European Heart Journal – Quality of Care and Clinical Outcomes (2015) **1**, 92–99
doi:10.1093/ehjqcco/qcv014

ORIGINAL ARTICLE

Angina frequency after acute myocardial infarction in patients without obstructive coronary artery disease

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Received 27 May 2015; revised 13 July 2015; online publish-ahead-of-print 23 July 2015

Aims Myocardial infarction (MI) patients without obstructive coronary artery disease (CAD) are at increased risk for recurrent ischaemic events, but angina frequency post-MI has not been described.

Methods and results Among MI patients who underwent angiography, we assessed angina at baseline, 1, 6, and 12 months using the Seattle Angina Questionnaire. A hierarchical repeated-measures-modified Poisson model assessed the association between the absence of obstructive CAD (defined as epicardial stenosis >70% or left main stenosis >50%) and angina. Among 5539 MI patients from 31 US hospitals (mean age 60, 68% male), 6.9% had no angiographic obstructive CAD. More patients without obstructive CAD (vs. obstructive CAD) were female (57 vs. 30%), non-white (51 vs. 24%), and had non ST elevation myocardial infarction (87 vs. 51%). In unadjusted analyses, patients without obstructive CAD had less angina prior to MI, but more angina and worse health status post-discharge. After adjustment for socio-demographic and clinical factors, the risk of post-MI angina was similar in patients without vs. with obstructive CAD [incidence rate ratio (IRR) = 0.89, 95% CI 0.77–1.02]. Among patients without obstructive CAD, depression and self-reported avoidance of care due to cost were independently associated with angina (IRR = 1.28 per 5 points on Patient Health Questionnaire, 95% CI 1.17–1.41; IRR = 1.34, 95% CI 1.02–1.1.74).

Conclusion Following MI, patients without obstructive CAD experience an angina burden at least as high as those with obstructive CAD, affecting 1 in 4 patients at 12 months. As these patients are not candidates for revascularization, other antianginal strategies are needed to improve their health status and quality of life.

Keywords Angina • Coronary artery disease • Acute myocardial infarction

Introduction

One in 10 patients presenting with an acute myocardial infarction (MI) do not have obstructive coronary artery disease (CAD) on coronary angiography, with the aetiology of the MI thought to be a combination of resolved thrombus, coronary spasm, and others.[1] Prior research has shown that these patients generally have lower rates of recurrent MI but similar rates of long-term mortality than those with obstructive CAD.[2] However, quality-of-life outcomes, such as post-MI angina, have not been evaluated in this patient population.

This is particularly relevant as patients without obstructive CAD can experience ischaemia-driven angina, presumably via mechanisms such as endothelial dysfunction and abnormal coronary vascular resistance. Residual angina after an MI is a particularly relevant outcome as it is associated with poor quality of life and is a major driver of repeat hospitalizations.[3] In addition, it is a potentially modifiable condition and therefore could be an ideal target to both improve patient symptoms and reduce healthcare costs.[4–6]

To address this knowledge gap, we compared the prevalence of post-MI angina, as well as rehospitalization rates, among MI patients

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with and without obstructive CAD in two large US multicentre MI registries. In addition, we evaluated predictors of residual angina among patients without obstructive CAD, so that efforts of more intense medical management could be directed towards those at highest risk.

Methods

Study design and participants

Details regarding the TRIUMPH (Translational Research Investigating Underlying disparities in acute Myocardial infarction Patients' Health status) and PREMIER (Prospective Registry Evaluating Myocardial Infarction: Events and Recovery) prospective observational registries have been described.[7,8] Briefly, from 2003 to 2004, 2498 MI patients from 19 US hospitals were enrolled in PREMIER, and between 2005 and 2008, 4340 MI patients from 24 US hospitals were enrolled in TRIUMPH (12 hospitals participated in both registries). Both registries had identical inclusion and exclusion criteria and follow-up protocols. Patients' 1-year mortality and angina outcomes were also similar between the two registries. To be included, patients were required to have a type 1 MI,[9] including biomarker evidence of myocardial necrosis and additional evidence supporting the clinical diagnosis of an MI such as prolonged ischaemic signs/symptoms ($\geq$20 min) or electrocardiographic ST changes.

Baseline data were obtained through chart abstraction and a structured interview by a trained research staff within 24–72 h following admission. Each participating site obtained Institutional Research Board approval, and all patients provided informed consent for baseline and follow-up assessments

Definition of obstructive coronary artery disease and angina

The reports of all angiograms performed during the MI were obtained and abstracted. In the primary analysis, obstructive CAD was defined as any epicardial coronary stenosis $\geq$70%, and/or left main stenosis $\geq$50%. We also performed a sensitivity analysis redefining obstructive CAD as any epicardial stenosis $>$50%. Patients with prior coronary artery bypass grafting, in-hospital percutaneous coronary intervention (PCI), or in-hospital CABG were also classified as having obstructive CAD. Patients were excluded from the analysis if they did not have a diagnostic coronary angiogram performed during the MI hospitalization.

Angina and health status were assessed during the MI hospitalization and at 1, 6, and 12 months following MI using the Seattle Angina Questionnaire (SAQ)[10] and the Medical Outcomes Study 12-Item Short Form (SF-12).[11] The SAQ is a reliable, responsive, and valid 19-item questionnaire with a 4-week recall that assesses five clinically important domains of health in patients with CAD: angina frequency, angina stability, disease perception/quality of life, physical limitations, and treatment satisfaction. The scores for each of the SAQ domains range from 0 to 100, with higher scores indicating less angina and better health status. The primary outcome of this study was the SAQ angina frequency domain, which quantifies the frequency and burden of angina and was categorized as absent (score = 100) or present (score $<$100).[12] The angina stability domain was not included in these analyses as it represents a short-term assessment of change and is not appropriate for longitudinal analyses. Generic health status was assessed with the SF-12,[13] which provides summary scales for overall physical and mental health status using norm-based methods that standardize the scores to a mean of 50 and a standard deviation of 10 (higher scores indicate better health status).[11]

Rehospitalization data

As part of the TRIUMPH study, patients were asked to report interval hospitalizations since their last study contact during the follow-up interviews. If a patient reported being hospitalized, records of that hospitalization were obtained to adjudicate cardiovascular events. Chart abstractions were sent to two cardiologists who independently classified the reason for hospitalization. If there was disagreement, the record was adjudicated by a third senior cardiologist and, if disagreement persisted, up to five cardiologists independently reviewed the charts until consensus was obtained. For this analysis, we examined both all-cause rehospitalizations and those due to chest pain, which included MI, unstable angina, stable angina, and non-cardiac chest pain. Rehospitalizations were not adjudicated in PREMIER, and thus, only TRIUMPH patients were included in this subanalysis.

Statistical analysis

Baseline characteristics—including socioeconomic status, demographic, and clinical factors—and health status scores at baseline and 12 months were compared between patients without vs. with obstructive CAD using the χ^2 test for categorical variables and *t*-test for continuous variables. The prevalence of angina (i.e. SAQ angina frequency score $<$100) was compared between groups at each follow-up time point using the χ^2 test. A hierarchical, multivariable repeated-measures Poisson model was used to assess the independent association between the absence of obstructive CAD and angina over the year following MI. As angina was a common outcome, we derived incidence rate ratios (IRRs) directly by using hierarchical modified Poisson regression models (as opposed to logistic regression) to avoid overestimating the effect size.[14,15] Covariates included in the multivariable model were selected a priori based on prior literature review and clinical judgment of factors that might confound the association between obstructive CAD and angina: age, sex, race, current smoking, diabetes mellitus, depressive symptoms [assessed with the Patient Health Questionnaire (PHQ)[16]], self-reported avoidance of care due to cost, type of MI (ST- or non-ST-elevation), and discharge Global Registry of Acute Coronary Events (GRACE) score[17] (a score calculated at the time of discharge from MI that incorporates several prognostically important factors including age, creatinine, heart failure, and in-hospital revascularization procedures).

To explore factors associated with angina among patients without obstructive CAD, we constructed a second repeated-measures model among only patients without obstructive CAD. After covariates independently associated with angina were identified, we then examined whether these predictors were unique to patients without obstructive CAD by testing the interaction between these covariates and the absence of obstructive CAD in the main model (which included patients both with and without obstructive CAD). In addition, we performed two sensitivity analyses. To ensure that our analytic cohort included only patients with MI, we performed a sensitivity analysis excluding patients without obstructive CAD who had a prior diagnosis of heart failure and a peak troponin of $<$1 ng/mL.[18] We also performed a sensitivity analysis redefining obstructive CAD as any epicardial stenosis $>$50% to evaluate angina outcomes in patients with a more intermediate burden of coronary disease. Finally, we compared the time to first all-cause rehospitalization and first chest pain rehospitalization over the year following MI between those without vs. with obstructive CAD using Kaplan–Meier curves.

Missing baseline data (mean number of missing items per patients of 0.08) were imputed using IVEware (Imputation and Variance Estimation Software; University of Michigan's Survey Research Center, Institute for Social Research, Ann Arbor, MI, USA). All remaining analyses were conducted using SAS v9.3 (SAS Institute, Inc., Cary, NC, USA), and statistical significance was determined by a two-sided *P*-value of $<$0.05.

Results

Study population

Among 6927 MI patients from 31 US hospitals enrolled in PREMIER and TRIUMPH, 519 (7.5%) patients did not have a coronary angiogram performed during the MI hospitalization, and were thus excluded from the analysis. Twenty-six patients (0.4%) were missing baseline SAQ data and 754 (10.9%) were missing SAQ follow-up data (98 of the 754 patients died prior to 1 month and thus had no opportunity to follow-up). This left our final analytic sample at 5539 patients (*Figure 1*). Patients who were missing were more likely to be younger, non-white, and unmarried (see Supplementary material online, *Table S1*). Missing patients were also less likely than analysed patients to have obstructive CAD (90 vs. 93%, $P = 0.003$), but obstructive CAD was not associated with missingness in a multivariable model adjusted for demographic and clinical factors ($P = 0.73$). The mean age of the cohort was 59.6 years, 68% were men, 74% were white, and 47% presented with an ST-elevation MI (*Table 1*).

Baseline characteristics

Among the 5539 patients with MI who underwent coronary angiography, 381 (6.9%) did not have obstructive CAD. The baseline demographic and clinical characteristics of patients without vs. with obstructive CAD are summarized in *Table 1*. Greater proportions of patients without obstructive CAD (vs. with obstructive CAD) were female (57 vs. 30%), and non-white (51 vs. 24%). Patients without obstructive CAD were more likely to present with a non-ST-elevation MI (87 vs. 51%) and had lower peak troponin levels (median 2.4 vs. 7.6 ng/mL). They were also less likely to have diabetes (21 vs. 29%), but more likely to have hypertension (69 vs. 63%) and chronic lung disease (14 vs. 8%). At discharge, guideline-recommended secondary prevention therapies were less commonly prescribed among patients without obstructive CAD, with lower use of aspirin (86 vs. 95%), clopidogrel (28 vs. 80%), beta-blockers (77 vs. 92%), statins (70 vs. 88%), and referral to cardiac rehabilitation (21 vs. 48%).

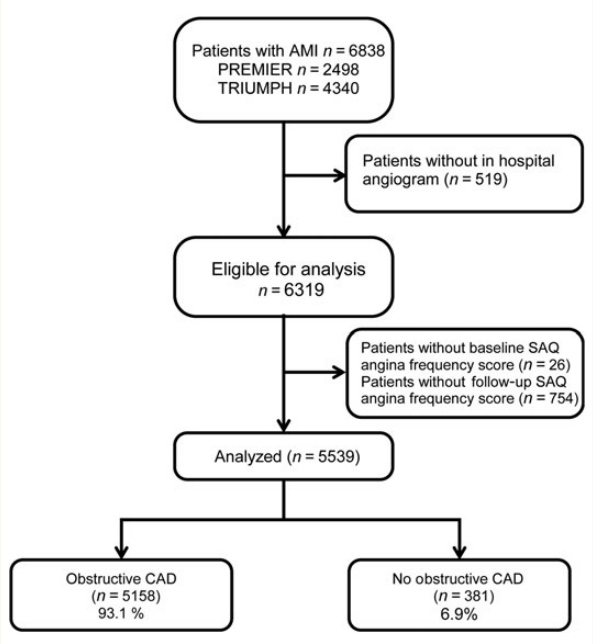

Figure 1 Flowchart of analytical cohort in the TRIUMPH and PREMIER registries.

Mortality outcomes

Survival rates were similar between patients with and without obstructive CAD at each follow-up time point (100 vs. 100%, 97.4 vs. 98.5%, and 96.1 vs. 96.9%, log-rank *P*-value = 0.08 at 1, 6, and 12 months in patients without vs. with obstructive CAD, respectively).

Angina and health status

Patients without obstructive CAD had a lower prevalence of angina over the 4 weeks prior to MI (without vs. with obstructive CAD: 42.5 vs. 48.0%, $P = 0.038$), but not at 12-month follow-up (24.6 vs. 21.4%, $P = 0.199$; *Figure 2*). In addition, they also reported worse disease-specific and generic health status at 12 months post-MI, including worse quality of life due to angina and lower satisfaction with the treatment of their angina (*Table 2*). Patterns of antianginal therapies differed between groups; patients without obstructive CAD were treated less frequently with beta-blockers and more frequently with calcium channel blockers during follow-up compared with those who had obstructive CAD (*Table 3*). In the multivariable repeated-measures model, the risk for post-MI angina was similar among patients without vs. with obstructive CAD over the 1-year follow-up period (IRR 0.89, 95% CI 0.77–1.02). In the first sensitivity analysis excluding patients without obstructive CAD who had prior heart failure and troponin levels <1 ng/mL, results were unchanged (IRR for post-MI angina in patients without vs. with obstructive CAD 0.90, 95% CI 0.78–1.03). In the second sensitivity analysis redefining obstructive CAD as any epicardial stenosis $>50\%$, results were also similar (IRR 0.96, 95% CI 0.82–1.11).

Predictors of post-myocardial infarction angina among those without obstructive coronary artery disease

We evaluated the association between demographic and clinical variables with the presence of post-MI angina within the subgroup of patients who did not have obstructive CAD. Depressive symptoms were independently associated with angina (IRR 1.28 per 5 points on PHQ, 95% CI 1.17–1.41) as was self-reported avoidance of care due to cost (IRR 1.34, 95% CI 1.02–1.74) (see Supplementary material online, *Table S2*). In the main model that included all patients, however, the interaction terms between the absence of obstructive CAD and these two variables were not significant (*P* for interaction 0.43 and 0.76, respectively), indicating that neither factor was uniquely associated with a greater risk for post-MI angina among those without (vs. with) obstructive CAD.

Rehospitalizations

Among the 3440 patients in our analytic cohort from the TRIUMPH registry, patients without vs. with obstructive CAD had

Table 1 Baseline characteristics of patients with and without obstructive CAD in the TRIUMPH and PREMIER registries

	No obstructive CAD (n = 381)	Obstructive CAD (n = 4941)	P-value
Mean age (years)	56.7 ± 12.6	59.8 ± 12.1	<0.001
Female sex	57.0%	30.0%	<0.001
Non-white race	51.1%	23.6%	<0.001
Married	46.5%	59.7%	<0.001
Low social support	19.7%	15.1%	0.017
High school education	76.9%	80.9%	0.057
Hypertension	68.8%	63.4%	0.037
Mean total cholesterol	178.3 ± 51.0	173.2 ± 40.0	0.074
Mean triglycerides	157.8 ± 167.4	125.7 ± 105.4	<0.001
Mean HDL cholesterol	41.9 ± 13.6	50.5 ± 18.5	<0.001
Mean LDL cholesterol	106.1 ± 41.3	98.9 ± 34.4	0.002
Prior MI	16.8%	20.2%	0.107
Current smoker	33.7%	37.3%	0.159
Diabetes mellitus	20.7%	28.5%	0.001
PHQ depression score	6.2 ± 5.8	5.2 ± 5.4	<0.001
ST-elevation MI	13.4%	49.0%	<0.001
Mean GRACE mortality score at discharge	106.7 ± 28.6	100.1 ± 29.4	<0.001
Troponin peak (ng/dL; median [IQR])	2.4 (0.6, 8.0)	7.6 (1.9, 37.7)	<0.001
In-hospital PCI	0.0%	76.7%	<0.001
In hospital CABG	0.0%	12.1%	<0.001
Discharge management			
Cardiac rehabilitation referral	21.3%	48.2%	<0.001
Aspirin prescription	85.6%	95.1%	<0.001
Clopidogrel prescription	28.1%	79.9%	<0.001
Beta-blocker prescription	76.6%	91.7%	<0.001
Statin prescription	70.3%	88.3%	<0.001
ACE-I or ARB	69.6%	75.1%	0.017
Eplerenone or spironolactone	6.3%	3.9%	0.025

CAD, coronary artery disease; MI, myocardial infarction; PHQ, Patient Health Questionnaire; GRACE: Global Registry of Acute Coronary Events; PCI, percutaneous coronary intervention; CABG: coronary artery bypass grafting; ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.

similar rates of all-cause rehospitalization over the 12 months after MI (Kaplan–Meier-estimated rates 28.8 vs. 30.0%, log-rank $P = 0.64$; *Figure 3*). In addition, rates of rehospitalization due specifically to chest pain were also similar between groups (without vs. with obstructive CAD: Kaplan–Meier-estimated rates 7.1 vs. 11.9%, log-rank $P = 0.07$; *Figure 3*).

Discussion

In two large, contemporary multicentre MI registries, we found that patients who presented with an MI and were found to be without obstructive CAD had a high prevalence of angina during follow-up, with one in four patients reporting angina at 1 year after MI. The burden of angina was at least as high in patients without obstructive CAD as in those who had obstructive CAD. Furthermore, patients without obstructive CAD experienced similar rates of rehospitalizations over the year following MI. Collectively, these findings highlight the importance of aggressive medical therapy and follow-up in patients with MI and without obstructive CAD, in order to potentially reduce their burden of angina, improve the quality of life, and prevent rehospitalizations in these patients with limited revascularization options.

Prior studies

Prior work exploring outcomes of patients without obstructive CAD has suggested that patients who experience MI in the absence of obstructive CAD experience lower rates of reinfarction despite being treated less aggressively with medical management when compared with patients with obstructive CAD.[19,20] Additionally, Roe *et al.*[21] reported lower adverse ischaemic events (death or non-fatal MI by 6-month follow-up) in patients without (vs. with) obstructive CAD. However, long-term all-cause mortality outcomes for patients without obstructive coronary disease have not been described. Previous studies exploring angina burden in patients with MI in the absence of obstructive coronary disease focused on pre-admission angina, and suggested that patients without obstructive CAD had angina less commonly prior to index MI than matched patients with obstructive CAD, similar to our findings.[22] Our study is unique in that to our knowledge, it is the first to focus on the burden

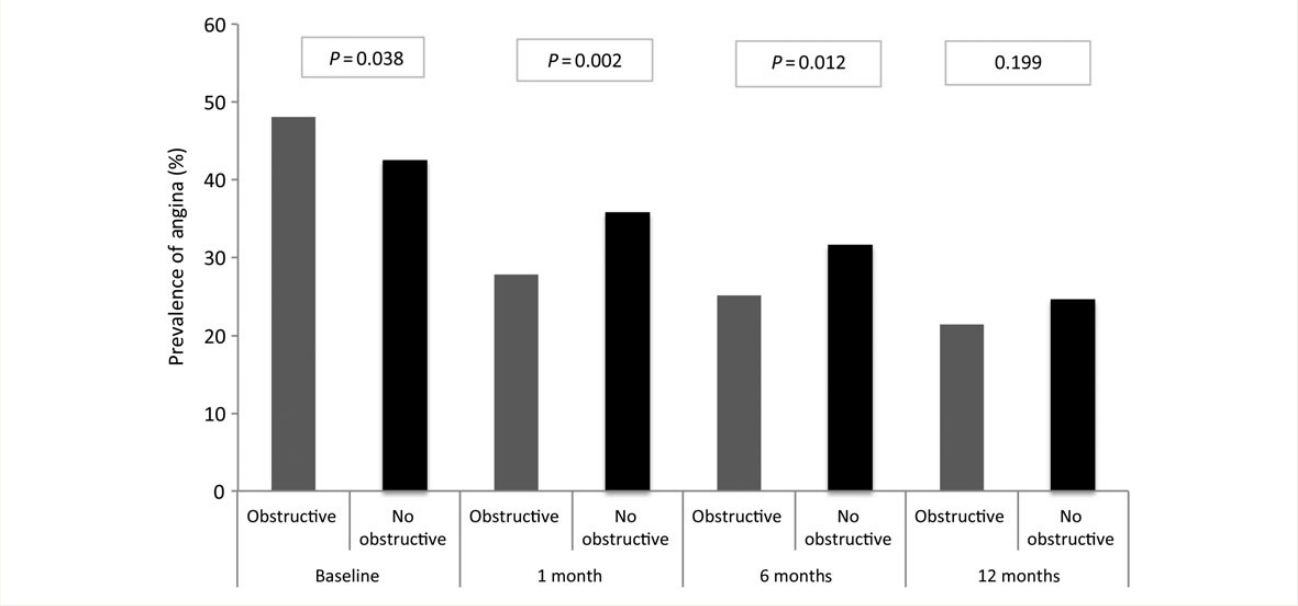

Figure 2 Rate of patient-reported angina in patients without vs. with obstructive coronary artery disease over the year following myocardial infarction.

Table 2 Health status comparisons at baseline and 12 months

	No obstructive CAD (n = 381)	Obstructive CAD (n = 4941)	P-value
Baseline			
SAQ angina frequency	85.2 ± 21.0	87.6 ± 19.7	0.031
SAQ disease perception/quality of life	60.5 ± 24.1	63.8 ± 23.2	0.006
SAQ physical limitation	84.4 ± 24.3	86.4 ± 21.9	0.101
SAQ treatment satisfaction	92.3 ± 11.9	94.4 ± 10.3	<0.001
SF-12 mental component score	47.4 ± 12.6	50.2 ± 11.3	<0.001
SF-12 physical component score	42.1 ± 12.9	43.4 ± 12.1	0.065
12 months			
SAQ angina frequency	93.3 ± 15.9	92.7 ± 16.2	0.559
SAQ disease perception/quality of life	79.6 ± 22.7	83.2 ± 19.5	0.004
SAQ physical limitation	91.6 ± 19.3	93.9 ± 16.0	0.066
SAQ treatment satisfaction	90.4 ± 15.4	92.9 ± 13.0	0.002
SF-12 mental component score	50.3 ± 11.5	52.8 ± 9.8	<0.001
SF-12 physical component score	41.3 ± 12.0	44.5 ± 11.8	<0.001

CAD, coronary artery disease; SAQ, Seattle Angina Questionnaire; SF-12, Medical Outcomes Study 12-Item Short Form.
Scores for the SAQ and SF-12 range from 0 to 100, with higher scores indicating less disease burden.

of residual angina post-MI and rehospitalizations in patients without vs. with obstructive CAD.

Potential mechanisms

The reasons as to why patients without angiographically evident obstructive CAD have a high burden of residual angina after an MI are unclear. It has been well established that patients can have myocardial ischaemia and angina in the absence of obstructive epicardial CAD.[23] Potential aetiologies include microvascular disease and/or epicardial artery spasm, although the underlying mechanisms for residual angina in these patients require further study. We found that depressive symptoms were associated with an increased risk of angina in patients without obstructive CAD. In patients with CAD, depression has been associated with increased angina, even after adjusting for the degree of myocardial ischaemia.[24,25] Whether or not increased angina occurs due to increased pain reporting or to observable differences in visceral pain processing within the nervous system among these patients is still unclear. Regardless of the

Table 3 Use of antianginal medication at discharge and 12 months following acute myocardial infarction

	No obstructive CAD (n = 381)	Obstructive CAD (n = 4941)	P-value
Discharge			
Beta-blocker	76.6%	91.7%	<0.001
Calcium channel Blocker	23.9%	9.4%	<0.001
Nitrate	26.2%	18.0%	<0.001
Mean # of antianginals	1.3 ± 0.7	1.2 ± 0.6	0.014
12 months			
Beta-blocker	62.0%	78.5%	<0.001
Calcium channel blocker	27.3%	10.3%	<0.001
Nitrate	18.8%	21.6%	0.303
Mean # antianginals	1.1 ± 0.8	1.1 ± 0.7	0.633

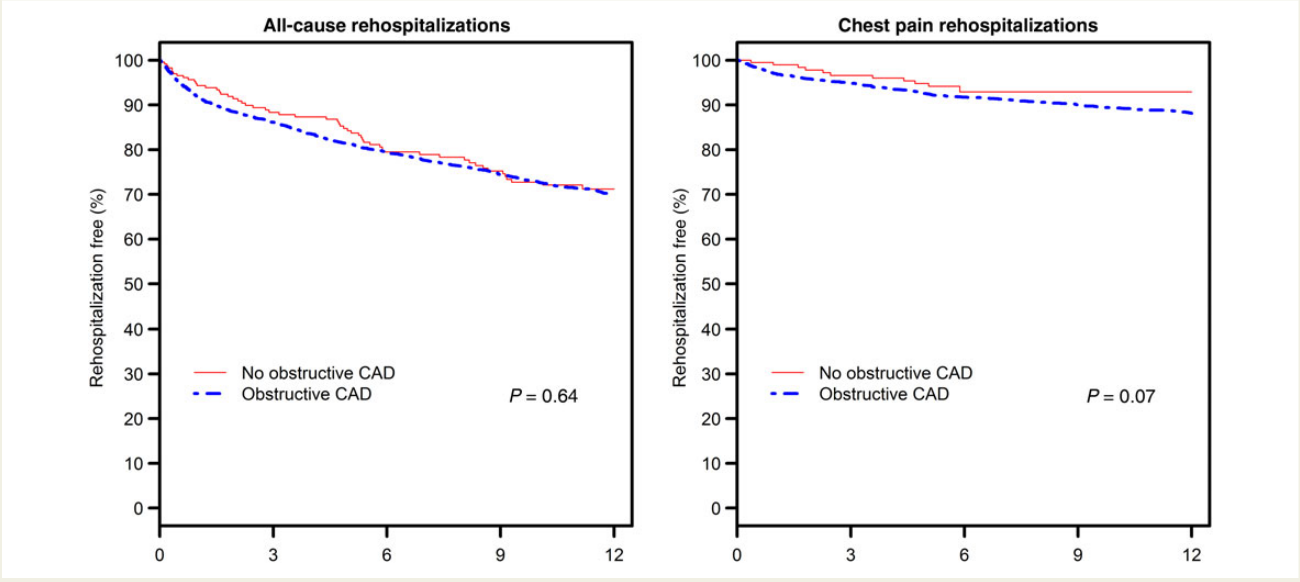

Figure 3 Rates of all-cause rehospitalizations and rehospitalization due to chest pain over the year following myocardial infarction according to the presence of obstructive coronary artery disease.

mechanism, patients without obstructive CAD had equivalent rates of all-cause and cardiac rehospitalization as those with obstructive CAD, indicating that the downstream effects of the patients' chest pain, whether truly ischaemic or not, were the same in these two groups.

Clinical implications

Given the high prevalence of residual angina and rehospitalization rates among post-MI patients who do not have obstructive CAD, we believe that these findings are of considerable clinical relevance. Importantly, angina is a potentially modifiable condition, and greater attention to surveillance and aggressive management of angina in post-MI patients without obstructive CAD may improve their symptoms and quality of life, and potentially reduce repeat hospitalizations. However, in concordance with prior studies,[26,27] we found that patients without obstructive CAD were less aggressively managed with secondary prevention strategies. As these patients are not candidates for coronary revascularization, non-interventional strategies are needed to improve their outcomes; yet, they appear to be prescribed guideline-directed treatments less often. For example, we found that referral to cardiac rehabilitation was far less frequent among those without vs. with obstructive CAD, highlighting one potential opportunity to improve outcomes. Additional potential targets for improvement of angina burden may include psychosocial issues, including mechanisms to decrease medication avoidance due to cost. Admittedly, the effectiveness of these secondary prevention strategies, such as clopidogrel and statins, among patients with MI and without obstructive CAD is not well established as these patients were infrequently included in the pivotal clinical trials.[28,29] With increasing scrutiny on reducing readmissions post-MI, however, a better understanding is needed of whether strategies such as more frequent follow-up, consideration

of aggressive angina management, or referral to cardiac rehabilitation could reduce angina in these patients and also reduce costly rehospitalizations.

Limitations

Our findings should be considered in the context of several potential limitations. First, we relied on adjudication of the coronary angiogram reports to determine the diagnosis of obstructive CAD and did not evaluate the angiograms in a core laboratory. It is possible that some patients without obstructive CAD could have been reclassified as having obstructive CAD if routinely evaluated with an intravenous ultrasound or other advanced interventional techniques. However, in the setting of an MI, we suspect that the search for a culprit lesion would likely lead to an over- (rather than under-) estimation of the degree of coronary stenosis of any moderate lesions that would then be treated with PCI. Secondly, our study was not designed to evaluate the mechanisms underlying the residual angina in these patients. Thirdly, although the entry criteria in our registries were expressly intended to ensure inclusion of patients with type 1 MI (including pre-specified requirements for troponin elevation and presentation within 24 h of ischaemic symptoms onset), it is possible that there could be a few non-type 1 MI patients in our study. Finally, although the absolute difference in the rate of chest pain-specific rehospitalization was only 4% between groups, it is possible that this difference was found not to be statistically significant due to sample size. Our findings should thus be confirmed in future, larger studies.

Conclusions

Patients who present with an MI and are found to have no obstructive CAD experience a burden of angina that is at least as high as those with obstructive CAD, with one in four patients reporting angina during 1-year follow-up. This underrecognized group of patients, with substantial angina burden, challenges us to aggressively medically manage their symptoms as they remain at high risk for rehospitalization. As these patients are not candidates for revascularization, non-invasive strategies to reduce angina burden could have a significant impact on their health status and quality of life. Further studies are needed to better determine the aetiology of angina as well the effectiveness of antianginal therapies and other treatments, such as cardiac rehabilitation and psychosocial interventions, in improving the symptoms and quality of life of these challenging patients.

Supplementary material

Supplementary material is available at *European Heart Journal — Quality of Care and Clinical Outcomes* online.

Funding

The PREMIER Registry was supported in part by CV Therapeutics, Palo Alto, CA, USA. Funding support for the TRIUMPH Registry was received from the National Heart, Lung and Blood Institute (P50 HL077113). A.G. was supported by a T32 training grant from the National Heart Lung and Blood Institute (T32HL110837). The funding agencies had no role in data collection, analysis, interpretation, or the decision to submit the results. The content is solely the responsibility of the authors and does not necessarily represent the official views of the funding agencies. J.A.S. owns intellectual property rights to the Seattle Angina Questionnaire.

Conflict of interest: J.A.S. reports significant grants from NIH/NHLBI, PCORI, ACCF, Gilead, Lilly, EvaHeart, and Amorcyte. J.A.S. has consulted for (all modest): United Healthcare, Genentech, Amgen, Janssen, and Novartis. He owns the copyright to the Seattle Angina Questionnaire (significant), Kansas City Cardiomyopathy Questionnaire (significant), and Peripheral Artery Questionnaire (modest), and has an equity interest in Health Outcomes Sciences (significant). J.A.M.F. has consulted for (all modest): Novartis, Merck, AstraZeneca, Amgen, Inc., Daiichi Sankyo, Sanofi, Janssen, Amarin, Lilly, Aegerion, Pfizer, Boehringer Ingelheim, Regeneron, and Genzyme. J.B. reports no direct conflicts of interest; potential disclosures include Servier Laboratories (modest). T.M.M. is supported with a VA HSR&D career development award. M.K. is a consultant for AstraZeneca , Edwards Life Sciences, Gilead Sciences, Roche, Genentech, Regeneron, Eli Lilly, Amgen, Takeda, and ZS Pharma. M.K. has received research support from the American Heart Association, Genentech, Gilead Sciences, Glumetrics, Optiscan, Astra Zeneca, and Sanofi.

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