Polypills for the Prevention of Cardiovascular Disease: A Promising Option for Global Cardiovascular Health

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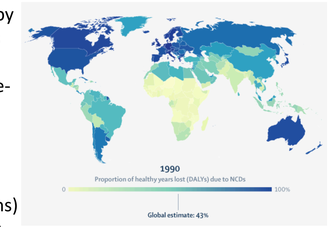
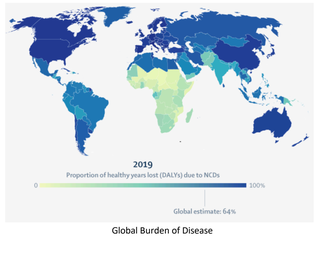
Background

- WHO Sustainable Development Goal 3.4: By 2030, reduce by 1/3 premature mortality from non-communicable diseases (NCDs) through prevention and treatment
- NCDs represent 71% of all deaths globally; Low- and middle-income countries (LMICs) disproportionately affected
  - 75% of global NCD burden, 85% of NCD-related "premature deaths"
- 80% of cardiovascular disease (CVD) is preventable, but it remains the leading cause of death worldwide (1 in 3 deaths)
- CVD increasingly prevalent in LMICs, likely due to rising risk factors (obesity, HTN, smoking, DM, HLD)
- <25% of patients w/ ASCVD in LMICs use guideline-directed drugs for 2º prevention
- Barriers to CVD management in LMICs: poor availability/ affordability of meds/healthcare, poor adherence, policy hurdles
- Significant funding/need mismatch per Global Burden of Disease
  - 2019: NCDs got only 1.8% of total global health funding

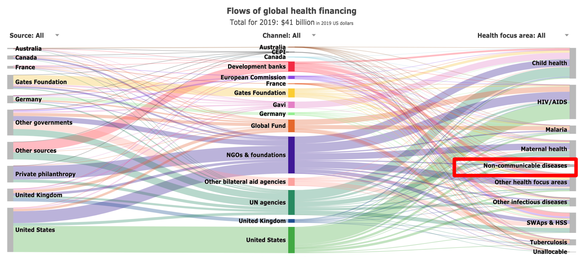




Global Burden of Disease

What is a Polypill?

Single fixed-dose combination pill containing at least one blood pressure-lowering drug and one lipid-lowering drug, +/- aspirin.



Global Burden of Disease

The Polypill—A Brief History

- Many fixed-dose combination pills since the 1980s—TB, HIV, malaria, Hepatitis C
- Wald and Law 2003: Initial concept of the CV polypill as something that should be given to those with known CVD AND everyone ≥55 years old
  - Initial claim that it would prevent 88% of heart attacks and 80% of strokes
  - Significant backlash/mockery—playing God, medicalization of society, "Gerifix"
- The first polypill: Caduet (amlodipine/atorvastatin)
  - Safe: No effect modification w/ dual dosing (AVALON, Respond)
  - Effective: 58% of patients achieved goal for both HTN and HLD (GEMINI)
  - Useful in underserved communities: 48% of African-Americans w/ HTN and HLD achieved dual goals, compared to <1% at baseline (CAPABLE)

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Polypill Efficacy

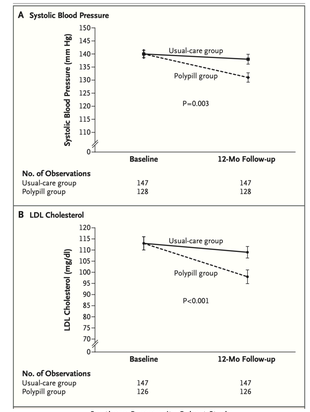
- Most studies "high" quality rating (based on Jadad score ≥3)
- **BP reduction**
  - 2017 systematic review: mean change in SBP -6.34 mmHg (95% CI -9.03 to -3.64)
  - 2022 systematic review: mean change in SBP -1.99 mmHg (95% CI -3.07 to -0.91), mean change in DBP -1.30 mmHg (95% CI -2.42 to -0.19)
- **LDL reduction**
  - 2017 systematic review: mean change in LDL -27 (95% CI -37.9 to -15.9)
  - 2017 systematic review: mean change in LDL -0.31 (95% CI -0.11 to -0.73)
- **Adherence**
  - 2017 systematic review: 44% higher in polypill group
  - 2022 systematic review: RR 1.31 (95% CI 1.11 to 1.55)—significantly increased

Polypill Outcomes

- **PolyIran (2019)-** 5-year follow-up
  - 34% reduction in risk of major adverse CVD events (MACE)
    - HR 0.66, 95% CI 0.55 to 0.80
  - Non-significant reduction in ischemic heart disease, stroke, heart failure, sudden death
  - Non-significant reduction in overall mortality
    - HR 0.93, 95% CI 0.77 to 1.11
  - 17% reduction in MACE in 2º prevention group vs 40% reduction in 1º prevention group
- **TIPS-3 (2021)-** 5-year follow-up
  - 33% reduction in risk of MACE
    - HR 0.79, 95% CI 0.63 to 1.0
  - Non-significant reduction in CV death, all-cause mortality
- **NEPTUNO (2022)-** 2-year follow-up
  - Focused on 2º prevention only
  - Significant reduction in incidence of recurrent MACE in polypill group compared to other groups (monocomponents, equipotent, other therapies)
- **2022 systematic review**
  - Non-significant reduction in risk of MACE overall, including 1º and 2º prevention trials together
    - RR 0.85, 95% CI 0.70 to 1.02
  - Significant reduction in risk of MACE in 1º prevention trials alone (30% decrease)
  - Most significant risk reduction in lower-risk cohorts
  - Significant reduction in risk of all-cause mortality
    - RR 0.90, 95% CI 0.81 to 1.00

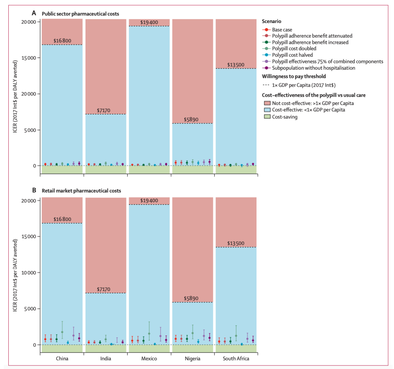
Polypills as a Vehicle for Health Equity

- Southern Community Cohort Study – Franklin Primary Health Ctr, Mobile, AL
  - Participants 96% black, 75% w/ annual income <$15,000
  - Polypill ($26/mo) vs usual care
  - SBP ↓9mmHg in polypill group (↓2 in usual care group)
  - LDL ↓15 in polypill group (↓4 in usual care group)
  - Adherence to polypill 86%
  - Estimated ↓25% incidence of CV events
- Most studies included in systematic reviews (including PolyIran and TIPS-3) done in LMICs



Southern Community Cohort Study

Cost-Effectiveness of Polypills



Lancet Global Health Study

- UMPIRE Study (India 2018) – 2º prevention
  - −$203 per person (95% CI: −286, −119, p < 0.01)
- Lancet Global Health study (2019) – 2º prevention
  - Polypill is cost-effective compared with current care in China, India, Mexico, Nigeria, and South Africa, particularly if available at public-sector pricing

Barriers to Polypill Availability

- Barriers to development
  - Low profit margins, low investment, technical challenges w/ bioequivalence
- Barriers to uptake
  - Paucity of evidence on major clinical outcomes, physician underestimation of true degree of med non-adherence, lack of gov't reimbursement, lack of inclusion in clinical guidelines and WHO Essential Medicines List