Risk Factors and Outcomes of Very Young Adults Who Experience Myocardial Infarction: The Partners YOUNG-MI Registry

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Abstract

BACKGROUND: Despite significant progress in primary prevention, the rate of myocardial infarction has not decreased in young adults. We sought to compare the risk factor profiles and outcomes between individuals who experienced a first myocardial infarction at a very young (40 years) and a young (age 41-50 years) age.

METHODS: We evaluated all patients 50 years of age admitted with a Type 1 myocardial infarction to 2 large academic hospitals from 2000 to 2016. Risk factors were determined by review of electronic medical records. The primary outcomes of interest were all-cause and cardiovascular mortality.

RESULTS: Among 2097 consecutive young patients with myocardial infarction, 431 (20.5%) were 40 years of age. When compared with their older counterparts, very young patients had similar risk profiles, with the exception of greater substance abuse (17.9% vs 9.3%, *P* < .001) and less hypertension (37.9% vs 50.9%, *P* < .001). Spontaneous coronary artery dissection was more prevalent in very young patients (3.1% vs 1.1%, *P* = .003). Over a median follow-up of 11.2 years, very young myocardial infarction patients had a similar risk of all-cause and cardiovascular mortality.

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CONCLUSIONS: Despite being, on average, 10 years younger and having a lower prevalence of hypertension, very young myocardial infarction patients had similar 1-year and long-term outcomes when compared with those aged 41 to 50 years at the time of their index infarction. Our findings suggest the need for aggressive secondary prevention measures in very young patients who experience a myocardial infarction.

Keywords

Premature coronary artery disease; Risk factors; Very young adults

INTRODUCTION

The incidence of myocardial infarction is increasing among younger individuals.[1–3] While developing a myocardial infarction at an early age is significant, as there are more productive years of life at risk, the source of this phenomenon is not well understood. One possible explanation is the rising prevalence of conventional cardiovascular disease risk factors such as hypertension, dyslipidemia, diabetes, and smoking among younger individuals.[4] Other studies focusing on young individuals, however, have explored the role of additional risk factors such as illicit substance use[5] and hemostatic dysfunction.[6]

Nonetheless, even in studies focused on younger populations, few studies have specifically focused on individuals younger than age 40 suffering from a myocardial infarction,[7,8] with most evaluating those younger than 50,[9] 55,[1] or even 60 years of age.[10] A better understanding of risk factors and outcomes among young patients is needed because age remains the dominant risk factor for 10-year atherosclerotic cardiovascular disease (ASCVD) risk prediction. In particular, the calculation of the ASCVD risk score and subsequent treatment with a statin are generally reserved for individuals over the age of 40 years, while for those under the age of 40 there is more emphasis on lifestyle interventions. Furthermore, it has been shown that current guidelines underestimate cardiovascular risk among individuals who developed a myocardial infarction at a young age.[11]

Therefore, our aim was to compare the baseline characteristics, risk factors, and outcomes of very young patients (age 40 years) who experienced a myocardial infarction with other, older patients (ages 41-50) within the Partners YOUNG-MI Registry. In addition, we evaluated angiographic characteristics of these patients to determine whether very young patients had a similar extent and severity of coronary artery disease when compared with those patients who were older at the time of their myocardial infarction.

METHODS

Study Population

The design of the YOUNG-MI registry has been previously described.[9] In summary, this is a retrospective cohort study from 2 large academic medical centers (Brigham and Women's Hospital and Massachusetts General Hospital) including all patients who experienced a first myocardial infarction at or prior to 50 years of age between the years 2000 and 2016. All medical records were adjudicated by a team of study physicians, as previously described[9]

using the Third Universal Definition of Myocardial Infarction.[12] For the present analysis, only patients who experienced a Type 1 myocardial infarction on index admission were included. Individuals with known coronary artery disease (defined as a prior myocardial infarction or revascularization) were excluded from this analysis.

Risk Factors

The presence of cardiovascular risk factors was ascertained through a detailed review of electronic health records corresponding to the period of time up to and including the index admission. The definitions of all risk factors, household income, and the Charlson Comorbidity Index have been previously described and are detailed in the online supplement.[9,11,13]

Angiographic Findings

Invasive angiographic findings were ascertained through a review of cardiac catheterization images by a single interventional cardiologist blinded to all patient outcomes and risk factors. Both culprit lesions and nonculprit lesions were identified. For each lesion, the location and severity of stenosis (assessed visually, ranging from 20% to 100%) were classified.[14]

The extent of coronary artery plaque was determined by the segment involvement score (SIS) calculated as the total number of coronary artery segments exhibiting plaque, irrespective of the degree of luminal stenosis. For each patient, the SIS ranged from 0 to 16. Additionally, the Gensini score was used as a method of quantifying the overall severity of coronary stenosis while accounting for lesion location, as previously described.[15] Patients with a Gensini score >20 (a score corresponding to approximately a single lesion of 70% in the proximal left anterior descending artery) were defined as possessing severe coronary artery disease.[16]

Outcomes

The primary outcomes of interest were all-cause and cardiovascular death. Vital status was assessed by means of the Social Security Administration Death Master File, the Massachusetts Department of Vital Statistics, and the National Death Index. Cause of death was adjudicated independently by 2 cardiologists, with instances of disagreement reviewed by an adjudication committee and decisions reached by consensus. Death was classified as cardiovascular or noncardiovascular, as per published criteria.[9,17] If death certificates were not available, deaths were conservatively classified as noncardiovascular.

In an exploratory secondary analysis, we also evaluated the incidence of a short-term composite outcome comprised of all-cause mortality and re-infarction within 1-year post-myocardial infarction. Ascertainment of re-infarction was determined by review of all available records following the index admission. For an event to be classified as a re-infarction, discharge with a hospitalization diagnosis of myocardial infarction was required.[18]

Statistical Analysis

All analyses were performed using Stata version 15.1 (StataCorp, College Station, Texas). Categorical variables are reported as frequencies and proportions, and compared with chi-squared or Fisher's exact tests, as appropriate. Continuous variables are reported as means or medians and compared with *t*-tests or Mann-Whitney *U* tests, as appropriate. The proportional hazards assumption was assessed by analyzing the Schoenfeld residuals. Survival curves were compared using the log-rank test.

To evaluate the impact of age on the 3 outcomes in question, individuals were stratified into 2 groups based on their age at the time of the index myocardial infarction. Specifically, those patients who were at or below the age of 40 years were classified as "very young," while others, all aged 41 to 50, were classified as "young." Univariate Cox proportional hazards modeling was performed for survival free from all-cause mortality, cardiovascular mortality, and a composite outcome consisting of all-cause mortality and re-infarction within 1-year post-myocardial infarction. In each case, multivariable adjustment was then made using all baseline covariates that had a significant (P .05) univariate association with the outcome in question. Individuals who died during their index hospital stay were excluded from both the univariate and multivariate analyses.

RESULTS

Proportion of Very Young Myocardial Infarction Patients

The cohort consisted of 2097 patients who experienced a Type 1 myocardial infarction, of whom 443 (21%) were at or below the age of 40 years (very young) at the time of their event (Table 1). The proportion of individuals presenting with a Type 1 myocardial infarction at or prior to the age of 40 increased over the study period (2000-2016), although the increase was statistically significant only during the last 10 years of the study (2007-2016), where there was an average increase of 1.7% per year (P for trend .022) (Figure 1).

Baseline Characteristics

The baseline characteristics of very young patients vs those who experienced their index myocardial infarction between the ages of 41 and 50 years are shown in Table 1. Patients who experienced their myocardial infarction at or below the age of 40 had a median age that was 10 years lower than that of their older counterparts (36 vs 46, $P < .001$). When compared with older patients, very young individuals were more likely to use both marijuana ($P < .001$) and cocaine ($P = .013$) and present with chest pain ($P = .012$). Conversely, patients aged 41 to 50 years upon admission were more likely to be diagnosed with hypertension ($P < .001$) or peripheral vascular disease ($P = .012$), use alcohol ($P = .049$), and have a higher ASCVD risk score ($P < .001$). A comparison of the full set of characteristics is provided in Table 1.

In-hospital cardiac procedures, including cardiac catheterization, coronary revascularization, and coronary artery bypass grafting, were similar across both groups (Table 2). While the use of antiplatelet therapies and beta-blockers, as well as angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers, was similar between the 2 groups, there was

a small but statistically significant difference in the rate of aspirin (P = .011), statin (P = .017), and diuretic (P = .012) prescriptions upon discharge between very young and older members of the cohort (Table 2).

Invasive angiography was performed in 1985 patients (95%; Table 3). Single-vessel disease was more common in those who experienced their index myocardial infarction at or prior to the age of 40 years (56% vs 64%, P = .006). Spontaneous coronary artery dissection was also more prevalent among the very young (1.1% vs 3.1%, P = .003). Finally, those individuals at or under the age of 40 had lower extent of plaque, as measured by the SIS (P < .001), and lower overall plaque burden, as measured by the Gensini score (P = .035), than patients aged 41 to 50 years. The full set of angiographic findings can be found in Table 3.

Long-Term Outcomes

All-cause death.—Of the original 2097 patients, 6 of the 431 patients (1.4%) classified as very young died during their hospital stay, compared with 37 (2.2%) of the patients aged 41 to 50 years at the time of their index admission (P = .49). The remaining 2054 patients had a median follow-up of 11.2 years, during which 36 (8.5%) of the very young patients and 175 (10.7%) of their older counterparts died (P = .17). The annual death rate post discharge among the very young was 0.85 deaths per 100 person-years, while the rate for the older members of the cohort was 1.06 deaths per 100 person-years (P = .23). Being at or below the age of 40 upon index admission had an unadjusted hazard ratio of 0.80 (95% confidence interval [CI], 0.56-1.15; P = .22) (Figure 2A). After adjusting for sex, income, presentation with ST-elevation myocardial infarction, length of stay, hypertension, diabetes mellitus, alcohol use, illicit substance use, angina, peripheral vascular disease, ASCVD risk score, Charlson Comorbidity Index (CCI), high-density lipoprotein, total triglycerides, creatinine, estimated glomerular filtration rate, cardiac catheterization, revascularization, and medications upon discharge, the hazard ratio (HR) remained nonsignificant (1.06; 95% CI, 0.69-1.64; P = .79) (Figure 2A).

Cardiovascular death.—Over the same follow-up period, very young individuals had a similar incidence of cardiovascular mortality post discharge compared with their older counterparts (4.2% vs 4.2%, P = 1.00). The cardiovascular death rate among those who experienced their myocardial infarction at or below the age of 40 years was 0.41 deaths per 100 person-years, while that of patients aged 41 to 50 was 0.42 deaths per 100 person-years (P = .93). The unadjusted hazard ratio of those experiencing a first myocardial infarction at or below the age of 40 was 1.02 (95% CI, 0.61-1.71; P = .95) (Figure 2B). Following adjustment for income, length of stay, hypertension, diabetes mellitus, obesity, alcohol use, illicit substance use, angina, peripheral vascular disease, ASCVD risk score, CCI, creatinine, estimated glomerular filtration rate, and medications upon discharge, the HR remained nonsignificant (1.40; 95% CI, 0.77-2.56; P = .270) (Figure 2B).

Short-Term Outcomes

Following discharge, 37 (8.7%) of the very young patients died or experienced a reinfarction within 1 year of their myocardial infarction, compared with 154 (9.5%) of those patients aged 41 to 50 years (P = .64). Those experiencing a myocardial infarction at or prior to the

age of 40 had an unadjusted hazard ratio of 0.96 (95% CI, 0.67-1.37; *P* = .82) for the composite outcome of death or reinfarction (Figure 2C). After adjusting for the CCI, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, creatinine, cardiac catheterization, and coronary revascularization, the hazard ratio remained nonsignificant (0.97; 95% CI, 0.67-1.44, *P* = .879) (Figure 2C).

DISCUSSION

Among the 2097 patients who experienced a myocardial infarction at or prior to the age of 50 years, we found that approximately 21% were at or below the age of 40 at the time of hospitalization. These very young patients were similar to their older counterparts within our cohort in terms of their baseline characteristics, with the exception of a lower prevalence of hypertension and more frequent use of both marijuana and cocaine. While the 2 age groups were similar with respect to in-hospital cardiovascular procedures, younger patients were less likely to be prescribed aspirin or statins upon discharge. Finally, relative to the older members of the cohort, very young patients demonstrated less extensive coronary artery disease. However, despite being, on average, 10 years younger, having similar risk factor profiles, and having less coronary artery disease, younger patients had a similar incidence of both all-cause and cardiovascular mortality over a median follow-up of more than 11 years.

To the best of our knowledge, this is the largest study to compare the baseline characteristics, angiographic findings, and long-term outcomes of very young (age ≤ 40 years) and young (age 41-50) adults with myocardial infarction. Although a number of other studies have examined patients who experienced a myocardial infarction at a young age, they do not specify the upper age limit of the older or control group, often leading to comparisons between individuals who differ significantly in age.[19–24] Even in those cases where very young individuals were compared with an intermediate-aged control group, not only was the division between the 2 groups higher at age 45[25] or 50,[26] but the upper limit of the control group was significantly higher.[25,26] Moreover, among studies focused on myocardial infarction in younger patients, ours represents one of very few that have included long-term outcomes.[19,27] Finally, our study is one of the largest to examine the angiographic findings encountered in such a patient population. In particular, prior works examining the angiographic characteristics of young patients with myocardial infarction have often been limited to samples of several hundred or fewer individuals.[8,19,22]

Clinical Implications

A concerning trend that we observed was a significant increase in the proportion of very young patients experiencing a myocardial infarction during the last 10 years of the study period. Because the overall burden of traditional risk factors was similar between very young and young patients, it is plausible that there are additional risk factors among the very young in our cohort. For example, in the present study, more substance use was detected among very young individuals who experienced a myocardial infarction. This is not only an important risk factor in very young adults,[28] but one that seems to be increasing over time.[5] However, the association between substance use and adverse outcomes can also be due to a correlation between substance use and other risky health-related habits (eg, sedentary

behavior and poor diet).[30] Another explanation for the excess risk in very young adults is a genetic predisposition; however, we would not expect the prevalence of this risk factor to change over time.[29]

In keeping with prior research, those patients who experienced their myocardial infarction at a very young age had a lower extent of coronary artery disease when compared with the older members of the cohort. [19,20,22] Additionally, we found that spontaneous coronary dissection was significantly more frequent in very young myocardial infarction adults, and mostly present in women. These findings are consistent with previous work, which has shown that spontaneous coronary dissection occurs at a mean age of 43 years, and mostly among young females.[31]

The vast majority of patients who experienced a myocardial infarction at or under the age of 40 years had a low ASCVD risk score prior to their event, and most had a low burden of traditional risk factors such as hypertension. These results highlight the challenges that are present in identifying risk in very young individuals and suggest that future research is needed to identify and treat cardiovascular risk in young adults, particularly those under the age of 40 who are only rarely candidates for statin therapy.

Limitations

The primary limitation of our study was its retrospective nature. However, this aspect provided us with the opportunity to examine a substantial number of individuals who experienced a myocardial infarction at a young age. A similar prospective study would have required at least 10 years to allow for the recruitment of the same number of patients. Our study was also restricted to those individuals who suffered a myocardial infarction. Therefore, it was not possible to examine either the prevalence of myocardial infarction within the full, at-risk population, or the relative rates of myocardial infarction among the 2 different age groups of at-risk individuals. In addition, we do not have data on genetics or lifestyle factors, which are known to be associated with cardiovascular risk, and which may be even more important in the determination of cardiovascular risk among younger individuals. Finally, in terms of methodology, our study was limited in that we relied on a visual analysis to determine the angiographic characteristics of all patients within the cohort. Although arguably less precise than a quantitative assessment of obstruction, visual assessment has been widely used in prior studies.

CONCLUSION

Despite being, on average, 10 years younger and having less extensive coronary artery disease, very young myocardial infarction patients had similar 1-year and long-term outcomes when compared with those who were aged 41 to 50 years. Our findings suggest the need for aggressive secondary prevention measures in very young patients who experience a myocardial infarction and underscore the need for future efforts to improve risk assessment among young adults, particularly those under the age of 40, who are only rarely candidates for statin therapy.

Acknowledgments

SUPPLEMENTAL MATERIAL

Definition of Risk Factors

Diabetes was defined as having a fasting plasma glucose >126 mg/dL, a hemoglobin A1c 6.5%, or a documented diagnosis and/or treatment for diabetes. Hypertension was defined as a systolic blood pressure 140 mmHg, a diastolic blood pressure 90 mmHg, or a documented diagnosis and/or treatment of hypertension. Dyslipidemia was defined as having a total cholesterol 240 mg/dL, a serum triglyceride 150 mg/dL, a high-density lipoprotein (HDL) cholesterol <40 mg/dL in men or <50 mg/dL in women, or a documented diagnosis and/or treatment of dyslipidemia. Obesity was defined as having a body mass index (BMI) 30 kg/m^2 or a documented diagnosis of obesity. Family history of premature CAD was defined as a fatal MI, a non-fatal MI, or a coronary revascularization occurring before 55 years of age in the case of first-degree male family members and before 65 years of age for first-degree female family members. Alcohol use was defined as having a positive toxicology report for alcohol during the index hospitalization or a documented diagnosis and/or treatment of alcohol use. Illicit substance use was defined as having a positive toxicology report during the index hospitalization for one or more of marijuana, cocaine, heroin, or methamphetamines or a documented diagnosis and/or treatment for use of these substances. Depression, anxiety, and psychotic disorders were defined as having a

documented diagnosis and/or treatment for these conditions. In addition, we also calculated the atherosclerotic cardiovascular disease (ASCVD) risk score for each individual whenever possible.

In order to adjust for comorbidities, we calculated the Charlson Comorbidity Index (CCI), a method of predicting the risk of mortality based on co-morbidities, for each patient as determined by International Classification of Diseases, 9th Revision (ICD-9) diagnosis and billing codes associated with the index hospitalization.[1] Additionally, because lower socioeconomic status is known to be associated with all-cause mortality, household income for each patient was estimated based on household zip codes in conjunction with the 2015 inflation adjusted median household income data provided by the US Census Bureau.[2]

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CLINICAL SIGNIFICANCE

- Despite comparable risk factor profiles, being, on average, 10 years younger, and having less extensive coronary artery disease, very young myocardial infarction patients (40 years of age) had a similar incidence of both all-cause and cardiovascular mortality over a median follow-up of more than 11 years.

- Our findings suggest the need for aggressive lifestyle and pharmacological secondary prevention therapies among individuals who experience a myocardial infarction at a young age.
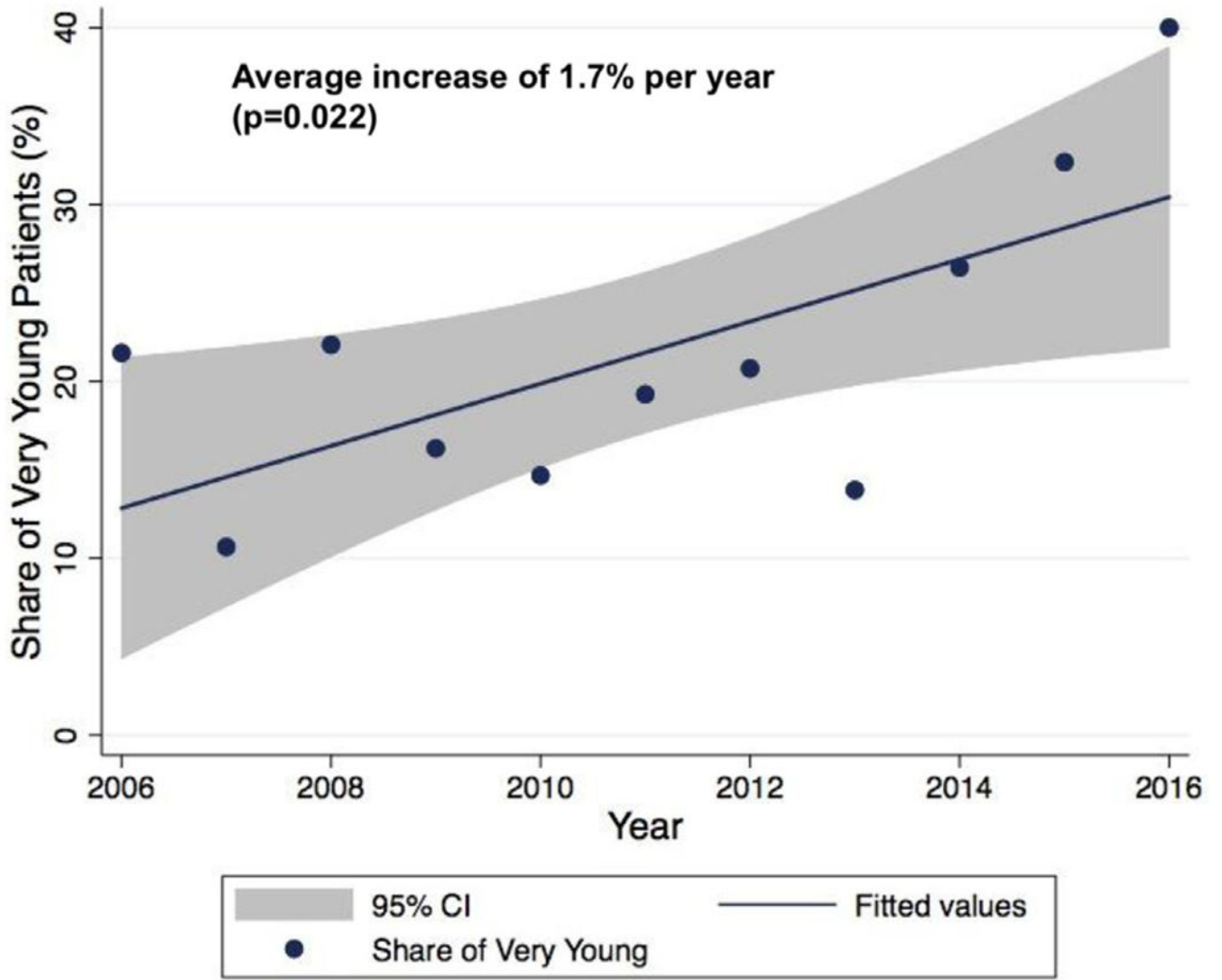
Figure 1.
Trend in the percentage of very young presenting with myocardial infarction from 2006-2016.
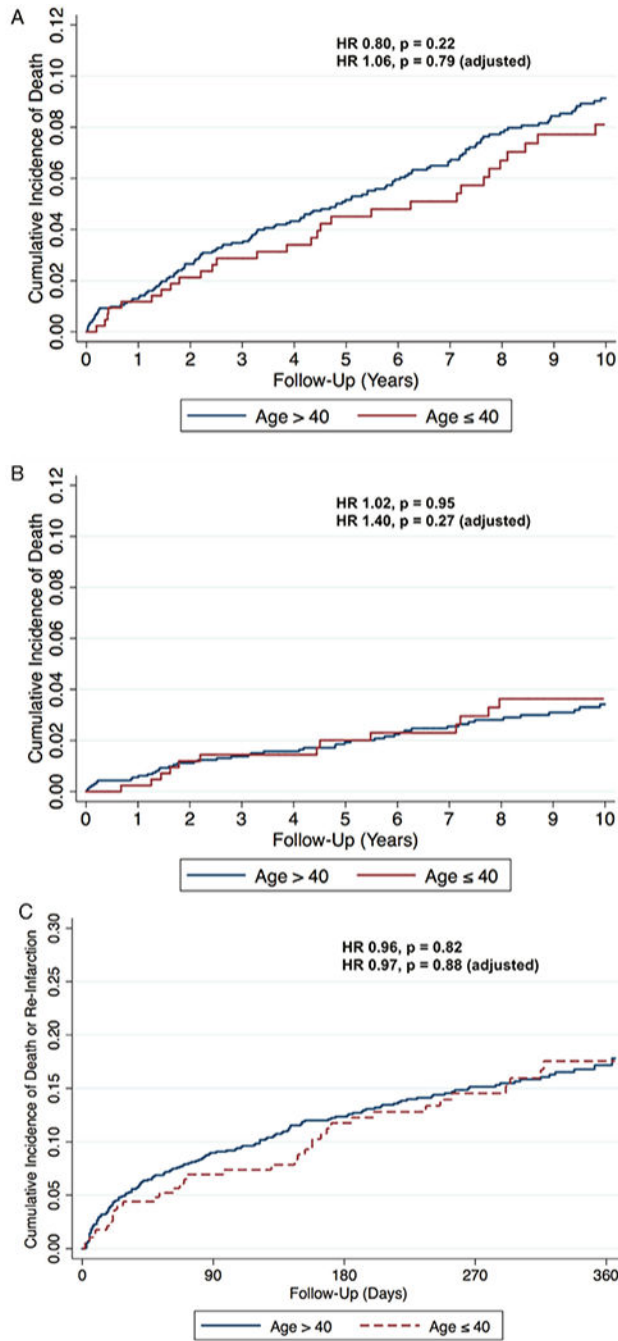
Figure 2.
(**A**) Kaplan-Meier survival curves for all-cause mortality stratified by age at index myocardial infarction (MI). (**B**) Kaplan-Meier survival curves for cardiovascular mortality stratified by age at index MI. (**C**) Kaplan-Meier survival curves for the composite of all-cause mortality and reinfarction within 1-year post-MI stratified by age at index myocardial infarction.

Table 1

Baseline Characteristics Stratified by Age at Index Myocardial Infarction

| Factor	40 < Age 50 Years (n = 1666, 79%)	Age 40 Years (n = 431, 21%)	P Value
Demographics			
Age at time of MI, median (IQR)	46 (44, 48)	36 (34, 39)	<.001
Female	317 (19.0%)	87 (20.2%)	.59
White	1225 (73.5%)	312 (72.4%)	.63
Income (thousands $), median (IQR)	71.4 (53.6, 87.4)	71.6 (50.9, 85.5)	.060
Insurance category			.15
None	148 (9.9%)	43 (11.7%)	
Public	239 (16.0%)	71 (19.2%)	
Private	1107 (74.1%)	255 (69.1%)	
ST-elevation myocardial infarction	884 (53.1%)	237 (55.0%)	.47
Length of stay, median (IQR)	3 (2, 5)	3 (2, 6)	.95
Risk factors			
Hypertension	841 (50.9%)	161 (37.9%)	<.001
Hyperlipidemia	1519 (91.2%)	391 (90.7%)	.77
Diabetes mellitus	335 (20.1%)	81 (18.8%)	.54
Premature CAD in 1st degree relative	478 (28.7%)	135 (31.3%)	.37
Obesity	591 (35.5%)	159 (36.9%)	.58
Current smoking	844 (51.1%)	222 (52.2%)	.68
Alcohol use	226 (13.7%)	43 (10.1%)	.049
Illicit substance use	154 (9.3%)	76 (17.9%)	<.001
Marijuana use	103 (6.3%)	58 (13.7%)	<.001
Cocaine use	69 (4.2%)	30 (7.1%)	.013
Angina	1444 (88.7%)	393 (92.9%)	.012
Peripheral vascular disease	39 (2.4%)	2 (0.5%)	.012
ASCVD score, median (IQR)	5.3 (3.2, 9.2)	3.9 (1.9, 6.7)	<.001
Charlson Comorbidity Index, mean (SD)	1 (1, 2)	1 (1, 2)	.099
Laboratory values			
Total cholesterol mg/dL, mean (SD)	192.7 (57.1)	190.6 (54.4)	.51

Factor	40 < Age 50 Years (n = 1666, 79%)	Age 40 Years (n = 431, 21%)	P Value
HDL cholesterol mg/dL, mean (SD)	37.3 (10.3)	35.4 (9.9)	.001
LDL cholesterol mg/dL, mean (SD)	118.9 (46.4)	119.9 (48.5)	.72
Triglycerides mg/dL, median (IQR)	150 (103, 223)	148 (102, 225)	.71
Creatinine mg/dL, median (IQR)	1 (0.9, 1.1)	1 (0.9, 1.1)	.13
Estimated glomerular filtration rate mL/min/1.73 m^2, mean (SD)	78.9 (20.5)	84.9 (22.3)	<.001

ASCD = atherosclerotic cardiovascular disease; CAD = coronary artery disease; HDL = high-density lipoprotein; IQR = interquartile range; LDL = low-density lipoprotein; MI = myocardial infarction.

Table 2

Medical Therapy Stratified by Age at Index Myocardial Infarction

Factor	40 < Age 50 Years (n = 1666, 79%)	Age 40 Years (n = 431, 21%)	P Value
Patient management			
Cardiac catheterization	1561 (93.7%)	410 (95.1%)	.27
Coronary revascularization	1382 (83.0%)	353 (81.9%)	.61
Coronary artery bypass grafting	147 (8.8%)	30 (7.0%)	.21
Factor	**40 < Age 50 Years (n = 1629, 79%)**	**Age 40 Years (n = 425, 21%)**	
Medical therapy			
Statin at discharge	1465 (89.9%)	365 (85.9%)	.017
Statin intensity			.056
None	164 (10.1%)	60 (14.1%)	
Low intensity/unknown dose	55 (3.4%)	16 (3.8%)	
Moderate intensity	619 (38.0)	140 (32.9%)	
High intensity	791 (48.6%)	209 (49.2%)	
Ezetimibe	19 (1.2%)	7 (1.6%)	.43
Aspirin at discharge	1550 (95.2%)	391 (92.0%)	.011
P2Y12 inhibitor at discharge	1338 (82.1%)	338 (79.5%)	.22
Beta-blocker at discharge	1490 (91.5%)	385 (90.6%)	.57
ACE inhibitor/ARBs at discharge	1002 (61.5%)	265 (62.4%)	.75
Diuretic at discharge	192 (11.8%)	32 (7.5%)	.012

ACE = angiotensin-converting enzyme; ARB = angiotensin II receptor blockers.

Table 3

Angiographic Findings Stratified by Age at Index Myocardial Infarction

Factor	40 < Age 50 Years (n = 1577, 79%)	Age 40 Years (n = 408, 21%)	P Value
Any plaque or stenosis	1517 (97.2%)	383 (96.2%)	.29
Spontaneous dissection	16 (1.1%)	12 (3.1%)	.003
Female	14 (5.1%)	11 (14.9%)	.009
Male	2 (0.2%)	1 (0.3%)	.50
MICAD			
No obstructive CAD	77 (4.9%)	29 (7.1%)	< .001
Single-vessel disease	885 (56.1%)	260 (63.7%)	
Multi-vessel disease	615 (39.0%)	119 (29.2%)	
Segment involvement score, median (IQR)	3 (1, 4)	2 (1, 3.5)	< .001
Gensini score			
Single-vessel disease	32 (20, 47)	32 (20, 43.5)	.83
Multi-vessel disease	58 (42, 83)	56 (42, 88)	.65
Total	40 (24, 62)	36.5 (20, 58)	.035

CAD = coronary artery disease; IQR = interquartile range; MICAD = myocardial infarction with CAD.