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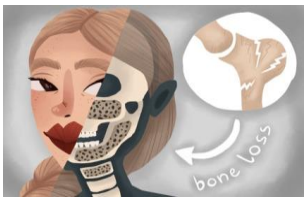
Combination of warfarin and aspirin. Warfarin and aspirin are widely used for the treatment or prevention of thromboembolic and atherosclerotic diseases. Indications for warfarin include stroke prevention in atrial fibrillation (AF) and the treatment/prevention of venous thromboembolism (VTE), while indications for aspirin include ischaemic heart disease, peripheral arterial disease and secondary prevention of stroke. Combination warfarin/aspirin use is limited to a number of therapeutic areas including acute coronary syndrome (ACS), recent percutaneous coronary intervention and patients with mechanical heart valves. Apart from these conditions, there is limited data to guide on deciding which patients should receive combination warfarin/aspirin. A US registry based cohort study assessed the frequency of warfarin/aspirin combination use in a community-based setting of patients anticoagulated for AF or VTE and compared the outcomes (bleeding and thrombosis) of patients receiving combination warfarin/aspirin with those receiving warfarin monotherapy ***(JAMA Intern Med doi:10.1001/jamainternmed.2018.7816)***. The study collected data from a cohort of adults who were enrolled in 6 anticoagulation clinics (from 1st January 2010 to 31st December 2017). The study included adults newly initiated on warfarin for AF or VTE (n=6539), without a history of a recent myocardial infarction (MI) (<6 months) or valve replacement. Patients receiving warfarin/aspirin combination and patients on warfarin monotherapy were propensity score matched based on patient demographics, anticoagulation indications, history of bleeding or thrombosis, medications, time in the therapeutic range and comorbidities. Outcomes for bleeding included any patient-reported bleeding, major bleeding, emergency department (ED) visits and hospitalisation for bleeding, while thrombotic outcomes included ischaemic strokes, transient ischaemic attack, VTE, ACS/MI, ED visits and hospitalisations for thrombosis. The study overall found that 37.5% of patients received combination warfarin/aspirin compared with 62.5% who received warfarin monotherapy. Data from the propensity score-matched groups (n=1844) found that **patients treated with combination warfarin/aspirin experienced significantly more overall bleeding compared with those receiving warfarin monotherapy** (cumulative incidence at 1 year: 26% [95% CI, 23.8% to 28.3%] versus 20.3% [95% CI, 18.3% to 22.3%) p<0.001); similarly the number of major bleeding events, ED visits and hospitalisations for bleeding was significantly higher for combination warfarin/aspirin than for warfarin monotherapy. **The rates of thrombosis were similar for both groups**; 2.3% of patients receiving combination warfarin/aspirin had a thrombotic event at 1 year compared with 2.7% of patients on warfarin monotherapy (p=0.40) and **mortality rates were similar for the 2 groups at 1 year**. The authors of the study conclude that combination warfarin/aspirin use in patients without recent ACS or a heart valve replacement is associated with an increased risk of bleeding however similar to other studies there was no observed benefit regarding thrombotic events. They advise that there is a need for greater awareness of the issue and for research to further determine those patients receiving warfarin for AF or VTE that would benefit from additional aspirin.

Keeping Medicines Safe. The European Medicines Agency recently launched a social media campaign (on Twitter and LinkedIn) to highlight how the EU medicines regulatory network works to keep medicines safe and effective (***www.ema.europa.eu/en/news/working-together-safe-medicines-eu)***. This occurs in various ways such as the pooling of resources for monitoring and analysing medicines safety information, the raising of safety standards and enabling patients to directly report adverse effects and to identify legally operating online pharmacies and retailers.



Medication-related osteonecrosis of the jaw (ONJ) is a rare but serious adverse event that has been reported in patients with osteoporosis and cancer who are treated with anti-resorptive (e.g. bisphosphonates or denosumab) and/or anti-angiogenic therapies (e.g. bevacizumab, sunitinib, aflibercept) ***(BMJ 2019;365:l1733)***. Patients with ONJ present with exposed jaw bone (mandible or maxilla), pain, swelling, pus, mucosal ulceration or erythema, loose teeth and altered sensation in the regional nerve distribution; the symptoms may be constant or cyclical and can affect eating, drinking, talking, and routine dental care. The pathogenesis of ONJ is unknown but likely to be multi-factorial; jaw bones have relatively high bone turnover and remodelling rates and are exposed to bacteria from the oral cavity through the oral mucosa or teeth. Anti-resorptive therapies reduce bone turnover by inhibiting osteoclast function, while anti-angiogenic therapies disrupt new blood vessel formation.

Risk factors for ONJ include **1) medication-related factors** – a higher risk is associated with patients treated for cancer (approximately 1%) than in those treated for osteoporosis (between 1 in 10,000 to 1 in 1,000), and a higher risk is associated with increased duration of anti-resorptive therapy (e.g. >4 years), **2) dental factors** – increased risk from dental surgery (e.g. tooth extraction, which is reported in up to 61% of patients with ONJ in studies), periodontal disease, trauma from poorly fitting dentures, **3) concomitant medications** – there is higher risk associated with dual therapy (anti-resorptive plus anti-angiogenic therapy) and an increased risk with corticosteroids and immunosuppressants (e.g. methotrexate, azathioprine), and **4) comorbidities** – increased risk in cancer patients with anaemia, diabetic patients and those with HIV infection.

Prevention of medication-related ONJ is the main management approach. Patients who are prescribed anti-resorptive and/or anti-angiogenic therapies should be informed of the small risk of developing ONJ, however they should not be discouraged from taking these effective medicines. They should be informed of measures to reduce the risk of ONJ which include 1) maintaining good oral hygiene, 2) having a nutritious diet, 3) reducing alcohol intake and 4) smoking cessation. **Patients should also be encouraged to attend for regular dental reviews** and to report any jaw symptoms. It is also strongly advised that patients (in particular those with cancer) should be referred to dental services for screening and remedial treatment before initiating these therapies. There is weak evidence that the risk of ONJ may be reduced by taking a "drug holiday". The authors refer to the American Association of Oral and Maxillofacial Surgeon guidelines which suggest that a 2 month drug-free period before invasive dental treatment for patients taking long-term (>4 years) oral bisphosphonates may be an option.

Treatment: patients with suspected medication-related ONJ should be referred promptly to dental or oral maxillofacial services in secondary care. The management is palliative and supportive to control infection, bone necrosis and pain; this includes dedicated oral hygiene regimens. Surgery may be required in severe cases, however there is a risk of exacerbating necrosis.

Osteoporosis in postmenopausal women guideline. Readers may be interested in a clinical practice guideline on the pharmacological management of osteoporosis in postmenopausal women that was recently published by the Endocrine Society ***(J Clin Endocrinol Metab 2019;104(5):1-28)***. It is available on https://www.endocrine.org/guidelines-and-clinical-practice/clinical-practice-guidelines/osteoporosis-in-postmenopausal-women

Every effort has been made to ensure that this information is correct and is prepared from the best available resources at our disposal at the time of issue. References are available on request. This ***newsletter is produced by the National Medicines Information Centre, St. James's Hospital (SJH) Dublin 8 and Dept of Therapeutics Trinity College, Trinity Centre, SJH.*** *Tel: Direct Line (01) 473 0589 or 1850 727 727 Email: nmic@stjames.ie @NationalNmic*