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CLINICAL RESEARCH

Long-term survival in patients with refractory angina

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Aims An increasing number of patients with severe coronary artery disease (CAD) are not candidates for traditional revascularization and experience angina in spite of excellent medical therapy. Despite limited data regarding the natural history and predictors of adverse outcome, these patients have been considered at high risk for early mortality.

Methods and results The OPtions In Myocardial Ischemic Syndrome Therapy (OPTIMIST) program at the Minneapolis Heart Institute offers traditional and investigational therapies for patients with refractory angina. A prospective clinical database includes detailed baseline and yearly follow-up information. Death status and cause were determined using the Social Security Death Index, clinical data, and death certificates. Time to death was analysed using survival analysis methods. For 1200 patients, the mean age was 63.5 years (77.5% male) with 72.4% having prior coronary artery bypass grafting, 74.4% prior percutaneous coronary intervention, 72.6% prior myocardial infarction, 78.3% 3-vessel CAD, 23.0% moderate-to-severe left-ventricular (LV) dysfunction, and 32.6% congestive heart failure (CHF). Overall, 241 patients died (20.1%: 71.8% cardiovascular) during a median follow-up 5.1 years (range 0–16, 14.7% over 9). By Kaplan–Meier analysis, mortality was 3.9% (95% CI 2.8–5.0) at 1 year and 28.4% (95% CI 24.9–32.0) at 9 years. Multivariate predictors of all-cause mortality were baseline age, diabetes, angina class, chronic kidney disease, LV dysfunction, and CHF.

Conclusion Long-term mortality in patients with refractory angina is lower than previously reported. Therapeutic options for this distinct and growing group of patients should focus on angina relief and improved quality of life.

Keywords Refractory angina • Chronic coronary artery disease

Introduction

As the population ages and mortality from coronary artery disease (CAD) decreases, a growing number of patients with severe CAD continue to experience angina which is not amenable to surgical or percutaneous coronary revascularization despite excellent medical therapy.[1–3] These patients with refractory angina are frequently labelled 'no option' patients with 'end-stage' CAD. The European Society of Cardiology Joint Study Group on the Treatment of Refractory Angina defined it as a chronic condition (more than 3 months in duration) characterized by angina caused by coronary insufficiency in the setting of CAD which cannot be controlled by a combination of medical therapy, angioplasty, and coronary bypass surgery, where the presence of reversible myocardial ischaemia has been clinically established to be the cause of the symptoms.[1] Anatomic reasons which preclude traditional revascularization include severe diffuse CAD, collateral-dependent myocardium, multiple coronary restenoses, chronic total coronary occlusions, degenerated saphenous vein grafts, poor distal targets, or lack of conduits due to prior coronary artery bypass grafting (CABG). Significant comorbidities may also preclude traditional revascularization. Currently, treatment options for this distinct and growing patient group are limited to traditional

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anti-anginal therapy and secondary risk-factor modification. This has stimulated interest in alternative strategies including myocardial angiogenesis (protein, gene, or stem cell therapy),[4–8] novel pharmacological agents (i.e. ranolazine),[9] enhanced external counterpulsation (EECP),[10–12] spinal cord stimulation,[1,13] and transmyocardial revascularization (TMR).[14–19]

Limited data exist regarding the natural history and predictors of mortality for patients with refractory angina. A retrospective study from the Cleveland Clinic in 500 consecutive patients undergoing cardiac catheterization found that 59 patients had ischaemia but were ineligible for revascularization. The 1-year mortality in this small cohort of patients was 17% and led many to believe refractory angina patients are at high risk for mortality following diagnosis.[20] Current ACC/AHA guidelines provide limited information on this patient population,[21] and no Medicare claims code identifies individuals with refractory angina. In 2002, the European Society of Cardiology expressed an 'urgent' need to clarify the epidemiology of this condition.[1] We established a dedicated clinic for refractory angina patients in 1996 and report here the long-term survival and predictors of mortality in 1200 patients followed a median of 5.1 years.

Methods

The study population consisted of 1200 consecutive patients with either refractory myocardial ischaemia and/or refractory angina who were considered not to be candidates for traditional revascularization and referred for alternative treatment strategies from 1996 to 2001 at Hennepin County Medical Center (Minneapolis, MN, USA) and, from 2002 on, at the OPTions In Myocardial Ischemic Syndrome Therapy (OPTIMIST) clinic at the Minneapolis Heart Institute at Abbott Northwestern Hospital (Minneapolis, MN, USA). Patients were predominantly referred from the upper Midwest region of the USA but the study population includes individuals from 40 states, Puerto Rico, and Canada. Referral sources included self-referral, primary care physicians, and cardiologists both within and outside the Hennepin County Medical Center and Minneapolis Heart Institute at Abbott Northwestern cardiology practices. At the time of initial consultation, physicians and clinical staff comprehensively reviewed medical records and assessed patients' angina symptoms, medical regimen for angina, and secondary risk-factor modification for CAD. Coronary angiography was reviewed to assess whether traditional surgical and percutaneous revascularization was possible. Patients deemed not to be candidates for traditional revascularization who were receiving appropriate medical therapy were included in the database (described subsequently) and considered for alternative therapies including novel pharmaceuticals, EECP, angiogenesis (patients enrolled in protein, gene, and stem cell clinical trials designed to promote angiogenesis), spinal cord stimulation, and TMR. No patients were excluded.

Baseline demographics, cardiovascular risk factors, medical history (cardiovascular and non-cardiovascular), cardiovascular medications, and tests (including left-ventricular function, stress testing, and coronary angiography) were recorded in a prospective database. Institutional Review Board approval for the database was obtained at both Hennepin County Medical Center and Abbott Northwestern. For mortality measurements, the patient's diagnosis of refractory angina was defined as either the date of angiography when the patient was determined to have 'no option' or the initial OPTIMIST clinic consultation. Left-ventricular (LV) function was defined as normal [left-ventricular ejection fraction (LVEF) $\geq$55%], mildly reduced (LVEF $>$40% but $<$55%), and moderately to severely reduced (LVEF $<$40%) as assessed by echocardiography, gated myocardial perfusion imaging, or left ventriculography. Categories were chosen for clinical relevance and to account for possible differences in measurement between different tests used to assess LV function. Congestive heart failure (CHF), myocardial infarction (MI), moderate/severe valvular heart disease, chronic kidney disease (CKD), peripheral arterial disease (PAD), and cerebrovascular disease (CVD) were based on patient history and confirmed with the medical record. Coronary artery stenoses $>$50% in diameter were considered significant and angiographic data were available on 87.4% of patients. Comprehensive data on baseline medications were available from patients enrolled at Abbott Northwestern Hospital beginning in 2006.

Vital status for all patients was determined using the Social Security Death Index (SSDI), considered to be a highly accurate and specific source of mortality data,[22,23] and by clinical follow-up. Cause of death was determined from medical records and clinical follow-up. If these were unavailable, death certificates were used to determine the cause of death. Deaths were classified in accordance with the 9th and 10th revision of the *International Classification of Diseases*.[24,25] 'Natural causes' was categorized as cardiovascular death, not otherwise classifiable.

Fractions surviving at each follow-up time are from Kaplan–Meier analysis with Wald-style confidence intervals. Individual predictors of mortality were tested using the log-rank test excluding persons with unknown predictor values. Multivariate analyses of time to death used Cox proportional-hazards regression and likelihood ratio tests, with Wald-style confidence intervals on the log-relative hazard scale back-transformed to relative hazards. A P-value < 0.05 was considered statistically significant, and P-values are two-sided whenever possible. All computations used JMP (v. 7, SAS Institute Inc., Cary, NC, USA).

Results

Table 1 summarizes the baseline characteristics of 1200 patients (mean age 63.5 years, 77.5% male). Common characteristics included 3-vessel CAD (78.3%), prior revascularization [PCI (74.4%), CABG (72.4%), or either (92.3%)], prior MI (72.6%), and Canadian Cardiovascular Society (CCS) Class III or IV angina (59.2%). History of diabetes mellitus (DM) (36.6%), CHF (32.6%), moderate-to-severe LV dysfunction (23.0%), PAD (22.8%), CVD (19.5%), CKD (14.8%), malignancy (11.5%), and moderate or severe valvular heart disease (9.9%) were also common. *Table 2* summarizes the categories of coronary anatomy defining poor candidacy for further revascularization; many patients met more than one criterion. Severe comorbidities which precluded further attempts at revascularization were present in 91 (7.6%) patients.

Comprehensive data regarding baseline medications was available for 616 patients with 91.4% on aspirin, 49.7% on another antiplatelet agent, 58.1% on angiotensin converting enzyme inhibitors or angiotensin receptor blockers, 86.9% on lipid lowering agents, 85.1% on beta blockers, and 37.5% on calcium channel blockers.

Median follow-up was 5.1 years (range 0–16years) with 176 (14.7%) patients followed for over 9 years. Overall, 241 (20.1%) patients died. From Kaplan–Meier analysis (*Figure 1*), mortality was 3.9% (95% CI 2.8–5.0) at 1 year, 17.5% (95% CI 15.2–19.9) at 5 years, and 28.4% (95% CI 24.9–2.0) at 9 years. Cause of death was determined for 213 (88.4%) patients, including 153 (71.8%) cardiovascular deaths, and 60 (28.2%) non-cardiovascular deaths. For individuals who died of cardiovascular causes, 45 (29.4%) died of progressive CHF/ischaemic cardiomyopathy, 33 (21.6%) died suddenly, 36 (23.5%) died of MI, and 39 (25.4%) were not classifiable (i.e. 'natural causes'). Periprocedural death occurred in 20 (9.3%),

Table 1 Univariate predictors of mortality in 1200 patients with refractory angina

	n (% of known)	5-year mortality % (95% CI)	*P*-value*
Demographics and medical history			
Age[a]			
<63.68 years	577 (50.0)	11.9 (9.0, 14.8)	<0.0001
≥63.68 years	577 (50.0)	23.8 (20.0, 27.6)	
Sex			
Female	270 (22.5)	18.2 (13.3, 23.1)	0.72
Male	930 (77.5)	17.3 (14.7, 20.0)	
Baseline smoking status			
Current	124 (13.6)	18.5 (11.1, 26.0)	0.33
Former	492 (53.9)	15.3 (11.8, 18.8)	
Never	296 (32.5)	14.3 (9.8, 18.8)	
History of hypertension			
No	366 (30.6)	20.7 (16.4, 24.9)	0.16
Yes	830 (69.4)	15.9 (13.2, 18.7)	
History of dyslipidaemia			
No	54 (5.3)	27.0 (14.3, 39.7)	0.030
Yes	964 (94.7)	15.3 (12.8, 17.8)	
History of diabetes			
None	761 (63.4)	14.9 (12.2, 17.7)	<0.0001
Type I	45 (3.7)	23.7 (9.8, 37.5)	
Type II	394 (32.8)	21.9 (17.5, 26.3)	
Family history of CAD			
No	297 (33.6)	14.6 (10.0, 19.3)	0.94
Yes	586 (66.4)	14.9 (11.8, 18.0)	
Prior CABG			
No	308 (27.6)	12.3 (8.2, 16.4)	0.005
Yes	806 (72.4)	19.0 (16.0, 21.9)	
Prior PCI			
No	263 (25.6)	12.5 (8.2, 16.8)	0.43
Yes	764 (74.4)	16.1 (13.2, 19.0)	
Any revascularization			
No	86 (7.7)	11.9 (4.6, 19.3)	0.21
Yes	1031(92.3)	17.6 (15.1, 20.1)	
History of MI			
No	284 (27.4)	8.4 (4.8, 12.1)	<0.0001
Yes	751 (72.6)	19.2 (16.2, 22.3)	
History of CHF			
No	653 (67.4)	10.6 (7.9, 13.3)	<0.0001
Yes	316 (32.6)	27.8 (22.5, 33.0)	
History of CVD			
No	960 (80.4)	16.2 (13.7, 18.7)	0.0001
Yes	233 (19.5)	22.7 (16.9, 28.6)	
History of PAD			
No	916 (77.2)	15.1 (12.6, 17.6)	<0.0001
Yes	270 (22.8)	25.9 (20.2, 31.7)	
History CKD			
No	1017 (85.2)	14.9 (12.5, 17.2)	<0.0001
Yes	177 (14.8)	34.2 (26.3, 42.1)	
History of malignancy			
No	1041 (88.5)	15.6 (13.3, 18.0)	0.0005
Yes	135 (11.5)	28.6 (20.3, 36.9)	
History of anaemia			
No	1032 (88.7)	15.3 (13.0, 17.7)	<0.0001
Yes	132 (11.3)	31.6 (22.6, 40.6)	
Clinical characteristics			
CAD, *n* vessels			
1 vessel	67 (6.8)	7.6 (1.2, 14.1)	0.021
2 vessel	147 (14.9)	9.9 (4.7, 15.1)	
3 vessel	774 (78.3)	18.2 (15.2, 21.2)	
Angina class, CCS			
1	67 (7.6)	9.1 (1.3, 16.9)	0.013
2	182 (20.5)	9.3 (4.8, 13.8)	
3	387 (43.6)	16.3 (12.1, 20.6)	
4	251 (28.3)	18.2 (13.1, 23.3)	
If CHF 'Yes', NYHA Class			
1	51 (23.2)	15.0 (4.7, 25.4)	0.19
2	78 (35.5)	20.6 (11.2, 30.0)	
3	60 (27.3)	19.3 (9.0, 29.6)	
4	31 (14.1)	35.6 (17.4, 53.7)	
Moderate or severe valvular heart disease			
No	1028 (90.1)	15.8 (13.4, 18.2)	<0.0001
Yes	113 (9.9)	31.0 (21.7, 40.4)	
LV dysfunction			
Normal	421 (44.4)	10.5 (7.1, 13.9)	<0.0001
Mild	310 (32.7)	14.7 (10.4, 19.1)	
Moderate/ severe	218 (23.0)	30.4 (23.8, 37.0)	
Number of anatomic criteria met			
0	152 (12.7)	17.6 (11.4, 23.8)	0.35
1	349 (29.1)	19.0 (14.5, 23.6)	
2	441 (36.8)	15.6 (12.0, 19.3)	
3	202 (16.8)	17.8 (12.0, 23.6)	
4	49 (4.1)	21.9 (9.0, 34.9)	
5	7 (0.6)	28.6 (0.0, 62.0)	
Comorbidities			
No	1109 (92.4)	16.0 (13.7, 18.4)	<0.0001
Yes	91 (7.6)	36.3 (25.3, 47.3)	

CAD, coronary artery disease; CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention; MI, myocardial infarction; CHF, congestive heart failure; CVD, cerebrovascular disease; PAD, peripheral arterial disease; CKD, chronic kidney disease; CCS, Canadian Cardiovascular Society; NYHA, New York Heart Association; LV, left ventricular.

*5-year survival percent from Kaplan–Meier analysis, with 95% confidence interval by Wald's method; *P*-value from log-rank test excluding persons with unknown value of the predictor.

[a]Mean 63.5, SD 11.1, range 26–101.

Table 2 Coronary anatomic reasons which preclude traditional revascularization and mortality hazard in 1200 patients with refractory angina

Anatomic feature	Patients (%)	Mortality relative hazard (95% CI)[a]
Collateral-dependent myocardium	581 (48.4)	0.81 (0.62–1.06)
Diffuse CAD	565 (47.1)	1.03 (0.79–1.35)
Multiple coronary restenoses	126 (10.5)	0.83 (0.52–1.31)
Severely degenerated/ occluded SVGs	418 (34.8)	1.17 (0.89–1.55)
Poor distal targets	244 (20.3)	1.16 (0.84–1.60)
No graft conduits	43 (3.6)	1.26 (0.71–2.23)

CAD, coronary artery disease; SVG, saphenous vein graft.
[a]From Cox regression including as predictors these conditions and also including co-morbidity as a predictor (relative hazard 2.72 with 95% confidence interval 1.89–3.91).

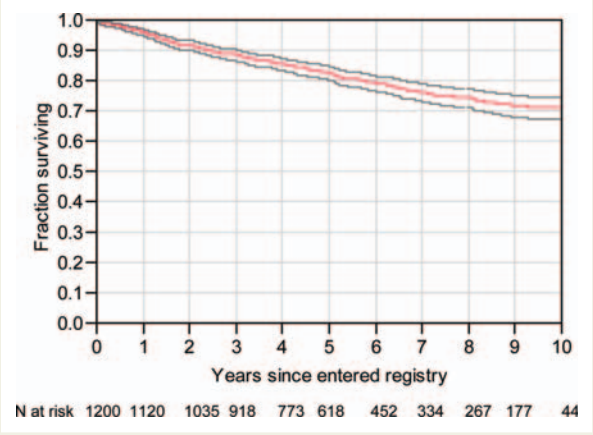

Figure 1 Kaplan–Meier survival curve in 1200 patients with refractory angina; centre line is the estimated fraction surviving, upper and lower lines are 95% pointwise confidence intervals.

including 13 (6.1%) following cardiac procedures (11 peri-CABG, two peri-PCI). *Table 1* summarizes the tests of univariate predictors of all-cause mortality; significant predictors were age ($P < 0.0001$), CVD ($P = 0.0001$), PAD ($P < 0.0001$), DM ($P < 0.0001$), CKD ($P < 0.0001$), malignancy ($P = 0.0005$), anaemia ($P < 0.0001$), multivessel CAD ($P = 0.021$), CHF ($P < 0.0001$), prior CABG ($P < 0.005$), angina class ($P = 0.013$), moderate/severe valvular heart disease ($P < 0.0001$), history of MI ($P < 0.0001$), LV dysfunction ($P < 0.0001$), and comorbidities ($P < 0.0001$). Variables with $P < 0.05$ for univariate associations were then entered into a Cox proportional-hazards regression model for multivariate analysis. *Table 3* summarizes the multivariate analysis of all-cause mortality: baseline age ($P < 0.0001$), DM ($P = 0.0032$), angina class ($P = 0.0041$), CKD ($P = 0.0115$), LV dysfunction ($P = 0.0354$), and CHF ($P = 0.0439$) were still significantly associated with mortality.

Use of alternative therapies was as follows: 255 (21.2%) patients had EECP, 185 (15.4%) were enrolled in studies of angiogenesis (protein, gene, stem cell), 78 (6.5%) had TMR, and 21 (1.8%) had spinal cord stimulation.

Discussion

This manuscript presents the first description of long-term follow-up of patients in a dedicated refractory angina clinic. Our results demonstrate that long-term mortality in patients with refractory angina is surprisingly low, under 4% per year, and approaches that of patients with chronic stable angina (1.5%) who tend to have fewer comorbidities and preserved LV function.[26] Our results are also comparable to patients undergoing revascularization in the SYNTAX trial which reported 5-year mortality of 11.4% in CABG patients and 13.9% in PCI patients.[27] The multivariate predictors of mortality in patients with refractory angina are similar to those in patients with other cardiovascular conditions: baseline age, DM, angina class, CKD, LV dysfunction, and CHF. Besides age, angina class (3 and 4) and LV dysfunction/CHF were the strongest predictors of mortality and therefore these patients deserve special focus for alternative treatment strategies.

Data on the incidence and prevalence of refractory angina are scarce and mainly derived from cardiac catheterization laboratory registries.[2,3] In 1994, a survey of patients referred for coronary angiography in Sweden found that 9.6% did not undergo revascularization despite significant symptoms.[28,29] Of 500 consecutive patients presenting for coronary angiography at the Cleveland Clinic in 1998, 59 (12%) had evidence of ischaemia and were not candidates for traditional revascularization;[30] this rate would imply ~100 000–200 000 patients identified per year in the USA. In a consecutive series of 493 patients undergoing coronary angiography at the Minneapolis Heart Institute in 2005, 6.7% were on optimal medical management and not candidates for revascularization ('no option' patients) and an additional 9.3% were not candidates for revascularization but received additional medical therapy.[31] From November 2001 to March 2002, 21% of 5767 patients in the Euro Heart Survey (130 hospitals in 31 countries) were medically managed following coronary angiography.[32] The same authors estimated that 14% of a subset of 4409 patients were ineligible for traditional revascularization.[33] Controversy remains regarding incidence, prevalence, and even the definition of refractory angina, but as individuals live longer with more extensive CAD, the number of patients is likely to increase. Currently, no Medicare claims code identifies individuals with refractory angina or refractory ischaemia, which contributes to a lack of knowledge regarding this condition's epidemiology.

Mortality estimates in this population have been limited by studies with small sample sizes, extrapolation from cohorts of patients referred for coronary angiography, and limited duration of follow-up. Annual mortality rates of highly selected patients in randomized trials of alternative therapies for patients with refractory angina (control groups) range from 3 to 21%.[1–8,14–19] One-year mortality in the Cleveland Clinic series was high (17%) but based on only 59 patients.[20] The Mediators of Social Support Study (MOSS), a longitudinal observational study of patients undergoing cardiac catheterization at Duke University between August 1992 and January 1996, also reported high mortality (38% at 2.2 year mean follow-up) in 487

Table 3 Multivariate predictors of mortality in 1200 patients with refractory angina

Predictor	DF	Hazard ratio (95% CI)	Likelihood-ratio ChiSquare	*P*-value
Age at time zero (years), (hazard ratio per year)	1	1.04 (1.02, 1.05)	28.56	<0.0001
History of diabetes				
None	1	1.00	8.71	0.0032
Any		1.54 (1.16, 2.06)		
History of CABG				
No	2	1.00	1.58	
Unknown		0.94 (0.50, 1.75)		0.4538
Yes		1.20 (0.84, 1.75)		
History of MI				
No	2	1.00	5.85	
Unknown		2.00 (1.11, 3.59)		0.0537
Yes		1.52 (0.98, 2.35)		
History of CHF				
No	2	1.00	6.25	
Unknown		1.35 (0.86, 2.12)		0.0439
Yes		1.54 (1.09, 2.18)		
History of CVD				
No	2	1.00	2.50	
Unknown		4.26 (0.63, 28.74)		0.2862
Yes		1.16 (0.84, 1.61)		
History of PAD				
No	2	1.00	3.02	
Unknown		0.93 (0.19, 4.47)		0.2210
Yes		1.32 (0.97, 1.81)		
History of CKD				
No	2	1.00	8.92	
Unknown		0.45 (0.06, 3.32)		0.0115
Yes		1.62 (1.17, 2.26)		
CAD, *n* vessels				
1 vessel	3	1.00	2.26	
2 vessel		1.01 (0.39, 2.64)		0.5201
3 vessel		1.28 (0.55, 3.00)		
n vessels unknown		1.54 (0.64, 3.72)		
Angina class, CCS				
1	5	1.00	17.24	
2		1.07 (0.45, 2.55)		
3		1.80 (0.83, 3.98)		0.0041
4		2.09 (0.93, 4.67)		
Angina status unknown		2.57 (1.14, 5.80)		
Angina, but class unknown		2.71 (1.16, 6.32)		
Moderate or severe valvular disease				
No	2	1.00	5.44	
Unknown		1.25 (0.67, 2.34)		0.0659
Yes		1.59 (1.08, 2.34)		

Continued

Table 3 *Continued*

Predictor	DF	Hazard ratio (95% CI)	Likelihood-ratio ChiSquare	*P*-value
LV dysfunction				
Moderate/severe	3	1.00	8.58	
Mild		0.68 (0.47, 0.99)		
Normal		0.55 (0.36, 0.83)		0.0354
Unknown		0.78 (0.48, 1.26)		

CABG, coronary artery bypass graft; MI, myocardial infarction; CHF, congestive heart failure; CVD, cardiovascular disease; PAD, peripheral artery disease; CKD, chronic kidney disease; CAD, coronary artery disease; CCS, Canadian Cardiovascular Society; LV, left ventricular.

patients who did not undergo revascularization within 30 days.[34] In contrast, 1-year mortality from the Euro Heart Survey for patients with stable angina treated medically was 5%.[32] In the group deemed ineligible for revascularization, 7% of patients died at 1 year compared with 3.7% in the cohort eligible for revascularization[33]; further details regarding reasons for ineligibility were unavailable. In a contemporary cohort of 1427 patients undergoing EECP for refractory angina, overall mortality at 3-year follow-up was 15.4%.[35] Consistent with these lower numbers, the results from our recent angiographic series reported a 14.8% mortality at 3 years in patients receiving incomplete revascularization.[31] Our results provide new insight into annual mortality and cause of death in the largest cohort in the literature consisting of patients referred specifically for refractory angina. The long follow-up and relatively low mortality argue that, as a group, patients who are not candidates for traditional revascularization do not suffer from excess mortality compared with other patients with CAD. Cause of death, though predominantly cardiovascular, was non-cardiac in nearly 30% of patients and the incidence of sudden cardiac death was low. Our estimate of cardiovascular death may be an overestimate since we included 'natural causes' (which may well represent other aetiologies) with cardiovascular death.

Improved secondary prevention strategies, better evidence-based medical therapy, and more advanced revascularization techniques all likely contribute to these results. Widespread and improved adherence to medical therapy (antiplatelet agents,[36] angiotensin converting enzyme inhibitors,[37] and statins[38]) combined with aggressive lifestyle modification[39] (diet change, exercise, smoking cessation) has contributed to lower overall mortality in patients with CAD.[40,41] Similar benefits likely apply to patients with refractory angina. Although longitudinal mortality data are not available on a population basis, comparison of annual mortality in the MOSS (August 1992 to January 1996, 19% per year) and OPTIMIST (January 1997 to present, under 4% per year) cohorts suggests an improvement in mortality over time. Medication use in the two populations reflects important historical trends. In the most recent enrolled OPTIMIST patients, 91% were on aspirin and 50% on an additional antiplatelet, 85% on beta-blockers, 87% on lipid-lowering agents, and 58% on angiotensin converting enzyme inhibitors/angiotensin receptor blockers. In comparison, in the MOSS cohort, medication use in patients who did not undergo revascularization was markedly lower with 58% on aspirin, 45% on beta-blockers, 23% on statins, and 20% on angiotensin converting enzyme inhibitors.[34]

There are several limitations to our study. This registry is observational, but still represents a large, diverse cohort of patients who are not candidates for revascularization with refractory angina. Referral bias is an inherent limitation. However, in spite of high rates of comorbid conditions such as PAD, CHF, and LV dysfunction, mortality for this group of patients remained low. Determination of when a patient has exhausted traditional revascularization options can be difficult and in many cases is subjective. Patients frequently had refractory angina before a 'definitive' cardiac catheterization laboratory or referral-based clinic determination; therefore, our baseline time of diagnosis was conservative. Anatomic descriptors of candidacy for traditional revascularization are also subjective and represent a simplification of complex anatomy and pathophysiology. Better characterization and research are clearly needed in this area, especially for 'diffuse' CAD and microvascular dysfunction.[42–44] We recently proposed a novel classification scheme and a validation study is underway to determine if classification can further risk-stratify these patients.[45] Advances in cardiovascular imaging which more accurately define the amount of myocardium at risk in individuals with refractory ischaemia may prove useful as well.

In conclusion, long-term mortality in patients with refractory angina who are not candidates for traditional revascularization is surprisingly low. Over 70% of patients with refractory angina can expect to survive 9 years from the time of diagnosis. Therapeutic options for this growing population should therefore focus on chest pain relief and improved quality of life.

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