education

FROM THE JOURNALS Edited highlights of weekly research reviews

Flu nudges

Persuading our most vulnerable patients into getting a flu jab is an annual headache for many GPs. In this trial of nearly 300 000 Danish patients aged 18-64 years with a chronic disease, participants were randomised to receive six different behaviourally informed electronic letters to encourage influenza vaccination or no letter. All the additional interventions were effective, with absolute effect sizes of 11-14% from a baseline of 27.9% vaccination uptake in the control group who received no letter.

The more nudges the better: 41.8% of those who received repeated digital letters had the vaccination. How to capture the 60% of non-responders remains unknown.

JAMA doi:10.1001/jama.2024.21060

Post MI beta blockade

How long do you need to stay on a beta blocker after a myocardial infarction (MI)? NICE recommends lifelong beta blockers for those with a reduced ejection fraction (EF), but possible discontinuation after 12 months in those with a decent EF. In this open-label, randomised, non-inferiority trial from 49 sites in France of patients taking long term beta blockers with a history of MI and an EF of ≥40% who had been free of any cardiovascular events in the previous six months, half of the patients were told to stop their beta blockers, and the other half continued.

A primary outcome event (MI, death, stroke, or hospital admission for a cardiovascular event during follow-up of ≥1 year) was similar in both groups (23.8% *v* 21.1%), and so non-inferiority couldn't be demonstrated. Stopping beta blockers seemed to be safe but was associated with an increased risk of angina with more hospital admissions and coronary procedures.

N Engl J Med doi:10.1056/NEJMoa2404204

HIV, statins, and diabetes—it's complicated

The REPRIEVE trial led to new guidelines for statin use among people with HIV even if their risk of atherosclerotic cardiovascular disease (ASCVD) is moderate or low. Statins are associated with a rise in blood glucose and diabetes, so does the liberal use of statins in people with HIV cause an excess in diabetes?

This phase 3, global, multicentre trial of nearly 8000 people with HIV aged 40-75 years with low to moderate ASCVD risk found that, over a median follow-up of 5.6 years, the statin pitavastatin (4 mg daily) was associated with a higher rate of new diagnoses of diabetes compared with placebo (0.34 *v* 0.27/100 person-years if no risk factors for diabetes (obesity, pre-diabetes, and metabolic syndrome), 3.24 *v* 2.66/100 person-years in individuals with multiple risk factors). Reducing the key metabolic risks for diabetes is a no-brainer, but weighing up the relative merits of statins in those who remain at high risk of diabetes is complicated.

Ann Intern Med doi:10.7326/ANNALS-24-00944

Improving the discontinuation of "benzos"

It's almost impossible to persuade a reputable doctor to prescribe even a handful of Valium if your back is in spasm. But you can still get cheap and plentiful "benzos" from online pharmacies, street dealers, and elsewhere. So the dependency on these drugs is still a major problem.

This small randomised trial of 188 US adults over 55 years old found that an intervention of masked tapering (in which participants don't know what daily dose they're on) alongside an augmented cognitive behavioural therapy for insomnia (CBTI) programme helped 73.4% of participants to discontinue all benzodiazepines for six months compared with 58.6% who underwent open taper and standard CBTI. These were quite light users (they had used the equivalent of <8 mg diazepam on two or more nights a week for at least three months), were middle-aged, and were followed up for only six months. But the results suggest that, when confronted by a dependent patient asking for a repeat prescription, effective help is possible.

JAMA Intern Med doi:10.1001/jamainternmed.2024.5020

PKU progress

Phenylketonuria (PKU) affects around 1 in 10 000 babies born in the UK, and—with prompt diagnosis with the newborn screening test, dietary advice, and follow-up—most will lead healthy lives. Untreated, neurotoxic levels of phenylalanine (Phe) can cause seizures and severe intellectual and developmental disabilities.

This important phase 3 multicentre trial (APHENITY) found oral sapropterin (a synthetic version of the deficient enzyme in PKU) was a safe and effective treatment in children and adults. It achieved a substantial reduction in blood Phe concentration compared with placebo across a broad range of patients (independent of age, sex, or ethnicity). Longer term studies are needed as the study period was only six weeks.

Lancet doi:10.1016/S0140-6736(24)01556-3

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PRACTICE POINTER

How to get started in medical leadership

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CPD READING 0.5 HOURS

Leadership is a core component of the work of any practising doctor. Good medical leadership is essential to the successful delivery of optimal clinical care,[1] and is associated with better team functioning, improved patient outcomes, and positive cultural change.[2-4]

Application of leadership has the potential to transform individuals, teams, working practices, and outcomes while improving job satisfaction.[5] Here, we offer an insight into potential leadership opportunities for doctors in training from local to national level, using case studies to illustrate how early career clinicians have built up their leadership skills.

Leadership at a local level

Early in your leadership development journey you should access the NHS Leadership Academy website (https://www.leadershipacademy.nhs.uk/), which contains valuable resources. It has a free self-assessment tool and a leadership 360—a tool that gathers anonymous views and opinions from your peers, multidisciplinary colleagues, and clinical supervisors—to identify your learning priorities and access a framework that can help you and your educational supervisor develop your leadership skills. Consider getting involved in local audits and quality improvement projects—these can help you fulfil your e-portfolio needs and are often a gateway to more formal leadership projects.

Local leadership opportunities are usually offered on an ad hoc basis. Approach your postgraduate medical centre to see if your trust has a consultant who acts as a leadership mentor or equivalent. They might be able to point you towards educational resources and courses, help organise shadowing opportunities, link you in with key trust-wide clinical and managerial leaders, and provide one to one mentoring. If your trust does not have such a dedicated role, many consultants will facilitate similar leadership experiences. Some trusts might also offer more formal resident doctor roles that include anywhere between 10% and 40% protected time for specific leadership activities alongside a part time clinical post—again, your postgraduate medical centre might be able to help you find these roles.

In 2016 the Royal College of Physicians introduced the chief registrar scheme to offer a more standardised and formal approach to leadership training at a trust level. Chief registrar posts are open to doctors in specialty training (year four and above) who are given 40-50% protected time to help deliver a wide range of local projects focused around areas such as workforce development, education, service improvement, and resident doctor engagement. Post holders are supported by a leadership development programme provided by the Royal College of Physicians. Although the post is run by the college it has now been expanded to include all physician and non-physician specialties. Some trusts have opted to set up similar roles independent of the college, often known as chief resident roles. If these roles interest you, early discussion with your departmental lead consultant is advisable, who can then help signpost you in the right direction.

Box 1 | How to develop your leadership skills

- Practise good leadership skills in your day job—make sure everyone feels part of the team, promote multidisciplinary team working, support those who are struggling, and always look to make a positive change
- Upskill in quality improvement—it is a great tool to help understand systems and how you might systematically lead and influence change. Your local quality improvement team will be able to guide you to local training. Alternatively, you might be able to access free online courses—for example, through the Improvement Academy (https://improvementacademy.org/we-can-help/doctors/)
- Seize local leadership opportunities—highlight to seniors that you are keen to get involved. One opportunity often leads to another
- Gain insight into your motivations—consider seeking coaching to help you understand your driving forces and pinpoint areas for future growth.
- Develop your coaching and mentorship skills—many deaneries offer courses that you can take in your protected study time. (https://www.leadershipacademy.nhs.uk/programmes/coaching-and-mentoring/regional-coaching-and-mentoring-offers/)
- Use the free Healthcare Leadership Model Self-Assessment Tool—use this tool at the start of your specialty training to identify your leadership development needs. (https://www.leadershipacademy.nhs.uk/healthcare-leadership-model/self-assessment-tool/)
- Review your leadership development at each appraisal—this link provides a framework to help guide you and your supervisor (https://www.leadershipacademy.nhs.uk/download/29659/)
- Complete a leadership programme—consider signing up to a free leadership development programme through the NHS Leadership Academy. Courses are available for every level of training—Edward Jenner (medical students and foundation years one and two), Rosalind Franklin (core trainees years one and two and specialist training years one to three) and Elizabeth Garrett Anderson (specialist training year four and above)

Case studies

Danielle Eddy

Faculty of Medical Leadership and Management, national clinical director's fellow at Public Health England, paediatric specialty trainee

During the covid-19 pandemic, I worked across government departments as part of their crisis response team. This opportunity gave me insight into national leadership during a crisis and exposed me to various leadership styles and challenges. I worked within Public Health England's acute response team, handling requests from various government departments and collaborating closely with the chief medical officer's team to deliver timely responses and actions. With reflection and coaching provided by the scheme, I was able to identify what type of leadership role appealed to me.

Jonny Gamble

Chief registrar, renal specialty registrar

I joined the Trainee Think Tank, a body of resident doctors in Wales that provides a direct link between the senior leadership of the medical deanery and resident doctors while sitting alongside the Specialist Training Committee structure of the deanery. I helped in raising matters that might have an impact on trainees with senior medical leaders, including proposed changes to less than full time working, study and educational leave provision, and the implementation of "speaking up safely" campaigns.

The post offers a similar advocacy role to that of regional royal college and BMA representatives, collecting voices across the spectrum of resident doctors in Wales and feeding relevant information back to those same diverse groups. I have learnt the importance of building trusting relationships to ensure that effective two way communication is possible.

Matthew Cowan

Trust-wide associate clinical leadership mentor, general practice specialty trainee

In 2022, I worked alongside our trust's clinical leadership mentor in an associate role on a novel project aimed at integrating resident doctor roles into trust-wide committees. A key aspect involved engaging with senior executives and clinical leaders as well as enthusing resident doctors. I also helped organise a trust-wide leadership study day aimed at enhancing resident doctors' insights into medical leadership and improving their competence and confidence in leadership skills. The day attracted a large number of resident doctors from a range of specialties and training grades, and now forms a key part of our trust's yearly education programme. This role was a stepping stone to gaining a research scholarship for my final year of general practice training.

Jonny Gamble

Chief registrar, renal specialty registrar

During my specialist training I pursued a one year out of programme experience as a Welsh clinical leadership fellow within our local health board. I engaged with the senior leadership team and the resident doctor body to identify areas of need and to improve two way communication. I joined leadership discussions across the health board, providing a resident doctor voice while learning and appreciating the work that occurs "behind the curtain." I established a forum for engaging resident doctors within local systems, with voluntary representative roles across training grades and specialties. I also had the opportunity to create referral policies, lead trainee feedback events, and sit in on deanery quality visits. The year gave me exposure to existing leadership structures and the barriers to implementing change as a leader.

Box 2 | How to expand your leadership knowledge

Reading material

- Kline R. Leadership in the NHS. BMJ Leader 2019: leader-2019.
- Coltart CE, Cheung R, Ardolino A, et al. Leadership development for early career doctors. *Lancet* 2012;379:1847-9.
- Warrant OJ, Carnall R. Medical leadership; why it's important, what is required, and how we develop it. *Postgrad Med J* 2011;87:27-32.

Attend leadership conferences

- For example, those of the Faculty of Medical Leadership and Management (https://www.fmlm.ac.uk/cpd)

Upskill in free leadership courses

- King's Fund (https://www.kingsfund.org.uk/leadership-development)
- NHS Leadership Academy (https://www.leadershipacademy.nhs.uk/)
- BMA leadership courses (BMA leadership programmes)
- NHS Wales Leadership programmes through their Gwella portal (https://nhswalesleadershipportal.heiw.wales/leadership-programmes). The Dragon Heart Institute also offers a 10 month programme (https://dragonsheart.org/learn/climb/)
- Northern Ireland—leadership courses available through Health and Social Care in Northern Ireland (https://leadership.hscni.net/Home/Index)
- Scotland —NHS Education for Scotland offer a range of leadership courses (https://learn.nes.nhs.scot/18217/leadership-and-management-programmes)

With reflection and coaching provided by the scheme, I was able to identify what type of leadership role appealed to me

Regional leadership opportunities

Regional leadership opportunities are often deanery based, and usually have a medical education or quality improvement angle to them. They can include elected positions, such as BMA regional committees, and appointed positions—for example, regional representatives for royal colleges, specialty training committees, and the Faculty of Medical Leadership and Management. Routes to these opportunities vary but monitoring your deanery and college websites and contacting your training programme director are good places to start. Regional representative roles require a different kind of leadership from local roles because you need to work as the representative voice and ear of a group that is more diverse and geographically spread. This can be a useful first step towards understanding some of the complexities of the wider National Health Service and give you an appreciation of the oversight roles within larger organisations. The experience often

Box 3 | Leadership roles—examples of local, regional, and national opportunities

Local opportunities

- Chair of Resident Doctors Forum—the 2016 resident doctors contract mandated each NHS trust in England to establish a forum to deal with contractual problems raised by doctors in training. The chair leads meetings, advocates for resident doctor interests, advises on fines and works with the guardian of safe working. Appointments typically last a year and might be combined with the role of mess president
- Mess committee—the Doctors' Mess Committee's primary roles are to manage on site facilities and organise social events. The make up of the committee varies between trusts, but core roles include president, social secretary, and treasurer. Other roles, such as representatives for international medical graduates and less than full time trainees are also common. Elections are usually held after the changeover time for doctors in training in August or early September

Regional opportunities

- Regional trainee networks—all deaneries are keen for trainee representation to present concerns and improve training opportunities. Foundation training grades through to all specialty schools have representatives. These roles provide an opportunity to appreciate medical education structures and to engage with multi professional groups
- BMA regional representatives—these roles allow you to represent colleagues at local negotiating committee meetings, regional, and national councils, and to participate in UK wide policy negotiations.
- Faculty of Medical Leadership and Management regional networks—there are eight regional networks, led by members of the faculty's council. All have regional trainee roles that require a wide range of abilities with a focus on increasing leadership opportunities
- College representatives—although varying approaches exist across the royal colleges, all have trainee committees to which deanery representatives are elected. This role would allow you to input on local and national matters, develop curriculum adjustments, and comment on national policy updates.

National opportunities

- Faculty of Medical Leadership and Management leadership schemes: national clinical director's fellowship (England)—a one year fellowship scheme for which all resident doctors are eligible. It involves working with senior clinical leaders across the NHS and allied organisations. It does not offer formal leadership courses, but there are opportunities for leadership development.
- Darzi fellowship—a one year fellowship scheme, where you are hosted by an organisation and able to complete a PGCert in healthcare leadership and management. Posts and eligibility vary
- Centre for Sustainable Healthcare: SusQI and education fellows—a one year fellowship scheme hosted by NHS organisations or by the centre with a focus on developing sustainable quality improvement skills and leading projects on sustainability.
- Centre for Peri-Operative Care fellowship—a one year fellowship for anaesthetic trainees. The post involves working half time (0.5 whole time equivalent) for the centre providing clinical support and knowledge to the development and delivery of their strategy
- Scottish Clinical Leadership Fellowship Scheme, Northern Ireland ADEPT Clinical Leadership Fellow Programme, and Welsh Clinical Leadership Training Fellowship—all three of these schemes provide one year fellowship scheme hosted by NHS organisations and allied organisations aiming to allow the postholders to learn about the practicalities of national leadership alongside formal training in healthcare leadership

includes working closely with senior leaders within the healthcare system. These posts offer the opportunity to ensure training standards are maintained, and to gain a better understanding of how feedback, such as the General Medical Council training survey, can be used to improve training and enact change.

Leadership at a national level

National leadership opportunities are garnering increasing attention as the value of contributions from doctors in training is becoming better acknowledged. Paid national leadership roles—although less common—offer resident doctors the chance to work alongside and collaborate with senior clinical leaders in a variety of organisations such as the Care Quality Commission and NHS England, providing valuable insights into high level policy decision making. These roles often entail leading projects or teams, developing or implementing change initiatives, shadowing senior leaders, and presenting at national meetings. They are available to anyone from medical students to doctors approaching the end of their specialty training. Some roles focus on project delivery, whereas others offer more formal training in leadership such as providing funding for a Postgraduate Certificate in Healthcare Leadership and Management, or providing an opportunity to learn about change implementation, coaching, and reflective practice. These positions afford time for self-reflection on personal leadership style, observing senior leaders' styles, assessing the effectiveness of different approaches, and shaping your future leadership style.

If you have an interest in leadership, it's never too late to gain experience and seek relevant training

Although previous leadership experience at the local or regional level can be beneficial when applying for a national role, it is not essential. These roles offer exposure to national leadership dynamics and allow you to explore whether this path aligns with your future aspirations. Some roles might require you to relocate whereas others can be performed remotely. Compensation varies, and accepting such roles might affect your salary.

If you have an interest in leadership, it's never too late to gain experience and seek relevant training. Notably, if leadership at a consultant level is an aspiration, previous experience at a national leadership level is not mandatory.

Competing interests: None declared.

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Sodium-glucose cotransporter-2 (SGLT-2) inhibitors for adults with chronic kidney disease: a clinical practice guideline

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CPD READING 0.5 HOURS

Clinical question

What is the impact of sodium-glucose cotransporter-2 (SGLT-2) inhibitors on survival and on cardiovascular and kidney outcomes for adults living with chronic kidney disease (CKD)?

Current practice

Few therapies slow kidney disease progression and improve long term prognosis for adults living with CKD. SGLT-2 inhibitors have demonstrated cardiovascular and kidney benefits in adults with CKD with and without type 2 diabetes. Existing guidance for SGLT-2 inhibitors does not provide fully stratified treatment effects and recommendations across all risk groups based on risk of CKD progression and complications.

Recommendations

The guideline panel considered evidence regarding benefits and harms of SGLT-2 inhibitor therapy for adults with CKD over a five year period, along with contextual factors, and provided the following recommendations:

1. For adults at low risk of CKD progression and complications, we suggest administering SGLT-2 inhibitors (weak recommendation in favour)
2. For adults at moderate risk of CKD progression and complications, we suggest administering SGLT-2 inhibitors (weak recommendation in favour)
3. For adults at high risk of CKD progression and complications, we recommend administering SGLT-2 inhibitors (strong recommendation in favour)
4. For adults at very high risk of CKD progression and complications, we recommend administering SGLT-2 inhibitors (strong recommendation in favour).

Recommendations are applicable to all adults with CKD, irrespective of type 2 diabetes status.

How this guideline was created

An international panel including patients, clinicians, and methodologists produced these recommendations following standards for trustworthy guidelines and using the GRADE approach. The panel identified typical risk strata of adults with CKD (from low to very high risk of CKD progression and related complications) using the classification system developed by Kidney Disease Improving Global Outcomes (KDIGO), and applied an individual patient perspective in moving from evidence to recommendations. The panel explicitly considered the balance of benefits, harms, and burdens of starting an SGLT-2 inhibitor, incorporating the values and preferences of adults with different risk profiles.

The evidence

A linked systematic review and pairwise meta-analysis (13 trials including 29 614 participants) of benefits and harms associated with SGLT-2 inhibitors in adults with CKD with or without type 2 diabetes informed guidance. Among individuals at very high risk of CKD progression and complications, moderate to high certainty evidence shows SGLT-2 inhibitors (relative to placebo or standard care without SGLT-2 inhibitors) decrease all-cause and cardiovascular mortality, hospitalisation for heart failure, kidney failure, non-fatal myocardial infarction, and non-fatal stroke. Among individuals at high risk, moderate to high certainty evidence shows SGLT-2 inhibitors result in similar benefits across outcomes except demonstrating little or no effect on hospitalisation for heart failure and kidney failure. Among individuals at moderate and low risk, moderate to high certainty evidence shows SGLT-2 inhibitors probably reduce all-cause mortality and non-fatal stroke, with little or no effect for other outcomes of benefit. SGLT-2 inhibitors are associated with little or no effect on acute kidney injury requiring dialysis, bone fractures, lower limb amputations, ketoacidosis, genital infections, or symptomatic hypovolaemia.

Understanding the recommendation

In order to apply recommendations, clinicians must appropriately identify adults with CKD, consider the underlying aetiology, and risk stratify them based on glomerular filtration rate (GFR) (estimated or measured) and degree of albuminuria. Further estimation of a given patient's risk based on the extent of their kidney disease and other comorbidities may be warranted to inform individual-level decisions and shared decision making.

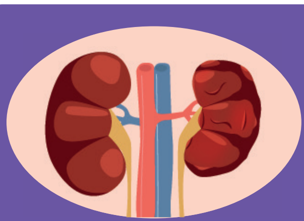
LINKED RESOURCES IN THIS *BMJ* RAPID RECOMMENDATIONS CLUSTER

- Zou X, Shi Q, Vandvik P, et al. Sodium glucose co-transporter-2 inhibitors in patients with chronic kidney disease with or without type 2 diabetes: a systematic review and meta-analysis. *BMJ Med* 2024;3:e001009
- MAGICapp: https://app.magicapp.org/#/guideline/EezrQj

Visual summary of recommendations

Population

Recommendations apply to:



Patients with chronic kidney disease

With or without diabetes

Recommendations may or may not apply to:

- People receiving kidney replacement therapy
- People who have received a kidney transplant
- People with polycystic kidney disease
- People with rare kidney diseases
- People with low estimated GFR not receiving kidney replacement therapy < 20 mL/min/1.73 m²

Age is not accounted for in the risk stratification approach, leading to possible overestimation of risk in older adults and underestimation of risk in younger individuals

See an interactive version of this graphic online

https://bit.ly/bmj-rr-ckd2

Risk stratification for recommendations:

Estimated GFR (Glomerular filtration rate): ≥ 60 mL/min/1.73 m² | 45-59 mL/min/1.73 m² | 30-44 mL/min/1.73 m² | < 30 mL/min/1.73 m²

Albuminuria (Albumin-creatinine ratio): < 3 mg/mmol | 3-30 mg/mmol | > 30 mg/mmol

Risk of kidney disease progression and complications: Low | Moderate | High | Very high

Recommendation strengths

W S

Weak Strong

Recommendations

People at low risk

No SGLT-2 inhibitors (S W) | SGLT-2 inhibitors (W S)

"We suggest administering SGLT-2 inhibitors"

Benefits
Moderate certainty of small but important reductions in risks of all-cause mortality and non-fatal stroke

People at moderate risk

No SGLT-2 inhibitors (S W) | SGLT-2 inhibitors (W S)

"We suggest administering SGLT-2 inhibitors"

Benefits
Moderate certainty of important reductions in risks of all-cause mortality and non-fatal stroke

People at high risk

No SGLT-2 inhibitors (S W) | SGLT-2 inhibitors (W S)

"We recommend administering SGLT-2 inhibitors"

Benefits
Moderate certainty of important reductions in risks of mortality and most cardiovascular and kidney outcomes

People at very high risk

No SGLT-2 inhibitors (S W) | SGLT-2 inhibitors (W S)

"We recommend administering SGLT-2 inhibitors"

Benefits
High certainty of an overall survival benefit and reduced risk of kidney failure, moderate certainty of important reductions in cardiovascular mortality and outcomes

Harms Moderate certainty of no important increase in the risk of harms

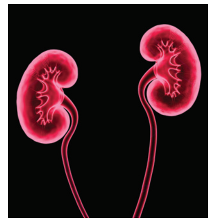
Why is the guideline needed?

CKD is classified based on aetiology, GFR, and degree of albuminuria.[1] CKD affects approximately 850 million individuals internationally, is the tenth leading cause of death, and is projected to be the fifth leading cause by 2050.[2-4] CKD is generally progressive, with declining GFR and progressive albuminuria associated with an increasing risk of cardiovascular complications, kidney failure, and premature death.[5 6]

SGLT-2 inhibitors have emerged—alongside renin-angiotensin system inhibitors, glucagon-like peptide 1 agonists, and non-steroidal mineralocorticoid receptor antagonists—as therapies with potential cardiovascular and kidney protective effects among individuals with type 2 diabetes and CKD.[7] Recently, two randomised trials have demonstrated similar cardiovascular and kidney benefits with the use of SGLT-2 inhibitors among non-diabetic individuals with CKD.[8 9]

Previous guidelines from KDIGO recommended the use of SGLT-2 inhibitors for patients with type 2 diabetes, CKD, and an estimated GFR (eGFR) of ≥20 mL/min per $1.73\ m^2$.[10] Their more recent guidance provides recommendations for SGLT-2 inhibitors more broadly for adults with CKD irrespective of diabetes status; however, recommendations are limited to specific risk groups (that is, an eGFR ≥20 mL/min per $1.73\ m^2$ with urine albumin to creatinine ratio (ACR) ≥20 mg/mmol (≥200 mg/g) with concurrent heart failure; or with an eGFR 20-45 mL/min per $1.73\ m^2$ with urine ACR <20 mg/mmol).[11] Moreover, these recommendations are primarily informed by a systematic review and meta-analysis of large double-blind, placebo-controlled trials of at least six months' duration evaluating SGLT-2 inhibitors across disease populations including CKD. The review included only four large trials including adults with CKD and did not account for the entirety of existing randomised trial evidence applicable to the CKD population. The review and practice guideline did not take into account treatment effects in absolute terms based on varying prognoses and baseline risks (that is, likelihood of events occurring without treatment), therefore failing to provide risk-stratified interpretations of the evidence and risk-stratified recommendations.[11 12]

We need trustworthy and actionable guidelines that consider all available randomised trial evidence. This international guideline panel of diverse healthcare professionals, patient partners, and methodologists experienced in guideline development provides the basis for practice guidance that can be used, adapted, and widely implemented.[13]



SGLT-2 inhibitors have demonstrated cardiovascular and kidney benefits in adults with CKD with and without type 2 diabetes

Context for recommendations

This practice guidance is intended to facilitate evidence-informed decision making for nephrologists, endocrinologists, internal medicine physicians, general practitioners, and patients with established CKD regardless of degree of kidney dysfunction and albuminuria. The recommendations take into account all available evidence regarding SGLT-2 inhibitors for adults with CKD; the expertise and experience of healthcare professionals, researchers, guideline methodologists, and people living with CKD; and the values and preferences of people with CKD when making treatment decisions, informed directly by patient partners on the guideline panel.

Approach to risk stratification

Risks of death, adverse cardiovascular outcomes, and progression to kidney failure vary across GFRs and degrees of albuminuria. No single prognostic model was identified that accurately risk-stratifies individuals with varying CKD profiles and produces reliable estimates for all prioritised cardiovascular and kidney outcomes and harms. Ultimately, the panel agreed to use the CGA classification, which incorporates underlying cause of CKD (C), GFR (G), and degree of albuminuria (A).[1 10 11] Data from a UK primary care database of records collected as part of routine care with general practitioners (99 129 patients) informed baseline risks and absolute effects across cardiovascular and kidney outcomes—specifically, all-cause and cardiovascular mortality, hospitalisation for heart failure, non-fatal myocardial infarction, non-fatal stroke, and kidney failure.[15] Absolute effects were estimated over a five year time-frame.

Applicability of recommendations

Recommendations apply to most adults with established CKD irrespective of type 2 diabetes status, heart failure status, sex, or ethnicity. In line with internationally accepted definitions, CKD is defined as abnormalities in kidney structure or function for a minimum of three months, with health implications. Either decreased GFR (<60 mL/min per $1.73\ m^2$) or one or more markers of kidney damage (such as albuminuria with an albumin to creatinine ratio ≥3 mg/mmol) must be present to establish the diagnosis. This guideline does not apply to adults meeting neither criterion and therefore not having CKD.

Recommendations may not be applicable to certain other groups based on specific clinical considerations and lack of representation in included studies:

- Individuals receiving kidney replacement therapy
- Individuals who have received a kidney transplant
- Individuals with polycystic kidney disease
- Individuals with rare kidney diseases
- Individuals with eGFR <20 mL/min per $1.73\ m^2$ and not receiving kidney replacement therapy.

Age is not accounted for in the definition and classification system published by KDIGO in 2012. This may result in possible overestimation of risk in older adults (≥65 years) and underestimation of risk in younger individuals (<40 years).[16]

The recommendations

Recommendation 1: For adults at low risk of CKD progression and complications, we suggest administering SGLT-2 inhibitors (weak recommendation in favour)

Understanding the recommendation—Moderate certainty of small but important reductions in risks of all-cause mortality and non-fatal stroke, balanced against moderate certainty of no important increase in the risk of harms, led to a weak recommendation in favour of treatment. The panel deliberated on whether treatment effects justified a weak recommendation in favour or against and ultimately concluded that most patients would be inclined to accept treatment.

Benefits and harms—In adults at low risk, SGLT-2 inhibitors probably decrease all-cause mortality (7 fewer per 1000 adults, 95% confidence interval 11 fewer to 1 fewer) and non-fatal stroke (10 fewer per 1000, 16 fewer to 2 fewer) (both moderate certainty) with little or no effect on cardiovascular mortality, hospitalisation for heart failure, kidney failure, and non-fatal myocardial infarction (all moderate to high certainty). Therapy is probably associated with little or no increased risk of harms, including acute kidney injury requiring dialysis (9 fewer per 1000, 14 fewer to 1 fewer), bone fracture (2 more per 1000, 10 fewer to 15 more), lower limb amputation (2 more per 1000, 4 fewer to 10 more), ketoacidosis (4 more per 1000, 1 more to 9 more), genital infection (27 more per 1000, 17 more to 39 more), and symptomatic hypovolaemia (32 more per 1000, 17 more to 49 more) (low certainty for lower limb amputation; moderate certainty for all other outcomes). Adverse events remained plausible at the individual patient level.

Values and preferences—Applying the values and preferences agreed on by the panel, the majority of individuals would be expected to accept SGLT-2 inhibitors, though a reasonable proportion would likely decline, given the marginal benefits, increased pill burden, medication costs, and a residual possibility of harms.

Recommendation 2: For adults at moderate risk of CKD progression and complications, we suggest administering SGLT-2 inhibitors (weak recommendation in favour)

Understanding the recommendation—Moderate certainty of important reductions in risks of all-cause mortality and non-fatal stroke, balanced against moderate certainty of no important increase in the risk of harms, justified a weak recommendation in favour.

Benefits and harms—In adults at moderate risk, SGLT-2 inhibitors probably decrease all-cause mortality (13 fewer per 1000, 95% CI 22 fewer to 2 fewer) and non-fatal stroke (13 fewer per 1000, 21 fewer to 3 fewer) (both moderate certainty), with little or no effect on cardiovascular mortality, non-fatal myocardial infarction (both moderate certainty), hospitalisation for heart failure, and kidney failure (both high certainty). Harms are the same as for adults in other risk strata, acknowledging uncertainty given lack of risk-stratified estimates and the residual possibility of adverse events at the individual patient level.

Values and preferences—Same as for recommendation 1.

Recommendation 3: For adults at high risk of CKD progression and complications, we recommend administering SGLT-2 inhibitors (strong recommendation in favour)

Understanding the recommendation—Moderate certainty of important reductions in risks of mortality and most cardiovascular and kidney outcomes, combined with moderate certainty of no important increase in the risk of harms, motivated a strong recommendation in favour of treatment.

Benefits and harms—In individuals at high risk, SGLT-2 inhibitors probably decrease all-cause mortality (24 fewer per 1000, 95% CI 41 fewer to 3 fewer) and cardiovascular mortality (6 fewer per 1000, 10 fewer to 1 fewer), non-fatal myocardial infarction (21 fewer per 1000, 34 fewer to 6 fewer), and non-fatal stroke (21 fewer per 1000, 34 fewer to 5 fewer) (all moderate certainty), with little or no effect on hospitalisation for heart failure and kidney failure (both high certainty). Harms are the same as for adults in other risk strata.

Values and preferences—Applying the values and preferences agreed on, the panel inferred that all or almost all individuals would be inclined to receive SGLT-2 inhibitors in light of benefits substantially outweighing potential harms and treatment burdens, and did not anticipate substantial variability in preferences.

Recommendation 4: For adults at very high risk of CKD progression and complications, we recommend administering SGLT-2 inhibitors (strong recommendation in favour)

Understanding the recommendation—High certainty of an overall survival benefit and reduced risk of kidney failure, moderate certainty of important reductions in cardiovascular mortality and outcomes, and moderate certainty of no important increase in the risk of harms, justified a strong recommendation in favour.

Benefits and harms—In individuals at very high risk, SGLT-2 inhibitors decrease all-cause mortality (48 fewer per 1000, 95% CI 84 fewer to 6 fewer) and kidney failure (58 fewer per 1000, 72 fewer to 42 fewer) (both high certainty), and probably decrease cardiovascular mortality (10 fewer per 1000, 17 fewer to 3 fewer), hospitalisation for heart failure (25 fewer per 1000, 32 fewer to 17 fewer), non-fatal myocardial infarction (32 fewer per 1000, 51 fewer to 9 fewer), and non-fatal stroke (25 fewer per 1000, 40 fewer to 6 fewer) (all moderate certainty). Harms are the same as for adults in other risk strata.

Values and preferences—Same as recommendation 3.

HOW PATIENTS WERE INVOLVED IN THE CREATION OF THIS ARTICLE

The panel included three patients with CKD. Their perspectives informed judgments regarding values and preferences associated with decision-making related to SGLT-2 inhibitors.

Competing interests: None delcared.

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CASE REVIEW

The often forgotten element: a key differential diagnosis for eczema, allergy, or infection

A five month old ex-26 week premature infant presented to the emergency department with a five week history of a rash, irritability, and diarrhoea. The rash consisted of erythematous, scaly, crusted skin lesions involving the head (figure), neck, perineal, and genital area. The infant was exclusively breastfed and had a history of chronic lung disease of prematurity. He had recently received a diagnosis of bronchiolitis and had been hospitalised in the paediatric intensive care unit for one week. He had a family history of psoriasis in a paternal aunt.

A diagnosis of superinfected eczema was suspected so systemic antibiotics were started resulting in initial improvement of the symptoms, but the skin lesions subsequently worsened. The infant had no response to various other treatments such as dairy exclusion from the mother's diet for suspected cow's milk protein allergy, topical emollients and steroids (eczema), topical miconazole, oral nystatin (fungal infection), oral aciclovir (viral infection), repeated oral co-amoxiclav (impetigo and cellulitis). He was receiving prophylactic iron and multivitamins, phosphate supplements, and alginic acid as regular medication.

Erythematous, scaly, crusted skin lesions

The results of repeated blood cultures and skin swabs for bacterial and fungal culture were negative, as were skin swab polymerase chain reaction tests for herpes viruses (herpes simplex viruses 1 and 2, varicella zoster virus). Erythrocyte sedimentation rate and C reactive protein were normal, full blood count unremarkable except for a mild thrombophilia (778 cells 10^9/L, normal range 150-350 cells 10^9/L). Alkaline phosphatase levels were low (105 U/L, normal range 134-518 U/L), with a normal kidney, liver, and bone profile. Zinc levels later came back as 1.8 μmol/L (normal range 5-21.5 μmol/L).

1 What are the differential diagnoses?

2 What is the most likely diagnosis?

3 What is the management?

Submitted by Amy Smit, Ibraheem Abdelhamid, Suzy Leech, Christian Harkensee, and Sushama Harikrishnan

Parental consent obtained.

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answers

CASE REVIEW

The often forgotten element: a key differential diagnosis for eczema, allergy, or infection

1 What are the differential diagnoses?

Atopic eczema, cow's milk protein allergy, psoriasis, and fungal, bacterial, or viral skin infections are the most common differential diagnoses. Atopic eczema in infants is characterised by dry, scaly lesions to the scalp, forehead, cheeks, perioral region, flexures, and more disseminated on the trunk. This might occur in conjunction with cow's milk protein allergy, which can also cause symptoms of reflux and diarrhoea with mucus and blood. Psoriasis in infants shows isolated or confluent plaque-like lesions often affecting the scalp, the lower back, and (unlike eczema) the extensor surfaces of the extremities.

2 What is the most likely diagnosis?

Zinc deficiency—in children, zinc deficiency can occur as a result of a low intake (nutritional deficiency), impaired absorption (general causes of malabsorption or defective zinc transporter protein caused by a genetic condition known as primary acrodermatitis enteropathica) owing to excess loss (increased loss in urine due to diuretics or renal diseases like nephrotic syndrome), or low albumin with high catabolic state (trauma, burns, extensive surgery). Primary acrodermatitis enteropathica and nutritional zinc deficiency can be clinically indistinguishable at initial presentation.

3 What is the management of this condition?

Replacement with elemental zinc for two months at doses recommended for age and weight by oral route mostly replenishes zinc stores. Zinc supplementation is known to reduce the severity and frequency of infectious diarrhoea in malnourished children and is recommended by the World Health Organization.The response to treatment is usually rapid with no need for additional skin treatment, though emollients may be helpful. Bacterial and fungal superinfections can be diagnosed with skin swabs and should be treated accordingly.

LEARNING POINTS

- Consider nutritional zinc deficiency in a premature infant presenting with erythematous scaly, well demarcated circumoral, anogenital, and acral skin changes unresponsive to treatments of common differential diagnoses.
- Risk factors for nutritional zinc deficiency include prematurity or exclusive breastfeeding especially with a deficient or restrictive maternal diet.
- Start zinc supplementation before confirmation with a low zinc level because test results can take time. In children unable to maintain zinc levels after stopping supplements, genetic testing for primary acrodermatitis enteropathica should be considered.

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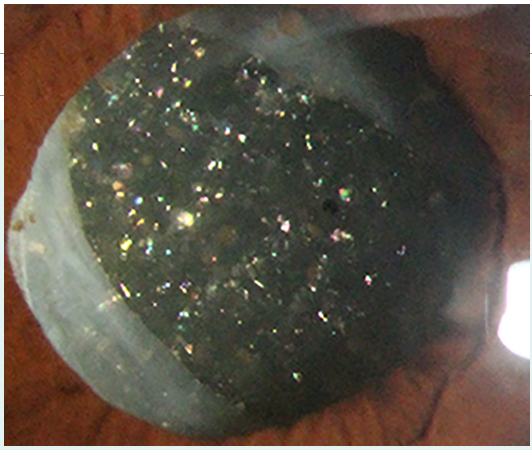
MINERVA

Iridescent crystals in the eye

These multi-coloured crystals were found in the vitreous cavity of the left eye of a woman in her 40s at a routine diabetic screening examination. She was asymptomatic but had a history of proliferative diabetic retinopathy with recurrent vitreous bleeds. Slit lamp examination of the left eye showed iridescent glistening crystals in the vitreous cavity that moved freely during ocular movements and fell to the vitreous floor with gravity. B-scan ultrasonography showed vitreous cavity opacity. Synchysis scintillans was diagnosed clinically.

Synchysis scintillans, or cholesterolosis bulbi, is a rare degenerative ocular condition characterised by the accumulation of small, freely moving, gravity dependent cholesterol crystals in the vitreous humour or cavity. It can be unilateral or bilateral and is derived from the breakdown of erythrocytes after vitreous haemorrhage. Synchysis scintillans must be differentiated from asteroid hyalosis, vitreous amyloidosis, and vitritis. Although secondary glaucoma is a notable complication, this patient had normal intraocular pressure, and was followed up regularly.



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Patient consent obtained.

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If you would like to write a Minerva picture case, please see our author guidelines at bit.ly/29HCBAL and submit online at bit.ly/29yyGSx

Dizziness and falls

No one will be surprised to learn that older adults who experience dizziness are at increased risk of falling. Any lingering doubt is resolved by a systematic review of 29 studies with data on 100 000 participants (*Age Ageing* doi.org/10.1093/ageing/afae177). A positive answer to the question, "Have you experienced episodes of feeling dizzy, unsteady, or as if you were spinning, moving, light headed, or faint?" was associated with a doubling of the risk of future falls.

Dementia in people with Parkinson's disease

Two prospective investigations come up with different estimates of the long term risk of developing dementia in people with Parkinson's disease (*Neurology* doi:10.1212/WNL.0000000000209699). An international study, which followed 420 patients, puts the probability at around 10%, 10 years after diagnosis. The other, a single site study from the University of Pennsylvania, estimated the probability at 27% after 10 years of disease duration, rising to 74% at 20 years.

Fluoroquinolones and seizures

Fluoroquinolones such as ciprofloxacin and moxifloxacin have acquired a reputation for being epileptogenic. A retrospective analysis of data from 53 000 hospitalised patients treated either with fluoroquinalones or with macrolides finds that it's probably unjustified (*J Antimicrob Chemother* doi:10.1093/jac/dkae255). The incidence of seizures was low in the group as a whole, and was no higher in patients treated with fluoroquinalones than those given macrolides.

Negative colonoscopy

Colonoscopy in people who screen positive on a fecal immunochemical test fails to find advanced neoplasia in more than half. One possible explanation is that the source of bleeding is a cancer in the upper gastrointestinal tract, oral cavity, or throat. When Dutch investigators linked data from a colorectal cancer screening programme to a national cancer registry they found that the incidence of a proximal cancer was raised in screen positive individuals regardless of whether their subsequent colonoscopy was positive or negative (*Gastroenterol* doi:10.1053/j.gastro.2024.04.028). Even so, the cumulative incidence over three years was less than 1%.

Comorbidity in multiple sclerosis

Data from 17 000 people with multiple sclerosis who took part in clinical trials indicate that those with co-morbidities at the time of trial recruitment were slightly more likely to show clinical or imaging evidence of disease activity during two years of follow-up (*JAMA Neurol* doi:10.1001/jamaneurol.2024.2920). The presence of three or more co-morbidities raised the likelihood of disease progression by around 10% when compared with those with no co-morbidity.

Hypertension and dementia

Among more than 30 000 people taking part in community based longitudinal studies of aging, those with untreated hypertension were more than a third more likely to develop Alzheimer's disease than normotensive people or people with treated hypertension (*Neurology* doi:10.1212/WNL.0000000000209715). People with hypertension were also at higher risk of forms of dementia other than Alzheimer's disease, but puzzlingly, this increased risk wasn't mitigated by anti-hypertensive treatment.

Fraud and falsification

As many as one in seven scientific papers in the field of biomedical research contain fabricated data or falsified results, according to a synthesis of the evidence available from investigations carried out in the past 10 years (OSF doi:10.17605/OSF.IO/5RF2M). Although this is a shockingly high figure, the scientific community seems unwilling to recognise the problem. The resources available to investigate and deal with fake science are seriously inadequate.

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