Risk factor reduction in progression of angiographic coronary artery disease

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Abstract

Introduction: To investigate differences between outpatients with progressive and nonprogressive coronary artery disease (CAD) measured by coronary angiography.

Material and methods: Chart reviews were performed in patients in an outpatient cardiology practice having ≥ 2 coronary angiographies ≥ 1 year apart. Progressive CAD was defined as 1) new non-obstructive or obstructive CAD in a previously disease-free vessel; or 2) new obstruction in a previously non-obstructive vessel. Coronary risk factors, comorbidities, cardiovascular events, medication use, serum low-density lipoprotein cholesterol (LDL-C), and blood pressure were used for analysis.

Results: The study included 183 patients, mean age 71 years. Mean follow-up duration was 11 years. Mean follow-up between coronary angiographies was 58 months. Of 183 patients, 108 (59%) had progressive CAD, and 75 (41%) had nonprogressive CAD. The use of statins, β-blockers, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, and aspirin was not significantly different in patient with progressive CAD or nonprogressive CAD Mean arterial pressure was higher in patients with progressive CAD than in patients with nonprogressive CAD (97 ±13 mm Hg vs. 92 ±12 mm Hg) ($p < 0.05$). Serum LDL-C was insignificantly higher in patients with progressive CAD (94 ±40 mg/dl) than in patients with nonprogressive CAD (81 ±34 mg/dl) ($p = 0.09$).

Conclusions: Our data suggest that in addition to using appropriate medical therapy, control of blood pressure and serum LDL-C level may reduce progression of CAD.

Key words: coronary artery disease, blood pressure, cholesterol.

Introduction

Progression of coronary artery disease (CAD) diagnosed by coronary angiography is associated with an increase in cardiovascular events [1-3]. The Coronary Artery Surgery Study (CASS) showed that diabetes and elevated serum total cholesterol level were associated with CAD progression [4]. Reduction of elevated serum low-density lipoprotein (LDL) cholesterol by statins reduces progression of CAD diagnosed by coronary angiography [5-7]. Hypertension increases progression of CAD diagnosed by coronary angiography [8, 9]. No significant difference in progression of CAD by

coronary angiography was found in patients treated with the angiotensin-converting enzyme inhibitor perindopril and placebo in the EUropean trial on Reduction Of cardiac events with Perindopril in stable coronary Artery disease (EUROPA) [10].

The primary aim of this study was to investigate differences between patients with progressive and nonprogressive CAD measured by coronary angiography who were followed in an academic cardiology outpatient practice.

Material and methods

Paper and electronic chart reviews were used to screen patients receiving two or more cardiac catheterizations with coronary angiography at least 1 year apart. The date of the first cardiac catheterization with coronary angiography could be any time during follow-up, but could not be any earlier than 3 months before the first visit. The 3-month criterion was chosen because many patients received cardiac catheterization with coronary angiography shortly before starting treatment at our cardiology outpatient practice. Coronary artery disease was diagnosed as previously described [11-19].

Of 1599 patients actively treated in the cardiology practice, 183 patients met the inclusion criteria and were included in the study. Follow-up coronary angiography was performed because of symptoms or an abnormal stress test with myocardial ischemia. The study population was divided into patients with progression of CAD and no progression of CAD. This grouping was based on the two coronary angiographic findings for each patient. Progression of CAD was defined as: 1) new non-obstructive or obstructive CAD in a previously disease-free vessel; or 2) new obstruction in a previously non-obstructive vessel. If a patient had more than two coronary angiographies, comparisons were made between the first coronary angiography and the earliest coronary angiography that followed at least a year later. The coronary arteries analyzed included left main, left anterior descending, left circumflex, and right coronary arteries. Graft and branch vessels were not included in the analysis. The mean duration between the two coronary angiographies was 58 ±41 months.

Patients treated with percutaneous coronary intervention during the first coronary angiography were considered to be completely revascularized. If a new obstructive or non-obstructive lesion developed subsequently, the patient was considered to have progression of CAD. Side branch stenosis was not considered because we could not reliably use side branches to determine progression of CAD and because side branch stenosis does not carry the same prognosis as major branch stenosis.

The reasons for the first coronary angiography were not recorded in the outpatient charts for all patients. The CAD was considered obstructive if the diameter stenosis was ≥ 50% and non-obstructive if the diameter stenosis was < 50%.

For every patient, progress notes of all interim visits, letters of correspondence, medication usage, blood pressure, and laboratory studies including all serum lipid levels from the time of initial presentation to the last follow-up were recorded. Patient co-morbidities were recorded, including CAD, hyperlipidemia, hypertension, diabetes mellitus, cigarette smoking history, congestive heart failure, angina, atrial fibrillation, chronic kidney disease, peripheral arterial disease, abdominal aortic aneurysm, carotid stenosis, transient ischemic attack, and stroke. Dates of the events as well as dates of medication initiation and discontinuation were recorded. Blood pressure was recorded at least once a year, and more frequently if a patient had active management for hypertension.

Statistical analysis

Characteristics between the two groups were then compared and analyzed. Medication use, blood pressure, serum LDL cholesterol levels, other coronary risk factors, and comorbidities at the time of the second coronary angiography were used for analysis.

Data were extracted by the physician authors and tabulated with Microsoft Access 2003 (Microsoft Corporation, Redmond, WA, USA). Data analysis was performed with Microsoft Excel 2003. A p-value of < 0.05 was considered statistically significant.

Student's t tests were used for continuous variables. χ^2 tests were used for dichotomous variables. Logistic regression analysis and Cox regression analysis were also used but were unable to predict progression of CAD because of the similar baseline characteristics and medication use between both groups.

Results

Table I shows the baseline characteristics including age, gender, follow-up time, time between the two coronary angiographies, coronary risk factors, and comorbidities in 108 patients with progression of CAD and in 75 patients with no progression of CAD. Table I also lists levels of statistical significance. The median time between the 2 coronary angiographies were 56 months for the progression of CAD group and 42 months for the group with no progression of CAD. Table II shows the prevalence of use of 23 medications in the patients with and without progression of CAD. There was no significant difference in use of any of these medications between the patients with and without progression of CAD.

Table III shows that patients with progression of CAD had an insignificantly higher systolic blood

Table I. Baseline characteristics of patients with and without progression of coronary artery disease

Parameter	Progressive coronary artery disease	No progressive coronary artery disease	Value of *p*
Number	108 (59%)	75 (41%)	
Age [years]	71 ±10	72 ±11	NS
Men	75 (69%)	56 (75%)	NS
Women	33 (31%)	19 (25%)	NS
Follow-up [months]	135 ±59	116 ±59	0.04
Time between two angiographies [months]	64 ±43	50 ±37	0.02
Years of follow-up	1978-2008	1985-2008	
Coronary artery disease	105 (97%)	73 (97%)	NS
Hyperlipidemia	104 (96%)	70 (93%)	NS
Hypertension	96 (89%)	57 (76%)	0.03
Diabetes mellitus	34 (31%)	24 (32%)	NS
Smoker	53 (49%)	29 (39%)	NS
Congestive heart failure	8 (7%)	21 (28%)	0.0006
Angina	16 (15%)	19 (25%)	0.09
Atrial fibrillation	16 (15%)	14 (19%)	NS
Carotid stenosis	6 (6%)	4 (5%)	NS
Stroke	10 (9%)	5 (7%)	NS
Transient ischemic attack	9 (8%)	6 (8%)	NS
Chronic kidney disease	2 (2%)	4 (5%)	NS
Peripheral arterial disease	3 (3%)	10 (13%)	0.01

NS – not significant

pressure ($p = 0.06$), a significantly higher diastolic blood pressure ($p = 0.01$), a significantly higher mean blood pressure ($p = 0.01$), and an insignificantly higher serum LDL cholesterol ($p = 0.09$) at the time of the second coronary angiography than the patients with no progression of CAD. The other coronary risk factors listed in Table I did not show a significant difference or borderline significant difference between both groups. Hemoglobin A_{1c} levels were not measured in all diabetics.

Discussion

The CASS Study showed that diabetes and elevated serum total cholesterol level were associated with CAD progression [4]. Reduction of LDL cholesterol by statins reduces progression of CAD diagnosed by coronary angiography [4-7]. Hypertension increases progression of CAD diagnosed by coronary angiography [8, 9]. No significant difference in progression of CAD by coronary angiography was found in patients treated with perindopril vs. placebo in the EUROPA trial [10]. The rate of progression of coronary atherosclerotic plaque diagnosed by intravascular ultrasound was similar in 251 women and in 727 men treated with intensive risk factor modification [20].

In 298 patients in the Emory Angioplasty Versus Surgery trial, native CAD progression was independently correlated with hypertension (odds ratio = 2.4, $p = 0.03$) and with percent of small LDL particles (odds ratio = 1.2 for every 5% increase, $p = 0.01$) [21]. At 5-year follow-up of 392 patients who underwent coronary artery bypass surgery, percutaneous coronary intervention, or medical therapy, multivariate Cox proportion regression analysis showed that hypertension was a significant independent risk factor for native CAD progression (hazard ratio = 1.3, $p = 0.048$) [9].

The Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial investigators stated that the extent to which recurrent events in patients with stable CAD is due to progression of a lesion with ≥ 50% diameter stenosis but not revascularized or < 50% diameter stenosis during optimal medical therapy is unknown [22]. The findings from this study underscore the need for improved therapies to arrest progression of CAD and reliable strategies for selecting stenoses warranting percutaneous coronary intervention [22].

The data from the present study shows that patients with progression of CAD had a significantly higher prevalence of hypertension at baseline ($p = 0.03$) than the patients with no progression of

Table II. Medication use in patients with and without progression of coronary artery disease

Parameter	Progressive coronary artery disease	No progressive coronary artery disease	Value of *p*
Statins	80 (74%)	55 (73%)	NS
Ezetimibe	19 (18%)	9 (12%)	NS
Nicotinic acid	1 (1%)	1 (1%)	NS
Bile acid sequestrants	0 (0%)	0 (0%)	NS
Fibrates	4 (4%)	4 (5%)	NS
Fish oil	2 (2%)	2 (3%)	NS
β-Blockers	85 (79%)	61 (81%)	NS
Diuretics	23 (21%)	25 (33%)	NS
Angiotensin-converting enzyme inhibitors	49 (45%)	32 (43%)	NS
Angiotensin receptor blockers	18 (17%)	18 (24%)	NS
Calcium channel blockers	43 (40%)	24 (32%)	NS
Aspirin	86 (80%)	60 (80%)	NS
Ticlopidine	2 (2%)	0 (0%)	NS
Clopidogrel	18 (17%)	11 (15%)	NS
Aspirin/extended-release dipyridamole	1 (1%)	1 (1%)	NS
Warfarin	10 (9%)	9 (12%)	NS
Nitrates	25 (23%)	23 (31%)	NS
Digoxin	11 (10%)	5 (7%)	NS
Cilostazol	0 (0%)	1 (1%)	NS
Insulin	5 (5%)	8 (11%)	NS
Thiazolidinediones	8 (7%)	8 (11%)	NS
Sulfonylureas	20 (19%)	9 (12%)	NS
Metformin	15 (14%)	10 (13%)	NS

NS – not significant

Table III. Blood pressure and serum low-density lipoprotein cholesterol levels in patients with and without progression of coronary artery disease

Parameter	Progressive coronary artery disease	No progressive coronary artery disease	Value of *p*
Systolic blood pressure	135 ±20	130 ±18	0.06
Diastolic blood pressure	77 ±12	73 ±11	0.01
Mean arterial blood pressure	97 ±13	92 ±12	0.01
LDL-C level	94 ±40	81 ±34	0.09

LDL-C – low-density lipoprotein cholesterol

CAD. At the time of the second coronary angiography, the patients with progression of CAD had an insignificantly higher systolic blood pressure ($p = 0.06$), a significantly higher diastolic blood pressure ($p = 0.01$), a significantly higher mean blood pressure ($p = 0.01$), and an insignificantly higher serum LDL cholesterol ($p = 0.09$) than the patients with no progression of CAD. These data are consistent with those previously reported [4-9, 21].

A limitation of this study is that it is a retrospective study. The long time gap between the two coronary angiographies is a strength of this study. However, the longer time may have contributed to the progression of CAD. Another strength of this study is that we knew the dosage of all drugs used, the duration of their administration, and the compliance of medication use as well as the blood pressure and serum lipid levels throughout the study.

On the basis of the previously reported data [5-9, 21] and the data from the present study, patients with CAD should have their blood pressure controlled according to recommended guidelines

[23] and their serum LDL cholesterol reduced according to recommended guidelines [24].

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