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PERSONALISED APPROACH TO ANTICOAGULATION

We were pleased to read of the integration of SIGN into Healthcare Improvement Scotland so as to take advantage of their health economic expertise.[1] The new team may wish to reflect on the review in the same journal issue of the use of direct oral anticoagulants (DOACs), formally known as NOACs, as an alternative to warfarin.[2] Though well researched in terms of the details on use of DOACs, there were a number of oversights. Dabigatran, like warfarin, is susceptible to interpersonal variation, something the makers failed to make public, leading to legal actions.[3,4] The reported non-inferiority of rivaroxaban rests on a study where the INR in the warfarin arm was measured using a device which was subsequently recalled by the FDA due to unreliability.[5] Prescribing DOACs costs the NHS around 25 times per patient more than warfarin and have not been shown to be substantially superior at stroke risk reduction. Indeed, well administered warfarin is superior. The enthusiasm for the new agents led to an increase of £100 million in NHS England expenditure in the year to November 2015. Even after allowing for the cost of routine INR surveillance, the cost of managing patients with DOACs is four times higher for no clear clinical gain. Furthermore, the new antidotes developed for DOACs' reversal cost between £2,500 and £5,000 per use, which is substantially more expensive compared to vitamin K injections to reverse a warfarin overdose.

The major oversight was the failure to reference the excellent European clinical trial (EU-PACT) of genotype-guided warfarin dosing[6] in the NICE 2014 guidelines. It has been known for 20 years that around 3% of the population carry two *CYP2C9* variants plus a variant in the vitamin K-related *VKORC1* which make them exquisitely sensitive to warfarin and more liable to overdose.[7–9] Around a third of the population have one or two of these variants, making the choice of warfarin a more finely balanced decision. Two-thirds of the population can be managed more effectively with warfarin, with much lower risk of overdose and the comfort of knowing that vitamin K is widely available as an antidote. For those who find the regular visits to the warfarin clinic problematic, self-monitoring with the Roche's CoaguCheck® device is now available and is essentially cost neutral. Many patients easily learn to move from monitoring with telephone guidance to self-management. The success of the EU-PACT trial was overshadowed by the failure of a similar US-based trial – COAG.[10] This trial failed to demonstrate a benefit due to the lack of point of care genotype testing device at the point of recruitment and, more importantly, failed to adequately allow for the fact that the dosing algorithm used was not effective for the substantial African American group involved in the study.

There is an opportunity for Scotland to adopt a 'multiple win' approach whereby the growing number of atrial fibrillation patients at risk of stroke are genotyped at referral or when they present with unstable INRs. This is a cheap and simple test easily developed in any genetic centre and is currently being developed by a number of companies for testing at or near the point of care. Those with three variants should use one of the DOACs not liable to interpersonal variation. Those with wild type for all three variants, who are of north European ancestry, should be offered warfarin as a first line with the option of self-monitoring. A publically available dosing algorithm, as used in the EU-PACT trial, allows rapid stabilisation on a maintenance dose rather than slow loading which leaves them at risk of a stroke for up to several weeks. People with one or two variants, or those of other ethnicities where the sensitivity genotypes are not fully understood, should be offered the option of slower loading warfarin plus the option of self-monitoring or use of a DOAC from the outset.

We are exploring the feasibility of this 'personalised' approach in Newcastle with other centres in development.

[1]J Burn, [2]H Sheth
[1]Professor of Clinical Genetics, [2]Research Fellow, Institute of Genetic Medicine, International Centre for Life, Newcastle University, Newcastle upon Tyne, NE1 3BZ, UK
Email john.burn@newcastle.ac.uk

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Author's reply

Professor John Burn and Dr Harsh Sheth raise important points for future consideration. In response, we would like to point out the following:

1. The idea behind our paper was to offer clinicians and especially primary care physicians a PRACTICAL guide to using NOACs, particularly as an increasing number of patients are expressing their preference for them. In addition, the recently published ESC guidelines also recommend the use of NOACs as first line in preference to warfarin in patients with NVAF, which is likely to increase the prescription further.
2. Our paper was not intended to be a cost-analysis/health economics paper and we did not make a reference to the economic impact of adopting NOAC/DOAC strategy
3. We did not advocate a wholesale adoption of the new agents instead of warfarin
4. The approach to genotype-based warfarin dosing trials appears to have potential for future research and we await with interest health economic analysis of its potential application in clinical practice

[1]S Bashir, [2]A Al-Mohammad, [3]S Gupta
[1]Cardiology Registrar, Castle Hill Hospital, Cottingham, UK; [2]Consultant Cardiologist and Honorary Senior Clinical Lecturer, Sheffield Teaching Hospitals NHS Foundation Trust, UK; [3]Consultant Cardiologist, York General Hospital, York, UK
Email shaza.khider@gmail.com

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FATAL HAEMORRHAGE FOLLOWING FNA

We read with interest and some concern the salutary case of fatal haemorrhage following fine needle aspiration (FNA) of a retrosternal thyroid lesion.[1] As mentioned by the authors, thyroid FNA is a widely performed procedure with a well-established safety record; the incidence of significant complications post thyroid FNA is extremely low. Serious bleeding, even in patients taking oral anticoagulants is unusual, although many radiologists will require cessation of oral anticoagulant medication prior to these procedures.

There is increasing evidence that ultrasound-guided core biopsy (USCB), a more invasive procedure, can also be safely used in thyroid nodule and parenchymal assessment, replacing FNA in some circumstances. Many thyroid lesions are highly vascularised and may contain sonographically visible arterial or venous vasculature. Using ultrasound guidance for needle biopsy should allow these to be avoided. On occasion the thyroid nodule under investigation may be low-lying in the neck or either partly or wholly contained within the superior mediastinum/retrosternal space – as was the case in the patient described.[1] Accessing retrosternal lesions from the neck sonographically for FNA/USCB is feasible but does raise potential issues.

The lesion may be difficult to fully visualise, intralesional vessels in particular may be less visible and it can be difficult to precisely determine the path of the biopsy needle due to angling of the needle away from the ultrasound beam. If a bleed occurs following needle biopsy of a thyroid lesion arising in the neck, this is usually rapidly obvious both clinically and on post-procedural check ultrasound. Pressure can be readily applied and the patient referred for urgent surgical assessment and airway protection if needed. A lesion which bleeds in the retrosternal region will not be apparent clinically until significant bleeding has occurred, there is no adjacent soft tissue to allow tamponade and perilesional bleeding may be difficult to visualise sonographically.

This case report is a timely reminder of the hazards that may be associated with needle biopsy of superior mediastinal lesions from the neck. I would suggest post-procedural management of this patient group should differ from that utilised for needle biopsy of thyroid lesions in the neck. Patients for biopsy of retrosternal, or low-lying, thyroid lesions from the neck should stop oral anticoagulants prior to the procedure; FNA should be the initial technique of choice rather than USCB due to the lower incidence of bleeding associated with FNAC; patients should be observed longer post-procedure than regular thyroid FNA patients, at least 30–45 min in the radiology department; all patients should have a post-procedural ultrasound to exclude significant bleeding prior to discharge, if the lesion is not well seen, or if there is clinical concern, then CT should be considered. Patients should be advised, as is mentioned in the paper, of the need to seek urgent medical help – this is likely to mean calling an ambulance, not the GP, if they experience breathing or swallowing difficulties when they get home.

[1]DC Howlett, [2]R Mortimer
[1]Consultant Radiologist, [2]FY2 ENT, Eastbourne District General Hospital, Eastbourne, East Sussex BN21 2UD
Email davidhowlett2@sky.com

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Author's reply

We are grateful to Professor Howlett for his comments. We were keen to share our experience so that other clinicians performing thyroid biopsy may be aware that although serious complications of thyroid biopsy are extremely rare, they can occur. Professor Howlett is absolutely correct to point out that biopsy of superior mediastinal masses, using a neck approach, is much more risky than a conventional neck biopsy. In our patient, the nodule was palpable in the midline of the neck and so the area biopsied was above the manubrium, but clearly the bleeding must have tracked down into the retrosternal space where it caused tracheal compression. No vessels were visualised by ultrasound during the procedure. The suggestions that Professor Howlett has made are very sensible and we would readily endorse them.

MWJ Strachan
Consultant in Diabetes and Endocrinology, Metabolic Unit, Western General Hospital, Edinburgh EH4 2XU

CORRECTION

In the paper entitled 'The Japanese Hospital in Broome, 1910–1926. A harmony of contrasts' by P Stride and A Louws, issue 2, 2015, pp 156–64, two of the doctors' names were incorrect, and are corrected below:

Tsukano Tojojiro

Masuyama Masayoshi

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