).

Discussion

Among this cohort of 3135 community-dwelling older men, 45% died during an average follow-up of 9.2 years with ≈35% of deaths adjudicated as due to CVD causes and 65% of deaths due to non-CVD causes. Frail men compared with

robust men had an increased risk of CVD mortality and non-CVD mortality. Traditional analytic methods that ignored the competing risk of non-CVD death among frail men substantially overestimated their long-term absolute probability and relative risk of CVD death. Findings regarding comparison of traditional and competing-risk approaches were similar when the analyses were restricted to men with prevalent CVD at baseline. These results suggest that the benefit of cardiovascular therapeutic interventions in reducing CVD mortality among frail older adults should be weighed against the high risk of competing non-CVD mortality.

Frailty or its individual components, such as slowness, have been associated with higher odds of clinical and subclinical CVD and a higher risk of CVD mortality.¹ In the Three-City study, slow gait speed was associated with an increased risk of CVD death (hazard ratio: 2.9) but not mortality from cancer or other causes (hazard ratio: 1.0).³² In the EPESE (Established Populations for Epidemiologic Studies of the Elderly) study, impaired mobility was associated with a higher risk of CVD death.³³ Among patients with peripheral arterial disease, frail men had a higher risk of CVD mortality.^{34–36} In our study, the multivariable-adjusted risk of CVD death was 1.84 times higher among frail compared with robust men; this risk was similar in magnitude to that reported in previous studies. Nevertheless, in the analyses that considered non-CVD death as a competing risk, the association between frailty and CVD death was reduced by 25% to 1.38. Considering the sizable burden of non-CVD mortality in frail patients, studies assessing the association of frailty or its individual components with risk of CVD death should account for the competing risk of non-CVD death.

Previous studies have shown that frailty is a factor in the decision of whether or not to implement a therapeutic cardiovascular intervention in frail patients with CVD. Compared with robust patients, frail patients with CVD are less likely to receive therapeutic CVD medications or be referred for invasive cardiovascular procedures.^{1,18} The decision

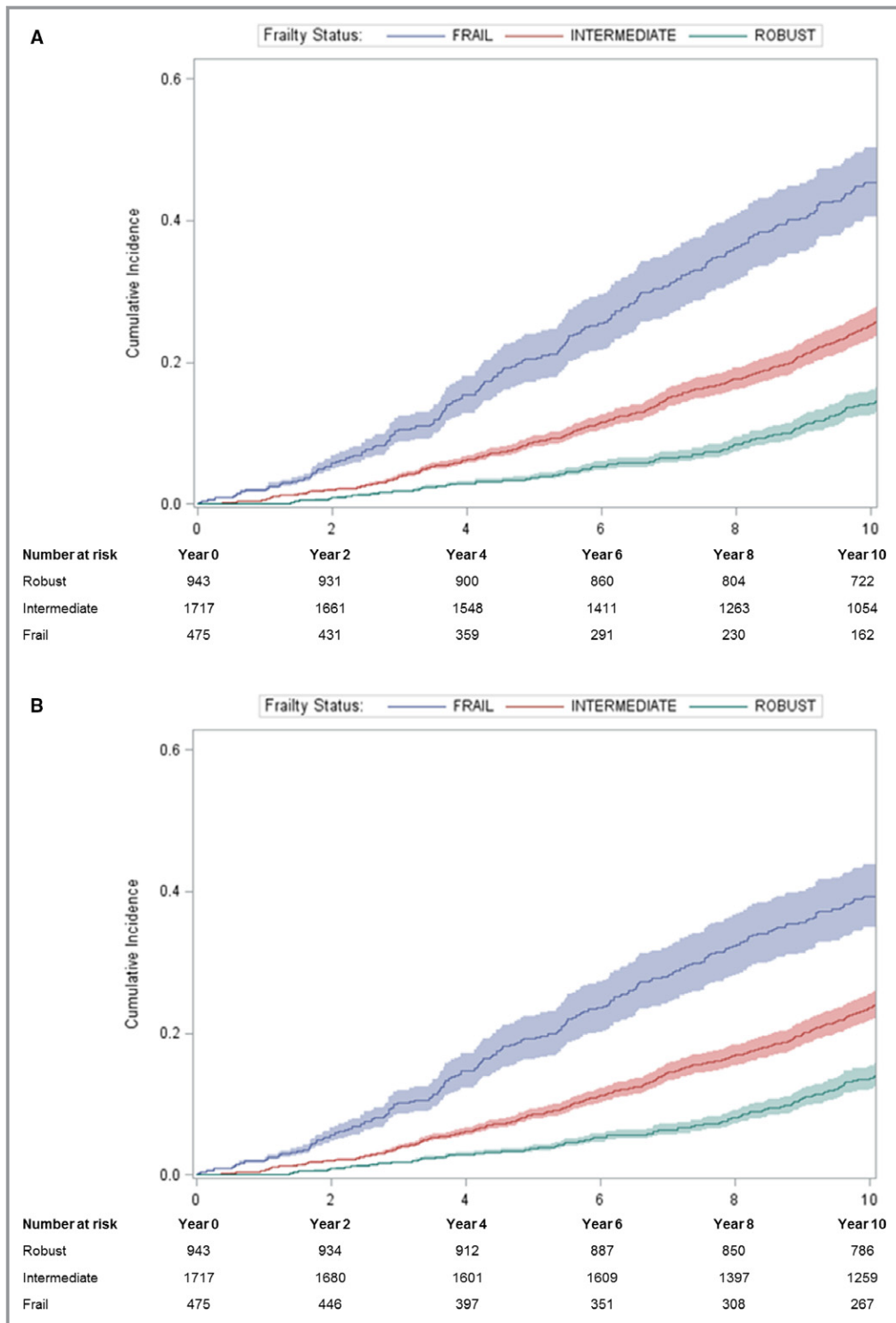


Figure 2. Cumulative absolute probabilities of non-CVD mortality in relation to frailty status using (A) the Kaplan–Meier method and (B) the competing risk method. CVD indicates cardiovascular disease.

regarding whether or not to initiate a treatment or refer a patient to a cardiovascular intervention is complex and involves the clinician’s personal intuition.³⁷ Although frailty is associated with a higher risk of CVD mortality despite taking into account the competing risk of non-CVD death, frail

patients also have a higher risk of adverse outcomes after therapeutic CVD interventions.¹ Previous studies have reported that preoperative frailty or gait speed was associated with higher postoperative mortality and morbidity.^{38–41} A post hoc analysis from SCD-HeFT (Sudden Cardiac Death in Heart

Failure Trial) showed that patients who were unable to cover 288 m in a 6-minute walk test were unlikely to have mortality reduction from implantable cardioverter–defibrillator implantation.⁴² Although the present analysis indicated that the likelihood of both CVD death and death from non-CVD causes was highest among frail men, the latter was nearly twice as likely to be the cause of death ($\approx 65\%$ versus 35% of deaths) in this community-dwelling cohort of older men. Our results suggest that the benefit of cardiovascular therapeutic interventions in reducing CVD mortality among frail older adults should be weighed against the high risk of competing non-CVD mortality with corresponding greater uncertainty of benefit. Furthermore, reporting for clinical trials evaluating efficacy of cardiovascular interventions in older adults should include absolute risks and risk ratios for non-CVD mortality in addition to total mortality to better ascertain study relevance to older frail adults and to evaluate possible non-CVD benefits of those interventions. Inclusion of these results would better inform clinical decision-making in the aged population.

More than 20 measures of frailty have been used in previous published reports, but no consensus exists about the best method to incorporate into clinical practice.¹ Most tools measure ≥ 1 of the 5 core domains that define frailty: slowness, weakness, low physical activity, exhaustion, and shrinking.¹ The method developed by Fried et al²⁶ from the Cardiovascular Health Study has been one of the most frequently cited frailty tools and has been associated with mortality and disability in large cohorts of community-dwelling older adults.¹ This method, however, is not easy to incorporate into a clinical setting, and the distribution of some of its measures such as weakness, slowness, and physical activity requires knowledge of the quartiles in each patient population. Consequently, simpler methods for assessment of frailty status, such as the Study of Osteoporotic Fractures scale and the Short Physical Performance Battery, have been developed and validated.^{4,43,44} In contrast to these multi-item frailty scales, 5-m gait speed has been advocated as a single component of frailty that has been associated with poor outcomes after CVD interventions.^{32,45,46} Recently, sarcopenia, assessed by psoas muscle area or pectoralis muscle volume, has been associated with poor outcomes after cardiac procedures.^{47–50} Future research needs to evaluate the validity and clinical utility of simple frailty assessment tools that fit in the time constraints and competing demands of busy clinical practice.

Strengths and Limitations

A strength of this study cohort is the inclusion of community-dwelling older men from 6 geographic locations in the United States, suggesting that the results can be generalized to other communities; however, the inclusion of only men (mostly

white) is a limitation. Although the adjudication of the cause of death was performed independently using a prespecified protocol, determining the cause of death in older individuals may be inherently prone to error. Furthermore, although the greatest impact of cardiovascular therapeutic interventions is expected to be on CVD mortality, it is possible that these interventions could affect (reduce or increase) the risk of non-CVD mortality. An intervention that prevents myocardial infarction, for example, could also reduce the risk of deconditioning and falls by way of maintaining mobility. Conversely, such an intervention (eg, coronary bypass surgery) could increase the risk of falls in the postoperative period by causing deconditioning.⁵¹

Conclusions

Among community-dwelling older men, $\approx 35\%$ of the deaths are due to CVD mortality and 65% are due to non-CVD causes. Frailty is associated with a higher risk of both CVD and non-CVD mortality in these men; therefore, CVD interventions may improve the survival of these patients. Nevertheless, non-CVD death is a major competing event to a CVD death among frail men. Not taking into account this competing risk among frail men overestimates their long-term absolute probability of CVD death and adjusted CVD mortality risk. The results of this study suggest that a competing-risk approach should be used among frail patients, including those with prevalent CVD, to better inform CVD-death risk assessment and clinical decision-making.

Sources of Funding

The MrOS (Osteoporotic Fractures in Men) study is supported by National Institutes of Health funding. The National Institute on Aging, the National Institute of Arthritis and Musculoskeletal and Skin Diseases, the National Center for Advancing Translational Sciences, and NIH Roadmap for Medical Research provide support under the following grant numbers: U01 AG027810, U01 AG042124, U01 AG042139, U01 AG042140, U01 AG042143, U01 AG042145, U01 AG042168, U01 AR066160, and UL1 TR000128. The National Heart, Lung, and Blood Institute provides funding for the MrOS Sleep (Outcomes of Sleep Disorders in Older Men) ancillary study under the following grant numbers: R01 HL071194, R01 HL070848, R01 HL070847, R01 HL070842, R01 HL070841, R01 HL070837, R01 HL070838, and R01 HL070839. This article is the result of work supported with resources and use of facilities of the Minneapolis VA Health Care System. The contents do not represent the views of the US Department of Veterans Affairs or the US Government.

Disclosures

None.

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SUPPLEMENTAL MATERIAL

Table S1. Characteristics of men who died due to CVD versus non-CVD causes.

Characteristic	CVD death (N=445)	Non-CVD death (N=828)	P-value CVD vs. non-CVD
Age, years, mean (SD)	79.6(5.6)	78.8(5.7)	0.02
Caucasian race, n (%)	412(92.6%)	756(91.3%)	0.43
Robust, n (%)	81(18.2%)	158(19.1%)	0.39
Pre-frail, n (%)	242(54.4%)	472(57.0%)	
Frail, n (%)	122(27.4%)	198(23.9%)	
Smoking status			0.06
Never	164(36.9%)	302(36.5%)	
Former	277(62.2%)	501(60.6%)	
Current	4(0.9%)	24(2.9%)	
Selected medical conditions, n (%)			
Stroke	27(6.1%)	44(5.3%)	0.58
Diabetes mellitus	85(19.1%)	122(14.8%)	0.05
Hypertension	347(78.0%)	508(61.4%)	<0.0001
Coronary heart disease*	212(47.6%)	286(34.5%)	<0.0001
Peripheral vascular disease†	63(14.2%)	95(11.5%)	0.17
Valvular heart disease‡	21(4.7%)	31(3.7%)	0.40
Congestive heart failure	66(14.8%)	55(6.7%)	<0.0001
Cancer	127(28.5%)	293(35.4%)	0.01
CKD	195(45.2%)	303(38.1%)	0.02
COPD	23(5.2%)	65(7.9%)	0.07

Abbreviations: COPD, chronic obstructive pulmonary disease; CKD= chronic kidney disease (estimated glomerular filtration rate < 60 ml/min)

*including myocardial infarction, bypass surgery, coronary angioplasty or angina

†including claudication, repair of abdominal aortic aneurysm, peripheral bypass

‡including heart valve replacement