REACT-AUS

REsistant And Hard-to-Control HyperTension in AUStralia

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LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
A2ARA	Alpha-2 adrenergic receptor agonist
ACEi	Angiotensin-converting enzyme inhibitor
ADEPT	Anonymised Data Ethics & Protocol Transparency Committee
ARB	Angiotensin-II receptor blocker
ASI	Selective aldosterone synthase inhibitor
BB	Beta blocker
CCB	Calcium channel blockers
CKD	Chronic kidney disease
CVD	Cardiovascular disease
DBP	Diastolic blood pressure
eGFR	Estimated Glomerular Filtration Rate
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
ESC	European Society of Cardiology
ESH	European Society of Hypertension
GDMT	Guideline Directed Medical Therapy
GP	General practitioner/practice
HbA1c	Glycated haemoglobin
MRA	Mineralocorticoid receptor antagonist
NSAID	Non-steroidal anti-inflammatory drug
OPCA	Optimum Patient Care Australia
OPCRDA	Optimum Patient Care Research Database Australia
PBAC	Pharmaceutical Benefits Advisory Committee
RAAS	Renin-aldosterone-angiotensin system (RAAS)
SBP	Systolic blood pressure
SNRI	Serotonin and norepinephrine reuptake inhibitors

1. BACKGROUND & RATIONALE

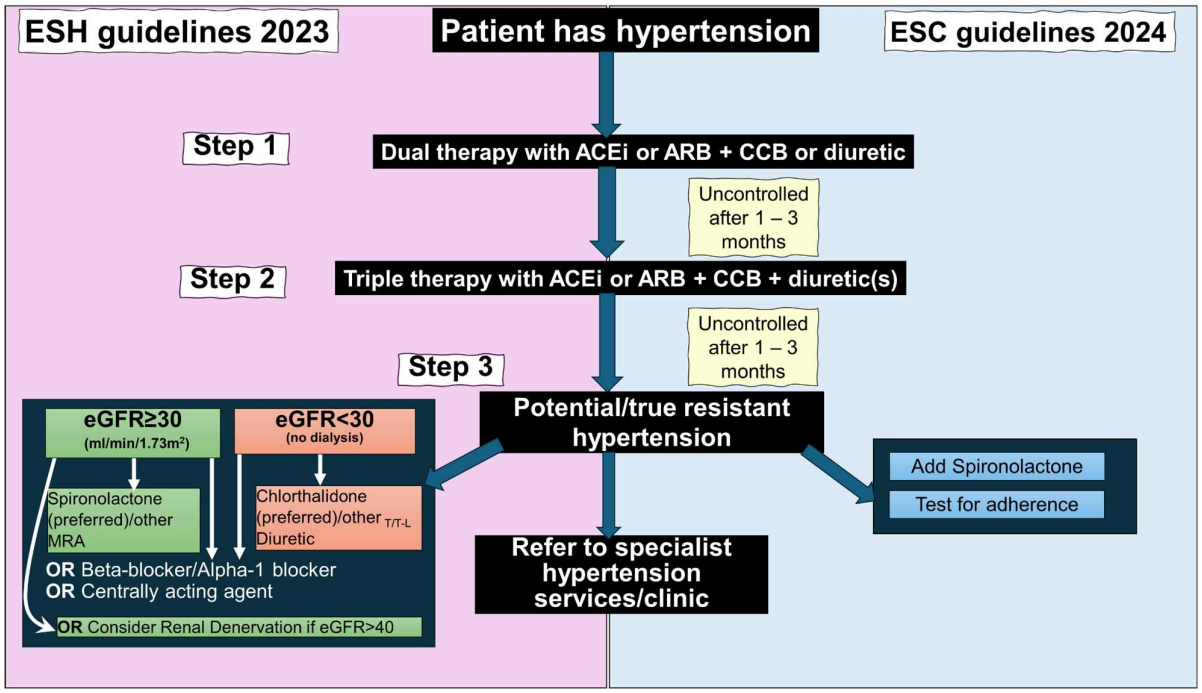
Hypertension, defined by the World Health Organisation as systolic blood pressure (SBP) readings on two consecutive days of ≥140mmHg and/or diastolic blood pressure (DBP) of ≥90mmHg [1], is a highly prevalent condition that is a well-known risk factor for heart failure, stroke, heart disease and kidney disease [2 3]. In 2022, 11.6% of people in Australia reported having hypertension and many more had high measured blood pressure but did not report having hypertension [4]. Blood pressure control is crucial for reducing cardiovascular disease (CVD) risk [5] so effective management and prevention of future complications rely on finding the right treatment strategies.

The most recent guidelines from the European Society of Hypertension (ESH) [6] and European Society of Cardiology (ESC) [7] recommend initiating patients aged under 85 years with newly diagnosed hypertension on dual therapy in the first instance using angiotensin-converting enzyme inhibitors (ACEi) or angiotensin-II receptor blockers (ARB) combined with calcium channel blockers (CCB) or a diuretic. If hypertension remains uncontrolled with these therapies for up to 3 months, a step up to triple therapy of ACEi or ARB combined with both CCB and a diuretic is indicated. If triple therapy fails to control the hypertension, the patient is said to have potentially resistant hypertension (**Figure 1**).

Distinguishing between resistant and hard-to-control hypertension can be challenging. Hard-to-control hypertension may be due to poor adherence of medication or drug interactions that affect the potency of antihypertensive medications, such as certain antidepressants (serotonin and norepinephrine reuptake inhibitors [SNRIs] or tricyclics) and over-the-counter medications, such as decongestants and non-steroidal anti-inflammatory drugs (NSAID; e.g. ibuprofen). Resistant hypertension is said to be present when a treatment strategy, in the absence of drug-drug interactions, that includes appropriate lifestyle measures and treatment with maximum or maximally tolerated doses of a (thiazide or thiazide-like) diuretic, ARB and CCB fail to lower SBP and DBP values (to <140 mmHg and/or <90 mmHg, respectively)[7]. For those with “true” resistant hypertension, ESH guidelines recommend add-on drug treatments including medications that target the renin-aldosterone-angiotensin system (RAAS), including mineralocorticoid receptor

antagonist (MRAs), such as spironolactone or a loop diuretic, and consultation with a hypertension specialist (**Figure 1**).

Figure 1: Guidelines on treatment for hypertension and identification of resistant and uncontrolled hypertension



Treatment with the new therapy, Baxdrostat, a highly selective aldosterone synthase inhibitor (ASI) [8], is in clinical development for uncontrolled and resistant hypertension. The treatment works by lowering the levels of the hormone aldosterone, which regulates potassium and sodium, but without affecting cortisol levels, to reduce blood pressure [9,10]. Evidence from Phase 3 trials has found that the addition of Baxdrostat to background therapy significantly lowers hypertension at 12 weeks compared with placebo [11].

Real-world clinical data can provide valuable insights into the nature and magnitude of patients in Australian primary care with resistant and hard-to-control hypertension, including current treatment pathways, the size of the population who might benefit from Baxdrostat as an add-on therapy, and whether there is any scope for earlier intervention in the patients' treatment pathway.

2. AIMS & OBJECTIVES

This overarching aims of this study are to quantify the nature, scale, prescribing patterns, and factors driving treatment choices over time for people with hard-to-control and resistant hypertension in Australian primary care settings. **Table 1** outlines the specific aims and objectives.

Table 1: Aims and objectives of the REACT-AUS study

Aims	Objectives
1) To quantify prescribing patterns and treatment trajectories of hypertension patients over time and how they align with Guidelines Directed Medical Therapy (GDMT)	1a) To describe current primary care treatment patterns for patients with hard-to-control hypertension 1b) To compare treatments for hard-to-control hypertension with GDMT 1c) To describe current primary care treatment patterns for patients with resistant hypertension 1d) To compare treatments for resistant hypertension with GDMT
2) To explore factors that drive treatment choices for hard-to-control/resistant hypertension	2a) To investigate the relationship between treatment choices for hard-to-control hypertension and blood pressure control, clinical characteristics, comorbidities and concomitant medications and time to step-up to add-on therapies 2b) Investigate the relationship between treatment choices for resistant hypertension and blood pressure control, clinical characteristics, comorbidities and concomitant medications and time to step-up to add-on therapies
3) To quantify the prevalence of hard-to-control/resistant hypertension and length of time with hypertension before meeting hard-to-control/resistant status	3a) To estimate the prevalence of hard-to-control hypertension 3b) To investigate length of time with hypertension prior to meeting hard-to-control hypertension status 3c) To estimate the prevalence of resistant hypertension from 3d) To investigate length of time with hypertension and hard-to-control hypertension prior to meeting resistant hypertension status

3. STUDY DESIGN AND POPULATION

3.1. Data sources

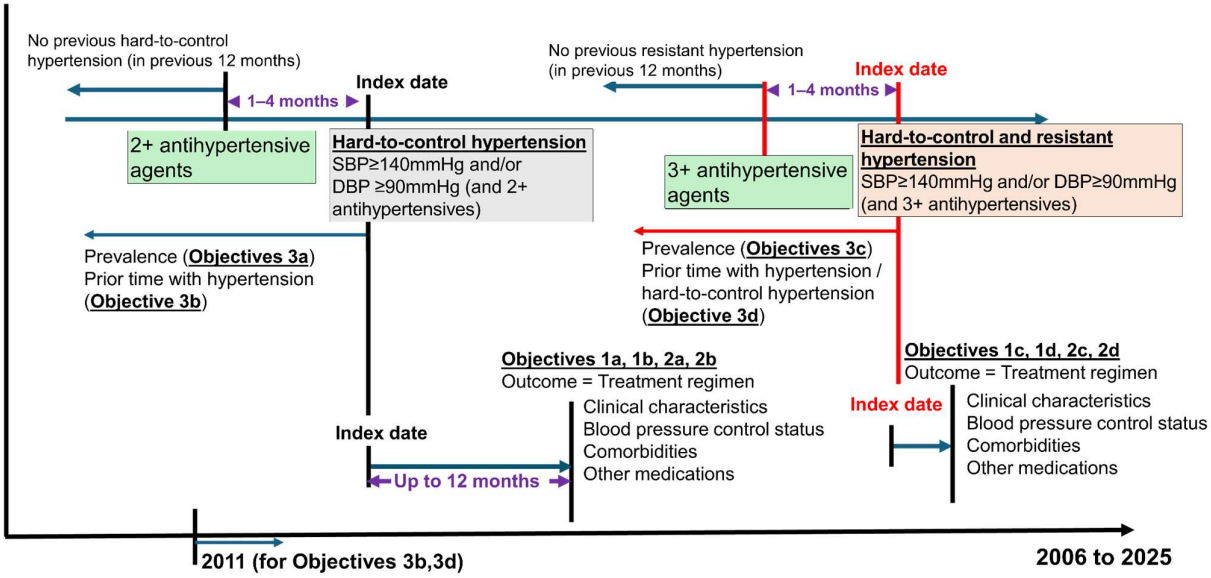
This is an observational cohort study using data from Australia primary care electronic medical records from the Optimum Patient Care Research Database Australia (OPCRDA) [12,13]. The OPCRDA is a real-world, longitudinal, research database that is maintained by Optimum Patient Care Australia (OPCA). It contains anonymised health data from over one million patients from primary care across Australia.

3.2. Study population

All adults (≥18 years and <85 years) with high blood pressure measurement (SBP ≥140mmHg and/or DBP≥90mmHg) with ≥2 antihypertension treatments in the previous 1–4 months between 2006 and 2025 will be identified. For hard-to-control hypertension, index date will be the first date of a high blood pressure measurement with ≥2 antihypertensive therapies in the previous 1–4 months. For resistant hypertension, index date will be the first date of a high blood pressure measurement with ≥3 antihypertensive therapies in the previous 1–4 months. The same patient can be included as having hard-to-control and resistant hypertension where they step up from 2 antihypertensive therapies, but their blood pressure remains uncontrolled (**Figure 2**).

We will investigate characteristics of patients within the first 12 months of receiving their first hard-to-control and/or resistant hypertension event in the observation window. Patients will be followed up for a maximum of 12 months.

Figure 2: Study Design of the REACT-AUS study



3.2. Eligibility criteria

Inclusion criteria

- Adults (≥18 years and <85 years) at index date
- 12 months registration at the participating GP surgery prior to index date
- High blood pressure measurement: SBP ≥140mmHg and/or DBP≥90mmHg
- Prescription for ≥2 antihypertensives 1–4 months before high blood pressure measurement

Exclusion criteria

- No hard-to-control or resistant hypertension within the 12-month period prior to index date (i.e. a new episode)

4. STUDY VARIABLES AND STUDY OUTCOME DEFINITIONS

The population will be stratified according to hypertension (i.e. hard-to-control hypertension and resistant hypertension) status, accepting that some patients will be included in both definitions.

4.1. Primary Outcome: Current primary care treatment (objective 1)

Antihypertensive medications and antihypertensive regimens prescribed during a maximum of 12-months period of follow-up from index date will be described (i.e. description of step-up medications) (**Table 2**).

Table 2: Anthypertensive medication collected for Objective 1 of REACT-AUS study

Antihypertensive medications	Collection of data
Beta blockers	Date of prescription during 12-month follow up
Calcium channel blockers (CCB)	Date of prescription during 12-month follow up
Diuretics	Date of prescription during 12-month follow up
Vasodilators	Date of prescription during 12-month follow up
Angiotensin-converting enzyme inhibitors (ACEi)	Date of prescription during 12-month follow up
Alpha blockers	Date of prescription during 12-month follow up
Angiotensin II receptor blockers (ARB)	Date of prescription during 12-month follow up
Mineralocorticoid receptor antagonist (MRA)	Date of prescription during 12-month follow up
Alpha-2 adreneregic receptor agonists (A2ARA)	Date of prescription during 12-month follow up
Angiotensin receptor-neprilysin inhibitor (ARNI)	Date of prescription during 12-month follow up

4.2. Additional Primary Outcome: Current primary care treatment (objective 2)

We will explore the relationship between treatment choices (step-up [Y/N] and the most common antihypertensive medication regimens and individual antihypertensive medication) by sociodemographics, lifestyle factors, clinical measurements, comorbidities and concomitant medications. We will also investigate guideline adherence data (see **Table 3**).

Table 3: Variables collected for Objective 2 of REACT-AUS study

Variable	Collection of data
Sociodemographics	
Practice ID	At index date
Age	At index date
Sex	At index date
Ethnicity	At index date (note: proxy = nationality)
Deprivation	At index date (practice-level deprivation measure based on postcode)
Patient reported outcome measures	
Side-effect reporting	12 months prior to index date
Quality of life measures	12 months prior to index date

Lifestyle and lifestyle modification	
Body mass index	Closest measure prior to index date
Smoking status	Closest measure prior to index date
Alcohol consumption	Closest measure prior to index date
Clinical measurements / indicators	
eGFR	Calculated from creatinine, age, sex, ethnicity (nationality proxy), height and weight, with date at baseline
Albuminuria	Most recent recordings prior to index date
Family history of CVD	Ever in patients' records
Electrolytes (sodium, potassium)	Most recent recordings prior to index date
Lipid profile	Most recent recordings prior to index date
HbA1c (for diabetic patients)	Most recent recordings prior to index date
Urinary albumin-to-creatinine ratio	Most recent recordings prior to index date
Comorbidities	
Number of comorbidities	Separated into: 2+; 3+; 4+
Diabetes	Ever
Chronic kidney disease	Ever
Heart failure	Ever
Stroke/TIA	Ever
Peripheral arterial disease	Ever
Myocardial infarction	Ever
Angina	Ever
Sleep apnoea	Ever
Primary Aldosteronism	Ever
Concomitant medications	
Psychiatric medications	
Tricyclic antidepressant	Within 12 months prior to index date
Serotonin-norepinephrine reuptake inhibitors (SNRIs)	Within 12 months prior to index date
Corticosteroids	Within 12 months prior to index date
Over the counter Medications	
Non-steroidal anti-inflammatory drugs (NSAIDs)	Within 12 months prior to index date
Ibuprofen	Within 12 months prior to index date
Decongestants that contain pseudoephedrine or phenylephrine	Within 12 months prior to index date
Other medications	
Hormonal therapies	Within 12 months prior to index date
Immunosuppressants	Within 12 months prior to index date
Sodium-glucose transport 2 (SGLT2) inhibitors	Within 12 months prior to index date
Anticoagulants: Warfarin (oral)	Within 12 months prior to index date
Rivaroxaban (direct oral [DOAC])	Within 12 months prior to index date
Apixaban (direct oral [DOAC])	Within 12 months prior to index date
Renal replacement therapies	Within 12 months prior to index date

4.3. Additional outcomes

We will describe prevalence of patients on dual and triple therapy and prevalence of patients with hard-to-control and resistant hypertension.

5. STATISTICAL ANALYSIS

5.1. Statistical Analysis Plan

The baseline characteristics of the study population will be described according to the characteristics in **Table 3**.

Aim 1: Prescribing patterns and treatment trajectories of hypertension patients

Individual antihypertensive therapies, antihypertensive drug classes (**Table 2**) and antihypertensive drug class regimens prescribed for patients with hard-to-control (**Objective 1a**) and resistant hypertension (**Objective 1c**) will be investigated during the 12-month follow-up period using proportions and Wilson confidence intervals. We will investigate if the distribution of medications has changed over calendar time to evaluate potential cohort effects. We will also compare treatment choices with guidelines (**Objectives 1b,1d**). These approaches will be mainly descriptive.

Aim 2: Factors driving treatment choices for hard-to-control/resistant hypertension

The relationship between the most common individual antihypertensive regimens (outcome measure) for hard-to-control/resistant hypertension, blood pressure control status, clinical characteristics, comorbidities and concomitant medications, patient adherence and time to step-up to add-on therapies will be investigated using multi-level generalised linear models (**Objectives 2a,2b**; see **Table 3** for all covariates), allowing for clustering by practice ID (random effect).

Aim 3: Prevalence of hard-to-control/resistant hypertension and length of time with hypertension before meeting hard-to-control/resistant status

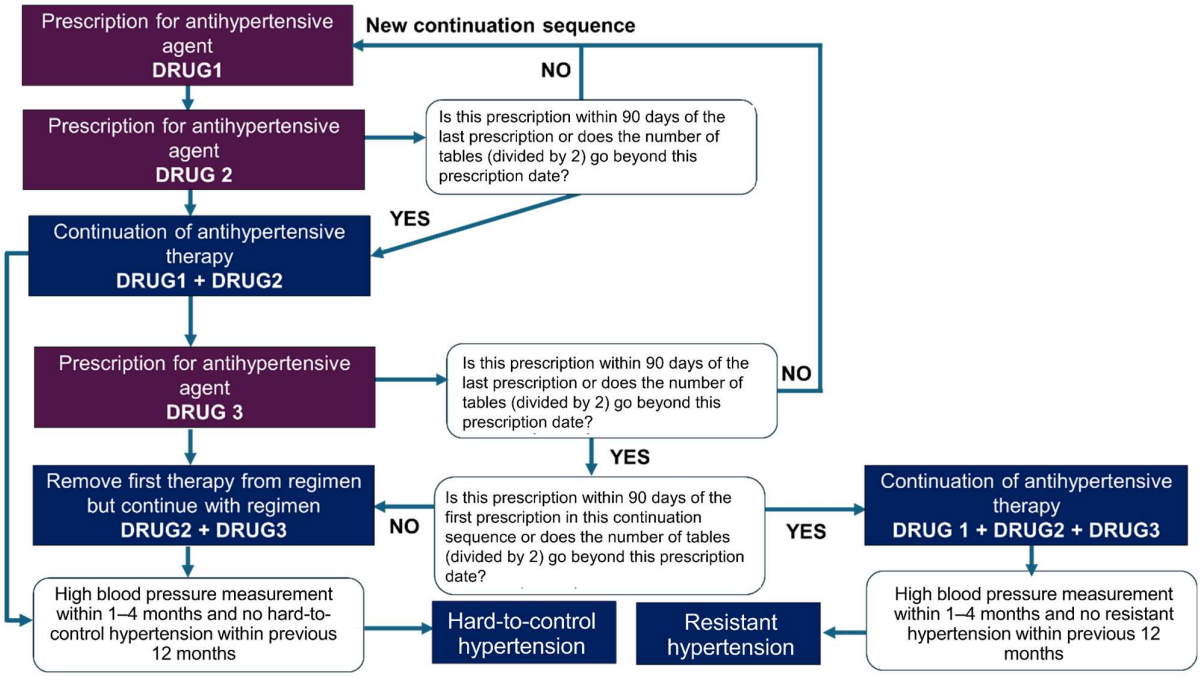
Additional objectives will be achieved using descriptive statistics of the number and characteristics of patients with hard-to-control hypertension and resistant hypertension, also looking at any differences across time and by age/gender distributions. Among those who have been clinically active (consultation/prescription) in previous 5 years (2011 onwards), we will investigate length of time (categorised) between first hypertension measurement and resistant/hard-to-control status and from hard-to-control to resistant hypertension status.

Sensitivity analyses

As therapy stop dates are not available for this primary care data set, we have assumed a continuation of antihypertensive medication if there is a previous prescription within 90 days of the new prescription or the number of tablets in the previous prescription exceeds the prescription date. Two sensitivity analyses will be conducted under the assumption that up to 180 days and up to 360 days constitutes a continuation in therapy. This is shown graphically in **Figure 3**. An example for a single patient is shown in **Table 4**. The table of the beginning of the patient's journey (note dates have been anonymised) show how hard-to-control and resistant hypertension are identified. The last record shows how switches between drug classes are treated (with the exception of 2 diuretics) – the patient is assumed to switch from the beta blockers bisoprolol to atenolol, even though the window falls within the 90-day continuation period.

The definition of hard-to-control and resistant hypertension is currently restricted to one measure entered on the database (or an average of the measures if more than one is entered on the same day). As an additional sensitivity analysis, we will investigate patients who meet a stricter definition and have persistent hypertension, as defined by ≥2 and ≥3 high blood pressure measurements over 3 months.

Figure 3: Study diagram to illustrate handling of continuations in antihypertensive therapies for the first three continuations of treatment* and definition of hard-to-control/resistant hypertension



* Subsequent drugs (e.g., fourth/fifth) are treated using the same algorithm such that 3+ drugs followed by a high blood pressure measurement constitutes resistant hypertension

Table 4: Example of identification of potential hard-to-control/resistant hypertension for a single patient

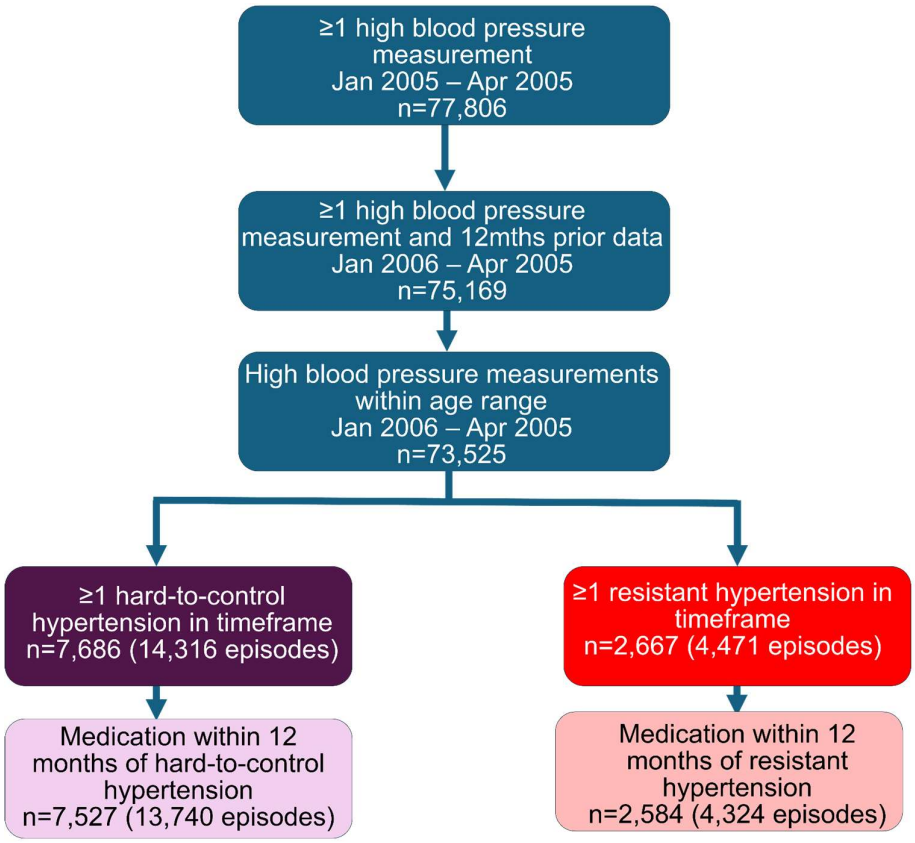
Date of prescription / measurement	Generic drug combination	Hard to control hypertension	Resistant hypertension
17/04/2005	telmisartan	0	0
23/12/2007	candesartan	0	0
21/11/2008	candesartan + lercanidipine	0	0
08/05/2009	candesartan + lercanidipine	0	0
26/06/2010	candesartan + lercanidipine	0	0
15/08/2010	candesartan + lercanidipine + moxonidine	0	0
15/08/2010	**HIGH BLOOD PRESSURE MEASUREMENT**	**1**	**0**
28/10/2010	candesartan + lercanidipine + moxonidine	0	0
13/03/2011	candesartan + lercanidipine + moxonidine	0	0
06/09/2011	candesartan + lercanidipine + moxonidine	0	0
28/10/2011	atenolol + candesartan + lercanidipine + moxonidine	0	0
13/01/2012	bisoprolol + candesartan + lercanidipine + moxonidine	0	0
13/01/2012	**HIGH BLOOD PRESSURE MEASUREMENT**	**1**	**1**

* note – figure is based on a real-life patient but the dates have been changed for anonymisation purposes

5.2. Feasibility counts

We have conducted initial feasibility counts for this study using real-life data on 77,806 individuals with high blood pressure measurements on the OPCRDA. **Figure 4** shows the data flow for these individuals. There were 7,686 people with hard-to-control hypertension (14,316 episodes) and 2,667 people with resistant hypertension (4,471 episodes) during the observation period.

Figure 4: Data flow chart



* Please note: within 12 months of hard-to-control/resistant hypertension refers to 12 months subsequent to the hypertension measurement

5.3. Sample size

A sample size of 500 is typically required for logistic regression of real-world observational studies with 50 events per predictor/confounding variables [16]. The sample size will depend

on the specific outcome variable (i.e. binary step-up variable, antihypertensive agent, drug class and drug class regimen) but will be sufficient to investigate the most common drugs prescribed. For example, taking the first hard-to-control hypertension measure in the observation period and drug regimen within 12 months follow-up (n=7,527 individuals have medication data) reveals that regimens containing hydrochlorothiazide are the most common (30%) followed by amlodipine (25%) and perindopril (23%). Among those with resistant hypertension, the most common regimens contain hydrochlorothiazide (43%), followed by amlodipine (29%) and perindopril (21%) (see **Table 5**). We will be able to investigate all of these antihypertensive agents for >26 covariates. We will also have sufficient power to investigate classes of drugs and common regimens (**Table 5**).

Table 5: Most common antihypertensive agents and classes prescribed within 12 months follow up of first episode of hard-to-control/resistant hypertension*

	Hard-to-control hypertension N	(%)	Resistant hypertension N	(%)
Total patients (first episode)	**7,527**	**100.0**	**2,584**	**100.0**
Most common antihypertensive agents prescribed after hard-to-control/resistant status				
hydrochlorothiazide	2,250	29.9	1,114	43.1
amlodipine	1,855	24.6	748	28.9
perindopril	1,729	23.0	547	21.2
telmisartan	1,437	19.1	530	20.5
candesartan	1,183	15.7	443	17.1
irbesartan	1,167	15.5	459	17.8
atenolol	894	11.9	467	18.1
lercanidipine	782	10.4	505	19.5
Most common regimens prescribed after hard-to-control/resistant status				
Most common 2-class regimens				
ARB + diuretic(s)	1,364	18.1	181	7.0
ARB + CCB	963	12.8	83	3.2
ACEi + CCB	696	9.2	59	2.3
Most common 3-class regimens				
ARB + CCB + diuretic(s)	424	5.6	443	17.1
ARB + beta blocker + diuretic(s)	184	2.4	178	6.9
ACEi + CCB + diuretic(s)	135	1.8	125	4.8
Most common 4-class regimens				
ARB + beta blocker + CCB + diuretic(s)	78	1.0	108	4.2
ACEi + beta blocker + CCB + diuretic(s)	33	0.4	49	1.9
Class of antihypertensive medications prescribed after hard-to-control/resistant status				
ARB	4,489	59.6	1,708	66.1
Diuretic	3,397	45.1	1,698	65.7
CCB	3,330	44.2	1,582	61.2
ACEi	2,732	36.3	880	34.1

Beta blocker	2,447 32.5	1,143 44.2
A2ARA	397 5.3	307 11.9
MRA	267 3.5	191 7.4
Alpha blocker	251 3.3	165 6.4
ARNI	43 0.6	33 1.3
Vasodilator	37 0.5	31 1.2

A2ARA: alpha-2 adrenergic receptor agonist; ACEi: angiotensin-converting enzyme inhibitor; ARB: angiotensin II receptor blocker; ARNI: angiotensin receptor-neprilysin inhibitor; CCB: Calcium Channel Blocker; MRA: Mineralocorticoid receptor antagonist

* Restricted to people with follow-up information on medication

5.3. Software

Analyses will be conducted in Stata v15.1 [17] for this programme of work.

6. REGULATORY AND ETHICAL COMPLIANCE

Approvals will be sought from the Anonymised Data Ethics & Protocol Transparency Committee (ADEPT) and registered with the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) prior to study commencement.

7. DATA DISSEMINATION

Findings from this study will be reported and presented at the Pharmaceutical Benefits Advisory Committee (PBAC) by May 2026.

8. TIMELINES

Action	Timeline
Protocol drafted and internal approvals	Nov 2025
Funder review	Nov 2025
Steering committee protocol review and kick-off meeting	Jan 2026
Study report	Mar 2026

9. VERSION HISTORY

Version	Date	Authors
1.0	25 Sep 2025	Freya Tyrer
1.1	29 Oct 2025	Ziggy Burnett-Kirton, Porsche le Cheng, Alexander Roussos, Freya Tyrer
2.0	23 Nov 2025	John Busby, Victoria Carter, Freya Tyrer
3.0	1 Dec 2025	Alexsandra Hughes, Freya Tyrer
4.0	4 Feb 2026	AstraZeneca market access team, Freya Tyrer, Steering committee, Porsche le Cheng, Ziggy Burnett-Kirton, Alexander Roussos, John Busby, David Price

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11. APPENDICES

Table A1: Drug classes and generic names of antihypertensive medication prescribed on the OPCRDA

Class	Number of prescription names
ACEi	**343**
captopril	16
enalapril	44
enapralil	4
fosinopril	11
lisinopril	39
perindopril	96
quinapril	10
ramipril	90
trandolapril	33
alpha blocker	**27**
alfuzosin	5
phenoxybenzamine	2
prazosin	20
alpha-2 adrenergic receptor agonist	**69**
clonidine	18
guanfacine	15
hydralazine	6
methyldopa	6
moxonidine	24
ARB	**247**
candesartan	71
eprosartan	6
irbesartan	70
losartan	5
olmesartan	38
telmisartan	34
valsartan	23
ARNI	**18**
sacubitril/valsartan	18
beta blocker	**280**
atenolol	22
bisoprolol	52
carvedilol	53
labetalol	8
metoprolol	81
nebivolol	27
pindolol	3

Class	Number of prescription names
diuretic(s)	**87**
amiloride	2
amiloride + hydrochlorothiazide	8
bumetanide	2
chlorthalidone	5
furosemide	33
hydrochlorothiazide	8
indapamide	27
tramterene + hydrochlorothiazide	2
MRA	**43**
eplerenone	16
finerenone	5
spironolactone	22
vasodilator	**62**
hydralazine	6
minoxidil	17
ACEi + CCB	**8**
enalapril + lercanidipine	5
trandolapril + verapamil	3
ACEi + diuretic	**51**
enalapril + hydrochlorothiazide	8
fosinopril + hydrochlorothiazide	5
perindopril + indapamide	35
quinapril + hydrochlorthiazide	3
ARB + diuretic	**187**
candesartan + hydrochlorothiazide	38
eprosartan + hydrochlorothiazide	3
irbesartan + hydrochlorthiazide	44
olmesartan + hydochlorothiazide	28
telmisartan + hydrochlorothiazide	45
valsartan + hydrochlorthiazide	29
beta blocker + diuretic	**4**
carvedilol + hydrochlorothiazide	4
CCB + ACEi	**46**
amlodipine + perindopril	19
amlodipine + valsartan	20
felodipine + ramipril	7
CCB + ARB	**44**

propranolol	26
sotalol	8
CCB	**245**
amlodipine	61
diltiazem	44
felodipine	37
lercanidipine	36
nifedipine	18
verapamil	49

amlodipine + olmesartan	21
amlodipine + telmisartan	23
CCB + ARB + diuretic	**34**
amlodipine + olmesartan + hydrochlorothiazide	14
amlodipine + valsartan + hydrochlorothiazide	20
vasodilator + MRA	**3**
minoxidil + spironolactone	3

A2ARA: alpha-2 adrenergic receptor agonist; ACEi: angiotensin-converting enzyme inhibitor; ARB: angiotensin II receptor blocker; ARNI: angiotensin receptor-neprilysin inhibitor; CCB: Calcium Channel Blocker; MRA: Mineralocorticoid receptor antagonist

Please note: Number of prescription names refers to trade names related to the prescription (e.g., phenoxybenzamine has 2 prescription names in the OPCRDA records “dibenyline 10mg capsule (100)” and “phenoxybenzamine 10mg capsule (100)”)