ORIGINAL RESEARCH

Frailty and Outcomes After Myocardial Infarction: Insights From the CONCORDANCE Registry

Ashish Patel, MD; Shaun G. Goodman, MD, MSc; Andrew T. Yan, MD; Karen P. Alexander, MD; Camilla L. Wong, MD; Asim N. Cheema, MD, PhD; Jacob A. Udell, MD, MPH; Padma Kaul, PhD; Mario D'Souza, PhD; Karice Hyun, MAppStat; Mark Adams, MD; James Weaver, MD; Derek P. Chew, MBBS, MPH, PhD; David Brieger, MBBS, PhD; Akshay Bagai, MD, MHS

***Background*—**Little is known about the prognostic implications of frailty, a state of susceptibility to stressors and poor recovery to homeostasis in older people, after myocardial infarction (MI).

***Methods and Results*—**We studied 3944 MI patients aged ≥65 years treated at 41 Australian hospitals from 2009 to 2016 in the CONCORDANCE (Australian Cooperative National Registry of Acute Coronary Care, Guideline Adherence and Clinical Events) registry. Frailty index (FI) was determined using the health deficit accumulation method. All-cause and cardiac-specific mortality at 6 months were compared between frail (FI >0.25) and nonfrail (FI ≤0.25) patients. Among 1275 patients with ST-segment–elevation MI (STEMI), 192 (15%) were frail, and among 2669 non-STEMI (NSTEMI) patients, 902 (34%) were frail. Compared with nonfrail counterparts, frail STEMI patients received 30% less reperfusion therapy and 22% less revascularization during index hospitalization; frail NSTEMI patients received 30% less diagnostic angiography and 39% less revascularization. Unadjusted 6-month all-cause mortality (STEMI: 13% versus 3%; NSTEMI: 13% versus 4%) and cardiac-specific mortality (STEMI: 6% versus 1.4%, NSTEMI: 3.2% versus 1.2%) were higher among frail patients. After adjustment for known prognosticators, FI was significantly associated with higher 6-month all-cause (STEMI: odds ratio: 1.74 per 0.1 FI [95% confidence interval, 1.37–2.22], $P<0.001$; NSTEMI: odds ratio: 1.62 per 0.1 FI [95% confidence interval, 1.40–1.87], $P<0.001$) but not cardiac-specific mortality (STEMI: $P=0.99$; NSTEMI: $P=0.93$).

***Conclusions*—**Frail patients receive lower rates of invasive cardiac care during MI hospitalization. Increased frailty was independently associated with increased postdischarge all-cause mortality but not cardiac-specific mortality. These findings inform identification of frailty during MI hospitalization as a potential opportunity to address competing risks for mortality in this high-risk population. **(*J Am Heart Assoc*. 2018;7:e009859. DOI: 10.1161/JAHA.118.009859.)**

Key Words: frailty • health services research • myocardial infarction • outcomes

Frailty is defined as state of susceptibility in which a person has decreased physical reserve that leads to a greater likelihood of an adverse outcome when a stressor is applied.[1] The overall prevalence of frailty in adults aged ≥65 years has been estimated at ≈10%. However, in patients with significant cardiovascular disease, the prevalence may be as high as 60%.[2] Frailty has been associated with increased major adverse cardiac events after myocardial infarction (MI).[3–6] Mechanisms proposed for worse outcomes are likely multifactorial. Compared with nonfrail patients, frail patients have delayed recognition of the symptoms delayed recognition of the symptoms and contact with medical care, less ability to adhere to medical treatment, risk of delirium with polypharmacy, and therapeutic nihilism toward invasive procedures. Understanding the impact of frailty on therapy selection and outcomes, particularly invasive therapies, is an important consideration in the context of a rapidly aging

From the Terrence Donnelly Heart Centre (A.P., S.G.G., A.T.Y., A.N.C., A.B.), and Division of Geriatric Medicine (C.L.W.), St Michael's Hospital, Toronto, Ontario, Canada; University of Toronto, Ontario, Canada (A.P., S.G.G., A.T.Y., C.L.W., A.N.C., J.A.U., A.B.); Duke Clinical Research Institute, Durham, NC (K.P.A.); Women's College Research Institute and Cardiovascular Division, Women's College Hospital and Peter Munk Cardiac Centre, University Health Network, Toronto, Ontario, Canada (J.A.U.); Canadian VIGOUR Centre, University of Alberta, Edmonton, Canada (S.G.G., P.K.); School of Public Health, University of Sydney, Clinical Research Centre, Sydney Local Health District, Sydney, Australia (M.D.); ANZAC Institute, Westmead Clinical School, Sydney Medical School (K.H.), University of Sydney, Australia; Department of Cardiology, Royal Prince Alfred Hospital, Sydney, Australia (M.A.); University of New South Wales, Sydney, Australia (J.W.); Department of Cardiology, Flinders University, Adelaide, Australia (D.P.C.); Department of Cardiology, Concord Hospital, University of Sydney, Sydney, Australia (D.B.).

Correspondence to: Akshay Bagai, MD, MHS, Terrence Donnelly Heart Center, St. Michael's Hospital, University of Toronto, Ontario, Canada. E-mail: bagaia@smh.ca

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Clinical Perspective

What Is New?

- Frail patients receive lower rates of invasive cardiac care during hospitalization for myocardial infarction.
- Increased frailty is independently associated with increased postdischarge all-cause mortality but not cardiac-specific mortality.

What Are the Clinical Implications?

- Older patients should be screened for frailty routinely during index hospitalization for myocardial infarction.
- Additional use of invasive cardiac therapies alone may not necessarily be sufficient to improve prognosis for frail patients.
- Management of noncardiac risk both during index hospitalization and after discharge presents a valuable opportunity to improve care and outcomes for this high-risk population.

population with increasing medical complexity.[7] Although technical and procedural innovations have expanded the therapeutic armamentarium available to treat patients, many of these therapies have not been explicitly tested in older frail patients. Consequently, at the bedside, there is limited guidance on whether and how metrics of frailty should be applied to influence risk–benefit decision-making for utilization of these interventions. The CONCORDANCE (Australian Cooperative National Registry of Acute Coronary Care, Guideline Adherence, and Clinical Events) registry presents an opportunity to evaluate the clinical characteristics, treatments, and outcomes of patients according to baseline frailty status on presentation at the hospital. In this study, we utilized the CONCORDANCE registry database to report the prevalence of frailty in older adults presenting with MI using a frailty index (FI) (deficit accumulation model). We specifically sought to explore the association of frailty in older MI populations with the use of evidence-based therapies and outcomes after MI.

Methods

The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure.

Data Source and Analysis Population

All patients aged ≥65 years with ST-segment–elevation MI (STEMI) or non-STEMI (NSTEMI) in the CONCORDANCE registry from 2009 to 2016 were included in the initial study population (n=5006 from 41 hospitals). CONCORDANCE (ACTRN12614000887673), a prospective, Australian registry of MI patients, was designed within a comparative effectiveness research framework to collect and report data from hospitals located in geographically diverse regions of Australia and has been described previously.[8] Information including patient demographics, presenting characteristics, past medical history, in-hospital management, and outcomes after discharge were entered into a Web-based database using an electronic clinical record form. Because data were primarily at the local site for quality improvement, an opt-out consent process was applied with a consent waiver for patients who were too ill to provide informed consent. Patients could be enrolled in the registry only once over a 12-month period. All participating hospitals secured institutional review board approval. Approval for this analysis was granted by the lead ethics committee, Concord Hospital, Sydney Local Health district.

Frailty Assessment

Twenty-eight variables were identified from the baseline data (see Table 1) to construct a FI using a deficit accumulation model, as described previously.[9,10] In brief, variables in a FI can be diseases or comorbidities, symptoms, signs, or laboratory measures, with each being age-related; not saturating too early (ie, not found in all individuals early on); associated with adverse outcomes; and, as a group, covering several bodily systems. Dichotomous variables (eg, presence of hypertension) were coded as 0 for absent and 1 for present. Dichotomous scores were assigned for continuous variables as appropriate. For number of cardiovascular medications, for example, ≥3 medications were coded as 1 and <3 medications were coded as 0. Each participant received a score between 0 and 28, and the FI was defined as the frailty score divided by 28, ranging between 0 and 1. While frailty in the deficit accumulation model is a continuum, similar prior analyses[3] have stratified patients into 2 groups: (1) *frail*, defined as a FI ≥0.25 (ie, frailty score ≥7) and (2) *nonfrail*, defined as a FI <0.25 (ie, frailty score <7).

Statistical Analysis

Continuous variables are reported as medians with 25th and 75th percentiles and compared using the Wilcoxon rank-sum test. Categorical variables are presented as proportions and compared using the χ^2 test. Baseline demographics, presentation characteristics, in-hospital management including invasive and medical therapy, and in-hospital outcomes (all-cause mortality, cardiac-specific mortality, and major bleeding) stratified by MI type (STEMI and NSTEMI) were compared between the 2 frailty groups.

Cardiac-specific mortality was defined as death due to MI, arrhythmia, cardiac rupture, cardiogenic shock, or other cardiac reasons provided by free text and adjudicated by

Table 1. Frailty Index Parameters

Variable	Scoring on Index
Weight <60 kg	Yes=1, No=0
Previous MI	Yes=1, No=0
Previous angiogram positive for coronary disease	Yes=1, No=0
Previous CHF	Yes=1, No=0
Previous PCI	Yes=1, No=0
Previous coronary bypass surgery	Yes=1, No=0
Previous AF	Yes=1, No=0
Previous DVT/PE	Yes=1, No=0
Previous major bleed	Yes=1, No=0
Permanent pacemaker	Yes=1, No=0
ICD	Yes=1, No=0
Chronic renal failure	Yes=1, No=0
Dialysis	Yes=1, No=0
Previous stroke or TIA	Yes=1, No=0
Diabetes mellitus	Yes=1, No=0
Hypertension	Yes=1, No=0
Dyslipidemia	Yes=1, No=0
Smoking history	Active=1, Former or Never=0
PAD	Yes=1, No=0
Dementia/cognitive impairment	Yes=1, No=0
Impaired mobility	Yes=1, No=0
Incontinence	Yes=1, No=0
Liver disease	Yes=1, No=0
Lung disease	Yes=1, No=0
Cancer limiting life expectancy	Yes=1, No=0
Polypharmacy (≥3 cardiovascular medications)	Yes=1, No=0
Hb <100 g/L	Yes=1, No=0
Prior mechanical valve replacement	Yes=1, No=0

AF indicates atrial fibrillation; CHF, congestive heart failure; DVT/PE, deep vein thrombosis/pulmonary embolism; ICD, implantable cardioverter-defibrillator; MI, myocardial infarction; PAD, peripheral arterial disease; PCI, percutaneous coronary intervention; TIA, transient ischemic attack.

the CONCORDANCE management committee. *Major bleeding* was defined as having intracranial bleeding, retroperitoneal bleeding, intraocular bleeding, gastrointestinal/genitourinary bleeding requiring intervention, (endoscopy/transfusion) or cessation of therapies, access-site hemorrhage requiring radiological or surgical intervention, ≥5-cm-diameter hematoma at puncture site, reoperation for bleeding, bleeding leading to a prolongation of hospitalization, decrease in Hb >2 g/dL in the presence of a bleeding source, decrease in Hb >3 g/dL in the absence of a bleeding source, or any bleeding event requiring a blood or blood product transfusion. Among patients discharged alive from the index hospitalization, clinical outcomes including all-cause and cardiac-specific mortality and rehospitalization for heart cause at 6 months were evaluated.

We then evaluated whether FI is a predictor of in-hospital all-cause and cardiac-specific mortality. The generalized estimating equation method with an exchangeable working correlation structure was used to account for within-site clustering of patients (ie, within-site correlation for response).[11] Multivariable logistic regression models were used to estimate the marginal effect of FI separately by MI type (NSTEMI and STEMI) after adjusting for age, sex, and covariates previously identified as significantly associated with in-hospital mortality among patients with MI.[12] These covariates include heart failure on presentation, cardiogenic shock, heart rate, systolic blood pressure, cardiac arrest, creatinine clearance, and initial troponin (as a ratio of the upper limit of normal). Finally, we evaluated whether FI is a predictor of 6-month all-cause and cardiac-specific mortality. Multivariable logistic regression models were used to estimate the marginal effect of FI separately by MI type (NSTEMI and STEMI) after adjusting for sex and GRACE (Global Registry of Acute Coronary Events) risk score.[13,14] Odds ratios (ORs) with 95% confidence intervals (CIs) were reported per 0.1 FI. A value of $P<0.05$ was considered significant for all tests. All statistical analyses were performed by the CONCORDANCE group within the ANZAC Institute with SAS software (v9.4; SAS Institute).

Results

The study population comprised 3944 patients; 1275 had STEMI, and 2669 had NSTEMI.

STEMI Patients

Frailty score distribution among the STEMI patients is shown in Figure 1A; the median FI was 0.11 (interquartile range; 0.04–0.18); 192 (15%) patients were considered frail. Compared with nonfrail counterparts, frail patients were older and had more cardiac and noncardiac comorbidities, cognitive impairment, impaired mobility, incontinence, and wish for no resuscitation (Table 2). Frail patients also had lower left ventricular function and more cardiac arrest and congestive heart failure on presentation (Table 3).

Use of fibrinolysis, cardiac catheterization, primary percutaneous coronary intervention, and revascularization overall, both percutaneous coronary intervention and coronary artery bypass grafting, was significantly lower among frail patients (Table 3). Among patients treated with primary percutaneous coronary intervention or fibrinolysis, duration from first

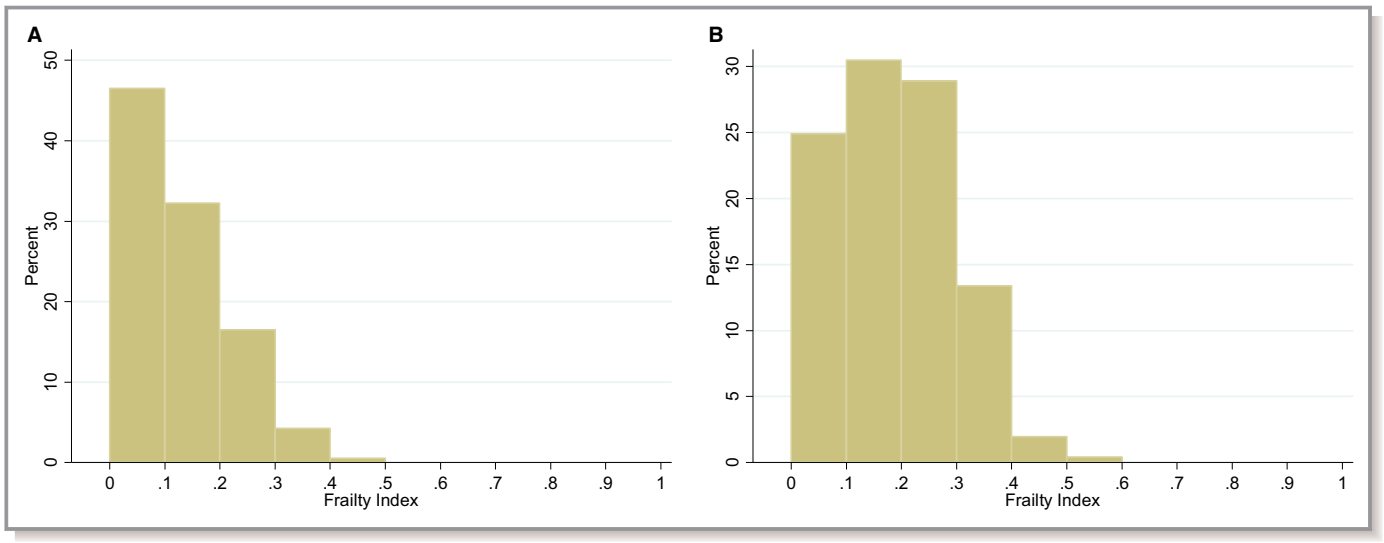

Figure 1. Frailty index distribution among patients with (A) STEMI (ST-segment–elevation myocardial infarction) (B) NSTEMI (non-ST-segment–elevation myocardial infarction).

medical contact to reperfusion therapy was significantly longer among frail patients. In-hospital use of aspirin, ADP receptor inhibitors, β-blockers, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, and statins was lower among frail patients (Figure 2). Among patients discharged from the hospital, however, use of only aspirin (not other cardiac medications) was lower among frail patients (Figure 3); frail patients were more likely to be treated with anticoagulants at discharge. At discharge, referral to cardiac rehabilitation was 34% lower among frail patients.

Clinical outcomes

All-cause and cardiac-specific mortality in hospital and major bleeding were higher among frail patients (Table 4). After adjustment, the FI was significantly associated with higher all-cause in-hospital mortality (OR: 1.38 per 0.1 FI; 95% CI, 1.05–1.83; *P*=0.02) but not cardiac-specific in-hospital mortality (OR: 0.54 per 0.1 FI; 95% CI, 0.24–1.21; *P*=0.13). Among patients discharged from the hospital, rates of all-cause and cardiac-specific mortality and readmission for heart disease were higher among frail patients at 6 months. After adjustment, the FI was associated with higher 6-month all-cause mortality (OR: 1.74 per 0.1 FI; 95% CI, 1.37–2.22; *P*<0.001) but not cardiac-specific mortality (OR: 1.00 per 0.1 FI; 95% CI, 0.53–1.90; *P*=0.99).

NSTEMI Patients

Frailty score distribution among the NSTEMI patients is shown in Figure 1B; the median FI was 0.18 (interquartile range: 0.11–0.25); 902 (34%) patients were considered frail. Compared with nonfrail NSTEMI patients, frail NSTEMI patients were older and had more cardiac and noncardiac comorbidities, cognitive impairment, impaired mobility, incontinence, and wish for no resuscitation (Table 2). Frail patients also had lower left ventricular function and more congestive heart failure on presentation (Table 3).

Use of cardiac catheterization, percutaneous coronary intervention, and coronary artery bypass grafting were significantly lower among frail patients (Table 3). In-hospital use of aspirin and ADP receptor inhibitor, but not other secondary cardiac medications, was lower among frail patients (Figure 4). Among patients discharged from the hospital, use of aspirin was lower, but use of ADP receptor inhibitors was higher among frail patients (Figure 5). At discharge, referral to cardiac rehabilitation was 23% lower among frail patients.

Clinical outcomes

All-cause and cardiac-specific in-hospital mortality rates were higher among frail patients (Table 4). There was no difference in major bleeding. After adjustment, the FI remained significantly associated with higher all-cause in-hospital mortality (OR: 1.49 per 0.1 FI; 95% CI, 1.34–1.95; *P*=0.004) but not cardiac-specific in-hospital mortality (OR: 1.10 per 0.1 FI; 95% CI, 0.66–1.85; *P*=0.71). Among patients discharged from the hospital, all-cause and cardiac mortality and readmission for heart disease were higher among frail patients at 6 months. After adjustment, the FI was associated with higher 6-month all-cause mortality (OR: 1.62 per 0.1 FI; 95% CI, 1.40–1.87; *P*<0.001) but not cardiac-specific mortality (OR: 1.01 per 0.1 FI; 95% CI, 0.78–1.32; *P*=0.93).

Table 2. Patient Characteristics

	STEMI			NSTEMI		
	Nonfrail (n=1083)	Frail (n=192)	*P* Value	Nonfrail (n=1767)	Frail (n=902)	*P* Value
Demographics						
Age, y	72 (68–79)	78 (71–84)	<0.001	74 (69–80)	77 (71–83)	<0.001
Sex, male	732 (67.6)	133 (69)	0.38	1114 (63)	624 (69.2)	0.004
Weight, kg	78 (68–87)	75 (62–87)	0.37	78 (68–90)	79 (68–92)	0.49
Private health insurance	322 (29.7)	42 (21.8)	0.001	459 (26)	189 (21)	0.01
Regular general practitioner / healthcare provider	978 (90.3)	184 (95.8)	0.18	1648 (93.2)	855 (94.8)	0.11
Past medical history						
Prior MI	94 (8.7)	127 (66.1)	<0.001	297 (16.8)	676 (74.9)	<0.001
Prior HF	26 (2.4)	45 (23.4)	<0.001	74 (4.2)	292 (32.4)	<0.001
Previous angiogram identifying coronary disease	96 (8.7)	133 (69.3)	<0.001	362 (20.5)	726 (80.5)	<0.001
Previous PCI	61 (5.6)	84 (43.8)	<0.001	147 (8.3)	419 (46.5)	<0.001
Previous CABG	14 (1.3)	51 (26.6)	<0.001	141 (8)	340 (37.7)	<0.001
Previous AF	69 (6.4)	54 (28.1)	<0.001	200 (11.3)	276 (30.6)	<0.001
Previous DVT/PE	30 (2.8)	21 (10.9)	<0.001	61 (3.5)	91 (10.1)	<0.001
Previous major bleed	9 (0.8)	12 (6)	<0.001	34 (1.9)	52 (5.8)	<0.001
Previous metal valve replacement	3 (0.3)	4 (2.1)	0.002	10 (0.6)	23 (2.5)	<0.001
Permanent pacemaker	8 (0.7)	13 (6.8)	<0.001	36 (2)	100 (11.1)	<0.001
ICD	4 (0.4)	3 (1.6)	0.01	5 (0.3)	27 (3)	<0.001
Chronic renal failure	37 (3.4)	59 (30.7)	<0.001	106 (6)	285 (31.6)	<0.001
Previous stroke/TIA	61 (5.6)	46 (24)	<0.001	113 (6.4)	199 (22.1)	<0.001
Diabetes mellitus	207 (19.1)	93 (48.4)	<0.001	422 (23.9)	480 (53.2)	<0.001
Hypertension	625 (57.7)	169 (88)	<0.001	1169 (66.2)	819 (90.8)	<0.001
Dyslipidemia	453 (41.8)	157 (81.8)	<0.001	925 (52.3)	759 (84.1)	<0.001
Smoking history			0.15			0.01
Never smoked	507 (46.8)	76 (39.6)		796 (45)	368 (40.8)	
Ex-smoker	372 (34.3)	79 (41.1)		796 (45)	417 (46.2)	
Current smoker	199 (18.4)	36 (18.8)		167 (9.5)	115 (12.7)	
PAD	38 (3.5)	35 (18.2)	<0.001	94 (5.3)	193 (21.4)	<0.001
Dementia/cognitive impairment	28 (2.6)	28 (14.6)	<0.001	45 (2.5)	95 (10.5)	<0.001
Impaired mobility	65 (6)	66 (34.4)	<0.001	133 (7.5)	292 (32.4)	<0.001
Incontinence	26 (2.4)	28 (14.6)	<0.001	36 (2)	85 (9.4)	<0.001
Liver disease	15 (1.4)	1 (0.5)	0.35	20 (1.1)	34 (3.7)	0.001
Lung disease	109 (10)	55 (28.6)	<0.001	206 (11.7)	242 (26.8)	<0.001
Cancer limiting life expectancy	31 (2.9)	13 (6.8)	0.01	40 (2.2)	37 (4.1)	<0.001
Not for resuscitation	61 (5.6)	39 (20.3)	<0.001	62 (3.5)	112 (12.4)	<0.001
Polypharmacy (≥3 cardiovascular medications) before admission	158 (15)	131 (68)	<0.001	495 (28)	719 (80)	<0.001
GRACE risk score	132.0 (120.4–148.6)	147.6 (133.2–170.8)	<0.001	121.7 (106.6–138.2)	133.7 (117.9–150.1)	<0.001

Data are shown as median (interquartile range) or number (percentage). AF indicates atrial fibrillation; CABG, coronary artery bypass grafting; DVT/PE, deep vein thrombosis/pulmonary embolism; GRACE, Global Registry of Acute Coronary Events; HF, heart failure; ICD, implantable cardioverter-defibrillator; MI, myocardial infarction; NSTEMI, non–ST-segment–elevation myocardial infarction; PAD, peripheral arterial disease; PCI, percutaneous coronary intervention; STEMI, ST-segment–elevation myocardial infarction; TIA, transient ischemic attack.

Table 3. Presentation Characteristics and In-Hospital Management

Variable	STEMI			NSTEMI		
	Nonfrail (n=1083)	Frail (n=192)	*P* Value	Nonfrail (n=1767)	Frail (n=902)	*P* Value
Presentation characteristics						
Ambulance called	681 (62.8)	139 (72.4)	0.003	967 (54.7)	612 (67.8)	<0.001
Heart rate, beats/min	75 (64–89)	80 (66–98)	0.003	79 (67–92)	81 (68–96)	0.002
SBP, mm Hg	135 (117–154)	137 (111–155)	0.50	140 (124–160)	140 (123–158)	0.10
Killip class			<0.001			<0.001
1	950 (87.7)	136 (70.8)		1543 (87.3)	619 (68.6)	
2	100 (9.2)	29 (15.1)		178 (10.1)	226 (25.1)	
3	20 (1.8)	14 (7.3)		42 (2.4)	50 (5.5)	
4	13 (1.2)	13 (6.8)		4 (0.2)	7 (0.8)	
Cardiac arrest on admission	92 (8.5)	24 (12.5)	0.10	29 (1.6)	22 (2.4)	
Hb <100 g/L	20 (1.8)	23 (12.0)	<0.001	55 (3.1)	111 (12.3)	<0.001
Ratio of initial creatinine/ULN	0.8 (0.7–1.0)	1.1 (0.8–1.5)	<0.001	0.8 (0.7–1.0)	1.0 (0.8–1.4)	0.54
In-hospital management						
Echocardiogram	816 (75.3)	133 (69.3)	0.11	1039 (58.8)	444 (40.2)	<0.001
LV function*			0.01			<0.001
Normal	211 (25.8)	26 (19.5)		606 (58.3)	165 (37.3)	
Mild impairment	178 (21.8)	26 (19.5)		184 (17.7)	71 (16.0)	
Moderate impairment	175 (21.4)	35 (26.3)		143 (13.8)	76 (17.1)	
Severe impairment	53 (6.5)	19 (14.2)		54 (5.2)	61 (13.7)	
Intra-aortic balloon pump	45 (4.2)	4 (2.1)	0.15	23 (1.3)	8 (0.9)	0.37
Ventilation	93 (8.6)	26 (13.5)	0.01	99 (5.6)	36 (2.9)	0.06
Cardiac catheterization	999 (92.2)	142 (74.0)	<0.001	1479 (83.7)	530 (58.8)	<0.001
Thrombolysis	340 (31.4)	36 (18.8)	<0.001	NA	NA	NA
First medical contact to lysis time, min	63 (43–95)	90 (62–139)	0.01	NA	NA	NA
Symptom onset to lysis time, h	2.7 (1.6–5.0)	3.2 (2.0–5.6)	0.16	NA	NA	NA
Primary PCI	528 (48.7)	68 (35.4)	0.007	NA	NA	NA
First medical contact to primary PCI time, min	127 (91–262)	156.5 (118–349)	0.03	NA	NA	NA
Symptom onset to primary PCI time, h	3.8 (2.4–9.9)	4.4 (2.7–13.4)	0.48	NA	NA	NA
PCI	773 (71.4)	101 (52.6)	<0.001	688 (38.9)	228 (25.3)	<0.001
CABG	90 (8.3)	7 (3.6)	0.01	218 (12.3)	58 (6.4)	<0.001
Revascularization (PCI or CABG)	936 (86.4)	129 (67.2)	<0.001	904 (51.2)	284 (31.5)	<0.001
Reperfusion (primary PCI or thrombolysis)	822 (75.9)	102 (53.1)	<0.001	NA	NA	NA
Referral to cardiac rehabilitation	815 (75.3)	94 (49)	<0.001	1118 (63.3)	435 (48.2)	<0.001

Data are shown as median (interquartile range) or number (percentage). CABG indicates coronary artery bypass grafting; LV, left ventricular; NA, not applicable; NSTEMI, non–ST-segment–elevation myocardial infarction; PCI, percutaneous coronary intervention; SBP, systolic blood pressure; STEMI, ST-segment–elevation myocardial infarction; ULN, upper limit of normal.
*LV function was determined among patients undergoing echocardiogram.

Discussion

In this large, contemporary evaluation of treatment and outcomes of older MI patients, several important observations regarding prevalence and outcomes associated with frailty emerge. Compared with nonfrail patients, frail patients presenting with MI receive less medical and invasive in-hospital care including diagnostic angiography, reperfusion therapy, and coronary revascularization. Referral to rehabilitation at discharge was also lower among frail patients. Although in-hospital and postdischarge all-cause and cardiac-specific mortality was significantly greater among frail

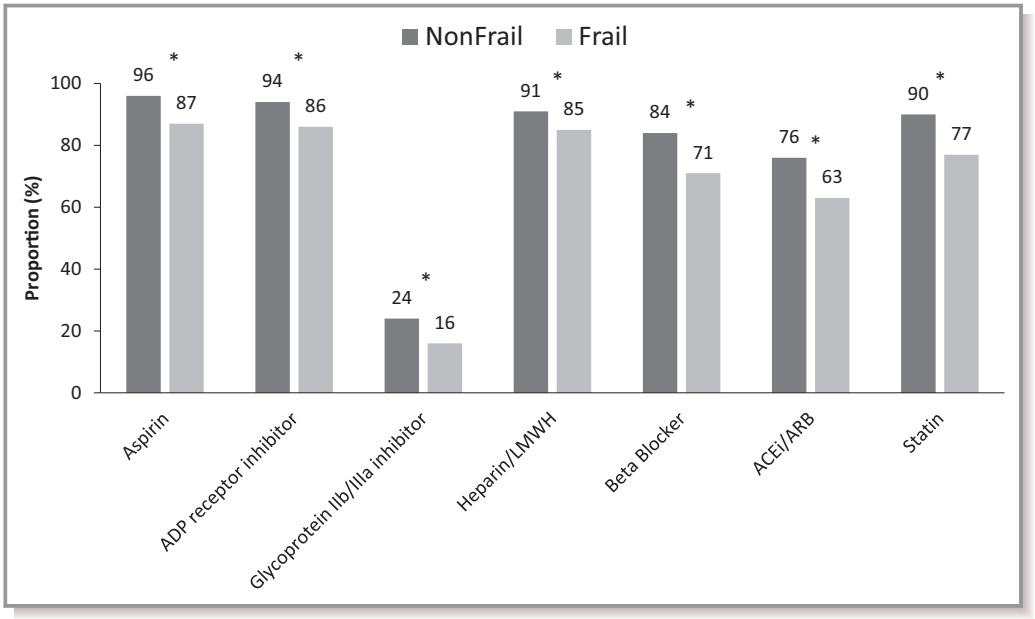

Figure 2. In-hospital medical therapy by frailty classification among patients with ST-segment–elevation myocardial infarction. **P*<0.05. ACEi indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; LMWH, low-molecular-weight heparin.

patients, after adjustment, frailty remained significantly associated with increased in-hospital and 6-month all-cause mortality but not cardiac-specific mortality. These findings reinforce that presence of frailty identifies patients who are at increased risk of death after MI. However, additional cardiac interventions—including invasive coronary interventions alone—may not necessarily be sufficient to improve the prognosis of this high-risk population. Improving the outcomes of this patient population will require understanding MI presentation in the context of other conditions and patient goals of care. It also requires addressing noncardiac reasons for mortality during and after hospitalization for MI.

Our study adds to the growing body of evidence on the implications of frailty in cardiovascular medicine. Frailty is of high priority given aging and the increasingly complex nature of cardiovascular patients. There is no gold standard for frailty assessment, with upward of 20 tools that have been developed to measure frailty.[15] Phenotypic assessment of frailty can be difficult in patients with acute illness and, in general, predicts mortality less well than measures that

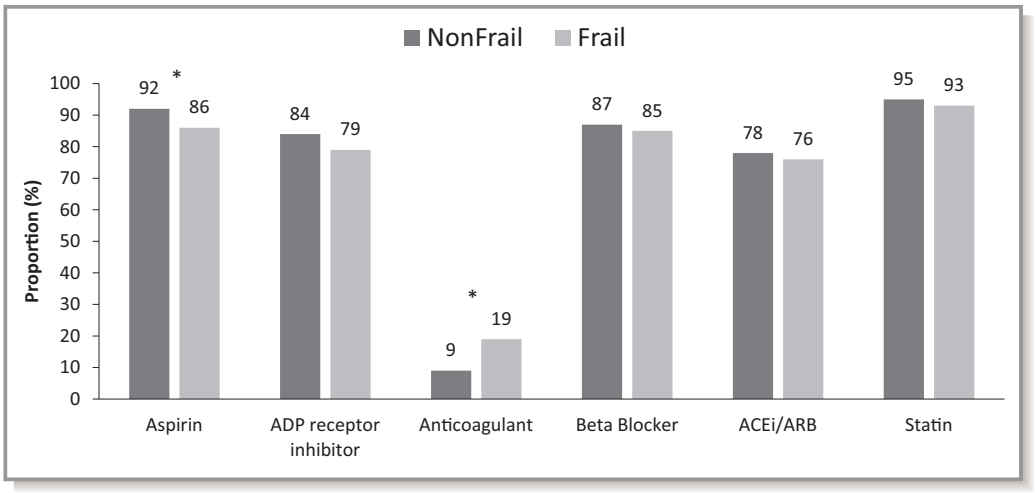

Figure 3. Discharge medical therapy by frailty classification among patients with ST-segment–elevation myocardial infarction. **P*<0.05. ACEi indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.

Table 4. In-hospital and 6-Month Postdischarge Outcomes for STEMI and NSTEMI Patients

	Nonfrail	Frail	*P* Value
In-hospital outcomes			
STEMI (n)	1083	192	
All-cause death	90 (8.3)	46 (24)	<0.001
Death due to cardiac causes	81 (7.5)	39 (20.3)	0.52
Major bleeding	110 (10.2)	30 (15.6)	0.02
NSTEMI (n)	1767	902	
All-cause death	50 (2.8)	63 (7)	<0.001
Death due to cardiac causes	43 (2.4)	52 (5.8)	0.59
Major bleeding	180 (10.2)	107 (11.9)	0.29
Six-month postdischarge outcomes			
STEMI (n)	810	117	
All-cause mortality	27 (3.3)	15 (12.8)	<0.001
Death due to a cardiac cause	11 (1.4)	7 (6.0)	<0.001
Rehospitalization for heart disease	158 (19.5)	34 (29.1)	0.01
NSTEMI (n)	1373	619	
All-cause mortality	54 (3.9)	78 (12.6)	<0.001
Death due to cardiac cause	16 (1.2)	20 (3.2)	<0.001
Rehospitalization for heart disease	278 (20.2)	182 (29.4)	<0.001

Data are shown as number (percentage) except as noted. NSTEMI indicates non–ST-segment–elevation myocardial infarction; STEMI, ST-segment–elevation myocardial infarction.

consider >5 deficits.[16] Dodson et al demonstrated that gait speed, a component of the frailty phenotype, measured 1 month after MI was associated with a 2-fold increase in mortality at 1 year, but its significance independent of clinical factors was unclear.[17] As such, in the present study we employed the health deficit accumulation method to assess for frailty. This approach recognizes that frailty is a continuum —it is not all or none; the more deficits a person has, across more organ systems and physiologic parameters, the more likely that person is to be frail. Although the idea and approach are relatively simple, the results yielded by the FI have been consistent across many settings, even though not every FI considers the same deficits, or even the same number of deficits.[10,18,19] The prognostic implications of FI have been demonstrated not only in a variety of different chronic conditions (osteoporosis,[20] human immunodeficiency virus and AIDS,[21] kidney disease[22]) but also in acute disease states (trauma[23]).

In patients with significant cardiovascular disease, the prevalence of frailty has been shown to be as high as 60%.[2] In this study of older Australian MI patients, 15% of STEMI patients and 34% of NSTEMI patients were classified as frail. In addition to greater cardiac and noncardiac comorbidities, frail patients had greater deficits in cognition, mobility, and continence. Our findings demonstrating that frailty is not only associated with increased in-hospital but also midterm all-cause mortality and hospitalizations following MI are consistent with prior analyses.[3–6] Despite this higher risk, frail patients were managed less aggressively compared with their nonfrail counterparts. Frail STEMI patients received 30% less reperfusion therapy and 22% less revascularization during index hospitalization. In-hospital use of aspirin, ADP receptor inhibitors, and other secondary prevention medications was also lower among frail patients. Findings were similar among frail NSTEMI patients who received 30% less diagnostic angiography and 39% less revascularization compared with nonfrail NSTEMI patients. This treatment-risk gap, in which evidence-based invasive and pharmacological therapies are, paradoxically, used less often in higher risk patients has been observed previously.[24] Elimination of this treatment-risk paradox has been advocated to fully realize the benefits of these therapies in high-risk patients.[25] Nevertheless, more often than not, including in our database, the reasons why certain evidence-based therapies were not offered are not ascertained. Furthermore, such patients are often not included in clinical trials of these therapies. Consequently, uncertainty remains about whether the overall outcomes of such frail patients who did not receive these therapies can be improved with increased their use.

We found that after adjustment for traditional factors associated with increased mortality after MI, frailty identified patients at increased risk of all-cause, but not cardiac-specific, mortality in hospital and after discharge, likely due to increased risk of competing noncardiac causes of death. Efforts to mitigate the treatment-risk paradox in such patients with additional use of invasive cardiac therapies alone may not necessarily be sufficient to improve prognosis. Management of frail patients with numerous health deficits is complex. In addition to identifying increased risk of cardiac mortality, FI, as determined by the accumulation of such health deficits that are easy to assess at the bedside, identifies patients at increased risk of noncardiac death after MI. Such patients may benefit from more comprehensive care (eg, geriatrics consultation, prevention of delirium and deconditioning) during hospital admission for MI and close follow-up after discharge. Compared with nonfrail counterparts, referral to rehabilitation was 34% and 23% lower for frail STEMI and NSTEMI patients, respectively. The benefit of multidisciplinary cardiac rehabilitation in terms of exercise capacity, obesity indexes, behavioral characteristics, and quality of life has been demonstrated in elderly patients.[26,27] Consequently, routine screening and identification of frailty during hospitalization for MI and management of noncardiac risk both during index hospitalization and after discharge

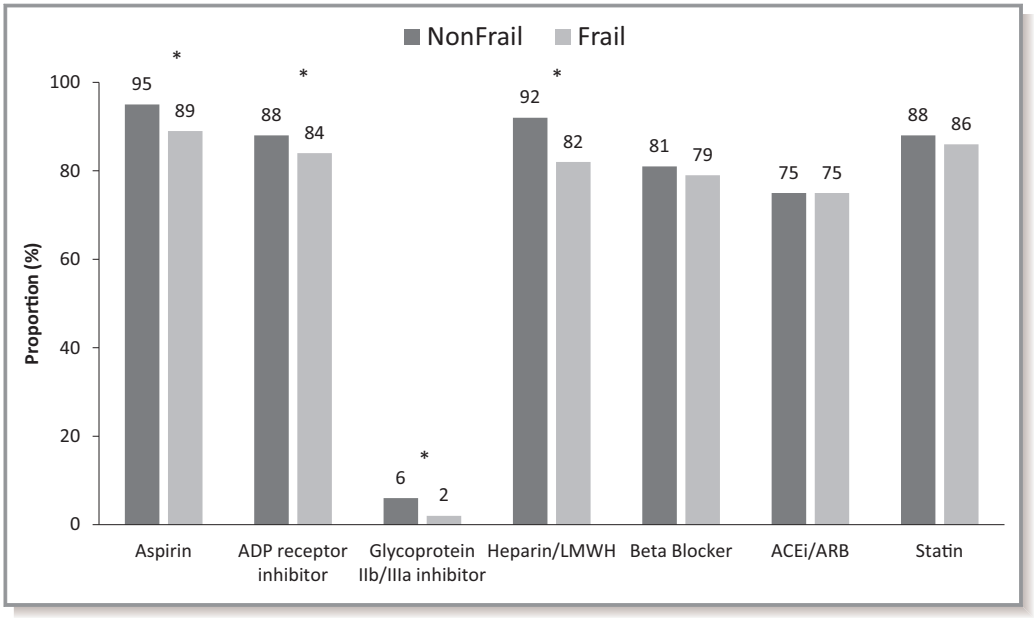

Figure 4. In-hospital medical therapy by frailty classification among patients without ST-segment–elevation myocardial infarction. *$P<0.05$. ACEi indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; LMWH, low-molecular-weight heparin.

present valuable opportunities to improve care for this high-risk population. Inclusion of frail patients in future studies of cardiac therapies will also inform how best to use such therapies in these patients.

Limitations

Several limitations should be considered. Although it has been suggested that at least 30 variables be included in the FI,[9] in the present study, the available number of candidate variables was 28; however, a variety of deficits were incorporated covering health attitudes and practices, function, comorbidity, and physical performance. Data were not available for frailty phenotype, in which frailty is defined as a clinical syndrome displaying ≥3 of the following criteria: unintentional weight loss, exhaustion, slow walking speed, low physical activity, and weakness.[28] Although the 2 approaches are conceptually similar, it has been shown that, at least when analyzed as a continuous variable, the FI can more precisely discriminate risk of death as well as measure change after an intervention.[15] Data were self-reported with the associated potential for inaccuracy. The data source also lacks precision

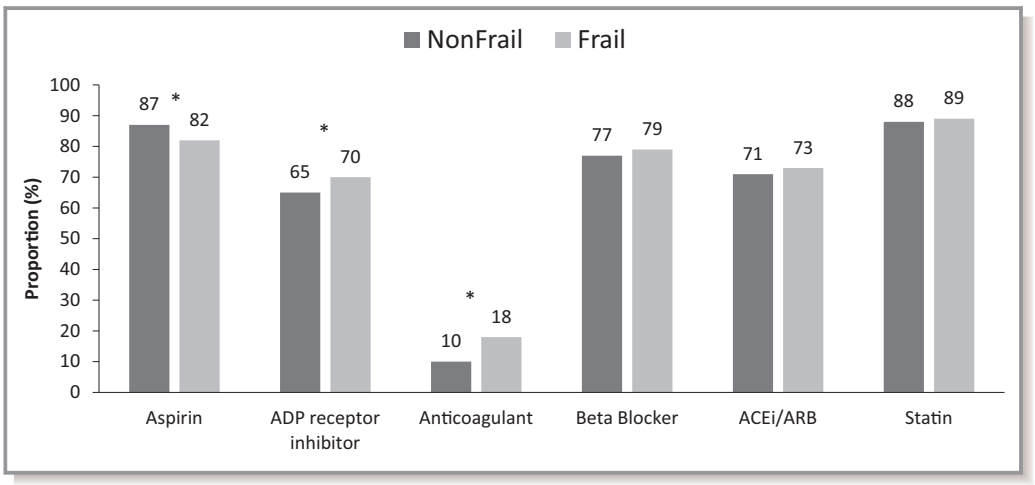

Figure 5. Discharge medical therapy by frailty classification among patients without ST-segment–elevation myocardial infarction. *$P<0.05$. ACEi indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.

regarding contraindications and reasons (eg, patient preference) for not using individual medications and procedures. Factors beyond those captured on the data collection form may represent unmeasured confounders that contributed to the discrepancy in therapies provided to frail patients; future registries should collect data on reasons why certain therapies are not used in individual patients.

Conclusion

In a contemporary cohort of Australian MI patients, ≈1 in 6 older STEMI patients and 1 in 3 older NSTEMI patients are frail. Frail patients receive less medical and invasive cardiac care during index hospitalization. After adjustment for traditional factors associated with increased risk for mortality after MI, increased frailty was associated with increased in-hospital and midterm postdischarge all-cause, but not cardiac-specific, mortality. These findings help inform clinicians pay particular attention to and manage competing noncardiac risk in frail patients with MI.

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References

1. Clegg A, Young J, Iliffe S, Rikkert MO, Rockwood K. Frailty in elderly people. *Lancet*. 2013;381:752–762.
2. 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.
3. Myers V, Drory Y, Gerber Y; Israel Study Group on First Acute Myocardial I. Clinical relevance of frailty trajectory post myocardial infarction. *Eur J Prev Cardiol*. 2014;21:758–766.
4. Ekerstad N, Swahn E, Janzon M, Alfredsson J, Lofmark R, Lindenberger M, Carlsson P. Frailty is independently associated with short-term outcomes for elderly patients with non-ST-segment elevation myocardial infarction. *Circulation*. 2011;124:2397–2404.
5. Purser JL, Kuchibhatla MN, Fillenbaum GG, Harding T, Peterson ED, Alexander KP. Identifying frailty in hospitalized older adults with significant coronary artery disease. *J Am Geriatr Soc*. 2006;54:1674–1681.
6. Sanchis J, Bonanad C, Ruiz V, Fernandez J, Garcia-Blas S, Mainar L, Ventura S, Rodriguez-Borja E, Chorro FJ, Hermenegildo C, Bertomeu-Gonzalez V, Nunez E, Nunez J. Frailty and other geriatric conditions for risk stratification of older patients with acute coronary syndrome. *Am Heart J*. 2014;168:784–791.
7. Singh M, Stewart R, White H. Importance of frailty in patients with cardiovascular disease. *Eur Heart J*. 2014;35:1726–1731.
8. Aliprandi-Costa B, Ranasinghe I, Turnbull F, Brown A, Kritharides L, Patel A, Chew D, Walters D, Rankin J, Ilton M, Meredith I, Cass A, Brieger D. The design and rationale of the Australian Cooperative National Registry of Acute Coronary Care, Guideline Adherence and Clinical Events (CONCORDANCE). *Heart Lung Circ*. 2013;22:533–541.
9. Searle SD, Mitnitski A, Gahbauer EA, Gill TM, Rockwood K. A standard procedure for creating a frailty index. *BMC Geriatr*. 2008;8:24.
10. Rockwood K, Mitnitski A. Frailty in relation to the accumulation of deficits. *J Gerontol A Biol Sci Med Sci*. 2007;62:722–727.
11. Zeger SL, Liang KY. Longitudinal data analysis for discrete and continuous outcomes. *Biometrics*. 1986;42:121–130.
12. McNamara RL, Kennedy KF, Cohen DJ, Diercks DB, Moscucci M, Ramee S, Wang TY, Connolly T, Spertus JA. Predicting in-hospital mortality in patients with acute myocardial infarction. *J Am Coll Cardiol*. 2016;68:626–635.
13. Fox KA, Dabbous OH, Goldberg RJ, Pieper KS, Eagle KA, Van de Werf F, Avezum A, Goodman SG, Flather MD, Anderson FA Jr, Granger CB. Prediction of risk of death and myocardial infarction in the six months after presentation with acute coronary syndrome: prospective multinational observational study (GRACE). *BMJ*. 2006;333:1091.
14. Elbarouni B, Goodman SG, Yan RT, Welsh RC, Kornder JM, Deyoung JP, Wong GC, Rose B, Grondin FR, Gallo R, Tan M, Casanova A, Eagle KA, Yan AT; Canadian Global Registry of Acute Coronary Events I. Validation of the global registry of acute coronary event (GRACE) risk score for in-hospital mortality in patients with acute coronary syndrome in Canada. *Am Heart J*. 2009;158:392–399.
15. de Vries NM, Staal JB, van Ravensberg CD, Hobbelen JS, Olde Rikkert MG, Nijhuis-van der Sanden MW. Outcome instruments to measure frailty: a systematic review. *Ageing Res Rev*. 2011;10:104–114.
16. Theou O, Brothers TD, Mitnitski A, Rockwood K. Operationalization of frailty using eight commonly used scales and comparison of their ability to predict all-cause mortality. *J Am Geriatr Soc*. 2013;61:1537–1551.
17. Dodson JA, Arnold SV, Gosch KL, Gill TM, Spertus JA, Krumholz HM, Rich MW, Chaudhry SI, Forman DE, Masoudi FA, Alexander KP. Slow gait speed and risk of mortality or hospital readmission after myocardial infarction in the translational research investigating underlying disparities in recovery from acute myocardial infarction: patients' health status registry. *J Am Geriatr Soc*. 2016;64:596–601.
18. Rockwood K. Conceptual models of frailty: accumulation of deficits. *Can J Cardiol*. 2016;32:1046–1050.
19. Mitnitski A, Song X, Skoog I, Broe GA, Cox JL, Grunfeld E, Rockwood K. Relative fitness and frailty of elderly men and women in developed countries and their relationship with mortality. *J Am Geriatr Soc*. 2005;53:2184–2189.
20. Kennedy CC, Ioannidis G, Rockwood K, Thabane L, Adachi JD, Kirkland S, Pickard LE, Papaioannou A. A frailty index predicts 10-year fracture risk in adults age 25 years and older: results from the Canadian Multicentre Osteoporosis Study (CaMos). *Osteoporos Int*. 2014;25:2825–2832.
21. Guaraldi G, Brothers TD, Zona S, Stentarelli C, Carli F, Malagoli A, Santoro A, Menozzi M, Mussi C, Mussini C, Kirkland S, Falutz J, Rockwood K. A frailty index predicts survival and incident multimorbidity independent of markers of HIV disease severity. *AIDS*. 2015;29:1633–1641.
22. Hubbard RE, Peel NM, Smith M, Dawson B, Lambat Z, Bak M, Best J, Johnson DW. Feasibility and construct validity of a frailty index for patients with chronic kidney disease. *Australas J Ageing*. 2015;34:E9–E12.
23. Joseph B, Pandit V, Zangbar B, Kulvatunyou N, Tang A, O'Keeffe T, Green DJ, Vercruysse G, Fain MJ, Friese RS, Rhee P. Validating trauma-specific frailty index for geriatric trauma patients: a prospective analysis. *J Am Coll Surg*. 2014;219:10–17.e11.
24. Yan AT, Yan RT, Tan M, Fung A, Cohen EA, Fitchett DH, Langer A, Goodman SG, Canadian Acute Coronary S, Registry I. Management patterns in relation to risk stratification among patients with non-ST elevation acute coronary syndromes. *Arch Intern Med*. 2007;167:1009–1016.
25. Steg PG, Kerner A, deVan Werf F, Lopez-Sendon J, Gore JM, Fitzgerald G, Feldman LJ, Anderson FA, Avezum A; Global Registry of Acute Coronary Events

I. Impact of in-hospital revascularization on survival in patients with non-ST-elevation acute coronary syndrome and congestive heart failure. *Circulation*. 2008;118:1163–1171.

26. Stahle A, Mattsson E, Ryden L, Unden A, Nordlander R. Improved physical fitness and quality of life following training of elderly patients after acute coronary events. A 1 year follow-up randomized controlled study. *Eur Heart J*. 1999;20:1475–1484.

27. Lavie CJ, Milani RV. Effects of cardiac rehabilitation programs on exercise capacity, coronary risk factors, behavioral characteristics, and quality of life in a large elderly cohort. *Am J Cardiol*. 1995;76:177–179.

28. Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, Seeman T, Tracy R, Kop WJ, Burke G, McBurnie MA; Cardiovascular Health Study Collaborative Research G. Frailty in older adults: evidence for a phenotype. *J Gerontol A Biol Sci Med Sci*. 2001;56:M146–M156.