The developed world is experiencing a rapid demographic transition towards an older population. As people age, they develop more chronic conditions, known as multimorbidity. This creates difficulties for primary care physicians in the management of such patients, since clinical guidelines are typically limited to specific disease areas. Patients may end up being prescribed multiple medications for each condition, leading to polypharmacy. Sometimes this is necessary, but when multiple medications are prescribed inappropriately, individuals can be left at an increased risk of adverse events and hospitalisation.

One solution is to reduce the burden of medication through deprescribing. Deprescribing is defined as the process of withdrawal of an inappropriate medication, supervised by a healthcare professional, with the goal of managing inappropriate polypharmacy and improving outcomes. Cardiovascular medications such as antihypertensives, which are used for prevention rather than to alleviate symptoms or treat infection, are a common target for deprescribing. The evidence for prescribing antihypertensives in older people is limited to a few large clinical trials, which show benefit in terms of cardiovascular risk reduction. However, these trials failed to recruit frail patients with multimorbidity, who may be at greater risk of adverse events. Thus, in older patients with frailty and multimorbidity, it has been suggested that deprescribing of antihypertensives might be possible with little impact on the individual other than to reduce their risk of future drug harms.

Existing evidence for antihypertensive deprescribing
A recent Cochrane review found no evidence for an association between antihypertensive medication withdrawal in older people...
and mortality, myocardial infarction, stroke or hospitalisation. In total, just six trials enrolling a total of 1073 participants were identified in the review and follow-up was short (between four and 56 weeks). Blood pressure was increased by 10/4mmHg suggesting that longer follow-up may have revealed an increased risk of cardiovascular disease. The review found few data on side-effects, adverse events (including falls) or quality of life. Although the authors concluded that deprescribing may be possible without causing harm, the lack of data made it difficult to make any firm conclusions about the effect of deprescribing on clinical outcomes.

The OPTIMISE randomised controlled trial

The Optimising Treatment for Mild Systolic Hypertension in the Elderly (OPTIMISE) study was recently published in the *Journal of the American Medical Association* and examined the short-term safety and efficacy of antihypertensive deprescribing. The trial was limited to withdrawal of one antihypertensive medication, an intervention termed ‘medication reduction’. Patients were eligible if they were aged 80 years or older, with systolic blood pressure at baseline <150mmHg and prescribed two or more antihypertensive treatments for at least 12 months prior to enrolment. Patients with a history of heart failure, myocardial infarction/stroke in the preceding 12 months, secondary hypertension or lacking in capacity to consent were excluded from the trial.

Participants were randomised to either medication reduction or usual care. The choice of drug for withdrawal was made prior to randomisation by the primary care physician. The clinician was given a medication reduction algorithm (see Figure 1) to assist with this decision, which suggested that medications should be reduced if contraindications were present, or in reverse order of the NICE ‘Calcium-channel blocker + ACE inhibitor + Diuretic (C+A+D)’ approach to treating hypertension in patients aged 55 years or over. Physicians were encouraged to monitor patients following medication reduction, including by inviting them to a four-week safety follow-up visit.

Trial follow-up lasted for 12 weeks, and outcomes included between-group differences in blood pressure control (primary outcome), mean blood pressure, quality of life, frailty, side-effects, adverse events (post hoc outcome) and serious adverse events. The trial was designed to determine whether medication reduction was equivalent (or ‘non-inferior’) to usual care. The primary outcome was measured as a relative risk (RR), and an RR of close to 1.00 would mean blood pressure control was almost exactly the same in both groups. It was decided before the trial that equivalency could only be assumed if the 95% confidence interval (CI) around this RR did not fall below 0.90. If this was the case, it would suggest that for every 10 patients who have their medication reduced, nine would still have controlled blood pressure at 12-week follow-up.
Main findings of the OPTIMISE trial
A total of 569 participants were randomised in the trial, with a mean age of 85 years, 560 (98%) of whom were living with multimorbidity. Participants had mild frailty (mean electronic frailty index score of 0.14) and moderate cognitive impairment (Montreal Cognitive Assessment score of 24/30).
Overall, 229 (86.4%) participants in the medication reduction group and 236 (87.7%) in the usual care group had controlled blood pressure at follow-up (RR 0.98, 95% CI 0.92–1.05) (see Table 1). Since the lower 95% CI was greater than the 0.90 used to define equivalency, medication reduction could be assumed to be equivalent to usual care.
A total of 187 (66.3%) participants were still taking fewer antihypertensive medications at 12-week follow-up. Medication reduction was associated with a significant increase in blood pressure (3/2mmHg) but no differences in quality of life, frailty, side-effects or serious adverse events (see Table 1).
Post hoc analyses revealed an increase in (non-serious) adverse events such as increased blood pressure, chest pain, infections, ankle swelling, headache and back pain. Most were not thought to be related to the intervention and higher rates may have occurred because of the additional safety visit required for people in the intervention group, giving participants one additional opportunity to report adverse events, compared to the usual care group.

Clinical implications
In older patients with multimorbidity who have decided to reduce their antihypertensive medication, the findings of the OPTIMISE trial can be used to inform decisions about how to approach deprescribing. Medications should be reduced one at a time, beginning with those added most recently, reversing the NICE C+A+D approach for patients aged 55 years or older.10 Blood pressure should be carefully monitored at follow-up to identify those whose blood pressure increases above target, or in whom adverse events occur. For these patients, reintroduction of antihypertensive therapy should be considered. Beta-blockers should be first reduced in dose, prior to complete withdrawal, to avoid rebound tachycardia.
The OPTIMISE trial does not determine whether or not antihypertensive deprescribing should be attempted in older...
patients with multimorbidity. Follow-up was too short and the study was not powered to detect differences in clinical outcomes such as adverse cardiovascular events or death. A short study was necessary for ethical reasons and future large studies are now needed to determine the long-term clinical impact of antihypertensive deprescribing. Such trials should examine its effect on cardiovascular disease outcomes, serious adverse events and hospitalisation, as well as patient-focused outcomes such as cognitive and physical function and quality of life.

It is likely that those at the highest risk of medication harms are most likely to benefit from antihypertensive deprescribing. However, at present it is difficult to determine which individuals are at higher risk. Until this is established, along with the long-term outcomes from randomised controlled trials, antihypertensive deprescribing should not be widely practiced in routine primary care.

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