Outcome of patients with atrial fibrillation after intravenous thrombolysis for cerebral ischaemia

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Abstract  The question of whether i.v. rt-PA is beneficial in patients with ischaemic stroke and atrial fibrillation (AF) remains unresolved. Our objective was to evaluate the outcome of patients with AF who received i.v. rt-PA for stroke in the registries of Lille (France) and Belgrade (Serbia). End-points were poor outcome [modified Rankin Scale (mRS) 3–6], and symptomatic haemorrhagic transformation (sHT) according to ECASS3. Of 734 consecutive patients, 155 (21.2 %) had AF. The unadjusted comparison found patients with AF to be 12 years older, more likely to be women, to have hypertension, and baseline INR \([1.2\), and less likely to be smokers. They had higher baseline NIHSS scores, diastolic blood pressure, and serum glucose concentrations, and lower platelet counts. They did not differ for sHT (5.8 vs. 5.5 %; \(p = 0.893\)), but they more frequently had poor outcomes (52.3 vs. 35.2 %; \(p < 0.001\)) and death (21.9 vs. 9.0 %; \(p < 0.001\)). The only independent predictor of sHT was baseline NIHSS (adj OR 1.05 per 1 point increase; 95 % CI 1.01–1.10). Independent variables associated with poor outcome were age (adj OR 1.04 for 1 year increase; 95 % CI 1.03–1.06), baseline NIHSS (adj OR 1.17 per 1 point increase; 95 % CI 1.13–1.21), and sHT (adj OR 47.6; 95 % CI 10.2–250) but not AF. In patients treated with i.v. rt-PA for cerebral ischaemia, those with AF have worse outcomes because they are older and have more severe strokes at admission. This result suggests that we should focus on prevention and research of more aggressive strategies at the acute stage.

Keywords  Ischaemic stroke · Cerebral ischaemia · Thrombolysis · Atrial fibrillation · Haemorrhagic transformation · Outcome

Introduction

Intravenous (i.v.) recombinant tissue plasminogen activator (rt-PA) given within 4.5 h improves functional outcomes in patients with cerebral ischaemia [1]. I.v. rt-PA is also beneficial after the age of 80 years [2, 3], i.e. in an age-category where atrial fibrillation (AF) is frequent. AF-associated ischaemic strokes are more severe [4], more frequently associated with haemorrhagic transformation (HT) [5, 6], and have worse outcomes [7]. HT may be favoured by on-going antithrombotic therapies [8], delayed recanalisation, older clots being less likely to dissolve with rt-PA [9], or subclinical pre-existing brain changes frequent in the elderly such as microbleeds, leucaaraiosis, silent infarcts, or cerebral amyloid angiopathy [10, 11].

Three randomised controlled trials comparing rt-PA vs. placebo in cerebral ischaemia provided detailed results in patients with AF [2, 12, 13]: their results are conflicting, with a non-significant tendency in favour of placebo in
ECASS III [12], of rt-PA in IST-3 [2], and no difference in NINDS [13]. Observational studies conducted in patients treated with i.v. rt-PA provided also conflicting results: most suggested i.v. rt-PA is probably beneficial in patients with AF [14–16] despite worse outcomes and higher risks of HT [17–20], but another did not [21]. These discrepancies may be due to the association of AF with age and severity, two major predictors of poor outcome.

The aim of our study was to evaluate the outcome of patients with AF who received i.v. rt-PA for cerebral ischaemia in clinical practice.

Methods

We analysed data prospectively collected in two registries of patients treated with i.v. rt-PA for cerebral ischaemia.

Setting

Patients were recruited in the stroke centres of the university hospitals of Lille, France, and Belgrade, Serbia. The general organisation of these centres has already been described [22–26]. Magnetic resonance imaging (MRI) replaced computed tomography (CT) as first-line examination in Lille after May 2009. In both centres the recruitment of patients was stopped for this study on May 31, 2012, and patients were followed-up for 3 months.

Assessment of atrial fibrillation

We recorded the medical history, a 12-lead ECG at admission, a 48–72 h continuous ECG monitoring, and, when necessary, additional ECG recordings. We considered patients as having previously known AF when a previous ECG with AF or atrial flutter had been seen by a physician of the stroke team, or when there was a letter from a cardiologist stating that AF had been previously detected on ECG or Holter ECG. We considered as having de novo AF those patients without history of AF or atrial flutter, who had AF on the ECG recorded in the emergency room, or during hospitalisation, or on the 48–72 h continuous ECG monitoring. As it has been shown previously that outcomes do not differ between patients with de novo AF and previously known AF [17], we combined both types for the analysis.

Neurological assessment

The pre-treatment stroke severity was assessed by the National Institutes of Health Stroke Scale (NIHSS) [27] just before the bolus of rt-PA. The presumed cause of ischaemic stroke was determined according to the TOAST criteria [28]. Patients with AF were classified either in the “cardioembolic” subgroup when no other potential cause has been identified, or in the “unknown cause” subgroup when another potential cause of ischaemic stroke was present or when the diagnostic work-up has not been extensive enough. The outcome at 3 months was assessed with the modified Rankin scale (mRS) [29]: in both centres, survivors were examined 3 months after treatment by a senior neurologist, a specialist of rehabilitation, or both. When necessary, the face-to-face visit was replaced by a telephone interview with the patient, caregiver, local neurologist, or general practitioner.

Endpoints

The primary end point a “poor outcome” defined as a mRS score of 3–6 at the 3-month visit. The secondary end point was symptomatic HT (sHT) according to the ECASS 3 definition.

Statistical analysis

We performed the statistical analysis with the SPSS 15.0 package for Windows. We compared patients with and without AF for age, sex, baseline NIHSS, sHT and poor outcome at 3 months.

We used median values, interquartile ranges (IQR), and percentages with 95 % confidence intervals (CI). We compared groups for categorical variables, with the Chi Square test with Yates’ correction or Fisher exact test when appropriate, and odds ratios (OR) with 95 % CI. We compared continuous variables with the Mann and Whitney U test.

We performed two logistic regression analyses [30] with “poor outcome” at 3 months, and sHT as dependent variables. The independent variables included in these analyses were selected from a bivariate analysis, with a p value of 0.25 or less as a screening criterion for the selection of candidate variables [31]. The variables centre (quoted 1 for patients from Belgrade and 0 for patients from Lille), and atrial fibrillation, were forced into the model. Correlations between variables were checked for possible collinearity between variables (defined as $r > 0.6$). Adjusted OR (adjOR) and 95 % CI were calculated from the logistic regression analyses.

Ethics

In Belgrade the stroke database was approved by the professional collegium of the Association of Serbian neurologists. In Lille it was declared at the institutional data review board, and considered as observational. Patients gave an informed consent.
Results

Baseline characteristics and outcome

During the study period, we included 734 consecutive patients, 149 in Belgrade (20.3 %) and 585 in Lille (79.7 %). Of these, 155 patients had AF (21.2 %), previously known in 140 (90.3 %), de novo in 15 (9.7 %). Baseline characteristics of the study population, and outcomes, are detailed in Table 1 for the whole population and separately in patients with and without AF. In the 155 patients with atrial fibrillation, the presumed cause of stroke was “cardioembolic” in 135 (87.1 %) and “unknown” in 20 (12.9 %) patients who had another potential cause of stroke associated with AF. In the 579 patients without atrial fibrillation, the presumed causes of stroke were “large-artery atherosclerosis” in 105 (18.1 %), “cardioembolic” other than AF in 109 (18.8 %), “small-vessel occlusion” in 34 (5.9 %), “other definite cause” in 28 (2.8 %) and “unknown” in 295 (50.9 %). The unadjusted comparison showed that patients with AF were older, more likely to be women, to have history of arterial hypertension, and to have a baseline INR > 1.2, less likely to be current smokers, had higher baseline NIHSS scores, higher diastolic blood pressure, higher serum glucose concentration, and lower platelet count. They did not differ for sHT, but they were more likely to have a poor outcome or to be dead at 3 months. The analysis of the whole spectrum of mRS showed a worse overall outcome in patients with AF (Fig. 1).

Predictors of outcome

The only independent variable associated with sHT was baseline NIHSS scores (adjOR 1.05 per 1 point increase; 95 % CI 1.01–1.10). AF, age, arterial hypertension, smoking, previous myocardial infarction, and being under oral anticoagulant therapy were not independently associated with sHT (overall \( p \) value \(<0.048\); \( r^2 \) 0.043; 94.4 % prediction of the model). The other variables did not qualify for the model.

Table 1 Comparison of demographic and baseline characteristics, and outcome between patients with and without atrial fibrillation who were treated by i.v. rt-PA between the two centres

<table>
<thead>
<tr>
<th></th>
<th>With atrial fibrillation (( n = 155 ))</th>
<th>Without atrial fibrillation (( n = 579 ))</th>
<th>Unadjusted ( p ) values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic characteristics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>90 (58.1 %)</td>
<td>257 (44.4 %)</td>
<td>0.002</td>
</tr>
<tr>
<td>Age (years)*</td>
<td>76 (67–83)</td>
<td>64 (52–76)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Recruited in Belgrade</td>
<td>34 (21.9 %)</td>
<td>115 (19.9 %)</td>
<td>0.569</td>
</tr>
<tr>
<td>Medical history</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arterial hypertension</td>
<td>124 (80.0 %)</td>
<td>359 (62.3 %)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>31 (20.0 %)</td>
<td>91 (15.7 %)</td>
<td>0.203</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>70 (45.2 %)</td>
<td>266 (45.9 %)</td>
<td>0.863</td>
</tr>
<tr>
<td>Currently smoking</td>
<td>29 (18.7 %)</td>
<td>174 (30.1 %)</td>
<td>0.005</td>
</tr>
<tr>
<td>Alcohol use</td>
<td>11 (7.1 %)</td>
<td>58 (10.0 %)</td>
<td>0.268</td>
</tr>
<tr>
<td>Previous stroke</td>
<td>15 (9.7 %)</td>
<td>63 (10.9 %)</td>
<td>0.666</td>
</tr>
<tr>
<td>Previous myocardial infarction</td>
<td>22 (14.2 %)</td>
<td>52 (9.0 %)</td>
<td>0.056</td>
</tr>
<tr>
<td>Baseline clinical and biological characteristics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Onset to needle*</td>
<td>148 (114–178)</td>
<td>153 (120–192)</td>
<td>0.073</td>
</tr>
<tr>
<td>NIHSS score*</td>
<td>14 (8–18)</td>
<td>10 (6–16)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Systolic blood pressure*</td>
<td>155 (140–170)</td>
<td>150 (137–165)</td>
<td>0.110</td>
</tr>
<tr>
<td>Diastolic blood pressure *</td>
<td>83 (79–95)</td>
<td>80 (73–90)</td>
<td>0.018</td>
</tr>
<tr>
<td>INR &gt; 1.2</td>
<td>13 (8.4 %)</td>
<td>10 (1.7 %)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Blood glucose (mmol/l)*</td>
<td>7.06 (6.05–8.57)</td>
<td>6.66 (5.77–7.91)</td>
<td>0.036</td>
</tr>
<tr>
<td>Platelet count (10<em>9/L)</em></td>
<td>212 (179–244)</td>
<td>230 (194–270)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MRI as first line imaging</td>
<td>55 (35.5 %)</td>
<td>232 (40.1 %)</td>
<td>0.299</td>
</tr>
<tr>
<td>Middle cerebral artery territory infarct</td>
<td>136 (87.7 %)</td>
<td>503 (87.6 %)</td>
<td>0.970</td>
</tr>
<tr>
<td>Bridging therapy</td>
<td>1 (0.6 %)</td>
<td>19 (3.3 %)</td>
<td>0.120</td>
</tr>
<tr>
<td>Outcome</td>
<td></td>
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<tr>
<td>Symptomatic HT (ECASS3 criteria)</td>
<td>9 (5.8 %)</td>
<td>32 (5.5 %)</td>
<td>0.893</td>
</tr>
<tr>
<td>Poor outcome (mRS 0–2) at month-3</td>
<td>81 (52.3 %)</td>
<td>204 (35.2 %)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Death at month-3</td>
<td>34 (21.9 %)</td>
<td>52 (9.0 %)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Unless specified, values are number of patients (\( p \) values calculated with the Chi square test)

NIHSS national institutes of health stroke scale, MRI magnetic resonance imaging, INR international normalised ratio, MRI magnetic resonance imaging, mRS modified Rankin scale, HT haemorrhagic transformation

* Median and interquartile range (\( p \) values calculated with the Mann–Whitney \( U \) test)
Independent variables associated with poor outcome at 3 months were age (adjOR 1.04 for 1 year increase; 95 % CI 1.03–1.06), baseline NIHSS scores (adjOR 1.17 per 1 point increase; 95 % CI 1.13–1.21), and sHT (adjOR 47.6; 95 % CI 10.2–250). AF, arterial hypertension, smoking, previous myocardial infarction, and being under oral anticoagulant therapy were not independently associated with poor outcome at 3 months (overall \( p \) value \( \leq 0.001; r^2 \) 0.393; 75.4 % prediction of the model). The other variables did not qualify for the model. After removal of sHT from the model, age and NIHSS remained the only two variables available at baseline that were independently associated with a poor outcome.

Discussion

Our study has shown that after i.v. rt-PA for cerebral ischaemia, (1) patients with AF have worse outcomes than patients without AF, but no more sHT, (2) AF is not an independent predictor of death or poor outcome, (3) the main reason why patients with AF have worse outcomes are that they are older and have more severe strokes at baseline.

Our study population is representative of patients treated with i.v. rt-PA. Their baseline characteristics were close to those of patients included in registries [4, 32–35], except that our population was slightly older. The proportion of patients with AF was in the same range as in patients of similar age included in trials [2, 14, 27, 36–38] and registries [32–35], but we cannot exclude that AF was slightly under-diagnosed, cases of paroxysmal AF being potentially diagnosed after the end of the follow-up period. Other strengths are that patients were treated in 2 centres, in clinical practice in the real world, and has one of the largest samples of patients with AF treated with rt-PA.

Our study has several limitations. We did not evaluate factors that influence the outcome such as the volume of the lesion, and the presence and site of arterial occlusion, because our study was conducted in practice, and patients were treated either after an MRI scan or a CT scan, without standardisation of these factors. Another possible limitation is that the primary endpoint was based on a dichotomisation of the mRS with a cut-off value at 2, and such a dichotomisation may lead to the non-identification of differences within severely disabled patients, e.g. mRS 5 instead of 4 or 3. However, trials with rt-PA have also used dichotomisation, and the analysis within the whole spectrum of mRS showed also worse outcomes in patients with AF. We did not differentiate the types of AF, especially de novo AF and previously known AF, but this is probably not an important limitation, as both types has similar outcomes [17].

The main explanation why AF patients have worse outcomes in our study is that patients with AF were older and had a more severe neurological deficit at baseline, age and severity being the two major predictors of outcome. This finding is in line with the analysis in VISTA [14]. In our study the proportion of patients with a mRS 3–6 at 3 months was much smaller than in patients with AF treated in the placebo group of IST3 [2]. It is not possible to compare directly the results of IST3 [2] with those of our study because they were recorded in different settings, and had a slightly different definition of good outcome, two points difference in baseline NIHSS and a 6-year difference in age. If we compare our results with those of VISTA patients who did not receive i.v. rt-PA and had AF [14] the outcome was also better in our patients with a lower proportion of patients with poor outcome (51.6 vs. 68.9 %), as well as death (20.1 vs. 23.2 %), while our patients were less severe (median NIHSS 13 vs. 14) but older (76 vs. 74

![Fig. 1 Outcome at 3 months of patients with (n = 155) and without (n = 579) atrial fibrillation. Outcomes are measured by the modified Rankin Scale (mRS) with 0 meaning no disability and 6 meaning death. Values provided in each category are the numbers of patients. The overall comparison of outcomes using the whole range of mRS is statistically significant (Chi square test; \( p < 0.001 \))](image-url)
years). Again, although a direct comparison is not possible, these results do not exclude a benefit of i.v. rt-PA in AF patients.

On-going oral anticoagulant therapy was not found as independent predictor of outcome. This finding may have several explanations: (1) patients under oral anticoagulant therapy who were properly treated were not thrombolysed and therefore not included; (2) only few patients with an INR > 1.2 were treated with i.v. rt-PA, leading to a poor statistical power to detect its influence on sHT and, therefore, on outcome, and preventing any multivariate analysis; (3) the bleeding risk for patients who have an INR > 1.2 may have been overestimated, as shown by the Helsinki group [39].

Our study confirmed that, in patients treated with i.v. rt-PA, those with AF have more severe ischaemic strokes at baseline and worse outcomes than non-AF patient. However, a comparison with the placebo groups of IST3 [2] and VISTA [14], does not support the hypothesis that the benefit of i.v. rt-PA may be lost in patients with AF. This finding should encourage a strict adherence to preventative strategies and research on more aggressive strategies at the acute stage.

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Conflicts of interest Charlotte Cordonnier and Didier Leys have been investigators for the ECASS3 trial. The other authors declare no disclosure in relation with this manuscript.

References


