Effect of treatment delay, age, and stroke severity on the effects of intravenous thrombolysis with alteplase for acute ischaemic stroke: a meta-analysis of individual patient data from randomised trials


Summary

Background Alteplase is effective for treatment of acute ischaemic stroke but debate continues about its use after longer times since stroke onset, in older patients, and among patients who have had the least or most severe strokes. We assessed the role of these factors in affecting good stroke outcome in patients given alteplase.

Methods We did a pre-specified meta-analysis of individual patient data from 6756 patients in nine randomised trials comparing alteplase with placebo or open control. We included all completed randomised phase 3 trials of intravenous alteplase for treatment of acute ischaemic stroke for which data were available. Retrospective checks confirmed that no eligible trials had been omitted. We defined a good stroke outcome as no significant disability at 3–6 months, defined by a modified Rankin Score of 0 or 1. Additional outcomes included symptomatic intracranial haemorrhage (defined by type 2 parenchymal haemorrhage within 7 days and, separately, by the SITS-MOST definition of parenchymal type 2 haemorrhage within 36 h), fatal intracranial haemorrhage within 7 days, and 90-day mortality.

Findings Alteplase increased the odds of a good stroke outcome, with earlier treatment associated with bigger proportional benefit. Treatment within 3–0 h resulted in a good outcome for 259 (32·9%) of 787 patients who received alteplase versus 176 (23·1%) of 762 who received control (OR 1·75, 95% CI 1·35–2·27); delay of greater than 3–0 h, up to 4·5 h, resulted in good outcome for 485 (35·3%) of 1375 versus 432 (30·1%) of 1437 (OR 1·26, 95% CI 1·05–1·51); and delay of more than 4·5 h resulted in good outcome for 401 (32·6%) of 1229 versus 357 (30·6%) (OR 1·75, 95% CI 1·35–2·27); delay of greater than 4·5 h resulted in good outcome for 357 (30·6%) of 1166 (OR 1·19, 95% CI 0·95–1·40). Proportional treatment benefits were similar irrespective of age or stroke severity. Alteplase significantly increased the odds of symptomatic intracranial haemorrhage (type 2 parenchymal haemorrhage definition 231 [6·8%] of 3391 vs 44 [1·3%] of 3365, OR 5·55, 95% CI 4·01–7·70, p<0·0001; SITS-MOST definition 124 [3·7%] vs 19 [0·6%], OR 6·67, 95% CI 4·11–10·84, p<0·0001) and of fatal intracranial haemorrhage within 7 days (91 [2·7%] vs 13 [0·4%]; OR 7·14, 95% CI 3·98–12·79, p<0·0001). The relative increase in fatal intracranial haemorrhage from alteplase was similar irrespective of treatment delay, age, or stroke severity, but the absolute excess risk attributable to alteplase was bigger among patients who had more severe strokes. There was no excess in other early causes of death and no significant effect on later causes of death. Consequently, mortality at 90 days was 608 (17·9%) in the alteplase group versus 556 (16·5%) in the control group (hazard ratio 1·11, 95% CI 1·00–1·24, p=0·07). Taken together, therefore, despite an average absolute increased risk of early death from intracranial haemorrhage of about 2%, by 3–6 months this risk was offset by an average absolute increase in disability-free survival of about 10% for patients treated within 3–0 h and about 5% for patients treated after 3–0 h, up to 4·5 h.

Interpretation Irrespective of age or stroke severity, and despite an increased risk of fatal intracranial haemorrhage during the first few days after treatment, alteplase significantly improves the overall odds of a good stroke outcome when delivered within 4·5 h of stroke onset, with earlier treatment associated with bigger proportional benefits.

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Introduction Intravenous alteplase (recombinant tissue plasminogen activator) is approved for the treatment of acute ischaemic stroke. Previous analyses of pooled data from randomised trials concluded that alteplase is beneficial when administered to some patients within 4·5 h, but that the magnitude of benefit diminishes with increasing treatment delay.11,12 However, uncertainties remain about the balance of benefit and risk when alteplase is given later after onset of symptoms, to older patients, or to

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patients with very severe or mild strokes. Present guidance14–16 and marketing authorisation7 from Europe and elsewhere recommends the routine use of alteplase within 4·5 h of stroke onset but, in the USA, the Food and Drug Administration has approved the use of alteplase only within 3 h of stroke onset.7 Marketing authorisation for Europe2 and Australia,3 but not for the USA4 or Japan, cautions against the use of alteplase for severe and mild stroke. Marketing of alteplase in some European countries is also restricted to patients younger than 80 years5 (despite clinical guidelines based on observational studies that recommends its use in older patients6–10), whereas no such age restriction applies in many other countries, including the USA.

IST-311—designed to resolve some of these uncertainties—included 3035 patients randomly assigned to alteplase or control up to 6 h after the onset of stroke. The principal investigators from IST-3 and other trials of alteplase11–19 agreed to make their individual-patient data available for analysis. The chief goal of this analysis was to explore the extent to which treatment delay affected the effect of alteplase and to establish whether age or stroke severity affected treatment effects. These analyses assessing potential effect modification are only possible with individual patient data. Key secondary aims included estimating the effect of alteplase on symptomatic intracranial haemorrhage and on 90-day mortality.

### Methods

#### Study design and inclusion criteria

We established a collaboration to undertake this meta-analysis of individual patient data. We included all completed randomised phase 3 trials of intravenous alteplase for treatment of acute ischaemic stroke for which data were available. Retrospective checks confirmed that no eligible trials had been omitted. These checks included reference to a previous systematic review,20 an updated review of the Cochrane Stroke Group’s Specialised Register of Trials, and enquiry among collaborators and the manufacturer of alteplase (Boehringer Ingelheim, Ingelheim, Germany). Individual patient data were sought from eligible trials. Before accessing the combined dataset, the collaboration agreed on a statistical analysis plan.21 The study protocol is available online.

### Table 1: Baseline characteristics of patients in participating trials

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<th>NINDS A</th>
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<th>ECASS II</th>
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<th>ATLANTIS B</th>
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<td>333</td>
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<td>800</td>
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<td>821</td>
<td>210</td>
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<td>2·0 (0·6)</td>
<td>4·4 (1·1)</td>
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<td>4·9 (0·8)</td>
<td>4·2 (1·2)</td>
<td>4·0 (1·2)</td>
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<td><strong>≤3</strong></td>
<td>290 (99%)</td>
<td>333 (100%)</td>
<td>87 (14%)</td>
<td>158 (20%)</td>
<td>22 (15%)</td>
<td>39 (6%)</td>
<td>21 (4%)</td>
<td>39 (6%)</td>
<td>162 (4%)</td>
<td>159 (4%)</td>
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<tr>
<td><strong>&gt;3 0≤4·5</strong></td>
<td>1 (1%)</td>
<td>233 (38%)</td>
<td>265 (33%)</td>
<td>53 (37%)</td>
<td>249 (41%)</td>
<td>788 (96%)</td>
<td>31 (31%)</td>
<td>1148 (38%)</td>
<td>2768 (41%)</td>
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<td><strong>&gt;4.5</strong></td>
<td>295 (48%)</td>
<td>370 (46%)</td>
<td>67 (47%)</td>
<td>321 (52%)</td>
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<td>1 (&lt;1%)</td>
<td>3 (&lt;1%)</td>
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<td>45 (1%)</td>
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<td>19–24</td>
<td>279 (96%)</td>
<td>289 (87%)</td>
<td>615 (99%)</td>
<td>792 (99%)</td>
<td>142 (100%)</td>
<td>608 (+99%)</td>
<td>805 (98%)</td>
<td>76 (75%)</td>
<td>1417 (47%)</td>
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<td>12 (4%)</td>
<td>29 (12%)</td>
<td>38 (6%)</td>
<td>27 (5%)</td>
<td>31 (6%)</td>
<td>25 (5%)</td>
<td>25 (5%)</td>
<td>615 (20%)</td>
<td>1278 (26%)</td>
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</table>

### Notes

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2 Correspondence to: Prof Colin Baigent, Clinical Trial Service Unit & Epidemiological Studies Unit, Nuffield Department of Population Health, University of Oxford, Richard Doll Building, Old Road Campus, Roosevelt Drive, Oxford, OX3 7LE, UK. colin.baigent@ctsu.ox.ac.uk
Figure 1: Effect of timing of alteplase treatment on good stroke outcome (mRS 0–1)

The solid line is the best linear fit between the log odds ratio for a good stroke outcome for patients given alteplase compared with those given control (vertical axis) and treatment delay (horizontal axis; \( p_{\text{interaction}}=0.016 \)). Estimates are derived from a regression model in which alteplase, time to treatment, age, and stroke severity (handled in a quadratic manner) are included as main effects but the only treatment interaction included is with time to treatment. Only 198 patients (159 from IST−3) had a time from stroke onset to treatment of more than 6 h. The white box shows the point at which the estimated treatment effect crosses 1. The black box shows the point at which the lower 95% CI for the estimated treatment effect first crosses 0. mRS=modified Rankin Scale.

Outcomes

Our a-priori primary measure of treatment efficacy was the proportion of patients who had a good stroke outcome, defined by a modified Rankin score (mRS) of 0–1 (ie, symptom-free or residual symptoms with no loss of activity) at 3–6 months. 3-month outcome assessments were to be used if available, but for IST-3 we used a 6-month assessment because no 3-month assessment was done. We mapped the Oxford Handicap Scale outcome assessment used in IST-3 to equivalent mRS categories.

Key secondary outcomes were fatal intracranial haemorrhage within 7 days, any symptomatic intracranial haemorrhage, and 90-day mortality (separated by cause where possible). For a full list of secondary outcomes, see the pre-specified statistical analysis plan. For each of the three baseline characteristics, estimates were derived from a single logistic regression model stratified by trial, which enables separate estimation of the OR for each subgroup after adjustment for the other two baseline characteristics (but not for possible interactions with those characteristics). mRS=modified Rankin Scale.

Figures 2: Effect of alteplase on good stroke outcome (mRS 0–1), by treatment delay, age, and stroke severity

For each of the three baseline characteristics, estimates were derived from a single logistic regression model stratified by trial, which enables separate estimation of the OR for each subgroup after adjustment for the other two baseline characteristics (but not for possible interactions with those characteristics). mRS=modified Rankin Scale.

Statistical analysis

A full description of the analyses is provided in the pre-specified statistical analysis plan. Briefly, we used logistic regression, stratified by trial, to model the common linear dependence of the log odds of a particular outcome on allocation to alteplase, treatment delay (a linear variable), age (a linear variable), baseline stroke severity (National Institutes of Health Stroke Scale [NIHSS] score, modelled by both linear and quadratic terms), and interactions between allocation to alteplase and each of these other baseline covariates. (The odds ratio estimates presented here are of course more extreme than corresponding risk ratio estimates would be, but have the advantage that they may be more generalisable among patients with differing likelihood of a good stroke outcome.) We cross-checked individual data against previous publications. We imputed missing data with prespecified rules. We assessed the extent to which treatment delay, age, and stroke severity modified (individually or jointly) the proportional effects of treatment by assessing the statistical significance of the relevant treatment interaction terms using likelihood ratio tests (ie, through comparison of minus twice the log-likelihood statistic between appropriate nested models). Other pre-specified analyses included assessment of treatment effects separately according to categories of treatment delay that relate to present licence issues and previous trial time limits (≤3·0 h, >3·0h−4·5 h, >4·5 h), age (≤80 years, >80 years), and baseline stroke severity (handled in a quadratic manner).
Figure 3: Effect of alteplase on a good stroke outcome (mRS 0–1) by age, with different treatment delays. Effect of age on the interaction between treatment delay and treatment effect p<0.01 (ie, not significant but, if anything, in the direction of it lengthening, not shortening, the period during which alteplase is effective in older people). *All six estimates derived from a single stratified logistic regression model that enables the odds ratio to be estimated separately for each group (also adjusted for baseline National Institutes of Health Stroke Scale score). mRS=modified Rankin Scale.

Figure 4: Effect of alteplase on fatal intracranial haemorrhage within 7 days by treatment delay, age, and stroke severity.

*For each of the three baseline characteristics, estimates were derived from a single logistic regression model stratified by trial, which enables separate estimation of the OR for each subgroup after adjustment for the other two baseline characteristics (but not possible interactions with those characteristics). The overall effect in all patients is the trial-stratified logistic regression estimate adjusted only for treatment allocation. NE=not estimable.

Figure 5: Effect of alteplase on 90-day mortality by follow-up period.

Patients can only contribute to a particular risk period if they have already survived any preceding periods.

*Estimated by Cox proportional hazards regression stratified by trial (and adjusted only for treatment allocation).
†Includes 91 versus 13 deaths caused by intracranial haemorrhage (with evidence of parenchymal haemorrhage type 2; figure 4) and 191 versus 191 deaths from other causes.

7.14 (3.98–12.79)
10.94 (2.54–47.15)
5.00 (1.89–13.20)
10.94 (2.54–47.15)
5.71 (2.02–15.30)
5.00 (1.89–13.20)
greater proportional benefit (p=0.016 for trend of increasing proportional benefit with earlier treatment; figure 1). We estimated the time at which alteplase has no effect to be 6·3 h (95% CI 5·0–13·8) and the time at which the lower 95% CI for the estimated treatment benefit first crossed 1·0 to be 5·1 h (figure 1). When estimated in the three predefined subgroups of treatment delay, alteplase significantly increased the odds of a good outcome when given within 3·0 h (OR 1·75, 95% CI 1·35–2·27; p=0·0001) or after 3·0 h up to 4·5 h (OR 1·26, 95% CI 1·05–1·51; p=0·0132), but not after 4·5 h (OR 1·15, 95% CI 0·95–1·40; p=0·15; figure 2). The effect of alteplase on a good outcome was chiefly driven by treatment delay; after controlling for treatment delay, neither age nor severity of stroke contributed significant additional predictive value (appendix p 5). After allowing for differences explained by treatment delay, the effect of alteplase on a good outcome reported in IST-3 was consistent with that reported in the eight previous trials (p for inconsistency=0.92).

Age did not change the effect of alteplase on odds of a good outcome (p=0.53; appendix p 5). The effect of alteplase treatment was similar for patients aged 80 years or younger (mean treatment delay 4·1 h; 990 [39%] vs 853 [34%]; OR 1·25, 95% CI 1·10–1·42, p=0·0001) and for those older than 80 years (mean treatment delay 3·7 h; 155 [18%] vs 112 [13%]; OR 1·56, 95% CI 1·27–1·90, p=0·0023; figure 2). We found no evidence that old age shortened the period during which alteplase could effectively be given (p=0·08, in the direction of lengthening not shortening the period; figure 3). Nor did we find clear evidence that stroke severity modified the effect of alteplase (p=0·06). In particular, there was no evidence that alteplase was less effective for patients who had had the least or most severe strokes (figure 2, appendix p 5), reinforcing findings from one of the individual trials.19

Alteplase increased the likelihood of symptomatic intracranial haemorrhage. Type 2 parenchymal haemorrhage within 7 days occurred in 231 (6·8%) of 3391 patients assigned alteplase versus 44 (1·3%) of 3365 assigned control (OR 5·55, 95% CI 4·01–7·70; p<0·0001) and SITS-MOST-MOST criteria type 2 parenchymal haemorrhage within 36 h occurred in 124 (3·7%) of 3391 versus 19 (0·6%) of 3365 (OR 6·67, 95% CI 4·11–10·84; p<0·0001). Fatal type 2 parenchymal haemorrhage within 7 days occurred in 91 (2·7%) patients assigned alteplase versus 13 (0·4%) assigned control (OR 7·14, 95% CI 3·98–12·79; p=0·0001). The proportional increase in risk of fatal intracranial haemorrhage was much the same, irrespective of treatment delay, age, or stroke severity (p for trend=0·7 for all), but the absolute excess risk increased with increasing stroke severity (figure 4). Alteplase did not increase the risk of other early causes of death (ie, those other than intracranial haemorrhage), and had no significant effect on later causes of death (figure 5). Consequently, the early excess mortality caused by intracranial haemorrhage did not translate into a significant excess of overall mortality at 90 days (608 [17·9%] vs 556 [16·5%], HR 1·11 (95% CI 0·99–1·25); p=0·07; figure 5). The trend towards a larger relative increase in 90-day mortality with greater treatment delay was not statistically significant (p for trend=0·22; figure 6), although the statistical power to detect any true trend was limited by the number of deaths. The effects of alteplase on symptomatic intracranial haemorrhage, fatal intracranial haemorrhage, and 90-day mortality reported in IST-3 were consistent with those reported in the eight previous trials (all p values for inconsistency >0·1).

Overall, therefore, despite an average absolute increase in risk of early death caused by intracranial haemorrhage of about 2%, by 3–6 months this was offset by an average absolute increase in disability-free survival (ie, mRS 0–1) of about 10% for patients treated within 3·0 h and about 5% for patients treated between 3·1 and 4·5 h.

**Discussion**

Our data provide further evidence about the extent to which treatment delay alters the beneficial effect of alteplase for acute ischaemic stroke. We provide clear evidence for improved odds of a good stroke outcome when treatment is started within 4·5 h of ischaemic stroke, with earlier treatment resulting in bigger proportional and absolute benefits. The average benefit of alteplase might even extend beyond 4·5 h for some patients. The proportional benefits were similar for patients aged older than 80 years compared with younger patients, and for patients with minor or severe strokes compared with other patients.

This average expected benefit from giving alteplase within 4·5 h occurred in spite of an average absolute increase in the early risk of fatal intracranial haemorrhage of around 2%. Since alteplase had no significant effect on other early causes of death, or on later causes of death, by 90 days this 2% excess remained but was no longer statistically significant. Longer-term follow-up data are needed to test whether the effect of alteplase on patients who survive the first week after their stroke have reduced long-term risk of death. Contrary to analyses of individual patient data done before IST-3,3 the trend towards a bigger relative risk of 90-day mortality with increasing treatment delay was not
statistically significant in our analysis. However, if improvements in stroke outcome among survivors do lead to parallel improvements in mortality, then one would expect that long-term survival will be greatest among those treated earliest (ie, the group most likely to benefit from alteplase).

Our results support guidelines that recommend use of alteplase irrespective of age and up to 4·5 h after onset of stroke.28-30 In the USA, marketing authorisation has not been granted for use of alteplase after 3·0 h, while in some European countries marketing authorisation limits the use of alteplase to patients aged 80 years or younger. In the present analysis, the lower limit of the 95% CI for the time at which the proportional benefit on mRS 0–1 crossed the line of no effect was 5·0 h, with statistically significant evidence of benefit in the prespecified subset of patients with treatment delay after 3·0 h, up to 4·5 h. In addition, we found no evidence that age modified either the proportional benefits or the proportional hazards of alteplase, with clear evidence of overall benefit for mRS 0–1 among the 1729 patients aged older than 80 years at randomisation. Nor was there evidence that older age shortened the period during which such benefits were seen, according with a recent report.31

The availability of individual data for a large number of patients enabled us to make a more precise assessment of the relative effects of alteplase than has been possible previously. We also included more than 1700 patients aged older than 80 years. The number of older patients with stroke is increasing as a proportion of the general population and as a proportion of those with stroke, so our analyses provide a reliable assessment of the effects of alteplase in this group.32 Our analyses differ from previous pooled analyses of alteplase trials27 by including patients from IST-3, which almost doubles the number of patients available. They also differ from previous tabular meta-analyses29 through the use of individual data, which enables direct assessment of the potential for effect modification. Our prespecified analysis plan safeguarded against the potentially inappropriate combination of data from IST-3 with those from the previous studies. In fact, the results from IST-3 were consistent with earlier trials after adjustment for the main differences in patient characteristics.

Nonetheless, the open design of IST-3 and its broader definition of significant bleeding might have inflated our estimate of the risk of parenchymal type 2 symptomatic intracranial haemorrhage. However, the number of such events associated with early neurological deterioration or death was small, limiting the potential for this to be a source of major bias. Furthermore, the overall results from IST-3 for symptomatic intracranial haemorrhage were similar to those estimated from previous trials. Patients in IST-3 were also older on average than patients in the eight previous trials. However, this difference provides one of the main strengths of our analysis—the ability to compare the effect of alteplase reliably in old and young patients. Although unknown systematic differences might also have existed between patients in IST-3 and patients in the other trials, any such characteristics would have to be strong determinants of treatment effect (rather than just predictors of risk) to produce material bias in our overall results. Future work will investigate the potential independent effect on treatment effect of a range of other characteristics, including sex, blood pressure, and baseline imaging features.

In conclusion, despite early increases in fatal intracranial haemorrhage, alteplase significantly improves the overall likelihood of a good stroke outcome at 3–6 months. The proportional benefit increases with earlier treatment and remains statistically significant up to at least 4·5 h after initial stroke symptoms, irrespective of age or stroke severity.

** Contributors**

WH and EB had the original idea for this meta-analysis and implemented data definitions in 2004; KRL and EB refined the approach in 2010; CB, PS, and JW had the idea for this cycle of the meta-analysis and all authors contributed to the subsequent study protocol and statistical analysis plan. All authors contributed either to the acquisition of the original trial data or the creation of the combined dataset. JE and LB did the statistical analysis. JE and KRL wrote the first draft of the report. All authors contributed to the interpretation of the results, revision of the report, and have approved the final version of the manuscript.

**included trials**

- ATLANTIS A and B (Gregory Albers, James Grotta, Maarten Lansberg, Jean Marc Olivot; ECASS-1, ECASS-2, ECASS-3 (Erich Bluhmki, Werner Hacke, Markku Kaste, Kennedy Lees, Ruediger von Kummer, Danilo Toni, Nils Wahlgren); EPITHET (Stephen Davis, Geoffrey Donnan, Mark Parsons); IST-3 (Peter Sandrock, Joanna Wardlaw, Richard Lindeley, Gordon Murray, Geoff Cohen, William Whiteley); NINDS A and B (Thomas Brott, James Grotta, Patrick Lyden, John Marler, Barbara Tilley).

**STT Statistical Analysis Centre and Secretariat**


**Declaration of interests**

CB, LB, and JE have not accepted fees, honoraria, or paid consultancies but are involved in clinical trials of lipid-modifying treatment funded by Merck to the University of Oxford, with the University the trial sponsor in all cases. KRL has received speaker fees from and has served on the data monitoring committee of trials for Boehringer Ingelheim; his department has received research grant support from Genentech; GA has received research grant support from Lundbeck, fees for consultancy and advisory board membership from Lundbeck, Coviden, Codman, and Genentech; fees for acting as an expert witness, and owns stock in 1SchemaView. EB is employed by Boehringer Ingelheim. SD has received honoraria from Boehringer Ingelheim, EVER Pharma, and Sanofi and has received fees for consultancy and advisory board membership from Boehringer Ingelheim and Sanofi. GD has received research grant support from the NHMRC (Australia) and honoraria from Pfizer and Bristol-Myers Squibb. JC has received fees for consultancy and advisory board membership from Lundbeck. RVK has received speaker fees and honoraria from Penumbra and Lundbeck. RIL has received honoraria from Boehringer Ingelheim. JMO has received speaker fees from Boehringer Ingelheim. MP has received travel support from Boehringer Ingelheim. BT has received honoraria from Pfizer. DT has received speaker fees and fees for consultancy and advisory board membership from Boehringer Ingelheim and Bayer. KT has received research grant support from the Ministry of Health, Labour, and Welfare of Japan, and speaker fees from Mitsubishi Tanabe Pharma.

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References