

# The role of additional computed tomography in the decision-making process on the secondary prevention in patients after systemic cerebral thrombolysis

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**Introduction:** Patients with ischemic stroke undergoing intravenous (iv)-thrombolysis are routinely controlled with computed tomography on the second day to assess stroke evolution and hemorrhagic transformation (HT). However, the benefits of an additional computed tomography (aCT) performed over the next days after iv-thrombolysis have not been determined.

**Methods:** We retrospectively screened 287 Caucasian patients with ischemic stroke who were consecutively treated with iv-thrombolysis from 2008 to 2012. The results of computed tomography performed on the second (control computed tomography) and seventh (aCT) day after iv-thrombolysis were compared in 274 patients (95.5%); 13 subjects (4.5%), who died before the seventh day from admission were excluded from the analysis.

**Results:** aCTs revealed a higher incidence of HT than control computed tomographies (14.2% vs 6.6%;  $P=0.003$ ). Patients with HT in aCT showed higher median of National Institutes of Health Stroke Scale score on admission than those without HT (13.0 vs 10.0;  $P=0.01$ ) and higher presence of ischemic changes  $>1/3$  middle cerebral artery territory (66.7% vs 35.2%;  $P<0.01$ ). Correlations between presence of HT in aCT and National Institutes of Health Stroke Scale score on admission ( $r_{\text{phi}}=0.15$ ;  $P<0.01$ ), and the ischemic changes  $>1/3$  middle cerebral artery ( $\phi=0.03$ ) existed, and the presence of HT in aCT was associated with 3-month mortality ( $\phi=0.03$ ).

**Conclusion:** aCT after iv-thrombolysis enables higher detection of HT, which is related to higher 3-month mortality. Thus, patients with severe middle cerebral artery infarction may benefit from aCT in the decision-making process on the secondary prophylaxis.

**Keywords:** ischemic stroke, iv-thrombolysis, computed tomography, hemorrhagic transformation

## Introduction

Plain computed tomography (CT) is commonly used for the initial assessment of stroke patients.<sup>1</sup> CT rules out hemorrhage, visualizes the occluding thrombus, and identifies early tissue hypodensity and brain edema.<sup>2,3</sup> Therefore, CT findings have different implications for intravenous thrombolysis (iv-thrombolysis).<sup>4,5</sup>

Control CT is routinely performed 24–36 hours from the stroke onset for the evaluation of ischemic lesions and hemorrhagic transformation (HT) after iv-thrombolysis.<sup>5–7</sup> Symptomatic HT is the most feared complication of iv-thrombolysis that is routinely diagnosed by control CT, with a negative prognostic value and important implications for secondary prevention in patients who have suffered a cardio-embolic stroke.<sup>8</sup> However, it is not clear if the additional CT (aCT) assessment, performed in the next

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days after iv-thrombolysis, may benefit HT detection and help with the decision making in secondary stroke prevention.

Thus, the aim of our study was to assess the potential benefits of aCT performed on the seventh day after iv-thrombolysis for the diagnosis of HT and to assess its long-term prognostic value.

## Materials and methods

We retrospectively screened the medical records of 287 Caucasian patients with acute ischemic stroke who were consecutively treated with iv-thrombolysis from January 2008 to December 2012 in the Department of Neurology and the Stroke Unit of the Holy Spirit Specialist Hospital in Sandomierz (Poland). We analyzed the demographic, clinical, and radiological data of 274 patients (55.2% male, aged 41–92 years; mean age  $69.7 \pm 11.9$  years) and excluded data of 13 subjects (4.5%) who died before the seventh day from the admission. The stroke unit provided 24-hour stroke service, 7 days a week, according to the European Stroke Organization criteria with the use of appropriate monitoring and diagnostic facilities.<sup>9</sup> Acute stroke therapy and secondary prophylaxis were applied according to the current European Stroke Organization guidelines and Polish national regulations.<sup>4,5,9–11</sup> CT was performed in all patients upon admission to the hospital between 24 and 36 hours (control CT), and on the seventh day after iv-thrombolysis (aCT) with the use of GE Hi Speed; Head 4/2i+10/2i, according to the protocol of thrombolytic treatment applied in our stroke center. Experienced radiologists and stroke physicians evaluated all CT scans. HT rates were assessed according to the European Cooperative Acute Stroke Study II criteria.<sup>12</sup> All baseline CTs were additionally evaluated according to the Alberta Stroke Program Early CT score.<sup>13,14</sup> Stroke symptoms were assessed on admission using National Institutes of Health Stroke Scale (NIHSS), and the 90-day stroke outcomes were measured with the modified Rankin scale.<sup>15,16</sup> A favorable outcome was defined as an modified Rankin scale score  $\leq 2$  points. All patients treated with iv-thrombolysis in our stroke units were reported to the Safe Implementation of Thrombolysis in Stroke registry and the Pomeranian Stroke Register.<sup>7,17</sup> The ethics committee of Świętokrzyska Medical Chamber approved all data analyses.

## Statistical methods

This study was based on a retrospective data analysis. All statistical analyses were performed with STATISTICA v.9.1, and all continuous variables were tested for normal distribution and equality of variance. Because of the non-normality of the variables, non-parametric Mann–Whitney *U*-tests were used to perform the univariate analysis of the continuous

variables. Categorical data were compared using chi-square tests. Single variable correlations with the outcome of interest were performed with use of point-biserial and Phi correlation coefficients.

## Results

From the studied cohort of 274 patients with acute ischemic stroke treated with iv-thrombolysis, 56.6% were independent (modified Rankin scale 0–2), 17.8% died, and 15.7 % were diagnosed with HT (4.2% had a symptomatic intracerebral hemorrhage) after 3 months from the stroke onset.

aCT performed on the seventh day after iv-thrombolysis revealed a higher presence of HT compared to control CT scans performed after 24 hours; symptoms, not significant differences regarding the presence of ischemic changes, were found (Table 1). The HT rate in aCT did not differ between patients on anticoagulants prior to intravenous tissue plasminogen activator therapy and those without prior anticoagulation (9.5% vs 12.7%;  $P=0.68$ ).

The subgroup of patients with HT detected in aCT was characterized by a higher median on the NIHSS assessed on admission, a higher presence of ischemic changes  $>1/3$  middle cerebral artery (MCA) territory (66.7% vs 35.2%;  $P<0.01$ ), and a higher 3-month mortality rate than patients without HT in the aCT. Median NIHSS score on admission was higher in patients with ischemic changes  $>1/3$  MCA territory than in those with ischemic changes  $\leq 1/3$

**Table 1** Radiological findings in CTs performed on the second and seventh day after iv-thrombolysis

Variables (n)	Second day after iv-thrombolysis N=274	Seventh day after iv-thrombolysis N=274	P-value
Ischemic changes, n (%)			
Abnormal CT	166 (60.6)	187 (68.3)	0.07
<1/3 territory	68 (24.8)	75 (27.4)	0.40
MCA			
>1/3 territory	93 (33.9)	106 (38.7)	0.50
MCA			
Posterior territory	5 (1.8)	6 (2.2)	0.76
HT* n (%)	18 (6.6)	39 (14.2)	<b>&lt;0.01</b>
HT1	6 (2.2)	11 (4.0)	0.22
HT2	4 (1.5)	11 (4.0)	0.07
PH1	5 (1.8)	12 (4.4)	0.09
PH2	2 (0.7)	3 (1.1)	0.65
PHr1, PHr2	1 (0.4)	2 (0.7)	0.56

**Notes:** \*According to the ECASS II definition. Significant *P*-values are shown in bold. **Abbreviations:** CT, computed tomography; iv, intravenous; MCA, middle cerebral artery; HT1, hemorrhagic transformation type 1; HT2, hemorrhagic transformation type 2; PH1, parenchymal hemorrhage type 1; PH2, parenchymal hemorrhage type 2; PHr1, parenchymal hemorrhage remote type 1; PHr2, parenchymal hemorrhage remote type 2; ECASS, European Cooperative Acute Stroke Study.

MCA territory (15 [11–18] vs 9 [7–12] points;  $P<0.01$ ). No significant differences regarding other clinical and radiological parameters were found; however, hemoglobin levels and median diastolic blood pressures between the second and seventh day from the stroke onset tended to be higher in the subgroup of patients with HT detected in aCT (Table 2).

Correlations tests showed significant associations between baseline NIHSS and the presence of HT in the aCT ( $r_{\text{pbi}}=0.15$ ;  $P<0.01$ ) and infarction volume  $>1/3$  MCA territory and the presence of HT in the aCT ( $\phi=0.03$ ); no significant association between diastolic blood pressure between the second and seventh day and the presence of HT in the aCT ( $r_{\text{pbi}}=0.04$ ;  $P=0.52$ ) was found. Hemoglobin levels tended to

**Table 2** The clinical characteristics of the subgroups of patients with and without HT in the additional CT

n (%)	Patients with HT* in the additional CT N=21	Patients without HT* in the additional CT N=253	P-value
<b>Demographic data</b>			
Age (years), mean, SD	71.0±10.5	69.6±11.2	0.75
Male sex, n (%)	11 (52.4)	140 (55.3)	0.79
<b>Logistic factors</b>			
Onset to treatment time, median (IQR)	135 (125–165)	160 (135–180)	0.11
<b>Risk factors, n (%)</b>			
Arterial hypertension	18 (85.7)	167 (66.0)	0.64
Coronary heart disease	9 (42.9)	144 (56.9)	0.21
Atrial fibrillation	8 (38.1)	82 (32.5)	0.59
Diabetes mellitus	2 (9.5)	42 (16.6)	0.40
Dyslipidemia	18 (85.7)	193 (76.3)	0.32
Smoking	4 (19.1)	52 (20.6)	0.87
Prior stroke	2 (9.5)	43 (17.0)	0.37
Antiplatelet therapy before stroke	11 (52.4)	149 (58.9)	0.56
Anticoagulant therapy before stroke	2 (9.5)	32 (12.7)	0.68
<b>Clinical status</b>			
NIHSS on admission (pts), median (IQR)	13.0 (11.0–18.0)	10.0 (7.0–15.0)	<b>0.01</b>
Delta NIHSS first-seventh day (pts), median (IQR)	6 (3.5–10.5)	6 (3.0–9.0)	0.54
<b>Secondary prevention between the second and seventh day, n (%)</b>			
Antiplatelet	7 (33.3)	129 (60.0)	0.12
Anticoagulant orally	3 (14.3)	16 (6.3)	0.17
Antiplatelet + LMWH (prophylactic dose)	11 (52.4)	109 (34.1)	0.41
<b>Long-term outcome</b>			
Unfavorable outcome at 90 days (mRS 3–5)	7 (33.3)	70 (26.7)	0.58
Death (mRS 6)	6 (28.6)	21 (8.3)	<b>&lt;0.01</b>
<b>Blood pressure on admission</b>			
MAP (mmHg), median (IQR)	113.3 (106.7–123.7)	106.7 (96.7–116.7)	0.55
SBP (mmHg), median (IQR)	160.0 (146.0–171.0)	152.0 (140.0–170.0)	0.13
DBP (mmHg), median (IQR)	89.0 (80.0–99.0)	80.0 (80.0–90.0)	0.85
<b>Blood pressure on the first day</b>			
MAP (mmHg), median (IQR)	104.7 (96.7–106.7)	103.3 (98.3–108.7)	0.82
SBP (mmHg), median (IQR)	148.0 (138.0–156.0)	142.0 (135.0–156.0)	0.61
DBP (mmHg), median (IQR)	86.0 (76.0–88.0)	82.0 (80.0–87.0)	0.90
<b>Blood pressure between the second and seventh day</b>			
MAP (mmHg), median (IQR)	101.3 (97.3–103.7)	99.3 (95.3–102.3)	0.11
SBP (mmHg), median (IQR)	139.0 (130.0–146.0)	135.0 (130.0–142.0)	0.52
DBP (mmHg), median (IQR)	82.0 (80.0–86.0)	80.0 (77.0–84.0)	0.07
<b>Laboratory findings before thrombolysis</b>			
INR on admission, median (IQR)	1.05 (0.98–1.18)	1.02 (0.97–1.10)	0.27
Glucose level (mmol/L), median (IQR)	6.5 (5.4–8.3)	6.4 (5.6–7.5)	0.82
Hemoglobin level (g/L), median (IQR)	14.5 (13.4–15.4)	14.0 (13.1–15.0)	0.07
Creatinine level (μmol/L), median (IQR)	90.3 (75.2–101.6)	83.6 (69.0–96.9)	0.61
eGFR (mL/min/1.73 m <sup>2</sup> ), median (IQR)	67.0 (64.0–86.0)	75.0 (62.0–90.0)	0.44

(Continued)

**Table 2** (Continued)

n (%)	Patients with HT* in the additional CT 21	Patients without HT* in the additional CT 253	P-value
<b>Baseline CT</b>			
Old ischemic changes in baseline CT, n (%)	9 (42.9)	85 (33.6)	0.39
Early ischemic changes in baseline CT, n (%)	5 (23.8)	59 (23.3)	0.96
Median ASPECTS score (pts), median (IQR)	9.0 (8.0–10.0)	10.0 (8.0–10.0)	0.37
ASPECTS score $\leq 7$ pts, n (%)	29 (9.5)	24 (9.5)	0.99
<b>Additional CT</b>			
Ischemic changes $< 1/3$ territory MCA, n (%)	2 (9.5)	24 (9.49)	0.99
Ischemic changes $> 1/3$ territory MCA, n (%)	14 (66.7)	89 (35.2)	<b><math>&lt; 0.01</math></b>
Posterior territory stroke, n (%)	1 (4.7)	5 (1.98)	0.40

**Notes:** \*According to the ECASS II criteria. Significant *P*-values are shown in bold.

**Abbreviations:** HT, hemorrhagic transformation; mRS, modified Rankin scale; LMWH, low molecular weight heparin; MAP, mean arterial pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure; NIHSS, National Institutes of Health Stroke Scale; ECASS, European Cooperative Acute Stroke Study; SD, standard deviation; IQR, interquartile range ( $Q_1$ – $Q_3$ ); eGFR, estimated glomerular filtration rate; CT, computed tomography; pts, points; MCA, middle cerebral artery; ASPECTS, Alberta Stroke Program Early CT Score.

be associated with the presence of HT in the aCT ( $r_{\text{phi}} = 0.11$ ;  $P = 0.07$ ). The presence of HT in the aCT was associated with mortality rate at a 3-month follow-up ( $\text{phi} = 0.03$ ).

## Discussion

Our study shows that brain CT performed on the seventh day after iv-thrombolysis may detect significantly more HT than CT routinely performed on the second day after treatment. Our results also show that a higher baseline NIHSS score on admission, presence of ischemic changes  $> 1/3$  MCA territory, and higher hemoglobin levels may indicate the benefit from aCT scanning regarding HT detection as the presence of HT detected by aCT is associated with a higher 3-month mortality rate.

A brain CT is routinely performed in the Polish stroke unit during the qualification for iv-thrombolysis and the follow-up between 24 and 36 hours from the therapy.<sup>4,5,9</sup> It is highly sensitive in the detection of hemorrhagic complications of iv-thrombolysis; however, some authors show that protocol requiring repeated neuroimaging 24 hours after intravenous tissue plasminogen activator is not supported by clinical practice data and recommend it rather in case of clinical deterioration after iv-thrombolysis.<sup>4,5,9,18</sup> In our opinion, our findings may justify repeated neuroimaging and show potential benefit from the aCT performed on the seventh day after iv-thrombolysis in patients without clinical deterioration.

Our data show that acute ischemic stroke patients receiving iv-thrombolysis who had a greater initial severity of stroke symptoms according to their NIHSS score and those with ischemic changes  $> 1/3$  MCA territory are at a higher risk of HT presence. Both high NIHSS score on admission and ischemic area  $> 1/3$  MCA territory are well-known

predictors of long-term unfavorable outcome and symptomatic intracranial bleeding complications in acute ischemic stroke.<sup>13,19–25</sup> Our results show that both of them may be also associated with further presence of asymptomatic HT. Thus, we believe that patients with a high NIHSS score on admission and ischemic changes  $> 1/3$  MCA territory may benefit from the implementation of aCT imaging beyond routine procedures. We also notice the potential prognostic value of aCT regarding 3-month mortality.

We also believe that aCT imaging may bring benefit for secondary stroke prevention. Presence of HT may influence the implementation of anticoagulant or antiplatelet therapy; thus, aCT may help with the decision making on its applications. As 38% of patients with HT in the aCT suffered AF in our cohort, and 9.5% were on oral anticoagulants before the stroke, aCT results could help in specifying the terms of (dis)continuation of anticoagulation therapy after seventh day from the stroke onset. Our results show that patients with a high NIHSS score on admission and infarction area  $> 1/3$  MCA territory could be considered for aCT before initiation of antithrombotic therapy with oral anticoagulants, which are usually introduced in subacute phase of stroke, but are contraindicated even in asymptomatic bleeding. We believe that this issue emphasizes the practical impact of our study.

The tendency to associate higher hemoglobin levels with the presence of HT is another novel finding, which might be followed-up in future studies. Previous reports mainly showed that a low hemoglobin level on admission predicts short- and long-term outcomes in patients with acute ischemic stroke and is associated with the growth of infarction volume, stroke severity, and outcome.<sup>26–30</sup> However, it has been also previously reported that erythropoietin combined with tissue



plasminogen activator may exacerbate tPA-induced brain hemorrhage in rats due to upregulation of matrix metalloproteinase, necrosis factor, and interleukin-1 receptor-associated kinase.<sup>31</sup> A similar mechanism may potentially explain higher hemoglobin levels in patients with HT in aCT in our cohort; however, we realize that it may be a more complex effect, which needs further clinical and biochemical evaluation.

Our study is a retrospective observation study with a number of limitations. The sample population was narrow in scope, and the results of our study may not apply to patients treated with intra-arterial thrombolysis or endovascular treatment of stroke.<sup>32</sup> Additionally, the risk profile of the included patients might be lowered by exclusion of patients who died within 7 days from the analysis. Thus, we have to admit that the generalizability of our results performing CT only, without magnetic resonance imaging, can be considered another limitation of our study. Therefore, we find confirmation of our results by other reports with magnetic resonance imaging reasonable.

## Conclusion

Our data may suggest that an aCT performed on the seventh day after iv-thrombolysis is justified in selected patients because it allows additional detection of radiological signs of HT, which are associated with long-term mortality. Especially patients with an MCA infarction >1/3 MCA territory and severe stroke deficit reflected by a high NIHSS score on admission may be considered for an aCT and may benefit from repeated neuroimaging in decision-making process on secondary prophylaxis with antithrombotic therapy.

## Author contributions

Piotr Sobolewski contributed to the study design, patient selection, clinical work, data collection, analysis, interpretation, and writing of the manuscript. Grzegorz Kozera contributed to the study design, statistical analysis, and data interpretation. Wiktor Szczuchniak contributed to patient selection, clinical work, data collection, statistical analysis, and interpretation. Walenty M Nyka contributed to analysis and interpretation. All authors contributed toward data analysis, drafting and revising the paper and agree to be accountable for all aspects of the work.

## Disclosure

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