Analysis of Dual Combination Therapies Used in Treatment of Hypertension in a Multinational Cohort

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Abstract

IMPORTANCE More than 1 billion adults have hypertension globally, of whom 70% cannot achieve their hypertension control goal with monotherapy alone. Data are lacking on clinical use patterns of dual combination therapies prescribed to patients who escalate from monotherapy.

OBJECTIVE To investigate the most common dual combinations prescribed for treatment escalation in different countries and how treatment use varies by age, sex, and history of cardiovascular disease.

DESIGN, SETTING, AND PARTICIPANTS This cohort study used data from 11 electronic health record databases that cover 118 million patients across 8 countries and regions between January 2000 and December 2019. Included participants were adult patients (ages ≥18 years) who newly initiated antihypertensive dual combination therapy after escalating from monotherapy. There were 2 databases included for 3 countries: the Iqvia Longitudinal Patient Database (LPD) Australia and Electronic Practice-based Research Network 2019 linked data set from South Western Sydney Local

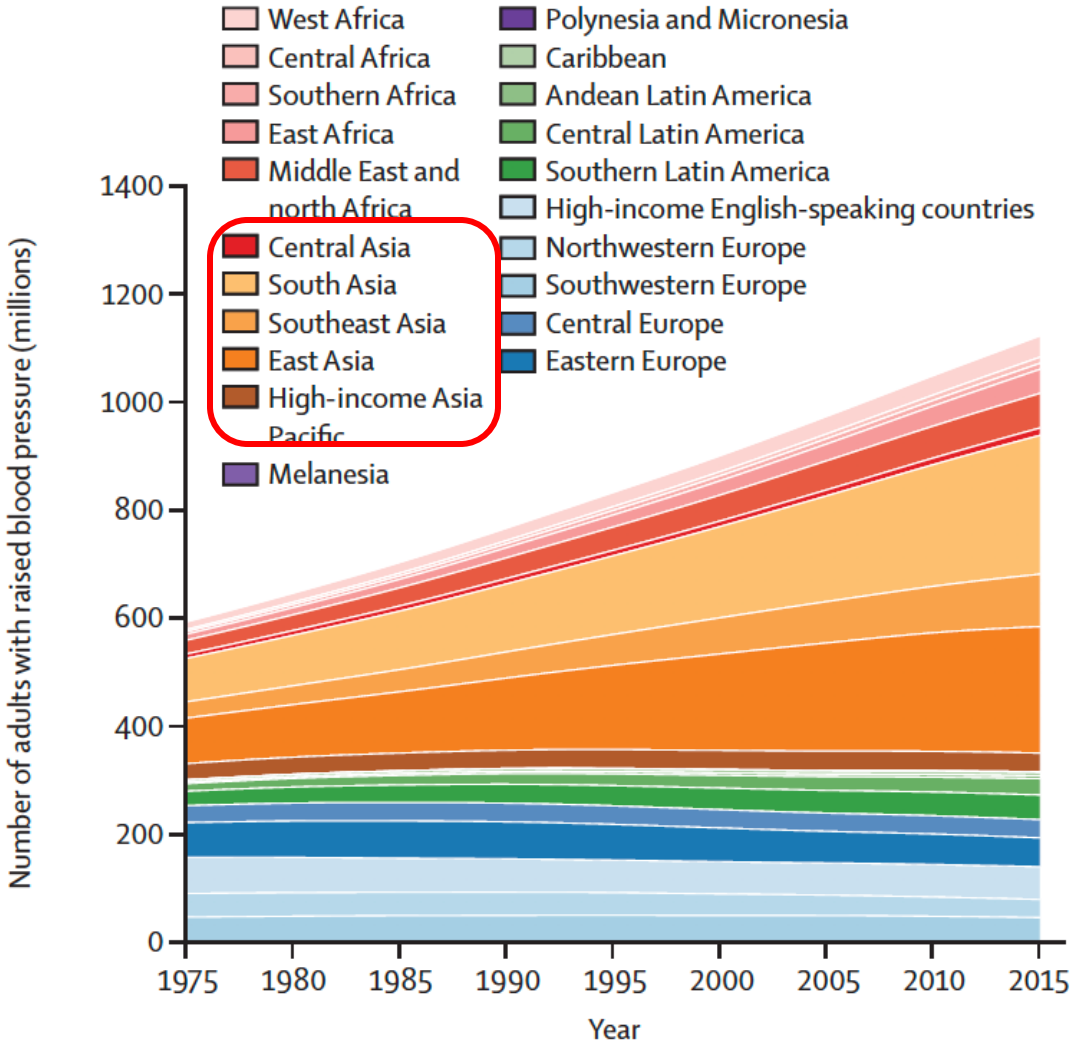
Key Points

Question What are the most common antihypertensive dual combinations prescribed to patients who escalate from monotherapy in clinical practice, and how do the combinations differ by country and patient demographic subgroup?

Findings In this cohort study of 970 335 individuals from 11 large databases, 12 dual combinations of antihypertensive drug classes were commonly used, with large variation across countries and

50% of the global hypertension population live in Asia

- Region with the largest population of hypertension
- Marked increase from 1975 to 2015
- Mostly due to change in population size and age structure



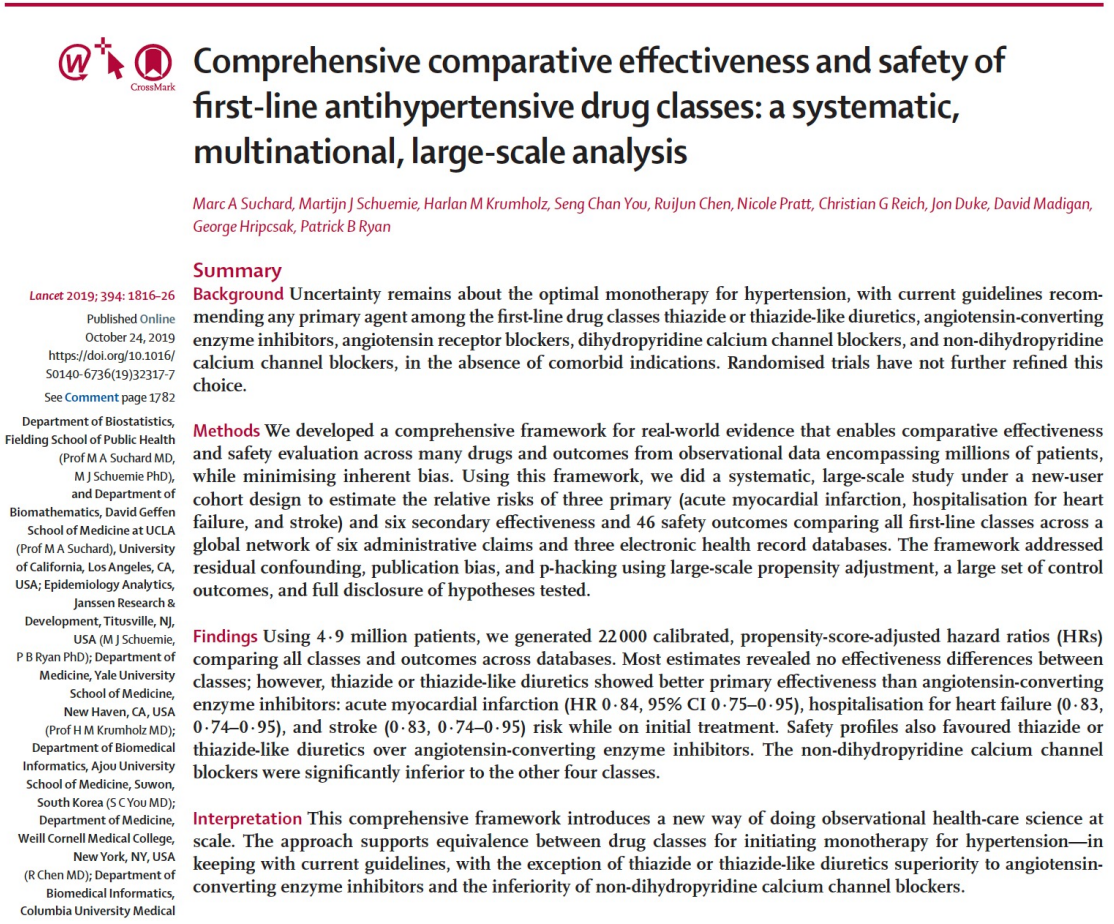
NCD Risk Factor Collaboration, Lancet, 2017

OHDSI in response to hypertension epidemic

OHDSI study on hypertension monotherapies (LEGEND-HTN)

However….

- For many patients, BP control goal not achieved by monotherapies
- Uncertainty about the optimal 2nd drug added to monotherapies
- Lack of high-quality evidence from RCT
- Inability for guideline to recommend preferred drug for treatment escalation



Comprehensive comparative effectiveness and safety of first-line antihypertensive drug classes: a systematic, multinational, large-scale analysis

Marc A Suchard, Martijn J Schuemie, Harlan M Krumholz, Seng Chan You, RuiJun Chen, Nicole Pratt, Christian G Reich, Jon Duke, David Madigan, George Hripcsak, Patrick B Ryan

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Summary

Background Uncertainty remains about the optimal monotherapy for hypertension, with current guidelines recommending any primary agent among the first-line drug classes thiazide or thiazide-like diuretics, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, dihydropyridine calcium channel blockers, and non-dihydropyridine calcium channel blockers, in the absence of comorbid indications. Randomised trials have not further refined this choice.

Methods We developed a comprehensive framework for real-world evidence that enables comparative effectiveness and safety evaluation across many drugs and outcomes from observational data encompassing millions of patients, while minimising inherent bias. Using this framework, we did a systematic, large-scale study under a new-user cohort design to estimate the relative risks of three primary (acute myocardial infarction, hospitalisation for heart failure, and stroke) and six secondary effectiveness and 46 safety outcomes comparing all first-line classes across a global network of six administrative claims and three electronic health record databases. The framework addressed residual confounding, publication bias, and p-hacking using large-scale propensity adjustment, a large set of control outcomes, and full disclosure of hypotheses tested.

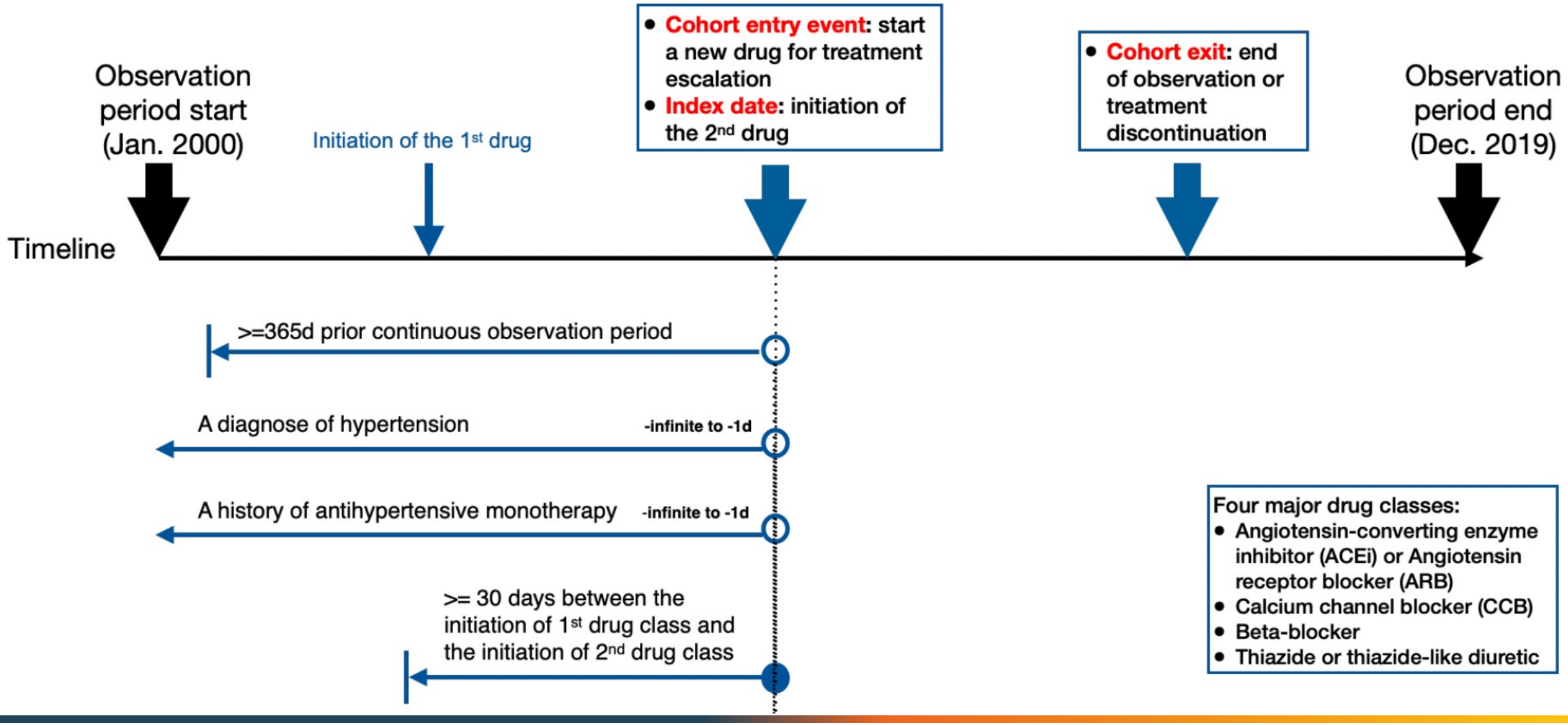
Findings Using 4·9 million patients, we generated 22 000 calibrated, propensity-score-adjusted hazard ratios (HRs) comparing all classes and outcomes across databases. Most estimates revealed no effectiveness differences between classes; however, thiazide or thiazide-like diuretics showed better primary effectiveness than angiotensin-converting enzyme inhibitors: acute myocardial infarction (HR 0·84, 95% CI 0·75–0·95), hospitalisation for heart failure (0·83, 0·74–0·95), and stroke (0·83, 0·74–0·95) risk while on initial treatment. Safety profiles also favoured thiazide or thiazide-like diuretics over angiotensin-converting enzyme inhibitors. The non-dihydropyridine calcium channel blockers were significantly inferior to the other four classes.

Interpretation This comprehensive framework introduces a new way of doing observational health-care science at scale. The approach supports equivalence between drug classes for initiating monotherapy for hypertension—in keeping with current guidelines, with the exception of thiazide or thiazide-like diuretics superiority to angiotensin-converting enzyme inhibitors and the inferiority of non-dihydropyridine calcium channel blockers.

Study objective

As an extension of the LEGEND-HTN initiative, we aim to conduct a large-scale observational study within the OHDSI collaborative community to characterize real-world utilization of dual antihypertensive combination therapies for treatment escalation among people with hypertension.

Cohort definition



Twelve exposure cohorts

Cohort #	1st Drug	2nd Drug
1	ACEi/ARB	CCB
2	CCB	ACEi/ARB
3	ACEi/ARB	Diuretic
4	Diuretic	ACEi/ARB
5	ACEi/ARB	B-blocker
6	B-blocker	ACEi/ARB
7	CCB	Diuretic
8	Diuretic	CCB
9	CCB	B-blocker
10	B-blocker	CCB
11	Diuretic	B-blocker
12	B-blocker	Diuretic

OHDSI APAC Data Network

Data Source	Data Type	Country/District	Time Period	No. of Patients
IQVIA LPD Australia	EHR	Australia	2006-2020	3,101,500
ePBRN SWSLHD 2019 Linked Dataset (ePBRN SWSLHD)	EHR	South Western Sydney, Australia	2012-2019	139,346
Ajou University School of Medicine (AUSOM)	EHR	Suwon, Korea	1995-2019	3,109,677
Kyung Hee University Hospital (KHMC)	EHR	Seoul, Korea	2008-2018	2,010,456
Khoo Teck Puat Hospital (KTPH)	EHR	Singapore	2010-2016	290,074
National University Hospital (NUH)	EHR	Singapore	2015-2018	750,270
China Jiangsu Province Hospital (CJSPH)	EHR	China	2005-2015	6,230,000
Taiwan Taipei Medical University Clinical Research Database (TMUCRD)	EHR	Taiwan	2004-2020	3,659,572
IQVIA US Ambulatory EMR	EHR	United States	2006-2020	78,526,000
IQVIA LPD France	EHR	France	1994-2020	18,118,000
IQVIA LPD Italy	EHR	Italy	2004-2020	2,209,600

Together, the committed data sources cover:
118 millions patients in 8 countries and districts

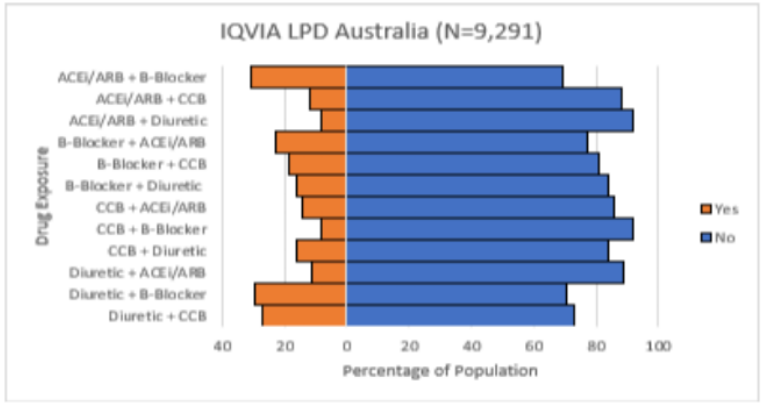
Use of 12 dual antihypertensive combinations

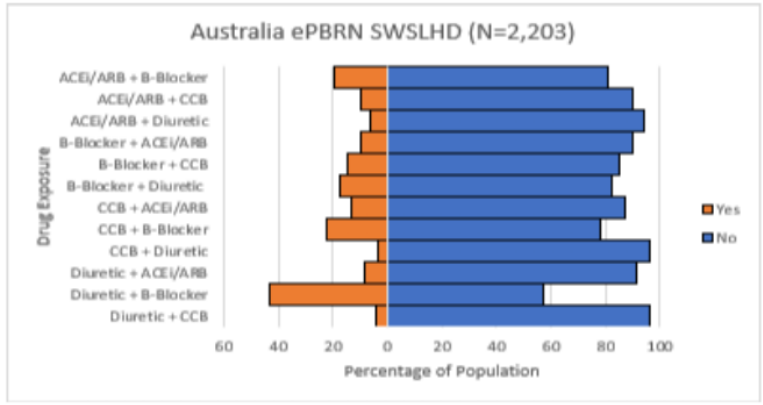
Cohort #	Dual combination	Data Sources										
		Australia		Korea		Singapore		China	Taiwan	France	Italy	United States
		Australia LPD	ePBRN SWSLHD	Ajou University	KHMC	KTPH	NUH	Jiangsu	TMUCRD	France LPD	Italy LPD	US AmbEMR
1	ACEi/ARB + Beta-blocker	1,184	268	392	49	105	144	46	1,464	11,236	11,844	110,579
2	ACEi/ARB + CCB	4,254	698	1,216	147	216	439	3,127	2,812	22,523	14,628	95,284
3	ACEi/ARB + Diuretic	2,066	508	474	12	16	31	111	8	22,399	16,988	123,940
4	Beta-blocker + ACEi/ARB	717	210	386	98	68	128	26	2,357	11,116	8,264	106,380
5	Beta-blocker + CCB	159	54	614	199	97	243	19	2,484	5,972	2,755	41,388
6	Beta-blocker + Diuretic	27	17	51	10	5	7	1	1	4,316	2,967	36,303
7	CCB + ACEi/ARB	1,339	246	1,487	191	191	133	3,312	5,015	15,749	5,841	54,297
8	CCB + Beta-blocker	190	41	814	217	120	101	34	2,518	3,866	2,475	30,593
9	CCB + Diuretic	74	28	259	15	11	6	78	4	1,660	1,103	21,108
10	Diuretic + ACEi/ARB	251	94	154	2	8	7	114	-	3,281	5,749	84,275
11	Diuretic + Beta-blocker	27	14	43	5	1	8	-	-	779	1,929	27,422
12	Diuretic + CCB	50	25	139	6	4	7	140	-	1,097	1,539	22,568

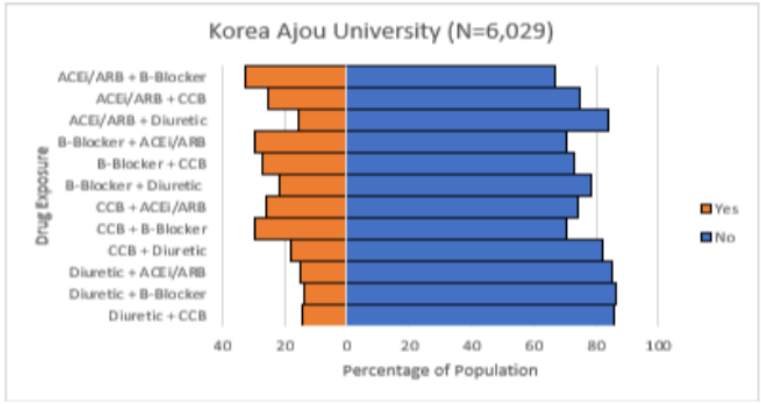
- Significant variations in use across country
- ACEI/ARB + CCB most commonly prescribed in Australia and Singapore
- In South Korea, CCB + ACEI/ARB, CCB + β-blocker, and ACEI/ARB + CCB were the 3 most commonly prescribed combinations.

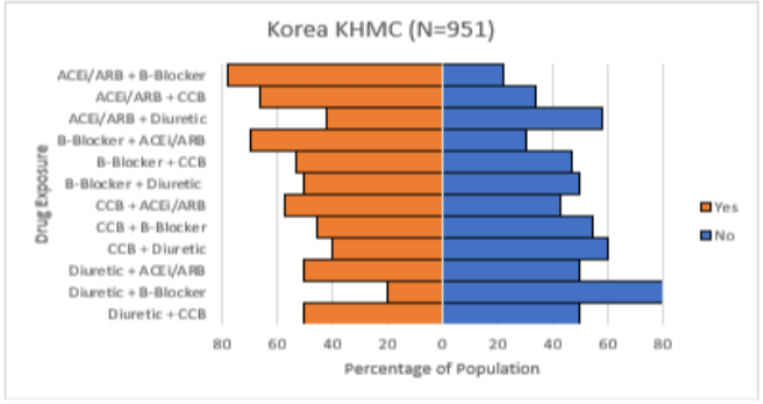
Cohort characterization by age

- Younger patients were more likely to be prescribed ACEi/ARB then a CCB or a diuretic compared with older patients.



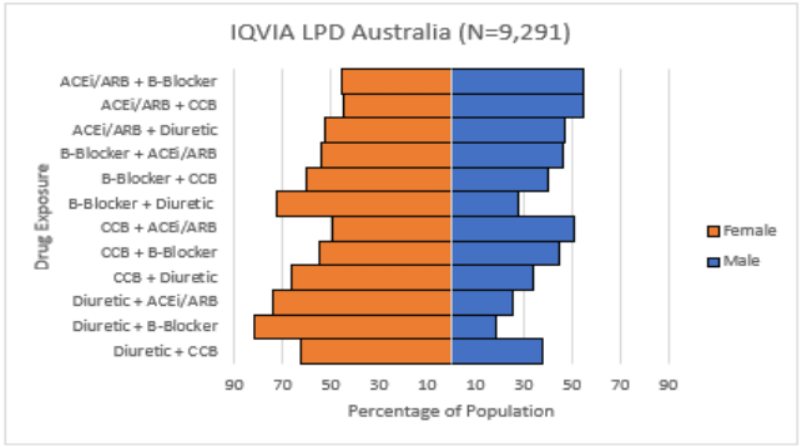


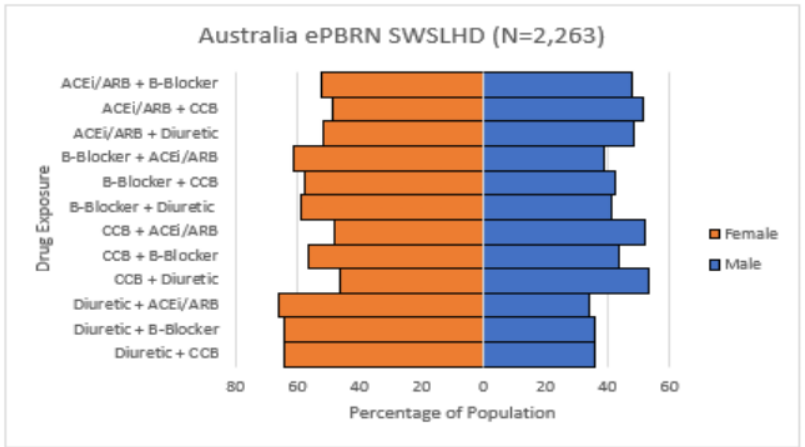


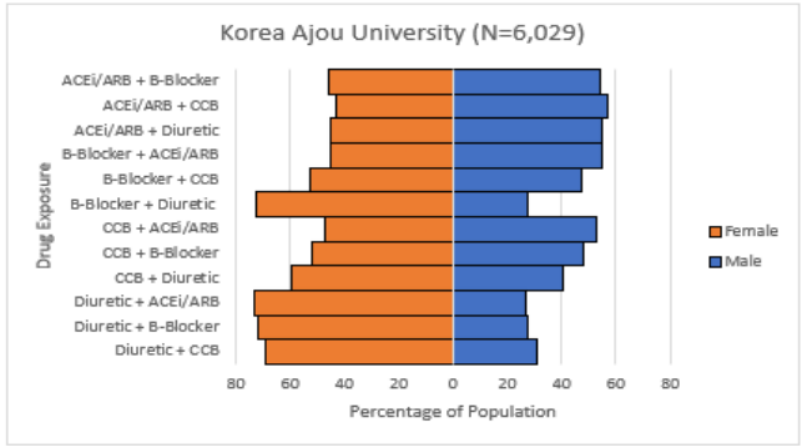


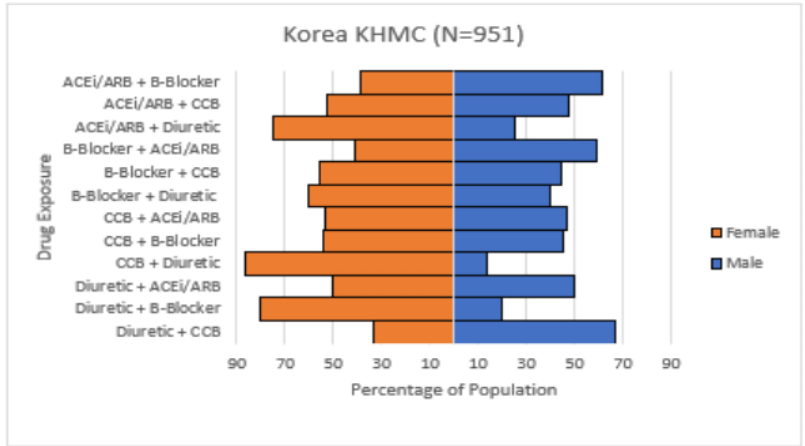
Cohort characterization by gender

- Women were more likely to be prescribed diuretics then an ACEi/ARB or a CCB compared with men.



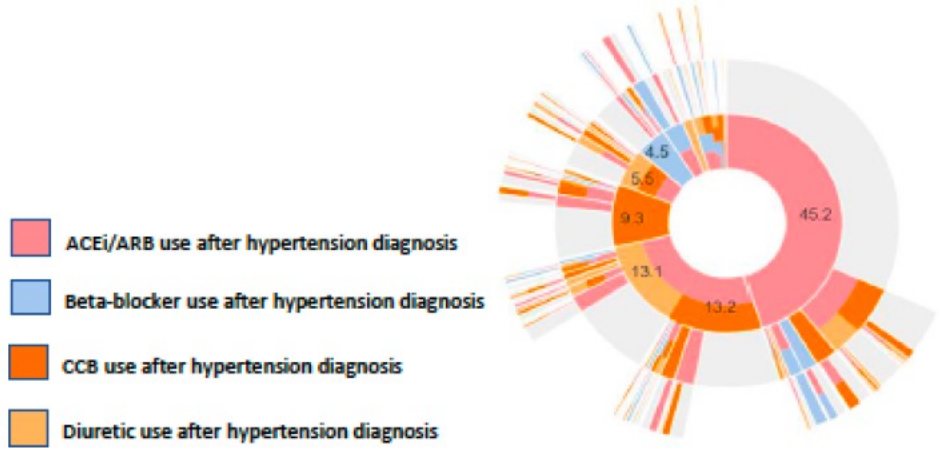




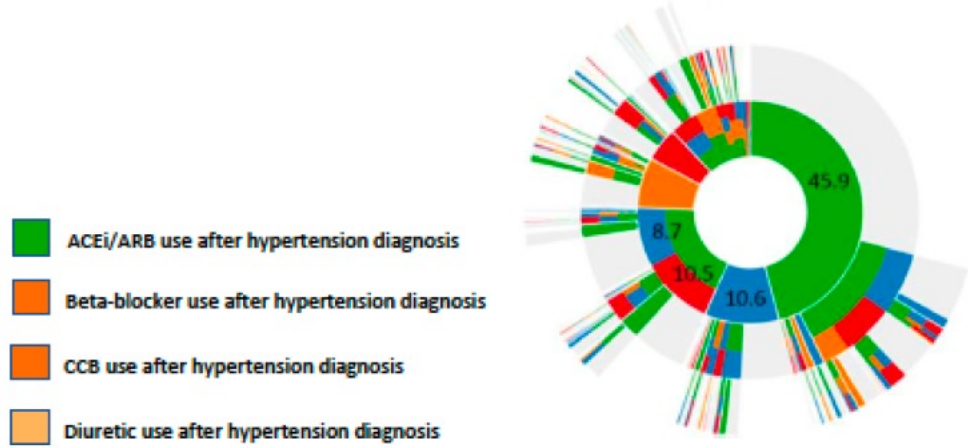


Diverse array of treatment trajectories across countries

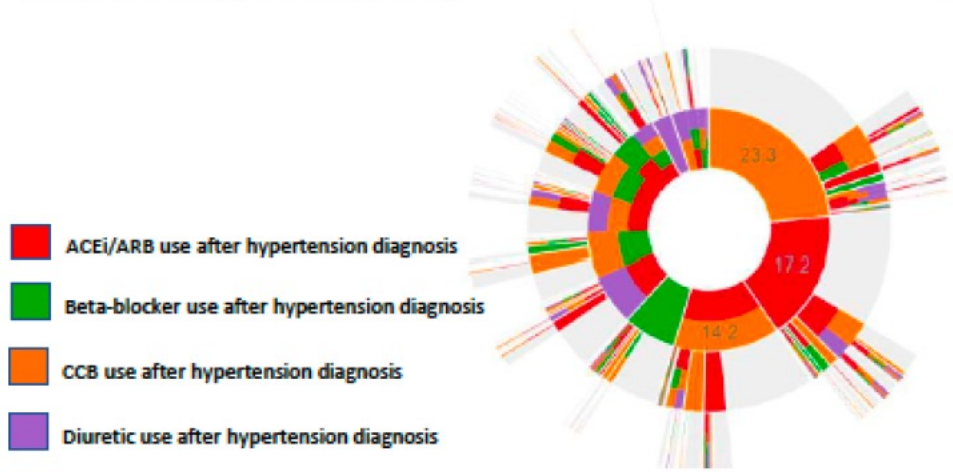
(A) IQVIA LPD Australia



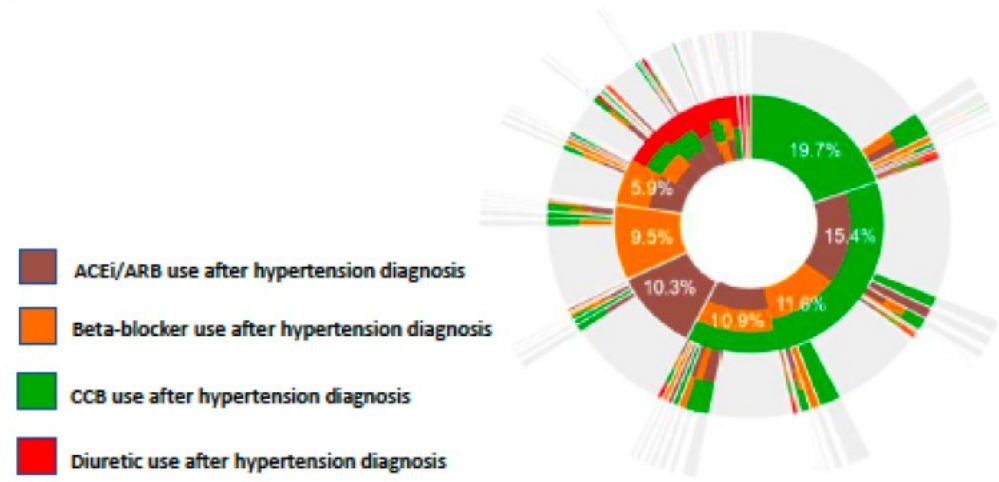
(B) Australia ePBRN SWSLHD



(C) Korea Ajou University

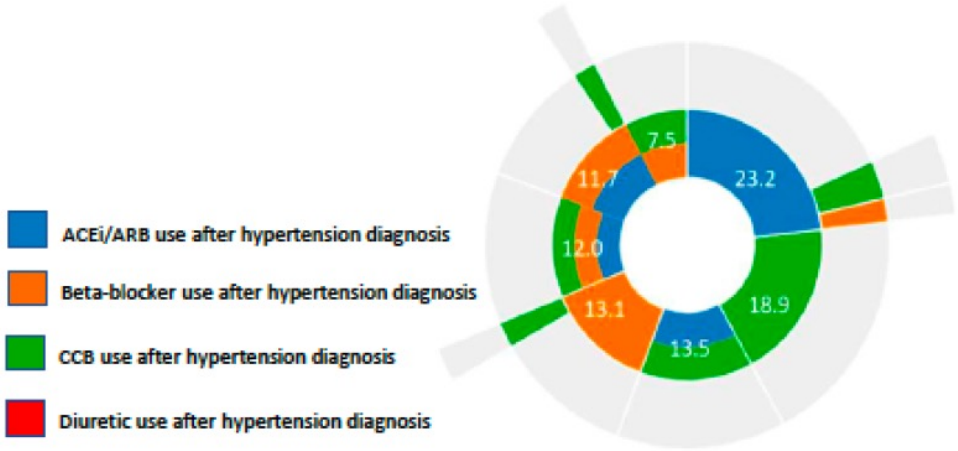


(D) Korea KHMC

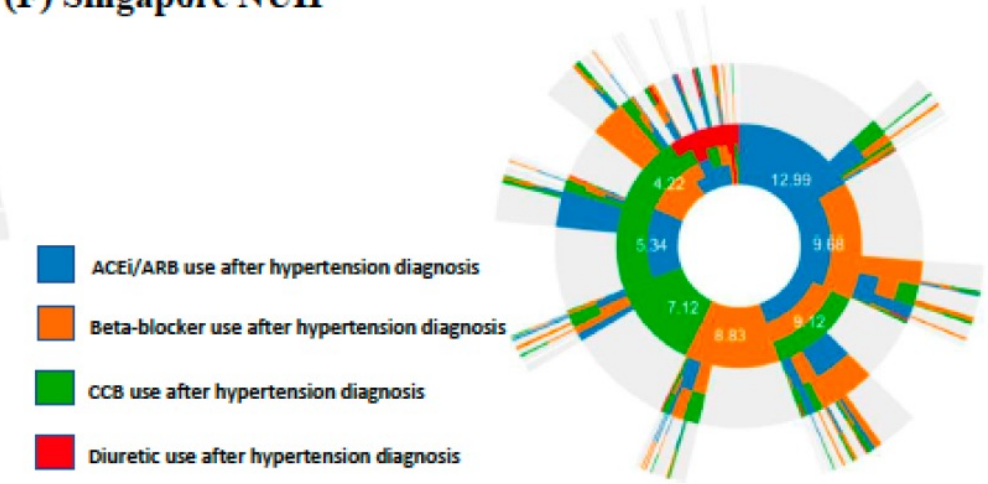


Diverse array of treatment trajectories across countries

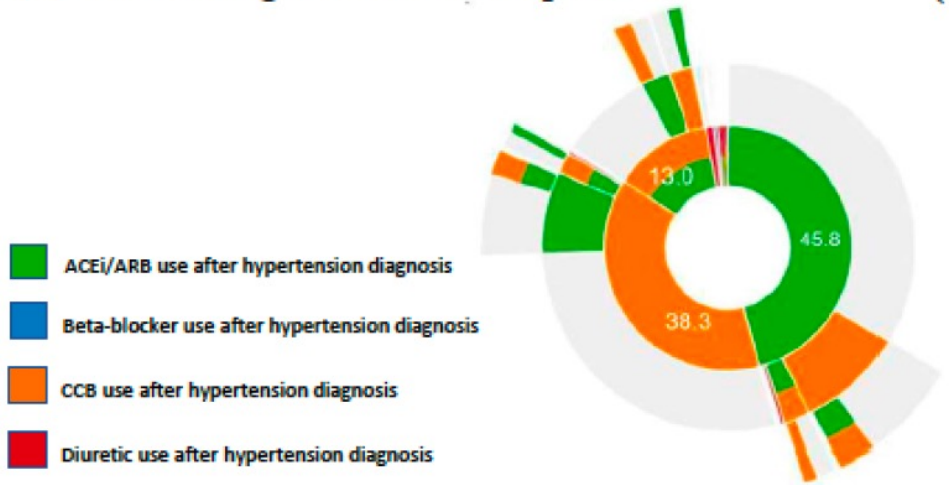
(E) Singapore KTPH



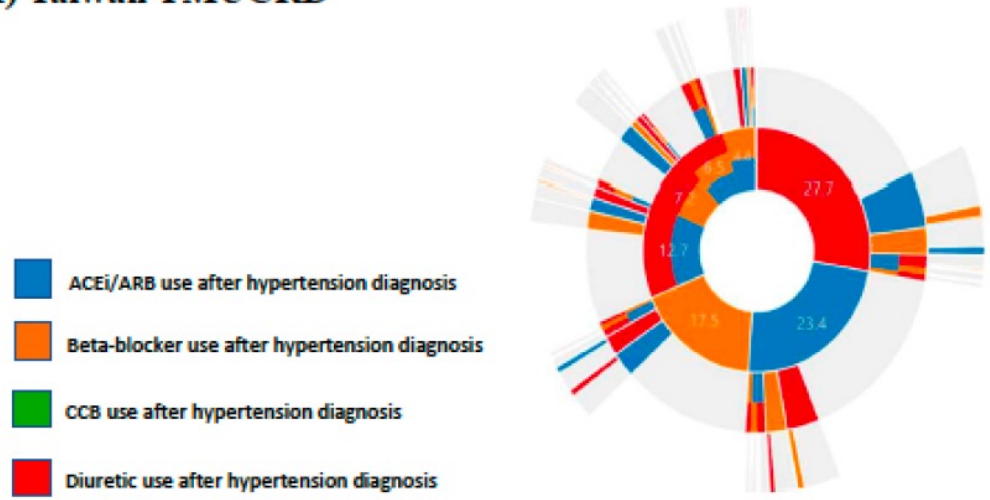
(F) Singapore NUH



(G) China Jiangsu Province Hospital

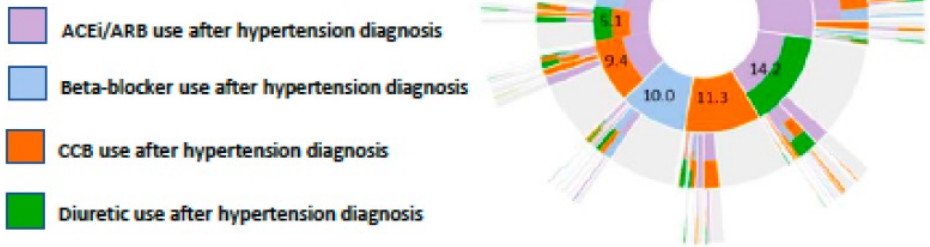


(H) Taiwan TMUCRD

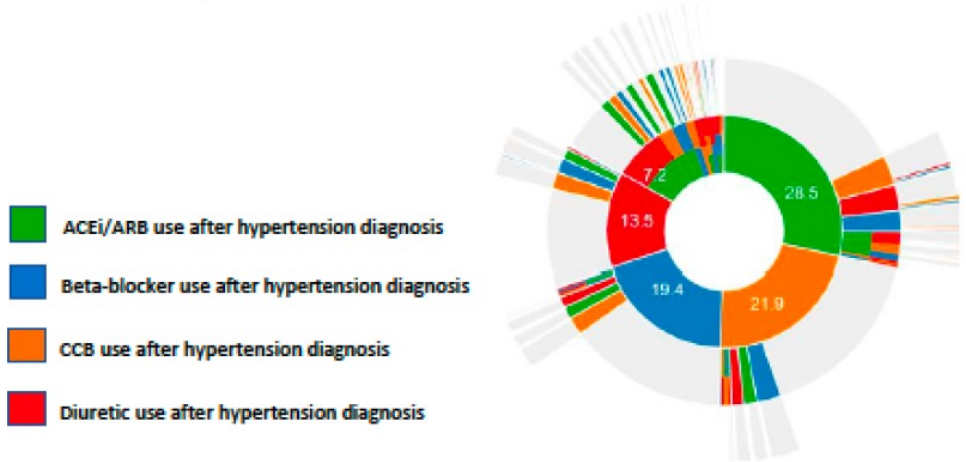


Diverse array of treatment trajectories across countries

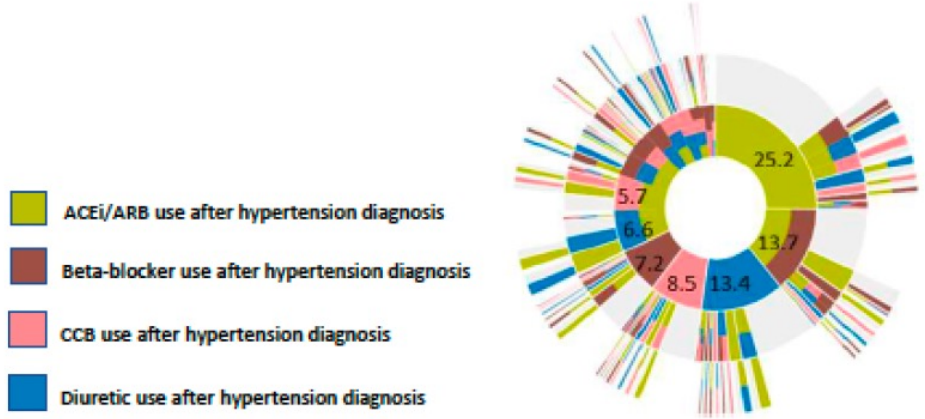
(I) IQVIA LPD France



(J) IQVIA Italy LPD



(K) IQVIA US AmbEMR



Main findings and lessons learned

- Large variation in the transition between monotherapy and dual combination therapy for hypertension across countries and by demographic groups.
- Future research is needed to identify what dual combinations work best for which patients.
- Using LEGEND principles can help mobilize collaboration with OHDSI data partners, but substantial effort was required to ensure data quality and alignment of methods across data sources.