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*TASIGNA is the only TKI to significantly protect more patients from disease progression (vs. imatinib; P=0.0059; on core treatment).1,2,3

CML-CP=Chronic Myeloid Leukaemia-Chronic Phase. EMR=Early Molecular Response. PFS=Progression-Free Survival. TKI=Tyrosine Kinase Inhibitor.

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EDITORIALS

The AMC of medicine

While physicians are inherently inquisitive, wanting to know about the details of disease and its care, we rarely question the need for accreditation of our education programmes or understand the way in which it occurs. The specialities of medicine are clearly delineated to reflect contemporary practice, and they ebb and flow with the emergence of new trends and technology. Think for a minute how this is incorporated into training of new physicians. Ponder how this will be part of the practice of contemporary physicians. The cornerstones of competent physician practice are knowledge, skill and information (and arguably emotional intelligence). To provide the stakeholders in the treatment chain (patients, carers, doctors, institutions and government) with the reassurance that these are achieved, institutions are now the custodians of trust. Universities are accredited for training doctors. Colleges are accredited for training specialists. It is the Australian Medical Council (AMC) and Medical Council of New Zealand (MCNZ) that have the authority to do the accrediting.

The AMC notes the origins of accreditation of specialist medical education and continuing professional development (CPD), including the most recent change in 2010 when accreditation became a mandatory requirement for Colleges – previously it was a voluntary quality assurance activity. Details of the process and history are available from the AMC website.¹

We need a licence to drive a car, practise medicine and get married. But where does a physician’s licence come from? The Royal Australasian College of Physicians (RACP) currently has the single right to train doctors to become consultant physicians, in a predetermined pathway (chosen by the trainee) to award Fellow of the Royal Australasian College of Physicians (FRACP). In turn, the Australian Health Practitioners Regulation Agency and the MCNZ recognise the FRACP qualification for the purposes of specialist registration (Australia) or recognition in a vocational scope of practice (New Zealand). Credentialling committees rely on this qualification as a marker of quality training at the level of a medical specialist and in Australia, the FRACP is recognised by Medicare, for consultant physician billing purposes. Recognition of the College as a training institution by the AMC or MCNZ is critical to the mission of the RACP and involves a defined process of application, external review and recognition.

Most physicians would not be aware of the importance of the AMC in the life of health-training institutions. Awareness of responsible bodies, such as the RACP, comes from a lifetime of learning, awareness and annual accountability. There is no CPD report to the AMC for the physician at work. Nor is there any need for trainees to understand the reporting lines to the AMC. In fact, the RACP will continue to provide up-to-date information for members on the importance of meeting accreditation standards. The AMC is therefore the body that gives the RACP a licence to train physicians.

The RACP has recently undergone a lengthy and searching accreditation process to meet AMC standards. The standards are similar across medical colleges and are relatively succinct and directed to community needs. They are not determined by the RACP and are an important roadmap for the strategic direction of the College in future years (Table 1).

Of relevance to the recent AMC review (2014), a public document that is available on the College website,³ specific issues raised in relation to standard 1 included the following:

- Interaction with the specialty societies and the Memoranda of Understanding
- Implementation of governance reform
- Interaction between education committees of the RACP
- Educational expertise and partnerships
- Challenges facing the College and the health sector

While there are potentially many responses that might be developed for the reviewers around these topics, eventually there must be one position and direction for the future. Consultation is a vital component of this strategic plan, as are resources. There is a multitude of drivers for change affecting stakeholders, all of which therefore affect the RACP and Board decisions. Like other systems, such as evaluation of proposals for research funding, there are many faults in accreditation systems; however, the goals and objectives of assessors remain the same.
The RACP has conducted numerous internal and external reviews of its areas of activity, including training and education. Often, the response from members to these exercises is ‘if it isn’t broken, don’t fix it’. Generally speaking, the area of education appears to change little from year to year. In fact, there have been major changes in accreditation of sites, assessment (both summative and formative), CPD, overseas trained physicians assessment, and teaching and learning methods. The reviews are as important as health checks, to ensure the optimal function of the organisation and that performance remains at the forefront of international practice.

The AMC accreditation exercise is a major collaboration between stakeholders, principally staff and members involved in education. In 2014, it is likely to have cost the RACP over $1 million in direct and indirect costs for activities around and preparation for the assessment. In addition, the generation of policies, data and structure to underpin the status of a complex, accredited body may cost over $1 million per year. It is imperative that the RACP strive for the highest standards in performance to guarantee accreditation of training pathways for the future.

The assessment has resulted in accreditation of the RACP for 6 years until March 2021, the maximum period of accreditation that can be awarded to a College by the AMC. AMC accreditation is usually associated with conditions for performance, which are made known to the College at the culmination of the review. These may be time-restricted and may require ‘development’ of initiatives or ‘implementation’ of programmes or policies. These are not suggestions for improvement that the RACP may elect to implement. The next report to the AMC (usually in September each year) must address progress in these areas. The work of the College’s Education Services Department and the Office of the Dean is focussed on these conditions and progress achieved to date in responding to them. In times gone by, many of these tasks were trivial; however, the complex and technical nature of this work demands specialist input by expert staff, while reflecting the work of RACP members on committees.

A major challenge is for all of us involved in training and education to understand our role. It would be difficult to imagine anyone but physicians training physicians. However, as specialty society members, we have a stake in the progress of advanced trainees by involvement in training for, training committees, accreditation of sites, policy development and the divisional structure of the College. Ideally, there exists a collaborative approach to education, originally stated in the Memoranda of Understanding documents from some years ago, now being redeveloped as Models of Collaboration between the College and the specialty societies. Through the training pathways, the Societies have representation on committees and form the planks of the Adult Medicine Division Council. Akin to a university, the Societies form the faculties of the College and this is recognised by the RACP.

The link to New Zealand has been strengthened through the Educational Governance Review and through changes to training committees. The AMC equivalent in New Zealand (MCNZ) has undertaken a simultaneous appraisal and will be aligned with the AMC recommendations. The binational nature of the Board, divisions, faculties and chapters of the College has called for alignment of policies and efficiencies in decision-making, addressed by the Educational Governance Review. Almost completed, the overview is compelling. While the United Nations has 30 committees (including ad hoc and advisory committees), the RACP had some hundreds of education committees before the governance review. The result has been a leaner and more efficient training and education service for members, with robust policy and structure to justify the College’s successful accreditation outcome.

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EDITOR’S NOTE

This is the third in the editorial series on the barriers to innovation and reform of healthcare. Dr Benny is the Director of the Health Workforce New Zealand business unit in the Ministry of Health. It has been his task to lead an innovation programme. Several barriers to such reform have become evident during this process, of which one is the subject of this editorial. That is, healthcare remains very provider-centric. A substantive change to patient-owned healthcare is essential if healthcare is to be sustainable and fit for purpose.

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D. Gorman
IMJ Editor (Editorials)

Provider-centric models of care in which most consumers of healthcare are passive

Patient-centred care has been the holy grail of healthcare systems for at least 30 years. The vision was of motivated and informed patients involved and consulted on their healthcare, actively participating in choosing from the services offered and interventions available. However, progress towards this vision has been slow and erratic, and health systems and professionals have not only struggled to articulate how such a vision could be made to work, but also how it could be sustainably implemented.

Despite these difficulties, many advances have been made and today patients are better informed and more involved in their care, and the clinical decision-making processes of their healthcare providers. There are many examples of good holistic patient-centred-care systems. However, Nirvana remains elusive, and most western healthcare systems still deliver care largely from a provider-centric perspective. For much of their journey through the healthcare system, patients are still passive consumers/recipients of interventions.

In previous decades, health professionals were often perceived as, and accused of, being egocentric, paternalistic and even patronising towards their patients. It was felt that the health professional was the expert in a very complex area of science that was beyond the comprehension or capability of most patients to understand. The natural corollary of this position was that one would not expect that patients would either want to know, need to know or have any pressing desire to be involved in complex clinical decision-making.

As we have made progress towards improving patient-centric care, it has become clear that many patients are well informed and do want to be actively involved and consulted on clinical decision-making; however, this is not true for all patients, nor has it proven to be easy for all health professionals.

Medicine is a complex and rapidly changing science, and to the layperson often very confusing. Making sense of the myriad of rapid advancements in clinical options, technological devices and diagnostic treatments can be a daunting task for a layperson. Patients also have access to a plethora of ‘expert opinions’ offered through the popular media which often leave them confused, uncertain and sometimes downright misinformed. Medicine and healthcare are not perfect sciences. Is it reasonable to expect that every patient will be able to navigate competently and successfully the complexities of this system? Is it even ethically appropriate to place the burden of responsibility for making potentially crucial clinical decisions on to every patient (or their family)? Many patients just want to be ‘made better’, they do not wish to have the pressure or responsibility of defining the ‘what’ or deciding the ‘how’. This dilemma will not be easily addressed and not for every patient at every course of their life.

Clearly, there is no instant recipe that can be used to transform rapidly our practitioner-centred system from what it is today to what we have aspired it to be, but in recent years there is an additional emerging imperative to do so.

The imperative is the rapidly growing need for different clinical options or interventions in order to reduce or control the dramatic increase in lifestyle-related/
generated diseases. Action to halt these diseases requires interventions that are beyond the capability of the current health system in its current provider-centric, facility-based form. The system has little direct ability to intervene to prevent the development of lifestyle-related diseases. Moreover, as more often, the patient presents late and in an advanced stage of disease, the system is increasingly limited to only providing symptomatic care.

In order to respond to this imperative does the health system of the future need to be profoundly and drastically different than the system of today? There is much talk of ‘new-models-of-care’ required to respond to ageing populations, limited or declining budgets, new technologies and rising expectations of a burgeoning global middle class. But just how new and profound do these really need to be? The traditional health teaching and training programmes, and silos within which health professionals learn and practise, have encouraged and reinforced provider-centric behaviours that result in a narrowness of intervention with patients. Such interventions have been very effective for acute and communicable diseases, but are proving to be much less successful in dealing with diseases of lifestyle. Most patient contact with professional healthcare providers is still usually within health-centric practices, hospitals and outpatient clinics that best suit the efficient utilisation of the health professional.

However, the mechanism to respond to this imperative is already all around us. An extensive range of social and health sector workers already work in the community and healthcare continuum. These resources are not currently the traditional general practitioners (GP) and hospital-based clinicians. By using these resources in different and coordinated ways and by linking them through technology, these almost universally passionate, committed and highly expert individuals could significantly enhance the efficacy of the overall healthcare system.

There are already many innovative ideas and approaches, new technologies and novel applications of health interventions being tried, tested and proven in hospitals, clinics and communities. Thus, in fact the change needed may not be as profound, far reaching or massive as many may think, because many of the ideas and ways in which the system needs to change already exist. At its simplest level, the future model of care may just need to be a broader base of utilisation of an existing workforce. It may simply be a case of actively seeking out and utilising the skills of all members of a much wider healthcare community and aligning them in connected ways to enable holistic care for the patient (and their families).

Homes and communities are often visited by education and social sector support workers and educators, but in guises other than health, health support or lifestyle management. Leveraging workforces that already have existing relationships with communities through cross-training and enhancing their profiles is likely to be one of the few viable options for extending the reach of the healthcare system, particularly given the continuing fiscal limitations and international shortages of health professionals. Upskilling these workers as part of the health intervention framework that reaches from the hospital through the GP into the home has real potential to be able to reach and respond to the epidemic of lifestyle diseases.

Topol has neatly encapsulated the questions and opportunities that we need to consider and act on in his book *The patient will see you now*. Technology and the Internet provide the active consumer with information that enables greater levels of knowledge and clinical understanding than has heretofore been possible. Health professionals are regularly confronted by patients armed with in-depth information on their condition, or perceived condition, possible treatments and likely outcomes. The role of the health professional inevitably will change from that of being the holder of the knowledge, options and potentially decisions, to more one of wise counsel. In short, ‘control/power’ in the relationship is largely shifted from the health professional to the patient.

Mate and Salinas have described an approach involving the concept of ‘flipping’ the interactions with the patient. They have highlighted how many interventions of health professionals come from the health professional-centric context. While in fact, many of these actions or interventions could actually be supported and/or performed remotely, often by the patients themselves (or by family members), via technology that already exists.

The Royal College of General Practitioners published a recent inquiry into *Patient Centred Care in the 21st Century* (RCGP (2014)). This report not only highlights that generally current care practices are mostly certainly not yet truly patient centric, but also that multiple new elements and interventions will be necessary in order to truly achieve this nirvana. In short, while an empowered supported patient served by a flexible and responsive health workforce is still an important goal, it is one that remains to be achieved.

Life in the 21st century is busy and people access complex services as and when they need them, and often in a cursory and inconsistent or poorly informed way. Most of the time, people rely on the wisdom of service experts or agents (e.g. mortgage brokers, service managers for our vehicles, real estate agents, personnel consultants, career consultants, project managers). It appears increasingly likely that the role of the medical professional will also move in this direction.
There is no single solution for ensuring that our future health care system is fit for purpose or sustainable. The current model of our healthcare system is likely to require some sort of change. Profound change is difficult, but possibly not necessary. A relatively simple route to achieve this change could be to utilise the services of the wider health/social/education workforce and how we train and leverage the skills and increase the span of patient interaction to include much more community and in-the-home contact. It must also ensure we find ways to maximise the benefit of the growing number of consumers who are accessing the health system already well informed and with clear expectations for their healthcare.

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References


Advances in endovascular treatment of acute ischaemic stroke

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Key words
acute ischaemic stroke, endovascular intervention, stent retriever, Solitaire, Penumbra.

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Abstract
Over the past decade, there have been rapid advancements in ischaemic stroke reperfusion treatments. However, clear clinical benefit is yet to be shown in large clinical trials. In this review, the major studies in different types of endovascular treatments including intra-arterial thrombolysis, aspiration devices, mechanical clot retrievers and the new stent retrievers are discussed. First-generation mechanical thrombectomy devices such as the MERCI Retriever (Stryker, Kalamazoo, MI, USA) and Penumbra aspiration device (Penumbra Inc., Alameda, CA, USA) demonstrated safety and higher rates of recanalisation in the MERCI and Penumbra Pivotal Stroke Trial; however, there was no significant improvement in clinical outcome. Second-generation endovascular stent retrieval devices Solitaire (ev3 Neurovascular, Irvine, CA, USA) and Trevo (Stryker) have shown promising results. In preliminary trials, SOLITAIRE with the Intention for Thrombectomy (SWIFT) and Thrombectomy Revascularization of Large Vessel Occlusions (TREVO), both showed rates of recanalisation close to 90% and significantly improved clinical outcomes compared with the MERCI study, but the recent landmark studies for endovascular treatment (Interventional Management of Stroke (IMS III), Mechanical Retrieval and Recanalisation of Stroke Clots Using Embolectomy (MR-RESCUE) and SYNTHESIS) did not show any clinical benefit from endovascular treatment compared with standard intravenous therapy. However, moving forward, the recent Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischaemic Stroke in the Netherlands (MR-CLEAN) study results have shown marked improvements in recanalisation, reperfusion and functional outcome in patients receiving endovascular treatment (97% using stent retrievers) within 6 h in addition to standard medical care. Overall, although evidence regarding the efficacy of endovascular treatment in acute stroke has been equivocal, recent publications of large multicentre randomised controlled trials indicate benefit of intra-arterial stent retriever reperfusion in patients selected by appropriate imaging and treated early by experienced operators, and it will likely remain an important adjunct to established medical treatment with intravenous tPA.

Introduction
Stroke is a major public health problem worldwide and is considered the third most costly health condition in developed countries.1 Approximately 800 000 strokes are reported in the United States every year leading to 200 000 deaths, almost one out of every 16 deaths.2 For those who survive, it is the most common cause of adult disability in the modern world and associated with expensive long term rehabilitation care.2 More than 80% of stroke victims suffer an ischaemic stroke due to a thrombus or thromboembolism, with the remainder haemorrhagic.2

Intravenous recombinant tissue plasminogen activator (tPA) was approved for administration within 3 h of stroke onset over 18 years ago. Despite the relative success of intravenous thrombolysis, limitations in recanalisation of large vessel occlusions with overall recanalisation of less than 50% and the short proven therapeutic window have spurred development of various endovascular therapeutic techniques.1,3 The main
forms of endovascular treatments are illustrated in Figure 1.

Overall, urgent reperfusion of the ischaemic brain remains the paramount goal for treatment either by intravenous medical therapy or endovascular interventional techniques. These treatments focus on vascular recanalisation and restoration of the blood flow to the ischaemic tissue, which has been shown to improve functional outcome and decrease mortality at 3 months compared with no recanalisation.4

This paper will review the advances in endovascular stroke treatment over the past decade and discuss the implications for future research and treatment.

Endovascular treatment

Current recommendations for endovascular stroke intervention can be found in the Standards of Practice Committee report of the Society of Neurointerventional Surgery. Some recommendations (class 1 evidence) include:2

- Availability of intra-arterial techniques should not preclude or delay initiation of the proven intravenous thrombolysis.
- Endovascular treatment should only be performed in a tertiary referral stroke centre with the required equipment and expertise available.

- Intra-arterial thrombolysis can be a suitable option for treatment of patients with major ischaemic stroke due to an occlusion of the middle cerebral artery within 6 h from onset.

Endovascular intervention for stroke requires the infrastructure for rapid assessment, diagnosis and stabilisation of the patients by a multidisciplinary team or alternatively transportation to a comprehensive stroke centre where the specialist care and technology are available. Such a model has been previously proposed as the Stroke Systems of Care. This also necessitates the implementation of a set of guidelines and the establishment of a system for quality control and assessment.2,5

Intra-arterial thrombolysis

The efficacy of intra-arterial thrombolysis was demonstrated in the Prolyse in Acute Cerebral Thromboembolism (PROACT II) and Interventional Management of Stroke (IMS II) trials.

The PROACT II study was a randomised controlled trial, using intra-arterial recombinant pro-urokinase (r-proUK) versus intravenous heparin given 6 h from symptom onset. The study showed that 66% of cases treated with r-proUK achieved partial or complete recanalisation compared with 18% in controls (P-value < 0.001). However, complete recanalisation (Thrombolysis in Myocardial Infarction (TIMI 3)) was only achieved in 19% of cases, and occlusions within the internal carotid artery (ICA) terminus, which are the most resistant to treatment, were also excluded from the study.6 This result questions the true efficacy of intra-arterial thrombolysis in achieving complete reperfusion.7

The IMS II trial is a single arm study comparing the efficacy and safety of low dose intravenous tPA (0.6 mg/kg) and intra-arterial tPA (up to 22 mg) delivered through an EKOS (Bothell, WA, USA) microinfusion catheter to historical results from the National Institute of Neurological Disorders and Stroke (NINDS) study. The trial had higher numbers of patients with modified Rankin scale (mRS) 0–2 at 3 months, 46% versus 39% in the NINDS tPA arm. However, the study did report higher rates of symptomatic intracerebral haemorrhage but lower mortality. Interestingly, in the study the rate of complete recanalisation (TIMI 3) was only 4%, and partial (TIMI 2/3) was 60%. The authors attributed the low complete recanalisation rate to an underestimation because some lesions were already recanalised by the intravenous tPA prior to endovascular therapy. The EKOS catheter was found to have similar efficacy at reperfusion as a standard microcatheter.8

![Figure 1 Endovascular treatments.](image-url)
Mechanical thrombectomy devices

Rapid mechanical clot extraction devices gained huge interest with the theoretical advantage of accelerated recanalisation, potentially lower rates of haemorrhagic transformation as well as possibly extending the time window in stroke intervention.1

US Food and Drug Administration (FDA) approval for the MERCI Retrieval (Stryker, Kalamazoo, MI, USA) and Penumbra Stroke Systems (Penumbra Inc., Alameda, CA, USA) as the first generation of mechanical thrombectomy devices was followed by the introduction of Solitaire (ev3 Neurovascular, Irvine, CA, USA) and Trevo (Stryker, Kalamazoo, MI, USA) stent retrievers. Pioneering studies like MERCI, multi-MERCI, Penumbra and SOLITAIRE with the Intention for Thrombectomy (SWIFT) have further strengthened the importance of the mechanical devices in large vessel occlusion.9–12

The safety and efficacy of the MERCI device was initially scrutinised in two prospective single arm, MERCI and multi-MERCI trials.9,11 MERCI is a corkscrew shape device with helical Nitinol loops specifically designed and tested for distal placement into the thrombus for en bloc removal. The target vessels were the proximal segments of major cerebral arteries, predominantly M1 segments of the middle cerebral and vertebrobasilar arteries. Clots located more distally are not removable by MERCI.

Overall analysis of the pooled MERCI data showed that patients with TIMI 2 or 3 recanalisation had improved mortality and functional outcome. However, overall patients treated with MERCI retriever did not have improved outcome at 90 days compared with PROACT II historical control subjects, and the overall mortality was higher in MERCI (44% vs 27%), which may be due to the more severe stroke baseline scores in their patients.2,13

Adjunctive anticoagulation has been shown useful in prevention of instrument related embolism, preventing acute re-occlusion and providing a synergistic effect to thrombolysis. The multi-MERCI trial showed an increased recanalisation rate with the MERCI retriever combined with intra-arterial tPA, approaching 70%, compared with clot retrieval alone, which was approximately 55%.9

The Penumbra Thrombus Perturbation and Aspiration device compared with the MERCI retriever works proximally to the thrombus. It utilises mechanical clot separators coupled with clot aspiration from a reperfusion catheter. Safety and effectiveness of this device was assessed in a multicentric single arm phase II study, the Penumbra Pivotal Stroke Trial. Although proven safe for use in patients presenting up to 8 h from stroke onset and despite a more than 82% recanalisation rate, the study showed no significant improvement in the clinical outcome compared with PROACT II control group.10

Self-expanding stents

Parallel to the advancement in clot retrieval techniques, the self-expanding stent was introduced as a means to assist and maintain revascularisation. Self-expanding stents or angioplasty alone has been described in retrospective studies for treatment of intra-arterial atherosclerosis and even in acute ischaemic stroke.2,14,15 However, despite high technical success of the permanent stent placement, potential immediate and delayed complications are not quite clear. While in-stent stenosis has been shown in approximately 30% of cerebral arteries receiving a stent for intracranial atherosclerosis, the exact incidence for stents inserted in acute stroke is unknown. The potential haemorrhagic risk of concurrent prophylactic antiplatelet and anticoagulation therapy has also not been thoroughly investigated.2,16

The Stent-Assisted Recanalisation Acute Ischaemic Stroke pilot study evaluated the efficacy of the Wingspan stent in patients who had contraindication to or did not improve with intravenous thrombolysis, showing close to 100% recanalisation and 45% excellent clinical outcome at 90 days. However, the downside was more than 10% stent-related complications, requiring aggressive antiplatelet therapy, which in turn increased the rate of subsequent haemorrhagic transformation.17,18

Stent retrievers

The introduction of stent retrievers was a major advancement in endovascular management of stroke, allowing the advantage of navigability and rapid recanalisation of a stent without the possible long-term complications. Stent retrievers utilise a temporary stent that captures thrombus, displaces it peripherally against the vessel wall thus restoring blood flow. The stent is then withdrawn and the thrombus is removed along with the stent, trapped within its interstices. Two such stent retrieval devices currently approved by the FDA for treatment of stroke due to large vessel occlusion are the Solitaire FR (Covidien, Dublin, Ireland) and Trevo (Stryker) retrievers; other devices including Trevo-ProVUE (Stryker) and Revive (Johnson & Johnson, New Brunswick, NJ, USA) are also in the process of approval.

The SWIFT trial is an open-label, randomised controlled, blinded, multicentre trial evaluating the efficacy of Solitaire FR revascularisation device against the MERCI Retrieval in revascularisation of large vessel occlusions. The Solitaire group demonstrated significantly higher overall recanalisation of 89%, compared
with MERCI 67%, *P*-value <0.0001. The final clinical outcome was also better in the Solitaire group with 58% of patients having mRS 0–2 at 3 months after treatment compared with 33% in the MERCI group.\(^{19}\)

Trevo is another stent retriever, designed and introduced by Stryker, which showed superior capability in recanalising large vessel occlusions when compared to MERCI in the Thrombectomy Revascularisation of Large Vessel Occlusions in Acute Ischaemic Stroke trial. The results of this randomised control trial were released almost at the same time as the final results of SWIFT and showed better recanalisation, with TICI 2 or greater in 86% of treated patients compared with 60% in the MERCI group. The Trevo group also achieved better clinical outcome assessed by mRS 0–2 at 90 days, 40% of patients versus 22% for MERCI.\(^{20}\)

Despite the success of stent retrievers, three recent randomised controlled studies comparing endovascular therapy versus standard intravenous therapy for acute stroke failed to demonstrate any clinical benefit and raised concerns about its use in the future. These studies are: IMS III, Mechanical Retrieval and Recanalisation of Stroke Clots Using Embolectomy and Synthesis Expansion: A Randomized controlled Trial on Intra-Arterial Versus Intra-venous Thrombolysis in Acute Ischaemic Stroke (SYNTHESIS Expansion) trials.

The IMS III study was a randomised multicentre trial, comparing combined intravenous and intra-arterial treatment, including mechanical endovascular techniques with intravenous therapy alone. The study was designed to be discontinued if a 10% difference was considered unlikely in favour of one arm of the study. The trial was stopped early after enrolment of 656 of the intended 900 patients because of the decision of the independent data monitoring board when the preliminary results (3-month clinical outcome) were against an underlying significant difference between the two groups (mRS 0–2 in 40.8% in the endovascular group vs 38.7% in the intravenous treatment group, *P* = 0.25).\(^{21}\)

There are multiple potential pitfalls in the study that could change the interpretation of the results. Selection was not targeted to those with large vessel occlusion or large clot burden ≥8 mm, as no vascular imaging was required prior to inclusion into the study, the dose of IV tPA used was less in the combined IV/IA group than in the IV group (0.6 vs 0.9 mg/kg).\(^{1,22}\) These limitations would certainly influence the accuracy of the IMS III study in evaluation of clot retrieval techniques. On subsequent subanalysis of patient who had confirmed large vessel occlusion, patients who had intravenous tPA and endovascular treatment had better recanalisation and outcomes compared with intravenous tPA alone (*P* = 0.01).\(^{23}\) Most of the patients in the endovascular arm received intra-arterial thrombolysis or clot retrieval using MERCI retrievers, as the stent retrievers were included in the study very late, with estimated less than 2% of the 434 cases randomised to endovascular intervention, treated using second generation devices (e.g. Solitaire).

The study does not give a good representation of the current capabilities of mechanical thrombectomy devices, for which stent retrievers are considered superior and are associated with the highest reperfusion rate. In the IMS III study, reperfusion after endovascular treatment only occurred in 65–81% depending on the site of occlusion, lower than rates reported with newer-generation devices. In particular, while subgroup analyses provided insight into the importance of the TICI 2b recanalisation threshold in meaningfully impacting clinical outcomes, TICI 2b or 3 scores were obtained in only 27–40% of patients, which is dramatically worse than the 68–70% TICI 2b or 3 reperfusion seen in subsequent prospective randomised trials.\(^{7,20}\)

There was also a significant delay of more than 2 h between initiation of intravenous tPA and intra-arterial intervention, which was longer compared with earlier studies (IMS I/II) and could have diminished the effects of the intra-arterial intervention.\(^{7}\)

The SYNTHESIS Expansion trial likewise compared endovascular treatment within 4.5 h of onset with intravenous thrombolysis alone. The trial did not show any significant difference in good neurological outcome at 3 months between the groups (30.4% in the endovascular group and 34.8% in the intravenous treatment group, *P* = 0.37) and no difference in symptomatic intracranial haemorrhage.\(^{24}\) Similar to the IMS III trial, confirmation of large-vessel occlusion by imaging was not performed prior to randomisation, allowing patients without proximal vessel occlusion, to enter that treatment arm. Intravenous tPA was withheld from all patients in the endovascular group, and the mean time to treatment was longer in that group, 3.75 h compared with 2.75 h in the intravenous tPA group. Stent retrievers were only used in 23 patients out of 181 randomised for endovascular intervention, which is approximately 13%, and the majority were treated with wire manipulation and intra-arterial thrombolysis. Part of the protocol also allowed intra-arterial thrombolysis in the suspected affected vascular territory in cases where angiography did not show an occlusion, which is no longer considered a first line intra-arterial treatment protocol.\(^{7}\)

The MR-RESCUE trial investigated the effect of endovascular treatment versus standard treatment in patients with a favourable penumbra and no penumbra pattern of large vessel stroke on imaging within 8 h of onset. The study showed no difference in the between...
treatment groups in neurological outcome at 90 days and no difference in outcome of patients who had embolectomy with a favourable penumbra pattern. The trial recruited 127 patients over 22 centres between 2004 and 2011. The number of patients in each treatment group ranged from 20 to 34 patients, which raises concerns about the trial being underpowered to show a significant difference. The mean time to groin puncture was more than 6 h after the onset of symptoms, beyond the 6-h window used in many previous studies and likely to contribute to lack of treatment efficacy. Patients with large infarct core volumes, as large as 90 mL, were also included into the study, although they have been shown to be associated with poor outcomes following revascularisation. The study also had low revascularisation rates, resulting in only 16 of 64 patients (27%) achieving TICI 2b or 3 reperfusion. This rate of endovascular recanalisation is lower than that achieved by the new generation endovascular devices. Study enrolment was completed before the introduction of the stent retrievers. When subanalysis of functional outcomes of patients who had partial/complete recanalisation was performed, patients with recanalisation showed lower mRS at 90 days ($P$-value = 0.04) and lower volume of infarct growth at day 7 imaging ($P$-value = 0.1).

The recent Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischaemic Stroke in the Netherlands (MR-CLEAN) trial results presented at the 9th World Stroke Congress is the first to show clear benefit from endovascular therapy compared with standard medical therapy.

The study randomised 500 patients with National Institutes of Health (NIH) score ≥ 2 and anterior circulation large artery occlusion on CT angiography to standard medical care or endovascular treatment within 6 h of stroke onset. Both groups received optimum medical stroke care, including intravenous tPA within 4.5 h if indicated. The median National Institutes of Health Stroke Score (NIHSS) was 17 in the intervention and 18 in the control groups, indicating a population with severe stroke comparable with many of the other large ischaemic stroke trials. The results were that rates of recanalisation at 24 h with endovascular treatment were higher (80% vs 32%, odds ratio = 6.9, 95% confidence interval 4.3–10.9), median stroke volume at 1 week was smaller (49 mL vs 80 mL) and mRS at 3 months was better in the endovascular group (mRS < 2, 33% vs 19%).

In this study, 97% of patients in the endovascular arm were treated with a stent retriever. The positive result from this study is extremely promising, and we anticipate the results of upcoming trials to confirm these findings further.

Although it is worth considering that at this stage, these results are yet to be peer reviewed and published.

**Upcoming trials**

The findings and shortcomings of previous trials have highlighted important aspects of trial execution and design to guide future trials. The current ethos of endovascular management and our recommendations for future trials:

- Stent retrievers should be the first-line treatment device for endovascular treatment as they have shown the highest rates of recanalisation.
- Appropriate selection of candidates with imaging guidelines (computed tomography angiography (CTA) or magnetic resonance angiography (MRA)) to confirm presence of large vessel occlusion.
- Minimise delays to treatment with catheter intervention and not impeding intravenous thrombolysis as per standard care – the two treatments should ideally proceed concurrently.
- Endovascular treatments should ideally be performed in tertiary stroke centres of high volume with experienced multidisciplinary stroke teams. Interventional neuroradiologists should have sufficient experience/training.
- Given the lack of standardisation of perfusion data, the current role of perfusion imaging is more to ‘rule-in’ late presenters on the basis of penumbra rather than ‘rule-out’ early presenters. Attainment of perfusion data also should not significantly delay potential treatments.

The authors of this review are now involved in an ongoing multicentre randomised controlled trial of intrartrial reperfusion therapy after standard dose intravenous t-PA called Extending the Time for Thrombolysis in Emergency Neurological Deficits – Intra-Arterial. The goal of this study is to identify whether intra-arterial intervention combined with intravenous tPA has a better outcome over intravenous thrombolysis alone in carefully selected cases with both large vessel occlusion and small core infarct.

Consented patients, older than 18 years, presenting with anterior circulation (ICA, M1 or M2) acute ischaemic stroke proven on CTA or MRA, who are eligible to receive intravenous tPA, with core/penumbra mismatch ratio of greater than 1.2, or alternatively absolute mismatch volume of greater than 10 mL, or infarct core less than 70 mL, were randomised into the experimental group for intra-arterial clot retrieval after intravenous tPA using Solitaire device, or control group only treated with intravenous tPA.

Primary outcome measures of the study were defined as reperfusion at 24 h and favourable clinical response at
3 days using NIHSS. The secondary outcome measures are defined as reperfusion at 24 h post-stroke without symptomatic intracerebral haemorrhage, recanalisation at 24 h post stroke, infarct growth within 24 h, symptomatic intracranial haemorrhage, final functional outcome as per mRS at 3 months and death due to any cause. This study is expected to finish within the next 2 years.\(^29\)

A large number of endovascular trials are either currently enrolling or stopped for data analysis:
- **ESCAPE:** Endovascular Treatment for Small Core and Proximal Occlusion Ischaemic Stroke (http://www.ClinicalTrials.gov identifier NCT01778335)
- **REVASCAT:** Endovascular Revascularisation with Solitaire Device versus Best Medical Therapy in Anterior Circulation Stroke Within 8 Hours (http://www.ClinicalTrials.gov identifier NCT01657461)\(^30\)
- **SWIFT PRIME:** Solitaire FR as Primary Treatment for Acute Ischaemic Stroke (http://www.ClinicalTrials.gov identifier NCT01657461)
- **PISTE:** Pragmatic Ischaemic Stroke Thrombectomy Evaluation (http://www.ClinicalTrials.gov identifier NCT01745692)
- **DAWN:** Trevo and Medical Management versus Medical Management Alone in Wake Up and Late Presenting Strokes (http://www.ClinicalTrials.gov identifier NCT02142283)
- **THERAPY:** The Randomized, Concurrent Controlled Trial to Assess the Penumbra System's Safety and Effectiveness in the Treatment of Acute Stroke (http://www.ClinicalTrials.gov identifier NCT01429350)

**Posterior circulation**

Although causing only 6–10% of large vessel strokes, posterior circulation occlusions have a relatively different course. Failure of recanalisation, particularly in comatose patients or those with basilar trunk involvement, carries a very poor prognosis. Randomised controlled trials are limited by the rarity of the incidence of posterior circulation strokes, and the results are potentially influenced by the heterogeneity of the presentations and the cause. At this stage, the rationale for aggressive treatment is mainly based on anecdotal evidence.\(^2,31\)

The Basilar Artery International Cooperation Study, an observational registry of 592 posterior circulation stroke patients, did not show a definite superiority for intraarterial intervention over intravenous thrombolysis with recanalisation rates of 72% and 67% respectively. It did show that recanalisation was protective of poor outcome (mRS 4–5 or death).\(^32\)

There have been several recent case series showing high rates of recanalisation with endovascular treatment. Baek \textit{et al.} reported a series of 25 patients treated with Solitaire stent retriever within 8 h of stroke that achieved 96% recanalisation and 48% good outcome at 3 months. Higher baseline stroke severity score was associated with poor outcome.\(^33\) Broussalis \textit{et al.} analysed the outcome of 99 patients who had either endovascular treatment or medical treatment. The endovascular group had better 3-month mRS 0–2, 45% versus 0% (\(P\)-value = 0.012) as well as higher rates of complete recanalisation (TICI 3), 36% versus 9% (\(P\)-value = 0.017) compared with medical management. However, it is important to note that only 23% of patients in the medical management group had intravenous thrombolysis.\(^34\)

**Conclusions**

Despite the large health impact and devastating consequences, the optimum treatment for acute ischaemic stroke currently remains unclear. The common goal in urgent chemical or mechanical recanalisation is to establish the flow to the ischaemic area while avoiding the risk of intracranial bleeding.

Intravenous thrombolysis has the benefits of being relatively easy to use and has shown good efficacy in small vessel occlusion, while endovascular interventions have the potential to achieve improved revascularisation in large vessel occlusions as well as extending the time frame for treatment.

Stent retrievers have shown promising results in achieving high rates of recanalisation in preliminary studies. The late introduction of the stent retrievers and difficulties in appropriate patient screening in the major clinical trials could explain the equivocal results of endovascular therapy compared with standard treatment. The recent studies have been a step forward providing us with knowledge and target areas for improvement in trial design and execution. It is likely that the optimum treatment in future will rely on a combination of intravenous thrombolysis as well as endovascular treatment.

The recent positive preliminary results from the MR CLEAN study, presented in the World Congress of Stroke, have demonstrated improvement in recanalisation, stroke size and functional outcome. These results, although yet to be peer reviewed and published, are of great significance and undoubtedly increase the hope and expectation for further confirmation with the results of similar upcoming studies.

This is an exciting time in stroke care with parallel advancements in endovascular technologies, neuroimaging as well as investigation of other non-invasive therapies.
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When a patient’s ethnicity is declared, medical students’ decision-making processes are affected

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Key words
Aboriginal health, bias, clinical decision-making, health disparity, Indigenous health, medical curriculum.

Abstract

Background: Disparity in health status and healthcare outcomes is widespread and well known. This holds true for Indigenous peoples in many settings including Australia and Hawaii. While multi-factorial, there is increasing evidence of health practitioner contribution to this disparity. This research explored senior medical students’ clinical decision-making processes.

Methods: A qualitative study was conducted in 2014 with 30 final year medical students from The University of Melbourne, Australia, and The John Burns Medical School, Hawaii, USA. Each student responded to questions about a paper-based case, first in writing and elaborated further in an interview. Half the students were given a case of a patient whose ethnicity was not declared; the other half considered the patient who was Native Hawaiian or Australian Aboriginal. A systematic thematic analysis of the interview transcripts was conducted.

Results: The study detected subtle biases in students’ ways of talking about the Indigenous person and their anticipation of interacting with her as a patient. Four main themes emerged from the interview transcripts: the patient as a person; constructions of the person as patient; patient–student/doctor interactions; and the value of various education settings. There was a strong commitment to the patient’s agenda and to the element of trust in the doctor–patient interaction.

Conclusion: These findings will help to advance medical curricula so that institutions graduate physicians who are increasingly able to contribute to equitable outcomes for all patients in their care. The study also draws attention to subtle biases based on ethnicity that may be currently at play in physicians’ practices.
Introduction

Disparity in health status and healthcare outcomes is widespread and well known. This holds true for Indigenous peoples of many countries, including Australia and Hawaii. While we know that this disparity is multifactorial, there is increasing evidence of health practitioner contribution. This research explored senior medical students’ clinical decision-making processes. The findings can be used to advance medical curricula so that medical schools graduate practitioners who are increasingly able to contribute to equitable outcomes for all patients in their care. The findings also draw attention to decision-making biases based on ethnicity that may be currently influencing medical practice.

Unequal treatment of patients according to their ethnicity has been shown in decades of clinical and vignette-based research. Among the range of factors known to contribute to inequitable outcomes is healthcare provider behaviour. Moscowitz et al. found an implicit association of certain diseases and social behaviours with African American patients; they also found that this implicit stereotyping altered physician behaviour. Diagnostic and treatment decisions as well as feelings about patients are also influenced by the healthcare providers’ bias, prejudice and stereotyping. One feasible explanation is that while practitioners attempt to view patients without bias, their efforts often fail in the context of clinical decision-making pressure, so the power of unconscious stereotypes prevails.

Furthermore, a systematic review of international research found statistically significant evidence of racist beliefs, emotions and practices among physicians in relation to minority groups. The authors concluded, however, that ‘we still know little about the extent of healthcare-provider racism’. This is also true for Australia where there is clear evidence that Aboriginal and Torres Strait Islander peoples experience a greater burden of socio-economic disadvantage and poor health than do non-Indigenous Australians. In past attempts to explain this disparity, there was an assumption that improved practitioner skills, knowledge and attitudes will bring about improvements in health outcomes for these patients. However, more recently, it has been proposed that a better understanding is needed of the very nature of clinical interactions between Indigenous people and health professionals. For the most part, these two parties have limited prior shared experience of each other’s life circumstances and often experience the interactions as difficult. This study is one step towards a better understanding of these patient–doctor interactions.

Our study continued investigations of the ways that practitioners’ behaviour may contribute to the disparities in healthcare and health outcomes. Our responsibility for the education of students led us to investigate senior medical students’ decision-making in encounters with paper-based patient scenarios. The research was guided by the question: ‘In what ways does identifying ethnicity influence clinical decision-making?’. We also sought answers to three subquestions:

1. What are the factors/assumptions that influence clinical decisions?
2. What is the influence of declared ethnicity in chronic disease management decisions and processes?
3. What contexts influence participant responses?

Methods

The overview of the methodology provides a basis for the reader to make judgements about the ‘transferability’ (generalisability) of the study in terms of the usefulness of the findings in other contexts.

We conducted a qualitative study at the Melbourne Medical School, Australia (MMS), and the John A. Burns School of Medicine (JABS), Hawaii, USA, and involved medical students from the final year of their post-graduate (graduate entry) medical course. Email invitations were sent to the whole final year student group at each of the two sites (a total of approximately 370 students). Students who responded were recruited by email and provided with written information about the study. Recruitment stopped when 30 students had participated and saturation achieved, that is, no new factors were emerging and there were sufficient data to enable thematic analysis.

This is an exploratory study. It required a methodology that would draw participants into discussions, allowing the interviewer to listen to and explore their perspectives. A semi-structured written and interview-based approach was therefore preferable to the use of, for example, a semi-quantitative instrument that would have directed the students more than necessary for the purposes of an exploratory study. We consulted with clinicians, educators and researchers with expertise in Indigenous health to develop a one-page written vignette. The same patient case was given to all participants except for one factor: for half the students, the patient was described as ‘Aboriginal’ (Liz A for Australian students) or ‘Native Hawaiian’ (Liz H

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Conflict of interest: None.

*We use the terms ‘Indigenous patients’ and ‘Indigenous peoples’ to refer to Australian Aboriginal, Torres Strait Islanders and Native Hawaiian peoples.
Table 1 Questions for written responses

1. Write a summary of what is going on for Liz.
2. Based on the information available what would you do now?
3. What additional information do you want to know to enable you to develop Liz’s care plan for the next 12 months?
4. What would be in your ideal preliminary healthcare plan for Liz?
5. What assumptions have you made to develop this healthcare plan?

Table 2 Interview guide

1. Can you describe Liz to me and tell me about her situation? Consider how you imagine she looks, for example some details about how she looked in the waiting room, how she’s dressed/presented, the way she interacted with you, her demeanour.
2. What do you think being well means for Liz?
3. What do you think good quality care is for Liz?
4. What do you think Liz wants from this consultation?
5. Looking at your responses to the questions, tell me what you were thinking when you made those decisions?
6. Additional question to some interviewees:
   (a) If a participant who was given the Liz A or Liz H case does not mention her ethnicity in the written responses or the interview, the interviewer will ask: ‘Do you think your approach to Liz was influenced by her [Aboriginality/being Native Hawaiian]?’
   (b) If a participant who was given the Liz case (i.e. where no ethnicity is declared) does not mention ethnicity in the written responses or the interview, the interviewer will ask: ‘Do you have assumptions in your head about this patient’s ethnicity given that it wasn’t mentioned in the script?’

Results

Saturation was reached when 30 medical students had participated, 20 at the Australian site and 10 in Hawaii. Fourteen of the participants were female and 16 male, and the average age was 27 (range 23–35). We present the results as one group, referring to participants as ‘P1’–‘P30’.

Medical student bias

Students considering Liz (whose ethnicity was not declared) are referred to with odd numbers (P1, P3, etc); those considering Liz A (Aboriginal) or Liz H (Native Hawaiian) are referred to with even numbers (P2, P4, etc).

The clinical decisions that students made for the patient will be discussed in a separate paper. The focus here is on the subtle effects of declared ethnicity on the students’ approaches to the patient and the consultation. Four themes emerged from the analysis of the interview transcripts:

- Perceptions of the patient as a person
- Constructions of the person as a patient
- Anticipations of dynamics and priorities in the patient–student/doctor interactions
- The value of particular teaching and learning experiences and settings

The patient as person

When asked to describe Liz, participants mostly stopped after identifying her roles as a mother and wife, only one mentioned that she may work, and most were unwilling or unable to imagine her in detail. Two participants offered descriptions of what she might look like. However, in their responses to the subsequent three
Table 3 Four themes: evidence/illustrative quotations

<table>
<thead>
<tr>
<th>Themes with illustrative quotations</th>
<th>P#</th>
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<tbody>
<tr>
<td>Theme – The patient as a person</td>
<td></td>
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<tr>
<td>... there's too much going on and [she's] not managing it or in control in some sense. So, you know, four kids, don't know where the 23 year old is, the 20 year old has just had a baby, the 16 year old is not certain about completing school and struggling with the moves and her youngest child's deaf and has got some learning difficulties so I can see that even on that front you'd feel a little overwhelmed by all of that. And then moving, I mean five times in 15 years . . .</td>
<td>P12</td>
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<tr>
<td>Theme – Construction of the patient</td>
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<tr>
<td>Describing Liz A</td>
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<td>I imagined her to be a friendly, middle-aged patient but one of the very common sort of heart-sink patients that have multiple co-morbidities, and um yeah just the real triad of chronic diseases. ... I didn't even get a good sense of whether she had come voluntarily ... Or whether she was coming because she got told to come back. ... her patient agenda would be really important for setting the tone of the interview, how co-operative she was and how open she was with history-taking.</td>
<td>P6</td>
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<tr>
<td>Theme – Education settings</td>
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<tr>
<td>[What the consultation might be like]</td>
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<td>It would obviously be rather frustrating because this is a long, time-consuming sort of case, um to be undertaken in the 10 minute medicine of General Practice. ... she's a complex patient and it's going to be very time consuming, um yeah, it's sort of there are a number of these patients out there that people colloquially refer to as 'heartsink' patients, where they've got lots of things wrong with them, and you don't know where to start sort of and how to make a positive improvement in their health because it seems that everything that can go wrong, does go wrong, yeah, they can just be really frustrating . . .</td>
<td></td>
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<tr>
<td>Theme – The patient–doctor interaction: patient agenda; trust</td>
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<td>I like to ask the patients what their priorities are . . . And then I can work from there . . . just because my priorities are different doesn't mean that her priorities are less important. They're equally as important and I should base my priorities on what she also thinks is important because if I don't consider her priorities then she's not going to listen to what I tell her, and ... Nothing will work.</td>
<td>P25</td>
</tr>
<tr>
<td>I think if she can trust you it'll work.</td>
<td>P12</td>
</tr>
<tr>
<td>You know I just think with every patient they look for trust. I mean trust, a physician that's willing to listen, actively listen, also give, you know, great advice. A physician or a clinic that's willing to follow up and actually play an active role in her physical and social wellbeing. ... I think that's the, I think along with the medical recommendations I think her being comfortable and actually feeling that she can trust the physician will kind of determine her return and actually compliance as well. In other words, I don't know what she's got or I don't know what kind of care they're going to provide. And, without assuming too much, I know that sort of history with the Stolen Generations. People just don't get that. That's another factor that could cause mistrust of bringing kids to sort of non-Indigenous Australians or fronting up there. So, you know, I admit that I'm kind of ignorant overall for how . . . So, yeah, I don't want to assume too much but, you know, I'd probably sort of want to see how much, yeah, they trust that sort of system. ... I guess then I'd try and gain her trust and sort of convince her of the seriousness of the situation and how I'd like to help her</td>
<td>P16</td>
</tr>
<tr>
<td>Theme – Education settings</td>
<td></td>
</tr>
<tr>
<td>I've always wanted to be, or always thought, you know, I'd be a physician or be a specialist of some sort but, and I thought general practice was quite boring, but after doing that and I was given a lot of autonomy as well ... in this particular practice the students had their own rooms and we got to see our patients before [the GP who was] such a great mentor as well ... I think they had a good work ethic there ... it wasn't like a super clinic or anything like that. Even though the patients ... were poor people, they had an appreciation for coming to the doctors even though it was bulk billed, you know and they really valued your opinion and they love their GP so much that, you know like if they wanted to see that particular doctor they had to see students (first)</td>
<td>P11</td>
</tr>
<tr>
<td>I can't remember where I picked it up from. I think it might be sort of some other, some friends of mine who have done a fair bit of placement in Indigenous communities and what they've kind of shared with me about the distrust that people in those communities have for, I guess, non-Indigenous Australians sometimes and the kind of care they can provide. And, without assuming too much, I know that sort of history with the Stolen Generations. People just don't get that. That's another factor that could cause mistrust of bringing kids to sort of non-Indigenous Australians or fronting up there. So, you know, I admit that I'm kind of ignorant overall . . .</td>
<td>P16</td>
</tr>
</tbody>
</table>

questions, almost all of the participants characterised her life as stressful, seeing her as feeling ‘overwhelmed’ by her four children and perhaps not feeling ‘in control’ of things (Table 3). Two students considered the possibility of marital discontent particularly given that she had wanted to move closer to her family, and four students considered the possibility of domestic abuse.

All MMS participants were alert to Liz’s statement that she was ‘having trouble coping’. The spectrum of responses to this cue ranged from the benign to the extreme: ‘just by virtue of human nature running into obstacles in the course of their daily lives.’ (P26) ‘maybe she’s feeling overwhelmed . . . feeling anxious.’ (P20)
Participants from JABSoM were more likely to respond at the benign end of the spectrum, seeing troubles as part of daily life: only half of them made comment on this cue, and only one suggested screening for depression. In contrast, all of the MMS group made comment on this cue: two considered the need for psychiatric assessment, two thought the problem was minor and the other responses were between these extremes. We did not detect bias based on the patient’s ethnicity here.

**Constructions of ‘the patient’**

Two subthemes relate to the way participants talked about the person as their patient and the patient’s ethnicity. Indigenous status was associated with commentary that assumed low health literacy where statements about the patient’s ‘understanding’ or ‘education’ dominated the participants’ constructions of the person as their patient. Many students extrapolated from the information in the paper case that the patient thought her last HbA1c test was about 12 months ago and that she thinks the result was 9%; they used these facts to evaluate and comment on ‘her understanding’. There was more concern about this among MMS students than in the JABSoM group. Across the whole participant group, students who considered Liz A were more likely than those considering Liz to see her as not understanding relevant features of her situation – her medical condition or the doctor’s rationale for treatment or the medical system. Importantly, this perspective on the patient appeared to influence their priorities. For example, if ‘this patient just doesn’t have a full grasp of the issues . . . [then] just to educate them’ was one participant’s priority (P10). Furthermore, if the patient was seen not to ‘understand the importance of these different services . . . you could give her lots of referrals but unless she realises how important it is . . . ’ she will not follow up (P14) – and if a patient does not attend a referral that a doctor has made it will ‘look bad on me’ (P28).

**Features of the patient–doctor interaction**

All participants emphasised the importance of appreciating the patient’s ‘priorities’ and ‘agenda’, and many had a related commitment to establishing and maintaining a foundational ‘trust’ in the clinical relationship (Table 3). Many participants were also alert to the likelihood of the interaction uncovering ‘mismatches’ between doctors and their patients in relation to:

- Cultural views of medicine
- Levels of knowledge/education
- Conceptualisations of wellness
- Perspectives on the seriousness of the condition of diabetes and its place in an individual’s life
- Patients’ beliefs and preferences

Where the patient’s ethnicity was declared, participants noted even more potentially complex mismatches, including:

- A social history of negative experiences resulting in distrust of medical practitioners and the health system
- The use of (alternative) traditional healing practices that are or are not declared
- A more holistic/less individualised conceptualisation of wellness.

The notion of ‘trust’ was presented as embedded in the interaction as students promoted different behaviours:

- Hearing what this patient wants
- Comprehending both the risks and strengths in her life situation
- Gently guiding her to do what the doctor knows is important (medication, investigations, specialist consultations) but within the constraints of her personal resources
- Negotiating starting points and priorities for the longer term.

Ultimately, the role of trust was seen as directed towards ensuring that the patient returns to the doctor: for this patient, this was seen as critical because without agreed priorities and trust, as one said, ‘nothing will work’ (P25). While this essential feature of doctor–
patient interactions was common across many transcripts, the extra layer of historical mistrust and perceived additional ‘mismatches’ with the Indigenous patient positions ‘trust’ at the centre of the interaction (Table 3).

**Education settings**

There are references in the transcripts to the emphasis in formal teaching programmes on the importance of a holistic approach to clinical practice, particularly on the psychosocial aspects of care. Also, several participants spoke passionately and at length about the value of their rotations in general practice settings. It was in ‘good’ clinics that they were able to observe practitioners as well as see patients themselves, sometimes experiencing the rewards of working with the patient’s agenda (Table 3). In contrast, hospital wards offered only ‘walk in, walk out’ experiences.

Here too, the serendipity that dominates clinical learning was highlighted and this randomness was particularly evident when participants were considering the Indigenous patient. There was luck in having had a friend who had undertaken a rotation in a remote Indigenous health service, or to have been awakened by one’s own life experience to do the same or just to have read a book about Indigenous health. Participants also highlighted the good luck of being allocated to a well-supervised (‘good’) GP clinic or the bad luck of being allocated to one that does brief consultations where the student is no more than an observer in the corner. Some MMS students ‘admitted’ that their knowledge of Aboriginal and Torres Strait Islander peoples (and/or their health) is poor (Table 3).

**Discussion**

**Patients, ethnicity and decision-making**

This qualitative study with senior medical students aimed to generate insights into ways that a patient’s declared ethnicity influences processes of clinical decision-making. The study did not explicitly explore the interaction of ethnicity and gender in clinical consultations although we acknowledge that this is important. We found that subtle biases influenced the ways the participants thought about Aboriginal patients and these biases affected some of the priorities they had for the patients. We also identified small differences between students from the two medical schools. The findings suggest that medical curriculum reforms are necessary to address ways students learn about Indigenous health, about patient–doctor interactions and about their own biases. These reforms will be both general as well as particular to the school.

We did not find evidence of the extent of unequal treatment of the Indigenous patient that has previously been reported and explained by the presence of implicit bias. However, we did find important differences in the ways that these senior medical students talked about the Indigenous patient and how they would approach a consultation with her. Biases were evident in many of the commentaries on the patient’s medical condition, her health literacy and/or assumptions they made about her social situation. Furthermore, if the patient was viewed as having multiple social problems in addition to the chronic medical condition, participants were more likely to construct the consultation and their interaction with her as difficult. Here, several students anticipated feeling overwhelmed, or out of their depth; as a consequence, they might focus on educating the patient before treating her or referring her to a range of specialists rather than working out their own approach. The subtile of these expressions requires attention across the medical curricula to help students identify their own (and others’) biases and if necessary modify their approaches to practice. It is here, too, that the medical schools need to ensure that students are adequately equipped with a framework to approach what they anticipate as or encounter as difficult consultations: as a specific curriculum reform, this is especially important given the likely increase in complex, chronic conditions that patients bring to them.

The value of the two-school study is apparent in finding differences between the two student groups: students’ knowledge of Indigenous health; biased inferences about patients’ health literacy; and their responses to the patient ‘having trouble coping’. While we do not know the reasons for these differences, we presume they result from complex interactions of formal, informal and hidden curricula as well as societal and cultural differences. It is not possible in this paper to deliberate on or suggest curriculum changes for schools; rather, this exploratory study highlights the need to place the goal of equitable outcomes for all patients as an underpinning principle of curriculum.

There is evidence in this study that medical students anticipate many ‘mismatches’ at play between doctors and their patients regardless of ethnicity, different views of motivations for attending clinic, beliefs about health, attitudes to medical treatment and personal/professional priorities. Here, in recognising these mismatches, the students drew attention to the value they place on attending to the patient’s agenda, and to the centrality of ‘trust’ in the therapeutic relationship. In relation to interactions with Indigenous patients, trust was endowed with even more significance because of the extra layer of potential mismatches given the historically poor relationship
between Indigenous peoples and the medical profession. Therefore, the study highlights an awareness of these issues (‘mismatches’, trust and ethnicity) in doctors’ interactions with Indigenous peoples. This is clearly a positive finding, though not a cause for complacency given that these good intentions and patient-centred values (attention to the patient’s agenda and the creation of trust) are often and easily overpowered when decisions are made under pressure of time and clinical workloads. In such contexts, unconscious stereotypes are likely to influence decisions more than they influence in the quiet of a paper case. Here we note the wisdom and caution that the prejudices of good people are those that should concern us.

At the heart of the matter here is the subtlety and persistence of the findings: biases appear to affect how students think about different patients and biases seem to influence how they shape their consultations with Indigenous patients. These preconceptions might generate in their negative expectations of the encounters with Indigenous patients, possibly influencing these future health practitioners to engage less with Indigenous patients than they do with other patients. Curriculum developers, teachers and medical practitioners alike can heed these findings as they work to recognise their own biases and influence students’ biases. The goal is equitable treatment of patients and equitable patient outcomes – equitable, not equal.

The findings of this research indicate that further research with more complex methodologies is required into the perceptions and biases that students bring to medical school as well as the impact on these students of medical school and subsequent experiences in vocational medical training programmes and associated clinical/hospital rotations. The research also signals the value of a longitudinal study with these students as clinical/hospital rotations. The research also signals the value of a longitudinal study with these students as the paper. These principles need to pervade medical curricula at university and training institutions so that students and trainees become conscious of their own biases as well as knowledgeable about different patient groups. Perhaps the approaches we found in this study – a move away from treating all patients the same, to treating each patient according to need – reflect the gains being made after more than a decade of the inclusion of Indigenous health curricula in medical education at university.

**Conclusion**

This was an exploratory study that suggests ways of thinking that senior medical students bring to their clinical decision-making. Indigenous patients need practitioners who are sensitive to the consequences of historical and ongoing mistreatment, who can acknowledge difference and disadvantage and bring that knowledge into their plans for these patients. They need practitioners who interact with them equitably – not equally. These approaches we found in this study – a move away from treating all patients the same, to treating each patient according to need – reflect the gains being made after more than a decade of the inclusion of Indigenous health curricula in medical education at university.

**Acknowledgements**

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**References**

8 Green AR, Carney DR, Pallin DJ. Implicit bias among physicians and its prediction and thrombolysis decisions
Using quality indicators to compare outcomes of permanent cardiac pacemaker implantation among publicly and privately funded patients

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Abstract

Background: Funding source/insurance status has been associated with disparity in the management and outcomes of cardiovascular disease, with poorer outcomes among disadvantaged groups.

Aim: Using proposed quality indicators for permanent pacemaker (PPM) implantation and administrative data, this study aimed to determine whether quality indicator-based outcomes of PPM implantation were comparable for publicly and privately funded patients within Australia’s two-tier health system.

Methods: A population-based cohort study of adults implanted with a PPM between 1995 and 2009 in Western Australia. The association of funding outcomes derived from linked administrative data was tested in multivariate logistic regression models.

Results: There were 9748 PPMs implanted, 48% being among privately funded patients. The mean age was 75 years for both public and private patients. Private patients had better health status (fewer with cardiac conditions and lower non-cardiac comorbidity scores), were less likely to be an emergency admission (33% vs 60%, P < 0.001) and more likely to have dual- or triple-chamber pacing. Mean length of stay was significantly greater for private patients (4.3 (standard deviation 6.3) vs 5.1 (6.8) days <0.001), related to longer elective admissions. Crude mortality was lower for private patients in-hospital (0.7 vs 1.3%), 30-day post-procedure (1.3 vs 2.1%) and at 1 year (7.3 vs 9.5%). Emergency admission, comorbidity and other demographic and clinical factors, not funding source, were significant predictors of these outcomes.

Conclusions: There was no difference between publicly and privately funded patients in study outcomes, after adjustment for demographic and clinical factors. The exception was longer hospital stay for elective PPM among privately funded patients.

Introduction

Variation in the use of cardiac permanent pacemakers (PPM) based on socio-demographic factors and funding source (insurance or primary payer status, re-imbursement methods) are reported from several countries.1-4 In one of the few outcomes studies, the greater use of dual-chamber pacing in more advantaged patients, including those treated in private hospitals in the United States (US), was associated with improved survival at 1 and 2 years.7

Differences in funding are a potential source of variation in care in Australia with its two-tier health system. There have been reports of greater use of coronary angiography and revascularisation procedures among private patients than in those admitted as public patients,8,9 but there is little information on the relative use of other cardiac interventions that may be influenced by funding source.

We sought to compare the use of and outcomes following PPM implantation in an Australian population using indicators of quality of care. Expert guidelines for
the selection of patients and devices, and for ongoing management of patients are available but do not include specific performance indicators. Several indicators of the safety and quality of care related to the implantation of a PPM have been proposed by various groups and institutions in Australia, the United States and Europe, although none set specific benchmarks. For example, while a delay in implanting a non-elective PPM has been identified as a risk to the safety of patients, the European Society of Cardiology guidelines recommend only that ‘every effort should be made to implant a pacemaker as soon as possible’.10

As Australians can access both universal (publicly funded) and private healthcare, we used linked administrative data and published quality indicators to evaluate the use and outcomes of PPM implantation to determine whether funding source was associated with quality of care.

Methods

The data for the study were prepared by the Data Linkage Branch of the Health Department of Western Australia. Individual records for all public and private hospital admissions and separations within the state are collated under a unique identifier, using computerised probabilistic matching of patient names and other identifiers.

Ascertainment of cases

The study cohort was extracted from the Western Australia hospital morbidity data) using World Health Organization International Classification of Disease (ICD) versions ICD-9, ICD-9-CM and ICD-10, Australian Modification, editions 1–10 diagnosis and procedure codes for insertion or management of a cardiac PPM (available from the author). All admissions from the beginning of 1980 for individuals aged 18 years or more who were identified as recipients of a PPM to 31 December 2009 were included in the study database. Incident cases of first implantation of a PPM device from 1 January 1995 were identified using 15 years of look back. The date of death to 31 December 2011 was linked to these index cases.

Of the 9764 cases identified, 16 (<0.2%) without an admission-type record were excluded. There were incomplete procedure data for 411 (4%) patients of whom 44 had no procedure date recorded. The others had a date for ‘procedure one’ only, which was not necessarily a PPM insertion code; other first procedures included cardiac surgery such as coronary artery bypass graft (CABG) or cardiac valve surgery, non-cardiac surgery, other procedures such as angiography and cardioversion, and non-cardiac procedures. Among these, the cases with a length of hospital stay (LOS) ≤2 days were assigned the single available procedure date and were categorised at having their PPM inserted without delay (on the day of admission or the following day). There were 334 (3%) remaining cases with missing or uncertain PPM procedure dates; these patients were excluded from the estimation of delay in time from admission to procedure.

Selection of quality indicators

The key indicators that can be measured using administrative data were in-hospital, 30-day post procedure and 1-year mortality, time delay to procedure, in-hospital complications, LOS and re-admissions to 30-days post-discharge. The following information was collected from the linked data: index admission type and date, separation (discharge) mode and date, principal diagnosis, up to 19 secondary diagnoses, and up to 11 in-hospital procedures. Re-admissions to 30 days for a PPM-related condition were identified.

Admission type was categorised in the hospital morbidity database as ‘emergency’ or ‘elective’ at the index PPM admission.

LOS was calculated from the admission to discharge dates for the whole ‘episode of care’, including transfers between hospitals, but excluding in-hospital deaths.

Pacemaker type (single, dual, triple chamber or ‘not otherwise specified’) was identified from Health Intervention (procedure) codes for the insertion of the device. Each PPM type was assigned a specific code to July 2008. From then ‘pacemaker type’ and lead placement were each only assigned a single code, making certain identification of PPM type difficult. Patients who had codes for both pacing and a cardiac defibrillator were included but not those with a cardiac defibrillator alone. ‘Not otherwise specified’ was coded when the pacemaker type was not evident or no code was assigned due to a lag between the introduction of new devices and the revision of codes.

The major indications for pacing were categorised, using diagnosis and procedure codes, as in the 11th World Survey of Cardiac Pacing (2009), and in a hierarchical fashion (major indication in principal diagnosis, secondary diagnosis etc.). Indications such as sick sinus syndrome or high-level atrio-ventricular block are given precedence over conditions such as acute myocardial infarction (AMI), heart failure (HF) or syncope.

Conditions other than arrhythmias recorded as principal and other diagnoses were identified, as well as complications of pacemaker insertion (mechanical, surgical, infective or inflammatory).
A Charlson Comorbidity Index score was calculated from the hospital morbidity data using the index admission and admissions in the previous 5 years to identify comorbidities such as stroke, cancer and chronic kidney disease. Weights were assigned according to the methods published by Quan et al.19,20 AMI and HF were excluded as comorbidities as they were frequently the primary disorder. The final score was categorised as zero (no non-cardiac comorbid conditions recorded), a score of 1–2 or of 3 or more.

Histories of AMI and HF within 5 years were recorded as independent variables.

The funding source recorded during the index admission was used to categorise funding status; patients transferring between public and private hospitals were categorised according to the funding source at the institution in which the device was inserted. Publicly funded patients were all those who elected treatment under the Australian Health Care Agreements and Reciprocal Health Care Agreements. Privately funded patients included those funded through private health insurance organisations, are self-funded or funded through the Department of Veterans’ Affairs. Sixteen patients (0.2%) with no data on funding were excluded.

Time delay was counted from admission date to the date of the PPM insertion procedure and categorised as ≤1 day (procedure on the day of admission or following day), 2–4, 5–7, and 8 or more days and used as a bivariate outcome (≤1 day and ≥2 days) to test factors associated with delay.

Primary outcomes were time delay to implantation, LOS, early (in-hospital) complications, a PPM-related readmission within 30 days of separation and mortality in-hospital, within 30 days of procedure (for patients with PPM date) and at 1 year.

Statistical analysis
The recipients of a PPM are described, with differences between privately and publicly funded patient groups defined by decade of age compared with those <65 years of age, sex, indication for PPM implantation, other cardiac diagnoses, admission type (emergency or elective), pacemaker type and comorbidity scores and outcomes were tested with the Chi-squared test for categorical variables. The differences between dual- and triple-chambered pacing for public and private patients were not subjected to significance testing as the proportion of ‘not otherwise specified’ type exceeded the differences between the groups. Similarly, ‘first procedure type’ was not tested due the overwhelming disparity in numbers in each procedure type. Differences in mean values of age and LOS were tested using Student’s t-test and one-way analysis of variance. A two-sided P value of <0.05 was considered statistically significant. Logistic regression analysis was undertaken to identify factors associated with each of the outcomes. Analyses were performed using SPSS Version 21 (IBM Corp., Armonk, NY, USA).

Ethics
The study was approved by the Human Research Ethics Committees at the University of Western Australia and Health Department of Western Australia.

Results
There were 9748 first PPM implants identified between 1995 and 2009, of which 5032 (52%) were publicly funded and 4716 patients were treated as private cases, including 760 veterans (16%). The mean age for the cohort was 75.0 (standard deviation (SD) 11.7) years and for both public and privately funded patients. After excluding veterans, who were on average 10 years older, the mean age for private patients was 73.3 (SD 11.3) years.

The proportion of people treated as private patients increased from 35% in 1995–1999 to 60% in 2005–2009, and the proportion of elective to emergency cases also rose, from 50% to 56% for the same eras. The characteristics of the patients are shown in Table 1.

Admission type
Of all admissions 4607 (47%) were emergency cases. Private cases were 34% of all emergency admissions but 61% of elective admissions (Fig.1). Of the publicly funded patients, the majority of emergency implants (94%) took place at one of three public metropolitan tertiary/teaching hospitals, as did almost half (44%) of the privately funded patients. Elective admissions for private patients were mostly to private tertiary hospitals (87%), while 8% of ‘publicly funded’ elective admissions for PPM insertion were treated in a private hospital.

Patients admitted as emergencies were older (76.5, SD 11.2 years vs 73.6, SD 11.9 years, <0.001), had a greater burden of comorbidities and were nearly twice as likely to have a PPM inserted for high-level atrio-ventricular block (50%) than those admitted electively (28%). Emergency cases admitted as private patients were slightly older than public patients 77.04 versus 76.3 years (P = 0.03); however, public patients suffered greater comorbidity with 38% in the highest category, Charlson score ≥3, versus 32% of privately funded emergency patients (P ≤0.001). Charlson scores were very similar for
public and private patients who underwent an elective PPM implantation (25% with Charlson score ≥ 3 for both).

Pacemaker type

Public patients were more likely to have single-chamber pacing than private patients in both the emergency and elective setting (Table 1). In addition to more dual- or triple-chamber pacing, a greater proportion of PPMs used for private patients were coded as ‘not otherwise specified’ which may have widened the gap in multi-chamber pacing use according to insurance status, but this cannot be quantified with certainty.

Pacing type was significantly associated with age; those treated with a single-chamber device (mean 78.7 (SD 10.7) years) were on average 5 years older than those with dual-chamber pacing (73.8 (SD 11.6) years) and around 8 years older than those with triple-chamber pacing (70.8 (SD 12.2) years, \( P < 0.001 \)).

Delay to permanent pacemaker implantation

The majority of patients with a PPM procedure date (\( n = 9414 \)) had the PPM implanted on the day of admission (\( n = 4053, 43\% \)) or the following day (\( n = 1679, 18\% \)), that is \( \leq 1 \) day. The proportion overall of PPM implantations \( \leq 1 \) day was higher for elective admissions (84%) than emergency admissions (35%) and for private patients (67%), the majority of whom were elective admissions, than for public patients (55%).

For elective cases who did not have AMI or acute coronary syndrome (ACS) as a principal diagnosis and whose first procedure was a PPM (\( n = 4526 \)), 90% of public patients and 84.2% of private patients had their procedure \( \leq 1 \) day (\( P < 0.001 \)). This difference in favour of public patients was not seen among emergency patients (Table 2).

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**Table 1** Characteristics of 9748 patients managed with implantation of a permanent cardiac pacemaker according to funding source (public or private)

<table>
<thead>
<tr>
<th></th>
<th>Public</th>
<th>Private</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>( n = 5032 )</td>
<td></td>
<td>( n = 4716 )</td>
<td></td>
</tr>
<tr>
<td>Men, ( n (%) )</td>
<td>2939 (58)</td>
<td>2868 (61)</td>
<td>0.008</td>
</tr>
<tr>
<td>Age mean (SD) years</td>
<td>75.0 (11.7)</td>
<td>75.0 (11.5)</td>
<td>0.84</td>
</tr>
<tr>
<td>Emergency admission, ( n (%) )</td>
<td>3040 (60)</td>
<td>1567 (33)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Charlson score n (%)</td>
<td>0</td>
<td>1279 (25)</td>
<td>1387 (29)</td>
</tr>
<tr>
<td>1</td>
<td>1213 (24)</td>
<td>1191 (25)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>902 (18)</td>
<td>858 (18)</td>
<td></td>
</tr>
<tr>
<td>3 or more</td>
<td>1638 (33)</td>
<td>1280 (27)</td>
<td></td>
</tr>
<tr>
<td>Medical history, ( n (%) )</td>
<td>AMI (5 years prior)</td>
<td>1192 (24)</td>
<td>982 (21)</td>
</tr>
<tr>
<td>Heart failure (5 years prior)</td>
<td>2022 (40)</td>
<td>1770 (38)</td>
<td>0.004</td>
</tr>
<tr>
<td>Index admission†</td>
<td>AMI (principal diagnosis)</td>
<td>124 (2.5)</td>
<td>74 (1.6)</td>
</tr>
<tr>
<td>Bundle branch block</td>
<td>507 (10)</td>
<td>518 (11)</td>
<td>0.15</td>
</tr>
<tr>
<td>Sick sinus syndrome</td>
<td>744 (15)</td>
<td>788 (17)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>567 (11)</td>
<td>602 (13)</td>
<td>0.29</td>
</tr>
<tr>
<td>Other dysrhythmia‡</td>
<td>574 (11)</td>
<td>682 (14)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CSS/NCGS</td>
<td>157 (3)</td>
<td>271 (6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ablation</td>
<td>143 (3)</td>
<td>89 (2)</td>
<td>0.002</td>
</tr>
<tr>
<td>Cardiomyopathy</td>
<td>99 (2)</td>
<td>83 (2)</td>
<td>1.00</td>
</tr>
<tr>
<td>Heart failure</td>
<td>33 (&lt;1)</td>
<td>76 (2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>No indication recorded</td>
<td>41 (&lt;1)</td>
<td>47 (1)</td>
<td>0.39</td>
</tr>
<tr>
<td>Pacemaker type, ( n (%) )</td>
<td>Single</td>
<td>1431 (28)</td>
<td>778 (16)</td>
</tr>
<tr>
<td>Dual</td>
<td>2968 (59)</td>
<td>2875 (61)</td>
<td>Not tested</td>
</tr>
<tr>
<td>Triple</td>
<td>161 (3)</td>
<td>248 (5)</td>
<td></td>
</tr>
<tr>
<td>‘Not otherwise specified’</td>
<td>472 (9)</td>
<td>815 (17)</td>
<td></td>
</tr>
<tr>
<td>First procedure type</td>
<td>PPM-related</td>
<td>4573 (91)</td>
<td>4248 (90)</td>
</tr>
<tr>
<td>CABG</td>
<td>61 (1)</td>
<td>36 (&lt;1)</td>
<td></td>
</tr>
<tr>
<td>PCI</td>
<td>26 (&lt;1)</td>
<td>30 (&lt;1)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>372 (7)</td>
<td>402 (9)</td>
<td></td>
</tr>
</tbody>
</table>

†Recorded as principal or one of 19 secondary diagnoses. ‡Other dysrhythmias including paroxysmal tachycardia, ventricular fibrillation and flutter; sinus bradycardia and other specified and unspecified rhythm disorders. ACS, acute coronary syndrome; AMI, acute myocardial infarction; AV, atrioventricular; CABG, coronary artery bypass graft; CSS/NCGS, carotid sinus syncope/neurocardiogenic syncope; PCI, percutaneous coronary intervention; PPM, permanent pacemaker; VF, ventricular fibrillation.
Mortality for emergency cases (n = 4421) at 30 days post-procedure increased with time from admission to PPM implantation (≤1 day, 2 or more days) being 1.9, 2.5, 3.7 and 4.7% (P < 0.001) and at 1 year 8.4, 10.9, 13.7 and 18.2% (P < 0.001).

AMI or ACS as the ‘principal diagnosis’, and a first procedure that was not for implantation of a PPM, significantly increased the delay to PPM implantation for emergency admissions. Excluding these, only other comorbid conditions such HF (odds ratio (OR) 3.24, confidence interval (CI) 1.83–5.76, P < 0.001), atrial fibrillation (OR 2.00, CI 1.70–2.32, P < 0.001) and a non-cardiac Charlson score of 3 or more (OR 1.68, CI 1.41–2.00, P < 0.001) were independently associated with delay: age was not. Treatment as a private patient was not significantly associated with a reduced risk for delay (Table 3).

Length of hospital stay

The median LOS was 3 days overall, and the mean LOS significantly greater for private patients who were elective admissions (Table 2). All the clinical and demographic predictor variables included in the models were significantly associated with LOS ≥ 3 days – increasing age, female sex, AMI as a principal diagnosis, HF, non-cardiac comorbidity, ventricular fibrillation/cardiac arrest (VF/arrest), complications and first procedures ‘other’ than PPM implantation. There was also a significant association with admission type. For those whose first procedure was a PPM and did not have AMI or ACS as a principal diagnosis, private funding was an independent predictor of great LOS for elective, but not emergency, admissions (Table 3).

Readmission within 30 days of hospital discharge

Readmission within 30 days for a PPM-related condition that required adjustment, removal or replacement of any part of a pacing system was 2.2% (n = 211). There was no difference between public and privately funded patients (Table 2). Only an in-hospital complication (OR 2.04, CI 1.32–3.15, P = 0.001) increased the risk for readmission. The oldest patients, 85 years (OR 0.41, CI 0.21–0.79, P = 0.008, compared to <65 years of age) and those whose first procedure was a PPM implantation, rather than ‘other’ surgery or procedure (OR 0.42, CI 0.20–0.87, P = 0.02) were less likely to be re-admitted. Funding source was not associated with readmission (Table 3).

In-hospital mortality

There were 96 deaths in hospital (1% overall) (Table 2). Most deaths (n = 85) were among patients treated as emergency admissions, with the rate being 1.3% in public patients and 0.7% in privately funded patients (P = 0.002). Independent predictors included age ≥85 years (OR 5.16, 95% CI 2.68–11.69 P = 0.02), VF/cardiac arrest in the index admission (OR 5.49, CI 3.33–9.06, P < 0.001), emergency admission (OR 5.16, CI 2.63–10.11, P < 0.001), Charlson score ≥3 (OR 3.81, CI 1.46–9.95,
Post-PPM mortality (Table 3). Delay nor funding source was associated with 30-day mortality (6.9% and 8.6%) or ‘not other specified’ (6.9%) (OR 0.20, 0.05–0.84, P < 0.001), this was not significant after adjustment for other factors.6,7

30-day post-procedure mortality

There were 163 (1.7%) deaths overall to 30 days from the procedure date, mortality being higher for public patients (Table 2). There were no deaths among the 334 patients with no PPM procedure date and their inclusion in the multivariate models had no significant effect on the associations between the predictor variables and the outcome. Independent predictors of death to 30 days after implantation included age ≥85 years (OR 4.15, 95% CI 1.48–11.60, P = 0.007), VF/arrest (OR 3.40, CI 2.13–5.41, P < 0.001), a principal diagnosis of AMI (OR 2.38, CI 1.32–4.30, P = 0.004) or HF recorded in the index admission (OR 3.24, CI 2.28–4.58, P < 0.001), emergency admission (OR 1.80, CI 1.25–2.71, P = 0.002), Charlson score ≥3 (OR 2.74, CI 1.52–4.92, P = 0.001). Neither delay nor funding source was associated with 30-day post-PPM mortality (Table 3).

One-year mortality

Among 9652 patients discharged alive, 814 (8.4%) died within 1 year. Mortality was highest among patients with reported HF (19.7%) and with AMI as a principal diagnosis (16.4%). For the major indications of atrioventricular or bundle-branch block, 1-year mortality was ≈10%, and was lowest (≈5%) for patients diagnosed with syncope or those post-ablation. Mortality for public patients was greater than among private patients (Table 2).

The risk for death within a year of discharge increased with each decade of age from 65 years, exceeding sevenfold for those aged 85 years or more (OR 4.12–12.0, P < 0.001) while women at lower risk overall (OR 0.56, 0.48–0.66, P < 0.001), HF (OR 2.24, CI 1.86–2.69, P < 0.001), VF/arrest (OR 1.55, 1.11–2.17, P = 0.01), an emergency admission (OR 1.46, CI 1.23–1.72, P < 0.001) and Charlson scores of ≥3 (OR 2.24, CI 1.79–2.82, P < 0.001) were each associated with increased risk. Patients whose first procedure was CAGB surgery were at lower risk (OR 0.20, 0.05–0.84, P = 0.03) for death within 1 year. Although PPM type was significantly associated with mortality, being 13.9% for patients with single-chamber devices compared with dual or triple chamber (6.9% and 8.6%) or ‘not other specified’ (6.9%) (P < 0.001), this was not significant after adjustment for decade of age (37.5% of patients aged ≥85 years had a single-chamber PPM compared with 13.5% for those <65 years). A reduced risk for private patients failed to meet statistical significance (Table 3).

Discussion

In this study of PPM implantation and outcomes from Western Australia, private patients had better health status (lower non-cardiac comorbidity scores and fewer concomitant cardiac diagnoses), were less likely to be an emergency admission and to have an AMI as a principal diagnosis.

Private patients were less likely to have a single-chamber PPM implanted, and the difference in dual- and triple-chamber pacing may have been more pronounced if not for a greater frequency of procedure coding of PPM type as ‘not otherwise specified’ among private patients. Studies from the United States using administrative data also found greater use of dual-chamber pacing among patients with private insurance, after adjustment for age and other factors.6,7

Among the outcomes used to evaluate safety and quality of care (delay to PPM, LOS, early complications, 30-day readmission, and in-hospital death, 30-day and 1-year mortality), almost all were significantly worse for public patients except for LOS for emergency cases, and 30-day readmissions. The 30-day readmissions were device-related readmissions only; readmissions for other reasons may have differed between the groups.

However, after adjustment for demographic and clinical factors, private insurance was predictive only of increased LOS for elective admissions. The shorter LOS for publicly funded elective cases is probably a reflection of the higher turn-over and early discharge protocols/policies for patients treated in a public hospital. The less delay to PPM procedure for elective admissions was also noted in a study from teaching hospitals in New South Wales.14 There was a trend to lower risk for mortality of ≈15% for private patients at each time-point, but none reached statistical significance. The equivalence of age among private and public patients in this generally older cohort may have contributed to the similarity of outcomes.

Use of performance/quality indicators

The proposed indicators for evaluation of quality-of-care outcomes using linked administrative provided a credible framework for comparing outcomes by patient funding in the Western Australian population. However, without benchmarks for quality care, we were not able to use...
In-hospital mortality in this study from 1995 to 2009 was 1% overall, lower than the <2% found among US Medicare patients (aged ≥65 years) in the year 2000, and an earlier 1992 Nationwide Inpatient Sample. However, without some mechanism for adjusting for demographic, clinical and process differences, such comparisons are not meaningful. The development of a valid measure of risk adjustment for patients undergoing cardiac device implantations, such as the EuroScore for risk assessment for cardiac surgery, or the American College of Cardiology/American Heart Association recommendations for performing percutaneous coronary intervention used to track mortality in US cardiac procedures registries, would enable the performance of health systems at various level to be compared. For those countries or regions fortunate enough to have comprehensive and well-maintained implantable device registries, the capacity to evaluate important indicators such as complications, readmissions and 1-year mortality requires the capacity to couple the registry data to morbidity and mortality data.

**Strengths**

This study used more than 30 years of high-quality, well-validated, population-based, person-level linked data. Validation of the matching of individuals in the hospital morbidity data estimated invalid links (false positives) and missed links (false negatives) at 0.11% each. In a contemporaneous validation study of morbidity coding of principal diagnosis of HF compared with the medical chart diagnosis, the positive predictive value of the hospital morbidity data was 99.5%.

**Limitations**

Administrative data do not provide detailed clinical information, limiting the range of possibly important factors available for some analyses, such as the severity of comorbid conditions, the urgency of need for a PPM and the selection of the device. This allows potential confounding from unknown factors. Similarly, indications for pacing derived from patients’ medical records more accurately reflect clinical decisions than administrative data, where multiple competing indications may be coded. Hierarchical categorisation of clinical codes did allow the major indications for pacing to be estimated for the cohort.

Insufficiently precise codes to identify pacemaker types in ICD-10-AM codes since 2008 and the lag in the introduction of codes for new cardiac pacing technology, leading to excessive use of ‘not otherwise specified’ for PPM type, reduced the reliability of statistical comparisons.

**Conclusions**

There was no difference between publicly and privately funded patients in study outcomes, except for days spent in hospital. Despite most outcomes favouring private patients before adjustment for demographic and clinical variables, care as a private patient was associated only with a longer LOS for an elective admission. While this has implications for hospital costs, none of the indicators of quality and safety including early complications, readmission or mortality in-hospital, at 30-days post-procedure or at 1 year was independently associated with funding source. These findings suggest that the quality of care provided to publicly funded patients, principally in public teaching hospitals, is not inferior to that for privately funded patients.

**Acknowledgements**

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Icatibant in angiotensin-converting enzyme (ACE) inhibitor-associated angioedema

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Key words
icatibant, angiotensin-converting enzyme inhibitor, airway angioedema, intubation, emergency department.

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Abstract

Background: Angioedema occurs in up to 2% of those taking angiotensin-converting enzyme (ACE) inhibitors. Upper airway angioedema may potentially require endotracheal intubation or cricothyrotomy, and is usually unresponsive to adrenaline. The bradykinin receptor antagonist icatibant is proven to be effective in the treatment of acute attacks of hereditary angioedema, and has also been reported effective in the treatment of angioedema associated with ACE inhibitors.

Aim: To describe the use of icatibant for ACE inhibitor-associated airway angioedema.

Methods: We treated 13 consecutive emergency department (ED) patients, who had not improved with adrenaline and/or corticosteroids, with icatibant 30 mg subcutaneously for ACE inhibitor-associated upper respiratory tract angioedema according to an agreed protocol.

Results: Four patients were intubated in the ED either before or after receiving icatibant; three of these were extubated within 24 h of treatment. Eight patients received early icatibant and did not require intubation. The time from onset of airway angioedema to ED presentation ranged from 1 h to 3 days (median 4 h); from ED presentation to receiving icatibant, from 30 minutes to 3 days (median 3 h); and to onset of symptom improvement after icatibant, 15 minutes to 7 h (median 2 h). One patient received a second dose of icatibant.

Conclusion: All patients improved after receiving icatibant, consistent with its bradykinin receptor blocking mechanism. Icatibant rapidly reversed symptoms, and appeared to avert the need for intubation or expedite extubation. Timely use of icatibant in ACE inhibitor-associated angioedema may avert the need for invasive airway procedures and intensive care unit admission.

Introduction

Angioedema is characterised by localised and self-limiting subcutaneous and submucosal oedema caused by increased vascular permeability.1 Angioedema may be mediated by histamine, for instance in anaphylaxis, or by bradykinin. Bradykinin is thought to be the principal mediator of hereditary angioedema (HAE), acquired angioedema secondary to C1 inhibitor deficiency, and angiotensin-converting enzyme (ACE) inhibitor-associated angioedema.

ACE inhibitors are commonly prescribed for hypertension, cardiac failure, myocardial infarction and diabetic nephropathy, and may cause angioedema as a side-effect by inhibiting bradykinin degradation. Angioedema is reported to occur in 0.1–2.5% of patients taking ACE inhibitors,2–5 and is potentially life threatening when it involves the airway, with fatalities reported.6 Standard treatments for histamine-mediated or anaphylactic angioedema such as adrenaline, antihistamines and corticosteroids are usually not effective in bradykinin-mediated angioedema. Icatibant, a bradykinin-2 receptor antagonist, is an established treatment for HAE attacks and has been reported to be effective in ACE inhibitor-associated angioedema.7

Progressive airway angioedema can cause asphyxia, and endotracheal intubation or cricothyrotomy may be required for emergency airway management. While life saving, intubation is technically challenging and
necessitates admission to the intensive care unit (ICU) often with a prolonged hospital stay. Recognition of ACE inhibitor use as the potential aetiology of the angioedema allows consideration of targeted effective medical therapy.

We describe the use of icatibant for ACE inhibitor-associated airway angioedema in 13 consecutive cases in two Australian hospital emergency departments (EDs).

Methods

We developed a protocol for the management of angioedema in the ED according to its presumed aetiology, whether histamine mediated, or non-histaminergic (Fig. 1). When the angioedema was considered likely to be related to ACE inhibitor use and involved the upper airway, the ED physician contacted the immunology consultant on call to approve the use of icatibant in suitable cases. Thirteen consecutive patients administered icatibant according to the protocol were identified at the Royal Adelaide Hospital (RAH), South Australia and Campbelltown Hospital, New South Wales from mid-2012 to September 2014.

All patients presented to ED with varying degrees of orofacial or laryngeal angioedema were on an ACE inhibitor at presentation, and were considered to have

Figure 1 Management algorithm for angioedema cases presenting to Royal Adelaide Hospital; a similar procedure was in place at Campbelltown Hospital. Diagnosis of angioedema assumed; flowchart provided in conjunction with written information on location, severity markers for angioedema and details on treatment. *A minority of cases of idiopathic angioedema do not respond to adrenaline/antihistamines and may be bradykinin mediated.
some degree of airway threat. These patients did not have urticaria or other features of anaphylaxis and, in general, there was no clear allergic trigger. Four patients were examined by the ear, nose and throat (ENT) team with direct flexible nasoendoscopy (FNE) at the request of the senior ED physician.

Demographic data of patients including sex, age, co-morbidities and the duration of ACE inhibitor use as well as presenting symptoms, signs and severity of airway swelling were recorded. The severity of the angioedema was scored based on the scheme suggested by Grant et al.\(^7\) type 1 angioedema involved the lip and anterior tongue, type 2 the floor of mouth, palate or oropharynx, and type 3 the hypopharynx or larynx. Scoring was based on observations recorded in the ED notes, adjusted according to symptoms and confirmed by FNE when available. All patients had serum complement factor 4 (C4) measured to exclude HAE and acquired C1 inhibitor deficiency.

Mean times from symptom onset to ED presentation, ED presentation to receiving icatibant and icatibant to first symptom relief were recorded.

This report using de-identified patient data was approved by the RAH human research ethics committee.

**Results**

Thirteen patients received icatibant. Seven were female (54%) and six were male. Eleven were Australian Caucasian (85%) while two were Australian Aboriginal. Ages ranged from 40 to 81 years. All patients had hypertension as the indication for an ACE inhibitor. Of the 13 cases, perindopril was implicated in eight (62%), fosinopril in two (15%), ramipril in two (15%) and enalapril in one (8%). The duration of ACE inhibitor use ranged from 1 day to more than 20 years, including five cases of undetermined duration likely to have been several years (Table 1).

Regional swelling accounted for the main symptomatology, except for one patient whose chief complaint was sore throat and drooling.

Five cases were characterised from ED records as type 1 angioedema (38%), six as type 2 (46%) and two as type 3 (16%). Symptoms suggested that three of five type 1 cases may have had type 2 angioedema although this was not possible to assess from recorded observations. All four cases examined by FNE demonstrated either type 2 or type 3 angioedema.

The duration from time of onset to ED presentation ranged from 1 h to 3 days, with a median time of 4 h. Of the 13 patients, 11 received adrenaline and corticosteroid as initial therapy in ED for angioedema. Two patients received icatibant as first-line treatment.

Twelve patients received a single dose of subcutaneous icatibant 30 mg in 3 mL, and one received a second 30 mg subcutaneous dose due to persistent stridor. Four patients (31%) were intubated in the ED, either before or shortly after icatibant was given, on the judgement of the ED or ICU team on concern of impending airway closure.

The time from the initial ED physician review to receiving icatibant ranged from 30 minutes to 3 days (with a median time of 3 h). Of note, patient A had an initial diagnosis of crustacean allergy and received multiple doses of adrenaline without improvement. She was intubated and transferred to the ICU, where the immunology team was consulted 3 days later, and icatibant was given.

The time between ED presentation to endotracheal intubation (when indicated) ranged from 1 to 14 h (median time of 2 h).

Table 2 summarises the time intervals (in hours) between symptom onset to ED presentation, ED presentation to intubation, ED presentation to receiving icatibant, and times after icatibant to first symptom resolution, with median values and airway swelling severity on presentation.

The time from receiving icatibant to first symptom resolution ranged from 15 min to 7 h in the 12 patients who received only one dose of icatibant. Patient J remained symptomatic with a loud inspiratory stridor and moist cough 2 h after receiving the first dose of icatibant. A repeat FNE by the ENT team showed persistent significant arytenoid and uvular oedema. On the recommendation of the immunologist, this patient received a second dose of 30 mg icatibant subcutaneously, with symptomatic improvement 2 h later.

There was no apparent relationship between the time taken to present to hospital after the onset of angioedema, or the time to administer icatibant, and whether or not the patient was intubated. Endotracheal intubation was performed in patients with both type 2 and type 3 angioedema, but none with type 1 involving the lips and anterior tongue alone. The major determinant of the need for intubation appeared historical with presentation early in the series, before the availability and efficacy of icatibant was widely appreciated by ED staff.

**Discussion**

ACE plays a key role in bradykinin degradation; therefore, inhibition of ACE results in excessive bradykinin accumulation. ACE inhibitor-associated angioedema, like HAE, is thought to be mediated by bradykinin activation of vascular bradykinin B2 receptors.\(^6\) Therefore, the
<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age</th>
<th>Co-morbidities</th>
<th>Duration and type of ACE inhibitor</th>
<th>Presenting symptoms</th>
<th>Presenting signs</th>
<th>Severity of airway swelling†</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Female</td>
<td>75</td>
<td>Hypertension</td>
<td>20 years (Fosinopril)</td>
<td>Lip and tongue swelling</td>
<td>(Flexible nasoendoscopy)</td>
<td>Type 3</td>
</tr>
<tr>
<td>B</td>
<td>Male</td>
<td>49</td>
<td>Hypertension</td>
<td>1 day (Perindopril)</td>
<td>Drooling and facial swelling</td>
<td>(Flexible nasoendoscopy)</td>
<td>Type 2</td>
</tr>
<tr>
<td>C</td>
<td>Female</td>
<td>40</td>
<td>Hypertension, DM, Renal failure</td>
<td>2 years (Perindopril)</td>
<td>Sore throat and drooling</td>
<td>(Flexible nasoendoscopy)</td>
<td>Type 2</td>
</tr>
<tr>
<td>D</td>
<td>Female</td>
<td>62</td>
<td>Hypertension, Scleroderma</td>
<td>4 years (Perindopril)</td>
<td>Tongue swelling and hoarse voice</td>
<td>Gross submental and tongue swelling</td>
<td>Type 2</td>
</tr>
<tr>
<td>E</td>
<td>Female</td>
<td>70</td>
<td>Hypertension, IHD, Dyslipidaemia</td>
<td>2 weeks (Ramipril)</td>
<td>Tongue swelling and speech disturbance</td>
<td>Swollen tongue</td>
<td>Type 1</td>
</tr>
<tr>
<td>F</td>
<td>Male</td>
<td>76</td>
<td>Hypertension, IHD, Dyslipidaemia</td>
<td>‘years’ (Fosinopril)</td>
<td>Tongue and facial swelling; Swallowing and speaking difficulty</td>
<td>Swollen tongue</td>
<td>Type 1(2)</td>
</tr>
<tr>
<td>G</td>
<td>Male</td>
<td>87</td>
<td>Hypertension, Stroke</td>
<td>1 day (Perindopril)</td>
<td>Tongue and lip swelling Swallowing difficulty</td>
<td>Tongue and submandibular swelling</td>
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</tr>
<tr>
<td>H</td>
<td>Female</td>
<td>38</td>
<td>Hypertension, DM</td>
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<td>Tongue swelling</td>
<td>Swollen tongue</td>
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</tr>
<tr>
<td>I</td>
<td>Female</td>
<td>59</td>
<td>Hypertension</td>
<td>Unknown duration (Perindopril)</td>
<td>Submandibular swelling Speaking and breathing difficulty</td>
<td>Swelling of tongue, floor of mouth and submandibular area</td>
<td>Type 2</td>
</tr>
<tr>
<td>J</td>
<td>Male</td>
<td>68</td>
<td>Hypertension, AF, Dyslipidaemia</td>
<td>Unknown duration (Ramipril)</td>
<td>Tongue swelling Voice change</td>
<td>(Flexible nasoendoscopy) Swollen soft palate, uvula, epiglottis and false cords</td>
<td>Type 3</td>
</tr>
<tr>
<td>K</td>
<td>Male</td>
<td>81</td>
<td>Hypertension, Baker's asthma, IHD</td>
<td>Unknown duration (Perindopril)</td>
<td>Lip and tongue swelling</td>
<td>Swollen tongue</td>
<td>Type 2</td>
</tr>
<tr>
<td>L</td>
<td>Female</td>
<td>81</td>
<td>Hypertension, Stroke, AF</td>
<td>&gt;10 years (Enalapril)</td>
<td>Tongue and neck swelling Swallowing and speaking difficulty</td>
<td>Tongue, floor of mouth and neck swelling</td>
<td>Type 2</td>
</tr>
<tr>
<td>M</td>
<td>Male</td>
<td>80</td>
<td>Hypertension, IHD</td>
<td>Unknown duration (Perindopril)</td>
<td>Tongue swelling and speaking difficulty Sore throat</td>
<td>Swollen tongue</td>
<td>Type 1(2)</td>
</tr>
</tbody>
</table>

†Airway swelling severity based on a scheme suggested by Grant et al., assessed by ED observation records, figure in brackets ( ) inferred from symptoms.
Type 1 angioedema – lip and anterior tongue involvement.
Type 2 angioedema – floor of mouth, palatal or oropharyngeal oedema.
Type 3 angioedema – laryngeal or hypopharyngeal oedema.
Patients A, B, C and J had flexible nassoendoscopy by the ENT team.
Patients A, B, C and D were intubated.
Patient J had two doses of icatibant.
DM, diabetes mellitus; IHD, ischaemic heart disease; AF, atrial fibrillation.
selective bradykinin B2 receptor antagonist icatibant has a clear pharmacological role. Icatibant has proven effective in randomised controlled trials for HAE attacks\(^9\) and is approved for this purpose by the Therapeutic Goods Authority (TGA) in Australia. Single reports and a small case series suggest that icatibant is effective in ACE inhibitor-associated angioedema,\(^{10-14}\) as expected. Although it does have ‘orphan drug status’ for ACE inhibitor-associated angioedema in Australia, its use for this indication has not been approved by the TGA and therefore remains ‘off label’.

The increased use of ACE inhibitors in hypertension, myocardial infarct and diabetic nephropathy makes it unsurprising that they account for a substantial proportion of angioedema cases presenting to the ED.\(^{15,16}\) Angioedema may occur with any ACE inhibitor. In our series, perindopril accounted for the majority of cases. This reflects prescribing patterns, as perindopril constituted 54% of all ACE inhibitor prescriptions in Australia in 2012/2013.\(^{17}\)

Triggers for angioedema attacks in patients taking an ACE inhibitor are seldom identified. Angioedema may occur within 24 h of the first dose, or after as long as 20 years.\(^{18}\) Susceptibility may be genetically determined.\(^{19-21}\) ACE inhibitor-associated angioedema has a predilection for the lips, tongue, face and upper airway, with the pharynx, larynx and supraglottis often involved, as seen in our series. Similarly, the lip and anterior tongue were the most common sites of involvement (63.5%) in ACE inhibitor-associated angioedema in a series of 228 emergency room visits reported by Grant et al.\(^7\)

For reasons that are not understood, bradykinin-mediated angioedema responds poorly or not at all to standard therapy used in allergic or idiopathic (histamine-mediated) angioedema such as adrenaline, antihistamines and corticosteroids. It is reasonable to treat cautiously acute airway angioedema with a standard dose of intramuscular adrenaline, because a patient on an ACE inhibitor may still have allergic or idiopathic angioedema, and because our experience is that there may be some marginal adrenaline responsiveness in some cases of ACE inhibitor-associated angioedema. However repeated doses of adrenaline are not recommended in this situation, as they are likely to be futile, and increase the potential for adverse events particularly since many of those who are taking ACE inhibitors have additional cardiovascular risk factors. Lack of response to adrenaline is an important clue that the angioedema is bradykinin mediated.

With the potential availability of targeted therapy with a bradykinin antagonist, identification of an ACE inhibitor as the underlying cause of angioedema is important to facilitate optimal management. Barriers to the recognition of ACE inhibitors as the cause of angioedema include

<table>
<thead>
<tr>
<th>Patient</th>
<th>Symptom onset to ED presentation</th>
<th>ED presentation to intubation</th>
<th>ED presentation to icatibant</th>
<th>Icatibant to first symptom resolution</th>
<th>Severity of airway swelling†</th>
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<tr>
<td>A</td>
<td>1</td>
<td>2</td>
<td>72</td>
<td>7</td>
<td>Type 3</td>
</tr>
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<td>24</td>
<td>2</td>
<td>2</td>
<td>3</td>
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<tr>
<td>C</td>
<td>6</td>
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<td>2</td>
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<td>D</td>
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<td>14</td>
<td>14</td>
<td>2</td>
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<td>1</td>
<td>2</td>
<td>Type 1(2)</td>
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<tr>
<td>G</td>
<td>3</td>
<td>NA</td>
<td>1</td>
<td>1</td>
<td>Type 1(2)</td>
</tr>
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<td>H</td>
<td>3</td>
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</tr>
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<td>3</td>
<td>3.5</td>
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</tr>
<tr>
<td>J</td>
<td>5</td>
<td>NA</td>
<td>6</td>
<td>2</td>
<td>Type 3</td>
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<td>NA</td>
<td>0</td>
<td>0.25</td>
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<tr>
<td>L</td>
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<td>NA</td>
<td>11</td>
<td>3</td>
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</tr>
<tr>
<td>M</td>
<td>4</td>
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<td>0.5</td>
<td>4</td>
<td>Type 1(2)</td>
</tr>
<tr>
<td>Median</td>
<td>4</td>
<td>2</td>
<td>3</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>

†Airway swelling severity based on a scheme suggested by Grant et al.\(^7\); assessed by ED observation records, figure in brackets ( ) inferred from symptoms.

Type 1 angioedema – lip and anterior tongue involvement.

Type 2 angioedema – floor of mouth, palatal or oropharyngeal oedema.

Type 3 angioedema – laryngeal or hypopharyngeal oedema.

Patients A, B, C and J had flexible nasoendoscopy by the ENT team.

Patients A, B, C and D were intubated.

Patient J had two doses of icatibant. ED, emergency department; ENT, ear, nose and throat.

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lack of reliable history in a patient presenting acutely, lack of knowledge of the association of ACE inhibitors with angioedema, misattribution to an allergic cause and poor understanding of the time course of angioedema in those taking ACE inhibitors, in particular that the angioedema can occur after many years of use.

Patients presenting with a threatened airway need immediate assessment and monitoring in a resuscitation area. Senior ED physician involvement is mandated, with urgent consideration for airway protection by endotracheal intubation or even emergency cricothyrotomy. When airway obstruction is not deemed imminent, a trial of medical therapy is justified and if successful may avert the need for such procedures. Intubation and airway management necessitate ICU admission and carry significant morbidity and even mortality.22 Prompt recognition and targeted management of ACE inhibitor-associated angioedema with icatibant have the potential to obviate the need for airway intervention and ICU admission (either after intubation or for airway observation), and to reduce morbidity, mortality and overall hospital length of stay.

Although type 1 angioedema is not itself dangerous and may stabilise and regress without active treatment, in some cases, it can progress to more extensive airway involvement. Type 2 or 3 angioedema threatens the airway,7 and icatibant is likely to avert the need for intubation if given early. As icatibant is a high-cost product (currently AUD $2571.70), our protocol required ED consultation with the immunologist for a joint decision on the appropriateness of its use. Since icatibant is currently registered only for HAE, its use for ACE inhibitor angioedema is ‘off-label’ and informed consent must be obtained and documented in the patient’s clinical records.

Almost one third of patients (n = 4) were intubated at the discretion of either the emergency physician or intensivist, based on their clinical progression. Icatibant would be unsuitable in any patient with imminent airway closure, due to the time to onset of action of around 30–60 min, and cannot replace immediate experienced airway support.

Our study is consistent with the report of Bas et al. in 2010.21 In that series, none of the eight patients with acute ACE inhibitor-associated angioedema successfully treated with a single subcutaneous injection of icatibant required tracheal intubation or tracheotomy. The mean time to first symptom improvement and to complete symptom relief was 50.6 min and 4.4 h respectively. The same study also retrospectively assessed the clinical course of 47 consecutive patients with ACE inhibitor-associated angioedema, and found that without icatibant, the mean time to complete symptom relief was 33 h. Among those 47 patients, two required intubation and three received a tracheotomy.

There is an unmet need for novel therapies targeted to treatment of acute ACE inhibitor-associated angioedema.24 This need is potentially met by icatibant, which is likely to be cost-effective compared with ICU admission. Icatibant is generally well tolerated with only minor local injection site irritation. Despite the theoretical cardiovascular risks associated with bradykinin blockade, there have been no reported serious adverse events.

Conclusion

This is the first Australian case series reporting icatibant for severe ACE inhibitor-associated angioedema, under a standard protocol with consultation between senior ED physicians and immunologists. Our experience suggests that icatibant is effective for adrenaline-unresponsive acute upper airway angioedema involving the larynx or oropharynx in a patient on an ACE inhibitor. This is now supported by a recent small randomised controlled trial25 that found that the time to complete resolution of oedema was significantly shorter with icatibant than with glucocorticoid and antihistamine. Currently, the use of icatibant for this indication is off-label and it is an expensive product although with timely and appropriate use it may be cost-effective. This report provides information to guide the optimal clinical pathway for the use of appropriate medical therapy and procedural intervention in acute ACE inhibitor-associated airway angioedema.

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Conditions associated with extreme hyperferritinaemia (>3000 μg/L) in adults
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Key words
haemophagocytic lymphohistiocytosis, ferritin, hyperferritinaemia.

Abstract

Background: The clinical significance of extreme hyperferritinaemia has come under scrutiny with the increasing recognition of haemophagocytic lymphohistiocytosis (HLH) in adults. Most studies of hyperferritinaemia have focused on serum ferritin greater than 1000 μg/L, often in ambulatory patients. The conditions associated with more extreme hyperferritinaemia are poorly understood.

Aims: To examine conditions associated with extreme hyperferritinaemia greater than 3000 μg/L in acutely ill adults at a quaternary care hospital.

Methods: Patients with serum ferritin greater than 3000 μg/L at Vancouver General Hospital between 1 August 2011 and 1 August 2012 were identified. Those over 18 years of age and with clinical data available were included in the study.

Results: Eighty-three subjects were identified. Twenty-one cases (25%) were due to transfusional iron overload, 16 (19%) due to liver disease and 15 (18%) due to mixed factors. Haemophagocytic lymphohistiocytosis (HLH) was diagnosed in six of 83 patients (7%) with ferritin greater than 3000 μg/L, but six of eight patients (75%) with ferritin greater than 20 000 μg/L.

Conclusions: Extreme hyperferritinaemia greater than 3000 μg/L is uncommon in adult patients. The highest serum ferritin values are seen in HLH, but the differential diagnosis for serum ferritin greater than 3000 μg/L remains broad with iron overload and liver disease being the most common causes.

Introduction

Ferritin is the major intracellular iron storage protein responsible for sequestering iron to prevent oxidative damage.1 Small amounts of ferritin are also present in serum where the reference range varies greatly (e.g. 15–300 μg/L) and the distribution best fits a log-normal model.2,3 Low serum ferritin is specific for iron deficiency, whereas high serum ferritin, or hyperferritinaemia, is non-specific and associated with iron overload, inflammation, liver disease or some combination thereof. Traditionally, the source of serum ferritin has been a mystery,1 but is now known in murine models to derive primarily from macrophages through a non-classical lysosomal secretory pathway.4 Thus, although serum ferritin is generally used to measure body iron stores, it may more specifically reflect macrophage iron status. Extreme hyperferritinaemia, which for the purpose of this report will be defined as serum ferritin greater than 3000 μg/L, is garnering increasing interest as a diagnostic test for haemophagocytic syndromes. In children, serum ferritin greater than 3000 μg/L is considered suspicious for haemophagocytic lymphohistiocytosis (HLH),5 and greater than 10 000 μg/L is highly specific for HLH.6

In adults, ferritin greater than 10 000 μg/L has also been described as ‘pathognomic’ for haemophagocytic syndromes, histiocytic malignancies and adult-onset Still disease.7 However, the perceived specificity of extreme hyperferritinaemia in adults for haemophagocytic syndromes is based on expert opinion and extrapolation from paediatric studies rather than published data. More specific markers of T-cell expansion and macrophage activity, such as sIL2rα and sCD163, have been studied in haemophagocytic syndromes, but are not as readily available in most centres as serum ferritin.

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In fact, numerous case reports and small studies describe extreme hyperferritinaemia in adults in a variety of conditions other than HLH (Table 1). A wider range of conditions associated with highly elevated ferritin is expected in adults compared to children, given the higher baseline iron stores, as well as the higher prevalence of iron overload, liver disease and inflammatory conditions. Historically, studies of hyperferritinaemia in adults have focused on the association of mild to moderate hyperferritinaemia with liver disease and haemochromatosis. One retrospective study of 95 patients with ferritin greater than 1000 μg/L revealed liver and renal disease to be the most common associated conditions and did not report any cases of HLH. Another study of 199 patients with ferritin over 1500 μg/L also emphasised the prevalence of renal disease and haematologic conditions and did not mention any cases due to haemophagocytic syndromes. Given the increasing recognition of HLH in adults and the perceived specificity of highly elevated ferritin as a commonly available marker of haemophagocytosis, a careful examination of the various causes of extreme hyperferritinaemia is warranted. A retrospective study at Vancouver General Hospital was therefore performed to examine conditions associated with serum ferritin >3000 μg/L.

### Methods

The Vancouver General Hospital (VGH) Sunset laboratory database was searched retrospectively for all ferritin values over 3000 μg/L between 1 August 2011 and 1 August 2012 with no knowledge as to the clinical indication for ordering the test. The VGH Patient Care Information System (PCIS) clinical database, British Columbia Cancer Agency database and VGH Division of Haematology patient records were then searched to obtain clinical information. Inclusion criteria were age over 18, clinical data available in the above databases and peak serum ferritin >3000 μg/L. Descriptive statistics were collected for patient age, sex, peak ferritin, blood counts at time of ferritin peak and liver profile. The study was approved by the University of British Columbia Clinical Research Ethics Board. The study was exempt from requiring individual patient consent. All patient data were de-identified and unique patient numbers generated for data analysis.

Conditions associated with hyperferritinaemia were identified from the literature (Table 1) and used to generate a list of 14 categories: Haemophagocytic lymphohistiocytosis, infection, inflammation, liver disease, haemochromatosis (hereditary), transfusions (defined as a transfusion history ≥10 units of red cells), adult-onset Still disease, renal failure, haematologic malignancy, solid organ malignancy, autoimmune/connective tissue disease, haemoglobinopathy, mixed and unknown. Following the review on clinical and laboratory data, patients were assigned by AW and LC to one of these categories by most likely reason for ferritin evaluation, and significant contributing factors were noted. Additional secondary diagnoses were recorded. When it was unclear why the ferritin was elevated patients were assigned to the ‘unknown’ category, while patients with multiple reasons without a likely primary aetiology were assigned to the ‘mixed’ category.

Ferritin assays were performed on a Siemens Vista chemistry analyser using an immunoassay sandwich with luminescent oxygen channeling assay (LOCI) technology. Linear data are available to 2000 μg/L followed by automated dilutions up to 1/20 giving a ferritin of 40 000 μg/L with confirmed linearity. Manual dilutions further than 1/20 (i.e. for values beyond 40 000 μg/L) were not routinely done, and these values were only reported as >40 000 μg/L.

### Results

There were 25 600 ferritin assays performed at Vancouver General Hospital during the study period, and 141 patients had peak ferritin values over 3000 μg/L.
Patients had a serum ferritin greater than 3000 μg/L. Clinical data were available for 83 patients, and these were included in the study. Demographic data are shown in Table 2.

Fifty-seven of 83 patients (69%) had multiple conditions associated with their hyperferritinaemia with a mean of 2.2 associated conditions per patient. The most common conditions associated with ferritin over 3000 μg/L (Fig. 1) were transfusions (21 patients, 25%), liver disease (16 patients, 19%; Table 3), mixed causes (15 patients, 18%) and infection (10 patients, 12%). HLH accounted for only six patients (7%). Three patients had solid organ malignancy (metastatic), and two had haematologic malignancy as the primary cause, although another 17 patients had haematologic malignancy as contributing factors. Two cases of haemochromatosis (hereditary) were identified. One patient had newly diagnosed human immunodeficiency virus complicated by tuberculosis. Of the four unknown cases, one patient died from bone marrow failure and distributive shock from colchicine toxicity, and one had a complex history of mechanical heart valves, haemodialysis dependence, stable hepatitis B and vasculitis, but the cause of his acute final illness was not clear. Two patients were suspected of having haemochromatosis (hereditary) with transferrin saturations >90%, but HFE gene testing results were not available.

The number of associated conditions decreased with higher ferritin cut-offs. There were 25 patients with a ferritin over 10 000 μg/L (Fig. 2), and the most common associated conditions in this group were liver disease (seven patients, 28%), HLH (six patients, 24%) and transfusions (four patients, 16%). The remaining cases were associated with infection (n = 4), mixed (n = 2), adult onset Still disease (n = 1) and inflammation (n = 1) related to a vancomycin drug reaction. Eight patients had hyperferritinaemia >20 000 μg/L. HLH was the associated condition in six (75%), infection due to clostridial myonecrosis and septic shock in one, and mixed in one

Table 2. Clinical features of patients

<table>
<thead>
<tr>
<th>Ferritin &gt;3000 μg/L</th>
<th>Ferritin &gt;10 000 μg/L</th>
<th>Ferritin &gt;20 000 μg/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total patients</td>
<td>83</td>
<td>25</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>47</td>
<td>11</td>
</tr>
<tr>
<td>Female</td>
<td>36</td>
<td>14</td>
</tr>
<tr>
<td>Mean age (range)</td>
<td>58 (19–86)</td>
<td>58 (20–82)</td>
</tr>
<tr>
<td>Mortality</td>
<td>26 (31%)</td>
<td>10 (40%)</td>
</tr>
<tr>
<td>Bone marrow biopsy</td>
<td>18 (22%)</td>
<td>10 (40%)</td>
</tr>
<tr>
<td>Transfusion dependent</td>
<td>29 (35%)</td>
<td>9 (36%)</td>
</tr>
</tbody>
</table>

Figure 1. Cause of ferritin elevation >3000 μg/L. Category: Haemophagocytic lymphohistiocytosis 7% (n = 6); infection 12% (n = 10); inflammation 4% (n = 3); liver disease 19% (n = 16); haemochromatosis 3% (n = 2); transfusions 25% (n = 21); mixed 18% (n = 15); unknown 5% (n = 4); adult onset Still disease 1% (n = 1); haematologic malignancy 2% (n = 2); solid organ malignancy 4% (n = 3).

Table 3. Patients with hyperferritinaemia due to liver disease

<table>
<thead>
<tr>
<th>Cause of liver disease</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viral hepatitis</td>
<td>4 (2 required liver transplant)</td>
</tr>
<tr>
<td>Acetaminophen overdose</td>
<td>3</td>
</tr>
<tr>
<td>Ischaemic hepatitis</td>
<td>2</td>
</tr>
<tr>
<td>Alcoholic liver disease</td>
<td>2</td>
</tr>
<tr>
<td>Idiopathic</td>
<td>2</td>
</tr>
<tr>
<td>Tuberculosis medications, metastatic adenocarcinoma, Epstein–Barr virus</td>
<td>3 (1 each)</td>
</tr>
</tbody>
</table>

Figure 2. Cause of ferritin elevation greater than 10 000 μg/L. Category: Haemophagocytic lymphohistiocytosis 24% (n = 6); infection 12% (n = 3); inflammation 4% (n = 1); liver disease 24% (n = 6); transfusions 16% (n = 4); mixed 12% (n = 3); adult onset Still disease 4% (n = 1); haematologic malignancy 4% (n = 1).
intensive care unit patient with multiple-system organ failure with baseline muscular dystrophy, transfusion-dependent bone marrow failure and recurrent infections.

Of the six patients with confirmed haemophagocytic lymphohistiocytosis, four had Epstein–Barr virus or cytomegalovirus-related HLH, one had macrophage activation syndrome associated with rheumatoid arthritis, and one had angioimmunoblastic T-cell lymphoma. Five of the patients died within 3 months of diagnosis. Several other patients were considered for possible HLH. One had rheumatoid arthritis with acute liver failure and cytopenias, positive Epstein–Barr virus titres and fungaemia, with some haemophagocytosis on bone marrow biopsy and a maximum ferritin of 8453 μg/L, but rapidly declined and died. Another patient died from disseminated intravascular coagulation from Staphylococcus aureus bacteraemia with ferritin 13 450 μg/L, cytopenias and a working diagnosis of leukaemia versus HLH. Marrow biopsy and a maximum ferritin of 8453 μg/L were not routinely diluted to report an exact value, which prevented calculation of median and mean in categories that included these values. The highest ferritin values were seen in HLH with peak ferritin greater than 40 000 μg/L in four of six patients, and >20 000 μg/L in all HLH patients with the lowest peak ferritin of 23 448 μg/L (Fig. 3). The next highest peak ferritins occurred in the mixed and infection groups, although the majority of ferritin elevations were significantly less than 10 000 μg/L. The only patient with adult onset Still disease had a ferritin of 11 836 μg/L. Using a value of 40 000 μg/L for the values above this threshold resulted in a median of 40 000 μg/L for HLH, 5631 μg/L for infection and 4905 μg/L for mixed.

**Discussion**

Prior to this study, the literature on hyperferritinaemia has focused on relatively healthy outpatients with serum ferritin >1000 μg/L. This is likely because the disease of interest has historically been HFE-related hereditary haemochromatosis, and ferritin greater than 1000 μg/L is the threshold that implies an increased risk of liver fibrosis in haemochromatosis. Increasing recognition of adult HLH in recent years has produced greater interest in the significance of highly elevated ferritin in acutely or critically ill patients. Historically, based on expert opinion and paediatric data, ferritin ≥3000 μg/L was considered specific for HLH, but this study provides empirical evidence that in adults, a wide variety of conditions, such as transfusional iron overload, liver disease and infection are associated with extreme hyperferritinaemia. The likelihood of HLH increases with hyperferritinaemia greater than 10 000 μg/L, but other conditions remain in the differential diagnosis even at this higher threshold. In fact, a recent study has shown that even hyperferritinaemia greater than 50 000 μg/L in adults is not specific for HLH, and thus the notion that extreme hyperferritinaemia at any threshold can be ‘pathognomonic’ for haemophagocytic syndromes in adults should be abolished.

This study establishes an association rather than a mechanism for extreme hyperferritinaemia. In iron overload, hyperferritinaemia is mediated by the iron responsive element, but the mechanisms of increased serum ferritin in other conditions, such as inflammation, liver disease and macrophage/histiocyte disorders is incompletely understood. Serum ferritin has been considered an acute phase reactant that increases with induction by tumour necrosis factor alpha (TNF-α) and interleukin 1-α in inflammation. Traditionally, ferritin is thought to increase five to 10-fold as an acute phase reactant, and thus a patient with a normal baseline ferritin (e.g. 15–300 μg/L for a male) would be expected to have a ferritin no higher than 3000 μg/L due to inflammation alone. However, in acute liver failure and haemophagocytic syndromes, ferritin can become markedly elevated to over 10 000 μg/L within hours. Recently, the GDF-15 pathway has been implicated in downregulating the hepcidin-ferroportin axis in HLH, facilitating efflux of iron from macrophages. The extreme hyperferritinaemia in liver failure, sepsis and 

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Figure 3 Peak ferritin for each diagnostic category. Green bars represent the patient with the highest peak ferritin level in each group. Red bars represent the patient with the lowest peak ferritin in each group. CTD, connective tissue disease; ESRD, end-stage renal disease; HLH, haemophagocytic lymphohistiocytosis; IHD, intermittent haemodialysis. 

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other inflammatory conditions may be related to macrophage expansion and activation.40,41 Whether this ‘physiological’ macrophage activation is on a spectrum with the pathological immune activation in HLH deserves further exploration.

The key limitation of this study is the lack of diagnostic certainty. Although each case was reviewed by clinicians experienced in the diagnosis and management of iron overload, haemophagocytic syndromes, liver disease and other causes of hyperferritinaemia, determining the contribution of these causes requires a degree of subjective clinical judgment. In particular, excluding haemophagocytic syndromes in acutely ill adults is very difficult and relies on pattern recognition. The finding of haemophagocytosis in bone marrow and other tissues is notoriously neither sensitive nor specific in isolation.41 Despite these limitations, this study broadens our understanding of the conditions associated with extreme hyperferritinaemia and justifies prospective studies in adult patients with extreme hyperferritinaemia examining the significance of macrophage and T-cell activation, including markers, such as sCD25 (sIL2rα) and sCD163.

**Conclusion**

Extreme hyperferritinaemia ≥3000 μg/L is uncommon in adult patients. The highest serum ferritin values are seen in HLH, but the differential diagnosis for serum ferritin over 3000 μg/L remains broad with iron overload and liver disease being the most common causes.

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Weighing up the benefits and harms of a new anti-cancer drug: a survey of Australian oncologists

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Key words
bevacizumab, everolimus, preference, decision-making, Australia.

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Abstract

Background: Little is known about the relative importance that oncologists attribute to the benefits and harms of anti-cancer drugs when considering treatment options with their patients.

Aim: To quantify the trade-offs made between overall survival, progression-free survival and adverse effects.

Methods: A web-based survey elicited importance weights for the benefits and harms of bevacizumab or everolimus. Combining the importance weights with trial-based probabilities produced a score and ranking for each treatment option.

Results: A total of 40 responses was received for the bevacizumab scenario and 32 for the everolimus scenario. All respondents regarded overall survival and progression-free survival as the most important attributes – more important than avoiding the potential harms regardless of drugs. Among the potential harms, respondents allocated the highest mean importance weight to gastrointestinal (GI) perforation and rated absolute improvement in overall survival as 1.6 times and 2.3 times as important as avoiding GI perforation in the two versions of the bevacizumab scenario respectively. For the everolimus scenario, stomatitis and pneumonitis were allocated the highest mean importance weights with absolute improvement in overall survival rated as 2.2 times as important as avoiding stomatitis/pneumonitis. All 40 respondents (100%) favoured treatment option with bevacizumab to no bevacizumab based on respondents’ determined weights for treatment attributes. The converse was found for everolimus with 22 (69%) of respondents preferring the ‘no everolimus’ option.

Conclusion: Oncologists’ preferences over the benefits and harms of treatment do, when combined with evidence of effect, influence treatment decisions for anti-cancer drugs.

Introduction

Many new anti-cancer drugs have been shown to prolong significantly progression-free survival with only a small improvement in overall survival. With those benefits comes the chance of an adverse effect. Yet patients may value small survival benefits (or the hope of small gains) sufficiently to outweigh the side effects of treatment. There are, however, limited data on how oncologists view the benefits versus harms of anti-cancer drugs.

Medical oncologists play a pivotal role in a shared decision-making process. Mismatch between physician and patient viewpoints has the potential to result in sub-optimally informed treatment decisions and could have implications for the way that information about treatment and likely subsequent outcomes is presented to patients. Therefore, it is important to understand how clinicians view the different treatment attributes of anti-cancer drugs and the value they place on benefits versus harms when considering treatment option for patients. This is especially important in situations where clinical
equipoise is sensitive to the relative preferences for benefits and harms as well as the evidence of effect.

The aim of this study was to determine the factors influencing the oncologist’s attitudes to two new anti-cancer drugs, namely bevacizumab and everolimus. Specifically, the objectives of our study were to quantify the trade-offs oncologists made between the different attributes (overall survival, progression-free survival and adverse effects) of two anti-cancer drugs and to demonstrate if there was any variability in the allocation of importance weights based on different evidence being presented.

Methods

Participants and recruitment

We surveyed members of the Medical Oncology Group Australia (MOGA), the representative body of medical oncologists in Australia to elicit their preferences for treatment attributes for bevacizumab and everolimus. Email invitations including a hyperlink to a web-based version of the survey were sent to 535 members of MOGA (comprising 70% consultants and 30% trainees) in August 2013. A reminder email was sent 1 week after the initial invitation to increase the response rate.

Questionnaire design

A web-based survey was used to ascertain a numeric weighting of the importance of overall survival, progression-free survival and adverse effects relating to a decision to start a patient on either of these anti-cancer drugs. The numeric weighting of the benefit or harm on a scale from 0 to 1 was then combined with a numeric rating of the evidence for each event (probability of an event or outcome expressed as a number from 0 to 1 derived from randomised controlled trials) to produce a score to generate a ranked list of treatment options. The higher the score, the better the option. This is an evidence- and preference-based approach to medical decision-making that was implemented using an online decision tool (known as Annalisa).

The online survey required approximately 10 min to complete. It comprised two clinical scenarios to two anti-cancer drugs: one for bevacizumab and another for everolimus. Each participant was asked to weight the importance of key attributes including overall survival, progression-free survival and adverse effects for bevacizumab and then as a separate exercise for everolimus. The survey included a demonstration video on how to use the online decision aid prior to asking respondents to completing the clinical scenarios (see Appendix for a copy of audio visual transcript on how to use Annalisa to assign importance weights for treatment attributes for bevacizumab and everolimus). Ethics approval was obtained from the ethics committee at Sydney University (protocol number: 2012/2792) as well as the Ethics Sub-Committee and Executive Committee of MOGA.

Clinical scenarios for bevacizumab and everolimus

Two versions of the bevacizumab scenario were used to test whether different sources of evidence (and hence probabilities of events occurring) made any difference to the ‘Scores’ (i.e. expected values) given oncologists’ weightings for the treatment attributes. One version was based on Hurwitz’s study of bevacizumab combined with irinotecan, fluorouracil and leucovorin (IFC) versus IFC alone in metastatic colorectal cancer. The other version was based on Saltz’s study of bevacizumab with capecitabine and oxaliplatin versus capecitabine and oxaliplatin alone in metastatic colorectal cancer. Medical oncologists who consented to participate in the study were randomly allocated to either the Hurwitz or Saltz version.

The everolimus scenario was based on a study comparing everolimus versus placebo in renal cell carcinoma.

Decision tool

The decision tool consists of three panels: (i) Weightings panel (Preferences) (ii) Ratings panel (Evidence) and (iii) Scores panel (Score) (Fig. 1).

Unlike other decision tools, Annalisa is an evidence- and preference-based approach to medical decision-making. It combines both the evidence and preferences to provide a score based on maximising the expected value. The assumed goal of this decision-making framework is to maximise benefits relative to potential harms/ side effects.

Weightings panel (preferences)

The bevacizumab scenario comprised seven key treatment attributes that described the benefits and harms of treatment with or without bevacizumab including overall survival, progression-free survival, gastrointestinal (GI) perforation (Grade 3+), bleeding (Grade 3+), venous thrombotic event, hypertension (Grade 3+) and proteinuria (Grade 3+). The everolimus scenario comprised nine key treatment attributes including overall survival, progression-free survival, stomatitis, rash, asthenia, diarrhoea, nausea and vomiting, infections and pneumonitis.
Ratings panel (evidence)

The evidence for each benefit and harm for each option was derived from published randomised controlled trials. Table 1 summarises the probability for each of the treatment attributes associated with the bevacizumab and everolimus scenarios. In the web-based survey, probabilities for treatment attributes representing the potential harms of an anti-cancer drug were expressed as a chance of avoiding that adverse event because all treatment attributes were required to be expressed as a positive attribute.

Table 1 Evidence: summary of probabilities for outcomes events† (i.e. treatment attributes) as presented in the bevacizumab and everolimus clinical scenarios

<table>
<thead>
<tr>
<th></th>
<th>Bevacizumab Hurwitz version</th>
<th>Chemotherapy with bevacizumab</th>
<th>Chemotherapy without bevacizumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>OS at 12 month</td>
<td>0.75</td>
<td>0.63</td>
<td>0.63</td>
</tr>
<tr>
<td>PFS at 6 month</td>
<td>0.75</td>
<td>0.52</td>
<td>0.52</td>
</tr>
<tr>
<td>GI perforation‡</td>
<td>0.01</td>
<td>0.00</td>
<td>0.00</td>
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<tr>
<td>G3+ bleeding‡</td>
<td>0.03</td>
<td>0.02</td>
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<td>VTE‡</td>
<td>0.19</td>
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<td>0.16</td>
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<td>G3+ hypertension‡</td>
<td>0.11</td>
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<td>0.02</td>
</tr>
<tr>
<td>G3+ proteinuria‡</td>
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<table>
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<tr>
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<th>Chemotherapy with bevacizumab</th>
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<tr>
<td>PFS at 6 month</td>
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<td>0.68</td>
<td>0.68</td>
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<tr>
<td>GI perforation‡</td>
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<tr>
<td>G3+ bleeding‡</td>
<td>0.02</td>
<td>0.01</td>
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<td>VTE‡</td>
<td>0.08</td>
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<tr>
<td>G3+ hypertension‡</td>
<td>0.04</td>
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<tr>
<td>OS at 6 month</td>
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<td>0.72</td>
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<tr>
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<tr>
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<td>0.40</td>
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<td>Rash‡</td>
<td>0.25</td>
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<td>Nausea and vomiting‡</td>
<td>0.37</td>
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<tr>
<td>Pneumonitis‡</td>
<td>0.08</td>
<td>0.00</td>
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</table>

†Bevacizumab Hurwitz version was based on Hurwitz et al. Bevacizumab Saltz version was based on Saltz et al. and everolimus scenario was based on Mortzer et al. ‡Probabilities of all adverse events were expressed as a chance of avoiding the event, that is as a probability of an event’s complement. G3+, grade 3 or worse; GI, gastrointestinal perforation; OS, overall survival; PFS, progression-free survival; VTE, venous thromboembolism.
Scores panel (scores)

The score is based on an expected value calculation; the sum of the products of the probability for each attribute (i.e. probability associated with each benefit and harm for bevacizumab or everolimus) multiplied by an individual’s importance weight for that attribute. The higher the score (expected value), the better the option.

Demographic characteristics

Respondents were asked to provide information on their gender, age, job description, years since graduation from medical school and percentage of time of working week spent in direct patient care.

Data (statistical) analysis

Descriptive statistics were used to summarise demographic variables and to describe the frequency of responses. Chi-squared tests were used to determine association between respondent characteristics and importance weights. The t test was used to determine the significance of differences between the means of relevant variables.

Results

Respondents

Overall, 98 medical oncologists went online to the survey website. Of the 60 oncologists consented to participate in the survey, 40 completed the survey. In total, 40 responses were received for the bevacizumab scenario (23 for Hurwitz version and 17 for Saltz version respectively) and 32 for the everolimus scenario. There were 31 respondents who provided demographic information, which was summarised in Table 2.

Evidence, preference-based decision-making

Bevacizumab scenario

The mean respondents’ determined importance weights for each treatment attribute for the bevacizumab scenario are summarised in Table 3. The order of importance weights from highest to lowest was identical in both versions of the bevacizumab scenario: (i) overall survival, (ii) progression-free survival, (iii) GI perforation, (iv) grade 3+ bleeding, (v) VTE (vi) grade 3+ hypertension and (vii) grade 3+ proteinuria. Moreover, the importance weights assigned by respondents for overall survival and progression-free survival were numerically higher in the Saltz version than Hurwitz version ($P = 0.05$ and $P = 0.107$ for overall survival and progression-free survival respectively). Figures 2 and 3 show the distribution of respondents’ determined importance weights for each of the treatment attributes for both versions of the bevacizumab scenario. As shown in the box plots, responding medical oncologists displayed variability in how they viewed the importance of different treatment attributes especially for overall survival and progression-free survival (note the top and bottom whiskers showing the maximum and minimum values).

Figure 4 plots each respondent’s determined importance weights for overall survival and progression-free survival. As illustrated, the scatter plot describes a positive trend between overall survival and progression-free survival regardless of clinical scenarios (i.e. for bevacizumab or everolimus). Interestingly, respondents in both versions of the bevacizumab scenario assigned similar mean relative importance weights between overall survival and progression-free survival. In summary, respondents rated absolute improvement in overall survival as 1.2 times as important as absolute improvement in progression-free survival (i.e. 0.24/0.20 = 1.2 and 0.30/0.25 = 1.2 for the Hurwitz version and Saltz version respectively).

Of all the treatment attributes representing potential harms for bevacizumab treatment, respondents allocated the highest mean importance weight to GI perforation in both versions of the bevacizumab scenario. In terms of relative importance of overall survival or progression-free survival to GI perforation, respondents in the Hurwitz

<table>
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<th>Characteristics</th>
<th>n (%)</th>
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<tbody>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>24 (77)</td>
</tr>
<tr>
<td>Female</td>
<td>7 (23)</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
</tr>
<tr>
<td>30–39</td>
<td>13 (42)</td>
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<tr>
<td>40–49</td>
<td>7 (23)</td>
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<tr>
<td>50–59</td>
<td>7 (23)</td>
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<tr>
<td>60–69</td>
<td>3 (10)</td>
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<tr>
<td>≥70</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Job type</td>
<td></td>
</tr>
<tr>
<td>Oncologist registrar/fellow</td>
<td>6 (19)</td>
</tr>
<tr>
<td>Consultant oncologist</td>
<td>23 (74)</td>
</tr>
<tr>
<td>Other</td>
<td>2 (6)</td>
</tr>
<tr>
<td>% of time of working week spent in direct patient care</td>
<td></td>
</tr>
<tr>
<td>0–50%</td>
<td>14 (45)</td>
</tr>
<tr>
<td>51–100%</td>
<td>17 (55)</td>
</tr>
<tr>
<td>Years since graduation from medical school</td>
<td></td>
</tr>
<tr>
<td>0–20 years</td>
<td>15 (48)</td>
</tr>
<tr>
<td>&gt;21 years</td>
<td>16 (52)</td>
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version rated absolute improvement in overall survival and progression-free survival as 1.6 times and 1.3 times as important as avoiding GI perforation respectively. Compared with the Hurwitz version, respondents in the Saltz version rated absolute improvement in overall survival and progression-free survival as 2.3 times and 1.9 times as important as avoiding GI perforation respectively.

The treatment option score in the decision aid is the sum of a product of evidence (probability) multiplied by
the preference weight. Combining the two components yielded the following results. For the Hurwitz version, the average score for treatment option with bevacizumab was 0.852 and without bevacizumab was 0.793 (mean difference = 0.058, 95% confidence interval (CI) = 0.045 to 0.071, P < 0.001). However, in the Saltz version, the average scores were 0.868 and 0.835 respectively (mean difference = 0.033, 95% CI = 0.025 to 0.041, P < 0.001). The mean differences in scores observed between the Hurwitz and Saltz versions were influenced by both the size of potential benefits and harms of bevacizumab (i.e. evidence, see Table 1) and the relative importance weights that respondents attached to each of the treatment attributes (i.e. clinician’s preferences, see Table 3).

During the survey, respondents were offered the opportunity to view the evidence-based probabilities in the ‘Ratings’ panel and to revise their importance weights. However, revealing the scores and or evidence-based probabilities did not alter the oncologist’s assessment of the importance of each individual attribute.

**Everolimus scenario**

A total of 32 oncologists completed the everolimus scenario. The mean respondents’ determined importance weights for each of treatment attributes are summarised in Table 3. The average scores for treatment option with everolimus and without everolimus were 0.755 and 0.766 respectively (mean difference = −0.011, 95% CI = −0.031 to 0.009, P = 0.28). Overall, there was no strong preference for treatment option with or without everolimus with 22 (69%) of respondents preferring the ‘no everolimus’ option. However, respondents who favoured treatment option with everolimus were found to attach higher importance weights to both overall survival and progression-free survival relative to attributes representing potential harms of everolimus.

Similar to the bevacizumab scenario, all respondents in the everolimus scenario rated the importance of overall survival and progression-free survival higher than any other treatment attributes of everolimus. In summary, overall survival was rated above all treatment attributes including progression-free survival. The distribution of importance weights for each of the treatment attributes associated with everolimus as assigned by the responding medical oncologists is shown in Figure 5. As with the bevacizumab scenario, the box plots show that there was variability between respondents in terms of how they weighted the treatment attributes especially for overall survival and progression-free survival.

Further, respondents in the everolimus scenario rated absolute improvement in overall survival as 1.1 times as important as absolute improvement in progression-free survival. Of all the treatment attributes representing potential harms of everolimus treatment for renal cell carcinoma, stomatitis and pneumonitis were allocated the highest mean importance weight by responding medical oncologists. In summary, respondents rated absolute improvement in overall survival and progression-free survival as 2.2 times and 2.0 times as important as avoiding stomatitis/pneumonitis.

Similar to the bevacizumab scenario, revealing the scores and or evidence-based probabilities did not alter the oncologist’s assessment of the importance of each individual attribute.

**Relationship between respondent characteristics and importance weights**

Univariate analyses were carried out to assess the relationship between respondent characteristics and the individual’s preferences (weights) for treatment attributes associated with everolimus. Results suggested that respondents’ preferences for different treatment attributes were not influenced by their individual characteristics and circumstances.

**Usefulness of Annalisa as a decision tool**

Of the respondents (n = 21), 68% agreed that an online decision tool like Annalisa could definitely or possibly
be useful in talking through treatment options with patients. Similarly, 65% of respondents \( (n = 20) \) said that their patients would find tools like Annalisa useful.

**Discussion**

Currently, there are limited data on how oncologists view the different treatment attributes of anti-cancer drugs. This paper reports on an experimental, interactive online survey used to elicit medical oncologists' preferences for treatment attributes for bevacizumab and everolimus. Respondents to our survey attached more importance to achieving the benefits (overall survival and progression-free survival) than avoiding the potential harms. Overall survival is the most important consideration in thinking about starting a new anti-cancer drug for a patient. These results highlight the importance of demonstrating survival advantage for new anti-cancer drugs and the potential implication of perceived value on new treatments that do not significantly prolong life. Recently, difficulty in demonstrating survival benefit for new anti-cancer drugs in randomised controlled trials due to confounding of cross-over/switching and availability of subsequent chemotherapies post-progression has become a contentious issue.

In addition, results of our study indicated a clear preference for using bevacizumab in first-line treatment of colorectal cancer. All 40 respondents (i.e. 100% of respondents in both versions of the bevacizumab scenario) favoured treatment option with bevacizumab to no bevacizumab. It is worth noting that although there was variability between respondents’ determined importance weights for individual treatment attributes in the Hurwitz and Saltz versions, this has no/minimal influence on the ranked treatment option for bevacizumab.

In contrast, medical oncologists in our study exhibited some degree of clinical equipoise about using everolimus as second-line treatment in renal cell carcinoma. Based on the respondents’ determined importance weights, 69% of respondents rated treatment option with everolimus ahead of no treatment with everolimus. Our study showed that respondents \( (n = 10) \) preferring treatment option with everolimus assigned higher importance weights to overall survival and progression-free survival compared with those preferring the ‘no everolimus’ option.

Based on the results of our study, it appears that respondents’ preferences for treatment option with or without everolimus were influenced by both the size of the potential benefits and harms of everolimus and the relative importance weights they assigned to each of the treatment attributes. In addition, it appears that where there are uncertainties in the evidence regarding potential benefits and harms of an anti-cancer drug, the importance weights are more likely to influence the ranked treatment options. Therefore, the value represented by an anti-cancer drug may be different in diverse individuals/groups even when presented with the same clinical evidence, that is an anti-cancer drug may not be perceived to confer as much benefit by some groups/individuals.

**Conclusion**

Ultimately, what is considered a benefit in cancer treatment should be guided by clinical evidence, as well as the preference of the patient and the clinician for the treatment option in the relevant clinical context. Given the influence that preferences for different treatment attributes could have on the perceived value of anti-cancer drugs, it is important that we have a better...
understanding of how clinicians and patients value and trade off the various benefits and harms of anti-cancer treatments. As shown in this study, treatment decision can be influenced by clinicians’ preferences and values. This is especially important in circumstances where the clinical evidence does not strongly and clearly support a particular treatment option or where a preference-sensitive decision is involved.9 Under these circumstances, the value represented by an anti-cancer drug may be different in diverse individuals/groups.

Although much effort has gone into the research of effectiveness and safety of medicines, there is limited information currently available on clinicians’ and patients’ preferences for the different treatment attributes associated with anti-cancer drugs. The elicitation of preferences for treatment options was very much part of Sackett’s original conception of evidence-based medicine.10 Therefore, it is important that clinicians’ and patients’ preferences for different treatment attributes for anti-cancer drugs are available to inform clinical decision-making.

Acknowledgements

We thank the staff from MOGA (Medical Oncology Group of Australia) who assisted with the distribution of this web survey and the oncologists who participated in the study. We also thank Professor Jack Dowie (London School of Hygiene and Tropical Medicine) for assisting with the setup of the Annalisa scenarios and Associate Professor Patrick Kelly (School of Public Health, University of Sydney) for reviewing the statistical analysis of this paper.

References


Appendix

The audiovisual transcript on how to use Annalisa to assign importance weights for treatment attributes in the clinical scenarios

We are interested in how oncologists weigh up the benefits and harms of anti-cancer drugs. On the screen in front of you is a tool for eliciting the views of expert medical oncologists about the relative importance of various attributes of the anti-cancer drug bevacizumab. The tool consists of three panels. The ratings of probabilities panel captures the evidence; the weightings panel captures the importance or preferences that you as a clinician or the patients attach to the benefits and harms of the drugs and the Scores panel presents an opinion about which options is best. But the first task is to outline the benefits and harms of treatment with the drug. Here we capture those in term of progression-free survival at 6 month, overall survival at 12 month, avoiding a grade 3 or worse gastrointestinal perforation, avoiding grade 3 or worse gastrointestinal perforation, avoiding grade 3 or worse gastrointestinal perforation, avoiding grade 3 or worse gastrointestinal perforation.
worse bleed, avoiding venous thromboembolism and avoiding grade 3 or worse hypertension and proteinuria. So the first and most important task is to summarise the evidence of the benefits and harms of bevacizumab. We do this in the bottom panel. The numbers here represent the probabilities of events associated with each of the benefits and the evidence of effects. So in this particular example, the probability of a patient taking bevacizumab achieving progression-free survival at 6 months is 75% in the group taking the drug and 52% for those who do not take the drug. The probability of avoiding a GI perforation is 98.5% in the beva group and 100% in the no beva group. In other words, there is approximately 1% risk of a GI perforation when taking bevacizumab but we are expressing the number as a chance of avoiding a perforation. The probabilities for all the adverse events are expressed as a chance of avoiding the event. So where do the numbers come from? In this particular example, the numbers come from a study published by Hurwitz et al. of bevacizumab. So having summarised the probabilities of the benefits and harms at the bottom panel, we turn our attention next to the middle panel-Weightings. The weightings represent the relative importance that you attach to each attribute compared with other benefits and adverse effects. For example, if you rate importance of progression-free survival at 0.8 and importance of avoiding Grade 3 hypertension or worse at 0.4, then you are saying that progression-free survival is twice as important as avoiding G3 hypertension when thinking of whether to include bevacizumab with chemotherapy treatment. You are weighing up the relative importance of benefits versus harms. The top panel, the Scores show which option is best. The score is a straight multiplication of the probabilities in bottom panel and your importance weights from the middle panel all summed together. The longer the bar, the better the option. Note what happens when you move the blue bar to the left or the right, the Scores panel change. So the relative importance that you attach to each of the attributes will influence which option is best. How much the score changes is going to depend on the difference in the probabilities between the options as well as your own importance weights. So your task in this survey is to set importance weights for each of the benefits and harms and tell us what’s important to you in thinking about whether to include bevacizumab to the chemotherapy regimen.
Long-term effectiveness of a community-based model of care in Māori and Pacific patients with type 2 diabetes and chronic kidney disease: a 4-year follow up of the DElay Future End Stage Nephropathy due to Diabetes (DEFEND) study

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Key words community care, dialysis, hypertension, survival, type 2 diabetes.

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Abstract

Background/Aim: The Delay Future End Stage Nephropathy due to Diabetes study was a randomised controlled trial of Māori and Pacific patients with advanced diabetic nephropathy, comparing a community-based model of care with usual care. The intervention group achieved lower blood pressure (BP), proteinuria and less end-organ damage. After the intervention ended, all patients reverted to usual care, and were followed to review the sustainability of the intervention.

Methods: A retrospective observation of 65 patients (aged 47–75 years) with type 2 diabetes, hypertension, chronic kidney disease 3/4 and proteinuria (>0.5 g/day) previously randomised to intervention/community care or usual care for 11–21 months. Follow up thereafter was until death, end-stage renal disease (ESRD) (estimated glomerular filtration rate (eGFR) ≤ 10 mL/min/1.73 m²)/dialysis or 1 February 2014. Primary end-points were death and ESRD/dialysis. Secondary outcomes were annualised glomerular filtration rate decline, non-fatal vascular events and hospitalisations.

Results: Median (interquartile ranges (IQR)) post-trial follow up was 49 (21–81) months and similar in both groups. The median (IQR) eGFR decline was −3.1 (−5.5, −2.3) and −5.5 (−7.1, −3.0) mL/min/year in the intervention and usual care groups respectively (P = 0.11). Similar number of deaths, renal and vascular events were observed in both groups. At the end of follow up, the number of prescribed antihypertensive medications was similar (3.4 ± 1.0 vs 3.3 ± 1.4; P = 0.78). There were fewer median (IQR) hospital days (8 (3, 18) vs 15.5 (6, 49) days, P = 0.03) in the intervention group.

Conclusions: Short-term intensive BP control followed by usual care did not translate into reduction in long-term mortality or ESRD rates, but was associated with reduced hospitalisations.

Introduction

In New Zealand, diabetic kidney disease is the most common cause of end-stage renal disease (ESRD) requiring renal replacement therapy (RRT). It is particularly prevalent in Māori and Pacific people, with a 12–14-fold increased incidence of ESRD compared with non-Māori. Furthermore, patients with diabetes have a greater risk of cardiovascular mortality compared with non-diabetic patients, with an excess risk in those with renal dysfunction.

Progression to ESRD is strongly associated with proteinuria and hypertension. These are characteristics commonly found in Māori and Pacific patients with diabetic nephropathy, who have a faster rate of glomerular filtration rate (GFR) decline and are more likely to develop ESRD than other ethnic groups in New Zealand. This increased risk is attributed to a higher prevalence of obesity, poorer glycated haemoglobin (HbA1c), higher
smoking rates in Māori, family history of renal disease, higher levels of albuminuria and earlier onset of type 2 diabetes. Poorer health outcomes in Māori and Pacific patients may be associated with a high proportion of unmet need for primary healthcare due to transport and cost limitations, and inability to get appointments with their usual primary care physicians in a timely fashion. Previous community-based interventions have shown promising results when compared with conventional approaches in the management of chronic diseases. Hill et al. demonstrated a beneficial effect on blood pressure control, surrogate cardiac and renal markers in disadvantaged African American men following a 3-year intervention. However, no long-term outcomes have been reported. Similarly, cultural considerations in implementing healthcare interventions in Māori and Pacific patients which involved family or community groups were more likely to succeed with improved patient involvement and adherence.

Proteinuria is an important predictor of ESRD and attaining remission of this has been observed to reduce substantially the development of ESRD and improve life expectancy in patients with diabetes and overt proteinuria. Patients with type 2 diabetes have a high prevalence of left ventricular hypertrophy (LVH) which heightens their risk of premature cardiac mortality and may be reduced with normalisation or regression of LVH, associated with BP and weight reduction.

The DElay Future End Stage Nephropathy due to Diabetes (DEFEND) study was a 12-month randomised controlled trial (RCT) that tested a novel community approach to try and overcome some of these recognised barriers to care that lead to poor health outcomes in Māori and Pacific people. Sixty-five Māori and Pacific patients, with uncontrolled hypertension and stage 3 or 4 chronic kidney disease (CKD) secondary to diabetic nephropathy, were randomly assigned either to a community-based intervention (n = 33) or usual care (UC) (n = 32). The intervention group received monthly home visits from ethnic-concordant healthcare assistants who were supervised by a nurse coordinator to optimise BP. Both groups continued to receive care by primary healthcare providers, and secondary care specialist diabetologists and renal clinics.

At the start of the study, all patients received comprehensive education and advice on regular exercise, smoking cessation, reduced dietary salt intake, and the importance of optimal BP control and medication adherence. At 12 months, the intervention group achieved a significantly lower BP compared with patients managed solely by UC (140/78 vs 149/77 mmHg, P < 0.05). This short-term community intervention resulted in a reduction in 24 h urinary protein excretion from baseline (−1.4 ± 2.6 g vs +0.1 ± 2.8 g, P = 0.04), and statistically significant echocardiographic changes from baseline. The mean LV mass of patients in the intervention group remained unchanged compared with an increased mean LV mass in the UC group at 12 months – two important determinants of renal and cardiovascular outcomes. Following the completion of the intervention, all patients reverted to UC only.

The aim of this follow-up post-trial study was to compare the longer-term outcomes between the intervention and UC groups so as establish whether the effect of the short-term community intervention would translate into measurable longer term benefits despite return to usual care.

Methods

The DEFEND trial was conducted at the University of Auckland, Department of Medicine. The details of the study’s design and methods have been previously published. The original study was planned as a 2-year intervention, but due to slow recruitment, it was curtailed and outcomes for patients following the first 12 months of intervention were reported in the DEFEND study. Some patients had however been in the intervention study for up to 21 months (median 17 months, range 11–21 months).

We report on the outcomes after the intervention was completed and when all patients had reverted to UC. Ethics approval was obtained from both the local ethics committee, and Māori and Pacific Island Health Services in the community and hospital. Patients had previously provided written informed consent.

Data source and patients

Three patients in the intervention group had reached study end-points during the 12 months of the initial study. One patient was commenced on dialysis within 7 months of recruitment, one died of cancer at 6 months and another had a cardiac arrest at 10 months. We conducted a retrospective follow-up study of the remaining 62 patients from the DEFEND cohort.

Each patient had a unique hospital identifier that was linked to their hospital and clinic records, dispensed prescriptions and mortality data. Using these hospital records, we recorded clinic HbA1c, retinopathy and smoking status, serum creatinine, estimated GFR (eGFR) and prescribed antihypertensive medications. We measured eGFR using the four-component Modification of Diet in Renal Disease equation and recorded HbA1c measurements only when corresponding haemoglobin
levels were >100 g/L to correct for renal anaemia in patients with CKD. Patients were followed up until a renal event (a composite outcome of ESRD defined as eGFR ≤10 mL/min/1.73 m² or RRT), death or 1 February 2014.

**Study outcomes**

The primary end-points were all-cause mortality or a composite renal event (ESRD or RRT). Secondary outcomes included annualised eGFR decline (defined as the difference between eGFR at recruitment to the DEFEND study and at the end of follow up, divided by the duration of follow up), inpatient hospital days and a composite end-point of macrovascular complications prior to ESRD. The latter consisted of cardiovascular events (non-fatal myocardial infarction, heart failure, coronary artery bypass graft and percutaneous coronary angioplasty), cerebrovascular events (ischaemic strokes and transient ischaemic attacks) and peripheral vascular disease (angioplasty, bypass and amputation). Patients were censored when they had reached the composite end-point of RRT/ESRD, death or when lost to follow up.

**Statistical analysis**

Statistical analysis was performed using STATA software (version 13.1; StataCorp, College Station, TX, USA). Continuous variables are expressed as mean (± standard deviation) and were compared using Student’s t-tests or analysis of variance as appropriate. Medians are presented with interquartile ranges (IQR) and compared using Mann–Whitney test. Categorical variables are expressed as proportions and were compared using the X² test. P < 0.05 was considered significant and all tests were two tailed. Kaplan–Meier cumulative estimates were conducted to compare the primary end-points of death and renal event between the two groups, censoring for loss of follow up or the end of this post-trial study.

**Results**

The median length of intervention during the RCT was 17 months (range 11–21 months) with subsequent median post-trial follow up of 48 (IQR 20–83) and 52 months (IQR 25–68) in the intervention and UC groups respectively (P = 0.98). Characteristics of the patients at recruitment, at 12 months of the study and at the end of follow up are shown in Table 1. No significant intergroup differences were observed for HbA₁c, haemoglobin level, eGFR, number of antihypertensive medication prescribed, smoking and retinopathy status at the end of the post-trial follow up. At the end of the follow up, the proportion of patients with a smoking history and retinopathy status were similar to that at baseline.

**Primary outcomes**

Four years following the DEFEND study and cessation of intervention, the event rate for the composite outcome of all-cause mortality or renal events was high, affecting 46 (74%) patients in this cohort and was similar in both groups (Table 2). Six patients in the intervention group had died – four of malignancy, one cardiac and one unknown. Ten patients in the UC group had died – four related to ESRD, one malignancy, one cardiac, one multi-organ failure, one sepsis and two from unknown causes, with a trend towards an increased ESRD-related mortality in the UC group (P = 0.045).

A similar proportion of patients from both groups were established on dialysis or reached ESRD: 15 of 30 (50%) patients from the intervention group, and 15 of 32 (47%) patients from the usual care group.

**Table 1** Comparison of HbA₁c, eGFR and number of antihypertensive agents between the intervention and usual care group at baseline, 12 months and at the end of follow up after the completion of intervention, and when all patients had reverted to usual care

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<th>Usual care group</th>
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<td></td>
<td>Baseline (n = 33)</td>
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<tr>
<td>Follow up, months (IQR)</td>
<td>47.5 (20.25, 82.5)</td>
<td>52 (24.5, 68)</td>
</tr>
<tr>
<td>HbA₁c, %</td>
<td>8.3 ± 1.6</td>
<td>8.0 ± 1.9</td>
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<tr>
<td>eGFR, mL/min/1.73 m²</td>
<td>67 ± 17</td>
<td>63 ± 20</td>
</tr>
<tr>
<td>No. of antihypertensive agents, n</td>
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<td>33 ± 17</td>
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</tbody>
</table>

*P < 0.05 (Intervention vs usual care group at 12 months). Findings are expressed as mean ± SD unless otherwise stated. eGFR, estimated glomerular filtration rate (4-point Modification of Diet in Renal Disease (MDRD) calculation); HbA₁c, glycated haemoglobin; IQR, interquartile range. Baseline and 12 months characteristics have been previously reported in the DEFEND study. Four patients in the usual care group who had initially been lost to follow up at 12 months had available medical records and are reported in this follow-up study.
patients from the UC group ($P = 0.81$). At the end of post-trial follow up, the median rate of annualised eGFR decline from baseline was similar in both groups ($−3.1 \text{ (−5.5, −2.3)} \text{ mL/min/year}$, $P = 0.11$) (Table 2). There was no survival or renal advantage demonstrated for patients who received community-based intervention over UC during follow up from the time of recruitment (Fig. 1).

Patients in the intervention group were divided into three groups according to the duration of the intervention received. Ten patients received 11–16 months, 12 patients 17 months and 8 patients 18–21 months of intervention. There was no significant difference observed for outcomes of all-cause mortality ($P = 0.90$) or renal events ($P = 0.067$) between both groups.

**Secondary outcomes**

A total of 33 macrovascular complications occurred, affecting 28 patients (11 from the intervention group and 17 patients from the UC group). These were predominantly cardiovascular events and occurred equally in both groups ($P = 0.13$). Two patients in the intervention group and three in the UC group suffered from two separate vascular events respectively.

There were fewer inpatient hospital days in the intervention group (median (IQR) 8 (3–18) vs 16 (6–49) days; $P < 0.05$) compared with that observed in the UC group during the post-trial follow up (Table 2). The number of antihypertensive medications prescribed in both groups was comparable at the end of the study ($P = 0.71$) (Table 1), with a similar proportion of patients in both groups on either angiotensin-converting-enzyme inhibitors (ACEi) or angiotensin II receptor blockers (ARB) (97% vs 88%, $P = 0.19$) and diuretics (63% vs 66%, $P = 0.85$).

**Table 2.** Comparison of clinical outcomes between the intervention and usual care groups at the end of post-trial follow up

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Intervention (n = 30)</th>
<th>Usual care (n = 32)</th>
<th>$P$-value</th>
<th>Relative risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary composite end-points†</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. patients (%)</td>
<td>6 (20%)</td>
<td>10 (31%)</td>
<td>0.31</td>
<td>0.65 [0.3–1.5]</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>0 (0%)</td>
<td>4 (12.5%)</td>
<td>0.045</td>
<td></td>
</tr>
<tr>
<td>Renal deaths</td>
<td>1 (3%)</td>
<td>1 (3%)</td>
<td>0.96</td>
<td></td>
</tr>
<tr>
<td>Cardiovascular deaths</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal events</td>
<td>15 (50%)</td>
<td>15 (47%)</td>
<td>0.81</td>
<td>1.1 [0.6–1.8]</td>
</tr>
<tr>
<td><strong>Secondary composite end-point‡</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. patients (%)</td>
<td>11 (37%)</td>
<td>17 (53%)</td>
<td>0.12</td>
<td>0.7 [0.4–1.2]</td>
</tr>
<tr>
<td>Total no. macrovascular complications</td>
<td>13 (43%)</td>
<td>20 (62.5%)</td>
<td>0.13</td>
<td>0.7 [0.4–1.1]</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>8 (27%)</td>
<td>12 (37.5%)</td>
<td>0.36</td>
<td>0.7 [0.3–1.5]</td>
</tr>
<tr>
<td>Cerebrovascular</td>
<td>2 (7%)</td>
<td>2 (6%)</td>
<td>0.95</td>
<td>1.1 [0.2–7.1]</td>
</tr>
<tr>
<td>Peripheral vascular</td>
<td>3 (10%)</td>
<td>6 (19%)</td>
<td>0.33</td>
<td>0.53 [0.2–1.9]</td>
</tr>
<tr>
<td><strong>Annualised eGFR decline, mL/min/1.73 m²/year, median (IQR range)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline-12 months</td>
<td>$−1.8 \text{ (−6.9, 1.8)}$</td>
<td>$0.3 \text{ (−5.7, 6.7)}$</td>
<td>0.15</td>
<td></td>
</tr>
<tr>
<td>Baseline-end of study</td>
<td>$−3.1 \text{ (−5.5, −2.3)}$</td>
<td>$−5.5 \text{ (−7.1, −3.0)}$</td>
<td>0.11</td>
<td></td>
</tr>
<tr>
<td>Inpatient hospital days, median (IQR range)</td>
<td>$8 \text{ (3, 18)}$</td>
<td>$15.5 \text{ (6, 49)}$</td>
<td>0.025</td>
<td></td>
</tr>
</tbody>
</table>

†Primary composite end-point: all-cause mortality or renal events (composite of ESRD defined as $<10 \text{ mL/min/1.73 m²}$ and/or RRT). ‡Secondary composite end-point = non-fatal and fatal cardiovascular, cerebrovascular or peripheral vascular disease. eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; RRT, renal replacement therapy.

Discussion

In this 4-year post-trial follow up of the DEFEND study, we evaluated the longer term impact of intensive BP control over 11–21 months in patients with type 2 diabetes and CKD 3/4, delivered through an integrated, community-based model compared with UC.

Although patients in the intervention group achieved lower BP, less proteinuria and no progression of LV hypertrophy at 12 months when compared with those in the UC group, this did not translate into sustained and improved clinically meaningful outcomes after reverting to routine care.

In our study, 74% of patients reached the end-points of mortality or ESRD/RRT with no survival or renal difference between both groups. Although less than 20% of patients had documented pre-existing cardiac disease at baseline, 32% of patients had suffered a cardiovascular event by the end of our follow up, with a non-significant 28% relative reduction in event risk for patients who had received the intervention. The proportion of cardiovascular events in the DEFEND cohort, particularly in the intervention group, was similar to that seen in the
Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) study that affected 33% of patients. The high renal event rate was unsurprising as high levels of albuminuria and lower GFR are independent and synergistic predictors of progression of renal disease. The mean rate of GFR decline in this population appears to be comparable to that observed in a similar cohort with type 2 diabetes and macroalbuminuric CKD 2, but who had higher renal reserve at baseline. In that study, an annual eGFR decline of 5.2 mL/min/1.73 m² was reported, with only 54% of patients on an ACEi or ARB. When compared with a subgroup of patients from the DIYabetes MElitus Treatment for Renal Insufficiency Consortium (DIAMETRIC) database with similar baseline eGFR, renal events occurred at a higher rate in our study.

Overall, we found a 26% mortality rate over the 4.8-year follow up, which is similar to the annualised total mortality of 4.6% observed in the follow-up study from the DIAMETRIC database where only 25% of their patients had macroalbuminuria and eGFR ≤ 45 mL/min/1.73 m². On the contrary, the ADVANCE cohort showed a statistically significant but perhaps a less clinically meaningful 9% reduction in mortality in patients who had received BP lowering intervention.

The poorer renal outcomes in our study were likely related to the advanced CKD stages at the time of recruitment. The improved management of cardiovascular diseases in patients with type 2 diabetes in recent years has also increased patient survival long enough to reach ESRD such that it now exceeds fatal cardiovascular events to become a common outcome in those with advanced diabetic nephropathy. Furthermore, Māori

Figure 1 (a) Kaplan–Meier cumulative survival estimates of community (n = 33) and usual care (n = 32) groups from recruitment, adjusted for HbA₁₀₀, eGFR and presence of diabetic retinopathy (P = 0.53), and (b) Kaplan–Meier cumulative renal survival estimates of community (n = 33) and usual care (n = 32) groups from recruitment, adjusted for HbA₁₀₀, eGFR and presence of diabetic retinopathy (P = 0.80). (—), Intervention/community care; (---), usual care.
and Pacific people have additional metabolic risk factors associated with poorer renal prognosis.\textsuperscript{6,19} Severe retinopathy, a marker of microvascular damage, was also present in more than half of our patients. Diabetic retinopathy, together with high levels of proteinuria, is associated with higher rates of ESRD and mortality.\textsuperscript{12,20}

The number of prescribed anti-hypertensive medications between both groups was similar at the completion of the post-trial follow up. It would appear that in the period after the trial, both primary and secondary care clinicians have taken a more active approach in achieving BP targets. While this may partly be a consequence of their patients’ involvement in the DEFEND trial, it more likely relates to an increase in the overall awareness of the importance of BP control. As a result, this may have minimised the difference in study outcomes between the intervention and UC groups upon return to routine care.

We found fewer inpatient days in the intervention group associated with fewer hospitalisations during the post-trial follow up. The significance of this finding is unclear and it did not lead to any survival or renal advantage. It is conceivable that the more intensive education provided to the intervention group resulted in improved health literacy, leading to better overall personal care and timely access to primary healthcare. Based on this finding, implementation of community-based interventions could lead to greater healthcare savings. Community-based programmes are integral to the management of chronic illness. A systematic review of 15 studies involving home visiting programmes (of varying duration and intensity) in older people showed that such interventions were effective in reducing mortality and admissions into permanent institutional care, and possibly fewer hospitalisations although the latter was not statistically significant.\textsuperscript{17} Further research is still required to establish an optimal duration and intensity of community-based interventions in delivering effective and efficient healthcare to high-risk groups.

There are several limitations to this study. Firstly, the small sample size limits interpretable significance of associated treatment effects. However more than 50\% of patients in the DEFEND study had reached ESRD by the end of the post-trial follow up, confirming the poor prognosis normally associated with diabetes and CKD. Secondly, the lack of systematic post-trial BP and urine PCR measurements prevents correlation of these clinical parameters to outcomes. However, this study was aimed at reviewing concrete and meaningful outcomes which could emerge from a short-term trial of intensive BP control. Thirdly, it is not possible to assess medication adherence during the follow-up phase, which would affect the success of the intervention.

**Conclusion**

Current efforts are targeted towards identification and prediction of CKD progression\textsuperscript{17} which needs to be matched by a systematic, effective and economical management process to retard the progression towards ESRD. The cardiovascular and renal benefits seen at 12 months in the DEFEND cohort did not translate into longer term improved clinical outcomes and highlights the management difficulties faced with these high-risk patients in clinical practice. To achieve improved outcomes, intensive community-based interventions may need to be commenced earlier and maintained longer term. However, the costs and benefits of such a strategy would need to be explored before wider adoption of this approach can be recommended.

**Acknowledgements**

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Patients’ estimates of their sleep times: reliability and impact on diagnosis of obstructive sleep apnoea

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Key words
apnoea–hypopnoea index, obstructive sleep apnoea, sleep latency, total sleep time, type 2 polysomnography.

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Abstract
Background: Home polysomnography (PSG) is an alternative method for diagnosis of obstructive sleep apnoea (OSA). Some types 3 and 4 PSG do not monitor sleep and so rely on patients’ estimation of total sleep time (TST).

Aim: To compare patients’ subjective sleep duration estimation with objective measures in patients who underwent type 2 PSG for probable OSA.

Methods: A prospective clinical audit of 536 consecutive patients of one of the authors between 2006 and 2013. A standard questionnaire was completed by the patients the morning after the home PSG to record the time of lights being turned off and estimated time of sleep onset and offset. PSG was scored based on the guidelines of the American Academy of Sleep Medicine.

Results: Median estimated sleep latency (SL) was 20 min compared with 10 min for measured SL (P < 0.0001). There was also a significant difference between the estimated and measured sleep offset time (median difference = −1 min, P = 0.01). Estimated TST was significantly shorter than the measured TST (median difference = −18.5 min, P = 0.002). No factors have been identified to affect patients’ accuracy of sleep perception. Only 2% of patients had a change in their diagnosis of OSA based on calculated apnoea–hypopnoea index.

Conclusions: Overall estimated TST in the patients with probable OSA was significantly shorter than measured with significant individual variability. Collectively, inaccurate sleep time estimation had not resulted in significant difference in the diagnosis of OSA.

Introduction
Obstructive sleep apnoea (OSA) is a common sleep disorder with recurrent complete or partial collapse of the upper airway leading to intermittent hypoxaemia and arousals with sleep fragmentation. This condition is estimated to affect at least 2–9% of the adult population.1,2 A questionnaire-based study found that 26% of American adults were at high risk of OSA, who could benefit from the evaluation for OSA.3 In addition to daytime somnolence and its secondary effects such as motor vehicle and work accidents, OSA has been found to be associated with cardiovascular and metabolic disease if untreated. With increasing recognition of this syndrome, the referrals for diagnostic evaluations of suspected OSA have increased dramatically over the last two decades.

In-laboratory (type 1) polysomnography (PSG) is the gold standard for the diagnosis of OSA; however, this approach is restricted by inadequate infrastructure leading to limited accessibility with extended waiting period prior to testing. An alternative method for the diagnosis of OSA is portable or home PSG. Portable sleep studies are classified into three different types (type 2, 3 and 4) based on the degree of sleep and respiratory variable measurements. Type 2 portable PSG has similar respiratory and sleep measurements as in-lab PSG, apart from being unattended by a sleep technician. On the other hand, type 3 and 4 studies are more simplified without sleep measurements by electroencephalography (EEG) and are also unattended.

The apnoea–hypopnoea index (AHI) on PSG is used to quantify the diagnosis and assess the severity of OSA. AHI represents the number of obstructive events occurring per hour of sleep. The calculated total sleep time (TST) in types 3 and 4 PSG is based on the patient’s estimation as these studies do not measure sleep. Inaccurate estimation of TST would translate into overestimation or under-estimation of AHI. Previous studies in specific populations have revealed inconsistent correlation between subjective estimation and objective measurement of sleep duration.4,5 However, there have been no studies on the relationship between subjective and objective sleep estimation in a population with
probable OSA. The aim of this analysis was to compare patients’ estimated sleep duration with objective measures in patients who underwent type 2 home PSG for diagnosis of OSA.

Methods
A prospective audit was conducted in a tertiary hospital. Participants were consecutive patients who had been assessed at the Sleep Clinic by one of the authors and referred for type 2 home PSG for probable OSA. The recruitment period was between November 2006 and January 2013. Type 2 home PSG was performed using Somte PSG devices (Compumedics, Melbourne, Victoria, Australia) administered by trained sleep scientists. The recorded montage consisted of electrocardiogram (lead II), EEG (F4/M1, C4/M1, O2/M1), electrooculography, submental electromyography, oximetry, nasal pressure, oronasal temperature, thoracic and abdominal chest wall movements (using inductance plethysmography), leg movements, and body position. Measurements and analysis of sleep stages and associated events were performed in accordance with the American Academy of Sleep Medicine (2007) scoring manual. A standard questionnaire was completed by the patients the morning after the study. The questions included were time of lights being turned off, estimated time of sleep onset and estimated time of sleep offset. Patients were informed during the evening setup procedure of the need for them to make these estimates upon awakening in the morning. The estimated sleep latency (SL) was derived from time of lights being turned off, estimated time of sleep onset and estimated time of sleep offset. Patients were informed during the evening setup procedure of the need for them to make these estimates upon awakening in the morning. The estimated sleep latency (SL) was derived from time of lights being turned off, estimated time of sleep onset and estimated time of sleep offset. The estimated TST was calculated based on estimated time of sleep onset and sleep offset (without estimation of wake after sleep onset). Clinically significant difference between subjective and objective measures was defined as 10 min.

Ethics approval was not required given that it was an audit and the approval of using patients’ records was granted as patients’ confidentiality was maintained.

Statistical methods
Statistical analysis was performed using Graphpad Prism (v5, Graphpad Software, San Diego, CA, USA). Data distributions were tested for normality using the Kolmogorov–Smirnov test, followed by the Dallal and Wilkinson approximation to Lilliefors’ method to obtain a p-value. Parametric distributions were analysed with t-tests for comparisons of two groups, and expressed as mean (standard deviations). Correlations were assessed using Pearson’s test. For non-parametric data, Mann–Whitney or Kruskal–Wallis tests followed by Dunn’s post-test were used for two or multiple comparisons, respectively, and expressed as median (range or interquartile range). Non-parametric correlations were assessed using Spearman’s test.

Results
A total of 536 patients was included in the study. There was no exclusion from the data analysis. The majority of patients were male (63%) with a median (range) age of 50 (15–81) years. The mean (range) body mass index was 30.2 (17.9–74.2) kg/m². The median (range) Epworth Sleepiness Scale score was 8 (5–24). The demographic characteristics are presented in Table 1.

Sleep perception
Median estimated SL was significantly longer compared to measured SL (20 min (interquartile range: 10–30 min) vs 10 min (interquartile range: 3–22 min), P < 0.0001). A total of 223 (42%) patients estimated their SL within 10 min of measured SL. There were 227 (43%) patients who overestimated their SL, whereas 15% underestimated it. Bland–Altman analysis showed mean difference of 13 min with wide limits of agreement (95% limits of agreement: −89 and 116 min; Fig. 1). The plot indicated that the variability between the estimated and measured SL increased as the average values increased.

For sleep offset time, the median difference between the estimated and measured values was −1 min (range: −415 to 355 min, P = 0.01). Of the patients, 33% underestimated their sleep offset time, whereas 22% overestimated it. Bland–Altman analysis showed mean difference

Table 1 Patient demographics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Age [years]</td>
<td>50 (15–81)</td>
</tr>
<tr>
<td>Gender (F : M)</td>
<td>196 : 340</td>
</tr>
<tr>
<td>Body mass index [kg/m²]</td>
<td>30.2 (17.9–74.2)</td>
</tr>
<tr>
<td>Epworth sleepiness scale</td>
<td>8 (5–24)</td>
</tr>
<tr>
<td>Measured TST [minutes]</td>
<td>381.5 (85–679)</td>
</tr>
<tr>
<td>Estimated TST [minutes]</td>
<td>360 (20–720)</td>
</tr>
<tr>
<td>Measured AHI [events/hour]</td>
<td>19 (9–185)</td>
</tr>
<tr>
<td>Patients with measured AHI score (%)</td>
<td></td>
</tr>
<tr>
<td>• 5–15</td>
<td>29</td>
</tr>
<tr>
<td>• &gt;15–30</td>
<td>27</td>
</tr>
<tr>
<td>• &gt;30</td>
<td>31</td>
</tr>
<tr>
<td>Patients with calculated AHI score (%)</td>
<td></td>
</tr>
<tr>
<td>• 5–15</td>
<td>27</td>
</tr>
<tr>
<td>• &gt;15–30</td>
<td>24</td>
</tr>
<tr>
<td>• &gt;30</td>
<td>36</td>
</tr>
</tbody>
</table>

Results are expressed as median (range) unless specified. Calculated AHI: AHI score calculated based on patients’ estimated total sleep time. AHI, apnoea–hypopnoea index; TST, total sleep time.
of 13 min with wide limits of agreement (95% limits of agreement: −107 and 132 min; Fig. 2). On the contrary to SL, the plot revealed that the variability between the estimated and measured sleep offset time increased as the average values decreased. Overall, the median difference between the estimated and measured TST was −18.5 min (interquartile range: −80.5 to 42.75 min) ($P = 0.002$).

However, there was no correlation between estimation for SL and sleep offset time. For both SL and sleep offset time estimations, there were no significant correlations with patient factors, including age, body mass index, Epworth sleepiness scale, AHI and sleep efficiency.

### Apnoea-hypopnoea index

Of the patients, 87% had an AHI of 5 or more events per hour based on both the TST measured by PSG and patients’ estimated TST. Of the patients, 31% had a measured AHI of more than 30 events per hour, whereas 36% of the AHI-based patients estimated TST. Bland–Altman analysis showed mean difference of 4 events/h with wide limits of agreement (95% limits of agreement: −46 and 38 events/h; Fig. 3). Based on calculated AHI, 10 patients (2%) had a change in their diagnosis of OSA when compared with using their measured AHI.

### Discussion

This is the first study, to our knowledge, to evaluate the accuracy of subjective estimates of sleep time compared with PSG measured sleep time in patients referred for investigation of OSA. In this study, the patients generally overestimated their SL and underestimated their sleep offset time. Together, this led to the overall underestimation of TST. However, a key finding was that there was significant individual variability in estimation of sleep time without any identified factors that influenced the sleep perception. Our findings are consistent with the previous studies on sleep perception in pregnant women and patients with psychiatric disorders.4,5

Over the past decades, there has been a steady increase in the referrals to sleep physicians for assessment of possible OSA. Although in-laboratory PSG is the gold standard for diagnosis of OSA, there are often waiting lists in sleep laboratories. Based on Australian Medicare data, there were 6400 sleep laboratory PSG per month from January 2009 to February 2011.7 Of these, the proportion of Medicare-funded home PSG has increased from approximately 20% in early 2009 to 32% by December 2010.7 There is a wide variety of portable monitor devices...
with different measured parameters. Based on the available studies, the systematic review by Flemons and colleagues has not been able to recommend unattended portable monitor device use of any type for most patients with suspected OSA. However, recent studies that compared home-based and in-laboratory assessments in patients with high clinical suspicion of OSA suggested that there was no significant difference in the patient outcomes in terms of clinical symptoms and therapy adherence.

The absence of sleep monitoring for types 3 and 4 PSG can lead to erroneous sleep assessment of TST and so errors in the AHI. The use of patients’ inaccurate estimated sleep onset time could also be inaccurate. The measured SL is the time from lights off to sleep recorded on the EEG. We have demonstrated that patients’ estimates of SL were inaccurate. Obviously, the estimates of sleep onset time could also be inaccurate. However, because our objective measure of SL was only partially objective because of the lack of a light sensor to detect light off, our results will likely be an underestimate of the range of differences between objective and subjective SL. Thus, any inaccuracy in lights off time is unlikely to alter our conclusion about the patients’ SL and sleep duration times being inaccurate.

It is important to appreciate that there are several other limitations with our study. The study was conducted in a single centre with recruitment by a single sleep physician. However, we were able to include all patients from the particular physician for the study. In addition, the study was based on a single-night PSG. It would be worthwhile assessing the intra-individual variability in addition to the inter-individual variability in sleep perception. In addition, the calculated AHI was derived from the total number of events divided by patients’ estimated TST, without considering the estimation of wake after sleep. It is noted that some calculated AHI were significantly higher than the measured AHI because of considerable patients’ underestimation of TST.

**Conclusion**

In conclusion, self-estimation of sleep times was not accurate compared with PSG-measured sleep time in patients with suspected OSA. There was significant individual variability. Subjective estimation of sleep perception should be interpreted with caution. Collectively, inaccurate sleep time estimation had not resulted in significant difference in the diagnosis of OSA in patients with suspected OSA in our study. Thus, home PSG may play a role in the assessment of selected patients with high pre-test probability of OSA.

**References**


Pretreated baseline neutrophil count and chemotherapy-induced neutropenia may be conveniently available as prognostic biomarkers in advanced gastric cancer

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Key words
neutrophil count, neutropenia, prognostic factor, chemotherapy, myelosuppression, gastric cancer.

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Abstract

Background: Increasing evidence suggests that neutrophils play a critical role in tumorigenesis, tumour cell proliferation and metastasis. The prognostic significance of such inflammation-associated markers has been explored in different cancers.

Aim: To evaluate the prognostic effect of baseline neutrophil counts and nadir neutrophils on advanced gastric cancer (AGC) patients who were treated with two different chemotherapy regimens in our institution.

Methods: Data were collected retrospectively for 260 AGC patients treated between 1 February 2009 and 31 December 2011. The prognostic effect of baseline neutrophil counts and nadir neutrophils on AGC patients was evaluated.

Results: Approximately 79% of the patients experienced neutropenia during chemotherapy. The median survival was 369 days for patients with neutrophil counts \( \leq 7.5 \times 10^9/L \) and 326 days for patients with neutrophil counts \( >7.5 \times 10^9/L \) (\( P < 0.001 \)). The median survival was 340 days for patients with no neutropenia (grade 0), 422 days for patients with mild neutropenia (grade 1–2) and 339 days for patients with severe neutropenia (grade 3–4) (\( P < 0.001 \)). The adjusted hazard ratios (HR) for mild and severe neutropenia compared with absent neutropenia were 0.572 (\( P = 0.002 \)) and 1.246 (\( P = 0.219 \)) respectively. Furthermore, it was suggested that pretreatment baseline neutrophil counts \( \leq 7.5 \times 10^9/L \) may be an independent predictor (HR = 0.683; \( P = 0.005 \)). We also observed that other factors were independently associated with worse survival, such as higher performance status, stage IV and the presence of ascites.

Conclusion: Our findings suggest that baseline neutrophil count and chemotherapy-induced neutropenia can be conveniently available as clinical biomarkers in AGC. Mild myelosuppression in patients with AGC most likely leads to better overall survival, whereas a high baseline neutrophil count may be associated with a worse prognosis.

Introduction

Gastric cancer has become the fourth most frequently occurring cancer and the second leading cause of cancer-related death worldwide.\(^1\) In developing countries, including China, the morbidity and mortality of gastric cancer remains high. Chemotherapy can provide palliation, improved survival and improved quality of life compared with the best supportive care in patients who have advanced and metastatic disease.\(^2,3\) Unfortunately, there is currently no global standard regimen for advanced gastric cancer (AGC) treatment. Thus, new therapeutic strategies are crucially needed to improve the dismal prognosis of AGC.

Traditionally, chemotherapy-induced neutropenia has been considered a harmful side-effect that should be avoided and resolved. However, several retrospective studies have suggested that patients who fail to achieve mild neutropenia during chemotherapy have inferior survival.\(^4,4\)

It is quite often clinically observed in advanced cancer that the neutrophil count increases in the terminal stage.
of cancer. Several studies have indicated that an elevated neutrophil count before treatment suggests a short progression-free survival and short overall survival (OS).9,10

We conducted this retrospective study to evaluate the prognostic effect of baseline neutrophil counts and nadir neutrophils on AGC patients who were treated with two different chemotherapy regimens in our institution. Our major goal was to provide some initial evidence to confirm that pretreatment baseline neutrophil count and the presence of chemotherapy-induced neutropenia have strong prognostic value in Chinese patients with AGC.

**Methods**

A search of the hospital computerised database was used to locate all patients diagnosed with gastric cancer who were registered at the second affiliated hospital of Soochow University between 1 February 2009 and 31 December 2011. This study identified 260 patients who met the following inclusion criteria: aged 18–75 years; histologically and cytologically confirmed AGC; an Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1 or 2; adequate bone marrow function (leukocytes $\geq 4.0 \times 10^9/L$, neutrophil $\geq 2.0 \times 10^9/L/\mu L$, platelet $\geq 100 \times 10^9/L$, haemoglobin $\geq 9.0$ g/dL); and no previous or other concomitant malignant disease. Exclusion criteria were as follows: incomplete medical records or refusal to follow up.

Patients underwent one of two treatment regimens: intravenous fluorouracil 2600 mg/m² through 24-h infusion, leucovorin 200 mg/m² and oxaliplatin 85 mg/m² every 2 weeks (FLO arm, $n = 128$)11 or liposome-paclitaxel 80 mg/m² administered on days 1, 8, 15 and 22 by intravenous infusion, and S-1 given 60 mg twice a day orally on days 1–28 for a body surface area (BSA) $>1.5$ m² and 50 mg for BSA $<1.5$ m² every 6 weeks (liposome-paclitaxel + S-1 (L-PS) arm, $n = 132$).12 The cycles were repeated every 2 weeks for at least six cycles (FLO arm) and were repeated every 6 weeks for at least two cycles (L-PS arm); treatment was stopped if there was evidence of disease progression or unacceptable toxicity.

The information collected included patient demographics, clinico-pathologic features, chemotherapy protocol, laboratory evaluation and survival outcomes. Routine complete blood counts were conducted every chemotherapy cycle, at day 1 before treatment and subsequently weekly. Chemotherapy-induced neutropenia was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), version 3. The patients were separated into three groups according to the worst degree of neutropenia observed throughout the chemotherapy cycle: absent (grade 0), mild–moderate (grade 1–2) and severe (grade 3–4). Patients with neutropenia were evaluated and compared with non-neutropenic patients in terms of OS. This study was approved by the Ethics Committee of the second affiliated hospital of Soochow University. Written informed consent was obtained from all patients.

Overall survival was the primary endpoint of the analysis. Survival curves were computed using the Kaplan–Meier method. Cut-off levels of $7.5 \times 10^9/L$ for neutrophils were identified as representative upper reference levels.13 The hazard ratios (HR) of death and 95% confidence interval (CI) were estimated using Cox multivariable regression analysis. All statistical tests were two-tailed, and $P$ values lower than 0.05 were considered to indicate statistical significance. Analyses were performed using the SPSS software, version 19.0 (SPSS Inc. IBM, Chicago, IL, USA).

**Results**

A total of 260 patients who had AGC and met the inclusion criteria was identified for the present study. A total of 128 patients was treated with the FLO regimen, and 132 patients were treated with the L-PS regimen. Patient baseline demographics and clinical characteristics were balanced between the different arms (Table 1).
Approximately 79% of the patients (n = 206) had experienced neutropenia at least once during chemotherapy, whereas the remaining 54 patients had not. Mild neutropenia (grade 1–2) occurred in 100 (38%) of the 260 patients, whereas severe neutropenia (grade 3–4) was noted in 106 (41%) patients. Approximately 46 patients with severe neutropenia received granulocyte colony-stimulating factor treatment. Febrile neutropenia occurred in 12 (4.6%) of the 260 patients, 5 of whom died of infection related to neutropenia.

**Impact of baseline neutrophil count in univariate analyses**

In the FLO arm, according to the baseline neutrophil count level, the median OS in patients with a neutrophil count $\leq 7.5 \times 10^9/L$ was 370 days (95% CI, 351–389 days), which was significantly higher than that in patients with a neutrophil count $>7.5 \times 10^9/L$ (median survival 323 days, 95% CI, 293–352 days, $P = 0.002$; Fig. 1A). In the L-PS arm, the median OS in patients with a baseline neutrophil count $\leq 7.5 \times 10^9/L$ was 367 days (95% CI, 348–385 days), which was also significantly higher than that in patients with a neutrophil count $>7.5 \times 10^9/L$ (median survival 329 days, 95% CI, 276–381 days, $P = 0.012$; Fig. 1B). For all 260 patients, the median survival was 369 days (95% CI, 357–381 days) for patients with a neutrophil count $\leq 7.5 \times 10^9/L$ and 326 days (95% CI, 293–359 days) for patients with neutrophil count $>7.5 \times 10^9/L$. The log–rank test showed that the differences between the curves were statistically significant ($P < 0.001$; Fig. 1C).

**Impact of nadir neutrophils in univariate analyses**

In the FLO arm, according to the severity of neutropenia, the median survival was 339 days (95% CI, 256–422 days) for patients with no neutropenia (grade 0), 407 days (95% CI, 363–451 days) for patients with mild neutropenia (grade 1–2) and 335 days (95% CI, 310–360 days) for patients with severe neutropenia (grade 3–4) (Fig. 2A). The log–rank test showed that the differences among the three curves were statistically significant ($P = 0.0001$). In the L-PS arm, the median survival was 355 days (95% CI, 297–412 days) for patients with no neutropenia (grade 0), 422 days (95% CI, 378–466 days) for patients with mild neutropenia (grade 1–2) and 341 days (95% CI, 323–358 days) for patients with severe neutropenia (grade 3–4) ($P = 0.007$) (Fig. 2B). For all the 260 patients, the median survival was 340 days (95% CI, 288–392 days) for patients with no neutropenia (grade 0), 422 days (95% CI, 397–446 days) for patients with mild neutropenia (grade 1–2) and 339 days (95% CI, 321–356 days) for patients with severe neutropenia (grade 3–4) ($P < 0.001$) (Fig. 2C).

**Multivariate analyses**

A multivariate Cox regression model also demonstrated that a mild grade of chemotherapy-induced neutropenia was independently associated with a longer OS (Table 2). The adjusted HR for mild and severe neutropenia compared with absent neutropenia were 0.572 (95% CI, 0.405–0.807; $P = 0.002$) and 1.246 (95% CI, 0.878–1.768; $P = 0.219$) respectively. Furthermore, it was shown that pretreatment baseline neutrophil counts $\leq 7.5 \times 10^9/L$ were independent predictors of better OS (HR = 0.683; 95% CI, 0.524–0.892; $P = 0.005$). We also observed that other factors were independently associated with worse survival, such as higher PS status, stage IV and the presence of ascites.

![Figure 1](image-url) 

**Figure 1** High baseline neutrophil count is associated with poor survival. Kaplan–Meier survival analysis for patients: (A) FLO arm, (B) L-PS arm, overall patients; significance was assessed by the log–rank test. *Baseline $\leq 7500/\mu L$; †Baseline $>7500/\mu L$.**
Discussion

Increasing evidence suggests that neutrophils play a critical role in tumorigenesis, tumour cell proliferation and metastasis through the production of cytokines and chemokines. Some studies have disclosed that the elevation of pretreatment neutrophil counts is associated with poor outcome in some types of cancer, such as advanced non-small-cell lung cancer, metastatic melanoma, AGC, metastatic renal cell carcinoma, nasopharyngeal carcinoma and non-metastatic upper urinary tract carcinoma.

In this study, we showed that the pretreatment peripheral blood neutrophil count is significantly associated with OS in patients with AGC. Moreover, multivariate analysis demonstrated that the pretreatment neutrophil count is an independent predictor of longer OS in patients with ADC, and the same conclusion could be drawn in the two subgroups of the FLO arm and L-PS arm.

It is well known that chemotherapy-induced neutropenia is a common adverse event during the course of cancer treatment. It is now proposed that the current method of calculating a drug dose for chemotherapy using the patient’s BSA, which does not consider individual differences in drug metabolism, is inaccurate. In other words, the determined standard dose may be conservatively low for some patients who exhibit faster drug elimination times and high for those who exhibit slower drug elimination times. The hypothesis that chemotherapy-induced neutropenia may be a surrogate marker of the drug’s biological activity has been supported in several studies, although no acceptable explanations for the mechanisms of these associations have emerged.

Several retrospective studies have suggested that mild neutropenia during chemotherapy achieves a more favourable prognosis, such as longer progression-free survival and OS. In our study, we found that patients with mild neutropenia have the longest OS, compared with the other two groups (mild neutropenia, 422 days; no neutropenia, 340 days; severe neutropenia, 339 days $P < 0.0001$). However, the severity of neutropenia does not correlate with survival, most likely because patients with severe neutropenia have more complications, thus potentially delaying subsequent chemotherapy treatment.

Neutrophils play an important role in cancer-related inflammation, infiltration, polarisation and are of prognostic significance in human cancer. Recently, Donskov reported that a high pretreatment neutrophil count correlated well with poor outcomes of surgery, chemotherapy and chemoradiotherapy in several human cancers.
cancers, notably in colorectal cancer, hepatocellular carcinoma, renal cell carcinoma, melanoma, gastrointestinal stromal tumors, gastric, oesophageal, lung, ovarian and head and neck cancer (reviewed in Donskov22). One meta-analysis that included 20 studies and a total of 3946 patients with various solid tumours revealed that high levels of intratumoral neutrophils (tumour-associated neutrophils, TAN) are associated with unfavourable recurrence-free, cancer-specific and OS.23 This meta-analysis may suggest that TAN are likely the main explanation for pretreated baseline neutrophil count and chemotherapy-induced neutropenia as a prognostic marker.

Furthermore, some clinical trials have proposed adjusting chemotherapy doses based on the severity of myelosuppression as a rational method for calculating a patient’s optimal chemotherapy drug dose. This method was confirmed in a randomised clinical trial that disclosed a significantly improved relapse-free survival compared with marrow-supported high-dose chemotherapy in primary breast cancer.24 However, in another multicentre, randomised clinical trial,25 the approach of tailoring and escalating the carboplatin dose according to the myelosuppression provided no benefit in progression-free survival or OS compared with flat dosing in ovarian cancer.

Some limitations of this study should be acknowledged. As a retrospective study, patients were not randomly assigned to a chemotherapy procedure, which means that patient selection bias existed. Another limitation was the low sample size included in this study. Finally, in this study, we chose OS as the primary endpoint. We know that OS may be confounded by some different subsequent therapies, including different chemotherapy regimens, radiology treatment and mortality unrelated to cancer.

Conclusion
This study demonstrated that pretreated baseline neutrophil count and chemotherapy-induced neutropenia are independent predictive markers in advanced gastric carcinoma, regardless of the different chemotherapy regimens implemented. It may be utilised as a surrogate marker for risk stratification and provide better treatment allocation. More large multicentre, randomised clinical trials of individualised subsequent doses based on the level of chemotherapy-induced myelosuppression are urgently needed.

Acknowledgement
We thank our collaborators for their useful suggestions.

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17 He JR, Shen GP, Ren ZF, Qin H, Cui C, Zhang Y et al. Pretreatment levels of peripheral neutrophils and lymphocytes as independent prognostic factors in patients with nasopharyngeal carcinoma. Head Neck 2012; 34: 1769–76.


Excessive range of statin dose in Western Australian primary care


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Key words
statin, dose, hypercholesterolaemia, coronary disease, side-effect.

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Abstract
Background: Statins are very effective in reducing coronary disease and ischaemic stroke but guidelines although evolving have not been clear on statin dose.
Aim: To audit and review community statin prescribing.
Methods: A retrospective audit of the type and dose of statin dispensed was undertaken at five pharmacies in and around Perth, the capital city of Western Australia. Patients were de-identified.
Results: Statins made up 6.5% of all prescriptions. Statin dose when adjusted for different potency effectively varied 64-fold between patients. Rosuvastatin and atorvastatin accounted for 79% of prescriptions, at a mean dose of 10 times the effective dose 50.
Conclusion: The extraordinarily wide variation in statin dose is at odds with the more consistent doses of other drugs used in the management of arterial disease. Unnecessarily high statin dosing increases side-effects and may not improve clinical outcomes appreciably. Rational prescribing of statins based on the pharmacodynamic evidence, with lower doses in most patients, combined with close attention to reduction of smoking, blood pressure and weight, is likely to reduce arterial disease most efficiently and safely.

Introduction
Ischaemic heart disease will develop in more than one half of adults and continues to account for over one quarter of all deaths.1 Mortality rises exponentially with increasing serum cholesterol.2 Statins (3-hydroxy-3-methyl-glutaryl-CoA reductase inhibitors) lower cholesterol very effectively and have a major role in the prevention of coronary and other arterial disease, in concert with attention to other risk factors, in particular smoking, blood pressure and weight. The relationship with coronary events weakens with lower levels of cholesterol2 and clinicians may inadvertently prescribe unnecessarily high doses that increase side-effects without adding significant clinical benefit.

Independent audits3–5 and earlier randomised clinical trials show that statin side effects are common and include fatigue,6 myopathy,7 hepatic8–9, cerebral haemorrhage,10 subtle cognitive impairment,10,11 neuropathy,12 acute renal failure,13,4 diabetes mellitus14 and cataracts.6 Side-effects are dose related,3,5,7 often appear before cardiovascular benefits are obtained and may explain poor compliance, up to 50% in some studies.14

Given the paucity of clear guidelines on optimal dosing, we undertook an audit of statin doses prescribed in and around Perth, Western Australia.

Methods
We audited statins dispensed at five pharmacies through the month of July 2013. Three pharmacies were located in inner metropolitan Perth, two in nearby regional centres. The doses of the different statins prescribed were obtained from electronic records at each pharmacy. Data were de-identified. The study was approved by a human research ethics committee.

Results
The statins prescribed and the range of doses were similar at each of the five pharmacies. The aggregate findings are

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Conflict of interest: None.
summarised in Table 1, along with the effective dose that lowers low density lipoprotein (LDL) cholesterol by 50% (effective dose 50 (ED50)) for each statin, determined from published extensive systematic review and meta-analysis. Seventy-nine per cent (79%) of prescriptions were for either rosuvastatin or atorvastatin. Fluvastatin, pravastatin and simvastatin made up the remaining 21%.

The mean statin dose, expressed equivalent to simvastatin, was 116 mg. When allowance is made for the efficacies of the different agents, statins were prescribed over a 64-fold range of dose. The doses of individual statins also varied widely, for example 16-fold in the case of simvastatin. Prescribing appeared bimodal, with atorvastatin and rosuvastatin each prescribed at a mean of 12 times the ED50, while simvastatin, pravastatin and fluvastatin were prescribed near their respective ED50s.

### Discussion

Our audit revealed that prescribed statin doses varied enormously, effectively up to 64-fold overall. This is in stark contrast to the relatively uniform doses of other drugs used in the long-term management of coronary disease. For example, the recommended dose of aspirin is 50–150 mg daily after an arterial event (secondary prevention), and antihypertensive agents important in the primary prevention16 and management of coronary disease are typically prescribed over a fourfold dose range. We did not ascertain which patients were on a statin for primary prevention.

The mean statin dose in our audit, 116 mg daily expressed as equivalent to simvastatin, was almost five times the mean of 24 mg in a large Japanese outpatient audit, in which the newer agents, atorvastatin and rosuvastatin, similarly dominated, comprising 72% of prescriptions. The new statins are broadly eight times as potent as the older statins, partly related to their much longer half-lives. Highly significant reductions in mortality and around 30% reduction in total cardiovascular events were seen with just 20–40 mg of simvastatin in earlier landmark clinical trials (the Scandinavian Simvastatin Survival Study17 and the Heart Protection Studies18). The ED50 of simvastatin is about 12 mg. By comparison, irbesartan, commonly used in the treatment of hypertension, has an ED50 of around 75 mg daily19 and is not prescribed above 300 mg. Marketing of the new potent agents has been based on greater cholesterol lowering with similar doses. For comparison, doses of 60 mg of simvastatin, 15 mg atorvastatin or 8 mg of rosuvastatin are all at or near the top of the dose–response curve and appear likely to be more than sufficient.

Although higher drug doses may seem necessary in more severe coronary disease, lower dose long-term pharmacotherapy provides sufficient benefits in many other chronic diseases, with significantly lower risk of side-effects and thereby often better overall outcomes, for example aspirin, diuretics, digoxin and psychotropics. Convincing analyses have demonstrated equivalent or superior outcomes with lower doses of antihypertensive pharmacotherapy used in combination, in particular, beta-adrenoceptor blockers. It seems likely that lower doses were employed in some patients in our audit because of side-effects. Known statin-intolerant patients are excluded from clinical trials. Higher doses of statins have been promoted because of the greater reduction in coronary events, albeit small, with 80 compared with 10 mg atorvastatin daily in the highly publicised Treating to New Targets (TNT) study. The higher dose was associated with 23% lower LDL cholesterol and was marketed as grounds to aim for the on-treatment LDL cholesterol in TNT, 2.0 mmol/L, even though the study was not designed to establish a specific target cholesterol level. The higher dose had no impact on mortality but increased abnormal liver function sixfold. Similarly, many clinicians persist with high dose statins started for acute coronary syndrome, even though the demonstrated outcome benefits appear small. Most

### Table 1 Statin doses prescribed

<table>
<thead>
<tr>
<th>Statin</th>
<th>5 mg</th>
<th>10 mg</th>
<th>20 mg</th>
<th>40 mg</th>
<th>80 mg</th>
<th>Total</th>
<th>Mean Dose (mg)†</th>
<th>ED50 (mg)‡</th>
<th>Dose range around ED50</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluvastatin</td>
<td></td>
<td>2</td>
<td>0</td>
<td>3</td>
<td>5</td>
<td>5</td>
<td>56</td>
<td>50</td>
<td>0.4–1.6</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>9</td>
<td>33</td>
<td>92</td>
<td>11</td>
<td>145</td>
<td>37</td>
<td>55</td>
<td>24</td>
<td>0.4–3.3</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>1</td>
<td>26</td>
<td>114</td>
<td>155</td>
<td>351</td>
<td>37</td>
<td>55</td>
<td>12</td>
<td>0.4–6.7</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>170</td>
<td>299</td>
<td>373</td>
<td>160</td>
<td>1002</td>
<td>35</td>
<td>160</td>
<td>3</td>
<td>3.3–27</td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>119</td>
<td>409</td>
<td>233</td>
<td>138</td>
<td>899</td>
<td>17</td>
<td>899</td>
<td>1.5</td>
<td>3.3–27</td>
</tr>
<tr>
<td>Total</td>
<td>240</td>
<td>564</td>
<td>1396</td>
<td>860</td>
<td>5539</td>
<td>177</td>
<td>2402</td>
<td>1.5</td>
<td>3.3–27</td>
</tr>
</tbody>
</table>

†Rounded to a whole number.
‡ED50 = Dose that lowers LDL-cholesterol 50% of maximum.
of the reduction in cardiovascular events with statin pharmacotherapy in fact does not appear until after several years\(^\text{13}\) and appears not to require high dose.\(^\text{17,18}\) The reported poor adherence to statins\(^\text{14}\) is likely to be related to side-effects that are more frequent with the higher doses.\(^\text{23}\) Quality of life has not been fully addressed in statin clinical trials. Close clinical monitoring for side-effects is essential.

Targeting individuals at higher risk is important.\(^\text{24}\) Statins are clearly effective in preventing recurrent events in individuals with a history of symptomatic arterial disease.\(^\text{17,18}\) although benefits may be exaggerated.\(^\text{25}\) The role of statins in asymptomatic individuals (primary prevention) has been more controversial.\(^\text{26}\) Studies to date have shown a small survival benefit\(^\text{27}\) but reliable modelling of poorly quantified risks compared with benefit is problematic.\(^\text{28}\) The last American Heart Association/American College of Cardiology guidelines noted that there is no evidence to support titration of dose against cholesterol levels.\(^\text{29}\) Serum cholesterol can be unreliable because of variation with diet, posture and intercurrent illness.\(^\text{30}\) The severity of coronary disease can be determined with computed tomography,\(^\text{31,32}\) which may provide a more reliable basis for ascertaining coronary risk and guiding statin treatment and dose. The negative predictive value of a low or negative coronary calcium score is high\(^\text{32}\) and even if the cholesterol is elevated, a low dose of statin is probably sufficient.

### Conclusion

The very wide variation in statin dosing disclosed in this audit is of concern and reflects a paucity of evidence-based dosing guidelines. Excessive dose increases side-effects, insufficient dose risks avoidable cardiovascular events. Dose might be adjusted according to body size and liver function. Although our findings may be peculiar to Western Australia, we found similar wide dose variation at each of the five pharmacies audited. An at least eightfold variation in statin dose was reported in a large Japanese audit\(^\text{2}\) and a 32-fold variation in a smaller UK audit.\(^\text{31}\) Lower dose statin has been shown to be sufficient for primary prevention even in severe hypercholesterolaemia\(^\text{14}\) and higher doses may only be appropriate in symptomatic arterial disease. A single antihypertensive agent reduces coronary risk over 20%\(^\text{18}\) and many patients are prescribed two or three antihypertensive agents, especially in secondary prevention. The substantial impact of these, along with antiplatelet anti thrombotic therapy, smoking cessation and weight reduction, is likely to circumvent the need for high statin dose in most patients.

### References


BRIEF COMMUNICATIONS

What is the evidence status of Appropriate Use Criteria (AUC)? Insight from a matching exercise with the guidelines for echocardiography

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Key words
echocardiography, appropriate use criterion, guideline.

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Abstract
There is interest in adapting the American Appropriate Use Criteria (AUC) for transthoracic echocardiography to Australian practice. We matched 90 of 98 AUC with the guidelines (53 appropriate, 12 sometimes appropriate, 25 rarely appropriate), but eight lacked any match. Among the matched criteria, 76 (82%) indications were concordant with the guidelines. A stronger evidence base would be desirable to settle these discrepancies before Australian adoption of AUC.

The growth of cardiac imaging has paralleled advances in the therapeutic options for cardiovascular disease and improvements in imaging technology. However, the cost of this growth has necessitated a reduction in the heterogeneity of practice and provision of high-quality health services. The Appropriate Use Criteria (AUC) were developed in the United States to align better the expense and value of cardiac imaging. However, some have expressed concern that the selection of AUC on the basis of expert opinion using a modified Delphi process risks the provision of unscientific guidance, because their evidence base is insufficiently robust. In contrast, clinical guidelines have become a cornerstone of cardiology, optimising patient outcomes through facilitating clinical decision relating to the diagnosis, prevention or treatment of diseases or conditions. These documents have classed recommendations according to the level of available scientific evidence, which has helped the calculation of risk and outcomes in clinical practice.

In Australia, growth in the performance of cardiovascular imaging continues, with substantial regional variation in utilisation, suggesting that need and performance are not well matched. For this reason, the adoption of AUC to Australian practice has been proposed as a means of containing the growth of imaging. However, current Australian practice relies heavily upon the published American College of Cardiology Foundation (ACCF), American Heart Association (AHA), American Society of Echocardiography (ASE) and European Society of Cardiology (ESC) guidelines on the diagnosis and management of cardiovascular illnesses. Consequently, any conflicting messages between the published guidelines and the appropriate use criteria would result in difficulties for the attending physician. We hypothesised that the differing ways of formulating AUC and the guidelines may be responsible for discordances between these entities. In order to elucidate the relation between the class of recommendation and the appropriate designation for transthoracic echocardiography, we sought to find a match for each item of ACCF/ASE/AHA AUC from published cardiology guidelines. Given the paucity of relevant guidelines in the Australian literature, we compared both European and American guidelines with the existing (American) AUC.

We searched for the matched items for each of the 98 criteria for transthoracic echocardiography in the 2011 AUC in the following manner: When a specific indication contained in the AUC lacked a match in the 2003 Guidelines for the Clinical Application of Echocardiography, other guidelines were used, principally in those related to management of heart failure, aortic disease, pulmonary hypertension, pulmonary embolism, cardiac devices, syncope, perioperative evaluation.
supraventricular arrhythmias\textsuperscript{18} and valvular diseases.\textsuperscript{19} We defined concordance if usually appropriate items (A) had Class I or IIa recommendation in the guidelines; rarely appropriate had Class III; or usually appropriate had Class IIb.\textsuperscript{1}

Among the 98 AUC indications for the use of transthoracic echocardiography (TTE), the majority (90 items, 92\%) had a match in the different guidelines: 53 usually appropriate, 12 sometimes appropriate, 25 rarely appropriate. Four of the usually appropriate indications and the same number of rarely appropriate indications did not have a counterpart in the guidelines (8\% of the indications of the AUC for TTE) (Fig. 1). Among the 90 matched criteria, 76 (82\%) indications were concordant with the guidelines, but there were 14 indications with discordance.

Four indications categorised as ‘Usually Appropriate’ in the AUC had Class III recommendations in the guidelines. They were on syncope without cardiovascular signs and symptoms, routine surveillance of mild valvular stenosis and prosthetic valve without suspected valve dysfunction, and monitoring for rejection in cardiac transplant recipients. Another two ‘appropriate’ indications on re-evaluation of known aortic dilation or history of aortic dissection where the concept was found in the guidelines did not have any recommendation numbered and suggested limited use of transoesophageal echocardiography (TEE) only to the root or those with Marfan syndrome (Table 1).

There were 5 (20\%) discords in ‘rarely appropriate’ indications (four class I and one class IIa in guidelines), concerning the use of echocardiography in screening for heart disease, re-evaluation of pulmonary hypertension with no change in clinical status, routine surveillance of moderate or severe valvular stenosis without a change in clinical status or cardiac exam and diagnosis of endocarditis or pulmonary embolism (Table 2).

Additionally, there were three ‘sometimes appropriate’ indications (25\%) with class I recommendations in guidelines. These inconsistencies were related to evaluation of critically ill patients, re-evaluation of known heart failure with a change in clinical status or cardiac exam with a clear precipitating change in medication or diet and routine surveillance (<1 year) of adult congenital heart disease, following incomplete or palliative repair with residual structural or haemodynamic abnormality without a change in clinical status or cardiac exam (Table 3).

In this matching exercise, we found important inconsistencies with published guidelines in 15\% of the 98 AUC for transthoracic echocardiography – 1\% without indications in guidelines and 14\% that contradict the guidelines. The incorporation of clinical evidence into guidelines is a fundamental pillar of clinical practice, although the proliferation of guidelines, their variable quality and sometimes contradictory messages, make it a struggle for clinicians to incorporate these documents in their clinical practice.\textsuperscript{20} Not all guidelines show a clear connection between evidence and recommendations.\textsuperscript{9} Surprisingly – given the role of echocardiography as one of the most commonly used imaging techniques – the guidelines for the clinical application of echocardiography do not incorporate level of evidence.\textsuperscript{9,10}

The AUC for echocardiography have been developed to help clinicians to choose testing more appropriately to improve quality of care.\textsuperscript{3} The contradictions between AUC and guidelines are awkward and confusing. This finding highlights the shortcomings of a process, whereby rating of appropriateness is based on expert opinion.\textsuperscript{4,5} A stronger evidence base is needed in order to settle these discrepancies in future updates of the AUC.

Given the number of guidelines evaluating the use of echocardiography in different diseases and scenarios, our study results do not show all the possible relationships between the AUC criteria and the published guidelines. We showed the main differences between American AUC and American and European guidelines, but it is likely that more discrepancies might be apparent if more guidelines were compared. Cardiology practice in Australia parallels and is informed by the practices of the American and European cardiology societies. If AUC (or some modification) are to be adopted in Australia, it seems important to develop a greater degree of internal consistency between guidelines and the AUC.

The Appropriate Use Criteria for Transthoracic Echocardiography are not consistent with the guidelines for the use of echocardiography. The potential incorporation of an AUC process into Australian practice might still improve patient outcomes, reduce variation and contain costs, but should be informed by these limitations.

\section*{Appendix A}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure1}
\caption{Appropriate Use Criteria (AUC) indications with and without a counterpart in guidelines. Blue: with matching. Yellow: no counterpart.}
\end{figure}
Table 1: Discrepancies between Usually Appropriate indications and guidelines

<table>
<thead>
<tr>
<th>AUC table</th>
<th>Item no.</th>
<th>AUC indication</th>
<th>Appropriate Use score</th>
<th>Guidelines†</th>
<th>Recommendation</th>
<th>Class</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>TTE for general evaluation of cardiac structure and function</td>
<td>9</td>
<td>Syncope when there are no other symptoms or signs of cardiovascular disease</td>
<td>A 7</td>
<td>1</td>
<td>Syncope in a patient for whom there is no clinical suspicion of heart disease.</td>
</tr>
<tr>
<td>3</td>
<td>TTE for evaluation of valvular function</td>
<td>39</td>
<td>Routine surveillance (≥3 years) of mild valvular stenosis without a change in clinical status or cardiac exam</td>
<td>A 7</td>
<td>1</td>
<td>Routine re-evaluation of asymptomatic adult patients with mild aortic stenosis having stable physical signs and normal LV size and function.</td>
</tr>
<tr>
<td>3</td>
<td>TTE for evaluation of valvular function</td>
<td>49</td>
<td>Routine surveillance (≥3 years after valve implantation) of prosthetic valve if no known or suspected valve dysfunction</td>
<td>A 7</td>
<td>1</td>
<td>Routine re-evaluation of asymptomatic patients with mild to moderate mitral stenosis and stable physical signs.</td>
</tr>
<tr>
<td>6</td>
<td>TTE for evaluation of hypertension, heart failure or cardiomyopathy</td>
<td>84</td>
<td>Monitoring for rejection in a cardiac transplant recipient</td>
<td>A 7</td>
<td>2</td>
<td>Routine re-evaluation of patients with valve replacements without suspicion of valvular dysfunction and unchanged clinical signs and symptoms.</td>
</tr>
<tr>
<td>5</td>
<td>TTE for evaluation of aortic disease</td>
<td>64</td>
<td>Re-evaluation of known ascending aortic dilation or history of aortic dissection to establish a baseline rate of expansion or when the rate of expansion is excessive</td>
<td>A 9</td>
<td>3</td>
<td>Because TTE does accurately visualise the aortic root, its primary role as an imaging method for serial follow-up is in patients with aortic disease limited to the root, particularly those with Marfan syndrome. TEE is preferred.</td>
</tr>
<tr>
<td>5</td>
<td>TTE for evaluation of aortic disease</td>
<td>65</td>
<td>Re-evaluation of known ascending aortic dilation or history of aortic dissection with a change in clinical status or cardiac exam or when findings may alter management or therapy</td>
<td>A 9</td>
<td>3</td>
<td>Because TTE does accurately visualise the aortic root, its primary role as an imaging method for serial follow-up is in patients with aortic disease limited to the root, particularly those with Marfan syndrome. TEE is preferred.</td>
</tr>
</tbody>
</table>


AUC, Appropriate Use Criteria; EMB, endomyocardial biopsy; LV, left ventricle; TEE, transoesophageal echocardiography; TTE, transthoracic echocardiography.
Table 2 Discrepancies between Rarely Appropriate indications and guidelines

<table>
<thead>
<tr>
<th>AUC table</th>
<th>Item no.</th>
<th>AUC indication</th>
<th>Appropriate Use score</th>
<th>Guidelines†</th>
<th>Recommendation</th>
<th>Class</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>TTE for general evaluation of cardiac structure and function</td>
<td>10 Initial evaluation of ventricular function (e.g. screening) with no symptoms or signs of cardiovascular disease</td>
<td>I 2 1</td>
<td>Patients with a family history of genetically transmitted cardiovascular disease.</td>
<td>I</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1 Patients with phenotypic features of Marfan syndrome or related connective tissue diseases.</td>
<td>I</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1 First-degree relatives (parents, siblings, children) of patients with unexplained dilated cardiomyopathy in whom no etiology has been identified.</td>
<td>I</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>TTE for general evaluation of cardiac structure and function</td>
<td>16 Routine surveillance (&lt;1 year) of known pulmonary hypertension without change in clinical status or cardiac exam</td>
<td>I 3 1</td>
<td>Follow-up of pulmonary artery pressures in patients with pulmonary hypertension to evaluate response to treatment.</td>
<td>I</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>TTE for evaluation of valvular function</td>
<td>40 Routine surveillance (&lt;1 year) of moderate or severe valvular stenosis without a change in clinical status or cardiac exam</td>
<td>I 3 1</td>
<td>Re-evaluation of asymptomatic patients with severe stenosis.</td>
<td>I</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>TTE for evaluation of valvular function</td>
<td>54 Transient bacteraemia with a pathogen not typically associated with infective endocarditis and/or a documented non-endovascular source of infection</td>
<td>I 3 4</td>
<td>Transthoracic echocardiography to detect valvular vegetations with or without positive blood culture is recommended for the diagnosis of infective endocarditis.</td>
<td>I</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>TTE for cardiovascular evaluation in an acute setting</td>
<td>28 Suspected pulmonary embolism in order to establish diagnosis</td>
<td>I 2 1</td>
<td>Pulmonary emboli and suspected clots in the right atrium or ventricle or main pulmonary artery branches</td>
<td>IIa</td>
<td></td>
</tr>
</tbody>
</table>


AUC, Appropriate Use Criteria; TTE, transthoracic echocardiography.
Table 3  Discrepancies between Sometimes Appropriate Indications and guidelines

<table>
<thead>
<tr>
<th>AUC Table</th>
<th>Item no.</th>
<th>AUC indication</th>
<th>Appropriate Use score</th>
<th>Guidelines†</th>
<th>Recommendation</th>
<th>Class</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>20</td>
<td>Assessment of volume status in a critically ill patient</td>
<td>U 5</td>
<td>1</td>
<td>The haemodynamically unstable patient.</td>
<td>I</td>
</tr>
<tr>
<td>6</td>
<td>72</td>
<td>Re-evaluation of known heart failure (systolic or diastolic) with a change in clinical status or cardiac exam with a clear precipitating change in medication or diet</td>
<td>U 4</td>
<td>1</td>
<td>Re-evaluation of LV function in patients with established cardiomyopathy when there has been a documented change in clinical status or to guide medical therapy.</td>
<td>I</td>
</tr>
<tr>
<td>7</td>
<td>97</td>
<td>Routine surveillance (&lt;1 year) of adult congenital heart disease following incomplete or palliative repair + with residual structural or haemodynamic abnormality + without a change in clinical status or cardiac exam</td>
<td>U 5</td>
<td>1</td>
<td>Periodic echocardiography in patients with surgically repaired (or palliated) congenital heart disease with the following: change in clinical condition or clinical suspicion of residual defects, obstruction of conduits and baffles, or LV or RV function that must be followed, or when there is a possibility of haemodynamic progression or a history of pulmonary hypertension</td>
<td>I</td>
</tr>
</tbody>
</table>

†Guidelines: 1, ACC/AHA Guidelines for the Clinical Application of Echocardiography.9

AUC, Appropriate Use Criteria; LV, left ventricle; RV, right ventricle; TTE, transthoracic echocardiography.

References


Development of postgraduate research supervisors within a teaching hospital setting

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Key words
postgraduate supervision, professional, research higher degree, student, teaching hospital.

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Abstract
The recent trend to embed medical research at point of care has created a need for postgraduate research supervisors in hospitals who are practising clinicians and lab-based researchers. We explored the training needs of supervisors to inform the design and evaluation of a hospital-based development programme. We found that if hospital-based supervisors are to improve their practice, the programme needs to be on-site to ensure access and relevance to local issues.
The training of clinician researchers is crucial for promoting translational research in medicine. Supportive supervisors and mentors have been shown to enable clinical research; however, the supervision of medical research at a doctoral level remains a challenge. Over the past decade, there has been an increasing number of PhD students, interest in health-related research outside university campuses, including hospitals, and demands for translation. More postgraduate research supervisors in hospitals with local discipline knowledge and skills are needed.

There have been calls for better support for postgraduate research supervisors to improve quality. Although universities offer training courses, conflicting priorities and time limitations may restrict hospital-based supervisors from attendance and completion. Flexible professional development that meets supervisors’ needs is required.

We identified limited uptake of a generic university course by potential hospital-based postgraduate research supervisors, who could not complete lengthy online tasks in isolation or attend on-campus classes. To determine supervisor training needs, we undertook research with existing supervisors to inform development of a hospital-based development programme (the Programme), which we then evaluated. The research question was: Does a hospital-based supervisor development programme influence supervisory practice and involvement in supervision in a teaching hospital?

Between June and September 2008, postgraduate research supervisors at the Children’s Hospital at Westmead Clinical School were invited to participate in semi-structured, audio-recorded interviews. Supervisors were asked what important, manageable training would help them provide students with effective guidance and support. Interview transcriptions were analysed by the researchers following a grounded theory approach.

Common themes were identified and classified, and formed the basis of the Programme design, which has been implemented annually since 2008.

To evaluate the Programme’s effectiveness and identify further training needs, all who had completed it between 2008 and 2011 (50 in total: 23 clinicians) were invited to complete a quantitative survey with additional comments. Analysis was undertaken using descriptive statistics, focusing on common themes. The research was approved by the University of Sydney Ethics Committee and Hospital Quality Assurance Committee.

Out of 75 supervisors (19% of cohort), with a range of supervisory experience, 14 participated in the interviews (Table 1). Interview analysis identified 19 themes, grouped into four categories (Table 2). The categories concerning supervisors’ training needs received the highest number of comments, including critical issues in supervision and managing problems. The challenges of supervision in a hospital were evident for clinical and laboratory-based staff, with their team-based work practices. Difficulties arose, for example, when supervisors were perceived to favour students over colleagues. The Programme therefore included setting supervisor and student expectations, monitoring progress and supporting writing.

### Table 1 Demographics of participants of the interview

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Participants n = 14 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender:</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>8 (57%)</td>
</tr>
<tr>
<td>Research focus:</td>
<td></td>
</tr>
<tr>
<td>Clinic-based research</td>
<td>8 (57%)</td>
</tr>
<tr>
<td>Laboratory-based research</td>
<td>4 (29%)</td>
</tr>
<tr>
<td>Both clinic- and laboratory-based research</td>
<td>2 (14%)</td>
</tr>
<tr>
<td>Length of supervisory experience:</td>
<td></td>
</tr>
<tr>
<td>More than 5 years</td>
<td>7 (50%)</td>
</tr>
<tr>
<td>Type of supervisory experience:</td>
<td></td>
</tr>
<tr>
<td>Primary</td>
<td>7 (50%)</td>
</tr>
<tr>
<td>Auxiliary</td>
<td>6 (43%)</td>
</tr>
<tr>
<td>Not yet supervised at postgraduate research level</td>
<td>1 (7%)</td>
</tr>
</tbody>
</table>

### Table 2 Categories, themes and quotations illustrative of themes in interview data

<table>
<thead>
<tr>
<th>Categories</th>
<th>Themes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Critical issues in successful postgraduate research supervision</td>
<td>Expectations, requirements, time commitments, management communication feedback meetings types of students writing</td>
</tr>
<tr>
<td>Managing problems that arise in postgraduate supervision</td>
<td>Failure to progress planning, preparation feelings, motivation conflict supporting supervisor and student</td>
</tr>
<tr>
<td>Features of an effective postgraduate supervisor development programme in a hospital setting</td>
<td>Positives meeting supervisor’s needs</td>
</tr>
<tr>
<td>Need for ongoing professional development of postgraduate supervisors</td>
<td>Training mentoring</td>
</tr>
</tbody>
</table>

Funding: None.

Conflict of interest: None.
A total of 32 participants completed the Programme evaluation survey (response rate 64%; 16 clinicians). Participants reported an increase in supervisory involvement: most had registered to supervise and expected to supervise more students and become a primary supervisor. All participants reported that through the Programme, they developed supervisory expertise and skills, and increased policy awareness. Almost all reported clarifying thinking about supervision and developing management skills (31/32). Most reported developing a critical self-reflective approach to supervision (28/32). Issues not previously considered had been highlighted (26/32), prompting them to seek advice (24/32). Just over half (17/32) indicated it would be useful to develop further skills through mentorship, discussion with other supervisors and experience, and that more assistance was needed with student progress problems, university policies and thesis completion. Participants indicated they would recommend the Programme to early career (32/32) and senior researchers (24/32).

Of the 23 participants supervising students, half (12/23) reported their improved strengths involved personal qualities, such as approachability, fostering independent thinking, helping students conceptualise projects, giving feedback and availability. Other improved skills included teaching technical skills and scientific writing, taking a structured approach to supervision and clarifying expectations. Most (20/23) reported that the Programme had an enduring influence on their supervisory practice, with some ongoing difficulties (21/23), including student preparedness, performance and progress, and writing and communication.

A key result of our research was the accreditation of many new researchers as primary supervisors, who previously could not take on this role because of lack of time to complete online activities and attend university classes. This is an important outcome, given increasing students at our site.

New clinical academics are commonly keen to learn about doctoral supervision, which can lead to an expanded research programme and promotion. Reflecting prior research, the participants reported that the Programme had highlighted the importance of adapting supervision to individual students’ needs, and discussions of critical issues promoted a reflective approach to supervision. It is important for supervisors to learn about university policies and management skills; however, problems in research supervision can require a more complex approach. Drawing on key literature, the Programme builds on participants’ knowledge and skills, includes disciplinary knowledge by involving local presenters and facilitators, and promotes critical analysis of practice through small group discussion.

Participants reported ongoing difficulties common to postgraduate research supervision, including managing student progress, communication and scientific writing. Other issues specific to hospitals are indicative of the increasing diversity of students and locations. For example, supervisors reported conflicts of interest when students worked alongside the supervisor’s colleagues in a team-based environment, and supervisors were accused of favouritism. However, team-based approaches provide mentorship to inexperienced supervisors and can reduce intense, traditional, individual supervisory relationships. Combining postgraduate research with heavy workloads in hospitals is difficult, highlighting the need for support and education. It is difficult for supervisors to supervise on top of demanding hospital and academic roles. Similarly, it is difficult to supervise students who have heavy clinical commitments or change training hospital. A limitation of the research is that development of supervisors is influenced by a range of factors that is difficult to isolate and measure. However, it appears the Programme helped participants improve their ability to self-reflect and be explicit about supervision issues, knowledge and skills development, and supervisory approach.

If postgraduate research supervisors in hospitals are to improve their practice and involvement through a development programme, it needs to meet local needs. For hospital-based supervisors, an on-site programme ensures local needs are met and access facilitated.

**Acknowledgement**

We thank the participants of this research.

**References**


6 Brew A, Peseta T. Changing postgraduate supervision practice: a
Mobilisation of haemopoietic stem cells in teriparatide-treated patients

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Key words
teriparatide, haemopoietic stem cell, osteoporosis.

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Abstract

Parathyroid hormone (PTH) is the predominant regulator of calcium/phosphate homeostasis in the human body. Beside this classical function, preclinical and clinical studies indicated a relevant role for PTH in mobilisation of bone marrow-derived cells into peripheral blood. In addition, recombinant PTH (teriparatide) was recently approved for the treatment of severe osteoporosis. Therefore, it was the aim of the present study to investigate the dynamics of haemopoietic stem cells and corresponding in peripheral blood of 13 patients with osteoporosis during treatment with teriparatide. We were able to show that administration of teriparatide is sufficient to mobilise haemopoietic stem cells into the bloodstream accompanied by an alteration of mobilising cytokines. In conclusion, teriparatide might be a useful tool in the context of stem cell mobilisation.

Parathyroid hormone (PTH) is a peptide hormone secreted from the parathyroid glands and exerts its main function on calcium/phosphate homeostasis and on bone formation and resorption.1,2 Chronic exposure to high-serum PTH in patients with primary hyperparathyroidism (PHPT) is associated with increased bone resorption.3 In contrast, intermittent administration of recombinant parathyroid hormone (rhPTH), has been demonstrated to stimulate bone formation.4,5 These observations guided the approval of rhPTH for the treatment of severe osteoporosis in postmenopausal women and in men.6,7 Yet, recent preclinical and clinical studies provided evidence that PTH also influences proliferation and mobilisation of haemo-
Clinical application of rPTH in the field of haemopoiesis

G-CSF administration, indicating a possible role of PTH in mobilising HSC in vivo. Additionally, PTH exerts mobilising effects by endogenous release and stabilisation of cytokines and chemokines like granulocyte-colony stimulating factor (G-CSF), stromal cell-derived factor 1 (SDF-1) and vascular endothelial growth factor (VEGF). More recently, it has been demonstrated that at high and escalating dosages, PTH was able to induce stem cell mobilisation in patients which previously failed to mobilise a sufficient number of CD34+ stem cells following G-CSF administration, indicating a possible clinical application of rPTH in the field of haemopoiesis. We therefore sought to investigate in the present study whether rPTH (teriparatide, Forsteo, Lilly, Indianapolis, IN, USA) administered once daily at the dose of 20 μg in osteoporotic patients is able to mobilise haemopoietic stem cells into the bloodstream and whether rPTH treatment is associated with elevated levels of mobilising cytokines.

To address this question, we prospectively investigated 13 patients with osteoporosis who are on therapy with teriparatide at baseline and during treatment and analysed circulating HSC and a selection of chemokines and cytokines involved in stem cell mobilisation and homing.

The patients included in the study were recruited from the Medical Department II (Endocrinology) of the University Hospital Grosshadern in Munich, Germany. The inclusion criteria comprised patients suffering from severe osteoporosis without a concomitant allergic diathesis, calcium abnormalities and drug use that may affect bone marrow cells. Severe osteoporosis is defined as a T-score of less than −2.5 standard deviation with fragility fracture(s). After enrolment and after taking the first blood samples, patients self-administered an injection of teriparatide 20 μg/day subcutaneously and took calcium (1 g) and vitamin D (400–1200 IU) as daily supplements. For comparison of stem cell numbers with healthy controls, CD45+ /CD34+ HSC were investigated in seven healthy adults.

The purpose, nature and potential risks of the study were explained to the patients before their informed consent was obtained. The protocol was approved by the Ethics Committee on Human Research of the Ludwig-Maximilians University of Munich, Germany.

Cytometric analyses were performed using a flow cytometer (FACScan, Becton Dickinson, Heidelberg, Germany) according to International Society for Hematotherapy and Graft Engineering (ISHAGE) guidelines and to a standard protocol. Each analysis included 100 000 events. For immunophenotyping, the following monoclonal antibodies were used: CD45 (conjugated with Peridinin-chlorophyll-protein, clone 2D1, #345809, BD Biosciences, Heidelberg, Germany), CD34 (conjugated with Fluorescein isothiocyanate (FITC), clone 581, #IM 1870, Beckman Coulter Immunotech, Marseille, France). Samples were excluded from evaluation in case of high amounts of cell detritus (>20%), no exact delimitable population in any dot plot or high numbers of positive cells in the isotype control (>2%). Exact numbers of evaluated subjects are included in the figures and tables respectively.

After enrolment, the following routine laboratory parameters were assessed: serum concentration of intact PTH, total calcium (Ca), inorganic phosphate (PO4), creatinine (Cr), 25OH-Vitamin D3 (25OH Vit D3) and thyroid-stimulating hormone (TSH). Serum levels of stem cell factor (SCF), SDF-1 and VEGF were analysed using enzyme-linked immunosorbent assay (R&D Systems, Wiesbaden, Germany). Values represent mean of two measurements.

Results are expressed in mean ± standard error of mean (SEM) as indicated. Data were evaluated for normal distribution by the Anderson–Darling test. All values were significantly different from normal distribution. Therefore, Mann–Whitney U-test was used for statistical testing. Values of P < 0.05 were considered statistically significant. Statistics were calculated using Microsoft Excel (Microsoft Office 2010), PAST v2.17c.

Thirteen patients (12 women and 1 man) with severe osteoporosis were prospectively enrolled to the study. The median age of the patients was 78 years old (range 56–86 years old). Osteoporosis was diagnosed by bone mineral density at the lumbar spine or the hip. All patients had a history of bone fractures. Furthermore, one patient suffered from polymyalgia rheumatica, and another patient suffered from atrial fibrillation. All patients showed normal laboratory findings for PTH, calcium, phosphate, 25OH-Vitamin D3, creatinine and TSH (Table 1).

Escalating dosages of PTH combined with subsequent G-CSF administration were shown to induce sufficiently

Table 1 Laboratory parameters

<table>
<thead>
<tr>
<th>Osteoporosis patients (n = 13)</th>
<th>Normal limits</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTH, pg/mL</td>
<td>32.9 ± 2.2</td>
</tr>
<tr>
<td>Ca, mmol/l</td>
<td>2.47 ± 0.02</td>
</tr>
<tr>
<td>PO4, mg/dl</td>
<td>3.55 ± 0.13</td>
</tr>
<tr>
<td>25OH-Vit D3, ng/mL</td>
<td>29.4 ± 2.6</td>
</tr>
<tr>
<td>Cr, mg/dl</td>
<td>0.88 ± 0.04</td>
</tr>
<tr>
<td>TSH, μU/mL</td>
<td>1.34 ± 0.19</td>
</tr>
</tbody>
</table>

Values are mean ± SE for n = 13 osteoporosis patients. Relevant laboratory parameters in our study population. 25OH-Vit D3, 25OH Vitamin D3; Ca, calcium; Cr, creatinine; PO4, phosphate; PTH, parathyroid hormone; TSH, thyroid-stimulating hormone.
mobilisation of CD34+ cells in G-CSF non-responders. Therefore, we assessed the mobilisation capacity of rPTH in dosages routinely used for the treatment of osteoporosis. Before starting treatment with teriparatide, peripheral blood of patients suffering from osteoporosis contained 0.06 ± 0.01% CD45+/CD34+ stem cells and did not differ significantly from that of healthy controls (n = 7, 0.09 ± 0.06%, non-significant). Peripheral blood was examined again 37 ± 7 days after initiation of treatment in these patients. The number of CD45+/CD34+ HSC significantly increased to 0.23 ± 0.02% (P < 0.01; 3.8-fold; Fig. 1).

PHPT has been previously shown to be associated with elevated cytokines and chemokines involved in stem cell mobilisation and migration. We therefore investigated the levels of three important cytokines VEGF, SDF-1 and SCF in our cohort. Compared to healthy controls from literature, our study cohort showed similar serum levels for VEGF (442.2 ± 119.8 pg/mL vs 260 ± 135 pg/mL in the publication of Senel et al.14), SCF-1 (851.2 ± 87.3 pg/mL vs 979 ± 181 pg/mL in the publication of Kitoh et al.4) and SDF-1 (2832.3 ± 227.2 pg/mL vs a median of 2851 (range 2642–3237) in the publication of Moniuszko et al.23) before treatment with teriparatide. Serum levels of VEGF showed a trend versus elevation during treatment with teriparatide compared to levels measured before starting treatment (683.9 ± 143.9 pg/mL vs 442.2 ± 119.8 pg/mL, P = 0.11; Fig. 2a,b). In addition, SDF-1 serum levels were elevated (3394.1 ± 159.8 pg/mL vs 2832.3 ± 227.2 pg/mL, P = 0.06; Fig. 2c,d). Furthermore, SCF serum levels were increased without significance (1008.6 ± 42.6 pg/mL vs 851.2 ± 87.3 pg/mL, P = 0.22, Fig. 2e,f).

In the present study, we were able to show that teriparatide administered at a dose of 20 μg s.c. once daily is sufficient to mobilise haemopoietic CD45+ /CD34+ stem cells into peripheral blood. Additionally, cytokines which are involved in stem cell mobilisation and homing, in particular SDF-1, were increased in peripheral blood.

Our findings confirm previous preclinical studies showing mobilisation of HSC after administration of PTH. Regarding the mobilisation capacity, our results are consistent with recent findings of Yu et al., who reported a –2-fold increase of HSC after teriparatide treatment. Nevertheless, in rodents as well in humans, the mobilising effect of G-CSF is more distinct. As we reported previously, G-CSF led to a 3.8-fold increase of Lin−/Sca-1−/c-kit+ bone marrow-derived stem cells in hearts of mice with acute myocardial infarction, whereas PTH only led to a 3.3-fold increase. Furthermore, patients with myocardial infarction showed a sixfold increase of CD34+ cells after treatment with G-CSF. Whereas our cohort showed normal serum levels of VEGF, SCF and SDF-1 at baseline, treatment with teriparatide led to an increase of SDF-1. Also serum levels of VEGF and SCF showed a slight increase during teriparatide treatment. The fact that results reached no significance – as previously described for VEGF and SDF-1 in patients with PHPT – might be due to the small number of patients analysed. Furthermore, patients with PHPT show a constant PTH stimulation, which might lead to a more pronounced cytokine response. VEGF, SCF and SDF-1 are known to stimulate mobilisation of bone marrow-derived stem cells. Therefore, enhanced endogenous secretion of these factors might represent a mechanism of action of teriparatide induced mobilisation of HSC. Nevertheless, VEGF has been shown to correlate with bone marrow density in mini pigs with glucocorticoid-induced osteoporosis. Furthermore, parathyroid hormone is known to act as a dipeptidyl peptidase IV inhibitor, therefore stabilising the serum level of SDF-1. Thus, it cannot be excluded that the augmented levels observed in our study during teriparatide treatment might simply represent an epiphenomenon.

In summary, our study shows that daily teriparatide treatment is able to mobilise HSC. Teriparatide-induced endogenous secretion of mobilising cytokines might represent a possible mechanism of action. Therefore, teriparatide might be a useful tool in the context of stem cell mobilisation.

Acknowledgements

We thank Mrs J. Arcifa (Medical Department I, Campus Grosshadern, Ludwig-Maximilians-University) for excellent technical assistance.
References


Figure 2. Cytokine serum levels. Cytokine serum levels of (a,b) vascular endothelial growth factor (in pg/mL), (c,d) stromal cell-derived factor 1 (in pg/mL) and (e,f) SCF (in pg/mL) in patients before and during treatment (37 ± 7 days after initiation of treatment) with teriparatide. Error bars showing standard error of the mean. n = 13.
Brief Communications


Clinical-scientific notes

An unusual cardiovascular adverse effect of donepezil

A 56-year-old woman was admitted to our emergency room with presyncope and dizziness. Her cardiovascular history was unremarkable. On admission, vital signs were respiratory rate of 22/min, blood pressure of 90/50 mmHg and pulse rate of 40/min. She looked exhausted and sweaty. She was using only donepezil as a drug that was started from the neurology department for dementia 1 week earlier. Electrocardiogram (ECG) revealed different P wave morphology heart rate of 40 b.p.m. (Fig. 1) was compatible with wandering atrial pacemaker. Laboratory examination showed normal electrolyte and troponin levels. The patient was admitted to coronary care unit and was decided to follow up with cessation of donepezil. After 48th follow up, the rhythm was resolved. ECG showed normal sinus rhythm with heart rate of 67 b.p.m. The patient discharged without any problem, she was well at 1 month follow up and was using another drug for her disease other than donepezil.

Cholinesterase inhibitors (ChEI) are the first-line treatment of Alzheimer disease. Heart rate and cardiac function are mainly dominated by the parasympathetic system.1 Increased level of acetylcholine enhances gamma-aminobutyric acid and glycinergic inhibitory receptors by triggering vagal activity. The heart is well supplied with cholinesterase. ChEI can cause adverse effects, especially in elderly patients with underlying conduction disorder.2 The side-effects of ChEI are consistent with bradycardia, QT interval prolongation and heart block. Vagotonic effect is an acceptable mechanism.2

Donepezil is a second generation, a reversible inhibitor of cholinesterase that is generally used for the treatment of Alzheimer disease.2 It is mostly thought as a well-tolerated drug; however, case studies related with cholinergic cardiovascular side-effects have been reported.3–5

The sinoatrial node is the primary pacemaker of the heart. The pacemaker shift is responsible for changed P wave morphology and PR interval duration on ECG.6 Wandering atrial pacemaker (WAP) is an arrhythmia, with at least three different P wave morphologies, which is also called ectopic atrial pacemaker. It is a less-known dysrhythmia than the others. WAP is generally caused by changing vagal tone. With increased vagotonic effect, the sinoatrial node burst slowly, allowing a pacemaker in the atria or atrioventricular nodal area. After the vagal tone decreases or secondary causes go away, the sinoatrial node assumes its natural pace. Ventricular conduction is normal with WAP, and thus the QRS complex is usual.

In conclusion, ChEI have cholinergic side-effects, and elderly people, especially those who are using digoxin or beta blockers, are more susceptible to adverse effects of ChEI. Cessation of the drugs provides normal rhythm in most patients. To our knowledge, this is the first case report related with donepezil and its rare cardiovascular adverse effect.

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Figure 1 Electrocardiogram demonstrating wandering atrial pacemaker with different P waves.
Beware the dog that didn’t bark: a tale of creatinine in acute kidney injury

A rapid reduction in creatinine concentration within 24 h of cardiac arrest is reported to associate with better clinical outcomes while stable or increasing creatinines are associated with higher mortality.1

We reviewed the records of all adults (>17 years) suffering out of hospital cardiac arrest followed by induced hypothermia in the Christchurch Hospital intensive care unit (ICU) in 2013. Sequential plasma creatinine results for the first 36 h were grouped according to percentage change in creatinine at admission baseline, at 3–7 h, at >7–11 h and at >11–36 h. Increased creatinine (pCr_increase) was defined as a ≥20% increase from baseline, stable creatinine (pCr_stable) as neither an increase (<20%) nor decrease (>9%), and decreased creatinine (pCr_decrease) as a ≥10% reduction from baseline (Fig. 1). Baseline creatinine was defined as the first available creatinine after cardiac arrest. Mortality data were collected in ICU and at hospital discharge.

Of a total of 57 patients, nine were in the pCr_increase group of whom five died (56%), 15 were pCr_stable of whom 10 died (67%), and 33 in the pCr_decrease group of whom 12 died (36%) (Fig. 1). The mortality rate was greater in the pCr_stable group compared with the pCr_decrease group (P = 0.018). We were unable to distinguish whether the cause of death was due to cardiogenic shock or severe hypoxic brain injury, because many individuals had both conditions, often with other pathologies, such as aspiration pneumonia.

However, these results highlight concerns with the use of plasma creatinine as a biomarker and in creatinine-based guidelines for acute kidney injury (AKI) diagnosis2,3 as the definitions assume creatinine generation is constant. If creatinine generation is con-

Figure 1 Changes in plasma creatinine concentration (%) relative to the first creatinine measured after cardiac arrest. Solid lines represent mean percentage change in plasma creatinine for each group; dotted lines depict 95% confidence limits. The mean baseline creatinine concentration for the pCr_increased group was 168 μmol/L (SD: 99), for the pCr_decreased group; 145 μmol/L (SD: 65) and for the pCr_stable group; 111 μmol/L (SD: 23). In the pCr_increased group, two patients died before the third sample (>7–11 h) was collected. In the pCr_decreased and pCr_stable groups, one and two patients in each group died, respectively, before 7 h post-admission to the emergency department. , increase; , stable; , decrease.

References

stant, an increase in concentration is expected with reduced renal perfusion following cardiac arrest. AKI is complex and heterogeneous in aetiology, with manifestations varying from minimal or no elevation in creatinine to anuric renal insufficiency with large increases in creatinine concentration. Although reduced urine output is in the consensus definitions of AKI, a decrease in urine output may follow structural or obstructive kidney disease, and recent evidence suggests the urine output criteria are too liberal. Urine creatinine excretion has been shown to be decreased in those requiring longer hospital stay suggesting the presence of decreased creatinine production. We hypothesise that creatinine generation decreases post-cardiac arrest. The pCrdecrease group can then be explained by clearance with near-normal glomerular filtration rate (GFR). In this scenario, the unchanging creatinine in the pCrstable group is attributable to the combination of decreased creatinine production with GFR impairment.

Prowle et al. recently documented a reduction in creatinine in patients who survived critical illness. Like Arthur Conan Doyle’s Sherlock Holmes (in *The Hound of the Baskervilles*), we caution clinicians (to ‘beware’) that plasma creatinine concentrations (‘the dog’) may not alert us to underlying AKI as is shown in the pCrstable (‘that didn’t bark’) group. Therefore, this suggests the need for intervention when creatinine does not decrease immediately after cardiac arrest. Future research could be aimed at measuring creatinine production to assess its role in patients with acute illness.

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**References**


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**Unusual presentation of Epstein–Barr virus encephalitis in an older patient with a dramatic clinical response to intravenous immunoglobulin**

Epstein–Barr virus (EBV) usually presents non-specifically, or with infectious mononucleosis, a clinical syndrome characterised by lymphadenopathy, pharyngitis and fever, with atypical lymphocytosis. EBV is less common in adults, as 90–95% already have antibodies. Central nervous system complications, including encephalitis, are uncommon.

A 66-year-old independent woman with no significant past history presented alert and oriented after a complex partial seizure. She experienced chills, lethargy, nausea, anorexia and a dull frontal headache 4 days prior. Physical examination was unremarkable.

Investigations are displayed in Table 1. She was commenced on oral levetiracetam 1 g t.d.s. and intravenous (IV) acyclovir 740 mg t.d.s. Two days post admission, she became acutely confused, disoriented, tachycardic, hypertensive and pyrexic.

She was found to have hospital-acquired pneumonia and mild cellulitis, so she was administered IV cefazolin 1 g daily and a single dose of gentamicin 5 mg/kg.

She was commenced on IV amoxicillin 2 g t.d.s. for queried leptospirosis or listeria and a 5-day course of intravenous immunoglobulin (IVIG) 0.4 g/kg daily for
Table 1 Investigation results

<table>
<thead>
<tr>
<th>Test (Unit of measurement)</th>
<th>Normal range</th>
<th>Day 0</th>
<th>Day 3</th>
<th>Day 4</th>
<th>Day 7</th>
<th>Day 12</th>
<th>Day 15</th>
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<tbody>
<tr>
<td>CT head scan</td>
<td>–</td>
<td>NAD</td>
<td>–</td>
<td>–</td>
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<tr>
<td>MRI head scan</td>
<td>–</td>
<td>–</td>
<td>Mesial temporal T2 hyperintensity</td>
<td>–</td>
<td>Mesial temporal T2 hyperintensity</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Neck to pelvis CT scan</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Biaxillary and mediastinal lymphadenopathy and hepatomegaly</td>
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</tr>
<tr>
<td>Whole body PET scan</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Low-grade lymphoproliferative process involving bilateral axillary nodes, inguinal nodes and spleen</td>
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</tr>
<tr>
<td>Electroencephalography</td>
<td>–</td>
<td>Epileptiform</td>
<td>–</td>
<td>Encephalo-pathic</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>White cell count (×10^9 L)</td>
<td>4–11</td>
<td>6.39</td>
<td>12.5</td>
<td>10.5</td>
<td>12.2</td>
<td>8.37</td>
<td>5.85</td>
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<tr>
<td>Lymphocytes (×10^9 L)</td>
<td>1.30–3.50</td>
<td>1.41</td>
<td>4.14 (reactive lymphocytes)</td>
<td>4.29</td>
<td>8.29</td>
<td>4.09</td>
<td>3.51</td>
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<tr>
<td>C-reactive protein (mg/L)</td>
<td>&lt;5</td>
<td>140</td>
<td>240</td>
<td>230</td>
<td>48</td>
<td>–</td>
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<td>Creatinine (μmol/L)</td>
<td>50–120</td>
<td>51</td>
<td>51</td>
<td>205</td>
<td>41</td>
<td>68</td>
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<tr>
<td>Bilirubin (μmol/L)</td>
<td>6–24</td>
<td>13</td>
<td>25</td>
<td>43</td>
<td>33</td>
<td>15</td>
<td>12</td>
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<td>Gamma-glutamyl transferase (U/L)</td>
<td>0–60</td>
<td>325</td>
<td>731</td>
<td>1084</td>
<td>2219</td>
<td>1606</td>
<td>1203</td>
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<tr>
<td>Alkaline phosphatase (U/L)</td>
<td>30–110</td>
<td>203</td>
<td>456</td>
<td>584</td>
<td>956</td>
<td>910</td>
<td>647</td>
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<tr>
<td>Alanine transaminase (U/L)</td>
<td>5–40</td>
<td>254</td>
<td>240</td>
<td>302</td>
<td>310</td>
<td>76</td>
<td>38</td>
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<tr>
<td>Aspartate aminotransferase (U/L)</td>
<td>0–45</td>
<td>325</td>
<td>232</td>
<td>240</td>
<td>385</td>
<td>90</td>
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<tr>
<td>Lactate dehydrogenase (U/L)</td>
<td>110–230</td>
<td>777</td>
<td>598</td>
<td>632</td>
<td>534</td>
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<td>Serum autoimmune hepatitis antibodies</td>
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<td>–</td>
<td>Negative</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
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<td>Liver ultrasound</td>
<td>–</td>
<td>Fatty liver</td>
<td>–</td>
<td>–</td>
<td>–</td>
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<tr>
<td>Cerebrospinal fluid</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
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<tr>
<td>Mononuclear cells (×10^6 L)</td>
<td>&lt;5</td>
<td>2</td>
<td>–</td>
<td>10</td>
<td>–</td>
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<tr>
<td>Polymorphonuclear cells (×10^6 L)</td>
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<td>–</td>
<td>1</td>
<td>–</td>
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<tr>
<td>Red blood cells (×10^6 L)</td>
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<td>–</td>
<td>5</td>
<td>–</td>
<td>–</td>
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<tr>
<td>Protein (g/L)</td>
<td>0.10–0.65</td>
<td>0.45</td>
<td>0.66</td>
<td>–</td>
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<tr>
<td>Cultures</td>
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<td>Negative</td>
<td>–</td>
<td>Negative</td>
<td>–</td>
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<tr>
<td>EBV DNA PCR</td>
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<td>–</td>
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<td>Not detected</td>
<td>–</td>
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<td>Enterovirus RNA</td>
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<td>–</td>
<td>Not detected</td>
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<tr>
<td>Herpes simplex virus 1 and 2 DNA</td>
<td>–</td>
<td>Not detected</td>
<td>–</td>
<td>Not detected</td>
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<tr>
<td>Varicella/Zoster virus DNA</td>
<td>–</td>
<td>Not detected</td>
<td>–</td>
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<td>–</td>
<td>–</td>
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<tr>
<td>EBV IgG antibody†</td>
<td>&lt;1.0</td>
<td>0.08</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>5.28</td>
<td>4.32</td>
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<tr>
<td>EBV IgM antibody†</td>
<td>&lt;1.0</td>
<td>0.22</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>1.36</td>
<td>1.47</td>
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<tr>
<td>Serum EBV PCR (×10^4 copies/mL)</td>
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<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>1.5</td>
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<td>Cytomegalovirus serology</td>
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<td>–</td>
<td>–</td>
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<tr>
<td>Hepatitis A, B, C serology</td>
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<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
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<tr>
<td>HIV serology</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
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<tr>
<td>N-methyl-D-aspartate receptor autoantibodies</td>
<td>–</td>
<td>–</td>
<td>Not detected</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

†Immunooassay results are expressed as signal to cut-off ratios (S/Co). Ratios ≥1.0 are considered reactive. CT, computed tomography; DNA, deoxyribonucleic acid; EBV, Epstein–Barr virus; HIV, human immunodeficiency virus; MRI, magnetic resonance imaging; NAD, no abnormality detected; PCR, polymerase chain reaction; PET, positron emission tomography.
suspected limbic encephalitis. The next day, her confusion significantly improved, and she clinically improved to baseline over several days.

Morphology and immunophenotyping of excisional lymph node biopsy material was consistent with acute EBV infection. Blood and serum EBV immunoglobulin G (IgG) and immunoglobulin M (IgM) antibodies, which were negative on admission, were detected.

A diagnosis of encephalitis and hepatitis secondary to EBV was made based on the histopathology and immunohistochemistry, positron emission tomography scan, viral polymerase chain reaction (PCR), and serology results.

This case illustrates an unusual presentation of EBV. The initial seizure, cerebrospinal fluid (CSF) pleocytosis and subsequent encephalopathy, developing prior to severe liver function tests derangement, were demonstrative of encephalitis, as opposed to hepatic encephalopathy. Autoimmune encephalitis triggered by EBV was unlikely in the absence of an anti-EBV immune response at encephalitis presentation, as evidenced by initially negative serology and absent CSF pleocytosis.

A limitation was the negative CSF EBV PCR. However, in a previous review of EBV-associated encephalitis cases, this was detected in only 48%.1

The changes caused by EBV encephalitis on brain imaging, specifically magnetic resonance imaging, are non-specific,2 as was the case in our patient.

The rapid improvement of encephalopathy following IVIg suggested a therapeutic benefit. Viral encephalitis is not an approved indication for use in Australia.4 Use in EBV encephalitis has not been previously documented.

IVIg has been reported to treat successfully encephalitides of other viral aetiologies.5

Our patient displayed delayed EBV seroconversion. It is possible the IVIg could have resulted in a positive IgG titre. However, it is unlikely to explain the formation of IgM antibodies, particularly at the titre found, in combination with positive serum EBV PCR.6 The lymph node pathology and previously negative serology confirmed acute primary infection.

We report an immunocompetent adult patient who presented with a seizure and progressive encephalopathy secondary to EBV encephalitis. EBV is uncommon in adults and encephalitis is a rare presentation. A negative CSF EBV PCR does not preclude diagnosis. Full clinical recovery occurred coincident with IVIg therapy. This rapid improvement was potentially serendipitous, and an IVIg treatment effect is biologically plausible.

Acknowledgements
The authors thank Dr Geoffrey Higgins (Microbiologist and Infectious Diseases Physician, The Royal Adelaide Hospital) for review of the serology results, and Dr Daniel Kearney (Pathologist, The Royal Adelaide Hospital) for review of the pathology relating to our case report.

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References

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Cardiac findings in obesity hypoventilation syndrome: is there a need for specific approach and evaluation?

Despite research, the exact pathophysiological mechanisms that are responsible for causing obesity hypoventilation syndrome (OHS) have not been clearly defined.1–3 The syndrome may result from complex interactions among impaired respiratory mechanics, abnormal central ventilator control, possible sleep-disordered breathing and neurohormonal aberrancies.4 Additionally, little is known concerning OHS-associated morbidity, in particular cardiovascular morbidity.

We read with great interest the results of Alawami et al.5 and consider that some aspects could be analysed for proper practice extrapolation. In this article, Alawami et al. attempt to establish a correlation between OHS and cardiovascular disease (CVD) with a retrospective analysis of 47 clinical records from a Sleep Disordered Breathing Service in Auckland.3 A small number of patients, high prevalence of right ventricular impairment, pulmonary hypertension, diastolic dysfunction and arrhythmias were noted in patients with OHS. These are interesting aspects to take into account.

First, cardiac function assessment was limited in this study due to the fact that a retrospective consultation carried poor quality of images, limited data and heterogeneity of echo systems that were used. Trained technicians performed echocardiograms; however, examination results are always dependent of the observer, which can pose as a limitation. Nonetheless, discrepancies found between the assessments of left ventricular hypertrophy by echocardiogram present an interesting finding. This information is useful for physicians to recall that mechanical limitations imposed by obesity can limit the information given by complementary examinations in this particular population. As such, there can be an occurring underestimation of cardiac problems.

Second, previous studies had documented the propensity of cardiac arrhythmias (atrial fibrillation) to occur more frequently in obstructive sleep apnoea (OSA) patients.6 This study draws the attention to the probable association of OHS and cardiac arrhythmias, describing other recurrent arrhythmias, including supraventricular and ventricular tachycardia not described before. However, a causal relationship between arrhythmia and OHS could not be established in this study as there are many other predisposing factors (e.g. OSAs, myocardial remodelling). Third, an interesting aspect that should be emphasised is the fact that all patients in this study were already under nocturnal treatment with non-invasive ventilation (NIV) (although no information is given whether these patients are compliant and well adapted to treatment), which means that perhaps these cardiovascular findings might be even more accentuated and/or prevalent in patients naïve of treatment.

Fourth, it would be interesting to know some key relevant aspects such as: (i) information on severity of OSA and nocturnal hypoxia; (ii) there is neither information on NIV mode, continuous positive airway pressure (CPAP) and automatic CPAP (APAP), nor efficacy on duration of therapy, (iii) information regarding efficacy of NIV/CPAP plays a major prognostic role in patients with heart failure7 and this point should be addressed.

Last, the study by Alawami et al.5 study poses an important starting point that shows a tendency for higher prevalence of CVD in OHS receiving NIV, although this study is limited by its small size. As such, further large-scale prospective studies are needed to determine specific cardiovascular risks for OHS patients, which might eventually lead to a different approach to this syndrome.

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References

Author reply

We read with interest the letter from Esquinas et al.,1 who commented on our paper2 regarding the cardiac findings in patients with obesity hypoventilation syndrome. We agree that the finding from echo can easily be discrepant when compared with the electrocardiogram (ECG) findings and that left ventricular hypertrophy can be missed when assessed by an ECG only. We also agree that prospective study of this group of patients would be very beneficial to try to identify the risks in terms of cardiovascular risk, especially arrhythmias, such as atrial fibrillation and ventricular tachycardia in these patients, and to study the effects of effective non-invasive ventilation.

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References


Improving ambulatory patient-centred practice with a patient teaching associate programme

Fiddes et al. reported impressive emerging qualitative evidence of favourable patient-centred outcomes achievable through patients’ active role in education programmes.1 We believe that learning through direct patient contact is an essential practical step to envision a patient-centred, team-based professionalism. However, the current changing acute healthcare models have shortened patient stay and increased devolution from acute to ambulatory care. Hence, medical students’ access to patients is contracting, threatening the sound development of foundation clinical skills. This is in the face of increased complexity of managing chronic illness in an ageing population and increased health literacy requiring the future workforce to provide patient-centred, personalised medicine.

We incorporate multisource feedback from patient volunteers, tutors and peer students to provide immediate oral feedback on student performance during consultation style teaching in a student-led clinic. This programme is closely modelled on the novel Patient Partner Programme (P3) in the University of Tasmania2 and was translated to Monash University’s Eastern Health Clinical School as the ‘P3 PTA’ programme. The Patient Teaching Associates (PTA) are enthusiastic ambulatory patient volunteers living with chronic conditions who provide their personal stories and an unhurried and safe learning environment for junior clinical medical students.3 Besides oral feedback based on a suggested framework, PTA volunteers also provide written structured consumer feedback using patient satisfaction scores to enhance patients’ active participation in their healthcare.

teaching role and to promote reflective learning in realistic settings.

Logistic and educational challenges of implementation highlighted the value of starting small and having a clear plan, defined expectations, experienced mentors, key staff with necessary skills, and supportive faculty and associates. True partnerships, developing close rapport with the programme coordinator and regular contacts, are driving factors to engage PTA volunteers. Adequate briefing is crucial to put PTA at ease of telling their stories as ‘real patients’ in the simulated teaching clinic.

The programme has successfully trained 71 students enrolled in 2013. Learner and teacher feedback was very positive, favourably contrasting the P3 PTA learning environment to experiences in the acute setting. Feedback from multiple modalities suited learners with different styles. This innovation lessened the impact of changes in acute care on clinical education.

There is little evidence that patient feedback provides measurable benefits in medical students.1 Therefore, we are evaluating the effectiveness of additional written patient feedback with guided self-reflection in a randomised controlled trial.4 We hope to identify critical elements necessary to support recruiting patients as teachers in educating future doctors about professionalism and chronic conditions, so that the benefits can be replicated.

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References

Author reply

The letter by Lai et al.1 describes an encouraging study involving medical students and patient teaching associates in a simulated teaching setting in which students receive direct feedback that has the potential to guide their developing professionalism. The letter refers to a review article published by myself, Brooks and Komesaroff,2 concerning interprofessional education (IPE) involving mixed health discipline students collaborating to learn from patients with the aim of improving healthcare.2

The ‘impressive emerging qualitative evidence’ in our paper referred to by Lai et al. consisted of outcomes from IPE engagements that had been identified by patients who indicated that they ‘felt more able to manage their health’ and enjoyed being involved in medical student education. Their outcomes were provided to the educators who subsequently gave constructive feedback to the mixed students as carefully considered comments about their clinical engagement that took into account both the patients’ responses and other factors.

It will be of importance to assess the impact of direct patient feedback to students on their learning outcomes and behaviours. We look forward with interest to seeing the outcomes of Lai et al.’s further investigations.

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References

Sustainability of deprescribing post discharge

It is with great interest I read the timely article on deprescribing by Scott and Le Couteur\(^1\) in the March issue of *Internal Medicine Journal*.

The authors have identified several key barriers to deprescribing, such as variable knowledge, skills and attitude, and have provided the readers with a practical framework while considering deprescribing.

Other barriers, may I add, is the questionable sustainability of deprescribing post discharge, and whether the hospital is the best milieu to start the deprescribing process, which needs effective engagement, communication and understanding (consent) on the patient’s part, all of which may be compromised in an acutely unwell patient. Besides, with pressures for timely discharge and rapid turnover of patients in busy hospitals, time constraints may not permit for effective monitoring of withdrawal or rebound symptoms, and carries a risk of misadventure.

Evidence is also limited regarding the long-term outcomes of deprescribing as most studies are of short duration. One study, namely the ‘Discontinuing Inappropriate Medication in Nursing Home Residents’ (DIM-NHR), a cluster randomised controlled trial, will examine the efficacy using a multidisciplinary multistep medication review and may shed light on how stakeholders other than geriatricians view deprescribing.\(^2\)

In the community, cessation of medicine is the most common yet the least enacted recommendation by general practitioners following a medication review,\(^1\) again due to resource constraints.

Given the above limitations, it is vital to consider diligent deprescribing as part of routine practice by all prescribers in all settings rather than an isolated or opportunistic activity in an acute setting.

From a systems perspective, deprescribing alerts may be built into the prescribing software and random audits undertaken to ascertain uptake.

Evidence needs to be built on both long- and short-term outcomes of deprescribing. Importantly, patient engagement is vital.

As the adage goes, ‘medicines are but poisons in small doses’, why start them let alone stop them?

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References


Author reply

We are gratified that our article\(^1\) has provoked the interests and thoughts of training physicians, such as Ramanathan.\(^2\) We concede deprescribing is challenging and competes in terms of time with other care imperatives in busy acute hospital settings. Nonetheless, we feel hospital physicians, as overseeing specialists, do need to provide guidance to general practitioners (GP) who may otherwise be loath to consider deprescribing in the absence of empowerment by treating specialists. We recognise that deprescribing needs to be continued in consultation with GP post-discharge, as some drugs will require slow weaning, and in other cases, ongoing indications for drugs, flagged for possible discontinuation, while the patient is in hospital, need to be confirmed by the GP in consultation with patients. As a compromise, deprescribing efforts may be best aimed at patients with longer lengths of stay which allows more time for collation of background information and involvement of patients and family during the convalescent period. Having said this, some drugs (e.g. statins) can be ceased quickly and safely even during a short hospital stay if thought appropriate. In all cases of deprescribing early follow up with the patient’s GP or review at a hospital clinic should be arranged to monitor for any withdrawal or rebound effects, and patients should be educated about recognising and notifying members of the treating team.
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of such occurrences. We feel good inpatient care does oblige physicians to appraise systematically the clinical utility of long-standing medication lists, especially in regards to older patients with eight or more medications or who are frequent hospital attenders or have been admitted with drug-related problems. Hospital clinical pharmacists can also assist in the identification and withdrawal of drugs that are considered inappropriate.

References


Endovascular treatment of acute ischaemic stroke

Patient ethnicity and medical student bias

Pacemaker outcomes by funding

Extreme hyperferritinaemia – clinical significance

Anti-cancer drugs: benefits and harms

Guidelines for Echocardiography