Comprehensive comparative effectiveness and safety of second-line antihypertensive agents: utilizing the LEGEND principles to mobilize collaboration across the OHDSI APAC network

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#OHDSIAPAC

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Agenda

- Why this study?
- Objectives & Methods
- Data sources
- Findings to date

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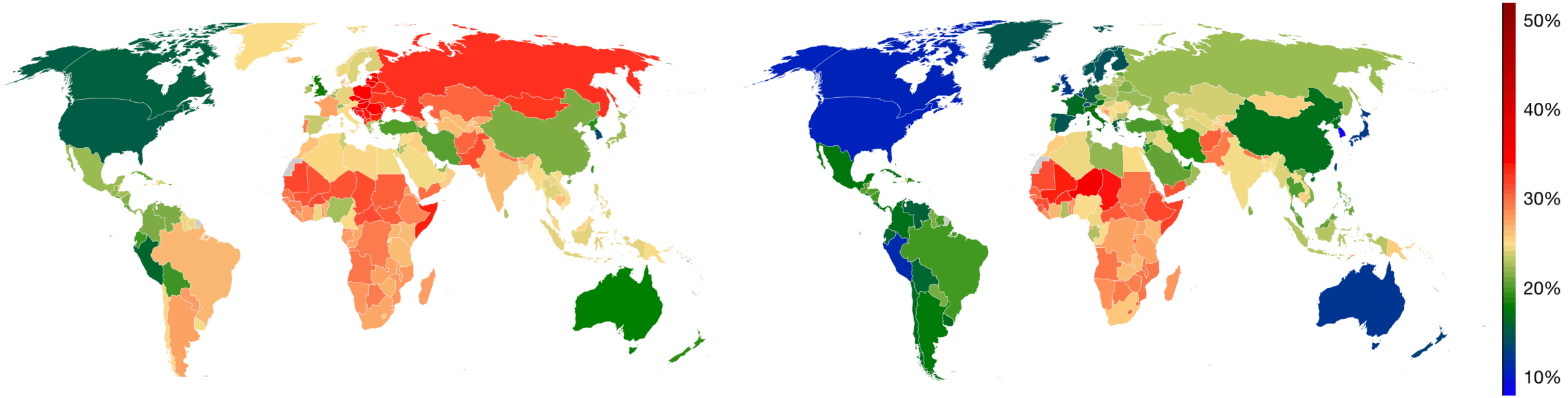
Global epidemic of hypertension

Age-adjusted prevalence of hypertension in adults, 2015

Men

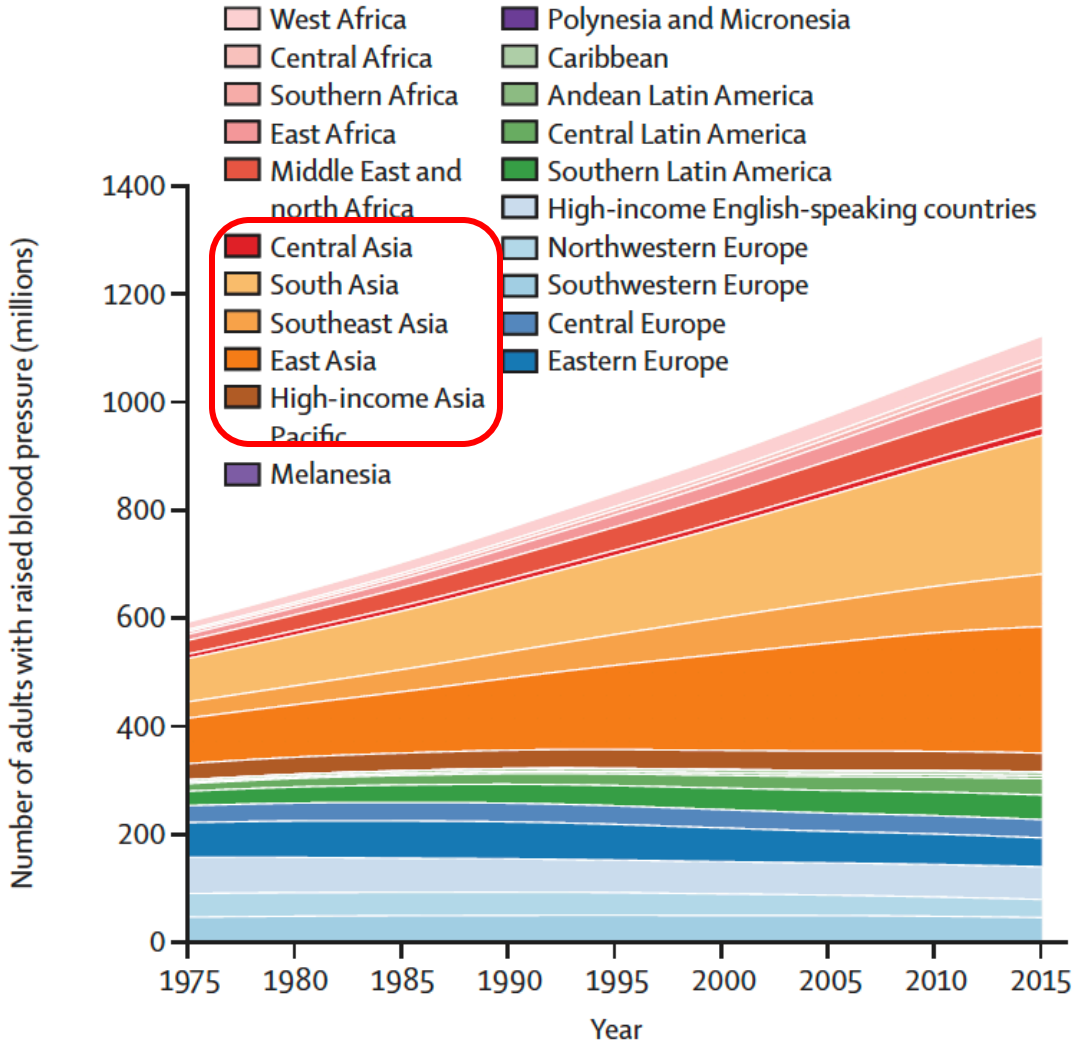
Women



NCD Risk Factor Collaboration, Lancet, 2017

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)

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

Lancet 2019; 394: 1816–26

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See Comment page 1782

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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.

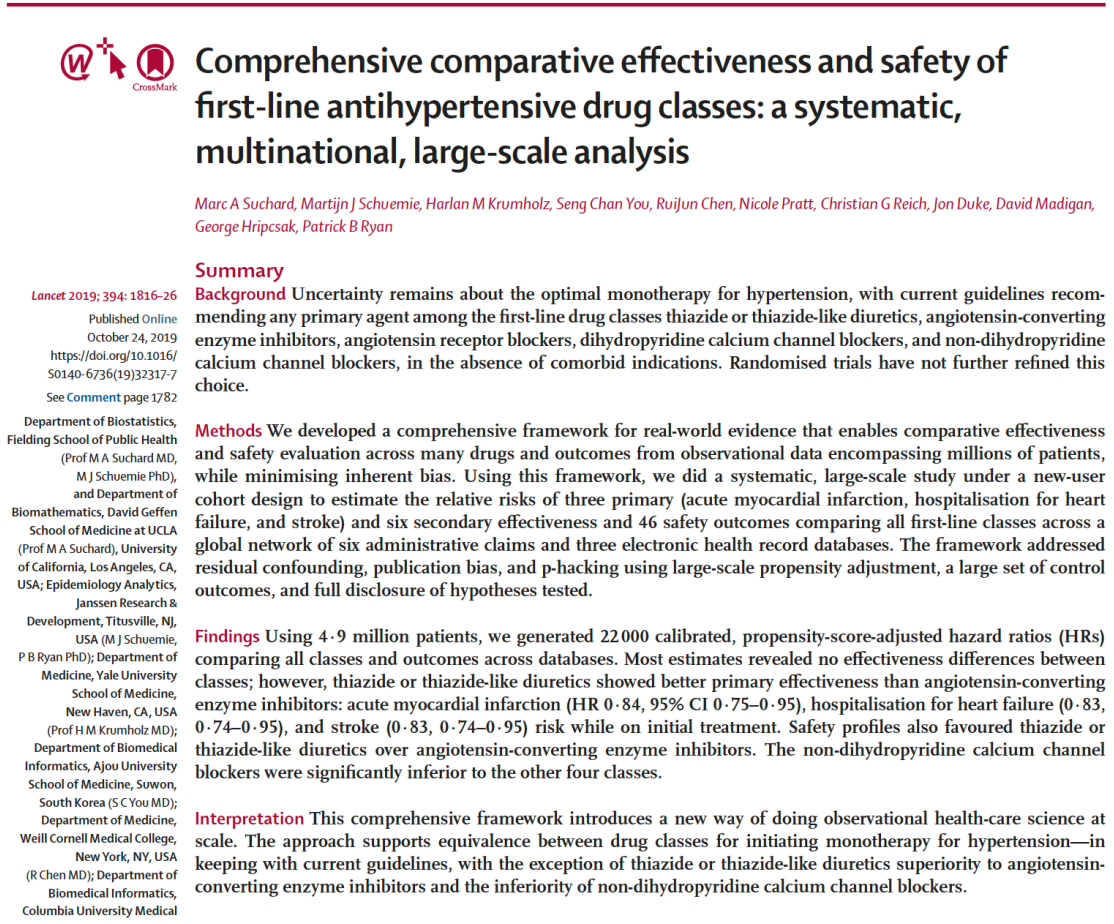
Interpretation This comprehensive framework introduces a new way of doing observational health-care science at scale. The approach supports equivalence between drug classes for initiating monotherapy for hypertension—in keeping with current guidelines, with the exception of thiazide or thiazide-like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

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



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- Objectives & Methods
- Data sources
- Findings to date

Study objective

As an extension of the LEGEND-HTN initiative, we aim to develop, implement and execute a systematic, large-scale observational study that provides comprehensive comparisons of dual combinations of four major antihypertensive agent classes for treatment escalation.

Study Aims

- Aim 1: To describe real-world utilization of dual antihypertensive combination therapies for treatment escalation among people with hypertension, overall and across subgroups by age, sex, history of CVD, and country.

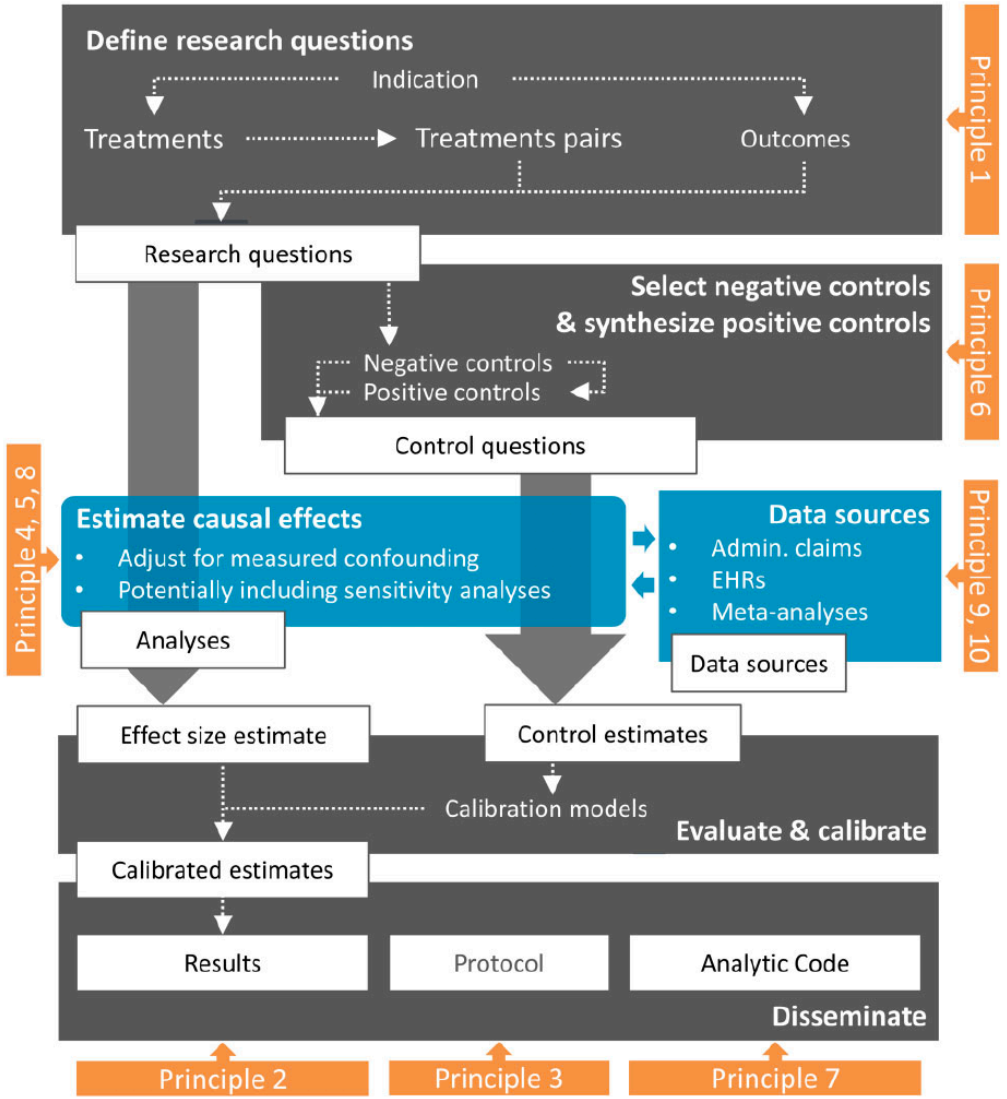
- Aim 2: To determine real-world effectiveness of dual antihypertensive combination therapies for treatment escalation on nine effectiveness outcomes.

- Aim 3: To determine real-world risks of adverse events and benefits on 46 safety outcomes.

Full study protocol will be available on GitHub soon.

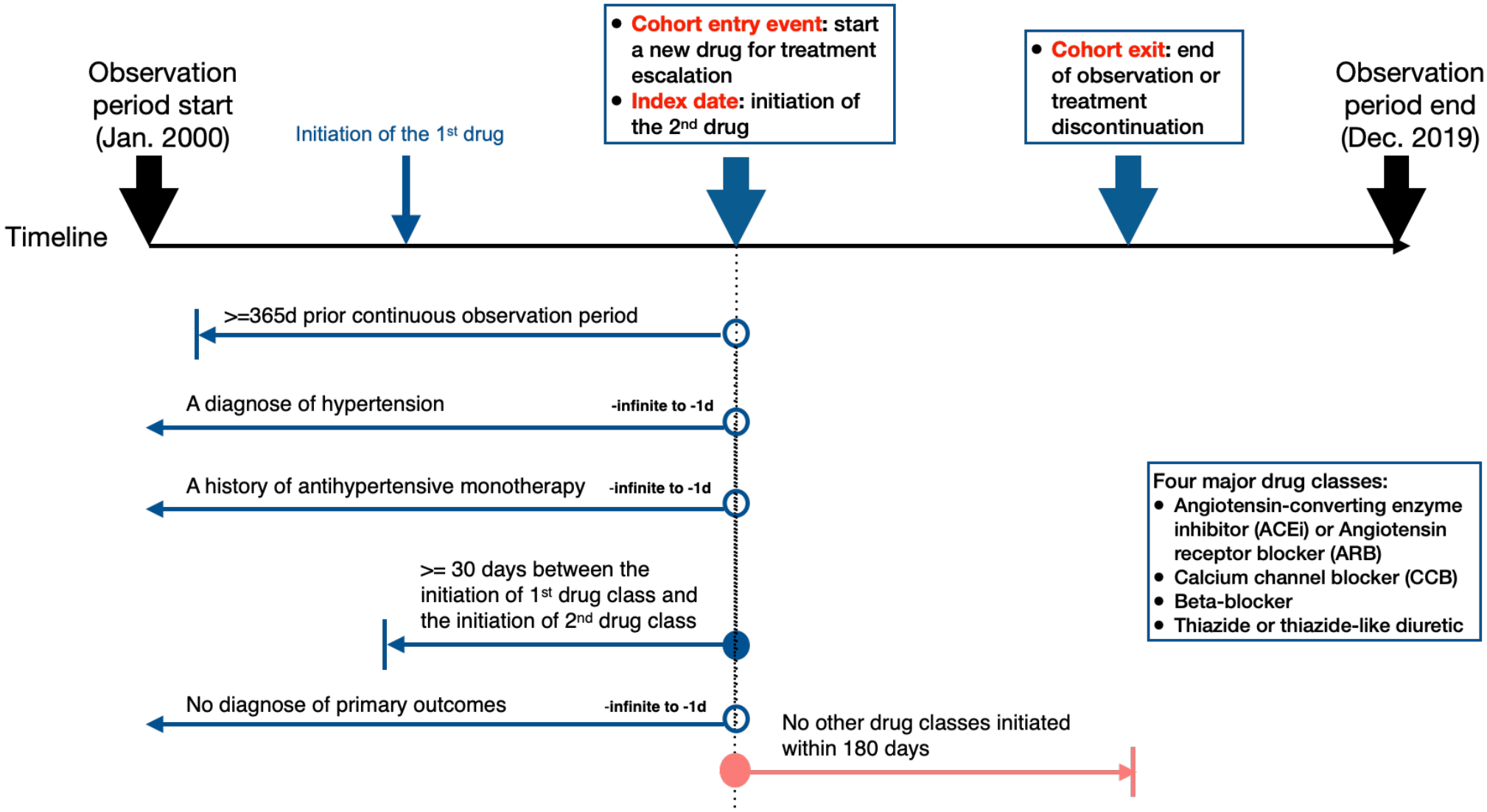
Study design

- Active comparator, new-user cohort design
- Model the study on LEGEND-HTN Lancet paper
- Apply LEGEND guiding principles



Schuemie et al, JAMIA, 2020

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

Public Atlas Links to 12 Cohorts

Cohort #	1st Drug	2nd Drug	Atlas Cohort links
1	ACEi/ARB	CCB	http://atlas-demo.ohdsi.org/#/cohortdefinition/1775040
2	CCB	ACEi/ARB	http://atlas-demo.ohdsi.org/#/cohortdefinition/1775041
3	ACEi/ARB	Diuretic	http://atlas-demo.ohdsi.org/#/cohortdefinition/1775042
4	Diuretic	ACEi/ARB	http://atlas-demo.ohdsi.org/#/cohortdefinition/1775043
5	ACEi/ARB	B-blocker	http://atlas-demo.ohdsi.org/#/cohortdefinition/1775044
6	B-blocker	ACEi/ARB	http://atlas-demo.ohdsi.org/#/cohortdefinition/1775045
7	CCB	Diuretic	http://atlas-demo.ohdsi.org/#/cohortdefinition/1775046
8	Diuretic	CCB	http://atlas-demo.ohdsi.org/#/cohortdefinition/1775047
9	CCB	B-blocker	http://atlas-demo.ohdsi.org/#/cohortdefinition/1775048
10	B-blocker	CCB	http://atlas-demo.ohdsi.org/#/cohortdefinition/1775049
11	Diuretic	B-blocker	http://atlas-demo.ohdsi.org/#/cohortdefinition/1775050
12	B-blocker	Diuretic	http://atlas-demo.ohdsi.org/#/cohortdefinition/1775051

Eight comparisons

Target cohort	Comparator cohort
ACEi/ARB + CCB	ACEi/ARB + Diuretics
ACEi/ARB + CCB	ACEi/ARB + B-blocker
B-blocker + ACEi/ARB	B-blocker + CCB
B-blocker + ACEi/ARB	B-blocker + Diuretics
CCB + ACEi/ARB	CCB + Diuretics
CCB + ACEi/ARB	CCB + B-blocker
Diuretics + ACEi/ARB	Diuretics + B-blocker
Diuretics + ACEi/ARB	Diuretics + CCB

Outcomes

- Three primary effectiveness outcomes based on 2017 AHA/ACC guidelines systematic review
- Six secondary effectiveness outcomes that major hypertension treatment RCTs have considered

Primary effectiveness outcome	Secondary effectiveness outcome
Acute myocardial infarction	Cardiovascular event
Hospitalization for heart failure	Ischemic stroke
Stroke	Hemorrhagic stroke
	Heart failure
	Sudden cardiac death
	Unstable angina

- 46 safety outcomes

Phenotype definitions available at: https://data.ohdsi.org/LegendBasicViewer/

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OHDSI APAC Data Network

Committed Data Sources
Australia LPD
Australia ePBRN SWSLHD
Korea KHMC
Korea Ajou University School of Medicine
China Jiangsu Province Hospital
China iHeart
Singapore NUH
Singapore KTPH
Japan Medical Data Center (JMDC)

Together, the committed data sources cover:
21 millions patients in 5 countries

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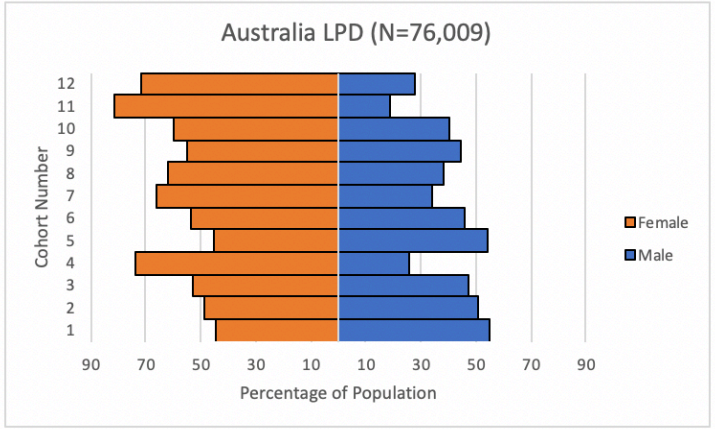
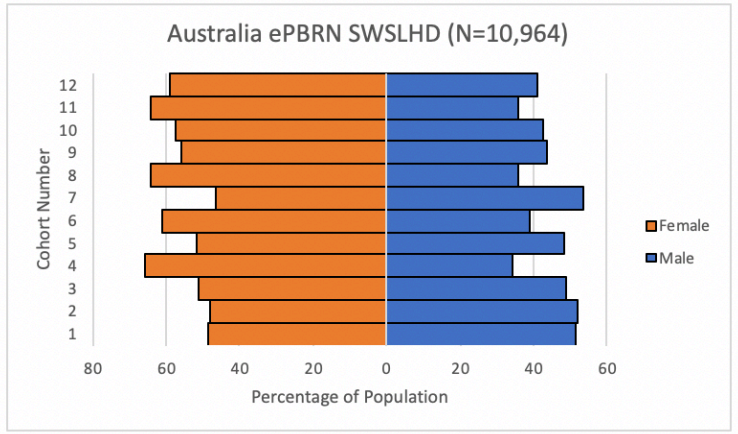
Patient counts for 12 exposure cohorts

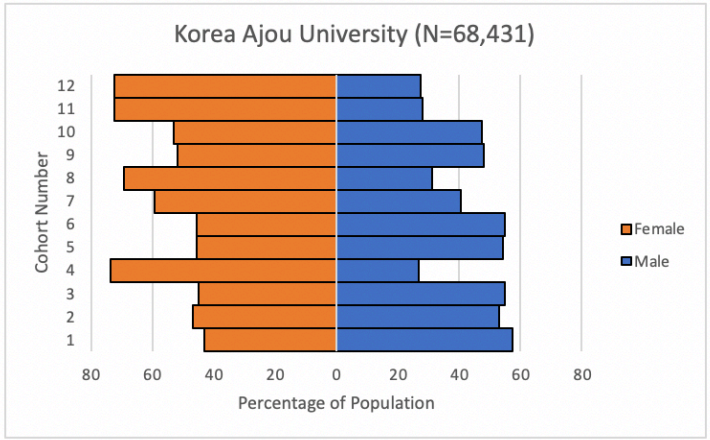
Cohort #	1st Drug	2nd Drug	APAC Data Sources					
			Australia		Korea		Singapore	
			IQVIA Australia	ePBRN SWSLHD	Ajou University	KHMC	SG_KTPH	SG_NUH
1	ACEi/ARB	CCB	4,254	698	1,216	147	257	439
2	CCB	ACEi/ARB	1,339	246	1,487	191	217	133
3	ACEi/ARB	Diuretic	2,066	508	474	12	19	31
4	Diuretic	ACEi/ARB	251	94	154	2	8	7
5	ACEi/ARB	B-blocker	1,184	268	392	49	177	144
6	B-blocker	ACEi/ARB	717	210	386	98	154	128
7	CCB	Diuretic	74	28	259	15	14	6
8	Diuretic	CCB	50	25	139	6	5	7
9	CCB	B-blocker	190	41	814	217	156	101
10	B-blocker	CCB	159	54	614	199	130	243
11	Diuretic	B-blocker	27	14	43	5	3	8
12	B-blocker	Diuretic	27	17	51	10	6	7

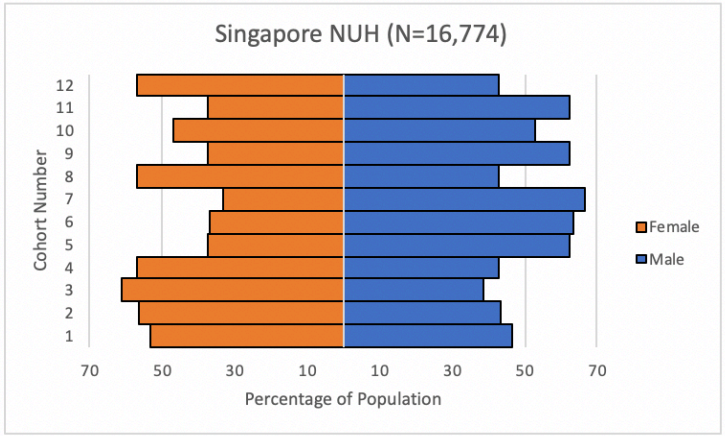
Cohort characterization by gender

- Gender ratio of hypertension patients is 1:1
- Women are more likely to be in Cohort #4 (Diuretic + ACEi/ARB), Cohort #8 (Diuretic + CCB), Cohort #12 (B-blocker + Diuretic)



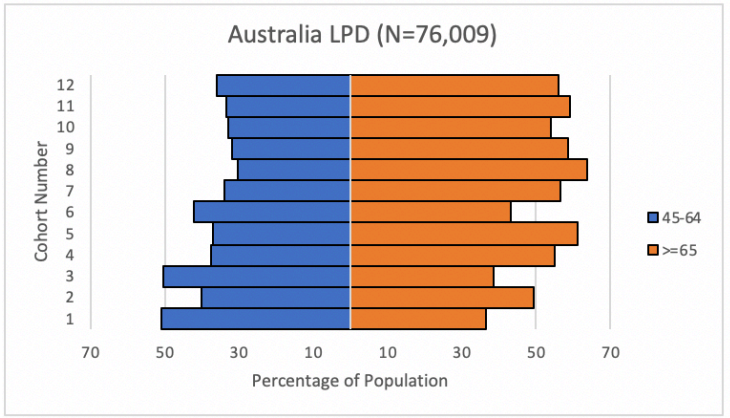


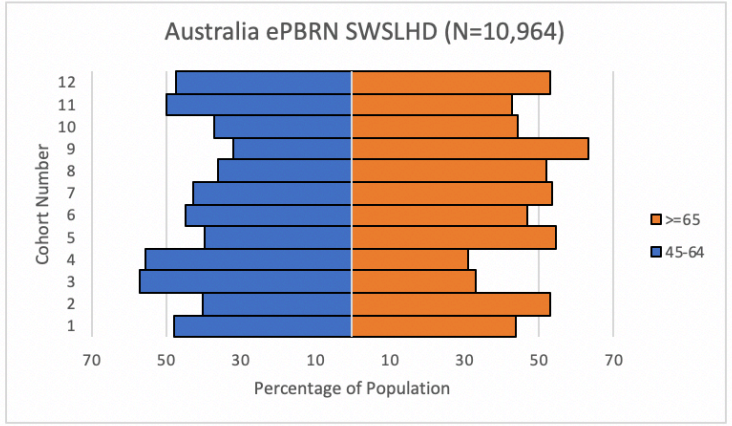


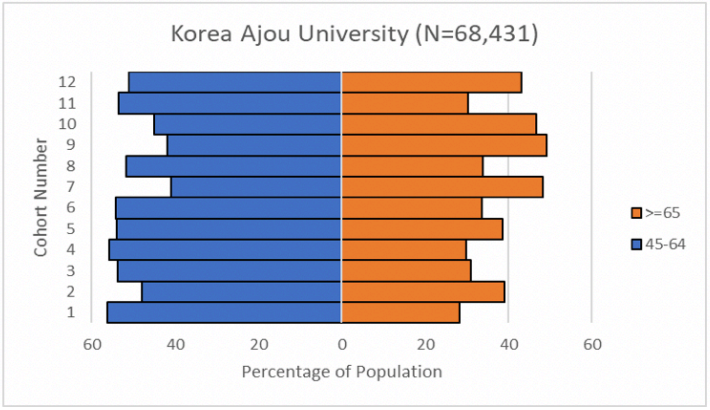


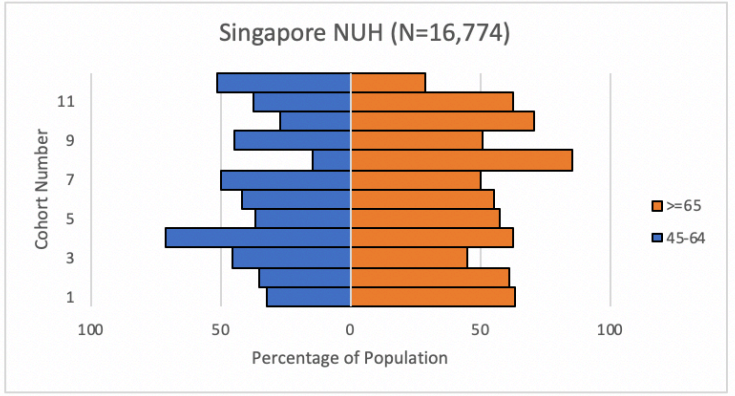
Cohort characterization by age

- Majority of cohort #1 (ACEi/ARB + CCB), cohort #3 (ACEi/ARB + Diuretic) are in age 45-64.
- Majority of cohort #7 (CCB + Diuretic), cohort #9 (CCB + B-blocker), cohort #10 (B-blocker + Diuretic) are in age >=65.
- Drug utilization in Australia and Singapore is higher in age >=65, in Korea is higher in age 45-64.



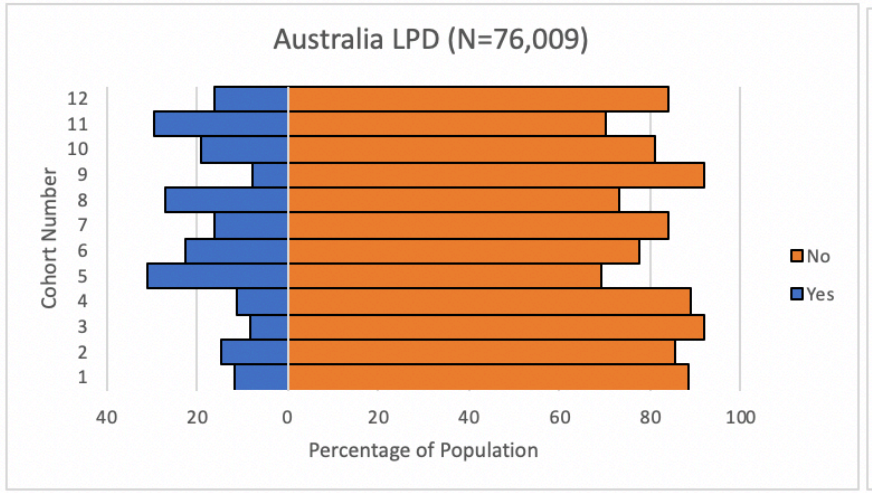


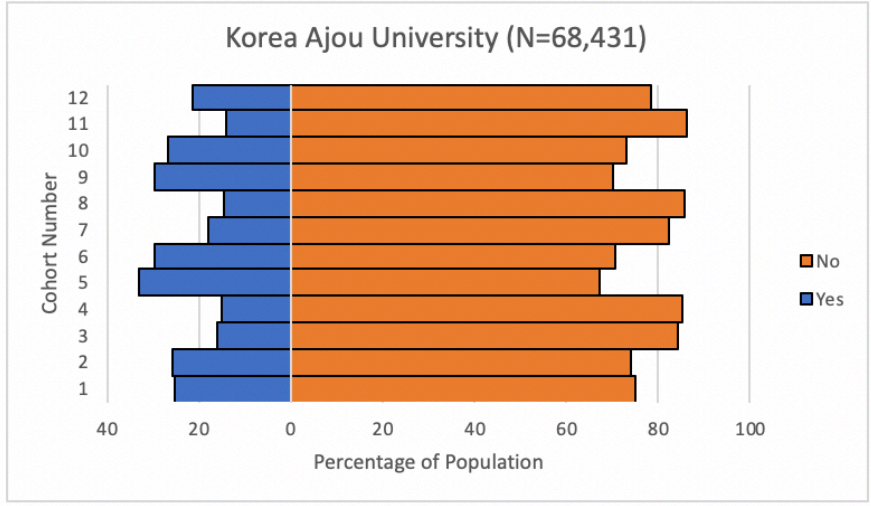




Cohort characterization by history of CVD

- Most patients do not have history of CVD.
- Among people with history of CVD, cohort #5 (ACEi/ARB + B-blocker) and cohort #6 (B-blocker + ACEi/ARB) are prevalent, consistent with guidelines for secondary prevention of CVD





Treatment pathway (Australia LPD)

Target Cohort

[APAC HTN] APAC overall population

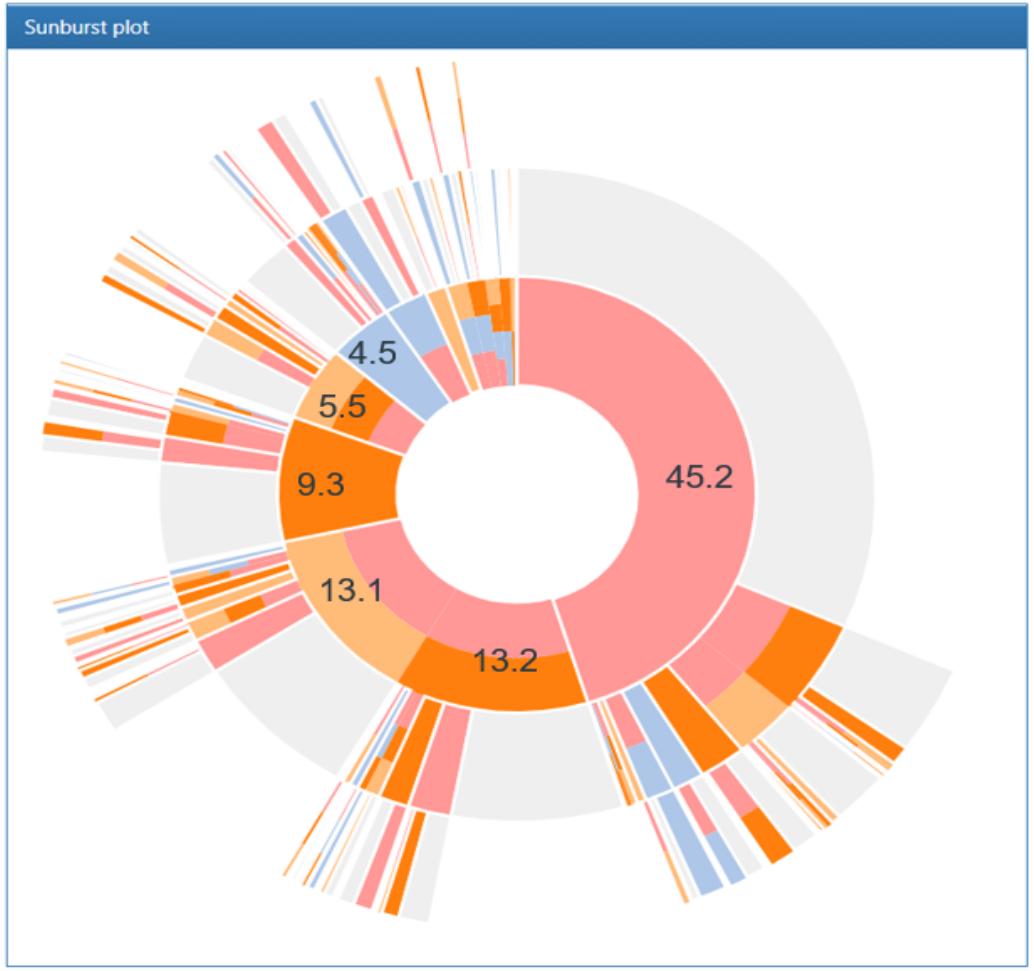
- Target cohort count: 78,840
- Persons with pathways count: 69,213
- Persons with pathways portion: 87.8%

[APAC HTN] Beta-blocker use after hypertension diagnosis

[APAC HTN] CCB use after hypertension diagnosis

[APAC HTN] Diuretic use after hypertension diagnosis

[APAC HTN] ACEi/ARB use after hypertension diagnosis



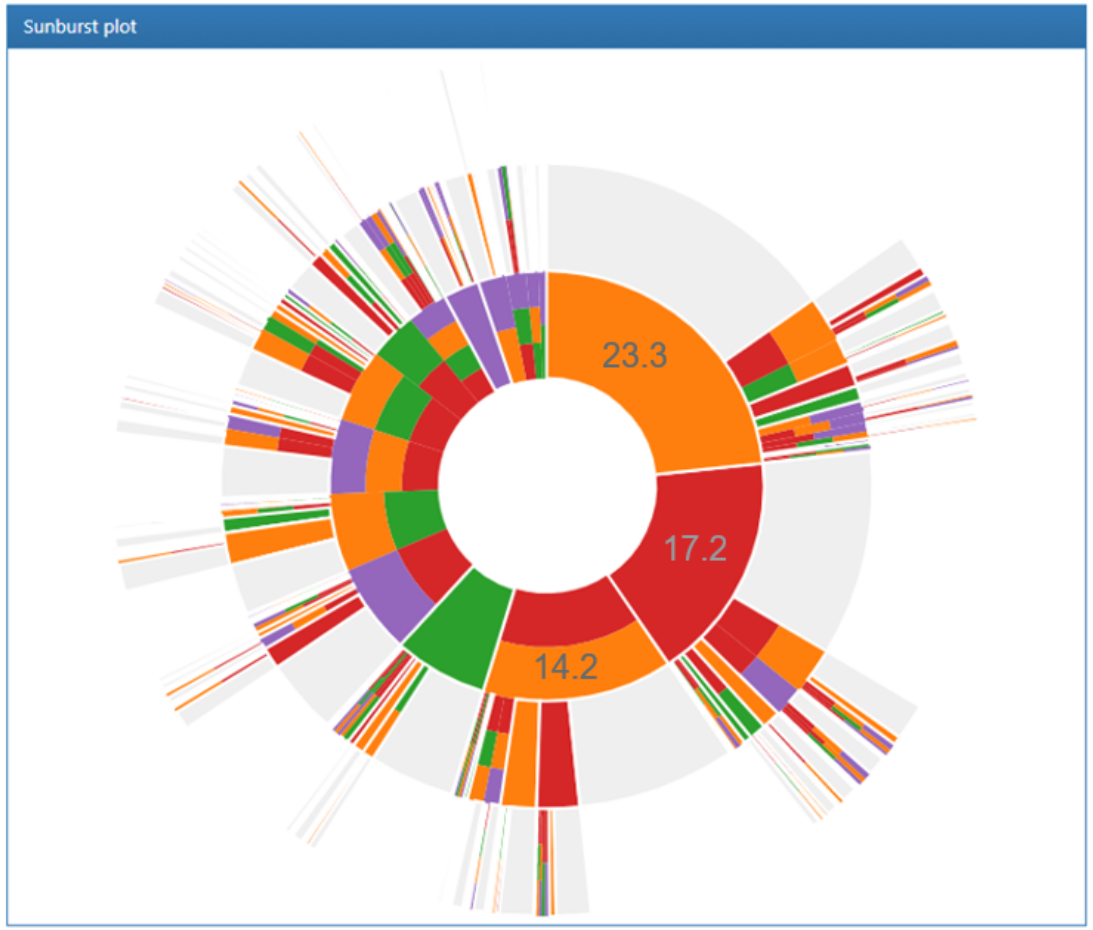
Treatment pathway (Korea Ajou University)

Target Cohort

[APAC HTN] APAC overall population

- Target cohort count: 68,431
- Persons with pathways count: 52,250
- Persons with pathways portion: 76.4%

- [APAC HTN] CCB use after hypertension diagnosis
- [APAC HTN] Beta-blocker use after hypertension diagnosis
- [APAC HTN] ACEi/ARB use after hypertension diagnosis
- [APAC HTN] Diuretic use after hypertension diagnosis



Treatment pathway (Singapore NUH)

Legend

Target Cohort

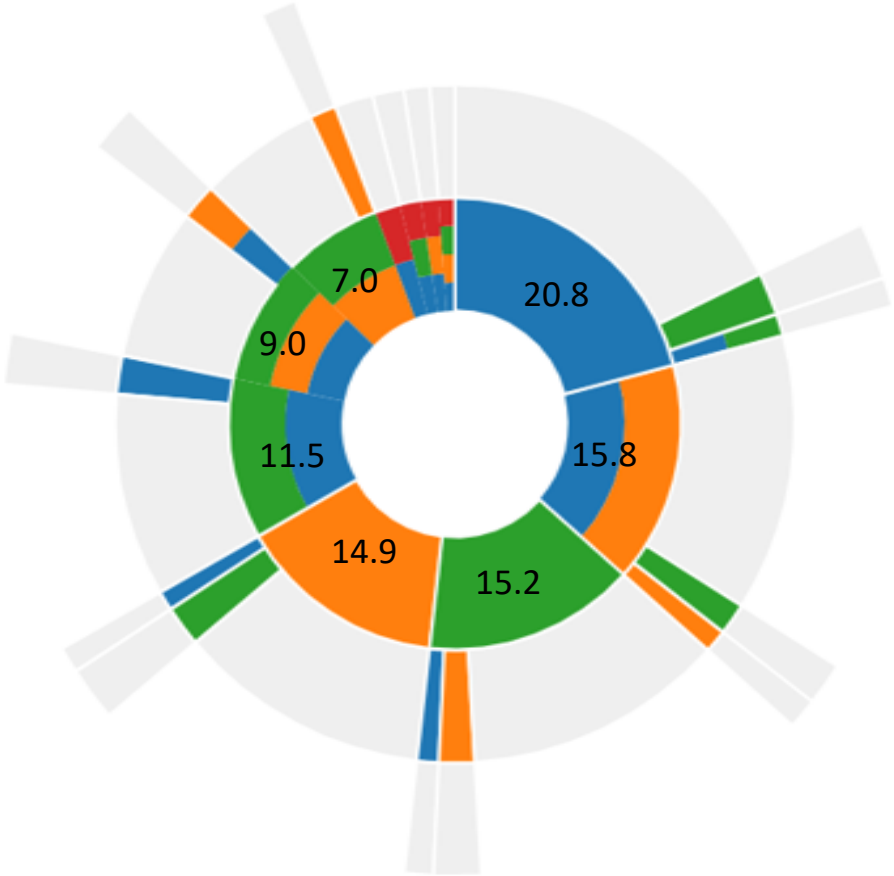
[APAC HTN] APAC overall population

- Target cohort count: 16,774
- Persons with pathways count: 14,707
- Persons with pathways portion: 87.7%

Event Cohorts

- [APAC HTN] ACEi/ARB use after hypertension diagnosis
- [APAC HTN] Beta-blocker use after hypertension diagnosis
- [APAC HTN] CCB use after hypertension diagnosis
- [APAC HTN] Diuretic use after hypertension diagnosis

Sunburst plot



Treatment pathway

Significant variations in drug utilization across countries

- Most common first-line therapy of patients in Australia and Singapore is ACEi/ARB.
- Most common first-line therapy of Korean patients is CCB.
- More patients in Australia had second-line treatment than Korean patients.

JOIN the OHDSI APAC team

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