# Hyperglycemia and cerebral perfusion in acute ischemic stroke

Merel Luitse

| | |
|---|---|
| Cover photo | Ruta Nacional 52, Jujuy, Argentina |
| Layout | Renate Siebes \| Proefschrift.nu |
| Printed by | Proefschriftmaken.nl |
| ISBN | 978-90-393-6829-9 |

# Hyperglycemia and cerebral perfusion in acute ischemic stroke

Hyperglycemie en cerebrale perfusie bij een acuut herseninfarct
(met een samenvatting in het Nederlands)

PROEFSCHRIFT

ter verkrijging van de graad van doctor aan de
Universiteit Utrecht op gezag van de rector magnificus,
prof.dr. G.J. van der Zwaan, ingevolge het besluit van het
college voor promoties in het openbaar te verdedigen
op dinsdag 26 september 2017 des middags te 2.30 uur

door

Merel Janna Adriana Luitse

geboren op 11 september 1982
te Naarden

Promotoren: Prof.dr. G.J. Biessels
Prof.dr. L.J. Kappelle
Prof.dr. B.K. Velthuis

The research described in this thesis was supported by a grant of the Dutch Heart Foundation (DHF2008T034). Additional funding was provided by a grant of the NutsOhra Foundation (0903-012).

Financial support by the Dutch Heart Foundation for the publication of this thesis is gratefully acknowledged.

*Voor mijn ouders*

# TABLE OF CONTENTS

# CHAPTER 1

## General introduction

## ISCHEMIC STROKE

Ischemic stroke is a leading cause of mortality and long-term disability.[1,2] In 2010, 16.9 million people suffered from a first stroke worldwide.[2] Risk factors associated with ischemic stroke are advanced age, smoking, obesity, hypertension, dyslipidemia and diabetes mellitus.[3,4] In recent years, significant advances have been made in the management of acute ischemic stroke, including the implementation of stroke units, intravenous thrombolysis and endovascular treatment, with beneficial effect on functional outcome.[5–9] Nonetheless, a substantial number of patients still suffers from death and disability on the long-term.[2] To further improve long-term outcome after acute ischemic stroke, better understanding of underlying pathophysiology and enhanced diagnostic options and prediction of prognosis are needed.

This thesis focuses on two aspects of acute ischemic stroke. The first part concerns the application of CT imaging in the emergency setting and the prognostic value of CT angiography and CT perfusion in acute ischemic stroke. The second part addresses the importance of hyperglycemia as a vascular risk factor, its relation to poor outcome after ischemic stroke and its influence on cerebral perfusion, building on the CT techniques that are the focus of the first part of this thesis.

## CT IMAGING IN ACUTE ISCHEMIC STROKE

In patients with suspected ischemic stroke, CT imaging plays a critical role in the emergency setting. As treatment aimed at reperfusion should be administered as soon as possible, several questions concerning etiology, diagnosis, prognosis, and therapy need to be answered in a short period of time. CT imaging may help to answer these questions.

Non-contrast CT is used to exclude intracranial hemorrhage as cause of the symptoms. Furthermore, early ischemic changes, such as cortical swelling, loss of grey-white matter differentiation and a hyperdense vessel sign, may be visible on non-contrast CT and may support the diagnosis of ischemic stroke.[10] However, early ischemic changes are often still absent at the time of CT scanning, as it may take several hours before these changes become apparent.

In addition to non-contrast CT, CT angiography and CT perfusion are increasingly used in the diagnostic work-up of patients with suspected ischemic stroke in the emergency setting.[11,12] These techniques can easily be performed after the non-contrast CT within a 5- to 10-minute examination and are faster and more feasible than MRI and have around the clock availability in stroke clinics worldwide.

CT angiography provides information about the location and extent of intracranial and extracranial occlusions or stenosis.[13–15] In addition, the presence and patency of the collateral circulation can be identified.[16–18] CT perfusion can help to detect ischemia even when the non-contrast CT is still normal.[19] Perfusion abnormalities can be identified on the basis of an area with decreased cerebral blood flow and cerebral blood volume, and increased mean transit time and time to peak enhancement. These measures can help identify the infarct core and the penumbra, which is the part of the ischemic area that can still recover if adequate reperfusion is restored within hours after stroke onset.[20–23] Furthermore, CT perfusion may also help to distinguish ischemic stroke from stroke mimics such as a brain tumor, epilepsy or migraine.[24,25]

Yet, possible disadvantages and risks of the implementation of CT angiography and CT perfusion in the emergency setting also need to be considered, such as allergic reactions to CT contrast material and increased radiation exposure.[26–28] Another important safety concern regarding the use of CT contrast material is the potential development of acute nephropathy.[29,30] Acute nephropathy after contrast administration is associated with increased mortality rates and prolonged hospital stay.[30]

CT angiography and CT perfusion thus make it possible to support the diagnosis and extent of ischemic stroke and may help to reject alternative causes. These techniques may also have additional value in prediction of outcome after ischemic stroke. To assess this prognostic value, the Dutch acute Stroke Study (DUST) was initiated in 2009.[31] The DUST is a prospective multicenter cohort study in The Netherlands including almost 1400 patients with acute ischemic stroke.[32] With the large amount of prospective data of DUST, several questions related to the use of CT angiography and CT perfusion and acute ischemic stroke and related risk factors can be answered.

In **PART I** of this thesis, the following questions related to the use of CT angiography and CT perfusion are addressed:

1. Can CT angiography and CT perfusion improve prediction of outcome in patients with acute ischemic stroke?
2. How often does an occluded extracranial carotid artery in the acute stage of ischemic stroke recanalize and how often does a residual high-grade stenosis remain after recanalization in patients with acute ischemic stroke?
3. What is the occurrence of acute nephropathy after CT angiography and CT perfusion in patients with acute ischemic stroke?

## HYPERGLYCEMIA AND ACUTE ISCHEMIC STROKE

Disturbed glucose metabolism is common in patients with ischemic stroke. Chronic hyperglycemia as a condition can represent diabetes type I, type II, or prediabetic stages. The risk of stroke is already higher in prediabetic stages, and diabetes is associated with a two times increased risk of ischemic stroke.[33,34] Apart from being a risk factor for the occurrence of ischemic stroke, chronic hyperglycemia may also affect functional outcome after ischemic stroke. Long-term functional outcome is worse in patients with diabetes compared to those without.[35] However, controversy still exists about the association between all cause chronic hyperglycemia and poor outcome after acute ischemic stroke.

Ischemic stroke itself can also give rise to abnormalities in glucose metabolism. Hyperglycemia on admission occurs in 30–40 percent of the patients presenting with ischemic stroke.[36] Most of these patients are not known with diabetes.[37]

This acute hyperglycemia on admission may reflect pre-existent, unrecognised diabetes or prediabetic stages of impaired glucose metabolism. However, more often it is the result of a stress response, typically named stress hyperglycemia.[38] Glucose concentrations are raised in people with stress hyperglycemia but revert to normal after discharge from hospital.[38] Although high levels of glucose on admission do not distinguish between stress hyperglycemia and diabetes, raised amounts of hemoglobin A1c in the acute stage could help to identify people with pre-existent chronic hyperglycemia (e.g., diabetes or prediabetic stages).[38,39]

High glucose levels in the acute stage of ischemic stroke are associated with increased mortality and poor functional outcome.[37] Moreover, patients with admission hyperglycemia tend to have larger infarct volumes than patients with normal glucose levels.[40,41] Several mechanisms have been identified through which hyperglycemia could aggravate cerebral damage in ischemic stroke, including impaired recanalization and reperfusion injury.[42] With regard to abnormalities in cerebral perfusion, hyperglycemia is likely to affect salvage of the penumbra. However, the course and timing of this process are still unknown.[42]

PART II of this thesis focuses on two questions related to hyperglycemia in patients with acute ischemic stroke:

1. Is *chronic* hyperglycemia prior to acute ischemic stroke related to poor functional outcome and how is acute hyperglycemia on admission involved in this relation?
2. What is the influence of *acute* admission hyperglycemia on cerebral perfusion, final infarct volume and outcome in acute ischemic stroke?

# OUTLINE OF THE THESIS

## PART I – CT imaging in acute ischemic stroke

**Chapter 2** addresses whether CT angiography and CT perfusion can predict clinical outcome after acute ischemic stroke. We first relate several individual CT angiography and CT perfusion parameters to clinical outcome. Next, we determine if CT angiography and CT perfusion have additional value on top of other predictors of clinical outcome that can easily be collected in the emergency setting.

With the availability of CT angiography in the emergency setting, an acute occlusion of the extracranial carotid artery is regularly found. Recanalization after an occlusion in the acute stage may occur more commonly than previously assumed.[43] If a high-grade stenosis persists after recanalization, this may have important implications for subsequent treatment because the recurrence rate of ischemic stroke in patients with high-grade stenosis is significant.[44,45] Therefore in **Chapter 3**, we study the frequency of residual high-grade stenosis on follow-up imaging in patients with an acute symptomatic occlusion of the extracranial carotid artery.

As CT angiography and CT perfusion are increasingly used in the emergency setting, this increases the risk of potential complications. **Chapter 4** addresses the occurrence of acute nephropathy as one of the possible complications after CT angiography and CT perfusion. In the emergency setting, renal function is often still unknown when patients with suspected ischemic stroke undergo CT angiography and CT perfusion. However, waiting for the renal function laboratory results before starting treatment may cause unacceptable delay in the acute stage of ischemic stroke. Therefore, more clarity is needed regarding the risk of acute nephropathy after contrast administration after CT imaging in the acute stage of ischemic stroke.

## PART II – Hyperglycemia and acute ischemic stroke

**Chapter 5** provides an overview of the interplay between glucose metabolism and acute ischemic stroke and focuses on clinical implications for prevention and management in the acute stage. We address the epidemiology of the association between diabetes, admission hyperglycemia and ischemic stroke, highlighting potentially modifiable risk factors and long-term outcome.

Acute hyperglycemia on admission is an independent predictor of poor functional outcome.[37] By comparison, there is conflicting evidence on the association between

chronic hyperglycemia and poor outcome.[46–50] In **Chapter 6**, we sought to determine if chronic hyperglycemia is associated with poor functional outcome in patients with acute ischemic stroke. In addition, we evaluate the role of vascular risk factors and acute hyperglycemia on admission in this context.

While the association between acute hyperglycemia on admission and poor outcome after ischemic stroke is well established,[37] the pathophysiology underlying this association remains unclear. Abnormalities in cerebral perfusion, such as reduced penumbral salvage, have been suggested to play an important role.[42]

It is unknown if cerebral perfusion is already compromised in the acute stage of ischemic stroke and how this is related to final infarct volume. For the development of future therapeutic interventions, further insight in the underlying mechanism of hyperglycemia and cerebral perfusion is required. In **Chapter 7** and **Chapter 8**, we explore the association between hyperglycemia on admission and cerebral perfusion in the acute stage of ischemic stroke. **Chapter 8** additionally assesses the effect of hyperglycemia on admission on final infarct volume and functional outcome.

In **Chapter 9**, we discuss the research presented in this thesis and its implications for clinical practice and future research.

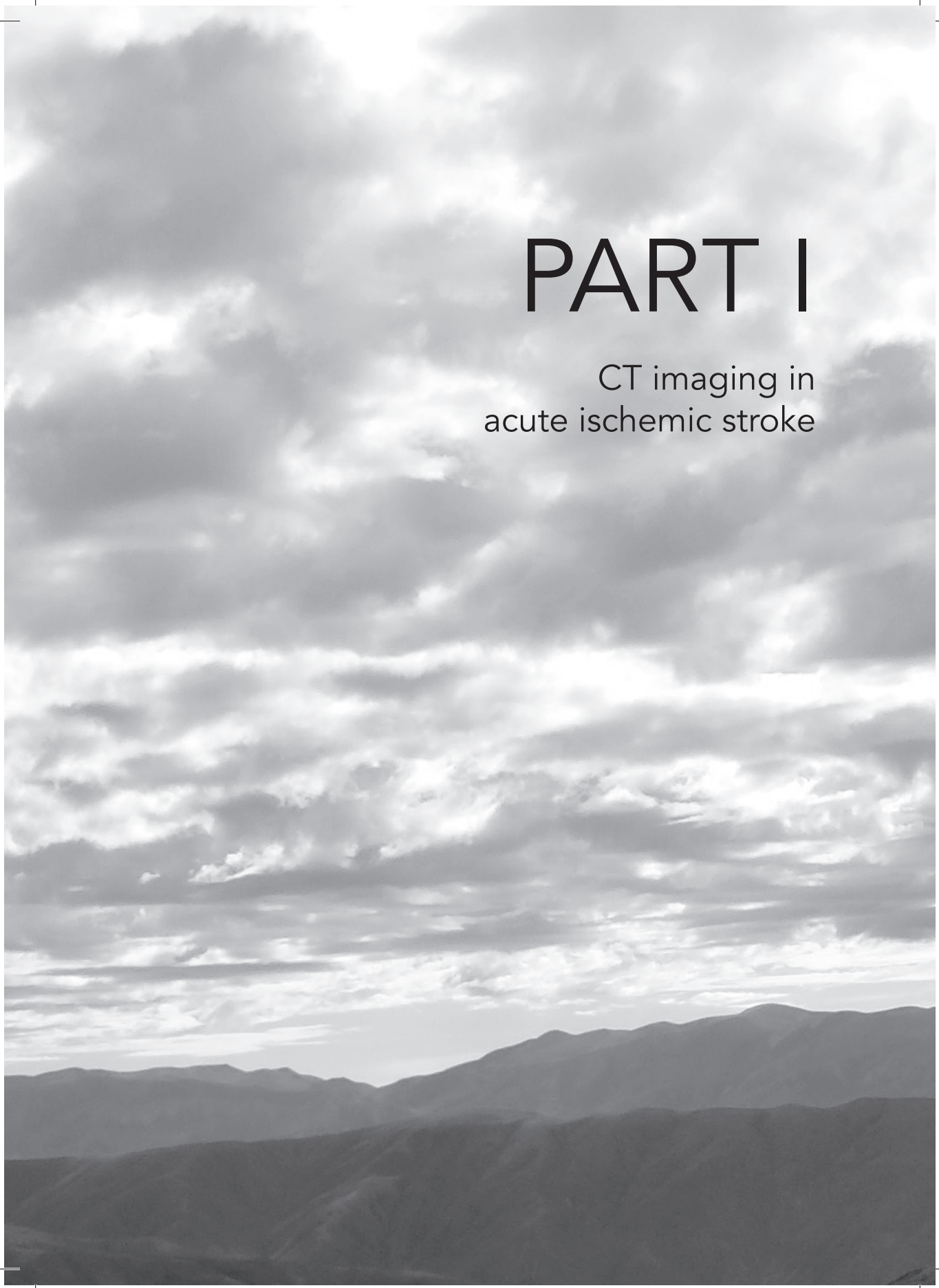
# REFERENCES


1. Feigin VL, Krishnamurthi R V., Parmar P, Norrving B, Mensah GA, Bennett DA, et al. Update on the Global Burden of Ischemic and Hemorrhagic Stroke in 1990-2013: The GBD 2013 Study. Neuroepidemiology. 2015;45:161–176.
2. Feigin VL, Forouzanfar MH, Krishnamurthi R, Mensah GA, Connor M, Bennett DA, et al. Global and regional burden of stroke during 1990-2010: Findings from the Global Burden of Disease Study 2010. Lancet. 2014;383:245–255.
3. O 'Donnell MJ, Chin SL, Rangarajan S, Xavier D, Liu L, Zhang H, et al. Global and regional eff ects of potentially modifi able risk factors associated with acute stroke in 32 countries (INTERSTROKE): a case-control study. Lancet. 2016;388:761–775.
4. Feigin VL, Roth GA, Naghavi M, Parmar P, Krishnamurthi R, Chugh S, et al. Global burden of stroke and risk factors in 188 countries, during 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet Neurol. 2016;15:913–924.
5. Candelise L, Gattinoni M, Bersano A, Micieli G, Sterzi R, Morabito A. Stroke-unit care for acute stroke patients: an observational follow-up study. Lancet. 2007;369:299–305.
6. Lees KR, Bluhmki E, von Kummer R, Brott TG, Toni D, Grotta JC, et al. Time to treatment with intravenous alteplase and outcome in stroke: an updated pooled analysis of ECASS, ATLANTIS, NINDS, and EPITHET trials. Lancet. 2010;375:1695–1703.
7. Hacke W, Kaste M, Bluhmki E, Brozman M, Davalos A, Guidetti D, et al. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. N. Engl. J. Med. 2008;359:1317–1329.
8. Emberson J, Lees KR, Lyden P, Blackwell L, Albers G, Bluhmki E, et al. Effect of treatment delay, age, and stroke severity on the effects of intravenous thrombolysis with alteplase for acute ischaemic stroke: A meta-analysis of individual patient data from randomised trials. Lancet. 2014;384:1929–1935.

9. Goyal M, Menon BK, Van Zwam WH, Dippel DWJ, Mitchell PJ, Demchuk AM, et al. Endovascular thrombectomy after large-vessel ischaemic stroke: A meta-analysis of individual patient data from five randomised trials. Lancet. 2016;387:1723–1731.
10. von Kummer R, Meyding-Lamade U, Forsting M, Rosin L, Rieke K, Hacke W, et al. Sensitivity and prognostic value of early CT in occlusion of the middle cerebral artery trunk. AJNR. Am. J. Neuroradiol. 1994;15:8–9.
11. Smith WS, Roberts HC, Chuang NA, Ong KC, Lee TJ, Johnston SC, et al. Safety and feasibility of a CT protocol for acute stroke: combined CT, CT angiography, and CT perfusion imaging in 53 consecutive patients. AJNR.American J. Neuroradiol. 2003;24:688–690.
12. Wintermark M, Flanders AE, Velthuis B, Meuli R, van Leeuwen M, Goldsher D, et al. Perfusion-CT assessment of infarct core and penumbra: receiver operating characteristic curve analysis in 130 patients suspected of acute hemispheric stroke. Stroke. 2006;37:979–985.
13. Josephson SA, Bryant SO, Mak HK, Johnston SC, Dillon WP, Smith WS. Evaluation of carotid stenosis using CT angiography in the initial evaluation of stroke and TIA. Neurology. 2004;63:457–460.
14. Saarinen JT, Rusanen H, Sillanpää N. Collateral score complements clot location in predicting the outcome of intravenous thrombolysis. Am. J. Neuroradiol. 2014;35:1892–1896.
15. Tan IYL, Demchuk AM, Hopyan J, Zhang L, Gladstone D, Wong K, et al. CT angiography clot burden score and collateral score: Correlation with clinical and radiologic outcomes in acute middle cerebral artery infarct. Am. J. Neuroradiol. 2009;30:525–531.
16. Lima FO, Furie KL, Silva GS, Lev MH, Camargo ÉCS, Singhal AB, et al. The pattern of leptomeningeal collaterals on ct angiography is a strong predictor of long-term functional outcome in stroke patients with large vessel intracranial occlusion. Stroke. 2010;41:2316–2322.
17. Menon BK, Smith EE, Coutts SB, Welsh DG, Faber JE, Goyal M, et al. Leptomeningeal collaterals are associated with modifiable metabolic risk factors. Ann. Neurol. 2013;74:241–248.
18. Miteff F, Levi CR, Bateman GA, Spratt N, McElduff P, Parsons MW. The independent predictive utility of computed tomography angiographic collateral status in acute ischaemic stroke. Brain. 2009;132:2231–2238.
19. Biesbroek JM, Niesten JM, Dankbaar JW, Biessels GJ, Velthuis BK, Reitsma JB, et al. Diagnostic Accuracy of CT Perfusion Imaging for Detecting Acute Ischemic Stroke: A Systematic Review and Meta-Analysis. Cerebrovasc. Dis. 2013;35:493–501.
20. Wintermark M, Reichhart M, Cuisenaire O, Maeder P, Thiran JP, Schnyder P, et al. Comparison of admission perfusion computed tomography and qualitative diffusion- and perfusion-weighted magnetic resonance imaging in acute stroke patients. Stroke. 2002;33:2025–2031.
21. Schaefer PW, Souza L, Kamalian S, Hirsch JA, Yoo AJ, Kamalian S, et al. Limited reliability of computed tomographic perfusion acute infarct volume measurements compared with diffusion-weighted imaging in anterior circulation stroke. Stroke. 2015;46:419–424.
22. Schramm P, Schellinger PD, Klotz E, Kallenberg K, Fiebach JB, Kulkens S, et al. Comparison of perfusion computed tomography and computed tomography angiography source images with perfusion-weighted imaging and diffusion-weighted imaging in patients with acute stroke of less than 6 hours' duration. Stroke. 2004;35:1652–1658.
23. Muir KW, Halbert HM, Baird TA, McCormick M, Teasdale E. Visual evaluation of perfusion computed tomography in acute stroke accurately estimates infarct volume and tissue viability. J. Neurol. Neurosurg. Psychiatry. 2006;77:334–339.
24. Nieuwkamp DJ, Van Der Schaaf IC, Biessels GJ. Migraine aura presenting as dysphasia with global cognitive dysfunction and abnormalities on perfusion CT. Cephalalgia. 2010;30:1007–1009.
25. Huisman MHB, Velthuis BK, Kappelle LJ, Biessels GJ. Perfusion CT in suspected ischaemic stroke: Red flags that should have been blue. J. Neurol. 2011;258:155–158.
26. Diekmann S, Siebert E, Juran R, Roll M, Deeg W, Bauknecht HC, et al. Dose exposure of patients undergoing comprehensive stroke imaging by multidetector-row CT: Comparison of 320-detector row and 64-detector row CT scanners. Am. J. Neuroradiol. 2010;31:1003–1009.
27. Tong E, Wintermark M. CTA-enhanced perfusion CT: an original method to perform ultra-low-dose CTA-enhanced perfusion CT. Neuroradiology. 2014;955–964.

28. Namasivayam S, Kalra MK, Torres WE, Small WC. Adverse reactions to intravenous iodinated contrast media: A primer for radiologists. Emerg. Radiol. 2006;12:210–215.
29. Dittrich R, Akdeniz S, Kloska SP, Fischer T, Ritter MA, Seidensticker P, et al. Low rate of contrast-induced Nephropathy after CT perfusion and CT angiography in acute stroke patients. J. Neurol. 2007;254:1491–1497.
30. Hopyan JJ, Gladstone DJ, Mallia G, Schiff J, Fox AJ, Symons SP, et al. Renal safety of CT angiography and perfusion imaging in the emergency evaluation of acute stroke. AJNR. American J. Neuroradiol. 2008;29:1826–1830.
31. van Seeters T, Biessels GJ, van der Schaaf IC, Dankbaar JW, Horsch AD, Luitse MJ, et al. Prediction of outcome in patients with suspected acute ischaemic stroke with CT perfusion and CT angiography: the Dutch acute stroke trial (DUST) study protocol. BMC Neurol. 2014;14:37.
32. Van Seeters T, Biessels GJ, Kappelle LJ, Van Der Schaaf IC, Dankbaar JW, Horsch AD, et al. The Prognostic Value of CT Angiography and CT Perfusion in Acute Ischemic Stroke. Cerebrovasc. Dis. 2015;40:258–269.
33. Unwin N, Shaw J, Zimmet P, Alberti KG. Impaired glucose tolerance and impaired fasting glycaemia: the current status on definition and intervention. Diabet. Med. 2002;19:708–723.
34. Sarwar N, Gao P, Seshasai SR, Gobin R, Kaptoge S, Di AE, et al. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. Lancet. 2010;375:2215–2222.
35. Megherbi SE, Milan C, Minier D, Couvreur G, Osseby G V, Tilling K, et al. Association between diabetes and stroke subtype on survival and functional outcome 3 months after stroke: data from the European BIOMED Stroke Project. Stroke. 2003;34:688–694.
36. Uyttenboogaart M, Koch MW, Stewart RE, Vroomen PC, Luijckx GJ, De KJ. Moderate hyperglycaemia is associated with favourable outcome in acute lacunar stroke. Brain. 2007;130:1626–1630.
37. Capes SE, Hunt D, Malmberg K, Pathak P, Gerstein HC. Stress hyperglycemia and prognosis of stroke in nondiabetic and diabetic patients: a systematic overview. Stroke. 2001;32:2426–2432.
38. Dungan KM, Braithwaite SS, Preiser JC. Stress hyperglycaemia. Lancet. 2009;373:1798–1807.
39. American Diabetes Association et al. Standards of medical care in diabetes—2014. Diabetes Care. 2014;37 Suppl 1:S14-80
40. Baird TA, Parsons MW, Phanh T, Butcher KS, Desmond PM, Tress BM, et al. Persistent poststroke hyperglycemia is independently associated with infarct expansion and worse clinical outcome. Stroke. 2003;34:2208–2214.
41. Parsons MW, Barber PA, Desmond PM, Baird TA, Darby DG, Byrnes G, et al. Acute hyperglycemia adversely affects stroke outcome: a magnetic resonance imaging and spectroscopy study. Ann. Neurol. 2002;52:20–28.
42. Kruyt ND, Biessels GJ, Devries JH, Roos YB. Hyperglycemia in acute ischemic stroke: pathophysiology and clinical management. Nat.Rev.Neurol. 2010;6:145–155.
43. Meves SH, Muhs A, Federlein J, Büttner T, Przuntek H, Postert T, et al. Recanalization of acute symptomatic occlusions of the internal carotid artery. J. Neurol. 2002;249:188–192.
44. Blaser T, Hofmann K, Buerger T, Effenberger O, Wallesch C-W, Goertler M. Risk of Stroke, Transient Ischemic Attack, and Vessel Occlusion Before Endarterectomy in Patients With Symptomatic Severe Carotid Stenosis. Stroke. 2002;33:1057–1062.
45. J Johansson E, Wester P. Recurrent stroke risk is high after a single cerebrovascular event in patients with symptomatic 50-99% carotid stenosis: a cohort study. BMC Neurol. 2014;14:23.
46. Kuwashiro T, Sugimori H, Ago T, Kuroda J, Kamouchi M, Kitazono T. The impact of predisposing factors on long-term outcome after stroke in diabetic patients: The Fukuoka Stroke Registry. Eur. J. Neurol. 2013;20:921–927.
47. Kamouchi M, Matsuki T. Prestroke Glycemic Control Is Associated With the Functional Outcome in Acute Ischemic Stroke. Stroke. 2011;42:2788-2794
48. Lei C, Wu B, Liu M, Chen Y. Association between hemoglobin A1C levels and clinical outcome in ischemic stroke patients with or without diabetes. J Clin Neurosci. 2015;22:498-503.
49. Wu S, Wang C, Jia Q, Liu G, Hoff K, Wang X, et al. HbA1c is associated with increased all-cause mortality in the first year after acute ischemic stroke. Neurol. Res. 2014;36:444–452.

50. Hjalmarsson C, Manhem K, Bokemark L, Andersson B. The role of prestroke glycemic control on severity and outcome of acute ischemic stroke. Stroke Res Treat. 2014;2014:694569.



# PART I

## CT imaging in acute ischemic stroke

# CHAPTER 2

## The prognostic value of CT angiography and CT perfusion in acute ischemic stroke

Tom van Seeters, Geert Jan Biessels, L. Jaap Kappelle, Irene C van der Schaaf, Jan Willem Dankbaar, Alexander D. Horsch, Joris M. Niesten, Merel J. Luitse, Charles B. Majoie, Jan Albert Vos, Wouter J. Schonewille, Marianne A. van Walderveen, Marieke J. Wermer, Lucien E. Duijm, Koos Keizer, Joseph C. Bot, Marieke C. Visser, Aad van der Lugt, Diederik W. Dippel, F. Oskar Kesselring, Jeannette Hofmeijer, Geert J. Lycklama à Nijeholt, Jelis Boiten, Willem Jan van Rooij, Paul L. de Kort, Yvo B. Roos, Ewoud J. van Dijk, C. Constantijn Pleiter, Willem P. Mali, Yolanda van der Graaf, Birgitta K. Velthuis, on behalf of Dutch acute Stroke Study (DUST)

Cerebrovascular Diseases. 2015;40:258–226

# ABSTRACT

## Background

CT angiography (CTA) and CT perfusion (CTP) are important diagnostic tools in acute ischemic stroke. We investigated the prognostic value of CTA and CTP for clinical outcome and determined whether they have additional prognostic value over patient characteristics and non-contrast CT (NCCT).

## Methods

We included 1374 patients with suspected acute ischemic stroke in the prospective multicenter Dutch acute stroke study. Sixty percent of the cohort was used for deriving the predictors and the remaining 40% for validating them. We calculated the predictive values of CTA and CTP predictors for poor clinical outcome (modified Rankin Scale score 3–6). Associations between CTA and CTP predictors and poor clinical outcome were assessed with odds ratios (OR). Multivariable logistic regression models were developed based on patient characteristics and non-contrast CT predictors, and subsequently CTA and CTP predictors were added. The increase in area under the curve (AUC) value was determined to assess the additional prognostic value of CTA and CTP. Model validation was performed by assessing discrimination and calibration.

## Results

Poor outcome occurred in 501 patients (36.5%). Each of the evaluated CTA measures strongly predicted outcome in univariable analyses: the positive predictive value (PPV) was 59% for Alberta Stroke Program Early CT Score (ASPECTS) ≤7 on CTA source images (OR 3.3; 95% confidence interval (CI) 2.3–4.8), 63% for presence of a proximal intracranial occlusion (OR 5.1; 95% CI 3.7–7.1), 66% for poor leptomeningeal collaterals (OR 4.3; 95% CI 2.8–6.6), and 58% for a >70% carotid or vertebrobasilar stenosis/occlusion (OR 3.2; 95% CI 2.2–4.6). The same applied to the CTP measures, as the PPVs were 65% for ASPECTS ≤7 on cerebral blood volume maps (OR 5.1; 95% CI 3.7–7.2) and 53% for ASPECTS ≤7 on mean transit time maps (OR 3.9; 95% CI 2.9–5.3). The prognostic model based on patient characteristics and NCCT measures was highly predictive for poor clinical outcome (AUC 0.84; 95% CI 0.81–0.86). Adding CTA and CTP predictors to this model did not improve the predictive value (AUC 0.85; 95% CI 0.83–0.88)). In the validation cohort, the AUC values were 0.78 (95% CI 0.73–0.82) and 0.79 (95% CI 0.75–0.83), respectively. Calibration of the models was satisfactory.

## Conclusions

In patients with suspected acute ischemic stroke, admission CTA and CTP parameters are strong predictors of poor outcome and can be used to predict long-term clinical outcome. In multivariable prediction models, however, their additional prognostic value over patient characteristics and NCCT is limited in an unselected stroke population.

# INTRODUCTION

Ischemic stroke is an important cause of death and long-term disability. When a patient is admitted to the hospital with symptoms of acute ischemic stroke, the possibilities for acute treatment need to be considered and the underlying cause should be identified. Early individualized assessment of expected clinical outcome can help to guide treatment decisions.

CT angiography (CTA) and CT perfusion (CTP) may play an important role in answering these questions. CTA offers the possibility to visualize the location, extent, and aspect of an arterial occlusion, may reveal important information about the collateral circulation, and depicts the extracranial vessels from the aortic arch.[1–3] With CTP, various tissue perfusion parameters can be used to differentiate reversible from irreversible ischemic brain tissue.[4–6] Moreover, CTA and CTP can guide patient selection for intra-arterial treatment.[7–11]

In addition to providing diagnostic information and guiding therapy, CTA and CTP can also be used to predict clinical outcome. However, this has not been studied in large prospective series of unselected patients with acute ischemic stroke. We aimed to assess the prognostic value of CTA and CTP, and whether they could improve the prediction of clinical outcome in prognostic models also including patient characteristics and non-contrast CT (NCCT) measures.

# METHODS

## Study population

The Dutch acute stroke study (DUST) was a prospective observational cohort study in 6 university and 8 non-university hospitals in The Netherlands. Patients older than 18 years were included between May 2009 and August 2013 if they had symptoms suspected to be caused by ischemic stroke. Inclusion criteria were symptom duration <9 hours, and National Institutes of Health Stroke Scale (NIHSS) ≥2, or ≥1 if intravenous thrombolysis with recombinant tissue type plasminogen activator (IV-rtPA) was indicated. Patients were not eligible if another diagnosis on NCCT such as intracranial hemorrhage explained the symptoms. Patients with an unknown onset time were included if the elapsed time between the time they were last seen without symptoms and imaging was <9 hours. All patients underwent neurological examination, NCCT, CTA, and CTP.

The cohort was split in 2 separate groups. The first group was used to perform all univariable analyses and to make the multivariable prediction models (derivation set). This group

consisted of the first 60% of the patients, based on the date of inclusion. The second group consisted of the remaining 40% of the patients and was used for the validation of the models (validation set). With this approach, we were able to develop the prediction models and to assess their validity in one single study. Ethical approval was obtained from the medical ethics committee of the University Medical Center Utrecht, The Netherlands, in addition to obtaining local approval from participating hospitals. Informed consent was obtained from patients or their legal representatives. The medical ethics committee waived the need for informed consent for patients who died before informed consent could be obtained. A detailed description of the study protocol has been published previously.[12]

## Patient characteristics

Patient characteristics that were used as predictors were age, stroke severity (quintiles of NIHSS), time from onset to imaging (hours), dependency prior to the stroke symptoms (modified Rankin Scale (mRS) score of 3–6), glucose level (in mmol/L), and whether treatment had been given (either IV-rtPA, intra-arterial thrombolysis (IAT), mechanical thrombectomy (MT), or any combination).[13–18]

## Imaging predictors

All admission scans were assessed in the University Medical Center Utrecht, The Netherlands, by an observer with at least 5 years of experience in neurovascular imaging (from a pool of 3 observers). Except for the side of the symptoms, observers were blinded for all clinical information, including follow-up scans and clinical outcome.[12] CTA and CTP imaging were performed on 40- to 320-detector CT scanners (Philips, Siemens, GE, Toshiba). Depending on the hospital and CT scanner, NCCT was performed with 120 kV, 300–375 mAs, and 5 mm slice thickness. CTP scans were generally performed with 80 kV, 150 mAs, and 5 mm slice thickness. Forty milliliter of non-ionic contrast material followed by 40 ml of saline were injected with a flow of 6 ml/s. Images were acquired every 2 seconds for 50 seconds after the initiation of contrast injection. The Alberta Stroke Program Early CT Score (ASPECTS) was used to quantify the amount of ischemia.[19,20] CTP coverage, ranging from 40 mm to full brain coverage, included at least the basal ganglia up to the lateral ventricles to ensure that both ASPECTS levels were included. If a stroke in the posterior circulation was suspected, the CTP slab was lowered to include the posterior circulation ASPECTS (pcASPECTS) levels.[3,12] For CTA, from aortic arch to cranium vertex, 50–70 ml of contrast material followed by 40 ml of saline was injected with a flow of 6 ml/s. The scan delay after contrast injection was calculated either from the time to peak arterial enhancement on CTP, or by a trigger based on Hounsfield unit threshold measurement in the aortic arch.

### NCCT predictors

NCCT predictors included the presence of a hyperdense vessel sign and an ASPECTS ≤7.[18–21] In case of a posterior circulation stroke, pcASPECTS was used.[3]

### CTA predictors

CTA source images (CTA-SI) were evaluated to detect brain tissue with diminished contrast enhancement, corresponding to ischemic areas with diminished tissue perfusion. ASPECTS ≤7 on these CTA-SI was used as a predictor (or pcASPECTS in case of a posterior circulation stroke). Other CTA predictors included the presence of a proximal intracranial occlusion (either intracranial internal carotid artery, M1 segment, P1 segment, or basilar artery), poor enhancement of leptomeningeal collateral circulation (<50% of affected territory), and the presence of a >70% stenosis/occlusion in either the internal carotid, vertebral, or basilar artery, supplying the affected (symptomatic) brain area.[1–3,22,23]

### CTP predictors

CTP predictors were ASPECTS ≤7 on cerebral blood volume (CBV) and mean transit time (MTT) maps (or pcASPECTS in case of a posterior circulation stroke), penumbra and infarct core size ($cm^2$), and penumbra/infarct core index (penumbra size / (penumbra + infarct core size)).[6,24] The software for CTP post-processing (Extended Brilliance Workstation version 4.5, Philips Healthcare) has been validated previously.24 Based upon previously reported MTT and CBV thresholds for this CTP post-processing software, threshold-defined penumbra and infarct core maps were calculated.[24] The total ischemic area was defined as the area with an MTT ≥145% compared to the contralateral hemisphere. Within this area, infarct core was separated from the penumbra by a CBV value <2.0 ml/100 g. Differences in CTP coverage were accounted for by using the sum of penumbra and infarct core size on both ASPECTS levels, and by calculating the penumbra/infarct core index for these 2 levels. In the multivariable analyses, the infarct core size was used instead of the penumbra size and penumbra/infarct core index, because it had the strongest predictive value for poor clinical outcome in univariable analyses.

### Clinical outcome

The primary outcome measure was poor clinical outcome after 90 days. Poor outcome was defined as a score of 3–6 on the mRS.[25] The 90-day mRS was collected over phone by a trained research nurse or neurologist.[26]

# ANALYSES

## Univariable models

In the derivation set, logistic regression was used to assess the relation between each of the patient characteristics and CT predictors, and clinical outcome. This was expressed in odds ratios with 95% confidence interval (CI). We calculated the positive predictive value (PPV) for all predictors, indicating the probability of poor clinical outcome if the predictors are abnormal. Single imputation was performed to deal with missing values. To minimize the effect of outliers, continuous predictors were truncated at the first and 99$^{th}$ percentile.[27]

## Multivariable prediction models

To assess whether CTA and CTP could improve the predictive value of patient characteristics and NCCT measures, different multivariable logistic regression models were fitted in the derivation set. The first model included patient characteristics and NCCT measures. In the next 2 models, we added either CTA or CTP predictors to the first model. In the final model, we added both CTA and CTP predictors to the model with patient characteristics and NCCT. Penalized maximum likelihood estimation was used to correct for optimism and shrink the model coefficients. The optimal penalty factor was obtained by maximizing the penalized Akaike's Information Criterion.[27]

Discrimination, which is the ability to differentiate between patients with good and poor outcome, was assessed with receiver operator characteristics (ROC) analyses and their corresponding area under the curve (AUC). Differences in AUC values were tested for statistical significance.[28] Calibration, which reflects the agreement between predicted probabilities and actual (observed) outcomes, was evaluated with calibration plots. Goodness-of-fit was tested with the Hosmer-Lemeshow test. The multivariable prediction models were validated in the validation set. Statistical analyses were performed with R version 3.0.2.

# RESULTS

In total, 1476 patients were included in the study (Figure 2.1). Eighty-three patients (6%) were excluded because scan data were incomplete and 19 patients (1%) were excluded because of missing mRS scores at 90-day follow-up. The remaining study population consisted of 1374 patients. Poor clinical outcome at 90 days occurred in 501 patients

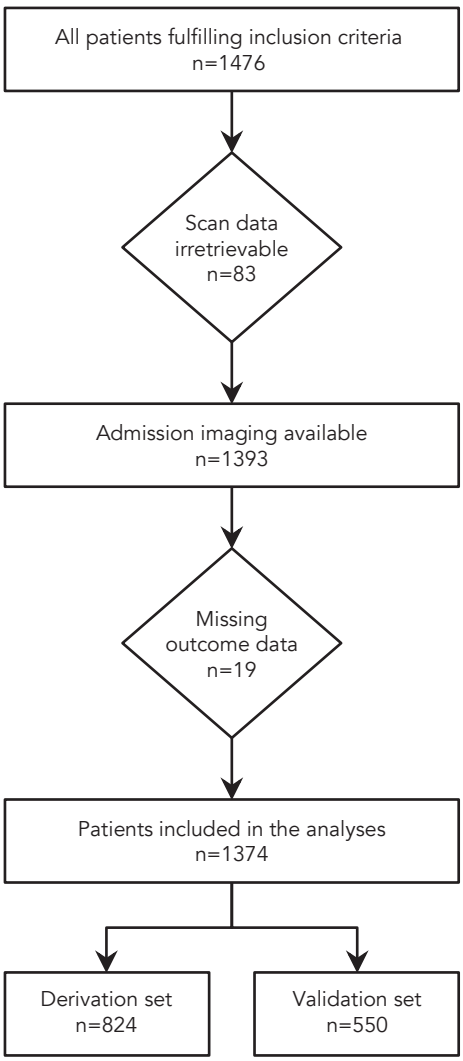



Figure 2.1. Flowchart depicting the number of patients included in the study and remaining for the analyses.

(36%). Abnormalities on CTA and CTP were very common and ranged from 13% (172 patients) for the presence of poor leptomeningeal collaterals to 39% (510 patients) for ASPECTS ≤7 on MTT maps. The discharge diagnosis was ischemic stroke in 1223 patients (89%). The proportion of patients with a posterior circulation stroke was 18% (247 patients). Additional baseline characteristics are presented in Table 2.1.

Table 2.1. Baseline characteristics

| | All patients (n=1374) | Derivation set (n=824) | Validation set (n=550) |
|---|---|---|---|
| Age (years) | 67.2 (14.2) | 67.7 (14.1) | 66.5 (14.1) |
| Male sex | 788 (57.4) | 480 (58.3) | 308 (56.0) |
| Stroke severity (NIHSS) | 6 (3-12) | 7 (3-13) | 5 (3-11) |
| Pre-admission mRS >2 | 82 (6.0) | 48 (5.9) | 34 (6.2) |
| Time from symptom onset to scan (minutes) | 118 (74–189) | 115 (73–182) | 124 (76–197) |
| IV-rtPA | 861 (62.7) | 526 (63.8) | 335 (60.9) |
| Endovascular treatment (with or without IV-rtPA) | 80 (5.8) | 53 (6.4) | 27 (4.9) |
| Smoking | 372 (29.8) | 226 (30.2) | 146 (29.1) |
| Glucose (mmol/L) | 6.6 (5.8–8.0) | 6.6 (5.8–7.9) | 6.7 (5.8–8.3) |
| Systolic blood pressure (mmHg) | 157.6 (28.9) | 156.5 (27.9) | 159.2 (30.3) |
| Diastolic blood pressure (mmHg) | 85.8 (17.2) | 85.2 (17.0) | 86.6 (17.6) |
| Medical history | | | |
| Ischemic stroke or TIA | 335 (24.6) | 204 (24.9) | 131 (24.2) |
| Hypertension | 711 (52.4) | 447 (54.8) | 264 (48.8) |
| Diabetes | 206 (15.1) | 127 (15.5) | 79 (14.5) |
| Hyperlipidemia | 447 (33.6) | 266 (33.2) | 181 (34.2) |
| Atrial fibrillation | 175 (12.9) | 101 (12.5) | 74 (13.6) |
| Non-contrast CT findings | | | |
| Hyperdense vessel sign | 283 (20.6) | 190 (23.1) | 93 (16.9) |
| ASPECTS† | 10 (10–10) | 10 (10–10) | 10 (10–10) |
| ASPECTS ≤7† | 123 (9.1) | 83 (10.2) | 40 (7.4) |

| | | | |
|---|---|---|---|
| CT angiography findings | | | |
| CT angiography source images ASPECTS† | 10 (9–10) | 10 (9–10) | 10 (9–10) |
| CT angiography source images ASPECTS ≤7† | 247 (18.3) | 149 (18.4) | 98 (18.1) |
| Proximal intracranial occlusion | 347 (25.6) | 219 (27.0) | 128 (23.6) |
| Poor leptomeningeal collaterals | 172 (12.7) | 108 (13.3) | 64 (11.8) |
| Significant carotid or vertebrobasilar stenosis/occlusion | 245 (18.3) | 149 (18.6) | 96 (17.9) |
| CT perfusion findings | | | |
| CBV ASPECTS† | 10 (8–10) | 10 (8–10) | 10 (8–10) |
| CBV ASPECTS ≤7† | 286 (21.9) | 178 (22.8) | 108 (20.7) |
| MTT ASPECTS† | 9 (5–10) | 9 (5–10) | 9 (5–10) |
| MTT ASPECTS ≤7† | 510 (39.1) | 317 (40.5) | 193 (37.0) |
| Perfusion deficit in MCA territory | 648 (49.3) | 396 (50.4) | 252 (47.7) |
| Penumbra size ($cm^2$)* | 21.5 (8.5–39.0) | 20.5 (8.3–37.6) | 24.7 (8.7–43.5) |
| Infarct core size ($cm^2$)* | 6.4 (1.5–20.5) | 7.0 (1.7–22.2) | 4.9 (1.0–19.4) |
| Penumbra/infarct core index* | 0.84 (0.55–1.00) | 0.81 (0.51–0.99) | 0.87 (0.60–1.00) |
| Discharge diagnosis | | | |
| Ischemic stroke | 1223 (89.4) | 734 (89.4) | 489 (89.4) |
| Transient ischemic attack | 85 (6.2) | 49 (6.0) | 36 (6.6) |
| Non-ischemic | 60 (4.4) | 38 (4.6) | 22 (4.0) |
| Clinical outcome | | | |
| Poor outcome at 90 days (mRS 3–6) | 501 (36.5) | 292 (35.4) | 209 (38.0) |

All data are displayed as mean (SD), median (interquartile range) or n (%). †ASPECTS was used for patients with suspected anterior circulation stroke, and posterior circulation ASPECTS was used for patients with suspected posterior circulation stroke. * In patients with perfusion deficit in the MCA territory. NIHSS indicates National Institutes of Health Stroke Scale; mRS, modified Rankin Scale; IV-rtPA, intravenous thrombolysis with recombinant tissue type plasminogen activator; IAT, intra-arterial thrombolysis; ASPECTS, Alberta Stroke Program Early CT Score; CBV, cerebral blood volume; MTT, mean transit time; MCA, middle cerebral artery.

## Univariable models

Results of the univariable analyses showed that all evaluated CTA measures strongly predicted clinical outcome (Table 2.2). On CTA, the strongest predictors were poor leptomeningeal collaterals and the presence of a proximal intracranial occlusion, which had PPVs of 66% and 63% for poor clinical outcome, respectively. The investigated CTP measures were also highly predictive for poor clinical outcome (Table 2.2) with the highest PPVs for ASPECTS/pcASPECTS ≤7 on CBV and MTT maps, and infarct core size ≥4.8 $cm^2$ (PPV 65%, 53%, and 55%, respectively).

The strong predictive value of CTA and CTP measures across the full spectrum of mRS scores is illustrated in Figure 2.2. Results of the univariable analyses for the predictive value of patient characteristics and NCCT measures are provided in Table 2.3.

**Table 2.2. Univariable analyses between CT angiography and CT perfusion measures and poor clinical outcome (n=824)**

| Predictor | OR (95% CI) | PPV |
|---|---|---|
| CT angiography measures | | |
| CT angiography source images ASPECTS ≤7† | 3.32 (2.31–4.78)*** | 59% |
| Proximal intracranial occlusion | 5.13 (3.69–7.14)*** | 63% |
| Poor leptomeningeal collaterals | 4.30 (2.80–6.59)*** | 66% |
| Significant carotid or vertebrobasilar stenosis/occlusion | 3.21 (2.23–4.60)*** | 58% |
| CT perfusion measures | | |
| CBV ASPECTS ≤7† | 5.14 (3.66–7.22)*** | 65% |
| MTT ASPECTS ≤7† | 3.90 (2.89–5.27)*** | 53% |
| Penumbra size (per SD; 18.7 $cm^2$) | 1.70 (1.46–1.97)*** | |
| Lowest tertile (0.0 $cm^2$) | | 23% |
| Middle tertile (0.0–11.5 $cm^2$) | | 41% |
| Highest tertile (≥11.5 $cm^2$) | | 51% |
| Infarct core size (per SD; 13.7 $cm^2$) | 1.93 (1.65–2.25)*** | |
| Lowest tertile (0.0 $cm^2$) | | 22% |
| Middle tertile (0.0–3.9 $cm^2$) | | 36% |
| Highest tertile (≥3.9 $cm^2$) | | 55% |
| Penumbra/infarct core index (per SD; 28.4%) | 0.60 (0.52–0.69)*** | |
| Lowest tertile (≤82.3%) | | 53% |
| Middle tertile (82.3–100%) | | 41% |
| Highest tertile (100%) | | 22% |

†ASPECTS was used for patients with suspected anterior circulation stroke, and posterior circulation ASPECTS was used for patients with suspected posterior circulation stroke. OR indicates odds ratio; CI, confidence interval; PPV, positive predictive value; ASPECTS, Alberta Stroke Program Early CT Score; CBV, cerebral blood volume; MTT, mean transit time. *** p<0.001.

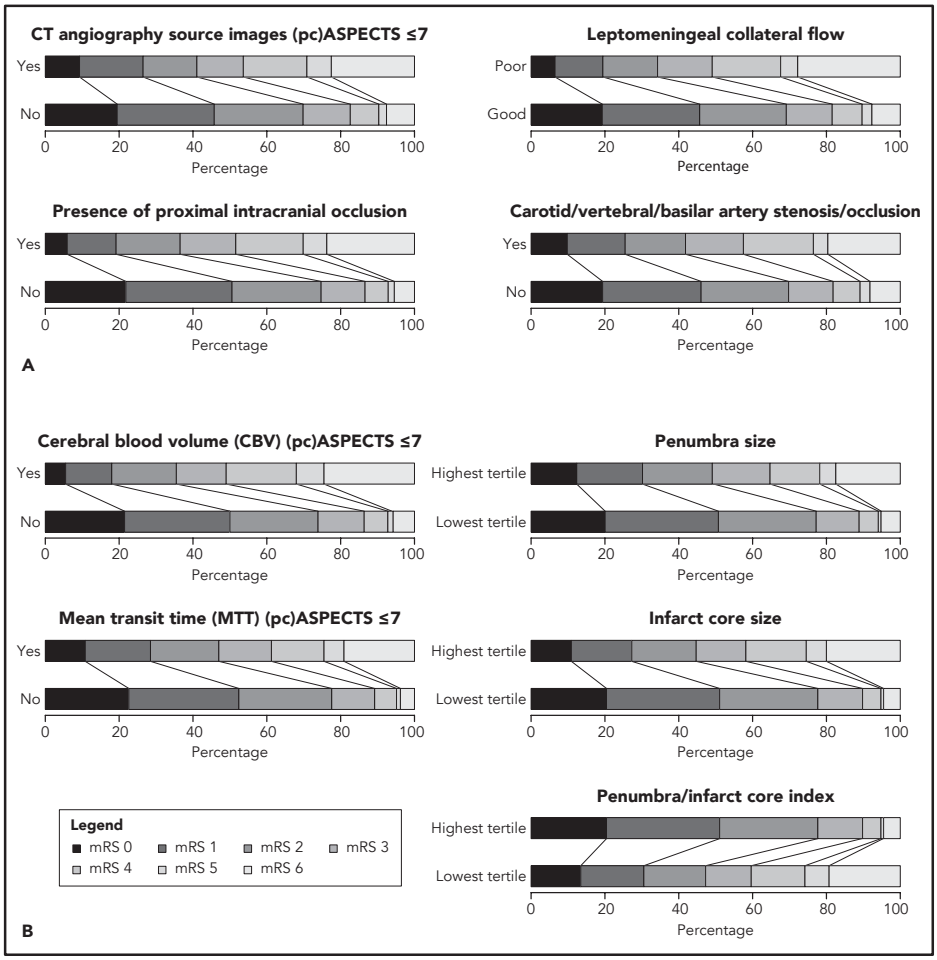



Figure 2.2. Distribution of mRS scores after 90 days in patients with normal and abnormal admission CTA (a) and CTP predictors (b).
When CTA and CTP predictors are abnormal, patients have higher mRS scores than when CTA and CTP predictors are normal, indicating a strong predictive value of CTA and CTP measures for poor clinical outcome.

## Multivariable prediction models

As expected, stroke severity (NIHSS) had a very strong predictive value for clinical outcome in the multivariable model including only patient characteristics and NCCT (Table 2.4). Age, admission glucose level, and NCCT measures were other variables that predicted clinical outcome. Obviously, the small subgroup of patients with prior disabilities (mRS ≥2) was also likely to have poor clinical outcome.

Table 2.3. Univariable analyses between patient characteristics and non-contrast CT measures and poor clinical outcome, within derivation set (n=824)

| Predictor | OR (95% CI) | PPV |
|---|---|---|
| Patient characteristics | | |
| Age (per decade) | 1.42 (1.27–1.59)*** | |
| Lowest tertile (<63.0 years) | | 26% |
| Middle tertile (63.0–75.1 years) | | 31% |
| Highest tertile (≥75.1 years) | | 49% |
| Stroke severity (NIHSS) | | |
| NIHSS 1–2 | 1.00 (reference) | 6% |
| NIHSS 3–4 | 3.64 (1.67–7.96)** | 20% |
| NIHSS 5–7 | 6.04 (2.85–12.79)*** | 29% |
| NIHSS 8–13 | 10.14 (4.84–21.23)*** | 41% |
| NIHSS >13 | 34.88 (16.52–73.67)*** | 71% |
| Time from symptom onset to scan (per hour) | 1.03 (0.96–1.11) | |
| Lowest tertile (≤84 minutes) | | 39% |
| Middle tertile (84–142 minutes) | | 33% |
| Highest tertile (≥142 minutes) | | 34% |
| Pre-admission mRS >2 | 10.40 (4.80–22.54)*** | 83% |
| Admission glucose level (per mmol/L) | 1.14 (1.07–1.22)*** | |
| Lowest tertile (≤6.1 mmol/L) | | 28% |
| Middle tertile (6.1–7.3 mmol/L) | | 36% |
| Highest tertile (≥7.3 mmol/L) | | 44% |
| IV-rtPA, intra-arterial thrombolysis, or mechanical thrombectomy | 1.07 (0.79–1.45) | 36% |
| Non-contrast CT measures | | |
| Hyperdense vessel sign | 3.78 (2.70–5.30)*** | 60% |
| ASPECTS ≤7† | 4.21 (2.62–6.75)*** | 66% |

†ASPECTS was used for patients with suspected anterior circulation stroke, and posterior circulation ASPECTS was used for patients with suspected posterior circulation stroke. OR indicates odds ratio; CI, confidence interval; PPV, positive predictive value; NIHSS, National Institutes of Health Stroke Scale; mRS, modified Rankin Scale; IV-rtPA, intravenous thrombolysis with recombinant tissue type plasminogen activator; ASPECTS, Alberta Stroke Program Early CT Score. * p<0.05; ** p<0.01; *** p<0.001.

After addition of CTA or CTP measures to this model, CTA measures, but not CTP measures, predicted outcome. The presence of a proximal intracranial occlusion (odds ratio (OR) 1.8 (95% CI 1.1–3.0)) and the presence of a >70% stenosis/occlusion of the internal carotid, vertebral, or basilar artery, supplying the symptomatic brain area (OR 2.3 (95% CI 1.5–3.6)) were independently related to outcome (Table 2.4).

The basic prognostic model with patient characteristics and NCCT proved to be highly predictive for clinical outcome and had an AUC value of 0.84 (95% CI 0.81–0.86; Table 2.5). Adding both CTA and CTP measures to the basic model did not improve the predictive value (AUC value 0.85 (95% CI 0.83–0.88; p=0.004)).

Validation of the models in the validation set showed similar results with an AUC value of 0.78 (95% CI 0.73–0.82) for the basic model and 0.79 (95% CI 0.75–0.83) after addition of both CTA and CTP predictors (p=0.01). When only CTA predictors were added to the basic model (Table 2.4 and Table 2.5) the AUC value was 0.79 (95% CI 0.75–0.83; p=0.01), whereas the AUC was 0.78 (95% CI 0.74–0.82) when CTP predictors were added to the basic model (p=0.37).

Calibration plots showed adequate calibration for all models (Figure 2.3) and we concluded that model fit was sufficient. See Table 2.5 for additional measures of model performance, including AUC values for subgroup analyses. Subgroup analyses in patients with more severe stroke symptoms, anterior circulation stroke, posterior circulation stroke, in patients with and without thrombolysis, and in patients with a confirmed proximal occlusion, showed a similar added prognostic value of CTA and CTP as was seen in the overall cohort. A nomogram based on the basic model is provided to predict the risk of poor clinical outcome for individual patients (Figure 2.4). Moreover, automated risk prediction sheets for the basic model and for the model including CTA and CTP predictors can be found online (https://www.karger.com/Article/FullText/441088).

## DISCUSSION

Abnormalities on CTA and CTP were common in patients suspected of ischemic stroke and were highly predictive for poor clinical outcome at 90 days. When added to patient characteristics and NCCT, CTA and CTP proved to have only limited additional prognostic value.

Our findings that individual CTA and CTP measures have a strong predictive value for clinical outcome are largely consistent with previous studies. These studies also showed that ASPECTS and pcASPECTS on CTA-SI,[3,22,29,30] the presence of a proximal occlusion,[2,31] leptomeningeal collateral status,[31–35] the presence of a significant internal carotid artery stenosis,[23] ASPECTS on CBV maps,[6,30,36–39] and penumbra size[40] were predictors of clinical outcome. However, while these studies focused on one or a few CTA or CTP measure(s), often in small patient groups,[6,22,30,36–39] this study evaluated the predictive value of several CTA and CTP measures in one large prospective patient cohort.

Table 2.4. Multivariable analyses between patient characteristics and imaging findings, and poor clinical outcome, within derivation set (n=824)

| | Patient characteristics and NCCT | | Addition of CTA | | Addition of CTP | | Addition of CTA and CTP | |
|---|---|---|---|---|---|---|---|---|
| Predictor | Coefficient | OR (95% CI) | Coefficient | OR (95% CI) | Coefficient | OR (95% CI) | Coefficient | OR (95% CI) |
| Age (per decade) | 0.368 | 1.44 (1.26–1.66)*** | 0.374 | 1.45 (1.26–1.67)*** | 0.355 | 1.43 (1.24–1.64)*** | 0.370 | 1.45 (1.26–1.67)*** |
| Stroke severity (NIHSS) | | | | | | | | |
| NIHSS 1–2 | 0.000 (ref) | 1.00 (ref) | 0.000 (ref) | 1.00 (ref) | 0.000 (ref) | 1.00 (ref) | 0.000 (ref) | 1.00 (ref) |
| NIHSS 3–4 | 1.371 | 3.94 (1.70–9.14)** | 1.122 | 3.07 (1.43–6.61)** | 1.140 | 3.13 (1.47–6.67)** | 1.134 | 3.11 (1.44–6.70)** |
| NIHSS 5–7 | 1.940 | 6.96 (3.06–15.79)*** | 1.653 | 5.23 (2.48–10.99)*** | 1.640 | 5.16 (2.47–10.76)*** | 1.630 | 5.10 (2.42–10.76)*** |
| NIHSS 8–13 | 2.304 | 10.02 (4.40–22.83)*** | 1.956 | 7.07 (3.33–14.99)*** | 1.883 | 6.57 (3.12–13.85)*** | 1.892 | 6.63 (3.11–14.14)*** |
| NIHSS >13 | 3.573 | 35.62 (15.13–83.86)*** | 2.998 | 20.05 (9.07–44.29)*** | 2.931 | 18.74 (8.46–41.52)*** | 2.860 | 17.46 (7.76–39.25)*** |
| Time from symptom onset to scan (per hour) | 0.073 | 1.08 (0.97–1.19) | 0.045 | 1.05 (0.95–1.16) | 0.072 | 1.07 (0.97–1.19) | 0.053 | 1.05 (0.95–1.17) |
| Pre-admission mRS >2 | 2.674 | 14.50 (5.82–36.11)*** | 2.492 | 12.09 (5.32–27.47)*** | 2.472 | 11.85 (5.24–26.77)*** | 2.514 | 12.35 (5.44–28.05)*** |
| Admission glucose level (per mmol/L) | 0.116 | 1.12 (1.04–1.22)** | 0.117 | 1.12 (1.04–1.22)** | 0.116 | 1.12 (1.04–1.22)** | 0.118 | 1.13 (1.04–1.22)** |
| IV-rtPA, IAT or MT | -0.321 | 0.73 (0.45–1.17) | -0.426 | 0.65 (0.41–1.05) | -0.281 | 0.75 (0.48–1.20) | -0.387 | 0.68 (0.42–1.09) |
| Non-contrast CT predictors | | | | | | | | |
| Hyperdense vessel sign | 0.601 | 1.82 (1.18–2.83)** | 0.196 | 1.22 (0.75–1.96) | 0.371 | 1.45 (0.91–2.32) | 0.103 | 1.11 (0.67–1.83) |
| ASPECTS ≤7† | 0.868 | 2.38 (1.33–4.27)** | 0.757 | 2.13 (1.12–4.06)* | 0.609 | 1.84 (1.02–3.31)* | 0.670 | 1.95 (1.02–3.74)* |

| | | | | | | |
|---|---|---|---|---|---|---|
| CT angiography predictors | | | | | | |
| CTA-SI ASPECTS ≤7† | -0.315 | 0.73 (0.42–1.28) | | | -0.500 | 0.61 (0.34–1.10) |
| Proximal intracranial occlusion | 0.651 | 1.92 (1.19–3.09)** | | | 0.589 | 1.80 (1.10–2.97)* |
| Poor leptomeningeal collaterals | 0.617 | 1.85 (1.08–3.18)* | | | 0.503 | 1.65 (0.95–2.88) |
| Significant carotid or vertebrobasilar stenosis | 0.804 | 2.23 (1.42–3.51)** | | | 0.836 | 2.31 (1.46–3.64)*** |
| CT perfusion predictors | | | | | | |
| CBV ASPECTS ≤7† | | | 0.379 | 1.46 (0.81–2.63) | 0.436 | 1.55 (0.84–2.86) |
| MTT ASPECTS ≤7† | | | 0.176 | 1.19 (0.73–1.95) | -0.082 | 0.92 (0.55–1.55) |
| Penumbra size (per SD; 18.2 $cm^2$) | | | | | | |
| Infarct core size (per SD; 13.9 $cm^2$) | | | 0.125 | 1.13 (0.90–1.43) | 0.116 | 1.12 (0.87–1.44) |
| Penumbra/infarct core index (per SD; 37.8%) | | | | | | |

†ASPECTS was used for patients with suspected anterior circulation stroke, and posterior circulation ASPECTS was used for patients with suspected posterior circulation stroke OR indicates odds ratio; CI, confidence interval; NIHSS, National Institutes of Health Stroke Scale; mRS, modified Rankin Scale; IV-rtPA, intravenous thrombolysis with recombinant tissue type plasminogen activator; IAT, intra-arterial thrombolysis; MT, mechanical thrombectomy; ASPECTS, Alberta Stroke Program Early CT Score; CTA-SI, CT angiography source images; CBV, cerebral blood volume; MTT, mean transit time.
* p<0.05; ** p<0.01; *** p<0.001.

Table 2.5. Model performance with and without addition of CT angiography and CT perfusion predictors

| | Patient characteristics and NCCT | Model with addition of CTA | Model with addition of CTP | Model with addition of CTA and CTP |
|---|---|---|---|---|
| Derivation set (n=824) | | | | |
| $R^2$ | 0.422 | 0.445 | 0.421 | 0.451 |
| Brier score* | 0.153 | 0.146 | 0.151 | 0.145 |
| AUC value | 0.837 (0.809–0.865) | 0.852 (0.825–0.878) | 0.841 (0.813–0.868) | 0.853 (0.826–0.880) |
| Goodness-of-fit p-value† | 0.99 | 0.80 | 0.69 | 0.87 |
| Internal validation (n=824)‡ | | | | |
| $R^2$ | 0.399 | 0.425 | 0.401 | 0.423 |
| Brier score* | 0.159 | 0.153 | 0.158 | 0.153 |
| AUC value | 0.828 (0.800–0.856)§ | 0.839 (0.813–0.866)§ | 0.829 (0.801–0.856)§ | 0.839 (0.812–0.866)§ |
| Validation set (n=550) | | | | |
| $R^2$ | 0.302 | 0.343 | 0.310 | 0.342 |
| Brier score* | 0.184 | 0.175 | 0.182 | 0.175 |
| AUC value | 0.776 (0.735–0.817) | 0.793 (0.753–0.833) | 0.777 (0.736–0.819) | 0.793 (0.753–0.833) |
| Goodness-of-fit p-value† | <0.001 | <0.001 | <0.001 | <0.001 |
| Goodness-of-fit p-value after updating intercept† | 0.001 | 0.09 | 0.003 | 0.01 |

| | | | | |
|---|---|---|---|---|
| AUC in subgroups of patients in the validation cohort | | | | |
| Anterior circulation stroke (TACS or PACS; n=361) | 0.778 (0.730–0.826) | 0.795 (0.749–0.842) | 0.780 (0.732–0.828) | 0.795 (0.749–0.841) |
| Posterior circulation stroke (POCS; n=80) | 0.748 (0.620–0.877) | 0.808 (0.695–0.921) | 0.746 (0.618–0.874) | 0.805 (0.690–0.920) |
| NIHSS ≥5 (n=315) | 0.745 (0.692–0.799) | 0.778 (0.728–0.829) | 0.747 (0.693–0.800) | 0.779 (0.728–0.829) |
| NIHSS ≥8 (n=215) | 0.742 (0.677–0.807) | 0.774 (0.713–0.836) | 0.748 (0.684–0.812) | 0.779 (0.718–0.840) |
| Pre-admission mRS 0–2 (n=515) | 0.749 (0.703–0.795) | 0.769 (0.724–0.813) | 0.751 (0.705–0.796) | 0.768 (0.723–0.812) |
| Treatment with IV-rtPA, IAT, or MT (n=343) | 0.750 (0.695–0.805) | 0.772 (0.718–0.825) | 0.752 (0.698–0.807) | 0.772 (0.719–0.825) |
| No treatment with IV-rtPA, IAT, or MT (n=207) | 0.817 (0.755–0.878) | 0.828 (0.769–0.887) | 0.818 (0.757–0.879) | 0.826 (0.767–0.886) |
| Proximal intracranial occlusion (n=130) | 0.780 (0.702–0.859) | 0.811 (0.738–0.885) | 0.792 (0.716–0.869) | 0.815 (0.742–0.888) |

* Quadratic score for differences between actual outcomes and predictions, range from 0 for a perfect model to 0.25 for a non-informative model. †Goodness-of-fit p-values are calculated with the Hosmer-Lemeshow test.‡Internal validation with 1000 bootstraps resamples. §Assuming the same standard error applies as estimated for model development.NCCT indicates non-contrast CT; CTA, CT angiography; CTP, CT perfusion; AUC, area under the curve; mRS, modified Rankin Scale; TACS, total anterior circulation syndrome; PACS, partial anterior circulation syndrome; POCS, posterior circulation syndrome; NIHSS, National Institutes of Health Stroke Scale; IV-rtPA, intravenous thrombolysis with recombinant tissue type plasminogen activator; IAT, intra-arterial thrombolysis; MT, mechanical thrombectomy.

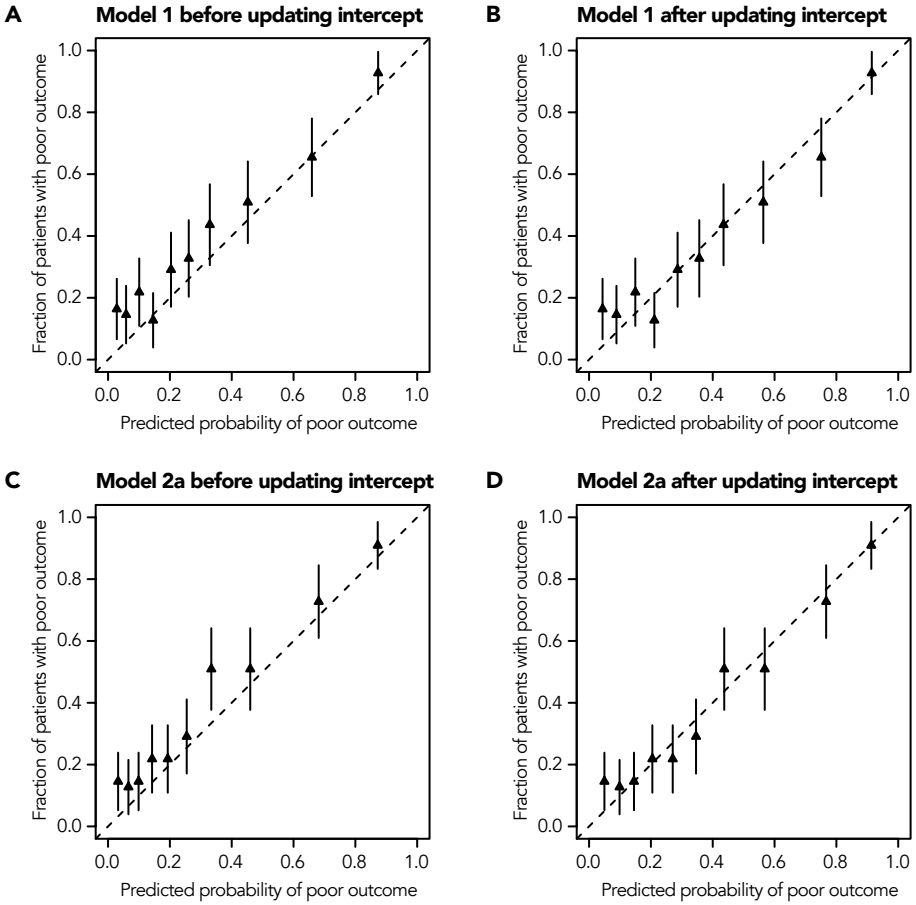



Figure 2.3. Calibration plots for all models in the validation set.
The calibration plots depict the observed fraction of patients with poor clinical outcome within deciles of predicted risk. Calibration plots are presented before (left) and after updating the model intercept (right), for the models based on patient characteristics and non-contrast CT (model 1; A, B), and with addition of CT angiography measures (model 2a; C, D), CT perfusion measures (model 2b; E, F), and both CT angiography and CT perfusion measures (model 3; G, H).

Furthermore, the patient characteristics and NCCT measures we identified as predictors of clinical outcome including age,[13,14,18,41–52] stroke severity,[13,14,18,41–43,45–53] pre-admission dependency,[18,41–44] glucose,[18,42,45,47,54] hyperdense vessel sign,[18] and ASPECTS on NCCT[45] are in correspondence with the literature, supporting the external validity of our study.

However, the study populations of the previous studies were somewhat different and consisted of patients with a confirmed large-vessel occlusion[29,34,35,40] or otherwise confirmed ischemic stroke,[2,22,31,38,39] patients with evidence of recanalization at follow-up,[30]

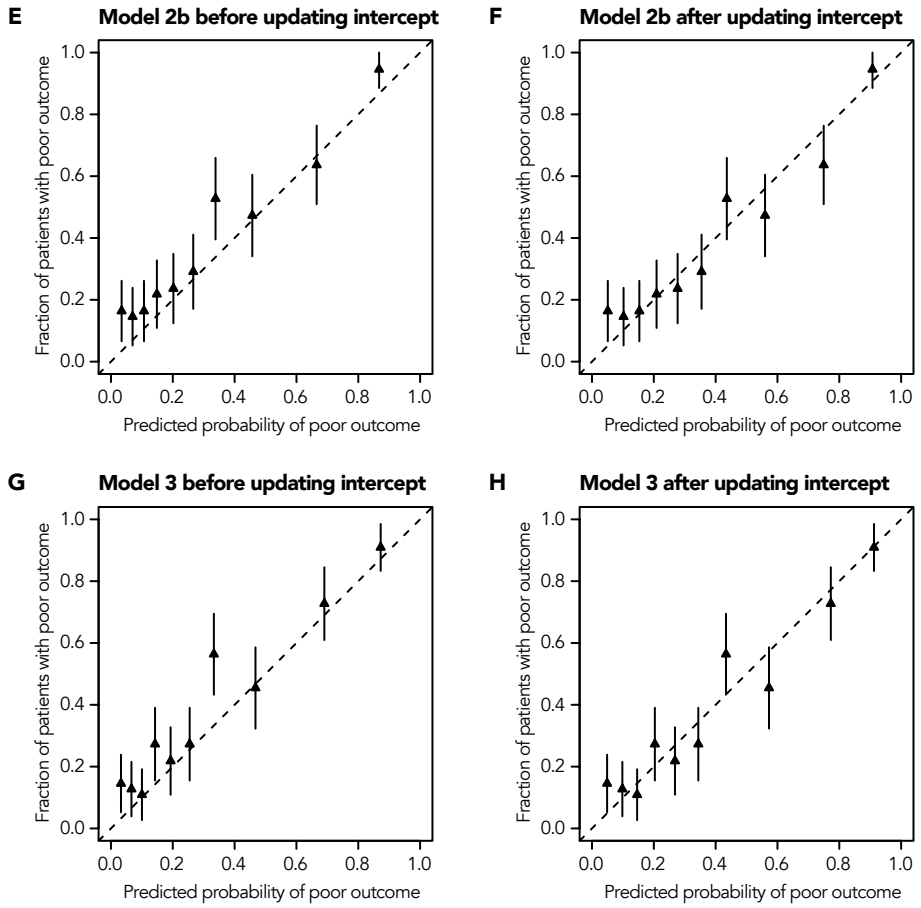



Figure 2.3. *Continued.*

or only patients treated with IV-rtPA.[6,32,36–38] An important strength of our study is that we included all patients with a clinical diagnosis of acute ischemic stroke instead of a certain subgroup of stroke patients, which often can only be identified in retrospect. Because treatment decisions are made in the acute stage when the final diagnosis is still unclear, prediction of outcome as guideline for further treatment is needed for all patients who are suspected of acute ischemic stroke. For similar reasons, another strength of our study is that we selected predictors that are readily available to the neurologist in the acute stage, at the emergency room, before he/she needs to decide on treatment with IV-rtPA or one of the intra-arterial treatment options. While information on recanalization and reperfusion potentially can also improve outcome prediction, these measures can be assessed only

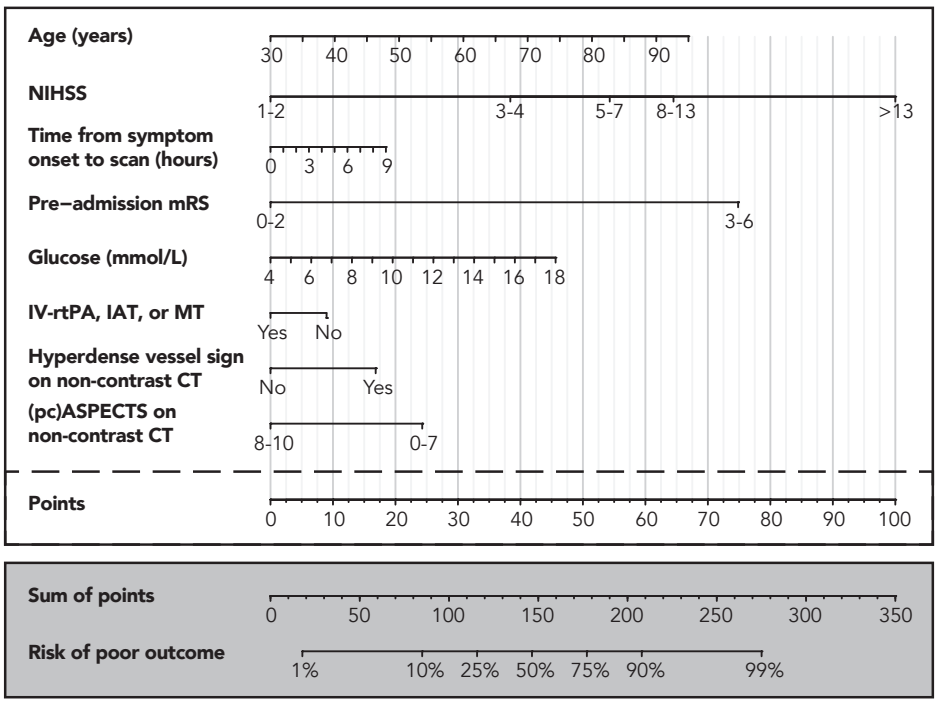



Figure 2.4. Nomogram for prediction of the risk of poor clinical outcome (mRS 3–6), based on patient characteristics and non-contrast CT measures.
Determine the points for each predictor by locating the predictor value on its axis, and find the amount of points on the corresponding 'Points' axis. Add the points for the individual predictors together and locate this number on the 'Sum of points' axis to find the predicted risk of poor clinical outcome. Abbreviations: NIHSS, National Institutes of Health Stroke Scale; mRS, modified Rankin Scale; IVrtPA, intravenous thrombolysis with recombinant tissue type plasminogen activator; IAT, intra-arterial thrombolysis; MT, mechanical thrombectomy; (pc)ASPECTS, (posterior circulation) Alberta Stroke Program Early CT Score.

on repeat imaging, hours or days after the acute event, and therefore cannot contribute to a model for outcome prediction in the emergency setting. Furthermore, the validation set that was used in the multivariable analyses was separated from the derivation set based on inclusion date instead of a random selection, which resulted in some variation between the 2 datasets. This shifts the results of the validation toward 'real' external validation, and improves generalizability of our results.

Prediction models based on CTA and CTP parameters in addition to patient characteristics and NCCT have never been developed and validated before in a large prospective study of unselected patients with a suspected ischemic stroke. One recently published study retrospectively evaluated the prognostic value for individual CTA and CTP measures

added to patient characteristics.[55] This study showed that some imaging measures were independent predictors of clinical outcome, but the additional prognostic value of combined imaging parameters was not investigated. Another retrospective study assessed whether outcome prediction could be improved by addition of CTP to patient characteristics, NCCT and CTA.[40] While several CTP predictors in that study were statistically significant in multivariable analyses, receiver operator characteristics analyses were not performed to assess prognostic performance.

One could argue that the prognostic value of CTA and CTP can be improved further by changing the way the imaging data are obtained. For example, certain CTA parameters could be improved with better reconstruction techniques such as CTA reconstruction from CTP data.[5] Addition of the dimension 'time' from CTP data makes the reconstructed CTA independent from timing of contrast administration and scan acquisition, and improves the assessment of the collateral circulation.[56] Furthermore, it has been shown that the use of different CTP algorithms, including time-insensitive CTP analysis, results in different quantitative CTP parameter maps.[57] In addition, the currently established CBV and MTT thresholds to obtain penumbra and infarct core size are suitable for use in the middle cerebral artery (MCA) territory,[24] but have not been validated for the posterior circulation.

Of note, the use of CTA and CTP is not restricted to the prediction of outcome. CTA and CTP have been shown to increase the diagnostic accuracy for acute ischemic stroke. A simple and quick assessment by means of visual information from CTA and CTP provides information about the presence and location of the occlusion and ischemia, the likely etiology (e.g. large or small vessel occlusion, carotid stenosis, dissection), and it helps the clinician in urgent decision making on which treatment should be administered, including endovascular therapy.[7–11,58,59] Therefore, one should not conclude that CTA and CTP should be omitted from the work-up of patients with acute ischemic stroke symptoms based on our multivariable prediction models. CTA and CTP have a prognostic value with a clear defined quantification, which we showed for the first time in this study. However, in an unselected population of patients with stroke symptoms, their additional prognostic value over patient characteristics and NCCT is limited. In post-hoc analyses, the same applied to subgroup analyses in patients with more severe stroke, anterior circulation stroke, or confirmed proximal occlusion. Nevertheless, further studies in patients with more severe stroke and patients with proximal occlusions are warranted, especially in the context of endovascular treatment.

Treatment with IV-rtPA, IAT, or MT did not predict clinical outcome in our analyses. This might be explained by differences between treated and non-treated patients, that is, confounding by indication. For example, treated patients have more severe stroke

symptoms and more imaging abnormalities than untreated patients. As patients were not randomized for treatment in our study, our study is not suited to appraise the relation between treatment and clinical outcome.

Our study has some limitations. Many patients received IV-rtPA in our study. Although the proportion of patients who arrive in hospitals within 4.5 hours that receive IV-rtPA has increased up to 50% in The Netherlands in recent years,[60] this proportion is even higher in our study, which could indicate selection bias. In addition, ASPECTS was used for assessment of ischemia in the anterior circulation and pcASPECTS for the posterior circulation. We assumed that the predictive values of ASPECTS and pcASPECTS are equal, which is not necessarily true. Moreover, ischemic changes in the anterior cerebral artery territory are not assessed with either ASPECTS or pcASPECTS. However, this only concerns an extremely small patient group. Finally, most of our CTP scans did not cover the entire brain, which leads to an underestimation of infarct core and penumbra volumes.

In conclusion, our study showed that CTA and CTP measures are strong predictors of clinical outcome. Besides their proven diagnostic use and their importance for guidance of therapeutic decisions, the prognostic value of CTA and CTP measures in addition to patient characteristics and NCCT is limited in an unselected stroke population.

## REFERENCES


1. Tan JC, Dillon WP, Liu S, Adler F, Smith WS, Wintermark M. Systematic comparison of perfusion-CT and CT-angiography in acute stroke patients. Ann Neurol 2007;61:533–543.
2. Puetz V, Dzialowski I, Hill MD, Subramaniam S, Sylaja PN, Krol A, O'Reilly C, Hudon ME, Hu WY, Coutts SB, Barber PA, Watson T, Roy J, Demchuk AM. Intracranial thrombus extent predicts clinical outcome, final infarct size and hemorrhagic transformation in ischemic stroke: the clot burden score. Int J Stroke. 2008;3:230–236.
3. Puetz V, Sylaja PN, Coutts SB, Hill MD, Dzialowski I, Mueller P, Becker U, Urban G, O'Reilly C, Barber PA, Sharma P, Goyal M, Gahn G, von Kummer R, Demchuk AM. Extent of hypoattenuation on CT angiography source images predicts functional outcome in patients with basilar artery occlusion. Stroke. 2008;39:2485–2490.
4. Schramm P, Schellinger PD, Klotz E, Kallenberg K, Fiebach JB, Kulkens S, Heiland S, Knauth M, Sartor K. Comparison of perfusion computed tomography and computed tomography angiography source images with perfusion-weighted imaging and diffusion-weighted imaging in patients with acute stroke of less than 6 hours' duration. Stroke. 2004;35:1652–1658.
5. Schaefer PW, Barak ER, Kamalian S, Gharai LR, Schwamm L, Gonzalez RG, Lev MH. Quantitative assessment of core/penumbra mismatch in acute stroke: CT and MR perfusion imaging are strongly correlated when sufficient brain volume is imaged. Stroke. 2008;39:2986–2992.
6. Parsons MW, Pepper EM, Chan V, Siddique S, Rajaratnam S, Bateman GA, Levi CR. Perfusion computed tomography: Prediction of final infarct extent and stroke outcome. Ann Neurol. 2005;58:672–679.

7. Berkhemer OA, Fransen PS, Beumer D, van den Berg LA, Lingsma HF, Yoo AJ, Schonewille WJ, Vos JA, Nederkoorn PJ, Wermer MJ, van Walderveen MA, Staals J, Hofmeijer J, van Oostayen JA, Lycklama a Nijeholt GJ, Boiten J, Brouwer PA, Emmer BJ, de Bruijn SF, van Dijk LC, Kappelle LJ, Lo RH, van Dijk EJ, de Vries J, de Kort PL, van Rooij WJ, van den Berg JS, van Hasselt BA, Aerden LA, Dallinga RJ, Visser MC, Bot JC, Vroomen PC, Eshghi O, Schreuder TH, Heijboer RJ, Keizer K, Tielbeek AV, den Hertog HM, Gerrits DG, van den Berg-Vos RM, Karas GB, Steyerberg EW, Flach HZ, Marquering HA, Sprengers ME, Jenniskens SF, Beenen LF, van den Berg R, Koudstaal PJ, van Zwam WH, Roos YB, van der Lugt A, van Oostenbrugge RJ, Majoie CB, Dippel DW. A randomized trial of intraarterial treatment for acute ischemic stroke. N Engl J Med. 2015;372:11–20.
8. Campbell BC, Mitchell PJ, Kleinig TJ, Dewey HM, Churilov L, Yassi N, Yan B, Dowling RJ, Parsons MW, Oxley TJ, Wu TY, Brooks M, Simpson MA, Miteff F, Levi CR, Krause M, Harrington TJ, Faulder KC, Steinfort BS, Priglinger M, Ang T, Scroop R, Barber PA, McGuinness B, Wijeratne T, Phan TG, Chong W, Chandra RV, Bladin CF, Badve M, Rice H, de Villiers L, Ma H, Desmond PM, Donnan GA, Davis SM. Endovascular therapy for ischemic stroke with perfusion-imaging selection. N Engl J Med. 2015;372:1009–1018.
9. Goyal M, Demchuk AM, Menon BK, Eesa M, Rempel JL, Thornton J, Roy D, Jovin TG, Willinsky RA, Sapkota BL, Dowlatshahi D, Frei DF, Kamal NR, Montanera WJ, Poppe AY, Ryckborst KJ, Silver FL, Shuaib A, Tampieri D, Williams D, Bang OY, Baxter BW, Burns PA, Choe H, Heo JH, Holmstedt CA, Jankowitz B, Kelly M, Linares G, Mandzia JL, Shankar J, Sohn SI, Swartz RH, Barber PA, Coutts SB, Smith EE, Morrish WF, Weill A, Subramaniam S, Mitha AP, Wong JH, Lowerison MW, Sajobi TT, Hill MD. Randomized assessment of rapid endovascular treatment of ischemic stroke. N Engl J Med. 2015;372:1019–1030.
10. Saver JL, Goyal M, Bonafe A, Diener HC, Levy EI, Pereira VM, Albers GW, Cognard C, Cohen DJ, Hacke W, Jansen O, Jovin TG, Mattle HP, Nogueira RG, Siddiqui AH, Yavagal DR, Baxter BW, Devlin TG, Lopes DK, Reddy VK, du Mesnil de Rochemont R, Singer OC, Jahan R. Stent-Retriever Thrombectomy after Intravenous t-PA vs. t-PA Alone in Stroke. N Engl J Med. 2015;372:2285–2295.
11. Jovin TG, Chamorro A, Cobo E, de Miquel MA, Molina CA, Rovira A, San Roman L, Serena J, Abilleira S, Ribo M, Millan M, Urra X, Cardona P, Lopez-Cancio E, Tomasello A, Castano C, Blasco J, Aja L, Dorado L, Quesada H, Rubiera M, Hernandez-Perez M, Goyal M, Demchuk AM, von Kummer R, Gallofre M, Davalos A. Thrombectomy within 8 Hours after Symptom Onset in Ischemic Stroke. N Engl J Med. 2015;372:2296–2306.
12. van Seeters T, Biessels GJ, van der Schaaf IC, Dankbaar JW, Horsch AD, Luitse MJ, Niesten JM, Mali WP, Kappelle LJ, van der Graaf Y, Velthuis BK. Prediction of outcome in patients with suspected acute ischaemic stroke with CT perfusion and CT angiography: the Dutch acute stroke trial (DUST) study protocol. BMC Neurol. 2014;14:37.
13. Weimar C, König IR, Kraywinkel K, Ziegler A, Diener HC. Age and National Institutes of Health Stroke Scale Score within 6 hours after onset are accurate predictors of outcome after cerebral ischemia: development and external validation of prognostic models. Stroke. 2004;35:158–162.
14. König IR, Ziegler A, Bluhmki E, Hacke W, Bath PM, Sacco RL, Diener HC, Weimar C, Virtual International Stroke Trials Archive I. Predicting long-term outcome after acute ischemic stroke: a simple index works in patients from controlled clinical trials. Stroke. 2008;39:1821–1826.
15. Luitse MJ, Biessels GJ, Rutten GE, Kappelle LJ. Diabetes, hyperglycaemia, and acute ischaemic stroke. Lancet Neurol. 2012;11:261–271.
16. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. N Engl J Med. 1995;333:1581–1587.
17. Hacke W, Kaste M, Bluhmki E, Brozman M, Davalos A, Guidetti D, Larrue V, Lees KR, Medeghri Z, Machnig T, Schneider D, von Kummer R, Wahlgren N, Toni D. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. N Engl J Med. 2008;359:1317–1329.
18. Strbian D, Meretoja A, Ahlhelm FJ, Pitkaniemi J, Lyrer P, Kaste M, Engelter S, Tatlisumak T. Predicting outcome of IV thrombolysis-treated ischemic stroke patients: the DRAGON score. Neurology. 2012;78:427–432.

19. Barber PA, Demchuk AM, Zhang J, Buchan AM. Validity and reliability of a quantitative computed tomography score in predicting outcome of hyperacute stroke before thrombolytic therapy. Lancet. 2000;355:1670–1674.
20. Pexman JH, Barber PA, Hill MD, Sevick RJ, Demchuk AM, Hudon ME, Hu WY, Buchan AM. Use of the Alberta Stroke Program Early CT Score (ASPECTS) for assessing CT scans in patients with acute stroke. AJNR Am J Neuroradiol. 2001;22:1534–1542.
21. von Kummer R, Meyding-Lamade U, Forsting M, Rosin L, Rieke K, Hacke W, Sartor K. Sensitivity and prognostic value of early CT in occlusion of the middle cerebral artery trunk. AJNR Am J Neuroradiol. 1994;15:9–15.
22. Coutts SB, Lev MH, Eliasziw M, Roccatagliata L, Hill MD, Schwamm LH, Pexman JH, Koroshetz WJ, Hudon ME, Buchan AM, Gonzalez RG, Demchuk AM. ASPECTS on CTA source images versus unenhanced CT: added value in predicting final infarct extent and clinical outcome. Stroke. 2004;35:2472–2476.
23. Rothwell PM, Eliasziw M, Gutnikov SA, Fox AJ, Taylor DW, Mayberg MR, Warlow CP, Barnett HJ. Analysis of pooled data from the randomised controlled trials of endarterectomy for symptomatic carotid stenosis. Lancet. 2003;361:107–116.
24. Wintermark M, Flanders AE, Velthuis BK, Meuli R, van Leeuwen MS, Goldsher D, Pineda C, Serena J, van der Schaaf IC, Waaijer A, Anderson J, Nesbit G, Gabriely I, Medina V, Quiles A, Pohlman S, Quist M, Schnyder P, Bogousslavsky J, Dillon WP, Pedraza S. Perfusion-CT assessment of infarct core and penumbra: receiver operating characteristic curve analysis in 130 patients suspected of acute hemispheric stroke. Stroke. 2006;37:979–985.
25. van Swieten JC, Koudstaal PJ, Visser MC, Schouten HJ, van Gijn J. Interobserver agreement for the assessment of handicap in stroke patients. Stroke. 1988;19:604–607.
26. Janssen PM, Visser NA, Dorhout Mees SM, Klijn CJ, Algra A, Rinkel GJ. Comparison of telephone and face-to-face assessment of the modified Rankin Scale. Cerebrovasc Dis. 2010;29:137–139.
27. Steyerberg EW. Clinical prediction models: a practical approach to development, validation, and updating. New York, Springer. 2009.
28. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. Biometrics. 1988;44:837–845.
29. Bhatia R, Bal SS, Shobha N, Menon BK, Tymchuk S, Puetz V, Dzialowski I, Coutts SB, Goyal M, Barber PA, Watson T, Smith EE, Demchuk AM. CT Angiographic source images predict outcome and final infarct volume better than noncontrast CT in proximal vascular occlusions. Stroke. 2011;42:1575–1580.
30. Lum C, Ahmed ME, Patro S, Thornhill R, Hogan M, Iancu D, Lesiuk H, Dos Santos M, Dowlatshahi D. Computed tomographic angiography and cerebral blood volume can predict final infarct volume and outcome after recanalization. Stroke. 2014;45:2683–2688.
31. Tan IY, Demchuk AM, Hopyan J, Zhang L, Gladstone D, Wong K, Martin M, Symons SP, Fox AJ, Aviv RI. CT angiography clot burden score and collateral score: correlation with clinical and radiologic outcomes in acute middle cerebral artery infarct. AJNR Am J Neuroradiol. 2009;30:525–531.
32. Kucinski T, Koch C, Eckert B, Becker V, Kromer H, Heesen C, Grzyska U, Freitag HJ, Rother J, Zeumer H. Collateral circulation is an independent radiological predictor of outcome after thrombolysis in acute ischaemic stroke. Neuroradiology. 2003;45:11–18.
33. Maas MB, Lev MH, Ay H, Singhal AB, Greer DM, Smith WS, Harris GJ, Halpern E, Kemmling A, Koroshetz WJ, Furie KL. Collateral vessels on CT angiography predict outcome in acute ischemic stroke. Stroke. 2009;40:3001–3005.
34. Miteff F, Levi CR, Bateman GA, Spratt N, McElduff P, Parsons MW. The independent predictive utility of computed tomography angiographic collateral status in acute ischaemic stroke. Brain. 2009;132:2231–2238.
35. Lima FO, Furie KL, Silva GS, Lev MH, Camargo EC, Singhal AB, Harris GJ, Halpern EF, Koroshetz WJ, Smith WS, Yoo AJ, Nogueira RG. The pattern of leptomeningeal collaterals on CT angiography is a strong predictor of long-term functional outcome in stroke patients with large vessel intracranial occlusion. Stroke. 2010;41:2316–2322.

36. Aviv RI, Mandelcorn J, Chakraborty S, Gladstone D, Malham S, Tomlinson G, Fox AJ, Symons S. Alberta Stroke Program Early CT Scoring of CT Perfusion in Early Stroke Visualization and Assessment. AJNR Am J Neuroradiol. 2007;28:1975–1980.
37. Kloska SP, Dittrich R, Fischer T, Nabavi DG, Fischbach R, Seidensticker P, Osada N, Ringelstein EB, Heindel W. Perfusion CT in acute stroke: prediction of vessel recanalization and clinical outcome in intravenous thrombolytic therapy. Eur Radiol. 2007;17:2491–2498.
38. Lee JY, Kim SH, Lee MS, Park SH, Lee SS. Prediction of clinical outcome with baseline and 24-hour perfusion CT in acute middle cerebral artery territory ischemic stroke treated with intravenous recanalization therapy. Neuroradiology. 2008;50:391–396.
39. Gasparotti R, Grassi M, Mardighian D, Frigerio M, Pavia M, Liserre R, Magoni M, Mascaro L, Padovani A, Pezzini A. Perfusion CT in patients with acute ischemic stroke treated with intra-arterial thrombolysis: predictive value of infarct core size on clinical outcome. AJNR Am J Neuroradiol. 2009;30:722–727.
40. Zhu G, Michel P, Aghaebrahim A, Patrie JT, Xin W, Eskandari A, Zhang W, Wintermark M. Computed tomography workup of patients suspected of acute ischemic stroke: perfusion computed tomography adds value compared with clinical evaluation, noncontrast computed tomography, and computed tomography angiogram in terms of predicting outcome. Stroke. 2013;44:1049–1055.
41. Reid JM, Gubitz GJ, Dai D, Kydd D, Eskes G, Reidy Y, Christian C, Counsell CE, Dennis M, Phillips SJ. Predicting functional outcome after stroke by modelling baseline clinical and CT variables. Age Ageing. 2010;39:360–366.
42. Saposnik G, Kapral MK, Liu Y, Hall R, O'Donnell M, Raptis S, Tu JV, Mamdani M, Austin PC. IScore: a risk score to predict death early after hospitalization for an acute ischemic stroke. Circulation. 2011;123:739–749.
43. O'Donnell MJ, Fang J, D'Uva C, Saposnik G, Gould L, McGrath E, Kapral MK. The PLAN score: a bedside prediction rule for death and severe disability following acute ischemic stroke. Arch Intern Med. 2012;172:1548–1556.
44. Counsell C, Dennis M, McDowall M, Warlow C. Predicting outcome after acute and subacute stroke: development and validation of new prognostic models. Stroke. 2002;33:1041–1047.
45. Kent DM, Selker HP, Ruthazer R, Bluhmki E, Hacke W. The stroke-thrombolytic predictive instrument: a predictive instrument for intravenous thrombolysis in acute ischemic stroke. Stroke. 2006;37:2957–2962.
46. Solberg OG, Dahl M, Mowinckel P, Stavem K. Derivation and validation of a simple risk score for predicting 1-year mortality in stroke. J Neurol. 2007;254:1376–1383.
47. Ntaios G, Faouzi M, Ferrari J, Lang W, Vemmos K, Michel P. An integer-based score to predict functional outcome in acute ischemic stroke: the ASTRAL score. Neurology 2012;78:1916–1922.
48. Williams GR, Jiang JG. Development of an ischemic stroke survival score. Stroke. 2000;31:2414–2420.
49. Johnston KC, Connors AF, Jr., Wagner DP, Knaus WA, Wang X, Haley EC, Jr. A predictive risk model for outcomes of ischemic stroke. Stroke. 2000;31:448–455.
50. Saposnik G, Guzik AK, Reeves M, Ovbiagele B, Johnston SC. Stroke Prognostication using Age and NIH Stroke Scale: SPAN-100. Neurology. 2013;80:21–28.
51. Muscari A, Puddu GM, Santoro N, Zoli M. A simple scoring system for outcome prediction of ischemic stroke. Acta Neurol Scand. 2011;124:334–342.
52. Smith EE, Shobha N, Dai D, Olson DM, Reeves MJ, Saver JL, Hernandez AF, Peterson ED, Fonarow GC, Schwamm LH. Risk score for in-hospital ischemic stroke mortality derived and validated within the Get With the Guidelines-Stroke Program. Circulation. 2010;122:1496–1504.
53. Baird AE, Dambrosia J, Janket S, Eichbaum Q, Chaves C, Silver B, Barber PA, Parsons M, Darby D, Davis S, Caplan LR, Edelman RE, Warach S. A three-item scale for the early prediction of stroke recovery. Lancet. 2001;357:2095–2099.
54. Wang Y, Lim LL, Levi C, Heller RF, Fischer J. A prognostic index for 30-day mortality after stroke. J Clin Epidemiol. 2001;54:766–773.

55. Ntaios G, Papavasileiou V, Faouzi M, Vanacker P, Wintermark M, Michel P. Acute imaging does not improve ASTRAL score's accuracy despite having a prognostic value. Int J Stroke. 2014;9:926–931.
56. Smit EJ, Vonken EJ, van Seeters T, Dankbaar JW, van der Schaaf IC, Kappelle LJ, van Ginneken B, Velthuis BK, Prokop M. Timing-invariant imaging of collateral vessels in acute ischemic stroke. Stroke. 2013;44:2194–2199.
57. Kudo K, Sasaki M, Yamada K, Momoshima S, Utsunomiya H, Shirato H, Ogasawara K. Differences in CT perfusion maps generated by different commercial software: quantitative analysis by using identical source data of acute stroke patients. Radiology. 2010;254:200–209.
58. Biesbroek JM, Niesten JM, Dankbaar JW, Biessels GJ, Velthuis BK, Reitsma JB, van der Schaaf IC. Diagnostic accuracy of CT perfusion imaging for detecting acute ischemic stroke: a systematic review and meta-analysis. Cerebrovasc Dis. 2013;35:493–501.
59. Khan R, Nael K, Erly W. Acute stroke imaging: what clinicians need to know. Am J Med. 2013;126:379–386.
60. Lahr MM, Luijckx GJ, Vroomen PC, van der Zee DJ, Buskens E. Proportion of patients treated with thrombolysis in a centralized versus a decentralized acute stroke care setting. Stroke. 2012;43:1336–1340.

# CHAPTER 3

## Residual high-grade stenosis after recanalization of extracranial carotid occlusion in acute ischemic stroke

Merel J.A. Luitse
Birgitta K. Velthuis
Meenakshi Dauwan
Jan Willem Dankbaar
Geert Jan Biessels
L. Jaap Kappelle
on behalf of Dutch acute Stroke Study (DUST)

Stroke. 2015;46:12–15

# ABSTRACT

## Introduction

Residual stenosis after recanalization of an acute symptomatic extracranial occlusion of the internal carotid artery (ICA) might be an indication for carotid endarterectomy. We evaluated the proportion of residual high-grade stenosis (≥70%, near occlusions not included) on follow-up imaging in a consecutive series of patients with an acute symptomatic occlusion of the extracranial ICA.

## Methods

We included patients, participating in the Dutch Acute Stroke study (DUST) who had an acute symptomatic occlusion of the extracranial ICA that was diagnosed on CT-angiography (CTA) within 9 hours after onset of neurological symptoms. Follow-up imaging of the carotid artery had to be available within 7 days after admission.

## Results

Of the 1021 patients participating in DUST between May 2009 and May 2013, an acute symptomatic occlusion of the extracranial ICA was found in 126 (12.3%). Follow-up imaging was available in 86 (68.3%) of these patients. At follow-up, a residual stenosis <30% was found in 15 patients (17.4%; 95% CI 10.8–26.9); a 30–49% stenosis in 3 (3.5%; 95% CI 0.8–10.2) patients; a 50–69% stenosis in 2 (2.3%; 95% CI 0.1–8.6) patients; and a ≥70% stenosis in 14 (16.3%; 95% CI 9.8–25.6) patients. A near or persistent occlusion was present in the remaining 52 (60.5%) patients.

## Discussion

A residual high-grade stenosis of the extracranial ICA occurs in one out of six patients with a symptomatic occlusion in the acute stage of cerebral ischemia. As this may have implications for secondary prevention, we recommend follow-up imaging in these patients within a week after the event.

# INTRODUCTION

Acute occlusion of the internal carotid artery (ICA) can lead to a large ischemic stroke with severe disability and poor prognosis in the long-term.[1] Recanalization after an occlusion of the ICA in the acute stage may occur more commonly than previously assumed.[2] If after recanalization a high-grade stenosis persists, this may have important implications for subsequent treatment, as the recurrence rate of ischemic stroke in patients with high-grade stenosis within 7 days is around 8%.[3,4] Carotid endarterectomy has proven to be beneficial in patients with a ≥70% stenosis without near occlusions and is recommended within two weeks after the first symptoms.[5–7]

The combination of non-contrast computed tomography (NCCT), CT Perfusion (CTP) and CT Angiography (CTA) is increasingly used to determine the extent and severity of cerebral ischemia and to localize intra- and extracranial vascular stenosis, occlusion and recanalization in patients with acute ischemic stroke.[8]

The aim of our study was to determine the frequency of residual high-grade stenosis of ≥70% on follow-up imaging in patients with an acute symptomatic occlusion of the extracranial ICA.

# METHODS

## Study population

All patients participated in the multicenter prospective Dutch acute stroke study (DUST) between May 2009 and May 2013. Inclusion criteria for the DUST were (1) clinical diagnosis of acute ischemic stroke, (2) NCCT, CTP and CTA examination performed within 9 hours of symptom onset, and (3) no known history of renal failure or allergy to contrast agents. Follow-up assessment with preferably NCCT, CTA and CTP was recommended within three days after stroke onset. Institutional review boards approved the trial, and written informed consent was obtained for each patient. Detailed information on the DUST has been described earlier.[9]

For the current study, we included patients with signs or symptoms that originated from an ischemic lesion in the supply territory of the ICA and a symptomatic occlusion of the extracranial ICA on the initial CTA. Furthermore, follow-up imaging of the carotid artery with CTA or alternatively magnetic resonance angiography (MRA), duplex ultrasound (DUS) or digital subtraction angiography (DSA) had to be available within 7 days after admission.

## Imaging protocol

The admission CT examination included NCCT, CTP of the brain, and cervical and intracranial CTA. Detailed information on the CT imaging and analysis protocol has been described previously.[9] The initial CTA and follow-up imaging (CTA, MRA, DUS, DSA) were evaluated by a radiologist experienced in neurovascular imaging who was blinded for the clinical features. The carotid arteries were evaluated for presence and degree of stenosis or occlusion on admission and follow-up imaging.

## Clinical assessment

Information was collected on the patients' medical history of ischemic stroke or TIA, vascular risk factors and the use of antithrombotic medication. Stroke severity on admission was assessed by means of the National Institute of Health Stroke Scale (NIHSS) and stroke subtype by means of the TOAST classification.[10] Treatment categories included intravenous recombinant tissue plasminogen activator (rtPA), endovascular treatment (intra-arterial thrombolysis with rtPA, mechanical clot disruption or retrieval, or a combination of these approaches). Clinical outcome at 3 months was assessed by means of the Modified Rankin Scale (mRS).[11] A Rankin score of 0–2 was defined as good outcome, a score of 3–6 as poor outcome. Finally, information was collected on subsequent treatment as carotid endarterectomy or carotid stenting after the ischemic stroke.

## Outcome measures

The primary outcome measure was the proportion of patients with a residual high-grade stenosis on follow-up imaging who might be eligible for carotid endarterectomy (CEA) or carotid artery stenting. A residual high-grade stenosis was defined as a stenosis of ≥70% not including near occlusions.[6,12] It was determined how many patients had complete or partial recanalization of the extracranial ICA on follow-up imaging and what the degree of residual stenosis was according to the following categories: 1) <30%; 2) 30–49%; 3) 50–69%; 4) (≥70%; 5) near occlusion and 6) persistent occlusion.[6,12] A near occlusion was defined as a severe stenosis with caliber reduction of the ICA distal to the stenosis.[13,14] The categories were labeled for the different treatment types, e.g. intravenous rtPA, endovascular treatment or conservative treatment.

### Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics, version 20. Descriptive analysis was used to determine the frequency of occurrence of categories of residual stenosis with 95% confidence intervals (95% CI) on follow-up imaging. Mean values were compared with analysis of variance (ANOVA). Differences in proportions were evaluated by the Pearson's chi squared test. Differences at the level of $p < 0.05$ were considered statistically significant. Finally, for the relation between residual stenosis and outcome, odd ratios (OR) and the corresponding 95% CIs were calculated by means of logistic regression.



## RESULTS

From May 2009 until May 2013, 1021 patients were included in DUST. A symptomatic occlusion of the extracranial ICA was found 126 (12.3%) patients. From these 126, all 86 patients (68.3%) with adequate follow-up carotid imaging were included in the analysis. There were no differences in baseline characteristics between patients with and without adequate follow up. The mean age was 63 (SD ±12.9) years and 74% of the patients was male (Table 3.1). The mean time from admission until follow-up imaging was 3.2 (SD ±1.6) days. Follow-up imaging consisted of CTA in 83.7%, DUS in 9.3%, MRA in 3.5% and DSA in 3.5% of the patients.

Forty-seven (54.7%) patients were treated with intravenous rtPA and 11 (12.8%) patients underwent endovascular treatment. The baseline characteristics stratified for the different treatment modalities are presented in Table 3.2. The majority of ICA occlusions (76.7%) was considered to be caused by large artery atherosclerosis, while 16.3% was attributed to carotid dissection. Cardiac embolism and unknown cause each accounted for 3.5%.

In 34 (39.5% (95% CI 29.9–50.1)) of the 86 patients the occluded extracranial ICA was completely or partially recanalized at follow-up. Near occlusions were not included in this group. Characteristics of patients with a near or persistent occlusion (n=52) and patients with an open extracranial ICA at follow up (n=34) are shown in Table 3.1. In the group with CTA follow-up only, the occluded carotid artery recanalized in 40.3%. For the remaining follow-up imaging modalities together, this was 35.7% (p=0.75).

Figure 3.1 shows the proportion of the residual stenosis according to the different categories. A residual stenosis of <30% occurred in 15 (17.4%; 95% CI 10.8–26.9) patients; a 30–49% stenosis in 3 (3.5%; 95% CI 0.8–10.2) patients; a 50–69% stenosis in 2 (2.3%; 95% CI 0.1–8.6) patients; a residual high-grade stenosis of ≥70% in 14 (16.3%; 95% CI

Table 3.1. Occurrence of recanalization on follow-up imaging

| Variable, No. (%) | ICA occlusion on admission N=86 | Persistent occlusion at follow-up N=52 | Recanalization at follow-up N=34 | p-value |
|---|---|---|---|---|
| Male | 64 (74.4) | 40 (76.9) | 24 (70.6) | 0.51 |
| Age (years), mean ±SD | 63.8±13 | 64±12 | 61±14 | 0.09 |
| Hypertension | 37 (43.0) | 28 (53.8) | 9 (26.5) | 0.01 |
| Diabetes mellitus | 10 (11.6) | 8 (15.4) | 2 (5.9) | 0.18 |
| Hyperlipidemia | 24 (27.9) | 14 (26.9) | 10 (29.4) | 0.80 |
| Smoking | 33 (38.4) | 21 (40.4) | 12 (35.3) | 0.64 |
| Previous use of antithrombotic medication | 33 (38.4) | 24 (46.2) | 9 (26.5) | 0.07 |
| NIHSS on admission, median (IQR) | 11 (4–15) | 8 (3–15) | 12 (7–16) | 0.36 |
| Time from onset to CTA (minutes), mean ± SD | 163±112 | 175±122 | 143±92 | 0.39 |
| Time to follow-up imaging (days), mean ± SD | 3.2±1.6 | 3.5±1.6 | 2.7±1.4 | 0.34 |
| Treatment with intravenous rtPA | 47 (54.7) | 25 (48.1) | 22 (64.7) | 0.13 |
| Endovascular treatment | 11 (12.8) | 3 (5.8) | 8 (23.5) | 0.02 |

ICA indicates internal carotid artery; NIHSS, National Institutes of Health Stroke Scale; IQR, interquartile range; CTA, computed tomography angiography; rtPA, recombinant tissue plasminogen activator; SD, standard deviation.

Table 3.2. Baseline characteristics stratified for treatment modalities

| Variable, No. (%) | No treatment N=28 | Intravenous rtPA N=47 | Endovascular treatment N=11 |
|---|---|---|---|
| Male | 21 (75.0) | 35 (74.5) | 8 (72.7) |
| Age (years), mean ± SD | 65±13 | 62±12 | 58±13 |
| Hypertension | 19 (67.9) | 18 (38.3) | 0 (0.0) |
| Diabetes mellitus | 7 (25.0) | 3 (6.4) | 0 (0.0) |
| Hyperlipidemia | 14 (50.0) | 9 (19.1) | 1 (9.1) |
| Smoking | 14 (50.0) | 16 (34.0) | 3 (27.3) |
| Previous use of antithrombotic medication | 17 (60.7) | 14 (29.8) | 2 (18.2) |
| NIHSS on admission, median (IQR) | 4 (3–8) | 12 (7–17) | 12 (11–18) |
| Time from onset to CTA (minutes), mean ± SD | 228±137 | 119±69 | 184±109 |
| Time to follow-up imaging (days), mean ± SD | 3.3±1.3 | 3.5±1.6 | 1.8±1.6 |

ICA indicates internal carotid artery; NIHSS, National Institutes of Health Stroke Scale; IQR, interquartile range; CTA, computed tomography angiography; SD, standard deviation.

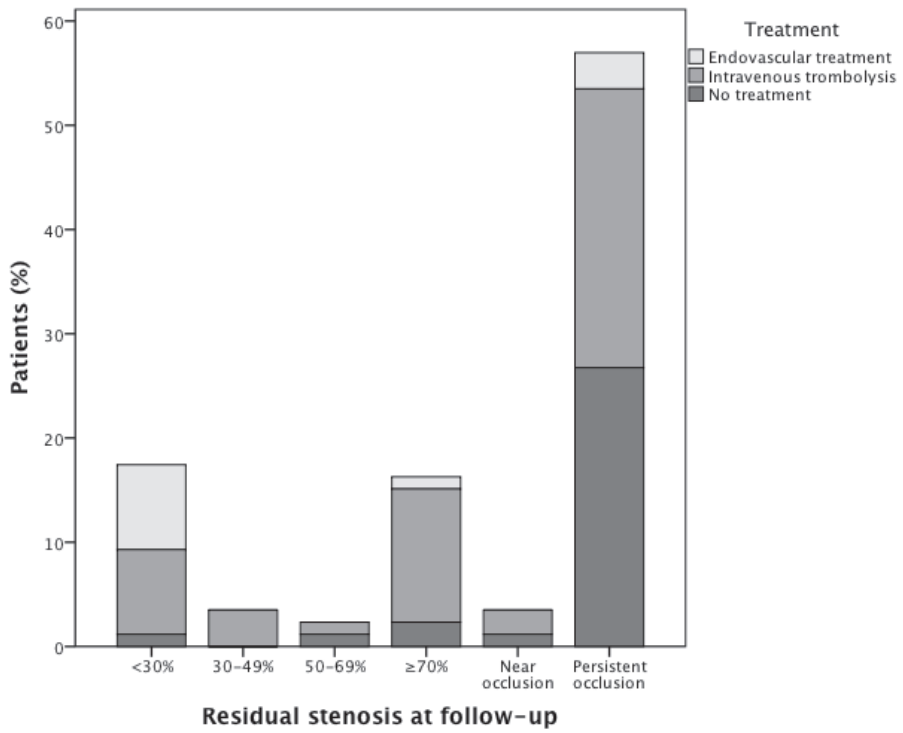



Figure 3.1. Proportion of the residual stenosis of the extracranial ICA at follow-up subdivided into the categories, stratified for treatment types.

9.8–25.6) patients; a near occlusion was found in 3 (3.5%; 95% CI 0.8–10.2) patients and a persistent occlusion in 49 (57.0%; 95% CI 46.4–66.9) patients.

With regard to acute treatment, a residual high-grade stenosis of the extracranial ICA was found in 2 (7.1%; 95% CI 0.9–23.7) of the 28 untreated patients and in 11 (23.4%; 95% CI 13.5–37.4) of the 47 patients treated with intravenous rtPA. In one (9.1%; 95% CI -0.6–40.0) of the 11 patients with endovascular treatment a residual high-grade stenosis was present, but this patient also underwent stenting of the occluded extracranial ICA during endovascular treatment.

Of the 14 patients with a residual high-grade stenosis, 8 were later treated with carotid endarterectomy. Two patients were diagnosed with carotid artery dissection and therefore not eligible for carotid endarterectomy. The two patients with a residual stenosis of 50–69% did not undergo carotid endarterectomy.

Good clinical outcome (mRS ≤2) three months after stroke did not differ significantly in patients with either a residual high-grade stenosis (OR 2.1 (95% CI 0.6–7.1, p=0.23), or patients with a residual stenosis <70% (OR 1.3 (95% CI 0.5–3.7) p=0.64) compared to patients with a near or persistent occlusion.

## DISCUSSION

In one out of six patients with an occlusion of the extracranial ICA in the acute stage of ischemic stroke a residual high-grade stenosis remains after recanalization. Our findings have implications for secondary prevention, since carotid endarterectomy or stenting might be indicated in a selected group of these patients.

The proportion of patients with ischemic stroke and acute carotid occlusion in our study concurs with findings in previous studies in which rates between 6–15% have been reported.[1,2,15] Our recanalization rate of acute carotid occlusion (39.5%) also falls within the range (15.8 to 62.5%) described in other studies.[2,16–18] The rate of recanalization is dependent on several factors, such as the type of acute treatment and the segment affected.[17,19]

This is the first study with a prospective design on the occurrence of a residual high-grade stenosis after recanalization of an extracranial ICA occlusion in the acute stage of cerebral ischemia. One previous retrospective study showed that a high-grade stenosis remained in 13 (25%) of 52 patients with an acute occlusion.[18] Two smaller studies reported a residual high-grade stenosis in one out of 12 (8.3%) patients and two out of 20 (10.0%) patients

respectively.[2,16] More than half of the patients with a residual high-grade stenosis in our study population underwent carotid endarterectomy or carotid stenting. In addition, carotid endarterectomy could also be considered in patients with a residual stenosis of 50–69%.[6] This emphasizes the importance of follow-up imaging of a carotid artery that is found to be occluded in the acute phase.



Our study has several strengths, including the prospective design, the use of a standardized CTA imaging protocol and review of the imaging data, blinded to clinical findings. A possible limitation might be that baseline and follow-up imaging was not performed in all patients with a carotid occlusion. This was due to a contra-indication for iodinated contrast administration at baseline of follow-up, early discharge of the patients or no permission to perform a follow-up CTA. However, baseline characteristics did not differ between patients with and without follow up imaging. Furthermore, DUST was designed as a diagnostic and prognostic observational study on the value of CTA and CTP in acute ischemic stroke. There was no standardized collection of recurrent strokes, additional therapeutic strategies or outcome other than the modified Rankin Score. In addition, follow-up examinations consisted of four different modalities (CTA, MRA, DUS, DSA). Although standardization of the follow-up imaging would have increased the validity of our study, previous studies have shown that the accuracy of CTA is comparable to MRA, DSA and DUS in grading carotid stenosis.[20] In our study we found no differences in recanalization of the occluded carotid artery between the group with CTA follow-up only and the other imaging modalities. Furthermore, follow-up imaging was not performed at standardized time-intervals, but mostly performed within three days. Therefore, we were not able to assess at what time recanalization occurred and if recanalization was temporary or persistent. Although, three days may be considered a fairly tight time window, this time window may be relatively short for the subgroup with a near occlusion at follow-up. In this subgroup, it is possible that the recanalization process may still be ongoing and repeated follow-up imaging at later time-intervals might be indicated.

In conclusion, follow-up carotid imaging of patients with an acute symptomatic ICA occlusion on admission identifies a potentially treatable residual high-grade stenosis in one out of six patients. We therefore recommend follow-up imaging within a week after the event in all patients with an acute symptomatic ICA occlusion.

# REFERENCES


1. Burke MJ, Vergouwen MDI, Fang J, Swartz RH, Kapral MK, Silver FL et al. Short-term outcomes after symptomatic internal carotid artery occlusion. Stroke. 2011;42:2419–2424.
2. Meves SH, Muhs A, Federlein J, Büttner T, Przuntek H, Postert T et al. Recanalization of acute symptomatic occlusions of the internal carotid artery. J. Neurol. 2002;249:188–192.
3. Blaser T, Hofmann K, Buerger T, Effenberger O, Wallesch C-W, Goertler M. Risk of Stroke, Transient Ischemic Attack, and Vessel Occlusion Before Endarterectomy in Patients With Symptomatic Severe Carotid Stenosis. Stroke. 2002;33:1057–1062.
4. Johansson E, Wester P. Recurrent stroke risk is high after a single cerebrovascular event in patients with symptomatic 50–99% carotid stenosis: a cohort study. BMC Neurol. 2014;14:23.
5. Rothwell PM, Eliasziw M, Gutnikov SA, Warlow CP, Barnett HJM. Endarterectomy for symptomatic carotid stenosis in relation to clinical subgroups and timing of surgery. Lancet. 2004;363:915–924.
6. Barnett HJ, Taylor DW, Eliasziw M, Fox AJ, Ferguson GG, Haynes RB et al. Benefit of carotid endarterectomy in patients with symptomatic moderate or severe stenosis. North American Symptomatic Carotid Endarterectomy Trial Collaborators. N Engl J Med. 1998; 339:1415–1425.
7. Rothwell PM, Algra A, Amarenco P. Medical treatment in acute and long-term secondary prevention after transient ischaemic attack and ischaemic stroke. Lancet. 2011;377:1681–1692.
8. Bivard A, Spratt N, Levi C, Parsons M. Perfusion computer tomography: imaging and clinical validation in acute ischaemic stroke. Brain. 2011;134:3408–3416.
9. Van Seeters T, Biessels GJ, van der Schaaf IC, Dankbaar JW, Horsch AD, Luitse MJ et al. Prediction of outcome in patients with suspected acute ischaemic stroke with CT perfusion and CT angiography: the Dutch acute stroke trial (DUST) study protocol. BMC Neurol. 2014;14:37.
10. Adams HP, Bendixen BH, Kappelle LJ, Biller J, Love BB, Gordon DL et al. 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.
11. Van Swieten JC, Koudstaal PJ, Visser MC, Schouten HJ, van Gijn J. Interobserver agreement for the assessment of handicap in stroke patients. Stroke. 1988;19:604–607.
12. Rothwell P, Eliasziw M, Gutnikov S, Fox A, Taylor D, Mayberg M, et al. Analysis of pooled data from the randomised controlled trials of endarterectomy for symptomatic carotid stenosis. Lancet. 2003;361:107–116.
13. Bartlett E. Diagnosing carotid stenosis near-occlusion by using CT angiography. Am. J. Neuroradiol. 2006;27:9–10.
14. Chen C-J, Lee T-H, Hsu H-L, Tseng Y-C, Lin S-K, Wang L-J, et al. Multi-Slice CT angiography in diagnosing total versus near occlusions of the internal carotid artery: comparison with catheter angiography. Stroke. 2004;35:83–85.
15. Paciaroni M, Caso V, Venti M, Milia P, Kappelle LJ, Silvestrelli G, et al. Outcome in patients with stroke associated with internal carotid artery occlusion. Cerebrovasc. Dis. 2005;20:108–113.
16. Szabo K, Kern R, Gass A, Griebe M, Lanczik O, Daffertshofer M et al. Early spontaneous recanalization following acute carotid occlusion. J. Neuroimaging. 2008;18:148–153.
17. Zangerle A, Kiechl S, Spiegel M, Furtner M, Knoflach M, Werner P et al. Recanalization after thrombolysis in stroke patients: predictors and prognostic implications. Neurology. 2007;68: 39–44.
18. Pechlaner R, Knoflach M, Matosevic B, Ruecker M, Schmidauer C, Kiechl S et al. Recanalization of extracranial internal carotid artery occlusion after i.v. thrombolysis for acute ischemic stroke. PLoS One. 2013;8:e55318.
19. Eckert B, Kucinski T, Neumaier-Probst E, Fiehler J, Rother J, Zeumer H et al. Local Intra-Arterial Fibrinolysis in Acute Hemispheric Stroke: Effect of Occlusion Type and Fibrinolytic Agent on Recanalization Success and Neurological Outcome. Cerebrovasc. Dis. 2003;15:258–263.
20. Nederkoorn PJ, van der Graaf Y, Hunink MGM. Duplex ultrasound and magnetic resonance angiography compared with digital subtraction angiography in carotid artery stenosis: a systematic review. Stroke.2003;34:1324–1332.

# CHAPTER 4

## Acute nephropathy after CT angiography and CT perfusion in acute ischemic stroke

Merel J.A. Luitse
Meenakshi Dauwan
Tom van Seeters
Alexander D. Horsch
Joris M. Niesten
L. Jaap Kappelle
Geert Jan Biessels
Birgitta K. Velthuis
on behalf of Dutch acute Stroke Study (DUST)

Adapted from:
International Journal of Stroke. 2015;10:E35–36

# ABSTRACT

## Introduction

Development of acute nephropathy is a safety concern when using Computed Tomography Perfusion (CTP) and Angiography (CTA) for acute ischemic stroke. We assessed the occurrence of acute nephropathy after CTP and CTA in patients with acute ischemic stroke.

## Methods

Patients with a suspected ischemic stroke and without known renal dysfunction, were recruited from the Dutch acute Stroke Study (DUST). All patients underwent CTP and CTA within 9 hours after stroke onset. Creatinine levels were measured at admission and again within 3 days. Admission renal dysfunction was defined as an estimated glomerular filtration rate (eGFR) of <60 mL/min/1.73 $m^2$. Acute nephropathy was defined as an increase in creatinine level of >25% or >44 µmol/L.

## Results

Baseline and follow-up creatinine levels were available in 731 patients. Acute nephropathy occurred in 27 (3.7%) patients. In 16 of these patients, the creatinine rise did not reach the threshold of impaired renal function. The occurrence of acute nephropathy was not increased in patients with renal dysfunction on admission.

## Conclusion

Acute nephropathy is infrequent in patients with suspected acute ischemic stroke who received intravenous iodinated contrast, even in patients with renal dysfunction on admission. CTP and CTA imaging can be safely performed without prior knowledge of renal function.

# INTRODUCTION

Non-contrast computed tomography (NCCT), CT perfusion (CTP) and CT angiography (CTA) are increasingly used in the diagnostic work-up of patients with acute ischemic stroke in the emergency setting.[1] CTP helps to differentiate between reversible and irreversible ischemia and CTA can identify arterial occlusions, which may require immediate treatment.[2] A safety concern regarding the use of CTP and CTA is the potential development of contrast-induced-nephropathy (CIN).[3,4] However, waiting for the renal function laboratory results before starting treatment may cause unacceptable delay in the acute stage of ischemic stroke.



CIN develops within 72 hours after contrast administration and elevated creatinine levels usually normalize within 2 weeks.[5] However, a minority of the affected patients develops chronic renal failure.[4] Moreover, CIN has been associated with prolonged hospital stay and increased mortality rates.[4] The aim of our study was to evaluate the occurrence of acute nephropathy after CTP and CTA in the emergency setting in patients with suspected acute ischemic stroke. A secondary aim was to evaluate the relation of acute nephropathy to renal function on admission.

# METHODS

## Study population

All patients participated in the multicenter prospective Dutch acute Stroke Study (DUST) between May 2009 and July 2013. Inclusion criteria for the DUST were 1) clinical diagnosis of acute ischemic stroke, 2) NCCT, CTP and CTA examination performed within 9 hours of symptom onset and 3) no known renal disease on admission. Institutional review boards approved the study, and written informed consent was obtained for each patient. Detailed information on the DUST has been described previously.[6] For the present study, creatinine levels at admission and follow-up were required.

## Imaging protocol

NCCT, CTP, and cervical and cranial CTA were performed at admission. Detailed information on the CTA and CTP imaging protocol has been described previously.[6] As per institutional protocol, a total of 90–110 ml non-ionic contrast agent was administered for CTA (50–70 ml) and CTP (40 ml).

## Clinical assessment

Information on patients' medical history including hypertension, diabetes, coronary artery disease, and type of treatment applied, e.g. intravenous thrombolysis or endovascular treatment was collected. Creatinine levels were measured on admission before CT examination (baseline) and within 3 days after admission (follow-up). The estimated glomerular filtration rate (eGFR) was calculated with the MDRD (Modification of Diet in Renal Disease) equation by using the admission creatinine value.[7]

Routinely, patients were screened for a history of renal disease based on information from the patient or hospital records. If there was no known history of renal disease, treating physicians were advised to perform CT examinations as soon as possible, also before baseline creatinine levels were available. There was no standardized hydration protocol before or after contrast administration. Patients who were diagnosed with impaired renal function after the CTP and CTA were performed were treated at the discretion of their physician.

Renal dysfunction on admission was defined as an eGFR <60 mL/min/1.73 $m^2$. Acute nephropathy was defined according to the standard definition of CIN: (a) a relative increase in serum creatinine level by >25% or (b) an absolute increase of >44 μmol/L within 3 days after admission.[5]

## Outcome measures

The primary outcome measures was the development of acute nephropathy within 3 days after admission. Furthermore, we assessed the occurrence of renal dysfunction after the development of acute nephropathy for which treatment was required. In a second analysis, we assessed the occurrence of acute nephropathy separately for patients with and without renal dysfunction on admission.

## Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics, version 20. All data are expressed as means ± standard deviation (SD) or as medians with interquartile ranges (IQR) when they were not normally distributed. Mean values were compared by analysis of variance (ANOVA). Differences in proportions were evaluated by the $\chi^2$ test. Differences at the level of $p<0.05$ were considered statistically significant.

Descriptive statistics were used to analyse the proportion of patients with renal dysfunction and the patients who developed acute nephropathy and persistent renal dysfunction.

# RESULTS

## Baseline characteristics

From May 2009 until July 2013, 1393 patients were included in DUST. Follow-up creatinine levels at any time after admission were available in 883 of these patients; in 82.8% of the patients these follow-up creatinine levels were measured within 3 days after admission. As a result, 731 patients were included in the analyses. In the majority of these patients (89.9%) creatinine levels were measured after 48–72 hours. The baseline characteristics are shown in Table 4.1. Renal dysfunction on admission was present in 155 (21.2%) patients. These patients were significantly older than patients with normal renal function and hypertension occurred more frequently.



Table 4.1. Baseline characteristics, stratified for renal function on admission

| Variable, No. (%) | Study population (N=731) | Renal dysfunction on admission (N=155) | Normal renal function on admission (N=576) | p |
|---|---|---|---|---|
| Age (years) mean±SD | 66±14 | 74±11 | 64±14 | <0.001 |
| Male | 441 (60.3) | 78 (50.3) | 363 (63.0) | 0.004 |
| Hypertension | 345 (47.2) | 103 (66.5) | 242 (42.0) | <0.001 |
| Diabetes | 95 (13.0) | 23 (15.9) | 72 (12.5) | 0.434 |
| Coronary artery disease | 99 (13.5) | 30 (19.4) | 69 (12.0) | 0.018 |
| Intravenous rtPA | 485 (66.3) | 100 (64.5) | 385 (66.8) | 0.587 |
| Endovascular treatment | 56 (7.7) | 9 (5.8) | 47 (8.2) | 0.323 |
| Admission creatinine (mmol/L) mean±SD | 85±23 | 114±25 | 77±15 | <0.001 |
| Admission eGFR (mL/min/1.73 $m^2$) median±IQR | 75 (61–88) | 52 (43–57) | 80 (69–92) | <0.001 |

eGFR indicates estimated Glomerular Filtration Rate; rtPA, recombinant tissue plasminogen activator; SD, standard deviation; IQR, interquartile range.

## Outcome

According to the definitions for acute nephropathy, 27 patients (3.7%) had a relative increase in creatinine of >25%, including 4 patients (0.7%) who also had an absolute increase of creatinine of >44 μmol/L (Figure 4.1). The median increase of the creatinine level in the 27 patients was 22 μmol/L (IQR 17–37μmol/L). The occurrence of acute nephropathy was not increased in patients with renal dysfunction on admission (1.3%),

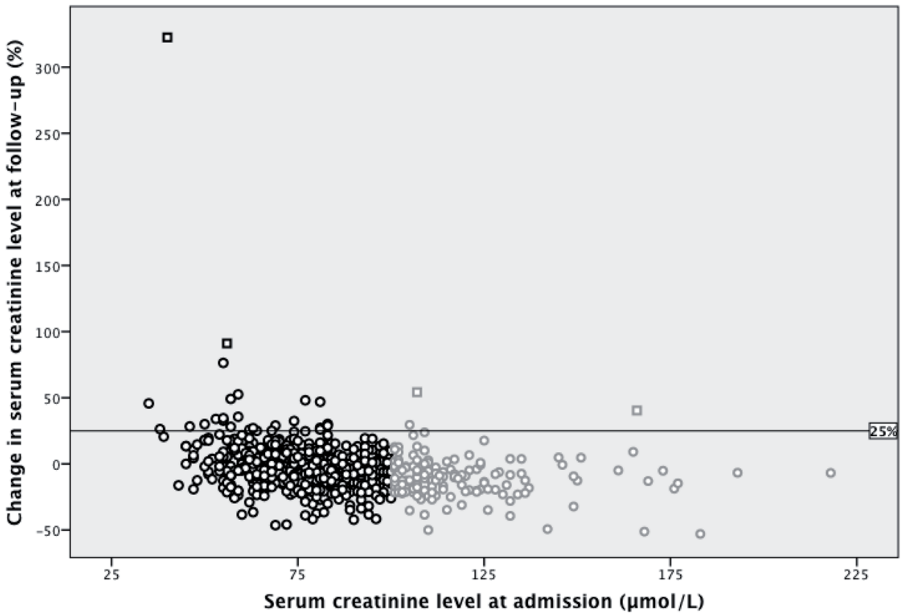



Figure 4.1. Relative change in follow-up serum creatinine levels (%) with respect to serum creatinine levels at admission.
The horizontal line represents the cut-off point of 25% above which acute nephropathy is present. The red dots represent the patients with >25% increase. The yellow dots with red borders represent the 4 patients with also an absolute increase of >44 µmol/L.

compared to those with normal renal function (4.3%). Of the 152 patients with follow-up creatinine levels measured beyond 3 days after admission, two patients met the definition of acute nephropathy. These creatinine levels were measured after 4 and 6 days respectively.

Sixteen of the 27 patients (63.0%) who met the criteria of acute nephropathy did not reach the threshold of impaired renal function (eGFR <60 mL/min/1.73 $m^2$) at follow-up. None of these patients required further treatment. Eight patients were diagnosed with acute nephropathy at follow-up, but did not require treatment according to their physician and their renal function recovered spontaneously.

Three patients (0.4%) developed persistent renal dysfunction after acute nephropathy for which treatment was required. In one of them, acute urinary retention and cystitis were considered to be contributory factors. He was treated with intravenous fluids. In another patient, NSAID's were stopped and renal function was closely monitored. In both patients, renal function recovered to admission levels. The third patient proved to have

a history of pre-existing renal disease unrecognized at admission, which was in violation with the study protocol. This patient developed acute renal insufficiency, considered to be caused by the combination of contrast administration and antibiotics use. Hemodialysis was planned, but the patient died of myocardial infarction before dialysis was started.

## DISCUSSION

This study demonstrates that the risk of acute nephropathy is low in patients with a diagnosis of acute ischemic stroke who underwent diagnostic CTP and CTA in the emergency setting, even in those with unknown renal dysfunction on admission. In one patient that developed acute nephropathy, a history of renal disease was missed at admission, which emphasizes the importance of a high vigilance for obtaining a history of renal function when this protocol is used in the acute stage of ischemic stroke.



Our study is the first prospective cohort study that assessed the risk of acute nephropathy stratified on the basis of renal function on admission. Our results concur with observations from previous retrospective studies, the largest of which (N=1075) reported an incidence of CIN in 52 patients (4.8%) of whom four (0.37%) patients needed additional treatment.8 Several smaller studies reported a similar incidence of CIN.[3,4,9,10] In our study, baseline creatinine levels were mostly unknown at the time of contrast administration, whereas in some of the other studies baseline creatinine levels were known before CT scanning.[3,8] This may have led to an underestimation of acute nephropathy, as patients with impaired renal function at admission may not have received iodinated contrast.

A limitation of our study is that we did not include a reference group of stroke patients who did not receive iodinated contrast. Therefore, it was not possible to determine the proportion of patients with acute nephropathy who did not receive iodinated contrast in the acute stage of ischemic stroke. Consequently, we chose the term "acute nephropathy" instead of CIN, because the term "CIN" implies causality and therefore cannot be used in absence of a reference group. With regard to safety of contrast administration this limitation is probably of minor importance since our definition includes both patients with CIN and acute nephropathy due to other causes. Moreover, studies focusing on the acute stroke setting in which a reference group was included, found similar rates of acute nephropathy and report no difference between patients who underwent imaging examinations with contrast administration and controls.[11,12] It had therefore been suggested that CIN may be overdiagnosed and is confounded by alternative explanations for renal dysfunction in hospitalized patients.[13,14]

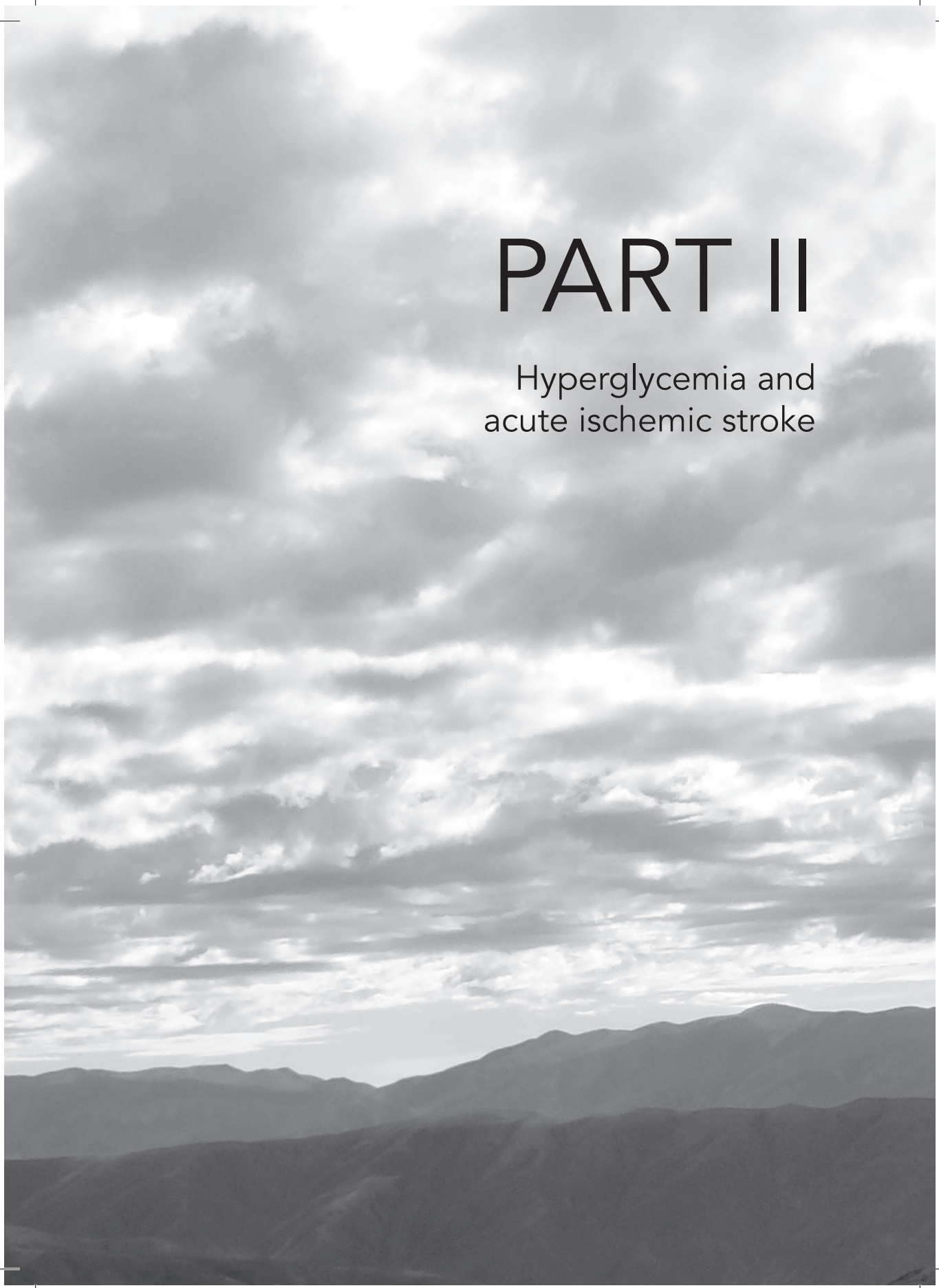
Another limitation of our study is that in 510 patients participating in DUST no follow-up creatinine levels were available. The risk of acute nephropathy may therefore be underestimated, although it is unlikely that cases of acute nephropathy that required treatment would have been missed.[9]

### Conclusion

The occurrence of acute nephropathy is low in patients with acute ischemic stroke without a known history of renal disease, even if renal dysfunction is present on admission. Therefore, it appears to be safe to perform CTP and CTA before creatinine levels are known. Nevertheless, we do recommend follow-up of renal function in the first days after admission.

## REFERENCES


1. Gonzalez RG. Current State of Acute Stroke Imaging. Stroke. 2013;44:3260–3264.
2. Bivard A, Spratt N, Levi C, et al. Perfusion computer tomography: imaging and clinical validation in acute ischemic stroke. Brain. 2011;134:3408–3416.
3. Dittrich R, Akdeniz S, Kloska SP, et al. Low rate of contrast-induced Nephropathy after CT perfusion and CT angiography in acute stroke patients. J Neurol. 2007;254:1491–1497.
4. Hopyan JJ, Gladstone DJ, Mallia G, et al. Renal safety of CT angiography and perfusion imaging in the emergency evaluation of acute stroke. American J Neuroradiol. 2008;29:1826–1830.
5. Stacul F, van der Molen AJ, Reimer P, et al. Contrast induced nephropathy: updated ESUR Contrast Media Safety Committee guidelines. Eur Radiol. 2011;21:2527–2541.
6. Van Seeters T, Biessels GJ, van der Schaaf IC, et al. Prediction of outcome in patients with suspected acute ischemic stroke with CT perfusion and CT angiography: the Dutch acute stroke trial (DUST) study protocol. BMC Neurol. 2014;14:37.
7. Morcos SK, Thomsen HS, Webb JA. Contrast-media-induced nephrotoxicity: a consensus report. Contrast Media Safety Committee, European Society of Urogenital Radiology (ESUR). Eur Radiol. 1999;9:1602–1613.
8. Josephson SA, Dillon WP, Smith WS. Incidence of contrast nephropathy from cerebral CT angiography and CT perfusion imaging. Neurology. 2005;64:1805–1806.
9. Krol AL, Dzialowski I, Roy J, et al. Incidence of radiocontrast nephropathy in patients undergoing acute stroke computed tomography angiography. Stroke. 2007;38:2364–2366.
10. Mehdiratta M, Schlaug G, Kumar S, et al. Reducing the delay in thrombolysis: is it necessary to await the results of renal function tests before computed tomography perfusion and angiography in patients with code stroke? J Stroke Cerebrovasc Dis. 2008;17:273–275.
11. Aulicky P, Mikulík R, Goldemund D, et al. Safety of performing CT angiography in stroke patients treated with intravenous thrombolysis. J Neurol Neurosurg Psychiatry. 2010;81:783–787.
12. Lima FO, Lev MH, Levy RA, et al. Functional contrast-enhanced CT for evaluation of acute ischemic stroke does not increase the risk of contrast-induced nephropathy. American J Neuroradiol. 2010;31:817–821.
13. Davenport MS, Cohan RH, Khalatbari S, et al. The challenges in assessing contrast-induced nephropathy: where are we now? Am J Roentgenol. 2014;202:784–789.
14. Sinert R, Brandler E, Subramanian RA, et al. Does the current definition of contrast-induced acute kidney injury reflect a true clinical entity? Acad Emerg Med. 2012;19:1261–1267.



# PART II

## Hyperglycemia and acute ischemic stroke

# CHAPTER 5

## Diabetes, hyperglycemia, and acute ischemic stroke

Merel J.A. Luitse
Geert Jan Biessels
Guy E.H.M. Rutten
L. Jaap Kappelle

Lancet Neurology. 2012;11:261–271

## ABSTRACT

Diabetes and ischemic stroke often arise together. People with diabetes have more than double the risk of ischemic stroke after correction for other risk factors, relative to individuals without diabetes. Multifactorial treatment of risk factors for stroke—in particular, lifestyle factors, hypertension, and dyslipidemia—will prevent a substantial number of these disabling strokes. Hyperglycemia occurs in 30–40% of patients with acute ischemic stroke, also in individuals without a known history of diabetes. Admission hyperglycemia is associated with poor functional outcome, possibly through aggravation of ischemic damage by disturbing recanalization and increasing reperfusion injury. Uncertainty surrounds the question of whether glucose-lowering treatment for early stroke can improve clinical outcome. Achievement of normoglycemia in the early stage of stroke can be difficult, and the possibility of hypoglycemia remains a concern. Phase 3 studies of glucose-lowering therapy in acute ischemic stroke are underway.

# INTRODUCTION

Diabetes and ischemic stroke are common disorders that often arise together. Worldwide, 347 million people have diabetes,[1] and the type 1 and type 2 forms are the most typical (Panel 5.1). Diabetes is a leading cause of renal failure, coronary heart disease, non-traumatic lower limb amputations, and visual impairment (Figure 5.1). Stroke is the second leading cause of long-term disability in high-income countries and the second leading cause of death worldwide.[18] In 2005, 16 million people had a first stroke and

**Panel 5.1. Update on diabetes**

**Type 1 diabetes**
Type 1 diabetes is a cell-mediated autoimmune disease with destruction of β cells that leads to absolute insulin deficiency, resulting in hyperglycemia and lipolysis.[2] The disorder accounts for 5–10% of the total diabetes population.[3] Onset of type 1 diabetes usually happens before age 30 years. Incidence is 16.4 per 100000 in men and 8.9 per 100000 in women.[4] All patients need insulin treatment.

**Type 2 diabetes**
Type 2 diabetes is characterised by insulin resistance and relative insulin deficiency and accounts for 90% of patients with diabetes.[5] The progression from normal glucose metabolism to type 2 diabetes is gradual and happens over many years. When the pancreas fails (after a compensatory increase in insulin secretion), the patient develops hyperglycemia. The estimated global prevalence of type 2 diabetes is 3.8%.[6] Prevalence does not differ by sex[7] and increases with age, to 20–25% in patients older than 65 years.[8] Over past decades, type 2 diabetes has become more prevalent in younger age groups, including adolescents.[9] Insulin resistance develops because of environmental factors, particularly obesity and a sedentary lifestyle.[10] Moreover, a family history confers a 2.4-times risk of the disorder.[5] Treatment is aimed at reduction of insulin resistance and increasing endogenous insulin secretion. In more advanced stages of type 2 diabetes, treatment with exogenous insulin could be necessary.

**Prediabetic stages**
People whose glucose levels are raised but are still below the diabetes threshold are at higher risk for progression to type 2 diabetes than are individuals with normal values. Stages of elevated glucose are defined as impaired glucose tolerance (i.e., 2 h after glucose loading, a glucose concentration of 7.8–11.1 mmol/L) or impaired fasting glucose (i.e., a fasting glucose level of 6.1–6.9 mmol/L).[11] Both impaired glucose tolerance and impaired fasting glucose are associated with cardiovascular disease.[12] These prediabetic disorders sometimes occur with obesity, dyslipidaemia, hypertension, and prothrombotic and proinflammatory states.[9]

**Vascular complications in diabetes**
Prolonged hyperglycemia is associated with microvascular complications, such as retinopathy (Figure 5.1A and 5.1B),[13] neuropathy, and nephropathy, and with macrovascular complications caused by atherosclerosis (Figure 5.1C).[3] Despite intensive treatment, most patients with type 1 diabetes develop microvascular complications before midlife.[14] Type 1 diabetes is also a risk factor for macrovascular complications later in life.[15] In patients with type 2 diabetes, microvascular complications develop as exposure to hyperglycemia increases.[16] Macrovascular complications might already start to develop in prediabetic stages.[17]

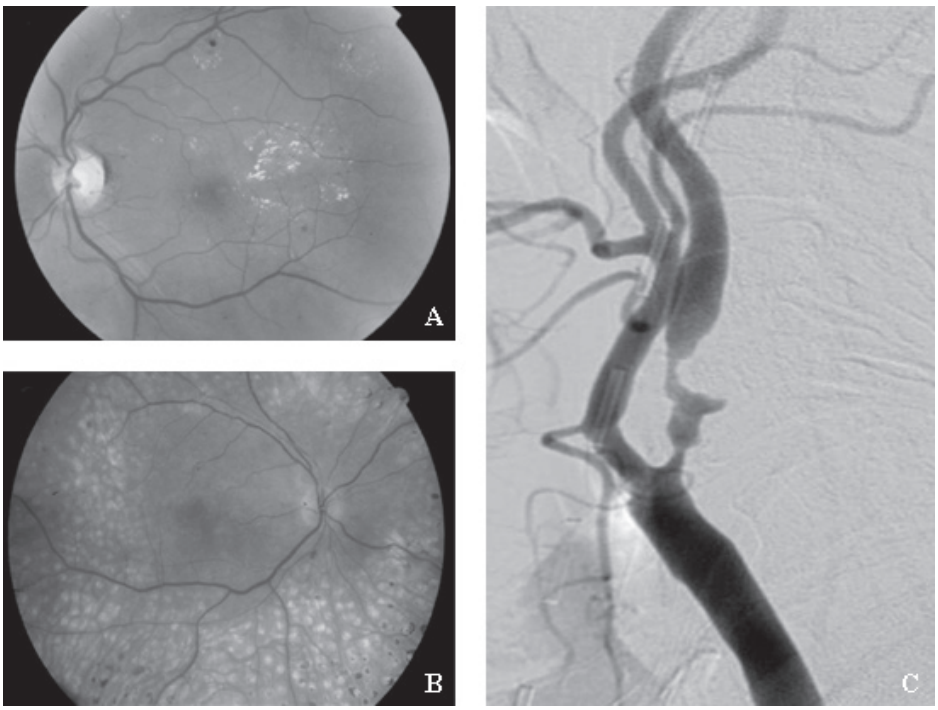



**Figure 5.1. Microvascular and macrovascular complications of diabetes.**
(A) Non-proliferative diabetic retinopathy showing microhemorrhage and hard exudates. (B) Proliferative diabetic retinopathy with neovascularisation. Reproduced from Cheung and colleagues,[13] by permission of Elsevier. (C) Large-vessel atherosclerosis.

5.7 million died because of the effects of stroke.[19] The relation between disturbed glucose metabolism and ischemic stroke is bidirectional. On the one hand, people with diabetes have more than double the risk of ischemic stroke after correction for other risk factors, compared with people without diabetes.[20] On the other hand, acute stroke can give rise to abnormalities in glucose metabolism, which in turn could affect outcome.[21] Importantly, the relation between disturbed glucose metabolism and cerebrovascular disease is not restricted to acute ischemic stroke. Diabetes is also associated with more insidious ischemic damage to the brain, mainly manifesting as small-vessel disease and increased risk of cognitive decline and dementia.[22] Moreover, a relation between admission hyperglycemia and poor outcome has been noted for hemorrhagic stroke, in particular aneurysmal subarachnoid hemorrhage.[23]

In this Review, we describe the interplay between glucose metabolism and acute ischemic stroke and focus on clinical implications for prevention and management in the acute

stage. We address the epidemiology of the association between diabetes and stroke, highlighting potentially modifiable risk factors and long-term outcome. We review findings from many trials on prevention of stroke in people with diabetes, which suggest that rigorous assessment and treatment of associated risk factors can substantially reduce the risk of stroke in patients with diabetes. We then describe the cause, outcome, and management of hyperglycemia at the time of an acute ischemic stroke. Admission hyperglycemia is a common risk factor for poor outcome after ischemic stroke. However, much uncertainty surrounds the question of whether intensive glucose-lowering treatment after stroke benefits clinical outcome.

## DIABETES AND RISK OF STROKE

Diabetes is an important risk factor for ischemic stroke. In a meta-analysis of prospective studies (including 530083 participants), the reported hazard ratio for ischemic stroke was 2.3 (95% CI 2.0–2.7) in people with versus those without diabetes.[20] Assuming a population-wide prevalence of diabetes of around 10%, these findings indicate a diabetes-attributable risk of stroke of around 12% (i.e., one in eight or nine cases of stroke is attributable to diabetes). The risk of stroke associated with diabetes is assessed predominantly in people with type 2 diabetes, because in the age group in which most strokes take place, type 2 diabetes is much more common than type 1 diabetes. Studies that allow direct comparison between both types of diabetes show that the relative risk of stroke in people with type 1 diabetes is at least similar or maybe even higher than in individuals with type 2 diabetes.[24,25] In patients younger than 60 years, the relative risk of stroke in those with versus those without diabetes is double that of individuals older than 70 years.[20] Sex and ethnic origin also modulate the risk of stroke in people with diabetes. The risk is higher in women (hazard ratio 2.8, 95% CI 2.4–3.4) than in men (2.2, 1.8–2.5).[20] In US populations, people of African-American origin are over-represented among patients with diabetes who have a stroke.[26] Diabetes causes atherosclerotic changes in the heart and the cerebropetal arteries and is associated with different subtypes of ischemic stroke, including lacunar, large artery occlusive, and thromboembolic strokes.[27–29] Moreover, the risk of atrial fibrillation—a major cause of thromboembolic stroke—is increased by 40% in individuals with diabetes.[30] Diabetes-associated risk factors for stroke include not only diabetes-specific factors (e.g., hyperglycemia) and vascular risk factors (e.g., hypertension, dyslipidemia) but also genetic, demographic, and lifestyle factors. The contribution of these factors, many of which are strongly inter-related, is likely to differ according to diabetes type and age. Nevertheless, after adjustment for the above-mentioned risk

factors, diabetes is associated with a doubling in the risk of ischemic stroke (hazard ratio 2.2, 95% CI 1.9–2.6) compared with those without diabetes.[20] The risk of stroke is already raised in prediabetic stages. Insulin resistance is a risk factor for stroke,[31] but whether insulin concentrations themselves or markers of glucose tolerance convey the highest risk is debatable.[32,33] Therefore, amounts of HbA1c have also been investigated.[34] HbA1c concentrations of greater than 42 mmol/mol (6%) increased the risk of stroke between two and three times in adults without diabetes, taking the potential confounding effects of other vascular risk factors into account.[34]

## DIABETES AND LONG-TERM OUTCOME AFTER STROKE

During the first 3 months after ischemic stroke, mortality is not increased in patients with diabetes compared with those without.[35,36] However, mortality more than 1 year after stroke was slightly increased (hazard ratio 1.2, 95% CI 1.1–1.2); a similar finding was reported in patients younger than 50 years.[36,37] Furthermore, risk of recurrent stroke is raised (1.8, 1.2–2.8),[38] which could be even more striking in patients with diabetes younger than 50 years.[37] Finally, diabetes is associated with augmented risk of long-term functional deficits after stroke (odds ratio 1.5, 95% CI 1.1–1.9),[35] including an increased risk of post-stroke dementia (1.5, 1.1–2.3).[39]

## DIABETES AND PREVENTION OF STROKE

Several risk factors for stroke in patients with diabetes are potentially modifiable, in particular lifestyle factors, glucose concentrations, blood pressure, and dyslipidemia, which have been targeted in several large randomised controlled trials (Panel 5.2). Neurologists typically distinguish between primary prevention (e.g., prevention of first stroke) and secondary prevention (e.g., prevention after transient ischemic attack or ischemic stroke). However, this distinction is not always made in published work on prevention of cardiovascular events in people with diabetes. Lifestyle probably has the largest effect on risk of stroke, and smoking, obesity, inactivity, excessive alcohol intake, and unhealthy diets should be strongly discouraged in people with diabetes. Lifestyle modification in this population is associated with a substantial decline in stroke incidence (hazard ratio 0.62, 95% CI 0.39–0.98).[42] Moreover, modest weight loss (5–10% of bodyweight) in individuals with type 2 diabetes has been associated with substantial improvement of cardio vascular risk factors and glycemic control.[43,44]

Panel 5.2. Stroke prevention in diabetes

- Regulate blood pressure below 130/80 mm Hg; angiotensin-converting-enzyme inhibitors or angiotensin II receptor blockers are recommended as first-line treatment[40,41]
- Prescribe statins[40]
- Discourage smoking, inactivity, excessive alcohol intake, and obesity[42–44]
- Prescribe platelet-aggregation inhibitors in patients with clinically manifest vascular disease and sinus rhythm[45]
- Apply the CHA2DS2-VAS score and prescribe warfarin in patients with clinically manifest vascular disease and with atrial fibrillation[40,46]
- Undertake carotid surgery in patients with symptomatic high-grade carotid stenosis[47]

CHA2DS2-VAS = congestive heart failure/left-ventricular dysfunction (1 point); hypertension (1); age ≥75 years (2); diabetes mellitus (1); stroke/transient ischemic attack/thromboembolism (2); vascular disease, i.e., previous myocardial infarction/ peripheral artery disease/aortic plaque (1); age 65–74 years (1); female sex (1).



## Glucose-lowering treatment

Three large long-term trials have compared the effects of intensive versus standard glycemic control in participants at fairly high risk of stroke with longstanding type 2 diabetes. In two of these trials, no difference in cardiovascular outcomes was reported with intensive glycemic control.[48,49] In the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study,[50] the glycemic control study was terminated after 3.7 years owing to increased mortality in the intensive treatment group (HbA1c <42 mmol/mol [6%]). Participants assigned to the intensive therapy group were subsequently switched to the standard control group (HbA1c 53–64 mmol/mol [7–7.9%]) and were followed up for about 1.2 years. Both before and after the transition, risk for non-fatal stroke was similar (hazard ratio 0.99, 95% CI 0.77–1.1, and 0.87, 0.65–1.2, respectively). At the end of the study, the rate of death from any cause was 19% higher in the intensive treatment group (hazard ratio 1.5 vs 1.3, 95% CI 1.0–1.4). Reasons for the higher mortality in the intensive therapy group in the pretransition period remain unclear.[51] In a meta-analysis of 34533 patients with type 2 diabetes, no beneficial effects of tight glycemic control versus standard glycemic control could be seen on stroke rates during a mean treatment period of 5 years (hazard ratio 0.96, 95% CI 0.83–1.1).[52] Similar findings were noted in a Cochrane review, in which the effects of targeting intensive versus conventional glycemic control were assessed in 29986 patients with type 2 diabetes from 20 randomised controlled trials, with a duration of intervention of between 3 days and 12.5 years.[53] Targeting intensive glycemic control did not reduce the risk of cardiovascular mortality (risk ratio 1.1, 95% CI 0.90–1.3) or non-fatal stroke (0.96, 0.80–1.2).[53] Heterogeneity between trials

did not affect the results. Of 837 non-fatal strokes, 423 were reported from one trial.[48] In a separate meta-analysis dealing exclusively withglycemic control in usual care settings, the effect estimate on prevention of non-fatal stroke remained non-significant (risk ratio 1.0, 95% CI 0.87–1.2). Risk of severe hypoglycemia was increased significantly when intensive glycemic control was targeted (relative risk 2.0, 95% CI 1.4–3.0).[53] Findings of the Diabetes Control and Complications Trial (DCCT) showed that 1422 patients with type 1 diabetes who were treated with intensive control of glucose concentration for 6.5 years had a 57% reduced risk of cardiovascular events over a mean follow-up period of 17 years (95% CI 12–79), compared with individuals receiving conventional treatment.[54] However, strokes were rare, with only one event in the intensive treatment group and five in the conventional treatment group.[54]

To date, insufficient evidence is available to show that stroke prevention will be improved by intensive glucose-lowering treatment, in people with either type 1 or type 2 diabetes. Clinicians should balance risk of (recurrent) hypoglycemia against the advantages of a lower amount of HbA1c, taking into account patient's age, duration of diabetes, and comorbidities.

## Vascular risk factors

In patients with type 2 diabetes, lowering of blood pressure has a large effect on risk of future stroke.[55–58] In a meta-analysis of 37736 patients (13 trials) with type 2 diabetes, impaired fasting glucose or impaired glucose tolerance assessed the effects of blood pressure control (≤135 mm Hg vs ≤140 mm Hg).[59] More intensive control of blood pressure was associated with a 10% reduction in all-cause mortality (odds ratio 0.90, 95% CI 0.83–0.98) and a 17% reduction in strokes (0.83, 0.73–0.95), compared with standard treatment. This difference was mainly driven by trials in which the aim was to achieve systolic pressure of 130–135 mm Hg. Control of blood pressure below 130 mm Hg was associated with a greater reduction in stroke but a 40% increase in serious adverse events, with no benefit for cardiac, renal, and retinal outcomes.[59] Most guidelines recommend a blood pressure of less than 130/80 mm Hg for patients with diabetes.[40] The choice of antihypertensive drugs is probably less important than the target levels. Currently, angiotensin-converting-enzyme (ACE) inhibitors or angiotensin II receptor blockers are typically recommended as first-line drugs.[40,41] In a post-hoc analysis of the Heart Protection Study, a daily dose of 40 mg simvastatin administered to 5963 patients with type 2 diabetes, of whom half did not have any evidence of arterial occlusive disease, was associated with a 28% (95% CI 8–44) reduction in ischemic stroke, independent of baseline lipid levels.[60] In people with type 2 diabetes with no history of cardiovascular

disease, daily use of 10 mg atorvastatin was associated with a 37% (17–52) reduction in cardiovascular events and with a 48% (11–69) reduction in all types of stroke.[61] In 9795 patients with type 2 diabetes, of whom 7664 had no history of cardiovascular disease, micronized fenofibrate 200 mg once daily versus placebo reduced the risk of cardiovascular events (hazard ratio 0.89, 95% CI 0.80–0.99), including ischemic stroke (0.91, 0.73–1.1).[62] The combination of fenofibrate and simvastatin did not reduce the rate of fatal or non-fatal cardiovascular events more than simvastatin alone.[63] On the basis of this evidence, statins are recommended for secondary prevention in all individuals with type 2 diabetes—and in most for primary prevention—depending on their 10-year cardiovascular risk.[40] Consensus on choice of statin has not been reached. In three trials,[64–66] multifactorial prophylactic treatment was assessed in people with type 2 diabetes. Of 160 high-risk individuals with longstanding type 2 diabetes and microalbuminuria who participated in the Steno-2 study,[64] a multifactorial approach—including use of statins, ACE inhibitors, angiotensin II receptor blockers, or an antiplatelet drug as appropriate, and modification of lifestyle—was associated with reduction of cardio vascular events by 59% (hazard ratio 0.41, 95% CI 0.25–0.67), compared with conventional treatment. The number of all types of stroke during a mean follow-up period of 8 years was five times higher in the group receiving conventional treatment.[64] In 3488 patients participating in the Euro Heart Survey on Diabetes and the Heart,[65] intensive treatment of vascular risk factors had an independent protective effect on 1-year mortality and cardiovascular events (relative risk 0.61, 95% CI 0.40-0.91, and 0.61, 0.39–0.95, respectively). No effect on stroke rate was recorded, but cerebrovascular revascularisation procedures were reduced by half.[65] The benefits of combined control of many vascular risk factors immediately after early diagnosis of type 2 diabetes were investigated in 3055 patients with diabetes, in the Anglo-Danish-Dutch Study of Intensive Treatment In People with Screen Detected Diabetes in Primary Care (ADDITION-Europe).[66] During a mean follow-up period of 5.3 years, stroke rates did not differ between groups. A non-significant reduction of cardio vascular events (hazard ratio 0.83, 95% CI 0.65–1.1) was noted in the intensive treatment group versus the routine care group.[66] Intensive monitoring of vascular risk factors is important in the long term, as shown by follow-up of individuals participating in the UK Prospective Diabetes Study (UKPDS).[67] Reported differences in blood pressure and stroke rate disappeared 2 years after termination of the trial. Training programmes for patients aimed at acquiring the skills for a healthy lifestyle and self-monitoring of blood glucose and blood pressure can be useful.[68]

## Antithrombotic treatment

Findings of a trial in which the efficacy of aspirin was assessed specifically in patients with type 2 diabetes with no history of cardiovascular disease did not show a protective effect on atherosclerotic events (hazard ratio 0.80, 95% CI 0.58–1.1).[69] This trial was not powered to detect an effect on stroke. In a meta-analysis on use of aspirin for primary prevention in patients with diabetes, no benefits were recorded with respect to reduction of serious vascular events, including stroke.[70] The effectiveness of antithrombotic drugs for secondary prevention of stroke has not been studied in a major trial, specifically in people with diabetes. In the Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) trial,[71] in which clopidogrel was compared with aspirin in patients with atherosclerotic disease (including minor disabling ischemic stroke), the benefit of clopidogrel for prevention of ischemic events was higher in individuals with diabetes than in those without (relative risk reduction 12.9%, 95% CI -3.0 to 26.4).[71] However, the conclusions of a meta-analysis of the efficacy of antithrombotic agents in more than 5000 patients with diabetes showed that these drugs reduced both coronary events and ischemic stroke to a similar degree as in people without diabetes.[45] Although the effect of antithrombotic treatment on prevention of future cardiovascular events is relatively low compared with rigorous control of risk factors, this type of drug should be considered in every patient with diabetes who is at risk of future vascular complications. Diabetes not only is a risk factor for atrial fibrillation[30] but also increases the risk of embolic complications in individuals with atrial fibrillation, as indicated by the CHA2DS2-VAS score (a measure of the risk of stroke, in which 1 point is assigned to each factor, unless otherwise noted: congestive heart failure or left-ventricular dysfunction; hypertension; age 75 years or older [2 points]; diabetes mellitus; stroke, transient ischemic attack, or thromboembolism [2 points]; vascular disease [previous myocardial infarction, peripheral artery disease, or aortic plaque]; age 65–74 years; and female sex).[46] Therefore, patients with diabetes and atrial fibrillation should receive platelet aggregation inhibitors if they have none of the other risk factors included in CHA2DS2-VAS46 and warfarin in all other cases.[72] Dabigatran, rivaroxaban, and apixaban are proven to protect patients with atrial fibrillation as well as—or even better than—warfarin, but the definite role of these new antithrombotic drugs in patients with a recent transient ischemic attack or minor ischemic stroke remains to be established.[73]

## Carotid surgery

Carotid endarterectomy for secondary stroke prevention in patients with high-grade stenosis of the carotid artery is effective, but has not been investigated specifically in

patients with diabetes. Both peri-procedural and long-term risks are higher in individuals with diabetes than in those without,[74,75] but this increased risk should not be a reason to withhold surgery in this group.

## HYPERGLYCEMIA IN ACUTE ISCHEMIC STROKE

Hyperglycemia arises in 30–40% of people with acute ischemic stroke.[76] Most of these individuals do not have a known history of diabetes mellitus.[21] In some patients, hyperglycemia reflects pre-existing but unrecognised diabetes, but more often it is the result of an acute stress response, typically named stress hyperglycemia (Panel 5.3). Glucose concentrations are raised in people with stress hyperglycemia but revert to normal after discharge from hospital.[77] Therefore, high levels of glucose on admission do not distinguish between stress hyperglycemia and diabetes, but under these conditions, raised amounts of HbA1c (≥48 mmol/mol [6.5%]) could help to identify people with previously undiagnosed diabetes.[40,77] Stress hyperglycemia usually resolves spontaneously after dissipation of the acute illness. The stress reaction that results in hyperglycemia is initiated by activation of the hypothalamic-pituitary-adrenal axis, which leads to raised amounts of glucocorticoids (cortisol) and activation of the sympathetic autonomic nervous system. Increased levels of stress hormones stimulate glucose production by glycogenolysis, gluconeogenesis, proteolysis, and lipolysis. Augmented epinephrine also can result in insulin resistance and hyperinsulinemia.[77,78]



**Panel 5.3. Differential diagnosis of hyperglycemia in acute ischemic stroke**

- Known pre-existing diabetes
  - Newly diagnosed diabetes
  - Fasting glucose >6.9 mmol/L or random glucose >11.1 mmol/L, persisting after discharge[77]
- HbA1c ≥6.5% at admission indicates pre-existing type 2 diabetes[40]
- Stress hyperglycemia
  - Fasting glucose >6.9 mmol/L or random glucose >11.1 mmol/L, reverting to normal range after discharge[77]

### Outcome

Compared with patients with normoglycemia, the unadjusted relative risk of in-hospital or 30-day mortality after an ischemic stroke in individuals who are hyperglycemic at admission is 3.3 (95% CI 2.3–4.7) in those without known diabetes and 2.0 (0.04–90.1) in those with

a known history of diabetes.[21] This increased risk is independent of other predictors of poor outcome. By contrast, for persistent hyperglycemia, at 24–48 h after stroke the relation with poor outcome is less clear.[79] The association between hyperglycemia and poor outcome after stroke is mainly relevant to patients with large vessel infarction.80 In lacunar stroke, moderate hyperglycemia has even been associated with good rather than poor outcome.[76,81]

## Pathophysiology

Both experimental and clinical studies have investigated extensively the potential mechanisms underlying the relation between hyperglycemia and poor outcome after stroke.[78] Results of a meta-analysis of experimental studies[82] showed that infarcts were larger in animal models of hyperglycemia, and this effect was more striking for streptozotocin than after dextrose infusion (140% larger vs 48% larger). The authors expressed concerns about the validity of experimental observations for the clinical situation,[82] because studies either include models with prolonged hyperglycemia before stroke (streptozotocin) or with very high glucose loads. Although hyperglycemia—in amounts that can be encountered in patients—has not been proven definitively to be a causal factor for impaired outcome after stroke, several mechanisms have been identified through which hyperglycemia could aggravate cerebral damage in ischemic stroke, including impaired recanalization and reperfusion injury (Figure 5.2).[78] Impaired recanalization has been attributed to disturbances in coagulation and in fibrinolytic pathways.[83,84] These pathways have been investigated extensively in people with diabetes, at prediabetic stages, with persistent dysglycemia, and who are resistant to insulin[85] but infrequently in those with acute stroke. Amounts of plasminogen activator inhibitor 1 and tissue-type plasminogen activator antigens, for example, were higher in individuals with glucose intolerance compared with those with normal glucose tolerance.[85] Hyperinsulinemia is associated mainly with impaired fibrinolysis in people with glucose intolerance.[86] Moreover, raised levels of fasting insulin are linked to impaired fibrinolysis and hypercoagulability in individuals with normal glucose tolerance.[86] Acute and chronically raised glucose concentrations show important similarities in their effects on coagulation activation and impaired fibrinolysis.[85] In patients with acute stroke, such disturbances could impinge on the efficacy of fibrinolytic treatment. Indeed, findings of transcranial Doppler imaging studies show that hyperglycemia is associated with persistent arterial occlusion after thrombolytic treatment in individuals with ischemic stroke.[87,88] Both acute and chronic hyperglycemia are associated with widespread abnormalities in blood vessels that can affect blood flow and vascular reactivity.[89,90] Disturbances in metabolism of

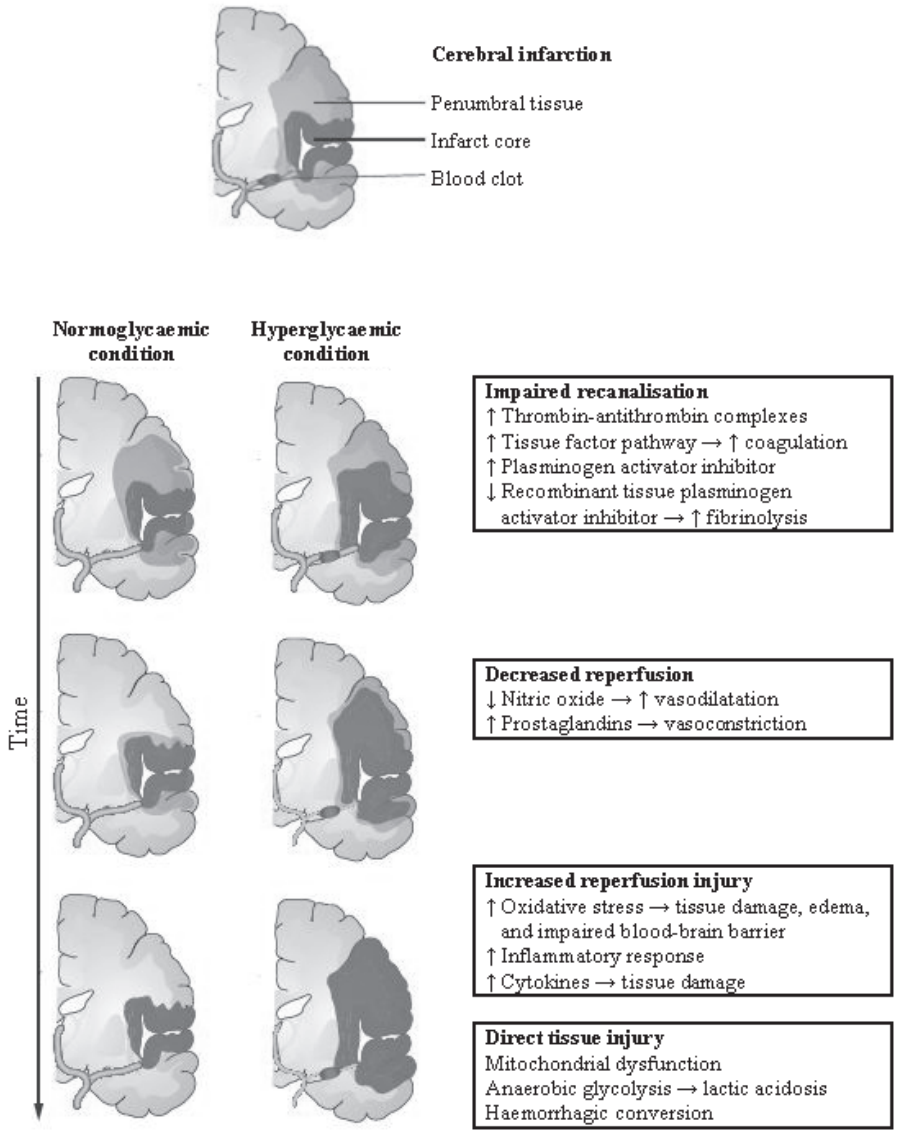



Figure 5.2. Potential effects of hyperglycemia over time on pathophysiological processes entailed in development of cerebral infarction.
Reproduced from Kruyt and colleagues,[78] by permission of Nature Publishing Group.

endothelium-derived nitric oxide probably have a key role in these vessel abnormalities,[91,92] which can become especially detrimental when blood flow is acutely compromised—e.g., during acute cerebral ischemia. Even when perfusion is restored, hyperglycemia could

further threaten the tissue, through augmented reperfusion injury.[90,93] This process is mediated by increased oxidative stress and inflammation,[94,95] both of which are affected by hyperglycemia. Moreover, admission hyperglycemia has been linked to increased risk of haemorrhagic complications after thrombolytic treatment.[78] In an observational study of a large series of patients with acute ischemic stroke treated with intravenous thrombolysis, the increased risk of haemorrhage was only raised significantly when admission glucose concentrations were greater than 10 mmol/L.[96] In another study, this increased risk was more evident in patients who had persistent hyperglycemia during the first 48 h after admission compared with those with admission hyperglycemia only.[97] Tight control of blood glucose could be indicated in the hyperacute phase after thrombolysis, but data from randomised trials are needed.[96] In patients with large-vessel thromboembolic stroke, hyperglycemia-related mechanisms are likely to affect salvage of the penumbra, the part of the ischemic area that can still potentially recover if adequate reperfusion is restored within hours after stroke onset (Figure 5.3). Indeed, findings of MRI studies indicate that reduced penumbral salvage is a key contributor to increased infarct size in patients with hyperglycemia at admission.[98,99] This effect on the penumbra might also explain why hyperglycemia is not associated with worse outcome in lacunar stroke, since a penumbra is usually not present in this stroke subtype. Moreover, lactate produced by astrocytes has been suggested to be an important rescue source of energy for axons in the basal ganglia region.[76] Enhanced lactate production due to hyperglycemia in lacunar stroke might fuel and salvage axons.[76]

## Management

Amounts of glucose in plasma should be measured on admission in all patients suspected of acute stroke, because they direct diagnosis and treatment. Exclusion of patients with a known history of diabetes from receiving thrombolytic treatment is unnecessary. The odds of improvement after thrombolysis are similar in people with or without a history of diabetes (odds ratio 1.5, 95% CI 1.3–1.6 vs 1.53, 1.4–1.6).[100] Severe hyperglycemia can cause focal neurological deficits with sudden onset, thus mimicking stroke.[101,102] For this reason, patients with glucose concentrations of greater than 22.2 mmol/L have been excluded from trials on intravenous thrombolysis. Therefore, whether intravenous thrombolysis is safe and useful in such patients is unclear. Modern imaging techniques, such as perfusion CT scanning, can help to differentiate acute cerebral ischemia from hyperglycemia-related focal neurological deficits (Figure 5.3). This method might make neurologists less reluctant to withhold intravenous thrombolysis in patients with severe hyperglycemia, although the risk of hemorrhagic transformation remains a concern.[96]

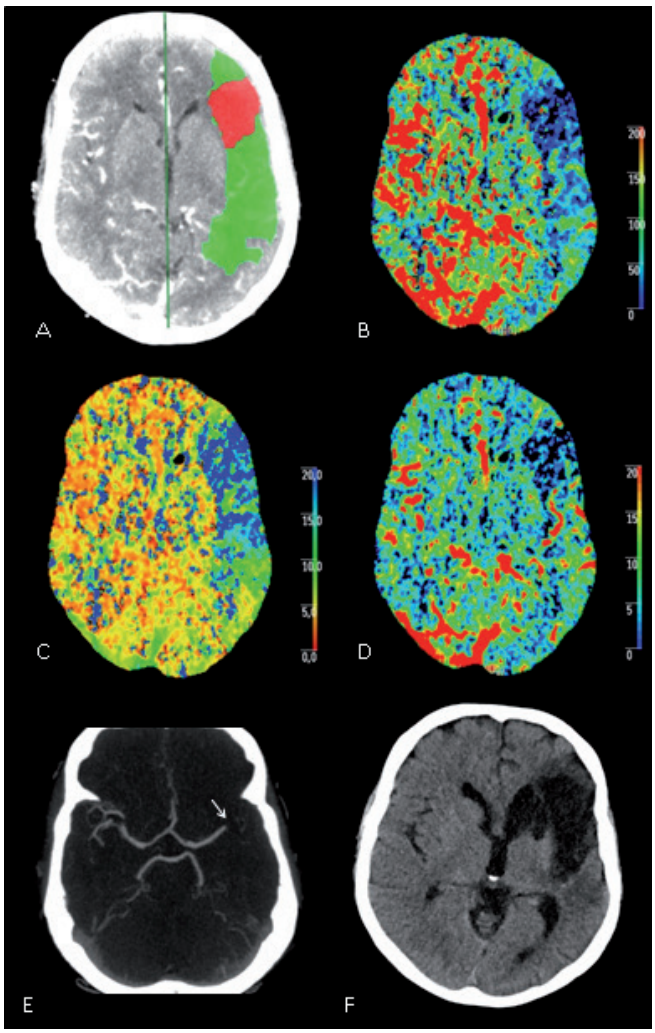



**Figure 5.3. Perfusion CT in acute ischemic stroke.**
Perfusion abnormalities can be identified on the basis of an area with decreased cerebral blood flow (B), increased mean transit time (C), and decreased cerebral blood volume (D). With these measures, the infarct core (A, red) and the potentially salvageable ischemic penumbra (A, green) can be identified. CT angiography (E) shows occlusion of the middle cerebral artery. Follow-up CT (F) shows the final lesion at 3 months.

The observed relation between hyperglycemia and poor outcome in patients with ischemic stroke raises the question of whether outcome can be improved by glucose-lowering treatment. Experience in disorders other than stroke suggests that glucose-lowering treatment might be effective.[103–105] Trial findings suggested that intensive insulin therapy

Table 5.1. Overview of phase 2 and 3 glucose-lowering trials in acute ischemic stroke

| Study | Phase | Patients | Intervention | Outcome | Results |
|---|---|---|---|---|---|
| Bruno et al.[107] | 2 | Ischemic stroke <12 h, all with diabetes mellitus; n=46 (31 intervention, 15 controls) | Continuous intravenous insulin infusion for 72 h (target 5–7.2 mmol/L); monitor every 1 h | Mean glucose difference between the two groups | Significantly lower glucose concentrations in intervention group (p=0.001); 35% hypoglycemia |
| Gray et al.[108] | 3 | All stroke; n=933 (464 intervention, 469 controls) | Glucose-insulin-potassium continuous intravenous infusion for 24 hours (target capillary 4-7 mmol/L, plasma glucose 4.6–8 mmol/L); monitor every 8 h | European Stroke Scale and modified Rankin scale at 90 days | No significant reduction in mortality at 90 days (glucose-insulin-potassium vs control, odds ratio 1.14, 95% CI 0.86–1.51, p=0.37) |
| Johnston et al.[109] | 2 | Ischemic stroke <24 h; n=74 (24 intervention, 50 controls) | Intravenous insulin infusion and subcutaneous insulin (target 3.9–11.1 mmol/L, loose control) or continuous intravenous insulin infusion for 5 days (target 3.9–6.1 mmol/L, tight control); monitor every 1–4 h | Within-target success at 24 h; hypoglycemia | Within-target success 90% in loose control group, 44% in tight control group; 4% hypoglycemia in loose control group, 30% in tight control group, 4% in controls |
| Kreisel et al.[110] | 2 | Ischemic stroke <24 h; n=40 (20 intervention, 20 controls) | Continuous intravenous insulin infusion for 5 days (target 4.4–6.1 mmol/L); monitor every 1-4 h | Hypoglycemia; severe hyperglycemia | Significantly lower glucose levels in intervention group (p=0.0005); significantly more hypoglycemia (incidence rate ratio 5.3, 95% CI 1.2–22.4) in intervention group |
| Kruyt et al.[111] | 2 | Ischemic stroke <24 h; n=38 (10 insulin CTF, 13 insulin, 15 controls) | Continuous intravenous insulin infusion and CTF for 5 days (target 4.4–6.1 mmol/L); monitor every 1–2 h | Time spent within target range | Median time within target, 55% in insulin CTF group, 19% in insulin group, and 58% in controls; 20% hypoglycemia in insulin CTF group, 31% in insulin group |

| | | | | | |
|---|---|---|---|---|---|
| Staszewksi et al.[112] | 2 | Ischemic stroke <12 h; n=50 (26 intervention, 24 controls) | Continuous intravenous insulin infusion (target 4.5–7 mmol/L); monitor every 1 h, every 4 h once stable for 24 h | Time spent within target range; hypoglycemia | 6.0 vs 6.8 mmol/L (p=0.03)<br>8% hypoglycemia in intervention, 0% in control |
| Vinychuk et al.[113] | 2 | Ischemic stroke <12 h; n=128 (61 intervention, 67 controls) | Continuous intravenous infusion 100 mL/h per 4 h with insulin doses (target: <7 mmol/L); monitor every 4 h | Reduction in plasma glucose concentration | Significant improvement in neurological status in intervention group (p=0.05); no reports on hypoglycaemia |
| Vriesendorp et al.[114] | 2 | Ischemic stroke <24 h; n=49 (13 basal insulin, 10 meal-related insulin,<br>10 hyperglycemic control,<br>16 normoglycemic control) | Basal insulin using intravenous insulin, or strict glucose control with predominantly meal-related insulin using subcutaneous insulin (target 4.4–6.1 mmol/L); monitor every 1-4 h | Time spent within target range | Two insulin-dosing regimens with a different basal to bolus insulin ratio failed to lower glucose in intermittently fed patients in the first 2–5 days after stroke |
| Walters et al.[115] | 2 | Ischemic stroke <24 h; n=25 (13 intervention, 12 controls) | Continuous intravenous insulin infusion for 48 h (target 5–7.9 mmol/L); monitor every 2 h | Time spent within target range | Significant reduction in mean area under glucose/time curve in intervention group (p=0.04); one event of hypoglycemia |

CTF = continuous tube feeding.

had a beneficial effect on outcome of critically ill patients with hyper glycaemia in the intensive-care unit (ICU) and, subsequently, intensive glucose treatment protocols were implemented on ICUs worldwide. Data from later studies, however, could not confirm these earlier positive results. A systematic review of 21 trials of intensive insulin therapy in the ICU, perioperative care, myocardial infarction, and stroke or brain injury settings concluded that evidence was inconsistent to show improvement of health outcomes in admitted patients, and such treatment was associated with an increased risk of severe hypoglycemia.[106] Several studies have assessed specifically the feasibility and safety of glucose-lowering treatment in patients with acute stroke (Table 5.1). Although glucose concentrations can be lowered by various insulin treatment regimens, achievement of stable normoglycemia can be difficult in the first few days after stroke onset, probably because oral food intake causes fluctuations in glucose levels.[114] A possible solution was reported in a study that used continuous tube feeding in combination with intravenous insulin administration.[111] However, important safety issues remain with respect to glucose-lowering treatment, because even with intensive monitoring, many patients can experience one or more episodes of hypoglycemia.[78,114] To facilitate control of hyperglycemia and to counter the risk of hypoglycemia, various computer-guided treatment protocols have been developed.[111,116] Introduction of continuous glucose monitoring devices might also help to improve treatment protocols and enhance safety. As yet, no evidence shows that glucose-lowering treatment improves clinical outcome in patients with acute ischemic stroke. Findings of randomised controlled trials specifically targeting individuals with stroke have failed to show beneficial effects. In a meta-analysis of 1296 patients with acute stroke from seven trials, intensively monitored intravenous insulin treatment (aimed at maintenance of glucose concentrations between 4.0 and 7.5 mmol/L) was compared with usual care.[117] No difference was seen with respect to poor outcome (odds ratio 1.0, 95% CI 0.8–1.3), and the risk of symptomatic hypoglycemia was significantly higher in the group treated with insulin (25.9, 9.2–72.7).[117] It is noteworthy that the results of this meta-analysis mainly came from 926 participants in the UK Glucose Insulin in Stroke Trial (GIST-UK).[108] Although this trial was important it did have some limitations. Patients were treated for only 24 h, during which time mean amounts of glucose in plasma were only 0.57 mmol/L lower in the intensively treated group than in the saline-treated group. Moreover, 22% of participants had lacunar stroke. A large randomised controlled trial is planned, in which 1400 patients will be randomly allocated to either standard care (aiming at glucose levels of <10 mmol/L) or intravenous insulin treatment (aiming at glucose concentrations of 4.4–7.2 mmol/L) for 72 h after stroke (ClinicalTrials.gov identifier NCT01369069). An insulin infusion protocol will be used that has proven safe and feasible in a pilot study.[109] Several questions remain regarding management of hyperglycemia in patients with acute

ischemic stroke. Should we monitor and lower glucose concentrations and, if so, how? How long should we maintain strict glucose management after stroke? Furthermore, should we account for stroke subtype when deciding whether to treat hyperglycemia? Current American Heart Association and European Stroke Organisation guidelines for management of ischemic stroke advise that glucose concentrations exceeding 11.1 mmol/L[118] or 10.0 mmol/L[119] should trigger the administration of insulin (Panel 5.4).

**Panel 5.4. Management of hyperglycemia in acute ischemic stroke**

- Treat hyperglycemia (recommended cut-offs 10.0 mmol/L or 11.1 mmol/L)[118,119] and consider that:
  - benefit on clinical outcome is not yet established
  - phase 2 studies show that glucose regulation is feasible, but fluctuations in glucose concentrations and risk of hypoglycemia are a concern[111,114]
- Differentiate between stress hyperglycemia and newly diagnosed diabetes (Panel 5.3)[77]



## CONCLUSIONS

Diabetes is associated with a doubling of the risk of stroke and with poor long-term outcome after ischemic stroke. Therefore, neurologists should monitor glucose metabolism in all patients with ischemic stroke. All individuals should be classified as either normoglycemic or with stress hyperglycemia, and with either newly diagnosed type 2 diabetes or known diabetes. Although the effectiveness of glucose-lowering treatment on clinical outcome has yet to be established, protocols are becoming available for patients with ischemic stroke. The possibility of hypoglycemia remains a concern. Neurologists and primary-care doctors should collaborate with respect to treatment of vascular risk factors for stroke prevention.

**Search strategy and selection criteria**

We searched PubMed from 1975 to Dec 15, 2011, with the terms (and synonyms) "stroke", "cerebral ischemia", "cerebral infarction", "hyperglycemia", "diabetes", "glucose", and "insulin", in combination with the key terms "epidemiology", "risk factors", "treatment", "prevention", and "outcome". We only searched for papers published in English. We also searched reference lists of reports identified with this strategy for relevant publications. Furthermore, we searched the Stroke Trials Registry, and ClinicalTrials.gov. From the large amount of published work on these topics we selected mainly randomised controlled trials, observational studies, and systematic reviews or meta-analyses published in core clinical journals over the past 5 years. Our final selection was based on originality and relevance to topics covered in this Review.

# REFERENCES


1. Danaei G, Finucane MM, Lu Y, et al, on behalf of the Global Burden of Metabolic Risk Factors of Chronic Diseases Collaborating Group (Blood Glucose). National, regional, and global trends in fasting plasma glucose and diabetes prevalence since 1980: systematic analysis of health examination surveys and epidemiological studies with 370 country-years and 2.7 million participants. Lancet. 2011;378:31–40.
2. Eisenbarth GS. Update in type 1 diabetes. J Clin Endocrinol Metab. 2007;92:2403–2407.
3. Daneman D. Type 1 diabetes. Lancet. 2006;367:847–858.
4. Ostman J, Lonnberg G, Arnqvist HJ, et al. Gender differences and temporal variation in the incidence of type 1 diabetes: results of 8012 cases in the nationwide Diabetes Incidence Study in Sweden 1983–2002. J Intern Med. 2008;263:386–394.
5. Stumvoll M, Goldstein BJ, van Haeften TW. Type 2 diabetes: principles of pathogenesis and therapy. Lancet. 2005;365:1333–1346.
6. Green A, Christian Hirsch N, Pramming SK. The changing world demography of type 2 diabetes. Diabetes Metab Res Rev. 2003;19:3–7.
7. Gale EA, Gillespie KM. Diabetes and gender. Diabetologia. 2001;44:3–15.
8. Mainous AG III, Baker R, Koopman RJ, et al. Impact of the population at risk of diabetes on projections of diabetes burden in the United States: an epidemic on the way. Diabetologia. 2007;50:934–940.
9. Eckel RH, Grundy SM, Zimmet PZ. The metabolic syndrome. Lancet. 2005;365:1415–1428.
10. Choi BC, Shi F. Risk factors for diabetes mellitus by age and sex: results of the National Population Health Survey. Diabetologia. 2001;44:1221–1231.
11. Gerstein HC, Santaguida P, Raina P, et al. Annual incidence and relative risk of diabetes in people with various categories of dysglycemia: a systematic overview and meta-analysis of prospective studies. Diabetes Res Clin Pract. 2007;78:305–312.
12. Unwin N, Shaw J, Zimmet P, Alberti KG. Impaired glucose tolerance and impaired fasting glycaemia: the current status on definition and intervention. Diabet Med. 2002;19:708–723.
13. Cheung N, Mitchell P, Wong TY. Diabetic retinopathy. Lancet. 2010;376:124–136.
14. Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study Research Group. Long-term effect of diabetes and its treatment on cognitive function. N Engl J Med. 2007;356:1842–1852.
15. Orchard TJ, Stevens LK, Forrest KY, Fuller JH. Cardiovascular disease in insulin dependent diabetes mellitus: similar rates but different risk factors in the US compared with Europe. Int J Epidemiol. 1998;27:976–983.
16. Donnelly R, Emslie-Smith AM, Gardner ID, Morris AD. ABC of arterial and venous disease: vascular complications of diabetes. BMJ. 2000;320:1062–1066.
17. DeFronzo RA, Abdul-Ghani M. Assessment and treatment of cardiovascular risk in prediabetes: impaired glucose tolerance and impaired fasting glucose. Am J Cardiol. 2011;108:3B–24B.
18. Lopez AD, Mathers CD, Ezzati M, Jamison DT, Murray CJ. Global and regional burden of disease and risk factors, 2001: systematic analysis of population health data. Lancet. 2006;367:1747–1757.
19. Strong K, Mathers C, Bonita R. Preventing stroke: saving lives around the world. Lancet Neurol. 2007;6:182–187.
20. The Emerging Risk Factors Collaboration. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. Lancet. 2010;375:2215–2222.
21. Capes SE, Hunt D, Malmberg K, Pathak P, Gerstein HC. Stress hyperglycemia and prognosis of stroke in non-diabetic and diabetic patients: a systematic overview. Stroke. 2001;32:2426–2432.
22. Biessels GJ, Deary IJ, Ryan CM. Cognition and diabetes: a lifespan perspective. Lancet Neurol. 2008;7:184–190.
23. Kruyt ND, Biessels GJ, DeVries JH, et al. Hyperglycemia in aneurysmal subarachnoid hemorrhage: a potentially modifiable risk factor for poor outcome. J Cereb Blood Flow Metab. 2010;30:1577–1587.

24. Fuller JH, Stevens LK, Wang SL. Risk factors for cardiovascular mortality and morbidity: the WHO Mutinational Study of Vascular Disease in Diabetes. Diabetologia. 2001;44: S54–64.
25. Janghorbani M, Hu FB, Willett WC, et al. Prospective study of type 1 and type 2 diabetes and risk of stroke subtypes: the Nurses' Health Study. Diabetes Care. 2007;30:1730–1735.
26. Kissela BM, Khoury J, Kleindorfer D, et al. Epidemiology of ischemic stroke in patients with diabetes: the greater Cincinnati/Northern Kentucky Stroke Study. Diabetes Care. 2005;28:355–359.
27. Jackson C, Sudlow C. Are lacunar strokes really different? A systematic review of differences in risk factor profiles between lacunar and non-lacunar infarcts. Stroke. 2005;36:891–901.
28. Cui R, Iso H, Yamagishi K, et al. Diabetes mellitus and risk of stroke and its subtypes among Japanese: the Japan public health center study. Stroke. 2011;42:2611–2614.
29. Ohira T, Shahar E, Chambless LE, Rosamond WD, Mosley TH Jr, Folsom AR. Risk factors for ischemic stroke subtypes: the Atherosclerosis Risk in Communities study. Stroke. 2006;37:2493–2498.
30. Huxley RR, Filion KB, Konety S, Alonso A. Meta-analysis of cohort and case-control studies of type 2 diabetes mellitus and risk of atrial fibrillation. Am J Cardiol. 2011;108:56–62.
31. Dekker JM, Girman C, Rhodes T, et al. Metabolic syndrome and 10-year cardiovascular disease risk in the Hoorn Study. Circulation. 2005;112:666–673.
32. Rundek T, Gardener H, Xu Q, et al. Insulin resistance and risk of ischemic stroke among nondiabetic individuals from the northern Manhattan study. Arch Neurol. 2010;67:1195–1200.
33. Thacker EL, Psaty BM, McKnight B, et al. Fasting and post-glucose load measures of insulin resistance and risk of ischemic stroke in older adults. Stroke. 2011;42:3347–3351.
34. Selvin E, Steff es MW, Zhu H, et al. Glycated hemoglobin, diabetes, and cardiovascular risk in nondiabetic adults. N Engl J Med. 2010;362:800–811.
35. Megherbi SE, Milan C, Minier D, et al. Association between diabetes and stroke subtype on survival and functional outcome 3 months after stroke: data from the European BIOMED Stroke Project. Stroke. 2003;34:688–694.
36. Kamalesh M, Shen J, Eckert GJ. Long term post-ischemic stroke mortality in diabetes: a veteran cohort analysis. Stroke. 2008;39:2727–2731.
37. Putaala J, Liebkind R, Gordin D, et al. Diabetes mellitus and ischemic stroke in the young: clinical features and long-term prognosis. Neurology. 2011;76:1831–1837.
38. Hillen T, Coshall C, Tilling K, et al. Cause of stroke recurrence is multifactorial: patterns, risk factors, and outcomes of stroke recurrence in the South London Stroke Register. Stroke. 2003;34:1457–1463.
39. Pendlebury ST, Rothwell PM. Prevalence, incidence, and factors associated with pre-stroke and post-stroke dementia: a systematic review and meta-analysis. Lancet Neurol. 2009;8:1006–1018.
40. American Diabetes Association. Standards of medical care in diabetes: 2011. Diabetes Care. 2011;34:S11–61.
41. Goldstein LB, Bushnell CD, Adams RJ, et al. Guidelines for the primary prevention of stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2011;42:517–584.
42. Sone H, Tanaka S, Iimuro S, et al. Long-term lifestyle intervention lowers the incidence of stroke in Japanese patients with type 2 diabetes: a nationwide multicentre randomised controlled trial (the Japan Diabetes Complications Study). Diabetologia. 2010;53:419–428.
43. The Look AHEAD Research Group. Long-term effects of a lifestyle intervention on weight and cardiovascular risk factors in individuals with type 2 diabetes mellitus: four-year results of the Look AHEAD trial. Arch Intern Med. 2010;170:1566–1575.
44. Wing RR, Lang W, Wadden TA, et al. Benefits of modest weight loss in improving cardiovascular risk factors in overweight and obese individuals with type 2 diabetes. Diabetes Care. 2011;34:1481–1486.
45. Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. BMJ. 2002;324:71–86.

46. Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the Euro Heart Survey on Atrial Fibrillation. Chest. 2010;137:263–272.
47. Rerkasem K, Rothwell PM. Carotid endarterectomy for symptomatic carotid stenosis. Cochrane Database Syst Rev. 2011;4:CD001081.
48. The ADVANCE Collaborative Group. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med. 2008;358:2560–2572.
49. Duckworth W, Abraira C, Moritz T, et al. Glucose control and vascular complications in veterans with type 2 diabetes. N Engl J Med. 2009;360:129–139.
50. The Action to Control Cardiovascular Risk in Diabetes Study Group. Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med. 2008;358:2545–2559.
51. The ACCORD Study Group. Long-term effects of intensive glucose lowering on cardiovascular outcomes. N Engl J Med. 2011;364:818–828.
52. Boussageon R, Bejan-Angoulvant T, Saadatian-Elahi M, et al. Effect of intensive glucose lowering treatment on all-cause mortality, cardiovascular death, and microvascular events in type 2 diabetes: meta-analysis of randomised controlled trials. BMJ. 2011;343:d4169.
53. Hemmingsen B, Lund SS, Gluud C, et al. Targeting intensive glycemic control versus targeting conventional glycemic control for type 2 diabetes mellitus. Cochrane Database Syst Rev. 2011;6:CD008143.
54. The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study Research Group. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. N Engl J Med. 2005;353:2643–2653.
55. UK Prospective Diabetes Study Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. BMJ. 1998;317:703–713.
56. Lindholm LH, Ibsen H, Dahlöf B, et al, for the LIFE study group. Cardiovascular morbidity and mortality in patients with diabetes in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. Lancet. 2002;359:1004–1010.
57. Patel A, ADVANCE Collaborative Group. Effects of a fixed combination of perindopril and indapamide on macrovascular and microvascular outcomes in patients with type 2 diabetes mellitus (the ADVANCE trial): a randomised controlled trial. Lancet. 2007;370:829–840.
58. Cushman WC, Evans GW, Byington RP, et al. Effects of intensive blood-pressure control in type 2 diabetes mellitus. N Engl J Med. 2010;362:1575–1585.
59. Bangalore S, Kumar S, Lobach I, Messerli FH. Blood pressure targets in subjects with type 2 diabetes mellitus/impaired fasting glucose: observations from traditional and bayesian random-effects meta-analyses of randomized trials. Circulation. 2011;123:2799–7810.
60. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 5963 people with diabetes: a randomised placebo-controlled trial. Lancet. 2003;361:2005–2016.
61. Colhoun HM, Betteridge DJ, Durrington PN, et al, on behalf of the CARDS investigators. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. Lancet. 2004;364:685–696.
62. The FIELD study investigators. Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomised controlled trial. Lancet. 2005;366:1849–1861.
63. Ginsberg HN, Elam MB, Lovato LC, et al. Effects of combination lipid therapy in type 2 diabetes mellitus. N Engl J Med. 2010;362:1563–74.
64. Gaede P, Lund-Andersen H, Parving H-H, Pedersen O. Effect of a multifactorial intervention on mortality in type 2 diabetes. N Engl J Med. 2008;358:580–591.
65. Anselmino M, Malmberg K, Öhrvik J, Rydén L, on behalf of the Euro Heart Survey Investigators. Evidence-based medication and revascularization: powerful tools in the management of patients with diabetes and coronary artery disease: a report from the Euro Heart Survey on diabetes and the heart. Eur J Cardiovasc Prev Rehabil. 2008;15:216–223.

66. Griffin SJ, Borch-Johnsen K, Davies MJ, et al. Effect of early intensive multifactorial therapy on 5-year cardiovascular outcomes in individuals with type 2 diabetes detected by screening (ADDITION-Europe): a cluster-randomised trial. Lancet. 2011;378:156–167.
67. Holman RR, Paul SK, Bethel MA, Neil HA, Matthews DR. Long-term follow-up after tight control of blood pressure in type 2 diabetes. N Engl J Med. 2008;359:1565–1576.
68. Gary TL, Genkinger JM, Guallar E, Peyrot M, Brancati FL. Meta-analysis or randomized educational and behavioural interventions in type 2 diabetes. Diabetes Educ. 2003;29:488–501.
69. Ogawa H, Nakayama M, Morimoto T, et al. Low-dose aspirin for primary prevention of atherosclerotic events in patients with type 2 diabetes: a randomized controlled trial. JAMA. 2008;300:2134–2141.
70. De Berardis G, Sacco M, Strippoli GF, et al. Aspirin for primary prevention of cardiovascular events in people with diabetes: meta-analysis of randomised controlled trials. BMJ. 2009;339:b4531.
71. Bhatt DL, Marso SP, Hirsch AT, Ringleb PA, Hacke W, Topol EJ. Amplified benefit of clopidogrel versus aspirin in patients with diabetes mellitus. Am J Cardiol. 2002;90:625–628.
72. Camm AJ, Kirchhof P, Lip GYH, et al. Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). Europace. 2010;12:1360–1420.
73. Rothwell PM, Algra A, Amarenco P. Medical treatment in acute and long-term secondary prevention after transient ischemic attack and ischemic stroke. Lancet. 2011;377:1681–1692.
74. Cunningham EJ, Bond R, Mehta Z, et al. Long-term durability of carotid endarterectomy for symptomatic stenosis and risk factors for late postoperative stroke. Stroke. 2002;33:2658–2663.
75. Debing E, Aerden D, Van den Brande P. Diabetes mellitus is a predictor for early adverse outcome after carotid endarterectomy. Vasc Endovascular Surg. 2011;45:28–32.
76. Uyttenboogaart M, Koch MW, Stewart RE, Vroomen PC, Luijckx GJ, De Keyser J. Moderate hyperglycemia is associated with favourable outcome in acute lacunar stroke. Brain. 2007;130:1626–1630.
77. Dungan KM, Braithwaite SS, Preiser J-C. Stress hyperglycemia. Lancet. 2009;373:1798–1807.
78. Kruyt ND, Biessels GJ, Devries JH, Roos YB. Hyperglycemia in acute ischemic stroke: pathophysiology and clinical management. Nat Rev Neurol. 2010;6:145–155.
79. Ntaios G, Abatzi C, Alexandrou M, et al. Persistent hyperglycemia at 24-48 h in acute hyperglycemic stroke patients is not associated with a worse functional outcome. Cerebrovasc Dis. 2011;32:561–566.
80. Kruyt ND, Nys GM, van der Worp HB, van Zandvoort MJ, Kappelle LJ, Biessels GJ. Hyperglycemia and cognitive outcome after ischemic stroke. J Neurol Sci. 2008;270:141–147.
81. Bruno A, Biller J, Adams HP Jr, et al. Acute blood glucose level and outcome from ischemic stroke: Trial of ORG 10172 in Acute Stroke Treatment (TOAST) Investigators. Neurology. 1999;52:280–284.
82. MacDougall NJ, Muir KW. Hyperglycemia and infarct size in animal models of middle cerebral artery occlusion: systematic review and meta-analysis. J Cereb Blood Flow Metab. 2011;31:807–818.
83. Gentile NT, Vaidyula VR, Kanamalla U, DeAngelis M, Gaughan J, Rao AK. Factor VIIa and tissue factor procoagulant activity in diabetes mellitus after acute ischemic stroke: impact of hyperglycemia. Thromb Haemost. 2007;98:1007–1013.
84. Vaidyula VR, Rao AK, Mozzoli M, Homko C, Cheung P, Boden G. Effects of hyperglycemia and hyperinsulinemia on circulating tissue factor procoagulant activity and platelet CD40 ligand. Diabetes. 2006;55:202–208.
85. Lemkes BA, Hermanides J, Devries JH, Holleman F, Meijers JC, Hoekstra JB. Hyperglycemia: a prothrombotic factor? J Thromb Haemost. 2010;8:1663–1669.
86. Meigs JB, Mittleman MA, Nathan DM, et al. Hyperinsulinemia, hyperglycemia, and impaired hemostasis: the Framingham Off spring Study. JAMA. 2000;283:221–228.
87. Pandolfi A, Giaccari A, Cilli C, et al. Acute hyperglycemia and acute hyperinsulinemia decrease plasma fibrinolytic activity and increase plasminogen activator inhibitor type 1 in the rat. Acta Diabetol. 2001;38:71–76.

88. Ribo M, Molina C, Montaner J, et al. Acute hyperglycemia state is associated with lower tPA-induced recanalization rates in stroke patients. Stroke. 2005;36:1705–1709.
89. Kawai N, Keep RF, Betz AL, Nagao S. Hyperglycemia induces progressive changes in the cerebral microvasculature and blood-brain barrier transport during focal cerebral ischemia. Acta Neurochir Suppl. 1998;71:219–221.
90. Quast MJ, Wei J, Huang NC, et al. Perfusion deficit parallels exacerbation of cerebral ischemia/reperfusion injury in hyperglycemic rats. J Cereb Blood Flow Metab. 1997;17:553–559.
91. Fleming I, Busse R. Molecular mechanisms involved in the regulation of the endothelial nitric oxide synthase. Am J Physiol Regul Integr Comp Physiol. 2003;284:R1–12.
92. Melikian N, Seddon MD, Casadei B, Chowienczyk PJ, Shah AM. Neuronal nitric oxide synthase and human vascular regulation. Trends Cardiovasc Med. 2009;19:256–262.
93. Kamada H, Yu F, Nito C, Chan PH. Influence of hyperglycemia on oxidative stress and matrix metalloproteinase-9 activation after focal cerebral ischemia/reperfusion in rats: relation to blood-brain barrier dysfunction. Stroke. 2007;38:1044–1049.
94. Bemeur C, Ste-Marie L, Montgomery J. Increased oxidative stress during hyperglycemic cerebral ischemia. Neurochem Int. 2007;50:890–904.
95. Esposito K, Nappo F, Marfella R, et al. Inflammatory cytokine concentrations are acutely increased by hyperglycemia in humans: role of oxidative stress. Circulation. 2002;106:2067–2072.
96. Ahmed N, Davalos A, Eriksson N, et al. Association of admission blood glucose and outcome in patients treated with intravenous thrombolysis: results from the Safe Implementation of Treatments in Stroke International Stroke Thrombolysis Register (SITS-ISTR). Arch Neurol. 2010;67:1123–1130.
97. Putaala J, Sairanen T, Meretoja A, et al. Post-thrombolytic hyperglycemia and 3-month outcome in acute ischemic stroke. Cerebrovasc Dis. 2011;31:83–92.
98. Parsons MW, Barber PA, Desmond PM, et al. Acute hyperglycemia adversely affects stroke outcome: a magnetic resonance imaging and spectroscopy study. Ann Neurol. 2002;52:20–28.
99. Els T, Klisch J, Orszagh M, et al. Hyperglycemia in patients with focal cerebral ischemia after intravenous thrombolysis: influence on clinical outcome and infarct size. Cerebrovasc Dis. 2002;13:89–94.
100. Mishra NK, Ahmed N, Davalos A, et al. Thrombolysis outcomes in acute ischemic stroke patients with prior stroke and diabetes mellitus. Neurology. 2011;77:1866–1872.
101. English P, Williams G. Hyperglycemic crises and lactic acidosis in diabetes mellitus. Postgrad Med J. 2004;80:253–261.
102. Lavin PJ. Hyperglycemic hemianopia: a reversible complication of non-ketotic hyperglycemia. Neurology. 2005;65:616–619.
103. van den Berghe G, Wouters P, Weekers F, et al. Intensive insulin therapy in the critically ill patients. N Engl J Med. 2001;345:1359–1367.
104. van den Berghe G, Wilmer A, Milants I, et al. Intensive insulin therapy in mixed medical/surgical intensive care units: benefit versus harm. Diabetes. 2006;55:3151–3159.
105. Furnary AP, Gao G, Grunkemeier GL, et al. Continuous insulin infusion reduces mortality in patients with diabetes undergoing coronary artery bypass grafting. J Thorac Cardiovasc Surg. 2003;125:1007–1021.
106. Kansagara D, Fu R, Freeman M, Wolf F, Helfand M. Intensive insulin therapy in hospitalized patients: a systematic review. Ann Intern Med. 2011;154:268–282.
107. Bruno A, Kent TA, Coull BM, et al. Treatment of hyperglycemia in ischemic stroke (THIS): a randomized pilot trial. Stroke. 2008;39:384–389.
108. Gray CS, Hildreth AJ, Sandercock PA, et al, for the GIST Trialists Collaboration. Glucose-potassium-insulin infusions in the management of post-stroke hyperglycemia: the UK Glucose Insulin in Stroke Trial (GIST-UK). Lancet Neurol. 2007;6:397–406.
109. Johnston KC, Hall CE, Kissela BM, Bleck TP, Conaway MR. Glucose Regulation in Acute Stroke Patients (GRASP) trial: a randomized pilot trial. Stroke. 2009;40:3804–3809.
110. Kreisel SH, Berschin UM, Hammes HP, et al. Pragmatic management of hyperglycemia in acute ischemic stroke: safety and feasibility of intensive intravenous insulin treatment. Cerebrovasc Dis. 2009;27:167–175.

111. Kruyt ND, Biessels GJ, Vriesendorp TM, et al. Subjecting acute ischemic stroke patients to continuous tube feeding and an intensive computerized protocol establishes tight glycemic control. Neurocrit Care. 2010;12:62–68.
112. Staszewski J, Brodacki B, Kotowicz J, Stepien A. Intravenous insulin therapy in the maintenance of strict glycemic control in nondiabetic acute stroke patients with mild hyperglycemia. J Stroke Cerebrovasc Dis. 2011;20:150–154.
113. Vinychuk SM, Melnyk VS, Margitich VM. Hyperglycemia after acute ischemic stroke: prediction, significance and immediate control with insulin-potassium-saline-magnesium infusions. Heart Drug. 2005;5:197–204.
114. Vriesendorp TM, Roos YB, Kruyt ND, et al. Efficacy and safety of two 5 day insulin dosing regimens to achieve strict glycemic control in patients with acute ischemic stroke. J Neurol Neurosurg Psychiatry. 2009;80:1040–1043.
115. Walters MR, Weir CJ, Lees KR. A randomised, controlled pilot study to investigate the potential benefit of intervention with insulin in hyperglycemic acute ischemic stroke patients. Cerebrovasc Dis. 2006;22:116–122.
116. Vogelzang M, Loef BG, Regtien JG, et al. Computer-assisted glucose control in critically ill patients. Intensive Care Med. 2008;34:1421–1427.
117. Bellolio MF, Gilmore RM, Stead LG. Insulin for glycemic control in acute ischemic stroke. Cochrane Database Syst Rev. 2011;9:CD005346.
118. Adams HP Jr, del Zoppo G, Alberts MJ, et al. Guidelines for the early management of adults with ischemic stroke: a guideline from the American Heart Association/American Stroke Association Stroke Council, Clinical Cardiology Council, Cardiovascular Radiology and Intervention Council, and the Atherosclerotic Peripheral Vascular Disease and Quality of Care Outcomes in Research Interdisciplinary Working Groups. Circulation. 2007;115:e478–534.
119. European Stroke Organisation (ESO) Executive Committee, ESO Writing Committee. Guidelines for management of ischemic stroke and transient ischemic attack 2008. Cerebrovasc Dis. 2008;25:457–507.

# CHAPTER 6

## Chronic hyperglycemia is related to poor functional outcome after acute ischemic stroke

Merel J.A. Luitse
Birgitta K. Velthuis
L. Jaap Kappelle
Yolanda van der Graaf
Geert Jan Biessels
on behalf of the DUST study group

International Journal of Stroke. 2017;12:180–186

# ABSTRACT

## Introduction

Acute hyperglycemia (HG) is associated with poor functional outcome after ischemic stroke, but the association between chronic antecedent HG and outcome is unclear. We assessed the association between chronic HG, measured by hemoglobin A1c (HbA1c), and functional outcome in patients with acute ischemic stroke.

## Methods

We included 812 patients with acute ischemic stroke (mean age 66±14 years; 61.5% male). Patients were categorized per HbA1c level: no (<39 mmol/mol), moderate (39–42 mmol/mol) or severe chronic HG (>42 mmol/mol). Poor functional outcome was defined as Modified Rankin Scale score >2 after 3 months. The relation between chronic HG and functional outcome was assessed with a Poisson regression analysis and expressed as risk ratios (RR) with 95% confidence intervals (95% CI) with no chronic HG as the reference.

## Results

Moderate chronic HG was present in 234 (28.8%) patients and severe chronic HG in 183 (22.5%) patients. Acute HG on admission was present in 338 (41.6%) patients. Severe chronic HG was associated with poor outcome (RR 1.40; 95% CI 1.09–1.79). After adjustment for age, sex, stroke severity, vascular risk factors and acute HG on admission the RR was 1.35 (95% CI 1.04–1.76). Moderate chronic HG was not associated with poor outcome (RR 1.12; 95% CI 0.87–1.44).

## Conclusion

Severe chronic HG is associated with poor functional outcome in patients with acute ischemic stroke. This association is independent of HG in the acute stage of stroke and of an unfavourable vascular risk factor profile.

# INTRODUCTION

Admission hyperglycemia (HG) is frequently observed in patients with acute ischemic stroke, also in the absence of a known history of diabetes.[1,2] This admission HG may be the result of an acute stress response, but may also reflect pre-existent, sometimes unrecognised diabetes or pre-diabetic stages of impaired glucose metabolism.[3]

Acute HG on admission is an independent predictor of poor functional outcome and increased mortality, and is also associated with larger infarct sizes.[2,4] It has been suggested that chronic HG prior to ischemic stroke is also associated with poor functional outcome, but evidence is inconsistent.[5–9] Multiple mechanisms are probably involved, but an unfavorable vascular risk factor profile or insulin resistance linked to chronic HG may be possible explanations.[1,10] Furthermore, it is unclear if and how acute HG influences the possible association between chronic HG and poor outcome.

Chronic HG over the past 3 months prior to stroke is most accurately measured with hemoglobin A1c (HbA1c).[11] The objective of our study was to determine if chronic HG, measured by HbA1c, is associated with poor functional outcome in patients with acute ischemic stroke. In addition, we evaluated the role of vascular risk factors and acute HG in this context.



# METHODS

## Patients

All patients participated in the multicenter prospective Dutch acute Stroke Study (DUST) between May 2009 and August 2013.[12] Inclusion criteria for the DUST were (1) clinical diagnosis of acute ischemic stroke, (2) non-contrast Computed Tomography (CT), CT Perfusion and CT Angiography examination performed within 9 hours of symptom onset, and (3) no known history of renal failure or allergy to contrast agents. Institutional review boards approved the trial. All patients or family gave signed informed consent, unless a patient died before consent could be obtained, in which case the medical ethics committee waived the need for consent. Detailed information on the DUST has been described earlier.[13]

For the current study, patients with the diagnosis of an ischemic stroke or transient ischemic attack (TIA) at discharge and with a pre-admission modified Rankin Score (mRS) ≤2 were included.[14] Furthermore, a HbA1c level, measured within 72 hours after admission, had to be available.

## Clinical assessment

Information was collected about hypertension, dyslipidemia, smoking, atrial fibrillation, previous myocardial infarction, peripheral artery disease, previous vascular interventions, treatment with intravenous recombinant tissue plasminogen activator (rtPA) or endovascular treatment. Stroke severity on admission was assessed by means of the National Institute of Health Stroke Scale (NIHSS) and stroke subtype by means of the TOAST classification.[15] Pre-existing diabetes was defined as a self-reported history of diabetes, reports in the medical records or use of insulin or oral glucose lowering medication.

HbA1c levels were measured within 72 hours after admission as part of routine testing. There are no generally accepted criteria to define chronic HG in patients with ischemic stroke. The American Diabetes Association defines prediabetes as an HbA1c value ≥39 mmol/mol; diabetes as >48 mmol/mol and a value >42 mmol/mol for prediabetes requiring interventions.[16] For our study we used the following cut-offs: 1) no chronic HG (HbA1c <39 mmol/mol); 2) moderate chronic HG (HbA1c 39–42 mmol/mol) and 3) severe chronic HG (HbA1c >42 mmol/mol).[16,17] In a sensitivity analysis, we separately considered HbA1c values between 42–48 mmol/mol for severe chronic HG, excluding the group >48 mmol/mol.

Acute HG was defined as a serum glucose level on admission of ≥7.0 mmol/L.[18]

## Outcome measures

Functional outcome at 3 months was assessed with the Modified Rankin Scale (MRS), which was obtained by telephone interview by a trained research nurse or neurologist.[14] This approach was chosen to ensure maximum follow-up rate and limited attrition. A MRS score of 0–2 was defined as good outcome, a score of 3–6 as poor outcome.

## Statistical analyses

Statistical analyses were performed using IBM SPSS Statistics, version 22. All data are expressed as means ± standard deviation (SD) or as medians with interquartile ranges (IQR) when they were not normally distributed. Mean values were compared with analysis of variance (ANOVA). Differences in proportions were evaluated by the Pearson's $\chi^2$ test. Differences at the level of $p<0.05$ were considered statistically significant and variables were checked for collinearity.

For the association between chronic HG and functional outcome, a Poisson regression analysis with robust standard errors was performed to calculate adjusted risk ratios (RR)

with 95% confidence intervals (95% CI).[19] The group with no chronic HG was used as the reference group. Risk ratios were adjusted for age, sex, vascular risk factors, NIHSS on admission and admission glucose levels. A subgroup analysis for patients without known diabetes was performed. Risk ratios were also calculated for the relation between acute HG and poor functional outcome, adjusted for age, sex, vascular risk factors, HbA1c levels and NIHSS on admission.

## RESULTS

From May 2009 until July 2013, 1393 patients were included in DUST. We enrolled 812 DUST participants in the current study (Figure 6.1). The main reason for exclusion for this substudy was missing HbA1c values (n=495). Of note, assessment of HbA1c levels was not part of the DUST core protocol and was not standard practice in all participating centers. Mean age was 66±14 years and 61.5% of the patients was male.

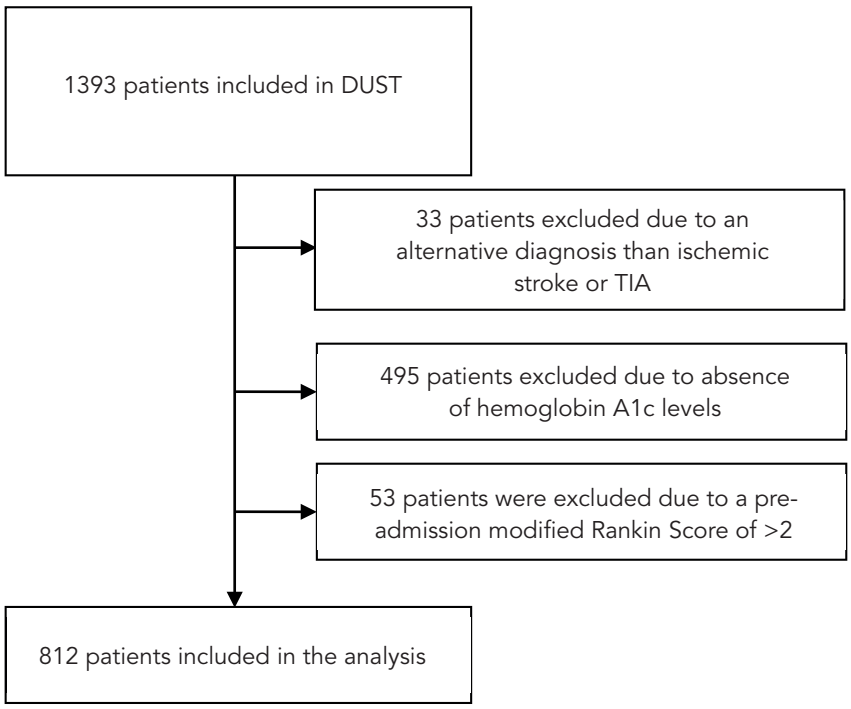



Figure 6.1. Flow of patients through the study.

The median HbA1c level was 38.8 mmol/mol with a range of 19–107 mmol/mol. In 395 (48.6%) patients there was no chronic HG. Moderate chronic HG was present in 234 (28.8%) patients. The remaining 183 (22.5%) patients had severe chronic HG. Known pre-existent diabetes was present in 11.7% of the total population and more frequently present in the group with severe chronic HG (43.7%). Acute HG on admission was present in 338 of the 812 patients (41.6%).

The baseline characteristics for the complete study population and stratified by HbA1c level are shown in Table 6.1. Patients with severe chronic HG were significantly older and had more vascular risk factors than patients without chronic HG. Admission HG occurred more frequently in the moderate and severe chronic HG group than in the no chronic

Table 6.1. Baseline characteristics

| | | Chronic HG | | |
|---|---|---|---|---|
| Variable (%) n | All patients (N=812) | No chronic HG (N=395) | Moderate chronic HG (N=234) | Severe chronic HG (N=183) |
| Age±SD | 66±14 | 63±14 | 68±13 | 70±12 |
| Male | 499 (61.5) | 244 (61.8) | 131 (56.0) | 124 (67.8) |
| Diabetes | 95 (11.7) | 4 (1.0) | 11 (4.7) | 80 (43.7) |
| Hypertension | 377 (46.4) | 137 (34.7) | 127 (54.3) | 113 (61.7) |
| Hypercholesterolemia | 209 (25.7) | 65 (16.5) | 43 (29.9) | 74 (40.4) |
| Smoking | 238 (29.3) | 117 (29.6) | 79 (33.8) | 42 (23.0) |
| Prior vascular event | 226 (27.8) | 86 (21.8) | 74 (31.6) | 66 (37.9) |
| Atrial fibrillation | 102 (12.6) | 25 (10.2) | 26 (10.3) | 37 (14.3) |
| SBP on admission (mmHg) ±SD | 158 (28) | 156±28 | 159±29 | 160±28 |
| NIHSS on admission ±IQR | 6 (3–11) | 5 (2–10) | 6 (3–11) | 6 (3–12) |
| Admission glucose (mmol/L) ±IQR | 6.7 (5.8–8.0) | 6.2 (5.6–7.2) | 6.7 (5.9–7.5) | 8.4 (6.7–10.2) |
| Admission HG | 338 (41.6) | 115 (29.1) | 94 (40.2) | 129 (70.5) |
| Fasting glucose (mmol/L) ±IQR | 6.0 (5.3–7.0) | 5.6 (5.2–6.2) | 6.0 (5.3–6.9) | 7.5 (6.3–9.4) |
| HbA1c (mmol/mol) ±IQR | 39 (35–42) | 35 (33–37) | 40 (39–41) | 49 (45–58) |
| Intravenous rtPA | 525 (64.7) | 256 (64.8) | 160 (68.4) | 109 (59.6) |
| Endovascular treatment | 50 (6.2) | 27 (6.8) | 13 (5.6) | 10 (5.7) |

HG indicates hyperglycemia; SBP, systolic blood pressure; NIHSS, National Institutes of Health Stroke Scale; HbA1c, hemoglobin A1c; rtPA, recombinant tissue plasminogen activator; IQR, interquartile range; SD, standard deviation.

HG group. Moreover, fasting glucose levels after 24 hours were also higher in the groups with moderate and severe chronic HG. Stroke severity on admission (NIHSS) did not differ between the groups (p=0.3). Between the groups, no differences were observed in treatment with intravenous rtPA (p=0.2) or endovascular treatment (p=0.7). Concerning stroke subtypes, no significant differences were observed between the groups in patients with large vessel disease (p=0.3), cardio-embolism (p=0.05) and small vessel disease (p=0.09). Information about follow-up at 3 months was available in 775 patients (95.4%).

Functional outcome stratified for HbA1c level is shown in Figure 6.2. In patients with severe chronic HG, the risk of poor functional outcome at 3 months was significantly increased as compared with the group with no chronic HG (RR 1.40; 95% CI 1.09–1.79 adjusted for age and sex; Table 6.2). Additional adjustment for vascular risk factors or NIHSS on admission did not influence this finding. Patients with moderate HG did not have an increased risk of poor functional outcome (RR 1.12; 95% CI 0.87–1.44).

Since chronic hyperglycemia is strongly related to acute hyperglycemia, we analysed the influence of acute hyperglycemia separately. Acute HG on admission itself was also associated with poor functional outcome with an RR of 1.43 (95% CI 1.16–1.75; adjusted for sex, age, vascular risk factors and NIHSS on admission). In patients with severe chronic HG, adjustment for admission glucose levels attenuated the risk of poor outcome (RR 1.27; 95% CI 0.96–1.67).



In the multivariate analysis, in which we adjusted for age, sex, NIHSS, vascular risk factors and admission glucose levels, an overall RR of 1.35 (95% CI 1.04–1.76) was found for patients with severe chronic HG compared with the group without chronic HG.

In a sensitivity analysis in patients with HbA1c values between 42 and 48 mmol/mol, there were no differences in risk ratios in between the complete group with severe chronic HG (age and sex adjusted RR 1.40; 95% CI 1.09–1.79) and the subgroup with HbA1c values of 42–48 mmol/mol (age and sex adjusted RR 1.43; 95% CI 1.06–1.93). Similar results were found in the multivariate analysis between these groups.

In 746 patients, fasting glucose levels after 24 hours were available. In these patients, adjustment for fasting glucose attenuated the risk of poor outcome associated with chronic HG (age and sex adjusted RR 1.47; 95% CI 1.13–1.91), additionally adjusted for fasting glucose RR 1.24 (95% CI 0.92–1.67)). In a subgroup analysis in the patients without diabetes (N=717) after adjustment for age, sex, vascular risk factors, NIHSS on admission and admission glucose levels the RR for poor functional outcome was 1.26 (95% CI 0.93–1.71).

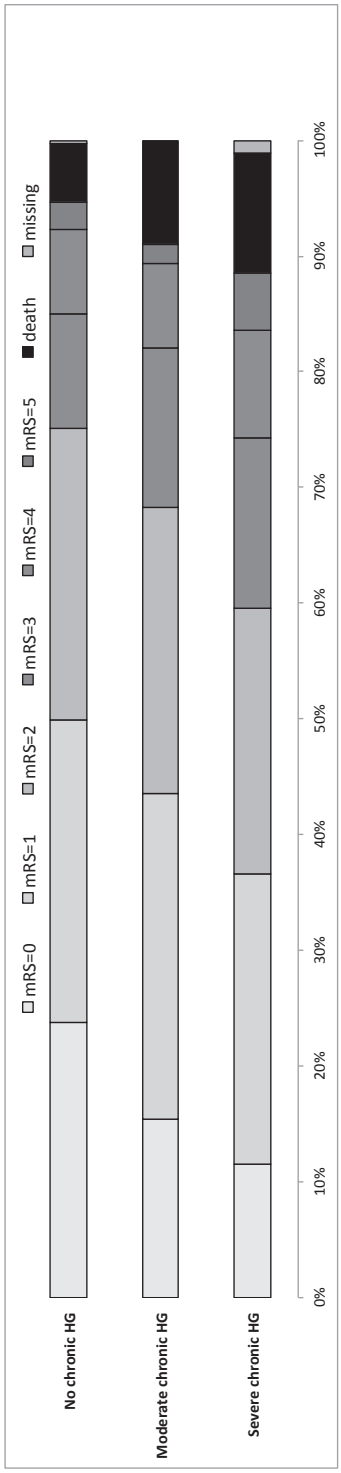



Figure 6.2. Functional outcome stratified for HbA1c level.

Table 6.2. Risk ratios for poor functional outcome according to chronic hyperglycemia

| Poor functional outcome | | | Age and sex adjusted | | Age, sex and vascular RF* adjusted | | Age, sex and admission NIHSS adjusted | | Age, sex and admission glucose adjusted | | Multivariate model§ | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | No. patients/ total | No. poor outcome | RR | 95% CI | RR | 95% CI | RR | 95% CI | RR | 95% CI | RR | 95% CI |
| No chronic HG | 395/812 | 97/395 | 1.00 | reference | 1.00 | reference | 1.00 | reference | 1.00 | reference | 1.00 | reference |
| Moderate chronic HG | 234/812 | 74/234 | 1.12 | (0.87–1.44) | 1.12 | (0.87–1.45) | 1.12 | (0.87–1.45) | 1.10 | (0.85–1.42) | 1.11 | (0.86–1.43) |
| Severe chronic HG | 183/812 | 72/183 | 1.40 | (1.09–1.79) | 1.41 | (1.10–1.81) | 1.44 | (1.14–1.82) | 1.27 | (0.96–1.67) | 1.35 | (1.04–1.76) |
| p for trend# | | | | 0.028 | | 0.024 | | 0.007 | | 0.240 | | 0.068 |

HG indicates hyperglycemia; RR, risk ratios; CI, confidence interval; NIHSS, National Institutes of Health Stroke Scale; RF; risk factors; * vascular risk factors are hypertension, hypercholesterolemia, smoking, atrial fibrillation and prior vascular event; § adjusted for age, sex, vascular RF, admission NIHSS and admission glucose; # applies to reference, moderate and severe chronic HG group in total.

# DISCUSSION

This prospective study demonstrates that severe chronic HG prior to stroke is an independent risk factor for poor functional outcome in patients with acute ischemic stroke. Admission HG in the acute stage of ischemic stroke was also associated with an increased risk of poor outcome.

While the association between acute HG and poor outcome after ischemic stroke is well established, less is known about the association between chronic HG and stroke outcome. Currently available studies show heterogeneity in design and study population.[5–9] In some studies, the study population consisted of patients with known diabetes only,[5] or older patients who did not receive intravenous rtPA.[9] Other studies had a retrospective design.[6,9] The overall picture that emerges is that chronic HG indeed is associated with poor outcome, which is in line with the findings of the present study. Earlier studies that evaluated the role of admission glucose in the relation between chronic HG and outcome, included patients that were admitted up to 7 to 14 days after symptom onset.[5,7,8] These studies do not allow to assess the possible mediating role of the acute hyperglycemic stress response. Only one previous retrospective study specifically addressed acute HG, within 24 hours after symptom onset, in relation to chronic HG and outcome.[6] In this study an association between chronic HG and poor outcome was found, with only a limited effect of glucose levels on admission,[6] which is in line with our findings.

Our findings indicate that chronic HG is an independent risk factor for poor outcome after ischemic stroke. Therefore, the association between chronic HG and poor outcome cannot be attributed to the adverse vascular risk factors, such as hypertension, hypercholesterolemia, atrial fibrillation and prior vascular events that are linked to chronic HG. There are several possible explanations why chronic HG might be linked to poor functional outcome. First of all, chronic HG may be associated with pre-existent cerebral changes that predispose to worse outcome when a stroke occurs. It is known that chronic HG may lead to changes in the cerebral tissue and cerebral vasculature, such as cerebral atrophy and small vessel disease.[20] In addition, patients with chronic HG may be predisposed to more severe acute HG in case of a stroke, as was also observed in our cohort. This could be explained by the pre-existent glucose abnormalities in patients with chronic HG involving insulin resistance and subsequent acute HG when exposed to an acute stressor like stroke.[21] Acute HG itself was associated with poor functional outcome and adjustment for this factor attenuated the association between chronic HG and poor outcome. This could possibly be caused through aggravation of ischemic damage by disturbing recanalization and increasing reperfusion injury caused by acute HG.[21] Other

factors associated with chronic HG may also negatively influence the course of stroke. Chronic HG may lead to a protrombotic condition, caused by elevated coagulation factors and impaired fibrinolysis.[22] Amounts of plasminogen activator inhibitor 1 and tissue-type plasminogen activator antigens, for example, were higher in individuals with glucose intolerance than in those with normal glucose tolerance. In addition, hyperinsulinemia is associated with impaired fibrinolysis in patients with chronic HG. In patients with acute ischemic stroke, these factors may affect vessel recanalization or the efficacy of fibrinolytic treatment.[22,23]

It is still uncertain if acute and chronic HG are targets for treatment to improve outcome after ischemic stroke. In patients with acute HG and ischemic stroke, randomized-controlled trials have not provided evidence that glucose-lowering treatment improves clinical outcome.[24] Achievement of normoglycemia in the early stage of stroke seems to be difficult, and the possibility of inadvertently causing hypoglycemia is a concern.[25] A large phase III trial of glucose-lowering therapy in acute ischemic stroke that is currently underway will provide more insights.[26] Additionally, presence of chronic HG in patients with ischemic stroke may identify patients who may benefit from additional interventions, targeting some of the mechanisms mentioned above. This should be explored in further studies.



### Limitations

A limitation of our study is that HbA1c levels were not available in 581 of the 1393 patients included in DUST, but no significant differences were found in patient characteristics, NIHSS on admission and outcome after 3 months between the included and excluded patients. Another point is that chronic and acute HG are interrelated as they may share underlying mechanisms and could even be collinear. In addition, dysglycemia is linked to an adverse vascular risk profile. However, it is unlikely that collinearity influenced our findings since none of the variables had a correlation coefficient above 0.7.

Measurement of HbA1c level was performed only once and therefore may be less reliable. Furthermore, there was no standardized protocol of follow-up glucose measurement or treatment of hyperglycemia. Possible treatment of hyperglycemia was also not standardly collected.

## CONCLUSION

Severe chronic HG is associated with poor functional outcome after acute ischemic stroke. This finding is not due to effects of concomitant acute HG on admission. Possibly,

processes other than the acute HG response may also provide targets for treatment to prevent secondary damage in patients with ischemic stroke and chronic HG.

## REFERENCES


1. Sarwar N, Gao P, Seshasai SR, et al. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. Lancet. 2010;375:2215–2222.
2. Capes SE, Hunt D, Malmberg K, Pathak P, Gerstein HC. Stress hyperglycemia and prognosis of stroke in nondiabetic and diabetic patients: a systematic overview. Stroke. 2001;32:2426–2432.
3. Dungan KM, Braithwaite SS, Preiser JC. Stress hyperglycaemia. Lancet. 2009;373:1798–1807.
4. Baird TA, Parsons MW, Phanh T, et al. Persistent poststroke hyperglycemia is independently associated with infarct expansion and worse clinical outcome. Stroke. 2003;34:2208–2214.
5. Kuwashiro T, Sugimori H, Ago T, Kuroda J, Kamouchi M, Kitazono T. The impact of predisposing factors on long-term outcome after stroke in diabetic patients : the Fukuoka Stroke Registry. Eur J Neurol. 2013;921–927.
6. Kamouchi M, Matsuki T. Prestroke Glycemic Control Is Associated With the Functional Outcome in Acute Ischemic Stroke. Stroke. 2011;42:2788-2794
7. Wu S, Wang C, Jia Q, et al. HbA1c is associated with increased all-cause mortality in the first year after acute ischemic stroke. Neurol Res. 201;36:444-52
8. Lei C, Wu B, Liu M, Chen Y. Association between hemoglobin A1C levels and clinical outcome in ischemic stroke patients with or without diabetes. J Clin Neurosci. 2015;22:498-503
9. Hjalmarsson C, Manhem K, Bokemark L, Andersson B. The Role of Prestroke Glycemic Control on Severity and Outcome of Acute Ischemic Stroke. Stroke Res Treat. 2014;2014:694569.
10. Meigs JB, Mittleman MA, Nathan DM, et al. Hyperinsulinemia, hyperglycemia, and impaired hemostasis: the Framingham Offspring Study. JAMA. 2000;283:221–228.
11. Goldstein D, Little R, Lorenz R, Malone J, Nathan. Tests of glycemia in diabetes. Diabetes Care. 2004;27:2003–2005.
12. van Seeters T, Biessels GJ, Kappelle LJ, et al. The Prognostic Value of CT Angiography and CT Perfusion in Acute Ischemic Stroke. Cerebrovasc Dis. 2015;40:258–269.
13. van Seeters T, Biessels GJ, van der Schaaf IC, et al. Prediction of outcome in patients with suspected acute ischaemic stroke with CT perfusion and CT angiography: the Dutch acute stroke trial (DUST) study protocol. BMC Neurol. 2014;14:37.
14. van Swieten JC, Koudstaal PJ, Visser MC, Schouten HJ, van Gijn J. Interobserver agreement for the assessment of handicap in stroke patients. Stroke. 1988;19:604–607.
15. Adams HP, Bendixen BH, Kappelle LJ, et al. 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.
16. Silverman R, Thakker U, Ellman T. Hemoglobin A1c as a screen for previously undiagnosed prediabetes and diabetes in an acute-care setting. Diabetes Care. 2011;34:1908-12
17. American Diabetes Association et al. Standards of medical care in diabetes—2014. Diabetes Care. 2014;37 Suppl 1:S14-80
18. Kruyt ND, Nys GM, van der Worp HB, van Zandvoort MJ, Kappelle LJ, Biessels GJ. Hyperglycemia and cognitive outcome after ischemic stroke. J Neurol Sci. 2008;270:141–147.
19. Knol MJ, Le Cessie S, Algra A, Vandenbroucke JP, Groenwold RHH. Overestimation of risk ratios by odds ratios in trials and cohort studies: Alternatives to logistic regression. CMAJ. 2012;184:895–899.
20. Ritchie K, Touchon J. Mild cognitive impairment: conceptual basis and current nosological status. Lancet. 2000;355:225–228.
21. Kruyt ND, Biessels GJ, Devries JH, Roos YB. Hyperglycemia in acute ischemic stroke: pathophysiology and clinical management. Nat Rev Neurol. 2010;6:145–155.

22. Lemkes BA, Hermanides J, Devries JH, Holleman F, Meijers JC, Hoekstra JB. Hyperglycemia: a prothrombotic factor? J Thromb Haemost. 2010;8:1663–1669.
23. Gentile NT, Vaidyula VR, Kanamalla U, DeAngelis M, Gaughan J, Rao AK. Factor VIIa and tissue factor procoagulant activity in diabetes mellitus after acute ischemic stroke: impact of hyperglycemia. Thromb Haemost. 2007;98:1007–1013.
24. Bellolio MF, Gilmore RM, Stead LG. Insulin for glycaemic control in acute ischaemic stroke. Cochrane Database Syst. Rev. 2011;9:CD005346.
25. Luitse MJ, Biessels GJ, Rutten GE, Kappelle LJ. Diabetes, hyperglycaemia, and acute ischemic stroke. Lancet Neurol. 2012;11:261–271.
26. Bruno A, Durkalski VL, Hall CE, et al. The Stroke Hyperglycemia Insulin Network Effort (SHINE) trial protocol: A randomized, blinded, efficacy trial of standard vs. intensive hyperglycemia management in acute stroke. Int. J. Stroke. 2014;9:246–251.

# CHAPTER 7

## Admission hyperglycemia and cerebral perfusion deficits in acute ischemic stroke

Merel J.A. Luitse
Tom van Seeters
Alexander D. Horsch
Hieke A. Kool
Birgitta K. Velthuis
L. Jaap Kappelle
Geert Jan Biessels

Cerebrovascular Diseases. 2013;35:163–167

# ABSTRACT

## Introduction

Hyperglycemia (HG) occurs in 30–40% of the patients with acute ischemic stroke and is associated with larger infarct size and poor functional outcome. It is unknown whether HG is also associated with larger perfusion deficits in the acute stage of ischemic stroke. As computed tomography perfusion (CTP) is a reliable technique to determine the infarct core and ischemic penumbra, we aimed to determine if patients with acute ischemic stroke and HG have larger perfusion deficits or infarct cores on admission perfusion CT than patients with normoglycemia (NG).

## Methods

We identified 80 consecutive patients (mean age 69±11 years, 58% men) with acute supratentorial non-lacunar ischemic stroke in whom CT showed a perfusion deficit within 24 h after stroke onset. The size of the total perfusion deficit area (mean transit time of >145% compared to the contralateral hemisphere) and the infarct core area (cerebral blood volume of <2.0 ml/100 g) at the level of the basal ganglia (level 1) and at the level of the corona radiata (level 2) were compared between patients with HG (admission glucose ≥7.0 mM) and patients with NG with a MANOVA. Clinical outcome [modified Rankin Scale (mRS) score] after 6 months was correlated to glucose levels at admission.

## Results

Admission HG was present in 33 of the 80 patients (41%). A perfusion deficit was present in 79 (40% HG) patients at level 1 and 75 (43% HG) at level 2. The total area with a perfusion deficit (level 1 HG 22.1±11.3 and NG 23.3±12.3 $cm^2$; level 2 HG 27.1±12.3 and NG 25.4±12.0 $cm^2$) and the proportion of the infarct core (level 1 HG 31±30% and NG 25±22%; level 2 HG 33±27% and NG 26±23%) did not differ significantly between the groups. HG was associated with worse outcome (mRS ≥3) at 6 months (OR 2.6, 95% CI 0.72–9.1).

## Conclusion

As compared to patients with NG, patients with HG did not have larger perfusion deficits in the acute stage of ischemic stroke. Nevertheless, functional outcome was worse in patients with HG, which means that poor clinical outcome in stroke patients with HG could not be explained by a larger perfusion deficit in the acute stage. Therefore, our study suggests that there might be a window of opportunity for glucose-lowering therapy in the future.

# INTRODUCTION

Hyperglycemia (HG) occurs in approximately 30–40% of the patients with acute ischemic stroke.[1,2] The majority of patients with post-stroke HG do not have a known history of diabetes mellitus.[3] HG in the acute stage of stroke is associated with increased mortality and worse functional outcome.[4] In patients receiving thrombolysis, it was observed that this association may be even stronger if HG persists during the first 48 h after stroke.[5] Moreover, patients with high serum glucose levels tend to have larger final infarct size than patients with normal serum glucose levels.[6] Although the pathophysiology underlying this association remains unclear, reduced penumbral salvage has been reported to play an important role.[7–9] It is unknown whether HG is also associated with larger perfusion deficits in the acute stage of ischemic stroke. If the perfusion deficit on admission in patients with HG is not larger than in patients with normoglycemia (NG), treatment of HG might be a window of opportunity in preventing poor outcome in patients with HG.

CT perfusion (CTP) is a reliable technique to determine the infarct core and ischemic penumbra. In the acute stage, non-contrast CT is used to exclude intracerebral hemorrhage. Non-contrast CT can easily be extended with CTP and CT angiography (CTA) within a 10-min examination. CTP compares well to magnetic resonance imaging (MRI) for imaging of penumbra and infarct core.[10–12] The objective of our study was to determine if a larger total perfusion deficit and a larger infarct core in the acute stage can explain the worse outcome of patients with HG on admission and acute ischemic stroke as compared to normoglycemic patients.



# METHODS

## Inclusion criteria

Patients were retrieved from a prospectively established database of all patients with an acute ischemic stroke who were admitted to the Utrecht University Medical Centre, The Netherlands, between January 2007 and June 2008. Inclusion criteria for the present study were (1) a diagnosis of acute non-lacunar ischemic stroke of the anterior circulation; (2) a non-contrast CT scan and CTP performed on admission within 24 h after stroke onset; (3) a National Institutes of Health Stroke Scale (NIHSS) score ≥2 at the time of the CT scan, and (4) a serum blood glucose sample (mM) taken on admission. We included only patients with large-vessel strokes of the anterior circulation because lacunar strokes and strokes of the posterior circulation are difficult to visualize well on CTP.[13]

## Imaging protocol

The admission CT examination included a non-contrast brain CT, CTP and cervical and intracranial CT angiography. Detailed information on the CTP imaging and analysis protocol has been described earlier.[14] The CTP data were transferred to a workstation with commercially available CTP analysis software (EBW workstation version 4.5, Philips medical systems, The Netherlands) for analysis of the total perfusion deficit and the infarct core. The total perfusion deficit area ($cm^2$) was defined as the area with a mean transit time (MTT) >145% compared to the MTT of the contralateral hemisphere.[15] This area includes both the irreversibly damaged infarct core as well as the potentially salvageable penumbra. The infarct core area ($cm^2$) was de- fined as the area within the perfusion deficit area with a cerebral blood volume of <2.0 ml/100 g.[15] CTP analysis software computed these areas automatically using these thresholds for normal and decreased perfusion.[15] Brain perfusion was measured at two levels of the brain, in the same way as has been described for the Alberta Stroke Program Early CT Score (ASPECTS).[16] The first assessment was performed at the level where the thalamus and basal ganglia are visible, and the second measurement was performed just cranial to the basal ganglia at the level of the corona radiata. This two-level method was used because these measurements were available as part of the standard scan protocol of CTP in all patients, and the CTP protocol did not have whole-brain coverage. The CTP slab was positioned to cover at least the basal ganglia up to the lateral ventricles to ensure that both ASPECTS levels were included. For the analysis, we measured the total perfusion deficit and the infarct cores in square centimetres at both levels.

## Clinical assessment

We collected information on medical history, use of medication, stroke severity on admission by means of the NIHSS, treatment with intravenous thrombolysis and serum glucose levels on admission. HG was defined as a blood glucose level of ≥7.0 mM.[17,18]

## Outcome measures

Our primary outcome measures were the area (in $cm^2$) of total perfusion deficit and infarct core, as well as the ratio of infarct core to perfusion deficit (index infarct core) on both levels separately and both levels combined. Our secondary outcome measure was the modified Rankin Scale (mRS) at 6 months after admission, which was obtained by telephone interview by a trained research nurse.[19] A mRS score of 0–2 was defined as good outcome, a score of 3–6 as poor outcome.

## STATISTICAL ANALYSIS

Admission glucose levels were dichotomized at the value of 7.0 mM. All data (the total perfusion area, infarct core, and infarct core/perfusion deficit ratio) are expressed as means ± standard deviation (SD) or as medians when they were not normally distributed.

Mean values were compared by analysis of variance (ANOVA). Differences in proportions were evaluated by the $\chi^2$ test. Differences at the level of $p<0.05$ were considered statistically significant. Secondly, the values of the perfusion deficits were entered in a multivariable regression analysis (MANOVA). In all analyses, we adjusted for disease characteristics when they influenced the mean difference by >5%. Finally, odds ratios (OR) and the corresponding 95% confidence intervals (CI) were calculated by means of logistic regression for the relation between HG and poor outcome. Adjustment for disease characteristics was performed when they influenced the OR by >5%.

## RESULTS

### Baseline characteristics

From January 2007 until June 2008, 227 patients presented with an acute ischemic stroke at our emergency unit. We enrolled 80 consecutive patients who met our inclusion criteria (Figure 7.1). Of the included 80 patients, 33 patients (41%) had HG on admission.

Table 7.1 shows the characteristics of patients with and without admission HG. Mean admission blood glucose level was 5.9±0.57 mM in the normoglycemic group and 9.5±3.7 mM in the hyperglycemic group. The proportion of patients treated with intravenous thrombolysis did not differ between the normoglycemic (47%) and hyperglycemic group (46%).

### Primary outcome

Brain perfusion was measured on the level of the basal ganglia (level 1) and on the level of the corona radiata (level 2). A perfusion deficit was present in 79 (41% HG) patients at level 1 and in 75 patients (43% HG) at level 2. Seventy-four patients had a perfusion deficit on both levels. The results of the perfusion measurements are shown in Table 7.2. No significant difference between the groups was found for the total mean perfusion deficit, the infarct core and the ratio of infarct core to perfusion deficit on either level 1 or 2, or on a combined analysis for both levels. Adjustment for age, gender and NIHSS did not influence the results. The range of the infarct core index in the patients with NG

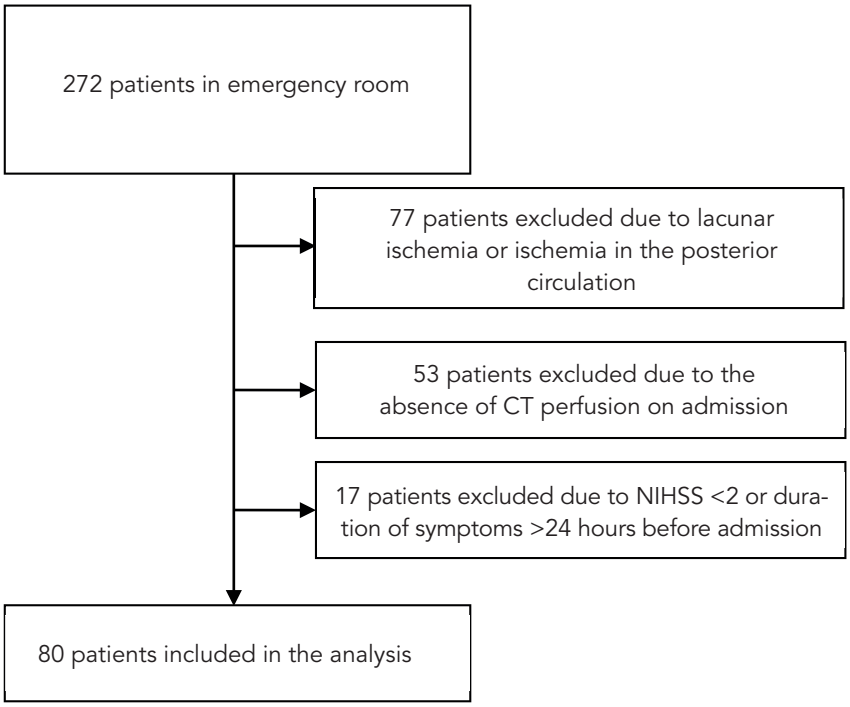



Figure 7.1. Flow chart of the inclusion process.

Table 7.1. Baseline characteristics

| Characteristics (N=80) | Normoglycemia N=47 No. (%) | Hyperglycemia N=33 No. (%) |
|---|---|---|
| Male | 47 (58.8) | 33 (41.3) |
| Age (years) mean±SD | 59±15.3 | 69±10.9 |
| Diabetes mellitus | 4 (8.5) | 9 (27.3) |
| Hypertension | 16 (34.0) | 17 (51.5) |
| Systolic BP† (mmHg) mean±SD | 143±29.3 | 155.2±25.5 |
| Diastolic BP† (mmHg) mean±SD | 79.7±15.9 | 83.3±16.8 |
| NIHSS§ on admission mean±SD | 9.9±5.6 | 13.2±6.2 |
| Blood glucose (mmol/L) mean±SD | 5.9±0.57 | 9.5±3.7 |
| Stroke subtype | | |
| Atherothrombotic | 11 (23.4) | 7 (21.2) |
| Cardio embolic | 10 (21.3) | 12 (36.4) |
| Dissection | 2 (4.3) | 3 (9.1) |
| Unknown | 23 (48.9) | 11 (33.3) |
| Other | 1 (2.1) | 0 (0.0) |
| Intravenous thrombolysis | 22 (46.8) | 15 (45.5) |

† BP indicates blood pressure; § NIHSS indicates National Institutes of Health Stroke Scale.

Table 7.2. MANOVA for the total perfusion deficits and infarct cores in HG and NG

| | Hyperglycemia Mean (SD) | Normoglycemia Mean (SD) | Model I* (95% CI) | Model II** (95% CI) | Model*** (95% CI) |
|---|---|---|---|---|---|
| Total perfusion deficit ($cm^2$) | | | | | |
| Level 1 (N=79) | 22.1±11.3 | 23.3±12.3 | | | |
| Level 2 (N=75) | 27.1±12.3 | 25.4±12.0 | | | |
| Level 1 and 2 (N=74) | | | F=1.94 (p=0.15) | F=1.23 (p=0.30) | F=1.26 (p=0.29) |
| Infarct core ($cm^2$) | | | | | |
| Level 1 (N=79) | 6.66±7.18 | 5.92±6.63 | | | |
| Level 2 (N=75) | 9.24±8.94 | 6.31±7.47 | | | |
| Level 1 and 2 (N=74) | | | F=2.18 (p=0.12) | F=1.69 (p=0.19) | F=0.99 (p=0.38) |
| Index infarct core | | | | | |
| Level 1 (N=79) | 0.31±0.30 | 0.25±0.22 | | | |
| Level 2 (N=74) | 0.33±0.27 | 0.26±0.23 | | | |
| Level 1 and 2 (N=73) | | | F=1.07 (p=0.35) | F=0.91 (p=0.41) | F=0.29 (p=0.75) |

* Unadjusted; ** Adjusted for age and sex; *** Adjusted for age, sex and NIHSS.

was 0.0–0.8 and 0.0–1.0 in the patients with HG. In additional analyses, with a higher glucose cut-off point of 9.0 mM, HG was still not associated with larger perfusion deficits.

### Secondary outcome

In total, 18 patients died during their hospital stay (17% of the patients with NG and 30% of the patients with HG). Follow-up at 6 months by means of the mRS score [18] was obtained in all surviving patients. The crude OR for poor outcome associated with HG was 4.2 (95% CI 1.6–11.3). After multivariate adjustment for age, gender and NIHSS, the OR for poor outcome associated with HG was 2.6 (95% CI 0.72–9.1).

## DISCUSSION

This study demonstrates that HG is not associated with the size of the total perfusion deficit and infarct core in the acute stage of ischemic stroke. In accordance with previous research, where HG was found to be an independent predictor for poor outcome,[1] we demonstrated the relation between HG and poor clinical outcome. We therefore believe that reduced penumbral salvage in patients with HG may be a possible explanation for the relatively poor outcome of these patients.

Although definitive evidence for a direct causal relation between HG on admission and poor outcome is lacking, experimental and clinical studies have identified several mechanisms through which HG could aggravate cerebral damage in ischemic stroke, including impaired recanalisation and reperfusion injury.[7] In patients with large-vessel thromboembolic stroke, these HG-related mechanisms are likely to have an impact on the salvage of the penumbra, the part of the ischemic area that is still potentially salvageable if adequate reperfusion is restored within hours after stroke onset. In fact, MRI studies have shown that reduced penumbral salvage appears to be a key contributor to increased infarct size in patients with HG at admission.[8,20] Parsons et al. have studied the association between HG and the penumbra by acute perfusion-diffusion lesion mismatch on MRI.[8] They found that in 63% of the patients with acute perfusion-diffusion lesions, acute HG was correlated with reduced penumbra salvage. Moreover, studies using animal models suggest that HG leads to decreased reperfusion to the ischemic tissue due to inhibition of vasodilatation and increased vasoconstriction, which might in turn lead to reduced penumbral salvage.[21–24]

However, it was not clear if HG was associated with a proportionally smaller penumbra already in the acute stage. Based on our results, we have reason to believe that there

are no perfusion differences in the acute stage, which may have implications for glucose-lowering therapy in patients with an acute ischemic stroke and HG.

### Limitations

The thresholds used in this study to define the total ischemic defect (relative MTT difference of 145%) and infarct core (cerebral blood volume <2 ml/100 g) on ad- mission CTP are based on a study of final infarct size in patients with and without recanalization.[15] A point of concern might be that the final infarct size and recanalization was not measured in our study and we have no information on how the perfusion deficits develop over time. Another limitation might be that perfusion was only measured on two levels of the brain, which may have caused an underestimation of the perfusion deficits. In addition, our results are based on a relatively small sample size and therefore our findings need to be confirmed in a larger cohort study in the future.

One of the strengths of our study is the prospective collection of patients and the large number of patients who underwent CTP on admission in the acute phase of ischemic stroke. Our study population and data are therefore representative for the population of acute ischemic stroke. Furthermore, our study is the first to evaluate HG and the size of perfusion deficits on admission at CTP.

## CONCLUSION

Although functional outcome is worse in acute stroke patients with HG compared to patients with NG, the perfusion deficit on admission is not larger in patients with HG. This suggests that there might be a window of opportunity for glucose-lowering therapy in the future in order to improve clinical outcome in patients with HG.



## REFERENCES

1. Capes SE, Hunt D, Malmberg K, Pathak P, Gerstein HC. Stress hyperglycemia and prognosis of stroke in nondiabetic and diabetic patients: a systematic overview. Stroke. 2001;32: 2426–2432.
2. Uyttenboogaart M, Koch MW, Stewart RE, Vroomen PC, Luijckx GJ, De Keyser J. Moderate hyperglycemia is associated with favourable outcome in acute lacunar stroke. Brain. 2007;130:1626–1630.
3. Bruno A, Williams LS, Kent TA. How important is hyperglycemia during acute brain infarction? Neurologist. 2004;10:195–200.
4. Luitse MJ, Biessels GJ, Rutten GE, Kappelle LJ. Diabetes, hyperglycemia, and acute ischemic stroke. Lancet Neurol. 2012;11:261–271.

5. Putaala J, Sairanen T, Meretoja A, Lindsberg PJ, Tiainen M, Liebkind R, et al. Post-thrombolytic hyperglycemia and 3-month outcome in acute ischemic stroke. Cerebrovasc Dis. 2011;31:83–92.
6. Baird TA, Parsons MW, Phanh T, Butcher KS, Desmond PM, Tress BM, et al. Persistent poststroke hyperglycemia is independently associated with infarct expansion and worse clinical outcome. Stroke. 2003;34:2208–2214.
7. Kruyt ND, Biessels GJ, Devries JH, Roos YB. Hyperglycemia in acute ischemic stroke: pathophysiology and clinical management. Nat Rev Neurol. 2010;6:145–155.
8. Parsons MW, Barber PA, Desmond PM, Baird TA, Darby DG, Byrnes G, et al. Acute hyperglycemia adversely affects stroke outcome: a magnetic resonance imaging and spectroscopy study. Ann Neurol. 2002;52:20–28.
9. Alvarez-Sabin J, Molina CA, Montaner J, Arenillas JF, Huertas R, Ribo M, et al. Effects of admission hyperglycemia on stroke outcome in reperfused tissue plasminogen activator-treated patients. Stroke. 2003;34:1235–1241.
10. Wintermark M, Reichhart M, Cuisenaire O,Maeder P, Thiran JP, Schnyder P, et al. Comparison of admission perfusion computed tomography and qualitative diffusion- and perfusion-weighted magnetic resonance imaging in acute stroke patients. Stroke. 2002;33:2025–2031.
11. Wintermark M, Meuli R, Browaeys P, Reichhart M, Bogousslavsky J, Schnyder P, et al. Comparison of CT perfusion and angiography and MRI in selecting stroke patients for acute treatment. Neurology. 2007;68:694–697.
12. Schramm P, Schellinger PD, Klotz E, Kallen- berg K, Fiebach JB, Kulkens S, et al. Comparison of perfusion computed tomography and computed tomography angiography source images with perfusion-weighted imaging and diffusion-weighted imaging in patients with acute stroke of less than 6 hours' duration. Stroke. 2004;35:1652–1658.
13. Wintermark M. Brain perfusion-CT in acute stroke patients. Eur Radiol. 2005;15:D28–D31.
14. Dankbaar JW, Rijsdijk M, van der Schaaf IC, Velthuis BK, Wermer MJ, Rinkel GJ. Relationship between vasospasm, cerebral perfusion, and delayed cerebral ischemia after aneurysmal subarachnoid hemorrhage. Neuroradiology. 2009;51:813–819.
15. Wintermark M, Flanders AE, Velthuis B, Meuli R, van Leeuwen M, Goldsher D, et al. Perfusion-CT assessment of infarct core and penumbra: receiver operating characteristic curve analysis in 130 patients suspected of acute hemispheric stroke. Stroke 2006;37:979–985.
16. Pexman JH, Barber PA, Hill MD, Sevick RJ, Demchuk AM, Hudon ME, et al. Use of the Alberta stroke program early CT score (AS- PECTS) for assessing CT scans in patients with acute stroke. AJNR Am J Neuroradiol. 2001;22:1534–1542.
17. Kruyt ND, Nys GM, van der Worp HB, van Zandvoort MJ, Kappelle LJ, Biessels GJ. Hyperglycemia and cognitive outcome after ischemic stroke. J Neurol Sci. 2008;270:141-147
18. Scott JF, Robinson GM, French JM, O'Connell JE, Alberti KG, Gray CS. Glucose potassium insulin infusions in the treatment of acute stroke patients with mild to moderate hyperglycemia: the glucose insulin in stroke trial (GIST). Stroke. 1999;30:793–799.
19. van Swieten JC, Koudstaal PJ, Visser MC, Schouten HJ, van Gijn J. Interobserver agreement for the assessment of handicap in stroke patients. Stroke. 1988;19:604–607.
20. Els T, Klisch J, Orszagh M, Hetzel A, Schulte-Monting J, Schumacher M, et al. Hyperglycemia in patients with focal cerebral ischemia after intravenous thrombolysis: influence on clinical outcome and infarct size. Cerebrovasc Dis. 2002;13:89–94.
21. Duckrow RB, Beard DC, Brennan RW. Regional cerebral blood flow decreases during chronic and acute hyperglycemia. Stroke. 1987;18:52–58.
22. Kawai N, Keep RF, Betz AL, Nagao S. Hyperglycemia induces progressive changes in the cerebral microvasculature and blood-brain barrier transport during focal cerebral ischemia. Acta Neurochir Suppl. 1998;71:219–221.
23. Quast MJ, Wei J, Huang NC, Brunder DG, Sell SL, Gonzalez JM, et al. Perfusion deficit parallels exacerbation of cerebral ischemia/ reperfusion injury in hyperglycemic rats. J Cereb Blood Flow Metab. 1997;17:553–559.
24. Yip PK, He YY, Hsu CY, Garg N, Marangos P, Hogan EL. Effect of plasma glucose on infarct size in focal cerebral ischemia-reperfusion. Neurology. 1991;41:899–905.

# CHAPTER 8

## Admission hyperglycemia in acute ischemic stroke is associated with poor penumbral salvage

Merel J.A. Luitse
Birgitta K. Velthuis
L. Jaap Kappelle
Tom van Seeters
Yolanda van der Graaf
Geert Jan Biessels
on behalf of the DUST study group

Submitted

# ABSTRACT

## Introduction

Patients with acute ischemic stroke and admission hyperglycemia (HG) are known to have larger final infarct size and poorer outcome than normoglycemic (NG) patients. Yet, the relation between HG and cerebral perfusion in the acute stage of stroke is largely unknown. We assessed the association between HG and cerebral perfusion, infarct size and functional outcome.

## Methods

We included 617 patients with ischemic stroke and an anterior circulation perfusion deficit (mean age 66±14 years, 55% male) within 9 hours after symptom onset. Total perfusion deficit, penumbra and infarct core areas on admission and infarct volume after 3 days were compared between hyperglycemic and normoglycemic patients with an ANCOVA. Functional outcome (Modified Rankin Scale (mRS) at 3 months was related to admission HG.

## Results

Admission HG was present in 43% of the patients. In the acute stage, HG was independently associated with larger total perfusion deficits (mean difference 3.1 $cm^2$; 95% CI 0.73–5.5) and larger penumbra areas (mean difference 3.2 $cm^2$; 95% CI 1.3–5.0), but not with larger infarct cores (mean difference -0.04 $cm^2$; 95% CI -1.8–1.7). After 3 days, patients with HG had significant larger infarct sizes (median 23.6 ml; IQR 4.6–86.9) than patients with NG (11.4 ml; IQR 2.1–59.5). HG was also associated with poor functional outcome (mRS 3–6) (RR 1.39; 95% CI 1.18–1.65).

## Conclusion

In the acute stage of ischemic stroke, HG is associated with larger penumbras, but not with a larger infarct cores when compared to NG. However, infarct size after 3 days is larger in patients with HG, indicating that penumbral salvage is worse in patients with HG.

# INTRODUCTION

Admission hyperglycemia (HG) occurs in 30–40% of people with acute ischemic stroke.[1] Most of these individuals do not have a known history of diabetes mellitus.[2] HG in the acute stage of ischemic stroke is associated with increased mortality and with worse long-term functional outcome.[1,3] Moreover, patients with HG tend to have a larger final infarct size than patients with normal glucose levels.[3] The pathophysiology underlying this association remains unclear, but reduced penumbral salvage has been suggested to play an important role.[4,5] It is unknown, however, if cerebral perfusion is already compromised in the acute stage of ischemic stroke in patients with HG and how this is related to final infarct size.

The objective of our study was to determine the effect of acute HG on cerebral perfusion using CT perfusion (CTP) in a large prospective cohort of patients with acute ischemic stroke. Furthermore, we assessed the effect of admission HG on final infarct size and functional outcome.

# METHODS

## Inclusion criteria

All patients participated in Dutch acute stroke study (DUST), a prospective multi-center cohort study including adult patients with a clinical diagnosis of acute ischemic stroke within nine hours after symptom onset between May 2009 and August 2013.[6] A detailed description of the DUST study protocol and the main results have been published previously.[6,7] Institutional review boards approved the study, and written informed consent was obtained for each patient. In case the patient died before consent was acquired, the ethics committee waived the need for consent.

For the current study, we selected patients with a visible perfusion deficit in the anterior circulation on at least one of the two Alberta Stroke Program Early CT Score (ASPECTS) levels on the admission CTP[8,9] and with known serum blood glucose levels measured on admission.

## Clinical assessment

Patient characteristics were collected at admission and included age, medical history, presence of vascular risk factors, use of antithrombotic medication and treatment of ischemic stroke. Stroke severity on admission was assessed by means of the National Institutes of Health Stroke Scale (NIHSS)[10] and stroke subtype by means of the TOAST classification.[11]

HG on admission was defined as a blood glucose level of 7 mmol/L or higher. Clinical management of admission HG was left at the discretion of the treating physician. Treatment of HG was not recorded for the present study.

## Imaging protocol

The admission CT examination included a non-contrast CT (NCCT), CTP, and CT angiography (CTA) of the cervical and intracranial arteries. Detailed information on the CT imaging and analysis protocol has been described earlier.[7] All scans were evaluated by one of three experienced observers, who were blinded for all clinical data except for the side of symptoms.

CTP coverage varied according to the type of CT scanner, with minimal coverage of both ASPECTS levels in all patients with anterior circulation stroke symptoms.[8,9] The first level was where the thalamus and basal ganglia are visible, and the second level was just cranial to the basal ganglia at the corona radiata and the centrum semiovale. Threshold-defined penumbra and infarct core maps were calculated for both ASPECTS levels based upon previously reported mean transit time (MTT) and cerebral blood volume (CBV) thresholds for this CTP post-processing software.[12] The total perfusion deficit area was defined as the area with an MTT ≥145% compared to the contralateral hemisphere. Within this area, infarct core was separated from the penumbra by a CBV value <2.0 ml/100g.[12]

Follow-up imaging was performed after 3 (±2) days with NCCT or MRI, according to the decision of the treating physician.

## Outcome measures

Imaging outcome measures for the present study were perfusion metrics at admission and infarct size at follow-up imaging. Perfusion metrics, including mean area in $cm^2$ of the total perfusion deficit, the penumbra and the infarct core, were measured on the ASPECTS levels. If CTP data were available of both ASPECTS levels, the mean area was calculated. In case perfusion data were missing on one of the two ASPECTS levels, only the data at the available level were used in the analysis. Infarct size was measured in millilitres (ml). This was obtained by manually tracing the infarct area(s) on the axial NCCT slices or on the axial diffusion weighted imaging slices on the MRI. The surface of these area(s) was subsequently multiplied by the slice thickness to obtain an infarct volume per slice. The infarct volumes of all slices on which the infarct was visible were added up to obtain the total infarct volume.

Our functional outcome measure was the modified Rankin Scale (mRS) at 3 months after admission, which was obtained by telephone interview by a trained research nurse.[13] A mRS score of 0–2 was defined as good outcome, a score of 3–6 as poor outcome.

### Statistical analyses

Statistical analyses were performed using IBM SPSS Statistics, version 22. All data are expressed as means ± standard deviation (SD) or as medians with interquartile ranges (IQR) when they were not normally distributed. Mean values were compared with analysis of variance (ANOVA). Differences in proportions were evaluated by the Pearson's $\chi^2$ test. Differences at the level of $p<0.05$ were considered statistically significant.

The association between HG and the area of the total perfusion deficit, penumbra, infarct core on admission, and final infarct size after 3 days was calculated by analysis of covariance (ANCOVA). Mean differences between NG and HG were calculated with corresponding 95% confidence intervals. Patients with no visible penumbra area (only infarct core) or no visible infarct core area (only penumbra) on admission or no visible infarct after 3 days were included in the analyses with an area of 0 $cm^2$ for the admission scan or volume of 0 ml for the follow-up scan. In a sensitivity analysis, penumbra and infarct core areas on admission and infarct volumes after 3 days were log-transformed after addition of 1 ml to secure a normal distribution of the variables.

We adjusted for age, sex, NIHSS on admission, hypertension, hyperlipidemia, myocardial infarction, atrial fibrillation, previous use of antithrombotic medication, time from symptom onset to scan, treatment with intravenous rtPA and stroke subtype according to the TOAST classification.

The association between HG and functional outcome was calculated by means of Poisson regression analysis with a robust standard error. The relation was expressed as a relative risk (RR) with corresponding 95% confidence intervals (CI), respectively.



## RESULTS

### Patient characteristics

Between May 2009 and August 2013, 1393 patients were included in DUST. For the present study we selected 617 DUST participants with a visible perfusion deficit in the anterior circulation on at least one of the two ASPECTS levels (Figure 8.1). Reasons for exclusion from the current study were the absence of a perfusion deficit (n=659), missing

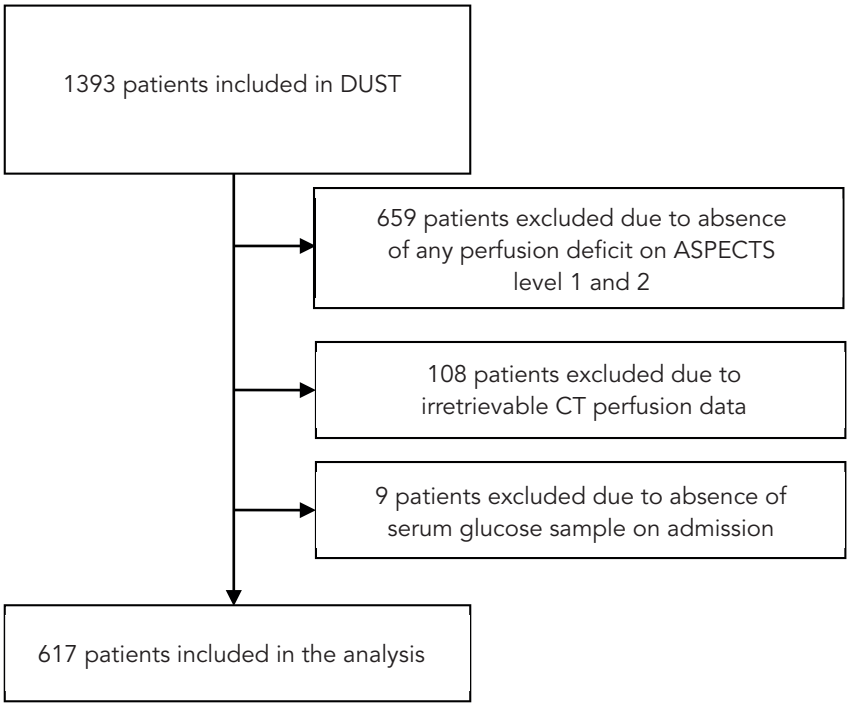



Figure 8.1. Flow of patients through the study.

or incomplete CTP data (n=108) or no glucose sample on admission (n=9). The 776 excluded patients had a significantly lower median NIHSS score on admission (NIHSS 4; IQR 2–7 versus NIHSS 10; IQR 5–15) and better functional outcome at 2 months than included patients (73% versus 57%). However, there was no difference in the occurrence of HG (included patients 43%; excluded patients 42%). Mean age for included patients was 66±14 years and 55.4% of the patients was male.

Admission HG was present in 264 (42.8%) patients. Known pre-existent diabetes was present in 13.0% of the study population. The median total perfusion deficit area was 20.8 $cm^2$ (9.0–29.8); median penumbra area 13.3 $cm^2$ (IQR 4.2–20.1) and median infarct core area 7.5 $cm^2$ (IQR 7.4–11.1). Follow-up imaging was available in 523 (84.4%) of the patients. Median infarct volume after 3 days was 16.1 ml (IQR 2.8–73.2). There were 65 (24.3%) patients without a visible infarct on follow-up imaging. Information about functional follow-up at 3 months was available in 612 (99.2%) patients.

The baseline characteristics for the study population and stratified by admission HG are shown in Table 8.1. Patients with admission HG had a worse vascular risk profile

(i.e. diabetes, hypertension and hyperlipidemia) and slightly higher NIHSS scores at admission. With regard to stroke subtypes, large-artery atherosclerosis occurred more often in the HG group, whereas strokes of undetermined cause occurred less frequently in the HG group compared to the NG group. There was no difference in the occurrence of small vessel occlusion, cardioembolic strokes or stroke of other causes. Fewer patients with admission HG were treated with intravenous rtPA compared with patients with NG (60.3% in HG; 70.8% in NG).

Table 8.1. Patient characteristics

| Characteristics<br>n | All patients<br>N=617 | Normoglycemia<br>N=353 | Hyperglycemia<br>N=264 |
|---|---|---|---|
| Age, years | 66±14 | 66±15 | 67±13 |
| Male | 342 (55.4) | 197 (55.8) | 145 (54.9) |
| Previous stroke or TIA | 128 (20.7) | 76 (21.5) | 52 (19.7) |
| Hypertension | 324 (52.5) | 167 (47.3) | 157 (60.6) |
| Diabetes | 80 (13.0) | 17 (4.8) | 63 (23.9) |
| Hyperlipidemia | 182 (29.5) | 79 (22.4) | 103 (39.0) |
| Myocardial infarction | 108 (17.5) | 53 (15.0) | 55 (20.8) |
| Atrial fibrillation | 84 (13.6) | 42 (11.9) | 42 (15.9) |
| Peripheral artery disease | 37 (6.0) | 16 (4.5) | 21 (8.0) |
| Smoking | 173 (28.0) | 99 (28.0) | 74 (28.0) |
| Previous use of antithrombotics | 241 (39.1) | 129 (36.6) | 112 (42.4) |
| Median NIHSS on admission (IQR) | 10 (5–15) | 9 (5–15) | 11 (5–16) |
| Median time from onset to scan, min (IQR) | 108 (68–182) | 102 (65–171) | 115 (69–210) |
| Systolic BP, mmHg | 155±28 | 153±28 | 157±27 |
| Diastolic BP, mmHg | 85±17 | 85±18 | 84±17 |
| Admission glucose, mmol/L | 7.3±2.5 | 6.0±0.6 | 9.1±2.9 |
| Intravenous rtPA | 410 (66.5) | 250 (70.8) | 160 (60.3) |
| Endovascular treatment | 62 (10.0) | 31 (8.8) | 31 (11.7) |
| Stroke subtype | | | |
| Large-artery atherosclerosis | 247 (40.0) | 127 (36.0) | 120 (45.5) |
| Small vessel occlusion | 27 (4.4) | 14 (4.0) | 13 (4.9) |
| Cardioembolism | 137 (22.2) | 78 (22.1) | 59 (22.3) |
| Unknown | 165 (26.7) | 110 (31.2) | 55 (20.8) |
| Other | 41 (6.6) | 24 (6.8) | 17 (6.4) |

Data are expressed as means ± standard deviation or numbers with percentages in parentheses unless otherwise indicated. NIHSS, National Institutes of Health Stroke Scale; IQR, interquartile range; ER, emergency room; BP, blood pressure; rtPA, recombinant tissue plasminogen activator.

Table 8.2. Mean differences for perfusion parameters on admission in patients with HG and NG

| Parameters on admission | n | HG mean±SD | NG mean±SD | Model I[a] (95% CI) | Model II[b] (95% CI) | Model III[c] (95% CI) |
|---|---|---|---|---|---|---|
| Total perfusion deficit ($cm^2$) | 617 | 23.2±17.6 | 19.0±13.8 | 4.1 (1.7–6.6) | 2.8 (0.58–5.1) | 3.1 (0.69–5.5) |
| Penumbra area ($cm^2$) | 617 | 15.4±12.8 | 11.7±9.9 | 3.8 (2.0–5.6) | 3.2 (1.4–5.0) | 3.0 (1.1–4.8) |
| Infarct core area ($cm^2$) | 617 | 7.8±12.6 | 7.4±9.8 | 0.32 (-1.5–2.1) | -0.37 (-2.0–1.3) | 0.2 (-1.6–1.9) |

[a] Adjusted for age and sex [b] Adjusted for age, sex and NIHSS on admission [c] Adjusted for age, sex, NIHSS on admission, hypertension, hyperlipidemia, myocardial infarction, atrial fibrillation, previous use of antithrombotics, time symptom onset to scan, treatment with rtPA and stroke subtype. HG indicates hyperglycemia; NG, normoglycemia; SD, standard deviation; 95% CI, 95% confidence interval.

Table 8.3. Log transformed mean differences for perfusion parameters on admission in patients with HG and NG

| Parameters at baseline | n | HG mean±SD | NG mean±SD | Model I[a] (95% CI) | Model II[b] (95% CI) | Model III[c] (95% CI) |
|---|---|---|---|---|---|---|
| Total perfusion deficit ($cm^2$) | 617 | 23.2±17.6 | 19.0±13.8 | | | |
| Log total perfusion deficit ($cm^2$) | | 3.2±0.52 | 3.1±0.57 | 0.11 (0.02–0.20) | 0.08 (0.00–0.17) | 0.10 (0.01–0.19) |
| Penumbra area ($cm^2$) | 617 | 15.4±12.8 | 11.7±9.9 | | | |
| Log penumbra area ($cm^2$) | | 2.9±0.66 | 2.8±0.64 | 0.14 (0.04–0.25) | 0.12 (0.01–0.22) | 0.12 (0.01–0.23) |
| Infarct core area ($cm^2$) | 617 | 7.8±12.6 | 7.4±9.8 | | | |
| Log infarct core ($cm^2$) | | 2.3±0.91 | 2.2±1.1 | 0.13 (-0.31–0.29) | 0.08 (-0.66–0.23) | 0.13 (-0.02–0.30) |

[a] Adjusted for age and sex [b] Adjusted for age, sex and NIHSS on admission [c] Adjusted for age, sex, NIHSS on admission, hypertension, hyperlipidemia, myocardial infarction, atrial fibrillation, previous use of antithrombotics, time symptom onset to scan, treatment with rtPA and stroke subtype. HG indicates hyperglycemia; NG, normoglycemia; SD, standard deviation; 95% CI, 95% confidence interval.

### Perfusion metrics and infarct size

In patients with HG on admission, the total perfusion deficit areas were larger compared to patients with NG (adjusted mean difference 3.1 $cm^2$; 95% CI 0.73–5.5). The penumbral areas on admission were also significantly larger in patients with HG (adjusted mean difference 3.2 $cm^2$; 95% CI 1.3–5.0). In contrast, the infarct core areas on admission were not larger in patients with HG than in patients with NG (adjusted mean difference -0.04 $cm^2$; 95% CI -1.8–1.7). The results are shown in Table 8.2. A sensitivity analysis, in which these variables were log-transformed, showed no different findings (Table 8.3).

Patients with HG on admission had a median infarct size after 3 days of 23.6 ml (IQR 4.6–86.9). In patients with NG, the median infarct size after 3 days was 11.4 ml (IQR 2.1–59.5) ml (adjusted log mean difference 0.20; 95% CI 0.08–0.33)). In the subgroup of patients with a visible infarct on follow-up, the infarct size was still larger in the HG group (adjusted log mean difference 0.18 ml; 95% CI 0.07–0.30). The results are shown in Table 8.4.

### Functional outcome

Poor outcome occurred in 290 patients (57% of the patients with HG and 40% in the patients with NG). HG was independently associated with poor functional outcome with a RR of 1.39 (1.18–1.65) after adjustment of age, sex, NIHSS on admission, vascular risk factors, previous use of antithrombotic medication, time from onset of symptoms to scan and treatment with rtPA. Functional outcome stratified for HG and NG is shown in Figure 8.2.

## DISCUSSION

This large prospective study in patients with acute ischemic stroke demonstrates that penumbral areas on admission are larger in patients with HG than in patients with NG whereas there was no difference in the size of the infarct cores between the groups. Yet, after 3 days final infarct size is larger in patients with HG, indicating that penumbral salvage is reduced. Functional outcome at 3 months is also worse in patients with HG.

Few previous studies have addressed the association between HG and cerebral perfusion disturbances in the acute stage of ischemic stroke. In a study of 69 patients, the association between HG and the penumbra was assessed by acute perfusion-diffusion lesion mismatch on MRI.[14] They found that in the 63% of patients with acute perfusion-diffusion lesions, acute HG was correlated with reduced penumbra salvage. In an earlier study performed in

Table 8.4. Log transformed mean differences for infarct size after 3 days in patients with HG and NG

| Infarct size after 3 days | n | HG mean±SD | NG mean±SD | Model I[a] (95% CI) | Model II[b] (95% CI) | Model III[c] (95% CI) |
|---|---|---|---|---|---|---|
| All patients with follow-up | 523 | | | | | |
| Infarct volume (ml) | | 68.0±102.9 | 51.9±84.1 | | | |
| Log Infarct volume (ml) | | 1.3±0.76 | 1.1±0.79 | 0.20 (0.07–0.33) | 0.19 (0.07–0.31) | 0.20 (0.07–0.33) |
| Patients with visible infarct | 458 | | | | | |
| Infarct volume (ml)[$] | | 75.9±106.0 | 60.3±87.8 | | | |
| Log Infarct volume (ml)[$] | | 1.5±0.65 | 1.3±0.69 | 0.17 (0.05–0.30) | 0.17 (0.06–0.28) | 0.18 (0.07–0.30) |

[a] Adjusted for age and sex [b] Adjusted for age, sex and NIHSS on admission [c] Adjusted for age, sex, NIHSS on admission, hypertension, hyperlipidemia, myocardial infarction, atrial fibrillation, previous use of antithrombotics, time symptom onset to scan, treatment with rtPA and stroke subtype. [$] Patients with a visible infarct (i.e an infarct volume >0 ml at follow-up). HG indicates hyperglycemia; NG, normoglycemia; SD, standard deviation; 95% CI, 95% confidence interval.

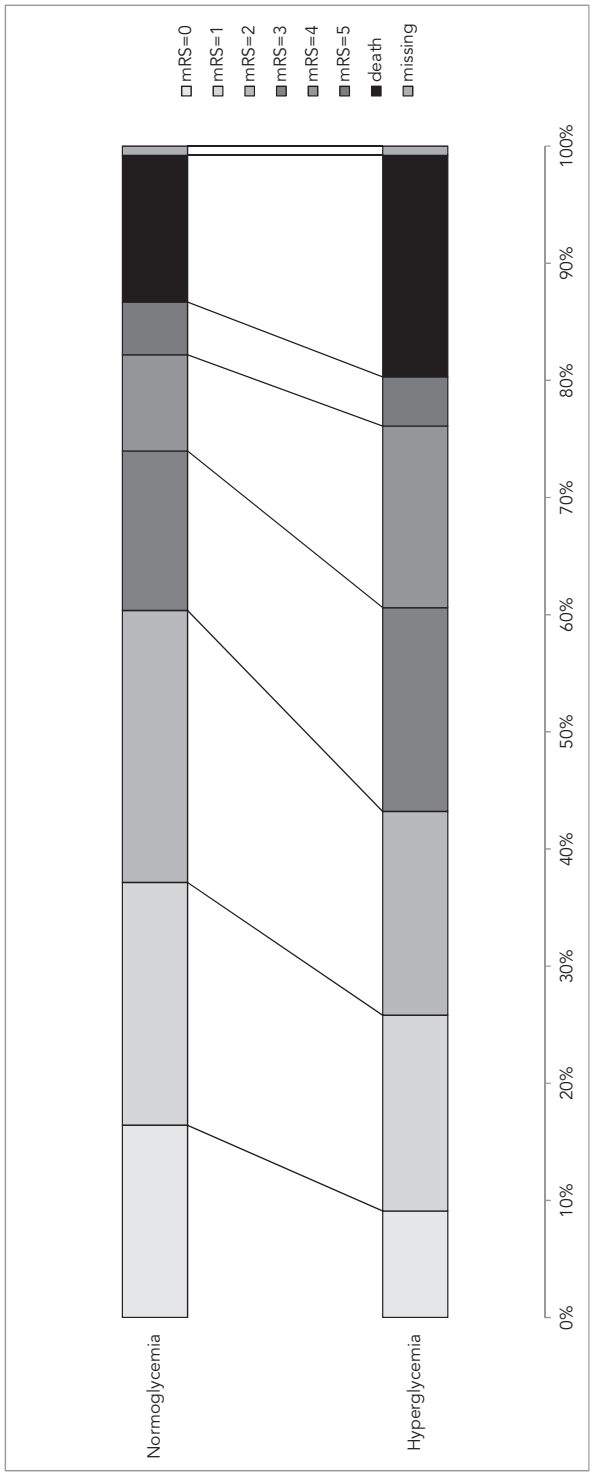



Figure 8.2. Functional outcome stratified for HG and NG.

2007–2008, we showed no differences in perfusion deficits between patients with HG and those with NG.[15] The use of earlier generation CT-scanners, the lower portion of patients with large vessel atherosclerosis (22%) and the small sample size (n=80) in that previous study are likely to explain the differences in results compared with the present study.

Our findings that patients with HG in the acute stage of ischemic stroke had a larger total perfusion deficit, but a similar infarct core compared with patients with NG, imply that in patients with HG there is relatively more penumbral tissue at admission. In other words, the part of the ischemic area that is at risk but still potentially salvageable if adequate reperfusion is restored within hours after stroke onset is larger than in patients with NG. Whether the increased perfusion deficit in relation to HG is a consequence of compromised blood flow or worse leptomeningeal collaterals due to HG,[16] or whether a larger perfusion deficit and worse condition at admission induce HG cannot be derived from our data. However, previous experimental studies have suggested that induction of HG may lead to metabolic derangements, decreased reperfusion and inflammation, and adversely influence cerebral perfusion already in the acute stage of ischemic stroke (30–120 minutes).[17,18]

We also demonstrated that HG is independently associated with larger infarcts at follow-up and worse functional outcome. These findings are in line with previous studies.[1,5,19] As the infarct core at admission is not different between patients with HG or NG, this suggests that after admission there is more infarct growth due to reduced penumbral salvage. Our results suggest that a detrimental, but potentially reversible, influence of HG is already present in the acute stage of ischemic stroke, but leads to irreversible damage in the first days after ischemic stroke by affecting the salvage of the penumbra. This is in line with earlier smaller MRI studies that indicated that reduced penumbral salvage is a key contributor to increased final infarct size in patients with HG in the acute stage.[19,20] Other studies using animal models have also suggested that HG could aggravate cerebral damage and reduced penumbral salvage through mechanism as impaired recanalization, decreased reperfusion and increased reperfusion injury.[17,21–23]

In patients with ischemic stroke and acute HG, randomized-controlled trials have not provided evidence that glucose-lowering treatment improves clinical outcome.[24,25] One factor in this lack of effect may be that achieving NG in the early stage of stroke can be difficult, and the possibility of inadvertently causing hypoglycemia remains a concern.[4,26] Moreover, the optimal duration of glucose-lowering treatment has not yet been determined. The present results do indicate that at admission there is still a larger amount of potentially salvageable tissue in people with HG, offering a window of opportunity for glucose-lowering therapy, at least in a subgroup of patients. Previous studies on glucose-

lowering therapy also included patients with lacunar strokes. In these patients HG has not been linked to worse outcome in observational studies.[27] Therefore, glucose-lowering therapy might be particularly beneficial in patients with non-lacunar infarcts with larger perfusion deficits. Hopefully, a large phase III trial of glucose-lowering therapy in acute ischemic stroke that is currently underway will provide more information on this topic.[28]

### Limitations

Our study has limitations. CTP coverage did not include the whole brain. Therefore, the perfusion deficit was assessed two dimensionally on the two ASPECTS levels, whereas infarct volumes were assessed in three dimensions at follow-up. Consequently, this implies that penumbral salvage cannot be measured directly. In addition, infarct volume was measured after 3 days, which could have led to an overestimation of the true infarct volume due to the presence of cytotoxic oedema, as it has been shown that infarct volume is smaller after 3 months.[29] Finally, there was no standardized protocol of follow-up glucose measurement or treatment of HG and possible treatment of HG was also not recorded.

## CONCLUSION

HG is independently associated with larger penumbra areas in the acute stage of ischemic stroke, but not with larger infarct cores. HG is also associated with larger final infarcts and with worse functional outcome in these patients. Apparently, HG negatively influences penumbral recovery. This implies that glucose-lowering therapy in patients with acute ischemic stroke and HG deserves reappraisal.

## REFERENCES

1. Capes SE, Hunt D, Malmberg K, Pathak P, Gerstein HC. Stress hyperglycemia and prognosis of stroke in nondiabetic and diabetic patients: a systematic overview. Stroke. 2001;32:2426–2432.
2. Bruno A, Williams LS, Kent TA. How important is hyperglycemia during acute brain infarction? Neurologist. 2004;10:195–200.
3. Baird TA, Parsons MW, Phanh T, Butcher KS, Desmond PM, Tress BM, et al. Persistent poststroke hyperglycemia is independently associated with infarct expansion and worse clinical outcome. Stroke. 2003;34:2208–2214.
4. Kruyt ND, Biessels GJ, Devries JH, Roos YB. Hyperglycemia in acute ischemic stroke: pathophysiology and clinical management. Nat.Rev.Neurol. 2010;6:145–155.
5. Parsons MW, Barber PA, Davis SM. Relationship between severity of MR perfusion deficit and DWI lesion evolution. Neurology. 2002;58:1707.
6. Van Seeters T, Biessels GJ, Kappelle LJ, Van Der Schaaf IC, Dankbaar JW, Horsch AD, et al. The Prognostic Value of CT Angiography and CT Perfusion in Acute Ischemic Stroke. Cerebrovasc. Dis. 2015;40:258–269.

7. van Seeters T, Biessels GJ, van der Schaaf IC, Dankbaar JW, Horsch AD, Luitse MJ, et al. Prediction of outcome in patients with suspected acute ischaemic stroke with CT perfusion and CT angiography: the Dutch acute stroke trial (DUST) study protocol. BMC Neurol. 2014;14:37.
8. Pexman JH, Barber PA, Hill MD, Sevick RJ, Demchuk AM, Hudon ME, et al. Use of the Alberta Stroke Program Early CT Score (ASPECTS) for assessing CT scans in patients with acute stroke. AJNR.American J. Neuroradiol. 2001;22:1534–1542.
9. Puetz V, Dzialowski I, Hill MD, Demchuk AM. The Alberta stroke program early ct score in clinical practice: What have we learned? Int. J. Stroke. 2009;4:354–364.
10. Brott T, Adams HP, Olinger CP, Marler JR, Barsan WG, Biller J, et al. Measurements of acute cerebral infarction: A clinical examination scale. Stroke. 1989;20:864–870.
11. Adams HP, Bendixen BH, Kappelle LJ, Biller J, Love BB, Gordon DL, et al. 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.
12. Wintermark M, Flanders AE, Velthuis B, Meuli R, van Leeuwen M, Goldsher D, et al. Perfusion-CT assessment of infarct core and penumbra: receiver operating characteristic curve analysis in 130 patients suspected of acute hemispheric stroke. Stroke. 2006;37:979–985.
13. van Swieten JC, Koudstaal PJ, Visser MC, Schouten HJ, van Gijn J. Interobserver agreement for the assessment of handicap in stroke patients. Stroke. 1988;19:604–607.
14. Parsons MW, Barber PA, Desmond PM, Baird TA, Darby DG, Byrnes G, et al. Acute hyperglycemia adversely affects stroke outcome: a magnetic resonance imaging and spectroscopy study. Ann. Neurol. 2002;52:20–28.
15. Luitse MJA, Van Seeters T, Horsch AD, Kool HA, Velthuis BK, Kappelle LJ, et al. Admission hyperglycaemia and cerebral perfusion deficits in acute ischaemic stroke. Cerebrovasc. Dis. 2013;35:163–167.
16. Menon BK, Smith EE, Coutts SB, Welsh DG, Faber JE, Goyal M, et al. Leptomeningeal collaterals are associated with modifiable metabolic risk factors. Ann. Neurol. 2013;74:241–248.
17. Quast MJ, Wei J, Huang NC, Brunder DG, Sell SL, Gonzalez JM, et al. Perfusion deficit parallels exacerbation of cerebral ischemia/reperfusion injury in hyperglycemic rats. J. Cereb. Blood Flow Metab. 1997;17:553–559.
18. Gisselsson L, Smith M, Siesjo BK. Hyperglycemia and Focal Brain Ischemia. J. Cereb. Blood Flow Metab.1999;288–297.
19. Els T, Klisch J, Orszagh M, Hetzel A, Schulte-Monting J, Schumacher M, et al. Hyperglycemia in patients with focal cerebral ischemia after intravenous thrombolysis: influence on clinical outcome and infarct size. Cerebrovasc. Dis. 2002;13:89–94.
20. Parsons MW, Barber PA, Chalk J, Darby DG, Rose S, Desmond PM, et al. Diffusion- and perfusion-weighted MRI response to thrombolysis in stroke. Ann. Neurol. 2002;51:28–37.
21. Duckrow RB, Beard DC, Brennan RW. Regional cerebral blood flow decreases during chronic and acute hyperglycemia. Stroke. 1987;18:52–58.
22. Kawai N, Keep RF, Betz AL, Nagao S. Hyperglycemia induces progressive changes in the cerebral microvasculature and blood-brain barrier transport during focal cerebral ischemia. Acta Neurochir. 1998;71:219–221.
23. Yip PK, He YY, Hsu CY, Garg N, Marangos P, Hogan EL. Effect of plasma glucose on infarct size in focal cerebral ischemia-reperfusion. Neurology. 1991;41:899–905.
24. Gray CS, Hildreth AJ, Sandercock PA, O'Connell JE, Johnston DE, Cartlidge NE, et al. Glucose-potassium-insulin infusions in the management of post-stroke hyperglycaemia: the UK Glucose Insulin in Stroke Trial (GIST-UK). Lancet Neurol. 2007;6:397–406.
25. Bellolio MF, Gilmore RM, Stead LG. Insulin for glycaemic control in acute ischaemic stroke. Cochrane Database Syst. Rev. 2011;9:CD005346.
26. Vriesendorp TM, Roos YB, Kruyt ND, Biessels GJ, Kappelle LJ, Vermeulen M, et al. Efficacy and safety of two 5 day insulin dosing regimens to achieve strict glycaemic control in patients with acute ischaemic stroke. J. Neurol. Neurosurg. Psychiatry. 2009;80:1040–1043.
27. Kruyt ND, Nys GM, van der Worp HB, van Zandvoort MJ, Kappelle LJ, Biessels GJ. Hyperglycemia and cognitive outcome after ischemic stroke. J. Neurol. Sci. 2008;270:141–147.

28. Bruno A, Durkalski VL, Hall CE, Juneja R, William G, Janis S, et al. The Stroke Hyperglycemia Insulin Network Effort (SHINE) trial protocol: a randomized, blinded, efficacy trial of standard vs. intensive hyperglycemia management in acute stroke. Int. J. Stroke. 2014;9:246–251.
29. Brott T, Marler JR, Olinger CP, Jr HPA, Tomsick T, Barsan WG, et al. Measurements of Acute Cerebral Infarction: Lesion Size by Computed Tomography. Stroke. 1989;20:871-875.

# CHAPTER 9

## General discussion

Ischemic stroke carries a significant risk of death and long-term disability.[1,2] Better understanding of underlying pathophysiology, enhanced diagnostic options, and better estimation of prognosis are needed to improve long-term outcome. In my thesis, I have focused on the application of CT angiography and CT perfusion in acute ischemic stroke. Furthermore, I have explored the role of hyperglycemia in relation to prognosis and cerebral perfusion in acute ischemic stroke. In this final chapter, I review the main findings and discuss perspectives for future research.

# PART I – CT IMAGING IN ACUTE ISCHEMIC STROKE

In recent years, significant advances have been made in imaging and management of acute ischemic stroke.[3–7] In many stroke centers, multimodal CT imaging has now become standard practice in the diagnostic evaluation of patients with acute ischemic stroke. CT angiography and CT perfusion can easily be incorporated in the emergency setting and have broader availability compared to MRI imaging.

## Diagnostic value of CT angiography

In acute ischemic stroke, CT angiography can identify intracranial occlusions in large and medium size arteries, such as the distal internal carotid artery, proximal middle cerebral artery or basilar artery.

In the past when intravenous thrombolysis was the only treatment option proven to be beneficial for patients with acute ischemic stroke,[4–6] CT angiography was not routine practice in most stroke centers. This has changed considerably after endovascular thrombectomy has been shown to have beneficial effect on outcome.[7] CT (or MR) angiography should now always be performed in patients with suspected acute ischemic stroke who are eligible for intravenous thrombolysis or endovascular treatment.

CT angiography can also be used to identify an extracranial occlusion of the carotid artery. Acute occlusions of the extracranial carotid artery are associated with poor outcome and substantial risk of recurrent stroke.[8,9] Spontaneous recanalization of an acute occlusion may occur.[10,11] However, little is known about the natural course of such an occlusion, and the influence of acute treatment on recanalization.[11] Detection of recanalization may be particularly important when a high-grade stenosis remains. In this situation, subsequent treatment such as carotid endarterectomy might be indicated. In the DUST cohort, all patients underwent CT angiography within 9 hours after symptom onset and a substantial number of these patients received follow-up imaging after three days. In **Chapter 3**, we

showed that in 12% of the study population, an acute symptomatic occlusion of the extracranial carotid artery was present. In one out of every six patients with an occlusion, we found a residual high-grade stenosis on follow-up imaging. More than half of these patients underwent subsequent carotid endarterectomy after the acute phase. Based on these results, I suggest follow-up imaging in all patients with an acute occlusion of the extracranial carotid artery. Since the natural course and possible recanalization of an occluded carotid artery is unknown, the timing of follow-up imaging remains unclear. In our study, mean follow-up time was 3 days. Especially in patients with persistent or near occlusions, this time-window may be too short if the recanalization process is still ongoing. Repeated follow-up might be indicated in those patients with persistent or near occlusions who are eligible for subsequent treatment if a high-grade stenosis would be found. Hence, the optimal strategy of follow-up imaging and cost-effectiveness needs to be established.

## Diagnostic value of CT perfusion

Whereas CT angiography is crucial for identifying patients with intracranial and extracranial vessel occlusions, the position of CT perfusion in the diagnostic work-up of acute ischemic stroke is debated. CT perfusion has a high sensitivity and specificity for the detection of ischemic stroke,[12] and is suggested to increase the diagnostic accuracy in patients suspected of posterior circulation ischemia.[13] Furthermore, CT perfusion is used to differentiate between penumbra and the irreversible ischemic core,[14–17] which may have implications for treatment selection. However, variations in software, imaging protocols and post-processing techniques may hinder widespread implementation of CT perfusion.[18] Threshold values by which the infarct core is distinguished from the penumbra are based on a limited number studies.[19–21] Moreover, other studies found that these CT perfusion threshold measures cannot substitute for diffusion weighted imaging with MRI in measuring the infarct core.[15,22] Another important issue is the limited brain coverage on many of the CT scanners currently in use. Whereas CT angiography typically covers the aortic arch up to the top of the head, the CT perfusion brain coverage depends on the type of CT and can vary from a few centimeters to full brain coverage in modern scanners. Because of these limitations, at present, perfusion and diffusion weighted imaging on MRI is probably still the best approach to identify infarct core and penumbra.

Despite the ongoing debate about the implementation of CT perfusion in daily practice, my personal view is that CT perfusion in combination with CT angiography has the potential to become the first-choice approach in the diagnostic work-up of patients with acute ischemic stroke. The 24-hour availability of MRI is difficult to reach in most centers.

MRI is also more time-consuming and not as easily combined with CT angiography in the acute setting compared to CT perfusion and is less cost-effective compared to adding CT perfusion to the standard CT stroke protocol. Furthermore, better access to CT scanners with full brain CT perfusion coverage will probably only be a matter of time. In addition, new CT perfusion techniques are being developed that can extract multiphase CT angiography and CT perfusion, and even the non-contrast CT, from a single whole-brain dynamic acquisition during contrast injection.[23]

However, CT perfusion first needs to be validated further, especially for identifying penumbra and infarct core, before it can be implemented in the routine diagnostic work-up of patients with acute ischemic stroke.

## Prediction of outcome with CT angiography and CT perfusion

Accurate prediction of clinical outcome in patients with acute ischemic stroke is essential. When a patient suffers from ischemic stroke, obviously the most frequently asked question is: "how will the patient recover?" When initiating the DUST study, we hypothesized that CT angiography and CT perfusion are of additional prognostic value in prediction of clinical outcome on top of patient characteristics and non-contrast CT (**Chapter 2**). Previous prediction models for clinical outcome after acute ischemic stroke mostly relied on patient characteristics with or without non contrast CT[24–39] or individual parameters of CT angiography and CT perfusion.[40–55] At the time the DUST study was initiated, no information was available about the predictive value of the combination of clinical and different CT-modalities. In the model that we developed with the data of the DUST study we investigated the prognostic value of individual CT angiography and CT perfusion measures on clinical outcome after three months. For CT angiography, the strongest predictors for poor clinical outcome were the presence of a proximal intracranial occlusion and poor leptomeningeal collateral flow. The Alberta Stroke Program Early CT Score on cerebral blood volume maps and mean transit time maps and the size of the infarct core were the strongest CT perfusion predictors for poor clinical outcome. Next, we developed multivariable models for the prediction of clinical outcome. The basic prediction model, based on clinical information, including the National Institutes of Health Stroke Scale (NIHSS), and non-contrast CT, already had a high prognostic performance, similar to the models in previous studies.[24–39] Addition of CT angiography and CT perfusion parameters improved the prognostic performance of the basic model only slightly. Therefore, we had to conclude that CT angiography and CT perfusion have only limited additional prognostic value when added to patient characteristics and non-contrast CT.

Based on these findings, it might be questioned whether CT angiography and CT perfusion should always be performed in patients with suspected acute ischemic stroke. However, CT angiography has clearly shown its value in identifying occlusions in large to medium size vessels and the potential of CT perfusion is promising.[18] As in other studies, we confirmed that NIHSS was a very strong predictor of outcome.[28,32] However, in a time where treatment has to be initiated as quickly as possible, performing an relatively extensive neurological examination in order to obtain a complete NIHSS is rather time consuming whereas CT angiography and CT perfusion parameters provide a rapid and simple visual assessment of the acute pathology and may therefore replace NIHSS for the prediction of outcome. In addition, in selected subgroups of patients, CT angiography and CT perfusion may be useful for the selection of patients that should receive treatment in the acute stage. For example, patients with wake-up strokes or with unknown time of symptom onset can often not be treated with intravenous thrombolysis or endovascular thrombectomy.[56,57] It would be interesting to determine whether CT angiography and CT perfusion measurement can help to identify these subgroups who may benefit from treatment. Moreover, studies using perfusion-weighted imaging to randomize patients with a mismatch profile to endovascular treatment or no treatment in the 6- to 24-hour window are currently underway (ClinicalTrials.gov: identifier NCT02142283 and NCT02586415) These efforts may deliver a window of opportunity for acute treatment in patients who are currently untreated because they have exceeded the current time limits for acute stroke treatment.

## Clinical implementation of CT angiography and CT perfusion

As discussed in the previous sections, implementation of CT angiography and CT perfusion in the emergency setting may have important benefits. Moreover, CT angiography and CT perfusion have shown to be cost-effective in selecting patients for intravenous thrombolysis and endovascular treatment.[58,59] Yet, the benefits must be weighed against the potential harms of the techniques, such as allergic reactions, increased radiation exposure and the administration of contrast material. Allergic reactions are a risk in every contrast enhanced CT examination, but without a positive medical history, this risk is limited.[60] Currently, CT angiography can be derived from CT perfusion data with a technique referred to as "timing-invariant CT angiography".[61] This technique combines the whole 4D-CT angiography dataset derived from CT perfusion source data into one high-quality 3D-CT angiography dataset by displaying maximum contrast enhancement with time. Such an approach allows the improvement of patient safety by reducing the total scanning time, radiation dose, and amount of contrast material needed.[61] Although there is a modest

increase in radiation dose, most clinicians agree that this limited increase in radiation dose is well worth the additional information provided by CT angiography and CT perfusion.

Another potential harm of CT angiography and CT perfusion that needs to be mentioned is the risk of acute nephropathy after contrast administration, also known as contrast-induced nephropathy.[62,63] In the elective setting, this risk is limited as renal function is mostly known before contrast administration, and preventive measures, such as pre-hydration, can be taken. However, when a patient with a suspected ischemic stroke is admitted to the emergency department, renal function is generally unknown before imaging. Waiting for renal function is unacceptable as it may delay treatment. Therefore, in **Chapter 4**, we assessed the occurrence of acute nephropathy after CT angiography and CT perfusion in the DUST cohort. Our study showed a low incidence (3.7%) of acute nephropathy after contrast administration in patients with suspected ischemic stroke, even in patients with renal dysfunction on admission. Only three patients (0.4%) developed persistent renal dysfunction after acute nephropathy for which treatment was required. In one of these three patients, a history of renal disease was missed at admission and renal function did not recover to admission values.

Recently, the causal relation of contrast administration and the development of acute nephropathy has become increasingly controversial.[64–67] Based on the results of our study, I assume that the causal relation is questionable. A meta-analysis showed that controlled contrast medium–induced nephropathy studies demonstrate a similar incidence of acute kidney injury, dialysis, and death between the contrast medium group and the control group.[66] A recent large cohort study even showed that there was no increased risk in patients with impaired renal function.[67] These findings need to be confirmed in prospective case controlled cohort studies in patients with acute ischemic stroke. Until then, I suggest follow-up of renal function after CT angiography and CT perfusion and high vigilance of obtaining a history of renal dysfunction before contrast administration. Currently, there is no reason to wait for renal function before performing CT angiography and CT perfusion in the emergency setting.

## Topics of future research

- To assess the optimal timing of follow-up imaging in patients with an acute symptomatic occlusion of the extracranial carotid artery
- To further improve the CT perfusion technique with regard to brain coverage and ischemia detection thresholds

- To explore the additional value of CT angiography and CT perfusion in the selection of patients who may benefit from acute stroke treatment, in particular intravenous thrombolysis and endovascular treatment
- To confirm that contrast administration is not associated with an increased risk of acute nephropathy in patients with suspected ischemic stroke

## PART II – HYPERGLYCEMIA AND ACUTE ISCHEMIC STROKE

Hyperglycemia is a common finding in acute ischemic stroke. It may reflect a chronic condition like diabetes or a prediabetic stage; an acute condition such as stress hyperglycemia; or a combination of both.[68]

### Chronic hyperglycemia

Chronic hyperglycemia is most commonly found in patients with diabetes. It may also be present in patients not yet diagnosed with diabetes or a prediabetic stage. Measurement of hemoglobin A1c is a common method to establish diabetes or prediabetes. Hemoglobin A1c concentrations of greater than 42 mmol/mol (6%) are associated with a two to three times increased risk of stroke in adults without diabetes.[69] Yet, evidence regarding to the association between chronic hyperglycemia prior to ischemic stroke and poor functional outcome is inconsistent. In **Chapter 6**, we identified severe chronic hyperglycemia, defined by a hemoglobin A1c concentration >42 mmol/mol, as an independent risk factor for poor outcome after ischemic stroke. Patients with chronic hyperglycemia may be predisposed to more severe acute hyperglycemia in case of ischemic stroke, as was also observed in our cohort. Nevertheless, the relation between chronic hyperglycemia and long-term poor outcome cannot solely be attributed to this acute hyperglycemia. Hence, the pathophysiological mechanism still remains unclear.

### Acute hyperglycemia

Acute hyperglycemia on admission is indisputably associated with poor outcome in acute ischemic stroke.[70,71] Poor outcome may even be more pronounced in patients without known diabetes, with persistent hyperglycemia or large cortical infarcts.[70–72] Several mechanisms are proposed by which acute hyperglycemia may lead to adverse outcomes.[73] Hyperglycemia may result in aggravated cerebral damage, and subsequent reduced penumbral salvage due to hyperglycemia is likely to be a key factor in association with poor outcome. Few studies have addressed the association between hyperglycemia and

cerebral perfusion disturbances in the acute stage of ischemic stroke.[74] In our small study performed in 2007–2008 (**Chapter 7**), we found no differences in the initial perfusion deficits between patients with hyperglycemia and those with normoglycemia. In our larger study based on the DUST cohort, we showed that on admission the perfusion deficits and penumbras were larger in patients with hyperglycemia, but not the infarct cores. In concordance with previous research,[70,75,76] we showed in **Chapter 8** that patients with hyperglycemia had larger infarct volumes at follow-up compared to patients with normoglycemia. The difference in findings between our two cohorts is not completely understood. Nonetheless, differences in sample size, patient selection, CT perfusion protocols and the lower proportion of patients with large vessel atherosclerosis in the smaller study may be possible explanations. The findings in our large cohort study support the concept of reduced penumbral salvage due to hyperglycemia in the acute stage of ischemic stroke. A limitation is that CT perfusion used in our study did not have full brain coverage. Therefore, it was not possible to directly compare the perfusion deficits on admission with the infarct volumes on follow-up non-contrast CT. The increasing availability of whole brain coverage CT perfusion will probably overcome this problem in the near future. Despite this limitation, our results suggest that there might be a window of opportunity for glucose-lowering therapy. To date, however, randomized-controlled trials in patients with hyperglycemia and acute ischemic stroke have not provided evidence that glucose-lowering treatment improves clinical outcome.[77,78] One factor in this lack of effect may be that achieving normoglycemia in the early stage of stroke can be difficult, and the possibility of inadvertently causing hypoglycemia remains a concern.[73,79] Moreover, the optimal duration of glucose-lowering treatment has not yet been determined. Hopefully, a large phase III trial of glucose-lowering therapy in acute ischemic stroke that is currently underway will provide more information on this topic.[80]

There are possible alternative explanations why glucose lowering therapy has failed to show a beneficial effect on clinical outcome. One could even question whether hyperglycemia on admission should be considered an etiological factor, or solely represents a risk marker of poor outcome in patients with acute ischemic stroke. In the latter case, no effort should be spent on determining the effect of glucose lowering therapy. On the other hand, previous studies on glucose-lowering therapy also included patients with lacunar strokes. In these patients, hyperglycemia was not linked to worse outcome in observational studies.[72,81] Therefore, glucose-lowering therapy may only be beneficial in patients with non-lacunar infarcts with larger perfusion deficits. Future research is needed to either confirm or reject this hypothesis.

### Hyperglycemia and secondary prevention of stroke

Beyond glucose lowering treatment in patients with acute hyperglycemia on admission, the diagnosis of chronic hyperglycemia in acute ischemic stroke may have implications for secondary prevention. The risk of recurrent stroke and cardiovascular complications in patients with chronic hyperglycemia is significant, even in patients with prediabetic stages.[82–86] If chronic hyperglycemia is detected in patients with acute ischemic stroke, clinicians should be triggered to intensive risk factor management in order to prevent cardiovascular complications of impaired glucose metabolism and recurrent stroke.[87] Furthermore, treatment with pioglitazone is promising in reducing the risk of recurrent stroke in patients with insulin resistance, but its safety needs to be confirmed in future trials.[88] Hemoglobin A1c is not standardly measured in many stroke centers in the Netherlands. Since the risk of recurrent stroke and cardiovascular complications of chronic hyperglycemia is considerable, I recommend measurement of hemoglobin A1c in every patient with acute ischemic stroke. Subsequent treatment should follow if chronic hyperglycemia is diagnosed and follow-up of glucose levels and hemoglobin A1c should establish whether or not chronic hyperglycemia is treated accurately.

### Topics of future research

- To study the concept and mechanisms of reduced penumbral salvage due to hyperglycemia in patients with acute ischemic stroke in more depth
- To investigate whether glucose-lowering therapy is effective in subgroups of patients with acute hyperglycemia on admission
- To explore treatment options in patients with prediabetes to reduce the risk of recurrent stroke

## REFERENCES

1. Feigin VL, Forouzanfar MH, Krishnamurthi R, Mensah GA, Connor M, Bennett DA, et al. Global and regional burden of stroke during 1990-2010: Findings from the Global Burden of Disease Study 2010. Lancet. 2014;383:245–255.
2. Feigin VL, Krishnamurthi R V., Parmar P, Norrving B, Mensah GA, Bennett DA, et al. Update on the Global Burden of Ischemic and Hemorrhagic Stroke in 1990-2013: The GBD 2013 Study. Neuroepidemiology. 2015;45:161–176.
3. Candelise L, Gattinoni M, Bersano A, Micieli G, Sterzi R, Morabito A. Stroke-unit care for acute stroke patients: an observational follow-up study. Lancet. 2007;369:299–305.
4. Hacke W, Kaste M, Bluhmki E, Brozman M, Davalos A, Guidetti D, et al. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. N. Engl. J. Med. 2008;359:1317–1329.

5. Lees KR, Bluhmki E, von Kummer R, Brott TG, Toni D, Grotta JC, et al. Time to treatment with intravenous alteplase and outcome in stroke: an updated pooled analysis of ECASS, ATLANTIS, NINDS, and EPITHET trials. Lancet. 2010;375:1695–1703.
6. Emberson J, Lees KR, Lyden P, Blackwell L, Albers G, Bluhmki E, et al. Effect of treatment delay, age, and stroke severity on the effects of intravenous thrombolysis with alteplase for acute ischaemic stroke: A meta-analysis of individual patient data from randomised trials. Lancet. 2014;384:1929–1935.
7. Goyal M, Menon BK, Van Zwam WH, Dippel DWJ, Mitchell PJ, Demchuk AM, et al. Endovascular thrombectomy after large-vessel ischaemic stroke: A meta-analysis of individual patient data from five randomised trials. Lancet. 2016;387:1723–1731.
8. Damania D, Kung NT-M, Jain M, Jain AR, Liew JA, Mangla R, et al. Factors associated with recurrent stroke and recanalization in patients presenting with isolated symptomatic carotid occlusion. Eur. J. Neurol. 2016;23:127–132.
9. Burke MJ, Vergouwen MDI, Fang J, Swartz RH, Kapral MK, Silver FL, et al. Short-term outcomes after symptomatic internal carotid artery occlusion. Stroke. 2011;42:2419–2424.
10. Morris-Stiff G, Teli M, Khan PY, Ogunbiyi SO, Champ CS, Hibberd R, et al. Internal carotid artery occlusion: its natural history including recanalization and subsequent neurological events. Vasc. Endovascular Surg. 2013;47:603–607.
11. Nguyen-Huynh MN, Lev MH, Rordorf G. Spontaneous recanalization of internal carotid artery occlusion. Stroke. 2003;34:1032–1034.
12. Biesbroek JM, Niesten JM, Dankbaar JW, Biessels GJ, Velthuis BK, Reitsma JB, et al. Diagnostic accuracy of CT perfusion imaging for detecting acute ischemic stroke: A systematic review and meta-analysis. Cerebrovasc. Dis. 2013;35:493–501.
13. van der Hoeven EJRJ, Dankbaar JW, Algra A, Vos JA, Niesten JM, van Seeters T, et al. Additional diagnostic value of computed tomography perfusion for detection of acute ischemic stroke in the posterior circulation. Stroke. 2015;46:1113–1115.
14. Wintermark M, Reichhart M, Cuisenaire O, Maeder P, Thiran JP, Schnyder P, et al. Comparison of admission perfusion computed tomography and qualitative diffusion- and perfusion-weighted magnetic resonance imaging in acute stroke patients. Stroke. 2002;33:2025–2031.
15. Schaefer PW, Souza L, Kamalian S, Hirsch JA, Yoo AJ, Kamalian S, et al. Limited reliability of computed tomographic perfusion acute infarct volume measurements compared with diffusion-weighted imaging in anterior circulation stroke. Stroke. 2015;46:419–424.
16. Schramm P, Schellinger PD, Klotz E, Kallenberg K, Fiebach JB, Kulkens S, et al. Comparison of perfusion computed tomography and computed tomography angiography source images with perfusion-weighted imaging and diffusion-weighted imaging in patients with acute stroke of less than 6 hours' duration. Stroke. 2004;35:1652–1658.
17. Muir KW, Halbert HM, Baird TA, McCormick M, Teasdale E. Visual evaluation of perfusion computed tomography in acute stroke accurately estimates infarct volume and tissue viability. J. Neurol. Neurosurg. Psychiatry. 2006;77:334–339.
18. Heit JJ, Wintermark M. Perfusion Computed Tomography for the Evaluation of Acute Ischemic Stroke: Strengths and Pitfalls. Stroke. 2016;47:1153–1158.
19. Bandera E, Botteri M, Minelli C, Sutton A, Abrams KR, Latronico N. Cerebral blood flow threshold of ischemic penumbra and infarct core in acute ischemic stroke: a systematic review. Stroke. 2006;37:1334–1339.
20. Kudo K, Sasaki M, Yamada K, Momoshima S, Utsunomiya H, Shirato H, et al. Differences in CT perfusion maps generated by different commercial software: quantitative analysis by using identical source data of acute stroke patients. Radiology. 2010;254:200–209.
21. Dani KA, Thomas RGR, Chappell FM, Shuler K, MacLeod MJ, Muir KW, et al. Computed tomography and magnetic resonance perfusion imaging in ischemic stroke: definitions and thresholds. Ann. Neurol. 2011;70:384–401.
22. Copen WA, Morais LT, Wu O, Schwamm LH, Schaefer PW, González RG, et al. In acute stroke, can CT perfusion-derived cerebral blood volume maps substitute for diffusion-weighted imaging in identifying the ischemic core? PLoS One. 2015;10:1–16.

23. Jia B, Scalzo F, Agbayani E, Woolf GW, Liu L, Miao Z, et al. Multimodal CT techniques for cerebrovascular and hemodynamic evaluation of ischemic stroke: occlusion, collaterals, and perfusion. Expert Rev. Neurother. 2016;16:515–525.
24. Reid JM, Gubitz GJ, Dai D, Kydd D, Eskes G, Reidy Y, et al. Predicting functional outcome after stroke by modelling baseline clinical and CT variables. Age Ageing. 2010;39:360–366.
25. Saposnik G, Guzik AK, Reeves M, Ovbiagele B, Johnston SC. Stroke Prognostication using Age and NIH Stroke Scale: SPAN-100. Neurology. 2013;80:21–28.
26. Strbian D, Meretoja A, Ahlhelm FJ, Pitkaniemi J, Lyrer P, Kaste M, et al. Predicting outcome of IV thrombolysis-treated ischemic stroke patients: the DRAGON score. Neurology. 2012;78:427–432.
27. O'Donnell MJ, Fang J, D'Uva C, Saposnik G, Gould L, McGrath E, et al. The PLAN score: a bedside prediction rule for death and severe disability following acute ischemic stroke. Arch. Intern. Med. 2012;172:1548–1556.
28. Weimar C, Konig IR, Kraywinkel K, Ziegler A, Diener HC. Age and National Institutes of Health Stroke Scale Score within 6 hours after onset are accurate predictors of outcome after cerebral ischemia: development and external validation of prognostic models. Stroke. 2004;35:158–162.
29. Counsell C, Dennis M, McDowall M, Warlow C. Predicting outcome after acute and subacute stroke: development and validation of new prognostic models. Stroke. 2002;33:1041–1047.
30. Kent DM, Selker HP, Ruthazer R, Bluhmki E, Hacke W. The stroke-thrombolytic predictive instrument: a predictive instrument for intravenous thrombolysis in acute ischemic stroke. Stroke. 2006;37:2957–2962.
31. Solberg OG, Dahl M, Mowinckel P, Stavem K. Derivation and validation of a simple risk score for predicting 1-year mortality in stroke. J. Neurol. 2007;254:1376–1383.
32. Konig IR, Ziegler A, Bluhmki E, Hacke W, Bath PMW, Sacco RL, et al. Predicting long-term outcome after acute ischemic stroke: a simple index works in patients from controlled clinical trials. Stroke. 2008;39:1821–1826.
33. Smith EE, Shobha N, Dai D, Olson DM, Reeves MJ, Saver JL, et al. Risk score for in-hospital ischemic stroke mortality derived and validated within the Get With the Guidelines-Stroke Program. Circulation. 2010;122:1496–1504.
34. Muscari A, Puddu GM, Santoro N, Zoli M. A simple scoring system for outcome prediction of ischemic stroke. Acta Neurol. Scand. 2011;124:334–342.
35. Ntaios G, Faouzi M, Ferrari J, Lang W, Vemmos K, Michel P. An integer-based score to predict functional outcome in acute ischemic stroke: the ASTRAL score. Neurology. 2012;78:1916–1922.
36. Wang Y, Lim LL, Levi C, Heller RF, Fischer J. A prognostic index for 30-day mortality after stroke. J. Clin. Epidemiol. 2001;54:766–773.
37. Williams GR, Jiang JG. Development of an ischemic stroke survival score. Stroke. 2000;31:2414–2420.
38. Baird AE, Dambrosia J, Janket S, Eichbaum Q, Chaves C, Silver B, et al. A three-item scale for the early prediction of stroke recovery. Lancet (London, England). 2001;357:2095–2099.
39. Johnston KC, Connors AFJ, Wagner DP, Knaus WA, Wang X, Haley ECJ. A predictive risk model for outcomes of ischemic stroke. Stroke. 2000;31:448–455.
40. Coutts SB, Lev MH, Eliasziw M, Roccatagliata L, Hill MD, Schwamm LH, et al. ASPECTS on CTA source images versus unenhanced CT: added value in predicting final infarct extent and clinical outcome. Stroke. 2004;35:2472–2476.
41. Tan JC, Dillon WP, Liu S, Adler F, Smith WS, Wintermark M. Systematic comparison of perfusion-CT and CT-angiography in acute stroke patients. Ann. Neurol. 2007;61:533–543.
42. Puetz V, Dzialowski I, Hill MD, Subramaniam S, Sylaja PN, Krol A, et al. Intracranial thrombus extent predicts clinical outcome, final infarct size and hemorrhagic transformation in ischemic stroke: the clot burden score. Int. J. Stroke. 2008;3:230–236.
43. Puetz V, Sylaja PN, Coutts SB, Hill MD, Dzialowski I, Mueller P, et al. Extent of hypoattenuation on CT angiography source images predicts functional outcome in patients with basilar artery occlusion. Stroke. 2008;39:2485–2490.

44. Bhatia R, Bal SS, Shobha N, Menon BK, Tymchuk S, Puetz V, et al. CT angiographic source images predict outcome and final infarct volume better than noncontrast CT in proximal vascular occlusions. Stroke. 2011;42:1575–1580.
45. Tan IYL, Demchuk AM, Hopyan J, Zhang L, Gladstone D, Wong K, et al. CT angiography clot burden score and collateral score: Correlation with clinical and radiologic outcomes in acute middle cerebral artery infarct. Am. J. Neuroradiol. 2009;30:525–531.
46. Kucinski T, Koch C, Eckert B, Becker V, Kromer H, Heesen C, et al. Collateral circulation is an independent radiological predictor of outcome after thrombolysis in acute ischaemic stroke. Neuroradiology. 2003;45:11–18.
47. Maas MB, Lev MH, Ay H, Singhal AB, Greer DM, Smith WS, et al. Collateral vessels on CT angiography predict outcome in acute ischemic stroke. Stroke. 2009;40:3001–3005.
48. Miteff F, Levi CR, Bateman GA, Spratt N, McElduff P, Parsons MW. The independent predictive utility of computed tomography angiographic collateral status in acute ischaemic stroke. Brain. 2009;132:2231–2238.
49. Lima FO, Furie KL, Silva GS, Lev MH, Camargo ÉCS, Singhal AB, et al. The pattern of leptomeningeal collaterals on ct angiography is a strong predictor of long-term functional outcome in stroke patients with large vessel intracranial occlusion. Stroke. 2010;41:2316–2322.
50. Lum C, Ahmed ME, Patro S, Thornhill R, Hogan M, Iancu D, et al. Computed tomographic angiography and cerebral blood volume can predict final infarct volume and outcome after recanalization. Stroke. 2014;45:2683–2688.
51. Lee J-Y, Kim SH, Lee MS, Park SH, Lee SS. Prediction of clinical outcome with baseline and 24-hour perfusion CT in acute middle cerebral artery territory ischemic stroke treated with intravenous recanalization therapy. Neuroradiology. 2008;50:391–396.
52. Gasparotti R, Grassi M, Mardighian D, Frigerio M, Pavia M, Liserre R, et al. Perfusion CT in patients with acute ischemic stroke treated with intra-arterial thrombolysis: predictive value of infarct core size on clinical outcome. AJNR. Am. J. Neuroradiol. 2009;30:722–727.
53. Parsons MW, Pepper EM, Chan V, Siddique S, Rajaratnam S, Bateman GA, et al. Perfusion computed tomography: prediction of final infarct extent and stroke outcome. Ann. Neurol. 2005;58:672–679.
54. Aviv RI, Mandelcorn J, Chakraborty S, Gladstone D, Malham S, Tomlinson G, et al. Alberta Stroke Program Early CT Scoring of CT perfusion in early stroke visualization and assessment. AJNR. Am. J. Neuroradiol. 2007;28:1975–1980.
55. Kloska SP, Dittrich R, Fischer T, Nabavi DG, Fischbach R, Seidensticker P, et al. Perfusion CT in acute stroke: prediction of vessel recanalization and clinical outcome in intravenous thrombolytic therapy. Eur. Radiol. 2007;17:2491–2498.
56. Dorado L, Ahmed N, Thomalla G, Lozano M, Malojcic B, Wani M, et al. Intravenous Thrombolysis in Unknown-Onset Stroke: Results From the Safe Implementation of Treatment in Stroke-International Stroke Thrombolysis Registry. Stroke. 2017;48:720–725.
57. Wahlgren N, Moreira T, Michel P, Steiner T, Jansen O, Cognard C, et al. Mechanical thrombectomy in acute ischemic stroke: Consensus statement by ESO-Karolinska Stroke Update 2014/2015, supported by ESO, ESMINT, ESNR and EAN. Int. J. Stroke. 2016;11:134–147.
58. Young KC, Benesch CG, Jahromi BS. Cost-effectiveness of multimodal CT for evaluating acute stroke. Neurology. 2010;75:1678–1685.
59. Jackson D, Earnshaw SR, Farkouh R, Schwamm L. Cost-effectiveness of CT perfusion for selecting patients for intravenous thrombolysis: a US hospital perspective. AJNR. Am. J. Neuroradiol. 2010;31:1669–1674.
60. Namasivayam S, Kalra MK, Torres WE, Small WC. Adverse reactions to intravenous iodinated contrast media: A primer for radiologists. Emerg. Radiol. 2006;12:210–215.
61. Smit EJ, Vonken E-J, Meijer FJA, Dankbaar JW, Horsch AD, van Ginneken B, et al. Timing-Invariant CT Angiography Derived from CT Perfusion Imaging in Acute Stroke: A Diagnostic Performance Study. AJNR. Am. J. Neuroradiol. 2015;36:1834–1838.
62. Dittrich R, Akdeniz S, Kloska SP, Fischer T, Ritter MA, Seidensticker P, et al. Low rate of contrast-induced Nephropathy after CT perfusion and CT angiography in acute stroke patients. J. Neurol. 2007;254:1491–1497.

63. Hopyan JJ, Gladstone DJ, Mallia G, Schiff J, Fox AJ, Symons SP, et al. Renal safety of CT angiography and perfusion imaging in the emergency evaluation of acute stroke. AJNR. American J. Neuroradiol. 2008;29:1826–1830.
64. Davenport MS, Cohan RH, Khalatbari S, Ellis JH. The challenges in assessing contrast-induced nephropathy: where are we now? AJR. Am. J. Roentgenol. 2014;202:784–789.
65. Sinert R, Brandler E, Subramanian RA, Miller AC. Does the current definition of contrast-induced acute kidney injury reflect a true clinical entity? Acad. Emerg. Med. 2012;19:1261–1267.
66. McDonald J, McDonald R, Comin J. Frequency of acute kidney injury following intravenous contrast medium administration: a systematic review and meta-analysis. Radiology. 2013;267:119–128.
67. McDonald JS, McDonald RJ, Lieske JC, Carter RE, Katzberg RW, Williamson EE, et al. Risk of Acute Kidney Injury, Dialysis, and Mortality in Patients With Chronic Kidney Disease After Intravenous Contrast Material Exposure. Mayo Clin. Proc. 2015;90:1046–1053.
68. Dungan KM, Braithwaite SS, Preiser JC. Stress hyperglycaemia. Lancet. 2009;373:1798–1807.
69. Selvin E, Steffes MW, Zhu H, Matsushita K, Wagenknecht L, Pankow J, et al. Glycated hemoglobin, diabetes, and cardiovascular risk in nondiabetic adults. N. Engl. J. Med. 2010;362:800–811.
70. Capes SE, Hunt D, Malmberg K, Pathak P, Gerstein HC. Stress hyperglycemia and prognosis of stroke in nondiabetic and diabetic patients: a systematic overview. Stroke. 2001;32:2426–2432.
71. Baird TA, Parsons MW, Phanh T, Butcher KS, Desmond PM, Tress BM, et al. Persistent poststroke hyperglycemia is independently associated with infarct expansion and worse clinical outcome. Stroke. 2003;34:2208–2214.
72. Kruyt ND, Nys GM, van der Worp HB, van Zandvoort MJ, Kappelle LJ, Biessels GJ. Hyperglycemia and cognitive outcome after ischemic stroke. J. Neurol. Sci. 2008;270:141–147.
73. Kruyt ND, Biessels GJ, Devries JH, Roos YB. Hyperglycemia in acute ischemic stroke: pathophysiology and clinical management. Nat.Rev.Neurol. 2010;6:145–155.
74. Parsons MW, Barber PA, Desmond PM, Baird TA, Darby DG, Byrnes G, et al. Acute hyperglycemia adversely affects stroke outcome: a magnetic resonance imaging and spectroscopy study. Ann. Neurol. 2002;52:20–28.
75. Parsons MW, Barber PA, Davis SM. Relationship between severity of MR perfusion deficit and DWI lesion evolution. Neurology. 2002;58:1707; author reply 1707.
76. Els T, Klisch J, Orszagh M, Hetzel A, Schulte-Monting J, Schumacher M, et al. Hyperglycemia in patients with focal cerebral ischemia after intravenous thrombolysis: influence on clinical outcome and infarct size. Cerebrovasc. Dis. 2002;13:89–94.
77. Gray CS, Hildreth AJ, Sandercock PA, O'Connell JE, Johnston DE, Cartlidge NE, et al. Glucose-potassium-insulin infusions in the management of post-stroke hyperglycaemia: the UK Glucose Insulin in Stroke Trial (GIST-UK). Lancet Neurol. 2007;6:397–406.
78. Bellolio MF, Gilmore RM, Stead LG. Insulin for glycaemic control in acute ischaemic stroke. Cochrane Database Syst. Rev. 2011;9:CD005346.
79. Vriesendorp TM, Roos YB, Kruyt ND, Biessels GJ, Kappelle LJ, Vermeulen M, et al. Efficacy and safety of two 5 day insulin dosing regimens to achieve strict glycaemic control in patients with acute ischaemic stroke. J. Neurol. Neurosurg. Psychiatry. 2009;80:1040–1043.
80. Bruno A, Durkalski VL, Hall CE, Juneja R, Barsan WG, Janis S, et al. The Stroke Hyperglycemia Insulin Network Effort (SHINE) trial protocol: A randomized, blinded, efficacy trial of standard vs. intensive hyperglycemia management in acute stroke. Int. J. Stroke. 2014;9:246–251.
81. Miedema I, Luijckx G, Brouns R, De Keyser J, Uyttenboogaart M. Admission hyperglycemia and outcome after intravenous thrombolysis: is there a difference among the stroke-subtypes? BMC Neurol. 2016;16:104.
82. Donnelly R, Emslie-Smith AM, Gardner ID, Morris AD. ABC of arterial and venous disease: vascular complications of diabetes. BMJ. 2000;320:1062–1066.
83. DeFronzo RA, Abdul-Ghani M. Assessment and treatment of cardiovascular risk in prediabetes: impaired glucose tolerance and impaired fasting glucose. Am. J. Cardiol. 2011;108:3B–24B.
84. Putaala J, Liebkind R, Gordin D, Thorn LM, Haapaniemi E, Forsblom C, et al. Diabetes mellitus and ischemic stroke in the young: clinical features and long-term prognosis. Neurology. 2011;76:1831–1837.

85. Hillen T, Coshall C, Tilling K, Rudd AG, McGovern R, Wolfe CD, et al. Cause of stroke recurrence is multifactorial: patterns, risk factors, and outcomes of stroke recurrence in the South London Stroke Register. Stroke. 2003;34:1457–1463.
86. Vermeer SE, Sandee W, Algra A, Koudstaal PJ, Kappelle LJ, Dippel DWJ. Impaired glucose tolerance increases stroke risk in nondiabetic patients with transient ischemic attack or minor ischemic stroke. Stroke. 2006;37:1413–1417.
87. Luitse MJ, Biessels GJ, Rutten GE, Kappelle LJ. Diabetes, hyperglycaemia, and acute ischaemic stroke. Lancet Neurol. 2012;11:261–271.
88. Kernan WN, Viscoli CM, Furie KL, Young LH, Inzucchi SE, Gorman M, et al. Pioglitazone after Ischemic Stroke or Transient Ischemic Attack. N. Engl. J. Med. 2016;374:1321–1331.

# CHAPTER 10

## Summary
## Nederlandse samenvatting

Ischemic stroke is a leading cause of mortality and long-term disability. Although significant advances have been made in the management of acute ischemic stroke, a substantial number of patients still suffers from death and disability on the long-term. To further improve long-term outcome, better understanding of underlying pathophysiology, enhanced diagnostic options and better prediction of prognosis are needed.

This thesis focuses on two aspects of acute ischemic stroke. The first part describes the application of CT imaging in the emergency setting and the prognostic value of CT angiography and CT perfusion in acute ischemic stroke. The second part addresses the importance of hyperglycemia as a vascular risk factor and its relation to poor outcome after ischemic stroke. Furthermore, the second part evaluates the influence of hyperglycemia on cerebral perfusion, building on the CT techniques that were the focus of the first part of this thesis.

## PART I – CT IMAGING IN ACUTE ISCHEMIC STROKE

**Chapter 2** describes the prognostic value of CT angiography and CT perfusion for clinical outcome in addition to patient characteristics and non-contrast CT. Poor leptomeningeal collateral flow and the presence of a proximal intracranial occlusion were the strongest predictors of clinical outcome on CT angiography. The strongest predictors on CT perfusion were the extent of ischemic changes on cerebral blood volume maps and mean transit time maps and the size of the infarct core. The multivariable prediction models that were developed showed that the combination of clinical information and non-contrast CT already had a high prognostic value. When CT angiography and CT perfusion parameters were added to the multivariable prediction models, there was only a small improvement of the prognostic value. Therefore, we concluded that in an unselected stroke population the additional prognostic value of CT angiography and CT perfusion is limited.

An acute occlusion of the extracranial carotid artery is regularly found in patients with acute ischemic stroke with CT angiography performed in the emergency setting. If a high-grade stenosis remains after recanalization, this may have important implications for subsequent treatment, because the recurrence rate of ischemic stroke in patients with high-grade stenosis is significant.

In **Chapter 3**, we evaluate the proportion of residual high-grade stenosis (≥70%) on follow-up imaging patients with an acute symptomatic occlusion of the extracranial carotid artery. An occlusion of the extracranial carotid artery was present in 12% of our study population. We found that a residual high-grade stenosis of the extracranial carotid

artery persists in one of six patients with a symptomatic occlusion in the acute stage of ischemic stroke. As this may have implications for secondary prevention, we recommend follow-up imaging in these patients within a week after the event.

When CT angiography and CT perfusion are used in the emergency setting, without prior knowledge of renal function, the development of acute nephropathy is a possible complication. **Chapter 4** addresses the occurrence of acute nephropathy after CT angiography and CT perfusion in patients with suspected ischemic stroke. We found that acute nephropathy after CT angiography and CT perfusion occurred in 3.7% of the patients. Only three patients (0.4%) developed persistent renal function after acute nephropathy for which treatment was required. Moreover, the occurrence of acute nephropathy was not increased in patients with renal dysfunction on admission. Therefore, we conclude that CT angiography and CT perfusion can be safely performed without prior knowledge of renal function.

### To conclude

- The additional prognostic value of CT angiography and CT perfusion on top of patient characteristics and non-contrast CT is limited in patients with suspected ischemic stroke
- A residual high-grade stenosis of the extracranial carotid artery occurs in one of six patients with a symptomatic occlusion in the acute stage of ischemic stroke
- The occurrence of acute nephropathy after CT angiography and CT perfusion is low in patients with acute ischemic stroke, even if renal dysfunction is present on admission.

## PART II – HYPERGLYCEMIA AND ACUTE ISCHEMIC STROKE

In **Chapter 5**, we provide a general review of the interplay between glucose metabolism and ischemic stroke. We address the epidemiology of the association between diabetes and stroke, highlighting potentially modifiable risk factors and long-term outcome. Diabetes is associated with a doubling of the risk of stroke and with poor long-term outcome after ischemic stroke and rigorous assessment and treatment of associated risk factors may substantially reduce the risk of stroke in patients with diabetes. Furthermore, we describe the cause, outcome, and management of hyperglycemia at the time of acute ischemic stroke. Admission hyperglycemia is a common risk factor for poor outcome after ischemic stroke. Therefore, glucose metabolism should be monitored in all patients with ischemic stroke. All individuals should be classified as either normoglycemic or with stress hyperglycemia, and with either newly diagnosed type 2 diabetes or known diabetes.

Although the effectiveness of glucose-lowering treatment on clinical outcome has yet to be established, protocols are becoming available for patients with ischemic stroke. The possibility of hypoglycemia remains a concern. Neurologists and primary-care doctors should collaborate with respect to treatment of vascular risk factors for stroke prevention.

Acute hyperglycemia is associated with poor functional outcome after ischemic stroke, but the association between chronic hyperglycemia prior to stroke and outcome is unclear. In **Chapter 6**, we assess the association between chronic hyperglycemia, measured by hemoglobin A1c and functional outcome in patients with acute ischemic stroke. We found that moderate chronic hyperglycemia (hemoglobin A1c 39–42 mmol/mol) was not associated with poor outcome (risk ratio 1.12; 95% confidence interval 0.87–1.44). However, severe chronic hyperglycemia was associated with poor functional outcome in patients with acute ischemic stroke (risk ratio 1.35; 95% confidence interval 1.04–1.76). This association is independent of acute hyperglycemia on admission and of an unfavourable vascular risk factor profile.

**Chapter 7** and **Chapter 8** focus on acute hyperglycemia on admission and its influence on cerebral perfusion in the acute stage of ischemic stroke. In **Chapter 7**, we found that patients with hyperglycemia on admission did not have larger perfusion deficits and infarct cores in the acute stage of ischemic stroke compared to patients with normoglycemia. However, in **Chapter 8** we showed that hyperglycemia on admission was indeed associated with larger perfusion deficits and penumbras, but not with larger infarct cores. Infarct volumes at follow-up were larger in patients with hyperglycemia. These findings suggest that penumbral salvage is worse in patients with hyperglycemia on admission and that glucose lowering therapy deserves reappraisal at least in a subgroup of patients.

## To conclude

- Chronic hyperglycemia prior to ischemic stroke is associated with worse functional outcome
- Acute hyperglycemia on admission is associated with larger final infarcts and worse functional outcome
- Acute hyperglycemia on admission negatively influences recovery of the penumbra

# NEDERLANDSE SAMENVATTING

## Achtergrond

Een herseninfarct is een van de belangrijkste oorzaken van overlijden en langdurige invaliditeit. Bij een acuut herseninfarct sluit een bloedstolsel een bloedvat af waardoor een deel van de hersenen onvoldoende zuurstof krijgt. Hierdoor wordt de functie van dit gedeelte van de hersenen belemmerd en kunnen er neurologische uitvalverschijnselen ontstaan, zoals verlamming, taal- of spraakstoornissen, gevoelsstoornissen en/of gezichtsvelduitval. Wanneer de afsluiting van het bloedvat te lang duurt, raakt het hersenweefsel onherstelbaar beschadigd. Risicofactoren voor het krijgen van een herseninfarct zijn roken, overgewicht, hoge bloeddruk, een verhoogd cholesterol en hyperglycemie (verhoogde bloedsuiker). Indien het vermoeden bestaat op een herseninfarct, zal er op de spoedeisende hulp direct een CT- of MRI-scan van de hersenen worden gemaakt. De behandeling van het herseninfarct richt zich op het verwijderen van het bloedstolsel. Dit is mogelijk door middel van intraveneuze trombolyse, waarbij medicatie die stolsels oplost per infuus wordt toegediend. Een nieuwe behandelingsmogelijkheid is de endovasculaire behandeling, waarbij het stolsel kan worden verwijderd met een katheter die via een bloedvat in de lies wordt opgevoerd naar de hersenen.

Ondanks de recente vooruitgang wat betreft de behandelingsmogelijkheden van het herseninfarct, houdt een aanzienlijk deel van de patiënten blijvende restverschijnselen. Om de uitkomst na een herseninfarct te verbeteren is snelle diagnostiek en behandeling cruciaal, maar ook kennis van de onderliggende mechanismen en de prognose.

## Dit proefschrift

In dit proefschrift worden twee aspecten van het acute herseninfarct belicht. In het eerste deel onderzoeken we de toepasbaarheid en de toegevoegde waarde van aanvullende beeldvorming in de acute situatie van het herseninfarct. Het tweede deel van dit proefschrift richt zich op de risicofactor hyperglycemie voor een herseninfarct en op de invloed van hyperglycemie op de doorbloeding van de hersenen en het functioneel herstel na een herseninfarct.

# DEEL I – BEELDVORMING MET CT BIJ EEN ACUUT HERSENINFARCT

Bij patiënten met de verdenking op een acuut herseninfarct speelt beeldvorming van de hersenen door middel van CT-scan een belangrijke rol. Met een CT-scan van de hersenen zonder contrast (blanco CT) is het mogelijk om andere oorzaken van acute neurologische uitvalsverschijnselen uit te sluiten. Naast een blanco CT worden tegenwoordig in veel ziekenhuizen in Nederland aanvullende CT-scans gemaakt, zoals CT-angiografie en CT-perfusie. Met CT-angiografie worden de bloedvaten in de hersenen en de hals in beeld gebracht. Hierdoor kan de locatie van de afsluiting in het bloedvat bepaald worden en kunnen de alternatieve routes voor bloed naar het aangedane hersenweefsel (collateralen) in kaart worden gebracht. CT-perfusie wordt gebruikt om de doorbloeding van het hersenweefsel, de cerebrale perfusie, zichtbaar te maken. Daarmee is het mogelijk een uitspraak te doen over het hersenweefsel dat al onherstelbaar beschadigd is (infarctkern) en het omringende hersenweefsel dat nog te redden is wanneer de afsluiting van het bloedvat op tijd wordt opgeheven (penumbra).

CT-angiografie en CT-perfusie maken het dus mogelijk de diagnose en uitgebreidheid van het herseninfarct te ondersteunen en dragen bij aan het verwerpen van een alternatieve diagnose (zoals een tumor of epileptische aanval). Daarnaast zijn deze technieken mogelijk ook van toegevoegde waarde in het voorspellen van de uitkomst na een herseninfarct. Om dit te onderzoeken is in 2009 de 'Dutch Acute Stroke Study (DUST)' opgezet. De DUST is een grootschalig onderzoek in 14 ziekenhuizen in Nederland waaraan bijna 1500 patiënten met de verdenking op een herseninfarct hebben deelgenomen.

In **hoofdstuk 2** wordt de toegevoegde waarde van CT-angiografie en CT-perfusie bovenop de blanco CT en klinische gegevens zoals leeftijd, risicofactoren, mate van uitval en glucose onderzocht om de klinische uitkomst te voorspellen. De klinische uitkomst is drie maanden na het ontstaan van het herseninfarct vastgesteld. Patiënten met een slechte klinische uitkomst hadden na drie maanden hulp van anderen nodig bij het uitvoeren van alledaagse handelingen zoals eten, drinken, opstaan, aankleden en wassen. Wanneer patiënten deze handelingen zelfstandig konden uitvoeren, werd dit als een goede klinische uitkomst beschouwd.

Een belangrijke voorspeller voor een slechte uitkomst in beeld gebracht met CT-angiografie blijkt het ontbreken van collateralen. Daarnaast blijkt de kans op een slechte klinische uitkomst ook groter wanneer de afsluiting van het bloedvat zich meer proximaal bevindt, oftewel in het voorste gedeelte van de aftakkingen van de bloedvaten in de hersenen. Hierdoor is de doorbloeding in een groot gebied van de hersenen verminderd.

Wat betreft de CT-perfusie, zijn een grote infarctkern en een grote penumbra voorspellers voor een slechte klinische uitkomst.

In multivariate modellen die ontwikkeld zijn om de uitkomst te voorspellen, bleek dat de klinische gegevens van een patiënt en de blanco CT al een hoge voorspellende waarde hebben. Wanneer de parameters van CT-angiografie en CT-perfusie aan deze modellen worden toegevoegd, blijkt dat de voorspellende waarde slechts in beperkte mate wordt verbeterd. Hoewel de voorspellende waarde van CT-angiografie en CT-perfusie groot is wanneer hun parameters afzonderlijk worden onderzocht, is de toegevoegde waarde van CT-angiografie en CT-perfusie voor het voorspellen van de klinische uitkomst op basis van ons onderzoek beperkt.

Bij patiënten met een acuut herseninfarct die een CT-angiografie ondergaan, wordt regelmatig een afsluiting (occlusie) van een halsslagader (arterie carotis interna) gevonden. Het komt voor dat een occlusie in een later stadium weer open gaat (recanalisatie). Wanneer er na recanalisatie een ernstige vernauwing (hooggradige stenose) van de a. carotis interna overblijft kan een aanvullende behandeling nodig zijn (o.a. carotis-endarteriectomie). Patiënten met een hooggradige stenose van de a. carotis interna hebben namelijk een hoog risico op een recidief herseninfarct.

In **hoofdstuk 3** hebben we onderzocht in hoeveel patiënten met een occlusie van de a. carotis interna in het acute stadium een hooggradige stenose overbleef na herhaalde beeldvorming. In 12% van de patiënten in onze studiepopulatie was er sprake van een occlusie van de a. carotis interna. Bij één op de zes van deze patiënten bleef er een hooggradige stenose over bij de herhaalde beeldvorming. Deze bevinding kan consequenties hebben voor het beleid aangezien deze patiënten mogelijk in aanmerking komen voor een carotis-endarteriectomie. Daarom adviseren wij bij deze patiënten herhaalde beeldvorming binnen één week na het herseninfarct.

Naast de voordelen van CT-angiografie en CT-perfusie, zijn er ook potentiële risico's, zoals de schadelijke effecten van blootstelling aan röntgenstraling en het optreden van een allergische reactie na toediening van contrastmiddel. Daarnaast is er een risico op het ontwikkelen van nierschade (acute nefropathie) na contrasttoediening. Bij patiënten met de verdenking op een herseninfarct is er meestal geen tijd om te wachten met de CT-angiografie en CT-perfusie totdat de nierfunctie bekend is. In **hoofdstuk 4** wordt het vòòrkomen van acute nefropathie na CT-angiografie en CT-perfusie onderzocht bij patiënten met de verdenking op een herseninfarct. Een acute nefropathie na CT-angiografie en CT-perfusie trad op bij 3,7% van de patiënten. Daarnaast was het aantal gevallen van acute nefropathie niet verhoogd bij patiënten met een verminderde

nierfunctie voor opname in het ziekenhuis. Slechts drie patiënten (0,4%) hadden een blijvend verminderde nierfunctie waarvoor een aanvullende behandeling noodzakelijk was. Op basis van dit onderzoek concluderen we daarom dat CT-angiografie en CT-perfusie veilig kan worden verricht voordat de nierfunctie bekend is.

### Conclusies

- De toegevoegde waarde van CT-angiografie en CT-perfusie bovenop klinische patiëntgegevens en de blanco CT is beperkt bij patiënten met een acuut herseninfarct.
- Bij 1 op de 6 patiënten met een acuut herseninfarct en een occlusie van de a. carotis interna blijft er een hooggradige stenose over. Deze patiënten komen mogelijk in aanmerking voor een aanvullende behandeling.
- De incidentie van acute nefropathie na CT-angiografie en CT-perfusie is laag in patiënten met de verdenking op een herseninfarct, zelfs wanneer de nierfunctie al verminderd is voor opname.

## DEEL II – HYPERGLYCEMIE BIJ EEN ACUUT HERSEN-INFARCT

Ontregeling van het glucosemetabolisme komt regelmatig voor bij mensen met een acuut herseninfarct. Er wordt onderscheid gemaakt in chronische hyperglycemie en acute hyperglycemie. Chronische hyperglycemie is een situatie waarbij het glucosegehalte in het bloed al langere tijd verhoogd is, zoals bij diabetes mellitus of een voorloperstadium van diabetes, zogenaamde pre-diabetes. Chronische hyperglycemie is een risicofactor voor het ontwikkelen van een herseninfarct en heeft mogelijk ook invloed op de uitkomst na een herseninfarct.

Een herseninfarct zelf kan ook verstoring van het glucosemetabolisme veroorzaken. Acute hyperglycemie komt voor bij 30 tot 40% van de patiënten met een herseninfarct. Het merendeel van deze patiënten is niet bekend met diabetes. Acute hyperglycemie is geassocieerd met een slechte uitkomst en een hoger sterftecijfer na een herseninfarct. Patiënten met acute hyperglycemie lijken ook grotere herseninfarcten te hebben dan patiënten met normale glucosewaarden. Hoewel dit mechanisme nog niet opgehelderd is, speelt een verminderd behoud van de penumbra een mogelijke rol in dit proces.

In **hoofdstuk 5** geven we een overzicht van de interactie tussen het glucosemetabolisme en een herseninfarct. We bespreken de epidemiologie van de associatie tussen diabetes

en het herseninfarct, met nadruk op behandelbare risicofactoren en de uitkomst op de lange termijn.

Diabetes is geassocieerd met een tweemaal verhoogd risico op een herseninfarct en met slechtere uitkomst op de lange termijn. Agressieve behandeling van risicofactoren draagt bij aan het reduceren van het risico op een herseninfarct bij patiënten met diabetes.

Daarnaast beschrijven we de oorzaak, uitkomst en behandeling van hyperglycemie in het acute stadium van een herseninfarct. Aangezien acute hyperglycemie bij opname een bekende risicofactor is voor een slechte uitkomst na een herseninfarct, is het monitoren van glucosewaarden noodzakelijk in alle patiënten met een herseninfarct. Hoewel het effect van glucoseverlagende therapie op de klinische uitkomst nog moet worden vastgesteld, zijn er protocollen beschikbaar voor patiënten met een acuut herseninfarct. Het optreden van hypoglycemie (verlaagde bloedsuiker) is tijdens deze behandeling een risico waarvoor speciale aandacht nodig is. Tenslotte is samenwerking tussen neurologen en huisartsen van belang voor wat betreft preventie van herseninfarcten.

Hoewel de associatie tussen acute hyperglycemie en een slechtere uitkomst duidelijk is vastgesteld, is dit voor chronische hyperglycemie en een slechte uitkomst nog onduidelijk. In **hoofdstuk 6** hebben we de associatie tussen chronische hyperglycemie en een slechte uitkomst na een herseninfarct onderzocht. Om de mate van chronische hyperglycemie vast te stellen, hebben we gebruik gemaakt van hemoglobine A1c. Dit is een bepaling in het bloed die de gemiddelde waarde van de bloedsuikerspiegel van de afgelopen drie maanden weergeeft. We stelden vast dat matige chronische hyperglycemie (hemoglobine A1c-waarde tussen 39 en 42 mmol/mol) niet geassocieerd was met een slechte uitkomst (relatief risico 1,12; 95% betrouwbaarheidsinterval 0,87–1,44). Ernstige chronische hyperglycemie was echter wel geassocieerd met een slechte uitkomst (relatief risico 1,35; 95% betrouwbaardheidsinterval 1,04–1,76). Deze associatie was onafhankelijk van acute hyperglycemie bij opname en een ongunstig vasculair risicofactorprofiel.

**Hoofdstuk 7** en **hoofdstuk 8** zijn gericht op acute hyperglycemie bij opname en de invloed hiervan op de cerebrale perfusie in het acute stadium van een herseninfarct. In **hoofdstuk 7** hebben we gevonden dat patiënten met acute hyperglycemie geen grotere perfusiedefecten en infarctkernen hadden bij opname ten opzichte van patiënten met normale glucosewaarden. Echter, uit de grotere studie in **hoofdstuk 8** blijkt dat acute hyperglycemie wel was geassocieerd met grotere perfusiedefecten en penumbra's bij opname, maar niet met grotere infarctkernen. Het verschil in resultaten in **hoofdstuk 7** en **hoofdstuk 8** kan niet volledig worden verklaard, maar waarschijnlijk speelt het verschil in populatiegrootte een belangrijke rol. In **hoofdstuk 8** was het uiteindelijke infarct ook groter

bij patiënten met acute hyperglycemie. Deze bevindingen suggereren dat het herstel van de penumbra verminderd is bij patiënten met acute hyperglycemie bij opname. Dit geeft wellicht in de toekomst nieuwe mogelijkheden voor glucoseverlagende therapie.

## Conclusies

- Chronische hyperglycemie voorafgaand aan een herseninfarct is geassocieerd met een slechtere uitkomst.
- Acute hyperglycemie bij opname is geassocieerd met grotere uiteindelijke herseninfarcten en een slechte uitkomst na een herseninfarct.
- Acute hyperglycemie leidt tot een verminderd herstel van de penumbra.

# CHAPTER 11

Acknowledgements
Dankwoord
Curriculum vitae
List of publications

# ACKNOWLEDGEMENTS


## Chapter 2

We gratefully acknowledge the contribution of the DUST investigators.

The DUST investigators are: Academic Medical Center, Amsterdam, The Netherlands (C.B. Majoie, Y.B. Roos); Catharina Hospital, Eindhoven, The Netherlands (L.E. Duijm, K. Keizer); Erasmus University Medical Center, Rotterdam, The Netherlands (A. van der Lugt, D.W. Dippel); Gelre Hospitals, Apeldoorn, The Netherlands (K.E. Droogh-de Greve, H.P. Bienfait); Leiden University Medical Center, Leiden, The Netherlands (M.A. van Walderveen, M.J. Wermer); Medical Center Haaglanden, The Hague, The Netherlands (G.J. Lycklama à Nijeholt, J. Boiten); Onze Lieve Vrouwe Gasthuis, Amsterdam, The Netherlands (D.A. Duyn- dam, V.I. Kwa); Radboud University Medical Center, Nijmegen, The Netherlands (F.J. Meijer, E.J. van Dijk); Rijnstate Hospital, Arnhem, The Netherlands (F.O. Kesselring, J. Hofmeijer); St. Antonius Hospital, Nieuwegein, The Netherlands (J.A. Vos, W.J. Schonewille); St. Elisabeth Hospital, Tilburg, The Netherlands (W.J. van Rooij, P.L. de Kort); St. Franciscus Hospital, Rotterdam, The Netherlands (C.C. Pleiter, S.L. Bakker); VU University Medical Center, Amsterdam, The Netherlands (J.C. Bot, M.C. Visser); University Medical Center Utrecht, Utrecht, The Netherlands (B.K. Velthuis, I.C. van der Schaaf, J.W. Dankbaar, W.P. Mali, T. van Seeters, A.D. Horsch, J.M. Niesten, G.J. Biessels, L.J. Kappelle, M.J. Luitse, Y. van der Graaf).

This study was supported by the Dutch Heart Foundation (2008T034) and the NutsOhra Foundation (0903-012). J.W. Dankbaar is supported by the Dutch Heart Foundation (2012T061). A. van der Lugt is supported by grants and personal fees from GE Healthcare.

## Chapter 3

We gratefully acknowledge the contribution of the DUST investigators. The DUST study was supported by the Dutch Heart Foundation (2008T034) and the NutsOhra Foundation (0903-012).

## Chapter 4

We gratefully acknowledge the contribution of the DUST investigators. The DUST study was supported by the Dutch Heart Foundation (2008T034) and the NutsOhra Foundation (0903-012).

## Chapter 5

We thank M.D.I. Vergouwen for valuable comments on an earlier version of this Review. M.J.A. Luitse and G.J. Biessels are supported by a high potential grant from Utrecht University to G.J. Biessels. G.J. Biessels is also supported by grant 2010T073 from the Netherlands Heart Foundation.

## Chapter 6

We gratefully acknowledge the contribution of the DUST investigators. The DUST study was supported by the Dutch Heart Foundation (2008T034) and the NutsOhra Foundation (0903-012).

## Chapter 8

We gratefully acknowledge the contribution of the DUST investigators. The DUST study was supported by the Dutch Heart Foundation (2008T034) and the NutsOhra Foundation (0903-012).

# DANKWOORD

Hoewel ik weleens heb getwijfeld of het zou lukken, is het toch echt gebeurd: mijn boekje is af! Dit proefschrift had niet tot stand kunnen komen zonder de hulp en steun van velen. Daarom wil ik een aantal van hen persoonlijk bedanken.

Allereerst wil ik alle patiënten en hun naasten bedanken voor deelname aan de DUST. Ondanks dat zij zich in een moeilijke situatie bevonden, vlak na een herseninfarct, hebben zij deelgenomen aan het onderzoek. Dat zij de moeite hebben genomen om zich in te zetten voor wetenschappelijk onderzoek waardeer ik zeer.

Prof. dr. L.J. Kappelle, beste Jaap, jij weet als geen ander het overzicht te houden en de grote lijnen van het onderzoek te blijven zien. De kritische en inhoudelijke discussies waren erg leerzaam. Dank voor je begeleiding, persoonlijke interesse en dat je me soms wist af te remmen waar nodig.

Prof. dr. G.J. Biessels, beste Geert Jan, jouw wetenschappelijke inzicht en doelgerichtheid zijn bewonderenswaardig . Hoewel ik in het begin soms moest wennen aan je directheid, heb ik veel van je geleerd. Jouw vermogen om iets ingewikkelds terug te brengen tot een eenvoudig stroomschema heeft me enorm geholpen. Dank voor je begeleiding in de afgelopen jaren.

Prof. dr. B.K. Velthuis, beste Birgitta, drijvende kracht achter de DUST, jouw toewijding aan het onderzoek is een voorbeeld voor velen. Dank voor je betrokkenheid, jouw oog voor detail hebben mijn stukken alleen maar beter gemaakt.

Leden van de beoordelingscommissie, geachte prof. dr. E.W.M. ter Braak, prof. dr. A. van der Lugt, prof. dr. G.E.H.M. Rutten, prof. dr. Y.T. van der Schouw en prof. dr. J.H. Veldink. Hartelijk dank voor de bereidheid tot het beoordelen van mijn proefschrift.

Mijn opleiders, prof. dr. J.H.J. Wokke, prof. dr. L.J. Kappelle en dr. T Seute, wil ik bedanken voor de mogelijkheid om mijn opleiding tot neuroloog in het UMC Utrecht te volgen. Dank voor de persoonlijke betrokkenheid, zeker in de periode waarin ik dit extra nodig had.

Mijn dank gaat uit naar alle neurologen, radiologen, arts-assistenten, onderzoeks-verpleegkundigen en laboranten van de aan DUST deelnemende ziekenhuizen. Uw inspanningen om zoveel mogelijk patiënten te includeren en data te verzamelen waardeer ik zeer. Zonder u was het niet mogelijk geweest om de DUST tot een goed einde te brengen.

De overige leden van de DUST-groep in het UMC Utrecht, prof. dr. W.P.Th.M. Mali en prof. dr. Y. van der Graaf, dank voor uw inspanningen om de DUST tot een succes te

maken. Prof. dr. Y. van der Graaf, beste Yolanda, bedankt voor je bijdrage aan twee hoofdstukken van mijn proefschrift.

Mede DUST-onderzoekers in het UMC Utrecht, Jan Willem Dankbaar, Irene van der Schaaf, Alexander Horsch, Joris Niesten en Tom van Seeters, ik wil jullie bedanken voor jullie hulp bij het includeren van patiënten, het verzamelen van alle gegevens voor de database en de bijdrage aan mijn manuscripten.

Meenaskhi Dauwan, hartelijk dank voor je bijdrage als student-onderzoeker aan de DUST en twee manuscripten in dit proefschrift.

Ans de Ridder, Daniëlle Derks, Berber Zweedijk, Marrit van Buuren, Paut Greebe en Dorien Slabbers van het trialbureau neurologie, hartelijk dank voor het bijhouden van de DUST-database en de vele telefoontjes voor de follow-up van de patiënten.

Trialbureau radiologie, Saskia van Amelsvoort, Anneke Hamersma en Cees Haring, hartelijk dank voor jullie inspanningen om de radiologische database zo compleet mogelijk te maken.

Angela van Rossum en Cora Dircks van het stafsecretariaat neurologie, dank voor jullie inspanningen om in de overvolle agenda's van mijn promotoren toch altijd een plekje te vinden voor een overleg.

Collega-assistenten en -onderzoekers van de neurologie, het is een voorrecht om tot deze assistentengroep te behoren. Bedankt voor de gezelligheid en collegialiteit. De Babinski's (vooral die met Oh Oh Tirol), congressen, de weekenden, maar ook de Basketborrels waren een feest.

Kamertje 1, Willem, Manon, Rachel, Eduard, Janneke, Yael en Sophie, de koffiemomenten, ontbijtjes, het eitjes koken en vooral de foute hitjes op de vrijdagmiddag maakten ook de minder productieve onderzoeksdagen draaglijker. Dank voor de gezelligheid.

Year of 2011, lieve Celine, Femke, Marjolein en Oliver, wat heb ik het getroffen met jullie als jaargenootjes. Ik weet niet of er andere jaren zijn die weekenden weg en hele diners organiseren zoals wij. Laten we volgend jaar met z'n allen naar New York gaan!

Damesch' 2002, na al die jaren nog steeds een ploeg!

Marjolein, lieve Ek, co-schapmatties van het eerste uur en een onvergetelijke tijd in Suriname. Er is veel koffie nodig geweest om al onze onderzoeksperikelen te bespreken. Succes met jouw laatste loodjes, als ik het kan, kan jij het ook!

Lieve jaarclub, het begon op 14-10… Ik kijk terug op een mooie studententijd met jullie. Ik hoop dat we ondanks onze drukke levens toch de tijd blijven vinden voor een goede borrel op zijn tijd.
Lieve Anne en Rian, dank voor jullie interesse in mijn promotie-onderzoek, maar nog meer voor de gezellige avondjes en vakanties, Kirchberg blijft memorabel.
Lieve Noor, vanaf het begin van de jaarclub delen we lief en leed. Onze reis naar Australië en Azië was fantastisch. Ik hoop dat we samen nog veel mooie momenten gaan beleven.

Lieve Marjolein, wat begonnen is als buddy's op het werk, is in korte tijd uitgegroeid tot een hechte vriendschap. Geen onderwerp blijft onbesproken en er is altijd ruimte voor een kop koffie, een wijntje of een avondje eten met of zonder de mannen. Je betrokkenheid en oprechtheid zijn erg waardevol.

Lieve Geneco's, wat is het bijzonder om zo'n hechte groep vriendinnetjes te hebben. Of we nu met veel of weinig zijn, elkaar vaak of minder zien, het is altijd een feest. Ik waardeer onze goede gesprekken over werk en leven, humor en interesse in elkaar. Ik kijk altijd uit naar de etentjes, weekendjes weg en borrels met jullie. Ik hoop dat er nog veel mooie momenten mogen volgen!

Mijn paranimfen, Kim Boshuisen en Virginie Verhoeven. Ik ben heel blij dat jullie naast me willen staan op 26 september. Je zou zeggen dat het met twee keer een doctor naast me toch wel goed zou moeten komen…
Lieve Kim, jij schreef het al eerder: wij doen wel heel veel hetzelfde. Hoewel we nu toch echt allebei een andere kant op gaan, hoop ik dat we niet ophouden met koffie drinken, mooie momenten en frustraties delen en feestjes vieren. Onze vriendschap is erg waardevol.
Lieve Vir, werkgroepgenootjes in het eerste jaar; huisgenootjes (meerdere malen); op vakantie naar Australië en rally's in de gele banaan. Wat hebben we veel samen meegemaakt! Bij jou kan ik altijd aankloppen voor een spontane date of een goede woordgrap.

Lieve Stan en Hanneke, het is fijn om zulke lieve en zorgzame schoonouders te hebben. Dank voor jullie interesse en betrokkenheid.

Lieve Oma, wat is het bijzonder dat je op je 93e nog getuige kunt zijn van mijn promotie. Je hebt al veel mijlpalen in mijn leven meegemaakt en hopelijk komt hier nog een aantal bij.

Lieve Daan, grote kleine broer, het is verhelderend dat er binnen ons gezin iemand is die niets opheeft met het doktersvak. Ik bewonder je eigenheid en wat je allemaal weet te bereiken. Dank voor je steun, je bent er altijd als dat nodig is.
Lieve Roos, dank voor alle gezelligheid en interesse. We moeten snel weer een keer gaan varen.

Lieve pap en mam, dat ik hier nu sta, is dankzij jullie. Dank jullie wel voor alle mogelijkheden die jullie me hebben gegeven en voor jullie onvoorwaardelijke steun, vertrouwen en liefde. Mam, ik weet niet wat ik zonder jou had gemoeten. Je bent er altijd voor me en springt in waar nodig. Ik vind het fantastisch om te zien hoeveel jullie van Phileine genieten. Pap, dat perfectionisme ook soms een valkuil kan zijn, weten wij maar al te goed. Je goede adviezen en betrokkenheid bij mijn opleiding en onderzoek zijn ontzettend waardevol. Ik hoop dat ik net zo goed in mijn vak zal worden als jij bent.

Lieve Menno, wat ben ik blij met jou. Jij hebt de gave om rust en stabiliteit te creëren in chaotische tijden. Met jou is geen berg te hoog en geen dal te diep, samen lukt het ons wel. Ik ben trots op je, je bent een superpapa voor Phileine. Ik heb heel veel zin in onze toekomst samen.

Lieve Phileine, lief klein meisje. Ik smelt elke dag opnieuw bij het zien van je vrolijke, ondeugende koppie!

# CURRICULUM VITAE

Merel Luitse was born on the 11th of September 1982 in Naarden, the Netherlands. In 2001 she finished secondary school (Gymnasium) at de Bataafse Kamp in Hengelo (OV) and started at University College in Utrecht. In 2002 she started her medical training at the Utrecht University. She travelled to Paramaribo, Surinam, in 2006 for her gynaecology internship. In 2007 she worked on a research project on subarachnoid hemorrhages (prof. dr. G.J.E. Rinkel). She performed her 6th year scientific internship on intracerebral hemorrhages under supervision of dr. C.J.M. Klijn and prof. dr. G.J.E. Rinkel. After obtaining her medical degree in 2009 she worked on the Pearl String Initiative focused on Cerebrovascular diseases. Simultaneously, she started working on the research projects described in this thesis under supervision of prof. dr. G.J. Biessels, prof. dr. B.K. Velthuis and prof. dr. L.J. Kappelle. In 2011, she started her training in Neurology at the University Medical Center under supervision of prof. dr. J.H.J. Wokke and dr. T Seute. Merel is married to Menno and they live in Utrecht with their daughter Phileine who was born in July 2016.

# LIST OF PUBLICATIONS

## This thesis

**Luitse MJ**, Velthuis BK, Kappelle LJ, van der Graaf Y, Biessels GJ; DUST Study Group. Chronic hyperglycemia is related to poor functional outcome after acute ischemic stroke. Int J Stroke. 2017;12:180–186.

**Luitse MJ**, Dauwan M, van Seeters T, Horsch AD, Niesten JM, Kappelle LJ, Biessels GJ, Velthuis BK; Dutch acute Stroke Study (DUST). Acute nephropathy after contrast agent administration for computed tomography perfusion and computed tomography angiography in patients with acute ischemic stroke. Int J Stroke. 2015;10:E35–6.

van Seeters T, Biessels GJ, Kappelle LJ, van der Schaaf IC, Dankbaar JW, Horsch AD, Niesten JM, **Luitse MJ**, Majoie CB, Vos JA, Schonewille WJ, van Walderveen MA, Wermer MJ, Duijm LE, Keizer K, Bot JC, Visser MC, van der Lugt A, Dippel DW, Kesselring FO, Hofmeijer J, Lycklama À Nijeholt GJ, Boiten J, van Rooij WJ, de Kort PL, Roos YB, van Dijk EJ, Pleiter CC, Mali WP, van der Graaf Y, Velthuis BK; Dutch acute stroke study (DUST) investigators. The Prognostic Value of CT Angiography and CT Perfusion in Acute Ischemic Stroke. Cerebrovasc Dis. 2015;40:258–269.

**Luitse MJ**, Velthuis BK, Dauwan M, Dankbaar JW, Biessels GJ, Kappelle LJ; Dutch Acute Stroke Study Group. Residual high-grade stenosis after recanalization of extracranial carotid occlusion in acute ischemic stroke. Stroke. 2015;46:12–15.

**Luitse MJ**, van Seeters T, Horsch AD, Kool HA, Velthuis BK, Kappelle LJ, Biessels GJ. Admission hyperglycaemia and cerebral perfusion deficits in acute ischaemic stroke. Cerebrovasc Dis. 2013;35:163–167.

**Luitse MJ**, Biessels GJ, Rutten GE, Kappelle LJ. Diabetes, hyperglycaemia, and acute ischaemic stroke. Lancet Neurol. 2012;11:261–271.

## Other publications

Horsch AD, Dankbaar JW, van Seeters T, Niesten JM, **Luitse MJ**, Vos PC, van der Schaaf IC, Biessels GJ, van der Graaf Y, Kappelle LJ, Mali WP, Velthuis BK. Relation between stroke severity, patient characteristics and CT-perfusion derived blood-brain barrier permeability measurements in acute ischemic stroke. Clin Neuroradiol. 2016;26:415–421.

van Seeters T, Biessels GJ, Kappelle LJ, van der Schaaf IC, Dankbaar JW, Horsch AD, Niesten JM, **Luitse MJ**, Majoie CB, Vos JA, Schonewille WJ, van Walderveen MA, Wermer MJ, Duijm LE, Keizer K, Bot JC, Visser MC, van der Lugt A, Dippel DW, Kesselring FO, Hofmeijer J, Lycklama À Nijeholt GJ, Boiten J, van Rooij WJ, de Kort PL, Roos YB, Meijer FJ, Pleiter CC, Mali WP, van der Graaf Y, Velthuis BK; Dutch acute stroke study (DUST) investigators. CT angiography and CT perfusion improve prediction of infarct volume in patients with anterior circulation stroke. Neuroradiology. 2016;58:327–337.

de Bresser J, Schaafsma JD, **Luitse MJ**, Viergever MA, Rinkel GJ, Biessels GJ. Quantification of structural cerebral abnormalities on MRI 18 months after aneurysmal subarachnoid hemorrhage in patients who received endovascular treatment. Neuroradiology. 2015;57:269–274.

van Seeters T, Biessels GJ, van der Schaaf IC, Dankbaar JW, Horsch AD, **Luitse MJ**, Niesten JM, Mali WP, Kappelle LJ, van der Graaf Y, Velthuis BK; DUST investigators. Prediction of outcome in patients with suspected acute ischaemic stroke with CT perfusion and CT angiography: the Dutch acute stroke trial (DUST) study protocol. BMC Neurol. 2014;14:37.

Niesten JM, van der Schaaf IC, van der Graaf Y, Kappelle LJ, Biessels GJ, Horsch AD, Dankbaar JW, **Luitse MJ**, van Seeters T, Smit EJ, Mali WP, Velthuis BK. Predictive value of thrombus attenuation on thin-slice non-contrast CT for persistent occlusion after intravenous thrombolysis. Cerebrovasc Dis. 2014;37:116–122.

Niesten JM, van der Schaaf IC, Biessels GJ, van Otterloo AE, van Seeters T, Horsch AD, **Luitse MJ**, van der Graaf Y, Kappelle LJ, Mali WP, Velthuis BK; DUtch acute Stroke Trial (DUST). Relationship between thrombus attenuation and different stroke subtypes. Neuroradiology. 2013;55:1071–1079.

**Luitse MJ**, van Asch CJ, Klijn CJ. Deep coma and diffuse white matter abnormalities caused by sepsis-associated encephalopathy. Lancet. 2013;381:2222.

Persoon S, **Luitse MJ**, de Borst GJ, van der Zwan A, Algra A, Kappelle LJ, Klijn CJ. Symptomatic internal carotid artery occlusion: a long-term follow-up study. J Neurol Neurosurg Psychiatry. 2011;82:521–526.

Kruyt ND, Biessels GJ, DeVries JH, **Luitse MJ**, Vermeulen M, Rinkel GJ, Vandertop WP, Roos YB. Hyperglycemia in aneurysmal subarachnoid hemorrhage: a potentially modifiable risk factor for poor outcome. J Cereb Blood Flow Metab. 2010;30:1577–1587.

van Asch CJ, **Luitse MJ**, Rinkel GJ, van der Tweel I, Algra A, Klijn CJ. Incidence, case fatality, and functional outcome of intracerebral haemorrhage over time, according to age, sex, and ethnic origin: a systematic review and meta-analysis. Lancet Neurol. 2010;9:167–176.

Dorhout Mees SM, **Luitse MJ**, van den Bergh WM, Rinkel GJ. Fever after aneurysmal subarachnoid hemorrhage: relation with extent of hydrocephalus and amount of extravasated blood. Stroke. 2008;39:2141–2143.