EDITORIALS

Editorials are usually commissioned. We are, however, happy to consider and peer review unsolicited editorials

Guideline recommended treatments in patients with multimorbidity

New evidence is reassuring, but every patient is different

Christiane Muth senior researcher, Institute of General Practice, Johann Wolfgang Goethe University, Frankfurt, Germany muth@allgemeinmedizin.uni-frankfurt.de
Paul P Glasziou professor of evidence based medicine, The Centre for Research in Evidence-Based Practice, Bond University, Robina, Queensland, Australia

Multimorbidity is an increasing problem for both clinicians and patients. Ageing populations, the increased complexity of managing chronic illness, and the tendency of guidelines to focus on a single disease have created a "perfect storm" of treatment burden. Consider the following patient: "Mrs S is a 79 year old woman with osteoporosis, osteoarthritis, type 2 diabetes mellitus, hypertension, and chronic obstructive pulmonary disease who takes 12 separate drugs in 19 doses five times during a typical day. A drug review revealed three drug-disease interactions, nine drug-drug interactions, and eight potential drug-food interactions."

With this hypothetical case, a decade ago one study showed that applying multiple guidelines to a patient with multimorbidity creates three problems[1]: firstly, as comorbidity is a common reason for exclusion in clinical trials it is not known whether treatment effects in patients with multimorbidity are equivalent to those in patients with single diseases.[2 3] Secondly, the application of multiple disease oriented guidelines bears the risks of potentially harmful interactions between diseases and treatments.[4 5] Thirdly, an uncritical application of multiple guidelines adds to the burden of treatment of patients with multimorbidity, which may exceed patients' willingness or capability to cope.[6]

Pointing in the same direction?

In a linked paper, pioneering work by Tinetti and colleagues tackles the first of these three problems.[7] Using three years' follow-up of population data representative of older US citizens who had at least two out of nine common chronic conditions, the authors investigated the effects on survival of nine guideline recommended and frequently prescribed drugs in older patients with multimorbidity taking multiple drugs. In line with the high prevalence of cardiovascular diseases, drugs recommended for these conditions were at the core of their analyses.

RADIUS/ALAMY

Treatment burden

In comparison with effects shown in randomised trials, the authors found a similar mortality reduction associated with four drugs (β blockers, calcium channel blockers, renin-angiotensin system blockers, and statins), variable effects with respect to comorbidity in one drug (warfarin), and a lack of effects on survival with the remaining three drugs (metformin, clopidogrel, and selective serotonin reuptake inhibitors or serotonin norepinephrine (noradrenaline) reuptake inhibitors).[7]

These findings are in line with those from previous studies. For instance, an individual patient data meta-analysis of randomised trials found comparable effects of statins on major coronary and vascular events in patients with or without previous coronary heart disease, type 2 diabetes mellitus, and hypertension.[8] In observational studies, statins reduced mortality also in older and very old patients, with or without diabetes or frailty, irrespective of the presence or absence of coronary heart disease or of glucose lowering drugs.[9-11] Tinetti and colleagues' work adds another important piece of evidence: statins and other guideline recommended cardiovascular drugs seem to be effective in complex patients with multiple conditions taking a mean number of 10 drugs daily.

> This study reassures us that treatments may be broadly as effective in patients with multimorbidity as they are in patients with single diseases

The effectiveness of treatment strategies may be attenuated in certain subpopulations and may vary with age. Patterns of comorbidity may play a role when considering the generalisability of Tinetti and colleagues' results: with more than 10 000 known diseases, there are vast numbers of potential combinations within individual patients, and attempts to identify patterns (or clusters) of diseases have yielded inconsistent results.[14 15]

Most of the medical conditions selected by Tinetti and colleagues have concordant therapeutic pathways and treatment goals. Potentially harmful interactions may occur more often in discordant coexisting conditions such as asthma and chronic heart failure. Although some patients in the study did not receive guideline recommended treatment, this may have been a doctor's deliberate choice rather than mere variation in practice, and this introduces the possibility of confounding. The real benefits of β blockers in heart failure could be exaggerated, for example, because some unexposed patients had comorbid asthma. These patients were unable to take β blockers[16] and at the same time had a higher mortality due to their asthma.[17]

As the authors point out, such unmeasured confounding cannot be excluded in observational studies. Since we cannot conduct randomised controlled trials evaluating treatments in all relevant combinations of comorbidities, we have to accept some uncertainty.

As discussed by Tinetti and colleagues, many questions remain about the effects of guideline recommended treatments in different patient groups with other conditions and outcomes of interest. However, the new study reassures us that treatments may be broadly as effective in patients with multimorbidity as they are in patients with single diseases, so guidelines may be safe and effective, as "we have little with which to replace them."[18] But the other two problems of interactions and treatment burden remain. We cannot assess whether a specific treatment is beneficial for a patient without considering potential interactions between diseases and treatments. We must also establish a clear understanding of each patient's circumstances, preferences, and treatment goals, along with close follow-up of goal attainment.[19] Only then will patients avoid being "left confused and even tyrannised when their clinical management is inappropriately driven by algorithmic protocols, top-down directives, and population targets."[20]

Cite this as: *BMJ* 2015;351:h5145

RESEARCH, p 13

Women with small, node negative breast cancers now have a five year survival rate close to that of the general population

thebmj.com Read more breast cancer articles at bmj.co/breast-cancer

With better adjuvant therapy, does breast cancer stage still matter?

Catching cancers when they are small still makes a difference to survival

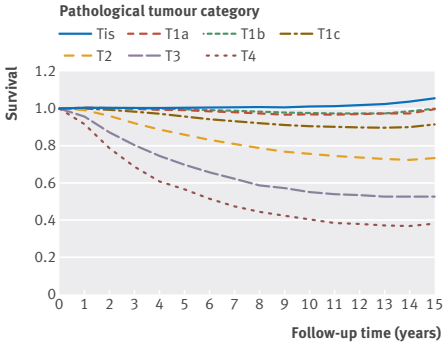
Ines Vaz-Luis instructor in medicine
Harold J Burstein associate professor of medicine, Dana Farber Cancer Institute, Harvard Medical School, Boston, MA, USA hal_burstein@dfci.harvard.edu

Breast cancer mortality is declining throughout the Western world.[1-3] If, as J F Kennedy said, "victory has a thousand fathers," then progress in breast cancer surely has a lot of parents. In the late 1970s, guidelines recommended screening mammography for women over the age of 40, resulting in implementation of national and regional screening programmes in most developed countries. Soon after, adjuvant endocrine therapy and chemotherapy were found to reduce the risk of breast cancer recurrence and death.[4 5] Meanwhile, the combination of early detection and effective radiation therapy enabled breast conserving surgery as an option for most women.[6] The implementation of these truly multidisciplinary treatment programmes, combining local and systemic treatments with public health screening initiatives and health awareness campaigns, revolutionised and improved breast cancer care.

Getting better all the time

The linked paper by Saadatmand and colleagues brings that progress forward into the 21st century.[1] Using a population based cohort of 173 797 patients and comparing patterns of care and outcomes in two time periods (1999-2005 *v* 2006-12), they document steadily improving survival for women with breast cancer in the Netherlands. Dutch women with non-metastatic breast cancer diagnosed during 2006-12 had a five year survival rate exceeding 95% of the survival rate in the general population (relative survival). Overall survival exceeded 85%. Compared with patients treated during 1999-2005, those treated during 2006-12 were diagnosed at earlier stages, were more likely to have breast conservation, and received more aggressive systemic treatment. The net result was improved survival.

Interestingly, the classic prognostic factors of tumour stage, grade, and hormone receptor status still influence survival estimates. However, human epidermal growth factor receptor 2 (HER2) expression—previously a marker for more virulent forms of breast cancer—is no longer an independent prognostic factor, a testament to the efficacy of adjuvant trastuzumab, which was introduced in 2005 and neutralised the historically adverse prognosis.



Staging matters

Among women with cancers measuring less than 1 cm, the five year relative survival was 100%, a population estimate that corroborates findings from cohorts at academic cancer centres in the United States.[7] Yet there is still work to do. At the other end of the spectrum, patients with substantial nodal disease still had a five year relative survival of 71% compared with the general population. Clearly, these patients need therapeutic innovation to achieve better results.

Like those of all registry reports, the findings and conclusions are constrained by the observational nature of the study. Nonetheless, there are powerful takeaway lessons from this extensive, population based report. Firstly, ongoing refinements in breast cancer treatment are providing persistent, incremental improvement in outcomes. Trastuzumab, taxane based chemotherapy, adjuvant use of aromatase inhibitors, and biological refinements in decisions about adjuvant therapy are all contributing to steady progress.

Secondly, certain cohorts of patients are achieving astonishingly good outcomes. Women with small, node negative breast cancers now have a five year survival rate close to that of the general population. Prospective studies in similar cohorts have shown remarkably low risks of cancer recurrence—less than 5% over five years.[8] In Western countries with mammography screening programmes, small node negative cancers constitute more than 40% of all breast cancers, and, as the Dutch experience shows, the likelihood of diagnosis of such a cancer is increasing. From a population point of view a recurrence rate of less than 5% at five years is great news; from a clinical trials point of view it is a dealbreaker as the recurrence rate is so low that it makes further randomised trials nearly impossible.

Finally, these data suggest that early detection is still vital in improving outcomes for breast cancer. Of late, there has been debate about whether mammography saves lives or whether, in a modern era of effective therapy, detecting cancers when they are smaller makes any meaningful difference to patients. Saadatmand and colleagues' study does not specifically answer the question. But it strongly suggests that, even after accounting for biological variation and enhanced treatments, tumour stage at diagnosis still matters. That is a powerful albeit indirect argument in favour of screening mammography. Catching cancers when they are smaller still makes a difference.

It is surely no coincidence that, while the Netherlands reports superior breast cancer outcomes, it also has very high rates of screening mammography. More than 80% of eligible women in the Netherlands have regular mammography, a compliance rate higher than that achieved in most other developed countries.[9 10] Given those high rates of screening, and the sophisticated, multidisciplinary care available in the Netherlands, this study offers a contemporary benchmark that other nations can aspire to when measuring outcomes in breast cancer.

Unfortunately, few countries have rates of mammography or breast cancer survival that match those of the Netherlands. Five year survival for breast cancer has increased overall around the globe and is 85% or higher in 17 of the 59 countries with data in the global surveillance cancer programme (CONCORD-2).[3] For the rest, marked disparities and inadequacies in outcomes persist, with some countries experiencing a recent rise in breast cancer mortality and others with projected five year survival lower than 70%.[2 3] For those nations, prioritising the main known drivers for success is essential.

Cite this as: *BMJ* 2015;351:h5273

RESEARCH, p 11

In north Holland AEDs are used in 60% of out-of-hospital cardiac arrests; in a UK study, they were used in fewer than 2%

thebmj.com Read more cardiology articles at bmj.co/cardiology

Improving survival after out-of-hospital cardiac arrest

Adopting the Institute of Medicine's strategies could save hundreds of thousands of lives worldwide

Jerry P Nolan professor, University of Bristol and Royal United Hospital, Bath BA1 3NG, UK jerry.nolan@nhs.net
Gavin D Perkins professor, University of Warwick and Heart of England NHS Foundation Trust, Coventry, UK
Jasmeet Soar consultant, Southmead Hospital, North Bristol NHS Trust, Bristol, UK

Sudden cardiac arrest results in millions of deaths worldwide each year and is a leading cause of premature death, with large disparities in survival between less privileged and more privileged groups.[1] Despite this, there has been relatively little attention given to policies and strategies to improve the outcomes of cardiac arrest.

Cardiac arrest is commonly associated with low survival rates and poor functional outcome in survivors, but recent data show that both are improving.[2 3] Nevertheless, there remains much scope for communities to improve outcomes to match those in the best performing places.[4]

The US Institute of Medicine's report on strategies to improve survival from cardiac arrest is therefore timely.[5] It focuses on five areas: cardiopulmonary resuscitation (CPR) and the use of automated external defibrillators (AEDs); emergency medical systems and hospital systems of resuscitation care; national cardiac arrest statistics; resuscitation research; and future treatments and strategies for improving outcomes. The main recommendations are familiar to those involved in healthcare systems and quality improvement. They include establishing a national cardiac arrest registry, fostering a culture of action through public awareness and training, enhancing the capabilities and performance of emergency medical systems, setting accreditation standards for hospitals and healthcare systems, adopting continuous quality improvement programmes, accelerating research into new treatments, and creating a national cardiac arrest collaborative.

Measuring processes and patient outcomes can help quantify whether change has led to improvement and enable comparisons between settings. Internationally agreed templates for recording cardiac arrest data already exist to enable comparisons.[7] Some national registries of cardiac arrests already collect these data—for example, the out-of-hospital cardiac arrest outcomes project and the national cardiac arrest audit in the UK.

The chain of survival (figure) provides a framework for improving outcome. The first link—early recognition and calling for help—requires training the public to recognise cardiac arrest and immediately call the emergency services. Call dispatchers must also be trained to quickly recognise the possibility of cardiac arrest and instruct the caller to provide compression-only CPR, unless the caller is already trained in conventional CPR. Bystander CPR at least doubles the chance of survival,[8] and one way to increase rates is to use mobile phone positioning systems to dispatch nearby lay volunteers.[9]

Put it on the school curriculum

In the UK a bystander starts CPR in about 40% of cases.[10] Campaigns to train more people in the technique are fundamental to increasing survival from out-of-hospital cardiac arrest. Countries with the highest bystander rates teach it to schoolchildren, and the "kids save lives" campaign, endorsed by the World Health Organization, aims to put CPR on the school curriculum.

The presenting cardiac arrest rhythm is shockable (ventricular fibrillation or pulseless ventricular tachycardia) in about a quarter of patients, 25-30% of whom survive to hospital discharge. The remainder of cases are non-shockable—asystole in about 50% and pulseless electrical activity in about 25% of cases—and have much poorer survival (less than 5%).[2 3] The third link in the chain of survival, early defibrillation for shockable rhythms, can be strengthened through public access to AEDs, allowing a bystander to deliver the first shock before an ambulance arrives. Defibrillation within 3-5 minutes of collapse can produce survival rates of 50-70%.[11]

Chain of survival

Increasing use of public access defibrillators in the Netherlands has been associated with improved survival.[12] Lay rescuers, alerted by text messages, can retrieve a nearby AED and take it to the person affected.[13] The use of an on-site AED doubles neurologically intact survival compared with no defibrillation, but the benefit is reduced if the defibrillator has to be brought from elsewhere.[14] In North Holland, AEDs are used in 60% of out-of-hospital cardiac arrests; in a UK study, they were used in fewer than 2% of arrests before an ambulance arrived.[10]

The role of many commonly used advanced resuscitation interventions is uncertain. For example, large randomised controlled trials have shown that routine use of mechanical chest compression devices does not improve outcome.[15] Ongoing trials are studying the role of adrenaline, amiodarone and lidocaine, and tracheal intubation.

Developments in the final link in the chain, post-resuscitation care, are also contributing to improved survival. Most notable are the increasing use of primary percutaneous coronary intervention in patients with ST elevation in the post-arrest 12 lead electrocardiogram, use of targeted temperature management, and multimodal prognostication in patients who are comatose after cardiac arrest.[16]

The next International Liaison Committee on Resuscitation consensus on CPR science with treatment recommendations will be published in October. These systematic reviews form the basis for simultaneously published resuscitation guidelines, including those from the American Heart Association, European Resuscitation Council, and Resuscitation Council (UK).[17] These guidelines should reinforce the principles in the Institute of Medicine report. The institute's strategies to improve survival from cardiac arrest can save hundreds of thousands of lives. Policy makers around the world should review these findings because now is the time to act.

Cite this as: *BMJ* 2015;351:h4989

Ongoing contact with tertiary centres, which is part of the surgical trajectory, may seem preferable to parents if the alternative is to be sent home with no help at all

thebmj.com Read responses to this article at thebmj.com/content/351/bmj.h5124/rapid-responses

Parental choice on normalising cosmetic genital surgery

Between a rock and a hard place

Lih-Mei Liao consultant clinical psychologist
Dan Wood consultant adolescent and reconstructive urologist
Sarah M Creighton consultant gynaecologist, University College London Hospitals, London NW1 2PG, UK
sarah.creighton@uclh.nhs.uk

About 1 in 2000 children is born with genitalia considered atypical enough to prompt medical investigation. Underlying causes include complex genetic and hormonal conditions as well as unexplained anatomical anomalies such as hypospadias.

Paediatricians have previously stated that the determining factor in deciding to raise a child as a boy is the "size of the phallus."[1 2] Newborn penile size charts were used in the 1960s, and any child with a penis of stretched length less than 2.5 cm was likely to be assigned to female sex regardless of the underlying diagnosis; feminising genital surgery usually followed.[1] Gender assignment has become less simplistic but normalising surgery remains common. As a result, little is known about the physical, psychological, social, and sexual effects of untreated atypical genitalia associated with different diagnoses. It has been impossible to determine to what extent difficulties reported by adults are caused by the anatomical difference, other aspects of the diagnosis, the imperfect results of surgery, poor psychological care, or a combination of these factors.

Paediatricians' confidence in the ability to construct genital anatomies to meet cultural expectations of appearance and function has not been borne out. The intended outcomes of these interventions can be known only when individuals reach puberty and adulthood, and reliable longitudinal research does not exist. Persistent concerns from adults who have had surgery in childhood have prompted research with adolescents and adults. In a landmark study with 44 adolescent girls born with atypical genitalia, despite multiple feminising genitoplasties in childhood, almost all participants required further surgery to facilitate menstrual flow, vaginal intercourse, or both.[3]

Subsequent research has identified increased difficulty with orgasm among women who had had clitoral surgery[4] and diminished genital sensitivity specific to the site of surgery.[5] Similar doubts have been cast over surgery for hypospadias.[6] Patient narratives point to the potential harm of multiple operations and repeated genital examinations.[7] The rate of female assigned and surgically feminised children who are reassigned as male is of concern.[8]

Surgical techniques for childhood conditions can change long before adult outcomes are known, and experts in surgery have so far been unable to reach a consensus about the best operation. Parents may not realise that they are de facto opting for experimental surgery on their children. Furthermore, their emotional states during decision making may not be optimal. Research suggests that medicalised presentations of genital difference have undue influence on parental decisions[9] and that parental regret can be high.[10]

Credible alternative

In 2012 the law in Germany was changed to allow parents to leave the gender of their baby blank on the birth certificate. The aim was to remove pressure to make premature decisions on irrevocable sex assignment surgery. However, such an aim can be met only if clinical services are able to provide a credible alternative to surgery. There is no evidence that parents are given sufficient time to appreciate their child, effective psychosocial support to manage their emotional reactions, or help to slowly digest the highly complex medical information and implications.

Recently, less straightforward

There is no identifiable psychoeducational care pathway to help parents deal with situations that may feel daunting, such as talking to nursery staff and babysitters or discussing with siblings and eventually the affected child about diversity in sex and gender. Skills and confidence will increase with practice, and parents need practical resources and mentoring not verbal instructions that are easier said than done.

Lack of funding is often cited as the reason for the absence of consistent psychosocial follow-up. However, such support may amount to no more than the team nurse and psychologist offering telephone follow-ups and educating community based care providers such as the general practitioner or health visitor to assist the family. The hospital payment structure encourages controversial, invasive, and expensive surgical interventions rather than low cost alternatives. Ongoing contact with tertiary centres, which is part of the surgical trajectory, may seem preferable to parents if the alternative is to be sent home with no help at all. To improve clinical practice, an additional, non-surgical care protocol is required to enable parents to cope with what may feel like insurmountable pressure to appear normal. Without this, most parents may find it impossible to delay surgery.

In April 2015, the European Union Agency for Fundamental Rights deliberated on the rights of intersex people and recommended that member states "avoid non-consensual sex normalising medical treatments on intersex people," mirroring earlier recommendations by the European parliament and the United Nations. Earlier this year Malta became the first nation to put a moratorium on "non-vital" childhood genital surgery.

In the UK, genital surgery for children with atypical genitalia remains part of standard medical care.[11] Given the contentious scientific issues and in light of recent international recommendations, audit of all such surgery should become mandatory. Furthermore, a credible non-surgical care pathway for affected families should be a performance indicator against which standards of care are judged. Given the increasingly adversarial atmosphere in this field, more of the same is not an option.

Cite this as: *BMJ* 2015;351:h5124