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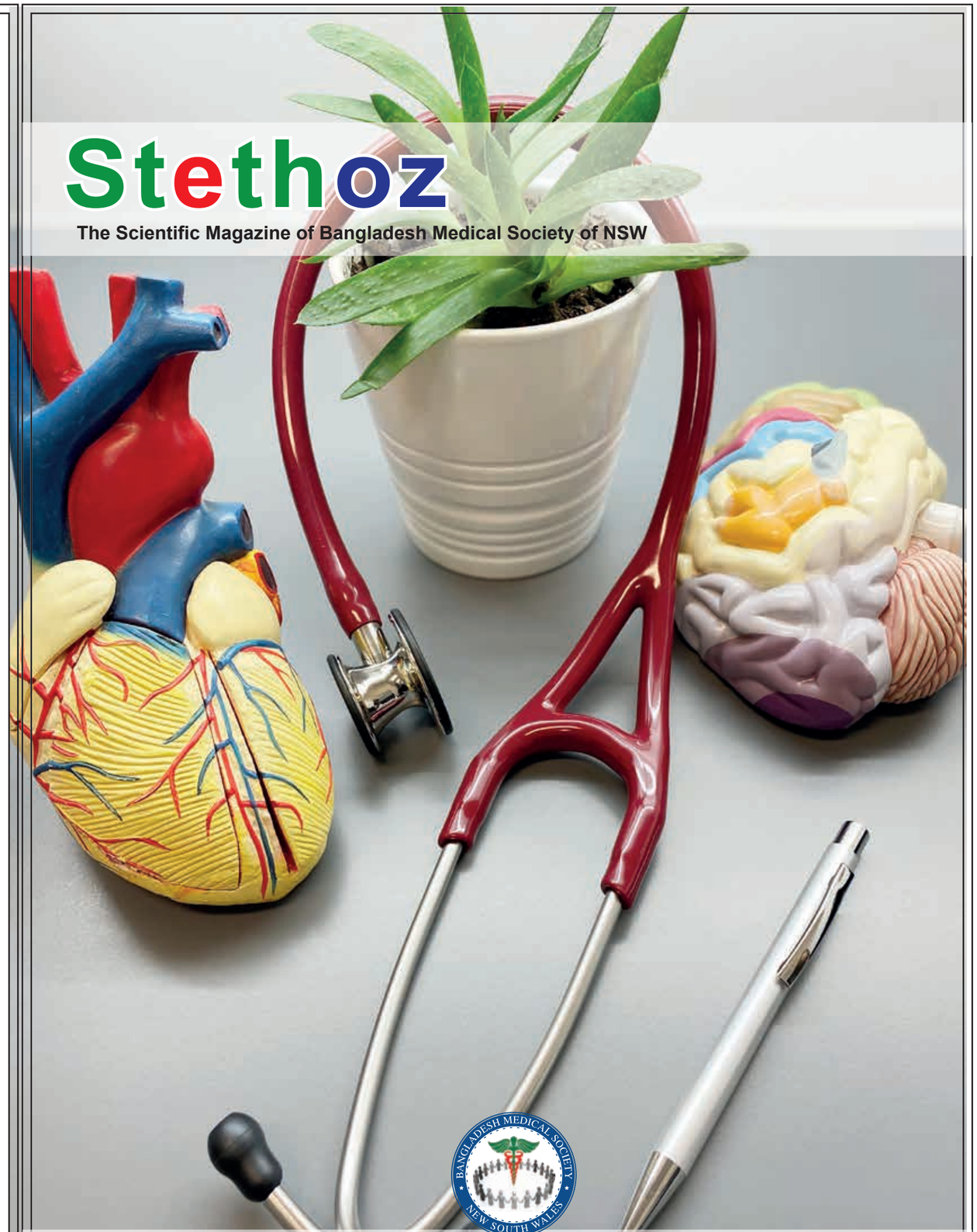
Stethoz

The Scientific Magazine of Bangladesh Medical Society of NSW



BANGLADESH MEDICAL SOCIETY OF NSW

Executive Committee
2022-2023

Medico Legal Workshop 2022

The First

Scientific Magazine

from

Bangladesh Medical Society of New South Wales Australia

EDITORIAL

It gives me an intense pleasure and privilege to write the editorial for the first scientific magazine of Bangladesh Medical Society of NSW. It is the success of a great family of teams of BMS NSW.

Bangladesh Medical Society of NSW is a society, we call family, of doctors of NSW established in 2010. Since then, this has grown enormously and brought a large number of doctors together in professional developments through to social cohesiveness and bonding. Since the beginning, BMS of NSW has been conducting various educational activities including annual scientific meetings. We aspired to publish a scientific magazine for some time now to show the flourishing talents of our doctors in multiple faculties in Australian Health Care.

Finally, we started to talk of publishing a scientific magazine this year. It almost felt impossible at the start. What would be the structure, what would be the writings like, who would write, who would edit etc etc! It seemed like a mammoth task. But we were hopeful, because we have a wonderful team who work together in such a collegial manner that we thought this team could do it. So, we sat down, meetings after meetings, selected a working group, made some criteria on how to write and what to write, as a guideline. We decided that all the writings would be evidence based scientific writings including the list of references cited, if possible. We also created an editorial board to ensure minimal standard of writings were maintained. However, we were clear from the beginning that this would be a "Magazine", not a "Journal". Because we did not think we were experienced enough to publish a journal, yet (!). Then we received a few interests – as if someone had shone light on us. We had to work hard, I must say, to finally collect the articles. Then the struggle to find a name of our magazine and one was selected from few suggestions, all stars started to align and finally we are here!

I am not going to go in detail about the articles here. I must say this will be a collection of good knowledge useful to all doctors and students, as the magazine has included writings on diverse subjects. The article by Dr Shafiq Majumdar discusses a culturally sensitive issue of 'close the gap' for indigenous population, the article by Dr Tanveer Ahmed and Dr Halim Chowdhury discuss about important issues like depression and its related complications, particularly during covid period. The article by Dr A H Milton teaches us how to read a scientific article. How to improve outcomes of chronic kidney disease was explained by Dr Shafiqul Bar Chowdhury. How metformin can be a problem drug in acute renal failure was nicely presented by Dr Iqbal Chowdhury. Common issues like managing rectal bleeding by Dr Faizur Reza, sleep disordered breathing by Dr Faisal Chowdhury, update on migraine management by Dr Abul Mamun, diabetic management by Dr Mohiuddin, how to recognise and treat delirium by Dr Muzahid Hossain, osteoporosis by Dr Jessie Chowdhury is amazing. Last but not the least are the articles on cancer immunotherapy by Dr Nahar and stroke management in the acute care setting by Dr Ali were mind bogging for all doctors.

A lot of people have put a lot of effort on this. Please congratulate our team for such a success. I want to thank the whole team from the bottom of my heart for such an amazing achievement. I am proud of being a part of this team. Thanking you

Dr M A Sayek Khan MBBS FCICM
Senior Intensivist
Blacktown-Mt Druitt Hospital, NSW
General Secretary
Bangladesh Medical society of NSW

Message from

THE PRESIDENT

Dear all
Bangladesh Medical society of NSW was established in 2010 by a group of dedicated, enthusiastic doctors. It is an organised, not for profit, non political, professional and friendly organisation with many members. From the onset BMS has been assisting newly immigrated doctors from Bangladesh find employment within Australia. BMS has been involved with different educational, sociocultural activities both locally and abroad. BMS is committed to help local Australian communities and other countries during natural calamities and crisis. BMS has organised a day long annual scientific seminar each year except during the Covid pandemic.

On behalf of BMS NSW it is my great pleasure to declare the inauguration of 'Stethoz' first scientific magazine of Bangladesh Medical Society of NSW. I would like to express my sincere congratulations to all members of BMS, executive committee, education subcommittee and writers who are involved with this publication. My special thanks to Dr. Sayek Khan, General Secretary of BMS NSW and Dr Ishrat Jahan, Education Secretary of BMS NSW who worked hard to make this dream a reality. I offer my heartfelt thanks to the writers who are involved with this magazine by providing their writings. We have a good number of medical experts and authors who are contributing their knowledge to medical science and I believe BMS will be able to publish a proper journal in the near future. I would like to thank Dr. Fazle Rabbi, Publication Secretary who has spent much time and effort to publish this magazine and give the magazine it's name. I also like to offer my thanks to Mr Kamrul Hai of 'Touch Printing' for his fabulous contribution for publishing BMS magazines.

Best wishes for all of you.
Proud to be a member of BMS

Dr. Md Mirjahan Mia,
President, Bangladesh Medical Society of NSW

Message from EDUCATION SECRETARY

I feel very proud to be a member of Bangladesh Medical Society of NSW. As a society, we always strive to grow and reach our full potential. As education secretary, these values align with my own belief in lifelong learning.

This year, we have made the effort to publish a scientific magazine, consisting of write ups from our very own Bangladeshi doctors. Doctors of Bangladeshi origin are now working in every sector of the Australian health care system. Hence, we felt it was important to collect these various scientific writings from our colleagues and have them reviewed by a board of editors!

My heartfelt thanks to general secretary Dr. Sayek Khan for initiating this new chapter of BMS NSW to enrich our educational activities.

My sincere gratitude to President Dr. Mirjahan Maju for helping me implement diverse educational activities throughout the year.

Thanks to publication secretary Dr. Fazle Rabbi for assistance with the final phase of this publication.

Most importantly, I would like to thank all the writers and editors who dedicated their valuable time to help this dream come to life. I hope all our readers find the articles intriguing and enriching.

I am sure in the future we will come up with even more ideas that will help us become a stronger and better BMS NSW.

Ishrat Jahan
Education Secretary
BMS NSW

Message from PUBLICATION SECRETARY

Salam everyone.

It is my pleasure to welcome you all to see and enjoy reading the first scientific magazine published from the Bangladesh Medical society of NSW on this grand occasion of Annual Scientific Meeting 2022. With this publication BMS has uplifted the status to the next level. BMS - NSW has been consistently improving and broadening the ways we the doctors' community of NSW act, interact, socialise, donate, and deliver. Since birth, BMS has been arranging different educational activities to enrich our members and also improving the understanding of young doctors to be integrated into the health system in Australia. It is very satisfying to see our Bangladeshi doctors are doing great in their respective fields. This scientific magazine is the recognition of that excellence.

Stethoz, the name that has come to my mind as we doctors carry a stetho which distinguish us from the crowd. This is such a word that we readily get connected with, and oz simply means Australian. My publication experience in BMS has helped me through the cumbersome process, yet very satisfying at the end. I had proposed Dr Sayek Khan to write the editorial to acknowledge his efforts. Well deserved thanks to Dr Ishrat Jahan for her enthusiasm in each and every educational activity including this one. And of course, the hard-working Dr Md Mirjahan Mia Maju who has been coordinating this Annual Scientific Meeting and this magazine.

The cover design I have done, the concept of which is based on the symbol of medicine, and I have made the theme flow over the rest of the magazine. My effort was to give this magazine the standard look of a journal as much as I could.

I hope you like this magazine and sincerely looking forward to get your kind feedback.

Warm Regards

Dr Mohammad Fazle Rabbi MBBS FRACGP
Publication Secretary of BMS-NSW

EDITORIAL BOARD

TABLE OF CONTENTS

ANNUAL SCIENTIFIC MEETING 2022

3RD SEPTEMBER 2022
NOVOTEL, SYDNEY OLYMPIC PARK

8.30 AM PROCEDURAL WORKSHOP FOR AMC
10 AM - 5PM ASM

BMS-NSW IS PROUDLY PUBLISHING 1ST SCIENTIFIC MAGAZINE

- PROCEDURAL WORKSHP
- SPECIALIST SPEAKERS
- PLENARY
- SPONSORS EXHIBITION
- CERTIFICATES

REGISTRATION IS ESSENTIAL

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EDUCATION SECRETARY	PRESIDENT, BMS NSW	GS, BMS NSW
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Insight into general practice training – 'close the gap' for Indigenous population

Dr. Shafiq Rahman FRACGP, FAUS, DUROC(London)
GP Supervisor (GP synergy), Clinical Lecturer University of Sydney

Background

A strong foundation of becoming a skilled independent general practitioner (GP) depends on quality of training they receive as GP registrars. Both the supervisors and trainees need to fully grasp the scope of knowledge, skills and experience that are required of the trainees. Availing quality supervision with strong learner-centred approach is critical to achieve skills in providing safe medical care at the community level, obtain patient satisfaction and enjoy the career as general practitioners [O'Sullivan et al]. Strong commitment to a reliable and acceptable atmosphere with efficient teaching-learning environment is crucial in the community setting in Australia, especially in the areas with diverse population including Aboriginal and Torres Strait Islander population.

General Practice Education and Training Limited (GPET), an initiative of the Australian Government in collaboration with Royal College of General Practitioners (RACGP) and other vested organisations developed a guideline that emphasized the following 6 principles for a successful training in Aboriginal Health, these are 1. Culturally appropriate general practice training, 2. Leadership and advocacy, 3. Support for registrars, 4. Partnerships and collaboration, 5. Quality standards and 6. Evidence based approaches. These all principles are interdependent and application of these in results in delivery of a culturally aware clinically competent service with successful outcomes in closing the gap between Aboriginal Australians and Australians of non-Aboriginal background [AGPT].

Challenges

Indigenous Australians comprise Aboriginal and Torres Strait Islander population with hundreds of groups that have their own distinct set of languages, history, and cultural traditions. In general, they have lower use of preventive health services, higher rates of long and complex primary care consultations and a higher rate of potentially preventable hospitalisations compared to non-Indigenous population that relates to poorer access to appropriate primary care services [Bywood et al].

Kidney and cardiovascular diseases are widely prevalent amongst Indigenous population in Australia [AIHW]. A large proportion of younger indigenous patients have significant mental health issues including self-harm, suicidal tendency, substance abuse, history of previous mental and physical abuse, fear of loss of connection with their families and homelessness [Hunter E]. All these are day to day problems faced in the general practice environment with only limited time and resources available for individual patients, especially, in the urban setting. This poses a challenge sometimes for trainees in the busy practices with limited supervision facilities.

Miscommunication is a major challenge involving Aboriginal health in medical practices. A qualitative survey done amongst Indigenous population in Canberra found out health professional's enquiries about their Indigenous status without proper explanation of the identifying question creates apprehension and mistrust amongst the patients [Scotney et al].

Successful Approach

Educational resources are needed to facilitate a shared understanding not only health issues but also of the cultural, social, and economic dimensions of the illness experience of

Indigenous people. Dedicated training facilities targeting Indigenous population is an integral part of general practice training [O'Sullivan et al]. There is a need to improve identification of Indigenous patients, improve respectful health service delivery with good communication, building up trust, ensure access to subsidised medication and provide well trained indigenous and culturally safe health workforce with adequate resource allocation for the serving community. Along with clinical support improved family support, community support and connection with the land are also key components of integrated primary health care of Aboriginal population [Bywood et al].

General practice supervisors experienced in communicating and caring for Aboriginal patients should encourage and guide trainees for culturally sensitive and empathetic personal contact, acknowledgement and respect for family structures, culture and life circumstances, an understanding of the significant role of non -verbal communication and acknowledging the importance of history, land and community [AGPT]. After building a trusting relationship, regular follow-ups including nine monthly health check, chronic disease management plan, involvement of Aboriginal health workers from PHN (Primary health Network) with patient's permission, Allied health (e.g. podiatry) and specialist services input could be ensured. The improved acceptance amongst the community lead to more compliant health seeking behaviour.

Conclusion

General practice trainees with cultural awareness, good communication skills and non-judgemental unbiased style are successful in gaining the trust of Aboriginal patients leading to increase in their participation in the chronic disease management plans with regular follow ups. This leads to better health outcomes in the long run and improved health statistics amongst Indigenous population closing the gap with non-Indigenous population.

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COVID-19 Mental health impact on Australians

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Background

The COVID-19 pandemic has become the forefront of global health problems, leading to over six million deaths worldwide affecting humans on a multi-organ level. In response, Australia along with many other countries has faced many social and economic challenges that have negatively impacted mental health (NMHC, 2020). Challenges including employment loss, lockdown restrictions along with the stressors of adjusting to remote work and schooling have emerged as major factors in poor mental health for many Australians (AIHW, 2022). As a result, this has placed extreme pressure on the healthcare system and It is important to analyse the impacts on patients and doctors in order toc improve mental health treatment and outcomes in Australia.

Reported effects on Australians

A national survey of Patient Health Questionnaire 9 (PHQ-9; symptoms of depression) and the Generalised Anxiety Disorder Scale (GAD-7) was performed during the first Australian lockdown in early 2020. Of the 13,829 surveys conducted, almost 1 in 4 respondents reported mild to moderate symptoms of depression (Fisher et al., 2020). Those affected by COVID-19 directly or through loss of jobs, isolation from family, death of loved ones and worried about contracting COVID-19 were more likely to report clinically significant anxiety (Fisher et al., 2020). Another survey of 5,070 Australian adults found elevated psychological distress, with 62%, 50%, and 64% of respondents reporting elevated depression, anxiety and stress levels, respectively (Newby, O'Moore, Tang, Christensen, & Faasse, 2020). Contrary to prior research, the survey found that higher engagement in precautionary behaviours (e.g., hand sanitisation, hand washing, and avoidance of social events) was associated with higher stress and anxiety levels. Participants with mental health diagnosis were also associated with exacerbation of their conditions. Similar reports of elevated negative emotions of stress, anxiety and depression were found in Europe (Pérez, Masegoso, & Hernández-Espeso, 2021), and the USA/Canada (Klaiber, Wen, DeLongis, & Sin, 2021).

Furthermore, while comparing the four-week period from January 9, 2022 to January 9, 2020, the use of several national helplines increased consistently (Table 1). This further highlights a greater need for mental health support following the pandemic and may give rise to an increased focus on telehealth in providing mental health support.

Support Line	January 2020 contacts	January 2022 contacts	
Lifeline	77,309	89,679	(↑16.0%)
Kids Helpline	22,843	22,935	(↑0.4%)
Beyond Blue	16,910	21,425	(↑26.7%)

Mental health admissions during COVID-19

The restrictions caused by the COVID-19 pandemic has led to a decrease in many healthcare-seeking behaviour from Australians. Healthcare data from NSW suggests that in March to June 2020, primary care in person consultations, ambulance incidents, emergency department visits, and public hospital inpatient episodes had all markedly decreased compared to 2019 (Sutherland et al., 2020). Change in specific NSW health service use varied by chronic conditions, with a large decrease (40-78%) in respiratory conditions while mental health disorders had non-significant change (Hu et al., 2022). Following the lockdown, the majority of these services reverted to their pre-COVID-19 levels. However, the usage of mental health disorders related services increased by 30-55% between June 2020 and February 2021, with the greatest increase among young females aged 12 to 17 years old. As a result, mental health professionals must look towards addressing this rise with adequate changes to meet this demand especially in young adolescents.

Providing Adolescent Mental Health support during COVID-19

During the COVID-19 pandemic, social and schooling constraints have had a significant impact on adolescents.. The increasing use of technology among younger people has aided the emergence of digital intervention, most notably during the pandemic. Cognitive Behavioural Therapy, health promotion and other face-to-face psychotherapies that are effective for improving anxiety have been converted into Internet-based programs. This may provide an alternative intermediate option for young people awaiting in-person treatment and potentially reduces the service gap in a setting with lack of resources by improving efficiency and access to care (Das et al., 2016; McGorry et al., 2022). However, formal investigations quantifying their efficacy is necessary.

Healthcare worker burnout

Healthcare workers (HCWs) as well have not been immune to the increased levels of mental health issues during the COVID-19 pandemic. The pandemic has created increased workplace demands and stressors on HCWs whilst minimising the importance of their mental health. Despite prior knowledge that physicians and nurses suffer from higher rates of burnout, anxiety, depression, and suicide compared to other occupations, this phenomenon persists (Smallwood & Willis, 2021). Meta-analyses comparing HCWs with the general population found that the pandemic had a greater increase in prevalence of mental illness for HCWs (Deng, Chen, & Zhang, 2021; Krishnamoorthy, Nagarajan, Saya, & Menon, 2020).

A nationwide survey of Australian junior doctors found that a difficult workplace culture, challenging working conditions and disrupted career trajectories were major difficulties faced during the pandemic (Hunter, Willis, & Smallwood, 2022). HCW burnout is also a major concern to patient care as it has been predisposed to poor clinical decision-making and increased risk of medical errors (Heath, Sommerfield, & von Ungern-Sternberg, 2020). This indicates the need to increase support for HCWs mental health in order to improve patient outcomes as well as creating tangible changes that allow for healthy working culture, and clearer career projection post-pandemic.

Future Management

The COVID-19 pandemic has exacerbated mental health illness worldwide, including Australians, and our general practitioners (GPs) are likely the first point of contact for such issues. Apart from a through history of presenting complaints and family history of mental health, it is essential for GPs to assess the impact of the pandemic on the individuals mental health. Mental health risk assessment is particularly important in patients who are HCWs, adolescents or exhibiting signs of maladaptive coping mechanisms (e.g., alcoholism) (Munindradasa, Blashki, Hall Dykgraaf, Desborough, & Kidd, 2021). Management should be focused on fostering resilience by helping patients keep perspective and encourage positive behaviours. In addition, curbing lifestyle factors such as

smoking, harmful alcohol use, and physical inactivity has shown to improve mental health (Bartlem et al., 2015).

Treatment

Cognitive behavioural therapy has shown good evidence of treating common mental health conditions such as depression and anxiety (Morgan, 2019). It is the practice of helping patients identify and challenge unhelpful thoughts and to create practical self-help strategies to bring about positive changes to one's quality of life. Pharmacological treatment is also important to consider if required. Broadly speaking, GPs must know few medication's short and long term side effects, contraindications and medical interactions to provide more accurate and early administration.

Overall, the COVID-19 pandemic has posed a great challenge for the Australian healthcare system. Learning from the trends that have occurred particularly in mental health aspects of the general population as well as HCWs is integral to creating policies to help prepare for future events should they occur.

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Critical appraisal of evidence: Why it is essential for general practitioners?

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2 Director, Research and Training International, NSW, Australia

Australians' access to primary health care (PHC) largely relies on general practice. Approximately 85 percent of the Australian population annually uses Medicare for at least one general practice service. The general practitioner (GP) is crucial to delivering health care to the Australian people. Many Bangladeshi Australian physicians work as General Practitioners in Australia. The practice of evidence-based medicine (EBM) is essential for GPs. In this article, I will discuss about EBM, that our GP community may find useful.

What is evidence-based medicine in general practice?

In general practice, EBM is the application of the best available evidence, the patient's preferences, and the GP's clinical expertise in making treatment decisions. (Welink LS et al 2020).

When utilised in a consistent manner, it is more likely that optimal patient outcomes will be achieved. Using EBM means abandoning outdated care delivery practices in favour of effective, scientifically validated alternatives to meeting the specific needs of each patient. EBM practitioners must be able to assess the relevance of research to their specific patient groups.

Why EBM is important in general practice

EBM strives to assess the quality of evidence supporting medical therapies in terms of risks and benefits and may thus be used to influence clinical decision-making on an individual and population level. As a result, EBM is critical for maintaining high-quality medical care and achieving good clinical outcomes. EBM involves several stakeholders. Firstly, researchers and publishers are involved in conducting and disseminating medical evidence. Then, policymakers and clinicians are in charge of implementing changes in healthcare decisions that may occur (Lin Lee 2013).

Critical appraisal is an essential part of the Evidence-Based Practice approach. Critical appraisal aims to identify possible risks to the validity of research findings in the literature and to provide consumers with the information based on research evidence they need to make informed decisions regarding the quality of research evidence.

How to apply EBM in general practice

It would be practically challenging to evaluate all the available evidence on a topic. Fortunately, various Evidence-Based Practice (EBP) approaches have been established to assist healthcare professionals in implementing EBP in the work place.

The most common process consists of six steps:

1. ASK a question. Is there something in your clinical setting about which you have questions? Perhaps you are curious whether a new intervention is more effective than the current one. First, consider what works well and what may be improved. And, most significantly, WHY? Next, evaluate the processes and workflow that influence the identified practice gap or are impacted by it. We will utilise the PICO(T) (pronounced "pee ko") format. If this phrase is new, we need to learn more about PICO(T).

2. ACQUIRE the current evidence. You will do this through a literature search. Your search will be directed by the clinical question you have.

3. APPRAISE the literature. Or, in other words, sort, read, and critique literature that has been peer-reviewed. In the next section, I will discuss the critical evaluation of evidence.

4. APPLY your findings to clinical decision-making. Integrate the evidence with medical expertise and the preferences and values of the patient. Then, make recommendations for daily practice based on research.

5. EVALUATE your outcomes. Review the data and record your approach. Include any edits or modifications. Maintain close track of the outcomes of your intervention. Assess and summarise the result.

6. DISSEMINATE the information. Share your project's outcomes with others. Sharing assists in promoting best practices and avoiding duplication of effort. Additionally, it contributes to the existing resources that support or criticise the practice.

Participating in project-based work may teach us how to apply EBP, but incorporating EBP into our everyday practice can help us achieve the best possible patient outcomes. It demands us to be deliberate with our practice and to ask the appropriate questions.

It is essential to stress that while using evidence at the bedside can be done alone, teamwork is more likely to result in long-lasting benefits.

How to critically appraise a journal article?

Various groups have developed frameworks to assist researchers and clinicians in detecting bias and evaluating the quality of studies. Of them, the following three frameworks are important:

1.The Critical Appraisal Worksheet (CAW)

2. Users' Guides

3. Fowkes and Fulton Method

The first framework (CAW) and the third framework (Fowkes and Fulton) are general frameworks applicable to all types of study designs; the second framework (Users' Guides) is really a set of frameworks, each tailored to a specific research question. I shall describe the CAW in this article, since I have found this framework helpful in my work.

The Critical Appraisal Worksheet (CAW)

The Critical Appraisal Worksheet (CAW) is one method for evaluating scientific literature critically. In a series of Clinical Epidemiology and Health Services Workshops that began in Newcastle in 1979, it has been refined over a number of years. The Critical Appraisal Worksheet (CAW) is essentially a set of questions you should ask yourself about various areas of the article you are reading. It is a matrix consisting of nine rows and three columns of questions that you must consider:

1. Whether the information is present in the paper;

2. Whether there was a problem in what was presented; and

3. Whether any problem(s) identified were sufficient to affect either the internal or external validity of the study.

4. The CAW can be applied to a range of topics and study designs.

5. The Critical Appraisal Worksheet is displayed on the next page. A detailed explanation of how to use the CAW checklist is presented in the paper by Darzins et al, 1992

Table 1: The Newcastle Critical Appraisal Worksheet		
Can you find the information in the paper?	Is the way this was done a problem?	Does this problem threaten the validity of the study?
What is the research question and/or hypothesis?	Is it concerned with the impact of an intervention, causality, or determining the magnitude of a health problem?	
What is the study type?	Is the study type appropriate to the research question?	If not, how useful are the results produced by this type of study?
What are the outcome factors and how are they measured?	• Are all relevant outcomes assessed? • Is there measurement error ?	• How important are omitted outcomes? • Is measurement error an important source of bias?
What are the study factors and how are they measured?	Is there measurement error ?	Is measurement error an important source of bias?
What important potential confounders are considered?	Are potential confounders controlled for?	Is confounding an important source of bias?
What is the reference population and source population? What is the sampling frame and sampling method?	Is there selection bias?	Does this threaten the external validity of the study?
• In an experimental study how were the subjects assigned to groups? • In a longitudinal study how many reached final follow-up? • In a case-control study are the controls appropriate?		Does this threaten the internal validity of the study?
Are statistical tests considered?	Were the tests appropriate for the data? Are confidence intervals given? Is the power given if a null result?	Do the conclusions drawn follow logically from the results of the analyses?
Are the results clinically/socially significant?	Was the sample size adequate to detect a clinically/socially significant result?	
What conclusions did the authors reach about the study question?	Do the results apply to the population in which you are interested?	Do you accept the results of this study ?

Conclusions:

General practitioners must improve their research abilities to maximise their efficiency as primary care physicians. However, health and medical research appear to be inadequately focused from the general practice perspective. Aside from the government programme, several physician groups and individual GPs canmay acquire research training.

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Improving outcomes of chronic kidney disease

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The burden of Chronic Kidney Disease (CKD) continues to increase on a global level. The reasons are phenomenal increase in Type 2 Diabetes Mellitus, obesity, and the ageing general population. [1]

CKD poses a substantial burden to the health care system. The immense morbidity, reduced life expectancy of ESRD (End Stage Renal Disease) patients and economic burden of CKD have prompted CKD prevention program globally. Appropriate screening, diagnosis and management are paramount importance to prevent CKD related outcomes and primary care physicians can play a significant role

CKD is defined as abnormalities of kidney structure or function that persist for more than 3 months. [2]

CKD is classified based on estimate Glomerular Filtration Rate (eGFR) and albuminuria as per KDIGO (Kidney Disease Improving Global Outcomes) and it helps to risk stratify patients.

CKD is largely asymptomatic until late stages. Medical and lifestyle intervention at early stage of CKD may slow the progression of CKD and reduce its morbidity and mortality. [3]

Screening high-risk populations for CKD has shown to be cost effective. Clinical practice guidelines strongly recommend screening people with any of the following indications such as diabetes, hypertension, established cardiovascular disease, family history of kidney disease, obesity, age >60 years, Aboriginal or Torres Strait islander origin aged ≥30 years and hose with prior history of AKI (Acute Kidney Injury).[4 5]

Kidney Health Australia has recommended a kidney profile test that includes measuring both serum creatinine for estimating GFR and urine ACR (Albumin Creatinine Ratio). Albuminuria is an indicator of increased glomerular permeability. ACR is preferred to PCR (Protein Creatinine Ratio) because albumin assay has better precision at lower levels and some proteins such as uromodulin exclusively produced in kidney are most abundant in normal urine.

Microalbuminuria is defined as persistent elevation of ACR (> 2.5 mg/mmol in Male and ACR > 3.5 mg/mmol in Female) in 2 out of 3 urine samples in 3 months. Guidelines recommended using first morning urine sample because of diurnal variation of urinary albumin excretion. Random spot urine sample is also acceptable if first morning urine sample is not available. [6] There are conditions associated with transient albuminuria such as decompensated heart failure, vigorous exercise, fever, and urinary tract infection. Therefore, urine ACR should not be measured when these conditions are present.

The strategy of CKD management is to reduce risks of kidney disease progression and cardiovascular diseases. The goal directed treatment is to optimise blood pressure control, glycaemic control, and albuminuria/proteinuria reduction. There are supporting evidence that Lifestyle modifications are cornerstone of CKD management. Therefore, CKD patients should receive counselling on healthy lifestyle such as weight management, smoking cessation, physical activity and diet.[7 8]

Avoidance potential nephrotoxins (e.g. NSAID Non-Steroidal Anti Inflammatory Drug) and adjustments to drug doing according to eGFR are also important aspects of CKD management.

Diabetes is the leading cause of CKD worldwide. Several landmark trials have demonstrated the benefits of glycaemic control in preventing microvascular complications. Glycaemic control may mitigate the progression of CKD. Several guidelines including KDIGO recommended the target HbA1c of approximately 7% for most patients with CKD. However higher glycaemic target (HbA1c 7% to 8%) has been endorsed by KDIGO for advanced CKD patients for shorter life expectancy, higher comorbidity burden and high risk of hypoglycaemia. In advanced CKD, risk of hypoglycaemia is driven by failure of gluconeogenesis in the kidney and reduce clearance of many antihyperglycemic agents particularly insulin. The value of HbA1c has its limitation in advanced CKD due to high urea level, metabolic acidosis, anaemia, use of erythropoietin stimulating agents and reduced erythrocytes life span for uraemia. Therefore, HbA1c should be interpreted with caution in advanced CKD. [9]

KDIGO recommended first line treatment for type 2 diabetes with metformin and SGLT2 (Sodium-Glucose-cotransporter 2) inhibitor. SGLT2 inhibitor has proven benefit of reducing risks of CKD progression which is independent of glycaemic effect and the lower cut off eGFR for its use is ≥ 20ml/min/1.73m[10]. It is of note that in Australia lower cut off eGFR value varies according to type of SGLT2 inhibitor and its therapeutic indication. SGLT2 inhibitor will be a game changer in the management of diabetic and non-diabetic kidney disease because of its proven reno-protective effect. Precaution should be taken in elderly patients and those on diuretics because of a greater risk of volume depletion with SGLT2 inhibitor.

Aggressive blood pressure control has demonstrated to delay the progression of CKD. In general, guidelines recommended target BP of <130/80 mmHg for all adults with hypertension and CKD regardless of proteinuria.[11]

Recently the Systolic Blood Pressure Intervention Trial (SPRINT) showed a reduction of cardiovascular events by lowering systolic BP to 120 mmHg. KDIGO in recent guidelines published in2021 adopted this lower target BP goal for CKD patients which is controversial and is also associated with higher risks of adverse kidney outcomes.

RAAS (Renin Angiotensin Aldosterone System) inhibitor such as Angiotensin Converting Enzyme (ACE) inhibitor or Angiotensin Receptor Blocker (ARB) is the preferred agent for hypertension treatment and those with microalbuminuria. It is of note that microalbuminuria is a poor prognostic marker for progression of CKD. Combination treatment with ACEi and ARB is not recommended due to lack of superiority and increase risk of hyperkalaemia and AKI (Acute Kidney Injury). RAAS inhibitors should be titrated at its highest approved dose if tolerated. Renal function and potassium need to be monitored within 2 to 4 weeks of treatment initiation or titration. If hyperkalaemia develops with RAAS inhibitors, dietetic review for low potassium diet and potassium binders are recommended. RAAS inhibitors will need to be ceased in case of resistant hyperkalaemia or rise of creatinine greater than 30% within 4 weeks of treatment initiation or dose titration.

Anaemia is a common complication of CKD. It usually starts to develop when eGFR is less than 60 ml/min/1.73m^2. Anaemia

has a deleterious effect on cardiac structure and function. Before commencement of ESA (Erythropoietin Stimulating Agent), initial workup of anaemia should include iron studies, other haematinics, and thyroid function test to exclude other causes of anaemia. Current recommendation is to initiate ESA when haemoglobin is between 90 to 100 g/L and the target Hb is between 100 and 115 g/L. Studies have shown that fully corrected anaemia in CKD increases cardiovascular morbidity and mortality in comparison to partially corrected anaemia.[12]

In conclusion, CKD management warrants multidisciplinary approach that may facilitate early detection and improve management of CKD for high-risk cohorts in the primary health care setting. A systematic approach by Primary care physician can play a significant role. To share the burden of the disease, guidelines recommended that patients with CKD be referred to a nephrologist when eGFR falls below 30 ml/min/1.73m^2 or persistent albuminuria of ≥ 30 mg/mmol or rapid CKD progression such as a decrease in eGFR 25% from baseline or a sustained decline in eGFR > 5ml/min/1.73m^2.

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An overview of sleep disordered breathing

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Sleep disordered breathing (SDB) is a term used to describe a spectrum of respiratory disturbances that occur during sleep.

Classification of Sleep disordered breathing

International Classification of Sleep Disorders (ICSD-3) has defined four major categories of SDB:

1. Obstructive sleep apnoea syndrome (OSAS)
2. Central sleep apnoea syndrome (CSAS)
3. Sleep-related hypoventilation disorders
4. Sleep-related hypoxemia disorder.

The fundamental difference between the first two major categories is the pathophysiological mechanism that causes the respirator disturbance. In OSAS, the upper airway obstruction is most often caused by abnormal anatomy and/or abnormal control of the muscles that maintain the patency of the upper airway. In CSAS, dysfunction of ventilatory control in the central neurons is involved, resulting in loss of ventilatory effort **(Fig. 1).**

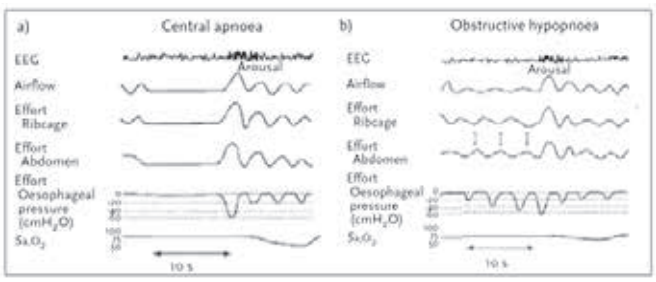


Figure 1: a – central apneas as characterized by apneas with absent respiratory and abdominal muscle effort. b- Obstructive apneas despite chest wall and abdominal muscle effort.

Central sleep apnea syndromes

1. Central sleep apnea with Cheyne-Stokes breathing
2. Central sleep apnea due to a medical disorder without Cheyne-Stokes breathing
3. Central sleep apnea due to high altitude periodic breathing
4. Central sleep apnea due to a medication or substance
5. Primary central sleep apnea
6. Primary central sleep apnea of infancy
7. Primary central sleep apnea of prematurity
8. Treatment-emergent central sleep apnea

Sleep-related hypoventilation disorders

- Obesity hypoventilation syndrome
- Congenital central alveolar hypoventilation syndrome
- Late-onset central hypoventilation with hypothalamic dysfunction
- Idiopathic central alveolar hypoventilation
- Sleep-related hypoventilation due to a medication or substance
- Sleep-related hypoventilation due to a medical disorder

OBSTRUCTIVE SLEEP APNOEA (OSA)

•OSA is a disorder characterized by repetitive apneas (total cessation of flow) and hypopnoeas (reduction in flow) due to partial or total collapse of the upper airway during sleep. OSA Syndrome (OSAS) = Apnea Hypopnea Index (AHI) > 5 plus symptoms.

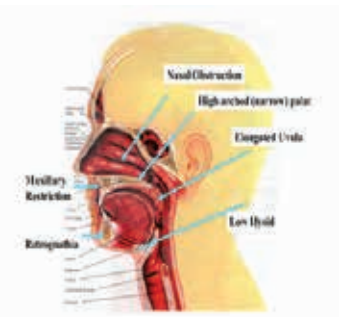


Figure 2: Anatomical abnormality contributing to OSA

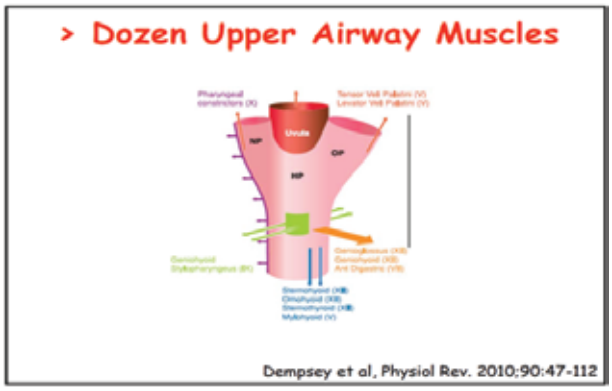
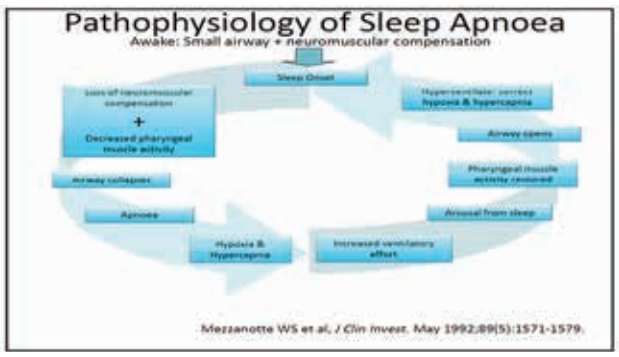


Figure 3: Poor neurogenic control of upper airway muscle contributes to OSA

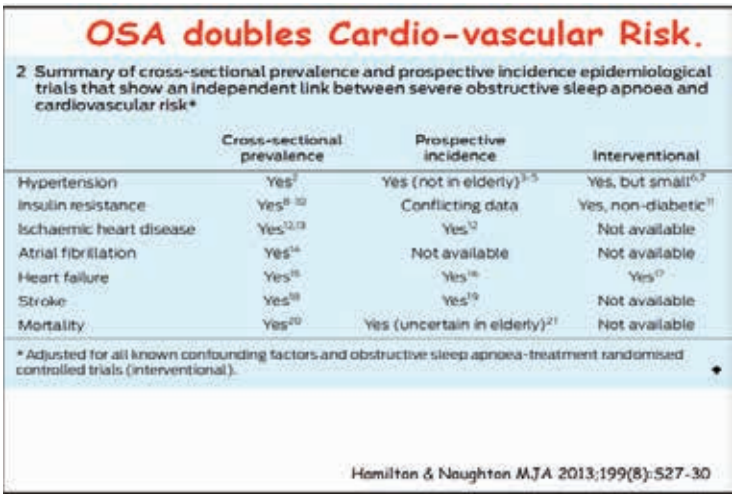


- OSA is associated with:
- Excessive daytime sleepiness, impaired daily function, inattention, depression.
- May be brought in by bed partner – witnessed apnoea, choking or gasping episodes.
- May present with poor work performance, falling asleep in meetings/lectures, etc.
- Increased driving risk, 2-3 times increased risk of motor vehicle accident (1).
- Cardiovascular disease: coronary artery disease, stroke, HT, pulmonary hypertension, arrhythmias (2).
- T2DM and Non-alcoholic fatty liver disease (Independent of obesity).
- Perioperative complication.
- Mortality -severe untreated OSA has a 2-3x increased all-cause mortality (3).

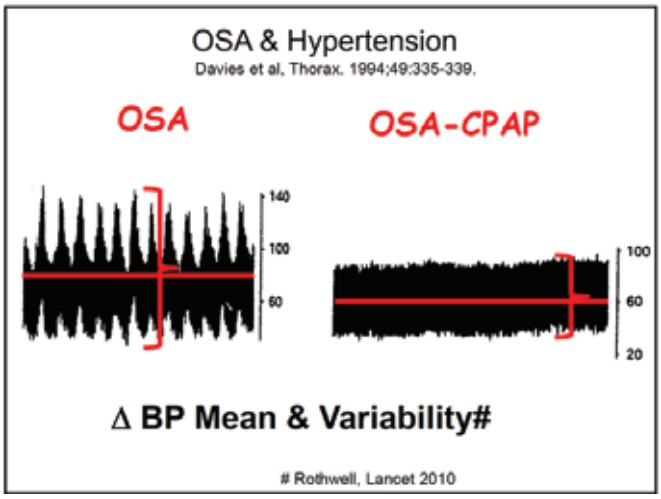
Epidemiology: OSA is one of the most common medical disorders in the general population. Prevalence in adults ranges from 9% to 38% (higher in men and older people) when OSA is defined as disordered breathing present on a sleep study, although prevalence is in the range of 4% to 6% when OSA on sleep study is combined with symptoms of excessive daytime sleepiness (4).

Screening tools:

• STOP BANG: (Snoring, Tiredness, Observed apnoeas, blood Pressure, BMI, Age, Neck circumference, Gender)
• Score of 3 or more has a good sensitivity for OSA diagnosis (88-93% depending on OSA severity cut off) (5).
• Others: OSA50, Berlin Questionnaire
• Most have reasonable sensitivity but not so good specificity which is why we use further diagnostic evaluation (sleep studies).
• Specificity of these tests is increased (up to 92-95%) by adding Epworth Sleepiness scale >/=8 (5).



Treatment strategy of OSA



Sleep disordered breathing in cardiac failure

The desired outcomes of treatment include resolution of signs and symptoms of OSA and the normalization of sleep quality, the apnea-hypopnea index (AHI), and oxyhemoglobin saturation levels. A variety of effective behavioral and airway-specific therapies are available for the treatment of OSA, including weight loss, positive airway pressure therapy, oral appliances, and surgical procedures. Behavior modification is indicated for most patients who have OSA. This includes losing weight (if overweight or obese), exercising, changing the sleep position (if OSA is positional), abstaining from alcohol, and avoiding centrally acting medications.

- For patients with severe OSA (AHI ≥30 events per hour), nocturnal continuous positive airway (CPAP) pressure is recommended as initial therapy (6).

- For patients with mild to moderate OSA, CPAP is preferred as initial therapy rather than an oral appliance for example mandibular advancement splint (Figure 3). For patients who are reluctant or intolerant to CPAP, an oral appliance is a reasonable alternative as first-line therapy (7).

Surgical therapy is generally reserved for selected patients in whom positive airway pressure, or an oral appliance was either declined, not an option, or ineffective. A notable exception is patients whose OSA is due to a surgically correctable obstructing lesion e.g., severe tonsillar hypertrophy, adenoid hypertrophy (pediatrics), or craniofacial abnormalities. Hypoglossal nerve stimulation via an implantable neurostimulator device is a novel treatment strategy (Fig 4) that may have a role in selected patients with moderate to severe OSA who decline or fail to adhere CPAP, but further data are required.

• May be either OSA or Cheyne Stokes Respiration – Central Sleep Apnea (CSR - CSA) or a mix. CSR is the cyclic crescendo decrescendo pattern of respiratory effort and airflow (Figure 5).

• CSA (AHI >15 events per h sleep) occurs in 21–37% of patients with stable congestive heart failure with reduced ejection fraction (HFrFE) (8). The prevalence of CSA in heart failure with preserved ejection fraction (HFpEF) is less defined. Estimates vary from 18% to 30%(8). The severity of CSA is related to the severity of HFrEF and HFpEF. In HFrEF, the presence of CSA is associated with an increased risk of death or risk of cardiac transplant, risk of ventricular arrhythmias.

• First line of treatment is to always optimize heart failure therapy.

• There is nil strong evidence that continuous positive airway pressure (CPAP) reduces mortality in heart failure (although CANPAP study (NEJM 2005) post hoc analysis suggested if AHI suppressed <15, survival may be improved with CPAP).

• If OSA present, CPAP may improve EF, BP, exercise capacity and quality of life.

• If CSR present, can consider trialing CPAP, oxygen or Bilevel positive airway pressure (NIV) therapy.

• Adaptive Servo Ventilation (ASV), a special type of CPAP therapy is now contraindicated in CSR with EF <45% as the SERVE HF study (NEJM 2015) randomized controlled trial.

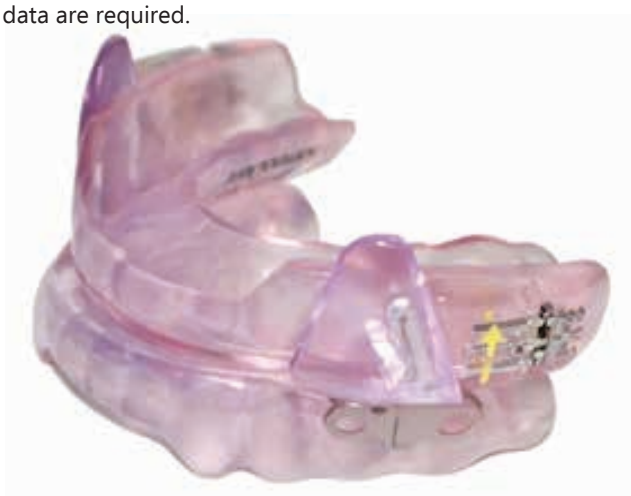


Figure 4: Mandibular advancement splint

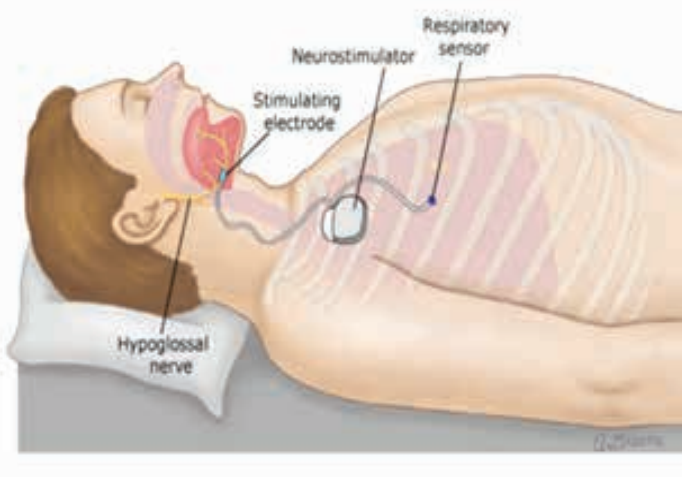


Figure 5: Hypoglossal nerve stimulation

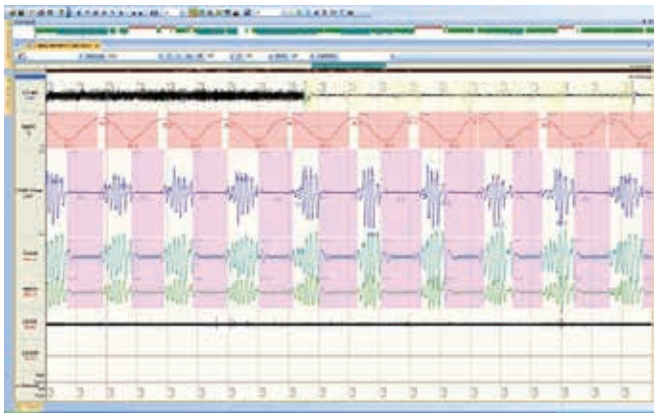
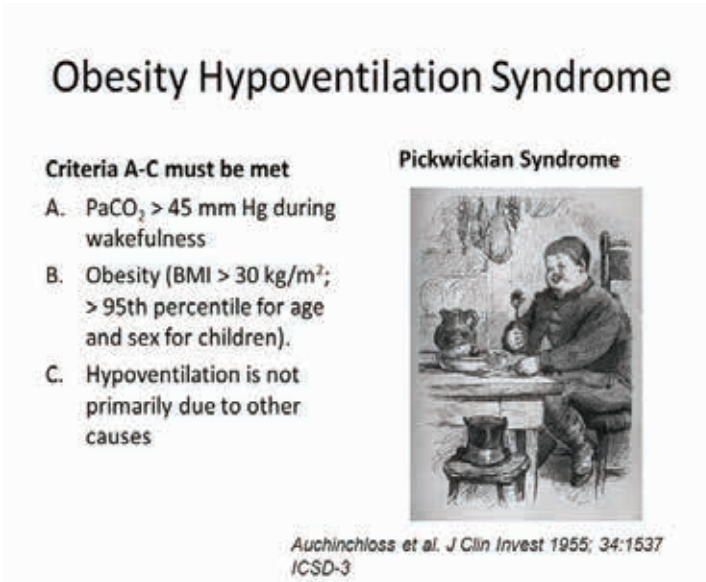


Figure 6: Polysomnography of Cheyne Stokes respiration-waxing and waning pattern of breathing as reflected on CPAP flow and thoraco-abdominal muscle movement.



Epidemiology: The majority of patients with OHS have concurrent OSA while pure sleep hypoventilation alone (nonobstructive events) is present in around 10 percent of individuals. 90% patients with OHS have at least mild OSA (apnea-hypopnea index [AHI] >5 events per hour), with severe disease (AHI >30 events per hour) seen in 70% (9,10).

Pathophysiology of Obesity Hypoventilation Syndrome

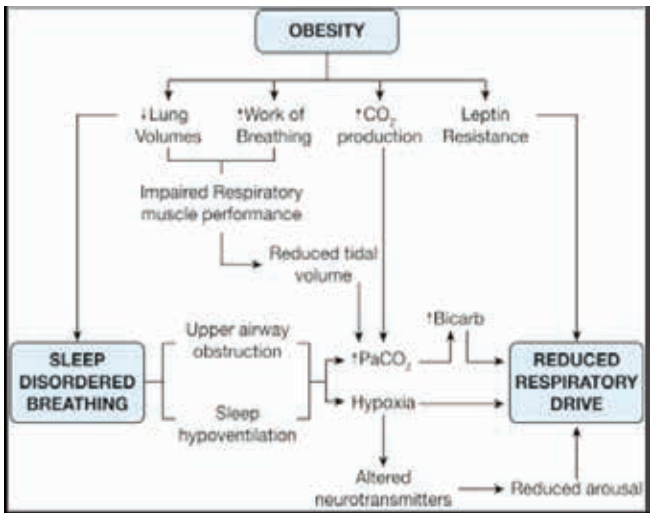


Figure 7: Pathophysiology of OHS (Ref: Pépin JLLancet Respir Med 2016; 4:407-418)

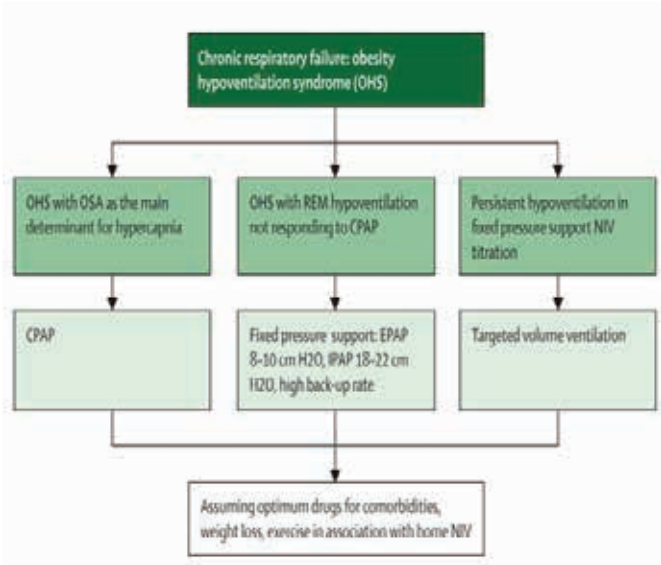


Figure 8 : Rx of OHS (Ref : Pépin JL et alLancet Respir Med 2016;4:407-418)

Conclusion : Sleep disodreded bretahing encomapsses a range of respiratory disturbances that can occur in sleep. WIth the growing bariatric population and increased co-morbidities in the face of global post pandemic phase , this is postulated that SDB will be be more prevalent in our demography in the coming years. A systemic approach for screening the sleep disorder in higly susceptible and high risk population is quite crucial to prevent future cardio-respiratory complications, hospitalizations and mortality.

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Altered mental state – Is it Delirium or something else?

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Delirium is an acute neuropsychiatric condition affecting global cognitive function, primarily attention, working memory, and consciousness.1 It is often confused with dementia or other psychiatric illnesses. Patients presenting with an acute and fluctuating altered mental state, which is associated with a lack of attention, disorganised thinking, and perceptual disturbance, are diagnosed with delirium.[2]

Among older adults who are hospitalized, 14%–56% presents with delirium.3 In fact, 10%–30% of older patients present to the emergency department with delirium as a symptom of a potentially serious medical illness.4 Delirium is often multi-factorial in nature. A recent study investigated the most common aetiologies of altered mental state; this multicenter, prospective study (which examined involving 822 older patients with an altered mental state) found that 50% patients had delirium. Among them infection (39.5%) and neurological diseases (36.5%), which were the most common aetiologies underlying the development of altered mental state.5 In another study, sepsis and metabolic abnormalities were the most common aetiologies of delirium at about 36.5% and 35%, respectively.6 Most patients had more than one aetiology and the predisposing and precipitating factors are summarised in the table below.

Delirium is typically thought to be transient in nature, as most patients are expected to make a full recovery once the underlying aetiology (such as the presence of an illness or drug-related toxicity) is addressed or managed.2 It is critical to note, however, that certain patient populations – primarily frail and older adults – frequently experience ongoing delirium that does not resolve. Delirium is associated with a number of adverse outcomes, including worsening of one's cognitive function, the onset of functional disability, increased hospitalization/institutionalization, and death.7,8 The one-year mortality rate among patients with delirium is 35%–40%.9

The pathophysiology of delirium is still not well understood. As delirium is multifactorial a single mechanism is unlikely to delineate its pathogenesis. Among multiple hypothesis the two dominant theories regarding delirium pathophysiology are direct brain insult and aberrant stress response leading to neuroinflammation.10,11 These mechanisms resulted in impairment of oxidative cerebral metabolism with defective neuotransmitter release affecting various intracranial structures including prefrontal cortex,thalamus,fusiform cortex,posterior parietal cortex and basal ganglia,particularly on the non-dominant side.12,13

Proinflammatory cytokines such as interleukin-1, interleukin-2, interleukin-6, tumor necrosis factor α (TNF-α), and interferon, may contribute to delirium14,15,16 by increasing the permeability of the blood– brain barrier and altering neurotransmission. Cytokine activation may account for delirium (particularly hyperactive forms of the disturbance) in situations such as sepsis (where mental changes may actually precede fever), cardiopulmonary bypass17, and acute hip fracture18. Insults from acute medical intercurrent illnesses such as hypoxia,hypoglycaemia,thiamine deficiency etc may abate acetylcholine synthesis in CNS which in turn precipitate delirium. It is also noted that serum anticholinergic activity correlates with the severity of delirium in postoperative and medical patients [19,20].

Table: 1

Predisposing factors	Precipitating factors
1.Demographic characteristics - Age of 65 or older - Male sex 2. Cognitive status - Dementia or cognitive impairment - Depression - History of delirium 3. Functional status - Immobility - History of falls 4. Sensory impairment - Visual impairment - Hearing impairment 5. Reduced oral intake - Dehydration - Malnutrition 6. Drugs - Polypharmacy - Alcohol abuse 7. Coexisting medical conditions - Severe illness - History of stroke and Neurologic disease - Metabolic derangements - Multiple coexisting conditions - Chronic renal or hepatic disease - Fracture or trauma - Terminal illness	1. Drugs - Sedatives and narcotics - Anticholinergic - Polypharmacy - Alcohol or drug withdrawal 2. Primary neurologic disease - stroke - Intracranial haemorrhage - Meningitis or encephalitis 3. Intercurrent illness - Infection -Iatrogenic complications - Severe acute illness - Hypoxia - Shock - Fever or hypothermia - Anaemia - Dehydration - Poor nutrition - Low serum albumin - Metabolic derangements 4.Surgery - Orthopaedic and cardiac surgery - Prolonged cardiopulmonary bypass 5. Environmental - Admission to ICU - Use of physical restraint - Use of bladder catheter - Use of multiple procedures - Pain -Emotional stress 6. Prolonged sleep deprivation

Source: Inouye SK Delirium in older persons. N Engl J Med 2006;354:1157-65.

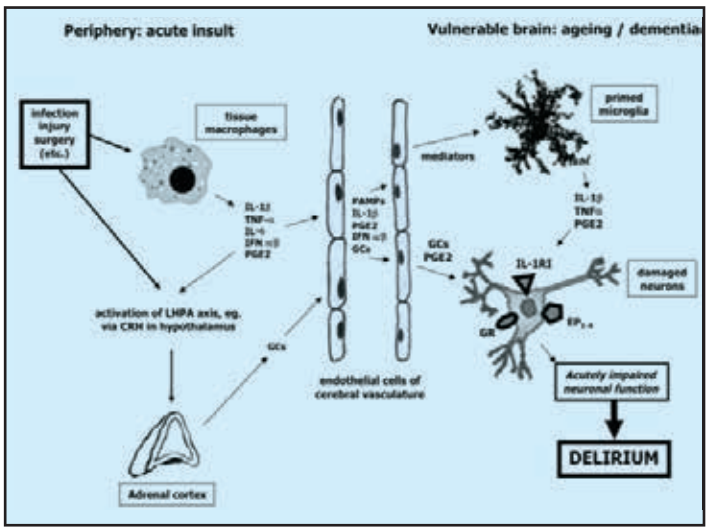

Figure: 1 Mechanism how peripheral insults cause delirium Source: MacLullich A,,Ferguson K et al. Unravelling the pathophysiology of delirium: a focus on the role of aberrant stress responses. J Psychosom Res. 2008 Sep;65(3):229-38

Delirium due to cholinergic deficiency is based on extensive research. Any drugs with anticholinergic property can induce or precipitate delirium in human. Physostigmine reverses delirium associated with anticholinergic drugs, and there is beneficial role of cholinesterase inhibitors in patients with delirium that are not induced by drugs.15,21,22 Dopamine excess has regulatory influence on the release of acetylcholine which in turn may contribute to delirium.15 Dopaminergic drugs (e.g., levodopa and bupropion) are recognized precipitants of delirium, and dopamine antagonists (e.g., antipsychotic agents) effectively treat delirium symptoms. Alteration of other neurotransmitters, such as norepinephrine, serotonin, γ-aminobutyric acid, glutamate, and melatonin, may also have a role in the pathophysiology of delirium,14,15,16 through interactions with the cholinergic and dopaminergic pathways However this mechanism is still uncertain due to lack of strong evidence.

To identify delirium is crucial as it can often be unrecognised. Delirium can be assessed using bedside tools. There are several tools that can be used to identify it. Among those, the Confusion Assessment Method (CAM) is highly sensitive and specific.23 In 2010, Wong et al24 performed a systematic review examining the evidence on the accuracy of 11 bedside instruments in diagnosing delirium. It was found that CAM has the best available supportive data showing a positive likelihood ratio of 9.6 (95% confidence interval [CI]: 5.8–16.0) and a negative likelihood ratio of 0.16 (95% CI: 0.09–0.29).24

There are four major features of delirium used in the algorithm of CAM, which are as follows: acute onset and fluctuating course, inattention, disorganized thinking, and altered level of consciousness.23 Among these four features, the presence of both the first and second, and either the third or fourth criteria are required to form a diagnosis of delirium.23

Determining the precipitating and predisposing factors of delirium warrants a systematic approach that starts with obtaining a detailed patient history, performing a physical examination, and conducting laboratory investigations that include a patient's full blood count, erythrocyte sedimentation rate (ESR), C-reactive protein, midstream urine microscopy and culture, and chest X-ray to identify infective causes; biochemistry, blood glucose, and thyroid function tests are used to rule out metabolic causes; and computed tomography scans of the brain (CT Brain) are warranted to rule out intracranial pathology in the appropriate clinical setting. A review of the patient's medication is also essential to assess if any antipsychotic, antidepressant, or other psychotropic mediations are interfering with the patient's cognition. If the diagnosis is still uncertain and the patient's clinical condition does not resolve, further investigation is necessary, which needs to be tailored according to the patient's history, clinical examination, and the evolution of his or her clinical progress.25,26

It can be sometimes challenging to distinguish delirium from dementia and other psychiatric illnesses. It is particularly difficult when one person may suffer from more than one condition. Dementia is a well-known predisposing factor for delirium. However having delirium does not mean that a person has dementia. Hence an attempt to assess dementia during an episode of delirium is of limited value.

The cognitive changes in dementia,particularly in Alzheimer disease are typically insidious, progressive with minimal fluctuation, and occurs over a much longer time (months to years). Attention is relatively intact, as are remote memories in the earlier stages.

Dementia with Lewy bodies (DLB) is particularly difficult as fluctuations and visual hallucinations are common and prominent which is also present in delirium. It is important to remember that the visual hallucination in DLB is more formed and persistent.

Delirium is often confused with depression. Both are associated with alteration of sleep rhythm and difficulty with attention or concentration. Agitated depression can be specifically difficult due to its mode of presentation. However, depression is associated with dysphoria, and there is less fluctuation than in delirium. Mania is another differential diagnosis for hyperactive delirium with restlessness, delusions, and psychotic behaviour. However, mania is usually associated with a pre-existing history of manic episode or depression. The unique fixed and systematised delusions in Schizophrenia are the main contrasting feature for delirium.

Delirium is a serious medical condition that is associated with significant morbidity and mortality. As this is often unrecognised, clinicians should be mindful of the occurrence of it when someone presents with altered mental state.

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Self harm summary article

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Self-harm is one of the most challenging aspects of working in mental health. Every day I see patients with cuts on their Chaney illustrates that self-harm has always occurred in a cultural and historical context. This is important for those of us who work more closely with Bangladeshis or South Asians more generally as rates vary. The online context is also more significant with many self harm groups on the internet which can be both beneficial in forging a sense of support but can also normalise some pathological behaviours.

Self-harm often has overlaps with what is known as borderline syndrome, a personality type that is acutely sensitive to feeling abandoned, criticised or rejected. This was even more pronounced amid the peer relations and need for group belonging that exist in adolescence. Such patients often have a history of trauma in their childhood or a disrupted bonding with their mothers. Medications such as anti-depressants and mood stabilisers can help to manage some of the complications, such as reducing anxiety, providing better impulse control and helping to regulate mood. Patients often complain of wildly gyrating moods, a feature of borderline personality that often makes sufferers think they suffer bipolar disorder.

The vast majority of self-harmers speak of feeling a wave of relief when they self-harm. The urge is not always conscious, which frustrates parents and loved ones who start becoming resentful of the cutting behaviours. The vast majority of self-harmers speak of their sense of frustration or tension. While they are not always aware of it, many experience an overwhelming rage, usually because something they wanted was not received. While few will admit it, the act is often an expression of rage in those who have not learned to deal with frustration. Sometimes self-harm is a way to manipulate the environment, to get what they want from those who have power, be they parents, nurses or prison wardens.

The other complicating factor about self-harm, and a clue about its origins, is that the patients show little visible emotion during interviews. They might be talking about the most horrific things, but there is barely a change in their facial expression. In psychiatry we label this as a lack of reactivity in affect. Its wider significance is a kind of roadblock between what is being experienced at an emotional level and what is expressed outwardly. This is very much the case in self-harm, where sufferers have adapted in the context of either abusive, highly conflicted or emotionally constricted environments to repress difficult emotions like anger or aggression.

One of the key treatments for self-harm, especially for those who have a diagnosis of borderline personality disorder, is dialectical behavioural therapy (DBT). This was developed by American psychologist Marsha Linehan, who describes her treatment as a modification of cognitive behavioural therapy incorporating elements of acceptance and mindfulness inspired by Buddhist meditation.

When I ask patients about the most useful concepts they learn from the DBT treatment, a regular reply is the notion of "being comfortable with the uncomfortable". Another way of thinking about the expression is the skill of handling difficult or problematic emotions, especially those associated with anger, aggression or disgust.

There are many factors contributing to the current spike in psychological distress. They include the decline of communal structures, the dilution of uniting moral systems such as religion, and the greater social comparison that comes with a media-rich environment combined with a meritocratic system.

I want to cover some specifics about the South Asian population, a group widely studied in the United Kingdom. This will be especially for local communities given they have the similarity of living in the Western context. The studies are below were collated by the Annals of General Psychiatry in Britain, in a 2006 article authored by Husain and Wahid.

One major precipitating factor in South Asian Women who harm themselves is marital problems. In a study by Merrill and Owens [8], in Birmingham, UK, South Asian women reported marital problems more frequently and the majority of these problems were due to cultural conflicts. A few of the Asian women in the study reported that their husbands demanded them to behave in a less westernised fashion. Also, they reported that their mother in laws interfered with the way they ran their lives and marriages. Such factors, along with arranged marriages, rejections of arranged marriage proposals and other marital problems place pressure on South Asian women, and thus were reported as precipitating factors for self-harm by the participants.

In 1999, Bhugra et al [19] compared two groups of South Asian women to study various cultural and social factors associated with attempted suicide in South Asians. From the study, it was found that those attempting suicide were more likely to have history of a past psychiatric disorder, more likely to repeat the attempt and more likely to be in an interracial relationship. It was also found that those South Asian women attempting suicide were more likely to have changed religion and spent less total time with their families. In the same study, when South Asians attempting suicide were compared with white attempters it was found that South Asians were more likely to have no psychiatric disorder, were less likely to have used alcohol in their attempt and were more likely to have been assaulted verbally or physically.

In the study in Manchester [9] higher proportion of South Asians (particularly women) cited an interpersonal problem with family members, as the main precipitant of the self-harm episode and a higher proportion were married despite being younger.

Some of the social and cultural factors that influence rates of self-harm in South Asian women are summarised in Table 1.

The high rates of self-harm displayed by South Asian women is not a trend that is displayed by South Asian adolescents; in a study of South Asian female adolescents Bhugra et al [21] reported that rates of attempted suicide among teenagers were no different from their white counterparts. Nonetheless, South Asian female adolescents were more likely to report a family history of suicide and were more likely to recognise a cultural conflict. Otherwise white and South Asian female adolescents (aged 16–17 years) had similar adjustment reactions, alcohol and drug use, peer and relationship problems.

Kingsbury [22], in a study of adolescents who had taken overdoses showed that social and parental relationships were

a key cause of isolation and as a result, attempted suicide. He found that South Asian adolescents had fewer problems with boy or girlfriends and were more likely to have problems with siblings. It was also reported that South Asian adolescents were less likely to be in contact with their friends, saw them less frequently and for shorter periods, and their relationships with their parents did not compensate for this. A school based self report survey [23] of deliberate self harm carried out in England also show that 6.7% of Asian girls as compared to 11.6% of white girls had reported self harming. Among the boys 2.7% Asian and 3.3% whites reported such behaviour.

Most South Asian communities maintain their traditional cultural identity and place great importance on academic and economic success, the stigma attached to failure, the overriding authority of elders and an unquestioning compliance from the younger members. Such cultural attitudes place hard-to-meet expectations on Asian youth leading to increased pressure and stress.

As South Asian female adolescents grow older, the rates of self-harm increase; particularly the rates of self-harm for Asian females aged 18–24 are significantly higher [9, 21]. This suggests that they come under more stress. The stress may relate to gender role expectations, pressure for arranged marriage, individualisation and cultural conflict, which may precipitate attempts of self-harm.

A qualitative study of South Asian women in Manchester [24] found that issues such as racism, stereotyping of Asian women, Asian communities, and the concept of "izzat" (honour) in Asian family life all led to increased mental distress. The women in this study saw self-harm as a way to cope with their mental distress.

The concept of izzat (i.e. honour/respect) is a major influence in Asian family life. (In Bangladeshi cultures this might be called “shomaan”).

According to the women in the study, izzat was pervasive and internalised and it prevented other community members from listening and getting involved. The burden of izzat was unequally placed upon the women in Asian families and as a result this created hard-to-achieve high expectations of women as daughters, daughters-in-law, sisters, wives and mothers.

Furthermore, many Asian families are critical about the behaviour of women and it is very important whether this is seen as 'good' behaviour according to the community since it is essential in gaining status and prestige for the family. The women in the study reported that a community grapevine often develops in Asian communities in the UK due to this. This grapevine then results in a lack of privacy and space for women. Many women in the study felt as though they had nobody to trust and thus could not speak to anyone in the community. This leads to an increasing sense of isolation for Asian women.

In assessment of self harm, it is important to exclude co-morbid disorders such as a depression or anxiety. Any association with substances increases the lethality of any attempt, especially in overdose. It also increases risk by worsening impulsivity. One question to ask is how long they had planned the attempt. As soon as it is more than a few hours, it is much higher risk. Whether there was actually suicidal intent or not is important to verify. Many deaths are associated with self harm gone wrong, without suicidal intent. Psychiatric admissions can be useful if brief and for crises only, but a challenge can be explaining to parents and sufferers that hospital admissions don’t tend to help and that unfortunately for self harm thoughts can be chronic. The vast majority of episodes are due to feelings of being abandoned or rejected which those with borderline personality in particular are especially sensitive to.

The aim of treatment is to better cope with difficult emotions and improve function in relationships and work/study. Patients usually require a psychologist, ideally a DBT program and some medications- usually an anti-depressant and mood stabiliser such as lamotrigdine. Family therapy can be useful also if they are a teenager.

A brief overview and update on migraine

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Introduction:
Migraine is a common disabling headache disorder that causes significant morbidity and has socioeconomic and personal impacts. This is characterised by recurrent attacks of moderate to severe headaches and a host of neurological, gastrointestinal, cognitive and emotional symptoms 1. Migraine is often underdiagnosed and not adequately treated.

How common is migraine?
Migraine affects approximately 1 billion people worldwide, predominantly females 2,3. This is the second most prevalent neurologic disorder (after tension-type headache), with a female-to-male ratio of 3:1 and an estimated 1-year prevalence of approximately 15% in the general population 2,3.

Is migraine vascular or neurological disorder?
The debate whether migraine is a vascular or neurological disorder has largely been settled. Vascular changes represent an epiphenomenon, and migraine is best thought of as a disorder of brain excitability and sensory dysmodulation causing head pain plus associated features. Migraine is usually a hereditary brain abnormality, although it can occur in other settings, such as after head trauma 5.

How much do we know about the pathophysiology?
The pathophysiology of migraine is not well understood. In general, it is considered to involve the trigeminal nerve and its axonal projections to the intracranial vasculature (termed the trigeminovascular system). Nociceptive signals from the trigeminovascular system are relayed to areas in the brain that yield the perception of migraine pain3.

Sensitisation: This is the process in which neurons become increasingly responsive to nociceptive and non-nociceptive stimulation. Peripheral sensitization in the primary afferent neurons and central sensitization within second-order neurons in the trigeminal nucleus caudalis and higher-order neurons in the central nervous system are thought to play a role within individual migraine attacks and, perhaps, even in the transformation of episodic migraine to chronic migraine (Uptodate).

What is migraine aura?
Aura is a suboptimal term because it can occur before or during the headache, in the absence of a headache. This usually lasts for 15-20 minutes but can last longer. There are many types of aura and can be present in one third of migraineurs.

CSD: Cortical spreading depression, is the physiological basis of the aura phase of migraine. This is self-propagating wave of depolarization across the cerebral cortex that is followed by cerebral hypoperfusion which occurs at rate of 3mm/minute.

How do I diagnose Migraine?
International Classification of Headache Disorders (ICHD- 3), has brought greater clarity to the field of headache diagnosis4. The following two tables show diagnostic criteria for migraine without aura and chronic migraine based on ICHD-3. For details of other subtypes of migraine, please refer to ICHD-III website (https://ichd-3.org) for full details. This website also includes exhaustive lists of other headache disorders which can be very useful and informative

Table 1:

Migraine without Aura
Description: Recurrent headache disorder manifesting in attacks lasting 4–72 hours Typical characteristics of the headache are unilateral location, pulsating quality, moderate or severe intensity, aggravation by routine physical activity and association with nausea and/or photophobia and phonophobia.
Diagnostic Criteria:
A. At least five attacks fulfilling criteria B–D
B. Headache attacks lasting 4–72 hours (when untreated or unsuccessfully treated)
C. Headache has at least two of the following four characteristics: 1. unilateral location 2. pulsating quality 3. moderate or severe pain intensity 4. aggravation by or causing avoidance of routine physical activity (e.g. walking or climbing stairs)
D. During headache at least one of the following: 1. nausea and/or vomiting 2. photophobia and phonophobia
E. Not better accounted for by another ICHD-3 diagnosis.

Table 2:

Chronic Migraine
Description: Headache occurring on 15 or more days/month for more than three months, which, on at least eight days/month, has the features of migraine headache.
Diagnostic Criteria:
A. Headache (migraine-like or tension-type-like1) on 15 days/month for >3 months, and fulfilling criteria B and C
B. Occurring in a patient who has had at least five attacks fulfilling criteria B–D for 1.1 Migraine without aura and/or criteria B and C for
1.2 Migraine with aura C. On 8 days/month for >3 months, fulfilling any of the following: 1. criteria C and D for 1.1 Migraine without aura 2. criteria B and C for 1.2 Migraine with aura 3. believed by the patient to be migraine at onset and relieved by a triptan or ergot derivative
D. Not better accounted for by another ICHD-3 diagnosis.

How to treat migraine?
The approach to treatment depends of many factors such as migraine type i.e. episodic or chronic; abortive vs preventative therapy; patient co-morbidities and personal choice.

In general, abortive therapies should be used early in the headache phase to be more effective. The first line therapy is over the counter NSAIDs. Triptans are considered second-line agents, and there are many to choose from. For more severe cases, combination of triptan and NSAIDs can be helpful. Antiemetic medication can be used in combination or by itself, especially for patients who have nausea/vomiting. Opioids should be avoided for acute therapy due to adverse effects and risk of dependency. Opioid use can contribute to development of chronic daily headache and can interfere with other preventive therapies. More recently, small-molecule CGRP receptor antagonists, called gepants, and the 5-hydroxytryptamine type 1F (5-HT1F) receptor agonists, called ditans, show promising benefit in the treatment of acute migraine3. Caution should be taken for patient taking excessive amounts of acute abortive therapies as there is a risk of development of medication overuse headache.

Should I treat episodic migraine with prophylactics?
This can be quite a tricky question. Few studies have examined indications which are[7]:

• Two severe or disabling or four less disabling migraine attacks per month
• Acute migraine treatment is ineffective or contraindicated
• Medication-overuse headache is present
• Highly disabling migraine attacks (eg, hemiplegic migraine or migraine with brainstem aura)
• Patient preference

What are the options for preventative therapies?
Choosing the right prophylactic medication can be very challenging. These medications often have a variety of adverse effects and adherence is a big issue. It is best to start at low dose and slowly increase the dose towards effective dose. The following table7 shows the classes of prophylactic medication available.

Table 3:

Class	Drugs
Antiepileptic drugs	Divalproex sodium, topiramate, gabapentin
Antidepressant drugs	Amitriptyline and others TCAs, venlafaxine and other SNRIs
Beta-blockers	Propranolol, metoprolol, timolol
Other antihypertensive drugs	Verapamil, lisinopril, candesartan
Neurotoxins	OnabotulinumtoxinA
Calcitonin gene-related peptide monoclonal antibodies	Erenumab, fremanezumab, galcanezumab, eptinezumab
Other	Memantine, cyproheptadine
Herbal & nutritional supplements	Magnesium, vitamin B2 (riboflavin), feverfew, coenzyme Q10, melatonin

Which agent should I used first?
First-line prophylactic medications for chronic migraine include:
* Propranolol
* Amitriptyline
* Topiramate
* Valproic acid and its derivatives (for males and for females who do not have childbearing potential)

What other oral therapies can I use if first line therapy fails or cannot be used?

One of the following medications can be considered: Venlafaxine, Verapamil, Other beta blockers (atenolol, metoprolol), Gabapentin, Magnesium, Riboflavin, Candesartan and other tricyclic antidepressants such as nortriptyline

Antidepressants:
TCA Amitriptyline is better tolerated is started lower dose such as 10 mg. The target dose is 25-50mg. SNRI venlafaxine has moderate evidence for prevention of migraine. Venlafaxine can have a significant withdrawal syndrome. Duloxetine has less severe withdrawal symptoms.

Antihypertensive medications:
The most commonly prescribed antihypertensive agent is the nonselective beta-blocker propranolol. This is contraindicated in people with asthma. Evidence that beta-blockers worsen depression has been challenged in recent years. The target dose is 60 mg once daily or 2 times a day.

The calcium channel blocker verapamil has relative benign side effects profile, though constipation can be bothersome. Verapamil may also be helpful in patients with migraine aura. Other antihypertensive (ACE-I/ARB) such as Candesartan and Lisinopril also showed some efficacy.

Antiepileptic medications:
This group has higher efficacy but also causes higher side effects. Topiramate has the best evidence, but has side effects such as cognitive slowing, including perceived memory deficits and word-finding difficulties.

Sodium valproate is also highly effective but is limited by a high side effect burden and teratogenicity. Gabapentin has lower sided effects and can be useful in medication overuse headache.

Do I have any other options if first and second line fail?
Essentially, there are 2 options, which include Botulinum toxinA treatment and Monoclonal antibodies directed against CGRP receptor or ligand. To meet the PBS criteria in Australia, patients have to fail 3 prophylactic medication. At present, there are two CGRP monoclonal antibodies available on PBS, Fremanezumab and Galcanezumab.

What is the evidence of Botulinum toxin treatment?
Two randomized controlled trial (PREEMPT1 and PREEMPT2) found that onbotulinumtoxinA was effective in chronic migraine. Overall, this treatment is moderately effective therapy in chronic migraine. This treatment has relatively low adverse effects, done in the right clinical setting.

Is there anything new in treatment paradigm?
The CGRP (calcitonin gene-related peptide) antibodies are new kid in the block. CGRP is a neuropeptide found throughout the central and peripheral nervous systems that is intrinsically involved in migraine pathogenesis. CGRP is a therapeutic target in migraine because of its role in mediating trigeminocervical pain transmission and the vasodilatory component of neurogenic inflammation. Drugs directly antagonizing the CGRP receptor were initially evaluated as preventive treatments in the 2000s but were associated with an increased risk of liver toxicity. This ultimately led to the development of monoclonal antibodies to CGRP or its receptor[7].

Erenumab was the first in these group that became available in 2018, followed by other agents, Fremanezumab and Galcanezumab. The latter 2 have been approved by PBS since June 2021. The latest medication in this group, Eptinezumab, is administered IV and has quick onset of action. Multiple randomized controlled trials have proven the benefit8. The common side effects are injection site reaction, nasopharyngeal infection and constipation. The relative low adverse effects has the potential for better medication adherence.

Botulinum toxin vs CGRP MAB – which one should I choose? There is no head to head studies between treatments with Botulinum toxin and CGRP monoclonal antibodies. However, ICER (Institute for clinical and economical review) network meta-analysis shows roughly equivalent efficacy7. A systematic review and meta-analysis by Broessner et al in 2021 examined comparative overview of efficacy of topiramate, Botulinum toxin and CGRP antibodies9. All these showed higher odds ratios in achieving a 50% response rate compared to placebo. Topiramate numerically demonstrated the greatest effect size but also the highest drop-out rate.

Conclusion:

This is an exciting time to be in the field of headache as the understanding of underlying mechanism of migraine is evolving. The advent of new CGRP antibodies, a disease-specific and mechanism-based treatment for migraine, has expanded the treatment paradigm. Moreover, further research is being undertaken to find new target and to develop biomarkers and in future more targeted therapy will be available.

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Acute renal failure and metformin-associated lactic acidosis following colonoscopy

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Abstract
Two patients with type 2 DM developed acute kidney injury and lactic acidosis following colonoscopy despite withholding metformin for a few days. We recommend that DM patients on metformin withhold angiotensin converting enzyme inhibitor (ACEI), angiotensin receptor blocker (ARB) until their dehydration is reversed after colonoscopy. This should reduce the risk of acute renal failure (ARF) and of lactic acidosis due to reduced renal clearance of metformin.

1. Presentation of cases

The first patient was a 67 year old man who had a 22 year history of Type 2 diabetes and had many complications of diabetes, including diabetic nephropathy with mild chronic kidney disease. Six weeks prior to colonoscopy his serum creatinine was 118µmol/L, eGFR 57 ml/min/1.73m2, microalbumin:creatinine ratio 11.6mg/mmol creatinine [reference range (RR), ≤2.5]. His HbA1c was 7.9% (63mmol/mol). Other diabetes associated complications included diabetic retinopathy, peripheral neuropathy, cerebrovascular disease and ischaemic heart disease. He had undergone surgery for a rectal adenocarcinoma 2 years prior.

He presented to emergency with 7 hours of central chest pain, and 5 days of nausea and vomiting. A colonoscopy 12 days prior found 2 adenomas that were removed. The bowel preparation used included sodium picosulphate. Metformin 1000mg bd was withheld the day prior to and of the colonoscopy. He was continued on his other regular medication of gliclazide 160mg bd, isophane insulin 30 units nocte, perindopril 5mg, indapamide 2.5mg, pantoprazole 40mg, allopurinol 300mg, felodopine2.5 mg, warfarin 5mg, atorvastatin 80mg and fluoxetine 20mg.

At presentation he was dehydrated and his heart rate was 110 beats/minute, blood pressure 140/90mmHg and respiratory rate 40/minute. His serum sodium was 139mmol/L (RR, 135-145), potassium 6.4mmol/L (RR, 3.5-5.0), chloride 92mmol/L (RR, 97-109), bicarbonate <5mmol/L (RR, 24-32), glucose 4.2mmol/L and creatinine 630µmol/L (RR, 70-110). Arterial blood gas levels showed a metabolic acidosis with pH 6.91 (RR, 7.36-7.44), partial pressure of oxygen (PaO2) 87mmHg (80-100), partial pressure of carbon dioxide (PaCO2) 17mmHg (35-45), base excess (BE) -29mmol/L (-2 to 2), and lactate 16.8mmol/L (RR, 0.36-1.25 mmol/L). His ECG demonstrated sinus tachycardia with new ST depression in lateral leads with initial troponin of 0.06µg/L (RR, ≤0.01). Liver function tests were within the reference range. Metformin and perindopril were ceased.

Despite supportive care, four hours after presentation his blood pressure fell to 70/40mmHg and his oxygen saturation was 89%, his Glasgow Coma Score was 10 and he was anuric. Inotropes were commenced and he was intubated for mechanical ventilation. Both were required for three days. Continuous veno-venous haemodialysis (CVVHD) was carried out for 57 hours. A diuresis commenced after 5 days. Metformin and perindopril were ceased and he was switched to a bolus insulin regimen. Arterial lactate normalised after 40 hours.

A dipyridamole sestimibi myocardial perfusion study showed a small reversible area at the basal inferior wall of the left ventricle. He was discharged after 17 days, with serum creati nine 148µmol/L.

The second patient was a 68 year old woman with a 18 year history of Type 2 DM who was managed with metformin 750 mg bd (withheld on the day of procedure), gliclazide MR 120mg and isophane insulin 50 units nocte. She had hypertension that was controlled by irbesartan 300mg, indapamide 2.5mg, amlodipine 5mg. She was also taking meloxicam 15mg. Three weeks prior to colonoscopy her serum creatinine was 90µmol/L, eGFR 55ml/min/1.73m2, protein:creatinine ratio 14.8mg/mmol and HbA1c 6.9% (mmol/mol).

She had a colonoscopy to investigate an altered bowel habit, for which she had a sodium picosulphate bowel preparation. A caecal polyp was removed. Five days later, she presented with a four day history of vomiting and diarrhoea and was oliguric. She appeared dehydrated but was normotensive, and her serum sodium was 129mmol/L, potassium 4.6mmol/L, chloride 87mmol/L, bicarbonate 12mmol/L, glucose 5.1mmol/L and creatinine 730µmol/L. Arterial blood gases revealed a metabolic acidosis with pH 6.81, PaO2 142mmHg, PaCO2 11mmHg, BE -32mmol/L, and lactate 18.0mmol/L. Liver transaminases were within the reference range.

She was admitted to intensive care for haemodynamic and ventilatory support. Metformin, irbesartan and indapamide were ceased. Although initially normotensive, her blood pressure fell to 83/53mmHg and inotropes were commenced. She was commenced on CVVHD, which continued for 24 hours. She was extubated after 30 hours. Arterial lactate normalised by 48 hours. A diuresis commenced after 4 days. Serum creatinine on discharge 10 days later was 147µmol/L.

2. Discussion

Acute renal failure (ARF) in both of these cases is likely to be multi-factorial; however, there was a temporal relationship with the colonoscopy and bowel preparation. Both patients had hypertension managed with either an angiotensin converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB), and the diuretic indapamide, which are likely to have also contributed to the development of ARF. The second patient was also on a non- steroidal anti-inflammatory drug, that may also have contributed to her risk of ARF [1]. The bowel preparation may lead to dehydration and hypovolaemia, which would have been exacerbated by the diuretics. The presence of the ACEI or ARB blocked the rennin-angiotensin compensation required to reduce sodium and water loss when there is hypovolaemia, thereby worsening the hypovolaemia and acute renal failure. The acute renal impairment and fall in GFR led to accumulation of metformin and lactic acidosis. The lactic acidosis predominantly was a result of the metformin and renal impairment, but hypoperfusion of tissues may also have contributed.

Both early and late renal dysfunction subsequent to bowel preparation with oral sodium phosphate has been described

[1]. To our knowledge, this is the first report of ARF occurring subsequent to the use of picosulfate. Patients managed with ARB or ACEI, are vulnerable to acute renal failure if dehydration occurs [2]. In one series of ARF arising in patients managed with ACEI, 20% had precedent vomiting and diarrhoea [3]. A series of patients with metformin related lactic acidosis and acute renal failure found that acute gastroenteritis was a frequent precipitating event [4]. With colonoscopy, the bowel preparation and any following diarrhoea could similarly induce acute renal failure especially if ACEI/ARB and diuretics are continued.

Cases of metformin associated lactic acidosis have been described where there was no antecedent contra-indication to the use of metformin [5]. Many of these cases were on ACEI or ARB with acute renal injury from a diarrhoeal illness and hypovolaemia [6, 7]. These two cases are the first described arising after colonoscopy.

These cases suggest that in patients having a colonoscopy, metformin, combined with ACEI or ARB increases the risk of metformin associated lactic acidosis, even in patients with no renal contra-indication to metformin. The author suggests that metformin should be withheld at the time of colonoscopy [8], similar to recommendations to withhold metformin when patients are acutely unwell and at risk of dehydration [6,7]. In those with diabetes, it has been recommended that therapy such as ACEI or ARB should be withheld with acute illness [7]. The author suggests that it would be prudent to withhold ACEI or ARB a day prior to colonoscopy in patients with renal impairment and in all patients if diarrhoea or vomiting follows colonoscopy. Patients should also be counselled to stop ACEI or ARB and diuretics, as well as to seek medical review if hydration cannot be maintained with bowel preparation after colonoscopy. Care also needs to be given to the avoiding dehydration with bowel preparation for those with diabetes and older patients who also have renal impairment or are on ACEI or ARB.

These cases suggest that dehydration with sodium picosulphate use in patients with chronic renal disease, on ARB or ACEI and metformin increases the risk of acute renal failure and lactic acidosis. In such patients it is necessary to avoid dehydration, hold metformin and ACEI or ARB and diuretics until the patient is rehydrated.

Conflict of interest

No conflict to declare

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The new kid on the block: What should we know about cancer immunotherapy and immure-related toxicities.

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Introduction

Immunotherapy has revolutionized modern medicine, more precisely, modern cancer treatment. It has introduced a novel concept in combating cancer that is different from decade-old conventional cancer treatments like cytotoxic chemotherapy. It targets and stimulates the body's immune system which eventually attacks cancer cells. Although the history of cancer immunotherapy dates back to as far as 1976 when Bacillus Calmette-Guerin (BCG) was introduced in the treatment of superficial bladder cancer[1], the real success of immunotherapy commenced with the addition of immune checkpoint inhibitors. The checkpoint molecules such as CTLA-4 (cytotoxic T-lymphocyte antigen 4) and PD-1 (Programmed cell death receptor 1) are protein molecules located on the surface of T lymphocytes or T cells (found in blood and lymphoid organs) and act as negative regulators of immune activation against cancer and inflammation[2]. The monoclonal antibodies against CTLA-4 such as ipilimumab and PD-1 or PDL1 (ligand of PD-1, found in macrophages, dendritic cells, epithelial cells) such as nivolumab and pembrolizumab, block the action of these checkpoint inhibitors and re-invigorate immune system[3]. The checkpoint inhibitors take the break-off immune system and thus reactivate immune cells against cancer. The first checkpoint inhibitor, ipilimumab was approved in 2011 for treatment of metastatic melanoma which showed superior survival benefit over chemotherapy[4]. Subsequently, pembrolizumab was approved for metastatic melanoma in 2014 and nivolumab for non-small cell lung cancer in 2015 [5-7]. Since then, anti-PD-1 and anti-PD-L1 antibodies have been approved for a growing list of cancers including Merkel cell cancer, bladder cancer, renal cell cancer, Head and Neck cancer, cutaneous squamous cell cancer, liver cancer, stomach cancer, and Hodgkin's lymphoma. Moreover, hundreds of clinical trials in different types of cancer are performed worldwide where immunotherapy remains the backbone of therapy combined with other types of cancer therapy.

Efficacy of immunotherapy

The efficacy of checkpoint inhibitors reflects the unique mechanism by which they control cancer. They stimulate the immune system against cancer and mount a response that continues to work for months to years by providing a sustained benefit. This is in contrast to most conventional cancer therapies where continuation of therapy is needed to maintain response. The concept of cure in advanced cancer is possible now with the establishment of immunotherapy. The unprecedented success of checkpoint inhibitors can be explained by several factors. Firstly, the ability of checkpoint inhibitors to enable durable response and long-term survival for at least a subset of patients. The patients can continue to sustain response even on discontinuation of treatment. Secondly, checkpoint inhibitors target the immune system, regardless of tumour histology or the presence of any mutation. Thirdly, their efficacy can be improved by combining other agents or immunotherapy. Fourthly, the side effects of immune therapy are distinct from conventional chemotherapy and targeted agents enabling them to be used in a wide range of cancer patients.

Side effects of immunotherapy

The unique mechanism of action of checkpoint inhibitors gives rise to unique side effects known as immune-related adverse effects. The boosted immune system can give rise to a generalized inflammatory response which can affect other organs of the body. Almost any organ can get affected although the most commonly involved are the skin, endocrine glands, gastrointestinal system, and liver. Less commonly, the lungs, nervous system, cardiovascular system, eye, and hematological system can get involved in an aberrant inflammatory response. Most importantly, the inflammatory response can resemble classic autoimmune diseases and thus becomes a challenge for physicians. The wide spectrum of irAEs can be manifested as an inflammatory rash (skin), gastritis, colitis (gastrointestinal tract), thyroiditis leading to hypo or hyperthyroidism (thyroid gland), hypophysitis (pituitary gland), pneumonitis (lungs), hepatitis (liver), pancreatitis and diabetes (pancreas), meningitis and encephalitis (central nervous system), neuropathy (peripheral nervous system), nephritis (kidney) and myocarditis (cardiac). The severity of side effects can range from mild self-limiting rash to life-threatening myocarditis. The pattern of organ involvement and timing and severity of side effects depends on the type of immune checkpoint used and their specific role in immune awakening. For example, anti-PD-1 antibodies have a more favourable toxicity profile compared to anti-CTLA-4 antibodies. The most common toxicities from anti-PD-1 therapy are thyroiditis and pneumonitis whereas colitis and hypophysitis are common with anti-CTLA-4 antibodies [8]. The combination of anti-CTLA-4 and anti-PD-1 has a higher incidence of toxicities compared to monotherapy. This particularly demands meticulous care and supervision from treating physicians when patients undergoing treatment with combination therapy. Some organs affected by irAEs can sustain permanent tissue damage (for example thyroid gland, pituitary gland, and pancreatic B cells) requiring lifelong hormone replacement. Other iRAEs can affect organs that have the inherent capability for regeneration (for example liver, gastrointestinal tract, skin) and thus can be reversible. This underpins the diversity of mechanisms of action of immune checkpoint inhibitors used and the underlying physiology of affected organs. Nevertheless, a biopsy of the affected organs to study tissue-specific mechanisms is not routinely done due to either limited accessibility of the tissue (myocarditis, pneumonitis,

nervous system, uveitis) or various patient-related issues (unwellness, disease progression). The severity of irAEs necessitates discontinuation of treatment which ultimately affects the overall cancer outcome of patients. Therefore, prompt recognition and early management are the cornerstones of management for irAEs. To guide the management of irAEs, several international groups have set standard guidelines which provide directions regarding the diagnosis and treatment of irAEs [9-11]. The guidelines set directions on how to establish the diagnosis of irAEs by ruling out differentials and initiating prompt management. Discontinuation of immunotherapy and initiation of corticosteroids are usually the mainstay of management. For severe or higher-grade toxicities, hospitalization is usually necessary for investigation, supportive management, and escalation of therapy to monoclonal antibodies targeting inflammatory cytokines or immunosuppressive drugs. Most importantly, the involvement of multiple specialties such as pathologists, surgeons, immunologists, cardiologists, gastroenterologists, endocrinologists, and neurologists is commonly needed to ensure optimal management of irAEs.

Response and toxicity relationship

As the development of irAEs can occur as a result of a hyperactive immune system, the response to immunotherapy can be regarded to be related to irAEs. Although the relationship between response and irAEs is not clear and may depend on multiple other factors such as type of checkpoint inhibitor used, type of cancer, organ involved, and severity of irAEs; some studies showed that patients treated with anti-PD-1/anti-PD-L1 antibodies had better response and survival benefits if they developed irAEs. This relationship was not clear with anti-CTLA-4 antibodies [12-14]. Another important confounding factor that needs to be taken into account is the use of the high-dose corticosteroids required to suppress the overactive immune system. Studies have shown conflicting data on the negative effect of corticosteroids on anti-tumour response [15, 16].

Conclusion

Immune checkpoint inhibitors are promising novel therapeutic tools in modern cancer medicine that undoubtedly opened new hope for cancer patients. The durability of response, better tolerability, and relatively safe toxicity profile made them on top of the list for a cancer treatment algorithm. It must be emphasized that patients can get serious toxicities from immunotherapy so high suspicion, prompt recognition, and immediate management are essential to avoid complications.

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Current trend in diabetes management with focus on prevention of Complications

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Background:
Incidence and prevalence of diabetes mellitus is on the rise for both type 1 and type 2 diabetes. In particular, T2D associated with obesity and metabolic syndrome has become a significant challenge for clinicians and policymakers. This is true for both developed and developing countries.

Complications of diabetes result from two major factors, duration of disease and suboptimal management which in turn is due to inertia of treatment escalation and choice of agents. The most dreaded complications resulting from long-standing suboptimal management of diabetes that have a significant impact on morbidity and mortality are those that affect the vital organ systems such as the cardiovascular system, and renal and eye complications. Other complications that affect the quality of life are diabetic foot disease and neuropathies (peripheral and autonomic). In 2008 FDA mandated cardiovascular safety trials for all glucose-lowering agents prior to marketing. In compliance with this regulation, manufacturers needed to conduct cardiovascular safety trials for all DPP4 inhibitors, SGLT-2 inhibitors, modified release GLP-1 receptor agonists, and newer generations of insulins prior to FDA approval.

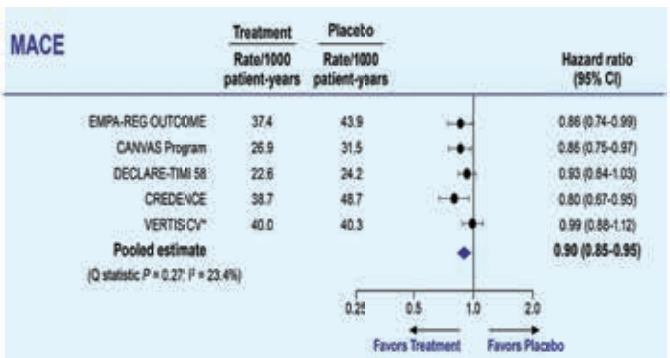
Discussion:
Over the last ten to fifteen years there has been significant progress in new drug classes approved for the management of T2D that has proven cardio-renal benefits by mechanisms other than glucose lowering effects. The two most notable of these classes are the SGLT-2 inhibitors1,2 and GLP-1 receptor agonists 1,2. With the introduction of these agents and evolving evidence of their benefits through a number of clinical trials, most management guidelines have updated their recommendations as to the choice of add-on therapy in T2D to achieve target glycaemic control. In the arena of type 1 diabetes, progress has predominantly been made with respect to technological advances in better glucose monitoring and insulin delivery systems. Examples of such technological advances are flash glucose monitoring and continuous glucose monitoring compatible with smartphones, and advanced insulin delivery systems including closed-loop pumps. All these devices have improved patients' quality of life enormously. It is also worth mentioning that newer long, ultra-long, and rapid-acting insulins have simplified multi-dose insulin regimes for type 1 patients. These advances not only improved quality of life but also made a positive impact on overall diabetes control thereby preventing or delaying complications.

I now would like to discuss more in detail the roles of SGLT-2 inhibitors and GLP-1 receptor agonists in the treatment cascade of T2D and what special benefits these agents have over any other agents including insulin when used in the right patient, at the right time, and in appropriate combination with other agents.

SGLT-2 inhibitors: Major outcomes trials with SGLT2 inhibitors in people with T2D at varying levels of CV risk include EMPA-REG OUTCOME2, CANVAS program3, CREDENCE4, DECLARE-TIMI5, and VERTIS- CV6. These trials were done with currently available various members of the SGLT-2 inhibitor class.

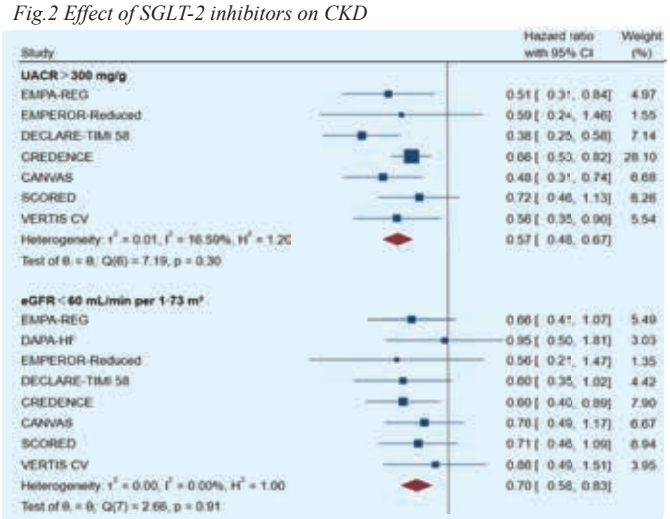
EMPA-REG OUTCOME, CANVAS, and CREDENCE demonstrated superiority with respect to MACE, and DECLARE-TIMI found superiority with respect to the combined outcome of cardiovascular death and hospitalization from heart failure (HFH). EMPA-REG and CREDENCE have demonstrated improved mortality with SGLT-2 inhibitors. Although MACE was the primary outcome in these trials, reduction in HFH in T2DM patients with ASCVD appears to be a class effect. The benefit of SGLT-2 inhibitors in reducing HFH is also evident among patients with heart failure and reduced ejection fraction (HFrEF) regardless of diabetes status as shown in DAPA-HF7 and EMPEROR-Reduced8. There are ongoing trials such as EMPA-Preserved and DELIVER to look at the benefits of use of SGLT-2 inhibitors in HFpEF irrespective of diabetes status. However, reduction in major adverse cardiac events (MACE) has only been limited to empagliflozin and canagliflozin in clinical trials in T2DM patients with ASCVD

Fig.1 Effect of SGLT-2 inhibitors on Major Adverse Cardiovascular Events



In regards to renal outcome, CREDENCE and DAPA-CKD9 were among the early trials showing significantly reduced risk of the primary outcome in CKD patients. A subsequent systematic review and meta-analysis of nine included studies10 showed that SGLT2 inhibitors significantly reduced the risk of primary renal outcomes in patients with CKD, and this benefit was consistent across the spectrum of different levels of eGFR. Additionally, consistent benefits were observed in patients with type 2 diabetes.

Fig.2 Effect of SGLT-2 inhibitors on CKD



The observed renal and cardiovascular benefits of SGLT-2 inhibitors are independent of the HbA1c lowering effects of these agents in people with type 2 diabetes and eGFR >45 ml/min11. In people with diabetes and eGFR<45 mL/min, treatment with SGLT-2 inhibitors do not lower HbA1c

significantly. SGLT-2 inhibitors can be initiated or continued for cardio-renal protection, however, if further glucose lowering is required adding another class of medications to optimize diabetes control is recommended.

It is worth mentioning some important precautions to bear in mind while considering the use of SGLT-2 inhibitors. Genito-urinary infections are well known and more common in women. These need to be explained. The mild initial decline in renal function during the first couple of weeks should not be a cause for concern and it is not recommended at present to monitor renal function within 6-8 weeks after initiation of treatment. Product information has now been revised for use of SGLT-2 inhibitors with eGFR >45ml/min. Another important caution for use of SGLT-2 inhibitors is to avoid it in patients prone to sepsis and during the peri-operative period to reduce the risk of euglycaemic keto-acidosis.

GLP-1 receptor agonists: GLP-1 RAs have emerged as an important class of medications to consider in the treatment of patients with T2D. Certain GLP-1 RAs have shown benefits compared with placebo in decreasing the risk of composite cardiovascular outcomes in patients with type 2 diabetes12.

Current guidelines have changed to recommend GLP-1 RA as the preferred therapy after metformin in patients with T2D with established cardiovascular disease.

The European Association for the Study of Diabetes and the American Diabetes Association consensus statements recommend that SGLT2 inhibitors and GLP-1 RAs should be considered as add-on therapies in patients with T2DM and established ASCVD. If HF or chronic kidney disease predominates, SGLT2 inhibitors are preferred. However, if SGLT-2 inhibitors cannot be tolerated or are contraindicated, the statement suggests that GLP-1 RAs are reasonable to use.

Fig.3 Meta-analysis of eight CVOTs with GLP-1 RA on MACE

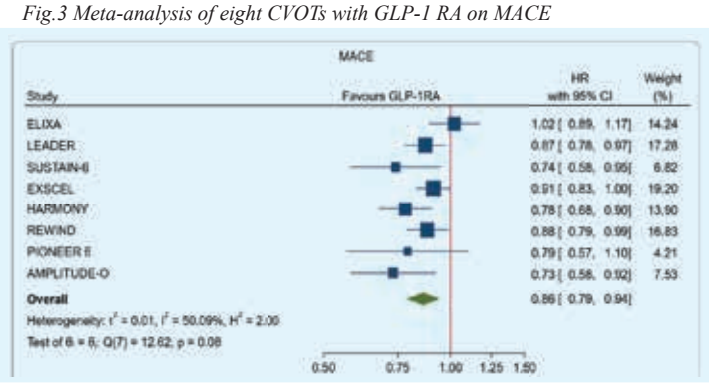
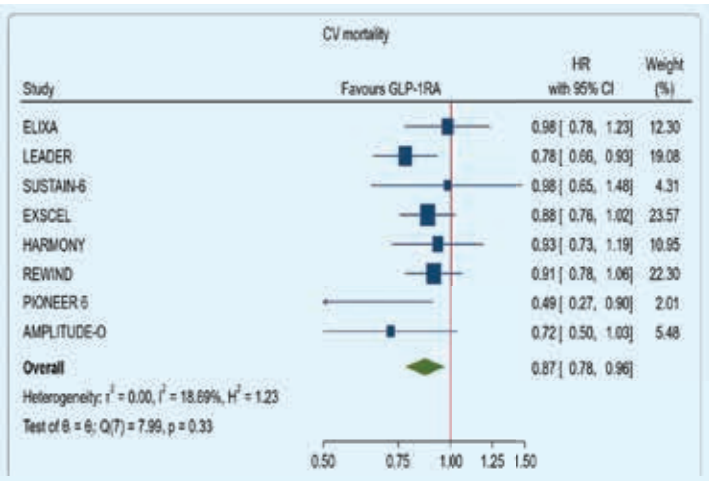
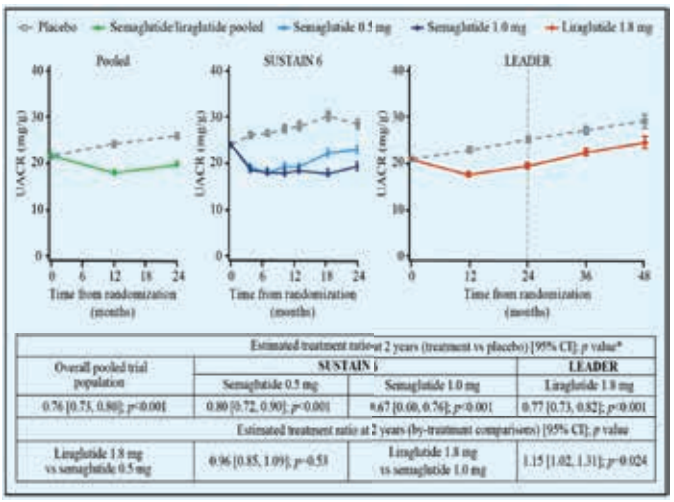


Fig.4 Meta-analysis of eight CVOTs with GLP-1 RA on CV mortality



GLP-1 receptor agonists have also been shown to improve renal events in DKD13. GLP-1RA can be used up to eGFR of 15 mL/min, therefore offering the potential for adequate glycaemic control in multiple stages of DKD without an increased risk of hypoglycemia, preventing the onset of macro albuminuria and slowing the decline of glomerular filtration rate (GFR) in diabetic patients and with additional benefits in weight reduction.

Fig.5 Effects of once-weekly semaglutide and once-daily liraglutide versus placebo on albuminuria



Estimated treatment ratio at 2 years (treatment vs placebo) [95% CI]; *p* value*			
Overall pooled trial population	SUSTAIN 6		LEADER
	Semaglutide 0.5 mg	Semaglutide 1.0 mg	Liraglutide 1.8 mg
0.76 [0.75, 0.80]; *p*<0.001	0.80 [0.72, 0.90]; *p*<0.001	0.67 [0.60, 0.76]; *p*<0.001	0.77 [0.73, 0.82]; *p*<0.001
Estimated treatment ratio at 2 years (by-treatment comparisons) [95% CI]; *p* value			
Liraglutide 1.8 mg vs semaglutide 0.5 mg	0.96 [0.85, 1.09]; *p*=0.53	Liraglutide 1.8 mg vs semaglutide 1.0 mg	1.15 [1.02, 1.31]; *p*=0.024

Importance of non-glucose-lowering agents: It is important not to ignore the role of lipid lowering agents and anti-platelet agents in specific patient groups when aiming for prevention of diabetes complications. Statins and aspirin/clopidogrel have proven benefits in T2D with established cardiovascular disease. Fenofibrate, in addition to its role in lowering triglycerides, has also been shown in the FIELD14 study to slow the progression of diabetic retinopathy.

Conclusion: The above discussion has predominantly focused on glucose-lowering agents that have proven benefits in cardio-renal protection by mechanisms other than glycaemic control. Two classes of drugs have been discussed, SGLT-2 inhibitors and GLP-1 RA. These are approved for add-on agents, not as primary or sole agents. One or the other should be chosen early when the indication is clear to get the maximum benefit from it. Simultaneous use of both agents in the appropriate patient cohort does not have any safety concerns but is not on the PBS subsidy list in Australia.

This discussion by no means indicates that the use of other oral agents and insulin should be discouraged. They have specific roles in achieving target glycaemic control in specific patient cohorts. It is to be kept in mind the very important findings of the 'legacy effect' of two landmark trials in diabetes, UKPDS15 (T2D) and DCCT16 (T1D). Both of these trials demonstrated that good glycaemic control even for the short to medium term lowers the risk of long-term complications, predominantly microvascular but also macrovascular complications.

Issues for consideration: As doctors of Bangladeshi origin and working overseas, it is our desire to implement our knowledge and expertise in our respective fields so at least our relatives and friends and thereafter the population in Bangladesh can benefit from evidence-based treatment. It is easy said than done. We can explore ways at a personal level and more importantly through initiatives taken by organizations like BMS NSW in collaboration with various government and non-governmental organizations in Bangladesh. I would leave this matter at present time to the office-bearers of BMS NSW for consideration in future planning.

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Rectal bleeding: What do i do?

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Rectal bleeding is a common symptom and occurs in adults of all ages. Approximately 15-25 per cent of adults experience this symptom by the age of 50, and most of this will not be reported. It is more common in younger adults who may be less likely to seek medical consultation for this problem as they tend to believe it is secondary to haemorrhoids or benign peri-anal conditions. It has also been noted that only 40% of patients with rectal bleeding seek medical care, and most of these patients hail from more than 60 years old. Women have higher rates of rectal bleeding in the age groups of 18 to 39, whereas men have a higher incidence of bleeding in the age group of 40 to 49.

It is imperative to understand the difference between haematochezia and melaena. Passage of minimal bright red blood per anus most commonly occurs in a chronic intermittent pattern and is referred to as intermittent haematochezia. It could be secondary to a lesion or pathology near the anal canal. Melaena implies upper gastrointestinal or slow proximal colonic bleeding. It refers to black tar-like stool (due to enzyme breakdown and digesting the blood as it moves through the GI tract) and is often accompanied by a strong, foul smell and sticky stool. The cause of maroon stool intermixed with bright red blood is likely secondary to the proximal colonic or small intestinal source. However, patients' and clinicians' perceptions of stool colour vary widely, even when assisted by a standardized colour chart.

Aetiology

The age of the patient and the onset of symptoms give a clue to aetiology. Those under 30 presenting with rectal bleeding are more likely to have haemorrhoids, an anal fissure or inflammatory bowel disease. Those over 50 should have a higher suspicion of colorectal cancer. It should, however, not be forgotten that nearly one-third of rectal cancer patients are younger than 55.

More common	Less common
Benign anorectal disease:	Infectious gastroenteritis
· Haemorrhoids	Coagulopathies
· Anal fissure	Arteriovenous malformation
· Perianal fistula	Ischaemic colitis
Diverticular disease	Radiation proctitis
Inflammatory bowel disease	Solitary rectal ulcer
· Ulcerative colitis	Dieulafoy's lesion (Small or large bowel)
· Crohn's disease	Endometriosis
Diverticular disease	Trauma (e.g., sexual abuse)
Colorectal polyps	Sexually transmitted infection
Colorectal cancer	
Anal cancer	

Presentation

The pattern, amount of bleeding, and the initial symptom can give clues to the likely aetiology and severity of bleeding. It is, for example, important to assess the amount of bleeding. There are three classifications according to the amount of bleeding:

- Occult bleeding - presenting with anaemia.
- Moderate bleeding - presenting with rectal bleeding (fresh or dark) or melaena in a haemodynamically stable patient.
- Massive bleeding - presenting with large amounts of blood passed rectally (may be dark but often fresh).

History & differentiation

A thorough history taking and physical exam are essential to rule out the different causes of rectal bleeding. Direct questions regarding onset, duration, amount, frequency, and passage of clots should be foremost during the consultation. Associated symptoms of abdominal pain, weight loss, change in bowel habits, and a previous history of any recent pelvic surgery or abdominal-pelvic radiation should also be included.

A comprehensive review of the patient's comorbidities and medications is warranted. Special attention should be given to comorbidities contributing to bleeding tendencies or requiring the patient to take anticoagulants such as an artificial heart valve or atrial fibrillation. Regarding medications, special attention should be given to NSAIDs, anticoagulants, and antiplatelet agents as possible contributing factors to rectal bleeding.

The most common cause of rectal bleeding in the middle-aged and elderly population is haemorrhoids, which are often asymptomatic. They may be described as soft, painless protrusions in the anal canal. In essence, there is a downward displacement of the hemorrhoidal cushions, which causes venous dilatation and, hence, symptoms. Common symptoms include bleeding with or without defecation, swelling, and mild discomfort or irritation. Other symptoms may include mucous discharge, pruritis, difficulties with hygiene, and a sense of incomplete evacuation. Internal haemorrhoids are only painful if they are thrombosed, have prolapsed with oedema, and/or strangulated. External haemorrhoids only cause pain when they become thrombosed. Anal pain associated with defecation may suggest anal fissures. A change in bowel habits and significant weight loss in older patients may hint at a malignancy.

Haemorrhoids

The most common symptom is bleeding, which tends to be painless, bright and following defaecation; may drip into the bowl. An associated prolapse can lead to mucus or liquid stool leakage and pruritis. Pain is uncommon in internal haemorrhoids but can occur if associated external component with acute thrombosis.

Anal fissure

Severe pain accompanies bowel movements and persists as intense throbbing for hours afterwards. Patient complaints of bright red blood, usually on toilet paper or surface of stool; pruritis or skin irritation may also occur.

Infective colitis

Profuse watery diarrhea with or without blood is the cardinal clinical symptom. Lower abdominal pain and cramping and low-grade fever, and leukocytosis. High fever is a more severe disease. Symptoms may begin during antibiotic therapy or 5-10 days later.

Ischaemic colitis

It usually affects the elderly and is caused by a reduction in intestinal blood flow, commonly arising from occlusion, vasospasm and/or hypoperfusion of the mesenteric vasculature. In the Hyperactive phase, the patient experience severe pain and passage of loose, bloody stools due to mucosal and submucosal injury. In the paralytic phase. Pain can be diminished, but more diffuse and continuous tenderness, distended abdomen with reduced bowel sounds.

Diverticular disease
Most patients with diverticulosis are asymptomatic; however, a small proportion will have intermittent colicky pain or lower abdominal discomfort, constipation, distension or a sensation of incomplete evacuation. Most patients come to clinical attention because of complications (diverticulitis, bleeding, or stricture causes colonic obstruction. They present with left lower abdominal pain, low-grade fever, nausea, diarrhoea and rarely rectal bleeding. The risk factors for diverticular disease leading to complications are smoking, NSAIDs, obesity, low fibre diet and constipation.

Colorectal cancer
Symptoms depend on the site, size and location of the tumour. The patient with a left sided cancer experiences rectal bleeding and a change in bowel habits. On right-sided tumours, the patient can be asymptomatic or may present with iron-deficiency anaemia or palpable mass. In colonic cancer, unintentional weight loss and anorexia are also common. An obstruction, perforation or fistula suggests an advanced disease and needs emergency surgical attention.

Physical Examination
The physical exam should begin with assessing hemodynamic status via measuring vital signs. Attention should be paid to low blood pressure, tachycardia, and/or a high respiratory rate, as these may indicate hemodynamic instability and necessitate rapid escalation of care.

A focused exam for lower GI bleeding should include an abdominal exam with an assessment for pain, masses, distention, and signs of cirrhosis, which might hint toward rectal varices. Perineum inspection should be carried out with the patient lying in the left lateral decubitus position under a light source to evaluate for old blood, thrombosed vessels, prolapsing haemorrhoids, fissures, or protruding masses.

The rectal exam should follow an inspection of the anus for any skin tags protruding, sentinel piles, fissures, protruding piles, or any other apparent abnormalities that could be causing the bleed. External haemorrhoids may thrombose, causing extensive pain and discomfort.

A rectal exam can be uncomfortable and painful for patients, particularly in the case of acute fissures. In this case, inspection, while gently spreading the buttocks, helps visualise most anal fissures and is sufficient for diagnosis. A digital rectal exam should be done to assess for masses and internal haemorrhoids. However, it is contraindicated in immunocompromised patients, given the possibility of introducing pathogens, which could potentially cause life-threatening infections.

Investigation
A full blood count (FBC) should be ordered with any complaint of bleeding to assess the severity and help direct the management. Other important lab tests are the international normalized ratio (INR) and the partial thromboplastin time (PTT), which will help assess any bleeding tendencies. A cross-match test may be needed to reserve blood for transfusion in cases of severe bleeding. A stool MCS and inflammatory markers should be done if suspected infective or inflammatory condition.

CT angiography may be pursued if there is a large bleeding volume or the patient is too unstable to undergo anaesthesia for endoscopic intervention. If there is a large blood volume in the gut, it may be difficult to isolate the specific site of where the blood is coming from.

Technetium 99 labelled red blood cell scintigraphies are an accurate investigation for localizing the bleeding vessels and identifying the site into which they bleed. It can be utilized in recurrent and persistent rectal bleeding of an unknown cause.

Management
A patient above 40 years with rectal bleeding or any age with unusual presentation or unknown aetiology should be referred to a specialist. The management depends on the age, the severity and the suspected cause of the bleeding. Endoscopies are the gold standard for investigating rectal bleeding, which should be performed in patients who are older than 40 years of age regardless of other clinical symptoms

An anoscope or rigid procto-sigmoidoscope can be used to evaluate for a distal source of bleeding, such as internal haemorrhoids, proctitis, rectal ulcers, malignancies, or varices. A colonoscopy should be done if there is a concern for proximal lower GIT pathology.

Acute, severe rectal bleeding requires initial hemodynamic assessment and the initiation of haemostatic resuscitation to control the patient's vital signs. Rectal bleeding severe enough to compromise the hemodynamic system is rare. It is usually due to severe upper GI bleeding such as bleeding varices, perforated ulcer, or an aorto-enteric fistula and may mandate an upper GI endoscopy. If the patient undergoes endoscopy, bleeding can be controlled by endoscopic cauterization, ligation, or direct injection to the bleeding site with either adrenaline or sclerosing agents.

Management of haemorrhoids can be divided into conservative and surgical categories. Conservative management revolves around incorporating high fibre options in the diet to minimize the risk of constipation and hence straining while defecating. Daily consumption is highly recommended. Fibre therapy can take up to 6 weeks to improve the haemorrhoids. Increased fluid intake is also important to prevent constipation. Stool softeners and hyperosmolar supplements, such as glycerine and sorbitol, which can be given as rectal suppositories, or oral milk of magnesia and polyethylene glycol 3350, can be used as adjuncts to a high fibre diet. Sitz baths help to decrease pain, burning, and itching following a bowel movement for active, symptomatic haemorrhoids. Symptom relief can also be achieved using topical local anaesthetics, cortico steroids, and anti-inflammatory drugs. One of the most commonly used drugs is 0.2% glyceryl trinitrate (GTN) rectal ointment (mostly in grade 1 or 2 haemorrhoids), which relieves symptoms of haemorrhoids associated with high resting anal canal pressures. The efficacy of topical steroids is currently unproven.

Rubber band ligation is the most widely used office technique for internal haemorrhoids. The procedure involves the application of a rubber band at the apex of internal haemorrhoids. This will cause the fixation of haemorrhoids in the anal canal, correcting the prolapse, with the additional benefit of decreasing blood flow resulting in a decrease in size. It is beneficial for grade one and two haemorrhoids and is considered the most effective non- excisional treatment in the literature. However, up to 30% of patients will have recurrences requiring repeated treatment. Another treatment option is the injection of sclerotherapy, which requires injecting a sclerosing agent at the base of the internal hemorrhoidal complex. This causes scarring, fibrosis, and

ultimately fixation of the hemorrhoidal complex. Sclerotherapy is not as successful as rubber band ligation for grade 3 haemorrhoids. Arterial embolization procedures of the superior and inferior rectal arteries have also proven effective in controlling severe and persistent bleeding.

Operative management is reserved for patients who fail medical management or continue to have symptoms despite undergoing office-based procedures, present with extensive thrombosed haemorrhoids, or have other manifestations of advanced disease. Moreover, strangulated or gangrenous haemorrhoids will require immediate operative intervention as well. Closed excisional hemorrhoidectomy is the most commonly performed operation in Australia.

Prognosis

The prognosis depends on the cause of rectal bleeding, the severity, and the patient's underlying health. Approximately 95% of rectal bleeding cases will regress spontaneously.

Deterrence and patient Education

It is important for patients to seek medical consultation in cases of rectal bleeding, especially in middle and older-aged individuals, as the risk of malignancy is higher in these groups. Patients should be educated to seek medical assistance immediately if they experience vomiting or coughing up blood associated with rectal bleeding. This may indicate a potentially life-threatening upper gastrointestinal bleed or the presence of a bleeding tendency such as thrombocytopenia or anti-coagulant toxicity.

Pearls and other issues

The full blood count and, more specifically, the haemoglobin and haematocrit values may not immediately reflect the severity of an acute bleed. Patients with previous cardiac conditions taking low-dose aspirin as secondary prevention should not stop taking it.

Enhancing healthcare team outcome

Rectal bleeding frequently poses a diagnostic dilemma and is best managed with an interprofessional team approach. These patients may exhibit non-specific signs and symptoms. Interprofessional team communication and patient care coordination between general practitioners, gastroenterologists, and general & colorectal surgeons plays a critical role in optimizing management strategies.

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Stroke management in the acute care setting

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Stroke management is continuously evolving.

Endovascular clot retrieval is gradually coming into being a leading contender in the management of large vessel occlusion strokes.

Following is some review of articles that have been published internationally describing the rational and benefits vs harm.

IS THROMBOLYSIS NEEDED PRIOR TO CLOT EXTRACTION IN STROKE?

Since the broad acceptance of endovascular therapy (EVT) for large vessel occlusion (LVO) stroke, the co- or preadministration of thrombolysis to improve the yield of EVT has been standard. Meanwhile, the contribution of this yyyresource-intensive addition to an already cumbersome and rushed, time-sensitive process was never proven. Recent research has therefore concentrated on whether adding thrombolysis to EVT improves outcomes.

QUESTION: WHAT DO RECENT TRIALS SAY ABOUT THROMBOLYSIS FOR STROKE, GENERALLY?

It's hard to find a more controversial or debated topic. In one sense the issue is already decided since thrombolysis is now standard of care for eligible stroke patients. But the debate rages on. And for those who prefer black-or-white to shades of grey, the last few years have only made things worse. Below is a brief review of highly publicized and much discussed publications on thrombolysis for ischemic stroke.

Good news first: This first study is a randomized trial from 2018 called the 'WAKE-UP' trial. WAKE-UP was an effort to determine if patients with an unknown stroke onset time could benefit from thrombolytics if MRI suggests onset <4.5 hours. This fits the mold of common contemporary research, since few seem interested in attempting totruly replicate NINDS, the one trial that showed a benefit with thrombolytics. Instead, most efforts focus on extending timewindows or identifying amenable strokes with new imaging.

Basically, in the WAKE-UP trial stroke patients at centers with 24-hour neurologist, radiologist, and MRI capability whisked stroke patients with an unknown onset to MRI, had readings done instantly, and if their stroke appeared to be <4.5h patients were randomized to thrombolysis or placebo. This wasn't easy, and eligible patients were difficult to find, as participating centers enrolled roughly 1.6 patients/year each.

The trial was stopped early at 503 subjects despite a plan for 800, because they ran out of funding. And while the study found a roughly 11% benefit in 'favorable outcome' (modified Rankin scale 0-1) with thrombolytics (p=0.02), they also found a 3% increase in deaths (p=0.07) and, more concerning, no difference in 'death or dependence'. Advocatessay the trial suggests that for strokes amenable on MRI, there is an outcome benefit. Critics note the trial was stopped early, the outcome patients care about (not being dead or dependent) was unchanged, and thrombolysis increased deaths.

The highlights:

- Patients 18-80 years old at 61 centers in 8 European countries with clinical stroke were eligible if they noted stroke signs on waking (94%) or could not report onset due to aphasia/confusion (6%)
- Of 1362 screened 503 were enrolled; 10% were excluded because no stroke was found (i.e., stroke mimics) and 33% were excluded because their infarct was completed
- As many editorialists noted, this means patient selection must be done carefully, since >40% with 'wake-up' stroke patients can only be harmed by thrombolysis
- Just over a third of subjects had a LVO or visible major vessel occlusion
- 53% v 42% experienced favorable outcomes (mRs 0-1) (p=0.02), and 4% v 1% died (p=0.07)
- Death or dependency was 14% v 18% (p=0.17)
- The authors conclude thrombolytics increased favorable outcomes.

1.MRI-GUIDED THROMBOLYSIS FOR STROKE WITH UNKNOWN TIME OF ONSET Thomalla G, et al. NEJM. 379(7): 611-622, AUGUST 2018

BACKGROUND: Under current guidelines, intravenous thrombolysis is used to treat acute stroke only if it can be ascertained that the time since the onset of symptoms was less than 4.5 hours. We sought to determine whether patients with stroke with an unknown time of onset and features suggesting recent cerebral infarction on magnetic resonance imaging (MRI) would benefit from thrombolysis with the use of intravenous alteplase. METHODS: In a multicenter trial, we randomly assigned patients who had an unknown time of onset of stroke to receive either intravenous alteplase or placebo. All the patients had an ischemic lesion that was visible on MRI diffusion-weighted imaging but no parenchymal hyperintensity on fluid-attenuated inversion recovery (FLAIR), which indicated that the stroke had occurred approximately within the previous 4.5 hours. We excluded patients for whom thrombectomy was planned. The primary end point was favorable outcome, as defined by a score of 0 or 1 on the modified Rankin scale of neurologic disability (which ranges from 0 [no symptoms] to 6 [death]) at 90 days. A secondary outcome was the likelihood that alteplase would lead to lower ordinal scores on the modified Rankin scale than would placebo (shift analysis). RESULTS: The trial was stopped early owing to cessation of funding after the enrollment of 503 of an anticipated 800 patients. Of these patients, 254 were randomly assigned to receive alteplase and 249 to receive placebo. A favorable outcome at 90 days was reported in 131 of 246 patients (53.3%) in the alteplase group and in 102 of 244 patients (41.8%) in the placebo group (adjusted odds ratio, 1.61; 95% confidence interval [CI], 1.09 to 2.36; P=0.02). The median score on the modified Rankin scale at 90 days was 1 in the alteplase group and 2 in the placebo group (adjusted common odds ratio, 1.62; 95% CI, 1.17 to 2.23; P=0.003). There were 10 deaths

(4.1%) in the alteplase group and 3 (1.2%) in the placebo group (odds ratio, 3.38; 95% CI, 0.92 to 12.52; P=0.07). The rate of symptomatic intracranial hemorrhage was 2.0% in the alteplase group and 0.4% in the placebo group (odds ratio, 4.95; 95% CI, 0.57 to 42.87; P=0.15). CONCLUSIONS: In patients with acute stroke with an unknown time of onset, intravenous alteplase guided by a mismatch between diffusion- weighted imaging and FLAIR in the region of ischemia resulted in a significantly better functional outcome and numerically more intracranial hemorrhages than placebo at 90 days.

The second study, the EXTEND trial published in 2019, attempts to use the promise of CT- or MR-perfusion imaging to find patients who might benefit from thrombolysis. In this

large, multinational trial patients with a stroke between 4.5h and 9h underwent perfusion imaging and, if a reversible area of ischemia was found, patients were randomly assigned to alteplase or placebo. About 2/3 had 'wake-up' type strokes, and this similarity between EXTEND and the WAKE-UP trial led the authors to create another similarity: they stopped the trial early, saying the results of WAKE- UP meant they no longer had 'equipoise' between groups (i.e., it was unethical to continue researching since another trial found a benefit).

That was an unfortunate and silly choice—the imaging technologies from the two trials are completely different, among other things, and replicating research findings is ALWAYS important. And frustratingly, it leads to yet another highly debatable result, this time even fuzzier. While the authors claim a benefit in favorable outcome (mRs of 0-1) at 35.4% vs 29.5%, based on a p-value of 0.04, it turns out they only found this difference in a post hoc adjusted analysis. The raw comparison leads to a p-value of 0.35 (no difference, not close), and even the adjusted analysis they planned in their protocol was nonsignificant (though closer at a p of 0.06).

All of these statistical shenanigans led to some serious blogger hand-wringing. But maybe this trial didn't matter much. It turns out the trial was done in 28 centers across Asia, Europe, and Australia, and each center managed to enroll just one patient per year—even less than WAKE-UP. That means stroke cases fitting the inclusion criteria were rare. How many centers are ready to make all the personnel and resources available 24/7 for perfusion imaging, MRI, radiology, neurology, and EM, in order to treat 1 patient a year? Moreover, in EXTEND 80% of patients had LVOs, and would therefore now be eligible for EVT, a much more effective therapy. The highlights:

•EXTEND was a large, 8-year, international, randomized trial using CT- and MR-perfusion imaging to identify patients with eligible strokes at 4.5-9h after onset

•The protocol called for 400, just 225 were enrolled; they do not tell us how many were screened

•**'Favorable outcome' of mRs 0-1, was 35.4 % vs 29.5%, (p=0.04 in a post hoc adjusted analysis, p=0.06 using the preplanned adjustment, p=0.35 unadjusted)**

•Mortality was statistically unchanged but numerically higher with alteplase (11.5% vs 8.9%)

•As expected ICH was higher with alteplase (6.2% vs 0.9%)

•The authors conclude alteplase benefited those with salvageable tissue on perfusion imaging

2.THROMBOLYSIS GUIDED BY PERFUSION IMAGING UP TO 9 HOURS AFTER ONSET OF STROKE Ma H, et al, NEJM 380(19):1795-1803, May 2019

BACKGROUND: The time to initiate intravenous thrombolysis for acute ischemic stroke is generally limited to within 4.5 hours after the onset of symptoms. Some trials have suggested that the treatment window may be extended in patients who are shown to have ischemic but not yet infarcted brain tissue on imaging. METHODS: We conducted a multicenter, randomized, placebo-controlled trial involving patients with ischemic stroke who had hypoperfused but salvageable regions of brain detected on automated perfusion imaging. The patients were randomly assigned to receive intravenous alteplase or placebo between 4.5 and 9.0 hours after the onset of stroke or on awakening with stroke (if within 9 hours from the midpoint of sleep). The primary outcome was a score of 0 or 1 on the modified Rankin scale, on which scores range from 0 (no symptoms) to 6 (death), at 90 days. The risk ratio for the primary outcome was adjusted for age and clinical severity at baseline. RESULTS: After 225 of the planned 310 patients had been enrolled, the trial was terminated because of a loss of equipoise after the publication of positive results from a previous trial. A total of 113 patients were randomly assigned to the alteplase group and 112 to the placebo group. The primary outcome occurred in 40 patients (35.4%) in the alteplase group and in 33 patients (29.5%) in the placebo group (adjusted risk ratio, 1.44; 95% confidence interval [CI], 1.01 to 2.06; P = 0.04). Symptomatic intracerebral hemorrhage occurred in 7 patients (6.2%) in the alteplase group and in 1 patient (0.9%) in the placebo group (adjusted risk ratio, 7.22; 95% CI, 0.97 to 53.5; P = 0.05). A secondary ordinal analysis of the distribution of scores on the modified Rankin scale did not show a significant etween-group difference in functional improvement at 90 days. CONCLUSIONS: Among the patients in this trial who had ischemic stroke and salvageable brain tissue, the use of alteplase between 4.5 and 9.0 hours after stroke onset or at the time the patient awoke with stroke symptoms resulted in a higher percentage of patients with no or minor neurologic deficits than the use of placebo. There were more cases of symptomatic cerebral hemorrhage in the alteplase group than in the placebo group.

A third, similar study called the THAWS trial was published in 2020. Again, the target was wake-up and other strokes of unknown onset, and perfusion imaging was performed in all subjects. If salvageable tissue was present, patients were randomized to alteplase or standard care (this time without placebo controls). Again, the trial was stopped early, this time at 131 subjects, and again the investigators claimed the WAKE-UP trial results prompted them to stop early.

Two important notes on this trial. First, most of the strokes were small vessel occlusions rather than LVOs, and second there was not even a hint of clinical benefit. The highlights:

•THAWS was a large, 4-year, nonblinded randomized trial across 40 centers in Japan using MR imaging to identify patients with eligible strokes and salvageable tissue

•The original protocol called for 278 subjects, 131 were enrolled, mostly wake-up strokes

•Roughly one third of enrolled strokes were LVO, the rest were small vessel

•Favorable outcome of mRs 0-1 occurred in 47% with alteplase vs 48% with standard care

•No adjustment, no subgroup, and no other analysis suggested any benefit

•Mortality was the same (3% vs 3%) and symptomatic ICH was rare (1 only in the alteplase group)

•Authors conclude alteplase showed no benefit, but "termination precludes definitive conclusions"

3.THROMBOLYSIS WITH ALTEPLASE AT 0.6 MG.KG FOR STROKE WITH UNKNOWN TIME OF ONSET: A RANDOMIZED CONTROLLED TRIAL. Koga M, et al, Stroke. 51(5):1530-1538, May 2020

BACKGROUND AND PURPOSE: We assessed whether lower-dose alteplase at 0.6 mg/kg is efficacious and safe for acute fluid-attenuated inversion recovery-negative stroke with unknown time of onset. METHODS: This was an investigator-initiated, multicenter, randomized, open-label, blinded-end point trial. Patients met the standard indication criteria for intravenous thrombolysis other than a time last-known-well >4.5 hours (eg, wake-up stroke). Patients were randomly assigned (1:1) to receive alteplase at 0.6 mg/kg or standard medical treatment if magnetic resonance imaging showed acute ischemic lesion on diffusion- weighted imaging and no marked corresponding hyperintensity on fluid-attenuated inversion recovery. The primary outcome was

a favorable outcome (90-day modified Rankin Scale score of 0–1). RESULTS: Following the early stop and positive results of the WAKE-UP trial (Efficacy and Safety of MRI-Based Thrombolysis in Wake-Up Stroke), this trial was prematurely terminated with 131 of the anticipated 300 patients (55 women; mean age, 74.4±12.2 years). Favorable outcome was comparable between the alteplase group (32/68, 47.1%) and the control group (28/58, 48.3%; relative risk [RR], 0.97 [95% CI, 0.68– 1.41]; P=0.892). Symptomatic intracranial hemorrhage within 22 to 36 hours occurred in 1/71 and 0/60 (RR, infinity [95% CI, 0.06 to infinity]; P>0.999), respectively. Death at 90 days occurred in 2/71 and 2/60 (RR, 0.85 [95% CI, 0.06–12.58]; P>0.999), respectively. CONCLUSIONS: No difference in favorable outcome was seen between alteplase and control groups among patients with ischemic stroke with unknown time of onset. The safety of alteplase at 0.6 mg/kg was comparable to that of standard treatment. Early study termination precludes any definitive conclusions.

To round out this update on thrombolysis-for-stroke-of-unclear-onset, a meta-analysis. Normally it isn't terribly helpful to look at a big blender filled with the same patients in trials we've already reviewed. But in this case the researchers not only did a rigorous meta-analysis, they obtained patient-level data from all four relevant trials— WAKE-UP, EXTEND, THAWS, and ECASS4, a fourth similar trial. All four used high-tech imaging to look for salvageable brain tissue, then randomized to alteplase vs control.

Having patient-level data allows for fancy subgroup analyses. The authors found a pooled 8% favorable outcome advantage with lytics, and a 3% increase in mortality, but they also report something novel: on close reading of subgroup results there was no statistical benefit in the subgroups of non-LVO strokes and those where no vessel was identified. This fits with the results of THAWS, which found no benefit in a patient mix where less than a third of subjects had LVOs.

Most of the trials were begun, it turns out, before EVT was standard for LVO. It may well be that the reason every trial in the meta-analysis was stopped early is that it became increasingly difficult to enroll those with a LVO—since halfway through, these patients started to be whisked off for EVT.

Now that we know EVT works best for LVO, efforts should be directed at EVT once an LVO is identified. And with small vessel strokes, based on the subgroups in this meta-analysis, it seems unlikely thrombolytics will help (despite an almost certain increase in mortality), even when perfusion imaging identifies salvageable tissue. The highlights:

• This international group of collaborative researchers conducted a rigorous, individual patient-level systematic review and meta-analysis of four RCTs of alteplase vs control for wake-up type stroke

• 843 stroke patients were included, and the primary endpoint was favorable outcome (mRs 0-1)

• 47% vs 39% of controls achieved a favorable outcome (p=0.01), while 6% vs 3% died (p=0.04)

• Subgroups that appeared to differentially benefit included those with LVO, those with any visible vessel occlusion; no benefit was seen in non-LVO and no-vessel strokes

• The authors conclude alteplase showed benefits for patients identified as having a perfusion or MRI- based DWI-FLAIR mismatch

4. INTRAVENOUS ALTEPLASE FOR STROKE WITH UNKNOWN TIME OF ONSET GUIDED BY ADVANCED IMAGING: SYSTEMATIC REVIEW AND META-ANALYSIS OF INDIVIDUAL PATIENT DATA. Thomalla G, et al. Lancet. 396(10262): 1574-1584, November 2020

BACKGROUND: Patients who have had a stroke with unknown time of onset have been previously excluded from thrombolysis. We aimed to establish whether intravenous alteplase is safe and effective in such patients

when salvageable tissue has been identified with imaging biomarkers. METHODS: We did a systematic review and meta-analysis of individual patient data for trials published before Sept 21, 2020. Randomised trials of intravenous alteplase versus standard of care or placebo in adults with stroke with unknown time of onset with perfusion-diffusion MRI, perfusion CT, or MRI with diffusion weighted imaging-fluid attenuated inversion recovery (DWI-FLAIR) mismatch were eligible. The primary outcome was favourable functional outcome (score of 0-1 on the modified Rankin Scale [mRS]) at 90 days indicating no disability using an unconditional mixed-effect logistic-regression model fitted to estimate the treatment effect. Secondary outcomes were mRS shift towards a better functional outcome and independent outcome (mRS 0-2) at 90 days. Safety outcomes included death, severe disability or death (mRS score 4-6), and symptomatic intracranial haemorrhage. This study is registered with PROSPERO, CRD42020166903. FINDINGS: Of 249 identified abstracts, four trials met our eligibility criteria for inclusion: WAKE-UP, EXTEND, THAWS, and ECASS-4. The four trials provided individual patient data for 843 individuals, of whom 429 (51%) were assigned to alteplase and 414 (49%) to placebo or standard care. A favourable outcome occurred in 199 (47%) of 420 patients with alteplase and in 160 (39%) of 409 patients among controls (adjusted odds ratio [OR] 1·49 [95% CI 1·10-2·03]; p=0·011), with low heterogeneity across studies (I2=27%). Alteplase was associated with a significant shift towards better functional outcome (adjusted common OR 1·38 [95% CI 1·05-1·80]; p=0·019), and a higher odds of independent outcome (adjusted OR 1·50 [1·06-2·12]; p=0·022). In the alteplase group, 90 (21%) patients were severely disabled or died (mRS score 4-6), compared with 102 (25%) patients in the control group (adjusted OR 0·76 [0·52-1·11]; p=0·15). 27 (6%) patients died in the alteplase group and 14 (3%) patients died among controls (adjusted OR 2·06 [1·03-4·09]; p=0·040). The prevalence of symptomatic intracranial haemorrhage was higher in the alteplase group than among controls (11 [3%] vs two [<1%], adjusted OR 5·58 [1·22-25·50]; p=0·024). INTERPRETATION: In patients who have had a stroke with unknown time of onset with a DWI-FLAIR or perfusion mismatch, intravenous alteplase resulted in better functional outcome at 90 days than placebo or standard care. A net benefit was observed for all functional outcomes despite an increased risk of symptomatic intracranial haemorrhage. Although there were more deaths with alteplase than placebo, there were fewer cases of severe disability or death.

Moving on to the thorny issue of thrombolysis as it is most often used in practice (without perfusion imaging, in the 0-4.5h window), the next trial is a rare gem. Published in 2018, it's about as close as we may ever get to replicating NINDS. In this brave trial the researchers randomly assigned patients with a non-disabling stroke, i.e., a NIHSS score of <6, in the first 3 hours of onset, to alteplase or aspirin. While in many centers such patients were routinely treated with thrombolysis the practice was controversial (though 10% of the original NINDS trial subjects were in this category). The primary endpoint, as in the trials above, was a mRs of 0-1.

Amazingly, this trial too was stopped early, also for lack of funding. Of a planned 948 subjects only 313 were enrolled. Still, this is the largest and most rigorous study done of thrombolytics vs placebo in the 0-3h time period. The results were a bit shocking for many, though for longtime naysayers perhaps less so. Thrombolytics didn't help. In fact, placebo performed numerically better than thrombolytics in every

category. Moreover, 26% of the lytics group vs 13% of the aspirin group experienced a serious adverse event (bleeding, ICH, etc.). This trial led to the first ever pullback in the American Heart Association's position on thrombolytics for stroke. The AHA now recommends flatly against thrombolytics for patients with a NIHSS<6. The highlights:

• The researchers enrolled non-disabling stroke patients at 58 stroke network hospitals across North America, randomizing to alteplase plus placebo or aspirin plus placebo in double blind fashion

• Eligible patients had non-disabling stroke, NIHSS 0-5, and were treatable in <3 hours from onset

• **A favorable outcome mRs 0-1 occurred in 78% (alteplase) vs 81% (placebo), no difference**

• Symptomatic ICH occurred in 3% vs 0%, serious adverse events occurred in 26% vs 13%, both differences statistically significant

• The authors conclude alteplase did not improve outcomes, but suggest early termination "precludes any definitive conclusions"

5. EFFECT OF ALTEPLASE VS ASPIRIN ON FUNCTIONAL OUTCOME FOR PATIENTS WITH ACUTE ISCHEMIC STROKE AND MINOR NONDISABLING NEUROLOGIC DEFICITS. Khatri P, et al, JAMA 320(2):156-166, July 2018

IMPORTANCE: More than half of patients with acute ischemic stroke have minor neurologic deficits (National Institutes of Health Stroke Scale [NIHSS] score of 0-5) at presentation. Although prior major trials of alteplase included patients with low NIHSS scores, few without clearly disabling deficits were enrolled. OBJECTIVE: To evaluate the efficacy and safety of alteplase in patients with NIHSS scores of 0 to 5 whose deficits are not clearly disabling. DESIGN, SETTING, AND PARTICIPANTS: The PRISMS trial was designed as a 948-patient, phase 3b, double-blind, double-placebo, multicenter randomized clinical trial of alteplase compared with aspirin for emergent stroke at 75 stroke hospital networks in the United States. Patients with acute ischemic stroke whose deficits were scored as 0 to 5 on the NIHSS and judged not clearly disabling and in whom study treatment could be initiated within 3 hours of onset were eligible and enrolled from May 30, 2014, to December 20, 2016, with final follow-up on March 22, 2017. INTERVENTIONS: Participants were randomized to receive intravenous alteplase at the standard dose (0.9 mg/kg) with oral placebo (n = 156) or oral aspirin, 325 mg, with intravenous placebo (n = 157). MAIN OUTCOMES AND MEASURES: The primary outcome was the difference in favorable functional outcome, defined as a modified Rankin Scale score of 0 or 1 at 90 days via Cochran-Mantel-Haenszel test stratified by pretreatment NIHSS score, age, and time from onset to treatment. Because of early termination of the trial, prior to unblinding or interim analyses, the plan was revised to examine the risk difference of the primary outcome by a linear model adjusted for the same factors. The primary safety end point was symptomatic intracranial hemorrhage (sICH) within 36 hours of intravenous study treatment. RESULTS: Among 313 patients enrolled at 53 stroke networks (mean age, 62 [SD, 13] years; 144 [46%] women; median NIHSS score, 2 [interquartile range {IQR}, 1-3]; median time to treatment, 2.7 hours [IQR, 2.1-2.9]), 281 (89.8%) completed the trial. At 90 days, 122 patients (78.2%) in the alteplase group vs 128 (81.5%) in the aspirin group achieved a favorable outcome (adjusted risk difference, −1.1%; 95% CI, −9.4% to 7.3%). Five alteplase-treated patients (3.2%) vs 0 aspirin-treated patients had sICH (risk difference, 3.3%; 95% CI, 0.8%- 7.4%). CONCLUSIONS AND RELEVANCE: Among patients with minor nondisabling acute ischemic stroke, treatment with alteplase vs aspirin did not increase the likelihood of favorable functional outcome at 90 days. However, the very early study termination precludes any definitive conclusions, and additional research may be warranted.

Perhaps the most unsettling, and potentially game-changing, recent publication is the now-infamous Alper reanalysis. The author group spent years requesting access to the original ECASS-3 data. ECASS3 remains the only trial ever to report a benefit of thrombolysis at 3-4.5h, and is thus cited by virtually all guidelines supporting thrombolysis at 3- 4.5h.

The authors' primary interest centered on two imbalances between groups in the trial, NIHSS score and history of prior stroke, both favoring thrombolysis. The authors long ago expressed concern these imbalances, based on rough calculations, appeared to eclipse the borderline benefit reported, even despite adjusted analyses in the original paper. The authors hoped to perform their own analyses, and to replicate published adjustments, using the original data.

After gaining access to the data the authors made a number of discoveries. First, they found no benefit in any outcome when performing standard adjustment for group imbalances. Second, and more shocking, when they attempted to replicate the original paper's adjusted analyses (those cited by guidelines), they found unusual statistical steps taken in the original paper. Without them—like altering how the NIHSS score, and time to stroke onset, are both normally tabulated and calculated—ECASS-3 failed to demonstrate benefit. Only using these very nonstandard statistics could thrombolysis appear to be superior to placebo.

In discussing their findings the authors use gentile language: "Previously reported adjusted analyses suggesting efficacy show statistical significance only under multiple conditions that do not represent the most informative use of the data. Seven other 'less selective' approaches to these adjusted analyses fail to replicate significant effects."

The highlights:

• The researchers, anchored by a Canadian family practitioner at EBSCO (DynaMed) Health, aimed to replicate comparisons between alteplase and placebo in ECASS-3, originally reported in 2008

• Imbalances between groups strongly favored the thrombolysis arm in ECASS-3

• Using original data they found no benefit in any comparison properly adjusted for imbalances

• They were also unable to replicate the published adjusted analyses

• On discussion with the original researchers they were informed special techniques had been used that, when applied, then allowed these authors to replicate the researchers' original calculations

• The techniques included 1) excluding patients with incomplete or missing baseline NIHSS scores, 2) altering NIHSS scores to be a 5-step scale (0-5, 6-10, 11-15, 16-20, or >20) rather than continuous numbers, and 3) doing the same with onset times (using 15 min windows)

• The authors note these techniques are not prespecified, or even described, in the original protocol, and none are common or accepted approaches

• The authors did, however, easily replicate statistically significant increases in symptomatic ICH

• The authors conclude their reanalysis "does not support any significant benefits and continues to support harms for the use of alteplase 3-4.5h after stroke onset"

6. THROMBOLYSIS WITH ALTEPLASE 3-4.5 HOURS AFTER ACUTE ISCHAEMIC STROKE: TRIAL REANALYSIS ADJUSTED FOR BASELINE IMBALANCES. Alper B, et al. BMJ Evidence-based Medicine 25(5):168-171, October 2020

OBJECTIVES: Alteplase is commonly recommended for acute ischaemic stroke within 4.5 hours after stroke onset. The Third

European Cooperative Acute Stroke Study (ECASS III) is the only trial reporting statistically significant efficacy for clinical outcomes for alteplase use 3-4.5 hours after stroke onset. However, baseline imbalances in history of prior stroke and stroke severity score may confound this apparent finding of efficacy. We reanalysed the ECASS III trial data adjusting for baseline imbalances to determine the robustness or sensitivity of the efficacy estimates. DESIGN: Reanalysis of randomised placebo- controlled trial. We obtained access to the ECASS III trial data and replicated the previously reported analyses to confirm our understanding of the data. We adjusted for baseline imbalances using multivariable analyses and stratified analyses and performed sensitivity analysis for missing data. **SETTING**: Emergency care. **PARTICIPANTS: 821** adults with acute ischaemic stroke who could be treated 3-4.5 hours after symptom onset. **INTERVENTIONS**: Intravenous alteplase (0.9 mg/kg of body weight) or placebo. **MAIN OUTCOME MEASURES:** The original primary efficacy outcome was modified Rankin Scale (mRS) score 0 or 1 (ie, being alive without any disability) and the original secondary efficacy outcome was a global outcome based on a composite of functional end points, both at 90 days. Adjusted analyses were only reported for the primary efficacy outcome and the original study protocol did not specify methods for adjusted analyses. Our adjusted reanalysis included these outcomes, symptom-free status (mRS 0), dependence-free status (mRS 0-2), mortality (mRS 6) and change across the mRS 0-6 spectrum at 90 days; and mortality and symptomatic intracranial haemorrhage at 7 days. **RESULTS:** We replicated previously reported unadjusted analyses but discovered they were based on a modified interpretation of the National Institutes of Health Stroke Scale (NIHSS) score. The secondary efficacy outcome was no longer significant using the original NIHSS score. Previously reported adjusted analyses could only be replicated with significant effects for the primary efficacy outcome by using statistical approaches not reported in the trial protocol or statistical analysis plan. In analyses adjusting for baseline imbalances, all efficacy outcomes were not significant, but increases in symptomatic intracranial haemorrhage remained significant. **CONCLUSIONS:** Reanalysis of the **ECASS III trial** data with multiple approaches adjusting for baseline imbalances does not support any significant benefits and continues to support harms for the use of alteplase 3-4.5 hours after stroke onset. Clinicians, patients and policymakers should reconsider interpretations and decisions regarding management of acute ischaemic stroke that were based on **ECASS III results.**

The Alper reanalysis is troubling for many reasons. For one, ECASS-3 was the one randomized trial that seemed to support the idea that NINDS found a true benefit. Even if the time windows were different (0-3h vs 3-4.5h) at least someone had replicated the finding of benefit with thrombolytics for stroke. With the Alper reanalysis NINDS now stands alone, the only trial ever to demonstrate a benefit, and NINDS has many detractors and doubters and at least one prominent reanalysis challenging its findings. Since then, despite 26 other trials of thrombolytic vs. control, none has found a benefit, including 12 large trials using alteplase. Nonetheless meta-analyses, including a Cochrane review, have suggested a favorable outcome benefit (and an increase in mortality), and it is these reviews that thrombolytic advocates point to.

Now, as the 25-year mark passes since the AHA recommending tPA for stroke based on NINDS, a number of author groups have attempted to tackle the controversy. Two publications, one in 2019, the other in 2021, summarize the big picture. One is pro, one is con, and both set the Twitterverse alight. Neither is peer-reviewed, instead both were posted on the high-minded, highly trafficked website TheNNT.com.

The first, titled 'tPA for Acute Ischemic Stroke' takes a narrow approach, reporting numbers from a 2014 meta- analysis of alteplase trials only. Their rationale is that alteplase is essentially the only agent used for stroke thrombolysis, and establishing a class effect for thrombolytics isn't as important as examining alteplase results. The review and numbers repre sent an optimistic view of alteplase. The highlights:

- This Canadian author group presents a summary and analysis of the data supporting alteplase for stroke, focusing on a meta-analysis published in 2014 pooling data from 9 trials of 6756 subjects
- The authors feel other agents (streptokinase, urokinase, etc.) have proven dangerous and therefore choose to exclude trials of these agents from their review
- The primary endpoint was a favorable outcome (mRs 0-1)
- Favorable outcomes <3h were 33% vs 23% (NNT 10); <4.5h were 35% vs 30% (NNT 20)
- Mortality was increased by 1.4%, at 17.9% vs 16.5% (NNH 71)
- ICH was increased by thrombolysis, but the effects of ICH are included in 'favorable outcomes'
- The authors emphasize that an organized, team-driven approach with stroke unit care is essential, and that benefits are not assured when thrombolysis is used outside of this paradigm
- The authors conclude alteplase is a beneficial drug when used correctly in the right setting

7. TISSUE PLASMINOGEN ACTIVATOR (tPA) FOR ACUTE ISCHEMIC STROKE. Hill M, et al.TheNNT.com. January, 2019

SOURCE: Emberson J, Lees KR, Lyden P, et al. Effect of treatment delay, age, and stroke severity on the effects of intravenous thrombolysis with alteplase for acute ischaemic stroke: a meta-analysis of individual patient data from randomised trials. Lancet 2014; 384(9958): 1929-35. **STUDY POPULATION:** 6756 patients in nine randomized trials comparing alteplase with placebo or open control for the treatment acute ischemic stroke. Trials of other thrombolytic agents (e.g. streptokinase, urokinase) were excluded. **EFFICACY ENDPOINTS:** Excellent functional outcome defined as a modified Rankin Scale (mRS) score of 0-1 assessed at 90-180 days after stroke. The mRS is an inclusive efficacy and harm outcome because it includes harm related to poor outcomes. **HARM ENDPOINTS:** Fatal intracerebral hemorrhage, all-cause mortality. (Note that harm endpoints are included in the efficacy endpoint because the mRS includes all- cause mortality as a poor outcome) **NARRATIVE:** Stroke is a devastating condition that leaves most survivors with permanent neurological disability. Worldwide, stroke is the second leading cause of death and has a declining age-adjusted incidence in high-income countries but a rapidly rising incidence and impact in lower- and middle-income countries. Ischemic stroke is the most common stroke type, accounting for roughly 85% of all strokes. Ischemic stroke is caused by an acute occlusion of an intracranial artery or one of four extracranial cervical arteries leading to the brain. Treatment with thrombolytic drugs targets the occlusion and is designed to restore blood flow to the brain. Thrombolytic drugs are effective in recanalizing occluded brain arteries only some of the time. Large proximal artery occlusions (e.g. carotid artery or middle cerebral artery stem) are opened 10-35% of the time, and smaller more distal arteries, up to 60-80% of the time. Large proximal artery occlusions are best treated with a combination of thrombolysis and endovascular thrombectomy.

The second NNT review is more cerebral, and less supportive, but leaves room for hope. The authors emphasize that most analyses, like the one above, focus on time windows and drug choice. This is an error they call the Texas sharpshooter fallacy, in which thrombolysis advocates selectively ignore dozens of trials that failed. The 3h time window, the authors note, is only

considered special because one trial (NINDS) using this window found a benefit. Alteplase is special only for being the drug in the two (of 26) trials that claimed benefit. But, citing a comprehensive review of 26 trials, they note many other trials in the 0-4.5h windows, and many others using alteplase, have failed to show benefit, and in fact some were stopped early for harm. Touting data based on characteristics from the two beneficial trials is a classic example of the fallacy.

Furthermore, they argue, meta-analyses on this topic are not trustworthy because they jumble together different strokes, severities, age ranges, prognoses, blood vessels, brain regions, treatment windows, and on and on. No meta- analysis, they argue, offers a reliable estimate at the bedside. The lack of successful trials (now there's just one) and the multitude of failures is discouraging, but they believe a benefit is still possible. The data are simply too uncertain to know where that benefit can be found. Rigorous replications of NINDS, ECASS3, and other trials will be the only way to know. The highlights:

• This (also) Canadian group presents a summary review of a 2016 meta-analysis examining 10,431 subjects in 26 trials of thrombolysis vs control (either placebo or standard care) for stroke

• The authors include all agents and time windows

• The primary endpoint was a 'good functional outcome' defined as mRs 0-3, meaning a range of zero deficit to a small residual deficit, but able to walk and care for personal needs independently

• By this measure there is a 3.2% increase in good outcomes, and a 2.5% increase in mortality

• The authors offer no NNT or NNH, they feel the numbers are too uncertain

• The authors conclude the impact of thrombolysis in ischemic stroke remains uncertain

8. TISSUE PLASMINOGEN ACTIVATOR (tPA) FOR ACUTE ISCHEMIC STROKE. Morgenstern J, et al. TheNNT.com. April, 2021

SOURCE: Donaldson L, Fitzgerald E, Flower O, Delaney A. **Review article:** Why is there still a debate regarding the safety and efficacy of intravenous thrombolysis in the management of presumed acute ischaemic stroke? A systematic review and meta-analysis. Emerg Med Australas 2016;28(5):496–510. STUDY POPULATION: 10,431 patients in 26 randomized trials comparing intravenous thrombolysis with placebo or standard care in acute ischemic stroke. EFFICACY ENDPOINTS: Good functional outcome, defined as a modified Rankin Score of 3 or less, i.e. some residual disability requiring assistance but able to walk and care for personal needs independently. HARM ENDPOINTS: Symptomatic intracranial hemorrhage (as defined by individual trials) and overall mortality. NARRATIVE: This is the third NNT summary of thrombolytics for acute ischemic stroke. The first gave thrombolytics, as a class, a "red color recommendation: no benefit." The second gave alteplase, a single agent, a "green color recommendation: benefit>harm." As no relevant trials were published between the two, both author groups examined essentially the same data and arrived at opposing conclusions. We believe it would be hubris to presume this third summary will arrive at the one true answer. We focus, therefore, on the uncertainty we believe leads to conflicting interpretations. The systematic review we chose to summarize includes 26 randomized trials of more than 10,000 participants, assessing the benefits of thrombolysis for acute ischemic stroke.1 The authors report a 3.2% improvement in good neurologic outcome, a 5.4% increase in symptomatic intracranial hemorrhage, and a 2.5% increase in mortality. However, we question the certainty implied by these summary numbers. There are multiple relevant systematic reviews with varying methods but similar findings. In one widely cited review, Emberson and colleagues reported only on alteplase (a problem we discuss below) and find a 5% improvement in neurologic outcomes, a 5.5% increase in intracranial hemorrhage, and a 1.4% increase in 90 day mortality that was not statistically significant.2 The 2014 Cochrane review by Wardlaw and colleagues arrives at similar conclusions with significant improvement in neurologic outcomes, increased intracranial hemorrhage, and increased mortality.3Thus our conclusions and discussion are unchanged by choice of review, and reflect our belief that pooling data on this topic is overly simplistic and masks profound uncertainty.

Bottom line: Some new data finds no advantage for thrombolysis and now we know some old data, on closer review, never showed an advantage; but meta-analyses continue to find small numerical benefits in disability for thrombolysis, despite higher mortality rates.

QUESTION: DOES THROMBOLYSIS IMPROVE OUTCOMES IN PATIENTS UNDERGOING EVT FOR LVO?

This question vexes all providers involved in the care of patients who undergo EVT. Fortunately, momentum is building, and the evidence is rolling in, and there is good reason to believe EVT without thrombolysis may become routine in the near future

Here's why. The original EVT trials demonstrated EVT is very beneficial. It is difficult to find an intervention—for stroke or anything else—with comparable benefits on death or disability. In experienced hands modern stent retrievers, when used for anterior circulation LVO stroke, produced absolute benefits in the 13-30% range (NNT 3-8), often with significant decreases in mortality and little or no increase in ICH. (That story may not hold for basilar artery strokes, but that's a topic for another time).

And in theory thrombolysis before EVT could occasionally avert the need for EVT, might facilitate EVT, and should help dissolve downstream micro-emboli generated by EVT. And in the big EVT trials co-administration of thrombolytics was common. Not universal, but common. This spotty use of thrombolysis in trials, and the fact that subgroups who didn't receive thrombolysis typically fared just as well (and sometimes better), has led to great interest in streamlining EVT to skip the thrombolytics.

The momentum for this approach is building mostly on the basis of four major trials. They are, in chronological order, the EXTEND-IA TNK part 2 study, the DIRECT-MT trial, the DEVT trial, and the SKIP trial.

EXTEND-IA TNK part 2 is a trial using Tenecteplase (TNK) as the pre-EVT thrombolytic of choice. However, the primary comparison was between a full dose and a reduced dose of TNK. Patients eligible for thrombolysis (<4.5h from onset) and also planned for EVT because of LVO were randomized to reduced- or regular-dose TNK. The trial found no differences in any outcome, producing the first major publication to hint at the possibility that thrombolysis may not be a meaningful factor in clinical outcomes with EVT. The highlights:

• This Australian group, funded by an Australian government grant, conducted a 27-hospital non- blinded RCT across Australia and New Zealand, of 0.25 mg/kg vs 0.4 mg/kg TNK prior to EVT

• 300 subjects were enrolled over 19 months, 95% with MCA or internal carotid occlusions

• The primary outcome was >50% reperfusion of ischemic territory, per neuroradiology reading

• Secondary outcomes included mRs. continuous and by cutoffs

• No differences were noted in primary outcome (19%, both groups)

• Secondary outcomes were also no different ('favorable' mRs of 0-1, 32% both groups), and no significant 'ordinal shift' was seen in the mRs outcomes when compared between groups

• The authors conclude higher dose TNK conferred no advantage over lower dose

9. EFFECT OF INTRAVENOUS TENECTEPLASE DOSE ON CEREBRAL REPERFUSION BEFORE THROMBECTOMY IN PATIENTS WITH LARGE VESSEL OCCLUSION ISCHEMIC STROKE: THE EXTEND-IA TNK PART 2 RANDOMIZED CLINICAL TRIAL. Campbell B, et al. JAMA. 323(13): 1257-1265. April, 2020

IMPORTANCE: Intravenous thrombolysis with tenecteplase improves reperfusion prior to endovascular thrombectomy for ischemic stroke compared with alteplase. OBJECTIVE: To determine whether 0.40 mg/kg of tenecteplase safely improves reperfusion before endovascular thrombectomy vs 0.25 mg/kg of tenecteplase in patients with large vessel occlusion ischemic stroke. DESIGN, SETTING, AND PARTICIPANTS: Randomized clinical trial at 27 hospitals in Australia and 1 in New Zealand using open- label treatment and blinded assessment of radiological and clinical outcomes. Patients were enrolled from December 2017 to July 2019 with follow-up until October 2019. Adult patients (N = 300) with ischemic stroke due to occlusion of the intracranial internal carotid, \basilar, or middle cerebral artery were included less than 4.5 hours after symptom onset using standard intravenous thrombolysis eligibility criteria. INTERVENTIONS: Open-label tenecteplase at 0.40 mg/kg (maximum, 40 mg; n = 150) or 0.25 mg/kg (maximum, 25 mg; n = 150) given as a bolus before endovascular thrombectomy. MAIN OUTCOMES AND MEASURES: The primary outcome was reperfusion of greater than 50% of the involved ischemic territory prior to thrombectomy, assessed by consensus of 2 blinded neuroradiologists. Prespecified secondary outcomes were level of disability at day 90 (modified Rankin Scale [mRS] score; range, 0-6); mRS score of 0 to 1 (freedom from disability) or no change from baseline at 90 days; mRS score of 0 to 2 (functional independence) or no change from baseline at 90 days; substantial neurological improvement at 3 days; symptomatic intracranial hemorrhage within 36 hours; and all-cause death. RESULTS: All 300 patients who were randomized (mean age, 72.7 years; 141 [47%] women) completed the trial. The number of participants with greater than 50% reperfusion of the previously occluded vascular territory was 29 of 150 (19.3%) in the 0.40 mg/kg group vs 29 of 150 (19.3%) in the 0.25 mg/kg group (unadjusted risk difference, 0.0% [95% CI, -8.9% to -8.9%]; adjusted risk ratio, 1.03 [95% CI, 0.66-1.61]; P = .89). Among the 6 secondary outcomes, there were no significant differences in any of the 4 functional outcomes between the 0.40 mg/kg and 0.25 mg/kg groups nor in all-cause deaths (26 [17%] vs 22 [15%]; unadjusted risk difference, 2.7% [95% CI, - 5.6% to 11.0%]) or symptomatic intracranial hemorrhage (7 [4.7%] vs 2 [1.3%]; unadjusted risk difference, 3.3% [95% CI, -0.5% to 7.2%]). CONCLUSIONS AND RELEVANCE: Among patients with large vessel occlusion ischemic stroke, a dose of 0.40 mg/kg, compared with 0.25 mg/kg, of tenecteplase did not significantly improve cerebral reperfusion prior to endovascular thrombectomy. The findings suggest that the 0.40-mg/kg dose of tenecteplase does not confer an advantage over the 0.25-mg/kg dose in patients with large vessel occlusion ischemic stroke in whom endovascular thrombectomy is planned.

Next came the real thing: DIRECT-MT, a trial comparing EVT with and without thrombolysis. At academic centers in China researchers performed a large trial using no alteplase vs. standard dose alteplase, given within 4.5h of stroke onset among 656 patients with LVO undergoing EVT. This was a 'non-inferiority' trial, statistically designed to prove EVT alone could be no worse than EVT with thrombolysis. This kind of endpoint is often more difficult to show than 'equivalence' but EVT alone was indeed found to be 'noninferior'.

The highlights:

• The Chinese group of researchers enrolled 656 LVO strokes within 4.5h of onset at 41 academic centers across China, randomizing to EVT alone or EVT plus preceding thrombolysis

• 1586 patients were screened, 656 enrolled, all with MCA or internal carotid occlusions

• The primary outcome was an odds ratio (OR) calculation comparing mRs in each group, and showing an OR of 1.07 (.95 CI: 0.81-1.4) for EVT alone to EVT plus thrombolysis

• Because the CI did not extend below 0.8, a preplanned margin, this was considered 'noninferior'

• All secondary outcomes were numerically the same or better in the EVT alone group

• The authors conclude EVT alone was noninferior to EVT plus thrombolysis

10. ENDOVASCULAR THROMBECTOMY WITH OR WITHOUT ALTEPLASE IN ACUTE STROKE. Yang P, et al. NEJM. 382(21): 1981-1993. May, 2020

BACKGROUND: In acute ischemic stroke, there is uncertainty regarding the benefit and risk of administering intravenous alteplase before endovascular thrombectomy. METHODS: We conducted a trial at 41 academic tertiary care centers in China to evaluate endovascular thrombectomy with or without intravenous alteplase in patients with acute ischemic stroke. Patients with acute ischemic stroke from large- vessel occlusion in the anterior circulation were randomly assigned in a 1:1 ratio to undergo endovascular thrombectomy alone (thrombectomy-alone group) or endovascular thrombectomy preceded by intravenous alteplase, at a dose of 0.9 mg per kilogram of body weight, administered within 4.5 hours after symptom onset (combination-therapy group). The primary analysis for noninferiority assessed the between-group difference in the distribution of the modified Rankin scale scores (range, 0 [no symptoms] to 6 [death]) at 90 days on the basis of a lower boundary of the 95% confidence interval of the adjusted common odds ratio equal to or larger than 0.8. We assessed various secondary outcomes, including death and reperfusion of the ischemic area. RESULTS: Of 1586 patients screened, 656 were enrolled, with 327 patients assigned to the thrombectomy-alone group and 329 assigned to the combination-therapy group. Endovascular thrombectomy alone was noninferior to combined intravenous alteplase and endovascular thrombectomy with regard to the primary outcome (adjusted common odds ratio, 1.07; 95% confidence interval, 0.81 to 1.40; P = 0.04 for noninferiority) but was associated with lower percentages of patients with successful reperfusion before thrombectomy (2.4% vs. 7.0%) and overall successful reperfusion (79.4% vs. 84.5%). Mortality at 90 days was 17.7% in the thrombectomy-alone group and 18.8% in the combination-therapy group. CONCLUSIONS: In Chinese patients with acute ischemic stroke from large-vessel occlusion, endovascular thrombectomy alone was noninferior with regard to functional outcome, within a 20% margin of confidence, to endovascular thrombectomy preceded by intravenous alteplase administered within 4.5 hours after symptom onset.

And finally, in early 2021, two more such efforts, the DEVT and SKIP trials arrived, one from China and the other from Japan. The results of both were nearly identical to each other and the same as the DIRECT-MT trial—except they looked even better

for EVT alone. The only rub was that the Japanese trial was unable to establish noninferiority, a statistical oddity that occurred because they set a difficult margin. It was particularly odd because just as in other trials the numerical results were better in the EVT-alone group, across the board. But the trial was the smallest in the group, at 204 subjects, suggesting they simply didn't have the necessary power.

Either way, done, right? A large rigorous trial replicated by two other groups. Here comes practice change… right?
Perhaps the one factor keeping these three trials from being adequate to drive a widespread change is not the noninferiority oddity from Japan—it was the geographical setting. Asian stroke pathology tends to be different from that seen in western settings. More strokes occurring in an Asian population are related to underlying CNS atherosclerotic disease than in western populations. Asian populations, according to some evaluations, also seem to have higher hemorrhage rates with thrombolysis for stroke, suggesting a potentially different harm/benefit profile.

Also, as noted in an editorial accompanying the DIRECT-MT trial, in China and Japan EVT centers can be the only places administering thrombolysis, therefore the same center provides both. In the DEVT trial thrombolysis began a mean of 40 minutes before thrombectomy began, and in the SKIP trial only 8 minutes. In a decentralized thrombolysis stroke system like the U.S., patients often receive immediate thrombolysis in a community hospital followed by thrombectomy after transfer to an academic center. The potential benefits may be optimized with this larger gap and earlier use of thrombolysis. On the other hand, an editorial accompanying the SKIP and DEVT trials (which were published in the same issue of JAMA), and written by a notoriously fervent advocate of IV thrombolysis, suggests for patients with LVO stroke presenting to EVT- capable centers it is now reasonable to forego thrombolysis.

Regardless, the results of the first three major trials firmly agreed: EVT alone was as effective for all endpoints as adding thrombolysis (and maybe better). A fourth trial, the last summarized below, was more equivocal, and muddies the waters a bit. And in the meantime two more major trials in western populations, one in Europe and one in Australia, are under way and expected to finish in the next two years. We may have to await these results before the stroke community is ready to consider prying its cold, dead hands from the alteplase vial.

Highlights from DEVT: Despite a plan for 970 subjects only 234 were enrolled when the trial was stopped early for efficacy. With a primary endpoint of functional independence (mRs 0-2) at 90 days, at the first interim analysis the research group found 54% of the EVT-alone group vs. 47% of the EVT-thrombolysis group had achieved functional independence (p for noninferiority 0.003). The trial was stopped and noninferiority declared.

- This research group in China enrolled 234 of a planned 970 strokes within 4.5h of onset at 33 academic centers, andomizing, non-blinded, to EVT alone or EVT plus thrombolysis
- 509 patients were screened, 234 enrolled, all with MCA or internal carotid occlusions
- The primary outcome was the proportion of patients with a mRs of 0-2 at 90 days
- The primary outcome was 54% for EVT alone, and 47% for both (noninferiority p=0.003)
- Mortality was similar between groups (17% EVT alone, 18% EVT-thrombolysis)
- All secondary outcomes were numerically the same or better in the EVT alone group
- The authors conclude EVT alone was noninferior to EVT plus thrombolysis

11. EFFECT OF ENDOVASCULAR TREATMENT ALONE VS INTRAVENOUS ALTEPLASE PLUS ENDOVASCULAR TREATMENT ON FUNCTIONAL INDEPENDENCE IN PATIENTS WITH ACUTE ISCHEMIC STROKE: THE DEVT RANDOMIZED CLINICAL TRIAL. Zi W, et al. JAMA. 325(3): 234-243. January, 2021

IMPORTANCE: For patients with large vessel occlusion strokes, it is unknown whether endovascular treatment alone compared with intravenous thrombolysis plus endovascular treatment (standard treatment) can achieve similar functional outcomes. OBJECTIVES: To investigate whether endovascular thrombectomy alone is noninferior to intravenous alteplase followed by endovascular thrombectomy for achieving functional independence at 90 days among patients with large vessel occlusion stroke. DESIGN, SETTING, AND PARTICIPANTS: Multicenter, randomized, noninferiority trial conducted at 33 stroke centers in China. Patients (n = 234) were 18 years or older with proximal anterior circulation intracranial occlusion strokes within 4.5 hours from symptoms onset and eligible for intravenous thrombolysis. Enrollment took place from May 20, 2018, to May 2, 2020. Patients were enrolled and followed up for 90 days (final follow- up was July 22, 2020). INTERVENTIONS: A total of 116 patients were randomized to the endovascular thrombectomy alone group and 118 patients to combined intravenous thrombolysis and endovascular thrombectomy group. MAIN OUTCOMES AND MEASURES: The primary end point was the proportion of patients achieving functional independence at 90 days (defined as score 0-2 on the modified Rankin Scale; range, 0 [no symptoms] to 6 [death]). The noninferiority margin was -10%. Safety outcomes included the incidence of symptomatic intracerebral hemorrhage within 48 hours and 90-day mortality. RESULTS: The trial was stopped early because of efficacy when 234 of a planned 970 patients had undergone randomization. All 234 patients who were randomized (mean age, 68 years; 102 women [43.6%]) completed the trial. At the 90-day follow-up, 63 patients (54.3%) in the endovascular thrombectomy alone group vs 55 (46.6%) in the combined treatment group achieved functional independence at the 90-day follow- up (difference, 7.7%, 1- sided 97.5% CI, -5.1% to ∞)P for noninferiority = .003). No significant between-group differences were detected in symptomatic intracerebral hemorrhage (6.1% vs 6.8%; difference, -0.8%; 95% CI, -7.1% to 5.6%)and 90-day mortality (17.2% vs 17.8%; difference, -0.5%; 95% CI, -10.3% to 9.2%). CONCLUSIONS AND

RELEVANCE: Among patients with ischemic stroke due to proximal anterior circulation occlusion within 4.5 hours from onset, endovascular treatment alone, compared with intravenous alteplase plus endovascular treatment, met the prespecified statistical threshold for noninferiority for the outcome of 90-day functional independence. These findings should be interpreted in the context of the clinical acceptability of the selected noninferiority threshold.

In the Japan-based SKIP trial the researchers enrolled 204 LVO stroke patients from 23 centers across Japan, aiming for noninferiority of EVT alone vs EVT-plus-thrombolysis. Their goal margin for inferiority was a lower confidence interval margin of 0.74 for the calculated OR. In this trial the alteplase dose was also slightly lower than in other trials (0.6 mg/kg instead of 0.9 mg/kg), a technique often used when administering thrombolysis in Japan because of a known higher tendency for hemorrhage among Asian patients. Otherwise, the protocols were very similar to the two China-based trials.

The highlights:

• This Japanese research group enrolled 204 (as planned) strokes within 4.5h of onset at 23 academic centers, randomizing, non-blinded, to EVT alone or EVT plus thrombolysis

• No screening was documented, and all patients had internal carotid or MCA strokes

• The primary outcome was the proportion of patients with a mRs of 0-2 at 90 days

• mRs of 0-2 was achieved in 59% with EVT alone and 57% with EVT-thrombolysis

• Calculation of the mRs OR (1.09, .95CI: 0.60 - ∞), meant noninferiority was not shown

• Mortality was similar between groups (8% EVT alone, 9% EVT-thrombolysis)

• All outcomes were numerically the same or better in the EVT alone group

• The authors conclude EVT alone was not noninferior to EVT plus thrombolysis

12. EFFECT OF MECHANICAL THROMBECTOMY WITHOUT VS WITH INTRAVENOUS THROMBOLYSIS ON FUNCTIONAL OUTCOME AMONG PATIENTS WITH ACUTE ISCHEMIC STROKE. Suzuki K, et al. JAMA. 325(3): 244-253. January, 2021

I**MPORTANCE:** Whether intravenous thrombolysis is needed in combination with mechanical thrombectomy in patients with acute large vessel occlusion stroke is unclear. OBJECTIVE: To examine whether mechanical thrombectomy alone is noninferior to combined intravenous thrombolysis plus mechanical thrombectomy for favorable poststroke outcome. DESIGN, SETTING, AND PARTICIPANTS: Investigator-initiated, multicenter, randomized, open-label, noninferiority clinical trial in 204 patients with acute ischemic stroke due to large vessel occlusion enrolled at 23 hospital networks in Japan from January 1, 2017, to July 31, 2019, with final follow-up on October 31, 2019. INTERVENTIONS: Patients were randomly assigned to mechanical thrombectomy alone (n = 101) or combined intravenous thrombolysis (alteplase at a 0.6-mg/kg dose) plus mechanical thrombectomy (n = 103). MAIN OUTCOMES AND MEASURES: The primary efficacy end point was a favorable outcome defined as a modified Rankin Scale score (range, 0 [no symptoms] to 6 [death]) of 0 to 2 at 90 days, with a noninferiority margin odds ratio of 0.74, assessed using a 1-sided significance threshold of .025 (97.5% CI). There were 7 prespecified secondary efficacy end points, including mortality by day 90. There were 4 prespecified safety end points, including any intracerebral hemorrhage and symptomatic intracerebral hemorrhage within 36 hours. RESULTS: Among 204 patients (median age, 74 years; 62.7% men; median National Institutes of Health Stroke Scale score, 18), all patients completed the trial. Favorable outcome occurred in 60 patients (59.4%) in the mechanical thrombectomy alone group and 59 patients (57.3%) in the combined intravenous thrombolysis plus mechanical thrombectomy group, with no significant between- group difference (difference, 2.1% [1- sided 97.5% CI, -11.4% to ∞]; odds ratio, 1.09 [1-sided 97.5% CI, 0.63 to ∞]; P = .18 for noninferiority). Among the 7 secondary efficacy end points and 4 safety end points, 10 were not significantly different, including mortality at 90 days (8 [7.9%] vs 9 [8.7%]; difference, -0.8% [95% CI, -9.5% to 7.8%]; odds ratio, 0.90 [95% CI, 0.33 to 2.43]; P > .99). Any intracerebral hemorrhage was observed less frequently in the mechanical thrombectomy alone group than in the combined group (34 [33.7%] vs 52 [50.5%]; difference, -16.8% [95% CI, -32.1% to -1.6%]; odds ratio, 0.50 [95% CI, 0.28 to 0.88]; P = .02). Symptomatic intracerebral hemorrhage was not significantly different between groups (6 [5.9%] vs 8 [7.7%]; difference, -1.8% [95% CI, -9.7% to 6.1%]; odds ratio, 0.75 [95% CI, 0.25 to 2.24]; P = .78). CONCLUSIONS AND RELEVANCE: Among patients with acute large vessel occlusion stroke, mechanical thrombectomy alone, compared with combined intravenous thrombolysis plus mechanical thrombectomy, failed to demonstrate noninferiority regarding favorable functional outcome. However, the wide confidence intervals around the effect estimate also did not allow a conclusion of inferiority.

The most recent trial ('MR CLEAN-NO IV') was performed across 20 centers in Europe, came to a slightly more confusing conclusion, finding EVT alone was neither superior nor noninferior, with numbers that leaned slightly toward adding thrombolysis. However, there was no statistically significant difference in virtually any primary or secondary outcome between groups. Highlights:

• This research group enrolled 539 stroke patients in a multicenter trial at 20 centers in France, Belgium, and the Netherlands, randomizing to EVT alone or plus thrombolysis within 4.5h

• As in other trials, only centers capable of performing both treatments were involved

• Median time to thrombolysis from onset was 98 minutes in the thrombolysis group

• Mean age was 71, 57% were male, and median NIHSS score was 16

• There was no detectable shift in mRs at 90 days (OR 0.84;, .95CI: 0.62-1.15)

• Because the OR confidence interval included 0.8, noninferiority was not statistically shown

• mRs 0-2 occurred in 49.1% (EVT alone) vs 51.1% (both), statistically no different

• Mortality was 20.5% (EVT alone) vs. 15.8% (both), also statistically not different

• The authors conclude EVT alone was not noninferior to EVT plus thrombolysis

13. A RANDOMIZED TRIAL OF INTRAVENOUS ALTEPLASE BEFORE ENDOVASCULAR TREATMENT FOR STROKE. LeCouffe N, et al. NEJM. 385(20): 1833-1844. November, 2021

BACKGROUND: The value of administering intravenous alteplase before endovascular treatment (EVT) for acute ischemic stroke has not been studied extensively, particularly in non-Asian populations. METHODS: We performed an open-label, multicenter, randomized trial in Europe involving patients with stroke who presented directly to a hospital that was capable of providing EVT and who were eligible for intravenous alteplase and EVT. Patients were randomly assigned in a 1:1 ratio to receive EVT alone or intravenous alteplase followed by EVT (the standard of care). The primary end point was functional outcome on the modified Rankin scale (range, 0 [no disability] to 6 [death]) at 90 days. We assessed the superiority of EVT alone over alteplase plus EVT, as well as noninferiority by a margin of 0.8 for the lower boundary of the 95% confidence interval for the odds ratio of the two trial groups. Death from any cause and symptomatic intracerebral hemorrhage were the main safety end points. RESULTS: The analysis included 539 patients. The median score on the modified Rankin scale at 90 days was 3 (interquartile range, 2 to 5) with EVT alone and 2 (interquartile range, 2 to 5) with alteplase plus EVT. The adjusted common odds ratio was 0.84 (95% confidence interval [CI], 0.62 to 1.15; P = 0.28), which showed neither superiority nor noninferiority of EVT alone. Mortality was 20.5% with EVT alone and 15.8% with alteplase plus EVT (adjusted odds ratio, 1.39; 95% CI, 0.84 to 2.30). Symptomatic intracerebral hemorrhage occurred in 5.9% and 5.3% of the patients in the respective groups (adjusted odds ratio, 1.30; 95% CI, 0.60 to 2.81). CONCLUSIONS: In a randomized trial involving European

patients, EVT alone was neither superior nor noninferior to intravenous alteplase followed by EVT with regard to disability outcome at 90 days after stroke. The incidence of symptomatic ICH was similar in the two groups.

Finally, to help elucidate why some leading authorities are holding fast to thrombolysis prior to EVT (despite results universally showing no statistical difference between groups), on the basis of this latest trial, the next paper is an editorial making the following points:

• This editorialist reviews MR CLEAN-NO IV and compares it to other similar trials

• MR CLEAN-NO IV used an ordinal shift as a primary outcome rather than dichotomizing scores

• The author prefers this because it "relates better to outcomes in which clinicians are interested"

• It also permitted patients with prior disability to be in the trial "as might occur in clinical practice"

• Time from hospital arrival to thrombolytics was 31 minutes, half that in other trials

• Prior trials were in Asian populations, which have a higher prevalence of intracranial stenosis

• Alteplase before EVT "has not increased mortality or symptomatic ICH, it is easy to administer, and its costs are negligible"

• Benefits of thrombolysis may be more evident when hospital transfer is required, delaying EVT

• The author concludes the thrombolytic bridge to EVT "is not ready to be dismantled"

ALTEPLASE AND THROMBECTOMY—NOT A BRIDGE TO DISMANTLE. Ciccone A, et al. NEJM.385(20): 1904-1905. November, 2021

In the past few years, thrombectomy—the removal of a thrombus under angiographic guidance—has become an accepted treatment for acute ischemic stroke caused by occlusion of a large cerebral vessel. Guidelines have included the use of intravenous alteplase preceding thrombectomy if there are no contraindications to its use, and most randomized, controlled trials of thrombectomy have used alteplase in this manner. After the efficacy of thrombectomy was established, the obvious question of whether it could be effective without preceding intravenous thrombolysis arose. In the somewhat parallel case of acute myocardial infarction, percutaneous coronary intervention (PCI) alone has been more effective than PCI preceded by intravenous thrombolysis. MR CLEAN (Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands)–NO IV, the results of which are reported in this issue of the Journal, is the fourth trial to test whether thrombolysis can be omitted before thrombectomy for stroke.

Bottom line: Adding EVT to thrombolysis in Asian cohorts was clearly unhelpful, while in western cohorts 'noninferiority' has been more difficult to show (though no statistical advantage to adding EVT is apparent, either)

KEY POINTS AND RECOMMENDATIONS

1. Four trials used imaging to extend the window for thrombolysis to wake-up (and 4.5- 9h) strokes, yielding more favorable outcomes, but also increased mortality.

2. It appears most of this benefit, however, was among patients with LVO strokes, who should have EVT.

3. In patients with NIHSS score 0-5, nondisabling strokes, thrombolysis is harmful, with no benefits.

4. The AHA now firmly recommends against thrombolysis in nondisabling strokes.

5. ECASS-3, which ostensibly showed a benefit with alteplase at 3-4.5h, did not show a benefit—by using highly unusual, questionable statistical methods the original report claimed a benefit where there was none.

6. The benefits of thrombolysis for stroke remain strongly supported by some while others robustly question the notion benefits are proven, and believe the right subgroup who truly benefits has yet to be identified.

7. EVT for large vessel occlusion is a proven intervention for anterior circulation strokes.

8. Thrombolysis as a pretreatment for EVT in LVO stroke is still routine practice and standard of care.

9. Three trials in Asian populations suggest adding thrombolysis does not improve outcomes.

10. A recent trial in Europe also showed no benefit, but couldn't show 'noninferiority.' which may be enough to stave off any major changes in current practice—for now.

On bones and bonds

Dr Jessie Chowdhury MBBS, DRANZCOG, FRACGP
General Practitioner

The earliest humans have stood upright for approximately 6-7 million years. The bond between our bones and human evolution is intricate. Evidence suggests that the Homo Erectus may have been fully bipedal for at least 2 million years which meant that our pace was faster, upper limbs were free for other essential functions such as picking and carrying which equated to survival in those times. It took us another 200,000 years to change from a tarzan boy to an urban man. We evolved and had healthier lives which extended our longevity and now we have the burden of chronic diseases.

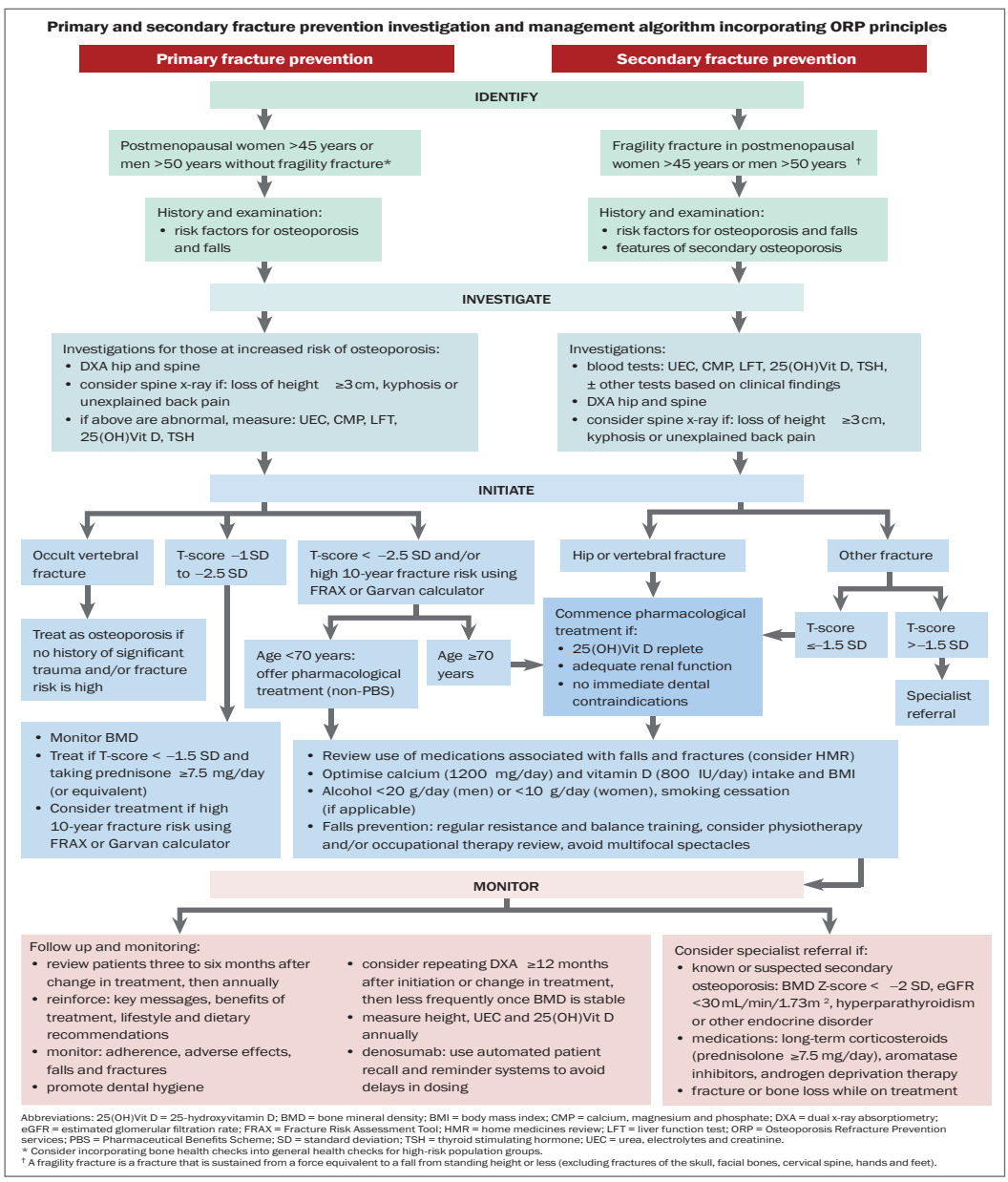
Osteoporosis is a chronic skeletal disease resulting in fragile bones and increased risk of fracture. Our bodies are designed around a framework made of 206 bones. The bone tissue is in a constant flux of breaking down and remodelling. The continual process of disintegration by the Osteoclast cells and fabrication of new tissue by the osteoblast cells keeps this vital organ pliable and strong. In infancy the Osteoblastic cells have an upper hand but in the late adulthood the resorptive process of the Osteoclasts take control and Osteoporosis sets in.

A baby born in Australia today has a 1 in 3 chance of being a centenarian resulting in increased risk of chronic disease. In females, osteoporosis is more common than breast and cervical cancer combined. 1 in 3 women over 50 will break a bone due to osteoporosis.

General Practitioners are the first port of call in the Australian healthcare system. The identification and management of osteoporosis in general practice is complex, which includes both primary and secondary prevention.

The first fracture puts the patient at a higher risk of a second fracture.Each fracture leads to more impairment in mobility and balance which leads to an increased need for care.Fractures also increase the risk of secondary cardiovascular and orthopaedic complications.

Some recently published flowcharts from Medicine Today and Healthy Bones Australia are excellent tools for GPs.



HEALTHY BONES AUSTRALIA

Bone density testing in general practice

A guide to Dual Energy X-ray Absorptiometry (DXA)

Scanning of the axial skeleton by dual energy X-ray absorptiometry (DXA) is the gold standard in Australia for the measurement of bone mineral density (BMD). DXA is a diagnostic tool for osteoporosis or osteopenia, enabling doctors to determine the extent of bone loss for clinical decision making. Who to refer for DXA and how to interpret a bone densitometry report, are outlined in this guide.

Poor bone health is common in Australia

An estimated 4.7 million Australians over the age of 50 currently have osteoporosis or osteopenia, with over 170,000 associated fractures (2020). Without major improvements in diagnosis and management, the rate of osteoporotic fracture will be around 30% higher by 2022, costing an estimated $33.6 billion over a decade.

In general practice, early detection can prevent a first fracture. For patients who have already fractured, investigation and initiation of osteoporosis medication is crucial to reduce the very high risk of subsequent fractures.

Who to send for a DXA scan

Patients over 50 with risk factors	MBS item
Family history – parent with hip fracture	No rebate
Early menopause	12312
Hypogonadism	12312
Glucocorticoids ≥ 3 months ≥ 7.5mg/day	12312
Coeliac disease/malabsorption disorders	12315
Rheumatoid arthritis	12315
Primary hyperparathyroidism	12315
Hyperthyroidism	12315
Chronic kidney or liver disease	12315
Androgen deprivation therapy	12312
Recurrent falls	No rebate
Breast cancer on aromatase inhibitors	No rebate
Treatment with antiepileptic medications	No rebate
Low body weight	No rebate
HIV and its treatment	No rebate
Major depression/ SSRI treatment	No rebate
Type 1 and type 2 diabetes mellitus	No rebate
Multiple myeloma/monoclonal gammopathy	No rebate
Organ or bone marrow transplant (item 12312 applies if treated with glucocorticoids or if kidney disease present)	No rebate

Patients with a minimal trauma fracture	MBS item
A minimal trauma fracture in a patient over 50 indicates probable osteoporosis. DXA is recommended to confirm low bone density and to establish a baseline BMD for treatment.	12306

Suspected vertebral fracture	MBS item
Refer for spinal X-ray when: – Height loss of 3cm or more – Thoracic kyphosis – New onset back pain suggestive of fracture	
If fracture confirmed, refer for DXA	12306
Vertebral fracture assessment (VFA) is offered with some DXA scans. VFA may be a useful screen for fractures in people with height loss. MBS rebate not available for VFA.	

Patients over 70 years of age	MBS item
For men and women over 70 years, MBS rebate applies (regardless of other risk factors)	12320
Patients with a normal result or mild osteopenia (as measured by a T-score down to -1.5) will be eligible for one scan every 5 years	12320
Patients with moderate to marked osteopenia (as measured by a T-score less than -1.5 and above -2.5) will be eligible for one scan every two years	12322

Acknowledgement: Bone Density Testing in General Practice, reproduced courtesy of Healthy Bones Australia, 2022.

The DXA report

The level of detail provided in a DXA report varies. To comply with guidelines, all reports should state the make and model of the DXA machine used, BMD (measured in g/cm^2), T-score and Z-score.

Medical Imaging Centre – Bone Densitometry Report

Dear Doctor

Re: [Patient] **DOB: .....**

This patient attended on ..... for bone densitometry of AP spine and left hip. Bone mineral density was measured by [DXA machine make and model]. The results are summarised below:

Scan date: ..... **Sex: Female**

Age at scan: ..... years **Ethnicity: .....**

L1–L4 or L2-L4 usually measured.

T-score compares the patient's BMD with that of young healthy adults of the same sex.

Scan site	Region	BMD	T-score	Z-score
AP spine	L2-L4	0.890	-2.6	-1.1
Left femur	Total	0.822	-1.5	-0.4
	Neck	0.831	-1.5	-0.0

Z-score compares the patient's BMD with that of adults of the same age and sex.

Total proximal femur combines femoral neck, shaft and trochanter.

Results

Lumbar spine: This patient has a BMD T-score of 2.6 SD below the mean for young females at this site. BMD is considerably reduced.

Left femur: This patient has a BMD measurement of 1.5 SD below the mean for young females at this site. BMD is mildly reduced.

Vertebral fracture assessment: VFA demonstrates a deformity of L3, indicating a probable vertebral fracture. Confirmation with X-ray is recommended.

VFA (vertebral fracture assessment) is offered by some imaging centres. It is a useful screening tool for asymptomatic vertebral fracture. Fractures detected by VFA should be confirmed by plain x-ray. VFA does not attract an MBS rebate.

T-score

The T-score compares the patient's bone density to the peak bone density of young adults. It is the number of standard deviations (SDs) of the BMD measurement above or below that of young healthy adults of the same sex. According to definitions agreed by the World Health Organisation, a T-score of -2.5 or lower at the spine or hip is indicative of osteoporosis.

Normal bone density	T-score -1.0 or above	BMD not more than 1.0 SD below young adult mean
Osteopenia	T-score between -1.0 and -2.5	BMD between 1.0 and 2.5 SDs below young adult mean
Osteoporosis	T-score -2.5 or below	BMD 2.5 or more SDs below young adult mean

Z-score

The Z-score compares the patient's bone density to that of adults of the same age. It is the number of SDs of the BMD measurement above or below that of adults of the same age and sex. Z-score is a useful indicator of possible secondary osteoporosis. A Z-score of -2.0 or below should trigger investigations for underlying disease to exclude other causes of bone mineral loss.

www.healthybonesaustralia.org.au

National toll-free number for patients **1800 242 141**

HEALTHY BONES AUSTRALIA | Protect Build Support

Acknowledgement: Bone Density Testing in General Practice, reproduced courtesy of Healthy Bones Australia, 2022.

2. Risk factors for and causes of osteoporosis [27,28]

Genetic factors
- Parent with osteoporosis

Medications associated with reduced bone density
- Corticosteroids* (long-term use of prednisolone ≥7.5 mg/day or equivalent)
- Excess thyroid hormone replacement*
- Aromatase inhibitors
- Androgen deprivation therapy
- Carbamazepine
- Phenytoin
- Heparin

Lifestyle and other risk factors
- Low body mass index (<30 kg/m^2), sarcopenia or malnutrition
- Physical inactivity
- Tobacco use
- Excessive alcohol intake (>40 g/day for men or >2 g/day for women)
- Inadequate dietary calcium intake
- Thiazolidinediones
- Tenofovir disoproxil fumarate

Conditions that increase fracture risk

Endocrine disorders
- Acromegaly
- Hyperparathyroidism*
- Hyperthyroxinaemia/hyperthyroidism*
- Hypercortisolaemia*
- Diabetes mellitus (especially type 1)
- Male hypogonadism*
- Female hypogonadism >6 months before 45 years*
- Hypopituitarism
- Hyperprolactinaemia

Inflammatory disorders
- Rheumatoid arthritis*
- Systemic lupus erythematosus
- Inflammatory bowel disease*

Malabsorption syndromes
- Coeliac disease*
- Pancreatic exocrine insufficiency*
- Pernicious anaemia
- Gastrectomy
- Eating disorders

Haematological conditions
- Multiple myeloma and monoclonal gammopathy
- Systemic mastocystosis

Other
- Chronic liver or kidney disease*
- Solid organ or bone marrow transplantation
- HIV infection
- 25-hydroxyvitamin D deficiency
- Metastatic malignancy

* Indications for which Medicare benefits for dual-energy x-ray absorptiometry scanning are payable. See Medicare Benefits Schedule items 12306, 12312, 12315, 12320, 12321, 12322.

Key points to cover with patients for a GP:

1. Use of evidence based osteoporosis treatment for optimal management.
2. Informing patients of all available pharmacological and nonpharmacological treatment modes.
3. Discussion of side effects related to each mode of treatment.
4. The crucial need for all patients diagnosed with Osteoporosis to have pretreatment dental assessment.
5. Reassuring patients of the benefits of fracture protection from osteoporosis medication versus the risk of osteonecrosis of the jaw (ONJ). ONJ can occur after dental treatment that involves bone.
6. Patients need to have regular dental care during treatment and maintain good personal dental hygiene.The dentist needs to be aware of the patients Osteoporosis treatment.
7. Importance of long term continuation and compliance with treatment plan.
8. Fracture prevention is the priority in osteoporosis patients and antiresorptive treatment benefits outweigh the low risk of ONJ.

Tips for Osteoporosis management for a GP

1. Identify the patient
2. Retrieve significant past history regarding old fractures, dental care status, long use of steroids, other endocrine disorder and family history of Osteoporosis. In females premature menopause, current menopausal state and previous breast and ovarian cancer treatment. Check smoking and alcohol intake status.
3. Investigate for Bone Density, serum Vit D and Serum Calcium in specific patients. Further tests may be ordered for other relevant chronic diseases.
4. Engage patients and discuss treatment options.
5. Commence Osteoporosis treatment.
6. Involve Allied Health professionals for exercise plans with exercise physiologists and physiotherapists. Connect patients with dietitians for a good diet plan and weight management as appropriate.
7. Organise regular follow up to check compliance with medication, weight management, exercise plan and lifestyle risk.
8. Specialist opinions may be sought in cases of complex patients.
9. Recall systems should be added in GP software programmes for 2-3 yearly BMD checks.

GPs are in a leading position to treat Osteoporosis. Early diagnosis and treatment reduces risk of fracture. Each fracture leads to increased need of hospital admission and rehabilitation care. The ageing population with its increased risk of osteoporosis adds extra encumbrance to our already fiscally challenged Health System. GPs should always be aware of this silent disease and manage patients accordingly.

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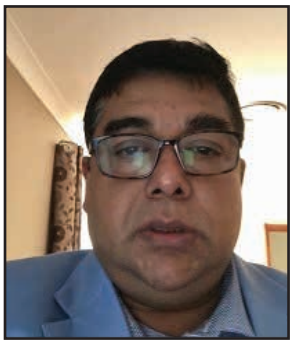

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Medico-Legal Workshop 2022

Information day for IMG and Mock interview 2022

Educational Events 2021

Educational Events 2021

Annual Scentific Meeting 2019

Annual Scentific Meeting 2018

Annual Scentific Meeting 2017

Annual Scentific Meeting 2016

Annual Scentific Meeting 2015

Annual Scentific Meeting 2012

Annual Scentific Meeting 2010

Educational Activities BMS NSW