Hypertension Treatment and Trials as Model Polypharmacy

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Conflict of Interest Statement.

Franz H. Messerli, MD currently has consultant or advisory relationships with the following companies :
, Menarini, Medtronic, WebMD, IPCA, ACC

“In the past 100 years, only during the 1918 flu pandemic was cardiovascular disease *not* the number-one cause of death”.

AHA Year End Statistics 2008

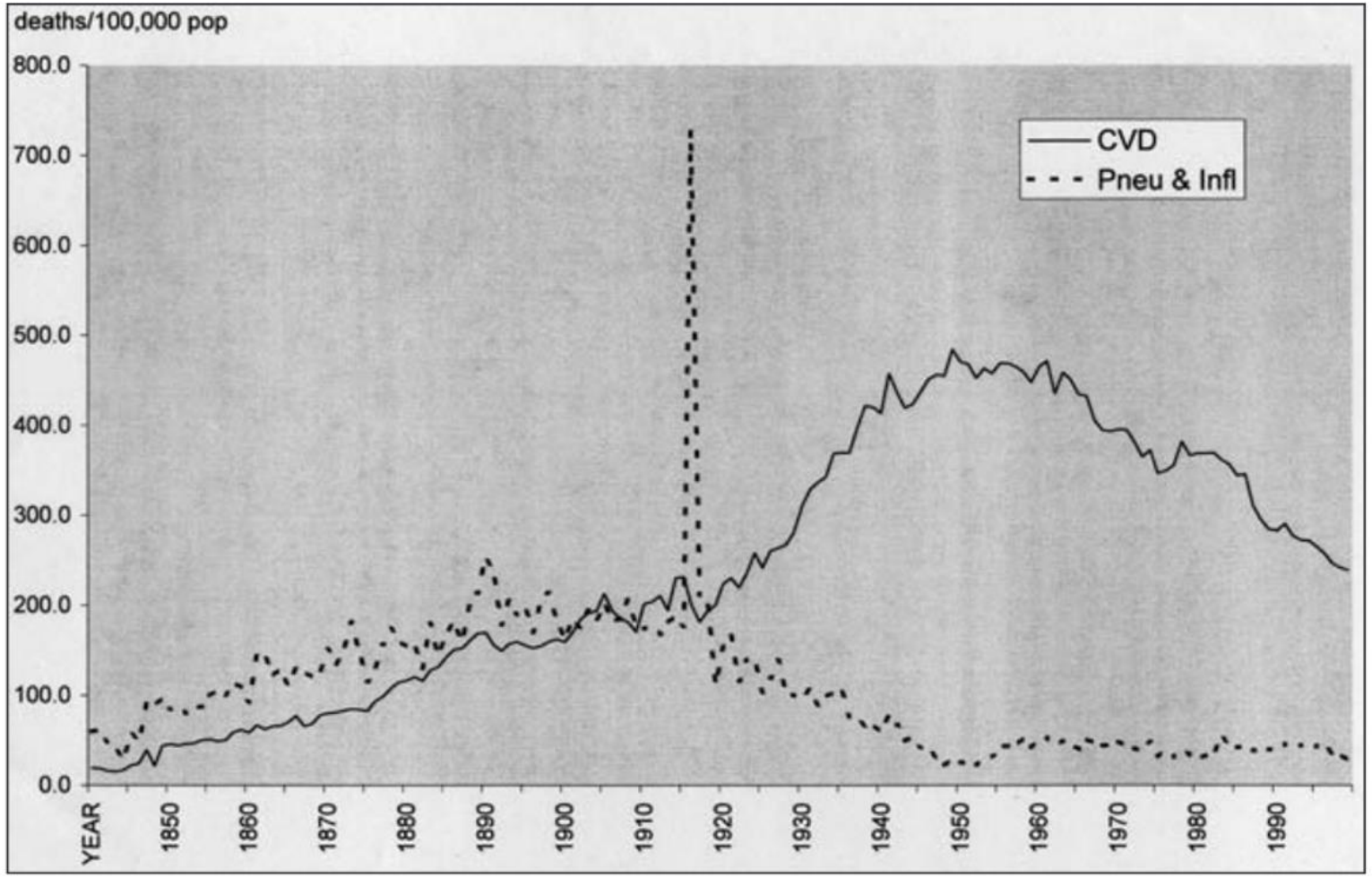
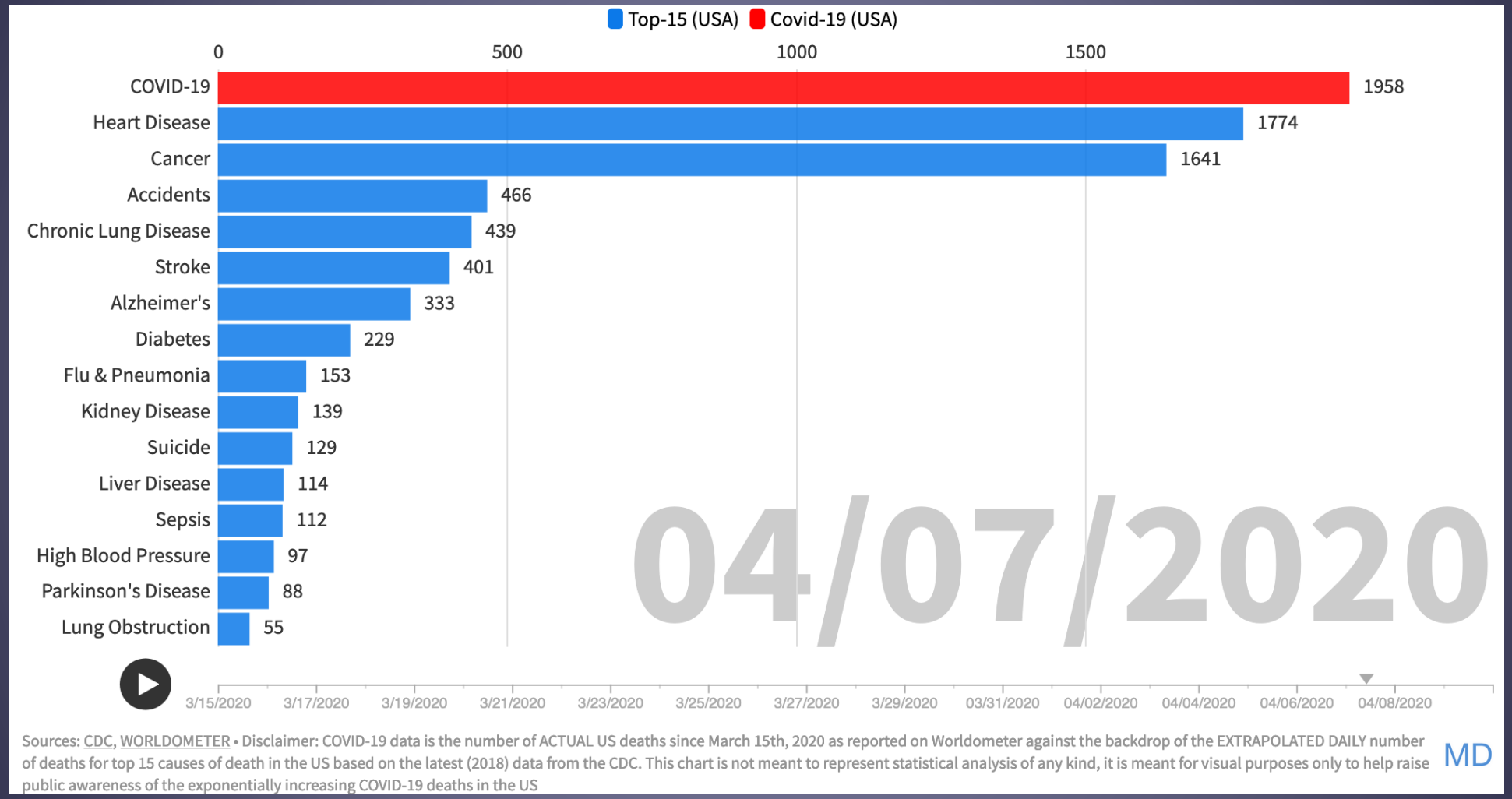
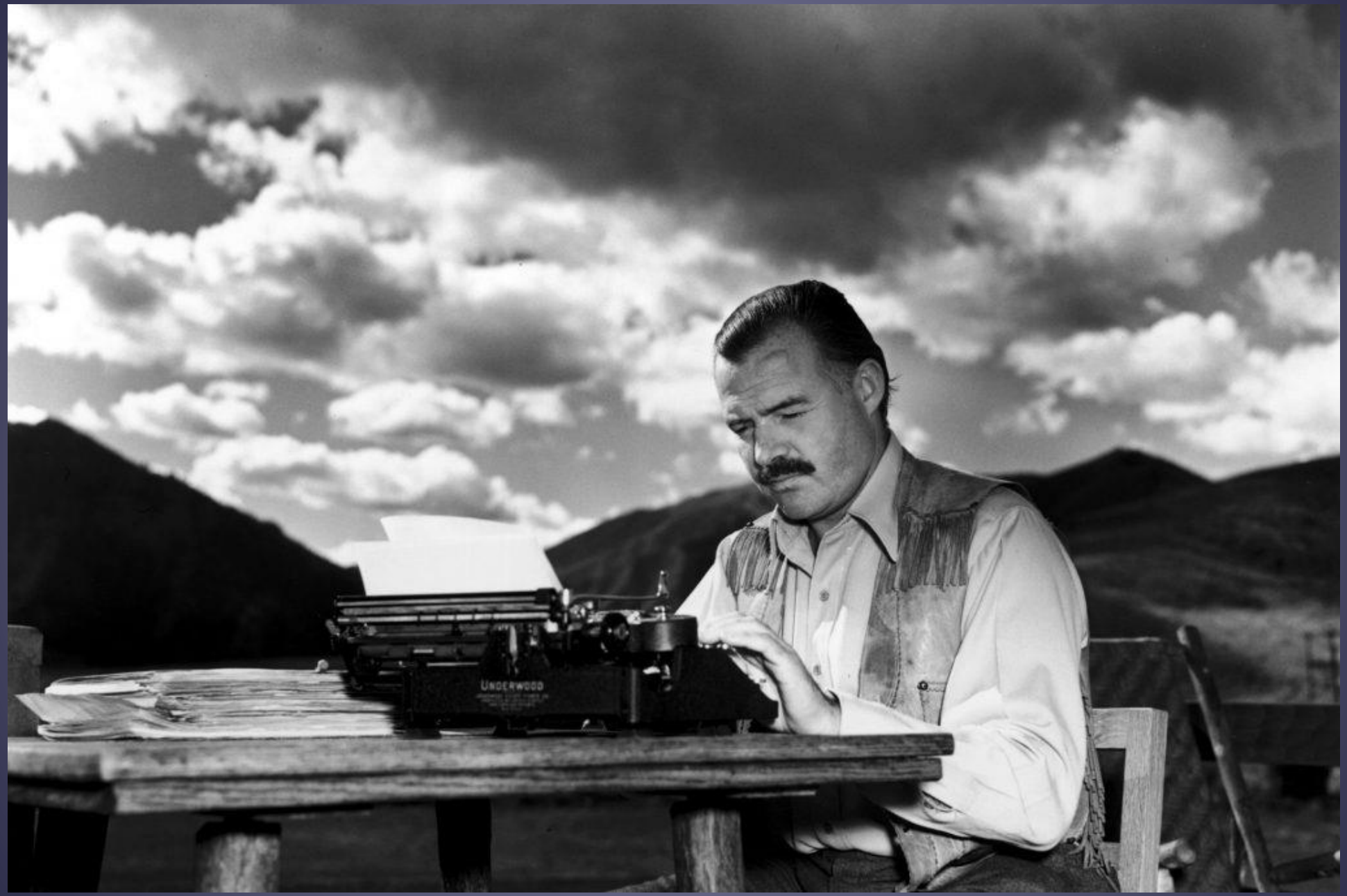
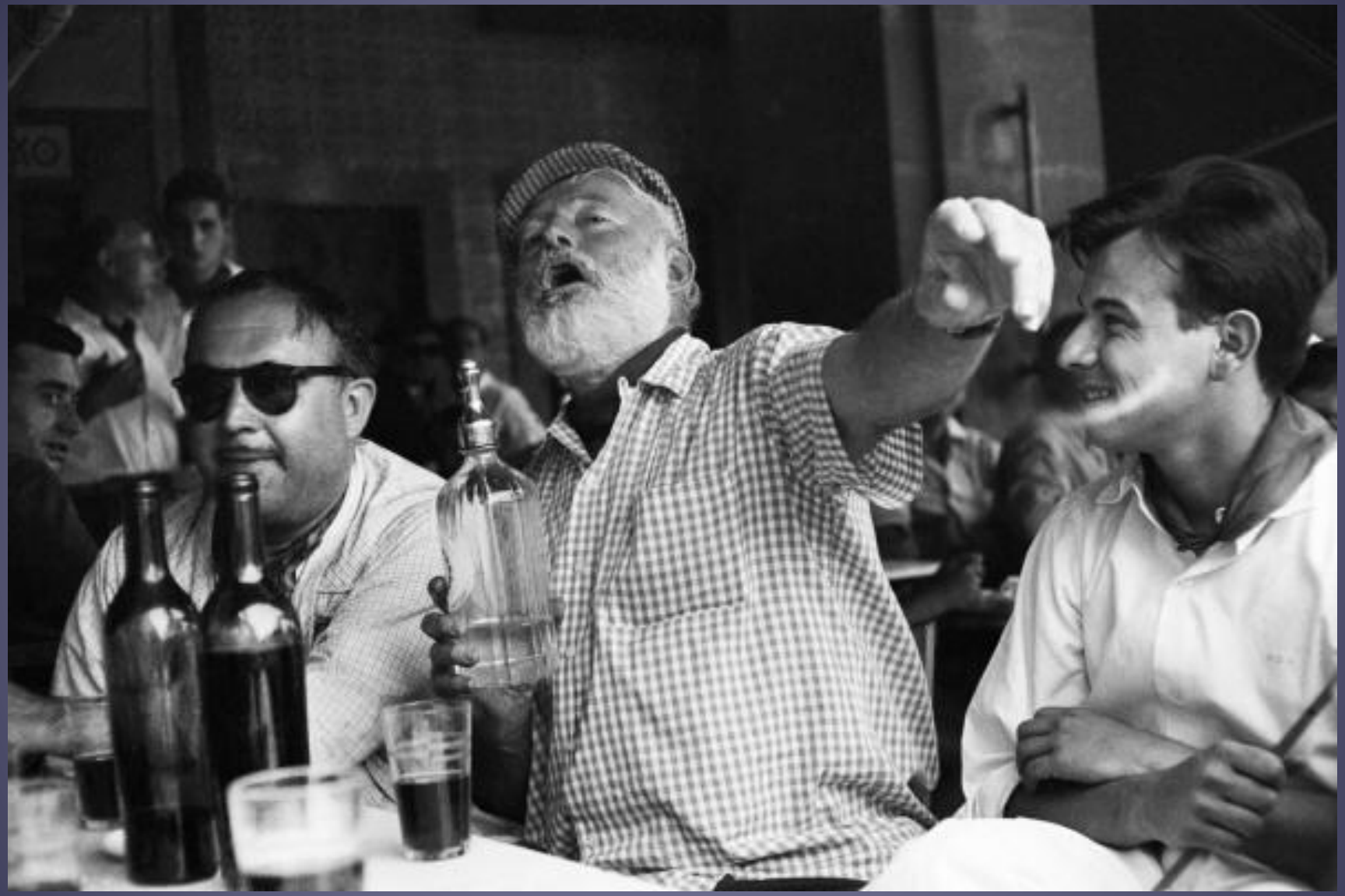


FIGURE 1

Temporal trends in cardiovascular diseases (CVD) and pneumonia and influenza (Pneu & Infl) mortality, Massachusetts, 1842–2000.


Top-15 (USA)
Covid-19 (USA)
0
500
1000
1500
COVID-19
1958
Heart Disease
1774
Cancer
1641
Accidents
466
Chronic Lung Disease
439
Stroke
401
Alzheimer's
333
Diabetes
229
Flu & Pneumonia
153
Kidney Disease
139
Suicide
129
Liver Disease
114
Sepsis
112
High Blood Pressure
97
Parkinson's Disease
88
Lung Obstruction
55
04/07/2020
3/15/2020
3/17/2020
3/19/2020
3/21/2020
3/23/2020
3/25/2020
3/27/2020
3/29/2020
03/31/2020
04/02/2020
04/04/2020
04/06/2020
04/08/2020
Sources: CDC, WORLDOMETER • Disclaimer: COVID-19 data is the number of ACTUAL US deaths since March 15th, 2020 as reported on Worldometer against the backdrop of the EXTRAPOLATED DAILY number of deaths for top 15 causes of death in the US based on the latest (2018) data from the CDC. This chart is not meant to represent statistical analysis of any kind, it is meant for visual purposes only to help raise public awareness of the exponentially increasing COVID-19 deaths in the US
MD


UNDERWOOD



“Never sit at a table when you can stand at the bar.”

Some of Hemingway's Diagnoses at Mayo

- Hypertension (Reserpine)
- Hyperlipidemia
- Hemochromatosis
- Diabetes
- Alcoholism
- Depression, bipolar disease (Ritaline, ECT)
- Paranoid delusions
- Chronic traumatic encephalopathy (dementia pugilistica)

- “they gave him 36 shock treatments at the Mayo Clinic in Rochester, Minnesota. After some of those shock treatments, he didn’t even know his name.
- Then he would be sent back home to recover, given that drug for high blood pressure, and it was only a matter of weeks before he was depressed again.”

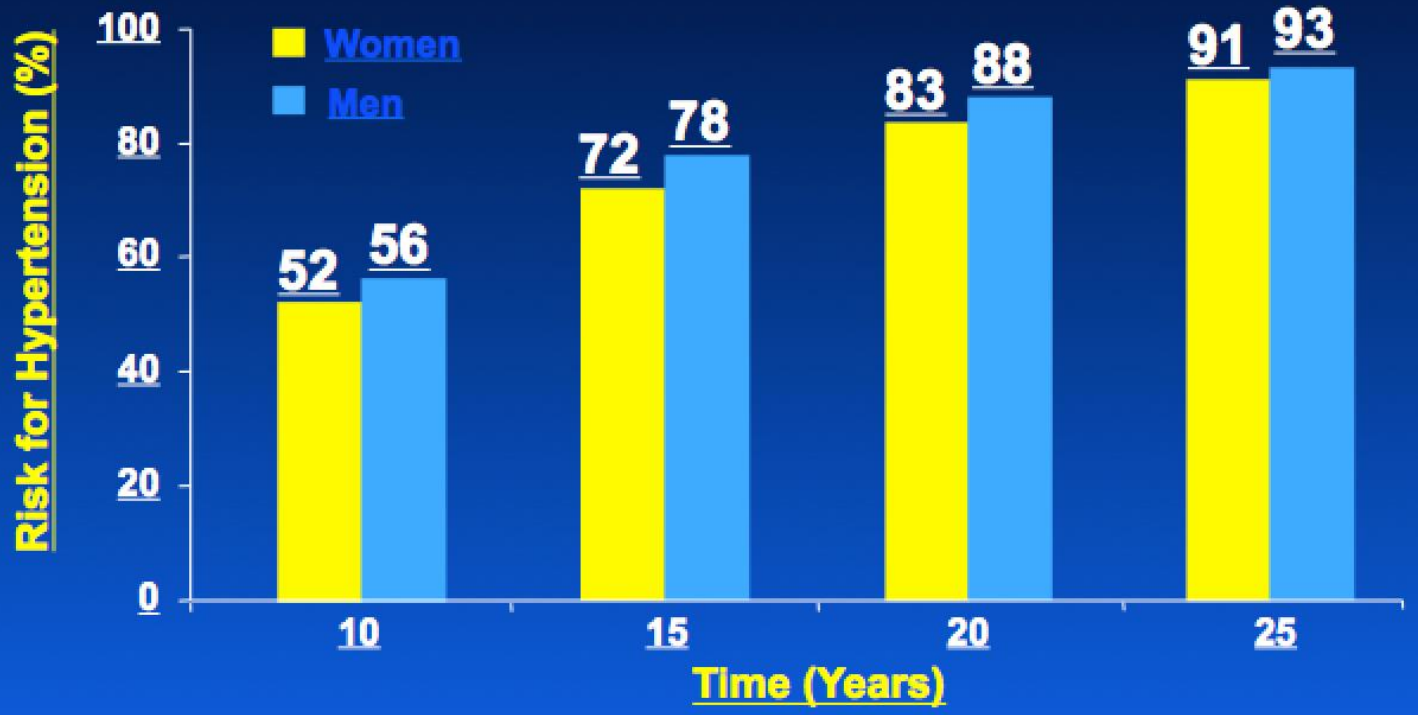
- Well, what is the sense of ruining my head and erasing my memory, which is my capital, and putting me out of business?
- It was a brilliant cure, but we lost the patient."

Ernest Hemingway, 1961

What is the residual lifetime risk of becoming hypertensive in a normotensive person at age 55?

- 10 – 30 %
- 30 – 50 %
- 50 – 70 %
- 70 – 90 %
- >90 %

Residual Lifetime Risk for Hypertension From Age 55



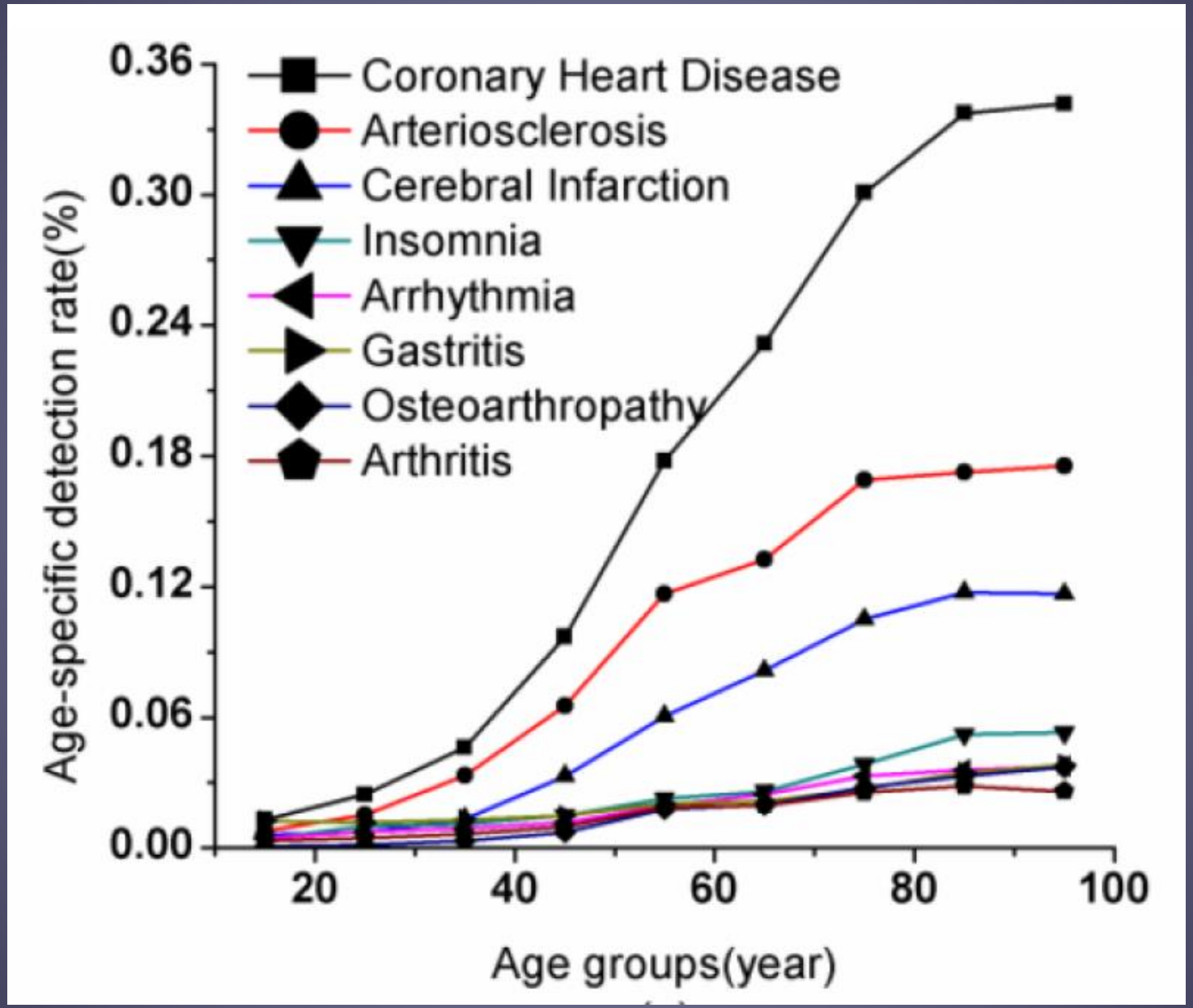
Individuals who are normotensive at age 55 have a > 90% lifetime risk of developing hypertension

Vasan RS et al. *JAMA*. 2002;287:1003-1010 **Framingham.**

Table 1. Detection rates of the top 20 comorbidities of hypertension in China.

No.	Comorbidity	Detection Rate(%)	95% CI
1	Coronary Heart Disease	21.71	21.68-21.74
2	Diabetes	16.00	15.97-16.03
3	Hyperlipemia	13.81	13.78-13.84
4	Arteriosclerosis	12.66	12.63-12.68
5	Cerebral Infarction	7.53	7.51-7.55
6	Move With Difficulty	4.35	4.34-4.37
7	Nephropathy	4.24	4.23-4.26
8	Respiratory Tract Infection	3.95	3.94-3.97
9	Cerebral Circulation Insufficiency	3.87	3.85-3.88
10	Upper Respiratory Tract Infection	3.43	3.42-3.45
11	Renal Insufficiency	3.25	3.23-3.26
12	Tracheitis	3.10	3.09-3.12
13	Osteoporosis	3.04	3.03-3.05
14	Insomnia	2.86	2.85-2.87
15	Uremia	2.73	2.82-2.74
16	Anemia	2.42	2.41-2.44
17	Arrhythmia	2.39	2.38-2.40
18	Gastritis	2.26	2.25-2.27
19	Osteoarthropathy	2.00	1.99-2.01
20	Arthritis	1.96	1.95-1.97

Liu et al. Int J Med Sci 2016; 13(2): 99-107.



Liu et al. Int J Med Sci 2016; 13(2): 99-107.

Hypertension and Polypharmacy: Take home messages

1. Lone Hypertension doesnt exist – comorbidities abound.

2018 ESC/ESH Guidelines

"The above considerations …encourages the use of two-drug single pill combinations as initial therapy for most patients, because monotherapy is insufficient in all but some patients with stage 1 hypertension…"

Polypharmacy compared

Clinical and biological characteristics of the study population

Variables	All participants (n=2545)	Polypharmacy (n=2545)		
		Drugs < 4	Drugs ≥ 4	p
Number	2545	1785 (70.1%)	760 (29.9%)	≤ 0.01
Gender (Women)	46.2	42.4	55.0	≤ 0.01
Age (years)	66.4 ± 4.8	66 ± 4.6	68 ± 5.0	≤ 0.01
Education level (High %)	13.0	14.7	8.4	≤ 0.01
BMI (kg/m²)	27.0 ± 4.2	26.5 ± 3.9	27.9 ± 4.5	≤ 0.01
Waist circumference (cm)	89.6 ± 12,3	88.8 ± 12.0	91.7 ± 12.8	≤ 0.01
MMSE (0 - 30)	27.7 ± 2.0	27.8 ± 1.9	27.5 ± 2.2	0.14
Self-perceived health status (0 - 10)	7.02 ± 1.61	7.31 ± 1.50	6.31 ± 1.65	≤ 0.01
Despair (%)	5.6	4.5	8.4	≤ 0.01
Psychological follow-up (%)	2.5	1.60	4.67	≤ 0.01
Sense of being elderly (%)	18.7	15.5	26.5	≤ 0.01
Memory problems (%)	21.8	17.7	31.4	≤ 0.01
History of falls (%)	19.1	15.8	26.7	≤ 0.01

Husson et al. 2014 J Nutrition, Health & Aging

Polypharmacy compared

Analysis of factors associated with polypharmacy using multiple logistic regression models

Variable	Regression Coefficient (Standard Deviation)	Odds Ratio	95% Confidence Interval	p
Intercept	-2.79 (0.38)			≤ 0.01
Age > 65	0.46 (0.21)	1.58	1.05 - 2.38	0.03
Poor self-perceived health status	1.03 (0.22)	2.79	1.80 - 4.31	≤ 0.01
History of falls	0.51 (0.25)	1.66	1.02 - 2.71	0.04
Lack of a physical activity	0.41 (0.21)	1.50	1.00 – 2.26	0.05
Metabolic Syndrome	1.15 (0.25)	3.17	1.95 - 5.15	≤ 0.01
Low or Medium education Level	0.79 (0.35)	2.20	1.24 - 4.30	0.02

Model $R^2 = 0.134$

“polypharmacy cannot be considered as the sole consequence of several diseases”.

Husson et al. 2014 J Nutrition, Health & Aging

Hypertension and Polypharmacy: Take home messages

1. Lone Hypertension doesnt exist – comorbidities abound.
2. Treatment of hypertension per se requires polypharmacy

Is Blood Pressure Control for Stroke Prevention the Correct Goal?

The Lost Opportunity of Preventing Hypertension

George Howard, DrPH; Maciej Banach, MD, PhD; Mary Cushman, MD;
David C. Goff, MD, PhD; Virginia J. Howard, PhD; Daniel T. Lackland, DrPH;
Jim McVay, DrPA; James F. Meschia, MD; Paul Muntner, PhD; Suzanne Oparil, MD;
Melanie Rightmyer, DNP; Herman A. Taylor, MD

Background and Purpose—Although pharmacological treatment of hypertension has important health benefits, it does not capture the benefit of maintenance of ideal health through the prevention or delay of hypertension.

Methods—A total of 26875 black and white participants aged 45+ years were assessed and followed for incident stroke events. The association was assessed between incident stroke and: (1) systolic blood pressure (SBP)categorized as normal (<120 mm Hg), prehypertension (120–139 mm Hg), stage 1 hypertension (140–159 mm Hg), and stage 2 hypertension (160 mm Hg+), and (2) number of classes of antihypertensive medications, classified as none, 1, 2, or 3 or more.

Results—During 6.3 years of follow-up, 823 stroke events occurred. Nearly half (46%) of the population were successfully treated (SBP<140 mm Hg) hypertensives. Within blood pressure strata, the risk of stroke increased with each additional class of required antihypertensive medication, with hazard ratio [HR], 1.33; 95% confidence interval, 1.16 to 1.52 for normotensive, HR, 1.15; 95% confidence interval, 1.05 to 1.26 for prehypertension, and HR, 1.22; 95% confidence interval, 1.06 to 1.39 for stage 1 hypertension. A successfully treated (SBP<120 mm Hg) hypertensive person on 3+ antihypertensive medication classes was at marginally higher stroke risk than a person with untreated stage 1 hypertension (HR, 2.48 versus HR=2.19; relative to those with SBP <120 on no antihypertensive medications).

Conclusions—Maintaining the normotensive status solely through pharmacological treatment has a profound impact, as

Howard et al. Stroke, 2015;46:1595-1600.

Table 2. HR for Incident Stroke (95% Confidence Interval) After Adjustment for Age, Race, Age-By-R Deviation From the Mean SBP Level for the Category

	Normotensive (<120 mm Hg)	Prehypertension (120 mm Hg–139 mm Hg)	Stage 1 Hypertension (140 mm Hg–159 mm Hg)	Stage 2 Hypertension (160+ mm Hg)
No antihypertensive medications	1.0 (Ref)	1.44 (1.04–2.01)	2.19 (1.45–3.31)	3.35 (1.78–6.28)
1 Antihypertensive medication				
2 Antihypertensive medications				
3+ Antihypertensive medications				

Howard et al. Stroke, 2015;46:1595-1600.

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No antihypertensive medications	1.0 (Ref)	1.44 (1.04–2.01)	2.19 (1.45–3.31)	3.35 (1.78–6.28)
1 Antihypertensive medication	1.42 (0.94–2.15)	2.00 (1.44–2.77)	1.67 (1.09–2.54)	3.00 (1.71–5.26)
2 Antihypertensive medications	1.60 (1.06–2.42)	1.88 (1.35–2.62)	2.84 (1.95–4.13)	1.42 (0.67–2.99)
3+ Antihypertensive medications	2.48 (1.63–3.77)	2.34 (1.66–3.32)	3.35 (2.28–4.92)	4.62 (2.84–7.51)

Howard et al. Stroke2015;46:1595-1600.

Conclusions

“Maintaining the normotensive status solely through pharmacological treatment…. failed to return to risk levels similar to normotensive individuals. Even with successful treatment, there is a substantial residual risk.”

Howard et al. Stroke2015;46:1595-1600.

ESC European Society of Cardiology

European Heart Journal (2021) **42**, 750–757
doi:10.1093/eurheartj/ehaa756

CLINICAL RESEARCH
Imaging

Midlife blood pressure is associated with the severity of white matter hyperintensities: analysis of the UK Biobank cohort study

Karolina Agnieszka Wartolowska * and Alastair John Stewart Webb

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Received 7 April 2020; revised 3 June 2020; editorial decision 18 August 2020; accepted 9 September 2020; online publish-ahead-of-print 26 November 2020

See page 758 for the editorial comment on this article (doi: 10.1093/eurheartj/ehaa971)

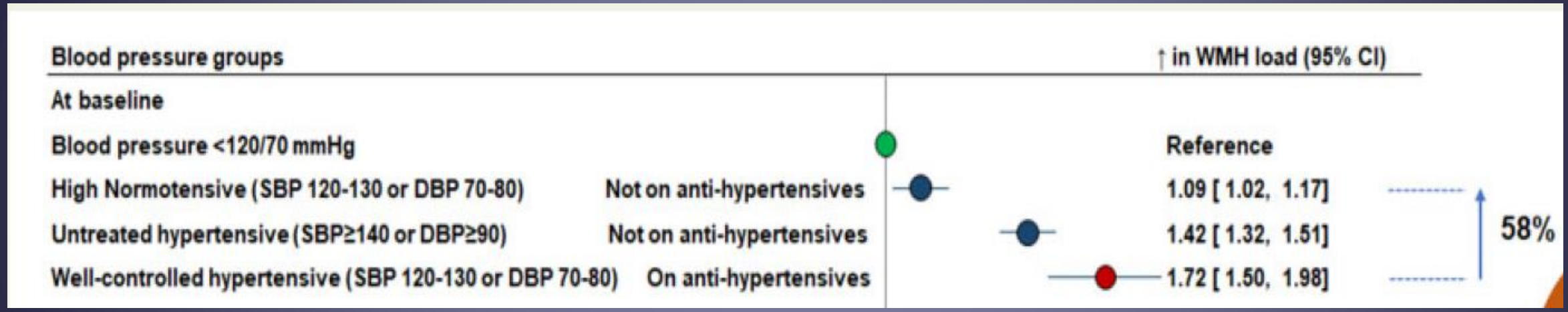
Aims White matter hyperintensities (WMH) progress with age and hypertension, but the key period of exposure to elevated blood pressure (BP), and the relative role of systolic BP (SBP) vs. diastolic BP (DBP), remains unclear. This study aims to determine the relationship between WMH and concurrent vs. past BP.

Methods and results UK Biobank is a prospective community-based cohort of 40–69-year olds from 22 centres, with magnetic resonance imaging in a subgroup of over 40 000 people at 4–12 years after baseline assessment. Standardized

- **Methods: UK Biobank is a prospective community-based cohortof 40-69 year-olds from 22 centres, with MRI imaging in a subgroup of over 40,000 people at 4-12 years after baseline assessment.**
- **Conclusions: Our results suggest that to ensure maximal prevention of WMH in late life, control of DBP may be required in early mid-life, even for DBP below 90 mmHg**

Wartolowska et al. EHJ 2020, in press

BP Groups and White Matter Hyperintensities (WHM load)



“antihypertensive therapy per se, independent of its effect on BP was a powerful risk factor for WMH. Apparently, antihypertensive therapy must be cerebrotoxic!”

Messerli et al. EHJ in press

Supplementary Table 13: **Increase in WMH in relation to people not on antihypertensive medication and with blood pressure < 120/70 mmHg at follow-up.** NT – normotensive, HT – hypertensive.

Group at follow-up	BP [mmHg]	AntiHT	Increase in WMH load (95% CIs)	N
High NT	SBP: 120-130 or DBP: 70-80	No	1.079 (1.032 to 1.127)	5463
Untreated pre-HT	SBP: 130-140 or DBP: 80-90	No	1.180 (1.130 to 1.232)	6053
Untreated HT	SBP ≥ 140 or DBP ≥ 90	No	1.398 (1.341 to 1.457)	9226
Very well-controlled HT	SBP < 120 or DBP: < 70	Yes	1.545 (1.374 to 1.738)	285
Well-controlled HT	SBP 120-130 or DBP 70-80	Yes	1.603 (1.495 to 1.719)	949
Controlled HT	SBP: 130-140 or 80-90	Yes	1.604 (1.516 to 1.697)	1879
Uncontrolled HT	≥ 140 or DBP ≥ 90	Yes	1.774 (1.693 to 1.858)	5156

Regardless of BP level, treated hypertension is associated with significantly more WMH than untreated hypertension !

Wartolowska et al. EHJ 2020, in press

ESC European Society of Cardiology

European Heart Journal (2020) **00**, 1–3
doi:10.1093/eurheartj/ehaa971

EDITORIAL

On cerebrotoxicity of antihypertensive therapy and risk factor cosmetics

Franz H. Messerli[1,2,3]*, Chirag Bavishi [4], Adrian W. Messerli[5], and George C.M. Siontis [1]

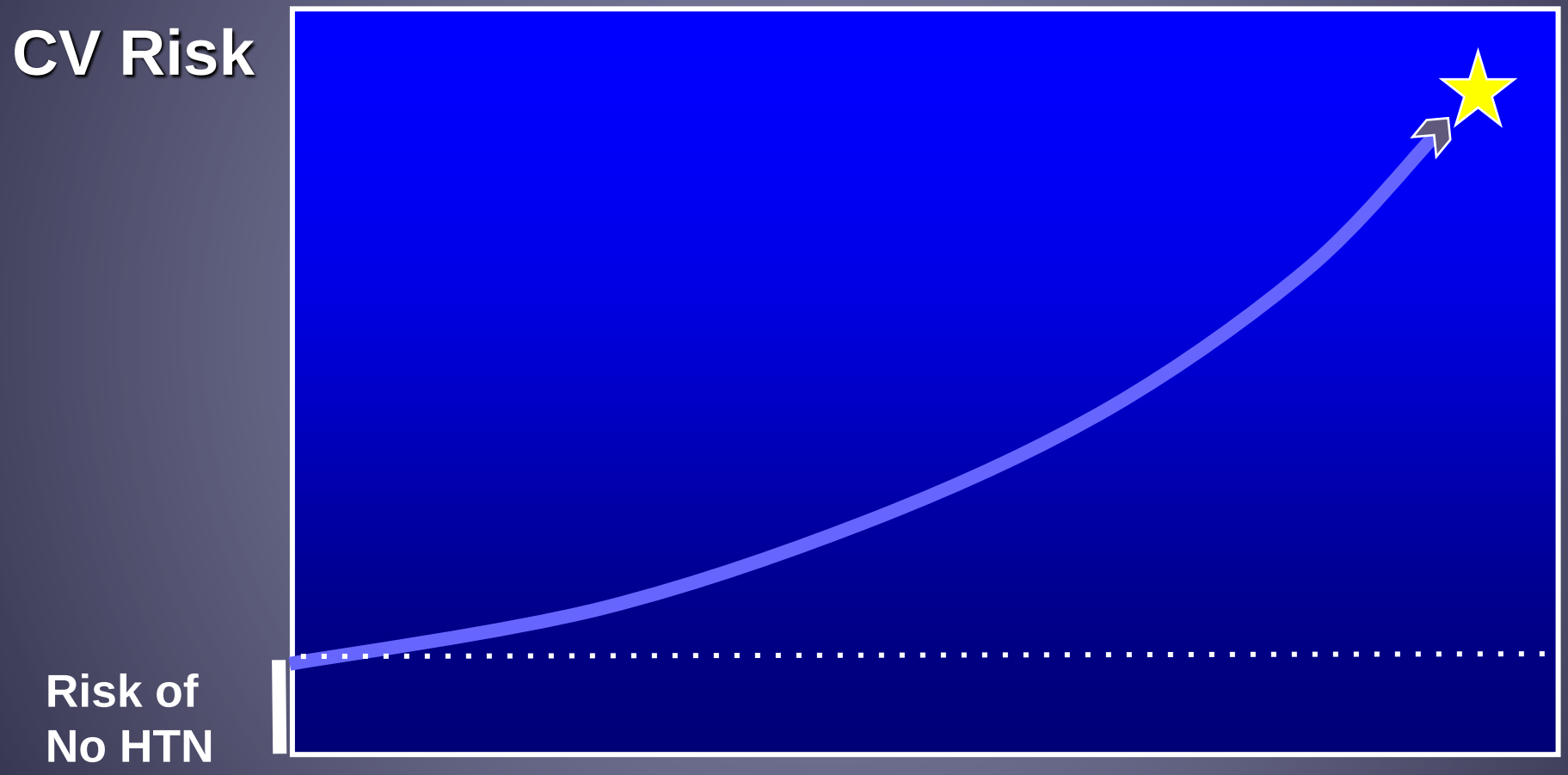
[1]Department of Cardiology, Bern University Hospital, University of Bern, Switzerland; [2]Jagiellonian University, Krakow, Poland; [3]Division of Cardiology, Mount Sinai Health Medical Center, Icahn School of Medicine, New York, NU, USA; [4]Lifespan Cardiovascular Institute, Warren Alpert Medical School at Brown University, Providence, RI, USA; and [5]Gill Heart and Vascular Institute, University of Kentucky, Lexington, KY, USA

This editorial refers to 'Midlife blood pressure is associated with severity of white matter hyperintensities: analysis of the UK Biobank cohort study', by K.A. Wartolowska and A.J.S. Webb, doi:10.1093/eurheartj/ehaa756.

documented WMH load to be more strongly associated with past DBP than with past SBP, especially under the age of 50. WMH load was also strongly associated with concurrent BP, both systolic and diastolic, following adjustment for the other BP measure, age, sex,

antihypertensive therapy per se, independent of its effect on BP, was a powerful risk factor for WMHs.
Apparently, antihypertensive therapy must be cerebrotoxic!

Risk of Hypertension and its Reduction by Antihypertensive Therapy



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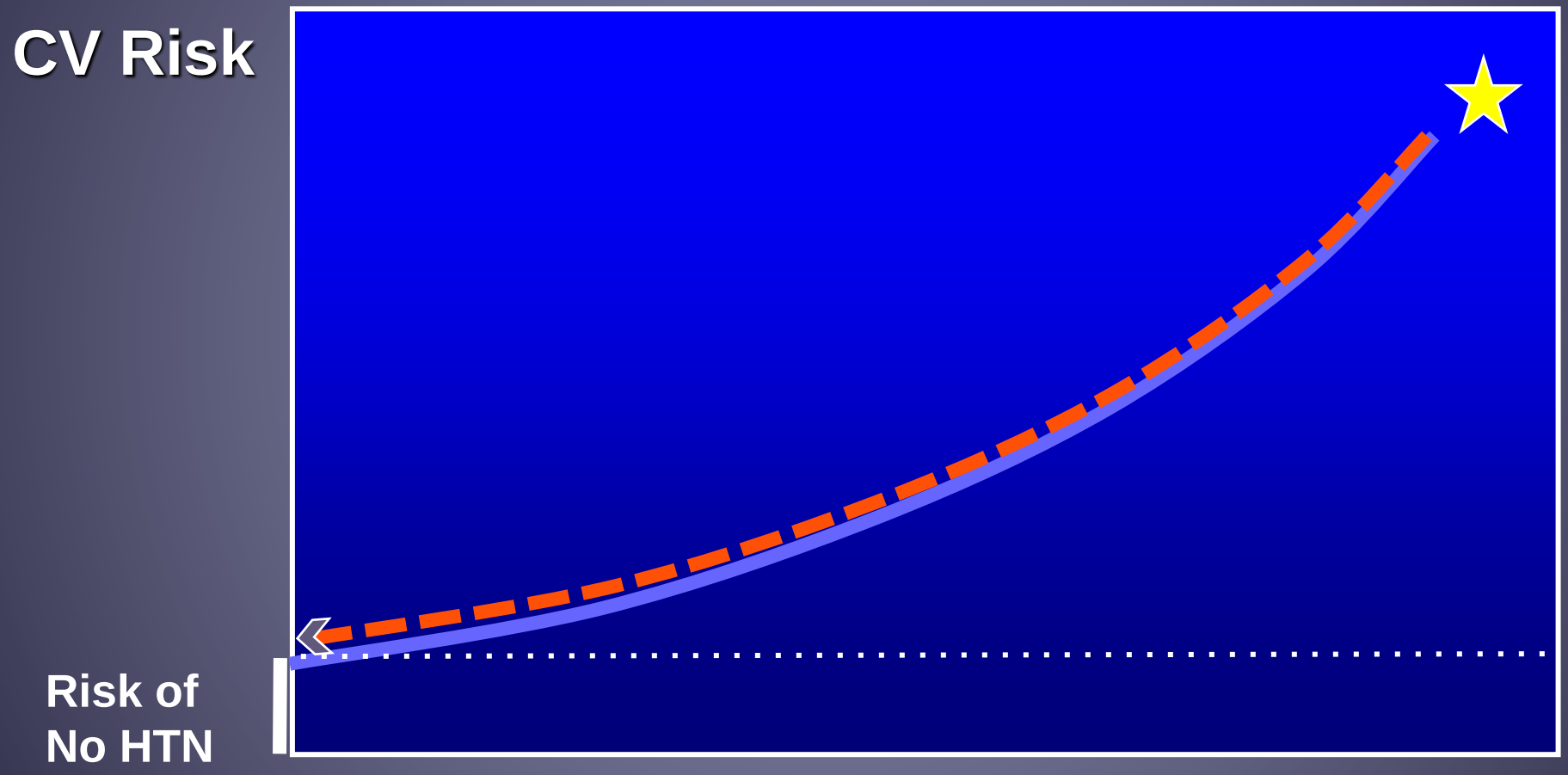

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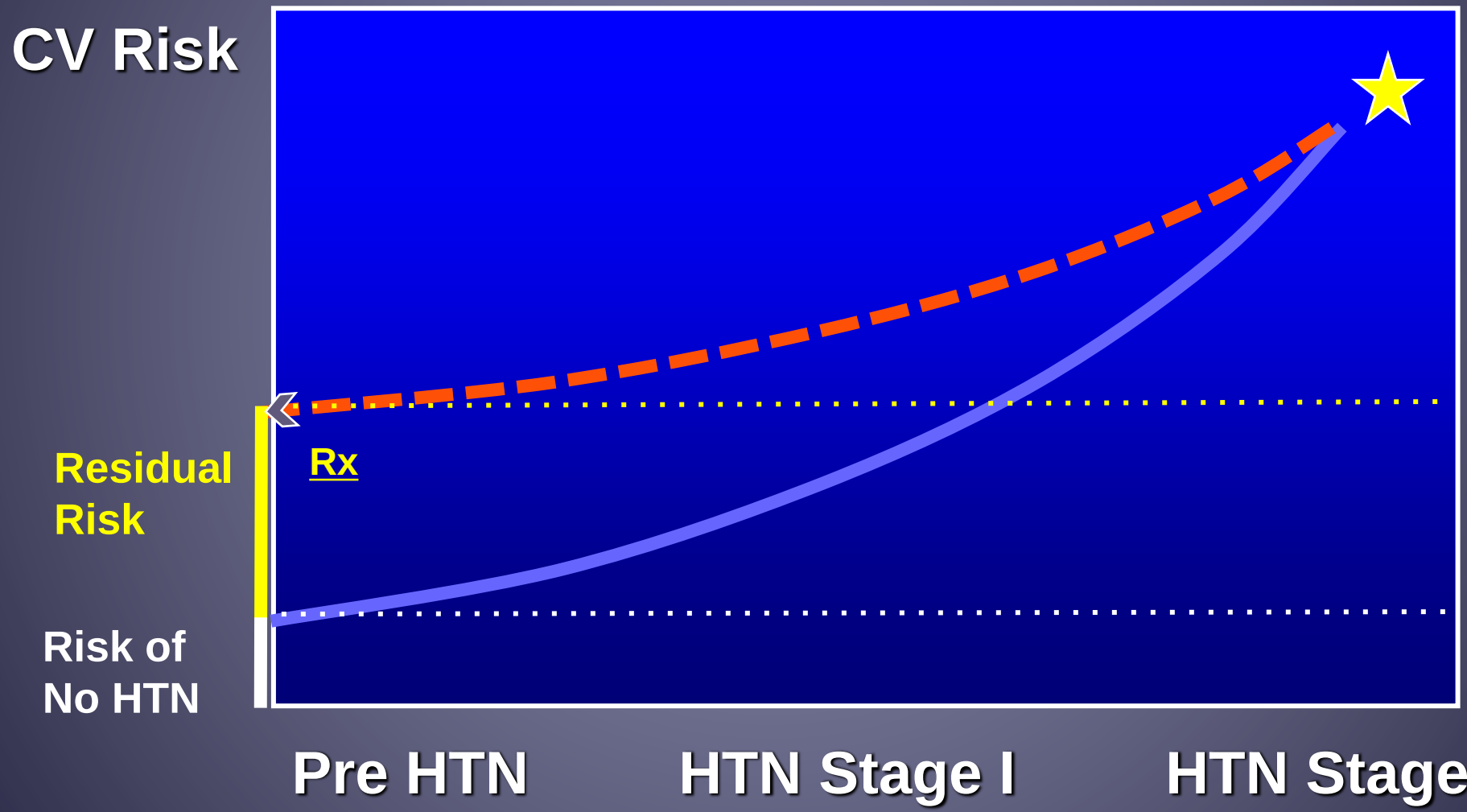

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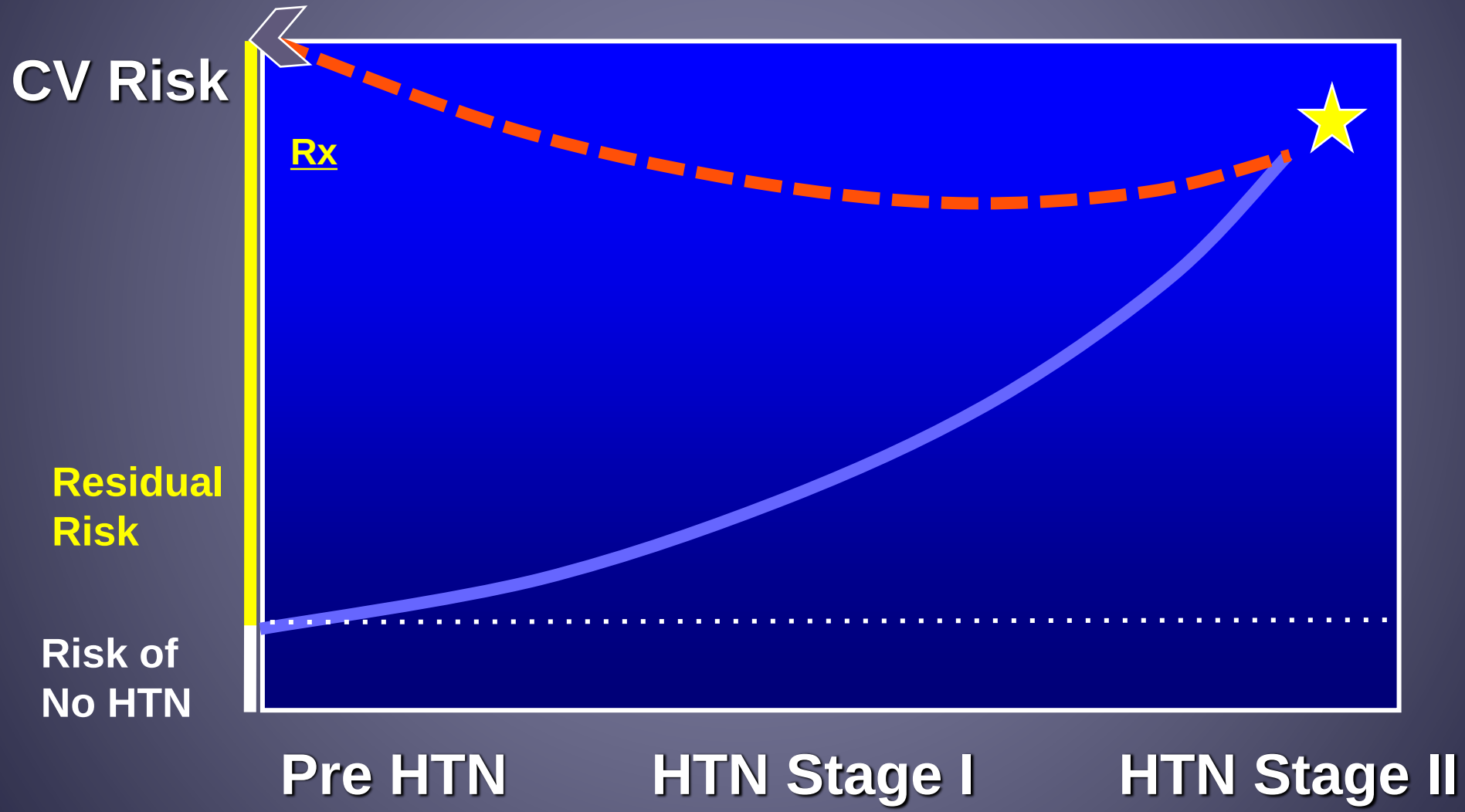
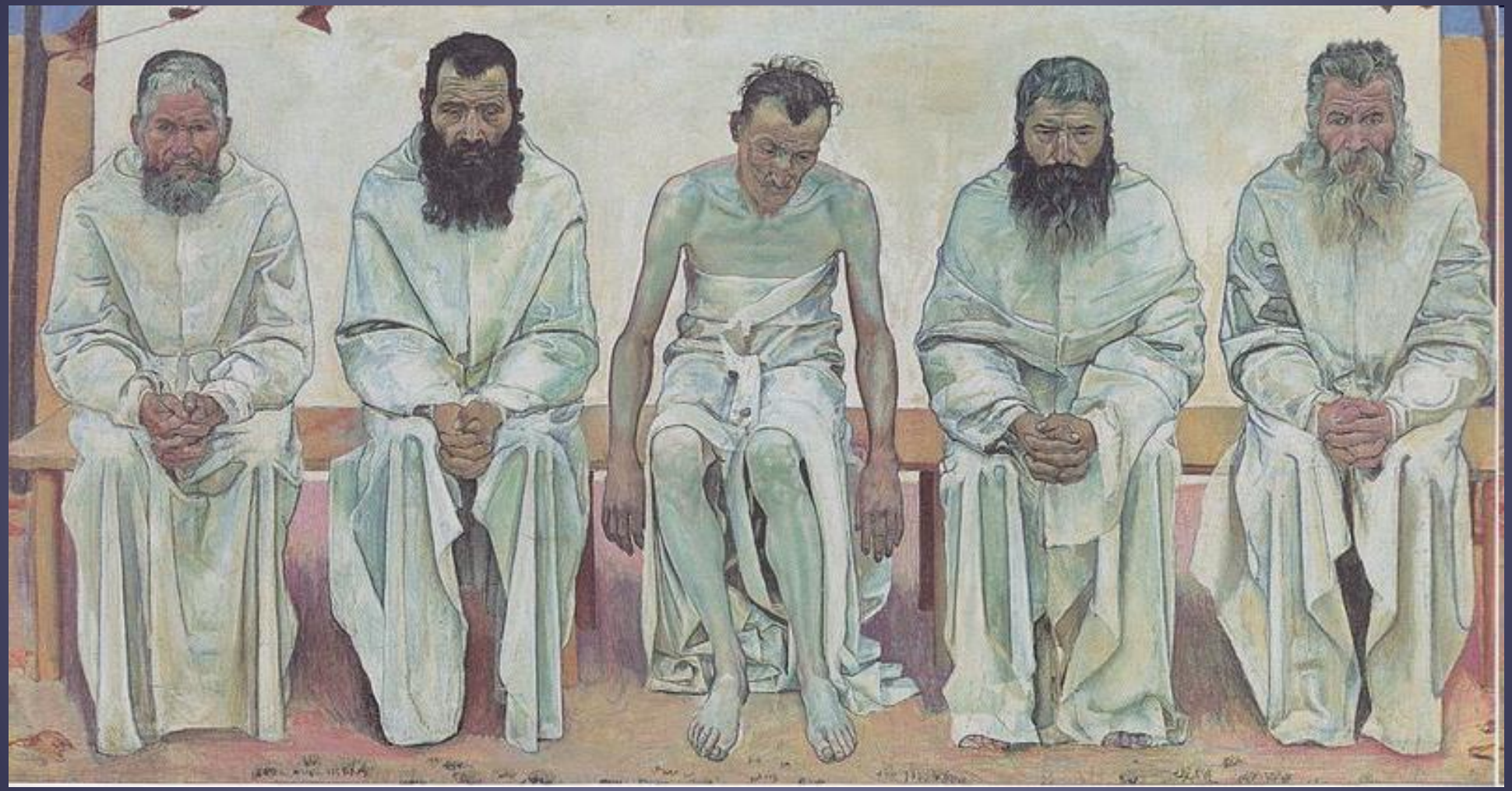


Point of No Return

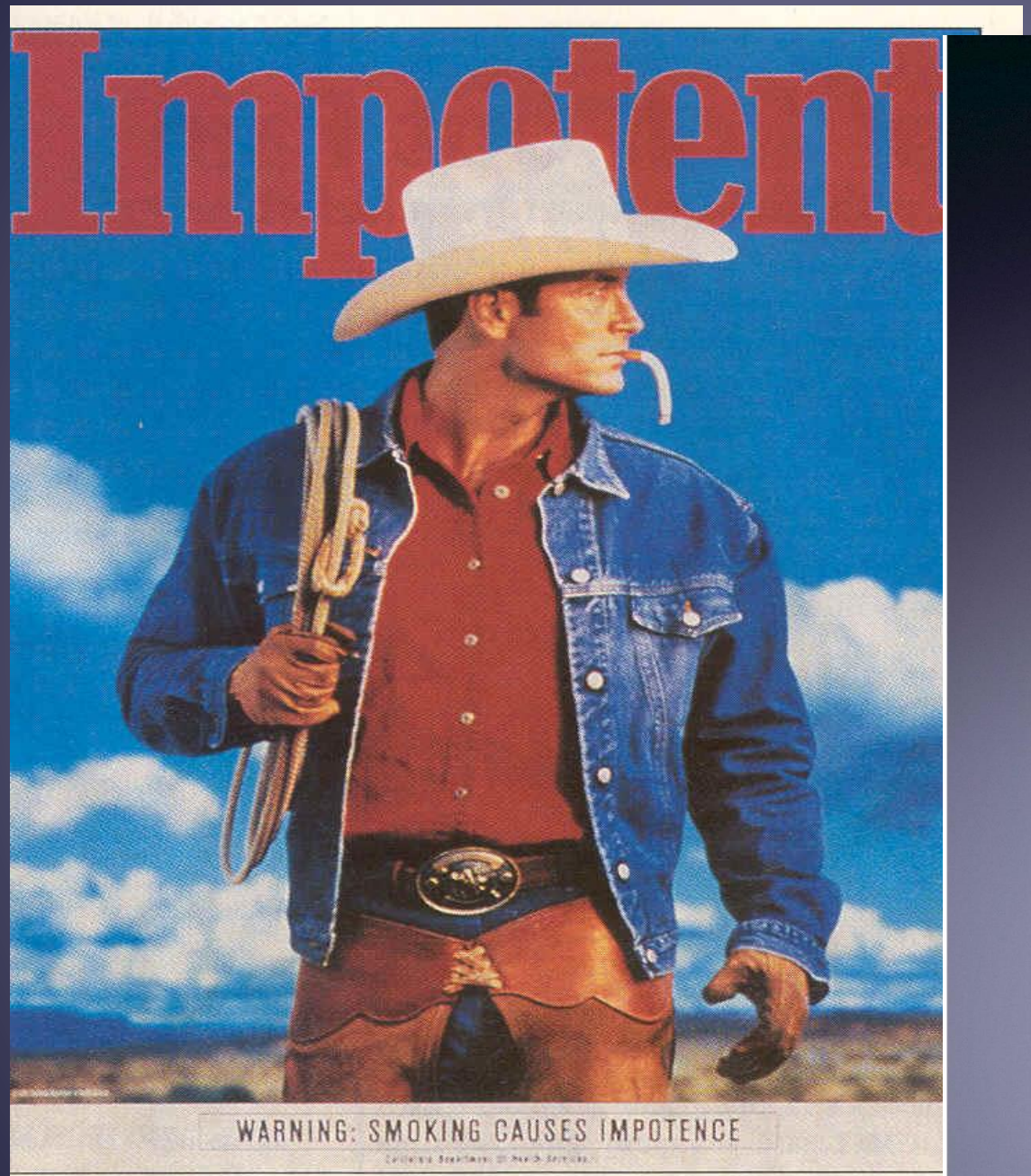
Hypertension and Polypharmacy: Take home messages

1. Lone Hypertension doesnt exist – comorbidities abound.
2. Treatment of hypertension per se requires polypharmacy.
3. Reduction of BP may not be beneficial – residual risk remains.

Die Lebensmüden, [Tired of Life]



Ferdinand Hodler, 1892



A $21 million antismoking campaign in California features billboard linking smoking to impotence. Public-health advocat

Josef Koudelka, geboren 1938, Tschechoslowakei/Frankreich: „Irland“, 1976 (Silbergelatine, 36 x 54 cm)

Hypertension and Polypharmacy: Take home messages

1. Lone Hypertension doesnt exist – comorbidities abound.
2. Treatment of hypertension per se requires polypharmacy.
3. Reduction of BP may not be beneficial – residual risk remains.
4. Adverse events of antihypertensive therapy may require treatment

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Polypill with or without Aspirin in Persons without Cardiovascular Disease

S. Yusuf, P. Joseph, A. Dans, P. Gao, K. Teo, D. Xavier, P. López-Jaramillo, K. Yusoff, A. Santoso, H. Gamra, S. Talukder, C. Christou, P. Girish, K. Yeates, F. Xavier, G. Dagenais, C. Rocha, T. McCready, J. Tyrwhitt, J. Bosch, and P. Pais, for the International Polycap Study 3 Investigators*

ABSTRACT

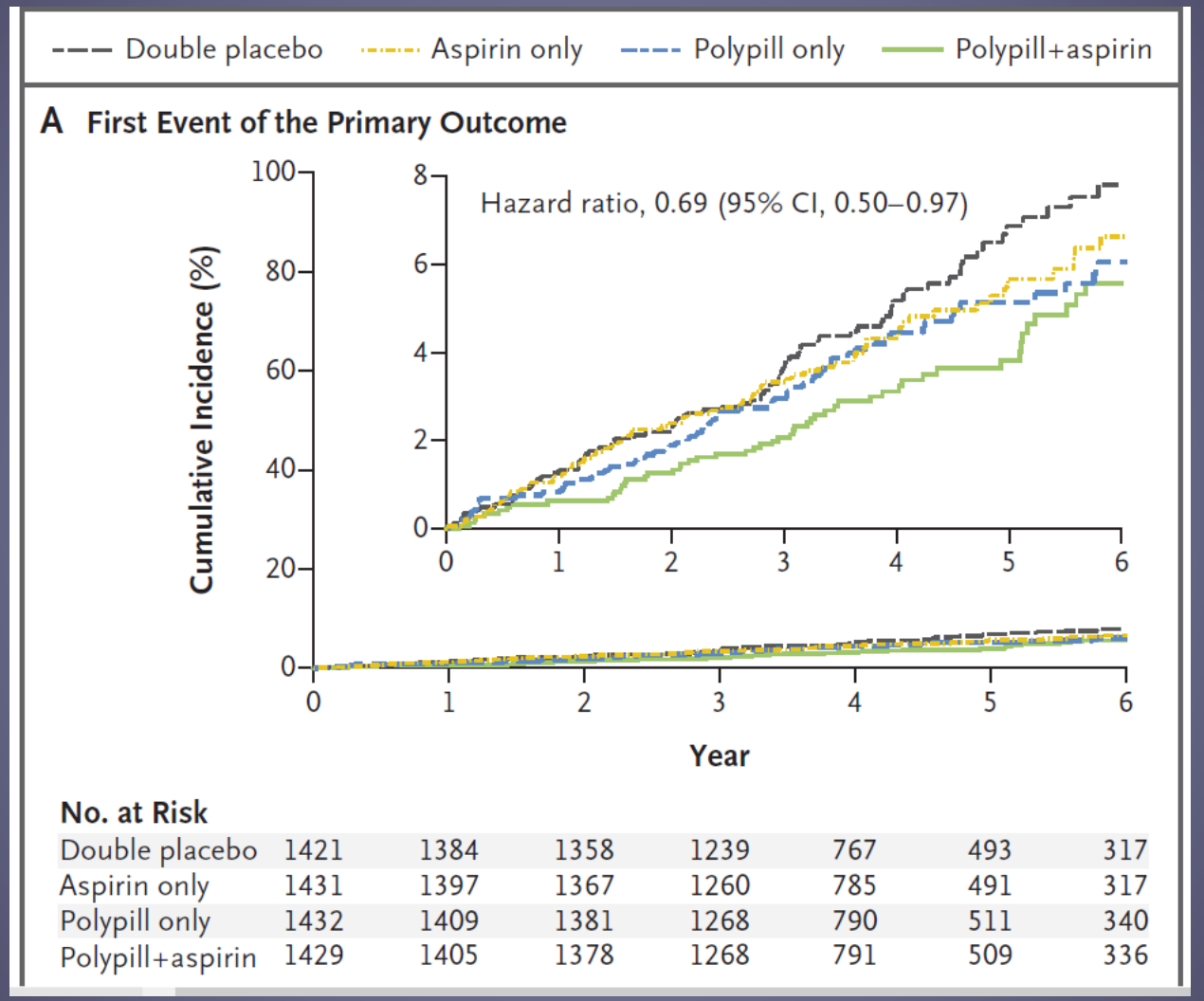
BACKGROUND

A polypill comprising statins, multiple blood-pressure–lowering drugs, and aspirin has been proposed to reduce the risk of cardiovascular disease.

METHODS

Using a 2-by-2-by-2 factorial design, we randomly assigned participants without cardiovascular disease who had an elevated INTERHEART Risk Score to receive a polypill (containing 40 mg of simvastatin, 100 mg of atenolol, 25 mg of hydrochlorothiazide, and 10 mg of ramipril) or placebo daily, aspirin (75 mg) or pla-

Yusuf et al. NEJM January 2021



Yusuf et al. NEJM January 2021

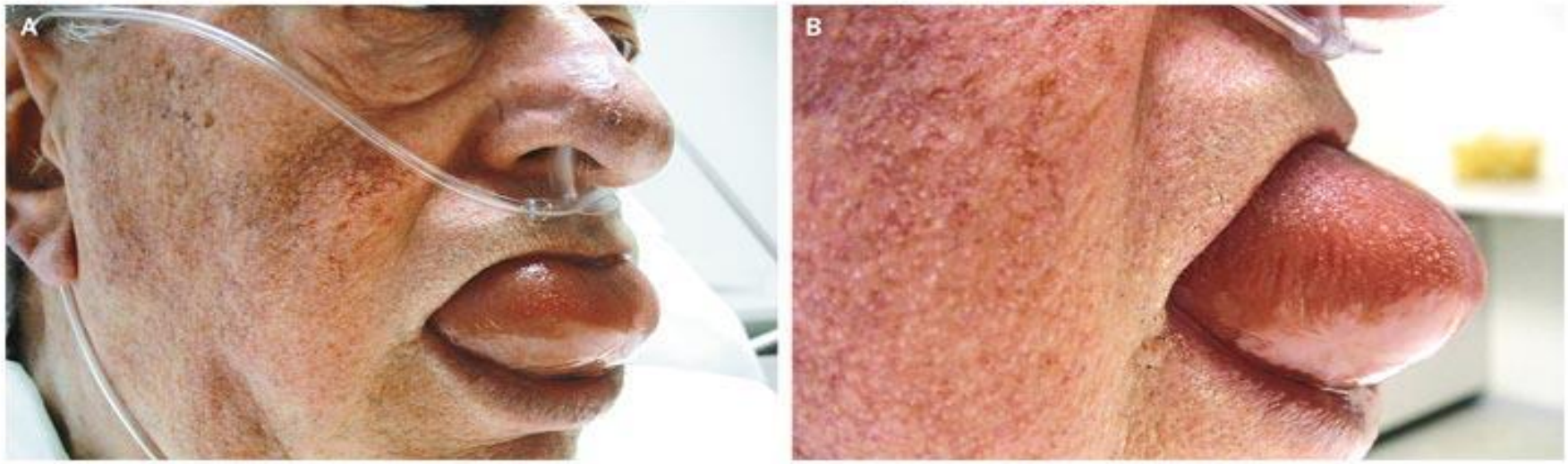
THE LANCET
Volume 390, Issue 10089, 1–7 July 2017, Page 26

Correspondence

Are ACE inhibitors acceptable ingredients in polypills?

Franz H Messerli [a, c, d] ✉, Sripal Bangalore [b], Stefano F Rimoldi [c], Jerzy Gąsowski [d], Juerg Nussberger [e]

A 75-year-old man treated with captopril for more than 3 years presented to the emergency department with diffuse swelling of his tongue that had begun a few hours earlier



Westra S and de Jager C. N Engl J Med 2006;355:295, July 20

The NEW ENGLAND JOURNAL of MEDICINE

ACE-Inhibitors and Angioedema (AE)

	# of patients
Worldwide ACE-I use	> 30,000,000
Episodes of AE/year	60,000
Episodes of life-threatening AE/year	12,000
Episodes of fatal AE/year	>1,000

Messerli FH, Nussberger J
Lancet 2000, 356: 608-609

Are ACE Inhibitors acceptable ingredients in polypills?

We estimated that exposing the 30 million people to ACE inhibitors, as The Lancet would welcome, could result in several hundred fatalities per year. Admittedly, some of these numbers are extrapolations, but they still beg the question of *whether ACE inhibitors are acceptable ingredients in polypills*.

Messerli et al. Lancet, March 2017

Hypertension and Polypharmacy: Take home messages

1. Lone Hypertension doesnt exist – comorbidities abound.
2. Treatment of hypertension per se requires polypharmacy.
3. Reduction of BP may not be beneficial – residual risk remains.
4. Adverse events of antihypertensive therapy may require treatment
5. Polypills reduce pill burden but one size does not fit all!

- **Medicine is still all about treating populations, not people - one-size-fits all treatments and diagnoses.**

Eric Topol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