ACE inhibitors in covid-19—yes or no?
If you are confused about the role of angiotensin converting enzyme (ACE) and ACE inhibitors in covid-19 you’re forgiven.
There’s so much back and forth it’s difficult to keep track. Luckily, this week JAMA heard our call.
This retrospective cohort study of 4480 patients in Denmark found no association between prior use of ACE inhibitors or angiotensin receptor blockers and a covid-19 diagnosis, having severe covid-19, or dying from covid-19. This is reassuring for those with hypertension who are taking these drugs. (Although death rates were higher in those who had been using the drugs, the association became non-significant after adjustment for confounders including age, sex, and medical history.)

Covidophilic environments in New York City
The first thing to notice about this study is that it is a cohort study of almost 400 pregnant women who were tested in a universal testing programme at a New York hospital delivery unit during March and April. So, whatever the findings, fascinating and damning as they may be, it is important to remember the sample from which the data were collected. Pregnant women are not representative of the general population. But on to the findings.
Emeruwa and colleagues found significant variation in the likelihood of getting the SARS-CoV-2 virus based on differences in the urban environment (although they concede that they could not perform a multivariable analysis owing to the small sample size and highly correlated neighbourhood level variables). Empirically, there was higher risk with more residents per unit, more units per building, lower median income, and higher unemployment rate. I am not sure how feasible it is to reduce the risk related to built environments and socioeconomic status, but it is still useful to identify those at risk and why this may be.

High covid-19 rates in Latin American populations
I was not surprised by the statistic that people from Latin American populations were more likely to test positive for the virus than any other ethnic group, especially as testing rates would have differed between groups. Until I saw the numbers. At Johns Hopkins Hospital in Baltimore, the percentage of those tested who were positive was 8.8% in white people, 17.6% in black people, 17.2% in other ethnicities, and a giant 42.6% in Latino people. It’s hard to pass off such a huge difference as Latin American people being less likely to get tested (as they are known to be less likely to have insurance and less likely to access healthcare). It is likely that the difference in risk is due to differences in lifestyle between the ethnic groups and/or to genetic susceptibility factors.
The authors suggest that Latino populations may live in more densely populated accommodation, which makes it less likely that they could follow physical distancing measures, and that they are more likely to work in jobs that put them at higher risk of infection. I agree with Martinez and colleagues’ conclusion that, “Addressing the unique needs of the Latino community may help mitigate the spread of SARS-CoV-2 infection and prevent covid-19 disease.”

Diet dogma doesn’t change
The word diet originates from the Greek diaita, meaning way of life. The more one thinks about the concept of diet as a way of life, the more meaningless studies of individual diet components seem. Hence I’m pleased that Shan and colleagues’ US cohort study looks at the cardiovascular risk reduction with patterns of eating. This study’s strengths are large numbers of participants (although they were all healthcare professionals, making the study less applicable to the general public) and long length of follow-up. I’m not sure these features help to make up for the limitations of diet surveys based on self-reporting. The authors found that greater adherence to any of the four healthy eating patterns assessed was associated with a lower risk of myocardial infarction and strokes—which sounds good, but what is lacking from this analysis is all cause mortality. This is important because cancer and dementia, for example, are also affected by diet and also cause a lot of deaths.

Covid cruise ship revisited
We learnt a lot from the outbreak of covid-19 on the cruise ship Diamond Princess, and not just why not to go on a cruise. For example, we learnt it is possible to have the virus without being symptomatic. More than half of those who tested positive for SARS-CoV-2 were asymptomatic at the time. This formed a 96 person cohort. Sakurai and colleagues now report what happened to these people after they disembarked. The time to resolution of the infection was a median of nine days, and the time increased with age. Eleven of the cohort developed symptoms, thereby reclassifying them to pre-symptomatic. The sample is very small so the findings aren’t that robust, but they are interesting.

Alex Nowbar is a clinical research fellow at Imperial College London
Computerised speech and language therapy can help people with aphasia find words following a stroke

Why was this study needed?

Aphasia is usually caused by damage to the left side of the brain, most commonly after a stroke. Around 110,000 people in England have a stroke each year. About a third of survivors will have aphasia. Between 30% and 43% of those affected have symptoms in the long term.

Most people make some improvement with speech and language therapy, and some people recover fully. However, speech and language therapy is resource intensive and difficult to obtain in the NHS. Some small studies have suggested that computerised therapy might be an effective way to provide additional support for those who need it. Computer programs allow patients to complete exercises to help with word retrieval and other language problems. They can be tailored for individuals and are readily available.

This study aimed to assess the clinical and cost-effectiveness of self-managed computer speech and language therapy used in addition to usual care.

What did this study do?

Big CACTUS was a randomised controlled trial that recruited 278 adults with aphasia from 20 NHS trusts in the UK.

Participants were randomly assigned to one of three groups. The "usual care" group received usual care plus six months of using a computer program daily at home. This was a self-managed set of word-finding exercises, tailored for each individual.

There was also an "attention control" group, who received usual care in addition to completing paper based puzzle book activities (such as sudoku, or word searches) daily for six months. This last group helped to ensure that any effect could be attributed to the computer intervention rather than just increased attention from a therapist.

This was a robust, albeit relatively small, trial, but it was limited to English speakers as the computer program was only available in English.

What did it find?

- On average, participants in the group using a computer had improved word finding of 16.2% more than those in the usual care group (95% confidence interval 12.7 to 19.6), and 14.4% more than those in the attention control group (10.8 to 18.1). This was greater than the pre-specified clinically important difference of 10%. This improvement was maintained at nine and 12 months.

- The computer therapy did not improve functional communication. Nor did it have an impact on participants’ own perceptions of their communication, social participation, or quality of life.

- The mean cost per person for the computer therapy was £733. The cost for the equivalent amount of face-to-face time with a speech and language therapist would be approximately £1400.

What does current guidance say on this issue?

The National Institute for Health and Care Excellence published guidance on stroke rehabilitation in adults in 2013. Its section on communication states that speech and language therapists should provide direct impairment based therapy for communication impairments such as aphasia. It doesn’t specify what that therapy should be, or how it should be delivered. The Royal College of Speech and Language Therapists’ resource manual for commissioning and planning services for aphasia states that computer based therapy directed by a speech and language therapist is beneficial, cost effective, and acceptable.
Initial assessment

What are the symptoms of recurrent vulvovaginal candidiasis? Typical symptoms of RVVC are vulval itching and a non-offensive vaginal discharge. Other common symptoms include soreness, superficial dyspareunia, and a cyclical pattern of symptoms. Although a curd-like discharge is typical, discharge can be thin or absent altogether. A green or yellow discharge, or one with an offensive odour, may indicate other causes of infection.

What else should you cover in the history? Ask if the patient has a history of skin problems such as psoriasis or eczema. Does she have poorly controlled diabetes or symptoms of undiagnosed diabetes? Does she have any medical conditions or take any medications that might cause immunosuppression? Patients are often keen to explore any underlying causes or contributing factors, to help avoid further recurrences. These are listed in the box.

What impact does recurrent vulvovaginal candidiasis have? RVVC often has a profoundly negative impact on the quality of life and productivity of women affected, comparable to conditions such as asthma, chronic obstructive pulmonary disease, or migraine. We recommend exploring and validating this throughout the consultation.

Is an examination required? A key part of the assessment is examination and laboratory testing. Our experience in a community gynaecology clinic has highlighted how often recurrent thrush is misdiagnosed when relying on symptoms alone. According to one study of 95 women who self diagnosed with RVVC, over half had another condition, including dermatitis, lichen sclerosis, other infections (such as herpes simplex and trichomonas vaginalis), and vulvodynia. The table summarises the key findings on examination.

WHAT YOU NEED TO KNOW

- If symptoms of recurrent vulvovaginal candidiasis occur, offer a full examination and laboratory tests as other diagnoses such as bacterial vaginosis, sexually transmitted infections, and dermatitis are common
- Consider testing for non-albicans species, which may be more effectively treated with nystatin
- Common predisposing factors and triggers include recent antibiotic use, higher oestrogen states, diabetes, vaginal douching, and sexual activity

Can self swabs be offered? When an examination is not possible or declined, we offer self swabs for women to take home. These are also useful if the history is suggestive of RVVC but the examination and initial swabs are unremarkable.

Are blood tests needed? We offer testing for diabetes to all patients in order to exclude this long term condition. BASHH recommend considering testing for iron deficiency anaemia, although evidence of a possible link is conflicting and inconclusive.
Management of recurrent vulvovaginal candidiasis

How is it diagnosed?
BASHH define RVVC as at least four episodes in 12 months, with two episodes confirmed by microscopy or culture when symptomatic (at least one must be culture). In clinic we make a clinical decision about treatment with the woman based on the severity of her symptoms, her preference for empirical treatment, and the likelihood of an alternative diagnosis. This will determine whether we start treatment that day or await laboratory confirmation.

Are culture results reliable?
Asymptomatic colonisation with candida species is common (up to 20% of women of reproductive age). A culture result of candida in the absence of microscopy findings of neutrophils is likely to represent asymptomatic colonisation. Be cautious of results that quantify candida growth, since quantification of candida isn’t reliable in samples kept in transport medium for over 12 hours.

What is the treatment for confirmed recurrent vulvovaginal candidiasis?
Begin with general skincare advice: avoid scented soaps and instead encourage external use of emollients as soap substitutes. Discuss how the patient might address any causes or triggers identified (box).

Causes and triggers for recurrent vulvovaginal candidiasis (RVVC)

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about any unwanted effects, and we do discuss this option with many patients.\textsuperscript{33,34} Tea tree oil is not currently recommended because there is no evidence to suggest that it works in RVVC.\textsuperscript{35} Furthermore, there are studies that highlight the potentially severe adverse reactions of its use.\textsuperscript{36}

Although the media have often advocated dietary changes (such as a yeast-free diet or garlic-rich diet), studies have not documented any efficacy of this approach.\textsuperscript{36,37,38} In practice, we often see patients with RVVC seeking dietary exclusion advice, and in response we aim to discuss lifestyle and diabetes-reducing strategies.

Should partners also seek testing or treatment?

BASHH state that uncomplicated vulvovaginal candidiasis does not require treatment of asymptomatic male partners of affected women. Treatment of male sexual partners does not prevent the recurrence of candidiasis in women.\textsuperscript{39}

Cite this as: BMJ 2020;369:m1995

Find the full version with references at http://dx.doi.org/10.1136/bmj.m1995


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COMMON QUESTIONS FROM PATIENTS

What is it?

Candida is a yeast which normally lives in our bodies in small amounts and is harmless. Vaginal thrush is when the amount of yeast increases in the vagina and cause symptoms.

Why does it keep coming back?

We can take a look at some common triggers but in most people we do not know why it keeps coming back.

It often comes back after I have sex. Am I getting it from my partner?

Vaginal Thrush is not a sexually transmitted infection, so you can still have sex when you have thrush. The creams used to treat thrush can sometimes weaken condoms so apply the cream after sex.

Do anti-candida diets and supplements help?

This has been looked at in studies, which found that dietary changes do not prevent thrush. The yeasts found in foods such as bread are a completely different type of yeast from those that cause vaginal thrush.

Is it safe to take these medications for so long?

Reactions are rare, and it is generally a safe treatment. The rare risk of reaction can be abnormal liver blood results.

WHAT YOU NEED TO KNOW

- Hypospadias is a common congenital condition characterised by a ventral meatus
- Hypospadias should be identified at the newborn baby check, but can be missed
- Refer to a hypospadias surgeon when the abnormality is identified, to plan for surgery at 1 year

A 6 week old boy is brought into clinic. His parents are concerned about the way he passes urine. They say the opening of his penis is on the underside. He appears otherwise healthy.

Hypospadias is the most common congenital defect of the penis,\textsuperscript{1} and occurs in approximately one in 250 infant boys in Europe.\textsuperscript{2} It is characterised by a urethral meatus on the ventral aspect of the penis or scrotum, dorsal winged prepuce (foreskin), and ventral curvature of the penis (chordee). These features can be present in varying degrees of severity.

In this article we offer a guide for assessing hypospadias in primary care. As soon as a baby with hypospadias is identified, he should be referred to secondary care. This is often following a newborn baby check, before mother and baby are discharged from maternity care.

What you should cover

History

When was the abnormality first noticed? Hypospadias is usually identified at the newborn baby check and referred directly. However, some cases are missed and identified later, or the general practitioner is asked by the neonatal team to refer. This might be after the parents have noticed an abnormality.

Have you noticed any erections? If so, were they straight?

Reassure the parents that erections are perfectly normal from birth. In hypospadias they are commonly curved ventrally. The greater the severity of the curvature the more challenging the surgery, and a two-stage repair is more likely. It is usually not possible to assess this in clinic, and therefore a report from the parents is very helpful.
What you should do

Explain to the parents what hypospadias means. Stress that the abnormality is fairly common and that it occurs spontaneously. Advise the parents that you are referring them to a specialist clinic where their child will be assessed and examined, and probably offered surgery. Hypospadias surgery is performed by a plastic surgeon or urologist, depending on the geographical area of referral.

The surgery will be undertaken when the child is around 1. This is because he will be developed enough for the surgery to be undertaken, but still young enough not to have awareness of his genitals and will not remember the surgery. Historically the surgery was performed at a later stage (up to the age of 4), but this trend has changed.

In most cases the child will have only one operation, but in the more proximal cases or the cases with more severe curvature, two stages may be required.

The skin from the prepuce, or occasionally the buccal mucosa, can be utilised as a graft. Therefore advise parents not to have their child circumcised preoperatively.

Most affected children are treated successfully with no problems in later life. The main complications of surgery are fistula, stenosis, and dehiscence. A systematic review and meta-analysis that included 6603 patients found an incidence of fissure of 7.5%, stenosis or stricture 4.4%, and dehiscence 2.1%. 7

Most boys grow up not knowing there was ever a problem, although most are followed up into their second decade to check for these complications. Complications of fistula or stenosis are more common in the more severe cases (more proximal meatus or greater curvature). These cases require further surgery, which is usually successful.8,9

Competing interests: None declared.

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Find the full version with references at http://dx.doi.org/10.1136/bmj.m2070

Most affected children are treated successfully with no problems in later life

Examination

Assess location of the meatal opening

When referring, it is useful to detail if the meatus is distal or proximal. The more proximal the meatus, the more challenging the surgery, and is a further reason for a two-stage procedure. Figure 1 describes the Duckett classification, which classifies hypospadias based on the location of the urethral meatus.

Examination of testes to ensure descent

Cryptorchidism is present in 9.3% of cases.6

Exclude inguinal hernias

Approximately 9.1% of cases are associated with inguinal hernias.4

The foreskin is adherent to the glans in children, and adhesions should not be separated during clinical examination. In hypospadias the foreskin is incompletely formed ventrally. This is referred to as a dorsal hood or dorsal winged prepuce.
Pedometers can help people get more active as part of an exercise programme

Why was this study needed?

Metabolic conditions such as type 2 diabetes are closely linked to conditions such as overweight and obesity, and to cardiovascular disease. Improved diet and more physical activity are recommended as the first steps in managing these conditions.

The use of wearable technology is becoming a popular way to encourage people with cardiovascular or metabolic conditions to become more active.

What did this study do?

This was a systematic review and meta-analysis including 36 randomised controlled trials and 5208 participants. Twenty studies assessed accelerometers and 16 used pedometers. Six studies were from the UK and nine from the US.

Eligible studies included adults aged 18 or over, with at least one of:

- type 2 diabetes or risk factors for type 2 diabetes
- obesity or overweight
- cardiovascular disease.

What did it find?

- Interventions including monitoring devices (accelerometers or pedometers) resulted in a small to medium increase in physical activity over eight months compared with usual care or other interventions (SMD 0.39, 95% confidence interval 0.28 to 0.51; 22 studies, 4856 participants).

- Pedometer-based interventions resulted in a medium increase in physical activity (0.52, 0.32 to 0.72; 15 studies, 1741 participants). This was an average increase of 1703 steps per day compared with the control group (1067 to 2339). Accelerometer-based interventions resulted in a small increase in physical activity compared with controls (0.30, 0.16 to 0.44; 20 studies, 3115 participants).

- Pedometer-based interventions that included face-to-face consultations with a healthcare professional showed the largest improvement in physical activity levels (0.73, 0.50 to 0.97; 10 studies). The effect was smaller for accelerometer studies including consultations (0.29, 0.14 to 0.43; 12 studies). Without support, pedometers had a small effect, and accelerometers were ineffective.

What are the implications?

The study suggests that staff setting up physical activity programmes for people with cardiometabolic disease might want to consider using pedometers as motivational tools, within a wider programme. Accelerometers seem less successful. Also, monitoring devices used without coaching or support from healthcare professionals do not work as well as those used within a programme.

Pedometers might be a relatively quick and cheap way to enhance a physical activity programme, but cannot replace such a programme on their own.
**Trichotillomania**

People with trichotillomania pull out hair from their scalp, eyebrows, and other areas of their body. For some, the condition is mild and manageable—no worse than the need some people feel to bite their nails. In others, the urge to pull out hair is overwhelming, leaving bald spots, and interfering with social and work activities. A systematic review of 24 trials reckons that behavioural therapy is the best option. Among pharmacological treatments, clomipramine, olanzapine, and N-acetylcysteine had some benefit, while selective serotonin reuptake inhibitors did not (Depress Anxiety doi:10.1002/da.23028).

**Kidney transplant outcomes**

Outcomes of renal transplants vary by age of the recipient, according to an analysis of Hospital Episode Statistics data from England. Young adults aged 14 to 23 lose their transplanted kidneys and require dialysis about 50% more often than transplant recipients in other age groups (Nephrol Dial Transplant doi:10.1093/ndt/gfaa059). Young adults also had a higher non-attendance rate for clinic appointments and more emergency admissions to hospital after transplantation. It’s likely that their poorer outcomes are linked to poor compliance with medication.

**Orexin antagonists**

Orexin is a brain neuropeptide involved in the regulation of sleep, wakefulness, and appetite. Low levels are implicated in the pathology of some forms of narcolepsy. Blockade of orexin signalling has the potential to induce sleep and might be an alternative to benzodiazepines and Z drugs. Daridorexant, an orexin receptor antagonist with the right sort of pharmacokinetics, gave promising results in both polysomnography and subjective sleep measures in a phase II trial (Neurology doi:10.1212/WNL.0000000000009475). However, adverse effects included fatigue, cold-like symptoms, gait disturbance, and headache.

**Aspirin doesn’t prevent depression**

The ASPREE (Aspirin in Reducing Events in the Elderly) trial was a large placebo-controlled randomised controlled trial in community living people over the age of 70 which took place in the US and Australia. A couple of years ago it reported no benefit from low dose aspirin (100 mg daily) as far as a primary endpoint of disability-free survival was concerned (N Engl J Med doi:10.1056/NEJMoa1803955). A secondary analysis of data from the same trial now finds that low dose aspirin has no useful effect in preventing depression (JAMA Psychiatry doi:10.1001/jamapsychiatry.2020.1214).

**Anti-inflammatory diets**

An anti-inflammatory diet containing foods rich in n-3 fatty acids, fibre, antioxidants, and probiotics failed to produce improvement in people with rheumatoid arthritis in a 10 week Swedish trial. Disease activity scores (a composite score that included a count of tender and swollen joints, erythrocyte sedimentation rate or C reactive protein, and a visual analogue scale of global health) were no lower while patients were on the anti-inflammatory diet than while they were eating a control diet similar to a typical Swedish diet (Am J Clin Nutr doi:10.1093/ajcn/nuaa019).

**Wittenoom**

Mining and milling of crocidolite asbestos in the town of Wittenoom in Western Australia ceased in 1966, but the legacy of malignant mesothelioma, lung cancer, and asbestosis continues. The first case of malignant mesothelioma was diagnosed in 1960 and since then 373 cases have emerged in former asbestos workers and 158 cases in people who lived in the town. Half the cases among the ex-residents occurred in people who were children when they were living in Wittenoom. There’s a compelling account of the history of this industrial disaster in the International Journal of Epidemiology (doi:10.1093/ije/dyz204).

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**MINERV A**

**Aggressive multiple sclerosis**

A small proportion of people who develop multiple sclerosis experience a rapid progression of their disease and become severely disabled within a few years. A bayesian analysis of an international database attempted to identify predictors of this aggressive form of multiple sclerosis (Brain doi:10.1093/brain/awaa081). The three strongest predictive factors were age 35 or older at symptom onset, rapid progression of disability in the first year, and the presence of pyramidal signs. The findings were validated in a second group of patients from the Swedish Multiple Sclerosis Registry.

**Exercise and mortality**

Many studies have shown that people who are physically active are less likely to have diabetes, hypertension, or depression. Evidence also suggests that exercise protects against dementia, accidental falls, coronary heart disease, and some types of cancer.

So the finding from Taiwan that all-cause mortality is lower in older people with high levels of physical activity isn’t a surprise (Age Ageing doi:10.1093/ageing/afa172). The size of the reduction is substantial. Among 40,000 people followed for six years, mortality in people who took exercise several times a week was nearly 40% lower than in people who took no exercise.

**Kidney transplant outcomes**

Outcomes of renal transplants vary by age of the recipient, according to an analysis of Hospital Episode Statistics data from England. Young adults aged 14 to 23 lose their transplanted kidneys and require dialysis about 50% more often than transplant recipients in other age groups (Nephrol Dial Transplant doi:10.1093/ndt/gfaa059). Young adults also had a higher non-attendance rate for clinic appointments and more emergency admissions to hospital after transplantation. It’s likely that their poorer outcomes are linked to poor compliance with medication.

**Orexin antagonists**

Orexin is a brain neuropeptide involved in the regulation of sleep, wakefulness, and appetite. Low levels are implicated in the pathology of some forms of narcolepsy. Blockade of orexin signalling has the potential to induce sleep and might be an alternative to benzodiazepines and Z drugs. Daridorexant, an orexin receptor antagonist with the right sort of pharmacokinetics, gave promising results in both polysomnography and subjective sleep measures in a phase II trial (Neurology doi:10.1212/WNL.0000000000009475). However, adverse effects included fatigue, cold-like symptoms, gait disturbance, and headache.

**Aspirin doesn’t prevent depression**

The ASPREE (Aspirin in Reducing Events in the Elderly) trial was a large placebo-controlled randomised controlled trial in community living people over the age of 70 which took place in the US and Australia. A couple of years ago it reported no benefit from low dose aspirin (100 mg daily) as far as a primary endpoint of disability-free survival was concerned (N Engl J Med doi:10.1056/NEJMoa1803955). A secondary analysis of data from the same trial now finds that low dose aspirin has no useful effect in preventing depression (JAMA Psychiatry doi:10.1001/jamapsychiatry.2020.1214).