Antihypertensive Treatment Evaluation in Multimorbidity and Polypharmacy Trial (ATEMPT): A decentralised open-label pilot trial

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Summary

Background

Older patients with multimorbidity and polypharmacy have been underrepresented in previous clinical trials. This study aimed to assess the effect of different intensities of antihypertensive treatment on changes in blood pressure (BP), major safety outcomes and patient-reported outcomes in a home-based decentralised trial.

Methods

ATEMPT was a home-based, two-armed, parallel-group, open-label randomised controlled clinical pilot trial. Individuals aged 65 years or over with multimorbidity (three or more chronic conditions) or polypharmacy (five or more types of medications) with a systolic BP of 115-165 mmHg were recruited. Participants were randomised to up to two more classes of antihypertensive medications versus up to two fewer. The primary outcome of the trial was change in home-measured BP and prescribed antihypertensive drugs. Secondary outcomes included cognitive function, frailty status and health-related quality of life measured with validated instruments.

Findings

The changes in antihypertensive medications corresponded to an 11 mmHg difference in systolic BP between the two groups 122 mmHg (10.5) vs 133 mmHg (15.3), respectively (p=0.002). There was no meaningful difference in cognitive function, health-related quality of life, frailty score or the occurrence of serious adverse events between treatment arms. The remote trial design achieved a high satisfaction rate among participants, with 96.3% (222/230) of participants expressing their willingness to participate in a trial using a similar approach again.

Interpretation

Intensive antihypertensive therapy substantially reduced BP levels in older adults less represented in trials, with no increase in the risk of serious adverse events or measurable effects on participants' quality of life, cognitive function, medication adherence, and frailty status. The results of this trial will inform a larger clinical trial focussing on major cardiovascular events, safety, physical functioning and cognitive function that is in the planning stages at present. Additionally, these results underscore the efficiency of decentralised study designs, which might be of broader interest.

Funding

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Research in context

Evidence before this study

We conducted a literature search on PubMed for trials published between January 1, 1966, and August 2023. Search terms included hypertension, antihypertensives, multimorbidity, polypharmacy, frailty and randomised controlled trials. Clinical trials highlight the effectiveness of blood pressure reduction in reducing cardiovascular risks overall, but uncertainties persist, particularly in older individuals with multiple health issues and medications and normal or mildly elevated blood pressure. This uncertainty is reflected in inconsistent recommendations for systolic blood pressure thresholds. The limitation of evidence in this area arises from challenges in recruiting older, multimorbid patients for clinical trials due to strict inclusion criteria, logistical issues, and concerns about short-term side effects.

Added value of this study

The ATEMPT trial successfully achieved a substantial reduction in systolic blood pressure, to 122 mmHg in the intervention arm. With an average one antihypertensive drug difference between arms, a difference of 11 mmHg in systolic blood pressure was achieved. This intervention did not significantly affect participants' quality of life, cognitive function, medication adherence, or frailty status, though there were reports of increased dizziness and fatigue with more antihypertensive drugs. The trial demonstrated the feasibility and acceptability of remote medication delivery. These results will inform a larger clinical trial focusing on major cardiovascular events, safety, physical functioning, and cognitive function.

Implications of all the available evidence

The decentralised trial design proved effective in engaging older individuals with multiple health conditions and medication regimens, allowing them to participate from the comfort of their homes. The intervention successfully achieved a significant decrease in systolic blood pressure without adversely affecting the participants' quality of life or cognitive function. This provides some reassurance about intensive blood pressure lowering in this underrepresented patient group and informs the design of future studies.

Introduction

Hypertension is one of the main risk factors for premature death and disability globally, and it is affecting over a billion individuals, resulting in an estimated 9.4 million deaths per year.[1] Numerous clinical trials have demonstrated that pharmacological blood pressure (BP) reduction effectively reduces the risk of cardiovascular events in at-risk populations and that the relative risk reduction afforded by treatment is proportional to the intensity of BP reduction.[2] However, due to restrictions in participant selection in most clinical trials, the importance of BP-lowering treatment in specific patient populations remains uncertain. One growing patient population in whom there is uncertainty about treatment effects is older patients with multimorbidity and polypharmacy, particularly when their BP is not highly elevated.[3,4] This uncertainty is also mirrored in inconsistent recommendations about the systolic BP threshold in older patients by clinical practice guidelines.[5–7] While a systolic BP target of less than 130 mmHg is favoured for older and multimorbid patients by the American College of Cardiology /American Heart Association guideline,[5] European guidelines recommend a range between 130 and 139 mmHg,[6] and the National Institute for Health and Care Excellence in the United Kingdom suggests maintaining the treatment target between 140 to 159 mmHg.[7]

One major cause for the significant gap in evidence of BP treatment effects and optimal target threshold is the challenge of recruiting a sufficient number of older and multimorbid patients into clinical trials.[8] A systematic review that evaluated phase III clinical trials between 1965 and 2015 showed that patients were either explicitly excluded by age or did not pass the eligibility criteria due to the presence of several comorbidities, concomitant medications or cardiac conditions.[8] Apart from applying restrictive inclusion criteria, another challenge is to overcome the burdensome trial procedures which often require regular travel to study clinics that may lead to logistical difficulties for older and multimorbid patients.[9] With regards to BP-lowering treatment, another difficulty is the concern about short-term side effects of the treatment, which episodic clinic assessments might not be able to capture appropriately. This concern is of particular importance in older and multimorbid patients, given their altered drug metabolism, which could lead to an exaggerated and fluctuating response to treatment.[10]

A potential way to overcome the challenges of participant recruitment, monitoring and follow-up in the growing population of older and multimorbid patients is to design and conduct patient-centred home-based trials. The promise of this strategy was recently shown in a trial of multimorbid patients with heart failure who despite little or no experience in using digital technologies could be supported

to use a tablet computer with a bespoke study application at home.[11,12] The remote communication system employed in the trial was found to achieve high acceptability and satisfaction rates among older patients with multimorbidity whilst reducing the burden of monitoring on participants and study staff.[12,13]

Thus, the Antihypertensive Treatment Evaluation in Multimorbidity and Polypharmacy Trial (ATEMPT) was set to test the effectiveness of a similar decentralised home-based approach with little direct physical contact between participants and the study team. We aimed to test the hypothesis that in older multimorbid patients with average BP readings, a substantial change in BP can be achieved remotely without detrimental effects on safety or tolerability.

Methods

Study design

ATEMPT was a decentralised single-centre, two-armed, parallel-group, open-label randomised controlled pilot trial. The trial was led by the University of Oxford, United Kingdom (UK). The trial was funded by the Oxford Martin School and the UK National Institute for Health Research Oxford Biomedical Research Centre (BRC). The funders had no role in the study design, data collection, analysis or publication. The trial is registered with ISRCTN (ISRCTN17647940) and ethics approval (reference number 20/NW/0344) was obtained prior to commencement. The trial was overseen by an independent Trial Steering Committee including lay members to guide the research agenda, advise on the plan of investigation, and monitor the execution of the project on behalf of the Sponsor and project funder. A Data Monitoring Committee (DMC) was responsible for monitoring the trial data and the continued safety of research participants, with permission to access unblinded comparative data during the trial. Safety reviews of already collected trial data by the DMC were conducted on the 12th of November 2021 and the 12th of September 2022. The final version of the trial protocol (version 3.0 issued on the 26th of April 2021) can be found in the supplementary material. There has been one approved amendment to the protocol and the amendment included changes to the trial team and Steering Committee members as well as updated trial team contact details **(Supplementary material, trial protocol).**

Participants

From December 2020 to December 2021, participants living in the Thames Valley area, UK, were recruited and screened for eligibility. The inclusion criteria focussed on patients aged 65 years or over

with multimorbidity (three or more underlying chronic conditions) or polypharmacy (five or more types of non-antihypertensive medications) with a systolic BP of 115-165 mmHg. Comorbid conditions were defined as long-term medical conditions for which patients received active medical treatment or follow-up throughout the trial. Further inclusion criteria were participants' willingness to monitor their BP at home and their or their carer's ability to use the web-based trial system. Patients with a history of admission to hospital with heart failure or known systolic heart failure, or self-reported orthostatic hypotension were excluded. Complete inclusion and exclusion criteria are provided in the trial protocol (**Supplementary material, trial protocol**). The ethnicity details of participants were not collected.

The entire study workflow, data and participant management as well as safety and clinical monitoring were implemented in a modular clinical trial management platform, Zeesta™ (www.zeesta.ai). Potentially eligible participants were identified via three main routes: search of national hospital discharge databases, patients registered with an online pharmacy, and targeted advertising on social media platforms. Potential participants were invited by mail or digitally to log into Zeesta's online personal participant portal to learn more about the study via an interactive participant information sheet including a video infographic, to self-screen their eligibility, and to provide e-consent. Participants unsure of or unwilling to use the online portal could nominate a friend or carer to assist them with accessing and using the website during the registration process and throughout study participation if required. Additionally, a free phone line and email were available if participants or their carers preferred to contact the study team directly for further information.

Run-in period

Screened and consented participants entered a run-in phase to assess full eligibility before randomisation. This involved a home visit to provide an upper arm cuff-based BP monitor (A&D model UA-651BLE or UA-767 Plus BT-Ci) unless participants wished to use their own validated device and to collect further information about participants' demographics, medical conditions and treatment. The baseline assessment also included the evaluation of participants' frailty status using the PRISMA-7 questionnaire,[14] quality of life index by EQ-5D-5L,[15] cognitive function assessment using T-MoCA,[16] and a medication adherence assessment. Participants were asked to measure their BP and pulse once a day during run-in (and once weekly afterwards) and to submit these via Zeesta's participant portal. The process of taking BP measurements was standardised by advising patients to measure their BP at the same time of the day and to rest for at least five minutes in a seated position before taking the measurement. A mean value of all day-time measurements over a week was automatically calculated

by Zeesta, and served as the baseline pre-randomisation home BP. To estimate clinic BP values for eligibility assessment, 5 mmHg was added to mean home BP values.[7]

During the baseline home visit, blood samples were taken to check participants' renal function and electrolytes. Further blood analyses were conducted after randomisation according to participants' treatment allocation and treatment regimen throughout the trial.

Randomisation and Interventions

A difference of two antihypertensive drugs between treatment arms was targeted, with an expected 10-mmHg difference in systolic BP.[17] Aiming for a fixed difference in intensity of BP-lowering treatment has the advantage that participants with a wide range of pre-randomisation BP and antihypertensive medication use could be included. This also obviated the need for a single BP target which would be difficult to achieve across all baseline BP groups, and enabled reliable testing of the study hypothesis.

Eligible participants were assigned to either more antihypertensive drugs or fewer antihypertensive drugs using the trial's electronic concealed randomisation system in Zeesta. This was based on a dynamic biased-coin minimisation algorithm using the categories of participant's age (≤80 years versus >80 years) and baseline clinic systolic BP (<130 mmHg, 130-140 mmHg and >140 mmHg). Once the imbalances of these factors were estimated as a score, the participant was allocated to the group with the lowest score using a probability greater than 0.75. This method was employed to dynamically minimize the imbalance between the groups. Once all relevant information had been collected, Zeesta triggered an alert to authorised central trial staff to perform the randomisation. A full audit trail of actions including the randomisation seed was recorded by Zeesta.

Depending on the number of antihypertensive medications and systolic BP at baseline, Zeesta then automatically divided participants in each randomised arm into three strata to guide the treatment implementation aiming for a minimum difference of two drug classes between randomised groups (Table 2, Supplementary Table 6, page 8). The trial management system restricted access to treatment allocation as per the protocol and according to user roles.

The selection of antihypertensive medications followed the recommended order of the European Society of Hypertension guidelines.[6] The antihypertensive agents were provided at no cost to participants and were directly delivered to their homes using the services provided by an online

pharmacy. Drugs were added at each assessment point every four weeks, after checking for known intolerances, drug interactions and contraindications. A maximum of one up-titration for each newly allocated drug with the aim of achieving half the daily recommended dose was targeted.[18,19] For those where deprescribing was recommended, one drug was reduced in dose or removed at each assessment point following the reverse order of guideline recommendations. Any antihypertensive agents prescribed for other compelling indications were not reduced or discontinued. Participants' GPs were kept informed about any treatment changes, either reduction or intensification, initiated by the trial team throughout the study and asked to update participants' repeat prescription lists.

Procedures

The trial did not involve routine clinic assessments and all communication, monitoring and management of participants by the trial team was conducted remotely, and, where necessary home visits by a trained clinician were arranged. To examine the medication changes, participants' BP values and treatment changes were reviewed remotely by a clinician and adjusted accordingly in four-weekly intervals. Participants were encouraged to report any changes in their well-being or adverse events at any point during the follow-up period via Zeesta's participant portal or directly to the trial team via a freephone line. In addition, medication changes were automatically retrieved from record changes held by the online pharmacy, which was electronically linked to Zeesta. Every three to six months, a phone call assessment by blinded trial personnel was conducted for further treatment review, completion of quality of life, medication adherence, cognitive function, and frailty questionnaires as well as for reporting of any adverse events.

Outcomes

The primary objective of this pilot study was to estimate the effectiveness of the intervention on change in BP and prescribed antihypertensive drugs. Secondary outcomes included the assessment of the acceptability and tolerability of the intervention, using patient-reported outcomes, and to rule out any major excess harms. Also, cognitive function, frailty status and health-related quality of life were measured with validated instruments. The trial also aimed to assess the feasibility of a planned large-scale trial. This included the identification and recruitment of participants, remote monitoring and follow-up procedures and evaluation of the resources needed for the pilot trial.

Occurrences of myocardial infarction, strokes or transient ischaemic attacks (TIA), heart failure or vascular procedures were investigated at each assessment point. Similarly, all serious adverse events (SAE) and adverse events of interest, events such as falls, fractures, dizziness, or confusion were

captured at each assessment point. Participants were further encouraged to report any other events which they felt might be related to any antihypertensive treatment changes via the participant portal. User experience and treatment adherence were also investigated. In a survey that was conducted at the end of the follow-up period, participants were asked about their experience with the decentralised trial involving minimal physical contact with the trial team. The survey responses were collected using a Likert scale using the following response options: 1 = very dissatisfied, 2 = dissatisfied, 3 = neither satisfied or dissatisfied, 4 = satisfied, and 5 = very satisfied. For each question, participants also had the option to provide additional feedback that was captured as free text.

Statistical analysis

Assuming a standard deviation (SD) of 20 mmHg in systolic BP, a total sample size of 200 patients was calculated to provide 80% power to detect a mean difference of 8 mmHg or more, and 90% power for a mean difference of 10 mmHg. Mean change in systolic BP from baseline to end of follow-up between the treatment arms was estimated using an independent sample T-test for each month. To plot the trajectory of systolic BP change and count of antihypertensives drug classes during follow-up time and between two treatment arms, a linear mixed effects modelling approach was utilised to take account of the irregularly spaced time points or data missingness at certain time points. The model included a random intercept and slope for time. The fixed effects included interaction of treatment and time and cubic effect of time, with an unstructured covariance structure of the model. For the secondary outcomes, descriptive statistics were computed using mean and median for normal distributed and skewed continuous outcomes, respectively, and counts and percentages for categorical outcomes. All analyses were conducted using R statistical software version 3.4.4 and IBM SPSS Statistics version 29.0.1.0.

To monitor safety aspects and the overall progress of the trial, interim analyses were conducted that were monitored by the DMC. Before each planned DMC meeting, an interim database lock was performed, and the trial statistician obtained blinded trial data for analysis. The preparation of the DMC reports was done to an agreed standard analysis and reporting format developed by the trial statistician with the support of the trial team and under the direction of the DMC. The reports were shared with the DMC members at least five days prior to scheduled meetings with a password-protected file. Operational bias was minimised by keeping trial statisticians blinded to participants' treatment allocation and by the oversight of independent DMC members.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between December 2020 and December 2021, 436 participants gave their consent for participation. Of these, 206 were ineligible and a total of 230 participants were randomised (126 vs 104 in more vs fewer antihypertensive arms, respectively) (**Figure 1**). Taking account of pre-randomisation systolic BP and the number of anti-hypertensive classes that could potentially get stopped, the randomised participants were further divided into three strata, aiming for a two-drug class difference in each stratum. 59% (136/230) of participants were allocated to stratum 1 (2 drug classes added vs no change), 33% (75/230) to stratum 2 (1 drug class added vs 1 drug class stopped), and 8% (19/230) to stratum 3 (no change vs 2 drug classes stopped).

The characteristics of study participants are shown in **Table 1** and were well balanced between the two trial groups. The mean age of participants was 76.0 years (SD 6.1), and 51% (118/230) were women. The mean systolic BP was 134.5 mmHg (SD 10.7) with 1.5 classes of antihypertensives (SD 1.1) at baseline. Participants were on average on 5.7 (SD 2.4) non-antihypertensive classes of drugs and 80% (184/230) had 3 to 5 comorbidities (excluding hypertension). The quality-of-life indices (**Supplementary Table 8, page 10**), cognitive function (**Supplementary Table 7, page 9**), frailty score, and medication compliance (**Supplementary Tables 2-3, pages 4-5**) were comparable between both arms at baseline.

Mean systolic BP was gradually reduced in the more antihypertensives group and remained largely unchanged in the fewer antihypertensives group (**Figure 2**). Thirteen months after randomisation, the mean systolic BP was 122.1 mmHg (SD 10.5) and 132.9 mmHg (SD 15.3), in the groups allocated to more and fewer antihypertensives, respectively (**Supplementary Table 4, page 6**). Mean difference in systolic BP between groups at 8 months and the end of the trial were -10.8 mmHg (95% CI -14.4 and -7.2) and -10.7 mmHg (95% CI -17.5 to -4.0), respectively. This was achieved with an increase in number of antihypertensive classes from 1.5 (SD 1.1) to 3.0 (SD 1.4) in the more antihypertensives group, compared with a change from 1.5 (SD 1.1) to 1.9 (1.5 SD) in the fewer antihypertensive group

(**Supplementary Table 5, page 7, Figure 3**). Stratified analyses according to the three strata were generally in line with the overall findings, however, there were too few participants in stratum 3 (no change vs reduction of 2 antihypertensive drugs) to enable reliable comparison (**Table 1, Supplementary Figures 1-2, pages 11-14**).

Frailty scores, as assessed with PRISMA-7 questionnaires show no change in the more antihypertensive group with a numerically worsening score in the fewer antihypertensive groups but with large uncertainty around the estimates (**Supplementary Table 3, page 5**). Similarly, T-MoCA questionnaire did not reveal any material changes in overall or subscale cognitive function assessment. However, the classification of participants into those with or without cognitive impairment seemed unreliable due to large within-group variations (**Supplementary Table 7, page 9**). Health-related quality of life as assessed by EQ-5D-5L remained stable in both groups throughout the follow-up duration (**Supplementary Table 8, page 10**). Self-reported drug compliance was high with no material change over the follow-up duration in either group (**Supplementary Table 2, page 4).**

During the follow-up of 13 months, no cardiovascular events occurred in the more antihypertensive group, compared with 6 cardiovascular (fatal and non-fatal) events in the fewer antihypertensive group, of which two were fatal (**Table 3**). A total of three deaths occurred during the follow-up period – one death in the group allocated more antihypertensives and the two cardiovascular deaths in the group allocated fewer antihypertensives (**Table 3)**. 33 participants had at least one other type of admission to hospital with no difference between the allocated groups (14.2% vs 14.4%, p=0.97). A high number of non-serious adverse events were reported by participants (**Table 3)**. Noticeably, the rate of dizziness and fatigue was higher among those allocated more antihypertensives (**Table 3)**. Other event categories, including falls, fainting, fracture, and confusion did not differ between the groups. A more detailed breakdown of all clinical events can be found in **Supplementary Table 1, page 3.** Those allocated an ACE-inhibitor, ARB or diuretics were followed up with a blood test as per routine clinical recommendations. Analysis showed no worsening renal function or electrolyte abnormalities, and average values were stable during the entire study period (**Supplementary Figures 3 a-d, pages 17-20)**.

Overall, 87.4% (201/230) of participants described their experience with the trial as very satisfying, and 96.3% (221/230) would consider participating in a trial using a similar approach again. The decentralised design of the trial and not needing to attend appointments at GPs or hospital sites were rated as very satisfying by 97.2% (223/230) of participants. The online registration process and the

information available on the designated participant website were rated as very satisfying by 80.9% (186/230) and 79.1% (181/230) of participants, respectively.

Discussion

ATEMPT showed that in a study of older patients with multimorbidity and polypharmacy – a growing patient group that has been previously underrepresented in trials focussing on antihypertensive treatment [3,4] - and using an IT-system for remote recruitment, trial monitoring and intervention a substantial lowering of BP down to a systolic BP of 122 mmHg could be achieved. On average, a change of one antihypertensive drug difference was achieved, which corresponded to an 11-mmHg systolic BP difference between the treatment arms. There was no evidence to suggest that this relatively short-term intervention had an impact on participants' quality of life, cognitive function, frailty status or medication adherence. However, there were more reports of dizziness and fatigue among those allocated more antihypertensive drugs. Although the recruitment phase fell into the second and third wave of the COVID-19 pandemic in the UK, the pilot trial exceeded the anticipated recruitment rate with a final number of 230 randomised participants. Remote delivery of drugs to patients' homes was feasible and acceptable by participants.

How to handle BP treatment in older multimorbid and often frail people has been subject to much controversy. A systematic review and meta-analysis of non-randomised studies that investigated associations between BP and risk of mortality in older patients found evidence for interaction by frailty status, suggesting that low BP might be harmful in this patient group.[20] However, these findings were only hypothesis-generating due to the limitations of the study design. SPRINT and HYVET are two randomised trials that have reported outcomes stratified by frailty status.[21,22] Although these studies showed no evidence of interaction by categories of frailty, SPRINT has been criticised for its method in measuring BP and HYVET was confined to patients with very high BP at baseline. Individual participant meta-analyses of large-scale RCTs have not shown any important treatment interaction by age or predicted cardiovascular risk, as proxies for disease burden and frailty.[23,24] In the meantime, a few studies have assessed the effect of deprescribing in older multimorbid patients. Although these studies have overall concluded that deprescribing is feasible and safe, the findings have not been conclusive for several reasons. First, like our study, they have been too small or too short to detect modest differences in important clinical outcomes. Second, intervention fidelity has been suboptimal. For instance, in the ECSTATIC trial, 67% of participants stopped the study-allocated intervention and only 27% were able to maintain this throughout the 2-year follow-up.[25] Similarly, in OPTIMISE, while

initial deprescribing was complete, there was a 44% re-prescription over the relatively short 12-week follow-up period.[26] Unsurprisingly, these studies have not been able to detect a meaningful difference in BP and are therefore prone to type 2 statistical error.

By contrast, we aimed for a two-drug class difference between groups which led to a significant reduction in systolic BP of about 10 mmHg. However, this change was largely due to the successful addition of drugs in the more antihypertensives group rather than any deprescribing effect. Indeed, the BP in the fewer antihypertensive group remained largely the same throughout the trial. One reason for this was that similar to previous deprescribing trials, patients were less willing to have their long-term antihypertensive treatment stopped than new medications added. In some cases, stopping medication led to participants expressing concern about negative consequences arising from an increase in systolic BP and asked their doctor to restart treatments. Another reason for the limited contribution of deprescribing to the treatment differences is the fact that the proportion of participants with at least one or two antihypertensives that could get potentially be stopped was much lower than those in whom treatment could be intensified. Only 8% (19/230) of participants belonged to the stratum of 'no change vs reduction of two antihypertensives' and contributed little weight to the overall results.

The relatively low number of antihypertensives at baseline is consistent with epidemiological studies of representative UK patient populations. An observational study investigating multimorbidity and temporal BP trajectories in hypertensive patients showed that only 2.7% of such UK patients were prescribed three or more antihypertensive medications.[27] On average, patients with hypertension and 3 comorbidities were prescribed 1.5 (SD 0.9) antihypertensives, which is identical to the 1.5 antihypertensive medications at baseline in ATEMPT.

Our results did not show a significant difference in the occurrence of serious adverse events between the treatment groups. While four cases of myocardial infarction, stroke, and transient ischemic attack were reported in the group with fewer antihypertensive medications, the low number of events did not allow us to test for a statistical difference between the two treatment arms. Clinical trials with a larger number of participants focussing on major cardiovascular events as outcomes are needed to complement the results of our pilot trial. Participants in the group of more antihypertensive medications reported a greater number of non-serious adverse events compared to the treatment group of less antihypertensive medications. Under those events, the occurrence of dizziness and fatigue was shown to be statistically significantly different between the treatment arms. In the context

of an open-label trial, the discrepancy in the reporting of dizziness and fatigue may be attributed to participants' awareness of the changes in their antihypertensive medications and potential expectations of side effects. Although the remote assessments during the follow-up period were equally scheduled in both treatment arms, participants in the treatment group of more antihypertensive drugs had additional contact with the trial team to evaluate the remote delivery of initiated medications and instructions for increasing the dosage, which may also explain the overall greater number of reports in this group. We tried to minimise the risk of adverse effects by favouring the combination of multiple antihypertensive drugs at a low or moderate dose over the full up-titration of single drugs,[18] although acknowledging that this approach may not prevent the occurrence of short-lasting adverse effects. The occurrence of dizziness was, however, not associated with an increased reporting of falls, fractures, or episodes of fainting and did not translate into a meaningful difference in participants' quality of life, cognitive function, frailty status and medication adherence. Hence, our findings suggest that it is safe to intensify participants' antihypertensive treatment, even in a home-based environment to thresholds below the typical guideline recommendations for this group.

Key strengths of ATEMPT are the recruitment of an underrepresented patient group and being able to achieve the anticipated systolic BP difference between the two intervention groups. Overall, the remote design of the trial achieved a high satisfaction rate among randomised participants. However, we acknowledge that the study was not sufficiently powered to detect more modest differences in safety outcomes and quality of life. Future studies could adopt the decentralised design of ATEMPT and employ digital endpoints for assessment of physical and cognitive functioning. Such outcomes are more sensitive to change and potentially less intrusive. Future studies could also explore enriching recruitment for the very old (>85 years) and those with at least moderate frailty in whom treatment uncertainty is substantial.[24]

The trial also has some limitations. Whilst it demonstrated that a substantial change in participants' systolic BP can be achieved in this patient population, the durability of these changes remains unclear due to the relatively short follow-up period of the trial. Future studies with longer-term follow-ups and larger sample sizes could assess the impact of the intervention on clinical outcomes. A further limitation of the pilot trial is its open-label design. However, several measures were implemented to reduce bias. With regard to the clinical frailty assessment using the PRISMA-7 questionnaire, a limitation can be seen in the lower specificity for detecting frailty in patients compared to other assessment tools, such as the Clinical Frailty Scale. However, the questionnaire was deemed most

feasible for a decentralised home-based trial as participants were able to complete it on their own without the direct input of a clinician. Future studies could adopt alternative ways of measuring physical functioning, including with wearables.

Overall, ATEMPT highlighted that patient-centred trials using digital technologies can successfully recruit and monitor older patients with multimorbidity and polypharmacy. The antihypertensive intervention resulted in a substantial change in systolic BP in older and multimorbid patients, and this did not translate into an increased risk of serious adverse events or measurable effects on participants' quality of life, cognitive function, medication adherence and frailty status. The results of this trial will provide some reassurance about antihypertensive use in this patient group and will inform a larger clinical trial focussing on major cardiovascular events, safety, physical functioning and cognitive function that is in the planning stages at present.

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Conflict of Interest

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Data availability statement

The full dataset underlying this article cannot be shared publicly due to the privacy of individuals who participated in the study. Aggregate and anonymised data will be shared on reasonable request to the corresponding author.

Contribution of authors

KR, DH, WT, APC and JM conceived the study. BG and MMA provided support for the study design from a patient point of view. KR, DH, WT wrote the trial protocol and JM helped with amendments. KR, DH, WT, APC, JM, NA, MA were responsible for the conduction of the trial and the collection of the data. MN, ZB, RR and JM verified the data and conducted the statistical analyses. CCA, LB, DK, JP supported the trial as DMC and SC. JM and KR drafted the manuscript. All authors contributed to the critical revision of the manuscript and approved the final version. The corresponding authors attest that all listed authors meet authorship criteria.

References:

1. World Health Organisation. A global brief on hypertension | A global brief on Hypertension - Silent killer, global public health crisis. https://www.who.int/publications/i/item/a-global-brief-on-hypertension-silent-killer-global-public-health-crisis-world-health-day-2013 (accessed 20 Aug 2022).

2. Ettehad, D., Emdin, C. A., Kiran, A., Anderson, S.G., Callender, T., Emberson, J., et al. Blood pressure lowering for prevention of cardiovascular disease and death: A systematic review and meta-analysis. *The Lancet* 387, 957–967 (2016).

3. Collerton, J., Davies, K., Jagger, C., Kingston, A., Bond, J., Eccles, M. P., et al. Health and disease in a UK cohort of 85-year-olds: the Newcastle 85+ study. *J Epidemiol Community Health (1978)* 63, (2009).

4. Pinho-Gomes, A. C., Rahimi, K. Blood pressure management in the elderly: The need for more randomised evidence. *Heart* 105(14): 1055-6, (2019).

5. Whelton, P. K., Carey, R. M., Aronow, W. S., Casey, D. E., Collins, K.J. Himmelfarb, C. D., et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults. *J Am Coll Cardiol* 71, (2018).

6. Williams, B., Mancia, G., Spiering, W., Rosei, E. A., Azizi, M., Burnier, M., et al. 2018 ESC/ESHGuidelines for themanagement of arterial hypertension. *European Heart Journal* 2018; 39(33): 3021-104.

7. National Institute for Health and Care Excellence (NICE). Diagnosis and management of hypertension in adults: NICE guideline update 2019. https://www.nice.org.uk/guidance/ng136 (accessed 23 Aug 2022).

8. Lockett, J., Sauma, S., Radziszewska, B., Bernard, M. A. Adequacy of Inclusion of Older Adults in NIH-Funded Phase III Clinical Trials. *J Am Geriatr Soc* 67, (2019).

9. Forsat, N. D., Palmowski, A., Palmowski, Y., Boers, M., Buttgereit, F. Recruitment and Retention of Older People in Clinical Research: A Systematic Literature Review. *J Am Geriatr Soc* 68, 2955–2963 (2020).

10. Bobrie, G., Chatellier, G., Genes, N., Clerson, P., Vaur, L., Vaisse, B., Menard, J., Mallion, J.-M. Cardiovascular Prognosis of 'Masked Hypertension' Detected by Blood Pressure Self-measurement in Elderly Treated Hypertensive Patients. *J Am Med Assoc* 291, (2004).

11. Rahimi, K., Velardo, C., Triantafyllidis, A., Conrad, N., Shah, S. A., Chantler, T., et al. A user-centred home monitoring and self-management system for patients with heart failure: A multicentre cohort study. *Eur Heart J Qual Care Clin Outcomes* 1, (2015).

12. Triantafyllidis, A., Velardo, C., Chantler, T., Shah, S. A., Paton, C., Khorshidi, R., et al. A personalised mobile-based home monitoring system for heart failure: The SUPPORT-HF Study. *Int J Med Inform* 84, 743–753 (2015).

13. Rahimi, K., Nazarzadeh, M., Phino-Gomes, A.-C., Woodward, M., Salimi-Khorshidi, G., Ohkuma, T., et al. Home monitoring with technology-supported management in chronic heart failure: A randomised trial. *Heart* 106, 1573–1578 (2020).

14. Higginbotham, O., O'Neill, A., Barry, L., Leahy, A., Robinson, K., O'Connor, M., et al. The diagnostic and predictive accuracy of the PRISMA-7 screening tool for frailty in older adults: A systematic review protocol. *HRB Open Res* 3, 26 (2020).

15. Zhou, T., Guan, H., Wang, L., Zhang, Y., Rui, M., Ma, A. Health-Related Quality of Life in Patients With Different Diseases Measured With the EQ-5D-5L: A Systematic Review. *Frontiers in Public Health* vol. 9, (2021).

16. Hobson, J. The Montreal Cognitive Assessment (MoCA). *Occupational Medicine* vol. 65 764–765, (2015).

17. Rahimi, K., Bidel, Z., Nazarzadeh, M., Copland, E., Canoy, D., Ramakrishnan, R., et al. Pharmacological blood pressure lowering for primary and secondary prevention of cardiovascular disease across different levels of blood pressure: an individual participant-level data meta-analysis. *The Lancet* 397, 1625–36 (2021).

18. Benetos, A., Petrovic, M., Strandberg, T. Hypertension Management in Older and Frail Older Patients. *Circ Res* 124, (2019).

19. Chow, C. K., Thakkar, J., Bennett, A., Hillis, G., Burke, M., Usherwood, T., et al. Quarter-dose quadruple combination therapy for initial treatment of hypertension: placebo-controlled, crossover, randomised trial and systematic review. *The Lancet* 389, (2017).

20. Todd, O. M., Wilkinson, C., Hale, M., Wong, N. L., Hall, M., Sheppard, J.P., et al. Is the association between blood pressure and mortality in older adults different with frailty? A systematic review and meta-analysis. *Age and Ageing* vol. 48 627–635, (2019).

21. Warwick, J., Falaschetti, E., Rockwood, K., Mitnitski, A., Thijs, L., Beckett, N. et al. No evidence that frailty modifies the positive impact of antihypertensive treatment in very elderly people: An investigation of the impact of frailty upon treatment effect in the HYpertension in the Very Elderly

Trial (HYVET) study, a double-blind, placebo-controlled study of antihypertensives in people with hypertension aged 80 and over. *BMC Med* 13, (2015).

22. Williamson, J. D., Supiano, M. A., Applegate, W. B., Berlowitz, D. R., Campbell, R. C., Chertow, G. M. et al. Intensive vs standard blood pressure control and cardiovascular disease outcomes in adults aged ≥75 years a randomized clinical trial. *JAMA - Journal of the American Medical Association* 315, 2673–2682 (2016).

23. Blood Pressure Lowering Treatment Trialists' Collaboration. Blood pressure-lowering treatment based on cardiovascular risk: a meta-analysis of individual patient data. *Lancet: Elsevier Ltd* 591–598 (2014).

24. Blood Pressure Lowering Treatment Trialists' Collaboration. Age-stratified and blood-pressure-stratified effects of blood-pressure-lowering pharmacotherapy for the prevention of cardiovascular disease and death: an individual participant-level data meta-analysis. *The Lancet* 398, 1053–1064 (2021).

25. Luymes, C. H., Poortvliet, R. K. E., van Geloven, N., de Waal, M., W., M., Drewes, Y., M., Blom, J. W., et al. Deprescribing preventive cardiovascular medication in patients with predicted low cardiovascular disease risk in general practice - the ECSTATIC study: A cluster randomised non-inferiority trial. *BMC Med* 16, (2018).

26. Sheppard, J. P., Burt, J., Lown, M., Temple, E., Lowe, R., Fraser, R., et al. Effect of Antihypertensive Medication Reduction vs Usual Care on Short-term Blood Pressure Control in Patients with Hypertension Aged 80 Years and Older: The OPTIMISE Randomized Clinical Trial. *JAMA - Journal of the American Medical Association* 323, 2039–2051 (2020).

27. Tran, J., Norton, R., Canoy, D., Solares, J. R. A., Conrad, N., Nazarzadeh, M., et al. Multi-morbidity and blood pressure trajectories in hypertensive patients: A multiple landmark cohort study. *PLOS Medicine* 17, (2021).

Table 1. Baseline characteristics of analysed participants in ATEMPT trial.

	Total (n=230)	More antihypertensives (n=126)	Fewer antihypertensives (n=104)
Age, mean (SD)	76.0 (6.1)	75.8 (6.3)	76.2 (6.0)
SBP, mean (SD)	134.5 (10.7)	134.3 (10.2)	134.8 (11.2)
Age categories, n (%)			
≤80 years	177 (77.0)	95 (75.4)	82 (78.8)
> 80 years	53 (23.0)	31 (24.6)	22 (21.2)
SBP categories, n (%)			
<130 mmHg	86 (37.4)	49 (38.9)	37 (35.6)
130-140 mmHg	77 (33.5)	42 (33.3)	35 (33.7)
>140 mmHg	67 (29.1)	35 (27.8)	32 (30.8)
Sex, n (%)			
Men	111 (48.5)	67 (53.2)	44 (42.7)
Women	118 (51.5)	59 (46.8)	59 (57.3)
Treatment stratum after randomisation, n (%)			
Stratum 1: Increase of two vs no change	136 (59.1)	80 (63.5)	56 (53.9)
Stratum 2: Increase vs reduction of one	75 (32.6)	37 (29.4)	38 (36.5)
Stratum 3: No change vs reduction of two	19 (8.3)	9 (7.1)	10 (9.6)
Number of anti-hypertensive medications, mean (SD)	1.54 (1.10)	1.53 (1.12)	1.54 (1.09)
Anti-hypertensive drug class, n (%)			
None	42 (10.8)	23 (10.9)	19 (10.6)
ACE inhibitors	62 (15.9)	39 (18.5)	23 (12.8)
ARBs	66 (16.9)	31 (4.7)	35 (19.6)
Beta-blockers	56 (14.4)	34 (16.1)	22 (12.3)
Calcium-channel blockers	96 (24.6)	50 (23.7)	46 (25.7)
Diuretics	48 (12.3)	24 (11.4)	24 (3.4)
Alpha1-receptor blockers	18 (4.6)	9 (4.3)	9 (0.05)
Potassium-sparing diuretics	2 (0.5)	1 (0.5)	1 (0.6)
Dose of anti-hypertensive drugs[a], n(%)			
ACE inhibitors	57 (20.7)	37 (25.2)	20 (15.6)
ARB	50 (18.2)	21(14.3)	29 (22.7)
Beta-blockers	24 (8.7)	16 (10.9)	8 (6.3)
Calcium-channel blockers	88 (32.0)	46 (33.3)	42 (32.8)
Diuretics	38 (13.8)	19 (12.9)	19 (14.8)
Alpha1-receptor blockers	17 (6.2)	8 (5.4)	9 (7.0)
Potassium-sparing diuretics	1 (0.04)	0 (0)	1 (0.8)
Number of non-antihypertensive medications, mean (SD)	5.7 (2.4)	5.7(2.5)	5.8 (2.3)
Comorbid conditions, n(%)			
≤2	11 (4.8)	5 (4)	6 (5.8)
3-5	184 (80)	99 (78.6)	85 (81.7)
>5	35 (15.2)	22 (17.5)	13 (12.5)
Comorbid diseases			
Stroke	8 (0.8)	4 (0.7)	4 (0.9)
CHD	42 (4.1)	30 (5.3)	12 (2.7)
Diabetes	45 (4.4)	17 (3.0)	28 (6.2)
CKD	20 (2.0)	11 (1.9)	9 (2.0)
AF	42 (4.1)	26 (4.6)	16 (3.5)
EQ-5D-5L score, mean (SD)			
Health state index	7.8 (2.6)	7.6 (2.6)	7.9 (2.6)
VAS (perceived health status)	78.0 (13.9)	78.1 (13.2)	77.9(14.7)
EQ-5D value set	0.7(0.1)	0.7(0.1)	0.7(0.1)
T-MoCA score (cognitive function), mean (SD)	19.5(2.0)	19.7(1.8)	19.3 (2.2)
Cognitive impairment, n(%)	59 (25.7)	28 (22.2)	30 (29.1)
PRISMA frailty scale, mean (SD)	2.7 (1.6)	2.6(1.4)	2.8 (1.7)
Drug compliance, mean (SD)	4.2 (1.5)	4.2 (1.5)	4.1 (1.6)
Laboratory measurements, mean(SD)			
Blood urea, mmol/L	7.6 (7.5)	7.3 (3.9)	7.9 (9.7)
Serum creatinine, µmol/L	86.2 (31.4)	86.1 (32.2)	86.3 (30.9)
Serum sodium, mmol/l	139.6 (2.8)	140.1 (2.1)	139.2 (3.2)
Serum potassium, mmol	4.8 (0.5)	4.7 (0.5)	4.8 (0.5)

a. Number (%) of participants who met the minimal dose recommended by the British National Formulary (BNF).

n: number, SBP: systolic blood pressure, SD: standard deviation, ACEs: angiotensin-converting-enzyme inhibitors, ARBs: angiotensin receptor blockers, AF: atrial fibrillation, CHD: coronary heart disease, CKD: chronic kidney disease

Table 2. Randomisation and stratum allocation.

	Randomised group allocation	
	Arm A	**Arm B**
Stratum 1	Add 2 new drugs	No change
Stratum 2	Add 1 new drug	Stop 1 drug
Stratum 3	No change	Stop 2 drugs

Table 3. Serious adverse events and clinical outcomes of interest.

	More antihypertensives (n=126)	Fewer antihypertensives (n=104)
Serious adverse event, n (%)		
Hospitalisation		
MI/ACS	0	1
Stroke/TIA	0	3
Heart failure	0	0
Coronary revascularization	0	0
Other hospitalisations	18 (14.2)	15 (14.4)
Deaths		
MI/ACS	0	1
Stroke/TIA	0	1
Heart failure	0	0
Coronary revascularization	0	0
Other causes of death	1	0
Non-serious adverse event, n (%)		
Falls	20 (15.8)	17 (16.3)
Fracture	4 (3.1)	2 (1.9)
Dizziness (feeling unsteady, lightheaded)	47 (37.3)	19 (18.2)
Fainting (collapse, syncope, brief loss of consciousness)	8 (6.3)	4 (3.8)
Fatigue	13 (10.3)	1 (0.96)
Loss of consciousness (longer episode of unconsciousness)	4 (3.1)	2 (1.9)
Delirium/confusion (feeling disorientated, having difficulty paying attention, remembering and making decisions)	6 (4.7)	6 (5.7)
Loss of balance	4 (3.1)	7 (6.7)
Nausea	4 (3.1)	1 (6.9)
Itching	3 (2.3)	0 (0)
Flushing	1 (0.79)	1 (0.96)
Headache	3 (2.3)	4 (3.8)
Fluid retention or leg swelling	6 (4.7)	3 (2.8)
Bruising (due to fall or other reasons)	5 (3.9)	3 (2.8)
Shortness of breath	1 (0.79)	2 (1.92)
Rash	2 (1.58)	1 (0.96)
Other	41 (32.5)	25 (24.0)

MI: myocardial infarction; ACS: acute coronary syndrome; TIA: transient ischaemic attack

Figure 1. CONSORT flow diagram

SBP: systolic blood pressure

Figure 2. Mean systolic blood pressure in the two treatment groups over the course of the trial.

The trajectory was plotted using the linear mixed-effects model. The model included random intercept and slope of time. The fixed effects included treatment and interaction of treatment and cubic effect of time. The covariance structure of the model was unstructured. Vertical error bars indicate confidence intervals.

Figure 3. Count of antihypertensive drug classes in the two treatment groups over the course of the trial.

The trajectory was plotted using the linear mixed-effects model. The model included a random intercept and slope of time. The fixed effects included treatment and interaction of treatment and cubic effect of time. The covariance structure of the model was unstructured. Vertical error bars indicate confidence intervals.