Polypill - ¿una solución para la falta de adherencia en la prevención cardiovascular?

José R. González Juanatey
Servicio de Cardiología y UCC
Hospital Clínico Universitario. IDIS
Santiago de Compostela
Disclosures:
Research Grants: AZ, Boehringer Ingelheim, Pfizer, Novartis, Daichii-Sankyo, Sanofi-Aventis, Bayer, MSD, Servier, Ferrer
Consultant/Honorarium. AZ, Boehringer-Ingelheim, Bayer, Pfizer, BMS, MSD, Daichii-Sankyo, Servier, Menarini, Ferrer, Angem
## IHD 2ªPrev. An Extraordinary Journey

<table>
<thead>
<tr>
<th>Innovation</th>
<th>Year</th>
<th>Impact</th>
</tr>
</thead>
<tbody>
<tr>
<td>B-Blockers</td>
<td>70´</td>
<td>Mortality</td>
</tr>
<tr>
<td>ASA</td>
<td>80´</td>
<td>Mortality</td>
</tr>
<tr>
<td>Life-style changes/Rehab</td>
<td>70-15´</td>
<td>Mortality</td>
</tr>
<tr>
<td>ACE Ih</td>
<td>80-90´</td>
<td>Morbi-mortality</td>
</tr>
<tr>
<td>Statins</td>
<td>90´</td>
<td>Morbi-Mortality</td>
</tr>
<tr>
<td>Empaglifocin/Liragutide</td>
<td>16´</td>
<td>Morbi/mortality</td>
</tr>
<tr>
<td>Revasc (subgroups)</td>
<td>00´</td>
<td>Morbi-mortality</td>
</tr>
<tr>
<td>Vorapaxar</td>
<td>13´</td>
<td>Morbi-mortality</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>13´</td>
<td>Morbi-mortality</td>
</tr>
<tr>
<td>Ticagrelor</td>
<td>15´</td>
<td>Morbi-mortality</td>
</tr>
<tr>
<td>Ezetimibe</td>
<td>15´</td>
<td>Morbi-mortality</td>
</tr>
</tbody>
</table>

10 %/y for Innovation Year Impact

2 %/y for Life-style changes/Rehab
Potential Cumulative Impact of 4 Simple Secondary Prevention Treatments

*Risk Factors Control and Direct CV and Kidney Protection*

<table>
<thead>
<tr>
<th>Treatment</th>
<th>RRR</th>
<th>Event rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>8%</td>
<td>8%</td>
</tr>
<tr>
<td>ASA</td>
<td>25%</td>
<td>6%</td>
</tr>
<tr>
<td>β-Blockers</td>
<td>25%</td>
<td>4.5%</td>
</tr>
<tr>
<td>Lipid lowering</td>
<td>30%</td>
<td>3.0%</td>
</tr>
<tr>
<td>ACE-inhibitors</td>
<td>25%</td>
<td>2.3%</td>
</tr>
</tbody>
</table>

*CUMULATIVE BENEFITS ARE LIKELY TO BE IN EXCESS OF 75% RRR, WHICH IS SUBSTANTIAL*
Rationale for the selection of “Polypill” components for secondary prevention

**ACETYLSALCYLIC ACID 100mg**
- 22% RRR of stroke
- 20% RRR of coronary events

*AT trialists collaboration. Baignent. BMJ 2002;324:71-86*

**ATORVASTATIN 20mg**
- 43% RRR of total mortality
- 52% RRR of non fatal MI
- 47% RRR of coronary mortality
- 47% RRR of stroke


**RAMIPRIL 10mg**
- 26% RRR of cardiovascular death
- 20% RRR of AMI
- 31% RRR of stroke

*HOPE Yusuf S et al. NEJM 2000;342(3):145-53*

RRR: relative risk reduction
Main results


*A* outcome significantly reduced as compared to placebo (p<0.005)
Picking Plaques That Pop!
Narula & DeMaria
*J Am Coll Cardiol [Editorial] 2005*

From Virmani, Narula, Leon, Willerson; The Vulnerable Atherosclerotic Plaques: 2007
LDLc reduction and CV Protection

Ballantyne CM. Am J Cardiol 1998; O’Keefe JH et al, JACC 2004
Evidence based treatments in EUROASPIRE

WHY ARE WE FAILING TO IMPLEMENT KNOWLEDGE:
A GLOBAL GAP IN TREATMENT OF CARDIOVASCULAR DISEASE

Knowledge

System

Accessibility

Physician

Adherence

Patient

Adherence
Medication Non-Adherence

"Adherence is the degree to which a person’s behavior in taking medication corresponds with agreed recommendations from a health care provider"
Importance of Age on Adherence to Cardiovascular Medications

Incidence (%) of Cardiovascular Disease by sex and age

Go A. et al. AHA Statistical Update, Circulation, 2013; 129, 24-292
Direct association between dosing frequency and medication adherence

Adherence drops after first six months

By the end of the first year of treatment, 50-90% of patients stopped taking their prescribed medications

Castellano JM, et al. , Global Heart. 2013 ;8:263
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>Medication Type</th>
<th>No. of Studies</th>
<th>No. of Participants</th>
<th>Proportion (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adherence to any CVD Medication</td>
<td>34</td>
<td>1,230,382</td>
<td>0.60 (0.52-0.68)</td>
</tr>
<tr>
<td>Adherence to STATINS</td>
<td>12</td>
<td>771,323</td>
<td>0.54 (0.41-0.67)</td>
</tr>
<tr>
<td>Adherence to ANTIHYPERTENSIVES</td>
<td>11</td>
<td>363,819</td>
<td>0.54 (0.42-0.77)</td>
</tr>
<tr>
<td>Adherence to ASPIRIN</td>
<td>2</td>
<td>11,068</td>
<td>0.70 (0.49-0.91)</td>
</tr>
<tr>
<td>Adherence to ANTIDIABETIC AGENTS</td>
<td>2</td>
<td>1112</td>
<td>0.69 (0.59-0.78)</td>
</tr>
</tbody>
</table>

Prevalence of Good Adherence (%)
Time to Major cardiac Event by Adherence Levels

Adherence Levels and MACE
(Hospitalizations per 100 Patient – years)

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

Impact on Health Care Costs

n=137227 DM, HT, Hchol, CHF


Medication Non-Adherence

Direct Costs (USD)

<table>
<thead>
<tr>
<th>Adherence levels (%PDC)</th>
<th>Direct Costs</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-19</td>
<td>15186</td>
</tr>
<tr>
<td>20-39</td>
<td>11200</td>
</tr>
<tr>
<td>40-59</td>
<td>11008</td>
</tr>
<tr>
<td>60-79</td>
<td>9363</td>
</tr>
<tr>
<td>80-100</td>
<td>6377</td>
</tr>
</tbody>
</table>
Adherence to Medication in the Guidelines

From “get on with the guidelines” to “strategies to improve adherence”


2016 European Guidelines on cardiovascular disease prevention in clinical practice

The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and invited experts)

Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR)

Authors/Task Force Members: Massimo F. Piepoli* (Chairperson) (Italy), Arno W. Hoeks (Co-Chairperson) (The Netherlands), Stefan Agewall (Norway)*, Christian Albus (Germany)*, Carlos Brotons (Spain)*, Alberico L. Catapano (Italy)*, Marie-Therese Cooney (Ireland)*, Ugo Corra (Italy)*, Bernad Cosyns (Belgium)*, Christi Deaton (UK)*, Ian Graham (Ireland)*, Michael Stephen Hall (UK)*, Frédéric Haude (France)*, Maja Luchen (Norway)*, Herbert Lüscher (Switzerland)*, Pedro Marques-Vidal (Switzerland)*, Josef Swedova (Denmark)*, Josep Redon (Spain)*, Dimitrios J. Richter (Greece)*, Naved Satter (UK)*, Yvo Smulders (The Netherlands)*, Monica Tiberi (Italy)*, H. Bart van der Werf (The Netherlands)*, Ineke van Dis (The Netherlands)*, W. M. Monique Verschuren (The Netherlands)*

Additional Contributor: Simone Binne (Italy)*

* Corresponding author. Heart Unit, University Hospital, University of Milan, Via Celoria 11, 20122 Milan, Italy. Tel.: +39 02 5033 8851; Fax: +39 02 5033 8886. E-mail: simone.binne@unimi.it

ESC Committees having participated in the development of this document:

- Committee for Practice Guidelines (CPG) and National Cardiac Society Reviewers can be found in the Appendix.

ESC/EAS guidelines for the management of dyslipidaemias

2016 ESC/EAS Guidelines for the management of dyslipidaemias

The Task Force for the Management of Dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS)

Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR)

Authors/Task Force Members: Alberico L. Catapano* (Chairperson) (Italy), Ian Graham* (Chairperson) (Ireland), Guy De Backer (Belgium), Olov Wiklund (Sweden), M. John Chapman (France), Heinz Drexel (Austria), Arno W. Hoeks (The Netherlands), Catriona S. Jennings (UK), Ulf Landmesser (Germany), Terje R. Pedersen (Norway), Željko Reiner (Croatia), Gabriele Riccardi (Italy), Marja-Rita Taskinen (Finland), Late Yokoogulu (Turkey), W. M. Monique Verschuren (The Netherlands), Charalampos Vlachopoulos (Greece), David A. Wood (UK), Jose Luis Zamorano (Spain)

Additional Contributors: Marie-Therese Cooney (Ireland), W. M. Monique Verschuren (The Netherlands)

Document Reviewers: Lisa Badimon (CPG Review Coordinator) (Spain), Christian Funk-Brentano (CPG Review Coordinator) (France), Stefan Agewall (Norway), Goesla Barin-Esquerris (Spain), Jan Boren (Sweden), Eric Brukkert (France), Alberto Cordero (Spain), Alberto Corrini (Italy), Paola Grazioso (Italy)

© 2016 European Society of Cardiology and European Atherosclerosis Society. All rights reserved. For permissions please email: journals.permissions@oxfordjournals.org
Polypill for Cardiovascular Prevention
From Research to Clinical Practice

- Increases Patient/Physician Compliance
- Reduces Health Care Costs
- Improves accessibility to proven medication

Acetylsalicylic acid
Platelet antiaggregation

Atorvastatin
Plaque stabilisation

Ramipril
Myocardial remodelling

galenic innovation

Treatment and adherence available for everyone

trinomia
acetylsalicylic acid + atorvastatin + ramipril

cnïc ferrer
RCTS USING A POLYPILL TO STUDY THE EFFECT ON ADHERENCE

KANYINI GAP
RR=1.49

IMPACT
RR=1.75

UMPIRE
RR=1.33

Selak et al. BMJ. 2014

Castellano JM et al, J Am Coll Cardiol. 2014;64(6):613-621
A Polypill Strategy to Improve Adherence
Results From the FOCUS Project

José M. Castellano, MD, PhD,*† Ginés Sanz, MD, PhD,* José L. Peñalvo, PhD,* Sameer Bansilal, MD, MS,† Antonio Fernández-Ortiz, MD, PhD,*† Luz Alvarez, BSc,∗ Luis Guzmán, MD,§ Juan Carlos Linares, MD,§ Fernando García, MD, PhD,∥ Fabiana D’Aniello, PhD,∥ Joan Albert Arnáiz, MD, PhD,¶ Sara Varea, BSc,¶ Felipe Martínez, MD,# Alberto Lorenzatti, MD,# Iñaki Imaz, MD, PhD,** Luis M. Sánchez-Gómez, MD, MSc,** Maria Carla Roncaglioni, Biol Sci Dr,†† Marta Baviera, PharmD,†† Sidney C. Smith, Jr, MD,∥∥ Kathryn Taubert, PhD,∥∥ Stuart Pocock, PhD,*§§ Carlos Brotons, MD, PhD,∥∥ Michael E. Farkouh, MD, MSc,¶¶ Valentin Fuster, MD, PhD*†
10% adherence increase with the CNIC-Ferrer polypill (Trinomia ASR) in patients with long-term evaluated CV disease.

Intention to treat

Per Protocol

FOCUS Project: Phase 2, Results

secure
SECONDARY PREVENTION OF CARDIOVASCULAR DISEASE IN THE ELDERLY
Poor adherence leads to poor outcomes and a polypill strategy leads to better adherence. Hence the implementation of a polypill strategy in post MI setting should lead to better clinical outcomes.
Study Overview

n=3200
Post MI >65

FU: 2-4 years

MACE
Cardiovascular death
Nonfatal myocardial infarction
Nonfatal ischemic stroke
Urgent revascularization
A step ahead in secondary prevention of cardiovascular risk

Consensus document on clinical use of the polypill
Polypill in CV secondary prevention. Clinical criteria related with a preferential access

- *Patients with history of non-compliance* or with predictors of drug non-compliance.

- Patients *treated and controled with the individual polypill components.*

- Patients with history of *non-compliance and good control with equivalent doses of the individual polypill components.*

- Patients with *several co-morbidities and poly-pharmacy.*
Clinical situations when can be started the Polypill treatment

- During hospital admission for an **Acute CV event** when are expected difficulties with*:
  - Patient compliance,
  - Treatment accessibility,
  - Follow-up

In stable patients after a CV event, when **low compliance** was identified during the follow-up.

- **In patients with ply-pharmacy** or when asking for reduction in the number of pills, independent to the patient compliance status.

*Plypill prescription during hospital admission or after hospital discharge is related to the health care system/hospital characteristics.
The "New Polypill" for Cardiovascular Prevention
From Hospital to Outpatient Care

Increases Patient/Physician Compliance from Hospital Discharge

Reduces Health Care Costs

Improves accessibility to proven medication

Atorvastatin 40 mgs

Acetylsalicylic acid Platelet antiaggregation
Ramipril Myocardial remodelling

Galenic innovation

Treatment and adherence available for everyone
Polypill in patients with high- and very-high CV Risk with Subclinical CV Disease?

1. *Hypertensive patients with high CV Risk*: hypertensive patients + any of the clinical characteristics:
   - LVH, microalbuminuria / proteinuria or kidney dysfunction, or high pulse wave velocity or increased carotid IMT or atherothrombotic plaque or ABI<0.9

2. *Diabetic or hypertensive patients with microalbuminuria / proteinuria* irrespective to the presence of other markers of subclinical CV disease**.

*In patients without a high bleeding risk
** Also can be considered in normotensive patients.
Aspirin Therapy in Primary Cardiovascular Disease Prevention

A Position Paper of the European Society of Cardiology Working Group on Thrombosis

<table>
<thead>
<tr>
<th>Step 1: Assess 10 year risk of major CV events</th>
<th>&lt;10%</th>
<th>10-20%</th>
<th>&gt;20%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Step 2: history of bleeding without reversible causes, concurrent use of other medications that increase bleeding risk</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Consider family history of GI (especially colon) cancer /patient values and preferences

- Stop
- Go ahead with caution
- Proceed

Low-dose aspirin

Halvorsen S et al JACC 2014; 64:319 - 327
Compliance Challenge

Patient compliance

Get with the pills

Physician compliance

Get with the guidelines

Polypill
"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"