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The cardiovascular risk of patients with carotid artery stenosis

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SOUHRN

Souvislost mezi postižením koronárních a karotických tepen je všeobecně uznávána. Studie sledující přítomnost ischemické choroby srdeční u pacientů s postižením karotických tepen popisují prevalenci až 77 % v závislosti na studované populaci. Zvýšené kardiovaskulární (KV) riziko je popisováno jak u pacientů s asymptomatickou, tak i symptomatickou stenózou karotidy. Pacienti s asymptomatickou stenózou karotické tepny mají zhruba třikrát vyšší riziko úmrtí z kardiovaskulárních příčin nebo infarktu myokardu v porovnání s referenční populací bez postižení karotických tepen, a toto riziko může být u pacientů se symptomatickou stenózou karotické tepny dokonce ještě vyšší. U těchto pacientů je proto indikována protidestičková a hypolipidemická terapie nejen z důvodu prevence cévní mozkové příhody, ale zejména ke snížení celkového kardiovaskulárního rizika. Revaskularizační výkony na karotických tepnách jsou zavedenou metodou léčby pacientů se symptomatickou stenózou karotické tepny, u kterých vedou k významnému absolutnímu snížení rizika recidivy cévní mozkové příhody. U pacientů s významnou, ale asymptomatickou stenózou karotické tepny zůstává indikace k revaskularizaci sporná. V tomto případě se zdá revaskularizace nejvíc přínosná u těch pacientů, kteří mají přítomny specifické klinické nebo zobrazovací charakteristiky, jež značí zvýšené riziko rozvoje cévní mozkové příhody.
Screening a léčba asymptomatické ischemické choroby srdeční může být prospěšná pro pacienty s nedávno symptomatickou stenózou karotické tepny, zejména v případě, že je v plánu provedení revaskularizačního výkonu na karotických tepnách. Z důvodu nedostatku důkazů o přínosnosti rutinní profylaktické karotické revaskularizace u pacientů s karotickou stenózou podstupujících aortokoronární bypass – CABG (ve smyslu snížení výskytu perioperační cévní mozkové příhody), se jeví jako přínosné omezení profylaktické karotické revaskularizace před CABG pouze na pacienty v nejvyšším riziku perioperační cévní mozkové příhody, tedy ty s významnými bilaterálními stenózami obou karotických tepen nebo s anamnézou předchozí CMP/TIA.

ABSTRACT

It is commonly accepted that a relationship exists between coronary and carotid arterial disease, given that the prevalence of coronary artery disease (CAD) in patients with carotid stenosis is as high as 77%, depending on the population studied. Elevated cardiovascular (CV) risks are apparent in patients with either asymptomatic or symptomatic carotid stenosis. Patients with asymptomatic carotid stenosis are at about a three-fold higher risk of CV death/myocardial infarction compared with a matched population without carotid stenosis, and this risk may be even higher among patients with symptomatic carotid stenosis. Thus, antiplatelet and lipid-lowering therapies are indicated not only to prevent stroke, but also especially to lower elevated CV risks. Carotid revascularization has become well established in patients with symptomatic carotid stenosis, which is associated with significant absolute risk reductions in terms of recurrent stroke, but remains controversial for patients with significant but asymptomatic carotid stenosis. Carotid revascularize-

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tion in those with asymptomatic carotid stenosis seems to principally benefit patients with specific clinical/imaging features indicating a high risk of stroke. Screening and treatment of asymptomatic CAD can be beneficial for patients with recently symptomatic carotid stenosis and especially for those for whom surgical or endovascular carotid revascularization is planned. Because evidence of the benefits afforded by prophylactic revascularization of asymptomatic carotid artery stenosis in all CABG candidates (in terms of reducing perioperative stroke) is lacking, it may be reasonable to restrict prophylactic carotid revascularization to patients at the highest risk of postoperative stroke, thus those with severe bilateral lesions or a history of prior stroke/transient ischemic event.

Introduction

When treating a patient with significant carotid artery disease, it is important to realize that atherosclerosis is a systemic inflammatory vascular disorder involving multiple arterial beds. These patients are threatened not only by stroke; the presence of carotid artery disease places them into very high-risk group for any of several atherosclerotic cardiovascular (CV) events, especially coronary events. The presence of atherosclerotic disease in more than one arterial system is associated with a higher risk of recurrent symptoms and complications, and patients with detectable disease in the coronary and peripheral arteries are at twice the risk of those presenting with coronary artery disease (CAD) alone [1].

Although modern pharmacotherapy and revascularization techniques have markedly improved the prognosis of patients with atherosclerotic vascular disease, atherosclerosis-related CV events and cerebrovascular events remain the causes of death in almost 46% of all cases in developed countries [2]. Detection and treatment of preclinical CAD in patients with significant carotid artery stenosis may improve long-term outcomes and survival, because CAD is a major cause of death not only during follow-up in stroke patients, but also in patients with asymptomatic carotid stenosis [3–6].

The purpose of this review is to summarize the known levels of association between carotid and coronary atherosclerosis, to present the CV risk profile of patients with carotid stenosis, and to summarize recommendations for the investigation and treatment of asymptomatic coronary artery disease among patients with carotid stenosis.

Association between carotid and coronary atherosclerosis

A relationship between coronary and carotid arterial disease is commonly accepted, confirming that atherosclerosis is a systemic condition. Similar plaque morphology at both vascular sites and predominant plaque location at the branch points of arteries suggest that development of atherosclerotic changes at both sites share similar systemic factors [3,7]. The prevalence of concomitant atherosclerosis in the carotid and coronary arteries has been studied under different circumstances, and the proportions vary widely (Table 1).

Most clinical studies have sought to determine the prevalence of carotid artery atherosclerosis in patients with known CAD. This prevalence differs depending on the study population and is highly dependent on the extent of CAD [8]. The weighted mean prevalences of carotid stenosis greater than 50, 60, 70, and 80% described in an earlier review were 14.5, 8.7, 5.0, and 4.5%, respectively [9]. Risk factors most commonly associated with carotid stenosis in patients with CAD are extension of CAD, older

Table 1 – Prevalence of carotid stenosis in patients with known CAD.

Author	No. of patients	Population	Method	Prevalence of carotid stenosis > 50%	Prevalence of carotid stenosis > 70%	Ref.
Brevetti et al. (2009)	169	Patients with stable CAD	DUS	20.7%		14
Fassiadis et al. (2008)	117	Patients 65–75 years of age with histories of PCI	DUS	13.7%	3.7%	19
Fichet et al. (2008)	152	Patients admitted to the ICU for ACS	DUS	2.6%*		20
Steinvil et al. (2011)	1116	Consecutive patients with confirmed CAD undergoing same-day coronary angiography and carotid Doppler studies	DUS	14.5%	5.2%	8
Tanimoto et al. (2005)	433	Consecutive patients with confirmed CAD on clinically driven coronary angiography	DUS + angiography confirmation	25.4%		21

* Stenosis > 60%. ACS – acute coronary syndrome; CAD – coronary artery disease; DUS – duplex ultrasonography; ICU – intensive care unit; PCI – percutaneous coronary intervention.

Table 2 – Prevalence of CAD in patients with carotid artery disease or after ischemic stroke.

Author	No. of patients	Study population	Method	Any CAD (at least 1 > 50%) or a history of CAD	1 VD	2 VD	3 VD	LM disease	Ref.
Amarenco et al. (2011)	378	Consecutive patients with acute cerebral infarctions	Coronary angiography	38%					22
Calvet et al. (2010)	274	Patients examined after noncardioembolic ischemic strokes or TIA	CT angiography	18%					23
Enomoto et al. (2013)	112	Consecutive patients undergoing elective CAS	Coronary angiography	49.1*	17.8%	6.2%	8%	2.7%	16
Gongora-Rivera et al. (2007)	341	Patients after fatal strokes	Autopsy	37.5%					24
Hofmann et al. (2005)	420	Consecutive patients undergoing elective stenting of the carotid artery	Coronary angiography	77.1%	16.7%	15.2%	22.1%	7.4%	15
Hoshino et al. (2008)	104	Patients with cerebral infarctions with no history of CVD	CT angiography	37.5%					25
Yoo et al. (2012)	1304	Consecutive patients admitted because of acute ischemic stroke	CT angiography	32.3%					26

* Includes patients with CAD treated via percutaneous coronary intervention and/or coronary artery bypass graft, or angiographically documented stenosis ≥ 75%. CAD – coronary artery disease; CAS – carotid artery stenting; CT – computed tomography; CVD – cardiovascular disease; LM – left main stem coronary artery; No. – number; Ref. – reference; TIA – transient ischemic attack; VD – vessel disease.

age, and a history of cerebrovascular disease and concomitant peripheral artery disease [10–13]. The presence of peripheral artery disease may also be associated with more high-risk hypoechogenic carotid lesions [14].

Few studies have been performed to determine the prevalence of CAD in patients presenting with carotid artery disease. Hofmann et al. described the prevalence of CAD (defined as stenosis ≥ 50% or previous percutaneous intervention/coronary artery bypass grafting) in a population of patients (both symptomatic and asymptomatic) admitted for elective carotid artery stenting as being as high as 77.1% [15]. Enomoto et al. described the prevalence of CAD in 112 patients undergoing elective carotid artery stenting 49.1%. Almost 60% of these patients were neurologically symptomatic [16]. The prevalence of concomitant CAD has also been studied in stroke patients using both noninvasive and invasive tools (Table 2). The prevalence of CAD in this population was lower, likely because atherosclerotic stenosis of the carotid artery is a minor cause of stroke in such patients. The literature states that only 10–12% of strokes involve acute occlusion or thromboembolism caused by 50–99% stenosis of the carotid artery [17,18].

These numbers tell us that patients with known CAD and who are neurologically asymptomatic are at a relatively low risk of critical carotid stenosis, but this risk rises with the extent of CAD. On the other hand, patients with confirmed carotid stenosis are at a high risk of significant concomitant CAD.

Cardiovascular risk profiles of patients with asymptomatic carotid artery stenosis

Asymptomatic carotid artery stenosis is defined as narrowing of the common or internal carotid artery in the absence of ipsilateral neurological symptoms referable to the carotid artery, or if such symptoms occurred more than 6 months prior. Asymptomatic carotid artery stenosis is not only an established risk factor for stroke and transient ischemic attack but is also a marker of elevated CV morbidity and mortality.

The risks of stroke in patients with asymptomatic carotid artery stenosis have been described in many studies. Data from randomized trials show an interesting trend in which the incidence of stroke has reduced over time in patients with asymptomatic carotid artery stenosis, likely because of improvements in medical therapy and lifestyle measures. In 1995, the ACAS (Endarterectomy for asymptomatic carotid artery stenosis) trial reported that the 5-year risk of any stroke in patients with 60–99% stenosis who were treated medically was 17.5% (3.5% per year) [27]. In 2004, the 5-year risk of any stroke reported in the ACST (Asymptomatic Carotid Surgery Trial) trial declined to 11.8% (2.4% per year) [28]. This trend was confirmed in a meta-analysis of 41 studies, where the rate of ipsilateral stroke was 2.3/100 person-years in studies for which patients were recruited before 2000, compared with 1.0/100 person-years during the 2000–2010 period [29]. This trend, together with the low absolute risk reduction (4.6% at 10

years) of stroke observed in trials comparing optimal medical treatment with endarterectomy in patients with asymptomatic carotid stenosis, has currently rendered the indications for revascularization more controversial [30]. The aim is to select subgroups of patients with asymptomatic carotid stenosis who are at high risk of stroke, using specific clinical/imaging features. These include contralateral transient ischemic attack/stroke, an ipsilateral silent infarction evident on cerebral imaging, stenosis progression (> 20%), spontaneous embolization evident on transcranial Doppler, an impaired cerebral vascular reserve, large plaques (> 40 mm^2 on digital analysis), echolucent plaques, intraplaque hemorrhage, and lipid-rich necrotic cores evident on magnetic resonance imaging [31–37].

As already mentioned, patients with asymptomatic carotid artery stenosis are threatened not only by stroke, but also have a higher overall CV risk. Some studies suggest that patients with asymptomatic carotid stenosis are at higher risk for myocardial infarction than stroke [38]. The higher age- and sex-adjusted 1-year rates of adverse CV events recorded in a large registry were reported on follow-up of high-risk atherosclerotic patients with or without asymptomatic carotid artery stenosis. Patients with asymptomatic carotid artery stenosis (compared with patients without carotid stenosis) did not have higher rates of stroke or transient ischemic attack, but were at significantly higher risk of CV death (2.29% vs. 1.52%, $p = 0.002$) and a higher level of the composite end-point of CV death/myocardial infarction/stroke (6.03% vs. 4.29%, $p < 0.0001$) [6]. A meta-analysis of studies comparing the risk of CV events among patients with or without carotid bruits showed that the odds ratio for myocardial infarction was 2.15 (1.67–2.78) and that for CV death 2.27 (1.49–3.49) [39].

Another meta-analysis analyzing mortality among 11,391 patients with asymptomatic carotid artery disease found that the 5-year cumulative all-cause mortality was 23.6% (95% confidence interval [CI], 20.50–26.80), and 62.9% of deaths (95% CI, 58.81–66.89) were cardiac-related, mainly due to myocardial infarction or heart failure developing subsequent to ischemic episodes. The 5-year all-cause mortality rate of 23% as revealed by the meta-analysis in patients with asymptomatic carotid artery stenosis was three-fold higher than mortality in the general population of the same age [40].

A few studies have stratified patients with asymptomatic carotid artery stenosis by their CV risk. Identified risk factors associated with increased all-cause late mortality were age, diabetes, smoking status, CAD, an abnormal electrocardiogram, congestive heart failure, chronic obstructive pulmonary disease, impaired renal function, lack of statin therapy, contralateral internal carotid stenosis or occlusion, intermittent claudification, lacunar infarcts, and a history of previous vascular surgery [41–45].

The atherosclerotic risk profile of patients with symptomatic carotid artery stenosis

Symptomatic carotid artery stenosis (SCAS) is defined as narrowing of the common or internal carotid artery in the presence of ipsilateral neurological symptoms referable to the carotid artery if the symptoms occurred less than 6 months prior. Although symptomatic carotid artery stenosis is a high-risk factor for recurrent ipsilateral stroke, patients with SCAS are also at an elevated CV risk and CAD is a major cause of death during follow-up in stroke patients [3–5].

According to one meta-analysis, the 5-year risk of stroke in symptomatic patients with 50–69% carotid stenosis who were treated medically was 27.7%. The 5-year risk of stroke in symptomatic patients with 70–99% carotid stenosis treated medically was 32.7% [46]. A significant benefit of carotid revascularization in terms of preventing recurrent stroke in patients with symptomatic carotid artery stenosis was confirmed in the meta-analysis. Carotid endarterectomy (CEA) conferred a significant 7.8% absolute risk reduction for stroke at 5 years in patients with 50–69% stenosis, and the maximum benefit was observed in patients with 70–99% stenosis, for whom the absolute risk reduction for stroke was 15.6%; equivalent to 156 strokes prevented over 5 years per 1,000 CEAs [46].

In the early years after a stroke, the most common vascular event is another stroke. However, at 5 years, twice as many deaths are due to myocardial infarction than recurrent stroke [47,48]. Patients with a history of previous ischemic stroke are at a well-documented risk of myocardial infarction, ranging from 4% within 3 months of stroke onset to 1% per year thereafter [47–51]. However, we need to realize that only 10–12% of strokes involve acute occlusion or a thromboembolism from a 50–99% carotid stenosis [17,18]. Patients with symptomatic carotid stenosis are certainly at a higher risk of myocardial infarction than the general ischemic stroke population. However, the CV risk of this population is not well documented. Amarenco et al. found that the prevalence of CAD among patients after stroke was 38%. This cohort was followed-up in terms of CV events by the presence or absence of CAD. The 2-year Kaplan–Meier estimates for combined major vascular events were 3.4% (95% CI, 1.3–8.9) in patients with no CAD compared with 16.2% (95% CI, 9.7–26.3) in patients with asymptomatic coronary stenosis ≥ 50%, and 24.1% (95% CI, 15.3–36.8) in patients with previously described coronary heart disease [52]. Considering that patients with carotid artery stenosis develop CAD at almost twice the rate of the overall population of stroke patients, their CV risk appears to be extremely high [15,23,26].

Investigation and treatment of CAD in patients with carotid artery stenosis

In an effort to lower the high rate of CV events, low-dose aspirin is recommended for patients with extracranial carotid atherosclerosis even if any benefit in terms of stroke prevention in asymptomatic patients has not been well established [53]. Dual antiplatelet therapy (DAPT) is not recommended for those with asymptomatic carotid artery disease, as no benefit was observed in a randomized trial involving high-risk patients [54].

Patients with carotid artery disease are considered to be at very high risk of CV events and, according to recognized guidelines on CV disease prevention, should be treated with statins to a target LDL-cholesterol level of < 1.8 mmol/L [55]. Considerable evidence indicates that

statin therapy reduces the stroke risk in patients with cerebrovascular disease. In a meta-analysis of randomized trials of statins in combination with other preventative strategies, every 1 mmol/L decrease in LDL-C level was associated with a reduction in the relative risk of stroke of 21% ($p = 0.009$). In terms of the secondary prevention of non-cardioembolic stroke, intensive reduction of the LDL-C level (using statins) significantly prevented both stroke and major CV events (0.80, $p = 0.002$) [56].

Further investigation of CAD among patients with asymptomatic carotid artery stenosis who are not scheduled for revascularization should depend on the symptoms and should follow appropriate guidelines [57,58]. However, the situation is different in patients with symptomatic carotid artery stenosis after a recent stroke/transient ischemic event. According to an American Heart Association/American Stroke Association statement, stroke/transient ischemic attack patients should undergo routine noninvasive testing for CAD in the presence of significant carotid disease [59]. Although some studies, including the COURAGE trial, have shown that asymptomatic CAD can be addressed only with optimal medical therapy, the residual risks in studies investigating CV risks in stroke patients with documented asymptomatic CAD were markedly increased in comparison with those of patients without CAD, despite optimal medical therapy, suggesting that additional interventions may play useful roles. Such interventions could include revascularization in patients after recent stroke with asymptomatic CAD. However, this remains to be tested [52,60].

The indications for coronary angiography and coronary revascularization prior to elective revascularization of asymptomatic carotid artery stenosis remain controversial. The risk of myocardial infarction during CEA was 2.25% in the CREST trial and was the same in symptomatic and asymptomatic carotid artery stenosis patients. The trial also revealed that the presence of either myocardial infarction or (only) elevation in cardiac biomarkers was associated with a significantly higher risk of subsequent mortality – the unadjusted hazard ratios were 3.40 (95% CI, 1.67–6.92, $p < 0.001$ for myocardial infarction) and 3.57 (95% CI, 1.46–8.68, $p = 0.005$ for the biomarkers) [61]. Consistent evidence about relatively high risk of MI during carotid endarterectomy and an effort to lower this risk led to an idea of routine preoperative coronary angiography to select extremely high risk cardiovascular patients and perform coronary revascularization prior to elective carotid surgery. In a trial that randomized 426 patients planned for CEA without a history of CAD to either systematic coronary angiography (with subsequent revascularization) or not, significant CAD was found (and treated via PCI) prior to CEA in 39% of those randomized to angiography. These patients suffered no postoperative myocardial infarction, in contrast to 2.9% of the no-angiography group ($p = 0.01$). Importantly, PCI delayed CEA only by a median of 4 days (range 1–8 days), without any neurological event or bleeding complication in patients on DAPT [62]. Six years later, patients allocated to the systematic coronary angiography had a lower rate of myocardial infarction (1.4% vs. 15.7%; $p < 0.01$) and exhibited better survival (95% vs. 90%; $p < 0.01$) [63]. These results suggest that routine coronary angiography and revascularization can significantly improve the prognosis of patients undergoing carotid endarterectomy.

In randomized trials, the rate of myocardial infarction after carotid stenting was about half that after CEA [61,64]. However, in real practice, where patients subjected to carotid stenting are usually high-risk surgical patients, the absolute risk of myocardial infarction can be higher. Thus, routine coronary angiography for high-risk patients undergoing carotid stenting may improve the periprocedural and long-term outcomes. A few studies have suggested that coronary revascularization combined with carotid stenting in high-risk patients yields favorable results [65,66].

Other controversial topics include the optimal screening for, and treatment of, asymptomatic carotid artery stenosis in patients undergoing coronary artery bypass graft (CABG). Ultrasound screening is recommended for patients with recent neurological symptoms and those at higher risk of perioperative stroke during CABG; these factors include age ≥ 70 years, multivessel coronary artery disease, concomitant lower extremity artery disease, or carotid bruits [9,67].

The impact of asymptomatic carotid artery stenosis on the stroke risk after CABG is modest, except in patients with bilateral stenosis or unilateral occlusion; 86% of postoperative strokes are not attributable to carotid disease. A systematic review found that the prevalence of ipsilateral stroke in patients with unilateral asymptomatic 50–99% stenosis undergoing CABG was 2.0% (1.0–3.8%), whereas the risk of any stroke was only 2.9% (2–5.7%). Patients with bilateral, asymptomatic 50–99% stenosis, or 50–99% stenosis and contralateral occlusion, incurred a 6.5% stroke risk after cardiac surgery, whereas the risk of death/stroke was 9.1% (3.8–20.6%) [68].

Because evidence of the benefits afforded by prophylactic revascularization of asymptomatic carotid artery stenosis in all CABG candidates (in terms of reducing perioperative stroke) is lacking, it may be reasonable to restrict prophylactic carotid revascularization to patients at the highest risk of postoperative stroke, thus those with severe bilateral lesions or a history of prior stroke/transient ischemic event [69].

Conclusion

This review showed the evidence of elevated cardiovascular risk among patient with carotid artery disease. "Panvascular" approach in these patients with a special emphasis put on screening and treatment of coronary artery disease is advised. Best medical therapy in patients with carotid disease is strongly advised to prevent CV events. Revascularization of asymptomatic CAD can be beneficial among patients with recently symptomatic carotid stenosis and patients scheduled for surgical or endovascular carotid revascularization.

Conflict of interest
The authors declare no conflict of interest.

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Ethical statement

The authors have respected publishing ethics.

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