Large-Scale Evidence Generation and Evaluation in a Network of Databases (LEGEND)

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

OHDSI Symposium

12 October 2018

OHDSI's mission

To improve health by empowering a community to collaboratively generate the evidence that promotes better health decisions and better care

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Hypertension

The New York Times

TheUpshot

THE NEW HEALTH CARE

Why New Blood Pressure Guidelines Could Lead to Harm

Fear is typically not effective in getting people to adopt healthier habits. A more likely outcome is overtreatment.

By Aaron E. Carroll

Dec. 18, 2017

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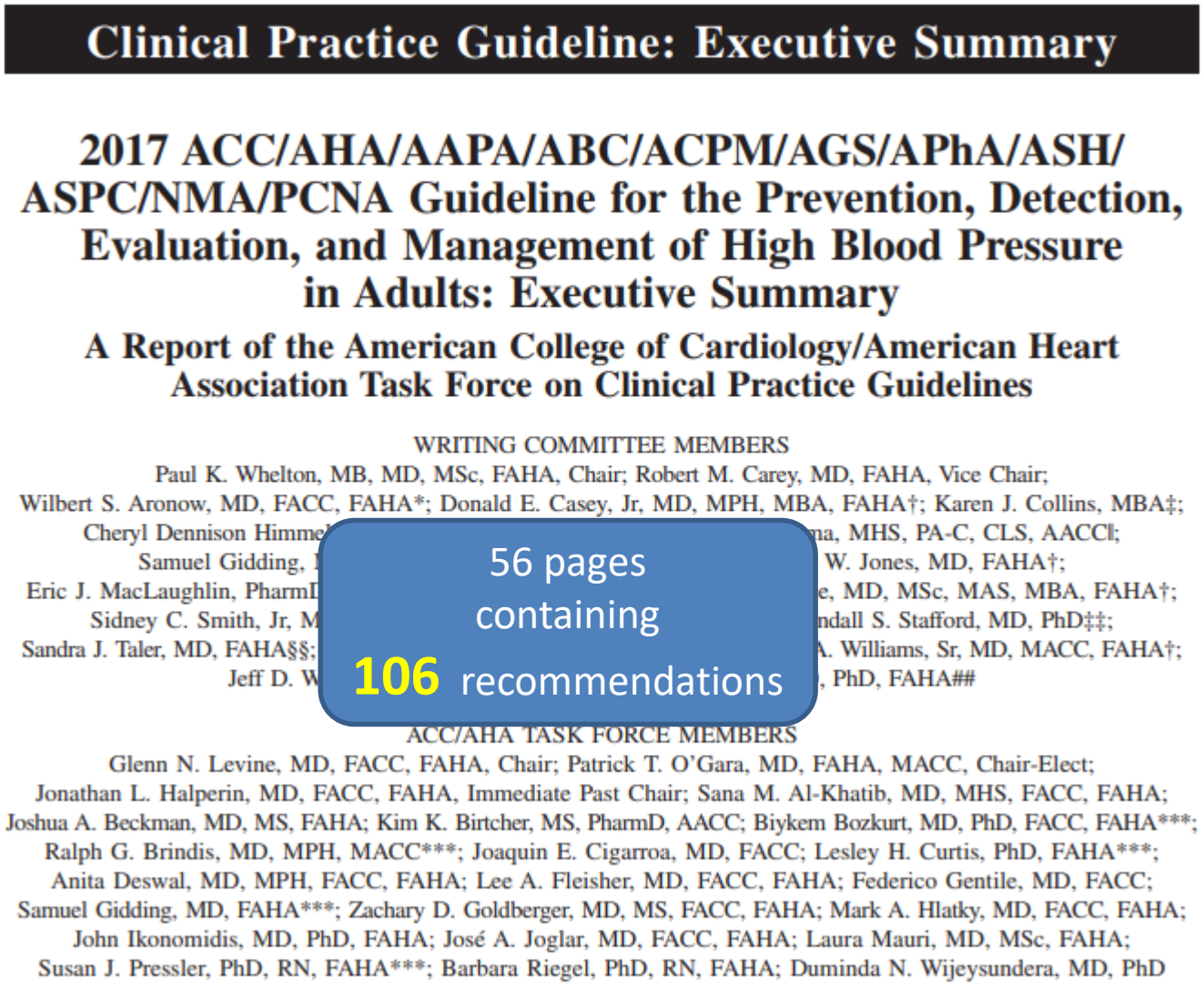
The potential upside from this change is that because of "awareness," more people might make lifestyle changes that lead to lower cardiovascular risk in the future. The potential downside is that more people may receive a diagnosis of high blood pressure, be overtreated with medication, and endure side effects or adverse outcomes. It's not irrational to fear that these new guidelines might lead to more of the latter than the former.

What's in a guideline?



Clinical Practice Guideline: Executive Summary

2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: Executive Summary

A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines

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56 pages containing **106** recommendations

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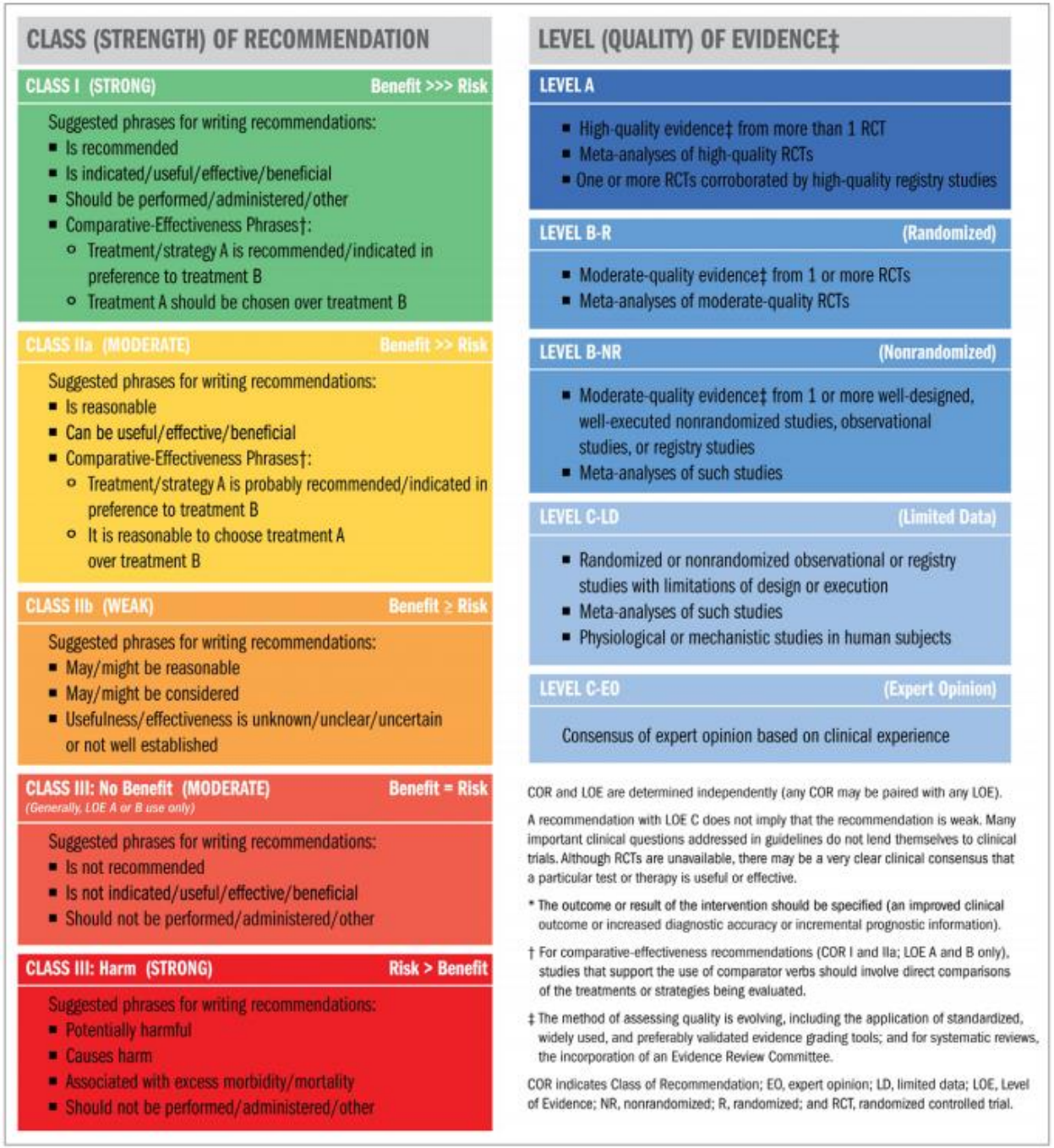


CLASS (STRENGTH) OF RECOMMENDATION

CLASS I (STRONG) — Benefit >>> Risk

Suggested phrases for writing recommendations:
- Is recommended
- Is indicated/useful/effective/beneficial
- Should be performed/administered/other
- Comparative-Effectiveness Phrases†:
  - Treatment/strategy A is recommended/indicated in preference to treatment B
  - Treatment A should be chosen over treatment B

CLASS IIa (MODERATE) — Benefit >> Risk

Suggested phrases for writing recommendations:
- Is reasonable
- Can be useful/effective/beneficial
- Comparative-Effectiveness Phrases†:
  - Treatment/strategy A is probably recommended/indicated in preference to treatment B
  - It is reasonable to choose treatment A over treatment B

CLASS IIb (WEAK) — Benefit ≥ Risk

Suggested phrases for writing recommendations:
- May/might be reasonable
- May/might be considered
- Usefulness/effectiveness is unknown/unclear/uncertain or not well established

CLASS III: No Benefit (MODERATE) — Benefit = Risk
(Generally, LOE A or B use only)

Suggested phrases for writing recommendations:
- Is not recommended
- Is not indicated/useful/effective/beneficial
- Should not be performed/administered/other

CLASS III: Harm (STRONG) — Risk > Benefit

Suggested phrases for writing recommendations:
- Potentially harmful
- Causes harm
- Associated with excess morbidity/mortality
- Should not be performed/administered/other

LEVEL (QUALITY) OF EVIDENCE‡

LEVEL A
- High-quality evidence‡ from more than 1 RCT
- Meta-analyses of high-quality RCTs
- One or more RCTs corroborated by high-quality registry studies

LEVEL B-R (Randomized)
- Moderate-quality evidence‡ from 1 or more RCTs
- Meta-analyses of moderate-quality RCTs

LEVEL B-NR (Nonrandomized)
- Moderate-quality evidence‡ from 1 or more well-designed, well-executed nonrandomized studies, observational studies, or registry studies
- Meta-analyses of such studies

LEVEL C-LD (Limited Data)
- Randomized or nonrandomized observational or registry studies with limitations of design or execution
- Meta-analyses of such studies
- Physiological or mechanistic studies in human subjects

LEVEL C-EO (Expert Opinion)

Consensus of expert opinion based on clinical experience

COR and LOE are determined independently (any COR may be paired with any LOE).

A recommendation with LOE C does not imply that the recommendation is weak. Many important clinical questions addressed in guidelines do not lend themselves to clinical trials. Although RCTs are unavailable, there may be a very clear clinical consensus that a particular test or therapy is useful or effective.

* The outcome or result of the intervention should be specified (an improved clinical outcome or increased diagnostic accuracy or incremental prognostic information).

† For comparative-effectiveness recommendations (COR I and IIa; LOE A and B only), studies that support the use of comparator verbs should involve direct comparisons of the treatments or strategies being evaluated.

‡ The method of assessing quality is evolving, including the application of standardized, widely used, and preferably validated evidence grading tools; and for systematic reviews, the incorporation of an Evidence Review Committee.

COR indicates Class of Recommendation; EO, expert opinion; LD, limited data; LOE, Level of Evidence; NR, nonrandomized; R, randomized; and RCT, randomized controlled trial.

Whelton et al., Hypertension 2018

8.1.6. Choice of Initial Medication

Recommendation for Choice of Initial Medication

References that support the recommendation are summarized in Online Data Supplement 27 and Systematic Review Report.

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]

SR indicates systematic review.

Table 18. Oral Antihypertensive Drugs

Class	Drug	Usual Dose, Range (mg/d)*	Daily Frequency	Comments
Primary agents				
Thiazide or thiazide-type diuretics (4)	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	2.5–10	1	
ACE inhibitors (10)	Benazepril	10–40	1 or 2	• Do not use in combination with ARBs or direct renin inhibitor. • There is an increased risk of hyperkalemia, especially in patients with CKD or in those on K^+ supplements or K^+-sparing drugs. • There is a risk of acute renal failure in patients with severe bilateral renal artery stenosis. • Do not use if patient has history of angioedema with ACE inhibitors. • Avoid in pregnancy.
	Captopril	12.5–150	2 or 3	
	Enalapril	5–40	1 or 2	
	Fosinopril	10–40	1	
	Lisinopril	10–40	1	
	Moexipril	7.5–30	1 or 2	
	Perindopril	4–16	1	
	Quinapril	10–80	1 or 2	
	Ramipril	2.5–10	1 or 2	
	Trandolapril	1–4	1	
ARBs (8)	Azilsartan	40–80	1	• Do not use in combination with ACE inh… direct renin inhibitor. • There is an increased risk of hyperk… in those on K^+ supplements or K^+-sp… • There is a risk of acute renal failure in patie… severe bilateral renal artery stenosis. • Do not use if patient has history of angioedem… with ARBs. Patients with a history of angioedema with an ACE inhibitor can receive an ARB beginning 6 weeks after ACE inhibitor is discontinued. • Avoid in pregnancy.
	Candesartan	8–32	1	
	Eprosartan	600–800	1 or 2	
	Irbesartan	150–300	1	
	Losartan	50–100	1 or 2	
	Olmesartan	20–40	1	
	Telmisartan	20–80	1	
	Valsartan	80–320	1	
CCB—dihydropyridines (5)	Amlodipine	2.5–10	1	• Avoid use in patients with HFrEF; … felodipine may be used if required. • They are associated with dose-rel… which is more common in women.
	Felodipine	5–10	1	
	Isradipine	5–10	2	
	Nicardipine SR	5–20	1	
	Nifedipine LA	60–120	1	
	Nisoldipine	30–90	1	
CCB—nondihydropyridines (2)	Diltiazem SR	180–360	2	• Avoid routine use with beta block… increased risk of bradycardia and h… • Do not use in patients with HFrEF. • There are drug interactions with diltiazem and verapamil (*CYP3A4* major substrate and moderate inhibitor).
	Diltiazem ER	120–480	1	
	Verapamil IR	40-80	3	
	Verapamil SR	120–480	1 or 2	
	Verapamil-delayed onset ER (various forms)	100–480	1 (in the evening)	

Only **29** different drugs in **5** different classes to choose from!

Distinguished from **28** drugs in **12** other classes that are classified as potential secondary agents **(including Beta Blockers)**

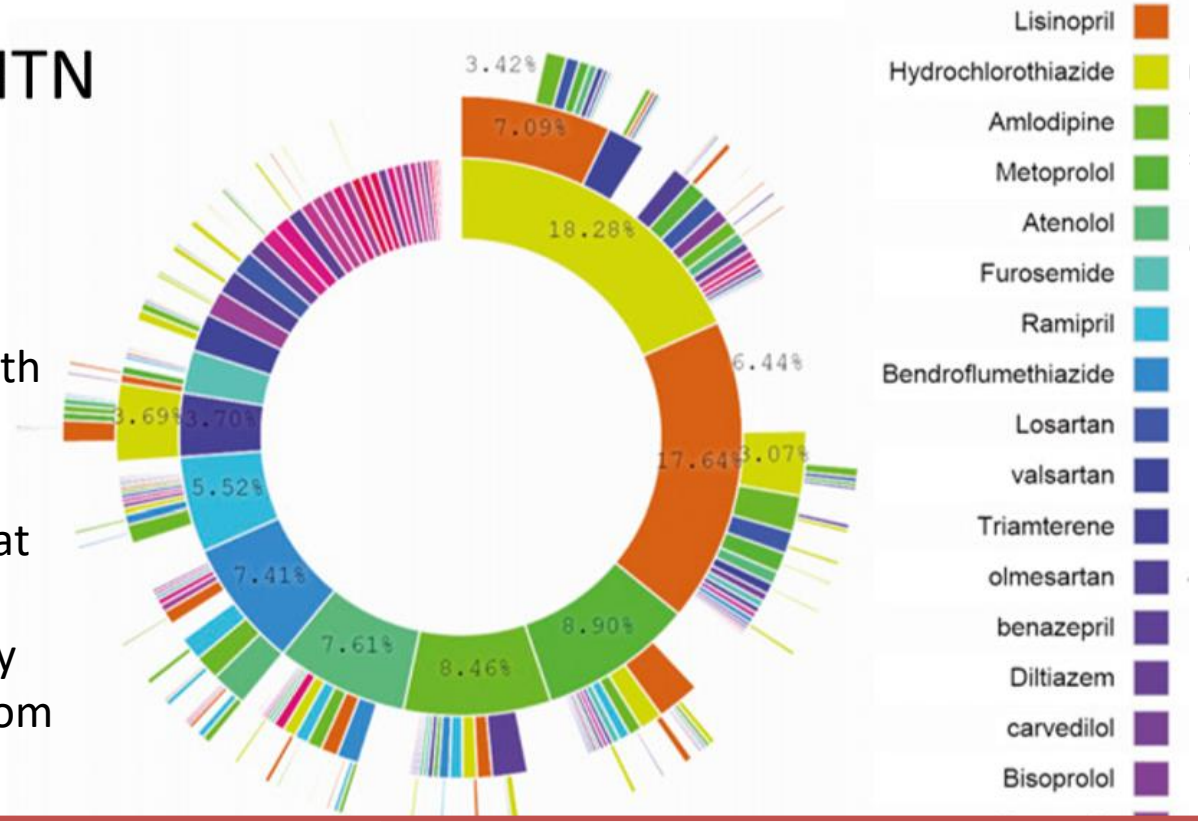
Whelton et al., Hypertension 2018

How are patients with hypertension *ACTUALLY* treated in the real world?

PNAS
COLLOQUIUM PAPER

Characterizing treatment pathways at scale using the OHDSI network

George Hripcsak[a,b,c,1], Patrick B. Ryan[c,d], Jon D. Duke[c,e], Nigam H. Shah[c,f], Rae Woong Park[c,g], Vojtech Huser[c,h],



- 1,182,792 patients with hypertension with at least 1 year of history before first drug and at least 3 years of uninterrupted therapy
- Results aggregated from 11 data sources in 4 countries

That is, for almost one quarter of hypertension patients, the response to the question, "In an underlying population of 250 million, based on my 3-y treatment pathway, what patients are like me?" would be "No one."

New capability in ATLAS: Cohort pathway!

Pathways Analysis for [LEGEND HTN] Hypertension treatment sequence

Legend

Target Cohort

[LEGEND HTN] First HTN drug use

- Target cohort count: 1,364,108
- Persons with pathways count: 1,320,017
- Persons with pathways portion: 96.8%

Event Cohorts

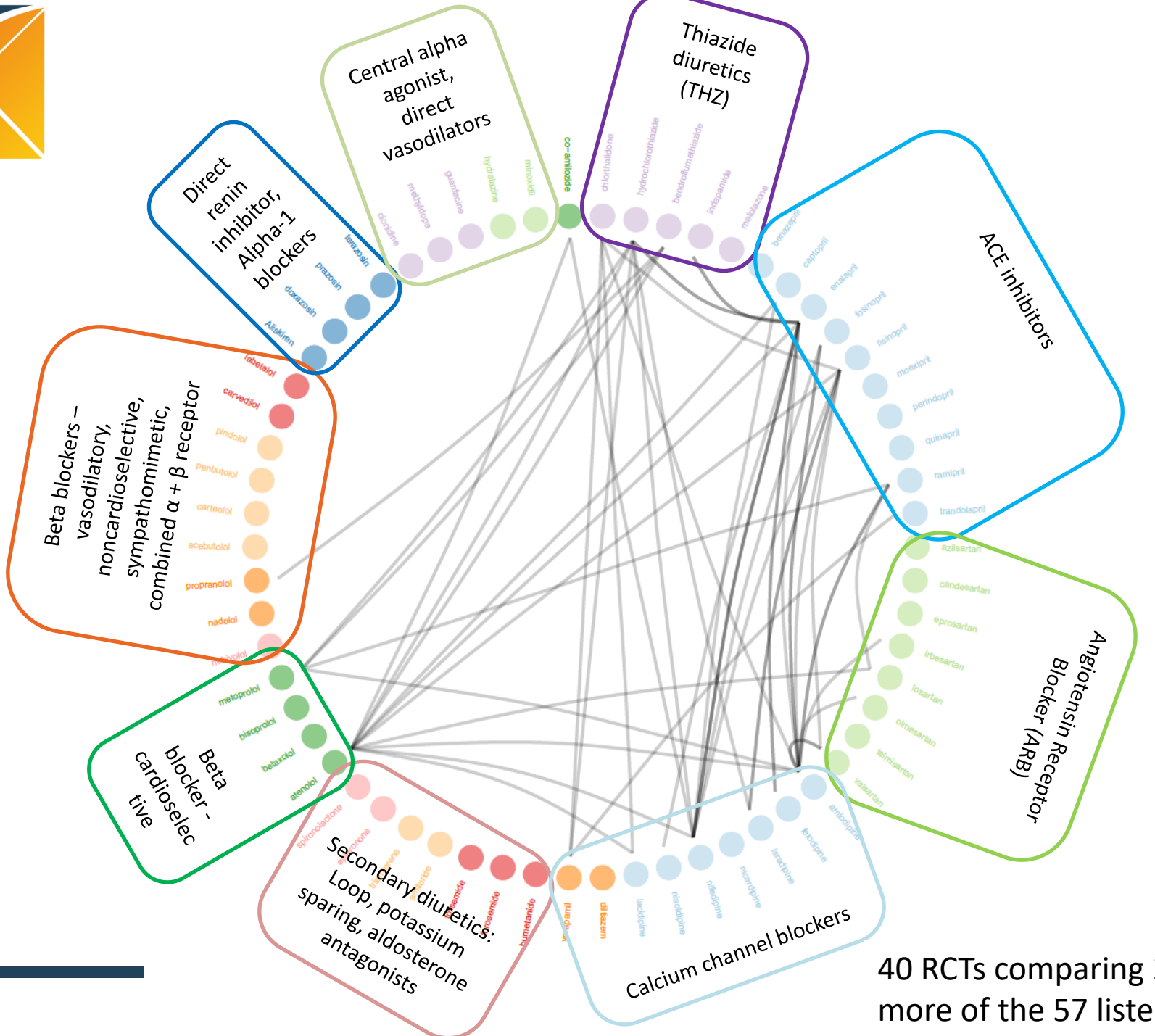
- First use of ACE inhibitor
- First use of Angiotensin Receptor Blocker (ARB)
- First use of Beta blocker - cardioselective (cBB)
- First use of Calcium Channel Blocker - dihydropyridine (ndCCB)
- First use of Calcium Channel Blocker - nodihydropyridine (ndCCB)
- First use of Thiazide diuretic

Sunburst plot

Check out the software demo by Chris Knoll during the Collaborator Showcase!

For initiation of antihypertensive drug therapy, how *SHOULD* patients be treated?

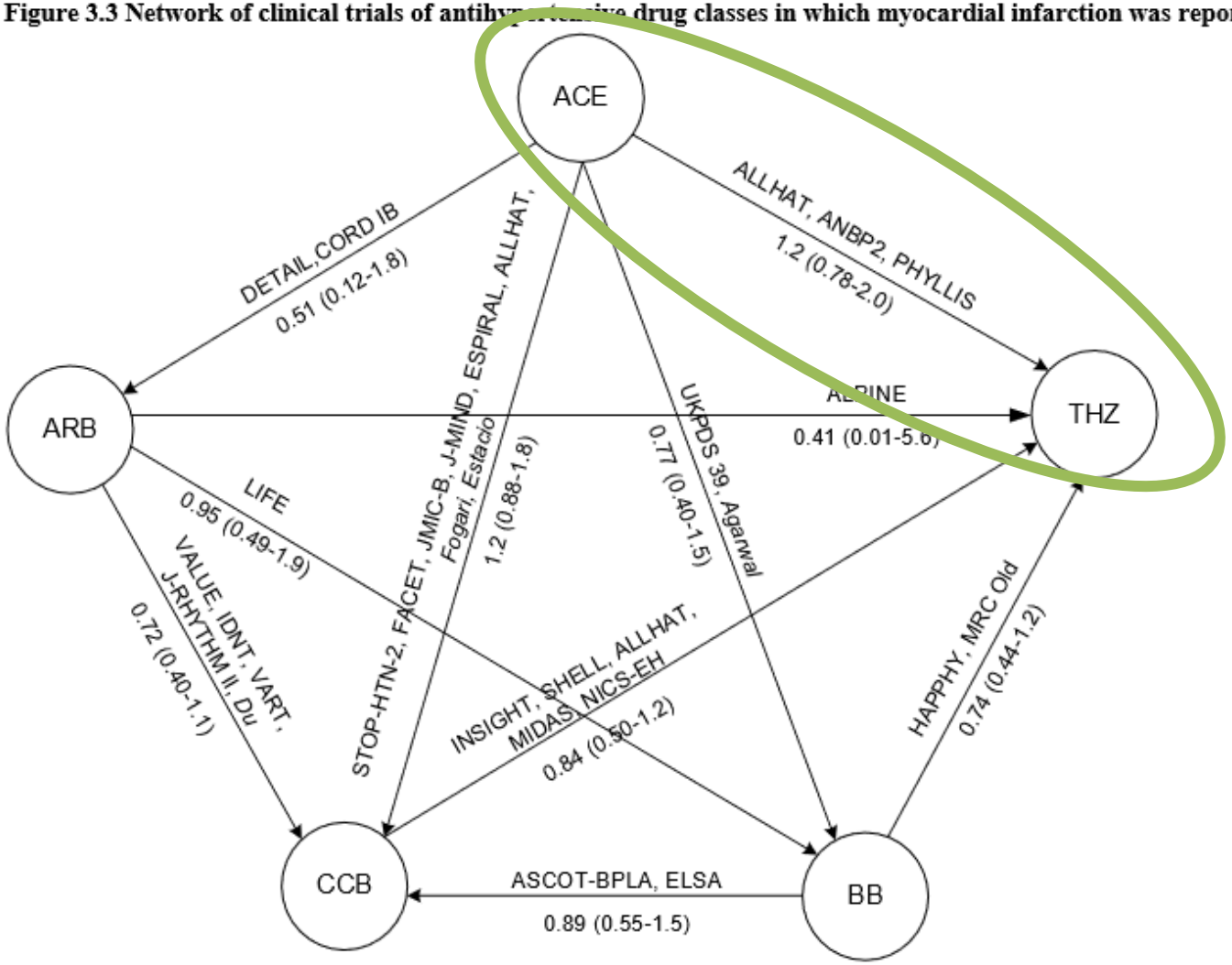
What evidence do we have about the comparative effects about alternative antihypertensive drugs?



40 RCTs comparing 2 or more of the 57 listed drugs

RCT evidence about comparative effectiveness for myocardial infarction

Figure 3.3 Network of clinical trials of antihypertensive drug classes in which myocardial infarction was reported (N=29). *



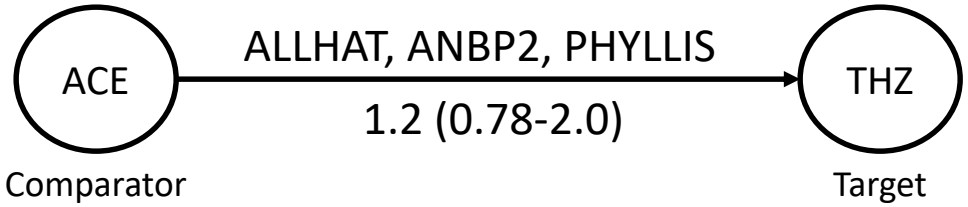
RCTs used in meta-analysis

C → T

Random-effects MA RR (95% CI)

Reboussin et al., Hypertension 2018

Dissecting the comparative evidence of ACE vs THZ on AMI



		Target			Comparator			Effect estimate		
Study	Population	Drug	Exposed	Events	Drug	Exposed	Events	RR	LB95CI	UB95CI
ALLHAT	Prior (treated) stage 1/2 hypertension with >=1 CVD risk factor	Chlorthalidone	15,255	1,362	Lisinopril	9,054	796	1.01	0.93	1.10
ANBP2	Australians aged 65-84 with SBP > 160mmHg (62% previously treated)	Hydrochlorothiazide	3,039	82	Enalapril	3,044	58	1.47	1.02	2.13
PHYLLIS	Italians age 45-70 with hypertension and hypercholesterolemia	Hydrochlorothiazide	127	3	Fosinopril	127	-	not reported		

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Practice of Epidemiology

Using Big Data to Emulate a Target Trial When a Randomized Trial Is Not Available

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* Correspondence to Dr. Miguel A. Hernán, Department of Epidemiology, 677 Huntington Avenue, Boston, MA 02115 (e-mail: miguel_hernan@post.harvard.edu).

Initially submitted December 9, 2014; accepted for publication September 8, 2015.

Ideally, questions about comparative effectiveness or safety would be answered using an appropriately designed and conducted randomized experiment. When we cannot conduct a randomized experiment, we analyze observational data. Causal inference from large observational databases (big data) can be viewed as an attempt to emulate a randomized experiment—the target experiment or target trial—that would answer the question of interest. When the goal is to guide decisions among several strategies, causal analyses of observational data need to be evaluated with respect to how well they emulate a particular target trial. We outline a framework for comparative effectiveness research using big data that makes the target trial explicit. This framework channels counterfactual theory for comparing the effects of sustained treatment strategies, organizes analytic approaches, provides a structured process for the criticism of observational studies, and helps avoid common methodologic pitfalls.

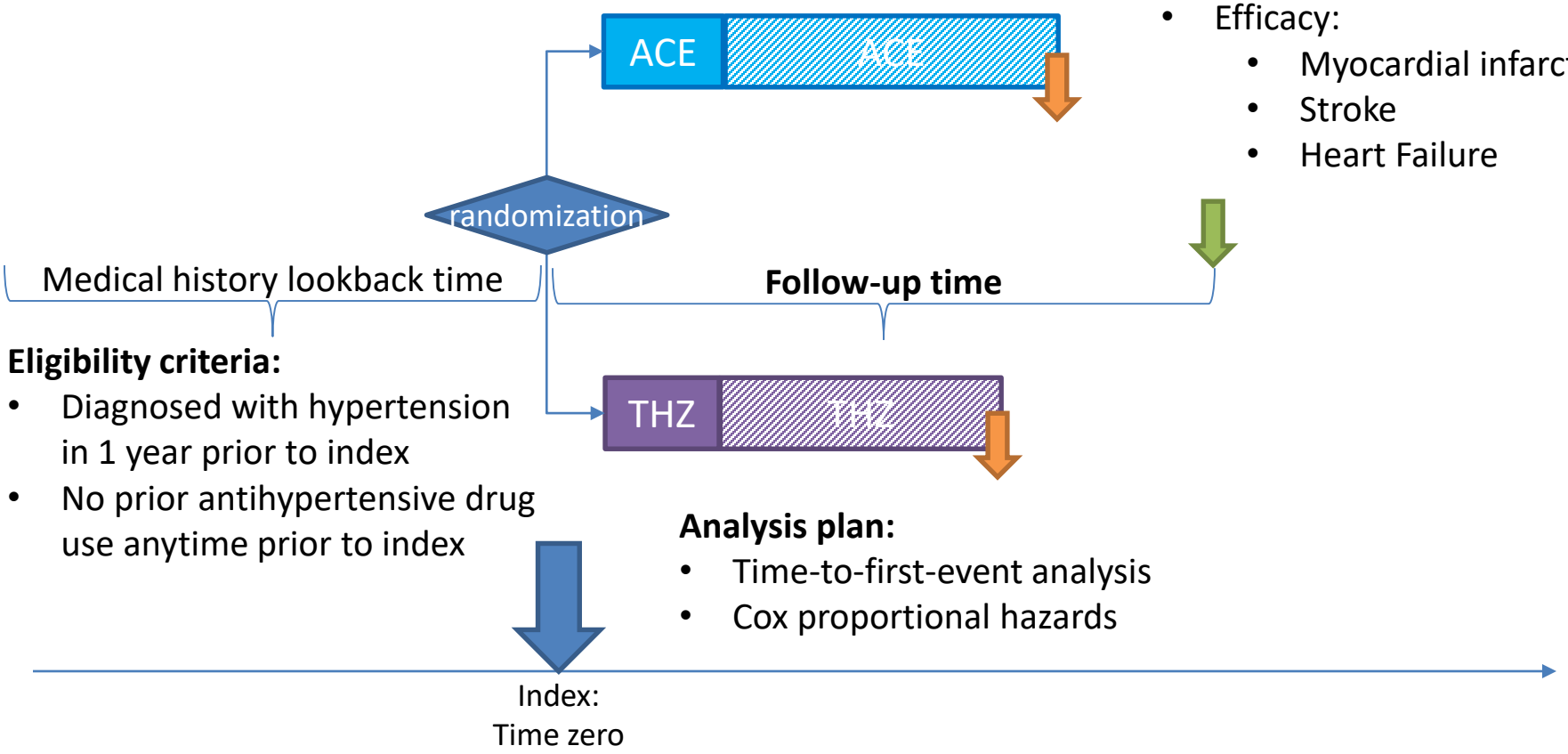
big data; causal inference; comparative effectiveness research; target trial

What would the 'target trial' look like to compare efficacy of two initial therapies?

Treatment strategies:
- Monotherapy with ACE
- Monotherapy with THZ

Causal contrasts of interest:
- Intent-to-treat effect
- On-treatment effect

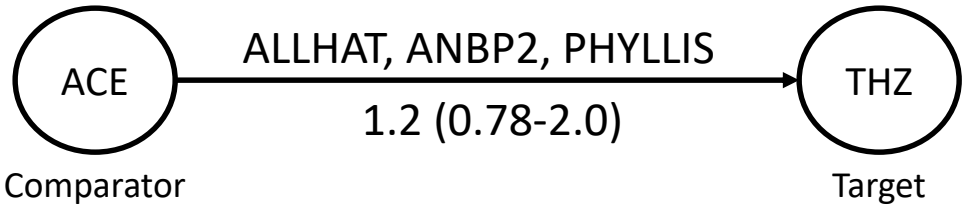
Outcomes:
- Efficacy:
  - Myocardial infarction
  - Stroke
  - Heart Failure



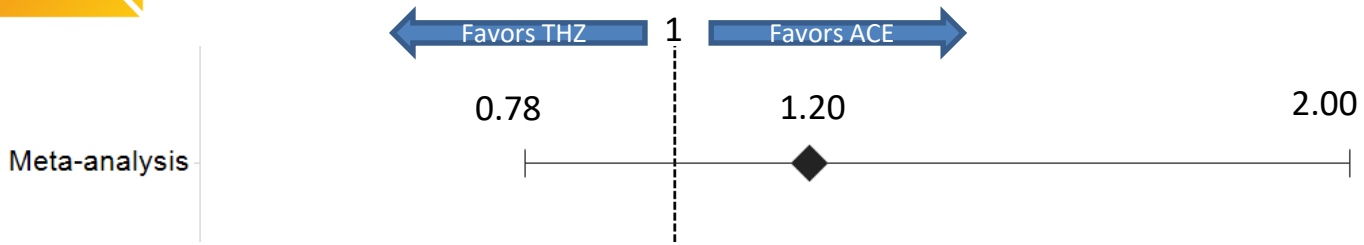
Eligibility criteria:
- Diagnosed with hypertension in 1 year prior to index
- No prior antihypertensive drug use anytime prior to index

Analysis plan:
- Time-to-first-event analysis
- Cox proportional hazards

What if we assumed the current evidence came from RCTs that were *close enough* to the 'target trial'?



Interpreting uncertainty

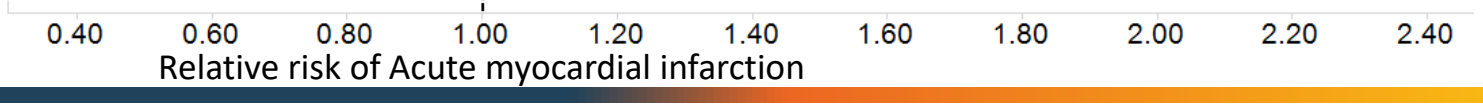


1) Stand up if you think this estimate shows no statistically significant difference.

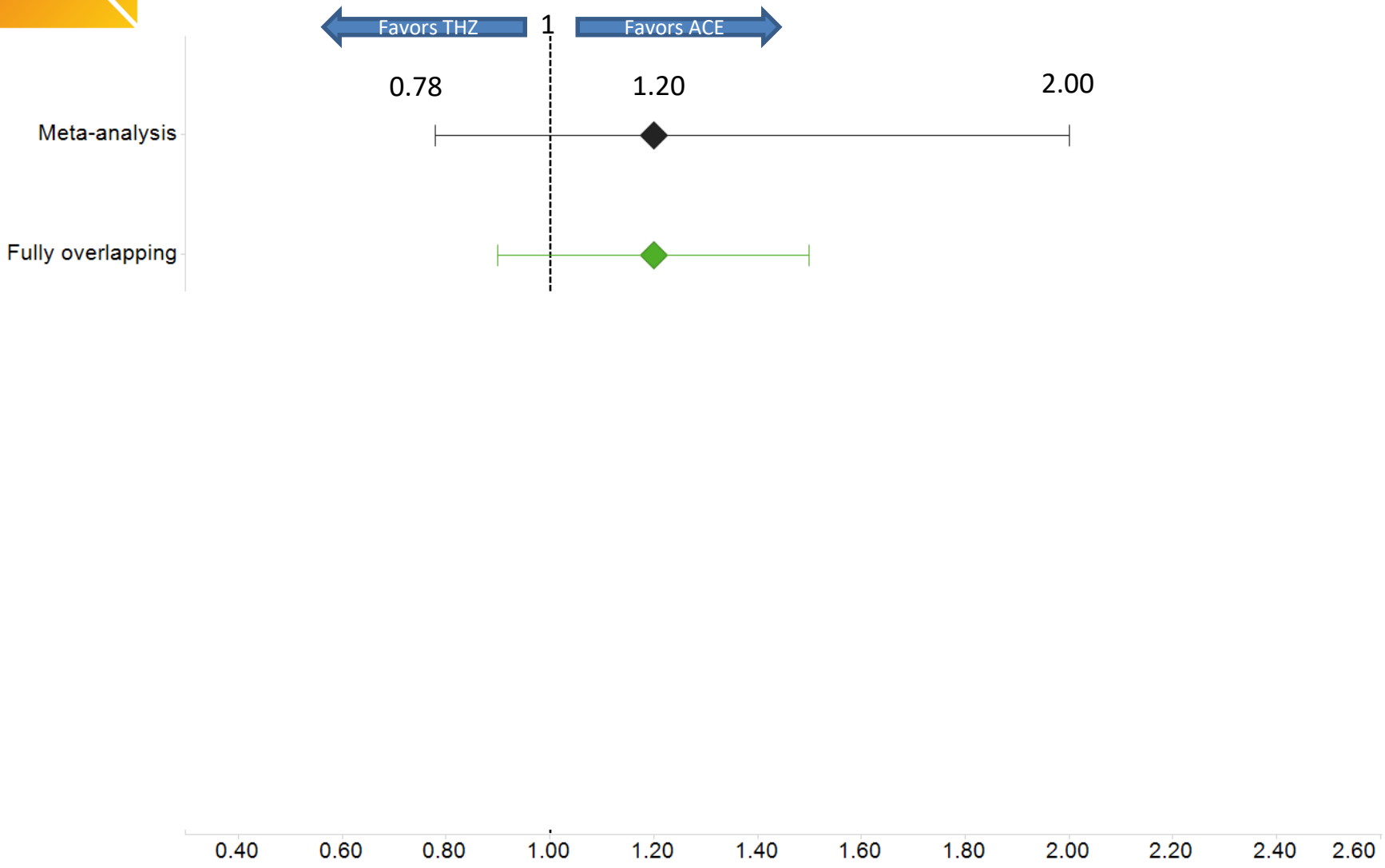
2) Sit down if you think this estimate suggests the expected average treatment effect is 20% increased risk for TZD.

3) Raise your left hand if you think this estimate suggest the risk associated with TZD vs. ACE could be as large as 100% increase (RR=2).

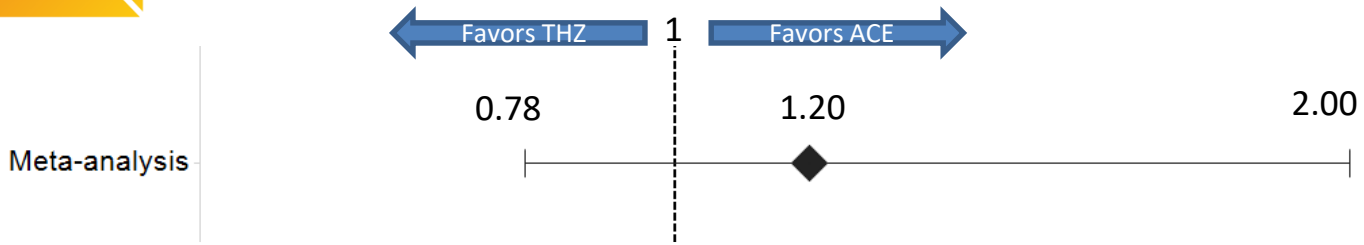
4) Raise your right hand if you think this estimate suggest the risk associated with TZD vs. ACE could be as large as 28% decrease (RR=0.78).



Evaluating concordance between estimates



Interpreting uncertainty



Would this estimate be concordant with RCT meta-analysis?
How would it be interpreted?

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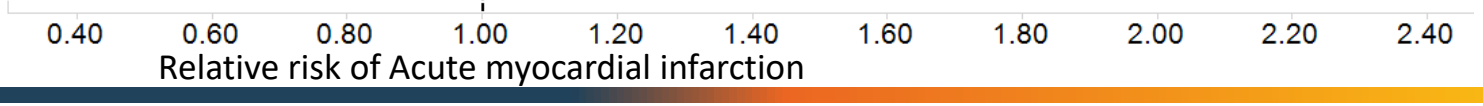
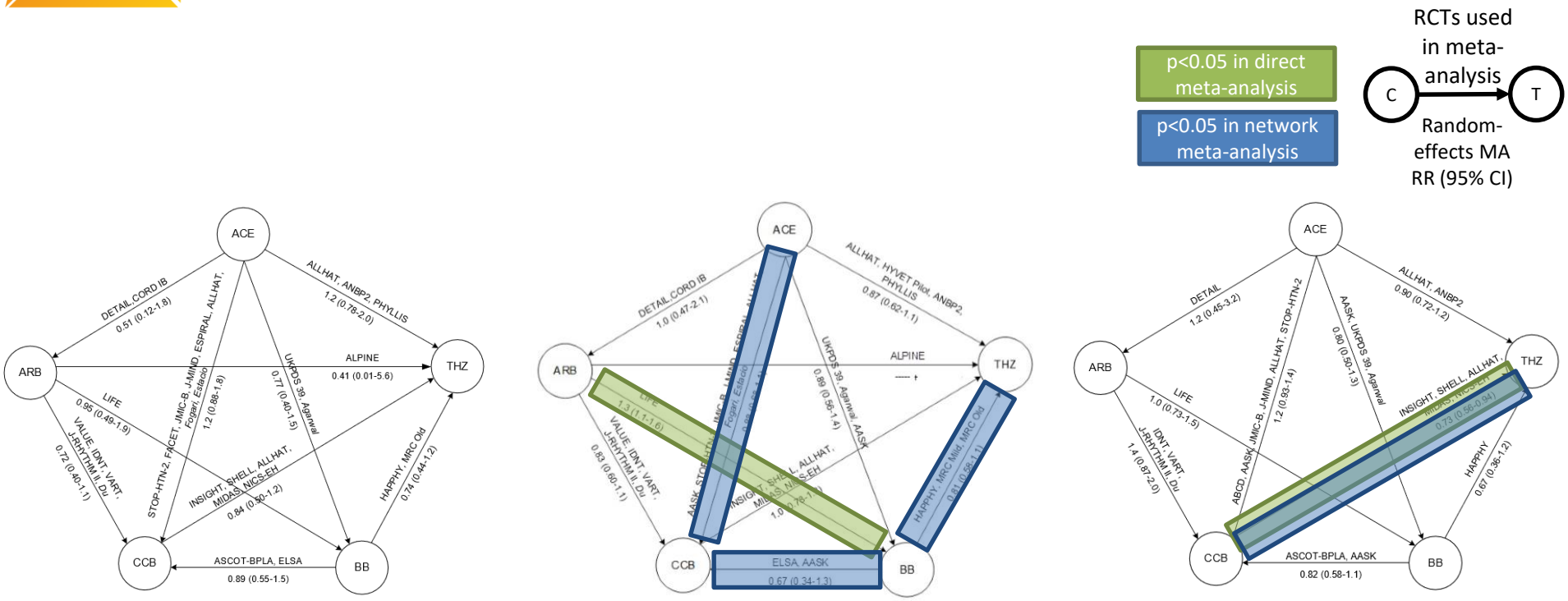


RCT evidence about comparative effectiveness for cardiovascular outcomes



Myocardial infarction

- 8/10 DMA comparisons cannot rule out possibility of 2x risk

Stroke

- 1/10 DMA comparisons cannot rule out possibility of 2x risk

Heart failure

- 4/10 DMA comparisons cannot rule out possibility of 2x risk

Reboussin et al., Hypertension 2018

8.1.6.1. Choice of Initial Monotherapy Versus Initial Combination Drug Therapy

Recommendations for Choice of Initial Monotherapy Versus Initial Combination Drug Therapy*

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	

*Fixed-dose combina

Data Supplement D.

Synopsis

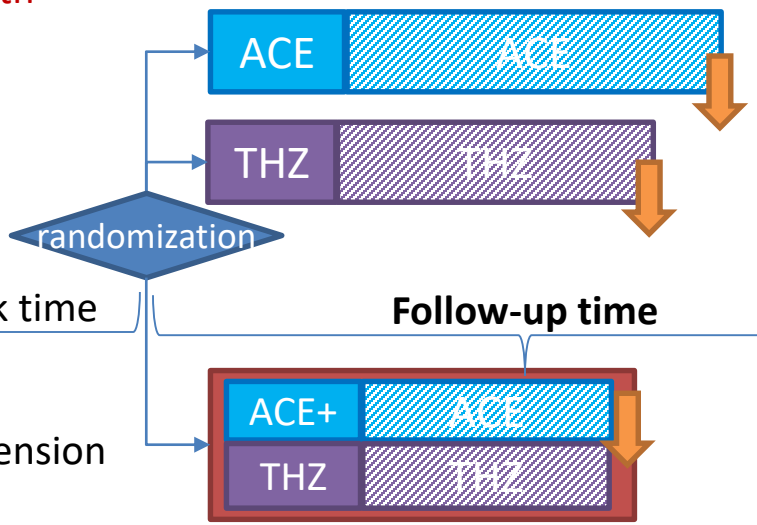
Systematic review of the evidence comparing the initiation of antihypertensive treatment with monotherapy and sequential (stepped-care) titration of additional agents versus initiation of treatment with combination therapy (including fixed-dose combinations) did not identify any RCTs meeting the systematic review questions posed in the PICOTS format (P=population, I=intervention, C=comparator, O=outcome, T=timing, S=setting). However, in both ACCORD and SPRINT, 2-drug therapy was recommended for most participants in the intensive- but not standard-therapy groups.

Whelton et al., Hypertension 2018

What would the 'target trial' look like to compare mono vs combination therapy?

Treatment strategies:
- Monotherapy with ACE
- Monotherapy with THZ
- Combination therapy with ACE+THZ

Causal contrasts of interest:
- Intent-to-treat effect
- On-treatment effect



Outcomes:
- Efficacy:
  - Myocardial infarction
  - Stroke
  - Heart Failure
- Safety:
  - Known or potential adverse events, e.g.
  - Acute renal failure
  - Angioedema
  - Cough
  - Diarrhea
  - Fall
  - Gout
  - Headache
  - Hyperkalemia
  - Hyponatremia
  - Hypotension
  - Impotence
  - Syncope
  - Vertigo

Eligibility criteria:
- Diagnosed with hypertension in 1 year prior to index
- No prior antihypertensive drug use anytime prior to index

Analysis plan:
- Time-to-first-event analysis
- Cox proportional hazards
- Two pairwise comparisons:
  - ACE vs. ACE+THZ
  - THZ vs. ACE+THZ

Are drugs within the same class truly equivalent?

Table 18. Oral Antihypertensive Drugs

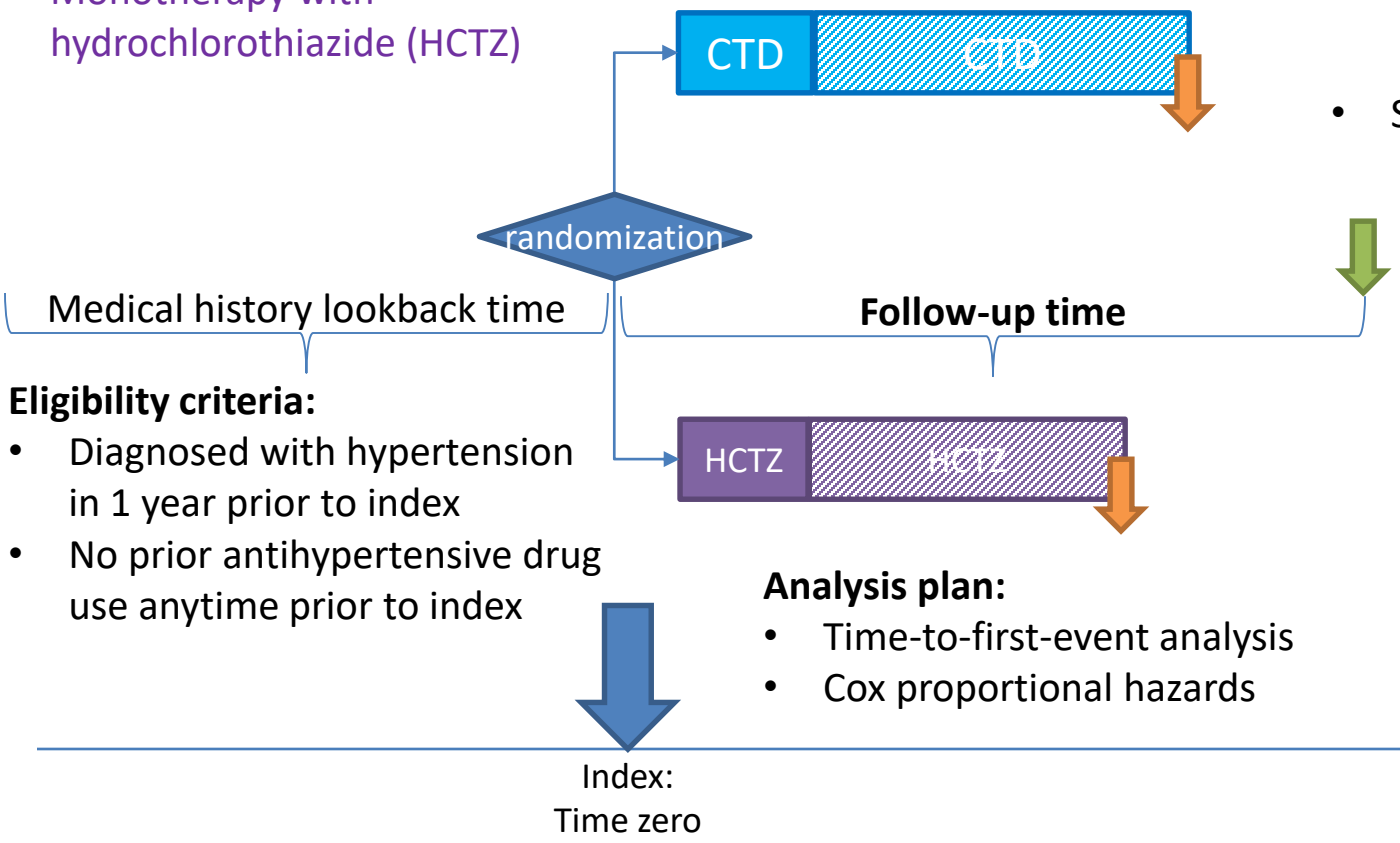
Class	Drug	Usual Dose, Range (mg/d)*	Daily Frequency	Comments
Primary agents				
Thiazide or thiazide-type diuretics	Chlorthalidone	12.5–25	1	• Chlorthalidone is preferred on the basis of prolonged half-life and proven trial reduction of CVD. • Monitor for hyponatremia and hypokalemia, uric acid and 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	2.5–10	1	
ACE inhibitors	Benazepril	10–40	1 or 2	• Do not use in combination with ARBs or direct renin inhibitor. • There is an increased risk of hyperkalemia, especially in patients with CKD or in those on K^+ supplements or K^+-sparing drugs. • There is a risk of acute renal failure in patients with severe bilateral renal artery stenosis. • Do not use if patient has history of angioedema with ACE inhibitors. • Avoid in pregnancy.
	Captopril	12.5–150	2 or 3	
	Enalapril	5–40	1 or 2	
	Fosinopril	10–40	1	
	Lisinopril	10–40	1	
	Moexipril	7.5–30	1 or 2	
	Perindopril	4–16	1	
	Quinapril	10–80	1 or 2	
	Ramipril	2.5–10	1 or 2	
	Trandolapril	1–4	1	
ARBs	Azilsartan	40–80	1	• Do not use in combination with ACE inhibitors or direct renin inhibitor. • There is an increased risk of hyperkalemia in CKD or in those on K^+ supplements or K^+-sparing drugs. • There is a risk of acute renal failure in patients with severe bilateral renal artery stenosis. • Do not use if patient has history of angioedema with ARBs. Patients with a history of angioedema with an ACE inhibitor can receive an ARB beginning 6 weeks after ACE inhibitor is discontinued. • Avoid in pregnancy.
	Candesartan	8–32	1	
	Eprosartan	600–800	1 or 2	
	Irbesartan	150–300	1	
	Losartan	50–100	1 or 2	
	Olmesartan	20–40	1	
	Telmisartan	20–80	1	
	Valsartan	80–320	1	
CCB—dihydropyridines	Amlodipine	2.5–10	1	• Avoid use in patients with HFrEF; amlodipine or felodipine may be used if required. • They are associated with dose-related pedal edema, which is more common in women than men.
	Felodipine	5–10	1	
	Isradipine	5–10	2	
	Nicardipine SR	5–20	1	
	Nifedipine LA	60–120	1	
	Nisoldipine	30–90	1	
CCB—nondihydropyridines	Diltiazem SR	180–360	2	• Avoid routine use with beta blockers because of increased risk of bradycardia and heart block. • Do not use in patients with HFrEF. • There are drug interactions with diltiazem and verapamil (*CYP3A4* major substrate and moderate inhibitor).
	Diltiazem ER	120–480	1	
	Verapamil IR	40-80	3	
	Verapamil SR	120–480	1 or 2	
	Verapamil-delayed onset ER (various forms)	100–480	1 (in the evening)	

Whelton et al., Hypertension 2018

What would the 'target trial' look like to compare efficacy of two initial therapies?

Treatment strategies:
- Monotherapy with chlorthalidone (CTD)
- Monotherapy with hydrochlorothiazide (HCTZ)

Causal contrasts of interest:
- Intent-to-treat effect
- On-treatment effect



Eligibility criteria:
- Diagnosed with hypertension in 1 year prior to index
- No prior antihypertensive drug use anytime prior to index

Analysis plan:
- Time-to-first-event analysis
- Cox proportional hazards

Outcomes:
- Efficacy:
  - Myocardial infarction
  - Stroke
  - Heart Failure
- Safety:
  - Known or potential adverse events, e.g.
  - Acute renal failure
  - Angioedema
  - Cough
  - Diarrhea
  - Fall
  - Gout
  - Headache
  - Hyperkalemia
  - Hyponatremia
  - Hypotension
  - Impotence
  - Syncope
  - Vertigo

Diuretic Comparison Project (DCP)

U.S. Department of Veterans Affairs

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VA CSP Study No. 597: Diuretic Comparison Project

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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.

In this study, we will compare the effectiveness of two common diuretics, hydrochlorothiazide and chlorthalidone, on reducing the risk of cardiovascular events among Veterans over the age of 65 years who are currently taking hydrochlorothiazide to treat their hypertension. Both of these medications are FDA approved and have been used to treat high blood pressure for more than 50 years. Although hydrochlorothiazide is more commonly used, some evidence suggests that chlorthalidone may be more effective at preventing heart attacks and strokes. The DCP will be the first large-scale research study that uses the POC study design for a direct comparison between hydrochlorothiazide and chlorthalidone. By leveraging the VA's electronic medical record (EMR) system, DCP plans to enroll 13,500 veterans and record heart attacks, strokes, and other cardiovascular events while each VA healthcare provider continues to treat their patients as usual. No additional study visits are needed.

What is the Diuretic Comparison Project study design?

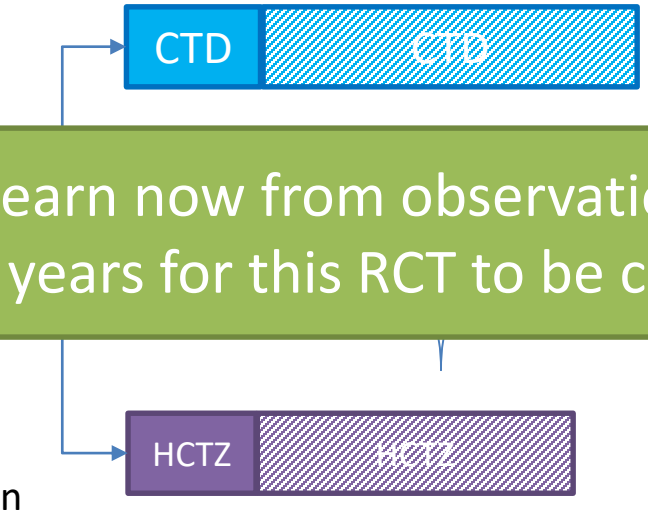
Treatment strategies:
- Monotherapy with chlorthalidone (CTD)
- Monotherapy with hydrochlorothiazide (HCTZ)

Causal contrasts of interest:
- Intent-to-treat effect

Outcomes:
- Myocardial infarction
- Stroke
- Hospitalization for Heart Failure
- Coronary

What can we learn now from observational data while we wait 4 years for this RCT to be completed?

Eligibility criteria:
- Age >= 65
- Diagnosed with hypertension
- Currently treated with hydrochlorothiazide
- Potassium/sodium imbalance
- Death expected in 6 months



Analysis plan:
- Time-to-first-event analysis
- Cox proportional hazards

Estimated enrollment:
13,500
Study start:
June2016
Estimated completion:
Oct2022

Index:
Time zero

https://clinicaltrials.gov/ct2/show/NCT02185417

Summarizing the opportunity

- Many different opportunities to generate observational evidence that could promote better health decisions and better care
  - Confirm LOE-A evidence in ‘real world’
  - Improve the level of evidence for ‘C-EO’ recommendations
  - Enable greater specificity in guidelines, based on both comparative effectiveness and safety
  - Reduce uncertainty and fill gaps in our existing knowledge
- But first, we need to prove that observational evidence can be considered reliable enough to be used to inform decision-making
  - Doing so requires fundamentally re-thinking how observational evidence is generated, evaluated, and disseminated