NICE National Institute for Health and Care Excellence

2021 exceptional surveillance of stroke and transient ischaemic attack in over 16s (NICE guideline NG128)

Surveillance report
Published: 1 April 2021

www.nice.org.uk

Contents

Surveillance decision

We will update the NICE guideline on stroke and transient ischaemic attack in over 16s.

The update will focus on blood pressure control for people with acute intracerebral haemorrhage.

Reason for the exceptional review

An enquirer to NICE highlighted differences in recommendations on blood pressure control in acute intracerebral haemorrhage between NICE's guideline on stroke and transient ischaemic attack in over 16s, and the following 2 guidelines:

- Guidelines for the management of spontaneous intracerebral hemorrhage (American Heart Association [AHA]/American Stroke Association [ASA] 2015).
- Guidelines for the management of arterial hypertension (European Society of Cardiology [ESC]/European Society of Hypertension [ESH] 2018).

Current NICE recommendations on blood pressure lowering in acute intracerebral haemorrhage were substantially informed by 2 large randomised controlled trials (RCT): INTERACT2 (2013) and ATACH-2 (2016). We are now also aware of a 2019 pooled analysis of individual participant data from these trials, which was published after the NICE guideline.

The purpose of this exceptional review was to consider any impact of the new pooled analysis on NICE's guideline, while considering differences between recommendations from NICE and other guideline developers.

Methods

The exceptional surveillance process consisted of:

- Considering the evidence used to develop the NICE guideline in 2019.

- Considering the new evidence and information that triggered the exceptional review. This was sufficient for decision making and full updated literature searches were not needed.
- Discussion with the clinical lead (a consultant in stroke medicine) on the development committee for the NICE guideline, and with the NICE clinical adviser.

For further details about the process and the possible update decisions that are available, see ensuring that published guidelines are current and accurate in developing NICE guidelines: the manual.

Information considered when developing the guideline

The NICE guideline on stroke and transient ischaemic attack in over 16s states: for people with acute intracerebral haemorrhage: 'Aim for a systolic blood pressure target of 130 mmHg to 140 mmHg within 1 hour of starting treatment and maintain this blood pressure for at least 7 days'. The guideline recommends offering rapid blood pressure lowering to this target for people who present within 6 hours of symptom onset **and** have a systolic blood pressure between 150 mmHg and 220 mmHg, but recommends considering rapid blood pressure lowering to this target for people who present beyond 6 hours of symptom onset **or** have a systolic blood pressure greater than 220 mmHg.

The guideline's evidence review (E) on blood pressure (maintenance of homeostasis) found moderate quality evidence from a meta-analysis of 3 trials (including INTERACT2, n=2,839; and ATACH-2, n=1,000) that intensive blood pressure lowering led to an improvement (although non-significant) in post-stroke functional status on the modified Rankin Scale (mRS; relative risk 1.06, 95% confidence interval [CI] 0.99 to 1.13). Despite the non-significant result, the committee considered the absolute benefit to be sufficiently clinically meaningful.

However, moderate quality evidence from a meta-analysis of 4 trials (including ATACH-2 but not INTERACT2) showed that intensive blood pressure lowering was accompanied by increased renal failure at 90 days (relative risk 2.07, 95% CI 1.08 to 3.99). This finding was driven almost entirely by ATACH-2, which had a more aggressive systolic blood pressure target (110 mmHg to 139 mmHg) than INTERACT2 (less than 140 mmHg, with cessation of blood pressure-lowering treatment at less than 130 mmHg). INTERACT2 did not report renal failure outcomes and so was not included in the meta-analysis. However, its

predecessor (INTERACT, n=404), which used the same intervention and comparator as INTERACT2 did not show any significant effect of the intensive strategy on renal failure.

The guideline committee concluded: 'Regarding the target range, this was consistent with what was achieved in the INTERACT2 trial and also avoids the potentially harmful aggressive reduction to a lower target, as in ATACH-2, that could be associated with renal failure'.

They further concluded: 'Lowering the systolic blood pressure below 130 mmHg was noted to risk excessive reduction, requiring intervention to raise the blood pressure back to a safe level in these patients and so should be avoided'. However, the committee did not include any caveats on maximum size of blood pressure reduction in the recommendations.

Information considered in this exceptional surveillance review

Pooled analysis of individual participant data from INTERACT2 and ATACH-2

INTERACT2 (2013; n=2,839) was an RCT comparing an intensive systolic blood pressure target (less than 140 mmHg within 1 hour of randomisation) with a less-intensive target (less than 180 mmHg) in patients with acute intracerebral haemorrhage and systolic blood pressure of 150 mmHg to 220 mmHg within 6 hours of presentation.

ATACH-2 (2016; n=1,000) was an RCT comparing an intensive systolic blood pressure target (110 mmHg to 139 mmHg) with a less-intensive target (140 mmHg to 179 mmHg) in patients with acute intracerebral haemorrhage and systolic blood pressure of 170 mmHg to 200 mmHg within 4.5 hours of presentation.

Both trials were considered by the NICE guideline committee during development of the original guideline.

The new 2019 study, published after the NICE guideline, was a pre-planned pooled analysis of individual patient-level data from the above 2 trials. The primary analysis looked for independent associations between 3 post-randomisation systolic blood pressure measures (size of blood pressure reduction in 1 hour, mean systolic blood

pressure achieved between 1 hour and 24 hours, and systolic blood pressure variability between 1 hour and 24 hours) and the primary outcome of functional status (defined by distribution of scores on the mRS at 90 days post-randomisation).

In the first hour, the mean reduction in systolic blood pressure was 29 mmHg (standard deviation [SD] 22). In the first 24 hours, the mean systolic blood pressure achieved was 147 mmHg (SD 15), and variability in systolic blood pressure was 14 mmHg (SD 8). Achieved mean systolic blood pressure from 1 hour to 24 hours was continuously associated with a favourable shift in ordinal scores on the mRS (improvement per 10 mmHg increase adjusted odds ratio [aOR] 0.90, 95% CI 0.87 to 0.94; p<0.0001). That is, every 10-mmHg reduction in systolic blood pressure was associated with a 10% increase in the odds of better functional recovery.

A secondary assessment of the systolic blood pressure summary measures as categories produced variation in the shape and significance of associations with outcomes. When plotted graphically, the general pattern was that lower categories of achieved systolic blood pressure (down to 120 mmHg to 130 mmHg) seemed to be associated with better outcomes, though the only significant linear trend (p=0.0002) among the outcomes was for early neurological deterioration (defined as an increase of 4 or more points on the National Institute of Health stroke scale or a decline of 2 or more points on the Glasgow coma scale within 24 hours post-randomisation).

A further analysis found that, compared with a reference category of reduction in systolic blood pressure of less than 20 mmHg, a large reduction of 60 mmHg or more within 1 hour was significantly associated with lower odds of a good outcome, defined as scores 0 to 3 on the mRS (aOR 0.63, 95% CI 0.47 to 0.84; p=0.0018), and had no significant effect on functional independence, defined as scores 0 to 2 on the mRS; whereas more moderate reductions in systolic blood pressure of 20 mmHg to 40 mmHg and 40 mmHg to 60 mmHg within 1 hour were significantly associated with functional independence (aOR 1.36, 95% CI 1.13 to 1.64; p=0.0012; and aOR 1.35, 95% CI 1.07 to 1.69; p=0.0101 respectively). Blood pressure reduction of 20 mmHg to 40 mmHg was also significantly associated with a good outcome (aOR 1.29, 95% CI 1.06 to 1.57; p=0.0096).

Adverse events included symptomatic hypotension in 28 (1%) patients, serious renal adverse events in 26 (1%) patients, and serious cardiac adverse events in 99 (3%) patients.

Recommendations in other guidelines

The AHA/ASA guidelines for the management of spontaneous intracerebral hemorrhage (2015) state: 'For intracerebral haemorrhage patients presenting with systolic blood pressure between 150 mmHg and 220 mmHg and without contraindication to acute blood pressure treatment, acute lowering of systolic blood pressure to 140 mmHg is safe and can be effective for improving functional outcome'.

The rationale for the recommendation states: 'Overall, current evidence indicates that early intensive blood pressure lowering is safe and feasible and that surviving patients show modestly better functional recovery, with a favourable trend seen toward a reduction in the conventional clinical endpoint of death and major disability. It is therefore reasonable for intracerebral haemorrhage patients similar to those enrolled in INTERACT2 to receive early treatment targeted to a systolic blood pressure level less than 140 mmHg'. This guideline was published in 2015 and so does not refer to ATACH-2 (which found no benefit of intensive blood pressure lowering for death and major disability and was associated with more renal adverse events), and therefore its recommendations are based mainly on the findings of INTERACT2. This guideline does not refer to the 2019 pooled analysis of ATACH-2 and INTERACT2.

The ESC/ESH guidelines for the management of arterial hypertension (2018) state: 'In patients with acute intracerebral haemorrhage: Immediate blood pressure lowering is not recommended for patients with systolic blood pressure less than 220 mmHg. In patients with systolic blood pressure of 220 mmHg or more, careful acute blood pressure lowering with intravenous therapy to less than 180 mmHg should be considered'.

The rationale for the recommendation states: 'Results from an RCT (INTERACT2) suggested that immediate BP lowering (within 6 hours) to less than 140/90 mmHg did not show benefit on the primary outcome of disability or death at 3 months, but might reduce haematoma expansion and improve functional recovery, and was generally safe. A subsequent RCT (ATACH-2), in which systolic blood pressure was immediately reduced (within 4.5 hours) from a mean of 200 mmHg to 2 different target intervals (140 mmHg to 170 mmHg versus 110 mmHg to 139 mmHg), showed that more intensive blood pressure lowering had no benefit on the same primary outcome and was associated with more renal adverse events. Thus, we do not recommend treatment to immediately lower blood pressure in patients with acute intracerebral haemorrhage. One possible caveat to this recommendation is patients with acute intracerebral haemorrhage and very severe hypertension (systolic blood pressure of 220 mmHg or more), for whom there are much

fewer data'. This guideline was published in 2018 and so refers to both INTERACT2 and ATACH-2, which explains its more conservative approach to blood pressure management compared with the AHA/ASA. The NICE guideline also included both these trials but came to different, less conservative conclusions about blood pressure targets. The ESC/ESH guideline does not refer to the 2019 pooled analysis of ATACH-2 and INTERACT2.

Topic expert feedback

We contacted the clinical lead (a consultant in stroke medicine) on the development committee for the NICE guideline to ask if they believed that the pooled analysis of individual patient-level data from INTERACT2 and ATACH-2 affected current recommendations.

They noted that the moderate quality evidence informing the current NICE-recommended blood pressure target (130 mmHg to 140 mmHg within 1 hour of starting treatment) was not statistically significant regarding post-stroke functional status, though it was deemed clinically meaningful. They recalled that recommendations were based on the target in INTERACT2 because it was not associated with renal impairment as seen with the more aggressive target in ATACH-2. They noted the consensus at the time was that a relatively low target was worth recommending, because people with intracerebral haemorrhage would get more intensive overall management, the drugs used are inexpensive, and staff are already in place to deliver it. However, they noted that in clinical practice, it is difficult to reduce blood pressure to the recommended target, because if people cannot swallow then intravenous labetalol is used, which at higher doses can cause serious bradycardia.

The clinical adviser highlighted results from the 2019 patient-level pooled analysis that the mean systolic blood pressure achieved was 147 mmHg following a mean reduction of 29 mmHg, and that harms may exist with reductions of 60 mmHg or more within 1 hour of treatment. They believed that current NICE recommendations should therefore be amended, and suggested raising the currently recommended blood pressure target of 130 mmHg to 140 mmHg, with a caveat that very large reductions in blood pressure within the first hour may be harmful. They indicated that this would give clinicians more leeway.

Equalities

No equalities issues were identified during the surveillance process.

Overall decision

The NICE guideline on stroke and transient ischaemic attack in over 16s currently recommends a systolic blood pressure target of 130 mmHg to 140 mmHg for people with acute intracerebral haemorrhage (based on benefits seen with this target in INTERACT2, while avoiding potential harms from more aggressive reductions to lower levels seen in ATACH-2); whereas the AHA/ASA recommend a higher target of 140 mmHg (which did not include consideration of ATACH-2), and the ESC/ESH do not recommend immediate blood pressure lowering at all for patients with systolic blood pressure less than 220 mmHg. The ESC/ESH only recommend acute blood pressure lowering for patients with systolic blood pressure of 220 mmHg or more, but the recommended target is less than 180 mmHg. Like the NICE guideline, the ESC/ESH considered both INTERACT2 and ATACH-2, but made more cautious recommendations.

New evidence from a pooled analysis of individual patient-level data from INTERACT2 and ATACH-2 showed that the systolic blood pressure achieved is often higher than targets, but achieved systolic blood pressure was continuously associated with functional status improvement. Lower categories of achieved systolic blood pressure (potentially down to 120 mmHg to 130 mmHg) were associated with better outcomes, which is broadly aligned with current NICE recommendations, although the association with better outcomes was only significant for early neurological deterioration.

However, the clinical adviser noted that achieving such low targets can be challenging in practice because of the need to use intravenous drugs with serious adverse effects. The new evidence also found that a large reduction of 60 mmHg or more within 1 hour might cause harm (whereas NICE recommendations currently make no statement on avoiding large drops in blood pressure). The clinical adviser believed that overall, these findings warrant reconsideration of the current NICE recommendations, and suggested raising the current blood pressure target and adding warnings about large reductions. The potential need for a more cautious approach is reflected in the ESC/ESH recommendations, which considered the same key trials as NICE, but did not recommend immediate blood pressure lowering if systolic blood pressure is less than 220 mmHg.

In summary, although there is evidence of benefit for lowering blood pressure following intracerebral haemorrhage, discrepancies with other guidelines in this area, and topic expert feedback about practical and safety issues of intensive targets with a suggestion to update recommendations (to raise the current target and add warnings about large reductions) also need consideration. New evidence re-analysing data from 2 trials (which

had a substantial bearing on current NICE recommendations) may have an impact on the guideline in relation to systolic blood pressure targets after acute intracerebral haemorrhage.

ISBN: 978-1-4731-4114-8