Observed and expected serious adverse event rates in randomised clinical trials of antihypertensives; comparing trials which do and do not focus on older people

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# Abstract

## Introduction

Representativeness of trials of antihypertensive drugs is uncertain. Some trials specifically recruit older participants to address this. If ‘older people’ trials are representative, we would expect rates of hospitalisation and death in each trial to be similar to rates in the community, and higher than rates in ‘standard’ trials.

## Methods

We identified trials of Renin-Angiotensin-Aldosterone system (RAAS) drugs for hypertension. Serious Adverse Events (SAEs) are routinely included in trial reports and are predominantly accounted for by hospitalisations and death. We compared SAE rates in ‘older-people’ and ‘standard’ trials, adjusting for trial characteristics (phase/drug/comparison/outcome). We identified a community cohort of adults with hypertension commencing similar drugs to obtain an expected rate of hospitalisations/deaths, and compared this to observed SAE rates in each trial.

## Results

Included 110 trials: 11 focused exclusively on people over 60 years (‘older-people trials’); 99 also included younger people (‘standard trials’). ‘Older-people’ trials had higher SAEs rate than ‘standard' trials (IRR 1.74, 95% CI 1.03-2.92). The hospitalisation and death rate in the community for those taking RAAS antihypertensives was greater than the rate of SAEs reported in ‘standard’ (ratio 4.16 (3.57-5.26)) and ‘older-people’ trials (5.26 (3.03-9.09)), adjusting for age and sex.

## Discussion

Trials report substantially fewer SAEs than would be expected from the rate of hospitalisations and deaths among similar-aged people receiving equivalent treatments 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 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 (“representative\*” or “serious adverse events”). Four 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 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 to 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 other trials; or that compared SAEs in the trial population to similar events in community populations.

## 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 than comparator trials which did not focus specifically on older people. As would be expected, this suggests that trials focussing on older people recruited people with a greater risk of adverse health outcomes than trials including all ages. However, the rate of hospitalisations and deaths (which, by definition, would be SAEs in trial populations) 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, like ‘standard’ trials, they are not representative of community populations. Our findings also indicate that SAE rates should be considered 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 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 estimates of treatment efficacy. However, there are concerns that trial participants are often not representative of people treated for hypertension in routine clinical practice.5 Specifically, older people are often excluded from trials.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 often only enrol a fraction of those invited to participate.10 Consequently, It remains unclear whether conducting trials specifically among ‘older people’ is sufficient to overcome the difficulties in applying trial evidence to older people encountered in routine clinical practice.

Older people have a greater risk of adverse health outcomes in routine care setting, and in trials.11 This is likely to be driven by characteristics such as frailty, multimorbidity (increasing the risk of drug-disease interactions) and polypharmacy (increasing risk of drug interactions) and decreased kidney and liver function which are more common in older age, associated with poor health outcomes, and often under-represented within trials.12-16

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 trials.5,6,10,17 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, whilerecording SAEs is also part of the CONSORT statement for the publication of trial findings.18 Importantly, SAEs are required to be reported irrespective of the susepcted cause, as well as for 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 trial 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 hope to apply the trial results. We would also expect trials involving ‘older people’ to have higher SAE rates than other trials for the same indication.

The aim of this paper is to compare the rates of SAEs in trials of ‘older people’ with the rates in trials not focussing specifically on older people (‘standard trials’) and compare these findings to the rate of SAEs (i.e. rate of hospitalisation and death) in people with hypertension starting a similar treatment in routine clinical practice, adjusting for age and sex. As an exemplar, here we focus on drugs to treat hypertension acting on the renin-angiotensin-aldosterone system (RAAS).

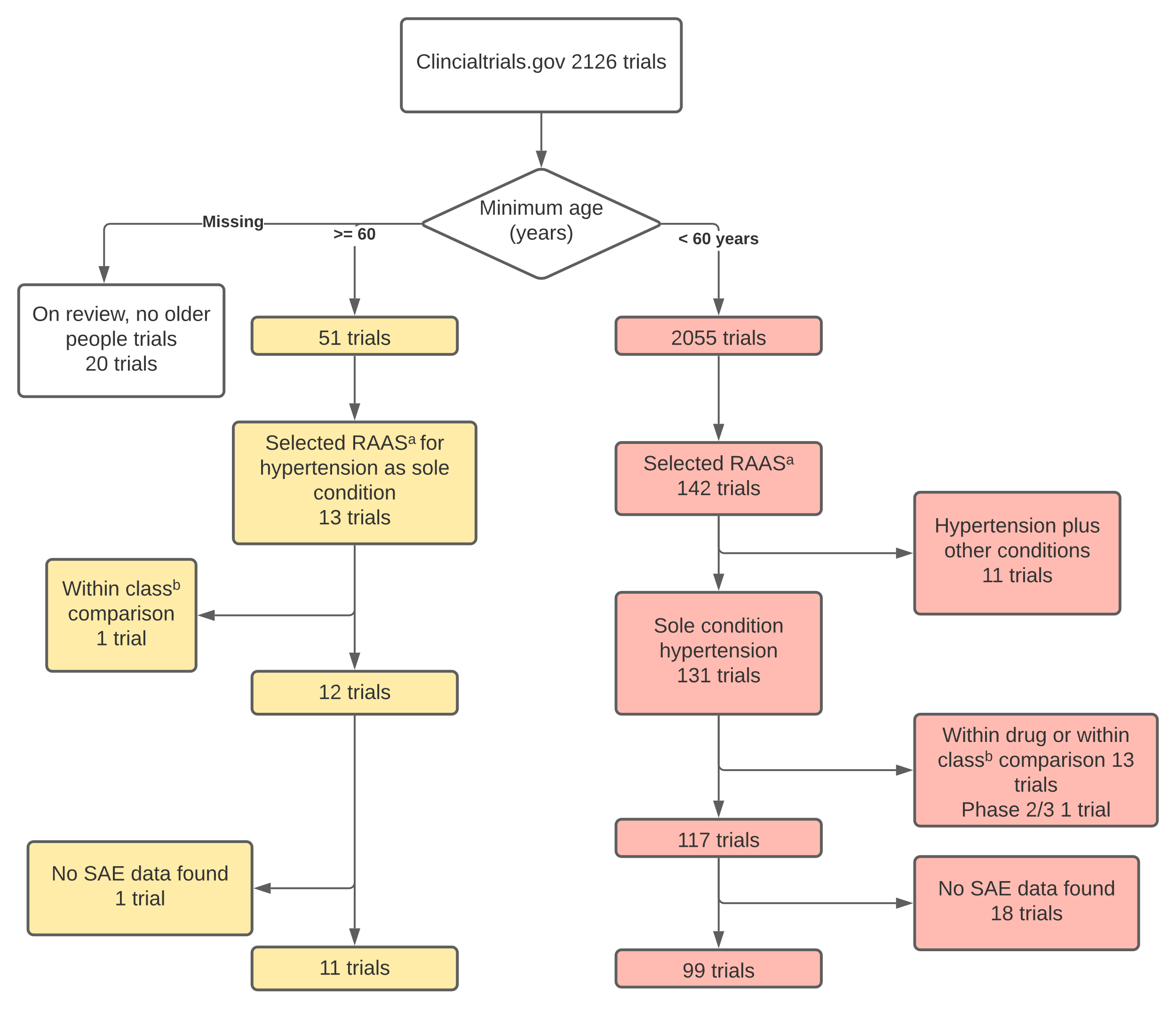
# Methods

This study compares SAE rates in registered randomised controlled trials 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 World Health Organisation Anatomic Therapeutic Chemical (WHO ATC) drug classes for all interventions.12 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 trials of ‘older people’. We reviewed these to identify drugs and indications for which such trials were commonly undertaken. We found that trials of drugs acting on the RAAS for the treatment of hypertension were relatively commonly focused on ‘older people’. As optimal treatment of hypertension in older people is also a clinically important question, we selected on trials of RAAS drugs for hypertension which focused on ‘older people’. Secondly, we obtained, as a comparator group, all trials for the same indications and drugs regardless of age-based inclusion criteria. To be eligible, trials (both older people and the ‘standard’ comparator 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



“Missing” refers to the fact that the entry for the specific field in clincialtrials.gov for the minimum age was missing. The full text of the trial registration was then reviewed to identify if the trial was targeted specifically at older participants. 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 Welsh 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 12 months 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 SAIL participants with a previous code for diabetes mellitus, chronic kidney disease, 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 12 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

12-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 https://github.com/dmcalli2/adverse\_events\_older\_people): 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). We also recorded whether the trial outcome was a ‘hard outcome’ (i.e. a clinical endpoint such as major adverse cardiovascular event or mortality), or ‘soft outcome’ (i.e. a surrogate marker such as change in blood pressure). For trials with hard outcomes, the number of clinical endpoint events was added to the number of SAEs before comparing event rates to the community population (as both endpoint and SAEs are likely to represent hospitalisation or deaths).

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 trials of ‘older-people’ with ‘standard’ trials, adjusting for trial characteristics. We modelled SAEs on older people trial status using hierarchical Poisson regression models (random intercept, Poisson likelihood); unadjusted (calculated as follow-up \* (offset by estimated person time calculated as the follow-up time x number of participants - 0.5 \* number of SAEs) 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 adjusted model was the pre-specified primary analysis. Models were fit using Rstanarm to allow fitting of the 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 fitted 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. Having calculated the expected rate of hospitalisations and deaths (as a proxy for SAEs), we calculated the ratio of expected to observed SAEs. 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 trials of ‘older people’, we re-ran the regression models having excluded each trial in turn to examine the sensitivity of the findings to trial characteristics. The second sensitivity analysis explored the impact of possible 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 repository https://github.com/dmcalli2/adverse\_events\_older\_people.

# Results

We included 110 trials, of which 11 were trials in ‘older people’ and 99 were standard trials which did not focus specifically on older people. 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 |  |  |
| Angiotensin receptor blocker | 66 (67%) | 8 (73%) |
| Renin inhibitor | 33 (33%) | 3 (27%) |
|  |  |  |
| Comparison |  |  |
| Placebo | 22 (22%) | 1 (9%) |
| Drug of different class | 77 (78%) | 10 (91%) |
|  |  |  |
| Phase |  |  |
| 3 | 67 (68%) | 5 (46%) |
| 4 | 32 (32%) | 6 (54%) |
|  |  |  |
| Trial outcome was clinical endpoint |  |  |
| Yes | 1 (1%) | 2 (18%) |
| No | 98 (99%) | 9 (82%) |
|  |  |  |
| Trial sample size | Median 722 (474 to 1124) | Median 754 (388 to 884) |
|  |  |  |
| Trial follow-up (days) | Median 63 (56 to 98) | Median 98 (56 to 252) |
|  |  |  |
| Mean trial age | Median 55.6 (53.7 to 57.0) | Median 73.1 (71.6 to 74.2) |
|  |  |  |
| % women in trial | Median 45% (40% to 49%) | Median 55% (52% to 55%) |

The comparison of SAE rates between trials of ‘older people’ and standard trials is shown in table 2. 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) than did standard trials. This demonstrates that, for an equivalent trial comparison, trials focussing on older people appear to 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: Unadjusted | Model 2: Adjusted\* |
| Incident rate ratio (older versus standard trials) | 1.57  (0.95-2.57) | 1.74  (1.03-2.92) |
| 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 (clinical endpoint or not)  \*Model 2 is the pre-specified primary analysis | | |

The relationship between age and rates of hospitalisation and death among people with hypertension starting RAAS drugs in routine clinical practice is shown by the line on figure 3. Coloured points show the observed rate of SAEs in each 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 connecting these are not shown for clarity). The observed rates were consistently lower than the expected rates (shown by the coloured points in figure 3).

|  |
| --- |
| 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 specific rates from SAIL applied to the age/sex distribution of the trial, is shown by the black points. Trial sample size is indicated by the size of the coloured points. |

A formal comparison of the ratio between the observed SAE rate and the expected rate of hospitalisation and death for each trial (adjusted for age and sex) is shown in figure 4. For all but one of the trials, the rate of SAEs was lower than the expected rate of hospitalisation and deaths given the age/sex distribution of trial participants. There was considerable heterogeneity in the calculated ratios, both within the trials of ‘older people’ 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 standardised ratio (SR) was 4.16 (3.57-5.26) for ‘standard trials’ and 5.26 (3.03-9.09) for ‘older people trials’, indicating that hospitalisations and deaths occurred more than four times more frequently among people taking RAAS drugs in the community than SAEs occurred in trials. There was no evidence of a difference between the ‘standard trials’ and ‘older people’ trials with respect to the SR (ratio of SRs - 0.82; 95% CI 0.46-1.47). The results were similar on adjusting for agent, type of outcome (clincal endpoint yes/no), type of comparison and phase (adjusted SR 4.55; 95% CI 2.77-7.14 for ‘standard trials’, 5.00; 95% CI 2.44-11.11 and ratio of SRs 0.88; 95%CI 0.48-1.64 for standard trials, older trials and the ratio between the two).

In the first sensitivity analysis, the effect estimates were similar on leaving out each trial in turn. In the second sensitivity analysis, 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.

|  |
| --- |
| Figure 4 |

Figure 4 legend: Each point (with 95% confidence intervals) shows the ratio of expected hospitalisations and deaths (given the estimated age/sex distribution of each trial) to the observed SAE count in each trial. Four trials reported no SAEs and the ratio was therefore infinite, and are excluded from this plot. The plot also excludes a further 7 trials with only one reported SAE and ratios >50.

# Discussion

In this analysis of trials of RAAS drugs for hypertension, trials specifically recruiting older people (all >60 years, mean age >70) had a significantly higher incidence of SAEs than ‘standard’ trials after adjusting for trial characteristics. This suggests that trials of ‘older people’ do recruit participants with a higher baseline risk of adverse health outcomes.

Nonetheless, in both trials of ‘older people’ and ‘standard’ trials, the rate of SAEs was substantially lower than one would expect, given the incidence of hospitalisation and death (which, within a trial would be classed as SAEs) in people with hypertension being 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. This suggests that, even accounting for age and sex, participants in hypertension trials and people with hypertension in the community are very different populations. This difference between trial and community populations was similar for ‘older-people trials’ and for ‘standard trials’. This does not necessarily 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.19 Nonetheless, it does suggest that clinical guideline developers are correct to be cautious when applying trial evidence to community populations. This is particularly true for older, multimorbid or frailer populations, and remains true even when trials aredeliberately targetted at 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,18 there is inconsistency in how SAEs are reported.20 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 populations 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 trial participants.

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 older people at a higher risk of serious adverse events than standard trials, thus capturing some of the increased risk experienced. However, concerns about trial representativeness are still 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 trials of ‘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 higher risk of adverse health outcomes, such as people living with frailty.

The higher rate of hospitalisations and deaths in the community population has some important implications for managing hypertension in older people. First this finding is likely to reflect a higher prevalence and severity of frailty in community populations 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 in trials.13 Furthermore, frailty in participants in cardiovascular trials is associated with adverse cardiovascular outcomes independently of traditional risk factors.21 While frailty has been shown to be present in trials 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 such individuals are commonly prescribed these medications in the community, often in the context of polypharmacy. The applicability of trial evidence, even those recruiting older people, needs careful consideration when applied to a broader population. It is also likely that such evidence is insufficient to inform treatment decisions in some patient groups, such as people living with severe frailty.

Second, the difference in SAEs between trial and community populations may impact the net benefit of treatment when used in routine clinical practice.22 For example, higher mortality risks in the community may mean that absolute treatment effects (based on trial participants) are overestimated.23 Also, if drug-related SAEs were more common in the community (for example, among people living with frailty) this may reduce the net benefit of treatment.24,25 For example, even if drugs reduce cardiovascular outcomes, the net benefit may get smaller if SAE rates increase rapidly with age. Quantifying the net benefit would require analysis of differential treatment effectiveness and also treatment-related SAEs, neither of which are possible with this data. However, our findings do indicate that clinicians and guideline developers should be cautious when applying trial estimates of benefit to the wider population.

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 registry and trial pre-registration is required both for publication in high-impact journals and to qualify as evidence for regulatory agencies such as the United States Food and Drug Administration. 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 any bias is very likely towards under-estimating the difference between trial and community rates. 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 estimated 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.24

## Conclusion

Our study shows that participants in hypertension trials experience substantially lower rates of adverse health outcomes than people with hypertension treated with similar drugs in the community. Our work suggests assessment of the rate of SAEs, when compared to the expected rate from representative “target” populations, may be a useful metric of trial representativeness. Our findings also show that the problem of under-representativeness is not resolved by recruiting older people to trials, as ‘older people’ trials and ‘standard’ trials were also under-representative in terms of SAEs. This observation emphasises highlights the need for developing approaches to design and execution which enable frail older people to become trial participants..

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