LEGEND: Clinical insights for hypertension

Patrick Ryan, Martijn Schuemie, Marc Suchard
on behalf of the LEGEND team

OHDSI Symposium
12 October 2018

Current knowledge base for hypertension

Head-to-head antihypertensive drug comparisons

- Driven primarily by ALLHAT
  - just 3 individual drugs
- Focus: efficacy $\gg$ safety

Can LEGEND provide

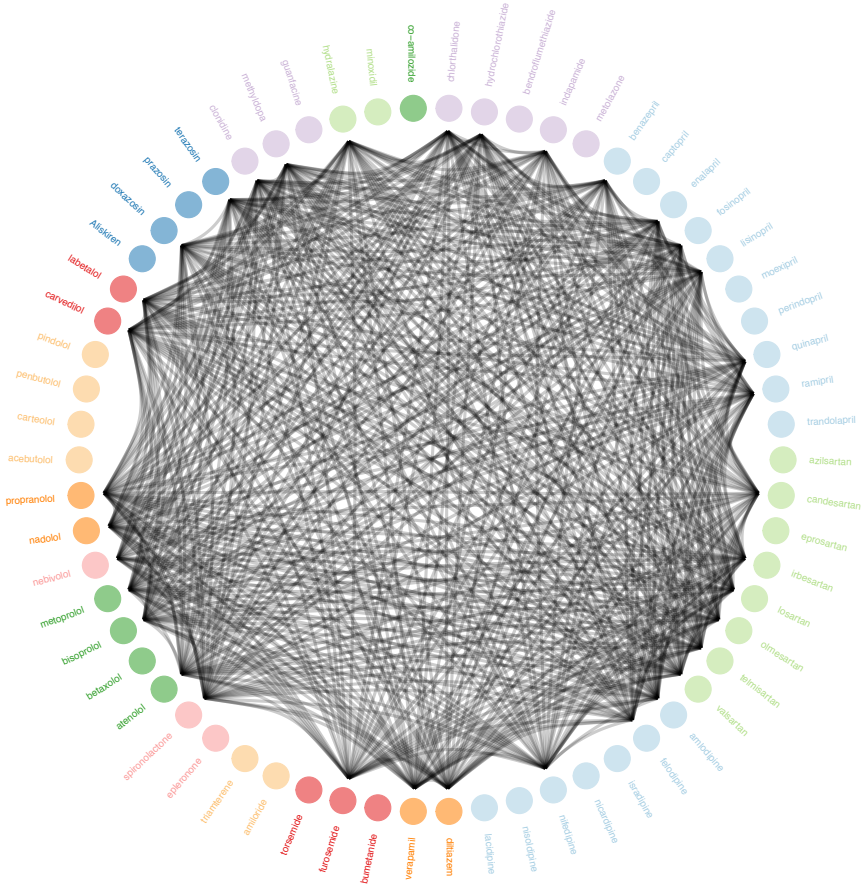
1. reliable – concordant w/ RCTs
2. rich – across "all" comparators
3. relevant – inform practice

evidence?

- Trials: 40
- $N = 102 - [1148] - 33K$

LEGEND knowledge base for hypertension

Head-to-head HTN drug comparisons



- Trials: 40
- $N = 102 - [1148] - 33K$

- Comparisons: 10,278
- $N = 3502 - [212K] - 1.9M$

First-line agents

2017 ACC/AHA Guidelines

COR	LOE	RECOMMENDATION
I	A^{SR}	1. For initiation of antihypertensive drug therapy, first-line agents include thiazide diuretics, CCBs, and ACE inhibitors or ARBs. (S8.1.6-1,S8.1.6-2)

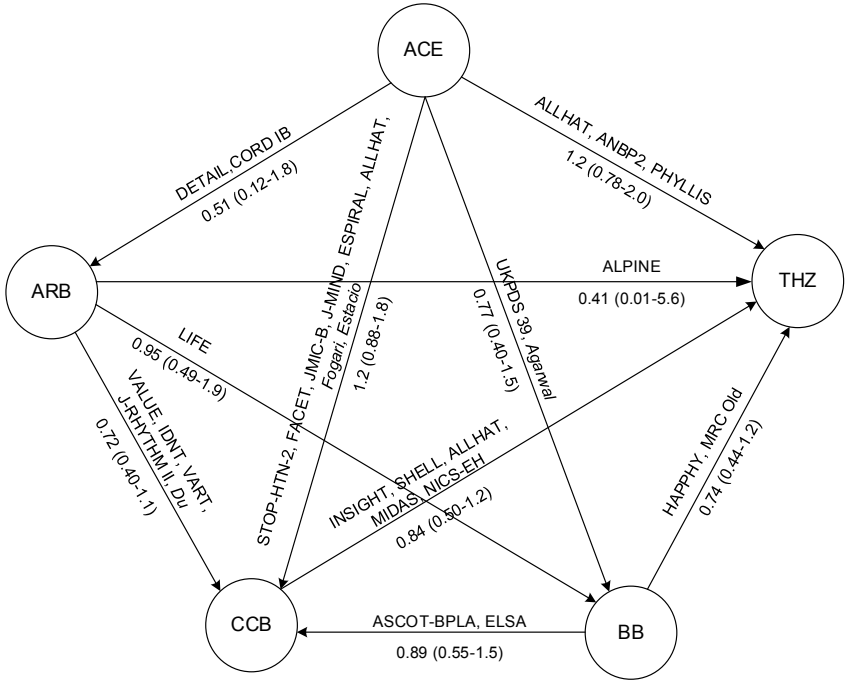
"In particular, there is inadequate evidence to support the initial use of beta blockers for hypertension in the absence of specific cardiovascular comorbidities."

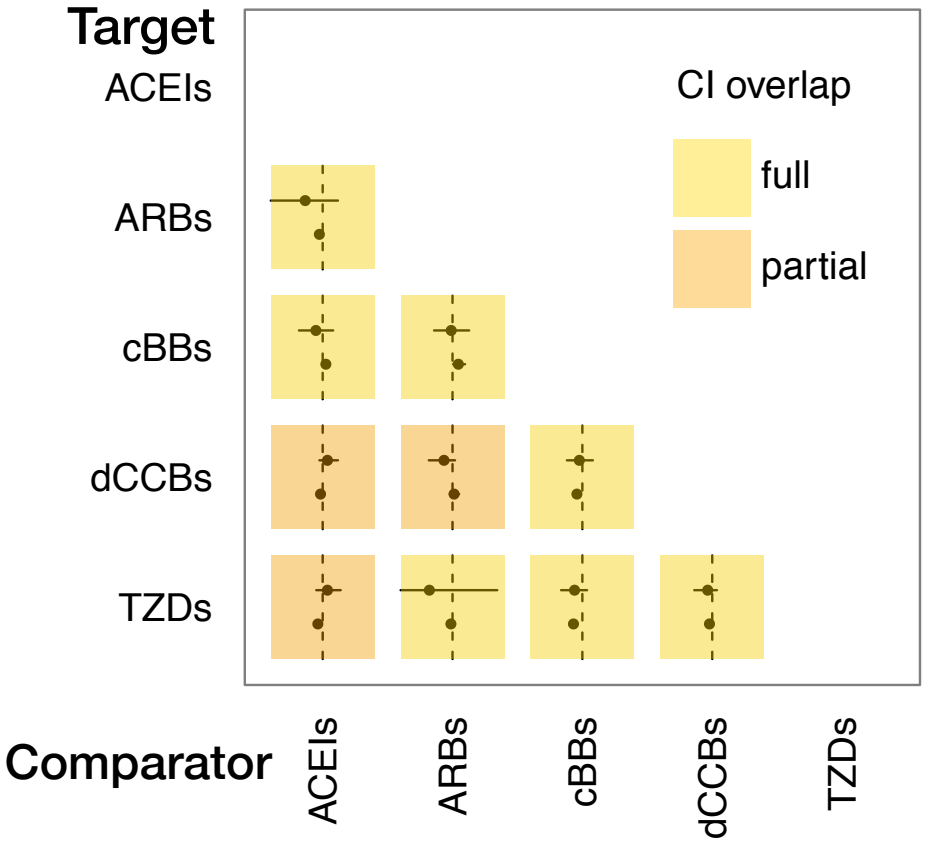
2018 ESC/ESH Guidelines: Class I, Level A

"Among all antihypertensive drugs, ACE inhibitors, ARBs, beta-blockers, CCBs, and [thiazide] diuretics . . . have demonstrated effective reduction of BP and CV events in RCTs, and thus are indicated as the basis of antihypertensive treatment strategies." ". . . beta-blockers are usually equivalent in preventing major CV events, except for less effective prevention of stroke . . ."

First-line agents: comparisons from RCTs

Efficacy outcomes: **myocardial infarction**, heart failure, stroke

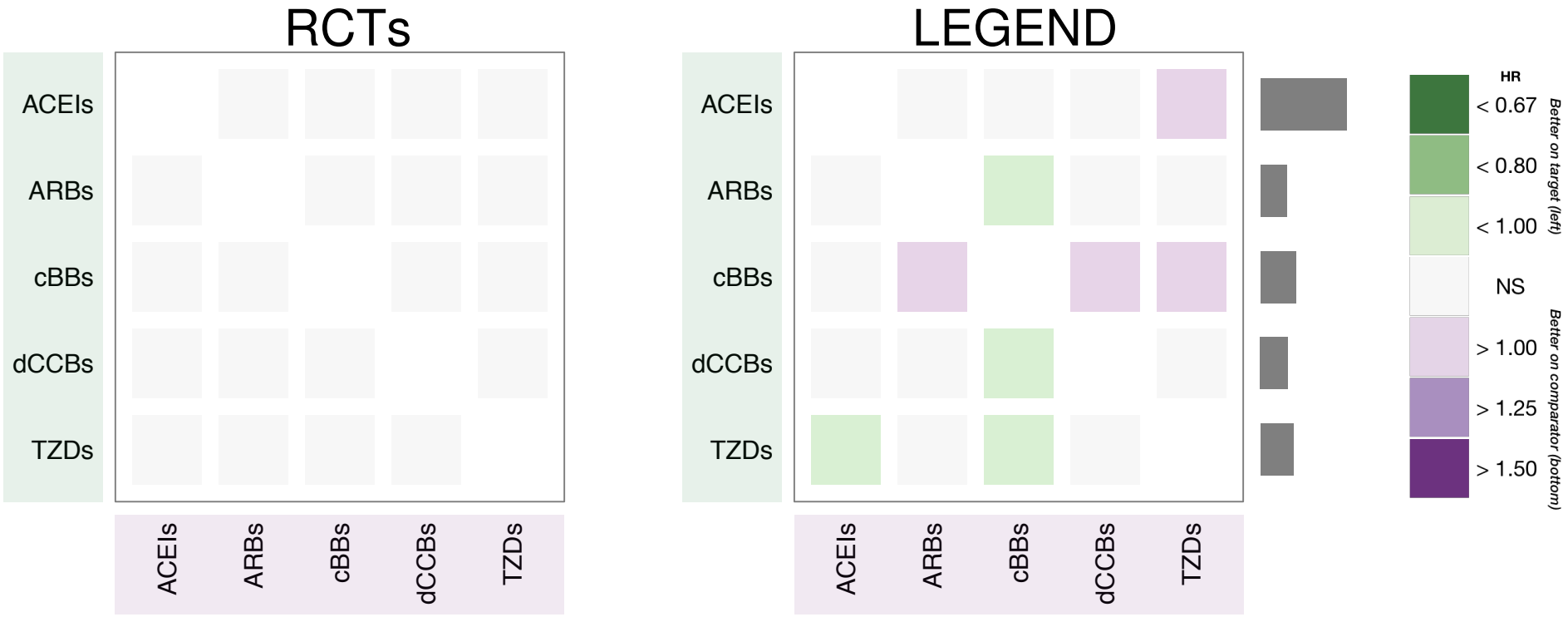




- 28 / 30 estimates are concordant (discordant in BBs for HF)

First-line agents: comparisons from LEGEND

Efficacy outcome: **myocardial infarction**, heart failure, stroke



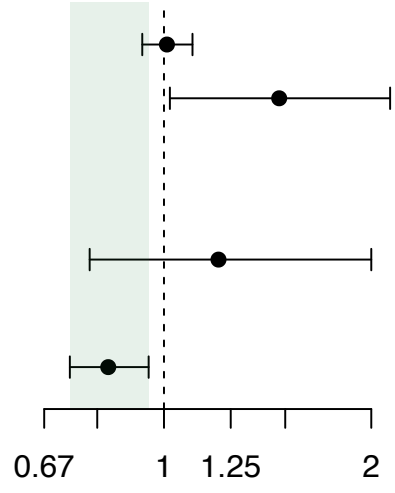
Data source: meta-analysis, $\sim 1 - 2$M total patients per study

- Beta blockers underperform alternatives
- Unexpected: TZDs $>$ ACEIs. Reliable?

TZDs vs. ACEIs: hazard ratio

Efficacy outcome: **myocardial infarction**

		Patients	Events		Patients	Events
ALLHAT	CTD	15,255	1,362	lisinopril	9,054	796
ANBP2	HCTZ	3,039	82	enalapril	3,044	58
PHYLLIS	HCTZ	127	-	fosinopril	127	-
Review		18,421	1,447		12,225	854
LEGEND	TZDs	631,154	1,122	ACEIs	1,666,241	5,073



- TZDs vs. ACEIs calibrated HR: 0.83, 95% CI 0.73 - 0.95, $p = 0.01$
- Is concordant with systematic review, but shows effect difference
- Suspect previous studies lack power

TZDs vs. ACEIs: study diagnostics

Large-scale propensity score model controls for observed confounding

Fig. 2. Preference score distribution for TZDs and ACEIs new-users. The preference score is a transformation of the propensity score that adjusts for prevalence differences between populations. A higher overlap indicates that subjects in the two populations are more similar in terms of their predicted probability of receiving one treatment over the other.

Cohort stratification / balance:

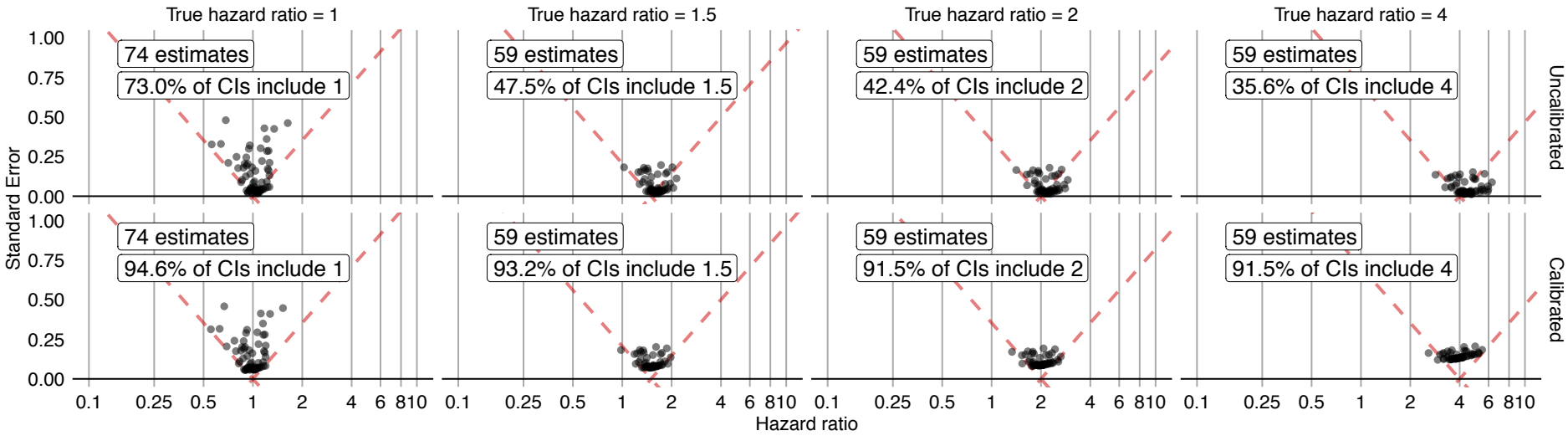
- Achieved across all 10,868 baseline characteristics (CCAE)
- Blood pressure (pop. means in mmHg) (Panther)

	TZDs	ACEIs	$\lvert\Delta\rvert$
before	145/89	145/87	0.13
after	145/88	145/87	0.02

No BP measurements used in PS model, but still balanced after stratification

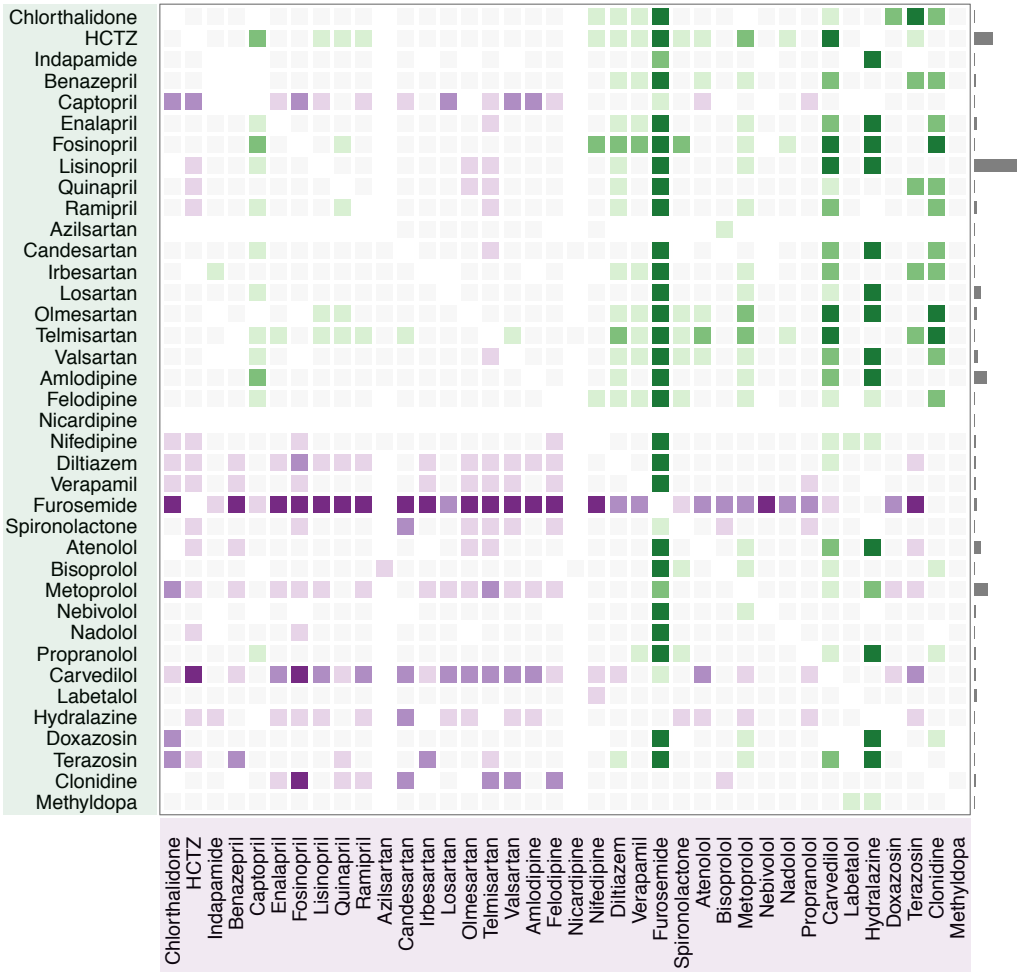
TZDs vs. ACEIs: study outcomes

Calibration returns near nominal HR estimate coverage



- Good diagnostics $\rightarrow$ comparable cohorts (observed and unobserved); calibration $\rightarrow$ controls for residual systematic bias
- TZDs are more effective than ACEIs in preventing MI

Cardiovascular efficacy by drug



Composite (MI, HF, stroke) outcome in meta-analysis

Prescriptions are not written at the class-level; must choose an individual drug for the patient

- 1^{st}-line $>$ 2^{nd}-line
- Some within-class differences failed diagnostics, e.g. captopril

Initiating mono- vs. combination-therapy

2017 ACC/AHA Guidelines

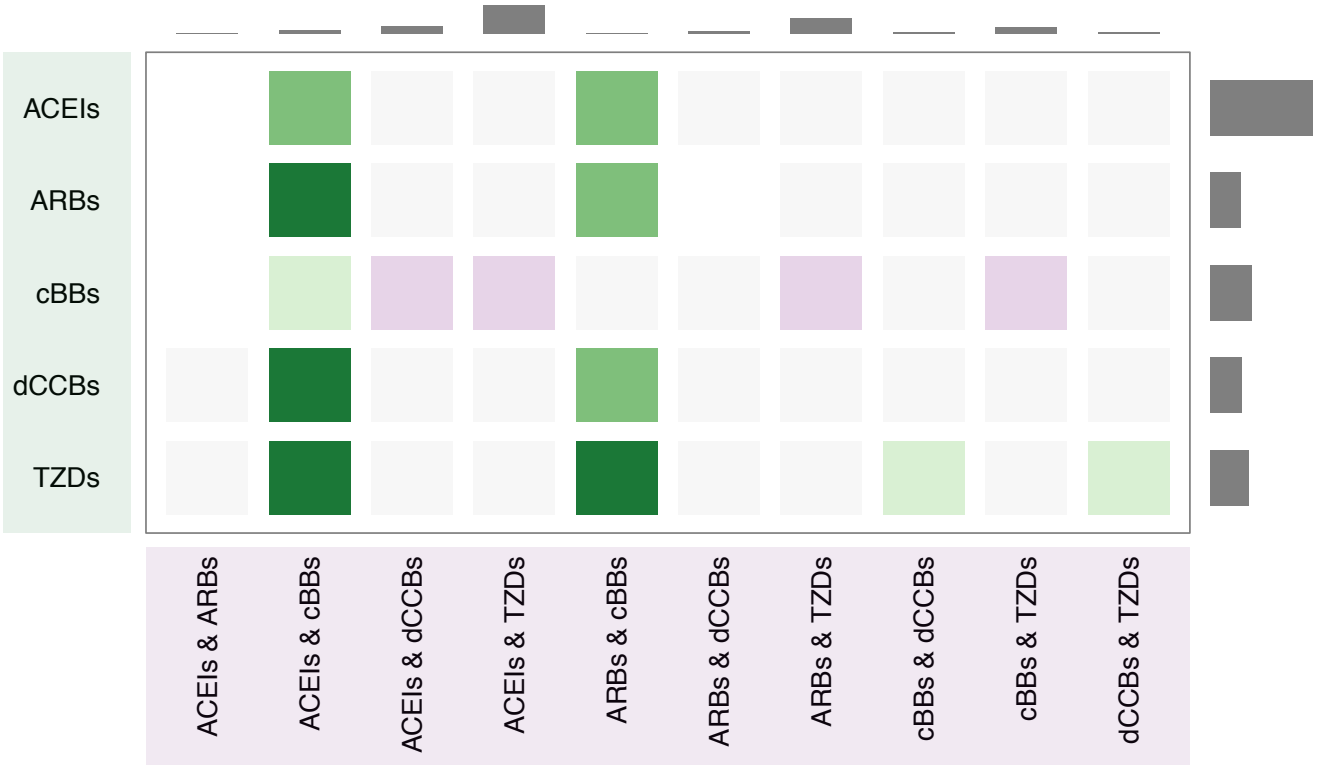
COR	LOE	RECOMMENDATIONS
I	C-EO	1. Initiation of antihypertensive drug therapy with 2 first-line agents of different classes, either as separate agents or in a fixed-dose combination, is recommended in adults with stage 2 hypertension and an average BP more than 20/10 mm Hg above their BP target.
IIa	C-EO	2. Initiation of antihypertensive drug therapy with a single antihypertensive drug is reasonable in adults with stage 1 hypertension and BP goal <130/80 mm Hg with dosage titration and sequential addition of other agents to achieve the BP target.

2018 ESC/ESH Guidelines: Class I, Level A

"Combination treatment is recommended for most hypertensive patients as initial therapy." "...no RCT has compared major CV outcomes between initial combination therapy and monotherapy ..."

Mono- vs. combo-therapy

Efficacy outcome: **myocardial infarction**, heart failure, stroke



Similar efficacy for HF and stroke

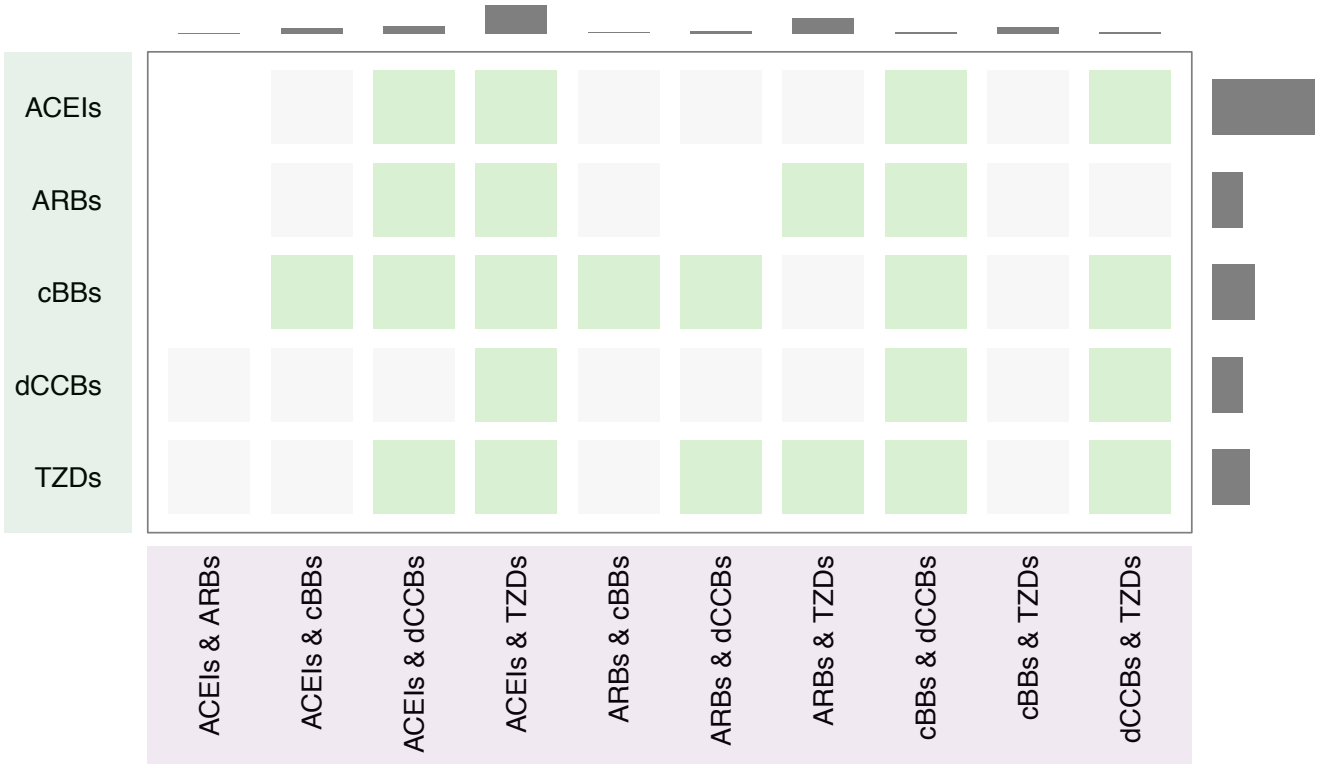
Recommended: no ACEIs + ARBs combos

ACEIs + TZDs combos are most prevalent

- ACEIs vs. ACEIs + TZDs
- TZDs vs. ACEIs + TZDs

Mono- vs. combo-therapy

Safety outcome: **kidney disease**



Antihypertensives tend to affect kidney function

Initiating combo increases risk

- **ACEIs vs. ACEIs + TZDs** – ACEIs are more prevalent
- TZDs vs. ACEIs + TZDs

Kidney disease in CCAE

Table 1. Patient cohorts. Target (T) cohort is ACEIs new-users. Comparative (C) cohort is ACEIs and TZDs new-users. We report total number of patients, follow-up time (in years), number of chronic kidney disease events, and event incidence rate (IR) per 1,000 patient years (PY) in patient cohorts, as well as the their minimum detectable relative risk (MDRR). Note that the IR does not account for any stratification or matching.

	Patients		PYs		Events		IR		
Design	T	C	T	C	T	C	T	C	MDRR
PS stratification, on-treatment	767,571	231,312	579,641	153,465	3,473	980	5.99	6.39	1.10
PS stratification, intent-to-treat	769,659	232,022	2,089,649	635,031	11,872	3,673	5.68	5.78	1.05

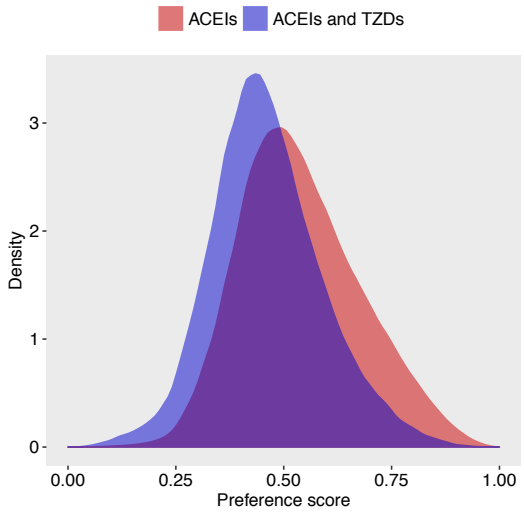


Fig. 2. Preference score distribution for ACEIs and ACEIs and TZDs new-users. The preference score is a transformation of the propensity score that adjusts for prevalence differences between populations. A higher overlap indicates that subjects in the two populations are more similar in terms of their predicted probability of receiving one treatment over the other.

Cohort stratification / balance:

- Achieved across all 8,541 baseline characteristics
- Remarkable overlap in cohorts

Kidney disease in CCAE

Table 4. Hazard ratio (HR) estimates and their confidence intervals (CIs) and p-value to reject the null hypothesis of no difference (HR = 1) under various designs.

Design	Uncalibrated		Calibrated	
	HR (95% CI)	p	HR (95% CI)	p
PS stratification, on-treatment	0.78 (0.72 - 0.84)	0.00	0.78 (0.71 - 0.87)	0.00
PS stratification, intent-to-treat	0.79 (0.76 - 0.82)	0.00	0.80 (0.73 - 0.89)	0.00

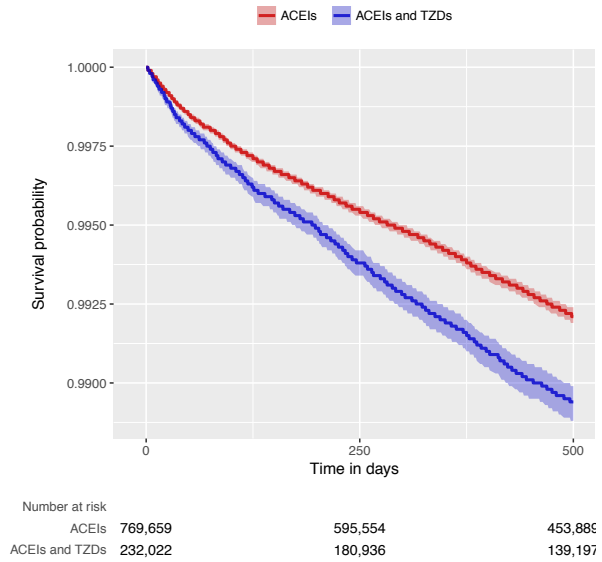


Fig. 4. Kaplan Meier plot of chronic kidney disease-free survival. This plot is adjusted for the propensity score stratification; the ACEIs curve shows the actual observed survival. The ACEIs and TZDs curve applies reweighting to approximate the counterfactual of what ACEIs survival would look like had the ACEIs cohort been exposed to ACEIs and TZDs instead. The shaded area denotes the 95% CI.

Meta-analysis safety estimates:

	HR
ACEIs	0.84 (0.77 - 0.91)
TZDs	0.80 (0.67 - 0.96)

Mono vs. combo-therapy:

- Comparable efficacy
- Greater safety risk

Chlorthalidone vs. hydrochlorothiazide

2017 ACC/AHA Guidelines

TABLE 18 Oral Antihypertensive Drugs

Class	Drug	Usual Dose, Range (mg/d)*	Daily Frequency	Comments
Primary agents				
Thiazide or thiazide-type diuretics	Chlorthalidone	12.5–25	1	■ Chlorthalidone is preferred on the basis of prolonged half-life and proven trial reduction of CVD. ■ Monitor for hyponatremia and hypokalemia, uric acid and calcium levels. ■ Use with caution in patients with history of acute gout unless patient is on uric acid–lowering therapy.
	Hydrochlorothiazide	25–50	1	
	Indapamide	1.25–2.5	1	
	Metolazone	2.5–5	1	

Diuretic Comparison Project (2022)

VA CSP Study No. 597: Diuretic Comparison Project

| Diuretic Comparison Project Home Page | Information for Veterans | Information for VA Providers | Study Team and Contact Information |

DCP is a national, voluntary research study funded by the VA Cooperative Studies Program (CSP), with the Department of Veterans Affairs Office of Research and Development. The goal of the DCP study is to compare the benefits of two commonly used medications, using an innovative study design. DCP uses Point of Care (POC) methodology, which embeds as much of the study procedures as possible into the routine medical care of Veterans. The result is a streamlined and efficient trial that follows clinical practice, thereby enhancing the ability to learn the answers to important questions directly within the VA healthcare system, thus supporting the goal for VA to be a Learning Healthcare System.

CTD vs. HCTZ: risk of MI in CCAE

Table 1. Patient cohorts. Target (T) cohort is chlorthalidone new-users. Comparative (C) cohort is hydrochlorothiazide new-users. We report total number of patients, follow-up time (in years), number of acute myocardial infarction events, and event incidence rate (IR) per 1,000 patient years (PY) in patient cohorts, as well as the their minimum detectable relative risk (MDRR). Note that the IR does not account for any stratification or matching.

	Patients		PYs		Events		IR		
Design	T	C	T	C	T	C	T	C	MDRR
PS stratification, on-treatment	14,077	287,092	8,513	200,715	11	348	1.29	1.73	2.01
PS stratification, intent-to-treat	14,098	288,073	32,565	888,405	72	1,806	2.21	2.03	1.36

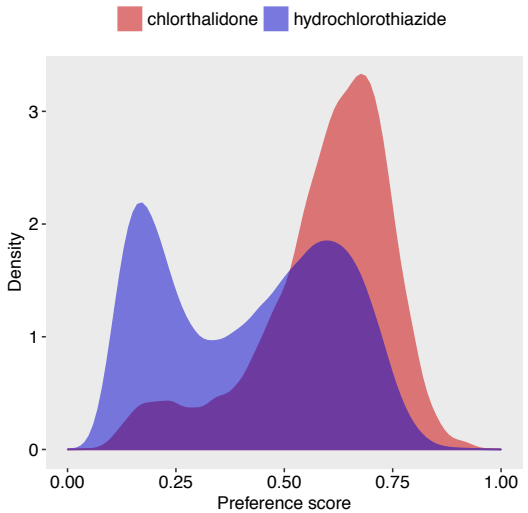


Fig. 2. Preference score distribution for chlorthalidone and hydrochlorothiazide new-users. The preference score is a transformation of the propensity score that adjusts for prevalence differences between populations. A higher overlap indicates that subjects in the two populations are more similar in terms of their predicted probability of receiving one treatment over the other.

Cohort stratification / balance:

- Achieved across all 8,773 baseline characteristics
- Sufficient overlap in cohorts

CTD vs. HCTZ: risk of MI in CCAE

Table 4. Hazard ratio (HR) estimates and their confidence intervals (CIs) and p-value to reject the null hypothesis of no difference (HR = 1) under various designs.

	Uncalibrated		Calibrated	
Design	HR (95% CI)	p	HR (95% CI)	p
PS stratification, on-treatment	0.65 (0.33 - 1.14)	0.17	0.66 (0.37 - 1.19)	0.18
PS stratification, intent-to-treat	1.00 (0.78 - 1.26)	0.99	1.01 (0.79 - 1.30)	0.93

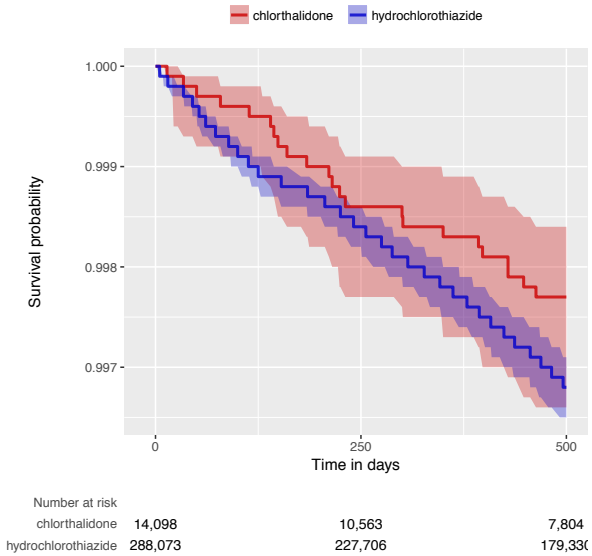


Fig. 4. Kaplan Meier plot of acute myocardial infarction-free survival. This plot is adjusted for the propensity score stratification; the chlorthalidone curve shows the actual observed survival. The hydrochlorothiazide curve applies reweighting to approximate the counterfactual of what chlorthalidone survival would look like had the chlorthalidone cohort been exposed to hydrochlorothiazide instead. The shaded area denotes the 95% CI.

Not shown: Calibration plots demonstrate (and control for) only minimal systematic residual bias

CTD vs. HCTZ: risk of MI

Risk estimates and meta-analysis across LEGEND databases:

Analysis	Data source	HR	LB	UB	P	Cal.HR	Cal.LB	Cal.UB	Cal.P
PS stratification, on-treatment	CCAE	0.65	0.33	1.14	0.17	0.66	0.37	1.19	0.18
PS stratification, on-treatment	Meta-analysis	0.79	0.54	1.16	0.24	0.81	0.56	1.17	0.30
PS stratification, on-treatment	Optum	0.90	0.52	1.44	0.67	0.93	0.57	1.53	0.82
PS stratification, on-treatment	Panther	0.98	0.05	5.06	0.99	0.91	0.26	3.42	0.96

Showing 1 to 4 of 4 entries

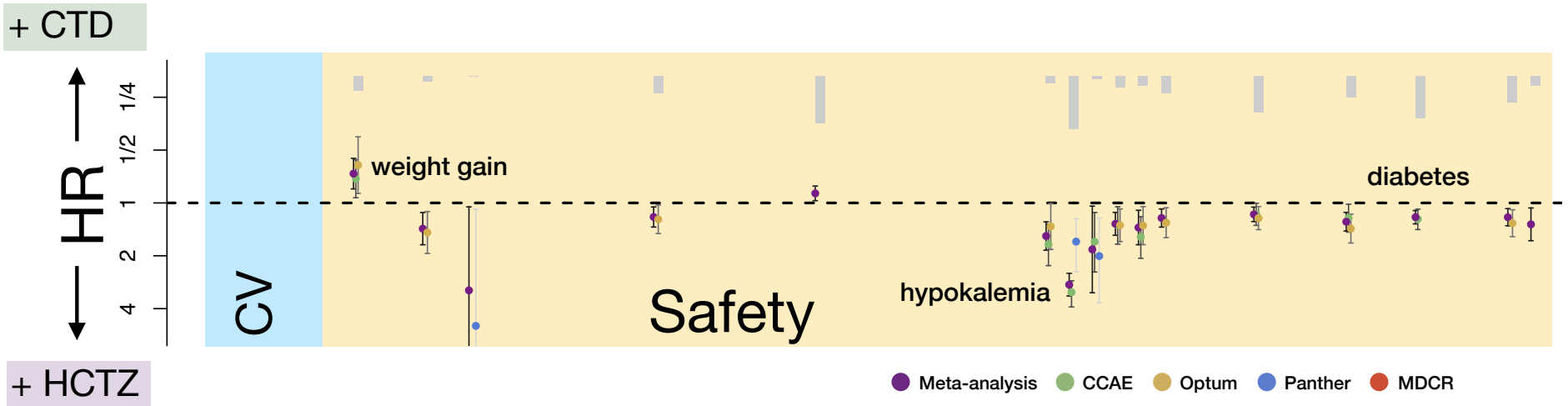
Previous 1 Next

Power | Systematic error | Subgroups

Table 1a. Number of subjects, follow-up time (in years), number of outcome events, and event incidence rate (IR) per 1,000 patient years (PY) in the target (*Chlorthalidone*) and comparator (*Hydrochlorothiazide*) group after stratification, as well as the minimum detectable relative risk (MDRR). Note that the IR does not account for any stratification.

Target subjects	Comparator subjects	Target years	Comparator years	Target events	Comparator events	Target IR (per 1,000 PY)	Comparator IR (per 1,000 PY)	MDRR	i2
25,566	528,202	14,047	339,516	<32	819	<2.28	2.41	>1.58	0.00

CTD vs. HCTZ: safety profile



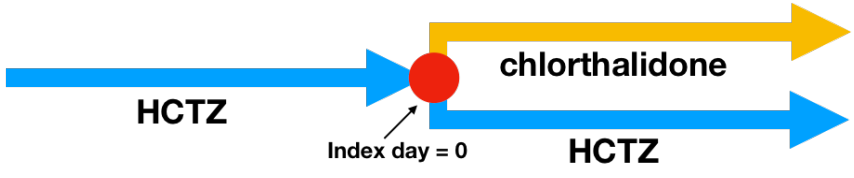
- Safety favors HCTZ – electrolyte imbalance
- CTD is more potent, longer half-life

CTD vs. HCTZ: prediction

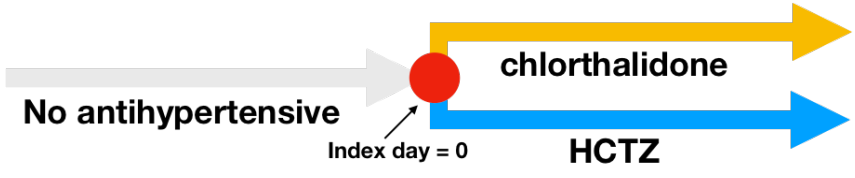
	DCP-RCT	LEGEND
CTD-users	6,750	25,566
HCTZ-users	6,750	528,202
avg/median follow-up	3 years	2 years
maximum follow-up	4.5 years	16 years
HR for MI	(anticipated in 2022)	0.81 (0.56 - 1.17) NS

- 25% of LEGEND patients have follow-up $>$ 4 years

Caveat: design differences (similar vis-a-vis ALLHAT)



DCP

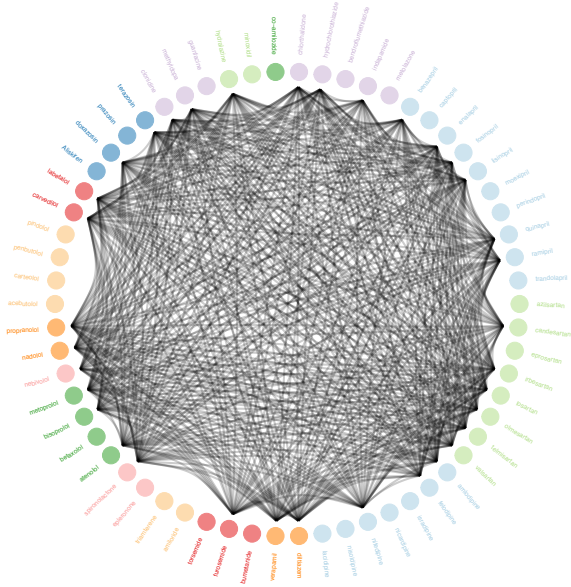


LEGEND

Clinical lessons for hypertension

LEGEND evidence is concordant with RCTs:

- Where RCT results exist, but many unanswered questions remains
- More outcomes, comparisons, data sources

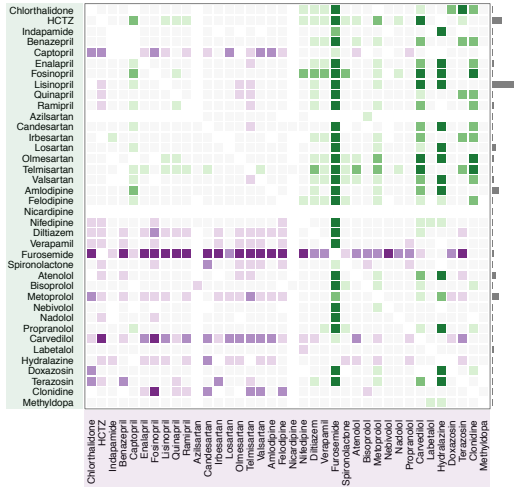


Not all 1st-line agents are equivalent:

- ↓ BBs, TZDs > ACEIs

Combo-therapy initiation:

- ↓ evidence that combo-therapy is better
- Evidence of ↑ safety risk



DCP trial prediction:

- CTD vs. HCTZ – no efficacy difference

Acknowledgments

LEGEND Scientific Group:

- Martijn J. Schuemie
- Patrick B. Ryan
- Seng Chan You
- Nicole Pratt
- David Madigan
- George Hripcsak
- Marc A. Suchard

Clinical Advisory Team:

- RuiJun Chen
- Jon Duke
- Rae Woong Park
- Christian Reich
- Peter R. Rijnbeck