Observed and expected serious adverse event rates in randomised clinical trials of antihypertensives; a comparison between standard trials and trials in older people

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# Abstract (250 word limit – currently 255)

## Introduction

The representativeness of clinical trials of antihypertensive drugs are uncertain, even where such trials specifically recruit older participants. If such “older people” trials are representative, we would expect rates of hospitalisation and death in such trials to be similar to rates in the community, and higher than rates in “standard” trials not targeted at older people.

## Methods

We identified registered RCTs for Renin-Angiotensin-Aldosterone system drugs for hypertension, both ‘older-people trials’ (recruiting people over 60, (n=11)) and ‘standard trials’ (n=99). In adults, SAEs (whether caused by the study drug or not) are routinely included in trial reports and are predominantly accounted for by hospitalisations and death. Therefore, we compared the SAE rate in older-people trials and standard trials, adjusting for trial characteristics (phase/drug/comparison/outcome). We also identified a community cohort of adults with hypertension starting similar drugs (n=36,021, mean age 64) to obtain an expected rate of hospitalisations/deaths, and compared this to observed SAE rates in each trial.

## Results

Older people trials had a higher rate of SAEs than standard trials (1.74, 95% CI 1.03-2.92). However, the rate of SAEs in trials was substantially lower than the rate of hospitalisations and deaths in the community (median ratio 4.2). This was the case for both standard trials and older people trials.

## Discussion

Trials report substantially fewer SAEs than would be expected from the rate of hospitalisations and deaths among people in the community. SAE rates may be a useful metric to assess trial representativeness. Clinicians should be cautions when applying recommendations from trials to older people, even when those trials have been designed to study older participants.

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# Research in Context

## Evidence before this study

We searched Medline on 5th November 2020 using terms for “hypertension” and “trials”, and (“repesentativeness” or “serious adverse events”). 4 studies, including 24 different trials, assessed the representativeness of hypertension trials by applying trial exclusion criteria to people with hypertension in routine clinical practice. The proportion of people who were ineligible for trials was between 50% and 100% in most cases. This was true of trials specifically focussing on older adults (e.g. HYVET, SPRINT and OPTiMISE trials) in which uncontrolled blood-pressure, polypharmacy, multimorbidity and frailty were associated with ineligibility. This suggests that trial participants are likely to be ‘healthier’ overall than people treated in the community, previous studies have not directly compared health-related outcomes of trial participants real-world populations. Older adults have been shown to have higher rates, and a greater diversity, of adverse events in the trial setting. However, we did not identify any previous studies that systematically assessed rates of SAEs in hypertension trials; that compared SAEs in trials focussing on older people with ‘standard trials’; or that compared SAEs in the trial setting to similar events in routine clinical practice.

## What this study adds

After systematically identifying hypertension trials of drugs acting on the renin-angiotensin-aldosterone system, we demonstrated that trials focussing on older people had a significantly higher rate of SAEs. This suggests that trials focussing on older people recruited people with a greater risk of adverse health outcomes than trials including all ages, as would be expected. However, the rate of hospitalisations and deaths (which, by definition, would be SAEs in the setting of a trial) among people with hypertension treated in the community was on average four-fold higher than the SAE rate in the trials, after adjusting for age and sex. This difference was similar for ‘standard’ trials and trials focusing on older people. Therefore, despite having a higher risk of SAEs than in ‘standard’ trials, people included in hypertension trials focused on older people have a considerably lower incidence of adverse health outcomes than people of a similar age, receiving similar treatment in the community.

## Implications of all the available evidence

Our findings demonstrate that people in hypertension trials experience substantially lower rates of adverse health outcomes than people with hypertension treated with similar drugs in the community. This adds weight to the body of evidence showing that hypertension trials are under-representative of their target populations. However, our findings also add nuance to this statement, as trials focussing on older people do have a significantly higher rate of SAEs than standard trials. Therefore, trials focussing on older people do, at least in part, reflect the increased risk of adverse outcomes seen in older populations. Trials focussing on older people therefore have an important role in informing treatment decisions in older people, but should be viewed with caution as the degree of under-representativeness appears to be similar to ‘standard’ trials. Our findings also indicate that SAE rates may be used as a novel metric with which to assess the representativeness of trial populations, through comparison with the incidence of similar events in routine clinical care. Such an approach could facilitate more direct quantification of the consequences of trial under-representativeness, however this would require consistent and complete recording and reporting of SAEs as well as reliable estimates of event rates in the community.

# Introduction

Hypertension is a common and important modifiable risk factor for major cardiovascular disease. Hypertension is associated with age, with over 75% of people over 80 years old being diagnosed with hypertension.1 There is uncertainty, however, about how hypertension should best be managed in older people.2 The risk of cardiovascular disease associated with hypertension may reduce as people age,3 particularly in the context of frailty.4 Furthermore, antihypertensive treatment presents a range of potential risks which may disproportionately impact older people.

Randomised controlled trials (trials), which are the cornerstone of evidence-based clinical guidelines, provide the least biased assessments treatment efficacy. However, the representativeness of many trials is less clear.5 Specifically, older people are often excluded from RCTs.6 This can occur directly, through age-based exclusion criteria, or indirectly through other exclusion criteria (e.g. comorbidities) as well as the trial recruitment process.6,7 To address this problem and provide evidence to guide treatments of older people, some trials have focussed explicitly on older people.8,9 However, such trials tend to enrol only a fraction of those invited to participate.10 Older people have a greater risk of adverse health outcomes at a population level, and in the trial setting specifically.11 This is likely to be driven by characteristics such as frailty and multimorbidity which are more common in older age, associated with poor health outcomes, and often under-represented within RCTs.12,13 It is not clear, therefore, whether recruiting older people into such trials is sufficient to generate evidence applicable to older people encountered in routine clinical practice.

Previous studies assessing trial representativeness have tended to apply trial exclusion criteria to population samples derived from routine healthcare data or disease registries, concluding that many people living with long-term conditions would be ineligible for RCTs.5,6,10,14 However, such an approach does not directly assess the health outcomes in trial participants compared to those receiving routine care. One potential alternative approach is based instead on Serious Adverse Events (SAEs). SAEs in a trial setting are events which are either life threatening, lead to death, cause or prolong hospitalisation, result in serious or lasting impairment or disability, or cause a birth defect. Regulatory bodies require that trial sponsors record and report all SAEs and recording these is also part of the CONSORT statement for the publication of trial findings.15 Importantly, SAEs need not be related to the trial treatment and may occur in both treatment and control arms. Therefore, SAEs should provide a reliable measure of the rate of adverse health outcomes (particularly resulting in hospitalisation and death) within a trial population. Indeed, if a trials was perfectly representative, we would expect the SAE rate of that trial to be similar to hospitalisation and death rates among the “target” patients with the same condition to which we would expect the trial results to apply. We would also expect older people trials to have higher SAE rates than ‘standard’ or ‘unselected’ trials for the same indication.

Therefore, we will compare the rates of SAEs in older people trials with the rates in standard trials and compare the rate of SAEs in each both older people and standard trial to the rate of hospitalisation and death in people with hypertension starting RAAS in routine clinical practice, adjusting for age and sex. As an exemplar, we will focus on drugs to treat hypertension acting on the renin-angiotensin-aldosterone system (RAAS).

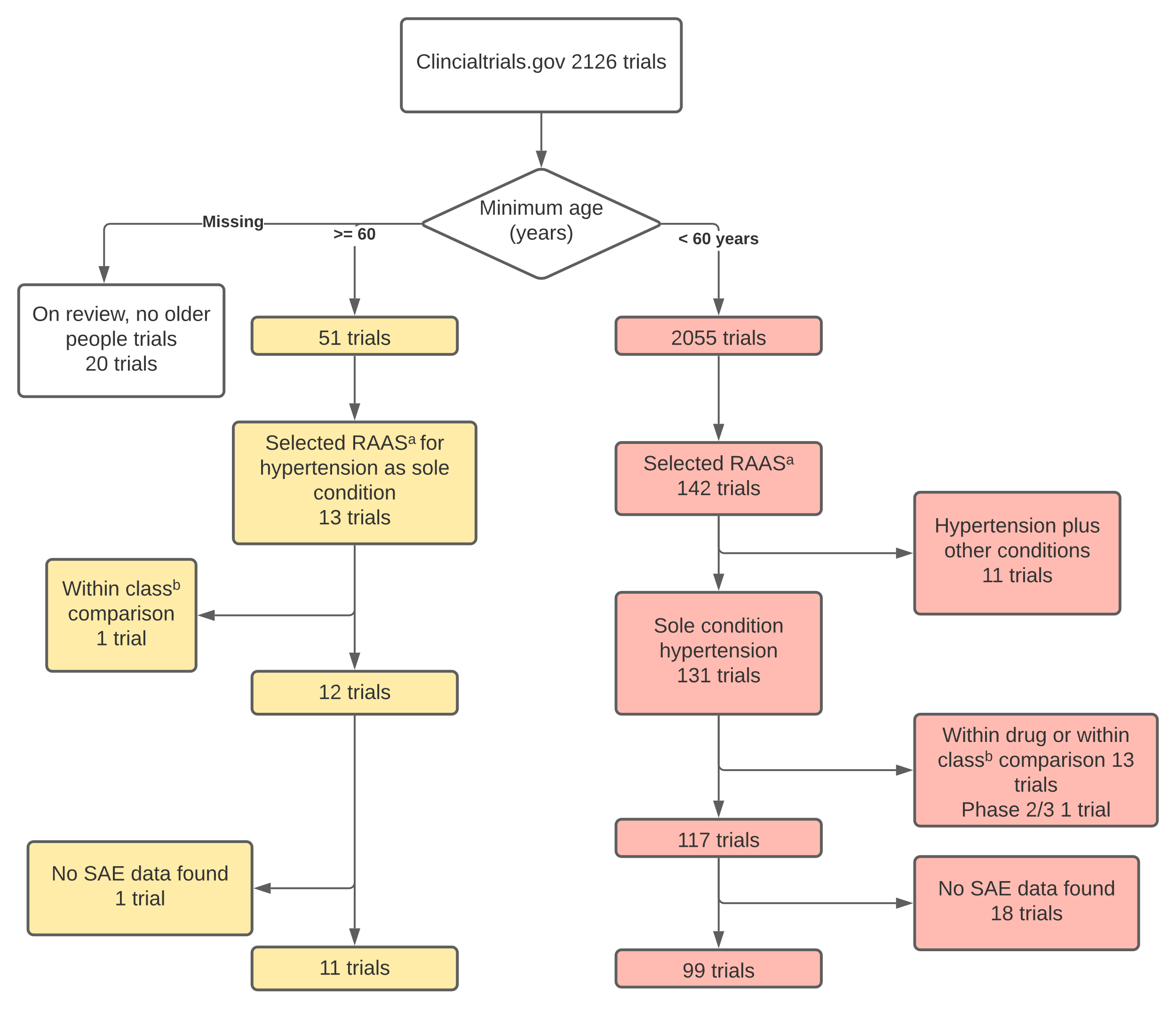
# Methods

This study compares SAE rates in registered RCTs of RAAS drugs to treat hypertension with a community sample of people with hypertension who were initiated on RAAS drugs

## Study design and participants

Trials were identified from clinicaltrials.gov, a registry of clinical trials from across the world managed by the United States National Institutes of Health based on an extract taken on August 2017 to which we had applied WHO ATC drug classes for all interventions [ref bmc paper]. We included trials in two stages (Figure 1). First, we identified all trials with a minimum inclusion age of 60-years or older, and defined these as older people trials, and reviewed these to identify drugs and indications for which older people trials were commonly undertaken, selecting drugs acting on the RAAS for the treatment of hypertension. Secondly, we obtained all trials for the same indications and drugs regardless of age-based inclusion criteria. To be eligible, trials had to be registered from 1999 onwards, be phase 2-3, 3, or 4, and have eligibility criteria published in English. We included trials undertaken in any country, single- or multi-centre trials, with published or unpublished results.

## Figure 1 Trial selection



a) All RAAS drugs were permitted for the selection of eligible older people trials. Only trials which were studied in one or more of the older person trials (aliskiren, irbesartan, olmesartan, telmisartan or valsartan) were selected for the comparator group of the standard trials. b) Within drug comparisons refers to trials where all arms included the same drug (eg trials of different dosages or regimens). Between class comparisons refers to trials where all arms included drugs with the same 5-character ATC class (eg drugs in WHO ATC class C09CA are all angiotensin II receptor blockers).

The community comparison sample was identified using the Secure Anonymised Information Linkage (SAIL) databank. SAIL collects routine healthcare data (including primary care diagnostic codes and prescriptions, with linked hospital and mortality data) from participating practices in Wales, UK (covering approximately 70% of the population). SAIL participants are representative of the wider population in terms of age, sex and socioeconomic status. We identified participants with a previous diagnostic code for hypertension in primary care who were prescribed a RAAS drug for the first time. We excluded participants who registered with a SAIL practice less than 1 year before starting the RAAS drug. We also excluded people with any coded myocardial infarction or stroke occurring in the 12 months prior to initiation (as these people were unlikely to be receiving the RAAS drug solely to treat hypertension, so are likely to have higher rates of hospitalisation and death). Figure 2 summarises participant selection and exclusions. As a sensitivity analysis, we also excluded all participants with a previous code for diabetes mellitus or heart failure.

Figure 2: Inclusion and analysis of SAIL participants for community comparison

Adult SAIL participants, initial prescription for RAAS drug 2011-2015

N=111,653

Diagnostic code of hypertension at any time before prescription

N=47,803

No myocardial infarction or stroke past 6 months

N=46,137

Registered for at least 6 months

N=36,021

36,021 participants with any previous hypertension code

Mean age: 64.6 (13.4)

19,230 (53.4%) female

20,100 events (hospitalization/death)

3 years follow-up

Mean observation time 2.8 years per person

Censored at death or de-registration

Time

Exclude recent

MI, stroke, or

recent

registrations

6-month Incident RAAS prescription 3 years follow-up

look-back

63,850 excluded

No hypertension

1,666 excluded

Recent MI/stroke

10,116 excluded

Recently registered with SAIL practice

## Measures

For the trials we extracted the following information from clinicaltrials.gov, clinical trial reports and published papers (all data on github): baseline characteristics of the trial participants (age, sex, body mass index), number of trial participants, trial phase, trial drug, comparison treatment, outcomes, follow up times, and the occurrence of serious adverse events (total number of events).

For each participant in the community sample we identified age and sex. We then calculated the number of emergency/urgent hospitalisations (excluding elective admissions) or deaths occurring over 3 years follow-up. Participants were censored at death or if they de-registered from a participating practice within the 3-year period.

## Statistical analyses

Our first analysis compared the SAE rate in ‘older-people trials’ with ‘standard trials’, adjusting for trial characteristics. We modelled SAEs on older people trial status with the following Poisson regression models; unadjusted (calculated as follow-up \* (offset by estimated person time calculated as the follow-up time x number of participants - 0.5 x) and adjusting for direct renin inhibitor trial (yes/no), comparison type (placebo, different ATC class to 3-character, different ATC class to 5-character), phase (3 or 4) and outcome type (hard or not). The latter was the pre-specified primary analysis. Models were fit using Rstanarm to allow a random intercept for the trials.

We also used Poisson regression to model the age and sex specific rate of unplanned hospital admission or death in the 3 years following initiation of RAAS drugs in SAIL. This model fit the data well (appendix) and the covariates and variance covariance matrix were exported from the SAIL secure platform to allow us to calculate the expected number of hospitalisations and deaths for each trial population. We used the truncated normal distribution to estimate the age distribution for each trial based on the reported mean age as well as any age cut-offs used as exclusion criteria. In a previous analysis of trial IPD (including trials with the same eligibility criteria as those in this sample) the truncated normal distribution was found to accurately represent the age distribution of trials in this context.12 We propagated uncertainty in the expected rates by performing the calculations of the expected rate of hospitalisation and deaths using coefficients sampled from a multivariate normal distribution (10,000 samples) and the observed rates by sampling from Poisson distributions (10,000 samples).

We performed two sets of sensitivity analyses. First, in view of the small number of older people trials, we examined the sensitivity of the findings to the inclusion of each trial by re-running the regression models having excluded each trial in turn. The first explored the impact of the trial characteristics included in the comparison between older-people and standard trials. The second sensitivity analysis explored the impact of possibly misclassification of the indication for RAAS treatment within the community cohort. For this, in addition to excluding participants with recent myocardial infarction or stroke (as in the main analysis), we also excluded any participant with a previous diagnosis of diabetes mellitus, heart failure, or chronic kidney disease. We then repeated all analyses comparing trials to the community cohort.

The full analysis code and all data are available at github\_repo.

# Results

We identified 110 trials, of which 11 were ‘older people’ trials and 99 were ‘standard trials’. A full list of trial characteristics is included in the supplementary appendix, with summary data shown in table 1. The median number of SAEs per trial was 7.5 (interquartile range [IQR] 3-14). The median rate of SAEs per person per year was 0.18 (IQR 0.12-0.29) in the older people trials and 0.11 (0.08-0.18) in the standard trials.

|  |  |  |
| --- | --- | --- |
| Table 1: Summary of included trials | | |
|  | Standard trials (n = 99) | Older-people trials (n = 11) |
| Drug under investigation |  |  |
|  |  |  |
| Comparison |  |  |
| Placebo |  |  |
| Drug of different class |  |  |
|  |  |  |
| Phase |  |  |
| 3 |  |  |
| 4 |  |  |
|  |  |  |
| Hard outcome |  |  |
| Yes |  |  |
| No |  |  |
|  |  |  |
| Mean trial age |  |  |
|  |  |  |
| % female in trial |  |  |

The comparison of SAE rates between older and standard trials is shown in table 2. In the unadjusted analysis older-people trials had a lower incidence of SAEs than standard trials. However, after adjusting for trial characteristics including trial drug, type of comparison, trial phase and type of outcome, older-people trials had a higher incidence of SAEs (IRR 1.74, 95% credible interval 1.03-2.92). This demonstrates that, for an equivalent trial comparison, trials focussing on older-people appear to successfully recruit participants with a greater risk of adverse health outcomes.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Table 2: Comparison of incidence of SAEs between older-people trials and standard trials | | | | | |
|  | Model 1 | Model 2\* | Model 3 | Model 4 | Model 5 |
| Incident rate ratio (older:standard trials) | 1.57  (0.95-2.57) | 1.74  (1.03-2.92) |  |  | 2.47 (0.73-8.33) |
| Model 1: Unadjusted, offset by estimated person time (calculated as follow-up \* (number of participants - 0.5 \* number of SAEs))  Model 2: Covariates in model 1 plus direct renin inhibitor trial (yes/no), comparison type (placebo, different ATC class to 3-character, different ATC class to 5-character), phase (3 or 4), outcome type (hard or not)  Model 3: Covariates in model 2 plus age  Model 4: Covariates in model 2 plus sex  Model 5: Covariates in model 2 plus age and sex  \*Model 2 was pre-specified as the primary analysis | | | | | |

The relationship between age and rates of hospitalisation and death among people with hypertension starting RAAS drugs within routine clinical practice is shown by the line on figure 2. Coloured points show the observed rate of SAEs in the trial, while the black points show the expected SAE rate obtained by applying community hospitalisation and death rates to the age and sex distribution of each trial (each coloured point has a black point which is its pair, but lines are not shown joining these for clarity). The observed rates were consistently lower than the expected rates (shown by the coloured points in figure 2).

|  |
| --- |
| Figure 3: Observed versus expected SAEs per trial |
|  |
| Legend: The observed rate of SAE per trial is shown by the coloured points (red = standard, blue = older people). Points are plotted at the mean age for the trial. The expected number of hospitalisations and deaths for each trial, based on the age/sex distribution of the trial applied to SAIL, is shown by the black points. The grey line shows the predicted rate of hospitalisations and deaths by age in people with hypertension in SAIL following incident RAAS use. |

A formal comparison of the ratio between the observed SAE rate and the expected rate of hospitalisation and death (taking account of the full age/sex distribution of each trial) is shown in figure 3. For all but one of the trials, the rate of SEAs was lower than the expected rate of hospitalisation and deaths given the age/sex distribution of trial participants. The median ratio was 4.23 (95% CI 2.03-8.68) indicating that hospitalisations and deaths occurred 4 times more frequently among people taking RAAS drugs in the community than did SAEs in the trial setting. There was considerable heterogeneity in the calculated ratios, both within the ‘older-people’ trials and the ‘standard trials’. However, for all trials, the reported rate of SAEs was significantly lower than would be expected to occur if the trials were representative of people with hypertension taking RAAS drugs in the community.

The effect estimates were similar across multiple models leaving out each trial in turn. The difference between trials and the community was similar after further excluding people with diabetes mellitus, heart failure or chronic kidney disease from the community sample, to minimise the risk of misclassification of the indication for RAAS treatment.

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# Discussion

In this analysis of trials of RAAS drugs for hypertension, trials specifically recruiting older people had a significantly higher incidence of SAEs than standard trials after adjusting for trial characteristics. This suggests that older-people trials are at least partly successful in recruiting participants with a higher baseline risk of adverse health outcomes. Nonetheless, in both older-people and standard trials, the rate of SAEs was substantially lower than one would expect, given how common of hospitalisations and deaths (which, in a trial setting, would be classed as SAEs) were in people with hypertension treated in the community.

The difference was large, with rates of hospitalisations and death in the community on average four times greater than the rate of SAEs in the trials suggesting that participants in older people trials and older people with similar conditions in the community are very different populations. This does not mean trial findings are inapplicable; treatment benefits obtained from trials, especially relative treatment benefits, may be applicable even where there are differences between trial and target populations. Nonetheless, it does suggest that clinical guideline developers are correct to be cautious when applying trial evidence to older, multi-morbid or frailer populations, even when the trials were deliberately conducted among older people.

While these findings suggest that trials are under-representative in terms of underlying risk of adverse health outcomes, there are two alternative explanations which could also contribute to the difference between trials and the community sample. First, trials may under-report the true incidence of SAEs. Despite reporting guidelines,15 there is inconsistency in how SAEs are reported.16 Second, our community sample may include people taking RAAS for other indications, for whom the risk of hospitalisations and deaths may be higher. For this reason, we excluded people with recent myocardial infarction or stroke, as the indication for RAAS drugs in these people is clearly different from in the hypertension trials and the risk of subsequent hospitalisation or death will be predictably higher. The results were also similar after additionally excluding people with a history of diabetes, chronic kidney disease, or heart failure. Nonetheless, we cannot be certain about the true indication for starting RAAS drugs from routine data alone. Both underreporting of SAEs and misclassification of the community comparison may bias our estimation of the difference between trials and community samples in the direction that we observed. However, the difference between trials and community was large (median 4-fold higher rate in the community than in trials) and so would be unlikely to be the result of under-reporting of SAEs alone. Similarly, while it is not possible to be certain of the indication for community prescribing, our analysis does reflect ‘real-world’ use of these drugs, in which indication may not be as clear-cut as in a trial setting.

Our findings have implications for interpreting trials that specifically recruit older people. On one hand, trials focusing on older people are likely to be helpful in informing treatment decisions as they successfully recruit people at a higher risk of serious adverse events than standard trials, thus capturing some of the increased risk experienced by older people. However, concerns about trial representativeness are still likely to be well founded, as suggested by the difference between SAEs and hospitalisation and death rates in the community. We observed that the difference between trials and community event rates were similar in both older-people and standard trials, suggesting they were similarly under-representative. This suggests that trials focussing on older people present only part of the solution to informing treatment decisions in older people, particularly those at high risk of adverse health outcomes, such as people living with frailty.

The higher rate of hospitalisations and deaths in the community setting has some important implications for managing hypertension in older people. First, the incidence of competing risks is likely to be higher in the community than in the setting of a trial. This would concur with previous studies showing that the range of adverse events experienced by older trial participants tends to be more diverse than in younger participants.17 This may lead to the absolute treatment effect estimates (eg the absolute risk reduction or numbers needed to treat) being lower than suggested by trial evidence.

Second, this finding is likely to reflect a higher prevalence and severity of frailty in the community setting compared to trials, which may modify the relationship between hypertension and cardiovascular risk.4 We previously showed, in an individual-level participant data analysis, that frailty is associated with SAEs within the trial setting.13 Furthermore, frailty within the setting of cardiovascular trials is associated with adverse cardiovascular outcomes independently of traditional risk factors.18 While frailty has been shown to be present in trials concerning treatment strategies for hypertension in older people,8,9 frailty in these trials is thought to be less severe than in the community.2 It is likely that people living with severe frailty are excluded from clinical trials, however these people are routinely prescribed these medications in the community, often in the context of polypharmacy. Evidence from existing trials, even those recruiting older people, is likely insufficient to inform these treatment decisions.

Strengths of this study include a systematic identification of registered trials. By searching using a trial register and hand-searching clinical study reports we were able to include both published and unpublished trials, limiting publication bias. Limiting our search to clincaltrials.gov may have resulted in a small proportion of studies not being included in our investigation. However, clinicaltrials.gov is the largest international trial repository and trial pre-registration is required both for publication in high-impact journals and to qualify as evidence for regulatory agencies such as the FDA. Moreover, it provided a single sampling frame from which we could draw all older people and standard trials. The systematic comparison of SAE rates with hospitalisation and death rates in the community for people with hypertension is novel, and builds upon previous studies of trial representativeness by comparing actual health-related outcomes rather than inclusion criteria. Nonetheless, comparing SAEs to hospitalisations and deaths is not an exact like-for-like comparison. SAEs have a broader definition which includes events perceived to be life threatening as well as events leading to impairment or disability (which may not necessarily result in hospitalisation). However, hospitalisations and deaths are, by definition, SAEs and so our estimation of the community incidence is, if anything, an underestimate. Trial data were reported inconsistently and for some trials, we had to estimate the observation time in the trial (based on follow-up length and the SAE rate). This calculation is a conservative estimate of the observation time, and therefore the rate of SAE may be slightly lower than was estimates for some trials. Also, as we have highlighted above, we were not able to verify the indication for RAAS drugs in the community. While we excluded participants with recent events which would be alternative indications, there may be some participants prescribed RAAS drugs for reasons other than hypertension. This study focussed on RAAS drugs for hypertension, and the findings may not necessarily be generalisable to other drugs or indications. Indeed, trials of angiotensin receptor blockers may have lower rates of adverse events and discontinuations than other antihypertensives.

## Conclusion

Hypertension trials focussing on older people appear to be more representative than “standard” trials; such trials include more participants with a higher risk of adverse health outcomes, are so are useful for informing treatment decisions in older age. Nonetheless, like participants of standard trials, participants of older people trials with hypertension have substantially lower rates of hospitalisation and death than do patients with hypertension in the community. More widely, assessment of the rate of SAEs, especially when compared to the expected rate from representative “target” populations, may be a useful metric of trial representativeness.

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