Frailty Trajectories After Treatment for Coronary Artery Disease in Older Patients

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Background—Frailty is an independent risk factor for cardiovascular outcomes. However, its trajectory after coronary artery disease treatment is unknown.

Methods and Results—Three hundred seventy-four patients undergoing nonemergent cardiac catheterization followed by treatment (ie, 128 coronary artery bypass graft [CABG], 150 percutaneous coronary intervention [PCI], 96 medical therapy only) were observed for 30 months. A frailty index (FI) score was calculated at baseline (before initial treatment) and 6, 12, and 30 months after treatment. Random-effects models compared FI score trajectories by sex, age, and treatment group. Mean baseline FI scores were 0.170, 0.154, and 0.154 for CABG, PCI, and medical therapy only, respectively. FI scores decreased (improved) 6 months after initial treatment, then increased (worsened) at 12 and 30 months ($P<0.001$ for differences over time). Women had nonsignificantly higher FI scores than men ($P=0.097$) but followed the same trajectory ($P=0.352$ for differences over time). In patients aged ≥75 years, FI scores increased postbaseline for CABG and medical therapy only and after 6 months for PCI patients. Patients <75 years assigned to PCI and CABG experienced a sustained frailty reduction, whereas those assigned to medical therapy only showed stable frailty over the 30-month follow-up period (P value for differences over time by age and treatment group=0.041).

Conclusions—With coronary artery disease treatment, frailty generally follows a U-shaped trajectory, but the pattern may differ by age and treatment. Further investigation is needed to confirm these observations and determine whether patients might benefit from consideration of frailty status. **(*Circ Cardiovasc Qual Outcomes*. 2016;9:230-238. DOI: 10.1161/CIRCOUTCOMES.115.002204.)**

Key Words: aging ■ coronary artery disease ■ follow-up studies ■ frailty

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Significant improvements in survival rates among patients with coronary artery disease (CAD), including those aged ≥75 years, have led to a greater focus on functional and quality of life outcomes.[1] In this area, the concept of frailty has attracted increased attention as a means of identifying patients more prone to worse outcomes with coronary care.[2] Bergman et al[3] defined frailty as enhanced vulnerability to stressors because of impairments in multiple, interrelated systems that lead to decline in homeostatic reserve and resiliency. Understanding the dynamic nature of frailty may assist healthcare providers in providing more appropriate patient care for the entire course of management.

Editorial, see p 194

Recent systematic reviews note >40 studies that address frailty in patients with cardiovascular disease published between 2010 and 2014.[2,4,5] Research has primarily focused on the association between baseline frailty and both short-term[6] and long-term[7] mortality after an event or procedure.[2,4,5] Other outcomes considered include disability,[8,9] cardiovascular events,[10,11] and institutionalization,[12,13] as well as the association between frailty and cardiovascular risk factors.[14–16] Few studies have focused on frailty as a primary outcome and described it over time in cardiovascular patients.[16,17]

Frailty scores are generally higher in women than men[18,19] and rise exponentially with increasing age.[20–22] Frailty trajectories may also vary by the type of coronary treatment (ie, coronary artery bypass graft [CABG] surgery, percutaneous coronary intervention [PCI], or medical therapy only [MT]) patients receive. Although a cardiac intervention might lead to an improvement in the person's frailty status by improving their

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WHAT IS KNOWN

- Frailty is a dynamic, independent risk factor for cardiovascular outcomes.
- The frailty index (FI) is a valid, continuous measure of the severity of frailty, which has been frequently used in later-life frailty research.

WHAT THE STUDY ADDS

- After the initiation of coronary artery disease therapy, the trajectory of FI scores followed a U-shaped curve where frailty temporarily decreased but then increased after 6 months to 1 year.
- However, patients ≥75 years of age assigned to coronary artery bypass surgery or only medical treatment did not on average experience this reduction in their frailty severity with treatment.
- Patients ≥75 years of age, coronary artery bypass surgery patients, and women trended toward higher FI scores overall compared with other subgroups.

clinical symptoms, a more invasive procedure might also precipitate the onset or the deterioration of their frailty status.[23–25] Using data from cardiac patients undergoing coronary angiography at a tertiary care center, we sought to determine the patterns of frailty change postprocedure and the influence on frailty trajectories of the sex, age, and treatment group of patients.

Methods

Study Design and Sample

This was a substudy of the Calgary Cardiac and Cognition (3C) Study, a prospective cohort investigation of the effect of physical, neurocognitive and psychological factors on health outcomes and functional recovery in older patients undergoing coronary treatments.[26] Three hundred seventy-four subjects aged ≥60 years were enrolled between October 2003 and February 2007. All underwent coronary angiography for CAD at an urban tertiary care hospital providing centralized cardiac services for southern Alberta. Recruitment was stratified according to 3 initial treatments assigned after the coronary angiogram: CABG (n=128), PCI (n=150), and MT (n=96). Potential participants were excluded if they underwent an emergency catheterization, had previous revascularization, or were unable to complete the assessment because of language difficulties or mental or physical impairments. Ethical approval was received from the Conjoint Health Research Ethics Board, University of Calgary, and participants provided informed consent.

Trained research nurses and associates administered a standardized assessment battery collecting neuropsychological and physical performance, sociodemographic, health behavior, activity of daily living, and health-related quality of life measurements at baseline (preprocedure) and 6, 12, and 30 months after the procedure. The 3C database was linked with the Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease (APPROACH),[27] a registry of all patients undergoing cardiac catheterization in the province, for baseline clinical information. Three patients could not be linked because of out-of-province catheterizations (n=2) or missing linkage (n=1). Blood samples were collected for 357 of the 374 participants (95.5%) at the time of catheterization for patients receiving MT or at the time of revascularization for patients who underwent PCI and CABG. Figure 1 illustrates the subject flow for 3C.[26] Retention of participants was 89% during the course of the study. All patients were categorized according to their originally assigned treatment group.

Frailty Index

The outcome, frailty index (FI) score, was used because it is a widely employed, validated approach to the assessment of frailty[28] that is flexible in its implementation.[29,30] Also, as a continuous measure, it would be expected to be more sensitive than a categorical one for assessing change over time. An FI is the proportion of age-related health deficits an individual has accumulated. A deficit can be any disease, symptom, laboratory abnormality, or a functional or cognitive impairment associated with health decline that accumulates but does not saturate with age.[29–31] The index does not require a prespecified list of deficits as variables but can be implemented by anyone using any list of potential deficits, provided that they are at least 40 in number and that they come from a wide range of domains (physical, cognitive, disability, comorbidity, emotional, and social).[30] Individual frailty is scored as a proportion of actual deficits divided by total possible deficits, a decimal number between 0 and 1. The FI score is higher when there are more deficits.[29–31] A higher FI is associated with an increased risk for institutionalization and short-term mortality.[29,30]

In 3C, 53 potential deficits were derived from the clinical assessments, APPROACH data, and blood work obtained on participants, based on the criteria described above. Our selection covers a range of systems: physical, cognitive, emotional, health-related quality of life, disability, and medical condition,[30] and are described in Appendix A in the Data Supplement. The FI score was calculated as the number of deficits present in an individual divided by the number of potential deficits where data were available (ie, <53 if the data were not complete).

Statistical Analysis

Descriptive analyses were conducted to compare baseline sociodemographic and clinical characteristics by treatment group and across visits. To compare change by initial level of frailty, categories were created, the first 4 of equal width (0.06 in FI score), and all scores >0.24 for the last category. Equal-ranged categories were used, rather than sample-derived quintiles, to better compare the distribution and movement of data over time by comparing equal-sized ranges. For each of 3 transitions (baseline to 6 months, 6 to 12 months, and 12 to 30 months), proportions were estimated for FI score decrease (≥0.02 decrease in FI score), stable FI score (change of <0.02), FI score increase (≥0.02 increase in FI score), deaths, and withdrawals.[32] A change of 0.02 was used as it corresponds with slightly more than a gain or loss of one deficit and is similar to the threshold used by other researchers.[33]

To compare age, sex, and treatment group differences associated with change over time, we fitted FI scores to linear mixed models with a random intercept. Visit was modeled as a repeated categorical measure to accommodate a possible nonlinear relationship between

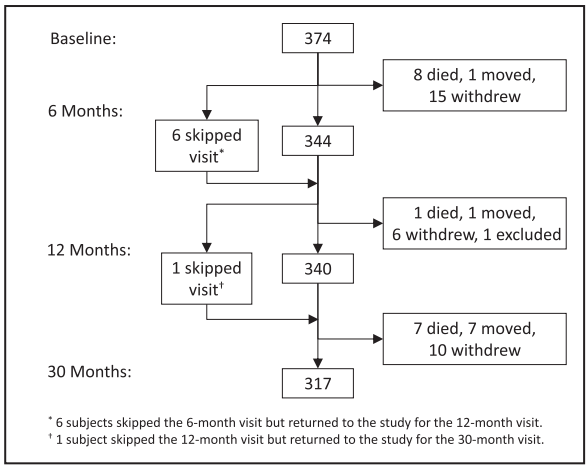

Figure 1. Calgary Cardiac and Cognition (3C) study flow. Reproduced from Freiheit et al[26] with permission of the publisher. Copyright © (2012) American Medical Association. All rights reserved.

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score and time. For the age comparison, age was categorized into quartiles based on the sample distribution, to isolate the oldest and youngest quartiles. For the age by treatment group comparison, 2 categories were used, ≥75 and <75 years, as the 3 lower age quartiles had similar results and were combined. Models were adjusted by age, sex, and education as appropriate because all have associations with frailty criteria.[18–22,34] Ethnic differences were not examined because 95% of the sample was of European or unknown ethnicity.

Adjusted least-square means (ie, predicted marginal means estimated over a balanced population), their standard errors, and accompanying *P* values based on the tests of fixed effects[35] were recorded for each model. A *P* value is given for change in score across visits, for mean score differences between groups overall, and for differences between groups in mean score changes across visits. Residuals were reviewed to check on assumptions of homoscedasticity and normal distribution. SAS 9.4 (SAS Institute, Cary, NC) was used for all analyses.

Results

Baseline Characteristics

The study sample was 26.7% female, with an average age of 71.4 years (Table 1). The MT group had a significantly higher proportion of women (39.6%) compared with the PCI group (27.3%) and CABG group (16.4%). The CABG group had a significantly higher proportion of patients with stable angina (74.4%), high-risk coronary anatomy (90.4%), and diabetes

Table 1. Baseline Characteristics of 3C Study Sample by Initial Treatment Group*

Characteristic	All (n=374)	CABG (n=128)	PCI (n=150)	MT (n=96)	*P* Value†
Age, mean±SD	71.4 (5.9)	71.3 (6.5)	71.0 (5.5)	72.3 (5.5)	0.193
Female sex, number (%)	100 (26.7)	21 (16.4)	41 (27.3)	38 (39.6)	<0.001
Education years, mean±SD	12.8 (3.8)	13.1 (3.8)	12.7 (3.7)	12.6 (3.8)	0.506
Frailty index deficit sum, mean±SD‡	8.4 (4.2)	8.9 (4.2)	8.1 (3.8)	8.2 (4.9)	0.239
Frailty index score, mean±SD‡	0.160 (0.080)	0.170 (0.080)	0.154 (0.071)	0.154 (0.093)	0.173
Cardiovascular disease, %					
Admitted with stable angina§	246 (65.3)	93 (74.4)	92 (61.3)	58 (60.4)	0.036
Acute coronary syndrome‖	145 (38.9)	45 (35.4)	64 (42.7)	36 (37.5)	0.446
Congestive heart failure§	38 (10.0)	10 (8.0)	16 (10.7)	12 (12.5)	0.537
Canadian Cardiovascular Society angina class>II§	178 (48.0)	53 (42.4)	74 (49.3)	51 (53.1)	0.269
High-risk coronary anatomy§¶	174 (46.9)	113 (90.4)	45 (30.0)	16 (16.7)	<0.001
Ejection fraction <50%#	61 (18.2)	20 (18.7)	21 (14.8)	20 (22.0)	0.531
Vascular risk factors, %					
Smoking (former or current)	267 (72.0)	95 (74.2)	108 (72.0)	64 (66.7)	0.454
Hypertension‖	305 (81.8)	108 (85.0)	125 (83.3)	72 (75.0)	0.128
Diabetes mellitus (type I or II)‖	103 (27.5)	49 (38.3)	37 (24.7)	17 (17.7)	0.002
Hyperlipidemia§	312 (84.1)	103 (82.4)	129 (86.0)	80 (83.3)	0.699
Comorbidities, %§					
Cerebrovascular disease	39 (10.5)	17 (13.6)	11 (7.3)	11 (11.5)	0.227
Peripheral vascular disease	33 (8.9)	17 (13.6)	5 (3.3)	11 (11.5)	0.007
Pulmonary disease	83 (22.4)	25 (20.0)	31 (20.7)	27 (28.1)	0.289
Renal disease	11 (3.0)	4 (3.2)	4 (2.7)	3 (3.1)	0.961
Malignancy	19 (5.1)	6 (4.8)	7 (4.7)	6 (6.3)	0.843
Liver or gastrointestinal disease	28 (7.5)	9 (7.2)	12 (8.0)	7 (7.3)	0.963

3C indicates Calgary Cardiac and Cognition; CABG, coronary artery bypass graft surgery; MT, medical therapy only; and PCI, percutaneous coronary intervention

*Two MT patients had a subsequent PCI at 3 and 20 mo (respectively) after baseline. Three PCI patients had a subsequent CABG at 7, 8, and 12 mo (respectively) after PCI procedure.

†Based on *F* test for continuous variables and χ^2 test for categorical variables.

‡Frailty index deficit sum is the raw sum of deficits of 53 possible criteria. Frailty index score is the deficit sum divided by the number of nonmissing criteria, 53 if the data are complete. See Appendix A in the Data Supplement for more information.

§Sample size for all (n=371), CABG (n=125), PCI (n=150), and MT (n=96).

‖Sample combines information from Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease (APPROACH) and visit questionnaires; 373 (all), 127 (CABG), 150 (PCI), and 96 (MT).

¶High risk defined as double-vessel coronary artery disease with proximal left anterior descending artery involvement, any 3-vessel disease, or left main disease.

#Sample is 336 (all), 103 (CABG), 142 (PCI), and 91 (MT) because of ejection fraction not being measured in all catheterizations.

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mellitus (38.3%) compared with the other 2 treatment groups. Additional data describing the sample are shown in Table I in the Data Supplement. Mean baseline FI scores were not significantly different across the 3 treatment groups (0.170 for CABG and 0.154 for both PCI and MT; *P*=0.173). The mean FI score was 0.160 at baseline, 0.150 at 6 months, 0.151 at 12 months, and 0.162 at 30 months (Table I in the Data Supplement).

Proportions Showing Increases or Decreases in FI Score Over Time Intervals by Initial FI Score

Table 2 describes the proportions of the sample that increased, decreased, or maintained their FI score (±0.02) during each transition period. This is stratified by FI score at the beginning of each time interval. Overall, a greater proportion of FI scores decreased (ie, frailty levels improved) from baseline to 6 months,

Table 2. Proportion of 3C Study Sample Exhibiting an Increase, Decrease, or Stable Frailty Index Scores, Stratified by FI Score at Beginning of Time Interval*†‡

Frailty Score Range at Start of Time Interval (TI) [Change Over TI]	Baseline to 6 mo		6 mo to 12 mo		12 mo to 30 mo	
	Number	Proportion, %	Number	Proportion, %	Number	Proportion, %
FI score: 0 - 0.06 (lowest frailty)	n=18		n=33		n=37	
[Decrease]	2	11.1	0	0	0	0
[Stable]	11	61.1	25	75.8	18	48.7
[Increase]	4	22.2	8	24.2	15	40.5
[Death]	0	0	0	0	2	5.4
[Lost to follow-up]	1	5.6	0	0	2	5.4
FI score: >0.06 -0.12	n=109		n=124		n=119	
[Decrease]	25	22.9	10	8.1	14	11.8
[Stable]	67	61.5	85	68.6	77	64.7
[Increase]	15	13.8	24	19.4	22	18.5
[Death]	0	0	1	0.8	0	0
[Lost to follow-up]	2	1.8	4	3.2	6	5.0
FI score: >0.12-0.18	n=123		n=97		n=96	
[Decrease]	43	35.0	24	24.7	22	22.9
[Stable]	47	38.2	50	52.6	37	38.5
[Increase]	23	18.7	23	22.7	34	35.4
[Death]	2	1.6	0	0	2	2.1
[Lost to follow-up]	8	6.5	0	0	1	1.1
FI score: >0.18-0.24	n=65		n=44		n=42	
[Decrease]	27	41.5	15	34.1	11	26.2
[Stable]	20	30.8	16	36.4	13	30.1
[Increase]	10	18.7	11	25.0	14	33.3
[Death§]	4	6.2	0	0	1	2.4
[Lost to follow-up]	4	6.2	2	4.5	3	7.1
FI score: >0.24 (highest frailty)	n=53		n=45		n=46	
[Decrease]	23	43.4	17	37.8	11	23.9
[Stable]	15	28.3	12	26.7	12	26.1
[Increase]	12	22.6	14	31.1	16	34.8
[Death]	2	3.8	0	0	2	4.3
[Lost to follow-up]	1	1.9	2	4.4	5	10.9

3C indicates Calgary Cardiac and Cognition.

*Decrease and increase are defined as a change in >0.02 in the frailty index score.

†Note that 6 patients who skipped month 6 and 2 patients who skipped month 12 are not included in the intervals pertaining to those visits.

‡Stable is defined as a change of <0.02 over the period.

§There were only 2 perioperative deaths in the study. Both had frailty index (FI) scores in this category.

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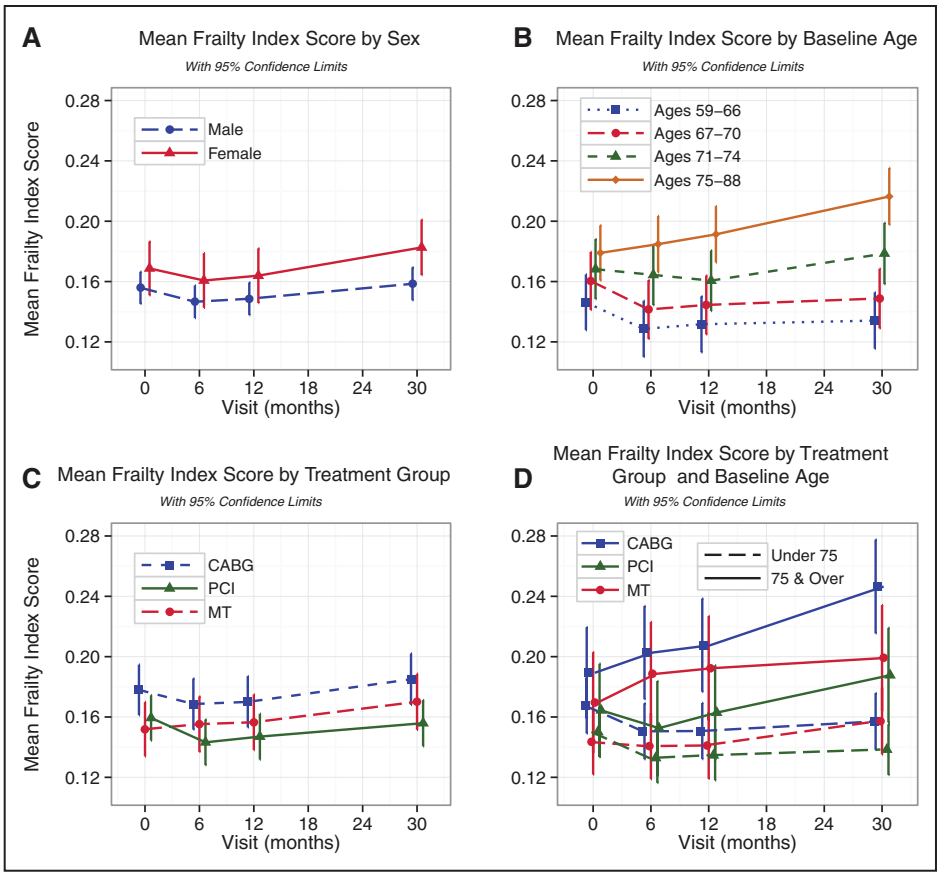

Figure 2. Mean frailty index scores over time by (**A**) sex, (**B**) baseline age category, (**C**) treatment group, and (**D**) treatment group and baseline age.

whereas a greater proportion of FI scores increased (ie, frailty levels worsened) during the later time intervals. The groups with the highest frailty levels (FI scores of 0.24+ and 0.18–0.24) were the most dynamic, with under a third maintaining stable FI scores during any transition period. By contrast, two-thirds of the 2 most robust groups maintained stable FI scores across any time interval. In the first 6 months postinitial treatment, there were more deaths in the highest frailty levels (>0.18), but no obvious pattern was observed during subsequent time intervals.

Frailty Trajectories by Sex, Age, and Treatment Groups

Figure 2 and Tables 3, 4, 5, and 6 present the adjusted mean FI scores at baseline, 6, 12, and 30 months postprocedure for the group overall and for 4 subgroup categories: (1) sex, (2) baseline age category, (3) initial treatment group, and (4) baseline age (≥75 years) by treatment group. Overall, the mean FI scores followed a U-shaped curve, with scores declining after the initial treatment and rising thereafter (P<0.001 for differences over time).

As illustrated in Figure 2A and Table 3, women showed a nonsignificantly higher mean FI score than men across all visits (P=0.097). For both sexes, the change in the FI score over time followed a U shape with an initial decline from baseline followed by an increase postprocedure. This change over time was statistically significant (P<0.001). Male and female trajectories did not differ from each other (P=0.352).

Frailty differed by age group overall (P<0.001), with older age groups showing consistently higher mean FI scores than younger ones across all visits (Figure 2B; Table 4). FI score trajectories also differed by age group (P<0.001), with the

Table 3. Mean Frailty Index Scores Over Time by Sex

	Sample Sizes at 0, 6, 12, 30 mo	Least-Square Means (Standard Error)*				Expected	*P* Values	
		Baseline	6 mo	12 mo	30 mo	30 mo†	Associated With Differences	
Overall	374, 344, 340, 317	0.163 (0.0052)	0.154 (0.0052)	0.156 (0.0052)	0.169 (0.0053)	0.178	Between visits	<0.001
							Between sexes	0.097
Female	100, 91, 91, 83	0.169 (0.0091)	0.161 (0.0092)	0.164 (0.0092)	0.183 (0.0093)	0.184	Between visits	<0.001
Male	274, 253, 249, 234	0.156 (0.0054)	0.147 (0.0055)	0.149 (0.0055)	0.159 (0.0056)	0.170	Sexes by visits	0.352

*Least-square means are predicted marginal means estimated over a balanced population, adjusted by age and education.
†Based on an annual rate of increase of 3.5% in community-dwelling persons. This is the baseline frailty index score times 1.09 (=$1.035^{2.5}$).[22]

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Table 4. Mean Frailty Index Scores Over Time by Baseline Age Category

	Sample Sizes at 0, 6, 12, 30 mo	Least-Square Means (Standard Error)*				Expected	*P* Values	
		Baseline	6 mo	12 mo	30 mo	30 mo†	Associated With Differences	
Baseline age 59–66 y	100, 94, 95, 91	0.146 (0.0094)	0.129 (0.0095)	0.132 (0.0095)	0.134 (0.0095)	0.159	Between age groups	<0.001
Baseline age 67–70 y	91, 84, 81, 73	0.160 (0.0098)	0.142 (0.0099)	0.145 (0.0099)	0.149 (0.0100)	0.174	Between visits	<0.001
Baseline age 71–74 y	87, 81, 80, 73	0.168 (0.0101)	0.164 (0.0102)	0.161 (0.0102)	0.179 (0.0103)	0.183	Age groups by visits	<0.001
Baseline age 75–88 y	96, 85, 84, 80	0.179 (0.0093)	0.185 (0.0095)	0.191 (0.0095)	0.216 (0.0096)	0.195		

*Least-square means are predicted marginal means estimated over a balanced population, adjusted by sex and education.
†Based on an annual rate of increase of 3.5% in community-dwelling persons. This is the baseline frailty index score times 1.09 (=$1.035^{2.5}$).[22]

oldest quartile (75+) failing to show the early improvement observed in the younger age groups.

Overall, 3C participants who underwent CABG as their initial treatment trended toward higher mean FI scores across all visits than those who underwent PCI or received MT only (*P*=0.053; Figure 2C; Table 5). U-shaped curves were observed for both PCI and CABG groups. For the PCI group, the decrease in mean FI score was greater at 6 and 12 months. FI scores were still slightly lower than baseline at 30 months. For the CABG group, the decrease in mean FI score was not as great at 6 and 12 months, and the score at 30 months was greater than baseline. By contrast, the mean FI score for patients assigned to MT tended to increase over time. However, the *P* value for treatment differences in FI score trajectories was 0.090.

Treatment group trajectories did not vary by sex (results not shown, *P*=0.579); however, they did vary by age (Figure 2D; Table 6). Specifically, mean FI scores for CABG patients aged <75 years decreased in months 6 and 12, but mean FI scores for CABG patients aged ≥75 years increased steadily from baseline. Similarly, mean FI scores increased steadily for MT patients aged ≥75 years, whereas mean FI scores for those aged <75 years did not. Mean FI scores declined from baseline to 6 months for all PCI patients regardless of age. However, after month 6, mean FI scores increased for those aged ≥75 years receiving PCI but not for the younger PCI group. These age differences between treatment groups in change over time were statistically significant (*P*=0.041).

The seventh column of Tables 3, 4, 5, and 6 shows what the mean FI score would have been if the rate of increase from the baseline score had been 3.5% per year, as observed in adult, community-dwelling populations who do not necessarily have cardiovascular disease.[22] In comparison with the adjusted mean FI scores at 30 months, patients overall had a lower average FI score than would be expected (0.169 compared with 0.178). Looking at the subgroups, those who had lower FI scores than would be expected were men, those <75 years of age, and those who had CABG and PCI. Those >75 years with CAD become frailer at a faster rate than predicted for community-dwelling seniors regardless of treatment assignment. This comparison is speculative as we are comparing patients with CAD to a general population, but it does provide context to the rate of change within this sample.

All analyses done using the FI were also performed using a frailty screening tool developed on the study sample.[36] Similar patterns with regard to sex, treatment, and age differences were observed. These results are not shown but are available on request.

Discussion

This is one of the first studies to determine frailty in patients before and after implementation of invasive therapy (CABG and PCI) or assignment to MT for CAD. It provides a guide as to the anticipated frailty trajectory for patients diagnosed with and treated for CAD. Frailty took on a U-shaped trajectory for the whole sample. However, different patterns emerged within particular age and treatment groups. Trends did not vary based on initial frailty status. However, frailty was more dynamic in frailer groups as the 2 frailest categories had the smallest proportion with stable FI scores across any of the 3 intervals.

Table 5. Mean Frailty Index Scores Over Time by Treatment Group

	Sample Sizes at 0, 6, 12, 30 mo	Least-Square Means (SE)*				Expected	*P* Values	
		Baseline	6 mo	12 mo	30 mo	30 mo†	Associated With Differences	
CABG	128, 120, 119, 111	0.178 (0.0085)	0.169 (0.0086)	0.170 (0.0086)	0.185 (0.0087)	0.194	Between treatments	0.053
PCI	150, 139, 137, 126	0.159 (0.0076)	0.143 (0.0077)	0.147 (0.0077)	0.156 (0.0078)	0.173	Between visits	<0.001
Medical therapy	96, 85, 84, 80	0.152 (0.0092)	0.155 (0.0094)	0.157 (0.0094)	0.170 (0.0094)	0.166	Treatments by visits	0.090

CABG indicates coronary artery bypass graft; and PCI, percutaneous coronary intervention.
*Least-square means are predicted marginal means estimated over a balanced population, adjusted by age, sex, and education.
†Based on an annual rate of increase of 3.5% in community-dwelling persons. This is the baseline frailty index score times 1.09 (=$1.035^{2.5}$).[22]

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Table 6. Mean Frailty Index Scores Over Time by Treatment Group and Baseline Age

	Sample Sizes at 0, 6, 12, 30 mo	Least-Square Means (SE)*				Expected	*P* Values	
		Baseline	6 mo	12 mo	30 mo	30 mo†	Associated With Differences	
CABG, age <75 y	94, 90, 89, 82	0.168 (0.0094)	0.151 (0.0094)	0.151 (0.0095)	0.157 (0.0096)	0.183	Between treatments	0.0338
CABG, age ≥75 y	34, 30, 30, 29	0.189 (0.0154)	0.203 (0.0158)	0.208 (0.0158)	0.247 (0.0158)	0.206	Between age <75/≥75+ y	<0.001
PCI, age <75 y	117, 108, 106, 96	0.150 (0.0083)	0.133 (0.0084)	0.135 (0.0084)	0.138 (0.0085)	0.164	Between visits	<0.001
PCI, age ≥75 y	33, 31, 31, 30	0.164 (0.0158)	0.153 (0.0159)	0.163 (0.0159)	0.188 (0.0160)	0.179	Treatments by visit	0.080
Medical therapy, age <75 y	117, 108, 106, 96	0.144 (0.0110)	0.141 (0.0112)	0.141 (0.0112)	0.157 (0.0112)	0.157	Age <75/≥75+ y by visit	<0.001
Medical therapy, age ≥75 y	29, 24, 23, 21	0.170 (0.0170)	0.189 (0.0175)	0.192 (0.0176)	0.199 (0.0178)	0.185	Treatments by age <75/≥75+ y	0.519
							Treatments by age <75/≥75+ y by visits	0.041

CABG indicates coronary artery bypass graft; and PCI, percutaneous coronary intervention.

*Least-square means are predicted marginal means estimated over a balanced population, adjusted by sex and education.

†Based on an annual rate of increase of 3.5% in community-dwelling persons. This is the baseline frailty index score times 1.09 (=$1.035^{2.5}$).[22]

Older participants were less likely to experience an improvement in frailty after implementation of their treatment plan and tended to have steeper increases than younger age groups. This is also consistent with literature that describes an exponential relationship between frailty and age.[20–22] The interaction between age and treatment plan has important implications for individual patient care. Despite significant improvements in survival for CAD patients undergoing coronary treatments, including older patients, these differences may impact important functional and quality of life outcomes. For example, the negative effects of hospitalization, because of prolonged loss of mobility, may impact older age groups more than younger groups, overriding health improvements after CABG and leaving a patient with a reduced resilience.[23–25,37]

Consistent with the literature, women trended toward higher FI scores than men.[18,38] However, men and women followed parallel courses during the 30-month period, and treatment group differences did not vary by sex. Some researchers have asserted that in the general population, women have less risk of unfavorable outcomes than men at similar frailty levels.[29] Others have concluded that women have more risk because of higher frailty measurements.[18] Previous research has found sex differences in acute coronary syndrome presentation and outcomes, which could not be accounted for by baseline clinical differences.[39] The inclusion of frailty measures may help to account for some of these differences.

Numerous publications have looked at frailty longitudinally in general populations: characterizing frailty transitions,[22,32,33,40] examining potential predictors of transitions,[41–43] testing interventions to limit worsening frailty,[44] and comparing static versus dynamic frailty measures to predict functional decline.[45] However, few have looked longitudinally at a cohort of patients with cardiovascular disease. A literature search revealed only one previous study looking at frailty at more than one time point in patients with cardiovascular disease. Myers et al[17] categorized an FI at baseline postacute myocardial infarction and 10 to 13 years postbaseline using 32 variables and found an association between the 2 FI measurements with mortality. Our study made use of the FI as a continuous measurement and focused on describing the trajectory of frailty as patients progressed from treatment through recovery and beyond.

Study Strengths and Limitations

A particular strength of our study is the large clinical sample, the detail of repeat measurements, and the 30-month length, relative to other clinical prospective studies that examined cardiovascular interventions. We compared 3 treatment plans including MT and had high retention. Our FI incorporated criteria from a wide range of domains, including cognitive, emotional, quality of life, as well as physical performance criteria.

One limitation of the study is that a clinically meaningful FI score change has not been established. Rockwood et al[46,47] did report mean FI scores for frailty categories based on other scales. For example, 0.22 was the mean FI score for people categorized as apparently vulnerable, and 0.27 was the mean FI score for people categorized as mildly frail on the Canadian Study of Health and Aging Clinical Frailty Scale. Individuals assigned to both categories have been shown to have worse survival than those in less frail categories. However, there was a large variance for FI scores within each category.[46] No minimum meaningful difference has yet been established for this continuous measurement to help guide interpretation of change. This represents an area for future research.

Another limitation is that this study was based in a single tertiary care center. Because the revascularization practices at this center may differ from other centers performing CABG and PCI,[48] generalizability may be limited. In addition, this study was not a randomized controlled trial. Some differences seen may be attributable to confounders not included in the analysis. In this population, mortality was too rare to include as an outcome in this analysis. The 3C study participants were younger and healthier than typical prospective cohorts included in frailty studies. Nevertheless, this analysis gives us important information about frailty at an early stage, when individuals may be less burdened by disabilities, but resilience is beginning to erode. Although this study is larger than many clinical prospective cohort studies of this type, it is smaller than some other community-based frailty studies.

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Conclusions

This study is one of the first to describe the different frailty trajectories for patients with CAD undergoing different approaches to their therapy. We found that frailty was more dynamic in frailer patients in this group. Women, older patients, and those undergoing CABG trended toward higher levels of frailty overall. In our sample, frailty followed a U-shaped curve after revascularization. However, relatively older patients (aged ≥75 years) initially assigned to MT or CABG did not experience this temporary decrease (or improvement). They showed continuous increases in their frailty level from baseline during the 30 months. If confirmed by other studies, frailty trajectories could be used to inform individualized decision making about initial treatment choices and allow more tailored subsequent patient care and monitoring once effective therapeutic approaches have been demonstrated.[2]

Further research is needed to confirm our findings and extend them to more diverse patient populations. Examining frailty as a time-varying covariate within larger and longer-term studies would provide additional information about the differences in trajectories in terms of outcomes and provide a more nuanced context for possible interventions. A major gap in our current understanding of the management of frailty is the need for effective therapeutics. Studying the impact of interventions[49,50] on frailty trajectories could speed up the development process and allow comparisons between studies and approaches.

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Disclosures

None.

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Frailty Trajectories After Treatment for Coronary Artery Disease in Older Patients

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SUPPLEMENTAL MATERIAL

eAppendix A: Frailty Index Construction

Missing data, value assignment

A neuropsychologist and a geriatrician reviewed all available data for persons with intermittent missing test values. A value was assigned indicating a deficit if a participant was deemed too impaired in that particular domain to complete the test. If no such deduction could be made, a single conditional mean based on a Monte-Carlo Markov Chain imputation process was used to assign a value.[1] Only 0.1% to 1.7% of any given criteria were completed based on imputation. No assignments were made for missed visits, missing APPROACH or bloodwork data.

Frailty Index (FI) Construction

The following criteria were used to determine which data would be included as deficits in the FI:[2]

1) The deficit is associated with health status.

2) The prevalence of the deficit in the population increases with the age of the population.

3) The deficit does not saturate within a population until very old age, if at all.

4) The deficits overall cover a range of systems.

5) The measurement collected for an entire sample is comprised of the same deficits.

One point was given for any of the following 53 deficits to create the FI score. Partial points were given as indicated below. Measurements were taken at all visits unless otherwise indicated. Physical characteristics (5 deficits) included body mass index, two questions and two tests from the Macarthur Studies of Successful Aging.[3, 4] Health-related quality of life criteria (6 deficits) included a self-rated health question, and five items from the EuroQOL EQ-5D questionnaire.[5, 6] Cognitive criteria (6 deficits) were age, sex, and education-adjusted scores from the animal naming test[7], "FAS" letter naming test[7], a global cognition test[8], a trail-making executive function test[7], a verbal delayed recall test[9] and a visual-spatial delayed recall test[10]. Mood criteria (4 deficits) include an anxiety scale[11], the 15-item Geriatric Depression Scale[12], and two subscales based on the Geriatric Depression Scale.[13] Self-reported activities of daily living (7 deficits) and instrumental activities of daily living (7 deficits) provided functional

criteria.[14] Baseline diseases (12 deficits) and medical conditions (5 deficits) such as ejection fraction were provided by APPROACH. Of these, diabetes, acute coronary syndrome, and hypertension were updated during caregiver interviews.[15] Self-reported strokes and TIAs were collected using a validated stroke questionnaire.[16] Collected blood samples provided homocysteine and B12 levels. Living arrangements (1 deficit) were self-reported.

For the 53 criteria, data was complete for 87.2-87.8% of the study population across all visits. For between 11.0% and 11.7% of the sample, across all visits, 51 or 52 criteria were present. The denominator was between 40 and 50, due to missing data, for approximately 1% of the study sample across all visits.

Physical Characteristics and Performance[3, 4, 17]

1. Abnormal body mass index (< 21 or >30 kg/m^2) based on self-reported height and weight
2. Unable or didn't know if able to walk up stairs without help (self-reported)
3. Unable or didn't know if able to walk half a mile without help (self-reported)
4. Balance test: unable to hold full tandem for >10 sec
5. Gait test: unable to walk 8 feet in <4 sec

Health-Related Quality of Life [5, 6]

6. Response of "fair" or "poor" to question, "In general, would you say your health is excellent, very good, good, fair, or poor?"
7. Some problems with washing/dressing (0.5); unable to wash/dress (1.0)
8. Some problems performing usual activities (work, study, housework, leisure) (0.5); unable (1.0)
9. Has moderate pain/discomfort (0.5); has extreme pain/discomfort (1.0)
10. Is moderately anxious or depressed (0.5); is extremely anxious or depressed. (1.0)
11. Self-rated health on scale of 0 to 100 (thermometer) less than or equal to 65.

SUPPLEMENTAL MATERIAL

Cognition[7-10]

12. Animal Naming Test: 1.5 standard deviations below age and education adjusted norms

13. FAS Test: 1.5 standard deviations below age and education adjusted norms

14. MMSE: in the bottom 10 percentile of age, sex, education-adjusted norms

15. Trails B: Test 1.5 standard deviations below age, sex, and education adjusted norms

16. CERAD Verbal Memory Delayed Recall: 1.5 standard deviations below age, sex, and education adjusted norms

17. Brief Visuospatial Memory-Revised Delayed Recall Test: 1.5 standard deviations below age-adjusted norms

Mood[11-13]

18. Current anxiety: 1.5 standard deviations below sex and education-adjusted norms

19. Geriatric Depression Scale score > 4

20. Mood/hope score >1

21. Withdrawal/apathy/vigor score = 3

Functional Status[14]

22. Eats with some help = 0.5; completely unable = 1

23. Dresses with some help = 0.5; completely unable = 1

24. Cares for appearance with some help = 0.5; completely unable = 1

25. Walks with some help = 0.5; completely unable = 1

26. Transfers with some help = 0.5; completely unable = 1

27. Bathes with some help = 0.5; completely unable = 1

28. Uses toilet with some help = 0.5; completely unable = 1

29. Uses telephone with some help = 0.5; completely unable = 1

30. Travels with some help = 0.5; completely unable = 1

31. Shops with some help = 0.5; completely unable = 1

32. Prepares meals with some help = 0.5; completely unable = 1

33. Does housework with some help = 0.5; completely unable = 1

34. Takes medicine with some help = 0.5; completely unable = 1

35. Handles money with some help = 0.5; completely unable = 1

Diseases and medical conditions recorded at time of catheterization[18]

36. Pulmonary disease at baseline

37. Cerebrovascular disease at baseline

38. Renal disease at baseline

39. Congestive heart failure at baseline

40. Diabetes mellitus (type I or II), self-reported updates at follow up visits

42. Dialysis at baseline

43. Hypertension, self-reported updates at follow up visits

44. Hyperlipidemia at baseline

45. Severe/debilitating liver or gi disease at baseline

46. Malignancy at baseline

47. Peripheral vascular disease

48. Acute coronary syndrome, self-reported updates at follow up visits

49. Ejection fraction at baseline <50%

Self-Reported Stroke and TIA[16]

50. Stroke prior to visit, self-reported

51. TIA prior to visit, self-reported

SUPPLEMENTAL MATERIAL

Bloodwork

52. High homocysteine at baseline

53. B12 deficiency at baseline

Social Support

54. Lives alone, self-reported

SUPPLEMENTAL MATERIAL

eTable 1: Baseline Characteristics of Study Sample by Visit

	Baseline **N=374**	**6 Months** **N=344**	**12 Months** **N=340**	**30 Months** **N=317**
Age at baseline, mean ± SD	71.4 ± 5.9	71.3 ± 5.9	71.3 ± 5.9	71.3 ± 6.0
Female sex, number (%)	100 (26.7)	91 (26.4)	91 (26.8)	83 (26.2)
Education years, , mean ± SD	12.8 ± 3.8	12.8 ± 3.9	12.8 ± 3.9	12.8 ± 3.8
Baseline treatment group, number (%)				
CABG	128 (34.2)	120(34.9)	119 (35.0)	111 (35.0)
PCI	150 (40.1)	139 (40.4)	137 (40.3)	126 (39.8)
MT	96 (25.7)	85 (24.7)	84 (24.7)	80 (25.2)
Frailty Index deficit sum, mean ± SD*	8.41 (4.22)	7.93 (4.89)	7.97 (4.96)	8.52 (5.79)
Frailty Index Score, mean ± SD†	.160 (0.080)	.150 (.093)	.151 (.094)	.162 (.110)
Frailty Index Score, minima - maxima	.019 - .596	0 - .547	.019 - .557	019 - .692
Frailty Index Score above 0.3, number (%)	21 (5.6)	26 (7.6)	30 (8.8)	24 (7.6)

Abbreviations: SD=standard deviation, CABG =coronary artery bypass graft, PCI = percutaneous coronary intervention, MT=medical therapy.

* Frailty Index deficit sum is the raw sum of deficits of 53 possible criteria.

† Frailty Index score is the deficit sum divided by the number of nonmissing criteria, 53 if the data is complete.

SUPPLEMENTAL MATERIAL

The table below describes the average change among those increasing or decreasing in frailty. Cross-sectional studies in older community dwelling populations describe average increase in frailty to be approximately .02 to .03 per year of age increase.[19-21] More recent longitudinal studies have depicted the rate of increase to be exponential, with the number of deficits increasing by a factor of 1.035 over a person's lifetime.[22]

eTable 2: Mean Change in Score for Those Increasing or Decreasing in FI Scores, Stratified by FI Score at Beginning of Time Interval

FI Score category	Change Type	Baseline to Month 6 Mean change in score (Standard deviation)	Month 6 to Month 12 Mean change in score (Standard deviation)	Month 12 to Month 30 Mean change in score (Standard deviation)
0-.06	Decrease*	-.028 (0)	NA	NA
	Increase	.047 (.011)	.048 (.018)	.051 (.021)
.06-.12	Decrease	-.043 (.013)	-.039 (.013)	-.041 (.009)
	Increase	.055 (.053)	.042 (.016)	.057 (.031)
.12-.18	Decrease	-.051 (.020)	-.041 (.015)	-.045 (.016)
	Increase	.064 (.044)	.052 (.027)	.063 (.033)
.18-.24	Decrease	-.068 (.026)	-.053 (.021)	-.043 (.011)
	Increase	.073 (.091)	.057 (.038)	.059 (.036)
.24+	Decrease	-.084 (.034)	-.064 (.036)	-.070 (.027)
	Increase	.100 (.067)	.063 (.041)	.108 (.065)

* The standard deviation is 0 in the first time interval, and the means and standard deviations are not available in second and third time intervals due to insufficient sample in this category.

SUPPLEMENTAL MATERIAL

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