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Background: The association between psoriasis and the risk of stroke is not clearly understood.

Objectives: To investigate whether psoriasis is independently associated with stroke after adjusting for risk factors.

Methods: An inception cohort of patients with psoriasis and matched controls (1:5) was identified for the interval 1994-2009 using the CPRD. Patients were at least 20 years old with no history of cardiovascular disease (CVD) or diabetes. Risk factors explored included psoriasis, severe psoriasis (exposure to systemic therapy or biologics), inflammatory arthritis, diabetes, chronic kidney disease, hypertension, hyperlipidaemia, transient ischaemic attack (TIA), myocardial infarction (MI), atrial fibrillation (AF), angina, valvular heart disease, thromboembolic disease, congestive heart failure and smoking as time-varying covariates; depression, age, gender and calendar year as baseline characteristics. Cox proportional hazard regression using shared frailty models and a stepwise forward approach ($p = 0.05$) estimated hazard ratios (HRs) with 95% confidence intervals for the risk of incident (fatal and non-fatal) stroke.

Results: 48,523 psoriasis patients and 208,187 controls were identified (mean (SD) age at diagnosis 48 years (16); 56% female). During a median follow-up of 5.2 years, 522 (1.08%) incident stroke events occurred in patients with psoriasis and 2,018 (0.97%) in controls. Crude HRs associated with psoriasis and severe psoriasis were 1.10 (1.00-1.21) and 1.21 (0.74-1.98) respectively. The stepwise regression model included: age HR 1.08 (1.08-1.08); TIA HR 4.85 (4.18-5.62); smoking HR 1.68 (1.53-1.85); AF HR 2.13 (1.84; 2.48); calendar year HR 0.95 (0.94-0.96); hypertension HR 1.45 (1.34-1.57); male gender HR 1.40 (1.29-1.51); MI HR 1.81 (1.45-2.25); and thromboembolic disease HR 1.40 (1.18-1.66). Neither psoriasis nor severe psoriasis were selected in the multivariable model as important predictors for stroke. When entered, their adjusted HRs were 1.05 (0.95-1.16) and 1.21 (0.73- 1.99) respectively.

Conclusions: Neither psoriasis nor severe psoriasis were associated with an increased risk of stroke after adjusting for known risk factors.

830. Spontaneous Reports of Thromboembolic Events Associated with Cyproterone/Ethinylestradiol after Media Attention

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Background: After extensive media attention on thromboembolic adverse drug reactions (TE-ADRs) and the use of cyproterone/ethinylestradiol (CE), the Netherlands Pharmacovigilance Centre Lareb received a high number of reports about this association, which prompted for detailed analyses.

Objectives: To analyse reports of thromboembolic events associated with the use of cyproterone/ethinylestradiol submitted to Lareb, focusing on the indication of use, presence of risk factors and time between the initial symptoms and the actual diagnosis of the TE.

Methods: Reports submitted to Lareb till 11 February 2014 were analysed. The analysis was focussed on reporter type, seriousness of the reaction, age of the patient, BMI, indication, ADRs classified as arterial thrombosis and venous thrombosis, pulmonary embolism, latency period, outcome of the reaction, treatment of the ADR, delay between the first symptoms and diagnosis of the ADR, presence of risk factors.

Results: On 11 February 2014, Lareb had received a total of 786 reports about CE, including 41 cases with a fatal outcome. Of all reports, 438 reports considered TE-ADRs which were analysed in more detail. Reported ADRs consisted of arterial thrombosis (N = 74), venous thrombosis (N = 63), pulmonary embolism (N = 219) and thrombosis with an unspecified location (N = 172). Patient's mean age was 30.5 years (range 14-57 years). The primary indications for use were acne (N = 193), oral contraceptive (N = 181), hirsutism (N = 13), other (N = 18) or the indication was unknown (N = 33). The median time to onset was

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4 years, although many patients reported a longer latency period. There was no distinction between the time of onset in respect to the reported ADR. No differences in risk factors seem to exist between labeled and off-label indications. In 382 out of 438 reports (87%), the reporter was a consumer. Some reports mentioned the fact that thrombosis or embolism were not recognized in an early stage.

Conclusions: The reported thromboembolic ADRs are a known risk related to the use of CE, but may be misdiagnosed initially. From the reports that Lareb received it is evident that off-label use is frequent.

831. Bisphosphonate and Adverse Cardiovascular Events: Meta-Analysis of Randomized Placebo-Controlled Trials

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Background: Some animal experiments and randomized controlled trials in humans suggest that bisphosphonates may inhibit progression of atherosclerosis. Whether bisphosphonates reduce clinical cardiovascular (CV) events is not known.

Objectives: To evaluate the cardiovascular effects of bisphosphonate treatment.

Methods: We conducted a systematic search of MEDLINE and EMBASE, from inception to August 2013, without language restriction, to identify randomized placebo-controlled trials of bisphosphonates that had longer than 6-month duration and reported adverse CV events. Two independent reviewers screened papers and extracted data on any CV events, atrial fibrillation (AF), myocardial infarction (MI), stroke, and CV death. The effect of bisphosphonates was combined using the Mantel-Haenszel risk difference (RD) over 7-12 months, 13-24 months, and ≥25 months.

Results: Of 2,520 records, 34 records reported at least one type of CV events from 22,213 patients treated with bisphosphonate and 18,965 placebo patients (mean age: 63.8 years; female: 81.7%) in 31 trials. Per 1,000 patients treated for 7-12 months, bisphosphonate use may cause 21 excess any CV events (95% confidence interval: 2, 39), including 15 strokes (95% CI: 0, 30), and 8 CV deaths (95% CI: 0, 17). There was no clear link with AF (RD: 12; 95% CI: -5, 30) or MI (RD: 4; 95% CI: -6, 14). There was no statistically significant difference in CV events over 13-24 months or ≥25 months, except an excess of 5 cases of AF (95% CI: 2, 8) per 1,000 patients treated with zoledronic acid for ≥25 months.

Conclusions: We found no evidence of reduction in CV events with bisphosphonate treatment. A possible excess risk of stroke and CV deaths was observed in the first 7-12 months of treatment and AF among long-term users. These data warrant a large-scale surveillance study to better estimate possible risks.

832. Potential Signals for Cardiovascular-Related Adverse Events with COX Inhibitor Use: Analysis of the WHO Global ICSR Database System (VigiBase)

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Background: Recent meta-analyses of RCTs and observational studies have suggested a positive association between the use of Cox-2 inhibitors and the risk of myocardial infarction (MI). It remains unclear whether an early detection of signals for CV events would have been possible through the disproportionality analysis (DA) of spontaneous reporting databases (SRDs) such as the WHO Global ICSR Database System (VigiBase).

Objectives: To examine how soon the positive association between MI and Cox-2 inhibitors could have been detected in VigiBase.

Methods: We identified all ADR-drug combinations that contain the ATC code for coxibs (M01AHxx: celecoxib, etoricoxib, lumiracoxib, rofecoxib, valdecoxib, parecoxib). DA was performed for the 6 substances separately and the entire class (M01AH) against other NSAIDS (ATC code M01A). Reporting odd ratios (ROR) adjusted for sex and age (<41, 41-60, 61-80, >80) were calculated for MI which was performed sequentially for each year (1999-2013). A positive signal (PS) and a strong PS were defined as the absolute value of the standardised ROR >2 or >3 respectively.

Results: A total of 20,712,802 ADR-drug combinations with 83,877 MIs were found. Of the 484,792 reports that contained coxib substances, 21,044 had MI.