Interaction between clopidogrel and smoking

Dear Editor

General practitioners (GPs) should be aware of an important interaction between clopidogrel and smoking, the so-called 'smokers' paradox', which was not mentioned in the article by Jayasinghe et al, 'Dual antiplatelet therapy – management in general practice' (*AFP* October 2013).[1] The interaction is common and has important clinical implications.

There is now good evidence that smokers have an enhanced antiplatelet response to clopidogrel, whereas the drug is of little benefit to non-smokers.[2,3] A recent meta-analysis found that smokers taking clopidogrel had a 25% reduction in cardiovascular events and non-smokers had a modest 8% reduction.[2]

Like atorvastatin and omeprazole, cigarette smoking seems to induce the cytochrome P450 enzyme 1A2, increasing the availability of the active metabolite of clopidogrel. Smoking does not seem to significantly alter the efficacy of prasugrel or ticagrelor;[2] however, it does increase the risk of aspirin resistance.[3] As a result, smokers may get more effect from clopidogrel and less benefit from aspirin treatment than non-smokers. On the other hand, aspirin, prasugrel and ticagrelor may be better choices for non-smokers.[3] If clopidogrel is used in non-smokers, larger doses may need to be considered, although there is no evidence at present to support this.

Another clinically important issue is that smokers may have an increased risk of major bleeding from clopidogrel[2] and the drug should be used with caution in smokers at high risk of bleeding.

The message for GPs is that the patient's smoking status should now be taken into account when selecting an antiplatelet agent.[3] Antiplatelet medications should also be reviewed after a change in smoking status, for example, after quitting smoking or relapse.

Dr Colin Mendelsohn
Camperdown, NSW

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Reply

Dear Editor

We thank Dr Mendelsohn for his response regarding the relationship between clopidogrel and smoking. It is clear that these relationships are becoming more apparent as the evidence base expands. Our paper was mainly focusing on the pivotal trials and the guidelines published by the international and national peak bodies. However, smoking status is of relevance when deciding on the optimal antiplatelet regimen according to the emerging evidence base and we therefore agree with the points made by Dr Mendelsohn. Furthermore, we prescribe complete cessation of smoking for those patients presenting with acute coronary syndrome who are current smokers.

Professor Rohan Jayasinghe
Gold Coast, QLD

Hypovitaminosis D: criteria, complications, concerns

Dear Editor

Drs Lucas and Neale have commendably highlighted important dilemmas with respect to hypovitaminosis D and related problems:[1] first, defining hypovitaminosis D – the upper limit for blood vitamin D level, below which hypovitaminosis D is considered present; second, defining the safe upper limit for blood vitamin D level that would avoid potential overdosing and complications of hypervitaminosis D; and third, the need to screen and provide vitamin D supplements to populations that can scarcely afford screening tests let alone the cost of long-term supplements.

With respect to the definition of hypovitaminosis D, the Institute of Medicine (IOM), National Institute of Health has defined the optimal range of 25(OH)D as 20–50 ng/mL; anything <20 ng/mL is deemed inadequate for bone and overall health in healthy individuals.[2] But there is evidence from a recent meta-analysis that the IOM criterion for sufficiency may not be adequate for bone health.[3] The IOM's definition of 20 ng/mL is not acceptable and could potentially be dangerous to some. A study on vitamin D levels and mortality found that a 25(OH)D level of 30–49 ng/mL was associated with the lowest mortality, and a significant increase in risk above 50 ng/mL in women.[4] A study has found that serum 25(OH)D levels above 50–60 ng/mL should be avoided, as even lower serum levels (30–48 ng/mL) are associated with increases in all-cause mortality, greater risk of cancer at some sites such as the pancreas, greater risk of cardiovascular events and more falls and fractures among the elderly.[2] Consequently, it would be more advisable to adopt a 25(OH)D level below 30 ng/mL as hypovitaminosis D and a level above 50 ng/mL as potential hypervitaminosis D. Hypovitaminosis D is a major public health issue worldwide, especially in Asia, the Middle East and Africa where there prevalence is high. A program of sensible exposure to the sun coupled with change in dietary patterns, introduction of fortified food staples, dietary supplements and vitamin D supplementation are essential to promote health. The problem of funding such an undertaking needs the support of the World Health Organization, donor nations and wealthy altruistic individuals.

Professor Davendralingam Sinniah
Seremban, Malaysia

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Reply

Dear Editor

This is a valuable opportunity for further discussion of this important topic. Some older studies did suggest that higher 25(OH)D levels were required to avoid poor health outcomes. However, the most recent meta-analyses[1–3] do not support that vitamin D supplementation has a beneficial effect on health outcomes, including fracture prevention. This is in agreement with results of our own meta-analysis where only studies of vitamin D supplementation alone (not vitamin D with calcium, since calcium supplementation itself may decrease fracture risk) were included and there was careful consideration of study quality.[4]

It is worth reiterating the concern noted in our paper[5] about trying to define an adequate level of 25(OH)D on the basis of meta-analysis data that combine measurements from a range of different assays and generally combine results from quantiles of 25(OH)D that are inconsistently defined. Since the 2009 meta-analyses cited by Bischoff-Ferrari and Willett,[6] the more recent reviews[7,8] cited in our paper provide further support for a level of a 25(OH)D level of 50 nmol/L (20 ng/mL) or higher as denoting vitamin D adequacy, rather than the higher cut-off suggested by Professor Sinniah.

Increasingly, research studies are reporting the results of analyses where 25(OH)D has been assayed using an LC-MS/MS method. This method tends to give higher absolute numbers than many immunoassays, as was reported in our paper. Yet many past studies have examined health outcomes in relation to 25(OH)D assayed by immunoassay. It is possible that the old 50 (20) is the new 75 (30) in research studies – indeed, we have shown almost exactly this shift from assays in Australia.[9] We need to be mindful that most pathology laboratories are still using an immunoassay for vitamin D testing. Adopting <75 nmol/L (30 ng/mL) as measured by immunoassay as reflecting hypovitaminosis D may be equivalent to aiming for an LC-MS/MS measured 25(OH)D of 100 nmol/L (40 ng/mL) or more – and venturing into the realm of adverse effects if such levels are maintained long term.

In a very recent study, there was a U-shaped relationship between the pre-admission level of 25(OH)D level and risk of all-cause 90-day mortality: an approximate 2-fold increase in risk for <25 nmol/L (10 ng/mL) as well as for >175 nmol/L (70 ng/mL), compared with the 75–124.75 nmol/L (30–49.9 ng/mL) reference category.[10] Although the evidence suggests that levels 75–125 nmol/L (30–50 ng/mL) provide the lowest risk, several points are worth noting. First, it is unusual to see these very high 25(OH)D levels (>175 nmol/L [70 ng/mL]) within the normal population (with the study set in Boston), raising the possibility that pre-existing ill health had led to vitamin D supplementation, with the measured levels reflecting this prior treatment. Second, this was a retrospective analysis, with 25(OH)D assayed by three different methods across 18 years and no measure of inter-assay variability available. Finally, samples were taken 7–365 days prior to hospital admission – with the shorter time interval, patients were probably already ill; with the longer time interval there was presumably some health reason to test for vitamin D status, and possible follow-up with vitamin D supplementation.

On 15 April 2014, the Australian Bureau of Statistics released the 25(OH)D results (measured using a standardised LC-MS/MS assay) from the Australian Health Survey. Our challenge is how to interpret these in terms of vitamin D status (deficiency, insufficiency, adequacy), when the work defining those categories has arisen using older assays so that those definitions may not now be relevant. The consensus from the IOM report was that there was no well-defined health outcome against which to assess vitamin D adequacy, and that situation remains.

Professor Robyn Lucas
Canberra, ACT

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Is the evidence limited for the exchangeability of new oral anticoagulants and warfarin for the treatment of symptomatic venous thrombosis or pulmonary embolism?

Dear Editor

In their review,[1] David Brieger and Jenny Curnow report that the efficacy of rivaroxaban, apixaban and dabigatran is comparable to that of warfarin for treatment of deep venous thrombosis (DVT) and pulmonary emobolism (PE).

In *Table 3* of their paper the question of whether initial heparin was administered in the two EINSTEIN[2,3] and AMPLIFY[4] studies is answered with 'No'. This statement seems to be incorrect. In these three studies, participants in both study arms had been pretreated before randomisation with heparin, low molecular

weight heparin (LMWH) or fondaparinux:

- in the Oral Rivaroxaban for Symptomatic Venous Thromboembolism study[2] in 73% and 71%
- in the Oral Rivaroxaban for the Treatment of Symptomatic Pulmonary Embolism study[3] in 92.5% and 92.1%
- in the Oral Apixaban for the Treatment of Acute Venous Thromboembolism study[4] in 86.7% and 85.1%.

Subcutaneously administered LMWH reaches an earlier maximal plasma concentration (1–2 hours) than rivaroxaban (2–4 hours), apixaban (3 hours) or dabigatran (2–4 hours).[5]

Considering these data, there seems to be rather scanty evidence for the exchangeability of new oral anticoagulants and warfarin (with prior administration of heparin) for the treatment of symptomatic venous thrombosis or pulmonary embolism.

Michael Kochen
University of Goettingen, General Practice
Goettingen, Germany

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Dear Editor

We would like to thank the author for his comments on heparin use in venous thromboembolism (VTE) trials comparing new orally active anticoagulants (NOACs) to heparin and warfarin.

Our comments in *Table 3* of our article[1] regarding heparin use refer to an important difference in design of these clinical trials. The RECOVER 1 and RECOVER 2 studies utilising dabigatran were designed to include an initial period of parenteral anticoagulation for both VTE treatment groups; thus, the mean duration of parenteral anticoagulation prior to use of dabigatran was 10 days and 9.4 ± 3.8 days in these studies.[2,3] The single-agent approach to treatment of VTE has not been tested with dabigatran.

By contrast, the EINSTEIN and AMPLIFY studies, utilising rivaroxaban and apixaban, were deliberately designed to test the single-agent approach to VTE treatment. The designs of these studies did not include any therapy with parenteral anticoagulation after randomisation for patients receiving oral direct Xa inhibitors.[4–6] In order to allow time for patients to have the diagnosis of VTE confirmed followed by an appropriate informed consent process, it was necessary to allow some pre-randomisation treatment with standard parenteral anticoagulation, predominantly low molecular weight heparin (LMWH). This is entirely consistent with standard clinical practice pending confirmation of VTE diagnoses. Patients were ineligible for study enrolment if they received more than brief treatment with parenteral anticoagulants (36 hours for apixaban and 48 hours for rivaroxaban). In fact, the majority of patients received no more than 24 hours of treatment with parenteral anticoagulation before subsequent treatment with an oral direct Xa inhibitor.[4–6] It is highly unlikely that this transient heparin exposure would have a significant impact on study outcomes.

In contrast to warfarin, the NOACs have a rapid onset of action. Although the differences in time to peak plasma concentration with NOACs (2–4 hours), compared with LMWH (1–2 hours), may influence the choice of agent for first dose in life-threatening VTE, for the majority of patients with VTE, this minor difference may be offset by the ease of administration of an oral drug and the time saved by avoiding the need to obtain access to and learn to inject a parenteral anticoagulant.

With 6841 patients receiving either rivaroxaban or apixaban in the Phase III EINSTEIN and AMPLIFY studies, of whom 5075 patients received no more than 24 hours parenteral anticoagulation, there is considerable evidence that a single-agent approach to VTE management with oral direct Xa inhibitors is as efficacious as warfarin for patients who would have met inclusion criteria for these studies. Patients treated with thrombectomy, fibrinolytic therapy or inferior vena cava filters were notable exclusions, in addition to other selection criteria discussed in our article.

Jennifer Curnow and David Brieger
Concord Hospital
Sydney, NSW

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Letters to the Editor

Letters to the Editor can be submitted via:
Email: afp@racgp.org.au
Mail: The Editor, Australian Family Physician
100 Wellington Parade
East Melbourne VIC 3002 Australia