Reduction in atherosclerotic events: a retrospective study in an outpatient cardiology practice

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Abstract

Introduction: Although atherosclerotic disease cannot be cured, risk of recurrent events can be reduced by application of evidence-based treatment protocols involving aspirin, beta blockers, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, and statin medications. We studied atherosclerotic event rates in a patient population treated before and after the development of aggressive risk factor reduction treatment protocols.
Material and methods: We performed a retrospective chart review of patients presenting for follow-up treatment of coronary artery disease in a community cardiology practice, comparing atherosclerotic event rates and medication usage in a 2-year treatment period prior to 2002 and a 2-year period in 2005-2008. Care was provided in both the early and later eras by 7 board-certified cardiologists in a suburban cardiology practice. Medication usage was compared in both treatment eras. The primary outcome was a composite event rate of myocardial infarction, cerebrovascular events, and coronary interventions.
Results: Three hundred and fifty-seven patients were studied, with a follow-up duration of 12.1 (±3.5) years. There were 132 composite events in 104 patients (29.1%) in the early era compared to 40 events in 33 patients (9.2%) in the later era ($p < 0.0001$). From the early to the later eras, there was an increase in use of β-blockers (66% to 83%, $p < 0.0001$), angiotensin-converting enzyme inhibitors or angiotensin receptor blockers (34% to 80%, $p < 0.0001$), and statins (40% to 90%, $p < 0.0001$).
Conclusions: Application of aggressive evidence-based medication protocols for treatment of atherosclerosis is associated with a significant decrease in atherosclerotic events or need for coronary intervention.

Key words: atherosclerosis, myocardial infarction, cerebrovascular events, cardiovascular drugs.

Introduction

While mortality statistics still point to coronary heart disease as the number one killer in the United States [1], many cardiologists have perceived a dramatic change in this disease over the last 20 years, with reductions in incidence and severity noted by community physicians in clinical practice. In our practice of 7 cardiologists in a suburban New York City community, we noticed that the incidence of myocardial infarction and

need for percutaneous coronary intervention and coronary artery bypass surgery seemed to be decreasing in recent years compared with time periods prior to the late 1990s. Since use of statin medications and angiotensin-converting enzyme (ACE) inhibitors increased during the late 1990s and early 2000s, we hypothesized that the decrease in incidence of coronary heart disease events we were seeing was due to newer and more aggressive treatment regimens for outpatients, especially in secondary prevention. Multicenter studies have shown that aspirin, β-blockers, ACE inhibitors, and statin medications can be used to reduce the risk of coronary events. We decided to test our hypothesis in our own patient population by performing a retrospective review of patient charts to determine whether changes in medical therapy were associated with a decrease in the incidence of myocardial infarction and need for coronary interventions.

Material and methods

We examined paper and electronic chart records of 1770 randomly selected patients who presented to our outpatient cardiology practice in 2003-2006, and carried a diagnosis of coronary artery disease. We identified 357 patients in that group who initially presented with symptoms or signs of coronary artery disease before January 1, 2000 and were treated continuously through 2005-2008. For each patient, we looked at progress notes of all interim office visits and recorded medication usage, blood pressure, laboratory studies including lipid levels, and occurrence of adverse cardiovascular events from the time of initial presentation to last follow-up. Adverse events included occurrence of acute myocardial infarction or stroke, or need for coronary intervention, either percutaneous or surgical.

We compared the earliest 2-year periods for each patient during the first era, to the latest 2-year period of follow-up in the second era. A total of 1748 visits in those 2 two-year periods were abstracted. If a patient presented initially with an adverse cardiovascular event, that event was not included as an event in the early era. For baseline data collection, comorbidities of coronary artery disease, hyperlipidemia, diabetes mellitus, hypertension, congestive heart failure, angina, atrial fibrillation, carotid stenosis, transient ischemic attack, cerebrovascular accident, chronic kidney disease, cigarette smoking history, peripheral vascular disease, abdominal aortic aneurysm, and previous coronary event or intervention were recorded. Occurrence of subsequent myocardial infarction, transient ischemic attack, or cerebrovascular accident was recorded, as well as requirement for percutaneous coronary intervention or coronary artery bypass grafting. Dates of the events as well as dates of all medication initiation and discontinuation were recorded. Coronary artery disease was diagnosed as previously described [2-5]. Cerebrovascular accident was diagnosed as previously described [6-8].

Table I. Characteristics of patients and study eras

Number of patients	357
Age at first date of therapy [years]	62.7 ±10.8
Age at second era [years]	74.7 ±10.6
Men	246 (69%)
Women	111 (31%)
Duration of follow-up [years]	12.1 ±3.5
Year range for early era	1977-2001
Year range for later era	2003-2008

The data were extracted from paper and electronic charts by the physician authors. Data collection was tabulated with Microsoft Access 2003, and statistical analysis was performed in Microsoft Excel 2003 (Microsoft Corporation, Redmond, WA, USA). Paired *t*-testing was used to analyze for statistical significance. A p-value of < 0.05 was considered statistically significant.

Results

Demographics and associated clinical characteristics are shown in Tables I and II. The group consisted of 246 males (69%) and 111 females. Average age at the time of the first visit was 62.7 ±10.8 years and at the last visit was 74.7 ±10.6 years. All patients had evidence for coronary artery disease at the time of presentation (angina, positive stress test, coronary artery disease on cardiac catheterization, or prior history of myocardial infarction, percutaneous coronary intervention (PCI), or coronary artery bypass surgery (CABS)). Other comorbidities included hyperlipidemia in 322 (90%) of the patients, diabetes in 80 (22%), hypertension in 295 (83%), congestive heart failure in 58 (16%), angina in 47 (13%), and atrial fibrillation in 69 (19%). One hundred and fifty-six (44%) of the patients were smokers. Other comorbidities are shown in Table II. The primary endpoint of the study was a composite of myocardial infarction, cerebrovascular event (transient ischemic attack or stroke), or requirement for coronary intervention (either PCI or CABS).

One hundred and thirty-five (37.8%) of the patients had myocardial infarction prior to (126 patients) or at their first visit, 67 (18.8%) had PCI prior to (62 patients) or at their first visit, 59 (16.5%) had CABS prior to (55 patients) or at their first visit, 4 patients had transient ischemic attack prior to (3 patients) or at their first visit, and 8 patients had history of cerebrovascular accident prior to their first visit. Only events or interventions that occurred

after the first visit in the early era were counted as an event in that era. The early follow-up era consisted of 2-year periods which were completed before December 31, 2001 (range of start dates from March 3, 1977 to December 27, 1999). The later follow-up era consisted of 2 year periods which were completed before November 7, 2008 (range of start dates September 21, 2003 to November 6, 2006).

The composite endpoint of myocardial infarction, cerebrovascular event (transient ischemic attack or stroke), and requirement for coronary intervention was significantly reduced in the later follow-up era compared to the early follow-up era (Table III, Figure 1). The need for CABS and PCI decreased from the early era to the later era. Percutaneous coronary interventions decreased from 63 interventions in 50 patients (14%) in the early era to 17 interventions in 16 patients (4.5%) in the later era ($p < 0.0001$). Requirement for CABS decreased from 53 procedures in 53 patients (14.8%) in the early era to 8 procedures in 8 patients (2.2%) in the later era ($p < 0.0001$). Five patients of 50 who underwent PCI in the early era required CABS in the early era, and 2 required CABS in the later era. Three patients who had a PCI in the early era required a repeat PCI in the later era. Only 1 patient of 53 who had a CABS in the early era required a CABS in the later era. In the early era, 9 patients (2.5%) experienced a total of 10 myocardial infarctions, while in the later era, 5 patients (1.4%) experienced myocardial infarctions, a result that was not statistically significant. Incidences of transient ischemic attack and cerebrovascular accident were also statistically unchanged. Of note, 4 of the 5 patients (80%) who experienced a myocardial infarction in the later era were not on statin medications.

Medication treatment regimens during these 2 follow-up periods changed significantly (Table IV). Statin use increased between the early era and the later era from 142 patients (39.8%) to 323 patients (90.5%, $p < 0.0001$). β-Blocker use increased from 235 patients (65.8%) to 295 patients (82.6%, $p < 0.0001$). Angiotensin converting enzyme inhibitor use increased from 101 patients in the early era (28.3%) to 216 in the later era (60.5%, $p < 0.0001$). Use of angiotensin receptor blockers also increased from 25 patients (7.0%) in the early era to 98 (27.5%, $p < 0.0001$) in the later.

Therefore, use of either ACE inhibitors or angiotensin receptor blockers increased from 34% to 80%. Although use of ezetimibe also increased from none in the early era to 100 patients (28.0%) in the later era, all but 3 of these patients were placed on ezetimibe together with a statin medication. Aspirin and calcium channel blocker use did not change. Use of other agents also increased (clopidogrel, warfarin, insulin, thiazolidinediones,

Table II. Associated clinical characteristics and comorbidities of patients in the study

Comorbidity	*n* (%)
Coronary artery disease	357 (100)
Hyperlipidemia	322 (90)
Diabetes mellitus	80 (22)
Hypertension	295 (83)
Clinical congestive heart failure	58 (16)
Angina	47 (13)
Atrial fibrillation	69 (19)
Carotid stenosis	19 (5)
Transient ischemic attack	22 (6)
Cerebrovascular accident	39 (11)
Chronic kidney disease	10 (3)
Smoker at time of presentation	156 (44)
Peripheral vascular disease	40 (11)
Aortic abdominal aneurysm	16 (4)
Prior myocardial infarction	135 (38)
Prior percutaneous coronary intervention	67 (19)
Prior coronary artery bypass surgery	59 (17)
Prior transient ischemic attack	4 (1)
Prior cerebrovascular accident	8 (2)

Table III. Outcomes in the patient group in the early era vs. later era

Outcomes	Early era		Later era		Value of *p*
	Adverse events, *n*	Patients with adverse events, *n* (%)	Adverse events, *n*	Patients with adverse events, *n* (%)	
MI	10	9 (2.5)	5	5 (1.4)	0.29
PCI	63	50 (14.0)	17	16 (4.5)	< 0.001
CABS	53	53 (14.8)	8	8 (2.2)	< 0.001
TIA	2	2 (0.6)	1	1 (0.3)	0.56
CVA	4	4 (1.1)	9	8 (2.2)	0.25
Composite	132	104 (29.1)	40	33 (9.2)	< 0.001

MI – myocardial infarction, PCI – percutaneous coronary intervention, CABS – coronary artery bypass surgery, TIA – transient ischemic attack, CVA – cerebrovascular accident

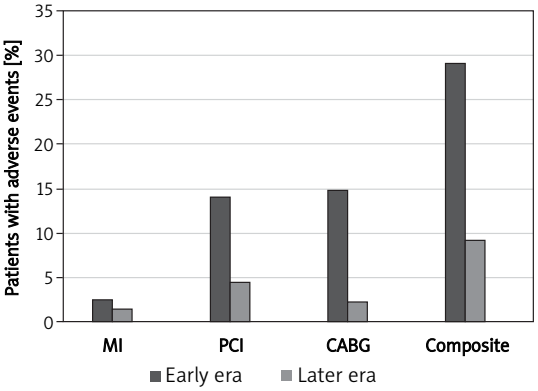

Figure 1. Percent of patients with events in early era and later era
MI – myocardial infarction, PCI – percutaneous coronary intervention, CABG – coronary artery bypass grafting

Table IV. Medication use for at least one visit in the earlier and later eras

Medications	Earlier era *n* (%)	Later era *n* (%)	Value of *p*
Statins	142 (40)	323 (90)	< 0.001
Ezetimibe	0 (0)	100 (28)	< 0.001
Nicotinic acid	11 (3)	13 (4)	0.67
Bile acid sequestrants	2 (1)	1 (0.3)	0.56
Fibrates	17 (5)	18 (5)	0.84
Fish oils	2 (1)	22 (6)	< 0.001
β-Blockers	235 (66)	295 (83)	< 0.001
Diuretics	115 (32)	202 (57)	< 0.001
ACE-I	101 (28)	216 (61)	< 0.001
ARB	25 (7)	98 (27)	< 0.001
ACE-I or ARB	123 (34)	285 (80)	< 0.001
Calcium channel blocker	161 (45)	148 (41)	0.24
Aspirin	278 (78)	282 (79)	0.67
Ticlopidine	17 (5)	0 (0)	< 0.001
Clopidogrel	18 (5)	62 (17)	< 0.001
Aspirin/ extended-release dipyridamole	1 (0.3)	7 (2)	0.03
Warfarin	50 (14)	95 (27)	< 0.001
Nitrates	108 (30)	64 (18)	< 0.001
Digoxin	56 (16)	64 (18)	0.29
Cilostazol	0 (0)	6 (2)	0.01
Insulin	15 (4)	30 (8)	< 0.001
Thiazolidinediones	8 (2)	38 (11)	< 0.001
Sulfonylureas	32 (9)	49 (14)	0.006
Metformin	20 (6)	48 (13)	< 0.001
Sitagliptin	0 (0)	2 (1)	0.16

ACE-I – angiotensin converting enzyme inhibitors, ARB – angiotensin receptor blockers

and metformin), but these drugs were used in only a small percentage of the patients in both eras. Clopidogrel was used with aspirin in all but 2 patients in the early era, and in all but 8 patients in the later era. Use of long-acting nitrates declined from 30% to 18%.

Discussion

Coronary atherosclerosis is still a major cause of morbidity and mortality in the United States population, but our data shows that with aggressive treatment using evidence-based protocols, even patients with overt coronary artery disease can reduce their chance of developing subsequent events or requirement for interventions. Peroxisome proliferator-activated receptor-gamma and retinoid X receptor-α expression down-regulation in both macrophages and smooth muscle cells was associated with more pronounced disease progression in patients with advanced carotid atherosclerotic lesions [9]. Further studies need to be performed to investigate the value of modulating vitamin D signaling [10], using serotonin reuptake inhibitor antidepressants [11], and postprandial use of verjuice [12] in treatment of atherosclerosis.

The patients in this trial acted as their own controls, and although the group had a high prevalence of angina, myocardial infarction, positive stress tests, and need for coronary intervention prior to the year 2002, their chance of requiring coronary intervention decreased in later years, and incidence of myocardial infarction did not increase. Since coronary atherosclerosis is a progressive disease process, one would expect the incidence of events to increase over time; the opposite happened to the patients in this study, and the most likely reason is use of more aggressive preventive treatment protocols. This study shows that such aggressive therapies can be implemented successfully in a community cardiology practice. For the most part, these protocols involve medications such as statins, ACE inhibitors (and to a lesser extent angiotensin receptor blockers), aspirin, and β-blockers. While the use of aspirin did not increase significantly, there was a high rate of use of aspirin in both groups, and the use of clopidogrel increased significantly during this time.

Numerous studies have shown the benefits of statin drugs [13-15], ACE inhibitor [16-18], β-blockers [19-21], and aspirin [22, 23] for reducing events in patients with documented coronary artery disease, but there are little data examining the application of these evidence-based protocols in community clinical practice and over long periods of time. A randomized, blinded trial to investigate the application of these protocols in community practice is not possible for ethical reasons. Although this study is a retrospective analysis, it provides pre-

sumptive data that changes in the practice of treating coronary disease over the past 20 years have significantly reduced event rates and the need for coronary interventions in this population.

Other possible contributing factors to the reduction in events include improved coronary intervention (CABS and PCI) and lifestyle changes. However, even patients without interventions in the early era had no increase in the need for interventions in the later era. It is also unlikely that improved interventional techniques resulted in reduced need for repeat procedures, since only 6 patients who had PCI or CABS in the first era required a second procedure in the later era. While the physicians in our practice recommend lifestyle changes strongly to our patients, it is our experience that many patients do not follow these changes, and that many who do cannot maintain them over long periods of time; unfortunately, compliance with lifestyle changes is difficult to measure and quantify.

There are limitations to a retrospective study such as this one. Patients were not randomized to treatment protocols, but this study more closely mimics actual clinical treatment among community-based cardiologists. Adherence to medication treatment could not be determined, since techniques such as pill counts were not employed, but it is our experience that our patient population tends to follow medication regimens. Mortality differences were not examined in this study since the criteria for entry was attendance at the later era visit. It is possible that very sick patients who were seen in the early era could have died before they would have presented for follow-up in the later era. A part of benefit, possibly small, should be attributed to this factor.

This retrospective study should give community practitioners, both specialists and primary care providers, the encouragement to pursue aggressive cardiovascular risk reduction strategies as a means for reducing the need for cardiovascular procedures in their patients. More importantly, it provides patients with the knowledge that, while coronary artery disease cannot be cured, there is hope that with proper and aggressive risk factor reduction therapies it can be controlled.

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