ORIGINAL RESEARCH

Predictors of Long-term Clinical Endpoints in Patients With Refractory Angina

Thomas J. Povsic, MD, PhD; Samuel Broderick, MS; Kevin J. Anstrom, PhD; Linda K. Shaw, MS; E. Magnus Ohman, MD; Eric L. Eisenstein, DBA; Peter K. Smith, MD; John H. Alexander, MD, MHS

***Background*—**Clinical outcomes in patients with refractory angina (RA) are poorly characterized and variably described. Using the Duke Database for Cardiovascular Disease (DDCD), we explored characteristics that drive clinical endpoints in patients with class II to IV angina stabilized on medical therapy.

***Methods and Results*—**We explored clinical endpoints and associated costs of patients who underwent catheterization at Duke University Medical Center from 1997 to 2010 for evaluation of coronary artery disease (CAD) and were found to have advanced CAD ineligible for additional revascularization, and were clinically stable for a minimum of 60 days. Of 77 257 cardiac catheterizations performed, 1908 patients met entry criteria. The 3-year incidence of death; cardiac rehospitalization; and a composite of death, myocardial infarction, stroke, cardiac rehospitalization, and revascularization were 13.0%, 43.5%, and 52.2%, respectively. Predictors of mortality included age, ejection fraction (EF), low body mass index, multivessel CAD, low heart rate, diabetes, diastolic blood pressure, history of coronary artery bypass graft surgery, cigarette smoking, history of congestive heart failure (CHF), and race. Multivessel CAD, EF<45%, and history of CHF increased risk of mortality; angina class and prior revascularization did not. Total rehospitalization costs over a 3-year period per patient were $10 185 (95% CI 8458, 11912) in 2012 US dollars.

***Conclusions*—**Clinically stable patients with RA who are medically managed have a modest mortality, but a high incidence of hospitalization and resource use over 3 years. These findings point to the need for novel therapies aimed at symptom mitigation in this population and their potential impact on health care utilization and costs. **(*J Am Heart Assoc*. 2015;4:e001287 doi: 10.1161/JAHA.114.001287)**

Key Words: angina • chronic ischemic heart disease • coronary artery disease • outcomes • refractory angina • resource use

Refractory angina resulting in continued symptoms despite maximal medical therapy and without revascularization options is estimated to affect 600 000 to 1.8 million Americans, with 50 000 to 100 000 new cases per year.[1] Despite great interest in the development of new therapies for these patients, this remains a poorly characterized and studied population and descriptions of their long-term outcomes have been variable.[2] New therapies have largely targeted patient symptoms, although, in some cases, an effect on cardiovascular events has trended in a favorable direction.[3] Nonetheless, there is a poor understanding of the long-term outcomes of these patients. A number of factors might be responsible for the variable outcomes reported, including requirements for clinical stability, limits on ejection fraction (EF), angina class, extent of coronary disease, and degree of congestive heart failure (CHF). The degree to which these factors predict outcomes has not been directly tested.

The Duke Database of Cardiovascular Disease (DDCD) is a unique resource used to capture angiographic and clinical data on all patients undergoing cardiac catheterization at Duke University Medical Center. The DDCD has been used in 2 previous studies to assess outcomes in medically treated patients with significant coronary disease.[2,4] These analyses suggested mortality rates in medically treated patients with angina that exceed those observed in other studies or randomized trials of new therapies for refractory angina.[5–7]

In order to reconcile these observations, we used the DDCD to model patients with class II to IV angina who

From the Duke Clinical Research Institute, Durham, NC (T.J.P., S.B., K.J.A., L.S.S., E.M.O., E.L.E., P.K.S., J.H.A.); Program for Advanced Coronary Disease, Duke Medicine, Durham, NC (E.M.O.).

Correspondence to: Thomas J. Povsic, MD, PhD, Duke Clinical Research Institute, Duke Medicine, 2400 Pratt Street, Durham, NC 27705. E-mail: thomas.povsic@duke.edu.

Received July 28, 2014; accepted October 19, 2014.

remained clinically stable without cardiovascular events for 60 days, mimicking entry criteria for clinical trials. In addition, we used this population to model the effect of key criteria (history of revascularization, extent of coronary disease, EF, history of CHF, and angina class) on long-term clinical endpoints, including mortality, myocardial infarction (MI), and rehospitalization. We also modeled rehospitalization costs for this cohort over the 3-year follow-up period.

Methods

Methodology on data collection and analysis in the DDCD has been previously published.[8,9] In brief, all patients undergoing cardiac catheterization, percutaneous coronary intervention (PCI), or cardiac surgery undergo systematic collection of demographic, clinical, angiographic, medication use, and procedural data. All cardiac catheterizations are systematically reviewed in a standardized fashion by 2 operators and the extent of coronary disease is defined on an individual segment basis.

Patients are contacted at 6 and 12 months after their initial procedure, and then annually thereafter. Medication use, death, rehospitalization, and revascularization status are determined using mailed questionnaires. Hospitalization and discharge records were used to supplement these data. Indications for hospitalization were determined through review of diagnosis-related groups (DRG) used for billing purposes (Duke University-affiliated hospitals) or through follow-up questionnaires (outside facilities). DRG code review was done in a blinded fashion. Vital status was supplemented through a search of the National Death Index.[10] Follow-up in this study was assessed as 98.6% complete.

The Duke University Institutional Review Board approved this analysis.

Patient Selection

All catheterization records from 1997 to 2010 were queried for inclusion after initial review indicated that use of broad periods of inclusion resulted in a significant impact on year of catheterization with outcomes. Unique patient records of those undergoing cardiac catheterization with class II to IV angina who remained clinically stable for 60 days were included. Clinical stability was defined as remaining alive without recurrent hospitalization, MI, stroke, or revascularization during the 60-day period following index catheterization. Patients with concomitant illness such as malignancy, HIV, or those who underwent cardiac catheterization for non-ischemic evaluation including severe valvular heart disease were also excluded. In the event that a patient had several catheterizations that met entry criteria, the earliest of the catheterizations was used to allow for longer follow-up.

Statistical Analysis

Unadjusted Kaplan-Meier overall event rates were calculated at various time points for the composite endpoint (defined as occurrence of any of the components). Cumulative incidence estimates for each of the components used Kaplan-Meier methods. The time until the composite event is the time until the first occurrence of a component that occurred during the follow up period.

The event rates for each endpoint and component were also stratified by the pre-specified analysis strata (history of revascularization, extent of coronary disease, EF, history of CHF, and angina class) at each time point (6 months, 1, 2, and 3 years after 60 days post-index catheterization).

To determine the characteristics affecting clinical endpoints, a multivariable Cox regression analysis was conducted using a set of candidate characteristics to determine variables with statistically significant relationships with clinical endpoints of interest. A single model incorporating 30 baseline characteristics (available in the Appendix) was constructed. Follow-up for these models began at 60 days following the index catheterization and ended 3 years later. The model for each endpoint was determined using both stepwise and backwards selection processes and the results were compared to develop a robust model. Patients with missing data for any of the variables in the analysis were not included in this analysis. Transformations were performed to assure that each variable satisfied the linearity assumption of the Cox model. Factors that were statistically significant are reported.

Cost Analysis

Rehospitalization rates were obtained, and costs of all hospitalizations at Duke were calculated. Medical costs for hospitalizations at Duke were obtained by mapping DRGs on DDCD hospitalization records into their 2012 Medicare Severity (MS)-DRG equivalents, and multiplying each 2012 MS-DRG relative weight by Medicare's fiscal year 2012 base payment amount. The missing costs associated with non-Duke hospitalizations were imputed using multiple imputation methods.[11]

To address differential follow-up in this patient population, a partitioned estimator of the mean hospitalization costs was calculated[12] and the standard error of the estimator was estimated using bootstrap methods.[13] Reported confidence intervals (CIs) account for both the variation in the partitioned estimate and variation due to the imputation of missing cost data.

Results

Patient Population

Of 77 257 patients undergoing cardiac catheterization between 1997 and 2010 at Duke University Medical Center, 11 106 unique patients met all inclusion criteria for the study (Figure 1). Patients were excluded for the following reasons: catheterization performed for congenital heart disease (n=1360); primary valvular heart disease (n=3663); evaluation of cardiomyopathy or pericardial disease (n=870); the presence of AIDS or metastatic cancer (n=314); lack of significant coronary artery disease (n=26 999); grade IV mitral insufficiency (n=68); Killip class >2 (n=5); presence of a tumor, lymphoma, severe liver disease, leukemia, dementia, or connective tissue disease (n=951); lacking class II, III, or IV angina (n=21 815); or an MI within 3 days of catheterization (n=2872).

Patients were further excluded if they had a revascularization up to 3 days prior to index catheterization; revascularization at or within 60 days post-index catheterization (n=8324); or a cardiac event within 60 days of index catheterization, including MI (n=8), stroke (n=43), cardiac rehospitalizations (n=194), or death (n=55). We excluded patients who had no follow-up information up to 60 days after index catheterization (n=6), did not have some assessment of EF (n=406), had an EF <25% (n=92), or had a baseline creatinine of >2.5 mg/dL or a baseline creatinine clearance <30 mL/min (n=70). The final study population consisted of 1908 unique patients.

Patient demographics are displayed in Table 1. Patients had a median (25th, 75th) age of 63 (55, 72) years and were mostly male (67.2%) and white (77.8%). A majority of patients had multivessel disease (64.8%), a preserved left ventricular EF (80.2%), and other cardiac risk factors such as hypertension (73.1%), hyperlipidemia (73.2%), tobacco use (58.3%), and diabetes (34.2%).

Endpoints

Kaplan-Meier survival analysis of cardiovascular endpoints

During the 3-year period, 227 deaths occurred, 300 patients experienced death or MI, and 934 observed the composite

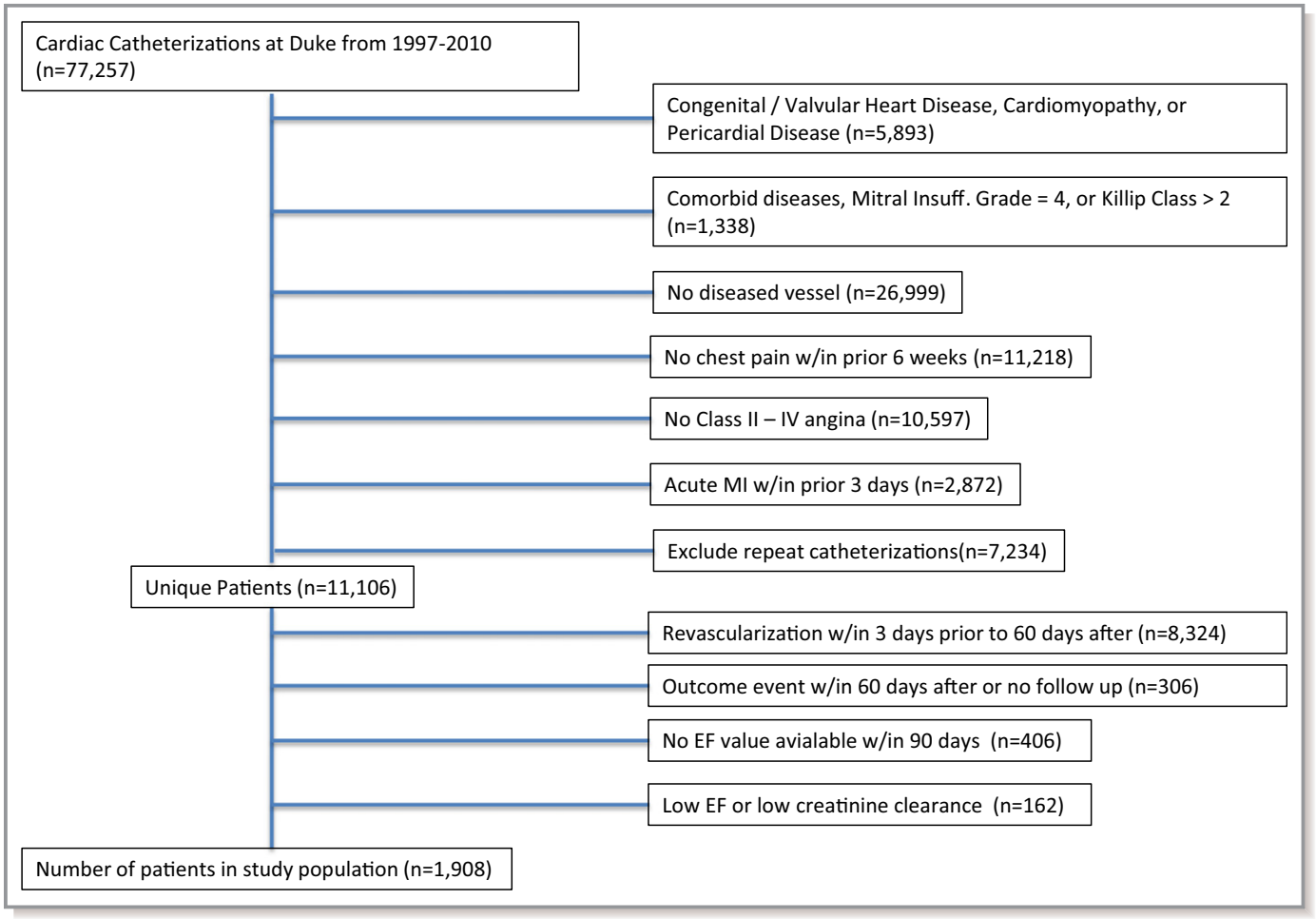

Figure 1. Patient selection.

Table 1. Patient Demographics

Demographics		
Continuous variables	N	Median (25th, 75th)
Age, y	1908	63 (55.0, 72.0)
BMI, kg/m^2	1898	28.7 (25.4, 32.5)
Duration of CAD, mos	1891	65.2 (11.9, 147)
EF, %	1908	57.8 (47.7, 65.5)
Diastolic blood pressure, mm Hg	1807	79.0 (70.0, 88.0)
Systolic blood pressure, mm Hg	1818	148 (131, 165)
Heart rate, beats/min	1901	67.0 (59.0, 77.0)
Categorical variables	n/N	%
Female	626/1908	32.8
White	1484/1908	77.8
Black	295/1908	15.5
Native American/Other	96/1908	5.0
Hypertension	1394/1908	73.1
Diabetes	653/1908	34.2
Hyperlipidemia	1397/1908	73.2
Family history of premature CAD	909/1908	47.6
History of cerebrovascular disease	275/1908	14.4
History of tobacco use	1113/1908	58.3
History of CHF	540/1862	29.0
EF >45%	1530/1908	80.2
Coronary disease		
1 vessel	672/1908	35.2
2 vessel	473/1908	24.8
3 vessel	763/1908	40.0
Multivessel	1236/1908	64.8
Angina class		
Class II	448/1908	23.5
Class III	362/1908	19.0
Class IV	1098/1908	57.6
History of MI	716/1908	37.5
History of revascularization	1145/1908	60.0
History of PCI	495/1908	25.9
History of CABG	900/1908	47.2
History of PAD	276/1908	14.5
NYHA class		
None	1433/1837	78.0
I	43/1837	2.3
II	138/1837	7.5
III	160/1837	8.7
IV	63/1837	3.4

Continued

Table 1. Continued

Demographics		
COPD	140/1908	7.3
Mild/moderate liver disease	11/1908	0.6
Renal disease	3/1908	0.2
Bruits	210/1900	11.1
Killip class		
N/A	1901/1905	99.8
I	4/1905	0.2
Mitral insufficiency		
Absent	1554/1852	83.9
1+	171/1852	9.2
2+	94/1852	5.1
3+	33/1852	1.8

BMI indicates body mass index; CABG, coronary artery bypass graft; CAD, coronary artery disease; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; EF, ejection fraction; MI, myocardial infarction; NYHA, New York Heart Association; PAD, peripheral artery disease; PCI, percutaneous coronary intervention.

ischemic events endpoint. The 3-year mortality rate was 13.0%, and the rate for cardiac rehospitalization was 43.5% of patients (Table 2). Overall event rates at 3 years for the composite ischemic endpoint and key components, as well as results by key clinical characteristics, are provided (Table 2). Kaplan-Meier curves demonstrating event rates for death, death or MI, and the composite ischemic endpoint and event rates for all individual components are shown in Figures 2 through 4.

Death

Overall 3-year death rates, as well as by key clinical characteristics, are listed in Table 2. Death was independently associated with 11 of 30 (see Online Supplement) baseline characteristics (Table 3). Notably, coronary artery bypass graft (CABG) surgery was protective, while EF was associated with an increased risk of mortality (hazard ratio [HR] 1.15 per 5% decrease in EF). Other factors associated with a >1.5-fold higher risk of death include the presence of multivessel coronary artery disease (HR 2.28), age per decade (HR 2.64), history of diabetes (HR 1.61), and a history of cigarette use (HR 1.52).

Composite of death or MI

The rate of death or MI at 6 months, 1, 2, and 3 years was 3.8%, 6.3%, 11.5%, and 17.1%, respectively (Table 2 and Figure 3). An analysis of the relationship between death or MI with 30 baseline characteristics revealed 12 factors that had an independent relationship (Table 4), 7 of which were common with predictors of death. Catheterization after 2005, a history of peripheral artery disease (PAD), duration of coronary artery disease, and a history of hyperlipidemia were identified as predictors of death or MI, while a history of CHF, heart rate, a history of smoking, and race were not associated with the death or MI endpoint.

Composite of death, MI, stroke, cardiac rehospitalization, and revascularization

The event rate for the ischemic composite endpoint at 6 months, 1, 2, and 3 years was 17.8%, 28.0%, 41.3%, and 52.2% (Table 2 and Figure 4). Rates for each individual component are shown (Figure 4). Sixteen factors were associated with the composite ischemic endpoint (Table 5). Compared with predictors of death, 5 factors (body mass index, history of CABG, diastolic blood pressure, heart rate, and history of tobacco use) were not predictors of the composite ischemic endpoint, while a history of PCI, angina class, year of catheterization, coronary artery disease duration, presence of chronic obstructive pulmonary disease, history of cerebrovascular disease, history of PAD, renal disease, and presence of mitral insufficiency were now significantly associated with the endpoint.

Cost of rehospitalizations

During 3 years of follow-up, 776 patients had a total of 1639 cardiovascular hospitalizations, with 1035 hospitalizations at Duke used to estimate costs. The median cost per hospitalization was $10 080 (25th, 75th [4564, 11465]). After accounting for differential follow-up and imputation of costs for rehospitalizations outside of Duke, the partition estimates with 95% confidence intervals (CIs) (rounded to 2012 US

Table 2. Rates of 3-Year Outcomes According to Key Clinical Criteria

Parameter	Death	Death/MI	CV Rehospitalization	Revascularization	Composite
Overall	13.0	17.1	43.5	14.5	52.2
History of revascularization					
No	14.8	18.1	37.3	12.2	47.8
Yes	11.8	16.5	47.5	15.9	55.1
History of CABG					
No	14.0	17.6	39.4	14.8	49.8
Yes	11.9	16.6	48.0	14.1	54.9
History of PCI					
No	13.5	16.8	40.6	11.8	49.8
Yes	11.6	17.9	51.6	21.8	59.0
CAD					
1V	7.5	10.5	38.9	11.6	45.9
2-3V	16.0	20.7	46.1	16.1	55.6
EF >45%					
No	25.0	29.0	49.1	11.4	61.4
Yes	10.1	14.2	42.1	15.2	50.0
History of CHF					
No	10.0	14.0	40.0	14.1	48.4
Yes	20.7	25.0	53.2	14.7	62.5
Angina					
Class II	11.8	14.9	36.7	13.0	43.3
Class III	10.9	15.1	38.8	13.2	47.5
Class IV	14.2	18.7	47.9	15.5	57.4

CABG indicates coronary artery bypass graft; CAD, coronary artery disease; CHF, congestive heart failure; CV, cardiovascular; EF, ejection fraction; MI, myocardial infarction; PCI, percutaneous coronary intervention.

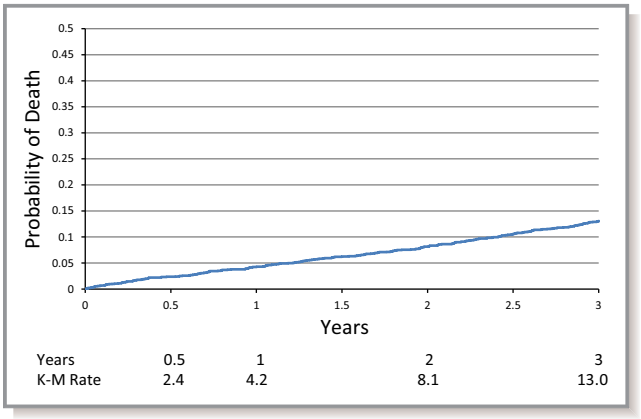

Figure 2. Unadjusted Kaplan-Meier event rate plot for death after 60 days.

dollars) was $10 622 per patient (95% CI 8860, 12384) in 2012 US dollars. Estimated rehospitalization costs based on prespecified variables (history of revascularization, multivessel coronary artery disease, EF, and CHF) are listed (Table 6).

Discussion

Our analysis from the DDCD in a broad population of patients undergoing catheterization indicates that patients with advanced angina from significant coronary disease lacking revascularization options but who are clinically stable have low rates of mortality (~4% per year), but a high rate of hospitalization and resource use.

Comparison With Other Studies

Previous descriptions of outcomes in refractory angina patient populations have reached variable conclusions, possibly due to large variations in how these patients are defined. Consistent across all studies are requirements for obstructive coronary disease (>70% obstruction of at least 1 epicardial coronary vessel) with a minimum of class II angina. Reviews of randomized clinical studies in this population report mortality rates of 3 to 21% in placebo-treated patients,[14,15] with only a single study (n=41) reporting a 1-year mortality of >11%.[14]

Table 3. Predictors of Death

Parameter	X^2	HR	95% CI	*P* Value
Age (per 10-y increase)	58.8	2.64	2.06, 3.38	<0.0001
EF (per 5% increase)	32.1	0.87	0.83, 0.91	<0.0001
BMI ≤22 kg/m^2	22.4	0.75	0.67, 0.85	<0.0001
Multivessel CAD	20.6	2.28	1.60, 3.26	<0.0001
Heart rate <80 (per 5 bpm increase)	14.7	1.14	1.07, 1.23	0.0001
Diabetes	11.8	1.61	1.23, 2.12	0.0006
Diastolic BP (per 5 mm Hg increase)	10.37	0.93	0.89, 0.97	0.0013
History of CABG	10.28	0.62	0.46, 0.83	0.0013
History of tobacco use	8.37	1.52	1.14, 2.01	0.0038
History of CHF	6.17	1.42	1.08, 1.87	0.013
White	4.45	0.72	0.53, 0.98	0.0350

BMI indicates body mass index; BP, blood pressure; bpm, beats per minute; CABG, coronary artery bypass graft; CAD, coronary artery disease; CHF, congestive heart failure; CI, confidence interval; EF, ejection fraction; HR, hazard ratio.

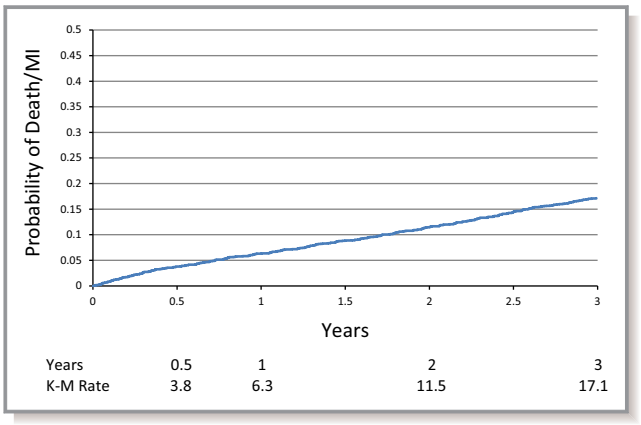

Figure 3. Unadjusted Kaplan-Meier event rate plot for death or MI after 60 days. MI indicates myocardial infarction.

Indeed, in non-surgical studies, mortality rates are consistently below 6%, although in many cases the follow-up period is short.[3,16–21] This is consistent with what is observed in studies of patients with stable angina.

Early registries largely reported higher mortality rates: 37.8% at a median follow-up of 2.2 years (MOSS study),[4] 16.9% at 1 year (Cleveland Clinic),[6] and 11% at 1 year in a separate analysis from the DDCD.[2] More recently, Williams et al reported 1- and 3-year mortality rates of 5% and 15% for patients undergoing cardiac catheterization who were treated medically and on maximal medical therapy.[7] A separate analysis of 1200 patients referred to an outpatient clinic specifically for refractory angina with 1- and 5-year mortality rates of 3.9% and 17.5%.[5] These rates are remarkably similar to those described here (4.2% at 1 year, 13.0% at 3 years).

The reasons for this variability in rates remain poorly understood. One proposed explanation is the improvement in medical therapy over time.[22] While more aggressive statin therapy may contribute, the only new therapy for angina, ranolazine, has not been demonstrated to improve clinical outcomes. In our study, year of catheterization was not associated with changes in mortality, but was associated with some composite endpoints. Furthermore, a different analysis from the DDCD demonstrated a 1-year mortality almost 3 times the rate in this study even though years of enrollment largely overlapped (1996–2005 versus 1997–2010),[2] suggesting that patient selection plays a key role. Trials frequently stipulate a period of clinical stability without changes in medical therapy, revascularization, or other acute events prior to enrollment. We selected patients that met such criteria, excluding those who died or required rehospitalization or revascularization within 60 days of the index catheterization. Referral to an outpatient refractory angina clinic, whose population was drawn from over 40 US states, likely reflected a similar stable population. This analysis suggests that even in this patient population, rates of rehospitalization and presentation with unstable symptoms remains high over time, although rates of mortality and MI are modest.

Our study also corroborates the findings of Henry et al[5] in identification of predictors of mortality, including age, diabetes, history of CHF, extent of coronary artery disease, and degree of left ventricular dysfunction with the notable exception that a history of CABG was protective in our study.

Comparison with 2 studies is of special interest because they involve patients from the same institution and database. Notably, both Cavender et al[2] and the MOSS study[4] excluded patients who had revascularization, but not other events, within 30 days. The studies of Mukherjee, Williams, and

Table 4. Predictors of Death and Myocardial Infarction

Parameter	X^2	HR	95% CI	*P* Value
EF (per 5% increase)	41.6	0.87	0.83, 0.91	<0.0001
Multivessel CAD	25.3	2.20	1.62, 2.98	<0.0001
Age ≥73 y (per 10-y increase)	24.5	2.11	1.57, 2.84	<0.0001
History of CABG	17.1	0.57	0.44, 0.75	<0.0001
History of PAD	13.5	1.65	1.26, 2.15	0.0002
BMI ≤22 kg/m^2	12.8	0.80	0.70, 0.90	0.0003
Year of index catheterization ≥2006	9.9	0.70	0.56, 0.87	0.0016
Diabetes	9.2	1.44	1.14, 1.83	0.0025
Diastolic BP (per 5 mm Hg increase)	7.5	0.95	0.91, 0.98	0.006
Hypertension	6.2	1.43	1.08, 1.89	0.0127
CAD duration (y)	5.5	1.02	1.00, 1.03	0.0187
Hyperlipidemia	4.5	0.77	0.60, 0.98	0.0336

BMI indicates body mass index; BP, blood pressure; CABG, coronary artery bypass graft; CAD, coronary artery disease; CI, confidence interval; EF, ejection fraction; HR, hazard ratio; PAD, peripheral artery disease.

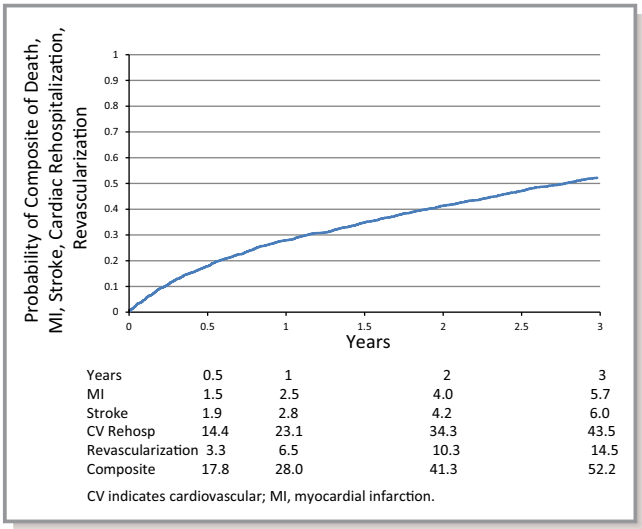

Figure 4. Unadjusted Kaplan-Meier event rate plot for death, MI, cardiovascular rehospitalization, revascularization, or stroke after 60 days. CV indicates cardiovascular; MI, myocardial infarction.

Cavender also describe an early hazard rate, which exceeds that observed during the follow-up period.[2,6,7] In contrast, we observed a near-linear relationship over time for the incidence of the composite and its individual components. The higher event rates reported in these cohort studies likely reflect the impact that a prolonged period of clinical stability has on lowering projected future event rates, as well as the distribution of events over time. These observations have important implications as therapies studied in more stable populations enrolled in clinical trials become implemented in broader classes of patients. It is notable that patients in these registries had extremely high resource utilization averaging 1.3 to 2.3 hospitalizations/patient per year. In the MOSS study, medically treated patients expended an average of $28 500 in hospital costs per year; thus, therapies that are effective at lowering angina burden in this patient population might have a profound impact on resource use.[4]

One factor that might be expected to increase events in clinical studies is the frequent criterion for the presence of inducible ischemia on stress testing. The role of stress testing in accurately identifying significant coronary disease has recently been called into question.[23] Nonetheless, patients with inducible ischemia on stress testing might be expected to have a larger area of under-perfused myocardium and higher risk. Nonetheless, the event rates in most cohort studies remain higher, perhaps because all patients had significant untreated stenosis in at least 1 major coronary or branch artery and would be expected to have significant ischemia.

Definition of Refractory Angina

Identification of patients with refractory angina is challenging. The European Society of Cardiology Joint Study Group on the Treatment of Refractory Angina required 3 months of angina not controlled by medical or interventional therapy where ischemia has been documented as the cause of symptoms.[24] Studies of these patients have largely been based on catheterization lab series where documentation of medical therapy and continued symptoms has been lacking. In our study, the percentage of patients undergoing catheterization

Table 5. Predictors of Composite Endpoint of Death, Myocardial Infarction, Stroke, Cardiac Rehospitalization, and Revascularization

Parameter	X^2	HR	95% CI	*P* Value
Age <62 y (per 10-y increase)	19.6	0.76	0.68, 0.86	<0.0001
Cerebrovascular disease	16.3	1.43	1.20, 1.69	<0.0001
Age ≥62 y (per 10-y increase)	13.2	1.22	1.10, 1.36	0.0003
EF (per 5% increase)	12.8	0.95	0.93, 0.98	0.0003
Renal disease	12.0	12.0	2.93, 48.7	0.0005
African American	10.2	1.32	1.12, 1.57	0.0014
History of PCI	10.2	1.26	1.09, 1.45	0.0014
CAD duration ≥18.5 y	9.0	1.04	1.01, 1.06	0.0027
Angina class 2 vs 3/4	8.9	0.78	0.66, 0.92	0.0029
COPD	7.5	1.37	1.09, 1.72	0.0061
Diabetes	6.7	1.20	1.04, 1.37	0.0099
History of CHF	6.6	1.2	1.05, 1.39	0.0104
Year of index catheterization	6.1	0.98	0.96, 1.0	0.0132
No MR	5.2	0.82	0.69, 0.97	0.0230
Multivessel CAD	5.04	1.18	1.02, 1.36	0.0247
PAD	4.1	1.20	1.01, 1.43	0.0430

CAD indicates coronary artery disease; CHF, congestive heart failure; CI, confidence interval; COPD, chronic obstructive pulmonary disease; EF, ejection fraction; HR, hazard ratio; MR, mitral regurgitation; PCI, percutaneous coronary intervention; PAD, peripheral artery disease.

who fulfilled our selection criteria was only 2.5%, lower than many previous series (6 to 15%). This is reflective of our selection process and inclusivity of all patients undergoing catheterization including those with non-cardiac conditions and those not related to coronary disease, and is similar to other series from the DDCD.[2,4] Notably 38% of patients did not have significant coronary artery disease and 49% of the remaining patients were excluded because they did not have sufficient angina.

Our study is strengthened by the numbers of patients selected, inclusion of all patients undergoing catheterization in a comprehensive database, and specific phenotyping of angina class and clinical risk factors and outcomes. Enrollment in clinical trials likely more rigorously selects for patients on optimal medical therapy with stable symptoms, as does referral to a clinic specializing in treatment of this condition. The concordance of our findings with these analyses validates our patient selection strategy and the outcomes described.

Impact of Angina, CHF, and Revascularization History

The current study models, for the first time, the impact of specific prespecified criteria on expected cardiovascular events. For instance, enrollment of patients with decreased EF and history of CHF is likely to have a significant impact on expected mortality rates. This has important implications for the development of angiogenic therapies aimed at improving symptoms in patients with ischemic cardiomyopathy in which

Table 6. Estimates of Hospitalization Costs Based on Presence of Absence of Prespecified Risk Factors*

Baseline Factor	Yes	No
Revascularization	11355 (9463, 13246)	8430 (6348, 10511)
Multivessel CAD	11103 (9240, 12967)	8469 (6341, 10650)
EF <45%	12333 (8426, 16239)	9654 (8183, 11126)
History of CHF	14044 (10642, 17455)	8590 (7073, 10107)

*Partitioned estimates with 95% confidence intervals are shown.
CAD indicates coronary artery disease, CHF, congestive heart failure; EF, ejection fraction.

preventing rehospitalizations as well as improving hard cardiac endpoints (mortality, MI) may be a feasible goal. In addition, restricting enrollment to patients with multivessel coronary artery disease may significantly impact event rates. Our analysis, unlike that of Henry et al[5] suggests that exclusion of class II angina patients would not significantly impact expected rates of clinical outcomes (3-year mortality 14.3 versus 13.4 [class III/IV versus II to IV], or composite ischemic endpoint 48.9% versus 46.0%). These contrasts may relate to differences in the clinical setting in which angina class was measured.

Cost Analysis

We determined the costs associated with cardiovascular hospitalizations in this patient population. It is difficult to compare the costs observed here with those reported in other patient populations, which calculated total medical costs over different time periods. Nonetheless, the costs and re-hospitalization rates in these patients are comparable with those of other high-risk patient populations.[25–28] Costs in our analysis are almost certainly underestimated for the following reasons: hospitalizations outside of Duke were not captured, only costs of cardiovascular hospitalizations were included, we relied on self-reporting of hospitalization, and we did not attempt to account for Medicare Part B costs. Estimates of the incidence of patients with refractory angina indicate that this population includes up to 1.8 million patients in the United States, suggesting that the costs of cardiovascular hospitalizations alone account for over $6 billion in health care expenditures per year.

Limitations

This is a single-center study reflecting endpoints in patients undergoing catheterization at a tertiary medical center, and may not reflect rates across other regions or countries. Nonetheless, our results are similar to results obtained from other US[5,29] and out-of-US registries.[30]

Patients were selected based on a referral for cardiac catheterization, which may have resulted in a more acute population with an accelerating clinical course. The reason for not proceeding with revascularization in our cohort is not captured and significant comorbidity adding to the risk of revascularization strategies may have played a role. However, each of these concerns would be expected to result in selecting patients at higher risk for future events.

We were unable to assess the impact of variables not collected in the DDCD that may be of significant interest in this patient population, including quality of life measures, angina burden, productivity loss, or resource use. We excluded patients with an EF <25%, serum creatinine of >2.5 mg/dL, or patients with a cardiovascular event within 60 days of the index catheterization to obtain a clinically stable patient population primarily limited by angina. However, these exclusions among others may bias the results and may not reflect rates of outcomes in a broader and more inclusive population. Similar to other series,[5–7] we did not assess for optimization of therapy and the persistence of angina after index catheterization.

Conclusions

Patients with class II or greater angina, significant coronary disease, and who are not candidates for further revascularization but remain stable for a period of 60 days appear to have low rates of death and MI but high resource use. In contrast, populations restricted to those with multivessel coronary artery disease and especially a history of CHF or a decreased EF have a markedly higher incidence of death and MI. Additional research on resource utilization and quality of life in these patients is needed.

Source of Funding

This work was partially funded by a grant from Baxter Healthcare Inc.

Disclosures

Povsic reports research funding from Baxter Healthcare Inc, Regado Biosciences and consulting (modest) fees from Pluristem. Broderick has no disclosures to report. Anstrom reports research support from AstraZeneca (significant), Eli Lilly & Company (significant), and Medtronic (significant); has served as a consultant for Abbott Vascular (modest), AstraZeneca (modest), Bristol-Meyers Squibb (modest), Pfizer (modest), GSK (modest), and Ikaria (modest); and has served on Data Monitoring Committees for Pfizer (modest) and Vertex (modest). Shaw has no disclosures to report. Ohman reports research funding from Daiichi Sankyo, Eli Lilly & Company and Gilead Services. He also reports consulting/speaking fees from Abiomed (modest), AstraZeneca (modest), Daiichi Sankyo (modest), Eli Lilly & Company (modest), Gilead Services (modest), Pozen, Inc (modest), Sanofi Aventis (modest), The Medicines Company (modest), WebMed (significant). Eisenstein reports research support from Medtronic Endovascular. Smith reports consulting fees from CSL Behring (modest). Alexander reports research funding from Bristol-Myers Squibb, Boehringer Ingelheim, CLS Behring, Duke Health System, National Institutes of Health, and Regado Biosciences; consulting/speaking fees from Bristol-Myers Squibb (modest), CLS Behring (modest), Daiichi Sankyo

(modest), GlaxoSmithKline (modest), Moerae Matrix (modest), Ono Pharmaceuticals (modest), Sohmalution (modest), and VA Cooperative Studies Program (modest).

Appendix

Initial List of Baseline Characteristics

History of any revascularization
Multi- versus single-vessel coronary artery disease
History of congestive heart failure
Age at time of catheterization
Body mass index
History of hypertension
Duration of CAD (months)
Presence of COPD
Diastolic blood pressure
Systolic blood pressure
History of diabetes
History of CABG
History of PCI
Ejection fractions
Family history of coronary artery disease
History of cerebrovascular disease
History of myocardial infarction
History of peripheral arterial disease
History of hyperlipidemia
Liver disease
Heart rate
Renal disease
Sex
History of cigarette smoking
Presence of bruits
Race
Killip class
Degree of mitral insufficiency (1 to 4+)
Class II angina versus Class III or IV angina
Year of index catheterization

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