Medicines Evidence Commentary

commentary on important new evidence from Medicines Awareness Weekly

Published: April 2013

Statin treatment at stroke onset associated with improved functional outcome

Document as included in MAW

A systematic review and meta-analysis, chiefly of observational studies, has found that people who have a stroke while being treated with a statin are more likely to have a better outcome than those who were not taking a statin. The outcomes specifically in statin-treated people who also receive thrombolysis are unclear. These findings appear to be in line with the recommendations in the NICE Clinical Guideline on Stroke.

Overview and current advice

The NICE Clinical Guideline on Stroke from 2008 recommends that people with acute stroke who are already receiving statins should continue their statin treatment but does not recommend immediate initiation of statin treatment after a stroke. At the time, no evidence was available on the safety and efficacy of initiating lipid lowering statin therapy for patients with an acute stroke, although the consensus of the Guideline Development Group was that it would be safe to start statins after 48 hours. However, there was evidence to support continuing statin treatment in those who were taking statins prior to stroke, and clearly a benefit in vascular risk reduction from initiation of statins after the acute phase of stroke.

See the NICE Evidence topic page on stroke for a general overview of the condition. The NICE Pathway – Stroke brings together all related NICE guidance and associated products on the condition in a set of interactive topic-based diagrams.

New evidence

A systematic review and meta-analysis of published and unpublished studies has investigated the relationship between statin treatment and outcome after ischaemic stroke. Twenty-seven studies (n=113,148) were identified for inclusion: 24 observational studies and 3 RCTs. A large proportion (76.6%) of the patients came from the Swedish stroke registry. Not all studies provided data for all outcomes.
The primary analysis investigated the association between statin treatment at the time of the stroke onset (that is, patients on statin treatment immediately before stroke onset) and good functional outcome or death at different time points after stroke (30 days or hospital discharge; 90 days: 1 year), compared with no statin therapy. Good functional outcome was defined as a score of 0–2 on the modified Rankin Scale (mRS). This scale ranges from 0 (no symptoms at all), through 2 (slight disability) to 5 (severe disability).

Prespecified secondary analyses included: data for patients who received thrombolysis, data for patients who received statins in the acute post-stroke period (0 to 72 hours after stroke), irrespective of whether this was a continuation of pre-stroke therapy or whether it was initiated within this period. Analysis was conducted separately in observational studies and RCTs.

Among the observational studies, statin treatment at the time of stroke onset was associated with an increased chance of good functional outcome at 30 days or hospital discharge (unadjusted pooled odds ratio [OR] 1.64, 95% confidence interval [CI] 1.14 to 2.36, p=0.008) and at 90 days (unadjusted pooled OR 1.41, 95% CI 1.29 to 1.56, p=0.001) but not at 1 year (pooled OR 1.12; 95% CI 0.90 to 1.40; p=0.31). Statin treatment at the time of stroke onset was associated with reduced risk of death at 30 days or hospital discharge, 90 days and 1 year (unadjusted pooled OR 0.80, 95% CI 0.67 to 0.95, p=0.01).

In the one RCT (n=492) that reported functional outcome at 90 days, statin treatment at the time of stroke onset was associated with an increased chance of good functional outcome at 90 days (OR 1.595% CI 1.0 to 2.24 p=0.05) in the single RCT reporting on this. There was no statistically significant difference in mortality at any of the 3 time points in the meta-analysis of data from the 3 RCTs (pooled OR for death at 1 year 0.87, 95% CI 0.57 to 1.31, p=0.5).

Five observational studies were included in the secondary analysis on statin treatment at stroke onset among patients treated with intravenous thrombolysis. No data were available on rates of death or good functional outcome at 30 days or 1 year. There was no statistically significant difference in the chance of good functional outcome at 90 days (unadjusted pooled OR 1.01, 95% CI 0.88 to 1.15, p=0.93, 5 studies, n=4993). Statin treatment was associated with increased risk of all-cause death at 90 days (pooled OR 1.25 95% CI 1.02 to 1.52; p=0.03, 3 studies, n=4339). However this association was no longer present after adjusting for age and stroke severity in the largest study (adjusted OR 1.14; 95% CI 0.90 to 1.44, n=4012).

Nine studies (5 observational studies and 4 RCTs) were included in the secondary analysis on statin therapy continued or initiated within 72 hours after the stroke. Among the observational studies, such statin treatment was associated with a greater chance of good functional outcome (unadjusted pooled OR 1.84, 95% CI 1.37 to 2.48, p<0.001) and reduced risk of death (unadjusted pooled OR 0.29, 95% CI 0.19 to 0.45, p<0.001) at 90 days (3 studies, n=1324). This association was not seen to a statistically significant extent in the RCTs: pooled OR for good functional outcome at 90 days was 1.57 (95% CI 0.88 to 2.81, p=0.12, 3 RCTs, n=211) and for death at 90 days was 1.71 (95% CI 0.74 to 3.97, p=0.2, 3 RCTs, n=146).

This study had several limitations. Few RCTs were available and therefore most data included were from nonrandomised observational studies. Observational studies can only suggest an association not prove causation and are prone to confounding. Unlike in the setting of an RCT, in ‘real life’, treatment plans are chosen, changed, or actively not chosen in the light of individual patients’ risk factors, preferences and tolerability or response to other drugs. Thus observed differences in outcomes may be due to differences among the patients, not only the different treatments. In observational studies it is usual to adjust for confounding variables (such as age, severity of stroke, etc.) However, individual patient data were not available so adjusted pooled analyses could not be performed, nor was it possible to pool the adjusted results of individual studies because different variables were used in each one.
Generally, a large, well-conducted RCT provides more reliable evidence than observational studies because it is much less likely to be confounded. However, the small size of the RCTs in this analysis means they may have lacked statistical power to detect a difference that truly exists: it is important to remember that ‘no statistically significant difference’ does not necessarily mean ‘no difference’, just that no difference could be established ‘beyond reasonable doubt’.

In addition, the authors acknowledge a number of other limitations such as the lack of information regarding cause of death and stroke recurrence stratified by statin treatment and the lack of individual patient data to establish the influence of statin withdrawal and dose-response relationships. Unpublished data were also included within the study and the authors acknowledge that this could limit the reproducibility of their analysis but comment that these data came from well-recognised large registries.

**Commentary**

While there is clear benefit from using statins to reduce the risk of further events in those who have had an ischaemic stroke (secondary prevention), there remains a concern that statin treatment may increase the risk of early haemorrhagic expansion or haemorrhagic transformation (bleeding into the ischaemic area) in the acute phase.

In this new meta-analysis, observational data suggest an association between statin treatment either started before stroke onset or within 72 hours and improved outcome; this is partially supported by RCT data. Nevertheless, the authors emphasise that they do not recommend routine prescription of statins for acute neuroprotection. They say that it remains unclear whether initiating statin treatment very early after a stroke is better than doing so later during the person’s hospital stay.

Given the concerns about the possible effects of statins on the risk of haemorrhagic transformation, the results of the subgroup analysis in people treated with thrombolysis are of interest. However, given the limitations of the analysis, the authors state that the data do not indicate that thrombolysis should be withheld in people taking statins who have had an acute ischaemic stroke, who would otherwise receive it.

The authors go on to say that their analyses underline the need for large RCTs to investigate further the efficacy and safety of statin treatment in acute ischaemic stroke.

**Study sponsorship**

The lead author’s institution received funding from the Irish Health Services Executive, National Lottery of Ireland and an unrestricted educational grant from Servier. However, the authors state that funding sources were not involved in the design, conduct, analysis or reporting of the study findings.

**References**

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