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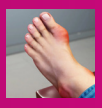
Volume 9 | Issue 1 | Apr-May 2024



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Health Digest

Dear Doctor,

We are proud to publish the next issue of the "Health Digest" written exclusively for medical professionals for their education and well-being.

Enjoy reading…

Editor:
Dr. Juma Venkatesh

Email:
md@glocarelabscro.com

Secondary prevention of cardiovascular disease, including cholesterol targets: summary of updated NICE guidance

What you need to know

- Offer 80 mg atorvastatin (unless contraindicated or previously not tolerated) as soon as possible to people with atherothrombotic cardiovascular disease (CVD)
- 2.0 mmol LDL-C (or 2.6 mmol/L non-HDL) is the most cost effective target for patients with established atherothrombotic CVD
- Consider ezetimibe for patients with atherothrombotic CVD, even if their cholesterol level is below the target

While mortality from acute cardiovascular disease (CVD) has been falling in most developed countries, more people are now living with established CVD, including coronary heart disease, peripheral arterial disease, and stroke or transient ischaemic attack. These individuals remain at high risk of subsequent cardiovascular events and mortality.

Statins, ezetimibe, bempedoic acid, and injectable therapies are approved as lipid lowering therapies in the UK. However, use of these agents is variable, with about one fifth of people with CVD in England receiving no lipid lowering therapy.

This is partly because of the absence of nationally agreed LDL-C targets for people with CVD to inform need for therapeutic escalation. Targets between 1.4 mmol/L and 1.8 mmol/L have been advocated by specialist societies and expert consensus, based on data from randomised controlled trials (RCTs).

Achievement of these targets has been poor, and as of September 2023, in England, only about one third of people with CVD who had a cholesterol test in the last 12 months had either LDL-C below 1.8 mmol/L or non-HDL-C below 2.5 mmol/L.

This article summarises the most recent recommendations from the National Institute

for Health and Care Excellence (NICE), first published in 2014, and updated in December 2023, incorporating for the first time LDL-C targets for people with CVD. This guideline is the first to incorporate economic modelling and cost effectiveness in the calculation of cholesterol targets, which could mean that it is more easily implemented.

Recommendations

NICE recommendations are based on systematic reviews of best available evidence and explicit consideration of cost effectiveness. When minimal evidence is available, recommendations are based on the Guideline Committee's experience and opinion of what constitutes good practice. Evidence levels for the recommendations are given in italics in square brackets. Evidence certainty is based on GRADE criteria (box 1).

Box 1

GRADE Working Group grades of evidence

- High certainty-we are very confident that the true effect lies close to that of the estimate of the effect.
- Moderate certainty-we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
- Low certainty-our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
- Very low certainty-we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Initial treatment

The evidence for these recommendations has not been revisited since the last update; however the wording has been updated to ensure consistency across the guideline. Randomised controlled trials have shown consistently that reduction of LDL-C by prescribing statins reduces the risk of major cardiovascular events and cardiovascular mortality by approximately one fifth for each 1 mmol/L reduction in LDL-C. For people with established CVD, cost utility analysis in an NHS setting showed that high intensity statins are highly cost effective when compared with no treatment or any other statin regimen.

- Offer atorvastatin 80 mg to people with CVD, whatever their cholesterol level.

[Based on randomised trial data, high to very low certainty, and economic modelling]

- Offer a lower dose of atorvastatin if any of the following apply:
- It could react with other drugs
- There is a high risk of adverse effects
- The person would prefer to take a lower dose.

[Based on randomised trial data, high to very low certainty, and the experience and opinion of the guideline committee (GC)]

- Do not delay statin treatment for secondary prevention of CVD but discuss lifestyle changes at the same time if appropriate.

[Based on the experience and opinion of the GC]

- If a person has acute coronary syndrome do not delay statin treatment. Measure full lipid profile on admission and two to three months after starting treatment.

[Based on the experience and opinion of the GC]

Lipid targets for people with CVD taking lipid lowering treatments

In people with CVD, LDL-C should be as low as possible to minimise the risk of re-admission to hospital and mortality, based on data from RCTs, genetic studies, and observational cohorts. At a population level, however, this is not cost effective, given that many potent non-statin therapies are expensive.

To inform this new recommendation, a cost utility analysis was developed using estimates

of the impact of lipid lowering treatments on LDL-C (from an original network meta-analysis of RCTs), combined with estimates of the impact of LDL-C reduction on major cardiovascular events (from a published meta-analysis of statin RCTs). The economic model measured the impact of lipid lowering treatments across a range of baseline LDL-C levels (0.3 to 4.0 mmol/L), on reduced admissions to hospital (stroke, myocardial infarction, and cardiovascular procedures), increases in life expectancy, and improvements in quality of life. Hospitalisation cost savings were offset against the cost of lipid lowering treatments and associated monitoring costs. The lowest LDL-C target that was cost effective at the benchmark pre-specified in NICE's principles of £20 000 per quality adjusted life year gained, was 2.0 mmol/L or an equivalent non-HDL of 2.6 mmol/L.

- For secondary prevention of CVD aim for LDL-C levels of 2.0 mmol per litre or less, or non-HDL cholesterol levels of 2.6 mmol per litre or less.

[Based on randomised trial data, high to very low certainty, and economic modelling]

Escalating treatment for people treated with statins

For people who are above the LDL-C target while already being treated with statin monotherapy, the GC refers healthcare practitioners to NICE's relevant technology appraisals to allow an informed choice to be made on the basis of the treatment specific expected LDL-C lowering that would achieve the LDL-C target, local availability, and patient preference.

This guideline newly recommends healthcare practitioners consider use of ezetimibe for people at or below the target. The low acquisition price (£1.51 for 28 tablets, at one tablet a day) and its effectiveness (an average 7% reduction in major cardiovascular events) makes ezetimibe highly cost effective for use in people with CVD at all cholesterol levels, and supports the principle of lowering LDL-C as much as possible for maximal risk reduction.

- Make decisions about escalating lipid lowering treatment after an informed discussion between the clinician and the person about the risks and benefits of additional lipid lowering treatments.

[Based on the experience and opinion of the GC]

- Take into account potential benefits from lifestyle changes, the person's preferences, the presence of any comorbidities, whether they are on multiple medications, whether they are frail, and their life expectancy (see also NICE's guideline on multimorbidity).

[Based on the experience and opinion of the GC]

- If the person is taking the maximum tolerated dose and intensity of statin but the lipid target for secondary prevention of CVD is not met (see above), consider additional lipid lowering treatments (see the NICE technology appraisals on alirocumab, evolocumab, ezetimibe, and inclisiran).

[Based on randomised trial data, high to very low certainty, and economic modelling]

- Consider ezetimibe in addition to the maximum tolerated intensity and dose of statin to reduce CVD risk further, even if the lipid target for secondary prevention of CVD is met (see above).

[Based on randomised trial data, high to very low certainty, and economic modelling]

Secondary prevention of cardiovascular disease when statins are contraindicated or not tolerated

People with CVD should take statins when they can be tolerated safely. However, approximately 9% of patients report an intolerance to all forms of statin therapy, commonly muscle ache and myalgia. In this context, this guideline newly recommends ezetimibe as a cost effective alternative first line therapy.

- Offer ezetimibe instead of a statin to people for whom statins are contraindicated or if after documented discussion, it is recognised the person cannot tolerate statins of any intensity or dose. This applies whatever the person's

cholesterol level (see the NICE technology appraisal on ezetimibe).

[Based on economic modelling and the experience and opinion of the GC]

- If the person is taking ezetimibe but the lipid target for secondary prevention is not met, consider alternative or additional lipid lowering treatments (see the NICE technology appraisals on alirocumab, bempedoic acid, evolocumab, and inclisiran).

[Based on randomised trial data, high to very low certainty, economic modelling, and the experience and opinion of the GC]

Annual medication review

This recommendation has been updated to focus treatment on people at greatest risk. Healthcare practitioners should measure a full lipid profile annually, to allow estimation of LDL-C, as well as evaluation of familial hypercholesterolaemia and quantification of triglycerides that could inform use of additional approved cholesterol lowering therapies, such as icosapent ethyl.

- Offer an annual full lipid profile to inform discussions about secondary prevention of CVD.

[Based on the experience and opinion of the GC]

Implementation

The high resource costs of some lipid lowering therapies, including acquisition and healthcare staff time, may create a barrier to implementation, but are likely to be offset by costs related to cardiovascular events prevented. The economic model for this guideline showed that many people can achieve the target with modestly priced oral medicines, such as statins alone or when combined with ezetimibe.

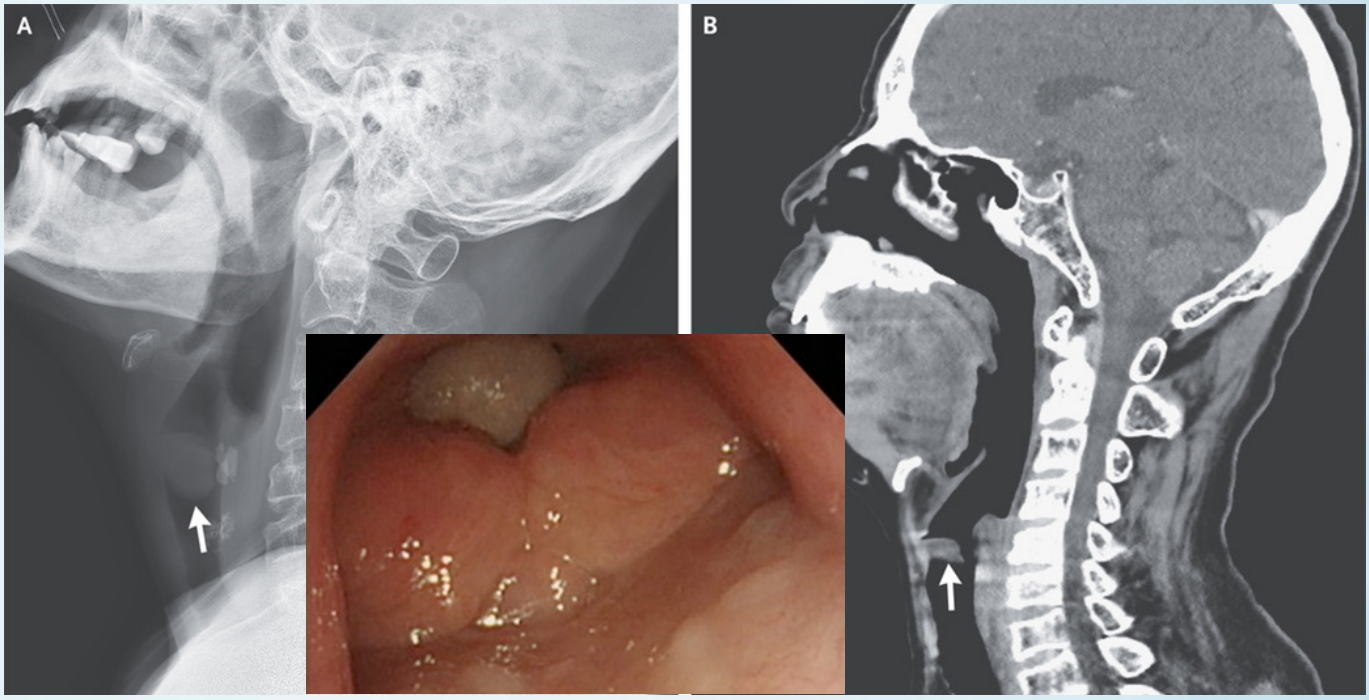
The slightly lower LDL-C target in existing guidelines, 1.8 mmol/L, seems close to the 2.0 mmol/L newly presented in this guideline; however, the economic model suggests that the additional cost to achieve a target of 1.8 mmol/L for everyone with CVD was considerable. We anticipate the Qualities and Outcome Framework indicator CHOL002 will be realigned to the guideline target in the 2024/25 GP contract, which will incentivise implementation in primary care. This guideline does not preclude aiming for a lower LDL-C target on an individual basis, with wider use of ezetimibe with statin therapy.

Healthcare practitioners might find it difficult to provide further escalation to patients taking maximal statin and ezetimibe therapy who have LDL-C between 2.0 and 2.6 mmol/L. No national funding mandate exists for advanced therapies, such as inclisiran or PCSK9 inhibitors, for use in patients in this range. Therefore, the escalation option of ezetimibe or inclisiran should be chosen carefully to reduce the occurrence of this scenario.

Although the strongest trial evidence was reported for LDL-C and a recommendation was made to carry out a full lipid profile annually, LDL-C testing varies across the country, and therefore, a corresponding non-HDL-C value was also recommended.

IMAGES IN CLINICAL MEDICINE

Vocal-Cord Polyp Causing Airway Obstruction



BRONCHOSCOPY

A 69-year-old man presented to the emergency department with a 2-week history of progressive, intermittent dyspnea that worsened when he was lying down. He also reported a 2-year history of hoarseness and a 30-pack-year smoking history. He worked in a noisy factory and frequently yelled to communicate with coworkers. On physical examination, there were normal inspiratory breath sounds and loud expiratory wheezes that were heard best over the neck. Owing to concern for upper-airway obstruction, radiography and computed tomography of the neck were performed, both of which showed a mass causing partial obstruction of the upper airway (Panels A and B, respectively, arrows). Bronchoscopy was subsequently performed, during which a large vocal-cord polyp was found to be causing intermittent airway obstruction in a ball-valve fashion during expiration. Vocal-cord polyps commonly manifest with hoarseness. Such polyps result from chronic irritation of the vocal cords, such as from smoking, reflux, or vocal strain. Immediately after bronchoscopic polypectomy, the patient's dyspnea resolved. Histopathological analysis confirmed the lesion to be a benign vocal-cord polyp. At the 1-month follow-up, his voice had returned to normal. Counselling on smoking cessation and vocal-strain avoidance was given.

Serum Urate and Recurrent Gout

Key Points

Question In patients with a history of gout, are higher levels of serum urate associated with a higher incidence of subsequent gout flares?

Introduction

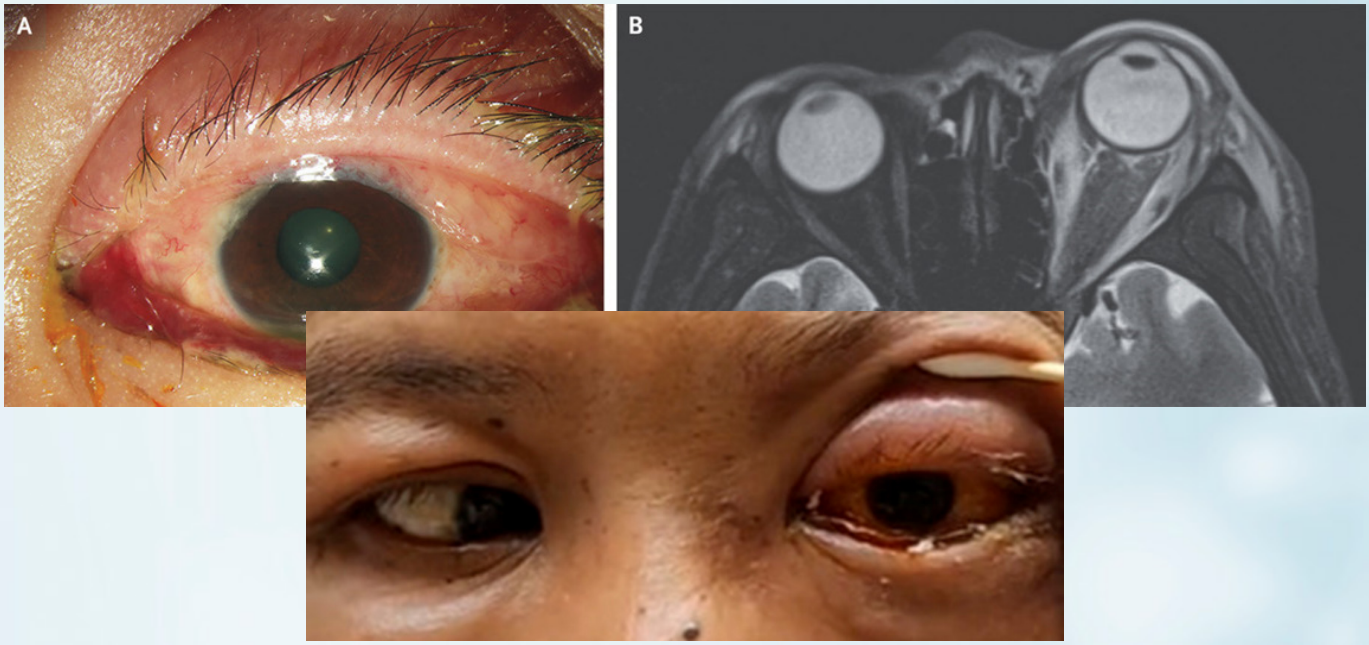
- Gout affects more than 12 million adults in the US.
- *Acute gout is typically episodic and associated with severe pain, reduced quality of life, and a transient increase in major cardiovascular and venous thrombotic events.
- Acute gout is caused by accumulation of monosodium urate crystallization in the joints, typically due to chronic hyperuricemia, with serum urate levels exceeding the saturation point of approximately 6.8 mg/dL for monosodium urate crystallization in the body.
- Among people without a history of gout, population-based studies reported graded associations between baseline serum urate levels above the saturation point and the risk of gout even after 10 or more years following the initial serum urate measurement.

Findings In this retrospective population-based study of 3613 patients with gout with a mean follow-up of 8.3 years, higher urate levels at baseline were associated with higher rates of recurrent gout. Overall, 95% of gout flares occurred in people with serum urate greater than or equal to 6 mg/dL and 98% occurred in people with serum urate greater than or equal to 5 mg/dL.

Meaning Among patients with a history of gout, these findings support using a baseline serum urate value to assess risk of subsequent gout flares.

Conclusions and Relevance In this retrospective study of patients with a history of gout, serum urate levels at baseline were associated with the risk of subsequent gout flares and rates of hospitalization for recurrent gout. These findings support using a baseline serum urate level to assess risk of recurrent gout over nearly 10 years of follow-up.

Ischemic Retinopathy from Prolonged Orbital Compression



PROPTOSIS AND OPHTHALMOPLEGIA OF THE LEFT EYE

A 44-year-old man presented to the emergency department with a 3-day history of vision loss and pain in the left eye. The symptoms had started after he had passed out for 3 hours in a position that put pressure on his left eye; before losing consciousness, he had taken insomnia medications and consumed alcohol. On physical examination, a relative afferent pupillary defect and an absence of light perception were found in the left eye. Proptosis and complete ophthalmoplegia of the left eye were also present. An anterior segment examination showed hemorrhagic chemosis and a fixed, mid-dilated pupil (Panel A). The intraocular pressure in the left eye was normal. Funduscopy showed diffuse retinal whitening, a finding consistent with infarction, and optical coherence tomography revealed full-thickness retinal edema. Magnetic resonance imaging of the orbit showed engorgement of the extraocular muscles and orbital tissue (Panel B). A diagnosis of ischemic retinopathy and choroidopathy owing to prolonged orbital compression was made. Historically, this condition has been known as "Saturday night retinopathy" because of its association with the use of alcohol and sedating substances. There is no consensus on management of the condition. The patient received treatment with systemic high-dose glucocorticoids and topical agents to prevent elevation of intraocular pressure; however, during follow-up by telephone 4 months after the initial assessment, the patient reported that he remained blind in his left eye.

IRRITABILITY IN AN INFANT- DIFFERNTIAL DIAGNOSIS

Irritability in an infant can be caused by common, easily reversible conditions but also by life-threatening conditions that require rapid recognition and treatment. Symptoms may not be clear in infants, and signs can be easily missed. A systematic approach that involves an evaluation of each body system sequentially can be helpful. However, given the immunocompromised and unimmunized status of infants, I will first consider infections.

Infections

A localized infection in an infant can easily spread to cause an invasive disease, such as bacteremia or meningitis,common infections, such as acute otitis media and skin and soft-tissue infections, that may have served as initial foci of invasive disease.

Neurologic Causes

Neurologic causes of irritability in an infant - including stroke, hydrocephalus, cerebral edema, and masses

Ocular Causes

Pain from a corneal abrasion can cause irritability in an infant. A fluorescein test could be considered to further evaluate for this possibility.

Cardiopulmonary Causes

Cardiomegaly, pulmonary edema, heart failure and myocarditis, arrhythmia, foreign-body ingestion, choking

Gastrointestinal Causes

Parents and pediatricians frequently anchor on the gastrointestinal system

when trying to find a reason for irritability. Common diagnoses include constipation, gas, reflux, and colic, appendicitis, intussusception, pancreatitis, hepatobiliary disease, and other causes of obstruction

Genitourinary Causes

Testicular torsion, hernia, or hair tourniquet, nephrolithiasis.

Skin and Soft-Tissue Causes

To rule out irritability associated with pain, an examination of all parts of the skin and musculoskeletal system for any signs of injury is essential. Fractures, which can be accidental or possibly signify child abuse, may be associated with swelling, bruising, or decreased movement

Cancer

Infants with leukemia or neuroblastoma can present with irritability. The presence of fever, hepatomegaly, cytopenia, and peripheral blasts should be checked. Presence of opsoclonus–myoclonus syndrome and ecchymoses around the eyes makes neuroblastoma likely, as do the abnormal abdominal ultrasound image and chest radiograph.

Metabolic Causes

Acute dehydration may be associated with irritability and associated with the reported decreased oral intake and the decreased bicarbonate level with an elevated anion gap, presumably from ketosis. Congenital conditions involving inborn errors of metabolism are important considerations in an infant with irritability..

Ingestions and Toxidromes

Paediatricians would consider ingestions and toxidromes in any patient with irritability. However, these conditions are more likely to occur in toddlers.

HYPOTONIA IN AN INFANT- DIFFERNTIAL DIAGNOSIS

The evaluation of an infant with hypotonia centers on conditions that affect either the central nervous system (CNS), including the brain and spinal cord, or the peripheral nervous system (PNS), including the motor neurons, muscles, nerves, and neuromuscular junction. Two rare causes of hypotonia that do not quite fit into this physiologic model are tick paralysis and paralytic shellfish poisoning

CNS Disease

In infants, 60 to 80% of cases of hypotonia are attributed to CNS diseases, specifically hypoxic–ischemic encephalopathy and cerebral palsy, spinal cord injury.

Other infectious or postinfectious conditions - such as transverse myelitis, acute disseminated encephalomyelitis

PNS Disease

The Guillain–Barré syndrome is an acquired demyelinating syndrome that is typically associated with ascending weakness, a loss of reflexes, and an elevated CSF protein level without pleocytosis.

Diseases of the neuromuscular junction can also cause hypotonia.

PRENATAL EXPOSURE TO SEVERE STRESS AND THE RISK OF HEART FAILURE UP TO MIDDLE-AGE

Background

Prenatal stress is a potential risk factor for cardiovascular disease, but its association with heart failure (HF) is unknown.

Objectives

The purpose of this study was to investigate whether prenatal stress, defined as maternal bereavement, was associated with HF risk up to middle-age.

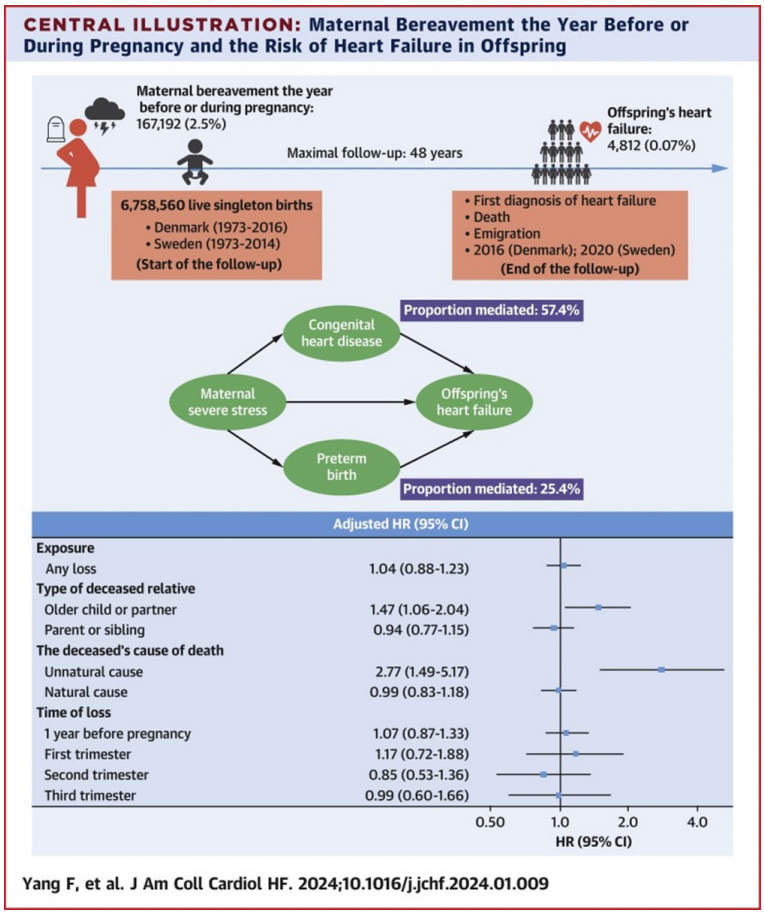
Methods

This cohort study included 6,758,560 live singleton births from the Danish (1973-2016) and the Swedish (1973-2014) Medical Birth Registers. The authors retrieved information on death of the mothers' close family members (partner, older children, parents, and siblings) and offspring's HF (up to 2016 in Denmark and 2020 in Sweden) from nationwide registers. They estimated HRs and 95% CIs for HF in the offspring according to maternal bereavement.

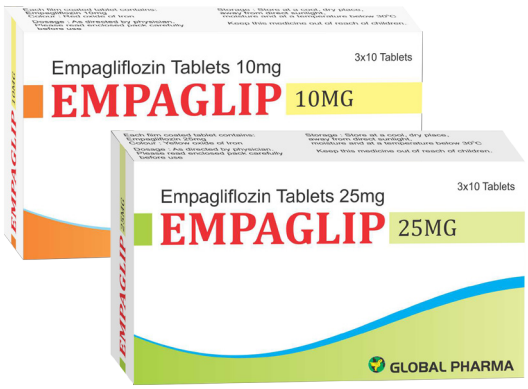
Conclusions

Maternal loss of a partner or older child and loss of a close relative caused by unnatural causes the year before or during pregnancy were associated with increased risk of HF in offspring.

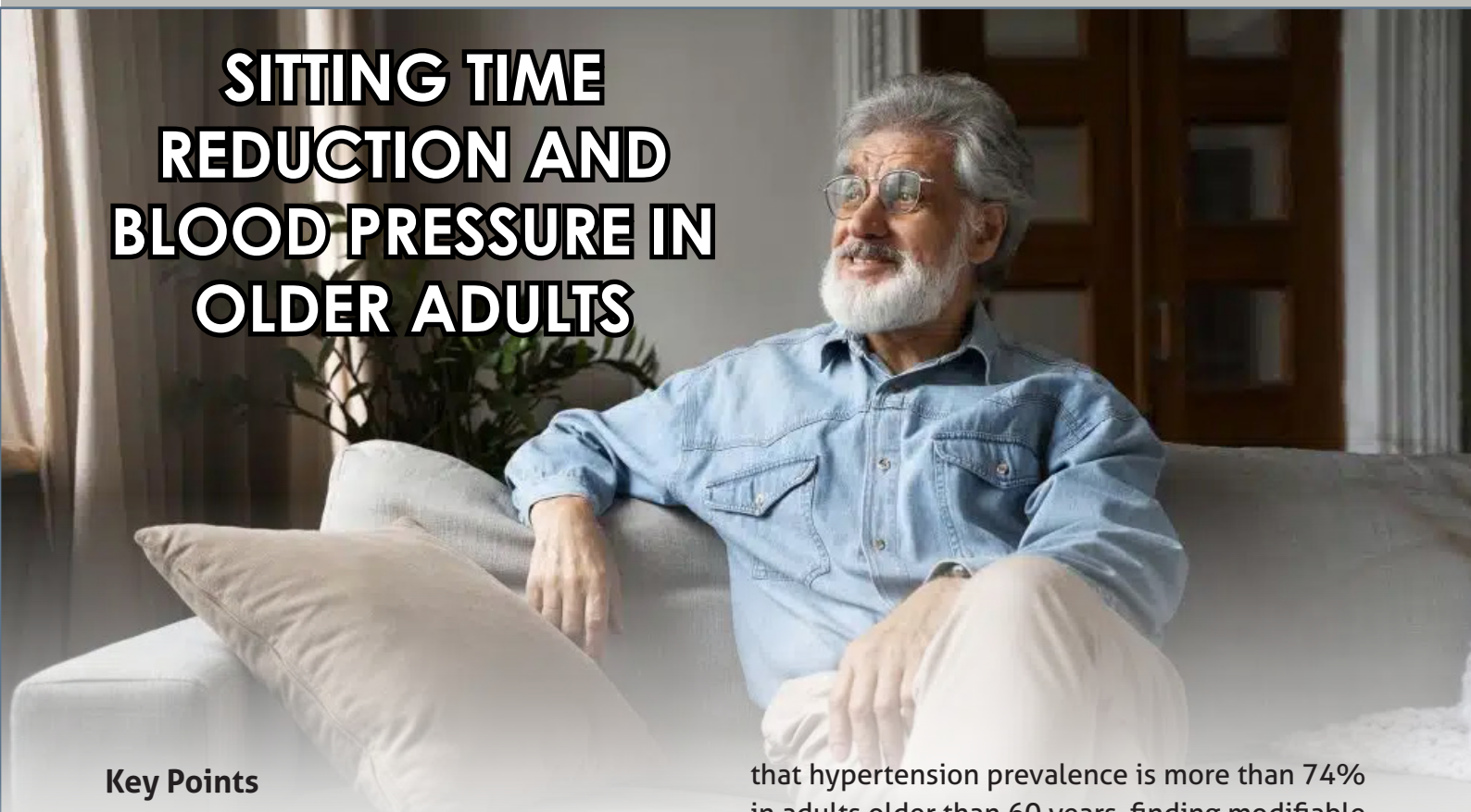
CENTRAL ILLUSTRATION



Yang F, et al. J Am Coll Cardiol HF. 2024;10.1016/j.jchf.2024.01.009



SITTING TIME REDUCTION AND BLOOD PRESSURE IN OLDER ADULTS



Key Points

Question Is sitting time reduction an effective strategy for improving blood pressure?

Conclusions and Relevance In this study of a 6-month sitting reduction intervention, older adults in the intervention reduced sedentary time by more than 30 min/d and reduced systolic blood pressure. Sitting reduction could be a promising approach to improve health in older adults.

Introduction

Moderate to vigorous activity can benefit the physical, cognitive, emotional, and functional health of older adults. However, their levels of meeting physical activity guidelines are low, with older adults typically sitting for 65% to 80% of waking hours. Strong evidence from epidemiologic studies associates sedentary behavior with adverse health impacts, including type 2 diabetes, cardiovascular disease, poor physical function, and mortality. Reducing or breaking up sitting time leads to improved blood pressure (BP) in short-term experimental studies, particularly for those with hypertension. Given that hypertension prevalence is more than 74% in adults older than 60 years, finding modifiable factors to improve control of this cardiovascular disease risk factor is crucial.

Training included 4 hours of didactic training and at least 10 hours of shadowing and practice and ongoing supervision.

Discussion

The sitting reduction intervention was effective at reducing sitting time by more than a half-hour per day during 6 months. It also increased standing time and reduced prolonged sitting periods. There were meaningful improvements in SBP of nearly 3.5 mm Hg that were commensurate to the effects of aerobic physical activity interventions. For comparison, systematic reviews indicate that aerobic physical activity reduces SBP by 4 mm Hg, the Dietary Approach to Stop Hypertension (DASH) diet by 5.2 mm Hg, and weight loss by 3 mm Hg. Sitting reduction through standing more and taking more frequent breaks from sitting may be a novel lifestyle strategy for improving BP and easier for older individuals with chronic conditions to incorporate into their daily life. Potential physiologic reasons for SBP reductions

could include more frequent interruptions to the bent artery position, which could improve blood flow and vascular shear stress.

Our finding that sitting was reduced by approximately 31 minutes per day is slightly lower than others have found and did not meet the study goal of a reduction of 2 hours per day. A Cochrane review of interventions to reduce sitting in older adults, including 7 randomized clinical trials, found an overall reduction of approximately 45 minutes per day, favoring intervention groups. In addition, most of our participants were affected by COVID-19 pandemic restrictions. Furthermore, the amount of sedentary behavior reduction needed to confer health benefits is not known.

Nonetheless, our intervention resulted in significant improvements in BP. This may be because we recruited participants at high risk of hypertension and aimed to reduce sitting time as well as decrease prolonged sitting. Perhaps given a population with higher cardiovascular risk, small changes in sitting patterns were sufficient for improving BP. The promising finding of no significant effect modifiers indicated that people with lower physical function or physical activity or with chronic conditions, such as type 2 diabetes, can reduce their sitting time and reap BP benefits. Decreased sitting could serve as a gateway to more physical activity as people gain strength and confidence.

effects on BP might have been greater had we excluded normotensive individuals.

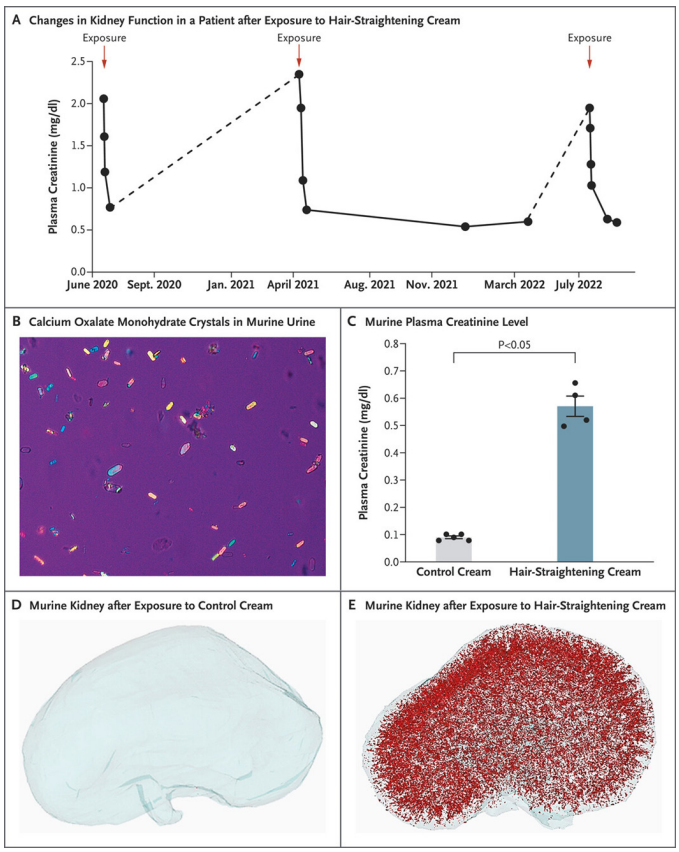
Conclusions

This randomized clinical trial showed that an intervention to reduce sitting time can be successfully delivered remotely and result in significant reductions in sitting time. These changes led to meaningful reductions in BP. Interventions that result in less sitting and more standing breaks deserve further study because they could lead to improved cardiovascular outcomes.

KIDNEY INJURY AND HAIR-STRAIGHTENING PRODUCTS CONTAINING GLYOXYLIC ACID

Hair treatments, particularly those aimed at straightening and smoothing, have garnered popularity in recent decades. Bnaya et al. recently described 26 patients in Israel who had acute kidney injury after a "Brazilian" hair-straightening procedure. The authors hypothesized that glycolic acid derivatives contained in hair-straightening products could be absorbed through the skin and metabolized into oxalate by the liver, thereby leading to calcium oxalate nephropathy

We report the case of a 26-year-old Tunisian woman without previous health issues who had three consecutive episodes of acute kidney injury (June 2020, April 2021, and July 2022)



after receiving hair-straightening treatments. She presented with vomiting, diarrhea, fever, and back pain. Laboratory studies showed increases in the plasma creatinine level during each episode. A computed tomographic (CT) scan indicated no evidence of obstructive uropathy, and urinalyses confirmed the presence of blood and leukocytes without proteinuria or infection.

Kidney function improved rapidly after each episode, and the plasma creatinine level was normal (0.78 mg per deciliter [69 µmol per liter]) at the last follow-up visit. No crystalluria or stone analyses were performed. A whole-exome sequencing analysis was negative.

Changes in Kidney Function in a Patient and a Murine Model of Crystalline Nephropathy after Cutaneous Application of a Hair-Straightening Product.

Each episode of acute kidney injury had coincided with a hair treatment at the same salon on the day the symptoms began. The patient reported a burning sensation during each procedure, followed by scalp ulcers. The cream used for the straightening procedure contained 10% glyoxylic acid but no glycolic acid.

These results provide evidence that hair-straightening cream containing glyoxylic acid is responsible for calcium oxalate–induced nephropathy after hair-straightening procedures of the type described here. Glyoxylic acid was patented and introduced recently in hair-straightening products as a seemingly safer alternative to formulations containing formaldehyde. In consideration of the potential nephrotoxicity of topical glyoxylic acid, products containing this compound should be avoided and, we would proffer, discontinued from the market.

USE OF PROGESTOGENS AND THE RISK OF INTRACRANIAL MENINGIOMA: NATIONAL CASE-CONTROL STUDY

ABSTRACT

Objective To assess the risk of intracranial meningioma associated with the use of selected progestogens.

Design National case-control study.

Participants Of 108 366 women overall, 18 061 women living in France who had intracranial surgery for meningioma between 1 January 2009 and 31 December 2018 (restricted inclusion periods for intrauterine systems) were deemed to be in the case group. Each case was matched to five controls for year of birth and area of residence (90 305 controls).

Main outcome measures Selected progestogens were used: progesterone, hydroxyprogesterone,

dydrogesterone, medrogestone, medroxy progesterone acetate, promegestone, dienogest, and intrauterine levonorgestrel. For each progestogen, use was defined by at least one dispensation within the year before the index date (within three years for 13.5 mg levonorgestrel intrauterine systems and five years for 52 mg). Conditional logistic regression was used to calculate odds ratio for each progestogen meningioma association.

Conclusions Prolonged use of medrogestone, medroxyprogesterone acetate, and promegestone was found to increase the risk of intracranial meningioma. The increased risk associated with the use of injectable medroxyprogesterone acetate, a widely used contraceptive, and the safety of levonorgestrel intrauterine systems are important new findings.

Introduction

Meningiomas account for 40% of primary tumours of the central nervous system. The incidence of meningioma in the United States is 9.5 per 100 000 person years. Meningiomas are mostly slow growing, histologically benign tumours but can nevertheless compress adjacent brain tissue and thus patients may require surgical decompression.

The incidence of meningiomas increases with age, rising sharply after the age of 65 years. Conversely, meningiomas are rare before the age of 35.

Other recognised risk factors for meningioma :

-are being female,

-intracranial exposure to ionising radiation,

- neurofibromatosis type 2,

-and, as shown only recently, prolonged use (≥one year) to high doses of three potent progestogens: cyproterone acetate, chlormadinone acetate, and nomegestrol acetate.

The link between female sexual hormones, in particular progesterone, and intracranial meningioma is biologically plausible.

Progesterone receptors are present in more than 60% of meningiomas and the volume of these tumours has been observed to increase during pregnancy and to decrease post partum. However, previous pregnancy does not appear to be an unequivocal risk factor for meningioma.

No significant association between exogenous female hormones and risk of meningioma has been shown to date for hormonal contraceptives (either combined or progestogen only pills).

Additionally, data for hormone replacement treatment for menopause are contradictory.

By contrast, the excess risk of meningioma observed with the use of high doses of cyproterone acetate among cis women, men, and trans women has been shown to be very high and somewhat lower, but still substantial, for chlormadinone acetate and nomegestrol acetate. Discontinuation of each of these three progestogens generally leads to a reduction in meningioma volume, which avoids the need for surgery and its associated risk of complications for most patients.

Whether progestogens other than these three oral progestogens at high doses have a similar effect depending on their route of administration is still unknown.

Our study aimed to assess the real-life risk of intracranial meningioma associated with the use of progestogens from an extensive list (progesterone, hydroxyprogesterone, dydrogesterone, medrogestone, medroxypro gesterone acetate, promegestone, dienogest, and levonorgestrel intrauterine systems) with different routes of administration (oral, percutaneous, intravaginal, intramuscular, and intrauterine). Although some of the progestogens studied are used in France (promegestone) or in only a few countries (medrogestone), others are widely used worldwide in various doses

and for various indications (progesterone, levonorgestrel, hydroxyprogesterone, medroxyprogesterone) (supplementary table A).

Certain progestogens may also be risky at some doses when used over a long period of time, but not at lower doses or when used for a short period of time. Our secondary objectives were to describe the characteristics of the women who were in the cases group (age, grade, and anatomical location of the meningiomas) and to approximate the number of surgically treated meningiomas attributable to the use of the concerned progestogens.

What this study adds

- Prolonged use of medrogestone (5 mg, oral), medroxyprogesterone acetate (150 mg, injectable), and promegestone (0.125/0.5 mg, oral) was found to be associated with an excess risk of intracranial meningioma
- In countries for which the use of medroxyprogesterone acetate for birth control is frequent (74 million users worldwide), the number of attributable meningiomas may be potentially high
- The results for oral, intravaginal, and percutaneous progesterone, as well as dydrogesterone and levonorgestrel intrauterine systems, are reassuring, supporting the absence of excess meningioma risk

Conclusions:

Prolonged use of medrogestone, medroxyprogesterone acetate, and promegestone was found to be associated with an increased risk of meningioma. Future studies should further clarify the association between the duration of use and risk for the progestogens studied, and extend the discussion of meningioma risk to dienogest and hydroxyprogesterone. Finally, no excess risk of meningioma was associated with the use of progesterone, dydrogesterone, or spironolactone, or the hormonal intrauterine systems used worldwide, regardless of the dose of levonorgestrel they contained.

Further studies are also needed to assess the meningioma risk with the use of medroxyprogesterone acetate, which, in this study, was considered at a dose of 150 mg and corresponded to a second line injectable contraceptive that is rarely used in France. Studies from countries with a broader use of this product, which, furthermore, is often administered to vulnerable populations, are urgently needed to gain a better understanding of its dose-response association.

Summarised / Edited for Internal Circulation:
GLOCARE LABS PVT LTD
Clinical Research Organisation

CLINICAL & BIOANALYTICAL UNIT:
2A, Ganga Nagar, 4th Street, Kodambakkam, Chennai - 600 024, INDIA.
Tel: +91-44-24726001 | Fax: +91-44-24726002 | Ph: +91-44-4857 3985
Email: md@glocarelabscro.com | Website: www.glocarelabscro.com