ORIGINAL RESEARCH

Cognitive Decline in Older Patients With Non-ST Elevation Acute Coronary Syndrome

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***Background*—**Dementia is a growing health burden of an aging population. This study aims to evaluate the prevalence of cognitive impairment and the predictors of cognitive decline at 1 year in older patients with non-ST–elevation acute coronary syndrome undergoing invasive care.

***Methods and Results*—**Older patients with non-ST–elevation acute coronary syndrome were recruited into the ICON1 study. Cognition was evaluated using Montreal Cognitive Assessment. The composite major adverse cardiovascular events comprised death, myocardial infarction, unplanned revascularization, stroke, and significant bleeding at 1 year. Of 298 patients, 271 had cognitive assessment at baseline, and 211 (78%) had follow-up Montreal Cognitive Assessment at 1 year. Mean age was 80.5±4.8 years. There was a high prevalence (n=130, 48.0%) of undiagnosed cognitive impairment (Montreal Cognitive Assessment score <26) at baseline. Cognitive impairment patients were more likely to reach major adverse cardiovascular events by Kaplan–Meier analysis (P=0.047). Seventy-four patients (35.1%) experienced cognitive decline (Montreal Cognitive Assessment score drop by ≥2 points) at 1 year. Recurrent myocardial infarction was independently associated with cognitive decline at 1 year (odds ratio 3.19, 95% confidence interval 1.18–8.63, P=0.02) after adjustment for age and sex.

***Conclusions*—**In older patients undergoing invasive management of non-ST–elevation acute coronary syndrome, there is a high prevalence of undiagnosed cognitive impairment at baseline. Recurrent myocardial infarction is independently associated with cognitive decline at 1 year.

***Clinical Trial Registration*—**URL: http://www.clinicaltrials.gov. Unique identifier: NCT01933581. **(*J Am Heart Assoc*. 2019;8: e011218. DOI: 10.1161/JAHA.118.011218.)**

Key Words: cognition • cognitive impairment • coronary artery disease • non-ST-segment–elevation acute coronary syndrome

Our population is rapidly aging. Dementia is a growing health burden of an aging population. Cognitive impairment (CI) is known to share many common risk factors with coronary artery disease (CAD) including age, smoking, genetics, hypertension, diabetes mellitus, dyslipidemia, metabolic syndrome, and inflammation.[1] The Cardiovascular Health Study reported a higher incidence of dementia in people with prevalent CAD.[2] The Rotterdam study showed higher incidences of dementia in those with prior myocardial infarction (MI).[3] The Bronx Aging Study found that women aged >75 years with a history of MI were more likely to develop dementia than those with no history of MI.[4] Possible mechanisms leading to cognitive impairment and dementia in patients with CAD might include cerebral hypoperfusion and ischemic brain injury as a result of cerebrovascular atherosclerosis.[1]

Older patients compared with young individuals experience more non-ST–elevation acute coronary syndrome (NSTEACS).[5,6] No previous study has evaluated whether the incident of NSTEACS or its management using invasive care leads to decline in cognitive function in older patients. The aim of this prospective cohort study is to determine the prevalence of cognitive impairment, the degree of cognitive

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Accompanying Tables S1 through S4 are available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.118.011218

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Clinical Perspective

What Is New?

- There is a high prevalence of cognitive impairment in older patients with non-ST–elevation acute coronary syndrome undergoing invasive care.
- Recurrent myocardial infarction is independently associated with cognitive decline at 1 year.

What Are the Clinical Implications?

- More aggressive contemporary therapeutic strategies to prevent recurrent events might play a role in reducing cognitive decline and subsequently delaying progression into dementia, and older patients should not be denied advanced care with contemporary treatment strategies.

decline over time, and to identify independent predictors of cognitive decline in older patients undergoing invasive management for NSTEACS.

Methods

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study Design

The ICON-1 study (A Study to Improve Cardiovascular Outcomes in High Risk Patients With Acute Coronary Syndrome) is a multicenter prospective cohort study consisting of older patients undergoing invasive management (coronary angiography with a view to revascularization) for NSTEACS. Ethical approval was gained from the appropriate Local Ethics Committee and National Research Ethics Service (NRES; 12/NE/0160). Written and informed consent was received from all participants before enrollment into the study. Details of the study design can be found in the previously published ICON1 study protocol.[7] Between November 2012 and December 2015, patients aged ≥65 years undergoing invasive management for NSTEACS, referred to 2 tertiary cardiac centers were recruited with 1-year follow-up completed in December 2016. Exclusion criteria were cardiac arrest, ventricular arrhythmia or cardiogenic shock, moderate to severe valvular heart disease, active infection, malignancy with expected survival <1 year, and lack of capacity to consent.[8]

Study Procedure, Measures of Cognitive Impairment, Frailty, and Comorbidity

All study participants underwent guideline-directed medical therapy, and invasive management at the discretion of the operating consultant interventional cardiologist. At baseline, participant demographics, medical history, and details of invasive management (coronary angiography, percutaneous coronary intervention, periprocedural complications) were obtained. Additional information on patient's cardiovascular status was assessed by ascertaining the New York Heart Association functional classification and Canadian Cardiovascular Society angina grade.

Cognitive function was assessed by using the Montreal Cognitive Assessment (MoCA) which has been developed and validated as a screening tool to accurately detect levels of CI. As a screening test, MoCA provides a practical assessment in the clinical setting to identify older adults who present with mild cognitive impairment. The MoCA assessment consists of tests in 7 domains (orientation, attention, recall, naming, visuospatial, language, and abstract reasoning) to give a representation of a person's current cognitive ability.[9] One point was used for education adjustment, in which an additional point can be added to the total score if patient's education years ≤12. It is administered over ≈10 minutes to patients at baseline during index NSTEACS hospital stay and at 1-year follow-up clinic. It gives a score ranging from 0 to 30, and a cut-off of 26 points has been used with scores ≥26 being normal, and scores <26 being cognitively impaired. Scores <26 can be subdivided to reflect degree of cognitive impairment (score 23–25: mild cognitive impairment; score 17–22: moderate cognitive impairment; scores ≤16: dementia).[9] A reduction in total MoCA score of 2 and more points is considered significant cognitive decline.[10] Patients who had a reduction of ≥2 points in MoCA at 1-year follow-up from baseline score are defined as "decliners," all the other patients with a MoCA score available at 1 year are "nondecliners."

All patients underwent assessment for frailty at baseline, using the Fried Frailty Criteria derived from the Cardiovascular Health Study, which consists of subjective and objective assessment in 5 domains: weight loss, exhaustion, physical inactivity, weakness, or slow walking.[11] Participants score 1 point for each criterion, a sum score of 0 to 2 is categorized, as nonfrail, and ≥3 as frail. The Charlson Co-morbidity Index was calculated taking into account age; this is based on a weighted index of the number and severity of comorbid medical conditions.[12] Laboratory blood testing including full blood count, urea and electrolytes, high-sensitivity cardiac troponin T, and high-sensitivity C-reactive protein were performed in all patients at baseline.

Clinical Outcomes and Follow-Up

The major adverse cardiovascular events (MACE) outcome was a composite of death, nonfatal MI, urgent unplanned repeat revascularization, stroke, and significant bleeding at 1

year. For time to MACE, only the first occurring event was counted. Significant bleeding was defined as per Bleeding Academic Research Consortium criteria. All 1-year outcomes were ascertained at follow-up appointment with the patient in the clinic, or by telephone consultation with the patient if unable to attend the clinic, or via interrogation of summary care records obtained from the patient's regular primary care physician. Discharge summaries provided by the patient or by their primary care physician and tertiary center electronic patient records were accessed to identify repeat revascularization procedures, or hospital readmission.

Statistical Methods

Baseline characteristics were summarized descriptively both overall and stratified by CI status using mean (±SD), median (interquartile range), or frequency (percentage) as appropriate. Baseline characteristics and procedural details were compared between those with and without cognitive impairment using the Student *t* test or Mann–Whitney *U* for continuous variables and the χ^2 test or Fisher exact test for categorical variables. Baseline and follow-up MoCA scores were compared using paired *t* test.

For time to event data, the Kaplan–Meier method was used to estimate survival function (ie, fraction of patients free of MACE for a certain amount of time from baseline) and comparisons between groups were made using the Log-rank test. Hazard ratios were estimated using Cox regression models. The proportional hazard assumption was tested. Logistic regression models were used to estimate the association of multiple covariates with cognitive decline, with the stepwise backward selection likelihood ratio method. Because of the nature of these hypothesis-generating analyses, a 2-tailed $P<0.05$ was used as the threshold for statistical significance. The Statistical Package for the Social Sciences (SPSS, version 23.0; IBM, New York) software was used for all statistical analyses.

Results

In total, 298 eligible patients were recruited to ICON-1. Of these, 271 (90.9%) participants underwent cognitive assessment using MoCA test at baseline, and 130 (48.0%) had cognitive impairment. A flow diagram of patient recruitment to ICON-1 is presented in Figure 1. The mean age of study participants was 80.5±4.8 years; 169 (62.4%) were male. With regard to diagnosis, 219 patients (80.8%) had non-ST–elevation myocardial infarction; 52 patients (19.2%) had troponin-negative unstable angina. All participants underwent coronary angiography; 225 (83%) underwent revascularization via percutaneous coronary intervention, 10 (3.7%) underwent coronary artery bypass graft, and the remaining 36 (13.3%) were managed with optimal medical therapy only.

Prevalence of CI

There is a high prevalence (n=130, 48.0%) of undiagnosed CI in this older patient group with NSTEACS determined by a MoCA score <26. Of these 130 patients, 92 (70.8%) had mild CI, 31 (23.8%) had moderate impairment, and 7 (5.4%) had severe impairment that can be considered in the dementia category. The baseline characteristics of the study population are presented in Table 1.

Presentation and Management of NSTEACS by Cognition Phenotype

CI patients were more likely to be managed with medical therapy only ($P=0.04$), and had more left mainstem disease ($P=0.03$). CI patients received less contrast load during a procedure compared with the normal cognition group ($P=0.006$). On discharge, fewer CI patients received ticagrelor ($P=0.04$). There is no difference in time from presentation to percutaneous coronary intervention (PCI), periprocedural complication rate, or the total length of hospital stay in CI patients compared with the normal group (Table S1).

Clinical Outcomes

One-year follow-up outcome was successfully ascertained for 270 study participants (Table 2), 1 patient was lost to follow-up. At 1 year, CI patients were associated with a significantly greater likelihood of reaching MACE outcome by Kaplan–Meier survival analysis (Figure 2) versus patients with normal cognition ($P=0.047$ by Log-rank test), and had a significantly increased hazard of incidence of MACE (hazard ratio 1.61, 95% confidence interval [95% CI] 1.00– 2.57, $P=0.049$). One patient in the CI group required dialysis at 1 year, and 2 individuals in the CI group became dependent on institutional care. There were 88 (32.6%) patients who had 1 or more hospital readmission events during the 1-year follow-up period; the first rehospitalization event was taken into account if multiple admissions occurred. Over a third (n=33, 37.5%) of admissions were because of problems with the cardiovascular system. No difference was found between the normal cognition group and the CI group in cardiovascular system readmission rate (12.8% versus 13.9%, $P=0.79$), or total any-cause readmission rate (33.8% versus 37.4%, $P=0.56$).

Cognitive Decline Analysis

Two hundred eleven patients completed the 1-year follow-up cognitive assessment. MoCA was not obtained in the

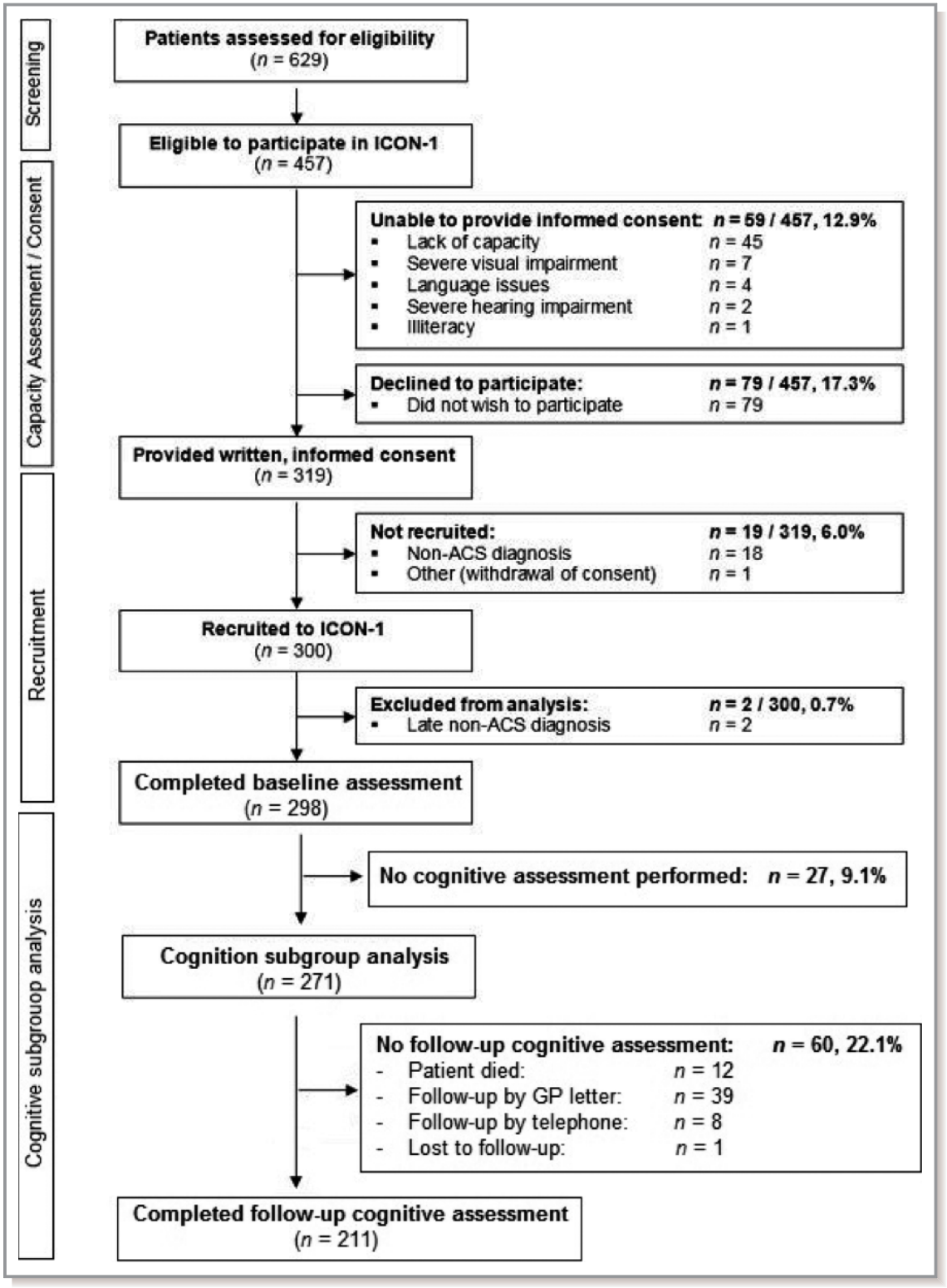

Figure 1. Flow diagram of ICON-1 screening, recruitment, and cognition subgroup analysis. ACS indicates acute coronary syndrome; GP, general practitioner; ICON-1, Study to Improve Cardiovascular Outcomes in High Risk Patients With Acute Coronary Syndrome.

remaining patients at 1 year for the following reasons: 12 died, 39 were followed up by general practitioner letter, 8 had telephone follow-up, and 1 patient was lost to follow-up. There is a significant reduction in overall MoCA score from baseline to 1-year follow-up (mean reduction in score: 0.6±3.3; 25.4±3.2 versus 24.7±3.7, baseline versus 1-year MoCA

Table 1. Baseline Characteristics Stratified by Baseline Cognitive Status

	Total (n=271)	Normal (n=141)	Cognitive Impairment (n=130)	*P* Value
Demographics				
Age, y (SD)	80.5 (4.8)	79.4 (4.8)	81.6 (4.5)	<0.001*
Male, n (%)	169 (62.4)	93 (66.0)	76 (58.5)	0.20
Clinical measures				
Height, m (SD)	1.66 (0.1)	1.67 (0.1)	1.65 (0.11)	0.25
Weight, kg (SD)	75.3 (14.3)	76.1 (14.5)	74.4 (13.8)	0.18
BMI, kg m^{-2} (SD)	27.4 (4.7)	27.5 (5.0)	27.3 (4.3)	0.74
Heart rate, bpm (IQR)	70 (21)	69 (18)	73.5 (21)	0.13
Systolic BP, mm Hg (SD)	144 (25)	143 (25)	145 (26)	0.67
Diastolic BP, mm Hg (SD)	77 (14)	76 (14)	78 (14)	0.30
Killip class II and above, n (%)	29 (11.7)	10 (7.6)	19 (16.4)	0.03*
ST changes present, n (%)	76 (32.1)	31 (25.2)	45 (39.5)	0.02*
NYHA III or IV, n (%)	55 (20.3)	16 (11.3)	39 (30.0)	<0.001*
CCS III or IV, n (%)	40 (14.8)	16 (11.3)	24 (18.5)	0.1
GRACE Score, points (SD)	129.9 (19.4)	125.9 (17.5)	134.5 (20.4)	0.001*
Medical history				
Hypertension, n (%)	195 (72.0)	102 (72.3)	93 (71.5)	0.88
Diabetes mellitus, n (%)	65 (24.0)	35 (24.8)	30 (23.1)	0.74
Hyperlipidemia, n (%)	158 (58.3)	85 (60.3)	73 (56.2)	0.49
Family history of IHD, n (%)	84 (31.2)	46 (33.1)	38 (29.2)	0.50
Renal impairment, n (%)	53 (19.6)	20 (14.2)	33 (25.4)	0.02*
Previous MI, n (%)	90 (33.2)	38 (27.0)	52 (40.0)	0.02*
Previous angina, n (%)	112 (41.3)	51 (36.2)	61 (46.9)	0.07
Previous PCI, n (%)	54 (19.9)	24 (17.0)	30 (23.1)	0.21
Previous CABG, n (%)	15 (5.5)	7 (5.0)	8 (6.2)	0.67
CCF, n (%)	21 (7.7)	7 (5.0)	14 (10.8)	0.07
AF, n (%)	40 (14.8)	19 (13.5)	21 (16.2)	0.54
PVD, n (%)	27 (10.0)	10 (7.1)	17 (13.1)	0.10
Previous TIA/stroke, n (%)	43 (15.9)	16 (11.3)	27 (20.8)	0.03*
Arthritis, n (%)	90 (33.2)	44 (31.2)	46 (35.4)	0.47
COPD, n (%)	48 (17.7)	22 (15.6)	26 (20.0)	0.34
Malignancy, n (%)	28 (10.0)	10 (7.1)	17 (13.1)	0.10
Peptic ulcer disease, n (%)	14 (5.2)	7 (5.0)	7 (5.4)	0.88
Bleeding problems, n (%)	7 (2.6)	4 (2.8)	3 (2.3)	1.0
Anemia, n (%)	20 (7.4)	6 (4.3)	14 (10.8)	0.04*
Smoking status				
Current smoker, n (%)	19 (7.1)	9 (6.5)	10 (7.7)	0.70
Ex-smoker, n (%)	132 (49.1)	67 (48.2)	65 (50.0)	0.77
Never-smoker, n (%)	117 (43.5)	64 (45.3)	54 (41.5)	0.53
Frailty indices				
Fried index, score (IQR)	1 (2)	1 (1)	2 (2)	0.003*
Weight loss, n (%)	73 (26.9)	34 (24.1)	39 (30.0)	0.28

Continued

Table 1. Continued

	Total (n=271)	Normal (n=141)	Cognitive Impairment (n=130)	*P* Value
Physical endurance/energy, n (%)	78 (28.8)	37 (26.2)	41 (31.5)	0.34
Low physical activity, n (%)	93 (34.3)	41 (29.1)	52 (40.0)	0.06
Weakness, n (%)	169 (62.4)	79 (56.0)	90 (69.2)	0.03*
Slow walking speed/TUG, n (%)	38 (14.1)	11 (7.8)	27 (21.1)	0.002*
Fried frailty status				
Robust, n (%)	53 (19.6)	29 (20.6)	24 (18.5)	0.002*
Prefrail, n (%)	148 (54.6)	88 (62.4)	60 (46.2)	
Frail, n (%)	70 (25.8)	24 (17.0)	46 (35.4)	
Rockwood index, score (IQR)	3 (2)	3 (1)	4 (1)	<0.001*
Rockwood frailty status				
Nonfrail	239 (88.2)	133 (94.3)	106 (81.5)	0.001*
Frail	32 (11.8)	8 (5.7)	24 (18.5)	
Blood results				
Hemoglobin, g L^{-1} (SD)	131.2 (19.1)	133.4 (20.7)	128.7 (16.9)	0.02*
Creatinine, μmol L^{-1} (SD)	101.9 (33.5)	97.1 (27.3)	107.1 (38.5)	0.07
eGFR, % (SD)	55.4 (20.3)	58.4 (18.3)	52.1 (22.0)	0.001*
Hs CRP, mg L^{-1} (IQR)	4.15 (8.3)	3.2 (6.9)	4.45 (10.3)	0.049*
Troponin T, ng L^{-1} (IQR)	120 (371)	124 (378)	119 (370)	0.43

AF indicates atrial fibrillation; BMI, body mass index; BP, blood pressure; bpm, beats per minute; CABG, coronary artery bypass graft; CCF, congestive cardiac failure; CCS, Canadian Cardiovascular Society angina score; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; GRACE, Global Registry of Acute Coronary Events; Hs CRP, high-sensitivity C-reactive protein; IHD, ischemic heart disease; IQR, interquartile range; MI, myocardial infarction; NYHA, New York Heart Association class; PCI, percutaneous coronary intervention; PVD, peripheral vascular disease; TIA, transient ischemic attack; TUG, timed up and go test.
*$P < 0.05$.

score, P=0.007 using paired t test) (Figure 3A and 3B). Seventy-four (35.1%) patients had cognitive decline (MoCA score dropped by ≥2 points), and they were defined as "decliners." The remaining 137 patients were defined as "nondecliners." Decliners had higher MoCA scores at baseline compared with nondecliners (26.2 versus 24.9, P=0.001), had less proportion of nonsmokers (P=0.001), more likely to be frail, with low physical activity (P=0.02) and slow walking speed (P=0.04) in Fried frailty measurement domains (Table S2). The presentation and management strategy were similar for decliners and nondecliners.

The rate of having an MI within 1-year follow-up was significantly higher in decliners (14.9% versus 5.1%, P=0.02), and they also had a higher proportion with congestive cardiac failure (14.9% versus 3.6%, P=0.003) (Table S3). In logistic regression analysis (Table S4), recurrent MI was an independent predictor of cognitive decline at 1 year (odds ratio 3.24, 95% CI 1.2–8.76, P=0.02), and this remained significant in age and sex adjusted model (odds ratio 3.19, 95% CI 1.18–8.63, P=0.02) and also after adjustment for other confounders. Other significant fully adjusted predictors of cognitive decline included new or worsening congestive cardiac failure within 1 year (P=0.008), all-cause rehospitalization within 1 year (P=0.02), and slow walking (P=0.045) at baseline. Additional linear regression analysis was also used to identify predictors of change in MoCA score at 1 year, controlling for baseline MoCA score. Recurrent MI was one of the significant predictors of MoCA change with a β coefficient of 2.63 (P=0.048) indicating patients who had a recurrent MI would expect to have a decline in MoCA score by 2.63 at 1 year.

Discussion

The present study demonstrates that in older patients undergoing invasive management of NSTEACS, there is a high prevalence of undiagnosed cognitive impairment at baseline. Our data showed that this group of NSTEACS patients had a lower than normal MoCA performance score (mean score 25.4 versus 25.7 from normative study[13]). Our study also shows that cognitive decline is present in over a third of all participants and recurrent MI is independently associated with cognitive decline at 1 year.

Very few prior studies have evaluated cognitive function in the setting of acute MI. Gharacholou and colleagues recruited patients who had survived an acute MI (mean age

Table 2. One-Year Outcomes, Stratified by Baseline Cognition Status

1-Year Outcomes	Total (n=270)	Normal (n=141)	Cognitive Impairment (n=129)	*P* Value
MACE outcome, n (%)	71 (26.3)	30 (21.3)	41 (31.8)	0.05*
Death, n (%)	13 (4.8)	4 (2.8)	9 (7)	0.16
Myocardial infarction, n (%)	30 (11.6)	13 (9.4)	17 (14)	0.25
Death/myocardial infarction, n (%)	39 (14.4)	15 (10.6)	24 (18.6)	0.06
Urgent revascularization, n (%)	21 (8.1)	7 (5.1)	14 (11.6)	0.06
Stroke, n (%)	2 (0.8)	0 (0)	2 (1.7)	0.22
Significant bleeding, n (%)	36 (14)	18 (13)	18 (15)	0.65
Stable angina, n (%)†	63 (26.8)	31 (24.6)	32 (29.4)	0.41
Elective PCI, n (%)†	26 (10.6)	16 (12.3)	10 (8.7)	0.36
CCF, n (%)†	24 (10)	10 (7.8)	14 (12.5)	0.23
TIA, n (%)†	2 (0.8)	1 (0.8)	1 (0.9)	1
Dialysis, n (%)†	1 (0.4)	0 (0)	1 (0.9)	0.47
Institutional care requirement, n (%)†	2 (0.9)	0 (0)	2 (1.9)	0.22

CCF indicates congestive cardiac failure; MACE, major adverse cardiac events (including death, myocardial infarction, urgent revascularization, stroke, significant bleeding); PCI, percutaneous coronary intervention; TIA, transient ischemic attack.
*Statistically significant $P < 0.05$.
†Secondary outcomes.
A full description of statistical methods is included in the main text. *Note:* the composite endpoint only counts the first event; some patients experienced multiple adverse outcomes.

73.2±6.3 years, 58.5% men) in the TRIUMPH (the Translational research investigating underlying disparities in acute myocardial infarction patients' health status) study, which showed a high rate of CI (55.6%) and a significant higher risk-adjusted 1-year mortality (hazard ratio 1.97, P=0.05).[14] Volonghi and colleagues compared cognitive outcomes in ACS to transient ischemic attack and minor stroke patients (ACS group: mean age 68.1±12.4 years, 73% men) in the OXVASC (Oxford Vascular Study). A high prevalence of CI (49%) at 1 year in ACS patients was found, and the ACS group had a higher risk of CI than transient ischemic attack patients but a risk similar to that of the minor stroke group.[15] A German study conducted by Salzwedel and colleagues recruited 496 younger patients (mean age 54.4±6.3 years, 79.8% men) who had a recent acute coronary event (ACE-MI or coronary artery bypass graft) and reported a CI rate of 36.7%, CI was also found to be associated with heavy workloads and a longer sick leave before ACE.[16] The TRIUMPH and OXVASC studies utilized a cognitive assessment tool, TICS-m (the Telephone interview for cognitive status-modified) different from MoCA to determine cognitive status. Salzwedel et al utilized MoCA as their cognitive assessment tool, but they studied a much younger patient group (mean age 54.4 years), which may explain the lower CI rate. Timing of the baseline cognitive assessment was also slightly different: ICON-1 at index NSTEACS event during hospitalization; TRIUMPH at 1 month after acute MI; OXVASC at 1-year post MI follow-up; and Salzwedel's study at 14 days after discharge following MI or coronary artery bypass graft.

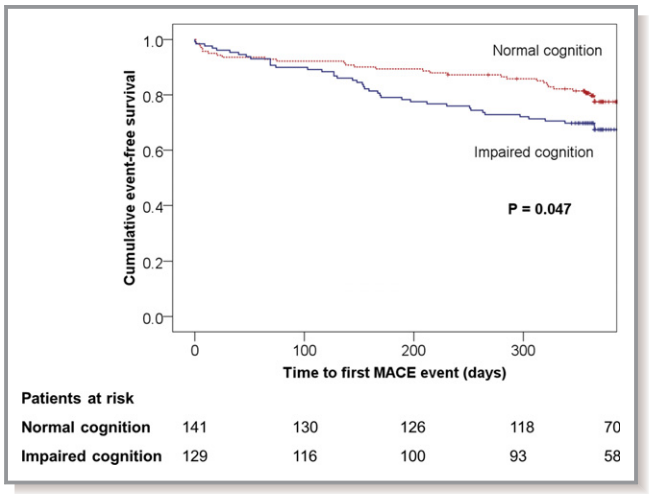

Figure 2. Kaplan–Meier plot, demonstrating time to first MACE stratified by baseline cognitive status. Log-rank test for equality of survival distributions demonstrates a significant difference between the survival curves (χ^2=3.96, 1 degree of freedom, P=0.047). MACE indicates major adverse cardiovascular events (death, nonfatal myocardial infarction, urgent revascularization, stroke, and significant bleeding).

The current study showed a significant reduction in overall MoCA score over 1 year with a mean reduction of 0.6. This is a more than expected decline in cognitive function compared with normative longitudinal studies on MoCA performance (annualized MoCA change of −0.37 from healthy elderly

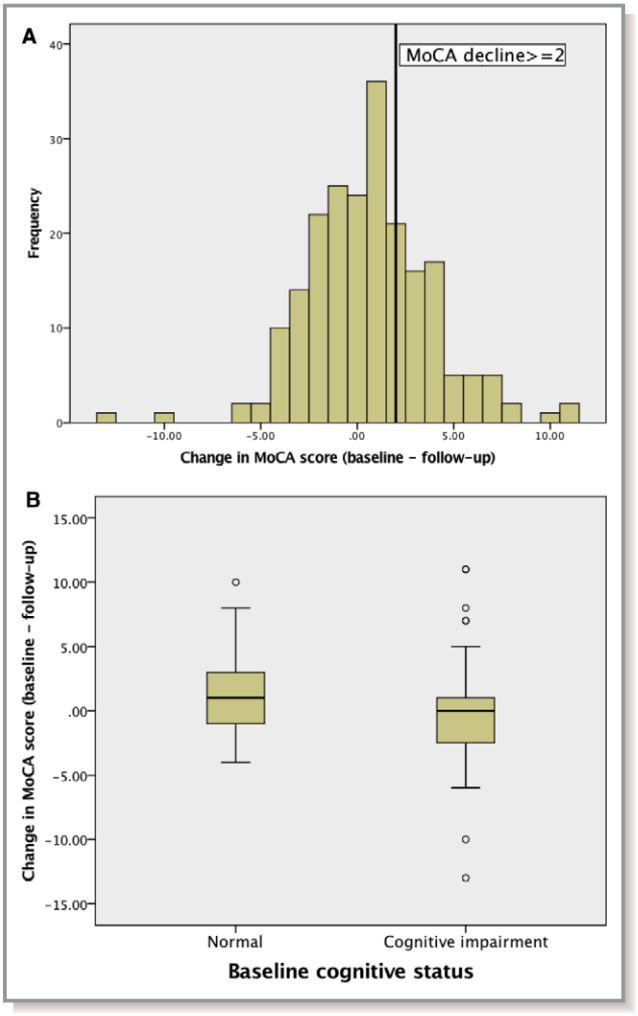

Figure 3. **A**, Histogram of the change in MoCA score from baseline to follow-up. **B**, Parallel boxplots of the overall change in mean MoCA score at 1 year from baseline split by baseline cognition. MoCA indicates Montreal Cognitive Assessment.

individuals[13]). Over one third of participants were identified as "decliners" with an overall MoCA reduction ≥ 2. Interestingly cognitive decline was common in patients who had a higher baseline cognitive function, those who were smokers, frail, had less physical activity, and slower walking speed. The important finding in the present analysis is that recurrent MI was independently associated with cognitive decline at 1 year. A recently published Danish large population-based cohort study demonstrated previous MI is associated with higher risk of vascular dementia (hazard ratio=1.35, 95% CI 1.28–1.43), and this association is strengthened for patients who had a stroke after MI (hazard ratio=4.48, 95% CI 3.29–6.12).[17] THORESCI (Tilburg Health Outcomes Registry or Emotional Stress after Coronary Intervention) study found that patients treated with acute PCI for ACS had poorer concentration (*P*=0.019) compared with elective PCI patients those who were more depressed and had a higher level of fatigue had poorer concentration and attention.[18] A recent systematic review found that coronary heart disease (CHD-MI and angina pectoris combined) was associated with a 45% increased risk of dementia, cognitive impairment, or cognitive decline (odds ratio 1.45, 95% CI 1.2–1.74, *P*<0.001), and MI was found to be associated with a 46% increased risk (odds ratio 1.46, 95% CI 1.16–1.84, *P*=0.001).[19]

The exact pathophysiological mechanism by which CAD is related to risk of cognitive decline or dementia is still unknown, but several possible pathways have been proposed. The association of dementia and CAD can be partly explained by their shared risk factors, such as diabetes mellitus, smoking, hypertension, hypercholesterolemia, and obesity. Higher platelet activation in CAD patients with cognitive impairment has been reported previously.[20] This leads to proposed hypothetical mechanisms involving increased platelet activity in CAD patients triggering perivascular inflammation in the brain and progression of carotid artery diseases and cerebral vasoconstriction contributing to dementia progression.[21] A recent study suggested immune activation might interconnect heart and brain dysfunction in the setting of MI.[22] CAD and associated vascular disease can lead to cerebrovascular changes and resulting in cerebral hypoperfusion, which in turn can lead to poor cognitive function and dementia. There are very few small studies evaluating PCI-related cognitive decline, and findings have been inconsistent. The passage of cardiac catheters in coronary angiography or PCI can potentially dislodge atheroma from the aortic wall, which leads to microemboli to the cerebral circulation causing stroke or cognitive decline.[23] Devapalasundarum et al found that cognitive function was worse in patients having elective coronary angiography compared with healthy controls: a rate of 39.6% new cognitive dysfunction was reported at discharge in coronary angiography patients. The group hypothesized that cognitive dysfunction may be exacerbated in some patients because of periprocedural microemboli.[24]

In our study, frail patients experienced CI, and this is particularly reflected in the domains of weak handgrip, slow walking, and low physical activity. This is possibly because of common underlying pathophysiologic mechanisms, and the concept of cognitive frailty has been proposed to emphasize the important role of brain aging. In the frail elderly population with cognitive deficits but without dementia, this may represent a prodromal phase for neurodegenerative diseases and is a potential target for early intervention to prevent disease progression.[25]

Dementia is associated with a huge burden on health and social care. Risk factor modification is crucially important in preventing cognitive decline to ensure good quality of life and to maintain functional independence, as well as to save healthcare costs. Our study has demonstrated the association of recurrent MI and cognitive decline. Thus, more aggressive

contemporary therapeutic strategies to prevent recurrent events might play a role in reducing cognitive decline and subsequently delaying progression into dementia, and the older patients should not be denied advanced care with contemporary treatment strategies.

Study Limitations

This study has limitations. ICON-1 recruited patients who had been referred to tertiary cardiac centers for coronary angiography, and thus the oldest, frailest, and more cognitively impaired patients who were not offered invasive management were not included in our study. Furthermore, the current study aimed to reflect real-world acute state of cognitive faculties at the time of NSTEACS, and cognitive impairment was assessed at the time of index hospitalization. Performing objective cognitive assessment could be challenging during acute illness, as patients are prone to acute confusional states or delirium. However, an effort was made to exclude conditions that may predispose patients to delirium (active infection, conditions that can cause brain hypoperfusion: cardiac arrest, ventricular arrhythmia or cardiogenic shock, and moderate to severe valvular heart disease). Moreover, applying a MoCA cut-off score of 26 to the older patients may seem to be too stringent, because normative studies in this elderly population suggest an age-adjusted or education-adjusted cut-off score to be applied.[13,26] There is currently no randomized controlled trial comparing cognitive function or decline in elderly patients with acute MI treated with PCI versus optimal medical therapy. The British Heart Foundation older patients in the SENIOR-RITA (non-ST segment elevation myocardial infarction randomized interventional treatment) trial (ClinicalTrials.gov identifier: NCT03052036) aims to compare invasive revascularization versus optimal medical treatment for older patients with non-ST–elevation myocardial infarction, and will provide some important insight into frailty and cognitive function affected by treatment strategy. Nevertheless, for the first time, our study provides key insights into baseline cognitive impairment and cognitive decline in this patient cohort (older patients undergoing invasive care for NSTEACS). Our study demonstrated the association between recurrent MI and cognitive decline, highlighting the importance and the need for risk factor modification addressing recurrent MI in preventing the decline in cognitive function and progression to dementia. There is also a proportion of patients whose cognition improved. This is not the focus of this study and may warrant further investigation.

Conclusions

In older patients undergoing invasive management of NSTEACS, there is a high prevalence of cognitive impairment at baseline. Recurrent MI is independently associated with cognitive decline at 1 year. The actual mechanisms responsible for cognitive decline in this patient cohort are not clear. Several hypothetical theories on the complex relationship between heart disease and long-term risk of dementia exist. These can be taken into account for the cognitive decline in this patient cohort. Early intervention and risk factor modifications are crucial in preventing cognitive decline.

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Author Contributions

Chief Investigator and Senior Author: Kunadian; First author: Gu; Co-investigators: Neely, Qiu; Statistician: Mossop; Clinical Research Fellows: Batty, Chan, Beska; Clinical Research Team: Adams-Hall.

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Disclosures

None.

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SUPPLEMENTAL MATERIAL

Table S1. Procedural details and medical management.

	Total (*n* = 271)	**Normal (*n* = 141)**	**Cognitive impairment (*n* = 130)**	**P value**
NSTEMI, *n* (%)	219 (80.8)	114 (80.9)	105 (80.8)	0.99
UA, *n* (%)	52 (19.2)	27 (19.1)	25 (19.2)	0.99
Time from admission to CA, days (IQR)	5 (4)	5 (3)	5 (4)	0.31
Length of hospital stay, days (IQR)	6 (5)	6 (4)	6 (4)	0.12
Medical management only, *n* (%)	36 (13.3)	13 (9.2)	23 (17.7)	**0.04**
PCI, *n* (%)	225 (83)	122 (86.5)	103 (79.2)	0.11
CABG, *n* (%)	10 (3.7)	6 (4.3)	4 (3.1)	0.75
Single-vessel PCI, *n* (%)	158 (58.3)	89 (63.1)	69 (53.1)	0.09
Multi-vessel PCI, *n* (%)	67 (24.7)	33 (23.4)	34 (26.2)	0.6
Left main stem disease, *n* (%)	16 (5.9)	4 (2.8)	12 (9.2)	**0.03**
LAD disease, *n* (%)	130 (48.0)	71 (50.4)	59 (45.4)	0.41
LCx disease, *n* (%)	75 (27.7)	37 (26.2)	38 (29.2)	0.58
RCA disease, *n* (%)	77 (28.4)	42 (29.8)	35 (26.9)	0.6
Number of stents, median (IQR)	1 (1)	1 (1)	1 (1)	0.68
Radial access, *n* (%)	235 (86.7)	125 (88.7)	110 (84.6)	0.33
Contrast volume, mL (SD)	160 (80)	171 (77)	148 (82)	**0.006**
Radiation dose, cGycm^2 (IQR)	5768 (5126)	6020 (5511)	5505 (5050)	0.16
Periprocedural complication*, *n* (%)	14 (5.2)	6 (4.3)	8 (6.2)	0.48
Duration of PCI, min (SD)	60.7 (29.8)	62.3 (29.1)	59.0 (30.6)	0.33
Medications on Discharge				
Aspirin, *n* (%)	268 (98.9)	140 (99.3)	128 (98.5)	0.61
Clopidogrel, *n* (%)	155 (57.2)	74 (52.5)	81 (62.3)	0.10
Prasugrel, *n* (%)	2 (0.7)	1 (0.7)	1 (0.8)	1
Ticagrelor, *n* (%)	105 (38.7)	63 (44.7)	42 (32.3)	**0.04**
Statin, *n* (%)	260 (95.9)	132 (93.6)	128 (98.5)	0.06
ACEi / ARB, *n* (%)	240 (88.6)	129 (91.5)	111 (85.4)	0.12
β-blocker, *n* (%)	219 (80.8)	110 (78.0)	109 (83.8)	0.22
Ca^{2+}-channel blocker, *n* (%)	90 (33.2)	48 (34.0)	42 (32.3)	0.76

Long-acting nitrate, *n* (%)	79 (29.2)	36 (25.5)	43 (33.1)	0.17
Nicorandil, *n* (%)	40 (14.8)	17 (12.1)	23 (17.7)	0.19
Proton pump inhibitor, *n* (%)	121 (44.6)	64 (45.4)	57 (43.8)	0.80
Warfarin, *n* (%)	18 (6.6)	8 (5.7)	10 (7.7)	0.51
NOAC, *n* (%)	8 (3.0)	3 (2.1)	5 (3.8)	0.49
Vitamin D supplement, *n* (%)	32 (11.8)	18 (12.8)	14 (10.8)	0.61

ACEi – angiotensin converting enzyme inhibitor, ACS – acute coronary syndrome, ARB – angiotensin II receptor blocker, CA – coronary angiography, Ca^{2+} – calcium, CABG – coronary artery bypass grafting, IQR – inter quartile range, LAD – left anterior descending artery, LCx – left circumflex artery, NOAC – novel oral anti-coagulant, NSTEMI – non-ST-elevation myocardial infarction, PCI – percutaneous coronary intervention, RCA – right coronary artery, SD – standard deviation, UA - unstable angina.

* – Periprocedural complications: 7 arterial dissection (5 coronary artery dissection, 1 aortic artery dissection treated conservatively,1 iliac artery dissection), 1 loss of side branch, 1 coronary artery perforation, 1 bleeding from radial artery puncture site, 1 pseudoaneurysm, 1 retroperitoneal bleed required blood transfusion, 1 pulmonary oedema, 1 ventricular fibrillation (VF) arrest.

Table S2. Baseline characteristics stratified by cognitive decliner (CD) or non-decliner (ND).

	Total (*n* = 211)	**ND (*n* = 137)**	**CD (*n* = 74)**	**P value**
Demographics				
Age, years (SD)	80.2 (4.9)	80.3 (4.6)	80.1 (5.4)	0.75
Male, *n* (%)	134 (63.5)	83 (60.6)	51 (68.9)	0.23
Clinical Measures				
Height, m (SD)	1.66 (0.1)	1.67 (0.1)	1.65 (0.1)	0.37
Weight, kg (SD)	75.9 (13.9)	76.1 (14.1)	75.5 (13.5)	0.79
BMI, kg m^{-2} (SD)	27.4 (4.3)	27.4 (4.4)	27.6 (4.0)	0.54
Heart rate, bpm (IQR)	70 (21)	71 (18)	67 (23)	0.24
Systolic BP, mmHg (SD)	144 (26)	144 (25)	144 (28)	0.87
Diastolic BP, mmHg (SD)	77 (13)	78 (13)	75 (14)	0.32
Killip class II and above, n (%)	22 (11.4)	13 (10.3)	9 (13.4)	0.52
ST changes present, n (%)	58 (30.9)	39 (31.5)	19 (29.7)	0.80
NYHA III or IV, *n* (%)	39 (18.5)	24 (17.5)	15 (20.3)	0.62
CCS III or IV, *n* (%)	29 (13.7)	17 (12.4)	12 (16.2)	0.44
GRACE Score, points (SD)	129.2 (19.4)	129.3 (18.4)	129.0 (21.4)	0.75
Medical History				
Hypertension, *n* (%)	150 (71.1)	92 (67.2)	58 (78.4)	0.09
Diabetes, *n* (%)	47 (22.3)	27 (19.7)	20 (27)	0.22
Hyperlipidaemia, *n* (%)	124 (58.8)	77 (56.2)	47 (63.5)	0.30
Family history of IHD, *n* (%)	65 (31.1)	45 (33.3)	20 (27)	0.35
Renal impairment, *n* (%)	42 (19.9)	32 (23.4)	10 (13.5)	0.09
Previous MI, *n* (%)	64 (30.3)	41 (29.9)	23 (31.1)	0.86
Previous angina, *n* (%)	81 (38.4)	48 (35)	33 (44.6)	0.17
Previous PCI, *n* (%)	41 (19.4)	26 (19)	15 (20.3)	0.82
Previous CABG, *n* (%)	8 (3.8)	4 (2.9)	4 (5.4)	0.46
CCF, *n* (%)	15 (7.1)	9 (6.6)	6 (8.1)	0.68
AF, *n* (%)	30 (14.2)	17 (12.4)	13 (17.6)	0.31
PVD, *n* (%)	19 (9)	13 (9.5)	6 (8.1)	0.74

Previous TIA/Stroke, *n* (%)	31 (14.7)	19 (13.9)	12 (16.2)	0.65
Arthritis, *n* (%)	72 (34.1)	43 (31.4)	29 (39.2)	0.25
COPD, *n* (%)	33 (15.6)	20 (14.6)	13 (17.6)	0.57
Malignancy, *n* (%)	23 (10.9)	12 (8.8)	11 (14.9)	0.17
Peptic ulcer disease, *n* (%)	10 (4.7)	5 (3.6)	5 (6.8)	0.33
Bleeding problems, *n* (%)	3 (1.4)	2 (1.5)	1 (1.4)	1
Anaemia, *n* (%)	14 (6.6)	10 (7.3)	4 (5.4)	0.78
Smoking Status				
Current smoker, *n* (%)	12 (5.7)	6 (4.4)	6 (8.2)	0.35
Ex-smoker, *n* (%)	102 (48.8)	59 (43.4)	43 (58.9)	**0.03**
Never-smoker, *n* (%)	94 (45)	70 (51.5)	24 (32.9)	**0.01**
Frailty Indices				
Fried index, score (IQR)	1 (1)	1 (1)	2 (2)	0.07
Weight loss, *n* (%)	54 (25.6)	32 (23.4)	22 (29.7)	0.31
Physical endurance/energy, *n* (%)	54 (25.6)	32 (23.4)	22 (29.7)	0.31
Low physical activity, *n* (%)	59 (28)	31 (22.6)	28 (37.8)	**0.02**
Weakness, *n* (%)	129 (61.1)	84 (61.3)	45 (60.8)	0.94
Slow walking speed/TUG, *n* (%)	24 (11.5)	11 (8.1)	13 (17.6)	**0.04**
Fried frailty status: Robust, *n* (%)	48 (22.7)	33 (24.1)	15 (20.3)	0.63
Prefrail, *n* (%)	116 (55)	76 (55.5)	40 (54.1)	
Frail, *n* (%)	47 (22.3)	28 (20.4)	19 (25.7)	
Charlson index, points (IQR)	5 (2)	5 (2)	5 (2.3)	0.87
Blood Results				
Haemoglobin, g L^{-1} (SD)	132.3 (19.4)	132.1 (20.4)	132.8 (17.6)	0.98
Creatinine, µmol L^{-1} (SD)	100.6 (32.7)	99.7 (32.0)	102.1 (34.2)	0.51
eGFR, % (SD)	56.8 (20.5)	57.5 (21.5)	55.5 (18.6)	0.69
Hs CRP, mg L^{-1} (IQR)	3.95 (8.5)	4.2 (9.8)	3.9 (7)	0.96
Troponin T, ng L^{-1} (IQR)	121 (381)	126 (360.5)	99 (431.8)	0.89

AF – atrial fibrillation, BMI – body mass index, BP – blood pressure, CABG – coronary artery bypass grafting, CCF – congestive cardiac failure, CCS – Canadian Cardiovascular Society angina score, COPD – chronic obstructive pulmonary disease, eGFR – estimated glomerular filtration rate, GRACE

– Global Registry of Acute Coronary Events, Hs CRP – high-sensitivity C-reactive protein, IHD – ischaemic heart disease, IQR – interquartile range, MI – myocardial infarction, NYHA – New York Heart Association class, PCI – percutaneous coronary intervention, PVD – peripheral vascular disease, SD – standard deviation, TIA – transient ischaemic attack, TUG – timed up and go test.

Table S3. 1-year outcomes, stratified by cognitive decline status.

1-year Outcomes	**Total (*n* = 211)**	**Non-decliner (*n* = 137)**	**Cognitive decliner (*n* = 74)**	***P*-value**
MACE outcome- *n* (%)	46 (21.8)	25 (18.2)	21 (28.4)	0.09
Myocardial infarction- *n* (%)	18 (8.5)	7 (5.1)	11 (14.9)	**0.02**
Urgent revascularisation- *n* (%)	14 (6.6)	7 (5.1)	7 (9.5)	0.25
Stroke- *n* (%)	1 (0.5)	1 (0.7)	0 (0)	1
Significant bleeding- *n* (%)	35 (16.6)	23 (16.8)	12 (16.2)	0.92
Stable angina- *n* (%)	53 (25.1)	30 (21.9)	23 (31.1)	0.14
Elective PCI- *n* (%)	20 (9.5)	14 (10.2)	6 (8.1)	0.62
CCF- *n* (%)	16 (7.6)	5 (3.6)	11 (14.9)	**0.003**
TIA- *n* (%)	2 (0.9)	1 (0.7)	1 (1.4)	1

CCF – congestive cardiac failure, MACE – major adverse cardiac events (including death, myocardial infarction, urgent revascularisation, stroke, significant bleeding), PCI – percutaneous coronary intervention, TIA – transient ischaemic attack.

A full description of statistical methods is included in the main text. Note: the composite endpoint only counts the first event; some patients experienced multiple adverse outcomes

Table S4. Predictors of cognitive decline at 1-year, unadjusted and adjusted logistic regression models.

Predictor	Unadjusted*		Adjusted†		Adjusted‡		Adjusted§	
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
Recurrent MI	3.24 (1.2, 8.76)	**0.02**	3.19 (1.18, 8.63)	**0.02**	3.17 (1.15, 8.79)	**0.03**	4.33 (1.48, 12.66)	**0.007**
Unplanned repeat revascularisation	1.94 (0.65, 5.76)	0.23	1.91 (0.64, 5.71)	0.25	2.08 (0.68, 6.36)	0.20	2.29 (0.73, 7.16)	0.15
Bleeding	0.96 (0.45, 2.06)	0.92	1.02 (0.46, 2.27)	0.96	1.03 (0.45, 2.33)	0.95	0.96 (0.41, 2.27)	0.93
CCF- new or worsening	4.61 (1.54, 13.83)	**0.006**	4.54 (1.51, 13.63)	**0.007**	5.22 (1.68, 16.27)	**0.004**	4.82 (1.51, 15.36)	**0.008**
All cause re-Hospitalisation	1.85 (1.03, 3.33)	**0.04**	1.88 (1.04, 3.39)	**0.04**	1.94 (1.06, 3.55)	**0.03**	2.15 (1.14, 4.06)	**0.02**
CVS hospitalisation	1.53 (0.66, 3.58)	0.32	1.57 (0.66, 3.72)	0.31	1.50 (0.62, 3.61)	0.37	1.70 (0.69, 4.20)	0.25
Baseline cognitive impairment	0.40 (0.22, 0.72)	**0.002**	0.41 (0.22, 0.74)	**0.003**	-	-	0.36 (0.19, 0.68)	**0.002**
Baseline Fried frailty	1.35 (0.69, 2.62)	0.38	1.44 (0.73, 2.84)	0.30	1.79 (0.87, 3.67)	0.11	1.09 (0.52, 2.27)	0.83
Weight loss	1.39 (0.74, 2.62)	0.31	1.50 (0.78, 2.86)	0.22	1.6 (0.83, 3.11)	0.16	1.33 (0.66, 2.68)	0.43
Physical endurance	1.39 (0.74, 2.62)	0.31	1.41 (0.74, 2.68)	0.29	1.51 (0.78, 2.92)	0.22	1.21 (0.61, 2.40)	0.59
Low physical activity	2.08 (1.12, 3.86)	**0.02**	2.04 (1.10, 3.79)	**0.023**	2.19 (1.16, 4.15)	**0.016**	1.62 (0.84, 3.13)	0.15
Weakness	0.98 (0.55, 1.75)	0.94	1.03 (0.57, 1.86)	0.93	1.17 (0.63, 2.14)	0.62	0.96 (0.51, 1.78)	0.89
Slow walking	2.40 (1.02, 5.67)	**0.046**	2.36 (1.0, 5.58)	**0.05**	3.27 (1.31, 8.19)	**0.011**	2.57 (1.02, 6.45)	**0.045**
Smoking history	2.17 (1.20, 3.92)	**0.011**	2.23 (1.23, 4.05)	**0.008**	2.51 (1.35, 4.64)	**0.004**	-	-
Vitamin D supplement	2.43 (1.06, 5.58)	**0.04**	3.07 (1.27, 7.45)	**0.013**	3.06 (1.24, 7.56)	**0.016**	-	-
Hypertension	1.77 (0.92, 3.43)	0.088	1.75 (0.91, 3.39)	0.096	1.80 (0.92, 3.52)	0.089	-	-
Renal impairment	0.51 (0.24, 1.11)	0.09	0.52 (0.24, 1.14)	0.10	0.59 (0.27, 1.31)	0.20	-	-

ACS – acute coronary syndrome, CCF – congestive cardiac failure, CI – confidence interval, CVS – cardiovascular system, MI – myocardial infarction, OR – odds ratio

* Unadjusted logistic regression models

† Logistic regression models adjusted for age (age≥85 vs. age<85) and sex (male vs. female)

‡ Logistic regression models adjusted for age (age≥85 vs. age<85), sex (male vs. female) and baseline MoCA (<26 vs. ≥26)

§ Logistic regression models adjusted for age (age≥85 vs. age<85), sex (male vs. female), smoking history (current/ex-smoker vs. never smoker), hypertension, renal impairment, and taking Vitamin D supplement

|| Linear regression models adjusted for age, sex, and baseline MoCA score