The Polypill for Secondary Prevention Is Entering the Cardiovascular Field: Worldwide Interest Based on Better Adherence and Economics

Jose M. Castellano, MD, PhD
Clinical Trials Coordinator, CNIC, Madrid, Spain
Adjunct Associate Professor, Mount Sinai School of Medicine
Nothing to disclose
A Polypill Strategy for Secondary Cardiovascular Prevention

1. A new Global CVD Scenario: focus on accessibility to CV drugs

2. A polypill strategy to improve adherence to CV Medication

3. A Cost effective strategy for CV Prevention

4. From Concept to Reality
A Polypill Strategy for Secondary Cardiovascular Prevention

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CARDIOVASCULAR DISEASE IN 2011

- Cardiovascular Disease (Total 32%)
  - Ischemic heart disease (13.4)
  - Cerebrovascular disease (11.2)
  - Other cardiovascular disease (4.16)
  - Hypertensive heart disease (1.92)
  - Inflammatory heart disease (0.64)
  - Rheumatic heart disease (0.32)

- Other Causes
  - Other non-cardiovascular disease (30)
  - Communicable diseases (29)
  - Injuries (9)
Global Cardiovascular Disease

8 out of 10 cardiovascular deaths occur in LMIC

Fuster, V. Nat. Rev. Cardiol. advance online publication 30 September 2014; doi:10.1038/nrcardio.2014.137
Global treatment rates with antiplatelet, statin and BP lowering

A Polypill Strategy for Secondary Cardiovascular Prevention

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A Polypill Strategy for Secondary Cardiovascular Prevention: from concept to reality

Reduces the number of components to simplify treatment regimen:
**Improves adherence**

Cost Effective Strategy
**Improves affordability**

Favors global accessibility to pharmacologic treatment
Medication Non-Adherence

...America’s other drug problem

Nearly 3 out of 4 Americans admit that they do not always take their medication as directed.

1/3 of medicine-related hospitalizations

Nearly 125,000 deaths in the U.S. each year

Almost $300 billion in avoidable costs to the health care system annually

Number of Americans affected by a chronic condition requiring medication therapy is expected to grow from 133 million to 157 million by 2020.
## Medication Non-Adherence

### The Five Dimensions of Non Adherence

<table>
<thead>
<tr>
<th>Social/Economic</th>
<th>Health Care System</th>
<th>Condition-Related</th>
<th>Therapy-related</th>
<th>Patient-related</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age and race</td>
<td>Patient Provider relationship</td>
<td>Comorbidities (depression)</td>
<td>Polypharmacy Side effects</td>
<td>Cognitive impairment</td>
</tr>
<tr>
<td>Family size</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Marital status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Socio economic status</td>
<td>Overworked HCP Communication</td>
<td>Asymptomatic condition</td>
<td>Complexity of treatment Lack of immediate benefit of therapy</td>
<td>Assumption once person feels better: discontinuation</td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
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<td>Employment</td>
<td></td>
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<tr>
<td>Income</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Health Illiteracy</td>
<td>Lack of incentives</td>
<td>Long duration, chronic disease</td>
<td>Social stigma</td>
<td>Media influence</td>
</tr>
<tr>
<td>Cost of medication</td>
<td>Lack of empathy</td>
<td>Frequent changes of treatment</td>
<td>Duration</td>
<td>Fear of side effects</td>
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**ADHERENCE TO LONG TERM THERAPIES: EVIDENCE FOR ACTION. WHO 2003**
# Medication Non-Adherence

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ADHERENCE TO LONG TERM THERAPIES: EVIDENCE FOR ACTION. WHO 2003
**Prevalence of Good Adherence to CV Medications**

Adherence to cardiovascular therapy: a meta-analysis of prevalence and clinical consequences

n=1,978,919 (135,627 CVD events and 94,126 cases of all-cause mortality)

<table>
<thead>
<tr>
<th>Adherence to</th>
<th>No. of Studies</th>
<th>No. of Participants</th>
<th>Proportion (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any CVD Medication</td>
<td>34</td>
<td>1.230.382</td>
<td>0.60 (0.52-0.68)</td>
</tr>
<tr>
<td>STATINS</td>
<td>12</td>
<td>771.323</td>
<td>0.54 (0.41-0.67)</td>
</tr>
<tr>
<td>ANTIHYPERTENSIVES</td>
<td>11</td>
<td>363.819</td>
<td>0.54 (0.42-0.77)</td>
</tr>
<tr>
<td>ASPIRIN</td>
<td>2</td>
<td>11.068</td>
<td>0.70 (0.49-0.91)</td>
</tr>
<tr>
<td>ANTIDIABETIC AGENTS</td>
<td>2</td>
<td>1112</td>
<td>0.69 (0.59-0.78)</td>
</tr>
</tbody>
</table>

Relative Risks for ANY CVD in good vs. poor adherence to major CV medication

n=1978919 (135 627 CVD events and 94 126 cases of all-cause mortality)

<table>
<thead>
<tr>
<th>Adherence to any CVD Medication</th>
<th>No. of Studies</th>
<th>No. of Participants</th>
<th>No. of CVD Events</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adherence to any CVD Medication</td>
<td>33</td>
<td>1.615.126</td>
<td>135.627</td>
<td>0.80 (0.77-0.84)</td>
</tr>
<tr>
<td>Adherence to STATINS</td>
<td>17</td>
<td>1,055,920</td>
<td>96,216</td>
<td>0.85(0.81-0.89)</td>
</tr>
<tr>
<td>Adherence to ANTIHYPERTENSIVES</td>
<td>13</td>
<td>552,143</td>
<td>36,186</td>
<td>0.81 (0.76-0.86)</td>
</tr>
<tr>
<td>Adherence to ACEI/ARB</td>
<td>4</td>
<td>68,780</td>
<td>4643</td>
<td>0.75 (0.55-1.01)</td>
</tr>
<tr>
<td>Adherence to ASPIRIN</td>
<td>3</td>
<td>15,253</td>
<td>2274</td>
<td>0.60 (0.31-1.16)</td>
</tr>
</tbody>
</table>
Relative Risks for ALL-CAUSE-MORTALITY
good vs. Poor adherence to major CV medication

n=1978919 (135 627 CVD events and 94 126 cases of all-cause mortality)

<table>
<thead>
<tr>
<th>Medication Type</th>
<th>No. of Studies</th>
<th>No. of Participants</th>
<th>No. of DEATHS</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adherence to any CVD Medication</td>
<td>23</td>
<td>533,381</td>
<td>94,126</td>
<td>0.65 (0.57-0.67)</td>
</tr>
<tr>
<td>Adherence to STATINS</td>
<td>11</td>
<td>291,864</td>
<td>29,605</td>
<td>0.55 (0.81-0.89)</td>
</tr>
<tr>
<td>Adherence to ANTIHYPERTENSIVES</td>
<td>11</td>
<td>205,598</td>
<td>12,228</td>
<td>0.71 (0.64-0.78)</td>
</tr>
<tr>
<td>Adherence to ACEI/ARB</td>
<td>4</td>
<td>62,196</td>
<td>886</td>
<td>0.74 (0.69-0.80)</td>
</tr>
<tr>
<td>Adherence to ASPIRIN</td>
<td>3</td>
<td>12,980</td>
<td>1573</td>
<td>0.45 (0.16-1.29)</td>
</tr>
</tbody>
</table>

9% of CV deaths EU attributable to poor adherence

Good adherence to CV therapies could be associated with a 20% lower risk of CVD and 35% reduced risk of all cause mortality

Assessing the Impact of Medication Adherence on Long-term Outcomes Post Myocardial Infarction

S. Bansilal, JM. Castellano, HG. Wei, EG. Vinado, A. Freeman, CM. Spettell, FG. Alonso, G. Steinberg, G. Sanz, V. Fuster

European Society Of Cardiology Congress 2014

Presented ESC 2014 Registry Hotline Aug 31, 2014
Adults following MI Between 1/1/2010 - 2/28/2013

14,119

Adults following MI & ACEI and statin fill in 6 months

7,107

Adults following MI & ACEI and statin fill in 6 months

5,776

Adults following MI & ACEI and statin fill in 6 months
With a 6 month pre-period

4,015

7,012 No fill of both ACEI and Statin during the 6 months after the MI

1,331 excluded (diagnostic codes)
- 29% mental disease
- 1% maternity or delivery
- 10% hospice or respite care
- 23% nursing facility
- 33% ARB fill during 6 months post-MI
- 4% MI as a subsequent episode

1,761 without a 6 month pre-period

Fully adherent
PDC > 80%

1,761 (43%)

Partially adherent
PDC 40-79%

1,263 (31%)

Non-adherent
PDC < 40%

1,031 (26%)
Time to Major cardiac Event by Adherence Levels

Cumulative Incidence

Time in Months

Log-Rank p-value=.0002

Number at Risk:
4015 3541 2421 1510 871 438 99 0
Strategies to Improve Adherence
Strategies to Improve Adherence

Medico Pak makes medication perfectly clear

See-through blister packs with the right dose, for the right time of day, so you don't forget to take your medication even if you're away from home.
Strategies to Improve Adherence
What Is Effective in Helping Chronic Non-Adherence: Sobering Findings

Annals of Internal Medicine Systematic Review 2012 and the Cochrane Review:

- 36 of 83 interventions in 70 RCTs improved adherence, but only 25 led to clinical improvement.
- Almost all were complex interventions but led to only modest improvements—case management and patient education with behavioral support.
- Cost effectiveness needs to be studied.
- Policy interventions aimed at co-payment costs or drug coverage were also effective.

Strategies to Improve Adherence

S — Simplify the regimen
I — Impart knowledge
M — Modify patient beliefs and behavior
P — Provide communication and trust
L — Leave the bias
E — Evaluate adherence

Primary Outcomes – Adherence at 12 months

UMPIRE: n= 2002, India & W. Europe
Kanyini-GAP: n=623 in Australia, half indigenous
IMPACT: n=513 in NZ, half indigenous

<table>
<thead>
<tr>
<th></th>
<th>Usual Care</th>
<th>Polypill</th>
<th>Risk Ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kanyini-GAP</td>
<td>96/249 (38.6%)</td>
<td>196/249 (78.7%)</td>
<td>2.04 (1.72,2.42)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>IMPACT</td>
<td>106/218 (48.6%)</td>
<td>172/233 (73.8%)</td>
<td>1.52 (1.30,1.78)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>UMPIRE</td>
<td>602/925 (65.1%)</td>
<td>827/935 (88.4%)</td>
<td>1.36 (1.29, 1.43)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td>1/4</td>
<td>4</td>
<td></td>
</tr>
</tbody>
</table>

Favors  Favors
Usual Care Polypill
Polypill Opens a Path for Improving Adherence*

K. Srinath Reddy, MSc, MD, DM

In September 2011, the United Nations called for concerted efforts to reduce global mortality from chronic noncommunicable diseases (NCDs) (1). In the hopes of achieving this goal, the World Health Organization adopted a strategy in May 2014. This message is especially pertinent for low- and middle-income countries (LMICs), which contribute to 80% of all NCD-related deaths and 90% of NCD-related deaths that occur in those younger than
Fixed-dose Combination Drug for Secondary Cardiovascular Prevention

FOCUS

64 Clinical Sites in Spain, Italy, Argentina, Brazil and Paraguay

Phase 1: Observational
- To determine the proportion of post-MI patients receiving appropriate secondary prevention
- To estimate the level of patient adherence
- To identify factors that contribute to poor adherence.

Morisky Green: Assessment of adherence

Phase 2: Prospective RCT
- To compare adherence to treatment in post MI patients receiving a FDC vs. those with conventional treatment (3 drugs provided separately)
- Primary Endpoint: Adherence measured by Morisky-Green and Pill Count combined
- To evaluate the effect of TRINOMIA on BP and LDL-C
- Safety and tolerability of TRINOMIA

FUSTER-CNİC-FERRER TRINOMİA
- Aspirin 100
- Ramipril 2,5-5-10
- Simvastatin 40

Adherence: MG + Pill Count

Castellano JM et al. *J Am Coll Cardiol.* 2014; 64
FOCUS Phase 1 – Results

MORISKY GREEN: EVALUATION OF ADHERENCE (N=2118)

<table>
<thead>
<tr>
<th>Country</th>
<th>% Adherent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paraguay</td>
<td>17.7%</td>
</tr>
<tr>
<td>Brazil</td>
<td>30.1%</td>
</tr>
<tr>
<td>Argentina</td>
<td>36.4%</td>
</tr>
<tr>
<td>America</td>
<td>36.4%</td>
</tr>
<tr>
<td>Spain</td>
<td>49.3%</td>
</tr>
<tr>
<td>Italy</td>
<td>50.3%</td>
</tr>
<tr>
<td>Europe</td>
<td>49.8%</td>
</tr>
<tr>
<td>Global</td>
<td>45.5%</td>
</tr>
</tbody>
</table>

% adherent (Original Morisky-Green = 20)

Castellano JM et al. J Am Coll Cardiol. 2014 Sept 1
FOCUS Phase 1 Results

FACTORS THAT INFLUENCE ADHERENCE

**Clinical**: AMI date, more pills*, complex treatments*

**Socio demographics**: Younger age, Illiteracy*, Distance from medical center†

**Risk factors**: BMI*, Smoking*, Sedentary lifestyle*

**Psychosocial**: Depression, Social Support†, lack of Insurance†

*Individual level intervention  †Systems intervention

Castellano JM et al. J Am Coll Cardiol. 2014 Sept 1
FOCUS Phase 1 Results

DETERMINANTS OF LACK OF ADHERENCE

Results from country-adjusted stepwise variable selection model

- Younger age <50
- Depression severity
- Complexity of tx
- % Insurance cover
- Degree social support

Castellano JM et al. J Am Coll Cardiol. 2014 Sept 1
**PROJECT OVERVIEW**

**Phase 1: Observational**
- To determine the proportion of post-MI patients receiving appropriate secondary prevention
- To estimate the level of patient adherence
- To identify factors that contribute to poor adherence.

**Morisky Green: Assessment of adherence**

**Phase 2: Prospective RCT**
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- Safety and tolerability of TRINOMIA

**FUSTER-CNIC-FERRER**
**TRINOMIA**
Aspirin 100
Ramipril 2,5-5-10
Simvastatin 40

**Adherence: MG + Pill Count**
FOCUS Phase 2 Results

POLYPILL VS. CONTROL AT 9 MONTHS: EFFECT ON ADHERENCE

MORISKY GREEN (20)

<table>
<thead>
<tr>
<th></th>
<th>Percentage</th>
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<tbody>
<tr>
<td>Control</td>
<td>59</td>
</tr>
<tr>
<td>Polypill</td>
<td>68</td>
</tr>
</tbody>
</table>

\[ p=0.049 \]

MORISKY (20) + PILL COUNT (80-110)

<table>
<thead>
<tr>
<th>Visit 1 (1m)</th>
<th>Visit 3 (9m)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>Polypill</td>
</tr>
<tr>
<td>p=0.364</td>
<td>p=0.012</td>
</tr>
<tr>
<td>59</td>
<td>65.7</td>
</tr>
<tr>
<td>54.8</td>
<td>55.7</td>
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Castellano JM et al. *J Am Coll Cardiol.* 2014 Sept 1
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AHA Policy Statement

Forecasting the Future of Cardiovascular Disease in the United States
A Policy Statement From the American Heart Association

Projections of Prevalence

Projections of Direct Cost (Billions USD)
Medication Non-Adherence
Impact on Health Care Costs

- Poor Medication Adherence
  - Costs passed on to patient
  - Increased Health Care Costs
  - Increased Service Utilization
  - Poor Health Outcomes
  - Costs passed on to patient
Impact of Medication Adherence in Chronic Vascular Disease on Health Services use (2005-2008)

Cardiovascular disease prevention with a multidrug regimen in the developing world: a cost-effectiveness analysis

Thomas A Gaziano, Lionel H Opie, Milton C Weinstein

Summary
Background Cardiovascular disease is the leading cause of death, with 80% of cases occurring in developing countries. We therefore aimed to establish whether use of evidence-based multidrug regimens for patients at high risk for cardiovascular disease would be cost-effective in low-income and middle-income countries.

Methods We used a Markov model to do a cost-effectiveness analysis with two combination regimens. For primary prevention, we used aspirin, a calcium-channel blocker, an angiotensin-converting-enzyme inhibitor, and a statin, and assessed them in four groups with different thresholds of absolute risks for cardiovascular disease. For secondary prevention, we assessed the same combination of drugs in one group, but substituted a β blocker for the calcium-channel blocker. To compare strategies, we report incremental cost-effectiveness ratios (ICER), in US$ per quality-adjusted life-year (QALY).

Findings We recorded that preventive strategies could result in a 2-year gain in life expectancy. Across six developing World Bank regions, primary prevention yielded ICERS of US$746–890/QALY gained for patients with a 10-year absolute risk of cardiovascular disease greater than 25%, and $1039–1221/QALY gained for those with an absolute risk greater than 5%. ICERS for secondary prevention ranged from $306/QALY to $388/QALY gained.

Interpretation Regimens of aspirin, two blood-pressure drugs, and a statin could halve the risk of death from cardiovascular disease in high-risk patients. This approach is cost-effective according to WHO recommendations, and is robust across several estimates of drug efficacy and of treatment cost. Developing countries should encourage the use of these inexpensive drugs that are currently available for both primary and secondary prevention.
The CV Polypill: A Cost Effective Strategy

Comparative Cost-Effectiveness of Interventions to Improve Medication Adherence after Myocardial Infarction

Kouta Ito, William H. Shrank, Jerry Avorn, Amanda R. Patrick, Troyen A. Brennan, Elliot M. Antman, and Niteesh K. Choudhry

© Health Research and Educational Trust
DOI: 10.1111/j.1475-6773.2012.01462.x
BEST OF THE ACADEMYHEALTH ANNUAL RESEARCH MEETING
A Polypill Strategy for Secondary Cardiovascular Prevention

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EVOLUTION OF THE POLYPILL CONCEPT

2002
Safety Bioequivalence Formulation
2006
RCT 1ary Prevention
Toleration, BP, LDL-Chol
TIPS-1 (2009)
PILL (2011)
TIPS-2 (2012)
2014
Adherence
UMPIRE
KANYINI-GAP
IMPACT
FOCUS
2014
WHO-EML
Adherence
Outcomes & Cost
PROPS
HOPE-3 (2016)
TIPS-3 (2019)
Stroke
MACE
Reduction > 80%
6 components > 55
Post MI
ASCVD
DM
Wald & Law
‘Vaccination Strategy’
PI: VALENTIN FUSTER
✓ Patients over 65
✓ First ever AMI
✓ n=3200
✓ 7 countries
✓ RCT: Polypill vs. Usual care
✓ Primary outcome: MACE CV death, recurrent MI, stroke, revascularization
✓ Secondary outcomes:
  ✓ Adherence
  ✓ Risk factor control
  ✓ Cost-effectiveness

Trinomia Atorvastatin 40mgs.
From Concept to Reality

Sweden, Greece, Belgium, Bulgaria, Finland, France
Poland, Ireland, Chez Republic

Marketed: TRINOMIA/SINCRONIUM (ASR y AAR)
Approved: TRINOMIA (AAR), launch 2015
TRINOMIA (AAR), registration, launch 2015 - 2017
Conclusions

1. The current global CV disease scenario demands **cost effective strategies to improve adherence and accessibility** to medications.

2. The perfect is enemy of the possible
   What can be done to assist the 50%+ patients not receiving recommended medications for secondary prevention?

3. Failure to address chronic disease global pandemic: **polypill as part of a comprehensive public health intervention**
   The undertreated are underrepresented in clinical trials.
Medication Non-Adherence

“Increasing the effectiveness of adherence interventions may have a far greater impact on the health of the population than any improvement in specific medical treatments”

ADHERENCE TO LONG-TERM THERAPIES: EVIDENCE FOR ACTION. WHO 2003