

# Risk of acute cerebrovascular and cardiovascular events among users of paracetamol or paracetamol-codeine combination: a case-control study nested in a cohort of patients with osteoarthritis

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Paracetamol is generally considered the first-line pharmacotherapy for osteoarthritis (OA),<sup>1</sup> particularly for patients at high risk for cerebro and cardiovascular events.<sup>2</sup> Nevertheless, evidence on cerebro and cardiovascular safety of acetaminophen is conflicting,<sup>3,4</sup> and little is known on the paracetamol-codeine combination, which is used to treat severe OA-related pain not responding to acetaminophen.

The aim of this study was to verify whether paracetamol or paracetamol-codeine combination is associated with an increased risk of acute cerebro and cardiovascular events (ACCEs) in patients with OA.

We used the Health Search – CSD Longitudinal Patient Database (HSD). A case-control analysis was nested in a cohort of new users of nonsteroidal anti-inflammatory drugs, and diagnosed with OA. Cases of ACCEs occurred between January 2002 and June 2013 (index date) were identified. Up to five controls per case were randomly selected within each risk set.<sup>5</sup> The risk of ACCEs was investigated with respect to the recency of use of paracetamol and/or paracetamol-codeine combination. Patients were classified as current (0-90 days preceding index date), recent (91-180 days), past (181-365 days) or non-users (>365 days), considering the latter as the reference category. Conditional logistic regression was estimated to calculate odds ratios (ORs) and 95% confidence intervals (95% CI).

In a cohort of 36,754 patients, the incidence rate of ACCEs was 117.6 per 10,000 person-years. No significant association between exposure to paracetamol-containing medicines and ACCEs was observed in current (OR=1.22; 95% CI: 0.96-1.55), recent (OR=1.12; 95% CI: 0.80-1.55) or past users (OR=1.13; 95% CI: 0.86-1.48). Similar results were obtained for current users exposed to paracetamol monotherapy or paracetamol-codeine combination, respectively.

Our findings indicate that there is no association between the use of paracetamol and/or paracetamol-codeine combination and the occurrence of ACCEs. This information contributes to support clinicians in the choice of therapy for OA-related pain.

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3 - Chan A et al. (2006) *Circulation*;113:1578-87.

4 - Fulton RL et al. (2015) *Hypertension*;65:1008-14.

5 - Breslow NE. (1996) *J Am Stat Assoc*;91:14-28