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Tom Nolan's research reviews—1 September 2022

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Remote ischaemic conditioning—an unlikely treatment for acute ischaemic stroke

JAMA reports a promising new treatment for acute ischaemic stroke that falls in the categories of "I would never have thought that might work" and "don't try this at home." Remote ischaemic conditioning (RIC) involves "brief, reversible episodes of ischaemia and reperfusion in one vascular bed to activate ischaemia tolerance in remote tissues and organs." In practice, this means inflating a blood pressure cuff on both arms to 200 mm Hg for five minutes, deflating for five minutes, and repeating this cycle four more times, and doing the whole thing again twice a day for two weeks. The largest randomised trial of RIC to date recruited adults with acute moderate ischaemic stroke who had not received thrombolysis or endovascular therapy. The primary endpoint—excellent neurological function after 90 days—was seen slightly more in those receiving RIC (67.4% versus 62% of controls, odds ratio 1.27, P=0.02), but the findings from this open label study need to be replicated before RIC can be said to be an effective treatment for acute ischaemic stroke (*JAMA* doi: doi:10.1001/jama.2022.13123).

Will LAAO ever be more than an appendage to atrial fibrillation guidelines?

Using minimally invasive surgical techniques to occlude the clot-prone left atrial appendage in people with atrial fibrillation makes sense. However, left atrial appendage occlusion (LAAO) is included in NICE's list of "do not dos": do not offer it as an alternative to anticoagulation unless anticoagulation is contraindicated or not tolerated. A new virtual trial, which runs data from published studies through a mathematical model, explored the role of LAAO in people with high bleeding risk from anticoagulation. Unfortunately, the data used did not include patients on direct oral anticoagulants, which have largely replaced warfarin in the treatment of atrial fibrillation, meaning the conclusion that LAAO may be of most benefit to those with a high bleeding risk and low stroke risk is very much up for debate (*Ann Intern Med* doi:10.7326/M21-4653).

Letters to clinicians about cause of death

If GPs get a letter for every single outpatient follow-up appointment, why is there typically so little communication between clinicians after someone dies? In the US a randomised control trial in 2018 saw medical examiners send letters (including a safe prescribing injunction) to clinicians informing them when one of their patients had a fatal overdose of a controlled drug. They found reductions in overall, high dose, and new opioid prescriptions associated with the intervention compared with a control group. A new secondary analysis found that the letter led to a modest (3.7%) reduction in dispensing of 2 mg benzodiazepine pills one to four months after the letters were sent compared with the three months before. This doesn't seem like a big effect, but I'm struggling to think of a reason why clinicians shouldn't be informed when a patient dies in these circumstances (*JAMA Intern Med* doi:10.1001/jamainternmed.2022.3372).

More drugs to cross off the covid treatment list

What endpoints should be used to determine the efficacy of treatments for covid-19? In a new US based study, looking at whether metformin, ivermectin, or fluvoxamine might be effective as treatment for people at high risk of complications of covid-19, 2% of a cohort of 1323 people testing positive for covid-19 with obesity or overweight were admitted to hospital within two weeks and two people (0.2%) died. Given the small sample size, the researchers chose a composite primary endpoint of death, hospitalisation, emergency department visit, or hypoxaemia (home oxygen saturation reading of 93% or under). No difference was seen in this primary endpoint compared with controls for either of the three repurposed drugs, adding to the existing evidence that they shouldn't be prescribed as treatments for covid-19. But what about that composite endpoint? What is the sensitivity and clinical value of a low home oxygen saturation reading when over 20% of participants in all study arms reported hypoxaemia, yet so few required hospital admission? (*N Engl J Med* doi:10.1056/NEJMoa2201662).

Did adenovirus cause the spike in acute hepatitis in children?

Remember the reports last year about a mysterious increase in the number of children with acute hepatitis, linked simultaneously by the press to both covid-19 and social distancing? *NEJM* publishes two case series that aim to shed light on the true cause, one from Birmingham, England, and one from Birmingham, Alabama. At first glance, human adenovirus type 41 seems a likely culprit, being found in 27 of the 30 children who had molecular testing in the UK study and all nine of the children in the US case series. But a linked editorial calls for more caution: no evidence has been seen of hepatocellular adenoviral infection on histological examinations in these cases: might the virus activity be an immunological response leading to acute hepatitis, or could adenovirus even be an "innocent bystander?" Better epidemiological data and registries of clinical studies are needed, it argues (*NEJM* doi:10.1056/NEJMoa2206704; 10.1056/NEJMoa2206294).

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