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Severity of Angina Pectoris and Risk of Ischemic Stroke

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Background and Purpose—Ischemic stroke and coronary heart disease (CHD) share risk factors and pathogenic process, ie, atherosclerosis and thrombosis. We examined the relationship between severity of angina pectoris and its accompanying characteristics and the risk of incident ischemic stroke.

Methods—We traced 3122 patients with stable CHD, included in a secondary prevention trial of lipid modification, the Bezafibrate Infarction Prevention trial. CHD was documented by a history of myocardial infarction ≥ 6 months and < 5 years before enrollment and/or stable angina pectoris with evidence of ischemia confirmed by ancillary diagnostic testing. Severity of angina pectoris was assessed according to the Canadian Cardiovascular Society angina classification, and heart failure functional class according to the New York Heart Association (NYHA) classification. Patients with severe heart failure or unstable angina on enrollment were excluded.

Results—During a mean follow-up period of 8.2 years, 186 patients developed an ischemic stroke. The cumulative rate of ischemic stroke increased in a dose-response manner from 4.7% in patients with no angina to 5.7%, 8.4%, and 12.9% in patients with angina classes 1, 2, and 3, respectively ($P < 0.001$). Patients with NYHA functional class 1 had a 5.5% rate of ischemic stroke versus 7.3% and 9.6% in patients with classes 2 and 3, respectively ($P = 0.05$). In a Cox proportional-hazard model adjusting for conventional risk factors and potential confounders, the hazard ratio associated with angina class 1 was 1.20 (95% CI, 0.83 to 1.74); class 2, 1.66 (95% CI, 1.12 to 2.45); and class 3, 2.35 (95% CI, 1.08 to 5.13), as compared with patients with no angina. Hazard ratios of ischemic stroke associated with conventional risk factors were 1.55 for a 10-year age increment, 2.16 for diabetes mellitus, 1.81 for current smoking, and 1.29 for a 20 mm Hg increase in systolic blood pressure.

Conclusions—Severity of angina pectoris in patients with stable CHD predicts an increased risk of subsequent ischemic stroke. The association between angina class and incident ischemic stroke is independent of traditional vascular risk factors. (*Stroke*. 2002;33:245-250.)

Key Words: angina pectoris ■ atherosclerosis ■ coronary heart disease ■ risk factors ■ stroke, ischemic

Ischemic stroke and coronary heart disease (CHD) are among the leading causes of morbidity, mortality, and health care expenditure in adults. Both diseases share risk factors and pathogenic processes, ie, atherosclerosis and thrombosis. The presence of cerebrovascular disease is strongly associated with the presence of symptomatic and asymptomatic CHD.¹⁻³ The risks of major thrombotic and thromboembolic complications are related to the extent of atherosclerosis but also to the stability of the atherosclerotic plaque.^{4,5} There are multiple additional specific cause-and-effect relationships between manifestations of ischemic heart disease such as left ventricular wall-motion abnormalities with thrombus formation, congestive heart failure, and risk of ischemic stroke. There are few data, however, on the association between severity of angina and functional capacity and the risk of ischemic stroke during long-term follow-up in a

large cohort of patients. We therefore prospectively assessed the risk of incident ischemic stroke associated with the severity and evolution of angina pectoris and its accompanying characteristics in patients with stable CHD. Analyses were based on the cohort of patients included in the Bezafibrate Infarction Prevention (BIP) study and poststudy follow-up, serving as an opportunity to investigate the risk of stroke associated with attributes of stable CHD.

Methods

The BIP study was a placebo-controlled randomized clinical trial investigating the efficacy of bezafibrate Retard 400 mg daily in secondary prevention in a cohort of patients with established chronic CHD.⁶ The study included 3122 men and women 45 to 74 years of age with a history of myocardial infarction at least 6 months and not longer than 5 years before enrollment and/or stable angina pectoris during the last 2 years confirmed by coronary angiography, and/or

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radionuclear studies or standard exercise tests. In addition, the lipid profile of participants at inclusion was as follows: serum total cholesterol 180 to 250 mg/dL, low-density lipoprotein-cholesterol ≤ 180 mg/dL (≤ 160 mg/dL for patients < 50 years), high-density lipoprotein-cholesterol ≤ 45 mg/dL, and triglycerides ≤ 300 mg/dL. Main exclusion nonlipid criteria were insulin-dependent diabetes mellitus, hepatic or renal failure, and disabling stroke.

Angina severity at baseline was classified according to the Canadian Cardiovascular Society classification (CCSC),⁷ and heart failure functional class according to the New York Heart Association (NYHA) classification.⁸ In the CCSC for angina, class 1 indicates no limitation to normal activity and angina provoked by prolonged exertion, whereas class 4 indicates severe limitation to normal activity and angina provoked by minimal activity or at rest. In the NYHA classification, class 1 indicates no limitation, ie, ordinary physical activity does not cause undue fatigue, dyspnea, or palpitation, whereas class 4 indicates inability to carry on any physical activity without discomfort, ie, symptoms of congestive failure are present even at rest, and with any physical activity, increased discomfort is experienced. Canadian angina class 4 or NYHA class 4 at baseline was also a criterion for exclusion.

The patients were routinely followed up every 4 months during the study period. Follow-up continued for an overall mean of 8.2 years (range 6.7 to 9.6 years). Myocardial infarction, hospitalization for unstable angina, percutaneous transluminal coronary angioplasty, and coronary artery bypass graft were prospectively monitored. A Critical Event Committee, whose members were blinded to the treatment assignment, reviewed primary end points and all cases of mortality to determine their likely underlying cause.

Data on the occurrence of new cerebrovascular events were routinely obtained during these evaluations. Records from hospital or emergency department discharge, primary care physician, or neurologist were reviewed. Clinical data related to the new cerebrovascular event, results of brain CT scan and other available ancillary tests for assessment of stroke classification, and functional outcome were recorded on standardized forms. Data were centrally reviewed by the study stroke neurologist (D.T). Stroke was defined according to World Health Organization criteria⁹ as rapidly developing clinical signs of focal disturbance of cerebral function with symptoms lasting > 24 hours or leading to death, with no apparent cause other than that of vascular origin. Stroke type was differentiated by results of CT scan into ischemic stroke and intracerebral hemorrhage. Cases in which brain imaging was not available were regarded as stroke of undetermined origin. Study physicians assessed functional outcome by the modified Rankin scale during follow-up visits.¹⁰ Stroke severity was defined as minor for cases in which the modified Rankin score was 0 or 1, major for a score of 2 or more, and fatal for 30-day case fatality.

Statistical Analysis

Statistical analysis was performed using SAS software.¹¹ The distributions of categorical and continuous variables were compared using χ^2 and *t* test or ANOVA test respectively. To categorize the type of cerebrovascular event, a single event was used for each patient, with stroke taking precedence over transient ischemic attack and intracerebral hemorrhage taking precedence over ischemic stroke. Cox proportional-hazard models of incident ischemic stroke were used (PHREG procedure), adjusting for differences in covariates comparing with all patients without an ischemic stroke. Adjustments were done for age, gender, diabetes mellitus, current smoking, systolic blood pressure, prior myocardial infarction, angina pectoris class, NYHA class, antihypertensive medications, antiplatelets, and BIP study arm (bezafibrate versus placebo). In additional models, we adjusted also to peripheral vascular disease and to plasma fibrinogen levels. Atrial fibrillation was present in $< 0.5\%$ of electrocardiograms performed at baseline and was therefore not included in further analyses. The cumulative incidence of ischemic stroke by angina pectoris class was computed using the Kaplan-Meier method.

TABLE 1. Baseline Characteristics of Patients With and Without Ischemic Stroke

	Ischemic Stroke (n=186)	Others (n=2936)	P
Age (years)	61.8 \pm 6.1	60.0 \pm 6.8	< 0.001
Male sex	173 (93%)	2362 (91%)	
Body mass index (kg/m ²)	26.8 \pm 3.4	26.7 \pm 3.3	0.63
Current smoking	32 (17%)	338 (12%)	0.02
Systolic BP (mm Hg)	138 \pm 20	133 \pm 18	< 0.001
Diastolic BP (mm Hg)	82 \pm 10	81 \pm 9	0.09
Total cholesterol (mg/dL)	213 \pm 18	212 \pm 18	0.56
LDL cholesterol (mg/dL)	149 \pm 16	149 \pm 17	0.95
HDL cholesterol (mg/dL)	34.2 \pm 5.2	34.6 \pm 5.5	0.34
LDL/HDL	4.4 \pm 0.8	4.4 \pm 0.9	0.58
Triglycerides (mg/dL)	151 \pm 53	145 \pm 51	0.11
Fibrinogen (mg/dL)	373 \pm 75	349 \pm 73	< 0.001
Leukocytes ($\times 10^3/\mu\text{l}$)	7.0 \pm 1.7	6.8 \pm 1.9	0.28
Angina class [*] ≥ 2	64 (34%)	665 (23%)	< 0.001
NYHA ≥ 2	58 (31%)	696 (24%)	0.029
Bezafibrate	92 (49%)	1472 (50%)	0.86
History of			
Diabetes	36 (20%)	275 (9%)	< 0.001
Hypertension	80 (43%)	930 (32%)	0.001
Peripheral vascular disease	12 (7%)	95 (3%)	0.02
Prior myocardial infarction	150 (81%)	2284 (78%)	0.30

NYHA indicates New York Heart Association functional class; BP, blood pressure; LDL, low-density lipoprotein, and HDL, high-density lipoprotein. Continuous data are expressed as mean \pm SD, noncontinuous data as number (%).

^{*}Angina class according to the Canadian Cardiovascular Society angina classification.

Results

During a mean follow-up period of 8.2 years, 253 of the 3122 patients with chronic CHD had experienced at least 1 cerebrovascular event (overall rate 8.1%). Fifty-one patients (1.6%) had transient ischemic attack, 186 patients (6.0%) ischemic stroke, 11 patients (0.4%) intracerebral hemorrhage, and 5 patients (0.2%) stroke of undetermined origin. More than 95% of cases with a determined cerebrovascular event were of ischemic origin (ischemic stroke or transient ischemic attack). There were no significant differences between the bezafibrate and placebo arms in the risk of ischemic stroke or transient ischemic attacks.⁶ Mortality during the overall follow-up period was 15% (419 of 2869) among patients with no cerebrovascular event, 27% (50 of 186) among patients with ischemic stroke, and as high as 64% (7 of 11) among patients with intracerebral hemorrhages.

Patients who subsequently experienced ischemic strokes were older; more often were smokers; had more frequently a history of diabetes mellitus, hypertension, or peripheral vascular disease; and had higher systolic blood pressure measurements and plasma fibrinogen levels (Table 1). Their angina severity according to the CCSC and functional class according to the NYHA were more often higher. Baseline characteristics by severity of angina are summarized in Table

TABLE 2. Baseline Characteristics of Patients by Angina Severity*

	No Angina (n=1476)	Angina Class 1 (n=917)	Angina Class 2 (n=667)	Angina Class 3 (n=62)	P
Age, y	59.8±6.9	60.3±6.8	60.4±6.4	60.8±5.7	0.13
Male sex	1374 (93)	837 (91)	588 (88)	56 (90)	0.02
Body mass index (kg/m ²)	26.4±3.2	26.9±3.2	27.0±3.5	28.0±3.9	<0.001
Current smoking	162 (11)	114 (12)	84 (13)	10 (16)	0.42
Systolic BP (mm Hg)	132±17	134±11	135±18	140±18	<0.001
Diastolic BP (mm Hg)	81±9	81±9	82±9	82±8	0.17
Total cholesterol (mg/dL)	213±18	212±17	213±18	212±20	0.78
LDL cholesterol (mg/dL)	149±16	148±16	149±17	148±17	0.22
HDL cholesterol (mg/dL)	34.7±5.6	34.6±5.5	34.3±5.4	34.4±5.3	0.56
LDL/HDL	4.4±0.9	4.4±0.9	4.5±0.9	4.4±0.9	0.41
Triglycerides (mg/dL)	143±50	147±51	146±52	148±45	0.25
Fibrinogen (mg/dL)	350±72	347±76	353±71	369±74	0.08
Leukocytes (×10 ³ /μL)	6.8±1.7	6.9±2.4	6.9±1.8	6.7±1.5	0.49
NYHA ≥2	176 (12)	192 (21)	336 (50)	50 (81)	<0.001
Bezafibrate	731 (50)	459 (50)	341 (51)	33 (53)	0.87
History of					
Diabetes	123 (8)	106 (12)	76 (11)	6 (10)	0.36
Hypertension	457 (31)	298 (33)	231 (35)	24 (39)	0.26
Peripheral vascular disease	41 (3)	34 (4)	28 (4)	4 (7)	0.16
Prior myocardial infarction	1297 (88)	619 (68)	474 (71)	44 (71)	<0.001

NYHA indicates New York Heart Association functional class; BP, blood pressure; LDL, low-density lipoprotein, and HDL, high-density lipoprotein. Continuous data are expressed as mean±SD, noncontinuous data as number (%).

*Angina class according to the Canadian Cardiovascular Society angina classification.

2. Patients with more severe angina were more often female, had higher mean body mass index, and had systolic blood pressure and a borderline trend toward higher plasma fibrinogen levels. They had less often a history of prior myocardial infarction and more often a NYHA functional class ≥2.

Rates of ischemic stroke increased significantly with higher angina class and NYHA functional class (Figure 1). The cumulative incidence of ischemic stroke increased in a dose-response manner from 4.7% in patients with no angina to 5.7%, 8.4%, and 12.9% in patients with angina classes 1, 2, and 3, respectively ($P<0.001$). Patients with NYHA functional class 1 had a 5.5% cumulative incidence of ischemic stroke versus 7.3% and 9.6% in patients with classes 2 and 3, respectively ($P=0.05$). The Kaplan-Meier curves for the cumulative incidence of ischemic stroke by the severity of angina pectoris are depicted in Figure 2.

In a Cox proportional-hazard model adjusting to conventional vascular risk factors, diabetes mellitus was associated with a >2-fold increased risk of ischemic stroke, and cigarette smoking with a nearly 2-fold increased risk (Table 3). Risks increased, as expected, with increasing age and blood pressure. Compared with patients with no angina, the hazard ratios associated with angina classes 1, 2, and 3 were 1.20, 1.66, and 2.35 respectively. In a separate model adjusting in addition to presence of peripheral vascular disease and to baseline plasma fibrinogen levels, the hazard ratios were mildly attenuated to 1.26 (95% CI, 0.86 to 1.85), 1.71 (95% CI, 1.14 to 2.54), and 1.56 (95% CI, 0.60 to 4.07), respectively. Because of the high colinearity between severity of

angina and NYHA class, adjusting for both may result in underestimation of the true risks. We therefore conducted, in addition, separate models for angina class and for NYHA class, adjusting for all other confounding variables. The hazard ratios associated with angina classes 1, 2, and 3, compared with no angina, were 1.22 (95% CI, 0.84 to 1.77), 1.79 (95% CI, 1.25 to 2.57), and 2.69 (95% CI, 1.28 to 5.65),

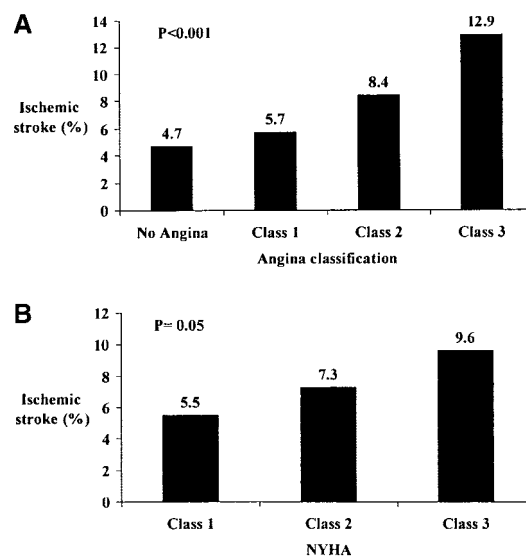


Figure 1. a, Rates of ischemic stroke by severity of angina pectoris, according to CCSC. b, Rates of ischemic stroke according to NYHA functional class.

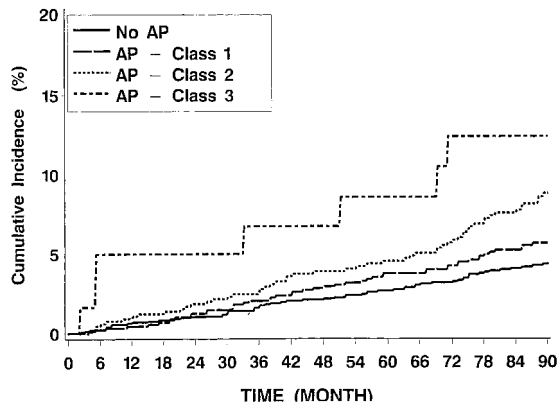


Figure 2. Kaplan-Meier curves for cumulative incidence of ischemic stroke by severity of angina pectoris according to CCSC. AP indicates angina pectoris.

respectively. The hazard ratio associated with NYHA class 2 or 3, compared with NYHA class 1, was 1.50 (95% CI, 1.10 to 2.05). No significant interactions were identified between angina severity and NYHA class.

During follow-up 277 patients were hospitalized for unstable angina. In 9 patients the unstable angina occurred after the index ischemic stroke. Among the remaining 268 patients the rate of ischemic stroke was 6.7% (18 patients), compared with 5.9% among patients free of unstable angina (168 patients; $P=0.60$). Higher angina class at baseline was associated with increasing risk of being hospitalized during follow-up for unstable angina, of developing a myocardial infarction, of requiring a percutaneous coronary intervention or a coronary bypass graft operation, or of dying from a cardiac cause ($P<0.05$ for all; data not tabulated). Unstable angina developing during follow-up did not predict independently subsequent ischemic stroke (hazard ratio=1.1; 95% CI, 0.67 to 1.78) in a Cox proportional-hazard model adjust-

TABLE 3. Cox Proportional Hazard Model for Prediction of Ischemic Stroke

		Hazard Ratio	95% CI
Age	Per 10 years	1.55	1.22–1.96
Male gender		1.55	0.87–2.74
Diabetes mellitus		2.16	1.49–3.12
Current smoking		1.81	1.23–2.68
Systolic BP	Per 20 mm Hg	1.29	1.10–1.51
Prior myocardial infarction		1.49	1.02–2.18
Angina class 1*		1.20	0.83–1.74
Angina class 2*		1.66	1.12–2.45
Angina class 3*		2.35	1.08–5.13
NYHA ≥ 2		1.21	0.86–1.72
Antihypertensive medications		0.93	0.23–3.79
Antiplatelets		0.85	0.62–1.15
Study medication (bezafibrate vs placebo)		0.94	0.70–1.25

BP indicates blood pressure.

*Angina pectoris class according to the CCSC compared with patients with no angina.

ing for conventional vascular risk factors and the angina class at baseline. Nonfatal myocardial infarction or need for revascularization during follow-up also did not predict independently an increased risk of incident ischemic stroke. No statistically significant differences were found in the distribution of ischemic stroke subtypes (cardioembolic or not), severity (according to the modified Rankin scale), or vascular territory involved (anterior versus posterior circulation) by angina severity.

Discussion

Our results demonstrate that, among patients with chronic CHD, higher severity of angina pectoris class predicted an increased risk of incident ischemic stroke. This relationship between angina class and subsequent ischemic stroke was independent of traditional cardiovascular risk factors. Approximately half of the strokes were severe with poor functional outcome. Mortality during follow-up was 2-fold higher among patients experiencing a stroke.

Atherosclerosis and thrombosis are important pathological processes underlying both CHD and ischemic stroke. Development of carotid atherosclerosis closely parallels coronary atherosclerosis, and both are associated with aortic arch atherosclerosis.^{12,13} Calcifications of the mitral and aortic valves, common in patients with CHD, are also associated with carotid atherosclerosis and may represent widespread systemic atherosclerosis.^{14,15} The presence of cerebrovascular disease is strongly associated with the presence of symptomatic and asymptomatic cardiac disease.^{1–3} Carotid artery stiffness, intima-media thickness, and early plaque formation are potentially useful predictors of the risk of both ischemic stroke and CHD.^{16–19} Carotid arterial wall disease is also a useful predictor of coronary artery disease on angiography and subsequent coronary vascular events in populations at risk of CHD.^{20,21} Myocardial infarction is a leading cause of death in patients who recover from strokes or transient ischemic attacks. Asymptomatic coronary artery disease is most often identified among patients with stroke due to large-vessel atherothrombosis.³

There are few data, however, on the relationship between severity of angina and functional capacity and the risk of ischemic stroke during long-term follow-up in a large cohort of patients. In the Framingham study, history of CHD almost tripled the risk of a stroke. CHD increased stroke risk in the absence of hypertension or cardiac failure, but risk was greatly augmented when these coexisted.²² Among men 40 to 59 years of age, randomly selected from 24 general practices in Britain and classified into CHD groups, the association of disease group with a range of fatal and nonfatal outcomes during 15 years of follow-up was assessed.²³ Different manifestations of prevalent CHD were associated with widely differing outcomes. There are specific etiologies for stroke after acute myocardial infarction. The risk of stroke is highest within the first weeks after an acute myocardial infarction.^{24,25} Strokes occurring several weeks after myocardial infarction may result from chronic left ventricular thrombi, an akinetic left ventricular segment, or left ventricular dysfunction, due to atrial fibrillation or due to atherosclerotic disease.²⁶ For every decrease of 5% in the ejection fraction, an

18% increase in the risk of long-term stroke has been found.²⁷ In our study cohort, higher NYHA class was associated with higher risk of ischemic stroke.

The development of atherosclerosis is a chronic process accelerated in part by hypertension, cigarette smoking, diabetes, and hyperlipidemia. However, the risks of the major thrombotic and thromboembolic complications of atherosclerosis appear to be related more to the stability of atheromatous plaques than to the extent of disease. Unstable angina, acute myocardial infarction, and sudden cardiac death are almost invariably associated with irregular or ruptured plaques. Similarly, in patients with carotid artery atherosclerotic disease, plaque irregularity and rupture are closely associated with the occurrence of cerebral ischemic events, and patients with irregular or ulcerated plaques on carotid angiography have a higher risk of ischemic stroke irrespective of the degree of stenosis of the vessel lumen.^{28,29} The factors that influence the stability of plaques include local factors and systemic factors such as inflammation, infection, autoimmune factors, or genetic susceptibility.^{4,30} Indeed, clustering of unstable atheromatous plaques within certain individuals was demonstrated.⁵

In our study cohort, the severity of angina predicted subsequent risk of ischemic stroke. This increased risk persisted after adjusting for conventional vascular risk factors. It was somewhat attenuated after adjusting for peripheral vascular disease, another manifestation of generalized atherosclerosis, and for plasma fibrinogen, a marker of inflammation. Therefore, widespread atherosclerosis and inflammation, and clustering of unstable atheromatous plaques, may underlie in part the increased risk observed.

The limitations of our study include lack of systematic ancillary laboratory investigations to assess the degree of coronary or cerebrovascular atherosclerosis, as well as to quantify left ventricular function and wall-motion abnormalities. The increased incidence of stroke early after myocardial infarction could potentially confound the association with severity of angina. Our study cohort included, however, patients with stable CHD, at least 6 months after their myocardial infarction, thereby excluding the possibility of these events influencing the rate of stroke. The current analysis is limited to patients with stable CHD included in a clinical trial and with a selected lipid profile. Atrial fibrillation, a strong established risk factor for ischemic stroke, was rarely present in the electrocardiograms performed at baseline in the current study cohort of selected patients with stable CHD. Atrial fibrillation was therefore not included in further analysis, and was an unlikely confounder of our findings. Despite these limitations, our study provides strong evidence for an association between severity of angina pectoris and incident ischemic stroke.

Our findings are in agreement with a large body of evidence demonstrating that atherothrombosis and its consequences are a generalized process. They provide indirect support to the contention that development of atherosclerotic plaque instability is influenced by systemic factors that are present in a proportion of patients, independent of traditional cardiovascular risk factors. Implications of the present study are that patients at high angina class should be regarded at

high risk also of ischemic stroke. Screening for cerebrovascular atherosclerosis should be considered in these patients, and aggressive preventive measures used to prevent both acute coronary syndromes and ischemic stroke in this high-risk population.

Acknowledgment

A complete list of the BIP Study Group members has been previously published.⁶

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