

**Paracetamol, ibuprofen, and recurrent major cardiovascular and major bleeding events in 19,120 patients with recent ischaemic stroke**

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## Summary

**Background and purpose** The presumed safety of paracetamol in high cardiovascular risk patients has been questioned. We determined whether paracetamol or ibuprofen use is associated with major cardiovascular events (MACE) or major bleeding in 19,120 patients with recent ischemic stroke or transient ischemic attack (TIA) of mainly atherothrombotic origin included in the PERFORM trial.

**Methods** We performed two, nested case-control analysis (2153 cases with MACE during trial follow-up and 4306 controls matched on **Essen Stroke Risk Score**; 809 cases with major bleeding matched with 1616 controls), and a separate time-varying analysis. **Results** 12.3% were prescribed paracetamol and 2.5% ibuprofen. Median duration of treatment was 14 (IQR 5–145) days for paracetamol and 9 (5–30) days for ibuprofen. Paracetamol, but not ibuprofen, was associated with increased risk of a MACE (odds ratio [OR] 1.21, 95% confidence interval [CI] 1.04–1.42) or a major bleeding (OR 1.60, 95% CI 1.26–2.03), with no impact of daily dose and duration of paracetamol treatment. Time-varying analysis found an increased risk of MACE with both paracetamol (HR 1.22, 95% CI 1.05–1.43) and ibuprofen (HR 1.47, 95% CI 1.06–2.03) and of major bleeding with paracetamol (HR 1.95, 95% CI 1.45–2.62)

**Conclusion** There was a weak and inconsistent signal for association between paracetamol or ibuprofen and MACE or major bleeding, which may be related to either a genuine but modest effect of these drugs, or to residual confounding.

Clinical Trial Registration Information [ISRCTN66157730](https://www.isrctn.com/ISRCTN66157730)

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<http://www.isrctn.com/ISRCTN66157730?totalResults=5&pageSize=10&page=1&searchType=basic-search&offset=3&q=&filters=conditionCategory%3ACirculatory+System%2CrecruitmentCountry%3ATaiwan%2CrecruitmentCountry%3AAustria&sort=>

## Introduction

The association between non-steroidal anti-inflammatory drugs (NSAIDs) and cardiovascular risk is well established, particularly in high-risk populations.<sup>1</sup> Paracetamol (acetaminofen) is the most widely used analgesic and antipyretic worldwide.<sup>2</sup> It is commonly accepted that it has a better safety profile than NSAIDs, and thus it is usually the treatment of choice in many medical conditions. In patients with a high cardiovascular risk, recommendations state that paracetamol should be chosen over NSAIDs.<sup>3</sup> Recently, this assumed safety profile has been questioned. First, Hinz et al. found that paracetamol produces a substantial selective cyclooxygenase 2 (COX-2) inhibition, to a degree comparable to non-selective NSAIDs and selective COX-2 inhibitors.<sup>4</sup> Considering the vascular risk associated with COX-2 inhibitors, these results suggest that the presumed safety of paracetamol should be revisited.<sup>5-7</sup> In addition, chronic paracetamol consumption may be related to hypertension, a major vascular risk factor.<sup>8-10</sup> Indeed some studies have shown an increased risk of cardiovascular events and stroke in patients treated with paracetamol, particularly in high-dose users.<sup>10, 11</sup> Nevertheless, the hypothesis of a paracetamol-associated cardiovascular risk remains controversial. Paracetamol intake was not associated with an increase in stroke rate in a recent population-based case-control study, nor to myocardial infarction in other studies.<sup>12-14</sup> In an acute stroke setting, paracetamol treatment to control mild-to-moderate hyperthermia (37–39°C) seemed to be associated with a better final outcome, reducing disability at 3 months according to the modified Rankin scale.<sup>15</sup> Although there is a more commonly accepted belief that other NSAIDs, such as ibuprofen, have a higher vascular risk, there are still conflicting data in the literature. While some authors claim that ibuprofen intake is associated with an increase in vascular risk,<sup>16</sup> others have found no such association.<sup>12, 13</sup> NSAIDs associated bleeding risk is well known, particularly of a gastrointestinal origin.<sup>16</sup> Their use represents an independent risk factor in patients with an antithrombotic treatment, even when prescribed for a short term.<sup>17</sup> Differences between NSAIDs have been noted, probably related to a variable COX-1 inhibition and different half-lives, but while some authors claim that ibuprofen could have a lesser risk, others have found a similar bleeding risk compared to other NSAIDs.<sup>16, 18</sup> Paracetamol has an excellent gastrointestinal tolerability and safety profile concerning bleeding complications.<sup>19,20</sup> It is hence again the preferred analgesic in cases of an elevated bleeding risk.

PERFORM (Prevention of cerebrovascular and cardiovascular Events of ischaemic origin with teRutroban in patients with a history of ischaemic strOke or tRansient ischaeMic attack) was a

randomised, double-blinded clinical trial comparing the efficacy of terutroban, a selective prostaglandin-thromboxane antagonist, against aspirin for the prevention of cardiovascular events after a cerebral vascular event.<sup>21</sup> By analysing paracetamol and ibuprofen use in patients who were all on a background of antiplatelet therapy, we aimed to clarify whether there was an attributable cardiovascular risk associated with paracetamol or ibuprofen use in this high vascular risk population.

## Methods

### Selection of cases and controls for the nested case-control study

Two nested case-control studies were performed. One addressed cardiovascular events (death, myocardial infarction or stroke) and a second, life threatening (defined by a fatal outcome, a reduction in haemoglobin of 50 g/L or more, symptomatic intracranial haemorrhage or transfusion of 4 units or more of red blood cells) and major bleeding events (defined by a significantly disabling bleeding, an intraocular bleeding leading to significant loss of vision, a transfusion of 3 units or less of red blood cells, or needing hospital admission or surgery). The same procedure was performed for both nested-case control study.

We defined cases as those with a first occurrence of a major cardiovascular (or major bleeding) event after randomisation in the PERFORM trial. Over a 4-year follow-up, 2153 cardiovascular events and 809 major bleedings were recorded. The date of the event was considered as the index date.

Based on incidence density sampling, we selected up to two control subjects for each case by random sampling from all members of the study cohort who were alive before the day the case subject had the event. With this design, all cohort members were eligible to serve as controls for more than one case subject; and case subjects before the event were eligible to serve as controls for other case subjects who had an earlier event. Control subjects were individually matched to each case subject by **Essen stroke risk score (ESRS)** (+/- 1), comprising age, arterial hypertension, diabetes mellitus, previous myocardial infarction, other cardiovascular disease, peripheral artery disease, smoking, previous transient ischaemic attack (TIA) or ischaemic stroke, in addition to qualifying event and duration of follow-up. Since individual components of **ESRS** were available for all of patients, no imputation to handle missing data was done before matching. Thus, all controls were alive, not previously diagnosed as having a recurrent major cardiovascular event (or major bleeding), and had an equal

duration of follow-up at the risk set date. The index date of controls was defined as the date of event of their matched case. In the analysis, estimates of paracetamol or ibuprofen exposure for each control subject were truncated at the date of the event of the matched case subject.

### **Exposure definition**

For all cases and controls, we obtained information on paracetamol and ibuprofen use between the date of enrolment in the study and the index date. We had information about the timeline of the prescription and the dose. Also patients were asked to record the frequency of their use. They were classified into one of three groups: no use; occasional use; and daily use (several intakes for >1 days).

### **Statistical analysis**

Data are expressed as mean  $\pm$  standard deviation or median (interquartile range [IQR]) for continuous variables and count (percentage) for qualitative variables. The same analyses were performed for both the nested case-control studies.

Baseline characteristics were described and compared between the cases and **ESRS** matched controls by using the McNemar test for binary variables and the paired Student t test or the Wilcoxon signed rank test for continuous variables.

We compared the paracetamol or ibuprofen exposures between cases and controls using conditional logistic regression for matched sets with and without adjustment for history of paracetamol or ibuprofen prior randomization. Using patients with no-exposure as reference, we derived from this model, the odds ratios (ORs) with their corresponding 95% confidence intervals (CIs) as effect size measure.

A second analysis was performed using a time-varying Cox regression analysis by using all paracetamol(or ibuprofen) exposure status recorded at baseline and at each follow-up visit. This secondary sensitivity analysis, attempted to account for change in paracetamol (or ibuprofen) use status over time by including a time-dependent covariate into the Cox model with and without adjustment for the **ESRS** and history of paracetamol or ibuprofen prior randomization.

Finally we performed a sensitivity analysis restricted to patients with aspirin treatment at randomisation. Statistical testing was conducted at the 2-tailed  $\alpha$ -level of 0.05. Data were analyzed using the SAS software version 9.3 (SAS Institute, Cary, NC).

## Results

### Nested case-control study

#### ✓ Major cardiovascular event

We identified 2153 cases with a major cardiovascular (cardiac death, myocardial infarction or stroke) event and 4306 matched controls. The baseline characteristics are described in Table 1. The mean age of cases was 69 years and 70 years for controls. 13.7% of cases used paracetamol at the index date compared with 11.7% of controls. Paracetamol treatment was associated with an increased risk of major cardiovascular events (OR 1.21, 95% CI 1.04–1.42).

Patients who used paracetamol daily had a higher risk of major cardiovascular events but the OR was not significant (adjusted-OR 1.20, 95% CI 0.89–1.63). In this group, the median duration of paracetamol treatment was 14 (IQR 5–145) days. No effect was found for daily dose and duration of treatment. The OR for a dose of  $\geq 3000$  mg/day was not significant (Fig. 1).

Patients who used ibuprofen had no significant increase in the risk of major cardiovascular events (OR 1.03, 95% CI 0.73–1.34) and there was no significant association with duration or dose of ibuprofen treatment (Fig. 2). The median treatment duration for patients with a daily use was 9 (IQR 5–30) days. In sensitivity analysis restricted to patients with aspirin treatment at randomisation (1047 cases and 2094 matched control), a similar association between paracetamol and major cardiovascular event was found (adjusted OR, 1.36, 95% CI 1.11–1.67). However, for ibuprofen, an association with increased risk of major cardiovascular events was close to significance level (adjusted-OR, 1.43, 95% CI 0.99–2.05).

#### ✓ Major bleeding

There were 809 cases with major bleeding matched with 1616 controls. Supplementary table I shows sites of major bleedings. The mean age was 69 years for cases and 68 years for controls and 60% of cases were men compared with 62% of controls. 18.4% of cases were paracetamol users at the index date, compared with 12.3% controls. Paracetamol treatment was associated with major bleeding (adjusted-OR 1.60, 95% CI 1.26–2.03, Fig 1). Daily users had a higher risk of major bleeding. In addition, the risk of major bleeding increased gradually with the daily dose ( $P$  for trend across dose levels=0.02, Fig 1).

4.8% of cases were ibuprofen users at the index date compared with 3.7% controls. Ibuprofen was not associated with major bleeding (Fig 2). We also found no association between dose or duration of treatment.

In sensitivity analysis restricted to patients with aspirin treatment at randomisation (406 cases and 812 matched controls), paracetamol remained associated with an increase in major bleedings event (adjusted OR, 1.58, 95% CI 1.16-2.14). For ibuprofen the association remained not significant (adjusted OR, 1.45, 95% CI 0.86-2.44).

### **Time-varying analysis**

Using all prescriptions of paracetamol or ibuprofen during follow-up, we found an increased risk of major cardiovascular events in patients who received paracetamol (HR 1.23, 95% CI 1.05–1.43) or ibuprofen (HR 1.42, 95% CI 1.03–1.96). After multiple adjustments, the same results were obtained (table 2). For paracetamol, we also found an increased risk among patients who used the drug occasionally (Fig. 3). A non-significant increased risk was observed for patients with a dose  $\geq 3000$  mg/d. For ibuprofen, similar to the previous analyses, there was no effect of daily use and no dose effect (Fig. 3).

There was also an increased risk of major bleeding with paracetamol treatment (adjusted-HR 1.95, 95% CI 1.45–2.62) but not with ibuprofen treatment (adjusted-HR 1.02, 95% CI 0.54–1.90). Daily use of paracetamol and ibuprofen was associated with a higher risk of major bleeding (Fig. 3). Also, a significant increase risk was observed for patients with a dose  $\geq 3000$

In sensitivity analysis restricted to patients with aspirin treatment at randomisation, only paracetamol was associated with an increase in major cardiovascular and major bleeding events (adjusted HRs [95%CI]: 1.27[1.04-1.55], 1.93[1.46-2.56], respectively).

## Discussion

In this high vascular risk population of nearly 20,000 patients with recent ischaemic stroke or TIA, we found a weak and inconsistent relationship between paracetamol or ibuprofen prescription and recurrent major cardiovascular events or major bleeding. Even if there was an association between paracetamol prescription and an increased risk of major cardiovascular events or major bleeding, a dose effect was only found in the time-varying analysis and not in the nested case-control analysis, and patients who had longer paracetamol prescription showed no increase in the rate of major cardiovascular events. The results were not concordant for ibuprofen: in the nested case-control analysis there was no association between ibuprofen prescription and the risk of major cardiovascular events but this association was significant in the time-varying analysis. **The results were consistent when only patients randomised to aspirin at baseline were taken into account.** Overall, the strength of these associations for both paracetamol and ibuprofen was low, making possible that other undetected confounding factors explained these weak associations.

There are some limitations to our study. First, this is a high vascular risk population, and all patients were on antiplatelet treatment, so these results cannot be extrapolated to the general population. Besides, as previously pointed out, there are possible confounding factors underlying paracetamol prescription. Finally, our population was selected for a different purpose and was not homogeneous in terms of paracetamol intake, even if we tried to avoid this kind of bias with the case-control design. We also performed a propensity score-adjusted analysis and found similar inconsistent results (data not shown). The weak association between occasional paracetamol use and cardiovascular events or bleeding was possibly confounded by the underlying pathology that justified the prescription. On one hand, paracetamol could have been taken for misdiagnosed chest pain related to coronary events. On the other, paracetamol prescription is often associated with diseases implying a systemic inflammatory response. There is evidence of a relationship between systemic inflammation and stroke pathogenesis. Atherosclerosis, a major cause of stroke, is partly an inflammatory disease.<sup>22</sup> Besides, many inflammatory conditions have been associated with stroke.<sup>23</sup> Chronic inflammatory diseases, such as rheumatoid arthritis, systemic lupus erythematosus, giant-cell arteritis, and atopic dermatitis imply an increased risk of stroke.<sup>24-26</sup> Finally, an increased risk of both myocardial infarction and stroke has been associated with previous infections, especially in the 7 days following a respiratory infection.<sup>27, 28</sup> The unexpected association between paracetamol and major bleeding in our study raises

concern about its safety in patients under antithrombotic treatment. Nevertheless there are also some confounding factors that should be considered. Most of the major bleeding were of gastrointestinal origin or related to a surgical intervention (supplementary data, table 1), Because of its alleged safety profile, paracetamol is often prescribed in patients with a pre-existing medical condition implying an important bleeding risk and in a postoperative setting as a painkiller, which constitutes an important prescription bias. Besides, paracetamol can be also used as a symptomatic treatment for gastrointestinal diseases with possible bleeding complications.<sup>29</sup> These bias have been already underlined by other authors, who found an association with major bleeding when paracetamol was prescribed for gastrointestinal discomfort, but not for other indications, like headaches.<sup>30, 31</sup> Our patients were under antithrombotic treatment, either terutroban or aspirin. If an analgesic or antipyretic was needed, their physicians may have chosen paracetamol over NSAIDs in regard of its tolerability. Ibuprofen would have been used only in low risk patients, and its use seems safe when used at doses of 1200mg/day or lower.<sup>32</sup>

In conclusion, there was a weak and inconsistent signal for an association between paracetamol and ibuprofen use and major vascular events or major bleedings, which may be related to either a genuine but modest effect of paracetamol and ibuprofen or to residual confounding. Given the uncertainty and the widespread use of paracetamol, the safety of paracetamol and ibuprofen among patients with ischaemic stroke should be elucidated in future randomised studies.

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**Table 1:** Characteristics of cases (with major vascular events) and controls.

	Major cardiovascular event		Major bleeding	
	Cases (n=2153)	Controls (n=4306)	Cases (n=809)	Controls (n=1618)
<b>Demographics</b>				
Age (years)	69.2±8.2	69.7±7.8**	69.2±8.0	68.3±8.0 **
Men	1449 (67.3)	2741 (63.7)*	536 (66.3)	1012 (65.4)*
Body mass index (kg/m <sup>2</sup> )	27.0±4.3	27.1±4.3	26.6±4.5	27.2±4.3
Systolic blood pressure (mmHg)	138.3±15.7	138.1±15.8	138.8±15.6	137.8±15.5
Diastolic blood pressure (mmHg)	79.4±8.5	79.2±8.5	79.4±8.7	79.6±8.4
Total cholesterol (mmol/L)	4.7±1.2	4.6±1.2	4.5±1.1	4.6±1.2
Low-density lipoprotein cholesterol (mmol/L)	1.2±0.3	1.2±0.3	1.3±0.4	1.2±0.3
High-density lipoprotein cholesterol (mmol/L)	2.8±1.0	2.8±1.0	2.7±0.9	2.8±1.0 *
<b>Risk factor</b>				
Hypertension	1842 (85.6)	3917 (91.0) *	703 (86.9)	1431 (88.4) **
Diabetes	742 (34.5)	1623 (37.7)*	234 (28.9)	559 (34.6)*
Hypercholesterolemia	1025 (47.6)	2145 (49.8)*	395 (48.8)	796 (49.2)
Current smoker	571 (26.5)	1326 (30.8)*	227 (28.1)	475 (29.4)
Previous stroke	492 (22.9)	945 (22.0)	161 (19.9)	294 (18.2)
Previous transient ischaemic attack	185 (8.6)	497 (11.5)*	61 (7.4)	140 (8.7)
Previous myocardial infarction	312 (14.5)	668 (15.5)	73 (9.0)	150 (9.3)
<b>Essen stroke risk score</b>	4 (3–5)	3 (3–4)	3 (2–4)	3 (2–4)
<b>Duration of follow-up (years)</b>	11 (4-19.5)	11 (4-19.5)	12 (5-20)	12 (5-20)

\*<0.005, \*\*<0.05

Data are number (%), mean±SD, or median (IQR) unless stated otherwise.

**Figure 1:** Effect of paracetamol on risk of major cardiovascular events or major bleedings

Data are number (%) unless otherwise specified. CI=confidence interval; OR=odds ratio. \*Adjusted on previous use of paracetamol.† Calculated for daily use. One confidence interval were truncated

Figure 2. Effect of ibuprofen on risk of major cardiovascular events or major bleedings

Data are number (%) unless otherwise specified. CI=confidence interval; OR=odds ratio. \*Adjusted on previous use of ibuprofen.† Calculated for daily use. One confidence interval were truncated

**Table2:** Time-dependent HR for paracetamol and ibuprofen and major cardiovascular events or major bleeding risks

	Unadjusted HR(95% CI)	<i>P</i> value	Adjusted* HR(95% CI)	<i>P</i> value
<b>Major cardiovascular event</b>				
Paracetamol	1.23 (1.05–1.43)	0.01	1.22 (1.05–1.43)	0.01
Ibuprofen	1.42 (1.03–1.96)	0.03	1.47 (1.06–2.03)	0.02
<b>Major bleeding</b>				
Paracetamol	1.84 (1.48–2.28)	<0.0001	1.89 (1.52–2.34)	<0.0001
Ibuprofen	1.02 (0.54–1.90)	0.96	1.05 (0.56–1.96)	0.88

CI=confidence interval; HR=hazard ratio. \*Adjusted on **Essen stroke risk score** and previous use of paracetamol or ibuprofen

**Figure 3:** Major cardiovascular events or major bleedings according to frequency of consumption of paracetamol or ibuprofen and to dose of paracetamol or ibuprofen in time-varying analysis

CI=confidence interval; HR=hazard ratio. \*Reference. † Calculated for daily use ‡Adjusted on **Essen stroke risk score** and previous use of paracetamol or ibuprofen. Note: there was no cardiovascular and bleeding event in the dose class 1500–2999 mg/d. One confidence intervals were truncated