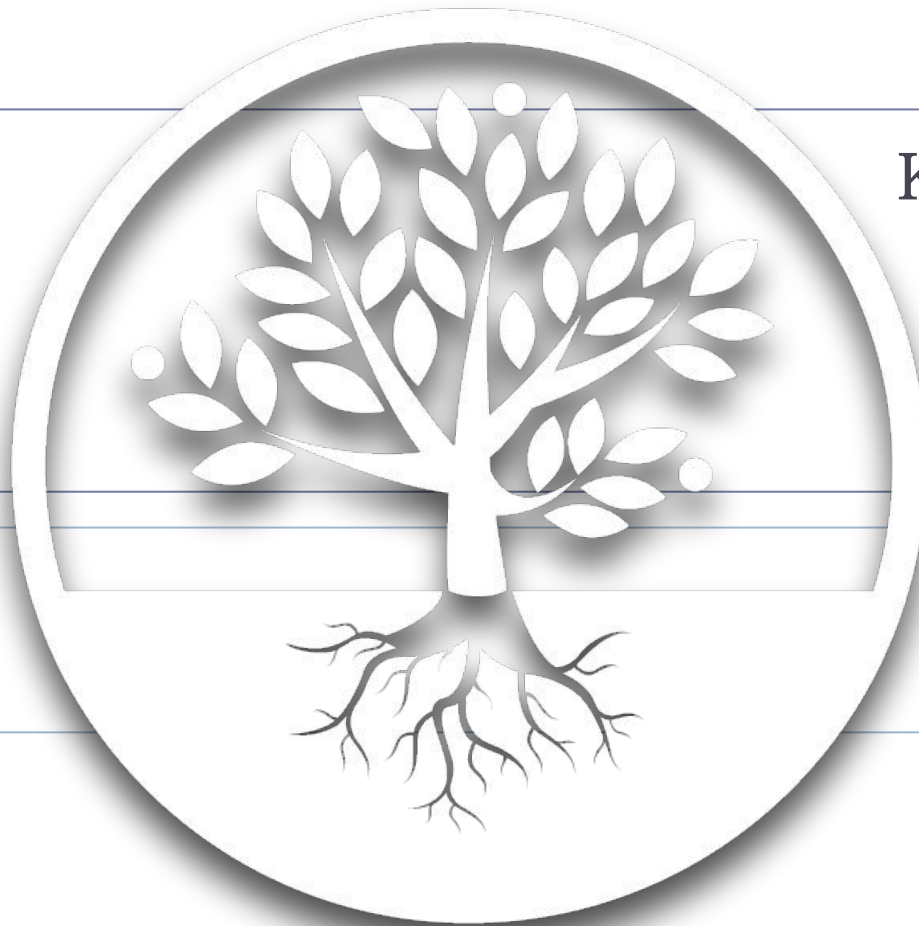


Preventive Care Anyone?

“Prevention is better than cure”

Is this true?



Kelly W. Jones, Pharm.D., BCPS
THE Pharmacy
kjones@thepharmacyrx.com



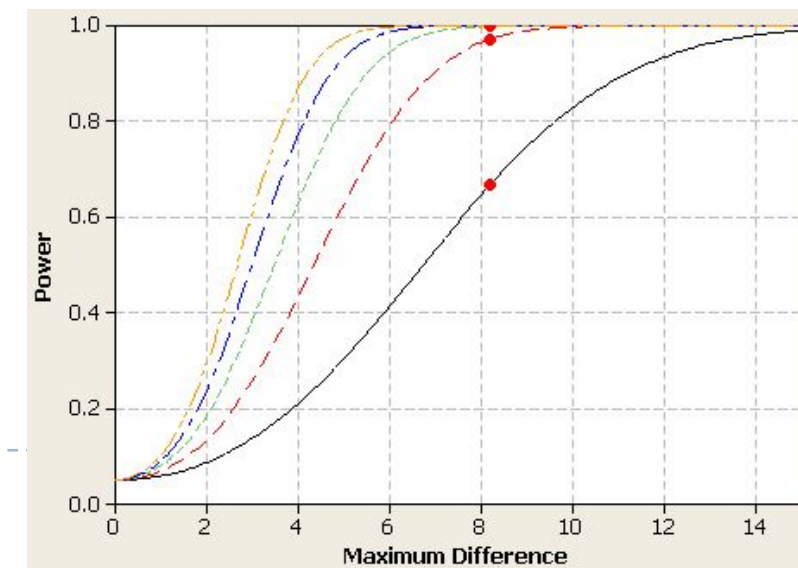
THE PHARMACY





DISCLAIMER

- I have no conflict of interest relating in the material covered today
- I do not serve on any speaker bureau
- I do not have any personal grants concerning the area of discussion today
- Some lame jokes included
- Lots of brand names mentioned, but no financial interest in any of them
- Promise: no ANOVA regression curves



Objectives - Pharmacists

- Define preventive medicine
- Discuss the risk benefit of preventive medicine
- Discuss the difference between primary and secondary prevention
- Understand the new primary prevention data concerning aspirin and cardiovascular risk (ARRIVE, ASCEND, ASPREE trials)
- Discuss the differences in primary and secondary prevention utilizing examples in cholesterol and hypertension research
- Discuss the use of vitamin D in preventive medicine



Don't miss this read!!

Foreword by Rod Dreher

THE RISE AND TRIUMPH *of the* MODERN SELF



Cultural Amnesia, Expressive Individualism,
and the Road to Sexual Revolution

CARL R. TRUEMAN

Popular Prevention Quotes

- The phrase '**prevention is better than cure**' is often attributed to the Dutch philosopher Desiderius Erasmus on or around 1500
- “An ounce of prevention is worth a pound of cure.”
— **Benjamin Franklin**
- “There is no medicine you can take that will replace what you can do for your own health.”
— **Aarti Patel** (from book called The Art of Health)
- “The Centers for Disease Control and Prevention (CDC) is a COVID-19 disaster.”
— **Steven Magee**



Popular Prevention Quotes

- “You can't prevent what you can't predict.”
– **K.M. Mac Aulay**
- “Pragmatism is good prevention for problems.”
– **Amit Kalantri**
- Pragmatism - truth being what works – success is therefore more important than truth (Chalcedon Report #102, 1974)



Preventive Medicine

- **Preventive medicine** is a **medical** specialty recognized by the American Board of **Medical** Specialties (ABMS), which focuses on the health of individuals and communities.
- The goal of **preventive medicine** is to promote health and well-being and prevent disease, disability and death.

Primary Vs Secondary Prevention

- Are we good at preventing disease?
- One issue is understanding disease vs dis-ease
- Primary Prevention
 - Primary prevention aims to prevent disease or injury before it ever occurs
- Secondary Prevention
 - Secondary prevention aims to reduce the impact of a disease or injury that has already occurred



Levels of Prevention Strategies



Disease
Onset

Clinical
Diagnosis

Primary

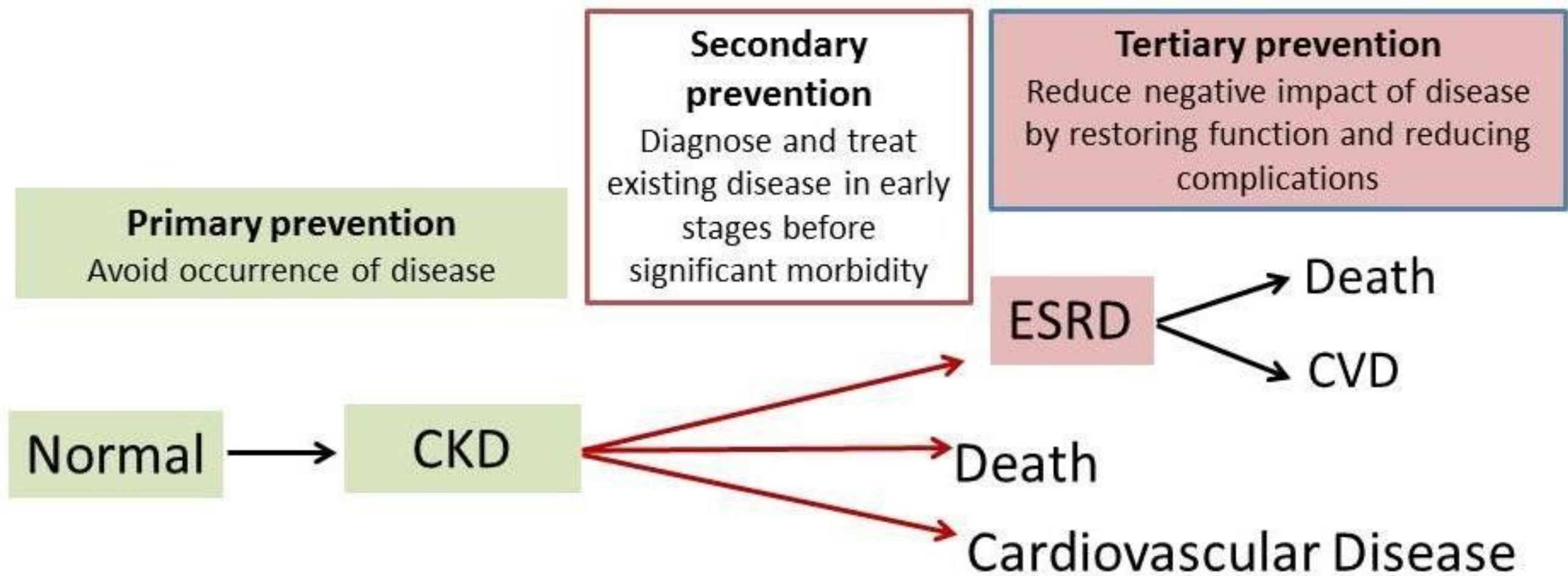
- Avoid development of a disease
- Remove Risk Factor

Secondary

- Early Detection
- Treatment
- Prevent Progression

Tertiary

- Reduce Complications of established disease



Secondary Prevention Trial

- **Randomized Trial of Estrogen Plus Progestin for Secondary Prevention of Coronary Heart Disease in Postmenopausal Women**
 - Stephen Hulley, MD; Deborah Grady, MD; Trudy Bush, PhD; Furberg, MD, PhD; David Herrington, MD; Betty Riggs, MD; Eric Vittinghoff, PhD; for the Heart and Estrogen/progestin Replacement Study (HERS) Research Group
- *JAMA*. 1998;280(7):605-613. doi:10.1001/jama.280.7.605



HERS Trail

- Study Type: POEM
 - Trial Design: randomized, double-blinded, placebo-controlled, multicenter (20), Prempro® (2.5 mg), follow-up visits every 4 mths
 - Patients: 2763 patients, mean age = 67, 89% white, 80% completed high school,
 - Purpose: Analyze the rate of cardiovascular events among postmenopausal women with coronary disease.
 - Inclusion: postmenopausal women < 80 with established CAD, no hysterectomy, no natural menses for 5 years, at least 55 years old,
 - no natural menses for 1 year with suitable levels
-



What were the results?

- Primary outcome: CHD death and nonfatal MI

Outcome	P value	ARI	NNH
□ Year 1-4	NS		
□ Year 1	.01	1.4%	71
□ Year 2	NS		
□ Year 3	NS		
□ Year 4 & 5	NS		
□ All secondary events	NS		

Harm Outcomes

Harm Outcomes	P value	ARI	NNH
□ Total death	NS		
□ DVT	.004	1.2	83
□ any thromboembolic	.002	1.6	63
□ Gallbladder disease	.05	1.6	63



Primary Prevention

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812

AUGUST 7, 2003

VOL. 349 NO. 6

Estrogen plus Progestin and the Risk of Coronary Heart Disease

JoAnn E. Manson, M.D., Dr.P.H., Judith Hsia, M.D., Karen C. Johnson, M.D., M.P.H., Jacques E. Rossouw, M.D., Annlouise R. Assaf, Ph.D., Norman L. Lasser, M.D., Ph.D., Maurizio Trevisan, M.D., Henry R. Black, M.D., Susan R. Heckbert, M.D., Ph.D., Robert Detrano, M.D., Ph.D., Ora L. Strickland, Ph.D., Nathan D. Wong, Ph.D., John R. Crouse, M.D., Evan Stein, M.D., and Mary Cushman, M.D., for the Women's Health Initiative Investigators*

METHODS

The WHI included a randomized primary-prevention trial of estrogen plus progestin in 16,608 postmenopausal women who were 50 to 79 years of age at base line. Participants were randomly assigned to receive conjugated equine estrogens (0.625 mg per day) plus medroxyprogesterone acetate (2.5 mg per day) or placebo. The primary efficacy outcome of the trial was CHD (nonfatal myocardial infarction or death due to CHD).

Risks and benefits of estrogen plus progestin in healthy postmenopausal women Women's Health Initiative (WHI Trial)

JAMA 2002;288(3):321-33 (July 17)

Study Type: POEM

Purpose: Does continuous-combined hormone replacement therapy reduce the incidence of heart disease, breast cancer, colorectal cancer and fractures in postmenopausal medicine?

Study Duration: 8.5 year trial, study stopped early, follow-up time was 5.2 years; NNTSFSC = $373,032/16,608 = 22$

Trial Design: randomized-controlled, primary prevention trial, multicenter (40 US centers), intention-to-treat

Drug: 0.625 conjugated equine estrogen + 2.5 mg medroxyprogesterone

Patients: 16,608 patients, mean age 63 +/- 7 yrs (~50% 60-69, only 21% 70-79), 84% white, ~74% were never user's of HRT; 70% HRT user's have been using < 5 yrs; BMI = 28.5; BP = 128/76; 50% never smoked; 90% had one or more pregnancies; 4% diabetic; 36% were being treated for HTN; 13% for treating cholesterol; 7% using a statin; 20% aspirin user's; History: MI (1.6%), Angina (2.8%), CABAG/PTCA (1.1% placebo grp verses 1.5% in placebo grp, $p > .04$), stroke (<1%); DVT/or PE (<0.8%); Relative with breast cancer (~16%); fracture at the age ≥ 55 (14%); no difference in the risk of breast cancer in each group (Gail model assessment)

What were the results?

Outcomes	Estrogen + progestin	placebo	ARI	NNH	10,000 pat-yrs
Cardiovascular					
CHD total	0.37%	0.30%	0.07%	1429	7
nonfatal MI	0.30%	0.23%	0.07%	1429	7
Stroke	0.29%	0.21%	0.08%	1250	8
DVT	0.26%	0.13%	0.13%	769	13
PE	0.16%	0.08%	0.08%	1250	8
Total CV dz	1.57%	1.32%	0.25%	400	25
Cancer					
Invasive breast	0.38%	0.30%	0.08%	1250	8
Colorectal	0.10%	0.16%	0.06%	1667	6 (NNT)
Fractures					
Hip	0.10%	0.15%	0.05%	2000	5 (NNT)
Vertebral	0.09%	0.15%	0.06%	1667	6 (NNT)
Total	1.47%	1.91%	0.44%	227	44 (NNT)



Problems with Preventive Care

- Overdiagnosis
 - “Making people sick in the pursuit of health”
- “Medical histories alert doctors before they get sick”
- We change the numbers (lab or BP) to pick up more patients with the potential issue – we often find that we have to be careful not to hurt the patient
- We pick up things that may never matter
 - They never progressed to sickness
 - They die of something else before the issue progresses to cause a problem

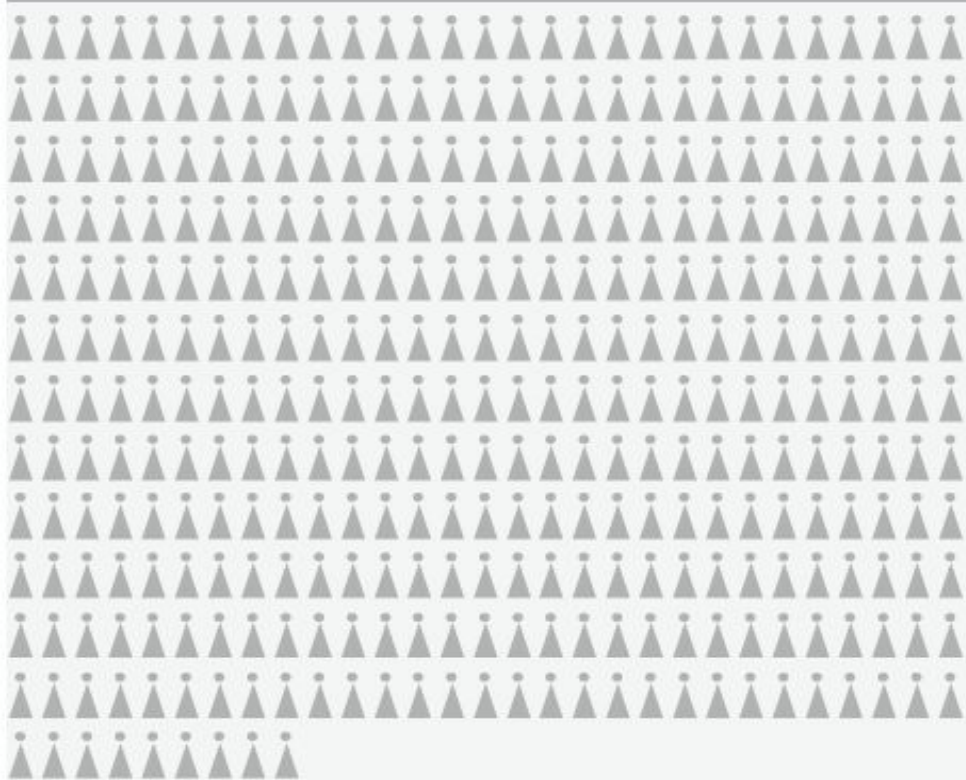


Problems with Preventive Care

- **Overdiagnosis**
 - “Making people sick in the pursuit of health”
- “Medical histories alert doctors before they get sick”
- We change the numbers (lab or BP) to pick up more patients with the potential issue – we often find that we have to be careful not to hurt the patient
- We pick up things that may never matter
 - They never progressed to sickness
 - They die of something else before the issue progresses to cause a problem

Estimates of Benefits and Harms of Annual Mammography Screening Over 10 Years of 10 000 50-Year-Old Women

3568 will have normal mammogram results for all 10 years



6130 will have at least 1 false-positive result during the 10 years



302 will be diagnosed as having breast cancer

173 will survive breast cancer regardless of screening

10 deaths averted

57 overdiagnoses

62 deaths despite screening



940 will have an unnecessary biopsy

Another Book to Recommend

OVER- DIAGNOSED

MAKING PEOPLE SICK IN
THE PURSUIT OF HEALTH

DR. H. GILBERT WELCH,

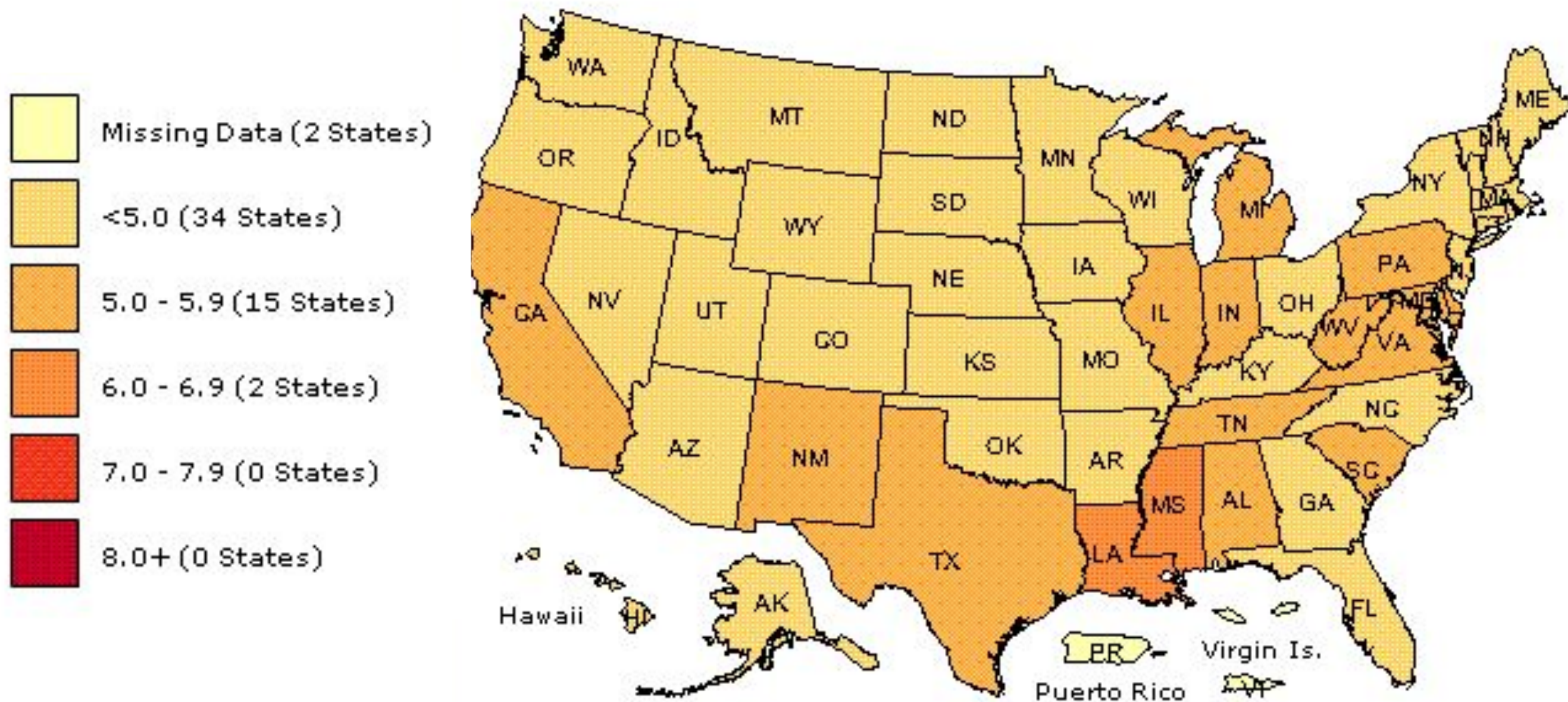
DR. LISA M. SCHWARTZ, AND DR. STEVEN WOLOSHIN

Problems with Preventive Care

- Overdiagnosis
- “Making people sick in the pursuit of health”
- “Medical histories alert doctors before they get sick”
- We change the numbers (lab or BP) to pick up more patients with the potential issue – we often find that we have to be careful not to hurt the patient
- We pick up things that may never matter
 - They never progressed to sickness
 - They die of something else before the issue progresses to cause a problem

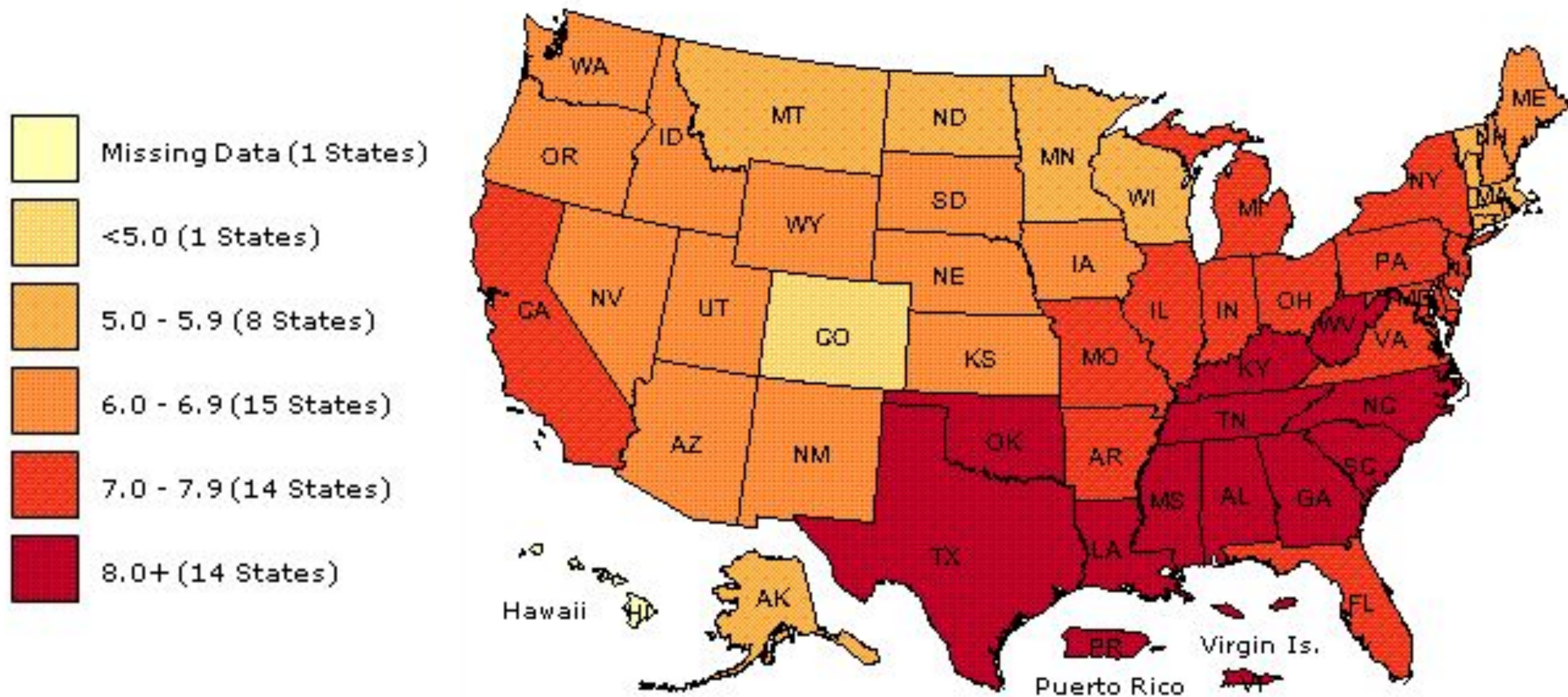
Age-Adjusted Percentage of Adults with Diagnosed Diabetes By State, 1995:

- Data from the National Diabetes Surveillance System -



Age-Adjusted Percentage of Adults with Diagnosed Diabetes By State, 2005:

- Data from the National Diabetes Surveillance System -



2 Types of Prevention

- Early Diagnosis – what a test will tell you to get ahead of the symptoms
 - Looking hard for things to be wrong
 - This can lead to over diagnosis
- Health Promotion – is what your Aunt Betty would tell you
 - Get rest
 - Eat the right foods
 - Go play outside
 - Don't ever smoke
 - Do something that you think is positive for yourself



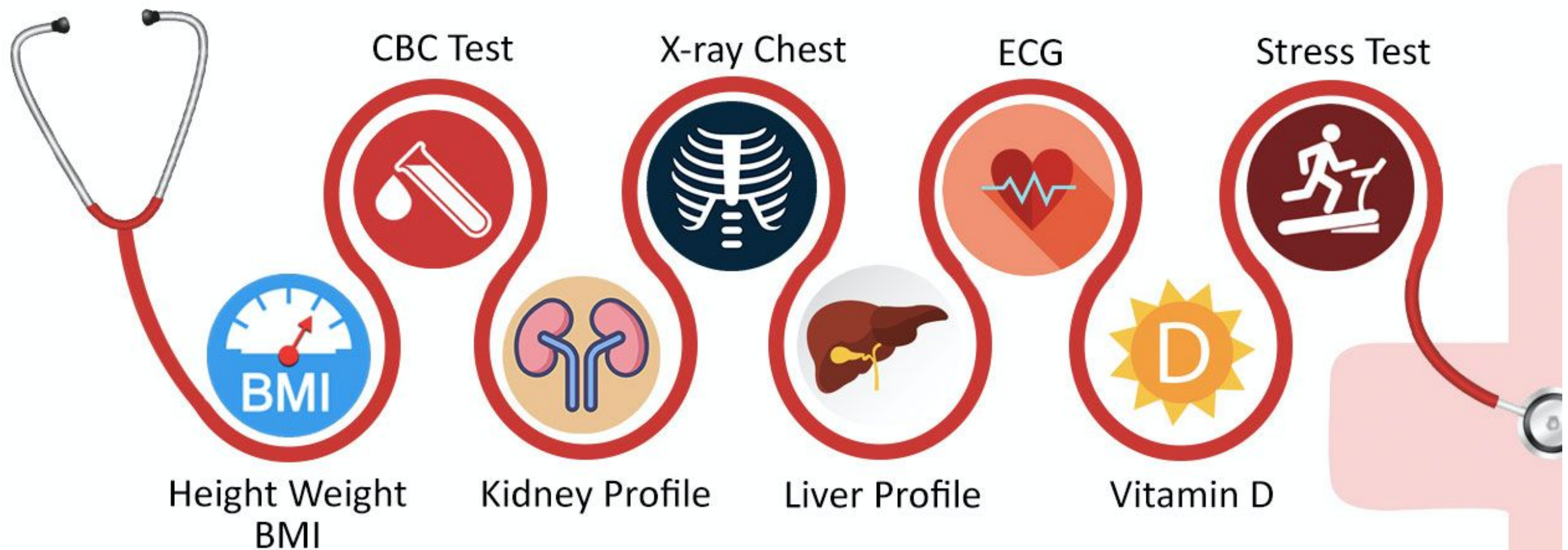
Biblical View of Preventive Medicine?

- And when Jesus heard it, he said to them, “Those who are well have no need of a physician, but those who are sick. I came not to call the righteous, but sinners.”
 - Mark 2:17
- Very traditional view
- Where did the idea of preventive medicine come from?



Would you believe High Blood Pressure?

Preventive Health Check Up



Picture is used only for example purpose

- 1905, Korotkoff described the systolic and diastolic sound he heard with the stethoscope
- Hypertension was described in two ways

1. White hypertension

- It was an adaptive process for pathology in the kidney

2. Red hypertension

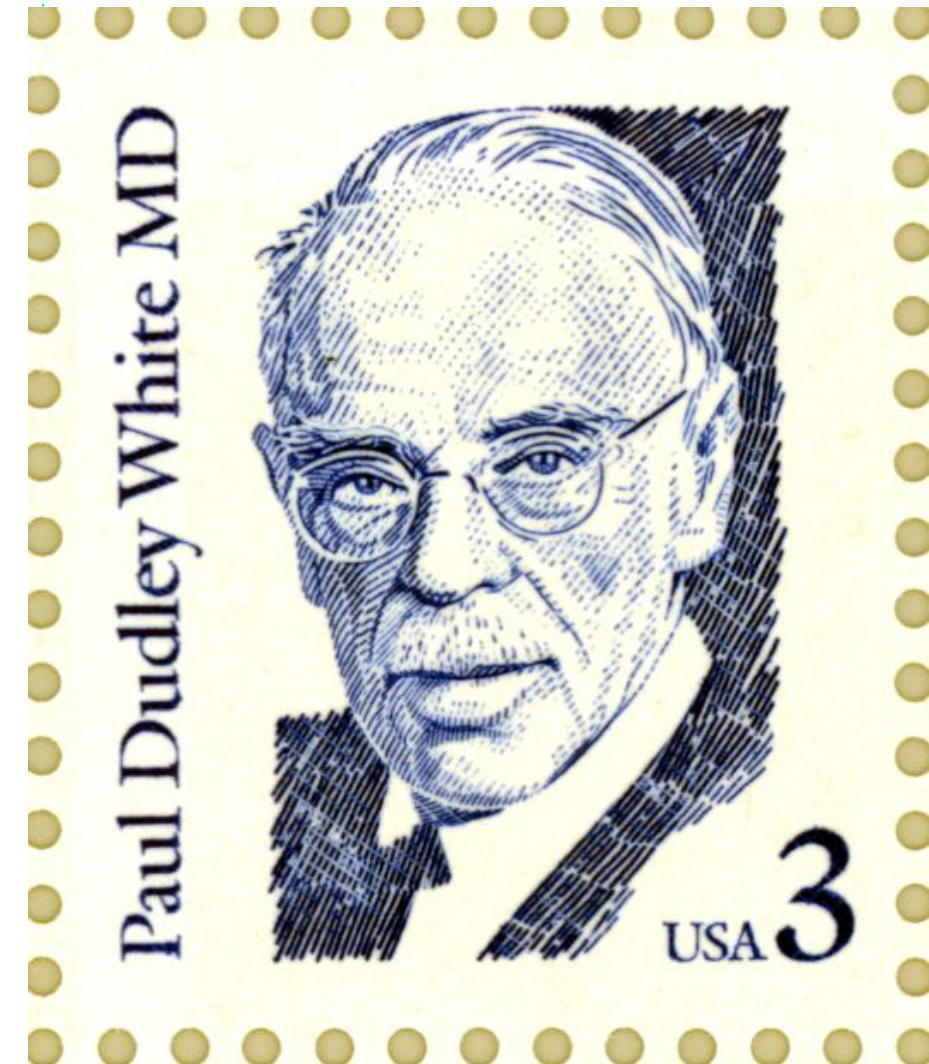
- It was an adaptive process for pathology in the blood vessels

History



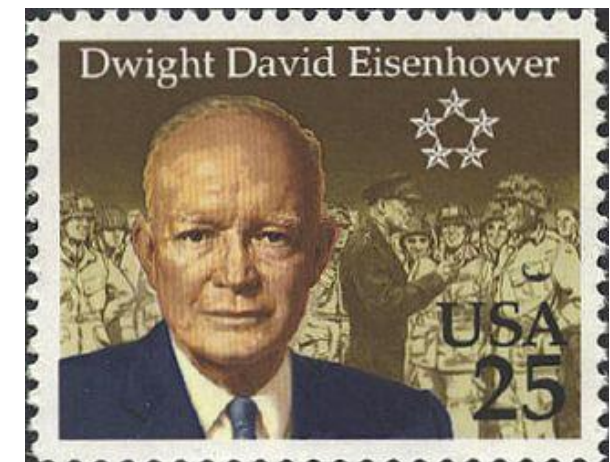
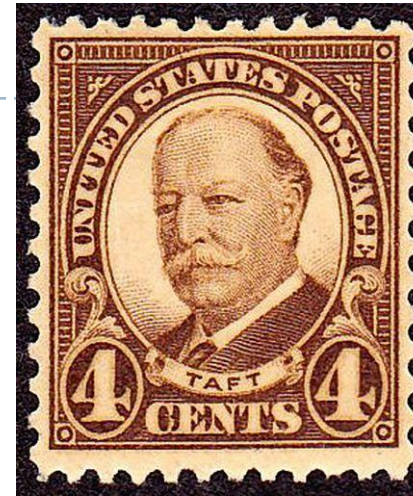
- 1937, Paul Dudley White
- He cared for many US Presidents
- “The treatment of hypertension itself is a difficult and almost hopeless task in the present state of knowledge, and in fact for aught we know... the hypertension may be an important compensation mechanism which should not be tampered with, even were it certain that we could control it.”

History



A Tale of 3 Presidents

- Howard Taft in 1910
- Franklin Delano Roosevelt or FDR
- Died at age 63 from a massive cerebral bleed in Warm Springs Georgia on April 12, 1945
- Dwight D. Eisenhower
- The heart attack heard all over the world!
- Dr. White presented his case publically at AHA Annual meeting in New Orleans in 1955.
- He had 8 heart attacks and died of heart failure on March 28, 1969 at the age of 78, fourteen years after his first heart attack.



- **The Framingham Study** resulted from:
- Post WWII reaction to increasing prevalence of heart disease
 - Fueled by media, President Roosevelt's death and the win against infectious disease!
 - President Roosevelt dedicated the NIH a new building in Bethesda, MD
 - Project of the NIH and NHLBI (was National Heart Institute at the time of the study)
- Just after WWI, the effort was to control infection
 - Sanitation
 - Penicillin for pneumonia
 - TB programs

**The Monument to
all this....**



▶ **President Roosevelt, NIH dedication, October 31, 1940**

Early Approach to Therapy

- Early treatment pioneers – 1940's
- Walter Kempner (Duke University)
 - Developed the Kempner diet – rice, fruits, low in sodium, fat, protein and calories
- Reginald Smithwick (Boston University)
 - Developed a surgical approach - lumbodorsal sympathectomy and splanchnicectomy, etc
- Robert Wilkins (Boston University)
 - Medication approach – he studied many of Smithwick's patients
 - He helped NIH and Squibb Institute to develop medications



Early Approach to Therapy

Wilkins was joined later by Edward Freis, his research fellow

Freis was later recruited to Georgetown VA hospital where he conducted the famous two VA Cooperative Trials

The VA Cooperative Study, 1967

Cohort	143 men
Mean age	51 years
Eligibility	Diastolic BP 115-129 mmHg
Design	Double blind; placebo control
Therapy	HCTZ, reserpine, hydralazine
Duration	1.5 years
BP change	-43/30 mmHg

HCTZ=hydrochlorothiazide

VA Cooperative Study Group. JAMA. 1967;202:1028-1034.

www.hypertensiononline.org

The VA Cooperative Study, 1967: Assessable Morbid/Fatal Events

	Placebo n=70	Active Rx* n=73
Accelerated hypertension	12	0
Stroke	4	1
Coronary event	2	0
CHF	2	0
Renal damage	2	0
Deaths	4	0

*P<0.001 active drug therapy vs placebo

VA Cooperative Study Group. JAMA. 1967;202:1028-1034.

www.hypertensiononline.org

The VA Cooperative Study, 1970

Cohort	380 men
Mean age	50 years
Eligibility	Diastolic BP 90-114 mmHg
Design	Double blind; placebo control
Therapy	HCTZ, reserpine, hydralazine
Duration	5.5 years (mean=3.8 yrs)
BP change	Diastolic BP -19 mmHg

VA Cooperative Study Group. JAMA. 1970;213:1143-1152.

www.hypertensiononline.org

II – trial was longer and involved lower diastolic BP for entry

The VA Cooperative Study, 1970: Assessable Morbid/Fatal Events

	Placebo n=194	Active Rx* n=186
Accelerated hypertension	4	0
Stroke	20	5
Total coronary event	13	11
Fatal coronary event	11	6
Congestive heart failure	11	0
Renal damage	3	0
Deaths	19	8

*P<0.001 active drug therapy vs placebo

VA Cooperative Study Group. JAMA. 1970;213:1143-1152.

www.hypertensiononline.org

Mary Lasker

Heis later won the Lasker Award for clinical research in 1971

Mary Lasker was so impressed with the research that she pushed the Secretary of Health, Education, and Welfare to establish a national program for hypertension education. In 1972, the National High Blood Pressure Education Program was developed by the NIH, which ultimately led to JNC reports. The first publication was in 1976.



Powerful Influence

- Now you can see where this all began. You need to go to the physician even if you feel well.
- This has led to:
 - Preventive care
 - Screening
 - Improved research to detect small differences to help make treatment decisions
 - Randomized controlled trials became the battlefield
 - Clinical impressions and clinical experience was sacrificed on the alter of clinical significance
 - Much more.....





Felix Hoffmann, a chemist at Bayer acetylated the phenol group of the willow bark structure of salicin to get Aspirin® or acetylsalicylic acid, August 10, 1897

Aspirin for Primary Prevention?
Shared Decision

“An ASA a day keeps the doctor away”?

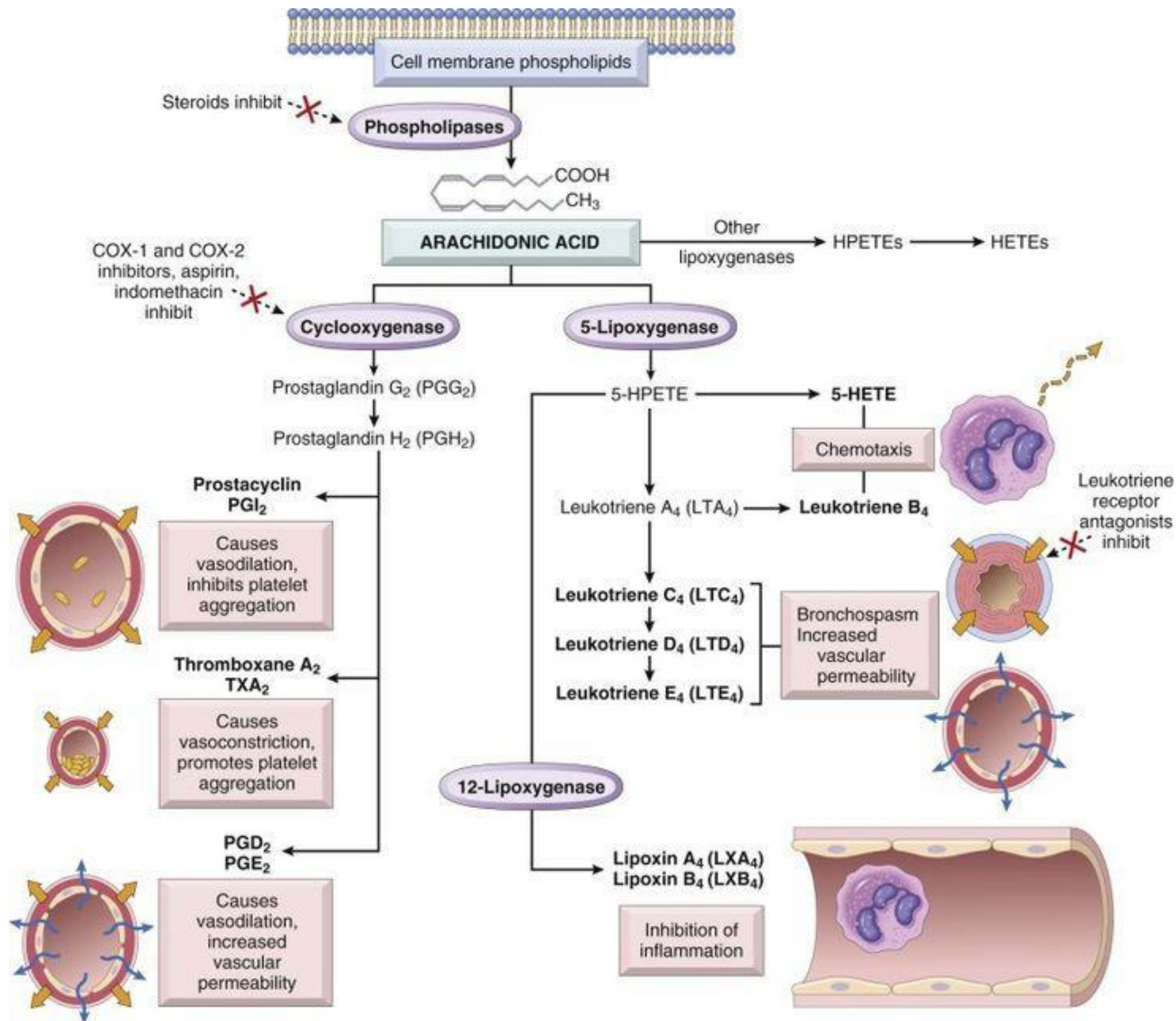
- **USPSTF 2016:** age 50 to 59 years with $\geq 10\%$ 10-year risk of CV disease, AND not at increased risk of bleeding, AND with a life expectancy of at least 10 years, AND willing to take low-dose aspirin for at least 10 years. Also consider for age 60 to 69 years with $> 10\%$ 10-year risk of CV disease
 - **ACCP 2012:** all persons age 50 and older
 - **AHA/ASA (2014):** adults with a 10-year CVD risk $> 10\%$ (i.e., potential benefit is high enough to outweigh potential aspirin risks); women with stroke risk high enough that aspirin benefits outweigh risks (to prevent stroke); or patients with chronic renal disease with eGFR 30 to 45 mL/min/1.73 m² (to prevent stroke)
 - **ADA (2018):** consider for patients with diabetes and increased CV risk (e.g., patients ≥ 50 years of age with at least one additional major risk factor: family history of premature atherosclerotic CV disease, hypertension, dyslipidemia, smoking or albuminuria) who are not at increased risk of bleeding
 - **CCS (Canada, 2011):** not routinely recommended in patients without evident vascular disease. Consider for select patients (e.g., multiple risk factors, radiographic evidence of vascular disease, elevated CRP)
-



Aspirin Dosing

- **USPSTF** (2016 recommendations): 81 mg daily
- **AHA/ASA**: dose not explicitly stated except that 81 mg daily or 100 mg every other day suggested for preventing first stroke in women
- **ADA**: 75 to 162 mg daily
- **ACCP**: 75 to 100 mg daily
- **CCS**: 75 to 162 mg daily





ASPREE Trial

- ASPREE Trial - primary prevention
- N = 19,114, 4.7 year follow-up
- Effect of aspirin on disability-free survival in healthy elderly
- USA and Australia, >65 yrs with no history of CV disease, AD, or physical disability
- ASA dose was 100 mg (EC) vs placebo for 5 years
- Patients taking antiplatelets or anticoagulants were excluded, as were patients with BP \geq 180/105 mmHg
- Patients were allowed short-term use of NSAIDs at the lowest dose
- Eleven percent of enrollees had diabetes

Table 1. Demographic Characteristics and Illness History of the Participants at Randomization, According to Prespecified Subgroups and Trial Group.*

Characteristic	Aspirin (N=9525)	Placebo (N=9589)
Age — no. (%) [†]		
65–73 yr	4719 (49.5)	4823 (50.3)
≥74 yr	4806 (50.5)	4766 (49.7)
Female sex — no. (%)	5373 (56.4)	5410 (56.4)
Country — no. (%)		
Australia	8322 (87.4)	8381 (87.4)
United States	1203 (12.6)	1208 (12.6)
Race or ethnic group — no. (%) [‡]		
White		
Australia	8169 (85.8)	8193 (85.4)
United States	539 (5.7)	549 (5.7)
Black	451 (4.7)	450 (4.7)
Hispanic	240 (2.5)	248 (2.6)
Other	126 (1.3)	149 (1.6)
Body-mass index [§]	28.1±4.8	28.1±4.7
Current smoking — no. (%)	352 (3.7)	383 (4.0)
Diabetes mellitus — no. (%) [¶]	1027 (10.8)	1030 (10.7)
Hypertension — no. (%)	7065 (74.2)	7148 (74.5)
Dyslipidemia — no. (%) ^{**}	6159 (64.7)	6308 (65.8)
Personal history of cancer — no. (%)	1827 (19.2)	1833 (19.1)
Previous regular aspirin use — no. (%) ^{††}	1053 (11.1)	1041 (10.9)
Frailty — no. (%) ^{‡‡}		
Not frail	5603 (58.8)	5643 (58.8)
Prefrail	3707 (38.9)	3740 (39.0)
Frail	215 (2.3)	206 (2.1)

Table 2. Composite Primary End Point, Including the Components, and Secondary End Points of Death, Dementia, Persistent Physical Disability, and Major Hemorrhage.*

End Point	Aspirin (N = 9525)		Placebo (N = 9589)		Hazard Ratio (95% CI)	P Value
	<i>no. of participants with event</i>	<i>rate per 1000 person-yr</i>	<i>no. of participants with event</i>	<i>rate per 1000 person-yr</i>		
Primary end point†	921	21.5	914	21.2	1.01 (0.92–1.11)	0.79
Death from any cause	480	11.2	431	10.0	—	—
Dementia	274	6.4	275	6.4	—	NS
Persistent physical disability	167	3.9	208	4.8	—	—
Secondary end points‡						
Death from any cause	558	12.7	494	11.1	1.14 (1.01–1.29)	—
Dementia	283	6.7	292	6.9	0.98 (0.83–1.15)	—
Persistent physical disability	188	4.9	224	5.8	0.85 (0.70–1.03)	—
Major hemorrhagic event	361	8.6	265	6.2	1.38 (1.18–1.62)	<0.001
Clinically significant bleeding	312	7.4	225	5.3	—	—
Hemorrhagic stroke	49	1.2	40	0.9	—	—

Major hemorrhagic event: 3.8%, 2.8%, ARI = 1%, NNH 100

ASPREE Trial

- ASPREE Trial - primary prevention
- Effect of aspirin on cardiovascular events and bleeding in the healthy elderly
- USA and Australia, >65 yrs with no history of CV disease, AD, or physical disability
- ASA dose was 100 mg (EC) vs placebo for 5 years
- This trial reports the secondary outcomes of ASPREE

Table 2. Cardiovascular Events.*

End Point	Overall (N = 19,114)	Aspirin (N = 9525)		Placebo (N = 9589)		Hazard Ratio (95% CI)
	<i>no. of participants with event</i>	<i>no. of participants with event</i>	<i>rate per 1000 person-yr</i>	<i>no. of participants with event</i>	<i>rate per 1000 person-yr</i>	NS
Cardiovascular disease†	922	448	10.7	474	11.3	
Major adverse cardiovascular event‡	701	329	7.8	372	8.8	0.89 (0.77–1.03)
Fatal cardiovascular disease§	159	78	1.8	81	1.9	0.97 (0.71–1.33)
Hospitalization for heart failure	171	88	2.1	83	1.9	1.07 (0.79–1.44)
Fatal or nonfatal myocardial infarction	355	171	4.0	184	4.3	0.93 (0.76–1.15)
Fatal or nonfatal ischemic stroke¶	315	148	3.5	167	3.9	0.89 (0.71–1.11)

Major hemorrhagic event: 3.8%, 2.8%, ARI = 1%, NNH 100

ASCEND Trial

- ASCEND Trial - primary prevention
- N = 15,480, 7.4 year follow-up
- patients ≥ 40 years of age **with diabetes** but **NO** evidence of cardiovascular disease
- ASA dose was 100 mg (EC) vs placebo for 5 years

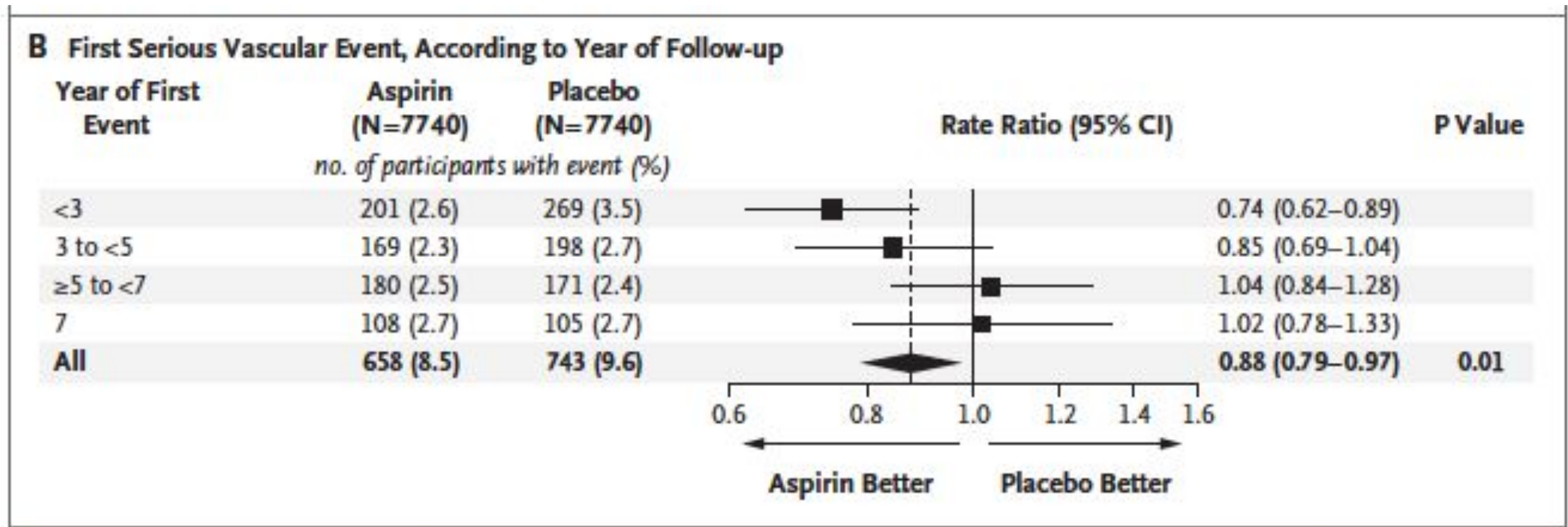


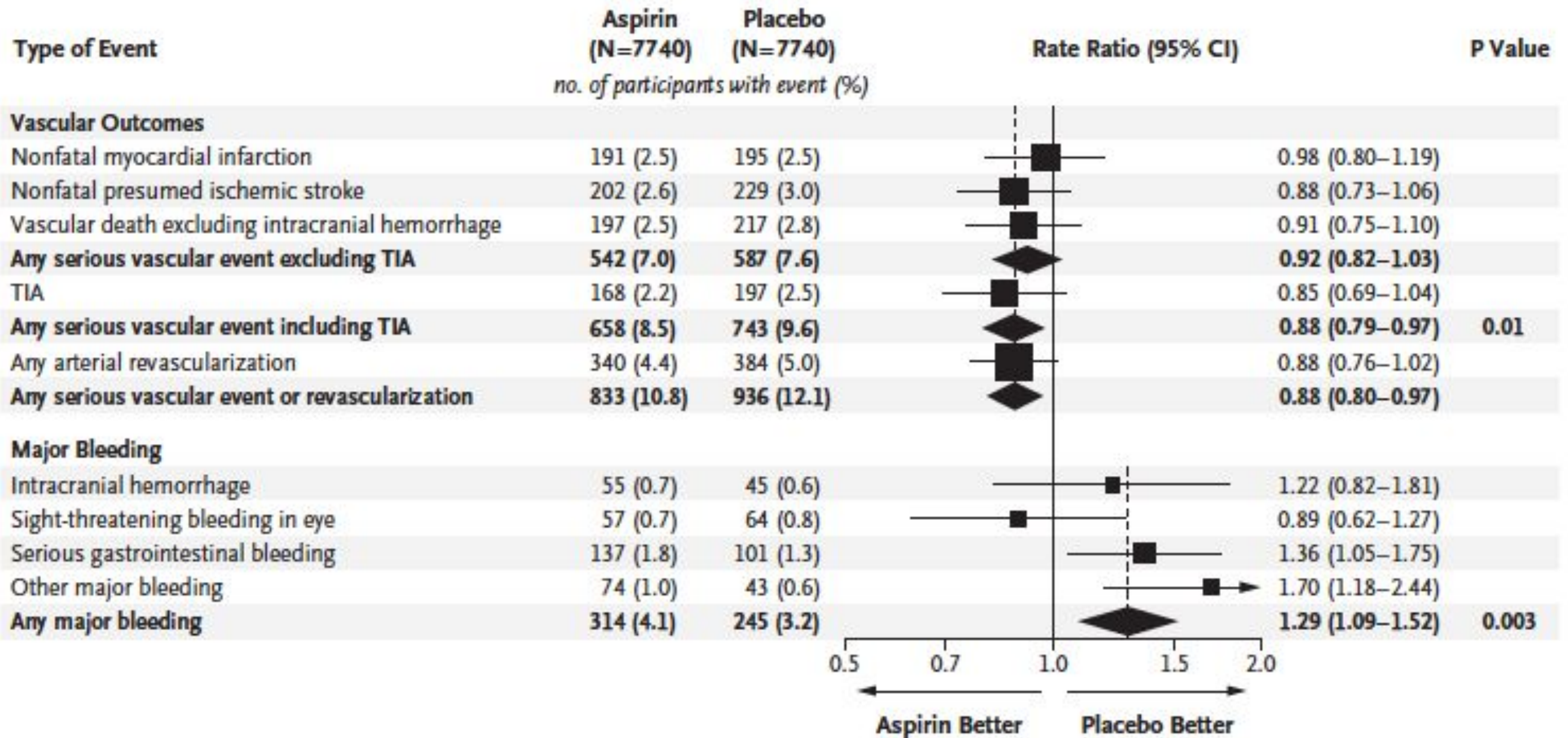
Table 1. Key Characteristics of the Participants at Baseline.*

Characteristic	Aspirin Group (N=7740)	Placebo Group (N=7740)
Age		
Mean — yr	63.2±9.2	63.3±9.2
Distribution — no. (%)		
<60 yr	2795 (36.1)	2795 (36.1)
60 to <70 yr	3123 (40.3)	3124 (40.4)
≥70 yr	1822 (23.5)	1821 (23.5)
Male sex — no. (%)	4843 (62.6)	4841 (62.5)
White race — no. (%)†	7467 (96.5)	7468 (96.5)
Body-mass index‡		
Mean	30.8±6.2	30.6±6.3
Distribution — no. (%)		
<25	1080 (14.0)	1169 (15.1)
25 to <30	2753 (35.6)	2776 (35.9)
≥30	3665 (47.4)	3536 (45.7)
Unknown	242 (3.1)	259 (3.3)
Smoking status — no. (%)		
Current smoker	639 (8.3)	640 (8.3)
Former smoker	3526 (45.6)	3525 (45.5)
Never smoked	3489 (45.1)	3488 (45.1)
Unknown	86 (1.1)	87 (1.1)
Participant-reported hypertension — no. (%)	4766 (61.6)	4767 (61.6)
Aspirin use before screening — no. (%)	2740 (35.4)	2768 (35.8)
Statin use — no. (%)	5854 (75.6)	5799 (74.9)
Type 2 diabetes — no. (%)§	7282 (94.1)	7287 (94.1)
Duration of diabetes		
Median (interquartile range) — yr	7 (3–13)	7 (3–13)
Distribution — no. (%)		
<9 yr	4337 (56.0)	4322 (55.8)
≥9 yr	2976 (38.4)	2989 (38.6)
Unknown	427 (5.5)	429 (5.5)
Systolic blood pressure		
Mean — mm Hg	136.1±15.2	136.2±15.3
Distribution — no. (%)		
<130 mm Hg	1694 (21.9)	1700 (22.0)
≥130 to <140 mm Hg	1550 (20.0)	1541 (19.9)
≥140 mm Hg	2263 (29.2)	2292 (29.6)
Unknown	2233 (28.9)	2207 (28.5)
Vascular risk score — no. (%)¶		
Low	3128 (40.4)	3136 (40.5)
Moderate	3294 (42.6)	3254 (42.0)
High	1318 (17.0)	1350 (17.4)

Results

- Overall benefit - ARR 1.1%, NNT 91
- Best in first 5 years





Major Bleeding: ARI 0.9%, NNH 111

Conclusion: The absolute benefits were largely counterbalanced

Table 2. Effect of Aspirin Use on the Incidence of Site-Specific Fatal or Nonfatal Cancer.*

Cancer Type	Aspirin Group (N=7740)	Placebo Group (N=7740)	Rate Ratio (95% CI)
	<i>no. of participants (%)</i>		
Gastrointestinal tract cancer	157 (2.0)	158 (2.0)	0.99 (0.80–1.24)
Other gastrointestinal cancer†	87 (1.1)	82 (1.1)	1.06 (0.78–1.43)
Respiratory cancer	101 (1.3)	103 (1.3)	0.98 (0.74–1.29)
Genitourinary cancer	332 (4.3)	294 (3.8)	1.13 (0.97–1.32)
Hematologic cancer	88 (1.1)	86 (1.1)	1.02 (0.76–1.38)
Breast cancer	97 (1.3)	96 (1.2)	1.01 (0.76–1.34)
Melanoma	50 (0.6)	59 (0.8)	0.85 (0.58–1.23)
Other cancer	25 (0.3)	30 (0.4)	0.83 (0.49–1.41)
Unspecified cancer	26 (0.3)	31 (0.4)	0.84 (0.50–1.41)
Any cancer‡	897 (11.6)	887 (11.5)	1.01 (0.92–1.11)

ARRIVE Trial Summary

- **ARRIVE Trial** (n = 12,546)
- multinational trial of enteric-coated aspirin 100 mg once daily vs placebo
- primary prevention of CV events (CV death, MI, unstable angina, stroke, or TIA) in men ≥ 55 with two to four risk factors
- women ≥ 60 years of age with three or more risk factors (an estimated 10-year CV risk of about 10% to 20% per the 2013 ACC/AHA pooled cohort equations calculator)
- Patients with a history of GI bleed, frequent NSAID use, antiplatelet or anticoagulant use, or **diabetes were excluded**
- Aspirin was not beneficial during 5 years of follow-up - event rate 4.29% vs 4.48%, HR 0.96, 95% CI 0.81 to 1.13, $p=0.6038$
- Risk of GI bleeding - 0.97% vs 0.46%, RRI 0.51, NNH 196/HR = 2
- The actual 10-year CV event rate in this study was lower than estimated (about 8% to 9%), perhaps due to optimization of modern medical therapies (e.g., statins, antihypertensives), making the study population essentially a low-risk population

“Now fear this: we are in the throes of a VD epidemic!”

The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

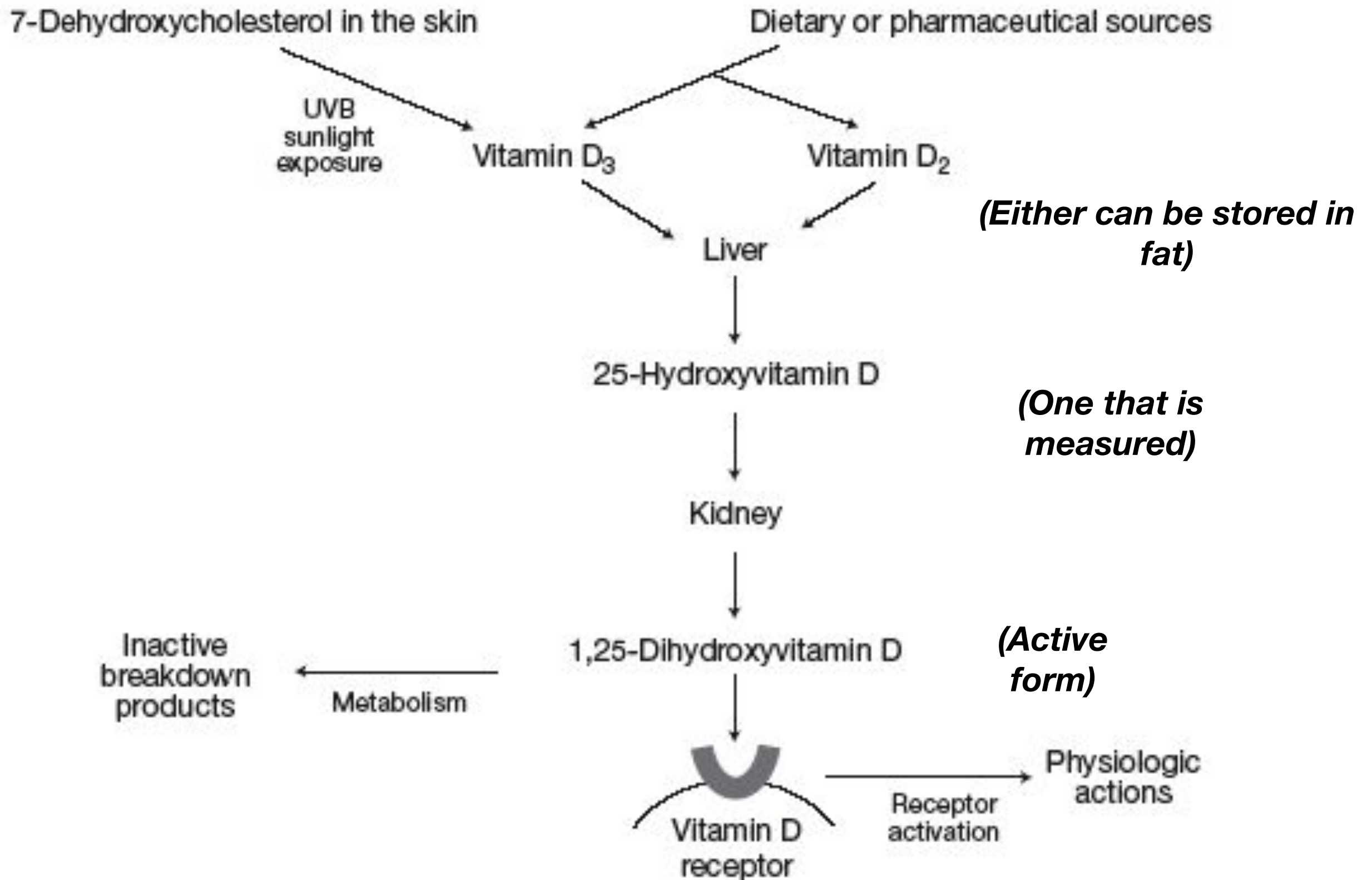
MEDICAL PROGRESS

Vitamin D Deficiency

Michael F. Holick, M.D., Ph.D.

The Wonder Drug?

Orally, vitamin D is used for treating or preventing vitamin D deficiency. It is also used for preventing osteoporosis, muscle weakness, enhancing immune function, preventing autoimmune diseases, multiple sclerosis, rheumatoid arthritis, fibromyalgia, chronic obstructive pulmonary disease (COPD), asthma, bronchitis, respiratory tract infections, tuberculosis, cancer, and the risk of dying from any cause. It is also used orally for rickets, premenstrual syndrome (PMS), seasonal affective disorder (SAD), and influenza. Vitamin D is also used orally for preventing falls and fractures in people at risk for osteoporosis, corticosteroid-induced osteoporosis, osteomalacia, anticonvulsant-induced osteomalacia, renal osteodystrophy, osteitis fibrosa in people on dialysis, hepatic osteodystrophy, and osteogenesis imperfecta. Vitamin D is also used for preventing and treating high parathyroid levels in patients with chronic kidney disease, hypocalcemia and tetany in premature infants' bone disorders in people with familial hypophosphatemia, hypophosphatemia associated with Fanconi syndrome, hypocalcemia associated with postoperative or idiopathic hypoparathyroidism or pseudohypoparathyroidism, and bone loss related to hyperparathyroidism. **Other uses include plaque-type psoriasis, actinic keratosis, lupus vulgaris, squamous cell carcinomas, bacterial vaginosis and vaginal atrophy, vitiligo, scleroderma, myelodysplastic syndrome, periodontal disease, prevention of cavities and retaining teeth in the elderly, hypertension, hyperlipidemia, cardiovascular disease, heart failure, metabolic syndrome, obesity and weight loss, and diabetes.** Vitamin D is also used orally to treat severe proximal myopathy associated with vitamin D deficiency or myopathy associated with the use of HMG-CoA reductase inhibitors (statin-induced myopathy), and to maintain bone density in prostatic cancer patients at risk for osteoporosis when treated with luteinizing hormone-releasing hormone analogue (LHRH-a). **It is also used to improve cognitive function, including in patients with Alzheimer's disease or dementia, and to prevent low birth weight infants.** Topically, vitamin D is used as calcitriol or calcipotriene for plaque-type psoriasis. Vitamin D as cholecalciferol is applied topically for seborrheic keratosis. A vitamin D derivative, maxacalcitol, is used topically for viral warts. Intravenously, vitamin D, administered as calcitriol, is used for hypocalcemic tetany in premature infants, hypocalcemia and hyperparathyroidism in renal dialysis patients, and osteitis fibrosa. Intramuscularly, vitamin D is administered as ergocalciferol for hepatic osteodystrophy, as an injectable source of vitamin D, and to treat severe proximal myopathy associated with vitamin D deficiency.



Why is Vitamin D deficiency so high?

- Depends on where you draw the line on serum levels
- No consensus on deficiency point
 - WHO <10 ng/ml
 - IOM < 20 ng/ml
 - Holick < 30 ng/ml
 - Lab reference range 30 to 76 ng/ml

NEJM 2007;357:266-81

NEJM 2011;364;3:248-54

Holick's case for 30 ng/ml

- Vitamin D levels are inversely related to parathyroid hormone levels until the vitamin D levels reach 30 to 40 ng/ml.
- As you approach 30 ng/ml, intestinal calcium transport increases by 45 to 65%.
- You get the greatest muscle strength and bone density - from letter (NEJM 2007;357:1981)
- Women who received 1100 units per day cut their risk of cancer 60% - from letter (NEJM 2007;357:1981)
 - That's 20 cases in those on placebo, 17 cases in those taking calcium only and 13 cases in those on Ca and VitD (Am J Clin Nut 2007;85:1586-91)

Main Vitamin D Source

- Sunshine - ultraviolet B radiation
- 3000 IU D₃ for every 5 to 10 minutes of direct sun exposure to the arms and legs
 - Based on time of day, latitude, season, skin tone



Dietary Sources of Vitamin D

- ❑ Greatest dietary source?
- ❑ Fresh wild salmon 1000 IU D₃
- ❑ Fish 4oz 300 IU D₃
 - ❑ Tuna, Salmon, Sardines
- ❑ Shiitake mushrooms 100 IU D₂
- ❑ Egg Yoke 20 IU D₂ or D₃
- ❑ Fortified foods 100 IU D₃/8oz
 - ❑ Milk, orange juice, yogurt, butter, cheese, cereal

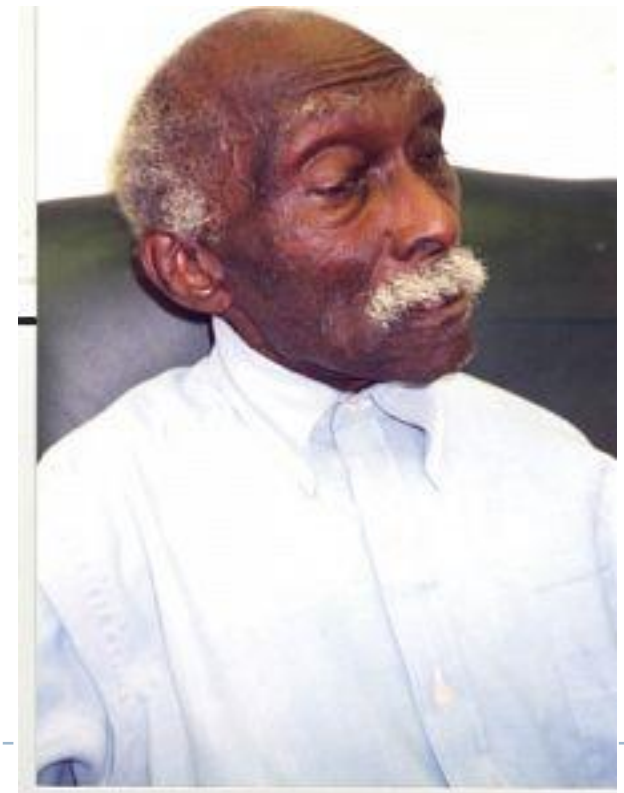


Who is Vitamin D Deficient?

- Pregnancy 73%
 - Child at birth (80%)
 - 70% on prenatal vitamin, 93% drank 2.3 glasses of milk per day, 90% ate fish
- Breast milk deficiency?
- Hispanic and Black in Boston 52%
 - Preadolescent Whites in Maine 48%
 - Black girls 15 to 49 yrs old 42%
- Healthy students, physicians, residents in Boston 32%
 - consuming glass of milk and multivitamin daily and salmon at least once a week

Who is Vitamin D Deficient?

- Everyone!!!! Or at least one out of three
 - It's not "Born in the USA" but "Born into deficiency"
- If the sun is the major source of vitamin D, then why are 28% of children in Costa Rica vitamin D deficient?
Medscape article, May 4, 2009
- 40 to 100% of community dwelling elderly deficient?
 - NEJM 2007;357:266-81



Vitamin D Receptors

- Brain
- Prostate
- Breast
- Colon tissue
- Immune cells
 - Monocytes and macrophages
- Controls > 200 genes
 - For apoptosis, angiogenesis, cell differentiation
 - Decreases cellular proliferation (e.g., why we use topical vitamin D)



Benefits of Vitamin D?

- Muscle weakness
- Falls
- Influenza
- Cancer
- Diabetes
- Cardiovascular disease (esp. HTN)
- Osteoarthritis
- Autoimmune disease
- Schizophrenia and depression
- Wheezing

Is it Fact or Fad?

Some thoughts to share....

- We live longer these days than we ever have, in spite of most of us being vitamin D deficient
- Society today has a magic bullet mentality, quick fix
- We are on a quest to live forever, in-spite of our fallen selves.
 - Very FDA-like
 - Thou shalt not die



Some thoughts to share....

- Are we really born into deficiency?
- Could mother's milk be inadequate?
 - God the Creator vs. Evolution
- “Should we bother drawing serum levels when most of us are deficient?”
- Normal results are not the norm
- It has a fad “flavor” like so many before!
 - Antioxidants, vitamin E, folic acid, homocysteine, vitamin C
 - Lots of similar publications in many journals by the same authors
 - The majority of research is not outcome-based, but disease-based
 - The cure-all!!!



And the research says?

Effect of High-Dose Vitamin D₃ on Hospital Length of Stay in Critically Ill

Patients With Vitamin D Deficiency

The VITdAL-ICU Randomized Clinical Trial

CONCLUSIONS AND RELEVANCE

Among critically ill patients with vitamin D deficiency, administration of high-dose vitamin D₃ compared with placebo did not reduce hospital length of stay, hospital mortality, or 6-month mortality. Lower hospital mortality was observed in the severe vitamin D deficiency subgroup, but this finding should be considered hypothesis generating and requires further study.



And the research says?

Calcium/Vitamin D Supplementation and Cardiovascular Events

Judith Hsia, Gerardo Heiss, Hong Ren, Matthew Allison, Nancy C. Dolan, Philip Greenland, Susan R. Heckbert, Karen C. Johnson, JoAnn E. Manson, Stephen Sidney, Maurizio Trevisan and for the Women's Health Initiative Investigators

Circulation 2007;115:846-854

Conclusions—Calcium/vitamin D supplementation neither increased nor decreased coronary or cerebrovascular risk in generally healthy postmenopausal women over a 7-year use period.

And the research says?

Effect of Vitamin D Supplementation on Blood Pressure

A Systematic Review and Meta-analysis

JAMA Intern Med. doi:10.1001/jamainternmed.2015.0237 Published online

March 16, 2015

CONCLUSIONS AND RELEVANCE Vitamin D supplementation is ineffective as an agent for lowering BP and thus should not be used as an antihypertensive agent.



And the research says?

Vitamin D and Cardiovascular Outcomes: A Systematic Review and
Meta-Analysis

Mohamed B. Elamin, Nisrin O. Abu Elnour, Khalid B. Elamin,

Conclusions: Trial data available to date are unable to demonstrate a statistically significant reduction in mortality and cardiovascular risk associated with vitamin D. The quality of the available evidence is low to moderate at best.

(J Clin Endocrinol Metab 96: 1931–1942, 2011)



And the research says?

Vitamin D shows no clear evidence of benefits despite hundreds of studies

BMJ 2014;348:g2489 doi: 10.1136/bmj.g2489 (Published 2 April 2014)

Vitamin D and Prevention of Cardiovascular Disease and Diabetes

Why the Evidence Falls Short

JAMA, June 22/29, 2011—Vol 305, No. 24



And the research says?

A Pooled Analysis of Vitamin D Dose Requirements for Fracture Prevention

Heike A. Bischoff-Ferrari, M.D., Dr.P.H., Walter C. Willett, M.D.

CONCLUSIONS

High-dose vitamin D supplementation (≥ 800 IU daily) was somewhat favorable in the prevention of hip fracture and any nonvertebral fracture in persons 65 years of age or older. (Funded by the Swiss National Foundations and others.)



And the research says?

Time for a moratorium on vitamin D meta-analyses

At least eight further meta-analyses have been performed, including that reported by Bischoff-Ferrari and colleagues.² Four reported a positive effect, and five no effect, or benefits limited to certain subgroups.

Similarly, there are at least 14 published meta-analyses on vitamin D and fracture prevention, but the most recent Cochrane review included only 22 RCTs.⁵

Again, conclusions differ substantially between reviews. Most reviews reported no effect of vitamin D overall, but positive effects in some subgroups.



New Trial this Year - VITAL Trial

- Vitamin D for the prevention of CV disease and cancer
- n= ~25,000, RCT

CONCLUSIONS

Supplementation with vitamin D did not result in a lower incidence of invasive cancer or cardiovascular events than placebo. (Funded by the National Institutes of Health and others; VITAL ClinicalTrials.gov number, [NCT01169259](https://clinicaltrials.gov/ct2/show/study/NCT01169259).)

Vitamin D and/or fish oil supplementation do not reduce the risk of atrial fibrillation (VITAL)

□ Bottom line

This study found no benefit to daily supplementation with vitamin D and/or marine omega-3 fatty acids in reducing the risk of new-onset atrial fibrillation (AF) in adults 50 years or older.

Vitamin D does not reduce the incidence nor the recurrence of depression in adults

□ **Bottom line**

This study found no benefit of vitamin D supplementation compared with placebo in reducing the incidence or recurrence of depression or depressive symptoms in adults, 50 years or older, who had no clinically significant depressive symptoms at baseline. Similarly, there was no benefit found regardless of baseline vitamin D level, race, or comorbid medical conditions. [\(LOE = 1b\)](#)

Vitamin D for the management of multiple sclerosis

- **Conclusions** For people with MS, vitamin D supplementation appears to have no effect on relevant clinical outcomes or new MRI lesions. Vitamin D supplementation at the doses and treatment durations used in the included trials appears to be safe, although available data are limited. Seven trials are ongoing; they will likely provide further evidence for a future update of this review.

Vitamin D supplementation does not prevent diabetes

□ **Bottom line**

There is no evidence that vitamin D supplementation prevents type 2 diabetes mellitus (T2DM) in patients with normal or mildly low vitamin D levels

Vitamin D not effective for reducing asthma exacerbations in children with asthma and low vitamin D levels (VDKA)

□ Bottom line

This study found that vitamin D supplementation did not reduce the risk of severe asthma exacerbations in children who meet the standard diagnostic criteria for persistent asthma and low vitamin D levels. [\(LOE = 1b\)](#)

Vitamin D supplementation does not improve survival in adults with digestive tract cancers

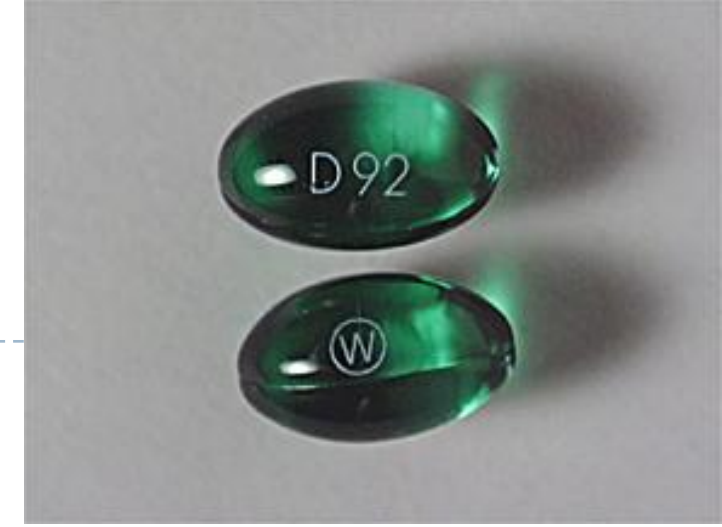
- In this trial, 2000 IU vitamin D supplementation per day did not significantly improve relapse-free survival in adults with surgically treated digestive tract cancers. A similar trial of high-dose vitamin D supplementation in the same journal issue also failed to find a survival benefit in adults with metastatic colorectal cancer. ([LOE = 1b](#))

And it goes on and on and on....

- **Vitamin D = placebo for preventing cognitive decline in African-American women with low vitamin D levels**
 - *J Am Geriatr Soc 2019;67(1):81-86*
 - **Additional prenatal vitamin D does not reduce risk of asthma in offspring**
 - *JAMA 2019;321(10):1003-1004*
 - **Vitamin D supplementation during pregnancy does not prevent asthma in offspring**
 - *N Engl J Med 2020;382(6):525-533*
-



Vitamin D₂ and D₃ Supplements



- Vitamin D₂ (ergocalciferol)
 - Manufactured through irradiation of ergosterol from yeast
 - Vitamin D₂ is 30% as effective as Vitamin D₃ in maintaining₂ serum levels.
 - Ergocalciferol 50,000 IU/capsule - Rx
 - Drisdol® liquid 8000 IU/ml - OTC
 - Vitamin D₃ (cholecalciferol) - All OTC
 - Manufactured through irradiation of 7-dehydrocholesterol from lanolin
 - Vitamin D₃ 400; 1,000; 2,000; 5,000; 10,000; 50,000 IU
 - Often used in multivitamins 400 IU
 - 40,000 units of vitamin D activity = 1 mg cholecalciferol or ergocalciferol
-



Dosing for Deficiency

- Treatment of deficiency and maintaining levels:
 - Vitamin D₂ 50,000 IU weekly for 8 weeks, then check level, repeat if < 30 ng/ml
 - Follow-up with 50,000 IU every 2 to 4 weeks for life
- Alternative regimens
 - 1000 IU vitamin D₃ daily
 - 100,000 IU vitamin D₃ once every three month



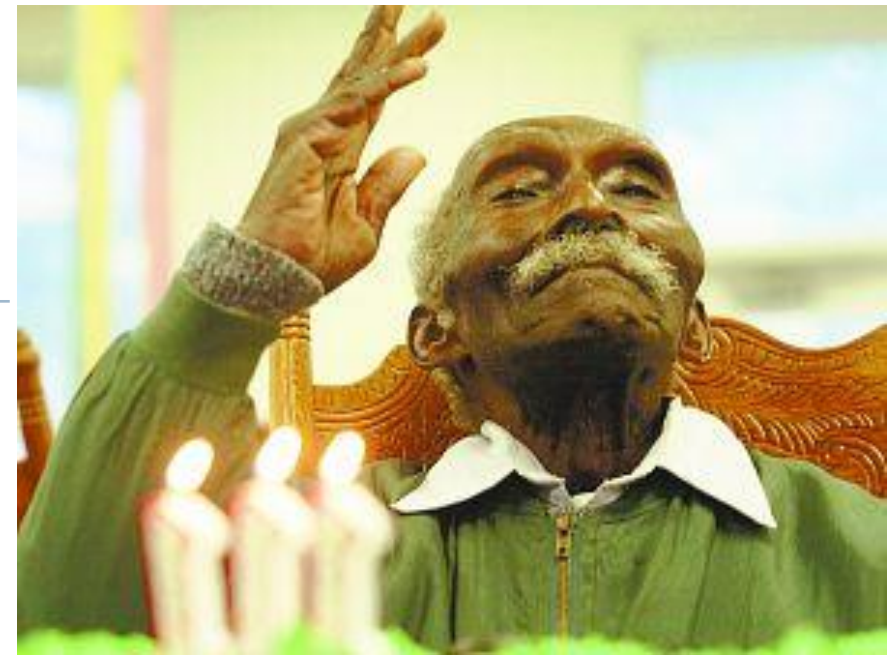
Dosing for Special Situations

- Lactation
 - 4000 IU vitamin D₃ daily
- Children
 - Canada recommends all infants and children get 400 IU vitamin D₃ daily
- In obesity or nephrotic syndrome
 - 1000 to 2000 IU daily



And then there is.....

- R.W. of Darlington County, SC
- One of the oldest men around
 - Born 1893
 - 116 years old when he died
 - Recognized by US Congress in 2001 as one of the oldest living American's
- Favorite foods?
 - PB & J with a side of pork and beans
 - Chicken and dumplings (“thicker the better”)
 - Fatback sandwich
- Vitamin D level on last admission?
- 6 ng/ml



Arrogance of Preventive Medicine

- Preventive medicine is *assertive* – pursuing symptomless individuals and telling them what they must do to stay healthy
- Preventive medicine is *presumptuous*, confident that on average will do more good than harm to those who accept and adhere to them
- Preventive medicine is *overbearing*, attacking those who question the value of its recommendations
- The real key is this...on the average the patient will be the better for it!

