ORIGINAL ARTICLE

Coronary artery disease is not associated with stroke recurrence

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Submitted: 2011-12-02 Accepted: 2012-02-15 Published online: 2012-05-27

Key words: **coronary artery disease; epidemiology; risk factors; stroke; recurrence**

Neuroendocrinol Lett 2012; **33**(3):294–297 **PMID:** 22635087 NEL330312C10

Abstract

BACKGROUND: Coronary artery disease (CAD) is a leading cause of long-term mortality in Europe and it negatively influences the outcome after stroke. However, its influence on stroke recurrence which endangers stroke patients mostly in the first months following stroke, is unclear. Previous studies have found no association between CAD and ischemic stroke recurrence. However, assessment of the relationship was not the primary endpoint of these investigations. The aim of this study was to assess the possible association between CAD and stroke recurrence.

PATIENTS AND METHODS: In a hospital-based, retrospective study, the set consisted of 190 patients – 105 patients with a first ever stroke (48 males; age 37–88, mean 70.7±12.5 years) and 85 patients with stroke recurrence (36 males; age 46–94, mean 88.0±9.6 years). CAD was correlated with the following other risk factors (age, sex, occurrence of arterial hypertension, atrial fibrillation, diabetes mellitus, plasma levels of total cholesterol, triglycerides, low-density cholesterol, high-density cholesterol, body mass index, presence of carotid plaques). Logistic regression analysis was used for the statistical evaluation.

RESULTS: No significant association was found between CAD and stroke recurrence. Of all of the other observed risk factors, only age showed a significant association with stroke recurrence (OR 1.04, 95% CI: 1.02–1.07).

CONCLUSION: The results of the presented study indicate that CAD does not influence stroke recurrence.

INTRODUCTION

Neurologists often tend to concentrate on the brain and do not give enough attention to patients´ cardiac condition. According to current knowledge, the presence of coronary artery disease (CAD) strongly influences the outcome and prognosis in patients who have suffered from an ischemic stroke (IS) (ESPS group 1990; Hass *et al.* 1989; Diener *et al.* 1996; CAPRIE Steering Committee 1996; Fischer *et al.* 2006). Additionally, CAD represents a major cause of long-term mortality in stroke patients. However, stroke recurrence endangers patients mostly in the first weeks after IS and CAD might have an important impact on this. If CAD is associated with higher stroke recurrence, effective CAD treatment might lead to more efficient secondary prevention and reduction of stroke recurrence. However, previous studies quite surprisingly indicate, that there might be no such association (Ois *et al.* 2008; Johnston *et al.* 2000; Johnston *et al.* 2003; Hillen *et al.* 2003). On the other hand, assessment of the relationship between CAD and stroke recurrence was not the primary endpoint in these investigations. The aim of the present study was to assess a possible association between stroke recurrence and CAD in IS patients.

PATIENTS AND METHODS

A retrospective, hospital based, single centre study was used. Discharge reports of 191 patients admitted to the Department of Neurology, Hospital Liptovský Mikuláš, Slovakia, from December 2007 to January 2009 with acute IS were systematically reviewed. The sample consisted of 190 patients – 105 patients with the first ever stroke – Subgroup 1 (48 males; age 37–88, mean 70.7±12.5 years) and 85 patients with stroke recurrence – Subgroup 2 (36 males; age 46–94, mean 88.0±9.6 years). The diagnosis of IS was based on the clinical and computed tomography (CT) findings (neurological deficit and corresponding acute ischemic area on CT scan) according to the WHO criteria (Aho *et al.* 1980) and was made by an experienced neurologist. The diagnosis of clinical manifest CAD was made by a senior internal medicine specialist on the basis of the clinical (history of angina pectoris symptoms) and electrocardiography (ECG) findings (ST segment changes, presence of Q wave) (Tunstall-Pedoe *et al.* 1994). Stroke recurrence was defined either as a new neurological deficit or a deterioration of the previous neurological deficit which had to match previously mentioned criteria. In both subgroups of patients, the following were recorded: age; sex; occurrence of arterial hypertension (diagnosis previously established by internist or previous antihypertensive treatment or blood pressure values >140/90 mm Hg during the last three days of hospitalization, but not earlier than on the 5th day), atrial fibrillation (AF), diabetes mellitus (either fasting blood glucose ≥6.1 mmol/l or treatment with insulin, oral anti-diabetics or on diet); plasma levels of total cholesterol (mmol/l), triglycerides (mmol/l), low-density cholesterol (mmol/l), high-density cholesterol (mmol/l) (Oravec *et al.* 2011); body mass index (weight/height^2) value; presence of carotid plaques on ultrasound examination. Other RF such as smoking or other medication were also recorded but they were later excluded due to missing data.

In order to control for confounding factors, multivariable logistic regression analysis (SAS Institute Inc., Cary, NC, USA) was used. The odds ratios for risk factors with confidence interval of 95% were calculated.

RESULTS

Based on the previously mentioned criteria, 190 consecutive IS patients were included in the study and divided into two subgroups – 105 patients with first ever IS (Subgroup 1) and 85 patients with recurrent stroke (Subgroup 2). All patients were Caucasians. Subgroups where quite homogenous, although Subgroup 2 patients were older than Subgroup 1 patients (mean 88.0±9.6 versus 70.7±12.5 years). Comparisons of the occurrence of the observed factors in the particular subgroups are shown in Table 1.

CAD was present in 65.7% of Subgroup 1 and in 82.4% of Subgroup 2 patients. In the univariable analysis, CAD showed no statistically significant association with stroke recurrence (χ^2=1.0185, p=0.3128), as shown in Table 2. However, the univariable statistical analysis included the confounding factors and did not take other

Tab. 1. Characteristics of the study participants and occurrence of the observed risk factors.

Characteristic	Subgroup 1 (first stroke)	Subgroup 2 (recurrent stroke)
Study participants #	105	85
CAD presence # (%)	69 (65.7%)	70 (82.4%)
Males # (%)	48 (45.7%)	36 (42.6%)
Age - years	70.7±12.5	88.0±9.6
BMI - (kg/m^2)	30.1±6.1	28.5±3.5
Total cholesterol - (mmol/l)	5.1±1.3	5.0±1.5
TG - (mmol/l)	1.8±1.3	1.3±0.9
LDL - (mmol/l)	3.4±1.1	3.2±1.5
HDL - (mmol/l)	1.1±0.4	1.2±0.3
Arterial hypertension - # (%)	91 (86.7%)	77 (90.6%)
Diabetes mellitus - # (%)	34 (32.4%)	31 (36.5%)
Carotid stenosis > 50% - # (%)	29 (27.6%)	27 (31.8%)
Atrial fibrillation - # (%)	30 (28.6%)	25 (29.4%)

Plus-minus values are means ± standart deviation,
BMI - body mass index, CAD denotes coronary artery disease,
HDL - high density lipoproteins, LDL - low density lipoproteins,
TG - triglicerides, no - number

Tab. 2. Univariable model for evaluation of association between coronary artery disease and stroke reccurence.

Risk Factor	χ^2	*p*-value
Coronary artery disease	1.0185	0.3128

Tab. 3. Multivariable analysis for evaluation of association between risk factors and stroke recurrence.

Risk Factor	Odds Ratio	95% Confidence Interval	*p*-value
Age (1 year)	1.04	1.02–1.07	0.003

risk factors into account. For this reason a multivariable model was used.

The multivariable logistic regression analysis model, including other observed risk factors, CAD showed no statistically significant association with stroke recurrence.

Of all other observed factors, only age (OR 1.04, 95% CI: 1.02–1.07) reached statistical significance considering stroke recurrence (Table 3). However, the statistical power was quite weak. No other risk factors showed a significant relationship to CAD occurrence in IS patients and the odds ratios could not be established.

DISCUSSION

The primary endpoint of the presented study showed, in agreement with previously published studies (Ois *et al.* 2008; Johnston *et al.* 2000; Johnston *et al.* 2003; Hillen *et al.* 2003), that stroke recurrence seemed not to be associated with CAD presence. However, the evaluation of this association was not the primary endpoint of the earlier reports.

The possible influence of CAD on stroke recurrence may be explained in two ways – via atherosclerosis and via AF. One may assume, their effect could sum, causing a statistically significant association between CAD and stroke recurrence.

CAD in stroke patients is associated with a more severe degree of atherosclerosis, as previously proven from autopsy studies (Gongora-Rivera *et al.* 2007). More severe atherosclerosis could represent a higher risk for stroke recurrence, for example by a plaque rupture (Ustrell & Pellisé 2010). Atherosclerosis is usually assessed using the intima media thickness measurement in the internal carotid (Barbarash *et al.* 2011; Peters *et al.* 2011; Mookadam *et al.* 2011) or using the measurement of the grade of stenosis (Owen *et al.* 2011). In the present study, the latter measurement was used. More than 50% stenosis of the internal carotid artery was observed in 27.6% of Subgroup 1 patients and in 31.8% of Subgroup 2 patients. No significant association could be found when these data were included in the multivariable analysis.

Non valvular AF may represent another way by which CAD could cause a higher rate of stroke recurrence (Deedwania & Huang 2011; Andersen *et al.* 2008; Aburto-Murrieta *et al.* 2005). AF has been repeatedly proven to be a cause for stroke recurrence by direct cardio-embolism (Gongora-Rivera *et al.* 2007). The association between CAD and AF is clear, as far as CAD may directly cause AF. In the Malmö study, CAD was present in up to 82% of AF patients (Elneihoum *et al.* 1998). In the present study, AF was present in 28.6% of Subgroup 1 and in 29.4% of Subgroup 2 patients. Nevertheless, in a multivariable analysis, AF, as an isolated risk factor, did not reach statistical significance.

As neither the AF nor carotid stenosis had any statistical significance in the multivariable analysis, the same could be expected from CAD in both the multi and univariable statistical model.

From our results, age might be a risk factor for stroke recurrence, although the strength of correlation is low (OR 1.04, 95% CI: 1.02–1.07). This can be again explained by a more severe atherosclerosis or by an accumulation of various risk factors at higher ages. However, previous studies did not identify age to be an independent risk factor for stroke recurrence (Ois *et al.* 2008; Hillen *et al.* 2003).

AF and diabetes mellitus have been repeatedly reported to be independent risk factors for stroke recurrence (Gongora-Rivera *et al.* 2007; Nucifora *et al.* 2009; Lai *et al.* 1994, Hier *et al.* 1991; Sacco *et al.* 1994; Hankey *et al.* 1998). However, their role was not confirmed in the present study. This could be caused by a relatively low number of patients which is the main limitation of the presented study. Its retrospective design should be mentioned as the second limitation.

CONCLUSION

Our results show no association between CAD and stroke recurrence. However, further population based prospective studies with larger numbers of patients are needed to confirm this finding.

ACKNOWLEDGEMENTS

Supported in part by the GAUK grant number 305-10/259079 and by the IGA MH CR grants number NT/11046-6/2010 and NT/11386-5/2010.

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