

**OPTIMAL DURATION OF ANTICOAGULATION IN IDIOPATHIC VENOUS THROMBOEMBOLISM SHOULD BE DETERMINED BY MULTIPLE VARIABLES**

I read with interest the article ‘What is the optimal duration for the management of patients with idiopathic deep venous thrombosis and pulmonary embolism?’ (TM Hyers, HG Shetty, IA Campbell. *J R Coll Physicians Edinb* 2010; 40:224–8) and would like to give some comments.

Firstly, I understand the authors’ views. The optimal duration of anticoagulation in this setting remains controversial due to several factors. Research studies were not perfect. Some included patients with both idiopathic venous thromboembolism (VTE) as well as secondary VTE. Some have small patient numbers. International normalised ratio (INR) control was different among studies. Some have a shorter anticoagulation duration comparison arm (e.g. three vs six months), while others have a longer duration comparison arm (three vs 27 months). The definitions of idiopathic VTE also vary from one study to another. Those variations in the study designs obviously could give varying results.

Secondly, even after idiopathic VTE diagnosis was made, we certainly do not know from the studies how many patients were subsequently screened for thrombophilia and how many actually had thrombophilia. From the studies, it was also unknown how many actually turned out to have occult malignancy on subsequent follow-ups. Population studies showed 4.4–7% of the Caucasian population carried heterozygous mutations for factor V Leiden, while 2% carried prothrombin gene mutations.<sup>1,2</sup> With this in mind, even in the absence of family history, 6.5–9% are expected to be positive for those mutations.

Recently, newly acquired thrombophilic risk factors such as JAK-2 mutation were discovered, which had not been taken into consideration in many idiopathic VTE studies.<sup>3,4</sup> Another important point is that occult cancers may present with idiopathic VTE several months before cancer diagnosis. In cohort series and population-based registries, subsequent cancer diagnoses were made in 7.3–17.1% of patients with idiopathic VTE.<sup>5,6</sup> If researchers who conducted the original randomised studies retrospectively look at their data now, I am certain that their figures will be different. Once patients are subsequently diagnosed with thrombophilia or cancers, the number of patients who were originally labelled as having idiopathic VTE will be down and this can certainly alter the numbers.

Thirdly, not all patients with idiopathic VTE carry the same VTE recurrence risk. Those with proximal deep vein thrombosis (DVT) carry a higher risk of recurrence compared with distal DVT. Presence of high D-dimer one month after the discontinuation of anticoagulants appears to have higher risk of recurrence than those with normal D-dimer. Male gender is associated with increased risk of

recurrence.<sup>7</sup> Patients with a first symptomatic idiopathic DVT have a higher risk of recurrence than those with a first symptomatic idiopathic isolated pulmonary embolism (PE).<sup>8</sup> Residual thrombus on follow-up ultrasonography may be associated with increased recurrence risk.

Fourthly, I agree with Dr Hyers’ statement that six months of anticoagulation seemed to offer little additional benefit compared with three months, whereas extended anticoagulation (e.g. 24 months) reduced the risk of recurrence during the period of anticoagulation and that the recurrent VTE rates begin to reach a plateau after two years of anticoagulation.<sup>9</sup>

Fifthly, the risk of recurrent VTE must be weighed against the risk of anticoagulant-associated bleeding. Major bleeding risk varies among various patient groups. Those with liver or renal diseases, alcohol abuse, age >75 years, uncontrolled hypertension, anaemia, excessive fall risk, prior stroke and concomitant thrombocytopenia appear to have a higher risk of bleeding than those without.<sup>7,10</sup>

Finally, the duration of anticoagulation in idiopathic VTE should be determined after carefully excluding thrombophilia, carefully determining the risk-versus-benefit ratio of bleeding risk versus reduction in VTE recurrence, and while watching out for occult malignancies. Factors such as age, sex, proximal versus distal DVT, D-dimer status, idiopathic DVT versus idiopathic isolated PE, residual thrombus, lifestyle, bleeding risk factors (co-morbidities), ease/compliance of INR monitoring and individual wishes have to be taken into account. I believe the anticoagulation management should be both evidence-based and individualised.

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## AN ALTERNATIVE VIEW OF CARDIAC RESYNCHRONISATION THERAPY

Especially in view of the fact that benefits of cardiac resynchronisation therapy (CRT) now appear to extend to patients who have symptoms belonging to the New York Heart Association (NYHA) Class I and II categories (in the presence of left ventricular ejection fraction of either <30% or <40%),<sup>1,2</sup> when taking stock of CRT, shortcomings of the procedure should be highlighted, as Cleland JG, Buga L, Ghosh J et al. have done in their recent paper (Applying evidence-based device care in cardiovascular patients: which patient with heart failure and what device? *J R Coll Physicians Edinb* 2010; 40:229–39). The opportunity should also be taken to focus on the apparently growing problem of device-related sepsis.

Over and above the fact that there has been limited success in the use of baseline variables to predict response,<sup>3,4</sup> the latter being characterised by a ‘continuous spectrum ranging from dramatic to disappointing’,<sup>4</sup> some failures of CRT are perceived to be attributable to suboptimal optimisation, although ‘both the technique and timing of optimization are contentious’.<sup>5</sup> Other unpredictable variables include an interruption of CRT (which occurred in 36% of 512 patients in one series) as a result of patients developing atrial tachyarrhythmias (18%), loss of left ventricular capture (10%), loss of right ventricular capture (2%), diaphragmatic stimulation (2%) and infection.<sup>6</sup>

Although in this study infection was documented as having a prevalence of 1%,<sup>6</sup> a more recent publication, dated January 2010, documented a 4.3% prevalence of infection of cardiac resynchronisation devices among 303 patients of a mean age of 70 years with a mean follow-up of 31 months.<sup>7</sup> In the same year data were published that showed that, in the US, the number of implantations of electronic devices had increased from 199,516 in 2004 to 222,940 in 2006 (representing a 12% increment), and that this had been paralleled by a 57% increment in device infections.

Also documented in that study was the observation that, in 2003, 8.9% of implanted electronic devices belonged to the CRT category and that, in 2006, this proportion had increased to 14.3%.<sup>8</sup>

Bearing in mind that ‘in the years after initial implantation, device replacement may be necessary’,<sup>9</sup> in some cases as a result of CRT interruption,<sup>6</sup> it is also worth noting that, in one study, complication rates (including infections) associated with replacements or upgrade procedures were highest (amounting to 18.7%; 95% confidence interval, 15.1–22.6) in patients who had an upgrade to or a revised CRT device.<sup>9</sup>

‘Optimal treatment of infected pacemaker and implantable defibrillator devices involves complete explantation of all hardware’,<sup>10</sup> and this should hold true also for CRT devices. The challenge, however, begins with determining the diagnosis because patients with device-related infections can present with a variety of manifestations, some of which appear to be atypical,<sup>11</sup> and the onset of symptoms of device-related infection can be as long as 2,920 days after device implantation or device change.<sup>12</sup> Device extraction is, itself, associated with some morbidity and fatality, evidenced in the US by 27 deaths attributable to device extraction during the period 2007–08,<sup>13</sup> hence the requirement for accreditation in the procedure.<sup>14</sup>

Accordingly, when asking patients to consent to CRT, it must be pointed out that device success is not predictable from baseline variables; that, in the event of device infection (the risk of which might, arguably, prevail for the entire duration of the patient’s remaining lifetime), a removal of the device will be necessary irrespective of its previous efficacy; and that device extraction is associated with some risk of morbidity and mortality.

Furthermore, especially in view of the likelihood that guidelines might be revised to include NYHA Class I and II as an indication for CRT, it should be part of good governance to document, prospectively, in a national database, all device-related complications so that, at any future date, there should never be an occasion to make the observation that ‘owing to underreporting the... database does not contain all adverse events’.<sup>13</sup>

Finally, given the fact that ‘with [the] surge of CIED (cardiac implantable electronic device) implants has come an increasing recognition of associated complications, of which infection is among the most important’,<sup>11</sup> device-related infection should feature in all assessment questionnaires based on CIEDs. The question of basing eligibility for CRT on the association of subnormal left ventricular ejection fraction (which does not necessarily equate with clinically overt cardiac failure)<sup>15</sup> and NYHA parameters (which have suboptimal specificity for heart failure)<sup>16</sup> is part of a different discussion, which need not concern us at this juncture.

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## CHURCHILL, MORAN AND THE STRUGGLE FOR SURVIVAL

Dr Wyn Beasley (Beasley AW. Churchill, Moran and the struggle for survival. *J R Coll Physicians Edinb* 2010; 40: 362–7) recounted the difficult problems of the medical care of Winston Churchill by Charles Wilson (Physician to St Mary's 1919–47, Dean 1920–45, knighted 1938, Baron Moran 1942, but to my knowledge never Professor) and Russell (later Lord) Brain.

However, when I discussed these problems two years ago,<sup>1</sup> I concentrated on the political consequences of his illnesses and those of his two successors, Attlee and Eden, as part of the overall issues raised in the last century about sick national leaders discussed by Lord Owen, a one-time physician before he became Foreign Secretary.<sup>2</sup>

Churchill's first stroke was in 1949 and he was told truthfully that it was a temporary impairment of the blood supply to his brain. He insisted that Moran and Brain conceal the diagnosis because he wanted to continue as Leader of the Opposition and fight the coming February 1950 general election, which he did in spite of a second stroke in January 1950. His third stroke was in May, but he went on to win the 1951 election.

His intimates found him forgetful and lacking tenacity, and Churchill had the insight to admit to 'a decline in mental and physical vigour', yet told his Conservative MPs: 'I would not stay if I found I was fading physically or mentally.' Even after his fifth and most severe stroke in 1953 he kept Eden from succeeding him until April 1955. Moran reminisced that his patient 'was hardly up to his job', and his family and friends pressed him to retire. Moran 'could have forced him to leave office, but did not because I held this was none of my business'. Churchill 'would feel that life was over when he resigned; it was my job as his doctor to postpone that day as long as I could'.

By contrast, when Eden's health was impaired, his physician Sir Horace (later Lord) Evans on 7 January 1957 called into consultation Thomas Hunt (my predecessor as senior physician and gastroenterologist at St Mary's) and Sir Gordon Gordon-Taylor. They agreed that Eden's 'health will no longer enable him to sustain the heavy burdens inseparable from the office of Prime Minister'. Eden resigned the next day.

The many doctors who have written about the major illnesses of world leaders concurred that the public are entitled to full disclosure of candidates' medical data. I agree. However, it is only fair to point out that all the *Standpoint* correspondents after my article disagreed with me, and when I sought the opinions of senior London physicians in private practice of the great and the good they too held that doctors had a duty of confidentiality to their distinguished patients and no duty to the political health of their country. I wonder if Dr Beasley knows of such problems in the Antipodes?

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### Author's reply

I am delighted that Dr JH Baron has entered the discussion generated by my paper on Churchill, Moran et al., because his definition of science: 'establish refutable hypothesis; test; publish' (Medical students and history of medicine. *J R Soc Med* 1996; 89:728) is one that I have quoted frequently over the 15 years since it was published.

In his latest letter he has traced Churchill's succession of strokes and his reluctance to retire in favour of Eden. This prompts me to offer a 'refutable hypothesis': was this reluctance due in part to a lingering concern about Eden's fitness for the job of prime minister? I listened once to each of the two men, in 1955. In April I heard Churchill deliver what was to be his last speech as prime minister – it was a masterly performance in which he even used his deafness as a weapon; a few weeks later Eden spoke on the corner of our High Street in Eltham during the course of the ensuing election campaign – he delivered Peter Sellers' 'election campaign speech' that afternoon, with all its lame rhetoric, years before Sellers recorded it!

The performance by an ailing Eden at Suez 1956 would tend to confirm my hypothesis that Britain 'traded down' when it gained him in place of the ailing Churchill.

Dr Wyn Beasley

### CIRCADIAN RHYTHM SLEEP DISORDERS

The disappointing thing about the recent case report 'A circadian rhythm sleep disorder: melatonin resets the biological clock' (Abbas A, Raju J, Milles J et al. *J R Coll Physicians Edinb* 40:311–3) is the large number of expensive investigations the patient underwent before the diagnosis was contemplated. Delayed sleep phase syndrome is common and the diagnosis should have been obvious on the history outlined in the opening two sentences of the case report. What abnormalities were being sought on the extensive endocrine investigations and brain magnetic resonance imaging is not clear. Once the diagnosis was suspected some totally unnecessary urinary melatonin metabolites (also probably very expensive) were ordered.

So far as treatment goes, melatonin in the evening was used. It is not clear whether the patient was advised to expose himself to bright light at a standardised time in the morning, but if he was not this was an error. Morning bright light is a much more powerful resetter of the body clock than melatonin as well as being essentially free.

The main messages of this case report are, in fact, that common sleep disorders are poorly understood by most physicians and that more attention needs to be given to proper history taking rather than knee-jerk recourse to multiple expensive investigations.

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### Authors' reply

Thank you for asking us to respond to Dr Simpson's interesting comments. As Dr Simpson points out most physicians, including us, have little experience in diagnosing and treating sleep disorders. We agree that an expert such as Dr Simpson may not have needed to investigate the case extensively. We referred to the American Academy of Sleep Medicine's *International classification of sleep disorders: diagnostic and coding manual*<sup>1</sup> to gain better understanding of the condition before investigating and treating our patient. It did suggest timed melatonin measurements. The cost of these assays was in the region of £100.

There have been reports of circadian sleep disturbances associated with lesions in the region of the suprachiasmatic nucleus and the hypothalamus.<sup>2–4</sup> Hence, in our view it was important to carry out a magnetic resonance imaging scan.

Dr Simpson highlights the lack of understanding of sleep disorders among clinicians. Presentation of our case locally and nationally generated considerable interest. We hope that your readership has gained greater awareness of sleep disorders from this case.

Dr John Milles  
Dr Sud Ramachandran

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