CVD Prevention: A Return To Virchow From The Polypill

Prof. K Srinath Reddy
President, Public Health Foundation of India
Bernard Lown Professor of Cardiovascular Health, Harvard School of Public Health
GLOBAL DEATHS BY CAUSE 2004

Preventing chronic diseases: a vital investment: WHO global report 2005
Projected global numbers of deaths by cause for high, middle and low income countries (WHO, 2008)
Multiple Drugs for CVD Prevention

Combination Pill (Peto; 2001)

Little Red Heart Pill (Rodgers; 2002)

Polypill (Wald and Law; 2003)

Multi-Drug Therapy (WHO, Gaziano, Beaglehole; 2008-12)

Polypharmacy (Yusuf, 2012)
Rationale

• Antihypertensive, lipid lowering and anti-platelet drugs are proven to reduce CVD events when used in primary and secondary prevention

• **BUT** their use is sub-optimal globally, particularly in LMICs where most CVD occurs

• CVD patients often require multiple drugs

• Leading to decreased compliance and increased costs

• Polypill may improve compliance, reduce costs

• Non-physician health workers in LMICs could potentially screen and treat high risk people
Joint Effects of Blood Pressure and Cholesterol on CHD Risk in MRFIT Screenees Cohort

CHD death rates per 100,000 per year

Total cholesterol (mmol/l)

BP lowering
Cholesterol lowering
Polypill “move down the diagonal”
Why will the polypill reduce cardiovascular risk by 65%?

- Cholesterol lowering reduces risk by about 30%, blood pressure lowering by 30% and aspirin by 25%
- It is increasingly clear that these benefits are independent of each other

Chance of developing heart attack or stroke

<table>
<thead>
<tr>
<th>Treatments</th>
<th>Percent Chance</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Rx</td>
<td>25.0%</td>
</tr>
<tr>
<td>BP</td>
<td>17.5%</td>
</tr>
<tr>
<td>BP+Chol</td>
<td>12.3%</td>
</tr>
<tr>
<td>BP+Chol+Asp</td>
<td>9.2%</td>
</tr>
</tbody>
</table>

Overall ↓65%
What is projected about Polypill?

• Treatment of several risk factors simultaneously; regardless of level and without screening for them

• Intervention for all at ‘increased risk’ (regardless of actual risk level)
  i.e. everyone ≥ 55 years and people at any age with existing cardiovascular disease, diabetes

• Estimated potential to reduce CVD risk by 80%

Wald and Law, BMJ, 2003
Issues of Uncertainty

- Potential benefits: reduction of cardiovascular complications; quality of life; patient motivation/compliance to medication?

- Benefits of Polypill model versus the traditional model of health screening, individual risk assessment and appropriate treatment?
Polypill: Questions

• Lack of evidence that polypill reduces CVD events: need for outcome trials

• Safety concerns of polypill in middle aged, low risk individuals

• Pharmaceutical formulation Issues
  – Bioavailability
  – Pharmacokinetics
  – Possible interactions
  – Effect on risk factors

• Composition of ‘ideal’ polypill
**Polypill: Questions**

- Dose adjustment
- Actual rate of side effects (on long term treatment and adequate adherence)
- Cost effectiveness
- Registration of products: Criteria would be more stringent in primary prevention
- Evaluation of polypill based therapy Vs. usual therapy for CVD
- Interference with lifestyle: neglect of exercise and healthy diet?
## Completed Primary Prevention Trials

<table>
<thead>
<tr>
<th>Study &amp; Formulations</th>
<th>BP (mmHg)</th>
<th>LDL-C (mmol/l)</th>
<th>Placebo Corrected Absolute Excess of Side Effects</th>
<th>Placebo Corrected Absolute Excess of Side Effects</th>
<th>Estimated Risk Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline level</td>
<td>Reduction</td>
<td>Baseline level</td>
<td>Reduction</td>
<td>Sufficient to stop treatment</td>
</tr>
<tr>
<td>TIPS (Yusuf et al) Sim 20mg, HTZ 12.5mg, atn 50 mg, ram 5 mg, asp 100mg</td>
<td>134/85</td>
<td>7/6</td>
<td>3.0</td>
<td>0.7</td>
<td>n/a</td>
</tr>
<tr>
<td>Malekzadeh et al (PolyIran) Atorvo 20mg, enla 2.5mg, HTZ 2.5mg, asp 81mg</td>
<td>128/79</td>
<td>5/2</td>
<td>3.0</td>
<td>0.5</td>
<td>n/a</td>
</tr>
<tr>
<td>PILL (Rodgers A) Sim 20mg, HTZ 12.5mg, lisi 10mg, aspi 75mg</td>
<td>134/81</td>
<td>10/5</td>
<td>3.7</td>
<td>0.8</td>
<td>5%</td>
</tr>
<tr>
<td>Wald and Law (Estimated)</td>
<td>150/90</td>
<td>20/11</td>
<td>4.8</td>
<td>1.8</td>
<td>2%</td>
</tr>
</tbody>
</table>
Lessons and Issues

Lessons From Primary Prevention Trials
Moderate to significant reduction in LDL-c and BP
Side effects: Yes, but not the major reason for discontinuation

Issues

- 6-27% non-attendance / discontinuation at follow-up in TIPS, PolyIran, PILL
- Side effects and potential drug interactions?
- Aspirin in primary prevention?
- Long term adherence?
- Likely benefit less than speculated in studies comparing treatment with no treatment
- Elderly with diseases are likely already to be on some treatment
Polypill Vs Polymeal

- A combined meal of seven food components (the Polymeal) could reduce cardiovascular disease by >75% as proposed by Franco et al, 2004

- Pharmacological interventions are not the only option for preventing heart disease; a healthy diet and an active lifestyle reduce cardiovascular disease as well

- Need Primary Prevention Trials of Polypill (Full) Vs. Lifestyle Vs. Polypill (Partial) + Lifestyle
Polypill for Prevention

• **Secondary Prevention:** Strong rationale; Enough evidence of multidrug therapy on outcomes; Drug development and trials needed for evaluating impact on intermediate variables, adherence, safety and cost-effectiveness

• **Primary Prevention:** Sufficient rationale to permit trials; Outcome based trials needed; Comparison and combination with lifestyle interventions needed
Polypill: Limitations for Prevention

• Life time exposure to risk not addressed – Intervention comes late in life

• Does not reduce the risk of diabetes (while diet & physical activity do)

• No inter-generational benefits – Does not create a healthy society where the next generation can grow up without acquiring risk

• Even in secondary prevention – Protection starts after the event
Statins For Children!

- American Academy of Paediatrics recommends statins for children as young as 8 years.
  (Guardian; July 9, 2008)

- Use of statins in childhood debated.
  (LA Times; July 9, 2008)

Storm Over Statins

“The intense media coverage of the new statin policy may have shined a light on the profound cultural disconnect between our willingness to treat disease with drugs and our reluctance to institute preventive measures”

- De Ferranti S, Ludwig DS, NEJM; Sept 25, 2008
Competing Visions

Do We Want:

• A society where every succeeding generation has lower risk of CVD due to an enabling social environment?

  OR

• A society where every succeeding generation has a larger number of persons at high risk, acquired at even younger ages, needing multi-drug therapy for most of life?
“Do we not always find the diseases of the populace traceable to defects in society?”

“If disease is an expression of individual life under unfavourable circumstances, then epidemics must be indicative of mass disturbances.”

- Rudolf Virchow
Rudolf Virchow [1821-1902]

• *Analysis of an epidemic of typhus in Prussia*: Put forth radically liberal ideas for that time

• Recommended self-government, free and unlimited democracy, tax reform, abolition of feudal duties and privileges, and a constitution of the people.

• Explained the need for progress in social medicine: “physicians are the natural attorneys of the poor”.
Risk factors: tobacco use on the rise in developing countries

Cumulative tobacco-related deaths, 2005–2030

Snack imports from the United States into Central America, 1989-2006

Source: FAO 2007
“HIGH” BLOOD PRESSURE OR “HYPERTENSION”?  

- Changing Definitions of “Normal”, “Abnormal”, “Optimal”  
  (Systolic Blood Pressure: 160 → 140 → 130 → 120 → 115)  

- Observational studies ↔ Clinical Trials  
  (Prevention Norms ↔ Clinical Norms)  

- High Risk AND population approach  

- Risk Factor ↔ Social cause  

- Clinical Medicine ↔ Public Health
Inequality is Bad for the Heart!
In High Income Countries

It is by now well established that persons with lower levels of

– Income
– Education
– Professional status
– Decision making power (control)

have higher burdens of cardiovascular disease

(Marmot M. 2005)
SES Gradient: Order of Reversal for CVD Risk Factors

Tobacco

Blood Pressure

Cholesterol

Physical Activity

Obesity

Health Transition

Reddy KS et al (PNAS, 2007)
Tanzania: Smoking & HT ↑ in low SES; BMI ↑ in High SES Group

(Bovet P, 2002)

China: Smoking, HT, Obesity inversely correlated with years of education in Chinese women

(Zhije Yu, 2000)

India: Higher risk of MI in urban residents with low level of education and income

(Rastogi T, 2004)

Brazil: Obesity rates declining in High SES; Rising in Low SES

(Bell, 2000)
“Health leaps out of science and draws nourishment from the society around it”

-Gunnar Myrdal
THE ROSE PRINCIPLE

“Sick Individuals Arise From Sick Populations”

- Geoffrey Rose

WITHIN EACH POPULATION

- The *number of persons* who will have undesirable levels of any risk factor is related to the *mean level* of the risk factor in the population.

- A shift of the whole distribution to the left would mean better health (less ‘cases’) and a shift to the right means worse health (more ‘cases’).
Address the bulk of the distribution through small shifts (Population Attributable Risk)

Address the individuals at the highest ‘absolute’ risk of a CVD event (Comprehensive Cardiovascular Risk)

Widespread Effect = Large Benefits

High Impact = Cost-Effective use of resources
Societal policies and processes influencing the population prevalence of obesity

COMMUNICATION TO CONSUMERS; MIS-MATCH BETWEEN SCIENCE AND COMMERCE

**NUTRITION PYRAMID**

- **Occasional**
  - Colas and other sugary drinks
  - Chips and salted snacks
  - Biscuits chocolates and other candy
  - Fast food (Burgers, pizzas etc.)

- **In Moderation**

- **Plenty**

**ADVERTISING PYRAMID**

- **Occasional**

- **In Moderation**

- **Plenty**
MOULDING THE MARKETS

INTERNATIONAL AGENCIES; TRANS-NATIONAL TRADE AND MEDIA

GLOBAL COVENANTS, COMMERCE & COMMUNICATIONS

NATIONAL POLICY FRAMEWORK
Political, Economic, Social Motivators

CONSUMER CONSCIOUSNESS
Health Professionals, Civil Society; Media

INDUSTRY PRACTICES
Private-Public Partnerships; Health Dividend
The compass of research must extend from MOLECULES to MARKETS
The arena of advocacy and action must expand from RISK FACTORS to HUMAN RIGHTS
ACQUISITION OF RISK

ELEVATED RISK FACTORS

ESTABLISHED DISEASE

INTERVENTIONS WITH A SOCIO-ECONOMIC FOCUS (Population)

INTERVENTIONS WITH A PREVENTIVE FOCUS (High Risk)

INTERVENTIONS WITH A CLINICAL FOCUS
ACQUISITION OF RISK

ELEVATED RISK FACTORS

ESTABLISHED DISEASE

INTERVENTIONS WITH A SOCIO-ECONOMIC FOCUS (Population)

INTERVENTIONS WITH A PREVENTIVE FOCUS (High Risk)

INTERVENTIONS WITH A CLINICAL FOCUS

“Politics Is Medicine On A Grand Scale”

- Rudolf Virchow
<table>
<thead>
<tr>
<th>Tobacco</th>
<th>Diet</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Taxes</td>
<td>• Salt</td>
</tr>
<tr>
<td>• Smoke Free Policies</td>
<td>• Trans-Fats</td>
</tr>
<tr>
<td>• Ad Bans</td>
<td>• Edible Oils</td>
</tr>
<tr>
<td>• Health Warnings</td>
<td>• Fruits &amp; Vegetables</td>
</tr>
<tr>
<td></td>
<td>• Regulation of Advertising</td>
</tr>
<tr>
<td></td>
<td>• Labeling</td>
</tr>
</tbody>
</table>
Perspective

• We need to address the “causes of causes” for CVD prevention at the population level

• Polypill/ “polypharmacy” can help reduce CVD risk – In 2º prevention and in high risk individuals requiring 1º prevention. It is not a panacea for prevention!
Complementary Strategies

• Create a society where social conditions help to reduce the acquisition or augmentation of risk over the life course.

• Use pharmacotherapy (including MDT) judiciously to reduce CVD risk in individuals at high risk.
POLICY APPROACHES (Global; National; Local)

- Financial
- Legal
- Regulatory
- Trade

Environment To Enable Individuals To Make and Maintain Healthy Choices

INDIVIDUAL

FAMILY

NEIGHBORHOOD, COMMUNITY

Enhancement of Knowledge, Motivation, and Skills of Individuals

Health Communication

- Media
- Community Interventions
- Settings Based

Health Care Delivery

- Wider Society
  - Preventive, Diagnostic, Therapeutic, Rehabilitative Services

Health Care Delivery Determinants

- Globalization
- Access to Care
- Quality of Care
- Drugs & Technologies

Health Care Delivery Determinants

- Demographic Change
- Social Determinants
- Health Workforce
- Health Workforce

Health Care Delivery Determinants

- Social Determinants
- Health Workforce
- Health Workforce
- Health Workforce

Health Care Delivery Determinants

- Biological Risk
- Behavioral Risk
- Behavioral Risk
- Behavioral Risk

Health Care Delivery Determinants

- Education
- Education
- Education
- Education

Health Care Delivery Determinants

- Cultural and Social Norms
- Cultural and Social Norms
- Cultural and Social Norms
- Cultural and Social Norms
We Live In A World

Where Food Systems Are Threatening The Environment

And

Environmental Degradation (From A Variety of Sources)

Is Threatening Food Systems

❖ This Will Get Worse If We Don’t CHANGE!
Meat Production

Millions of tons

Today: 310
2050: 518

Grain Production

Millions of tons

Today: 2.7
2050: 3.3
INDUSTRIAL SCALE LIVESTOCK BREEDING

- Obesity
- CVD
- Cancer

+ Food Crisis (Grain Diversion)

- Climate Change (↑ Methane; Deforestation)

+ Pandemics (Zoonotic Diseases rising)
Nutrition Policy

20\textsuperscript{th} Century
- Focus on Technology Aided PRODUCTION
- Emphasis on Individual Behaviour Change

21\textsuperscript{st} Century
- Focus on both PRODUCTION and CONSUMPTION patterns which are compatible with sustainable development
- Emphasis on Systems thinking for broader societal change
RESPONSE TO HEALTH TRANSITION

**POPULATIONS**

- Demographic and Social Determinants
  - Low Risk
  - High Risk

**INDIVIDUALS**

- Biology + Beliefs + Behaviors
  - Low Risk
  - High Risk

- Clinical + Behavioral Interventions
MEDICINE

PUBLIC HEALTH

SUSTAINABLE DEVELOPMENT

20th Century

+ NUTRITION

21st Century

+ AGRICULTURE & ENVIRONMENT
“Should medicine ever fulfill its great ends, it must enter into the larger political and social life of our time; it must indicate the barriers which obstruct the normal completion of the life cycle and remove them. Should this ever come to pass, Medicine, whatever it may then be, will become the common good of all”

- Rudolf Virchow (1821-1902)