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Tom Nolan's research reviews—20 October 2022

Tom Nolan *clinical editor; sessional GP, Surrey*

The first RCT on colonoscopy screening

Until now, recommendations supporting colonoscopy for colorectal cancer screening have been based on cohort studies. Now we have a randomised control trial—the results of which have caused quite a stir. The participants, aged 55-64 years, who received an invitation for colorectal cancer screening had an 18% lower 10 year risk of developing colorectal cancer compared with controls, but there was no significant effect on the risk of death from colorectal cancer. The per-protocol analysis is more optimistic, but controversial due to the risk of bias: for the 42% of people invited for colonoscopy who actually had one, the risk of colorectal cancer reduced from 1.22% to 0.84% over 10 years (a 31% reduction), and their risk of death from colorectal cancer reduced from 0.3% to 0.15% (a 50% reduction).

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Sigmoidoscopy gets a look in

To remind us that there have been several randomised controlled trials (RCTs) of sigmoidoscopy screening for colorectal cancer, here is a pooled analysis of four RCTs, with no per-protocol analysis and a follow-up of 15 years. Among the more than 200 000 study participants across four countries there was a reduction in colorectal cancer incidence and colorectal cancer mortality (by 21% and 20% respectively) and a small reduction in all-cause mortality (14.3 deaths per 100 person years in the screening group versus 14.6 in the usual care group, a 2% reduction (P=0.016)).

How either of these studies should impact policy—particularly in the UK, where the NHS has chosen faecal immunochemical test (FIT) testing—I'm not sure. Perhaps trials comparing the three main options for screening are now needed?

Ann Intern Med doi:10.7326/M22-0835

Cardiovascular screening finds people to treat but no survival benefit

Moving on to cardiovascular screening, in Denmark 46 611 men aged 65-74 years were randomised 1:2 to either be invited for cardiovascular screening (including a non-contrast electrocardiography-gated computed tomography to calculate a coronary-artery calcium score, ankle-brachial blood pressure index, and blood tests) or ignored. After a median follow-up of 5.6 years, a total of 2106 men (12.6%) in the invited group and 3915 men (13.1%) in the control group had died. That gave a hazard ratio of 0.95, with a 95% confidence interval of 0.9 to 1.0 (P=0.06). So, although the participants in the study who were offered screening aren't seeing a survival benefit yet, the number of positive test results and treatments subsequently initiated are quite something: from the 16 738 people invited to screening, 10 471 attended screening, 6381 of whom had a positive test, from which 4105 initiated a preventive treatment.

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Diabetes as a risk factor for cardiovascular events

As treatments improve, the risk of the "feared outcomes" (see last week's melanoma paper) from diseases may change. Diabetes has long been considered on a par with cardiovascular disease as a risk factor for cardiovascular events, but is this still the case with improvements in care, and earlier diagnosis? A research letter in *JAMA* reports on a retrospective, population based study of healthcare records in Canada that examined the association between diabetes and five year risk of cardiovascular events between 1994 and 2019. It found that the magnitude of the association has reduced: in 1994 diabetes was associated with a relative risk of cardiovascular events of 2.06, which had fallen to 1.58 in 2014.

JAMA doi:10.1001/jama.2022.14914

Antihypertensives won't give us the time of day

In 2010, the MAPEC study made a splash after it found that evening dosing of antihypertensives seemed to lead to better cardiovascular outcomes. After a sceptical reception from academics, who found the effect size to be implausible, the British Heart Foundation funded a randomised control trial that aimed to put the issue to bed. The Treatment In Morning versus Evening (TIME...oh, I get it) study, just published in the *Lancet*, found no difference in the primary endpoint of vascular death or hospital admission for non-fatal myocardial infarction or non-fatal stroke over a five year period between the more than 20 000 people allocated to either morning or evening dosing of antihypertensives. The authors conclude that patients "should be advised that they need not change their antihypertensive medication dosing time, but might choose to take their medication at a time that suits them best, because the timing makes no difference to cardiovascular outcomes."

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