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## TIA in the Swedish Stroke Register (Riksstroke). Aspects on diagnostic validation, risk factors, investigations, and therapies

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# Is carotid imaging underused in patients with transient ischemic attack or ischemic stroke? A Swedish Stroke Register (Riksstroke) study

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**Background and aim:** Carotid artery stenosis is one of the major causes of transient ischemic attack (TIA) and acute ischemic stroke (IS), and carotid surgery and stenting are used to reduce the risk of ipsilateral IS. However, the adherence to the recommendation of carotid imaging in clinical practice has not been well studied. We analyzed proportions of carotid imaging and determinants for its non-use in patients with TIA and IS with respect to baseline demographics, risk factors, hospital characteristics, and geographical region.

**Patients and methods:** Hospital-based data on TIA and IS events, registered from July 2011 to June 2013, were obtained from the Swedish Stroke Register (Riksstroke). Carotid imaging diagnostics included carotid Doppler ultrasound and computed tomography angiography.

**Results:** Carotid imaging was performed in 70% (10 545/15 021) of patients with TIA and 54% (23 772/44 075) of patients with IS. The most significant independent determinants for not undergoing carotid imaging were, in patients with TIA: age  $\geq 85$  year (odds ratio (OR), 7.3; 95% confidence interval (CI), 6.4-8.4) and a history of stroke (OR, 2.3; 95% CI, 2.1-2.5); and in patients with IS: age  $\geq 85$  year (OR, 9.8; 95% CI, 9.0-10.6), age 75-84 year (OR, 2.5; 95% CI, 2.3-2.7), and reduced level of consciousness at admission (OR, 3.4; 95% CI, 3.1-3.6). Care at a University hospital and in a stroke unit increased the likelihood of carotid imaging. There were substantial regional variations regarding proportions of carotid imaging.

**Conclusion:** Carotid imaging appears to be underused in patients with TIA and IS. Opportunities of secondary stroke prevention with carotid interventions are likely missed.

## KEYWORDS

carotid stenosis, cerebrovascular diseases, transient ischemic attack

## 1 | INTRODUCTION

Large-vessel disease including carotid artery stenosis is a major pathophysiological mechanism of transient ischemic attack (TIA) and acute ischemic stroke (IS).<sup>1</sup> Carotid surgery or stenting is used to reduce the risk of ipsilateral IS.<sup>2</sup> Current guidelines for TIA and IS recommend the use of carotid imaging to identify potential candidates for carotid

stenosis interventions.<sup>3-5</sup> Standard modalities are carotid Doppler ultrasound, computed tomography angiography (CTA), or magnetic resonance angiography (MRA). Varying proportions of carotid imaging have been reported in clinical practice. In studies performed at specialized single or multiple centers, proportions of any carotid imaging procedure could be as high as >95% in patients with TIA<sup>6-8</sup> and IS.<sup>6</sup> In population-based studies, reported proportions of carotid imaging

were lower; in a TIA study performed at all 13 public hospitals in Hong Kong, carotid Doppler ultrasound was done in 45% and MRA in 8%,<sup>9</sup> and in an Israeli study based on a national registry, any vascular investigation was performed in 47% of patients with TIA and 48% of minor IS.<sup>10</sup>

Reported factors associated with lack of any carotid imaging in mixed TIA and IS cohorts were older age, female sex,<sup>11,12</sup> and a higher Charlson score, which reflects comorbidity.<sup>11</sup> In TIA, direct discharge from emergency department,<sup>13</sup> and in IS, posterior circulation stroke, worse stroke severity,<sup>11</sup> and no stroke unit care<sup>14</sup> were associated with not being investigated for carotid disease.

There are only few studies assessing adherence to recommendation on carotid imaging and factors associated with not undergoing carotid imaging in a population-based perspective.

We therefore aimed to assess the proportion of carotid imaging and determinants for its non-use in patients with TIA and IS with respect to baseline demographics, risk factors, hospital characteristics, and geographical region, based on the Swedish Stroke Register for TIA (Riksstroke-TIA, RS-TIA) and stroke (Riksstroke, RS).

## 2 | METHODS

### 2.1 | Study population

Data on TIA events, registered from 1 July 2011 to 30 June 2013, were obtained from the Swedish Stroke Register TIA module (RS-TIA); 59 out of 72 Swedish hospitals contributed with data to this register.<sup>15</sup> TIA diagnosis was based on a time-based definition, ie, an acute focal neurological deficit of presumed vascular origin with complete remission of symptoms <24 hours irrespective of neuroimaging findings. Data on IS events, registered during the same period of time, were obtained from the Swedish Stroke Register (RS) to which all Swedish hospitals involved in acute stroke care contributed with data.<sup>16</sup>

Patients 18 years or older with ICD-10 diagnoses of TIA (G45, excluding G45.4) and IS (I63) were included. For patients with more than one stroke during the course of 28 days, only the first event was included. All patients included in this study were treated in hospital.

### 2.2 | Registered items

Both in RS-TIA and RS, data on demography, history of stroke, risk factors, and investigations were registered. Carotid imaging methods included carotid Doppler ultrasound, CTA, and MRA. These procedures were registered as (i) being performed within 4 weeks prior to 1 week after the current event leading to registration, (ii) being performed later than 1 week after the current event, or (iii) not being performed. In RS-TIA, the ABCD2 score<sup>17</sup> was registered; in RS, the severity of stroke based on the National Institutes of Health stroke scale (NIHSS), the level of consciousness at admission based on the Reaction Level Scale (RLS85),<sup>18</sup> and whether a stroke unit was the 1st level of care after emergency unit care. We had access to information at which hospital each patient was taken

care of, the type of hospital,<sup>19</sup> and in which region each hospital was located.

### 2.3 | Definition of items

Patients who underwent either carotid Doppler ultrasound or CTA or both of these diagnostic procedures within 4 weeks prior to or after the current event [(i) or (ii), see paragraph Registered items] had per definition undergone carotid imaging. We did not have reliable information whether MRA procedures included neck vessels or were restricted to intracranial vessel imaging. The proportion of patients who underwent MRA and no other vascular imaging modality was, however, only 0.7% (102/14 597) in TIA and 0.9% (392/43 847) in IS. Due to the uncertainty about included vascular territory and low proportions, we excluded MRA from further analysis. Atrial fibrillation (AF) was registered as present or absent without specification whether it was diagnosed during the current hospital admission or previously known; AF was not specified as permanent, persistent, or paroxysmal. For presence of hypertension, we used the recorded item of blood pressure lowering medication at hospital admission. The item of stroke unit care included care in a higher specialized unit (intensive or neurosurgery care).

### 2.4 | Descriptive and statistical analysis

SPSS 22.0 was used for all statistical analyses. Categorical variables were summarized as proportions and quantitative variables as medians or means. Age groups were reported in the intervals <45, 45-54, 55-64, 65-74, 75-84, and ≥85 years. Proportions were derived from the total of patients in whom the respective item was registered. Baseline data were tested by Chi-square and Student's *t* test as appropriate. Variables associated with not undergoing carotid imaging in univariate analyses were included in multivariate logistic regression models with stepwise elimination in order to assess independent association. Both in TIA and IS, references were defined as age <65 years, male sex, no AF, no hypertension, no diabetes, no smoking, no history of stroke, care at a University hospital, and care in the region with highest proportion of carotid imaging. In TIA, this was the southeastern region and in IS, the Stockholm region. References in variables only registered in patients with IS were defined as care at a stroke unit and being alert at admission. NIHSS score was not included in the multivariate logistic regression model as this item was registered in less than 50% of patients.

### 2.5 | Ethics

The study was approved by the local ethical review board (Dnr 2013/719).

## 3 | RESULTS

During the 2 year study period, 15 064 patients with TIA were registered in RS-TIA and 44 416 patients with IS in RS. Less than 1% of

patients with TIA and IS had missing data on carotid Doppler ultrasound and CTA.

In patients with TIA, carotid Doppler ultrasound was performed within 4 weeks prior to 1 week after the event in 58% (8762/15 020) of cases and CTA in 15% (2267/15 006). In 1.4% (208/15 020), carotid Doppler ultrasound was done later than 1 week after the current event and CTA in 0.2% (26/15 006). In IS, 40% (17 509/44 113) were examined with carotid Doppler ultrasound and 18% (7869/44 055) with CTA within 4 weeks prior to 1 week after the event leading to registration, and 1.6% (703/44 113) underwent carotid Doppler ultrasound and 0.5% (203/44 055) CTA at a later stage. Any carotid imaging procedure (ie, either carotid Doppler ultrasound, CTA, or both) was performed in 70% (10 545/15 023) of patients with TIA and in 54% (23 772/44 075) of patients with IS.

### 3.1 | Patient characteristics

Patients with TIA who did not undergo carotid imaging had a mean age of 78.7 y [standard deviation (SD) 12.1] compared to 70.8 year (SD 11.6) in those who were examined. In patients with IS, mean age in those who were not examined was 80.9 year (SD 10.8) compared to 71.2 year (SD 11.8) in patients who underwent carotid imaging. Proportions of carotid imaging decreased with increasing age in both patients with TIA and IS (Figure 1A and B).

According to univariate analyses in Table 1, female sex, hypertension, AF, diabetes mellitus, non-smoking, and a history of stroke were factors associated with not being investigated in both TIA and IS. In patients with IS, being alert at admission and care at a stroke unit were associated with getting carotid imaging.

In patients with IS, NIHSS was registered in 49% (21 629/44 075); in patients without carotid imaging, median NIHSS was 5 (interquartile range 2-11) compared to 3 (interquartile range 1-6) in those who underwent carotid imaging ( $P < .0001$ , univariate analysis).

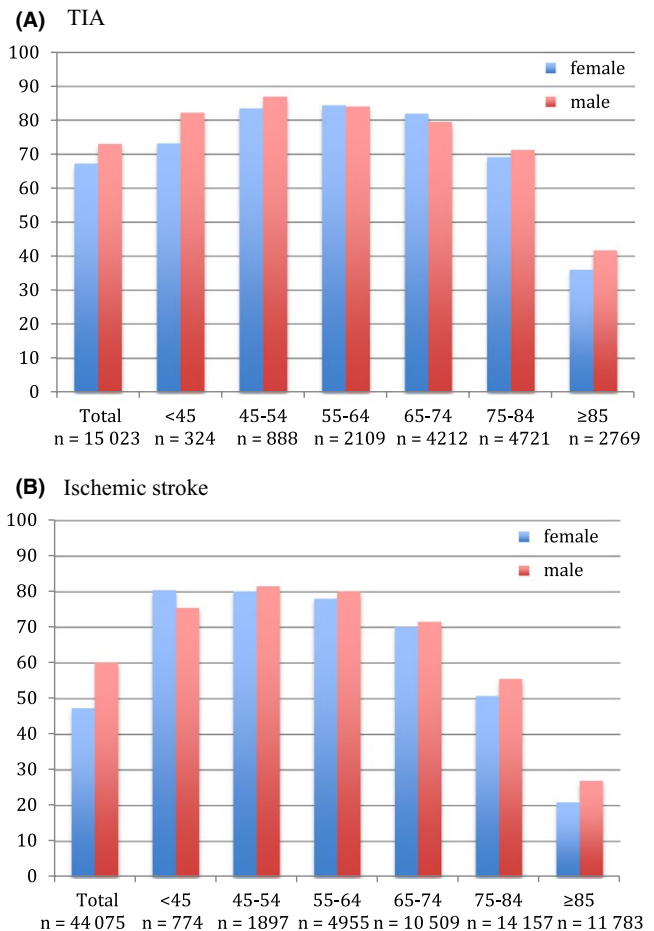
### 3.2 | Independent determinants for not undergoing carotid imaging

As detailed in Table 2, age  $\geq 85$  years, age 75-84 years, female sex, AF, and a history of prior stroke (Figure S1) were independently associated with not undergoing any carotid imaging, both in patients with TIA and IS; in patients with IS, in addition, age 65-74 years, diabetes mellitus, and reduced level of consciousness were associated with lack of carotid imaging. In IS, smoking and stroke unit care were associated with increased odds of being investigated.

After exclusion of patients with IS and decreased level of consciousness at admission (ie, patients with signs of severe ischemic stroke), proportions of carotid imaging and determinants for not undergoing this investigation were similar (Table S1 and Table S2).

### 3.3 | Hospital type and regional differences

In university hospitals, proportions of carotid imaging were larger than in specialized non-university and community hospitals; in the latter,



**FIGURE 1** Proportion of carotid imaging (%) in patients with A, Transient ischemic attack (TIA) and B, ischemic stroke in relation to age and sex

proportions were on similar levels. This applied both to patients with TIA and IS (Table 1). According to multivariate logistic regression models, care at specialized non-university or community hospitals were independent determinants for not undergoing any carotid imaging procedure, in both TIA and IS patients (Table 2).

Proportions of carotid imaging also differed dependent on geographical region. In patients with TIA, proportions varied from 58% (614/1066) in the northern to 78% (1384/1769) in the southeastern region of Sweden. In IS, proportions ranged from 41% (1878/4609) in the northern region to 65% (5590/8645) in the Stockholm region (Table 1). After adjustment for possible confounders, proportions of investigation still varied significantly between regions, both in TIA and IS (Table 2).

Corresponding multivariate logistic regression analyses were performed in patients with TIA aged  $<75$  years without AF and a history of stroke, and in patients with IS aged  $<75$  years without AF and a history of stroke, who were independent preadmission and alert at admission. Both in TIA and IS, ORs for no carotid imaging were on similar levels, ie, hospital-dependent and regional differences remained unchanged (data not shown).

As seen in Figure 2A and B, proportions of carotid imaging decreased with increasing age in all regions, both in TIA and IS. In patients

**TABLE 1** Carotid imaging in patients with transient ischemic attack (TIA) or ischemic stroke (IS) dependent on patient characteristics and risk factors

		TIA n = 15 023		IS n = 44 075	
		Carotid imaging n (%)	P value	Carotid imaging n (%)	P value
Sex	Female	4871/7252 (67)	<.0001	10 034/21 230 (47)	<.0001
	Male	5674/7771 (73)		13 738/22 845 (60)	
Hypertension <sup>a</sup>	Yes	6002/9050 (66)	<.0001	13 897/27 531 (51)	<.0001
	No	4503/5919 (76)		9785/16 324 (60)	
Atrial fibrillation	Yes	1509/2773 (54)	<.0001	4824/13 133 (37)	<.0001
	No	8984/12 171 (74)		18 843/30 745 (61)	
Diabetes mellitus	Yes	1605/2357 (68)	.015	4871/9319 (52)	.0002
	No	8890/12 591 (71)		18 855/34 646 (54)	
Smoking	Yes	1326/1661 (80)	<.0001	4198/5842 (72)	<.0001
	No	8521/12 265 (70)		18 264/35 119 (52)	
History of stroke	Yes	1530/2880 (53)	<.0001	4298/10 769 (40)	<.0001
	No	8982/12 094 (74)		19 375/33 099 (59)	
Level of consciousness <sup>b</sup>	Alert	-	-	22 051/37 413 (59)	<.0001
	Stuporous	-		1316/4737 (28)	
	Comatose	-		219/1399 (16)	
Care at stroke unit <sup>c</sup>	Yes	-	-	19 675/34 524 (57)	<.0001
	No	-		4017/9432 (43)	
Hospital type	University	2079/2654 (78)	<.0001	5704/9240 (62)	<.0001
	Specialized non-university	4815/7098 (68)		10 430/19428 (53)	
	Community	3651/5271 (69)		7638/14 977 (51)	
Region	Northern	614/1066 (58)	<.0001	1878/4609 (41)	<.0001
	Uppsala-Örebro	2305/3622 (64)		4566/10 036 (46)	
	Stockholm	914/1173 (78)		5590/8645 (65)	
	Southeastern	1384/1769 (78)		2734/4567 (60)	
	Western	2454/3753 (68)		3738/7874 (48)	
	Southern	2783/3640 (77)		5266/8344 (63)	

TIA, transient ischemic attack; IS, ischemic stroke.

<sup>a</sup>Defined by item blood pressure lowering medication at admission.

<sup>b</sup>Based on the Reaction Level Scale (RLS85).<sup>18</sup>

<sup>c</sup>Including care at intensive care or neurosurgical units.

with TIA aged <65 years, proportions of imaging spanned from 75% (191/256) in the northern to 91% (353/389) in the southeastern region compared to 3.6% (5/139) in the northern to 55% (196/354) in the southeastern region in those aged ≥85 years. In patients with IS aged <65 years, proportions varied from 69% (893/1300) in the western region to 88% (1499/1711) in the Stockholm region, and in patients ≥85 years, from 7.8% (77/989) in the northern region to 34% (818/2408) in Stockholm.

## 4 | DISCUSSION

Based on data from separate large national TIA and IS registers with unselected patients, our study shows that 30% of patients with TIA

and almost half of all patients with IS did not undergo carotid imaging. Proportions of investigation varied substantially within the cohorts; in patients with TIA as well as in patients with IS, the elderly, women, patients with a history of stroke, AF, and those taken care of at non-university hospitals were significantly less often investigated. In patients with IS, reduced level of consciousness at admission, and not being treated at a stroke unit were independent determinants of no imaging. Furthermore, there were substantial regional differences regarding proportions of carotid imaging.

In previous studies advanced age,<sup>11,12,20</sup> female sex,<sup>11,12,21</sup> stroke severity,<sup>11</sup> and a higher frequency of comorbid illnesses<sup>11</sup> were identified as factors of no imaging. However, those were mixed TIA and IS cohorts with predominantly stroke patients included based on data from single or multiple centers. Our study, based on separate large

**TABLE 2** Independent determinants for not undergoing carotid imaging in patients with transient ischemic attack (TIA) and ischemic stroke (IS) \*

	TIA		IS	
	OR (95% CI)	P value	OR (95% CI)	P value
Age <sup>a</sup>				
65-74 years	1.13 (1.00; 1.29)	.058	1.33 (1.23; 1.44)	<.0001
75-84 years	1.75 (1.54; 1.97)	<.0001	2.53 (2.34; 2.72)	<.0001
≥ 85 years	7.34 (6.42; 8.39)	<.0001	9.79 (9.00; 10.64)	<.0001
Female Sex	1.14 (1.05; 1.24)	.002	1.23 (1.18; 1.29)	<.0001
Atrial fibrillation	1.70 (1.54; 1.88)	<.0001	1.80 (1.71; 1.90)	<.0001
Diabetes mellitus	ns	ns	1.19 (1.12; 1.26)	<.0001
Smoking	ns	ns	0.91 (0.84; 0.97)	.007
History of stroke	2.30 (2.08; 2.54)	<.0001	2.10 (1.99; 2.21)	<.0001
Reduced LOC <sup>b</sup>	nr	nr	3.38 (3.14; 3.64)	<.0001
Care at stroke unit	nr	nr	0.56 (0.53; 0.59)	<.0001
Hospital type <sup>c</sup>				
Specialized non-university	1.57 (1.39; 1.78)	<.0001	1.38 (1.29; 1.47)	<.0001
Community	1.52 (1.33; 1.73)	<.0001	1.56 (1.45; 1.66)	<.0001
Region				
Northern	3.52 (2.91; 4.25)	<.0001	4.11 (3.76; 4.50)	<.0001
Uppsala-Örebro	2.37 (2.04; 2.76)	<.0001	2.78 (2.58; 3.00)	<.0001
Stockholm	0.95 (0.77; 1.17)	.606	Reference	-
Southeastern	Reference	-	1.26 (1.15; 1.39)	<.0001
Western	1.91 (1.64; 2.23)	<.0001	2.55 (2.36; 2.75)	<.0001
Southern	1.13 (0.97; 1.33)	.119	1.08 (1.00; 1.18)	.062

TIA indicates transient ischemic attack; IS, ischemic stroke; OR, odds ratio; CI, confidence interval; LOC, level of consciousness; ns, non-significant; nr, not registered.

\*Based on logistic regression with backward stepwise elimination including all associated variables in univariate analysis (<0.05, Table 1).

<sup>a</sup>With age <65 years as reference.

<sup>b</sup>Based on RLS85<sup>18</sup> with RLS 1, i.e. alert, as reference.

<sup>c</sup>With university hospital as reference.

national TIA and stroke registers, confirmed that advanced age and female sex are determinants of no imaging in both TIA and IS. In addition, we were able to show that AF and a history of stroke are independent factors associated with lack of carotid imaging. In IS, previous reports were confirmed that worse stroke severity<sup>11</sup> and not being admitted to a stroke unit contributed to no carotid imaging.<sup>14</sup>

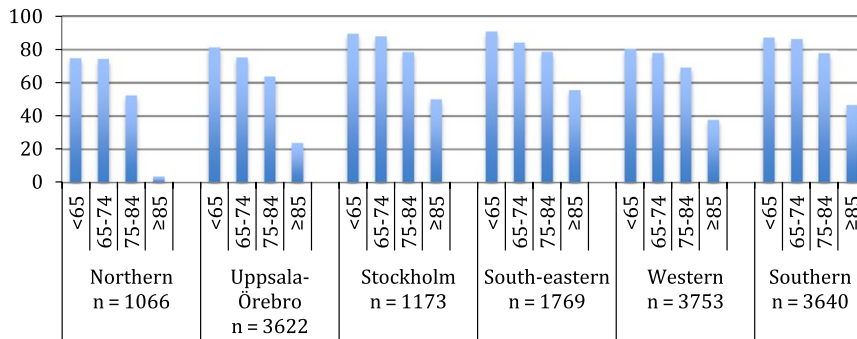
Our study is the first to report substantial variations in carotid imaging dependent on which type of hospital and in which region patients are taken care of. It is intriguing that non-university hospitals showed lower proportions of imaging than university hospitals, and that regional differences were so marked. According to a recent Swedish study, markers of quality of stroke care other than carotid imaging did not unanimously favor university hospitals.<sup>19</sup> Proportions of stroke units were comparable between university, specialized non-university, community hospitals, and number of stroke unit beds per capita actually higher in non-university hospitals. Poor outcome, ie, death and dependency 3 months after stroke was similar in patients taken care of in the three types of hospitals.<sup>19</sup>

In the northern region, only 3.6% of TIA patients ≥85 years were tested compared to 55% in the southeastern region. All Swedish

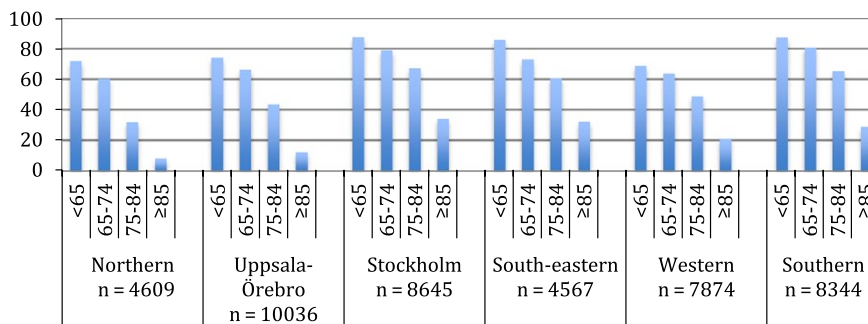
hospitals have access to either carotid Doppler ultrasound or CTA, or both. Geographical factors such as distance to hospital should not contribute to our findings as all patients in this study were taken care of in-hospital. Significant differences were observed between regions with comparable infrastructure, ie, the Stockholm and western region, the latter comprising Sweden's second largest city, Gothenburg. These regional and hospital-dependent differences remained when the same analysis was performed in patients without potential contraindications, ie, patients <75 years, and without AF, a history of stroke, pre-stroke dependency, or reduced LOC at admission. This indicates that local traditions rather than medical prioritizing or lack of funding may be responsible for these variations.

In our study, age ≥85 years was the statistically strongest determinant of no imaging. However, based on a report of 5 year cumulative risk of ischemic stroke, patients >75 years do benefit from carotid surgery.<sup>22</sup> In the presence of a contraindication to surgery, demonstration of large-vessel atherosclerosis as a potential cause of a TIA or IS might still be of added value, since it can result in more aggressive medical secondary preventive treatment such as statin therapy. The Swedish national guideline on TIA and stroke does not suggest any specific age

## (A) TIA



## (B) Ischemic stroke



**FIGURE 2** Proportion of carotid imaging (%) in patients with A, Transient ischemic attack (TIA) and B, ischemic stroke dependent on region divided in age groups <65, 65-74, 75-84, and ≥85 years

limits on carotid imaging. The guideline recommends admission of all patients with TIA and IS to hospital and a sound level of care in frail patients with severe comorbidity.<sup>23</sup>

Our results indicate that a substantial proportion of the very elderly patients are excluded from possible treatments that have been shown to be efficacious. Statins, eg, are underused in the elderly<sup>24</sup> although they are likely to be beneficial.<sup>25,26</sup> This might reflect differing opinions among treating physicians on the age-related effectiveness of secondary preventive therapies in these patients.

Patients with a prior history of stroke were less often investigated than those with first-time events although these patients appear to be at high risk of future stroke. Possible reasons for abstention might include poor functional state preadmission, a recent investigation in association with the prior stroke, or ischemic events in varying vascular territories indicating a cardio-embolic source.

There is a strong association between AF and TIA and AF and IS,<sup>27</sup> but there might be an overlap between diseases underlying cerebral ischemia,<sup>28</sup> therefore, patients with AF should not be excluded from carotid imaging.

Women underwent carotid imaging less often than men. In a previous study on patients with TIA, proportions of carotid imaging dependent on gender were comparable to ours.<sup>21</sup> Reasons for this gender difference remain to be clarified. In spite of lower proportions of investigation in women, 1 year mortality was in fact lower among them.<sup>21</sup> This might reflect differences in the severity of carotid disease.<sup>11</sup>

The rationale and decision to perform carotid imaging in an individual patient in clinical practice depends on several factors such as age, disability level, cognitive status, the subtype of a previous

stroke, ipsi- or contralateral location of a previous event in relation to the current cerebrovascular event, and comorbidities. A precise level of what proportion of patients that should undergo carotid imaging is therefore not possible to state. Riksstroke did not include items on reasons to abstain from carotid imaging. However, our data suggest that regional and hospital-dependent variations are better explained by traditions and local policies than by medical and patient-related factors.

The strength of this study is that data were obtained from the comprehensive Swedish Stroke Register (Riksstroke) with consistent data registration, high numbers of included patients, and separate databases for TIA and stroke.

There are limitations to our study. Although the national Swedish guideline recommends in-hospital care of patients with TIA and IS,<sup>23</sup> it is likely that some patients were taken care of as out-patients. Riksstroke is a hospital-based register, and these patients are not included in this study.

We were not able to assess precise reasons to why imaging was not performed. Possible reasons include posterior circulation events, cognitive deficits, perceived unfavorable short-term prognosis or patients' own preference. In order to achieve an equal and high quality of care, the impact of factors such as hospital type, region, and patient characteristics on carotid imaging needs to be further clarified.

Magnetic resonance angiography was excluded from our analysis but was performed in only 0.7% of our patients with TIA and in 0.9% of those with IS. It is unlikely that exclusion of this small patient group would have affected our results.

## 5 | CONCLUSIONS

Carotid imaging appears underused in patients with TIA and IS, especially in the elderly, those with a history of stroke, or AF. Regional variations are substantial and indicate management differences. It is likely that secondary preventive treatment opportunities are missed in a significant amount of cases.

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## DISCLOSURES

None.

## CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

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## SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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