

# Blood pressure medication and acute kidney injury after intracerebral haemorrhage: an analysis of the ATACH-II trial

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## ABSTRACT

**Background** Acute blood pressure (BP) reduction is standard of care after acute intracerebral haemorrhage (ICH). More acute BP reduction is associated with acute kidney injury (AKI). It is not known if the choice of antihypertensive medications affects the risk of AKI.

**Methods** We analysed data from the ATACH-II clinical trial. AKI was defined by the Kidney Disease: Improving Global Outcomes criteria. We analysed antihypertensive medication from two sources. The first was a case report form that specified the use of labetalol, diltiazem, urapidil or other. We tested the hypothesis that the secondary medication was associated with AKI with  $\chi^2$  test. Second, we tested the hypotheses the dosage of diltiazem was associated with AKI using Mann-Whitney U test.

**Results** AKI occurred in 109 of 1000 patients (10.9%). A higher proportion of patients with AKI received diltiazem after nicardipine (12 (29%) vs 21 (12%),  $p=0.03$ ). The 95%ile (90%–99%ile) of administered diltiazem was 18 (0–130) mg in patients with AKI vs 0 (0–30) mg in patients without AKI ( $p=0.002$ ). There was no apparent confounding by indication for diltiazem use.

**Conclusions** The use of diltiazem, and more diltiazem, was associated with AKI in patients with acute ICH.

## INTRODUCTION

Intracerebral haemorrhage (ICH), spontaneous bleeding into brain tissue, is frequently disabling or deadly. Most patients who present with ICH have elevated blood pressure (BP),<sup>1–2</sup> a risk factor for haematoma expansion, growth of the intracranial haematoma on repeated CT scans. Acute BP reduction is considered standard of care to reduce haematoma expansion, disability and death in patients with acute ICH.<sup>1–5</sup>

Acute kidney injury (AKI) complicates the management of acute ICH. AKI is independently associated with more dependence or death at follow-up.<sup>6</sup> More acute BP reduction after acute ICH increases the risk of AKI.<sup>4</sup> However, it is not known if the choice of antihypertensive medication is associated with AKI. We tested the hypothesis that the

## WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Acute kidney injury (AKI) is related to blood pressure reduction and worsens outcomes.

## WHAT THIS STUDY ADDS

⇒ Diltiazem after nicardipine increases the risk of AKI.

## HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Protocols might specify combinations of antihypertensive medication that minimise the risk of AKI.

choice of antihypertensive medication and dosage is associated with AKI in patients with acute ICH.

## MATERIALS AND METHODS

We used data from the Antihypertensive Treatment of Acute Cerebral Haemorrhage (ATACH)-II clinical trial (NCT01176565),<sup>7</sup> which randomised 1000 patients worldwide with acute ICH and systolic BP>180 mm Hg to a goal systolic BP of 120 mm Hg (intensive acute BP reduction) or 140 mm Hg (standard acute BP reduction) in a 1:1 ratio.<sup>4</sup> The protocol is available online and has been previously published.<sup>4</sup> Data were obtained from the NIH. Outcome assessment was blinded, although BP goals were not blinded. Nicardipine was the preferred first-line antihypertensive medication. Data are available online from the NIH.

We defined AKI as per the Kidney Disease: Improving Global Outcomes (KDIGO) criteria by serum creatinine values.<sup>8</sup> Incident AKI was defined as  $\geq 0.3$  mg/dL increase in baseline creatinine level over any 48-hour period during the first 7 days in the ICU or an creatinine level at least 1.5 times the baseline creatinine level within 7 days. Twenty-eight patients (2.8%) did not have two creatinine

**Table 1** Antihypertensive medications and outcomes stratified by acute kidney injury

| Variable                                     | No acute kidney injury | Acute kidney injury | P value |
|--|------------------------|---------------------|---------|
| Antihypertensive after nicardipine           |                        |                     | 0.03    |
| Labetalol                                    | 94 (56)                | 23 (56)             |         |
| Diltiazem                                    | 21 (12)                | 12 (29)             |         |
| Urapidil                                     | 13 (8)                 | 1 (2)               |         |
| Other  | 41 (24)                | 5 (12)              |         |
| Atrial fibrillation                          | 29 (3)                 | 6 (6)               | 0.4     |
| Diabetes type 2                              | 7 (1)                  | 4 (4)               | 0.002   |
| Coronary artery disease                      | 36 (4)                 | 8 (7)               | 0.2     |
| Cigarette use, current                       | 224 (26)               | 30 (28)             | 0.7     |
| Former                                       | 153 (18)               | 19 (17)             |         |
| Never  | 417 (48)               | 48 (44)             |         |
| Unknown                                      | 69 (8)                 | 12 (11)             |         |
| Days to hospital discharge                   | 15 (7 – 25)            | 18 (9 – 33)         | 0.03    |
| Days in intensive care unit                  | 4 (2 – 7)              | 6 (2 – 11)          | 0.003   |
| modified Rankin Scale in survivors           | 3 (1 – 4)              | 3 (1.25–4)          | 0.04    |
| EuroQOL-5D Utility Index for quality of life | 0.77 (0.52–0.84)       | 0.69 (0.39–0.83)    | 0.05    |

Data are N(%) or median (Q1–Q3).

values and so the presence of AKI could not be determined—to be conservative, they were considered to have no AKI. None of these 28 patients without two creatinine values had a renal adverse event documented, supporting the adjudication that these patients did not have AKI.

We compared continuous data with analysis of variance, non-normally distributed values with a Mann-Whitney U test (expressed as median (Q1–Q3)), and frequency of categorical variables with  $\chi^2$  test as appropriate. Calculations were performed with standard statistical software (R V.4, RStudio V.1.4, R Foundation for Statistical Computing, Boston, Massachusetts, USA).

## RESULTS

The data set contained 1000 patients, evenly assigned to goal systolic BP 120 or 140 mm Hg. Overall, 109 patients (10.9%) had AKI. There were 90 patients with KDIGO stage 1, 15 patients with KDIGO stage 2 and 4 patients with KDIGO stage 3 (most severe AKI).

Antihypertensive medications were associated with AKI. Antihypertensive medications in addition to nicardipine were generally needed only in patients randomised to intensive BP treatment. Patients with AKI were more likely to receive diltiazem as a secondary agent to nicardipine and to have type 2 diabetes (table 1).

We confirmed higher doses of diltiazem were administered in patients with AKI. Most patients received no diltiazem, so differences were at the extremes. The 95<sup>th</sup>ile (90%–99<sup>th</sup> ile) was 18 (0–130) mg in patients with AKI vs 0 (0–30) mg in patients without AKI ( $p=0.002$ ).

## DISCUSSION

We examined data from a large, prospective, randomised, clinical trial of patients with acute ICH. Different trials have allowed local clinicians wide latitude to choose antihypertensive medications.<sup>2</sup> These data associate diltiazem after nicardipine with an increased likelihood of AKI compared with other antihypertensive medications.<sup>6</sup> There was no evidence of confounding by an indication for diltiazem (eg, atrial fibrillation was uncommon). The consistent results between the summary of the use of diltiazem in a case report form and the analysis of dosages of administered medications is reassuring because the use of diltiazem was independently documented twice, reducing the potential of a chance finding. These data suggest that diltiazem should not be used as a second-line medication when nicardipine is inadequate for acute BP reduction in patients with acute ICH.

The mechanism for diltiazem's association with AKI is not clear from these data. Acute BP reduction and vasodilators are likely to reduce kidney blood flow. Doppler of kidney blood flow<sup>9</sup> might determine the magnitude of kidney blood flow associated with AKI. It is possible that kidney blood flow can be manipulated with different antihypertensive medications or different BP goals. Routine CT angiography typically does not lead to AKI in patients with acute stroke.<sup>10</sup> Thus, imaging is unlikely to explain our findings, and there is no evidence that CT angiography confounds our results. In other acute conditions (eg, sepsis), a variety of potential mechanisms exist for AKI. Sepsis was rare in this cohort, and would not explain our results. Type 2 diabetes was more common in patients with AKI; however, this affected too few patients to drive

our results overall. Potential explanations include diltiazem's inhibition of cytochrome P450, which could be synergistic with the effects of intravenous nicardipine. Although the use of labetalol was not different between patients with AKI or not, diltiazem (a calcium antagonist) could also potentiate bradycardia when used concurrently with labetalol (a beta/alpha antagonist).

There are limitations to these data. These data are from a trial that is relatively large for ICH, but not by the standards of other conditions. However, the results are in line with other clinical trials that have found some harm from antihypertensive medication.<sup>11</sup> ATACH-II was the last trial in patients with ICH to specify a BP goal below 140 mm Hg; the incidence of AKI may be lower with less intensive BP goals or general practice. The variety of antihypertensive medications used makes interpretation more challenging. We attempted to minimise the likelihood of a chance finding by comparing two sources of documentation of antihypertension medication use, a summary choice on a case report form and cleaned data from all medication administration dosages.

In sum, we found that diltiazem was associated with AKI in patients with acute ICH, particularly those randomised to intensive BP reduction. Future research could determine mechanisms by which acute BP reduction leads to AKI. Minimising the occurrence of AKI could improve the efficacy and safety of acute BP reduction, the only treatment administered to most patients with acute ICH.

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**Contributors** AMN and JM performed the analysis. AMN obtained the data from NIH and wrote the paper. MH, HW and YL revised the paper for analysis. JP and AS edited the manuscript regarding kidney injury. PB edited the manuscript. AMN acts as guarantor.

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**Competing interests** None declared.

**Patient consent for publication** Not applicable.

**Ethics approval** No IRB review was necessary (and thus no number was assigned) because the use of a publicly available data set of deidentified data fell outside the board's guidelines as human subjects research.

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**Data availability statement** Data are available in a public, open access repository. Data are available from the NINDS Clinical Trials Archive on request from the NIH, at <https://www.ninds.nih.gov/current-research/research-funded-ninds/clinical-research/archived-clinical-research-datasets>.

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