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Effects of ACE inhibitors and angiotensin receptor blockers: protocol for a UK cohort study using routinely collected electronic health records with validation against the ONTARGET trial

Paris J Baptiste ,[1] Angel Y S Wong,[1] Anna Schultze,[1] Marianne Cunnington,[2] Johannes F E Mann,[3,4] Catherine Clase,[5] Clémence Leyrat,[6] Laurie A Tomlinson,[1] Kevin Wing[1]

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For numbered affiliations see end of article.

Correspondence to
Paris J Baptiste;
paris.baptiste1@lshtm.ac.uk

ABSTRACT

Introduction Cardiovascular disease is a leading cause of death globally, responsible for nearly 18 million deaths worldwide in 2017. Medications to reduce the risk of cardiovascular events are prescribed based on evidence from clinical trials which explore treatment effects in an indicated sample of the general population. However, these results may not be fully generalisable because of trial eligibility criteria that generally restrict to younger patients with fewer comorbidities. Therefore, evidence of effectiveness of medications for groups underrepresented in clinical trials such as those aged ≥75 years, from ethnic minority backgrounds or with low kidney function may be limited. Using individual anonymised data from the Ongoing Telmisartan Alone and the Ramipril Global Endpoint Trial (ONTARGET) trial, in collaboration with the original trial investigators, we aim to investigate clinical trial replicability within a real-world setting in the area of cardiovascular disease. If the original trial results are replicable, we will estimate treatment effects and risk in groups underrepresented and excluded from the original clinical trial.

Methods and analysis We will develop a cohort analogous to the ONTARGET trial within the Clinical Practice Research Datalink between 1 January 2001 and 31 July 2019 using the trial eligibility criteria and propensity score matching. The primary outcome is a composite of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke and hospitalisation for congestive heart failure. If results from the cohort study fall within pre-specified limits, we will expand the cohort to include under represented and excluded groups.

Ethics and dissemination Ethical approval has been granted by the London School of Hygiene & Tropical Medicine Ethics Committee (Ref: 22658). The study has been approved by the Independent Scientific Advisory Committee of the UK Medicines and Healthcare Products Regulatory Agency (protocol no. 20_012). Access to the individual patient data from the ONTARGET trial was obtained by the trial investigators. Findings will be submitted to peer-reviewed journals and presented at conferences.

Strengths and limitations of this study

- ► Large cohort study giving power to look at effects within subgroups under represented in the clinical trial and novelty of studying treatment effects of dual therapy in real-world settings.
- ► Access to individual patient level data from a landmark trial to support creation of a trial-analogous cohort.
- ► There may be differences between the trial population and the observational cohort due to the level of detail on inclusion/exclusion criteria provided by the trial and misclassification by primary care coding.
- ► Study of drug class effects as opposed to drug-specific effects may lead to differences in results.
- ► Despite efforts to eliminate confounding and bias, unlikely to remove entirely due to the data setting.

INTRODUCTION

Hypertension, age, diabetes and poor diet contribute to cardiovascular disease (CVD), a leading cause of death worldwide.[1] Men have a higher incidence than women, despite women having higher mortality.[2] Angiotensin-converting enzyme (ACE) inhibitors and/or angiotensin II receptor blockers (ARBs) reduce blood pressure (BP) by targeting the renin–angiotensin system (RAS). They are commonly used drugs for the treatment of hypertension, stroke, heart failure, other CV outcomes and proteinuric kidney disease.[3]

Evidence underpinning the use of ACE inhibitors and ARBs comes from the results of landmark clinical trials. Although these international trials include a large number of participants, many have limited inclusion of subgroups, such as elderly patients, those from ethnic minority groups and people with impaired renal function, and thus have limited power to look for interactions in drug effects.[4] Activity of the RAS and response to drugs that inhibit this system differ between patients, for example among different genders and ethnic groups.[5] In the management of hypertension, there is a longstanding theoretical model that people of black African or African-Caribbean family origin, (subsequently referred to as 'black') have lower levels of renin and that some drugs which block the RAS such as ACE inhibitors and ARBs are less effective in black populations.[6] Despite the evidence supporting this, it is increasingly recognised that there are no clear genetic causes of underlying health differences between ethnic groups, and differences may be due to factors such as differences in socio-economic status and access to healthcare, indicating a level of underlying structural racism.[7] Poor representation of black populations in clinical trials limits the ability to examine variation in drug effects by ethnicity.[8] Information regarding drug effects in these underrepresented populations is frequently only available from non-interventional studies,[9] often limited to select patient groups or heavily confounded. Trial replication is a technique which can be used to address this issue.[10] By creating a ('trial-analogous') observational cohort that has similar characteristics to a trial population that has been randomised, and accounting for confounders using propensity score methods, residual confounding can be reduced.[11] Validation of the results generated by a trial-analogous cohort against the target randomised controlled trial (RCT), allows us to determine if patient selection and methods used to address confounding and bias can produce comparable results. If data agreement is shown between the RCT and observational study, these methods can then be applied to the analysis of the treatment effects in populations who would have been excluded or underrepresented in the original trial, and populations over a longer follow-up period.

Recent studies by Wing *et al* and Powell *et al* have explored whether validation against RCTs can support conclusions drawn from observational studies carried out in electronic health records (EHRs).[12 13] We aim to explore the validity of such methods for assessing treatment effectiveness and risk in non-interventional settings in the therapeutic area of CVD, by matching individual patient data from the Ongoing Telmisartan Alone and the Ramipril Global Endpoint Trial (ONTARGET) to a trial-analogous cohort developed in UK primary care data. We will then apply our validated methods to the estimation of:

- Treatment effects and risk in groups that were excluded from the trial due to prior comorbidities.
- Treatment effects in people aged 75 years and over, of black/Asian ethnicity, those with low kidney function and females who were underrepresented in the trial.

Early findings from Franklin *et al* from the RCT DUPLICATE initiative, which replicated 10 RCTs have shown promising results.[14] However, it was shown agreement in results relies largely on the comparator studied. Those studies which had an active comparator with similar indications were shown to increase the validity of the real-world evidence. Similar work was done by Matthews *et al*, emulating the VALIDATE study using the SWEDEHEART register, here it is was shown that accurate effect estimates can be obtained using real-world data to emulate a target trial, but results are not always replicable.[15] It is thought that using a similar protocol in the observational study to that used in the trial and harmonisation of the data analysis can lead to more comparable results.[16]

AIMS AND OBJECTIVES

Aim

To measure the association between ACE inhibitors and ARBs and cardiovascular outcomes within a trial-analogous cohort and within patients excluded and underrepresented from the ONTARGET trial using trial-replication methods.

Primary objective

To validate the effects of ACE inhibitors and ARBs found in an RCT-analogous cohort from UK routine primary care against those obtained from a randomised clinical trial.

Secondary objectives

- To estimate treatment effectiveness and risk in patients excluded from trials using EHRs.
- To estimate treatment effectiveness and risk in patients under represented in trials using EHRs.
- To investigate long-term outcomes and adverse events of patients treated with ACE inhibitors or ARBs beyond the duration of trials.

METHODS AND ANALYSIS

Study design

A historic cohort design using prospectively collected data will be used with a trial-replication component.

Patient and public involvement

Patients were not involved in the design or conduct of the protocol. We plan to disseminate the results through peer review publication.

Settings/data sources

Data used in the study will be obtained from the RCT, ONTARGET, and the UK Clinical Practice Research Datalink (CPRD) GOLD (linked to Hospital Episode Statistics (HES) database and Office for National Statistics (ONS data.

Ongoing Telmisartan Alone and the Ramipril Global Endpoint Trial

The global landmark ONTARGET trial compared the non-inferiority of an ARB (telmisartan 80 mg daily) with an ACE inhibitor (ramipril 10 mg daily) and the superiority of a combination of both therapies compared with ramipril alone.[17] Patients had established vascular disease or were at high risk of vascular disease.

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Table 1 Baseline characteristics from ONTARGET trial

Characteristic	Ramipril (N=8576)	Telmisartan (N=8542)	Combination therapy (N=8502)
Age—years	66.4±7.2	66.4±7.1	66.5±7.3
Female sex—n (%)	2331 (27.2)	2250 (26.3)	2250 (26.5)
Ethnic group—n (%)			
Asian	1182 (13.8)	1172 (13.7)	1167 (13.7)
Arab	102 (1.2)	106 (1.2)	106 (1.2)
African	206 (2.4)	215 (2.5)	208 (2.4)
European	6273 (73.1)	6213 (72.7)	6222 (73.2)
Native or aboriginal	747 (8.7)	756 (8.9)	728 (8.6)
Other	64 (0.7)	77 (0.9)	69 (0.8)
Missing	2 (<0.1)	3 (<0.1)	2 (<0.1)

Ethnic group was self-reported.
±, mean ± standard deviation; ONTARGET, Ongoing Telmisartan Alone and the Ramipril Global Endpoint Trial.

The primary outcome was a composite of: cardiovascular related death, non-fatal myocardial infarction (MI), non-fatal stroke or hospitalisation for heart failure.[18] Some baseline characteristics are displayed in table 1.

In the intention-to-treat (ITT) analysis, the trial found that telmisartan was non-inferior to ramipril in prevention of the primary composite outcome, hazard ratio (HR) 1.01, 95% CI 0.94 to 1.09) but was less likely to cause angioedema. In addition to this, it showed that combination therapy was no better than ramipril alone (HR 0.99, 95% CI 0.92 to 1.07) in preventing the primary composite outcome and significantly increased the risk of hypotension, syncope, renal dysfunction and hyperkalaemia. Similar results were shown under the per-protocol (PP) analysis.

Based on the findings of this trial and a smaller parallel trial, TRANSCEND, in October 2009 telmisartan was approved for cardiovascular risk reduction in patient's intolerant of ACE inhibitors, aged ≥55 years and with a high-risk of cardiovascular events, after already having been approved as an antihypertensive drug.

We assessed the bias present in the ONTARGET study using the Cochrane collaboration's tool for assessing risk of bias in randomised trials[19] and found the trial to have a low risk of bias. The results from the assessment are given in online supplemental material.

Clinical Practice Research Datalink

CPRD is an anonymised database of patient data from general practitioner (GP) practices across the UK. The data consist of 50 million patients with records dating back to 1987, of whom 14 million are currently registered at practices in the UK, ~20% of the UK population.[20] Patients have a median follow-up time of 10 years. The database contains demographic data, diagnoses and symptoms along with drug exposures, tests and vaccines. Linkage to Hospital Episode Statistics (HES) and other databases such as cancer registries and death registries from the ONS is also available. In August 2019, linkage data were available from ~74% of CPRD GOLD practices located in England and ~50% of practices in the UK, with 10 800 187 patients eligible for linkage.[21]

The validity of diagnoses captured in CPRD are described by Herrett *et al*.[22] In relevance to this study, the positive predictive value of acute MI recorded in primary care was 92.2% and 91.5% in HES data.[23] In 2004 the Quality and Outcomes Framework[24] encouraged the recording of key data such as smoking status by an incentive payment programme for English GPs. From this, completeness of a large number of variables showed a significant improvement.[25] Despite this, we acknowledge that missing data remains a challenge when analysing routinely collected data. Therefore, we will link the CPRD data to other databases to improve completeness, increase precision and reduce bias.[23] This is likely to improve the usage of key variables, such as ethnicity.[26] We also consider that part of this project is aiming to ascertain whether it is possible to obtain valid results using routinely collected data, despite the acknowledged challenges inherent in using such data.

Study population

Participants from CPRD with a prescription for an ACE inhibitor or ARB and eligible for HES linkage between 1 January 2001 and 31 July 2019 will be selected. To increase power, we will examine effects of drug classes, rather than specific drugs but we will report the proportion of each specific ACE inhibitor/ARB in our cohort. Prevalent users were included in the trial, and we will also include patients with previous prescriptions for ACE inhibitors or ARBs. Further detail related to the selection of participants for each objective is provided below.

Primary objective

To validate the effects of ACE inhibitors and ARBs found in an RCT-analogous cohort from UK routine primary care against those obtained from a randomised clinical trial.

For this objective, users of ARBs will be compared with users of ACE inhibitors.

Step 1: selection of exposed time periods

Prescriptions for an ACE inhibitor or ARB received at least 12 months after the patient has been registered with a general practice that meet prespecified standards for research-quality data (ie, be 'up-to-standard') for at least 12 months will be considered as exposed time periods. Exposed time periods will be defined as periods of continuous therapy, that is, receiving a repeat prescription, >90 days without a prescription after the previous prescription ending will result in the exposure period ending. Prescription duration will be calculated using quantity and daily dose. If this is missing, the median will be imputed. Patients can contribute more than one exposed time period for each drug, with the earliest prescription in each exposed time period denoted as the first eligible prescription.

Step 2: application of inclusion criteria

Exposed time periods where patients are aged ≥55 years and ever received a diagnosis of one of the following prior to the first eligible prescription will be included. This represents the inclusion criteria used in the trial.

- Aged ≥55 years
- At least one of the following of:
  Coronary artery disease
  Peripheral artery disease
  Cerebrovascular disease
  High-risk diabetes (defined by evidence of end-organ damage)

Step 3: application of exclusion criteria

The trial exclusion criteria will then be applied and time periods with any of the following exclusion criteria prior to the first eligible prescription will be excluded:

- Symptomatic heart failure
- Significant valvular heart disease
- Pericardial constriction
- Complex congenital heart disease
- Uncontrolled hypertension (BP >160/100)
- Elevated potassium above 5.5 mmol/L
- Heart transplant recipient
- Stroke due to subarachnoid haemorrhage
- Significant renal disease (defined as patients with codes for renal artery stenosis or renal artery atherosclerosis; or serum creatinine concentration above 265 µmol/L)
- Hepatic dysfunction
- Primary hyperaldosteronism
- Hereditary fructose intolerance
- Other major noncardiac illness expected to reduce life expectancy or interfere with participation (cancer, drug or alcohol dependence, mental illness)
- Hypotension

Further information of how these criteria will be interpreted in EHR is available in online supplemental material and code lists are available for download: https://doiorg/1017037/DATA00002112. Due to some of the criteria not being fully assessable using CPRD read codes, exclusion criteria are analogous with ONTARGET criteria but we acknowledge they are not identical.

Periods where all inclusion and exclusion criteria are met will be referred to as trial eligible periods and the start date of these periods will be denoted as the eligible for trial inclusion date. The ACE inhibitor exposed cohort will include those periods where a prescription for an ACE inhibitor was received. The ARB exposed cohort will include those periods where a prescription for an ARB is received.

Step 4: matching to trial participants

Having obtained individual patient data for ONTARGET participants, we will match patients within the ONTARGET study to the CPRD ACE inhibitor trial eligible exposure period with the closest propensity score for the probability of being included in the trial. Variables for the propensity score will be chosen based on those known or suspected to influence the likelihood of the outcomes of interest (see Covariates section for further details).

Exact selection of matching variables will depend on the quality and completeness of the data available. Characteristics will be measured at the eligible for trial inclusion date for the ACE inhibitor trial eligible period. Once a trial participant is matched to an ACE inhibitor exposure period from CPRD all other ACE inhibitor exposure periods in CPRD for that participant will be dropped, ensuring a patient can only be matched and included once in the resulting ACE inhibitor trial-analogous cohort. We anticipate matching all or the majority of ONTARGET participants to a CPRD ACE inhibitor-exposed patient, giving us a pool of ONTARGET analogous ACE inhibitor-exposed patients, with similar baseline characteristics to the trial participants at the point of randomisation. This step is outlined in figure 1.

Step 5: matching trial-eligible exposure groups

The ACE inhibitor trial-analogous patients selected by step 4 will be matched 1:1 to the ARB trial-eligible periods from step 3 with the closest propensity score considering the same variables considered for the propensity score model in step 4. This matching step will ensure the ARB trial-eligible group has similar characteristics to the telmisartan ONTARGET group due to randomisation in the trial. It will also help us to understand whether trial outcomes can be investigated in non-interventional settings alone, when access to the trial data is not available. Once an ARB exposure period has been matched, any other ARB exposure periods for that patient will be excluded so an ARB patient is matched only once. If a patient ends up contributing eligible exposure periods to both the ARB and ACE inhibitor groups, a restriction

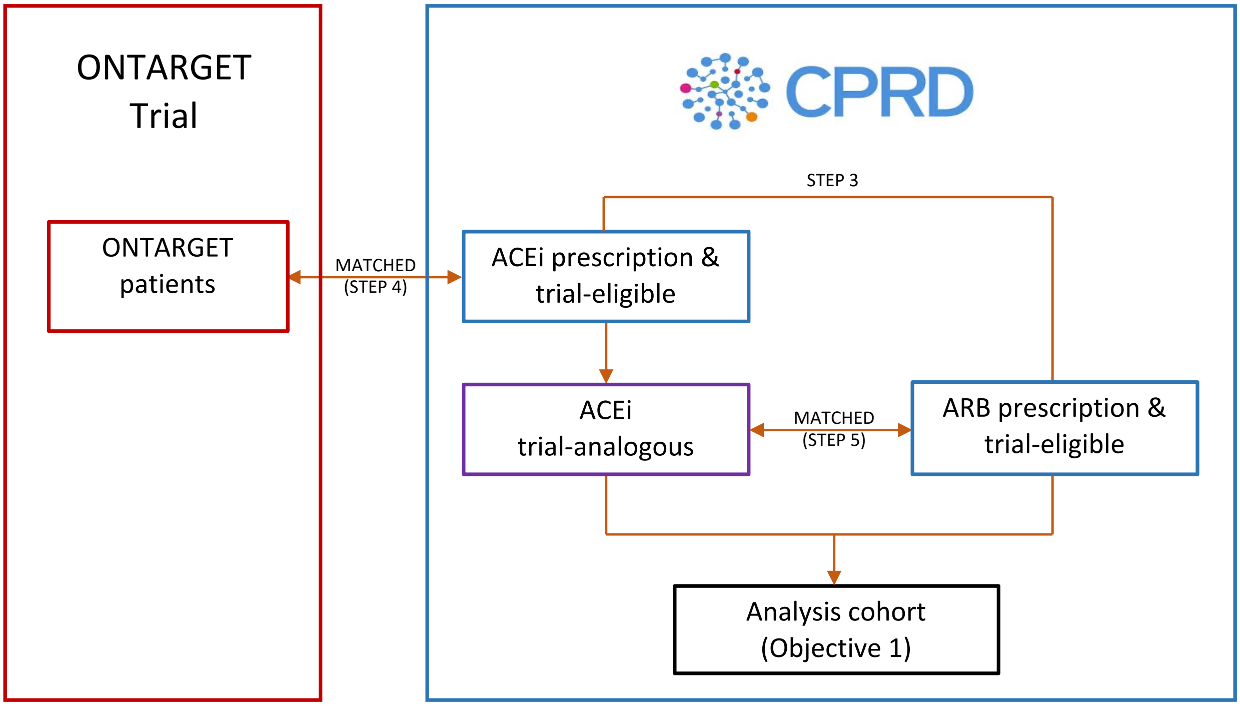

Figure 1 Simplified flow chart illustrating the planned steps in the selection of CPRD patients required to address the primary objective. Note double ended arrows denoted 'matched (step X)' indicates where two cohorts will be 1:1 matched using propensity score matching or some other similar method. ACEi, ACE inhibitor; ARBs, angiotensin II receptor blockers; CPRD, Clinical Practice Research Datalink; ONTARGET, Ongoing Telmisartan Alone and the Ramipril Global Endpoint Trial.

will be added that the patient cannot be matched to themselves.

The matched ACE inhibitor and ARB groups from step 5 will be the analysis cohort for the validation step.

To test the robustness of our findings, we will run the above propensity score model on the cohort of ARB and ACE inhibitor trial-eligible periods from step 3 (with removal of the trial-analogous ACE inhibitor group) and generate propensity scores. We will then run a propensity score weighted analysis to obtain the average treatment effects which will also be validated against the ONTARGET results. This will assess whether the trial-matching step is required in order to obtain results that are comparable to the trial.

Prior to the remaining objectives, we will check our findings from the validation step are generalisable to other settings. To do this we will repeat this step, matching the ACE inhibitor trial-analogous patients to the dual therapy trial-eligible group and see if results for the primary outcome are comparable with the trial. Dual therapy will be defined as explained in secondary objective 1.

Secondary objective 1

To estimate treatment effectiveness and risk in patients excluded from trials using EHRs.

Those patients who have one of the diagnoses listed in the trial diagnosis criteria in step 2, but who would have been excluded from the trial due to meeting specific exclusion criteria, such as those with significant renal disease. Exposure groups will be selected as in steps 1–3 with the inclusion/exclusion criteria modified to reflect that people with significant renal disease can be included. As the CPRD cohorts will include patients excluded from the trial, the cohorts will not be matched to the trial participants. The propensity score model developed in step 4 will be the basis for addressing confounding as validated in the primary objective.

Due to the difficulty of defining the dual therapy arm using routine data we will define dual ACE inhibitor/ARB users as patients with overlapping prescriptions who receive an additional prescription for the first agent after the second prescription for the second agent, this is shown in figure 2. Follow-up will then be started from the date of the first prescription of the second agent, with a sensitivity analysis planned where follow-up starts from the second prescription for the second agent (to evaluate the impact of using a prescription event occurring in the future for defining dual therapy users in the main analysis).

Secondary objective 2

To estimate treatment effectiveness and risk in groups underrepresented in trials using EHRs.

This will be applied as in secondary objective 1, with a focus on the groups of: black/Asian ethnicity, aged ≥75 years, and females who were underrepresented. All arms will be studied.

Secondary objective 3

To investigate long-term outcomes and adverse events of patients treated with ACE inhibitors or ARBs beyond the duration of trials.

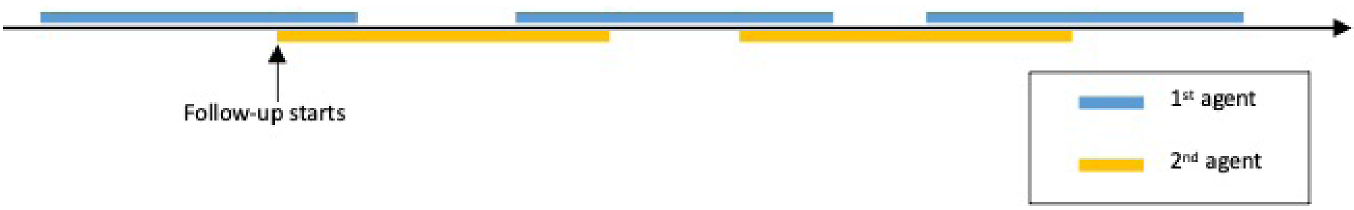

Figure 2 Example timeline of dual therapy user with overlapping prescriptions for two agents with follow-up starting at date of first prescription for second agent.

Adverse events such as cough, angioedema and renal impairment will be studied over a longer duration than that in the trial. This will be studied in the same cohort developed in step 5 to address the primary objective.

EXPOSURES, OUTCOMES AND COVARIATES

Exposures

Exposures will be determined using prescribing records in CPRD and code lists developed for ACE inhibitors and ARBs.

For the primary objective, ARBs are the primary exposure and will be compared with ACE inhibitors.

For the secondary objectives, dual therapy will also be considered as an exposure compared with ACE inhibitors, and will be defined as explained in the 'study population' section.

Outcomes

Outcomes to be measured are:

- Primary outcome: composite of cardiovascular death, non-fatal MI, non-fatal stroke or hospital admission for congestive heart failure.
- Secondary outcomes:
  - Components of primary outcome: (separately) cardiovascular death; non-fatal MI; non-fatal stroke; hospital admission for congestive heart failure.
  - (Separately) newly diagnosed congestive heart failure; revascularisation procedures; nephropathy (defined as 1. 50% reduction in estimated glomerular filtration rate (eGFR) or start of renal replacement therapy or eGFR <15 mL/min (for sensitivity analysis requires 50% reduction in eGFR on two occasions at least 3 months apart) and 2. Development of eGFR <15 or start of renal replacement therapy (for sensitivity analysis requires eGFR <15 on two occasions at least 3 months apart))
- Other outcomes: (separately) all-cause mortality or microvascular complications of diabetes mellitus.
- Safety outcomes: cough, angioedema, hyperkalaemia or renal impairment.

Outcomes will be identified using read codes and ICD-10 codes in CPRD and HES. Code lists are available for download: https://doiorg/1017037/DATA00002112.

Covariates

The propensity score models in step 4 and step 5 of the 'study population' section will consider a large range of variables including the following ONTARGET baseline characteristics:

- Age
- Sex
- Ethnicity
- CVD (categorised into—coronary, peripheral, cerebrovascular)
- Diabetes
- Prior treatment with RAS blockers
- Baseline systolic and diastolic BP within 6 months
- Smoking status
- Body mass index
- Renal function

In the propensity score model in step 5 of the 'study population' section variables such as calendar period and healthcare utilisation (eg, GP consultations, hospital appointments, procedures) will also be considered.

SAMPLE SIZE

In ONTARGET, there were 8576 in the ramipril arm, 8542 in the telmisartan arm and 8502 in the combination arm so we estimate a minimum of 14 000 CPRD patients exposed to an ACE inhibitor or an ARB are required for the individual patient matching to provide any benefit.

In a previous study,[27] the following counts were obtained: ACE inhibitor alone: n=281 204, ARB alone: n=83 850, both ACE inhibitor and ARB at the same time: n=39 548 between April 1997 and March 2014. Using data from an ongoing study (ISAC Protocol 19_072, using CPRD GOLD alone), we estimate that 37% of ACE inhibitor/ARB users are aged ≥55 years with previous cardiovascular or cerebrovascular disease and/or diabetes at drug initiation.

We have assumed a sample size of 80 000, 20 000 and 14 000 in the ACE inhibitor, ARB and dual therapy groups, respectively. We have chosen sample sizes smaller than those obtained from 37% of the cohort sizes described in the study by Mansfield *et al.*[27] since these are more likely to reflect the numbers found after applying the trial exclusion criteria. We have taken the upper and lower confidence limits for the risk ratio for the primary outcome in ONTARGET and the baseline risk of 16.5% in the ramipril group.[18] From this, we estimate 87.4% power for a risk ratio of 0.94, and 99.6% power for a risk ratio of 1.09, when comparing the non-inferiority of ARBs versus ACE inhibitors. For the superiority of dual therapy versus

ACE inhibitors, we estimate 94.6% power for a risk ratio of 0.92, and 87.0% power for a risk ratio of 1.07.

STATISTICAL ANALYSIS

Propensity score for addressing confounding

Multivariable logistic regression (on probability of being included in the trial for step 4, and on exposure status for step 5) will be used to generate the propensity score, with the variables selected for inclusion in the initial multivariable logistic regression model based on expert/prior knowledge of association with outcome. Those provisional variables listed in the 'Covariates' section along with other variables will be considered.

The propensity score model developed in the validation step in the primary objective will be the basis for the model used in the secondary objectives.

Methods of analysis

An ITT analysis will be carried out for the validation of results in the primary objective, which was used in ONTARGET[18] and the remaining objectives.

For the secondary objectives, a PP analysis will be carried out (in addition to ITT) for all comparisons. Patients who discontinue or switch treatment or start dual therapy, data for original treatment will be included up to and including their calculated date of last dose of the initially prescribed treatment +60 days, to account for repeat prescriptions and ensure exposure groups are correctly categorised. Therefore, patients may contribute more than one exposure period. The two analysis populations are shown in figure 3. Patients will be censored up to the earliest of: outcome of interest, death, leaving general practice date, or last data collection date from the general practice, or the derived date of last dose of study drug when using the PP analysis. If these dates do not occur the patient will be censored after 5.5 years of follow-up (reflecting the maximum follow-up time in the trial).

A Cox proportional hazards model will be used to address the primary composite outcome of time to cardiovascular death, non-fatal MI, non-fatal stroke or hospitalisation for congestive heart failure. Point estimates and two-sided 95% CIs for HRs will be provided for all efficacy outcomes with the bootstrap method used to estimate standard errors. Safety outcomes will be studied using logistic regression. If variability between practices is observed, a mixed effects model will be considered to account for this. A summary table of our protocol compared with the ONTARGET protocol is given in table 2.

Validation of results against ONTARGET

In the primary objective, we will validate the findings from our primary analysis against ONTARGET by determining whether results of the CPRD analysis are comparable with the ONTARGET trial results. The ONTARGET trial demonstrated non-inferiority of telmisartan over ramipril for the primary outcome (HR 1.01, 95% CI 0.94 to 1.09)

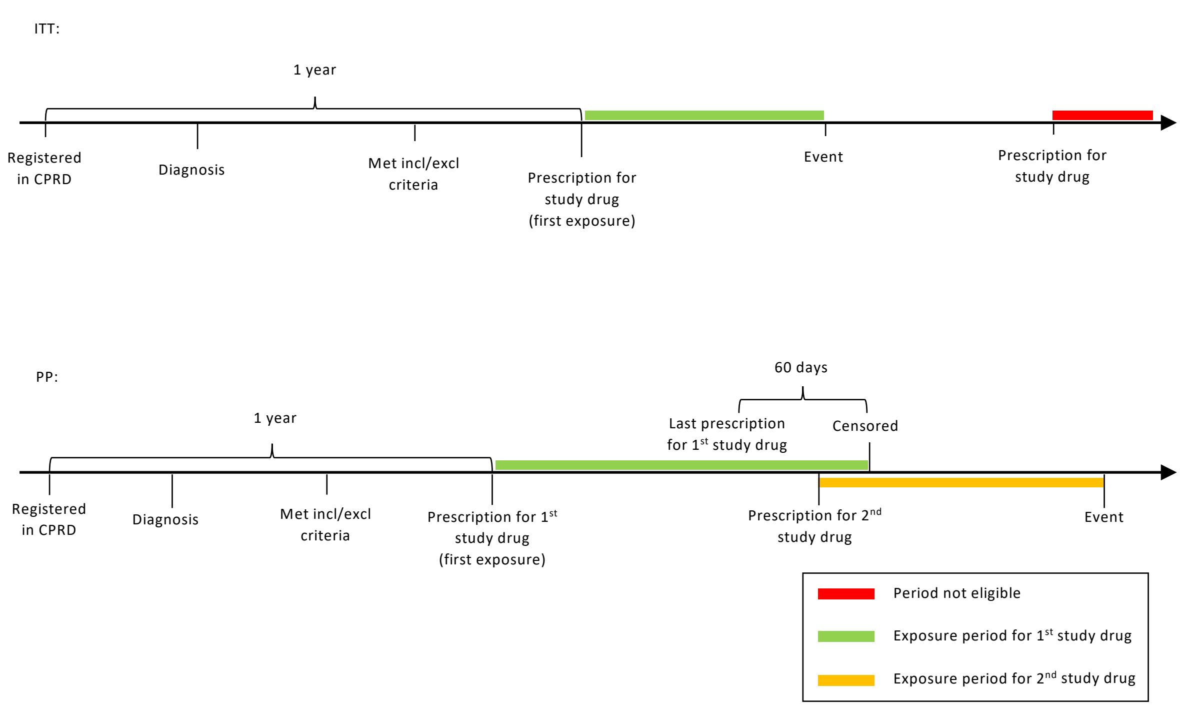

Figure 3 Figure illustration analysis groups to be used to address objectives. ITT timeline demonstrates order that criteria must be met for exposure period to be eligible, with patient no longer being able to contribute additional expose periods after being censored. PP timeline shows in green where patients exposure period can contribute to exposure group 1, then in yellow where a patient switches treatment and can contribute to second exposure group. There will be a small period of overlap, where the patient will contribute to both exposure groups as shown in the figure. CPRD, Clinical Practice Research Datalink; ITT, intention-to-treat; PP, per-protocol.

Table 2 Table of key design aspects of the ONTARGET trial and how these will be interpreted in our CPRD cohort

Protocol component	Description in ONTARGET	Description in CPRD
Eligibility criteria	Patients aged ≥55 years with coronary artery, peripheral vascular, or cerebrovascular disease or high-risk diabetes with end organ damage recruited up to 2004. No restriction on previous ACE inhibitor/ARB use except must be able to discontinue use.	Patients with a prescription for an ACE inhibitor or ARB between 01 January 2001 to 31 July 2019, eligible for HES linkage, aged ≥55 years with coronary artery, peripheral vascular, or cerebrovascular disease or high-risk diabetes.
Treatment strategies	Patients will enter 3-week single blind run-in period to check compliance then will be randomised to one of the three trial arms: ramipril 10 mg+telmisartan placebo, telmisartan 80 mg+ramipril placebo or ramipril 10 mg+telmisartan 80 mg.	Continuous courses of therapy with treatment gaps of <90 days. Dual therapy users defined as patients with overlapping prescriptions who receive additional prescription for the first agent after the second prescription for the second agent.
Assignment procedures	Randomly assigned and will receive a placebo for other drug so unaware which arm they are assigned to.	Based on prescriptions received. Patient can contribute to all three exposure groups at different timepoints.
Follow-up period	Follow-up starts at randomisation and ends at primary event, death, loss to follow-up or end of study. Close out planned in July 2007	Follow-up starts at start of trial-eligible period where exposure period meets trial inclusion/exclusion criteria. Ends at the earliest of: outcome of interest, death, transferred out of practice date, or last data collection from the general practice. If these dates do not occur the patient will be censored after 5.5 years of follow-up.
Outcome	Primary composite outcome of: cardiovascular death, non-fatal MI, non-fatal stroke, hospitalisation for heart failure	Primary composite outcome of: cardiovascular death, non-fatal MI, non-fatal stroke, hospitalisation for heart failure
Analysis plan	Primary analysis time-to-event counting first occurrence of any component of the composite outcome using Cox proportional hazards model.	Match to trial to obtain trial-analogous cohort then will match trial-eligible exposure groups. Cox proportional hazards model will be used for primary analysis.

ARB, angiotensin II receptor blocker; CPRD, Clinical Practice Research Datalink; HES, Hospital Episode Statistics; MI, myocardial infarction; ONTARGET, Ongoing Telmisartan Alone and the Ramipril Global Endpoint Trial.

under an ITT analysis and showed similar results under a PP analysis giving HR 1.00 (95% CI 0.92 to 1.09).[18]

Since the primary outcome comparing telmisartan vs ramipril showed clear non-inferiority of telmisartan and the upper limit of the 95% CI was within the non-inferiority boundary of 1.13, this will be used to validate results when testing ARB vs ACE inhibitors in the CPRD population. To conclude that our results are comparable with the ONTARGET trial results we have two criteria that must be met.

- First, the effect size for the two exposure groups must be clinically comparable with the ONTARGET findings; the HR for the composite primary outcome (time to cardiovascular death, non-fatal MI, non-fatal stroke, or hospitalisation for congestive heart failure) in the CPRD population under an ITT analysis must be between 0.9 and 1.12.
- Second, the 95% CI for the HR must contain 1.

Handling measurement of adherence to medication

A sensitivity analysis will be carried out to investigate the effect of a run-in period for compliance. The 3-week run-in period in the trial will be replicated by a 28-day period, reflecting a general prescription duration. Follow-up will be started from 28 days after first prescription and those patients who receive no subsequent prescriptions after 28 days will be excluded.

When using efficacy outcomes for validity we expect different adherence in routine clinical practice compared with the trial. Adherence will, therefore, be estimated in the CPRD cohort to enable comparisons with the trial and investigate the extent to which this may have influenced any observed differences in treatment effect. We will estimate the proportion of time covered by prescribing as a proxy measure for adherence in CPRD; this proxy measure assumes that all prescriptions are filled and that a patient takes all tablets in the prescription so is although not completely accurate, provides an indication of adherence.[28]

Missing data

CPRD data have few missing data for drug prescribing and mortality (partly through ONS linkage). Information on important comorbidity is also well recorded. Our approach for handling missing data in terms of the baseline characteristics will depend on the variable itself. Patients with variables missing that cannot be assumed to be missing at random will therefore be excluded from the trial-eligible cohort prior to step 4. In cases where missing data can be assumed to be missing at random or missing completely at random both a complete-case analysis and an analysis using multiple imputation in propensity score modelling to impute missing values will be used.[29]

ETHICS AND DISSEMINATION

Ethics

An application for scientific approval related to use of the CPRD data has been approved by the Independent Scientific Advisory Committee of the Medicines and Healthcare

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Products Regulatory Agency (protocol no. 20_012). CPRD are already approved via a National Research Ethnics Committee for purely non-interventional research of this type. Access to the secondary individual patient data from the ONTARGET trial was obtained by the trial investigators and complies with institutional review board approved informed consent forms provided by the individuals from whom the data were collected. Trial participants are identified by unique identifier and names and other personal identifiers other than age were not included in the data transfer.

Dissemination

The results of the study will be submitted to peer-reviewed journals and we anticipate three publications to arise directly from the planned work. Findings will also be presented at conferences such as the International Society for Pharmacoepidemiology Conference. Results will also be published on the London School of Hygiene & Tropical Medicine website and in the PhD thesis of the principal investigator. Results that may impact on treatment guidelines will be shared with policy-makers such as the Medicines and Healthcare products Regulatory Agency and the National Institute for Health and Care Excellence.

Author affiliations

[1]Department of Non-Communicable Disease Epidemiology, London School of Hygiene & Tropical Medicine, London, UK
[2]Epidemiology, Value & Evidence Outcomes, GlaxoSmithKline Research and Development Welwyn, Stevenage, UK
[3]Department of Medicine 4, Friedrich-Alexander-Universitat Erlangen-Nurnberg, Erlangen, Germany
[4]KfH-Nierenzentrum, München-Schwabing, Germany
[5]Department of Medicine and Health Research Methods, Evidence and Impact, McMaster University, Hamilton, Ontario, Canada
[6]Department of Medical Statistics, London School of Hygiene & Tropical Medicine, London, UK

Contributors PJB, LAT and KW contributed to the study question and design. PJB wrote the first draft of this protocol based on original scientific approval applications to ISAC that PJB, LAT, KW, JFEM and CC contributed to. PJB, LAT, KW, AYSW, CL, MC, AS, JFEM and CC contributed to further drafts and approved the final version.

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Competing interests PJB is funded by a GSK PhD studentship. CC has received consultation, advisory board membership or research funding from the Ontario Ministry of Health, Sanofi, Pfizer, Leo Pharma, Astellas, Janssen, Amgen, Boehringer-Ingelheim and Baxter. In 2018 she co-chaired a KDIGO potassium controversies conference sponsored at arm's length by Fresenius Medical Care, AstraZeneca, Vifor Fresenius Medical Care, relypsa, Bayer HealthCare and Boehringer Ingelheim. She co-chairs the cloth mask knowledge exchange, a stakeholder group that includes cloth mask manufacturers and fabric distributors. MC is an employee of, and own shares in, GSK.

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ORCID iD

Paris J Baptiste http://orcid.org/0000-0002-2565-8525

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