STRATEGIES FOR GETTING TO ZERO: DO WE NEED MORE THAN MEDICINE?

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DISCLOSURES

01
Employed by Stanford University

02
Retired from University of California System (UCLA/UCSD)

03
Retired from US Government (NIH/AHRQ)

04
Consultant to
• Purdue University (Regenstrief Center for Healthcare Engineering)
• Google/Verily
HEART DISEASE AND STROKE MORTALITY TRENDS, 1950-2015
Heart Disease and Stroke Mortality Trends, 1950-2015

STRATEGIES FOR REDUCING BURDEN OF CVD

The Nobel Prize in Medicine 1985:
Brown MS & Goldstein JL

"for their discoveries concerning the regulation of cholesterol metabolism"

1996: Brown and Goldstein forecast heart attacks will be “gone with the 20th century”
PROPOSALS TO ATTACK BURDEN OF CVD

- Million Hearts Campaign: Prevent 1 million heart attacks and strokes by 2022
- AHA: reduce deaths 20% by 2020
- WHO and World Heart Federation: 20% by 2025
- UN Sustainable Development Agenda: 33 1/3 by 2030
- Labarthe and Lloyd-Jones: Reduce risk factors by >50% among all individuals <50 years of age by 2050 (50X50X50)
Target Population

Total Population
281,000,000

TC
105,000,000

Smoking
53,000,000

HBP
50,000,000

DM
10,000,000

Stroke
500,000

MI
650,000

CHF
550,000

Goal 1
Increase Quality and Years of Healthy Life

Goal 2
Eliminate Disparities

Goal 3

Goal 4

A Vision of the Future

Social and Environmental Conditions Favorable to Health

Behavioral Patterns that Promote Health

Low Population Risk

Few Events/Only Rare Deaths

Full Functional Capacity/Low Risk of Recurrence

Good Quality of Life Until Death

Unfavorable Social and Environmental Conditions

Adverse Behavioral Patterns

Major Risk Factors

First Event/Sudden Death

Disability/Risk of Recurrence

Fatal CVD Complications/Decompensation

The Present Reality

The Healthy People 2010 Partnership Goals

Policy and Environmental Change

Behavior Change

Risk Factor Detection and Control

Emergency Care/Acute Case Management

Rehabilitation/Long-term Case Management

End-of-Life Care

Intervention Approaches

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Unfavorable Social and Environmental Conditions

Social and Environmental Conditions Favorable to Health
**Target Population**

- **TC**: 105,000,000
- **Smoking**: 53,000,000
- **HBP**: 50,000,000
- **DM**: 10,000,000
- **Stroke**: 500,000
- **MI**: 650,000
- **CHF**: 550,000
- **CVD**: 525,000

**The Healthy People 2010 Partnership Goals**

- **Goal 1**: Increase Quality and Years of Healthy Life
- **Goal 2**: Eliminate Disparities
- **Goal 3**: Action Framework For A Comprehensive Public Health Strategy To Prevent Heart Disease and Stroke

**TREATMENT $ .95**

**A Vision of the Future**

- **Good Quality of Life Until Death**
- **Full Functional Capacity/ Low Risk of Recurrence**
- **Few Events/ Only Rare Deaths**
- **Low Population Risk**
- **Behavioral Patterns that Promote Health**
- **Social and Environmental Conditions Favorable to Health**

**The Present Reality**

- **Unfavorable Social and Environmental Conditions**
- **Adverse Behavioral Patterns**
- **Major Risk Factors**
- **First Event/ Sudden Death**
- **Disability/ Risk of Recurrence**
- **Fatal CVD Complications/ Decompensation**

**Intervention Approaches**

- **Policy and Environmental Change**
- **Behavior Change**
- **Risk Factor Detection and Control**
- **Emergency Care/ Acute Case Management**
- **Rehabilitation/ Long-term Case Management**
- **End-of-Life Care**
- **Full Functional Capacity/ Low Risk of Recurrence**
- **Good Quality of Life Until Death**

**Adverse Behavioral Patterns that Promote Health**

- **Increase Quality and Years of Healthy Life**
- **Eliminate Disparities**
- **Healthy People 2010**
$ .05 PREVENTION
Target Population

Social and Environmental Conditions Favorable to Health
Behavioral Patterns that Promote Health
Low Population Risk
Few Events/Only Rare Deaths
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Unfavorable Social and Environmental Conditions
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The Present Reality

A Vision of the Future

The Healthy People 2010 Partnership Goals
Increase Quality and Years of Healthy Life
Eliminate Disparities

Goal 1
Goal 2
Goal 3
Goal 4

Target Population

<table>
<thead>
<tr>
<th>Target Population</th>
<th>Total Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC</td>
<td>105,000,000</td>
</tr>
<tr>
<td>Smoking</td>
<td>53,000,000</td>
</tr>
<tr>
<td>HBP</td>
<td>50,000,000</td>
</tr>
<tr>
<td>DM</td>
<td>10,000,000</td>
</tr>
<tr>
<td>Stroke</td>
<td>500,000</td>
</tr>
<tr>
<td>MI</td>
<td>650,000</td>
</tr>
<tr>
<td>CHF</td>
<td>550,000</td>
</tr>
<tr>
<td>Stroke</td>
<td>375,000</td>
</tr>
<tr>
<td>MI</td>
<td>450,000</td>
</tr>
<tr>
<td>CHF</td>
<td>450,000</td>
</tr>
<tr>
<td>CVD</td>
<td>525,000</td>
</tr>
</tbody>
</table>

Total Population

281,000,000
281,000,000
Action Framework For A Comprehensive Public Health Strategy To Prevent Heart Disease and Stroke

A Vision of the Future

Social and Environmental Conditions Favorable to Health

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Low Population Risk

Few Events/Only Rare Deaths

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CONTINUUM OF CARE

Policy and Environmental Change

Behavior Change

Risk Factor Detection and Control

Emergency Care/Acute Case Management

Rehabilitation/Long-term Case Management

End-of-Life Care

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Target Population

Total Population 281,000,000

TC 105,000,000

Smoking 53,000,000

HBP 50,000,000

DM 10,000,000

Stroke 500,000

MI 650,000

CHF 550,000

Stroke 375,000

MI 450,000

CHF 450,000

CVD 525,000
POPULATION BP AND EXCESS STROKE MORTALITY, THE WHITEHALL STUDY*

* MEN 40-64 YEARS OLD AT ENTRY, 18 YEAR FOLLOW-UP.


Do We Need More Than Medicine?
FROM PROSPECTIVE STUDIES COLLABORATION: 61 STUDIES, 1 MILLION ADULTS

Figure 2: Stroke mortality rate in each decade of age versus usual blood pressure at the start of that decade.
Rates are plotted on a floating absolute scale, and each square has area inversely proportional to the effective variance of the log mortality rate. For diastolic blood pressure, each age-specific regression line ignores the left-hand point (i.e., at slightly less than 75 mm Hg), for which the dot lies significantly above the fitted regression line (as indicated by the broken line below 75 mm Hg).
REDRAW OF 61 STUDIES ANALYSIS IN NORMAL UNITS

(from Kaplan & Ong, Annual Review of Public Health 2007, Kaplan 2009)
NHANES DISTRIBUTION OF SYSTOLIC BLOOD PRESSURE IN THE US
(KAPLAN, 2009)

Figure 6.4 Distribution of Systolic Blood Pressure in the United States: Data from NHANES III
COMPARISON OF JNC-8 AND 2017 ACC/AHA

- ACC/AHA labels 70.1 million people age 45-75 with hypertension
- Label would affect 63% of people in the age group
- Among people taking medications, new guidelines would intensify treatment for 13.9 million (from 24.0% to 54.4% of treated patients)
Relative Risk for Coronary Heart Disease (Log Scale)

LDL-Cholesterol (mg/dL)
6 YEAR CHD MORTALITY BY TOTAL SERUM CHOLESTEROL 356,222 MEN SCREENED FOR MRFIT, AGED 35-57 YRS
### All-cause mortality

<table>
<thead>
<tr>
<th>Study</th>
<th>Follow-up, y</th>
<th>Patients With Events, No./Total (%)</th>
<th>Patients With Events, No./Total (%)</th>
<th>Risk Ratio (95% C)</th>
<th>Favors</th>
<th>Favors</th>
<th>Weight in Analysis, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACAPS,10 1994</td>
<td>3</td>
<td>1 (460 (0.2)</td>
<td>8 (459 (1.7)</td>
<td>0.12 (0.02-0.99)</td>
<td></td>
<td></td>
<td>0.2</td>
</tr>
<tr>
<td>AFCAST/TeACAPS,16 1998</td>
<td>5</td>
<td>80 (3304 (2.4)</td>
<td>77 (3301 (2.3)</td>
<td>1.04 (0.76-1.41)</td>
<td></td>
<td></td>
<td>9.5</td>
</tr>
<tr>
<td>ASCOT-LLA,23 2003</td>
<td>3</td>
<td>185 (5168 (3.0)</td>
<td>212 (5137 (4.1)</td>
<td>0.87 (0.71-1.05)</td>
<td></td>
<td></td>
<td>24.3</td>
</tr>
<tr>
<td>ASPEN,21 2008</td>
<td>3</td>
<td>46 (959 (4.6)</td>
<td>41 (946 (4.3)</td>
<td>1.06 (0.76-1.50)</td>
<td></td>
<td></td>
<td>5.3</td>
</tr>
<tr>
<td>Brinazet et al,21 2004</td>
<td>2</td>
<td>3 (163 (2.9)</td>
<td>4 (179 (5.1)</td>
<td>0.58 (0.13-2.50)</td>
<td></td>
<td></td>
<td>0.4</td>
</tr>
<tr>
<td>Done et al,24 2011</td>
<td>1</td>
<td>0 (465 (0)</td>
<td>0 (119 (0)</td>
<td>Not estimable</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CARDS,20 2004</td>
<td>4</td>
<td>61 (1428 (4.3)</td>
<td>62 (1410 (5.8)</td>
<td>0.73 (0.51-1.01)</td>
<td></td>
<td></td>
<td>8.7</td>
</tr>
<tr>
<td>HOPE-1,16 2006</td>
<td>5</td>
<td>334 (6361 (5.3)</td>
<td>357 (6344 (5.8)</td>
<td>0.93 (0.81-1.08)</td>
<td></td>
<td></td>
<td>30.2</td>
</tr>
<tr>
<td>HYVINKÄ,20 2000</td>
<td>5</td>
<td>492 (560 (1.4)</td>
<td>307 (369 (0.9)</td>
<td>0.63 (0.44-0.89)</td>
<td></td>
<td></td>
<td>0.5</td>
</tr>
</tbody>
</table>

**Meta-analysis:** Statins vs Placebo and All-Cause Mortality, Cardiovascular Mortality, and Incident Diabetes. Size of data markers indicates weight of study in the pooled analysis.

### Cardiovascular mortality

<table>
<thead>
<tr>
<th>Study</th>
<th>Follow-up, y</th>
<th>Patients With Events, No./Total (%)</th>
<th>Patients With Events, No./Total (%)</th>
<th>Risk Ratio (95% C)</th>
<th>Favors</th>
<th>Favors</th>
<th>Weight in Analysis, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACAPS,10 1994</td>
<td>3</td>
<td>0/460 (0)</td>
<td>6/459 (1.3)</td>
<td>0.88 (0.004-1.36)</td>
<td></td>
<td></td>
<td>0.8</td>
</tr>
<tr>
<td>AFCAST/TeACAPS,16 1998</td>
<td>5</td>
<td>55 (3866 (1.4)</td>
<td>76 (3966 (2.0)</td>
<td>0.71 (0.51-1.00)</td>
<td></td>
<td></td>
<td>7.8</td>
</tr>
<tr>
<td>ASCOT-LLA,23 2003</td>
<td>3</td>
<td>745168 (1.4)</td>
<td>825137 (1.6)</td>
<td>0.59 (0.66-1.23)</td>
<td></td>
<td></td>
<td>1.1</td>
</tr>
<tr>
<td>HOPE-3,16 2008</td>
<td>2</td>
<td>2/163 (1.0)</td>
<td>12/79 (15.2)</td>
<td>0.13 (0.02-0.55)</td>
<td></td>
<td></td>
<td>7.8</td>
</tr>
</tbody>
</table>

**Meta-analysis:** Statins vs Placebo and All-Cause Mortality, Cardiovascular Mortality, and Incident Diabetes. Size of data markers indicates weight of study in the pooled analysis.

### Incident diabetes

<table>
<thead>
<tr>
<th>Study</th>
<th>Follow-up, y</th>
<th>Patients With Events, No./Total (%)</th>
<th>Patients With Events, No./Total (%)</th>
<th>Risk Ratio (95% C)</th>
<th>Favors</th>
<th>Favors</th>
<th>Weight in Analysis, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACAPS,10 1994</td>
<td>3</td>
<td>17/3004 (2.3)</td>
<td>27/3117 (2.4)</td>
<td>0.98 (0.71-1.35)</td>
<td></td>
<td></td>
<td>15.7</td>
</tr>
<tr>
<td>ASCOT-LLA,23 2003</td>
<td>3</td>
<td>154 (5168 (3.0)</td>
<td>134 (5137 (2.6)</td>
<td>1.14 (0.91-1.44)</td>
<td></td>
<td></td>
<td>21.4</td>
</tr>
<tr>
<td>HOPE-3,16 2008</td>
<td>2</td>
<td>232/6361 (3.6)</td>
<td>226/6344 (3.6)</td>
<td>1.02 (0.86-1.23)</td>
<td></td>
<td></td>
<td>20.9</td>
</tr>
<tr>
<td>JUPITER,23 2008</td>
<td>2</td>
<td>270 (6901 (3.0)</td>
<td>216 (6901 (2.4)</td>
<td>1.21 (0.95-1.55)</td>
<td></td>
<td></td>
<td>25.2</td>
</tr>
<tr>
<td>MEGA,11 2006</td>
<td>5</td>
<td>172 (10313 (5.7)</td>
<td>164 (10373 (5.3)</td>
<td>1.07 (0.87-1.32)</td>
<td></td>
<td></td>
<td>22.8</td>
</tr>
<tr>
<td>WOSCOPS,15 1995</td>
<td>5</td>
<td>57/2959 (2.1)</td>
<td>82/2975 (2.8)</td>
<td>0.69 (0.49-0.96)</td>
<td></td>
<td></td>
<td>15.0</td>
</tr>
</tbody>
</table>

**Meta-analysis:** Statins vs Placebo and All-Cause Mortality, Cardiovascular Mortality, and Incident Diabetes. Size of data markers indicates weight of study in the pooled analysis.

JUPITER
Multi-National Randomized Double Blind Placebo Controlled Trial of Rosuvastatin in the Prevention of Cardiovascular Events Among Individuals With Low LDL and Elevated CRP

No Prior CVD or DM
Men ≥50, Women ≥60
LDL <130 mg/dL
hsCRP ≥2 mg/L

Rosuvastatin 20 mg (N=8901)

Placebo (N=8901)

4-week run-in

MI
Stroke
Unstable Angina
CVD
Death
CABG/PT CA

Argentina, Belgium, Brazil, Bulgaria, Canada, Chile, Colombia, Costa Rica, Denmark, El Salvador, Estonia, Germany, Israel, Mexico, Netherlands, Norway, Panama, Poland, Romania, Russia, South Africa, Switzerland, United Kingdom, Uruguay, United States, Venezuela

Primary Trial Endpoint: MI, Stroke, UA/Revascularization, CV Death

HR 0.56, 95% CI 0.46-0.69
P < 0.00001

- 44%

Ridker et al NEJM 2008
JUPITER
Secondary Endpoint – All Cause Mortality

HR 0.80, 95%CI 0.67-0.97
P= 0.02

Placebo 247 / 8901 - 20 %

Rosuvastatin 198 / 8901

Ridker et al NEJM 2008
• Total number of fatal MIs was derived as the difference between 31 “any myocardial infarctions” and 22 (31-22=9) “nonfatal myocardial infarctions”) for Rosuvastatin and (68−62=6) in the placebo group.
  • Rosuvastatin 9
  • Placebo 6
FATAL STROKE
(LORGERI RECALCULATION)

• (the difference between “any stroke” and “nonfatal stroke”) It was actually only 3 (33–30) in the rosuvastatin group and 6 (64–58) in the placebo group.

  • Rosuvastatin 3
  • Placebo 6
TOTAL CVD MORTALITY (LORGERI RECALCULATION)

- Cardiovascular mortality
- Fatal stroke plus fatal myocardial infarction
  - Rosuvastatin 12
  - Placebo 12
### ANOTHER LOOK AT RESULTS FROM THE ASTRONOMER TRIAL (ROSUVASTATIN VS PLACEBO-
SPONSORED BY ASTRA-ZENECA)

<table>
<thead>
<tr>
<th>Outcome Event</th>
<th>Events (Patients), n</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rosuvastatin (n=134)</td>
<td>Placebo (n=135)</td>
<td>P*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any event</td>
<td>35 (29)</td>
<td>44 (35)</td>
<td>0.47</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AVR</td>
<td>28 (28)</td>
<td>27 (27)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coronary bypass surgery†</td>
<td>5 (5)</td>
<td>5 (5)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac death</td>
<td>2 (2)</td>
<td>5 (5)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>0 (0)</td>
<td>3 (3)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>0 (0)</td>
<td>1 (1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Angina</td>
<td>0 (0)</td>
<td>1 (1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*P* values were from the Fisher exact test based on the number of patients. Statistical tests were not done for subcategories because the numbers were too small to draw any meaningful conclusion.

†All coronary bypass surgery was performed in association with aortic valve replacement (AVR).

But, how about the big decline in CHD deaths after the introduction of statins?

**THE INCREASE IN STATIN PRESCRIPTIONS STARTED DECADES AFTER THE DECLINE IN CHD DEATHS**
Heart Outcomes Prevention Evaluation (HOPE)–3 trial
Systolic Blood Pressure over the Course of the Trial, According to Trial Group. Base line 138/82 mmHg

- 2-by-2 factorial trial
- 12,705 participants at intermediate risk who did not have cardiovascular disease
- randomly assigned to receive either
  - candesartan at a dose of 16 mg per day plus hydrochlorothiazide at a dose of 12.5 mg per day or
  - placebo.
(HOPE)–3 trial

Cumulative Incidence of Major Cardiovascular Events, According to Trial Group.

A Death from Cardiovascular Causes, Myocardial Infarction, Stroke, Cardiac Arrest, Revascularization, or Heart Failure

B Stroke

C Myocardial Infarction

D Coronary Revascularization

Both cigarette smoking and heart disease were relatively uncommon at the turn of the 20th Century.

Both began to rise sharply after 1910 and continued their ascent until about 1940.

In both cases, the peak occurs around 1950 and the plateau continues until the mid-1960s. Since then, both deaths from heart disease and cigarette smoking have steadily declined.
Cardiovascular and Bleeding Outcomes in all Participants

The composite cardiovascular (CV) outcome consisted of cardiovascular mortality, nonfatal myocardial infarction, and nonfatal stroke. Hazard ratios (HRs) and 95% credible interval variables (CrIs) were calculated using Bayesian meta-analysis of trial-level event counts. The absolute risk reductions and increases were calculated by multiplying the control event risk by the relative risk and 95% CIs derived by frequentist meta-analysis (eFigure 4 in Supplement 2).

GI indicates gastrointestinal.
WHAT DOES THIS MEAN?

- Treating risk factors is important......but
- Effects are limited
- To get to zero we need to think bigger
What About the Strategy of Preventing Risk Factors from Developing?

Cumulative incidence of CVD adjusted for the competing risk of death for men and women according to aggregate risk factor (RF) burden at 50 years of age.

Incidence of cardiovascular disease according to the number of ideal health behaviors and health factors. Reprinted from Folsom et al\textsuperscript{12} with permission from the American College of Cardiology Foundation. Copyright © 2011, the American College of Cardiology Foundation.
Ideal CVH – Present and Future

A. Today

B. 2020 – 2050

C. Beyond 2050

- 50x10 → 10x50
- 50x10 → 50x50
- 100x0 → 100x50+
CONCLUSIONS

• We are making important progress in the management of CHD risk factors.

• Improvements in risk factor profiles have resulted in reductions of events and deaths.

• Reductions in all-cause mortality have been more difficult to demonstrate.

• In order to move toward zero, we need more than medicine.
EXTRA SLIDES
Hospital discharges (International Classification of Diseases, 9th Revision) for the 10 leading diagnostic groups (United States: 2014). Source: Healthcare Cost and Utilization Project, Agency for Healthcare Research and Quality and National Heart, Lung, and Blood Institute
EFFECT OF AHA-ACC GUIDELINES ON HYPERTENSION PREVALENCE IN US AND CHINA

- In the USA
  - there will be 7.5 million new cases
  - 13.9 million will be candidates for treatment intensification

- In China
  - there will be 55.3 million new cases
  - 30 million will be candidates for treatment intensification

Adapted from data in Khera et al BMJ 2018, 362 posted July 2018
ARR FROM JUPITER

- \( \text{ARR} = \text{CER} - \text{EER} \)
- \( \text{ARR} = \frac{247}{8902} - \frac{198}{8901} \)
- \( \text{ARR} = 0.027 - 0.022, \text{or} \ 2.7\% - 2.2\% \)
- \( \text{ARR} = 0.005 \) (about .5 of 1%)
- \( \text{AAR for Fatal Stroke} = 0.0003 \)
- \( \text{AAR for Total Fatal CVD} = 0.0000 \)
CVD RATES DIFFER BY GEOGRAPHY

County-level percent change in heart disease death rates,
Ages 35-64, 2010-2015

Over 50% of counties had increases in heart disease mortality from 2010-2015.

Source: Adam Vaughan, PhD, MPH (email communication, December 11, 2017); Vaughan et al. Widespread recent increases in county-level heart disease mortality across age groups. Annals of Epidemiology. 2017;27:796-800