Stroke prevention: the role of carotid artery stenting and the management of antithrombotic therapy

PhD Thesis

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2008

List of original publications cited in the thesis

I. **Sztriha LK**, Vörös E, Sas K, Szentgyörgyi R, Pócsik A, Barzó P, Szikra P, Makai A, Szólics A, Elek P, Rudas L, Vécsei L. (2004) Favorable early outcome of carotid artery stenting without protection devices. *Stroke*. **35**, 2862-6. **IF: 5,748**

II. **Sztriha LK**, Sas K, Seres E, Boda K, Lenti L, Csifcsák G, Kovács N, Vécsei L. (2008) Optical platelet aggregometry does not appear useful as a means of assessing the risk of recurrent vascular events in aspirin-treated patients. *Acta Neurol Scand*. **117**, 250-4. **IF: 1,833**

III. **Sztriha LK**, Vécsei L. (2008) Current practice of antithrombotic treatment in ischemic stroke: a survey among Hungarian neurologists. *Ideggyogy Sz*. (accepted for publication).

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I. Szentgyörgyi R, Vörös E, Pócsik A, Makai A, Barzó P, **Sztriha L**, Szikra P, Palkó A. (2003) Stroke-prevenció: az arteria carotis interna stenosisának endovascularis ellátásával szerzett tapasztalataink. *Magyar Radiológia*. **77**, 6-14.

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List of abbreviations

ACAS	Asymptomatic Carotid Atherosclerosis Study
ACST	Asymptomatic Carotid Surgery Trial
CAS	carotid artery stenting
CEA	carotid endarterectomy
CT	computed tomography
ECST	European Carotid Surgery Trial
EVA 3S	Endarterectomy versus Stenting in Patients with Symptomatic Severe Carotid Stenosis
ICA	internal carotid artery
LMWH	low molecular weight heparin
MI	myocardial infarction
NASCET	North American Symptomatic Carotid Endarterectomy Trial
NIH	National Institutes of Health
SAPPHIRE	Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy
SPACE	Stent-protected Percutaneous Angioplasty of the Carotid vs Endarterectomy
TIA	transient ischemic attack

Summary

Stroke is a leading cause of death and long-term disability worldwide. Of all strokes, around 85% are ischemic. Some risk factors for ischemic stroke, such as age, gender, ethnicity and genetic factors, are nonmodifiable. Well-documented and modifiable risk factors include hypertension, diabetes, dyslipidemia, exposure to cigarette smoke, atrial fibrillation, internal carotid artery stenosis, obesity and physical inactivity. Survivors of a first stroke frequently suffer a further stroke. These stroke recurrences often cause substantial morbidity and greatly alter a patient's quality of life. Both primary and secondary (early and long-term) prevention of stroke are necessary. Effective prevention strategies seem to contribute to a decrease in incidence and to a milder presentation of the disease. The slow decrease in stroke mortality in developed countries may in part be related to declines in incidence and case fatality, the latter possibly resulting from better acute care and the presentation of less severe cases. Preventive measures include lifestyle modifications and various medical or surgical interventions. In this thesis, two important areas of stroke prevention are investigated: the endovascular treatment of extracranial carotid artery disease, a major cause of large-artery stroke; and antithrombotic (antiplatelet and anticoagulant) therapy.

In almost all cases, a stenosis of the internal carotid artery occurs secondary to atherosclerotic plaque formation. Although hemodynamic strokes can occasionally occur in patients with carotid stenoses, embolism rather than hypoperfusion is believed to be the primary mechanism causing stroke. The stenosis of a carotid artery is considered symptomatic if the patient has had a retinal or hemispheric TIA or ischemic stroke in the territory of the affected internal carotid artery. The risk of stroke in those with an asymptomatic ≥60% stenosis or occlusion is around 2% per year, whereas for subjects with a 70-99% symptomatic stenosis it is 26% during the 2 years following the ischemic episode. In addition to medical treatment, carotid endarterectomy (CEA) may be beneficial with a view to preventing a first or recurrent stroke in patients with carotid artery stenoses. Carotid artery stenting (CAS) is increasingly used as an alternative to CEA. However, the exact role of CAS in patients with carotid stenosis has not yet been fully established. Our study revealed that CAS without the use of protection devices can be performed with an acceptable overall rate of periprocedural complications; this procedure therefore may be a less invasive alternative to CEA in selected patients. Our results indicate that CAS may be associated with a high rate of complications among asymptomatic high-risk patients, possibly resulting in an unfavorable risk-benefit ratio. We observed that a significant proportion of embolization-related complications associated with CAS may occur after the

completion of the procedure, and are therefore not avoidable through the use of protection devices. We assessed the application of a novel covered stent in the carotid system, and concluded that the use of such covered stents for extracranial atherosclerotic carotid stenosis is feasible, and is possibly associated with a lower rate of embolization-related complications during the intervention and also postprocedurally. Developments in endovascular technology, pharmacological management and expertise should lead to further reductions in the complication rates associated with CAS.

Antiplatelet treatment is of great importance from the aspect of the prevention of ischemic episodes in patients with cardio- and cerebrovascular disease. Antiplatelet therapy reduces the overall risk of serious vascular events in high-risk patients by 22%. According to the US, European and Hungarian guidelines, aspirin, the combination of aspirin and extended-release dipyridamole, and clopidogrel are all acceptable antiplatelet options as initial therapy for the secondary prevention of stroke in patients with noncardioembolic ischemic stroke or TIA. The agent most commonly prescribed is aspirin. Despite the efficacy of aspirin in reducing the risk of ischemic vascular events, 12.9% of high-risk patients develop recurrent vascular episodes during aspirin treatment in the next 2 years. Aspirin fails to prevent around four-fifths (81%) of recurrences. The term aspirin treatment failure refers to recurrent ischemic clinical events during aspirin treatment. The inhibitory effect of aspirin on platelet activation can be measured by various *in vitro* methods, of which optical platelet aggregometry is one of the most frequent. Aspirin resistance refers to a condition when an inadequate inhibitory efficacy of aspirin is detected by an *in vitro* assay of the platelet function. Although some previous published studies have suggested that cerebro- and cardiovascular patients found by laboratory tests to be aspirin-resistant are at an increased risk of major vascular events, there is much uncertainty concerning the clinical relevance of platelet function testing. The main findings of our study were that results obtained by means of optical platelet aggregometry do not appear to be good indicators of the risk of recurrent vascular events in patients taking aspirin, and that conventional risk factors are more important predictors. The findings of our study are in contrast with some previous reports, and do not confirm the suitability of platelet aggregometry for assessment of the risk of vascular events during aspirin treatment. We agree with those who do not currently recommend routine testing for aspirin resistance and changing therapy on the basis of laboratory tests. In addition to the prescription of an antiplatelet drug, attention should not be diverted from other possibilities of secondary prevention because, unfortunately, conventional risk factors are poorly controlled in many patients who have suffered a stroke.

It is not always known how clinical practitioners adhere to the guidelines. On the other hand, there may be numerous clinical situations where no help is available from the guidelines. At present, insufficient data are available to allow evidence-based recommendations concerning choices among antiplatelet options after a first noncardioembolic cerebral ischemic event. For patients who suffer an ischemic stroke while taking a proven antiplatelet drug, no evidence-based proposals have been made as to further antiplatelet management. Our survey among practising neurologists indicated that the current strategies relating to the prescription of antithrombotic medications for patients with cerebrovascular disease in Hungary are largely in accordance with international and national guidelines, and are influenced both by the regulations of the health authorities and by patient preferences. Several reasons have emerged for choosing an alternative antiplatelet agent rather than aspirin following a first ischemic episode. Both clopidogrel and the combination of aspirin and dipyridamole are believed by many participants to be more effective than aspirin alone. Intolerance or allergy to aspirin are important factors in decisions in favor of clopidogrel. The combination of aspirin and dipyridamole is prescribed by some in the event of an intolerance to higher-dose aspirin. Clopidogrel is considered by some respondents to be well tolerated, while the combination of aspirin and dipyridamole is regarded as a less expensive alternative to clopidogrel. It is interesting that aspirin resistance determined by *in vitro* methods (e.g. optical platelet aggregometry) was a frequent reason for selecting alternative antiplatelet medication, despite the fact that at present such a practice may not be considered adequately evidence-based, and routine *in vitro* testing for aspirin resistance is usually not recommended by the guidelines. If a patient suffers a recurrent cerebrovascular ischemic attack while taking a given antiplatelet agent, some responders would not automatically modify that antiplatelet treatment: a higher proportion would do so when clopidogrel is given relative to the situation when aspirin is administered. Although not supported by clinical evidence, most practitioners answering this survey change the antiplatelet medication in the event of recurrent attacks. Similar findings have emerged from other studies, and this attitude appears to be rather common clinical practice.

Areas requiring further research include the long-term efficacy and durability of CAS, the validation of various *in vitro* platelet function assays, and antithrombotic management practices with novel agents or in certain specific situations.

1. Introduction

1.1. Ischemic stroke and TIA: risk factors, subtypes, recurrence and prevention

Stroke is a leading cause of death and long-term disability worldwide. Of all strokes, around 85% are ischemic. Some risk factors for ischemic stroke such as age, gender, ethnicity and genetic factors are nonmodifiable. Well-documented and modifiable risk factors include hypertension, diabetes, dyslipidemia, exposure to cigarette smoke, atrial fibrillation, internal carotid artery (ICA) stenosis, obesity and physical inactivity (Goldstein, 2006). A transient ischemic attack (TIA) has been defined as a brief episode of neurological dysfunction caused by a focal brain or retinal ischemia, with clinical symptoms typically lasting less than an hour, and without evidence of acute infarction (Albers, 2002).

The main pathophysiological classes of ischemic stroke are large-artery atherosclerosis, small-vessel disease (lacunes), cardioembolism, other determined causes (e.g. nonatherosclerotic vasculopathies or disorders of coagulation), and undetermined etiology (Adams, 1993). In large-artery stroke, occlusion or stenosis (>50%) of a large extra- or intracranial cerebral artery with ischemia in that arterial territory is present. Lacunar stroke is characterized by a characteristic lacunar syndrome with either no lesion on brain imaging or a deep infarct (≤1.5 cm in diameter) in a location consistent with the clinical syndrome. Cardioembolic stroke is a brain infarction that occurs in the presence of a potentially embologenic cardiac disease.

Survivors of a first stroke frequently suffer a further stroke. The most common vascular event during the first few years after a cerebral ischemic event is a recurrent nonfatal stroke. These early stroke recurrences often cause substantial morbidity and greatly alter a patient's quality of life (Albers, 2000). Among the estimated 700,000 people who suffer a stroke in the United States each year, 200,000 have a recurrent stroke (Sacco, 2006). Earlier studies have estimated the risk of recurrence after a stroke to vary from 1.7% to 4% in the first 30 days, from 6% to 13% in the first year, and from 5% to 8% per year for the next 2 to 5 years, culminating in a cumulative risk of stroke recurrence within 5 years of 19% to 42% (Rundek, 2004). More recently, the Oxford Vascular Study showed that the early risk of stroke after a TIA is relatively high, reaching 8.0%, 11.5% and 17.3% at 7 days, 1 and 3 months, respectively. The early prognosis after a minor stroke (National Institutes of Health [NIH] score ≤3) is similar (Coull, 2004). The early risk of stroke may depend on the underlying causal pathology. The early risk of recurrence is almost 8 times higher in patients with large-artery atherosclerotic etiology than in those with small-vessel stroke, and 3 times higher than in those with cardioembolic stroke

(Lovett, 2004). However, the long-term risk of stroke recurrence does not appear to be considerably different in the various subtypes of stroke (Burn, 1994, Rundek, 2004).

The slow decrease in stroke mortality in developed countries may in part be related to declines in incidence and case fatality, the latter possibly resulting from better acute care and the presentation of less severe cases. Effective prevention strategies seem to contribute to a decrease in incidence and to a milder presentation of the disease (Benatru, 2006; Carandang, 2006; Immonen-Räihä, 1997; Rothwell 2004a). Both primary and secondary (early and long-term) prevention of stroke are necessary. Primary prevention has the aim of reducing the risk of stroke in asymptomatic subjects, whereas the targets of secondary prevention are those who have survived a TIA or ischemic stroke. Preventive measures include lifestyle modifications and various medical or surgical interventions. Many preventive interventions reduce the risk not only of stroke, but also of other vascular outcomes, such as myocardial infarction (MI) or vascular death. The following sections will discuss two important areas of stroke prevention: the management of extracranial carotid artery disease, a major cause of large-artery stroke, and antithrombotic (antiplatelet and anticoagulant) therapy.

1.2. Extracranial carotid artery stenosis

In almost all cases, a stenosis of the ICA occurs secondary to atherosclerotic plaque formation (Fülesdi, 1999). There are various methods for measurement of the degree of carotid stenosis on angiographic images, the most widely used of which is the NASCET formula. This expresses stenosis as a percentage from the angiographic view showing the greatest stenosis. The diameter at the site of maximal narrowing (N) is compared with the luminal diameter (D) of the distal ICA where the vessel walls become parallel and beyond any area of post-stenotic dilatation. The percentage stenosis is calculated as (1–N/D)x100 (North American Symptomatic Carotid Endarterectomy Trial Collaborators, 1991). The stenosis of a carotid artery is considered symptomatic if the patient has had a retinal or hemispheric TIA or ischemic stroke in the territory of the affected ICA.

A detectable carotid stenosis is present in 75% of men and 62% of women aged ≥65 years, the prevalence of a ≥50% stenosis in these age groups being 7% in men and 5% in women (O'Leary, 1992). The risk of stroke in those with an asymptomatic ≥60% stenosis or occlusion is around 2% per year (Executive Committee for the Asymptomatic Carotid Atherosclerosis Study [ACAS], 1995; Inzitari, 2000), whereas for subjects with a 70-99% symptomatic stenosis it is 26% during the 2 years following the ischemic episode (NASCET Collaborators, 1991). In

symptomatic cases, the risk of a recurrent stroke is highest immediately following the index event; after about 2 years, it has returned to close to the level characteristic for asymptomatic cases (European Carotid Surgery Trialists' [ECST] Collaborative Group, 1998). The risk of stroke increases with the degree of stenosis in recently symptomatic patients, whereas such a relationship is less evident with an asymptomatic stenosis.

The reduced cross-sectional area is the main factor that makes a stenosis hemodynamically significant. This occurs when the vessel diameter is decreased by around 75%, a figure corresponding to a cross-sectional area reduction of 94% (Archie, 1981). Although hemodynamic strokes can occasionally occur in patients with carotid stenoses, embolism rather than hypoperfusion is believed to be the primary mechanism causing stroke. Plaque instability, rupture, local thrombus formation and distal embolization appear to be important in this process (Fisher, 1959; Forteza, 1996; Harrison, 1977; Markus, 2005a). The mechanisms whereby asymptomatic plaque becomes symptomatic are incompletely understood. Asymptomatic embolization is much more common than clinical events in patients with symptomatic carotid stenoses (Markus, 2005a). The occurrence of symptoms may depend not only on the character of the atherosclerotic plaque and the severity and progression of the stenosis, but also on the adequacy of the collateral vessels, and the presence or absence of other risk factors for stroke.

In addition to medical treatment, carotid endarterectomy (CEA) may be beneficial for patients with carotid artery stenoses to prevent a first or recurrent stroke. Several large studies have contributed to the establishment of the role of CEA in both symptomatic and asymptomatic patients (Barnett for the NASCET Collaborators, 1998; ECST Collaborative Group, 1998; Executive Committee for the ACAS, 1995; Halliday for the Asymptomatic Carotid Surgery Trial [ACST] Collaborative Group, 2004; NASCET Collaborators, 1991). The American Heart Association guidelines recommend CEA for patients who have suffered a TIA or ischemic stroke within the last 6 months and with an ipsilateral severe (70-99%) carotid artery stenosis; when performed by a surgeon with a perioperative morbidity and mortality rate of <6%. The recommendation of CEA for symptomatic patients with a moderate (50-69%) stenosis depends on various patient-specific factors. When CEA is indicated for patients with TIA or stroke, surgery within 2 weeks is suggested rather than delaying surgery (Sacco, 2006). Prophylactic CEA may be considered in carefully chosen patients with a 60-99% asymptomatic carotid stenosis; if it is carried out by a surgeon with a <3% morbidity and mortality rate (Goldstein, 2006). The benefits to be expected from CEA are not predicted by the degree of stenosis in asymptomatic patients. Carotid artery stenting (CAS) is increasingly used as an alternative to

CEA (Wholey, 2003). However, the exact role of CAS in patients with carotid stenosis has not yet entirely been established.

1.3. Antithrombotic therapy

Antithrombotic (antiplatelet and anticoagulant) treatment is of great importance with a view to preventing ischemic episodes in patients with cardio- and cerebrovascular disease. An important meta-analysis of 287 randomized antiplatelet trials documented that antiplatelet therapy reduced the overall risk of serious vascular events in high-risk patients by 22% as compared with the controls (Antithrombotic Trialists' Collaboration, 2002). Antiplatelet treatment is recommended for the secondary prevention of stroke in patients with noncardioembolic ischemic stroke or TIA (A Magyar Stroke Társaság, 2004, Hacke, 2003; Sacco, 2006). According to the US, European and Hungarian guidelines, aspirin, the combination of aspirin and extended-release dipyridamole, and clopidogrel are all acceptable options for the initial therapy. At present, insufficient data are available to allow evidence-based recommendations concerning choices between antiplatelet options. Although the addition of aspirin to clopidogrel is not routinely recommended for ischemic stroke or TIA patients, there may be situations when this combination is considered beneficial (Hacke, 2003; Markus, 2005). For patients who suffer an ischemic stroke while taking a proven antiplatelet drug, no evidence-based proposals have been made as to further antiplatelet management.

Although anticoagulation is not routinely advised for acute ischemic stroke, there may be situations when practitioners regard such treatment as favorable (Hacke, 2003). Chronic oral anticoagulation is generally indicated for most patients with ischemic stroke or TIA who have a cardiac source of embolism. However, it has been suggested that the use of chronic oral anticoagulation may be beneficial in certain special conditions, e.g. arterial dissections (Hacke, 2003). Moreover, there may be circumstances when a combination of oral anticoagulation and antiplatelet treatment is considered in stroke patients.

It is not always known how clinical practitioners adhere to the guidelines. On the other hand, there may be numerous clinical situations where no help is available from the guidelines. Furthermore, clinical practice may vary in the different centers and different countries.

1.4. Aspirin treatment failure and in vitro aspirin resistance

Aspirin exerts its antithrombotic activity by permanently inactivating cyclooxygenase-1, which results in the blockade of prothrombotic thromboxane A_2 production in the platelets (Patrono, 2004). Despite the efficacy of aspirin in reducing the risk of ischemic vascular events

(23% odds reduction, 19% relative risk reduction, 3.1% absolute risk reduction over 2 years), 12.9% of high-risk patients develop recurrent vascular episodes during aspirin treatment in the next 2 years. Aspirin fails to prevent around four-fifths (81%) of recurrences (Eikelboom, 2003). The term aspirin treatment failure refers to recurrent ischemic clinical events during aspirin treatment.

The inhibitory effect of aspirin on platelet activation can be measured by various *in vitro* methods, of which optical platelet aggregometry is one of the most frequent. Aspirin resistance refers to a condition when an inadequate inhibitory efficacy of aspirin is detected by an *in vitro* assay of the platelet function. Earlier investigations have indicated that aspirin treatment may not result in adequate *in vitro* antiplatelet efficacy in 5-60% of patients with vascular disease (Eikelboom, 2003). Although some previous published studies have suggested that cerebro- and cardiovascular patients demonstrated by laboratory tests to be aspirin-resistant are at an increased risk of major vascular events (Eikelboom, 2002; Grotemeyer, 1993; Gum, 2003), there is much uncertainty concerning the clinical relevance of platelet function testing.

2. Aims

The specific aims of our investigations were as follows:

- Study of the 30-day outcome of CAS, with an account of the rates of minor and major complications overall and in relation to the symptomatic or asymptomatic status, the high-risk or low-risk profile, and the time of the occurrence
- Evaluation of the safety of CAS without the use of protecting devices, and assessment of the application of a novel covered stent in the carotid system
- Investigation of the value of optical platelet aggregation studies in assessing the risk of recurrent vascular events in aspirin-treated patients
- Conduction of a national survey among Hungarian neurologists to obtain information on various aspects of their antiplatelet and anticoagulant treatment policies for patients with ischemic stroke

3. Materials and methods

3.1. Study of CAS

Patient selection: Between January 2001 and July 2003, 245 consecutive patients were enrolled in a single-center CAS study. They were included if they had symptomatic or asymptomatic, 60-99% (according to the NASCET measurement method) stenosis of a carotid artery. Exclusion criteria were the occurrence of a stroke within 6 weeks, a previous major stroke within the territory of the stenotic artery with no useful recovery of function, the presence of visible thrombus at the carotid lesion site, carotid artery dissection, vessel narrowing caused by external compression by a tumor, a life expectancy of <2 years due to a known pre-existing condition, and the inability or unwillingness of the patient to provide informed consent. Patient evaluation, intervention and follow-up were carried out by a team of radiologists, neurologists and neurosurgeons, in accordance with a standardized protocol. The patients gave their written informed consent to the procedures.

Patient evaluation: The relevant medical history was taken and a thorough neurological examination was performed on all patients. Patients demonstrating repetitive TIAs referable to an ipsilateral carotid stenosis were treated at the earliest opportunity. Duplex ultrasonography of the carotid arteries was utilized in all cases to reveal hemodynamically significant stenoses. Stenoses were considered significant if visible plaque and luminal narrowing were seen and the peak systolic velocity in the ICA exceeded 175 cm/s. Magnetic resonance (MR) angiography of the carotid arteries was performed in 21 patients (8.6%), and computed tomographic (CT) angiography in 5 cases (2.0%) because of uncertainty as to the presence of significant stenosis on ultrasonographic evaluation, due to plaque calcification or vessel tortuosity. CT or MR imaging of the brain was carried out in all cases. Criteria for patients at high risk included age ≥80 years, contralateral carotid occlusion, post-endarterectomy restenosis, cervical radiation treatment, severe cardiac dysfunction (New York Heart Association class III/IV chronic heart failure, acute MI within 4 weeks, unstable angina, or a coronary procedure within 4 weeks) and pulmonary disease causing a considerable functional limitation.

CAS protocol: Treatment with aspirin 100 mg plus clopidogrel 75 mg or ticlopidine 2x250 mg daily was started at least 4 days before the procedure and continued for a minimum of 4 weeks postprocedure. If this combined antiplatelet treatment had not been given before CAS, aspirin 100 mg and clopidogrel 300 mg were administered on the day of the intervention. All CAS procedures were performed under local anesthesia by the same neuroradiologist, with experience in >4000 diagnostic cerebral angiographies and 15 proctored CAS procedures prior

to this study. Percutaneous access was gained through the femoral artery. Brachiocephalic angiography with intracranial views and assessment of the collateral cerebral circulation always preceded the CAS. The extent of the carotid artery stenosis was measured with the NASCET method, and the plaque surface morphology was noted. All lesions found noninvasively to be hemodynamically significant proved to be ≥60% with the NASCET method. The final percentage stenosis was based on the angiographic findings. CAS was achieved by a standard technique (Vitek, 2000) with low-profile devices and gentle manipulation (Fig. 1). Heparin 5000 IU was given intraarterially 1-2 times during the intervention. No protection devices were utilized. The following appropriately-sized, self-expandable stents were implanted during the 257 successful procedures: 207 (80.5%) Carotid Wallstents (Boston Scientific), 31 (12.1%) Symbiot covered stents (Boston Scientific), 18 (7.0%) Precise stents (Cordis), and 1 (0.4%) Smart stent (Cordis). Predilatation was applied in 14 (5.4%) and postdilatation in 245 (95.3%) cases. Stent overdilatation was avoided. The residual stenosis in all successfully treated vessels was <30%. Covered stents were utilized at the discretion of the interventionalist. The covered stent (Symbiot) applied features a self-expanding nitinol stent encased in a thin porous polytetrafluoroethylene membrane. No such stent was used in 2001, 7 were implanted in 2002 and 24 were utilized from January to July, 2003. The vital signs were recorded regularly, the cardiac rhythm was monitored continuously, and neurological assessment was frequent during the intervention. Intravenous atropine, up to 2 mg, was administered as necessary for bradycardia. Control angiograms were recorded on procedure completion to evaluate recanalization and to exclude embolization into intracranial vessels. Three patients whose CAS failed technically subsequently underwent CEA.

Patient follow-up: Control neurological examination was performed routinely 24 hours and 30 days after CAS. If a patient exhibited a neurological deterioration, brain CT and control angiography (in the event of intraprocedural complications) or carotid ultrasonography were conducted without delay. Heart rate and blood pressure were checked regularly in the post-interventional period. Carotid duplex ultrasonography was carried out routinely 4 weeks postprocedure. The incidence of complications during the intervention and the subsequent 30-day follow-up period was recorded. A TIA was defined as a focal retinal or hemispheric event from which the patient made a complete recovery within 24 hours. Minor stroke was identified as a new neurological deficit that either resolved completely within 30 days or increased the NIH stroke scale score by ≤3. Major stroke was defined as a new neurological deficit that persisted after 30 days and increased the NIH stroke scale score by ≥4. Complications were considered ‘intraprocedural’ if they occurred between the attainment of femoral arterial access

and successful vascular access site hemostasis. Complications arising at any time up to 30 days after this period were regarded as 'postprocedural'. Eight patients (3.3%) missed the 30-day evaluation visit, but presented later. Follow-up information was obtained from their GPs on the 6 patients (2.4%) who did not attend for control.

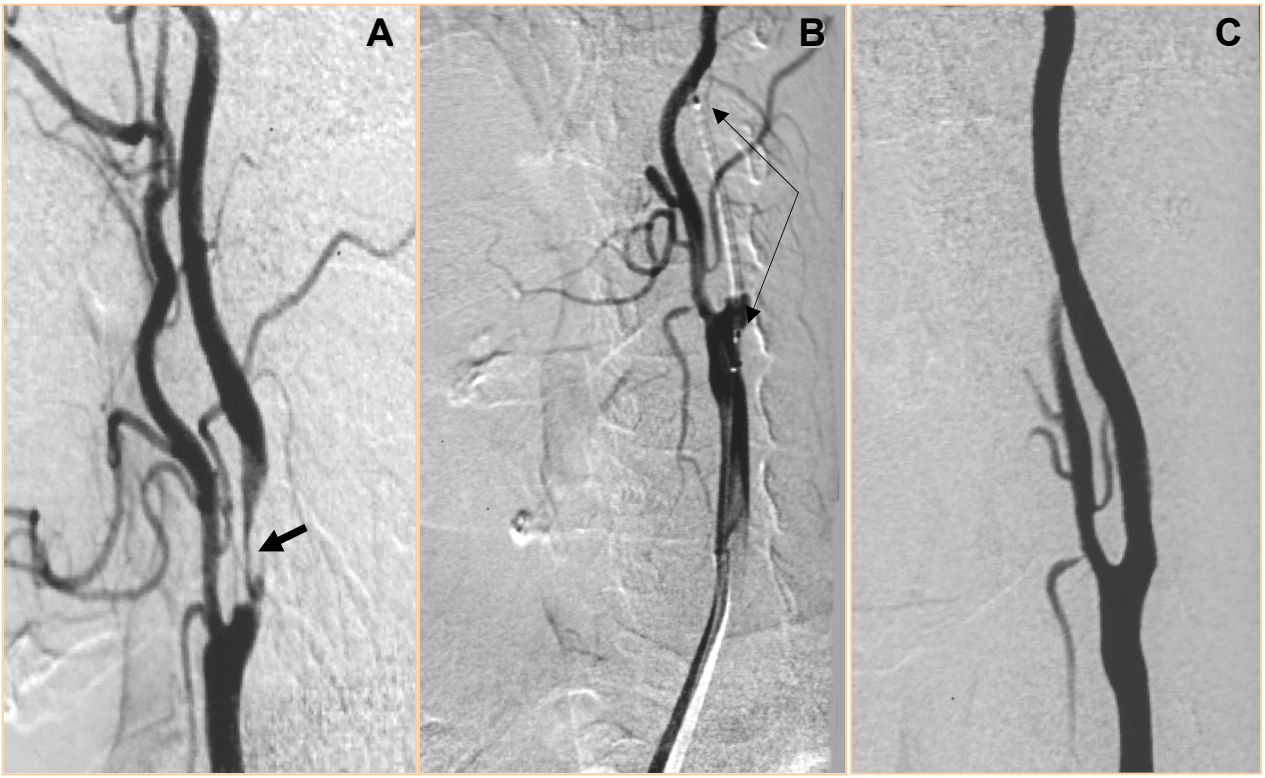

Fig. 1. CAS procedure. A. Diagnostic angiography revealing severe stenosis of the ICA (arrow). B. Deployment of a covered stent (arrows). C. Control angiography depicting a restored luminal diameter. (By courtesy of E. Vörös)

Statistical analysis: Proportions were compared by using chi-square or Fisher's exact tests, as appropriate. Two-sided p values are reported. $p<0.05$ was considered significant.

3.2. Study of the relationship between the degree of in vitro platelet aggregation and the risk of recurrent vascular events in aspirin-treated patients

Patient selection: The subjects of this retrospective study were selected from consecutive patients referred to our department for platelet function testing. The inclusion criteria were the occurrence of at least one vascular ischemic event (stroke, TIA, MI or angina pectoris) prior to testing, the chronic taking of aspirin for at least 30 days, and a physician's recommendation of a daily aspirin intake after the earliest ischemic event identified. The past medical history was evaluated via chart reviews, written questionnaires and telephone interviews covering the 5-year

period prior to the aggregation testing; and the occurrence of vascular events was screened and recorded. In a very small percentage of the patients, the first event had occurred more than 5 years before testing. The duration of aspirin treatment was calculated as the time difference between the first event (after which aspirin intake was recommended) and the aggregation testing. A recurrent ischemic episode was defined as stroke, TIA, MI or unstable angina occurring after the first event, during the 5-year period before aggregation testing. Among the recurrent ischemic events, stroke and MI were defined as "hard" events. Patients were not included if any of the following situations existed: the taking of oral anticoagulants or the presence of any condition that would have required oral anticoagulation rather than antiplatelet therapy; treatment with clopidogrel, ticlopidine or dipyridamole during the period analyzed; or heparin or glycoprotein IIb/IIIa inhibitor treatment within 14 days of the platelet function testing. Participants were reminded not to take nonsteroidal anti-inflammatory drugs for at least 10 days prior to aggregation testing. The aspirin doses among the patients in the study ranged from 100 to 250 mg daily. Compliance with aspirin treatment was ascertained by interviewing the patients; no blood or urinary tests were performed to check on compliance. The procedures followed were in accordance with institutional guidelines.

Platelet aggregation: Blood samples were drawn in the morning, 1 to 20 hours after the last aspirin intake. From each patient, whole blood for platelet aggregation analysis was collected in tubes containing 3.8% sodium citrate. One tube of blood anticoagulated with ethylenediaminetetraacetic acid was collected to determine the platelet count. Specimens were kept at room temperature and processed within 1 hour of collection. The whole-blood specimen was centrifuged at 150g for 10 minutes to obtain platelet-rich plasma (PRP). Platelet-poor plasma (PPP) was made by centrifuging the remaining sample at 2000g for 10 minutes. The platelet count of the PRP was adjusted to between 200 x 10^3/μl and 300 x 10^3/μl with autologous PPP. Platelet aggregation was measured by the method of Born (Born, 1962) with a Carat TX4 optical platelet aggregometer (Carat Diagnostics Ltd, Budapest, Hungary). The baseline optical density (100%) was set with PPP. PRP (which was assigned a light transmission of 0%) was incubated at 37 ^{o}C, stirred and evaluated following the addition of aggregating agents. Aggregation was induced with epinephrine at 10 μM and collagen at 2 μg/ml. The concentrations of stimuli are expressed as the final concentrations attained in the PRP. Optical density changes were detected photoelectrically as the platelets began to aggregate. Platelet aggregation was characterized with the maximal percentage of light transmission attained. A higher value indicates less platelet inhibition (Fig. 2). No threshold for aspirin resistance was

defined; the aggregation percentage was rather used as a continuous measure in the analyses. All platelet aggregation studies were interpreted by the same investigator, who was blind to the clinical histories.

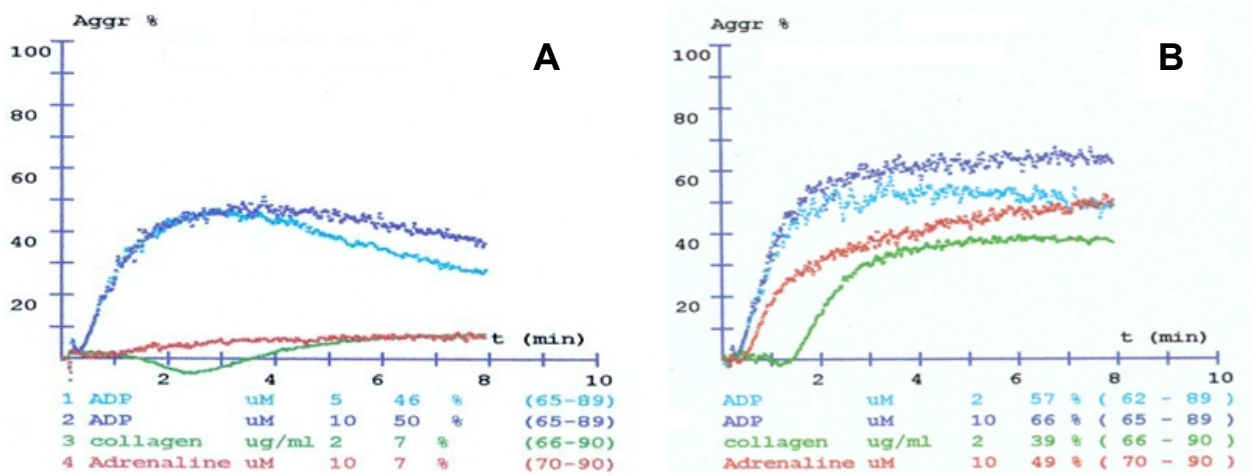

Fig. 2. Platelet aggregation curves in two patients taking 100 mg aspirin daily. Responses only to collagen and epinephrine (adrenaline) inducers were considered in this study (two lower curves). Examples of good (A) and poor (B) inhibition of platelet aggregation by aspirin. (By courtesy of E. Seres)

Statistical analysis: Categorical variables are presented as frequencies and percentages. As concerns categorical variables, the two groups were compared by using chi-square tests. Continuous variables are presented as means ± SD. For the continuous variables, t-tests for independent samples were utilized in the comparison of the two groups. Stepwise logistic regression modeling was carried out to investigate the factors contributing to all recurrent events and to "hard" recurrent ischemic episodes. The variables evaluated were age, sex, aggregation measures separately with collagen and epinephrine inducers, hypertension, diabetes, hyperlipidemia, smoking and obesity. A p value of <0.05 was considered statistically significant.

3.3. Survey on antithrombotic treatment

A structured questionnaire was mailed to the leaders of university departments and major hospital neurology wards throughout Hungary. English-language equivalents of the questions featuring in the questionnaire are listed in Appendix III. In order not to influence the participants, no fixed answers were suggested in the questionnaire. The participants were rather encouraged to express their opinions freely. It was necessary to categorize the answers to some questions during analysis for straightforward presentation of the data. Missing or overvague answers were regarded as invalid data and omitted from the evaluation. If more than one answer was given to a

question, each was treated as a separate record. Replies to the questionnaires were received between September 2005 and January 2006.

4. Results

4.1. Study of CAS

Of the 260 stenosed carotid arteries in the 245 patients, 124 (47.7%) were symptomatic. Sixty procedures (23.1%) were conducted on high-risk patients, 37 in symptomatic (29.8%) and 23 in asymptomatic (16.9%) cases. The CAS was performed successfully on 257 arteries of 242 patients (technical success rate: 98.8%). The procedure failed because of extreme vessel tortuosity in 2 cases, and because of the inability to guide the stent through a calcified subtotal occlusion in 1 patient.

Table 1. Complications within 30 days

Category	Symptomatic (n=124)	Asymptomatic (n=136)	Overall (n=260)
Death	0 (0.0)	1 (0.7)	1 (0.4)
Neurological complications			
Major strokes	2 (1.6)	1 (0.7)	3 (1.2)
Minor strokes	4 (3.2)	2 (1.5)	6 (2.3)
All ipsilateral strokes	5 (4.0)	3 (2.2)	8 (3.1)
TIAs	4 (3.2)	1 (0.7)	5 (1.9)
Other complications			
MI			0 (0.0)
Angina			1 (0.4)
Severe hypotension			1 (0.4)
Procedure-related bleeding			1 (0.4)
Stent occlusion			2 (0.8)
Restenosis			0 (0.0)
Femoral AV fistula			1 (0.4)

Values in parentheses are percentages.

The complications observed during the procedure and the 30-day follow-up are shown in Tables 1 and 2. The one postprocedural non-neurological death (0.4%), in a high-risk patient, occurred due to hemorrhagic shock resulting from uncontrollable bleeding of a previously unknown adenocarcinoma of the sigmoid colon. Neurological complications arose in 14 cases (5.4%, 95% confidence interval [CI] 2.6 to 8.1%). MI was not detected. The rate of major complications (death, major stroke and MI) was 1.6% among the symptomatic (low-risk, 1.1%; high-risk, 2.7%; p=0.51), and 1.5% among the asymptomatic (low-risk, 0%; high-risk, 8.7%; p=0.03) cases (p=1.0). The rate of minor strokes was 3.2% in the symptomatic (low-risk, 3.4%; high-risk, 2.7%; p=1.0) and 1.5% in the asymptomatic (low-risk, 1.8%; high-risk, 0%; p=1.0) group (p=0.43). The rate of major complications was 0.5% in the low-risk, and 5.0% in the high-risk group (p=0.04). The rate of minor strokes was 2.5% and 1.7% in the low- and high-risk populations, respectively (p=1.0).

Table 2. Neurological complications within 30 days

No.	Age y	Sex	Risk	Stenosis type	Plaque	Category	Side*	Time
1	55	M	H	sympt	irregular	minor stroke	ipsilateral	postprocedural
2	57	F	H	sympt	smooth	TIA	ipsilateral	intraprocedural
3	63	F	H	asympt	ulcerated	major stroke	ipsilateral	postprocedural
4	65	M	L	sympt	irregular	TIA	ipsilateral	postprocedural
5	66	F	L	sympt	irregular	TIA	ipsilateral	intraprocedural
6	68	F	L	asympt	smooth	TIA	ipsilateral	intraprocedural
7	69	M	L	sympt	irregular	minor stroke	ipsilateral	postprocedural
8	71	F	L	sympt	irregular	minor stroke	ipsilateral	postprocedural
9	72	M	L	sympt	irregular	minor stroke	contralateral	postprocedural
10	72	M	L	sympt	smooth	TIA	ipsilateral	postprocedural
11	74	M	L	asympt	smooth	minor stroke	ipsilateral	intraprocedural
12	78	F	L	sympt	irregular	major stroke	ipsilateral	postprocedural
13	79	M	L	asympt	irregular	minor stroke	ipsilateral	postprocedural
14	82	M	H	sympt	irregular	major stroke	ipsilateral	intraprocedural

M, male; F, female; H, high-risk; L, low-risk; asympt, asymptomatic stenosis; sympt, symptomatic stenosis

* Indicates whether the complication developed ipsi- or contralaterally to the stented carotid artery.

Of the 14 neurological complications, 5 (35.7%) occurred intraprocedurally, and the remainder after completion of the intervention. Thirteen (92.9%) neurological complications developed ipsilaterally to the stented carotid artery, 8 in cases with ≥90% stenosis (7.2%), and 5 in those with <90% stenosis (3.4%, p=0.16). The rate of ipsilateral neurological complications among the patients with irregular or ulcerated plaques was 4.5% (9 of 202), whereas among

those with smooth lesions it was 6.9% (4 of 58) (p=0.50). All strokes were ischemic. Stent occlusion was diagnosed in 2 patients within the 30-day follow-up; one of them (No. 3, Table 2) experienced a major stroke during coronary artery bypass surgery performed under anticoagulant but not combined antiplatelet treatment; the other remained symptom-free. Restenosis was not observed. One patient suffered severe hypotension requiring intensive care. Blood transfusion was necessary in 1 case because of a considerable blood loss from the femoral puncture site.

Of the 31 covered stents, 14 (45.2%) were implanted in symptomatic cases; 23 (74.2%) were used for irregular/ulcerated stenoses, and 8 (25.8%) in high-risk cases. No ipsilateral neurological complications developed in the patients receiving covered stents, as opposed to the 5.8% complication rate (13 ipsilateral neurological symptoms with 226 treated vessels) among those with regular stents (p=0.38). No technical difficulties were experienced with the use of covered stents.

The rate of neurological complications was 2.0% (1 during 49 procedures) in 2001, 5.9% (6 of 102) in 2002, and 6.4% (7 of 109) from January to July, 2003.

4.2. Study of the relationship between the degree of in vitro platelet aggregation and the risk of recurrent vascular events in aspirin-treated patients

Two hundred and forty-one patients were included in this study. The duration of aspirin treatment was <1 year in 119 (49.4%), 1-2 years in 45 (18.7%), 2-3 years in 14 (5.8%), 3-4 years in 27 (11.2%), 4-5 years in 11 (4.6%), and >5 years in 13 (5.4%) patients. In 12 (5.0%) cases, the duration of aspirin treatment was >30 days, but could not be determined more precisely. Seventy-eight (32.4%) patients suffered a recurrent ischemic episode, of which 21 were (8.7%) “hard” secondary events. The number of patients who displayed recurrent events of any type was 34 (28.6%) for a treatment duration <1 year, 15 (33.3%) for 1-2 years, 6 (42.9%) for 2-3 years, 12 (44.4%) for 3-4 years, 6 (54.5%) for 4-5 years, 4 (30.8%) for >5 years, and 1 (8.3%) for the group with an unknown treatment duration. The corresponding numbers of patients who experienced “hard” events were 9 (7.6%), 2 (4.4%), 2 (14.3%), 4 (14.8%), 1 (9.1%), 3 (23.1%) and 0 (0.0%), respectively.

Table 3 compares the features of the patients with a history of a single event as opposed to those with recurrent ischemic events of any type. The patients with recurrent ischemic episodes were significantly older and exhibited a higher rate of hypertension. In the group who suffered “hard” recurrent events, only the age was significantly higher (Table 4). The degree of platelet aggregation was not statistically significantly different with either collagen or

epinephrine between patients with single events as opposed to recurrent events of any type. This observation holds true for the comparison of the groups with or without "hard" recurrences (Tables 3 and 4 and Fig. 3).

Table 3. Characteristics of patients with single or recurrent events

	Only a single ischemic event (n=163)	Ischemia recurred (n=78)	p value
Age (yrs)	58.4±11.6	62.5±10.6	0.009*
Female	64 (39.3)	33 (42.3)	0.65
Hypertension	111 (68.1)	63 (80.8)	0.040*
Diabetes	36 (22.1)	25 (32.1)	0.096
Hyperlipidemia	66 (40.5)	37 (47.4)	0.31
Smoking history	66 (40.5)	29 (37.2)	0.62
Obesity	44 (27.0)	25 (32.1)	0.42
Platelet aggregation (%)			
collagen-induced	38±21	39±19	0.65
epinephrine-induced	30±18	32±18	0.43

Values in parentheses are percentages.
*Significant difference ($p<0.05$)

Table 4. Characteristics of patients with or without "hard" recurrent events

	Secondary "hard" ischemia did not occur (n=220)	Secondary "hard" ischemia occurred (n=21)	p value
Age (yrs)	59.3±11.4	64.5±10.8	0.048*
Female	90 (40.9)	7 (33.3)	0.50
Hypertension	156 (70.9)	18 (85.7)	0.15
Diabetes	53 (24.1)	8 (38.1)	0.16
Hyperlipidemia	96 (43.6)	7 (33.3)	0.36
Smoking history	88 (40.0)	7 (33.3)	0.55
Obesity	64 (29.1)	5 (23.8)	0.61
Platelet aggregation (%)			
collagen-induced	39±20	35±19	0.36
epinephrine-induced	31±18	28±13	0.45

Values in parentheses are percentages.
*Significant difference ($p<0.05$)

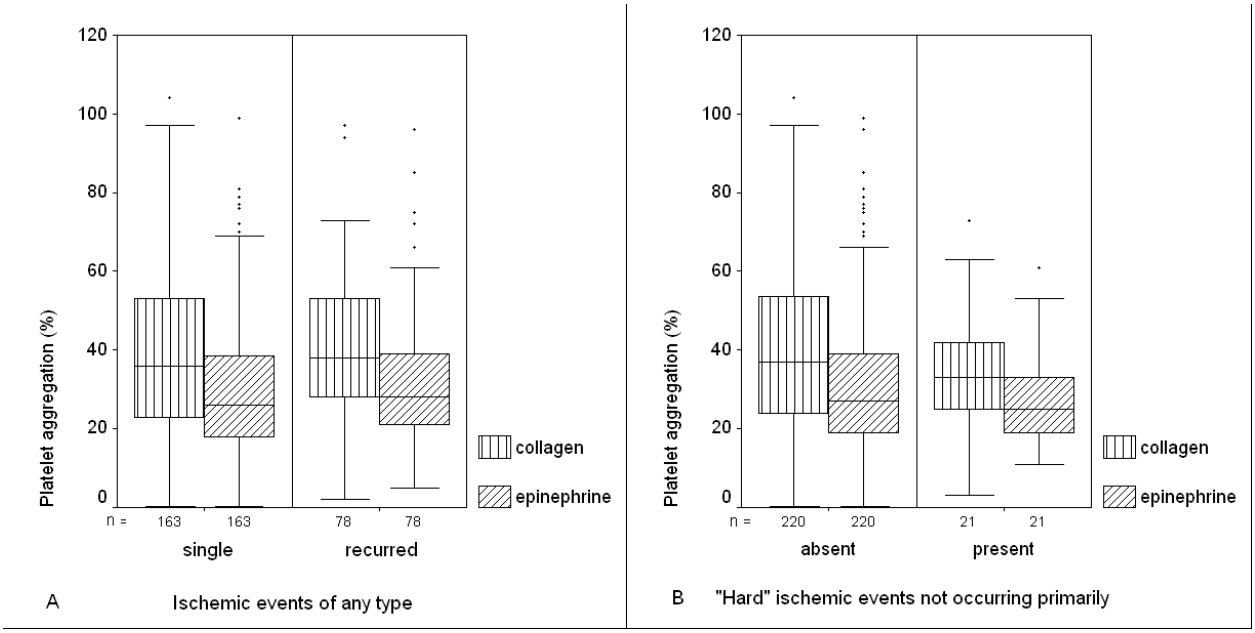

Fig. 3. Box and whisker plots indicating the distribution of platelet aggregation values for patients with recurrent ischemic events of any type (A) or "hard" recurrent events (B), as compared with cases without such episodes. All outliers and extremes are shown.

Stepwise logistic regression analysis identified age as a risk condition for all recurrent episodes (odds ratio [OR] 1.033 per year, 95% CI 1.008-1.058, p=0.010). For "hard" events, the impact of this variable was on the borderline of statistical significance (OR 1.041 per year, CI 1.000-1.084, p=0.051). The degree of platelet aggregation itself was not associated with an increased risk either of recurrent events of any type or of secondary "hard" events in the regression modeling.

4.3. Survey on antithrombotic treatment

Of the 40 mailed questionnaires, 26 (65%) were returned for evaluation. Those who returned the completed questionnaire are referred to below as responders.

It emerged that most of the responders (18 of 26; 69%) always wait until brain imaging has been performed before administering antithrombotic treatment in acute stroke.

Twenty-four (92%) responders identified specific conditions in which anticoagulation is applied in the acute phase of stroke. Such situations include cardiogenic embolism (named by 18 of the 24 experts; 75%), progressing stroke (6/24; 25%), a near-occlusive state of the carotid or basilar arteries (5/24; 21%), a coagulopathic state (3/24; 13%), arterial dissection (2/24; 8%), severe brain stem symptoms (1/24; 4%), a mobile thrombus (1/24; 4%), multiple ischemic lesions (1/24; 4%), and repeated TIAs (1/24; 4%). Of the 23 participants (88%) who answered

the question concerning the preferred anticoagulant formulation, 20 (87%) use only low molecular weight heparin (LMWH), while 3 (13%) apply either LMWH or heparin.

Table 5 demonstrates the relative frequencies with which antiplatelet agents are administered after a first noncardioembolic ischemic stroke. In the majority of the responders, aspirin is the most frequently prescribed antiplatelet agent; clopidogrel, the combination of aspirin plus dipyridamole, and ticlopidine feature less frequently as first choice. Of the 24 (92%) participants who reported the preferred dose of aspirin, 19 (79%) recommend 100 mg/day, while 5 (21%) prescribe a higher dose, in the range up to 300 mg/day.

Table 5. Choice of first antiplatelet agent after a first noncardioembolic ischemic stroke

	First choice	Second choice	Third choice	Number of responders
1.	aspirin	clopidogrel	aspirin+dipyridamole	10 (38)
2.	aspirin	aspirin+dipyridamole	clopidogrel	8 (31)
3.	aspirin	clopidogrel	ticlopidine	3 (11)
4.	aspirin	ticlopidine	clopidogrel	2 (8)
5.	aspirin	aspirin+dipyridamole	ticlopidine	1 (4)
6.	clopidogrel	aspirin+dipyridamole	aspirin	1 (4)
7.	aspirin+dipyridamole	clopidogrel	-------	1 (4)

Values in parentheses are percentages.

The reasons for choosing an alternative antiplatelet agent rather than aspirin following a first ischemic episode are listed in Table 6. Both clopidogrel and the combination of aspirin and dipyridamole are believed by many participants to be more effective than aspirin alone, and therefore more suitable for high-risk patients. Intolerance or allergy to aspirin are important factors in decisions in favor of clopidogrel and ticlopidine. The combination of aspirin and dipyridamole is prescribed by some in the event of an intolerance to higher-dose aspirin. The results of *in vivo* platelet aggregation studies frequently influence the drug selection. Clopidogrel is considered by some respondents to be well tolerated, while the combination of aspirin and dipyridamole is regarded as a less expensive alternative to clopidogrel. Many participants would leave patients on ticlopidine if no side-effects occurred.

Table 6. Common reasons for prescribing an alternative antiplatelet agent if not aspirin is given following a first ischemic cerebrovascular event.

	Clopidogrel	Aspirin + dipyridamole	Ticlopidine
No. of valid answers	26 (100)	20 (100)	21 (100)
Indication			
High-risk patient or more effective agent	12 (46)	10 (50)	---
Intolerance or allergy to aspirin	15 (58)	4 (20)*	9 (43)
Intolerance or allergy to clopidogrel	---	---	4 (19)
Intolerance or allergy to both aspirin and clopidogrel	---	---	3 (14)
Past or present PUD or GI bleeding	10 (38)	2 (10)	2 (10)
In vitro aspirin resistance	9 (35)	3 (15)	7 (33)
Good tolerability	3 (12)	---	---
Not so expensive	---	3 (15)	---
No CHD present	---	1 (5)	---
Small-vessel disease	---	1 (5)	---
The patient has been taking the drug without side-effects	---	---	7 (33)

The number (and percentage) of responders favoring a specific reason is indicated.
* Only intolerance to higher-dose aspirin
CHD coronary heart disease, GI gastrointestinal, PUD peptic ulcer disease

If a patient suffered a recurrent stroke or TIA while taking aspirin, 2 (8%) responders would not automatically change the antiplatelet treatment, and 2 (8%) would increase the dose of aspirin. Nineteen (73%) indicated a switchover to clopidogrel, 9 (35%) to aspirin plus dipyridamole, and 4 (15%) to ticlopidine. If a recurrent cerebrovascular ischemic event occurred during clopidogrel treatment, 6 (23%) neurologists would not automatically change the antiplatelet medication. Nine (35%) would switch to aspirin plus dipyridamole, and 6 (23%) to aspirin plus clopidogrel, while 6 (23%) would consider anticoagulation. Ticlopidine and aspirin would each be selected by 1 (4%) contributor, whereas dipyridamole would be chosen by 2 (8%).

The responses received from 21 (81%) neurologists indicate that, in addition to its administration after recurrent strokes, as reported in the previous paragraph, the combination of aspirin and clopidogrel is also held to be beneficial in other circumstances for the prevention of stroke. Such situations include a concomitant cardiological disease that otherwise requires

treatment with this combination (12/21 answers; 57%), high-risk patients (5/21; 24%), patients with severe carotid artery stenosis (3/21; 14%), and young individuals (1/21; 5%). The presence of a carotid artery stent was frequently mentioned (7/21; 33%) as a condition requiring the combination of aspirin and clopidogrel.

Oral anticoagulation is implemented in cardioembolic stroke (26/26; 100%), in hypercoagulable states (9/26; 35%), in intracranial stenosis (3/26; 12%), in cervical artery dissection (2/26; 8%), in inoperable severe carotid artery stenosis (1/26; 4%), in dolichoectasia of the basilar artery (1/26; 4%), and after certain recurrent strokes, as already mentioned above.

Sixteen (62%) neurologists listed their indications for the combination of oral anticoagulation with antiplatelet treatment for stroke prevention. Such medication may be an option in certain cardiological disorders (12/16; 75%), in very high-risk individuals (4/16; 25%), and in patients exhibiting both cardioembolic and atherothrombotic mechanisms (1/16; 6%). Fourteen of the 16 responders (88%) provided information on the antithrombotic agent they would use in combination with oral anticoagulation: aspirin only would be given by 7 (50%), and clopidogrel only by 1 (7%), and 6 (43%) would permit either aspirin or clopidogrel.

5. Discussion

5.1. Study of CAS

The rate of all strokes and death, 4.8% among the symptomatic and 2.9% among the asymptomatic cases in our study compares favorably with the results obtained in the NASCET (NASCET Collaborators, 2001) and ACAS (Executive Committee for the ACAS, 1995) investigations of CEA, in which the rate of all strokes and death was 5.8% for symptomatic ≥70%, and 2.3% for asymptomatic ≥60% cases, respectively. The Stent-protected Percutaneous Angioplasty of the Carotid vs Endarterectomy (SPACE) and Endarterectomy versus Stenting in Patients with Symptomatic Severe Carotid Stenosis (EVA 3S) studies recently compared the 30-day outcome of CAS with CEA in symptomatic patients in a multicenter, randomized fashion (Mas, 2006; SPACE Collaborative Group, 2006). The SPACE study, in which the primary outcome was periprocedural ipsilateral ischemic stroke or death, failed to prove the non-inferiority of CAS as compared with CEA. The rates of all strokes and death for both CAS (7.7%) and CEA (6.5%) slightly exceeded the desirable upper limit of 6%. In the EVA 3S trial, the 30-day incidence of any stroke or death was significantly higher in the CAS (9.6%) than in the CEA (3.9%) group. A recent Cochrane review of randomized studies of endovascular versus surgical treatment in symptomatic and asymptomatic patients concluded that the primary

outcome comparison of any stroke or death within 30 days of treatment favored CEA, a statistically significant difference being reached in one of the two applied models of analysis. Cranial nerve injury occurred significantly less frequently with endovascular treatment (Ederle, 2007).

High-risk conditions in our study included contralateral carotid occlusion and some exclusion criteria of the NASCET and ACAS studies: age ≥80 years, post-endarterectomy restenosis, cervical radiation treatment, and severe cardiac or pulmonary disease. It is an important observation of our study that the rate of observed major complications (death and major stroke) was significantly elevated in the high-risk as compared with the low-risk group. This was due to a significant difference between the two risk profile groups among the asymptomatic (but not among the symptomatic) patients. However, a chance of bias can not be fully excluded as the overall number of complications was relatively low. The Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) study compared the incidence of death, stroke or myocardial infarction within 30 days in symptomatic or asymptomatic high-risk patients randomized either to CAS or CEA (Yadav, 2004). High-risk conditions in that study, many of which were NASCET and ACAS exclusion criteria, are indicated in Table 7. The periprocedural composite rates of stroke, death or MI were 9.8% for CEA and 4.8% for CAS, a difference not statistically significant. It is of note that the rate of stroke or death at 30 days among asymptomatic patients was 4.6% for CEA and 5.4% for CAS, both of which are above the maximum 3% complication rate recommended by the guidelines. On the basis of our own findings and those of others, it is questionable whether asymptomatic patients at high risk of periprocedural complications achieve any benefit at all from either CAS or CEA, taking into account the relatively low rate of stroke on medical therapy in asymptomatic cases.

Many exclusion criteria applied in the NASCET and ACAS studies (Table 7) are commonly believed to convey an increased risk in CEA. However, there is evidence that CEA can be performed safely in such “high-risk” cases too (Mozes, 2004). In fact, many of these exclusion criteria have not actually been confirmed to increase the risk of stroke on medical therapy. Furthermore, as a result of exclusion, the applicability of the findings of these major studies of CEA to patients with such significant comorbidities is not well-defined.

Table 7. Identification of high-risk cases with medical or surgical therapy, the NASCET/ACAS exclusion and SAPPHIRE inclusion criteria

Risk conditions for stroke on medical therapy	Risk conditions for surgical complications	NASCET/ACAS exclusion criteria	SAPPHIRE inclusion criteria
Symptomatic stenosis	Symptomatic stenosis		
Male gender	Female gender		
Increasing age	Old age (>75 years)	Age > 80 years	Age > 80 years
Hemispheric event	Hemispheric TIA		
Ulcerated/irregular plaque	Ulcerated/irregular plaque		
Higher degree of stenosis			
Shorter interval since index event			
	Peripheral vascular disease		
	Contralateral occlusion		Contralateral occlusion
	Ipsilateral carotid siphon stenosis	Tandem lesions	
		Prior ipsilateral CEA	Prior ipsilateral CEA
		Neck irradiation	Neck irradiation
		Contralateral CEA within 4 months	
			Previous radical neck surgery
			Contralateral recurrent laryngeal nerve palsy
		Other lesion that could produce symptoms	
		Previous stroke with profound deficit	
		Contralateral symptoms within 45 days	
		Nonhemispheric symptoms	
		Significant cardiac disease:	Clinically significant cardiac disease:
		Atrial fibrillation	
		Unstable angina	
		Myocardial infarction within 6 months	
		Symptomatic congestive heart failure	Congestive heart failure
		Significant valve disease	
			Need for open-heart surgery
			Abnormal stress test
		Lung, liver or renal failure	Severe pulmonary disease
	Systolic hypertension	Uncontrolled hypertension or diabetes	
		Other major surgery within 1 month	
		Allergy to aspirin or active peptic ulcer	
		Warfarin use	
		Cancer with <50% 5-year survival	

A number of conditions increasing the risk of a stroke in patients with carotid stenosis, or associated with a higher complication rate from CEA have been identified in previous studies (Table 7). The distinction between these two groups of risk factors seems justified because CEA can be expected to be most beneficial for those at an increased risk of stroke on medical treatment, but at a relatively low risk of surgical complications. CAS may be more advantageous in patients at an increased risk in CEA, if performed with a lower complication rate.

Symptomatic patients have a more than 10-fold risk of stroke during the first 2 years after the index event as compared with asymptomatic individuals. In cases with recently symptomatic carotid stenosis, the 5-year risk of an ipsilateral stroke during medical treatment is elevated in males, and with increasing age, a higher degree of stenosis, a hemispheric as opposed to an ocular presenting event, ulcerated/irregular instead of smooth plaques, and a shorter interval since the last symptomatic event (Rothwell, 2005).

The risk of stroke or death as a complication of CEA is significantly lower for asymptomatic than symptomatic stenosis (Rothwell, 1996). Other risk factors of stroke and death associated with CEA include presentation with a cerebral TIA versus an ocular ischemic event, female sex, older age (>75 years), systolic hypertension, peripheral vascular disease, contralateral carotid occlusion, an ipsilateral ischemic lesion on CT scan, irregular or ulcerated ipsilateral plaque, and ipsilateral carotid siphon stenosis (Bond, 2002; Ferguson, 1999; Rothwell 1997).

It has been a significant observation that the operative risk of stroke and death is unrelated to the risk during medical treatment (Rothwell, 2005). It is important that some patients at high risk during CEA are not necessarily at a high risk of stroke on medical therapy, and therefore CEA may not be beneficial for them, whereas other patients with a high stroke risk on medical therapy may still benefit from CEA even if the risk involved in the surgery is increased. Benefit from CEA in symptomatic stenosis is greatest in men, patients aged >75 years, and individuals randomized within 2 weeks after their last ischemic event. Benefit from surgery is probably also the greatest in patients with stroke, intermediate in those with cerebral TIA, and the lowest in those with retinal events. There is also a trend toward greater benefit in patients with irregular rather than with smooth plaque. Surgery is not beneficial in various subgroups (e.g. women) with symptomatic 50-69% stenosis (Rothwell, 2004b). As concerns CEA for asymptomatic stenosis, an elevated surgical complication rate can obviate the relatively modest benefit of the surgery in this population. Asymptomatic women and patients with an occlusion contralateral to the asymptomatic side do not appear to benefit from surgery.

Risk factors for peri-interventional stroke or death associated with CAS include diabetes mellitus with inadequate glycemic control, age ≥80 years, ulceration of the carotid plaque, and contralateral stenosis of ≥50% (Hofmann, 2006). This observation indicates that many risk factors for an adverse outcome of CEA are also risk factors for CAS-related complications. Therefore, CAS may not necessarily be an appropriate alternative for all patients who are at high risk from CEA. According to current consensus, CAS may be beneficial chiefly in symptomatic patients with recurrent stenosis after CEA, previous cervical radiation, prior radical neck surgery, high bifurcation or distal plaque, stenoses involving the ostium or proximal portion of the common carotid or the innominate artery, neck immobility, the presence of a tracheostomy, a contralateral recurrent laryngeal nerve dysfunction, contralateral carotid occlusion, and significant cardiac or pulmonary disease. CAS may be complicated by severe atherosclerosis or calcification of the aortic arch, extreme angulation of the great-vessel origins from the aorta, severe tortuosity of the common or internal carotid artery, severe calcification of the target carotid stenosis, and the inability to obtain femoral artery access (Narins, 2006). It must be emphasized that, for many high-risk patients, a more crucial decision than deciding how to perform revascularization is to determine whether any form of revascularization is preferable to medical therapy. Moreover, the long-term efficacy of CAS as concerns stroke prevention also requires further evaluation.

Models based on previous observations in the medical arms of CEA trials might overestimate the risk in current patients because of improvements in medical treatment, such as the increased use of statins. It would take only a relatively modest improvement in the effectiveness of medical treatment to erode the overall benefit of CEA in patients with 50-60% symptomatic stenosis or in asymptomatic cases.

To resolve some of the above uncertainties, further trials comparing CAS, CEA or the best medical treatment are under way. The Carotid Revascularization Endarterectomy versus Stenting Trial (CREST) is a prospective, randomized, multicenter clinical trial assessing the relative efficacy of CEA versus CAS in the prevention of stroke, MI and death during a 30-day periprocedural period, and ipsilateral stroke thereafter in subjects with symptomatic and asymptomatic extracranial carotid stenosis (Major ongoing stroke trials, 2008). The International Carotid Stenting Study (ICSS) is a prospective, randomized, multicenter trial comparing the risks of treatment and benefits in the prevention of stroke in symptomatic individuals with primary CAS in comparison with conventional CEA (Major ongoing stroke trials, 2008). The Asymptomatic Carotid Stenosis, Stenting Versus Endarterectomy Trial (ACT I) plans to

compare CEA and CAS in asymptomatic patients in a randomized, multicenter fashion (www.strokecenter.org, accessed 02/03/2008). The ACST-2 would also randomize appropriate patients with asymptomatic disease to surgery versus stenting (www.acst.org.uk, accessed 02/03/2008). The Transatlantic Asymptomatic Carotid Intervention Trial (TACIT) will study all-risk patients who have asymptomatic carotid artery stenosis, and will assign these patients to one of three treatment arms. The first arm will provide optimal medical therapy alone, consisting of antiplatelet, antilipidemic and antihypertensive therapy, as well as tight glycemic control and tobacco cessation efforts. The second arm will provide optimal medical therapy plus CEA. The third arm will provide optimal medical therapy plus CAS, with embolic protection using commercially available devices at the time of trial initiation (www.evtoday.com, accessed 02/03/2008).

Endovascular management has been associated with a probably higher rate of procedural embolization than that for CEA (Jordan, 1999; Tedesco, 2007). In an attempt to reduce periprocedural complication rates during CAS, cerebral protection devices were developed, those most commonly used being distal filters and occlusive distal balloons. However, in addition to causing increases in the intervention time, the technical complexity and the cost, the application of protection devices may also lead to complications, including hemodynamic intolerance due to balloon occlusion or congested nets, spasm or dissection of the carotid artery, and difficulties with retrieval of the device (Cremonesi, 2003; Eckert, 2003; Reimers, 2001). Furthermore, predilatation, which is often necessary in protected CAS, and the removal of the protection devices may result in embolization. Not all particles may be removed from behind the balloon-occlusion type device, and small particles (even though probably clinically insignificant) may pass through the filter systems. Protection devices do not prevent the late embolization of particles trapped in the stent meshes. Interestingly, a study has reported more procedural microemboli, as detected by transcranial Doppler monitoring, during CAS in patients treated with filtering protection devices than in unprotected procedures (Vos, 2005). Our study indicates that CAS without protection devices appears to be safe. However, a systematic review of the early outcome of carotid angioplasty and stenting in both symptomatic and asymptomatic patients found that the combined stroke and death rate with cerebral protection was 1.8%, i.e. significantly lower than the 5.5% in those treated without protection devices (Kastrup, 2003), whereas the Cochrane review concluded that there was no significant difference in the 30-day stroke or death rate between endovascular treatment with or without a protection device (Ederle, 2007). The periprocedural stroke rate was lower with the use of protecting devices in the EVA 3S study (Mas, 2004). On the other hand, in the SPACE trial, where such devices were used in

27% of the CAS cases, there was no difference in the rate of ipsilateral ischemic stroke or death between patients treated with or without protection devices (SPACE Collaborative Group, 2006). Our results indicate that postprocedural embolization may be responsible for a significant proportion of the complications. Neurological complications could not have been prevented with a protection system in 9 (64.3%) cases in our series because these were not intraprocedural complications.

As far as we are aware, ours was the first published report on the application of covered Symbiot stents for carotid stenosis. Covered stents prevent the passage of atherosclerotic material through the stent mesh. Our results indicate that covered stents may safely and efficiently reduce neurological complications due to embolizations during stent deployment and postdilatation, and also postprocedurally. A significant reduction in ipsilateral microembolic signals by transcranial Doppler during the use of covered Symbiot stents has been reported, but a higher rate of restenosis has also been observed with such stents (Schillinger, 2006). Further studies are expected to provide more data on the use of covered stents for carotid stenosis, although relatively large case numbers would be necessary to demonstrate statistically significant differences in complication rates. Developments in endovascular technology, pharmacological management and expertise should lead to further reductions in the complication rates associated with CAS.

5.2. Study of the relationship between the degree of in vitro platelet aggregation and the risk of recurrent vascular events in aspirin-treated patients

The main findings of this study are that results obtained with optical platelet aggregometry do not appear to be good indicators of the risk of recurrent vascular events in patients taking aspirin, and that conventional risk factors are more important predictors.

Eikelboom et al. reported that patients in whom MI, stroke or cardiovascular death developed had a higher mean body mass index and baseline blood pressure and were more likely to be current smokers or to have a history of hypertension, diabetes, MI or peripheral vascular disease (Eikelboom, 2002). Gum et al. highlighted congestive heart failure, an elevated platelet count and advancing age as correlates of a poor outcome (Gum, 2003). Grotemeyer et al. demonstrated that an older age, the accumulation of vascular risk factors and pre-existing vascular disease had adverse impacts on the prognosis (Grotemeyer, 1993). After adjustment for other baseline characteristics, all three studies identified aspirin resistance as an independent predictor of adverse long-term events, although the methods used to examine aspirin resistance in the various studies differed.

The findings of the above reports are in contrast with our own. It should be mentioned, however, that the Gum study, which used optical platelet aggregometry as we did, drew its conclusions on the basis of relatively few events, especially in the aspirin-resistant group (4 events in 17 cases). Furthermore, information on how aspirin resistance had been defined was not provided.

There are advantages to our study. Aspirin resistance was not defined as aggregation above an arbitrary limit, but exact aggregation percentages were used as a continuous variable in the analyses. It has been suggested that aspirin resistance is a continuum, similarly to other biological variables such as age, blood pressure or blood cholesterol level (Hankey, 2006). In contrast with many studies that reported merely the prevalence of *in vitro* aspirin resistance in the population under investigation, we additionally evaluated the clinical outcome.

Our study has limitations, some of which are due to its retrospective nature. The duration of aspirin treatment could not be determined more precisely than presented in the Results section. Patients with a longer history of vascular disease are expected to undergo more recurrent events. Although aggregometry was performed at the end of the follow-up period, we do not consider this a disadvantage as the *in vitro* response to aspirin may vary with time (Helgason, 1994), and earlier testing would therefore not necessarily have been more informative. The possibility of a type II error can not be excluded due to the relatively small size of the study, and in particular the low number of "hard" events. However, the rate of such events among our patients is similar to that in the study by Gum et al. A further limitation of our study is the fact that compliance with aspirin taking was assessed by questioning, and salicylate levels were not measured.

We believe that our results are of considerable importance for everyday clinical practice. The findings of this study do not support the routine use of platelet aggregometry to assess the risk of vascular events during aspirin treatment. It is not known, however, whether a change in the aggregation value in response to aspirin administration (requiring measurements both before and during aspirin treatment) would be a better predictor instead of a single absolute value measured during aspirin administration. Platelet responsiveness to aspirin is variable. This variability in response to aspirin has been found to demonstrate consistent heritability (27-77%), and to be highly governed by the baseline platelet phenotype, indicating that pre- and post-aspirin phenotypes may be determined by the same genetic background (Faraday, 2007). Vascular risk factor covariates made only a minimal contribution to the variability observed. An important limitation of that study is that the correlation of risk factors and *in vitro* aggregation with the clinical outcome was not investigated.

The literature furnishes no evidence that patients exhibiting inadequate *in vitro* platelet inhibition while taking a given dose of aspirin benefit from a modified antiplatelet regime. In addition to the prescription of an antiplatelet drug, attention must not be diverted from other possibilities of secondary prevention. Unfortunately, conventional risk factors are poorly controlled in many patients who have suffered a stroke (Johnson P, 2007). Routine testing for aspirin resistance and changing therapy on the basis of laboratory tests can currently not be recommended (Michelson, 2005).

5.3. Survey on antithrombotic treatment

This is one of the very few published reports from Eastern Europe on the tendencies in the use of antithrombotic treatment in ischemic stroke. An obvious advantage of this study over previous reports of this kind (Lalouschek, 2001; Masuhr, 1998; Mayer, 2003; Török, 2003) is that it reflects more recent clinical practice.

In Hungary, some 42-50,000 people are hospitalized for acute stroke each year (Brainin, 2000; Gulácsi, 2007). Our survey revealed that 31% of the responders do not always wait for brain imaging to be performed before initiating antithrombotic treatment for patients with a diagnosis of suspected ischemic stroke. This may in part reflect the situation that a brain CT may not always be instantly available in an acute setting. An international survey published in 2000 reported that the rate of performance of acute CT examinations in hospitalized stroke patients displays great variability (0-100%) in the different countries (Brainin, 2000; Mihálka, 1999).

The American Heart Association guidelines on the early management of ischemic stroke do not recommend urgent anticoagulation for patients with acute stroke (Adams, 2007). The European Stroke Initiative recommendations list situations such as cardiac sources with a high risk of re-embolism, arterial dissections, coagulopathies, high-grade arterial stenoses prior to surgery, or high-grade stenoses with crescendo TIAs or stroke in progression, when full-dose heparin may be used (Hacke, 2003). The data stemming from our survey indicate that, as concerns the initiation of early anticoagulation, this group of practitioners tend to act mainly in line with the European guidelines, though the preferred agent is not heparin, but LMWH, probably in view of its easier and safe use.

Aspirin, the antiplatelet agent most commonly prescribed after a first stroke by these practitioners, is given within the dose range recommended by practice guidelines (50-325 mg/day) (A Magyar Stroke Társaság, 2004; Hacke, 2003; Sacco, 2006). The most common dose is 100 mg/day; lower doses are not prescribed at all, and higher doses (up to 300 mg/day) are recommended by approximately one-fifth of the responders. In Europe, daily aspirin doses are

usually in the range 100-350 mg, but some practitioners prefer less than 100 mg (Masuhr, 1998). Earlier studies indicated that most American neurologists appeared to favor 300-350 mg/day, and a significant proportion of them suggested an even higher level (Masuhr, 1998; Mayer, 2003).

As regards the selection of an antiplatelet agent after a first stroke, it is noteworthy that ticlopidine is chosen as second- or third-line agent by a considerable proportion of the participants (Table 5). This is in contrast with the Indiana University study (Mayer, 2003), which reported a total decline in the use of ticlopidine in recent years. Ticlopidine has a relatively unfavorable side-effect profile, and its use in many countries has largely been suppressed by the appearance of a newer thienopyridine, clopidogrel. Our finding of the continuing administration of ticlopidine in Hungary may be explained by the fact that, at the time of the survey, the Hungarian health insurance regulations relating to drug prescription actually encouraged the use of ticlopidine; additionally, patients pay somewhat less for ticlopidine than for clopidogrel.

Clopidogrel is frequently prescribed by virtue of its effectiveness. It is somewhat surprising that efficacy in our survey was not a reason in favor of the other thienopyridine, ticlopidine. A Cochrane Database review (Hankey, 2000) concluded that, in patients with TIA or ischemic stroke, there was a borderline statistically significant reduction in the odds of stroke, MI or vascular death among individuals allocated a thienopyridine as compared with those allocated aspirin, corresponding to the avoidance of 14 serious vascular events per 1000 patients treated for about 2 years. As concerns stroke of all types as an outcome in TIA/ischemic stroke patients, the odds in the group allocated a thienopyridine were significantly less than those in the group allocated aspirin, corresponding to 16 strokes avoided per 1000 patients treated for 2 years. The number needed to treat values obtained from the above review are unfortunately fairly high. The combination of aspirin plus dipyridamole is also frequently given for reasons of efficacy. In patients with a TIA or stroke, the European Stroke Prevention Study (ESPS-2) found that the combination of aspirin plus dipyridamole was more effective than aspirin alone in reducing the risk of a further stroke, preventing 30 strokes per 1000 patients treated for 2 years (Diener, 1996). As regards the clinical endpoint of stroke and/or death in stroke/TIA patients, the risk reduction observed with the combination of aspirin plus dipyridamole merely approached statistical significance as compared with aspirin alone, whereas for the prevention of death, this combination was not statistically significantly better than aspirin alone. The generalizability of the findings of the ESPS-2 study was brought into question by two important meta-analyses (Antithrombotic Trialists' Collaboration, 2002; De Schryver, 2006), mainly because this had

been the only available study to demonstrate the benefit of the combination of aspirin plus dipyridamole over aspirin. The recently published European / Australasian Stroke Prevention in Reversible Ischaemia Trial (ESPRIT Study Group, 2006), however, has furnished results similar to those of the ESPS-2 trial. The ongoing Prevention Regimen for Effectively Avoiding Second Strokes (PRoFESS) trial will help to assess the relative efficacy of aspirin plus dipyridamole versus clopidogrel (Diener, 2007).

The Vienna Stroke Study Group (Lalouschek, 2001) concluded that clopidogrel is more likely to be prescribed to diabetics, and to patients with concomitant coronary or peripheral arterial disease. Both clopidogrel and the combination of aspirin plus dipyridamole were preferred for those who had suffered a previous cerebrovascular event. Our study confirms that the high-risk status of a patient is an important factor in the selection of an alternative antiplatelet agent as first choice rather than aspirin, even though the evidence as to the unambiguous superiority of certain alternative antiplatelet regimes in such stroke/TIA patients may not be fully convincing (Warlow, 2002).

It is interesting that aspirin resistance determined by *in vitro* methods (e.g. optical platelet aggregometry) has been listed as a reason why many participants select alternative antiplatelet medication, despite the fact that at present such a practice may not be considered adequately evidence-based, and *in vitro* testing for aspirin resistance is usually not recommended on a routine basis (Michelson, 2005). Intolerance, allergy and an adverse side-effect profile were important arguments against a particular antiplatelet agent (Table 6). Our study has revealed that an important feature in favor of the use of clopidogrel was the view that it was well tolerated, whereas a significant point promoting the selection of the combination of aspirin plus dipyridamole was that it was considered affordable.

If a patient suffers a recurrent cerebrovascular ischemic attack while taking a given antiplatelet agent, some responders would not automatically modify that antiplatelet treatment: a higher proportion would do so when clopidogrel is given relative to the situation when aspirin is administered. Although not supported by clinical evidence, most practitioners answering this survey change the antiplatelet medication in the event of recurrent attacks. Since similar findings have emerged from other studies (Lalouschek, 2001; Mayer, 2003), this attitude may be considered rather common clinical practice. Conversion to the combination of aspirin plus clopidogrel, or to oral anticoagulation, was mentioned when the recurrent attack occurred during clopidogrel therapy; such options were not indicated for recurrences while aspirin was being taken.

Most participants in this study named situations in which they believe that the combination of aspirin plus clopidogrel may be beneficial. This survey was conducted after the results of the Management of Atherothrombosis with Clopidogrel in High-risk Patients with Recent TIA or Ischemic Stroke (MATCH) trial (Diener, 2004) had been published, but before the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management and Avoidance (CHARISMA) study (Bhatt, 2006) appeared. The most important outcome of those studies was that the combination of aspirin plus clopidogrel did not furnish a significant overall benefit in comparison with a single agent in patients without an acute coronary syndrome. Accordingly, the administration of the combination of aspirin plus clopidogrel in certain high-risk cases may not be supported by sufficient clinical evidence. The use of aspirin plus clopidogrel in patients with carotid artery stenosis may be explained by the findings of the Clopidogrel and Aspirin for Reduction of Emboli in Symptomatic Carotid Stenosis (CARESS) trial (Markus, 2005), in which the combination of aspirin plus clopidogrel was more effective than aspirin alone in reducing asymptomatic embolization as detected by transcranial Doppler monitoring in patients with recently symptomatic carotid artery stenosis. Results of the Fast Assessment of Stroke and Transient Ischemic Attack to Prevent Early Recurrence (FASTER) trial suggest that a combination of clopidogrel and aspirin administered within 24 hours of a TIA or minor stroke may be associated with a reduced risk of recurrent stroke relative to aspirin alone (Kennedy, 2007). Several trials are currently in progress to evaluate a combination of aspirin plus clopidogrel for specific stroke populations, such as lacunar stroke in the Secondary Prevention of Small Subcortical Strokes (SPS 3) trial, aortic arch atheromatous disease in the Aortic Arch Related Cerebral Hazard (ARCH) study, and acute ischemic stroke in the Clopidogrel in Acute Stroke and TIA (CASTIA) trial (Rothwell, 2006; www.strokecenter.org, accessed 02/03/2008).

The employment of oral anticoagulation in our sample is common evidence-based practice for cardioembolic conditions. Oral anticoagulation is selected, in accordance with the guidelines (Hacke, 2003; Sacco, 2006), in certain other situations too, including hypercoagulable states, cervical artery dissections, and basilar artery dolichoectasia (fusiform aneurysm). Although some studies (Lalouschek, 2001; Masuhr, 1998), similarly to ours, have revealed that an oral anticoagulant is frequently administered in large-artery atherosclerotic disease and after recurrent strokes during antiplatelet therapy, there is insufficient evidence in support of this practice.

The combination of oral anticoagulation and antiplatelet treatment may be an option in certain cardioembolic states, such as the recurrence of symptoms despite adequate levels of

anticoagulation (Sacco, 2006). Aspirin is the recommended antiplatelet agent; no data are available as concerns the usefulness of clopidogrel in combination with oral anticoagulation. Since the category of very high-risk individuals was not defined in detail by the responders, we can only presume that it may have overlapped with the group of cardiological disorders. Although it may appear logical, there is no evidence that the coexistence of atherothrombotic and cardioembolic etiologies may be an indication for simultaneous antiplatelet and anticoagulant regimes. The appropriateness of combined anticoagulant and antiplatelet therapy has not been well described in the guidelines. A recent study demonstrated that nearly 40% of patients receiving warfarin management care were on combined warfarin and antiplatelet therapy (Johnson SG, 2007). Clinicians should carefully assess the risks and benefits of therapy involving the combination of oral anticoagulation and antiplatelet treatment to ensure that patients are not exposed unnecessarily to an increased risk of bleeding.

There are some limitations to our study. We evaluated questionnaires completed by practising neurologists, and did not analyze individual patient data. The questionnaires were sent to only one person at each unit (usually the department chief), presuming that medical practice is homogenous among physicians at a given clinical center. We believe that the fact that there were no predefined answers to the questions allowed the responders to think freely, although it is possible that they simply forgot to mention some situations. In Hungary, stroke care is additionally provided in a number of non-neurological departments. This survey, however, was addressed only to specialist neurologists and neurological departments; it may therefore not demonstrate the attitude of other professionals to stroke care appropriately. We do not believe that a higher response rate would have led to appreciably different results.

In conclusion, we are of the opinion that this survey provides useful information for physicians working in the field of stroke prevention, especially in areas where hard evidence is lacking and the current guidelines provide little help. Topics requiring additional research have been highlighted. Further, this study may serve as a convenient source for comparisons of clinical practice in different countries.

6. Conclusions

- CAS without the use of protection devices can be performed with an acceptable overall rate of periprocedural complications, and this procedure may therefore be a less invasive alternative to CEA in selected patients.
- CAS may be associated with a high rate of complications among asymptomatic high-risk patients, possibly resulting in an unfavorable risk-benefit ratio.
- A significant proportion of embolization-related complications associated with CAS may occur after the completion of the procedure, and therefore not be avoidable through the use of protection devices.
- The use of covered stents for extracranial atherosclerotic carotid stenosis is feasible, and possibly associated with a lower rate of embolization-related complications during the intervention and also postprocedurally.
- The results of optical platelet aggregometry do not appear to indicate the risk of recurrent vascular events in aspirin-treated patients with vascular disease.
- The frequently observed dependence of antiplatelet selection on the results of *in vitro* platelet aggregation studies among practitioners does not appear to be fully justified by sufficient clinical evidence.
- Current prescription strategies of antithrombotic medications for patients with cerebrovascular disease in Hungary accord well with the international and national guidelines, and are also influenced both by the regulations of health authorities and by the patient preferences.
- Areas requiring further research include the long-term efficacy and durability of CAS, the validation of various *in vitro* platelet function assays, and antithrombotic management practices in certain specific situations.

Acknowledgments

I wish to express my deepest gratitude to Professor László Vécsei, Head of the Department of Neurology, University of Szeged, for his scientific guidance and continuous support throughout my research and clinical activities. I would also like to thank Professor György Benedek, Head of the Department of Physiology, University of Szeged, for arousing my interest in neuroscience research during my medical studies. I am grateful to Professor László Rudas at the Department of Intensive Care, University of Szeged, for broadening my knowledge in vascular medicine. I wish to thank Dr. Erika Vörös at the Department of Radiology, University of Szeged, for her help in research and also in everyday clinical practice. I would like to thank our patients and my colleagues for their cooperation and support during our investigations.

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APPENDIX