INTRACRANIAL and EXTRACRANIAL Atherosclerotic Disease

Assessed with Computed Tomography Angiography in patients with TIA or Ischemic Stroke

Philip J. Homburg

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Do not go gentle into that good night,
Old age should burn and rave at close of day;
Rage, rage against the dying of the light.

Dylan Thomas – *In Country Sleep, And Other Poems* (1952)

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Chapter 1

Introduction

Background

Stroke is an important cause of both death and physical and cognitive impairments. It has a sudden and often devastating impact on the patient and his family. Stroke poses a significant burden on healthcare and society, and is a preventable and treatable condition. The clinical presentation of stroke varies from mild neurological symptoms to syndromes of multiple and severe neurological deficits. About half of the patients survive with physical or cognitive impairments, which often lead to limitations in daily activities.[1,2] Consequently, the identification of patients who may benefit from early interventions - which are more effective shortly after the symptomatic event - is needed.

Definition and types of stroke

There are three pathological types of stroke: ischemic stroke, intracerebral hemorrhage, and subarachnoid hemorrhage. In the United States, the distribution of all strokes due to ischemia, intracerebral hemorrhage and subarachnoid hemorrhage is 87%, 10%, and 3%, respectively.[3] In Europe, the distribution of pathological stroke subtypes is 81.7% ischemic stroke, 12.4% intracerebral hemorrhage and 2.9% subarachnoid hemorrhage with 3.0% of the strokes undefined.[4] However, the worldwide relative frequency of ischemic stroke is 68%, with a higher proportion of hemorrhagic stroke of 32%.[5]

The World Health Organization (WHO) defines stroke as a syndrome of rapidly developing clinical signs of focal (or global) disturbance of cerebral function, with symptoms lasting 24 hours or longer or leading to death, with no apparent cause other than of vascular origin. A transient ischemic attack (TIA) is defined as a brief episode of neurologic dysfunction resulting from focal temporary cerebral ischemia not associated with cerebral infarction. However, these classic definitions are mainly based on clinical criteria and do not account for advances in vascular neurology and neuroimaging. Therefore, the American Heart Association/American Stroke Association published a scientific statement in 2009 redefining TIA as “a transient episode of neurological dysfunction caused by focal brain, spinal cord or retinal ischemia without acute infarction.[6] In 2013, the Stroke Council of the American Heart Association/American Stroke Association redefined ischemic stroke as an episode of neurological dysfunction caused by focal cerebral, spinal, or retinal infarction, based on 1) pathological, imaging, or other objective evidence of cerebral, spinal cord, or retinal focal ischemic injury in a defined vascular distribution; or 2) clinical evidence of cerebral, spinal cord, or retinal focal ischemic injury based on symptoms persisting ≥24 hours or until death, and other etiologies excluded.[7] For the studies in this thesis, TIA was defined clinically, as a sudden, focal neurological deficit presumed to be of vascular origin and confined to an area of

the brain perfused by a specific artery that lasted less than 24 hours. In addition, no relevant infarct (one that explains the deficit) should be present on the CT scan. Ischemic stroke was defined as a sudden focal neurologic deficit which lasted more than 24 hours or which was accompanied by a relevant infarct on the CT scan.

Epidemiology and burden of disease

Approximately 16 million first-ever strokes occur worldwide each year, leading to a total of 5.7 million deaths.[8] As a consequence, stroke is considered the second most frequent cause of mortality, and the third most common cause of disability.[5,9] According to the Hartstichting (Dutch Heart Foundation), the non-standardized incidence of hospitalization due to ischemic stroke in the Netherlands in 2018 was 173 per 100,000 inhabitants.[10] The ischemic stroke-related mortality in the Netherlands in 2018 was 32 per 100,000 inhabitants. Overall, stroke-related mortality is decreasing. However, the absolute number of patients with stroke, stroke survivors and the worldwide burden of stroke-associated disability is increasing.[11]

In terms of costs for society, stroke constitutes a considerable burden.[12] Within the European Union €18.5 billion is spent each year on the direct costs of medical care for stroke patients. In addition, an indirect cost of €8.5 billion results from loss of productivity as a consequence of a stroke morbidity and mortality.[13,14] A review of stroke cost studies demonstrated that an average 0.27% of gross domestic product was spent on stroke care by national healthcare systems, and that stroke care comprised approximately 3% of total health expenditure.[12] Strong motive therefore exists for better understanding of stroke pathophysiology, thereby striving to improved treatment and stroke prevention.

Causes of ischemic stroke and transient ischemic attack

Common causes of ischemic stroke as well as TIA comprise thrombosis, embolism, and local or systemic hypoperfusion. In addition, various rare causes of cerebral ischemia exist which include several blood disorders associated with increased blood coagulability.

Cerebral ischemia due to thrombosis can be categorized into either large vessel disease or small vessel disease. Differentiation between these two subtypes is important because the cause, resulting disability, mortality and potential treatments may differ.

In large vessel disease, pathological lesions in large extracranial and intracranial arteries may result in ischemic symptoms. Common pathological lesions in extracranial arteries include atherosclerosis, dissection and vasculopathies such as fibromuscular dysplasia. In large

intracranial arteries, pathological lesions comprise atherosclerosis, dissection, arteritis or vasculitis, non-inflammatory vasculopathy, and flow restriction due to localized vasoconstriction. Atherosclerosis is by far the most common cause of large vessel disease in both extracranial and intracranial arteries. Atherosclerotic lesions are often accompanied by superimposed thrombi.

Atherosclerotic lesions in large arteries may generate cerebral ischemia either by severely reducing blood flow distal of a local lesion, or by embolism of a fragment of thrombus migrating downstream to a more distant artery (artery-to-artery thromboembolism). Both processes may be present simultaneously, as severe stenosis creates a low flow environment distal to the lesion which promotes the formation of thrombus of which emboli can dislodge. At the same time the reduced blood flow caused by the vascular obstruction makes the intracranial circulation less capable in washing out and clearing these thromboemboli.[15]

In small vessel disease, obstruction of the deep penetrating arteries that arise from the distal vertebral artery, the basilar artery, the proximal middle cerebral artery, and the arteries of the circle of Willis leads to a lacunar infarction.[16] A stroke due to obstruction of these vessels is referred to as a lacunar stroke, and often presents with distinct combination of symptoms. The smaller arteries and arterioles penetrate at a right angle to supply the deeper structures within the brain, such as the basal ganglia, internal capsule, thalamus, and the pons.[16] Flow in these deep penetrating arteries may be obstructed due to lipohyalinosis and fibrinoid degeneration of the vessel wall, in which the media layer of the arterial wall becomes hypertrophic with depositions of lipid admixed with fibrinoid material. This process is most often related to hypertension. Other causes of small vessel disease are obstructions due to microatheromas in small penetrating arteries, and atherosclerotic plaques within the larger arteries that block or extend into the orifices of the deep penetrating branches.[17]

In ischemic events due to embolism, particles of debris originating from sources elsewhere block arterial access to a particular brain region.[18] Embolism from four different sources can be distinguished: cardiac embolism, artery to artery embolism, and embolism from an unknown source in which diagnostic tests for embolic sources are negative.[19-22]

Systemic hypoperfusion reflects a general failure in systemic circulation. Consequently, reduced perfusion does not affect a specific region restricted to distribution of a single affected artery. The most severe ischemia often occurs in border zone or watershed regions located at the borders of the major supplying arteries of the brain, since these areas are most vulnerable to systemic hypoperfusion.

Atherosclerosis and vulnerable plaques

Atherosclerosis is considered to be a dynamic process advancing in several phases starting with intima-media thickening, to proceed with fibrous cap atheroma (fibroatheroma) formation and thin-cap fibroatheroma formation. The process may ultimately lead to plaque rupture and ulceration.[23] The resulting degree of arterial stenosis, as well as plaque phenotype are suggested to influence risk of TIA or stroke. Stenotic atherothrombotic lesions of more than 70 percent at the carotid artery bifurcation are associated with embolic or low-flow TIA or ischemic stroke.[24-27] A significant drop in pressure is observed distal to these stenotic lesions.[28,29] In this situation of low and turbulent flow thrombus formation and subsequent embolism may occur.

Between intima-media thickening and the development of more advanced fibroatheromas, pathologic intima-media thickening occurs which is characterized by the formation of extracellular lipid pools.[23,30] In this stage necrosis within the plaque is still absent. The development of calcification may start, which is thought to arise from the demise of smooth muscle cells.[31] Alternatively, progression to advanced fibroatheromas may start with the development of a fibrous cap atheroma, featuring a lipid-rich necrotic core and a cap of fibrous tissue.[23,32] Fibrous cap atheroma progression may lead to a large plaque volume with a significant decrease in luminal diameter, especially after intra-plaque hemorrhage. This stage is succeeded by the thin-cap fibroatheroma, also designated as a *vulnerable plaque*. At this stage, lesions are distinguished by a large necrotic core of approximately 25% of the plaque volume and a thin fibrous cap of less than 65 µmin thickness. Typically, this thin cap is densely colonized by macrophages and T-lymphocytes, whereas smooth muscle cells are absent.[33,34] The thinning and infiltration of the fibrous cap is thought to prelude plaque rupture.[23,35] Following plaques rupture, the highly thrombogenic content of the plaque including tissue factor is exposed to the bloodstream, which can induce and sustain thrombus formation at the rupture site.[36]

Another type of plaque surface degeneration is plaque erosion, which constitutes an additional risk factor for thrombus formation. Plaque erosions are characterized by absence of surface endothelium.[37] Contrary to ruptured plaques, a prominent lipid core and interruption of the fibrous cap with exposure of the plaque interior to the lumen are absent. In addition, few macrophages and T-lymphocytes are typically present close to the lumen.[23] It is unclear why some lesions rupture and others erode.

Neo-angiogenesis within the lipid-rich necrotic core has been shown to be a source of intraplaque hemorrhage and is associated with plaque progression.[38] The origin of intraplaque hemorrhage is uncertain. It has been postulated that these hemorrhages may be related to rupture of the fibrous cap.[39,40] Another hypothesis of intraplaque hemorrhage development is

rupture of the vasa vasorum or of the immature newly formed vessels through neovascularization.[41] By contributing to the deposition of free cholesterol, macrophage infiltration, and enlargement of the necrotic core, the accumulation of erythrocyte membranes within an atherosclerotic plaque as a result of intraplaque hemorrhage may represent a potent atherogenic stimulus increasing the risk of plaque destabilization.[42]

Several imaging characteristics of atherosclerotic plaques in the carotid arteries have been associated with plaque vulnerability and subsequent the occurrence of clinical events. Examples of such imaging characteristics include degree of stenosis, plaque volume, plaque composition, plaque surface morphology, degree of inflammation, neovascularization, arterial stiffness, and shear stress.[43-47] Ulceration of carotid plaques as seen on vessel imaging is related to the presence of plaque rupture on pathological examination, and is seen most often in the proximal (upstream) part where shear stress is highest.[48]

Plaque healing

After plaque rupture healing of the affected plaque may occur. A basis of a disrupted fibrous cap with an overlying repair reaction has been observed during pathological examination.[49] Healed coronary plaques may reveal several alternating layers of necrotic core and fibrous tissue, with the older rupture sites located in the deeper layers and sequent lesion progression due to more recent superficial plaque ruptures.[50] Whereas plaque rupture promotes thrombus formation with the risk of thromboembolic ischemic stroke, lesion progression due to repeated rupture healing increases plaque volume and luminal narrowing. Plaque ruptures do not always lead to ischemic events and are often asymptomatic.[48]

Brain and vascular imaging in patients with TIA or stroke

Patients with TIA and minor ischemic stroke are at high risk of early recurrent stroke. Urgent clinical diagnosis is therefore needed to determine the pathophysiology of TIA or minor stroke thereby modifying risk factors and accomplishing tailored therapy. The risk of a recurrent ischemic stroke is increased in patients with a clinically defined TIA along with a recent infarct on CT.[51] Up to 20–50% of patients with a TIA based on clinical assessment may have acute ischemic lesions on diffusion weighted MRI, which is associated with an increased risk of stroke recurrence. [52-54] Nonetheless, at the time of writing of the studies in this thesis, it was not demonstrated yet that diffusion weighted MRI improves stroke recurrence risk prediction in addition to clinical risk scores.[55]

CT is the most widespread and cost-effective imaging modality used to assess patients with suspected stroke.[56] The technique is widely available, fast, easy to use, and less expensive than MRI. Several brain pathologies may present with transient neurological symptoms which are hard to distinguish from a TIA or ischemic stroke based on clinical presentation alone. Some of these mimicking pathologies include intracerebral hemorrhage, subdural hematoma and tumors, which can often be reliably diagnosed with CT.[56] In patients with moderate to severe stroke symptoms, ischemic changes are present on CT within the first few hours in up to two thirds of the patients.[57-61] On the other hand, in minor ischemic stroke ischemic changes are hardly seen on CT compared to MRI, especially within the first few hours after onset of symptoms.[57,61,62,64,65] In addition, several other conditions mimicking TIA or minor ischemic stroke such as multiple sclerosis, encephalitis, and hypoxic brain damage are better detected with MRI.[57]

In order to resolve the underlying pathophysiology of the event, vascular imaging should be performed promptly alongside brain imaging to identify pathological lesions in the large extracranial and intracranial arteries. The main aim is to identify patients with a significant symptomatic carotid artery stenosis who could benefit from endarterectomy or angioplasty. Traditionally, digital subtraction angiography (DSA) was used for this purpose. However, intra-arterial angiography has a 1–3% risk of causing a stroke in patients with symptomatic carotid lesions.[66,67] In comparison, non-invasive imaging with duplex imaging, CT angiography (CTA), or contrast-enhanced MR angiography (MRA) are relatively risk-free. The latter techniques are therefore currently used to screen for carotid artery stenosis. Contrast enhanced MRA is the most sensitive and specific non-invasive imaging modality for assessment of carotid artery stenosis, however it is closely followed by Doppler ultrasound and CTA. Non-contrast MRA is less reliable.[68,69] In addition, contrast enhanced MRA and CTA offer better non-invasive imaging of the intracranial vertebral and basilar arteries.[70]

Simultaneous assessment of the severity of stenosis and plaque characteristics with non-invasive imaging techniques may improve risk stratification for new and recurrent ischemic strokes. Ultimately, patients may benefit from tailored medical treatment reducing plaque vulnerability or from selective invasive revascularization therapy.

Digital subtraction angiography

This invasive imaging technique has been the gold standard technique for assessment of stenosis in large extracranial and intracranial arteries.[24,71] With DSA the contours of the lumen of arteries is depicted when filled with radiopaque contrast. It does not depict the atherosclerotic plaque itself, hereby limiting assessment of plaque vulnerability. Nonetheless

a number of studies have assessed plaque surface characteristics by means of DSA. Plaque surface irregularity and ulceration were independently associated with ipsilateral ischemic stroke.[72,73] DSA has a moderate sensitivity of 46-69% for the detection of ulcerations when compared to histology.[73,74]

Magnetic resonance imaging

Magnetic resonance imaging (MRI) has been shown to be capable of demonstrating several atherosclerotic plaque characteristics associated with plaque vulnerability. MRI allows the detection and quantification of the fibrous cap, lipid-rich necrotic core, and has a good sensitivity with a moderate-to-good specificity to detect and quantify intraplaque hemorrhage.[75-80] The delineation of the lipid-rich necrotic core from surrounding fibrous tissue can be improved using gadolinium contrast enhanced images.[81] Adventitial neovascularity can be visualize and quantified with dynamic contrast enhanced MRI which correlates with neovascularity and macrophages in histology specimens.[82]

Multidetector computed tomography angiography

MDCT has several advantages in comparison with conventional spiral CT. MDCT has a high acquisition speed. Importantly, MDCT acquires volume data instead of individual slice data with an increased coverage of the patient and a high spatial resolution. These characteristics combined with the capability to generate thin-slice acquisitions provide imaging voxels that are effectively isotropic (equal in size in all dimensions). Using these isotropic data, images can be reformatted and viewed in different planes without tradeoff in image integrity.

Multidetector computed tomography angiography (MDCTA) provides rapid and reliable evaluation of atherosclerotic steno-occlusive disease in extracranial and intracranial arteries, and is available in most European hospitals. [83-85] The technique is effective in the detection of carotid plaque ulceration with a sensitivity and specificity of 94% and 99% respectively.[86] Furthermore, distinct plaque components as well as plaque volume can be quantified in good correlation with histology.[87,88] Importantly, MDCTA has been demonstrated to be superior in the detection of intracranial as well as extracranial arterial stenosis. A sensitivity of 97% and a specificity of 99% have been reported.[84] In addition, MDCTA allows differentiation between calcified and non-calcified atherosclerotic plaques.[89]

Objectives of this thesis

This thesis aims to improve understanding of atherosclerotic carotid plaque ulcerations as a source of artery-to-artery thromboembolism in patients with TIA and ischemic stroke (Chapter 2). Furthermore, the prevalence of intracranial arterial stenosis (IAS) in patients with TIA or ischemic stroke was determined and the risk of recurrent ischemic stroke was assessed in patients with both symptomatic and asymptomatic IAS (Chapter 3).

Chapter 2

Besides the severity of carotid artery stenosis, atherosclerotic plaque ulceration on intra-arterial contrast angiography is a strong independent predictor of stroke.[73,90] Microscopic evaluation of atherosclerotic plaques has shown that ulceration and irregularities detected by angiography are strongly associated with the presence of plaque rupture, plaque hemorrhage, a large lipid core size and less fibrous tissue.[39] Plaque ulceration has been more frequently observed proximal to the point of maximum luminal stenosis, which is exposed to higher wall shear stress.[41,48] In *Chapter 2.1* we assess the associations between carotid artery atherosclerotic plaques surface morphology and severity of stenosis, cardiovascular risk factors, and type of ischemic cerebrovascular symptoms.

Whereas lacunar strokes are associated with local occlusive disease of the deep perforating arteries at the base of the brain, large deep and cortical ischemic strokes are frequently caused by thromboembolism from extracranial arteries or the heart.[91,92] However, no striking differences have been reported in cardiovascular risk profiles of these two stroke subtypes. Nonetheless, atrial fibrillation and carotid stenosis are both more common in non-lacunar stroke.[93] Plaque rupture with subsequent thrombus formation and embolization of plaque material or thrombus into the intracranial circulation may cause non-lacunar stroke. In *Chapter 2.2* we test this hypothesis by evaluating whether carotid plaque ulceration is more associated with non-lacunar stroke than with lacunar stroke.

Histological and non-invasive imaging studies assessing the relation of carotid plaque characteristics with plaque surface disruption has been limited to patients with a ≥50% carotid stenosis.[39,94] In patients with severe symptomatic stenosis, carotid plaque ulceration has been associated with the presence of fibrous cap rupture and distinct plaque components such as intraplaque hemorrhage, large lipid core, and less fibrous tissue.[39] However, a ≥50% carotid stenosis is present in only approximately 10% of patients with amaurosis fugax, TIA or minor ischemic stroke.[95] Whereas two-third of carotid plaque ulcerations is observed in carotid arteries with a low degree stenosis (0-49%),[96] little is known about the relation between carotid

plaque characteristics and plaque ulceration in these patients. Also, limited data are available on the association between plaque volume and carotid plaque surface disruption.[94] In *Chapter 2.3* we analyze the relation between atherosclerotic carotid plaques ulceration and plaque volume, degree of stenosis, and plaque components as assessed with MDCTA in both patients with ≥50% stenosis as well as in those with a low degree stenosis (0-49%).

While there is evidence of a healing process of ruptured atherosclerotic plaques in the coronary arteries which contributes to an increase in the degree of luminal narrowing, little is known about the healing process of plaque ruptures in carotid arteries.[49,50] Current knowledge about the evolution of atherosclerotic plaque rupture is mainly based on histological analysis of coronary arteries in autopsy studies or carotid plaque specimens obtained from carotid endarterectomy.[97-101] However, for extensive investigation of the temporal changes of plaque surface characteristics and their relation with recurrent thrombo-embolic events, longitudinal non-invasive serial imaging studies are required. To explore the natural history of ulcerated plaques and to assess whether plaque ulcerations heal, we study the temporal changes in plaque surface morphology on serial MDCTA in patients with TIA or minor ischemic stroke in *Chapter 2.4*.

Chapter 3

Intracranial arterial stenosis (IAS) in patients with TIA or ischemic stroke is associated with a high risk of recurrent stroke.[102] The prevalence of IAS seems to vary among ethnic groups.[103] Nevertheless, only limited studies have assessed the prevalence and associated risk factors for IAS in European stroke patients.[104-106] Moreover, the comparative value of studies available in European patients is limited by the use of multiple imaging modalities. Also, little is known about the composition of IAS lesions, which may point to a specific pathophysiological process.[107] The pathophysiology of intracranial atherosclerosis is suggested to differ from that of the extracranial arteries.[108] A prominent role for inflammatory factors is indicated in the atherosclerosis of the intracranial arteries.[109] Consequently, the pro-atherogenic influence of inflammatory reactions could be demonstrated by an association between the erythrocyte sedimentation rate (ESR) and IAS, as previously observed in a single study.[110] In addition, an accelerated intracranial atherogenesis could be reflected in differences in plaque calcification. In *Chapter 3.1* we evaluate a large cohort of patients with TIA or ischemic stroke for the prevalence, distribution and the calcification of IAS lesions using MDCTA. Furthermore, the association of IAS with the traditional risk factors for cerebrovascular disease as well as with ESR was investigated.

IAS accounts for around 8–10% of all ischemic strokes.[14,111] Recurrence rates of 10% to 14% per year have been reported in patients with previously symptomatic IAS.[102,104,112,113] A few studies have been published on the stroke recurrence risk in patients with asymptomatic IAS. However, these studies were limited to IAS in middle cerebral arteries alone or to coexisting asymptomatic IAS in patients with symptomatic IAS.[114-116] Thus far, the ischemic stroke recurrence risk for both symptomatic and asymptomatic IAS has not been compared in a consecutive of cohort transient ischemic attack (TIA) and ischemic stroke patients. In *Chapter 3.2*, we evaluate the occurrence of new ischemic strokes in patients with symptomatic and asymptomatic IAS as well as patients without IAS during long term follow-up.

Finally, in *Chapter 4*, we put our main findings in the context of current knowledge on extracranial and intracranial atherosclerotic disease.

References

1. Young J, Forster A. Review of stroke rehabilitation. BMJ. 2007 Jan 13;334:86-90.

2. Leys D, Hénon H, Mackowiak-Cordoliani MA, Pasquier F. Poststroke dementia. Lancet Neurol. 2005;4:752-759.

3. Roger VL, Go AS, Lloyd-Jones DM, et al. Heart disease and stroke statistics—2011 update: a report from the american heart association. Circulation. 2011;123:e18–e209.

4. European Registers of Stroke (EROS) Investigators, Heuschmann PU, Di Carlo A, Bejot Y, Rastenyte D, Ryglewicz D, Sarti C, Torrent M, Wolfe CD. Incidence of stroke in Europe at the beginning of the 21st century. Stroke. 2009;40:1557-1563.

5. Lozano R, Naghavi M, Foreman K, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet 2012; 380:2095-2128.

6. Easton JD, Saver JL, Albers GW, et al. Definition and evaluation of transient ischemic attack: a scientific statement for healthcare professionals from the American Heart Association/American Stroke Association Stroke Council; Council on Cardiovascular Surgery and Anesthesia; Council on Cardiovascular Radiology and Intervention; Council on Cardiovascular Nursing; and the Interdisciplinary Council on Peripheral Vascular Disease. The American Academy of Neurology affirms the value of this statement as an educational tool for neurologists. Stroke. 2009;40:2276-2293.

7. Sacco RL, Kasner SE, Broderick JP, et al. An updated definition of stroke for the 21st century: a statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2013;44:2064-2089.

8. Strong K, Mathers C, Bonita R. Preventing stroke: saving lives around the world. Lancet Neurol. 2007;6:182-187.

9. Warlow C, et al. Stroke. Lancet. 2003;362:121 1-24.

10. https://www.hartstichting.nl/getmedia/41cf66bf-2107-44d6-b2c3-739fc465ec73/cijferboek-hartstichting-hart-vaatziekten-nederland-2019-rp92.pdf.

11. Feigin VL, Forouzanfar MH, Krishnamurthi R, et al. Global and regional burden of stroke during 1990-2010: findings from the Global Burden of Disease Study 2010. Lancet 2014; 383:245.

12. Evers SM, Struijs JN, Ament AJ, van Genugten ML, Jager JH, van den Bos GA. International comparison of stroke cost studies. Stroke. 2004;35:1209-1215.

13. Roger VL, Go AS, Lloyd-Jones DM, et al. American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics--2012 update: a report from the American Heart Association. Circulation. 2012;125:e2-e220.

14. European Heart Network, Brussels. European cardiovascular disease statistics 2008.

15. Schreiber S, Serdaroglu M, Schreiber F, Skalej M, Heinze HJ, Goertler M. Simultaneous occurrence and interaction of hypoperfusion and embolism in a patient with severe middle cerebral artery stenosis. Stroke. 2009;40:e478-80.

16. Fisher CM. The arterial lesions underlying lacunes. Acta Neuropathol. 1968;12:1–15.

17. Caplan LR. Intracranial branch atheromatous disease: a neglected, understudied, and underused concept. Neurology 1989;39:1246.

18. Caplan LR, Manning W (Eds). Brain embolism. Informa Healthcare, New York 2006.

19. Amarenco P, Duyckaerts C, Tzourio C, et al. The prevalence of ulcerated plaques in the aortic arch in patients with stroke. N Engl J Med 1992;326:221-225.

20. Amarenco P, Cohen A, Tzourio C, et al. Atherosclerotic disease of the aortic arch and the risk of ischemic stroke. N Engl J Med 1994;331:1474-1479.

21. Cohen A, Tzourio C, Bertrand B, et al. Aortic plaque morphology and vascular events: a follow-up study in patients with ischemic stroke. FAPS Investigators. French Study of Aortic Plaques in Stroke. Circulation 1997;96:3838-3841.

22. Di Tullio MR, Russo C, Jin Z, et al. Aortic arch plaques and risk of recurrent stroke and death. Circulation 2009;119:2376–2382.

23. Virmani R, Kolodgie FD, Burke AP, et al. Lessons from sudden coronary death: a comprehensive morphological classification scheme for atherosclerotic lesions. Arterioscler Thromb Vasc Biol 2000;20:1262–1275.

24. North American Symptomatic Carotid Endarterectomy Trial Collaborators. Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade stenosis. N Engl J Med. 1991;325:445–453.

25. Kistler JP, Buonanno FS, Gress DR. Carotid endarterectomy--specific therapy based on pathophysiology. N Engl J Med 1991;325:505-507.

26. MRC European Carotid Surgery Trial: interim results for symptomatic patients with severe (70-99%) or with mild (0-29%) carotid stenosis. European Carotid Surgery Trialists' Collaborative Group. Lancet 1991;337:1235–1243.

27. Mayberg MR, Wilson SE, Yatsu F, et al. Carotid endarterectomy and prevention of cerebral ischemia in symptomatic carotid stenosis. Veterans Affairs Cooperative Studies Program 309 Trialist Group. JAMA 1991;266:3289–3294.

28. Suwanwela N, Can U, Furie KL, et al. Carotid Doppler ultrasound criteria for internal carotid artery stenosis based on residual lumen diameter calculated from en bloc carotid endarterectomy specimens. Stroke 1996;27:1965–1969.

29. Can U, Furie KL, Suwanwela N, et al. Transcranial Doppler ultrasound criteria for hemodynamically significant internal carotid artery stenosis based on residual lumen diameter calculated from en bloc endarterectomy specimens. Stroke 1997;28:1966–1971.

30. Stary HC, Chandler AB, Glagov S, et al. A definition of initial, fatty streak, and intermediate lesions of atherosclerosis. A report from the Committee on Vascular Lesions of the Council on Arteriosclerosis, American Heart Association. Circulation 1994;89:2462–2478.

31. Kolodgie FD, Burke AP, Nakazawa G, Virmani R. Is pathologic intimal thickening the key to understanding early plaque progression in human atherosclerotic disease? Arterioscler Thromb Vasc Biol 2007;27:986-989.

32. Stary HC, Chandler AB, Dinsmore RE, et al. A definition of advanced types of atherosclerotic lesions and a histological classification of atherosclerosis. A report from the Committee on Vascular Lesions of the Council on Arteriosclerosis, American Heart Association. Circulation 1995;92:1355-1374.

33. Burke AP, Farb A, Malcom GT, et al. Coronary risk factors and plaque morphology in men with coronary disease who died suddenly. N Engl J Med 1997; 336:1276-1282.

34. Naghavi M, Libby P, Falk E, Casscells SW, Litovsky S, Rumberger J, et al. From vulnerable plaque to vulnerable patient: a call for new definitions and risk assessment strategies: Part II. Circulation 2003;108:1772-1778.

35. Davies MJ, Thomas AC. Plaque fissuring--the cause of acute myocardial infarction, sudden ischaemic death, and crescendo angina. Br Heart J 1985;53:363-373.

36. Nemerson Y. A simple experiment and a weakening paradigm: the contribution of blood to propensity for thrombus formation. Arterioscler Thromb Vasc Biol 2002;22:1369.

37. Kolodgie FD, Burke AP, Farb A, et al. Differential accumulation of proteoglycans and hyaluronan in culprit lesions: insights into plaque erosion. Arterioscler Thromb Vasc Biol 2002;22:1642-1648.

38. Virmani R, Kolodgie FD, Burke AP, Finn AV, Gold HK, Tulenko TN, et al. Atherosclerotic plaque progression and vulnerability to rupture: angiogenesis as a source of intraplaque hemorrhage. Arterioscler Thromb Vasc Biol. 2005;25:2054-2061.

39. Davies MJ, Thomas AC: Plaque fissuring—the cause of acute myocardial infarction, sudden ischaemic death, and crescendo angina. Br Heart J 1985;53:363-373.

40. Kampschulte A, Ferguson MS, Kerwin WS, Polissar NL, Chu B, Saam T, et al. Differentiation of intraplaque versus juxtaluminal hemorrhage/thrombus in advanced human carotid atherosclerotic lesions by in vivo magnetic resonance imaging. Circulation 2004;110:3239-3244.

41. Saam T, Hatsukami TS, Takaya N, Chu B, Underhill H, Kerwin WS, et al. The vulnerable, or high-risk, atherosclerotic plaque: noninvasive MR imaging for characterization and assessment. Radiology 2007;244:64-77.

42. Kolodgie FD, Gold HK, Burke AP, Fowler DR, Kruth HS, Weber DK, et al. Intraplaque hemorrhage and progression of coronary atheroma. N Engl J Med 2003;349:2316-2325.

43. Naghavi M, et al. From vulnerable plaque to vulnerable patient: a call for new definitions and risk assessment strategies: Part I. Circulation. 2003;108:1664-1672.

44. Lovett JK, et al. Histological correlates of carotid plaque surface morphology on lumen contrast imaging. Circulation. 2004;1 10:2190-2197.

45. Shah PK. Mechanisms of plaque vulnerability and rupture. J Am Coll Cardiol. 2003;41:155-225.

46. Slager CJ, Wentzel JJ, Gijsen FJ, Thury A, van der Wal AC, Schaar JA, Serruys PW. The role of shear stress in the destabilization of vulnerable plaques and related therapeutic implications. Nat Clin Pract Cardiovasc Med. 2005;2:456-464.

47. Oliver JJ, et al. Noninvasive assessment of arterial stiffness and risk of atherosclerotic events. ArteriosclerThromb Vasc Biol. 2003;23:554-566.

48. Lovett JK, Rothwell PM. Site of Carotid Plaque Ulceration in Relation to Direction of Blood Flow: An Angiographic and Pathological Study. Cerebrovasc Dis 2003;16:369-375.

49. Mann J, Davies MJ. Mechanisms of progression in native coronary artery disease: role of healed plaque disruption. Heart 1999;82:265-268.

50. Burke AP, Kolodgie FD, Farb A, et al. Healed plaque ruptures and sudden coronary death: evidence that subclinical rupture has a role in plaque progression. Circulation 2001;103:934-940.

51. Douglas V, Johnston C, Elkins J, Sidney S, Gress D, Johnston GS: Head computed tomography findings predict short-term stroke risk after transient ischemic attack. Stroke 2003;34:2894-2898.

52. Gonzalez R, Koroshetz W: 'Footprints' of transient ischemic attacks: a diffusion-weighted MRI study. Cerebrovasc Dis 2002;14:177-186.

53. Crisostomo R, Garcia M, Tong D. Detection of diffusion-weighted MRI abnormalities in patients with transient ischemic attack: correlation with clinical characteristics. Stroke 2003;34:932-937.

54. Coutts S, Simon J, Eliasziw M, Sohn C, Hill M, Barber P, Palumbo V, Kennedy J, Roy J, Gagnon A, Scott J, Buchan A, Demchuk A. Triaging transient ischemic attack and minor stroke patients using acute magnetic resonance imaging. Ann Neurol 2005;57:848-854.

55. Redgrave J, Coutts S, Schulz U, Briley D, Rothwell P. Systematic review of associations between the presence of acute ischemic lesions on diffusion-weighted imaging and clinical predictors of early stroke risk after transient ischemic attack. Stroke 2007;38:1482-1488.

56. Wardlaw JM, Keir SL, Seymour J, Lewis S, Sandercock PA, Dennis MS, Cairns J: What is the best imaging strategy for acute stroke? Health Technol Assess 2004;8:1-180.

57. Chalela J, Kidwell C, Nentwich L, Luby M, Butmann J, Demchuk A, Hill M, Patronas N, Latour L, Warach S. Magnetic resonance imaging and computed tomography in emergency assessment of patients with suspected acute stroke: a prospective comparison. Lancet 2007;369:293-298.

58. Von Kummer R, Bourquain H, Bastianello S, Bozzao L, Manelfe C, Meier D, Hacke W. Early prediction of irreversible brain damage after ischemic stroke by computed tomography. Radiology 2001;219:95-100.

59. Von Kummer R, Allen K, Holle R, Bozzao L, Bastianello S, Manelfe C, Bluhmki E, Ringleb P, Meier D, Hacke W: Acute stroke: usefulness of early CT findings before thrombolytic therapy. Radiology 1997;205:327-333.

60. Barber P, Demchuk A, Zhang J, Buchan A. Validity and reliability of a quantitative computed tomography score in predicting outcome of hyperacute stroke before thrombolytic therapy. Lancet 2000;355:1670-1674.

61. Wardlaw J, Mielke O. Early signs of brain infarction at CT: Observer reliability and outcome after thrombolytic treatment – systematic review. Radiology 2005;235:444-453.

62. Fiebach JB, Schellinger PD, Gass A, et al. Stroke magnetic resonance imaging is accurate in hyperacute intracerebral hemorrhage: a multicenter study on the validity of stroke imaging. Stroke. 2004;35:502-506.

63. Grotta JC, Chiu D, Lu M, et al. Agreement and variability in the interpretation of early CT changes in stroke patients qualifying for intravenous rtPA therapy. Stroke. 1999;30:1528-1533.

64. Kidwell CS, Chalela JA, Saver JL, et al. Comparison of MRI and CT for detection of acute intracerebral hemorrhage. JAMA. 2004;292:1823-1830.

65. Wardlaw J, West T, Sandercock P, Lewis S, Mielke O. The International Stroke Trials Collaborative Group: Visible infarction on computed tomography is an independent predictor of poor functional outcome after stroke, and not of haemorrhagic transformation. JNNP 2003;74:452-458.

66. Forsting M, Wanke I. Funeral for a friend. Stroke 2003;34:1324-1332.

67. Willinsky R, Taylor S, TerBrugge K, Farb R, Tomlinson G, Montanera W. Neurologic complications of cerebral angiography: prospective analysis of 2,899 procedures and review of the literature. Radiology 2003;227:522-528.

68. Wardlaw J, Chappell F, Best J, Wartolowska K, Berry E. On behalf of the NHS R&D Health Technology Assessment Carotid Stenosis Imaging Group: Non-invasive imaging compared with intra-arterial angiography in the diagnosis of symptomatic carotid stenosis: a meta-analysis. Lancet 2006;367:1503-1512.

69. Wardlaw JM, Chappell FM, Stevenson M, et al. Accurate, practical and cost-effective assessment of carotid stenosis in the UK. Health Technol Assess 2006;10:1-182.

70. Khan S, Cloud G, Kerry S, Markus H. Imaging of vertebral artery stenosis: a systematic review. J Neurol Neurosurg Psychiatry 2007;78:1218-1225.

71. European Carotid Surgery Trialists' Collaborative Group. Randomised trial of endarterectomy for recently symptomatic carotid stenosis: Final results of the MRC European Carotid Surgery Trial (ECST). Lancet 1998;351:1379-1387.

72. Eliasziw M, et al. Significance of plaque ulceration in symptomatic patients with high- grade carotid stenosis. North American Symptomatic Carotid Endarterectomy Trial. Stroke. 1994;253:304-308.

73. Rothwell PM, et al. Interrelation between plaque surface morphology and degree of stenosis on carotid angiograms and the risk of ischemic stroke in patients with symptomatic carotid stenosis. On behalf of the European Carotid Surgery Trialists' Collaborative Group. Stroke. 2000;31:615-621.

74. Streifler JY, et al. Angiographic detection of carotid plaque ulceration. Comparison with surgical observations in a multicenter study. North American Symptomatic Carotid Endarterectomy Trial. Stroke. 1994;25:1130-1132.

75. Cai J, Hatsukami TS, Ferguson MS, Kerwin WS, Saam T, Chu B, et al. In vivo quantitative measurement of intact fibrous cap and lipid-rich necrotic core size in atherosclerotic carotid plaque: comparison of high-resolution, contrast-enhanced magnetic resonance imaging and histology. Circulation 2005;112:3437-3444.

76. Saam T, Ferguson MS, Yarnykh VL, Takaya N, Xu D, Polissar NL, et al. Quantitative evaluation of carotid plaque composition by in vivo MRI. Arterioscler Thromb Vasc Biol 2005;25:234-239.

77. Hatsukami TS, Ross R, Polissar NL, Yuan C. Visualization of fibrous cap thickness and rupture in human atherosclerotic carotid plaque in vivo with high-resolution magnetic resonance imaging. Circulation 2000;102:959-964.

78. Ota H, Yarnykh VL, Ferguson MS, Underhill HR, Demarco JK, Zhu DC, et al. Carotid intraplaque hemorrhage imaging at 3.0-T MR imaging: comparison of the diagnostic performance of three T1-weighted sequences. Radiology 2010;254:551-563.

79. Ota H, Yu W, Underhill HR, Oikawa M, Dong L, Zhao X, et al. Hemorrhage and large lipid-rich necrotic cores are independently associated with thin or ruptured fibrous caps: an in vivo 3T MRI study. Arterioscler Thromb Vasc Biol 2009;29:1696-1701.

80. Saam T, Hetterich H, Hoffmann V, Yuan C, Dichgans M, Poppert H, et al. Meta-analysis and systematic review of the predictive value of carotid plaque hemorrhage on cerebrovascular events by magnetic resonance imaging. J Am Coll Cardiol 2013;62:1081-1091.

81. Yuan C, Kerwin WS, Ferguson MS, Polissar N, Zhang S, Cai J, et al. Contrast-enhanced high resolution MRI for atherosclerotic carotid artery tissue characterization. J Magn Reson Imaging 2002;15:62-67.

82. Kerwin WS, Oikawa M, Yuan C, Jarvik GP, Hatsukami TS: MR imaging of adventitial vasa vasorum in carotid atherosclerosis. Magn Reson Med 2008;59:507-514.

83. Koelemay MJ, Nederkoorn PJ, Reitsma JB, Majoie CB. Systematic review of computed tomographic angiography for assessment of carotid artery disease. Stroke. 2004; 35:2306-2312.

84. Nguyen-Huynh MN, Wintermark M, English J, Lam J, Vittinghoff E, Smith WS, Johnston SC. How accurate is CT angiography in evaluating intracranial atherosclerotic disease? Stroke. 2008;39:1184-1188.

85. Balucani C, Leys D, Ringelstein EB, Kaste M, Hacke W. Executive Committee of the European Stroke Initiative. Detection of intracranial atherosclerosis: which imaging techniques are available in European hospitals? Stroke. 2009;40:726-729.

86. Saba L, Caddeo G, Sanfilippo R, Montisci R, Mallarini G. Efficacy and sensitivity of axial scans and different reconstruction methods in the study of the ulcerated carotid plaque using multidetector-row CT angiography: comparison with surgical results. AJNR Am J Neuroradiol. 2007;28:716-723.

87. de Weert TT, Ouhlous M, Meijering E, Zondervan PE, Hendriks JM, van Sambeek MR, Dippel DW, van der Lugt A. In vivo characterization and quantification of atherosclerotic carotid plaque components with multidetector computed tomography and histopathological correlation. Arterioscler Thromb Vasc Biol. 2006;26:2366-2372.

88. Wintermark M, Jawadi SS, Rapp JH, Tihan T, Tong E, Glidden DV, Abedin S, Schaeffer S, Acevedo-Bolton G, Boudignon B, Orwoll B, Pan X, Saloner D. High-resolution CT imaging of carotid artery atherosclerotic plaques. AJNR Am J Neuroradiol. 2008;29:875-882.

89. Cordeiro MA, Lima JA. Atherosclerotic plaque characterization by multidetector row computed tomography angiography. J Am Coll Cardiol. 2006;47;40-47.

90. Eliasziw M, Streifler JY, Fox AJ, Hachinski VC, Ferguson GG, Barnett HJ. Significance of plaque ulceration in symptomatic patients with high-grade carotid stenosis. North American Symptomatic Carotid Endarterectomy Trial. Stroke. 1994;25:304-308

91. Fisher CM. Lacunar strokes and infarcts: A review. Neurology. 1982;32:871-876.

92. Warlow C, Sudlow C, Dennis M, Wardlaw J, Sandercock P. Stroke. Lancet. 2003;362:1211–1224.

93. Jackson C, Sudlow C. Are Lacunar Strokes Really Different? A Systematic Review of Differences in Risk Factor Profiles Between Lacunar and Nonlacunar Infarct. Stroke. 2005;36:891-904.

94. Underhill HR, Yuan C, Yarnykh VL, Chu B, Oikawa M, Dong L, Polissar NL, Garden GA, Cramer SC, Hatsukami TS. Predictors of surface disruption with MR imaging in asymptomatic carotid artery stenosis. AJNR Am J Neuroradiol. 2010;31:487-493.

95. Tholen AT, de Monyé C, Genders TS, Buskens E, Dippel DW, van der Lugt A, Hunink MG. Suspected carotid artery stenosis: cost-effectiveness of CT angiography in work-up of patients with recent TIA or minor ischemic stroke. Radiology. 2010;256:585-597.

96. de Weert TT, Cretier S, Groen HC, Homburg P, Cakir H, Wentzel JJ, Dippel DW, van der Lugt A. Atherosclerotic plaque surface morphology in the carotid bifurcation assessed with multidetector computed tomography angiography. Stroke. 2009;40:1334-1340.

97. Finn AV, Nakano M, Narula J, Kolodgie FD, Virmani R: Concept of vulnerable/unstable plaque. Arterioscler Thromb Vasc Biol;30:1282-1292.

98. Kolodgie FD, Virmani R, Burke AP, Farb A, Weber DK, Kutys R, Finn AV, Gold HK: Pathologic assessment of the vulnerable human coronary plaque. Heart 2004;90:1385-1391.

99. Peeters W, Hellings WE, de Kleijn DP, de Vries JP, Moll FL, Vink A, Pasterkamp G: Carotid atherosclerotic plaques stabilize after stroke: Insights into the natural process of atherosclerotic plaque stabilization. Arterioscler Thromb Vasc Biol 2009;29:128-133.

100. Redgrave JN, Lovett JK, Gallagher PJ, Rothwell PM: Histological assessment of 526 symptomatic carotid plaques in relation to the nature and timing of ischemic symptoms: The Oxford Plaque Study. Circulation 2006;113:2320-2328.

101. Virmani R, Finn AV, Kolodgie FD: Carotid plaque stabilization and progression after stroke or TIA. Arterioscler Thromb Vasc Biol 2009;29:3-6.

102. Kasner SE, Chimowitz MI, Lynn MJ, Howlett-Smith H, Stern BJ, Hertzberg VS, Frankel MR, Levine SR, Chaturvedi S, Benesch CG, Sila CA, Jovin TG, Romano JG, Cloft HJ. Predictors of ischemic stroke in the territory of a symptomatic intracranial arterial stenosis. Circulation. 2006;113:555-563.

103. Sacco RL, Kargman DE, Gu Q, Zamanillo MC. Race-ethnicity and determinants of intracranial atherosclerotic cerebral infarction. The Northern Manhattan Stroke Study. Stroke. 1995;26:14-20.

104. Mazighi M, Tanasescu R, Ducrocq X, Vicaut E, Bracard S, Houdart E, Woimant F. Prospective study of symptomatic atherothrombotic intracranial stenoses: the GESICA study. Neurology. 2006;66:1187-1191.

105. Arenillas JF, Molina CA, Chacón P, Rovira A, Montaner J, Coscojuela P, Sánchez E, Quintana M, Alvarez-Sabín J. High lipoprotein (a), diabetes, and the extent of symptomatic intracranial atherosclerosis. Neurology. 2004;63:27-32.

106. Weimar C, Goertler M, Harms L, Diener HC. Distribution and outcome of symptomatic stenoses and occlusions in patients with acute cerebral ischemia. Arch Neurol. 2006;63:1287-1291.

107. Gorelick PB, Wong KS, Bae HJ, Pandey DK. Large artery intracranial occlusive disease: a large worldwide burden but a relatively neglected frontier. Stroke. 2008;39:2396-2399.

108. D'Armiento FP, Bianchi A, de Nigris F, Capuzzi DM, D'Armiento MR, Crimi G, Abete P, Palinski W, Condorelli M, Napoli C. Age-related effects on atherogenesis and scavenger enzymes of intracranial and extracranial arteries in men without classic risk factors for atherosclerosis. Stroke. 2001;32:2472-2478.

109. Arenillas JF, Alvarez-Sabín J, Molina CA, Chacón P, Montaner J, Rovira A, Ibarra B, Quintana M. C-reactive protein predicts further ischemic events in first-ever transient ischemic attack or stroke patients with intracranial large-artery occlusive disease. Stroke. 2003;34:2463-2468.

110. De Silva DA, Woon FP, Lee MP, Chen CP, Chang HM, Wong MC. South Asian patients with ischemic stroke: intracranial large arteries are the predominant site of disease. Stroke. 2007;38:2592-2594.

111. Wityk R, Lehman D, Klag M, Coresh J, Ahn H, Litt B. Race and sex differences in the distribution of cerebral atherosclerosis. Stroke. 1996;27:1974-1980.

112. Chimowitz MI, Kokkinos J, Strong J, Brown MB, Levine SR, Silliman S, et al. The Warfarin-Aspirin Symptomatic Intracranial Disease study. Neurology. 1995;45:1488-1493.

113. Chimowitz MI, Lynn MJ, Derdeyn CP, Turan TN, Fiorella D, Lane BF, et al. Stenting versus aggressive medical therapy for intracranial arterial stenosis. N Engl J Med 2011;365:993-1003.

114. Kern R, Steinke W, Daffertshofer M, Prager R, Hennerici M. Stroke recurrences in patients with symptomatic vs asymptomatic middle cerebral artery disease. Neurology. 2005;65:859–864.

115. Kremer C, Schaettin T, Georgiadis D, Baumgartner RW. Prognosis of asymptomatic stenosis of the middle cerebral artery. J Neurol Neurosurg Psychiatry. 2004;75:1300-1303.

116. Nahab F, Cotsonis G, Lynn M, Feldmann E, Chaturvedi S, Hemphill JC, et al; WASID Study Group. Prevalence and prognosis of coexistent asymptomatic intracranial stenosis. Stroke. 2008;39:1039-1041.

Chapter 2

Carotid artery plaque ulceration

Chapter 2.1

Atherosclerotic plaque surface morphology in the carotid bifurcation assessed with multidetector computed tomography angiography

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Abstract

Background and Purpose: Complicated (irregular or ulcerated) carotid plaques have proven to be independent predictors of stroke. We analyzed the frequency and location of plaque irregularities in a large cohort of patients with ischemic cerebrovascular disease and the relation with severity of stenosis, cardiovascular risk factors, and symptomatology.

Methods: Multidetector CT angiography images from 406 patients were evaluated. Plaque surface morphology was classified as smooth, irregular, or ulcerated. The location of the ulceration was defined as proximal or distal to the point of maximum stenosis.

Results: Atherosclerotic plaques with an open lumen were present in 448 carotid arteries; these plaques were classified as: smooth, 276 (62%); irregular, 99 (22%); and ulcerated, 73 (16%). Sixty-two (69%) of the ulcerations were located proximal to the point of maximum luminal stenosis. Complicated plaques were significantly ($P<0.001$) more common in carotid arteries with stenosis >30% than in those with stenosis <30%. There is an association between complicated plaques and hypercholesterolemia (OR, 3.0) and a trend toward an association with smoking (OR, 1.9). Complicated plaques are more often present in the symptomatic carotid artery than in the contralateral asymptomatic carotid artery; however, this is fully attributed to a significantly higher degree of stenosis in the symptomatic arteries.

Conclusions: Multidetector CT angiography allows the classification of atherosclerotic carotid plaque surface. Complicated plaques are frequent in atherosclerotic carotid disease, especially with higher stenosis degree. Ulcerations are mostly located in the proximal part of the atherosclerotic plaque. Hypercholesterolemia and smoking are related with the presence of complicated plaques.

Introduction

Cerebral infarction is one of the most important causes of death and the greatest cause of disability in the Western world. Approximately 20% to 30% of the infarcts can be related to carotid artery stenosis.[1,2] The severity of stenosis is an important predictor of (recurrent) ischemic cerebrovascular events and is used in therapeutic decision-making; patients with symptomatic or asymptomatic carotid stenosis above a certain degree are considered candidates for carotid intervention such as carotid endarterectomy or stent placement.

Besides the severity of stenosis, plaque ulceration on intra-arterial contrast angiography is a strong independent predictor of stroke.[3,4] It is current opinion that atherosclerotic plaque rupture plays an important role in acute events, like transient ischemic accidents (TIAs) and stroke.[5] Rupture-prone plaques have specific morphological features; the most frequently seen vulnerable plaque type has a large lipid-rich core with a thin fibrous cap and has proved to be an independent predictor of ischemic cerebrovascular events.[5-7] With microscopic evaluation of the plaque, it became clear that angiographic ulceration and irregularities were strongly associated with the presence of plaque rupture, plaque hemorrhage, a large lipid core size, and less fibrous tissue. These features are all closely related with the concept of a vulnerable plaque.[8] Plaque ulceration has been more frequently observed proximal to the point of maximum luminal stenosis, which is exposed to higher wall shear stress.[9,10]

The accuracy of digital subtraction angiography (DSA) in the detection of ulceration, with surgical observations as reference, has been reported to be low (sensitivity 46% and specificity 74%).[11] The first reports on the accuracy of CT angiography (CTA) compared with DSA in the assessment of plaque ulcers were disappointing, but this might be explained by the rather thick slice thickness used with single-section CT.[12] A later report demonstrated that CTA was superior to DSA in the detection of plaque irregularities and ulcerations.[13] Walker and colleagues evaluated 165 CTA studies, compared them with endarterectomy specimens, and reported a sensitivity of 60% and a specificity of 74%.[14] A recent multidetector CTA (MDCTA) study reported an even higher sensitivity and specificity for the detection of ulcerations (94% and 99%, respectively).[15]

The purpose of this study was to assess atherosclerotic plaque surface morphology in the carotid arteries with MDCTA in a large consecutive cohort of patients with ischemic cerebrovascular disease. Plaque surface morphology was related to severity of stenosis, cardiovascular risk factors, and type of ischemic cerebrovascular symptoms.

Materials and Methods

Study Population

Consecutive patients (n=406) with ischemic cerebrovascular disease, including amaurosis fugax or focal cerebral ischemia (TIA and minor ischemic stroke), were prospectively studied. Patients were enrolled from the neurology department's specialized TIA/stroke outpatient clinic or neurology ward. Patients underwent neurological examination on admission. Medical history was recorded from all patients. All patients underwent multidetector CT of the brain and MDCTA of the carotid arteries. In all patients, MDCTA has been performed as part of a research protocol that was approved by the Institutional Review Board and all patients had given written informed consent. The inclusion period ranged from November 2002 to January 2005.

Scanning and Image Reconstruction

Scanning was performed on a 16-slice multidetector CT scanner (Sensation 16; Siemens, Erlangen, Germany) with a standardized optimized contrast-enhanced protocol (120 kVp, 180 mAs, collimation 16×0.75 mm, pitch 1).[16,17] The MDCTA scan range reached from the ascending aorta to the intracranial circulation (2 cm above the sella turcica). All patients received 80 mL contrast material (320 mg/mL iodixanol, Visipaque; Amersham Health, Little Chalfont, UK) followed by 40 mL saline bolus chaser, both with an injection rate of 4 mL/s. Synchronization between the passage of contrast material and data acquisition was achieved by real-time bolus tracking at the level of the ascending aorta. The trigger threshold was set at an increase in attenuation of 75 Hounsfield units above baseline attenuation (approximately 150 Hounsfield units in absolute Hounsfield units value).

Image reconstructions were made with field of view 100 mm, matrix size 512×512 (real in-plane resolution 0.6×0.6 mm), slice thickness 1.0 mm, increment 0.6 mm, and with an intermediate reconstruction algorithm.[18]

Analysis of the Atherosclerotic Plaque

The MDCTA images were sent to a standalone workstation (Leonardo-Siemens Medical Solutions, Forchheim, Germany) with dedicated 3-dimensional analysis software. On the workstation, both carotid bifurcations were evaluated with multiplanar reformatting software. With this software, oblique planes can be adjusted to evaluate the carotid bifurcation in multiple reformations in the short axis and long axes with respect to the carotid artery.

First, the presence of an atherosclerotic plaque was evaluated. The criterion used for the presence of an atherosclerotic lesion was the presence of a calcification and/or thickening of the vessel wall. If a plaque was visible, the surface of the plaque was evaluated and classified as ulcerated, irregular, or smooth (Figures 1 and 2). Plaques were classified as ulcerated if extension of contrast material was present beyond the vascular lumen into the surrounding plaque. Ulcerated plaques were categorized according to the shape of the ulcer as Type 1 to 4 (Figure 2) as previously described by Lovett et al.[8] Type 1 is an ulcer that points out perpendicular to the lumen; Type 2 has a narrow neck and points out proximally and distally; Type 3 has an ulcer neck proximally and points out distally, and Type 4 has an ulcer neck distally and points out proximally. The location of the ulcer was defined as proximal or distal to the point of maximum luminal stenosis. Plaques were classified as irregular if pre- or poststenotic dilatation was present and/or if the plaque surface morphology showed irregularities without any sign of ulceration. If the plaque was not ulcerated or irregular, it was classified as smooth. To calculate interobserver reproducibility, a second observer reassessed 100 consecutive MDCTA scans.

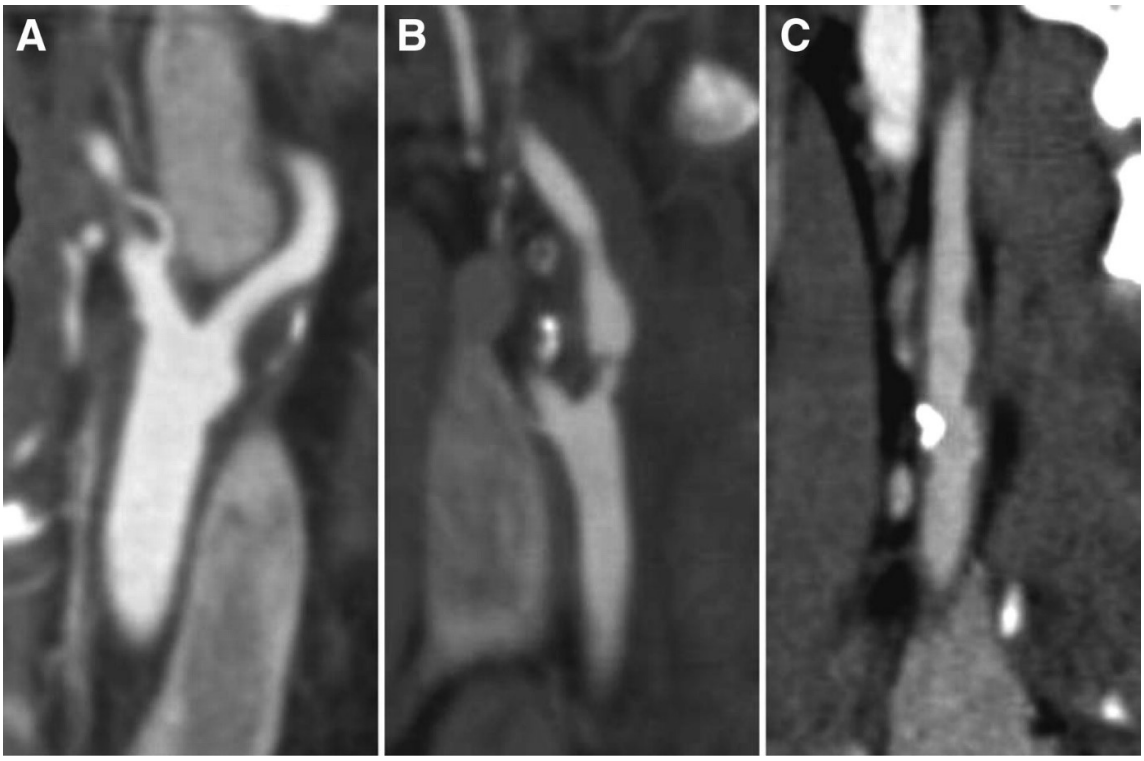

Figure 1. Multiplanar reformat images (1 mm thick). A, smooth atherosclerotic carotid plaque surface. B–C, irregular plaque surface.

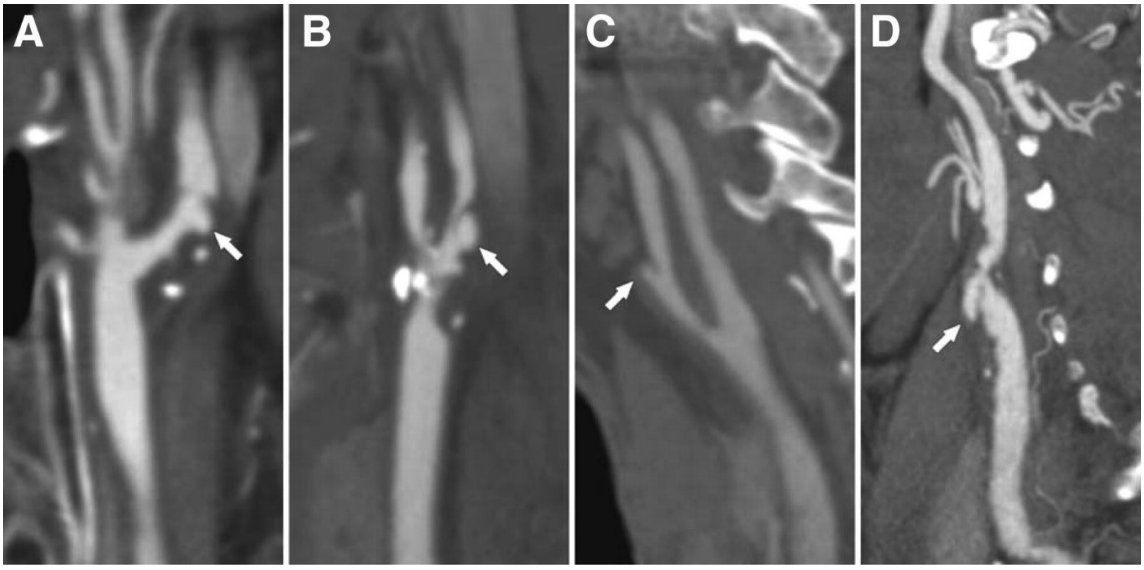

Figure 2. Multiplanar reformat images (1 mm thick) with (A) Type 1, (B) Type 2, (C) Type 3, and (D) Type 4 atherosclerotic carotid plaque ulceration.

Severity of Stenosis

The severity of stenosis on CTA was measured according to the North American Symptomatic Carotid Endarterectomy Trial (NASCET) criteria.[19] Oblique multiplanar reformatting images, parallel to the central lumen line, were used for measurements. The severity of stenosis was defined as the remaining lumen at the site of stenosis as percentage of the normal lumen distal to the stenosis and categorized into 0% to 29%, 30% to 49%, 50% to 69%, 70% to 99%, and 100%.

Cardiovascular Risk Factors

Clinical measures and information on risk factors and medication were obtained at admission to the hospital. Subjects were categorized as current, past, and never smokers. Hypertension was defined as systolic blood pressure over 140 mm Hg and/or diastolic blood pressure over 90 mm Hg during 2 episodes of at least 15 minutes of continuous noninvasive blood pressure measurement or treatment with antihypertensive medication. Blood pressure-lowering drugs comprised angiotensin-converting enzyme inhibitors, calcium antagonists, β-blockers, and diuretics.

Hypercholesterolemia was defined as fasting cholesterol >5.0 mmol/L or on treatment with cholesterol-lowering drugs. Diabetes was defined as fasting serum glucose levels >7.9 mmol/L, nonfasting serum glucose levels >11.0 mmol/L, or use of antidiabetic medication.

Information on previous cardiovascular disease (myocardial infarction, atrial fibrillation, angina pectoris, chronic heart failure, coronary artery bypass grafting) and previous ischemic cerebrovascular disease (TIA or ischemic stroke other than the event for which the patient was currently evaluated) was collected.

Symptoms

Amaurosis fugax was defined as a sudden, focal neurological deficit that was presumed to be of vascular origin and confined to the eye. TIA was defined as a sudden, focal neurological deficit that was presumed to be of vascular origin and was confined to an area of the brain perfused by a specific artery and that lasted <24 hours. In addition, no relevant infarct (one that explains the deficit) should be seen on the CT scan. An ischemic stroke was defined as a sudden focal neurological deficit that lasted >24 hours or which was accompanied by a relevant infarct on the CT scan.

Statistics

Data are presented as mean±SD. Analysis was performed for complicated (irregular or ulcerated) plaques. Reliability of assessment of plaque surface morphology was measured using the kappa statistics. Differences between categorical data and continuous data were analyzed with a χ^2 test and a Mann-Whitney test or Student *t* test, respectively. In exploratory analysis, we evaluated the association between the presence of complicated plaque and possible determinants: severity of stenosis and cardiovascular risk factors (smoking, hypertension, hypercholesterolemia, diabetes, previous cardiovascular disease, previous ischemic cerebrovascular disease). All determinants were included in a multiple logistic regression model to assess their association with complicated plaque independently from other determinants. No stepwise procedures were used. The associations were expressed as ORs with 95% CIs, which implies we used $P<0.05$ as the value for statistical significance. The same analysis was repeated for ulcerated plaques only. Finally, in the patients with symptoms in the territory of the carotid arteries, the association between the presence of complicated plaque and symptomatic side was evaluated with a logistic regression model after adjustment for severity of stenosis. All calculations were made with SPSS 14.0 for Windows.

Results

The MDCTA images and medical histories of 406 patients were evaluated. Two patients were excluded because of poor image quality due to dental artifacts. General patient characteristics are shown in Table 1. With respect to age, the symptomatic artery, and ischemic cerebrovascular disease, there were no significant differences between men and women.

However, men were more frequently smokers and had more frequently experienced previous cardiac disease, whereas women had more frequently hypercholesterolemia.

Table 1. Baseline characteristics of the study population.

	Patients	**Men**	**Women**	**p-value**
	404	**242 (60%)**	**162 (40%)**	
Age (mean ± SD; years)	62 ± 14	62 ± 13	62 ± 14	0.57
Symptomatic artery				
Carotid	350 (87%)	212 (88%)	138 (85%)	0.48
Vertebrobasilar	54 (13%)	30 (12%)	24 (15%)	
Cerebrovascular symptoms				
Amaurosis fugax	83 (21%)	50 (21%)	33 (20%)	0.94
Transient ischemic attack	122 (30%)	72 (30%)	50 (31%)	0.81
Minor stroke	199 (49%)	120 (50%)	79 (49%)	0.87
Risk factors				
Smoking	195 (48%)	136 (56%)	59 (36%)	<0.01
Hypertension	288 (71%)	177 (73%)	111 (69%)	0.31
Diabetes	61 (15%)	38 (16%)	23 (14%)	0.68
Hypercholesterolemia	317 (78%)	177 (73%)	140 (86%)	<0.01
Previous cardiac disease	107 (26%)	73 (30%)	34 (21%)	0.04
Previous cerebrovascular disease	105 (26%)	70 (29%)	35 (21%)	0.10

Data are number (percentage), or mean±SD.

In 142 patients (35%), both carotid arteries were free of atherosclerosis; in 68 patients (17%), presence of atherosclerosis was determined in one of the carotid arteries; in 190 patients (47%), both carotid arteries showed atherosclerosis and in 21 patients, at least one of the carotid arteries was occluded. Overall, from the 808 studied arteries, 337 (42%) were normal without atherosclerotic plaque, 448 (55%) were diseased, and 23 (3%) were occluded.

Table 2. Plaque surface morphology characteristics of 448 atherosclerotic carotid arteries with number, type (Type 1-4) and location of plaque ulceration.

Carotid arteries with atherosclerosis	
Smooth surface	276 (62%)
Irregular surface	99 (22%)
Ulcerated surface	73 (16%)
Number of ulcerations per carotid artery	
1	61 (84%)
2	8 (11%)
3	3 (4%)
4	1 (1%)
Type of ulceration	
1	43 (48%)
2	12 (13%)
3	24 (27%)
4	11 (12%)
Location of ulceration	
Proximal	62 (69%)
Distal	28 (31%)

Data are number (percentage).

Table 2 shows the plaque surface morphology characteristics of the 448 carotid arteries with atherosclerotic plaque. We found 90 ulcers in 73 carotid arteries of 61 patients. Both carotid arteries were ulcerated in 12 patients, and some patients had multiple (up to 4) ulcerations in the same carotid artery. The prevalence of ulceration among the patients with at least one atherosclerotic carotid artery (n=258) was 24%. Most of the ulcerations (69%) were located proximal to the point of maximum stenosis, and ulcer Type 1 and ulcer Type 3 were most frequently observed. An irregular plaque was demonstrated in 22% of the carotid arteries with atherosclerotic disease. The 2 observers agreed on the presence of complicated plaque in 93% of the cases (kappa=0.84; 95% CI, 0.70 to 0.97), on the presence of ulcerated plaque in all cases (kappa=1; 95% CI, 0.86 to 1.00), on the location of plaque ulceration in 96% of the cases (kappa=0.91; 95% CI, 0.54 to 1.00), and on the types of plaque ulceration in all cases (kappa=1; 95% CI, 0.95 to 1.00).

Table 3. Cross-table with the degree of stenosis according to the NASCET criteria compared with plaque surface morphology of 448 atherosclerotic carotid arteries. The presence of irregular and ulcerated plaques is significantly different between the lowest degree of stenosis (0-29%) and the higher degrees of stenosis (30-99%) (p-value for both <0.001).

	Number of carotids	**Smooth**	**Irregular**	**Ulcerated**
0% - 29%	346	265 (77%)	49 (14%)	32 (9%)
30% - 49%	48	8 (17%)	23 (48%)	17 (35%)
50% - 69%	29	1 (3%)	13 (45%)	15 (52%)
70% - 99%	25	2 (8%)	14 (56%)	9 (36%)
Total	448	276	99	73

Data are number (percentage)

Table 3 shows a crosstable with the degree of stenosis compared with the plaque surface morphology. It can be observed that ulcerated and irregular plaques are significantly (P<0.001) more common and smooth plaques less common among carotid arteries with a higher degree of stenosis (30% to 99%). There were not enough ulcerated plaques to determine significant differences in the distribution of ulcer type among the different degrees of stenosis.

Table 4. A. The multivariable adjusted odds ratios for associations between the complicated carotid plaques and cardiovascular risk factors for all patients with atherosclerosis (n=258). B. The multivariable adjusted odds ratios for associations between the ulcerated carotid plaques and cardiovascular risk factors for all patients with atherosclerosis (n=258). In both analyses the most severe stenosis per patient and the most severe plaque surface morphology per patient was used.

A. Complicated plaque	**Odds ratio (95% CI)**	**P-value**
Age (per increasing decade)	1.1 (0.8-1.5)	0.50
Gender	1.1 (0.5-2.3)	0.88
Previous cerebrovascular disease	1.8 (0.9-3.7)	0.12
Previous cardiac disease	0.8 (0.4-1.7)	0.55
Hypertension	0.9 (0.4-2.3)	0.87
Hypercholesterolemia	3.0 (1.0-8.9)	<0.05
Diabetes	0.6 (0.2-1.9)	0.43
Smoking	1.9 (0.9-4.1)	0.09
Degree of stenosis (per 10% increase)	2.3 (1.9-2.9)	<0.001
B. Ulcerated plaque		
Variable	Odds ratio (95% CI)	P-value
Age (per increasing decade)	1.0 (0.7-1.4)	0.92
Gender	1.2 (0.6-2.6)	0.61
Previous cerebrovascular disease	1.0 (0.5-2.0)	0.94
Previous cardiac disease	0.8 (0.4-1.6)	0.52
Hypertension	0.9 (0.4-2.2)	0.27
Hypercholesterolemia	0.9 (0.4-2.2)	0.89
Diabetes	0.5 (0.2-1.4)	0.21
Smoking	1.6 (0.8-3.3)	0.23
Degree of stenosis (per 10% increase)	1.5 (1.4-1.8)	<0.001

Data are OR (95% CI).

The OR for the association between complicated plaques and severity of stenosis (per 10% increase) adjusted for age and gender is 2.3 (95% CI, 1.9 to 2.9). The OR for the association between ulcerated plaques and severity of stenosis (per 10% increase) adjusted for age and gender is 1.5 (95% CI, 1.3 to 1.7).

The multivariable adjusted ORs for the association between cardiovascular risk factors and complicated plaque in one of the carotid arteries with at least atherosclerotic disease in one of the carotid arteries (n=258) are shown in Table 4. A significant association was found with hypercholesterolemia (OR, 3.0; 95% CI, 1.0 to 8.9) and a trend toward an association with smoking (OR, 1.9; 95% CI, 0.9 to 4.1).

The multivariable analysis for the association between cardiovascular risk factors and plaque ulceration in one of the carotid arteries showed no significant association between cardiovascular risk factors and plaque ulceration.

Table 5. Plaque surface morphology in symptomatic and asymptomatic carotid arteries stratified for cerebrovascular symptoms.

	Cerebrovascular symptoms		
	Total	Amaurosis fugax	TIA / Minor stroke
Symptomatic carotid artery (*ipsilateral*)	350	83	267
Atherosclerotic plaque (%)	193 (55%)	39 (47%)	154 (58%)
Complicated plaque (%)	89 (25%)	14 (17%)	75 (28%)
Asymptomatic carotid artery (*contralateral*)	458	83	267
Atherosclerotic plaque (%)	255 (56%)	41 (49%)	155 (58%)
Complicated plaque (%)	83 (18%)	14 (17%)	54 (20%)

For patients with vertebrobasilar symptoms both carotid arteries were considered asymptomatic. Symptomatic vs. asymptomatic complicated plaque for all patients: p = 0.01; Symptomatic vs. symptomatic complicated plaque surface for patients with TIA or minor stroke: p =0.03.

Table 5 shows that atherosclerotic plaques were present in both symptomatic and asymptomatic carotid arteries (55% versus 56%). Symptomatic carotid arteries more often harbored complicated plaques than asymptomatic carotid arteries (25% versus 18%, *P*=0.01, respectively). However, multivariable analysis showed that this can be attributed to the significantly higher degree of stenosis present in symptomatic arteries compared with asymptomatic arteries (*P*<0.01).

Complicated plaques were less often observed among patients with amaurosis fugax (17%) compared with patients with focal cerebral ischemia (28%); moreover, in the patients with amaurosis fugax, symptomatic arteries were not more often complicated than asymptomatic arteries (17% versus 17%) as opposed to patients with focal cerebral ischemia (28% versus 20%; *P*=0.03). Nonetheless, also in patients with focal cerebral ischemia, the difference in incidence of complicated plaques was attributable to the significantly higher stenosis degree present in symptomatic arteries.

Discussion

This study demonstrates that MDCTA can assess atherosclerotic carotid plaque surface morphology with differentiation between smooth, irregular, and ulcerated surfaces. It shows that the majority of ulcerations are located proximally to the maximum stenosis and that ulcerated and irregular plaques are more frequently encountered with a higher degree of stenosis. Of all cardiovascular risk factors, hypercholesterolemia was associated with complicated plaque, whereas smoking showed a trend toward an association with complicated plaque. Finally, it was shown that complicated plaque is more common in the symptomatic artery of patients with cerebrovascular symptomatology than in the asymptomatic artery; however, this can be ascribed to the significantly higher stenosis degree present in symptomatic arteries compared with asymptomatic arteries.

The present study found ulceration in 11% of the symptomatic carotid artery and in 40% of the carotid arteries with a moderate to severe degree of stenosis (30% to 99%). The proportion of ulcerated plaques is lower in high-grade stenosis (70% to 90%) compared with 50% to 69% stenosis. The difference is not statistically significant but it might indicate a real difference for which we have 2 possible explanations: (1) with severe stenosis, calcifications are larger, which hampers identification of ulcerations with MDCTA; and (2) the risk of rupture might differ with plaque composition, which may change with increasing severity of stenosis. Plaques with a moderate stenosis degree have a larger proportion of lipid, whereas plaques with severe stenosis are more calcified.

Based on the DSA data of the European Carotid Surgery Trialists (ECST) study, Lovett *et al.* reported a prevalence of ulceration of 14% in 3007 symptomatic carotid arteries in patients with TIA or minor stroke, and a prevalence of 18% for symptomatic carotid arteries with a stenosis >30%.[9] In the NASCET study, ulcerations were found in 35% of symptomatic carotid arteries with a stenosis >70%.[3] In the present study, complicated plaque was present in 89% of the carotid arteries with stenosis >30%, which exceeds the reported frequency (63%) of carotid plaque surface abnormality detected with DSA.[4] The discrepancy in the frequencies of ulceration with MDCTA and DSA can be explained by the higher sensitivity of MDCTA in the detection of ulcerations; MDCTA has a reported sensitivity of 60% to 94%, whereas DSA has a sensitivity of 46% to 69%.[4,11,13-15] The lower sensitivity for DSA might be a result of the limited viewing directions (usually 2). Besides MDCTA and DSA, MR angiography has been used for the assessment of atherosclerotic carotid plaque surface morphology. One study made a comparison between these techniques and concluded that luminal surface irregularities were most frequently seen at CTA and that with CTA and MR angiography, more ulcerations were detected than with DSA.[13] Saba *et al.* have recently showed that ultrasound has a high specificity (93%) but a low sensitivity (38%) for the detection of carotid ulceration, which is in concordance with previous studies. [15,20,21] The low sensitivity can be ascribed, in part, to the fact that acoustic shadowing from calcifications obscures the presence of ulcerations.

A recent histological study of symptomatic carotid endarterectomy specimens from 526 consecutive patients with a stenosis degree of 75% to 90% found ulceration in 58% of the specimens.[22] The discrepancy in the frequencies of ulceration between MDCTA and histology in patients with a severe degree of stenosis can be explained by the higher resolution of histology, which enables the detection of small ulcerations, and the higher volume of calcifications in severe stenosis, which hampers accurate detection of small ulcerations by MDCTA. In addition, thrombus formation on the location of a rupture may fill the ruptured site, which will lead to nonvisualization with MDCTA.

Lovett et al[8] characterized ulcerations as Type 1 to 4 and determined that Type 1 and Type 3 are the most frequent type of rupture; the present study confirms these findings. However, the categorization of ulcers is only important when their occurrence can be related to different clinical behavior; this has not yet been demonstrated.

Ulcerations were most frequently seen at the proximal site of the maximum stenosis. The ECST data revealed the same distribution of ulcer location in the carotid artery (71% at the proximal site) as in the present study.[9] An intracoronary ultrasound study found that 69% of the ulcerated ruptured plaques (80%) were proximal to the minimal lumen site.[23] The proximal site as a predilection site for ulceration is in concordance with shear stress theories. It is

thought that high shear stress on the plaque surface (due to the lumen narrowing) weakens the cap through numerous signaling pathways.[10] Indeed, in a recent case report, Groen *et al.* showed in a serial MRI study that the ulceration was located at the high shear stress region.[24] Shear stress may therefore play an important role in the rupture of plaques.

The present study showed that plaque ulceration is not only present in high-grade stenosis, but can also occur in hemodynamically insignificant stenosis. A similar observation was made on the ECST data.[4] Most of the patients with an ischemic stroke did not have severe stenosis despite the accumulation of a substantial amount of atherosclerotic plaque in the carotid bifurcation. Detection of plaque ulceration thereby provides a clue to the underlying pathophysiology of the previously occurring ischemic stroke; rupture of the plaque may have been accompanied by thrombus formation and embolization of plaque material or thrombus into the intracranial circulation. In addition, detection of plaque ulceration indicates that a patient has an increased risk of a new ipsilateral ischemic stroke.[4] Whether surgical or endovascular intervention in symptomatic patients without significant stenosis but with plaque ulceration is justified remains to be demonstrated in larger prospective studies. Ideally, these studies should use the noninvasive imaging tools that are currently available.

In the present study, hypercholesterolemia is positively and significantly associated with the presence of complicated plaques, whereas smoking had a positive (but not significant) association with the presence of complicated plaques. Previous studies with univariate analysis revealed associations between irregular plaques and gender, age, carotid stenosis, hypercholesterolemia, and previous myocardial infarction.[3,4] Because irregular plaques are related to the severity of stenosis, multivariable analysis with adjustment for the severity of stenosis is necessary to demonstrate whether certain cardiovascular risk factors are independently related to the presence of irregular plaques.

The association with hypercholesterolemia might be explained by the atherogenic effect of lipoprotein(a) in the presence of high plasma low-density lipoprotein cholesterol levels, which increases lipid deposition in atherosclerotic plaque,[25,26] making the plaque probably more vulnerable for rupture. Cigarette smoking is considered to influence inflammation and hemostasis in such a way that plaque inflammation and thrombogenicity increases with cap degradation, plaque rupture, and subsequent thrombus formation as a possible result.[27]

In the present study, ulcerated and irregular plaques are significantly more common in the ipsilateral symptomatic carotid artery than in the asymptomatic carotid artery, which is in line with the findings of Sitzer et al, who concluded that plaque ulceration is more common in carotid endarterectomy specimens from symptomatic arteries than from asymptomatic arteries.[28] However, multivariate analysis showed that this difference does not remain

significant when severity of stenosis was added to the model. This indicates that besides local factors like plaque composition or shear stress, also systemic factors are important in the occurrence of plaque rupture. A reasoning that is supported by the findings of Rothwell et al, who reported that patients with irregular plaque in the symptomatic carotid artery were more likely to have irregular plaques in the contralateral artery, and by a study from Fisher et al, which concluded that plaque ulceration was more common in symptomatic patients than in asymptomatic patients but that the prevalence of ulceration in the ipsilateral and contralateral carotid artery in symptomatic patients was the same. [29,30]

Although the recent paper by Saba et al[15] showed that MDCTA is an excellent technique to evaluate carotid ulceration, we realize that it is a limitation of our study that we do not have a gold standard (e.g., histological specimens). Unfortunately, correlation with histological results is troublesome, because only patients with severe stenosis (NASCET >70% stenosis) are eligible for intervention, which in our hospital includes stenting in approximately 50% of the cases. Therefore, it is not possible to obtain histology from a vast majority of patients.

A second limitation of our study is its cross-sectional design. The evaluation of the causal association between severity of stenosis and complicated plaques, between cardiovascular risk factors and complicated plaques, and between complicated plaques and ischemic cerebrovascular disease requires a prospective design in which the atherosclerotic plaque is evaluated serially to detect changes in plaque surface morphology.

Conclusion

This study shows that MDCTA can classify atherosclerotic carotid plaque surface morphology. Furthermore, it shows that the presence of a complicated plaque surface in an atherosclerotic plaque is strongly related with the severity of stenosis and that the site of ulceration is mostly proximal to the most stenotic site. In addition, it is shown that hypercholesterolemia and probably smoking are related to the presence of complicated plaques.

References

1. Caplan LR. Diagnosis and treatment of ischemic stroke. Jama. 1991;266:2413-2418

2. Warlow C, Sudlow C, Dennis M, Wardlaw J, Sandercock P. Stroke. Lancet. 2003;362:1211-1224

3. Eliasziw M, Streifler JY, Fox AJ, Hachinski VC, Ferguson GG, Barnett HJ. Significance of plaque ulceration in symptomatic patients with high-grade carotid stenosis. North American Symptomatic Carotid Endarterectomy Trial. Stroke. 1994;25:304-308

4. Rothwell PM, Gibson R, Warlow CP. Interrelation between plaque surface morphology and degree of stenosis on carotid angiograms and the risk of ischemic stroke in patients with symptomatic carotid stenosis. On behalf of the European Carotid Surgery Trialists' Collaborative Group. Stroke. 2000;31:615-621

5. Naghavi M, Libby P, Falk E, Casscells SW, Litovsky S, Rumberger J, Badimon JJ, Stefanadis C, Moreno P, Pasterkamp G, Fayad Z, Stone PH, Waxman S, Raggi P, Madjid M, Zarrabi A, Burke A, Yuan C, Fitzgerald PJ, Siscovick DS, de Korte CL, Aikawa M, Juhani Airaksinen KE, Assmann G, Becker CR, Chesebro JH, Farb A, Galis ZS, Jackson C, Jang IK, Koenig W, Lodder RA, March K, Demirovic J, Navab M, Priori SG, Rekhter MD, Bahr R, Grundy SM, Mehran R, Colombo A, Boerwinkle E, Ballantyne C, Insull W, Jr., Schwartz RS, Vogel R, Serruys PW, Hansson GK, Faxon DP, Kaul S, Drexler H, Greenland P, Muller JE, Virmani R, Ridker PM, Zipes DP, Shah PK, Willerson JT. From vulnerable plaque to vulnerable patient: a call for new definitions and risk assessment strategies: Part I. Circulation. 2003;108:1664-1672

6. Polak JF, Shemanski L, O'Leary DH, Lefkowitz D, Price TR, Savage PJ, Brant WE, Reid C. Hypoechoic plaque at US of the carotid artery: an independent risk factor for incident stroke in adults aged 65 years or older. Cardiovascular Health Study. Radiology. 1998;208:649-654

7. Takaya N, Yuan C, Chu B, Saam T, Underhill H, Cai J, Tran N, Polissar NL, Isaac C, Ferguson MS, Garden GA, Cramer SC, Maravilla KR, Hashimoto B, Hatsukami TS. Association between carotid plaque characteristics and subsequent ischemic cerebrovascular events: a prospective assessment with MRI--initial results. Stroke. 2006;37:818-823

8. Lovett JK, Gallagher PJ, Hands LJ, Walton J, Rothwell PM. Histological correlates of carotid plaque surface morphology on lumen contrast imaging. Circulation. 2004;110:2190-2197

9. Lovett JK, Rothwell PM. Site of carotid plaque ulceration in relation to direction of blood flow: an angiographic and pathological study. Cerebrovasc Dis. 2003;16:369-375

10. Slager CJ, Wentzel JJ, Gijsen FJ, Thury A, van der Wal AC, Schaar JA, Serruys PW. The role of shear stress in the destabilization of vulnerable plaques and related therapeutic implications. Nat Clin Pract Cardiovasc Med. 2005;2:456-464

11. Streifler JY, Eliasziw M, Fox AJ, Benavente OR, Hachinski VC, Ferguson GG, Barnett HJ. Angiographic detection of carotid plaque ulceration. Comparison with surgical observations in a multicenter study. North American Symptomatic Carotid Endarterectomy Trial. Stroke. 1994;25:1130-1132

12. Oliver TB, Lammie GA, Wright AR, Wardlaw J, Patel SG, Peek R, Ruckley CV, Collie DA. Atherosclerotic plaque at the carotid bifurcation: CT angiographic appearance with histopathologic correlation. AJNR Am J Neuroradiol. 1999;20:897-901

13. Randoux B, Marro B, Koskas F, Duyme M, Sahel M, Zouaoui A, Marsault C. Carotid artery stenosis: prospective comparison of CT, three-dimensional gadolinium-enhanced MR, and conventional angiography. Radiology. 2001;220:179-185

14. Walker LJ, Ismail A, McMeekin W, Lambert D, Mendelow AD, Birchall D. Computed tomography angiography for the evaluation of carotid atherosclerotic plaque: correlation with histopathology of endarterectomy specimens. Stroke. 2002;33:977-981

15. Saba L, Caddeo G, Sanfilippo R, Montisci R, Mallarini G. Efficacy and sensitivity of axial scans and different reconstruction methods in the study of the ulcerated carotid plaque using multidetector-row CT angiography: comparison with surgical results. AJNR Am J Neuroradiol. 2007;28:716-723

16. de Monye C, Cademartiri F, de Weert TT, Siepman DA, Dippel DW, van Der Lugt A. Sixteen-detector row CT angiography of carotid arteries: comparison of different volumes of contrast material with and without a bolus chaser. Radiology. 2005;237:555-562

17. de Monye C, de Weert TT, Zaalberg W, Cademartiri F, Siepman DA, Dippel DW, van der Lugt A. Optimization of CT angiography of the carotid artery with a 16-MDCT scanner: craniocaudal scan direction reduces contrast material-related perivenous artifacts. AJR Am J Roentgenol. 2006;186:1737-1745

18. de Weert TT, Ouhlous M, Zondervan PE, Hendriks JM, Dippel DW, van Sambeek MR, van der Lugt A. In vitro characterization of atherosclerotic carotid plaque with multidetector computed tomography and histopathological correlation. Eur Radiol. 2005;15:1906-1914

19. Rothwell PM, Gibson RJ, Slattery J, Warlow CP. Prognostic value and reproducibility of measurements of carotid stenosis. A comparison of three methods on 1001 angiograms. European Carotid Surgery Trialists' Collaborative Group. Stroke. 1994;25:2440-2444

20. Bluth EI, McVay LV, 3rd, Merritt CR, Sullivan MA. The identification of ulcerative plaque with high resolution duplex carotid scanning. J Ultrasound Med. 1988;7:73-76

21. Lammie GA, Wardlaw J, Allan P, Ruckley CV, Peek R, Signorini DF. What pathological components indicate carotid atheroma activity and can these be identified reliably using ultrasound? Eur J Ultrasound. 2000;11:77-86

22. Redgrave JN, Lovett JK, Gallagher PJ, Rothwell PM. Histological assessment of 526 symptomatic carotid plaques in relation to the nature and timing of ischemic symptoms: the Oxford plaque study. Circulation. 2006;113:2320-2328

23. Fujii K, Kobayashi Y, Mintz GS, Takebayashi H, Dangas G, Moussa I, Mehran R, Lansky AJ, Kreps E, Collins M, Colombo A, Stone GW, Leon MB, Moses JW. Intravascular ultrasound assessment of ulcerated ruptured plaques: a comparison of culprit and nonculprit lesions of patients with acute coronary syndromes and lesions in patients without acute coronary syndromes. Circulation. 2003;108:2473-2478

24. Groen HC, Gijsen FJ, van der Lugt A, Ferguson MS, Hatsukami TS, van der Steen AF, Yuan C, Wentzel JJ. Plaque rupture in the carotid artery is localized at the high shear stress region: a case report. Stroke. 2007;38:2379-2381

25. Baldassarre D, Tremoli E, Franceschini G, Michelagnoli S, Sirtori CR. Plasma lipoprotein(a) is an independent factor associated with carotid wall thickening in severely but not moderately hypercholesterolemic patients. Stroke. 1996;27:1044-1049

26. Rath M, Niendorf A, Reblin T, Dietel M, Krebber HJ, Beisiegel U. Detection and quantification of lipoprotein(a) in the arterial wall of 107 coronary bypass patients. Arteriosclerosis. 1989;9:579-592

27. MacCallum PK. Markers of hemostasis and systemic inflammation in heart disease and atherosclerosis in smokers. Proc Am Thorac Soc. 2005;2:34-43

28. Sitzer M, Muller W, Siebler M, Hort W, Kniemeyer HW, Jancke L, Steinmetz H. Plaque ulceration and lumen thrombus are the main sources of cerebral microemboli in high-grade internal carotid artery stenosis. Stroke. 1995;26:1231-1233

29. Rothwell PM, Villagra R, Gibson R, Donders RC, Warlow CP. Evidence of a chronic systemic cause of instability of atherosclerotic plaques. Lancet. 2000;355:19-24

30. Fisher M, Paganini-Hill A, Martin A, Cosgrove M, Toole JF, Barnett HJ, Norris J. Carotid plaque pathology: thrombosis, ulceration, and stroke pathogenesis. Stroke. 2005;36:253-257

Chapter 2.2

Atherosclerotic plaque ulceration in the symptomatic internal carotid artery is associated with non-lacunar ischemic stroke

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Abstract

Background and Purpose: Atherosclerotic carotid plaque ulceration is considered a marker of previous plaque rupture and subsequent thromboembolism, and can be accurately detected with multidetector computed tomography angiography (MDCTA). We hypothesized that atherosclerotic plaque ulceration is associated with non-lacunar ischemic stroke rather than lacunar stroke.

Methods: Prospectively, 750 consecutive patients with transient ischemic attack (TIA) or ischemic stroke symptoms in the anterior cerebral circulation were evaluated for the presence of atherosclerotic plaque ulceration in the symptomatic carotid artery with MDCTA. Patients with stroke due to cardiac embolism or other specific etiologies, and patients with amaurosis fugax were excluded. Ischemic strokes in the remaining 534 patients were classified as non-lacunar or lacunar based on clinical symptoms and MDCT of the brain. Ulceration was defined as extension of contrast material beyond the vascular lumen into the surrounding plaque.

Results: Plaque ulceration in the symptomatic carotid artery was more common in non-lacunar strokes (n=47, 20%) as compared to lacunar strokes (n=20, 7%) (P<0.001). After adjustment for age, sex, cardiovascular risk factors and degree of stenosis, ulcerations were independently associated with non-lacunar stroke, compared to lacunar stroke (OR 2.70, 95% CI 1.43-5.09).

Conclusions: Atherosclerotic carotid plaque ulceration is associated with non-lacunar ischemic stroke, independent of the degree of carotid stenosis. These results suggest that non-lacunar stroke and lacunar stroke are caused by different pathophysiological mechanisms.

Introduction

Whereas lacunar strokes are associated with local occlusive disease of the deep perforating arteries at the base of the brain,[1] large deep and non-lacunar ischemic strokes are frequently caused by thromboembolism from extracranial arteries or the heart.[2] However, no striking differences have been reported in cardiovascular risk profiles of these two stroke subtypes. Nonetheless, atrial fibrillation and carotid stenosis are both more common in non-lacunar stroke.[3]

Atherosclerotic carotid plaque ulceration is considered to be a marker of previous plaque rupture and an influential predictor of ischemic stroke besides degree of stenosis.[4,5] Plaque rupture with subsequent thrombus formation and embolization of plaque material or thrombus into the intracranial circulation may cause non-lacunar stroke. However, it is not known whether carotid plaque ulceration is more associated with non-lacunar stroke than with lacunar stroke.

Multidetector computed tomography angiography (MDCTA) has been demonstrated to be effective in the detection of carotid plaque ulceration with a sensitivity and specificity of 94% and 99% respectively.[6] CT angiography is superior to digital subtraction angiography in detecting ulcerations of the carotid atherosclerotic plaque.[7]

In the current study, the association between atherosclerotic plaque ulceration in the symptomatic carotid artery and non-lacunar stroke was evaluated by means of MDCTA in a large population of patients with ischemic stroke.

Materials and Methods

Study Population

From a prospective registry of 911 patients with amaurosis fugax, transient ischemic attack (TIA) or minor ischemic stroke (Rankin score <4) who did undergo a MDCTA of the carotid artery we selected all patients (n=750) with symptoms in the anterior circulation. Patients were enrolled from a specialized TIA/stroke outpatient clinic or the neurology ward. All patients underwent an interview, neurological examination, electrocardiography and laboratory analysis on admission. Medical history and cardiovascular risk factors were thereby recorded. On admission, patients underwent MDCT of the brain and MDCTA of the carotid arteries in a single session. In 3 patients the carotid artery could not be analyzed on MDCTA due to scan artifacts. Patients with a likely cardiac etiology (n=96) or other specific etiology according to the TOAST criteria (n=20) were excluded.[8] Patients with amaurosis fugax (n=79) were subsequently excluded as amaurosis fugax is associated with several non-vascular etiologies.[9] The remaining 534 patients were included in the study.

Cardiovascular Risk Factors

Hypercholesterolemia was defined as fasting cholesterol >5.0 mmol/l, or treatment with cholesterol-lowering medication. Hypertension was defined as a systolic blood pressure >140 mmHg and/or a diastolic blood pressure >90 mmHg, during two episodes of at least 15 minutes of continuous non-invasive blood pressure measurement or treatment with antihypertensive medication. Diabetes was defined as fasting serum glucose levels >7.9 mmol/l, HbA1c >6.5%, or use of antidiabetic medication.

MDCT and MDCTA Data Acquisition

Imaging was performed with a 16-slice MDCT scanner (Siemens, Sensation 16, Erlangen, Germany) or a 64-slice MDCT scanner (Siemens, Sensation 64, Erlangen, Germany) with a standardized optimized contrast-enhanced protocol (120 kVp, 180 mAs, collimation 16 x 0.75 mm or 64 x 0.6 mm, pitch ≤1).[10,11]

The MDCT brain scan ranged from the foramen magnum to the vertex. Image reconstructions were made with a 220 mm field of view, matrix size 512 x 512, (real in-plane resolution 0.5 x 0.5 mm), slice thickness 3 to 4.5 mm and with an intermediate reconstruction algorithm.

The MDCTA scan ranged from the ascending aorta to the intracranial circulation (2 cm above the sella turcica). All patients received 80 ml contrast material (Iodixanol 320 mg/ml, Visipaque, Amersham Health, Little Chalfont, UK), followed by a 40 ml saline bolus chaser, both with an injection rate of 4 ml/sec. Synchronization between the passage of contrast material and data acquisition was achieved by real time bolus tracking at the level of the ascending aorta. Image reconstructions were made with a 100 mm field of view, matrix size 512 x 512 (real in-plane resolution 0.6 x 0.6 mm), slice thickness 1.0 mm, increment 0.6 mm and with an intermediate reconstruction algorithm.[12]

MDCT and MDCTA Data Analysis

Relevant cerebral infarctions on MDCT of the brain related to the stroke symptoms were classified as non-lacunar infarction or lacunar infarction. A non-lacunar infarction was defined as an infarction with involvement of the cerebral cortex or a large deep infarction > 1.5 cm. A lacunar infarction was defined as an infarction in the deep brain structures (grey or white matter) with a size ≤ 1.5 cm.

The MDCTA images were sent to a stand-alone workstation (Leonardo – Siemens Medical Solutions, Forchheim, Germany) with dedicated 3D analysis software for further analysis. The symptomatic carotid bifurcation was evaluated with multi-planar reformatting (MPR) software. Herewith, oblique planes were adjusted to evaluate the carotid bifurcation in multiple reformations in the short axis and

long axes with respect to the carotid artery. Two experienced investigators blinded to clinical data and MDCT of the brain analyzed the MDCTA images. Discrepancies were solved by consensus.

Firstly, the degree of stenosis in the symptomatic carotid artery was determined according to the North American Symptomatic Carotid Endarterectomy Trial (NASCET) criteria.[13] Secondly, the symptomatic carotid artery was evaluated for the presence of occlusion, atherosclerotic plaque and atherosclerotic plaque ulceration. Presence of atherosclerotic plaque was defined as thickening of the vessel wall and/or the presence of calcification. Plaque ulceration was defined as extension of contrast media beyond the vascular lumen into the surrounding plaque.

Stroke Type and Etiology

All patients were analyzed for ischemic stroke etiology. The presence of a likely cardiac etiology or other specific etiology according to the TOAST criteria was determined.[8] The remaining patients were classified as having a non-lacunar stroke, lacunar stroke or amaurosis fugax based on clinical symptoms and findings on MDCT of the brain. Non-lacunar ischemic stroke was defined as a) ≥ two of following symptoms: 1. higher cerebral dysfunction (e.g. dysphasia, dyscalculia, visuospatial disorder), 2. homonymous visual field defect and 3. ipsilateral motor and/or sensory deficit *or* b) higher cerebral dysfunction alone and/or, a motor or sensory deficit more restricted than those classified as lacunar (e.g. confined to one limb, face and/or hand but not the complete arm). Lacunar ischemic stroke was defined as a pure motor stroke, pure sensory stroke, sensory-motor stroke, dysarthria clumsy hand syndrome, or ataxic hemiparesis without brainstem symptoms.[14] Amaurosis fugax was defined as a sudden, loss of vision that was presumed to be of vascular origin and confined to one eye.

Statistical Analysis

Data are presented as means ± SD or number of patients (%). Differences between categorical data were analyzed with a Chi-square test or Fisher's Exact Test where appropriate. Differences between continuous data were analyzed with a Mann-Whitney test. The association between degree of stenosis and plaque ulceration was evaluated in a multivariable logistic model adjusted for age and sex. The association between age, sex, cardiovascular risk factors, degree of stenosis (per 10% increase) and plaque ulceration with non-lacunar stroke (with lacunar stroke as reference) was first evaluated in a univariable logistic regression model. Thereafter, a multivariable logistic regression analysis was performed to identify variables independently associated with non-lacunar stroke. Patients with a symptomatic occluded carotid artery, wherein assessment of atherosclerotic plaque morphology was not possible, were not included in this analysis.

A multivariable logistic regression analyses was repeated with non-lacunar infarctions (versus lacunar infarctions) on MDCT of the brain to confirm the association of plaque ulcerations with clinically defined stroke subtype.

Statistical analyses were performed using SPSS software (version 15.0, Inc., Chicago, Illinois). *P*-values <0.05 were considered statistically significant.

Results

Patients Characteristics

Excluded patients with a likely cardiac etiology or other specific etiology (n=116) had less hypertension (56% versus 71%, *P*=0.002) and smoked less often (28% versus 39%, *P*=0.02) than patients included in the analysis. In this group, plaque ulceration in the symptomatic carotid artery was present in 9 patients (8%). Excluded patients with amaurosis fugax (n=79) smoked less often (28% versus 39%, *P*=0.04) and had less often a previous ischemic stroke (5% versus 14%, *P*=0.02) than included patients. Plaque ulceration in the symptomatic carotid artery was present in 7 patients (7%) with amaurosis fugax.

In the remaining 534 patients, non-lacunar stroke was present in 236 patients and lacunar stroke in 298 patients. Baseline characteristics of patients with non-lacunar and lacunar stroke are illustrated in table 1. The mean age of the study population was 62±13 years and 56% of the patients were male. Patients with non-lacunar stroke were significantly older than patients with lacunar stroke (64 versus 61 years, *P*=0.003). The prevalence of other cardiovascular risk factors was similar in the two groups.

Plaque Surface Morphology in the Symptomatic Carotid Artery

In 362 of the 534 patients (68%) atherosclerotic plaque was observed in the symptomatic carotid artery. In 23 patients (4%), the symptomatic carotid artery was occluded and in 149 patients (28%) the symptomatic carotid artery was normal. Plaque ulcerations were observed in 67 symptomatic carotid arteries (13%). The prevalence of ulcerations in symptomatic carotid arteries with atherosclerotic plaque was (19%).

The likelihood of plaque ulceration in the symptomatic carotid artery was increased with a higher degree of stenosis after adjustment for age and gender (OR 1.6, 95% CI 1.4-1.7).

Table 1. Characteristics of patients with non-lacunar and lacunar ischemic stroke.

	Non-lacunar Stroke n=236 (44%)	**Lacunar Stroke n=298 (56%)**	***P*-value**
Age (years)	64±13	61±13	0.003
Male Sex	128 (54%)	170 (57%)	0.52
Hypercholesterolemia	174 (74%)	215 (72%)	0.68
Hypertension	167 (71%)	212 (71%)	0.92
Diabetes Mellitus	50 (21%)	55 (18%)	0.43
Smoking	82 (35%)	126 (42%)	0.08
Peripheral Arterial Disease	17 (7%)	17 (6%)	0.48
Previous Ischemic Stroke	31 (13%)	42 (14%)	0.75
Previous TIA	36 (15%)	42 (14%)	0.71
Previous Intracerebral Hematoma	4 (2%)	5 (2%)	0. 99
History of Ischemic Heart Disease	37 (16%)	42 (14%)	0.61

Data are medians (lower quartile, upper quartile) or number of patients (%).

Risk Factors for Non-lacunar Ischemic Stroke

Atherosclerotic plaques in the symptomatic carotid artery were significantly more prevalent in patients with non-lacunar stroke as compared to patients with lacunar stroke (72% versus 65%, *P*<0.001). Occlusions of the symptomatic carotid artery were significantly more prevalent in patients with non-lacunar stroke as compared to patients with lacunar stroke (8% versus 1%, *P*<0.001) (table 2).

Table 2. MDCTA Plaque Characteristics of the symptomatic carotid artery in patients with non-lacunar and lacunar ischemic stroke.

	Non-lacunar Stroke n=236 (44%)	**Lacunar Stroke n=298 (56%)**	***P*-value**
Atherosclerotic Plaque	169 (72%)	193 (65%)	
Occluded carotid artery	19 (8%)	4 (1%)	<0.001
Normal carotid artery	48 (20%)	101 (34%)	
Degree of Stenosis			
0%	121 (56%)	207 (70%)	
1-29%	38 (18%)	57 (19%)	
30-49%	18 (8%)	17 (6%)	<0.001
50-69%	22 (10%)	5 (2%)	
≥70%	18 (8%)	8 (3%)	
Plaque Ulceration	47 (20%)	20 (7%)	<0.001

Data are means ± SD or number of patients (%).

Severe stenosis of the symptomatic carotid artery in patients with non-lacunar stroke was significantly more prevalent than in patients with lacunar stroke (*P*<0.001). Plaque ulceration in the symptomatic carotid artery was more common in non-lacunar strokes (n=47, 20%) as compared to lacunar strokes (n=20, 7%) (*P*<0.001). In patients with plaque ulcerations no significant differences in number of ulcerations per plaque, location of the ulceration and type of ulceration were observed between patients with non-lacunar and lacunar stroke.

Risk factors associated with non-lacunar stroke (as opposed to lacunar stroke) in univariable and multivariable analysis are provided in table 3. In univariable analysis age, degree of stenosis and plaque ulceration were found to be significantly associated with non-lacunar stroke, whereas smoking was found to be associated with lacunar stroke. Risk factors independently associated with

non-lacunar stroke in multivariable analysis were degree of stenosis (OR 1.19, 95% CI 1.07-1.32) and plaque ulceration (OR 2.70, 95% CI 1.43-5.09).

Table 3. Univariable- and multivariable odds-ratios for association between non-lacunar stroke (versus ischemic lacunar stroke) and cardiovascular risk factors, degree of stenosis and plaque ulceration.

	Univariable Analysis	**Multivariable Analysis**
Age (per decade)	1.23 (1.08-1.40)	1.11 (0.96-1.29)
Male Sex	0.84 (0.59-1.20)	0.70 (0.48-1.02)
Hypercholesterolemia	1.02 (0.69-1.51)	0.86 (0.56-1.33)
Hypertension	0.98 (0.66-1.44)	0.75 (0.48-1.15)
Diabetes Mellitus	1.27 (0.82-1.95)	1.24 (0.77-1.98)
Smoking	0.68 (0.47-0.98)	0.73 (0.49-1.10)
Peripheral Arterial Disease	1.04 (0.49-2.19)	0.81 (0.36-1.87)
Previous Ischemic Stroke	0.89 (0.53-1.49)	0.81 (0.46-1.42)
Previous TIA	1.17 (0.71-1.94)	1.05 (0.61-1.82)
Previous Intracerebral Hematoma	1.09 (0.29-4.09)	1.07 (0.27-4.27)
History of Ischemic Heart Disease	1.23 (0.75-2.00)	1.09 (0.63-1.89)
Degree of Stenosis (per 10%)	1.27 (1.16-1.40)	1.19 (1.07-1.32)
Plaque Ulceration	3.79 (2.17-6.61)	2.70 (1.43-5.09)

Data are OR (95% CI).

As illustrated by the forest plot in figure 1, multivariable analysis revealed an independent association between plaque ulceration and non-lacunar stroke after adjustment for age and sex; age, sex and cardiovascular risk factors; degree of stenosis alone and age, sex, cardiovascular risk factors and degree of stenosis.

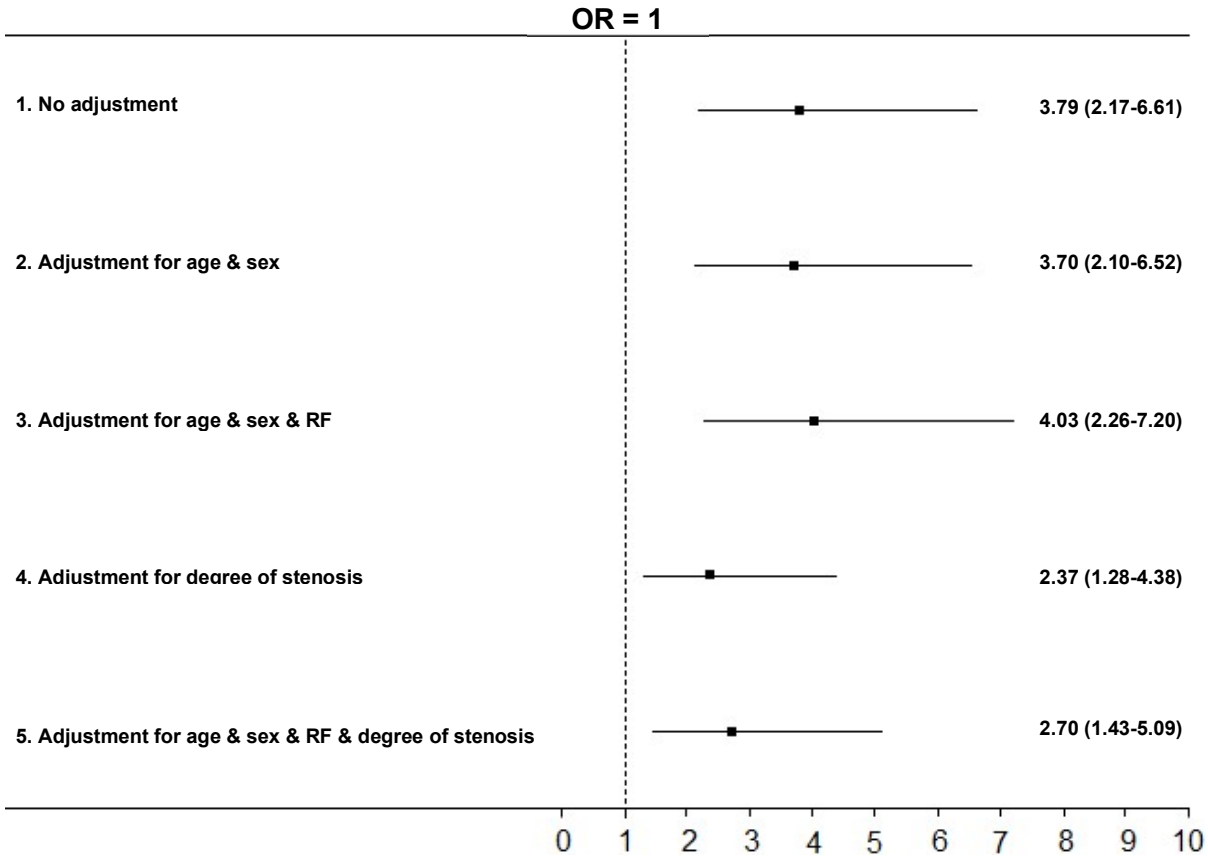

Figure 1. Symptomatic carotid plaque ulceration is independently associated with non-lacunar stroke after correction for age, sex, cardiovascular risk factors (RF) and degree of stenosis.

Risk Factors for Non-lacunar Infarction on MDCT of the brain

An infarction on MDCT of the brain was found in 162 patients (30%), including 82 patients with non-lacunar infarction and 80 patients with lacunar infarction. In patients with non-lacunar infarction as compared to patients with lacunar infarction, a higher prevalence of atherosclerotic plaques (n=60, 73% versus n=65, 81%) and occlusions (n=10, 12% versus n=1, 1%) (*P*=0.02), were observed in the symptomatic carotid artery. Plaque ulceration in the symptomatic carotid artery was more common in non-lacunar infarction (n=23, 28%) as compared to lacunar infarction (n=7, 9%) (*P*=0.002).

Risk factors associated with non-lacunar infarction (as opposed to lacunar infarction) in univariable and multivariable analysis are provided in table 4. Atherosclerotic plaque ulceration was independently associated with non-lacunar infarction in multivariable analysis (OR 4.31, 95% CI 1.49-12.50).

Table 4. univariable- and multivariable odds-ratios for association between CT confirmed non-lacunar infarctions (versus lacunar infarctions) and cardiovascular risk factors, degree of stenosis and plaque ulceration.

	Univariable Analysis	**Multivariable Analysis**
Age (per decade)	0.90 (0.69-1.18)	0.80 (0.58-1.09)
Male Sex	1.16 (0.61-2.20)	0.92 (0.44-1.91)
Hypercholesterolemia	0.70 (0.32-1.53)	0.75 (0.32-1.77)
Hypertension	0.60 (0.28-1.31)	0.44 (0.18-1.08)
Diabetes Mellitus	1.48 (0.72-3.03)	2.01 (0.89-4.50)
Smoking	0.95 (0.50-1.80)	0.76 (0.36-1.63)
Peripheral Arterial Disease	0.97 (0.35-2.67)	0.93 (0.29-3.04)
Previous Ischemic Stroke	1.47 (0.64-3.39)	1.56 (0.60-4.05)
Previous TIA	0.99 (0.38-2.58)	0.54 (0.17-1.80)
Previous Intracerebral Hematoma	1.10 (0.07-17.89)	1.48 (0.08-26.23)
History of Ischemic Heart Disease	1.11 (0.45-2.75)	1.01 (0.34-2.98)
Degree of Stenosis (per 10%)	1.23 (1.05-1.44)	1.19 (0.98-1.46)
Plaque Ulceration	4.83 (1.92-12.12)	4.31 (1.49-12.50)

Data are OR (95% CI).

Discussion

In the current study patients with ischemic cerebrovascular symptoms were classified according to presumed stroke etiology. Besides degree of stenosis, atherosclerotic carotid plaque ulceration was shown to be independently associated with non-lacunar stroke. This relation between plaque ulceration and clinically defined non-lacunar stroke was confirmed by an independent association between the presence of atherosclerotic carotid plaque ulceration and non-lacunar infarction on MDCT of the brain.

Etiology of ischemic stroke subtypes

The association of various risk factors with subtypes of ischemic stroke has been studied extensively.[3] Differences in cardiovascular risk factor profile would support a distinct arterial pathological process underlying different types of stroke. Previous studies had suggested lacunar strokes to be predominantly associated with hypertension and diabetes mellitus.[15,16]

However, in a recent review by Jackson and colleagues, only a marginal increase was shown in the prevalence of hypertension in patients with lacunar stroke as compared to non-lacunar stroke.[3] Whereas no difference was observed in the prevalence of diabetes mellitus. The authors suggested that the previously observed difference in risk factors between ischemic stroke subtypes was based on stroke classification bias, as most studies included risk factors in their ischemic stroke subtype definitions. In the present study, a risk factor free stroke subtype classification was used. Thereby, we differentiated between non-lacunar and lacunar ischemic stroke based on clinical symptoms and MDCT imaging of the brain. In concordance with Jackson et al, no significant difference in cardiovascular risk factors was observed between patients with non-lacunar and lacunar ischemic stroke. To further elucidate the pathophysiological mechanisms associated with subtypes of ischemic stroke we therefore evaluated the relation between parameters of carotid atherosclerosis as assessed by MDCTA of the symptomatic carotid artery.

Relation of Carotid Artery Stenosis and Plaque Ulceration with Non-lacunar Stroke

The relation of degree of stenosis and plaque ulceration with any ischemic stroke has been previously studied using conventional angiographic studies. Previous studies relating degree of stenosis with specific stroke subtypes have identified an association with non-lacunar stroke.[3,17,18] Accordingly, in the current study a significant relation was observed between the severity of carotid stenosis and presence of non-lacunar stroke. Plaque ulceration in the symptomatic carotid artery of patients with ischemic stroke has been shown to be independently associated with an increased risk of recurrent ipsilateral ischemic stroke in patients on medical treatment in the NASCET and ECST

study.[4,5] However, no previous studies have evaluated the association of plaque ulceration with non-lacunar stroke in particular.

Atherosclerotic carotid plaque ulcerations are thought to be a marker of previous plaque ruptures.[19] Following plaque rupture, thrombogenic material is exposed to blood initiating platelet aggregation and thrombus formation, ultimately leading to thromboembolism or local carotid artery occlusion.[20] Emboli from ruptured atherosclerotic carotid plaques may occlude the intracranial cerebral arteries, resulting in ischemia of cortical and subcortical brain tissue. Accordingly, Lovett *et al.* observed a strong correlation between atherosclerotic plaque ulceration in the carotid artery and histological characteristics of plaque instability including plaque rupture, intraplaque hemorrhage and large lipid core.[21] The results of the present study support this underlying mechanism by revealing an independent association between plaque ulceration in the symptomatic carotid artery and non-lacunar stroke. In addition, current results suggest a different pathophysiological mechanism in non-lacunar and lacunar stroke subtypes.

Clinical and Research Implications

Recent research on atherosclerosis has shifted from severity of stenosis towards parameters of plaque vulnerability. Plaque surface morphology and plaque ulcerations may reflect plaque vulnerability. Plaque surface evaluation of the symptomatic carotid artery has been recommended in an algorithm for clinical decision making concerning carotid endarterecomy.[22] That particular algorithm is based on the results of the NASCET and ECST data wherein plaque surface morphology was evaluated using conventional arterial angiography. However, in current clinical practice conventional angiography is increasingly replaced by non-invasive imaging modalities such as MDCTA and magnetic resonance angiography (MRA). Both techniques provide accurate non-invasive evaluation of carotid artery stenosis. In addition, MDCTA provides supplementary information on plaque surface morphology as compared to MRA.[7] Accordingly, for individual risk stratification assessment of plaque surface morphology could be based on MDCTA rather than conventional angiography.

The predominant association of plaques ulcerations with the presence of non-lacunar ischemic stroke in the current study suggests that risk stratification strategies using plaque ulceration should be developed with caution and potentially adjusted for type of clinically defined ischemic stroke. Furthermore, future studies relating atherosclerotic disease to clinical events or brain tissue damage should therefore take the heterogeneity of stroke etiologies into account.

Study Limitations

Firstly, the current study is based on carotid analysis by MDCTA, and findings were not confirmed by histological specimens. However, MDCTA has been validated for detection of plaque ulceration.[6,23] The applied stroke subtype classification was based on clinical symptoms and corrected for relevant infarctions seen on MDCT of the brain. Although a clinical approach results in an accurate classification in the majority of patients, some misclassifications are inevitable. Nonetheless, after replication of the analysis based on infarctions alone as a substitute for clinically defined stroke subtypes, the independent association between carotid plaque ulceration and non-lacunar infarction was confirmed. Finally, the present study has a cross-sectional design. Therefore, the prognostic value of carotid plaque ulcerations in different stroke subtypes remains to be determined in follow-up studies. Also, the incremental value of medical treatment adapted for plaque morphology needs to be determined in a randomized clinical study.[24]

Conclusion

Atherosclerotic plaque ulceration of the symptomatic carotid artery is strongly related with non-lacunar ischemic events as compared to lacunar ischemic events, independently of severity of stenosis. This finding was confirmed by an independent association between the presence of atherosclerotic carotid plaque ulceration and non-lacunar infarctions on MDCT of the brain. These results indeed suggest that non-lacunar ischemic stroke and lacunar stroke are caused by different pathophysiological mechanisms. Plaque ulceration is an important factor to evaluate in future prognostic and therapeutic studies of patients with carotid atherosclerotic disease.

References

1. Fisher CM. Lacunar strokes and infarcts: A review. Neurology. 1982;32:871-876.

2. Warlow C, Sudlow C, Dennis M, Wardlaw J, Sandercock P. Stroke. Lancet. 2003;362:1211–1224.

3. Jackson C, Sudlow C. Are Lacunar Strokes Really Different? A Systematic Review of Differences in Risk Factor Profiles Between Lacunar and Nonlacunar Infarct. Stroke. 2005;36:891-904.

4. Eliasziw M, Streifler JY, Fox AJ, Hachinski VC, Ferguson GG, Barnett HJ. Significance of plaque ulceration in symptomatic patients with high-grade carotid stenosis. North American Symptomatic Carotid Endarterectomy Trial. Stroke. 1994;25:304-308.

5. Rothwell PM, Gibson R, Warlow CP. Interrelation between plaque surface morphology and degree of stenosis on carotid angiograms and the risk of ischemic stroke in patients with symptomatic carotid stenosis. On behalf of the European Carotid Surgery Trialists' Collaborative Group. Stroke. 2000;31:615-621.

6. Saba L, Caddeo G, Sanfilippo R, Montisci R, Mallarini G. Efficacy and sensitivity of axial scans and different reconstruction methods in the study of the ulcerated carotid plaque using multidetector-row CT angiography: comparison with surgical results. AJNR Am J Neuroradiol. 2007;28:716-723.

7. Randoux B, Marro B, Koskas F, Duyme M, Sahel M, Zouaoui A, Marsault C. Carotid artery stenosis: prospective comparison of CT, three-dimensional gadolinium-enhanced MR, and conventional angiography. Radiology. 2001;220:179-185.

8. Adams HP Jr, Bendixen BH, Kappelle LJ, Biller J, Love BB, Gordon DL, Marsh EE 3rd. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in acute stroke treatment. Stroke. 1993;24:35-41.

9. Current management of amaurosis fugax. The Amaurosis Fugax Study Group. Stroke. 1990;21:201-208.

10. de Monyé C, Cademartiri F, de Weert TT, Siepman DA, Dippel DW, van der Lugt A. Sixteen-detector row CT angiography of carotid arteries: comparison of different volumes of contrast material with and without a bolus chaser. Radiology. 2005;237:555-562.

11. de Monyé C, de Weert TT, Zaalberg W, Cademartiri F, Siepman DA, Dippel DW, van der Lugt A. Optimization of CT angiography of the carotid artery with a 16-MDCT scanner: craniocaudal scan direction reduces contrast material-related perivenous artifacts. AJR Am J Roentgenol. 2006;186:1737-1745.

12. de Weert TT, Ouhlous M, Zondervan PE, Hendriks JM, Dippel DW, van Sambeek MR, van der Lugt A. In vitro characterization of atherosclerotic carotid plaque with multidetector computed tomography and histopathological correlation. Eur Radiol. 2005;15:1906-1914.

13. Rothwell PM, Gibson RJ, Slattery J, Warlow CP. Prognostic value and reproducibility of measurements of carotid stenosis. A comparison of three methods on 1001 angiograms. European Carotid Surgery Trialists' Collaborative Group. Stroke. 1994;25:2440-2444.

14. Bamford J, Sandercock P, Dennis M, Burn J, Warlow C. Classification and natural history of clinically identifiable subtypes of cerebral infarction. Lancet. 1991;337:1521-1526.

15. Mast H, Thompson JL, Lee SH, Mohr JP, Sacco RL. Hypertension and diabetes mellitus as determinants of multiple lacunar infarcts. Stroke. 1995;26:30-33.

16. Grau AJ, Weimar C, Buggle F, Heinrich A, Goertler M, Neumaier S, Glahn J, Brandt T, Hacke W, Diener HC. Risk factors, outcome, and treatment in subtypes of ischemic stroke: the German stroke data bank. Stroke. 2001;32:2559-2566.

17. Boiten J, Lodder J. Lacunar infarcts. Pathogenesis and validity of the clinical syndromes. Stroke. 1991;22:1374-1378.

18. Schmal M, Marini C, Carolei A, Di Napoli M, Kessels F, Lodder J. Different vascular risk factor profiles among cortical infarcts, small deep infarcts, and primary intracerebral haemorrhage point to different types of underlying vasculopathy. A study from the L'Aquila Stroke Registry. Cerebrovasc Dis. 1998;8:14-19.

19. Ross R. Atherosclerosis: an inflammatory disease. N Engl J Med. 1999;340:115-126.

20. Lammie GA, Sandercock PA, Dennis MS. Recently occluded intracranial and extracranial carotid arteries. Relevance of the unstable atherosclerotic plaque. Stroke. 1999;30:1319-1325.

21. Lovett JK, Gallagher PJ, Hands LJ, Walton J, Rothwell PM. Rothwell. Histological Correlates of Carotid Plaque Surface Morphology on Lumen Contrast Imaging. Circulation. 2004; 110:2190-2197.

22. Rothwell PM. Medical and surgical management of symptomatic carotid stenosis. Int J Stroke. 2006;1:140-149.

23. Walker LJ, Ismail A, McMeekin W, Lambert D, Mendelow AD, Birchall D. Computed tomography angiography for the evaluation of carotid atherosclerotic plaque: correlation with histopathology of endarterectomy specimens. Stroke. 2002;33:977-981.

24. van der Lugt A. From Case Study to Prospective Study. Stroke. 2005;36:2337-2338.

Chapter 2.3

Association between carotid artery plaque ulceration and plaque composition evaluated with multidetector CT angiography

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Abstract

Background and Purpose: Symptomatic carotid artery plaque ulceration is associated with distinct plaque components such as a large lipid-rich necrotic core (LR-NC) in ischemic stroke patients with a ≥50% carotid stenosis. We evaluated the associations between carotid artery plaque ulceration and plaque characteristics in ischemic stroke patients with ≥50% stenosis as well as in those with a low degree stenosis (0-49%).

Methods: Consecutive patients (n=346) with symptoms in the anterior circulation were evaluated with multi-detector CT angiography (MDCTA) for the presence of atherosclerotic plaque, degree of stenosis, and plaque ulceration in the symptomatic carotid artery. Plaque volume and plaque component proportions of LR-NC, fibrous tissue, and calcification were measured. The associations between plaque ulceration and plaque characteristics were analyzed using logistic regression.

Results: Atherosclerotic plaque was present in 185 patients. Plaque ulcerations were present in 38 (21%) patients, of which half had a low degree stenosis (0-49%). Plaque volume was significantly larger in ulcerated plaques. After adjustment for age, sex, and degree of stenosis, LR-NC proportion was strongly associated with plaque ulceration (OR 2.21; 95%CI 1.49-3.27), whereas calcification proportion was inversely associated with plaque ulceration (OR 0.60; 95%CI 0.40-0.89). These associations remained significant in patients with a low degree stenosis (0-49%).

Conclusion: Plaque volume, degree of stenosis, and LR-NC proportion evaluated non-invasively with MDCTA are associated with carotid artery plaque ulceration, even in patients with a low degree stenosis (0-49%). Plaque volume and composition analysis with MDCTA may identify rupture prone plaques, and improve risk stratification in ischemic stroke patients.

Introduction

Atherosclerotic carotid plaque ulceration is an independent marker of previous plaque rupture and an influential predictor of ischemic stroke.[1,2] Thus far, histological and non-invasive imaging assessment of the relation of carotid plaque characteristics with plaque surface disruption has been limited to patients with a ≥50% carotid stenosis.[3,4] In patients with severe symptomatic stenosis, carotid plaque ulceration has been associated with the presence of fibrous cap rupture and distinct plaque components such as intraplaque hemorrhage, large lipid core, and less fibrous tissue.[3] However, a ≥50% carotid stenosis is present in only approximately 10% of patients with amaurosis fugax, transient ischemic attack or minor ischemic stroke.[5] Whereas two-third of carotid plaque ulcerations is observed in carotid arteries with a low degree stenosis (0-49%),[6] little is known about the relation between carotid plaque characteristics with plaque ulceration in these patients. Also, limited data are available on the association between plaque volume and carotid plaque surface disruption.[4]

Analysis of atherosclerotic plaque volume and plaque composition using non-invasive imaging could be useful to identify rupture prone plaques. However, concomitant assessment of carotid plaque characteristics associated with plaque rupture cannot be advocated in the general population of ischemic stroke patients without knowledge of the relation between plaque characteristics and plaque surface disruption.

In the current study, we analyzed the relationship between the symptomatic carotid plaque characteristics, comprising of plaque component proportions and plaque volume, with plaque ulceration in consecutive patients with amaurosis fugax, transient ischemic attack or ischemic stroke using multi-detector CT angiography (MDCTA). The analysis included and compared the associations of plaque characteristics with plaque ulceration in symptomatic carotid arteries with significant stenosis (≥50%), as well as in those with a low degree stenosis (0-49%).

Materials and Methods

Study Population

From a prospective registry of 911 consenting patients with amaurosis fugax, transient ischemic attack or ischemic stroke (Rankin score <4) who underwent MDCTA of the carotid arteries, we selected a two-year cohort of consecutive patients (n=346) with symptoms in the anterior circulation. Patients were enrolled from a specialized transient ischemic attack/stroke outpatient clinic or the neurology ward. All patients underwent an interview, neurological examination, electrocardiography, laboratory analysis, and MDCTA on admission. Medical history and cardiovascular risk factors as defined previously were recorded.[7] Patients without atherosclerotic plaque (n=137), with carotid occlusion (n=20), and patients with an MDCTA of insufficient quality (n=4) were excluded from the analysis.

MDCTA Data Acquisition and Data Analysis

Imaging was performed with a 16-slice MDCT scanner (Sensation 16, Siemens, Erlangen, Germany) or a 64-slice MDCT scanner (Sensation 64, Siemens, Erlangen, Germany) with a standardized optimized contrast-enhanced protocol (120 kVp, 180 mAs, collimation 16x0.75 mm or 64x0.6 mm, pitch≤1).[8] Details of the MDCTA scan protocol have been described previously.[7,9]

MDCTA images were sent to a stand-alone workstation (Leonardo – Siemens Medical Solutions, Forchheim, Germany) with dedicated 3D-analysis software. The symptomatic carotid bifurcation was evaluated by two experienced investigators blinded to clinical data with multi-planar reformatting software, which allows reconstruction of sagittal, coronal, and oblique views from axial sections. Discrepancies were solved by consensus.

Symptomatic carotid arteries were evaluated for the presence of atherosclerotic plaque, defined as thickening of the vessel wall or the presence of calcification. Plaque ulceration was defined as extension of contrast media beyond the vascular lumen into the surrounding plaque. Degree of stenosis in the symptomatic carotid artery was determined according to the NASCET criteria on multi-planar reformatting images perpendicular to the central lumen line.[10]

Plaque volume and plaque component proportions were measured with custom-made software, programmed in MeVisLab (MeVis Research, Bremen, Germany). Using this software, the components of the atherosclerotic plaque within regions of interest drawn on axial MDCTA images can be determined from their corresponding Hounsfield values using thresholds determined previously.[11] The threshold for the distinction between fibrous tissue and lipid-rich necrotic core (LR-NC) was set at 60 Hounsfield units. The threshold for distinguishing calcifications from fibrous tissue

was set at 130 Hounsfield units; the value currently used for calcium scoring. Based on previous studies it may be assumed that intraplaque hemorrhage, if present, would be classified as LR-NC or fibrous tissue.[11,12]

Plaque volume and plaque component volumes were automatically calculated from the number and dimensions of voxels for different ranges of Hounsfield unit values within the regions of interest (Figure 1). Plaque component proportions were calculated from plaque component volumes as a percentage of the plaque volume.

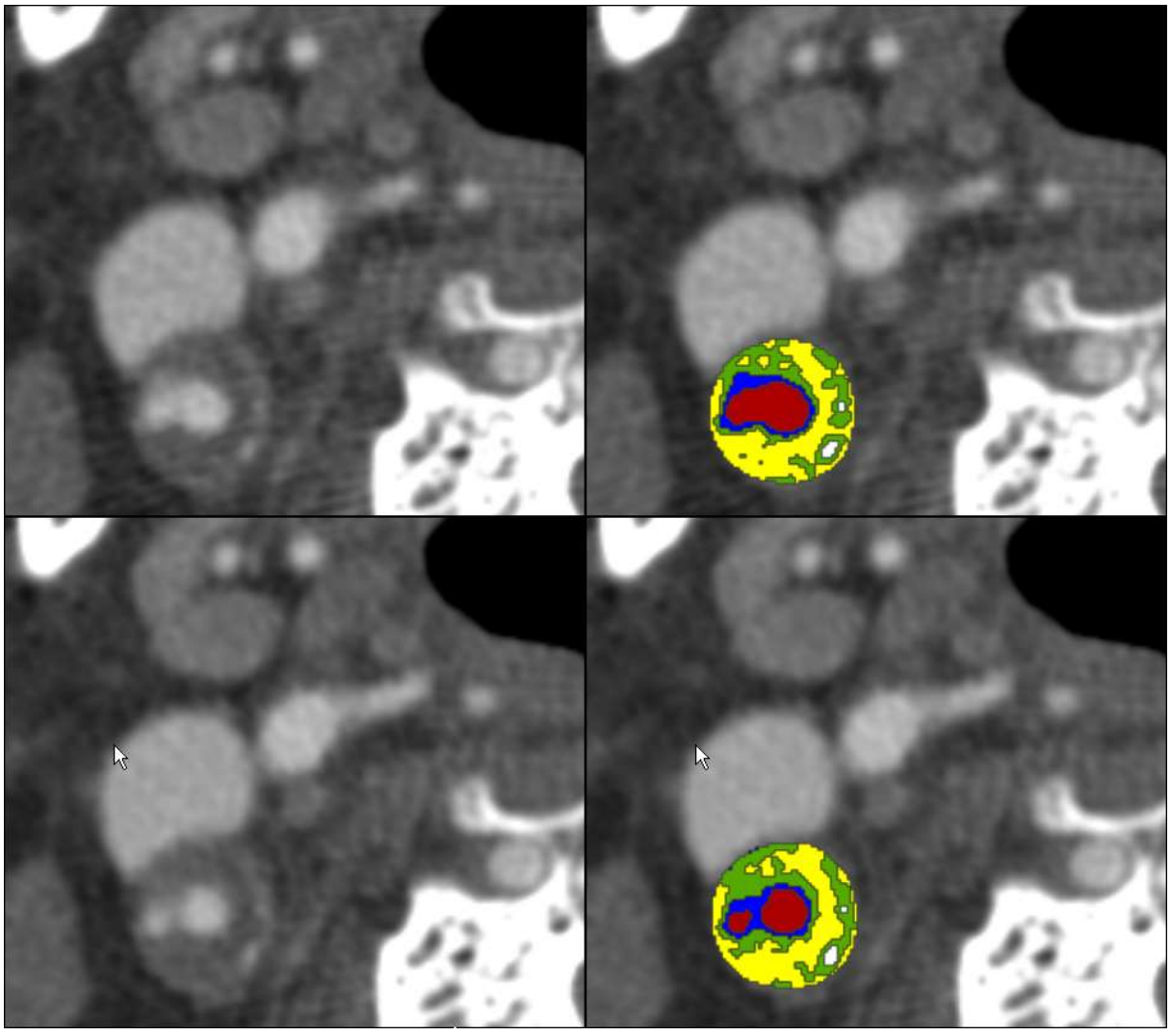

Figure 1. Two succeeding axial MDCTA images illustrating an ulcerated plaque in the internal carotid artery (left). The plaque composition is visible in the image overlay (right), with LR-NC (yellow), fibrous tissue (green), calcifications (white), and the contrast-filled lumen and plaque ulceration (red with blue border-zone).

Statistical Analysis

Baseline population and plaque characteristics are presented as mean±SD or number of patients (%). Differences were tested with chi-square tests, Fisher's Exact tests or Mann-Whitney tests when appropriate. For logistic regression analysis continuous data were divided by 10 or 100, as indicated in the relevant tables.

The correlation between degree of stenosis and plaque volume was evaluated by calculation of the Spearman's rank correlation coefficient. The associations between carotid plaque ulceration and degree of stenosis, plaque volume, and plaque component proportions were evaluated using logistic regression analysis. Two models were constructed. In model I, plaque characteristics were adjusted for age and sex. In model II, adjustments were made for age, sex, and degree of stenosis. Finally, in a stratified analysis the associations between carotid plaque ulceration and plaque characteristics were evaluated in patients with low (0-49%), and with significant (≥50%) carotid stenosis, with adjustment for age, sex, and degree of stenosis. *P*-values ≤0.05 were considered statistically significant. All analyses were performed using SPSS 15.0 statistical package for Windows (SPSS, INC., Chicago, Illinois, USA).

Results

Patients Characteristics

From the 346 evaluated patients, 185 patients with atherosclerotic plaque were included in all further analyses. Baseline characteristics of patients with and without atherosclerotic plaque ulceration in the symptomatic carotid artery are illustrated in Table 1. Atherosclerotic plaque ulceration in the symptomatic carotid artery was present in 38 (21%) patients. The prevalence of cardiovascular risk factors was not significantly different between the two groups.

Table 1. Characteristics of patients with and without symptomatic carotid artery plaque ulceration.

	Patients with Plaque Ulceration n=38 (21%)	**Patients without Plaque Ulceration n=147 (79%)**	***P*-value**
Age (years)	67±10	67±11	0.74
Male sex	28 (74%)	93 (63%)	0.26
Hypercholesterolemia	28 (74%)	124 (84%)	0.15
Hypertension	27 (71%)	120 (82%)	0.15
Diabetes mellitus	4 (11%)	30 (20%)	0.24
Smoking	17 (45%)	45 (31%)	0.10
Peripheral arterial disease	4 (11%)	15 (10%)	1.00
Previous ischemic stroke	7 (18%)	19 (13%)	0.43
Previous TIA	8 (21%)	27 (18%)	0.82
Previous intracerebral hematoma	2 (5%)	2 (1%)	0.19
History of ischemic heart disease	7 (18%)	42 (29%)	0.30

Data are number (percentage), or mean±SD.

Plaque Characteristics on MDCTA

Atherosclerotic plaque characteristics of patients with and without atherosclerotic plaque ulceration in the symptomatic carotid artery are illustrated in Table 2. Degree of stenosis was significantly higher in patients with plaque ulceration. In patients with carotid artery ulcerations, 19 had 0-49% stenosis, whereas the remaining 19 patients had ≥50% stenosis (Figure 2).

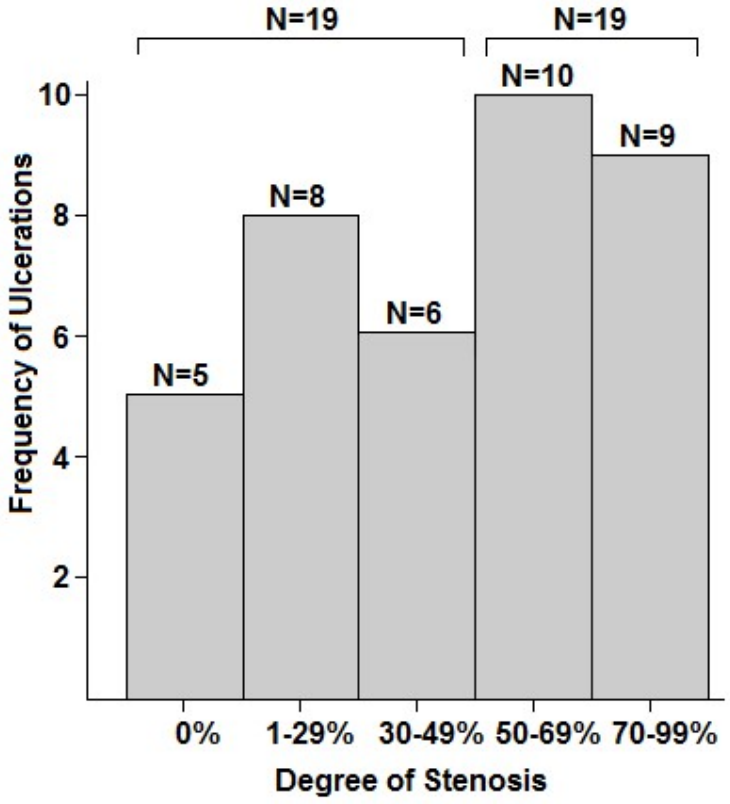

Figure 2. Bargraph illustrating the degree of stenosis of the symptomatic carotid artery in patients with atherosclerotic plaque ulcerations (n=38).

Plaque volume of ulcerated plaques was significantly larger as compared to non-ulcerated plaques. A moderate correlation was observed between degree of stenosis and plaque volume (r_s=0.57; *P*=0.01). Ulcerated plaques contained a significantly larger LR-NC volume, fibrous tissue volume, and LR-NC proportion. Fibrous tissue proportion was significantly lower in ulcerated plaques as compared to non-ulcerated plaques.

Table 2. Plaque characteristics of patients with and without symptomatic carotid artery plaque ulceration.

	Patients with Plaque Ulceration (n=38; 21%)	**Patients without Plaque Ulceration (n=147; 79%)**	***P*-value**
Degree of Stenosis	44±29%	18±27%	<0.001
Plaque volume	1320±708 mm^3	765±588 mm^3	<0.001
LR-NC volume	416±283 mm^3	168±197 mm^3	<0.001
Fibrous volume	736±333 mm^3	468±306 mm^3	<0.001
Calcification volume	163±178 mm^3	129±180 mm^3	0.196
LR-NC proportion	29±10%	18±10%	<0.001
Fibrous proportion	60±11%	67±13%	0.001
Calcification proportion	10±9%	15±14%	0.152

Data are means±SD.

Plaque Characteristics associated with Plaque Ulceration on MDCTA

Results of multivariable analyses relating plaque characteristics and plaque ulcerations are provided in Table 3 and 4. After adjustment for age and sex (model I), degree of stenosis, plaque volume, and the LR-NC proportion were associated with plaque ulceration, whereas fibrous proportion was inversely associated with plaque ulceration. After adjustment for age, sex, and degree of stenosis (model II), plaque volume and the LR-NC proportion remained significantly associated with plaque ulceration, whereas the calcification proportion was inversely associated with plaque ulceration.

Table 3. Multivariable analysis for the associations between symptomatic carotid artery plaque ulceration and plaque characteristics.

	Model I		**Model II**	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Degree of Stenosis (/10%)	1.33 (1.18-1.50)	<0.001	n.a.	n.a.
Plaque volume (/100mm^3)	1.14 (1.07-1.21)	<0.001	1.09 (1.02-1.16)	0.01
LR-NC proportion (/10%)	2.58 (1.77-3.78)	<0.001	2.21 (1.49-3.27)	<0.001
Fibrous proportion (/10%)	0.64 (0.48-0.87)	0.004	0.85 (0.60-1.20)	0.35
Calcification proportion (/10%)	0.75 (0.54-1.04)	0.08	0.60 (0.40-0.89)	0.01

Data are OR (95% CI).

Table 4. Stratified multivariable analysis for the associations between symptomatic carotid artery plaque ulceration and plaque characteristics in patients with low (0-49%) and with significant (≥50) carotid stenosis.

	Patients with 0-49% Stenosis (n=144)		**Patients with ≥50% Stenosis (n=41)**	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Plaque volume (/100mm^3)	1.06 (0.98-1.14)	0.15	1.23 (1.04-1.46)	0.02
LR-NC proportion (/10%)	3.04 (1.70-5.45)	<0.001	1.82 (0.98-3.40)	0.06
Fibrous proportion (/10%)	0.88 (0.57-1.36)	0.56	1.05 (0.53-2.08)	0.89
Calcification proportion (/10%)	0.34 (0.16-0.69)	0.003	0.68 (0.40-1.15)	0.15

Data are OR (95% CI).

In a stratified analysis of patients with a low degree stenosis of 0-49% (n=144), the LR-NC proportion remained strongly associated with plaque ulceration, whereas the calcification proportion remained inversely associated with plaque ulceration. In patients with significant stenosis of ≥50% (n=41), plaque volume was associated with plaque ulceration, whereas a trend towards a significant association between the LR-NC proportion and plaque ulceration was observed.

Discussion

In the current study of patients with amaurosis fugax, transient ischemic attack or ischemic stroke, half of the plaque ulcerations were identified in symptomatic carotid arteries with a low degree stenosis of 0-49%. Non-invasive carotid artery plaque analysis with MDCTA revealed that degree of stenosis, plaque volume, and the LR-NC proportion were associated with plaque ulceration in the symptomatic carotid artery. Of these plaque characteristics, the LR-NC proportion was most strongly associated with plaque ulceration. In contrast, the calcification proportion was inversely associated with plaque ulceration. The observed associations remained significant in patients with a low degree carotid stenosis of 0-49%. The current study is the first to evaluate the associations between plaque ulceration and plaque characteristics irrespective of the degree of stenosis.

Association of Atherosclerotic Plaque Characteristics with Ischemic Stroke

Several studies have evaluated the relation of carotid artery plaque characteristics with ischemic stroke.[13-19] In general, imaging studies with magnetic resonance and CT have identified positive associations between fibrous cap thickness, the size of the LR-NC, intraplaque hemorrhage and the presence of carotid plaque surface disruption with ischemic stroke in cross-sectional and follow-up studies.[13-16] Accordingly, in ultrasound studies echolucent carotid plaques were associated with increased risk of cerebrovascular events.[17,18] Echolucent plaques are known to have higher levels of lipid and hemorrhage compared with echogenic plaques, which contain more calcification and fibrous tissue. On the contrary, proportion of carotid plaque calcification is shown to be inversely associated with the occurrence of ischemic stroke.[16,19] However, results of histological analyses have been less consistent.[20] A review by Golledge *et al.* demonstrated the lack of an association between histologically defined LR-NC and intraplaque hemorrhage with ischemic stroke.[20]

The observed discrepancy may be a consequence of disparate etiology of ischemic stroke. Nevertheless, plaque rupture and subsequent thrombo-embolism are considered crucial elements in the pathophysiological cascade between the development of a heterogeneous plaque and thromboembolic stroke.[21] As a result, in the present study we evaluated the direct associations between plaque characteristics comprising of plaque stenosis, plaque volume and composition with plaque ulceration in patients with ischemic stroke.

Association of Atherosclerotic Plaque Characteristics with Carotid Plaque Surface Disruption

Previous research relating atherosclerotic carotid plaque characteristics with plaque surface disruption has focused on stenotic plaques corresponding with luminal narrowing of ≥50%.[3,4] In a magnetic resonance study, the LR-NC proportion of carotid plaques of ≥50% stenosis was the strongest predictor of new surface disruption, in form of an ulceration or a fibrous cap rupture.[4] In

that particular study, the calcification proportion was inversely related with plaque surface disruption. In addition, the presence of intraplaque hemorrhage as assessed with magnetic resonance is significantly associated with the presence of plaque ulceration on MDCTA.[22] Plaque ulceration on conventional angiography in symptomatic carotid arteries with ≥50% stenosis was associated with the presence of intraplaque hemorrhage, large lipid core and less fibrous tissue in carotid endarterectomy specimens.[3] Similarly, ultrasonographic examination of carotid arteries demonstrated a relation between echolucency of stenotic plaques and plaque ulceration.[23] However, conventional angiography and ultrasound provide no quantitative information on plaque volume. Therefore, only limited data are available on the relation of plaque volume with plaque surface disruption as assessed using magnetic resonance.[4]

MDCTA allows fast and reliable evaluation of steno-occlusive disease in extracranial and intracranial arteries and is widely available.[24-26] The technique is effective in the detection of carotid plaque ulceration with a sensitivity and specificity of 94% and 99% respectively.[27] Furthermore, distinct plaque components as well as plaque volume can be quantified in good correlation with histology.[11,12] In the current study, using MDCTA, the relation between plaque composition and plaque volume with plaque ulceration was evaluated in patients with a symptomatic carotid stenosis of ≥50% as well as in patients with a low degree of stenosis (0-49%). Interestingly, in line with previous reports, a substantial proportion of the plaque ulcerations were located in symptomatic carotid arteries with a low degree of stenosis.[5,6] The association between the LR-NC proportion with plaque ulceration was significant in ischemic stroke patients with a low degree of stenosis (0-49%), whereas a trend toward significance was observed in patients with a stenosis of ≥50%. The inverse association observed between the calcification proportion and plaque ulceration was significant in patients with a low degree stenosis. Furthermore, only a weak correlation was observed between the degree of carotid artery stenosis and plaque volume on MDCTA. Importantly, plaque volume was associated with plaque ulceration, even after adjustment for the severity of stenosis. Overall, these findings demonstrate that the associations between plaque composition and volume with plaque ulcerations are present in ischemic stroke patients irrespective of the degree of the carotid plaque stenosis. In addition, an etiological explanation is provided for the previously observed correlation of plaque characteristics with ischemic stroke events. Herein, a key role is suggested for plaque ulceration in the pathophysiological cascade between the development of a heterogeneous plaque and thromboembolic stroke. In consequence, apart from degree of stenosis, assessment of carotid plaque composition and volume which predispose ulceration could contribute to risk stratification for plaque instability or stroke recurrence.

Study Limitations

First, the study has a cross-sectional design. Indeed, the prognostic value of plaque composition analysis with MDCTA, and more specifically of the LR-NC proportion for the development of plaque ulceration and subsequent thromboembolic ischemic stroke should be confirmed in longitudinal serial imaging studies. Second, in the current study the presence of intraplaque hemorrhage was not evaluated as plaque composition analysis software used in the current study has not been validated for differentiation of intraplaque hemorrhage. As a result, both LR-NC and fibrous tissue assessed with MDCTA may contain intraplaque hemorrhage if present in the plaque. Finally, plaque composition analysis can be performed on routine MDCTA scans used for carotid stenosis evaluation. Nevertheless, every MDCTA leads to ionizing radiation exposure. Therefore, repeated examinations should not be advocated.

Clinical and Research Implications

To our knowledge, the present study is the first to examine the associations between carotid plaque characteristics and carotid plaque ulceration in ischemic stroke patients with a ≥50% stenosis, as well as in those with a low degree stenosis of 0% to 49%. The LR-NC proportion was identified as the strongest determinant for plaque ulceration. The association between the LR-NC proportion and carotid plaque ulceration was independent of the degree of stenosis. Plaque composition analysis with MDCTA may prove useful for detection of rupture-prone plaques and could potentially improve risk stratification in ischemic stroke patients.

References

1. Eliasziw M, Streifler JY, Fox AJ, Hachinski VC, Ferguson GG, Barnett HJ. Significance of plaque ulceration in symptomatic patients with high-grade carotid stenosis. North American Symptomatic Carotid Endarterectomy Trial. *Stroke*. 1994;25:304-308.

2. Rothwell PM, Gibson R, Warlow CP. Interrelation between plaque surface morphology and degree of stenosis on carotid angiograms and the risk of ischemic stroke in patients with symptomatic carotid stenosis. On behalf of the European Carotid Surgery Trialists' Collaborative Group. *Stroke*. 2000;31:615-621.

3. Lovett JK, Gallagher PJ, Hands LJ, Walton J, Rothwell PM. Histological correlates of carotid plaque surface morphology on lumen contrast imaging. *Circulation*. 2004;110:2190-2197.

4. Underhill HR, Yuan C, Yarnykh VL, Chu B, Oikawa M, Dong L, Polissar NL, Garden GA, Cramer SC, Hatsukami TS. Predictors of surface disruption with MR imaging in asymptomatic carotid artery stenosis. *AJNR Am J Neuroradiol*. 2010;31:487-493.

5. Tholen AT, de Monyé C, Genders TS, Buskens E, Dippel DW, van der Lugt A, Hunink MG. Suspected carotid artery stenosis: cost-effectiveness of CT angiography in work-up of patients with recent TIA or minor ischemic stroke. *Radiology*. 2010;256:585-597.

6. de Weert TT, Cretier S, Groen HC, Homburg P, Cakir H, Wentzel JJ, Dippel DW, van der Lugt A. Atherosclerotic plaque surface morphology in the carotid bifurcation assessed with multidetector computed tomography angiography. *Stroke*. 2009;40:1334-1340.

7. Homburg PJ, Rozie S, van Gils MJ, Jansen T, Dippel DW, van der Lugt A. Atherosclerotic plaque ulceration in the symptomatic internal carotid artery is associated with non-lacunar ischemic stroke. *Stroke*. 2010;41:1151-1156.

8. de Monyé C, Cademartiri F, de Weert TT, Siepman DA, Dippel DW, van der Lugt A. Sixteen-detector row CT angiography of carotid arteries: comparison of different volumes of contrast material with and without a bolus chaser. *Radiology*. 2005;237:555-562.

9. de Weert TT, Ouhlous M, Zondervan PE, Hendriks JM, Dippel DW, van Sambeek MR, van der Lugt A. In vitro characterization of atherosclerotic carotid plaque with multidetector computed tomography and histopathological correlation. *Eur Radiol*. 2005;15:1906-1914.

10. North American Symptomatic Carotid Endarterectomy Trial. Methods, patient characteristics, and progress. *Stroke*. 1991;22:711-720.

11. de Weert TT, Ouhlous M, Meijering E, Zondervan PE, Hendriks JM, van Sambeek MR, Dippel DW, van der Lugt A. In vivo characterization and quantification of atherosclerotic carotid plaque components with multidetector computed tomography and histopathological correlation. *Arterioscler Thromb Vasc Biol*. 2006;26:2366-2372.

12. Wintermark M, Jawadi SS, Rapp JH, Tihan T, Tong E, Glidden DV, Abedin S, Schaeffer S, Acevedo-Bolton G, Boudignon B, Orwoll B, Pan X, Saloner D. High-resolution CT imaging of carotid artery atherosclerotic plaques. *AJNR Am J Neuroradiol*. 2008;29:875-882.

13. Takaya N, Yuan C, Chu B, Saam T, Underhill H, Cai J, Tran N, Polissar NL, Isaac C, Ferguson MS, Garden GA, Cramer SC, Maravilla KR, Hashimoto B, Hatsukami TS. Association between carotid plaque characteristics and subsequent ischemic cerebrovascular events: a prospective assessment with MRI--initial results. *Stroke*. 2006;37:818-823.

14. Singh N, Moody AR, Gladstone DJ, Leung G, Ravikumar R, Zhan J, Maggisano R. Moderate carotid artery stenosis: MR imaging-depicted intraplaque hemorrhage predicts risk of cerebrovascular ischemic events in asymptomatic men. *Radiology*. 2009;252:502-508.

15. Serfaty JM, Nonent M, Nighoghossian N, Rouhart F, Derex L, Rotaru C, Chirossel P, Thabut G, Guias B, Heautot JF, Gouny P, de la Vega A, Pachai C, Ecochard R, Villard J, Douek PC; CARMEDAS Study Group. Plaque density on CT, a potential marker of ischemic stroke. *Neurology*. 2006;66:118-120.

16. Wintermark M, Arora S, Tong E, Vittinghoff E, Lau BC, Chien JD, Dillon WP, Saloner D. Carotid plaque computed tomography imaging in stroke and nonstroke patients. *Ann Neurol*. 2008;64:149-157.

17. Mathiesen EB, Bonaa KH, Joakimsen O. Echolucent plaques are associated with high risk of ischemic cerebrovascular events in carotid stenosis: the Tromso Study. *Circulation*. 2001;103:2171-2175.

18. Grønholdt ML, Nordestgaard BG, Schroeder TV, Vorstrup S, Sillesen H. Ultrasonic echolucent carotid plaques predict future strokes. *Circulation*. 2001;104:68-73.

19. Nandalur KR, Baskurt E, Hagspiel KD, Phillips CD, Kramer CM. Calcified carotid atherosclerotic plaque is associated less with ischemic symptoms than is noncalcified plaque on MDCT. *AJR Am J Roentgenol*. 2005;184:295–298.

20. Golledge J, Greenhalgh RM, Davies AH. The symptomatic carotid plaque. *Stroke*. 2000;31:774–781.

21. Virmani R, Ladich ER, Burke AP, Kolodgie FD. Histopathology of carotid atherosclerotic disease. *Neurosurgery*. 2006;59:S219-227.

22. U-King-Im JM, Fox AJ, Aviv RI, Howard P, Yeung R, Moody AR, Symons SP. Characterization of carotid plaque hemorrhage: a CT angiography and MR intraplaque hemorrhage study. *Stroke*. 2010;4:1623-1629.

23. Gray-Weale AC, Graham JC, Burnett JR, Byrne K, Lusby RJ. Carotid artery atheroma: comparison of preoperative B-mode ultrasound appearance with carotid endarterectomy specimen pathology. *J Cardiovasc Surg*. 1988;29:676–681.

24. Koelemay MJ, Nederkoorn PJ, Reitsma JB, Majoie CB. Systematic review of computed tomographic angiography for assessment of carotid artery disease. *Stroke*. 2004; 35:2306-2312.

25. Nguyen-Huynh MN, Wintermark M, English J, Lam J, Vittinghoff E, Smith WS, Johnston SC. How accurate is CT angiography in evaluating intracranial atherosclerotic disease? *Stroke*. 2008;39:1184-1188.

26. Balucani C, Leys D, Ringelstein EB, Kaste M, Hacke W; Executive Committee of the European Stroke Initiative. Detection of intracranial atherosclerosis: which imaging techniques are available in European hospitals? *Stroke*. 2009;40:726-729.

27. Saba L, Caddeo G, Sanfilippo R, Montisci R, Mallarini G. Efficacy and sensitivity of axial scans and different reconstruction methods in the study of the ulcerated carotid plaque using multidetector-row CT angiography: comparison with surgical results. *AJNR Am J Neuroradiol*. 2007;28:716-723.

Chapter 2.4

Evolution of atherosclerotic carotid plaque morphology: do ulcerated plaques heal? A serial multidetector CT angiography study

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Abstract

Background: Atherosclerotic carotid plaque rupture may lead to thromboembolization, causing transient ischemic attack or ischemic stroke. Carotid plaque ulceration on angiography is associated with plaque rupture. Although healing of ruptured plaques has been described in coronary arteries, little is known about the natural development of plaque ulcerations in carotid arteries. We therefore explored the evolution of carotid plaque surface morphology with serial multidetector CT angiography (MDCTA).

Methods: From a registry of patients with transient ischemic attack or minor ischemic stroke, we selected 83 patients who had undergone serial MDCTA of the carotid arteries. Arteries subjected to revascularization procedures between the two scans were excluded (n = 11). Plaque surface morphology was classified as smooth, irregular or ulcerated on both baseline and follow-up MDCTA. Progression (i.e. development of irregularities or ulceration) and regression (i.e. disappearance of irregularities or ulceration) in morphology were evaluated.

Results: The mean time interval between the MDCTA scans was 21 ± 13 months. At baseline, 28 (18%) arteries were normal, 124 (80%) contained atherosclerotic plaque and 3 (2%) were occluded. Plaque surface morphology was smooth in 86 arteries (55%), irregular in 23 (15%) and ulcerated in 15 (10%). At follow-up, surface morphology was unchanged in 88% of arteries, had progressed in 8% and regressed in 4%. Most importantly, plaque morphology remained unchanged in most ulcerated plaques (10/15; 67%). One ulcerated plaque had progressed, whereas 4 had regressed. New ulcerations had developed in 2 nonulcerated plaques.

Conclusion: MDCTA allows evaluation of temporal changes in atherosclerotic carotid plaque morphology. Plaque surface morphology remained unchanged in most arteries. Carotid ulcerations persist for a long time, and may remain a potential source of thromboembolism.

Introduction

Carotid plaque ulceration is associated with plaque rupture, which is an important element in the cascade between vulnerable plaque and the occurrence of thrombo-embolic events.[1-3] In addition to this, carotid plaque ulcerations may be an additional cause of embolic stroke due to local flow disturbances.[4-6] While there is evidence of a healing process of plaque ruptures in the coronary arteries which contributes to the degree of luminal narrowing, little is known about the healing process of plaque ruptures in carotid arteries.[7,8]

Current knowledge about the evolution of atherosclerotic plaque rupture is mainly based on histological analysis of coronary arteries in autopsy studies or carotid plaque specimens obtained from carotid endarterectomy.[9-13] However, for extensive investigation of the temporal changes of plaque surface characteristics and their relation with recurrent thrombo-embolic events, longitudinal non-invasive serial imaging studies are required. Computed tomography angiography (CTA) has been demonstrated to be superior to angiography in detecting plaque ulcerations and multidetector-CT angiography (MDCTA) has been found to have a high sensitivity and specificity (94% and 99%, respectively) in detecting plaque ulcerations.[14,15] Therefore MDCTA is an appropriate non-invasive imaging technique for studying plaque ulceration. As MDCTA is able to identify and classify plaque ulcerations with a very good interobserver agreement, it is also suitable for serial imaging.[16]

To explore the natural history of ulcerated plaques and to assess whether plaque ulcerations heal, we studied the temporal changes in plaque surface morphology on serial MDCTA in patients with transient ischemic attack (TIA) or minor ischemic stroke.

Materials and Methods

Study population

From November 2002 till January 2007, 911 consecutive patients with amaurosis fugax, TIA or minor ischemic stroke (Rankin score < 4) who underwent MDCTA of the carotid arteries were registered. From November 2002 until December 2004, MDCTA was performed as part of a research protocol approved by the Institutional Review Board. All patients gave written informed consent. Onwards of January 2005, MDCTA was performed as part of standard clinical workup. Patients were enrolled from the neurology department's specialized TIA/stroke outpatient clinic or neurology ward and underwent neurological examination on admission; symptoms, risk factors and medication use were reported. Follow-up MDCTA scans of the carotid arteries were registered.

For the present study we selected the patients from our registry who had undergone more than one MDCTA of the carotid arteries in the period November 2002 till December 2008 (n=84). One patient was excluded because of poor image quality caused by dental artifacts on both MDCTA scans. If more than two MDCTA scans per patient had been performed, the one with the largest lead time before any surgical treatment was evaluated in this study. Arteries subjected to revascularization procedures between the two scans were excluded (n=11).The present study was approved by the Institutional Review Board.

Cardiovascular risk factors

Hypercholesterolemia was defined as fasting cholesterol > 5.0 mmol/L or treatment with cholesterol-lowering medication. Hypertension was defined as a systolic blood pressure > 140 mmHg and/or a diastolic blood pressure >90 mmHg during two episodes of at least 15 minutes of continuous non-invasive blood pressure measurement, or treatment with antihypertensive medication. Diabetes was defined as serum glucose levels > 7.9 mmol/L, HbA1c > 6.5%, or use of anti-diabetic medication. Smoking was categorized as either current smoking or non-smoking. Information was collected on previous peripheral vascular disease (intermittent claudication and/or ankle/arm systolic blood pressure ratio < 0.85; or a history of related leg amputation, reconstructive surgery or angioplasty), previous ischemic TIA or stroke, and previous cardiovascular disease (myocardial infarction, angina pectoris, CABG) or otherwise previous cardiac disease (atrium fibrillation, chronic heart failure).

MDCTA data acquisition

Imaging was performed on a 16-slice multidetector CT scanner (Siemens, Sensation 16, Erlangen, Germany) or a 64-slice MDCT scanner (Siemens, Sensation 64) with a standardized, optimized contrast-enhanced protocol (120 kVp, 180 mAs, collimation 16 x 0.75 or 32 x 2 x 0.6 mm, pitch ≤1).[17,18] The scan range extended from the ascending aorta to the intracranial circulation. All patients received 80 mL of contrast material (Iodixanol 320 mg/ml, Visipaque, Amersham Health, Little Chalfont, UK), followed by 40 mL saline bolus chaser, both at an injection rate of 4 mL/sec. Real-time bolus tracking at the level of the ascending aorta was used to synchronize passage of contrast material and data acquisition. Image reconstructions were made with a 120 mm FOV, a matrix size of 512 x 512, a slice thickness of 1.0 mm, a slice increment of 0.6 mm, and intermediate reconstruction algorithms (B30 and B46).

Analysis of the atherosclerotic plaque

The MDCTA images were sent to a workstation (Leonardo-Siemens Medical Solutions, Forchheim, Germany) equipped with dedicated 3-dimensional analysis software. Multi-planar reformatting software was used to evaluate both carotid bifurcations in multiple reformations and different planes. Each carotid artery was evaluated for the presence of an atherosclerotic plaque, defined as the presence of thickening of the vessel wall and/or a calcification in the wall. Atherosclerotic plaque surface morphology was evaluated and classified as smooth, irregular or ulcerated. Plaques were classified as ulcerated if contrast material extended into the plaque, being visible in at least two perpendicular planes. The number of ulcerations per carotid artery was recorded. Irregularities were described as prestenotic or poststenotic dilatation and/or irregular plaque-surface morphology without extension of contrast material into the plaque. Plaques that were not ulcerated or irregular were classified as smooth. The interobserver agreement for the presence of plaque ulceration as described above was found to be good (kappa=1.00; 95% CI 0.86-1.00).[16]

In addition, plaque density was evaluated as previously described by Saba et al.[19] In atherosclerotic carotid plaques, the mean Hounsfield unit attenuation was measured within manually drawn regions of interest covering the plaque on three consecutive axial images at the level of largest plaque burden. Plaque density was classified as soft, mixed or calcified, according to cut-off values derived from a method validated by Schroeder et al: soft plaques with mean density values < 50 HU, intermediate plaques with mean density values between 50 and 119 HU and calcified plaques with a mean density value ≥ 120 HU.[20]

The number of calcifications in the investigated plaques was manually counted within a range of 3 cm above to 3 cm under the bifurcation point. An automated calcium scoring tool was used to assess calcium volumes within this same range, using a cut-off value of 600 HU to differentiate calcifications from contrast material in the lumen.

Assessment of changes in plaque morphology

The atherosclerotic plaque morphology at baseline and follow-up MDCTA were evaluated separately, with a time interval of more than one month between the two assessments. Two experienced observers blinded to clinical data analyzed the MPR images. Discrepancies were resolved by consensus. Additionally, temporal changes in morphology between baseline and follow-up MDCTA scans were verified by a consensus reading where necessary. Changes in atherosclerotic plaque morphology were considered as progression if irregularities, ulceration or occlusion had developed. Regression was defined as disappearance of ulceration or irregularities.

Statistics

Where appropriate, data are presented descriptively as numbers and percentages and means ± standard deviations (SD). We evaluated the association between cardiovascular risk factors and baseline plaque morphology and between cardiovascular risk factors and temporal change in plaque morphology. Differences between categorical data and continuous data were analyzed with a χ^2 test and a Mann-Whitney test or a Student *t* test, respectively. Temporal changes in continuous data on plaque characteristics were analyzed with a paired-samples *t* test.

Results

In total 83 patients who had undergone a baseline MDCTA as well as a follow-up MDCTA evaluation of the carotid arteries were included. The mean time period between the serial scans was 21 ± 13 months. The mean age in the study population was 60 ± 12 years, and the majority of patients were male (64%, Table 1). In 75 patients (90%), the indication for follow up MDCTA was recurrent TIA or ischemic stroke; in 39 (47%), the recurrent event was attributed to the same vascular distribution as the previous attack, and in 36 (43%) a different vascular territory was involved. In eight patients (10%) a follow-up MDCTA was performed for pre- and post-interventional indications or for neurological symptoms that could not be attributed to a specific vascular territory.

Table 1. Baseline characteristics of the study population

	Total Patients (N=83)
Age (years, mean ± SD)	59.8 ± 12.4
Gender (% male)	53 (64%)
Risk factors (%):	
- previous cerebrovascular disease	36 (43%)
- previous cardiovascular disease	16 (19%)
- peripheral vascular disease	6 (7%)
- hypertension	61 (73%)
- hypercholesterolemia	64 (77%)
- diabetes mellitus	22 (27%)
- smoking	29 (35%)
Cerebrovascular symptoms (%):	
Amaurosis fugax	8 (10%)
TIA	33 (40%)
Minor stroke	42 (51%)
Symptomatic artery (%):	
Carotid	68 (82%)
Vertebrobasilar	15 (18%)

Data are means±SD or number of patients (%).

Of the 166 carotid arteries in 83 patients, 11 arteries were excluded, because of treatment by carotid endarterectomy (n=3) or because of stent placement (n=8) in the period between the baseline and follow-up MDCTA. One-hundred-fifty-five carotid arteries were available for analysis of changes in atherosclerotic plaque characteristics on follow-up MDCTA.

Table 2. Plaque characteristics of 155 carotid arteries on baseline and on follow-up MDCTA

	Baseline MDCTA	**Follow-up MDCTA**
Occlusion	3 (2%)	4 (3%)
No plaque	28 (18%)	24 (15%)
Plaque	124 (80%)	127 (82%)
Plaque surface morphology		
Smooth plaque surface	86 (55%)	87 (56%)
Irregular plaque surface	23 (15%)	26 (17%)
Ulcerated plaque	15 (10%)	14 (9%)
Number of ulcerations		
1	12	11
2	2	2
3	1	1
Plaque density *		
Soft plaque	5 (4%)	6 (5%)
Mixed plaque	51 (41%)	46 (36%)
Calcified plaque	68 (55%)	75 (59%)
Calcifications **		
Mean number of calcifications	4.9 ± 3.5	4.6 ± 3.2
Mean calcium volume (mm^3)	44.7 ± 72.1	62.8 ± 92.2

** Assessed in carotid arteries containing plaque ** Assessed in carotid arteries containing plaques with calcification at baseline (n=102)*

Table 2 shows plaque characteristics of the carotid arteries on baseline and follow-up MDCTA scans.

At baseline, 28 (18%) carotid arteries were normal, 124 (80%) contained atherosclerotic plaque, and 3 arteries were occluded. The majority (n=86, 55%) of vessels had a smooth plaque surface, whereas 23 (15%) had irregular plaque surfaces. Fifteen of the 155 vessels (10%) had an ulcerated plaque surface; most arteries contained one ulceration. These ulcerated plaques were present in 15 patients. Most of the plaques (119/124; 96%) were mixed or calcified plaques, since the majority of carotid plaques (102/124, 82%) contained at least some calcifications. The mean HU density of the 124 plaques at baseline was 179 ± 147 HU, which increased to 216 ± 187 HU over time (p=0,001). The number of calcifications did not significantly change over time (4.9 ± 3.5 at baseline versus 4.6 ± 3.2 at follow-up, p=0.21), whereas calcium volume increased significantly (44.7 ± 72.1 mm^3 at baseline versus 62.8 ± 92.2 mm^3 at follow-up, p<0.001)

Table 3. Changes in plaque surface morphology between baseline and follow-up MDCTA in 155 carotid arteries

Plaque Morphology	**Baseline MDCTA**	**Follow-up MDCTA**	**Carotid arteries (N)**
Unchanged	No plaque	No plaque	24
N=137 (88%)	Smooth	Smooth	81
	Irregular	Irregular	19
	1 Ulceration	1 Ulceration	8
	2 Ulcerations	2 Ulcerations	1
	3 Ulcerations	3 Ulcerations	1
	Occlusion	Occlusion	3
Progression	No plaque	Smooth	4
N=12 (8%)	Smooth	Irregular	4
	Smooth	1 Ulceration	1
	Irregular	Occlusion	1
	Irregular	1 Ulceration	1
	1 Ulceration	2 Ulcerations	1
Regression	1 Ulceration	Irregular	3
N=6 (4%)	2 Ulcerations	1 Ulceration	1
	Irregular	Smooth	2

Data are number (%).

Changes in surface morphology between the baseline and the follow-up MDCTA are presented in Table 3. On the follow-up MDCTA the surface morphology was unchanged in 137 (88%) of the carotid arteries, whereas 12 (8%) had progressed and 6 (4%) had regressed. The 12 arteries that had progressed were present in 10 patients. The morphology of most ulcerated plaques (10 out of 15) had not changed over a mean time period of 20 ± 15 months, as illustrated by an example in figure 1.

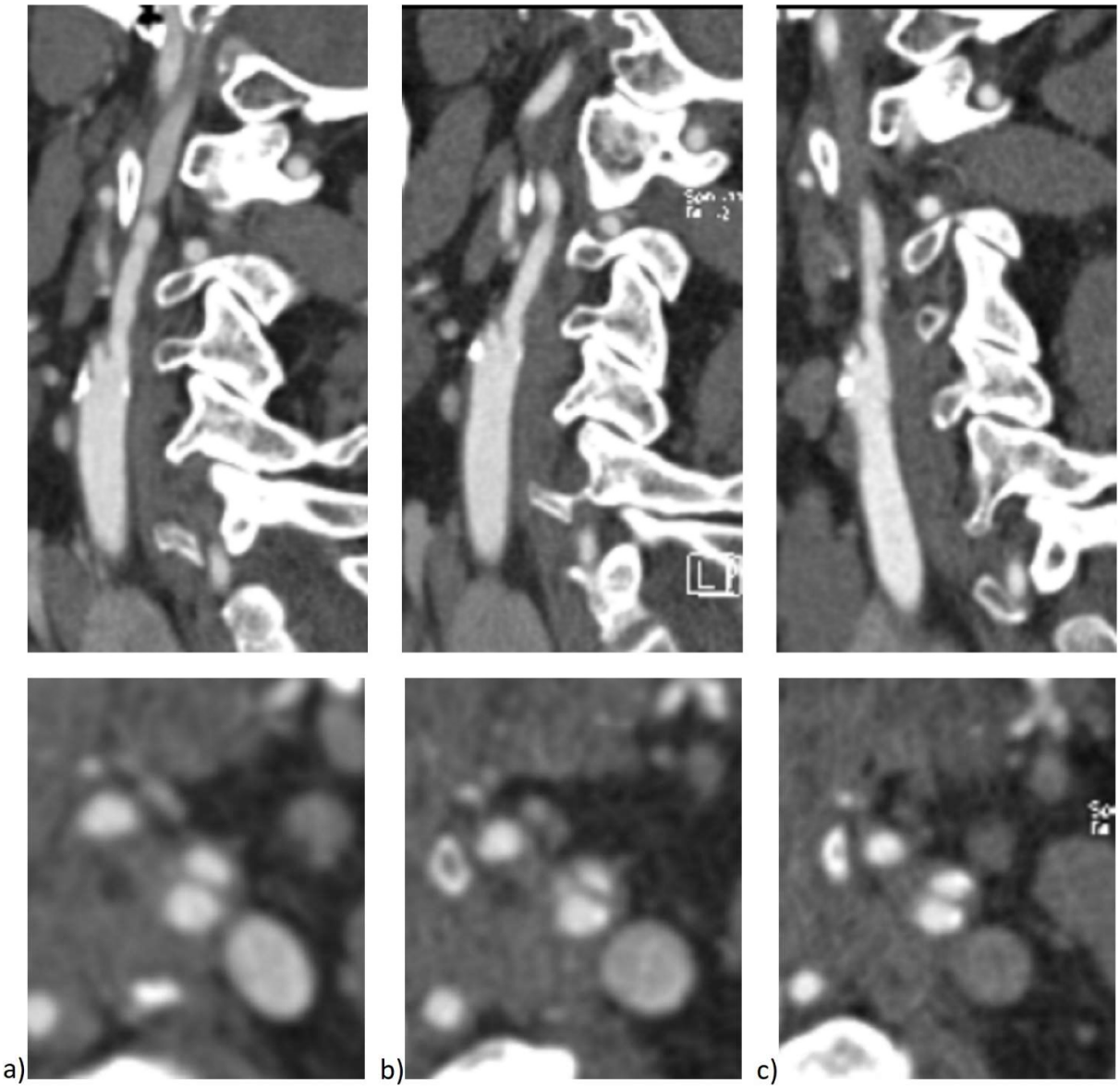

Figure 1. Multiplanar reformat images (on top) and axial images (below) showing a carotid bifurcation of the same patient with plaque ulceration (arrows) in the proximal internal carotid artery. The time delay between the MDCTA scans was 11 months (A → B) and 13 months (B → C) respectively. No change in appearance of plaque morphology is found.

A second ulceration evolved in one ulcerated plaque (over 21 months), whereas a new ulceration developed in two non-ulcerated plaques (over 29 and 40 months). Four ulcerated plaques regressed (over 3, 9, 14 and 44 months), of which an example is shown in figure 2.

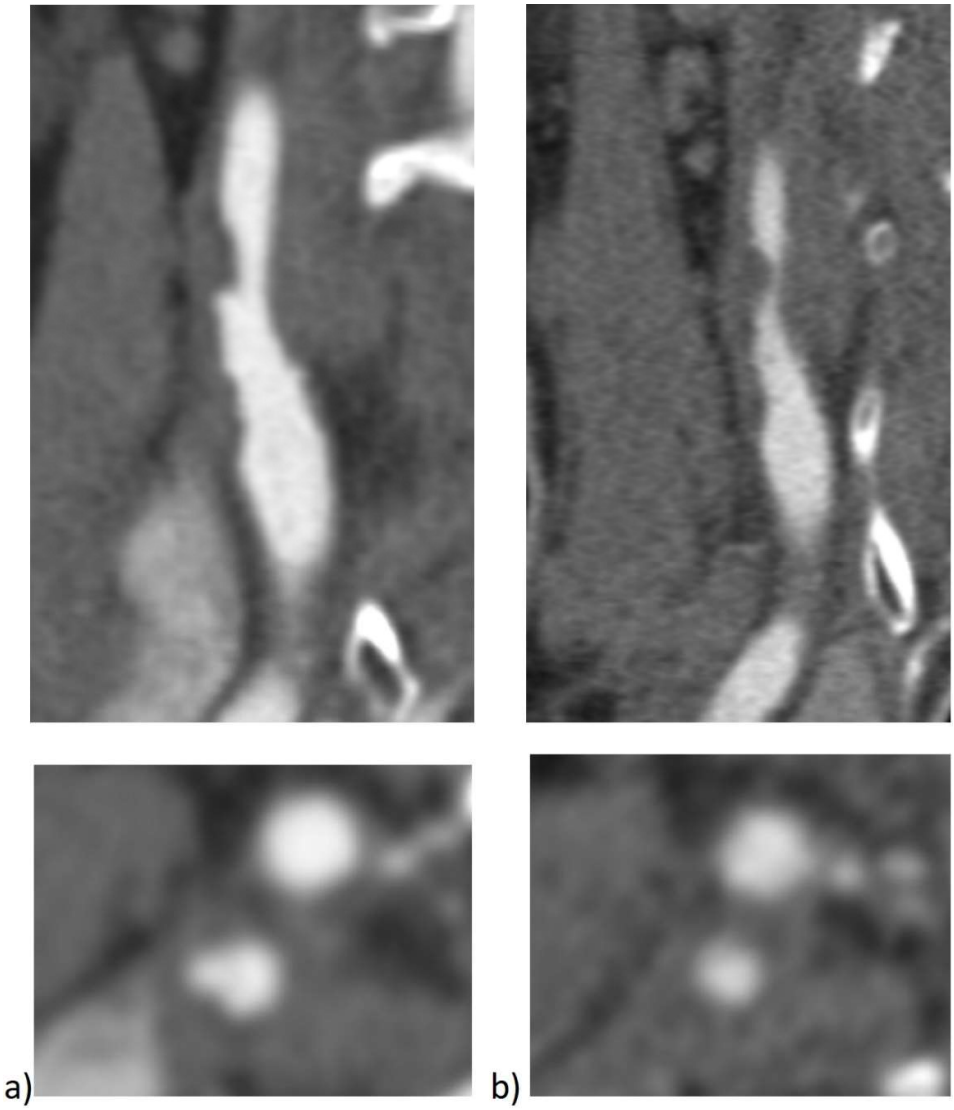

Figure 2. Multiplanar reformat images (on top) and axial images (below) of a carotid bifurcation with a time delay between the MDCTA scans of 9 months. The plaque ulceration (arrows) disappeared over time, leaving a smooth plaque surface.

We did not find any associations between cardiovascular risk factors and baseline plaque morphology and between cardiovascular risk factors and temporal change in plaque morphology. There was no relation between changes in plaque morphology and the occurrence of TIA or ischemic stroke at baseline or follow-up (Table 4).

Table 4. Relation between changes in plaque morphology and symptomatology of the carotid arteries. Shown are the number of carotid arteries presenting with a particular plaque morphology on baseline and on follow-up MDCTA and the number of these arteries that became symptomatic or asymptomatic (AS = asymptomatic, S = symptomatic).

Baseline	**Follow-up**	**N**	**AS → S**	**AS → AS**	**S → AS**	**S → S**
no plaque	no plaque	24	4	11	4	5
smooth	smooth	81	14	37	15	15
irregular	irregular	19	5	7	2	5
1 ulceration	1 ulceration	8	1	4	3	0
2 ulcerations	2 ulcerations	1	0	1	0	0
3 ulcerations	3 ulcerations	1	1	0	0	0
occlusion	occlusion	3	0	1	0	2
	Total unchanged	137	25	61	24	27
no plaque	smooth	4	1	2	1	0
smooth	irregular	4	1	0	3	0
smooth	1 ulceration	1	1	0	0	0
irregular	occlusion	1	0	0	0	1
irregular	1 ulceration	1	1	0	0	0
1 ulceration	2 ulcerations	1	0	1	0	0
	Total progression	12	4	3	4	1
1 ulceration	irregular	3	2	1	0	0
2 ulcerations	1 ulceration	1	1	0	0	0
irregular	smooth	2	0	1	0	1
	Total regression	6	3	2	0	1
	Total	155	32	66	28	29

Data are number.

Discussion

This is the first MDCTA study that longitudinally evaluates the natural evolution of carotid plaque surface morphology. Our results show that plaque surface morphology remains largely unchanged and that regression and progression occur in just a minority of plaques after a time period of 21 ± 13 months. Most importantly, plaque ulcerations do not disappear; 10 out of 15 ulcerated plaques had a similar appearance after 20 ± 15 months. Mean plaque density increased over time, while the number of calcifications did not change significantly. The increased density can be explained by the increase in volume and density of the calcifications.

Carotid plaque ulceration is associated with fibrous cap rupture, which is an important cause of thrombo-embolic events.[1,3,12] Current imaging modalities allow the visualization of carotid plaque ulceration, which is associated with cap rupture and other features of plaque instability.[1] The site of ulceration probably represents part of the plaque where fibrous cap and part of the necrotic core has disappeared and has most probably embolized.[13] However, our results show that plaque ulceration on MDCTA images does not necessarily suggest that the plaque rupture is recent.

Since a healing process of ruptured coronary plaques has been described in histological studies, our finding of temporarily unchanged carotid plaque ulcerations on serial MDCTA imaging was unexpected.[7,8] In coronary arteries a mechanism of plaque healing has been reported in which layers of collagen, proteoglycan-rich matrix and smooth muscle cells overly the ruptured cap and contribute to increased luminal narrowing.[7,8,13] One case report has described the concept of rupture and healing in a carotid atherosclerotic plaque visualized with magnetic resonance imaging (MRI).[21] We therefore expected that carotid plaque ulcerations might fill and disappear. Our findings may be explained by the differences in vessel size and hemodynamic forces in carotid arteries compared to coronary arteries, or by the possibility that ulcerations reflect the more severely ruptured plaques. It is uncertain which time interval should be regarded as sufficient to demonstrate long term changes in plaque morphology. However, we consider a mean follow-up period of almost two years sufficient to evaluate changes, since healing of ulceration as assessed with MRI has been reported to occur within two months.[21]

Our results are indirectly supported by some observations that also question the concept of healing of carotid plaque ulcerations. Whereas a histological study found plaque ulcerations to be more common in symptomatic carotid arteries than in asymptomatic arteries (36% versus 14%, $p<0.0001$), the prevalence of ulceration in the ipsilateral and contralateral carotid artery in symptomatic patients was the same.[22] Likewise, an MDCTA study reported that the prevalence of complicated plaques (i.e. irregularities and ulcerations) was 25% in symptomatic carotid arteries and 18% in asymptomatic carotid arteries.[16]

Whereas ulcerations seem to correlate with symptomatic arteries, they are also present in asymptomatic arteries. This might be explained either by the fact that not every plaque rupture leads to thrombosis and embolization, or that the embolized particles dissolve or cause clinically silent infarctions. Another explanation of the incidental detection of ulcerations in asymptomatic arteries may be that plaque ulcerations heal very slowly or do not disappear at all. The findings correspond with our own: ulcerations can persist unchanged for a long time in both symptomatic and asymptomatic carotid arteries.

Persisting plaque ulceration may be a potential imaging-based stroke-risk predictor. The presence of plaque ulceration on angiography has been found to be associated with recurrent stroke in patients with a previous ischemic cerebral event.[23] The question is whether persisting ulcer cavities should be regarded merely as a scar after a previous plaque rupture or also as a potential source of thromboembolization. Indeed, some local factors at the level of ulceration have been found to play an important role in the development of new thrombi. Firstly, plaque ulcerations may induce thrombus formation by disturbing the blood flow. In-vitro flow experiments with ultrasound showed that the flow downstream from ulcerated, moderate stenotic, carotid plaques was more disturbed than from non-ulcerated plaques.[21] Similarly, an experimental slipstream visualization technique showed that the introduction of an ulceration into a stenotic carotid bifurcation produced observable flow disturbances.[4] Further, color flow Doppler ultrasound, which uses detection of vortices, is useful in detecting ulcerated plaques.[25] Moreover, local flow disturbance caused by ulcerations is likely to favor thrombo-genesis.[5,6] Secondly, plaque ulcerations may induce thrombus formation by possessing an erosive surface. Whereas histological studies describe plaque healing as the deposition of a collagen matrix superimposing the ruptured cap they have not described re-endothelialization. Future studies should examine whether the surfaces of persistent ulcerations are pro-thrombotic.[7]

The clinical and pathophysiological importance of the distinction between ulcerations and irregularities is unknown. There is no evidence that ulcerated plaques on angiographic criteria are any more likely to lead to thrombus formation than irregular plaques. Rothwell *et al.* found that plaque-surface irregularities were highly predictive of ipsilateral ischemic stroke and significantly associated with macroscopic surface ulceration and thrombus formation.[26] Our results show that 19 out of 23 irregular plaques on the baseline MDCTA remained unchanged on follow-up MDCTA. Our considerations with regard to the consequences of persisting ulcerations might also apply to plaque irregularities.

The strength of this serial imaging study is that it presents a way to non-invasively study the development of atherosclerotic plaques in human beings. Serial MDCTA provides additional information that is otherwise difficult to achieve by enabling the investigation of the atherosclerotic plaque in earlier stages, at various time points in the same patient, and in patients in whom no histological material is available. MRI is potentially suitable for serially studying carotid plaque rupture in more detail. Although the status of the fibrous cap has been studied with MDCTA, no validation with histology is available.[27] MRI can distinguish intact, thick fibrous caps from intact thin and disrupted caps in human atherosclerotic carotid arteries in vivo.[28] By using MRI, Underhill *et al.* evaluated the predictive value of plaque characteristics for new plaque surface disruption.[29] Thin or ruptured fibrous caps have been associated with subsequent symptoms during follow-up.[30]

Our study has some limitations. First, the relatively small study population and the low overall prevalence of ulcerations meant that we found a small number of ulcerations. Nevertheless, we found a clear trend of mainly unchanged ulcerated plaque morphology. The second limitation was the study design and our selection of patients with follow-up scans that were performed for clinical reasons. These provided a relatively small and heterogeneous study population that was unsuitable for evaluating the correlation between changes in plaque morphology and symptomatology. Temporal changes in plaque ulceration should thus be correlated with recurrent thrombo-embolic events by including a larger number of patients in a prospective, long term follow-up study. The small selected study population may also underlie the absence of an association between classical cardiovascular risk factors and plaque morphology. Further, these limitations impeded the structural co-evaluation of other important plaque characteristics. The third limitation is that we evaluated temporal changes at the level of the carotid artery. Since atherosclerosis is a systemic disease and atherosclerotic plaques are thought to be liable to systemic influences, we might have expected progression or regression of plaque morphology to be clustered in particular patients. However, we did not find such clustering.

Summary

In conclusion, by demonstrating that ulcer cavities usually persist for a long time, the results of this serial MDCTA study contribute to the knowledge of the evolution of ulcerated plaques. Our findings suggest that the detection of plaque ulceration on MDCTA images may not have a direct diagnostic value as it may not represent a recent plaque rupture. However, persisting carotid ulcerations may remain a potential source of embolism. Further studies should reveal whether persisting plaque ulcerations constitute an important source of recurrent thrombo-embolism and whether they may aid future stroke-risk prediction and clinical decision-making in individual patients.

References

1 Lovett JK, Gallagher PJ, Hands LJ, Walton J, Rothwell PM: Histological correlates of carotid plaque surface morphology on lumen contrast imaging. Circulation 2004;110:2190-2197.

2 Virmani R, Kolodgie FD, Burke AP, Farb A, Schwartz SM: Lessons from sudden coronary death: A comprehensive morphological classification scheme for atherosclerotic lesions. Arterioscler Thromb Vasc Biol 2000;20:1262-1275.

3 Naghavi M, Libby P, Falk E, Casscells SW, Litovsky S, Rumberger J, Badimon JJ, Stefanadis C, Moreno P, Pasterkamp G, Fayad Z, Stone PH, Waxman S, Raggi P, Madjid M, Zarrabi A, Burke A, Yuan C, Fitzgerald PJ, Siscovick DS, de Korte CL, Aikawa M, Juhani Airaksinen KE, Assmann G, Becker CR, Chesebro JH, Farb A, Galis ZS, Jackson C, Jang IK, Koenig W, Lodder RA, March K, Demirovic J, Navab M, Priori SG, Rekhter MD, Bahr R, Grundy SM, Mehran R, Colombo A, Boerwinkle E, Ballantyne C, Insull W, Jr., Schwartz RS, Vogel R, Serruys PW, Hansson GK, Faxon DP, Kaul S, Drexler H, Greenland P, Muller JE, Virmani R, Ridker PM, Zipes DP, Shah PK, Willerson JT: From vulnerable plaque to vulnerable patient: A call for new definitions and risk assessment strategies: Part I. Circulation 2003;108:1664-1672.

4 Imbesi SG, Kerber CW: Why do ulcerated atherosclerotic carotid artery plaques embolize? A flow dynamics study. AJNR Am J Neuroradiol 1998;19:761-766.

5 Sitzer M, Muller W, Siebler M, Hort W, Kniemeyer HW, Jancke L, Steinmetz H: Plaque ulceration and lumen thrombus are the main sources of cerebral microemboli in high-grade internal carotid artery stenosis. Stroke 1995;26:1231-1233.

6 Stein PD, Sabbah HN: Measured turbulence and its effect on thrombus formation. Circ Res 1974;35:608-614.

7 Burke AP, Kolodgie FD, Farb A, Weber DK, Malcom GT, Smialek J, Virmani R: Healed plaque ruptures and sudden coronary death: Evidence that subclinical rupture has a role in plaque progression. Circulation 2001;103:934-940.

8 Mann J, Davies MJ: Mechanisms of progression in native coronary artery disease: Role of healed plaque disruption. Heart 1999;82:265-268.

9 Finn AV, Nakano M, Narula J, Kolodgie FD, Virmani R: Concept of vulnerable/unstable plaque. Arterioscler Thromb Vasc Biol;30:1282-1292.

10 Kolodgie FD, Virmani R, Burke AP, Farb A, Weber DK, Kutys R, Finn AV, Gold HK: Pathologic assessment of the vulnerable human coronary plaque. Heart 2004;90:1385-1391.

11 Peeters W, Hellings WE, de Kleijn DP, de Vries JP, Moll FL, Vink A, Pasterkamp G: Carotid atherosclerotic plaques stabilize after stroke: Insights into the natural process of atherosclerotic plaque stabilization. Arterioscler Thromb Vasc Biol 2009;29:128-133.

12 Redgrave JN, Lovett JK, Gallagher PJ, Rothwell PM: Histological assessment of 526 symptomatic carotid plaques in relation to the nature and timing of ischemic symptoms: The Oxford Plaque Study. Circulation 2006;113:2320-2328.

13 Virmani R, Finn AV, Kolodgie FD: Carotid plaque stabilization and progression after stroke or TIA. Arterioscler Thromb Vasc Biol 2009;29:3-6.

14 Randoux B, Marro B, Koskas F, Duyme M, Sahel M, Zouaoui A, Marsault C: Carotid artery stenosis: Prospective comparison of CT, three-dimensional gadolinium-enhanced MR, and conventional angiography. Radiology 2001;220:179-185.

15 Saba L, Caddeo G, Sanfilippo R, Montisci R, Mallarini G: CT and ultrasound in the study of ulcerated carotid plaque compared with surgical results: Potentialities and advantages of multidetector row CT angiography. AJNR Am J Neuroradiol 2007;28:1061-1066.

16 de Weert TT, Cretier S, Groen HC, Homburg P, Cakir H, Wentzel JJ, Dippel DW, van der Lugt A: Atherosclerotic plaque surface morphology in the carotid bifurcation assessed with multidetector computed tomography angiography. Stroke 2009;40:1334-1340

17 de Monye C, Cademartiri F, de Weert TT, Siepman DA, Dippel DW, van der Lugt A: Sixteen-detector row CT angiography of carotid arteries: Comparison of different volumes of contrast material with and without a bolus chaser. Radiology 2005;237:555-562.

18 de Monye C, de Weert TT, Zaalberg W, Cademartiri F, Siepman DA, Dippel DW, van der Lugt A: Optimization of CT angiography of the carotid artery with a 16-MDCT scanner: Craniocaudal scan direction reduces contrast material-related perivenous artifacts. AJR Am J Roentgenol 2006;186:1737-1745.

19 Saba L, Sanfilippo R, Montisci R, Mallarini G: Agreement between multidetector-row CT angiography and ultrasound echo-color doppler in the evaluation of carotid artery stenosis. Cerebrovasc Dis 2008;26:525-532.

20 Schroeder S, Kopp AF, Baumbach A, Meisner C, Kuettner A, Georg C, Ohnesorge B, Herdeg C, Claussen CD, Karsch KR: Noninvasive detection and evaluation of atherosclerotic coronary plaques with multislice computed tomography. J Am Coll Cardiol 2001;37:1430-1435.

21 Qiao Y, Farber A, Semaan E, Hamilton JA: Images in cardiovascular medicine. Healing of an asymptomatic carotid plaque ulceration. Circulation 2008;118:e147-148.

22 Fisher M, Paganini-Hill A, Martin A, Cosgrove M, Toole JF, Barnett HJ, Norris J: Carotid plaque pathology: Thrombosis, ulceration, and stroke pathogenesis. Stroke 2005;36:253-257.

23 Eliasziw M, Streifler JY, Fox AJ, Hachinski VC, Ferguson GG, Barnett HJ: Significance of plaque ulceration in symptomatic patients with high-grade carotid stenosis. North American Symptomatic Carotid Endarterectomy Trial. Stroke 1994;25:304-308.

24 Wong EY, Nikolov HN, Thorne ML, Poepping TL, Rankin RN, Holdsworth DW: Clinical doppler ultrasound for the assessment of plaque ulceration in the stenosed carotid bifurcation by detection of distal turbulence intensity: A matched model study. Eur Radiol. 2009;19:2739-2749

25 Furst H, Hartl WH, Jansen I, Liepsch D, Lauterjung L, Schildberg FW: Color-flow doppler sonography in the identification of ulcerative plaques in patients with high-grade carotid artery stenosis. AJNR Am J Neuroradiol 1992;13:1581-1587.

26 Rothwell PM, Gibson R, Warlow CP: Interrelation between plaque surface morphology and degree of stenosis on carotid angiograms and the risk of ischemic stroke in patients with symptomatic carotid stenosis. On behalf of the European Carotid Surgery Trialists' Collaborative Group. Stroke 2000;31:615-621.

27 Saba L, Mallarini G: Fissured fibrous cap of vulnerable carotid plaques and symptomaticity: Are they correlated? Preliminary results by using multi-detector-row CT angiography. Cerebrovasc Dis 2009;27:322-327.

28 Hatsukami TS, Ross R, Polissar NL, Yuan C: Visualization of fibrous cap thickness and rupture in human atherosclerotic carotid plaque in vivo with high-resolution magnetic resonance imaging. Circulation 2000;102:959-964.

29 Underhill HR, Yuan C, Yarnykh VL, Chu B, Oikawa M, Dong L, Polissar NL, Garden GA, Cramer SC, Hatsukami TS: Predictors of surface disruption with MR imaging in asymptomatic carotid artery stenosis. AJNR Am J Neuroradiol;31:487-493.

30 Takaya N, Yuan C, Chu B, Saam T, Underhill H, Cai J, Tran N, Polissar NL, Isaac C, Ferguson MS, Garden GA, Cramer SC, Maravilla KR, Hashimoto B, Hatsukami TS: Association between carotid plaque characteristics and subsequent ischemic cerebrovascular events: A prospective assessment with MRI--initial results. Stroke 2006;37:818-823.

Chapter 3

Intracranial arterial stenotic lesions

Chapter 3.1

Prevalence and calcification of intracranial arterial stenotic lesions as assessed with multidetector computed tomography angiography

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Abstract

Background and Purpose: Intracranial arterial stenosis (IAS) in patients with recent ischemic stroke is associated with a high risk of recurrent stroke. More insight into the pathophysiology of IAS could help identify high risk patients requiring more aggressive secondary prevention. We evaluated the prevalence, distribution, calcification and the risk factors predisposing IAS in a European stroke population.

Methods: Consecutive patients with a transient ischemic attack or ischemic stroke (n=786) were evaluated for the presence and distribution of IAS (≥30% luminal narrowing) by CT angiography. IAS were categorized as symptomatic or asymptomatic, and the presence of calcification was assessed. The association of traditional cerebrovascular risk factors and the erythrocyte sedimentation rate (ESR) with IAS was analyzed.

Results: In 178/786 patients (23%), 288 IAS were observed. Most stenoses (n=194/288, 67%) were located in the posterior circulation arteries. In 59/786 patients (8%) IAS were considered symptomatic. IAS in the basilar artery and arteries beyond the circle of Willis were mainly non-calcified. In addition to age, gender and several traditional cerebrovascular risk factors, ESR was independently associated with the presence of IAS (OR 1.20; 95%CI 1.06-1.36), and with the presence of non-calcified IAS in particular (OR 1.20; 95%CI 1.05-1.37).

Conclusions: IAS was observed in a noteworthy number of European stroke patients. Particularly, the majority of IAS was observed in the posterior circulation, possibly conferring worse prognosis. IAS in distal arteries were mainly non-calcified. Association of non-calcified IAS and ESR may indicate a prominent role for inflammatory factors in intracranial atherosclerotic disease.

Introduction

Intracranial arterial stenosis (IAS) in patients with transient ischemic attack (TIA) or ischemic stroke is associated with a high risk of recurrent stroke.[1] Angioplasty and stenting are feasible procedures for revascularization of vessels affected by IAS. However, insufficient evidence is available to recommend these treatments for the prevention of recurrent stroke in patients with IAS in clinical practice.[2] More insight into the prevalence, distribution and calcification of IAS lesions could help identify high risk patients requiring more aggressive secondary prevention.

The prevalence of IAS seems to vary among ethnic groups.[3] Nevertheless, only limited studies have assessed the prevalence and associated risk factors for IAS in European stroke patients.[4-6] Moreover, the comparative value of studies available in European patients is limited by the use of multiple imaging modalities.

Also, little is known about the composition of IAS lesions, which may point to a specific pathophysiological process.[7] The pathophysiology of intracranial atherosclerosis is suggested to differ from that of the extracranial arteries.[8] A prominent role for inflammatory factors is indicated in the atherosclerosis of the intracranial arteries.[9] Consequently, the pro-atherogenic influence of inflammatory reactions could be manifested as an association between the erythrocyte sedimentation rate (ESR) and IAS, as previously observed in a single study.[10] In addition, an accelerated intracranial atherogenesis could be reflected in differences in plaque calcification.

Multidetector computed tomography angiography (MDCTA) is reliable for the evaluation of both extracranial[11] as well as intracranial atherosclerotic disease.[12] Moreover, the technique is available for detection of IAS in most European hospitals.[13] As compared to digital subtraction angiography (DSA), MDCTA has been demonstrated to be effective in the detection of IAS with a sensitivity of 97% and a specificity of 99%.[12] In addition, MDCTA allows differentiation between calcified and non-calcified atherosclerotic plaques.[14]

In the current study we evaluated a large cohort of patients with TIA or ischemic stroke for the prevalence, distribution and the calcification of IAS lesions using MDCTA. Furthermore, the association of IAS with the traditional risk factors for cerebrovascular disease as well as with ESR was investigated.

Materials and Methods

Study Population

From a prospective registry of 911 consenting patients with amaurosis fugax, TIA or ischemic stroke (Rankin <4 at discharge) we selected all patients (n=795) with a recent ischemic stroke or TIA, but excluded patients with amaurosis fugax. Patients were enrolled from a specialized TIA/stroke outpatient clinic or the stroke unit. All patients were interviewed and examined by a vascular neurologist, and underwent electrocardiography and laboratory analysis. Medical history and cerebrovascular risk factors were recorded. On admission, patients underwent MDCT of the brain and MDCTA of the carotid and intracranial arteries in a single session. Three patients with an MDCTA of insufficient quality for reliable evaluation, and 6 patients with intracranial arteries outside the scan reconstruction area were excluded. Consequently, analyses were performed in the remaining 786 patients.

Risk Factors

Ethnicity of patients was determined through an algorithm, based on place of birth of the patients and their parents, as well as on name and surname.[15] For the purpose of this study, we distinguished between Asian and non-Asian ethnicities. History of ischemic heart disease was defined as previous chronic heart failure, angina pectoris, myocardial infarction or coronary artery bypass grafting. Hypercholesterolemia was defined as fasting cholesterol >5.0 mmol/L or treatment with cholesterol-lowering medication. Hypertension was defined as a systolic blood pressure >140 mmHg and/or a diastolic blood pressure >90 mmHg, during two episodes of at least 15 minutes of continuous noninvasive blood pressure measurement or treatment with antihypertensive medication. Diabetes was defined as fasting serum a glucose level >7.9 mmol/L, HbA1c >6.5%, or use of antidiabetic medication. Laboratory analysis included total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides and glucose, as well as ESR.

MDCT and MDCTA Data Acquisition and Analysis

MDCTA was performed with a 16-slice MDCT scanner (Siemens, Sensation 16, Erlangen, Germany) or a 64-slice MDCT scanner (Siemens, Sensation 64, Erlangen, Germany) with a standardized protocol.[16,17]

Intracranial arteries were evaluated on a stand-alone workstation (Leonardo – Siemens Medical Solutions, Forchheim, Germany) with multiplanar reformatting and maximum intensity projection images of 4 mm thickness (Figure 1). Since symptomatic ulceration with superimposed thrombus of intracranial atherosclerotic plaques is also present in low grade stenosis, we defined IAS as ≥30% luminal narrowing.[18] The degree of stenosis was measured according to the WASID criteria on oblique multiplanar reformatting images perpendicular to the central lumen line.[19] Stenoses were classified as 30-49%, 50-69% and 70-99%. The internal carotid arteries (ICA), the anterior cerebral arteries (ACA), the medial cerebral arteries (MCA), the vertebral arteries (VA), the basilar artery (BA), and the posterior cerebral arteries (PCA) were analyzed.

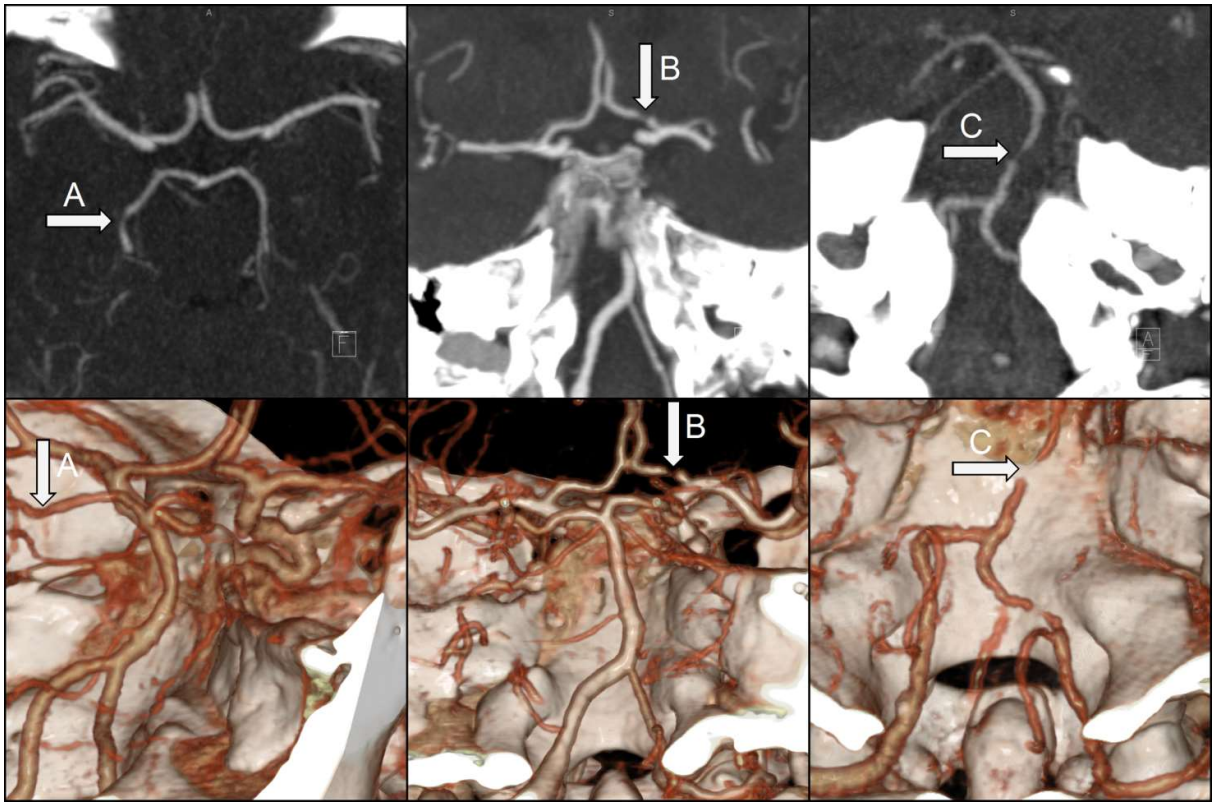

Figure 1. Assessment of IAS using MDCTA. Upper row: maximum intensity projection images of 4 mm thickness demonstrating an IAS of 30-49% in the right posterior cerebral artery (A), an IAS of 50-69% in the left anterior cerebral artery (B), and an IAS of 70-99% in the basilar artery (C). Lower row: volume rendering images demonstrating the same IAS lesions in 3D anatomy.

Blinded to clinical information, two trained observers (PJH and GJJP) independently analyzed the presence of IAS according the WASID method in the first 50 patients. After 4 weeks, the first observer analyzed the same 50 patients. Good interobserver agreement (κ=0.79; 95%CI 0.55-1.02) and intraobserver agreement (κ=0.79; 95%CI 0.60-0.99) was observed.

A calcified IAS lesion was defined as any intracranial stenosis (≥30%) containing plaque calcifications (>130 Hounsfield units). Symptomatic IAS was defined as any intracranial stenosis (≥30%) in an artery supplying the involved region of the brain, taking into account the configuration of the circle of Willis.

Statistical Analysis

Differences between variables were tested with the chi-square test, Fisher's exact test, Mann-Whitney test or a non-parametric rank test where appropriate. The association of traditional cerebrovascular risk factors and ESR with the presence of IAS was determined using regression analysis. The risk factors significantly associated with IAS ($P<0.05$) in the univariable regression analysis, which were not directly interrelated, were included in a multivariable regression model. Associations were expressed as odds ratio (OR) with 95% confidence interval (CI). The analysis was repeated for the presence of non-calcified IAS lesions, calcified IAS lesions and symptomatic IAS in patients. For the purpose of this analysis patients with solely non-calcified IAS lesions were considered as ‘patients with non-calcified IAS lesions’ whereas patients with any calcified IAS lesions were considered as ‘patients with calcified IAS lesions’. Statistical analyses were performed using SPSS software (version 15.0, Inc., Chicago, Illinois, USA). $P<0.05$ was considered statistically significant.

Results

Prevalence, Distribution and Calcification of IAS

Most patients were male (n=513; 56%) and the mean age was 62±14 years. Baseline characteristics of patients with and without IAS are illustrated in Table 1. The presence and severity of IAS in different arteries are shown in Table 2. IAS of ≥30% was observed in 178 patients (23%). IAS of ≥50% was present in 77 patients (10%), and IAS of ≥70% in 21 patients (3%). In total 288 IAS (≥30%) were observed.

Table 1. Baseline characteristics of the study population.

	No IAS (n=608; 77%)	**IAS (n=178; 23%)**	***P*-value**
Age	60±14	68±12	<0.001
Male sex	332 (55%)	110 (62%)	0.09
Asian ethnicity	20 (3%)	16 (9%)	0.001
Index event			
TIA	238 (39%)	47 (26%)	0.002
Ischemic stroke	370 (61%)	131 (74%)	
Time since onset (days)	5 (1-14)	5 (0-18)	0.40
Cerebrovascular history			
Previous ischemic stroke	77 (13%)	32 (18%)	0.07
Previous TIA> 6 months	85 (14%)	30 (17%)	0.34
History of ischemic heart disease	101 (17%)	33 (19%)	0.55
Cerebrovascular risk factors			
Hypercholesterolemia	440 (72%)	135 (76%)	0.36
Hypertension	389 (64%)	146 (82%)	<0.001
Diabetes mellitus	92 (15%)	53 (30%)	<0.001
Atrial fibrillation	39 (6%)	14 (8%)	0.50
Smoking	230 (38%)	56 (31%)	0.12
Laboratory results			
Cholesterol (mmol/l)	5.2±1.1	5.3±1.2	0.38
HDL cholesterol (mmol/l)	1.41±0.51	1.40±0.74	0.51
LDL cholesterol (mmol/l)	3.29±1.04	3.47±1.19	0.15
Triglycerides (mmol/l)	1.72±2.54	1.71±0.96	0.16
Glucose (mmol/l)	4.9±1.7	5.7±2.4	<0.001
ESR (mm/hr)	13±12	16±15	0.001
Extracranial carotid artery stenosis ≥50%	50 (8%)	38 (21%)	<0.001

Data are means±SD, median (interquartile range) or number of patients (%).

In 184/288 IAS (64%) the degree of stenosis ranged 30-49%, in 83/288 IAS (29%) 50-69%, and in the remaining 21/288 IAS (7%) 70-99%. Occlusions were present in 52 arteries. Interestingly, the majority of IAS (n=194/288; 67%) was located in the posterior circulation. Stenoses of ≥70% occurred mainly in the posterior circulation of the brain. Exclusively non-calcified IAS lesions were observed in 126 patients (16%). In total 221/288 IAS lesions (77%) were non-calcified. IAS lesions in the ACA, MCA and BA were exclusively non-calcified. Calcified IAS lesions were predominantly present in the proximal arteries (ICA and VA; n=64), whereas only 3 calcified IAS lesions were identified in the PCA. In 59 patients (8%) a total of 63 symptomatic IAS ≥30% was observed. Symptomatic IAS of ≥50% was present in 18 of the patients (3%). Overall, symptomatic IAS comprised of 39 stenoses in the anterior circulation and 24 stenoses in the posterior circulation.

Table 2. Distribution and severity of IAS (n=288)

Artery	Number of IAS	Degree of stenosis			Occlusions	Calcified IAS lesions	Symptomatic IAS
		30-49%	50-69%	70-99%			
Anterior (n=94; 33%)							
ICA	31 (11%)	24 (8%)	7 (2%)	0 (0%)	14	25 (9%)	15 (5%)
ACA	17 (6%)	11 (4%)	6 (2%)	0 (0%)	0	0 (0%)	4 (1%)
MCA	46 (16%)	30 (10%)	14 (5%)	2 (1%)	20	0 (0%)	20 (7%)
Posterior (n=194; 67%)							
VA	88 (31%)	57 (20%)	24 (8%)	7 (2%)	4	39 (14%)	8 (3%)
BA	30 (10%)	16 (6%)	8 (3%)	6 (2%)	5	0 (0%)	8 (3%)
PCA	76 (26%)	46 (16%)	24 (8%)	6 (2%)	9	3 (1%)	8 (3%)
Total	288 (100%)	184 (64%)	83 (29%)	21 (7%)		67 (23%)	63 (22%)

Data are number of IAS (% of all IAS).

Risk Factors associated with IAS

Multivariable analysis revealed an independent association between IAS and age, male sex, Asian ethnicity, hypertension, diabetes mellitus, LDL cholesterol and ESR (Table 3). Risk factors independently associated with non-calcified IAS lesions and calcified IAS lesions are provided in Table 4. Age, male sex, hypertension, diabetes mellitus, LDL cholesterol and ESR remained independently associated with non-calcified IAS lesions, whereas only age was independently associated with calcified IAS lesions. The median time since symptom onset and clinical and laboratory analysis was 5 days (1-14).

Table 3. Uni- and multivariable analysis of risk factors associated with IAS.

	OR (95% CI)	**OR (95% CI)**
Age (per 10 years)*	1.65 (1.43-1.90)	1.65 (1.40-1.94)
Male sex	1.34 (0.96-1.89)	1.55 (1.05-2.29)
Asian ethnicity	2.90 (1.47-5.73)	2.68 (1.20-5.98)
Index event		
Ischemic stroke	1.79 (1.24-2.60)	-
Cerebrovascular history		
Previous ischemic stroke	1.51 (0.96-2.37)	-
Previous TIA> 6months	1.25 (0.79-1.96)	-
History of ischemic Heart Disease	1.14 (0.74-1.76)	-
Cerebrovascular risk factors		
Hypercholesterolemia	1.20 (0.81-1.76)	-
Hypertension	2.57 (1.69-3.90)	1.87 (1.16-3.00)
Diabetes mellitus	2.38 (1.61-3.51)	2.08 (1.34-3.22)
Atrial fibrillation	1.25 (0.66-2.35)	-
Smoking	0.75 (0.53-1.08)	-
Laboratory results		
Cholesterol (mmol/l)*	1.13 (0.97-1.30)	-
HDL cholesterol (mmol/l)*	0.99 (0.74-1.34)	-
LDL cholesterol (mmol/l)*	1.17 (0.99-1.36)	1.33 (1.12-1.59)
Triglycerides (mmol/l)*	1.00 (0.93-1.08)	-
Glucose (mmol/l)*	1.19 (1.10-1.29)	-
ESR (per 10mm/h)*	1.22 (1.09-1.37)	1.20 (1.06-1.36)
Extracranial carotid artery stenosis ≥50%	3.03 (1.91-4.80)	-

**Ratio-per-unit increase. CI = confidence interval; OR = odds ratio.*

Table 4. Multivariable analysis of risk factors associated with exclusively non-calcified IAS lesions, calcified IAS lesions and symptomatic IAS.

	OR (95% CI) Non-calcified IAS lesions (n=126; 16%)	**OR (95% CI) Calcified IAS lesions (n=52; 7%)**	**OR (95% CI) Symptomatic IAS (n=59; 8%)**
Age (per 10 years)*	1.37 (1.15-1.63)	2.09 (1.56-2.82)	1.37 (1.07-1.75)
Male sex	1.56 (1.01-2.40)	1.29 (0.68-2.45)	1.60 (0.87-2.92)
Asian ethnicity	2.02 (0.88-4.62)	2.52 (0.76-8.36)	3.69 (1.49-9.14)
Hypertension	1.74 (1.02-2.96)	1.84 (0.79-4.31)	3.04 (1.23-7.49)
Diabetes mellitus	2.13 (1.32-3.42)	1.37 (0.67-2.81)	1.52 (0.80-2.86)
LDL cholesterol (mmol/l)*	1.29 (1.07-1.57)	1.25 (0.94-1.67)	1.08 (0.83-1.41)
ESR (per 10mm/h)*	1.20 (1.05-1.37)	1.09 (0.88-1.35)	1.23 (1.04-1.46)

**Ratio-per-unit increase. CI = confidence interval; OR = odds ratio.*

The association of ESR with IAS remained present after adjustment for time between onset of symptoms (OR 1.22; 95%CI 1.08-1.36). Interestingly, ESR increased with degree of intracranial stenosis (Figure 2). Age, Asian ethnicity, hypertension and ESR were independently associated with symptomatic IAS.

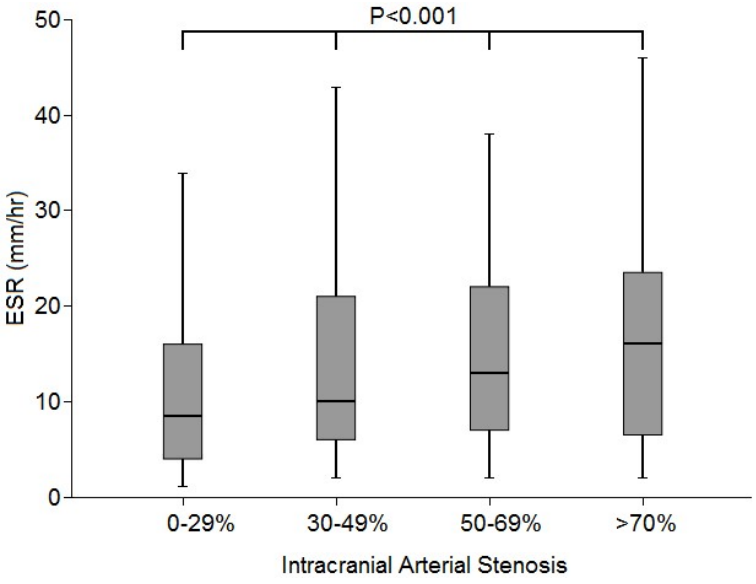

Figure 2. Boxplot illustrating higher median ESR rates with increase of severity of stenosis

Discussion

In the current study, IAS of ≥30% was observed in 178 patients (23%) with a recent ischemic stroke or TIA. The majority of all IAS was located in the posterior circulation arteries. Symptomatic IAS of ≥30% was observed in 59 patients (8%). Calcified IAS lesions were predominantly observed in the proximal intracranial arteries (ICA and VA), whereas IAS lesions in the distal intracranial arteries (BA, ACA, MCA and PCA) were mainly non-calcified. A number of traditional risk factors including age, male sex, Asian ethnicity, hypertension, diabetes mellitus, and LDL cholesterol were independently associated with the presence of IAS in multivariable analysis. An independent association was also observed between ESR and IAS. Equivalent traditional risk factors and ESR were also associated with non-calcified IAS lesions. However, age was the only risk factor associated with calcified IAS lesions.

Prevalence and Distribution of IAS

The comparability of studies on the prevalence of IAS in stroke patients is limited due to the variation in the studied populations, definition of IAS, and used imaging modalities. Thus far, large studies on the prevalence, distribution and risk factors predisposing IAS have been mainly performed in Asian stroke populations.[20-22] Relatively high prevalences of 26 to 54% were observed in studies of different Asian populations of stroke patients. In contrast, limited studies have evaluated the prevalence of IAS in Europe.[4-6] In a multicenter European study by Weimar *et al*., using various imaging modalities, symptomatic IAS of ≥50% was observed in 6.5% of the evaluated stroke patients.[6] In contrast, the results of the present study reveal a lower prevalence of symptomatic IAS of ≥50% in European stroke patients (3%). The difference in prevalence can be in part explained by the inclusion of a higher proportion of patients with a TIA and the exclusion of patients with severe ischemic stroke (Rankin <4 at discharge) in the current study.

Observed prevalence and distribution of IAS are also influenced by the applied imaging modality.[23] In general, transcranial doppler (TCD) is more operator dependent and obtained results vary according to operator skills. Moreover, TCD is suggested to be less sensitive than CT angiography for the detection of IAS in the posterior circulation.[23,24] However, in Asian patients with TIA and ischemic stroke, the anterior circulation seems to be the predilection site in the distribution of IAS irrespective of the imaging modality.[25-27] Distribution of IAS reported in European stroke patients has been less consistent. Using either DSA or ultrasonography for primary detection, Mazighi *et al*. reported a similar distribution of IAS in the anterior and posterior circulation.[4] In contrast, using Doppler/duplex ultrasonography in 99% of the studied patients, Weimar *et al.* observed a higher prevalence of IAS in the anterior (77%) versus the posterior (23%) circulation.[6]

Using MDCTA in current study, the majority of IAS (67%) was located in the posterior circulation. Indeed, the lower proportion of IAS in the posterior circulation in the previous European studies may be attributable to a detection bias, as investigators have mainly relied on ultrasonography. Of note, detection of IAS in the posterior circulation may be an important prognostic determinant as these lesions have been associated with a high risk of recurrent stroke.[1,28,29]

Composition of Intracranial Atherosclerotic Stenotic Lesions

Thus far, limited imaging studies have evaluated the composition of IAS lesions. CT brain studies have reported a predominant presence of calcification in the proximal arteries, but did not combine the evaluation of IAS and plaque calcification with MDCTA.[30,31] Our findings confirm the presence of calcified IAS lesions in the proximal intracranial arteries. However, a majority of non-calcified IAS lesions was demonstrated in the distal arteries, which would be neglected on CT brain. This implicates that absence of calcification on CT brain does not exclude the presence of IAS in the distal arteries. In line with the results of the current study, a previous postmortem histological analysis of atherosclerotic plaque composition in the MCA has demonstrated calcification in only a minority of the specimens, 31 of 111 (28%).[32]

The low prevalence of calcified IAS lesions on MDCTA in the distal intracranial arteries suggests a different pathophysiology of atherosclerotic disease in the proximal and distal intracranial arteries. The intracranial arteries show significantly greater antioxidant enzyme activities than the extracranial arteries.[8] Indeed, the greater activity of antioxidant enzymes in intracranial arteries may contribute to a greater resistance to atherogenesis. This antiatherogenic activity decreases significantly in older age, coinciding with accelerated atherogenesis.[8] Consequently, with age, intracranial arteries may respond with accelerated atherogenesis as their antioxidant protection decreases more significantly than that of the extracranial arteries. In the current study, the higher prevalence of extracranial stenosis in patients with IAS supports the loss of protective antioxidant capacity in the extracranial arteries at a younger age. In line with this observation, higher plasma C-reactive protein-levels have been previously noted in patients with extracranial stenosis as compared to those with isolated MCA stenosis.[33]

Furthermore, with age, plasma LDL becomes more susceptible to oxidation.[34] The oxidative modification of LDL may therefore play a key role in this atherogenic process through inflammatory reactions.[35,36] The presence of mainly non-calcified IAS lesions in the basilar artery and arteries beyond the circle of Willis in the current study might be a reflection of this accelerated atherogenesis.

Risk Factors Associated with IAS

A number of traditional risk factors for atherosclerotic disease have been previously related with IAS.[3,9,37] In addition, high-sensitivity C-reactive protein, a marker of inflammation is associated with recurrent ischemic events in the territory of the stenotic artery in stroke patients with IAS.[5] Also, ESR was shown to be independently associated of with the presence of IAS in a South Asian stroke population.[10] In the presents study of European patients, IAS lesions were not only associated with the traditional risk factors including hypertension, diabetes and LDL cholesterol, but also with ESR. Importantly, the association of ESR with IAS remained significant even after adjustment for the time since onset of symptoms. Thereby, the contribution of the acute phase reaction as a cause of ESR elevation was made less probable. As a result, an independent association was identified between ESR and LDL cholesterol with the presence of IAS, and more importantly with the presence of non-calcified IAS lesions in patients with a recent TIA or ischemic stroke. These findings may indicate a prominent role for inflammation in intracranial atherogenesis.[35,36]

Study Limitations

The design of the present study is cross-sectional. Indeed, the prognostic value of the presence, distribution and calcification of IAS lesions in patients with ischemic stroke or TIA remains to be determined in follow-up studies. The pathophysiological mechanisms initiating intracranial atherosclerosis were not evaluated. However, the predisposing risk factors and degree of calcification of IAS support the current hypothesis on the delayed development of intracranial atherosclerosis.

In the current study the association of IAS with the ESR was investigated as a marker of inflammatory processes in the atherosclerosis of the intracranial arteries. However, the ESR is only an indirect indicator of inflammatory processes and could be increased due to co-morbidity. We did not exclude patients with co-morbidity associated with ESR elevation to avoid additional bias. Evaluation of additional inflammatory markers such as high-sensitivity C-reactive protein and interleukins could have provided additional data on the role of inflammatory processes in intracranial atherosclerosis. Finally, the ESR was only measured at a single time point and during acute phase in part of the patients.

Conclusion and Implications

It has been suggested that atherosclerosis in the extracranial carotid artery is the primary source of ischemic stroke in Caucasian patients.[38] Indeed, we observed a low prevalence of IAS in the current study population of predominantly Caucasian ethnicity. However, most IAS were observed in the

posterior circulation, a location associated with a high risk of recurrent stroke.[1,28,29] Mainly non-calcified IAS lesions were observed in distal intracranial arteries. A strong association of LDL cholesterol as well as ESR was identified with the presence of IAS, and more importantly with the presence of non-calcified IAS lesions, in patients with a recent TIA or ischemic stroke. Accordingly, in the intracranial atherogenesis a prominent role is indicated for inflammation. Further research on non-invasive analysis of plaque components in IAS lesions could improve understanding of the pathophysiology of intracranial atherosclerosis. The additional evaluation of intraplaque hemorrhage using high-resolution magnetic resonance imaging, which is likely to convey strong prognostic value for recurrent stroke, may be of particular interest.[39]

Addendum

Subsequent to publication of this paper in *Stroke* (x-x-2010) we discovered that 5 patients were wrongly identified as having symptomatic IAS during reanalysis for chapter 3.2. Specifically, 54 instead of 59 patients with symptomatic IAS. Recalculation with the correct number of symptomatic patients did not change the significance of the outcomes. Results of the recalculation are illustrated in the Table 4.

Corrected version of Table 4. Multivariable analysis of risk factors associated with exclusively non-calcified IAS lesions, calcified IAS lesions and symptomatic IAS.

	OR (95% CI) Non-calcified IAS lesions (n=126; 16%)	**OR (95% CI) Calcified IAS lesions (n=52; 7%)**	**OR (95% CI) Symptomatic IAS (n=54; 7%)**
Age (per 10 years)*	1.37 (1.15-1.63)	2.09 (1.56-2.82)	1.38 (1.08-1.78)
Male sex	1.56 (1.01-2.40)	1.29 (0.68-2.45)	1.62 (0.87-3.03)
Asian ethnicity	2.02 (0.88-4.62)	2.52 (0.76-8.36)	3.57 (1.40-9.06)
Hypertension	1.74 (1.02-2.96)	1.84 (0.79-4.31)	2.79 (1.13-6.90)
Diabetes mellitus	2.13 (1.32-3.42)	1.37 (0.67-2.81)	1.21 (0.61-2.39)
LDL cholesterol (mmol/l)*	1.29 (1.07-1.57)	1.25 (0.94-1.67)	1.11 (0.84-1.46)
ESR (per 10mm/h)*	1.20 (1.05-1.37)	1.09 (0.88-1.35)	1.24 (1.04-1.47)

**Ratio-per-unit increase. CI = confidence interval; OR = odds ratio.*

References

1. Kasner SE, Chimowitz MI, Lynn MJ, Howlett-Smith H, Stern BJ, Hertzberg VS, Frankel MR, Levine SR, Chaturvedi S, Benesch CG, Sila CA, Jovin TG, Romano JG, Cloft HJ. Predictors of ischemic stroke in the territory of a symptomatic intracranial arterial stenosis. Circulation. 2006;113:555-563.

2. Cruz-Flores S, Diamond AL. Angioplasty for intracranial artery stenosis. Cochrane Database Syst Rev. 2006;3:CD004133.

3. Sacco RL, Kargman DE, Gu Q, Zamanillo MC. Race-ethnicity and determinants of intracranial atherosclerotic cerebral infarction. The Northern Manhattan Stroke Study. Stroke. 1995;26:14-20.

4. Mazighi M, Tanasescu R, Ducrocq X, Vicaut E, Bracard S, Houdart E, Woimant F. Prospective study of symptomatic atherothrombotic intracranial stenoses: the GESICA study. Neurology. 2006;66:1187-1191.

5. Arenillas JF, Molina CA, Chacón P, Rovira A, Montaner J, Coscojuela P, Sánchez E, Quintana M, Alvarez-Sabín J. High lipoprotein (a), diabetes, and the extent of symptomatic intracranial atherosclerosis. Neurology. 2004;63:27-32.

6. Weimar C, Goertler M, Harms L, Diener HC. Distribution and outcome of symptomatic stenoses and occlusions in patients with acute cerebral ischemia. Arch Neurol. 2006;63:1287-1291.

7. Gorelick PB, Wong KS, Bae HJ, Pandey DK. Large artery intracranial occlusive disease: a large worldwide burden but a relatively neglected frontier. Stroke. 2008;39:2396-2399.

8. D'Armiento FP, Bianchi A, de Nigris F, Capuzzi DM, D'Armiento MR, Crimi G, Abete P, Palinski W, Condorelli M, Napoli C. Age-related effects on atherogenesis and scavenger enzymes of intracranial and extracranial arteries in men without classic risk factors for atherosclerosis. Stroke. 2001;32:2472-2478.

9. Arenillas JF, Alvarez-Sabín J, Molina CA, Chacón P, Montaner J, Rovira A, Ibarra B, Quintana M. C-reactive protein predicts further ischemic events in first-ever transient ischemic attack or stroke patients with intracranial large-artery occlusive disease. Stroke. 2003;34:2463-2468.

10. De Silva DA, Woon FP, Lee MP, Chen CP, Chang HM, Wong MC. South Asian patients with ischemic stroke: intracranial large arteries are the predominant site of disease. Stroke. 2007;38:2592-2594.

11. Randoux B, Marro B, Koskas F, Duyme M, Sahel M, Zouaoui A, Marsault C. Carotid artery stenosis: prospective comparison of CT, three-dimensional gadolinium-enhanced MR, and conventional angiography. Radiology. 2001;220:179-185.

12. Nguyen-Huynh MN, Wintermark M, English J, Lam J, Vittinghoff E, Smith WS, Johnston SC. How accurate is CT angiography in evaluating intracranial atherosclerotic disease? Stroke. 2008;39:1184-1188.

13. Balucani C, Leys D, Ringelstein EB, Kaste M, Hacke W; Executive Committee of the European Stroke Initiative. Detection of intracranial atherosclerosis: which imaging techniques are available in European hospitals? Stroke. 2009;40:726-729.

14. Cordeiro MA, Lima JA. Atherosclerotic plaque characterization by multidetector row computed tomography angiography. J Am Coll Cardiol. 2006;47;40-47.

15. Bouwhuis CB, Moll HA. Determination of ethnicity in children in The Netherlands: two methods compared. Eur J Epidemiol. 2003;18:385-388.

16. de Monyé C, Cademartiri F, de Weert TT, Siepman DA, Dippel DW, van der Lugt A. Sixteen-detector row CT angiography of carotid arteries: comparison of different volumes of contrast material with and without a bolus chaser. Radiology. 2005;237:555-562.

17. Homburg PJ, Rozie S, van Gils MJ, Jansen T, Dippel DW, van der Lugt A. Atherosclerotic Plaque Ulceration in the Symptomatic Internal Carotid Artery is associated with Non-lacunar Ischemic Stroke. Stroke. 2010;41:1151-1156.

18. Mazighi M, Labreuche J, Gongora-Rivera F, Duyckaerts C, Hauw JJ, Amarenco P. Autopsy prevalence of intracranial atherosclerosis in patients with fatal stroke. Stroke. 2008;39:1142-1147.

19. Samuels OB, Joseph GJ, Lynn MJ, Smith HA, Chimowitz MI. A standardized method for measuring intracranial arterial stenosis. AJNR Am J Neuroradiol. 2000;21:643-646.

20. Bang OY, Kim JW, Lee JH, Lee MA, Lee PH, Joo IS, Huh K. Association of the metabolic syndrome with intracranial atherosclerotic stroke. Neurology. 2005;65:296-298.

21. Nam HS, Han SW, Lee JY, Ahn SH, Ha JW, Rim SJ, Lee BI, Heo JH. Association of aortic plaque with intracranial atherosclerosis in patients with stroke. Neurology. 2006;67:1184-1188.

22. De Silva DA, Woon FP, Pin LM, Chen CP, Chang HM, Wong MC. Intracranial large artery disease among OCSP subtypes in ethnic South Asian ischemic stroke patients. J Neurol Sci. 2007;260:147-149.

23. Rorick MB, Nichols FT, Adams RJ. Transcranial Doppler correlation with angiography in detection of intracranial stenosis. Stroke. 1994;25:1931-1934.

24. Graf J, Skutta B, Kuhn FP, Ferbert A. Computed tomographic angiography findings in 103 patients following vascular events in the posterior circulation: potential and clinical relevance. J Neurol. 2000;247:760-766.

25. Suh DC, Lee SH, Kim KR, Park ST, Lim SM, Kim SJ, Choi CG, Lee HK. Pattern of atherosclerotic carotid stenosis in Korean patients with stroke: different involvement of intracranial versus extracranial vessels. AJNR Am J Neuroradiol. 2003;24:239-244.

26. Huang YN, Gao S, Li SW, Huang Y, Li JF, Wong KS, Kay R. Vascular lesions in Chinese patients with transient ischemic attacks. Neurology. 1997;48:524-525.

27. Wong KS, Li H, Chan YL, Ahuja A, Lam WW, Wong A, Kay R. Use of transcranial Doppler ultrasound to predict outcome in patients with intracranial large-artery occlusive disease. Stroke. 2000;31:2641-2647.

28. Chimowitz MI, Kokkinos J, Strong J, Brown MB, Levine SR, Silliman S, Pessin MS, Weichel E, Sila CA, Furlan AJ, Kargman DE, Sacco RL, Wityk RJ, Ford G, Fayad, PB. The Warfarin-Aspirin Symptomatic Intracranial Disease Study. Neurology. 1995;45:1488-1493.

29. The Warfarin-Aspirin Symptomatic Intracranial Disease (WASID) Study Group. Prognosis of patients with symptomatic vertebral or basilar artery stenosis. Stroke. 1998;29:1389-1392.

30. Sohn YH, Cheon HY, Jeon P, Kang SY. Clinical implication of cerebral artery calcification on brain CT. Cerebrovasc Dis. 2004;18:332-337.

31. Chen XY, Lam WW, Ng HK, Fan YH, Wong KS. The frequency and determinants of calcification in intracranial arteries in Chinese patients who underwent computed tomography examinations. Cerebrovasc Dis. 2006;21:91-97.

32. Chen XY, Wong KS, Lam WW, Zhao HL, Ng HK. Middle cerebral artery atherosclerosis: histological comparison between plaques associated with and not associated with infarct in a postmortem study. Cerebrovasc Dis. 2008;25:74-80.

33. Bang OY, Lee PH, Yoon SR, Lee MA, Joo IS, Huh K. Inflammatory markers, rather than conventional risk factors, are different between carotid and MCA atherosclerosis. J Neurol Neurosurg Psychiatry. 2005;76:1128-1134.

34. Napoli C, Abete P, Corso G, Malomi A, Postiglione A, Ambrosio G, Cacciatore F, Rengo F, Palumbo G. Increased low-density lipoprotein peroxidation in elderly men. Coron Artery Dis. 1997;8:129-136.

35. Grønholdt ML. Age, Antioxidants, and Atherogenesis. Stroke. 2001;32: 2479-2480.

36. Ross R. Atherosclerosis--an inflammatory disease. N Engl J Med. 1999;340:115-126.

37. Bae HJ, Lee J, Park JM, Kwon O, Koo JS, Kim BK, Pandey DK. Risk factors of intracranial cerebral atherosclerosis among asymptomatics. Cerebrovasc Dis. 2007;24:355-360.

38 Wong LK. Global burden of intracranial atherosclerosis. Int J Stroke. 2006;1:158-159.

39. Turan TN, Bonilha L, Morgan PS, Adams RJ, Chimowitz MI. Intraplaque Hemorrhage in Symptomatic Intracranial Atherosclerotic Disease. J Neuroimaging. 2011;21:e159-161.

Chapter 3.2

Intracranial Atherosclerotic Stenosis assessed with Multidetector CT Angiography in TIA and Ischemic Stroke Patients is associated with increased risk of Ischemic Stroke

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Submitted - embargo

Chapter 4

General discussion

This thesis aims to improve understanding of atherosclerotic carotid plaque ulcerations as a source of artery-to-artery thromboembolism in patients with TIA and ischemic stroke. Furthermore, the prevalence of intracranial arterial stenosis (IAS) in patients with TIA or ischemic stroke was determined and the risk of recurrent ischemic stroke was assessed in patients with both symptomatic and asymptomatic IAS.

The thesis has six objectives:

I. To describe the frequency and location of plaque irregularities in patients with TIA or ischemic stroke, and the relationship of plaque irregularities with stenosis severity, cardiovascular risk factors and symptomatology.

II. To test the hypothesis whether carotid plaque ulceration is more associated with non-lacunar stroke than with lacunar stroke.

III. To analyze the relation between atherosclerotic carotid plaques ulceration and plaque volume, degree of stenosis, and plaque components in both patients with ≥50% stenosis as well as patients with a low degree stenosis (0-49%).

IV. To explore the natural history of ulcerated plaques and to assess whether plaque ulcerations heal by studying the temporal changes in plaque surface morphology on serial imaging in patients with TIA or minor ischemic stroke.

V. To investigate the prevalence, distribution and the calcification of IAS in a mainly European population of TIA and ischemic stroke patients.

VI. To assess the occurrence of new ischemic strokes in patients with symptomatic and asymptomatic IAS as well as without IAS during long term follow-up.

Main findings

Carotid artery atherosclerotic plaque ulceration

Chapter 2.1 describes the associations between carotid artery atherosclerotic plaques surface morphology assessed with MDCTA and severity of stenosis, cardiovascular risk factors, and type of ischemic cerebrovascular symptoms in patients with TIA or ischemic stroke. The presence of ulcerated or irregular plaques in the carotid artery was strongly related with the severity of stenosis, and ulcerations were more often present in severe stenotic carotid arteries. However, ulcerations were also present in 9% of carotid arteries with a stenosis of less than 30%. Ulcerations were predominantly located proximal to the site with the severest stenosis. This finding supports the hypothesis that shear stress plays a crucial role in the development of vulnerable plaque and plaque rupture. Complicated plaque surfaces were more frequently present in symptomatic carotid arteries compared to asymptomatic carotid arteries. However, this finding can be entirely attributed to the significantly higher degree of stenosis in the symptomatic arteries. Analysis of stroke symptoms revealed a lower frequency of complicated plaques among patients with amaurosis fugax compared to patients with cerebral ischemic events. Hypercholesterolemia was independently related to the presence of complicated plaques.

Carotid plaque ulceration is a marker of previous plaque rupture and may lead to subsequent thromboembolism in large intracranial arteries leading to deep or cortical infarcts. To test this hypothesis, we examined the association between atherosclerotic plaque ulceration with non-lacunar ischemic stroke compared to lacunar stroke in *Chapter 2.2*. This study revealed that atherosclerotic carotid plaque ulceration is associated with non-lacunar ischemic stroke, independent of the degree of carotid stenosis. These results suggest that non-lacunar stroke and lacunar stroke are indeed caused by different pathophysiological mechanisms.

Carotid plaque ulceration has been associated with the presence of fibrous cap rupture and distinct plaque components such as intraplaque hemorrhage, large lipid core, and less fibrous tissue in patients with severe symptomatic stenosis.[1] However, whereas a ≥50% carotid stenosis is present in only approximately 10% of patients with cerebral ischemic events, histological and non-invasive imaging studies assessing the relation of carotid plaque characteristics with plaque surface disruption have been limited to these patients with a ≥50% carotid stenosis.[1-3] In *Chapter 2.1* we demonstrated that plaque ulcerations are also present in carotid atherosclerosis with a stenosis <50%, which suggests that plaque composition could also play a role in plaque rupture of small plaques. Limited data are available on the association

between plaque volume and carotid plaque surface disruption.[3] This association is relevant as larger plaques may be more prone to ulceration. In addition, adjustment for plaque volume is needed when evaluating the association between plaque composition and plaque ulceration. In *Chapter 2.3* therefore we evaluated the relation between carotid artery atherosclerotic plaques ulceration and plaque volume, and plaque components as assessed with MDCTA in patients with ≥50% stenosis as well as in those with a lower degree stenosis of 0-49%. Plaque volume and LR-NC proportion, evaluated noninvasively with MDCTA, were associated with plaque ulceration in the carotid artery in both patients with ≥50% and <50% stenosis. This association between the LR-NC proportion and carotid plaque ulceration was independent of the degree of stenosis or plaque volume. Plaque composition analysis with MDCTA may prove useful for detection of rupture-prone plaques and could potentially improve risk stratification in ischemic stroke patients.

Carotid plaque ulcerations are considered to result from rupture of thin fibrous caps of atherosclerotic plaques. Persisting carotid plaque ulcerations may be an additional cause of thrombo-embolic stroke due to local flow disturbances.[4-6] Current knowledge on the evolution of atherosclerotic plaque rupture is primarily based on histological analysis of coronary arteries in autopsy studies or specimens obtained from carotid endarterectomies.[7-11] To explore the natural history of ulcerated plaques and to assess whether plaque ulcerations heal, we studied the temporal changes in plaque surface morphology on serial MDCTA in patients with TIA or minor ischemic stroke in *Chapter 2.4*. Plaque surface morphology remained unchanged in a large majority of arteries, whereas in a small minority of arteries new irregularities and ulceration occurred or existing irregularities or ulceration disappeared. Carotid plaque ulcerations may therefore persist for a long time and may not represent a recent plaque rupture. These persisting carotid ulcerations may remain a potential source of thrombo-embolism as a result of focal turbulence.

Intracranial arterial stenotic lesions

It is presumed that symptomatic IAS accounts for around 8–10% of all ischemic strokes.[12,13] More insight into the prevalence, distribution and calcification of IAS lesions could help identify high risk patients requiring more aggressive secondary prevention and improve effectiveness of therapies. In *Chapter 3.1* we evaluated a large cohort of patients with TIA or ischemic stroke for the prevalence, distribution and the calcification of IAS lesions using MDCTA. Furthermore, the association of IAS with the traditional risk factors for cerebrovascular disease as well as with ESR was investigated. IAS lesions were present in 23% of patients. Most stenoses were located in the arteries of the posterior circulation, which are associated with a high risk of

recurrent stroke.[14-16] IAS lesions in the basilar artery and arteries beyond the circle of Willis were mainly non-calcified. In addition to age, sex and several traditional cerebrovascular risk factors, ESR was independently associated with the presence of IAS and with the presence of non-calcified IAS in particular. This may indicate a prominent role for inflammation in intracranial atherogenesis.

Recurrence rates of 10% to 14% per year have been reported in patients with previously symptomatic IAS.[14,15,17,18] In *Chapter 3.2* we evaluated the occurrence of new ischemic strokes in patients with symptomatic and asymptomatic IAS as well as without IAS during long term follow-up. We observed a significantly increased ischemic stroke rate in patients with symptomatic IAS compared to patients without IAS. No increase in ischemic stroke rate was observed in patients with asymptomatic IAS. This study found a high risk of recurrent ischemic stroke in patients with symptomatic IAS, which is more than doubled compared to patients without IAS. This provides arguments for continued research efforts towards targeted therapeutic strategies and for intensive preventive treatment of patients with symptomatic IAS.

Clinical implications

Carotid artery atherosclerotic plaque ulceration

Pathophysiological mechanisms of cerebrovascular disease have been studied extensively. However, the nature of both transient as well as lasting ischemic cerebral symptoms remains unexplained in between 30 percent and 40 percent of ischemic strokes. Several mechanisms have been suggested for these so-called cryptogenic strokes, including occult paroxysmal atrial fibrillation, patent foramen ovale, aortic arch atherosclerosis, atrial cardiopathy, and substenotic atherosclerosis of the vertebrobasilar and extracranial carotid arteries.[19]

Artery-to-artery embolism is assumed to be an important pathophysiological mechanism in transient ischemic attacks (TIAs) or ischemic stroke ipsilateral to atherosclerotic plaques. Traditionally, two theories have been proposed to explain artery-to-artery embolism. The first is a hemodynamic concept which states that a high-grade stenosis produces symptoms by reduced and turbulent blood flow. The second theory explains ischemic cerebral symptoms as the result of cerebral emboli originating from irregular arteriosclerotic plaques frequently located in the extracranial arteries, principally in the common carotid artery bifurcation.[20-23] Since plaque irregularities are often present in atherosclerotic disease without stenosis greater than 50%, the conventional definitions relating ischemic stroke to a specific etiology must be

disputed, as large artery atherosclerosis is currently only considered the etiology of ischemic stroke in patients with carotid artery stenosis of more than 50%.

The clinical significance of ulcerated carotid plaques is supported by numerous studies. Strong associations have been found between plaque ulceration and downstream cerebral microemboli measured preoperatively with Transcranial Doppler (TCD).[5,24,25] Presence of ulcerations is a risk factor for ischemic stroke.[26-29] It increases the risk for neurologic symptoms by approximately four times.[30] Although the risk for ischemic stroke related to ulcerated carotid plaques increases with more severe stenosis, also ulceration of plaques with low-grade stenosis of ≤50% have been correlated with ischemic cerebral symptoms.[28,31]

In *Chapter 2.1* we demonstrated that although irregular or ulcerated plaques are more common in carotid arteries with stenosis of >50%, they are also present carotid arteries with stenosis of <50%. Furthermore, the study found that complicated plaques are more often present in the symptomatic carotid arteries than in the contralateral asymptomatic carotid artery, but this was fully attributed to a significantly higher degree of stenosis in the symptomatic arteries. These findings suggest that carotid artery plaque irregularities may be a cause of cryptogenic stroke in patients who do not fulfill the criteria of large artery atherosclerosis according to the TOAST classification.

In *Chapter 2.2* we demonstrated that carotid plaque ulcerations are indeed associated with non-lacunar ischemic strokes, which is confirmed by later reports.[32] This suggests that ulcerations are not just a marker of increased risk, but part of the pathophysiological cascade linking atherosclerotic disease to ischemic cerebral symptoms. For this reason, unstable and ulcerated plaques could be an important target for therapies to prevent (re-)ulceration. Although superficial irregularity of plaque surfaces without a clear ulceration have also been associated with an increased stroke risk,[23,27,33,34] these findings were not confirmed in a recent meta-analysis for US-detected plaque irregularities.[30]

Since ulcerations are related to ischemic stroke, the question arises of what causes plaque ulceration. Ulceration of atherosclerotic plaque is considered to be a remnant of plaque rupture which is related to a specific plaque components like intraplaque hemorrhage, large lipid core, and less fibrous tissue.[35] The study in *Chapter 2.3* reveals that plaque volume, degree of stenosis, and LR-NC proportion evaluated non-invasively with MDCTA are associated with carotid artery plaque ulceration, even in patients with a low degree stenosis (0-49%). In this study calcification volume as a proportion of the total plaque volume was inversely associated with plaque ulceration. A recent study, however, reported that surface and multiple calcifications and ulceration associated with intra-plaque hemorrhage in the carotid artery, which can lead to rupture of the plaque surface.[36] The latter study was performed with MRI,

which is an imaging modality that in contrast to CT is able to depict intraplaque hemorrhage. Our findings are supported by a recent systematic review and meta-analysis which reported that soft plaque and plaque ulceration on CTA are associated with ipsilateral cerebrovascular ischemia, while calcified plaque is negatively associated with downstream ischemic events.[37] Our study, which found that in addition to stenosis measurement, plaque volume and composition analysis with MDCTA may identify rupture prone vulnerable plaques, demonstrates that risk stratification in ischemic stroke patients could be improved with non-invasive imaging of atherosclerotic plaque features.

After plaque rupture, healing of the affected plaque may occur. A basis of a disrupted fibrous cap with an overlying repair response is observed in pathological examination of coronary artery specimens.[38] Although rupture healing may reduce the risk of thromboembolic ischemic stroke, repeated rupture healing increases plaque volume and degree of luminal stenosis in coronary arteries. Our study in *Chapter 2.4* on plaque evolution in carotid arteries with serial MDCTA in patients with TIA or minor ischemic stroke revealed that plaque surface morphology remains unchanged in a large majority of arteries. These results are in line with a prospective 3D ultrasound study which reported that the vast majority of plaques (76.5%) remained unchanged for more than a year, 23.5% of ulcerations regressed while only 5.8% of ulcerations progressed.[39] We therefore conclude that these persisting carotid artery plaque ulcerations may remain a potential source of new thrombo-embolism.

Intracranial arterial stenotic lesions

Several studies have elucidated the therapeutic management of IAS. Two main therapeutic strategies are available: revascularization combined with medical management or only medical management. Several trials have demonstrated the feasibility of revascularization through endovascular stenting.[40-42] However, two more recent randomized trials compared stenting combined with medical management to medical management alone in patients with symptomatic IAS.[43,44] Stenting was associated with an increased risk of TIA, stroke, death, or intracranial hemorrhage and showed no benefit in any subpopulation of patients. Patients already enrolled in the SAMMPRIS trial continued to be followed for a median of 32.4 months, during which 15% of those randomized to the medical management group and 23% of the stenting group had a primary endpoint.[43] Aggressive medical management in the control arm of the SAMPRISS trial resulted in a stroke risk comparable to that in similar patients in the WASID trial after adjustment of confounding characteristics. The authors concluded that the early benefit of aggressive medical management over stenting for high-risk patients with IAS persists during extended follow-up. Like the SAMMRPIS trial, the VISSIT trial showed a lower

than expected rate of stroke in the medical group and high procedural complication rates in the stent group.[44] The findings of these trials lend support to the use of aggressive medical management rather than stenting in high-risk patients with IAS.

Methodological considerations

The studies in this thesis were conducted in a cohort of consecutive TIA and stroke patients to investigate the associations between atherosclerotic plaque characteristics and ischemic symptoms. The studies aim to elucidate the pathophysiology relating atherosclerotic plaque development to ischemic stroke, to intervene in this process, and thereby prevent future ischemic strokes. However, all but one of the studies had a cross-sectional design, allowing for associations to be studied. In order to determine the precise importance of the findings in these cross-sectional studies, the value of image-based plaque characteristics for risk prediction should be confirmed in prospective studies.

The patient-based approach in this thesis differs from a population health approach, which aims to decrease the incidence of (primary) strokes through preventive measures in the general population. Longitudinal population-based studies could increase knowledge about atherosclerotic plaque progression and help improve risk stratification. Similarly, analysis of patient cohort studies could provide detailed estimates of recurrence risk based on clinical and imaging characteristics.

The applied stroke subtype classification in *Chapter 2.2* was based on clinical symptoms and corrected for relevant infarctions seen on brain CT. Although a clinical approach results in an accurate classification in most patients, some misclassifications are inevitable. Nonetheless, after replicating the analysis based on CT brain infarctions alone as a substitute for clinically defined stroke subtypes, the association between carotid plaque ulceration and non-lacunar infarction remained.

Although MDCTA has been shown to be an excellent technique to evaluate carotid ulceration,[45,46] a limitation of our studies on ulceration is the absence of conformation of the findings through histologic specimens. The correlation with histological results is troublesome because only patients with a severe stenosis (NASCET >70% stenosis) are eligible for surgical intervention. Furthermore, even in patients with >70% carotid artery stenosis histology was not always obtained, as stenting was performed in a large proportion of the patients in our cohort.

Fibrous cap thickness and rupture which are both related to atherosclerotic plaque instability cannot be reliably detected with MDCTA. The presence of intraplaque hemorrhage was not evaluated as the plaque composition analysis software used in *Chapter 2.3* has not been validated for differentiation of intraplaque hemorrhage. As a result, both LR-NC and fibrous tissue assessed with MDCTA may contain intraplaque hemorrhage. Furthermore, with the need of intravenous contrast material and ionizing radiation, MDCTA is not entirely non-invasive nor harmless.[47,48]

All patients in the study cohort received secondary preventive therapies including antiplatelet therapy and management of vascular risk factors. A recent systematic review and meta-analysis of studies using virtual histology on intravascular ultrasound found a significant effect of statin therapy on plaque and external elastic membrane volumes as well as fibrous and calcium volumes, whereas no effect was found on lumen volume, fibro-fatty and necrotic tissue volumes.[49] Secondary preventive therapies, particularly improved blood pressure control and antiplatelet therapy have contributed to a substantial decline in recurrent stroke and vascular event rates over the last 5 decades.[50] These therapies may have influenced outcomes in several studies in this thesis such as the development of extracranial carotid artery plaques in *Chapter 2.4* or the stroke recurrence risk in *Chapter 3.2*. However, we studied associations of clinical and imaging parameters with recurrence risk and plaque evolution in terms of relative risk, adjusted for confounders, which minimizes this bias.

Future directions

In recent years, MDCTA has emerged as an efficient medical imaging modality in acute stroke care. The Dutch guideline for stroke care recommends evaluating the cerebral arterial circulation from the aortic arch to the intracranial arteries with MDCTA to determine the presence and location of an arterial occlusion. This recommendation applies to all patients who may be eligible for intra-arterial treatment, i.e. with a clinical diagnosis of cerebral infarction without an intracranial hemorrhage on non-contrast cranial CT and without contraindications for intra-arterial thrombolysis (IAT). In addition to MDCTA, duplex ultrasonography or contrast MRA is recommended to detect carotid stenosis, replacing DSA as pre-intervention imaging.

This leading role of MDCTA in acute stroke care could be used to further investigate the role of CT imaging biomarkers such as plaque composition or ulcerations in the pathophysiology of thrombo-embolic stroke. Given the persistent presence of plaque ulceration found in this

thesis, their role in the pathogenesis of ischemic stroke and therapeutic management should be further explored in longitudinal studies.

The risk of recurrent ischemic stroke in patients with symptomatic IAS is high, and it is more than doubled compared to patients without IAS. This provides arguments for continued research efforts into focused therapeutic strategies, and also for intensive preventive treatment of these patients. Further research on non-invasive analysis of plaque components in IAS lesions could improve understanding of the pathophysiology of intracranial atherosclerosis. The additional evaluation of intraplaque hemorrhage using high-resolution magnetic resonance imaging, which is likely to convey strong prognostic value for recurrent stroke, may be of interest.

References

1. Lovett JK, Gallagher PJ, Hands LJ, Walton J, Rothwell PM. Histological correlates of carotid plaque surface morphology on lumen contrast imaging. Circulation. 2004;110:2190-2197.

2. Tholen AT, de Monyé C, Genders TS, Buskens E, Dippel DW, van der Lugt A, Hunink MG. Suspected carotid artery stenosis: cost-effectiveness of CT angiography in work-up of patients with recent TIA or minor ischemic stroke. Radiology. 2010;256:585-597.

3. Underhill HR, Yuan C, Yarnykh VL, Chu B, Oikawa M, Dong L, Polissar NL, Garden GA, Cramer SC, Hatsukami TS. Predictors of surface disruption with MR imaging in asymptomatic carotid artery stenosis. AJNR Am J Neuroradiol. 2010;31:487-493.

4. Imbesi SG, Kerber CW: Why do ulcerated atherosclerotic carotid artery plaques embolize? A flow dynamics study. AJNR Am J Neuroradiol 1998;19:761-766.

5. Sitzer M, Muller W, Siebler M, Hort W, Kniemeyer HW, Jancke L, Steinmetz H: Plaque ulceration and lumen thrombus are the main sources of cerebral microemboli in high-grade internal carotid artery stenosis. Stroke 1995;26:1231-1233.

6. Stein PD, Sabbah HN: Measured turbulence and its effect on thrombus formation. Circ Res 1974;35:608-614.

7. Finn AV, Nakano M, Narula J, Kolodgie FD, Virmani R: Concept of vulnerable/unstable plaque. Arterioscler Thromb Vasc Biol;30:1282-1292.

8. Kolodgie FD, Virmani R, Burke AP, Farb A, Weber DK, Kutys R, Finn AV, Gold HK: Pathologic assessment of the vulnerable human coronary plaque. Heart 2004;90:1385-1391.

9. Peeters W, Hellings WE, de Kleijn DP, de Vries JP, Moll FL, Vink A, Pasterkamp G: Carotid atherosclerotic plaques stabilize after stroke: Insights into the natural process of atherosclerotic plaque stabilization. Arterioscler Thromb Vasc Biol 2009;29:128-133.

10. Redgrave JN, Lovett JK, Gallagher PJ, Rothwell PM: Histological assessment of 526 symptomatic carotid plaques in relation to the nature and timing of ischemic symptoms: The Oxford Plaque Study. Circulation 2006;113:2320-2328.

11. Virmani R, Finn AV, Kolodgie FD: Carotid plaque stabilization and progression after stroke or TIA. Arterioscler Thromb Vasc Biol 2009;29:3-6.

12. Sacco RL, Kargman D, Gu Q, Zamanillo MC. Race-ethnicity and determinants of intracranial atherosclerotic cerebral infarction: the Northern Manhattan Stroke Study. Stroke. 1995;26:14-20.

13. Wityk R, Lehman D, Klag M, Coresh J, Ahn H, Litt B. Race and sex differences in the distribution of cerebral atherosclerosis. Stroke. 1996;27:1974-1980.

14. Kasner SE, Chimowitz MI, Lynn MJ, Howlett-Smith H, Stern BJ, Hertzberg VS, Frankel MR, Levine SR, Chaturvedi S, Benesch CG, Sila CA, Jovin TG, Romano JG, Cloft HJ. Predictors of ischemic stroke in the territory of a symptomatic intracranial arterial stenosis. Circulation. 2006;113:555-563.

15. Chimowitz MI, Kokkinos J, Strong J, Brown MB, Levine SR, Silliman S, et al. The Warfarin-Aspirin Symptomatic Intracranial Disease study. Neurology. 1995;45:1488-1493.

16. The Warfarin-Aspirin Symptomatic Intracranial Disease (WASID) Study Group. Prognosis of patients with symptomatic vertebral or basilar artery stenosis. Stroke. 1998;29:1389-1392.

17. Mazighi M, Tanasescu R, Ducrocq X, Vicaut E, Bracard S, Houdart E, et al. Prospective study of symptomatic atherothrombotic intracranial stenoses: the GESICA study. Neurology. 2006;66:1187-1191.

18. Chimowitz MI, Lynn MJ, Derdeyn CP, Turan TN, Fiorella D, Lane BF, et al. Stenting versus aggressive medical therapy for intracranial arterial stenosis. N Engl J Med 2011;365:993-1003.

19. Yaghi S, Bernstein RA, Passman R, Okin PM, Furie KL. Cryptogenic Stroke: Research and Practice. Circ Res. 2017;120:527-540.

20. Bonati LH, Nederkoorn PJ. Clinical perspective of carotid plaque imaging. Neuroimaging Clin N Am. 2016;26:175-182.

21. Fisher M, Paganini-Hill A, Martin A, et al. Carotid plaque pathology: thrombosis, ulceration, and stroke pathogenesis. Stroke. 2005;36:253-257

22. Wechsler LR. Ulceration and carotid artery disease. Stroke. 1988;19:650-653

23. Kessler C, von Maravic M, Bruckmann H, Kompf D. Ultrasound for the assessment of the embolic risk of carotid plaques. Acta Neurol Scand. 1995;92:231-234

24. Valton L, Larrue V, Arrue P, Geraud G, Bes A. Asymptomatic cerebral embolic signals in patients with carotid stenosis. Correlation with appearance of plaque ulceration on angiography. Stroke. 1995;26:813-815.

25. Orlandi G, Parenti G, Landucci Pellegrini L, et al. Plaque surface and microembolic signals in moderate carotid stenosis. Ital J Neurol Sci. 1999;20:179-182

26. A. Madani, V. Beletsky, A. Tamayo, C. Munoz, J.D. Spence. High-risk asymptomatic carotid stenosis: ulceration on 3D ultrasound versus TCD microemboli. Neurology. 2011;77:744-750

27. Rothwell PM, Gibson R, Warlow CP. Interrelation between plaque surface morphology and degree of stenosis on carotid angiograms and the risk of ischemic stroke in patients with symptomatic carotid stenosis. On behalf of the European Carotid Surgery Trialists' Collaborative Group. Stroke. 2000;31:615-621.

28. Eliasziw M, Streifler JY, Fox AJ, Hachinski VC, Ferguson GG, Barnett HJ. Significance of plaque ulceration in symptomatic patients with high-grade carotid stenosis. North American Symptomatic Carotid Endarterectomy Trial. Stroke. 1994;25:304-308

29. North American Symptomatic Carotid Endarterectomy Trial Collaborators Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis. N Engl J Med. 1991;325:445-453

30. Brinjikji W, Rabinstein AA, Lanzino G, et al. Ultrasound characteristics of symptomatic carotid plaques: a systematic review and meta-analysis. Cerebrovasc Dis. 2015;40:165-174

31. Ballotta E, Angelini A, Mazzalai F, Piatto G, Toniato A, Baracchini C. Carotid endarterectomy for symptomatic low-grade carotid stenosis. J Vasc Surg. 2014;59:25-31.

32. Nakamura T, Tsutsumi Y, Shimizu Y, Uchiyama S. Ulcerated carotid plaques with ultrasonic echolucency are causatively associated with thromboembolic cerebrovascular events. J Stroke Cerebrovasc Dis. 2013;22:93-9

33. Hokari M, Kuroda S, Yasuda H, et al. Lumen morphology in mild-to-moderate internal carotid artery stenosis correlates with neurological symptoms. J Neuroimaging. 2011;21:348-354

34. Prabhakaran S, Rundek T, Ramas R, et al. Carotid plaque surface irregularity predicts ischemic stroke: the northern Manhattan study. Stroke. 2006;37:2696-2701

35. van Dijk AC, Truijman MT, Hussain B, Zadi T, Saiedie G, de Rotte AA, Liem MI, van der Steen AF, Daemen MJ, Koudstaal PJ, Nederkoorn PJ, Hendrikse J, Kooi ME, van der Lugt A. Intraplaque Hemorrhage and the Plaque Surface in Carotid Atherosclerosis: The Plaque At RISK Study (PARISK). AJNR Am J Neuroradiol. 2015;36:2127-2133

36. Yang J, Pan X, Zhang B, Yan Y, Huang Y, Woolf AK, Gillard JH, Teng Z, Hui P. Superficial and multiple calcifications and ulceration associate with intraplaque hemorrhage in the carotid atherosclerotic plaque. European Radiology 2018;28:4968-4977.

37. Baradaran H, Al-Dasuqi K, Knight-Greenfield A, Giambrone A, Delgado D, Ebani EJ, Kamel H, Gupta A. Association between Carotid Plaque Features on CTA and Cerebrovascular Ischemia: A Systematic Review and Meta-Analysis. AJNR Am J Neuroradiol. 2017;38:2321-2326

38. Mann J, Davies MJ. Mechanisms of progression in native coronary artery disease: role of healed plaque disruption. Heart 1999;82:265-268.

39. Schminke U, Motsch L, Hilker L, Kessler C. Three-dimensional ultrasound observation of carotid artery plaque ulceration. Stroke. 2000;31:1651-1655

40. Chimowitz MI, Lynn MJ, Howlett-Smith H, Stern BJ, Hertzberg VS, Frankel MR, et al. Comparison of Warfarin and Aspirin for Symptomatic Intracranial Arterial Stenosis (WASID). N Engl J Med. 2005;352:1305-1316.

41. Mazighi M, Tanasescu R, Ducrocq X, Vicaut E, Bracard S, Houdart E, et al. Prospective Study of atherothrombotic intrancranial stenoses, the GESICA study. Neurology. 2006;66:1187-1191.

42. The SSYLVIA Study Investigators. Stenting of Symptomatic Atherosclerotic Lesions in the Vertebral or Intracranial Arteries (SSYLVIA). Stroke. 2004;35:1388-1392.

43. Derdeyn CP, Chimowitz MI, Lynn MJ, et al. Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis Trial Investigators. Aggressive medical treatment with or without stenting in high-risk patients with intracranial artery stenosis (SAMMPRIS): the final results of a randomised trial. Lancet. 2014 Jan 25;383:333-341.

44. Zaidat OO, Fitzsimmons B-F, Woodward BK, et al. VISSIT Trial Investigators. Effect of a balloon-expandable intracranial stent vs medical therapy on risk of stroke in patients with symptomatic intracranial stenosis: The VISSIT randomized clinical trial. JAMA. 2015;313:1240-1248.

45. Saba L, Caddeo G, Sanfilippo R, Montisci R, Mallarini G. Efficacy and sensitivity of axial scans and different reconstruction methods in the study of the ulcerated carotid plaque using multidetector-row CT angiography: comparison with surgical results. AJNR Am J Neuroradiol. 2007;28:716-723.

46. Walker LJ, Ismail A, McMeekin W, Lambert D, Mendelow AD, Birchall D. Computed tomography angiography for the evaluation of carotid atherosclerotic plaque: correlation with histopathology of endarterectomy specimens. Stroke. 2002;33:977-981.

47. Maaniitty T, Stenström I, Uusitalo V, Ukkonen H, Kajander S, Bax JJ, Saraste A, Knuuti J. Incidence of persistent renal dysfunction after contrast enhanced coronary CT angiography in patients with suspected coronary artery disease. Int J Cardiovasc Imaging. 2016;32:1567-1575.

48. Mielke D, Kallenberg K, Hartmann M, Rohde V.J Paraplegia after contrast media application: a transient or devastating rare complication? Case report. Neurosurg Spine. 2016;24:806-809.

49. Banach M, Serban C, Sahebkar A, Mikhailidis DP, Ursoniu S, Ray KK, Rysz J, Toth PP, Muntner P, Mosteoru S, García-García HM, Hovingh GK, Kastelein JJ, Serruys PW; Lipid and Blood Pressure Meta-analysis Collaboration (LBPMC) Group. Impact of statin therapy on coronary plaque composition: a systematic review and meta-analysis of virtual histology intravascular ultrasound studies. BMC Med. 2015;13:229.

50. Hong KS, Yegiaian S, Lee M, Lee J, Saver JL. Declining stroke and vascular event recurrence rates in secondary prevention trials over the past 50 years and consequences for current trial design. Circulation. 2011;123:2111-2119.

Chapter 5

Summary and Conclusions

Samenvatting en Conclusies

The general introduction (*Chapter 1*) of this thesis first outlines the relationship of both extracranial carotid artery and intracranial large artery atherosclerotic plaque characteristics with cerebral ischemic events. The concepts of atherosclerotic plaque vulnerability and healing of plaque rupture are described. The potential of different imaging techniques to assess atherosclerotic plaque characteristics is discussed. Finally, the objective and research questions of the thesis are explained.

Carotid artery atherosclerotic plaque ulceration

The studies in *Chapter 2* of the thesis focus on improving insight in carotid artery atherosclerotic plaque ulcerations as assessed with MDCTA, and the role of these ulcerations in TIA or ischemic stroke. *Chapter 2.1* describes the associations between carotid artery atherosclerotic plaques surface morphology assessed with MDCTA and severity of stenosis, cardiovascular risk factors, and type of ischemic cerebrovascular symptoms in patients with TIA or ischemic stroke. The presence of ulcerated or irregular plaques in the carotid artery was strongly related with the severity of stenosis. Ulcerations were predominantly located proximal to the site with the severest stenosis. Complicated plaque surfaces were more frequently present in symptomatic carotid arteries compared to asymptomatic carotid arteries, what can be fully attributed to the significantly higher degree of stenosis in the symptomatic arteries. A lower frequency of complicated plaques was present among patients with amaurosis fugax compared to patients with cerebral ischemic events. Hypercholesterolemia was independently related to the presence of complicated plaques. In *Chapter 2.2* the association of atherosclerotic plaque ulceration with non-lacunar stroke as compared to lacunar stroke was examined in patients with TIA or ischemic stroke. Atherosclerotic carotid plaque ulceration is associated with non-lacunar ischemic stroke, independent of the degree of carotid stenosis. In *Chapter 2.3* we evaluated the relation between carotid artery atherosclerotic plaques ulceration and plaque volume, degree of stenosis, and plaque components as assessed with MDCTA in both patients with ≥50% stenosis as well as in those with a low degree stenosis of 0-49%. Plaque volume, degree of stenosis, and lipid-rich necrotic core (LR-NC) proportion evaluated non-invasively with MDCTA were associated with carotid artery plaque ulceration, also in patients with a low degree stenosis (0-49%). This association between the LR-NC proportion and carotid plaque ulceration was independent of the degree of stenosis. In *Chapter 2.4* we assessed the temporal changes in plaque surface morphology on serial MDCTA in patients with TIA or minor ischemic stroke. Plaque surface morphology remained unchanged in a large majority (88%) of arteries, whereas in a small minority of arteries new irregularities and

ulcerations occurred (8%) or existing irregularities or ulcerations disappeared (4%). Plaque morphology remained unchanged in most ulcerated plaques (67%).

Intracranial arterial stenotic lesions

Chapter 3 of this thesis describes the prevalence, distribution and morphology of IAS in patients with TIA and ischemic stroke patients. Furthermore, the occurrence of new ischemic strokes in patients with symptomatic and asymptomatic IAS was evaluated during long term follow-up. In *Chapter 3.1* we evaluated a large cohort of patients with TIA or ischemic stroke for the prevalence, distribution and the calcification of IAS lesions using MDCTA. Furthermore, the association of IAS with the risk factors for cerebrovascular disease as well as with ESR was investigated. IAS were present in 23% of patients. Most stenoses were located in the posterior circulation arteries. IAS in the basilar artery and arteries beyond the circle of Willis were mainly non-calcified. In addition to age, gender and several traditional cerebrovascular risk factors, ESR was independently associated with the presence of IAS and with the presence of non-calcified IAS in particular. In *Chapter 3.2* we evaluated the occurrence of new ischemic strokes in patients with symptomatic and asymptomatic IAS as well as without IAS during long term follow-up. A significantly increased ischemic stroke rate was observed in patients with symptomatic IAS compared to patients without IAS. No increase in ischemic stroke rate was observed in patients with asymptomatic IAS.

De algemene inleiding (*hoofdstuk 1*) van dit proefschrift beschrijft de relaties tussen kenmerken van atherosclerotische plaques in zowel de extracraniële halsslagaders als de intracraniële slagaders met herseninfarcten en transient ischemic attacks (TIA's). De eigenschappen van de kwetsbare, instabiele atherosclerotische plaques en van genezing van atherosclerotische plaques na een plaqueruptuur worden beschreven. Na een ruptuur van een atherosclerotische plaque kan een holte in de plaque achterblijven met open verbinding naar het bloedvat lumen. Deze holtes worden ook wel ulceraties genoemd. De mogelijkheden om met verschillende beeldvormingstechnieken eigenschappen van atherosclerotische plaques te bestuderen worden besproken. Ten slotte worden de doelen en de onderzoeksvragen van het proefschrift beschreven.

Atherosclerotische plaque ulceratie van de halsslagader

Hoofdstuk 2 van het proefschrift richt zich op de associaties tussen atherosclerotische plaque ulceratie van de halsslagader en de ernst van stenose, cardiovasculaire risicofactoren, plaquevolume en -samenstelling, evenals herseninfarct subtypen. *Hoofdstuk 2.1* beschrijft de associaties tussen de oppervlakmorfologie van atherosclerotische plaques van de halsslagader beoordeeld met multidetector computed tomography angiography (MDCTA), en ernst van stenose (bloedvatvernauwing), cardiovasculaire risicofactoren en type ischemische cerebrovasculaire symptomen bij patiënten met een herseninfarct of TIA. De oppervlakmorfologie van atherosclerotische plaques van de halsslagader werd geclassificeerd als geulcereerd, onregelmatig of glad. Plaques met een geulcereerd of onregelmatig oppervlak werden samengevoegd geanalyseerd als gecompliceerde plaques. De aanwezigheid van plaque ulceraties of onregelmatige plaques in de halsslagader was sterk gerelateerd aan de ernst van stenose. Plaque ulceraties waren voornamelijk gesitueerd proximaal van het punt van de sterkste vernauwing van de halsslagader. Gecompliceerde oppervlakmorfologie was vaker aanwezig in symptomatische halsslagaders in vergelijking met asymptomatische halsslagaders. Dit kan volledig worden toegeschreven aan de significant hogere stenosegraad in de symptomatische halsslagaders. Gecompliceerde plaques waren minder vaak aanwezig bij patiënten met amaurosis fugax in vergelijking met patiënten met cerebrale ischemie. Hypercholesterolemie was onafhankelijk gerelateerd aan de aanwezigheid van gecompliceerde plaques. In *hoofdstuk 2.2* werden de associaties tussen atherosclerotische plaque ulceraties, niet-lacunaire herseninfarcten en lacunaire herseninfarcten vergeleken. Atherosclerotische plaque ulceraties van de halsslagader waren geassocieerd met niet-lacunaire herseninfarcten, onafhankelijk van de mate van vernauwing van de halsslagader. In *hoofdstuk 2.3* evalueerden we de relatie tussen ulceraties, plaque volume en plaque

compositie van atherosclerotische plaques in de halsslagader door middel van MDCTA bij zowel patiënten met ≥50% stenose als bij patiënten met een lage stenosegraad van 0-49%. Plaque volume, stenosegraad en lipid-rich necrotic core (LR-NC) percentage waren geassocieerd met plaque ulceratie, ook bij patiënten met een lage mate stenosegraad van 0-49%. Deze associatie tussen de LR-NC-percentage en plaque ulceratie was onafhankelijk van de mate van vernauwing van de halsslagader. In *hoofdstuk 2.4* hebben we de veranderingen in de tijd van oppervlaktemorfologie van atherosclerotische plaques in halsslagaders onderzocht met behulp van seriële MDCTA bij patiënten met TIA of een herseninfarct. De morfologie van het plaque-oppervlak bleef ongewijzigd in een grote meerderheid van de slagaders (88%). In een kleine minderheid van de slagaders ontstonden nieuwe ulceraties of onregelmatigheden (8%), of verdwenen bestaande ulceraties of onregelmatigheden (4%). De morfologie van geulcereerde atherosclerotische plaques bleef in 67% onveranderd.

Stenotische laesies van intracraniële arteriën

Hoofdstuk 3 van dit proefschrift beschrijft de prevalentie, distributie en morfologie van intracraniële atherosclerotische stenosen (IAS) bij patiënten met een herseninfarct of TIA. Daarnaast wordt het optreden van nieuwe herseninfarcten bij patiënten met symptomatische en asymptomatische IAS tijdens langdurige follow-up beschreven. In *hoofdstuk 3.1* evalueerden we patiënten met een herseninfarct of TIA voor de prevalentie, distributie en verkalking van IAS laesies met behulp van MDCTA. Verder werd de associatie van IAS met de cerebrovasculaire risicofactoren en met bezinking (ESR) onderzocht. IAS was aanwezig bij 23% van de patiënten. De meeste stenosen bevonden zich in het stroomgebied van de achterste intracraniële slagaders. IAS in de arteria basilaris en slagaders distaal van de cirkel van Willis waren hoofdzakelijk niet-verkalkt. Naast leeftijd, geslacht en verschillende cerebrovasculaire risicofactoren, was bezinking onafhankelijk geassocieerd met de aanwezigheid van IAS en met de aanwezigheid van niet-verkalkte IAS in het bijzonder. In *hoofdstuk 3.2* evalueerden we het optreden van nieuwe herseninfarcten bij patiënten met symptomatische IAS, asymptomatische IAS en patiënten zonder IAS tijdens langdurige follow-up. Een significant verhoogd aantal herseninfarcten werd waargenomen bij patiënten met symptomatische IAS in vergelijking met patiënten zonder IAS. Er werd geen toename van de herseninfarcten waargenomen bij patiënten met asymptomatische IAS.

Chapter 6

Appendices

Acknowledgements

Research described in this thesis is based on clinical data obtained through the fruitful co-operation of the departments of neurology and radiology at the Erasmus Medical Center in Rotterdam. I express my gratitude to all supervisors, personnel and fellow researchers.

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Dear colleagues at Rijndam rehabilitation center and at Leiden University Medical center, I express gratitude for your support and help in providing time needed for the completion of this thesis. The studies in this thesis do not cover the subject of stroke rehabilitation. They focus on the etiology and cure side of stroke treatment, whereas rehabilitation focuses on the care side. However, all complementary information will help provide better understanding of stroke etiology and tailored care in the individual stroke patient.

Dear committee members, thank you for assessing my thesis and serving on the doctoral committee.

Dear Kathy, thank you for your kind and creative involvement from the other side of the world, I really appreciate the cover! My paranymphes, Klaas and Marnix, thank you for your friendship and support in the final steps of this work.

I would like to thank my friends and family for their interest and heartfelt support. I especially thank my parents who have supported me in my studies and personal development, even when I made some radical choices in my career. Dear Rox, thank you for your unconditional love. Dear Mira, little scientist, know what you're getting into ...

List of publications

Homburg PJ, Plas GJJ, van der Lugt A, Dippel DWJ. Association of Intracranial Arterial Stenosis Assessed with MDCT Angiography with Risk of Recurrent Ischemic Stroke. Submitted

Homburg PJ, Plas GJJ, Rozie S, van der Lugt A, Dippel DWJ. Prevalence and Calcification of Intracranial arterial stenotic lesions as assessed with multidetector CT angiography. Stroke. 2011;42:1244-1250.

Homburg PJ, Rozie S, van Gils MJ, van den Bouwhuijsen QJA, Niessen WJ, Dippel DW, van der Lugt A. Association between carotid artery plaque ulceration and plaque composition evaluated with multidetector CT angiography. Stroke. 2011;42:367-372.

Homburg PJ, van Gils MJ, Rozie S, de Weert TT, Dippel DW, van der Lugt A. The evolution of atherosclerotic carotid plaque morphology: Do ulcerated plaques heal? A serial multidetector-CT angiography study. Cerebrovasc Dis. 2011;31:263-270.

Homburg PJ, Rozie S, van Gils MJ, Jansen T, de Weert TT, Dippel DW, van der Lugt A. Atherosclerotic plaque ulceration in the symptomatic internal carotid artery is associated with nonlacunar ischemic stroke. Stroke. 2010;41:1151-1156.

de Weert TT, Cretier S, Groen HC, Homburg P, Cakir H, Wentzel JJ, Dippel DW, van der Lugt A. Atherosclerotic plaque surface morphology in the carotid bifurcation assessed with multidetector computed tomography angiography. Stroke. 2009;40:1334-40.

Rozie S, de Weert TT, de Monyé C, Homburg PJ, Tanghe HL, Dippel DW, van der Lugt A. Atherosclerotic plaque volume and composition in symptomatic carotid arteries assessed with multidetector CT angiography; relationship with severity of stenosis and cardiovascular risk factors. Eur Radiol. 2009;19:2294-301.

PhD Portfolio

Specific courses offered by COEUR:	**Date**	**ECTS**
Imaging of carotid bifurcation atherosclerosis	2008	1,5
Cardiovascular imaging and diagnostics		1,5
Methodologie van patiëntgebonden onderzoek en voorbereiding van subsidie aanvragen (COEUR)	2007	1,5
Peripheral and Intracranial Aneurismal Disease	2008	1,5

Erasmus MC courses (Central courses and courses organized by other Research Schools):

Genetic Epidemiology of Complex Diseases (NIHES)	2007	1,4
Classical Methods for Data-analysis (CC02) (NIHES)	2007	5,7
Regression Analysis (NIHES)	2007	1,4
Course in Biomedical English Writing and Communication	2008	4,0

Other courses followed:

Study Design and Analysis, Leiden University	1998	4,3
Circulation, Leiden University	1999	4,3
Neurological Sciences, Leiden University	2000	5,7
Radiology and Introduction Clinical Methodology, Leiden University	2000	5,7

Lectures:

BIGR Research meetings 2007 - 2010	2007-2010	2,5
Research Lunch Presentation Radiology 2007 (1x)	2007	1,0
Research Lunches Radiology 2007 - 2010	2007-2010	2,5

Journal Club Radiology 2007 (5x)	2007	0,5
Research Lunch Presentation Radiology 2009 (1x)	2009	1,0

Teaching:

Vascular Imaging: Atherosclerosis and Biomechanics	2010	1,5
College BM1150R / KVR 8 "Vascular imaging in the clinic "	2010	0,4
Imaging of carotid bifurcation atherosclerosis	2008	1,5
Student supervision - Tessa Jansen	2008	0,6
Student supervision - Zabi Fanyar	2008	0,6
Student supervision - Gerben Plas	2008	0,6
Student supervision - Tiziana de Simone	2008	0,6
Student supervision - Sharda Anroedh	2009	0,6
Student supervision - Adam Kurz	2009	0,6
Student supervision - Fufa Tori	2010	0,6

Curriculum Vitae

The author of this thesis was born on December 28, 1977 in The Hague, the Netherlands. The weather that day was fairly typical for the location and time of the year: the temperature was between 2.3°C and 7.9°C, averaging 4.7°C; there was 4.9 mm of precipitation for 5.0 hours and 1.5 hours of sunshine; the average wind speed was 3 Bft and came mostly from the west-south-west. The United Kingdom had only recently voted to remain in the European Community in a referendum on June 5, 1975.

After graduating from the Hondsrug College in Emmen in 1996, he studied Medicine at Leiden University. During his study he was involved in several research projects. In the Hubrecht Institute (Utrecht) he designed and developed a transgenic zebrafish strain with the artificial gene construct *PCNA promoter- [d2] -EYFP* which encodes fluorescent proteins in proliferating neural stem cells. In collaboration with the Inter University Ophthalmic Institute (Amsterdam) and the Westfries Gasthuis (Hoorn) he investigated a quantification method for straylight after penetrating keratoplasty with the Straylight Meter V1.23-β. At Leiden University Medical Center, he performed a literature study and co-authored a coursebook for the elective doctoral course *Safe motherhood in different world regions*.

After receiving his medical degree in 2005, he worked at the Department of Neurology at the Groene Hart Ziekenhuis in Gouda. In 2006 he started a research fellowship on vascular imaging in TIA and ischemic stroke at the Department of Radiology of Erasmus Medical Center in Rotterdam under supervision of Prof.dr. A. van der Lugt and Prof.dr. D.W.J. Dippel. The results of studies performed during this research period are described in the present thesis. In 2010, he started his residency in Radiology at the Erasmus Medical Center in Rotterdam. However, in 2013 he switched to a residency in Physical Medicine and Rehabilitation at Rijndam Rehabilitation Center and Erasmus Medical Center, both in Rotterdam. As of 2017, he is working as a physiatrist in the Leiden University Medical Center.


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