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

Daniel Muñoz, MD, MPA
Thomas J. Wang, MD
NIH Collaboratory Grand Rounds
June 21, 2019
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 **unequally** distributed

Higher CV mortality in:
- Low SES populations
- African-Americans
- Rural areas
- Certain regions
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
What is the best way to reduce burden of cardiovascular disease?

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?
Comparison of 2 Treatment Models
Precision Medicine and Preventive Medicine

Psaty et al., JAMA; 2018
“…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.”
“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.”

Psaty et al., JAMA; 2018

Hemophilia B

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.”
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
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
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

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

Heart Protection Study

<table>
<thead>
<tr>
<th>Lipid levels at entry</th>
<th>SIMVASTATIN (10269)</th>
<th>PLACEBO (10267)</th>
<th>Rate ratio &amp; 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LDL cholesterol (mmol/l)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 3.0 (116 mg/dl)</td>
<td>598 (17.6%)</td>
<td>756 (22.2%)</td>
<td>STATIN better</td>
</tr>
<tr>
<td>≥ 3.0 &lt; 3.5</td>
<td>484 (19.0%)</td>
<td>646 (25.7%)</td>
<td></td>
</tr>
<tr>
<td>≥ 3.5 (135 mg/dl)</td>
<td>951 (22.0%)</td>
<td>1183 (27.2%)</td>
<td></td>
</tr>
<tr>
<td><strong>Total cholesterol (mmol/l)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 5.0 (193 mg/dl)</td>
<td>360 (17.7%)</td>
<td>472 (23.1%)</td>
<td></td>
</tr>
<tr>
<td>≥ 5.0 &lt; 6.0</td>
<td>744 (18.9%)</td>
<td>964 (24.5%)</td>
<td></td>
</tr>
<tr>
<td>&gt; 6.0 (323 mg/dl)</td>
<td>929 (21.6%)</td>
<td>1149 (26.8%)</td>
<td></td>
</tr>
<tr>
<td><strong>ALL PATIENTS</strong></td>
<td>2033 (19.8%)</td>
<td>2585 (25.2%)</td>
<td>24% SE 3 reduction (2P&lt;0.00001)</td>
</tr>
</tbody>
</table>
Adverse effects of most BP therapies are dose-dependent

Wald et al, BMJ 2003
Combination therapy is endorsed in the latest hypertension guidelines

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).

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>RECOMMENDATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>B-R</td>
<td>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).</td>
</tr>
<tr>
<td>Ila</td>
<td>B-NR</td>
<td>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).</td>
</tr>
</tbody>
</table>

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

Investigational Drug Service
The Polypill
Losartan 25mg
HCTZ 12.5mg
Amlodipine 2.5mg
Atorvastatin 10mg

Photo: courtesy C. Reynolds
Franklin Primary Health Center (Mobile, Alabama)

Per-capita income in Mobile: $22,401

Alabama: 49th in life expectancy
Polypill Study Schema

Eligible participants – Mobile, AL
   Age 45-75
   SBP ≥120 mm Hg
   Use of ≤ 2 anti-hypertensive medications
   No prior CVD, cancer, liver/kidney disease

Randomization

Polypill strategy
   (n=150)

Usual care strategy
   (n=150)

SBP, LDL-cholesterol at 12 months
Rx adherence
Process & operational considerations

Patients

• 3 free study visits
  – Baseline
  – 2-month
  – 12-month

• Data collected
  – Blood pressure
  – Labs (Lipids, BMP)
Process & operational considerations

Patients

- 3 free study visits
  - Baseline
  - 2-month
  - 12-month

- Data collected
  - Blood pressure
  - Labs (Lipids, BMP)

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

Original target: 300
Randomizations: 303
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*

<table>
<thead>
<tr>
<th></th>
<th>Polypill (=148)</th>
<th>Usual Care (n=155)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (years)</td>
<td>56 ± 6</td>
<td>56 ± 6</td>
</tr>
<tr>
<td>Male sex</td>
<td>65 (44%)</td>
<td>56 (36%)</td>
</tr>
<tr>
<td>African-American</td>
<td>141 (95%)</td>
<td>151 (97%)</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>31.3 ± 8.5</td>
<td>30.4 ± 8.4</td>
</tr>
<tr>
<td>Mean systolic BP, mm Hg</td>
<td>140 ± 18</td>
<td>140 ± 17</td>
</tr>
<tr>
<td>Mean LDL cholesterol, mg/dL</td>
<td>114 ± 32</td>
<td>112 ± 37</td>
</tr>
<tr>
<td>Diabetes</td>
<td>17 (11%)</td>
<td>22 (14%)</td>
</tr>
<tr>
<td>Annual income</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;$15,000</td>
<td>107 (72%)</td>
<td>120 (77%)</td>
</tr>
<tr>
<td>$15,000 to &lt;$25,000</td>
<td>28 (19%)</td>
<td>21 (14%)</td>
</tr>
</tbody>
</table>

*no significant differences*
Participant retention

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

303 subjects
baseline visit

290 subjects
2-month visit

275 subjects
12-month visit

Retention (visits): 91%
Pill counts: 86%
Results: systolic blood pressure (mm Hg)

Baseline 12 months
Systolic Blood Pressure, mm Hg
Polypill
Usual care

P=0.003
Results: LDL cholesterol (mg/dL)

- Baseline: Polypill 113, Usual care 98
- 12 months: Polypill 109, Usual care 98

P<0.001
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

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

• $\Delta$SBP $\rightarrow$ 17-20% reduction in MACE events

• $\Delta$LDL $\rightarrow$ 6-8% reduction in MACE events

• Overall, $\sim$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