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The following editorial by Dr Jonathan Coates, a lawyer who specialises in medicolegal law, is the last in the series on the barriers to innovation in healthcare. Although the risk of litigation is cited as a stimulant for defensive medical practice and as an inhibitor of innovation in high-tort-risk countries such as the US, England and Australia, the underpinning data in this regard are not robust. Dr Coates’ consideration of the situation in New Zealand provides an interesting insight in this context, given that New Zealand has a no fault compensation system, which makes it very difficult for anyone to sue a doctor for a treatment injury. He quite appropriately identifies alternative drivers of defensive medical behaviour such as reputational risk and fear of complaint.

As an aside, comparisons of treatment injury rates between New Zealand and tort-rich countries are difficult given that the monopoly corporation that exists in New Zealand enables a comprehensive and inclusive data set. It is nevertheless of some concern that within a decade, that treatment injury will be the single highest category of costs to New Zealand’s accident compensation scheme.

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D. Gorman
IMJ Editor (Editorials)

EDITORIAL

The threat of litigation as a possible barrier to innovation

The suggestion that the threat of litigation against health professionals may present a barrier to innovation in health is not new. Headlines in the mainstream media such as ‘The fear of being sued is ruining modern medicine’ have been supported, at least in part, by research that has suggested that defensive medical practice is common among doctors.

But to what extent are such claims supported by the experience in New Zealand, where there are extremely limited rights to sue for medical malpractice? Conversely, can it be claimed that innovation in health flourishes in New Zealand because of the inability to sue?

The threat of litigation and defensive medicine

Defensive medicine occurs where a health professional practises in a manner that is different from their usual practice, or different from accepted good practice, in order to reduce or prevent complaints, criticism or malpractice liability. In one UK study, 78% of doctors reported practising defensive medicine. Defensive medicine can often involve over-prescription of treatment or diagnostic procedures with obvious impacts on scare medical resources.

Defensive medicine is claimed to be an ‘innovation inhibitor’ with doctors unwilling to try new techniques and methods because of the fear of being sued if things go wrong. There have been moves in the United Kingdom to legislate to encourage innovation and advancement in medicine without the threat of being sued – most notably Lord Saatchi’s unsuccessful Medical Innovation Bill and its more recent successor the Access to Medical Treatment (Innovation) Bill 2015. Regardless of how the more recent Bill progresses, it seems clear that there is considerable support for moves to address what many regard as the impediment of defensive medicine. Others note that the underlying cause, being the fear of litigation, can only be removed by removing any possibility of litigation.

That brings us to consider the New Zealand model; where the possibility of litigation has been removed.

New Zealand’s model

The right to sue in New Zealand for medical malpractice was given up in exchange for a comprehensive no-fault compensation scheme run by the Accident Compensation Corporation (ACC). The ACC was established in 1974. The effect is to provide compensation and other support through the ACC to people who suffer personal
injury, with the social contract being that victims of personal injury give up the right to sue. While there have been several amendments to the scheme, the key principles remain. This means that, in its current form, patients who suffer a ‘treatment injury’ look to the ACC for compensation. It is only in extremely rare situations that doctors, other health professionals and healthcare provider organisations can be sued.

Perhaps in part because of the lack of clinical negligence litigation, New Zealand’s complaints resolution process and competence assurance regime are well entrenched. The Health and Disability Commissioner receives and investigates complaints about the provision of health services and has been an active and high profile office for two decades. New Zealand’s Health Practitioners Competence Assurance Act 2003 established a clear framework for the regulators to investigate and act on concerns and notifications about health practitioners’ competence, conduct and health.

Despite the no-fault compensation model, New Zealand has not been immune to claims of defensive medicine. Defensive medicine in New Zealand has tended to be linked to doctors changing their usual practice to avoid a complaint, rather than to avoid litigation. Defensive medicine has been described as an undesirable outcome of the complaints process in New Zealand.

It has been argued in New Zealand that defensive medicine is driven less by externalised factors and more by internalised mechanisms, such as the notion of shame. There is some intuitive attraction in that; a health professional’s reputation is everything – and likely more important to the individual than whether an indemnity insurer needs to pay out significant sums to settle litigation. The claims of defensive medicine in New Zealand have provoked an equally strong response, including questioning the validity of some of the research.

Conclusion

There are a lot of positives about the New Zealand no-fault compensation model and the regulatory framework for health services. However, it cannot clearly be concluded that the lack of malpractice litigation, and therefore the removal of the ‘fear of being sued’, has created an innovation nirvana where new models of healthcare are flourishing. Some might argue that the ‘fear of being sued’ in New Zealand has been replaced by the ‘fear of being complained about’. However, while there may have been some historical validity to such claims, as health professionals get more confidence in the integrity of the complaints process and regulatory system, it would seem harder to blame such fears for stifling innovation.

The practical steps needed to encourage and incentivise innovation will be multifaceted. Certainly, New Zealand does not have all the answers. However, what can be learned from New Zealand is that the lack of malpractice litigation will not eliminate the suggestion of defensive medicine, and that it is not at all clear that the threat of litigation itself is an obvious and major impediment to innovation in health. It would appear to be much more complicated than that.

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J. Coates
NZ’s Health Sector Lawyers, Claro Law, Christchurch, New Zealand

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4 The current legislation is the Accident Compensation Act 2001.
Cardiac resynchronisation therapy in 2015: keeping up with the pace

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Key words
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Abstract
Despite improved understanding of the pathophysiology of heart failure (HF) and availability of better medical therapies, HF continues to grow as a cause of morbidity and mortality in Australia and worldwide. Over the past decade, cardiac resynchronisation therapy (CRT), or biventricular pacing, has been embraced as a powerful weapon against this growing epidemic. However, much has changed in our understanding of dyssynchrony in HF, and this has led to a change in guidelines to ensure more appropriate selection of CRT candidates to improve the ‘non-response’ rate. More data have also emerged about the use of CRT in atrial fibrillation and in pacemaker-dependent patients. There has also been a growing focus on multimodality imaging to guide patient selection and lead positioning. Exciting new lead technologies are also emerging, with the potential to improve CRT outcomes further.

Introduction

Dysynchrony in heart failure (HF)

As HF progresses, pathological remodelling of the heart results in cellular and interstitial changes that also adversely affect the conduction system. Electrical dyssynchrony causes mechanical dyssynchrony, which refers to differences in the timing of contraction between different myocardial regions. This occurs at multiple levels in the failing heart, particularly atrioventricular (AV), interventricular and intraventricular. Intraventricular dyssynchrony is often manifested by QRS prolongation and occurs in approximately one third of cardiomyopathy patients. A left bundle branch block (LBBB) is the most common disturbance.

The presence of an LBBB results in delayed activation of the lateral wall relative to the right ventricle and septum, leading to reduced mechano-energetic efficiency of the heart. This is similar to the effects of chronic right ventricular (RV) pacing, with a slow depolarisation wavefront propagating through the myocardium, rather than the Purkinje system. There are numerous adverse haemodynamic sequelae of LBBB, including abnormal septal motion causing decreased regional ejection fraction, redistribution of myocardial fibre strain with altered regional blood flow, diastolic dysfunction due to shortened left ventricular (LV) filling time, depressed dP/dt and worsening mitral regurgitation. Further, LBBB, as either a contributor to, or simply a surrogate marker of, progressive cardiac dysfunction, is associated with increased morbidity and mortality.

Cardiac resynchronisation therapy (CRT)

CRT aims to reverse the deleterious effects of LBBB, as the right and left ventricular pacing leads generate two ventricular activation wavefronts that move towards each other. The benefit of CRT lies in the effective fusion of these two depolarisation wavefronts, synchronising the walls of the LV (Fig. 1).

Since implantation of the first transvenous CRT system in 1998, numerous large randomised multicentre trials have demonstrated significant benefit of CRT in appropriately selected HF patients with respect to multiple end-points. These have included functional class, exercise capacity, hospitalisation, quality of life, and reverse remodelling with improvement in ejection fraction, and reduction in LV size and mitral regurgitation. Since the
Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) and Cardiac Resynchronization–Heart Failure (CARE-HF) trials, there has also been a reproducible demonstration of mortality benefit (Table 1).

**Patient selection**

**Current guidelines**

While CRT is ‘life-changing’ for some, an estimated one third of patients derive little or no benefit.\(^2^0\) Given the heterogeneity of the various studies, it has taken time to develop a better understanding of which patients are most likely to benefit to improve patient selection. This has led to a change in the recommendations for CRT since 2006, when this topic was last reviewed in this journal.\(^2^1\) At that time, the widely accepted Class I indication was ‘severe systolic dysfunction’ (LV ejection fraction less than 35%) in sinus rhythm (SR) with QRS duration of at least 120 ms, and moderate-severe HF symptoms (New York Heart Association (NYHA) Class III–IV) despite optimal medical therapy.

Increasing data have emerged regarding the critical importance of a LBBB pattern in deriving clinical benefit from CRT. Patients with right bundle branch block (RBBB) do not have a dyssynchrony pattern suitable for CRT (activation of their lateral wall is already early), and often have concomitant RV dysfunction, pulmonary hypertension and more extensive conduction disease conferring a worse prognosis. Patients with RBBB undergoing CRT have significantly lower rates of symptomatic and echocardiographic response, and a lower survival free from heart transplantation or ventricular assist device placement.\(^2^2\) A recent meta-analysis reinforced this lack of benefit of CRT in patients with either RBBB or non-specific intraventricular conduction delay.\(^2^3\) In the recently published Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy (MADIT-CRT) long-term follow up,\(^2^4\) there was even the suggestion that CRT without LBBB was associated with harm (adjusted hazard for all-cause mortality 1.57; 95% confidence interval (CI): 1.03–2.39).

While the lack of CRT benefit in narrow QRS width (<120 ms) is widely accepted, there has been increasing debate about its benefit in those with ‘intermediate QRS width’ (120–149 ms), who have less mechanical intraventricular dyssynchrony than those with QRS width >150 ms.\(^2^5\) In a large meta-analysis of 5813 patients, there was no statistically significant reduction in death and HF hospitalisation with CRT in this ‘intermediate QRS width’ group.\(^2^6\) Only those with QRS duration ≥150 ms now receive a Class IA indication in major society guideline statements\(^6\),\(^7\) (Fig. 2). Unfortunately, studies utilising various imaging modalities to assess dyssynchrony have been largely disappointing, and electrocardiogram (ECG) still remains the gold standard for this purpose.

Also now receiving a Class I indication for CRT are mildly symptomatic patients (NYHA Class II). The Resynchronization–Defibrillation for Ambulatory Heart Failure Trial (RAFT)\(^2^7\) was the first study to show a significant reduction in mortality in this group (hazard ratio (HR) 0.75; 95% CI: 0.62–0.91) in addition to reduced hospitalisation for HF. This was reinforced by MADIT-CRT,\(^2^8\),\(^2^9\) the largest CRT trial to date, of whom 85% of patients were NYHA II, with significant reductions seen
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<td>Double-blinded, parallel arm, 19 months CRT-on versus CRT-off</td>
<td>≤35%</td>
<td>III/IV</td>
<td>&lt;130†</td>
<td>CRT arm: reduced all-cause mortality and HF hospitalisation, but increased device- or implantation-related complications</td>
</tr>
</tbody>
</table>

†With echocardiographic evidence of dyssynchrony. ‡Previously symptomatic. 6-MWD, 6-min walk distance; CRT, cardiac resynchronisation therapy; CRT-D, CRT with defibrillator; ICD, implantable cardioverter defibrillator; LBBB, left bundle branch block; LVEF, left ventricular ejection fraction; LVEF, left ventricular end-systolic volume index; MR, mitral regurgitation; NYHA, New York Heart Association; OMT, optimal medical therapy; QOL, quality of life; RETHINOQ, Resynchronization Therapy in Normal QRS.
in all-cause mortality and non-fatal HF events again (particularly in those with QRS duration ≥150 ms and LBBB).

**Atrial fibrillation (AF) and CRT**

Atrial tachyarrhythmias remain common in the HF population and interfere with CRT response by two mechanisms. First, they worsen the course of HF in general, by reducing cardiac output through loss of atrial contribution, while rapid ventricular rates interfere with diastolic filling and can result in a tachycardia-mediated cardiomyopathy. Second, critical to the efficacy of CRT is that the ventricles are solely activated by biventricular (BiV) pacing, with conduction through the atrioventricular node (AVN) completely pre-empted. Conduction of atrial tachyarrhythmias to the ventricles results in dysynchronous activation in patients with underlying LBBB, while competition with BiV capture can lead to fusion or pseudo-fusion beats.

While there are no large randomised trials looking directly at CRT in the AF population, a large meta-analysis of 23 observational studies involving 7494 CRT recipients showed that AF was associated with an increased risk of non-response to CRT (34.5% vs 26.7%; pooled relative risk 1.32, \( P = 0.01 \)). AVN ablation (AVNA) significantly reduced the risk of clinical non-response and death in this population. In a systematic review of 768 AF patients undergoing CRT, Ganesan et al. demonstrated significant reductions in mortality and improvement in symptoms with AVNA compared with pharmacological therapy. In the CERTIFY study, AVNA proved superior to pharmacological rate control at maximising CRT benefit, with the rate control group having a higher total and cardiac mortality than both the SR and AVNA groups. Interestingly, there was no mortality difference between the SR group and those with AF and AVNA.

Presently, the AHA guidelines give a Class IIa recommendation for CRT in persistent AF patients who otherwise meet CRT criteria in whom AVNA or pharmacological rate control will allow ‘near 100% pacing’ with CRT. Particularly in AF patients with QRS width >150 ms who otherwise satisfy the criteria, CRT is still better than no CRT (just not as beneficial as for SR patients with QRS width >150 ms). Unfortunately, Medicare does not currently provide a rebate for CRT in AF patients, regardless of ejection fraction or QRS duration. The Australian prospective randomised Cardiac Resynchronisation Therapy and AV Nodal Ablation Trial in Atrial Fibrillation (CAAN-AF) is currently recruiting patients to assess further the role of AVNA in AF patients with broad QRS and severe systolic dysfunction.

**Pacemaker induced dyssynchrony and the role of CRT**

RV apical pacing for patients with symptomatic AV block creates dyssynchrony, with QRS prolongation similar to an LBBB morphology, and results in adverse ventricular remodelling. Importantly, LV systolic dysfunction is seen in up to 40% of these patients and is related to the percentage of RV pacing. The detrimental effects of RV pacing on LV systolic function is well documented, with increased AF, as well as HF hospitalisation and mortality. In the Dual Chamber and VVI Implantable Defibrillator (DAVID) trial of 506 HF patients with implantable cardioverter defibrillator (ICD), patients randomised to a backup mode (VVI-40) had significantly superior outcomes (mortality and hospitalisation) compared with those with a dual-chamber pacing mode (DDDR-70). Various strategies have been employed to minimise RV apical pacing. These have included bradycardia prevention, programming long AV delays to promote intrinsic conduction and alternate pacing sites, such as the high RV septum or His bundle.

While undoubtedly the most physiological site, His-bundle pacing (HBP) is more technically challenging. Sharma et al. recently reported an 80% success rate in achieving permanent HBP (without a mapping catheter or backup RV lead) using the Medtronic Select Secure active fixation lead delivered through a fixed-shaped catheter. The majority of patients in this study had >40% ventricular pacing, and HF hospitalisation was significantly reduced in the HBP group compared with the RV-paced group (2% vs 15%; \( P = 0.02 \)). Disappointingly, the randomised Protection of Left Ventricular Function During Right Ventricular Pacing
(PROTECT-PACE) study of 240 patients did not demonstrate any difference in ejection fraction drop between RV apical and high RV septal positions at 2 years. However, in recent years, CRT has emerged as a promising option in these patients.

The largest trial of its kind, Biventricular versus Right Ventricular Pacing in Heart Failure Patients with Atrioventricular Block (BLOCK-HF), randomised 918 patients with AV block (with a need for significant ventricular pacing), ejection fraction (EF) <50% and NYHA I–III to receive either RV pacing or CRT. The primary composite outcome (all-cause mortality or HF requiring intravenous therapy or >15% increase in the left ventricular end-systolic volume index) occurred in 55.6% of RV-paced patients, compared with 45.8% of BiV-paced patients (HR 0.74; 95% CI: 0.60–0.90). Certainly, there remains a paucity of data to support the practice of routinely implanting CRT for all patients with indications for a pacemaker. Most will not develop LV dysfunction or HF, and subjecting them to a longer procedure with increasing peri-procedural complications is inappropriate. However, in RV-paced patients who, during follow up, develop symptoms of HF and have a deteriorating EF should be upgraded to CRT to reduce hospitalisation, and improve symptoms and cardiac function. Current international guidelines (Fig. 3) advocate ‘up-front’ implantation of a CRT device in patients with severe pre-existing systolic dysfunction (EF <35%) who are likely to require significant RV pacing (>40% RV-paced was found to be predictive of adverse outcomes in a substudy of the DAVID trial). While there are no Australian guidelines for this, the results of BLOCK-HF suggest this practice should even be considered in those with milder degrees of systolic dysfunction.

**Role of multimodality imaging**

As stated, electrical dyssynchrony results in mechanical dyssynchrony, and multiple imaging modalities have been used to confirm its presence and determine the site of latest LV activation. Studies have shown that up to 50% of patients with a narrow QRS (<120 ms) have echocardiographic evidence of dyssynchrony, and multiple early single-centre studies (employing predominantly M-mode and tissue Doppler) were able to variably demonstrate reverse remodelling with CRT in these patients. This sparked considerable interest in expanding the existing CRT indications, which mandated a broad QRS. The larger Resynchronization Therapy in Normal QRS (RETHINQ) and Evaluation of CRT in Narrow QRS Patients With Mechanical Dyssynchrony (ESTEEM-CRT) multicentre studies soon cast doubt on this notion as they failed to show improvement in exercise capacity in narrow QRS patients with echocardiographic evidence of dyssynchrony. More recently, the multicentre EchoCRT randomised trial assessed patients with QRS width <130 ms and echocardiographic dyssynchrony (defined by tissue Doppler opposing-wall delay in peak systolic velocity >80 ms or speckle tracking radial strain delay in anteroseptal-to-posterior wall >130 ms). After following 809 patients for a mean 19.4 months, the study was stopped early due to increased mortality in the CRT arm (11.1% vs 6.4%). This reinforced the notion that current dyssynchrony indices (apart from the ECG) are ineffective at selecting narrow QRS patients for CRT, and may worsen outcomes in patients with narrow QRS. Accordingly, QRS width (with or without mechanical dyssynchrony) remains the key determinant of clinical response to CRT, and the only Class I indication.

While availability is currently limited in many Australian centres, cardiac MRI (CMR) enables the assessment of both dyssynchrony and scar burden in a single study. It has been well established that pacing in regions of scar, as detected by delayed enhancement MRI, predicts lack of response to CRT. Combined with numerous validated measures of dyssynchrony (cine MRI, myocardial tagging, strain imaging), CMR is gaining increasing attention due to its excellent tissue characterisation, high spatial resolution and reproducibility. Like multidetector cardiac computed tomography (CT), CMR also enables the assessment of cardiac venous anatomy.
In patients with significant scar who may exhibit less extensive venous anatomy, this may mean a minimally invasive surgical approach rather than a transvenous approach. Notably, delineation of the precise number and location of tributaries of the coronary sinus by CT minimises peri-procedural venography, and has been shown to shorten procedural times and limit contrast and radiation exposure.52

Looking towards the future, myocardial imaging has the potential to individualise CRT. It can confirm candidacy by demonstrating significant mechanical dyssynchrony in an otherwise borderline candidate on ECG criteria. It can also guide lead placement by targeting an appropriate vein adjacent to the latest activated region of myocardium and away from scar.

**CRT leads: optimal position and new technologies**

**Lead positioning**

Appropriate positioning of the LV lead is a key determinant of CRT success. In the absence of additional information regarding activation sequence, the lead should be positioned in the lateral or posterolateral walls, which are usually activated last and are furthest away from the RV lead. In a retrospective analysis of 457 CRT recipients, Dong et al. demonstrated greater improvement in NYHA class with lateral LV lead positions compared with anterior locations.53 anterior LV lead positions also have a significantly higher risk of ventricular arrhythmias than posterior or lateral positions.54 Basal or mid-ventricular LV lead positions are superior to apical locations. In an analysis of 799 patients in the MADIT-CRT study, apical LV lead position was associated with a significantly increased risk of HF (HR 1.72; 95% CI: 1.09–2.71) and death (HR 2.91; 95% CI: 1.42–5.97).55

The location of the RV lead is less important, and there is certainly no clinical benefit of non-apical RV lead locations (i.e. septum, RV outflow tract) compared with apical locations.56 There is also some evidence that a larger horizontal inter-lead distance (as measured on a lateral chest X-ray), which correlates with a longer LV lead electrical delay, can improve LV anatomic reverse remodelling post-CRT.57 The amount of QRS shortening post-CRT (DeltaQRS), which relates to both inter-lead distance and LV lead electrical delay, is a strong predictor of improved outcomes post-CRT. Molhoek et al. demonstrated that a DeltaQRS >10ms has a high sensitivity (73%) while a DeltaQRS >50ms has a high specificity (88%) for CRT response.58

Showing promise is the use of echocardiography to guide lead placement. Unlike tissue Doppler, speckle tracking radial strain can distinguish between active and passive motion (scar tethering) and is able to determine the site of latest contraction. The Targeted Left Ventricular Lead Placement to Guide Cardiac Resynchronization Therapy (TARGET) study,59 randomised 220 patients to either standard unguided CRT or LV lead positioning at the site of latest peak contraction with an amplitude of >10% to signify freedom from scar. The latter group had a greater response rate (70% vs 55%, P = 0.031) with respect to reverse remodelling, as well as lower all-cause mortality and hospitalisation.

However, significant variability in coronary venous anatomy exists between patients, and the ability to target directly LV lead position is a limitation of the transvenous route. In a large series investigating distribution of venous anatomy and its effects on LV lead targeting, Khan et al. demonstrated that limitations of coronary venous anatomy restrict LV lead placement to a single vein with little scope for site selection in almost half of all patients.60 In patients with multiple target veins, intraprocedural coronary venous electroanatomic mapping has been assessed as a means of guiding LV lead placement to the latest activated region free from phrenic nerve stimulation. In a recently published series, Rad et al. demonstrated that this latest activated region (region with an electrical delay >75% of total QRS duration) was more often located anterolaterally, rather than the empirically targeted inferolateral vein.28

**Epacrdial leads**

Direct surgical epicardial approach may overcome these limitations, and should be considered in non-responders due to suboptimal lead placement, and in those with high thresholds or intractable phrenic nerve stimulation. Previously only performed by thoracotomy (or sternotomy), newer techniques have emerged to limit surgical morbidity, including left lateral mini-thoracotomy, video-assisted thoracoscopy and the use of robotic technology. While long-term outcomes with respect to mortality and functional improvement are similar to the transvenous route, these patients often have longer in-hospital length of stay29 and higher perioperative complications, including renal failure and infection.27

**Emerging lead technologies**

Compared with isolated RV pacing, patients undergoing CRT with standard bipolar leads have higher rates of LV lead complications, including lead dislodgement (5.7%) and coronary sinus complications (2.0%).61 In addition to loss of capture related to these problems, some patients also require reoperation due to phrenic nerve stimulation or increased LV pacing thresholds without obvious
dislocation. New quadripolar leads have four independent electrodes, which enable programming of additional different vectors for LV pacing. This provides the operator greater flexibility, as they can programme different electrode configurations, rather than having to reposition an entire lead. Down the track, they are more likely to find a stable position with reasonable pacing thresholds while minimising phrenic nerve stimulation.46,62

Quadripolar leads also enable multipoint pacing, which provides greater flexibility for optimal pacing configurations. This technology (MultiPoint Pacing, St. Jude Medical) delivers two LV pulses per pacing cycle from a single quadrupolar lead. Early studies show some promise in further optimising haemodynamics, improving contractility with echocardiographic guidance63 and reducing the rate of CRT non-response.64

Newer leads are also now being designed to monitor haemodynamic parameters, which will hopefully enable device optimisation, guide LV lead positioning and aid in clinical management. Intracardiac impedance reflects LV volume changes well in animal models, and early studies involving Biotronik’s intracardiac impedance sensing technology have demonstrated good correlation with LV stroke volume.65 Sorin’s SonR system utilises a sensor embedded in the lead tip that detects cardiac muscle vibrations (peak endocardial acceleration signal system). In a recent randomised study, automatic optimisation of AV and ventricle-ventricular (VV) delays based on this system resulted in improved CRT response, with significant improvement in NYHA class.48

Device programming and follow up

Improving %BiV pacing: arrhythmia suppression

The greatest benefit is derived from CRT when it is used maximally. Hayes et al. demonstrated a 24% reduction in mortality in patients receiving above 98.5% BiV pacing, as compared with those receiving <95% BiV pacing.66 Incremental increases in mortality benefit are seen with an increasing percentage of BiV pacing. Atrial tachyarrhythmias, predominantly AF, are significant contributors to loss of pacing. Santini et al. demonstrated that even a small burden of atrial arrhythmia in CRT patients resulted in higher rates of death or HF hospitalisation.67 Aggressive suppression of atrial tachyarrhythmias (with antiarrhythmics, cardioversion as required, and/or catheter ablation) to maintain SR may be beneficial in ensuring AV synchrony and achieving a high %BiV pacing. Frequent premature ventricular contractions (PVC) also contribute to CRT non-response. Lakkarireddy et al. demonstrated significant improvements to LV function, size and NYHA class by ablating PVC foci in CRT non-responders with >10 000 PVC in a 24-h period.68

Improving %BiV pacing: pacing algorithms

While routine optimisation of AV delay is controversial, an inappropriately programmed long AV delay may result in loss of BiV pacing in many patients.69 Avoidance of right atrial pacing is preferred, because pacing the right atrial appendage delays left atrial activation, which may impair LV preload and worsen myocardial performance. This can be achieved by programming a VDD mode, rather than a DDD mode.70

A novel adaptive CRT algorithm (AdaptivCRT, Medtronic) in patients with SR and normal AV conduction is also showing great promise. This algorithm provides LV pacing synchronised to produce fusion with intrinsic RV activation (to minimise RV pacing), with dynamic optimisation of AV and VV delays. It has been shown to be safe and at least as effective as BiV pacing with echocardiographic optimisation,71 with the suggestion of better clinical outcomes in those with a higher percentage of LV pacing.72

Echocardiographic optimisation

The use of echocardiography to assess mechanical dyssynchrony and select patients for CRT has been disappointing. However, modern CRT devices enable programming of AV and VV delays, which can be optimised based on echocardiographic evaluation of haemodynamics. With respect to optimising AV delay, numerous Doppler echocardiographic parameters have been studied. These include LV outflow tract velocity integral (VTI), diastolic filling time and transmitral flow (EA VTI), with the latter correlating best with invasive measurements (LV dP/dmax).73 However, the SmartDelay Determined AV Optimization (SMART-AV) randomised trial of 980 patients demonstrated no clinical benefit of an echocardiography-optimised AV delay over a fixed empirical AV delay of 120 ms.74 While many of the landmark CRT trials incorporated some form of echocardiography-guided AV delay optimisation (based on small haemodynamic studies), long-term randomised data supporting this practice are lacking.

Several small studies of echocardiography-guided VV optimisation have demonstrated acute haemodynamic improvements compared with simultaneous BiV pacing. Bordachar et al. demonstrated that improvements in intraventricular dyssynchrony (using tissue Doppler) correlated with an increase in cardiac output, with simultaneous BiV pacing being the optimal setting in only 15% of patients.75 In a randomised study of 238 patients with
VV intervals adjusted to minimise septal to posterior wall delay, significantly more patients improved based on a clinical composite score; however, no significant differences were found with respect to exercise capacity, quality of life or HF event rate. Again, simultaneous BiV pacing was the optimal setting in only 18%. In addition to a paucity of consistent clinical data demonstrating clear benefit, echocardiographic optimisation of AV and VV delays is time-consuming and resource-intensive, and requires significant skill. However, it may be useful in CRT non-responders.

**Integrated teams and remote monitoring**

With the burden of hospital readmission rates for HF rapidly increasing, multidisciplinary clinics encompassing nurse practitioners, physiotherapists, social workers, dieticians, psychologists and specialists are being developed to deliver holistic, patient-centred care. A multidisciplinary approach, coupled with individualised CRT optimisation (incorporating echocardiography-guided adjustment in device settings and optimisation of medical therapy), led to significant improvements in LV function and reduction in adverse events in 75 CRT non-responders. A reason for CRT non-response was identified in most patients, and multidisciplinary recommendations led to a change in treatment in 74%.

Remote monitoring of CRT devices, with the regular transmission of important data such as atrial and ventricular arrhythmia burden, heart rate histograms, device safety issues and ‘%BiV-paced’, enables regular ‘contact’ with cardiologists and earlier optimisation of therapy.

In the Implant-based Multiparameter Telemonitoring of Patients with Heart Failure (IN-TIME) randomised trial of 716 patients, most of whom had CRT-D (CRT and defibrillator) devices, those receiving automatic, daily multi-parameter tele-monitoring had a significantly lower incidence of the primary end-point (combined all-cause mortality, hospitalisation, change in NYHA class and symptoms). This was largely driven by earlier recognition of suboptimal device function, detection of arrhythmias and patient interview prompted by remote monitoring findings. Early results from the Patient Related Determinants of ICD Remote Monitoring Utilization and Outcomes (PREDICT-RM) study, which analysed registry data from 37 742 patients with new ICD or CRT-D implants, demonstrated lower mortality (HR = 0.67; 95% CI: 0.64–0.7) and hospitalisation (HR = 0.81; 95% CI: 0.79–0.83) in those who used remote monitoring. Despite its many benefits, remote monitoring is currently underutilised in Australia.

**Conclusion**

CRT remains one of the key successes of the ‘device era’ of HF therapy. The past decade has given us a greater understanding about the importance of appropriate patient selection, correct lead positioning and device optimisation to ensure a high percentage of BiV pacing. With novel indications, new lead technologies, better remote monitoring tools and integrated multimodality imaging showing great promise, CRT remains an exciting and rapidly evolving field.

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Characterisation and therapeutic manipulation of the gut microbiome in inflammatory bowel disease

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Key words
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Abstract
Inflammatory bowel diseases are thought to develop as a result of dysregulation of the relationship that exists between the gut microbiota, host genetics and the immune system. The advent of culture-independent techniques has revolutionised the ability to characterise the role of the gut microbiota in health and disease based on the microbiota’s genetic make-up. Inflammatory bowel diseases are characterised by dysbiosis which is an imbalance between pro- and anti-inflammatory bacteria and a reduction in bacterial diversity. Emerging data suggest that it is not only the presence of the gut microbiota but the functional activity of the microbiota that appears to play an important role in health and disease. Current strategies to manipulate therapeutically the gut microbiota using dietary modification, prebiotics, probiotics, antibiotics and faecal microbiota transplantation aim to restore the balance to a state of normobiosis. However, the ability of such strategies to correct dysbiosis and thereby achieve therapeutic benefit is yet to be fully characterised.

Introduction
Characterisation of the intestinal microbiome
From culture to metagenomics
The gut microbiota is a complex ecological environment, with each human harbouring up to 100 trillion \((10^{14})\) bacteria. Man can be considered a ‘supra-organism’ – a composite of human and microbial genes (the microbiome). The microbiome is estimated to encode 100-fold more genes than the human genome, and is currently being characterised as part of the Human Intestinal Tract (MetaHit) project. Seventy percent of the gut microbiota has not been cultured by standard, culture-based techniques. Metagenomics, the study of microbiota using culture-independent techniques, has greatly propelled forward our understanding of the role of the gut microbiota in health and inflammatory bowel disease (IBD). Metagenomics has been enabled by the presence of the bacterial \(16S\) ribosomal \((r)RNA\) gene in all bacteria which has revolutionised bacterial taxonomy through the identification of both known and novel bacteria based on sequence similarity to previously identified bacteria.

Owing to the large inter-individual variation, the normal spectrum of gut microbiota composition in healthy individuals is still unknown. There appears to be a small number of bacterial genes shared among individuals, referred to as the ‘phylogenetic core’. Although the phylogenetic core describes what is commonly ‘present’ in the gut among individuals, it does not explain the role of these bacteria. There is increasing focus on the elements of the microbiome that represent a functional core, a ‘core microbiome’, at a gene expression and organismal lineage level, related to the products and effects of the microbiota. With more than 1000 humans sampled from three different continents, the metagenomics integrated gene catalogue is now numbered at almost 10 million genes with data demonstrating some country-specific gut microbial signatures.

Characterisation of the gut microbiota in IBD

Two main approaches have been used to characterise the gut microbiota in IBD. Characterisation of the
microbial community as a whole has been referred to as the ‘global description strategy’ and led to the concept of ‘dysbiosis’ which refers to an imbalance between beneficial and harmful bacteria. The alternative approach has focused on single specific microorganisms that are thought to be pathogenic and this has been referred to as the ‘candidate microorganism strategy’. Dysbiosis in IBD is characterised by an overall reduction in microbial diversity, reduced abundance of the phylum *Firmicutes*, including *Faecalibacterium prausnitzii* as well as concurrent increases in *Bacteroidetes*. Differences in the bacterial communities between Crohn disease and ulcerative colitis (UC) suggest that the microbiome plays a different role in the pathogenesis of these diseases.

The search for a single specific pathogen as per the ‘candidate microorganism strategy’ in Crohn disease has largely focused on two organisms, *Mycobacterium avium* subsp. *Paratuberculosis* (MAP) and *Escherichia coli*. MAP has been suggested due to the similarity of Johne disease in cattle caused by MAP and Crohn disease in humans. However, results of studies have been inconsistent. *Escherichia coli* is a commensal organism in the gut; however, adherent invasive *E. coli* (AIEC) is a pathogenic strain of *E. coli* which has developed virulence factors that allow it to adapt, survive and colonise intestinal mucosa in up to a third of those with ileal Crohn disease and also is associated with early post-operative Crohn disease recurrence. Other organisms have been implicated and research assessing non-bacterial members of the microbiome including fungi and viruses suggests that these organisms too may have a significant role in gastrointestinal disease.

There is an ongoing debate as to whether changes in the intestinal microbiota precede or follow the development of colitis in IBD. Early work in mice has shown altered microbiota and composition changes preceding the onset of colitis in interleukin 10 knockout mice, thus suggesting that dysbiosis may in fact precede the development of IBD.

**Functional analysis: metagenomics, metatranscriptomics, metaproteonomics and metabolomics**

Although phylogenetic analysis using 16S rRNA technology provides us with information on the specific microbiota present in a given microbial community, it does not explain the specific functional role of the bacteria. Functional analyses of the microbiota are a rapidly evolving area of investigation, comprising various ‘omics’ technologies that characterise microbial activity at the level of DNA (metagenomics); RNA (metatranscriptomics), protein expression (metaproteonomics) and metabolites (metabolomics).

**Metagenomics: DNA**

Metagenomic sequencing characterises the metabolic and physiologic potential of the microbiota based on detailed DNA information. It is able to help identify which genes are present and therefore provides an insight into the functional capability of the microbiome by virtue of gene expression. Next-generation sequencing technologies have enabled widespread analyses beyond the 16S rRNA gene to sequencing the whole-genome of microbial communities en masse referred to as ‘shotgun metagenomics’. However, despite providing extremely detailed information on the microbiome and its DNA, the main current limitation of next generation metagenomics is the inability to correlate directly isolated bacterial DNA with gene expression. This in part relates to the absence of matches in the worldwide databases of the human microbiome which are still in their infancy. Nonetheless, it is anticipated that with the current microbiome sequencing projects the composition of human gut metagenomes will fast approach a saturation point whereby the level of characterisation involved in their ‘profiling’ will extend beyond a select number of taxonomic marker genes, and include a much greater depth of functional complexity, including the approaches described below. The vast majority of recent studies of the gut microbiota are based on 16S sequencing with only limited studies utilising shotgun metagenomics. Initial studies comparing 16S rRNA sequencing with shotgun metagenomics in IBD patients have found that microbial genetic expression, particularly in relation to fundamental microbial metabolic pathways, are seen to be far more perturbed than shifts in the microbiota at the genus level. In particular in IBD, genes involved in amino acid biosynthesis and carbohydrate metabolism appear to be down-regulated relative to genes involved in nutrient uptake.

**Metatranscriptomics: RNA**

Metatranscriptomics seeks to characterise the gene expression patterns of the microbiome and is thereby used to determine the activity of genes present. Significant qualitative compositional differences in rRNA expression have been seen in Crohn disease patients compared with controls, with *Bacteroidetes* being the most active in contrast to *Actinobacteria* and *Firmicutes* which were transcriptionally inactive in Crohn disease patients. Although the metatranscriptome provides a functional analysis of gene expression, it relies on mRNA
stability which is extremely low in prokaryotes, thus limiting its use.17

**Metaproteonomics: proteins**

Metaproteonomics refers to the set of all expressed proteins in a cell, tissue or organism. The gut proteome is dynamic and subject to interactions between genes, environment and the microbiome. There is distinct fluctuation in the expression of proteins in response to health and disease, thus making them attractive biomarkers and potential targets for molecular therapeutics.11 Most commonly, mass spectrometry is the technique used, measuring the mass-to-charge ratio of charged particles. These proteins, peptides or metabolites are then separated according to this ratio. Patients with ileal Crohn disease have been found to have a different metaproteome to healthy controls, including a generalised depletion of many proteins, alterations in bacterial carbohydrate metabolism, bacterial–host interactions, as well as human host-secreted enzymes. However, Gram-negative bacterial outer membrane proteins have been found to have a higher representation in the ileal microbiota of those with Crohn disease compared with healthy controls.18 Taken together these data illustrate that the alteration in the metaproteome may be reflective of underlying dysbiosis. DNA sequence databases that are as well as human host-secreted enzymes. However, Gram-negative bacterial outer membrane proteins have been found to have a higher representation in the ileal microbiota of those with Crohn disease compared with healthy controls.18 Taken together these data illustrate that the alteration in the metaproteome may be reflective of underlying dysbiosis. DNA sequence databases that are being rapidly produced should serve to improve the interrogative potential of proteomic methods, ensuring that more of these types of analyses successfully result in the identification of the specific gene (and microbe [s]) encoding that particular protein.

**Metabolomics: metabolites**

Metabolomics refers to the quantification of metabolites present in cells or organisms that participate in the metabolic reactions required for growth and maintenance of normal function. It not only includes the metabolites of the gut microbiota but also metabolites ingested from the external environment. Metabolome wide association studies have recently been shown to have potential in linking metabolic phenotypes with disease risk19 just as genome-wide association studies have found associations between genotype and disease phenotypes.20 Significant interdependence of the mucosal metabolome and microbiome has been found in patients with Crohn disease by McHardy et al.; however, it is not entirely clear whether the microbiota may be the source of and/or dependent upon gut epithelial metabolites. Current evidence suggests that the microbiome and metabolome have bi-directional influence, with bacteria influencing metabolite composition and metabolites contributing to microbial community architecture.21

**Variation in microbiota throughout life**

It has been traditionally thought that from birth a newborn’s gut is sterile and that following birth there is a rapid colonisation of microbes from the mother and surrounding environment in the newborn’s gastrointestinal tract.22 Initially, the gut microbiota of infants are unstable and highly variable. Abrupt changes in taxonomic groups can be linked to illness, dietary change and antibiotic therapy.23,24 A number of maternal and environmental conditions surrounding the birth, including before, during and early after birth has additionally resulted in differences in the composition of the gut microbiota in children. These include the time and mode of delivery, diet, mother’s age, body mass index, smoking status, household milieu, socio-economic status, breastfeeding and mother’s antibiotic use.25 This early period in the development of the gut microbiota is thought to be crucial in determining subsequent health or disease including IBD and other conditions such as eczema and asthma.11 Over time the phylogenetic diversity of the infant’s microbiome increases gradually with changes in microbial community composition increasing along a steady gradient.23 By the age of 2 years, an infant’s microbiota is established and thought to remain relatively stable throughout the remainder of life.26 It is likely that a so-called phylogenetic core exists among healthy humans of heterogeneous populations and this core microbiota likely has a key structural and therefore functional role in maintaining the health of the host. In contrast, individuals with disease may have aberrant gut microbial patterns leading to an unhealthy state of dysbiosis.27

**Host–bacterial mutualism**

Man’s co-evolution with microbiota over time has led to a finely balanced relationship which is referred to as host–bacterial mutualism.28 The host influences or determines the make-up and activity of the microbiota and the microbiota influences or determines aspects of host immunity.3

**Host effects on the microbiota**

The genetics of the host have been shown in several studies to have an effect on the gut microbial composition. Analysis of faecal samples from children has shown a greater similarity in the faecal-associated microbiota of monozygotic twins versus dizygotic twins and similarly
Microbiota and its effect on host immunity

It is not only the host genotype that dictates the development of the immune system. From early after birth, the gut microbiota also impacts on the development of the host intestinal immune system. The signals generated by exposure to the microbiota, influence maturation of the gut-associated lymphoid tissues. Lymphoid follicles in the gut mature following multiple signals from Gram-negative bacteria including that of Gram-negative peptidoglycans. The microbiota has also been shown to generate signals that promote recruitment of immunoglobulin A-secreting plasma cells and T-cells to the gut mucosa. This facilitates crosstalk between dendritic cells (DCs) and gut epithelial cells, thereby regulating the intensity of B- and T-cell responses. In addition to intestinal immunity, there is likely a significant modulatory effect of the intestinal microbiome on systemic immunity. This research is still in its infancy; however, systemic antibody production and cytokine levels have been shown to be affected by the nature of the commensal gut microbiome.

Environmental influences on gut microbiota

Geography and lifestyle

The gut microbiome has been compared in multiple studies between people of different countries and/or different lifestyles. In European infants 6 weeks from birth, country of birth had greater influence than both delivery mode and feeding method on the faecal microbiota. The microbiome of 6-month only infants living in rural Malawi has been compared with children of the same age living in urban Finland. Significant differences were seen in the relative abundance and species diversity across the two groups. In a large worldwide metagenomic study of adults by Li et al. looking for country specific differences, Chinese and Danish cohorts could be readily distinguished from each other based on specific signatures associated with their respective gut microbiomes. In data from our own group, geography and ethnicity both appeared to play a significant role in the composition of bacteria among people with and without IBD.

Diet

The influence of diet on the gut microbiota is often confounded by variation in the genetic make-up of the host as well as other environmental exposures and geography. Nevertheless, there is accumulating evidence that long-term diet is a primary driver of gut microbiota composition and function as demonstrated by Wu et al. in a study of 98 American subjects. The microbiota of American subjects was found to be clustered into ‘enterotypes’ distinguished primarily by levels of Bacteroides and Prevotella. Bacteroides was associated with a typical ‘Western’ diet high in protein and animal fat whereas Prevotella was enriched in people with high-fibre and high-carbohydrate diets. As part of that study, 10 subjects were placed for 10 days on a high-fat/low-fibre or low-fat/high-fibre controlled diet. There were detectable changes in the microbiome composition within 24 h of initiating the dietary modification; however, these changes were small and overall the ‘enterotype’ identity remained stable during the 10-day study. Long-term diet was therefore found to have a far stronger influence on the microbiome than short-term diet. Epidemiologic trends suggest that the rising incidence of IBD in Asia correlates with an increasing consumption of a ‘western’ diet in the East. However, despite the likely impact of diet on the microbiota and IBD pathogenesis in Crohn disease, the only dietary therapy that has been shown definitively to induce remission has been exclusive enteral nutrition therapy, the efficacy of which has been largely limited to paediatric patients.

Numerous observational studies have attempted to identify specific dietary patterns that may contribute to the risk of IBD. There is some suggestion of increased risk of IBD among those who consume greater quantities of meat and fats, particularly polyunsaturated fatty acids and omega-6 fatty acids, and lower risk among people with diets high in fibre, vegetables and fruits. However, clinical studies to date investigating various dietary interventions have had multiple limitations including recall bias, lack of placebo control and insufficient molecular microbiologic correlation.
Manipulation of the gut microbiota

Just as diet has been shown to enrich and influence the microbiome significantly, pharmacological and other interventions have aimed to ameliorate dysbiosis associated with intestinal and non-intestinal diseases.

Probiotics

Probiotics involve the use of live microorganisms that are believed to provide health benefits when consumed. Probiotics mediate their effect through exclusion of pathogens, maintenance of epithelial barrier function and induction of adaptive immunity. Probiotics have demonstrated efficacy in both induction and maintenance of remission in UC as well as maintenance of remission in pouchitis. A number of strains has been included in studies including Lactobacillus spp, Bifidobacteria spp, E. coli Nissle 1917 and Saccharomyces boulardii; however, the best evidence for efficacy in UC has been found in a combination probiotic VSL #3 which comprises eight separate organisms: three Bifidobacteria, one Streptococcus and four Lactobacilli. Meta-analyses have also demonstrated that probiotics are effective for the prevention of Clostridium difficile infection. However, there is no proven benefit for the use of probiotics in patients with Crohn disease.

Prebiotics

Prebiotics are generally regarded as non-digestible food ingredients that are fermented by intestinal bacteria in a selective manner which promote changes in the gut ecosystem that benefit the host. However, it should be noted that the literature contains no formal consensus regarding the specific definition of prebiotics. Prebiotics include oligofructose and inulin which are polymers of fructose found naturally and have been shown to increase commensal anti-inflammatory faecal and mucosal Bifidobacteria and Faecalibacterium prausnitzii in healthy humans. Prebiotic fermentation results in the production of short-chain fatty acids such as butyrate which appears to enhance epithelial integrity and promote regulatory DC function in vitro. While the use of prebiotics such as fructo-oligosaccharides in animal models of colitis and in healthy human subjects has shown multiple benefits, there have been conflicting results in two recent randomised placebo-controlled trials of patients with Crohn disease.

Antibiotics

The use of antibiotics has a substantial impact on the microbiome. During short-term antibiotic use, gut bacteria respond early with a significant reduction in susceptible organisms, an overall reduction in diversity and an increased likelihood of colonisation by ‘presumptive’ naturally resistant bacteria. The microbiome responds by activating systems to avoid the antimicrobial effects of the drugs. Major metabolic changes occur rapidly which reduce capacity to transport and metabolise bile acid, cholesterol, hormones and vitamins. However, following completion of antibiotic therapy, microbial interactions improve significantly. The long-term data on the effect of a course of antibiotics on the human microbiome are limited; however, recent animal studies have shown that antibiotic exposure early in life induces lasting effects on the microbiome, which may alter body composition and play a role in the development of obesity. In Crohn disease, modification of the microbiota with long-term antibiotics has proven efficacy in treatment of perianal Crohn disease as well as prevention of post-operative recurrence. In contrast it has been shown that prior exposure to antibiotics early in childhood predisposes to the risk of developing Crohn disease but not UC later in life. The evidence for antibiotic use in UC is relatively lacking except for in patients with acute severe colitis or induction of remission of pouchitis.

Faecal microbiota transplantation

Faecal microbiota transplantation (FMT) is highly efficacious in patients with refractory C. difficile infection. There have been two recent randomised controlled trials which have evaluated FMT in UC with conflicting results. In the study by Moayyedi et al. there was only a modest benefit of weekly FMT over a period of 6 weeks for inducing remission compared with placebo (24 vs 5%); however, most of the benefit was seen in those patients who received FMT from one individual donor perhaps suggesting that microbial characteristics from the donor was a significant factor in its efficacy. In contrast, Rossen et al. were not able to show a significant difference in outcome between FMT recipients and placebo-treated patients; only 41% of patients overall in the per protocol analysis who received donor faeces achieved clinical and endoscopic remission, suggesting that the two infusion protocols used in the study were insufficient to alter the microbiota in the majority of patients. Despite FMT’s relative lack of efficacy in UC, Rossen et al. found that at baseline UC patients had a significantly lower abundance of members of Clostridium clusters IV, XIVa and XVIII and higher abundance of Bacteroidetes, Bacilli, Proteobacteria and Clostridium clusters IX and XI compared with healthy donors. In those patients with UC who responded to the FMT infusions, the microbiota similarity shifted from the UC patient genotype (similar to UC patients who were non-FMT
responders) at baseline to a microbiome which was similar to the healthy donors, suggesting that FMT may have the potential to correct dysbiosis in a proportion of patients with UC. There have been no randomised trials of FMT to date in Crohn disease.

**Conclusion**

The advent of new high-throughput DNA sequencing technologies as well as functional analysis has revolutionised the characterisation of the microbiome in health and IBD. The microbiome and its relationship with the host play a central role in the pathogenesis of both Crohn disease and UC. The huge datasets that have emerged over the past few years will continue to grow and be refined to further help us evaluate the interaction between the host, diet, environment and microbiota. Therapeutic manipulation of the microbiome with bacteria-specific targeted therapies will now continue to be a focus of future therapeutic trials in IBD, which were previously dominated by strategies targeting the immune system alone.

**References**


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Regional challenges: evaluation of a hepatitis outreach programme using transient elastography (FibroScan) in Victoria

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Key words
hepatitis C, hepatitis B, outreach programme, transient elastography, liver fibrosis, rural.

Abstract
Background: Evaluation of an outreach programme using a mobile transient elastography (TE) device (FibroScan) to improve liver disease assessment in different clinical settings.
Aims: To evaluate a programme of liver fibrosis assessment by TE and to compare fibrosis scores between different sites and patient groups.
Methods: Prospective cohort study. TE was conducted at a tertiary hospital and during outreach clinics in three different settings: community clinics, clinics for people who use drugs (PWUD) and regional clinics in rural Victoria. All patients referred for TE at the participating locations were eligible during the study period.
Results: A total of 200 of 623 patients was assessed and evaluated during outreach sessions (regional 100; PWUD 18; community 82). While the majority of patients in community centres were infected with hepatitis B (68%), most patients in regional clinics and in PWUD settings had hepatitis C virus (HCV) (81 and 100%, respectively). Significantly more patients assessed at regional clinics and PWUD settings presented with severe fibrosis (F3-F4, F4): regional clinics 39%; PWUD 31%; tertiary 11%; community 7%, (P<0.001). Multivariable logistic regression analysis revealed that older age, alcohol consumption, male sex, increased alanine transferase levels, HCV infection and importantly, evaluation at regional sites were independently associated with severe fibrosis.
Conclusions: A TE-based outreach programme allows for assessment of liver fibrosis in varied and regional populations. The finding that patients in regional settings and PWUD presented with more advanced fibrosis should prompt improvements in healthcare to improve access for these populations.

Introduction

Despite concerted efforts to increase screening and notifications for viral hepatitis in Australia, it is estimated that around 45% of 218 000 patients living with chronic hepatitis B virus (HBV) are unaware of their disease and 40 000–50 000 of 230 000 people infected with chronic hepatitis C virus (HCV), remain undiagnosed.1,2

Funding: This study was supported by a grant from the Royal Melbourne Hospital and The University of Melbourne Centre for Excellence in Rural Sexual Health (CERSH). The grant included purchase of the mobile FibroScan device used in the study.
Conflict of interest: None.
Follow-up and management of patients with chronic hepatitis is often insufficient. It is estimated that in 2013 only 10% of the patients eligible for HBV treatment received antiviral medication and a total of 2550 patients with chronic HCV was treated.1,2

In Australia, the majority of individuals with chronic HBV are either migrants, originating from high prevalence countries or Aboriginal and Torres Strait Islanders.3 The majority of people with HCV have a current or prior history of intravenous drug use (IDU).4 For these vulnerable populations, access to medical care can be limited due to current or previously experienced stigmatisation, cultural differences, language difficulties and low health literacy.5–8

No studies have specifically addressed the provision of hepatitis care for people living in rural, regional or remote regions of Victoria, although several authors have emphasised the need for improved hepatitis care in regional and remote settings in Australia.9–11

In recent years, transient elastography (TE) has become the preferred method for non-invasive fibrosis screening allowing for prompt, point of care assessment.12 Outreach programmes using a mobile FibroScan are successful, can be integrated in harm-reduction strategies and engage patients who might otherwise not be able to commit to medical care.13,14 In 2012, a physician-initiated project was launched in Victoria, with the aim to provide onsite fibrosis assessment and disease evaluation for patients with chronic liver disease (primarily viral hepatitis) attending tertiary and non-tertiary healthcare facilities including clinics located in rural and regional Victoria. The aim of this study was to describe the specific characteristics of the populations reached through the programme, to identify risk factors associated with worse outcomes and to define specific needs for further shaping the programme.

Methods

This study was approved via the Melbourne Health human research and ethics committee as a quality assurance project with number QA2015105. Commencing in 2012, a mobile device for TE was used (FibroScan402, Echosens, Paris, France) at hepatitis clinics held at a tertiary hospital, a community clinic, a health centre servicing people who use drugs (PWUD) and at four regional clinic locations.

Using a standardised case report form, demographic (age, sex, region of origin), epidemiological (cause of liver disease, history of drug use, self-reported increased alcohol intake (not quantified)) and clinical information (height, weight, laboratory parameters including alanine transferase (ALT), results of TE) were collected during the clinical sessions. The database was censored on 31 May 2014, and patients with a complete set of data were included in the current analysis.

Results for median stiffness were used to categorise the level of fibrosis based on a published scoring system.15,16 For patients with underlying chronic hepatitis C: median stiffness 0–7 kPa (F0–1), median stiffness 7–9.5 kPa (F1–F2), median stiffness >9.5–14.5 kPa (F3–F4), median stiffness >14.5 (F4). For patients with chronic hepatitis B: median stiffness 0–7.3 (F0–F1), median stiffness 7.3–11 (F2–F3), median stiffness 11–18 (F3–F4), median stiffness >18 (F4). ALT levels were categorised as more than twice the upper limit of normal (UN) (>112 U/L) and less than 2× UN (<112 U/L).

To estimate the impact of age on the degree of liver fibrosis, age groups were defined based on age quartiles calculated for the entire population: age group 1: <33.7 years; age group 2: 33.7–<44.47 years; age group 3: 44.7–<53.94 years; age group 4: 53.94–84 years.

Data analysis was performed using Stata SE, v12. Due to non-normal distribution and the presence of outliers, continuous numerical variables (age, body mass index, median stiffness) were compared using either two-tailed Wilcoxon rank tests or Kruskal–Wallis tests. Depending on the sample size, categorical data were compared using either Fisher’s exact t test or Chi-squared test.

Results

Distinct populations are reached at different clinical sites

During the study period, a total of 680 patients was assessed for liver fibrosis using TE. Complete data collection was available for 623 patients and these were included in the analysis (Table 1).

The majority of patients (423 (68%)) were seen at a tertiary hospital; 254 (40%) of these were male and the median age was 45 years. Most were of either Asian or Australian origin (121 (28.6%) and 180 (43%), respectively) and were referred for evaluation of chronic hepatitis B (214, 51%) or for assessment of chronic hepatitis C 175 (41%).

Eighty-two patients were evaluated in urban community clinics, most of them were male (59 (72%)) and slightly younger (median age of 38 years). They were mostly of either Asian or African origin (45 (55%) and 20 (24%), respectively). The majority of these patients were referred for assessment of chronic hepatitis B infection (56 (68%)) (Table 1).

Of the 18 patients assessed at a health centre for PWUD, 11 (61.1%) were male, the median age was 39 years. Half of these patients were Australians and one
### Table 1 Population characteristics

<table>
<thead>
<tr>
<th></th>
<th>Total n (%)</th>
<th>Tertiary hospital n (%)</th>
<th>Community n (%)</th>
<th>PWUD n (%)</th>
<th>Regional clinic n (%)</th>
<th>P†</th>
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</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>623</td>
<td>423</td>
<td>82</td>
<td>18</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>Sex male</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td>0.191</td>
</tr>
<tr>
<td></td>
<td>390 (62.6%)</td>
<td>254 (60.1%)</td>
<td>59 (72.0%)</td>
<td>11 (61.1%)</td>
<td>66 (66.0%)</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>44</td>
<td>34</td>
<td>53</td>
<td>16</td>
<td>84</td>
<td></td>
</tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.259‡</td>
</tr>
<tr>
<td></td>
<td>24</td>
<td>21.6</td>
<td>27.5</td>
<td>16</td>
<td>52</td>
<td></td>
</tr>
<tr>
<td>Region of origin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asia</td>
<td>238 (38.2%)</td>
<td>180 (42.5%)</td>
<td>45 (54.9%)</td>
<td>6 (33.3%)</td>
<td>7 (7.0%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Australia</td>
<td>207 (33.2%)</td>
<td>121 (28.6%)</td>
<td>8 (9.8%)</td>
<td>9 (5.0%)</td>
<td>70 (70.0%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Africa</td>
<td>51 (8.2%)</td>
<td>28 (6.6%)</td>
<td>20 (24.4%)</td>
<td>1 (5.6%)</td>
<td>2 (2.0%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Europe</td>
<td>33 (5.3%)</td>
<td>27 (6.4%)</td>
<td>2 (2.4%)</td>
<td>2 (1.1%)</td>
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<td>America</td>
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<td>0</td>
<td>1 (1.0%)</td>
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<td>Unknown</td>
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<td>65 (15.4%)</td>
<td>7 (8.5%)</td>
<td>0</td>
<td>19 (19.0%)</td>
<td>0.065</td>
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<tr>
<td>Cause of hepatitis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>HBV</td>
<td>279 (44.8%)</td>
<td>214 (50.6%)</td>
<td>56 (68.3%)</td>
<td>0</td>
<td>9 (9.0%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HCV</td>
<td>285 (45.8%)</td>
<td>175 (41.4%)</td>
<td>16 (19.5%)</td>
<td>13 (71.2%)</td>
<td>81 (81.0%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HBV+ HCV</td>
<td>13 (2.1%)</td>
<td>8 (1.9%)</td>
<td>3 (3.7%)</td>
<td>0</td>
<td>2 (2.0%)</td>
<td>0.692</td>
</tr>
<tr>
<td>HIV (+HCV+ HBV)</td>
<td>27 (4.3%)</td>
<td>21 (5.0%)</td>
<td>1 (1.2%)</td>
<td>5 (27.8%)</td>
<td>0</td>
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</tr>
<tr>
<td>Alcohol</td>
<td>3 (0.5%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>3 (3.0%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Other</td>
<td>16 (2.6%)</td>
<td>5 (1.2%)</td>
<td>6 (7.3%)</td>
<td>0</td>
<td>5 (5.0%)</td>
<td>0.005</td>
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<td>Risk behaviour</td>
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<tr>
<td>IDU ever</td>
<td>169 (27.1%)</td>
<td>106 (25.06%)</td>
<td>9 (11.0%)</td>
<td>15 (83.3%)</td>
<td>39 (39.00%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Alcohol</td>
<td>81 (13.0%)</td>
<td>39 (9.2%)</td>
<td>6 (7.3%)</td>
<td>5 (27.8%)</td>
<td>31 (31.00%)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

†Comparing tertiary hospital, community, PWUD and remote clinics. §Kruskal–Wallis test. BMI, body mass index; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IDU, intravenous drug use; PWUD, people who use drugs.
third originated from Asia (9 (50%) and 6 (33%), respectively. Hepatitis C was the predominant cause for referral (13 (71%)); of note five (28%) were co-infected with human immunodeficiency virus (Table 1).

Of the 100 patients screened at regional clinics, 66 were male. They were older than patients in the other three settings (median age 47 years). The majority of these patients were of Australian origin (69 patients, including 15 individuals who identified as indigenous) and chronic hepatitis C was the predominant cause for liver disease (81 patients).

Compared with the two other non-PWUD-locations, more patients reported a history of IDU (39) and increased alcohol consumption (31) (Table 1).

**Higher median liver stiffness in patients with chronic hepatitis C and in patients evaluated at regional clinics**

Results of TE showed a wide range (2.5–72 kPa) with a median of 5.7 kPa for the entire population (Fig. 1A). Patients seen at the tertiary hospital and in community clinics had significantly lower levels of liver stiffness (median 5.6 and 5.3 kPa, respectively) compared with patients assessed at the PWUD centre or at regional clinics (median 6.2 and 6 kPa, respectively, $P < 0.001$, Fig. 1A).

Levels of median stiffness were lower in patients with chronic hepatitis B compared with patients not infected with HBV (median 5.3 vs 6.3 kPa, $P < 0.001$). No significant differences were observed when comparing HBV-infected patients assessed at different clinic locations (Kruskal–Wallis analysis of variance, $P = 0.696$) (Fig. 1B).

Levels of liver stiffness were higher in HCV-infected individuals, compared with patients not infected with HCV (median 6.4 vs median 5.3 kPa, $P < 0.001$) with highest values found in patients evaluated at regional clinics (8.6 vs 6.3 kPa, Mann–Whitney test $P < 0.001$) (Fig. 1C).

For the 564 patients infected with either hepatitis B or hepatitis C (HBV $n = 279$ and HCV $n = 285$) disease-specific levels of fibrosis were calculated based on TE results (Fig. 2). Of all patients included in this analysis, 88 (15.6%) were diagnosed with severe fibrosis (F3–F4) and 41 (7.3%) of these were cirrhotic. This proportion was markedly higher in the population evaluated at regional clinics: in 35 patients (38.9%) TE results were compatible with fibrosis levels of F3–F4, and 19 (21.11%) were cirrhotic (Fig. 2A).

![Figure 1](image_url) Transient elastography results (median stiffness in kilopascal) by location and cause of hepatitis. (A) Median stiffness for combined causes of underlying liver disease. All patients: tertiary patients evaluated at a tertiary hospital; community patients assessed at community clinics; PWUD patients examined at PWUD healthcare centre; regional patients examined at regional clinic location. (B) Patients mono-infected with hepatitis B. (C) Patients mono-infected with hepatitis C. * indicates median stiffness HBV (median 5.3 kPa) versus non-HBV (median 6.4 kPa): $P < 0.0001$ (Mann–Whitney test), median stiffness HCV (median: 6.4 kPa) versus non-HCV (median: 5.3 kPa): $P < 0.0001$ (Mann–Whitney test), median stiffness HCV (median: 6.4 kPa) versus HBV (median: 5.3 kPa): $P < 0.0001$ (Mann–Whitney test). ** indicates median stiffness HCV remote clinic (median 8.6 kPa) versus HCV non-remote clinic (median 6.3 kPa): $P = 0.0002$ (Mann–Whitney test).
Advanced fibrosis was rare among the patients infected with hepatitis B. Only a minority of 14 (5%) patients had TE results compatible with severe fibrosis; overt cirrhosis was found in four individuals (2.2%) (Fig. 2B); most patients had TE results compatible with no or only minimal liver fibrosis (F0–1: 241 individual (86.4%)).

In contrast, a significant proportion of 26% (74 individuals) of all patients infected with HCV showed signs of advanced fibrosis (F3–4, F4) (Fig. 2B), and 35 (12.3%) had TE results compatible with cirrhosis (Fig. 3C). This finding was most pronounced at regional clinic locations: 35 (43.2%) showed advanced liver fibrosis, and 19 of these (23.5%) had TE results compatible with cirrhosis.

**Distinct populations are infected with hepatitis B or hepatitis C**

In our study, people infected with chronic hepatitis C were significantly older compared with patients infected with chronic hepatitis B (median age 49 vs 39 years), results for median stiffness were higher (6.4 vs 5.3 kPa), alcohol consumption was more frequent (23.5 vs 2.5%)...
and a large proportion had a prior or current history of IDU (53.3 vs 0.7%, Table 2). Levels of ALT were significantly higher in HCV-infected patients and a larger proportion had ALT levels of more than 2× UN (Table 2), compatible with more inflammatory activity and potentially more inflammation-related liver injury in this group.

It has previously been shown that levels of fibrosis increase with age and our data were compatible with this observation (Fig. 3A). Although patients infected with HCV were markedly older than patients infected with HBV, this age difference did not fully explain the more severe fibrosis stage in HCV-infected patients. Age-stratified comparison of TE results revealed persistently increased levels of liver stiffness in HCV-infected individuals compared with HBV-infected patients of the same age group (Fig. 3B).

**Higher probability of cirrhosis in older patients, in male patients and in patients with chronic hepatitis C**

Overall, 91 of 623 (14.1%) patients assessed in this study had advanced liver fibrosis or cirrhosis (F3–F4, F4) (Fig. 2).

A multivariate logistic regression model revealed that for patients infected with HCV, age, increased alcohol consumption, ALT levels of >2× UN and screening at outreach clinics were associated with higher odds ratio (OR) for advanced liver fibrosis (Table 3).

Relevant fibrosis was rare among HBV-infected individuals. Multivariate logistic regression identified age as the only factor independently associated with increased OR for relevant fibrosis in this population.

**Discussion**

We demonstrate the feasibility of assessing liver fibrosis in distinct populations with chronic liver disease through an outreach programme using a mobile TE device.

Patients reached by this programme differed from the population seen at a tertiary hospital. The majority of people assessed in urban community healthcare settings had a migration background and a relevant proportion of patients reached at regional clinic locations had a history of drug use. Consistent with previous epidemiological findings, the underlying liver disease was largely determined by ethnic background or prior risk behaviour. Marked differences in levels of fibrosis were seen between clinical sites and underlying cause of liver disease.
Most advanced fibrosis was found at regional clinics, where patients were older and a higher proportion was infected with HCV. It has been demonstrated that both age and duration of disease contribute to progression liver fibrosis,17,18 and in our study, older patients had more advanced fibrosis. There was a significant age difference of 10 years between patients with HBV and HCV and the observed higher levels of median stiffness in HCV-infected patients might be age related. However, higher levels of median stiffness persisted in the age-stratified comparison of HCV- and HBV-infected individuals (Fig. 3B).

Despite the age difference between HCV- and HBV-infected patients, it is unlikely that longer disease duration would account for the increased levels of fibrosis observed in the HCV population. In our study, most HBV-infected patients originated from high-endemic countries and therefore presumably acquired HBV in early childhood. In contrast, large proportions of HCV-infected patients had a history of drug use and were likely infected with HCV during adult life. Thus, infection with HBV is likely to occur 15–20 years earlier than infection with HCV, suggesting overall shorter disease duration for HCV-infected individuals despite their older age.

Interestingly, a recent report comparing large cohorts of HCV- and HBV-infected patients found higher liver-associated hospital morbidity for HCV-infected patients, possibly reflecting a higher proportion of advanced liver fibrosis/cirrhosis in the HCV group.19 These results suggest that while age is a driver of fibrosis progression, additional factors, either disease-specific liver injury or individual characteristics and risk behaviour, must promote the accelerated fibrosis progression in HCV-infected patients.20

In our study, HCV-infected patients had significantly higher levels of ALT, compatible with more active inflammation. Elevated ALT levels can increase TE results and lead to an overestimation of fibrosis.21 In our study, multivariate analysis identified increased ALT levels as independent risk factor for relevant fibrosis in HCV-infected patients, and it is therefore possible that fibrosis levels were overestimated in some individuals.

ALT flares are not a common feature of chronic HCV and it is likely that additional factors such as increased alcohol intake are the cause of increased inflammation observed in the HCV population.

In addition to the discussed biological variables such as age, causative agent (HCV), increased ALT and ongoing liver injury due to alcohol, we found that assessment at outreach clinics was also independently associated with increased OR for advanced fibrosis. It is plausible that limited access to healthcare services, delayed specialist referral and evaluation only at an advanced stage account for this finding. Consistent with this interpretation, patients with chronic HCV, seen at a tertiary centre, had much milder fibrosis, a concerning observation, as patients with more advanced disease and higher risk for complication are more likely to benefit from tertiary care. Although

### Table 3 Risk factors for advanced fibrosis (F3–F4)

<table>
<thead>
<tr>
<th>Risk factors for advanced fibrosis in HCV-infected patients</th>
<th>Univariable</th>
<th></th>
<th></th>
<th>Multivariable</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>OR</td>
<td>CI</td>
<td>P</td>
<td>OR</td>
<td>CI</td>
<td>P</td>
</tr>
<tr>
<td>Male sex</td>
<td>2.058</td>
<td>[1.13–3.74]</td>
<td>0.018</td>
<td>1.446</td>
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<td>0.296</td>
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<td>1.842</td>
<td>[1.38–2.45]</td>
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<td>2.340</td>
<td>[1.64–3.33]</td>
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</tr>
<tr>
<td>Outreach†</td>
<td>2.557</td>
<td>[1.49–4.39]</td>
<td>0.001</td>
<td>2.743</td>
<td>[1.45–5.159]</td>
<td>0.002</td>
</tr>
<tr>
<td>BMI &gt; 25 kg/m²</td>
<td>1.400</td>
<td>[0.81–2.41]</td>
<td>0.230</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALT &gt; 2UN (U/L)</td>
<td>4.114</td>
<td>[2.25–7.52]</td>
<td>&lt;0.001</td>
<td>5.095</td>
<td>[2.43–10.64]</td>
<td>&lt;0.001</td>
</tr>
<tr>
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<td>3.831</td>
<td>[2.13–6.88]</td>
<td>&lt;0.001</td>
<td>2.844</td>
<td>[1.46–5.54]</td>
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<tr>
<td>Prior or current IDU</td>
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<td>[0.42–1.22]</td>
<td>0.227</td>
<td></td>
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</table>

<table>
<thead>
<tr>
<th>Risk factors for advanced fibrosis in HBV-infected patients</th>
<th>Univariable</th>
<th></th>
<th></th>
<th>Multivariable</th>
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</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR</td>
<td>CI</td>
<td>P</td>
<td>OR</td>
<td>CI</td>
<td>P</td>
</tr>
<tr>
<td>Male sex</td>
<td>4.743</td>
<td>[1.04–21.61]</td>
<td>0.044</td>
<td>4.145</td>
<td>[0.85–19.62]</td>
<td>0.073</td>
</tr>
<tr>
<td>Outreach†</td>
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<td>[0.24–3.30]</td>
<td>0.865</td>
<td>1.091</td>
<td>[0.27–4.33]</td>
<td>0.902</td>
</tr>
<tr>
<td>BMI &gt; 25 kg/m²</td>
<td>2.636</td>
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<td>0.109</td>
<td></td>
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<tr>
<td>ALT &gt; 2UN (U/L)</td>
<td>4.741</td>
<td>[0.92–24.38]</td>
<td>0.063</td>
<td>4.795</td>
<td>[0.75–30.85]</td>
<td>0.99</td>
</tr>
<tr>
<td>Alcohol yes</td>
<td>3.321</td>
<td>[0.37–29.64]</td>
<td>0.283</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

†Outreach: patients not assessed at tertiary hospital. ALT, alanine transferase; BMI, body mass index; CI, confidence interval; HCV, hepatitis C virus; IDU, intravenous drug use; OR, odds ratio.
Overt cirrhosis was rare in the entire population, 26% of all HCV-infected people had TE results compatible with advanced fibrosis/cirrhosis (F3–4, F4). This finding is important and should impact disease management. In an era when effective treatment may only be available to a limited number of patients, treatment access should be prioritised for those with more advanced disease and it is important to identify populations at risk.

The study was limited by being conducted in one Australian State and results may not be generalisable. Smoking status was not recorded, alcohol consumption was not evaluated quantitatively and patients were not routinely fasted prior to scanning. The programme represents a resource intensive approach to improving hepatitis care and might not be applicable in other settings. However, this audit illustrates that even in a well-functioning healthcare system gaps in care have been identified and should lead to improvements in care for neglected patient groups.

No data on disease duration were collected and therefore the impact of disease duration on fibrosis progression remains speculative. Also, no information on prior care was available, although for most of the patients seen in regional settings and at PWUD clinics the current assessment was their first (personal communication J. Sasa-deusz). Treatment data were scarce, and no statement can be made as to whether treatment might have influenced the observed fibrosis levels in this study. We cannot comment on the long-term impact of this outreach strategy on disease management and it remains unclear whether disease evaluation resulted in a higher rate of treatment uptake. Although PWUD represent the largest group of people affected by chronic hepatitis C, only a small group of people was evaluated at the PWUD clinic, reflecting remaining challenges to reach this patient group.

**Conclusion**

Overall, we have shown that an outreach programme using a mobile TE device improves access to evaluation of liver fibrosis in affected populations who might otherwise not be reached. The finding that patients seen at regional clinics presented with more advanced disease should reinforce attempts to further improve access to care for these individuals.

**References**


Baseline abnormal liver function tests are more important than age in the development of isoniazid-induced hepatotoxicity for patients receiving preventive therapy for latent tuberculosis infection

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Key words
latent tuberculosis, isoniazid, drug-induced liver injury, patient compliance, rifampicin.

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Abstract

Background: One of the cornerstones of Australia’s public health programmes to eliminate tuberculosis (TB) is the identification and treatment of latent tuberculosis infection (LTBI).

Aims: The main aim of this study is to determine the demographics, compliance, completion rates and adverse events of patients on preventive therapy (PT) for LTBI at our institution. The secondary aim is to determine the rates of isoniazid (INH) hepatotoxicity and identify any contributory factors.

Methods: The method used was an audit using medical records of 100 consecutive patients (2010–2014) treated with PT for LTBI.

Results: Seventy-two patients with confirmed LTBI started 9 months of INH and 22 started 4 months of rifampicin (RIF). The median age was 30 years. Half the patients were born in high TB-prevalence countries. Fifty-six per cent were contacts of index cases with confirmed TB, and 26% were pre-immunosupression. Seventy-seven per cent completed PT with adequate compliance. Thirty-three per cent on INH and 23% on RIF experienced some liver function test (LFT) abnormality while on treatment. INH was ceased in 3% due to asymptomatic hepatic dysfunction (transaminases >5x upper limit of normal). No patients had permanent liver damage. Significant risk factors for liver dysfunction during PT were risk factors for liver disease ($\chi^2 = 8.7; P = 0.03$) or abnormal pre-therapy LFT ($\chi^2 = 22.4; P < 0.001$). No patients developed active TB.

Conclusion: The completion rate of 77% and rate of INH-induced hepatic dysfunction of 3% is comparable with the literature. We found no age association with the risk of INH-induced hepatic dysfunction; however, there was a significant and linear association with the degree of liver function abnormality during INH therapy and the presence of abnormal baseline LFT. Routine LFT monitoring allowed early cessation of INH in those with significant but asymptomatic hepatitis who did not meet criteria for ATS/CDC LFT monitoring.
Introduction

Australia has a low incidence of tuberculosis (TB) with the majority of cases of active disease occurring due to reactivation of latent infection, most commonly acquired in high prevalence countries.\(^1\) One of the cornerstones of public health programmes to eliminate TB is the identification and treatment of latent tuberculosis infection (LTBI).\(^2\) Isoniazid (INH) preventive therapy (PT) has been used for many decades with its effectiveness a function of both duration of treatment and adherence. The optimal duration of therapy has been determined to be 9 months for immuno-competent adults, which provides a protective efficacy of up to a maximum of 90% against reactivation of TB.\(^3\) There is a wide range of estimates in the literature relating to completion rates of INH therapy. These range from 19 to 96% with higher compliance rates seen with 6 months of treatment.\(^4\)

INH-induced liver injury is idiosyncratic, independent of the presence of symptoms and is a diagnosis of exclusion.\(^5\) Historically, the incidence of INH-induced asymptomatic hepatitis has been reported in up to 10% of patients and overt hepatitis in 1%.\(^2,5\) The incidence is generally reported to be age-related, with those older than 35 years at increased risk.\(^6\) However, the lack of specific diagnostic criteria complicates comparisons across studies. The current American Thoracic Society/Centers for Disease Control and Prevention (ATS/CDC) recommendations are that routine blood testing of LFT is indicated only if baseline transaminases are abnormal or if the patient is at risk of hepatic disease, defined as having the human-immunodeficiency virus, chronic liver disease, being pregnant or postpartum, excessive alcohol consumption or an active intravenous drug user.

At our institution, PT is dispensed monthly by the TB clinic, free of charge to patients, and usually comprises 9 months of INH therapy. Patients greater than 30 years of age have baseline and then monthly blood tests looking for hepatotoxicity. Patients 16–30 years of age have baseline LFT testing; however, further monitoring is at the discretion of the clinician. All patients have clinical reviews at 3-month intervals after commencement of therapy. Patients are educated as to the side-effect profile of INH, isigns of hepatotoxicity (anorexia, nausea, vomiting and jaundice) and peripheral neuropathy in particular, and are instructed to contact the clinic if these symptoms occur.

Aims

The primary aim of this audit was to evaluate the demographics, compliance, completion rates and adverse events of patients on PT for LTBI. Secondly, we wanted to determine the rates of INH hepatotoxicity and to identify any contributory factors.

Methods

A retrospective audit was undertaken of 100 consecutive patients who commenced PT for LTBI at our institution from 15 July 2010 to 10 December 2013. The ethics was submitted but deemed not necessary by the committee. Patients were identified sequentially from the database kept in the chest clinic. Their medical records and pathology results were subsequently analysed.

At our institution, children less than 5 years of age who are deemed close TB contacts are offered INH whilst waiting for their second tuberculin skin test (TST), 10 weeks after the break of contact. If their second TST is negative, therapy is ceased at this time. During the study period, five children were commenced on INH and then ceased due to a second negative TST. As these children did not have LTBI, they were excluded from further analysis.

A 77-year-old female born in Greece had a negative TST and an initial positive QuantiFERON-TB Gold (QFT-G) prior to tumour necrosis factor (TNF)-alpha blockade. A decision was made to start INH therapy. Her QFT-G batch was subsequently recalled with the repeat test being negative. Therapy was stopped after 89 days of treatment. The patient experienced no adverse events. As she did not have LTBI, she was excluded from further analysis.

INH-induced hepatotoxicity was defined in this study as:

1. the presence of symptoms of hepatitis and laboratory evidence of hepatic dysfunction with aminotransferase (alanine aminotransferase (ALT) or aspartate aminotransferase (AST)) elevation greater than three times the upper limit of normal (ULN) with or without bilirubin elevation or
2. asymptomatic aminotransferase elevation greater than five times ULN with or without bilirubin elevation.

Statistical analysis

Statistical analysis calculations were carried out using IBM SPSS Statistics Version 22.0 (IBM, Armonk, NY, USA). Non-parametric analysis was undertaken. The Pearson chi-test was used to identify any demographic contributors to those who ceased therapy early, had any adverse event (grade 1–4 side-effect) or developed either mild or significant liver function test (LFT) abnormalities.
All $P < 0.05$ values were considered statistically significant.

**Results**

During the period of the audit, a prospective randomised controlled trial assessing the efficacy of 4 months rifampicin (RIF) therapy versus 9 months INH therapy was being conducted. Of the 94 patients commenced on PT for LTBI, 72 (77%) were started on INH and 22 (23%) on RIF (Fig. 1).

The clinical characteristics of the patients are shown below in Table 1. Of the 24 patients commencing PT prior to immunosuppression, 13 were pre-TNF-alpha therapy, seven were pre-solid-organ transplantation, two had systemic lupus erythematosus nephritis and two were pre-chemotherapy.

Patients who were commenced on therapy prior to immunosuppression were older (median 50 years; range 22–80 years) than those commenced for being close contacts (28 years; 3–69 years) or for other indications (27 years; 2–57 years) ($P < 0.001$; independent samples median test).

Of the 94 patients started on PT for LTBI, 88 met the appropriate TST criteria for LTBI for their indication (Table 2). Five patients did not have a TST performed as they had already tested positive for QFT-G. There were six discordant results (all TST+/QFT-G-).

Seventy-two (77%) patients completed therapy with adequate compliance, finishing 9 months of INH therapy within 10 or 4 months of RIF-therapy within 5 months of their start date. Twenty patients stopped prematurely (17 on INH, 3 on RIF) with two transferring to another service (Table 3). Those that stopped did so at a median of 95 days (7–221 days) after commencing therapy.

Patients taking INH were statistically no more likely than those taking RIF to cease prematurely ($\chi^2 = 1.5; P = 0.2$). However, the point estimate of early cessation

---

**Table 1 Clinical characteristics of patients**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>42 (45)</td>
</tr>
<tr>
<td>Female</td>
<td>52 (55)</td>
</tr>
<tr>
<td>Age at commencement of treatment</td>
<td></td>
</tr>
<tr>
<td>Age &gt;16 years</td>
<td>12 (13)</td>
</tr>
<tr>
<td>Age 16–35 years</td>
<td>44 (47)</td>
</tr>
<tr>
<td>Age &gt;35 years</td>
<td>38 (40)</td>
</tr>
<tr>
<td>Country of birth</td>
<td></td>
</tr>
<tr>
<td>High prevalence for TB†</td>
<td>50 (53)</td>
</tr>
<tr>
<td>Low prevalence for TB</td>
<td>18 (19)</td>
</tr>
<tr>
<td>Australia</td>
<td>26 (28)</td>
</tr>
<tr>
<td>BCG vaccination status</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>56 (60)</td>
</tr>
<tr>
<td>No</td>
<td>28 (30)</td>
</tr>
<tr>
<td>Unsure</td>
<td>10 (10)</td>
</tr>
<tr>
<td>Chest radiograph</td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>82 (87)</td>
</tr>
<tr>
<td>Apical thickening or granuloma</td>
<td>9 (10)</td>
</tr>
<tr>
<td>Abnormality unrelated to TB</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Indication for treatment</td>
<td></td>
</tr>
<tr>
<td>Healthcare worker</td>
<td>11 (12)</td>
</tr>
<tr>
<td>Pre-immunosuppression</td>
<td>24 (26)</td>
</tr>
<tr>
<td>Close contacts</td>
<td>53 (56)</td>
</tr>
<tr>
<td>Australian defence force</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Other</td>
<td>3 (3)</td>
</tr>
</tbody>
</table>

†Countries with an incidence of greater than or equal to 40 cases per 100 000 persons (WHO Global Tuberculosis Control Report 2013). TB, tuberculosis.
was higher in the INH group compared with the RIF group (22 vs 8%; \(P = 0.08\)).

Twenty-nine patients (24 of 72 (33%) on INH and 5 of 22 (23%) on RIF) experienced some LFT abnormality on treatment, with the peak occurring at a median of 3 months (0–8 months) after commencement of PT (Table 4). No patients experienced symptomatic INH-induced hepatotoxicity.

Significant risk factors for having LFT abnormalities while on INH included having a pre-existing risk factor for liver disease (\(\chi^2 = 8.7; P = 0.03\)) and having any LFT abnormality prior to commencing therapy (\(\chi^2 = 22.4; P < 0.001\)). In addition, both of these had statistically significant linear associations, with the degree of liver function abnormality increasing with the presence of baseline abnormal LFT (linear-by-linear association chi square test; \(\chi^2 = 22.2; P < 0.001\)) and risk factors for liver disease (\(\chi^2 = 3.8; P = 0.05\)). Regarding the risk of LFT abnormality during PT, there was no association with gender or concurrent hepatotoxic medications. Age was not associated with either any or major LFT abnormalities.

Two of the 19 patients who ceased INH prematurely did so due to INH-induced hepatotoxicity with the only significant risk factor being the presence of any baseline LFT abnormality (\(\chi^2 = 15.6; P < 0.001\)). There was no association with elevated transaminases (AST/ALT) at baseline and significant INH-induced hepatotoxicity (\(\chi^2 = 0.2; P = 0.7\)). No patients experienced RIF-induced hepatotoxicity.

Of the 24 cases with abnormal LFT on INH therapy, 19 demonstrated complete resolution of hepatic dysfunction at completion or after cessation of therapy. The remaining five had transaminase improvements to less than 3 × ULN. Males were twice as likely (95% confidence interval (CI) 1.3–3.0, \(\chi^2 = 5.3; P = 0.02\)) to have significant LFT abnormalities. There was no association with elevated transaminases (AST/ALT) at baseline and significant INH-induced hepatotoxicity (\(\chi^2 = 0.2\)); \(P = 0.7\)). No patients experienced RIF-induced hepatotoxicity.

Table 3 Outcomes of PT for LTBI

<table>
<thead>
<tr>
<th>Outcome</th>
<th>INH, number (%)</th>
<th>RIF, number (%)</th>
<th>Total, (n = 94)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment completed (%)</td>
<td>53 (74)</td>
<td>19 (86)</td>
<td>72 (77)</td>
</tr>
<tr>
<td>Stopped early (%)</td>
<td>16 (22)</td>
<td>2 (9)</td>
<td>18 (19)</td>
</tr>
<tr>
<td>Grade 3/4 side-effect</td>
<td>3</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Grade 1/2 side-effect</td>
<td>12</td>
<td>1</td>
<td>13</td>
</tr>
<tr>
<td>Became pregnant</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Social reasons</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Lost to follow up (%)</td>
<td>1 (1)</td>
<td>1 (5)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Transferred service (%)</td>
<td>2 (3)†</td>
<td>0</td>
<td>2 (2)</td>
</tr>
</tbody>
</table>

†One patient completed 3 months, and one patient completed 7 months prior to transferring to another TB clinic; GP, general practitioner; INH, isoniazid; LTBI, latent tuberculosis infection; PT, preventive therapy; RIF, rifampicin.

Table 4 INH-associated LFT abnormalities for the 61 patients who had LFT monitoring

<table>
<thead>
<tr>
<th></th>
<th>No abnormality</th>
<th>Mild LFT abnormality†</th>
<th>ALT/AST (3-5 \times \text{ULN})</th>
<th>ALT/AST (&gt;5 \times \text{ULN})</th>
<th>(P)-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>37</td>
<td>17</td>
<td>5</td>
<td>2</td>
<td>0.8</td>
</tr>
<tr>
<td>Median age (years)</td>
<td>33</td>
<td>41</td>
<td>30</td>
<td>39</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>15 (41%)</td>
<td>8 (47%)</td>
<td>3 (60%)</td>
<td>2 (100%)</td>
<td>0.4</td>
</tr>
<tr>
<td>Age ≥ 35 years</td>
<td>17 (46%)</td>
<td>10 (59%)</td>
<td>2 (40%)</td>
<td>1 (50%)</td>
<td>0.8</td>
</tr>
<tr>
<td>Abnormal baseline LFT</td>
<td>1 (3%)</td>
<td>6 (35%)</td>
<td>3 (60%)</td>
<td>2 (100%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Risk factors for liver disease</td>
<td>1 (3%)</td>
<td>2 (12%)</td>
<td>2 (80%)</td>
<td>0</td>
<td>0.03</td>
</tr>
<tr>
<td>Hepatotoxic meds</td>
<td>7 (19%)</td>
<td>3 (18%)</td>
<td>1 (20%)</td>
<td>1 (50%)</td>
<td>0.7</td>
</tr>
<tr>
<td>Pre-immunosuppression</td>
<td>13 (35%)</td>
<td>9 (53%)</td>
<td>1 (20%)</td>
<td>0</td>
<td>0.3</td>
</tr>
<tr>
<td>Peak month</td>
<td>n/a</td>
<td>3</td>
<td>4</td>
<td>0.3</td>
<td></td>
</tr>
<tr>
<td>Resolved</td>
<td>n/a</td>
<td>15 (88%)</td>
<td>3 (60%)</td>
<td>1 (50%)</td>
<td>0.2</td>
</tr>
</tbody>
</table>

†Mild LFT abnormality classified as transaminase elevation 1–3 × ULN (13 patients) or isolated gamma-glutamyl transferase (GGT) elevations (4 patients). ALT, alanine aminotransferase; AST, aspartate aminotransferase; INH, isoniazid; LFT, liver function test; ULN, upper limit of normal.
patients developed active pulmonary TB on therapy; chest radiographs remained stable on completion of treatment in all patients.

**Discussion**

Completion of 9 months of INH therapy, with an efficacy of approximately 90%, currently remains the standard therapy for the treatment of LTBI. Effective treatment is of particular importance for patients with a higher estimated risk of developing active TB, such as those with LTBI undergoing transplantation (RR 20–74) or TNF-alpha therapy (RR 1.7–9.0). However, there remain two main barriers to the acceptance of therapy, leading to poor adherence and consequently reduced effectiveness. The first is the long duration of therapy and the second is INH toxicity, particularly hepatotoxicity, which can be fatal.

Alternative regimens are available, including 4 months of RIF monotherapy and 3 or 4 months of combination RIF–INH. Randomised controlled trials have already shown that RIF monotherapy is consistently safer than INH, especially with regards to hepatotoxicity. Despite this, long-term follow-up data on both efficacy and acquired RIF resistance are relatively limited compared with the body of evidence supporting the use of INH. The results of a randomised controlled trial of 4 months RIF against 9 months of INH is due in the next couple of years and may provide some answers.

Our completion rate of 74%, with adequate compliance, for 9 months of INH therapy is on the higher end of the range in the literature. On post-hoc analysis, 78% completed at least 6 months of INH therapy. A systematic review of completion rates from 78 studies on LTBI PT showed highly variable rates of 19–96%. However, limiting this to the largest studies using INH only, the rates are more constant at 61–64%. There is some suggestion that ‘clinic factors’, such as intensive patient education, follow up and support, may lead to increased patient completion; however, this has not been formally examined. A recent audit at another Sydney TB clinic found completion rates of 75% for 6 months INH therapy; however, those that ceased due to adverse events were excluded from the analysis.

For patients commencing RIF, 86% completed therapy. This was not statistically different to the completion rates for INH; however, our study supports the current opinion of an improved safety profile of RIF, with a trend towards more adverse events experienced after 9 months of INH therapy.

Overall, there were no statistically significant demographic features that predicted either early cessation of PT or adverse events leading to cessation of PT. Our overall rates of 17% ceasing due to adverse events (including 3% grade 3/4 and 14% grade 1/2) are high compared with the literature (1.4–3.6%). The relatively high proportion of patients ceasing due to mild adverse events may be due to a change in the perceived risk/benefit ratio of PT in these patients, especially as half of the decisions to cease PT were initiated by the patient. We are prescribing potentially toxic medications to a relatively well cohort of asymptomatic patients. This combined with patients being more attuned to symptoms due to starting a new medication may have led to an over-representation of minor adverse events causing cessation of therapy. In addition, our 2% rate of loss to follow up is nearly 10 times lower than other retrospective audits. This may be due to the close monitoring of patients’ compliance and up to 10 phone calls for missed scheduled medication pick-ups or clinic appointments. Given that our overall non-completion rates are similar to other studies, approximately 20%, an alternative explanation is that patients in other studies may have experienced adverse events and decided not to continue on with therapy or follow up, leading to the different proportions of those lost to follow up compared with those experiencing adverse events.

In the literature, up to 20% of individuals treated with INH alone experience low-grade, asymptomatic and transient elevations of transaminases. INH-induced hepatotoxicity is reported in 1–4% of patients treated with LTBI in smaller studies, with larger reviews quoting the rates of 0.1–0.56%. Some of this difference pertains to the definition used and monitoring practices of the clinics involved. For example, rates of hepatotoxicity in a Seattle centre with careful patient selection (i.e. few patients older than 35 years) and monthly clinical monitoring were as low as 0.1%. However, the definition of hepatotoxicity used was based on aspartate aminotransferase (AST) levels only despite alanine aminotransferase (ALT) being more specific for hepatocellular injury. In addition, hepatotoxicity rates are higher (1.7%) in patients 35 years and older compared with younger patients (0.2%). Despite our older population group, our results are comparable with the existing body of literature.

In our study, we found that abnormal baseline LFT were associated with INH-induced hepatotoxicity. There was a significant linear association between the degree of hepatic dysfunction observed during treatment and the presence of both abnormal baseline LFT and risk factors for liver disease. We did not find an age or
potential for the increasing age of patients being offered solid-organ transplantation and TNF-alpha therapy in other areas of medicine. Although the safety data on RIF are promising, the long-term efficacy data will not be available for some years. In the interim, we have available a medication with a long history of use and efficacy.

**References**

Home medicines reviews in Australian war veterans taking warfarin do not influence international normalised ratio control

L. R. E. Bereznicki,1 E. C. van Tienen1 and A. Stafford2

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Abstract

Background: The clinical outcomes of warfarin are largely dependent on the international normalised ratio (INR) control achieved, and strategies to improve the time in therapeutic range (TTR) should be identified and widely implemented in practice.

Aims: To investigate the influence of pharmacist-led medication reviews on INR control and observe the quality of INR control in Australian veterans who take warfarin.

Methods: We undertook a retrospective cohort study using administrative claims data for Australian veterans and war-widows identified by the Department of Veterans’ Affairs who were regularly dispensed warfarin and invited them to contact the research team. Pathology providers were subsequently contacted to provide INR results.

Results: INR data were available for 344 of 818 (42.1%) veterans who consented to participate in the study; 64.4% were male and the median age was 83 years. The overall TTR for the veteran cohort during the study period was 64.0%. There was no difference in the TTR in the 6 months following home medicines review (HMR) compared with the control group (63.0% vs 67.0%, P = 0.27), with the TTR in patients with INR data available in the 6 months prior to, and the 6 months following HMR, remaining high (67.9% vs 69.6%, P = 0.63). Approximately, one-third of veterans in this study had a percentage TTR below 60%.

Conclusions: INR was well-controlled in this elderly cohort, comparable to that achieved in recent randomised trials involving warfarin. Pharmacist-led medication reviews were not associated with a change in INR control.

Introduction

Most individuals who receive warfarin therapy are elderly patients with atrial fibrillation and acute or recurrent venous thromboembolism. Anticoagulation in elderly people poses unique challenges because they are simultaneously at higher risk of recurrent thromboembolism and major bleeding, including catastrophic intracranial haemorrhage. The effectiveness of warfarin therapy is strongly linked to the proportion of time that patients spend in the target international normalised ratio (INR) range (time in therapeutic range, TTR).1,2 The risk of death, myocardial infarction, major bleeding and stroke or systemic embolism are all related to INR control.3

In Australia, the Department of Veterans’ Affairs (DVA) introduced a system of providing formal medication reviews for Australian veterans in 1999, which was followed by the home medicines review (HMR) program (available to all members of the Australian public) in 2001. For veterans taking warfarin, these reviews provide an opportunity for patient education and review of warfarin management in the community setting. General practitioners refer patients to an accredited pharmacist who undertakes a home visit, identifying any medication-related problems, including potential under-use, overuse, adverse effects, compliance and knowledge problems, or hoarding. The pharmacist provides a report to the doctor who has responsibility for follow-up with the patient. The potential benefits of patients receiving a pharmacist-conducted medication review were established in several large research projects performed in the
late 1990s. These studies found that HMR resulted in the resolution of medication-related problems and showed trends in reduced medication costs.

A study by Roughead et al. assessed the effect of HMR in Australian veterans and war widows taking warfarin retrospectively using administrative claims data. The study identified a 79% reduction in the likelihood of hospitalisation for bleeding between 2 and 6 months following the HMR (hazard ratio 0.21, 95% CI 0.05–0.87). This beneficial effect was not evident for 6–12 months following review. As INR testing and TTR were not assessed in the study, it is unclear whether improved INR control occurred as a result of the HMR, or whether the benefits occurred independently of improved INR control.

We aimed to determine whether HMRs are associated with improved INR control, and observe the degree of INR control in this population.

**Methods**

**The DVA database**

The Australian DVA claims databases contain details of all prescription medicines, medical and allied health services and hospitalisations provided for which DVA pay a subsidy. At the time of the study, the data file contained 140 million pharmacy records, 200 million medical and allied health service records and over 6 million hospital records for a treatment population of 310,000 veterans. The DVA maintains a client file, which includes data on gender, date of birth, date of death and family status. Medicines are coded in the dataset according to the World Health Organization (WHO) Anatomical Therapeutic Chemical (ATC) classification and the Schedule of Pharmaceutical Benefits item codes. Hospitalisations are coded according to the WHO International Classification of Diseases (ICD) classification.

**Study design and data collection**

A retrospective cohort study was undertaken to compare the degree of INR control in veterans taking warfarin who were exposed and not exposed to HMR. Eligible veterans were initially identified and selected by the DVA based on data from their patient database. To be eligible for inclusion into this study, veterans were screened by the DVA to meet the following inclusion criteria: possess a Gold repatriation benefit card (eligibility for full entitlements), dispensed warfarin during the study period (1 January 2007 to 31 December 2009), and residing at home (as opposed to a residential aged-care facility).

The DVA identified a list of veterans who met the inclusion criteria and who had also had an HMR prior to 30 June 2009. This allowed for data to be available for at least 6 months following the HMR in the group exposed to HMR. The DVA then randomly selected a matching number of veterans who met the inclusion criteria who had not been exposed to an HMR in the study period. The identified veterans were sent an information sheet and consent form. A list of veterans who consented to be involved in the study was generated and sent to the DVA for data extraction.

Data provided by the DVA included age, sex, remoteness, number of co-morbidities, dispensed medications, dates of HMR claims and health services utilisation (hospitalisations including diagnoses and procedures; general practitioner visits; and specialist visits). The research team then contacted pathology laboratories that had claimed payment from DVA for measuring the veteran’s INR.

**Formation of HMR and control groups**

The ‘HMR’ group were those who met the eligibility criteria, had received an HMR, and had at least two dispensings of warfarin in the 6 months prior to the HMR. The ‘control’ group comprised veterans who met the eligibility criteria and who had an average of at least two dispensings of warfarin per 6 months between the first and final dispensing during the study period (to identify regular warfarin use), had at least 3 months between their first and final dispensings of warfarin (to identify long-term warfarin use) and had a first warfarin dispensing date before 1 January 2009 (to allow adequate time for a minimum of 6 months follow-up within the study period).

Eligible veterans in the control group were randomly allocated to an index month in the study period to match the time of the HMR in the HMR group. Control group veterans were only matched once in the study period.

**Data handling and statistics**

Data were analysed using sss 19.0 for Windows (IBM Corporation, New York, NY, USA). Demographic variables were compared between the HMR and control groups using the following methods: paired and unpaired t tests were used for normally distributed continuous variables; the non-parametric Mann–Whitney test was used for non-normal data. Categorical variables were analysed using the Chi-squared test. Fisher’s exact test was used when at least one of the variables had fewer than five patients or events. Statistical significance was set at $P < 0.05$. 

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The primary outcome was the percentage TTR, calculated using Rosendaal’s linear interpolation method\textsuperscript{11} for the 6 months prior to the HMR or index date, compared to the 6 months following the HMR or index date. An INR target range of 2.0–3.0 was assumed for this analysis as specific diagnoses for the condition requiring anticoagulation were not available for the majority of patients and a range of 2.0–3.0 was considered to be appropriate for most elderly patients. The literature suggests that patients in the community spend 50–60% of their time within the target range. At a power of 80% and statistical significance set at 0.05, a minimum of 75 patients analysed before and after HMR was required to detect a 10% difference in the percentage TTR.

The composite incidence of major bleeding and major thrombotic events resulting in hospitalisation occurring within 6 months of the HMR or index date was a secondary outcome. The ICD codes used to determine the primary diagnosis of hospitalisation associated with a bleeding event or thrombotic event are available in Table S1, Supporting Information.

**Ethics**

Ethical approval for this project was provided by the DVA Human Research Ethics Committee (Reference No. E009-010) and the Tasmanian Health and Medical Human Research Ethics Committee (Reference No. H0010963) prior to the commencement of the study.

**Results**

Figure 1 shows a flow diagram of recruitment of veterans into the study. The DVA selected 3884 veterans according to the project methodology, from whom the research team received 1213 replies (31.2% response rate). A total of 1029 veterans who replied provided their consent and was eligible for inclusion in the project. There was a total of 818 veterans who were allocated to the HMR (n = 281) or control groups (n = 537). INR data were available for a total of 344 of 818 (42.1%) veterans. At least two INR results were required to allow calculation of the TTR; veterans with only one INR result in the specified timeframe were excluded from the respective analyses. A total of 321 veterans had at least two INR results within the 12-month study period; 265 veterans had two or more INR results recorded in the 6-month baseline period prior to their first HMR or index date, 279 veterans had two or more INR results recorded in the 6-month period following their first HMR or index date and 229 veterans had two or more INR results in each 6-month period.

Characteristics of the groups are shown in Table 1. The groups were well matched with respect to gender, prior hospitalisations, prior bleeding and thrombotic events and region. The median number of co-morbidities was statistically significantly higher in the HMR group. The median age was also 1 year older in the HMR group, which was of marginal statistical significance.

In the overall study cohort, the median testing interval was approximately 16 days (range 1.0–65.7) and the mean TTR was 64.0 ± 27.3% (n = 321). The proportion of veterans whose percentage TTR was >60% and >70% were 64.5 and 49.2% respectively. The mean percentage TTR following HMR and index date was 63.0 ± 30.1% (n = 98) and 67.0 ± 27.7% (n = 181) respectively (P = 0.27). There was no significant change in the TTR in either of the groups or the overall veteran cohort in the period following the HMR or index date from the 6-month baseline period (Table 2).

Veterans living in outer regional and remote areas had significantly poorer INR control than those living in inner regional areas and major cities (mean TTR 49.9 ± 30.7% vs 65.3 ± 30.7% for those living in outer regional/remote areas and those living in inner regional areas/major cities respectively; P < 0.01).

There was no change in the combined number of bleeding and thrombotic events leading to hospitalisation (4/281 (1.4%) in the HMR group vs 6/537 (1.1%) compared with the control group; P = 0.74). In the HMR group, there was no significant change in the combined number of bleeding and thrombotic events leading to hospitalisation before and after the HMR (1/281 (0.4%) vs 3/281 (1.1%) respectively; P = 0.62).

**Discussion**

The main finding of this study was that HMRs were not associated with a change in INR control, as estimated by the TTR. The degree of INR control in this study (mean TTR 64%) compares well with the mean TTR achieved in recent randomised trials comparing warfarin to the new anticoagulants dabigatran (64%), rivaroxaban (55%) and apixaban (62%)\textsuperscript{12–14} in a much older population, and exceeds the usual level of INR control achieved in the primary care setting in many countries.\textsuperscript{15}

A systematic review reported that INR control differed based on study site in community-based studies, anticoagulation clinics and RCTs; mean TTR was 56.7, 65.6 and 66.4% respectively.\textsuperscript{15} In the literature, appropriate TTR benchmarks for patients taking warfarin are suggested to be 60–70%.\textsuperscript{16} In a study comparing the outcomes of patients randomised to dual antiplatelet therapy or warfarin, the benefits of warfarin were predicted to be lost using a population model when the TTR fell below
If we accept the TTR benchmarks that have emerged internationally since our study, a TTR of 60% as a lower benchmark for acceptable INR control, around 35% of veterans in our study were below this figure. If upper benchmark of 70% is used, 51% of veterans were below this mark.

There is a strong correlation between TTR and clinical outcomes for patients taking warfarin. The generalisability of the trial results comparing new anticoagulants to warfarin depends to a large extent on the TTR achieved in the trials, as it has been established that the efficacy, safety and cost-effectiveness of comparators to warfarin changes depend on the quality of INR control. In the RE-LY trial, a 10% increase in TTR independently predicted a 20% lower rate (P < 0.001) of the composite clinical outcome (stroke, systemic embolism or major haemorrhage). The number of clinical events in this study was too low to enable a statistical comparison of the clinical event rate and the degree of INR control.

Noting that the study was underpowered to detect differences in hospitalisation for major bleeding and thrombosis, we did not identify any effect of HMR on hospital admission resulting from complications associated with warfarin therapy in veterans who had been taking warfarin for a period of at least 6 months.

Two studies in Australia involving a combination of a series of medication review and point-of-care INR monitoring have found that this combination reduces the risk of complications with warfarin therapy in the early post-discharge period. However, most of the beneficial effect of these interventions was due to a reduction in

**Figure 1** Patient recruitment flow diagram.
minor bleeding, and not events that resulted in hospitalisation. In the more recent study, the intervention was associated with significantly decreased rates of combined major and minor haemorrhagic events to day 90 compared to usual care. However, there were no significant differences in readmission and death rates in INR control between the groups. Furthermore, significant reductions in complications associated with warfarin therapy only occurred in the group of patients newly initiating, rather than continuing, warfarin therapy.

It is therefore difficult to extrapolate the benefits of these interventions involving multiple home visits to the effectiveness of a single HMR on people who are relatively stable on warfarin therapy (vs those recently discharged from hospital and/or recently initiated on warfarin). Additionally, the focus of the medication review in the studies was directly on warfarin, while this may often not be the reason for the initiation of a HMR in people who are stabilised on warfarin therapy. In a retrospective study by Roughead et al, using administrative claims data from the DVA, the effect of a single HMR on Australian veterans and war widows 65 years and older who were taking warfarin was investigated. The study identified a 79% reduction in the likelihood of hospitalisation for bleeding between 2 and 6 months following the HMR, but as this analysis did not include INR data, it was unclear whether the HMR influenced INR control. The results of the present study, albeit in a smaller subset of the veteran population, suggest that the reduction in hospitalisation occurred independently of improved INR control.

In order to obtain INR histories for patients included in the present study, the investigators were required to obtain consent from veterans. This meant that it was not possible to obtain information from veterans who had died either during the study period or in the time following the study period prior to the HMR or index date and subsequently died. Therefore, we were not able to investigate the data.
of the entire veteran cohort who were taking warfarin during the study period. It is possible that the more seriously ill veterans and perhaps those most likely to suffer from adverse events related to warfarin were not included as a result of this methodology. This may have underestimated any influence that HMR may have had on the clinical outcomes of warfarin therapy or on INR control. The low rate of major bleeding in this study (equivalent to 2% p.a.) might be explained by careful selection of veterans who are candidates for warfarin by prescribers, the relatively high standard of INR control, the exclusion of veterans who suffered major bleeding events and subsequently died (due to the nature of study methodology) or a combination of these factors.

**Limitations**

There were several methodological limitations to the study, which have largely been previously discussed. It should be acknowledged that while the percentage TTR is strongly associated with bleeding and thromboembolism in people taking warfarin, TTR is a surrogate measure of these clinical outcomes. Additionally, the data available from the DVA were limited in respect to the documentation of co-morbidities, which meant that it was impossible to determine the indication for warfarin from the data available. Therefore, a target INR of 2.0–3.0 was assumed for all veterans. It is likely that this would have resulted in an under-estimation of the TTR rather than an over-estimation of the degree of INR control. INR data were only available for approximately 40% of the included veterans. In some cases, the pathology provider did not comply with the joint request from the research team, the DVA and the veteran for the data to be released. In other cases the pathology provider only held a proportion of the INR data available; the veteran may have changed provider or of office-based INR testing was used (in which case it was not available to the pathology provider). It was not possible to identify which veterans may have received office-based point of care INR testing during the study period and it is therefore unknown whether their INR control is comparable to that of the veterans included in this study.

**Conclusions**

The overall level of INR control in the veterans participating in the study was good, and comparable to that achieved in RCT, which generally involve a younger, healthier cohort. However, there appear to be a relatively large group of patients who would benefit from interventions to improve their INR control. HMR did not appear to influence the INR control of veterans whose pathology data were available for analysis. The previously reported effect of pharmacist-led medication review on reducing hospital admission is likely to be due to other factors. It is clear there is an ongoing need to audit regularly INR control in veterans taking warfarin and intervene as appropriate to maximise the benefits and minimise the risks of warfarin therapy.

**Acknowledgements**

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**References**

6. Roughhead EE, Barratt JD, Ramsay E, Pratt N, Ryan P, Peck R et al. Collaborative home medicines review delays time to next hospitalization for warfarin associated bleeding in Australian

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Supporting Information
Additional supporting information may be found in the online version of this article at the publisher’s web-site:

Table S1 ICD-10 primary diagnosis codes used to identify hospitalisation due to haemorrhagic and thromboembolic events.
Do community hospice programmes reduce hospitalisation rate in patients with advanced chronic obstructive pulmonary disease?

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Key words
COPD, hospices, hospitalisation, terminal care, utilisation.

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Abstract

Background: Since Hinton first published his observations on the distress of patients dying on a medical ward in 1963, there has been increasing awareness of the palliative care needs in patients who have non malignant diseases. Patients with advanced chronic obstructive pulmonary disease (COPD) are known to have comparable symptom burden to lung cancer patients and are more likely receive invasive treatment at the end of life than patients with end stage lung cancer. They are also less likely to receive hospice services, and the benefit of such programmes in this key group of patients remain largely unknown, in particular what effect hospice programmes have on hospitalisation.

Aims: (i) To examine any effect of community hospice programmes on hospitalisation in patients with advanced COPD. (ii) To identify any association between utilisation of specific hospice services with hospitalisation. (iii) To describe key peri-mortem outcomes.

Methods: This was a retrospective study of consecutive patients with COPD admitted into community hospice programmes in the greater Wellington region, New Zealand between 1 October 2007 and 31 October 2013.

Results: A mean decrease of 2.375 (median decrease of 2; 95% confidence interval 1, 3) hospital admissions over a 12-month period was found after admission into hospice programme (P < 0.0005).

Conclusion: Community hospice programmes may be associated with reduction in hospitalisation in patients with advanced COPD.

Introduction

Chronic obstructive pulmonary disease (COPD) is a major cause of disability, hospital admission and premature death in Australia and New Zealand,¹ and the cost of hospital care for people with COPD is high.² Factors that have been shown to be associated with healthcare use, such as hospital admissions are: previous hospital admissions,³ dyspnoea⁴ and symptom cluster.⁵

Several international guidelines have highlighted the importance of palliative care in the management of patients with advanced COPD.¹ ⁶ ⁷ The benefit of specialist palliative care in these patients is being explored in the literature; in particular, it remains largely unknown whether these programmes have an effect on hospitalisation rates in these patients.⁸

End-of-life use of medications from this study will add to the wider literature as there is no acceptable dosage agreed currently. This is of particular importance when the use palliative sedation and hastening of death is in question.

Methods

Patients

Consecutive patients who were enrolled with Mary Potter Hospice and Te Omanga Hospice Programmes with a primary diagnosis of COPD between 1 October 2007 and 31 October 2013 were identified. Patients with concomitant cancer diagnosis were excluded. Health and Disability Ethics Committee online questionnaire was completed. Written permissions were obtained from the Ethics
Committee of Mary Potter Hospice, Te Omanga Hospice, Capital and Coast District Health Board and Hutt Valley District Health Board prior to data collection.

**Programme outline**

The combined serviced population of Mary Potter Hospice and Te Omanga hospice is 430,000, each hospice covering different geographical areas of the greater Wellington region. Both hospices provide in-patient-unit beds and community programmes, and are both staffed by specialist palliative care physicians and palliative care nurses. At Mary Potter hospice, each patient is designated to a palliative care coordinator (nurse) whose role is primarily that of case management during office hours with phone advice out of hours and working with other community services, such as primary care, district nursing services and ambulance service, all of whom contribute to out of hours care in the home. Each patient is seen by a palliative care physician as required after enrolment on designated ‘clinic’ days.

There are two community programmes at Te Omanga Hospice, General Practitioner (GP) Led and Hospice Led. Patients’ needs and their GP’s wishes and availability are the determinants for which programme the patient is to be enrolled in. Patients can move between the two programmes and patients at the end of life are usually on the Hospice Led programme with very few exceptions. Patients on hospice led programmes have 24-h access to both nursing and medical team advice and consultations. Patients on GP led programmes are case managed by a designated palliative care nurse and they have 24-h access to hospice nursing advice and visits. Palliative care physicians’ consultations are on request by their GPs or palliative care nurses.

Referrals were accepted if patients have a prognosis of 12 months or less and they have complex physical or psychosocial palliative needs.

There were no acceptance criteria specific to COPD during the study period.

**Data collected**

Data were retrospectively collected from electronic clinical records at the two hospices, Capital and Coast and Hutt Valley DHB. This comprises of patients’ demographics, baseline COPD characteristics and comorbidity. Outpatient management by specialist respiratory services (respiratory specialists and/or clinical nurse specialists) were noted. Patients who were on pulmonary rehabilitation programme only were not counted as receiving respiratory specialist services in this study. Reasons for referral to hospice service were identified, and service utilisation data were collected from patients’ enrolment to death or discharge. These include: total number of hospice doctors and nurses’ visits, allied health engagement, number of in-patient-unit (IPU) admissions and reasons for admissions. References to resuscitation status or ceiling of medical care for future exacerbations were noted.

Numbers of all hospital admissions 12 months before enrolment and the entire follow-up period up to 31 October 2013 were collected. For patients who survived for 12 months or more on the programme, the total number of hospitalisations up to 12 months after admission into hospice programme was also collected for comparison. Key peri-mortem data includes survival on the programme, places of death and end-of-life medication use. Only de-identified data were collected on the data form during the chart review.

**Statistical analysis**

Data were analysed using RStudio statistical software v0.98.1103. The number for all hospital admissions for patients before and after they were admitted onto the programme was analysed. For patients who survived on the programme for 12 months of more, we used a paired sample $t$ test to compare the number of hospital admissions 12 months before and after patients’ enrolment at the hospice. The 95% confidence interval for the difference in median was calculated using an empirical bootstrap method. Pearson’s product moment correlation coefficients were calculated to determine any relationship between the number of all hospital admissions after enrolment at the hospice (follow-up period until 31 October 2013) and number of IPU admissions, nursing visits and medical visits separately. Welch two sample $t$ test was used to determine any difference in hospital admissions between groups 1: with or without ceiling-of-care discussion; 2: with or without moving to higher level of care.

**Results**

**Baseline patients’ characteristics**

A total of 73 patients with a primary diagnosis of COPD was identified. Baseline patients’ demographics and characteristics are summarised in Table 1.

Reasons for referral were documented in 67 patients, and these include: symptom control ($n = 46$), patient did not wish to return to hospital ($n = 9$), end-of-life care (EOLC) ($n = 10$) and others ($n = 2$).

At the time of first assessment, the levels of support for all patients were documented, and these include: ‘Lives with others who provide support’ ($n = 50$ 68%), ‘Lives alone with external professional support’ ($n = 7$, 9%), ‘Lives at home with others with external professional support’ ($n = 6$, 8%), ‘Lives alone with external non professional support’ ($n = 2$, 3%), ‘Lives alone with
no care/support’ (n = 4, 5%), ‘rest home level care’ (n = 4, 5%) and ‘hospital level care’ (n = 1, 1%).

Results for baseline medication use in COPD were collected for all patients: short-acting bronchodilators 93% (n = 68), inhaled corticosteroid 88% (n = 64), long acting beta-agonists 85% (n = 62), long acting muscarinic antagonists 66% (n = 48) and long-term systemic steroid 19% (n = 14).

### Service utilisation

The mean number of hospice doctors’ visits and nurses visits was 2.2 (median = 1) and 20 (median = 12) respectively. There was a total of 97 IPU admissions over the 6-year period. Forty-three patients utilised in-patient service. The mean number of admission was 1.3 per patient (median = 1). The most common reason for admission was respiratory (n=45), followed by symptom control (n=25), EOLC (n=17) and others (n=4).

Fifty-seven out of 73 patients were noted to have received services from members of the hospice allied health.

### Hospital admissions

The total number of hospital admissions within the 12-month period before and after enrolment for the 73 patients was 267 and 97 respectively. The latter includes three of the 10 patients who did not wish to return to hospital on referral to the hospice programme. The mean number of all hospital admissions over a 12-month period prior to enrolment was 3.6 (median 3). There were 31 patients who remained on the hospice programme for 12 months or more. We used a paired sample t test to determine whether the number of hospital admissions before patients’ enrolment at the hospice differed from the number of admissions post hospice enrolment. Following admission into the hospice programme, a mean decrease of 2.375 (median 2; 95% confidence interval 1, 3) hospital admissions over a 12-month period was found. The difference was highly statistically significant, t (31) = 4.3813, P < 0.0005.

Pearson’s product moment correlation coefficients (95% confidence interval) for the number of all hospital admissions after enrolment with IPU admissions, nursing visits and medical visits were calculated, and no correlation between hospital admission and the number of IPU admissions, nursing visits or medical visits were found in all patients and in the subgroup of those who survived for more than 12 months.

The mean number of all hospital admissions after enrolment in patients with and without documented ceiling-of-care discussion was 2.0 and 1.63 respectively. The difference between the two groups was not statistically significant (P-value = 0.5386).

Similarly the differences in the number of admissions 12 months prior and after enrolment for patients who moved to higher level of care and those who did not were 2.67 and 2.32 respectively (P-value 0.77).

### Peri-mortem outcomes

The number of patients who died or were discharged from the programme was 64 (87.7%) and 5 (6.8%) respectively. The median survival on the hospice programme was 8 months (range 1 day to 45 months). Place of death is summarised in Table 2. There were no hospital deaths amongst patients who were referred for EOLC and those who did not wish to return to hospital.

Use of regular medications around the time of death was known in 46 (62%) patients and is summarised in Table 3. The median and mean regular total 24-h oral morphine equivalent dose was 25 mg and 41 mg respectively (range: 25–100 mg).

### Table 1 Baseline patients’ characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>n = 73</th>
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<tbody>
<tr>
<td>Age (range)</td>
<td>Mean 76.1 years (50–91)</td>
</tr>
<tr>
<td>Sex</td>
<td>Male 37 (51%)</td>
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<tr>
<td></td>
<td>Female 36 (49%)</td>
</tr>
<tr>
<td>Ethnicity</td>
<td>European 64 (87.7%)</td>
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<td></td>
<td>Maori 5 (6.8%)</td>
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<td></td>
<td>PI 3 (4.1%)</td>
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<td></td>
<td>Asian 1 (1.4%)</td>
</tr>
<tr>
<td>FEV1</td>
<td>Median 30.6% (14–59%)</td>
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<td>MRCDS (Medical Research Council Dyspnoea Score)</td>
<td>Median 5 (3–5)</td>
</tr>
<tr>
<td>Domiciliary oxygen</td>
<td>n = 33 (44.6%)</td>
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<tr>
<td>Significant co-morbidity (≥1)</td>
<td>n = 40 (55%)</td>
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<tr>
<td>Congestive heart failure (CHF)</td>
<td>n = 19</td>
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<td>Ischaemic heart disease (IHD)</td>
<td>n = 14</td>
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<tr>
<td>CHF and IHD</td>
<td>n = 2</td>
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<tr>
<td>Others</td>
<td>n = 5</td>
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<tr>
<td>NIV (within 12 months prior to enrolment)</td>
<td>n = 11 (15%)</td>
</tr>
<tr>
<td>Specialist respiratory services</td>
<td>n = 56 (76.7%)</td>
</tr>
<tr>
<td>At time of enrolment</td>
<td>n = 42 (57.5%)</td>
</tr>
<tr>
<td>Within 12 months prior</td>
<td>n = 14 (19.2%)</td>
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### Table 2 Place of death

<table>
<thead>
<tr>
<th>Place of death</th>
<th>Number of patient (n = 64)</th>
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<tbody>
<tr>
<td>Home</td>
<td>15 (23.4%)</td>
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<tr>
<td>Hospice</td>
<td>22 (34.4%)</td>
</tr>
<tr>
<td>Hospital</td>
<td>12 (18.8%)</td>
</tr>
<tr>
<td>Residential care facilities</td>
<td>15 (23.4%)</td>
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Table 3  End-of-life use of medications

<table>
<thead>
<tr>
<th>Use of</th>
<th>Number of patients (n = 46)</th>
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</thead>
<tbody>
<tr>
<td>Syringe driver</td>
<td>23 (50%)</td>
</tr>
<tr>
<td>Regular opioid</td>
<td>33 (72%)</td>
</tr>
<tr>
<td>Regular benzodiazepine</td>
<td>25 (54%)</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>23 (50%)</td>
</tr>
<tr>
<td>Systemic steroid</td>
<td>24 (52%)</td>
</tr>
</tbody>
</table>

0–240 mg). The median and mean regular total 24-h subcutaneous midazolam equivalent dose was 3.75 mg and 6 mg respectively (range: 0–30 mg). PRN use of opioids and benzodiazepines was documented in 25 (34%) patients. The median and mean 24-h PRN oral morphine equivalent dose was 7.5 mg and 11 mg respectively (range 0–45 mg). The median and mean 24-h PRN subcutaneous midazolam equivalent dose was 5 mg and 6.12 mg respectively (range 0–38 mg).

Discussion

The number of patients aged ≥40 years with COPD in the population captured by the two hospices is estimated to be 28,000.9,10 With the average of 12 patients per year, only a fraction of these patients received hospice care during the study period. This may be because of difficulty in prognostication resulting in physicians’ reluctance to discuss end-of-life issues, advance care planning or hospice referral.11,12 Alternatively patients may not want to commit themselves to a possibly dying trajectory.13 Fifty percent of patients were in the severe COPD category according to Global Initiative for Chronic Obstructive Lung Disease classification14 and yet the Medical Research Council Dyspnoea Score indicates much higher symptom burden than what the forced expiratory volume in 1 s (FEV1) measurements otherwise suggest. This is consistent with findings of other studies that showed a poor correlation between physiological measurements, such as FEV1 and severity of symptoms.15,16 Fifty five percent of patients have at least one co-morbidity which may account for some of the symptom burden of breathlessness and the lower than expected median survival observed if based on FEV1 alone.17

Results for baseline medications indicate the use of long acting muscarinic antagonists could be improved prior to referral. One possible explanation could be the requirement of application of special funding for these medications by providers in New Zealand.

Patients were most commonly referred from their GP and general physicians. Respiratory services were either involved at the time of or within 12-month period prior to referral in 76.7% of patients, which may imply patients referred having refractory symptoms despite management of the underlying disease by specialists. It is consistent with the finding of symptom management being most common reason for referral. Another underlying reason for referral not overtly identified could be carers’ stress given that 68% of patients were living at home with others. Unfortunately it was not possible to identify the actual triggers for referral because of lack of details in the referral data.

To the authors’ knowledge, this is the first study that describes hospice services utilisation for patients in New Zealand. The need for respite was found to be high, and this result is consistent with qualitative studies which highlighted the burden on caregivers.18,19 The median number of hospital admissions per patient over a 12-month period prior to enrolment into hospice programme was 3 (mean 3.6) and is consistent with New Zealand Palliative Council referral criteria.20 A decrease of 2,375 hospital admissions over a 12-month period was found for patients who remained on the programme for 12 months or longer. The 12-month period was selected to minimise confounding effect from seasonal variations in COPD exacerbations. The reduction is both highly statistically and clinically significant and could be attributable to hospice intervention. Results of other studies have been mixed. Young and Simpson observed a substantial drop in Emergency room visits and hospitalisations in patients with COPD who received home-based education and advanced care planning.21 In contrast, a randomised controlled study in COPD and chronic heart failure patients who received domiciliary palliative care service, while exhibited better outcomes on self management of illness and improved symptom control but failed to show a reduction in emergency department utilisation rate. Hospitalisation rate was not analysed in that study.22 Results of studies that examined the cost effectiveness of hospice programmes in non-malignant conditions have been mixed.22-23

One may argue the inclusion of patients who did not wish to return to hospital or were referred for EOLC for analysis could affect the results in hospitalisation. The effect of the latter group is offset by analysis of the subset of patients who survived for ≥12 months. As this study is an attempt to explore the effect of a community intervention in helping patients to stay in the community regardless of the reasons for referral and in providing an alternative to admission to hospital when they no longer were able to cope at home particularly around the time of an exacerbation, it is paramount such patients are not excluded from analysis as they constitute a significant group hospices generally cater for. Moreover patients’ wishes may change with
time as found in this study where 3 of such patients returned to hospital after enrolment.

No single component of hospice intervention alone was significantly associated with the reduction of hospital admissions, which could be because of the small study population. It may be that the broader psychosocial support makes a significant contribution that cannot be quantified in terms of medical or nursing interventions.\textsuperscript{24} Adequately powered controlled prospective studies are required to confirm the result of reduction in hospitalisation observed in this study and to identify determinants or specific hospice intervention(s) associated with hospitalisation. Results of a prospective study measuring outcomes of a community-based integrated palliative care programme for patients with COPD were inconclusive because of poor patient enrolment and incomplete data collection\textsuperscript{8} highlighting recruitment challenges in this area.

Our peri-mortem data help to fill the gap in current literature about important palliative care outcomes in advanced COPD. The mean and median survival on the hospice programme was 12 and 8 months respectively. In contrast, a subgroup analysis of COPD patients in an American hospice study reports a median survival of only 76.5 days.\textsuperscript{25} Almost half of the patients in this study died at their usual abode (25% at home and 23% at residential care facilities). Only 18% died in hospital, and by comparison a rate of 72% was reported in an Australian non hospice cohort.\textsuperscript{26} A potential explanation being patients who accept hospice care may also be more inclined to forego life-prolonging measures that can only be offered in hospitals. Future studies are required to confirm whether hospice care could reduce deaths occurring in hospitals in patients with end-stage COPD.

A significant influence of palliative care is the introduction of opioid for dyspnoea and benzodiazepines for dyspnoea related anxiety. The role of opioids and benzodiazepines in severe COPD has been extensively examined in the literature,\textsuperscript{27–30} and results of this study serve to describe their use outside research protocol. Furthermore there remains a paucity of end-of-life data.

The median 24-h oral morphine equivalent found in this study was 25 mg which is similar to the highest effective dosage of 30 mg demonstrated in the only dose ranging study published to date.\textsuperscript{31} Given that many patients are receiving greater than 30 mg, further consideration of whether this is being used appropriately for pain control, or for other reasons is warranted. Similar dosage has also been reported in studies of patients with motor neuron disease where the median dose for oral regular morphine 24 h before death ranged between 20 mg–30 mg.\textsuperscript{32,33}

Unlike opioid, the benefit of benzodiazepine in alleviating dyspnoea is not established, and its use in severe COPD has been associated with increased mortality.\textsuperscript{30} The median midazolam dose found in this study was 3.75 mg/24 h which is considerably less than 20 mg/24 h found in the above mentioned motor neuron disease study.\textsuperscript{33}

To our knowledge our study is the first to report on medication use in dying patients with COPD in New Zealand. Future benchmarking studies are important particularly when the issue of palliative sedation or hastening of death is raised.

Conclusions and limitations

Community hospice programmes may be associated with a reduction in hospitalisation. Most patients who did not wish to return to hospital managed to avoid hospitalisation, and there was no hospital death in this sub-group. No correlation was found between the numbers of hospital admissions after enrolment and utilisation of individual aspects of hospice services, including IPU, nurses and doctors’ visits. Neither did ceiling-of-care discussion nor moving patients to higher level of care during the enrolment period appears to have an effect on hospitalisation. This could be because of the small sample size in this study. This is a retrospective study, and the number of patients is very small and they are highly selected. Furthermore this study is limited by only two regional hospices being included, and community-based programmes may vary significantly between hospices. Therefore one would be cautious to generalise results from this study to a wider group of patients with COPD and other geographical areas. Further research in patients with advanced COPD receiving hospice care is warranted.

Acknowledgements

We thank clerical staff at Te Omanga Hospice, Mary Potter Hospice for their assistance for this study. We are grateful for statistical advice from Dr Dalice Sim; School of Mathematics, Statistics and Operations Research, Victoria University and Dr James Stanley; Department of Public Health, Wellington School of Medicine, University of Otago.

References


Alcohol use disorder hospitalisations over the last two decades: a population-based cohort study

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Abstract

Background: Alcohol use disorders are risk factors for almost all health conditions due to heavy alcohol use. The epidemiology of alcohol use disorders can be used to monitor harm from heavy alcohol consumption.

Aim: To estimate changes in the risk of alcohol use disorders over the last two decades among the Western Australian adult population.

Methods: This population-based cohort study used hospital separation records for Western Australian residents aged 18 years and older that occurred between 1990 and 2013 with a primary diagnosis of alcohol use disorder and annual estimated residential population to estimate the annual gender- and age-specific incidence rate. A random sample of emergency presentations to public hospitals in Western Australia between 2002 and 2013 was used to account for confounding effects, such as changes in patient access to medical care and overall improvement in healthcare service in the multivariable Poisson regression model.

Results: The risk of alcohol use disorder hospitalisations among the Western Australia population has increased considerably since 1998 with a decline in 2012 and 2013. The average rate remained significantly higher from 2010 to 2013 compared with previous years.

Conclusions: The trend of alcohol use disorder hospitalisations is indicative of an increase in harm due to heavy alcohol use in the population.

Introduction

Alcohol, a widely used psychoactive substance with dependence-producing properties, is a major risk factor for global mortality and morbidity.1,2 Alcohol has been widely consumed in Australia for more than 200 years,3 and about 80% of the population currently drink alcohol.4 Health conditions that can be caused by alcohol include various cancers, liver disease, injuries from falls, physical assaults, road traffic crashes and mental health disorders.5 Mental and behavioural disorders due to use of alcohol (defined by the International Classification of Diseases (ICD) developed by the World Health Organization)5 or alcohol-related disorders (defined by the Diagnostic and Statistical Manual of Mental Disorders developed by the American Psychiatric Association)6-7 are a cluster of neuropsychiatric conditions,6-7 and they are direct contributors to the alcohol-related burden.8 In 2010, the prevalence of harmful use of alcohol and alcohol dependence combined among the population 15 years and older was estimated to be 4.1% worldwide and 3.5% in Australia.2 To establish a diagnosis of an alcohol-related disorder requires evidence of alcohol use.5-7 For example, diagnostic criteria of alcohol use disorder includes ‘alcohol is often taken in larger amounts or over a longer period than was intended’, whereas a diagnosis of alcohol intoxication requires ‘clinically significant problematic behavioural or psychological changes after recent ingestion of alcohol’. Alcohol use is assessed based on self-reported data and/or objective analysis of specimens, such as breath, blood or urine.5-7 Because of the connection with heavy alcohol use, the epidemiology of alcohol-related disorders can therefore be used to monitor the harmful effects of heavy alcohol consumption8 including injuries and road traffic crashes; alcohol-induced mental disorders, such as depression;
multiple organ damage, such as liver disease; hypertension; development of cancer; unsafe sex; adverse social behaviours (such as violence) and suicidal behaviour.6,9 This study aimed to estimate changes in the risk of alcohol use disorders (mental and behavioural disorders due to use of alcohol) over the last two decades among the Western Australian adult population using a population-based approach.

Methods

The overall annual risk of hospitalisation for alcohol disorders was first estimated by calculating the annual age- and gender-specific incidence rate. In order to investigate changes in overall risk over time, a multivariable Poisson regression model was employed to adjust for changes in gender and age distribution of the Western Australian population. To account further for confounding effects, such as changes in patient access to medical care and improvement in medical treatments, a newly developed proxy outcome approach10–13 was used to offset possible biases using a random sample of emergency department admissions.

Three datasets were used in this study: (i) hospital morbidity data; (ii) emergency department data; and (iii) estimated residential population. The hospital morbidity data included all hospital admissions in Western Australia since 1970. This study includes all hospital separation records for Western Australian residents aged 18 years and older that occurred between 1990 and 2013 with a primary diagnosis of alcohol use disorder. The hospital morbidity data are coded using ICD-9-CM between 1990/1991 and 1998/1999 (fiscal year) and using the ICD-10-CM classification system between 1999 and 2013 in the data. The following codes were to extract alcohol use disorder hospitalisation records: ICD-9-CM codes 291.0–291.9, 303.0–303.9, 305.0 and ICD-10-AM codes F10.0–F10.9. Emergency department data covered emergency presentations to public hospitals in Western Australia from 2002. A random sample of 1.6 million presentations for Western Australian residents aged 18 years and older occurred between 2002 and 2013 was used in the analysis.

Data analysis

Gender- and age-specific (grouped into: 18–24 years then 10-year age groups from 25–74 years and 75+ years) as well as overall incidence rates of alcohol use disorder hospitalisations were estimated for each calendar year between 1990 and 2013. Gender- and age-specific incidence rate ratios were calculated to investigate changes in risk between each 4-year period and its previous 4-year period (e.g. 1994–1997 vs 1990–1993). As noted previously in the Methods, a multivariable Poisson regression model was employed to model changes in risk over time adjusting for changes in gender and age distribution of the Western Australian population and potential confounding effects.

Ethics

This study has been approved by the Department of Health Western Australia Human Research Ethics Committee and by the Human Research Ethics Committee, Curtin University (approval number NDRI-04-2013).

Results

A total of 3 526 563 person-years at risk was accumulated from the Western Australian adult population between 1990 and 2013, incurring 58 924 hospitalisations for alcohol use disorders. The risks (95% confidence intervals) per 1000 person-years of hospitalisation for alcohol use disorders were estimated to be 16.7 overall (16.6, 16.8) and 21.7 (21.5, 22.0) and 11.7 (11.5, 11.8) for males and females respectively. Figure 1 shows age- and gender-specific annual incidence rates. The risk of alcohol use disorders has increased from the late 1990s among both genders and all ages with the exception of those aged over 75 years.

Incidence rate ratios of alcohol use disorders were further estimated to compare the risk between each 4-year period and its previous 4-year period for each gender and age group (Fig. 2). In males, significant increases were observed for periods and ages as follows: 2002–2013 for 18–24 years; 2006–2013 for 25–35 years; 1998–2006 and 2010–2013 for 35–44 years; 1998–2001, 2010–2013 for 45–55 years; 2002–2009 for 55–64 years; 2010–2013 for 65–74 years; and no significant increase observed for 75+ years. In females, significant increases were observed for periods and ages as follows: 2002–2013 for 18–24 years; 1998–2001, 2006–2013 for 25–34 years; 1994–2013 for 35–44 years; 1998–2013 for 45–54 years; 2006–2013 for 55–64 years; 2002–2013 for 65 years; and no significant increase observed for 75+ years. Significant decrease in risk of alcohol use disorders was observed for males but not females and mainly observed in 1994–1997 (compared with 1990–1993) for 25–34, 35–34, 45–54 and 75+ years and in 2002–2005 for the 25–34 years age group.

Moreover, as shown in Figure 1, the risk of alcohol use disorders decreased in both genders and in most age groups in the last 2 years (2012 and 2013) within the latest 4-year period, 2010–2013. It was noted that the average risk was higher than the previous 4-year period,
2006–2009. Annual changes in the risk of alcohol use disorders for the whole population were further calculated for each year between 2011 and 2013 using a multivariable Poisson regression model. In keeping with Figure 1, significant decreases in risk from the previous year were observed in 2012 (5.5%) and 2013 (11%).

The average risk of alcohol use disorder for the whole Western Australia population has increased considerably in the last 10 years (Table 1), and the estimates remained similar after controlling for unmeasured confounding effects (Table 2). It was observed that participants aged 35–64 years have a higher risk of hospitalisation for alcohol use disorder.

**Discussion**

The incidence rate of hospitalisation for alcohol use disorders decreased in 1994–1997 then increased from 1998, peaked in 2011 and declined in 2012 and 2013. However, the average rate remained significantly higher from 2010 to 2013 compared with previous years (Tables 1 and 2). The incidence rate trend is in relatively good agreement with the national trend in per capita alcohol consumption among the 15+ year population, which showed a decrease in 1990–1996 and increased afterwards until about 2008, whereas the decrease in the risk of alcohol use disorders in 2012 and 2013 appeared to reflect the gradual decline in per capita alcohol consumption since 2009. In addition, a similar trend has been reported among national hospitalisations for alcohol-caused liver disease in Australia. The decline in incidence in 2012 and 2013 is in good agreement with data from the National Drug Strategy Household Survey (NDSHS) 2013, which showed that the prevalence of lifetime risky drinkers (≥2 standard drinks per day on average) among the 14+ year Australian population reduced to 18.2% (21.6% in WA) in 2013 from 20.0% (23.0% in WA) in 2010, and the prevalence of consuming ≥4 drinks on most days/everyday reduced to 6.7% in 2013 from 7.9% in 2010. The increased risk of hospitalisation for alcohol use disorders among the 35–64 year age group compared with the younger age groups appeared to be against the age-specific prevalence of lifetime risky drinkers (≥2 standard drinks per day on average) observed in the NDSHS, which was the highest in the 18–24 years age group. Alcohol use disorders are most likely developed among people who frequently use alcohol at the highest level, and data from the same survey showed that the prevalence of consuming ≥4 drinks on most days/everyday was higher among middle-age and older people compared with the youngest age groups. Nevertheless, it is possible that the age difference in the risk of alcohol use disorder hospitalisation
Figure 2 Changes in risk of alcohol use disorder hospitalisation between each 4-year period (measured as incidence rate ratio of each denoted 4-year period to its previous 4-year period) by age and gender.
was at least partly due to the delay between the onset of alcohol use disorders and treatment, which has been estimated to be about 18 years in Australia.\textsuperscript{17} Also noteworthy is that this study used unlinked hospitalisation data, and thus, repeated hospitalisation of the same patients are possible, that is, admission due to relapse in later life. In addition, the frequency of visits to general practitioners increases with age,\textsuperscript{18} and therefore, as has been observed for other medical conditions,\textsuperscript{18} alcohol use disorders may be more likely to be diagnosed among middle-aged and older people compared with younger populations.

The trends for risk of alcohol use disorder hospitalisation measured in this study indicated that the harmful effects caused by heavy alcohol use have been rising throughout most of the last two decades among Western Australians. Another finding with potential importance is that the risk of alcohol use disorders among women aged 35–54 years appeared to keep rising until 2011 with small reductions in 2012 and 2013. Similar findings have been reported in a US study, which showed that several older people requiring treatment for alcohol problems has been increasing in recent years.\textsuperscript{19} Concerns about heavy alcohol use behaviours and alcohol use disorders among middle-aged and older women in Australia have been discussed in recent studies.\textsuperscript{20,21} Findings from this study indicate that further research targeting middle-aged female daily alcohol users is important for the development of future prevention and treatment strategies.

**Conclusion**

The risk of alcohol use disorder hospitalisations among the Western Australia population has increased considerably over the last two decades. This is indicative of an increase in the harmful effects of heavy alcohol use in the population.

**Acknowledgements**

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Association between hepatitis B virus infection and risk of multiple myeloma: a systematic review and meta-analysis

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Key words
hepatitis B virus, multiple myeloma, meta-analysis.

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Abstract

Background: Hepatitis B virus (HBV) infection is a major global public health concern. Although recent findings suggest an inverse relationship between HBV infection and multiple myeloma (MM), the true relationship between these two conditions remains unclear.

Aim: The primary aim of this meta-analysis was to evaluate the association between HBV infection, defined as hepatitis B surface antigen positivity, and the incidence of MM.

Methods: We searched the PubMed/Medline, Cochrane Library and EMBASE databases from January 1975 to July 2014 and reviewed the reference lists of all retrieved articles. Odds ratios (OR) and 95% confidence intervals (CI) were calculated using fixed- and random-effects models.

Results: We identified nine case–control studies involving 30,646 patients with MM and 379,837 controls. HBV infection was not significantly associated with the development of MM (OR = 1.3; 95% CI: 0.92–1.82; P = 0.14). A similar risk of developing MM was present in different HBV-prevalent countries. However, significant heterogeneity was observed among studies (P = 0.01). A statistically significant relationship between HBV infection and increased MM risk was detected in sub-analyses evaluating high-quality studies and those with hospital-based controls (P < 0.05).

Conclusion: HBV infection may be associated with an increased risk of MM. However, confirmation of this relationship and the specific molecular mechanisms involved in the association between HBV infection and the development of MM require further exploration.

Introduction

Multiple myeloma (MM) is a B-cell malignancy characterised by the proliferation of clonal plasma cells within the bone marrow with the production of an abnormal monoclonal paraprotein and evidence of end-organ damage. On a global scale, an estimated 86,000 incident cases occur annually,1 accounting for approximately 1% of all cancers and 13% of all haematologic malignancies.2 Although the exact cause of MM is unknown, older age, obesity, male sex, exposure to ionising radiation, African ancestry and a history of monoclonal gammopathy of undetermined significance are established risk factors for MM.3 Some studies have suggested that human immunodeficiency virus and hepatitis C virus infections are related to an elevated risk of developing MM.4–8

The hepatitis B virus (HBV), a small DNA virus, is a member of the Hepadnaviridae family. HBV is the causative pathogen in most cases of acute and chronic hepatitis worldwide. The World Health Organization has estimated that more than 2 billion people exhibit serologic evidence of HBV infection and that 360 million of these people have chronic HBV infection.9 A mathematical model estimated that, globally, around 600,000 individuals die of HBV-related liver disease every year.10 HBV not only exhibits hepatotropic characteristics, but also a lymphotropic virus.11 HBV infection of and replication within lymphocytes is speculated to contribute to the development of lymphoproliferative disorders. Several studies have evaluated the potential associations between the presence of HBV infection and the development of lymphoproliferative disorders.12–14 A recent meta-analysis demonstrated an increased prevalence of HBV infection in patients with non-Hodgkin lymphoma.15 Although several recent studies have suggested
an association between the presence of HBV and the development of MM, this association remains controversial. The aim of the present meta-analysis of epidemiologic studies was to evaluate the association between HBV infection and MM.

**Methods**

**Literature search**

Two authors (Y.Y.L. and O.B.) independently searched the electronic databases of PubMed/Medline, EMBASE and the Cochrane Library for relevant studies published in English from January 1975 to July 2014. The combination term ‘hepatitis B and myeloma’ was used in the search. The titles and abstracts of all studies were reviewed to determine whether an article was relevant to the present meta-analysis. Relevant papers were retrieved and assessed, and the reference lists in these articles were screened to identify additional relevant studies.

**Study selection**

We included only case–control studies that investigated the association between the presence of HBV infection and the development of MM. Case series, case reports and review articles were excluded. HBV infection was defined as the presence of hepatitis B surface antigen (HBsAg) positivity. The definition of MM was based on either that described in the World Health Organization classification or by the International Myeloma Working Group. Any disagreements between the two reviewers were resolved by discussion among all of the authors. When the same study population was included in multiple publications, only the most informative study was selected for inclusion in the meta-analysis. Full-text versions of all eligible studies were obtained for quality assessment and data extraction.

**Data extraction**

Data extraction was independently performed by two reviewers (Y.Y.L. and O.B.). The previously designed data extraction form included the following items: authors, title, date of publication, country of origin, years of inclusion, method of determining HBV status, method of MM diagnosis, sources and definitions of patients and controls, sample size and sex and age of study participants. Disagreements between the two reviewers were resolved by consensus among all of the authors.

**Quality assessment**

The quality of each study was independently assessed by two reviewers (Y.Y.L. and O.B.) using the Newcastle–Ottawa scale (NOS) (Table S1, Supporting information). The NOS includes three quality parameters: study group selection (0–4 points), study group comparability (0–2 points) and determination of either the exposure or outcome of interest (0–3 points). The highest possible score is 9 points and is assigned to studies of the highest quality. In the present analysis, NOS scores of 1–3, 4–6 and 7–9 indicated low-, intermediate- and high-quality studies respectively.

**Data analysis**

Review Manager 5.3 software (RevMan 5.3; The Nordic Cochrane Center, The Cochrane Collaboration, Copenhagen, Denmark) and Stata 12.0 (StataCorp, College Station, TX, USA) were used to perform all statistical analyses. Heterogeneity between studies was assessed using the Q test (\(P<0.10\) indicated statistically significant heterogeneity) and \(I^2\) test (values of 25, 50 and 75% indicated mild, moderate and severe heterogeneity respectively). Either a random- or fixed-effects model was used for the meta-analysis depending on the heterogeneity between studies. The fixed-effects model was used in the absence of significant heterogeneity (\(I^2<50\%, \ P>0.10\)); otherwise, the random-effects model was used.

A contour-enhanced funnel plot and Egger’s test were used to evaluate publication bias. For Egger’s test, \(P<0.05\) was considered to indicate statistically significant publication bias. The primary outcome in this meta-analysis was the prevalence of HBV infection compared between patients with and without MM. Comparisons were made by calculating odds ratios (OR) and 95% confidence intervals (CI). Subgroup analysis of the HBV prevalence by country was performed. Countries were considered to have low, low-intermediate, high-intermediate and high HBV prevalence based on an HBV prevalence report previously published by the Centers for Disease Control and Prevention. Sensitivity analyses were performed to assess the stability of the results. For these analyses, individual studies were eliminated in turn in order to determine the influence of any given individual data set to the pooled OR.

**Results**

**Search results**

Our electronic database search initially identified 949 citations. We excluded 938 articles because they did
not meet the inclusion criteria. Nine case–control studies\(^\text{12,13,16,17,25–29}\) were selected for the meta-analysis. A flow chart of the search process is shown in Figure 1.

### Characteristics of studies

Table 1 lists the main characteristics of all nine case–control studies included in the meta-analysis. All studies were published from 1975 to 2012. The nine studies involved 30,646 patients with MM and 379,857 controls. One study originated from Africa,\(^\text{29}\) one from the United States,\(^\text{25}\) three from Europe\(^\text{12,26,28}\) and four from Asia.\(^\text{13,16,17,27}\) One study was prospective\(^\text{12}\) and eight were retrospective.\(^\text{13,16,17,25–29}\) Seven studies\(^\text{12,13,16,17,26,27,29}\) (78%) determined patients’ HBV status by seropositivity of at least the HBsAg. The other two studies\(^\text{25,28}\) (22%) did not test the HBsAg level; one determined patients’ HBV status based on their Medicare diagnosis and/or billing records,\(^\text{25}\) and the other used data obtained from the Swedish Inpatient Register.\(^\text{28}\)

### Quality assessment

According to the NOS, six studies\(^\text{12,13,16,26,27,29}\) (63%) were of high quality and three\(^\text{17,25,28}\) (33%) were of intermediate quality. Two studies\(^\text{17,29}\) (22%) did not describe how patients and controls were matched at the time of the trial design or whether confounders were adjusted for and during data analysis. The control groups in four studies were hospital-based controls,\(^\text{13,16,26,27}\) and five studies used population-based controls.\(^\text{12,17,25,28,29}\)

### Outcomes

The OR of detecting HBV infection in patients with MM versus controls using a random-effects model was 1.30 (95% CI: 0.92–1.82, \(P = 0.14\)), suggesting an increased prevalence of HBV infection in patients with MM, however the difference was not statistically significant (Fig. 2). A moderate degree of heterogeneity was observed (\(I^2 = 60\%\), \(P = 0.01\)). No evidence of publication bias was found on the funnel plots (Fig. 3) or by Egger’s test (\(P = 0.13\)).

### Subgroup analysis

The prevalence of HBV infection varied geographically. Countries with high (>8%), low-intermediate (2–4%), high-intermediate (5–7%) and low (<2%) HBsAg prevalence were identified.\(^\text{24,30}\) Subgroup analyses were performed in the countries with low, high and intermediate HBsAg prevalence. Among the studies performed in countries with high and intermediate HBV infection,\(^\text{13,16,17,27,29}\) the adjusted OR of MM in patients with HBV was 1.26 (95% CI: 0.72–2.19, \(P = 0.41\)) (Fig. 4A). A high degree of heterogeneity was observed (\(I^2 = 76\%\), \(P < 0.01\)), but no publication bias was evident (Egger’s test, \(P = 0.68\)). Studies performed in Europe and the United States\(^\text{12,25,26,28}\) regions with a
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<th>Controls Source of controls</th>
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<th>MM assessment</th>
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<td>2003–2007</td>
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<td>2 67</td>
<td>Patients recruited using records from university blood centre</td>
<td>Age and sex</td>
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<td>1993–1998</td>
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<td>Cohort participants who were cancer-free, alive and had blood samples available</td>
<td>Age, sex and time of blood collection and fasting status</td>
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<td>ELISA</td>
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<td>40 593</td>
<td>Patients undergoing general medical examinations at Asan Medical Center</td>
<td>Age, sex and year of serum collection</td>
<td>Pathologic confirmation</td>
</tr>
<tr>
<td>Lindqvist, 2011</td>
<td>Sweden (low)</td>
<td>Retrospective</td>
<td>NA</td>
<td>1965–2004</td>
<td>Nationwide Swedish Cancer Register</td>
<td>19 112</td>
<td>Cases in nationwide Swedish Cancer Register</td>
<td>Sex, age and country of residence</td>
<td>Pathologic confirmation</td>
</tr>
<tr>
<td>Becker, 2012</td>
<td>Europe (low)</td>
<td>Retrospective</td>
<td>Chemiluminescent microparticle immunoassay</td>
<td>1998–2004</td>
<td>Hospital- or clinic-based patients in Czech Republic, France, Germany, Ireland, Italy and Spain</td>
<td>27 171</td>
<td>Population registers in Germany and Italy; hospitalised patients with diseases other than lymphoma in Czech Republic, Ireland, Italy and Spain</td>
<td>Age, sex, country and education level</td>
<td>Pathologic confirmation</td>
</tr>
<tr>
<td>Huang, 2012</td>
<td>China (high-intermediate)</td>
<td>Retrospective</td>
<td>ELISA</td>
<td>1996–2008</td>
<td>Patients newly diagnosed with myeloma at the First Affiliated Hospital of Sun Yat-sen University in Guangzhou</td>
<td>58 299</td>
<td>Patients with newly diagnosed acute leukaemia at the First Affiliated Hospital of Sun Yat-sen University in Guangzhou</td>
<td>Age and sex</td>
<td>Pathologic confirmation</td>
</tr>
<tr>
<td>Teng, 2011</td>
<td>Taiwan (high-intermediate)</td>
<td>Retrospective</td>
<td>ELISA</td>
<td>2003–2008</td>
<td>Patients newly diagnosed with myeloma at Taipei Veterans General Hospital</td>
<td>17 155</td>
<td>Historical data from a large-scale survey in Taiwan</td>
<td>Not reported</td>
<td>Criteria proposed by the International Myeloma Working Group</td>
</tr>
<tr>
<td>Olutunji, 1991</td>
<td>Nigeria (high)</td>
<td>Retrospective</td>
<td>Reverse passive haemagglutination technique</td>
<td>1987–1989</td>
<td>Patients with lymphoproliferative malignancies at University College Hospital, Ilbadan, Nigeria</td>
<td>3 16</td>
<td>Healthy voluntary donors to the University College Hospital blood bank, Ilbadan, Nigeria</td>
<td>Not reported</td>
<td>Pathologic confirmation</td>
</tr>
</tbody>
</table>

ELISA, enzyme-linked immunosorbent assay; HBsAg, hepatitis B surface antigen; ICD, International Classification of Diseases; NOS, Newcastle-Ottawa Scale; PCR, polymerase chain reaction; SEER, Surveillance, Epidemiology, and End Results.
low prevalence of HBV infection, had an adjusted OR of MM in patients with HBV of 1.23 (95% CI: 0.91–1.67, \( P = 0.17 \)) (Fig. 4B). No significant heterogeneity was observed (\( I^2 = 17\% \), \( P = 0.30 \)), and no publication bias was found (Egger’s test, \( P = 0.25 \)).

### Sensitivity analysis and assessment of heterogeneity

Significant heterogeneity was present in the overall analysis. Thus, we performed the sensitivity analysis by excluding one study at a time and recalculating the OR in an attempt to detect the source of heterogeneity. Similar results were obtained after sequentially excluding each study, with exception of the Teng et al. study,\(^{17}\) where a significant relationship between HBV infection and increased risk of MM was observed when it was excluded (OR = 1.48, 95% CI: 1.16–1.88, \( P < 0.01 \)). The results were altered when we performed subgroup analyses according to the quality of the studies. After exclusion of the three studies with NOS scores <7,\(^{17,25,28}\) the pooled results showed that HBV infection was significantly associated with increased risk of MM (OR = 1.63, 95% CI: 1.30–2.05, \( P < 0.01 \)). No heterogeneity (\( I^2 = 4\% \), \( P = 0.39 \)) or obvious publication bias was found (Egger’s test, \( P = 0.33 \)). A similar outcome was observed after excluding the two studies that did not describe the comparability of patients and controls.\(^{17,29}\) The OR of MM in patients with HBV was 1.44 (95% CI: 1.13–1.85, \( P < 0.01 \)), the degree of heterogeneity was not significant (\( I^2 = 23\% \), \( P = 0.25 \)), and no publication bias was identified (Egger’s test, \( P = 0.14 \)). HBV infection was significantly associated with MM risk in the hospital-based control\(^{13,16,26,27}\) (OR = 1.57, 95% CI: 1.25–1.96, \( P < 0.01 \)), but not in the population-based controls.\(^{12,17,25,28,29}\) (OR = 1.20, 95%
CI: 0.64–2.28, \( P = 0.57 \)). There was no heterogeneity among the studies that included hospital-based controls \( (I^2 = 0, \ P = 0.42) \), but significant heterogeneity was found in those using population-based controls \( (I^2 = 62\%, \ P = 0.03) \).

**Discussion**

The main finding of this meta-analysis is that a relatively higher rate of seropositivity for HBV infection is observed among patients with than without MM. Patients with HBV infection have 1.3 times higher risk of developing MM than controls. This finding suggests that HBV infection may play a role in the pathogenic development of MM. The subtype analysis of studies performed in countries with a high, intermediate or low prevalence of HBV infection suggested that those infected in all countries had a similar increased risk of developing MM. However, the differences were not statistically significant, and high heterogeneity was present. Heterogeneity was reduced when evaluating studies with consideration of their quality and the source of controls, and the relationship between HBV infection and the risk of MM development achieved significance among the high quality and hospital-based control studies.

Another important point is that the high prevalence of HBV infection in patients with MM may cause a therapeutic dilemma in the clinical setting. Previous data show that HBV reactivation commonly occurs following chemotherapy, occurring in 21–53% of HBsAg carriers.\(^{31}\) All patients with HBV infection who subsequently develop MM are at risk for reactivation following chemotherapy, particularly following immunosuppressive chemotherapy. Several recent studies found a significantly higher occurrence of HBV reactivation and/or hepatic damage after patients with HBV infection underwent chemotherapy, especially protocols containing high doses of glucocorticoids or proteasome inhibitor bortezomib,\(^{32,35}\) which are the commonly used agents in the treatment of MM. The mechanism of HBV reactivation in association with chemotherapy is unclear. HBV DNA contains a glucocorticoid-responsive element that reportedly facilitates HBV replication.\(^{36,37}\) Bortezomib may alter the number and function of CD8 T cells and CD56 natural killer cells,\(^{38}\) and HBV reactivation may be attributable to the effect of bortezomib on cell-mediated immunity.\(^{32}\) In addition, patients with concurrent MM and HBV infection reportedly experience more and earlier hepatic adverse events while undergoing chemotherapy.\(^{37,39}\) The HBV status of patients with MM should be determined before chemotherapy or immunosuppressive therapy is initiated. Evidence suggests that patients with MM undergoing chemotherapy would benefit more from antiviral prophylaxis than from serial monitoring of HBV DNA.\(^{40}\)
Our meta-analysis has certain limitations. First, a significant degree of heterogeneity was detected among the studies evaluated. Moreover, some of the original studies had their own limitations, such as too few controls, relatively low sensitivity methods for detection of HBV or used hospital-based controls, which may have influenced the result of the meta-analysis. Indeed, a significant relationship was observed between HBV infection and the increased risk of MM when controlling for these factors. Second, we did not assess serum markers that are used to identify occult HBV infections, such as HBeAg or HBV DNA. Several recent studies showed a significant correlation between the presence of occult HBV infection and the development of chronic lymphocytic leukaemia/small lymphocytic lymphoma. These findings indicate that the presence of HBsAg seropositivity may lead clinicians to underestimate the risk of MM in patients with HBV infection. Further studies are needed to determine the relationship between the presence of occult HBV infection and the development of MM. Third, as mentioned above, MM patients are at a risk for HBV reactivation following treatment. The time interval between the HBsAg test and MM diagnosis may have affected the results. However, we could not assess the relationship due to the lack of accurate descriptions of this time interval in most of the studies. Finally, this meta-analysis included only studies published in English. HBV infection is highly endemic in Asia, Africa and the Middle East, and the populations in most regions of these countries do not speak English. This factor may have influenced the results.

Despite the above-mentioned limitations, our study has several strengths. First, to the best of our knowledge, this is the first meta-analysis to evaluate the association between the presence of HBV infection and the development of MM. Second, the NOS score indicated that most of the included studies were of high quality. In addition, the main association between HBV infection and MM became statistically significant after excluding studies with an NOS score of <7. Finally, our study showed that the association between the presence of HBV infection and the development of MM might not vary between countries with a high and low prevalence of HBV.

Conclusion

The present meta-analysis has shown that the presence of HBV infection may be associated with an increased risk of developing MM. However, the relatively low qualities of enrolled studies have affected the reliability of the results. Future studies on the risk of MM in patients with HBV infection are needed to elucidate fully the relationship between HBV infection in the whole population, including those with occult HBV infection, and the development of MM. Importantly, further studies should focus on elucidating the biologic relationship between the presence of HBV infection and the development of MM.

References


Supporting Information

Additional supporting information may be found in the online version of this article at the publisher’s web-site:

Table S1 Methodologic quality of studies included in the final analysis based on the Newcastle–Ottawa scale of quality of case–control studies.
Estimation of clinical and economic effects of prophylaxis against venous thromboembolism in medical patients, including the effect of targeting patients at high-risk

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Key words
thromboprophylaxis, medical patients, guidelines, selection criteria, cost-effectiveness.

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Abstract
Background: The clinical and economic effects of medical thromboprophylaxis (MT) using low molecular weight heparin in Australia are unknown. Aim: To estimate the effects of MT in Australia. Methods: A decision tree model of MT was populated with national data for medical admissions. The Prevention of Recurrent Venous Thromboembolism (PREVENT) trial was chosen as the primary data source because its design uniquely avoided bias caused by treatment of sub-clinical events. Clinical efficacy and costs were estimated compared with no prophylaxis, assuming full compliance and according to three definitions of eligibility. Effectiveness was estimated as thrombotic events saved, mortality from bleeding or pulmonary embolus (PE), cost and $/year of life saved. Model outputs were subjected to sensitivity analysis.

Results: MT decreased thrombotic events, and the numbers avoided increased as eligibility broadened (deep vein thrombosis (DVT): 2597, 2771 and 3232 at restricted, intermediate and broad eligibility; PE: 454, 484 and 565 respectively). The annual cost of no prophylaxis was $88.7 m. Costs were reduced at most restricted eligibility (−$7.9 m), but increased by $3.0 and $32.1 m at broader eligibility. PE deaths declined, but this was offset by deaths from haemorrhage, causing a net increase (158, 299 and 672 respectively). Estimates were sensitive to the incidence of venous thromboembolic event (VTE), case-fatality rates for PE and bleeds and the relative risk reduction for PE with prophylaxis.

Conclusions: Under PREVENT trial conditions, MT avoids up to 3200 DVT and 565 PE events annually, but may increase mortality.

Introduction

Thromboprophylaxis using low molecular weight heparin (LMWH) is widely promoted and practised in medical wards across Australia, but this activity occurs without evidence of benefit for clinical end-points in randomised controlled trials, all of which were powered to detect sub-clinical events detected by imaging.¹,² Obtaining secure knowledge for clinical end-points in the near future is unlikely without a major collaborative effort, given a sample size requirement of 200 000.³ In these circumstances, we considered whether data on clinical event rates reported in published trials could be used as an indicator of the likely clinical benefit of medical thromboprophylaxis (MT). However, in addition to being underpowered for clinical events, all trials save one were adversely affected by anticoagulant treatment given in response to the detection of sub-clinical thrombi, thereby altering the natural history. The exception is the Prevention of Recurrent Venous Thromboembolism (PREVENT) trial,⁴ which avoided this source of bias by deferring imaging until at least day 14 of the study. It is the largest trial of LMWH prophylaxis reporting clinical thrombotic end-points, but was underpowered for these events.

Several studies⁵–⁷ claim that MT is cost effective, but these estimates are affected by the same problem, being based mainly on the Prophylaxis in Medical Patients with Enoxaparin (MEDENOX) study, a randomised controlled trial of enoxaparin versus placebo⁸ in which the primary end-point was asymptomatic thromboses. The
The main incremental cost-effectiveness ratio obtained in these analyses (cost per asymptomatic venous thromboembolic event (VTE) avoided) is of questionable clinical significance and is not comparable with other medical interventions.

Australian guidelines for MT\textsuperscript{9,10} promote ‘consideration’ of MT in patients with any risk factor and no bleeding risk. However, an excess of major bleeding with LMWH has been reported in most trials in spite of the exclusion of patients at risk of bleeding.\textsuperscript{3} Thus broad eligibility for MT, which by definition includes patients with weak risk factors, may have a low benefit to risk ratio.\textsuperscript{11} Amending eligibility for MT to patients with only strong risk factors has been suggested,\textsuperscript{2,11–13} but the quantitative clinical and economic effects of such a change are uncertain. If eligibility is restricted, more VTE events will occur in non-eligible patients because their number will increase and those with weaker risk factors achieve sub-group membership, and this could compromise the potential gain in therapeutic efficiency.

With these points in view, and because of the importance of obtaining further information on the true value of MT, we decided to model its risks and benefits based on the PREVENT trial alone and to explore alternative methods to minimise its uncertainties.

**Methods**

We constructed a decision tree model of thromboembolic outcomes in adult medical patients admitted to all Australian public hospitals\textsuperscript{14} in 2011–2012, given or not given LMWH prophylaxis against VTE (Fig. 1), using an Excel spreadsheet (Microsoft Corporation, Redmond, WA, USA). The model treated deep vein thrombosis (DVT) and pulmonary embolus (PE) as separate events because they are reported as such in clinical trials, including PREVENT. Cost-effectiveness was assessed from the point of view of the public health system in Australia, assuming full compliance in order to estimate the maximum possible effects. The clinical outputs were DVT, PE, post-thrombotic syndrome (PTS), major bleeds and deaths from acute PE and major bleeds, and corresponding costs.

The model contained three levels of eligibility for MT according to the statistical weighting of known risk factors (Table 1): a relatively small population (25% of the total) carrying the strongest risk factors for thrombosis (malignancy, especially with chemotherapy; previous history of thromboembolism and some rarer high-risk conditions, such as acute inflammatory bowel disease)\textsuperscript{15}; an intermediate population with strong plus moderate risk factors, such as cardiac or respiratory failure, sepsis or inflammation (40%\textsuperscript{15}); and a larger group containing all putative risk factors (80%)\textsuperscript{16} equivalent to Australian guidelines\textsuperscript{9,10} and consisting essentially of the intermediate group plus patients satisfying an age-related criterion, such as ‘age > 40’ or ‘age > 60’.\textsuperscript{10} Thus, differences between estimates from the intermediate and broad eligibility criteria are a guide to the effect of including an age-related risk factor for MT. We refer to these subgroups by the proportion of the general inpatient medical population they represent, as above, or by the terms...
‘restricted’, ‘intermediate’ and ‘broad’. As no guidelines currently recommend MT after discharge in medical patients, our study was restricted to the inpatient phase of management. The comparator was no prophylaxis because enoxaparin is the only LMWH registered for MT in Australia and is the drug of choice in most Australian hospitals. In its absence, prophylaxis is unlikely. A minority of hospitals may use unfractionated heparin, but it is less effective17 and carries a higher risk of bleeding and heparin-induced thrombocytopenia.18 Orally active thrombin and factor Xa inhibitors (dabigatran, apixaban and rivaroxaban) are not registered for MT in Australia.

Costs in the model (AUS) were of acquisition and administration of enoxaparin, and treatment costs for DVT, PE, PTS and of major bleeds (Table 2). The model was populated by clinical outcome data from the PREVENT trial4 for reasons already stated and amplified in the Discussion. Administration of enoxaparin was assumed to occupy 5 min of nursing time, costed at $2.73 using level 1.5 of the WA nurses award. We assumed PTS did not curtail life expectancy, but PE was estimated to shorten survival from 13 to 11 years, using annual survival probabilities given in Australian Life tables19 after applying a survival hazard ratio of 1.4.22 With this adjustment, risk in non-eligible patients was two-thirds of the theoretical maximum, to an extent that is unknown. We assumed arbitrarily that the risk was zero in the low-risk group, but since events must occur increased with prophylaxis). Cost-effectiveness ratios for morbid events (e.g. $/DVT avoided) were estimated in all cases. No quality of life adjustments were made.

We assumed a baseline clinical DVT incidence across the general medical inpatient population of 0.0043 (0.43%) as reported by us23 for ‘VTE’ (PE + DVT). For the purposes of this study, we regarded this incidence as being due to DVT only. This compares with the PREVENT study placebo-group (a selected sub-population of the above) DVT incidence of 0.0063. The baseline PE incidence was estimated from the ratio of symptomatic PE to DVT incidence reported in the PREVENT study,4 giving a value of 0.0023. The relative risk reductions (RRR) for symptomatic DVT and PE with prophylaxis, major bleeding rates and case-fatality rates for PE and major bleeding were as reported in the PREVENT study.

We included an assessment of the contribution to overall clinical performance from non-eligible patients at each definition of eligibility. This in turn requires an estimate of the VTE risk in non-eligible patients, which was obtained from the known reciprocal relationship, reported by us, between the proportion of patients in a population selected by risk factor analysis and the maximum supplemental risk in that population.24 The derivation of this relationship assumes a limiting VTE risk of zero in the low-risk group, but since events must occur in that group, the actual supplemental risk in high-risk groups must be less than the theoretical maximum, to an extent that is unknown. We assumed arbitrarily that the risk was two-thirds of the theoretical maximum. With this adjustment, risk in non-eligible patients was calculated using the formula for weighted average.24

The model was challenged by sensitivity analysis for important assumptions, including baseline VTE risk up to the highest value reported,25 and likely sources of uncertainty (Table 4), including the uncertainty from the immediately above procedure and the effect of substituting independent literature values, such as the case-fatality rates for PE26–28 and major bleeding,29–31 where these values differed markedly from the PREVENT trial.
values or biased the results in a particular direction (Table 3). This research did not involve access to individual patients. Ethical approval was not required.

**Results**

The number of overnight medical admissions in Australia reported for 2012 by the Australian Institute of Health and Welfare were 1 458 600.14 Patients eligible for MT (Table 1) therefore numbered 364 650, 583 440 and 1 166 880 as eligibility criteria broadened.

**Base-case model**

**Clinical outcomes**

Estimated annual numbers of DVT, PE and PTS across Australia and deaths from PE and major bleeding, with associated costs and at 100% compliance are shown in Table 3 for the base-case from each data source and at each level of eligibility (25, 40 and 80%) and the comparator (no prophylaxis). This order of reporting is used throughout the paper. The model predicted that 6272 DVT and 3385 PE will occur annually without prophylaxis and that MT decreases these numbers under all definitions of eligibility under PREVENT conditions.

As expected, events including death in non-eligible patients increased as eligibility was progressively restricted (Table 3), because that group contains more untreated patients with risk factors for thrombosis, and the numbers of events increase. This effect contributed to the modestly greater total events seen under broad
eligibility, but did not reverse measures of performance expressed as total mortality, cost or $/YOLS.

Cost outcomes

Annual cost of treating thrombotic events without MT was $88.7 m. That cost was reduced modestly by MT by $7.9 m at 25% eligibility, but increased by $3.0 and $32.1 m at 40 and 80% eligibility. These trends were due to increases in drug acquisition and administration costs plus the cost of treating non-fatal major bleeds, at each level of eligibility ($21.4, $34.3 and $68.6 m/year respectively), offsetting the reduced cost of treating VTE events (Fig. 2).

Economic performance

The outcome variable $/YOLS was indeterminate in the base-case because of the excess of deaths and life years lost. In some runs of the model, YOLS was positive in spite of a small increase in mortality, because of the contribution to YOLS from the effect of MT on PE (Table 4). Negative costs (i.e. cost savings) per non-fatal VTE event (DVT plus PE) avoided were seen at 25% eligibility in the base-case ($2573/VTE avoided), but at 40 and 80% eligibility each VTE avoided came at a cost ($938 and $8463 respectively).

Sensitivity analyses

Table 4 displays the results of sensitivity analyses. We noted a general tendency for declining performance as eligibility was broadened, also seen clearly in Figure 2. Of particular interest were:

1. Baseline incidence of VTE. The VTE benefit of MT and aggregate costs was directly related to baseline VTE incidence. At the maximum reported VTE incidence of 1.58%, performance was improved compared with the base-case, but net mortality remained higher than comparator at intermediate (+93) and broad (+433) eligibility and showed only a modest decline (−34) at restricted eligibility. Costs increased substantially but the qualitative pattern in favour of restricted eligibility remained (−$1426, $841 and $51 308/YOLS). At an arbitrary value of half the base-case VTE rate (which is below the least reported incidence of 0.34%), total costs fell because there are fewer VTE events, but the pattern in mortality was exaggerated (Table 4). These trends arise because...
the number of events, and events prevented by MT at a fixed RRR, increases as the baseline incidence increases, but the cost and clinical effects of major bleeding are augmented as the treated population grows.

2. Case-fatality rates for PE and major bleeding. Both these rates appeared high in the PREVENT study compared with literature values. Substituting more likely (lower) values for PE case-fatality reduced deaths from major bleeding and hence had the opposite effect. Under an assumption of zero deaths from major bleeding, MT caused a reduction in deaths (Table 4), as expected, but increasing survivorship entailed an increase in costs from treatment of non-fatal major bleeds.

3. Assumption regarding VTE risk in non-eligible patients. Variation in this assumption altered the estimates of VTE events avoided, but had a modest effect only on mortality and no qualitative effect on cost-effectiveness expressed as $/YOLS (Table 4).

Discussion

The provenance of the PREVENT study

The main limitation of our study is that the precision of the PREVENT trial clinical data is low because of low event numbers, indicating the possibility of chance variation from reality. The study was underpowered for clinical events, and the differences in event rates with prophylaxis were not statistically significant. In addition, some PREVENT trial outcomes were inconsistent with results from independent studies. These facts make extrapolation to a relatively large population hazardous, because the uncertainty in the trial results is subject to a multiplier effect. However, another design characteristic of the PREVENT trial means, in our view, that it is the only valid data source for our study. Of several randomised controlled trials of MT using LMWH, it alone avoided bias caused by anticoagulant therapy for sub-clinical events, at least up to the 14th day of admission. These features make our study controversial. We make the following points:

1. The PREVENT study was a model randomised controlled trial, and the largest to date reporting clinical data on DVT, PE and major haemorrhage. The data represent real scientific measurements that confirm the very low frequency of clinical thrombotic events in medical patients. The trial DVT incidence is consistent with independent study estimates, and the reported RRR for DVT with prophylaxis is similar to the RRR for sub-clinical end-points. PE events were rare but, at about half the DVT rate, consistent with other studies, although ascertainment bias may apply to PE data. We believe that the PREVENT study clinical data deserve to be analysed and disseminated. On the whole, these results appear acceptable for modelling.

2. The preceding claim cannot be made with confidence for other PREVENT results used in our model. The incidence of major bleeding was greater than in other trials, and the case-fatality rate was at the upper range of
Table 4 Estimates of VTE (DVT + PE) events avoided in survivors, net deaths avoided and economic performance ($/YOLS) according to eligibility for VTE prophylaxis (see Methods) in sensitivity analysis for selected variables

<table>
<thead>
<tr>
<th>Variable (base-case value)</th>
<th>Variation</th>
<th>Rationale</th>
<th>Percentage of population eligible for prophylaxis</th>
<th>25%</th>
<th>40%</th>
<th>80%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>VTE Deaths</td>
<td>$/YOLS</td>
<td>VTE Deaths</td>
<td>$/YOLS</td>
</tr>
<tr>
<td>Population risk of DVT (0.0043)</td>
<td>0.00215</td>
<td>50% of base-case</td>
<td>25%</td>
<td>3051</td>
<td>−158</td>
<td>NC</td>
</tr>
<tr>
<td></td>
<td>0.0158</td>
<td>Ref 13</td>
<td>40%</td>
<td>1468</td>
<td>−204</td>
<td>NC</td>
</tr>
<tr>
<td>Major bleed incidence (0.0033)</td>
<td>0.0012</td>
<td>Ref 32</td>
<td>80%</td>
<td>10 786</td>
<td>34</td>
<td>−$1426</td>
</tr>
<tr>
<td></td>
<td>Zero</td>
<td>Exploratory</td>
<td>25%</td>
<td>2928</td>
<td>−14</td>
<td>−$6387</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>40%</td>
<td>2923</td>
<td>74</td>
<td>−$3531</td>
</tr>
<tr>
<td>Case-fatality rate after major bleed (18%)</td>
<td>11.1%</td>
<td>Ref 32</td>
<td>25%</td>
<td>2936</td>
<td>−58</td>
<td>−$10 668</td>
</tr>
<tr>
<td></td>
<td>Zero</td>
<td>Exploratory</td>
<td>40%</td>
<td>2936</td>
<td>75</td>
<td>−$3500</td>
</tr>
<tr>
<td>Case-fatality rate after PE (17.7%)</td>
<td>9.05%</td>
<td>50% of base-case</td>
<td>25%</td>
<td>2973</td>
<td>−204</td>
<td>NC</td>
</tr>
<tr>
<td></td>
<td>4.6%‡</td>
<td>See legend</td>
<td>40%</td>
<td>2991</td>
<td>−222</td>
<td>NC</td>
</tr>
<tr>
<td>RRR for PE with prophylaxis</td>
<td>32%</td>
<td>Twice base-case</td>
<td>25%</td>
<td>3268</td>
<td>−94</td>
<td>−$9647</td>
</tr>
<tr>
<td></td>
<td>55.5%</td>
<td>PREVENT RRR for DVT</td>
<td>40%</td>
<td>3746</td>
<td>12</td>
<td>−$2890</td>
</tr>
<tr>
<td>Combined plausible or literature-supported values</td>
<td>Major bleed incidence 0.0012 and CFR 11.1%; PE RRR 32% and CFR 4.6%</td>
<td>25%</td>
<td>3255</td>
<td>105</td>
<td>−$6896</td>
<td>3480</td>
</tr>
<tr>
<td>Risk adjustment for non-eligible group (66%)</td>
<td>33%</td>
<td>See Methods</td>
<td>40%</td>
<td>1957</td>
<td>−192</td>
<td>NC</td>
</tr>
</tbody>
</table>

†The upper limit of symptomatic DVT risk is the highest value reported to date and the lower limit is one-half the base-case value. For the other variables, the analysis was based on values present in the literature, or were exploratory values designed to establish a frame of reference. Otherwise, input variables have base-case values. Negative values for deaths avoided indicate an increase in deaths with thromboprophylaxis, and for $/YOLS, a cost saving per YOLS; ‘NC’ indicates that the ICER was not able to be calculated because MT caused an increase in life years lost; CFR, case-fatality rate; DVT, deep vein thrombosis; ICER, incremental cost-effectiveness ratio; MT, medical thromboprophylaxis; PE, pulmonary embolus; RRR, relative risk reduction; VTE, venous thromboembolic event; YOLS, year of life saved. ‡Weighted average of case-fatality rates reported.
reported values. However, all trials have reported an added major bleeding risk, it is reported as statistically significant. Major bleeding is unlikely to have a case-fatality rate of zero, but the effect of removing its contribution is nevertheless shown in Table 4. PE events were low, as was the reported RRR with prophylaxis, and the case-fatality rates were substantially higher than independently reported values. These are substantial difficulties with a potential to bias model outputs for reasons given above. Fortunately, independent high-quality epidemiological data exist for both PE and major bleeding. We felt that it was reasonable to apply the independent data in sensitivity analysis to determine the likely range of outputs (Table 4).

3. If the independent studies are reliable (which there is no reason to doubt), the model outputs should move closer to reality. When variables supporting reduced mortality are deployed together in the model, a net reduction is shown at 25 and 40% eligibility, but a finely balanced effect occurs at 80% eligibility, which we note is the eligibility described in current Australian guidelines.

4. The value of tentative extrapolation from uncertain data lies in the capacity to generate new hypotheses, a time-honoured scientific approach and indeed the main objective of a study such as ours. As a result of this study, we are able to confirm that morbid VTE events are likely to be reduced by MT, but also to express a novel hypothesis that it may be associated with net mortality due to major bleeding that offsets the expected mortality gain from reduced fatal PE, especially if broad eligibility criteria are applied. This hypothesis provides a possible alternative explanation of why no reduction in mortality from MT has so far been documented. We note that an identical offsetting and previously unrecognized effect of haemorrhage has been found recently in the related field, also involving LMWH, of bridging anticoagulation for surgery in patients with atrial fibrillation.

Qualitatively similar clinical details have been reported in various meta-analyses, including a recent Cochrane meta-analysis, which we initially considered as a data source for our study but ultimately rejected. All the trials but one (PREVENT) included in the Cochrane analysis applied treatment anticoagulation if imaging was positive for DVT. In addition, major bleeding results in active and placebo arms were in some cases unpaired, and the selected trials included studies of unfractionated heparin, which has a higher risk of bleeding than LMWH. These aspects would have introduced important additional sources of bias to our study, without easy remedy. Although we concluded in favour of proceeding with the PREVENT data, we recognize that the approach has limitations. We regard our results as tentative, to be interpreted cautiously after reasonable sensitivity analyses, used solely for hypothesis-generating activity, and confirmed or refuted by a future clinical trial. We are happy to provide results of any combination of input variables to our model on request.

Study results

Our modelling suggests that MT is complex and likely to reduce VTE events, but has a possible adverse effect on mortality. The results are due in turn to model input variables of uncertain validity from the PREVENT trial as discussed above. The effect of most of these values is to produce model outputs in favour of our emergent hypothesis, and the effect of substituting more likely values is to moderate but not eradicate the trends arising from the PREVENT trial results unless all are deployed together in the model or extreme assumptions are made, for example, major bleeds have a case-fatality rate of zero.

Trends in effectiveness across the range of eligibility were qualitatively similar in all runs of the model. Although associated with modestly greater numbers of VTE events prevented, broad eligibility carries the penalties of higher drug acquisition and nursing costs, with increasing cost and medical penalties from major haemorrhage, including possible death. Also, as eligibility for MT is broadened to include progressively weaker risk factors, one factor (increasing age) becomes important but is controversial. Although age appears as a risk factor for thrombosis in univariate analyses, the risk effectively disappears in multivariate analysis. Thus, it can be said that elderly patients have a predisposition to thrombosis because they suffer from diseases that are thrombogenic. On the other hand, age is a risk factor for bleeding in patients with PE, atrial fibrillation or myocardial infarction. It is possible that the increased major bleeding rates found in clinical trials were due to the deployment of prophylactic LMWH in elderly patients who were not at real risk of thrombosis because their only ‘risk factor’ was advanced age. The incidence of major bleeding caused by MT is uncertain and may have been unduly high in the PREVENT trial (0.0033). Major bleeding compromises the clinical and economic standing of MT because the events are important by definition, treatment is costly and death is a possible outcome. If age was removed as a risk factor, the proportion of patients eligible for prophylaxis would be about 40%.

Our results suggest that patients who are not eligible for prophylaxis at each level of eligibility contribute to a burden of VTE, an effect that expands as eligibility is restricted. In fact, this is an inevitable result in any area
of medical practice where patients are dichotomised on the basis of risk factor analysis as being at high or low risk, and treated on that basis. In such a system, the higher the risk threshold deemed to justify treatment, the larger the untreated group will be and the more events that will occur in that group. However, as we have shown here, the existence of this reciprocal trend does not have the effect of nullifying the increased efficiency of improved patient selection.

Clinical and economic performance improves as the baseline incidence of events of interest increases, because the number of events that can be avoided by prophylaxis increases, but so do costs. This is noted for VTE in our modelling even in the relatively narrow range reported (0.34%–1.58%). Therefore, the true performance of MT remains uncertain, but even at the highest reported VTE incidence excess mortality was found at intermediate and broad eligibility under PREVENT conditions in spite of greater benefit on morbidity events.

An important underlying assumption in this study is that MT is in fact effective. This has been questioned recently in the Journal. However, it appears likely that the RRR uniformly observed across all trials using asymptomatic end-points will apply to symptomatic disease, as one follows the other. Benefit in clinical end-points has been found in most trials in spite of them being substantially underpowered, but none has reported a mortality benefit. We are uncomfortable with the notion that the clinical data should not be examined, because this opinion causes the current uncertainty over the clinical value of MT to be perpetuated, perhaps indefinitely. We suggest that the necessary ethical equipoise has emerged to justify establishment of a national study to establish the true clinical effectiveness of MT.

Our study also assumes that MT guidelines are fully complied with, but in practice non-compliance is common. Non-compliance will compromise clinical benefits and cost-savings with MT, but will also reduce detrimental effects.

Conclusion

Our modelling of the PREVENT trial data suggests that MT decreases VTE events but may have an adverse effect on mortality. It also suggests that patient selection criteria for MT should be made more restrictive, possibly by removing current age-related criteria for MT as an independent risk factor.

References


A tertiary hospital audit of opioids and sedatives administered in the last 24 h of life

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Key words
opioid, sedative, benchmark, dying, tertiary hospital.

Abstract
Background/Aim: To audit the doses of opioids and sedatives administered to patients in the last 24 h of life in an Australian tertiary hospital and compare results with doses published in New Zealand (NZ) benchmarking studies and to examine the effect of caring for dying patients using a modified version of the Liverpool Care Pathway (mLCP) in respect to doses of opioids and sedatives.

Methods: A retrospective chart audit of 102 patients who died in a tertiary hospital was carried out over a 3-month period in 2011. Diagnosis, demographic patient characteristics, use of the mLCP, use of subcutaneous infusions and key symptoms were identified. Chi-squared and the non-parametric Mann–Whitney tests were applied to compare the group differences for categorical and continuous variables as appropriate. Parenteral morphine-equivalent daily dose (pMEDD) was calculated. A t-test assessed the variable mean doses of medication and patient characteristics.

Results: Of the audited patients, 76.5% died of non-malignant disease. The overall mean dose of midazolam was significantly lower compared with that of the NZ study pMEDD (6.0 vs 20.7 mg). The overall mean dose of morphine benchmarked closely with the NZ study (56.5 mg Australian study vs 47.8 mg NZ study). A total of 83% of patients with a malignant diagnosis was supported with the mLCP compared with 51% of patients with a non-malignant diagnosis.

Conclusion: The significance of the lower midazolam doses was postulated, including the possibility of inadequate symptom control for patients with a non-malignant diagnosis. The use of the mLCP did not lead to the provision of higher doses of medications.

Introduction
The provision of palliative care in supporting dying patients at the end of life is not a matter of debate and is now endorsed as an essential element of care for all by the World Health Assembly.1 This includes the recognition of the need to update, as appropriate, national essential medicines lists in light of the recent addition of sections on pain and palliative care medicines to the World Health Organization Model List of Essential Medicines.2 There is a large body of evidence for the use of opioids for the control of pain and dyspnoea.3 Similarly, benzodiazepines are considered essential in the practice of palliative care, and anti-psychotics, such as haloperidol, are commonly used for nausea, vomiting and delirium to best support the dying patient.

There is a paucity of literature regarding the practice of caring for the dying in the acute tertiary setting, with palliative care literature largely drawing on the population of patients under the care of specialist palliative care services in dedicated units.

In 2005, a dedicated specialist palliative care service was established in this 929-bed tertiary referral teaching hospital. To better support generalists caring for dying patients across a diverse and large clinical environment, a clinical pathway for the dying patient (modified from the Liverpool Care Pathway, mLCP)4 was implemented across all clinical areas in 2009. The mLCP reached full compliance with the Marie Curie Institute, Liverpool, UK and was described as modified due to local formatting requirements for documents. The mLCP utilised full clinician engagement processes, education and a clear governance model of support.

Medication guidelines to support the mLCP were developed by the specialist palliative care service in consultation with broad representation from across the facility to reflect the best practice palliation of dying...
patients. After the introduction of the mLCP, and despite rigorous governance to support the care of the dying, concerns were ‘voiced’ as to whether patients on the pathway might be medicated in excess of their needs. To understand better the validity of this concern, an audit of opioid and sedative prescribing for the dying patient was undertaken.

Two recent studies in New Zealand (NZ) across 14 hospices benchmarked the use of opioids and sedatives in the last 24 h of life to self-assess prescribing patterns. Patients in the NZ studies were admitted under the care of specialist palliative care teams. These studies also included the use of the LCP to support patients. The intention of this study was not to compare clinical practices across the two countries but to audit the doses of opioids and sedatives administered to a patient in the last 24 h of life in an acute tertiary hospital in Australia, with and without the utilisation of the mLCP, and to review these doses with those published in the NZ benchmarking studies.

**Methods**

A retrospective clinical chart audit was carried out over 3 months on 102 patients who died consecutively in a large tertiary teaching hospital in Australia. Following the death certification of a patient in the facility, a notification was made to the study team by the Mortality Review Officer. All deaths were included, regardless of their setting, including the intensive care unit and emergency department. A low-risk ethics approval was granted prior to the commencement of the audit. Charts were audited by a single medical practitioner to maximise reliability of the information obtained.

Data collected included gender, age, dates of admission and death, length of stay, primary diagnosis, comorbidities, utilisation of mLCP, utilisation of a continuous subcutaneous infusion (CSCI) and identification of clinical symptoms by descriptors of pain, dyspnoea and delirium. Demographic characteristics of patients and principal diagnoses were identified to compare malignant and non-malignant populations. The Chi-squared and the Mann–Whitney tests were applied for categorical and continuous variables as appropriate to compare these group differences.

All doses of opioids, midazolam and haloperidol administered in the last 24 h of life were recorded, including all ‘as required’ or prn doses. No other sedative medications were included in the audit. The morphine-equivalent daily dose (parenteral) (pMEDD) was calculated according to the Edmonton method. This method was chosen to allow comparison with other international studies. The patients’ characteristics and the variation in the mean doses of haloperidol, midazolam and parenteral morphine were assessed using the t-test. The distribution of the opioids was positively skewed. A logarithmic transformation was performed to approximate a normal distribution, and a parametric t-test was applied to compare the patients’ characteristics and the variation in the mean doses of haloperidol, midazolam and parenteral morphine. When patients were prescribed sedatives but were not administered during the last 24 h of life, the doses were treated as a nil dosage and excluded from the analysis to match the method used in the NZ study. Geometric mean was estimated and compared with the NZ benchmarking studies.

**Results**

Table 1 describes the demographic and clinical features of the 102 patients. The majority of patients studied died from non-malignant disease (76.5%).

The median age of the deceased patients was 79 years, with patients with a malignant diagnosis having a longer length of stay than those with a non-malignant diagnosis (13 vs 7 days; P-value = 0.024). Patients with a malignant diagnosis were more likely to be supported by the mLCP than those with a non-malignant diagnosis (79.2% vs 53.2%). Patients supported with the mLCP were also more likely to have symptom control medications delivered with a CSCI.

There was significant symptom prevalence in the last 24 h of life, with pain recorded in 46.5%, dyspnoea in 65.3% and signs of terminal agitation with descriptors of confusion, distress and agitation recorded in 74.3% of patients. The primary cause of death (from Death Certification) is shown in Figure 1.

Respiratory failure is listed as the major cause of death (27.8%) followed closely by the group defined as cerebrovascular accident (CVA) or stroke and cerebral haemorrhage (18.6%). The predominant underlying respiratory disease was pneumonia or chronic obstructive pulmonary disease.

A total of 84% of the patients audited received an opioid in the last 24 h of life. Figure 2 shows that the pattern of opioid use in this study follows patterns that are very similar to the NZ benchmarking study, noting that hydromorphone was not available for use in NZ. Methadone has historically been the second opioid of choice in NZ with the more recent introduction of fentanyl and oxycodone preparations. Morphine (52.0%) was the most commonly used opioid in the study facility followed by fentanyl (14%) and oxycodone (10.8%). Most of the patients in this study received a single opioid except one patient who received morphine and fentanyl simultaneously.
Table 1  Patients’ demographic and clinical characteristics

<table>
<thead>
<tr>
<th>Patients’ characteristics</th>
<th>Overall (n = 102)</th>
<th>Malignant (n = 24)</th>
<th>Non-malignant (n = 78)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (IQ)</td>
<td>79 (71.0, 86.0)</td>
<td>73.5 (63.5, 83.0)</td>
<td>79.5 (73.0, 86.0)</td>
<td>0.029</td>
</tr>
<tr>
<td>Gender†, (%) (n)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>50.0 (48)</td>
<td>43.5 (10)</td>
<td>52.1 (38)</td>
<td>0.473</td>
</tr>
<tr>
<td>Male</td>
<td>50.0 (48)</td>
<td>56.5 (13)</td>
<td>47.9 (35)</td>
<td></td>
</tr>
<tr>
<td>Length of stay, median (IQ)</td>
<td>8 (4.8,14.0)</td>
<td>13.0 (5.8,36.5)</td>
<td>7.0 (4.0,12.5)</td>
<td>0.024</td>
</tr>
<tr>
<td>mLCP‡, (%) (n)</td>
<td>59.4 (60)</td>
<td>79.2 (19)</td>
<td>53.2 (41)</td>
<td>0.024</td>
</tr>
<tr>
<td>CSCI§, (%) (n)</td>
<td>58.8 (57)</td>
<td>82.6 (19)</td>
<td>51.4 (38)</td>
<td>0.008</td>
</tr>
<tr>
<td>Dementia</td>
<td>14.7 (15)</td>
<td>0.0</td>
<td>19.2 (15)</td>
<td>0.020</td>
</tr>
<tr>
<td>Pain‡</td>
<td>46.5 (47)</td>
<td>66.7 (16)</td>
<td>40.3 (31)</td>
<td>0.024</td>
</tr>
<tr>
<td>Dyspnoea‡</td>
<td>65.3 (66)</td>
<td>66.7 (16)</td>
<td>64.9 (50)</td>
<td>0.876</td>
</tr>
<tr>
<td>Delirium/confusion/ agitation‡</td>
<td>74.3 (75)</td>
<td>75.0 (18)</td>
<td>74.0 (57)</td>
<td>0.766</td>
</tr>
</tbody>
</table>

†Gender has six missing values. ‡mLCP, pain, dyspnoea, delirium/confusion/ agitation each has one missing value. §CSCI has three missing values.

CSCI, continuous subcutaneous infusion; IQ, interquartile range; mLCP, modified Liverpool Care Pathway.

Figure 1  Cause of death (Death Certificate).
Note: Other malignancies including endometrial, colorectal, squamous cell carcinoma and glioblastoma multiforme. ACS, acute coronary syndrome; BMT-GVHD, bone marrow transplant graft versus host disease; COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident; MI, myocardial infarction.

Figure 2  Pattern of opioid use in an Australian tertiary hospital compared with the New Zealand benchmarking study.
The overall mean dose of pMEDD was close to that of the NZ benchmarking study (56.5 mg Australian study vs 47.8 mg NZ study) as shown in Table 2. Both studies showed that patients with malignant disease received on an average significantly higher doses of pMEDD than patients with non-malignant disease (Australian study: 99.1 vs 46.3 mg; \( P \)-value 0.002) and NZ study 53.8 vs 26.0 mg; \( P \)-value <0.001). In comparison with the NZ study, irrespective of diagnosis, all patients were administered higher doses of pMEDD (malignant diagnosis: 99.1 mg Australian study vs 53.8 mg NZ study; non-malignant diagnosis: 46.3 mg Australian study vs 26.0 mg NZ study). The mean pMEDD for those patients managed according to the mLCP was 61.1 mg, (range: 47.0–79.5 mg) with no significant difference from the pMEDD for those not managed on the mLCP (49.6 mg, range: 32.9–74.7 mg). There was a close correlation of pMEDD for patients cared for with the mLCP and LCP (NZ) (61.1 mg Australian study vs 63.1 mg NZ study).

Midazolam was the benzodiazepine provided to the majority of patients in this study. Two patients received clonazepam, and two patients received temazepam; both drugs were excluded from the calculations. As presented in Table 3, the overall mean midazolam dose in the Australian study setting was significantly lower than that in the NZ study (6.0 vs 20.7 mg). Patients with a non-malignant diagnosis received significantly lower doses of midazolam compared with patients with a malignant diagnosis (4.8 vs 9.2 mg; \( P \)-value = 0.006). The exclusion of 0 mg doses of medication (i.e. where prescribed but not administered) had the effect of significantly reducing the number of patients with non-malignant conditions included in the analysis of sedatives. Whilst the proportion of patients dying from non-malignant disease was much higher in this study, the actual total number included in the analysis of sedatives was similar between Australia and NZ (27 vs 22), but the mean doses were dissimilar (4.8 vs 12.5 mg).

Midazolam was the preferred benzodiazepine prescribed in association with the mLCP. There was no significant difference between patients managed on the mLCP who received a mean dose of 6.6 mg compared with those not managed on the mLCP who received 5.1 mg.

Haloperidol was the first-line antipsychotic prescribed at the study facility. No audited patients were prescribed levomepromazine or other major tranquillisers. The overall mean dose of haloperidol was very similar in both studies (2.4 mg NZ study vs 2.7 mg Australian study) as shown in Table 4. There was no significant difference between the doses of haloperidol for patients cared for with and without the mLCP (1.3 vs 2.3 mg).

### Discussion

The majority of Australians die each year in acute tertiary hospitals. In 2011–2012, 51% of all deaths occurred in an admitted-patient setting, and 39.5% had been a palliative care patient in their final admission.9

This study was unique in that there has been little evidence regarding the clinical characteristics and diagnoses of those admitted patients previously. This study included all consecutive deaths at a single site, an acute tertiary hospital where there is palliative care consultation only. This is in contrast to the NZ study where the audited patients were under the care of specialist palliative care teams in multiple settings, including at home and in-patient palliative care units.

### Table 2 Patients’ characteristics and the average doses of parenteral morphine (pMEDD) (in milligrams) comparison between the Australian tertiary hospital and the New Zealand benchmarking study

<table>
<thead>
<tr>
<th>Patients’ characteristics</th>
<th>Parenteral morphine daily dose (pMEDD)†</th>
<th>Tertiary hospital Australia</th>
<th>New Zealand benchmarking study</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Geometric mean (95% CI)</td>
<td>( P )-value</td>
<td>Geometric mean (95% CI)</td>
</tr>
<tr>
<td>Overall</td>
<td>77</td>
<td>56.5 (45.5, 70.1)</td>
<td>—</td>
</tr>
<tr>
<td>Gender‡</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>36</td>
<td>55.9 (39.8, 78.3)</td>
<td>0.877</td>
</tr>
<tr>
<td>Male</td>
<td>35</td>
<td>53.9 (39.4, 73.7)</td>
<td></td>
</tr>
<tr>
<td>Malignant§</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>20</td>
<td>99.1 (66.6, 147.2)</td>
<td>0.002</td>
</tr>
<tr>
<td>No</td>
<td>57</td>
<td>46.3 (36.3, 59.0)</td>
<td></td>
</tr>
<tr>
<td>mLCP §§</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>51</td>
<td>61.1 (47.0, 79.5)</td>
<td>0.374</td>
</tr>
<tr>
<td>No</td>
<td>25</td>
<td>49.6 (32.9, 74.7)</td>
<td></td>
</tr>
</tbody>
</table>

†pMEDD has one missing value. ‡Gender has six missing cases. §MlCP has one missing value. ; CI, confidence interval; mLCP, modified Liverpool Care Pathway; pMEDD, parenteral morphine-equivalent daily dose.
The majority of patients in this study had a non-malignant primary diagnosis (76.5%), with the majority dying of respiratory or cerebrovascular disease. Across Australia in 2011–12, 73.8% of patients with a primary diagnosis of malignancy received specialist palliative care in their final admission compared with 24% of patients with a primary non-malignant diagnosis.9

In both, this study and the NZ study, the mean dose of opioids for patients with malignant diagnoses is significantly higher than those with non-malignant diagnoses. This phenomenon might be explained by the longer-term use of opioids in patients with cancer, with the inherent pain and symptom burden leading to death. Whilst such a requirement has not been specifically studied, Sykes et al. have compared the rate of increase in opioid doses leading to death in four studies of patients mostly with malignancy in palliative care settings. They demonstrated that 42–76% of patients were using opioids prior to the dying phase.10

Patients supported by specialist palliative care were not specifically identified in this study, but the use of the mLCP acted as a surrogate marker. In the context of being dying in an acute hospital, the study examined the

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**Table 3** Patients’ characteristics and the average doses of Midazolam (in milligrams) comparison between the Australian tertiary hospital and the New Zealand benchmarking study

<table>
<thead>
<tr>
<th>Patients’ characteristics</th>
<th>Tertiary hospital Australia</th>
<th>New Zealand benchmarking study</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Geometric mean (95% CI)</td>
</tr>
<tr>
<td>Overall</td>
<td>41</td>
<td>6.0 (4.8, 7.6)</td>
</tr>
<tr>
<td>Gender‡</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>22</td>
<td>5.3 (3.7, 7.5)</td>
</tr>
<tr>
<td>Male</td>
<td>16</td>
<td>7.1 (4.8, 10.2)</td>
</tr>
<tr>
<td>Malignant§</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>14</td>
<td>9.2 (6.3, 13.2)</td>
</tr>
<tr>
<td>No</td>
<td>27</td>
<td>4.8 (3.6, 6.3)</td>
</tr>
<tr>
<td>mLCP¶</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>30</td>
<td>6.6 (4.9, 8.8)</td>
</tr>
<tr>
<td>No</td>
<td>10</td>
<td>5.1 (3.3, 7.5)</td>
</tr>
</tbody>
</table>

†95% CI of the geometric mean is not available in the New Zealand study. ‡Gender has three missing cases. §In the New Zealand study, malignant and non-malignant patients died under the care of hospice (variable settings including home). ¶mLCP has one missing case. mLCP, modified Liverpool Care Pathway.

**Table 4** Patients’ characteristics and the average doses of haloperidol (in milligrams) comparison between the Australian tertiary hospital and the New Zealand benchmarking study

<table>
<thead>
<tr>
<th>Patients’ characteristics</th>
<th>Tertiary hospital Australia</th>
<th>New Zealand benchmarking study</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Geometric mean (95% CI)</td>
</tr>
<tr>
<td>Overall</td>
<td>53</td>
<td>2.4 (2.0, 2.9)</td>
</tr>
<tr>
<td>Gender‡</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>27</td>
<td>2.4 (1.8, 3.1)</td>
</tr>
<tr>
<td>Male</td>
<td>23</td>
<td>2.4 (1.7, 3.3)</td>
</tr>
<tr>
<td>Malignant§</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>20</td>
<td>3.0 (2.3, 4.0)</td>
</tr>
<tr>
<td>No</td>
<td>33</td>
<td>2.1 (1.6, 2.7)</td>
</tr>
<tr>
<td>mLCP¶</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>36</td>
<td>1.3 (1.1, 1.4)</td>
</tr>
<tr>
<td>No</td>
<td>17</td>
<td>2.3 (1.5, 3.3)</td>
</tr>
</tbody>
</table>

†95% CI of the geometric mean is not available in the New Zealand study. ‡Gender has three missing cases. §In the New Zealand study, malignant and non-malignant patients died under the care of hospice (variable settings including home). CI, confidence interval; mLCP, modified Liverpool Care Pathway.
use of opioids and sedatives and the relationship of the use of the mLCP to these medications.

There has been more recently intense scrutiny of the LCP in the UK, resulting in an enquiry and its resultant phasing out. As a consequence, there have been significant international developments to ensure more robust and compassionate processes for the care of the dying.11 Of note in this study, having a non-malignant diagnosis demonstrated a reduced likelihood of care with the mLCP in comparison with patients with cancer diagnoses. The concerns initially voiced regarding the introduction of the mLCP within the acute facility and the administration of medications to support care with the mLCP were not supported by the results in this study. In relation to the effect on the pMEDD, with the use of the mLCP, there was no demonstrated difference in pMEDD. For those patients with malignancy, the mean doses of pMEDD were very similar to the NZ opioid benchmark study.

In this study, patients with malignancy were largely cared for within a designated cancer care unit and were more likely to have been supported with the mLCP. The transition to dying is more likely to be recognised in a patient with malignancy, thus meeting the criteria for dying with the mLCP.12

There was significant symptom burden in the study patients in the last 24 h of life. A total of 65.3% of the study patients experienced dyspnoea. Reassuringly, in respect to use of opioids, the overall mean pMEDD provided to these patients indicated recognition of the positive effect of an opioid to palliate dyspnoea.13

Evidence of distress and agitation in the last 24 h of life was predominant, with documentation in 74.3% of patients.

There were significant limitations with the interpretation of the audit data. Symptom recording and symptom relief were not able to be linked to the administration of a medication; hence, relief of a symptom was not able to be assessed.

The mean dose of midazolam administered in this study was 6.0 mg compared with 20.7 mg in the NZ study. It is postulated that this difference may have indicated a reluctance to administer sedatives for symptom control. Alternatively, the variance may reflect a difference in prescribing patterns between the NZ specialist palliative care or hospice providers and the generalist setting within an acute tertiary hospital. However, it is noted that in an international multi-centre study of sedation by Fainsinger et al.14 and an Australian study by Good et al.15 the mean midazolam doses were remarkably similar to the mean midazolam doses in NZ. The results may highlight a stigma related to use of sedatives15 and a resulting reluctance to manage dyspnoea and agitation in patients with a non-malignant diagnosis with sedatives. However, without more comprehensive symptom relief data, it is not possible to draw such a conclusion in this study.

It is recognised that prognostication in the group of patients with chronic disease or non-malignant diagnoses is more difficult due to the inherently unpredictable nature of end-stage chronic disease.16 The concept of a transition to dying or ‘diagnosing dying’ has been described previously as being essential to the provision of optimal symptom control in the context of treatment in an acute facility.12 However, for the patient with a non-malignant condition, this may not be achievable. Providing care that synchronously supports judicious active treatment that ameliorates the underlying condition with symptom control would obviate the need for determining whether a patient was in a terminal phase. Palliation and clinical management of a condition should not be mutually exclusive when the treatments are not burdensome or deemed futile. In this context, the recognition of a transition to dying would not be pivotal to the provision of a ‘good death’. There might rather be the recognition of clinical deterioration and the need for palliation, which identifies the palliative phase of the illness. Other research has demonstrated that there is a need to identify better the palliative phase of non-malignant conditions so as to undertake appropriately advance care planning, ensure access to symptom management and provide support to patients and their families.17

This study has implications for those caring for patients with chronic non-malignant disease with the evidence of significant symptom burden in the last 24 h of life. Whilst there are significant limitations within this study, a previous study in a large tertiary hospital in Australia confirmed that the majority of dying patients were not referred for palliative care support, and there were reported concerns regarding evidence of deficits in the care of these dying patients.18 Given that patients with a primary non-malignant diagnosis are significantly less likely to be referred to palliative care for symptom support, the onus to provide the best care of these patients ‘rests’ with the treating physician.

Conclusions

This study was initiated to understand the doses of opioids and sedatives administered to dying patients in an Australian tertiary facility and to review the doses prescribed to dying patients managed on the mLCP. A comparison was made with previous benchmarking studies of patients cared for by specialist palliative care. There was no significant difference of medication doses with the use of the mLCP. The diagnoses of CVA and
respiratory failure were the most common causes of death. Dyspnoea and distress were highly prevalent in the last 24 h of life. The most common opioid prescribed was morphine, and the overall mean pMEDD was comparable with the NZ study.

The lower doses of sedatives prescribed to patients with non-malignant disease in this study may be interpreted as a reluctance to administer sedatives but may also reflect differences between the management of malignant and non-malignant disease and between the generalist and specialist settings.

The difficulty in diagnosing the transition to dying in this group of patients, coupled with concerns of inducing deterioration, may have limited clinicians optimally prescribing and administering sedative medications for the management of distress and agitation. An alternative paradigm of dual care is suggested.

As the majority of Australians die in acute facilities, the results of this study may be significant. Whilst there is limited evidence of the effect of medication on symptom relief and the quality of these deaths, there is a need for further research, particularly in respect to the quality of deaths of patients with chronic, non-malignant disease.

Acknowledgements

The authors acknowledge the close support of Carol Parker, Mortality Review Coordinator and Marcella Choudhury, Interviewing Officer at the Royal Brisbane and Women’s Hospital

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Associations of demographic and behavioural factors with glycaemic control in young adults with type 1 diabetes mellitus

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Key words
type 1 diabetes, young adult, glycosylated haemoglobin A, psychosocial factor, behaviour.

Abstract
Background: Despite recognised benefits of optimal glycaemic control in patients with type 1 diabetes mellitus (T1DM), good control is still difficult to achieve, particularly for adolescents and young adults. Recognition of factors that may assist early optimisation of glycaemic control is therefore important.
Aims: We explored associations of demographic, social and behavioural factors with glycosylated haemoglobin (HbA1c) levels in participants with T1DM aged 18–25 years.
Methods: A cross-sectional analysis was performed on young adults attending a dedicated multidisciplinary clinic at Fremantle Hospital, Western Australia from January to August 2014.
Results: Data from 93 participants were analysed. Mean age was 21.4 ± 2.3 years, and 39.8% of the cohort were female. Longer duration of diabetes was associated with higher HbA1c (r = 0.25, P = 0.04). Men had lower HbA1c than women (8.2 ± 1.6 vs 9.2 ± 2.0%, P = 0.01). Increased frequency of clinic attendance was associated with lower HbA1c (r = −0.27, P = 0.02). Those engaged in work or study had better HbA1c compared with those who were not (8.9 ± 2.1 vs 10.5 ± 2.1%, P = 0.03). Socioeconomic disadvantage, risk-taking behaviour, insulin pump use and distance travelled to clinic were not associated with differences in HbA1c.
Conclusion: In young adults with T1DM, geographical separation, socioeconomic disadvantage and risk-taking behaviours did not influence glycaemic control. Longer duration of diabetes identifies young adults at higher risk of poor control, while attendance at a multidisciplinary clinic and engagement in work or study was associated with better glycaemic control. Additional studies are warranted to clarify the role of behavioural interventions to improve diabetes management in young adults.

Introduction
Australia is ranked amongst the top 10 countries in the world for its incidence and prevalence of type 1 diabetes mellitus (T1DM) in children and young adults.1 Diabetes as a whole represents the fourth largest contributor to the overall burden of disease in Australia, placing it within the top eight national health priority conditions.2 In adults with T1DM, glycaemic control reduces diabetic complications, which is one of the principal goals of diabetes management.3 Studies of young adults with T1DM have shown that a period of tight glucose control is associated with long-term reduction in micro- and macro-vascular complications and improved beta-cell function.4–6 The Australian Diabetes Society recommends a target glycosylated haemoglobin (HbA1c) of <7%; however, individualisation based on patient factors needs to be considered.3 Thus, it is important to identify factors that can positively or negatively influence glycaemic control and in turn modulate risk of complications and burden of disease.
The period of transition from a paediatric to adult diabetes clinic is marked with uncertainty and inconsistent behavioural patterns that may impact diabetes self-care.7 Adherence to treatment is suboptimal in the young adult population who are irregular attendees at outpatient clinics.7,8 Furthermore, young adults with T1DM have increased levels of psychological distress.9 Youth of lower socioeconomic status are less likely to use adaptive coping strategies, suggesting that this demographic may require additional support and services.10 These factors, amongst others, contribute to the higher HbA1c seen in many young adults7,11,12 and increase the likelihood of...
developing long-term complications. The transition between child and adult services is recognised as a high-risk period, although studies assessing the impact of healthcare transition on outcomes for young people with T1DM are limited.\(^8\) Thus, determining factors that act as barriers for achieving optimal glycaemic control in youth may help to improve the quality of services provided.

The aim of this study was to analyse physical, psychosocial and behavioural factors contributing to glycaemic control in patients aged 18–25 years with T1DM who attended a dedicated multidisciplinary diabetes clinic. We examined associations of socio-demographic factors, clinic attendance, mode of insulin delivery, engagement in risk-taking behaviours and occupational and educational status with glycaemic control in this population.

**Methods**

**Study cohort**

We conducted a systematic review of medical records for patients aged 18–25 attending the Fremantle Hospital Young Adult Clinic (YAC) with T1DM from 1 January 2014 to 31 August 2014. Fremantle Hospital is a tertiary adult teaching hospital that services the Southern Metropolitan Region of Perth, Western Australia. The Fremantle Hospital YAC population comprises direct referrals to a tertiary adult diabetes centre and the transition patients from Princess Margaret Hospital, the major tertiary paediatrics centre in Western Australia. The transition patients from Princess Margaret Hospital make up approximately 75% of the attendees at the YAC. A standardised data collection tool was used to record medical, social and behavioural information from medical records by study investigators. Exclusion criteria included those aged <18 or >25 and those who did not attend the YAC within the study time frame. For patients with repeat visits, data from the most recent visit were analysed. The study was approved by the Clinical Governance Unit, Fremantle Hospital.

Risk-taking behaviours (defined as smoking, excessive alcohol intake or illicit drug use), involvement in physical activity, eating behaviours (recorded as missing meals, body image issues or advice to change from healthcare professionals), polypharmacy and the use of an insulin pump versus injected insulin were assessed. Excessive alcohol consumption was defined as >14 standard drinks per week for males and >7 standard drinks per week for females. Illicit drugs were defined as illegal drugs of abuse. Smoking was recorded if it had been noted in the patient’s file within the previous year from the date of data collection. Other variables that were assessed include study or employment status, Index of Relative Socioeconomic Disadvantage (IRSD) – obtained through the Australian Bureau of Statistics (ABS)\(^13\) and distance of the patient’s primary residence from the YAC – obtained through Google maps (https://www.google.com.au/maps). Other social factors, such as relationship status, driver’s licence status, hobbies and several first-degree relatives with T1DM, were collated. HbA1c was used as a measure of glycaemic control.

**Data collection and statistical analysis**

Data were collected using a dedicated data collection tool (Appendix I). This data collection tool was developed by the Fremantle Hospital Department of Endocrinology and Diabetes and was designed to capture information regarding glycaemic control, diabetes-related complications, method of insulin administration and behavioural and social factors affecting diabetes care.\(^14\) This was used by the study investigators (JO, JP and MW) to extract and record relevant information from hard copy hospital medical records. Data entry methods were standardised and tested for reproducibility on a weekly basis by having each recorder assess the same medical record blinded to the results of the others. There was <10% variance in data collection between recorders over the course of the study. We used the Statistical Package for Social Sciences (version 22.0, IBM Corp, Armonk, NY, USA) to analyse the data. Comparison of means was performed using one-way analysis of variance. Bivariate correlations were performed using Spearman’s rank correlation coefficient. We considered two-tailed \(P\)-values <0.05 to be significant.

**Results**

**Baseline characteristics of the study cohort**

Between January and August, 97 patients attended the YAC at Fremantle Hospital. Of these patients, four were excluded as they were >25 years at the time of data collection, leaving 93 who were included in the analyses.

Of the 93 patients, 56 (60.2%) were male (Table 1). Mean age of participants was 21.4 ± 2.3 years, with the average duration of diabetes being 10.0 ± 6.0 years. Twenty patients were receiving insulin through a subcutaneous pump (21.5%). Mean duration of diabetes was lower in males (8.1 ± 5.7 for males vs 12.9 ± 5.4 for females). Retinopathy was recorded in three patients (one male, two female), and risk-taking behaviours, including excessive consumption of alcohol, smoking and illicit drug use, were recorded in 23 patients.
(excessive alcohol intake in 11, smoking in 13 and illicit drug use in 10). Participants lived an average of 12.3 km from the clinic.

**Associations of sex, occupational and educational status and method of insulin delivery with glycaemic control**

HbA1c was lower in males compared with females (8.2 ± 1.4 vs 9.2 ± 2.0%, \( P = 0.012 \)) (Table 2). Those engaged in full- or part-time work and/or study had lower HbA1c compared with those not engaged in either (8.4 ± 1.6 vs 9.7 ± 2.0%, \( P = 0.022 \)). There was no difference in HbA1c for those using insulin pumps compared with those who were on basal-bolus insulin (Table 2). There was no difference in HbA1c when comparing those reporting risk-taking behaviour to those who did not (8.4 ± 1.94 vs 8.7 ± 1.7, \( P = 0.574 \)). The male and female number of YAC clinic visits was comparable. Males missed fewer clinic visits compared with females (0.9 ± 1.1 vs 1.5 ± 1.4, \( P = 0.026 \)). Total daily insulin doses for those using insulin pumps were lower than those not using pumps (39.9 ± 19.1 vs 59.6 ± 19.9 units, \( P = 0.002 \)).

**Associations of socio-demographic factors, duration of diabetes and clinic attendance with glycaemic control**

There was a positive association between duration of diabetes and HbA1c (\( r = 0.247, P = 0.038 \)) (Table 3). There was an inverse association between the number of clinic visits and glycaemic control (\( r = -0.269, P = 0.020 \)). Age, distance of residence from clinic, IRSD, travel time and missed appointments were not associated with HbA1c (Table 3). Distance from clinic was not associated with either missed or total visits (\( r = 0.113, P = 0.291 \) and \( r = -0.009, P = 0.519 \) respectively).

**Discussion**

In this cross-sectional analysis of T1DM patients aged 18–25 years, several factors were associated with better glycaemic control. These include engagement in study or work, shorter duration of diabetes and frequency of clinic attendance. There was no association between glycaemic control and socioeconomic status, risk-taking behaviours, distance travelled to the outpatient clinic and use of insulin pumps.

Studies assessing the association between employment or education and glycaemic control in young adults with

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**Table 1** Baseline characteristics of the study cohort. Data expressed as number (%) and mean ± SD

<table>
<thead>
<tr>
<th></th>
<th>Males</th>
<th>Females</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (%)</td>
<td>56 (60.2)</td>
<td>37 (39.8)</td>
<td>93 (100)</td>
</tr>
<tr>
<td>Pump users (%)</td>
<td>8 (8.8)</td>
<td>12 (13.2)</td>
<td>20 (22.0)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>21.5 ± 2.4</td>
<td>21.2 ± 2.1</td>
<td>21.4 ± 2.3</td>
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<tr>
<td>BMI (kg/m²)</td>
<td>24.8 ± 4.5</td>
<td>23.8 ± 4.1</td>
<td>24.4 ± 4.4</td>
</tr>
<tr>
<td>Time since diagnosis (years)</td>
<td>8.0 ± 5.6</td>
<td>12.8 ± 5.4</td>
<td>9.9 ± 6.0</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>8.24 ± 1.35</td>
<td>9.23 ± 2.01</td>
<td>8.64 ± 1.71</td>
</tr>
<tr>
<td>Retinopathy (%) (n = 65)</td>
<td>1 (1.5)</td>
<td>2 (3.0)</td>
<td>3 (4.6)</td>
</tr>
<tr>
<td>Smoking (%) (n = 76)</td>
<td>9 (11.8)</td>
<td>4 (5.2)</td>
<td>13 (17.1)</td>
</tr>
<tr>
<td>High-risk alcohol (%) (n = 77)</td>
<td>7 (9.1)</td>
<td>4 (5.2)</td>
<td>11 (14.3)</td>
</tr>
<tr>
<td>Drug use (%) (n = 78)</td>
<td>7 (8.9)</td>
<td>3 (3.8)</td>
<td>10 (12.8)</td>
</tr>
<tr>
<td>All risk taking (%) (n = 93)</td>
<td>15 (16.1)</td>
<td>8 (8.6)</td>
<td>23 (24.7)</td>
</tr>
<tr>
<td>Distance from clinic (km) (n = 93)</td>
<td>10.65 ± 12.01</td>
<td>14.64 ± 22.94</td>
<td>12.31 ± 17.40</td>
</tr>
</tbody>
</table>

BMI, body mass index; HbA1c, glycosylated haemoglobin.

**Table 2** Factors associated with glycaemic control: between-group comparisons. Data are mean ± SD

<table>
<thead>
<tr>
<th>Outcome variable</th>
<th>Group 1</th>
<th>Group 2</th>
<th>( P )-value</th>
</tr>
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<tbody>
<tr>
<td>HbA1c (%)</td>
<td>Male 8.24 ± 1.35</td>
<td>Female 9.23 ± 2.01</td>
<td>0.012</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>Work/study 8.44 ± 1.60</td>
<td>No work/study 9.66 ± 1.95</td>
<td>0.022</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>Pump users 8.54 ± 1.31</td>
<td>Non-pump users 8.76 ± 1.74</td>
<td>0.654</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>Risk-takers 8.39 ± 1.92</td>
<td>Non-risk-takers 8.69 ± 1.70</td>
<td>0.574</td>
</tr>
<tr>
<td>Missed visits</td>
<td>Male 0.9 ± 1.0</td>
<td>Female 1.4 ± 1.3</td>
<td>0.026</td>
</tr>
<tr>
<td>Total visits</td>
<td>Male 3.1 ± 2.2</td>
<td>Female 3.0 ± 2.3</td>
<td>0.957</td>
</tr>
</tbody>
</table>

HbA1c, glycosylated haemoglobin.
Type 1 diabetes control in young adults

Our T1DM. Longer duration of T1DM increases the risk of complications related to worse glycaemic control. This is consistent with previous findings in young adults with T1DM.

The implications of this finding are that young adults with longer duration of T1DM should be monitored, supported and encouraged to maintain attention to diabetes self-care. Females in our cohort had worse glycaemic control compared with males. A systematic review of demographic and personal factors associated with glycaemic control and self-care in youth with T1DM showed a trend towards higher HbA1c in adolescent girls. Further studies are therefore required to clarify the role of gender on glycaemic control in youths with T1DM.

We found a significant relationship between the number of clinic visits and lower HbA1c. A previous study of patients with T1DM who were diagnosed before age 40 identified access to nurse educators as a determinant of glycaemic control. While we did not categorise clinic visits into appointments with the medical practitioner, nurse educator, dietitian or psychologist, many visits to the clinic involved patient interactions with more than one member of the diabetes team. Our findings support the importance of providing access to dedicated multidisciplinary care for young adults with T1DM, with encouragement to keep scheduled appointments.

Socioeconomic status and travel distance was not associated with glycaemic control in our cohort of patients. This is in contrast to findings from a systematic review reporting an inverse association between socioeconomic status and diabetes control in youths with T1DM. Similar inverse relationships have been demonstrated in older patients with T1DM. Socioeconomic status in our study was determined based on the IRSD developed by the ABS through the socio-economic indexes for areas survey. Chaturvedi et al. defined socioeconomic status based on level of education, while Secrest et al. utilised income level. The differences in our results may therefore be due to different definitions of socioeconomic status. IRSD is determined by Australian postcode and therefore does not describe the individual’s relative disadvantage but rather that of the area they lived in at the time of the study. Of note, travel distance was not associated with glycaemic control in our cohort. Therefore, within a metropolitan area, distance and classification of socioeconomic status based on residential location does not appear to be a barrier to diabetes care, possibly because our patients had access to appropriate transportation to attend clinic.

In our study, 20 of the participants received insulin through an insulin pump. The use of an insulin pump was not associated with improved glycaemic control compared with multiple daily injections. These findings differ with previous research. A meta-analysis of 23 studies containing 976 patients comparing continuous subcutaneous insulin infusion (CSII) and three or more insulin injections per day found a statistically significant difference in terms of glycaemic control between the two groups. Those using CSII had, on average, an HbA1c that was 0.3% less than those on insulin injections. Given this small difference, our cohort size may have been too small to reflect a subtle effect of pump use on glycaemic control in our cohort. While we did not find a difference in glycaemic control in patients on an insulin pump versus patients using multiple daily injections, the use of an

<table>
<thead>
<tr>
<th>Variables</th>
<th>Correlation coefficient (r)</th>
<th>P-value</th>
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<tbody>
<tr>
<td>Diabetes duration (years)</td>
<td>0.247</td>
<td>0.038</td>
</tr>
<tr>
<td>Visits (n)</td>
<td>−0.269</td>
<td>0.020</td>
</tr>
<tr>
<td>Age (years)</td>
<td>−0.155</td>
<td>0.185</td>
</tr>
<tr>
<td>Distance (km)</td>
<td>−0.153</td>
<td>0.199</td>
</tr>
<tr>
<td>IRSD</td>
<td>−0.101</td>
<td>0.399</td>
</tr>
<tr>
<td>Travel time (h)</td>
<td>−0.169</td>
<td>0.157</td>
</tr>
<tr>
<td>Missed visits (n)</td>
<td>0.177</td>
<td>0.317</td>
</tr>
</tbody>
</table>

HbA1c, glycosylated haemoglobin; IRSD, index of relative socioeconomic disadvantage.

T1DM are lacking. Interestingly, we identified an association between engagement in study and/or employment and better glycaemic control. It is plausible that the regular routine or cognitive functioning required for work or study facilitates executive functioning and motivation, lending itself to beneficial self-care behaviours. A systematic review of studies assessing the association of executive functioning and adherence and glycaemic control in youths with T1DM found a positive association between these variables. Furthermore, a study of patients with type 2 diabetes mellitus aged more than 25 years found that employment was associated with better health literacy and self-efficacy, both of which are thought to contribute directly and indirectly to self-care behaviours. Therefore, participation in work or study may be associated with psychological or other factors that facilitate improved self-care. Alternatively, better glycaemic control may allow for engagement in study or work due to improved confidence or well-being, or patients with good glycaemic control may be inherently highly motivated and more likely to be working or studying. It has previously been found that young adults with T1DM find diabetes management difficult in the workplace; however, our findings reassure that study and work can be encouraged in young adults with T1DM.

We found that longer duration of diabetes was associated with worse glycaemic control. This is consistent with findings from another observational study of youths with T1DM. Longer duration of T1DM increases the risk of developing diabetic complications. Pre-pubertal duration of disease contributes to the development of diabetic retinopathy in the adolescent and young adult years. The implications of this finding are that young adults with longer duration of T1DM should be monitored, supported and encouraged to maintain attention to diabetes self-care. Females in our cohort had worse glycaemic control compared with males. A systematic review of demographic and personal factors associated with glycaemic control and self-care in youth with T1DM showed a trend towards higher HbA1c in adolescent girls. Further

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insulin pump was associated with a lower total daily dose of insulin.

Adolescence is associated with a period of substance experimentation with the attendant risk of developing a substance use disorder. The developing adolescent brain may be vulnerable to negative impacts of substance abuse, and the likelihood of developing an addiction is inversely associated with the age of first substance use. Of note, risk-taking behaviours defined as a composite of substance use (smoking, excessive alcohol intake or illicit drug use) did not appear to affect glycaemic control. Other risk-taking behaviours, including insulin mismanagement and disordered eating behaviours, were not examined in this study. Previous studies assessing the associations between smoking and glycaemic control have reported contrasting results. Two large studies in children and adolescents consisting of 27,561 and 629 participants found that smoking was associated with worse glycaemic control. A further study consisting of participants with T1DM aged 18–59 years found that smoking was associated with higher HbA1c. Alcohol intake has been associated with increased glycaemic variability in adolescents and increased frequency of hypoglycaemia in adults; however, studies of alcohol intake and glycaemic control in adolescents are lacking. The effects of illicit drug use on diabetic control are unclear. Therefore, further studies would be needed to ascertain whether risk-taking behaviours, in particular alcohol and illicit drug use, affect glycaemic variability and their impact on other self-care behaviours. Our population was aged 18–25 years; however, studies suggest a significant increase in substance use with emerging adulthood and ongoing changes in trends associated with age. Furthermore, in industrialised societies, establishment of life-long behaviours may not occur until 25–30 years. Thus, risk-taking behaviours and their associations with diabetes self-care and control may continue to evolve above and beyond the age range that we studied.

Strengths of our study include the focus on young adults and the examination of current employment, education and risk-taking behaviours in relation to glycaemic control, which are relevant to this age group. There are several limitations to this study. As this was a cross-sectional analysis, causation cannot be inferred. Furthermore, this study was a convenience sample of clinic attendees. Patients who lack motivation or capacity to attend hospital-based clinics may be under-represented. The study focused on a single site, which was the referral centre for the Southern Metropolitan area of Perth, providing a reasonably representative sample of this group of patients. Our sample size was limited, which restricts the analyses we can conduct. As outpatient notes were the basis of our data collection, we relied on their accuracy and completeness. The use of novel instruments, such as ‘Google maps’, for distance calculations may lead to bias. While the distances were calculated using the same third-party software for all patients, comparisons were not made with other tools designed to make the same calculations.

Conclusion

The findings of this cohort study have several potential clinical implications. First, these results support encouraging young patients with T1DM to engage in employment and/or study given its association with better glycaemic control. Second, within a metropolitan area, socioeconomic status, travel duration and distance may not be a factor influencing glycaemic control; rather, the frequency of clinic appointments was more important. The provision of care in the form of dedicated multidisciplinary clinics for young adults with T1DM represents an appropriate means to support diabetes self-care in this age group. Therefore, young adults with T1DM should be given appropriate encouragement to maintain regular contact with these multidisciplinary clinics. Given the limited sample size in this study, further studies in other populations are required to confirm these findings and explore in greater depth the associations of substance use and gender with glycaemic control. Additional research is warranted to determine whether the influence of study and/or work on glycaemic control reflects underlying behavioural traits or represents an avenue for applied behavioural interventions to improve glycaemic control in this population.

Implications for practice

- Where appropriate, encourage young adults with type 1 diabetes to study or work; these behaviours are associated with better glycaemic control.
- Visits to a multidisciplinary clinic for young adults with type 1 diabetes are associated with better HbA1c values.
- Longer duration of type 1 diabetes in this age group identifies patients at risk of poorer control.

References

Type 1 diabetes control in young adults


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Appendix I

Date of data collection: __/__/__

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**Medical Information:**

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<td>Years with disease: ________</td>
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<td>Doctor concern? Y N</td>
<td>Patient concern? Y N</td>
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<td>Random glucose <em><strong>/</strong></em> <em><strong>/</strong></em></td>
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<td>Real time sensor? Y N</td>
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<td>HBA1c <em><strong>/</strong></em> <em><strong>/</strong></em></td>
<td># periods &lt;12 mths: __________</td>
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**Medications:**

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<td>Dose:</td>
<td>Frqcy:</td>
</tr>
<tr>
<td>3:</td>
<td>Dose:</td>
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Inaccurate risk perceptions contribute to treatment gaps in secondary prevention of cardiovascular disease

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Key words
risk perception, cardiovascular diseases, secondary prevention.

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Abstract

Background: All patients with cardiovascular disease (CVD) are at high risk of recurrent events. Despite strong evidence, large treatment gaps exist in CVD secondary prevention. We hypothesise that patients’ self-perception and general practitioner’s (GP) assessment of future cardiovascular (CV) risk may influence secondary prevention behaviours.

Aim: To examine in patients with known CVD the perceived risk of future CV events and its relationship with use of secondary prevention medications and risk factor control.

Methods: We examined patient and practitioner’s perceived risk and its relationship with the uptake of secondary prevention recommendations in adults with CVD participating in the Australian Hypertension and Absolute Risk Study.

Results: Among the 1453 participants, only 11% reported having a high absolute risk and 29% reported high relative risk of recurrent events. The GP categorised only 30% as having a 5-year risk ≥15%. After adjusting for covariates, hospitalisation within the preceding 12 months was the only significant predictor of patients’ accurate risk perception. Conventional CV risk factors were predictive of the GP’s risk estimates. Patients who accurately understood their risk reported higher smoking cessation rates (7 vs 3%, P = 0.003) and greater use of antiplatelet, blood pressure lowering therapy and statins (P ≤ 0.01). However, there was no relationship between GP’s risk perception and secondary prevention treatments.

Conclusion: Both patients and GP have optimistic bias and underestimate the risk of future CV events. Patients’ accurate self-perception, but not GP risk perception, was associated with improved secondary preventative behaviours. This suggests that helping patients to understand their risk may influence their motivation towards secondary prevention. Providing support to GP or programmes to help patients better understand their risks could have potential benefit on secondary prevention behaviours.

Introduction

Cardiovascular disease (CVD) is the leading cause of death globally and affects approximately one in six Australians.1,2 CVD is the most expensive disease group in Australia in terms of direct healthcare expenditure and is a major driver of escalating healthcare costs.3 Patients who have had a prior cardiovascular (CV) event are at a very high risk for repeat events with an estimated risk that exceeds 20% over 5 years.4 Almost half of the CV events occur in those with prior CVD,5 yet many of these events may have been prevented with intensive secondary prevention therapy.6 Preventative efforts are most efficient when directed at those patients with highest risk. Despite the strong evidence that treatment with secondary prevention medications, lifestyle modification and risk factor control decrease the risk of
repeat events, numerous studies have shown a gap in use of secondary prevention treatments.7,8 We have shown this in The Australian Hypertension and Absolute risk study (AusHEART).9 Several studies have suggested that patient and clinician attitudes towards their treatments may be a barrier to adherence,10 however, there is a little quantitative evidence that supports this.

The general practitioners (GP) assessment of their patients’ overall CV risk could impact on the prevention treatments they advise. Patients’ perceptions of their own CV risk may influence their own secondary prevention behaviours. The aims of this research paper was to examine, in patients with known CVD recruited in the AusHEART study through general practice; (i) the perceived future risk of CV events as estimated by patients and their GP in absolute and relative terms and (ii) the relationship between these perceptions and the uptake of secondary preventive measures.

Methods

Study design and population

AusHEART was a nationally representative, cluster-stratified, cross-sectional survey of CV risk management in patients aged 55 years or older presenting to primary healthcare centres that has been described previously.6,11 The study was approved by The Royal Australasian college of General Practitioners National Research and Evaluation Ethics Committee. All patients gave informed written consent for participation. Expression of interest letters was sent out to 21,074 GP registered to practise in Australia at the beginning of 2008. Of the 1416 GP who expressed interest in the study, 534 were randomly selected stratified by geographic location to ensure that distribution by state and rural-urban reflected the population distribution according to the data from 2004 census. GP were asked to recruit 15–20 consecutive adult patients (aged ≥55 years) presenting to their practices irrespective of the reasons for their consultation between April and June 2008. In total, 5,293 patients were recruited to AusHEART, 1,453 patients with history of CVD are the subjects of the current analysis.

Data collection

The GP completed a one-page questionnaire for each recruited patient on CV risk factors, use of cardiac medications, checked blood pressure with an electronic monitor (Omron HEM-907 when available). If certain key CV risk factors, including fasting blood lipids, blood glucose, estimated glomerular filtration rate and urine albumin-creatinine ratio, had not been measured within the National Heart Foundation of Australia guideline-recommended time frame, the GP were requested to repeat these tests and record the results, to allow a ‘forced capture’ of CV risk factor levels in all registered patients. GP were asked to estimate and record the patient’s absolute risk of a future CV event over the next 5 years.

Each patient completed a questionnaire that included questions on socio-economic status and physical activity. Each patient was asked to estimate their future risk of a CV event in the next 5 years and report this in absolute and relative terms. Specifically each patient was asked firstly ‘What do you think your chances of having a heart attack or stroke in the next 5 years are?’ and given six response options to select from – no chance, low, mild, moderate, high and very high. Secondly, they were asked – ‘How do you think your chances of having a heart attack or stroke in the next 5 years compare to chances of an average person the same age and sex as you?’ and given a scale from 1 to 5 (where 1–2, lower chance; 3, same chance; 4–5, higher chance). Finally, they were requested to provide a numeric risk estimate (range 0–100%) of the risk of an average person the same age and sex, and their risk of having a heart attack or stroke in the next 5 years.

Definitions

CVD was defined as patients with prior stroke, transient ischaemic attack (TIA), myocardial infarction (MI), angina or coronary revascularisation. Patients with established CVD are considered to be at high risk of a future CV event, that is, they are generally regarded to have a 5-year risk greater than 15%.12 We categorised GP’s risk estimates as an ‘accurate risk estimate’ if the GP reported the absolute CV risk of patients with CVD to be >15% over 5 years and otherwise an ‘underestimate of risk’.13 We categorised patients who indicated their future chances of heart attack or stroke was ‘high’ or ‘very high’ as ‘accurate high self-perception of risk’, whereas patients who indicated their risk as ‘no chance, low, mild or moderate’ were categorised into the ‘inaccurate low-moderate self-perception of risk’ group.

We defined good risk factor control as achieving three or more of the following five parameters: (i) physical activity of >30 min for 5 or more days per week, (ii) non-smoking status, (iii) LDL ≤2 mmol/L, (iv) BP ≤140/90 mm Hg and (v) body mass index (BMI) <25 kg/m². We defined good secondary prevention medication use as the use of statin, antiplatelet and BP lowering therapy.
Statistical analysis

We compared risk factor levels and use of secondary prevention treatments between groups with ‘accurate’ and ‘underestimated’ GP assessed risk and patients’ self-perception as ‘accurate high risk’ and ‘inaccurate low to moderate risk’. Descriptive statistics are presented as percentages or mean with standard deviation. Comparisons between groups were tested using t-tests for continuous variables and chi-squared tests for categorical variables. In all cases, a P-value of <0.05 was used to reject the null hypothesis. To examine the relationship of perception of risk with risk factor control and the use of secondary prevention treatments, we used a multivariable logistic regression model. Selection of parameters for inclusion into the multivariable model was based on clinical judgement and univariate statistical significance (P < 0.05). The covariates considered were: age, gender, smoking status, diabetes, obesity, systolic blood pressure control, diastolic blood pressure control, elevated total cholesterol (>4 mmol/L) and type of CVD (cardiac or cerebrovascular). All statistical analysis was conducted using STATA version 13.1 (Stata Corporation, College station, TX, USA).

Results

Of the 1453 AusHEART patients with a history of CVD, 743 (51%) had a history of coronary heart disease (CHD), 533 (37%) stroke or TIA and 177 (12%) had both. The mean age of participants with CVD was 70 years (SD: 9.1, range: 55–98 years) and 43% were females. Data on GP’s estimate of future risk and patient’s self-estimate of risk were available for 1260 (90%) and 1399 (96%) respectively. Larger proportion of patients with the history of CHD when compared with stroke was perceived to be at higher risk by the GP as well as patients.

Patients’ perceptions of their health and future CV risk

Patients with CVD reported their health as excellent (2%), very good (15%), good (45%), fair (32%) and poor (6%). With respect to their future chances of a CV event, 2% reported their risk to be very high, 9% high, 34% moderate, 23% mild, 28% low and 4% no chance. In relative terms to a person with the same age and sex, 29% reported themselves to be at much higher risk, 43% at the same risk and 28% at lower risk for a future event.

The risk perception for future events was similar by gender or age group (defined as age >65 years). Patients that accurately perceived their own risk to be high were more likely to have prior history of diabetes, hypertension, higher BMI, less physically active or had at least one hospital admission in preceding 12 months (Table 1). However, after adjusting for covariates recent hospitalisation within preceding 12 months (Table 2) remained a significant predictor of patients perceiving their risk as high.

Perception of risk by GP

GP categorised 30% of patients with established CVD as having a 5-year risk ≥15%, and thus 70% with an estimated absolute risk <15%. GP reported higher mean risk estimates in patients with CHD compared with stroke/TIA (17.0 vs 14.6%, P = 0.025). Patients that GP categorised accurately as high risk (>15%) were older, male, diabetic, hypertensive, had higher blood pressure, higher BMI, elevated total cholesterol and smokers (Table 1). After adjusting for covariates, age, male sex, diabetes, hypertension, obesity, elevated total cholesterol and smoking were significant predictors of GP accurately assessing risk as high (Table 2). There was poor correlation between the GP and patient risk estimates (coefficient 0.175, Spearman’s rho 0.187).

Risk perception and relation to risk factor control and management

Patients that perceived they were at increased risk for recurrent events reported a higher smoking cessation (quit) rate over the preceding 12 months (7 vs 3%, P = 0.03) (Table 1). There was no significant difference in the quit rates between patient groups based on GP perception (5 vs 4%, P = 0.53). Control of other risk factors was similar in patients that perceived their risk as high versus low/moderate (Figs 1,2).

After adjusting for covariates, patients’ perception of risk (adjusted Odds Ratio (aOR) 1.00, 95% CI 0.61–1.65, P = 0.985) and the GP’s estimate of risk (aOR 0.98, 95% CI 0.68–1.42, P = 0.93) were both not significantly associated with achieving risk factor control (≥3 of 5 risk factors controlled). With respect to the use of all secondary prevention medications, patients’ perception was significantly associated (aOR 1.64, 95% CI 1.12–2.43, P = 0.012) with receiving all therapy (aspirin plus BP lowering plus statin). The GP perception of the patients risk was not associated with receiving all CV preventative therapy (aOR 0.83, 95% CI 0.63–1.08, P = 0.174) (Figs 1,2).
Discussion

Our study found that the large majority of patients with established CVD recruited through primary care in Australia had inaccurate perception of their risk of future CV events. The GP of these patients tended to underestimate absolute numeric risk. Only 11% of patients with established CVD reported that they remained at high risk of future CV events. Nearly 70% of patients perceived their relative risk to be lower or similar to age and sex matched individuals. These findings support previous observations from the UK and USA, where the majority of participants have optimistic bias and underestimate their risk of having heart attack or stroke in future.\textsuperscript{14,15}

In general, subjects are optimistic and underestimate their risk, but an overestimate of the risk is also possible and was reported\textsuperscript{16} in a postal survey of over 2000 patients with hypertension and diabetes that reported more than 50% overestimated absolute risk of heart attack or stroke by more than 20%. The misperception of risk is evident in hospitalised patients, a study of 79 patients with acute MI admitted to coronary care unit in Auckland found patients’ risk perception were not congruent with estimates from established clinical indicators.\textsuperscript{17}

Table 1 Participant characteristics, risk factor control and treatment in patients with CVD as stratified by patient and GP perception of risk of future cardiovascular event

| Age ≥ 65 years | 101 (66%) | 838 (67%) | 0.667 | 276 (73%) | 573 (64%) | 0.001 |
| Male | 88 (58%) | 692 (57%) | 0.724 | 231 (62%) | 484 (55%) | 0.024 |
| Current smoker | 12 (8%) | 103 (8%) | 0.827 | 51 (14%) | 58 (7%) | <0.001 |
| Quit smoking in past year | 11 (7%) | 33 (3%) | 0.003 | 13 (5%) | 29 (4%) | 0.513 |

Table 1 Participant characteristics, risk factor control and treatment in patients with CVD as stratified by patient and GP perception of risk of future cardiovascular event

| Disease type | 0.353 | 0.021 |
| CAD/angina | 84 (55%) | 627 (50%) | 0.206 (55%) | 441 (50%) |
| Stroke/TIA | 44 (29%) | 472 (38%) | 0.115 (31%) | 342 (39%) |
| Both | 26 (16%) | 146 (12%) | 0.054 (14%) | 102 (12%) |
| Diabetes | 55 (36%) | 332 (27%) | 0.014 (38%) | 207 (23%) |
| Hypertension | 131 (86%) | 862 (71%) | <0.001 (81%) | 601 (69%) |
| Recent admission | 83 (54%) | 336 (27%) | <0.001 (32%) | 248 (29%) |

| <12 months | 0.017 |
| SBP (mm Hg) | 136 ± 17 | 134 ± 17 | 0.201 | 139 ± 19 | 132 ± 16 | <0.001 |
| DBP (mm Hg) | 74 ± 11 | 74 ± 11 | 0.605 | 76 ± 12 | 73 ± 10 | <0.001 |
| BMI (kg/m\textsuperscript{2}) | 29.17 ± 5.7 | 28.22 ± 5.6 | 0.033 | 29.5 ± 5.5 | 28.4 ± 4.9 | 0.002 |
| TC (mmol/L) | 4.49 ± 1.26 | 4.55 ± 1.01 | 0.448 | 4.62 ± 1.16 | 4.50 ± 1 | 0.07 |
| LDL (mmol/L) | 2.37 ± 0.85 | 2.51 ± 0.88 | 0.083 | 2.53 ± 0.05 | 2.47 ± 0.03 | 0.317 |
| HDL (mmol/L) | 1.30 ± 0.45 | 1.35 ± 0.01 | 0.177 | 1.27 ± 0.02 | 1.36 ± 0.01 | <0.001 |

| Risk factor control | 0.001 |
| Not smoking | 142 (92%) | 1137 (92%) | 0.827 | 323 (86%) | 824 (93%) | <0.001 |
| Regular exercise‡ | 26 (17%) | 301 (24%) | 0.041 | 87 (24%) | 211 (25%) | 0.657 |
| BMI < 25 | 37 (24%) | 320 (26%) | 0.571 | 89 (24%) | 235 (27%) | 0.284 |
| LDL < 2 mmol/L | 57 (40%) | 387 (33%) | 0.079 | 110 (32%) | 301 (35%) | 0.273 |
| BP < 140/90 | 95 (62%) | 851 (68%) | 0.118 | 211 (56%) | 653 (74%) | <0.001 |
| ≥3 risk factors controlled | 23 (20%) | 185 (19%) | 0.785 | 54 (20%) | 136 (19%) | 0.767 |

| Secondary prevention therapy | 0.110 |
| Antiplatelet | 128 (85%) | 850 (71%) | <0.001 | 280 (76%) | 616 (72%) |
| BP lowering | 133 (90%) | 934 (77%) | <0.001 | 301 (83%) | 661 (77%) | 0.012 |
| Statin | 121 (82%) | 872 (72%) | 0.010 | 269 (74%) | 631 (73%) | 0.695 |

\textsuperscript{†}34% moderate, 23% mild, 28% low, 4% no chance. Data are mean ± SD or number (%) and based on non-missing value. \textsuperscript{‡}≥30 min per day for >5 days per week. BMI, body mass index; BP, blood pressure; CHD, coronary heart disease; CVD, cardiovascular disease; DBP, diastolic blood pressure; GP, general practitioner; HDL, high density lipoprotein cholesterol; HT, hypertension; LDL, low density lipoprotein cholesterol; SBP, systolic blood pressure; TC, total cholesterol; TIA, transient ischaemic attack.
The GP underestimated the numeric risk of future CV events in patients with established CVD in 70% of cases. In addition, we noted that GP categorised more patients with CHD in high-risk subgroup compared with stroke. This disparity in differential risk perception towards cerebral compared with cardiac CVD may contribute towards gaps in secondary prevention therapies. Several studies have shown that doctors do not accurately estimate risk,\(^{18,19}\) nor do they discuss the CV risk with their patients.\(^{20}\) Higher risk estimates by the GP’s were associated with the presence of conventional risk factors. However, after adjusting for covariates, our study found that GP perceptions did not translate into improved control over their risk factors.

Our data have highlighted substantial lack of patients’ insight into their future CV risk. Several potential explanations exist. For example, patients’ under recognition of increased risk may be a symptom of poor health literacy in general and poor awareness of the risk factors.\(^{21}\) Inaccurate risk perception can result from lack of risk assessment by the physician and/or lack of communication. This can be due to inadequate consultation time, lack of financial incentive and low physician communication skills.\(^{22}\) A survey of 380 GP in Swiss cantons (Zurich and Aargau) found that 57% reported that numerical information resulting from risk prediction algorithms is not helpful.\(^{23}\) Misrepresentations in the media and by influential people may confuse the

| Table 2 Predictors of accurate perception of absolute CVD risk by patients with CVD and their GP as assessed by multivariable logistic regression model |
|-----------------|-----------------|-----------------|-----------------|
| Variables       | OR (95% CI)     | P-value         | OR (95% CI)     | P-value         |
| Age             | 1.02 (0.99–1.03) | 0.16            | 1.03 (1.02–1.05) | <0.01           |
| Male            | 1.02 (0.69–1.51) | 0.91            | 1.37 (1.03–1.84) | 0.03            |
| Obesity (BMI > 30 kg/m²) | 1.22 (0.82–1.84) | 0.33            | 1.56 (1.15–2.11) | 0.01            |
| CHD             | 1.13 (0.74–1.72) | 0.58            | 1.25 (0.92–1.67) | 0.15            |
| Diabetes        | 1.43 (0.96–2.14) | 0.08            | 2.16 (1.62–2.92) | <0.01           |
| Hypertension    | 1.84 (1.11–3.05) | 0.02            | 1.56 (1.12–2.18) | 0.01            |
| Elevated total cholesterol† | 0.85 (0.57–1.23) | 0.42            | 1.52 (1.12–2.06) | 0.01            |
| Regular physical activity | 0.69 (0.43–1.11) | 0.13            | 1.02 (0.74–1.41) | 0.86            |
| Smoking         | 1.14 (0.56–2.32) | 0.72            | 2.86 (1.81–4.52) | <0.01           |
| Recent hospitalisation‡ | 2.81 (1.94–4.06) | <0.01           | 1.01 (0.75–1.36) | 0.95            |

†>4 mmol/L ‡Hospitalisation in previous 12 months. BMI, body mass index; CHD, coronary heart disease; CVD, cardiovascular disease; GP, general practitioner; OR, odds ratio.

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information on CV risk. Erroneous perception can result from denial and tendency to compare themselves with persons who are worse off rather than an average matched person. Some studies have found that physicians overestimate patients’ knowledge with respect to their health. For example, in one large survey (REACT study) involving 754 primary care physicians and 5104 general public participants from five European countries, 92% physicians reported they believed that their patients associate high cholesterol with CHD, yet only 51% of public participants were aware that high cholesterol increases CHD risk.

The health belief model is a psychological health behaviour change theory that suggests that people’s beliefs about their health problem, for example, with respect to its severity or perceived benefits, are related to their engagement or lack of engagement with health-promoting behaviours. These theories underpin the potential importance of patients needing to have an accurate perception of their risk in order to engage effectively in behaviours, such as lifestyle change and medical adherence necessary for improving their condition. Intuitive recognition that a specific action will offer protection is central to theories surrounding health-related behaviour. Accurate perception of illness is probably a good motivation for self-care and influences the behaviour and risk factor control. Our study findings are consistent with this. We found that patients who accurately perceived their future risk as high, reported greater smoking cessation over the previous 12 months.

Medication adherence is an important patient behaviour that is influenced by beliefs. More benign perceptions of illness translate to lower medication adherence. This is reflected in our study. Patients who accurately perceived future risk as high were significantly more likely to be on secondary prevention medication. Information on health beliefs may be important at achieving concordance between patient and practitioner and can be a target for intervention to enhance adherence.

General practice is an ideal setting for providing preventative care. CV risk assessment in general practice can be helpful in motivating patients and reinforcing self-care. Even brief advice from the GP can act as a catalyst for change in an integrated model of disease prevention. One meta-analysis described significant increase in rates of smoking cessation with only brief advice. These highlight the importance of the physician’s role in risk quantification and knowledge translation.

Our study has some limitations. The assessment of risk perception for patients was drawn from self-reported responses to a Likert scale and quantitative questions about their risk relative to others in the community. The associations are estimates from cross-sectional survey data and as such we are unable to establish the direction of the associations found. Participants recruited were patients presenting to primary care for a variety of reasons, and GP were only a small proportion of all GP and while our study sample is likely to be broadly representative, it may represent a sample of patients that are...
more motivated about their health as they attend the doctor and their doctor is interested in patient audits.

**Conclusion**

This study has identified that both patients and GP underestimate risk of future CV events. Patients with an accurate understanding of their CV risk were more likely to observe treatment recommendations. The GP perceptions were not correlated with patients’ perceptions of their own risk and could reflect the challenges doctors face in communicating risk concepts to patients. As the findings in this study support, patients’ misperceptions of their risk may present a barrier to the implementation of secondary prevention. The potential implications of these findings are that increasing patients’ knowledge of their risk, for example, through supporting GP with tools or programmes to help educate patients about their risk, could translate into improved secondary prevention. Electronic decision support tools embedded in electronic health records, M-health tools or counselling programs may have a role.  

Further research, however, is required to identify effective strategies as well as to evaluate whether these can translate into improved clinical outcomes for individual patients.

**Acknowledgments**

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Substantial variation in post-engraftment infection prophylaxis and revaccination practice in autologous stem cell transplant patients

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Key words
prophylaxis, autologous stem cell transplant, Pneumocystis jirovecii, antiviral, revaccination.

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Abstract
There is a paucity of evidence supporting the necessity or duration of Pneumocystis jirovecii and antiviral prophylaxis as well as revaccination following autologous stem cell transplant (ASCT). A survey aimed at evaluating these policies was distributed to 34 ASCT centres across Australasia. The 26 survey respondents demonstrated significant heterogeneity in their infection prophylaxis and revaccination strategy post-transplant despite the availability of consensual guidelines.

Haemopoietic stem cell transplant patients are at risk of a range of opportunistic infections depending on their degree of immunosuppression and time since transplant. The majority of the current literature in this context focuses on allogeneic patients with a paucity of data on the risks of post-autologous transplant (ASCT).1–3 Despite this, guidelines for infection prophylaxis generally do not distinguish between these types of transplant.

To obtain an overview of local practice, we conducted a survey of prophylaxis policy in ASCT patients in Australasian autograft centres. We focussed on three specific areas: prophylaxis against Pneumocystis jirovecii (PJP), previously known as Pneumocystis carinii, Herpes simplex and varicella zoster infections and revaccination policies. A 15-item survey document (Appendix I) addressing these policies was emailed to 34 ASCT centres in Australia and New Zealand between May 2014 and June 2014. The survey allowed for descriptive comments. The responses were compared with the eviQ guidelines, a New South Wales online cancer service that serves as a point-of-care evidence-based clinical information resource relevant to local Australian practice; and international guidelines.5

Approval was obtained from the Austin Human Research Ethics Committee (LNR/14/Austin/659).

Twenty-six centres (76%) from across Australasia responded. A median of 30 ASCT (range 15–90) is performed in each centre annually. Table 1 describes the prophylaxis and revaccination policies in the various ASCT centres.

PJP prophylaxis was reportedly used routinely in the majority of centres (77%), most commonly commenced from the time of engraftment. Sulfamethoxazole/trimethoprim was the drug of choice, although the strength and dosing regimen varied, as did the duration of prophylaxis. Peripheral blood CD4+ count influenced the duration in only three centres. Only nine centres (35%) used prophylaxis during maintenance thalidomide- or prednisolone-based protocols.

Most centres (85%) reported the use of antiviral prophylaxis, with once daily valaciclovir or twice daily aciclovir being the commonest regimens, although the strength and dosing regimen varied, as did the duration of prophylaxis. Peripheral blood CD4+ count influenced the duration in only three centres. Only nine centres (35%) used prophylaxis during maintenance thalidomide- or prednisolone-based protocols.

Sixteen centres (62%) reported routine implementation of a revaccination policy post-ASCT, generally as per published European and local guidelines.5–7

Discussion
The results of this survey demonstrate significant heterogeneity among Australasian autograft centres in...
infection prophylaxis and revaccination strategy post-transplant despite the availability of published guidelines.1–3

The recommended drug option for PJP prophylaxis post-ASCT is sulfamethoxazole/trimethoprim, both due to its efficacy against PJP and its broad spectrum of activity providing protection against other pathogens, including toxoplasma, nocardia and other respiratory pathogens.4,5,8 While relatively safe, it can be associated with significant adverse drug effects, including significant myelosuppression and potentially fatal hypersensitivity syndromes; hence, its routine use post-ASCT should be based on evidence demonstrating its necessity. Our review of the literature, however, could not find convincing evidence to justify its routine use or the optimal duration of PJP prophylaxis in ASCT patients in the absence of risk factors, such as concomitant glucocorticoids or other immunosuppressants or previous PJP infection.

A recent retrospective study reported five cases of PJP pneumonia in 1191 ASCT patients (0.42%) over a 10-year period in the absence of prophylaxis (all cases occurred in patients receiving concomitant steroids), suggesting that routine prophylaxis may not be warranted.9 Moreover, in patients receiving immunomodulatory therapy post-ASCT for myeloma, commonly with thalidomide or lenalidomide with or without steroids, it remains unclear if this represents a higher risk group in whom PJP prophylaxis is clearly justified, although the reactivation of hepatitis B in patients receiving thalidomide suggest that these patients may be at risk of opportunistic infection.10 In human immunodeficiency virus (HIV) patients, a CD4+ count of less than 200/mm3 is associated with increased risk of PJP, and hence, this threshold determines prophylaxis use and its duration,11 but it remains unknown whether CD4+ can similarly be used as one of the surrogate laboratory parameters of immune recovery in a non-HIV setting and a possible guideline to optimal duration of prophylaxis in high-risk patients.5,12–15

Similar to antiviral prophylaxis, there was substantial variability in practice, particularly with respect to the duration. Previous studies suggest that in the absence of post-engraftment prophylaxis, the frequency of varicella zoster infection in ASCT patients is not insubstantial (16–28%), with the majority occurring within the first 12 months.16 Non-randomised studies suggest a potential benefit of an extended period of prophylaxis against varicella zoster viral reactivation for up to 12 months, although to our knowledge, there is no reported randomised trials addressing the issue of optimal duration.7,15,17,18

Immune reconstitution gradually occurs post-ASCT, although the CD4+ count remains low for at least the first year post-transplant despite reconstitution of total B and T cells to normal levels at 2–4 months.5,13

Table 1 Infection prophylaxis and vaccination policy in the 26 responding centres

<table>
<thead>
<tr>
<th>PJP prophylaxis n (%)</th>
<th>Antiviral prophylaxis n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. centres utilising</td>
<td></td>
</tr>
<tr>
<td>20 (77)</td>
<td>22 (85)</td>
</tr>
<tr>
<td>Drug options and dosing regimen</td>
<td></td>
</tr>
<tr>
<td>S/T DS† (18)</td>
<td>Valaciclovir 500 mg (16)</td>
</tr>
<tr>
<td>BD‡ twice weekly: 10 (50)</td>
<td>OD: 14 (64)</td>
</tr>
<tr>
<td>OD§ thrice weekly: 7 (32)</td>
<td>BD: 2 (9)</td>
</tr>
<tr>
<td>OD: 1 (5)</td>
<td>Aciclovir 400 mg (6)</td>
</tr>
<tr>
<td>S/T SS¶ (2)</td>
<td>OD: 1 (5)</td>
</tr>
<tr>
<td>OD: 2</td>
<td>BD: 5 (23)</td>
</tr>
<tr>
<td>Time of commencement</td>
<td></td>
</tr>
<tr>
<td>From admission</td>
<td>1 (5)</td>
</tr>
<tr>
<td>From engraftment</td>
<td>18 (90)</td>
</tr>
<tr>
<td>Other</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Duration of prophylaxis</td>
<td></td>
</tr>
<tr>
<td>≤3 months</td>
<td>11 (55)</td>
</tr>
<tr>
<td>&gt;3 to ≤6 months</td>
<td>9 (45)</td>
</tr>
<tr>
<td>12 months</td>
<td>0</td>
</tr>
<tr>
<td>Recommendations according to international guidelines5</td>
<td>3–6 months</td>
</tr>
<tr>
<td>3–6 months</td>
<td>17 (65)</td>
</tr>
<tr>
<td>12 months</td>
<td>4 (18)</td>
</tr>
<tr>
<td>% centres compliant</td>
<td></td>
</tr>
<tr>
<td>3–6 months</td>
<td>17 (65)</td>
</tr>
<tr>
<td>12 months</td>
<td>2 (9)</td>
</tr>
<tr>
<td>% centres compliant evIQ guidelines4</td>
<td></td>
</tr>
</tbody>
</table>

†S/T DS sulfamethoxazole/trimethoprim double strength (800/160 mg). ‡BD twice daily. §OD once daily. ¶S/T SS sulfamethoxazole/trimethoprim single strength (400/80 mg).
impact of this immunodeficiency on susceptibility to infectious complications, however, is not well documented, although previous studies have shown that antibody titres to vaccine-preventable diseases decline during the first decade after transplant.5,6 Moreover, to our knowledge, there are no published randomised trial data to support the efficacy of revaccination against any viruses, herpetic or otherwise. Despite this, largely based on extrapolation from the allogeneic setting, current guidelines advocate for revaccination against pneumococcus, Haemophilus influenzae type b, meningococcus, measles, mumps, rubella, hepatitis B, polio, tetanus, diphtheria and pertussis among others in ASCT patients.5–7 Ostensibly with the intention of reducing the risk of disease and to promote herd immunity where a vulnerable transplant patient could be a potential sentinel case.19,20 In our survey, not all the centres implemented this policy, which may reflect both the lack of evidence and the cost, noting that the vaccinations are not funded under the Australian Pharmaceutical Benefits Scheme and are estimated to cost more than AU$650 per patient.

Interpreting the results of our survey should be done with acknowledgement of its limitations. A quarter of invited centres did not respond, which may have biased the results in either direction. However, the centres that did accounted for approximately 900 out of the reported 1118 ASCT performed (80.5%) in Australasia in 2013,21 which represents the majority of the autograft centres and gives a good representation of current practice in this region. In approaching the centres, we directed our request to the heads of each unit. Accordingly, the survey was not designed to collect variability of individual physician practices within units without strict adherence to centralised unit protocols; however, we feel that this is unlikely to be a major factor influencing the validity of our results. Furthermore, the reasons behind non-adherence were not addressed in this survey due to the potential complexity involved in order to simplify the survey and maximise chances of response.

The heterogeneity within institutions identified from this practice survey and the not inconsiderable overall proportion of non-adherence to consensus guidelines may reflect a lack of strong evidence supporting the policies and hence a healthy scepticism towards their implementation in addition to patient and physician factors and economic costs. Prospective studies in these areas appear justified, and such a study investigating the use of no routine PJP prophylaxis post-ASCT in low-risk patients is being designed.

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## Appendix I

**A Survey of Infection Prophylaxis in Autologous Stem Cell Transplantation (ASCT)**

Use of PJP Prophylaxis post-ASCT

1. What is the average number of ASCT performed in your centre per year? ____________
2. Is PJP prophylaxis routinely used post-ASCT?
   a. Not routinely used (See Q7)
   b. Yes – in all patients
   c. Yes – in selected patients. Which groups? ____________
3. Does post-ASCT maintenance (eg thalidomide, thalidomide/steroids, rituximab) influence the use of PJP prophylaxis?
   a. No
   b. Yes – which maintenance regimen?
      i. Thalidomide alone
      ii. Thalidomide/Prednisolone
      iii. Rituxumab or other monoclonal antibodies
      iv. Other ____________
4. If used, what is the schedule of the first line PJP prophylaxis used? ____
   a. Cotrimoxazole DS BD twice a week
   b. Cotrimoxazole DS OD three times a week
   c. Cotrimoxazole 80/400 mg i OD daily
   d. Others (pls describe) _______
5. If used, how
   a. When is it started? _______
   b. How long is prophylaxis given for? _______
6. Does CD4+ count influence the duration of prophylaxis (eg in determining when to stop)?
   a. If yes (what is the cutoff ________)
   b. No
7. Can you recall any PJP complications in the first 12 months post-ASCT in the absence of other risk factors (eg high dose steroids)?
   a. Yes (how many ____ ) (see Q8)
   b. No (see Q10)
8. When did the PJP complications occur? ____
   a. Within first 6 months post-ASCT
   b. 6–12 months post-ASCT
9. Did the PJP complications occur while on PJP prophylaxis? ____
   a. Yes (which prophylaxis ____________)
   b. No
10. Would your centre be interested in participating in a prospective study to investigate the necessity of PJP prophylaxis post-autograft in the absence of other immunosuppressive therapy? ____
    a. Yes
    b. No

Use of Antiviral Prophylaxis post-ASCT in the absence of concomitant immunosuppressive therapy
1. Is antiviral prophylaxis used in this context post-engraftment? ____
   a. Yes
   b. No
2. Which antiviral prophylaxis is used? ____
   a. Aciclovir 400 mg oral BD
   b. Aciclovir 200 mg tds
   c. Valaciclovir 500 mg OD
   d. Others (please describe______________)
3. Describe the schedule of antiviral prophylaxis used.
   a. Time commenced______________
   b. Time ceased______________

Vaccination Policy post-ASCT
1. Is vaccination routinely given to ASCT patients? ____
   a. Yes
   b. No
2. If yes, which guidelines do you use?
   b. Others (please state_________________)
Thank you!
Are you willing for your answers to be anonymously included on a review of the use of infection prophylaxis in the haematological conditions discussed above? ______________
Other comments___________________________________________
Safety and efficacy of a novel short occlusive regimen of imiquimod for selected non-melanotic skin lesions in renal transplant patients

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Key words
imiquimod, renal transplant, non-melanotic skin cancer, BCC, Bowen disease, actinic keratoses.

Abstract
Australian patients remain at very high risk of non-melanotic skin cancer after renal transplantation. Surgical excision offers a cure but destroys tissue and may jeopardise function and cosmesis. We report excellent safety and efficacy using topical imiquimod in a novel short intensive regimen in 10 renal transplant patients with superficial basal cell carcinomas, Bowen disease or actinic keratosis. Outcomes compare well to those reported with extended-use imiquimod protocols.

While transplantation is undisputed as the treatment of choice for end-stage renal disease, chronic immunosuppression induces a significant risk of malignancy.1 While graft survival has almost doubled over the past 20 years, Australian renal transplant patients (RTP) remain at high risk of non-melanotic skin cancer (NMSC), mainly squamous cell carcinoma (SCC).2 In transplant patients, SCC occurs 65 times more frequently, and basal cell carcinomas (BCC) 10 times more frequently, than in the general population.1,4 NMSC incidence is cumulative over time; Australia has the highest incidence in the world at 38% at 10 years and 70% at 20 years, with the adjusted relative risk for development of NMSC in Australian compared with Dutch patients being 3.6.5 There is no evidence that newer immunosuppressive regimens have decreased cancer risks.6

Management of NMSC in RTP is identical to immunocompetent patients; surgery and histological confirmation of complete excision is the mainstay of therapy. However, due to the increased serial incidence of skin lesions, good cosmetic and functional results may be difficult to achieve surgically. In addition to destructive modalities, such as cryotherapy, surgical excision and curettage and diathermy, superficial malignancies are amenable to topical treatment, achieving the triple aims of cure, preservation of function and good cosmetic results.

Imiquimod is a topical treatment option approved by the Australian Therapeutic Goods Administration for the primary treatment of actinic keratosis (AK) and superficial BCC. A small molecule of the imidazoquinoline group of nucleoside analogues,4–9 imiquimod promotes anti-tumour activity through stimulation of toll-like receptors 7 and 8 on monocytes/macrophages and dendritic cells. This results in the activation of NF Kappa B and expression of multiple cytokines, chemokines and inflammatory mediators. Angiogenesis is inhibited, apoptosis is promoted and the anti-tumour immune response is enhanced.7–9 Imiquimod has been proven safe and efficient in both non-immunosuppressed7–13 and immunosuppressed patients,14–16 with an 83% clearance rate in Phase III studies for superficial BCC.6 In a randomised control trial of cryotherapy versus topical 5-fluorouracil versus topical imiquimod for multiple AK in non-immunosuppressed patients,17 imiquimod achieved comparable initial clearance rates to 5FU (85% vs 96%) and significantly better sustained clearance rates for both the lesion (73 vs 54%) and the total treatment field (73 vs 33%). Both creams out-performed cryotherapy when applied two to three times weekly for 4–8 weeks.17 This duration is shorter than the

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established regimen of applying two to three times weekly for 16 weeks.7–16

Imiquimod in Bowen disease (superficial SCC) is less studied, but efficacy is reported despite concomitant immunosuppression.15,16,18

Shorter-duration treatment protocols offer financial advantage and allow earlier recognition of treatment failure. We report here the safety and efficacy of a short-duration, lower-dose occlusive imiquimod regimen for treatment of superficial NMSC and AK in RTP.

Patients were selected for imiquimod treatment by a specialist dermatologist (BT) according to small lesion size, superficial depth and cosmetically sensitive site. All RTP treated with topical imiquimod between its first use in July 2004 and December 2013 were identified through pharmacy records. Clinical data were retrospectively collected from hospital records and our departmental database. All biopsy-confirmed NMSC treated with imiquimod were included in this study. Imiquimod (5% cream, Aldara, Meda Pharmaceuticals, Takeley, Bishop’s Stortford, UK) was applied daily for 7 consecutive days under plastic occlusion or tape. Between daily applications, the area was washed with mild soap and water. At 1 week, the dermatologist assessed the local inflammatory reaction and extended treatment for a further 5–7 days if none was present. If no response was achieved at 2 weeks, alternative treatment was initiated. Patients were assessed again at 3 months, when complete clinical response was defined as 100% clearance and partial response (PR) as clearance of at least 50%. All patients were followed up for at least 9 months.

Immunosuppression in all patients comprised a standard combination of corticosteroids, anti-proliferative agent (usually mycophenolate mofetil) and calcineurin inhibitor (usually Tacrolimus). Estimated GFR (e-GFR, MDRD equation) for each patient was recorded at baseline and 3 months post treatment with imiquimod, and patient records and biopsy databases were searched to identify rejection episodes.

Data were available for 12 NMSC treated with topical imiquimod in 10 RTP (six females, four males) with mean age 58.2 ± 12 years (range: 36.9–75 years). Targeted lesions were Bowen disease (five lesions in four patients), superficial BCC (five in four patients) and AK (two in two patients). No patient had a history of skin lesions prior to renal transplantation.

Anatomically, lesions were in sun-exposed areas: six head and neck lesions (in four patients); three arm lesions (three patients); two leg lesions (two patients) and a single trunk lesion in another patient. The mean follow-up time after imiquimod treatment was 5.2 ± 3.4 years (range: 0.8–8.9 years).

All lesions treated with imiquimod initially responded. None of the five superficial BCCs recurred, but one of the five Bowen lesions recurred after 12 months, and one of the two AK recurred after 4 months. Thus, complete response at 3 months was achieved in 10/12 lesions (83%), with ultimate treatment failure in 2 of 12 lesions (Table 1).

Renal function in all patients was stable throughout treatment with topical imiquimod (Fig. 1). No patient experienced any decline in renal allograft function during or after treatment; no graft biopsies were undertaken; and no patient reported any systemic symptoms.

Our results using this novel intensive therapeutic regimen of imiquimod for NMSC in RTP are comparable with reported data using an extended-use protocol.14 The earlier defined end point allows for timely identification of treatment failure and institution of alternative therapy if necessary, facilitates monitoring and compliance and reduces the required dose, improving cost efficacy.

Consistent with literature reports, side-effects were very well tolerated by all our patients and were confined to the local inflammatory reactions explained by local induction of pro-inflammatory cytokines and strongly linked to drug efficacy. No patient withdrew from therapy. It is possible that immunosuppression may reduce

<table>
<thead>
<tr>
<th>Patient</th>
<th>No. tumours</th>
<th>Type of lesions</th>
<th>Response</th>
<th>Recurrence/time of recurrence</th>
<th>Follow-up time (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>Bowen disease</td>
<td>PR/CR</td>
<td>Yes (&gt;1 year)/No</td>
<td>8.6</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>Bowen disease</td>
<td>CR</td>
<td>No</td>
<td>1</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>Bowen disease</td>
<td>CR</td>
<td>No</td>
<td>8.4</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td>Bowen disease</td>
<td>CR</td>
<td>No</td>
<td>8.9</td>
</tr>
<tr>
<td>5</td>
<td>1</td>
<td>sBCC</td>
<td>CR</td>
<td>No</td>
<td>8.2</td>
</tr>
<tr>
<td>6</td>
<td>1</td>
<td>sBCC</td>
<td>CR</td>
<td>No</td>
<td>6.6</td>
</tr>
<tr>
<td>7</td>
<td>2</td>
<td>sBCC</td>
<td>CR/CR</td>
<td>No/No</td>
<td>0.7</td>
</tr>
<tr>
<td>8</td>
<td>1</td>
<td>sBCC</td>
<td>CR</td>
<td>No</td>
<td>1.2</td>
</tr>
<tr>
<td>9</td>
<td>1</td>
<td>AK</td>
<td>CR</td>
<td>No</td>
<td>3.6</td>
</tr>
<tr>
<td>10</td>
<td>1</td>
<td>AK</td>
<td>PR</td>
<td>Yes (&gt;4 months)</td>
<td>4.3</td>
</tr>
</tbody>
</table>

AK, actinic keratosis; CR, clinical response; PR, partial response; sBCC, superficial basal cell carcinoma
the severity of the inflammatory response to imiquimod, but immunosuppression itself did not prevent the therapeutic response. None of our patients experienced the less commonly reported systemic adverse effects of fever, fatigue, headache, nausea, diarrhoea and muscle pain.

Our patient numbers do not allow for a comment on the relative efficacy of imiquimod for superficial BCC, AK and Bowen disease, although our results endorse the published levels of efficacy across all lesion types. Our 100% clearance rate of superficial BCC, without recurrence, is consistent with the high efficacy reported with longer-duration imiquimod protocols in both immunocompetent and immunosuppressed patients. Of our two patients treated for AK, one had a complete and the other a PR, although the latter had recurrence at 4 months. In our four BD patients, all five lesions initially responded. One lesion recurred at 12 months, did not then respond to 5-fluorouracil cream and was subsequently surgically managed. This experience is comparable with that of Smith et al., who reported total clinical and histological clearance of BD lesions in five immunosuppressed patients, using a combination of imiquimod 5% cream and 5% 5-fluorouracil gel. Clearance was achieved within 9 weeks, with no evidence of recurrence over the follow-up period of 3–15 months. Two additional studies reported similar results in biopsy-proven BD in transplant patients. Prinz et al. reported clearance of all four BD lesions after an average of 6 weeks using imiquimod 5% cream three times weekly, although one lesion recurred after 10 months, while Kovak and Stasko reported complete clearance of BD lesions in two transplant patients and PR in a third patient.

Few studies have comprehensively compared the cost-effectiveness of the newer treatment modalities for NMSC with surgical excision. A Spanish study of 209 patients analysed the cost of treating a single superficial BCC (<2 cm) with either surgery or imiquimod 5% cream, applied five times per week for 6 weeks and using 36 sachets. The use of imiquimod reduced the cost per patient cured compared to surgical excision, by 8.1% in dermatology and 36% in non-dermatology services, thus achieving cost-effectiveness. The efficacy of topical imiquimod was 82% at 1 year. However, the costs of treatment failures and of follow up of possible failures were not considered, and the study was not randomised.

As imiquimod works through immune stimulation, its use in RTP has induced concern regarding rejection risk. This theoretical concern has not been substantiated in our study or in the literature to date, probably because systemic drug effects are very low with topical administration. Renal function was stable for all our RTP, with no episodes of rejection throughout follow up.

Within the limitation of our retrospective study, the short occlusive regimen of imiquimod was very well tolerated; patient acceptance and compliance was high; and efficacy was excellent. We conclude that a protocol of 7-day self-application of imiquimod with occlusion is a safe and effective alternative to higher-dose regimens or surgery in selected cases of superficial BCC, Bowen disease and AK in RTP.

**Acknowledgement**

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Acute adrenal insufficiency: an aide-memoire of the critical importance of its recognition and prevention

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Key words
adrenal crisis, adrenal insufficiency, Addison’s disease, corticosteroids.

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Abstract
Adrenal crisis is a life-threatening emergency that causes significant excess mortality in patients with adrenal insufficiency. Delayed recognition by medical staff of an impending adrenal crisis and failure to give timely hydrocortisone therapy within the emergency department continue to be commonly encountered, even in metropolitan teaching hospitals. Within the authors’ institutions, several cases of poorly handled adrenal crises have occurred over the last 2 years. Anecdotal accounts from members of the Addison’s support group suggest that these issues are common in Australia. This manuscript is a timely reminder for clinical staff on the critical importance of the recognition, treatment and prevention of adrenal crisis. The manuscript: (i) outlines a case and the clinical outcome of sub-optimally managed adrenal crisis, (ii) summarises the clinical features and acute management of adrenal crisis, (iii) provides recommendations on the prevention of adrenal crisis and (iv) provides guidance on the management of ‘sick days’ in patients with adrenal insufficiency.

Our index patient was a 51-year-old woman with a 7-year history of autoimmune primary adrenal insufficiency. She usually took 20 mg hydrocortisone in the morning and 10 mg at 3 pm and 100 μg fludrocortisone twice daily. She had a MedicAlert bracelet (MedicAlert Foundation, Adelaide, SA, Australia) and an understanding of sick day management. She refused to have a parenteral hydrocortisone emergency kit at home, but was well aware of the need to present to hospital in the event of an impending crisis. She developed a gastrointestinal viral infection (of 24-h duration) with vomiting and diarrhoea. She tripled her oral hydrocortisone dose, but could not keep the tablets down. The ambulance service was called. At retrieval, her blood pressure was 80/60 mmHg, and 1 L of Hartmann’s solution was given en route to hospital. On arrival to the emergency department, her blood pressure was 101/62 mmHg, and she was labelled ‘normotensive’ and triaged to be medically reviewed within 60 min. Intravenous fluids and hydrocortisone were not administered despite repeated requests by the patient’s family. Three hours elapsed, and her condition deteriorated, eventuating in cardiorespiratory arrest. Her arterial pH was 7.06. She was resuscitated, intubated and transferred to the intensive care unit (ICU). Her treating endocrinologist was first notified of her hospital presentation and admission 5 h after the transfer to ICU. Her hospital length of stay was 16 days, and her admission was complicated by stress-induced cardiomyopathy and a broken tooth from intubation. The actual and optimal management of our index patient is summarised in Table 1.

Discussion
Adrenal crisis is a life-threatening emergency that causes significant excess mortality in patients with adrenal insufficiency. Epidemiological studies indicate an incidence of between 5 and 10 adrenal crises per 100 patient years each year; 1 in 200 patients will die from an adrenal crisis.1 A recent Australian study reviewed national databases over a 13-year period and identified an increase in adrenal crisis hospital admission rates (further highlighting the increasing importance of prompt medical staff recognition and treatment of adrenal crises) that was positively correlated with a rise in short-acting glucocorticoid prescription rates. In lieu of modern-day lower-dose glucocorticoid replacement regimens, this study suggests a possible causal relationship between...
adrenal crisis events and the increasing use of short-acting glucocorticoids +/- reduced effective doses. Although the treatment of an adrenal crisis should be straightforward, delayed recognition by medical staff of an impending or established adrenal crisis and failure to give timely hydrocortisone therapy within the emergency department continue to be commonly encountered even in metropolitan teaching hospitals. Within the authors’ institutions, several cases of poorly handled adrenal crises, such as the case above, have occurred over the last 2 years. Anecdotal accounts from members of the Addison’s support group suggest that these issues are common throughout Australia. Several clinical and sociological factors appear to account for these delays and potentially life-threatening omissions. Clinical staff commonly fail to recognise the severity of an impending adrenal crisis as hypotension develops rapidly. Emergency department staff are often concerned about precipitating harmful effects with the administration of hydrocortisone. However, such effects are unlikely, and the risks are considerably outweighed by the likely benefits. Perhaps of most concern is that there are many instances where glucocorticoid treatment is delayed even when patients (and/or their carers) clearly outline the need for treatment, and the need is emphasised in written materials or MedicAlert bracelets.

Suspected adrenal crisis requires immediate therapeutic intervention (in undiagnosed adrenal insufficiency, treatment usually precedes biochemical proof of diagnosis). Treatment is simple and entails parenteral hydrocortisone (an initial bolus dose of 100 mg hydrocortisone) and isotonic saline to correct volume depletion. Prompt recognition and treatment of an impending crisis generally results in clinical recovery within 24 h. It has been observed that clinical recovery from untreated adrenal insufficiency presenting with confusion and somnolence can take several days or even up to 1 week. Parenteral hydrocortisone followed by a timely change to an increased dose of oral glucocorticoids with subsequent tapering and overlap (generally 24–48 h following clinical improvement) is recommended, depending on the precipitant. Treatment of the inter-current illness and/or precipitant (e.g. with antibiotics etcetera) is required. Infections, particularly gastroenteritis, are the most frequent causes of an adrenal crisis. Patients on long-term exogenous glucocorticoids (for a non-endocrine condition) are at risk of an adrenal crisis.

Patient education is considered critical to prevent crises. Preventative strategies to ensure early recognition and timely intervention of an impending adrenal crisis are essential to reduce morbidity (including hospital length of stay and time to clinical recovery) and mortality from a crisis. Patients and carers of those with adrenal insufficiency commonly understand their condition very well, sometimes even better than the health professionals, and feel distressed and frustrated while encountering barriers to emergency care. Listening to a well-informed patient and/or carer in adrenal crisis who says that he or she needs steroids and taking urgent action will avoid unnecessary deaths from this treatable medical problem.

### Table 1

<table>
<thead>
<tr>
<th>Triage</th>
<th>Medical assessment</th>
<th>Parenteral hydrocortisone</th>
<th>Hydrocortisone dose</th>
<th>Endocrine consult</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Index patient</td>
<td>Addison’s disease noted but triaged as non-urgent</td>
<td>After 3 h</td>
<td>Administered after cardiac arrest</td>
<td>100 mg IV</td>
<td>5 h after ICU admission</td>
</tr>
<tr>
<td>Optimal management</td>
<td>Identify at risk of adrenal crisis</td>
<td>Rapid, ideally within 10 min</td>
<td>Administer immediately</td>
<td>100 mg IM or IV</td>
<td>Yes</td>
</tr>
</tbody>
</table>

ICU, intensive care unit.
Table 2: Sick day management for patients on glucocorticoid therapy

<table>
<thead>
<tr>
<th>Issue</th>
<th>Symptoms</th>
<th>Temperature</th>
<th>Dose adjustment</th>
<th>Duration of oral dose adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trivial illness</td>
<td>e.g. mild cold</td>
<td>No temperature (less than 37.4°C)</td>
<td>No change</td>
<td>N/A</td>
</tr>
<tr>
<td>Mildly unwell</td>
<td>e.g. mild infection (such as cystitis) with low grade temperature</td>
<td>37.5–38.5°C</td>
<td>2× normal oral dose</td>
<td>Until recovery plus 1–2 days</td>
</tr>
<tr>
<td>More unwell</td>
<td>e.g. high fevers</td>
<td>&gt;38.5°C</td>
<td>3× normal oral dose†</td>
<td>Until recovery plus 2 days</td>
</tr>
<tr>
<td></td>
<td>e.g. gastroenteritis with vomiting +/- diarrhoea or pneumonia etc</td>
<td>Could be normal or raised</td>
<td>Early parenteral hydrocortisone (50–100 mg IV bolus followed by 25–50 mg IV every 8 h till the condition stabilises) then 2–3× normal oral dose</td>
<td>Until recovery plus 2 days</td>
</tr>
<tr>
<td>Minor dental procedure (&gt;1 h under local anaesthetic), significant injury or major emotional stress</td>
<td></td>
<td></td>
<td>2× normal oral dose</td>
<td>24 h</td>
</tr>
<tr>
<td>Major surgery or procedure with general anaesthetic</td>
<td></td>
<td></td>
<td>Parenteral hydrocortisone (50–100 mg IV bolus at induction followed by 25–50 mg IV every 8 h till stable) then 2× normal oral dose</td>
<td>Continue for 48 h post procedure</td>
</tr>
</tbody>
</table>

†The ‘3 × 3 rule’ means tripling the patient’s usual oral dose for 3 days or for the duration of the illness after which the patient resumes their usual dose.6,7

Table 3: Ambulance service role in managing acute adrenal insufficiency

<table>
<thead>
<tr>
<th>Are there clinical practice guidelines and/or drug therapy protocols for acute adrenal insufficiency?</th>
<th>NSW</th>
<th>VIC</th>
<th>ACT</th>
<th>QLD</th>
<th>SA</th>
<th>NT</th>
<th>WA</th>
<th>TAS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Does the ambulance carry parenteral hydrocortisone?</td>
<td>No</td>
<td>No†</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No†</td>
<td>No†</td>
</tr>
<tr>
<td>Can paramedics administer patient’s own emergency parenteral hydrocortisone?</td>
<td>Yes</td>
<td>Yes‡</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes‡</td>
</tr>
</tbody>
</table>

†Only dexamethasone (adrenal insufficiency is not stated as an indication for its use).
‡If patient is carrying a letter stating it is required in the appropriate clinical setting.
insufficiency are encouraged to carry an emergency card and/or a MedicAlert bracelet that succinctly reflects glucocorticoid dependency. Every patient should be provided with an emergency kit for parenteral hydrocortisone self-administration (this injection can be administered by a trained relative and/or a healthcare professional, e.g. paramedic, prior to transfer to the hospital emergency department). Table 3 summarises whether each Australian state’s ambulance service has clinical practice guidelines and/or drug therapy protocols for managing acute adrenal insufficiency, whether parenteral hydrocortisone is available in the ambulance and, if unavailable, whether paramedics are able to administer the patient’s emergency parenteral hydrocortisone. Patient education group meetings may be an effective intervention. Hospital computer systems may be able to ‘flag’ patients with adrenal insufficiency.

In conclusion, prompt recognition and treatment of an impending adrenal crisis is critical to reduce its associated morbidity and mortality. Healthcare workers must be acutely aware of its presentation (including the initial false appearance of clinical stability with potential rapid deterioration) and appreciate the urgency of its treatment. Patients, carers and families must be well educated and updated on ‘sick day’ management using a structured and quality-controlled approach. A MedicAlert or emergency card and an emergency hydrocortisone kit ready for use by self or others are an essential part of patient management.

References
2. Rushworth RL, Torpy DJ. Adrenal insufficiency in Australia: is it possible that the use of lower dose, short-acting glucocorticoids has increased the risk of adrenal crisis? Horm Metab Res 2015; 47: 427–32.
Severe hypocalcaemia and hypophosphataemia following intravenous iron and denosumab: a novel drug interaction

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Key words
hypocalcaemia, hypophosphataemia, intravenous iron, iron polymaltose, denosumab, chronic kidney disease.

Abstract
We present the case of a 59-year-old woman with chronic kidney disease who suffered severe hypocalcaemia and hypophosphataemia after receiving denosumab and intravenous iron. This potentially life-threatening adverse drug interaction has never been reported before. We propose a mechanism to explain it with reference to the physiological derangements caused by both agents on calcium and phosphate homeostasis.

A 59-year-old woman who attended our nephrology clinic for routine review of stage 3 chronic kidney disease (CKD) due to ischaemic nephrosclerosis and type 2 diabetes mellitus was found to have a corrected calcium of 1.81 mmol/L (normal value: 2.20–2.60) and phosphate of 0.36 mmol/L (normal value: 0.80–1.50). She was admitted to the hospital and commenced on intravenous calcium and phosphate replacement. History revealed that 26 days prior to presentation, she had received 60 mg denosumab for osteoporosis and 5 days later she had received 1000 mg intravenous iron polymaltose for iron deficiency. This was her second denosumab infusion (the first had been 6 months previously and uncomplicated) and her first iron infusion. Her other comorbidities were dyslipidaemia and peripheral vascular disease. She was not taking calcium or vitamin D supplements. Further investigations on admission included a parathyroid hormone (PTH) of 40.2 pmol/L (normal value: 1.1–6.9), 25-OH vitamin D of 55 nmol/L (normal value: 25–150), creatinine of 166 μmol/L (normal value: 50–90; estimated glomerular filtration rate (eGFR) 27 mL/min/1.73 m² by CKD-EPI) and an elevated non-fasting urine fractional excretion of phosphate (FePO₄) of 71.6% (normal value: 10–20%). Seven weeks prior to presentation, her corrected calcium was 2.42 mmol/L, phosphate 1.41 mmol/L, creatinine 148 μmol/L (eGFR 31 mL/min/1.73m²), PTH 4.6 pmol/L and alkaline phosphatase 42 U/L (Figs 1, 2).

Her admission was uncomplicated. She remained asymptomatic and was discharged after 3 days on calcitriol 0.5 mcg BD, calcium carbonate 1.2 g daily and phosphate 500 mg daily. Phosphate, calcium and calcitriol replacements were weaned gradually and all supplements were ceased 3 months after the initial administration of iron and denosumab. At the final visit, the patient’s FePO₄ had reduced to 34.7% and her serum calcium and phosphate were within the normal range.

Discussion
Denosumab is a monoclonal antibody to the receptor activator of nuclear factor-κB ligand (RANK-L) used to treat osteoporosis and skeletal complications of metastatic solid organ malignancies. RANK-L is expressed by osteoblasts and stimulates osteoclastogenesis and bone resorption through interaction with RANK expressed on osteoclasts. Denosumab inhibits this interaction, thus suppressing osteoclast activity leading to increased bone mineral density.¹ ² RANK/RANK-L interactions are also found in the immune system where they have a role in lymph node growth, dendritic cell survival, T-cell activation, including regulatory T-cells and induction of tolerance.¹ The clinical relevance of these observations on the use of denosumab is debated as some, but not all, studies have shown a small absolute increase in risk of infection.
Side effects include eczema, hypercholesterolaemia, musculoskeletal pain, hypocalcaemia, hypophosphataemias and, rarely, osteonecrosis of the jaw. No previous drug interactions have been reported for denosumab. Unlike bisphosphonates, denosumab does not require dose reduction in renal impairment and is not associated with nephrotoxicity.2

Hypocalcaemia is a common complication of denosumab treatment for bony metastases, occurring in 5–10% of patients.3,4 It reflects inhibition of bone resorption and is accompanied by a compensatory increase in PTH.5 Trials of denosumab for post-menopausal osteoporosis have reported a much lower incidence of hypocalcaemia (<1%)6,7 reflecting both the higher doses used in malignancy and also the differing states of bone turnover in patients with metastases versus those with osteoporosis.1,8 Impaired renal function is a well-documented risk factor for denosumab-induced hypocalcaemia, which occurs in 15–45% of patients depending on degree of renal impairment.9,10 A nadir is typically reached around 10 days after the infusion and may be severe, requiring intravenous replacement. Serum calcium may take up to 8 weeks to return to the previous levels which correlate roughly with the mean half-life of denosumab of 28–32 days.2,3,6–12 Hypophosphataemia may also occur in patients with renal impairment given denosumab. In a series of 22 patients with malignancy and impaired renal function (eGFR < 30 mL/min/1.73 m²), in addition to 45% of patients with hypocalcaemia, 32% experienced hypophosphataemia following 120 mg denosumab.10

The increased incidence of hypocalcaemia after denosumab in patients with renal disease is attributable to CKD-bone and mineral disorder (CKD-MBD). CKD-MBD encompasses a wide spectrum of abnormalities of
bone turnover, vascular calcification and calcium and phosphate homeostasis that progress as renal function declines. Bone pathology (renal osteodystrophy) varies widely from low turnover (adynamic) bone disease to high turnover (osteitis fibrosa) bone disease with mixed disorders occurring. As denosumab acts to inhibit osteoclast activity, it is hypothesised that the disordered bone metabolism associated with CKD predisposes patients to varying degrees of ‘hungry bone syndrome’ causing hypocalcaemia and hypophosphataemia.9

Disordered phosphate metabolism is central to the pathophysiology of CKD-MBD. Elevated serum phosphate is not typically seen until the late stages of CKD (eGFR < 30 mL/min/1.73 m²). Rather, the earliest abnormality is an elevation in fibroblast growth factor 23 (FGF-23) which can be seen in stage 3 CKD (eGFR 30–60 mL/min/1.73 m²). FGF-23, produced by osteocytes, is the principal negative regulator of phosphate homeostasis. It acts on the proximal tubule to reduce renal phosphate reabsorption through the Na-Pi channel and inhibits 1-α-hydroxylase (thereby inhibiting the conversion of calcidiol to calcitriol). It also acts directly on the parathyroid to suppress PTH release.13

Hypophosphataemia following intravenous iron is well described and may be severe. It is thought to be due to the elevated levels of FGF-23.14–17 A low serum phosphate, high FePO₄ and elevated FGF-23 have been demonstrated in patients treated with intravenous iron polynaltose, including in haemodialysis patients.18,19 As would be expected from the physiological actions of FGF-23, reductions in PTH and serum 1,25(OH) vitamin D have also been demonstrated following intravenous iron highlighting the interdependence of calcium and phosphate metabolism. Hypophosphataemia may be more common in patients with CKD. Prats et al. demonstrated hypophosphataemia in 35 of 47 (74%) patients with renal impairment (mean eGFR 26 mL/min/1.73 m²) treated with ferric carboxymaltose. In contrast to other studies, however, C-terminal FGF-23 levels were reduced.20

We believe that the severity of denosumab-induced hypocalcaemia and the co-existence of severe hypophosphataemia in this patient were out of proportion to the probable degree of disordered bone metabolism. While this cannot be proven in the absence of a bone biopsy, her normal baseline serum phosphate, calcium, PTH, alkaline phosphatase and the context of stage 3 CKD make it unlikely that she had severe renal osteodystrophy. Instead, the constellation of biochemical abnormalities and her clinical course is best explained by the superposition of the iatrogenic disturbances of phosphate, calcium and bone metabolism by parenteral iron and denosumab. The pathophysiology of the interaction requires the pre-existence of CKD-MBD and is hypothesised to be as follows: denosumab caused hypocalcaemia through inducing a mild form of ‘hungry bone syndrome’ in a patient with abnormal bone metabolism. Intravenous iron then induced a rise in FGF-23 that blunted the homeostatic response to hypocalcaemia by inhibiting PTH secretion and activation of vitamin D. The result was a marked exaggeration of denosumab-induced hypophosphataemia. The severity of the patient’s hypophosphataemia is similarly explained by the conjunction of an increase in FGF-23-induced phosphaturia following the intravenous iron, reduced activation of vitamin D causing reduced phosphate absorption and a failure to buffer the fall in phosphate due to the antiresorptive activity of denosumab. Furthermore, the hypocalcaemia-induced increase in PTH would be expected to worsen the hypophosphataemia by promoting renal phosphate wasting.

This case demonstrates a novel and potentially serious drug interaction that is readily explained with reference to the current understanding of calcium and phosphate homeostasis. Impaired renal function, iron deficiency and osteoporosis are common and co-prevalent, meaning the number of patients at risk for similar complications is not insignificant. Furthermore, a similar interaction could be hypothesised to occur with intravenous bisphosphonates and iron. In summary, we suggest avoiding denosumab and intravenous iron in close temporal association in patients with impaired renal function. However if required, then provision of calcium and calcitriol supplementation and close monitoring of serum calcium and phosphate in the first 2 weeks after treatment are imperative to prevent life-threatening calcium or phosphate disturbance.

References

Cardiovascular risk reduction in hypertension: angiotensin-converting enzyme inhibitors, angiotensin receptor blockers. Where are we up to?

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Key words
angiotensin-converting enzyme inhibitor, angiotensin receptor antagonist, cardiovascular diseases, risk assessment, hypertension.

Abstract
Previously, management of hypertension has concentrated on lowering elevated blood pressure. However, the target has shifted to reducing absolute cardiovascular (CV) risk. It is estimated that two in three Australian adults have three or more CV risk factors at the same time. Moderate reductions in several risk factors can, therefore, be more effective than major reductions in one. When managing hypertension, therapy should be focused on medications with the strongest evidence for CV event reduction, substituting alternatives only when a primary choice is not appropriate. Hypertension management guidelines categorise angiotensin-converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB) interchangeably as first-line treatments in uncomplicated hypertension. These medications have different mechanisms of action and quite different evidence bases. They are not interchangeable and their prescription should be based on clinical evidence. Despite this, currently ARB prescriptions are increasing at a higher rate than those for ACEI and other antihypertensive classes. Evidence that ACEI therapy prevents CV events and death, in patients with coronary artery disease or multiple CV risk factors, emerged from the European trial on reduction of cardiac events with perindopril in stable coronary artery disease (EUROPA) and Heart Outcomes Prevention Evaluation (HOPE) trials respectively. The consistent benefit has been demonstrated in meta-analyses. The clinical trial data for ARB are less consistent, particularly regarding CV outcomes and mortality benefit. The evidence supports the use of ACEI (Class 1a) compared with ARB despite current prescribing trends.

Introduction
In the past, patients with hypertension have been managed by concentrating on reducing elevated blood pressure (BP). However, therapy is now targeted at reducing absolute cardiovascular (CV) risk through medications with proven reductions in fatal and non-fatal events. Current hypertension management guidelines recommend angiotensin-converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB) as interchangeable first-line pharmacological treatments in
uncomplicated hypertension (alongside calcium channel blockers (CCB)). Hypertension is the only parameter contributing to CV risk and should be considered as the ‘gateway to a cascade of CV risk’. When assessing patients with hypertension, absolute CV risk should be calculated using a risk calculator, as CV risk is often underestimated and patients with hypertension, or other CV risk factors, may miss the opportunity to have their CV risk profile measured and appropriately managed.

Management of hypertension focuses on improving CV morbidity and mortality, based on clinical trial data and meta-analyses. Therapy should concentrate on agents with the strongest evidence for CV event reduction, substituting alternatives only when a primary choice is not appropriate. Despite this, ARB prescriptions are increasing at a higher rate than those for ACEI and other antihypertensive therapies. The evidence base for ACEI and ARB is not the same, and difficulties may arise in applying this evidence to managing CV risk.

This article addresses the shift in antihypertensive management towards CV risk reduction by focusing on guidelines and their shortcomings, and the impact of multiple risk factor interventions to reduce CV risk. Within this context, the role of ACEI and ARB is explored, particularly their mechanisms of action and data supporting their use.

**Hypertension guidelines: where do you look?**

Clinicians have a plethora of guidelines to assist decisions about appropriate healthcare. The range of guidelines makes it difficult for clinicians to know which are the most appropriate for their patients. Whether regional, national or international, hypertension guidelines differ in recommendations for target BP, treatment options and recommendations for special groups, for example, the elderly, patients with diabetes or chronic kidney disease (CKD).

Guidelines rely on robust search strategies and methodologies. Disappointingly, some guidelines have fallen short of these standards and have been criticized. A systematic review of guidelines on the diagnosis, assessment and management of hypertension assessed the quality and consistency of recommendations of 11 guidelines. It highlighted methodological gaps, including clarifying the scope and purpose, ensuring representation of all stakeholders, including consumers, scientific rigour, supporting implementation and declaration of editorial independence. Across the 11 guidelines reviewed, the highest scores were for clarity of presentation and the lowest for rigour of development.

Several guidelines group ACEI/ARB agents inappropriately and interchangeably (e.g. National Heart Foundation of Australia: Guide to Management of Hypertension). Extrapolation from one drug class to another may not be based on clinical trial data. In addition, primary prevention hypertension guidelines and secondary cardiovascular disease (CVD) prevention guidelines differ in their recommendations. For example, while National Heart Foundation guides to the management of hypertension and diabetes, management in general practice guidelines for type 2 diabetes does not prefer ACEI or ARB choice. However, the American secondary CVD prevention guidelines recommend ACEI as first-line (with ARB utilised for ACEI intolerant patients) (Table 1).

BP targets worldwide may change following the early termination of the systolic blood pressure intervention trial (SPRINT), which determined a BP treatment regimen targeting a systolic BP target of 120 mm Hg, reduced the risk of CV events by 30% and all-cause

<table>
<thead>
<tr>
<th>BP in mmHg</th>
<th>NICE</th>
<th>ESH/ESC</th>
<th>AHA/ACC/CDC</th>
<th>JNC 8 and ASH/ISH</th>
</tr>
</thead>
<tbody>
<tr>
<td>‘Hypertension’ threshold</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BP targets</td>
<td>140/90 and ABPM 135/85</td>
<td>140/90</td>
<td>140/90</td>
<td>N/A</td>
</tr>
<tr>
<td>Drug treatment threshold in low risk patients</td>
<td>160/100 or ABPM 150/95</td>
<td>140/90</td>
<td>140/90</td>
<td>140/90</td>
</tr>
<tr>
<td>BP targets (elderly)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;80 years</td>
<td>&lt;150/90 Systolic BP 140–150</td>
<td>N/A</td>
<td>&lt;150/90</td>
<td></td>
</tr>
<tr>
<td>BP targets (diabetics)</td>
<td>N/A</td>
<td>&lt;140/85</td>
<td>&lt;140/90</td>
<td></td>
</tr>
</tbody>
</table>

Lower targets may be considered

ABPM, ambulatory blood pressure monitor; AHA/ACC/CDC, American Heart Association/American College of Cardiology/Centers for Disease Control and Prevention; ASH, American Society of Hypertension; BP, blood pressure; ESC, European Society of Cardiology; ESH, European Society of Hypertension; ISH, International Society of Hypertension; JNC8, Eighth Joint National Committee; N/A, not applicable; NICE, National Institute for Clinical Excellence (Adapted from Lindholm and Carlberg, with permission).
mortality by nearly 25% when compared with patients treated to a target of 140 mm Hg in high-risk hypertensive adults ≥50 years of age.

**CV mortality in Australia**

Over the past few decades, Australia has achieved major gains in CV survival, due to improvements in prevention, detection, management and lifestyle modification, such as dietary intake, physical activity and smoking cessation. Death rates have fallen from the late 1960s, when CVD was responsible for approximately 55% of annual mortality. Age-adjusted CV mortality fell by 76% from 1968 to 2007, a potential reduction of 140 000 lives if CV mortality was at 1968 levels.

**Multiple CV risk factor intervention**

In Australia, hypertension is one of the most common risk factors in people with CVD (Fig. 1). Two in three Australian adults have three or more CV risk factors (Fig. 2). Assessment of CV risk leads to a more effective intervention than assessment based on single risk factors (Fig. 3). Moderate reductions in several risk factors can, therefore, be more effective than major reductions in one. This is despite the fact that BP treatment recommendations have traditionally been based on BP targets rather than adjusting for associated CV risks. This is in contrast to more recent lipid lowering recommendations. The Blood Pressure Lowering Treatment Trialists’ Collaboration has now demonstrated progressively greater absolute risk reductions for BP treatment, as baseline risk increases.

Risk for CV events (including CV death) remains, despite treatment of hypertension. Studies have evaluated the efficacy of statins and their potential limitations in reducing risk of coronary disease. They have demonstrated the effectiveness of statins in reducing the combined primary end-point of coronary heart death, non-fatal myocardial infarction (MI) or cerebrovascular event. However, they have shown that it is insufficient to treat individual CV risk factors, because although this may diminish risk somewhat, risk for further events remains very high.

Statin use in patients with ≥15% risk of developing CVD in 10 years, regardless of lipid concentrations or BP, would avoid more CV deaths compared with a population health strategy. Under a population health strategy, reducing the total cholesterol concentration of each person in the population by 2% would lead to 42 fewer deaths per 100 000 people treated for 10 years. Treating only patients with cholesterol >6.2 mmol/L would prevent 125 deaths per 100 000 people treated for 10 years. Current guidelines recommend treating patients with increased CV risk at lower cholesterol thresholds. The most effective strategy is to treat those with 15% or greater risk of developing CVD in 10 years, which would prevent 290 deaths per 100 000 people treated for 10 years.
Achieved BP treatment targets and the J-curve

Observational studies have suggested a log-linear relationship between BP and risk of stroke, coronary heart disease and renal injury, through the normal range to the lowest levels of BP. The Blood Pressure Lowering Treatment Trialists’ Collaboration demonstrated progressively greater absolute risk reductions for BP treatment, as baseline risk increases. There was no observed BP below which continuous improvements in BP were not associated with risk reduction. This led to the hypothesis that control of hypertension with antihypertensive drugs should seek to achieve BP in the low-normal range.

The J-curve phenomenon was encountered in interventional studies designed to achieve tight BP control and describes the increased risk with BP reduction below the given threshold, but remains controversial. The J-curve was most apparent in studies relating achieved diastolic BP to outcomes, especially in patients with known heart disease. The effect may be mediated by impaired diastolic coronary blood flow in patients with coronary artery disease (CAD) and left ventricular hypertrophy.

Patients with significant postural BP drops, the elderly and those with low diastolic BP even prior to treatment may be at particular risk with further lowering of BP. The concern over the impact of the J-curve effect has led to the hypothesis that control of hypertension with antihypertensive drugs should seek to achieve BP in the low-normal range.

Mechanism of action

The mechanism of action of ACEI and ARB is not the same. Figure 4 depicts the classical description of the renin–angiotensin–aldosterone system (RAAS).

ACEI reduce angiotensin-2 (AT-2) synthesis by inhibiting ACE action. ACE has two enzymatic sites, one at the N-terminus and one at the C-terminus. The C-terminus is the domain responsible for the reduction in AT-2-mediated hypertension, and the N-terminus for the accumulation of bradykinin. ACEI block both functions, and consequently increase other bioactive peptides, notably bradykinin and angiotensin 1-7. Angiotensin 1-7 acting through the MAS receptor is important in the kidney, heart and muscle where it has anti-proliferative, anti-thrombotic and hypotensive effects by inducing nitric oxide.

ARB bind directly to the angiotensin-1 (AT-1) receptor, preventing its activation by AT-2. This results in a relative increase in circulating AT-2 which may stimulate ACE expression and inhibit the expression of ACE2. ACE2 is different from ACE and is not affected by ACEI. ACE2 is important under stress and converts AT-2 to angiotensin 1-7. Circulating AT-2 may then bind to other angiotensin receptors, particularly the AT-2 receptor. Several effects of AT-1 blockade could be due to the effects of increased availability of AT-2 to bind to the AT-2 receptor.

A further potential mechanism for the pleiotropic effects of ACEI is that ACEI (but not AT-1 blockers) regulate bradykinin BR2 receptor signalling which has effects on innate and adaptive immunity and renal tubular salt handling.

While there are similarities, there are many differences in how ACEI and ARB produce their therapeutic effects, which may account for the differences in clinical outcomes.

Effect of RAAS agents on glomerular filtration rate

The effect of RAAS agents on glomerular filtration rate (GFR) is context dependent. ACEI therapy is associated with a reduction in mean arterial pressure and peripheral vascular resistance, including renal vascular resistance. In most patients, there is an increase in renal blood flow. Despite a reduction in efferent glomerular vascular resistance and reduced intra-glomerular pressure, the net effect on GFR is minimal.
While ACEI improve renal blood flow and sodium excretion rates in chronic heart failure and reduce the rate of progressive renal injury in CKD, their use can be associated with a syndrome of ‘functional renal insufficiency’ and/or hyperkalaemia.²⁶ ACEI and ARB therapy may contribute to acute kidney injury (AKI) and reduced GFR in patients with volume insufficiency. In hypertensive patients with normal renal function (i.e. estimated GFR >90 mL/min/1.73 m²), there is little change. In patients with vascular disease, particularly renal artery stenosis, there may be a greater risk of deterioration in renal function. Patients who take non-steroidal anti-inflammatory agents with ACEI or ARB, and have pre-existing renal insufficiency, are particularly at risk of renal impairment.²⁷

A meta-analysis of patients taking ACEI and ARB prior to coronary angiography found an increased risk for AKI in patients taking ARB (odds ratio (OR) = 3.31; 95% confidence interval (CI) = 1.89–5.78; P < 0.0005), but not in patients taking ACEI. This may represent differential effects of AT-2 on various AT receptors compared with the inhibition of AT-2 production.²⁸

The combined arm of the ONTARGET study using ACEI and ARB therapy on CV outcomes and BP did not lead to a further reduction in MI or other CV events when compared with either agent alone, with some increase in hypotension.²⁹ ACEI and ARB are, therefore, not recommended in combination to reduce CV risk. A meta-analysis of patients receiving combined ACEI/ARB therapy for CKD showed that there was some benefit in reducing albuminuria, but at the expense of a small decrease in GFR.³⁰

**Evidence for ACEI use**

Evidence that ACEI prevent CV events and death in patients with multiple CV risk factors³¹ or CAD³² emerged with the Heart Outcomes Prevention Evaluation (HOPE)³¹ and European trial on reduction of cardiac events with perindopril in stable coronary artery disease (EUROPA)³² trials. The consistent benefit has been demonstrated in meta-analyses.³³–³⁵

In patients with high CV risk, a meta-analysis of 26 randomised controlled trials involving 108 112

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**Figure 4** The renin–angiotensin–aldosterone system. ACE, angiotensin converting enzyme; ACE2, angiotensin converting enzyme 2; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; AT-1, angiotensin-1; AT-2, angiotensin-2; AT-3, angiotensin-3; AT-4, angiotensin-4.
patients without heart failure reported that ACEI significantly reduced the composite outcome of CV death, MI and stroke by 17% (P = 0.001), MI by 19% (P < 0.001), stroke by 20% (P < 0.004), all-cause death by 9% (P = 0.008), new-onset heart failure by 21% (P = 0.001) and new-onset diabetes by 14% (P < 0.001).33 van Vark et al. completed a pooled analysis of 20 CV morbidity–mortality trials using RAAS inhibitors for the treatment of hypertension.34 They demonstrated that RAAS inhibitors were associated with a reduction in all-cause mortality of 5% (P = 0.032).35 In a post hoc analysis of ACEI and ARB separately, they found that the observed benefit was largely attributable to the beneficial effects of ACEI (10% relative risk reduction in all-cause mortality, P = 0.004). There was a significant statistical heterogeneity between ACEI and ARB effects on mortality (but not CV mortality).34 A South African study evaluating cost and outcomes found equal input costs for ACEI and ARB, but significant reduction in downstream events and costs.35 A meta-analysis of ACEI in patients with diabetes analysed 23 trials in 32 827 patients. ACEI significantly reduced all-cause mortality by 13% (P = 0.02), CV death by 17% (P = 0.04), MI by 21% (P = 0.01) and heart failure by 19% (P = 0.002).36

**Evidence for ARB use**

ARB have less compelling evidence pertaining to CV morbidity and mortality. A meta-analysis of 37 randomised controlled trials, including 147 020 patients showed that ARB reduce the relative risk of stroke by 10% (P = 0.007), heart failure by 13% (P < 0.001) and new-onset diabetes by 15% (P = 0.003) compared with placebo or an active comparator. Importantly, however, ARB did not reduce the risk of MI (1% reduction, P = 0.055), CV death (1% reduction, P = 0.090) or death from any cause (no reduction, P = 0.482).37 This meta-analysis included the ONTARGET trial that established that telmisartan (an ARB) was not inferior to ramipril (an ACEI) in the reduction of major CV events and CV mortality.29

The meta-analysis by van Vark et al. showed that ARB did not reduce overall or CV mortality in patients with hypertension. The paper was limited by the fact that it was an indirect comparison between studies and possible confounding attributable to additional parameters, including adjuvant treatment. Inter-trial comparisons are prone to epidemiological fallacies. Head-to-head comparisons are preferred. However, this meta-analysis directly compares these two classes in a predominantly hypertensive cohort.34

**Direct comparison**

The ONTARGET trial directly compared ACEI with ARB and showed that telmisartan (an ARB) was not inferior to ramipril (an ACEI) in the risk of major CV events, including CV death. Patients randomised to the ARB had less cough.29 In patients with hypertension, a meta-analysis of head-to-head trials found nine studies of more than 1 year in duration and demonstrated no difference between ACEI and ARB for total mortality (RR = 0.98), CV events (RR = 1.07) or CV mortality (RR = 0.98). This meta-analysis highlighted that ACEI have shown positive improvement in these outcomes over placebo, but these findings cannot be extrapolated to ARB.38 Two similarly designed studies have been performed in patients with multiple CV risk factors. The HOPE study31 evaluated the effect of ACEI and found a significant reduction in CV events. However, the TRANSCEND study39 assessed the effect of ARB in high-risk patients intolerant of ACEI and showed no significant reduction in CV events. The population demographics and concomitant medications varied between the trials.

A Cochrane review of ACEI versus ARB for hypertension noted substitution of an ARB for an ACEI, while supported by evidence on grounds of tolerability, must be made in consideration of the weaker evidence for the efficacy of ARB regarding mortality and morbidity compared with ACEI.38 However, in patients with renal impairment, diabetes and established vascular risk RAAS system intervention should be first-line.38

**Tolerability**

The most cited reason for discontinuation of ACEI therapy is cough. A meta-analysis of 27 492 ACEI-naïve patients with CVD treated with the ACEI perindopril or placebo found a 3.9% incidence of cough.40 It found no role for race in determining the incidence of cough for people of white people or Asian descent. The predictors of cough were female gender, older age and concomitant use of lipid lowering agents. This study cast doubt on the role of ethnicity in the genesis of cough, and further suggested that the switch from ACEI to ARB therapy should be no more than 4%.40 This is particularly so as ACEI have Class 1A evidence supporting their use.1

**Management of resistant hypertension**

Studies estimate that 10% of hypertensive patients have resistant hypertension.15 Primary hyperaldosteronism may occur in a significant proportion of this group.1
Spironolactone, an aldosterone antagonist, is considered a fifth-line agent for the treatment of hypertensive patients resistant to a combination of ACEI/ARB, CCB, a thiazide diuretic or a beta-blocker. Spironolactone may potentially benefit hypertensive patients with heart failure. Eplerenone, an aldosterone antagonist with less anti-progesterone and anti-androgenic effects, is effective in hypertension and post-MI heart failure.

Australian guidelines recommend several other fifth-line agents, including beta-blockers, clonidine, hydralazine, methyldopa, moxonidine and prazosin. Methyldopa, oxprenolol and labetalol may be used in pregnancy, whereas diuretics, ACEI and ARB are contraindicated.

Timing of antihypertensive therapy

Several studies have produced findings in favour of nocturnal dosing of antihypertensive medications. In patients with CKD whose BP did not fall during the night on ambulatory BP monitoring (non-dippers), changing antihypertensive therapy to the night time decreased nocturnal BP and decreased proteinuria.

In two studies by Hermida et al., patients with hypertension were randomised to receive all of their antihypertensive medications in the morning or at least one at night. In diabetic hypertensive patients, taking at least one antihypertensive medication at night reduced CV risk. In patients with hypertension and CKD, those who took at least one BP-lowering medication at night had an adjusted risk of CV events of less than one third of those who took all medications in the morning (adjusted hazard ratio (HR) = 0.31; 95% CI = 0.21–0.46; P < 0.001). Taking medications at night demonstrated a similar reduction in a composite outcome of CV death, MI and stroke (adjusted HR = 0.28; 95% CI = 0.13–0.61; P < 0.001).

These results may change timing of antihypertensive therapy, particularly as the majority of CV events occur in the morning hours, when night time medications exert their maximal effect, whereas morning medications may be losing efficacy.

Medication adherence and compliance

There has been a shift from the term ‘compliance’ to ‘adherence’, as the latter reflects the onus placed on the patient to take prescribed medication and implies the sharing of responsibility between doctor and patient.

The primary aim of antihypertensive medication is to reduce CV events, but non-adherence to medications may adversely affect the ability to control BP. In hypertensive patients, a meta-analysis demonstrated that the OR of achieving BP with adherence to dosing regimens versus non-adherence was 3.44 (95% CI = 1.60–7.37). Non-adherence may be a major contributor to ‘refractory hypertension’ in a subgroup of hypertensive patients. A middle group, referred to as the ‘white-coat’ compliers, take their medications prior to the doctor’s appointment, and others adhere on a ‘prn’ basis, with either wrong dosage or frequency.

Most hypertensive patients require at least two antihypertensive medications and some guidelines recommend initiation with dual therapy. Single tablet combinations, as opposed to prescription of two medications given separately (free drug components), were compared in a meta-analysis which found that single tablet combinations are associated with greater compliance (OR = 1.21; 95% CI = 1.03–1.43; P = 0.02). A reduction in systolic/diastolic BP of 4.1/3.1 mm Hg was seen; however, the change was not statistically significant.

Conclusion

Reducing CV morbidity and mortality is the focus of treating patients with hypertension. The means by which this is achieved is important. It is not simply about reaching a target BP, but about using medications which have been demonstrated to reduce CV events. The evidence supports the use of ACEI (Class 1A) in preference to ARB despite current prescribing trends. These medications have different mechanisms of action and quite different evidence bases. They are not interchangeable and their prescription should be based on clinical evidence.

Doctors are able to prescribe a range of medications which are able to lower BP. The key is to choose a management strategy which encompasses multiple risk factor reduction, is well tolerated, effective, economic and one which is likely to maximise patients’ adherence. This review has discussed the guidelines and evidence, as well as challenged current treatment paradigms in light of the available data to try and achieve maximal benefit for patients with increased CV risk.

Management of patients to reduce CV risk should include the evaluation of compliance with medications, whether medications are taken in the morning or at night and attempts to address modifiable risk factors, including hypertension, hyperlipidaemia, cigarette smoking, dietary intake and physical activity. This will enhance management and aims to reduce risk further.

The goal of CV therapy in hypertension management should focus on reducing CV events using medications with proven benefit. ACEI appear to have superior evidence over ARB and should be preferred to ARB.
Prescribers should only cease or change from an ACEI for a clearly confirmed side effect. Reducing CV morbidity and mortality in hypertension is not just about achieving a target BP. The class of medication used can affect outcomes, even though the same BP has been achieved. It is not just about the destination, but also about the journey.

References


Screening for coeliac disease in elderly inpatients with minimal trauma fracture is not indicated

It has been noted recently that in a Liverpool coeliac cohort,1 26% of tested coeliac patients had osteoporosis through bone mineral density. Due to this, some authorities recommend screening orthogeriatric populations for coeliac disease.1,2 However, this advice is at odds both with other literature3 and with our clinical experience – orthogeriatric patients with clinically defined osteoporosis (minimal trauma fracture) do not appear to have an increased incidence of coeliac disease.

Thus, we undertook a retrospective audit of the results of screening tests for coeliac disease obtained during 732 consecutive acute admissions from 2007 to 2009 with minimal trauma fracture to the orthogeriatric service of the Royal Melbourne Hospital (72.00% female, mean age of admission = 81.16 years). Tissue transglutaminase (tTG) levels were assessed in 290 (74.05% female) of the 732 admissions due to the lack of clear guidelines and differing practice. Some patients did not have any screening completed during their acute admission. Testing was not based on the presence or absence of signs, symptoms or other results suggestive of coeliac disease. Approval was subsequently obtained as a quality assurance activity from the Melbourne Health Human Research Ethics Committee. Testing data were obtained using the INOVA Diagnostics tTG assay (ref = 0–20 units). Three females and one male who presented with a fracture were tTG abnormal (1.38%). During their acute admission, none of the four went on to have gastroscopic confirmation of histologically evident coeliac disease or HLA DQ2/8 testing, and one died as a result of the fracture. In addition, none of the patients in our sample was completely IgA deficient (ref <0.05 g/L). These results could have been strengthened by additional serologic testing, including HLA DQ2/8 or for DGP-IgG, but this was not a part of routine screening at the time of admission.

The serologic prevalence of coeliac disease (1.38%) in our cohort closely approximates the prevalence of coeliac disease in a general Australian population of 1.3%.4

Recent work5 suggests a high rate of gluten or wheat exclusion in the general Australian population. While it is possible that this could lead to an increased rate of false negatives in this cohort, there are two potential mitigating factors. The first is the time this data were collected from – the fractures are from prior to 2009, where gluten avoidance may have been less frequent. Secondly, patients with a minimal trauma fracture are not representative of a general Australian population, with differences of age, residence, cognitive status and available nutrition such that gluten avoidance may have been less frequent.

In a review of the literature, several other authors have approached the association between coeliac disease and minimal trauma fractures with similarly low rates of association. Of particular note, our findings concord with a case series of 347 older patients with hip fracture which found no association with coeliac disease, although these authors used an older screening test (endomysial antibody) that has lower reported sensitivity than the test that we used (tTG-IgA).3

Given the low rates of coeliac autoantibody positive testing, there are at least four possibilities: first, that this test is for a previously unknown reason not useful in the diagnosis of coeliac disease in the elderly (despite various studies to the contrary); second, that coeliac disease is not associated with minimal trauma fracture; third, that the elderly represent a population with a low rate of coeliac disease compared with younger cohorts and therefore low rates of association (which is again contradicted by the literature) or finally that there is significant symptomatic and serologic control of coeliac disease through the voluntary adoption of a gluten-free diet in this population.

The lack of an increased autoantibody frequency in our cohort above general population prevalence supports our clinical impression that coeliac disease is not more common in the elderly suffering minimal trauma fracture. However, this finding may not necessarily apply to younger cohorts, where the contribution of reduced bone mineral density from coeliac disease may be relatively greater in the absence of other risk factors, such as age.

In summary then, we recommend against routine serological screening for coeliac disease in elderly inpatients with minimal trauma fracture. This is important given the lack of utility as described above, and the cost of screening a minimal trauma population with...
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relatively reduced QALY gains (compared with only symptomatic at-risk screening).6

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Traumatic superior gluteal artery pseudoaneurysm following a bone marrow biopsy

A 62-year-old man with recently diagnosed chronic myeloid leukaemia (CML) presented to the emergency department 2 h after a diagnostic bone marrow aspirate and trephine (BMAT) taken from the right posterior iliac crest. He described progressive pain and swelling in the right buttck and difficulty walking due to pain. He denied weakness or paraesthesia in the leg.

The man’s CML was in chronic phase, and he had not yet been started on treatment. His presenting blood tests showed haemoglobin of 86 g/L, platelet count of 616 × 10^9/L and a total white cell count of 376.50 × 10^9/L. His Sokal relative risk was high (1.63).1

Examination on admission revealed a superficial haematoma over the right buttck with no external bleeding from the biopsy site. There was no evidence of neurovascular compromise in the lower limbs. The man was initially treated with analgesia and observed; however, on the second day of his admission, his right buttck and leg were markedly more swollen. The man complained of severe pain mobilising and light-headedness on standing. Repeat blood tests showed a decline in the haemoglobin concentration to 60 g/L.

An urgent computed tomographic scan was requested, which showed a large haematoma in the right buttck and thigh with active haemorrhage at the level of the biopsy track in the right iliac crest.

The patient went forward for urgent endovascular treatment in view of active bleeding. Right internal iliac artery angiography demonstrated a pseudoaneurysm arising from a branch of the right superior gluteal artery (Fig. 1A). The branch of the superior gluteal artery supplying the pseudoaneurysm was accessed using a microcatheter, and the pseudoaneurysm was successfully coiled (Fig. 1B).

Following successful embolisation, the patient reported a dramatic improvement in his pain. He was discharged after 8 days in hospital when he was able to walk independently with the aid of crutches. His mobility was limited by pain only with no neurological complications detected.

Bone marrow biopsies are used extensively for the investigation of haematological diseases. They are considered a safe procedure with an adverse event rate of 0.08%.2 Complications are mostly limited to discomfort at the biopsy site, bruising and occasionally local bleeding. While infrequent, haemorrhage is the most common serious complication, and patients typically present within hours of the procedure.3 Haemorrhagic complications requiring surgical or endovascular intervention are rare with only a small number of cases reported in the literature.

Patients with myeloproliferative neoplasms have the greatest risk of haemorrhage following BMAT.2 Other risk factors for bleeding include antiplatelet and anticoagulant therapy, coagulation defects, platelet disorders, renal impairment, bone disease and obesity.2,3

Pseudoaneurysms arise from a defect in the artery wall with active bleeding into surrounding haematoma.4 Superior gluteal artery pseudoaneurysms are a rare but
known complication of bone marrow biopsies taken from the posterior iliac crest with a typical presentation of pain and swelling within the gluteal or retroperitoneal compartments.4,5 Morbidity following a superior gluteal artery pseudoaneurysm can be significant with prolonged hospital stays and case reports of patients having sciatic nerve injury.6 Endovascular treatment of traumatic pseudoaneurysms provides a fast, effective and minimally invasive method for patients who would otherwise require open surgery.3,4

We report a case of a BMAT resulting in severe haemorrhage from a traumatic superior gluteal artery pseudoaneurysm that was successfully treated with an embolisation procedure. Clinicians need to be aware of and minimise risk factors for bleeding following BMAT. In addition, knowledge of complications allows prompt diagnosis and treatment of patients who may present following a BMAT procedure.

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Liquid biopsies: advancing cancer research through drops of blood

Tissue biopsy has been the gold standard for diagnosis of cancer for years. Advances in the genotyping of tumour tissue acquired often through invasive procedures have led to development of several prognostic and predictive biomarkers to help facilitate complex decision-making in oncology clinics. However, the information acquired from a single biopsy only provides a limited snapshot at a single time point. We know that tumours evolve with time especially after exposure to various systemic therapies and can develop secondary mutations leading to drug resistance.1 Another major challenge in the era of personalised targeted therapy is that of intra-tumour heterogeneity. Gerlinger et al. took paired samples from various sites of the primary tumour specimen and its metastases and found that there was significant intra and inter-tumoural heterogeneity.2

Longitudinal tumour biopsies seem to be a rational approach, but are less practical due to several issues, including discomfort to the patient, risk of complications from invasive procedures and associated costs. In contrast, liquid biopsies obtained through a blood sample offer an attractive alternative despite its limitations. Liquid biopsy can potentially provide information regarding the genetic makeup of both primary tumour and metastases offering the opportunity to track systematically genomic evolution of the tumour. Analysis of circulating tumour cells (CTC) and circulating tumour DNA (ctDNA) in the plasma samples can provide extremely useful information through a non-invasive technique. CTC are cells of solid tumour origin that can be detected in the blood of cancer patients. ctDNA on the other hand can be detected in the peripheral blood specimen predominantly as a consequence of passive release of DNA fragments from necrotic and apoptotic malignant cells.

Serial liquid biopsies can be performed to give us a better understanding of the evolution of tumour with time, identify various prognostic and predictive biomarkers and identify mechanism of resistance to targeted therapy. Several studies in various tumour types have looked at evaluating the prognostic impact of CTC on patient outcomes.3 Results have however been conflicting. Studies have revealed a significant correlation between disease stage and the presence of tumour-associated genetic aberrations (including mutations in TP53, KRAS and APC) through ctDNA analysis in the blood of patients with breast, ovarian, pancreatic and colorectal cancer.4

One major issue with CTC and ctDNA analysis is the lack of standardisation of technique. This has led to conflicting results in different studies evaluating the prognostic impact of CTC and ctDNA.3,4 CellSearch assay is the most widely used method for CTC quantification.3 However, the CellSearch method of CTC identification relies heavily on epithelial surface markers (melanoma cell adhesion molecule (MCAM)) that is likely to be lost in the context of metastatic disease involving epithelial to mesenchymal transition meaning certain CTC subtypes can be missed. Others have evaluated a multi-marker approach involving stem cell markers (ABCB5, CD271 and RANK) along with epithelial surface markers (MCAM and modified citrus pectin (MCP)) that enriches the isolation of CTC in melanoma.5 Lack of standardised techniques in ctDNA analysis can be due to differences in the DNA extraction material (serum vs plasma) or in the techniques used for the quantification of ctDNA (digital polymerase chain reaction, next generation sequencing, BEAMing).4

Another promising application for liquid biopsies is the early detection of cancer relapse after curative surgery. Surveillance protocols vary for different tumour types and there is variable clinical practice globally. However, most surveillance protocols will include clinical examination that has a low sensitivity, tumour markers that can be non-specific or some patients can be non-secretors and various radiological assessments that are expensive and require injection of contrast media. A study by Diehl et al. showed that it was possible to identify disease recurrence with almost 100% sensitivity and specificity by monitoring tumour-specific aberrations (including APC, TP53 and KRAS) in the plasma of patients with colorectal cancer post-surgery.6

Role of liquid biopsies in situations where a biopsy might be difficult to obtain like patients with pancreatic cancer, deep abdominal or pelvic masses or patients with bony metastases needs to be explored. One of the most exciting areas of research is to investigate the predictive significance of CTC and ctDNA in determining response and resistance to treatment in various tumour types. Detection of androgen receptor splice variant-7 (AR-V7) in CTC from men with advanced prostate cancer is associated with resistance to both enzalutamide and abiraterone, as evidenced by inferior prostate specific antigen responses, progression-free survival and overall
survival. Sequist et al. recently reported the efficacy of rociletinib (CO-1686) in plasma-genotyped T790M-positive non-small-cell lung cancer patients and found T790M decrease in most patients.

In conclusion, liquid biopsies offer an exciting area of future research that has the potential to change clinical practice and make it more efficient. It will assist the clinicians in complex decision-making, and through serial liquid biopsies, we will be able to track an evolving tumour and identify predictive and prognostic biomarkers and study mechanisms of drug resistance. Several challenges remain before this is possible and these include lack of standardisation of quantification techniques, logistics of promptly processing the blood specimen after it is obtained and lack of widespread availability of laboratories with expertise in these techniques minimising the generalisability and uptake of liquid biopsies in routine clinical practice.

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Conflict of interest: real and perceived – a more mature consideration is needed

We were somewhat bemused to read the letter regarding conflict of interest (COI) statements in the Journal recently as it appeared to be a direct communication resulting from our publication, yet we had not been invited to respond prior to its publication, as would usually occur with correspondence arising. COI are an important issue as they are impossible to avoid completely and so reducing discussion of COI to a letter in which inaccurate statements are made and deceitful conduct implied is not helpful. We therefore felt compelled to put our views and open further more nuanced discussion on this important issue.

Niall says that our study exemplifies the fact that COI statements’ ‘purpose and interpretation remain unclear’. I fail to see that this is true. The purpose of a COI statement is to make the reader aware of (potential) biases of the authors (especially, but not only, financial) which may be of relevance to the subject matter. The interpretation is up to the readers – and each will have their own biases (otherwise also known as COI) that will lead each to a slightly different interpretation. A reader will see that authors on our paper made detailed disclosures, beyond this it is up to the readers to judge for themselves – having read the paper – whether they feel it is unduly biased.

Niall goes on to say that ‘The origin of these funds (to provide compassionate access therapy) is not clarified’. This is also inaccurate; our article clearly states that the origin of these funds was from hospital or industry funds. This means that either the hospital paid or the drug company forewent payment. We are not sure how this could have been more clearly written.

In the following paragraph, there is an indirect implication that we had funding to perform this study from pharma, which we have simply not yet declared. This is done by joining our study to a completely separate article in the same issue – yet the other article remains uncited, leaving us coloured by these comments – poor writing and sloppy editing.
Niall then appears to object to the fact that several of the authors on our paper declared their relationships with pharma – we can’t win, as they must be declared. Because we have involvement with pharma, does Niall propose that we should never publish on any inflammatory bowel disease-related issue?

Niall talks about ‘competing interests… hidden hand of the drug industry… quest for open trial data… over-diagnosis and overtreatment’. We fail to see how any of this is related to our paper: interests are declared; there is no hidden hand; it is openly declared that it is observational clinical audit. Moreover, there was certainly no issue with over-diagnosis or overtreatment as would be obvious to any clinician who has cared for someone with ulcerative colitis unresponsive to standard therapy. Allowing these comments to be made in reference to our paper implies that we are guilty of each of these heinous crimes. If one is to have a sensible discussion of these issues, one should at least pick discrete examples where each of these is an issue, rather than implying our paper is an excellent example of every possible sin where COI are concerned.

Furthermore, we find it ironic that Niall does not make any COI statement. Are we to understand he has never had any dealings with any industry involved in delivering medical services? This in itself may be an undeclared COI, as it is possible that this lack of recognition or engagement is resented. We are not implying this is true, yet rather suggesting that the issue is most constructively viewed from as broad a perspective as possible and not reduced to a simplistic concept involving only pharma companies and money.

From the broader view of healthcare, engagement with industries, such as pharma, is a necessary part of expert medical practice. Without such engagement in Australia, we would have submissions to the Pharmaceutical Benefits Advisory Committee and Medical Services Advisory Committee, which lacked any local clinical input. We would have educational meetings solely run by company employees (read ‘marketing departments’) and many patient support initiatives (some very useful, and not provided elsewhere by our public health system) would not exist. Perhaps in an ideal world, all of these roles would be funded without pharma – at an increased cost to the taxpayer – however, they are not, and so a lack of engagement by senior clinicians would appear to be counterproductive in our ‘user pays’ system especially with regard to Pharmaceutical Benefits Scheme and Medicare Benefits Schedule listings.

Having this sort of engagement does come with a high level of responsibility and all clinicians in this position do need to be careful about recognising their own and the pharmaceutical industry’s motives. Being naïve about company motives and failing to acknowledge where their interests diverge from our patients’ best interest are perhaps the biggest risks. However, the fact that such engagement entails risk does not mean that the best way to proceed is to have a lack of engagement. There is no other sector of work where anyone would genuinely propose that two of the biggest stakeholders would attempt to perform their roles without ever directly speaking to each other; to propose this in medicine appears illogical.

On a positive note, we wholeheartedly endorse Niall’s statement that ‘finance for healthcare is finite’ and this is the prime reason that several of us have been involved with and published on clinical outcomes through audit for some years. It is only by actually examining the outcomes of care that we can be informed as to how much value we get from our care and modify what we do in the future when deficiencies are discovered.

Personally, we feel that much more could be achieved by concentrating on evaluating outcomes of care actually achieved than sniping from the sidelines when people who are prepared to engage in consultation and declare their funding sources dare to audit their clinical results.

Our patients knew from whence extra drug doses came, and all were very grateful for and comfortable with the arrangement.

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Errata

The publisher would like to draw the readers’ attention to an error in the following article:


The following running headers were incorrect.

Optical diagnosis of polyp histology

Chandran et al.

They should have read:

Transfusion burden in allo-HSCT

Le Viellez et al.

The publisher apologises for this error.

The publisher would like to draw the readers’ attention to an error in the following article:


The full form of the first acronym in Table 2 was incorrect.

ASSIST, A Stop Smoking in Schools Trial.

It should have read:

ASSIST, American Scleroderma Stem Cell versus Immune Suppression Trial.

The publisher apologises for this error.
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