

# What is the Added Value of CT-angiography in Patients with Transient Ischemic Attack?

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## Research article

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# Abstract

## Background

Transient ischemic attack (TIA) is an important predictor for a pending stroke. Guidelines recommend similar workup for TIA-patients as for stroke patients to directly assess the extra- and intracranial arteries via Computed tomography angiography (CTA) regarding vascular pathologies with direct therapeutic implications. Aim of our study was a systematic analysis of CTA-findings in TIA-patients and evaluate possible predictive TIA scores for ipsilateral vascular pathology.

## Methods

We analysed data from TIA patients admitted to our University Medical Centre, between September 2015 and March 2018. Following subgroups were identified: 1) no- or low-grade-stenosis (<50%) 2) ipsilateral high-risk vascular pathology and 3) high risk findings needing surgical or interventional treatment. As predictive tools for ipsilateral vascular findings we used the ABCD2-, the ABCD3- and the SPI-II score.

## Results

Of 833 patients, 549 (65.9%) underwent initial CTA in the emergency department. In 126 (23.0%) patients, ipsilateral vascular findings were identified from which 40 (7.3%) needed treatment. The ABCD2-, ABCD3- and SPI-II-scores were not predictive for ipsilateral vascular pathologies. We identified male sex (OR 1.58, 1.06-2.36 95% CI; p=0.026), coronary heart disease (OR 1.88, 1.17-3.02 95% CI; p=0.009) and short duration of symptoms (OR 0.7, 0.55-0.89 95% CI; p=0.004) as predictors for ipsilateral vascular pathologies.

## Conclusion

More than every fifth TIA-patient had relevant vascular findings revealed by acute CTA. TIA-scores were not predictive for these findings. Male patients with a history of coronary heart disease and short duration of symptoms most likely might benefit from acute CTA to streamline further diagnostics and therapy.

## Introduction

TIA is a well-known predictor for a manifest ischemic stroke with an incidence over 10% within three months after the index TIA. Nearly half of the TIA-patients develop permanent ischemic stroke symptoms within the first 48 hours.[1] Scores have been developed to quantify the risk of a pending stroke after TIA like the ABCD2-Score[2], the ABCD3-Score[3] and the Stroke Prognosis Instrument-II (SPI-II)[4]. To reduce the risk for a pending ischemic stroke, it is important to perform a full diagnostic workup to identify common etiologic causes like ipsilateral vascular stenosis or occlusion.

Patients with TIA, based on intrinsic thrombolytic mechanisms and cerebral collateral status, can present with transient ischemic symptoms despite severe stenosis, dissection of brain supplying vessels, acute

occlusion of pre-existing stenosis or as a result of an acute embolic occlusion of large cerebral vessels. In this respect, current guidelines recommend treating TIA patients the same way as patients with a manifest stroke in the emergency department including the consideration to perform a CT-angiography of the brain supplying arteries.[5–7] However, macroangiopathic causes like arterial stenosis or occlusion only account for around 12% of all TIA-cases and clinical experience shows that most transient ischemic neurological deficits are caused by cardiac embolization.[8, 9] Moreover, only a minority of patients exhibit vascular findings in the CTA which have a direct impact on the acute treatment of the TIA-patient like a dissection with hemodynamic relevance, intravascular thrombi or an acute large vessel occlusion. Only the targeted diagnosis of one of those pathologies justifies possible side effects of CTA-imaging like nephrotoxicity and allergic contrast agent reaction as well as additional radiation exposure in the acute setting.[10–12]

The aim of our study was the systematic evaluation of the role of CTA imaging in the acute setting of TIA, to evaluate which subgroups of TIA patients benefit from the initial imaging with CTA and to test the predictive value of TIA scores regarding ipsilateral vascular pathologies.

## **Patients And Methods**

### **Patient population and study design**

In this retrospective study, clinical and neuroradiological data were collected from patients with the admission diagnosis TIA, being treated in a tertiary university hospital between September 2015 and March 2018. Patients with insufficient data and change of diagnosis during in hospital stay were excluded. Data was obtained by the Emergency Medical Service documentation, the clinics digital patient documentation system ixserv (ixmid Software Technologie GmbH) and the intensive care information system IntelliSpace Critical Care and Anaesthesia (Philips). The collected data included baseline characteristics like age and sex, initial assessment, kind of symptoms, symptom duration and National Institute of Health Stroke Scale (NIHSS), lab results, patient's medical history and pre-medication. The results of stroke-imaging and cranial doppler-ultrasound were included. Finally, we documented if the patients received intravenous thrombolysis (IVT), mechanical thrombectomy (MT), carotid endarterectomy (CEA) or carotid percutaneous transluminal angioplasty without stenting (PTA only) or with stenting (CAS). From all available data we calculated every patients ABCD2-Score, ABCD3-Score and Stroke Prognosis Instrument II. [2–4]

TIA-patients were categorised into three subgroups: 1) no- or low-grade stenosis (< 50% according to the North American Symptomatic Carotid Endarterectomy Trial (NASCET)) ipsilateral to the affected vascular territory, 2) patients with high risk ipsilateral vascular pathologies like high-grade ipsilateral stenosis (> 50% NASCET), dissection, occlusions or intraarterial thrombi and 3) patients receiving IVT, MT, surgical (CEA) or interventional treatment (CAS).

### **Statistical Analysis**

Statistical analysis was performed with Statistica (Version 13.3, TIBCO Software Inc.). Baseline characteristics were described using frequencies, means and median with standard deviation and interquartile range, as applicable. Groups were compared using Kruskal-Wallis test and  $\chi^2$  test, as appropriate. Predictors for ipsilateral vascular pathologies were included in a multivariate logistic regression model if they predicted the vascular pathology with a p-value  $\leq 0.2$  in a univariate logistic regression. A second regression model was developed for the need of interventional treatment. Items that would possibly cause interference, due to a certain causal similarity, were excluded.

## Results

In total, 1034 patients with the admission diagnosis 'TIA' were screened, from which 833 were finally included in the study. Of these 833 patients, 549 (65.9%) received immediate CTA in the emergency department. Baseline characteristics are given in Table 1. Patients with high grade, ipsilateral arterial pathology were more likely to be male ( $p = 0,044$ ), had lower duration of symptoms ( $p = 0.045$ ), were more likely to have a history of arterial hypertension ( $p = 0.096$ ), atrial fibrillation ( $p = 0.031$ ), coronary artery disease ( $p = 0.003$ ) and myocardial infarction ( $p = 0.001$ ) as well as were more likely to take antiplatelet ( $p < 0.001$ ), antihypertensive ( $p = 0.077$ ) and lipid-lowering medication ( $p < 0.001$ ).

Table 1  
Baseline characteristics (n = 833)

Item	No or Low-grade stenosis (n = 707)	Ipsilateral vascular pathology (n = 86)	Intervention (n = 40)	p-Value*
Sex, male (n, %)	372 (52.6)	54 (62.8)	25 (62.5)	0.044
Age, years $\pm$ SD	71 $\pm$ 14	72 $\pm$ 13	68 $\pm$ 11	0.172
Systolic blood pressure, mmHg $\pm$ SD	151 $\pm$ 27	152 $\pm$ 26	145 $\pm$ 21	0.549
NIHSS (median, IQR)	0 (0–1)	0 (0–1)	0 (0–1)	0.577
Duration of symptoms:				0.045
< 10 min	107 (15.1)	19 (22.1)	12 (30.0)	
< 60 min	19 (2.7)	18 (20.9)	11 (27.5)	
> 60 min	435 (61.5)	49 (57.0)	17 (42.5)	
Arterial hypertension (n, %)	568 (80.3)	73 (84.9)	36 (90.0)	0.096
Hyperlipidaemia (n, %)	604 (85.4)	72 (83.7)	37 (92.5)	0.433
Atrial fibrillation (n, %)	151 (21.4)	26 (30.2)	4 (10.0)	0.031
Diabetes mellitus (n, %)	173 (24.5)	20 (23.3)	10 (25.0)	0.956
Obesity (n, %)	120 (17.0)	15 (17.4)	12 (30.0)	0.110
Coronary heart disease (n, %)	103 (14.6)	22 (25.6)	9 (22.5)	0.003
Heart failure (n, %)	94 (13.3)	12 (14.0)	6 (15.5)	0.843
Myocardial infarction (n, %)	51 (7.2)	14 (16.3)	4 (10.0)	0.001
Aortic valve stenosis (n, %)	40 (5.7)	5 (5.8)	2 (5.0)	0.844
Chronic kidney disease (n, %)	108 (15.3)	15 (17.4)	7 (17.5)	0.665
PFO (n, %)	97 (13.7)	12 (14.0)	4 (10.0)	0.401
PFO + atrial aneurysm (n, %)	24 (3.4)	0 (0)	0 (0)	0.111
Pulmonal embolism (n, %)	9 (1.3)	1 (1.2)	1 (2.5)	0.796
DVT (n, %)	16 (2.3)	0 (0)	0 (0)	0.234

Item	No or Low-grade stenosis (n = 707)	Ipsilateral vascular pathology (n = 86)	Intervention (n = 40)	p-Value*
Procoagulant disease (n, %)	18 (2.5)	0 (0)	0 (0)	0.194
History of cancer (n, %)	78 (11.0)	10 (11.6)	3 (7.5)	0.766
History of ischaemic stroke (n, %)	142 (20.1)	25 (19.1)	9 (22.5)	0.152
TIA within the last seven days (n, %)	87 (12.3)	11 (27.5)	9 (10.4)	0.173
Antiplatelet medication (n, %)	247 (34.9)	41 (47.7)	22 (55.0)	< 0.001
Dual antiplatelet medication (n, %)	17 (2.4)	7 (8.1)	1 (2.5)	< 0.001
NOAK (n, %)	50 (7.0)	6 (7.0)	3 (7.5)	0.994
Marcumar (n %)	67 (9.5)	12 (14.0)	2 (5.0)	0.244
Antihypertensive medication (n, %)	525 (74.3)	69 (80.2)	34 (85.0)	0.077
Antihyperlipidemic medication (n, %)	254 (35.9)	47 (54.7)	22 (55.0)	< 0.001
NIHSS: National Institute of Health Stroke Scale; NOAK: new oral anticoagulants; SD: standard deviation; IQR: interquartile range; * via Kruskal-Wallis test				

Using the imaging data of the 549 patients receiving a CTA in the emergency department, 126 (23.0%) patients showed a high-grade ipsilateral arterial pathology: 94 (17.1%) were found with high-grade, ipsilateral arterial stenosis, 20 (3.6%) patients with a haemodynamic relevant, ipsilateral arterial occlusion, 6 (1.1%) patients with an arterial dissection and 2 (0.4%) patients with instable intraarterial thrombi. Of the 126 patients with high-grade ipsilateral arterial pathology, 40 (7.3%) received invasive treatment because of the diagnosed ipsilateral pathology: 20 (3.6%) patients received CEA, 11 (2%) received CAS, 4 (0.7%) patients received PTA without stenting, 4 (0.7%) patients received an IVT and one (0.2%) patient received subclavian-carotid bypass surgery. None of the patients received an MT on the basis of the acute CTA. In contrast, from all 284 patients without acute CTA, 3 (1.1%) patients were diagnosed with high-grade ipsilateral vascular pathology (stenosis) via doppler-ultrasound during in hospital stay; one (0.4%) patient underwent CEA.

Using the ABCD2-, ABCD3- and the SPI-II-Score, we found no significant difference between the three subgroups (Table 2). These TIA scores showed no predictive value for the diagnosis of high grade ipsilateral vascular pathologies or for the need of surgical or interventional treatment after the correction for possible confounders.

Table 2  
Comparison of TIA-Scores as a predictor for ipsilateral stenosis in need of therapy (n = 833)

TIA Scores	No or Low-grade stenosis (n = 707)	Ipsilateral vascular pathology (n = 86)	Intervention (n = 40)	p-Value*
ABCD2-Score (median, IQR)	4 (3–5)	4 (3–5)	4.5 (3,5–5,5)	0.577
ABCD3-Score (median, IQR)	4 (3–6)	4 (3–5)	5 (4–6)	0.199
SPI-II (median, IQR)	3 (1–5)	3 (2–6)	3 (1–5)	0.144
IQR: interquartile range, * via Kruskal-Wallis test				

From all possible clinical characteristics associated with high grade ipsilateral vascular pathology given in Table 1, univariate logistic regression revealed male sex (OR 1.64, 1.11–2.43 95% CI; p = 0.014), duration of symptoms (OR 0.74, 0.58–0.94 95% CI; p = 0.012), arterial hypertension (OR 1.84, 1.04–3.26, 95% CI; p = 0.035), coronary heart disease (OR 2.13, 1.36–3.34 95% CI; p = 0.002) and history of stroke (OR 1.47; 0.95–2.27 95% CI; p = 0.082) as possible predictors. In a multivariate logistic regression model including these items, male sex (OR 1.58, 1.06–2.36 95% CI; p = 0.026), coronary heart disease (OR 1.88, 1.17–3.02 95% CI; p = 0.009) and a short duration of the symptoms (OR 0.7, 0.55–0.89 95% CI; p = 0.004) remained as significant predictors for ipsilateral vascular pathologies (Table 3).

Table 3  
Multivariate logistic regression for ipsilateral vascular pathology

Item	Regression Coefficient for depending ipsilateral pathology	p-Value	OR	95%CI
Sex, male	0.457	0.026	1.579	1.056–2.360
Duration of Symptoms	-0.361	0.004	0.697	0.547–0.889
Arterial hypertension	0.528	0.081	1.696	0.937–3.070
Coronary heart disease	0.631	0.009	1.879	1.173–3.009
Ischaemic Stroke	0.298	0.191	1.348	0.862–2.108
<b>Intercept</b>	-1.776	< 0.001	0.169	0.076–0.375

A similar logistic regression model was developed to identify possible predictors for the need of any invasive treatment. The univariate logistic regression identified the items duration of symptoms (OR 0.61, 0.42–0.89 95% CI; p = 0,009), obesity (OR 2.09; 1.04–4.22 95% CI; p = 0.039), antiplatelet medication (OR

2.09; 1.1–3.97 95% CI; p = 0.025), antihyperlipidemic medication (OR 2.00; 1.05–3.79 95% CI; p = 0.034), hemiparesis (OR 2.52; 1.32–4.80 95%CI; p = 0.005) and pyramidal sign (OR 5.07, 1.62–15.87, p = 0.005) as possible predictors for intervention. A multivariate logistic regression model of these items identified duration of symptoms (OR 0.48; 0.32–0.72 95% CI; p < 0.001), obesity (OR 2.19, 1.04–4.60 95% CI, p = 0.038), hemiparesis (OR 2.66, 1.36–5.22 95% CI, p = 0.004) and pyramidal sign (OR 6.04, 1.70-21.47 95% CI, p = 0,005) as predictive items (Table 4).

Table 4  
Multivariate logistic regression for Intervention

Item	Regression Coefficient for depending intervention	p-Value	OR	95%CI
Duration of Symptoms	-0,741	< 0,001	0,476	0,316–0,719
Obesity	0,784	0,038	2,191	1,043 – 4,602
Antiplatelet medication	0,445	0,237	1,561	0,746–3,266
Antihyperlipidemic medication	0,486	0,191	1,626	0,783–3,378
Hemiparesis	0,979	0,004	2,662	1,358–5,220
Pyramidal sign	1,798	0,005	6,040	1,699 – 21,468
<b>Intercept</b>	-2,453	< 0,001	0,086	0,032 – 0,232

## Discussion

In our study, we found high grade, ipsilateral arterial pathologies in around 23% of all patients with TIA diagnosed by acute CTA and a need for invasive treatment in around 7% of cases. These numbers indicate that CTA in the acute setting of TIA is justified in selected patient subgroups. As predictors, we identified male sex, cardiovascular disease, a short period of symptoms, hemiparesis and pyramidal signs, which might be useful for patient selection. In contrast, established TIA-scores turned out to be not predictive for high risk vascular pathologies.

TIA and ischemic stroke, both indistinguishable in the acute setting in most cases, require vascular imaging. Besides CTA, there are other imaging methods to be considered for neurovascular status evaluation like magnetic resonance imaging and neurovascular ultrasound. Neurovascular ultrasound of the brain supplying arteries has a high spatial resolution and is able to detect atherosclerotic changes, as well as thrombi in the proximal carotid artery very well. However, it is limited by investigator dependency and availability. Neurovascular Ultrasound in the acute setting can also result in treatment delays due to



longer investigation times and patient factors like non-compliance, anatomical problems like insufficient transtemporal doppler window and the fact that distal intracranial arteries as well as distal parts of the internal carotid arteries cannot be visualized. [13] Therefore, neurovascular ultrasound is not recommended in the acute phase of ischemic stroke if fast and targeted therapy like IVT and EVT is available. Magnetic resonance imaging (MRI) is one of the most important methods to assess the brain tissue. However, it has been shown that CT combined with CTA provides a comparable quality to diffusion-weighted MRI in stroke patients.[14] Considering the fact that MRI resources are more limited compared to CT, which is available 24/7 in all stroke centres, also is significantly faster and has a high sensitivity for the diagnosis of vessel occlusions and haemorrhages, CT imaging is the technology of choice in the acute setting of stroke.[15]

The evaluated ABCD2-score, ABCD3-score and SPH-II, that stratify the risk for stroke after TIA, were not predictive for ipsilateral vascular pathologies or the need for invasive treatment in our study. This observation corresponds to findings from Lou et al. concerning the ABCD2-Score as a possible predictor for intervention. In their study, including 121 patients with TIA, they found that the ABCD2-Score was equally distributed in patients no matter if they received an intervention or not.[16] Reasons for the missing predictive value of these scores might be, that TIA scores have been developed to predict recurrence rates of TIA or stroke in those patients. Many factors incorporated in these scores (admission blood pressure, age, diabetes mellitus and heart failure) were equally distributed in our cohort, raising the suspicion, that these factors are likely to be usable to quantify instability (risk of recurrence) of the underlying pathology, but are not predictive for the underlying pathology itself. Also, most items are related to the neurologic symptoms presented at admission. As the most important predictors for vascular disease like chronic arterial hypertension, high heart rate, smoking habit and other vascular diseases are not considered in these scores, this might explain the lack of prediction. [17, 18]

Our results advise to consider a certain risk profile if to decide to perform a CTA or not.

Concerning the association between male sex and the incidence of cerebro- and cardiovascular diseases in general[19–23], the high prevalence of carotid stenosis in patients with coronary artery disease,[21, 24, 25] it is not surprising, these patient characteristics predict ipsilateral high-risk pathologies diagnosed by CTA in our study. Our findings suggest that patients at risk for macroangiopathic vessel disease and TIA should receive CTA in the acute setting to diagnose high risk vascular pathologies and to initiate targeted therapy. CTA in this case could contribute to a time gain to diagnosis and could contribute to reduce the risk for TIA recurrence or a manifest ischemic stroke.

A short duration of Symptoms in TIA patients is likely to be associated with macroangiopathic arterial disease of brain supplying arteries and can be found in most patients with carotid artery stenosis. A prototype of a short lasting neurologic deficit associated with carotid artery stenosis is the Amaurosis fugax, a special form of TIA.[26, 27] Already in the seventies Pessin et al. and Harrison et al. found that TIA-patients with a symptom duration under one hour were more likely to have a carotid artery stenosis and should get an angiography.[28, 29] These findings go in line with our finding, that a short duration of

symptoms increases the risk for a high grade, ipsilateral vascular pathology and the need for an invasive treatment in patients with TIA. In contrast, cardiac emboli are more likely to cause permanent and more severe focal neurological deficits.[24, 30, 31] The difference in duration of symptoms caused by arterial or cardiac emboli could be explained by a difference in spontaneous revascularization due to a variation of constitution and size of the thrombi.[29, 32, 33] Another point to consider is the collateralisation status in patients with arterial emboli caused by vessel stenosis compared to cardiac embolization with no associated vessel stenosis. Arterial stenosis formation take month to years inducing intracranial collateralization, which is not present in cardiac embolization. This fact could explain short symptom duration in patients with arterial stenosis, where hemodynamics can adapt in a few seconds.[34] Therefore, short duration of symptom should not be discarded as trivial by the clinician, but raise the suspicion of macroangiopathic disease with associated findings in CTA.

Strength of our study is the high number of patients included in our study cohort as well as the use of “real word” data from a large volume, tertiary stroke centre. Limitations include the monocentric, retrospective design of the study. Moreover, a selection bias must be assumed, as only 66% of patients with TIA received a CTA in the emergency department. The reason for the decision to perform or not to perform a CTA in the acute setting could be influenced by multiple factors like preference of the consultant neurologist in charge, patient factors like kidney disease and medical history of the patient.

## **Conclusion**

In this study CTA revealed high grade ipsilateral pathology in more than every fifth patient with TIA and therefore represents an important diagnostic tool in initial workup. Male sex, history of coronary heart disease and a short duration of symptoms may be useful to triage TIA patients for acute CTA. Our findings justify a prospective, randomized trial comparing patients receiving no acute vascular imaging, acute neurovascular ultrasound and acute CTA.

## **List Of Abbreviations**

CAS	carotid artery stenting
CEA	carotid endarterectomy
CTA	computed tomography angiography
IVT	intravenous thrombolysis
MRI	Magnetic resonance imaging
MT	mechanical thrombectomy
PTA	percutaneous transluminal angioplasty
SPI-II	stroke prognosis instrument II
TIA	transient ischaemic attack

## Declarations

### **Ethics approval and consent to participate:**

The ethics commission of the University Medicine Göttingen waived an ethical approval. Written informed consent was obtained from the patient(s) for their participation in this study.

### **Consent for publication:**

Not applicable

### **Availability of data and materials:**

All data generated or analysed during this study are included in this published article

### **Competing interests:**

The Authors declare that there is no conflict of interests.

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### **Authors' contributions:**

GH, IM, MP and JL conceived the study. GH and IM were involved in the protocol development. GH and IM wrote the first draft of the manuscript and qualify equally for the first authorship. All authors provided continuous evaluation during the study process. All authors reviewed and edited the manuscript and approved the final version of the manuscript.

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