Clarithromycin and cardiovascular outcomes

Current use of clarithromycin is associated with an increased risk of myocardial infarction (MI), arrhythmia and cardiac mortality in the short-term but not with long-term cardiovascular (CV) risk, according to results of this population-based study.

Clarithromycin is a macrolide antibiotic indicated for respiratory tract infections, *Mycobacterium avium* complex disease in patients with HIV, skin and soft tissue infections, and with amoxicillin or metronidazole and a PPI to treat *H. pylori* infections. Several randomised controlled trials and cohort studies have assessed CV outcomes but there is still uncertainty about whether the risk is short- or long-term.

CV outcomes in a cohort of 326,781 adults who received oral clarithromycin or amoxicillin between 2005 and 2009 in Hong Kong were analysed. Each clarithromycin user was matched to one or two amoxicillin users based on age, sex and calendar year at use. A self-controlled case series and case crossover analysis included those who received *H. pylori* eradication treatment containing clarithromycin. The observation period started on the date of first antibiotic prescription (index date) and ended at the earliest occurrence of the outcome, death, subsequent use of clarithromycin or amoxicillin, or end of study (December 2012). The primary outcome was first hospital recorded MI. Secondary outcomes were all-cause, cardiac, or non-cardiac mortality, arrhythmia and stroke.

The following results were reported:

- The propensity score adjusted rate ratio of MI 14 days after starting antibiotic treatment was 3.66 [95% CI 2.82 to 4.76] comparing clarithromycin use (132 events, rate 44.4 per 1,000 person-years) with amoxicillin use (149 events, 19.2 per 1,000 person-years), but no long-term increased risk was observed.
- Rate ratios of secondary outcomes increased significantly only with current use of clarithromycin vs. amoxicillin, except for stroke.
- In the self-controlled case analysis, there was an association between current use of *H. pylori* eradication treatment containing clarithromycin and CV events. Risk returned to baseline after treatment ended.
- The case crossover analysis showed an increased risk of CV events during current use of *H. pylori* eradication treatment containing clarithromycin. The adjusted absolute risk difference for current use of clarithromycin vs. amoxicillin was 1.90 excess MI events [1.30 to 2.68] per 1,000 patients.

The authors conclude that given the acute risk, clarithromycin should be prescribed with caution, especially to patients with a high baseline CV risk.

BMJ 2016; 352: h6926  (full text available)

Creatinine-based equations for adjusting drug dosage in obese patients

In patients with a BMI >30, body surface area (BSA) de-indexed Modification of Diet in Renal Disease (MDRD) equation appears to be the most suitable tool for estimating Glomerular Filtration Rate (eGFR) for the purpose of adjusting drug dosage, according to results of this study.

For adjusting drug dosing, the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines recommend using eGFR calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, after de-indexation by BSA. KDIGO, the FDA and EMA recommend using an eGFR value which is not adjusted to BSA. The formulae providing a BSA-adjusted GFR (ml min^-1 1.73m^-2) must therefore be ‘de-indexed’ to give the absolute GFR value, in ml/min, for each individual. This de-indexation has little impact in the general population as mean BSA is close to 1.73m^2 but impact is highly relevant in obese patients. In pharmacology, the Cockcroft-Gault (CG) equation is still recommended to adjust drug dosage. For obese patients, adjusted ideal body weight (AIBW) is sometimes preferred to actual body weight (ABW) for the CG equation. This study compared performance of different GFR-estimating equations, non-indexed or de-indexed by BSA, for the purpose of adjusting drug dosage in obese patients.

Data were assessed from 366 adults with a BMI >30 (51% female) who were undergoing GFR measurement. In patients without chronic kidney disease (CKD), the indication for GFR measurement was imminent living kidney transplant or patients being about to start a weight-loss diet. In patients with CKD, GFR was measured as part of CKD follow-up, and not because of obesity. eGFR was calculated using CKD-EPI and MDRD equations (de-indexed by BSA), and the CG equation, using either ABW, AIBW or lean body weight (LBW) for the weight variable and compared with measured GFR, expressed in ml/min. Patients treated with glucocorticoids, cimetidine or trimethoprim were excluded.

The following results were reported:

- Using AIBW instead of ABW markedly improved overall accuracy of the CG equation (57% for CGABW and 79% for CGAIBW; p<0.05).
- For high BMI (>40), accuracy of the CG equation is no different when using LBW than when using AIBW.
- The MDRD and CKD-EPI equations de-indexed by BSA also performed well, with an overall higher accuracy for the MDRD de-indexed equation (80% and 76%, respectively; p<0.05).

The authors conclude that performance of the CGABW equation is poor in the obese population. Using AIBW instead of ABW in the CG equation (non-indexed) drastically increases performance compared with that of other eGFR equations, especially when deciding whether or not the drug should be stopped (GFR <30ml/min). When adjustment of drug dosage needs to be carried out at GFR levels between 30ml/min and 45ml/min, MDRD,de-indexed and CKD-EPI,de-indexed equations are reasonably equivalent, with good performance. Currently, use of AIBW or other weight variables in the CG equation is still debated. Therefore, using creatinine-based equations such as MDRD and CKD-EPI de-indexed by BSA seems to be the easiest and most accurate way to estimate GFR and adjust drug dosage for obese patients to individual

Clarithromycin and cardiovascular outcomes

Current use of clarithromycin is associated with an increased risk of myocardial infarction (MI), arrhythmia and cardiac mortality in the short-term but not with long-term cardiovascular (CV) risk, according to results of this population-based study.

Clarithromycin is a macrolide antibiotic indicated for respiratory tract infections, *Mycobacterium avium* complex disease in patients with HIV, skin and soft tissue infections, and with amoxicillin or metronidazole and a PPI to treat *H. pylori* infections. Several randomised controlled trials and cohort studies have assessed CV outcomes but there is still uncertainty about whether the risk is short- or long-term.

CV outcomes in a cohort of 326,781 adults who received oral clarithromycin or amoxicillin between 2005 and 2009 in Hong Kong were analysed. Each clarithromycin user was matched to one or two amoxicillin users based on age, sex and calendar year at use. A self-controlled case series and case crossover analysis included those who received *H. pylori* eradication treatment containing clarithromycin. The observation period started on the date of first antibiotic prescription (index date) and ended at the earliest occurrence of the outcome, death, subsequent use of clarithromycin or amoxicillin, or end of study (December 2012). The primary outcome was first hospital recorded MI. Secondary outcomes were all-cause, cardiac, or non-cardiac mortality, arrhythmia and stroke.

The following results were reported:

- The propensity score adjusted rate ratio of MI 14 days after starting antibiotic treatment was 3.66 [95% CI 2.82 to 4.76] comparing clarithromycin use (132 events, rate 44.4 per 1,000 person-years) with amoxicillin use (149 events, 19.2 per 1,000 person-years), but no long-term increased risk was observed.
- Rate ratios of secondary outcomes increased significantly only with current use of clarithromycin vs. amoxicillin, except for stroke.
- In the self-controlled case analysis, there was an association between current use of *H. pylori* eradication treatment containing clarithromycin and CV events. Risk returned to baseline after treatment ended.
- The case crossover analysis showed an increased risk of CV events during current use of *H. pylori* eradication treatment containing clarithromycin. The adjusted absolute risk difference for current use of clarithromycin vs. amoxicillin was 1.90 excess MI events [1.30 to 2.68] per 1,000 patients.

The authors conclude that given the acute risk, clarithromycin should be prescribed with caution, especially to patients with a high baseline CV risk.

BMJ 2016; 352: h6926  (full text available)
The following results were reported:

- Overall number of adverse events leading to treatment interruption did not differ significantly between groups (64 events in the standard-treatment group and 95 events in the intensified-treatment group; \( p=0.08 \)).

The author of an accompanying editorial notes that, coupled with recent findings of fluoroquinolones failing to contribute to sterilisation of lesions and short duration of treatment for pulmonary tuberculosis, these results are disappointing. Although fluoroquinolones may replace isoniazid because of their good bactericidal activity and may assist in treating drug-resistant tuberculosis, they are not going to revolutionise treatment of pulmonary tuberculosis or tuberculosis meningitis. Usefulness of fluoroquinolones is also threatened by rising prevalence of fluoroquinolone resistance among \( M. \) tuberculosis isolates in many countries. Furthermore, new antituberculosis drugs (bedaquiline, delamanid and pretomanid) are highly protein-bound and unlikely to freely penetrate cerebrospinal fluid, and potential adverse events will probably limit any increase in their use.

### Intensified therapy for tuberculous meningitis

In adults with tuberculous meningitis, intensified antituberculosis treatment does not improve survival rate compared with standard treatment at nine months, according to results of this randomised controlled trial.

Tuberculous meningitis is often lethal. Early antituberculosis treatment and adjunctive glucocorticoids improve survival, but nearly one third of patients die. The authors hypothesised that intensified antituberculosis treatment would enhance killing of intracerebral \( M. \) tuberculosis organisms and decrease death rate.

817 patients with tuberculous meningitis (349 also had HIV infection) were randomised to a standard or intensified treatment regimen for nine months. All patients received isoniazid (5mg/kg/day; max 300mg per day), rifampicin (10mg/kg/day), pyrazinamide (25mg/kg/day; max 2g per day), and ethambutol (20mg/kg/day; max 1.2g per day) for three months, followed by rifampicin and isoniazid at the same doses for an additional six months. Patients who had previously received treatment for tuberculosis also received streptomycin (20mg/kg/day; max 1g per day) for the first three months. All patients received adjunctive treatment with dexamethasone for the first six to eight weeks of treatment. Intensified treatment consisted of the standard nine-month regimen with the addition for the first eight weeks of a weight-based dose of rifampicin (5mg/kg/day; to achieve a total dose of 15mg/kg/day) and levofloxacin (20mg/kg/day). The primary outcome was death by nine months. Secondary outcomes included neurologic disability at nine months, time to first new neurologic event or death, and serious adverse events.

The following results were reported:

- During nine months of follow-up, 113 patients in the intensified-treatment group and 114 patients in the standard-treatment group died (hazard ratio 0.94 [95% CI 0.73 to 1.22]; \( p=0.66 \)).
- There was no evidence of a significant difference between groups for any outcome in the overall population or in any subgroups, with the possible exception of patients infected with isoniazid-resistant \( M. \) tuberculosis.

### National guidelines for over-the-counter (OTC) sales of aspirin and paracetamol

National guidelines for over-the-counter (OTC) sales of aspirin and paracetamol appear to be poorly adhered to in non-pharmacy shops, according to results of this mystery shopper study.

Paracetamol misuse is the number one cause of overdose in the UK. Rising overdose rates in the 1990s, led to new legislation in 1998, restricting paracetamol pack size to 16-500mg tablets/capsules at non-pharmacy retail outlets. In 2009 the MHRA further restricted OTC drug sales in the UK stating “no retailer should sell more than two packets of paracetamol (500mg) in one transaction, retailers should be discouraged from promoting sale of more than one packet at a time and that it is illegal to sell more than 100 tablets of paracetamol (500mg) or aspirin (75 to 300mg) in one transaction. Since 2009 death rates in the UK from paracetamol overdose have dropped by 43%. Preliminary investigations suggest some non-pharmacy retail outlets are selling 48 tablets of paracetamol (500mg) and encouraging sale of three packets (3x16 tablets) as bargain offers. This study investigated the number of non-pharmaceutical retail outlets willing to break MHRA guidelines and the law for OTC sales of aspirin and paracetamol.

Data were collected across four geographical areas of Staffordshire and Shropshire from at least 50 stores. Data were collected in two stages in spring 2015. In Stage 1 eight medical students attempted to buy ≥96 tablets/capsules aspirin or paracetamol in one transaction in 62 shops. They were given the brief “I’m going away for a while and suffer migraines” to use if questioned by cashiers. In Stage 2, across the same area, four medical students attempted to purchase 2x16 packets of paracetamol 500mg along with a ‘flu remedy preparation also containing paracetamol in 54 shops. They were given the brief “My flat mate has ‘flu” to use if questioned. Mystery shoppers were asked in both stages to record whether cashiers willingly allowed transactions, if any questions were asked, why any sale was refused, if cashiers would accept multiple transactions of drugs to over-ride any obstruction in payment systems, and any remarks about sales made by cashiers.

The following results were reported:

- Stage 1 data revealed that 58% and 57% of retailers sold more than the MHRA guidelines recommended for paracetamol and aspirin, respectively.
- 23% and 28% of retailers were willing to sell ≥96 tablets of paracetamol or aspirin with no questions asked.
- Stage 2 results showed that 57% of retailers sold 2x16 packets of 500mg paracetamol in conjunction with a paracetamol-containing ‘flu preparation.
- 98% shops sold a 1x16 packet of paracetamol 500mg with a paracetamol-containing ‘flu remedy, without question and advice given.

The authors suggest that sales of aspirin and paracetamol OTC must be better regulated, recommending:

1. New laws:
   - a. Illegal to sell >32 paracetamol at non-pharmacy counters.
   - b. Non-pharmacy counters not permitted to sell paracetamol/paracetamol-containing medicines together.
2. Improved staff training for sale of paracetamol and/or aspirin.
3. Regulation of OTC medicine purchases internally/externally.
4. Amending till systems to prevent >32 paracetamol tablet sales with other products containing paracetamol.
5. Distancing OTC medicines from ‘everyday value’ signs/products.
6. Introduce a standardised logo to indicate if a product contains paracetamol or aspirin.

The information in this bulletin is based on resources available at time of publication. Any opinions are the author’s own and may not reflect those of the organisation. This is an NHS document. Do not use for commercial purposes.