A Polypill Strategy for Prevention of Cardiovascular Disease: Can We Bridge the Gap?

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NIH Collaboratory Grand Rounds

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Disclosures/Conflicts of Interest

- Dr. Wang: consulting fees from Novartis (unrelated to today's topic)

- No COI

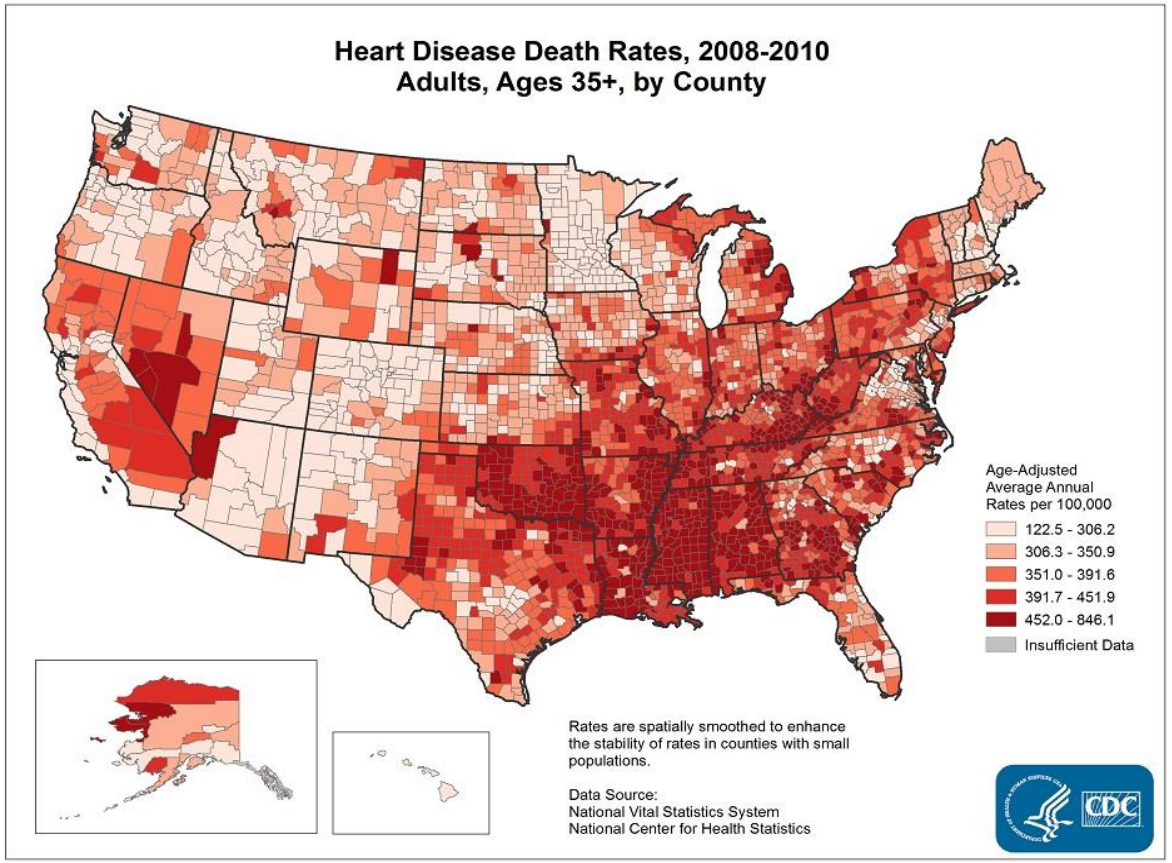
Agenda

- Highlight CVD disparities in U.S.
- Review broad approaches to prevention & the polypill concept
- Describe SCCS Polypill Trial
- Highlight key next-step considerations

U.S. cardiovascular health disparities

- ~75% reduction in CV mortality over past 60 years
- Gains <u>unequally</u> distributed

<u>Higher CV mortality in:</u>
Low SES populations
African-Americans
Rural areas
Certain regions



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Drivers of disparities

- Inadequate access to healthcare
- Economic barriers
- Lifestyle & cultural barriers
- Low adherence to medication

High prevalence & poor control of key risk factors (hypertension, hyperlipidemia, tobacco use)

Mensah et al. Circ Res, 2018

What is the best way to reduce burden of cardiovascular disease?

Precision Medicine

One size fits all

?

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Precision Medicine

One size fits all

?

What if the screening tests are invasive and/or inaccurate?

What if the best treatments are cheap and relatively safe?

VIEWPOINT

Comparison of 2 Treatment Models
Precision Medicine and Preventive Medicine

JAMA The Journal of the American Medical Association

Psaty et al., JAMA; 2018

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Hemophilia B


The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 DECEMBER 7, 2017 VOL. 377 NO. 23

Hemophilia B Gene Therapy with a High-Specific-Activity Factor IX Variant

"…10 patients with hemophilia who received gene therapy with a high specific activity factor IX variant demonstrated that gene transfer largely eliminated the need for prophylaxis, bleeding events, and factor use for a year."

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Hypertension

"Despite intense investigation for decades, no known procedure or biomarker makes it possible to select the subgroup patient for treatment, such as those with hypertension, whose cardiovascular event will be prevented."

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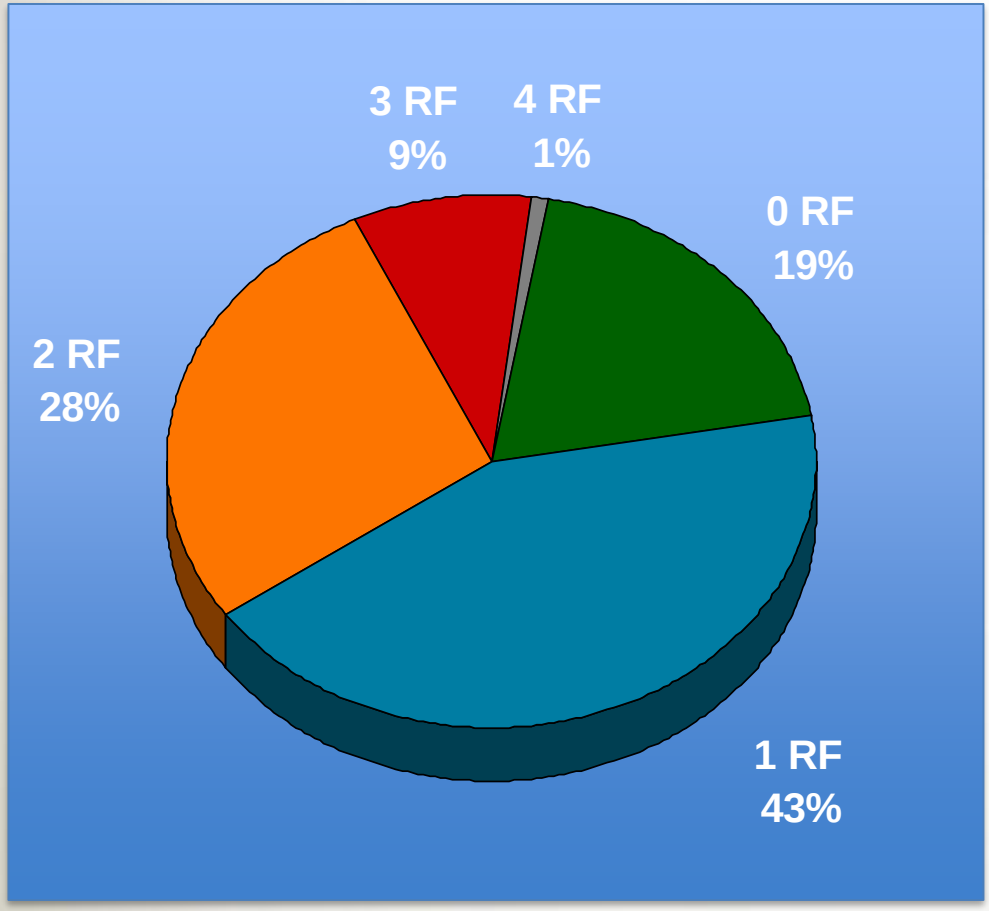
Psaty et al., JAMA; 2018

Most people who get heart disease are at low predicted risk: “prevention paradox”



- True, even with additional non-invasive testing
- Prediction models underestimate risk in low SES populations

Khot et al, JAMA 2003
Wang et al, NEJM 2006

Other barriers to primary prevention, especially in low-income populations

- Lifestyle modification
- Statin therapy
- Anti-hypertensive medications
- Anti-diabetic medications in some patients
- ASA in some patients

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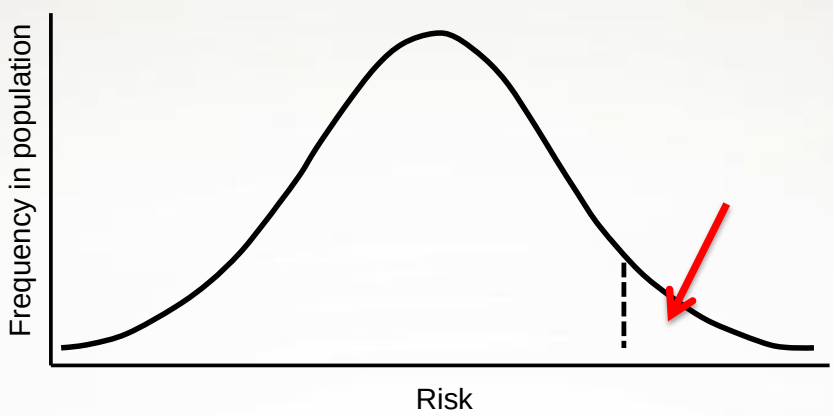
Multiple visits for testing and monitoring
< 50% stay on assigned CV meds for a year
< 50% of hypertensive pts are treated and controlled

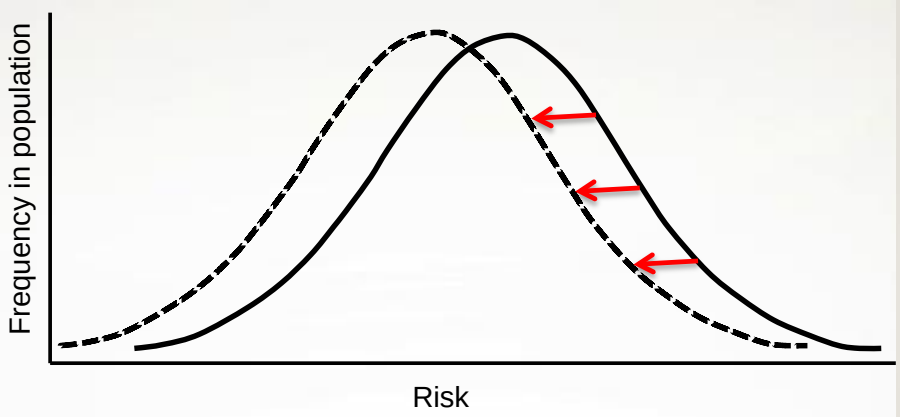
Approaches to CVD prevention

High-risk strategy



(+) Personalized, tailored approach
(+) Focus on subpopulation with highest predicted risk

Population strategy

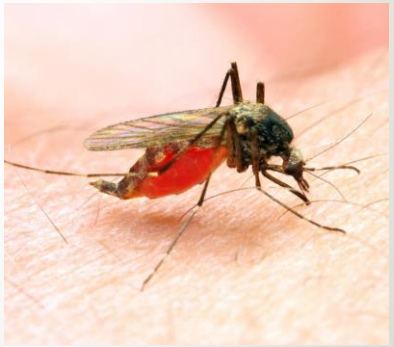


(+) Pragmatic, low-cost approach
(+) Focus on larger population

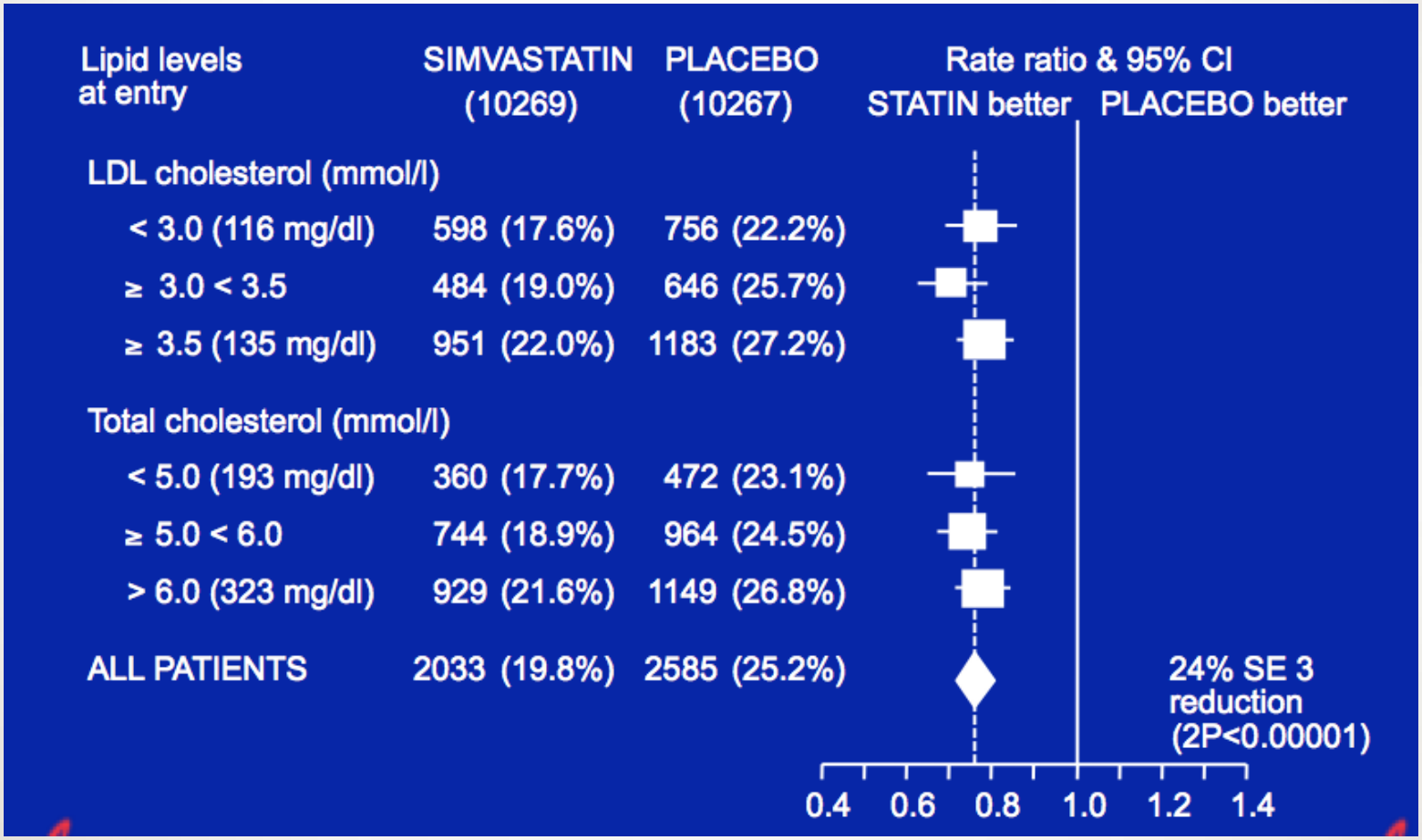
Rose, Int Journal Epi, 1985

The ‘polypill’ concept

- Polypill: once-daily, fixed-dose combination 4-5 medications
  - Fixed/low doses, no need to titrate
  - Low cost, generic only
- Goal
  - Simplify delivery of beneficial medications
  - Improve care & patient outcomes
- In cardiovascular prevention, historic focus:
  - Blood pressure control
  - Cholesterol improvement (i.e. statin)
  - Consideration of aspirin



Benefit of CV meds not clearly linked to baseline RF levels



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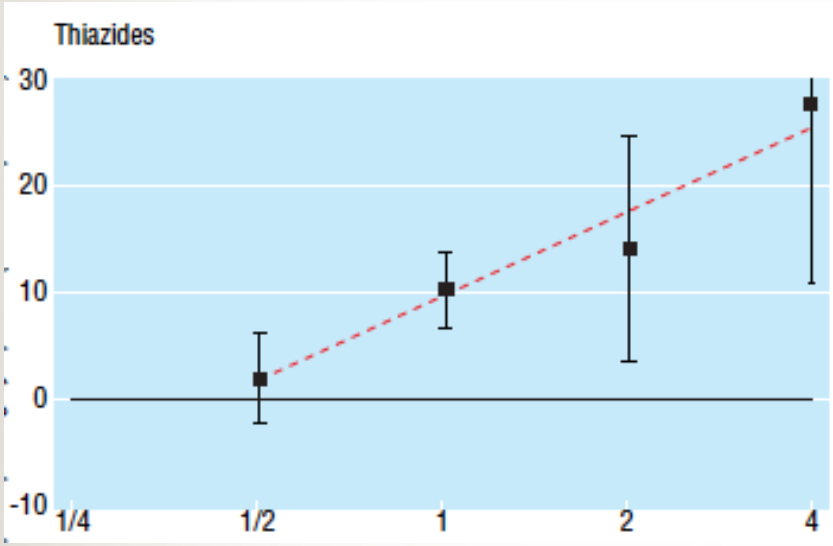
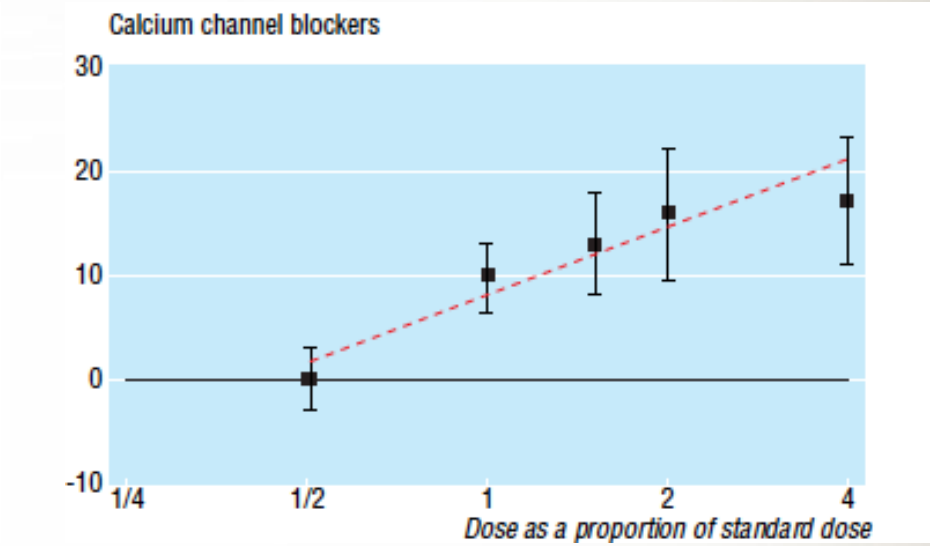
Heart Protection Study

Adverse effects of most BP therapies are dose-dependent





Wald et al, BMJ 2003

Combination therapy is endorsed in the latest hypertension guidelines

I	B-R	3. Adults with stage 2 hypertension should be evaluated by or referred to a primary care provider within 1 month of the initial diagnosis, have a combination of nonpharmacological and antihypertensive drug therapy (with 2 agents of different classes) initiated, and have a repeat BP evaluation in 1 month (1, 2).

Recommendations for Antihypertensive Medication Adherence Strategies
References that support recommendations are summarized in Online Data Supplements 59 and 60.

COR	LOE	RECOMMENDATIONS
I	B-R	1. In adults with hypertension, dosing of antihypertensive medication once daily rather than multiple times daily is beneficial to improve adherence (S12.1.1-1—S12.1.1-3).
IIa	B-NR	2. Use of combination pills rather than free individual components can be useful to improve adherence to antihypertensive therapy (S12.1.1-4—S12.1.1-7).

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Whelton et al, 2017

Prior trials of the polypill: the evidence gap

- No participating U.S. sites
- Very few individuals of African descent
- No deliberate focus on low SES groups
- No clear strategy for implementation
- Results of existing trials have not affected clinical practice in the U.S.

The Southern Community Cohort Polypill Trial

SCCS
Southern Community Cohort Study

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IEI International Epidemiology Institute

- Funded by National Cancer Institute, 2001
- Established to address root causes of cancer health disparities
- Prospective cohort of 85,000 adults in Southeastern U.S. – 2/3 African-American
- Opportunities to study cardiovascular disease

Source: www.southerncommunitystudy.org

Community Health Centers partnering with SCCS

Community Health Centers

- 1200+ Federally-Qualified Health Centers (FQHCs) in U.S. that serve:
  - 28 million patients annually
  - 1 in 6 residents in rural areas
- Provide important “safety net” in medically-underserved communities
- Individuals who receive care at FQHCs are poorly represented in clinical trials

SCCS Polypill Trial

- Primary hypothesis:
  - Use of a polypill will lead to better CV risk factor control compared with usual care in an at-risk U.S. primary prevention subpopulation

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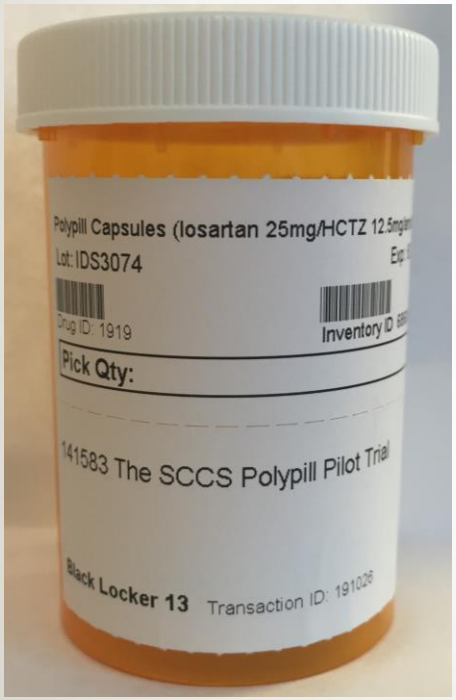

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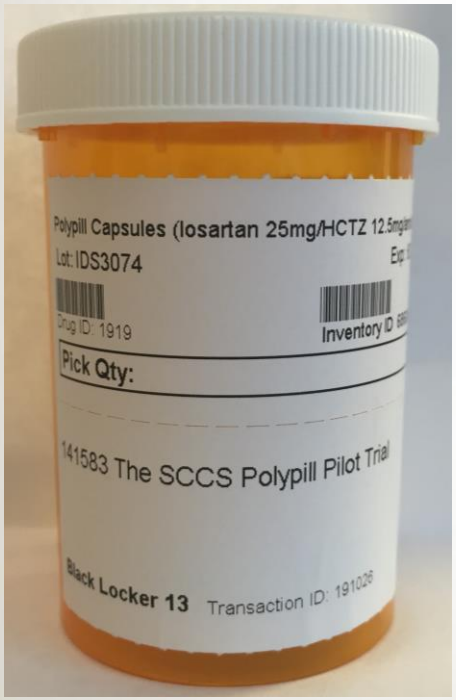

The Polypill

Losartan 25mg
HCTZ 12.5mg
Amlodipine 2.5mg
Atorvastatin 10mg

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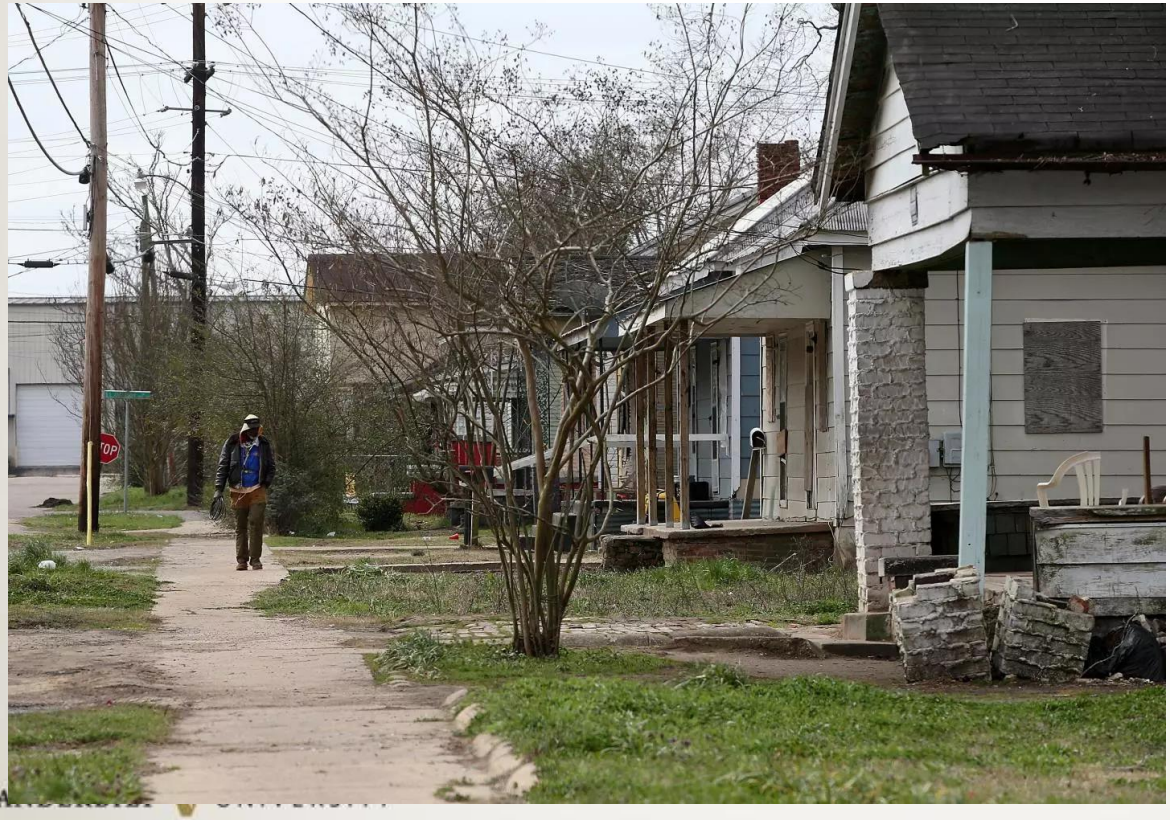
Photo: courtesy C. Reynolds

Franklin Primary Health Center (Mobile, Alabama)



Per-capita income in Mobile: $22,401

Alabama: 49th in life expectancy

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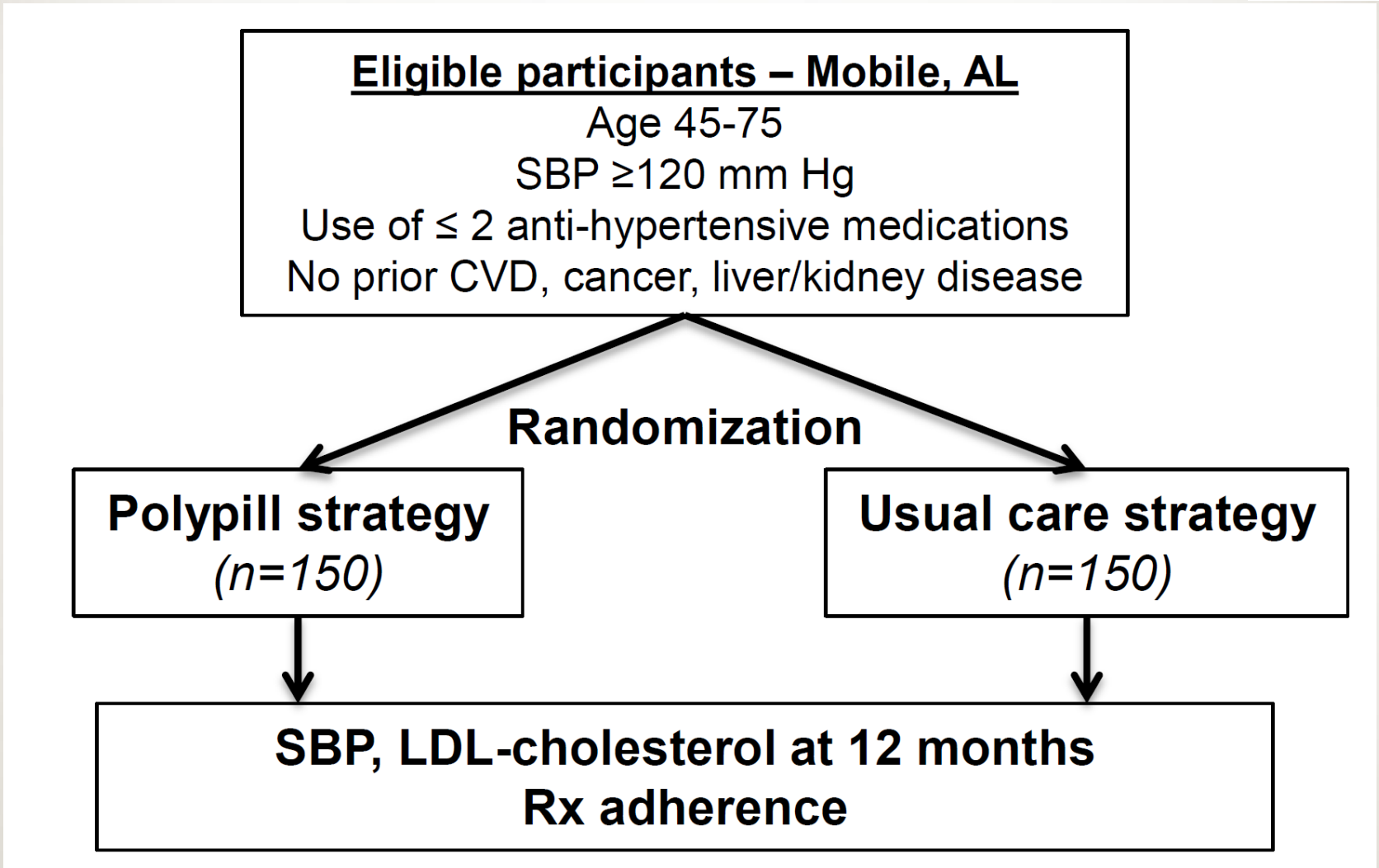
Polypill Study Schema



Process & operational considerations

Patients

- 3 free study visits
  - Baseline
  - 2-month
  - 12-month
- Data collected
  - Blood pressure
  - Labs (Lipids, BMP)

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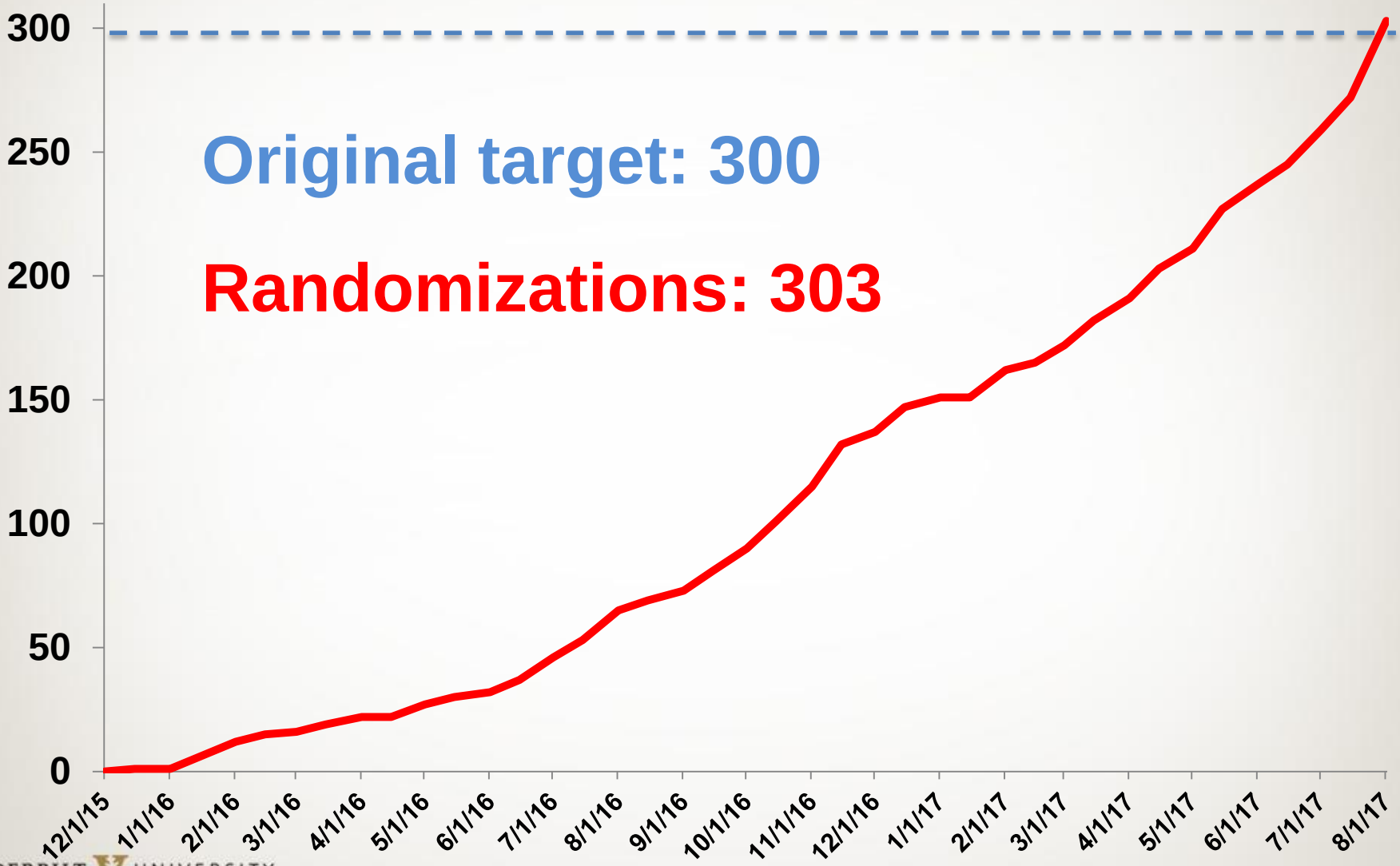
Clinicians/PCPs

- Notification from study team regarding:
  - Patient's enrollment
  - Study arm assignment
  - Any relevant lab findings
- Clear communication
- Consistent coordination
- Preservation of & respect for established doctor-patient relationships
  - *PCP* drives care decisions

Enrollment pace



SCCS Southern Community Cohort Study

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Key to enrollment: Community engagement

- Clinician-level initiatives
  - Educational sessions focused on local network of PCPs
- Patient-level initiatives
  - Local churches
  - Senior centers
  - Community fairs
  - Markets

Baseline Characteristics*

	Polypill (=148)	Usual Care (n=155)
Mean age (years)	56 ± 6	56 ± 6
Male sex	65 (44%)	56 (36%)
African-American	141 (95%)	151 (97%)
Body mass index, kg/m^2	31.3 ± 8.5	30.4 ±8.4
Mean systolic BP, mm Hg	140 ± 18	140 ± 17
Mean LDL cholesterol, mg/dL	114 ± 32	112 ± 37
Diabetes	17 (11%)	22 (14%)
Annual income <$15,000 $15,000 to <$25,000	107 (72%) 28 (19%)	120 (77%) 21 (14%)

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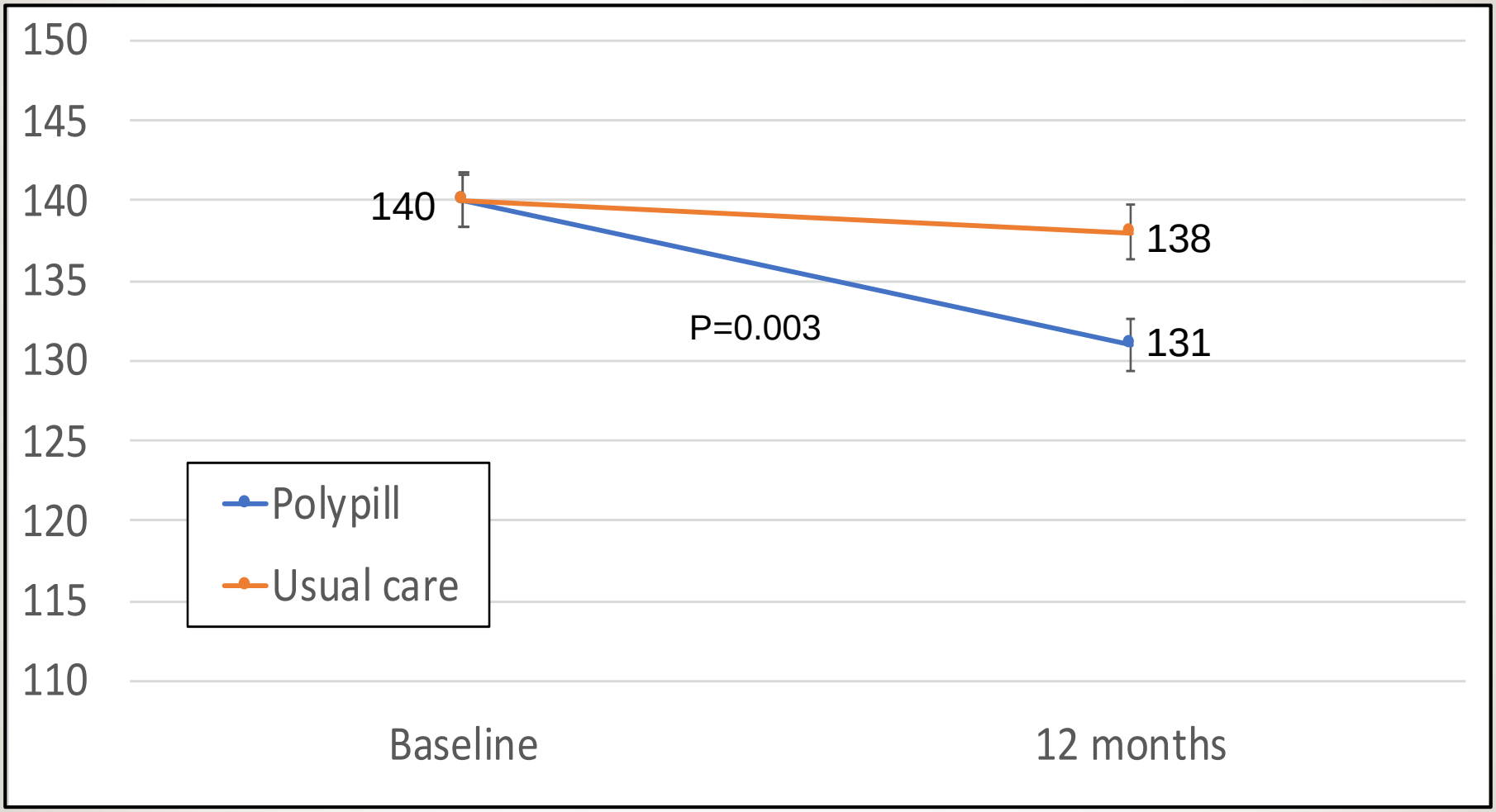
*no significant differences

Participant retention

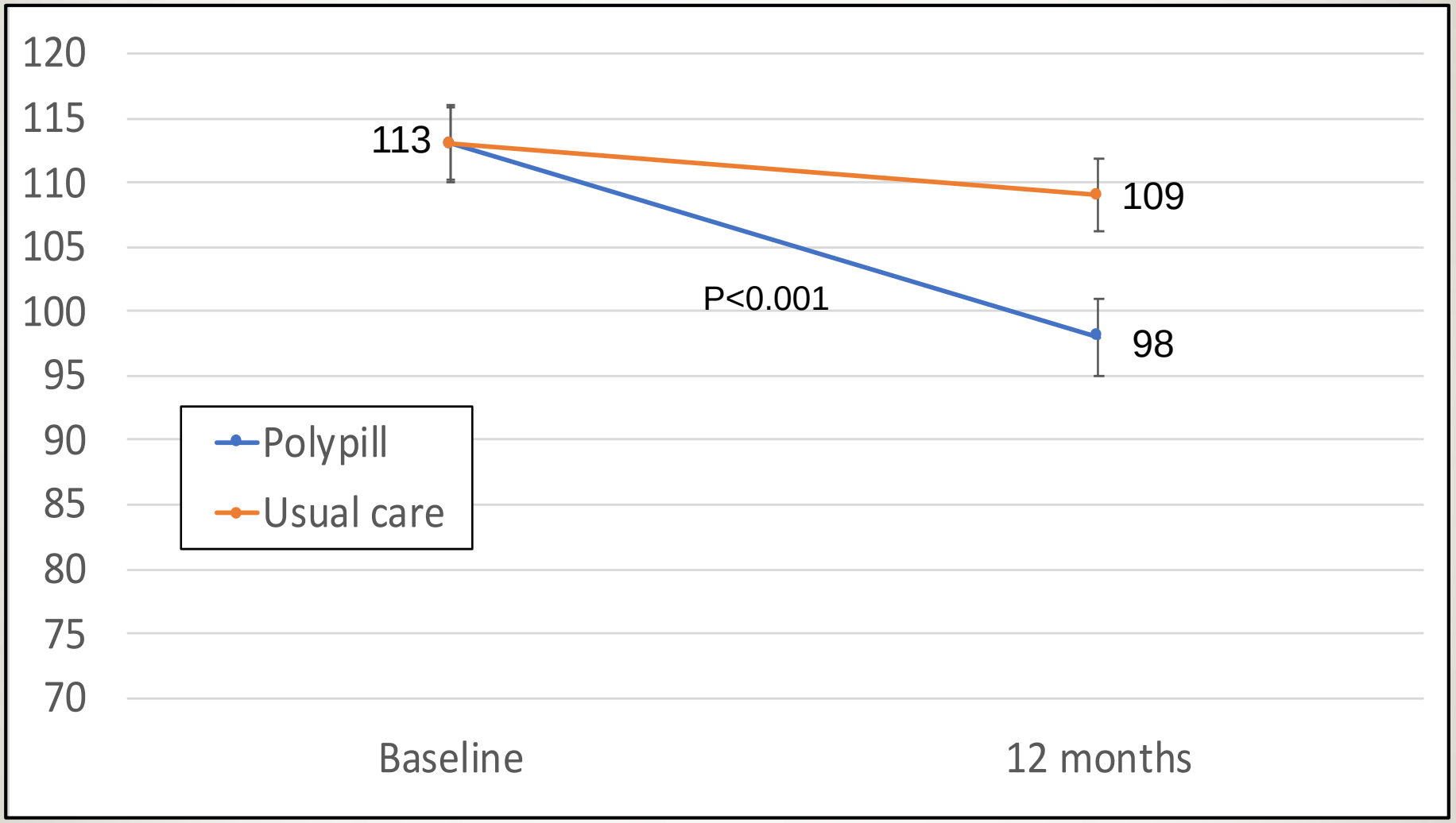
- Original assumption of up to 20% drop-out
  - ***Actual observed drop-out of 9%***

Retention (visits): 91%
Pill counts: 86%

Results: systolic blood pressure (mm Hg)



Results: LDL cholesterol (mg/dL)



SCCS Polypill Trial: key subgroups

- Polypill vs usual care treatment effects:
  - Baseline SBP > 140: - 11 mm Hg
  - On baseline BP therapy: - 5 mm Hg
  - Without baseline BP therapy: - 9 mm Hg
  - On baseline statin: - 7 mg/dl
  - Without baseline statin: - 16 mg/dl

Secondary endpoints

	Polypill		Usual Care		
	Baseline	**12 months**	**Baseline**	**12 months**	**Difference (95% CI)**
Total cholesterol, mg/dL	198	183	199	194	-11 (-19,-3)
HDL cholesterol, mg/dL	62	60	64	63	-1 (-4,2)
10-year ASCVD risk estimate	12.0%	9.4%	12.8%	13.3%	-3.1 (-4.6,-1.6)

Adverse events (AE)

Polypill arm

- Serious AEs
  - No CV deaths
  - 2 non-CV deaths
- Other AEs
  - 1.4% myalgias
  - 1.4% lightheadedness

Usual care arm

- Serious AEs
  - 1 CV death (stroke)
  - 1 non-CV death
  - 1 CABG

Translation of BP and LDL findings to potential hard endpoints

- △SBP → 17-20% reduction in MACE events
- △LDL → 6-8% reduction in MACE events
- Overall, ~25% reduction
  - MACE: death, stroke, myocardial infarction
  - Does not include heart failure

Other key considerations & potential limitations

- Open-label design
  - Intent: to preserve clinician flexibility to adjust other meds & to assess real world effectiveness
- Medication costs between arms
  - On-site 340B pharmacy program provides uninsured usual care participants with free or nearly free prescriptions
- Single-center study

Implications?

- FQHCs can be effectively leveraged to answer valuable research questions in traditionally-understudied populations

- Can a polypill strategy for CVD prevention be effectively scaled and deployed across a variety of settings?

Key Takeaways

- Despite therapeutic advances in CVD, risk factor & disease burdens remain high in vulnerable subpopulations
- Use of a polypill-based strategy is associated with improved control of BP and LDL cholesterol compared with usual care in a low-income population
- FQHC network may serve as an effective platform to study and address CVD health disparities

Thank you
&
Questions