Imaging of non-traumatic intracerebral and intraventricular haemorrhage

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Imaging of non-traumatic intracerebral and intraventricular haemorrhage

Beeldvormend onderzoek van niet-traumatische intracerebrale
en intraventriculaire bloedingen
(met een samenvatting in het Nederlands)

Proefschrift

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door

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"Rabbit's clever," said Pooh thoughtfully.
"Yes," said Piglet, "Rabbit's clever."
"And he has Brain."
"Yes," said Piglet, "Rabbit has Brain."
There was a long silence.
"I suppose," said Pooh, "that that's why he never understands anything."

A.A. Milne, The House at Pooh Corner

CONTENTS

LIST OF ABBREVIATIONS

AVM	arteriovenous malformation
CT	computed tomography
DAVF	dural arteriovenous fistula
DSA	digital subtraction angiography
DVA	developmental venous anomaly
ICH	intracerebral haemorrhage
IVH	intraventricular haemorrhage
MRA	magnetic resonance angiography
MRI	magnetic resonance imaging
mRS	modified Rankin Scale
NCCT	non-contrast computed tomography
SAH	subarachnoid haemorrhage
QALY	quality-adjusted life year

CHAPTER 1

General introduction

Epidemiology of intracerebral haemorrhage

In the Netherlands, intracerebral haemorrhage (ICH) accounts for 16% of all first strokes.[1] ICH is a devastating condition with a high case fatality rate and poor functional outcome.[2,3] Age-adjusted overall stroke incidence in high-income countries has decreased by 42% in the past four decades, which has been largely attributed to a decline in the incidence of ischemic stroke.[4] Whether the incidence of ICH had also changed is less clear; in some regions a decline has been reported[5,6] while in others the incidence of ICH has been stable.[7,8] Overall stroke case fatality appeared more or less stable during these four decades,[4] although case fatality of subarachnoid haemorrhage had decreased by 17% since 1972.[9]

Underlying causes of intracerebral and intraventricular haemorrhage

Non-traumatic ICH is often the result of rupture of small blood vessels, so-called spontaneous ICH, also referred to as primary ICH.[10] Small vessel disease is a condition in which small perforating blood vessels are damaged in the presence of arterial hypertension and other vascular risk factors such as smoking, excessive alcohol intake and increasing age.[11] This typically causes ICH in the deep grey matter or posterior fossa. In patients with cerebral amyloid angiopathy (CAA), a protein called β-amyloid is deposited in the wall of small cortical and leptomeningeal arteries. β-amyloid deposition can severely disrupt the structure of these vessel walls, which may lead to (recurrent) lobar ICH, microbleeds and superficial siderosis.[12,13]

Apart from damage of small vessels, the possibility of an underlying intracranial macrovascular cause should also be considered. An arteriovenous malformation (AVM), aneurysm, dural arteriovenous fistula (DAVF), cavernoma, or cerebral venous sinus thrombosis (CVST) is detected in 13-34% of patients with ICH.[14–16] Identification of these lesions has important therapeutic and prognostic consequences, since adequate treatment of the underlying macrovascular cause may prevent recurrent haemorrhage(s).[17,18] Among rare underlying causes of ICH are hypertensive encephalopathy, Moya Moya disease, vasculitis,[10] and capillary teleangiectasia.[19]

Isolated intraventricular haemorrhage (IVH) is a rare stroke subtype: it accounts for 3% of all intracranial haemorrhages.[20] Little is known about underlying aetiology. Causes of isolated IVH include hypertensive vasculopathy, and rupture of an AVM or aneurysm.[20–23]

Imaging in intracerebral haemorrhage

Non-contrast CT

Non-contrast computed tomography (NCCT) is widely available in developed countries for assessment of patients who present with focal deficits, sudden headache or a decreased consciousness. It has long been known that NCCT can reveal important clues on the presence of an underlying macrovascular cause of ICH.[24,25] More recently, the Secondary ICH (SICH) score was developed in the United States to estimate the probability of an underlying macrovascular cause in individual patients, based on patient characteristics and NCCT features (haematoma location, enlarged vessels or calcifications along haematoma margins, and venous hyperattenuation).[26] An external validation in another US hospital reported good performance of the SICH score,[27] but validation outside the US, e.g. in a European setting, has not yet been performed.

NCCT is also used to identify the cause of clinical deterioration in patients with ICH, such as hydrocephalus, rebleeding or an increase of mass effect by expansion of haematoma volume or surrounding oedema. Haematoma growth is associated with poor outcome in patients with ICH.[28] Since prevention of haematoma expansion is a potential treatment target, its prediction and treatment are currently major topics in research in patients with spontaneous ICH. The prevalence of haematoma growth in patients with a macrovascular cause, such as aneurysmal rupture, has not been investigated.

The role of angiographic modalities in ICH

For many decades, digital subtraction angiography (DSA) has been the modality of choice to detect or exclude the presence of an aneurysm, AVM, or DAVF in patients with ICH. Development of CT angiography (CTA) and of MR angiography (MRA) have facilitated non-invasive assessment of macrovascular aetiology of ICH in the past decades.

CTA and CT venography (CTV) have become increasingly available for rapid assessment of underlying macrovascular causes in patients with ICH.[29,30] With the introduction of MR imaging (MRI) in the eighties, cavernomas came to attention as a cause of ICH in patients with negative DSA.[31] Developmental venous anomalies (DVAs) are often incidental findings on MRI. In patients with ICH, a DVA can be seen adjacent to a cavernoma, which has bled. DVAs are very rarely the cause of ICH in isolation.[32] In patients in whom CVST is suspected as the cause of ICH, MR and CT venography have replaced DSA as less-invasive modalities.[33]

Data on comparison of the diagnostic value of CTA, MRI/MRA, and DSA are scarce,[34] and therefore it is unclear which of these investigations should be done, in which order, and in which patients. In clinical practice, diagnostic strategies in patients with ICH are highly variable, probably as a result of the aforementioned lack of data.[34]

The role of angiographic modalities in isolated IVH

Several observational studies have described the diagnostic value of DSA in the assessment of an underlying cause of isolated IVH, with a reported yield between 29 and 83%.[20,23,35–37] This wide range probably reflects differences in study design. Because isolated IVH is a rare condition, it is likely that differences in patient characteristics such as age and hypertension influence the reported yield. Data on the diagnostic value of less invasive modalities as CTA and MRI/MRA are lacking.

Cost-effectiveness

It is likely that differences in yield and accuracy of diagnostic strategies in patients with ICH will result in differences in total costs and effects of these strategies. For instance, CTA is cheaper than DSA but diagnostic accuracy of CTA is probably lower. Therefore, assessment with CTA may result in a higher proportion of initially missed macrovascular causes than assessment with DSA. The question then is whether morbidity and case fatality as a result of recurrent ICH in these patients outweighs morbidity and case fatality from diagnostic and therapeutic procedures in patients assessed with DSA.

Outline of this thesis

In **part I**, we assess the epidemiology of intracerebral haemorrhage.

Chapter 2 provides a systematic review and meta-analysis of population-based studies on ICH epidemiology. We analyse incidence, case fatality and functional outcome, with a focus on time trends, age, sex and ethnic origin.

In part II, we describe the role of imaging in patients with non-traumatic ICH and IVH.

In Chapter 3 we report on haematoma growth on sequential NCCT in aneurysmal ICH.

In Chapter 4 an external validation of the SICH score is performed.

Chapter 5 describes the diagnostic yield and accuracy of CTA, and of additional MRI/MRA and DSA, for the detection of an underlying (macrovascular) cause. We identify clinical and radiological predictors of an underlying macrovascular cause and construct a prediction rule.

Chapter 6 provides the results of a cost-effectiveness analysis in which a decision-analytic Markov model is used to estimate the consequences of finding or missing a potentially treatable macrovascular cause with CTA as a single modality, versus the combination of CTA and MRI/MRA , versus the combination of CTA, MRI/MRA, and DSA.

In Chapter 7 we study on the yield of angiographic modalities in isolated intraventricular haemorrhage. We report on the yield of CTA, MRI/MRA and DSA in a case-series of patients with isolated IVH, and perform a systematic review of the literature.

In Chapter 8 we discuss the research presented in this thesis and its implications for clinical practice and future research.

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PART I

Epidemiology of intracerebral haemorrhage

CHAPTER 2

Incidence, case fatality, and functional outcome of intracerebral haemorrhage over time, according to age, sex, and ethnic origin: a systematic review and meta-analysis

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ABSTRACT

Background and purpose: Since the early 1980s, imaging techniques have enabled population-based studies of intracerebral haemorrhage. We aimed to assess the incidence, case fatality, and functional outcome of intracerebral haemorrhage in relation to age, sex, ethnic origin, and time period in studies published since 1980.

Methods: From PubMed and Embase searches with predefined inclusion criteria, we identified population-based studies published between January, 1980, and November, 2008. We calculated incidence and case fatality. Incidences for multiple studies were pooled in a random-effects binomial meta-analysis. Time trends of case fatality were assessed with weighted linear-regression analysis.

Results: 36 eligible studies described 44 time periods (mid-year range 1983-2006). These studies included 8145 patients with intracerebral haemorrhage. Incidence did not decrease between 1980 and 2008. Overall incidence was 24.6 per 100 000 person-years (95% CI 19.7-30.7). Incidence was not significantly lower in women than in men (overall incidence ratio 0.85, 95% CI 0.61-1.18). Using the age group 45-54 years as reference, incidence ratios increased from 0.10 (95% CI 0.06-0.14) for people aged less than 45 years to 9.6 (6.6-13.9) for people older than 85 years. Median case fatality at 1 month was 40.4% (range 13.1-61.0) and did not decrease over time, and was lower in Japan (16.7%, 95% CI 15.0-18.5) than elsewhere (42.3%, 40.9-43.6). Six studies reported functional outcome, with independency rates of between 12% and 39%. Incidence of intracerebral haemorrhage per 100 000 person-years was 24.2 (95% CI 20·9-28·0) in white people, 22.9 (14.8-35.6) in black people, 19.6 (15.7-24.5) in Hispanic people, and 51.8 (38.8-69.3) in Asian people.

Conclusion: Incidence of intracerebral haemorrhage increases with age and has not decreased between 1980 and 2006. Case fatality is lower in Japan than elsewhere, increases with age, and has not decreased over time. More data on functional outcome are needed.

INTRODUCTION

Intracerebral haemorrhage is the second most common cause of stroke, and has a high case fatality.[1] Since 1980,[2] knowledge of the epidemiology of stroke has increased with the increasing availability of brain-imaging techniques.

Age-adjusted stroke incidence in high-income countries has decreased by 42% in the past four decades,[1] mostly owing to a reduction in incidence of ischaemic stroke. Whether incidence of intracerebral haemorrhage has also fallen is unclear. In Perth, Australia, the incidence of intracerebral haemorrhage decreased between 1989 and 2001.[3] Between 1981 and 2006, in Oxfordshire, UK, there was a decrease in incidence of intracerebral haemorrhage associated with premorbid hypertension in patients less than 75 years of age, whereas the incidence associated with antithrombotic medication and the incidence of non-hypertensive lobar bleed in patients over 75 years of age increased.[4] By contrast, incidence rates were stable between 1985 and 2004 in Dijon, France, and from 1983 to 1997 in Finland.[5,6]

Overall, stroke case fatality has not decreased substantially over the past four decades,[1] but crude case fatality of subarachnoid haemorrhage decreased by 17% between 1972 and 2002.[7] Whether the case fatality rate of intracerebral haemorrhage has changed has not been studied in detail. Although numerous population-based studies have reported intracerebral haemorrhage epidemiology,[1] few data are available from developing countries. Data on intracerebral haemorrhage incidence, case fatality, and functional outcome in age and sex subgroups are also scarce.

Although worldwide stroke epidemiology has been reviewed previously,[1] a more detailed analysis of intracerebral haemorrhage epidemiology is important for future research and management. We therefore did a meta-analysis on the incidence, case fatality, and functional outcome of intracerebral haemorrhage in relation to age, sex, ethnic origin, and time trends.

METHODS

Search strategy and selection criteria

We searched PubMed and Embase for population-based studies of intracerebral haemorrhage epidemiology from January, 1980, to November, 2008, with different combinations of the following key words: "h(a)emorrhagic stroke" or "intracranial" or "cerebral" or "intracerebral" or "intraparenchymal" and "h(a)emorrhage" or "h(a)ematoma" and "population (based)" or "region(al)" or "community (based)" or "stroke register/registry" and "incidence" or "fatality" or "mortality" or "trend" (see webappendix for syntaxes). Further studies were identified from the reference lists, related articles, and citation lists of each of the papers identified in the initial searches. This was repeated until no further studies were found.

We included population-based and prospective studies with designs that allowed calculation of crude incidence, case fatality, or functional outcome for first intracerebral haemorrhage. If the data provided in a study were not restricted to first ever occurrences of intracerebral haemorrhage or if data on first ever occurrences could not be extracted and analysed separately, the study was excluded.

Because clinical scoring systems do not reliably differentiate haemorrhagic stroke from ischaemic stroke (sensitivity for intracerebral haemorrhage <0.5)[8,9] we included only studies in which less than 20% of intracerebral haemorrhage cases were not confirmed with imaging or autopsy (so-called undefined strokes). We excluded studies that were hospital based, studies based only on international classification of diseases (ICD) codes, and retrospective studies because they are inadequate indicators of stroke incidence in a population.[2,10] If other types of intracranial haemorrhage (eg, subarachnoid haemorrhage or subdural haematoma) could have been included in the intracerebral haemorrhage group and could not be identified, these studies were excluded. Papers published in English, French, German, and Spanish were included in the meta-analysis.

Data extraction

Two authors (CJJvA and MJAL) did the data search and quality assessment independently and completed a data extraction form. Any disagreements in the data were resolved by a third reviewer (CJMK).

We aimed to study only data on non-traumatic intracerebral haemorrhage. Thus, for each study we assessed whether stroke was defi ned according to WHO criteria. WHO criteria for stroke exclude intracerebral haemorrhage from malignancy, trauma, and extracerebral

intracranial haemorrhage. Also, other criteria to exclude non-spontaneous and extracerebral haemorrhages were assessed. If data on the criteria used were not included in the publication we contacted the original investigators. If possible we recalculated incidence without other types of intracranial haemorrhage (eg, subarachnoid haemorrhage or subdural haematoma).

For each study included we analysed case-finding methods, proportion of ICH confirmed with imaging or autopsy, time from symptom onset to imaging, con firmation of diagnosis by study investigator, proportion of patients with undefined stroke, age limits, and demographic data of the study population and patients with intracerebral haemorrhage. Case-finding methods were categorised as excellent if all patients' data were obtained from regional hospitals, family doctors, or review of death certificates. For each time period we assessed the mid-calendar year, number of new cases of intracerebral haemorrhage, number of person-years, number of people with incident intracerebral haemorrhage who died within 1 month of diagnosis (and within 1 year if applicable), and outcome with either the modified Rankin scale (mRS) or Glasgow outcome scale (GOS), which are both validated disability scales.[11] Numbers of patients with intracerebral haemorrhage and person-years were also assessed in relation to age, sex, and ethnic subgroups. Populations were judged to be from Asia if they were from east or southeast Asia.

Statistical analysis

For each study we computed crude incidence per 100 000 person-years. Incidences for multiple studies were pooled by use of a random-effects binomial meta-analysis, with the number of intracerebral haemorrhages and the number of person-years for each study as variables (PROC NLMIXED, SAS Inc, Cary, NC, USA).[12] Random-effects models were used because of heterogeneity in incidence between studies. Incidence was calculated for age range, sex, and ethnic groups for studies that provided this information. To study sources of heterogeneity of incidence we did subgroup analyses and binomial meta-regression. We calculated the percentage of variance in incidence caused by age, sex, and ethnic origin by comparison of models with and without these characteristics.

Data on patients younger than 45 years of age were pooled. Because intracerebral haemorrhage is a rare condition before age 45 years,[13] we calculated age incidence ratios with the 45-54-year-old age group as the reference. For sex incidence ratios we used men as the reference, and for ethnic group incidence ratios we used the ethnic group with the largest number of events as the reference group.

Time trend was analysed at the mid-year of each study period and was expressed as the percentage change of the crude incidence rate per calendar year increase. We adjusted the relation between time period and intracerebral haemorrhage incidence for age, sex, and Asian versus non-Asian ethnic origin. The relation between intracerebral haemorrhage incidence and time period could not be adjusted for the demographics of the patients with intracerebral haemorrhage because these data were available for only three studies;[14-16] therefore, we used demographic data of the population in the region. The relations of age and sex with intracerebral haemorrhage incidence were analysed for studies that provided demographic data of all people at risk of intracerebral haemorrhage in the studied region, the proportion of people older than 65 years, and the proportion of women in the study population.

Case fatality was calculated as percentage of patients with intracerebral haemorrhage who died within a 1 month or 1 year time period. For 1 month case fatality, we pooled case fatality data assessed at 28 days or 1 calendar month after intracerebral haemorrhage. The case fatality for the various time periods was expressed as the median with range. Case fatality by sex, age range, and ethnic group was calculated with data from those studies that provided this information.

We used weighted linear regression to assess the relation between the case fatality rate and the mid-year of the study. The inverse of the standard error of the case fatality for each study was used as weight. We reported the percentage change of case fatality per calendar year increase.

Data regarding functional outcome was measured with the mRS or the GOS. Patients who survived to the end of study follow-up were grouped into dependent (mRS score 3-5 or GOS score 2-4) or independent (mRS 0-2 or GOS 5) from others for daily activities. We used SPSS 15.0 software (SPSS Inc, Chicago, IL, USA) for all statistical analyses, except for the random effects binomial regression, for which we used SAS 9.1 (SAS Institute Inc, Cary, NC, USA).

Role of the funding source

The sponsor had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all data in the study and had final responsibility for the decision to submit for publication.

RESULTS

47 articles reported 36 studies[3,6,13-57] (figure 1). A total of 9 151 929 people from 21 countries were studied. 8145 of the 9 151 929 people had had an intracerebral haemorrhage and were observed for a total of 28 034 233 person-years. All 36 studies reported incidence, 26 case fatality, and six functional outcome. Two studies were cohort studies;[17,18] the other were stroke registers, of which seven studies reported intracerebral haemorrhage incidence in two[13,19-28] or three[3] non-overlapping time periods. Case-finding methods were excellent in 28 of 36 studies reporting incidence,[3,13,16,19-51] 22 of 26 reporting case fatality,[3,13,16,19-23,25-30,32,33,37-45,47-50,52,53] and four of six reporting functional outcome.[13,19,41,54]

Nine studies provided data on the time interval from symptom onset to imaging (range of median 0-7 days). Review of death certificates was not mentioned as a case-finding method in three studies.[38,44,55] 30 studies used the WHO definition of stroke; additional criteria for the definition of (primary) intracerebral haemorrhage were numerous (webappendix). The 36 studies described 44 time periods (table 1).[3,6,13-52,55,56] Overall, intracerebral haemorrhage incidence was 24.6 per 100 000 person-years (95% CI 19.7-30.7). However, the incidence of intracerebral haemorrhage varied from 1.8 to 129.6 person-years between studies.(figure 2).

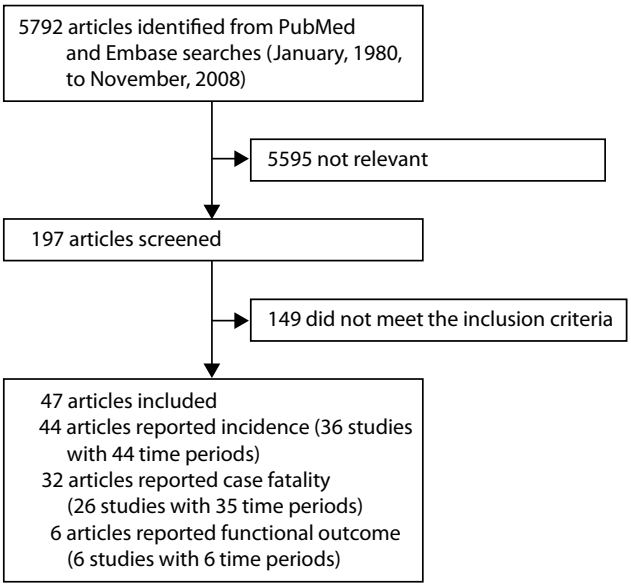

Figure 1 Literature search

Table 1 Characteristics of 36 studies reporting on intracerebral haemorrhage

	Mid-year	ICH n=	Person-years	Age limit	% imaging	%undefined	Case-finding methods	Review study investigator	Incidence ratio women vs. men (95% CI)
Oxford, UK[19]	1983	66	345948	no	80.0	4.6	ABCEFGHJKMN‡	yes	1.31 (0.80-2.12)
Florence, Italy[56]	1984	10	531597	15-44	91.4	4.3	ACKMN	yes	-
Oyabe, Japan[24]	1984	120	164295	>25	> 80	10.7	ABJLN‡	yes	0.64 (0.44-0.92)
Dijon, France[23]	1987	87	678560	no	88.0	11.0	ABDEHKN‡	yes	0.89 (0.58-1.36)
Jyvaskyla, Finland[14]	1987	158	502810	no	90.0	7.5	AHKN	yes	0.96 (0.70-1.31)
Frederiksberg, Denmark[37]	1989	17	85611	no	74.0	15.0	ABDHN‡	-	-
Okinawa, Japan[55]	1989	1412	3667194	no	98.4	0.6	ABDN	yes	-
Oyabe, Japan[24]	1989	115	164295	>25	>80	2.3	ABJLN‡	yes	0.62 (0.43-0.89)
Perth, Australia[3]	1989	32	131392	no	74.9	14.3	ABCDFHJMN‡	yes	-
Valle d'Aosta, Italy[21]	1989	33	114325	no	81.0	17.7	ABDEN‡	-	1.72 (0.85-3.49)
Belluno, Italy[40]	1992	93	211389	no	89.5	10.5	ABFJN‡	yes	1.20 (0.80-1.82)
Turku/Kuopio, Finland[6]	1993	506	1933660	25-74	86	2.7	AEHKN	yes	0.86 (0.73-1.03)
Hisayama, Japan[18]	1994	41	31644	>40	>80	0	BELM	yes	0.54 (0.29-0.99)
Arcadia, Greece[48]	1994	77	161548	>18	81.8	18.2	ABHJN‡	yes	0.58 (0.37-0.93)
l'Aquila, Italy[20]	1994	114*	297838	>18	89.0	2.0	ABCDFHN‡	yes	-
Erlangen, Germany[39]	1995	48	202900	no	95.5	4.5	ABCDJKN‡	yes	1.58 (0.88-2.84)
Innherred, Norway[33]	1995	45	138590	>15	87.5	12.0	ABDEHKN‡	yes	-
Izumo city, Japan[15]	1995	350	678832	no	100	0	AIN	-	0.75 (0.61-0.93)
Manhattan, USA[16,44]	1995	155	548000	>20	99.0	-	BDEFGJKLN‡	yes	0.75 (0.55-1.03)
Perth, Australia[3]	1995	22	136095	no	78.4	9.4	ABCDFHJMN‡	yes	-
Malmö, Sweden[38]	1995	699	2674144	no	>80	16.0	ABIN‡	yes	0.87 (0.75-1.01)
Dijon, France[28]	1996	37	429264	no	96.0	4.0	ABDEHKN‡	yes	-
l'Aquila, Italy[13]	1996	16*	874375	0-44	100.0	0.0	ABCDFHN‡	yes	-
Melbourne, Australia[27]	1996	40	133816	no	>80	8.7	ABDFGKN‡	yes	0.77 (0.41-1.43)

Vibo Valentina, Italy[32]	1996	62	179186	no	95.9	4.1	ABDEJKN‡	yes	0.92 (0.56-1.51)
Valle d'Aosta, Italy[22]	1997	36	118723	no	97.4	2.6	ABDEN‡	-	0.70 (0.36-1.36)
Jichi Medical School, Japan[17]	1998	102	131718	yes†	>80	0.2	AEFHLM	yes	0.63 (0.43-0.93)
China[50]	1998	2275	5657595	>25	92.0	8.3	ABHN‡	yes	-
Martinique[45]	1998	83	360000	no	92.8	2.4	ABEJKN‡	yes	-
Melbourne, Australia[27]	1998	151	613262	no	88.7	10.8	ABDFGKN‡	yes	1.01 (0.73-1.39)
North Portugal[31]	1999	108	243116	no	96.9	4.4	ABDFHIJKMN‡	yes	-
Örebro, Sweden[29]	1999	44	123503	no	84.0	15.2	ABDFHJKMN‡	yes	-
Scotland, UK[47]	1999	50	212704	no	91.9	8.1	ABEFKLN‡	yes	-
Perth, Australia[3]	2000	19	143417	no	89.1	7.7	ABCDFHJM‡N	yes	-
South London, UK[36,46]	2000	395	2701909	no	89.8	7.5	ABEFJKN‡	yes	0.87 (0.72-1.06)
Lund, Sweden[35]	2001	46	235505	>15	>80	6.0	ABDEJKMN‡	yes	-
Iquique, Chili[41]	2001	69	396712	no	91.0	7.9	ABDFHJKN‡	yes	0.62 (0.38-1.01)
Auckland, New Zealand[34]	2002	177	897882	>15	91.0	8.9	ABDE‡	yes	1.10 (0.82-1.48)
Barbados[30]	2002	42	239068	no	96.0	4.3	ABCFHJMN‡	yes	-
Puglia, Italy[42]	2002	24	77474	no	93.7	6.3	ABDIJKN‡	-	-
Tartu, Estonia[49]	2002	57	202244	no	90.0	10.0	ABJMN‡	yes	-
Oxford, UK[25,51]	2003	34	273318	no	96.0	4.0	ABCEFGHIJKMN‡	yes	0.95 (0.48-1.86)
Matão, Brazil[43]	2004	11	75053	no	100.0	0.0	ABFJN‡	yes	0.57 (0.17-1.95)
Mumbai, India[52]	2006	67	313722	>25	89.2	1.6	BDFHLN	yes	-

A death certificates. B family doctors. C rehabilitation. D nursing homes. E regular search. F review of radiology requests or reports. G media attention (campaign or newspaper). H outpatient clinics,health centres. I sudden deaths, very early death. J emergency, ambulance, on call medical services. K international classifi cation of diseases codes. L door-to-door, home visit, social services, phone calls. M autopsy reports. N all hospitals in the region. *Calculation of crude incidence of intracerebral haemorrhage after exclusion of cases with subdural haematoma. †Consisted of 12 communities, of which eight included only patients aged 40–69 years. ‡Case-finding methods categorised as excellent. ICH intracerebral haemorrhage, 95% CI 95% confidence interval.

[17,23] Two studies described only patients younger than 45 years,[13,56] and 11 studies reporting on 13 time periods also had age limitations.[6,16-19,20,24,33-35,44,48,50,52] The incidence of intracerebral haemorrhage in 29 time periods in studies without age limits[3,14,15,19,21-23,25-32,36-43,45-47,49,55] was 23.5 per 100 000 person-years (20.1-27.6).

Incidence could be calculated for men and women separately in 24 time periods (table 1).[3,6,14-19,21-25,27,32,34,36, 38-41,43,44,46,48] The incidence of intracerebral haemorrhage was not significantly lower in women than in men (overall incidence ratio 0.85, 95% CI 0.61-1.18), with sex explaining 2.1% of the variance in intracerebral haemorrhage incidence. The difference between the sexes was greatest in the five Japanese studies, with an incidence ratio of 0.65 (0.50-0.86) compared with 0.92 (0.72-1.19) in the other regions (p=0.14).

18 studies provided data on incidence of intracerebral haemorrhage in one or more mid-decade age bands (table 2).[13,19,20,23,26,27,29,30,32-34,38-41,43,46-48,52,56] 12 studies showed a continuous increase of intracerebral haemorrhage incidence with age,[20,26,27,29,30,32,38,40,43,46-48,52] whereas in six studies there was a stabilisation or a decrease of incidence for people older than 85 years of age.[19,23,33,34,39,41] 94% of the variance in intracerebral haemorrhage incidence between age and study strata was explained by age.

After exclusion of the two studies that included only patients with intracerebral haemorrhage who were up to 45 years old,[13,56] we noted an annual decrease in crude incidence of intracerebral haemorrhage of 2.9% (95% CI 0.1-5.6).[3,6,14-50,51,52,55] Year of study explained 9.2% of the variance in intracerebral haemorrhage incidence. These results were similar after adjustment for sex[3,6,14,16-19,21,23,24,26-30,32,34,35,37-44,48,51] or age.[14,16,19-23,27,29,30,32,33,37,39,40,42-45,47-49,51,55]

We assessed the influence of studies with a limited age range on the observed time trend by doing a sensitivity analysis with the 29 time periods used in studies that had no age limit. This analysis did not show an annual decrease in intracerebral haemorrhage incidence (1.2%, 95% CI -1.7 to 4.0).[3,14,15,19,21–23,25–32,36–43,45–47,49,55] When we restricted the analysis to the 26 time periods of studies that had excellent case-finding methods and no age limit, we also found no substantial decrease of intracerebral haemorrhage incidence over time (0.3%, –2·7 to 3·3).[3,19,21–23,25–32,36–43,45–47,49]

Incidence was comparable for white people (24.2, 95% CI 20.9–28.0, reference gro up),[3,6,13,14,16,19–22,25–29,31–40,42–44,46–49,56] black people (22.9, 14.8–35.6; incidence ratio 1.0, 95% CI 0.6–1.4),[16,30,44–46] Hispanic people (19.6, 15.7–24.5; incidence ratio 0.8, 0.5–1.3),[16,41,43,44] Indian people (21.4, 16.6–27.1; incidence ratio 1.1, 0.4–1.9),[52] and Maoris (22.2, 15.8–30.3; incidence ratio 0.9, 0.4–2.0),[34] but two times higher for east and southeast Asian people (51.8, 38.8–

69.3; incidence ratio 2.1, 1.6–2·[9,15,17,18,24,34,50,55] figure 3). Ethnic origin explained 42% of the variance in incidence of intracerebral haemorrhage between studies.

Incidence of intracerebral haemorrhage for black people was higher in northern Manhattan (49.5, 95% CI 35.1–67.9)[16,44] than in Martinique (23.1, 18.4–28.6),[45] south London (14.9, 12.1–18.3),[46] and Barbados (17.6, 12.7–23.7),[30] with an incidence ratio of 2.7 (1.7–4.3) for Manhattan versus elsewhere. Hispanic people in Manhattan also had a higher incidence of intracerebral haemorrhage (24.0, 19.2–29.6)[16,44] than did those in Chile or Brazil (14.5, 11.4–18.3),[41,43] however, the number of studies with data on Hispanic people was too small to analyse regional diff erences in incidence of intracerebral haemorrhage in this group. The incidence of intracerebral haemorrhage in white people in Manhattan (22.6, 15.2–32.5)[16,44] was similar to that in white people in general (incidence ratio 0.9, 0.4–2.1). In Auckland, incidence of intracerebral haemorrhage in east and southeast Asian immigrants (20.7, 13.5–30.3) was similar to that in white people (18.6, 15.3–22.4) and Maori people (22.2, 15.8–30.3) living in that region (incidence ratio 1.1, 0.7–1.6),[34] and lower than in Asian people living in China[50] and Japan[15,17,18,24,55] (57.6, 46.0–72.0; incidence ratio 0.36, 0.18–0.71).

Because the incidence in Asian people was higher than in people of other ethnic origins (figure 3), we investigated the influence of these populations on the observed time trend. After adjustment for Asian versus non-Asian studies, the decrease of intracerebral haemorrhage incidence was no longer significant (adjusted annual decrease of incidence 1.1%, 95% CI –1.1 to 3.3). In addition, we found no pronounced annual decrease of intracerebral haemorrhage incidence after exclusion of the Chinese study and the six Japanese studies (1.2%, –1.2 to 3.6),[3,6,14,16,19–23,25–49,52] or within the Chinese[50] and Japanese[15,17,18,24,55] studies (0.5%, –5.3 to 6.0).

Median case fatality at 1 month was 40.4% (range 13.1–61.0) for 26 study populations in 35 time periods (table 3).[3,13–16,19–23,25–27,29,30,32,33,38–45,47–50,53,55,56] Ten studies reported case fatality after 1 year (median 54.7%, range 46.0–63.6).[3,19,20,26,27,32,39,43,48,54,57]

Five studies provided data on 1 month case fatality in men and women separately (table 4)[27,38,48,50,55] and five studies provided data in age groups.[19,29,38,48,55] In Melbourne, Australia case fatality was higher in women than in men,[27] whereas the other regions reported similar case fatalities for men and women. The pooled case fatality was higher in patients older than 75 years (28.1%, 95% CI 24.9–31.2) than in younger patients (17.8%, 15.9–19.7; difference 10.3%, 95% CI 6.6–14.0). Case fatality at 1 month (table 3) was lower in the two Japanese studies (16.7%,15.0–18.5)[15,55] than in the other regions (42.3%, 40.9–43.6; difference 25.5%, 23.3–27.7).[3,13,14,16,19–23,25–27,29,30,32,33,38–45,47–50,53,56]

Table 2 Incidence of intracerebral haemorrhage according to age

	ICH n=	Person-years	Incidence per 100.000 person-years (95% CI)	Time periods n=	Incidence ratio (95% CI)
<44[13,19,23,26,27,30,32,39-41,43,46-48,52,56]	119	5958646	1.9 (1.6-2.2)	16	0.10 (0.06-0.14)
45-54[19,23,26,27,30,32,33,39-41,43,46-48,52]	164	725660	19.1 (13.4-27.4)	15	Reference
55-64[19,20,23,26,27,30,32,33,38-40,43,46-48,52]	305	865173	36.5 (28.4-46.7)	16	1.8 (1.3-2.6)
65-74[19,23,26,27,29,30,32-34,38-41,43,46-48,52]	597	812077	77.1 (65.0-91.5)	18	3.8 (2.7-5.4)
75-84[19,23,26,27,29,30,32–34,38-41,43,46-48,52]	665	531845	136.9 (111.3-168.4)	18	6.8 (4.8-9.6)
>85[19,23,26,27,29,30,32–34,38-41,46-48,52]	274	170580	196.0 (148.3-259.1)	17	9.6 (6.6-13.9)

ICH intracerebral haemorrhage. 95% CI 95% confidence interval.
Because intracerebral haemorrhage is rare in people under age 45 years, the incidence ratios were calculated with the 45–54 years age group as the reference.

We noted no change in case fatality over time[3,13–16,19–27,29,30,32,33,38–45,47–50,53,55] (annual increase of 0.4% per year, 95% CI –0.5 to 1.4), with a similar result after adjustment for age (0.3%, –0.7 to 1.3). Sensitivity analysis excluding the Japanese studies produced similar results (annual decrease 0.6% per year, –1.3 to 0.2). Sensitivity analysis including only the 22 time periods of studies with excellent case-finding methods also did not show a time trend for case fatality (annual decrease 0·2% per year, –1.1 to 0.7).[3,13,16,19–23,25–30,32,33,37–45,47–50,52,53]

Six studies reported functional outcome at some point after intracerebral haemorrhage (table 3).[13–15,19,41,54] The proportion of patients leading an independent life after intracerebral haemorrhage varied from 12% at 12 months in Estonia[54] to 39% at last follow-up visit in young Italian adults (mean follow-up period 50 months, range 19–79 months).[13] Because the study design and the timing of the functional outcome assessment in these six studies were variable, we did not do a formal meta-analysis.

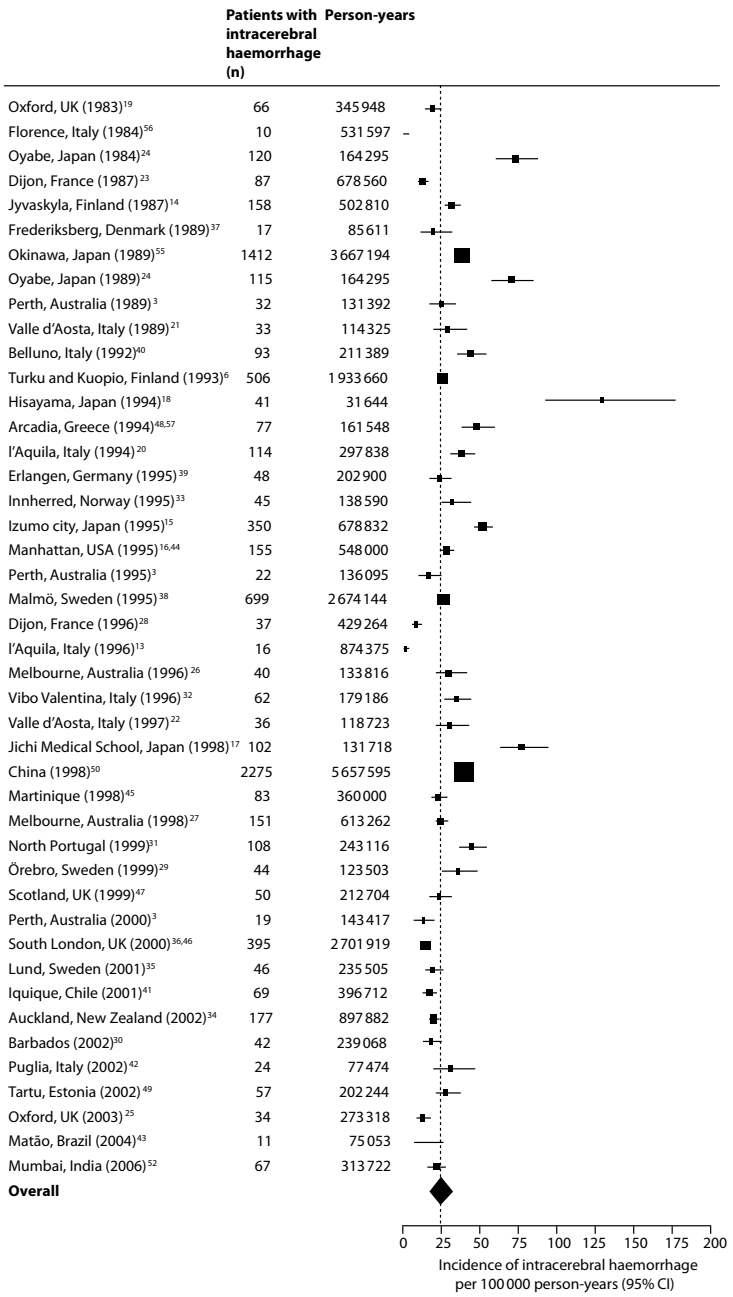

Figure 2 Incidence of intracerebral haemorrhage in 44 study periods
Size of the point estimates is proportional to the weight of the studies.

Table 3 Case fatality and functional outcome of intracerebral haemorrhage

	Mid-year of study	ICH n=	Age limit (years)	Case fatality at 1 month, % (95% CI)	Case fatality at 1 year, % (95% CI)	Patients living independently (%)
Oxford, UK[19]	1983	66	no	50.0 (37.4-62.6)	62.1 (49.3-73.8)	26 (at 12 months)
Florence, Italy[56]	1984	10	15-44	50.0 (18.7-81.3)	-	-
Dijon, France[23,53]	1987	87	no	42.6 (31.6-54.6)	-	-
Jyvaskyla, Finland[14]	1987	158	no	50.6 (42.8-58.4)	-	18*
Okinawa, Japan[55]	1989	1412	no	17.6 (15.6-19.6)	-	-
Perth, Australia[3]	1989	32	no	37.5 (21.1-56.3)	46.7 (29.1-65.3)	-
Valle d'Aosta, Italy[21]	1989	33	no	45.0 (28.1-63.7)	-	-
Belluno, Italy[40]	1992	93	no	34.4 (24.9-45.0)	-	-
Dijon, France[53]	1992	94	no	39.4 (29.4-50.0)	-	-
Arcadia, Greece[48,57]	1994	77	>18	46.8 (35.3-58.5)	53.2 (41.5-64.7)	-
l'Aquila, Italy[20]	1994	122	no	51.6 (46.1-64.4)	58.2 (49.4-66.9)	-
Erlangen, Germany[39]	1995	48	no	41.6 (27.6-56.8)	58.3 (43.2-72.4)	-
Innherred, Norway[33]	1995	45	>15	37.8 (23.8-53.5)	-	-
Izumo city, Japan[15]	1995	350	no	13.1 (9.6-16.7)	-	30†
Manhattan, USA[16,44]	1995	155	>20	35.0 (27.3-42.3)	-	-
Perth, Australia[3]	1995	22	no	45.4 (24.4-67.8)	-	-
Malmö, Sweden[38]	1995	699	no	23.3 (20.2-26.5)	-	-
l'Aquila, Italy[13]	1996	18	0-44	38.9 (17.3-64.3)	-	39‡
Melbourne, Australia[27]	1996	40	no	45.0 (29.3-61.5)	50.0 (33.8-66.2)	-
Vibo Valentina, Italy[32]	1996	62	no	40.3 (28.0-53.5)	56.5 (43.3-69.0)	-
Dijon, France[53]	1997	97	no	34.0 (24.7-44.3)	-	-
Valle d'Aosta, Italy[22]	1997	36	no	38.9 (23.1-56.5)	-	-
China[50]	1998	2275	>25	49.9 (47.3-51.4)	-	-
Martinique[45]	1998	83	no	37.3* (27.0-48.7)	-	-
Melbourne, Australia[27]	1998	151	no	40.4 (32.6-48.2)	49.7 (41.7-57.6)	-
Scotland, UK[47]	1999	50	no	46.0 (31.8-60.7)	-	-
Örebro, Sweden[29]	1999	44	no	20.5 (9.8-35.3)	-	-
Perth, Australia[3]	2000	19	no	47.4 (24.4-71.1)	-	-
Iquique, Chili[41]	2001	69	no	28.9 (18.7-41.2)	-	33 (at 6 months)
Puglia, Italy[42]	2002	24	no	20.8 (7.1-42.2)	-	-
Barbados[30]	2002	42	no	61.0 (44.5-75.8)	-	-
Dijon, France[53]	2002	102	no	24.5 (16.2-32.9)	-	-
Tartu, Estonia[49,54]	2002	57	no	40.4 (27.6-54.2)	54.4 (40.7-67.6)	12 (at 12 months)
Oxford, UK[25]	2003	34	no	55.8 (37.9-72.8)	-	-
Matão, Brazil[43]	2004	11	no	45.4 (16.8-76.6)	63.6 (30.8-89.1)	-

ICH intracerebral haemorrhage. 95% CI 95% confidence interval. *outcome at last follow-up visit, median follow-up 32 months (range 8 to 60 months). †Glasgow Outcome Score was assessed at discharge. ‡ outcome at last follow-up visit, mean follow-up period 50 months (range 19-79)

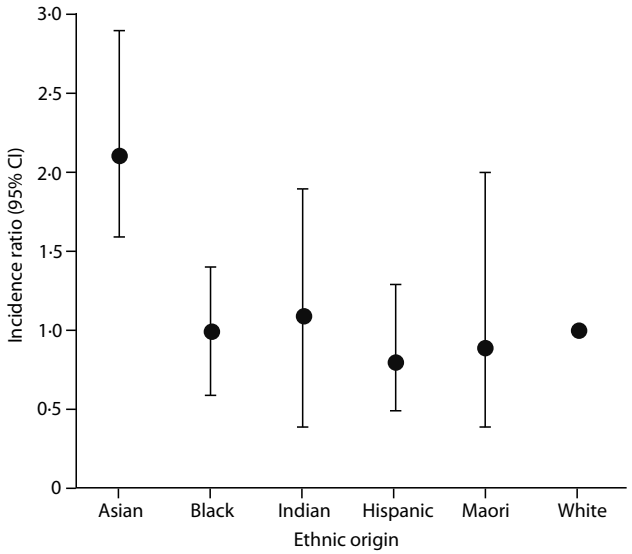

Figure 3 Intracerebral haemorrhage incidence ratios in ethnic groups

White ethnic origin was taken as reference because it was the ethnic group with the largest number of patients with intracerebral haemorrhage. Circles are means and bars are 95% CI.

Table 4 Intracerebral haemorrhage case fatality at 1 month according to sex and age

	Mid-year of study	ICH n=	CFR men	CFR women	CFR <65 yr	CFR 65-74 yr	CFR 75-84 yr	CFR >85 yr
Oxford, UK[19]	1983	66	-	-	42.0 (20.3-66.5)	44.4 (21.5-69.2)	58.0 (36.6-77.9)	80.0 (28.4-99.5)
Okinawa, Japan[55]	1989	1412	18.8 (16.1-21.5)	16.2 (13.3-19.1)	17.3 (14.6-19.9)	14.5 (10.4-18.7)	18.8 (13.8-23.7)	24.8 (17.1-32.5)
Arcadia, Greece[48*]	1994	77	44.0 (30.0-58.7)	51.8 (32.0-71.3)	33.3 (14.6-57.0)	31.8 (13.9-54.9)	63.2 (38.4-83.7)	60.0 (32.3-83.7)
Malmö, Sweden[38]	1995	699	23.9 (19.4-28.3)	22.7 (18.2-27.1)	14.3 (8.9-19.6)	18.9 (13.4-24.5)	29.8 (24.0-35.5)	31.3 (22.4-41.4)
China[50†]	1998	2275	48.4 (45.7-51.1)	50.7 (47.5-53.9)	-	-	-	-
Melbourne, Australia[27]	1998	151	29.2 (19.0-41.1)	50.6 (39.1-62.1)	-	-	-	-
Örebro, Sweden[29]	1999	44	-	-	25.0 (3.2-65.1)	21.4 (4.7-50.8)	12.5 (1.6-38.3)	33.3 (4.3-77.7)
Overall	-	-	35.4 (33.6-37.1)	35.3 (33.2-37.4)	17.6 (15.3-20.0)	18.1 (14.8-21.4)	26.8 (23.1-30.5)	30.9 (25.1-36.7)

Data are % (95% CI). CFR case fatality rate. 95% CI 95% confidence interval. *Patients older than age 18 years. †Patients older than age 25 years. ICH = intracerebral haemorrhage.

DISCUSSION

Overall, we did not find a substantial decrease in incidence of intracerebral haemorrhage between January, 1980, and November, 2008. We have reported overall higher incidence of intracerebral haemorrhage in men compared with women, especially in Japanese studies; a two times higher rate of intracerebral haemorrhage incidence in Asian people compared with other ethnic groups; and an increasing incidence of intracerebral haemorrhage with increasing age.

Case fatality at 1 month was low in Japanese studies compared with the other regions. Overall, case fatality was similar in men and women and increased with increasing age. We did not find a substantial time trend for 1 month case fatality.

The higher incidence of intracerebral haemorrhage in elderly patients has been attributed to high prevalences of amyloid angiopathy and hypertension, and to the use of antithrombotic drugs in this age group.[4] In a subset of studies we noted a stabilisation or decrease in intracerebral haemorrhage incidence in the oldest age groups. This is probably an anomaly because accurate community-based case finding in elderly patients is known to be difficult,[58] and stroke subtype is more likely to be categorised as undefined.[19]

Japanese men showed a higher incidence of intracerebral haemorrhage than Japanese women,[15,17,18,24] whereas in the other regions only small sex differences in intracerebral haemorrhage incidence were reported. Data from the Japanese Hisayama study[18,59] suggest that the effect of alcohol intake on incidence of intracerebral haemorrhage might be different in Japanese men and women, because the age-adjusted incidence of intracerebral haemorrhage increased more with higher daily alcohol intake in men than in women. In northern Manhattan, the risk of deep intracerebral haemorrhage was two times higher in men than in women, whereas the prevalence of hypertension was similar.[15] Inadequate treatment of hypertension in men, involvement of another risk factor for deep intracerebral haemorrhage, or a higher susceptibility of men to the effects of hypertension might contribute to this difference.[16]

Incidence of intracerebral haemorrhage is high in Japan and China, whereas the rate in Asian migrants in New Zealand is not different from that in white people or Maori people.[34] An opposite relation between ethnic origin and environment was found for black Caribbean people living in south London, who have higher intracerebral haemorrhage incidence than do those living in Barbados. This difference can probably be explained by a difference in cardiovascular risk factors after migration.[60] We found that intracerebral

haemorrhage incidence was two to three times higher in black people in Manhattan compared with those in other regions (Barbados, Martinique, and south London), whereas the incidence rate in white people in Manhattan was similar to the incidence rate in those elsewhere. These findings suggest environmental factors influence incidence of intracerebral haemorrhage.

Studies on time trends in intracerebral haemorrhage incidence have shown regional differences. In line with the results of our meta-analysis, the numbers of patients with intracerebral haemorrhage in all age groups did not decrease over time in Oxford and Dijon.[4,5,51] Interestingly, in Oxford, time trends differed according to age group and type of intracerebral haemorrhage.[4] A decrease in incidence of intracerebral haemorrhage was reported for Perth, Australia, which was most prominent in men.[3] No decline in incidence of intracerebral haemorrhage was found in Finland and France.[5,6] In Finland the intracerebral haemorrhage incidence in the 1980s might have been underestimated because only a small proportion of patients with stroke had CT scans at that time.[6] On the basis of our meta-analysis, the decrease in incidence of intracerebral haemorrhage is moderate at best and similar to that for subarachnoid haemorrhage[61] rather than that for ischaemic stroke.[1] Changes in incidence might be different for specific subtypes of intracerebral haemorrhage, but we could not assess changes in subgroup-specific incidence because these data were not available from the parent studies.

The overall intracerebral haemorrhage case fatality at 1 month of about 40% is much the same as that in a previous report.[1] Case fatality was similar between regions, except for the low case fatality of about 13%[15] and 18%[55] in the two Japanese studies. Japanese patients also have a high incidence and a low case fatality for subarachnoid haemorrhage.[7,61] The two Japanese studies reporting on case fatality did not meet our criteria for excellent quality because family doctors were not involved in case finding. Therefore, patients who died from intracerebral haemorrhage at an early stage were possibly missed, which might in part explain the low case fatality.[15,55] Also, differences in treatment strategies might explain the differences in case fatality after haemorrhagic stroke between Japan and the rest of the world. In theory, early referral to a stroke unit and surgical intervention for more patients might reduce intracerebral haemorrhage case fatality in Japan.[15] Six studies reported functional outcome after intracerebral haemorrhage,[13–15,19,41,49] one of which was from Japan.[15] Because these studies varied considerably in study design and time of assessment, no conclusions can be drawn from these data.

Several limitations of this meta-analysis should be mentioned. The definition of intrace-

rebral haemorrhage varied or was not specified in detail in the studies. Also, population-based stroke epidemiology data were limited for countries outside Europe and North America. A recent review, including ischaemic stroke, intracerebral haemorrhage, and subarachnoid haemorrhage, reported a decrease of stroke incidence in high-income countries and an increase of stroke incidence in low-income countries.[1] Investigation of the influence of known prognostic factors (eg, use of antithrombotics or anticoagulants, intracerebral haemorrhage size, or presence of intraventricular extension) on case fatality would be interesting. Unfortunately, there were few data on prognostic factors in these population-based studies and therefore we could not assess the influence of prognostic factors.

Age, sex, and ethnic background influence incidence of intracerebral haemorrhage. Environmental factors are probably also involved. The change in environmental factors, such as hypertension control, has probably led to a decreasing incidence of intracerebral haemorrhage in some regions. Because case fatality has not decreased, the best way to reduce mortality from intracerebral haemorrhage seems to be further treatment of risk factors. More data on functional outcome after intracerebral haemorrhage are needed.

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Webappendix MEDLINE and EMBASE syntaxes

MEDLINE syntax

"population"[MeSH Terms] OR "region"[Title/Abstract] OR "regional"[Title/Abstract] OR "population based"[Title/Abstract] OR "community based"[Title/Abstract] OR "community"[Title/Abstract] OR "stroke register"[Title/Abstract] OR "stroke registry"[Title/Abstract]
AND
"incidence"[Title/Abstract]OR "fatality"[Title/Abstract] OR "mortality"[Title/Abstract] OR "trend"[Title/Abstract] OR "incidence"[MeSH Terms] OR "mortality"[MeSH Terms]
AND
"hemorrhagic stroke"[Title/Abstract] OR "stroke"[Title/Abstract] OR "stroke"[MeSH Terms] OR "intracranial hemorrhage. hypertensive"[MeSH Terms] OR "cerebral hemorrhage"[MeSH Terms] OR (("intracerebral"[Title/Abstract] OR "intraparenchymal"[Title/Abstract]) AND ("hemorrhage"[Title/Abstract] OR "haemorrhage"[Title/Abstract] OR "hemorrhage"[MeSH Terms] OR "hematoma"[MeSH Terms] "haematoma"[Title/Abstract] OR "hematoma"[Title/Abstract]))

EMBASE syntax

'population'/syn OR 'region' OR 'regional' OR 'population based' OR 'community based' OR 'community'/syn OR 'stroke register' OR 'stroke registry'
AND
'incidence'/exp OR 'fatality'/exp OR 'mortality'/exp OR 'trend'
AND
'hemorrhagic stroke' OR 'stroke'/exp OR (('intracranial' OR 'cerebral' OR 'intracerebral'/exp OR 'intraparenchymal') AND ('hemorrhage'/exp OR 'haemorrhage'/exp OR 'hematoma'/exp OR 'haematoma'/exp))

Webtable Definition and terminology of (primary) intracerebral haemorrhage in population-based stroke studies

	WHO definition for stroke*	Term	Exclusion of certain causes of (P)ICH
Oxford, UK[19]	yes	PICH	Definite PICH: unrelated to tumour or trauma†
Florence, Italy[56]	yes	ICH	OCSP criteria
Oyabe, Japan[24]	yes	CH	Not specified, refers for full definition to article in Japanese‡
Dijon, France[23]	yes	PICH	"Spontaneous high density lesion without enhancement"
Jyvaskyla, Finland[14]	no	PICH	Exclusion trauma, AVM, aneurysm, neoplasm
Frederiksberg, Denmark[37]	yes	ICH	Not specified
Okinawa, Japan[55]	no	BH	Not specified
Perth, Australia[3]	yes	PICH	Exclusion trauma, hemorrhagic transformation infarct and aneurysm
Valle d'Aosta, Italy[21]	yes	CH	OCSP criteria
Belluno, Italy[40]	yes	PICH	Not specified
Turku/Kuopio, Finland[6]	yes	ICH	ICD (revision 8,9 and 10)§
Hisayama, Japan[18]	no	CH	Exclusion trauma, haematologic disorders etc.‖
Arcadia, Greece[48]	yes	ICH	Not specified
l'Aquila, Italy[20]	no	ICH	Exclusion trauma¶
Erlangen, Germany[39]	yes	ICH	Not specified
Innherred, Norway[33]	yes	ICH	ICD-9§
Izumo city, Japan[15]	no	PICH	Exclusion aneurysm, AVM, moyamoya disease, cavernous or venous haemangioma, hemorrhagic transformation of infarct, head trauma, brain tumour, severe bleeding tendency, coagulation disorder or malignancy.
Manhattan, USA[16,44]	yes	ICH	Exclusion trauma, underlying tumour or AVM
Malmö, Sweden[38]	yes	ICH	ICD-9§
l'Aquila, Italy[13]	no	ICH	ICD-9/-10 §, inclusion AVM and aneurysm
Melbourne, Australia[27]	yes	ICH	Not specified
Vibo Valentina, Italy[32]	yes	ICH	Not specified
Valle d'Aosta, Italy[22]	yes	CH	OCSP criteria
Jichi Medical School, Japan[17]	no	CH	Exclusion trauma (information from M. Kubo)
China[50]	yes	ICH	ICD-9§
Martinique[45]	yes	ICH	Not specified
Melbourne[27]	yes	ICH	Not specified
North Portugal[31]	yes	ICH	Not specified
Örebro, Sweden[29]	yes	ICH	OCSP criteria
Scotland, UK[47]	yes	ICH	Not specified
South London, UK[36,46]	yes	PICH	PICH includes hypertension, amyloid angiopathy, arterial aneurysm, and arteriovenous malformation

	WHO definition for stroke*	Term	Exclusion of certain causes of (P)ICH
Lund, Sweden[35]	yes	ICH	OCSP criteria
Iquique, Chili[41]	yes	ICH	Not specified
Auckland, New Zealand[34]	yes	ICH	Exclusion trauma, hemorrhagic transformation infarct and aneurysm
Barbados[30]	yes	ICH	See South London
Puglia, Italy[42]	yes	ICH	Not specified
Tartu, Estonia[49]	yes	ICH	Not specified
Oxford, UK[25,51]	yes	PICH	OCSP criteria
Matão, Brazil[43]	yes	ICH	Not specified
Mumbai, India[52]	yes	ICH	Not specified

AVM arteriovenous malformations. BH brain haemorrhage. CH cerebral haemorrhage. GHSDS Guy's Hospital Stroke Diagnostic Score. ICH intracerebral haemorrhage. PICH primary intracerebral haemorrhage
* WHO definition of stroke excludes cases of primary cerebral tumour, cerebral metastasis, subdural haematoma, postseizure palsy, brain trauma, and TIA. Aho K, Harmsen P, Hatano S, Marquardsen J, et al. Cerebrovascular disease in the community: results of a WHO collaborative study. Bull World Health Organ 1980;58:113-30.
† = "Primary intracerebral haemorrhage was defined as a stroke caused by non-traumatic bleeding, primarily into brain substance, with or without the presence of blood in the subarachnoid space. Intracerebral haematoma must be confirmed by CT or necropsy." Oxfordshire Community Stroke Project: Incidence of stroke in Oxfordshire: First year's experience of a community stroke register. No authors listed, Br Med J 1983;287:713-7.
‡ Okinaka S. Epidemiological study of stroke: three-year follow-up study of 17 districts in Japan [in Japanese]. Jpn Med J 1966;2221:19-28.
§ ICD-9 code 431:"Bleeding into a cerebral hemisphere of the brain, including lobar, subcortical white matter, and basal ganglia hemorrhages. Commonly associated conditions include HYPERTENSION; INTRACRANIAL ARTERIOSCLEROSIS; INTRACRANIAL ANEURYSM; CRANIOCEREBRAL TRAUMA; INTRACRANIAL ARTERIOVENOUS MALFORMATIONS; CEREBRAL AMYLOID ANGIOPATHY; and CEREBRAL INFARCTION."
|| "Cases of cerebrovascular disease due to rare causes such as collagen disease, hematologic disorders, trauma, cerebral arterial spasm after subarachnoid hemorrhage, chronic subdural hematoma, and moyamoya disease were not included in stroke cases." Tanizaki Y, Kiyohara Y, Kato I, Iwamoto H, Nakayama K, Shinohara N, Arima H, Tanaka K, Ibayashi S, Fujishima M.Incidence and risk factors for subtypes of cerebral infarction in a general population: the Hisayama study. Stroke 2000;31:2616-22.
¶"Two hundred twenty-eight patients were excluded because of nonfatal (n=23) or fatal (n=24) recurrent stroke, residence out of the district (n=53), transient ischemic attacks (n=86), stroke due to head trauma (n=41), and perinatal intraventricular hemorrhage (n=1)."

PART II

Imaging of intracerebral and intraventricular haemorrhage

CHAPTER 3

Early intracerebral haematoma expansion after aneurysmal rupture

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ABSTRACT

Background and purpose: Intracerebral haematomas (ICHs) often increase in size in the initial hours. It is unknown whether expansion of ICHs after aneurysmal rupture in the acute phase is always a sign of re-rupture of the original aneurysm.

Methods: We included patients with an ICH from a ruptured aneurysm who underwent computed tomography imaging within 24 hours of symptom onset and a repeat computed tomography within 48 hours. Haematoma growth was considered present when there was a 33% increase in haematoma volume, as assessed by the ABC/2 method. Clinical and radiologic characteristics were compared between patients with ICH growth, with and without clinical signs of re-rupture. Re-rupture was defined as a sudden deterioration in the level of consciousness in the absence of ventricular enlargement or a systemic cause.

Results: Haematoma expansion within 48 hours after onset occurred in 12 of the 49 included patients and was preceded by clinical evidence of re-rupture in 6 of these 12 patients. Of the 6 patients without an evident re-rupture, 3 had no clinical deterioration, 1 had respiratory failure due to pneumonia, another had temporal brain herniation, and the last had acute hydrocephalus.

Conclusion: Only half of the patients with early ICH expansion after aneurysmal rupture had clinical signs of re-rupture of the aneurysm. Early ICH expansion after aneurysmal rupture can be caused by other mechanisms, which are possibly comparable to those responsible for haematoma expansion in spontaneous ICH.

INTRODUCTION

In 20% of patients with aneurysmal subarachnoid haemorrhage (aSAH), the haemorrhage extends into the brain parenchyma. The presence of an intracerebral haematoma (ICH) in patients with aSAH is associated with a high case fatality and poor functional outcome.[1] Several studies have shown significant ICH expansion within 24 hours after onset of symptoms in approximately one third of patients with spontaneous ICH.[2,3] Contrast extravasation has been observed up to 48 hours after symptom onset of spontaneous ICH, which suggests active bleeding.[4]

In patients with ICH caused by a ruptured aneurysm, re-rupture of the aneurysm is an obvious cause of expansion, but whether ICH expansion can also occur in the absence of a re-rupture is unknown. We studied how often haematoma expansion in patients with ICH from a ruptured aneurysm is caused by re-rupture of the aneurysm.

METHODS

Patients

We included patients with ICH with or without SAH caused by a ruptured aneurysm from our prospectively collected database of patients with SAH admitted to the University Medical Center, Utrecht, The Netherlands, between January 2003 and November 2008. ICH had to be confirmed by non-contrast computed tomography (CT) within 24 hours after onset of symptoms. Patients had to have had a second CT within 48 hours after symptoms onset. The presence of an aneurysm had to be confirmed by CT angiography (CTA) or digital subtraction angiography. Exclusion criteria were age 18 years and craniotomy before the second CT. On the basis of the study protocol, the medical ethics committee of the University Medical Center Utrecht decided that no formal approval was needed for this study, because we only retrospectively reviewed data collected for clinical purposes, and we performed no additional tests or interviews of the patients.

We retrieved the following data for each patient: age, sex, daily use of antiplatelet agents, use of oral anticoagulants at the time of aneurysmal rupture (and if so, international normalized ratio at presentation), mean arterial pressure at presentation, clinical deterioration preceding the second CT scan, presumed cause of clinical deterioration, time interval between the first and second CT scans, location and size of the aneurysm, ICH location, and the pres-

ence of intraventricular or subdural blood. We defined re-rupture as the cause of ICH expansion when a patient had a sudden deterioration in the level of consciousness in the absence of ventricular enlargement or a systemic cause.

Measurement of ICH Volume

ICH volume was calculated with the ABC/2 method.[5] Perihaematomal oedema was not included in the measurements. Haematoma expansion was defined as an increase of ICH volume 33%, because changes in haematoma volume of 33% may reflect variability in CT imaging rather than actual haematoma expansion.[2]

Data Analysis

For the "expansion group" versus the "no-expansion group" and the"re-rupture group" versus the "no-re-rupture group," descriptive statistics were used for patient and ICH characteristics. We calculated overall proportions, mean values with standard deviation (SD) for normally distributed data, and median values with interquartile range for data with a skewed distribution. We refrained from a formal statistical comparison of patient and ICH characteristics between patients with ICH growth with and without re-rupture because the numbers of patients were small.

RESULTS

Of the 755 patients with aSAH admitted within the study period, 162 patients (21%) had an ICH, of whom 49 met our inclusion criteria (Figure 1). Patient and ICH characteristics are listed in the Table. In 12 patients (24%), the repeat CT showed ICH expansion within 48 hours of symptom onset. Median ICH volume increased from 13 mL (interquartile range, 7 to 24) on the admission CT to 26 mL (interquartile range, 12 to 65) on the second CT. In 3 patients with ICH expansion, no obvious clinical deterioration was present.

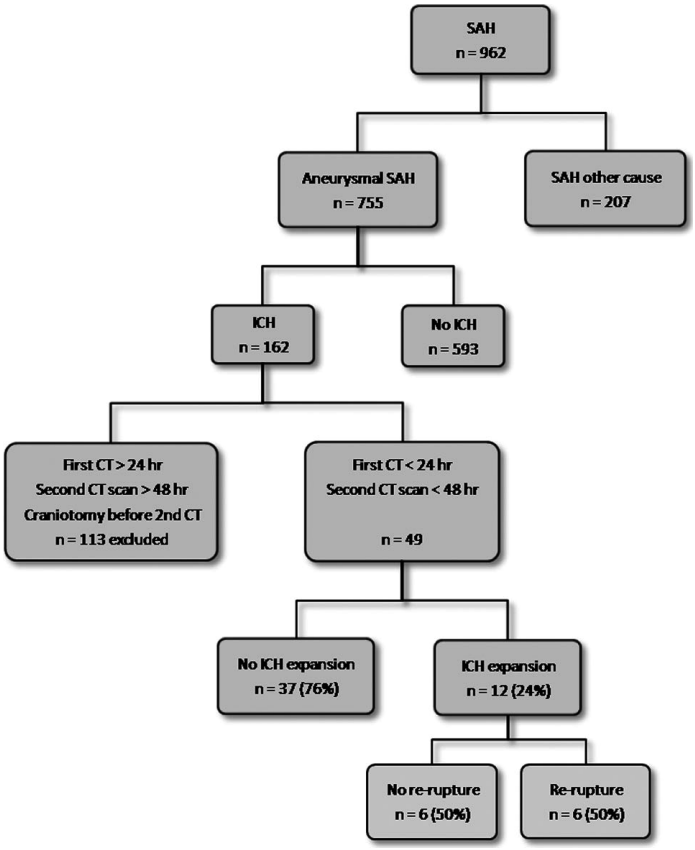

Figure 1 Flow chart of patient selection

Table Patient and ICH characteristics for patients with and without ICH expansion >33% and for patients with expansion due to re-rupture vs those without re-rupture

Characteristic	No ICH expansion n = 37	ICH expansion n=12	Expansion with re-rupture n=6	Expansion without re-rupture n=6
Mean age in years (SD), years	56.9 (11.7)	53.8 (13.0)	56.3 (12.6)	51.3 (14.3)
Women, n (%)	25 (68)	10 (83)	5 (83)	5 (83)
Medication at symptom onset, n (%)				
Anticoagulation	0 (0)	1 (8)	0 (0)	1 (17)
Antiplatelet agents	5 (14)	0 (0)	-	-
Median MAP at admission* (IQR)	102 (93-124)	118 (81-122)	105 (64-129)	120 (118-122)
Reason second CT (%)				
Routine CT before CTA	20 (54)	2 (17)	0 (0)	2 (33)
Clinical deterioration	16 (43)	9 (75)	6 (100)	3 (50)
Follow-up acute hydrocephalus	1 (3)	1 (8)	0 (0)	1 (17)
Median time between first and second CT in hours (IQR)	7.0 (3.9-17.3)	6.9 (2.4-22.1)	6.2 (1.8-11.0)	15.2 (3.5-31.6)
Aneurysm location, n (%)				
Anterior communicating artery	10 (27)	3 (25)	1 (17)	2 (33)
frontal	10 (100)	2 (67)	0 (0)	2 (100)
temporal	-	1 (33)	1 (100)	-
Middle cerebral artery	16 (43)	7 (58)	4 (67)	3 (50)
frontal	4 (25)	3 (43)	2 (50)	1 (33)
temporal	12 (75)	4 (57)	2 (50)	2 (67)
Internal carotid artery	11 (30)	2 (17)	1 (17)	1 (17)
frontal	2 (18)	1 (50)	1 (100)	-
temporal	8 (73)	1 (50)	-	1 (100)
occipital	1 (9)	-	-	-
Aneurysm size, mm (%)				
> 7.7 mm	19 (51)	6 (50)	4 (67)	2 (33)
Median ICH volume in mL (IQR)				
Admission CT	19 (6-41)	13 (7-24)	13 (8-28)	16 (5-27)
Second CT	17 (6-47)	26 (12-65)	42 (11-74)	26 (9-50)
Intraventricular haemorrhage (%)	29 (78)	8 (67)	5 (83)	3 (50)
Subdural haematoma (%)	8 (22)	1 (8)	0 (0)	1 (17)

CTA CT angiography. ICH intracerebral haemorrhage. IQR interquartile range. MAP mean arterial pressure. SD standard deviation. *MAP at admission was known for 8 patients in the expansion group and for 30 patients in the no-expansion group

Six of the 12 patients with ICH expansion fulfilled our criteria for re-rupture, but none of these 6 patients had a sudden aggravation of headache before the second CT was made. In 1 of the 6 patients with re-rupture, CTA showed contrast extravasation from a middle cerebral artery aneurysm (Figure 2). In the 6 patients without signs of re-rupture, 1deteriorated due to respiratory failure from pneumonia, a second from temporal brain herniation, and a third from acute hydrocephalus. One of the 3 patients without obvious clinical deterioration was stable but comatose, with a Glasgow Coma Scale score of E1M5Vtube.[6] The second patient was taking anticoagulants and was treated with a prothrombin complex concentrate (International Normalized Ratio 1.11 on admission to our hospital; Figure 3). The third patient was a 41-year-old woman who presented with a Glasgow Coma Scale score of E3M6V5 and subtle sensory dysphasia at a regional hospital. Her clinical condition had remained unchanged at the time of the CT and CTA performed at our institution. The CT showed expansion of a left frontal haematoma (Figure 4) and a left middle cerebral artery aneurysm, which was coiled successfully. In both patients, no active extravasation of contrast from the aneurysm was observed.

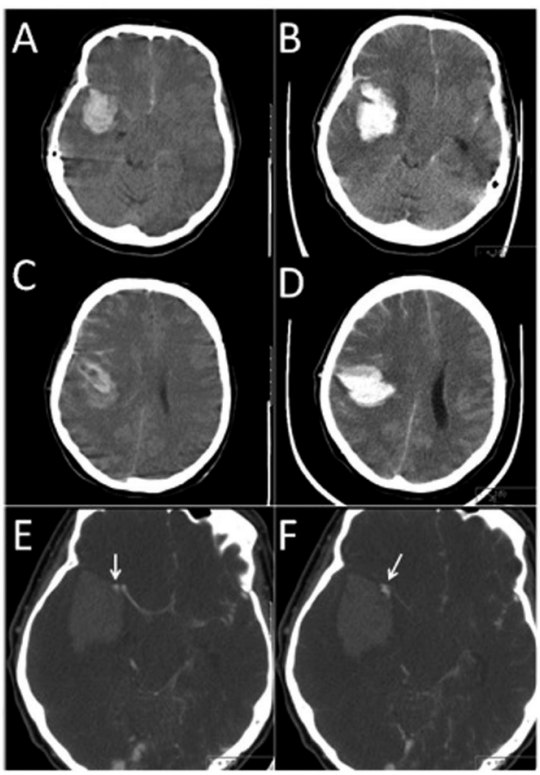

Figure 2 A 53-year-old man was admitted with SAH and a right temporal ICH adjacent to the sylvian fissure (A and C; the first CT was performed at a regional hospital). Initially, his clinical condition was stable, with a Glasgow Coma Scale score of E3M6V3 and a left-sided paralysis. A few hours later, the patient had to be intubated because of sudden neurologic deterioration accompanied by progressive respiratory failure; he was then transferred to our hospital. Subsequent CTA showed active extravasation (E and F, second CT; the arrow indicates contrast leakage into the haematoma) from a middle cerebral artery aneurysm into the expanding ICH (B and D, second CT). His neurologic condition worsened to a Glasgow Coma Scale score of E1M1Vtube with bilateral, fixed, dilated pupils and brainstem dysfunction, and he died soon after admission.

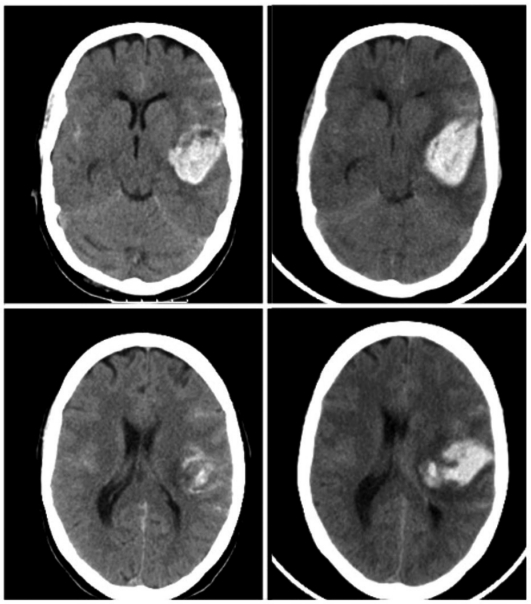

Figure 3 A 48-year-old woman presented to a local hospital with sudden headache, mild right-sided hemiparesis, and dysphasia. She was taking oral anticoagulants because of a history of deep vein thrombosis associated with a factor V Leiden mutation. Non-contrast CT showed an SAH and a left frontotemporal ICH adjacent to the sylvian fissure (left). After normalization of her International Normalized Ratio by administration of a prothrombin complex concentrate, the patient was transferred to our hospital. On admission, her clinical condition was unchanged. A repeat CT scan performed 7 hours after the first CT showed marked ICH expansion with a mass effect (right), and CTA detected a left middle cerebral artery aneurysm without active extravasation. The haematoma was evacuated and the aneurysm was clipped. A year later, the patient's right arm was still paretic, but she had regained independence in daily activities.

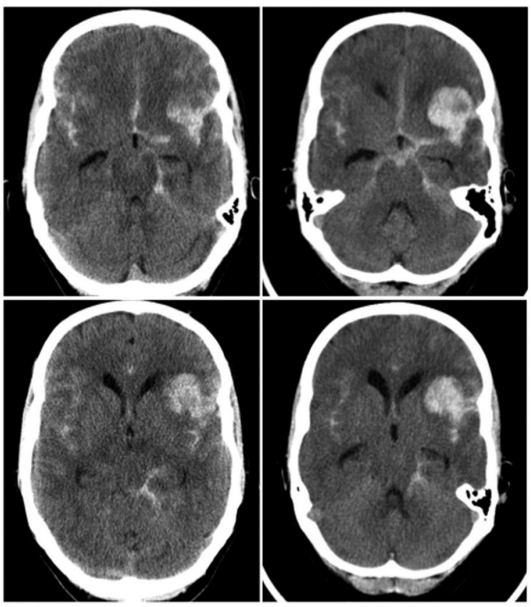

Figure 4 A 41-year-old woman with mild sensory dysphasia presented to a general hospital. Non-contrast CT showed an SAH and a left frontal ICH adjacent to the sylvian fissure (left).Her clinical condition was unchanged at the time of the CT and CTA performed at our institution. CT showed expansion of the left frontal haematoma (right) and a left middle cerebral arteryaneurysm that was later coiled successfully.

DISCUSSION

In only half of the patients with ICH expansion early after aneurysmal rupture, the expansion was explained by re-rupture of the aneurysm; in patients with expansion but without re-rupture, no clinical deterioration or obvious reasons other than re-rupture were present.

Little is known about ICH expansion in patients with aSAH. In 1 study of ICH in various vascular lesions including aneurysms, the proportion of patients with haematoma expansion within a median time of 7 hours after presentation was 20%.[7] However, in that study, the proportion of patients with a ruptured aneurysm who had ICH expansion and the proportion of patients with a re-rupture were not reported.[7] Another study did not find haematoma enlargement or contrast extravasation in 4 patients with ICH of a ruptured aneurysm who underwent a repeat CT and CTA within 24 hours after onset.[8] In patients with spontaneous ICH, haematoma expansion has been reported in approximately one third of patients within 24 hours after onset.[2,3] The cause of haematoma expansion in these patients remains unclear. Ongoing bleeding from a single source, breakdown of the blood-brain barrier, and delayed bleeding from a second source have all been suggested to be involved in contrast leakage and subsequent haematoma expansion.[9] Contrast extravasation has been observed up to 48 hours after symptom onset of a spontaneous ICH[4] and has been shown to be an independent predictor of haematoma expansion [4,9,10] and poor outcome.[10,11] The location of contrast leakage within the haematoma can be solely central, peripheral, or mixed.[9]

In patients with ICH after aneurysm rupture, re-rupture of the aneurysm is an obvious cause of haematoma expansion. In this study, we found haematoma expansion in the absence of clinical evidence of re-rupture of the aneurysm, suggesting that other mechanisms are responsible for haematoma expansion. Ongoing bleeding or bleeding from damaged vessels surrounding the haematoma, as suggested in spontaneous ICH, may cause haematoma expansion in aneurysmal bleeding in the absence of sudden clinical deterioration. Whether contrast extravasation is an independent predictor of haematoma expansion and poor outcome in aneurysmal ICH, similar to observations in spontaneous ICH, has not been studied. In addition, a high systolic blood pressure (that is, 200 mm Hg or higher) on admission has been shown to be a risk factor for haematoma expansion in spontaneous ICH.12 The small number of patients with ICH expansion in this study did not allow us to investigate the relation between hypertension and expansion in aneurysmal ICH.

A limitation of the present study is the retrospective design, especially the selection bias that occurred because a second CT scan was not performed routinely within 48 hours in all patients. For this reason, approximately two thirds of the 162 patients with aneurysmal ICH could not be included. In 22 of the 49 included patients (45%) in whom a second CT was performed, the CT was repeated for no reason other than performing a routine CT as part of the CTA protocol to locate the aneurysm in patients who had only non-contrast CT performed at the referring hospital. Of these 22 patients, 2 had haematoma expansion. The selection bias may have led to underestimation of the proportion of patients with ICH expansion unrelated to re-rupture of the aneurysm because patients whose clinical condition is stable are less likely to undergo repeat CT scanning. The proportion of patients with ICH due to aneurysmal rupture and the proportion of patients with re-rupture in our study are comparable to those in previous reports,[1,13] suggesting that the studied patients are a representative sample of aSAH patients.

A strength of our study is that we applied the strict criterion of a 33% increase in ICH volume for the expansion group; therefore, we are confident that the observed haematoma expansion was real in these patients and was not caused by variability in CT imaging technique. The ABC/2 method that we used to assess ICH volume has an excellent interrater and intrarater reliability.[5]

In conclusion, a substantial proportion of patients with ICH due to a ruptured aneurysm show an expansion of ICH volume within 48 hours, without evidence of re-rupture of the original aneurysm. Further studies are needed to more precisely determine the proportion of patients with aneurysmal ICH who develop ICH expansion and to define the effect of ICH expansion on clinical outcome. If patients at risk of haematoma expansion can be identified by, for example, the "spot sign," further studies should determine whether the outcome of patients with a high risk of ICH expansion may be improved by immediately occluding the aneurysm in combination with evacuation of the haematoma or by other measures to prevent haematoma expansion.

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CHAPTER 4

External validation of the Secondary Intracerebral Hemorrhage Score in the Netherlands

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ABSTRACT

Background and purpose: We aimed to validate externally in a setting outside the United States the Secondary IntraCerebral Hemorrhage (SICH) score that was developed to predict the probability of macrovascular causes in patients with non-traumatic intracerebral haemorrage (ICH).

Methods: Patients with non-traumatic ICH admitted to the University Medical Center Utrecht, the Netherlands, between 2003 and 2011 were included if an angiographic examination, neurosurgical inspection, or pathological examination had been performed. Secondary ICH score performance was assessed by calibration (agreement between predicted and observed outcomes) and discrimination (separation of those with and without macrovascular cause).

Results: Forty-eight of 204 patients (23.5%) had a macrovascular cause. The secondary ICH score showed modest calibration (P=0.06) and modest discriminative ability (c-statistic 0.73, 95% confidence interval 0.65-0.80). Discrimination improved slightly using only non-contrast computed tomography categorization (c-statistic 0.79, 95% CI 0.72-0.86).

Conclusion: The discriminative ability and calibration of the secondary ICH score are moderate in a university hospital setting outside the United States. Clues on non-contrast computed tomography are the strongest predictor of a macrovascular cause in patients with ICH.

INTRODUCTION

Non-traumatic intracerebral haemorrhage (ICH) is the subtype of stroke with the highest case fatality.[1] Approximately 15% to 20% of patients with non-traumatic ICH have an underlying macrovascular abnormality cause, such as an arteriovenous malformation, a dural arteriovenous fistula, or an aneurysm. Early identification of these lesions has important therapeutic and prognostic consequences.[2,3] Computed tomography (CT) angiography enables assessment of vascular pathology in the emergency setting, but it is unclear which patients with ICH should undergo angiographic examinations.[4] The secondary ICH (SICH) score was developed and validated in the United States to identify patients with a high risk of an underlying macrovascular cause on the basis of patient and haemorrhage characteristics (Table I in the Data Supplement).[5] The same investigators performed an external validation study in another US hospital, which indicated that the SICH score is an accurate tool in US settings.[6]

The discriminative power of the SICH score, however, may depend on population differences and local variation in which patients with ICH undergo angiographic studies to find a macrovascular cause. We, therefore, sought to validate externally the SICH score in a setting outside the United States and to assess the effect of the separate items of the SICH score on the probability of harboring an underlying vascular cause.

METHODS

Patients

From a prospectively collected database of patients with stroke admitted to the University Medical Center Utrecht, the Netherlands, we included patients admitted between February 2003 and May 2011 who met the following inclusion criteria: (1) non-traumatic ICH on non-contrast CT (NCCT); (2) ≥18 years; and (3) ≥1 angiographic study (CT angiography, MR angiography, or digital subtraction angiography), or pathological examination.

Predictors

Age, sex, and history of hypertension or impaired coagulation were retrieved.[5] NCCTs were reviewed independently by 2 observers blinded to clinical data and final diagnosis. Each NCCT was assessed by a neurology (C.J.J.v.A.) or radiology (P.J.v.L.) resident, and a neurology

(C.J.M.K.) or radiology (B.K.V.) staff member. NCCTs were classified as high probability of finding an underlying macrovascular cause when enlarged vessels or calcifications were present along the ICH margins, or visible hyperattenuation within a dural venous sinus or cortical vein. In low-probability NCCTs, none of these were present and the haematoma was located in basal ganglia or brain stem. Indeterminate probability NCCTs fulfilled neither high- nor low-probability criteria.[5] Differences in reader interpretations were resolved in consensus meetings.

Outcome

The outcome measure was a macrovascular cause of the ICH identified by CT angiography, MR angiography, or digital subtraction angiography, neurosurgical inspection, or pathological examination.

Data Analysis

Interobserver agreement for NCCT categorization was determined with κ statistics. To assess the effect of separate items of the SICH score on the probability of an underlying vascular cause, we performed univariable logistic regression analyses for all predictors separately in both the Boston derivation cohort and Utrecht validation cohort. Subsequently, we calculated the SICH score and predicted probability for each patient in the validation cohort on the basis of original regression coefficients of the final multivariable model on which the SICH score was based.[5]

We assessed performance of the SICH score by discrimination (separation of those with and without vascular cause) and calibration (agreement between observed and predicted outcomes). Discrimination was assessed using the area under the receiver-operating curve. For calibration, we constructed a calibration curve plotting the observed versus the predicted probability and performed the Hosmer–Lemeshow test.

RESULTS

From 517 patients admitted with non-traumatic ICH, we included 204 patients. Baseline characteristics of the Boston derivation and the Utrecht validation cohorts are listed in Table II in the Data Supplement. In our validation cohort, an underlying vascular cause was identified in 48 of 204 patients (23.5%), in comparison with 91 of 623 patients (14.6%) in the derivation cohort (Table III in the Data Supplement). In the derivation cohort 273 patients (43.8%) and in our validation cohort 46 patients (22.5%) were aged 71 to 94 years. The female preponderance in patients with a macrovascular cause in the derivation cohort was not observed in our validation cohort. Validation cohort patients less often had hypertension (59.1% versus 42.2%) or impaired coagulation (32.7% versus 21.6%) than derivation cohort patients.

Interobserver agreement for NCCT categorization in our validation cohort was substantial (κ statistic 0.64; 95% confidence interval [CI], 0.55–0.73). In our validation cohort, 66 NCCTs (32%) were categorized as low probability, 116 (57%) as indeterminate, and 22 (11%) as high probability.

In the univariable analyses, the effect of the predictors was of comparable magnitude in the derivation and the validation cohort with the except for sex (odds ratio derivation cohort, 1.6; odds ratio validation cohort, 0.7; Table II in the Data Supplement). The strongest predictor of harboring an underlying macrovascular cause was NCCT categorization.

In the validation cohort, the SICH score showed modest discriminative ability (*c*-statistic 0.73; 95% CI, 0.65-0.80), with a point estimate outside the 95% CI of the point estimate of the *c*-statistic in the derivation cohort (0.87; 95% CI 0.84-0.89; Table). Discrimination was much better when applying the original regression coefficients of the final multivariable model of the derivation group (*c*-statistic 0.81; 95% CI 0.75-0.88). The mean predicted probability of finding a macrovascular lesion (22.5%) was comparable with the mean observed presence of a macrovascular lesion (23.5%). Calibration was only modest (Hosmer–Lemeshow test, *P*=0.06; Figure in the Data Supplement). Discrimination was slightly better using only NCCT categorization (*c*-statistic 0.79; 95% CI 0.72–0.86).

Table Predictive value of the Secondary IntraCerebral Hemorrhage (SICH) score

	Derivation cohort ICH n=623	SICH n=91	Validation cohort ICH n=204	SICH n=48
SICH-score	ICH n (%)	SICH n (%)	ICH n (%)	SICH n (%)
0	37 (5.9)	0	3 (1.5)	0
1	145 (23.3)	2 (1.4)	33 (16.2)	0
2	209 (33.5)	11 (5.3)	56 (27.5)	9 (16.1)
3	138 (22.2)	25 (18.1)	55 (27.0)	15 (27.3)
4	61 (9.8)	24 (39.3)	45 (22.1)	19 (42.2)
5	28 (4.5)	24 (85.7)	8 (3.9)	2 (25)
6	5 (0.8)	5 (100)	4 (2.0)	3 (75)
AUC (95%CI)		0.86 (0.83–0.89)		0.73 (0.65-0.80)

AUC area under the curve. CI confidence interval. ICH intracerebral haemorrhage. SICH secondary intracerebral haemorrhage.

DISCUSSION

The SICH score has only moderate discriminative ability in a Dutch university hospital. NCCT classification, based on the presence of ICH characteristics suggestive of an underlying macrovascular cause and location of the ICH, was the strongest predictor of a macrovascular cause.

Our finding that the discriminative ability of the SICH score was lower in a Western European setting than in the United States is probably caused by differences in patient characteristics between the derivation and the validation cohort.

The patients in our cohort were younger and less often had impaired coagulation or hypertension. The yield of angiographic examinations is known to be higher in normotensive patients and those aged <55 years.[4,7] Indeed, the yield of angiographic examinations was higher in our cohort than in the derivation cohort.

A strength of our study is that we were able to study the external validity of the SICH score in a large cohort of patients with ICH on a different continent, with a different approach to performance of angiographic studies in patients with ICH. In addition, our study shows that NCCT characteristics suggestive of an underlying macrovascular cause may not always be easy to recognize and requires training.

A limitation of our study is that not all patients underwent digital subtraction angiography and small arteriovenous malformations and dural arteriovenous fistulas may have been missed.

In the Dutch setting, NCCT categorization should be used to determine whether there is a high likelihood of finding an underlying macrovascular cause in patients with ICH. Further studies are needed to determine whether performance of angiographic studies in patients with low-probability NCCT is cost-effective and to determine which type of angiographic study should preferably be applied.

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DATA SUPPLEMENT

Supplementary Table I Clinical and radiographic characteristics composing the Secondary IntraCerebral Hemorrhage (SICH) score.[1]

Determinant	Points
NCCT categorization	
High-probability*	2
Low-probability	0
Indeterminate	1
Age group	
18-45 years	2
46-70 years	1
≥ 71 years	0
Sex	
Female	1
Male	0
Neither known HTN nor impaired coagulation	
Yes	1
No	0

HTN hypertension. NCCT non-contrast computed tomography

* Criteria for high-probability NCCT: enlarged vessels or calcifications along the margins of the haematoma, or hyperattenuation within a dural venous sinus or cortical vein along the presumed venous drainage path of the haematoma.

Note:
Original regression coefficients: NCCT categorization 2.5345, age group 1.2657, sex 0.6192, Neither HTN nor impaired coagulation 1.5204

Kindly provided by dr. J.E. Delgado.

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Supplementary table II Baseline characteristics of the derivation and validation cohort and comparison of univariable odds ratios

		Derivation cohort			Validation cohort		
		Total ICH (%)	SICH (%)	OR (95% CI)	Total ICH (%)	SICH (%)	OR (95% CI)
All patients		623 (100)	91 (14.6)	n.a.	204 (100)	48 (23.5)	n.a.
Sex							
	Male	335 (53.8)	40 (11.9)	Ref.	120 (58.8)	31 (25.8)	Ref.
	Female	288 (46.2)	51 (17.7)	1.6 (1.0-2.5)	84 (41.2)	17 (20.2)	0.7 (0.4-1.4)
Age group							
	18-45 years	87 (14.0)	41 (47.1)	21.2 (10.2-44.3)	45 (22.1)	11 (24.4)	2.2 (0.7-6.5)
	46-70 years	263 (42.2)	39 (14.8)	4.2 (2.1-8.3)	113 (55.4)	31 (27.4)	2.5 (1.0-6.5)
	71-94 years	273 (43.8)	11 (4.0)	Ref.	46 (22.5)	6 (13.0)	Ref.
Haemorrhage site							
	Lobar	382 (61.3)	76 (19.9)	10.5 (3.8-29.2)	111 (54.4)	36 (32.4)	13.4 (3.1-58.2)
	Deep gray matter	173 (27.8)	4 (2.3)	Ref.	58 (28.4)	2 (3.4)	Ref.
	Infratentorial	68 (10.9)	11 (16.2)	8.2 (2.5-26.6)	35 (17.1)	10 (28.6)	11.2 (2.3-54.9)
Known HTN							
	Yes	368 (59.1)	21 (5.7)	Ref.	86 (42.2)	12 (14.0)	Ref.
	No	255 (40.9)	70 (27.5)	0.2 (0.1-0.3)	118 (57.8)	36 (30.5)	0.4 (0.2-0.8)
Impaired coagulation							
	Yes	204 (32.7)	8 (3.9)	Ref.	44 (21.6)	5 (11.4)	Ref.
	No	419 (67.3)	83 (19.8)	0.2 (0.1-0.4)	160 (78.4)	43 (26.9)	0.4 (0.1-0.9)
Neither HTN nor impaired coagulation							
	Yes	207 (33.2)	69 (33.3)	9.0 (5.3-15.1)	107 (52.5)	32 (29.9)	2.2 (1.1-4.3)
	No	416 (66.8)	22 (5.3)	Ref.	97 (47.5)	16 (16.5)	Ref.
NCCT categorization							
	Low	183 (29.4)	4 (2.2)	Ref.	66 (32.4)	2 (3.0)	Ref.
	Indeterminate	421 (67.6)	71 (16.9)	9.1 (3.3-25.3)	116 (56.9)	27 (23.3)	9.7 (2.2-42.3)
	High	19 (3.0)	16 (84.2)	238 (49-1161)	22 (10.8)	19 (86.4)	203 (32-1303)

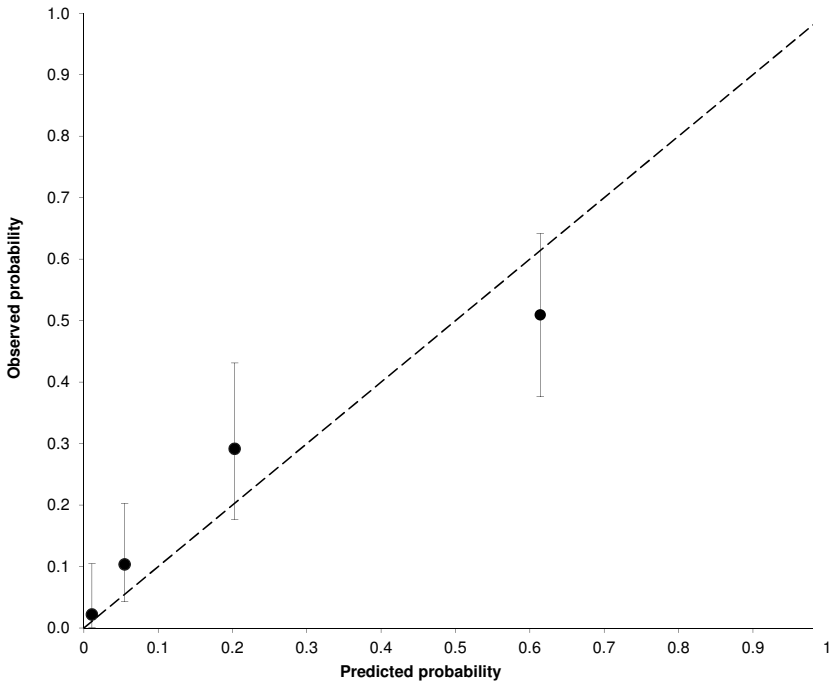
CI confidence interval. CTA CT angiography. HTN hypertension. ICH intracerebral haemorrhage. n.a. not applicable. NCCT non-contrast computed tomography. OR odds ratio. Ref. reference group. SICH secondary intracerebral haemorrhage

Supplementary Table III Identification of underlying vascular causes of intracerebral haemorrhage in the derivation and validation cohort

Vascular cause	Derivation cohort Number (% SICH)	Validation cohort Number (% SICH)
AVM	40 (44)	20 (42)
Aneurysm*	21 (23)	10 (21)
CVST	17 (19)	7 (15)
DAVF	8 (9)	10 (21)
Vasculopathy	3 (3)	0 (0)
Moyamoya	2 (2)	0 (0)
Other**	0 (0)	1 (2)
Total SICH (% total ICH)	91 (15)	48 (24)

AVM arteriovenous malformation. CVST cerebral venous sinus thrombosis. DAVF dural arteriovenous fistula. ICH intracerebral haemorrhage. SICH secondary intracerebral haemorrhage
* Includes mycotic aneurysms: 3 in the derivation cohort and 2 in the validation cohort
** Other: capillary teleangiectasia

Supplementary Figure Calibration plot of the predicted probabilities versus the observed proportions of patients with secondary intracerebral haemorrhage per quartile. The diagonal line reflects ideal calibration



Calibration plot of the predicted probabilities versus the observed proportions of patients with secondary intracerebral hemorrhage per quartile. The diagonal line reflects ideal calibration.

CHAPTER 5

Diagnostic yield and accuracy of CT angiography, MR angiography and digital subtraction angiography for detection of macrovascular causes of intracerebral haemorrhage – a prospective, multicentre cohort study

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ABSTRACT

Background and purpose: Assessment of the diagnostic value of early CT angiography (CTA), and of additional MR imaging/angiography (MRI/MRA) and digital subtraction angiography (DSA) in patients with non-traumatic intracerebral haemorrhage (ICH).

Methods: A prospective diagnostic cohort study was performed, with enrolment between July 2008 and July 2014, and one-year standardised follow up. Presence of a macrovascular cause was evaluated independently by three experienced neuroradiologists, unaware of clinical characteristics. We enrolled 298 patients, aged 18-70, excluding those >45 years with hypertension and ICH in basal ganglia, thalamus, or posterior fossa. Main outcome measures were diagnostic yield and positive predictive value (PPV) of CTA, and of additional MRI/MRA and DSA. We investigated clinical and radiological determinants of finding a macrovascular cause with logistic regression, and constructed a prediction score.

Results: We found a macrovascular cause in 69 of 298 patients (23%). Early CTA detected 51 of these, resulting in a yield of 17% (95% CI 13 to 22). On CTA+MRI/MRA we found two additional macrovascular causes (yield 18%, 14 to 23), and on CTA+MRI/MRA+DSA another 15 (yield 23%, 18 to 28). The most extensive strategy (CTA+MRI/MRA+DSA) failed to detect a cavernoma, which was identified on MRI during follow up (reference strategy). The PPV of CTA was 72% (60 to 82), of additional MRI/MRA 35% (14 to 62), and of additional DSA 100% (75 to 100). Predictors for a macrovascular cause were younger age, lobar or posterior fossa ICH location, and absence of signs of small vessel disease on non-contrast CT. The prediction score showed good discriminative ability for low, intermediate and high risk of a macrovascular cause (*c* statistic 0.83, 0.78 to 0.88).

Conclusion: CTA is an appropriate initial investigation to detect macrovascular causes in patients with ICH, but accuracy is modest. Additional MRI/MRA may find cavernomas or alternative diagnoses, but DSA is needed to diagnose macrovascular causes undetected by CTA or MRI/MRA. The DIAGRAM prediction score may be helpful for clinical practice to estimate the probability of finding a macrovascular cause.

INTRODUCTION

Non-traumatic intracerebral haemorrhage (ICH) accounts for 10-15% of all strokes[1,2] and is caused by an underlying macrovascular cause, including arteriovenous malformation (AVM), aneurysm, dural arteriovenous fistula (DAVF), cavernoma, and cerebral venous sinus thrombosis (CVST) in 1 of 4 to 7 patients.[3–5] Detection of these macrovascular causes is vital as this may have immediate therapeutic and prognostic implications.[6] The best strategy to identify a macrovascular cause in patients with ICH is unknown. CT angiography (CTA) for immediate angiographic assessment is easy to perform following identification of ICH on non-contrast CT (NCCT) and widely available in The Netherlands. The additional diagnostic value of magnetic resonance with MR imaging/angiography (MRI/MRA) in CTA negative patients is unknown, as is the additional value of digital subtraction angiography (DSA) after negative CTA, or after negative CTA and MRI/MRA. Baseline clinical and NCCT characteristics, such as age under 45 years and lobar ICH location, seem useful to identify patients with a high likelihood of an underlying macrovascular cause,[4,7–9] but there are no reliable data on how to select patients for (invasive) angiographic examination.[10–12] Consequently, large variability exists in the diagnostic approach in patients with ICH.[13]

In a prospective, multicentre study we aimed to determine diagnostic yield and accuracy of CTA as a single modality performed in the acute phase after NCCT, the yield of CTA and MRI/MRA combined, the yield of CTA, MRI/MRA, and DSA combined, and the additional accuracy of MRI/MRA and of DSA in CTA negative patients. We also investigated the influence of clinical and radiological characteristics on the probability of finding an underlying macrovascular cause and constructed prediction charts based on these characteristics for estimating the probability of finding a macrovascular cause in individual patients with ICH.

METHODS

Setting

The prospective, multicentre DIagnostic AngioGRAphy to find vascular Malformations (DIAGRAM) study included patients with non-traumatic ICH between 18 and 70 years of age, treated in 22 participating hospitals in the Netherlands between July 2008 and June 2014. Inclusion criteria were pre-stroke independence defined as a modified Rankin score <3[14] and the ability to undergo the investigations. Patients over 45 years with hyperten-

sion *and* ICH in the basal ganglia, the thalamus, or posterior fossa were excluded, because of the very low probability of finding an underlying macrovascular cause.[8]

Patients were considered to have hypertension when at least one of three criteria was met: documented history of hypertension, use of antihypertensive drugs prior to the ICH, or evidence of left ventricular hypertrophy on the electrocardiogram (ECG) on admission (Sokolow-Lyon criteria).[15] Other exclusion criteria were a diagnosis of a known macrovascular abnormality or tumour established before the ICH occurred, and use of oral anticoagulants with an INR >2.5 at the time of the ICH. For risk assessment we collected data on clinical condition at admission, smoking, alcohol consumption, drug abuse, patient and family history of cardiovascular disease, diabetes mellitus, use of anticoagulants or platelet inhibitors, use of antihypertensive drugs, and serum lipid levels. High alcohol intake was defined as consumption of four or more units per day.[16]

Approval was obtained from the medical ethics committee of the University Medical Center Utrecht, The Netherlands, as well as local approval from all participating hospitals. All participants had to provide written informed consent for inclusion in the study.

Procedures

CTA was performed within 7 days after the ICH, preferably within 48 hours after NCCT. If CTA was negative, MRI/MRA was performed four to eight weeks after the ICH, or earlier if indicated clinically. DSA was performed when CTA or MRI/MRA were inconclusive or negative. DSA was also performed in patients with an AVM or DAVF found on CTA or MRI/MRA, to plan treatment. DSA was not mandatory if an aneurysm,[17] CVST or an underlying cavernoma was identified on CTA or MRI/MRA.[18] All patients were followed for at least one year by telephone interviews at 4 weeks, 3 months and 12 months after ICH onset, to obtain information on complications of diagnostic procedures, recurrent ICH, and findings of angiographic assessment, follow-up imaging, neurosurgical inspection, and pathological examination. For patients who had during the study period a follow up of longer than 12 months as part of clinical practice, we collected data on recurrent ICH during this extended follow up and whether an underlying cause was found.

Imaging protocols

CTA was performed on a multidetector CT scanner with 16 or more slices. An unenhanced and late enhanced brain CT with 6 mm maximum slice thickness was performed as well as a CTA with contrast timing, from level C2 of the cervical spine upwards to the vertex.

MRI/MRA studies were done on 1.5T or 3T MR scanners and included a sagittal T1-weighted (T1W) scan, transversal T1W, T2 turbo-spin-echo (TSE), and T2 gradient-echo (GRE) scans, 3D multichunk gradient-echo time-of-flight (TOF) MRI/MRA after a single dose (0.1 mmol/kg) intravenous gadolinium contrast injection to increase distal vessel and venous opacification, and a transversal 3D T1W contrast-enhanced scan.

DSA consisted of selective catheterisation of the internal (ICA) and external (ECA) carotid artery or vertebral artery of the symptomatic hemisphere. On the asymptomatic side, catheterization of the common carotid artery was done with further catheterisation of the ICA and ECA if abnormalities were seen. Participating sites that did not routinely perform cerebral DSA referred their patients to centres with this expertise.

We collected data on complications of the investigations (type of complication and clinical consequences). All participating centres were asked to adhere to these imaging protocols with allowance of some local variation.

Patient involvement

No patients were involved in setting the research question or the outcome measures, nor were they involved in the design and implementation of the study. On inclusion, all patients were asked whether they wished to be informed about the findings of this study. If so, they will receive a letter with an outline of the main findings.

Radiologic assessment

Assessment of each NCCT, CTA, and MRI/MRA was performed independently by two of three experienced neuroradiologists (BKV, GAPdK or TDW), who were blinded for age, sex and clinical characteristics. The neuroradiologists reported on haematoma characteristics, signs of small vessel disease (SVD) or previous infarcts on NCCT (supplementary box 1), and presence of microbleeds or old ICH on MR imaging. Signs of SVD on NCCT was defined as the presence of white matter lesions, or an infarct in basal ganglia, thalamus or posterior fossa. Differences in reading were resolved by a third observer. When additional DSA was performed a third assessment was done reviewing the combination of CTA, MRI/MRA, and DSA (GAPdK). ICH volume was calculated with Analyze software (Biomedical Imaging Resource, Mayo Clinic, Rochester, MN), not including perihaematomal oedema.

Statistical analysis

Outcome was a macrovascular cause, including AVM, aneurysm, DAVF, developmental venous anomaly (DVA), CVST, and cavernoma. The reference standard was the best available evidence from all findings during follow-up.

Based on literature, the prevalence of macrovascular abnormalities in the study domain was estimated to be 40%.[8] We aimed to build a multivariable logistic regression model with 12 predictors. Based on the rule of thumb that each predictor would need 10 outcomes,[19] we would therefore need to include 120 patients with an underlying macrovascular cause, and thus 300 patients in total.

We calculated the probability of detection of a macrovascular cause in both the presence and absence of clinical and radiological characteristics (table 2), and calculated prevalence ratios with 95% confidence intervals (95% CIs) for each characteristic. Diagnostic accuracy measures were calculated twice: first with inconclusive results regarded as positive outcome, and subsequently with inconclusive results as negative outcome, with 95% CIs. We calculated the diagnostic yield of CTA as a single modality, of combined CTA and MRI/MRA, and combined CTA, MRI/MRA and DSA with 95% CIs. Patients in whom MRI/MRA or DSA was not performed because the previous modality had revealed a macrovascular cause, were incorporated in the calculation of yield of the diagnostic strategy.

With a multivariable logistic regression model we assessed which of six pre-defined determinants (patient characteristics: age as a continuous variable, hypertension, current smoking, heavy drinking and radiological characteristics: deep, lobar or posterior fossa location; and signs of small vessel disease on NCCT) discerned best between presence and absence of a macrovascular cause. Missing values were imputed for alcohol consumption and smoking.[20] We used restricted cubic spline functions and graphs to decide whether age could be analysed as a linear term or needed transformation.[21]

We selected variables for the final multivariable regression model with a backward selection procedure (exclusion if $p>0.20$). Subsequently, we used identified predictors of an underlying macrovascular cause in a prediction rule, and generated prediction charts to estimate the probability of the presence of a macrovascular cause in individual patients with ICH on admission. The point values of the risk score were based on the regression coefficients in the final multivariable regression model. For use in the prediction rule and charts, age was dichotomized at a value close to the mean.

Discrimination of both the original model and the prediction rule were assessed by *c* statistics with 95% CIs. The predicted probability of detection of a macrovascular cause within a

year after ICH was calculated per patient. A calibration curve was constructed by plotting the observed versus the predicted probability in quintiles, and the Hosmer–Lemeshow test was performed to assess goodness-of-fit of the model. Internal validation was done by a bootstrapping validation procedure; a shrinkage factor was applied to regression coefficients and the *c* statistic to correct for potential overestimation.[21,22] Analyses were performed with IBM SPSS Statistics (version 21.0) and R 2.15.2 software.
Results are reported according to the Standards for Reporting of Diagnostic Accuracy criteria for diagnostic tests.[23]

RESULTS

Between July 2008 and July 2014, 302 patients were included. In three patients CTA was not performed and in one patient MRI was contraindicated (protocol violations); these four patients were excluded from further analyses.
Mean age of the remaining 298 patients was 53.0 years (standard deviation 11.5), and median ICH volume 11 mL (interquartile range 4 to 26). Sixty-nine patients (23%) had an underlying macrovascular cause according to the reference standard (table 1). In 68 patients a macrovascular cause was identified by the diagnostic workup as described in the study protocol. This diagnostic workup failed to identify a cavernoma in one patient. This underlying cavernoma was identified by a repeated MRI during the follow-up period that was part of the reference strategy. The median duration of follow up of the 298 patients was 450 days (interquartile range (IQR) 371 to 1150). During this time seven patients had recurrent ICH, in none of these patients a macrovascular cause was found. One of these patients had been diagnosed with CAA after the initial diagnostic workup, another patient was diagnosed with CAA at the time of recurrent ICH, in two patients hypertensive vasculopathy was the presumed cause, and in three patients no underlying cause was found. Central reading detected one DAVF that was not detected at local reading.
Prevalences and prevalence ratios of a macrovascular cause according to presence or absence of clinical and radiological characteristics are listed in table 2.

Table 1 Aetiology of intracerebral haemorrhage in 298 patients

Aetiology	number of patients
Macrovascular causes	
Arteriovenous malformation	34
Dural arteriovenous malformation	13
Cavernoma	10
Cerebral venous sinus thrombosis	4
Aneurysm	7
Developmental venous anomaly (DVA)*	1
Subtotal	69
Other causes	
Probable cerebral amyloid angiopathy[30]	18
Hypertensive vasculopathy†	36
Neoplasm	3
Cocaine use	1
Haemorrhagic infarction	2
Unknown‡	169
Subtotal	229

* Partially thrombosed large DVA without evidence for an adjacent cavernoma
† Hypertensive vasculopathy was defined as an intracerebral haemorrhage in basal ganglia, thalamus or posterior fossa in the presence of hypertension
‡ In 30 of these patients a lobar haemorrhage was observed in the presence of hypertension

Table 2 Prevalences and prevalence ratios of a macrovascular cause in 298 patients with intracerebral haemorrhage according to presence or absence of clinical and radiological characteristics

	Prevalence macrovascular cause		
	characteristic present (%)	characteristic absent (%)	prevalence ratio (95%CI)
Clinical characteristics			
Age <50 years	42/112 (37.5)	27/186 (14.5)	2.58 (1.69 to 3.94)
Male sex	45/185 (24.3)	24/113 (21.2)	1.15 (0.74 to 1.77)
Glasgow coma score on admission			
3-11	10/28 (35.7)	34/165 (20.6)*	1.73 (0.97 to 3.10)
12-14	12/55 (21.8)	34/165 (20.6)	1.06 (0.59 to 1.90)
verbal score not applicable (aphasia)	13/50 (24.0)	34/165 (20.6)	1.26 (0.72 to 2.20)
Alcohol intake†			
none	24/114 (21.1)	41/144 (28.5)‡	0.74 (0.48 to 1.15)
high (≥4/day)	4/36 (11.1)	41/144 (28.5)	0.39 (0.15 to 1.02)
Current smoking	20/72 (27.8)	49/226 (21.7)	1.28 (0.82 to 2.00)
Drug abuse prior to ICH§	5/12 (41.7)	64/283 (22.6)	1.84 (0.91 to 3.73)
Hypertension	16/95 (16.8)	53/203 (26.1)	0.65 (0.39 to 1.07)
Diabetes mellitus I	1/18 (5.6)	68/279 (24.6)	0.23 (0.03 to 1.55)
Hypercholesterolemia¶	5/26 (19.2)	37/176 (21.0)	0.91 (0.40 to 2.12)
History of CVD†	2/12 (16.7)	67/282 (23.8)	0.70 (0.19 to 2.53)
Family history of CVD**	12/55 (21.8)	51/228 (22.4)	0.98 (0.56 to 1.70)
Oral anticoagulants§	0/5 (0.0)	69/291 (23.7)	P = 0.59††
Daily antiplatelet use	3/31 (9.7)	68/267 (25.5)	0.38 (0.13-1.14)
Radiological characteristics			
NCCT assessment			
ICH location			
basal ganglia or thalamus	5/85 (5.9)	49/178 (27.5)‡‡	0.21 (0.09 to 0.51)
posterior fossa	15/35 (42.9)	49/178 (27.5)	1.56 (0.99 to 2.44)
ICH volume > 11 mL (median)	34/148 (23.0)	35/150 (23.3)	0.98 (0.65 to 1.49)
Subarachnoid haemorrhage	21/56 (37.5)	48/242 (19.8)	1.89 (1.24 to 2.88)
Extension to frontal operculum	6/12 (50.0)	63/286 (22.0)	2.27 (1.24 to 4.16)
Intraventricular extension	23/71 (32.4)	46/227 (20.3)	1.60 (1.05 to 2.44)
Mass effect	45/191 (23.6)	24/107 (22.4)	1.05 (0.68 to 1.62)
Oedema	39/192 (20.3)	30/107 (28.0)	0.72 (0.48 to 1.10)
Haematoma density, homogeneous	55/239 (23.0)	14/59 (23.7)	0.97 (0.58 to 1.62)
White matter lesions	4/113 (3.5)	65/185 (35.1)	0.10 (0.04 to 0.27)
Hypodensity in basal ganglia, thalamus or posterior fossa	1/37 (2.7)	68/261 (26.1)	0.10 (0.01 to 0.72)
Small vessel disease§§	4/120 (3.3)	65/178 (36.5)	0.09 (0.03 to 0.24)
Enlarged vessels along ICH margins	11/13 (84.6)	58/285 (20.4)	4.16 (3.00 to 5.76)

	Prevalence macrovascular cause		
	characteristic present (%)	characteristic absent (%)	prevalence ratio (95%CI)
Hyperattenuation within dural venous sinus or cortical vein	6/10 (60.0)	63/288 (21.9)	2.74 (1.58 to 4.76)
MRI assessment			
Microbleeds II	0/63 (0.0)	40/163 (24.5)	P < 0.01††
Previous ICH II	0/30 (0.0)	40/196 (20.4)	P < 0.01††
White matter lesions¶¶	9/147 (6.1)	34/109 (31.2)	0.20 (0.10 to 0.39)
Previous infarct¶¶	1/70 (1.4)	42/186 (22.6)	0.06 (0.01 to 0.45)

CI confidence interval. CVD cardiovascular disease. ICH intracerebral haemorrhage

* GCS 15 was taken as reference
† Missing values for 4 patients
‡ Sporadic or moderate was taken as reference
§ Missing values for 3 patients
I Missing values for 1 patient
¶ Total cholesterol was available for 202 patients, cut-off value 217 mg/dL
** Missing values for 15 patients
†† P value Fisher's exact test
‡‡ Lobar was taken as reference
§§ Defined as the presence of white matter lesions, or an ischaemic lesion in the basal ganglia, thalamus or posterior fossa
II Assessment was possible for 226 patients
¶¶ Assessment was possible for 256 patients

Radiological assessment

CTA was assessed in 291 of 298 patients (98%). CTA was of insufficient quality to assess in seven patients (figure 1). CTA acquisition was stopped in one patient who was unable to lie still; in the other six patients the vessels in the area of the haematoma were not depicted because CTA was limited to the circle of Willis. MRI/MRA was successfully performed in 255 patients (86%). Three of 154 DSAs were of insufficient quality to assess. The main reason for not performing MRI/MRA was immediate diagnostic and therapeutic workup following positive CTA (supplementary box 2). The main reason for not performing DSA in patients with negative CTA was an alternative diagnosis on MRI/MRA, and reluctance of either patients or their treating physicians (supplementary box 3). The median interval between NCCT and CTA was 1 day (IQR 0 to 2), between CTA and MRI/MRA was 46 days (IQR 32 to 64), and between MRI/MRA and DSA was 33 days (IQR 3 to 60).

Of the 291 CTAs that were assessed, 59 were scored positive, 12 inconclusive, and 220 negative (figure 1). Including 'inconclusive' CTAs as a positive test result, positive predictive value (PPV) was 74% (95% CI 62 to 84), and negative predictive value (NPV) 92% (88 to 95%) (table 3A). In 51 of 298 patients a macrovascular cause was diagnosed with CTA, resulting in a yield of 17% (13 to 22), in 47 of these patients CTA was scored positive and in 4 patients inconclusive (table 3A).

Additional MRI/MRA was performed in 214 of 232 patients with a negative or inconclusive CTA test result. Of these 214 MRI/MRAs, 6 were scored positive, 11 inconclusive, and 197 negative. With inconclusive MRI/MRA included in the positive results, PPV was 32% (13 to 57%), and NPV was 93% (89 to 96%). In 53 of 298 patients a macrovascular cause was detected combined CTA and MRI/MRA, giving a yield of 18% (14 to 23). In 51 of these patients MRI/MRA (or CTA) was scored positive and in 2 patients MRI/MRA was inconclusive.

DSA was assessed in 103 of 232 patients with negative or inconclusive CTA test results, of whom 97 patients also had negative or inconclusive MRI/MRA test result. DSA was positive in 13 of these 97 patients (13%), resulting in a PPV of 100% (75 to 100%) and a NPV of 100% (96 to 100%) (table 3A). The yield of combined CTA, MRI/MRA and DSA was 23% (18 to 23), with a macrovascular cause detected in 68 of 298 patients. Accuracy of the combination of CTA and MRI/MRA, and of the combination of CTA, MRI/MRA and DSA are listed in table 3B.

An alternative explanation for the ICH was found, mainly on MRI, in 59 of 230 patients (26%) without a macrovascular cause (table 1). None of the 63 patients with microbleeds had an underlying macrovascular cause (table 2). In two patients an incidental aneurysm was found that was unrelated to the ICH

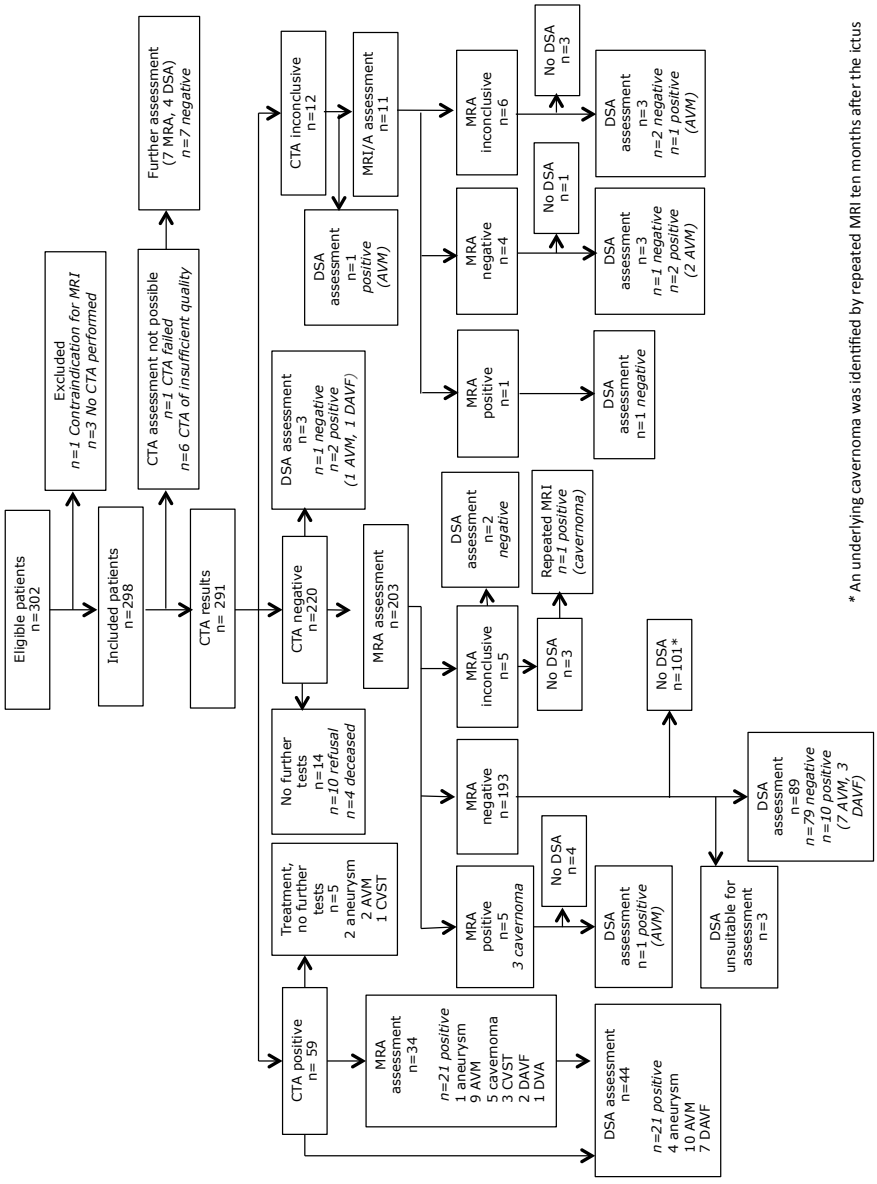

Figure 1 Flow chart of performed angiographic exams between July 2008 and July 2014

Table 3A Results of assessment of CTA, and of additional MRI/MRA and DSA

	Reference standard* positive	Reference standard* negative		Accuracy†, % (95%CI)	Accuracy‡, % (95%CI)
n=291					
CTA positive	47	12	Sensitivity	74 (62 to 84)	68 (56 to 79)
CTA negative	18	202	Specificity	91 (86 to 94)	95 (91 to 97)
CTA inconclusive	4	8	PPV	72 (60 to 82)	80 (67 to 89)
			NPV	92 (88 to 95)	91 (86 to 94)
CTA negative test result					
n=214§					
MRI/MRA positive	4	2	Sensitivity	32 (13 to 57)	21 (6 to 46)
MRI/MRA negative	13	184	Specificity	94 (90 to 97)	99 (96 to 100)
MRI/MRA inconclusive	2	9	PPV	35 (14 to 62)	67 (23 to 95)
			NPV	93 (89 to 96)	93 (88 to 96)
CTA negative test result					
n=103§					
DSA positive	17	0	Sensitivity	100 (80 to 100)	n.a.
DSA negative	0	86	Specificity	100 (96 to 100)	n.a.
DSA inconclusive	0	0	PPV	100 (80 to 100)	n.a.
			NPV	100 (96 to 100)	n.a.
CTA+MRI/MRA negative test results					
n=97I					
DSA positive	13	0	Sensitivity	100 (75 to 100)	n.a.
DSA negative	0	84	Specificity	100 (96 to 100)	n.a.
DSA inconclusive	0	0	PPV	100 (75 to 100)	n.a.
			NPV	100 (96 to 100)	n.a.

CI confidence interval. n.a. not applicable. NPV negative predictive value. PPV positive predictive value

* The reference standard was the best available evidence from all findings during follow-up
† Inconclusive result regarded as positive outcome
‡ Inconclusive result regarded as negative outcome
§ Only patients with negative or inconclusive CTA were included in these calculations
I Only patients with negative or inconclusive CTA and MRI/MRA were included in these calculations

Complications

None of the patients had a complication of CTA or MRI/MRA. DSA complications included three patients with a groin haematoma (2%) and three patients with (possible) thrombo-embolic complications (2%); one with transient aphasia, one with a permanent visual deficit (homonymous hemianopia), and one with transient decreased consciousness. The proportion of patients with a complication with permanent sequelae from the DSA was 0.6% (1/154).

Multivariable logistic regression, prediction rule and charts

In the multivariable logistic regression model ICH in the posterior fossa was the strongest predictor (OR 13.0, 95%CI 3.7 to 46.5, reference: basal ganglia or thalamus), followed by the absence of signs of small vessel disease on NCCT (OR 8.5, 95% CI 2.9 to 25.3), lobar ICH (OR 5.5, 95% CI 2.0 to 15.3), and age (OR 0.96, 95% CI 0.93 to 0.99).

After correction of the regression coefficients with the shrinkage factor (0.87), we found good discriminative ability for both the final model (c statistic 0.83, 0.78 to 0.88, see supplementary figure 1), and the prediction rule (c statistic 0.83, 0.78 to 0.88). The calibration plot showed a good model fit (supplementary figure 2), which was confirmed by non-significance of the Hosmer–Lemeshow test (p=0.99).

The point values of the prediction rule were based on the following regression coefficients: 1.2 for age ≤ 50 years (1 point), 2.1 for absence of small vessel disease (2 points) 1.8 for lobar ICH location (2 points), and 2.8 for posterior fossa ICH location (3 points); deep location was taken as reference. The prediction rule is presented in table 4, and plotted against predicted probability in figure 2.

We generated prediction charts for patients aged 18-50 years old and patients aged 51-70. Approximate probabilities of an underlying macrovascular cause for individual patients according to their age, ICH location, and absence of signs of small vessel disease can be found in figure 3.

Table 3B Results of assessment of CTA, of the combination of CTA and MRI/MRA, and of the combination of CTA, MRI/MRA, and DSA

	Reference standard* positive	Reference standard* negative		Accuracy†, % (95%CI)	Accuracy‡, % (95%CI)
CTA					
n=291					
Test result positive	47	12	Sensitivity	74 (62 to 84)	68 (56 to 79)
Test result negative	18	202	Specificity	91 (86 to 94)	95 (91 to 97)
Test result inconclusive	4	8	PPV	72 (60 to 82)	80 (67 to 89)
			NPV	92 (88 to 95)	91 (86 to 94)
Combination CTA+MRI/MRA					
n=273					
Test results positive	51	11	Sensitivity	82 (71 to 90)	76 (64 to 86)
Test results negative	12	179	Specificity	91 (86 to 95)	95 (91 to 97)
Test results inconclusive	4	16	PPV	77 (65 to 86)	82 (70 to 91)
			NPV	94 (89 to 97)	92 (88 to 96)
Combination CTA+MRI/MRA+DSA					
n=151					
Test results positive	99	0	Sensitivity	99 (95 to100)	n.a
Test results negative	1§	51	Specificity	100 (93 to100)	n.a
Test results inconclusive	0	0	PPV	100 (96 to100)	n.a
			NPV	98 (90 to 100)	n.a

CI confidence interval. n.a. not applicable. NPV negative predictive value PPV positive predictive value

* The reference standard was the best available evidence from all findings during follow-up
† Inconclusive result regarded as positive outcome
‡ Inconclusive result regarded as negative outcome
§ An underlying cavernoma was identified by repeated MRI ten months after the ictus

Table 4 Calculation of the DIAGRAM prediction score

	Points
Age ≤ 50 years	1
Absence of small vessel disease*	2
ICH location	
Deep	0
Lobar	2
Posterior fossa	3

ICH intracerebral haemorrhage
An individual DIagnostic AngioGRAphy to find vascular Malformations (DIAGRAM) prediction score is the sum of the points assigned to the predictors. The maximum score is 6 points.

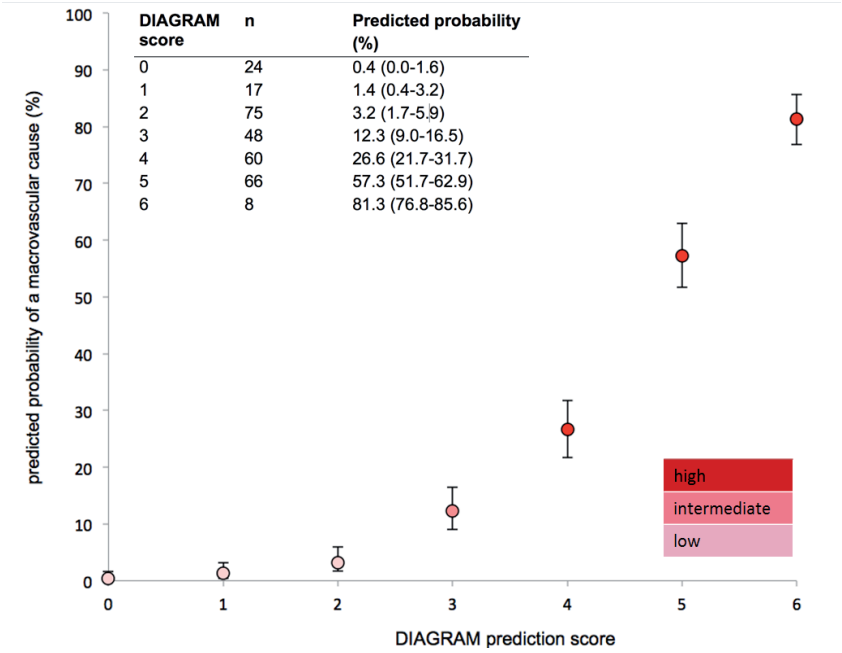

Figure 2 Predicted probability of a macrovascular cause of intracerebral haemorrhage according to the DIAGRAM prediction score

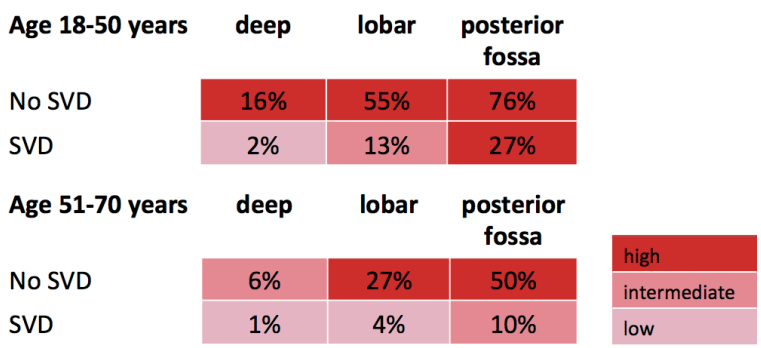

Figure 3 Prediction charts for assessment of the probability of an underlying macrovascular cause in individual patients with intracerebral haemorrhage

SVD = small vessel disease on non-contrast CT, defined as the presence of white matter lesions or an infarct in basal ganglia, thalamus or posterior fossa

DISCUSSION

This study shows that in preselected patients with non-traumatic ICH, the overall yield of CTA and MRI/MRA for detection of a macrovascular cause is slightly higher than the yield of early CTA as a single modality (18 versus 17%), whereas the combination of CTA, MRI/MRA and DSA increases the overall yield to 23%. DSA is accurate in detection AVMs and DAVF in patients in whom the underlying cause could not be found with CTA and MRI/MRA.

ICH location in the posterior fossa or lobar region is an important predictor of an underlying macrovascular cause, as is absence of small vessel disease on initial NCCT. The probability of finding an underlying macrovascular cause diminishes with increasing age.

The DIAGRAM prediction score showed good discriminative ability and calibration, and can help to select in which patients to proceed with angiographic assessment. The clinical implications of a low (<5%), intermediate (5-15%) or high (>15%) probability will depend on the available resources in a specific setting, and other factors such as age, clinical condition and comorbidity. In the Dutch situation, performance of CTA early after the haemorrhage is feasible in all patients with ICH. A negative CTA in patients with a low probability would then mean no further tests to look for a macrovascular cause, whereas additional DSA assessment to detect a small AVM or DAVF is indicated in patients with intermediate and high probability. After a negative CTA, MRI/MRA can identify patients with a cavernoma or an alternative diagnosis such as a neoplasm or cerebral amyloid angiopathy, but is not useful to exclude an AVM or DAVF.

Based on the finding that all but one macrovascular lesions were detected at local reading, a strategy with independent assessment of vascular imaging studies by a second reader is not indicated.

In 51 of 68 patients (74%), the underlying macrovascular cause was detected by CTA in the acute phase. A recent Cochrane review reported a high sensitivity (pooled estimate 0.95, 95% CI 0.90 to 0.97) and specificity (0.99, 95% CI 0.95 to 1.00) of CTA[24], but the authors noted that the test accuracy was likely inflated by methodological shortcomings in the included studies. In our study, CTA sensitivity (74%) and specificity (91%) were indeed lower than previously reported.[3,5,25] This can be related to differences in both study populations and outcomes between our study and others. In one previous study, the study population was younger (mean age 48 years), and thus more selected, resulting in a prevalence of macrovascular causes as high as 33%.[25] Two other studies,[3,5] both with a retrospective

design, reported on a less selected population with macrovascular cause and found prevalences of 13%[5] and 15%,[3] and therefore more true negative results. Another explanation for the lower sensitivity and specificity of CTA in our study compared to others is that we, unlike previous studies,[3,5,25] regarded an underlying cavernoma as a positive outcome; half of the detected cavernomas in our study were not identified on early CTA.

Diagnostic strategies in patients with ICH vary among specialties and countries.[13] Some have suggested CTA as initial exam,[26] whereas others prefer to start with MR.[27] The Cochrane review reported high accuracy for MRI/MRA for detection of macrovascular causes of ICH as a first diagnostic modality.[24] In our study, MRI/MRA was performed four to eight weeks after ICH in patients in whom CTA had not shown a cause of the ICH. Therefore, our study does not provide information on the diagnostic accuracy of MRI/MRA as an initial investigation after NCCT.

In this study, none of the patients with microbleeds had a macrovascular cause of the ICH. The predictive value of presence of microbleeds independently of signs of small vessel disease on NCCT cannot be determined from our study because DSA was not performed in all patients with negative CTA and microbleeds on MRI.

Absence of hypertension is a known predictor of an underlying macrovascular cause,[6-8] which could not be shown in the present study. This is not surprising since patients older than 45 years of age with a haemorrhage in basal ganglia, thalamus, or posterior fossa in the presence of hypertension were excluded, and therefore in our study prevalence of hypertension was relatively low compared with other studies.[5,8,28,29]

Strengths and weaknesses

Strengths of this study are the prospective design, and the standardised CTA, MRI/MRA and DSA workup in a relatively large cohort of patients in a large number of hospitals. Other strengths are centralized reading, including quality control of the scans at the same time allowing some variation in scanning parameters. The participation of both general and university hospitals and the pragmatic approach contribute to the external validity of our results. The pragmatic design of this study also has its limitations. We excluded patients older than 70 years, as there was little chance of finding a macrovascular cause.[7,8] Therefore, we could not assess if any determinants could identify which elderly patients should undergo additional DSA. Another limitation is that not all patients with negative CTA and MRI/MRA underwent DSA. This is largely attributable to reluctance of patients and treating physicians because of the (small) complication risk of DSA. Though prior

probability was lower in patients in whom no DSA was performed, as they were on average older and more often had a deep ICH location, we cannot rule out that some small AVMs or DAVFs may have been missed. Because of the lower prior probability a large effect on the prediction model is unlikely. Another limitation is the validity of 'best available evidence' as a reference standard, which incorporated the results of all performed tests, information from neurosurgical inspection, pathological examination and additional findings during one-year follow-up.

Longer-term follow-up data or repeated investigations in all patients could have provided additional information on detection of macrovascular causes after the initial diagnostic workup.

Findings in context of similar studies

Two prediction scores have been developed previously to identify patients with high risk of an underlying macrovascular cause of ICH. The DIAGRAM prediction score is the first to combine the prospectively and systematically collected diagnostic results of CTA, MRI/MRA, and DSA. The DIAGRAM prediction score is also the first to demonstrate the independent predictive value of absence of signs of small vessel disease on NCCT for finding a macrovascular cause.

Implications

Our results indicate that CTA is an appropriate initial investigation for non-traumatic ICH, as it identifies around three quarters of macrovascular causes of ICH, is widely available, feasible in patients with a poor clinical condition on admission, and has few complications (none in our study). However, we found that accuracy of CTA is lower than previously reported. Additional MRI/MRA rarely detects additional macrovascular causes after negative CTA but it does provide important information on alternative diagnoses such as cerebral amyloid angiopathy. DSA is able to detect with high accuracy small macrovascular causes that have not been detected by CTA. The proposed DIAGRAM prediction charts identify patients with a low, intermediate, or high risk of a macrovascular cause. The clinical implications of these estimated risks may depend on the available resources in different settings.

Unanswered questions and future research

It should be noted that our prediction score was made for a preselected domain, excluding hypertensive ICH in patients older than 45 years of age, patients taking anticoagu-

lant drugs, and those unable to undergo angiographic investigations. The score's generalizability needs to be confirmed by external validation in comparable domains in settings different from the Dutch healthcare system. Moreover, future research will be helpful to establish the diagnostic value of MRI/MRA as an initial diagnostic modality after NCCT, and to determine whether further evaluation with DSA is indicated in patients with microbleeds on MRI.

What is already known on this topic

- Detection of macrovascular causes in patients with intracerebral haemorrhage (ICH) has important therapeutic and prognostic implications
- Large variability exists in the diagnostic approach to identify a macrovascular cause in patients with ICH
- The diagnostic accuracy of both CTA and MRI/MRA - with digital subtraction angiography (DSA) as the reference standard - appears high, but methodological shortcomings of previous studies may have led to overestimation of diagnostic accuracy
- Baseline clinical and radiological characteristics seem useful to identify patients with a high likelihood of an underlying macrovascular cause

What this study adds

- Accuracy of CT angiography (CTA) for the detection of macrovascular causes of ICH is modest, less than previously assumed, and warrants DSA when CTA is negative, except in those with a low probability on the DIAGRAM prediction score.
- The additional value of MRI/MRA after negative CTA consists mainly of diagnosis of non-macrovascular causes of ICH
- The DIAGRAM prediction rule, based on age, location, and presence of signs of small vessel disease on non-contrast CT, can help selecting patients with ICH in whom angiographic workup is indicated

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Supplementary box 1 Assessed radiological characteristics on admission non-contrast CT (NCCT)

- Location of the haematoma (lobar, basal ganglia/thalamus, brain stem, or cerebellum), and extension to the ventricles, subarachnoid space, or frontal operculum if applicable (only for temporal lobe haematomas with extension to the Sylvian fissure[1]).
- Features of the haematoma itself: density (homogeneous or inhomogeneous), presence of mass effect and oedema.
- Clues of the presence of an underlying macrovascular cause: enlarged vessels or calcifications along ICH margins, or hyperattenuation within a dural venous sinus or cortical vein.[2]
- Presence of white matter lesions (WML), and if so: WML location (periventricular, subcortical, or both) and severity (<1 cm, >1 cm, or confluent); presence of a hypodensity elsewhere on NCCT, and if so: location. Signs of small vessel disease (SVD) on NCCT was defined as the presence of white matter lesions, or an ischaemic lesion in basal ganglia, thalamus or posterior fossa.

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Supplementary box 2 Sample size calculation

The prevalence or prior probability of a vascular malformation as cause of spontaneous ICH in this specific group of patients is estimated to be 40%.[1] Sensitivity and specificity of CTA, MRI/MRA and DSA for the detection of vascular malformations in patients with spontaneous ICH are not known. However, if we estimate, based on the (alas incomplete!) information of our retrospective pilot study (see below), a sensitivity of 50% and a specificity of 95% for the combination of CTA or MRI for detecting vascular malformations and for DSA of 95% and 98% respectively, we would be able to find a positive predictive value of 87% (95% CI 77 to 94%) for CTA or MRI and of 97% (95% CI, 92 to 99%) for DSA. This would mean an increase in positive predictive value of DSA in comparison with CTA or MRI of 10% (95% CI 1 to 18%). The negative predictive value would increase even more, by 23% (95% CI 17 to 29) comparing DSA (negative predictive value 97%, 95% CI 93 to 99) and the combination of CTA or MRI (negative predictive value 74%, 95% CI 68 to 80%).

Results pilot study
In a retrospective study of 451 patients admitted to the UMCU because of ICH between 1990 and 1998, DSA showed a vascular malformation as cause of the ICH in 30 (27%; 95% CI 19-35) of the 112 patients in whom either a CTA or MR investigation was negative. However, in this study CTA or MR studies and DSA were not performed in every patient and also patients with a history of hypertension and ICH in the basal ganglia, thalamus or posterior fossa were included. For these reasons it is impossible to draw any firm conclusions from this pilot study on what diagnostic tests should be performed in patients with ICH to find or exclude a vascular malformation.

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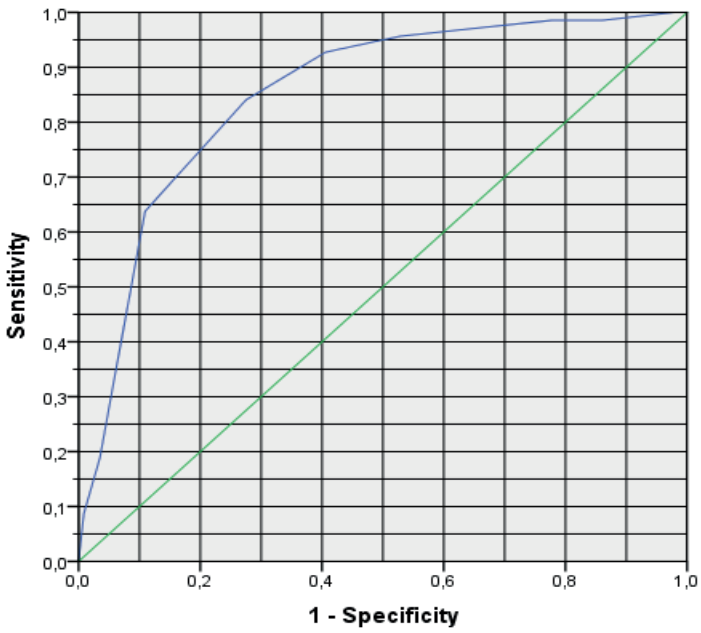
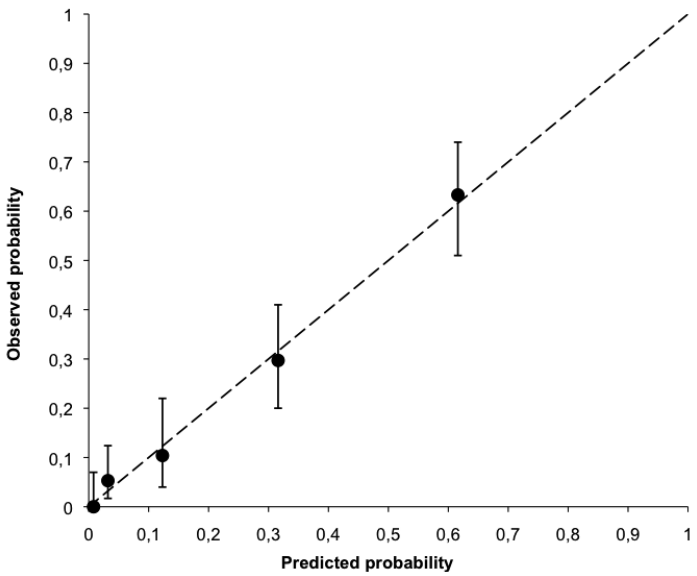


Supplementary figure 1 Receiver operating characteristic (ROC) curve of the final multivariable logistic regression model. The AUC reflects how well the model discriminates between patients with and without an underlying macrovascular cause of intracerebral haemorrhage

Area under the curve (AUC) 0.85 (95% CI 0.80-0.90). AUC after correction for optimism (0.02): 0.83 (0.78-0.88).



Supplementary figure 2 Calibration plot of the predicted probabilities versus the observed proportions of patients with an underlying macrovascular cause per quintile. Ideal calibration is reflected by the diagonal line

Reasons for not performing MRI/MRA (n=43)
- Direct performance of DSA after CTA (n=24)
- Refusal of further tests after negative CTA (n=10)
- Direct treatment after positive CTA (n=5)
- Deceased before MRI/MRA could be performed (n=4)

Reasons for not performing DSA (n=144)
- No additional value of DSA after CTA or MRI/MRA had revealed the diagnosis (n=52): an AVM (n=3, surgically treated), CVST (n=3), aneurysm (n=2), cavernoma (n=10), neoplasm (n=2), and haemorrhagic infarction (n=1). In the remaining 31 patients intracerebral haemorrhage was attributed to hypertensive vasculopathy (n=19) or cerebral amyloid angiopathy (n=12) by the treating physician.
- DSA was advised, patient refusal (n=27)
- Reluctance of treating physician to perform DSA (n=24)
- Death during hospital stay before further investigations were performed (n=4)
- Refusal of all further tests after CTA (n=8)
- Condition of the patient considered too poor for examination with DSA (n=3)
- Unclear (n=26)

Supplementary box 3 Reasons for not performing MRI/MRA and DSA in patients with negative or inconclusive CTA

CHAPTER 6

The optimal diagnostic strategy for non-traumatic intracerebral haemorrhage: a cost-effectiveness analysis

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ABSTRACT

Background and purpose: The optimal strategy to rule in or out macrovascular causes in patients with intracerebral haemorrhage (ICH) is unknown. We assessed the effects and costs of additional MR imaging/angiography (MRI/MRA) and additional digital subtraction angiography (DSA) following early CT angiography (CTA) in patients with ICH aged 18-70.

Methods: In a Markov decision-analytic model and Monte Carlo simulation we assessed differences in health outcomes and costs between four diagnostic strategies: CTA (strategy 1) vs. CTA and MRI/MRA (strategy 2) vs. CTA+MRI/MRA+DSA, with DSA in selected patients (strategy 3) and with DSA in all patients (strategy 4). Diagnostic accuracy and quality-adjusted life-years (QALYs) were derived from a prospective cohort study; other determinants were based on the literature. We compared QALYs, morbidity and mortality as a result of diagnostic procedures, treatment and adverse events, and costs, and assessed how these were influenced by prevalence of macrovascular causes.

Results: Compared with strategy 1, strategies 2-4 were not cost-effective: strategy 2 resulted in similar health outcomes at increased costs, strategies 3-4 resulted in health loss due to morbidity and mortality from diagnostic and therapeutic procedures at increased costs. Strategy 1 is less likely to be cost-effective when prevalence is as high as 40%.

Conclusion: Adding MRI/MRA and DSA to CTA as single investigation in the diagnostic workup of patients with ICH does not improve health outcomes but does increase healthcare costs.

INTRODUCTION

Non-traumatic intracerebral haemorrhage (ICH) accounts for 10-15% of all strokes.[1] Detection of macrovascular causes such as arteriovenous malformations (AVMs) and dural arteriovenous fistulae (DAVF) is important because of their therapeutic and prognostic implications.[2]

CT angiography (CTA), MR imaging/angiography (MRI/MRA) and digital subtraction angiography (DSA) can detect these and other macrovascular causes, but data on comparison of the diagnostic value of CTA, MRI/MRA, and DSA are scarce.[3–5] It is unclear which of these investigations should be done and when, to adequately detect the cause of the ICH. In a recent prospective multicentre study, we found a sensitivity of CTA of 74% and a specificity of 91%. We also found that the diagnostic value of additional MRI/MRA after negative CTA with respect to detection of macrovascular causes was minimal, although MRI enabled alternative diagnoses like cerebral amyloid angiopathy. DSA was highly accurate and detected small AVMs and DAVFs which had not been identified with CTA and MRI/MRA.(Chapter 5)

Differences in diagnostic yield and accuracy of CTA, MRI/MRA and DSA, as a single investigation or in combination as a diagnostic strategy, may result in differences in patient management, and thereby clinical outcome and costs. It is unknown whether performing MRI/MRA following negative CTA, and performing DSA following negative MRI/MRA improves health outcomes and at acceptable costs.

We therefore assessed in a Markov decision-analytic model the (long term) effectiveness, costs, and cost-effectiveness of three commonly used strategies to find or exclude the presence of a macrovascular cause: CTA as a single modality, versus the combination of CTA and MRI/MRA, versus the combination of CTA, MRI/MRA, and DSA in selected patients. To study the effect of selecting patients for DSA through MRI/MRA results, we added a fourth strategy to the model data in which DSA is performed in *all* patients with negative CTA and MRI/MRA.

METHODS

In a prospective cohort study of patients between 18 and 70 years of age (mean age 53 ± 11, 65% men), we assessed the diagnostic yield and accuracy of CTA, and of additional MRI/MRA and DSA, for detection of macrovascular causes in patients with non-traumatic ICH. 69 of 298 patients (23%) had a macrovascular cause.(Chapter 5) For the present study, the five most prevalent macrovascular causes were taken into account: aneurysm (7 patients), AVM (34 patients), cavernoma (10 patients), DVA (1 patient), CVST (4 patients), and DAVF (13 patients). Incidental findings, such as a DVA or aneurysm distant from the haematoma, were not taken into account.

CTA was performed in the acute phase, and MRI/MRA and DSA were performed four to eight weeks later. Questionnaires regarding quality of life (EQ-5D, www.euroqol.org) were administered by telephone interviews by a single assessor at 4 and 12 weeks, and 1 year after the ictus. The modified Rankin score (mRS)[6] was assessed at 12 weeks and 1 year by the same person.

Markov model

We developed a Markov decision-analytic model (TreeAge Software Pro 2014 version) to assess differences in health outcomes and costs between the diagnostic strategies.(Figure 1) Input parameters are listed in Table 1 and the Supplemental table.

Health states of this model were "well with treated macrovascular cause", "well with untreated macrovascular cause", "well with other cause of ICH", "disabled" and 'dead. All patients independent for activities of daily life (mRS ≤ 2) were classified as "well", dependent patients (mRS ≥3) were classified as "disabled", and utilities (i.e. quality of life values) were assigned accordingly.

Events causing transitions between health states were adverse events (recurrent ICH or focal deficits unrelated to recurrent ICH), disabling or fatal complications of diagnostic or therapeutic procedures, and death from other causes.

The health state "well with untreated macrovascular cause" was split in ten categories: independent patients in whom the outcome of the diagnostic strategy was false-negative (FN) started in one of the five "well with untreated macrovascular cause FN" health states (one health state of each macrovascular cause, i.e. "well with untreated aneurysm FN" etc); patients with true positive (TP) test results in whom treatment was not possible or had failed started in one of the five "well with untreated macrovascular cause TP" health states.

We incorporated higher medical costs for follow-up of patients with a known but untreated macrovascular cause than for follow up of patients in whom the macrovascular cause had been missed.

The effectiveness of the diagnostic strategies was expressed in terms of health outcomes as the number of quality-adjusted life years (QALY's). The utilities at 6 and 9 months were interpolated linearly using the utilities derived from the EQ-5D observations at 3 and 12 months. We assigned costs to each test, treatment, adverse event, and health state.

Additional DSA was performed in 49% of patients with negative CTA and MRI/MRA in our cohort study. The main reasons for not performing DSA were: no indication for DSA after CTA or MRI/MRA had revealed the diagnosis, and reluctance of the patient or treating physician to perform DSA.(Chapter 5) This observation was incorporated in strategy 3, whereas in strategy 4 we modeled that all patients with negative CTA and MRI/MRA underwent DSA.

Model parameters

The parameters in the Markov model, and their probability, distribution and source are listed in the Supplemental table. Utilities and the observed outcomes of the four diagnostic strategies were obtained from original cohort data.(Chapter 5) The TP and FN outcomes of each strategy were divided in 'moderate' (cavernoma, DVA, or the combination) and 'major' (aneurysm, AVM, CVST, and DAVF) categories, based on the impact of the detection of a specific macrovascular cause with regard to therapeutic interventions and outcome. Probabilities regarding morbidity and mortality as a consequence of testing or treatment were based on the literature.

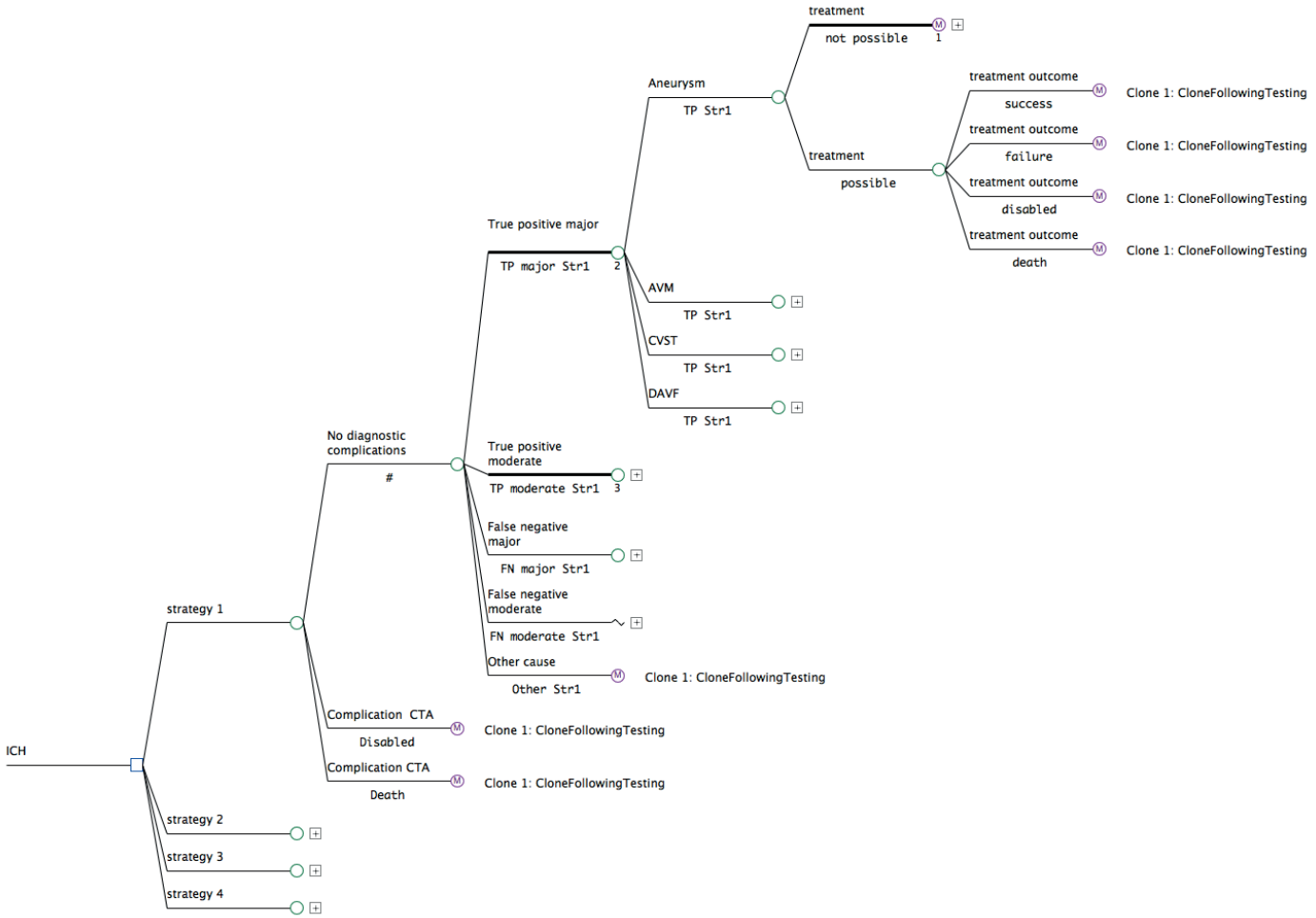

Figure 1 A part of the decision tree

Input parameters regarding probabilities of health state transitions and costs were derived from the literature, the Dutch health care system, and expert opinion. Age- and sex-specific mortality rates for the general population were obtained from Statistics Netherlands (statline.cbs.nl). Only direct medical costs were incorporated in the model. Costs for CTA, MRI/MRA and DSA, treatment of the macrovascular cause (neurosurgical, embolisation or radiation therapy), adverse events, and death were all allocated in the time cycle in which they occurred. Disabled patients residing in a nursing home induced costs every cycle, as did patients under treatment for an AVM up to three years following treatment initiation. All costs were updated to 2014 Euros with Dutch consumer price indices. Future costs were discounted with 4% and effects with 1.5% according to Dutch guidelines.[7,8]
Willingness-to-pay (WTP) was set at 20000 Euros/QALY as commonly used in the Netherlands.
Uncertainty about model parameters was reflected by statistical distributions (Table 1, Supplemental table). Uncertainty in model outcomes as a result of uncertainty in model input parameters was assessed using probabilistic sensitivity analysis. Results were visualised as incremental cost effectiveness planes and cost-effectiveness acceptability curves.

Assumptions

We assumed that all initial diagnostic tests were performed during the first cycle time, i.e. within 3 months after ICH onset. We considered the probability of an adverse event (AE) in patients with an untreated (small) aneurysm, AVM, DAVF, or CVST constant in time, whereas the probability of an AE in patients with an untreated cavernoma/DVA decreased in the first year after ICH and then remained constant.[9,10]
We assumed that in case of recurrent ICH, the underlying macrovascular cause would be detected in all surviving patients with previous false-negative tests. We assumed that patients in the "well with treated macrovascular cause" health state were protected from adverse events related to the macrovascular cause and could only die from other causes. Based on our patient cohort data, we estimated that 30% of patients who entered the "'disabled" health state, regained independence within 12 months, the other individuals were assumed to stay disabled.

Model Scenarios

Using Monte Carlo simulation we ran 2500 hypothetical cohorts each containing 5000 patients through the model, using a cycle time of three months and a lifetime horizon. Patients entered the model directly after ICH was observed on non-contrast CT. We estimated the number of diagnostic and therapeutic complications, life expectancy, QALYs and total costs per patient. The base-case scenario consisted of men and women aged 53 years, the mean age in the patient cohort. All patients with an untreated macrovascular cause were at risk of a related adverse event, and could die from unrelated causes.

Table 1 A selection of input parameters of the Markov model

Model parameter	Value	95% CI / range	Distribution	Source
Probabilities				
Strategy 1: CTA				
TP major	0.15	0.12-0.20	dirichlet	DIAGRAM cohort
TP moderate	0.02	0.01-0.04	dirichlet	DIAGRAM cohort
Strategy 2: MRI/MRA after negative CTA result				
TP major	0.004	0.00-0.01	dirichlet	DIAGRAM cohort
TP moderate	0.02	0.00-0.04	dirichlet	DIAGRAM cohort
Strategy 3: DSA after negative CTA+MRI/MRA results				
TP major	0.12	0.07-0.19	dirichlet	DIAGRAM cohort
TP moderate	0.00	0.00-0.01	dirichlet	DIAGRAM cohort
Complications				
CTA disability	0.00		beta	DIAGRAM cohort and [17,18]
CTA death	0.00		beta	DIAGRAM cohort and [17,18]
MRI/MRA disability	0.0000053		beta	[19,20]
MRI/MRA death	0.00		beta	[19,20]
DSA disability	0.0014		beta	[21]
DSA death	0.0006		beta	[21]
Costs (Euros)				
Costs CTA	200	174-229	gamma	‡
Costs MRI/MRA	201	173-229	gamma	‡
Costs DSA	606	558-653	gamma	‡ and [7]
Costs treatment aneurysm	12229	12013-12439	gamma	[22]
Costs treatment AVM*	30581	30235-30927	gamma	[23]
Costs treatment CA/DVA	12640	12423-12864	gamma	[23]
Costs treatment CVST	215	189-244	gamma	[24] and www.fk.cvz.nl
Costs treatment DAVF	21500	21223-21798	gamma	expert opinion

Costs adverse event	15759	15511-16000	gamma	DIAGRAM cohort, expert opinion
Costs nursing home per year	95376	94776-95956	gamma	[7]
Costs death	2870	2764-2977	gamma	[25]
Utilities†				
Well - treated cause	0.850	0.809-0.884	beta	DIAGRAM cohort
Well - other cause of ICH	0.822	0.804-0.838	beta	DIAGRAM cohort
Well - untreated AVM	0.838	0.784-0.887	beta	DIAGRAM cohort
Well - untreated aneurysm	0.838	0.783-0.885	beta	DIAGRAM cohort
Well - untreated cavernoma/DVA	0.838	0.785-0.883	beta	DIAGRAM cohort
Well - untreated DAVF	0.839	0.785-0.888	beta	DIAGRAM cohort
Well - untreated CVST	0.838	0.783-0.885	beta	DIAGRAM cohort
Dead	0	-	-	
Disabled (dependent)	0.694	0.659-0.727	beta	DIAGRAM cohort
Discounting				
Cost discount per year	4%	-	-	[7,8]
Effect discount per year	1.5%	-	-	[7,8]

The complete list of input parameters and sources is available in the Supplemental table.

AVM arteriovenous malformation. CA cavernoma. CI confidence interval. CTA computed tomography angiography. CVST cerebral venous sinus thrombosis. DAVF dural arteriovenous fistula. DVA developmental venous anomaly. DSA digital subtraction angiography. MRI/MRA magnetic resonance imaging/angiography. neg negative. TP true positive

* In three years
† Utility at 12 months after intracerebral haemorrhage
‡ www.dbc-zorgproducten-tarieven.nza.nl/nzaZpTarief/ZoekfunctieDot.aspx

Scenario analyses

Prevalence of an underlying macrovascular cause was 23% in the base-case scenario. To explore the influence of prevalence on the effects and costs of the different strategies, the analysis was repeated with a 15%, and with a 40% prevalence, based on the observed prevalence in two large cohort studies on the diagnostic value of angiographic exams in patients with ICH.[11,12]

RESULTS

EQ-5D and the modified Rankin scale were complete in 279 of 291 (94%) of the patients. Life-expectancy of the cohort of 53 year old patients was 24.78 years (95% CI 23.17 to 26.08) after strategy 1 vs 24.60 years (95% CI 22.98 to 25.90) after strategy 2. Life-expectancy was lower in strategy 3 (23.29 years), and in strategy 4 (23.30 years; Table 2). QALYs were comparable for all diagnostic strategies. Costs were lowest in diagnostic strategy 1 (CTA only), closely followed by strategy 3 (CTA, MRI/MRA, and selective DSA; Figure 2).
Differences in costs and effects of strategy 2, 3, and 4 compared with strategy 1 are displayed in Table 3.
In strategy 3 and 4, case fatality resulting from adverse events in patients with missed and untreated macrovascular causes was lower than in strategy 1 and 2. However, case fatality related to diagnostic and therapeutic procedures was higher in these strategies, which resulted in higher total case fatality and lower life-expectancy.
The strategy with CTA as a single investigation had the highest probability of being cost-effective, followed by the combination of CTA and MRI/MRA (Supplemental figure A). Costs of strategy 2 were higher than those of strategy 1 because of additional performance of MRI/MRA, whereas QALYs of strategy 1 and 2 were comparable. Excess case fatality of strategy 3 and excess case fatality and morbidity of strategy 4 resulted in higher costs and lower QALYs compared with strategy 1. The potential change in health outcome of strategy 2, 3, and 4 compared with strategy 1 is visualised in Figure 3.
The lower costs of only performing CTA, in comparison with strategy 2, 3 and 4, were influenced by the prevalence of macrovascular causes. A relatively low prevalence (15%) still favours strategy 1 for a wide range of values (Supplemental figure B), whereas in a setting with a high prevalence (40%), strategy 2 and 3 were favoured over strategy 1 in the lower range of WTP (Supplemental figure C).

Table 2 Estimated costs and effects of different diagnostic strategies for angiographic workup in 100000 hypothetical patients with intracerebral haemorrhage

	Strategy 1 CTA n=100000	Strategy 2 CTA-MRI/MRA n=100000	Strategy 3 CTA-MRI/MRA-DSA* n=100000	Strategy 4 CTA-MRI/MRA-DSA† n=100000
Mean costs per patient (Euros)	20799	21223	20899	21808
Life-expectancy per patient, y	24.78	24.60	23.29	23.30
Mean QALYs per patient	18.80	18.79	18.75	18.74
AE, n	8913	8335	4854	4846
Treatment, n	32596	32555	34148	34153
Case fatality test(s), n	0	0	23	48
Case fatality treatment, n	305	306	344	345
Case fatality AE, n	83	83	44	44
Total case fatality strategy, n	**388**	**389**	**411**	**437**
Morbidity test(s), n	0	0	55	114
Morbidity treatment, n	1512	1517	1618	1617
Morbidity AE, n	451	465	291	291
Total morbidity strategy, n	**1963**	**1982**	**1964**	**2022**

AE adverse event. CTA CT angiography. DSA digital subtraction angiography. MRI/MRA MR imaging/angiography. n number. QALYs quality-adjusted life years

The values in this table reflect the outcomes of a fictive cohort of 100000 patients recalculated from the original Monte Carlo simulation with 2500 samples of cohorts containing 5000 patients

* DSA was selectively performed in half of the patients with negative CTA and MRI/MRA
† DSA performed in all patients with negative CTA and MRI/MRA

Figure 2 Incremental cost effectiveness planes

The incremental cost effectiveness planes visualise the increment in QALYs versus the increment in costs induced by additional MRI/MRA (strategy 2, 2A), by MRI/MRA and selective DSA (strategy 3, 2B), and by MRI/MRA and DSA in all patients (strategy 4, 2C) for 2500 simulations. Strategy 1 is the reference. Each dot represents an estimate of cost-effectiveness from one of the 2500 simulation samples. Results indicating improved health outcomes at lower costs would be represented by dots in the lower right quadrant. The input values were sampled from parameter distributions, which can be found in the Supplemental table.

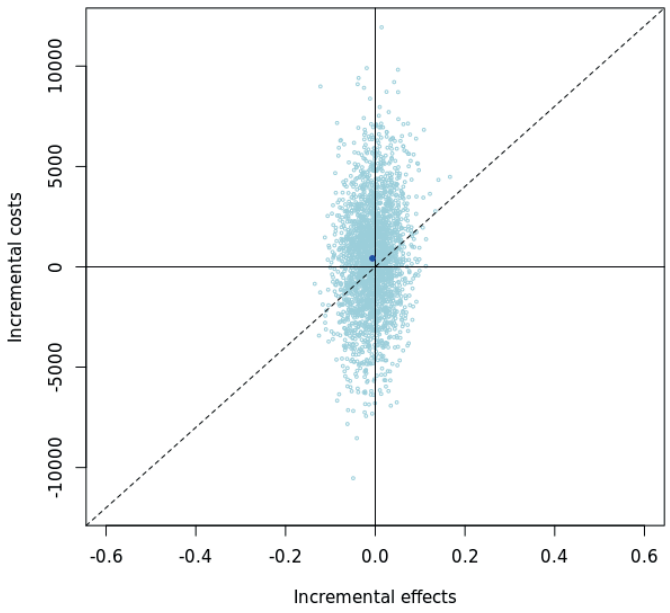

Figure 2A Strategy 2 compared with strategy 1

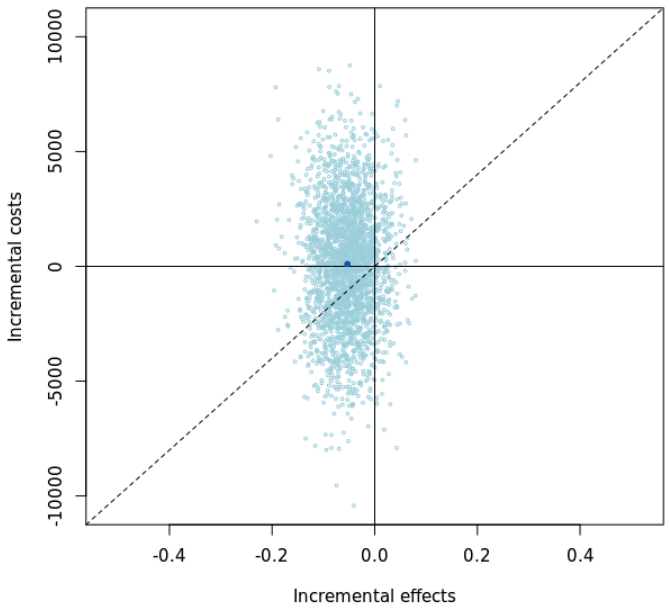

Figure 2B Strategy 3 compared with strategy 1

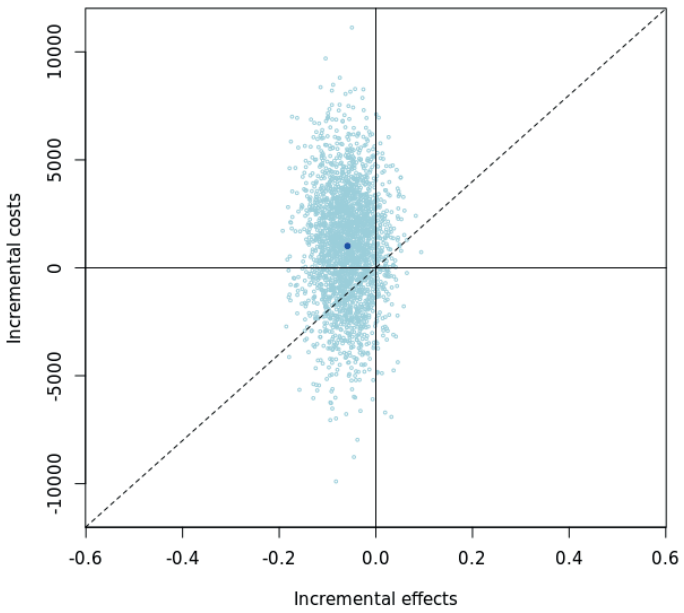

Figure 2C Strategy 4 compared with strategy 1

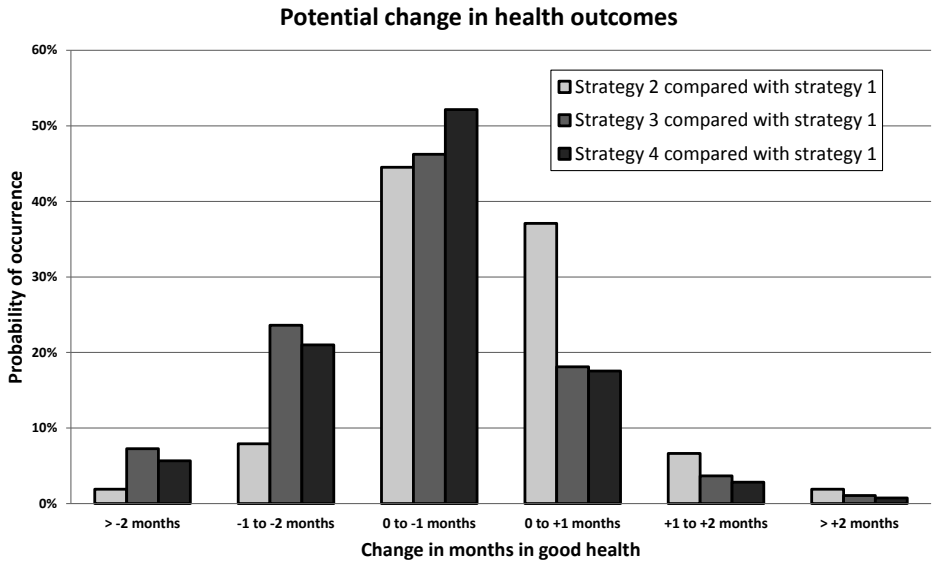

Figure 3 Potential change in health outcome of strategy 2, 3, and 4 compared with strategy 1

In this figure the expected differences in health outcome of strategy 2, 3 and 4 compared with strategy 1 are depicted, expressed in months in good health. Although strategy 1 had the highest probability of being cost-effective in comparison with the other strategies, this figure shows that absolute differences in health outcomes among strategies were small.

Table 3 Differences in costs and effects of strategy 2, 3, and 4 compared with strategy 1

	Str 2 vs 1		Str 3 vs 1		Str 4 vs 1	
	Costs (Euros)	Effects (QALYs)	Costs (Euros)	Effects (QALYs)	Costs (Euros)	Effects (QALYs)
Mean difference (95%CI)	578 (-4888 to 6284)	-0.005 (-0.16 to 0.15)	207 (-5049 to 5364)	-0.05 (-0.23 to 0.12)	577 (-3940 to 4816)	-0.04 (-0.21 to 0.10)
Proportion better (lower costs or higher effects)	42% dominated*	46%	47% dominated*	23%	40% dominated*	21%

CI confidence interval. QALYs quality-adjusted life years. Str Strategy. vs versus.

* Strategy 2, 3, and 4 are all dominated by strategy 1, indicating that these strategies are likely more costly and less effective than strategy 1. For example, the costs of strategy 3 are on average 207 Euros higher, and the effects on average -0.05 QALYs lower than those of strategy 1. It should be noted, however, that absolute differences are small and that the 95%CIs are broad. The data were derived from a Monte Carlo simulation with 2500 samples of cohorts containing 5000 patients. In 47% (proportion better) of the 2500 samples, strategy 3 was less costly than strategy 1, and in 23% of the samples strategy 3 was more effective than strategy 1. Thus, in the majority of the samples strategy 1 was less costly (53%) and more effective (77%) than strategy 3. This implies that overall strategy 3 is dominated by strategy 1.

DISCUSSION

In patients with non-traumatic ICH at the age of 70 years or younger, and excluding patients with hypertensive ICH older than 45 years of age, adding MRI/MRA and DSA to the diagnostic workup in patients with a negative CTA yields more macrovascular causes, but also extra costs and no actual health gain.

Though performance of DSA in selected patients with negative CTA and MRI/MRA (strategy 3) results in a more expensive diagnostic workup, the total costs of this strategy were lower than those of the CTA+MRI/MRA strategy (strategy 2). This is explained by the higher diagnostic yield of strategy 3, which leads to a significant reduction of adverse events in patients with macrovascular causes which otherwise would have been missed by CTA+MRI/MRA. On the other hand, excess mortality and morbidity of diagnostic and therapeutic procedures in a strategy with selective DSA results in a lower life-expectancy and QALYs, and therefore cost-effectiveness of this strategy is less favourable. The strategy least likely to be cost-effective is a strategy in which DSA is performed in all patients with negative CTA and MRI/MRA (strategy 4).

Costs and effects of CTA versus DSA as an initial exam after NCCT in patients with ICH have previously been studied in a cost utility study.[13] It was found that CTA in all patients was the optimal strategy when the risk of an underlying vascular lesion was below 12%; otherwise a strategy in which CTA was performed after risk stratification was optimal. Risk stratification was done by NCCT categorization as described by Delgado et al.[14] NCCT categorization (based on haematoma location, enlarged vessels or calcifications along haematoma margins, and venous hyperattenuation) may be useful to select patients with a high likelihood of an underlying macrovascular cause, though it should be noted that adequate training is required to assess NCCT characteristics suggestive of a macrovascular cause.[15]

Due to lack of evidence there is discussion about the optimal diagnostic workup in patients with ICH. This is reflected by two different diagnostic algorithms as recently proposed by experts in the field.[5,16] The first diagnostic algorithm starts with brain MRI, and if negative followed by DSA.[16] The second algorithm suggests to start with NCCT and CTA, followed by MR.[5] We provide a quantitative evidence-based analysis that supports a diagnostic strategy with CTA as a single exam. However, the sensitivity analyses suggest that in a setting with a high prevalence and low willingness-to-pay, the combination of CTA and MRI/MRA may be a cost-effective alternative, probably because of the slightly higher yield

of strategy 2 vs. strategy 1.

Cost effectiveness of diagnostic evaluation of ICH patients is influenced by age and by prevalence of macrovascular causes.[13] In this context, it should be noted that the DIAGRAM cohort included patients who were likely to benefit from diagnostic and therapeutic procedures, which is reflected by the relatively high proportion of macrovascular causes (23%) in this cohort. Selection of patients with a fairly good outcome is also evident from the EQ-5D assessments, which resulted in relatively high utilities for stroke patients.

An important strength of our study is that for the Markov model, we used parameters derived from the largest prospective cohort study to date on diagnostic workup in patients with ICH. Secondly, the developed model reflects clinical practice, although simplification was necessary to prevent the model from becoming too complex and requiring evidence that is currently lacking. The *additional* diagnostic value of MRI/MRA and DSA was assessed in the different strategies, which is of large clinical relevance as in many centers including those in The Netherlands, CTA is the first line diagnostic angiographic test performed immediately after NCCT in patients with ICH. A third strength is that the model distinguishes between the most relevant ICH causes, differences in subsequence treatment (for identified causes), and impact on quality of life. Finally, assessment of EQ-5D and the modified Rankin scale was available for the majority (94%) of the patients.

A limitation of this study is that not all patients have received all tests. Though inevitable, the cohort data are subject to selection by indication, in particular in strategy 3 in which DSA was performed in a selection of the patients with negative CTA and MRI/MRA. Selection for DSA in strategy 3 was not based on predefined criteria, but was an individual decision of patients and their treating physician. Patients in whom DSA was not performed were on average older and more often had a deep ICH location, resulting in lower prior probability of an underlying macrovascular cause.(Chapter 5) Small AVMs or DAVFs may have been missed, but we estimate that missed AVMs or DAVFs can only have had minor influence on our results as we have included recurrent ICH from missed macrovascular causes during follow-up in the reference standard. Another limitation is that indirect medical costs were not taken into account, which may have resulted in underestimation of costs in disabled patients. Moreover evidence on uncertainty in included direct medical costs was limited. Therefore uncertainty may have been underestimated in the cost-effectiveness results.

In conclusion, compared to CTA as a single investigation, performance of additional MRI/MRA and DSA increases healthcare costs without improving health outcomes. Additional MRI/MRA may still be indicated in some patients, eg. when an underlying cavernoma is suspected. The morbidity and case fatality from diagnostic and therapeutic procedures in the strategy that includes DSA are higher than those of adverse events in patients with a macrovascular causes missed by CTA. DSA can be indicated to detect or rule out a small AVM of DAVF in patients at high risk of an underlying macrovascular cause. With the DIAGRAM prediction rule, based on age, location, and presence of signs of small vessel disease on non-contrast CT, the probability of an underlying macrovascular cause can be estimated,(Chapter 5) which may be helpful in the selection of patients for additional DSA.

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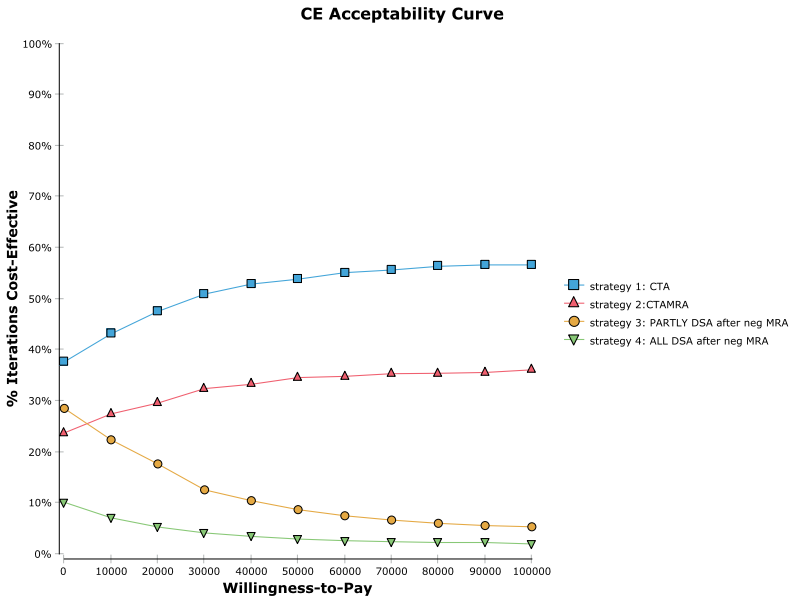
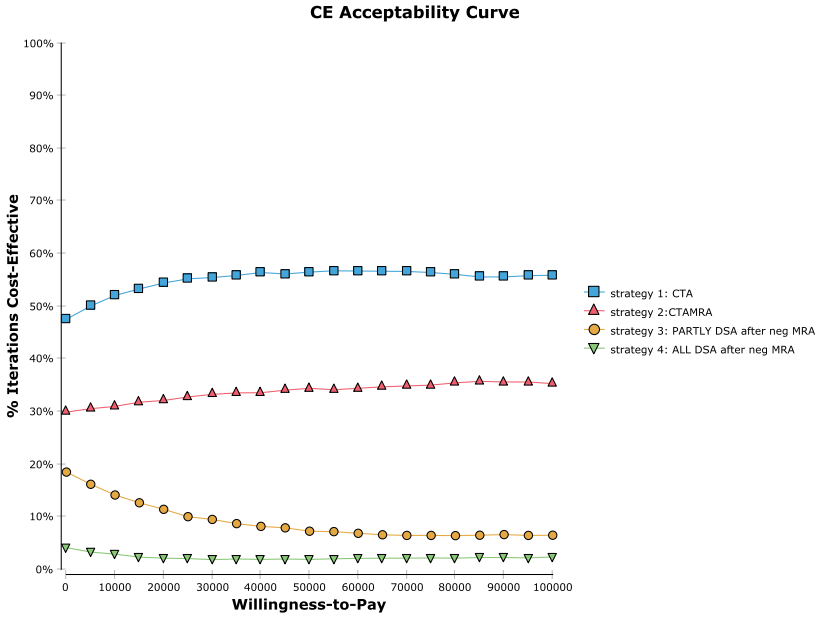


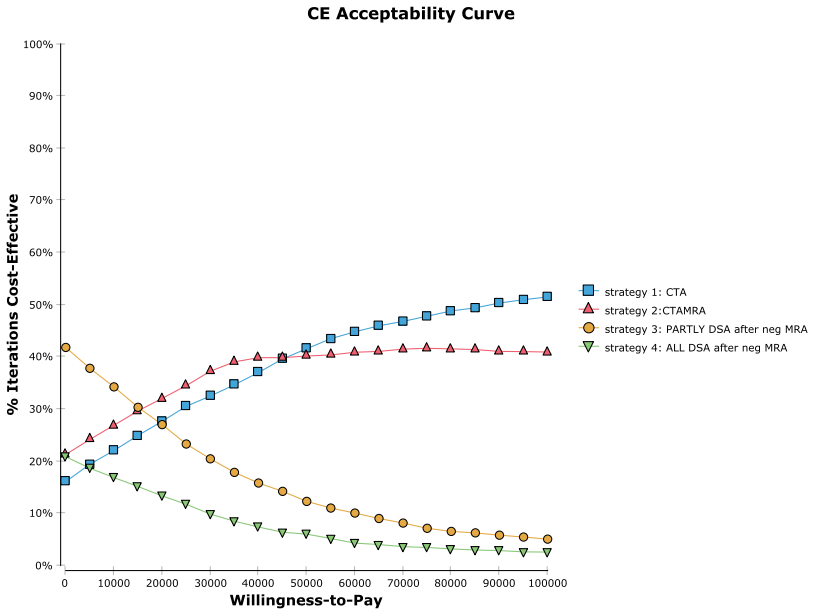
Supplemental figure A Prevalence 23%

Cost-effectiveness acceptability curves with different prevalences of macrovascular causes in cohorts of patients with intracerebral haemorrhage

Simulations were performed for 2500 hypothetical cohorts consisting of 5000 patients each. In the cost-effectiveness acceptability curves, the uncertainty in estimates of cost-effectiveness is visualized. The willingness-to-pay (WTP, in Euros) is plotted against the proportion of cost-effective iterations (n=2500) of the four diagnostic strategies. The estimates add up to 100%. Figure A (prevalence 23%, base-case scenario) depicts that strategy 1 has the highest probability of being cost-effective for a wide range of WTP values; this is also observed in the simulation with 15% prevalence (figure B). When the prevalence is higher (40%, figure C) and WTP is in the lower range, estimates of strategy 2 and 3 point out that these strategies have a higher probability of being cost-effective than strategy 1.



Supplemental figure B Prevalence 15%



Supplemental figure C Prevalence 40%

Supplementary table Parameters used in the Markov model, and their value, distribution and source

Variable	Cases/ population	Probability/ year or Probability/ Event*	Type of distribution	95% CI	Source
Strategy 1 (CTA)					
Probability TP major	45/291	0.15	dirichlet	0.12-0.20	DIAGRAM study cohort
Probability TP moderate	6/291	0.02	dirichlet	0.01-0.04	DIAGRAM study cohort
Probability FN major	13/291	0.04	dirichlet	0.02-0.07	DIAGRAM study cohort
Probability FN moderate	5/291	0.02	dirichlet	0.01-0.04	DIAGRAM study cohort
Probability other cause	222/291	0.76	dirichlet	0.71-0.81	DIAGRAM study cohort
Probability TP aneurysm	7/45	0.16	dirichlet	0.07-0.28	DIAGRAM study cohort
Probability TP AVM	25/45	0.56	dirichlet	0.41-0.69	DIAGRAM study cohort
Probability TP CVST	4/45	0.09	dirichlet	0.03-0.19	DIAGRAM study cohort
Probability TP DAVF	9/45	0.20	dirichlet	0.01-0.34	DIAGRAM study cohort
Probability FN aneurysm	-	0.01	dirichlet	0.00-0.07	DIAGRAM study cohort and [1]
Probability FN AVM	9/13	0.68	dirichlet	0.41-0.89	DIAGRAM study cohort
Probability FN CVST	-	0.00‖	dirichlet	0.00-0.07	DIAGRAM study cohort and expert opinion
Probability FN DAVF	4/13	0.30	dirichlet	0.10-0.57	DIAGRAM study cohort
Strategy 2 (CTA and MRI/MRA)					
Probability TP major CTA	45/291	0.15	dirichlet	0.12-0.20	DIAGRAM study cohort
Probability TP moderate CTA	6/291	0.02	dirichlet	0.01-0.04	DIAGRAM study cohort
Probability CTA negative	240/291	0.83	dirichlet	0.78-0.87	DIAGRAM study cohort
Probability TP major†	1/240	0.004	dirichlet	0.00-0.01	DIAGRAM study cohort
Probability TP moderate†	4/240	0.02	dirichlet	0.00-0.04	DIAGRAM study cohort
Probability FN major†	11/240	0.05	dirichlet	0.03-0.08	DIAGRAM study cohort
Probability FN moderate†	1/240	0.004	dirichlet	0.00-0.02	DIAGRAM study cohort
Probability strategy 2 FN other†	223/240	0.93	dirichlet	0.89-0.95	DIAGRAM study cohort
Probability TP aneurysm†	-	0.00‖	dirichlet	0.00-0.09	DIAGRAM study cohort
Probability TP AVM†	-	1.00	dirichlet	0.82-1.00	DIAGRAM study cohort
Probability TP CVST†	-	0.00‖	dirichlet	0.00-0.09	DIAGRAM study cohort
Probability TP DAVF†	-	0.00‖	dirichlet	0.00-0.09	DIAGRAM study cohort
Probability FN aneurysm†	0/11	0.00‖	dirichlet	0.00-0.08	DIAGRAM study cohort
Probability FN AVM†	7/11	0.64	dirichlet	0.38-0.88	DIAGRAM study cohort
Probability FN CVST†	0/11	0.00‖	dirichlet	0.00-0.07	DIAGRAM study cohort
Probability FN DAVF†	4/11	0.35	dirichlet	0.11-0.60	DIAGRAM study cohort
Strategy 3 (CTA, MRI/MRA and DSA)					
Probability CTA+MRI/MRA negative	235/240	0.98	dirichlet	0.97-1.00	DIAGRAM study cohort

Variable	Cases/ population	Probability/ year or Probability/ Event*	Type of distribution	95% CI	Source
Str3: Probability DSA	114/235	0.49	dirichlet	0.43-0.55	DIAGRAM study cohort
Str3: Probability refrained from DSA	121/235	0.51	dirichlet	0.45-0.57	DIAGRAM study cohort
Probability strategy 3 TP major‡	14/114	0.12	dirichlet	0.07-0.19	DIAGRAM study cohort
Probability strategy 3 TP moderate‡	0/114	0.00‖	dirichlet	0.00-0.01	DIAGRAM study cohort
Probability strategy 3 FN major‡	0/114	0.00‖	dirichlet	0.00-0.01	DIAGRAM study cohort
Probability strategy 3 FN moderate‡	1/114	0.01	dirichlet	0.00-0.03	DIAGRAM study cohort
Probability strategy 3 FN other‡	99/114	0.87	dirichlet	0.80-0.92	DIAGRAM study cohort
Probability TP aneurysm‡	0/14	0.00	dirichlet	0.00-0.07	DIAGRAM study cohort
Probability TP AVM‡	9/14	0.64	dirichlet	0.37-0.85	DIAGRAM study cohort
Probability TP CVST‡	0/14	0.00	dirichlet	0.00-0.06	DIAGRAM study cohort
Probability TP DAVF‡	5/14	0.36	dirichlet	0.14-0.61	DIAGRAM study cohort
Probability FN aneurysm‡	0/0	0.00‖	dirichlet	0.00-0.13	DIAGRAM study cohort
Probability FN AVM‡	0/0	0.83	dirichlet	0.52-0.99	Expert opinion and DIAGRAM study cohort
Probability FN CVST‡	0/0	0.00‖	dirichlet	0.00-0.14	DIAGRAM study cohort
Probability FN DAVF‡	0/0	0.17	dirichlet	0.00-0.44	Expert opinion and DIAGRAM study cohort
Complications test(s)					
Probability disabled CTA	-	0.00	beta		DIAGRAM study cohort and [2,3]
Probability dead CTA	-	0.00	beta		DIAGRAM study cohort and [2,3]
Probability disabled MRA*	-	0.0000053	beta		[4,5]
Probability dead MRA*	-	0.00	beta		[4,5]
Probability disabled DSA†	12/19826	0.0014	beta		[6]
Probability dead DSA†	27/19826	0.0006	beta		[6]
Probabilities per macrovascular cause					
Aneurysm detected					
Probability treatment not possible	1/100	0.01	beta	0.009-0.011	Expert opinion
Probability treatment possible	99/100	0.99	beta	0.99-1.00	
Treatment success		0.83	dirichlet	0.75-0.90	DIAGRAM data, expert opinion and [7–9]
Treatment incomplete		0.12	dirichlet	0.07-0.20	
Disabled		0.033	dirichlet	0.01-0.08	Expert opinion and [10]
Death		0.013	dirichlet	0.00-0.04	Expert opinion and [10]

Aneurysm not detected§					
Probability no AE		0.99	beta	0.99-1.00	
Probability AE		0.01	beta	0.009-0.011	[11,12]
Treatment success		0.83	dirichlet	0.76-0.89	
Treatment incomplete/failed		0.12	dirichlet	0.07-0.19	
Disabled		0.033	dirichlet	0.01-0.07	[13,14]
Aneurysm not detected§					
Probability no AE		0.99	beta	0.99-1.00	
Probability AE		0.01	beta	0.009-0.011	[11,12]
Treatment success		0.83	dirichlet	0.76-0.89	
Treatment incomplete/failed		0.12	dirichlet	0.07-0.19	
Disabled		0.033	dirichlet	0.01-0.07	[13,14]
Death		0.013	dirichlet	0.00-0.04	[15]
AVM detected					
Probability treatment not possible		0.05	beta	0.049-0.051	Expert opinion
Probability treatment possible		0.95	beta	0.94-0.95	
Treatment success		0.84	dirichlet	0.82-0.86	Expert opinion
Treatment incomplete		0.093	dirichlet	0.08-0.11	Expert opinion
Disabled	≈2927/46314	0.060	dirichlet	0.05-0.08	[16]
Death	315/46314 PY	0.0068	dirichlet	0.003-0.012	[16]
AVM not detected§					
Probability no AE		0.952	beta	0.951-0.953	
Probability AE	85/1771 PY	0.048	beta	0.047-0.049	[17]
Treatment success		0.84	dirichlet	0.82-0.86	Expert opinion
Treatment incomplete		0.093	dirichlet	0.08-0.11	Expert opinion
Disabled	≈2927/46314	0.060	dirichlet	0.05-0.08	[16]
Death	315/46314 PY	0.0068	dirichlet	0.003-0.013	[16]
Cavernoma/DVA detected					
Probability no treatment		0.81	beta	0.80-0.82	
Probability treatment	25/134	0.19	beta	0.18-0.20	[18]
Treatment successful		0.925	dirichlet	0.86-0.97	
Treatment not possible/failed	≈1/25 PY	0.040	dirichlet	0.01-0.09	[18]
Disabled	201/6290 PY	0.032	dirichlet	0.01-0.08	[19]
Death	28/10029 PY	0.003 (dummy)	dirichlet	0.000-0.019	[19]
Cavernoma/DVA not detected§					
Probability no AE		$1\text{-}P_{AE}$	beta	time de-pendent	
Probability AE		Table	beta	time de-pendent	[20]

Variable	Cases/ population	Probability/ year or Probability/ Event*	Type of distribution	95% CI	Source
Treatment successful		0.925	dirichlet	0.87-0.97	
Treatment not possible/failed		0.04	dirichlet	0.01-0.08	[18]
Disabled		0.032	dirichlet	0.01-0.07	[19]
Death		0.003 (dummy)	dirichlet	0.000-0.020	[19]
CVST					
Probability treatment not possible		0	beta	0.00-0.00	Expert opinion
Probability treatment possible		1	beta	0.99-1.00	
Treatment successful		0.90	dirichlet	0.88-0.92	[21,22]
Treatment failure		0.00#	dirichlet	0.000-0.001	[21,22]
Disabled		0.045	dirichlet	0.035-0.060	[21,22]
Death		0.055	dirichlet	0.042-0.070	[21,22]
CVST not detected§					
Probability no AE		0.977	beta	0.968-0.984	
Probability AE	≈23/1000 PY	0.023	beta	0.015-0.032	[21–23]
Treatment successful		0.90	dirichlet	0.88-0.92	[21,22]
Treatment not possible/failed		0.00#	dirichlet	0.000-0.001	[21,22]
Disabled		0.045	dirichlet	0.035-0.061	[21,22]
Death		0.055	dirichlet	0.041-0.070	[21,22]
DAVF					
Probability treatment not possible		0.01	beta	0.009-0.011	Expert opinion
Probability treatment possible		0.99	beta		
Treatment successful	≈61/79	0.80	dirichlet	0.72-0.87	DIAGRAM data and [24,25]
Treatment failure		0.17	dirichlet	0.10-0.25	
Disabled	3/236	0.013	dirichlet	0.001-0.041	[26]
Death	42/2572	0.016	dirichlet	0.001-0.049	DIAGRAM data and [26,27]
DAVF not detected§					
Probability no AE		0.921	beta	0.915-0.926	
Probability AE	3/40.4 PY	0.079	beta	0.073-0.085	[28]
Treatment successful		0.80	dirichlet	0.72-0.87	
Treatment not possible/failed		0.17	dirichlet	0.11-0.25	
Disabled		0.013	dirichlet	0.001-0.043	
Death		0.016	dirichlet	0.001-0.047	
Risk death other causes	age depen-dent	Table	5 years	age depen-dent	statline.cbs.nl

Costs		Euros			
CTA	-	200	gamma	174-229	DBC Zorgproducten ¶
MRA	-	201	gamma	173-229	DBC Zorgproducten ¶
DSA	-	606	gamma	558-653	DBC Zorgproducten ¶ and [29]
Aneurysm treatment	-	12229	gamma	12013-12439	[30]
AVM treatment		30581	gamma	30235-30927	[31] Costs were spread over three years
Cavernoma/DVA treatment		12640	gamma	12423-12864	[31]
CVST treatment	-	215	gamma	189-244	[32] and www.fk.cvz.nl
DAVF treatment	-	21500 Euro	gamma	21223-21798	Expert opinion
Healthstate Well untreated TP		800	gamma	640-979	Follow up imaging/visits during 10 years (expert opinion)
Healthstate Disability (dependent/year)	-	95376	gamma	94776-95956	[29]
Death	-	2870	gamma	2764-2977	[34]
Adverse event untreated macrovascular cause	-	15759	gamma	15511-16000	DIAGRAM cohort and expert opinion
	Cases/ population	**Utility**	**Type of distribution**	**95% CI**	**Source**
Utility – 3 month follow-up					
Well with treated macrovascular cause	27	0.829	beta	0.791-0.863	DIAGRAM study cohort
Well with other cause of ICH	153	0.829	beta	0.815-0.843	DIAGRAM study cohort
Dead	4	0	beta	-	DIAGRAM study cohort
Disabled after ICH	78	0.714	beta	0.688-0.740	DIAGRAM study cohort
Well with untreated AVM	24	0.840	beta	0.806-0.872	DIAGRAM study cohort
Well with untreated aneurysm	24	0.840	beta	0.806-0.872	DIAGRAM study cohort
Well with untreated cavernoma/ DVA	24	0.840	beta	0.805-0.872	DIAGRAM study cohort
Well with untreated DAVF	24	0.840	beta	0.806-0.872	DIAGRAM study cohort
Well with untreated CVST	24	0.840	beta	0.806-0.872	DIAGRAM study cohort
Utility – 12 month follow-up					
Well with treated macrovascular cause	34	0.850	beta	0.809-0.884	DIAGRAM study cohort
Well with other cause of ICH	169	0.822	beta	0.804-0.838	DIAGRAM study cohort
Dead	7	0	beta	-	DIAGRAM study cohort
Disabled after ICH	53	0.694	beta	0.659-0.727	DIAGRAM study cohort
Well with untreated AVM	16	0.838	beta	0.784-0.887	DIAGRAM study cohort
Well with untreated aneurysm	16	0.838	beta	0.783-0.885	DIAGRAM study cohort
Well with untreated cavernoma	16	0.838	beta	0.785-0.883	DIAGRAM study cohort

Utility – 12 month follow-up					
Well with untreated DAVF	16	0.839	beta	0.785-0.888	DIAGRAM study cohort
Well with untreated CVST	16	0.838	beta	0.786-0.887	DIAGRAM study cohort

Strategy 1: NCCT and CTA
Strategy 2: NCCT, CTA and MRA
Strategy 3: NCCT, CTA, MRA and DSA
Major: aneurysm, AVM, DAVF, CVST
Moderate: cavernoma, DVA
Other: non-macrovascular cause

AE adverse event. AVM arteriovenous malformation. CI confidence interval. CTA CT angiography. CVST cerebral venous sinus thrombosis. DAVF dural arteriovenous fistula. DSA digital subtraction angiography. FN false negative. ICH intracerebral haemorrhage. MRI/MRA MR imaging/angiography. n number. TP true positive. QALYs quality-adjusted life years

* Annual rates were converted to probabilities per 3 months.
† Result of MRA after negative CTA
‡ Result of DSA after negative CTA and MRA
§ The assumption is that undetected macrovascular cause are detected in case of an adverse event
| As the Dirichlet distribution cannot handle probability values of 0 a very small probability was used
AVM arteriovenous malformation, CVST cerebral venous sinus thrombosis, DAVF dural arteriovenous fistula, DVA developmental venous anomaly, FN false negative, ICH intracerebral haemorrhage, n.a. not applicable, TP true positive
¶ Website dbc-zorgproducten-tarieven.nza.nl/nzaZpTarief/ZoekfunctieDot.aspx

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6

CHAPTER 7

Yield of angiographic examinations in isolated intraventricular haemorrhage: a case series and systematic review of the literature

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ABSTRACT

Background and purpose: It is unknown which patients with non-traumatic isolated intraventricular haemorrhage (IVH) should undergo angiographic imaging to detect an underlying macrovascular cause and which modality has the highest yield. We aimed to study the yield of angiographic examinations in patients with IVH.

Methods: We reviewed medical records of patients with IVH admitted to the University Medical Center Utrecht between 2002 and 2012. We searched PubMed and Embase for studies on angiographic examinations in IVH until January 2014. We calculated yield of angiographic imaging and investigated influence of age, hypertension and anticoagulant use with meta-regression analysis.

Results: We identified 39 patients of whom 30 underwent an angiographic study. CT angiography (CTA) suggested a macrovascular abnormality in nine patients, which was confirmed by digital subtraction angiography (DSA) in seven. In the literature we found 15 studies describing 204 patients. Pooled analysis showed a yield of 58% for DSA (95% CI 47-68%; 15 cohorts; 142 patients). One small study described the yield of CTA or MR imaging/angiography (0%; 4 patients). Yield of angiographic imaging decreased with increasing age (-2.5%, 95% CI -5.0 to -0.2 per year increase) but was not affected by history of hypertension (-8.3%, -80.8 to 64.2) or anticoagulant use (-47.1%, -110.3 to 16.1).

Conclusion: The reported yield of DSA in isolated IVH is around 50% but varies considerably, probably due to confounding by indication. The yield is higher in younger patients but based on the available data it is not possible to set age or other criteria for patients in whom DSA can be safely omitted.

INTRODUCTION

Isolated intraventricular haemorrhage (IVH) accounts for around 3% of all non-traumatic intracranial haemorrhages in adults and is therefore a rare condition.[1,2] Isolated IVH can originate from rupture of an underlying macrovascular abnormality, e.g. an aneurysm, arteriovenous malformation (AVM) or arteriovenous fistula (AVF). Identification of such abnormalities has important therapeutic implications. Digital subtraction angiography (DSA) is the gold standard for detection of underlying macrovascular abnormalities, but less invasive computed tomography angiography (CTA) and magnetic resonance imaging/angiography (MRI/MRA) are increasingly applied. It is unclear in which patients with IVH angiographic studies should be performed and what the diagnostic accuracy is of non-invasive techniques. Also, yield of angiographic imaging might be influenced by patient characteristics, including age, pre-existing hypertension and use of oral anticoagulants.[3,4] The purpose of this study was to investigate the yield of angiographic modalities in patients with isolated IVH and to study the influence of patient characteristics on this yield.

METHODS

Case series

We reviewed the stroke database of the University Medical Center Utrecht for consecutive patients who had been admitted with isolated IVH between January 2002 and May 2012. We reviewed patient records for information on age, sex, diagnosis of hypertension, use of anticoagulants, and the number, type and yield of angiographic examinations. Patients were considered hypertensive when they had a medical history of hypertension, used antihypertensive agents on admission or were discharged on antihypertensive medication. The study was approved by the ethical review committee of the University Medical Center Utrecht.

Systematic literature search

We systematically searched PubMed and Embase up to January 2014 using synonyms of the following search terms 'intraventricular haemorrhage', 'digital subtraction angiography', 'magnetic resonance angiography' and 'computed tomography angiography'

(NH, Search strategy in Supplementary Data). No language restrictions were added. Title and abstract were screened for relevant articles based on predefined inclusion criteria. Inclusion criteria were 1) IVH defined as non-traumatic haemorrhage confined to the ventricles, 2) inclusion of at least three consecutive patients, 3) reporting results of CTA, MRI/MRA or DSA. References and related citations of relevant articles were screened until no additional studies were found. The quality of the selected studies was assessed using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS),[5] and the Standards for the Reporting of Diagnostic accuracy studies (STARD).[6]

Two authors (NH, CvA) independently retrieved information on case-finding methods, the number of included patients, age, sex, history of hypertension, use of anticoagulants, the applied angiographic modalities and their diagnostic yield. Diagnostic yield was defined as the proportion of angiographic examinations that identified a vascular abnormality as the cause of the IVH.

Statistical analysis

For each study we calculated mean age, proportion of men, proportion of patients with hypertension, proportion of patients on anticoagulants and the yield of angiographic examinations with 95% CI. In the case series we performed logistic regression to study the association between age and presence of vascular malformations. We pooled the yield of angiographic examinations obtained from the case series with the estimates from the literature review using a random effects model. To investigate the association between age, hypertension, use of anticoagulants, and the yield we performed meta-regression analysis weighted by the inverse variance. All statistical analysis were performed with SPSS version 22 or R version 3.0.3 for Windows (http://cran.r-project.org/).

RESULTS

Case series

In our case series we included 39 patients with isolated IVH (Webtable 1). In 30 patients one or more angiographic examinations had been performed: CTA in 28 patients, MRI/MRA in five patients and DSA in nine. In seven of 30 patients (23%) a macrovascular cause was found, in 2 patients an AVF, and in 5 patients an AVM. CTA had suggested the underlying macrovascular abnormality in nine patients, and it was confirmed by DSA in seven

patients. No DSA was performed in any of the 19 patients with a negative CTA. In the five patients who underwent MRI/MRA, we found no underlying macrovascular lesions; in three of these patients prior CTA had been negative as well. During a median follow up of 3 months (range 0-132 months), we found no macrovascular abnormalities nor recurrent haemorrhage among 24 patients with non-fatal IVH, who did not undergo DSA. The odds of having a vascular malformation decreased with each year increase in age (OR 0.91, 95% CI 0.85-0.97).

Systematic literature search

The literature search yielded 15 studies reporting on 204 patients with isolated IVH (Webfigure 1).[1,2,4,7-18] Thirteen studies described the yield of a single investigation, in all cases DSA. One study described DSA and performed MRI/MRA in one patient,[11] a single study reported on the diagnostic yield of CTA in addition to gadolinium-enhanced MRI.[7] Six studies had a prospective design.[1,7,8,10,16,17]

None of the included studies fulfilled all criteria for good quality of diagnostic studies according to the QUADAS-tool or STARD-checklist.[5,6] Apart from one, none of the studies assessed the yield of one modality in comparison with another that was used as a reference standard,[7] and most studies did not specify their selection criteria for angiography (Webfigure 2).

Baseline characteristics of studies are summarised and combined with the results of our case series in Table 1. Mean age was reported in eight studies and ranged from 46 to 61 years.[1,4,7,9,12,13,17] Median proportion of men was 58% (range 38 to 80%, 9 studies).[1,4,7,9,11-13,17] Median proportion of patients with hypertension was 50% (range 0 to 80%, 10 studies).[1,4,9-15] Yield of DSA in 15 studies ranged from 29 to 100%; a pooled analysis showed a yield of 58% (95% CI 47 to 68%) for DSA (Figure 1; I^2 43%). Yield of MRI/MRA and CTA, investigated in a study with four consecutive patients, was 0%.[7]

Overall, 81 macrovascular abnormalities were identified: in 49 patients (60%) the cause of IVH was an AVM, in 28 (35%) an aneurysm, in three (4%) a AVF and in one patient moyamoya disease (1%).

With each year increase in mean age per study, the yield of angiographic imaging decreased by -2.5% (95% CI -5.0 to -0.2%). We found no effect of the proportion of patients with hypertension (-8.3%; 95% CI -80.8 to 64.2) or of patients on anticoagulants (-47.1%; 95% CI-110.3 to 16.1).

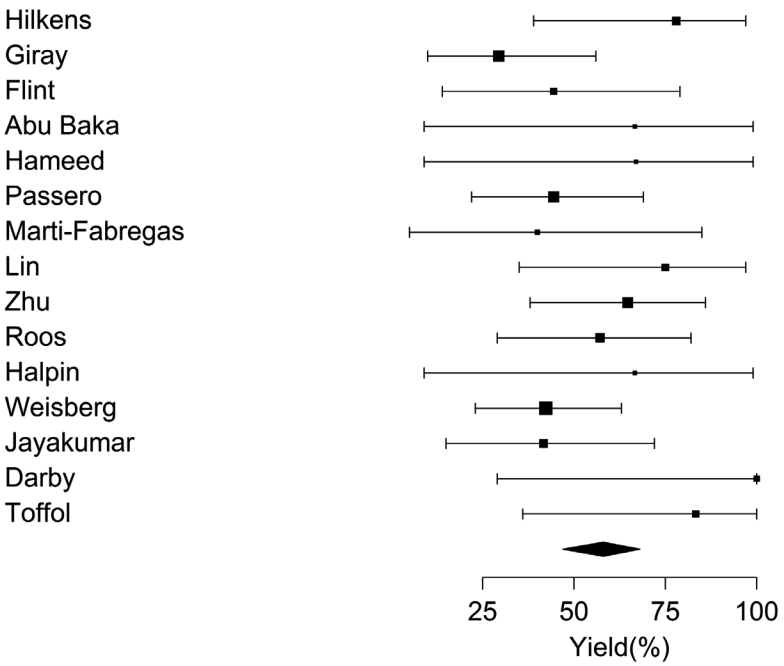

Figure Pooled analysis of 15 studies reporting on yield of digital subtraction angiography

Table Characteristics of 16 cohorts reporting on the yield of angiographic examinations in isolated intraventricular haemorrhage, including our own series.

Study (first author, year of publication)	Study design	Number of patients	Mean age	Male (%)	HT (%)	Use of OAC (%)	Angiographic modality	No. of patients undergoing angiographic studies	Macrovascular cause (%, 95% CI)
Hilkens, 2015	R	39	58	59	46	36	CTA-MRI/MRA-DSA	28-5-9	23 (10-42)
Snider, 2010[7]	P	4	61	50	-	-	CTA-MRI/MRA	4-4	0 (0-60)
Giray, 2009[4]	R	24	61	58	50	4	DSA	17	29 (10-56)
Flint, 2008[9]	R	15	60	47	80	7	DSA	9	44 (14-79)
Abu Bakar, 2005[8]	P	3	-	-	-	-	DSA	3	67 (9-99)
Hameed, 2005[11]	R	15	56	60	80	13	DSA-MRI/MRA	3-1	50 (7-93)
Passero, 2002[1]	P	26	58	50	38	4	DSA	18	44 (22-69)
Marti-Fabregas, 1999[13]	R	13	60	38	54	0	DSA	5	40 (5-85)
Lin, 1997[18]	R	8	15-40	-	-	-	DSA	8	75 (35-97)
Zhu, 1997[16]	P	17	-	-	-	-	DSA	17	65 (38-86)
Roos,1995[2]	R	24	-	-	-	-	DSA	14	57 (29-82)
Halpin,1994[10]	P	3	under 40	-	0	-	DSA	3	67 (9-99)
Weisberg, 1991[15]	R	26	-	-	50	-	DSA	26	42 (23-63)
Jayakumar,1989[12]	R	15	45	80	33	-	DSA	12	42 (15-72)
Darby, 1988[17]	P	5	46	60	-	-	DSA	3	100 (29-100)
Toffol,1986[14]	R*	6	-	-	50	-	DSA	6	83 (36-100)

* patients were selected by reviewing angiographic records.
CI confidence interval No. number P prospective. R retrospective. OAC oral anticoagulants. HT hypertension.

DISCUSSION

In around half of the patients with IVH undergoing DSA a macrovascular lesion is found, but the yield varies considerably between studies, which is probably explained by varying selection criteria. The yield of angiographic imaging increases in younger patients, whereas we found no effect of the presence of hypertension or the use of oral anticoagulants.

Accurate detection of underlying malformations is of great importance, since timely treatment may prevent recurrent haemorrhage. Although the yield was higher in younger patients, we could not set an age criterion for patients in whom DSA can be omitted based on our data; it is likely that also here bias by indication played a role in the studies included in the review and in our own cohort. Given the consequences of detection of an underlying malformation, DSA should probably be considered, in particular in younger patients, unless there are distinct contra-indications. Based on the available data, presence or absence of hypertension or use of oral anticoagulation should not be a criterion, but the lack of association is probably a result of indication bias.

CTA and MRI/MRA may be preferred imaging modalities due to their non-invasive character but their diagnostic accuracy in isolated IVH is unsettled. A recent Cochrane review investigated the yield of non-invasive imaging in patients with spontaneous parenchymal intracerebral haemorrhage.[19] This meta-analysis showed a high sensitivity and specificity for both CTA and MRI/MRA. However, the results were limited by methodological drawbacks in some of the included studies. Only if future studies show diagnostic accuracy of CTA and MRI/MRA as high as that of DSA, CTA and MRI/MRA can replace DSA.

Our study has several limitations. Most studies reported only on DSA, had small sample sizes, a retrospective design and lacked criteria for selecting patients for angiography. These methodological drawbacks of the included studies probably explain the wide variation of yield of DSA. Insufficient data are available to draw conclusions on the yield of CTA and MRI/MRA in isolated IVH. Also our case series had a retrospective design and not all patients underwent angiographic imaging (CTA, MRI/MRA, or DSA) nor was DSA performed in all patients with negative CTA. As a result small macrovascular abnormalities may have been missed.

Strengths of our study are that the described case series is the largest series published ever, and that we summarised the available evidence in a systematic way with pre-specified inclusion criteria and without applying any language restrictions.

The results of this study suggest that the yield of angiographic examination is higher in younger patients with isolated IVH. The available data are insufficient to provide firm recommendations regarding in which patients what type of angiographic examinations should be performed, or in which patients angiographic examinations are not needed. Data on the yield of CTA and MRI/MRA in patients with isolated IVH are urgently needed.

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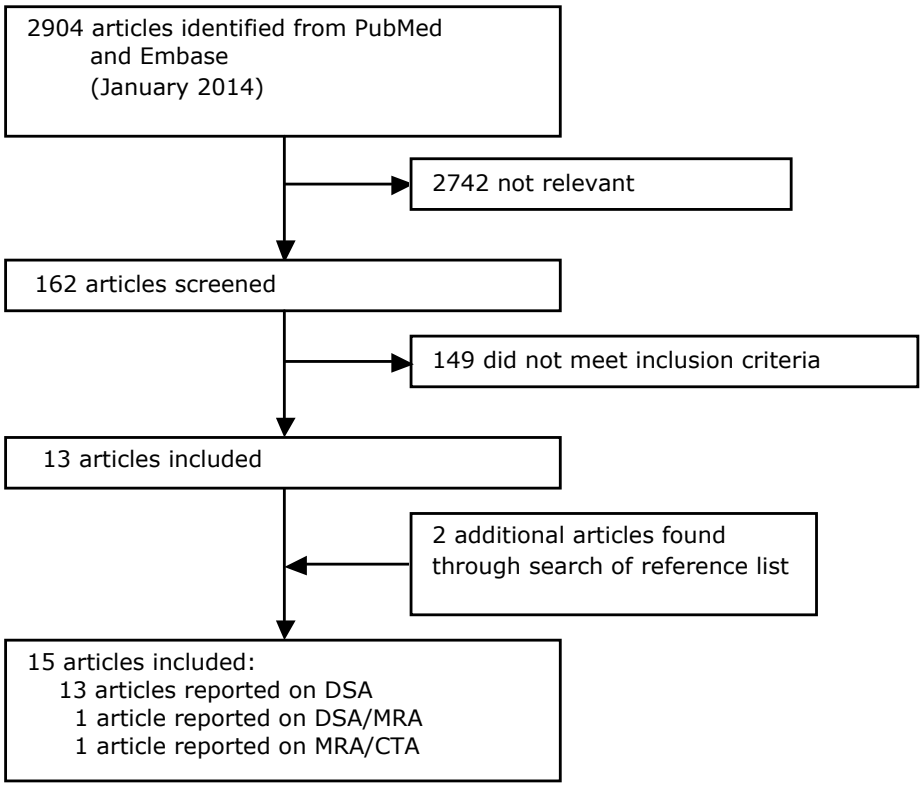
SUPPLEMENTAL DATA

Search strategy:
#1 'Intraventricular haemorrhage' OR 'Intraventricular haemorrhage' OR 'IVH'

AND

#2 'x-ray computed tomography' OR 'spiral computed tomography' OR 'magnetic resonance imaging' OR 'magnetic resonance angiography' OR 'cerebral angiography' OR 'catheter angiography' OR 'CT' OR 'CTA' OR 'MRA' OR 'IADSA' OR 'conventional angiography' OR 'catheter angiography'.



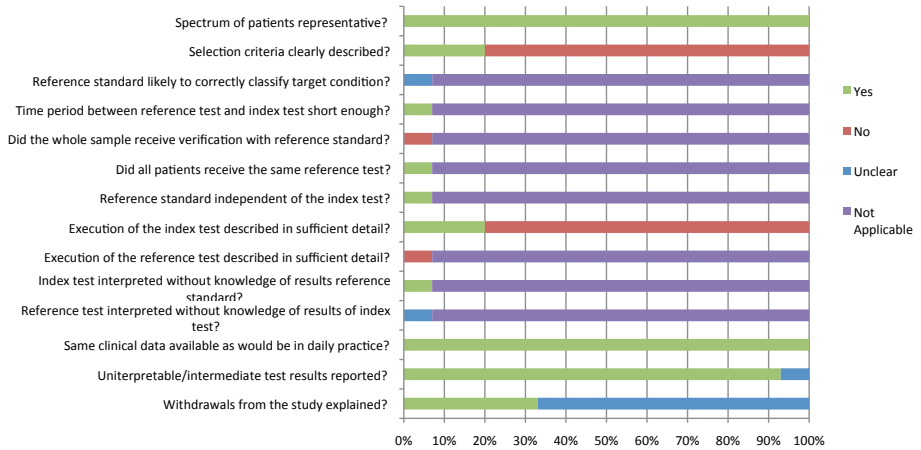
Webfigure 1 Flowchart

Webtable Patient characteristics and angiographic examinations in 39 patients with isolated intraventricular haemorrhage

Sex	Age (yrs)	CTA	Macrovasc	MRA	Macrovasc	DSA	Macrovasc	Med	INR	HT
M	16	yes	possible	no	-	Yes	AVM	No		no
M	20	yes	AVM	no	-	Yes	AVM	No		no
M	26	yes	AVF	no	-	Yes	AVM	No		no
M	33	yes	possible	no	-	Yes	No	No		yes
M	34	yes	no	yes	No	No	-	no†		no
F	36	yes	AVM	no	-	Yes	AVM	No		no
F	39	yes	no	no	-	No	-	OAC	4.7	yes
F	45	yes	AVM/AVF	no	-	Yes	AVF	No		no
M	46	no	-	no	-	No	-	No		no
F	49	yes	no	no	-	No	-	No		yes
F	52	yes	no	no	-	No	-	AP		no
M	52	no	-	yes	No	No	-	OAC	2.5	no
F	55	yes	no	no	-	No	-	OAC	unknown	no
M	57	yes	no	no	-	No	-	No		yes
F	57	yes	no	no	-	No	-	No		no
M	59	yes	no	no	-	No	-	OAC	1.2	no
F	59	yes	possible	no	-	No	-	No		no
M	59	yes	no	yes	No	No	-	OAC	4.6	yes
M	59	yes	no	no	-	No	-	OAC	1.9	no
F	60	yes	no	no	-	No	-	AP		yes
M	63	yes	possible	no	-	Yes	AVF	No		no
F	64	yes	no	no	-	Yes	No	No		yes
F	64	yes	no	yes	No	No	-	No		no
M	64	yes	AVM	no	-	Yes	AVM	No		no
F	65	yes	no	no	-	No	-	OAC	3.2	no
F	65	no	-	no	-	No	-	OAC	1.3	yes
M	65	no	-	no	-	No	-	No		yes
M	67	yes	no	no	-	No	-	No		no
F	68	yes	no	no	-	No	-	AP		yes
M	68	yes	no	no	-	No	-	OAC	3.8	yes
M	71*	yes	no	no	-	No	-	No		yes
M	72	no	-	no	-	No	-	OAC	3.0	
F	73	no	-	no	-	No	-	OAC	2.3	yes
M	73	yes	no	no	-	No	-	AP		yes

M	74	no	-	yes	No	No	-	OAC	1.7	yes
M	77	no	-	no	-	No	-	OAC	1.4	yes
M	80	no	-	no	-	No	-	U		yes
F	80	no	-	no	-	No	-	No		yes
M	80	no	-	no	-	No	-	OAC	4.4	no

AP antiplatelet drugs. AVF arteriovenous fistula. AVM arteriovenous malformation. CTA CT angiography. DSA digital subtraction angiography. F female. HT hypertension. INR international normalized ratio. M male. Macrovasc macrovascular cause. Med medication. MRA MR angiography. OAC oral anticoagulation. possible possible macrovascular cause. U treatment with urokinase. yrs years.
* patient had a recurrent intraventricular haemorrhage one year later, a metastasis was detected with MRI.
† known history of haemophilia.



Webfigure 2 Proportion of studies scoring ' Yes', 'No', 'Unclear', or 'Not applicable' on QUADAS tool criteria[5]

7

CHAPTER 8

General discussion

This thesis describes the epidemiology of non-traumatic intracerebral haemorrhage (ICH) and the role of brain imaging in the diagnostic workup of patients with ICH or isolated intraventricular haemorrhage (IVH). In this chapter we discuss the main findings of this thesis and the implications for clinical practice and future research.

Main findings of this thesis

1. Incidence of ICH has not decreased between 1980 and 2006. Overall incidence increases with age, is not significantly lower in women than in men, and is two times higher in Asian people compared with other ethnic groups. Case fatality is lower in Japan than elsewhere, increases with age, and has not decreased over time.
2. Early intracerebral haematoma expansion in patients with aneurysmal subarachnoid haemorrhage (aSAH) is not always related to aneurysmal re-rupture.
3. Application of the Secondary ICH score has moderate discriminative ability in a Dutch university hospital. The proposed non-contrast computed tomography (NCCT) classification was the strongest predictor of a macrovascular cause in Dutch patients with ICH.
4. The DIAGRAM prediction rule, based on age, ICH location, and presence of signs of small vessel disease on NCCT, can help selecting patients with ICH in whom angiographic workup is indicated.
5. Both posterior fossa location (in the absence of hypertension) and the absence of signs of small vessel disease on NCCT are independent predictors of an underlying macrovascular cause in patients with ICH.
6. Accuracy of CT angiography (CTA) for the detection of macrovascular causes of ICH is modest.
7. After a negative CTA, MR imaging/angiography (MRI/MRA) can identify patients with a cavernoma or an alternative diagnosis such as a neoplasm or cerebral amyloid angiopathy, but digital subtraction angiography (DSA) is needed to diagnose macrovascular causes that cannot be detected by CTA.
8. Adding MRI/MRA and DSA to CTA as single investigation in the diagnostic workup of patients with ICH does not improve health outcomes but does increase healthcare costs.
9. The probability that additional angiographic modalities after single CTA are cost-effective in comparison with single CTA, increases when prevalence of macrovascular causes is as high as 40%.

10. The reported yield of DSA in isolated IVH varies considerably, which is probably related to confounding by indication.

PART I: EPIDEMIOLOGY OF INTRACEREBRAL HAEMORRHAGE

The overall incidence of ICH or case fatality at one month has not decreased substantially in the past decades. Incidence rates were comparable for men and women, and incidence increased tenfold from 19.1 per 100.000 for people aged 45 to 54 years to 196.0 per 100.000 for people 85 years and older. We observed a two times higher incidence in Asian people in comparison with other ethnic groups. Case fatality was remarkably low in Japan.[1]

It has been suggested that changes in ICH incidence are different for deep and lobar intracerebral haemorrhage.[2,3] In the Oxford region, a decrease in incidence of deep, hypertension related ICH was observed, whereas the overall rate had remained stable over 25 years. In part this could be explained by an increased rate of ICH associated with antithrombotic use, and of lobar ICH attributed to cerebral amyloid angiopathy (CAA).[2] In our meta-analysis, we could not assess changes in incidence in lobar versus nonlobar ICH because of a lack of data. Data from a population-based registry in Dijon also showed a stable overall ICH incidence between 1985 and 2008, whereas the incidence in patients older than 75 years of age had increased markedly in this time period.[3] A Dutch study on ICH incidence, case-fatality and mortality rates between 1998 and 2010 demonstrated declined rates in patients under 75 years, but stable rates in patients of 75 years or older.[4] These findings suggest that effects of improved primary prevention on ICH incidence could have been neutralised by the effects of an aging population. In recent years, Direct Oral Anticoagulants (DOACs) have been introduced for the prevention of ischaemic events in patients with atrial fibrillation. The relative risk of ICH is substantially lower for DOACs than for warfarin (0.49, 95% confidence interval (CI) 0.38-0.64).[5] A reduced risk of ICH in this group of patients may manifest itself in a decrease of ICH incidence.

Several reports have suggested that haemorrhagic stroke is associated with genetic variants in Asian populations.[6-8] Environmental factors may also contribute to the high incidence of haemorrhagic stroke, as ICH incidence in Asian migrants in New Zealand is not different from that in white people or Maori people.[9] As discussed in Chapter 2, we found remarkable regional differences in incidence rates of Japanese, Chinese and black Caribbean people, which may be explained by changes in life style and socioeconomic

situation after migration. Among known risk factors for ICH are hypertension, smoking, and high alcohol intake.[10] Also dietary pattern, body mass index and kidney disease have been suggested as risk factors, whereas regular physical exercise may be protective of ICH.[10] An interesting observation is that Japanese men showed a higher incidence of ICH than Japanese women,[11-15] whereas in all other regions only small sex differences were reported. In the Hisayama Study, age-adjusted incidence of ICH increased with higher daily alcohol intake in men with known hypertension.[13,15] As high alcohol intake was uncommon among women in this study, the synergistic effect of alcohol and hypertension was solely observed in Japanese men.[15] More insight in the influence of environmental factors on ICH incidence may have implications for primary prevention in the future.

Lower case fatality in Japan is poorly understood. A possible explanation is that family doctors were not involved in case finding,[11,16] therefore patients who died soon after the ictus may have been missed. Also, the higher tendency to perform surgical intervention may explain lower ICH case fatality in Japan. A meta-analysis indicates that early surgery appears to have a small survival advantage in those with lobar ICH without intraventricular extension (OR 0.74, 0.64-0.86).[17] The question whether functional outcome is also better in Japanese patients remains unanswered because of a lack of data.[11] This underlines the need for more population-based data on functional outcome of ICH, specified by region. Potentially, a better understanding of the relatively low case-fatality in Japan may lead to improved clinical care of patients with ICH in other regions.

Future research

For better understanding of time trends in ICH incidence, there is need for more data on the epidemiology of ICH subtypes from population-based studies. The suggested influences of improved primary prevention on the one hand, and the increased prevalence of CAA and antithrombotic use in aging populations on the other, need further exploration.

Development of therapeutic strategies targeted at amyloid (Aβ40) deposition in blood vessel walls may reduce the risk of lobar ICH in patients with CAA. A first phase 2 randomized clinical trial (RCT) with ponezumab in patients with possible CAA (clinicaltrials.gov/ct2/show/NCT01821118) has been completed and results are eagerly awaited.

It has been shown that stroke unit care improves the outcome of patients with ICH,[18] and that functional outcome of patients with ICH is slightly better after rapidly lowering the blood pressure (odds ratio (OR) 1.13, 95% CI 1.00-1.26).[19] Other than this, no major advances in ICH management have been reported in recent years. Among several ongoing RCTs are inter-

vention studies on surgery versus best medical treatment (switch-trial.ch), the combination of minimally invasive surgery and recombinant tissue plasminogen activator (clinicaltrials.gov/ct2/show/NCT01827046), and tranexamic acid in the hyperacute stage (tich-2.org).

PART II: IMAGING OF INTRACEREBRAL AND INTRAVENTRICULAR HAEMORRHAGE

Haematoma expansion in aneurysmal ICH

Haematoma expansion within 48 hours after ICH from aneurysmal rupture could be attributed to aneurysmal re-rupture in only half of these patients.[20] Our study was subject to selection bias, and therefore the incidence and clinical relevance of this finding need to be established in prospective research. The pathophysiogical mechanisms underlying haematoma expansion in aSAH patients without re-rupture are unclear, and may be different from those in so-called primary ICH. In recent years, research has focused on the prediction of hematoma expansion in patients with primary ICH.[21-24] It is remarkable that the CTA spot sign has been shown to be a strong predictor of poor outcome in patients with primary ICH,[25] whereas it does not predict case fatality in patients with intraparenchymal extension of aSAH.[26]

Clinical implications and future research

- Prevention of haematoma expansion in the absence or presence of aneurysmal re-rupture might be a potential target for treatment. Possibly, patients with aSAH will benefit from new insights in the pathophysiology of the spot sign in primary ICH.

Prediction scores

To date, two prediction scores have been developed to identify patients with high risk of an underlying macrovascular cause of ICH: the Secondary ICH score (SICH), and the Simple Clinical Score.[27,28]we developed a scoring system based on baseline clinical characteristics (age group [0-2 points], sex [0-1 point], neither known HTN nor impaired coagulation [0-1 point] Both scores, derived from retrospective cohort studies, are based on a combination of patient and NCCT characteristics. Discrimination and calibration of the SICH score were modest in Dutch patients. In the validation cohort, NCCT categorization (panel) was the strongest predictor of a macrovascular cause. NCCT categorization may be used to identify patients in whom angiographic workup is indicated, though we found it more difficult than expected to recognize the signs that suggest a macrovascular cause.[29]

Panel NCCT categorization, as proposed by Delgado et al[31]

- *High-probability*
  Criteria: enlarged vessels or calcifications along the margins of the haematoma, or hyperattenuation within a dural venous sinus or cortical vein along the presumed venous drainage path of the haematoma
- *Low-probability*
  Absence of high-probability features and haematoma location in basal ganglia or brain stem
- *Indeterminate probability*
  Neither high- nor low-probability criteria

The Simple Clinical Score, with age, hypertension, ICH location, intraventricular extension, and oral anticoagulant use as predictors, showed modest discriminative ability in the validation cohort (*c*-statistic 0.67, 95%CI 0.55-0.79),[28] and external validation has not yet been performed.

In Chapter 5, the development and internal validation of the proposed DIAGRAM prediction score (table) is reported. The point values of the prediction rule were based on the regression coefficients of the independent predictors of a macrovascular cause: age ≤ 50 years, absence of small vessel disease (SVD) on NCCT, and lobar and posterior fossa location (reference: deep location). With the proposed DIAGRAM prediction score, the probability of an underlying macrovascular cause can be estimated as low (<5%), intermediate (5-15%) or high (>15%).

Table DIAGRAM prediction score

Determinants	Points
• Age ≤ 50 years	1
• Absence of small vessel disease*	2
• Haematoma location	
Deep	0
Lobar	2
Posterior fossa	3

* defined as the presence of white matter laesions or an ischaemic laesion in basal ganglia, thalamus or posterior fossa

In the absence of hypertension, macrovascular aetiology of posterior fossa ICH should be taken into account. Underlying macrovascular causes were mainly cavernomas, dural arteriovenous fistulae and arteriovenous malformations. Aneurysms and cerebral venous sinus thrombosis were less frequently identified as a cause of posterior fossa ICH.

Small vessel disease

A new finding in this thesis is that we found the absence of small vessel disease on NCCT to be an important predictor of an underlying macrovascular cause in patients with ICH. Macrovascular causes are more prevalent in younger patients,[29-31] but finding a macrovascular cause has equally relevant therapeutic and prognostic consequences in older patients. The DIAGRAM cohort study included patients up to 70 years of age. The prevalence of SVD rises with increasing age,[32,33] and angiographic workup is probably of little value when small vessel disease is present on NCCT.

The reason for the assessment of SVD on NCCT (and not on MRI) as a predictor in the DIAGRAM cohort was practical: NCCT was the first exam in all patients, followed by CTA. MRI/MRA was not performed in patients in whom DSA was performed directly after CTA, or in patients who underwent treatment of the underlying macrovascular cause immediately after CTA. In 43 patients (14%), of whom 29 patients (67%) had a macrovascular cause on CTA, no MRI/MRA was performed. NCCT was performed in all patients at admission and therefore less prone to selection bias.

MRI is more sensitive for detection of lacunar infarction than NCCT, and can also detect additional features of SVD such as microbleeds.[33] A diagnostic algorithm with early MRI has recently been proposed.[34] Absence of both ischaemic and microbleed signs of SVD on MRI may be an important predictor for finding a macrovascular cause. Therefore, we could not assess absence of signs of SVD reliably on MRI. None of the patients with microbleeds on MRI in the prospective study cohort had a macrovascular cause. As DSA was not performed in all patients with negative CTA and microbleeds on MRI, small macrovascular causes may have been missed.

Clinical implications and future research

- The DIAGRAM prediction score may be used to guide both clinicians and patients whether additional DSA is indicated after negative CTA. It should be noted that the DIAGRAM prediction score was established in a preselected domain of patients between 18 and 70 years of age, excluding hypertensive ICH in patients older than 45

years, and that external validation is still needed.

- Posterior fossa location as an independent predictor of an underlying macrovascular cause in patients with non-traumatic ICH needs to be confirmed in future studies. The observation that evidence of SVD on NCCT may be a strong predictor of macrovascular cause also needs confirmation. Whether angiographic evaluation is indicated in patients with microbleeds on MRI remains unclear.
- The pathophysiology of SVD and its exact role in ICH aetiology needs to be elucidated. The role of brain MRI in the assessment of SVD in patients with ICH is the subject of the Finding the ETiology in spontaneous Cerebral Haemorrhage Study (FETCH), in which patients are investigated with 3-Tesla and 7-Tesla MRI.

Angiographic modalities in ICH

The multicentre, prospective cohort study we describe in Chapter 5 demonstrates that CTA is a feasible and appropriate initial investigation in the diagnostic workup of patients with non-traumatic ICH. CTA was performed successfully (98%) in the vast majority of patients included in the DIAGRAM cohort study. Insufficient CTA quality was mostly due to incomplete depiction of vessels surrounding the haematoma because CTA acquisition had erroneously been limited to the circle of Willis. We chose CTA as the first modality after NCCT because of its wide around-the-clock availability in the Netherlands. Other potential advantages of CTA over MRI/MRA as an initial exam are the possibility to perform the CTA straight after the NCCT, the shorter scan time and lower sensitivity to motion artefacts in these acutely ill patients.

It should be noted that the CTA sensitivity (74%) and specificity (91%) we found are lower than in previous studies.[35-38] As discussed in Chapter 5, this can be explained by differences in study domain as well as in the definition of 'macrovascular cause'. Because of potential therapeutic[39] and prognostic[40] implications, detection of an underlying cavernoma was regarded as a positive outcome in the DIAGRAM cohort study, while it was not in previous studies. Half of these cavernomas were not identified on early CTA, which has contributed to relatively low sensitivity of CTA: when cavernomas are not taken into account, the sensitivity of CTA increases, albeit only slightly, from 74% to 78%.

The additional value of MRI/MRA after a negative CTA test result consisted mainly of diagnosis of non-macrovascular causes of ICH, which is in line with a previous report.[41] MRI should be performed in all patients in whom CAA, an underlying neoplasm, or cavernoma is suspected on clinical grounds or NCCT features. Though the detection of these aetio-

logies will not always have immediate therapeutic consequences, DSA can be omitted when the cause of the ICH is clear.

DSA remains the gold standard to detect or rule out the presence of (small) macrovascular causes, and should therefore be considered in all patients in whom the underlying cause of ICH is unclear.[34] Nevertheless, DSA was often omitted in the diagnostic workup of patients with ICH as described in Chapter 5. The single most important reason to refrain from DSA was reluctance of the patient or the treating physician (35%). The complication rate of DSA in the DIAGRAM cohort, with 0.6% permanent morbidity, is in line with previous reports.[42,43] Given the small but definite risk of complications of diagnostic DSA, the risk of recurrent ICH from a macrovascular cause missed by CTA or MRI/MRA should be carefully weighed against the risk of complications of DSA in individual patients.

Clinical implications and future research

- Diagnostic strategies in patients with ICH show great variability, reflecting the lack of evidence on the most appropriate diagnostic strategy in patients with non-traumatic ICH. The challenge is to translate the findings of the DIAGRAM cohort study to better-informed decisions on selection of patients for angiographic workup. The DIAGRAM prediction score may be helpful in patient selection. The prediction score is based on data from both general and academic hospitals in the Netherlands, where CTA is widely available. Additional MRI/MRA rarely detects macrovascular causes after negative CTA. The prediction score could thus be applied to patients with negative CTA to decide in whom DSA is indicated to assess the presence of a small AVM or DAVF. In a setting with limited resources, the prediction score could be used to select patients for assessment with CTA.
- It has been suggested that MRA is highly accurate for the detection of underlying macrovascular aetiology as a first diagnostic modality after NCCT.[35] Future research may establish the value of MRI/MRA as an initial diagnostic modality after NCCT. With the advent of fast MRI sequences, MRI/MRA is becoming a more viable option in the acute stage of stroke.
- Underlying macrovascular causes are highly prevalent in paediatric haemorrhagic stroke (54%)[44] though little is known on the diagnostic value of angiographic modalities in the assessment of children with non-traumatic ICH.[45] Only adult patients were included in the DIAGRAM cohort. Therefore the question remains whether the results of our prospective study can be applied to children.

- Future studies on the diagnostic value of angiographic modalities should take into account that work-up bias and reluctance to perform DSA were the most important reasons to refrain from DSA in the DIAGRAM cohort study.

The optimal diagnostic strategy

The results of the cost-effectiveness analysis are in favour of a diagnostic strategy with CTA as a single investigation (Chapter 6). Diagnostic strategies with additional MRI/MRA and DSA increase healthcare costs without improving health outcomes, though absolute differences in costs and effects were small among all investigated strategies. The least favourable strategy was the strategy in which DSA was performed in all patients with negative CTA and MRI/MRA.

A previous cost utility study explored costs and effects of CTA versus DSA as an initial exam after NCCT in patients with ICH.[46] Performance of CTA in all patients was shown to be the optimal strategy when the risk of an underlying macrovascular cause was below 12%, otherwise a strategy in which CTA was performed after risk stratification was optimal. Risk stratification was done by the formerly mentioned NCCT categorization in this study.[27] The key to optimal use of available angiographic resources may not lie in finding the optimal diagnostic strategy in the group of patients with ICH at large, but in optimal selection of patients for angiographic workup. The question is whether an approach with improved risk stratification, for example with the DIAGRAM prediction score, is cost-effective in comparison with the commonly used strategies that were explored in Chapter 6 (strategy 1, 2, and 3).

Clinical implications and future research

- A future study to integrate the DIAGRAM prediction rule in the current Markov decision-analytic model is planned.

Angiographic modalities in isolated IVH

The case series and systematic review described in Chapter 7 indicate that in patients with isolated IVH, predictors of an underlying macrovascular cause and the yield of angiographic investigations are largely unknown.

Studies that have been published to date are prone to selection by indication. Yield of DSA ranges from 29 to 100%, and is higher in younger patients. Higher yield in younger patients is also observed in patients with non-traumatic ICH, which is explained by a high

prevalence of macrovascular causes and a low prevalence of small vessel disease and use of anticoagulants. For this reason, patients older than 70 years of age were excluded from angiographic workup in the DIAGRAM cohort study. It remains unclear whether an age criterion can be set for the indication for angiographic work-up in patients with isolated IVH. Although clinicians generally appear to prefer less-invasive modalities as CTA and MRI/MRA to DSA, very little is known on the yield of these modalities in patients with isolated IVH.

Clinical implications and future research

- From the currently available data, it is not possible to derive clear recommendations with regard to patient selection and the type of angiographic examinations that should be performed in patients with isolated IVH. The results reported in Chapter 7 underline the need for more data on the diagnostic value of CTA and of MRI/MRA in patients with isolated IVH. Until then it will remain unclear whether DSA can be re placed by less-invasive modalities in these patients. Until further information is available, findings of the DIAGRAM cohort study could be applied to patients with isolated IVH, since there may be considerable overlap in aetiologies of ICH and isolated IVH.
- Isolated IVH is a rare condition, therefore an (international) registry of clinical characteristics and outcomes of diagnostic workup may be helpful to gain insight into underlying aetiologies and risk factors for an underlying macrovascular cause in these patients.

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CHAPTER 9

Summary
Samenvatting (Dutch summary)
Acknowledgements
Dankwoord (personal acknowledgements)
Curriculum Vitae
List of publications

SUMMARY

In this thesis the epidemiology of non-traumatic intracerebral haemorrhage (ICH) is described, as is the diagnostic value of non-contrast CT (NCCT) and angiographic modalities in the diagnostic workup of patients with ICH or isolated intraventricular haemorrhage (IVH).

PART I: Epidemiology of ICH

In **Chapter 2** we systematically reviewed studies on ICH epidemiology from January 1980 to November 2010, and performed a meta-analysis of population-based data on incidence, case-fatality and functional outcome. We selected 36 eligible studies, which described 44 time periods.

During 28 034 233 person-years of observation, 8145 persons had had a non-traumatic ICH, resulting in an overall ICH incidence of 24.6 per 100.000 person-years (95% confidence interval (CI) 19.7-30.7). We observed that ICH incidence had remained stable between 1980 and 2008, and was comparable in men and women. Incidence ratios increased with age: from 0.10 for people ≤ 45 years to 9.6 for people older than 85 years. We observed a two times higher rate for Asian people. We retrieved data on case fatality at 1 month from 26 study populations in 35 time periods. Median case fatality at 1 month was 40.4% (range 13.1-61.0) and did not decrease over time. Case fatality was much lower in Japan (16.7%) than elsewhere (42.3%). We found six studies that reported on functional outcome, the independency rates varied between 12% and 39%.

PART II: Imaging of non-traumatic ICH and IVH

In **Chapter 3** we studied early intracerebral haematoma expansion in patients with aneurysmal subarachnoid haemorrhage (aSAH). We selected 49 adult patients with ICH caused by aneurysmal rupture, who had been admitted in the University Medical Center Utrecht between January 2003 and November 2008. In all patients a second NCCT had been performed within 48 hours after the ictus. Haematoma expansion was present in 12 patients (24%), and was explained by aneurysmal re-rupture in 6 (50%) of these patients. We concluded that a substantial proportion of patients with aneurysmal ICH show haematoma expansion within 48 hours, without evidence of re-rupture of the original aneurysm.

External validation of the Secondary ICH (SICH) score was described in **Chapter 4.** In a Dutch validation cohort, an underlying macrovascular cause was identified in 48 of 204 patients (24%), while in the derivation cohort 91 of 623 patients (15%) had a macrovascular cause.
The SICH score showed modest calibration (Hosmer-Lemeshow test, *P*=0.06) and modest discriminative ability (*c* statistic 0.73; 95% CI 0.65-0.80). The strongest predictor of a macrovascular cause was the proposed NCCT categorization, with a slightly better discrimination than the SICH score (*c* statistic 0.79; 95% CI 0.72-0.86). We found a substantial interobserver agreement for NCCT categorization (κ statistic 0.64; 95% CI, 0.55–0.73), which implies that training may be required in order to use this tool to determine the probability of an underlying macrovascular cause in individual patients with ICH.

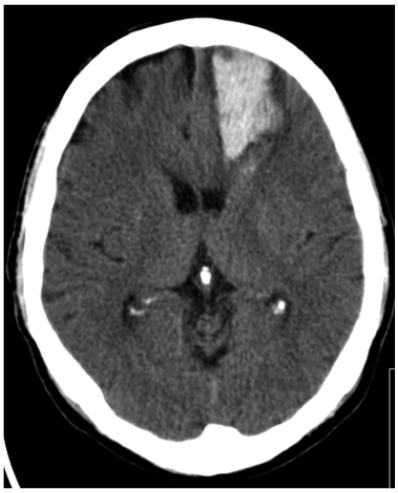
In **Chapter 5** we describe the diagnostic yield and accuracy of CT angiography (CTA), and of additional MR imaging/angiography (MRI/MRA) and digital subtraction angiography (DSA) for detection of macrovascular causes of ICH. The reference standard was the best available evidence from all findings during follow-up (median duration of 450 days). We enrolled 298 patients, aged 18 to 70 years, excluding those older than 45 years of age with hypertension and ICH in basal ganglia, thalamus, or posterior fossa. A macrovascular cause was identified in 69 patients (23%). The overall yield of CTA and MRI/MRA for detection of a macrovascular cause was slightly higher than the yield of early CTA as a single modality (18 versus 17%), whereas the combination of CTA, MRI/MRA and DSA increased the overall yield to 23%. The positive predictive value (PPV) of CTA was 72%, of additional MRI/MRA 35%, and of additional DSA 100%. The standardised diagnostic workup failed to identify a cavernoma in one patient, which was identified by a repeated MRI. Predictors for a macrovascular cause were younger age, lobar or posterior fossa ICH location, and absence of signs of small vessel disease on non-contrast CT. The discriminative ability of the proposed prediction score was good (*c* statistic 0.83, 95%CI 0.78-0.88) for estimation of low (<5%), intermediate (5-15%) and high (>15%) risk of a macrovascular cause. Prediction charts were generated for patients aged 18-50 years old and patients aged 51-70.
We conclude that CTA is an appropriate initial investigation and additional MRI/MRA may find cavernomas or alternative diagnoses, but DSA is indicated to find macrovascular causes undetected by CTA or MRI/MRA. The DIAGRAM prediction score may be helpful for clinical practice to estimate the probability of finding a macrovascular cause, and needs external validation.

In **Chapter 6** a Markov decision-analytic model was developed to examine the cost-effectiveness of different diagnostic strategies to find macrovascular causes in patients with ICH. We report on differences in health outcomes and costs between four diagnostic strategies: CTA (strategy 1) vs. the combination of CTA and MRI/MRA (strategy 2) vs. de combination of CTA, MRI/MRA and DSA, with DSA in selected patients (strategy 3) and with DSA in all patients (strategy 4). Input parameters were derived from a prospective cohort study (Chapter 5), the literature and expert opinion.
In the base-case scenario (prevalence of macrovascular causes of 23%), adding MRI/MRA and DSA to CTA as single investigation did not improve health outcomes but increased healthcare costs. Therefore strategy 1 has the highest probability of being cost-effective. A sensitivity analysis showed that strategy 1 is less likely to be cost-effective when prevalence of macrovascular causes is high (prevalence 40%).

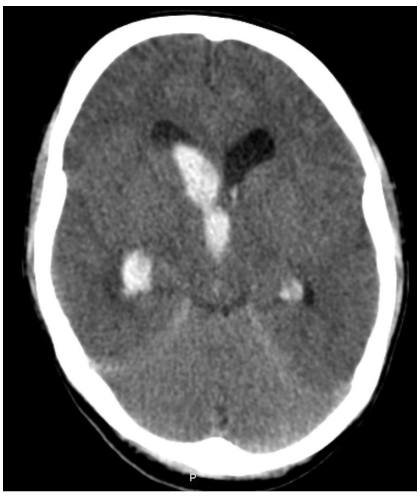
Chapter 7 provides a case series and systematic review of the literature on the yield of angiographic examinations in patients with isolated IVH. We reviewed medical records of patients with IVH admitted to the University Medical Center Utrecht and identified 39 patients of whom 30 underwent an angiographic study. CTA suggested a macrovascular cause in nine patients, which was confirmed by DSA in seven. In the literature we found 15 studies describing 204 patients. Pooled analysis showed a yield of 58% for DSA (95% CI 47-68%). One small study described the yield of CTA or MRI/MRA (0%; 4 patients). Yield of angiographic imaging decreased with increasing age but was not affected by presence of hypertension or anticoagulant use. In conclusion, the reported yield of DSA in isolated IVH varies considerably, which is probably related to confounding by indication. Data on the yield of CTA and MRI/MRA in patients with isolated IVH are urgently needed. The yield is higher in younger patients but based on the available data it is not possible to set age or other criteria for patients in whom DSA can be safely omitted.

SAMENVATTING

De term 'hersenbloeding' is een verzamelnaam voor bloedingen die in de verschillende ruimtes binnen de schedel kunnen optreden. Een intracerebrale bloeding (ICB) is een bloeding in het hersenweefsel zelf (figuur 1), een intraventriculaire bloeding (IVB) is een bloeding in met hersenvocht gevulde ruimtes (figuur 2), hersenkamers of ventrikels genoemd. Dit proefschrift richt zich op niet-traumatische hersenbloedingen, dit betekent dat hersenbloedingen als gevolg van hoofdhersenletsel buiten beschouwing worden gelaten.



Figuur 1 Intracerebrale bloeding



Figuur 2 Intraventriculaire bloeding

Door de toegenomen beschikbaarheid van verschillende beeldvormende technieken is het sinds begin jaren '80 veel beter mogelijk om epidemiologisch onderzoek te doen naar het optreden van ICB.

In deel I van dit proefschrift wordt de epidemiologie van ICB in de afgelopen decennia beschreven. Deel II gaat over het inzetten van beeldvormend onderzoek bij patiënten met een ICB of IVB, met een focus op het achterhalen van de onderliggende oorzaak van de bloeding.

Een belangrijke oorzaak van ICB, en waarschijnlijk ook van IVB, zijn vaatveranderingen in de kleinere hersenvaten. De verzamelnaam voor deze vaatveranderingen is microvasculopathie of 'small vessel disease'.

In afwezigheid van small vessel disease of een andere oorzaak voor de ICB of IVB kan nader onderzoek worden gedaan naar een zogenoemde macrovasculaire oorzaak. Met ma-

crovasculaire oorzaken bedoelen we afwijkingen van de grotere hersenvaten waaruit een bloeding kan ontstaan, zoals een aneurysma, arterioveneuze malformatie (AVM), durale AV fistel (DAVF), cavernoom, 'developmental venous anomaly' (DVA) en een cerebrale veneuze sinustrombose (CVST). Het op tijd ontdekken van een onderliggende macrovasculaire oorzaak is van belang omdat behandeling vaak mogelijk is en zo herhaalde hersenbloedingen voorkomen kunnen worden. Afwijkingen van hersenvaten kunnen in beeld worden gebracht met CT angiografie (CTA), MR imaging/angiografie (MRI/MRA) en digitale subtractie angiografie (DSA).

Verklarende woordenlijst

Incidentie	aantal nieuwe gevallen van een ziekte per tijdseenheid
Prevalentie	het aantal gevallen met een bepaalde aandoening op een specifiek moment
Hematoom	bloeding
Inclusie	een persoon laten deelnemen aan een onderzoek
Mediaan	het midden van een verdeling of gegevensverzameling

DEEL I: Epidemiologie van intracerebrale bloedingen

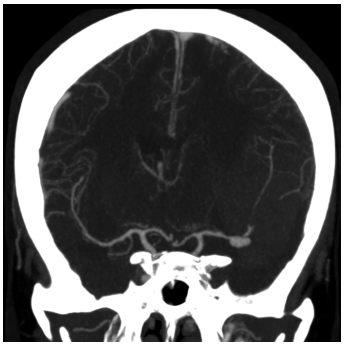
In **Hoofdstuk 2** onderzoeken we de incidentie, de kans op overlijden en het functionele herstel na een ICB in relatie tot leeftijd, geslacht, etniciteit, en veranderingen in de tijd sinds 1980. In PubMed en Embase werd met vooraf opgestelde selectiecriteria gezocht naar bevolkingsonderzoeken gepubliceerd tussen januari 1980 en november 2008. De geselecteerde 36 onderzoeken beschreven 44 tijdsperiodes (het middelste jaar van de onderzoeksperiode varieerde tussen 1983 en 2006), en 8145 patiënten met een ICB. De gemiddelde incidentie was 24,6 per 100.000 persoonsjaren (95% betrouwbaarheidsinterval (BI) 19,7-30,7), deze bleef gelijk in de periode tussen 1980 en 2008, en was niet duidelijk lager bij vrouwen dan bij mannen (gemiddelde incidentie ratio 0,85; 95% BI 0,61-1,18). In vergelijking met de leeftijdsgroep tussen 45 en 54 jaar oud nam de incidentieratio toe van 0,10 (95% BI 0,06-0,14) voor mensen jonger dan 45 jaar naar 9,6 (6,6-13,9) voor mensen ouder dan 85 jaar. De incidentie per 100.000 persoonsjaren was 24,2 (95% BI 20,9-28,0) voor blanken; 22,9 (14,8-35,6) voor zwarten; 19,6 (15,7-24,5) voor latino's en 51,8 (38,8-69,3) voor Aziaten. De mediane kans op overlijden was 40,4% na 1 maand (spreiding

13,1-61,0), nam niet af in de tijd en was lager in Japan (16,7%; 95% BI 15,0-18,5) dan elders (42,3%, 40,9-43,6). In de zes studies die rapporteerden over functioneel herstel lag de kans op goed functioneel herstel na een ICB tussen 12% en 39%.

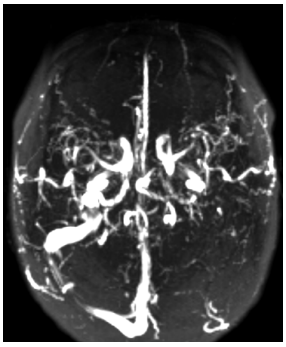
DEEL II: Beeldvormend onderzoek van intracerebrale en intraventriculaire bloedingen

In **Hoofdstuk 3** wordt beschreven hoe vaak hematoomgroei voorkomt bij patiënten met een intracerebraal hematoom uit een gebarsten aneurysma (aneurysmaruptuur). Er werden 49 patiënten geselecteerd met een intracerebraal hematoom na aneurysmaruptuur, het betrof patiënten die opgenomen waren in het Universitair Medisch Centrum Utrecht (UMCU) tussen januari 2003 en november 2008. Bij alle patiënten werd een tweede CT scan van de hersenen gemaakt binnen 48 uur na het ontstaan van de bloeding. Hematoomgroei werd gezien bij 12 patiënten (24%), en kon bij 6 patiënten (50%) verklaard worden door een recidiefbloeding uit het aneurysma. De conclusie luidt dat hematoomgroei na aneurysmaruptuur ook voorkomt als er geen aanwijzingen voor een recidiefbloeding zijn. De mechanismen die leiden tot hematoomgroei bij patiënten zonder recidiefbloeding na aneurysmaruptuur zijn nog onduidelijk.

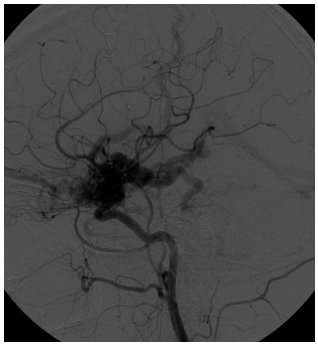
In de Verenigde Staten (VS) werd de Secondary IntraCerebral Hemorrhage (SICH) score ontwikkeld om de aanwezigheid van een macrovasculaire oorzaak van een ICB te voorspellen aan de hand van leeftijd, hoge bloeddruk, gebruik van bloedverdunners en diverse kenmerken van het hematoom zelf; de zogenoemde 'non-contrast CT (NCCT) categorization'. De SICH score bleek een goede voorspellende waarde te hebben voor de aanwezigheid van een macrovasculaire oorzaak van een ICB in twee ziekenhuizen in de VS. Om na te gaan of deze score ook toegepast kan worden bij Nederlandse patiënten werd een externe validatie van de SICH score verricht, dit wordt beschreven in **Hoofdstuk 4**. Het validatiecohort bestond uit 204 Nederlandse patiënten met een ICB, opgenomen in het UMCU tussen februari 2003 en mei 2011. Er werd een macrovasculaire oorzaak gevonden bij 48 van de 204 patiënten (24%) in het validatiecohort, en bij 91 van de 623 patiënten (15%) in het oorspronkelijke cohort. Het onderscheidend vermogen (discriminatie) van de SICH score was beperkt (c statistic 0,73; 95% BI 0,65-0,80), en dit gold ook voor de ijking (calibratie) van de score (Hosmer-Lemeshow test, P=0.06). De sterkste voorspeller voor een macrovasculaire oorzaak was de 'NCCT categorization', met een net wat betere discriminatie dan de SICH score zelf (c statistic 0,79; 95% BI 0,72-0,86). Er was een aanzienlijk



Figuur 3 Met een CT angiografie (CTA) wordt een aneurysma als oorzaak van een ICB gevonden



Figuur 4 Een MRI scan toont een stolsel in een hersenvat, hetgeen heeft geleid tot een ICB



Figuur 5 Een digitale subtractie angiografie (DSA) toont een AVM als oorzaak van een ICB

verschil in het scoren van 'NCCT categorization' tussen verschillende beoordelaars (κ statistic 0,64; 95% BI, 0,55-0,73). Dit betekent dat scholing nodig is voordat 'NCCT categorization' in de dagelijkse praktijk gebruikt kan worden om de waarschijnlijkheid van een onderliggende macrovasculaire oorzaak in te schatten bij patiënten met een ICB.

In **Hoofdstuk 5** beschrijven we de opbrengst en nauwkeurigheid van een diagnostische strategie met CTA, MRI/MRA en DSA voor het vinden van een onderliggende macrovasculaire oorzaak van een ICB. De uitkomst van deze onderzoeken (wel of geen macrovasculaire oorzaak) werd vergeleken met alle beschikbare gegevens gedurende het (poli) klinisch volgen van de patiënten. Patiënten werden mediaan gedurende 450 dagen gevolgd. Er werden 298 volwassen patiënten met een leeftijd van 70 jaar of jonger geïncludeerd. Patiënten ouder dan 45 jaar met een hoge bloeddruk en een bloeding in specifieke hersengebieden (basale kernen, thalamus of de achterste schedelgroeve) werden uitgesloten van deelname. Een macrovasculaire oorzaak werd bij 69 (23%) van de patiënten gevonden. De opbrengst van de combinatie van CTA en MRI/MRA was iets hoger dan de opbrengst van CTA alleen (18 versus 17%), terwijl de combinatie van CTA, MRI/MRA en DSA de opbrengst verhoogde naar 23%. De aanwezigheid van een macrovasculaire oorzaak werd correct aangeduid met CTA in 72% van de patiënten, met aanvullende MRI/MRA in 35%, en met aanvullende DSA in 100% van de patiënten. Met de diagnostische strategie werd één cavernoom gemist, dit cavernoom werd gedurende het poliklinisch vervolgen van de patiënt alsnog gezien op een herhaalde MRI scan. Voorspellers voor het vinden van een macrovasculaire oorzaak zijn jonge leeftijd, een bloeding in een hersenkwab (lobaire bloeding) of in de achterste schedelgroeve, en de afwezigheid van tekenen

van hersenschade op een CT scan passend bij 'small vessel disease'. De discriminatie van de voorgestelde predictieregel was goed (c statistic 0,83, 95%BI 0,78-0,88) om in te schatten of er een laag (<5%), matig (5-15%) of hoog (>15%) risico is op een onderliggende macrovasculaire oorzaak.
De conclusie is dat CTA geschikt is om macrovasculaire oorzaken op te sporen na het optreden van een ICB, daarnaast kunnen cavernomen of niet-macrovasculaire onderliggende oorzaken met MRI/MRA aangetoond worden. DSA is het meest nauwkeurige onderzoek en is nodig om de aanwezigheid van een onderliggende macrovasculaire oorzaak aan te tonen of uit te sluiten, ook als deze nog niet ontdekt werd met CTA of MRI/MRA. De DIAGRAM predictiescore kan artsen helpen om de waarschijnlijkheid van een onderliggende macrovasculaire oorzaak in te schatten bij een patiënt met een ICB. Wel is een externe validatie van de score noodzakelijk.

In **Hoofdstuk 6** beschrijven we het bouwen van een Markov-model, een computermodel waarmee de levensloop van patiënten na het overleven van een hersenbloeding gesimuleerd kan worden. Hiermee werd de kosteneffectiviteit geanalyseerd van verschillende diagnostische strategieën voor het opsporen van een onderliggende macrovasculaire oorzaak bij patiënten met een ICB. We rapporteren over verschillen in uitkomst en kosten tussen vier diagnostische strategieën: alleen CTA (strategie 1) versus de combinatie van CTA en MRI/MRA (strategie 2) versus de combinatie van CTA, MRI/MRA en DSA, met selectief toepassen van DSA (strategie 3) of DSA bij alle patiënten (strategie 4). De parameters die in het model zijn opgenomen, werden gebaseerd op de resultaten van het onderzoek dat wordt beschreven in **Hoofdstuk 5**, de wetenschappelijke literatuur en de mening van experts. In het uitgangsscenario gingen we uit van een prevalentie van macrovasculaire oorzaken van 23%. Het bleek dat het verrichten van MRI/MRA en DSA na CTA de uitkomst op lange termijn niet verbeterde, maar wel leidde tot hogere gezondheidszorgkosten. Om die reden is strategie 1 het meest waarschijnlijk kosteneffectief ten opzichte van de andere strategieën. Een extra analyse toonde dat de waarschijnlijkheid dat strategie 1 het meest kosteneffectief is afneemt als de prevalentie van macrovasculaire oorzaken in het cohort hoger is (prevalentie van 40%).

Hoofdstuk 7 gaat over de opbrengst van angiografische onderzoeken (CTA, MRI/MRA en DSA) bij patiënten met een geïsoleerde IVB, wat betekent dat er alleen bloed in de hersenkamers werd gezien en niet op andere plaatsen binnen de schedel. We doorzochten

de medische dossiers van patiënten die met een geïsoleerde IVB werden opgenomen in het UMCU en vonden 39 patiënten, waarvan 30 patiënten één of meer angiografische onderzoeken ondergingen. Met CTA werd bij negen patiënten een macrovasculaire oorzaak gezien, dit werd bij zeven patiënten bevestigd met DSA. In de wetenschappelijke literatuur vonden we 15 studies waarin 204 patiënten met een geïsoleerde IVB werden beschreven. Uit het samenvoegen van deze bevindingen bleek dat met DSA gemiddeld bij 58% (95% BI 47-68) van deze IVB-patiënten een macrovasculaire oorzaak wordt gevonden. Een kleine studie van 4 patiënten beschreef een opbrengst van 0% van CTA of MRI/MRA. De opbrengst van angiografische onderzoeken bij patiënten met een geïsoleerde IVB nam af met toenemen van de leeftijd, maar bleek niet te worden beïnvloed door de aanwezigheid van een hoge bloeddruk of het gebruik van bloedverdunners. We concluderen dat de gerapporteerde opbrengst van DSA bij patiënten met een geïsoleerde IVB erg variabel is, vermoedelijk als gevolg van verschillen in selectie van patiënten. Meer data over de opbrengst van CTA en MRI/MRA in deze groep patiënten is dringend noodzakelijk. De opbrengst is hoger bij jongere patiënten, maar op basis van de beschikbare data kan geen leeftijdsgrens getrokken worden waarboven angiografisch onderzoek niet meer zinvol is.

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Chapter 2

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Chapter 5

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Chapter 6

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[1] Deceased February 2013

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"Alice came to a fork in the road.
'Which road do I take?' she asked.
'Where do you want to go?' responded the Cheshire Cat.
'I don't know,' Alice answered.
'Then,' said the Cat, 'it doesn't matter."

Lewis Carroll, *Alice in Wonderland*

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CURRICULUM VITAE

Charlotte van Asch werd geboren op 16 maart 1980 te 's-Hertogenbosch. In 1998 behaalde zij haar VWO-diploma aan het Bisschoppelijk College Schöndeln te Roermond.
Zij studeerde van 1998 tot 2001 farmacie en vervolgens van 2001 tot 2007 geneeskunde aan de Universiteit Utrecht. In 2004 onderzocht zij tijdens een stage op de afdeling Kinderlongziekten van het Wilhelmina Kinderziekenhuis de relatie tussen uitgeademd stikstofoxide en atopie, onder begeleiding van dr. W.A.F. Balemans en prof.dr. C.K. van der Ent. Zij was van 2004 tot en met 2005 lid van de redactie van de Studenteneditie van het Nederlands Tijdschrift van Geneeskunde, in 2005 als eindredacteur. Tijdens het werk als afdelingsassistent op de afdeling Neurochirurgie van het UMC Utrecht en het coschap neurologie in het St. Antonius ziekenhuis te Nieuwegein groeide haar interesse in de neurologie. Zij deed tijdens een wetenschappelijke stage in het zesde studiejaar onderzoek naar het effect van acute hydrocephalus op de cerebrale perfusie van patiënten met een aneurysmale subarachnoïdale bloeding, onder begeleiding van dr. I.C. van der Schaaf en prof.dr. G.J.E. Rinkel. Tijdens het keuzecoschap neurologie maakte zij definitief de keuze voor neurologie en solliciteerde naar een opleidingsplaats. Na het behalen van het artsexamen begon zij in 2007 aan de opleiding tot neuroloog in het UMC Utrecht met als opleiders prof.dr. J.H.J. Wokke en prof.dr. L.J. Kappelle. In 2008 begon zij met het wetenschappelijk onderzoek dat in dit proefschrift wordt beschreven. In 2012 werd zij voorzitter van de Vereniging Arts-Assistenten Neurologie (VAAN) en was zij adviserend bestuurslid van het bestuur van de Nederlandse Vereniging van Neurologie (NVN). Tijdens de opleiding tot neuroloog werd haar interesse in epilepsie, slaapstoornissen en klinische neurofysiologie gewekt, zij volgde enkele cursussen op dit gebied en werkt van juli tot en met december 2015 als aios neurologie in expertisecentrum Kempenhaeghe. Zij zal de opleiding tot neuroloog begin 2016 afronden en zich daarna verder verdiepen in de epileptologie en klinische neurofysiologie in het Academisch Centrum voor Epileptologie Kempenhaeghe & Maastricht UMC+.

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