NUFFIELD DEPARTMENT OF PRIMARY CARE HEALTH SCIENCES

STAR Stratified Treatments Research

# Designing randomised controlled trials of deprescribing: learnings from the OPTiMISE trial

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NIHR | National Institute for Health Research

wellcome

THE ROYAL SOCIETY

British Heart Foundation

# CONFLICT OF INTEREST DISCLOSURE

**Related to this presentation:**

I have received funding from the National Institute for Health Research, British Heart Foundation and the Wellcome Trust / Royal Society to explore the risk of harm from antihypertensive therapy and the effects of antihypertensive deprescribing.

**Not related to this presentation:**

I have received consultancy payments from DoctorLink for critical reviews of their evidence synthesis exercises.

# Overview

1. Management of blood pressure in older adults
2. Why do a randomised controlled trial of deprescribing antihypertensives?
3. What should we consider when designing a deprescribing trial?
4. What was our experience in the OPTiMISE trial?
5. Summary

# Overview

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# Blood pressure lowering works

Previous trials have shown blood pressure lowering is very effective at preventing all CVD and death

## Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis

*Dena Ettehad, Connor A Emdin, Amit Kiran, Simon G Anderson, Thomas Callender, Jonathan Emberson, John Chalmers, Anthony Rodgers, Kazem Rahimi*

| | Studies | Intervention | | Control | | RR (95% CI) per 10 mm Hg reduction in systolic blood pressure |
|---|---|---|---|---|---|---|
| | | Events | Participants | Events | Participants | |
| Major cardiovascular events | 55 | 13209 | 137319 | 14068 | 128259 | 0·80 (0·77–0·83) |
| Coronary heart disease | 56 | 4862 | 136986 | 5301 | 128548 | 0·83 (0·78–0·88) |
| Stroke | 54 | 4635 | 136682 | 5378 | 128641 | 0·73 (0·68–0·77) |
| Heart failure | 43 | 3284 | 115411 | 3760 | 107440 | 0·72 (0·67–0·78) |
| Renal failure | 16 | 890 | 39888 | 834 | 39043 | 0·95 (0·84–1·07) |
| All-cause mortality | 57 | 9775 | 138298 | 9998 | 129700 | 0·87 (0·84–0·91) |

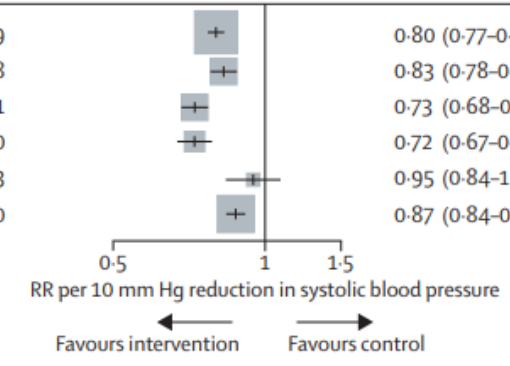



***Figure 3:*** **Standardised effects of a 10 mm Hg reduction in systolic blood pressure**
RR=relative risk.

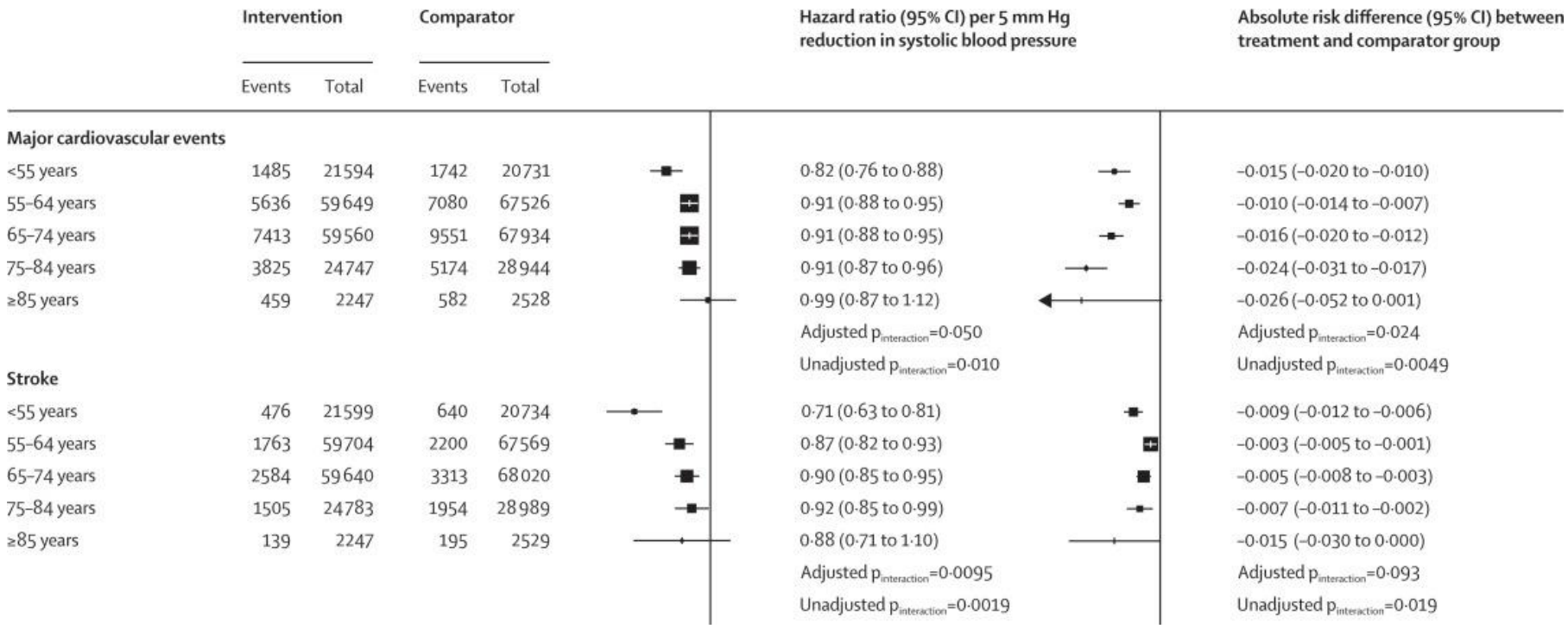
Ettehad *et al., Lancet* 2016; 387: 957–67

# Blood pressure lowering across age groups

Number needed to treat (NNT) to prevent one major CVD event over 5 years:

<55 years = **67**

>85 years = **38**



| | Intervention | | Comparator | | Hazard ratio (95% CI) per 5 mm Hg reduction in systolic blood pressure | Absolute risk difference (95% CI) between treatment and comparator group |
|---|---|---|---|---|---|---|
| | Events | Total | Events | Total | | |
| **Major cardiovascular events** | | | | | | |
| <55 years | 1485 | 21594 | 1742 | 20731 | 0·82 (0·76 to 0·88) | −0·015 (−0·020 to −0·010) |
| 55–64 years | 5636 | 59649 | 7080 | 67526 | 0·91 (0·88 to 0·95) | −0·010 (−0·014 to −0·007) |
| 65–74 years | 7413 | 59560 | 9551 | 67934 | 0·91 (0·88 to 0·95) | −0·016 (−0·020 to −0·012) |
| 75–84 years | 3825 | 24747 | 5174 | 28944 | 0·91 (0·87 to 0·96) | −0·024 (−0·031 to −0·017) |
| ≥85 years | 459 | 2247 | 582 | 2528 | 0·99 (0·87 to 1·12) | −0·026 (−0·052 to 0·001) |
| | | | | | Adjusted $p_{interaction}$=0·050 | Adjusted $p_{interaction}$=0·024 |
| | | | | | Unadjusted $p_{interaction}$=0·010 | Unadjusted $p_{interaction}$=0·0049 |
| **Stroke** | | | | | | |
| <55 years | 476 | 21599 | 640 | 20734 | 0·71 (0·63 to 0·81) | −0·009 (−0·012 to −0·006) |
| 55–64 years | 1763 | 59704 | 2200 | 67569 | 0·87 (0·82 to 0·93) | −0·003 (−0·005 to −0·001) |
| 65–74 years | 2584 | 59640 | 3313 | 68020 | 0·90 (0·85 to 0·95) | −0·005 (−0·008 to −0·003) |
| 75–84 years | 1505 | 24783 | 1954 | 28989 | 0·92 (0·85 to 0·99) | −0·007 (−0·011 to −0·002) |
| ≥85 years | 139 | 2247 | 195 | 2529 | 0·88 (0·71 to 1·10) | −0·015 (−0·030 to 0·000) |
| | | | | | Adjusted $p_{interaction}$=0·0095 | Adjusted $p_{interaction}$=0·093 |
| | | | | | Unadjusted $p_{interaction}$=0·0019 | Unadjusted $p_{interaction}$=0·019 |



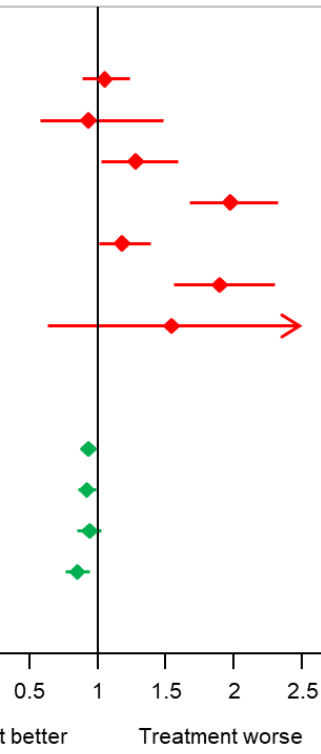
BPLTTC, *Lancet* 2021, S0140-6736(21)01921-8

# Harms of antihypertensive treatment

Trials across all age groups suggest a 18-97% increased risk of:

- Syncope
- Hypotension
- AKI
- Hyperkalaemia

| Outcome | No. of studies | Intervention group Sample size | Intervention group Events | Control group Sample size | Control group Events | Risk ratio (95% CI) | $I^2$ | $Tau^2$ |
|---|---|---|---|---|---|---|---|---|
| **Harm outcomes** | | | | | | | | |
| Falls | 7 | 14,719 | 913 | 14,762 | 877 | 1.05 (0.89, 1.24) | 31.5% | 0.009 |
| Fractures | 5 | 6,447 | 230 | 6,466 | 267 | 0.93 (0.58, 1.48) | 53.8% | 0.062 |
| Syncope | 16 | 51,072 | 644 | 51,189 | 543 | 1.28 (1.03, 1.59) | 42.9% | 0.050 |
| Hypotension | 35 | 88,575 | 5,390 | 93,547 | 3,121 | 1.97 (1.67, 2.32) | 85.1% | 0.132 |
| Acute kidney injury | 15 | 43,467 | 909 | 52,133 | 785 | 1.18 (1.01, 1.39) | 48.1% | 0.037 |
| Hyperkalaemia | 26 | 57,604 | 2,749 | 61,795 | 1,880 | 1.89 (1.56, 2.30) | 71.8% | 0.121 |
| Hypokalaemia | 12 | 19,748 | 517 | 19,528 | 274 | 1.54 (0.63, 3.75) | 94.3% | 1.612 |
| **Benefit outcomes** | | | | | | | | |
| All-cause mortality | 31 | 128,619 | 11,831 | 128,729 | 13,018 | 0.93 (0.89, 0.98) | 50.4% | 0.008 |
| Cardiovascular death | 21 | 92,676 | 6,341 | 92,733 | 6,890 | 0.92 (0.86, 0.99) | 54.6% | 0.011 |
| Myocardial infarction | 18 | 75,002 | 2,900 | 75,301 | 3,255 | 0.94 (0.85, 1.03) | 40.7% | 0.013 |
| Stroke | 16 | 104,153 | 3,220 | 104,366 | 3,733 | 0.85 (0.77, 0.94) | 44.8% | 0.013 |

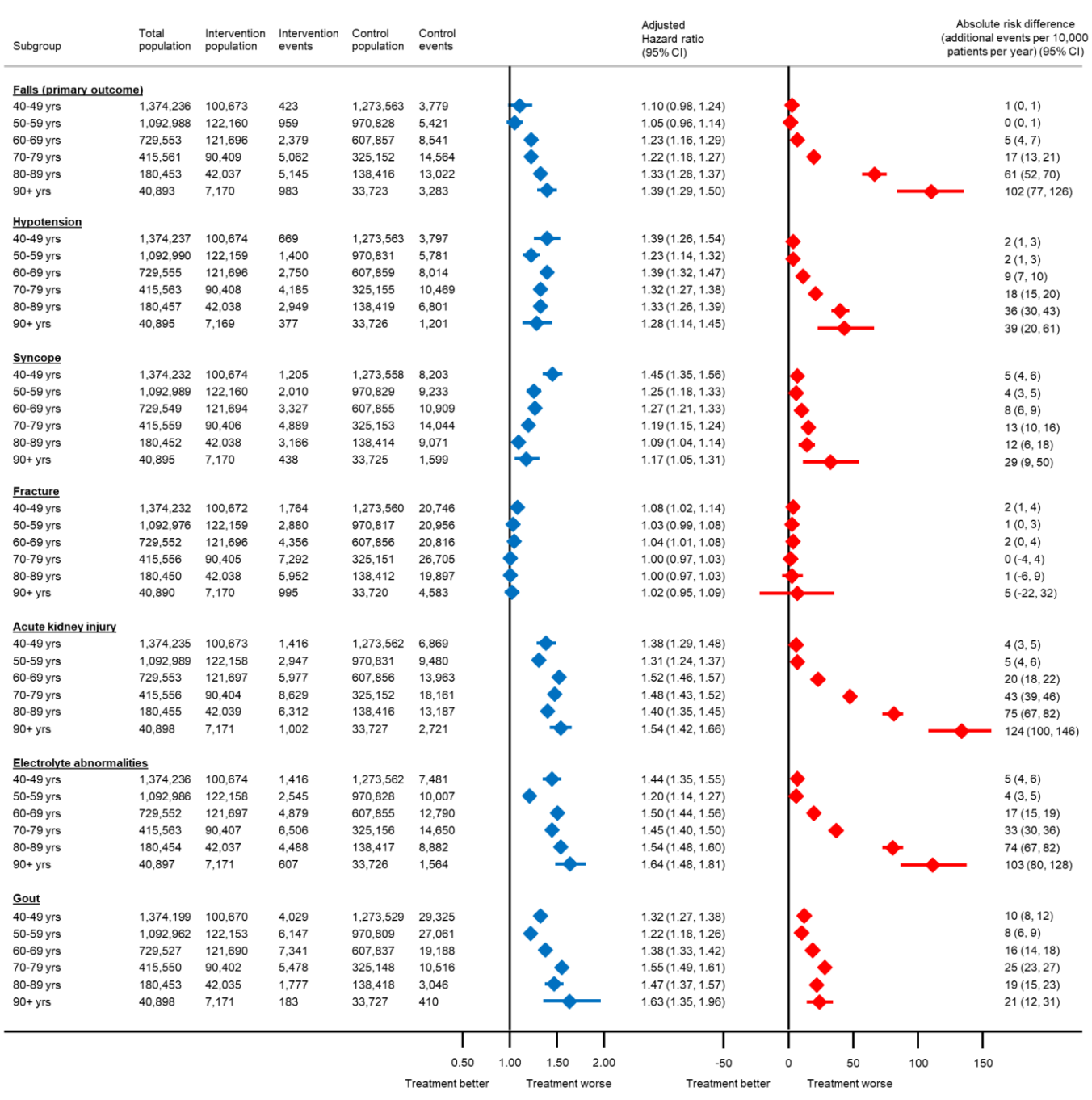





Albasri *et al., BMJ* 2021; 372:n189

# Adverse events by age group

| Subgroup | Total population | Intervention population | Intervention events | Control population | Control events | Adjusted Hazard ratio (95% CI) | Absolute risk difference (additional events per 10,000 patients per year) (95% CI) |
|---|---|---|---|---|---|---|---|
| **Falls (primary outcome)** | | | | | | | |
| 40-49 yrs | 1,374,236 | 100,673 | 423 | 1,273,563 | 3,779 | 1.10 (0.98, 1.24) | 1 (0, 1) |
| 50-59 yrs | 1,092,988 | 122,160 | 959 | 970,828 | 5,421 | 1.05 (0.96, 1.14) | 0 (0, 1) |
| 60-69 yrs | 729,553 | 121,696 | 2,379 | 607,857 | 8,541 | 1.23 (1.16, 1.29) | 5 (4, 7) |
| 70-79 yrs | 415,561 | 90,409 | 5,062 | 325,152 | 14,564 | 1.22 (1.18, 1.27) | 17 (13, 21) |
| 80-89 yrs | 180,453 | 42,037 | 5,145 | 138,416 | 13,022 | 1.33 (1.28, 1.37) | 61 (52, 70) |
| 90+ yrs | 40,893 | 7,170 | 983 | 33,723 | 3,283 | 1.39 (1.29, 1.50) | 102 (77, 126) |
| **Hypotension** | | | | | | | |
| 40-49 yrs | 1,374,237 | 100,674 | 669 | 1,273,563 | 3,797 | 1.39 (1.26, 1.54) | 2 (1, 3) |
| 50-59 yrs | 1,092,990 | 122,159 | 1,400 | 970,831 | 5,781 | 1.23 (1.14, 1.32) | 2 (1, 3) |
| 60-69 yrs | 729,555 | 121,696 | 2,750 | 607,859 | 8,014 | 1.39 (1.32, 1.47) | 9 (7, 10) |
| 70-79 yrs | 415,563 | 90,408 | 4,185 | 325,155 | 10,469 | 1.32 (1.27, 1.38) | 18 (15, 20) |
| 80-89 yrs | 180,457 | 42,038 | 2,949 | 138,419 | 6,801 | 1.33 (1.26, 1.39) | 36 (30, 43) |
| 90+ yrs | 40,895 | 7,169 | 377 | 33,726 | 1,201 | 1.28 (1.14, 1.45) | 39 (20, 61) |
| **Syncope** | | | | | | | |
| 40-49 yrs | 1,374,232 | 100,674 | 1,205 | 1,273,558 | 8,203 | 1.45 (1.35, 1.56) | 5 (4, 6) |
| 50-59 yrs | 1,092,989 | 122,160 | 2,010 | 970,829 | 9,233 | 1.25 (1.18, 1.33) | 4 (3, 5) |
| 60-69 yrs | 729,549 | 121,694 | 3,327 | 607,855 | 10,909 | 1.27 (1.21, 1.33) | 8 (6, 9) |
| 70-79 yrs | 415,559 | 90,406 | 4,889 | 325,153 | 14,044 | 1.19 (1.15, 1.24) | 13 (10, 16) |
| 80-89 yrs | 180,452 | 42,038 | 3,166 | 138,414 | 9,071 | 1.09 (1.04, 1.14) | 12 (6, 18) |
| 90+ yrs | 40,895 | 7,170 | 438 | 33,725 | 1,599 | 1.17 (1.05, 1.31) | 29 (9, 50) |
| **Fracture** | | | | | | | |
| 40-49 yrs | 1,374,232 | 100,672 | 1,764 | 1,273,560 | 20,746 | 1.08 (1.02, 1.14) | 2 (1, 4) |
| 50-59 yrs | 1,092,976 | 122,159 | 2,880 | 970,817 | 20,956 | 1.03 (0.99, 1.08) | 1 (0, 3) |
| 60-69 yrs | 729,552 | 121,696 | 4,356 | 607,856 | 20,816 | 1.04 (1.01, 1.08) | 2 (0, 4) |
| 70-79 yrs | 415,556 | 90,405 | 7,292 | 325,151 | 26,705 | 1.00 (0.97, 1.03) | 0 (-4, 4) |
| 80-89 yrs | 180,450 | 42,038 | 5,952 | 138,412 | 19,897 | 1.00 (0.97, 1.03) | 1 (-6, 9) |
| 90+ yrs | 40,890 | 7,170 | 995 | 33,720 | 4,583 | 1.02 (0.95, 1.09) | 5 (-22, 32) |
| **Acute kidney injury** | | | | | | | |
| 40-49 yrs | 1,374,235 | 100,673 | 1,416 | 1,273,562 | 6,869 | 1.38 (1.29, 1.48) | 4 (3, 5) |
| 50-59 yrs | 1,092,989 | 122,158 | 2,947 | 970,831 | 9,480 | 1.31 (1.24, 1.37) | 5 (4, 6) |
| 60-69 yrs | 729,553 | 121,697 | 5,977 | 607,856 | 13,963 | 1.52 (1.46, 1.57) | 20 (18, 22) |
| 70-79 yrs | 415,556 | 90,404 | 8,629 | 325,152 | 18,161 | 1.48 (1.43, 1.52) | 43 (39, 46) |
| 80-89 yrs | 180,455 | 42,039 | 6,312 | 138,416 | 13,187 | 1.40 (1.35, 1.45) | 75 (67, 82) |
| 90+ yrs | 40,898 | 7,171 | 1,002 | 33,727 | 2,721 | 1.54 (1.42, 1.66) | 124 (100, 146) |
| **Electrolyte abnormalities** | | | | | | | |
| 40-49 yrs | 1,374,236 | 100,674 | 1,416 | 1,273,562 | 7,481 | 1.44 (1.35, 1.55) | 5 (4, 6) |
| 50-59 yrs | 1,092,986 | 122,158 | 2,545 | 970,828 | 10,007 | 1.20 (1.14, 1.27) | 4 (3, 5) |
| 60-69 yrs | 729,552 | 121,697 | 4,879 | 607,855 | 12,790 | 1.50 (1.44, 1.56) | 17 (15, 19) |
| 70-79 yrs | 415,563 | 90,407 | 6,506 | 325,156 | 14,650 | 1.45 (1.40, 1.50) | 33 (30, 36) |
| 80-89 yrs | 180,454 | 42,037 | 4,488 | 138,417 | 8,882 | 1.54 (1.48, 1.60) | 74 (67, 82) |
| 90+ yrs | 40,897 | 7,171 | 607 | 33,726 | 1,564 | 1.64 (1.48, 1.81) | 103 (80, 128) |
| **Gout** | | | | | | | |
| 40-49 yrs | 1,374,199 | 100,670 | 4,029 | 1,273,529 | 29,325 | 1.32 (1.27, 1.38) | 10 (8, 12) |
| 50-59 yrs | 1,092,962 | 122,153 | 6,147 | 970,809 | 27,061 | 1.22 (1.18, 1.26) | 8 (6, 9) |
| 60-69 yrs | 729,527 | 121,690 | 7,341 | 607,837 | 19,188 | 1.38 (1.33, 1.42) | 16 (14, 18) |
| 70-79 yrs | 415,550 | 90,402 | 5,478 | 325,148 | 10,516 | 1.55 (1.49, 1.61) | 25 (23, 27) |
| 80-89 yrs | 180,453 | 42,035 | 1,777 | 138,418 | 3,046 | 1.47 (1.37, 1.57) | 19 (15, 23) |
| 90+ yrs | 40,898 | 7,171 | 183 | 33,727 | 410 | 1.63 (1.35, 1.96) | 21 (12, 31) |




Sheppard *et al.,* PLoS Med 20(4): e1004223

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# Clinical Guideline recommendations

| Recommendations and statements | CoR | LoE |
|---|---|---|
| **Patients ≥80 years old** | | |
| The recommended office SBP threshold for initiation of drug treatment is 160 mmHg. | I | B |
| However, a lower SBP threshold in the 140 to 159 mmHg range may be considered. | II | C |
| Office SBP should be lowered in the 140 to 150 mmHg range. | I | A |
| However, reduction of office SBP between 130 to 139 mmHg may be considered if well tolerated, albeit cautiously if DBP is already below 70 mmHg. | II | B |
| **Additional recommendations[a]** | | |
| In frail patients, initiation of drug treatment and the treatment target for office SBP and DBP should be individualized. | I | C |
| Initiation with monotherapy should be considered in patients with frailty and/or advanced age. | I | C |
| Do not actively aim to target office SBP below 120 mmHg or DBP below 70 mmHg during drug treatment. | III | C |
| However, in patients with low office DBP, i.e. below 70 mmHg, SBP should be still lowered, albeit cautiously, if on-treatment SBP is still well above target values | II | C |
| Reduction of treatment can be considered in patients age 80 years or older with a low SBP (<120mmHg) or in the presence of severe orthostatic hypotension or a high frailty level. | II | C |
| Withdrawal of BP-lowering drug treatment on the basis of age, even when patients attain an age of ≥ 80 years, is not recommended, if treatment is well tolerated. | III | B |
| In older patients, treatment may start with lower doses and uptitration should be slower. | II | C |
| The search for orthostatic hypotension in old patients should be systematic, even in the absence of symptoms. Back titration or discontinuation of BP lowering drugs should be considered in patients with orthostatic hypotension. | I | C |

**ESH Guidelines**
Mancia *et al., Journal of Hypertension* 2023; 41(12): p1874-2071

# Overview

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3. What should we consider when designing a deprescribing trial?
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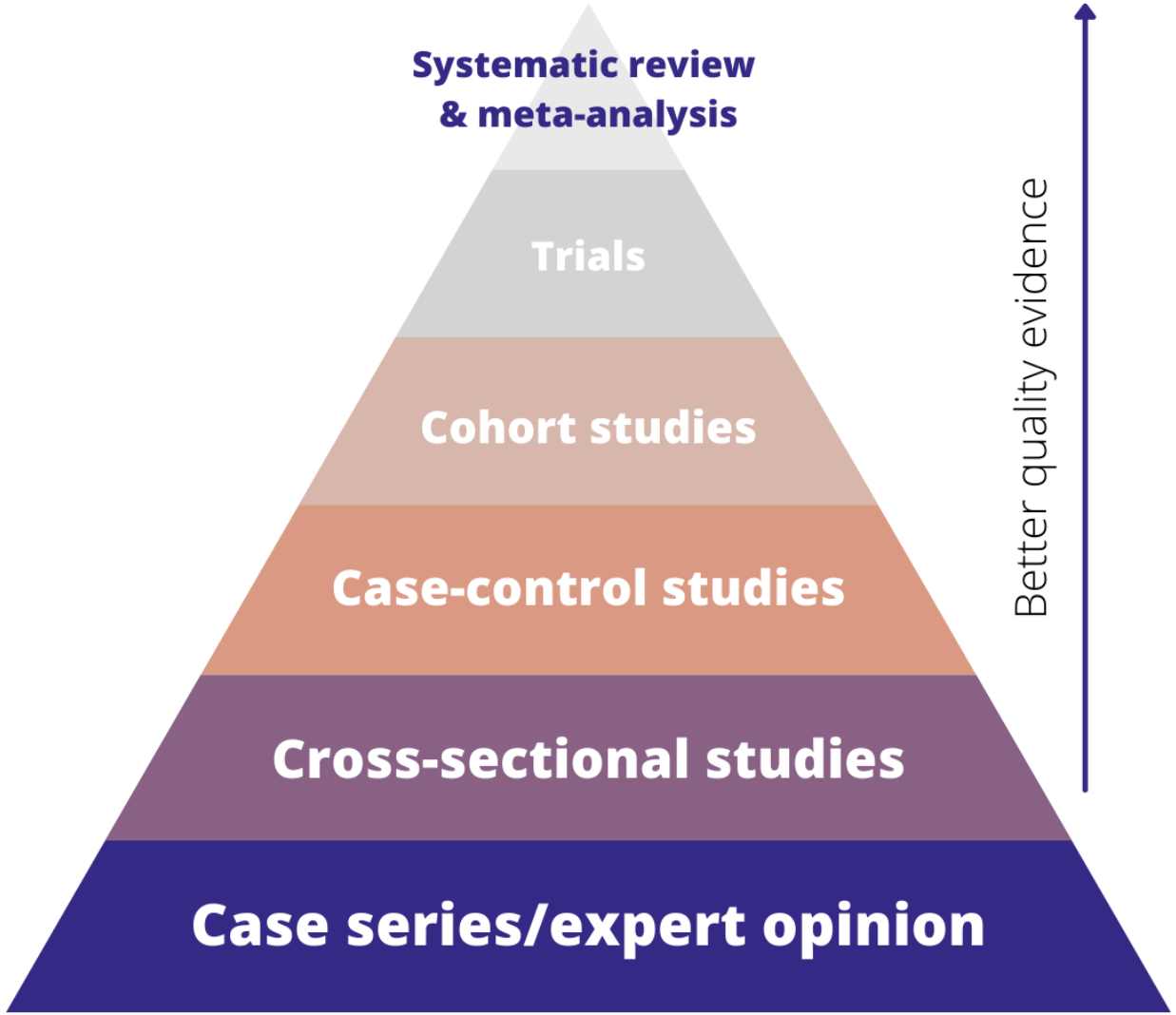
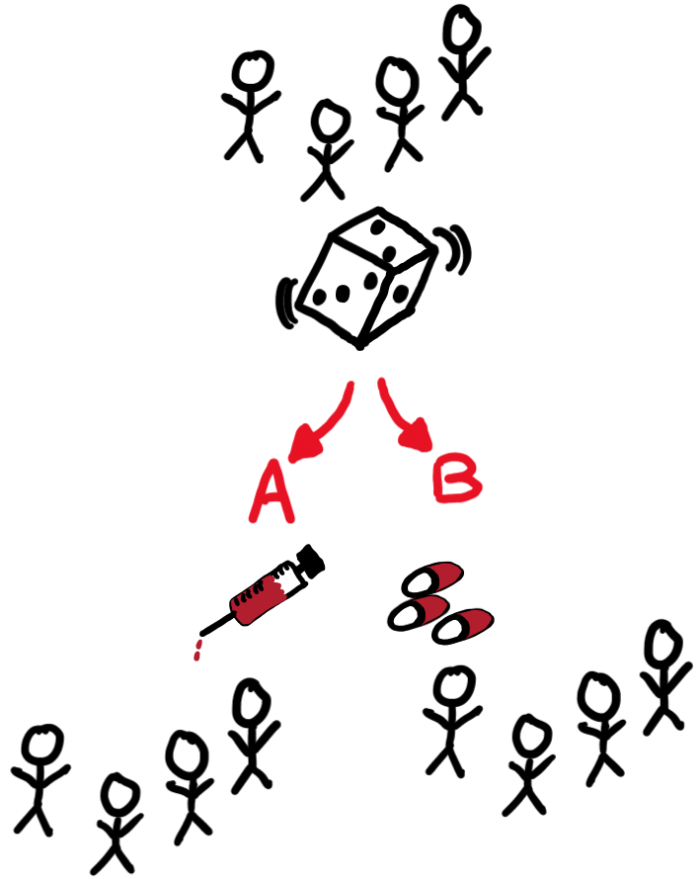

Systematic review
& meta-analysis
Trials
Cohort studies
Case-control studies
Cross-sectional studies
Case series/expert opinion
Better quality evidence

# Randomised controlled trials

**Randomisation** ensures the only difference between two groups is the intervention or drug being studied



# Why not do a randomised controlled trial?

Trials are expensive

Trials are time consuming

Some trials may not be feasible due to failure to recruit participants in the target population

# Target trial emulation

JAMA Network Open

Original Investigation | Geriatrics

## Antihypertensive Deprescribing and Cardiovascular Events Among Long-Term Care Residents

Michelle C. Odden, PhD; Laura A. Graham, PhD; Xiaojuan Liu, PhD, MS; Chintan V. Dave, PharmD, PhD; Sei J. Lee, MD, MAS; Yongmei Li, PhD; Bocheng Jing, MS; Kathy Fung, MS; Carmen A. Peralta, MD, MAS; Michael A. Steinman, MD

### Abstract

**IMPORTANCE** The practice of deprescribing antihypertensive medications is common among long-term care residents, yet the effect on cardiovascular outcomes is unclear.

**OBJECTIVE** To compare the incidence of hospitalization for myocardial infarction (MI) or stroke among long-term care residents who are deprescribed or continue antihypertensive therapy.

**DESIGN, SETTING, AND PARTICIPANTS** This comparative effectiveness research study used target trial emulation with observational electronic health record data from long-term care residents aged 65 years or older admitted to US Department of Veterans Affairs community living centers between October 1, 2006, and September 30, 2019, and taking at least 1 antihypertensive medication. Analyses were conducted between August 2023 and August 2024.

### Key Points

**Question** Is antihypertensive medication deprescribing associated with myocardial infarction and stroke in long-term care residents?

**Findings** In this comparative effectiveness research study using target trial emulation and including 13 096 US veterans residing in long-term care, no association between antihypertensive medication deprescribing and hospitalization for

**Table 1. Target Trial Protocol**

| Protocol component | Target trial | Emulation |
|---|---|---|
| Eligibility criteria | 1. VA nursing home resident aged ≥65 y at CLC admission<br>2. Admitted to CLC between October 1, 2006, and September 30, 2019<br>3. Had a CLC stay ≥90 days (to identify residents who were admitted for long-term care)<br>4. Had no acute hospital stays >30 days during CLC stay<br>5. Taking antihypertensive medications at admission<br>6. Systolic BP <160 mm Hg<br>7. No history of heart failure | Criteria 1-7 (except criterion 3) were the same as the target trial; for criterion 3, the target trial began at week 13 to eliminate the possibility of immortal time bias; residents at a low-volume CLC and those missing data on gender were excluded |
| Treatment strategies | Initiate antihypertensive deprescribing and maintain for 2 wk (deprescribed group) vs stable and/or increased antihypertensive use (nondeprescribed group) | Same as the target trial |
| Treatment assignment | Individuals were randomly assigned to a strategy at baseline | Individuals were assigned according to the strategy with which their data were comparable at baseline, and an attempt was made to emulate randomization by accounting for confounding and deviation from the assigned group |
| Outcome | Time to adjudicated MI or stroke | Time to MI or stroke hospitalization, based on EHR |
| Follow-up period | Follow up residents for 2 y from baseline or until discharge, death, loss to follow-up, or March 1, 2022 | Same as the target trial |
| Causal contrasts of interest | Intent-to-treat effect and per-protocol effect | Observational analogue of intent-to-treat and per-protocol effect |
| Analysis plan | Pooled logistic regression analysis of time to event compared across treatment strategies | Same as for the target trial, with additional adjustment for baseline covariates and preinitiation covariates using inverse probability weighting for treatment and adjustment for precensoring covariates using inverse probability weighting for censoring |

Abbreviations: BP, blood pressure; CLC, community living center; EHR, electronic health record; MI, myocardial infarction; VA, US Department of Veterans Affairs.

Table 3. HRs of Deprescribing Antihypertensive Medication and MI or Stroke Hospitalization Based on Target Trial Emulation

| Outcome | Intent-to-treat analysis | | | Per-protocol analysis | | |
|---|---|---|---|---|---|---|
| | Event rate, per 1000 person-years | | | Event rate, per 1000 person-years | | |
| | Deprescribed | Not deprescribed | HR (95% CI) | Deprescribed | Not deprescribed | HR (95% CI) |
| MI or stroke | | | | | | |
| Overall | 69.6 | 55.9 | NA | 75.9 | 62.1 | NA |
| Unadjusted | NA | NA | 1.21 (1.01-1.47) | NA | NA | 1.15 (0.88-1.51) |
| IPTW[a] | NA | NA | 1.03 (0.83-1.27) | NA | NA | 0.99 (0.74-1.31) |
| IPTW plus IPCW[a] | NA | NA | NA | NA | NA | 0.93 (0.71-1.23) |
| Expanded outcome definition[b] | | | | | | |
| Overall | 74.2 | 61.3 | NA | 81.6 | 67.4 | NA |
| Unadjusted | NA | NA | 1.18 (0.99-1.42) | NA | NA | 1.14 (0.88-1.48) |
| IPTW[a] | NA | NA | 1.01 (0.82-1.24) | NA | NA | 0.97 (0.73-1.30) |
| IPTW plus IPCW[a] | NA | NA | NA | NA | NA | 0.94 (0.70-1.26) |

No evidence of an association between antihypertensive deprescribing and MI or stroke leading to hospitalisation

**Could this be due to unmeasured confounding?**

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# Designing a deprescribing trial

**P**opulation – older people at risk of adverse events (deprescribing for prevention) or older people at the end of life (deprescribing due to futility)

**I**ntervention – deprescribing a specific drug class or an intervention which promotes/supports deprescribing inappropriate medication

**C**omparator – Placebo or usual care

**O**utcome – Medication changes, inappropriate medication prescriptions corrected, risk factor changes, clinical endpoints (adverse events, hospitalization, death)

# Designing a deprescribing trial

**P**opulation – Older people

**I**ntervention – Deprescribing an antihypertensive

**C**omparator – Usual care

**O**utcome – Mortality, hospitalization, cardiovascular disease

# Antihypertensive deprescribing trials

Previous trials of antihypertensive deprescribing are underpowered to determine the effect on health outcomes

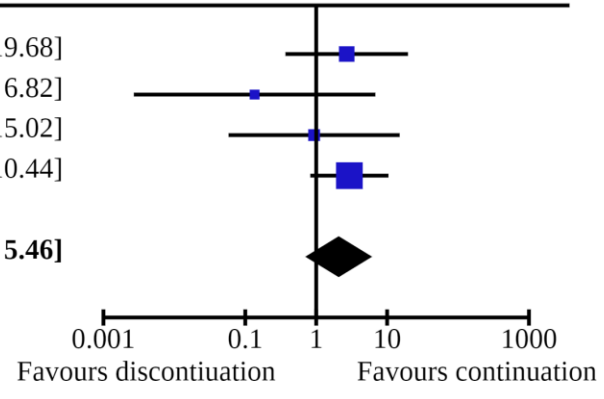
**Figure 4. Forest plot of comparison: 1 Continuation vs discontinuation by no treatment/placebo of antihypertensives, outcome: 1.1 All-cause mortality.**

| Study or Subgroup | Favours discontiuation Events | Total | Continuation Events | Total | Weight | Peto Odds Ratio Peto, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Burr 1977 (1) | 3 | 54 | 1 | 52 | 23.6% | 2.69 [0.37 , 19.68] |
| Maland 1983 (2) | 0 | 31 | 1 | 31 | 6.1% | 0.14 [0.00 , 6.82] |
| Moonen 2015 (3) | 1 | 199 | 1 | 186 | 12.1% | 0.93 [0.06 , 15.02] |
| Myers 1982 (4) | 8 | 38 | 3 | 39 | 58.1% | 2.94 [0.83 , 10.44] |
| **Total (95% CI)** | | **322** | | **308** | **100.0%** | **2.08 [0.79 , 5.46]** |
| Total events: | 12 | | 6 | | | |

Heterogeneity: Chi² = 2.53, df = 3 (P = 0.47); I² = 0%

Test for overall effect: Z = 1.48 (P = 0.14)

Test for subgroup differences: Not applicable




Reeve E *et al.*, Cochrane Database of Systematic Reviews 2020; No: CD012572

# Designing trials is about compromise

- Trials need to be **large** to be powered on clinical endpoints – this is expensive
- In the context of deprescribing, **safety** is a key consideration for patients and doctors involved in delivering the trial. Long-term follow-up may not be acceptable where there are significant concerns about safety.
- Consideration needs to be given as to the **size of effect** that would be expected from stopping one or more medications
- So a small, short trial, where we are not looking to demonstrate a difference between groups would be preferable

# Overview

1. Management of blood pressure in older adults
2. Why do a randomised controlled trial of deprescribing antihypertensives?
3. What should we consider when designing a deprescribing trial?
4. What was our experience in the OPTiMISE trial?
5. Summary

Research

JAMA | Original Investigation

# 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

James P. Sheppard, PhD; Jenni Burt, PhD; Mark Lown, MRCGP; Eleanor Temple, BSc; Rebecca Lowe, BSc; Rosalyn Fraser, MSc; Julie Allen, BSc; Gary A Ford, MB, BChir; Carl Heneghan, DPhil; F. D. Richard Hobbs, MBChB; Sue Jowett, PhD; Shahela Kodabuckus, MSc; Paul Little, MD; Jonathan Mant, MD; Jill Mollison, PhD; Rupert A. Payne, MRCGP; Marney Williams, BEd; Ly-Mee Yu, DPhil; Richard J. McManus, PhD; for the OPTIMISE Investigators

Sheppard *et al.,* JAMA. 2020;323(20):2039-2051

OPTiMISE Optimising Treatment for Mild Systolic Hypertension in the Elderly

# Design

Primary Care based, open-label, randomised controlled trial

**P**opulation: 569 older patients (≥80 years) with controlled systolic blood pressure (<150 mmHg), prescribed two or more antihypertensive medications

**I**ntervention: Medication reduction

**C**omparator: Usual care

**O**utcome: Non-inferior difference in the proportion of patients with systolic blood pressure levels below 150 mmHg of less than 10% at 12 week follow-up



Sheppard *et al.,* JAMA. 2020;323(20):2039-2051

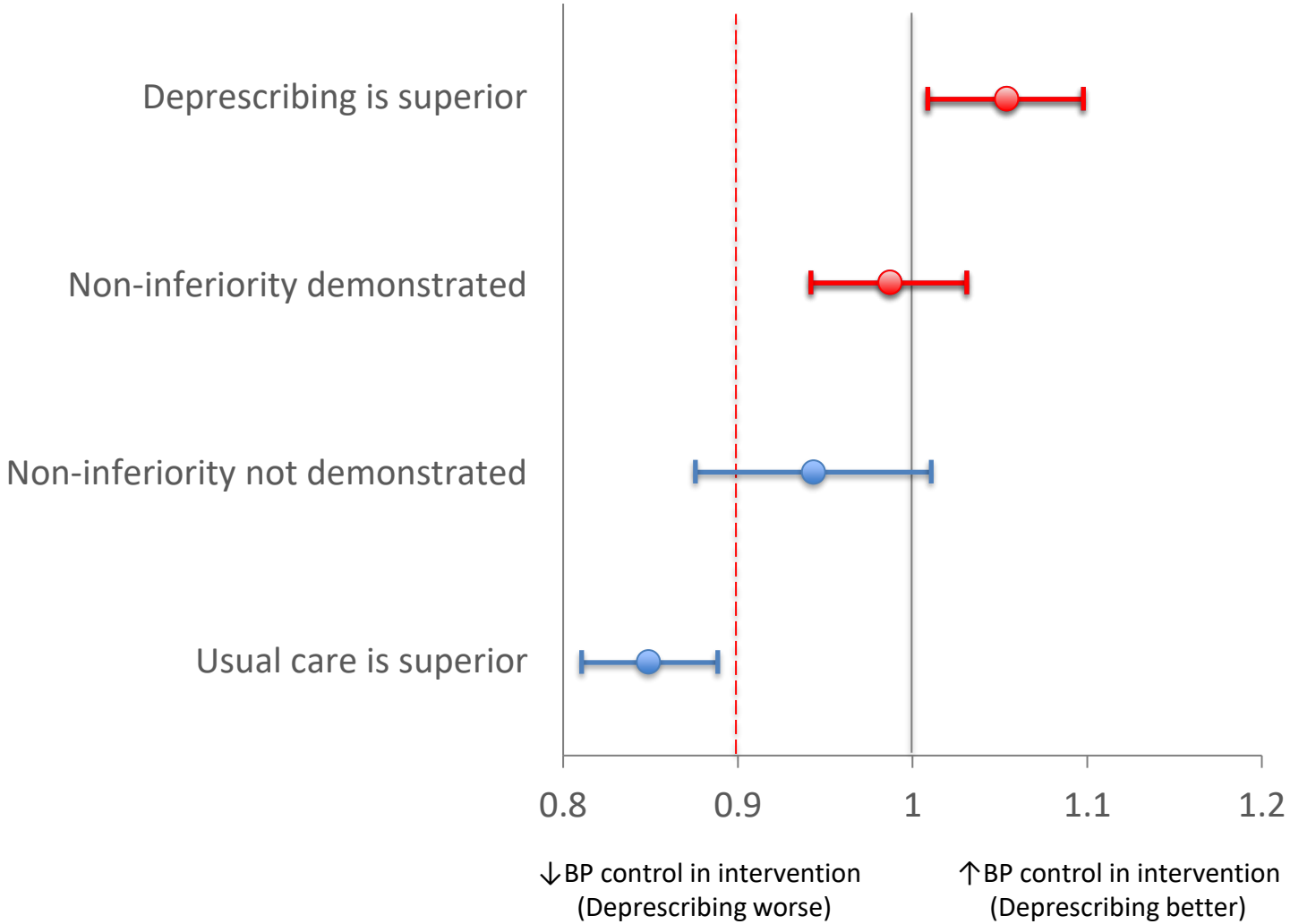
# Follow-up and outcomes

A follow-up of 12 weeks was made for ethical reasons to demonstrate the short-term effects of medication reduction on blood pressure and adverse events prior to embarking on a larger study with longer follow-up.

| Outcome type | Description |
|---|---|
| Primary | Relative risk of systolic BP control at 12 weeks |
| Secondary | Maintenance of medication reduction at 12 weeks |
| | Mean difference in change in systolic BP at 12 weeks |
| | Risk of side effects at 12 weeks |
| | Risk of serious adverse events at 12 weeks |



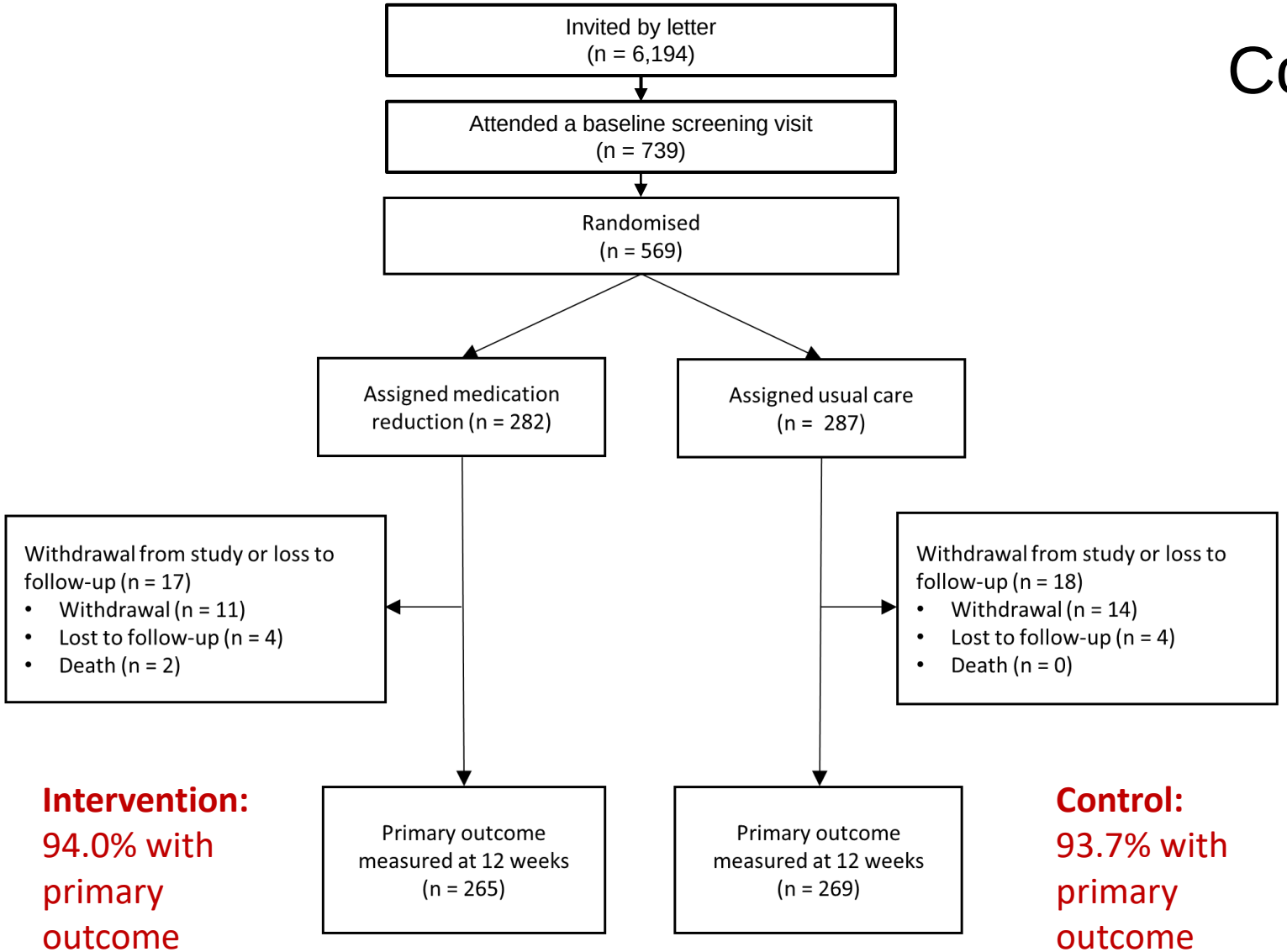
Sheppard *et al.*, JAMA. 2020;323(20):2039-2051


Deprescribing is superior
Non-inferiority demonstrated
Non-inferiority not demonstrated
Usual care is superior
0.8
0.9
1
1.1
1.2
↓BP control in intervention
(Deprescribing worse)
↑BP control in intervention
(Deprescribing better)

# Key elements to the OPTiMISE study design

1. Intervention involves stopping a single type of medication
2. Community based randomised controlled trial – delivering the intervention to the patients, in the same way as it would be delivered in practice
3. Non-inferiority design – deprescribing is no worse than usual care
4. Start small and build – intermediate outcomes to demonstrate safety, leading to more definitive trial

# Consort flow diagram




**Intervention:**
94.0% with primary outcome

**Control:**
93.7% with primary outcome



Sheppard *et al.*, JAMA. 2020;323(20):2039-2051

# Primary Outcome

## Relative risk of BP control at 12 weeks (ITT analysis)

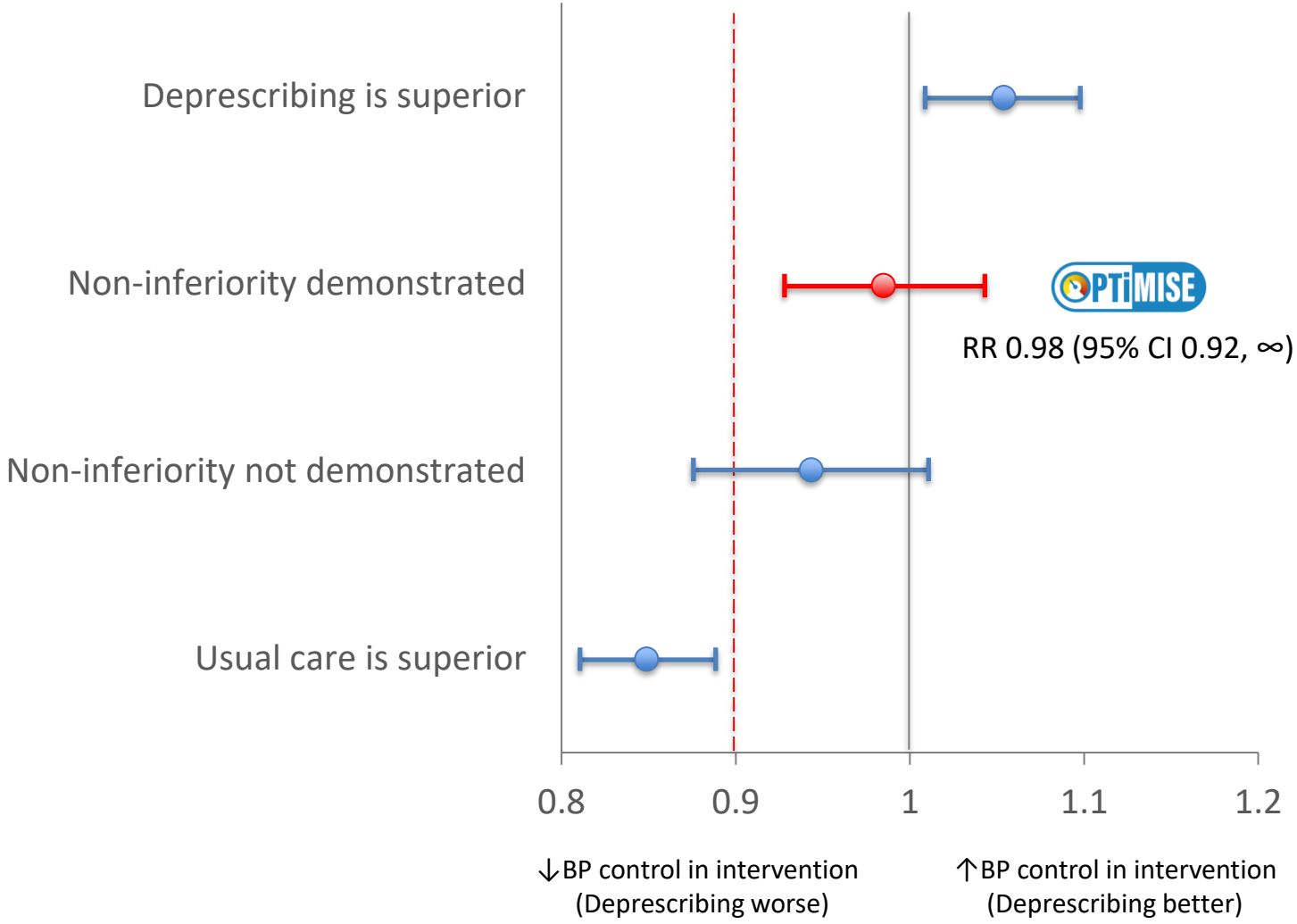
| SBP controlled at follow-up (SBP < 150 mmHg) | Intervention (N=265) | Control (N=269) | Adjusted Relative Risk[1] Intervention vs. Control (95% CI) |
|---|---|---|---|
| Yes, n(%) | 229 (86.4%) | 236 (87.7%) | 0.98 (0.92 to ∞) |

[1] Generalised linear mixed model with binomial error and log link, with baseline SBP as a fixed effect and GP practice as a random effect

Patients in the medication reduction group were 2% less likely to have controlled BP at 12 week follow-up



Sheppard *et al.*, JAMA. 2020;323(20):2039-2051






Sheppard *et al.,* JAMA. 2020;323(20):2039-2051

# Secondary Outcome

## Maintenance of medication reduction

| Antihypertensive | Yes | No | Unknown |
|---|---|---|---|
| Overall, n (%) | 187 (66.3%) | 91 (32.3%) | 4 (1.4%) |
| **Antihypertensive class:** | | | |
| ACE Inhibitor / ARB, n (%) | 45 (73.8%) | 16 (26.2%) | 0 |
| Calcium Channel Blockers, n (%) | 32 (50.0%) | 31 (48.4%) | 1 (1.6%) |
| Thiazide and related diuretics, n (%) | 59 (67.1%) | 28 (31.8%) | 1 (1.1%) |
| Beta blockers, n (%) | 29 (80.6%) | 7 (19.4%) | 0 |
| Other antihypertensives, n (%) | 22 (66.7%) | 9 (27.3%) | 2 (6.1%) |



Sheppard *et al.,* JAMA. 2020;323(20):2039-2051

# Secondary Outcome

## Change in blood pressure

| Change in blood pressure | Intervention | Control | Mean diff.[1] Intervention vs. Control (95% CI) |
|---|---|---|---|
| **ITT analysis** | N=265 | N=269 | |
| Systolic[2], mean (mmHg) | 133.7 (131.7 to 135.6) | 130.8 (128.9 to 132.7) | 3.4 (1.0 to 5.8) |
| Diastolic[2], mean (mmHg) | 70.9 (69.6 to 72.1) | 69.7 (68.5 to 70.8) | 2.2 (0.9 to 3.6) |

[1] Linear mixed effect model of the changes in the outcome from baseline to follow up, modelled against randomised group, with a random effect for practice and adjusted for baseline level of the outcome, baseline SBP, gender, Cognitive Function (MoCA Score), EQ-5D-5L Index and Searle Frailty Index.

[2] Change from baseline computed as BP at 12 weeks – BP at baseline. A positive change indicates a increase in BP.



Sheppard *et al.*, JAMA. 2020;323(20):2039-2051

# Secondary Outcome

## Difference in reporting of AEs and SAEs at 12 weeks

| Adverse Events | Intervention (N=282) | Control (N=287) | Adjusted risk ratio Intervention vs. Control (95% CI)[2] |
|---|---|---|---|
| At least 1 reported adverse event (%)[1] | 139 (49.3%) | 113 (39.4%) | 1.28 (1.06 to 1.54) |
| At least 1 reported serious adverse event (%) | 12 (4.3%) | 7 (2.4%) | 1.74 (0.68 to 4.29) |

[1]Outcome not pre-specified

[2]Adjusted for baseline systolic blood pressure and baseline adverse effects for adverse effect outcomes. The reporting of adverse effects and adverse events involved classifying the number into a binary variable in which 0 indicates no reported adverse effect or event and 1 indicates at least 1 reported adverse effect or event.

Hypertension

ORIGINAL ARTICLE

# Cost-Effectiveness of Antihypertensive Deprescribing in Primary Care: a Markov Modelling Study Using Data From the OPTiMISE Trial

Sue Jowett, Shahela Kodabuckus, Gary A. Ford, F.D. Richard Hobbs, Mark Lown, Jonathan Mant, Rupert Payne, Richard J. McManus*, James P. Sheppard*; for the OPTiMISE investigators

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UNIVERSITY OF OXFORD

Jowett *et al.,* Hypertension. 2022;79:1122–1131

STAR Stratified Treatments Research

# Health economic analyses

- A Markov patient-level simulation
- Effects of antihypertensive medication reduction examined of a life-time horizon.
- Model population characteristics were estimated using data from the OPTiMISE trial
- Long term effects of blood pressure changes on outcomes were derived from the literature.
- Health-related quality of life was modelled in Quality-Adjusted Life Years (QALYs) and results were expressed as costs per QALY gained



Jowett *et al.,* Hypertension. 2022;79:1122–1131

**Table 2**. Results of Base-Case and Threshold Cost-Effectiveness Analyses (Table view)

| Analysis | Strategy | Costs per patient | Incremental cost | QALYs gained | Incremental QALYs | ICER (£/QALY) | Interpretation |
|---|---|---|---|---|---|---|---|
| Base-case analysis | Reduced medication | £4560 | | 3.343 | | | Usual care is cost-effective. The reduced medication strategy is not cost-effective (cost savings not worth loss of QALYs). |
| | Usual Care | £4745 | £185 | 3.405 | 0.062 | £2975 | |
| Threshold analysis: Absolute risk of SAEs=7.7% per year.* Willingness to pay=£20 000/QALY | Reduced medication | £7275 | | 3.301 | | | Usual care no longer the preferred strategy if risk >7.7% year (cost savings worth the loss of QALYs with reduced medication). |
| | Usual Care | £8069 | £794 | 3.340 | 0.039 | £20 613 | |

# Health economic analyses

**Table 3**. Estimated Incidence of Outcome Events in the Base-Case Analysis Over the Life-Time Time Horizon (Table view)

| Outcome event type | Outcome events per 100 000 patients over the life-time (20 years) time horizon | | |
|---|---|---|---|
| | Medication reduction | Usual care | Difference between groups* |
| Heart failure | 22 160 | 19 421 | 2739 |
| Coronary heart disease | 18 177 | 18 606 | −429 |
| Stroke/transient ischemic attack | 19 376 | 18 692 | 684 |
| Serious drug-related adverse event | 4938 | 6376 | −1438 |
| Minor drug-related adverse event | 39 859 | 51 568 | −11 709 |

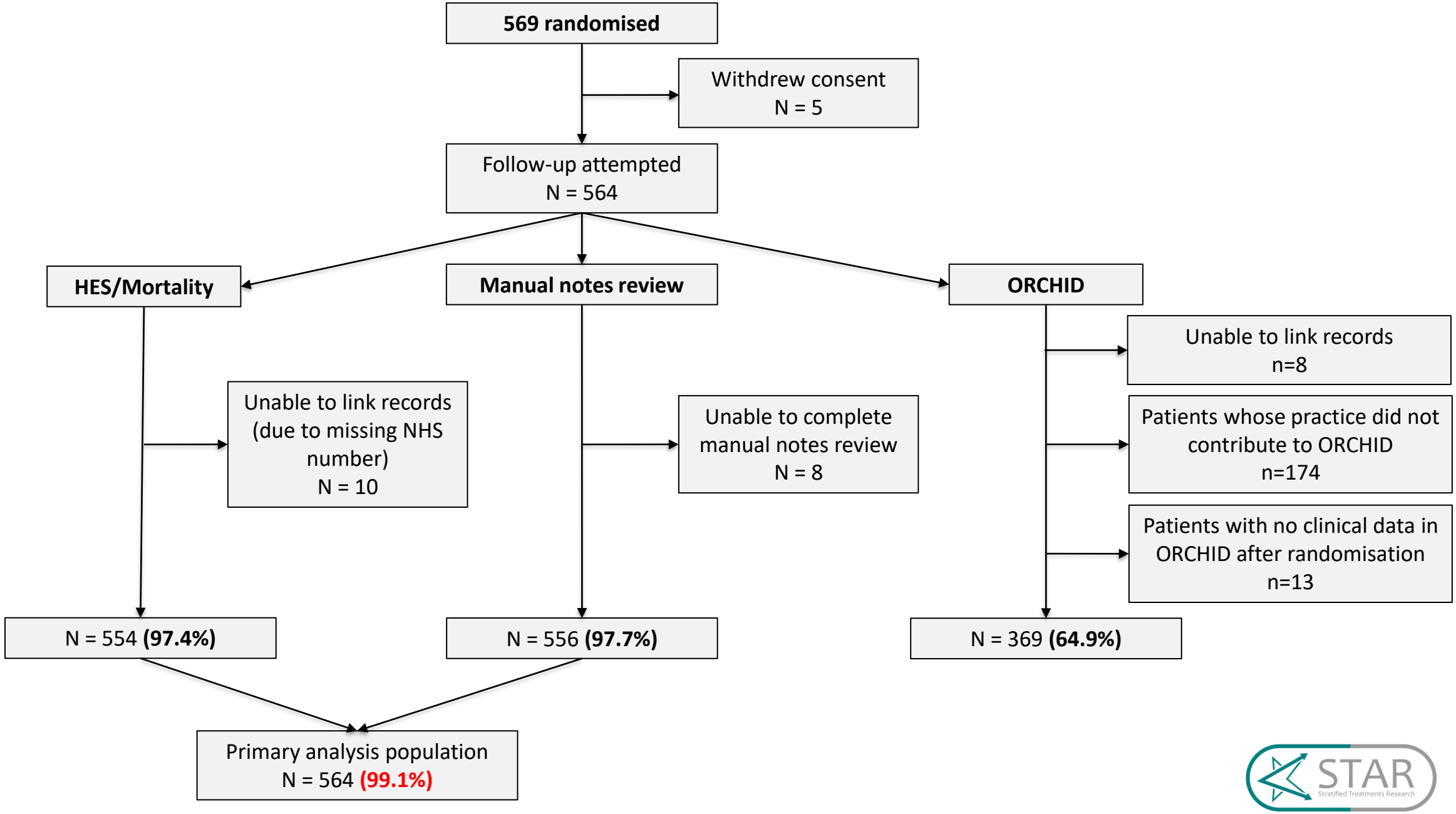
* Positive integer indicates more events in the medication reduction group.



Jowett *et al.,* Hypertension. 2022;79:1122–1131

# OPTIMISE-eXtension: Long-term follow-up study

- Aim to follow-up all participants at least 3 years after randomisation using data from their electronic health records
- Data were collected via three approaches:
  - Linked Hospital Episode Statistics and Civil Registration Death data via NHS England
  - Manual notes review of primary care records directly from practices
  - Automated data extraction from primary care records via ORCHID (in participating practices only)


569 randomised
Withdrew consent
N = 5
Follow-up attempted
N = 564
HES/Mortality
Manual notes review
ORCHID
Unable to link records
n=8
Unable to link records
(due to missing NHS
number)
N = 10
Unable to complete
manual notes review
N = 8
Patients whose practice did not
contribute to ORCHID
n=174
Patients with no clinical data in
ORCHID after randomisation
n=13
N = 554 (97.4%)
N = 556 (97.7%)
N = 369 (64.9%)
Primary analysis population
N = 564 (99.1%)
STAR
Stratified Treatments Research

# Effect on medication prescriptions

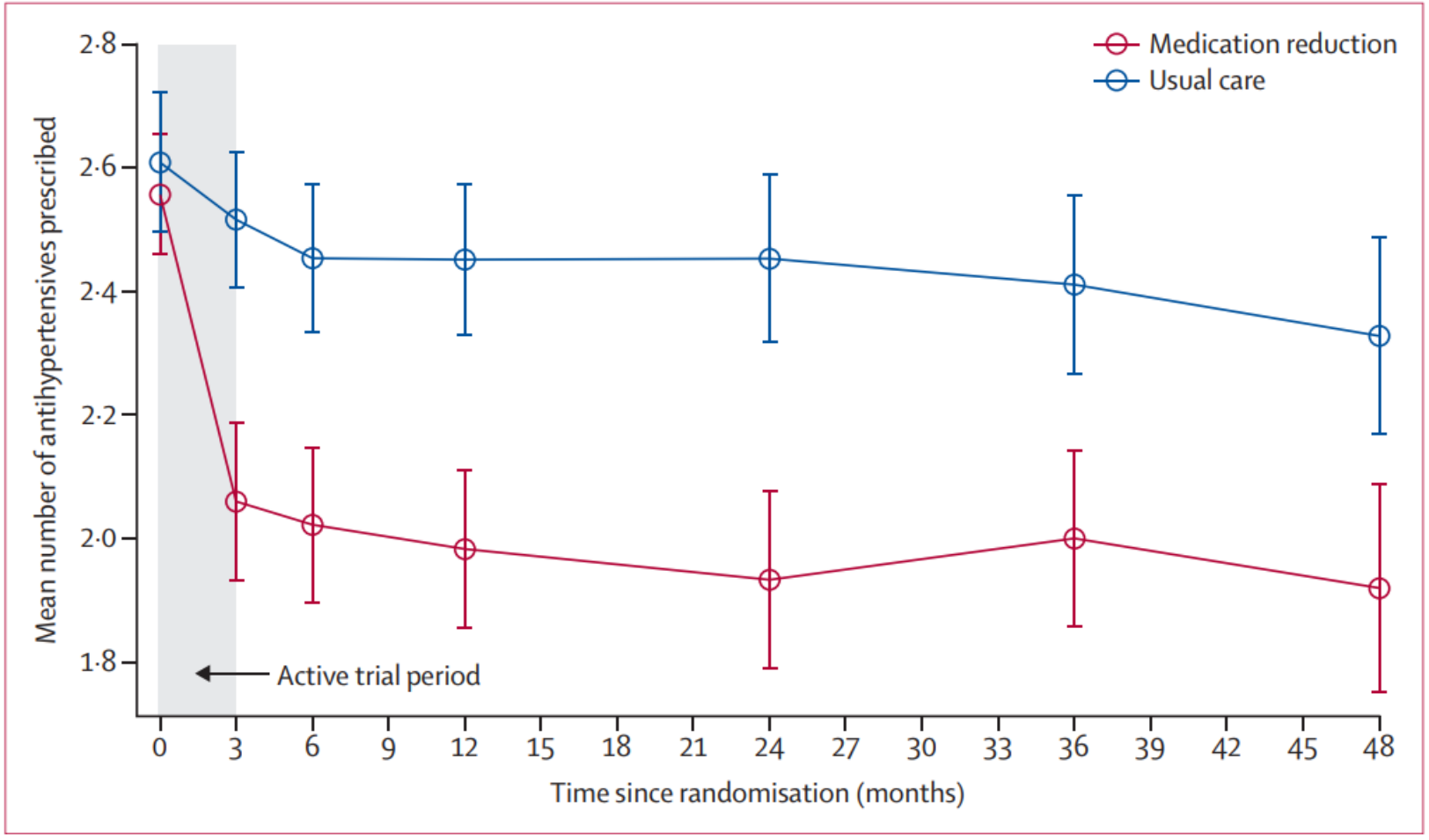
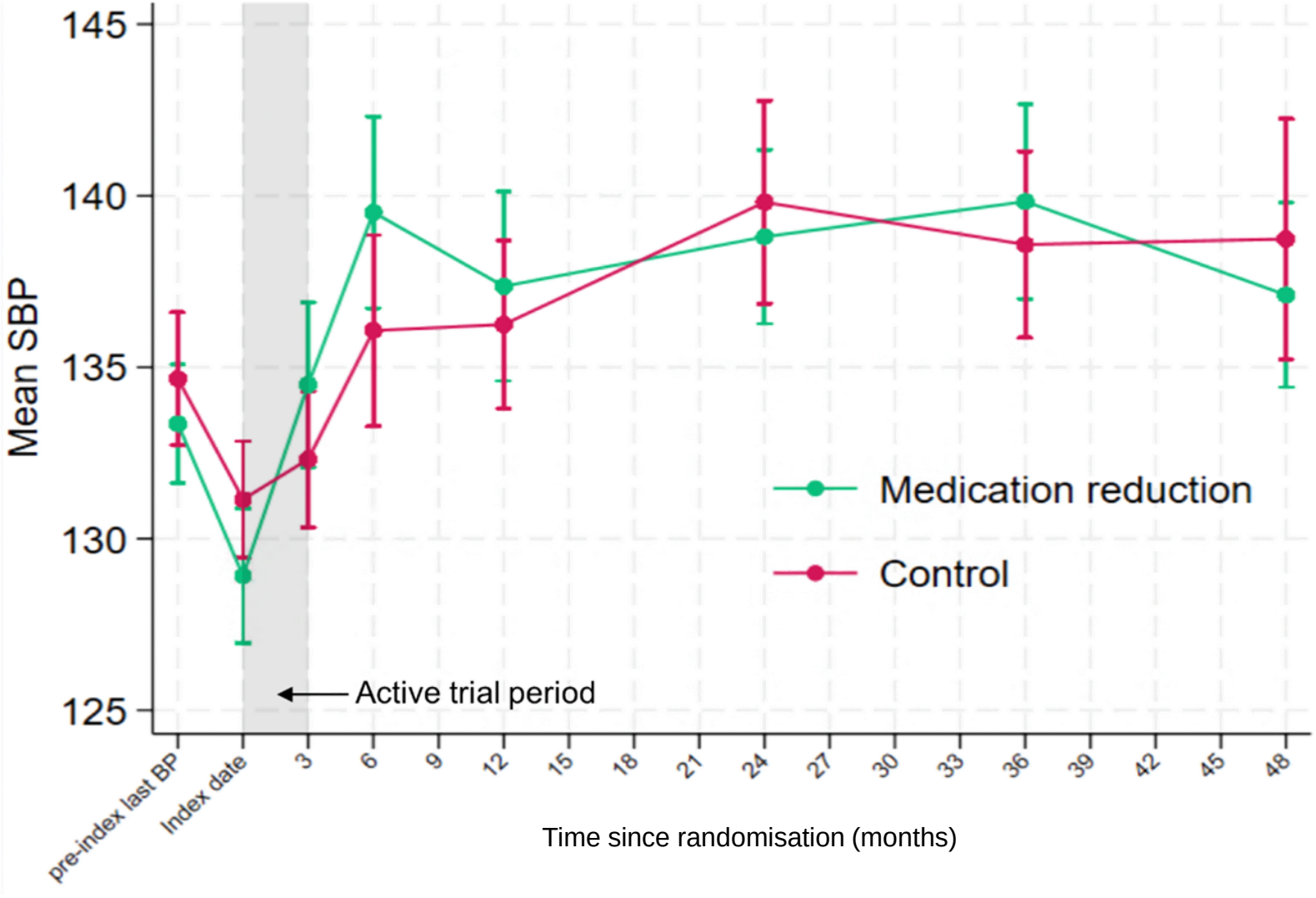



***Figure 2*: Antihypertensive medication prescription changes over time in participants registered to practices contributing to ORCHID (n=369)**

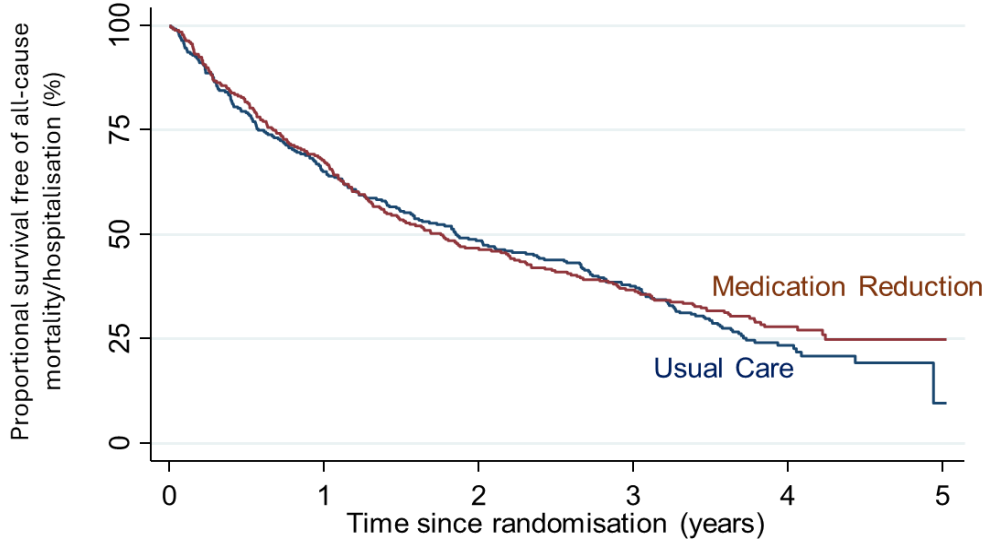
Error bars indicate 95% CIs.

# Effect on systolic blood pressure



# Effect on clinical outcomes

## All-cause hospitalisation and death (primary outcome)




| | | | | | | |
|---|---|---|---|---|---|---|
| **Medication reduction** | | | | | | |
| Alive/not hospitalised | 280 | 188 | 129 | 102 | 43 | 0 |
| Censored | 0 | 0 | 0 | 0 | 38 | 78 |
| Died/hospitalised | 0 | 92 | 151 | 178 | 199 | 202 |
| **Usual Care** | | | | | | |
| Alive/not hospitalised | 284 | 184 | 137 | 106 | 31 | 0 |
| Censored | 0 | 0 | 0 | 0 | 40 | 66 |
| Died/hospitalised | 0 | 100 | 147 | 178 | 213 | 218 |

| | Intervention (n=280) | Control (n=284) | Adjusted hazard ratio (95% CI) |
|---|---|---|---|
| **ITT** | **202 (72%)** [593; 34.1] | **218 (77%)** [595; 36.7] | 0.93 (0.76 to 1.12) |
| **PP** | **126 (67%)** [425; 29.6] | **218 (77%)** [595; 36.7] | 0.80 (0.64 to 1.00) |

Data are n (%) [Number of person-years at risk; incidence rate]

ITT = Intention to treat analysis

PP = Per protocol analysis

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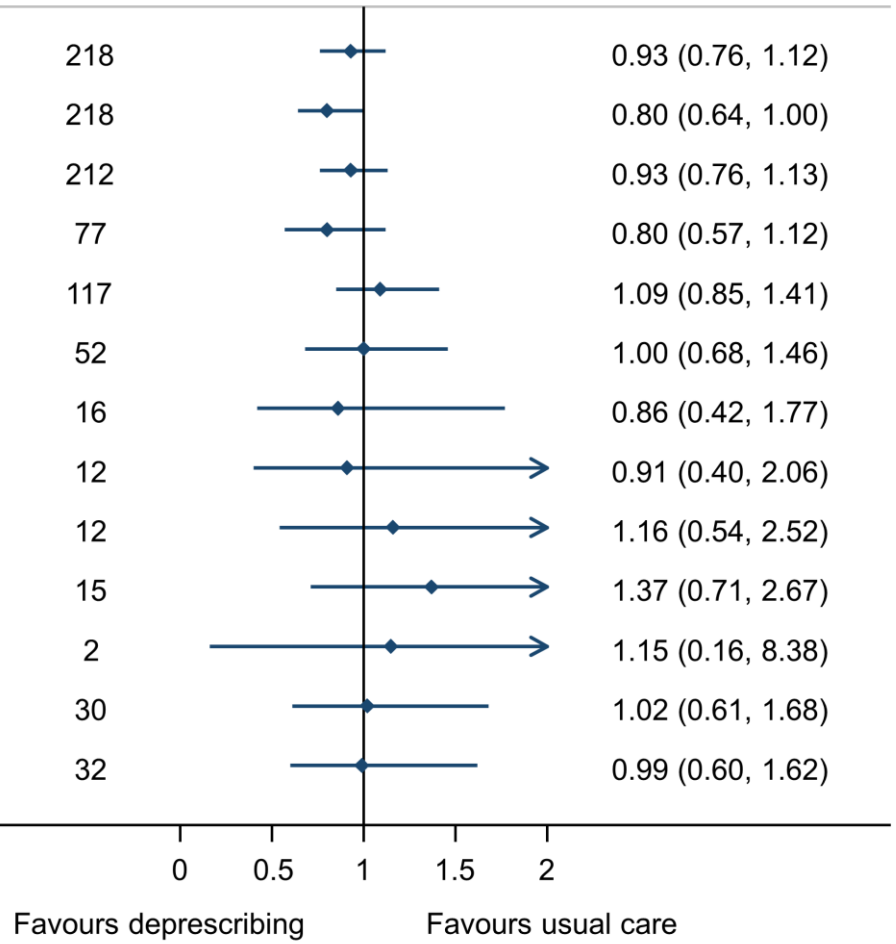
# Effect on clinical outcomes

| Outcome | Total population | Deprescribing group events | Usual care group events | Hazard ratio (95% CI) |
|---|---|---|---|---|
| All-cause hospitalisation or mortality (ITT) | 564 | 202 | 218 | 0.93 (0.76, 1.12) |
| All-cause hospitalisation or mortality (PP) | 471 | 126 | 218 | 0.80 (0.64, 1.00) |
| All-cause hospitalisation | 564 | 197 | 212 | 0.93 (0.76, 1.13) |
| All-cause mortality | 564 | 67 | 77 | 0.80 (0.57, 1.12) |
| Emergency hospitalisation | 564 | 123 | 117 | 1.09 (0.85, 1.41) |
| Major cardiovascular events | 564 | 52 | 52 | 1.00 (0.68, 1.46) |
| Myocardial infarction | 564 | 14 | 16 | 0.86 (0.42, 1.77) |
| Stroke | 564 | 11 | 12 | 0.91 (0.40, 2.06) |
| Dementia | 564 | 14 | 12 | 1.16 (0.54, 2.52) |
| Hypotension | 564 | 21 | 15 | 1.37 (0.71, 2.67) |
| Fracture | 564 | 2 | 2 | 1.15 (0.16, 8.38) |
| Electrolyte abnormalities | 564 | 31 | 30 | 1.02 (0.61, 1.68) |
| Acute kidney injury | 564 | 32 | 32 | 0.99 (0.60, 1.62) |




ITT = Intention to treat analysis
PP = Per protocol analysis

# Summary

Despite taking fewer antihypertensives, there was no evidence of an increased risk of the following:


All-cause hospitalisation or death


All-cause mortality


Cardiovascular disease


Adverse events usually associated with prescribing treatment

# Why bother with trials of deprescribing?

| Cardiovascular disease | Odden et al., 2024 | | | Sheppard et al., 2024 | | |
|---|---|---|---|---|---|---|
| | Event rate (deprescribed) | Event rate (not deprescribed) | Adjusted Hazard ratio | Event rate (deprescribed) | Event rate (not deprescribed) | Adjusted Hazard ratio |
| Intention to treat analysis | 69.6 | 55.9 | 1.03 (0.83 to 1.27) | 52.9 | 51.9 | 1.00 (0.68 to 1.46) |
| Per protocol analysis | 75.9 | 61.1 | 0.99 (0.74 to 1.31) | - | - | - |

- Those who don't believe in deprescribing will always question effect estimates from observational studies (due to unmeasured confounding)
- Guideline and policy markers use trials to make decisions
- Even these long-term follow-up data are considered observational in nature


# Optimising Prescription of Treatment In older patients with Mild hypertension at Increased risk of Serious adverse Events

UNIVERSITY OF OXFORD
NUFFIELD DEPARTMENT OF PRIMARY CARE HEALTH SCIENCES

OPTIMISE 2

# **OPTIMISE2** - Aims

This trial will establish whether deprescribing common drugs that lower blood pressure is safe in older people.

1. What is the effect of deprescribing blood pressure lowering drugs on hospital admissions and death?

2. Does deprescribing improve quality of life and/or save money for the NHS?

# **OPTIMISE2** - Design

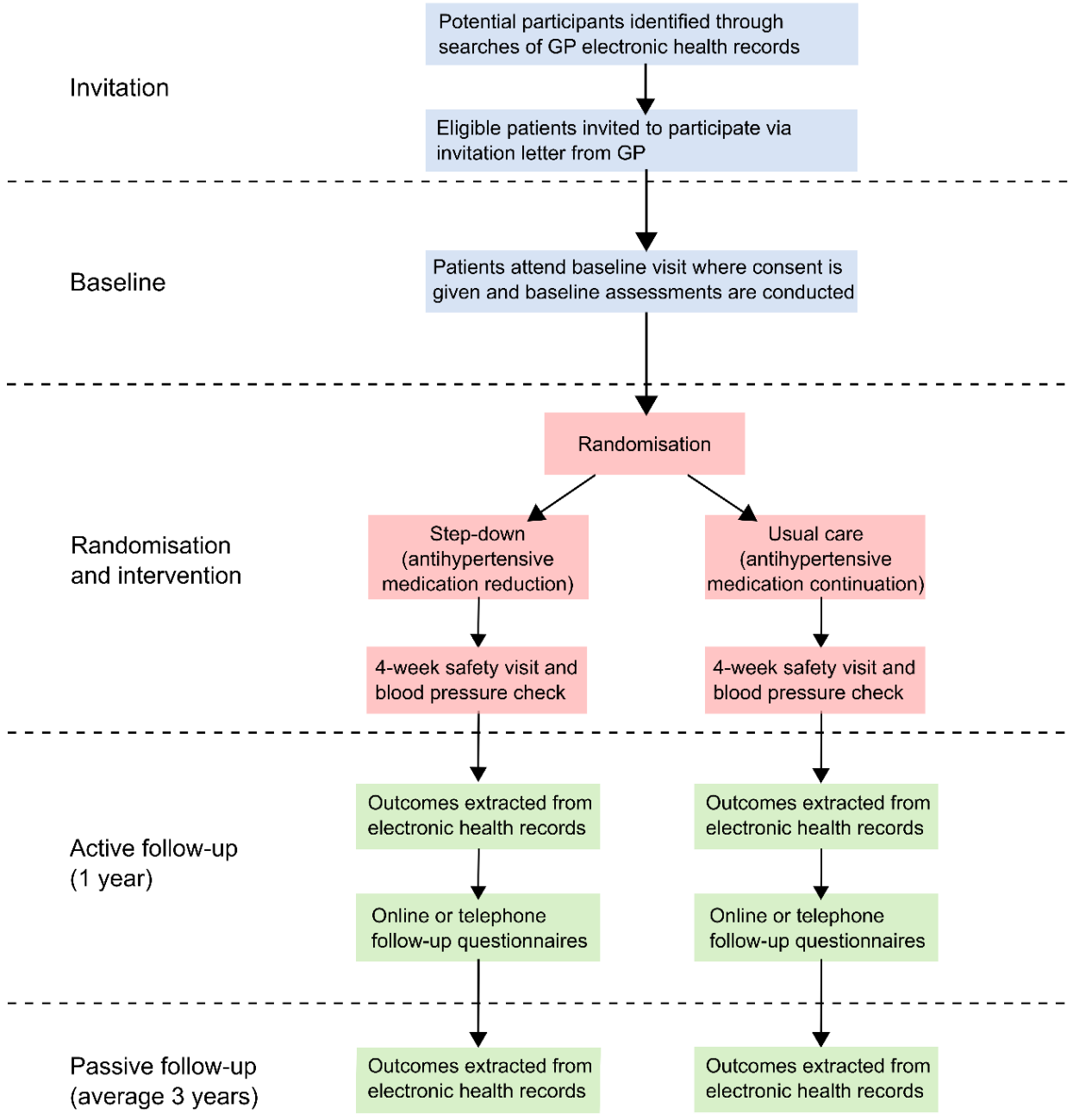
Primary Care based, open-label, randomised controlled trial

**P**opulation: 3,014 older patients (≥75 years) with controlled systolic blood pressure (<140/150 mmHg), prescribed two or more antihypertensive medications and at high risk of serious adverse events

**I**ntervention: Step down medication reduction

**C**omparator: Usual care

**O**utcome: Non-inferior difference in the proportion of patients experiencing emergency hospitalisation or death of less than 5% at 12 month follow-up


Potential participants identified through searches of GP electronic health records
Invitation
Eligible patients invited to participate via invitation letter from GP
Baseline
Patients attend baseline visit where consent is given and baseline assessments are conducted
Randomisation
Randomisation and intervention
Step-down (antihypertensive medication reduction)
Usual care (antihypertensive medication continuation)
4-week safety visit and blood pressure check
4-week safety visit and blood pressure check
Active follow-up (1 year)
Outcomes extracted from electronic health records
Outcomes extracted from electronic health records
Online or telephone follow-up questionnaires
Online or telephone follow-up questionnaires
Passive follow-up (average 3 years)
Outcomes extracted from electronic health records
Outcomes extracted from electronic health records

# Summary

- Antihypertensives are associated with an increased risk of adverse events in older people and those with frailty
- In some patients, deprescribing is recommended despite limited evidence regarding safety and efficacy
- Our data suggest antihypertensives can be stopped safely with no evidence of harm
- The benefits of deprescribing remain unknown
- Generating data from randomised controlled trials is the best way to influence policy and practice

# Our team

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