Updates on Statins and Aspirin in the Treatment and Prevention of Cardiovascular Disease

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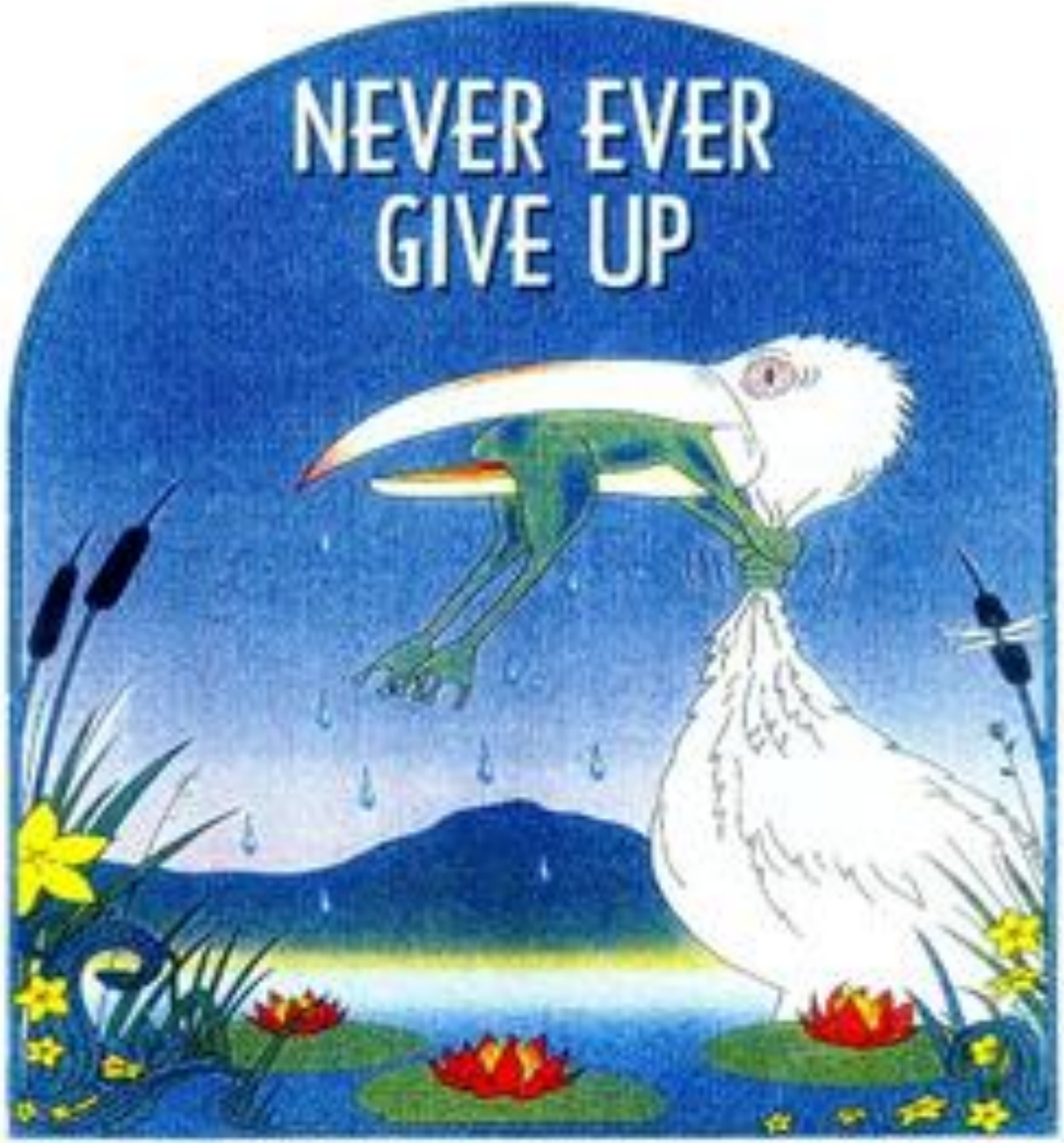
FINANCIAL DISCLOSURES

- I am funded as a 0.61FTE by the Charles E. Schmidt College of Medicine at Florida Atlantic University (FAU).
- I serve as an independent scientist in an advisory role to investigators and sponsors as Chair or Member of Data and Safety Monitoring Boards for Amgen, British Heart Foundation, Cadila, Canadian Institutes of Health Research, and the Wellcome Foundation.
- I serve as an independent scientist in an advisory role to the United States (U.S.) Food and Drug Administration as a Special Government Employee (SGE) , U.S. National Institutes of Health, and UpToDate.
- I receive royalties for authorship or editorship of three textbooks as well as for being co-inventor on patents concerning inflammatory markers and cardiovascular disease which are held by Brigham and Women's Hospital and co-authored the Collaborative Institutional Training Initiative (CITI) module on public health research.
- I have an investment management relationship with The West-Bacon Group within SunTrust Investment Services who has discretionary investment authority.
- I do not own any common or preferred stock in any pharmaceutical or medical device company.


NEVER EVER
GIVE UP

CLIFF NOTES

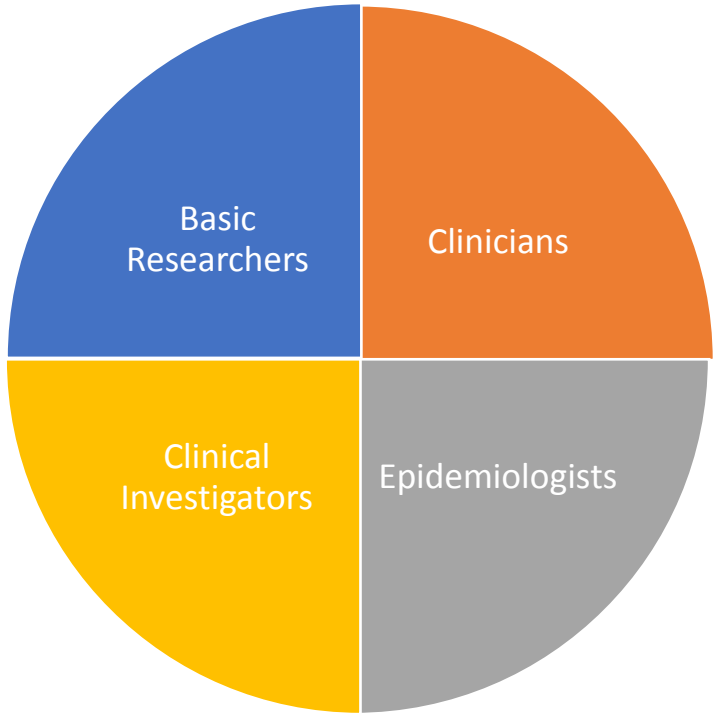
- STATINS: Hennekens CH, Lieberman E, Rubenstein M, Hebert P, DeMets D, Pfeffer M: Lipid Modification in the Treatment and Prevention of Cardiovascular Diseases: Emerging clinical and public health challenges. In Handbook of Cholesterol. Ed. Watson RR. AOCS Press, Urbana, IL., 2016, Chapter 9: 155-181. 2008 6(1): 95-107.

- ASPIRIN: Wood S, Lanas A, Hennekens CH. Utilization of aspirin: need for individual clinical judgements Chapter 18: 153-171 in the textbook Nonsteroidal anti-inflammatory drugs and aspirin: Recent advances and implications for clinical management. Lanas A (Ed), 2016, Springer

If you wish a PDF of either document, please contact me at chenneke@health.fau.edu

Totality of Evidence: importance of complementary sources

- Basic researchers (why)
- Clinicians
- Clinical Investigators
- Epidemiology (whether)
  - Descriptive studies
    - case reports
    - case series
    - ecological studies
  - Analytic studies
    - observational
      - case-control
      - cohort
    - randomized trials



Hennekens CH, Buring JE: *Epidemiology in Medicine*. Boston, Mass: Little, Brown & Co.;1987.
Hennekens CH and DeMets D: Statistical Association and Causation: Contributions of Different Types of Evidence, JAMA, 2011:304:1134-1136.

U.S. LIFE EXPECTANCY AT BIRTH: The Good News

- US life expectancy at birth is at an all time high of 78 years
  - (75.6 in men and 80.8 in women)

- Improvements in coronary heart disease and stroke mortality
  - Leading causes of death
  - Improvements in treatment account for over 90% of increased life expectancy.

- Improvements in cancer mortality
  - Second leading cause of death
  - Due mainly to improvement in treatment of patients with leukemia, lymphoma, breast and prostate cancer.

U.S. LIFE EXPECTANCY AT BIRTH:
The Bad News

- The state of our health is not at an all time high.
  - Improvements are due mainly to earlier diagnosis and aggressive treatment, not primary prevention.

- Improvements in life expectancy are no longer continuing in the US.
  - Increasing rates of obesity, diabetes, and physical inactivity.

CORONARY HEART DISEASE

- Leading cause of death in the US
  - among men by age 45 years with sudden cardiac death as the first presenting symptom in 1 in 4
  - among women by age 65 years

- Causes 1 in 3 deaths(325,00 in men and 350,000 in women) or 750,000 fatalities each year

- Coronary Heart Disease deaths in women
  - far higher than lung cancer deaths (70,500)
  - far higher than breast cancer deaths (40,610)
    - kills 1 in 25 women or about 1/3 of the afflicted 1 in 8

OBESITY IN THE US AND WORLDWIDE: A LEADING CAUSE OF PREMATURE DEATH

- The Nurse's Health Study enrolled 121,764 female registered nurses aged 30 to 55 years, whose average height was about 5'4" and average weight was 164 pounds.

- The average American gains almost 10 pounds in every decade of adult life. Thus, in the US today an unexplained weight loss of 10 or more pounds is a harbinger of death.

- The misconceptions about the hazards of obesity derive from failure to:
  - control confounding by smoking,
  - control for direct effects of obesity, and/or
  - exclude those with preclinical fatal illnesses at baseline in prospective cohort studies.

Hennekens CH, Andreotti F: The leading avoidable cause of premature death in the world: the case for obesity. AJM, 2012

METABOLIC SYNDROME: THE NEW SILENT KILLER

- Obesity causes abnormalities of lipids, blood pressure and insulin resistance, a precursor of diabetes.
- Apparently healthy men and women with these abnormalities have metabolic syndrome.
- In the U.S. 40% of adults aged 40 and older have metabolic syndrome.
  - -30% in 40-49,
  - - 40% in 50-59,
  - - 50% in 60-69
  - - and then begins to decline due to selective early mortality

Sherling D., Perumareddi P., Hennekens CH: Metabolic Syndrome: The new silent killer. JCPT. Published online ahead of print. January 30, 2017.

METABOLIC SYNDROME: THE NEW SILENT KILLER

- Patients with metabolic syndrome have a 10 year risk of a first coronary event of 16-18% which is almost as high as those who survived a prior MI of about 20% or more

- Significant weight loss is essential whether by

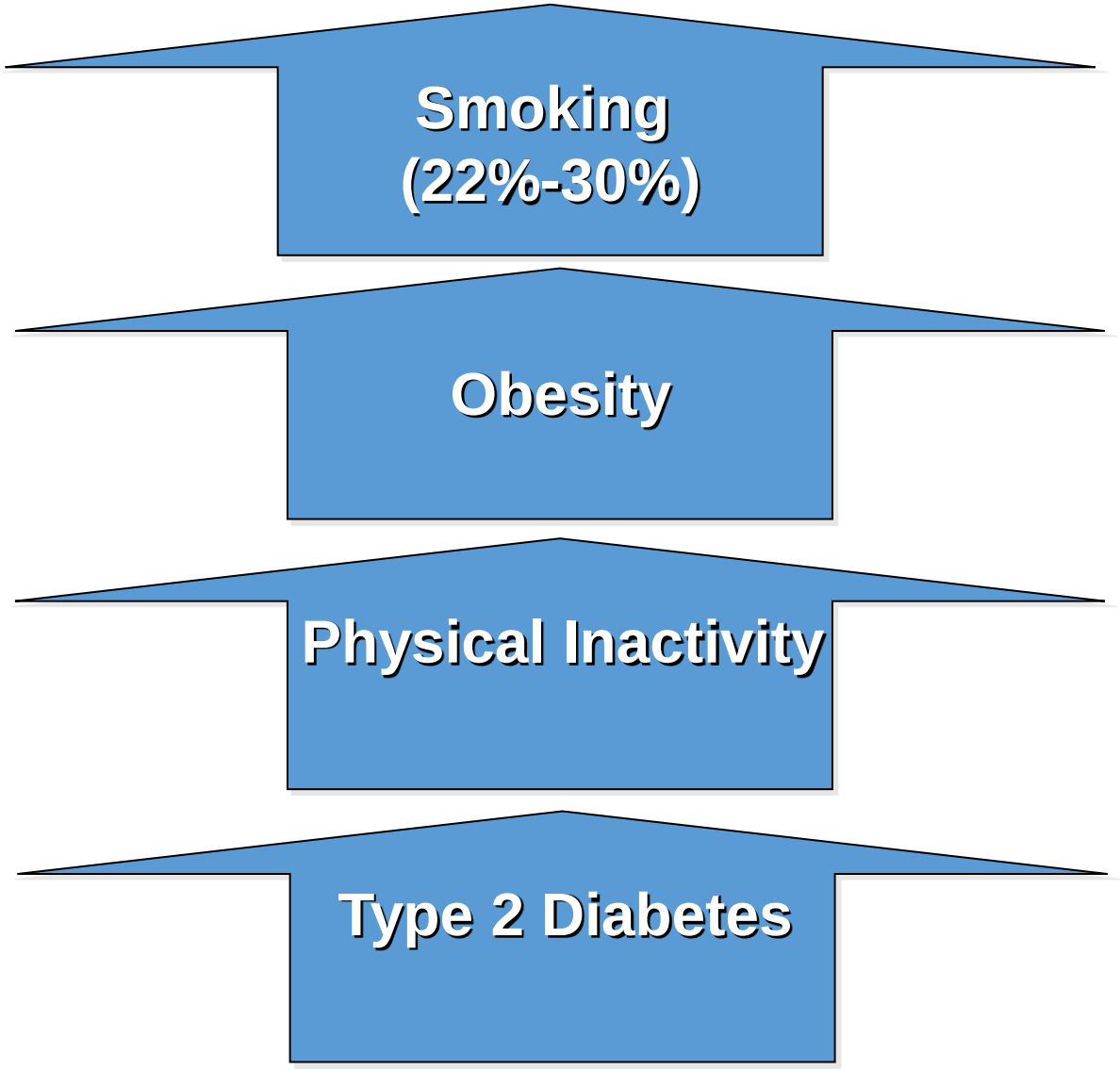
  diet and increased physical activity,

  drug therapies

  bariatric surgery

Sherling D., Perumareddi P., Hennekens CH: Metabolic Syndrome: The new silent killer. JCPT. Published online ahead of print. January 30, 2017.

US ADOLESCENTS:ALARMING TRENDS



Hennekens CH, Schneider W, Barice EJ: Childhood Obesity: General Considerations, Ped Res, 2007, 61(6):634-635.

Question: WHAT IS THE CLOSEST THING TO A MAGIC PILL IN THE US AND WORLDWIDE? (HELPFUL HINTS BELOW)

- Improves:
  - weight
  - blood pressure,
  - cholesterol and triglycerides.
  - risks of diabetes, heart attacks, strokes, colon and possibly breast and prostate cancer.
  - degenerative and inflammatory arthritis
  - mood
  - energy
  - sleep
  - sex life

Answer: SMALL AMOUNTS OF REGULAR PHYSICAL ACTIVITY

- Increase the quality and quantity of Life

- Men and women who walk for 20 minutes daily (or even every other day)
  - 35 to 55% reduction in risk of myocardial infarction and stroke
  - significant reduction in risk of deaths from cardiovascular disease

- This level of regular physical activity can be continued for most people for almost all their life, including the oldest old.

- 80% of Americans do not achieve this level of regular physical activity.

Lewis S, Hennekens CH: Regular physical activity: a necessity to curb the epidemic of obesity. Cardiology, 2016, 134:360-63

CHALLENGES FOR CLINICIANS

- For many US adults (especially the 60% without metabolic syndrome) therapeutic lifestyle changes (TLCs) may avoid the need for drugs of lifesaving benefit.

- In theory, TLCs, especially diet, in conjunction with regular physical activity, would reduce LDL cholesterol by 30-40%

- In practice, TLC's achieve reductions of <5%.

Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). JAMA. 2001 May 16;285(19):2486-97

GUIDE FOR CLINICIANS:
DON'T LET THE PERFECT BE THE ENEMY OF THE POSSIBLE

- The perfect is therapeutic lifestyle changes (TLCs) which are not often achieved by patients in clinical practice.

- The possible is the early diagnosis and aggressive management of secondary prevention patients and primary prevention subjects, especially those with metabolic syndrome, with evidence based doses of statins, aspirin, as well as angiotensin converting enzyme (ACE) inhibitors or blockers (ARB)

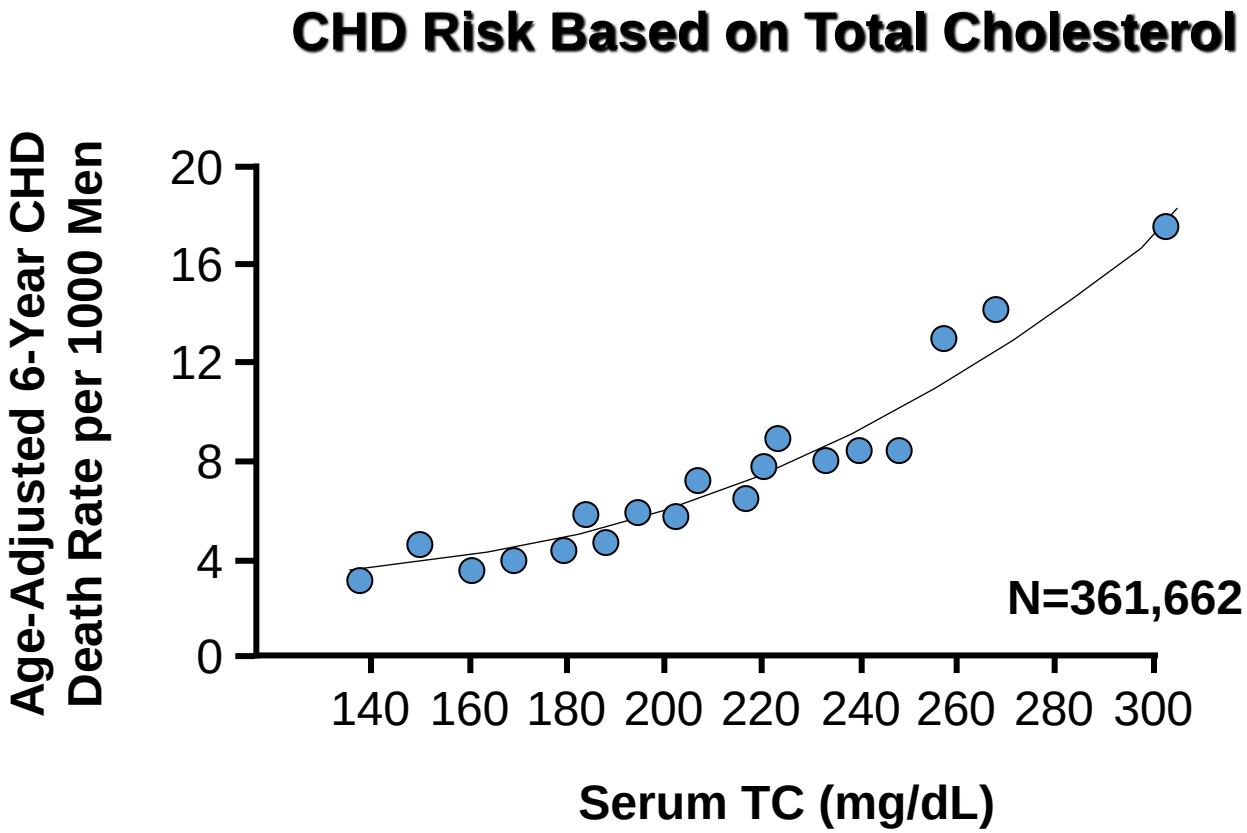
- Drugs of lifesaving benefit will avoid premature death and morbidity even in the absence of TLCs.

- At present, however, we have better living through chemistry not healthy lifestyles for large segments of the US population.

- The biggest clinical and public health challenges in the US are that for many segments of the population, especially primary prevention patients with metabolic syndrome, they have neither TLC nor get prescribed the drugs of lifesaving benefit.

Hennekens CH, Lieberman E, Rubenstein M, Hebert P, DeMets D, Pfeffer M: Lipid Modification in the Treatment and Prevention of Cardiovascular Diseases: Emerging clinical and public health challenges. In Handbook of Cholesterol. Ed. Watson RR. AOCS Press, Urbana, IL., 2016, Chapter 9: 155-181. 2008 6(1): 95-107.

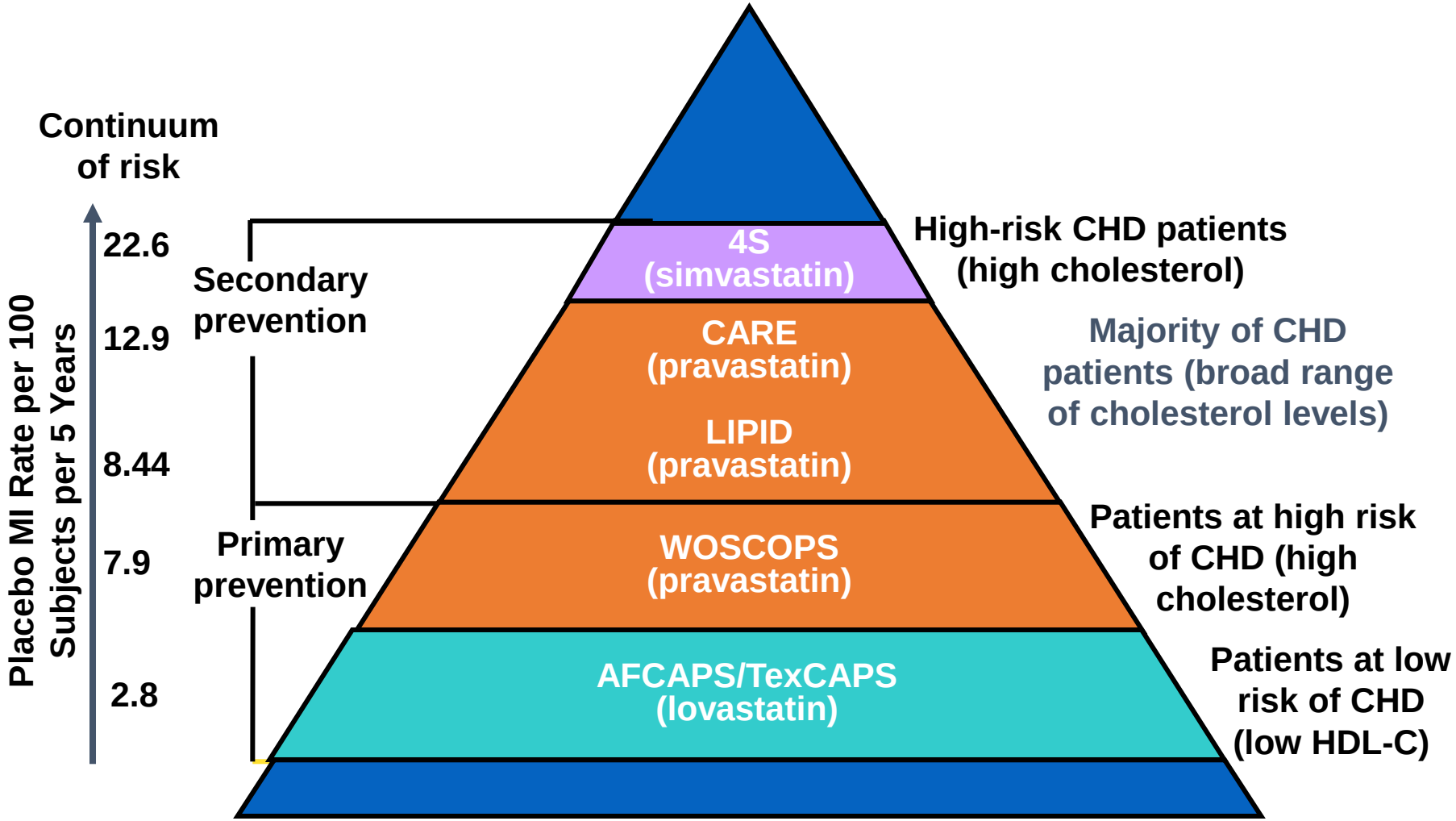
CHOLESTEROL AND RISK OF CORONARY HEART DISEASE (CHD)
MRFIT (Multiple Risk Factor Intervention Trial)



- Each 10% decrease in total cholesterol level is associated with a 20-30% reduction in coronary events
- In rural China where average cholesterol is about 140mg/dL, those with cholesterol of 126 have significantly lower risks of coronary events
- Epidemological evidence suggests no threshold below which a lower cholesterol is not associated with lower risk.

Hennekens CH, Lieberman E, Rubenstein M, Hebert P, DeMets D, Pfeffer M: Lipid Modification in the Treatment and Prevention of Cardiovascular Diseases: Emerging clinical and public health challenges. In Handbook of Cholesterol. Ed. Watson RR. AOCS Press, Urbana, IL., 2016, Chapter 9: 155-181. 2008 6(1): 95-107.

EARLY LANDMARK TRIALS OF STATINS
CLINICAL BENEFITS APPEAR @ 2-3 YEARS



THE LOWER THE LDL CHOLESTEROL THE GREATER THE BENEFITS: ALL APPARENT WITHIN 1 MONTH OF STARTING THERAPY

NAME OF TRIAL	LDL ACHIEVED	
	HIGH DOSE	USUAL DOSE
PROVE-IT (atorvastatin 80mg)	62	97
High risk secondary prevention		(pravastatin 40mg)
TNT (atorvastatin 80mg)	77	101
Usual risk secondary prevention		(atorvastatin 10mg)
JUPITER (rosuvastatin 20mg)	55	109
Moderate risk primary prevention		(placebo)

Hennekens CH, Lieberman E, Rubenstein M, Hebert P, DeMets D, Pfeffer M: Lipid Modification in the Treatment and Prevention of Cardiovascular Diseases: Emerging clinical and public health challenges. In Handbook of Cholesterol. Ed. Watson RR. AOCS Press, Urbana, IL., 2016, Chapter 9: 155-181. 2008 6(1): 95-107.

BENEFITS OF STATIN THERAPY: 170,000 PARTICIPANTS RANDOMIZED AND TREATED 5 YEARS

- **MI REDUCED BY ABOUT 30%**
- **STROKE REDUCED BY ABOUT 15%**
- **STENTS AND BYPASSES REDUCED BY 25%**
- **CORONARY DEATH REDUCED BY 22%**
- **IN 40,000 ADDITIONAL RANDOMIZED PATIENTS MORE INTENSIVE STATIN THERAPY PRODUCED LARGER REDUCTIONS IN LDL AND EVEN GREATER BENEFITS ON MI, STROKE, AND CORONARY DEATH**
- **STATIN THERAPY IN LOW RISK MEN AND WOMEN WITH NO HISTORY OF VASCULAR DISEASE OR RISK FACTORS PRODUCED SIMILAR BENEFITS ON MI, STROKE, AND CORONARY DEATH**

Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170 000 participants in 26 randomised trials, Cholesterol Treatment Trialists' (CTT) Collaborators. *Lancet* 2010; 376: 1670-1681

The effect of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials, Cholesterol Treatment Trialists' (CTT) Collaborators. *Lancet* Published online May 12, 2012

Hennekens CH, Lieberman E, Rubenstein M, Hebert P, DeMets D, Pfeffer M: Lipid Modification in the Treatment and Prevention of Cardiovascular Diseases: Emerging clinical and public health challenges. In Handbook of Cholesterol. Ed. Watson RR. AOCS Press, Urbana, IL., 2016, Chapter 9: 155-181.

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Proportional effects on major vascular events among low risk participants (10 year risk <10%) in 27 randomized trials of statins versus control

End point	Treatment-arm events, %	Control-arm events, %	Relative risk (95% CI)
Any major vascular event	0.38	0.56	0.62 (0.47-0.81)
Any major coronary event	0.11	0.19	0.57 (0.36-0.89)
Any coronary revascularization	0.16	0.30	0.52 (0.35-0.75)
Any stroke	0.16	0.20	0.74 (0.46-1.19)

The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials, Cholesterol Treatment Trialists' (CTT) Collaborators. *Lancet* published online May 17, 2012

STATIN INTOLERANCE: A SCOURGE FOR CLINICIANS AND PATIENTS: HEPATIC SIDE EFFECTS

-Initial FDA concerns about enzyme elevations were raised by high dose simvastatin in 4S and have been largely mitigated by reassuring evidence concerning atorvastatin and rosuvastatin

-May 2015: **FDA** has determined that serious liver injury with **statins** is a rare adverse event and that periodic monitoring of **liver enzymes**is not useful

- Many subjects with metabolic syndrome have nonalcoholic fatty liver disease (NAFLD) whose enzyme elevations return to normal with TLCs and statins, alone or in combination

Hennekens CH, Lieberman E, Rubenstein M, Hebert P, DeMets D, Pfeffer M: Lipid Modification in the Treatment and Prevention of Cardiovascular Diseases: Emerging clinical and public health challenges. In Handbook of Cholesterol. Ed. Watson RR. AOCS Press, Urbana, IL., 2016, Chapter 9: 155-181. 2008 6(1): 95-107.

STATIN INTOLERANCE: A SCOURGE FOR CLINICIANS AND PATIENTS: MUSCLE SIDE EFFECTS

There remains large discrepancies between randomized evidence and self reports by patients of muscle symptoms

Claims data suggest a positive relationship of statin use with muscle pain but suffer from confounding by indication that is larger than the effect sizes

Claims data, no matter how large, are useful only to formulate, not test hypotheses

If you torture the data enough, they will confess!

Hennekens CH, Lieberman E, Rubenstein M, Hebert P, DeMets D, Pfeffer M: Lipid Modification in the Treatment and Prevention of Cardiovascular Diseases: Emerging clinical and public health challenges. In Handbook of Cholesterol. Ed. Watson RR. AOCS Press, Urbana, IL., 2016, Chapter 9: 155-181. 2008 6(1): 95-107.

Safety Findings in TNT

	No. of patients (%)	
	Atorvastatin 10 mg (n = 5006)	Atorvastatin 80 mg (n = 4995)
Treatment-related myalgia	234 (4.7)	241 (4.8)
Rhabdomyolysis*	3 (0.06)	2 (0.04)

MUSCLE PAIN: HYPOTHESIS ABOUT RANDOMIZED EVIDENCE AND CLINICAL IMPRESSIONS

METEOR: 984 patients with carotid occlusions randomized to rosuvastatin 40mg daily or placebo for 2 years

Significant reduction in progression of atherosclerosis as measured by ultrasound.

1 in 8 patients on rosuvastatin 40mg experienced moderate to severe muscle pain

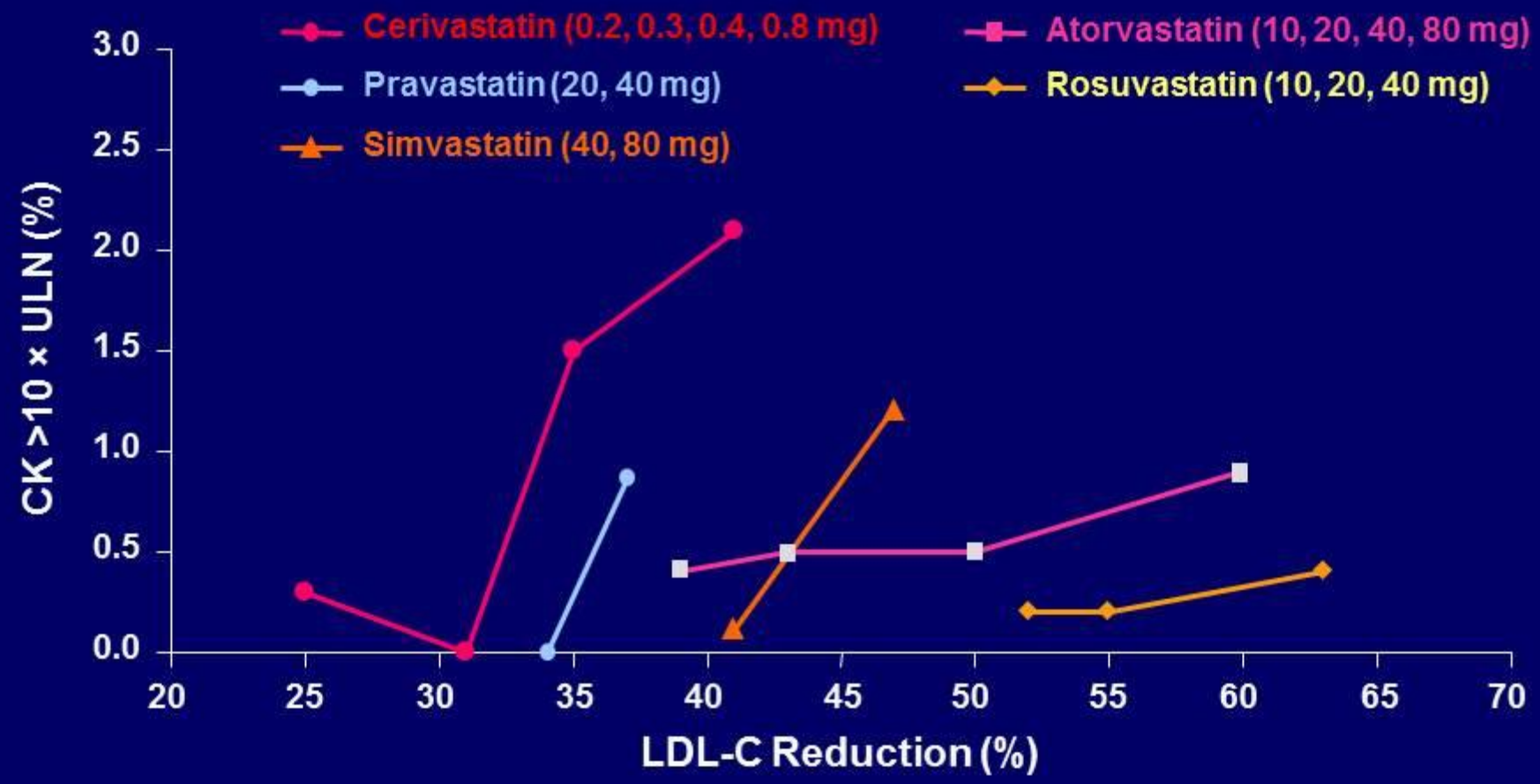
1 in 8 patients on placebo experienced moderate to severe muscle pain

Potential consequences of direct to consumer ads.

Possible analogies with aspirin

Hennekens CH: Statin-induced myopathy: Hypothesis about randomized evidence and clinical impressions AJM, 2009, 122(1):4-5.

Elevations in CK and LDL-C Reduction



Brewer B, *Am J Cardiol.* 2003;92(suppl)23K-29K.

CLINICAL MANAGEMENT OF STATIN INTOLERANCE

- **Stop the statin being prescribed**
- **Switch to a different statin:**

  -Lipophilic statins include atorvastatin,lovastatin, and simvastatin

  -Hydrophilic statins include pravastatin and rosuvastatin
- **Decrease the daily dose (Choose lower doses for Asians and all subjects of smaller stature)**
- **Alternate day dosing**
- **Addition of Coenzyme Q10**

Randomized Patients in Trials of Lipid Modifying Drugs and Clinical Cardiovascular Disease Outcomes

- Statins ~210,000
- Nicotinic Acid 6,249(2,835(CDP)+3414(AIM-HIGH))
- Omega-3-FA 11,324(GISSI PPT) + 18,645 (JELIS) showed a significant 19% added benefit to 10mg pravastatin or 5mg simvastatin
- Fibrates
  - Gemfibrozil 2,531(VA HIT)
  - Fenofibrate 15,373 (9795(FIELD)+5518(ACCORD))
- Ezetimibe 18,144 post ACS patients treated for 6 years showed a significant 6% added benefit to 40 mg simvastatin(IMPROVE-IT)

Hennekens CH, Lieberman E, Rubenstein M, Hebert P, DeMets D, Pfeffer M: Lipid Modification in the Treatment and Prevention of Cardiovascular Diseases: Emerging clinical and public health challenges. In Handbook of Cholesterol. Ed. Watson RR. AOCS Press, Urbana, IL., 2016, Chapter 9: 155-181. 2008 6(1): 95-107.

CLINICAL MANAGEMENT: GENERAL GUIDELINES

- Evidence based doses of a statin should be the first choice of drug therapy for virtually all patients who require pharmacologic therapy for the management of their lipids, including LDL, triglycerides and HDL.
- Statins produce net benefits in secondary and primary prevention. While there is debate about absolute benefit to risk and benefit to cost in low risk primary prevention subjects, women have the same benefit as men at equivalent risks and 40% of US adult men and women have metabolic syndrome.
- Statins should be prescribed as an adjunct , not alternative, to therapeutic lifestyle changes

Hennekens CH, Lieberman E., Rubenstein M., Hebert P., DeMets D., Pfeffer M.: Lipid Modification In Treatment and Prevention of CVD: Clinical and Public Health Challenges. Ch. 9 in Handbook of Cholesterol, 2016.

Sherling D., Perumareddi P., Hennekens CH: Metabolic Syndrome: The new silent killer. JCPT. Published online ahead of print. January 30, 2017.

Pung M, Robishaw J, Pfeffer M, Hennekens CH: Prescription of statins to women pose new clinical challenges, AJM, 2018, in press

CLINICAL MANAGEMENT: GUIDELINES FOR EVIDENCE BASED DOSES OF STATINS

RISK OF PATIENT	ATORVASTATIN	ROSUVASTATIN
HIGH	80MG	40MG
MODERATE	20-40MG	10-20MG
LOW	10-20MG	5-10MG

There is no level of LDL below which there are no incremental benefits

-randomized data primarily in patients treated with statins

-randomized data achieve LDL levels of 50-60mg/dl

-population data suggest LDLs of 50mg/dl

Gitin A, Pfeffer MA, Hennekens CH: The Lower the LDL the better-but how and how much? TCM, 2018, published online ahead of print in March 2018.

PCSK9 (PROPROTEIN CONVERTASE SUBLEXIN/KEXIN TYPE 9) INHIBITORS

PCSK9 IS AN ENZYME ENCODED BY THE PCSK9 GENE IN HUMANS ON CHROMOSOME 1

PCSK9 INHIBITORS ARE MONOCLONAL ANTIBODIES THAT INACTIVATE A SPECIFIC PROTEIN IN THE LIVER THAT MARKEDLY REDUCES LDL

WHEN ADDED TO 80MG ATORVASTATIN IN PATIENTS WHOSE LDLs REMAIN ELEVATED THEY LOWER LDL 60% FURTHER AND REDUCE CLINICAL CVD EVENTS BY 15% OVER 26 MONTHS WHEN GIVEN AS A MONTHLY INJECTION

THE RANDOMIZED SAFETY DATA INCLUDE ABOUT 26 WEEKS OF TREATMENT AND FOLLOW-UP

THE MOST COMMONLY REPORTED SIDE EFFECTS ARE JOINT PAIN, ALLERGIC REACTIONS AND FATIGUE

THE ANNUAL COST, WHICH IS NOT COVERED BY INSURANCE, IS $14,000

Gitin A, Pfeffer MA, Hennekens CH: The Lower the LDL the better-but how and how much? TCM, 2018, published online ahead of print in March 2018.

DIABETES AND CVD

- Diabetes is a major risk factor for CVD and can be a component to the metabolic syndrome which markedly increases risks of CVD
- Diabetes increases risks of CVD about 2-3 fold in men and 4-6 fold in women
- The CARDS trial of diabetics in primary prevention was terminated early due to a statistically extreme 37% reduction in the primary pre-specified outcome
- With respect to statins and diabetes, even assuming causality, the benefits of statins far exceed the potential risks.
- The US National Cholesterol Education Program (NCEP) III elevated diabetes from a major risk factor to a CHD risk equivalent and recommends that all patients with diabetes should be treated as aggressively as survivors of a CVD event (i.e., MI or stroke)

Hennekens CH, Pfeffer M, Newcomer J, Jellinger P, Garber A: Treatment of Diabetes Mellitus: The urgent need for multifactorial Interventions. Am J Manag Care. 2014 May;20(5):357-9.

Hennekens CH, Pfeffer, M, Teng B: Statins and diabetes: Current perspectives and implications for clinicians. AJM, 2017, published online ahead of print.

PREVENTION AND TREATMENT OF DIABETES: MULTIFACTORIAL APPROACH

THERAPEUTIC LIFESTYLE CHANGES (TLC)

- Avoidance and treatment of obesity: In the Nurse's Health Study, compared to women of usual weight the obese women had over 40X the risk of developing type 2 diabetes
- Maintaining an active lifestyle: In the NHS and PHS, compared to those who were inactive, those who walked for 20minutes daily had lower risks of developing diabetes at all levels of body weight

DRUG THERAPIES OF PROVEN BENEFIT:

- Statins, aspirin, ACE inhibitors or ARBS primarily to avoid macrovascular complications in the heart, brain and peripheral arteries
- Control of blood sugar while avoiding hypoglycemia, primarily to avoid microvascular complications in the eyes and kidneys.

Hennekens CH, Pfeffer M, Newcomer J, Jellinger P, Garber A: Treatment of Diabetes Mellitus: The urgent need for multifactorial Interventions. Am J Manag Care. 2014 May;20(5):357-9.

HYPOTHESIS FORMULATION: ADDITIVE BENEFITS OF STATINS AND ASPIRIN ON CVD

ATHEROSCLEROSIS

The principal underlying cause of occlusive CVD events

which is inhibited by statins

THROMBOSIS

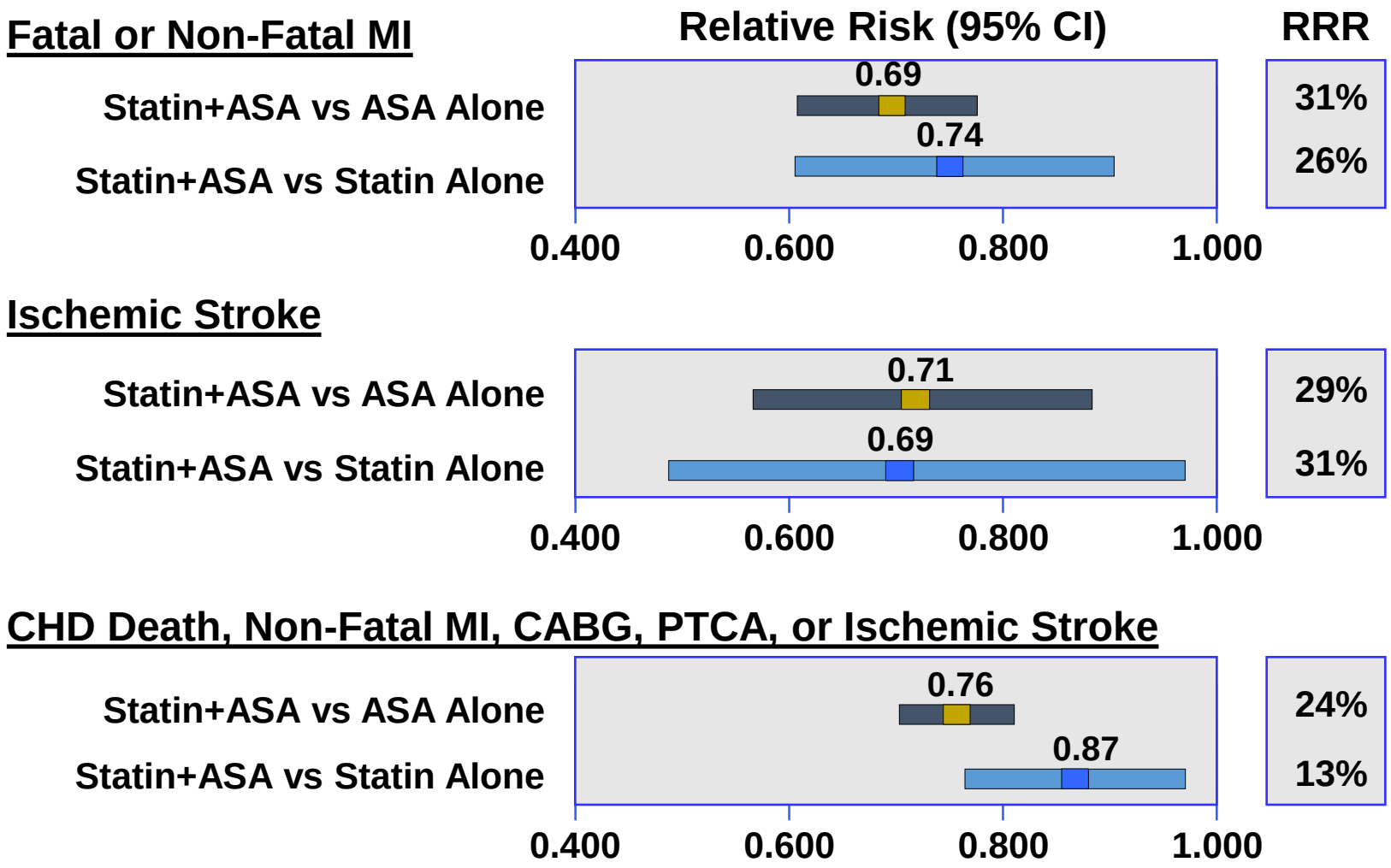
The principal proximate cause of occlusive CVD events

which is inhibited by aspirin

Hebert P, Pfeffer MA, Hennekens CH: Use of Statins and Aspirin to Decrease Risks of CVD J CV Pharm Ther, 7:77-80, 2002

ADDITIHYPOTHESIS TESTING: ADDITIVE BENEFITS

ADDITIVE BENEFITS OF STATINS AND ASPIRINSTATINADDS AND ASPIRIN ON CVD

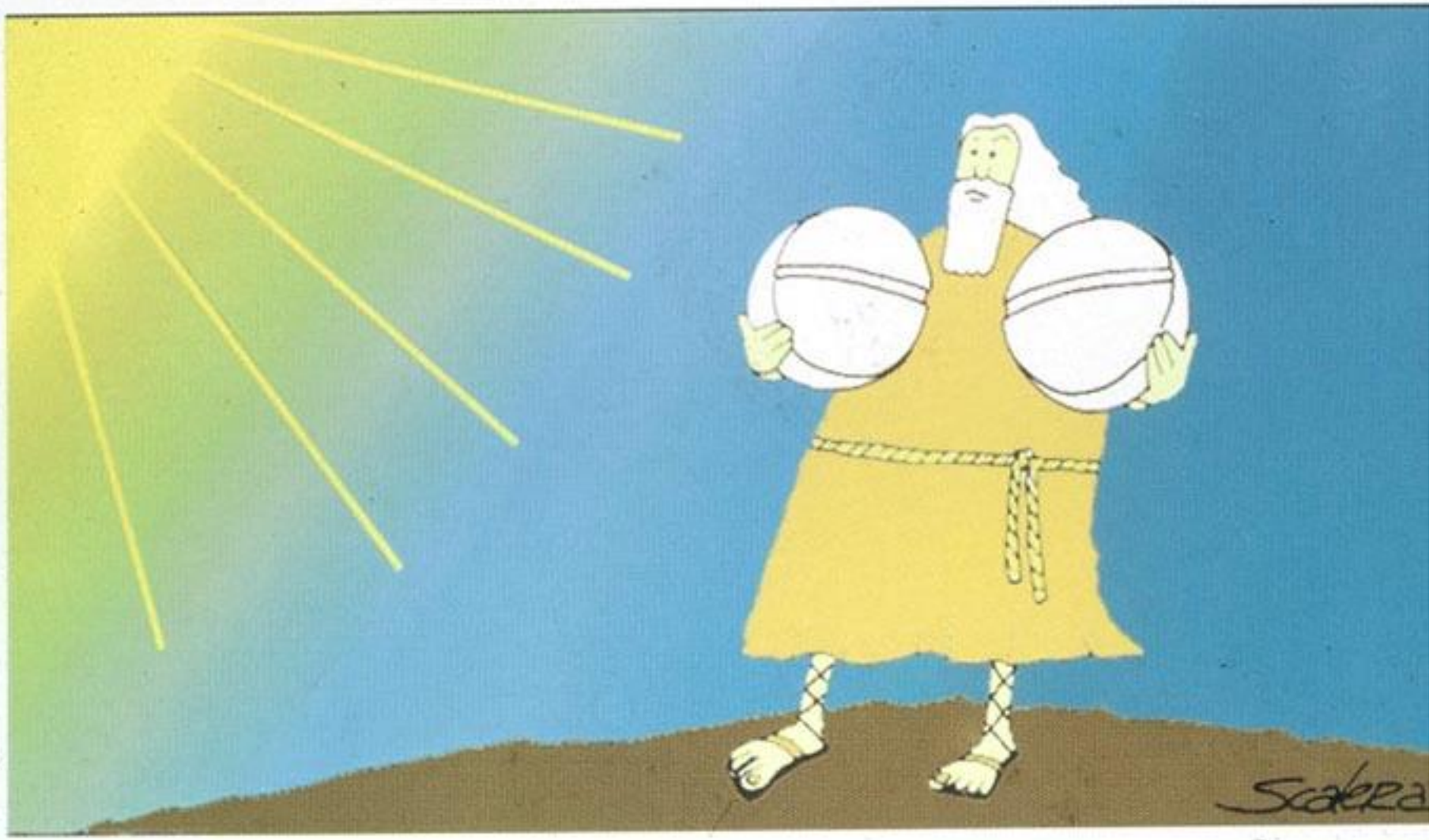


Hennekens CH et al. Arch Int Med 2004; 164:945-948.

MILESTONES FOR ASPIRIN

5th century BC	Hippocrates
1897 AD	Felix Hoffmann/Friedrich Bayer
1900 – Present	Most widely used drug in the world
1971	Sir John Vane

MOSES RECEIVING THE TABLETS FROM GOD

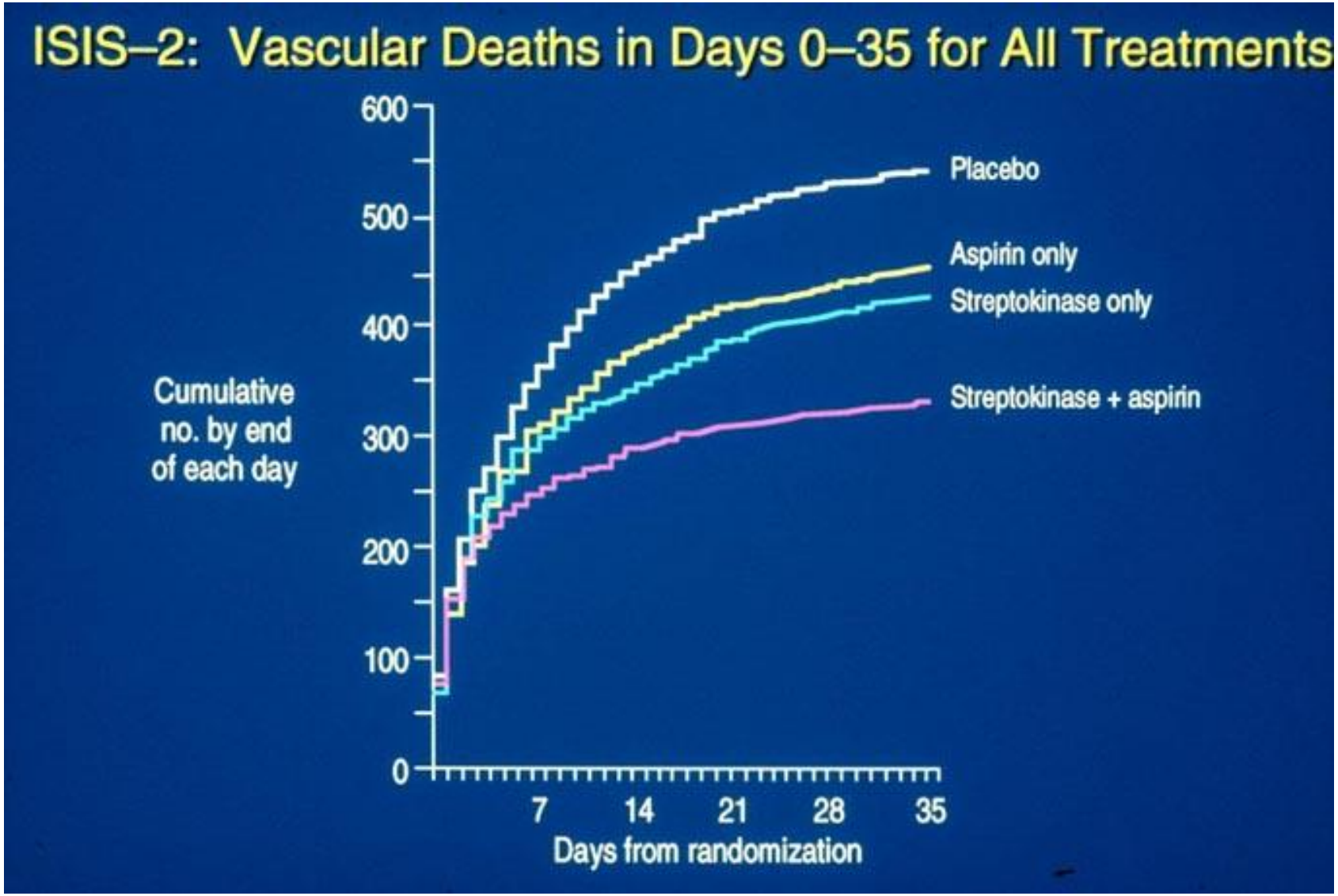


ASPIRIN IN TREATMENT OF CVD: NEEDS FOR WIDER UTILIZATION

Based on the totality of evidence including numerous randomized trials aspirin should be far more widely used in:

- A very wide range of patients who have suffered a prior occlusive vascular event, including myocardial infarction, stroke, transient ischemic attack, as well as stable and unstable angina
- All patients suffering acute myocardial infarction
- All patients suffering acute occlusive stroke

Second International Study of Infarct Survival



ISIS-2 Collaborative Croup Lancet. 1988 Aug 13;332: 349-60.

IN SUBGROUP ANALYSES ASPIRIN WAS OF SIMILAR BENEFIT TO

- Women and Men
- Elderly and Middle aged
- Diabetics and Non-Diabetics
- Hypertensives and Non-hypertensives

SECOND INTERNATIONAL STUDY OF INFARCT SURVIVAL (ISIS-2)

Subgroup Analyses of Aspirin and 35-Day Vascular Mortality

	Vascular Mortality Reduction	P-value
TOTAL	23%	< 0.00001
Patients born under all birth signs except Gemini and Libra	28%	< 0.00001
Patients born under Gemini and Libra	9% ↑	NS

ASPIRIN IN SECONDARY PREVENTION OF CVD

	Risk Ratios (RRs)
Major coronary events	
secondary prevention	**0.80** *(0.72, 0.92)*
Strokes	
secondary prevention	**0.78** *(0.61, 0.99)*
All serious vascular events	
secondary prevention	**0.81** *(0.75, 0.87)*

Antithrombotic Triallists Collaboration. *Lancet.* 2009;373:1849–60

ASPIRIN IN TREATMENT OF CVD: UNDERUTILIZATION AND MISMEDICATION

Of those prescribed aspirin

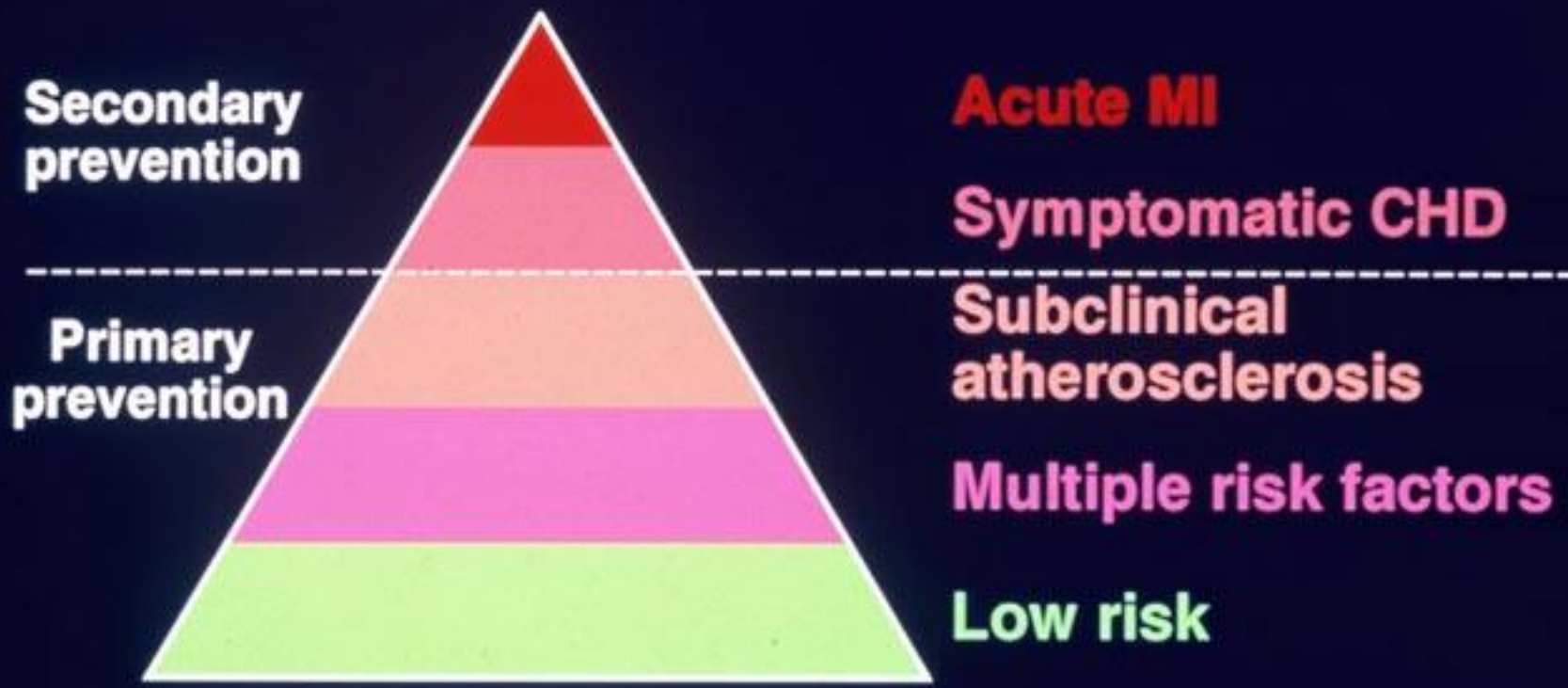
- 50% were taking medication

Of those who thought they were taking aspirin

- 10% were on NSAIDS
- 11% were on acetaminophen
- 21% were mismedicated

(Cook NR, Chae CU, Mueller FB, Landis S, Saks AM, Hennekens CH. Mismedication and underutilization of aspirin in the prevention and treatment of cardiovascular disease. MedGenMed 1999; http://www.medscape.com/medscape/GeneralMedicine/journal/1999/v01.n11/mgm1122.cook/mgm1122.cook-01.html)

Symptomatic CHD: The Tip of the Iceberg



Furberg et al. *Circulation.* 1994;90:1679

ASPIRIN IN SECONDARY AND PRIMARY PREVENTION OF CVD

	Risk Ratios (RRs)
Major coronary events	
secondary prevention	**0.80** *(0.72, 0.92)*
primary prevention	**0.82 (0.75, 0.90)**
Strokes	
secondary prevention	**0.78** *(0.61, 0.99)*
primary prevention	**0.86** ***(0.74, 1.00)***
All serious vascular events	
secondary prevention	**0.81** *(0.75, 0.87)*
primary prevention	**0.88** ***(0.82, 0.94)***

Antithrombotic Triallists Collaboration. *Lancet.* 2009;373:1849–60

ASPIRIN IN SECONDARY AND PRIMARY PREVENTION

- ABSOLUTE BENEFIT
  SECONDARY PREVENTION: HIGH
  PRIMARY PREVENTION: LOW

- ABSOLUTE RISK
  SECONDARY PREVENTION: LOW vs ABSOLUTE BENEFIT
  PRIMARY PREVENTION: SIMILAR vs ABSOLUTE BENEFIT

- NUMBER NEEDED TO TREAT (a function of absolute benefit and absolute risk of the population studied)
  SECONDARY PREVENTION: LOW
  PRIMARY PREVENTION: HIGH

Baigent C, Blackwell L, Buring J, Collins R, Emberson J, Godwin J, Hennekens C, Kearney P, Meade T, Patrono C, Peto R, Roncaglioni R, Zanchetti A. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data. Lancet. 2009;373:1849-1860.

ASPIRIN IN PRIMARY PREVENTION: NEEDS INDIVIDUAL CLINICAL JUDGMENTS

- The Physician's Health Study in 1988 of 22, 071 was the first to demonstrate that aspirin prevents a first MI and virtually all subsequent trials show similar results.
- In meta analyses of trials over 90,000 men and women the 10 year absolute risks are less than 5%
- The absolute benefits are far lower than those in secondary prevention but the side effects, mainly major extracranial bleeding, are the same and are similar to the absolute risks.
- Thus, for apparently healthy men and women the reduction in risk of a first heart attack needs to be weighed against any increase in major bleeds.
- The decision to use aspirin in primary prevention should be an individual clinical judgment by the healthcare provider.
- Aspirin should be considered by the healthcare provider on an individual basis as an adjunct, not alternative, to management of other modifiable major risk factors for cardiovascular disease, especially statins for which the benefits are at least additive to aspirin and the probability of synergy is 0.92.

Baigent C, Blackwell L, Buring J, Collins R, Emberson J, Godwin J, Hennekens C, Kearney P, Meade T, Patrono C, Peto R, Roncaglioni R, Zanchetti A. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data. Lancet. 2009;373:1849-1860.

EFFECTS ON PLATELETS

ASA	Irreversible inhibition for the life of the platelet GI and bleeding risks No liver or renal risks
NSAIDS	Reversible inhibition on vessel wall ▪Possible explanation for lack of CVD risk of long acting naproxen ▪Possible but unproven inhibition of clinical CVD benefits of aspirin by ibuprofen ▪Liver and renal risks More GI risks
COXIBS	Prothrombotic effects: CVD risks of slightly lower magnitude than ibuprofen and diclofenac but higher than naproxen which is neutral Significantly less GI complications than ASA or NSAIDS
Acetaminophen	No anti-inflammatory or effects on platelets but serious liver and renal risks

Rane M, Foster J, Wood S, Hebert P, Hennekens CH: Benefits and Risks of Nonsteroidal Anti-inflammatory Drugs (NSAIDs): Methodologic Limitations Lead to Clinical Uncertainties Ther Inn & Reg Sci, 2018, submitted

POSSIBLE ADDITIONAL BENEFITS OF ASPIRIN

- Prevention of certain cancers, principally colorectal but also possibly breast, prostate, lung, stomach, esophagus and melanoma
- Prevention or delay of loss of cognitive function with aging or Alzheimer's disease

Hennekens CH, Schuttenberg N, Baigent C, Pfeffer MA: Adjunctive Drug Therapies in Primary Prevention, Chapter in Primary Care Clinics in Office Practice, 2018, in press
.

Sturmer T, Glynn RJ, Field TS, Taylor JO, Hennekens CH. Aspirin use and cognitive function in the elderly. Am J Epidemiol 1996; 143:683-91.

CLINICAL CONSIDERATIONS

Blood cholesterol
10% ↓ = 20%-30% ↓ in CHD

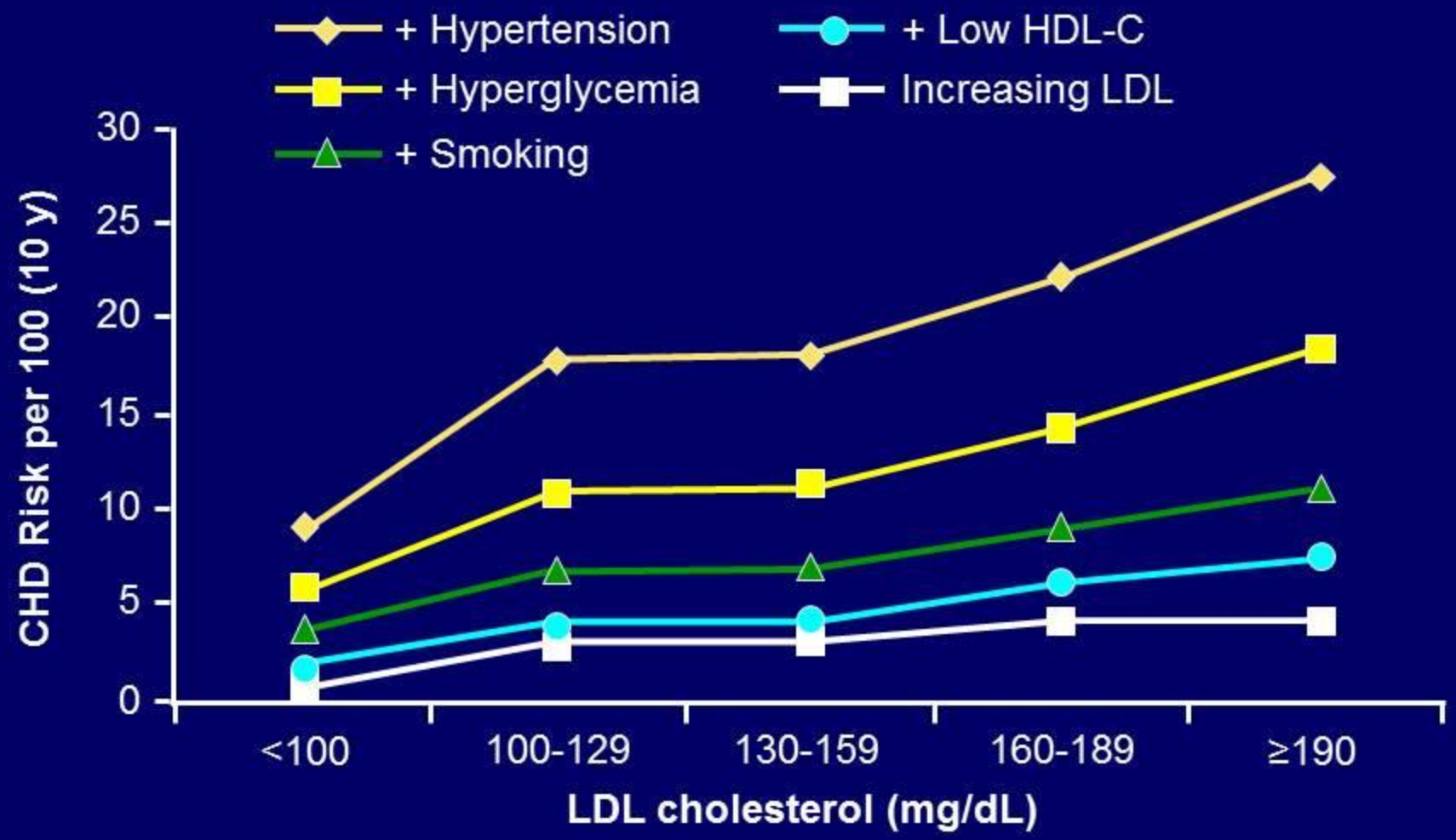
High blood pressure
5-6 mm Hg ↓ = 42% ↓ in Stroke
= 16% ↓ in CHD

Cigarette smoking
Cessation = 50%-70% ↓ in CHD

Body weight
BMI<25 vs BMI>27 = 35%-55% ↓ in CHD

Physical activity
20-minute brisk walk daily = 35%-55% ↓ in CHD

Importance of Assessing Multiple Risk Factors for CHD



Assessing CHD Risk in Men

Age Years	Pts
20-34	-9
35-39	-4
40-44	0
45-49	3
50-54	6
55-59	8
60-64	10
65-69	11
70-74	12
75-79	13

Systolic Blood Pressure	Untreated	Treated
<120	0	0
120-129	0	1
130-139	1	2
140-159	1	2
≥160	2	3

57 YO male
BP 152/94
T-Chol 264
TG 350
HDL-C 32
LDL-C 162
Nonsmoker
No DM
No CHD

Pts	10-Yr CHD Risk
<0	<1%
0	1%
1	1%
2	1%
3	1%
4	1%
5	2%
6	2%
7	3%
8	4%
9	5%
10	6%
11	8%
12	10%
13	12%
14	16%
15	20%
16	25%
≥17	≥30%

HDL-C (mg/dL)	Pts
>60	-1
50-59	0
40-49	1
<40	2

Total Cholesterol (mg/dL)	20-39	40-49	50-59	60-69	70-79
<160	0	0	0	0	0
160-199	4	3	2	1	0
200-239	7	5	3	1	0
240-279	9	6	4	2	1
3280 11	8	5	3	1	
Cigarette Smoking					
Nonsmoker	0	0	0	0	0
Smoker	8	5	3	1	1

ATP III. *JAMA*. 2001;285:2486-2497.

ADDITIONAL NEEDS FOR ASTUTE CLINICAL JUDGMENTS

- Most algorithms for risk calculators are based on the Framingham Risk Score so risks of Blacks and Hispanics are underestimated

- Most algorithms for risk calculations do not include:
  - BMI
  -Level of physical activity
  - Family history of premature events
    -<55 in male first degree relatives
    -<65 in female first degree relatives

Family history of premature events will roughly double the risk score independent of the risk factors of the patient.

Hennekens CH, Lieberman E, Rubenstein M, Hebert P, DeMets D, Pfeffer M: Lipid Modification in the Treatment and Prevention of Cardiovascular Diseases: Emerging clinical and public health challenges. In Handbook of Cholesterol. Ed. Watson RR. AOCS Press, Urbana, IL., 2016, Chapter 9: 155-181.

A MAJOR ISSUE FOR HEALTHCARE PROVIDERS AND PATIENTS

Unfortunately, for healthcare providers and their patients, most patients prefer the PRESCRIPTION of pills to the PROSCRIPTION of harmful lifestyles.

Charles H. Hennekens, MD

New York Times Magazine

New Yorker Magazine 1988.

"Take an aspirin every day, but before you swallow it, take it out for a five-mile walk."

There is ABSOLUTELY no substitute for astute clinical judgment.

Randomized trials are necessary to develop guidelines.

Guidelines are of crucial importance to provide guidance but are not the sole factor in astute clinical judgment.

The responsible clinician knows more about his or her patient than anyone else in the entire world