A Comprehensive Comparative Effectiveness and Safety Study of the Second Antihypertensive Agent after Monotherapy at scale using the OHDSI AP Network

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Background

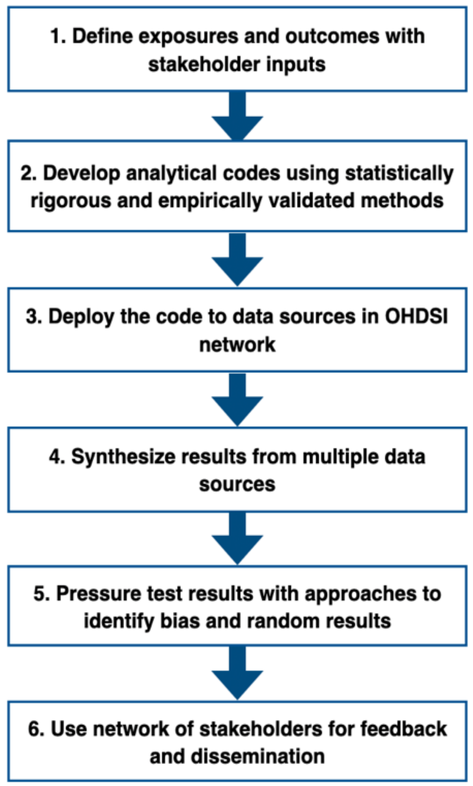
Hypertension is a leading cause of death and disability across the world[1]. Although many antihypertensive agents are available to treat hypertension, there remains considerable uncertainty regarding the optimal choice of a second agent to added monotherapy for hypertension, which is necessary for a substantial proportion of patients. Clinical trials have not provided head-to-head comparisons of the effectiveness and safety associated with the second line antihypertensive agents after monotherapy to control blood pressure[3,4]. The lack of high-quality evidence addressing this question means that guidelines are unable to provide recommendations about the preferred choice of medication for treatment escalation[5,6]. A better understanding of the comparative effectiveness and safety of different classes of second antihypertensive agents added to monotherapy, with attention to relevant subgroups of patients defined by demographic, geographic and clinical factors, has a great potential to inform clinical decisions.

Methods

This study is an extension of the Large-Scale Evidence Generation and Evaluation across a Network of Databases for Hypertension (LEGEND-HTN) initiative. We pursued three aims: (1) to describe real-world treatment variation in common antihypertensive agents added to monotherapy among patients with hypertension by demographic, clinical, and geographic subgroups; (2) to determine real-world effectiveness of common antihypertensive agents added to monotherapy for three primary (acute myocardial infarction, heart failure, and stroke) and six secondary effectiveness outcomes; and (3) to determine real-world risks of adverse events and benefits on 46 safety outcomes.

We developed and implemented a systematic, large-scale observational study that provided comprehensive pairwise comparisons between dual combinations of any of the four major antihypertensive agent classes to answer questions in Aims 1-3. In contrast to a single comparison approach, this study provided a comprehensive view of the findings and their consistency across populations, drugs, and outcomes. We modelled the study on the LEGEND-HTN collaborative research evaluating the comparative effectiveness of first-line antihypertensive monotherapies recently published in The Lancet[2]. The study followed a workflow described in Figure 1.

Figure 1. Overview of work process



Results

We have designed 12 cohorts based on the different combinations of the four main antihypertensive agents as the first-step feasibility study. Below are the results from the committed APAC data sources.

Cohort #	1st Drug	2nd Drug	APAC Data Sources									
			Australia		Korea		Singapore		China		Taiwan	Japan
			IQVIA Australia*	ePBRN SWSLHD*	Ajou Univ*	KHMC*	SG_KTPH*	SG_NUH*	iHeart - Jinan*	Jiangsu*	TMUCRD*	JMDC
1	ACEi/ARB	CCB	4,425	698	1,216	147	257	439				
2	CCB	ACEi/ARB	1,418	246	1,487	191	217	133				
3	ACEi/ARB	Diuretic	2,204	508	474	12	19	31				
4	Diuretic	ACEi/ARB	268	94	154	2	8	7				
5	ACEi/ARB	B-blocker	1,249	268	392	49	177	144				
6	B-blocker	ACEi/ARB	765	210	386	98	154	128				
7	CCB	Diuretic	72	28	259	15	14	6				
8	Diuretic	CCB	53	25	139	6	5	7				
9	CCB	B-blocker	199	41	814	217	156	101				
10	B-blocker	CCB	163	54	614	199	130	243				
11	Diuretic	B-blocker	28	14	43	5	3	8				
12	B-blocker	Diuretic	27	17	51	10	6	7				

*committed data sources

ACEi: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker; CCB: calcium channel blocker; B-blocker: beta-blocker.

Conclusions

This is the first collaborative effort of the newly established OHDSI Asia Pacific group. Although the project is still undergoing, the initial analyses support the feasibility of the study and show significant variations in treatment utilization across countries. Following the LEGEND principles of open, reproducible and reliable science, this work will bridge important knowledge gaps in treatment escalation for hypertension. The contribution will be significant as it provides critical information to inform treatment decisions facing patients with hypertension, their caregivers, clinicians, policymakers and healthcare system leaders in Asia Pacific region.

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