education

FROM THE JOURNALS Edited highlights of weekly research reviews on https://bit.ly/2PLtil8

Encouraging exercise for older people

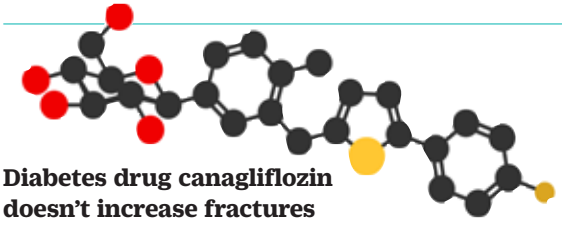
Exhorting older people to exercise has become standard advice for a wide range of conditions, but do we have evidence to support this? This meta-analysis of 40 long term randomised clinical trials including 21 868 participants found that long term exercise (a year or more), particularly moderate intensity multicomponent training with balance exercises, performed 2 to 3 times per week, appears to be safe and effective and reduces the risk of falling in older people. The effect is modest; to prevent one older person from falling or being injured in a fall, 20 and 27 individuals, respectively, would need to participate in a long term exercise intervention and 100 would need to take part to prevent a fracture. There was no overall reduction in mortality and exercise did not reduce the risk of multiple falls and hospitalisation.

JAMA Intern Med doi:10.1001/jamainternmed.2018.5406

Pain caused by knee osteoarthritis: what helps?

Older people come into GP surgeries with pain caused by knee osteoarthritis and GPs have so little to offer. So, I welcome this systematic review and meta-analysis of 33 pharmacological interventions which included 22 037 patients with knee osteoarthritis in 47 randomised clinical trials lasting at least 12 months. Unfortunately, the conclusion is that nothing works convincingly. The authors say: "there was uncertainty around the estimates of effect size for change in pain for all comparisons with placebo, including the two medications that were associated with improved pain (celecoxib and glucosamine sulfate)."

JAMA doi:10.1001/jama.2018.19319



Diabetes drug canagliflozin doesn't increase fractures

Canagliflozin is used in the treatment of diabetes. It has been approved by the National Institute for Health and Care Excellence as monotherapy if metformin is inappropriate, or as an add on to insulin or other diabetes drugs. But canagliflozin can affect calcium, phosphate, and vitamin D homeostasis and is associated with decreased bone mineral density. The question is whether taking the drug increases the risk of fractures? This cohort study of nearly 80 000 people has reassuring news. In middle aged patients with type 2 diabetes and relatively low risk of fracture (just over 2/1000 person years), canagliflozin was not associated with an increased risk of fractures compared with GLP-1 agonists.

Ann Intern Med doi:10.7326/M18-0567

Drink-driving—no easy solutions

Fatal road traffic incidents in the UK have fallen substantially (72% reduction from 1979-2017), but alcohol remains a major risk factor for deaths related to driving. Scotland lowered the legal blood alcohol concentration limit for drivers from 0.08 g/dL to 0·05 g/dL in 2014. This study looked at data on road traffic incidents and alcohol consumption in Scotland and in England and Wales—where the limit has not been lowered. It didn't find any reduction in road traffic incidents, but there was a small fall in alcohol sales. Just lowering the legal blood alcohol concentration limit may not be enough to prevent deaths. Other public health measures, such as better legal enforcement and social attitudinal shifts, may help.

Lancet doi:10.1016/S0140-6736(18)32850-2

Fixing secondary mitral regurgitation

Mitral regurgitation is often secondary to a diseased left ventricle rather than a primary problem with the mitral valve itself. Early surgery for severe primary mitral regurgitation is accepted practice, but it's unclear what to do in secondary mitral regurgitation. Two new studies come to different conclusions. One found that percutaneous mitral valve repair with medical therapy was no better than medical therapy alone in preventing death or hospital admission with heart failure at 1 year. A second study found the opposite. Transcatheter mitral valve repair resulted in a lower rate of hospitalisation for heart failure and lower all cause mortality within 24 months of follow-up than medical therapy alone.

N Engl J Med doi:10.1056/NEJMoa1805374

N Engl J Med doi:10.1056/NEJMoa1806640

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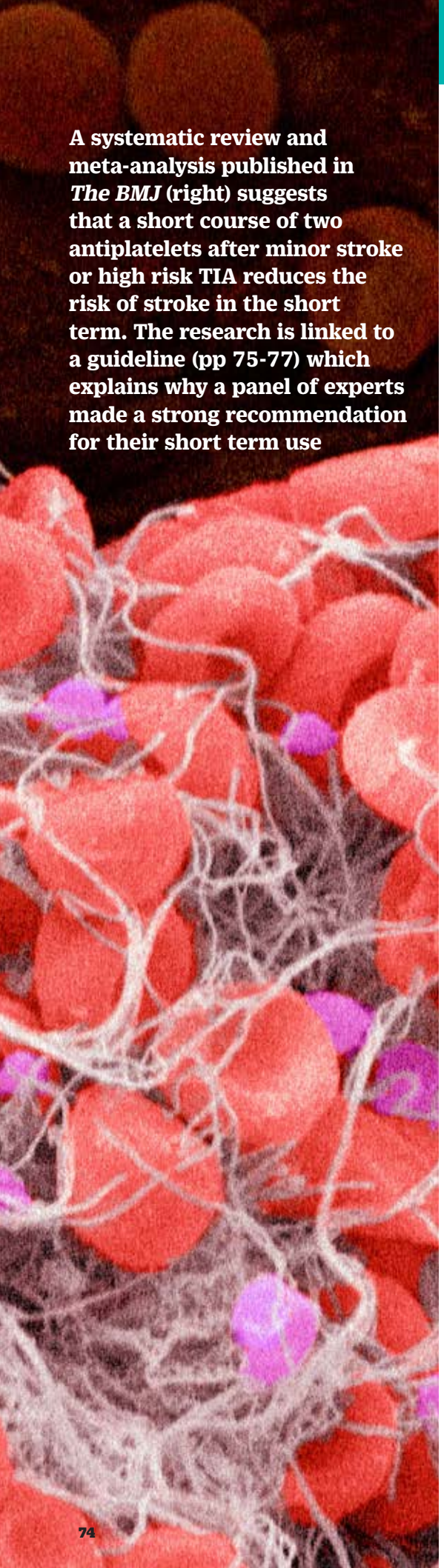


A systematic review and meta-analysis published in *The BMJ* (right) suggests that a short course of two antiplatelets after minor stroke or high risk TIA reduces the risk of stroke in the short term. The research is linked to a guideline (pp 75-77) which explains why a panel of experts made a strong recommendation for their short term use

ORIGINAL RESEARCH Systematic review and meta-analysis

Clopidogrel plus aspirin versus aspirin alone for acute minor ischaemic stroke or high risk transient ischaemic attack

Hao Q, Tampi M, O'Donnell M, Foroutan F, Siemieniuk RAC, Guyatt G

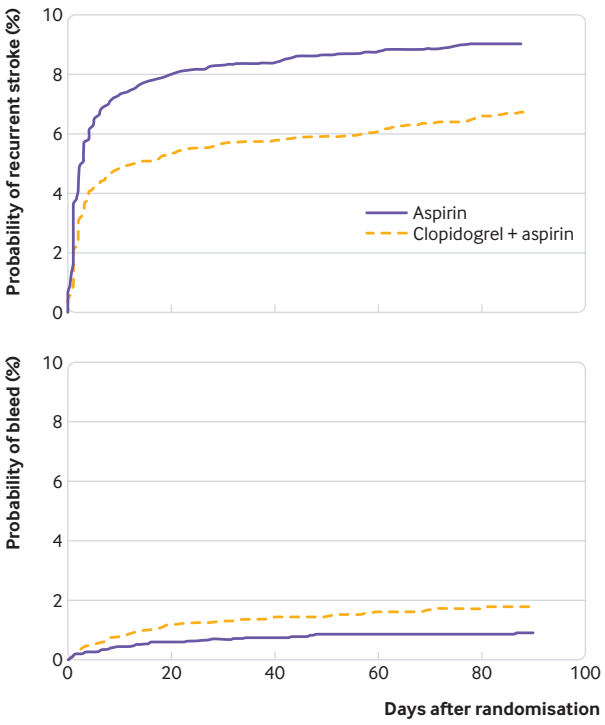
Cite this as: *BMJ* 2018;363:k5108
Find this at: http://dx.doi.org/10.1136/bmj.k5108

STUDY QUESTION How effective and safe is dual agent antiplatelet therapy combining clopidogrel and aspirin to prevent recurrent thrombotic and bleeding events compared with aspirin alone in patients with acute minor ischaemic stroke or transient ischaemic attack.

METHODS The authors carried out a systematic review and meta-analysis of randomised, placebo controlled trials on the effects of dual antiplatelet therapy using clopidogrel combined with aspirin compared with aspirin alone in patients with minor ischaemic stroke or high risk transient ischaemic attack. Three eligible trials involving 10 447 participants were identified. The main primary outcomes were recurrent thrombotic and bleeding events.

STUDY ANSWER AND LIMITATIONS Compared with aspirin alone, dual antiplatelet therapy with clopidogrel and aspirin commenced within 24 hours of symptom onset reduced the risk of non-fatal recurrent stroke (relative risk 0.70, 95% confidence interval 0.61 to 0.80, I^2=0%, absolute risk reduction 1.9%, high quality evidence), without apparent impact on all cause mortality (1.27, 0.73 to 2.23, I^2=0%, moderate quality evidence) but with a likely increase in moderate or severe extracranial bleeding (1.71, 0.92 to 3.20, I^2=32%, absolute risk increase 0.2%, moderate quality evidence). Most stroke events, and the separation in incidence curves between dual and single antiplatelet therapy arms, occurred within 10 days of randomisation; any benefit after 21 days is extremely unlikely. One limitation of this review was that it did not address other populations of potential interest, including those who have experienced low risk transient ischaemic attack and populations with moderate to severe ischaemic stroke.

WHAT THIS STUDY ADDS Pooled data showed a benefit of dual antiplatelet therapy started within 24 hours of presentation in reducing the absolute risk of recurrent stroke by about 2%. Stopping clopidogrel within 21 days, and possibly within 10 days, is likely to maintain the full benefits of dual antiplatelet therapy while minimising harms.



Pooled Kaplan-Meier time-to-event curves for stroke and bleeding

Competing interests, funding, and data sharing There are no relationships or activities that could appear to have influenced our review. This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors. No additional data are available.

RAPID RECOMMENDATIONS

Dual antiplatelet therapy for acute transient ischaemic attack and minor ischaemic stroke: a clinical practice guideline

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What is the role of dual antiplatelet therapy after high risk transient ischaemic attack or minor stroke? Specifically, does dual antiplatelet therapy with a combination of aspirin and clopidogrel lead to a greater reduction in recurrent stroke and death over the use of aspirin alone when given in the first 24 hours after a high risk transient ischaemic attack or minor ischaemic stroke? An expert panel produced a strong recommendation for initiating dual antiplatelet therapy within 24 hours of the onset of symptoms, and for continuing it for 10-21 days. Current practice is typically to use a single drug.

The recommendations in this clinical practice guideline are based on a linked systematic review[1] triggered by a randomised controlled trial published in the *New England Journal of Medicine* in August 2018.[2] This trial and the linked review found that dual antiplatelet therapy (DAPT) with clopidogrel and aspirin (acetylsalicylic acid) during the first 21 days after the index event reduced the risk of recurrent major ischaemic events compared with aspirin monotherapy.

Box 1 | Linked articles in this *BMJ* Rapid Recommendations cluster

- Hao Q, Tampi M, O'Donnell M, Foroutan F, Siemieniuk RAC, Guyatt G. Clopidogrel plus aspirin versus aspirin alone for acute minor ischaemic stroke or high risk transient ischaemic attack: systematic review and meta-analysis. *BMJ* 2018;363:k5108. doi:10.1136/bmj.k5108 (p 74)
- Review of all available randomised trials that assessed dual antiplatelet therapy (clopidogrel and aspirin) versus aspirin monotherapy after a high risk transient ischaemic attack or minor stroke

WHAT YOU NEED TO KNOW

CPD READING 0.5 HOURS

- People with high risk transient ischaemic attack or minor ischaemic stroke are at an increased risk of recurrent stroke and death
- Aspirin and clopidogrel decrease this risk, even more so when used in combination
- We make a strong recommendation for dual antiplatelet therapy (DAPT) with clopidogrel and aspirin to be started within 24 hours in patients who have had a high risk transient ischaemic attack or minor stroke
- We make a strong recommendation for DAPT to be continued for 10-21 days, at which point patients should continue with single antiplatelet therapy
- DAPT is not to be used for major stroke because of the increased risk of intracranial bleeding in these patients

Current practice

Single antiplatelet therapy with aspirin or clopidogrel is an effective intervention for both short and long term secondary prevention of stroke and transient ischaemic attack after an index event. Clinicians sometimes use alternatives of cilostazole or a combination of dipyridamole and aspirin, both referred to for this recommendation as single agent therapy.[6-9]

Aspirin and clopidogrel have synergistic action to inhibit platelet aggregation. So it is plausible that the two drugs together may provide better secondary prevention of stroke than one. However, they are not in widespread use for various reasons:

- They are not useful in the long term after stroke
- They are considered too risky after major stroke
- The balance of benefit and harm is uncertain for short term use after minor stroke or high risk transient ischaemic attack.

Table 1 on bmj.com outlines how international guidelines vary. A minority make a weak recommendation or suggestion for short term DAPT. The NICE guideline favours clopidogrel over others, and combined aspirin and dipyridamole over aspirin, whereas most guidelines consider all three as equivalent options.

The ABCD2 score and NIHSS score are typically used to help assess the severity of a transient ischaemic attack or stroke and can help to guide future care. Around one in 10 people go on to have a stroke after high risk transient ischaemic attack (box 2). The chance of a further stroke soon after minor stroke is less clear but is likely to be around 10-12% range.

Box 2 | Assessment of severity of transient ischaemic attack and minor stroke and subsequent risk of stroke

Transient ischaemic attack

- Severity assessed by ABCD2 score:
  - *Age*—1 point if ≥60 years
  - *Blood pressure*—1 point if ≥140/90 mm Hg
  - *Clinically*—1 point if speech disturbance only, 2 points if unilateral weakness
  - *Duration*—1 point if 10 minutes to 1 hour, 2 points if ≥1 hour
  - *Diabetes*—1 point if present
- Subsequent risk of stroke based on ABCD2 score:
  - Score 1-3 (low) = 1.2% at 7 days
  - Score 4-5 (moderate) = 5.9% at 7 days
  - Score 6-7 (high) = 11.7% at 7 days

Minor stroke

- Severity defined as NIHSS score ≤3
- Subsequent risk of stroke not well characterised but likely equal to that of a high risk transient ischaemic attack

NIHSS = National Institute of Health Stroke Scale.[14]

The evidence

The linked systematic review p 74[1] found three RCTs examining DAPT versus aspirin alone reporting on a total of 10 447 patients.[2-16] Figure 2 (see bmj.com) provides an overview of the RCTs and RCT participants. Overall, patients included in these trials were similar to those seen in everyday practice. Mean age varied from 62 to 68.1 years. In the FASTER trial 1/6 of the patients were older than 81 years; in CHANCE 1/4 of patients were over 72; and in POINT 1/4 were over 85. Just over half of participants (52.8-66.2%) were male.

Understanding the recommendation

Absolute benefits and harms

The infographic p 77 provides an overview of the recommendation, the benefits and harms, and our certainty in the evidence.

Overall, the panel was confident that DAPT, when started within 24 hours of symptom onset and used for 10-21 days:

- Reduces non-fatal recurrent stroke (ischaemic and haemorrhagic) in the first 90 days by 1.9%
- Reduces the incidence of moderate or severe functional disability by 1.4%
- Reduces the incidence of poor quality of life by 1.3%.

However, DAPT has little or no impact on:

- All-cause mortality
- Incidence of myocardial infarction or recurrent transient ischaemic attack.

DAPT also has some harms:

- A small (0.2%) increase in moderate to major extracranial bleeding events
- A small increase in the risk of minor extracranial bleeding events by 0.7%.

Duration of DAPT with clopidogrel and aspirin

The panel was confident that DAPT given for 10-21 days compared with 22-90 days results in:

- Absolute risk decrease of 0.4% in recurrent ischaemic stroke
- Absolute risk decrease of 0.3% in moderate to major bleeding events.

Values and preferences

The panel believed that most patients would consider a stroke considerably worse than a bleed and so would choose DAPT over single agent therapy. There was no published evidence to support this from patients considering DAPT, but this view is consistent with a systematic review of values and preferences in decision making for antithrombotic therapy.[18] In that scenario patients considered non-fatal stroke (thrombotic or haemorrhagic) to be two to three times worse than serious gastrointestinal bleeding.

The panel believed that all or almost all patients would choose 10-21 days of therapy rather than 22-90 days as shorter therapy is associated with equivalent benefit and less harm.

Practical issues

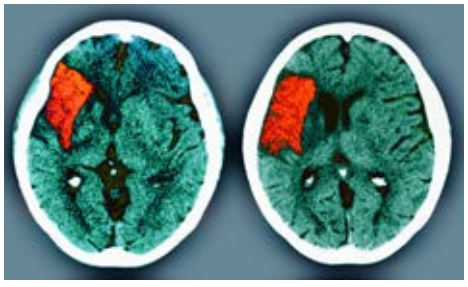
When should patients begin their DAPT?

If brain imaging is done within 24 hours of onset of symptoms, patients should begin DAPT as soon as the imaging results exclude intracranial haemorrhage or stroke-mimicking lesions. If a delay of 24 hours or more in imaging is suspected, then patients should begin DAPT as soon as a clinician makes a diagnosis of minor ischaemic stroke or transient ischaemic attack, be the clinician a primary care doctor or stroke neurologist, and be the setting inpatient or outpatient. Such patients should have imaging as soon as possible.

Dosing of antiplatelets

There were no head to head comparisons in the studies to give clear guidance on what loading and maintenance dose to offer. However, the following considerations may be useful:

- *For clopidogrel*—A loading dose of 300 mg and a dose of 75 mg thereafter seem reasonable because bleeding was marginally greater in the POINT trial,[2] which used a higher loading dose
- *For aspirin*—A dose between 75 mg and 345 mg seems reasonable. The results of the trials do not offer particular insights.



Competing interests: All authors have completed the *BMJ* Rapid Recommendations interests disclosure form, and a description of all disclosures is reported in appendix 1 on bmj.com. As with all *BMJ* Rapid Recommendations, the executive team and *The BMJ* judged that no panel member had any financial conflict of interest. Professional and academic interests are minimised as much as possible, while maintaining necessary expertise on the panel to make fully informed decisions.

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Find the full version with references at http://dx.doi.org/10.1136/bmj.k5130

RESEARCH, p 74

HOW PATIENTS WERE INVOLVED IN THE CREATION OF THIS ARTICLE

Three people with lived experience of stroke, and one person with lived experience as a carer for a patient with stroke, were full panel members.

We thank them for their time and valuable input.

EDUCATION INTO PRACTICE

- For prevention of recurrent stroke in patients with recent transient ischaemic attacks or minor stroke, which antiplatelet or combination of antiplatelets do you prescribe?
- How do you identify patients with transient ischaemic attacks as high risk or low risk?
- How do you classify stroke as minor or major?
- Based on this article, how do you think your personal practice might change?

HOW THIS RECOMMENDATION WAS CREATED

The scope of the recommendation and the patient-important outcomes were defined by an international guideline panel consisting of three patients with lived experience of stroke, one adult who cared for someone with a stroke, five stroke neurologists, one vascular surgeon, one health research methodologist, five general internists (four who are also methodologists), one nurse, one physiotherapist, and one critical care physician (who is also a methodologist). The panel then met online to discuss the evidence and to formulate recommendations. In our judgment no panel member had relevant financial conflicts of interest; intellectual and professional conflicts were minimised and transparently described.

The panel followed the *BMJ* Rapid Recommendations procedures for creating a trustworthy recommendation,[20 21] including using the GRADE approach to critically appraise the evidence and translate it to recommendations.[4] Following the GRADE based approach, recommendations can be strong or weak for or against a specific course of action.[23] The recommendations take a patient-centred perspective that de-emphasises public health, societal, and health payer points of view.

Recommendation 1: Dual *v* single antiplatelet therapy

See an interactive version of this graphic online
http://bit.ly/BMJrrDAPT

Population

Patients that have experienced:

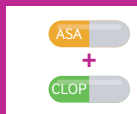
High risk transient ischaemic attack (TIA)
A score of 4 or more on the ABCD2 scale

or

Minor ischaemic stroke
A score of 3 or less on the National Institutes of Health Stroke Scale

Interventions compared

Dual antiplatelet therapy
Aspirin and clopidogrel



or

Single agent therapy
All identified trials compared with aspirin alone

Recommendation

Strong | Weak | Weak | Strong

We recommend dual antiplatelet therapy over single agent therapy. Start as soon as possible after index event.

Comparison of benefits and harms

Favours dual antiplatelets | No important difference | Favours single agent

Within 90 days	Events per 1000 people			Evidence quality
Non-fatal recurrent stroke	44	19 fewer	63	★★★★ High
All cause mortality	6	No important difference	5	★★★☆ Moderate
Functional disability	128	14 fewer	142	★★★☆ Moderate
Poor quality of life	55	13 fewer	68	★★★☆ Moderate
Recurrent TIA	36	No important difference	40	★★★☆ Moderate
Moderate or major bleeds	5	2 fewer	3	★★★☆ Moderate
Minor bleeds	13	7 fewer	6	★★★★ High

Key practical issues

Dual antiplatelets
Two different tablets taken once daily at same time

Single agent
A single aspirin tablet once daily

Both interventions
Aspirin tablet should be swallowed whole, but clopidogrel tablet can be crushed or split

Dosing

Although dosing varied slightly in the included trials, for clopidogrel, most physicians and patients would probably prefer a loading dose of 300 mg rather than a higher dose. For aspirin, a daily dose between 75 mg and 81 mg represents a reasonable choice.

Values and preferences

The panel believes almost all patients place a high value on avoiding a recurrent stroke and a lower value on avoiding moderate or major bleeding.

Recommendation 2: Duration of dual antiplatelet therapy

Interventions compared

Shorter duration
Dual antiplatelet therapy for 10-21 days after TIA or minor stroke

or

Longer duration
Dual antiplatelet therapy for 22-90 days after TIA or minor stroke

Recommendation

Strong | Weak | Weak | Strong

We recommend administering dual antiplatelet therapy for 10-21 days after the index event

Comparison of benefits and harms

Favours 10-21 days | No important difference | Favours 22-90 days

Within 90 days	Events per 1000 people			Evidence quality
Ischaemic stroke	10	No important difference	14	★★★☆ Moderate
Moderate or major bleeds	3	3 fewer	6	★★★★ High

Key practical issues

All people taking dual antiplatelets

Most patients should probably remain on single antiplatelet therapy indefinitely

Switch to anticoagulation instead of antiplatelet therapy when stroke management reveals an indication (such as atrial fibrillation or patent foramen ovale without plans for closure)

Herpes zoster infection

Phuc Le, Michael Rothberg

CPD READING 0.5 HOURS

LEARNING MODULE See http://learning.bmj.com for linked learning module

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Herpes zoster is caused by reactivation of a primary infection with varicella zoster virus.[1] After a primary infection, the virus lies dormant in the dorsal root or cranial nerve ganglia. Reactivation causes the typical dermatomal pain and vesicular rash (fig 1).

Varicella zoster (commonly known as chickenpox) and herpes zoster (commonly known as shingles) are caused by the same herpes virus. Varicella follows the initial infection and causes a generalised rash, whereas herpes zoster occurs after reactivation, years later, and symptoms are usually localised to a specific dermatome.

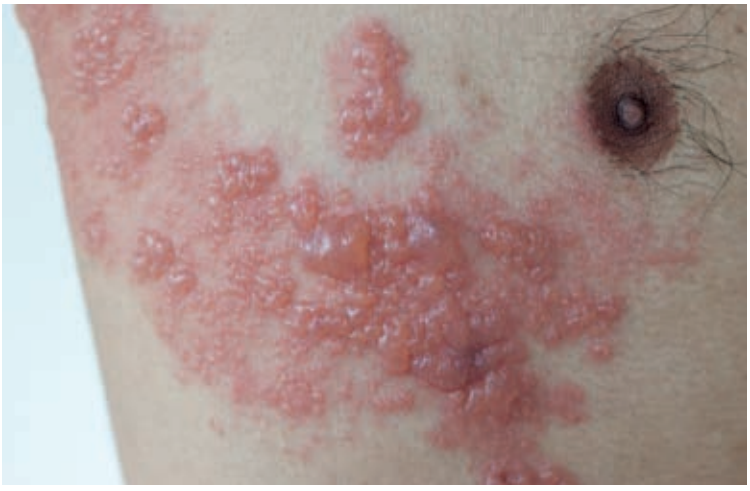

Fig 1 | Vesicular rash caused by herpes zoster

WHAT YOU NEED TO KNOW

- A typical history for herpes zoster might include neuropathic pain for around three days followed by a vesicular rash in a dermatomal distribution
- Consider treatment with an antiviral for those over 50, or with evidence of trigeminal nerve involvement (ideally within 72 hours of symptoms), and refer those who are immunocompromised and/or have eye involvement
- The rash takes around two weeks to resolve and can scar
- Post-herpetic neuralgia is the most common complication and is more likely in older people, where it can take six months or more to resolve
- In some areas a new recombinant zoster vaccine has been licensed; there is variation in whether the new or previous vaccine is recommended

HOW PATIENTS WERE INVOLVED IN THIS ARTICLE

Best Practice did not routinely ask for patient involvement at the time that the article was commissioned, and so no patients were involved

Who is at risk?

Over 90% of adults in the US have serological evidence of primary varicella zoster virus infection and are therefore at risk of reactivation.[5]

Risk of herpes zoster increases with age, and with any condition or treatment causing immunosuppression.[2 6]

Herpes zoster is not seasonal. Women have a higher risk than men,[4 7] and one study suggests that black people are less likely to develop herpes zoster than those of other ethnicities.[8]

Principal risk factors for developing herpes zoster are listed in box 1.

Box 1 | Risk factors

Strong

Age over 50[3]

HIV: herpes zoster incidence is up to 15 times higher in people infected with HIV than in those uninfected[9-11]

Other immunosuppression: eg, chronic use of corticosteroids,[12] lymphoproliferative malignancies,[13] or chemotherapy[6]

Weak

Gender: studies suggest women have a greater risk of developing herpes zoster than men[4 7]

White ethnicity: one study suggests that black people are substantially less likely than white people to develop herpes zoster[8]

How does herpes zoster typically present?

Herpes zoster is characterised by a prodromal period with burning pain for two to three days, then a vesicular eruption (fig 1) in the dermatomal distribution of the infected ganglion (fig 2). In immunocompetent people, the infection usually affects a single dermatome. In immunocompetent people, the infection usually affects a single dermatome. The most commonly affected dermatomes are T1 to L2.[20]

The pain usually lasts two to three days (more rarely up to a week) before the appearance of a rash. The pain can be constant or intermittent and is typically burning, stabbing, or throbbing. Pain can be severe enough to interfere with sleep and quality of life.[22] Persistent post-herpetic pain is a common complication.[23]

The rash is initially erythematous with a macular base and is followed rapidly by the appearance of

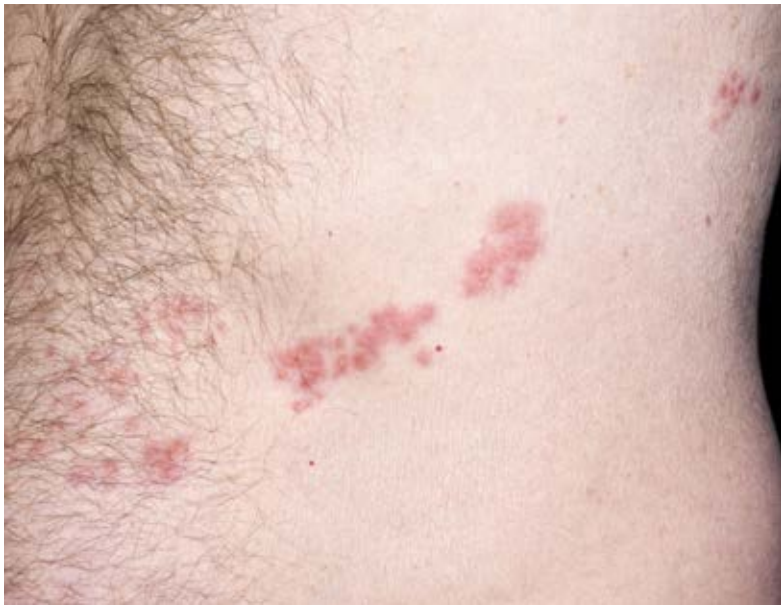

Fig 2 | Herpes zoster rash showing dermatomal distribution

Box 2 | Differential diagnoses

Rash	Pain	Herpes zoster ophthalmicus
Contact dermatitis: localised rash or irritation of the skin caused by contact with a foreign substance. The pain and the rash usually occur simultaneously	Cholecystitis: pain in the right upper quadrant of the abdomen	Ulcerative keratitis: pain and redness in the affected eye, with visual changes dependent on the ulcer location
Herpes simplex: grouped vesicles in a non-dermatomal pattern, often preceded by pruritis and pain. Oral and genital lesions most common	Acute appendicitis: pain in the right lower abdominal quadrant	Acute angle closure glaucoma: periorbital pain, blurred vision, and headache
	Renal calculi: severe colicky pain and inability to lie still; flank pain on examination	Trigeminal neuralgia: intense, stabbing, electric shock like pain in the areas of the face innervated by the trigeminal nerve

vesicles within one to two days. The lesions tend to be clustered along the branches of the cutaneous sensory nerve (fig 2).

The hallmark of a herpes zoster rash is that it does not cross the midline, whereas other rashes can. The dermatomal distribution is specific to herpes zoster.

The presence of a few skin lesions outside the primary or adjacent dermatome is not unusual.

Healing occurs over two to four weeks, and often results in scarring and permanent pigmentation in the affected area.

Approximately 20% of patients present with systemic symptoms such as fever, headache, malaise, or fatigue.[21]

Herpes zoster can almost always be diagnosed clinically. Confirmatory diagnostic tests may be necessary to differentiate genital herpes zoster from herpes simplex (polymerase chain reaction (PCR)) of samples from lesions), or to diagnose herpes zoster in patients with typical pain but no rash (blood PCR).

Possible differential diagnoses are given in box 2.

What are the complications?

The commonest complication of herpes zoster is post-herpetic neuralgia, the pain that persists long beyond cutaneous healing. Depending on the definition of post-herpetic neuralgia (the number of days of persistent pain after the onset of the rash), the risk ranges from 5% to 32%[2] and increases with patients' age. The duration of pain also varies widely and can extend for years, although it usually resolves within six months. People over 70 are at increased risk of more persistent pain.

Ocular complications are common and occur when the virus infects the ophthalmic division of the trigeminal nerve. Infection may cause conjunctivitis, keratitis, corneal ulceration, iridocyclitis, glaucoma, and blindness if untreated.[28-30]

Other complications include bacterial superinfections (1.1%), peripheral nerve palsies (1.8%), sensory loss (1.8%), encephalitis, and disseminated herpes zoster (1.7%).[31] Herpes zoster is rarely fatal in patients who are immunocompetent but can be life threatening in immunocompromised people.

Is it infectious?

Patients can transmit the virus through fluids from the lesions to people who have not had chickenpox, so direct body contact should be avoided. Covering lesions that are not usually covered by clothing may also decrease transmission.

When should I prescribe antivirals?

Herpes zoster is usually self limiting, but consider antivirals in all patients—especially those who have severe disease, are over 50, are immunocompromised, or have evidence of trigeminal nerve involvement.

Treatment is usually a seven day (or 10 day for patients with eye involvement) course of an oral antiviral drug such as aciclovir, famciclovir, and valaciclovir. Treatment is most effective when started within 72 hours of rash onset. Intravenous aciclovir is an option for patients who cannot tolerate oral treatments. Topical antivirals are not recommended. Treatment aims to reduce viral replication, stop the formation of new lesions, manage pain, prevent ocular complications, and reduce the risk of post-herpetic neuralgia.

Advise patients to keep the rash clean and dry to reduce the risk of bacterial superinfection. Patients should also avoid topical antibiotics, or dressings with adhesive that may cause irritation and may delay healing of the rash.

Which antiviral to prescribe?

Famciclovir, valaciclovir, and aciclovir have been shown to be superior to placebo in reducing the amount of time to complete cessation of pain.[32-35]

Studies report no differences between famciclovir and valaciclovir on cutaneous and pain end points.[36]

The treatment of herpes zoster during pregnancy is the same as for any other patient with the condition. Among antivirals, aciclovir has been the most extensively studied among pregnant women and is most commonly used.

Who requires referral?

People who are immunocompromised

Herpes zoster is common and often more complicated in immunocompromised people, so refer such patients to secondary care. The main objective of treatment is to reduce the incidence of cutaneous and visceral dissemination that can lead to life threatening complications. Immunocompromised patients require prompt antiviral therapy within one week of rash onset or at any time before full crusting of lesions. Treat localised disease with oral valaciclovir, famciclovir, or aciclovir, with close outpatient follow-up. Reserve intravenous aciclovir for patients with disseminated infection, ophthalmic involvement, severe immunosuppression, or the inability to take oral medications.

People with eye involvement (herpes zoster ophthalmicus)

Patients with eye manifestations require prompt referral to an ophthalmologist. Begin antiviral treatment as soon as possible, and before referral.[21] Give aciclovir, famciclovir, or valaciclovir for seven to 10 days, started preferably within 72 hours of rash onset. Supply lubricating eye ointment to patients with an impaired blinking reflex to prevent damage to the corneal epithelium. Other treatments include analgesia, antibiotic ophthalmic ointment to protect the ocular surface, and topical corticosteroids.

How should I approach analgesia?

Acute herpetic pain

For mild pain, analgesics such as paracetamol and ibuprofen are appropriate. For severe pain, opioid analgesics are an option. Topically administered lidocaine and nerve blocks are also effective.[28-38] Lotions containing calamine may also be used on open lesions to reduce pain and pruritus.

Warn patients about the possibility of post-herpetic pain and offer advice on how to psychologically manage chronic pain (eg, with relaxation techniques and counselling). Referral to a pain management consultant is indicated if the pain interferes with daily living.

Post-herpetic pain

Treat mild to moderate pain with non-steroidal anti-inflammatory drugs or paracetamol, alone or in combination with a weak opioid analgesic such as codeine or tramadol.[39-43] Topical capsaicin can also provide pain relief.[44-47] Patients with moderate to severe pain can be treated in the short term with a stronger opioid analgesic such as oxycodone or morphine. Where these treatments are ineffective, offer a tricyclic antidepressant such as amitriptyline[48] or an anticonvulsant such as gabapentin or pregabalin.[49-51] A meta-analysis showed no difference in pain relief between gabapentin and tricyclic antidepressants.[52] For those intolerant of opioids, one or a combination of anticonvulsants, tricyclic antidepressants, or corticosteroids are appropriate.

What are the latest vaccine recommendations?

Two vaccines are licensed for the prevention of herpes zoster and post-herpetic neuralgia in older adults: Zostavax, a live attenuated vaccine, and Shingrix, a recombinant subunit vaccine. Shingrix was approved in the US in 2017 and in Europe in January 2018.

Zostavax is still recommended in the UK for adults aged 70-79; however, the US Advisory Committee on Immunization Practices (ACIP) updated its guidance in January 2018 and now recommends Shingrix for adults aged 50 or older.[53] The latest guidelines are outlined on bmj.com.

What's the difference between Zostavax and Shingrix?

Zostavax is a lyophilised or freeze dried preparation of live, attenuated varicella zoster virus. The vaccine is given as a single subcutaneous dose and can reduce the risk of herpes zoster by 51%, post-herpetic neuralgia by 67%, and the overall burden of illness by 61%.[31]

This live vaccine is contraindicated in severely immunosuppressed people, pregnant women, and children.

Zostavax becomes less effective with increasing age, and efficacy wanes completely approximately 10 years after vaccination.[55]

Shingrix is a recombinant subunit vaccine containing the AS01B adjuvant system and glycoprotein E antigen from the varicella zoster virus. Shingrix requires two intramuscular doses 2 to 6 months apart, and has a substantially higher efficacy than Zostavax, reducing risk of herpes zoster infection by 97%[56 57] (mean duration of follow-up was 3.2 years).

Early studies suggest a single dose does not produce a robust immune response,[58] so attendance for both doses is important.

Unlike Zostavax, the efficacy of Shingrix is high even for patients over 70. Protection declines slightly four years after vaccination[59] but longer term efficacy is unknown.

Shingrix causes more reactions at the injection site than Zostavax.[57] Grade 3 systemic vaccine reactions, defined as symptoms that prevent normal everyday activities, are more frequent after the second dose than after the first.[56] Shingrix is safe and effective in patients previously vaccinated with Zostavax.[60] It can be safely given at the same time as the influenza vaccine.[61]

Competing interests PL has read and understood the BMJ policy on declaration of interests and declares the following interests: none. Since writing this module MR has done a single consultancy on herpes zoster vaccines for Health Advances. A *BMJ* editor chose which parts of the module to include in this adaptation. MR approved the final content.

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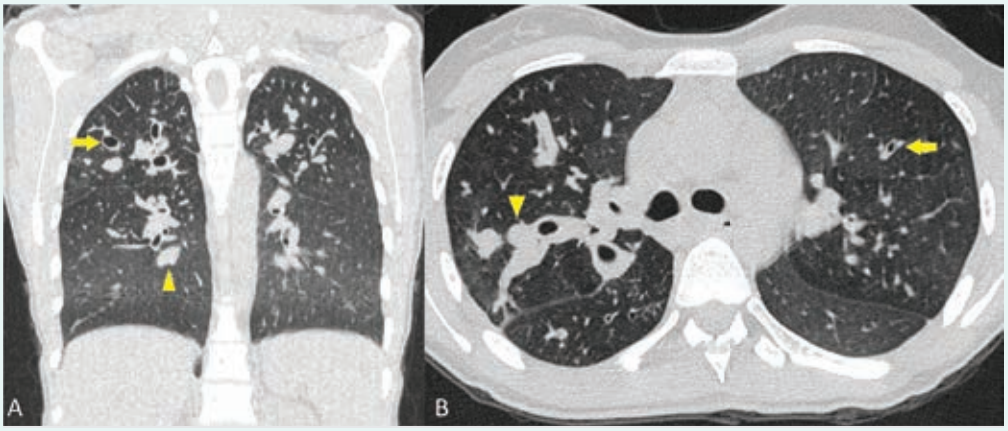
Find the full version with references at http://dx.doi.org/10.1136/bmj.k5095

EDUCATION INTO PRACTICE

- What information do you share with patients about what to expect with herpes zoster infection? Does this article offer you ideas on additional information to share?
- Does your organisation routinely offer older adults vaccination in line with local or national policies?
- What might you do differently for a patient with herpes zoster who is immunocompromised?

SPOT DIAGNOSIS **A young woman with upper lobe predominant bronchiectasis**

A 26 year old woman presented with a 10 year history of recurrent lower respiratory tract infections, productive cough, progressive dyspnoea on exertion, and difficulty gaining weight. She had no history of loose or frequent bowel movements, or abdominal pain, and did not smoke. She had not been in contact with any sources of tuberculosis and had no family members with chronic pulmonary conditions. Her body mass index was 18.9 kg/m^2, lung sounds were clear, and there was no evidence of nail clubbing. Chest radiography and computed tomography revealed upper lobe predominant bronchiectasis (figure, arrows) and airways with mucoid impaction (figure, arrowheads). Test results were normal for immunoglobulin studies, sweat chloride, faecal pancreatic elastase, and aspergillus antibodies. Sputum cultures grew oxacillin susceptible *Staphylococcus aureus*.



Non-contrast computed tomography scan of the chest in coronal (A) and transverse (B) planes. The lung window shows multiple bilateral dilated bronchi with a signet ring sign (arrows) and airways with mucoid impaction (arrowheads) with a mid to upper lung zone predominance

What is the most likely diagnosis?

Submitted by Leonard E Riley and Anupa P Nadkarni

Patient consent obtained.

Cite this as: *BMJ* 2019;364:k5244

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MINERVA WELCOMES SUBMISSIONS

Minerva pictures are cases which offer an educational message, and are of interest to a general medical audience (see p 82). Please submit as "Minerva" via our online editorial office (see bmj.com) and follow our advice on submitting images. Please provide two or three sentences (no more than 100 words) explaining the picture, and send us the signed consent to publication from the patient. We require written consent from every patient, parent, or next of kin, regardless of whether the patient can be identified or not from the picture. For more information see http://www.bmj.com/about-bmj/resources-authors/article-types

answers

For extra material, including patient outcome, go to bmj.com/endgames

SPOT DIAGNOSIS

A young woman with upper lobe predominant bronchiectasis

Upper lobe predominant bronchiectasis due to cystic fibrosis.

Bronchiectasis is the permanent dilatation of bronchi. Features of bronchiectasis on computed tomography imaging include bronchi extending to within 1 cm of the pleura, lack of airway tapering, and bronchi that appear larger than their adjacent artery (the signet ring sign) (figure).

Upper lobe predominant bronchiectasis can be seen in cystic fibrosis, allergic bronchopulmonary aspergillosis, tuberculosis, sarcoidosis, and post-radiation scarring. Other diseases that manifest bronchiectasis in early adulthood include post-infectious conditions, hypogammaglobulinaemia, ciliary dysfunction disorders, foreign body aspiration, and endobronchial malignancy.

In cystic fibrosis, a cycle of infection (commonly with *Staphylococcus aureus* and *Pseudomonas aeruginosa*), inflammation, and enzymatic/lytic enzyme release leads to bronchial destruction and eventual irreversible dilatation.

Cystic fibrosis is reported to occur one in 3200 births of white ethnicity and one in 15 000 of black ethnicity in the US.

Approximately 7% of patients with cystic fibrosis are ≥18 years at the time of diagnosis.

LEARNING POINT

Consider serum genetic testing to rule out cystic fibrosis in patients with symptoms and signs of cystic fibrosis in at least one organ system and a normal or borderline sweat chloride test.

PATIENT OUTCOME

Genetic testing revealed less common mutations (I507del and D1152H) of the CFTR gene, and a diagnosis of cystic fibrosis was reached.

CPD READING

0.5 HOURS

You can record CPD points for reading any article. We suggest half an hour to read and reflect on each.

LEARNING MODULE

Articles with a "learning module" logo have a linked BMJ Learning module at http://learning.bmj.com.

A sparkling cataract

Ophthalmoscope and slit lamp examination of a 73 year old man with progressive vision loss in his left eye showed an age related cataract and "sparkling" crystals in the lens (figure)

Sparkling cataract opacities (also known as Christmas tree cataracts) have been described as "glittering," "multicoloured," and "of polychromic lustre." Proposed causes include defective lens metabolism, cholesterol formation, cystine accumulations, and light diffraction from fused cell membranes.

Prognosis is the same as for other types of cataracts. However, a sparkling cataract may indicate the presence of associated metabolic conditions—for example, myotonic dystrophy, chronic liver disease, and renal dysfunction. This patient had a history of chronic hepatic cirrhosis caused by schistosomiasis and left renal atrophy.

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Patient consent obtained.

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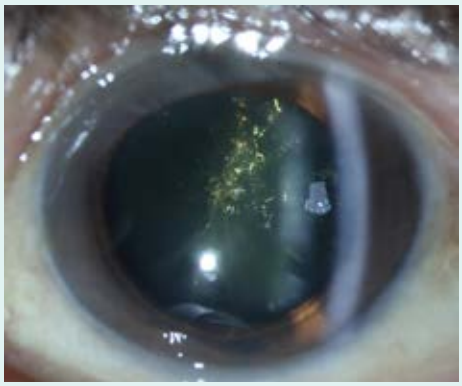

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Physical activity in children

As children get older, they gradually become less active. This is the finding from a longitudinal study of children in a European birth cohort that used accelerometer armbands to measure daily activity (*Paediatrics*). Between the ages of 6 and 11, the amount of time children spent in physical activity each day decreased by more than an hour. This decrease was mirrored by an increase in sedentary behaviour. Children with the highest body mass index were the least active.

Lignocaine

Although lignocaine is a safe and effective topical anaesthetic, subcutaneous injection sometimes causes uncomfortable burning sensations. A randomised trial finds that the discomfort can be diminished by dripping a couple of millilitres of lignocaine on the skin before the injection (*Chest*). The investigators invoke the gate theory of pain to explain why it works. The cold wet skin stimulus closes a neuronal gate in the afferent sensory pathway and reduces pain perception.

Prostate cancer

Inhibitors of the enzyme 5α-reductase prevent the conversion of testosterone to the more potent androgen dihydrotestosterone. They're an effective treatment for symptomatic benign prostatic hyperplasia and you'd expect that they would also protect against prostate cancer. A few years ago however, a large randomised controlled trial raised the possibility that they actually increased the risk of high grade tumours. Two further studies, one a long term follow-up of participants in the original trial, the other a population based cohort from Sweden, show that this was a false alarm (*JNCI*). Both report a protective effect of 5α-reductase inhibitors for all grades of prostate cancer.

Simpler than it seems

Complexity theory is often mentioned when discussing systems of healthcare, but it can be surprisingly difficult to pin down what the authors are actually talking about. An essay in the *Postgraduate Medical Journal* makes the paradoxical argument that the fundamentals of complexity are rather simple and already understood by most people (*Postgrad Med J*). If you can appreciate the law of unintended consequences, and have realised that the whole is sometimes greater than the sum of its parts, your grasp of the practical applications of complexity theory may well be as good as that of people who use terms such as linear thinking, emergent properties, and self-similarities.

Lymphopaenia

Neutropaenia increases risk of infection and it looks as if lymphopaenia does too. Among nearly100 000 participants in the Copenhagen General Population study who were followed up for a median of six years, rates of hospitalisation because of infection and infection related deaths were roughly 50% higher in people with lymphopaenia at the start of the study (*PLoS Med*). However, the investigators warn that the observational nature of the study design means that it can't address questions of causality. Minerva thinks that this is taking caution too far. If observational studies can't tell us anything about causation, there's no point in doing them.

Cite this as: *BMJ* 2019;364:l3