

REVIEW



## What are the images used to diagnose and assess suspected strokes?: A systematic literature review of care in four European countries

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### ABSTRACT

**Introduction:** The cost-effectiveness of clinical interventions is often assessed using current care as comparator. However, evidence suggests practice variation in stroke imaging across countries. For the purpose of feeding into cost-effectiveness analysis, this research aims to describe the patterns of stroke imaging, examine practice variations across countries and, as such, obtain results reflecting current care.

**Areas covered:** A systematic literature review was conducted to identify original studies reporting the imaging workup used in acute stroke care in clinical practice in Hungary, Germany, Sweden and the UK. Information regarding the type and frequency of stroke imaging was analysed. Computed Tomography (CT) was reported as the main diagnostic imaging modality used in stroke care (78–98% across patient profiles and time periods). This review revealed patterns that were not observed in individual studies. Comparisons of UK studies revealed considerable variations in the proportion of scanned patients and timing of imaging.

**Expert commentary:** While the evidence about thrombectomy is difficult to translate in clinical practice, the evidence regarding the optimal imaging approach to diagnose stroke patients is lacking. The heterogeneity in stroke imaging reinforces the need to compare the quality of stroke care within and between countries.

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## 1. Introduction

The rapid evolution of stroke treatment over the past years has been geared toward thrombolysis and more recently thrombectomy. Patients presenting with stroke-like symptoms in the hospital require a quick assessment of brain damage and perfusion impairment, making the use of neuroimaging essential. Besides common modalities such as computed tomography (CT), CT angiography (CTA), and magnetic resonance imaging (MRI), advanced imaging techniques such as perfusion-computed tomography (CTP) and magnetic resonance angiography (MRA) are available and able to provide relevant information during the diagnostic workup in stroke care. Among the new emerging technologies, dual energy CT, and more recently, spectral photon-counting CT (SPCCT) are innovative imaging tools expected to improve stroke treatment decision-making in emergency settings by better quantification of brain perfusion impairment [1]. However, the potential added value of these new techniques in acute stroke care is currently unknown and can only be determined by comparison with the modalities used in current clinical care.

In the management of complex diseases, such as stroke, diagnostic imaging tests influence outcomes indirectly by determining the treatment choice and clinical decision-making [2]. Thus, the relation between the use of an imaging test and the health outcomes is uncertain, making cost-effectiveness

evaluations of diagnostic tests sometimes difficult [3]. A crucial first step in assessing the potential value of an imaging technology is to understand the specific clinical context and the current level of provision of competing technologies used in clinical practice: Who and how do we image? Why do we image? For these reasons, assessing the relative value of new technologies such as SPCCT, both in terms of patient outcome and costs, requires an exact understanding of the current imaging practice in acute stroke care. Clinical guidelines are often assumed to represent current practice and used as a proxy in cost-effectiveness evaluations. The European Stroke Organisation (ESO) guidelines for the management of ischemic stroke recommend that patients with suspected transient ischemic attack (TIA) or stroke receive urgent axial brain imaging (cranial CT or MRI). Urgent vascular imaging, such as ultrasound, CTA or MRA, is recommended for patients with a TIA or minor stroke [4].

The assumption that current care is aligned on guidelines is inappropriate when clinical practice substantially differs from guidelines and problematic when clinical practice differs between hospitals or countries. Evidence suggests differences in stroke care [5] and outcomes [6–9] within European countries. The scarcity of and the need for international comparisons and databases have been pointed out by different authors [6–8], suggesting that variations in care need to be understood better.

In this context, we conducted a systematic literature review to identify studies informing of the diagnostic patterns in acute stroke imaging and to examine variations between countries.

## 2. Method

### 2.1. Search strategy

A *de novo* search strategy for finding relevant papers was designed by the researcher (ACP) together with the biomedical information specialist of the medical library of Erasmus Medical Centre of Rotterdam, The Netherlands. The search strategy can be found in the supplemental online material number 1. The following databases were researched on the 18 August 2016: Embase, Medline, Web of Science, the Cochrane Library and Google Scholar. All records retrieved from the databases were merged into one database and duplicates were removed. The remaining studies were screened by title and abstract by two independent reviewers (ACP and either KR or JLS) and ineligible publications were excluded based on predefined criteria (described below). The results of both reviewers were compared and any discrepancies were discussed and resolved by consensus. After title/abstract selection, all remaining publications were read in their entirety to determine which ones met all inclusion and exclusion criteria (ACP).

### 2.2. Inclusion and exclusion criteria

Non-English-language publications were excluded, as were conference abstracts, editorials, letters, reviews and books. Articles published before 2008 were also excluded since that was the year in which the latest ESO guidelines for the management of ischemic stroke were published. Non-observational studies such as pilot studies, experimental studies, and RCTs (randomized controlled trials) which did not include an arm focusing on current care were excluded.

Because we were interested in examining a range of healthcare systems, articles were eligible for inclusion only if they reported information on the diagnosis pattern of suspected stroke patients in the real-life practice of all types of hospitals (university, non-university, specialized, community, county) or clinics of Germany, Hungary, Sweden or the UK. Whereas Sweden is known for its early adoption of medical technologies, Hungary tends to be a late adopter. Besides, the UK is of major interest for its publicly funded system while Germany is characterized by its decentralized healthcare organization in which private practitioners play a relatively important role.

The therapeutic scope of the selected studies included ischemic or hemorrhagic stroke, TIA, cerebellar infarction, intracerebral hemorrhage or subarachnoid hemorrhage. Studies based on a patient population were included only if the sample contained more than an arbitrary cut off of 100 patients. Articles using data collected before and after 2008 were only included if the results after 2008 could be separated from the previous years.

### 2.3. Data extraction

One reviewer extracted the main characteristics from the included studies: first author's name, year of publication,

country, clinical setting, study population, study design, origin of data, data collection period and the study goal.

Data extracted with the aim of describing and analyzing the state of care included timing indicators related to the process of stroke care and information on the imaging techniques used. Whenever the data was available, the proportion of patients benefiting from each technology was reported. Extracted data were then analyzed and aggregated in a qualitative and quantitative synthesis. The extraction, calculation and reporting method is detailed in the supplementary material 2.

## 3. Results

### 3.1. Search results

Figure 1 provides an overview of the search steps based on the Preferred Reported Items for Systematic Review and Meta-Analysis (PRISMA) guidelines [10]. The literature search using the Embase, Medline, Web of Science, the Cochrane Library and Google Scholar databases yielded 1565, 1636, 666, 59 and 200 records, respectively. After duplicates were removed, 2481 records remained for title and abstract selection, which eventually resulted in the selection of 122 records. The full-text assessment identified 15 articles that met all the inclusion criteria.

### 3.2. Study characteristics

The general characteristics of the included studies are presented in Table 1. Three studies were conducted in Germany [6,11,12], three in Sweden [13–15], and 10 in the UK [5,12,16–23]; no study conducted in Hungary met the inclusion criteria for the final analysis. One of the three studies conducted in Germany reported results based on a combination of German and Austrian hospitals [11]. Nevertheless, given the detailed level of information provided, the choice was made to include this study for final analysis. Another study [12] describing care in both the UK and Germany was included for analysis based on the fact that information for each country was available.

Most selected articles were observational studies based on national registries, among which the Stroke Improvement National Audit Program (SINAP) and the Swedish stroke register that were found in 4 [17,18,20,21] and 2 studies [13,15], respectively. All the studies reported individual patient data, except the one from Jäkel et al. that was designed on data collected from telephone interviews with clinicians [12]. Since this study reported data related to TIA patients only, we decided to include it for the final quantitative synthesis. The study populations in the different publications differed slightly across studies. Most of them focused on stroke patients [5,6,13–19,21–23], two on ischemic stroke patients [11,20] and one on TIA patients [12]. Most of the studies based on a patient population database focused on adults, with the exception of one paper on children from 29 days to 15.99 years [23]. Among the adult populations studied, the mean reported ages varied slightly.

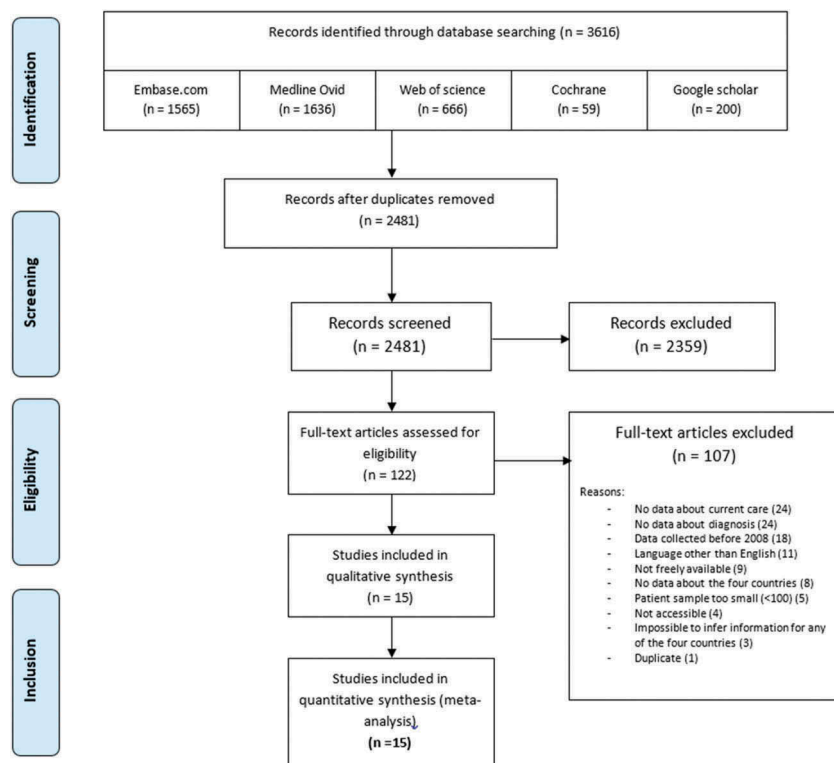


Figure 1. Preferred reporting items for systematic review and meta-analysis (PRISMA) flowchart.

Data found in the different studies were related to a wide range of hospital groups. While two studies included all hospitals in a country [13,15], the other studies focused on a geographic or institutional subgroup of hospitals. Public hospitals were the center of investigation in two studies [5,22] while emergency hospitals were selected for analysis in one study [14]. Finally, one studies restricted the observations to stroke centers [11].

The aims widely varied across the different studies and covered a wide range of topics from a qualitative and/or quantitative perspective. The most frequent topics covered the relationship between the process of care and mortality, the pattern and magnitude of variation of care over the week, inequalities in the delivery of care and outcomes associated with a reconfiguration of care, and real-world trends in the management of acute stroke patients.

The level and amount of information regarding the type and frequency of imaging technique used are heterogeneously documented across studies. While detailed data were extracted from the studies conducted in Germany and the UK, more general information was found in the Swedish studies. Furthermore, the majority of the papers focusing on the UK reported information about the timing of the imaging workup in clinical settings. Nevertheless, after consolidation of the data originating from different authors, it was possible to present results that go beyond the findings provided by individual studies and identify patterns per country.

Studies performed in the UK often attempted to assess the quality of care by examining the use of imaging tests over time. Figure 2 plots the proportion of patients tested with a brain scan per time range after admission to the hospital in the UK. Data related to different investigated periods, different

time categories of hospital admission (in hours or out of hours), and different geographic areas are presented and can be compared. Based on Figure 2, 51–70% of patients underwent a brain scan within 3 h following hospital admission and that 78–95% of the patients had undergone a brain scan within 24 h. Differences in the reported values can arise for various reasons. That is, since the results are drawn from different studies, some of the observed variations could be attributed to differences in study design, the period of investigation, geographical area, type of investigated health center and chance (due to sampling error). To minimize the effect of potential bias, focus on the results reported in a same publication might be relevant. For example, looking at the results by Ramsay, the frequency of brain scan use at 3 h varies from 56% in Greater Manchester to 70% in London which most likely reflects true differences in the way imaging is delivered to stroke patients across the UK. Ramsay also reports the frequency of brain scan use at 3 h and 24 h for two different areas. Strong variations are observed between London (70% of patients scanned at 3 h and 95% at 24 h) and urban areas of England where acute stroke services were not centralized (54% scanned at 3 h and 91% at 24 h).

Overall, both Lazzarino and Palmer reported lower proportions than the other authors, partly because they looked at the time in days after admission rather than in hours after admission. Their results are partly due to the fact that they used a timing indicator which reflects the time in days after admission rather than in hours. Thus, they reported that 35–48% of patients received a head scan during the day of admission. This low proportion might be partially influenced by the fact that some patients arriving at the hospital later in the day

Table 1. Study characteristics of the selected papers.

Authors	Publication year	Country of research	Health center	Number of patients	Patients' characteristics	Type of study/study design	Origin of data	Data collection period	Study goal	Ref.
Wiedmann et al.	2014	Germany	627 hospitals	260,800	Stroke patients, Mean age: 73 Male: 50%	Analysis of collected data	Regional quality assurance projects cooperating in the framework of the German Stroke Registers Study Group	2012	To present the quality indicators for acute hospital care of stroke patients in Germany.	[6]
Singer et al.	2013	Germany and Austria	12 stroke centers in Germany and Austria	734	Ischemic patients undergoing EVT Median age: 70 Male: 55% Median NIHSS at admission: 16	Observational registry study	EndoStroke	January 2011–November 2012	To focus on preprocedural imaging, patient handling and referral, as well as on different treatment modalities in mechanical recanalization.	[11]
Jäkel et al.	2012	Germany and United Kingdom	Unknown	NA	Suspected TIA patients	Analysis of data collected from tele-interviews	125 interviews (number not provided for the countries of interest) of ER physicians, neurologists and geriatricians	Not reported	To gain insights into real-world global trends of the current management approaches for patients with suspected and diagnosed TIA and highlight the unmet need and areas of improvement.	[12]
Asplund et al.	2015	Sweden	All hospitals in Sweden admitting acute stroke patients (72 hospitals)	49,144	Stroke patients Mean age: 73.9–76.2 Male: 50.8–52.8% (ranges across subgroups)	Clinical data collected during hospital stay + structural data collected from a questionnaire completed by hospital staff	Riks-Stroke, the Swedish stroke register	January 2012–December 2013	To explore to what extent differences in stroke care procedures and outcomes among university, large nonuniversity, and community hospitals exist.	[13]
Sundström et al.	2015	Sweden	9 emergency hospitals in Western Sweden (each with a stroke unit and the emergency medical services)	1,376	Stroke patients Mean age: 76 Male: 51%	Observational retrospective design	Data gathered from hospital and emergency medical service records, including the hospital diagnosis register	December 2010–April 2011	To identify weak links in the early chain of care for acute stroke.	[14]
Appelros et al.	2014	Sweden	All hospitals in Sweden (80 hospitals)	320,181	Stroke patients	Observational study	Riks-Stroke, the Swedish stroke register	1995–2010	To describe time trends for treatment and outcome data and to discuss if changes could be attributed to quality changes in stroke care.	[15]
Bray et al.	2016	United Kingdom	199 hospitals in England and Wales	74,307	Stroke patients older than 16 Median age: 77	Nationwide, registry-based, prospective cohort study	Sentinel Stroke National Audit Programme (SSNAP)	April 2013–March 2014	To describe the pattern and magnitude of variation in the quality of acute stroke care across the entire week.	[16]

(Continued)



Table 1. (Continued).

Authors	Publication year	Country of research	Health center	Number of patients	Patients' characteristics	Type of study/study design	Origin of data	Data collection period	Study goal	Ref.
Mallick et al.	2015	United Kingdom	All acute NHS hospitals in the South of England	139	Stroke patients, children (aged 29 days to 15.99) Group of AIS: median age 3.8, male: 51% Group of HS: median age 9, male: 62%	Prospective population-based cohort study	Case notes, electronic hospital admission databases and radiology records	July 2008–June 2009	To assess pre-hospital and in-hospital delays to the diagnosis of AIS and HS in children in the UK and to evaluate factors influencing delays.	[23]
Ramsay et al.	2015	United Kingdom	51 hospitals precentralization and 44 hospitals postcentralization	38,623	Adults stroke patients Mean age: 73 Male: 49.9%	National audit	Precentralization: National Sentinel Stroke Clinical Audit Postcentralization: Stroke Improvement National Audit Program (SINAP)	Precentralization: April 2008–April 2012 Postcentralization: April 2010–December 2012	To explain differences in stroke mortality after centralization of care in the UK.	[17]
Campbell et al.	2014	United Kingdom	130 hospitals in England	45,726	Stroke patients Median age = 77 Male: 49.1%	Prospective national clinical audit	Stroke Improvement National Audit Programme (SINAP)	April 2010–January 2012	To identify if inequalities in the quality of care and mortality exist in contemporary stroke care in England.	[18]
Power et al.	2014	United Kingdom	24 National Health Service hospitals and 9 control hospitals in the Northwest of England	6,592	Stroke patients Male: 47.3% (control group)	Randomized trial (with one arm being current care)	Registry of discharged patients coded for stroke	July 2008–December 2010	To determine whether hospitals participating in the QIC improved more than the control group on bundle compliance.	[19]
Bray et al.	2013	United Kingdom	106 hospitals	36,197	Ischemic stroke adult patients Median age: 77 Male: 49%	Observational prospective cohort study	Two national clinical audits, the Stroke Improvement National Audit Programme (SINAP) and the National Sentinel Stroke Audit	April 2010–November 2011	To estimate the relations between the organization of stroke services, process measures of care quality, and 30 day mortality in patients admitted with acute ischemic stroke.	[20]
Hunter et al.	2013	United Kingdom	After phase: 8 HASUS in London (complemented by SUS for ongoing inpatient care if necessary after 72 h)	3,463	Stroke patients Mean age: 71.6 Male: 53% ('after' period sample)	Prospective registry (SLSR), retrospective datasets (SINAP and LMDS) and national audit (Sentinel)	South London Stroke Register (SLSR), audit from two North London hospitals, London Minimum Dataset (LMDS), Stroke Improvement National Audit Programme (SINAP), national Sentinel Stroke Audit and London Ambulance Service	Before: July 2007–July 2008 After: July 2010–June 2011	To investigate differences in clinical outcomes and costs between the new centralized and old models.	[21]

(Continued)

Table 1. (Continued).

Authors	Publication year	Country of research	Health center	Number of patients	Patients' characteristics	Type of study/study design	Origin of data	Data collection period	Study goal	Ref.
Palmer et al.	2012	United Kingdom	English National Health Service public hospitals	93,621	Stroke patients Mean age: 73.8–74.5 (weekday versus weekend) Male: 47.2–48.5%	Retrospective cohort study	Hospital Episode Statistics (HES)	April 2009–March 2010	To examine the association between day of admission and measures of the quality and safety of the care received by patients with stroke.	[22]
Lazzarino et al.	2011	United Kingdom	Any English public hospital	209,174	Stroke patients older than 17	Database analysis	Hospital Episode Statistics (HES)	April 2006–March 2009	To describe the variation in use of BIS (Brain Imaging Scan (CT or MRI) among English public hospitals and identify any patient groups being excluded from appropriate care.	[5]

HASU: Hyper acute stroke unit.

would receive a head scan after midnight and be registered as 'the day after' in the study. However, this consideration can probably not fully explain the low frequency that they reported. That is, by reporting 59% of patients tested during their day of admission or the day after, Lazzarino et al. present a lower frequency than Bray, Campbell, Power and Ramsay, who report 78–95% of patients scanned within 24 h. It is worth mentioning that Lazzarino's results refer to the period of 2008–2009, which might partly explain why the frequencies they report are lower than those from authors who investigated more recent periods. Furthermore, Campbell and Palmer examined the association between the time of admission during the week and the proportion of scanned patient. They report disparities between the rate of scans delivered in hours or during the weekdays compared to the rate of scans delivered out of hours or during the weekend. Their results show that patients seen out of hours or during the weekend experience longer delays to receive a scan. Finally, it is worth mentioning that no association was found between the patient populations and the reported differences in the frequency of imaging. The inclusion criteria determining the characteristics of the patients from the different studies can be found in the supplementary material 2.

Figure 3 provides more detailed information regarding the type of imaging technologies used in clinical practice in the UK. As such, it illustrates the frequency of usage of different modalities by subgroups of patients during different periods. CT appeared to be the most frequently used modality across the investigated periods (2008–2011), places and patient profiles. While Power reported that 78% of the stroke patients received a CT scan within 24 h of hospital admission in 2009, Hunter reported that same technology was used for 94% of the stroke patients in 2010–2011. Mallick et al. also found that CT was the most common initial imaging modality for children: in their study population, 98% of the cases of hemorrhagic stroke received a CT as first imaging workup. In contrast, MRI was the initial imaging modality for 29% of the children with ischemic stroke and only 2% of the children with hemorrhagic stroke. Another notable result presented by Hunter et al. is the relatively high proportion (68%) of stroke patients imaged with MRI in the London Hyperacute Stroke Units over 2010 and 2011. Conversely, only 2–29% of the patients in the other subgroups were reported to be imaged with this modality. Of the stroke patients recorded in the study by Hunter et al., 63 and 49% received a CT angiography and echocardiogram, respectively.

Figure 4 illustrates the frequency of usage of CT, MRI, and carotid artery imaging in Sweden across different settings and time periods. CT appeared to be the most reported imaging modality in Sweden from 2010 through 2013. Across the observed periods and types of hospitals, 98–99% of the patients received a CT scan. In contrast, studies reported considerably smaller proportions of patients who received an MRI in the same period. In addition, variations in the proportion of patients who received an MRI were seen, with the highest rate recorded for the years 2012–2013 and in university hospitals. Use of carotid artery imaging was characterized by intermediate frequencies of usage varying between 52 and 63% of the ischemic stroke patients over 2010 and 2011. Again, it is in



Figure 2. Proportion of stroke patients tested with a brain scan per time range over various periods and categories of settings in the UK.

The vertical bars represent the 95% confidence intervals.

\*: proportion of patients tested with a brain scan during the same day of admission. \*\*: proportion of patients tested with a brain scan during the same day of admission or the day after. \*\*\*: end of hospitalization. NHS: National Health Service.

Definitions applied to the time of patient admission to the hospital:

- **Weekday:** period from midnight on Sunday to midnight on Friday, leaving all other times defined as weekend;
- **In hours:** period from Monday to Friday, 8am to 6pm, leaving all other times defined as out of hours.

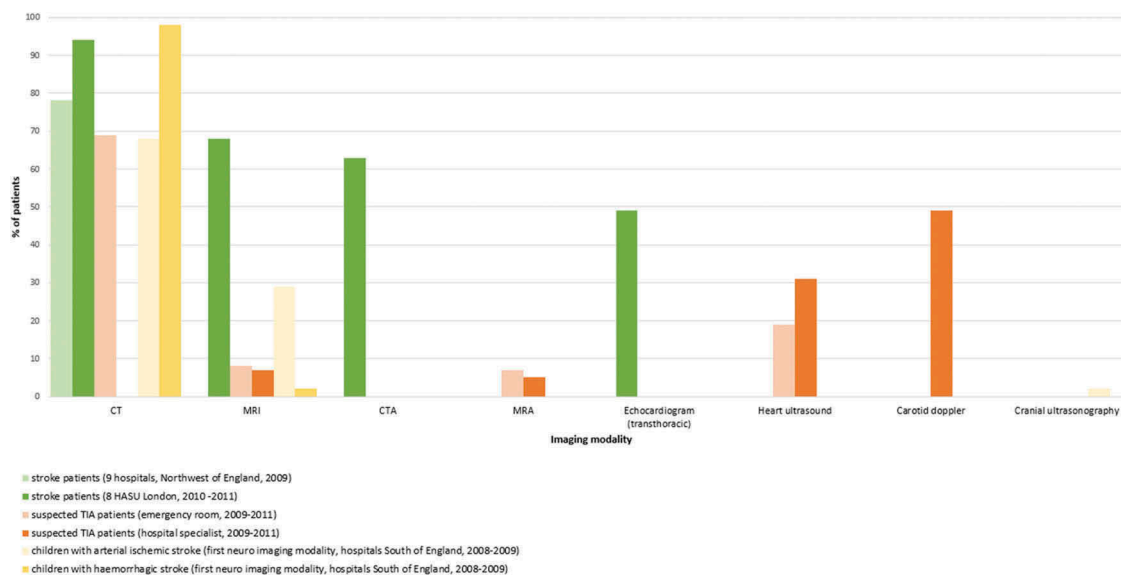


Figure 3. Frequency of different imaging modalities in the UK.

university hospitals that the proportion of patients examined with carotid artery imaging was the highest. It is worthwhile to note that both Asplund and Sundström [13,14] investigated the frequencies of more than a single imaging modality. Their comparative results might be more accurate than results compared across different studies. Indeed, variations in imaging frequency could arise for various reasons such as different study populations and study methodologies. However, the

individual studies investigating the frequency of CT, MRI, and carotid artery imaging found differences in the use of these imaging modalities. This observation demonstrates that the differences in frequency are caused by actual heterogeneity in clinical practice.

The frequency of usage of various imaging modalities per subgroup of stroke patients in Germany is depicted in Figure 5. Different clinical settings were covered over the

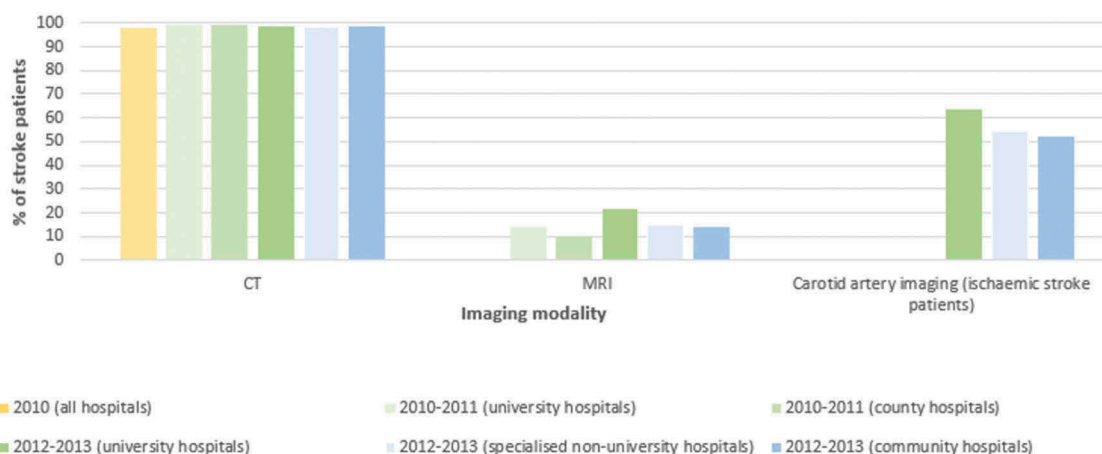


Figure 4. Proportion of stroke patients receiving different imaging modalities over various periods and categories of hospital in Sweden.

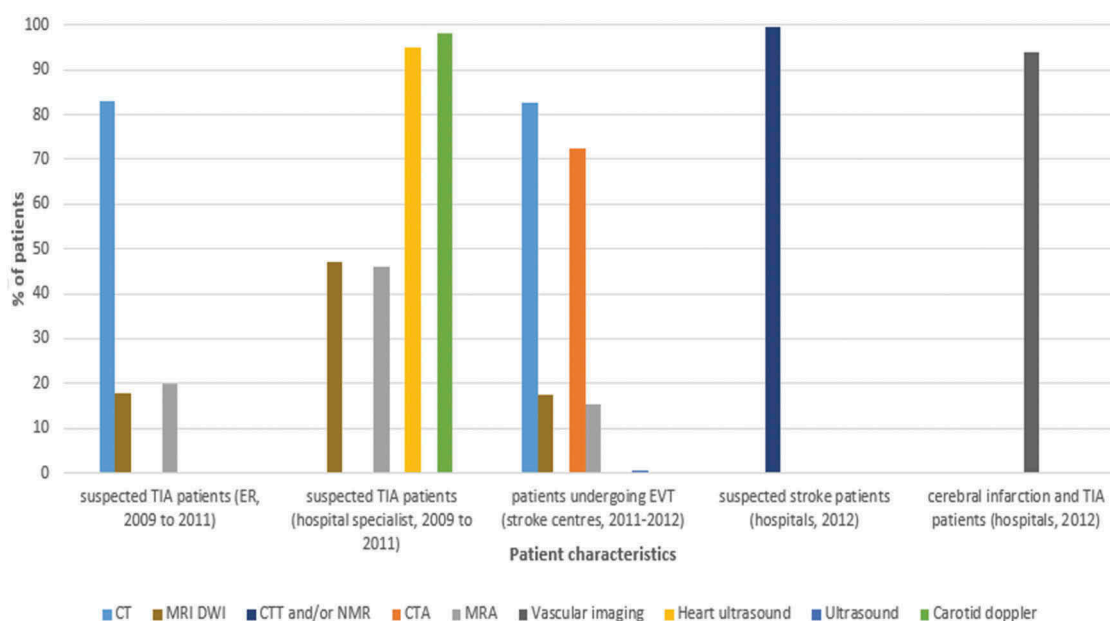


Figure 5. Proportion of subgroups of patients receiving different imaging modalities over time and categories of hospital in Germany. MRI DWI: magnetic resonance imaging diffusion weighted imaging; CTT: cranial computed tomography; NMR: nuclear magnetic resonance.

years 2009–2012 in the set of selected studies. More than 99% of the suspected stroke patients were reported to have received either a CT or an MRI in 2012. The frequency of CT also appeared to exceed 80% in the groups of suspected TIA patients (emergency room setting) and endovascular stroke treatment (EVT) patients. Whereas the frequency of MRA and MRI differed substantially between the different groups of patients, the two modalities appeared to be relatively evenly used within the groups. The suspected TIA patients (hospital specialist setting) are associated with the highest MRI and MRA frequency of 47 and 46%, respectively. Within the groups of suspected TIA patients (ER and EVT patients), the rates of MRI and MRA slightly varied between 15 and 20%, similarly to the level observed in Sweden. Finally, heart ultrasound and carotid Doppler were reported for the group of TIA patients (hospital specialist) only and accounted for a rate exceeding 95%. The study by Jakel et al. shows how frequencies of

imaging tests vary across clinical settings (emergency room versus hospital specialist). Their comparative results reinforce the evidence that the differences in frequency are caused by actual heterogeneity in clinical practice rather than by the differences in study characteristics.

#### 4. Discussion

This systematic review included published studies reporting data about the diagnosis workup of acute stroke patients in routine clinical practice in four selected European countries. Routine clinical data related to the diagnosis of stroke appeared to be unevenly reported across countries for the investigated period. The vast majority of the selected studies was conducted in the UK, while 3 papers related to the Swedish practice and 2 papers related to the German practice were identified. No study about Hungarian clinical practice was found.



The studies found in this review often reported limited or heterogeneous clinical data on the routine practice of stroke diagnosis. While most studies provided the proportion of patients receiving a brain scan across varying timeframes during the acute phase, the entire range of imaging modalities used during the diagnosis workup was reported in only one study [11]. The limitation of data found in hospital-based registries could be the reason why most studies focused on just one test [15,19]. The fact that a single head scan is the preferred strategy in some health centers where clinicians try to minimize the delay to treatment could also explain why most studies do not report data about the full range of tests. However, recent studies suggest that another approach, which consists of a more comprehensive imaging workup, is also advocated [24]. This comprehensive approach includes a combination of imaging modalities which improves patient selection for treatment. In this context, we hypothesize that the current practice is divided between the strategy of a single test and one involving a more comprehensive imaging workup. Since our analysis is constrained by the limited available data, more complete data would be needed to validate this assumption and assess the frequency at which these two approaches are used. For instance, the exhaustive list of imaging modalities routinely used for diagnosis would need to be analyzed.

Moreover, gaining insights into real-world trends of the current diagnosis approaches is hampered by the heterogeneity of the indicators used in the different studies. The imaging performance can be captured by indicators assessing the number of CT scans or MRIs. The performance is also assessed through more generic indicators tracking the number of head scans, without specifying the imaging modalities that are part of it. Likewise, time performance (the use of scans at different time points following a stroke) is assessed via a broad variety of indicators. To start with, time might be measured from symptom onset, from the patient's call for assistance or from hospital admission. Then, delays might be measured starting at any of these points in time and ending at the first head scan, the admission to the stroke unit, the first encounter with a specialist or the start of treatment. Time might be reported as a mean or median. Performance might be expressed in terms of unit of time (minutes, days, weeks) or proportion of patients tested or receiving care by a certain time threshold. This multiplicity of options found in the studies impeded a more comprehensive comparative analysis.

Furthermore, none of the included studies provided information about the time for imaging interpretation or the time between scanning and reporting. However, Mallick et al. acknowledged a study limitation in choosing the time when the diagnostic imaging is performed as an end point [23]. That is, the time of imaging differs from the time of diagnosis based on interpretation of the images and from the time of communication of the results to other clinicians. None of the 15 included studies provides the method used to report the imaging findings in clinical practice. However, the information used from an imaging test and the manner, content and level of details of imaging reports might differ across radiologists, health centers and countries. The frequency and extent to which radiologists use the reporting standards by imaging modality [25] would need to be analyzed. It might be worth

investigating the frequency at which radiologists report the Alberta Stroke Program Early CT Score (ASPECTS) after performing a CT, as this indicator has proven to be useful in predicting outcomes and reperfusion [25–27].

Despite these obstacles, the strength of this review is to reveal patterns that could not be observed in individual studies. First, the consolidated results support the assumption that CT scan is the most common modality for stroke diagnosis in Germany, Sweden and the UK. Remarkably, high rates of CT scan use (from 68 to 99%) are reported across different time periods, clinical settings and patient subgroups (including children). This finding is consistent with previous studies [24] and is presumably seen because access to CT is more rapid and requires less organization, logistics and resources than access to MRI [24]. Whether the widespread use of CT is the most effective way of dealing with stroke patients is a legitimate question. Interestingly, not all patients are imaged with CT despite its wide availability. Conversely, MR imaging, despite being reported in six studies [11–14,21,23], appears to be used less frequently for the diagnosis of stroke patients in these countries.

Second, we have confronted results from different authors that reflect disparities across studies. Time, space and patient selection criteria were reported and discussed as potential reasons why these differences could arise. Given the degree of variation found in the results, it seems unlikely that changes over years alone can fully explain these differences. Besides, no association was found between the patient populations and the reported differences in the frequency of imaging. Although we cannot exclude the influence of change over years, our analysis supports the hypothesis that large variations exist in the imaging management of stroke patients across category of hospitals (university versus non-university) in Sweden, across geographical areas and across the time of day and day of week in the UK. These findings are also consistent with the conclusions from several of the individual studies and suggest that inequalities exist in the provision of stroke imaging for patients admitted out of hours, during the weekend, in non-university hospitals and in areas where acute stroke services are not centralized. According to our results, these patients are less likely to receive (timely) access to imaging.

Guidelines uniformly claim that timely brain imaging and interpretation are critical in the diagnosis and management of stroke patients. However, previous studies in the UK reported that 'more than 60% of neurosurgical centers did not have an interventional radiologist available 7 days a week ... and 90% of all hospitals did not have access to computed tomography scanning 24 h per day and 7 days every week' [28]. A recent report describes the mismatch in the UK between the increase in clinical demand for CT scans (29%) and the growth in workforce (5%) from 2012 and 2015 [29]. An even more drastic gap is reported for Scotland. Overall, the UK is known to have the second lowest number of radiologists per capita across all European countries.

## 5. Limitations

Our study encountered some limitations which include the heterogeneity of studies included, the lack of data regarding the use of multiple modalities and the lack of comparative data.

For feasibility reasons, we did not include studies written in German, Swedish, and Hungarian and might have missed part of the existing literature. Besides, we did not have access to 13 studies out of 122 that were selected based on title/abstract reading. An important inherent limitation of any systematic literature review is that it only describes what happened in the past and not what is currently taking place in clinical practice. This is worth mentioning as clinical practice in the field of stroke imaging is expected to evolve considerably fast. Whether the results we present are still relevant would need to be investigated, preferably via other complementary research methods. Finally, the proportions and frequency of imaging tests are subject to different types of bias derived from the original studies. Inconsistent coding of imaging tests within and across hospitals and data originating from both voluntary and involuntary hospital participation might affect the validity of the reported results. However, in countries where coding is being used for reimbursement purposes, it is likely that coding errors are minimal and that coding is rather consistent across hospitals. Finally, while Wiedmann reported no major differences between voluntary and non-voluntary participating hospitals [6], Asplund reported no systematic differences in data quality from the different types of hospitals [13]. Nevertheless, the value of this systematic review is that we determined what is currently known about the current imaging practices in stroke care in order to inform future modeling on the potential added value of new diagnostic modalities. Our results, by showing that access to imaging varies across settings, implies that disparities will need to be reflected in the imaging strategies included in the modeling exercises. Our results also suggest that some scanning strategies might not be relevant for a specific hospital or country.

## 6. Conclusion

To our knowledge, our study is the first to focus on a comparative analysis of the imaging workup used to diagnose and assess strokes across different European healthcare systems. This systematic literature review allows synthesizing the work done in the field and draws attention to the obstacles preventing a more complete analysis and synthesis. The evidence from the scientific literature is scarce and thus insufficient for an accurate between-country comparison of the imaging workup used in stroke care. Alternative research methods (i.e. survey) might be relevant to provide comprehensive data on current access to imaging for stroke patients and to inform the cost-effectiveness modeling. Further consideration should also be given to investigate the optimal imaging workup to diagnose stroke patients and select a more personalized therapy for individual patients. Given the heterogeneity of stroke care, further research is also needed to identify the causes for the variations seen in our study and to assess the quality of stroke care.

## 7. Expert commentary

A major weakness in clinical management lies in the slow and difficult translation and implementation of the evidence in routine clinical practice. The first proof of principle for

intravenous thrombolysis arose in 1995 with the National Institute of Neurological Disorders and Stroke (NINDS) study [30]. After years of RCTs showing conflicting evidence [31] (and leaving the stroke community divided), the Cochrane review of 2014 [32] clearly demonstrated the efficacy and safety of intravenous thrombolysis. Although thrombolysis has been proven effective in acute ischemic strokes, its dissemination in routine clinical practice in various countries has been slow and limited to only a small proportion of eligible patients [33–36]. In 2014, the MR-CLEAN trial [37] provided the proof of principle for endovascular treatment and was followed by several RCTs which all confirmed the efficacy of this intervention. Evidence [38] shows that thrombectomy should be the standard of care for acute stroke caused by a large vessel occlusion and now needs to be translated in routine clinical practice across the world. While thrombolysis is relatively easy to implement, the use of thrombectomy in clinical practice faces logistical constraints that many hospitals have not overcome yet. The heterogeneity of stroke treatments delivered in clinical practice makes the need for neuroimaging different across health centers.

Furthermore, there is a lack of evidence regarding the optimal imaging approach for the diagnostic of stroke patients. Opening the artery only leads to a positive clinical outcome when viable brain tissue remains to be saved. The ideal neuroimaging method to be used to identify salvageable tissue in acute stroke patient is largely debated [39]. Although perfusion imaging is theoretically the best method to assess brain tissue viability [40], huge variations exist between commercial and academic imaging softwares. In practice, a set of clinical data (age, National Institutes of Health Stroke Scale (NIHSS), time from onset) combined to radiological data (ASPECTS, non-contrast-enhanced CT and grading of collaterals) are used by clinicians to assess tissue viability. Technology assessments of diagnostic tests for stroke are lacking [41] and would be needed to harmonize clinical practices and allow for a more systematic approach.

Further research is needed to understand the causes and drivers to heterogeneous clinical practice patterns in stroke imaging. Beyond these considerations, it would certainly be worth comparing the quality of stroke care within and between countries and to investigate to what extent the lack of harmonization creates inequalities in terms of health outcomes between patients. Since imaging tests do not directly affect long-term patient outcomes, the real impact of these tests on patients is not easily quantifiable. The benefits from imaging tests in stroke care depend not only on test performance characteristics, but also on the prevalence of strokes and on the effectiveness of the existing treatments.

Cost-effectiveness analyses could provide a framework to compare different stroke imaging strategies through the prism of maximizing health benefit within the constraint of limited resources. There are various challenges in performing cost-effectiveness studies of stroke imaging. In stroke care, the decision-making process and resource utilization that follows imaging tests is complex and driven by many factors that can be difficult to model. Parameters (test accuracy, efficacy of treatment options, costs, health states values, etc.) are

assessed based on multiple assumptions that can cause bias and inaccuracy of results. Comprehensive and complete data from large sample sizes are needed. It is not enough to capture the frequency of CT scan received by stroke patients. Studies should inform on the complete imaging workup used in stroke care and compare alternative strategies.

## 8. Five-year view

Imaging tests are valuable tools only when they influence the decision-making process and treatment choice. In current stroke care, the value of imaging is mainly found in its ability to identify and better select ischemic patients for intravenous thrombolysis or thrombectomy. The rise of these new treatment modalities has been changing the role of imaging in the stroke care pathway. Ruling out brain hemorrhage (most often by means of CT) is still needed in the first place to identify ischemic stroke patients but no longer sufficient to decide how to treat them. Information regarding the size of the occlusion should be obtained before clinicians decide to perform endovascular intervention. A CTA of the circle of Willis and ideally of the aortic arch and the neck vessels provides valuable information for treatment decision-making [42].

As mentioned above, the key challenge remains on implementing accessible and effective thrombectomy centers where both patients and relevant information must be transferred in a timely manner. This could be achieved by organizing networks of stroke care that would rely on a strong collaboration between health centers and on the definition of brain imaging standards. Thus, endovascular treatment would be performed only in high-volume centers where interventional radiologists would be available 24/24. Technical solutions already exist to allow neurologists in a given hospital to be in contact with neuroradiologists from another hospital regarding the management of an acute stroke patient [43]. Developing such collaboration would contribute to a more efficient use of the imaging equipment and workforce and would erase part of the dramatic variations observed in stroke care.

If CT remains the mainstay of the imaging workup in stroke, it is probably because its access is fast, requires little organization, logistics, and resources. The speed of acquisition and the large volume coverage provided by modern multislice CT allow for an almost instant examination of the whole brain and for an assessment of the feeding arteries with a high spatial and temporal resolution. Some researchers have evaluated the feasibility of a 'one-stop' machine combining CT acquisition of the heart with ECG synchronization [44] and imaging of great vessels. By using this technology, they were able to inform on the origin of stroke (clot in the left atrium generating brain embolism for example) while generating a neck and brain CT image. An opportunity of development lies in hybrid systems, combining CT and angiography suite in one unique room which would minimize the time of stroke imaging work-up. Furthermore, some companies are investigating how to miniaturize CT to make it a mobile and transportable device [45]. These developments will certainly shape the future of stroke care and imply considerable changes in the logistic organization, by allowing early scan of patients from even remote places and fast transfer of data to clinicians via the Internet.

Given the shortage of radiologists, another area for development may lie in the use of artificial intelligence in stroke care. Automated techniques have already been tested for stroke diagnosis and prognosis purposes and have shown variable performances across applications [46]. Interestingly, automated diagnosis based on the assessment of the ASPECTS by means of an e-ASPECTS software has been attempted [47,48]. This software showed a non-inferior performance in comparison to conventional human assessment of the score.

Finally, photon counting is likely to be the next breakthrough in CT technology [49]. Although time-to-market is kept confidential by manufacturers, it is suggested that the technology could be commercially available within 2–4 years [49]. Assuming this timeline, early health technology assessment (HTA) [50] of SPCCT is necessary to assess its potential added-value in stroke care imaging in comparison to the currently used technologies.

## Key issues

- The number and quality of studies devoted to the evaluation of the process and quality of stroke care seem to vary greatly across countries.
- Variability was found with regards to the indicators reported in the different studies. Large-scale international studies that use standardized methodological approaches are needed to assess the process of stroke care and compare it across countries.
- Ascertaining the use of imaging modalities in current stroke care requires a combination of research approaches. As such, it would be worth complementing our systematic review by an extensive and detailed international survey to clinicians in order to obtain the most recent and complete data regarding the use of imaging modalities.

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## Declaration of Interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties. Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

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