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Clinical Research

Sex And Prognostic Significance of Self-Reported Frailty in Non–ST-Segment Elevation Acute Coronary Syndromes: Insights From the TRILOGY ACS Trial

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ABSTRACT

Background: The effect of sex on self-reported frailty in acute coronary syndromes (ACS) is unclear. We examined the prevalence of self-reported frailty and its association with all-cause death among men and women.

Methods: Elderly (≥ 65 years) male (n = 2691) and female (n = 2305) patients with ACS enrolled in the **T**argeted **P**latelet **I**nhibition to **C**larify the **O**ptimal **S**trategy to **M**edically **M**anage **A**cute **C**oronary **S**yndromes (TRILOGY ACS) trial were screened using the Fried Frailty Index. Sex differences in prevalence of frailty symptoms

RÉSUMÉ

Introduction : On ignore les effets du sexe sur la fragilité autorapportée lors de syndromes coronariens aigus (SCA). Nous avons examiné la prévalence de la fragilité autorapportée et de son association avec la mortalité toutes causes confondues chez les hommes et les femmes.

Méthodes : Le Fried Frailty Index a servi à dépister les patients (n = 2691) et les patientes (n = 2305) âgés (≥ 65 ans) atteints d'un SCA qui étaient inscrits à l'étude TRILOGY ACS (***T**argeted **P**latelet **I**nhibition to **C**larify the **O**ptimal **S**trategy to **M**edically **M**anage **A**cute*

The number of people above the age of 65 years is expected to double over the next 2 decades in North America and Europe.[1-3] As health care systems around the world brace themselves for this demographic shift, issues specific to older adults, such as frailty, have taken centre stage. Frailty identifies a subset of older patients who are particularly susceptible to adverse events. Often referred to as a syndrome, the causes of frailty are multifactorial, culminating in an increased vulnerability to stressors and a higher risk of morbidity and mortality.

Although many frailty scores and indices have been published, there is no consensus regarding a single best tool for assessing frailty.[4-6] Instead, the diagnosis of frailty requires a geriatric assessment across various domains, perhaps involving one or more established frailty indices.[7,8] Concerns about the subjectivity and reproducibility of frailty assessments across providers and clinical settings have not been fully addressed.

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and categories (not frail; prefrail [1 to 2 symptoms]; and frail [≥ 3 symptoms]) and their prognostic importance were examined.

Results: Women were older and had higher rates of comorbidities than men. A total of 739 (27.5%) men and 645 (28%) women reported ≥ 1 frailty symptom. Prevalence of frailty increased with age among men but not women. During a median follow-up of 17.3 months, 353 (13.1%) men and 266 (11.5%) women died. After adjusting for age, prefrail men had a 35% increased risk (hazard ratio [HR] 1.35; 95% confidence interval [CI], 1.07-1.71), and frail men had an 80% increased risk (HR 1.80; 95% CI, 1.22-2.67) of death relative to not-frail men. The age-adjusted HR for death in prefrail women was 1.40 (95% CI, 1.07-1.84), and 1.55 (95% CI, 0.96-2.49) in frail women relative to not-frail women. Self-reported slow walk time and decreased physical activity appeared to provide the most prognostic information.

Conclusion: Self-reported frailty was similar among men and women with ACS. Frailty increased with age only among men, in whom it added more prognostic information. Patient-reported frailty may identify elderly patients with ACS, particularly men, at high-risk of mortality.

Coronary Syndromes). Nous avons examiné les différences entre les sexes quant à la prévalence des symptômes de fragilité et aux catégories de fragilité (non fragile, préfragile [de 1 à 2 symptômes] et fragile [≥ 3 symptômes]), et leur importance pronostique.

Résultats : Les femmes étaient plus âgées et avaient des taux plus élevés de comorbidités que les hommes. Un total de 739 (27,5 %) hommes et de 645 (28 %) femmes ont rapporté ≥ 1 symptôme de fragilité. La prévalence de la fragilité augmentait avec l'âge chez les hommes, mais non chez les femmes. Durant le suivi médian de 17,3 mois, 353 (13,1 %) hommes et 266 (11,5 %) femmes sont morts. Après l'ajustement de l'âge, les hommes préfragiles avaient un risque accru de mortalité de 35 % (risque relatif [RR] 1,35; intervalle de confiance [IC] à 95 %, 1,07-1,71), et les hommes fragiles avaient un risque accru de mortalité de 80 % (RR 1,80; IC à 95 %, 1,22-2,67) par rapport aux hommes non fragiles. Le RR ajusté selon l'âge pour ce qui est de la mortalité chez les femmes préfragiles était de 1,40 (IC à 95 %, 1,07-1,84), et de 1,55 (IC à 95 %, 0,96-2,49) chez les femmes fragiles par rapport aux femmes non fragiles. Le temps de marche lente et la diminution de l'activité physique autorapportés semblaient constituer les renseignements les plus utiles au pronostic.

Conclusion : La fragilité autorapportée était similaire chez les hommes et les femmes atteints d'un SCA. La fragilité qui augmentait avec l'âge seulement chez les hommes constituait un renseignement additionnel utile au pronostic. La fragilité rapportée par le patient peut aider à reconnaître les patients âgés atteints d'un SCA, notamment les hommes, qui sont exposés à un risque élevé de mortalité.

Despite a clear need for a less resource-intensive and efficient way to assess frailty, very few studies have examined the value of patient self-report, particularly among patients with cardiovascular disease.

The **Tar**geted Platelet **I**nhibition to C**l**arify the **O**ptimal Strate**g**y to Medically Manage **A**cute **C**oronary **S**yndromes study (TRILOGY ACS) was a randomized trial of aspirin plus prasugrel vs aspirin plus clopidogrel for the long-term medical management of patients with unstable angina or non–ST-segment elevation myocardial infarction (UA/NSTEMI). The trial collected self-reported frailty for all patients ≥ 65 years of age using the 5-symptom Fried Frailty Index.[9-11] Frail patients—that is, those who reported 3 or more of the 5 symptoms—had a significantly higher hazard of all-cause death relative to patients without any symptoms of frailty.[12] However, the effect of age and sex on the prognostic importance of frailty has not been examined previously. Accordingly, we examined the prevalence of frailty and its individual symptoms by age and sex and the association between frailty and all-cause death among men and women.

Methods

Patient population

Our study population consisted of 4999 patients aged ≥ 65 years of 9326 patients enrolled in the TRILOGY ACS trial. Details of the study design, patient population, and results of TRILOGY ACS have been published.[9] In brief, from June 2008 to September 2011, 9326 patients in 52 countries, who had been selected for medical management without revascularization within 10 days of their index ACS events, were randomly assigned to prasugrel or clopidogrel therapy in a double-blind, double-dummy fashion. All participants provided written informed consent, and the study protocol conformed to the Declaration of Helsinki guidelines.

Frailty assessment

Self-reported frailty was collected at baseline for all patients aged ≥ 65 years in the TRILOGY ACS trial. Components of the Fried Frailty Index were captured on the case report form. Patients were asked to report unintentional weight loss ≥ 5 kg; decreased grip strength; increased fatigue/lethargy or declining endurance; reduced normal walking speed over short distances (eg, 5 m); or decline in typical physical activity level, within the last 12 months.[11]

Statistical analysis

Descriptive statistics included percentages for discrete variables and medians with 25th, 75th percentiles for continuous variables. Baseline characteristics of men and women ≥ 65 years of age were compared using the Wilcoxon test for continuous variables and χ^2 tests for discrete variables. We examined the distribution of each component of frailty across all men and women and within specific age groups. We used the Fried criteria to categorize patients as "not frail" if they did not report having any of the 5 symptoms, "prefrail" if they had 1 or 2 of the symptoms, and "frail" if they had 3 or more of the symptoms.[11] The distribution of frailty categories among men and women, overall and by age, was examined. The primary outcome of interest was all-cause death. The likelihood of all-cause death by age within each frailty category and sex group was estimated by the robust locally weighted regression method.[13]

To examine whether the prognostic significance of each self-reported symptom of frailty was equivalent, we

categorized patients into mutually exclusive groups based on their responses to the 5 frailty symptoms. For example, patients who reported a decline in physical activity, but none of the other symptoms, were categorized separately from those who had experienced a decline in both physical activity and grip strength. Cox proportional hazard models were used to model time to death for each frailty group relative to patients who were not frail (ie, who did not report having any of the 5 symptoms). These analyses were restricted to only those groups with 20 or more patients. Of the 32 possible unique combinations of the 5 frailty symptoms, 28 were reported by TRILOGY ACS patients, with 15 combinations being reported by more than 20 patients.

Cox proportional hazard models were also used to examine the association between the individual symptoms of frailty and time to death. These analyses were conducted in 2 steps: first, the univariate association between the individual frailty symptom and outcome of interest was calculated, and second, previously developed TRILOGY ACS risk models were used to examine the baseline-adjusted association of the frailty symptom and outcome.[12] To assess the stability of our estimated associations between frailty components and all-cause mortality, we conducted bootstrap analyses by selecting 1000 samples without replacement from the study cohort. We fit the unadjusted and adjusted models and calculated the frequency with which the associations were statistically significant at level $P < 0.05$ over the 1000 samples. In addition to the main effects, a frailty-sex-interaction term was included in the adjusted models to examine whether the association between each frailty symptom and all-cause death was significantly different between men and women.

Results

Self-reported frailty was available for 4996 of 4999 older patients (aged ≥ 65 years) enrolled in TRILOGY ACS. Baseline characteristics of the 2691 (54%) men and 2305 (46%) women are presented in Table 1. Women were older, weighed less, and were more likely to present with unstable angina and Killip class $>$ I, and had lower creatinine clearance compared with men. Rates of comorbidities—including hypertension, hyperlipidemia, diabetes, and atrial fibrillation—were also significantly higher among women than men. Compared with women, men were more likely to smoke; to have a history of MI, peripheral arterial disease (PAD), previous percutaneous coronary intervention (PCI), or coronary artery bypass graft (CABG) surgery; and to undergo angiography prior to randomization. Despite these differences, the median **G**lobal **R**egistry of **A**cute **C**oronary **E**vents (GRACE) risk score at presentation was similar among men and women. There were no significant differences in rates of concomitant medication use between the 2 groups.

Overall, there was no difference in the distribution of frailty symptoms across men and women (Fig. 1). In addition, the prevalence of self-reported frailty categories did not differ across men and women: 72.5% not frail (no symptoms), 23.1% prefrail (1 to 2 symptoms), and 4.4% frail ($\geq$ 3 symptoms) among men and 72% not frail, 22.5% prefrail, and 5.2% frail among women. Decline in physical activity level was the most common symptom reported by both sexes and weight loss the least common. When patients were stratified by age, we observed an increasing trend in loss of grip strength, increased fatigue/lethargy, slow walk, and decreased physical activity among men. In contrast, with the exception of slow walk, there was no significant trend in increasing frailty by age among women. When stratified by age, the percentage of those categorized as prefrail and frail increased significantly among men but not among women (Fig. 2).

During a median follow-up of 17.3 months, 353 (13.1%) men and 266 (11.5%) women died. We have previously reported that relative to not-frail patients, patients who were prefrail had a 45% increased risk of all-cause death (hazard ratio [HR] 1.45, 95% confidence interval [CI], 1.22-1.73), whereas risk of all-cause death was nearly doubled for frail patients (HR 1.98, 95% CI, 1.47-2.68).[12] In our study, although the association between frailty and all-cause death did not appear to differ by sex (sex-frailty interaction was not significant), there was a "dose-response" among men with respect to risk of mortality with increasing frailty across the age spectrum (Fig. 3). After adjusting for age, prefrail men had a 35% increased risk (HR 1.35, 95% CI, 1.07-1.71), and frail men had an 80% increased risk (HR 1.80, 95% CI, 1.22-2.67) of mortality relative to men who were not frail. However, no such pattern was observed among women. Relative to not-frail women, the age-adjusted HR for prefrail women was 1.40 (95% CI, 1.07-1.84) and 1.55 for frail women (95% CI, 0.96-2.49).

Among the 5 individual frailty symptoms, decrease in physical activity and slow walk appeared to provide the most prognostic information (Supplemental Table S1). Patients who reported slow walk alone had an 82% higher hazard of all-cause death (HR 1.82, 95% CI, 1.22-2.71) relative to patients who did not report having any of the 5 frailty symptoms, and the HR associated with physical activity alone was 1.50 (95% CI, 1.18-1.91). These associations between slow walk alone and physical activity alone and mortality were confirmed in 69% and 81% of bootstrap analyses of 1000 samples, respectively. In combination, the effect of these 2 symptoms was not additive; patients who reported both decreased physical activity and slow walk had an 86% higher hazard of all-cause death (HR 1.86, 95% CI, 1.17-2.95). Although the combined presence of loss of physical activity, slow walk, and decreased grip strength was associated with the highest mortality hazard (HR 3.31, 95% CI, 1.48-7.41), this profile occurred only once in the 1000 bootstrap samples.

In multivariable analyses adjusting for all clinical characteristics included in the TRILOGY ACS risk models, slow walk and decreased physical activity were significantly associated with all-cause death (Table 2). These findings were confirmed in 29% and 67% of 1000 bootstrap samples, respectively (Supplemental Table S2). None of the interaction terms between the individual frailty symptoms and sex was significant, suggesting that the association of frailty with all-cause death was similar among men and women.

Discussion

Our study is the first to examine sex differences in self-reported frailty and its symptoms in a large contemporary cohort of medically managed patients with UA/NSTEMI that includes an almost equal number of men and women. The 2691 men and 2305 women aged 65 years and older enrolled in the TRILOGY ACS trial were asked whether they had experienced any of the 5 frailty symptoms included in the

Table 1. Baseline characteristics between elderly (≥ 65 years) men and women enrolled in TRILOGY ACS

	Women (n = 2305)	Men (n = 2691)	*P* value
Demographics			
Median age, y (25^{th}, 75^{th} percentiles)	74 (69, 79)	72 (68, 78)	< 0.01
Weight < 60 kg, n (%)	620/2302 (26.9)	292/2689 (10.9)	< 0.01
Mean weight kg, (SD)	68.4 (14.2)	77.6 (15.5)	< 0.01
Median weight, kg (25^{th}, 75^{th} percentiles)	67 (59, 77)	76 (67, 87)	< 0.01
Presentation characteristics, n (%)			
NSTEMI	1615/2305 (70.1)	2028/2691 (75.4)	< 0.01
Unstable angina	690/2305 (29.9)	663/2691 (24.6)	
Killip class II-IV	397/2304 (17.2)	366/2689 (13.6)	< 0.01
Medical history, n (%)			
Hypertension	2058/2305 (89.3)	2226/2684 (82.9)	< 0.01
Hyperlipidemia	1329/2194 (60.6)	1473/2559 (57.6)	0.04
Diabetes	875/2304 (38.0)	867/2685 (32.3)	< 0.01
Current/recent smoking	138/2283 (6.0)	442/2651 (16.7)	< 0.01
Previous MI	708/2287 (31.0)	1153/2660 (43.3)	< 0.01
Previous PCI	414/2291 (18.1)	708/2668 (26.5)	< 0.01
Previous CABG	219/2300 (9.5)	580/2685 (21.6)	< 0.01
Previous PAD	145/2265 (6.4)	275/2625 (10.5)	< 0.01
Previous AF	284/2240 (12.7)	280/2618 (10.7)	0.03
Previous CHF	458/2294 (20.0)	490/2665 (18.4)	0.16
Baseline risk assessment			
Median GRACE risk score (25th, 75th)	135 (122, 151)	136 (122, 150)	0.80
Median creatinine clearance, mL/min (25^{th}, 75^{th})	56 (42, 71)	64 (49, 80)	< 0.01
Angiography performed before randomization, n (%)	816/2305 (35.4)	1131/2691 (42.0)	< 0.01
Medications at randomization, n (%)			
β-Blocker	1789/2305 (77.6)	2028/2691 (75.4)	0.06
ACE-I/ARB	1819/2305 (78.9)	2073/2691 (77.0)	0.11
Statin	1887/2305 (81.9)	2248/2691 (83.5)	0.12
Proton-pump inhibitor	635/2305 (27.5)	766/2691 (28.5)	0.47

ACE-I, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blocker; CABG, coronary artery bypass grafting; CHF, congestive heart failure; GRACE, Global Registry of Acute Coronary Events; MI, myocardial infarction; NSTEMI, non-ST-segment elevation MI; PAD, peripheral arterial disease; PCI, percutaneous coronary intervention; SD, standard deviation; TRILOGY ACS, **T**a**r**geted Platelet **I**nhibition to C**l**arify the **O**ptimal Strate**gy** to Medically Manage **A**cute **C**oronary **S**yndromes.

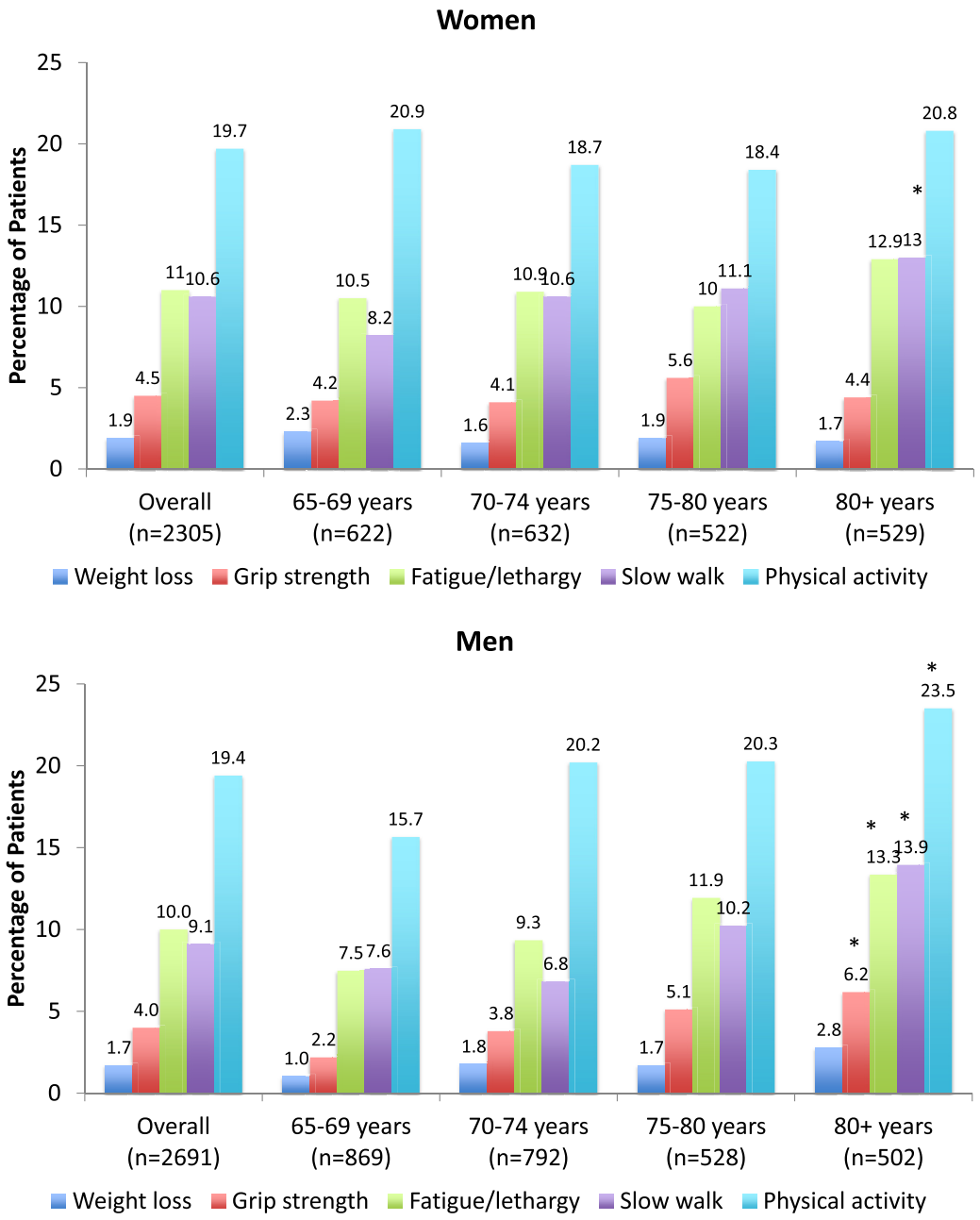
Fried Frailty Index during the previous 12 months: unintentional weight loss, decreased grip strength, increasing fatigue/lethargy or declining endurance, slower pace of walking, or decline in typical physical activity level. Despite similar overall prevalence of frailty, the prevalence of frailty increased significantly with increasing age among men, whereas no such relationship was observed among women. Although sex did not modify the overall effect of frailty on mortality, the impact of frailty appeared more pronounced for men. Self-report of frailty may not only offer important information for the management of older patients with cardiovascular disease but also allows for the capture of this information at a population level, providing unique information on its incidence, prevalence, and association with morbidity and mortality.[5,6,14]

Previous studies have consistently reported higher prevalence of frailty in women than men.[15,16] However, sex differences in prevalence have been shown to vary significantly in community-dwelling elderly, ranging from 2.1% to 16.3%, depending on the frailty phenotype and how it is measured.[16] Although they were older and had higher rates of comorbidities, self-reported prevalence of frailty and its individual symptoms in women was similar to men in our study population consisting of elderly patients enrolled in a large international randomized clinical trial. Despite the lack of sex differences in prevalence of frailty, our finding that the impact of frailty is more pronounced in men is consistent with previous reports. In a meta-analysis of 37,426 participants from 5 studies, Gordon et al. found frailty in men to be associated with higher mortality than in women, even after controlling for age.[15] Similarly, in the 712 participants enrolled in the Norwegian Tromsø 5 Study between 2001 and 2002 and followed until 2016, the mortality HR associated with frailty was 7.09 (95% CI, 3.03-16.58) for men and 2.93 (95% CI, 1.38-6.22) for women.[17]

Among the individual frailty symptoms, slow walk and decreased physical activity appeared to have the most prognostic significance before and after adjustment for clinical characteristics. These findings are consistent with those reported by previous small studies in patients with heart failure and in hospitalized patients with significant coronary disease.[18-20] When present in combination, the association between slow walk and decreased physical activity on outcomes was not additive. These findings suggest that the weighting of frailty symptoms to categorize patients as prefrail and frail deserves re-examination.

Limitations

Our study lacks the validation of self-report of frailty against the gold standard of a clinical examination by a geriatrician.



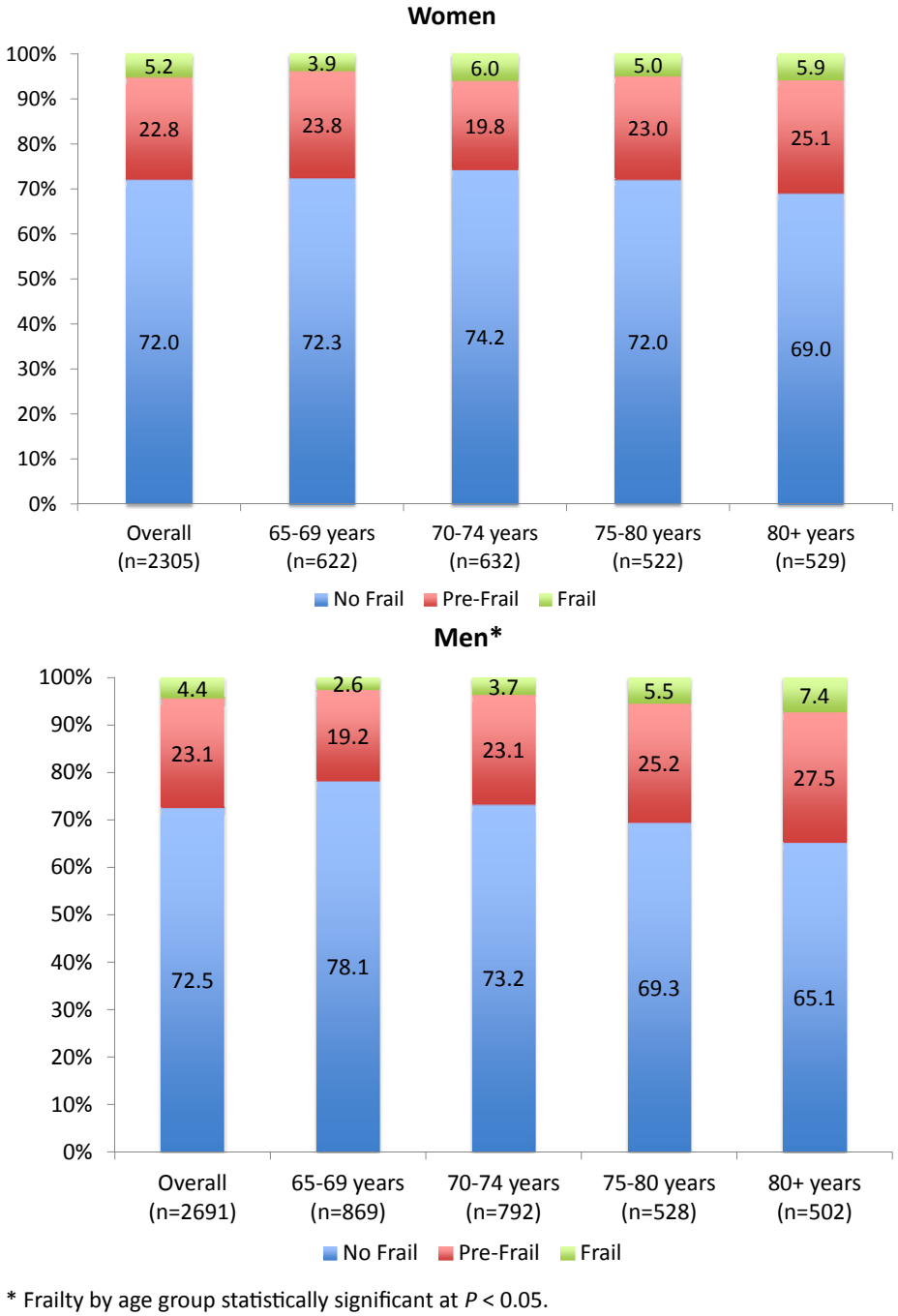
* Frailty measure by age group statistically significant at $P < 0.05$.
Confidence level was adjusted for multiple comparisons.

Figure 1. Distribution of individual frailty symptoms by sex and age.

However, several studies have demonstrated the validity of using self-reported frailty.[21,22] Our study population consists of patients enrolled in a large international clinical trial. Although this ensures that the patients are relatively homogeneous because of strict inclusion/exclusion criteria, they may not be representative of all patients with ACS. Finally, patients were asked to assess their frailty symptoms at baseline only. Therefore, information on whether patients developed frailty symptoms during the extended follow-up period of the trial is not known and accounted for.

Conclusions

The prevalence of self-reported frailty and its symptoms are similar among men and women presenting with ACS. Frailty increased with age among men only, and the association between frailty and all-cause mortality was more pronounced among men compared with women. Self-reported slow walk time and decrease in physical activity, whether or not related directly to biologic frailty, appeared to have the most prognostic significance in this patient population. Patient-reported



* Frailty by age group statistically significant at $P < 0.05$.

Figure 2. Distribution of frailty categories by sex and age.

frailty may be a useful marker to identify elderly patients with ACS at high risk of mortality.

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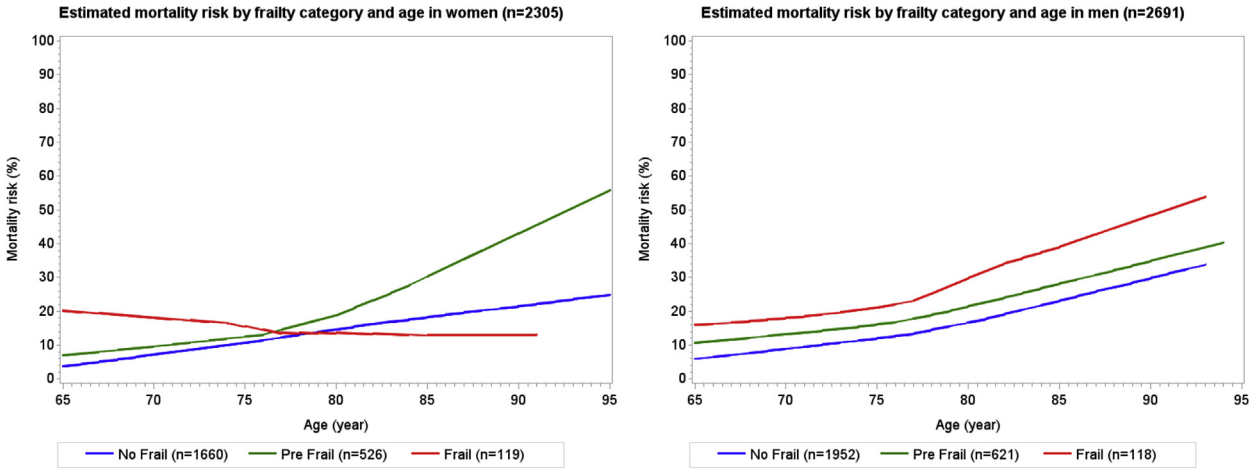

Figure 3. Estimated likelihood of primary end point and mortality by sex and age.

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Table 2. Association between individual frailty symptoms and all-cause death

Frailty component	Unadjusted HR (95% CI)	*P* value	Adjusted HR (95% CI)*	*P* value
Weight loss	1.96 (1.22, 3.15)	< 0.01	1.35 (0.81, 2.25)	0.25
Grip strength	1.29 (0.89, 1.88)	0.19	1.02 (0.69, 1.51)	0.93
Fatigue/lethargy	1.53 (1.22, 1.94)	< 0.01	1.17 (0.91, 1.51)	0.23
Slow walk	1.78 (1.41, 2.32)	< 0.01	1.28 (1.00, 1.63)	0.05
Physical activity	1.64 (1.37, 1.97)	< 0.01	1.31 (1.08, 1.58)	< 0.01
Prefrail	1.45 (1.22, 1.73)	< 0.01	1.2 (0.99, 1.44)	0.05
Frail	1.98 (1.47, 2.68)	< 0.01	1.35 (0.98, 1.84)	0.06

CI, confidence interval; HR, hazard ratio; TRILOGY ACS, **T**ar**g**eted Platelet **I**nhibition to C**l**arify the **O**ptimal Strate**gy** to Medically Manage **A**cute **C**oronary **S**yndromes.

*Adjusted for TRILOGY risk model, which includes age, sex, weight, region, acute coronary syndrome classification, Killip class, blood pressure, heart rate, time to treatment, hypertension, hyperlipidemia, diabetes, smoking, previous myocardial infarction, previous percutaneous coronary intervention, previous coronary artery bypass grafting, previous peripheral arterial disease, previous atrial fibrillation, previous congestive heart failure, family history of coronary artery disease, hemoglobin, creatinine, angiography before randomization, treatment, and concomitant medications.

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Supplementary Material

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