Effect of Right Insular Involvement on Death and Functional Outcome After Acute Ischemic Stroke in the IST-3 Trial (Third International Stroke Trial)

Luciano A. Sposato, MD, MBA*; Geoffrey Cohen, MSc*; Joanna M. Wardlaw, MD; Peter Sandercock, DM; Richard I. Lindley, MD; Vladimir Hachinski, CM, MD, FRCPC, DSc; on behalf of the IST-3 Expert Reading Panel and the IST-3 Collaborative Group†

Background and Purpose—In patients with acute ischemic stroke, whether involvement of the insular cortex influences outcome is controversial. Much of the apparent adverse outcome may relate to such strokes usually being severe. We examined the influence of right and left insular involvement on stroke outcomes among patients from the IST-3 study (Third International Stroke Trial) who had visible ischemic stroke on neuroimaging.

Methods—We used multiple logistic regression to compare outcomes of left versus right insular and noninsular strokes across strata of stroke severity, on death, proportion dead or dependent, and level of disability (ordinalized Oxford Handicap Score) at 6 months, with adjustment for the effects of age, lesion size, and presence of atrial fibrillation.

Results—Of 3035 patients recruited, 2099 had visible ischemic strokes limited to a single hemisphere on computed tomography/magnetic resonance scans. Of these, 566 and 714 had infarction of right and left insula. Six months after randomization, right insular involvement was associated with increased odds of death when compared with noninsular strokes on the left side (adjusted odds ratio, 1.83; 95% confidence interval, 1.33–2.52), whereas the adjusted odds ratio comparing mortality after insular versus noninsular strokes on the left side was not significant. Among mild/moderate strokes, outcomes for right insular involvement were worse than for left insular, but among more severe strokes, the difference in outcomes was less substantial.

Conclusions—We found an association between right insular involvement and higher odds of death and worse functional outcome. The difference between right- and left-sided insular lesions on outcomes seemed to be most evident for mild/moderate strokes.


(Stroke. 2016;47:2959-2965. DOI: 10.1161/STROKEAHA.116.014928.)

Key Words: cerebral infarction ■ death ■ functional laterality ■ insula ■ insular cortex ■ prognosis ■ stroke

Strokes involving the insular cortex tend to be more severe.1,2 Preliminary evidence suggests that insular involvement is associated with poorer functional outcome after ischemic stroke regardless of infarct size,3,4 as well as with higher case fatality rates.5,7 However, these associations are controversial.2,8,9 The pathophysiological mechanisms explaining the apparent association of insular involvement with poor ischemic stroke outcome remain unknown. Differences in outcomes between left and right insular cortex strokes arise because of the laterality of autonomic representation in the brain,10 although there is disagreement whether the right or left insula is the one most associated with poor prognosis.2,3,11-14 We therefore examined the associations between insular involvement, its laterality, and outcome at 6 months after stroke in the large prospective data set provided by the IST-3 study (Third International Stroke Trial).

Methods

Study Cohort and Neuroimaging Studies
The IST-3 was an international, multicenter, open-label, randomized controlled trial of intravenous recombinant tissue-type plasminogen

Received August 2, 2016; final revision received August 25, 2016; accepted October 5, 2016.
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Guest Editor for this article was Gregory W. Albers, MD.
*Dr Sposato and G. Cohen contributed equally and are joint first authors.
†A list of all IST-3 reading panel is given in the Appendix.
The online-only Data Supplement is available with this article at http://stroke.ahajournals.orglookup/suppl/doi:10.1161/STROKEAHA.116.014928/eDC1.
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Stroke is available at http://stroke.ahajournals.org DOI: 10.1161/STROKEAHA.116.014928

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activator versus control within 6 hours of ischemic stroke onset, enrolling 3035 patients at 156 centers in 12 countries.\textsuperscript{18} A detailed description of the study is provided elsewhere\textsuperscript{15–17} and in the online-only Data Supplement. Computed tomography (CT) or magnetic resonance imaging scans were obtained before enrollment and were repeated 24 to 48 hours after stroke and again if there was evidence of neurological deterioration within the first 7 days. To increase the odds of detecting acute lesions, we used available follow-up scans. This study cohort included 2099 ischemic stroke patients showing unilateral acute ischemic changes in follow-up neuroimaging studies according to the expert central review (Figure I in the online-only Data Supplement).\textsuperscript{18} All scans were systematically assessed by neuroradiologists or stroke neurologists expert in stroke imaging, masked to all clinical data.\textsuperscript{19}

The definitions for cerebral infarcts involving the insular cortex, stroke severity, and lesion size are provided in the online-only Data Supplement.

**Outcomes**

The main outcome measure was death from all causes by 6 months. The Oxford Handicap Score (OHS) is a commonly used variant of the modified Rankin scale.\textsuperscript{19} We defined 2 measures of functional outcome: (1) the proportion of patients dead or dependent at 6 months, with dependency defined as OHS 3–5\textsuperscript{20} and (2) the level of disability, with the OHS considered as an ordinal outcome because it is statistically more efficient\textsuperscript{21} (OHS levels 4–6 were pooled to strengthen the analysis against substantial deviations from the proportional odds assumption).\textsuperscript{22} We used level of disability instead of dependency for the ordinalized OHS to avoid confusion with the other measure of functional outcome proportion of patients dead or dependent. For all deaths within 7 days of randomization, the IST-3 adjudication committee reviewed, blind to treatment allocation, all relevant data to assign the cause of death. For deaths >7 days after randomization, although the stated cause of death from the death certificate was available for most cases, it was generally not feasible, from the data available, to reliably ascertain the cause.

**Statistical Analysis**

We fitted logistic regression models for 6-month mortality and for the 2 secondary outcome measures: death or dependency and level of disability (ordinalized OHS) with terms for age, time to randomization, treatment (recombinant tissue-type plasminogen activator versus control), atrial fibrillation, National Institutes of Health Stroke Scale (NIHSS) score, lesion size, and laterality (right versus left) and insular involvement. The odds of each outcome for insular strokes on the right and left sides and noninsular strokes on the right side were compared with odds for noninsular strokes on the left side (reference level). We also tested adding a term for interaction between laterality and insular involvement. The analyses were performed for all cases and separately for mild/moderate (NIHSS score of ≤15) and severe (NIHSS score of >15) strokes. We used Kaplan–Meier curves to compare death in the first 6 months after right noninsular, left noninsular, right insular, and left insular strokes.

**Results**

Of 3035 patients recruited, 2134 had computed tomography/magnetic resonance evidence of cerebral infarction on baseline or follow-up scans. For the present analysis, we excluded patients with midline (n=34) and bilateral (n=1) infarcts. As a result, the study cohort comprised 1280 patients with strokes involving the insular cortex and 819 without insular involvement. Left-sided strokes were significantly more prevalent (55.6%; 95% confidence interval [CI], 53.4–57.7); 566 (44%) and 714 (56%) cases had right and left insula infarcts, respectively; but the proportions with insular involvement were similar between left and right sides (61.2% and 60.7%, respectively; Figure I in the online-only Data Supplement). Mean age was 77.4 years, and 1083 patients were women (51.6%). Table I shows the baseline characteristics of patients according to the insular involvement and side of lesion.

Among all ischemic strokes (mild/moderate+severe), unadjusted death at 6 months was higher for both right insular (40.5%; 95% CI, 36.4–44.5) and left insular (38.5%; 95% CI, 34.9–42.1) involvement than for right noninsular (18.8%; CI, 14.8–22.8) and left noninsular (20.8%; 95% CI, 17.1–24.5) infarcts (Figure 1).

Figure 2 shows death and death or dependency at 6 months as a function of insula involvement, stroke severity, and presence of atrial fibrillation, three of the most stable predictors of worse outcome in the regression models. For mild/moderate strokes, right insular involvement had higher proportion of deaths and death or dependency than any other stroke localization, both in patients with and without atrial fibrillation. For severe strokes, both left and right insular infarcts had worse outcomes than those not involving the insula, both for patients with and without atrial fibrillation.

After adjusting for age, stroke severity (NIHSS), delay time, lesion size, atrial fibrillation, and treatment group, the main effects of insular involvement and laterality were significant for all 3 outcomes. However, their interaction was only significant for death (P=0.035) but not for secondary outcomes (Table I in the online-only Data Supplement). In comparison with strokes on the left side with no insular involvement, cases with right insular infarcts were independently associated with nearly 2-fold higher odds of death 6 months after ischemic stroke (Table 2, adjusted odds ratio, 1.83; 95% CI, 1.33–2.52). The effect of left insular involvement versus left noninsular was only significant for level of disability (odds ratio, 1.35) but not for death alone or death or dependency.

For patients with mild/moderate strokes, left insular involvement was not associated with any of the 3 outcomes, whereas insular involvement on the right was significantly associated with death or dependency (adjusted odds ratio, 1.98; 95% CI, 1.33–2.95) and level of disability (adjusted odds ratio, 1.44; 95% CI, 1.05–1.98). Among patients with severe strokes, both right and left insular involvement showed significantly higher level of disability and risk of being dependent than left noninsular strokes, but in regard to death only right insular involvement had significantly higher risk than the reference group (Table 2).

The most frequent cause of death at 7 days and 6 months was cerebrovascular (Table II in the online-only Data Supplement). Overall, both right and left insular strokes showed a higher proportion of cerebrovascular deaths, but this was most striking for patients with right insular strokes, among whom cerebrovascular deaths accounted for 97.1% and 64.2% of deaths at 7 days and 6 months.

**Discussion**

Our chief finding was an association of right but not left insular involvement with higher 6-month case fatality. Also, right insular strokes showed a higher proportion dead or dependent and higher level of disability in both severity strata, after adjustment for age, lesion size, stroke severity, time to...
randomization, treatment (recombinant tissue-type plasminogen activator versus control), and atrial fibrillation—variables usually considered as potential confounders in the association between insular strokes and worse prognosis. Left insular involvement was only associated with a higher level of disability for all strokes but not with death or death/dependency.

### Table 1. Baseline Study Cohort Characteristics of 2099 of 3035 Patients Enrolled in IST-3 Trial (Third International Stroke Trial) With a Visible Ischemic Lesion on Computed Tomography or Magnetic Resonance Brain Imaging

<table>
<thead>
<tr>
<th></th>
<th>Left Noninsular, n=452 (%)</th>
<th>Right Noninsular, n=367 (%)</th>
<th>Left Insular, n=714 (%)</th>
<th>Right Insular, n=566 (%)</th>
</tr>
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<tbody>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>18−50</td>
<td>26 (6)</td>
<td>11 (3)</td>
<td>31 (4)</td>
<td>22 (4)</td>
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<tr>
<td>51−60</td>
<td>37 (8)</td>
<td>25 (7)</td>
<td>37 (5)</td>
<td>31 (5)</td>
</tr>
<tr>
<td>61−70</td>
<td>54 (12)</td>
<td>57 (16)</td>
<td>80 (11)</td>
<td>68 (12)</td>
</tr>
<tr>
<td>71−80</td>
<td>115 (25)</td>
<td>89 (24)</td>
<td>173 (24)</td>
<td>127 (22)</td>
</tr>
<tr>
<td>81−90</td>
<td>190 (42)</td>
<td>170 (46)</td>
<td>336 (47)</td>
<td>275 (49)</td>
</tr>
<tr>
<td>&gt;90</td>
<td>30 (7)</td>
<td>15 (4)</td>
<td>57 (8)</td>
<td>43 (8)</td>
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<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>212 (47)</td>
<td>189 (51)</td>
<td>375 (53)</td>
<td>307 (54)</td>
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<tr>
<td>NIHSS score</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>≥15</td>
<td>131 (29)</td>
<td>74 (20)</td>
<td>473 (66)</td>
<td>286 (51)</td>
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<td>Delay in randomization, h</td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>0–3</td>
<td>119 (26)</td>
<td>101 (28)</td>
<td>232 (32)</td>
<td>176 (31)</td>
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<tr>
<td>3–4.5</td>
<td>169 (37)</td>
<td>137 (37)</td>
<td>279 (39)</td>
<td>228 (40)</td>
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<td>4.5–6</td>
<td>164 (36)</td>
<td>129 (35)</td>
<td>201 (28)</td>
<td>162 (29)</td>
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<td>0 (0)</td>
<td>2 (0)</td>
<td>0 (0)</td>
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<tr>
<td>Atrial fibrillation</td>
<td>130 (29)</td>
<td>100 (27)</td>
<td>247 (35)</td>
<td>205 (36)</td>
</tr>
<tr>
<td>Previous stroke or TIA</td>
<td>104 (23)</td>
<td>87 (24)</td>
<td>144 (20)</td>
<td>112 (20)</td>
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<tr>
<td>Systolic BP, mm Hg</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>≤143</td>
<td>133 (29)</td>
<td>124 (34)</td>
<td>236 (33)</td>
<td>202 (36)</td>
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<tr>
<td>144–164</td>
<td>159 (35)</td>
<td>132 (36)</td>
<td>253 (35)</td>
<td>181 (32)</td>
</tr>
<tr>
<td>≥165</td>
<td>160 (35)</td>
<td>111 (30)</td>
<td>225 (32)</td>
<td>183 (32)</td>
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<tr>
<td>Diastolic BP, mm Hg</td>
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<td></td>
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<tr>
<td>≤74</td>
<td>115 (26)</td>
<td>111 (30)</td>
<td>242 (34)</td>
<td>173 (31)</td>
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<tr>
<td>75–89</td>
<td>164 (37)</td>
<td>140 (38)</td>
<td>255 (36)</td>
<td>216 (38)</td>
</tr>
<tr>
<td>≥90</td>
<td>170 (38)</td>
<td>115 (31)</td>
<td>214 (30)</td>
<td>177 (31)</td>
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<tr>
<td>Lesion size</td>
<td></td>
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<td></td>
</tr>
<tr>
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<td>297 (66)</td>
<td>249 (68)</td>
<td>241 (34)</td>
<td>205 (36)</td>
</tr>
<tr>
<td>Small/medium</td>
<td>119 (27)</td>
<td>92 (25)</td>
<td>221 (31)</td>
<td>189 (33)</td>
</tr>
<tr>
<td>Large/very large</td>
<td>33 (7)</td>
<td>24 (7)</td>
<td>248 (35)</td>
<td>171 (30)</td>
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<tr>
<td>Acute treatment group</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>r-tPA</td>
<td>210 (46)</td>
<td>178 (49)</td>
<td>379 (53)</td>
<td>286 (51)</td>
</tr>
<tr>
<td>Antiplatelets in previous 48 h</td>
<td>234 (52)</td>
<td>174 (47)</td>
<td>383 (54)</td>
<td>287 (51)</td>
</tr>
<tr>
<td>Previous use of anticoagulants</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>427 (94)</td>
<td>350 (95)</td>
<td>682 (96)</td>
<td>544 (96)</td>
</tr>
<tr>
<td>Oral anticoagulants</td>
<td>22 (5)</td>
<td>16 (4)</td>
<td>26 (4)</td>
<td>19 (3)</td>
</tr>
<tr>
<td>Heparin (low dose)</td>
<td>3 (1)</td>
<td>1 (0)</td>
<td>6 (1)</td>
<td>3 (1)</td>
</tr>
</tbody>
</table>

Data are number (%). Percentages exclude missing values from denominators. Lesion size was missing for 5 insular and 5 noninsular cases; diastolic BP was missing for 3 insular and 4 noninsular cases. Patients with midline (n=34) and bilateral (n=1) infarcts were excluded. BP indicates blood pressure; NIHSS, National Institutes of Health Stroke Scale; r-tPA, recombinant tissue-type plasminogen activator; and TIA, transient ischemic attack.
Moreover, there were no differences between left insular and left noninsular strokes among mild/moderate strokes. These findings suggest that among mild/moderate strokes outcomes for right insular involvement are worse than for left insular, but among more severe strokes the difference in outcomes is less substantial.

**Right Insular Involvement and Increased Case Fatality**

Only right insular involvement was consistently associated with 6-month death across all strata of stroke severity. Importantly, this association was independent of stroke severity and infarct size. Identifying the cause of death after stroke is difficult, especially for cases that die after discharge from hospital, where no autopsy is performed. Although we did not find a clear excess of deaths attributable to cardiovascular causes in right insular infarcts either within 7 days or within 6 months, inaccuracies in death certificates may have obscured a difference. Although speculative, deaths classified as death from initial stroke (Table II in the online-only Data Supplement) may have comprised patients with sudden death with or without undetected fatal cardiac arrhythmias. The highest proportion of such deaths was documented among patients with right insular infarcts. Nonetheless, the difference in deaths from all causes is striking. There are some clues supporting the role of cardiac arrhythmias as the cause of right insular stroke-associated deaths. Cardiac arrhythmias are usually triggered by imbalance of sympathetic and parasympathetic activity rather than by either one or the other component. Hence, increased death might be explained by damage...
to the right insula constituting a key pathophysiological trigger of cardiac arrhythmias because of autonomic imbalance. Differences on the influence of right and left insular involvement on increased death may be explained by the lateralization of insular regulation of the autonomic nervous system. Lesions to the right insula result in a shift toward sympathetic tone leading to tachycardia and elevation of blood pressure, and cardiac arrhythmias and sudden death. We did not record information on way ascertainment of the cause of such deaths outside hospital death could not be independently verified and because any- 7 days and 6 months because the death certificates’ cause of death was unavailable for only 24 of 3035 (0.8%). The baseline and follow-up scans were read by an independent expert panel, blinded to all clinical data and blinded to the hypothesis tested here. We may have overlooked some small infarcts involving the insula as these may be difficult to identify on computed tomography, but no more so than small infarcts elsewhere, and the analysis compared visible infarcts in all brain regions. The use of scans obtained at 24 to 48 hours after stroke will have increased sensitivity to detect tiny lesions that are not visible on computed tomography, confounding the hypothesis tested here. We may have overlooked some small infarcts involving the insula as these may be difficult to identify on computed tomography, but no more so than small infarcts elsewhere, and the analysis compared visible infarcts in all brain regions. The use of scans obtained at 24 to 48 hours after stroke will have increased sensitivity to detecting small infarcts beyond that of computed tomography scans obtained within 6 hours of stroke. A clear limitation is that we could not reliably determine the cause of death between 7 days and 6 months because the death certificates’ cause of death could not be independently verified and because any- way ascertainment of the cause of such deaths outside hospital is notoriously unreliable. We did not record information on auto- nomic function during the study either. Second, despite the systematic use of the OHS in our study, we were not able to assess whether there was a specific cause of disability (eg, cognitive impairment, behavioral changes, and motor deficits). This may be assessed in future studies.


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Strengths and Limitations
The IST-3 study provides a large, prospective clinical cohort study, with complete baseline clinical and imaging measures and complete clinical follow-up. Indeed, vital status at 6 months was unavailable for only 24 of 3035 (0.8%). The baseline and follow-up scans were read by an independent expert panel, blinded to all clinical data and blinded to the hypothesis tested here. We may have overlooked some small infarcts involving the insula as these may be difficult to identify on computed tomography, but no more so than small infarcts elsewhere, and the analysis compared visible infarcts in all brain regions. The use of scans obtained at 24 to 48 hours after stroke will have increased sensitivity to detecting small infarcts beyond that of computed tomography scans obtained within 6 hours of stroke. A clear limitation is that we could not reliably determine the cause of death between 7 days and 6 months because the death certificates’ cause of death could not be independently verified and because any- way ascertainment of the cause of such deaths outside hospital is notoriously unreliable. We did not record information on auto- nomic function during the study either. Second, despite the systematic use of the OHS in our study, we were not able to assess whether there was a specific cause of disability (eg, cognitive impairment, behavioral changes, and motor deficits). This may be assessed in future studies.

Conclusions
We found an association between right insular cortex ischemic stroke and increased death and poor functional outcome at 6 months. Our findings have implications for research
and practice. Our results are exploratory and require further confirmation. Future research may investigate whether right insular strokes are related to fatal cardiac arrhythmias and sudden death, and how these arrhythmias are triggered by brain lesions. In clinical practice, patients with insular infarctions, especially those on the right side, should be considered as a specific high-risk population perhaps warranting closer cardiac monitoring. Our study also contributes to the understanding of functional stroke prognosis beyond well-known markers of poor outcome. Indeed, patients with less severe strokes or relatively smaller infarcts may still have poor outcomes if highly strategic areas such as the insular cortex are compromised.1

Appendix: IST Reading Panel
Rudiger von Kummer, MD, (Department of Neuroradiology, University Hospital, Technische Universität Dresden, Germany); Anders von Heijne, MD, (Danderyd Hospital. Stockholm, Sweden); Nick Bradely, FRCR, (Neuroradiology, James Cook University Hospital, South Tees Hospital NHS Trust, Middlesbrough, United Kingdom); Andre Peeters, MD, (CliniquesUniversitariesSaint-Luc, Bruxelles, Belgium); Lesley Cala, MD, FRCR, (School of Pathology and Laboratory Medicine, The University of Western Australia, Crawley, Western Australia); Alessandro Adami, MD, (Stroke Center, Department of Neurology, Ospedale Sacro Cuore-Don Calabria, Via Sempreboni 6, 37024, Negar, Verona, Italy); Zoe Morris, FRCR, (NHS Lothian, Edinburgh, Scotland); Andrew Farrall, FRCCR, (University of Edinburgh, Edinburgh, Scotland); Gillian Potter, MD, FRCR, (Salford Royal NHS Foundation Trust, Salford, Greater Manchester).

Acknowledgments
Dr Saposko commented on the analysis and wrote the first draft of the report. G. Cohen performed the statistical analyses and edited the report. P. Sandercoc and Dr Lindinger were IST-3 cochief investigato and designed IST-3 with Dr Wardlaw, who developed and managed the image reading and reviewed the report. All 3 commented on the analysis and edited the report. Dr Hachinski conceived the study and edited the report.

Sources of Funding
We thank the funding organizations for supporting the trial. The University of Edinburgh and the Lothian Health Board are cosponsors. The start-up phase was supported by a grant from Stroke Association, United Kingdom. The expansion phase was funded by Health Foundation, United Kingdom. The main phase of the trial is funded by the UK Medical Research Council (MRC) and managed by the National Institute for Health Research (NIHR) on behalf of the MRC–NIHR partnership. Further funding by: Research Council of Norway; AFA Insurances (Dina kollektivvård forskärings, Sweden); Swedish Heart Lung Fund; Foundation of Marianne and Marcus Wallenberg; Stockholm County Council and Karolinska Institute Joint ALF-project grants (Aval om likartabildning och Forskning, Sweden); Government of Poland; Australian Heart Foundation; Australian National Health and Medical Research Council (NHMRC); Swiss National Research Foundation; Swiss Heart Foundation; Foundation for health and cardiovascular/neurovascular research (Basel, Switzerland); Assessorato alla Sanita (Regione dell’Umbria); and Danube University (Krems, Austria). Alteplase and placebo for 300 patients in the double-blind component of the start-up phase were supplied by Boehringer Ingelheim. IST-3 acknowledges the extensive support of the NIH Stroke Research Network, National Health Service (NHS) Research Scotland, through the Scottish Stroke Research Network, and the National Institute for Social Care and Health Research Clinical Research Centre. Imaging work was undertaken at the Brain Imaging Research Centre, a member of the SINAPSE collaboration (Scottish Imaging Network – A Platform for Scientific Excellence, Division of Clinical Neurosciences, University of Edinburgh, Edinburgh, United Kingdom). SINAPSE is funded by the Scottish Funding Council and the Chief Scientist Office of the Scottish Executive. Additional support was received from Chest Heart and Stroke Scotland, Des/Acc, University of Edinburgh, Danderyd Hospital R&D, Department, Karolinska Institutet, Oslo University Hospital, and the Dalhousie University Internal Medicine Research Fund. This report presents independent research supported by the NHMR through the UK Stroke Research Network. The views expressed in this publication are those of the authors and not those of the NHS, the NIHR, or the Department of Health. Dr Saposko was supported by the Edward and Alma Saraydar Neurosciences Fund and by the Opportunities Fund of the Academic Health Sciences Centre Alternative Funding Plan of the Academic Medical Organization of Southwestern Ontario (AMOSO).

Disclosures
Dr Saposko received support from Boehringer Ingelheim, P. Sandercoc and Dr Wardlaw received support from the Medical Research Council, the Stroke Association, the Health Foundation, and Boehringer Ingelheim. Dr Wardlaw received support from Chest Heart Stroke Scotland. Dr Lindinger received support from Boehringer Ingelheim and Coviden. The other authors report no conflicts.

References


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Stroke. 2016;47:2959-2965; originally published online November 15, 2016;
doi: 10.1161/STROKEAHA.116.014928

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2016 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

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Effect of Right Insular Involvement on Death and Functional Outcome after Acute Ischemic Stroke in the IST-3 Trial

Study Cohort and Neuroimaging Studies
The IST-3 was an international, multicenter, open-label, randomized controlled trial of intravenous recombinant tissue plasminogen activator (rtPA) vs. control within 6 hours of ischemic stroke onset, conducted at 156 centers in 12 countries. Patients were eligible for the study if the treating physician felt there was no clear indication for or contraindication to rtPA and considered the treatment promising but unproven, and if they were 18 years-old or older (no upper age limit) and presented with symptoms of cortical, lacunar, and posterior circulation stroke, of all severities. The IST-3 enrolled 3035 patients who either had a computed tomography (CT) or magnetic resonance imaging (MRI) brain imaging before randomization to Alteplase or control groups. To ensure that all brain scans were of diagnostic quality for acute stroke (CT) and included the minimum correct sequences (MRI), all participating centers had to fulfill a minimum image acquisition standards before being approved for inclusion in IST-3. Brain scans were repeated 24 to 48 hours after stroke and again if there was evidence of neurological deterioration within the first 7 days. To increase the odds of detecting acute lesions, we used available follow-up scans. The present study cohort included 2099 ischemic stroke patients showing unilateral acute ischemic changes in follow-up neuroimaging studies (CT with tissue hypoattenuation, lesion size, swelling, and hyperattenuated artery or MRI with restricted diffusion) according to expert central review. All scans were systematically assessed by neuroradiologists or stroke neurologists expert in stroke imaging, masked to all clinical data, including assessment of lesion extent according to the one-third middle cerebral artery and location using the IST-3 method, as well as the Alberta Stroke Program Early CT Stroke (ASPECTS) score.

Definitions
Cerebral infarcts were considered to involve the insular cortex when at least a portion of the insula was compromised, regardless of whether they also affected other brain regions. We determined whether there was insular involvement based on the identification of the appropriate ASPECT region. We used the National Institutes of Health Stroke Scale (NIHSS) to determine ischemic stroke severity. We classified strokes as mild/moderate (NIHSS <15) or severe (NIHSS ≥15). To define the size of ischemic strokes, we condensed the full IST-3 lesion extent score into three groups for analysis as previously: (a) no visible lesion, (b) small/medium (small infarcts: lacunar, small cortical, small cerebellar, less than half of brainstem, or less than half of the anterior cerebral artery or posterior cerebral artery territory; medium infarcts: striatocapsular, the anterior or posterior half of the peripheral middle cerebral artery territory, or more than half the anterior cerebral artery or posterior cerebral artery territory), and (c) large/very large (large: whole of the peripheral middle cerebral artery territory, all the middle cerebral artery territory; very large: whole middle cerebral artery and posterior cerebral artery territory, all the middle cerebral artery and anterior cerebral artery territory, or all three territories).

Trial Registration
This trial is registered at ISRCTN.com, number ISRCTN25765518.
References


Table I. P-values for Insular Involvement, Laterality and their Interaction in Logistic Regression Analyses of three 6-month Outcomes

<table>
<thead>
<tr>
<th>Interaction term</th>
<th>Death</th>
<th>Proportion dead or dependent</th>
<th>Level of disability</th>
</tr>
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<tbody>
<tr>
<td>Insula involvement</td>
<td>0.0038</td>
<td>0.0068</td>
<td>0.0029</td>
</tr>
<tr>
<td>Brain side, right vs. left</td>
<td>0.0444</td>
<td>0.0025</td>
<td>0.0102</td>
</tr>
<tr>
<td>Brain side x insula involvement</td>
<td>0.0345</td>
<td>0.3219</td>
<td>0.8828</td>
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</table>

Adjusted for age, NIHSS, delay from stroke to randomization, lesion size, and atrial fibrillation.
<table>
<thead>
<tr>
<th></th>
<th>Left-Non-insular n=14</th>
<th>Right-Non-insular n=13</th>
<th>Left-Insular n=106</th>
<th>Right-Insular n=69</th>
<th>All n=202</th>
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</thead>
<tbody>
<tr>
<td><strong>Death at 7 days, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Cerebrovascular</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatal massive swelling of original infarct</td>
<td>2 (14.3)</td>
<td>0 (0.0)</td>
<td>40 (37.7)</td>
<td>26 (37.7)</td>
<td>68 (33.7)</td>
</tr>
<tr>
<td>Fatal intracranial hemorrhage</td>
<td>4 (28.6)</td>
<td>3 (23.1)</td>
<td>27 (25.5)</td>
<td>17 (24.6)</td>
<td>51 (25.2)</td>
</tr>
<tr>
<td>Death from initial stroke, other</td>
<td>4 (28.6)</td>
<td>3 (23.1)</td>
<td>28 (26.4)</td>
<td>23 (33.3)</td>
<td>58 (28.7)</td>
</tr>
<tr>
<td>Fatal recurrent ischemic stroke</td>
<td>1 (7.1)</td>
<td>2 (15.4)</td>
<td>2 (1.9)</td>
<td>1 (1.4)</td>
<td>6 (3.0)</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infection</td>
<td>3 (21.4)</td>
<td>3 (23.1)</td>
<td>6 (5.7)</td>
<td>1 (1.4)</td>
<td>13 (6.4)</td>
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<tr>
<td>Other or Multiple</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>1 (0.9)</td>
<td>0 (0.0)</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td>Unknown</td>
<td>0 (0.0)</td>
<td>1 (7.7)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>1 (0.5)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Left-Non-insular n=94</th>
<th>Right-Non-insular n=69</th>
<th>Left-Insular n=275</th>
<th>Right-Insular n=229</th>
<th>All n=667</th>
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<tr>
<td><strong>Death at 6 Months, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cerebrovascular</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Infection</td>
<td>35 (37.2)</td>
<td>30 (43.5)</td>
<td>175 (63.6)</td>
<td>147 (64.2)</td>
<td>387 (58.0)</td>
</tr>
<tr>
<td>Other or Multiple</td>
<td>23 (24.5)</td>
<td>13 (18.8)</td>
<td>23 (8.4)</td>
<td>17 (7.4)</td>
<td>76 (11.4)</td>
</tr>
<tr>
<td>Unknown</td>
<td>22 (23.4)</td>
<td>16 (23.2)</td>
<td>49 (17.8)</td>
<td>38 (16.6)</td>
<td>125 (18.7)</td>
</tr>
<tr>
<td>Unknown</td>
<td>10 (10.6)</td>
<td>6 (8.7)</td>
<td>16 (5.8)</td>
<td>11 (4.8)</td>
<td>43 (6.4)</td>
</tr>
<tr>
<td>Unknown</td>
<td>4 (4.3)</td>
<td>4 (5.8)</td>
<td>12 (4.4)</td>
<td>16 (7.0)</td>
<td>36 (5.4)</td>
</tr>
</tbody>
</table>
Figure I. Study Cohort

3035 patients recruited in IST-3 Trial

2,134 with visible cerebral infarction

901 without visible cerebral infarction

2,099 with right or left cerebral infarction

933 right

1,166 left

2,099 with right or left cerebral infarction

35 with bilateral or midline infarctions

34 midline

1 bilateral

Study Cohort

566 insular

367 non-insular

714 insular

452 non-insular

34 midline

31 non-insular

0 insular

1 non-insular