**“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 2005

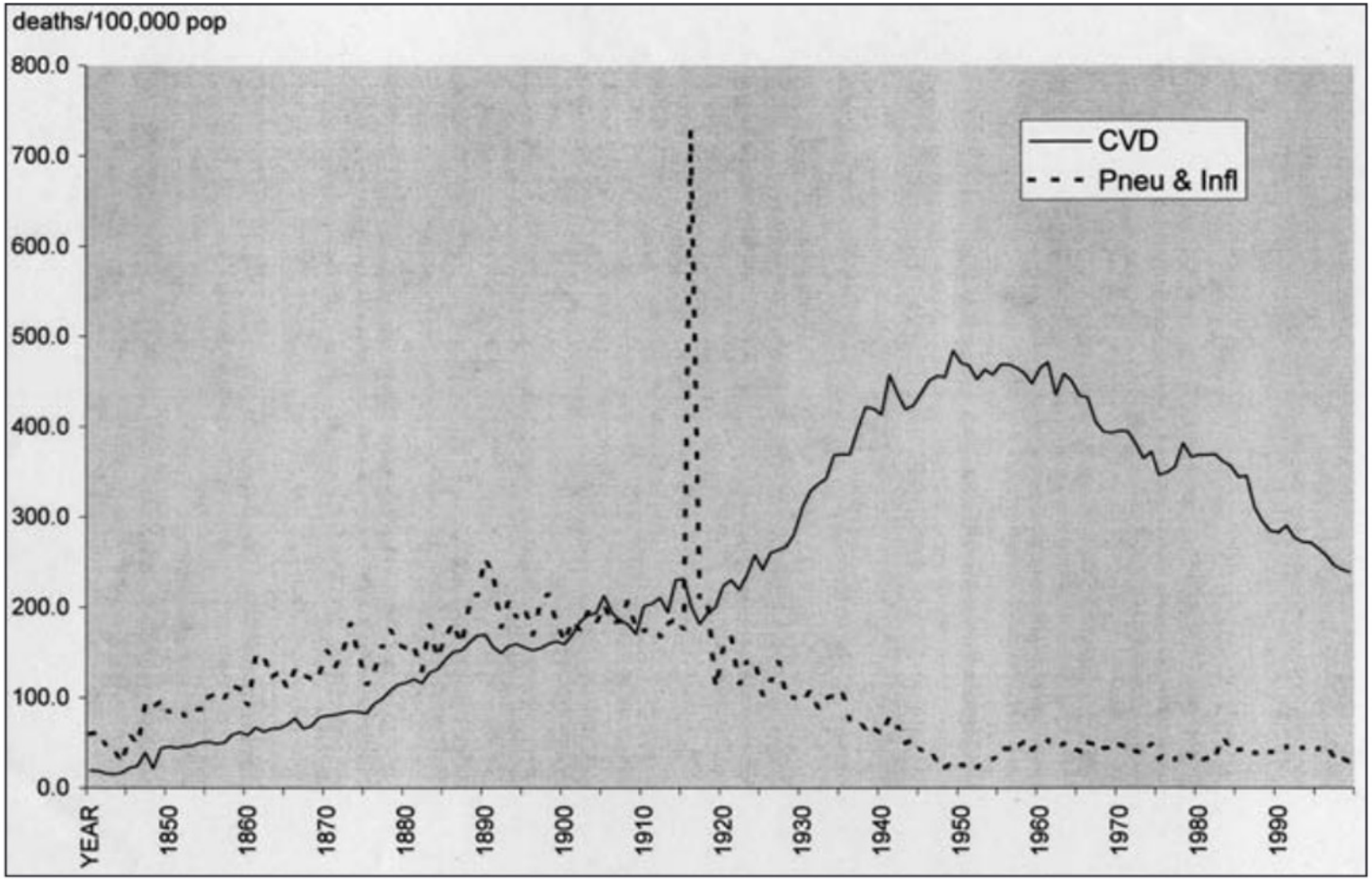
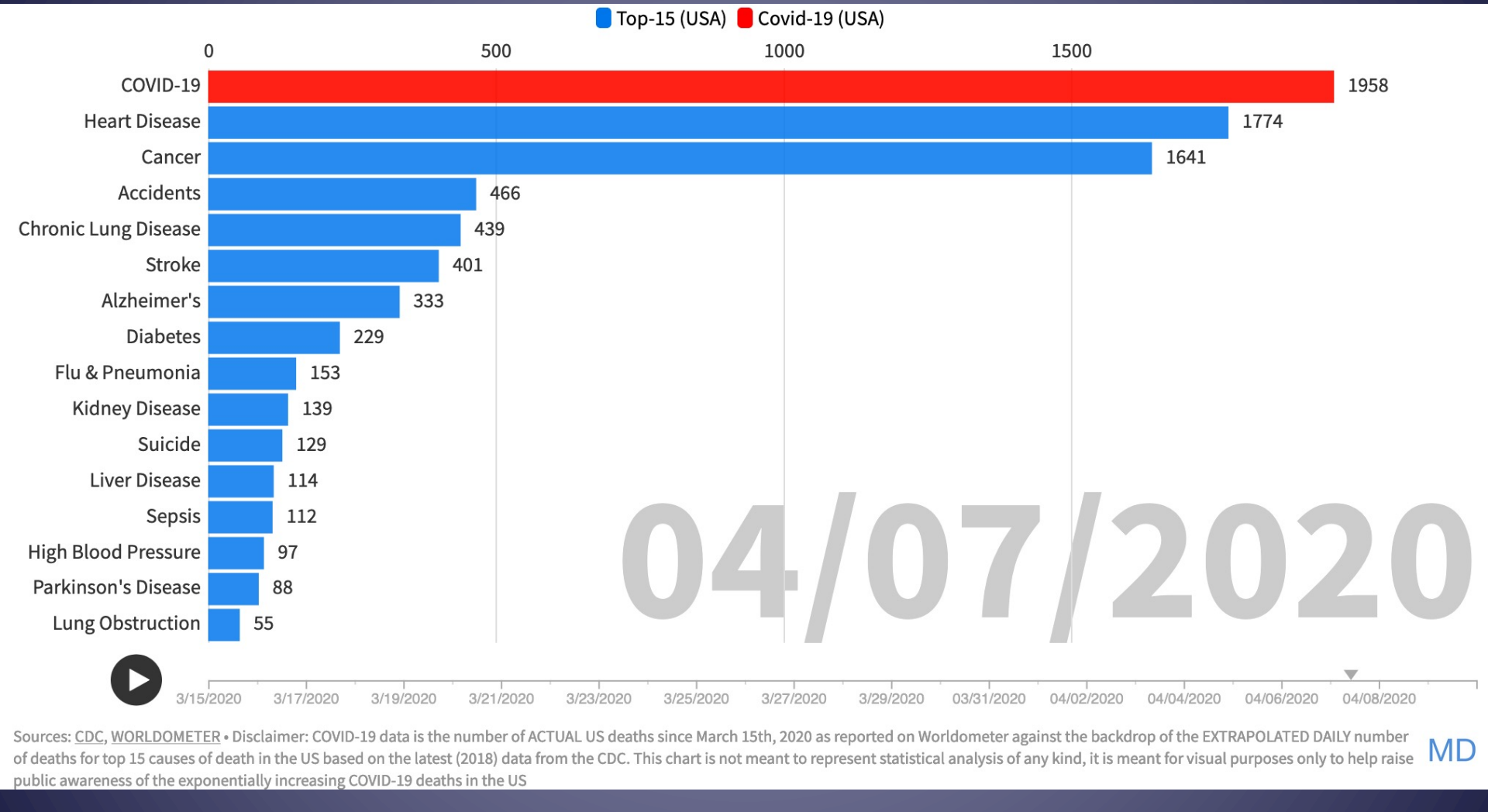



**FIGURE 1**

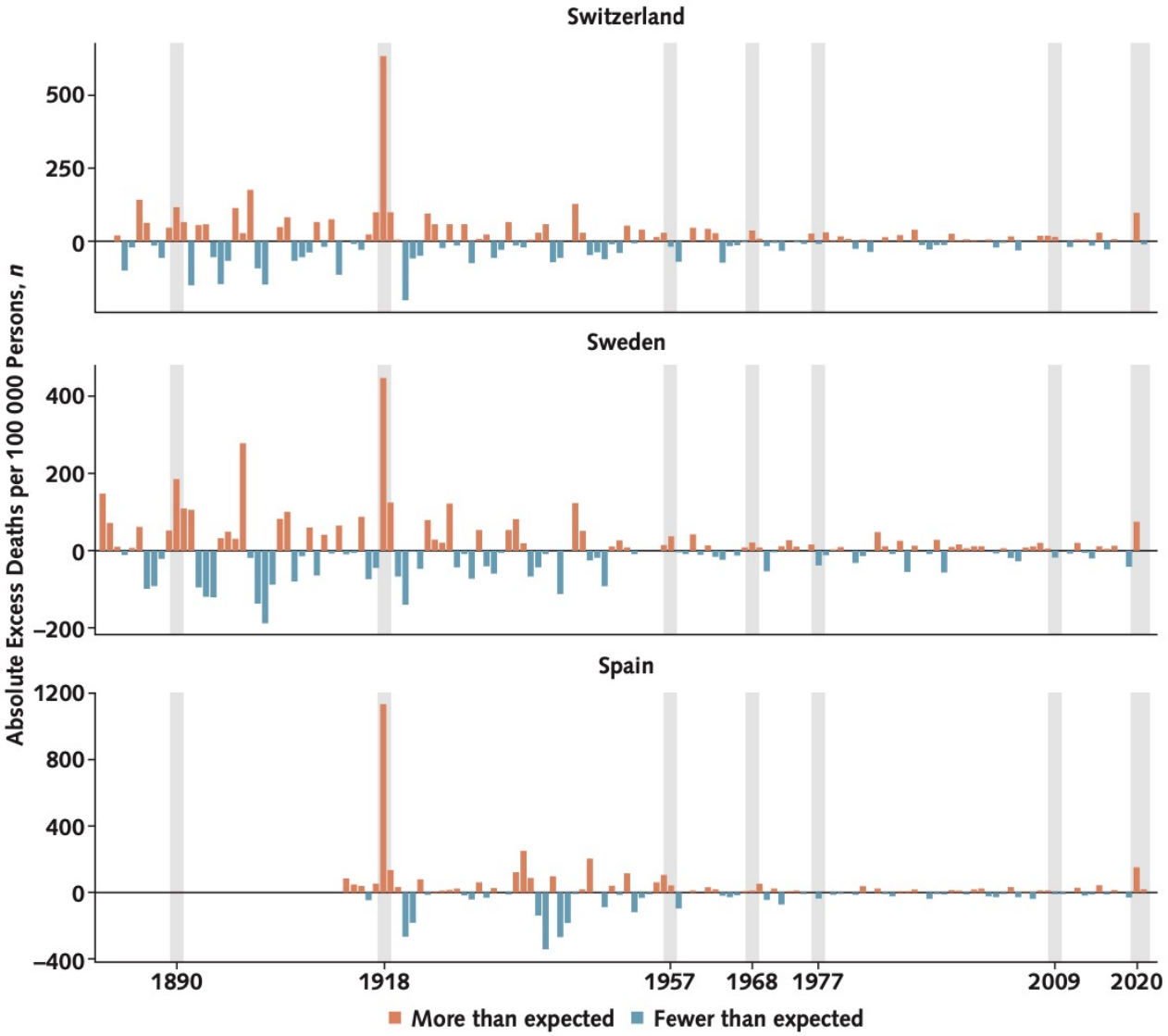
*Temporal trends in cardiovascular diseases (CVD) and pneumonia and influenza (Pneu & Infl) mortality, Massachusetts, 1842–2000.*




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

***Figure 1.*** Yearly numbers of excess deaths from all causes per 100 000 persons in Switzerland, Sweden, and Spain.




Staub et al. Annals Int Med Feb. 2022

- The patient in the vignette was a 56-year-old woman presenting for elevated blood pressure, which was noted at a job-site screening. She took naproxen sodium for joint pain (at a dose of 220 mg daily) and had gained 20 lb during the past 5 years, having now a body-mass index of 29. On examination, the sitting blood pressure was 162/94 mm Hg in both arms.

# You would initiate treatment with

- 1. ACE- Inhibitor, i.e. lisinopril 20 mg
- 2. CCB , i.e. amlodipine 5 mg
- 3. ARB , i.e. olmesartan 40 mg
- 4. Thiazide, i.e. HCTZ 12.5 mg
- 5. Combination

?

CLINICAL PRACTICE

Caren G. Solomon, M.D., M.P.H., *Editor*

# Initial Treatment of Hypertension

Sandra J. Taler, M.D.

*This Journal feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the author's clinical recommendations.*

From the Division of Nephrology and Hypertension, Mayo Clinic, Rochester, MN. Address reprint requests to Dr. Taler at the Division of Nephrology and Hypertension, Mayo Clinic, 200 First St. SW, Rochester, MN 55905, or at taler.sandra@mayo.edu.

N Engl J Med 2018;378:636-44.
DOI: 10.1056/NEJMcp1613481


A 56-year-old woman presents for elevated blood pressure, which was noted at a job-site screening. She has gained 20 lb (9.1 kg) during the past 5 years and takes naproxen sodium (at a dose of 220 mg daily) for joint pain. She has never smoked, and she consumes one or two alcoholic drinks daily. Both of her parents received a diagnosis of hypertension in their 50s. On examination, the blood pressure is 162/94 mm Hg in both arms while the patient is seated and 150/96 mm Hg while the patient is standing. The body-mass index (the weight in kilograms divided by the square of the height in meters) is 29. Her examination is notable only for abdominal obesity without bruits or masses. The serum level of sodium is 138 mmol per liter, potassium 3.8 mmol per liter, calcium 9.4 mg per deciliter (2.35 mmol per liter), fasting glucose 105 mg per deciliter (5.8 mmol per liter), and creatinine 0.8 mg per deciliter (71 μmol per liter). Urinalysis is negative. How would you further evaluate and treat this patient?

## THE CLINICAL PROBLEM

HYPERTENSION, THE ELEVATION OF SYSTOLIC BLOOD PRESSURE, DIASTOLIC blood pressure, or both above normal levels, is common in developed and developing countries and increases in prevalence with age. The thresh-

**Dr. Talor was one of the authors of ACC/AHA Guideline**

The NEW ENGLAND JOURNAL of MEDICINE

As to the management, the author, Dr. Talor suggested

"A thiazide-type diuretic **or** ACE-inhibitor is a reasonable first agent to prescribe, with follow-up blood-pressure and electrolyte measurements in 3 to 4 weeks".

**Dr. Talor was one of the authors of ACC/AHA Guideline**

# Lisinopril – a no brainer

## The most commenly prescribed antihypertensive worldwide

# Lisinopril

## Drug Usage Statistics, United States, 2013 - 2019

ClinCalc.com » Pharmacy » ClinCalc DrugStats » Lisinopril

## Lisinopril Summary for 2019

| | |
|---|---|
| Top drug rank | #3 (0) |
| Estimated number of prescriptions in the United States (2019) | 91,862,708 |
| Estimated number of patients in the United States (2019) | 19,990,170 |

# The ARB – MI Paradox



Editorials

## Angiotensin receptor blockers and myocardial infarction

*BMJ* 2004 ; 329 doi: https://doi.org/10.1136/bmj.329.7477.1248 (Published 25 November 2004)
Cite this as: *BMJ* 2004;329:1248



*Subodh Verma (subodh.verma@sympatico.ca), scientist, Marty Strauss (Dr.marty@bellnet.ca), consultant cardiologist*

Author affiliations

*These drugs may increase myocardial infarction—and patients may need to be told*

**Logic dictates that practice guidelines should recognize the unique cardiovascular benefits of ACEIs and their preferential use compared with ARBs. Were such advice to be given, the predicted impact on lives saved would be profound.**

**Strauss and Hall, Circulation 2021**

JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
VOL. 71, NO. 13, 2018

PUBLISHED BY ELSEVIER

THE PRESENT AND FUTURE

REVIEW TOPIC OF THE WEEK

# Angiotensin-Converting Enzyme Inhibitors in Hypertension

## To Use or Not to Use?

Franz H. Messerli, MD,[a,b] Sripal Bangalore, MD, MHA,[c] Chirag Bavishi, MD, MPH,[d] Stefano F. Rimoldi, MD[a]

**ABSTRACT**

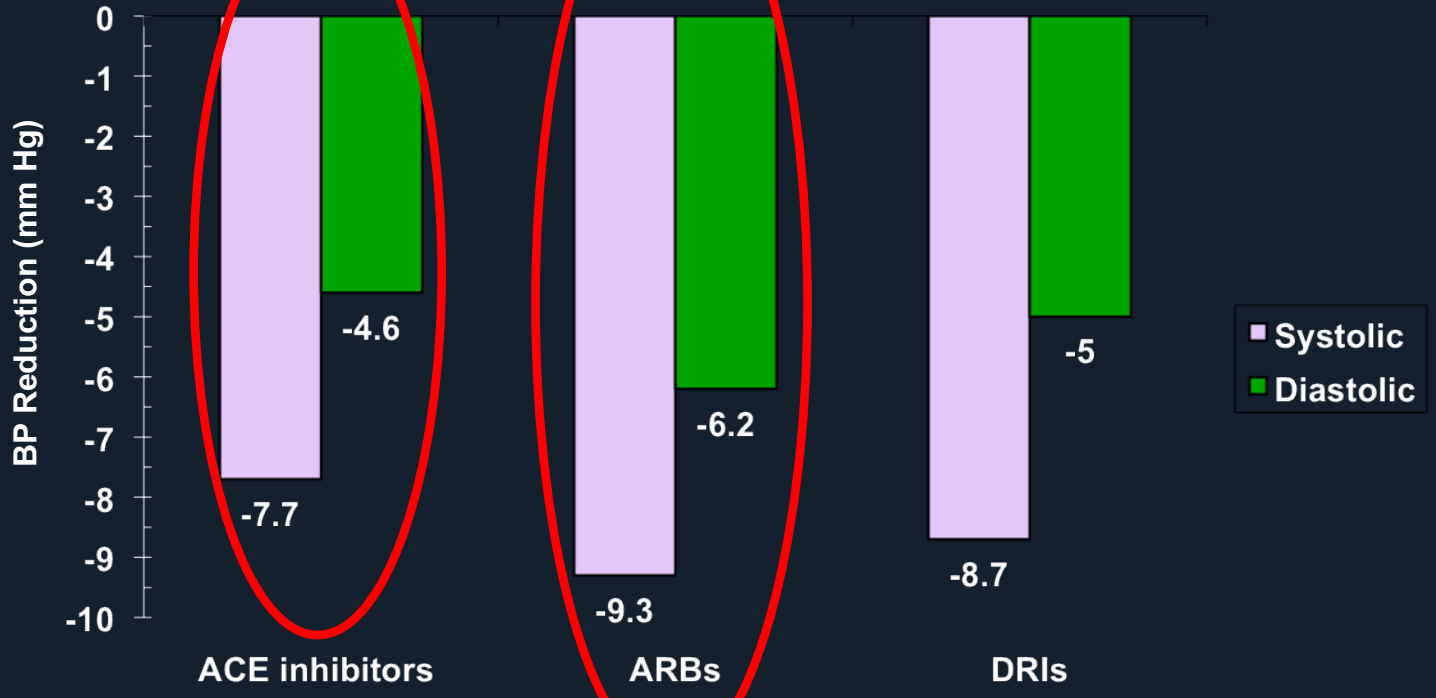
Most guidelines for the management of patients with cardiovascular disease recommend angiotensin-converting enzyme (ACE) inhibitors as first-choice therapy, whereas angiotensin receptor blockers (ARBs) are merely considered an alternative for ACE inhibitor–intolerant patients. The aim of this review was to compare outcomes and adverse events between ACE inhibitors and ARBs in patients. In patients with hypertension and hypertension with compelling indications, we found no difference in efficacy between ARBs and ACE inhibitors with regard to the surrogate endpoint of blood

# ACEi vs. ARBs

- **Antihypertensive Efficacy**
- **Tolerability**
- **Outcomes evidence**

# Are ACEi more potent antihypertensive agent than ARBs?

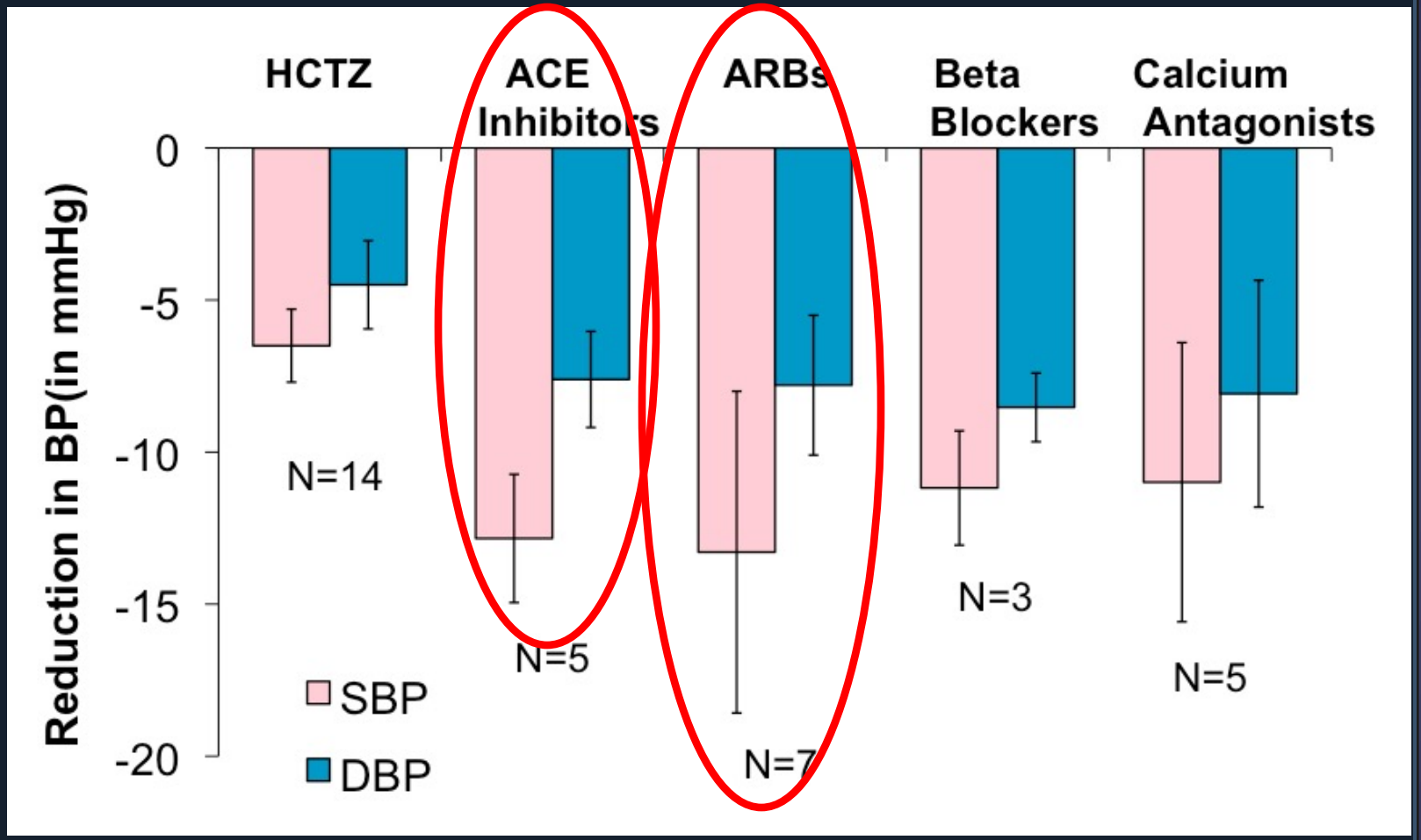
# Blood Pressure Reduction
## (Placebo Subtracted)




| | | | |
|---|---|---|---|
| # of Studies | 92 | 46 | 6 |
| # of Patients | 12954 | 13451 | 3694 |
| # of Drugs | 14 | 9 | 11 |

Messerli FH and Bangalore S. Circulation. 2009;119(3):371-3

# Ambulatory BP

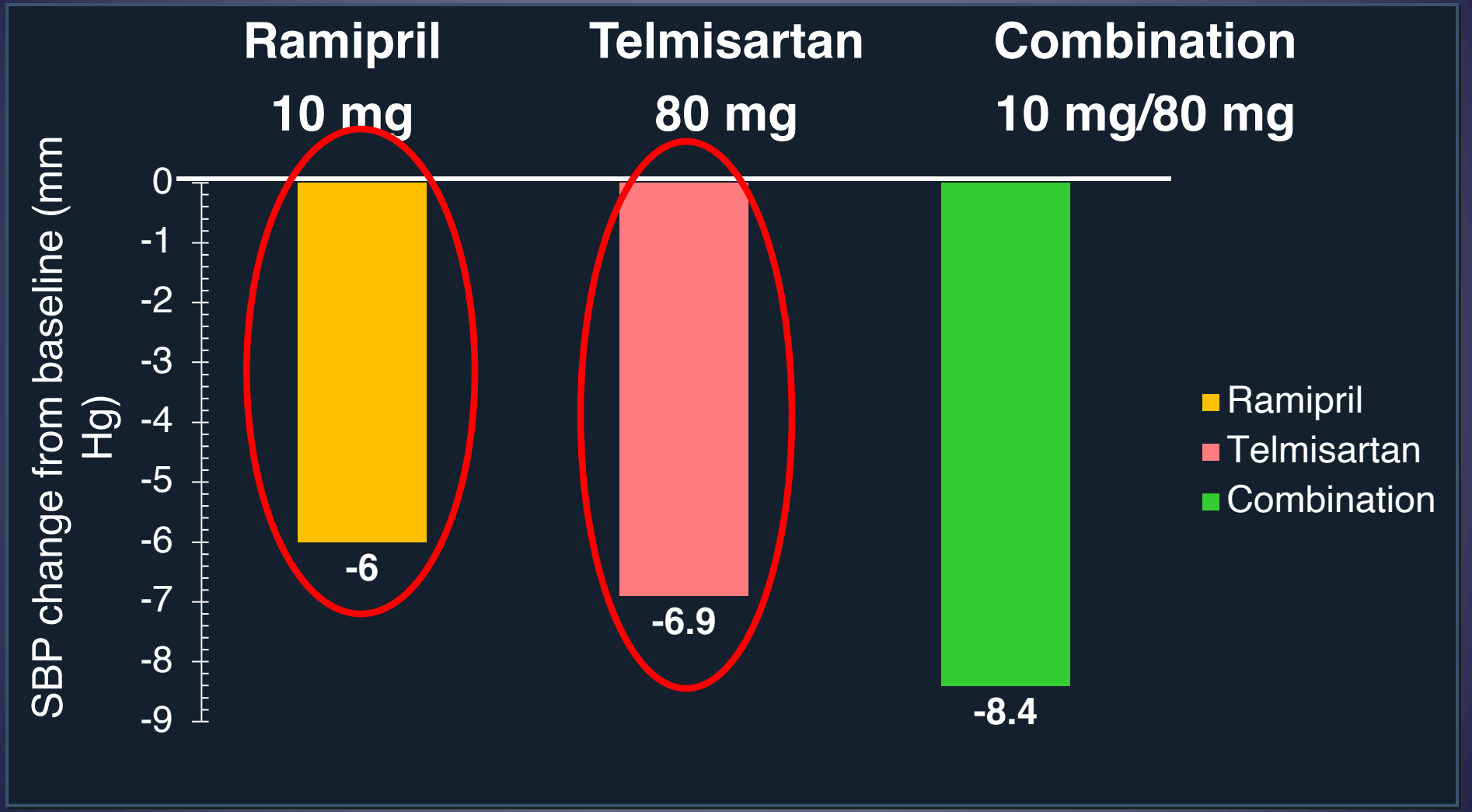



* Data from 19 trials and 1400 patients

Messerli, FH……Bangalore et al. J Am Coll Cardiol. 2011 Feb 1;57(5):590-600

ONTARGET

# Antihypertensive Efficacy



# ACEi vs. ARBs

- Antihypertensive Efficacy
- Tolerability
- Outcomes evidence

CLINICAL RESEARCH STUDY

THE AMERICAN JOURNAL of MEDICINE®

# Angiotensin-Converting Enzyme Inhibitor Associated Cough: Deceptive Information from the *Physicians' Desk Reference*

**Sripal Bangalore, MD, MHA,[a] Sunil Kumar, MD,[b] Franz H. Messerli, MD[b]**

*[a]Brigham and Women's Hospital, Harvard Medical School, Boston, Mass; [b]St. Luke's Roosevelt Hospital, Columbia University College of Physicians & Surgeons, New York, NY.*

**Bangalore et al. Am J Med, 2010, 123:1016-1030**

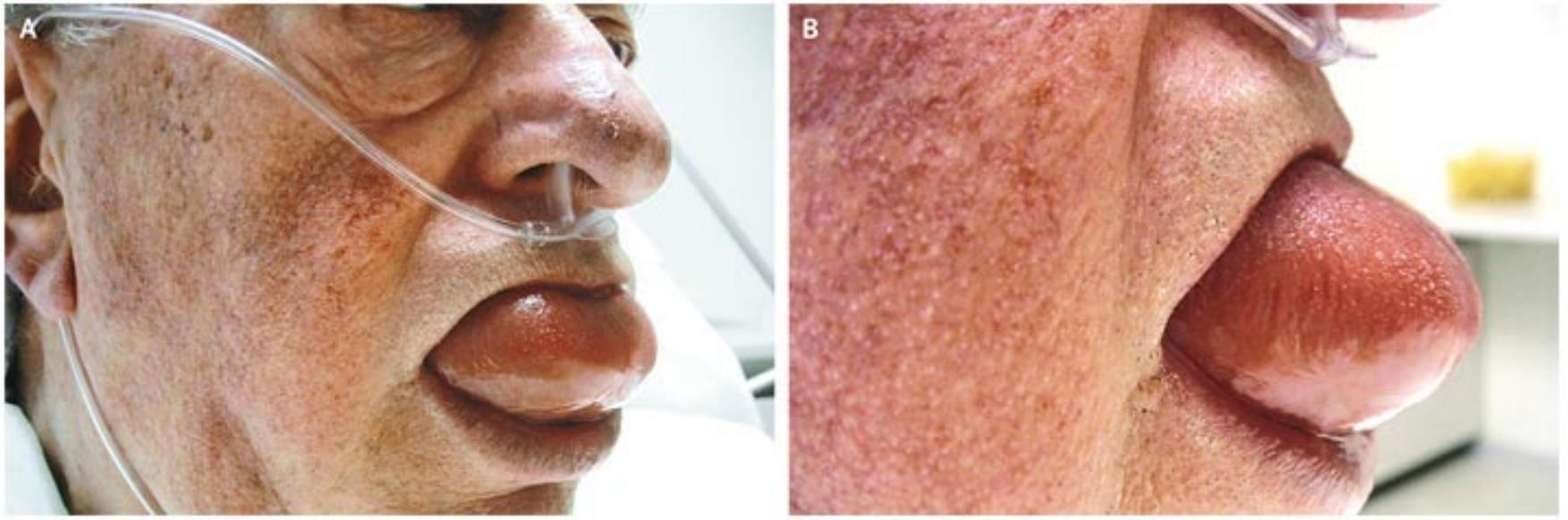
**“In Asian patients prevalence of ACEI – associated cough is more than 2.5 times higher than in Caucasian patients, and withdrawal rates exceed 30% (40,41). For this reason, many Asian physicians are no longer prescribing ACE inhibitors.”**

**Messerli et al. JACC 2018. April 3 : 1 4 7 4 – 8 2**


41. Tseng DS, Kwong J, Rezvani F, Coates AO. Angiotensin-converting enzyme-related cough among Chinese-Americans. Am J Med 2010;123: 183.e11–5.

42. Su M, Zhang Q, Bai X, et al. Availability, cost, and prescription patterns of antihypertensive medications in primary health care in China: a nationwide cross-sectional survey. Lancet 2017; 390:2559–68.

**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-Inhibitor Related Angioedema -- How Uncommon?

| | |
|---|---|
| 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

- A 63-year old, 71 in., 163 lb. man was running onto the front lawn waving a white towel and pointing toward his throat.  He collapsed, was attended to by neighbors and transported to a hospital emergency room…

- A tracheostomy was performed in the ED, but was of no avail and the patient was pronounced dead shortly thereafter. Medical history revealed **HTN treated with enalapril for at least eight months.**

# Asphyxia Due to ACE Inhibitor Mediated Angioedema

| Age | Sex | Race | Diagnosis | ACE Inhibitor | Duration of Exposure | Angioedema |
|---|---|---|---|---|---|---|
| 56 | F | AA | HTN, DM, CHF | fosinopril | 5 months | Tongue |
| 51 | F | AA | HTN, DM, CHF | benazepril | 21 months | Tongue, Lips |
| 63 | M | AA | HTN | enalapril | 8 month | Tongue, Oropharynx, Hypopharynx, Larynx |
| 54 | M | AA | HTN Nephr. Syn. | lisinopril | 10 hours | Tongue, Oropharynx |
| 65 | M | AA | HTN | enalapril | chronic | Tongue, Larynx |
| 71 | F | AA | HTN | lisinopril | chronic | Tongue, Larynx |

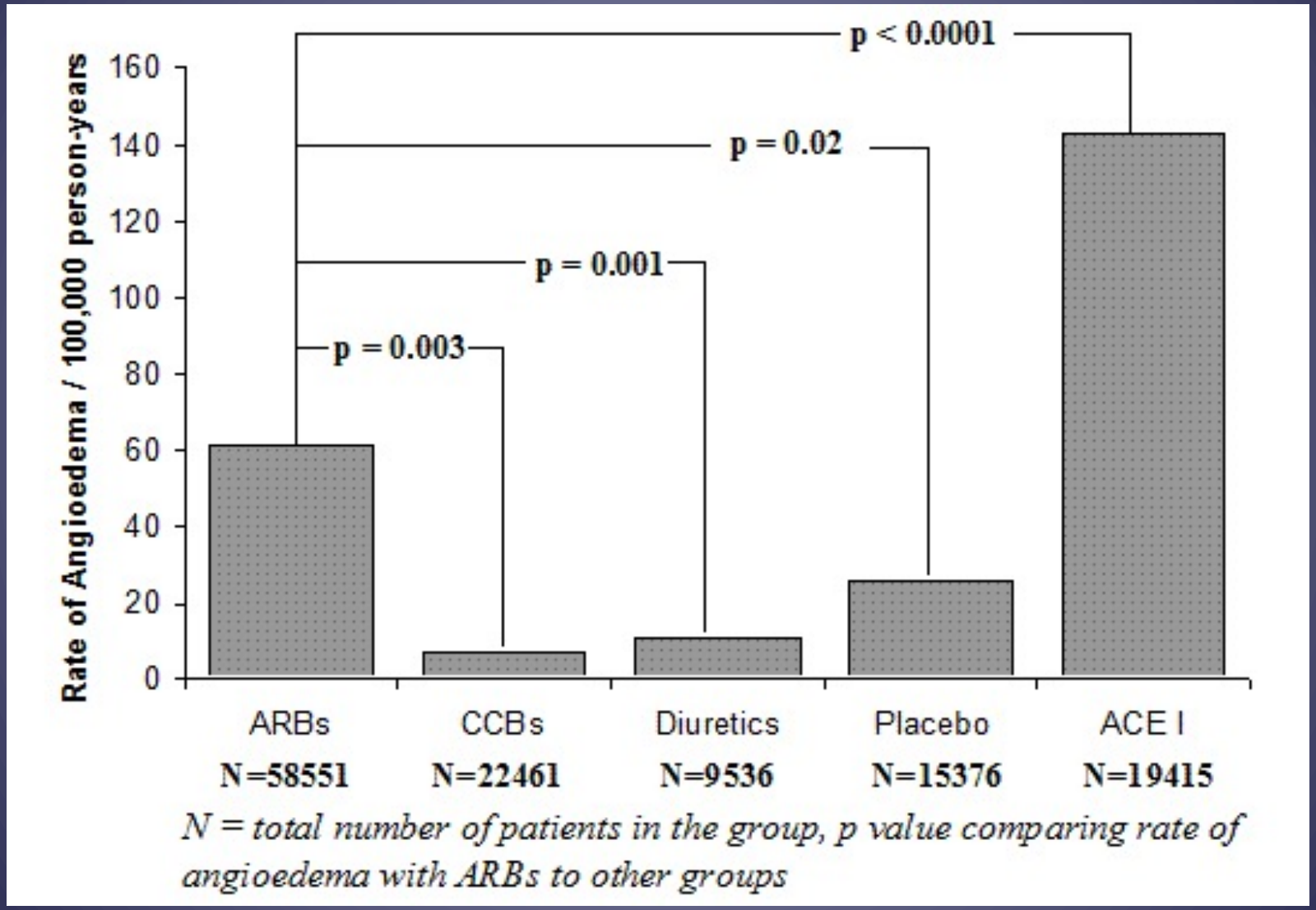
Dean DE, et al. J Forensic Science 2001;46:1239–43

# Angioedema with ACE-Inhibitors

- n = 85
- Rx for Hypertension  n = 82
- Rx for Heart Failure  n = 3
- Median duration of ACE-I Rx : 12 months.
- Range: 1 day – 13 years.
- Median time between 1st attack and ACE-I Rx withdrawal: 12 months.
- Range: 1 day – 12 years.

Lorenza et al. CMJ, 2006, 175, 1065

# Risk of Angioedema with Antihypertensive Therapy




Makani H, Messerli FH, et al. Am. J .Cardiol. 2012 May

# ACEi vs. ARBs

- Antihypertensive Efficacy
- Tolerability
- Outcomes evidence

**Angiotensin converting enzyme (ACE) inhibitors versus angiotensin receptor blockers for primary hypertension (Review)**

Li ECK, Heran BS, Wright JM

- 9 head-to-head trials- 11,007 participants
- Total mortality- No difference
- CV mortality- No difference
- CV events- No difference
- Withdrawal due to adverse effect- Favors ARB

Li et al. Cochrane Database of Systematic Reviews 2014,

Mayo Clinic Proceedings

Volume 91, Issue 1, January 2016, Pages 51–60

Original article

# Angiotensin-Converting Enzyme Inhibitors or Angiotensin Receptor Blockers in Patients Without Heart Failure? Insights From 254,301 Patients From Randomized Trials

Sripal Bangalore, MD, MHA[a], Robert Fakheri, MD[a], Bora Toklu, MD[b], Gbenga Ogedegbe, MD[a], Howard Weintraub, MD[a], Franz H. Messerli, MD[c, d]

Show more

http://dx.doi.org/10.1016/j.mayocp.2015.10.019



**Referred to by** Jean-Jacques Mourad

**The Different Effects of Angiotensin-Converting Enzyme Inhibitors and Angiotensin Receptor Blockers on Mortality**

*Mayo Clinic Proceedings, Volume 91, Issue 7, July 2016, Page 972*

# Outcomes in head-to-head comparison trials of ARBs vs ACEis.

| Outcome | No. of Studies | ARBs Events | ARBs Participants | ACEi Events | ACEi Participants | Heterogeneity ($I^2$) | RR (95% CI) (Random) | RR (95% CI) (Fixed) |
|---|---|---|---|---|---|---|---|---|
| All-cause mortality | 7 | 1003 | 11,211 | 1027 | 11,211 | 0.0% | 0.98 (0.90-1.07) | 0.98 (0.90-1.07) |
| Cardiovascular mortality | 5 | 601 | 8990 | 605 | 8990 | 0.0% | 1.00 (0.89-1.12) | 1.00 (0.89-1.12) |
| MI | 5 | 457 | 10,781 | 429 | 10,781 | 0.0% | 1.07 (0.94-1.22) | 1.07 (0.94-1.22) |
| Angina | 1 | 536 | 8542 | 567 | 8542 | NA | 0.95 (0.84-1.07) | 0.95 (0.84-1.07) |
| Stroke | 4 | 386 | 10,729 | 421 | 10,729 | 0.0% | 0.92 (0.80-1.06) | 0.92 (0.80-1.06) |
| Heart failure | 3 | 549 | 8842 | 524 | 8842 | 0.0% | 1.05 (0.93-1.19) | 1.05 (0.93-1.19) |
| Revascularization | 1 | 1290 | 8542 | 1269 | 8542 | NA | 1.02 (0.94-1.10) | 1.02 (0.94-1.10) |
| New-onset diabetes | 2 | 404 | 10,429 | 372 | 10,429 | 0.0% | 1.09 (0.95-1.26) | 1.09 (0.95-1.26) |
| Drug withdrawal | 8 | 558 | 11,317 | 738 | 11,317 | 77.2% | 0.78 (0.49-1.25) | 0.72 (0.65-0.81) |
| ESRD | 2 | 67 | 8648 | 76 | 8648 | 69.3% | 0.80 (0.41-1.53) | 0.88 (0.63-1.22) |
| Doubling of creatinine | 1 | 155 | 8542 | 140 | 8542 | NA | 1.11 (0.88-1.40) | 1.11 (0.88-1.40) |
| Hyperkalemia | 4 | 295 | 8938 | 292 | 8938 | 0.0% | 1.01 (0.86-1.19) | 1.01 (0.86-1.19) |

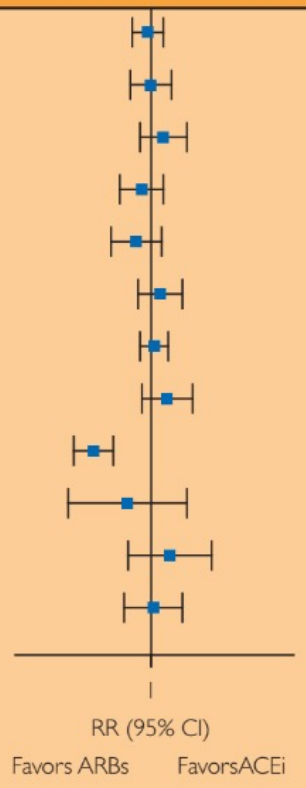



**FIGURE 6.** Outcomes in head-to-head comparison trials of ARBs vs ACEis. ARB = angiotensin receptor blocker; ESRD = end-stage renal disease; MI = myocardial infarction; RR = relative risk.

Bangalore, Messerli et al. Mayo Clinic Proceedings January 2016, 91, 51–60

# Conclusions

## ACEi vs. ARBs

- Antihypertensive efficacy: Similar
- Tolerability: ARBs better
- Outcomes: Largely similar

# ACEI trials versus ARB trials – the Generation GAP

| | ACEI trials | ARB trials |
|---|---|---|
| **Timing** | 1990's | 2000's |
| **CVD event rates in placebo arm** | 10.5% | 5.0% |
| **Concomitant Statin Therapy** | rare | common |
| **RAS blockade naivety before randomization** | most | rare |
| **Concomitant RAS Blockade in both study arms** | rare | common |
| **aggressive concomitant risk factor control** | rare | common |

**Messerli FH, Bangalore S, Circulation in press 2017**

Hypertension

ANTIHYPERTENSIVE TREATMENT

# Comparative First-Line Effectiveness and Safety of ACE (Angiotensin-Converting Enzyme) Inhibitors and Angiotensin Receptor Blockers

## A Multinational Cohort Study

RuiJun Chen, Marc A. Suchard, Harlan M. Krumholz, Martijn J. Schuemie, Steven Shea, Jon Duke, Nicole Pratt, Christian G. Reich, David Madigan, Seng Chan You, Patrick B. Ryan, George Hripcsak

**ABSTRACT:** ACE (angiotensin-converting enzyme) inhibitors and angiotensin receptor blockers (ARBs) are equally guideline-recommended first-line treatments for hypertension, yet few head-to-head studies exist. We compared the real-world effectiveness and safety of ACE inhibitors versus ARBs in the first-line treatment of hypertension. We implemented a retrospective, new-user comparative cohort design to estimate hazard ratios using techniques to minimize residual confounding and bias, specifically large-scale propensity score adjustment, empirical calibration, and full transparency. We

Chen et al. Hypertension. 2021;78:591–603.

- We included all patients with hypertension initiating monotherapy with an ACE inhibitor or ARB between 1996 and 2018 across 8 databases from the United States, Germany, and South Korea.
- We identified 2 29881 patients initiating treatment with ACE inhibitors and 673 938 patients with ARBs

Chen et al. Hypertension. 2021;78:591–603.

**Table 2. Primary Effectiveness Outcomes for ACE Inhibitors Compared With ARBs (on-Treatment, PS Stratification, Excluding NHIS/NSC)**

| Outcome | HR (95% CI) | *P* value | Calibrated HR (CI) | Calibrated *P* value |
|---|---|---|---|---|
| Acute myocardial infarction | 1.10 (1.04–1.17) | <0.01 | 1.11 (0.95–1.32) | 0.19 |
| CVEs | 1.04 (0.99–1.10) | 0.12 | 1.06 (0.90–1.25) | 0.49 |
| Heart failure | 1.02 (0.94–1.11) | 0.64 | 1.03 (0.87–1.24) | 0.68 |
| Stroke | 1.06 (1.00–1.12) | 0.06 | 1.07 (0.91–1.27) | 0.40 |

Calibrated hazard ratios (HRs), CIs, and *P* value are calibrated empirically using the distributions of positive and negative control outcomes to minimize residual systematic error (see Methods for detailed description). ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CVE, composite cardiovascular event; HR, hazard ratio; NHIS, National Health Insurance Service; NSC, National Sample Cohort; and PS, propensity score.

Chen et al. Hypertension. 2021;78:591–603.

- Summary
- ARBs demonstrate no statistically significant difference in real-world effectiveness at the class level and a significantly better safety profile as compared with ACE inhibitors in the first-line treatment of hypertension.
- despite their equal standing in guidelines … physicians and patients should consider preferentially starting ARBs rather than ACE inhibitors when initiating treatment for hypertension.

Chen et al. Hypertension. 2021;78:591–603.

article-commentary

Circulation

ON MY MIND

# Why Are We Still Prescribing Angiotensin-Converting Enzyme Inhibitors?

Franz H. Messerli, MD, HonD; Chirag Bavishi, MD, MPH; Sripal Bangalore, MD, MHA

*The human understanding when it has once adopted an opinion (either as being the received opinion or as being agreeable to itself) draws all things else to support and agree with it.*

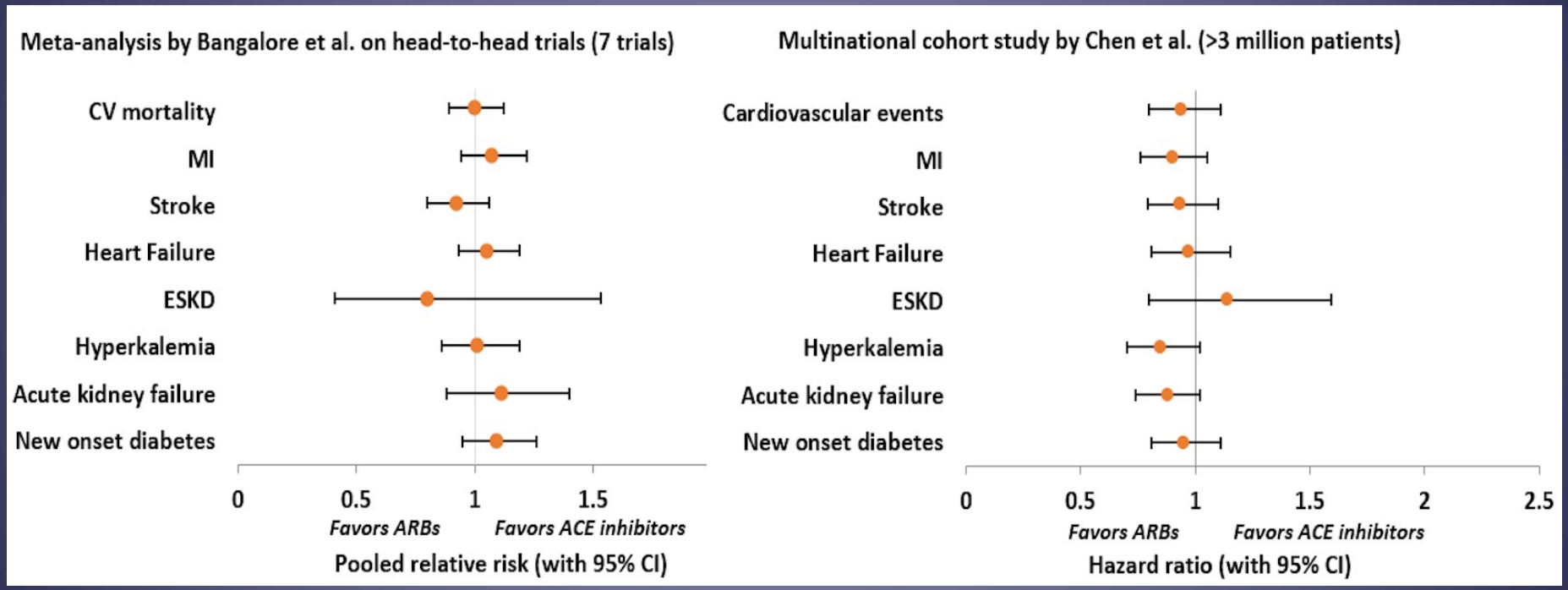
—Sir Francis Bacon, 1620

Prospective randomized controlled trials remain the gold standard in medicine because, when well performed, they provide us with knowledge untainted

head-to-head randomized trials suggested that ARBs are as efficacious and safe as ACE inhibitors but have fewer adverse effects and a lower risk of angioedema.

The recent comprehensive data set from Chen et al[2] corroborates and extends these findings. Across 8 databases, the authors identified 2297881 patients initiating treatment with ACE inhibitors and 673938 patients with ARBs. They documented no significant differences in the primary outcomes of acute MI (hazard ratio, 1.11 for ACE

# Outcome Evidence: ARBs vs ACEIs




Messerli et al. Circulation; February 8. 2022

- **For practicing clinicians this means that there is no longer any good reason to subject patients to ACEI's adverse effects.**
- **ACEIs may rapidly become a drug class of historical interest only.**

**Messerli et al. Circulation; February 8. 2022**

# Antihypertensive Drugs of Mostly Historical Interest

| | |
|---|---|
| Antiadrenergics | 1990's |
| Short-acting nifedipine | 1997 |
| Beta-blockers (Atenolol) | 1998 |
| Doxazosin | 2000 |
| Losartan | 2002 |
| Renin Inhibitors (Aliskiren) | 2015 |
| ACE-Inhibitors (Lisinopril | 2020 ??? |

# Dirty Laundry?

**Logic dictates that practice guidelines should recognize the unique cardiovascular benefits of ACEIs and their preferential use compared with ARBs. Were such advice to be given, the predicted impact on lives saved would be profound.**

**Strauss and Hall, Circulation 2021**

## DISCLOSURES

Dr Strauss has received speaker honorarium from and participated in advisory boards for Servier. Dr Hall has received speaker honorarium from Servier.

The NEW ENGLAND JOURNAL of MEDICINE

As to the management, the author, Dr. Talor suggested

"A thiazide-type diuretic **or** ACE-inhibitor is a reasonable first agent to prescribe, with follow-up blood-pressure and electrolyte measurements in 3 to 4 weeks".

**Dr. Talor was one of the authors of ACC/AHA Guideline**

# we have 4 simple questions regarding the management of this patient :

1. Since the patient's presenting BP was 32/14 mmHg above the target of 130/80 mmHg, why was treatment not initiated with 2 drugs as the ACC/AHA guidelines recommend?

Messerli et al. Hypertension, June 2018

# Choice of Initial Monotherapy Versus Initial Combination Drug Therapy

| COR | LOE | Recommendations for Choice of Initial Monotherapy Versus Initial Combination Drug Therapy* |
|---|---|---|
| I | C-EO | Initiation of antihypertensive drug therapy with 2 first-line agents of different classes, either as separate agents or in a fixed-dose combination, is recommended in adults with stage 2 hypertension and an average BP more than 20/10 mm Hg above their BP target. |
| IIa | C-EO | Initiation of antihypertensive drug therapy with a single antihypertensive drug is reasonable in adults with stage 1 hypertension and BP goal <130/80 mm Hg with dosage titration and sequential addition of other agents to achieve the BP target. |

## 2018 ESC/ESH Guidelines

"The above four 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…"

# we have 4 simple questions regarding the management of this patient :

1. Since the patient's presenting BP was 32/14 mmHg above the target of 130/80 mmHg, why was treatment not initiated with 2 drugs as the ACC/AHA guidelines recommend?

**How are we to expect practicing physicians to follow guidelines when their own authors demonstratively ignore them at the first possible opportunity?**

Messerli et al. Hypertension, June 2018

# we have 4 simple questions regarding the management of this patient :

2. Since the patient needed naproxen for joint pain, why was treatment initiated with a renin angiotensin blocker, the antihypertensive efficacy of which repeatedly has been documented to be reduced or abolished by NSAIDs (3, 4)?

Messerli et al. Hypertension, in press 2018

# we have 4 simple questions regarding the management of this patient:

3. Since outcome efficacy and antihypertensive efficacy has been shown to be equal for ACE inhibitors and ARBs (5, 6), why was, as the author emphasized, the drug class with more adverse effects, selected to initiate treatment?

Messerli et al. Hypertension, June 2018

JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY VOL. 71, NO. 13, 2018

PUBLISHED BY ELSEVIER

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Most guidelines for the management of patients with cardiovascular disease recommend angiotensin-converting enzyme (ACE) inhibitors as first-choice therapy, whereas angiotensin receptor blockers (ARBs) are merely considered an alternative for ACE inhibitor–intolerant patients. The aim of this review was to compare outcomes and adverse events between ACE inhibitors and ARBs in patients. In patients with hypertension and hypertension with compelling indications

Messerli et al. JACC 2018, 71, 1474-81

# we have 4 simple questions regarding the management of this patient :

4. “thiazide-type diuretic”.

Why was the recommendation for a “thiazide-type diuretic” and not specific for chlorthalidone, since the guidelines state “Chlorthalidone preferred based on prolonged half-life and proven trial reduction of CVD”?

Messerli et al. Hypertension, in press 2018

COMMENTAAR

# Bij hypertensie liever chloortalidon dan hydrochloorthiazide

Albertus J. Kooter en Yvo M. Smulders

Enkele decennia nadat melding was gemaakt van het diuretische effect van het antibacteriële middel sulfanilamide, werd in 1957 het derivaat chloorthiazide geïntroduceerd, gevolgd door hydrochloorthiazide (HCT) en het aan thiazides verwante chloortalidon. Inmiddels is HCT wereldwijd het meest voorgeschreven thiazidediureticum. Van de 8 thiazideprescripties in Nederland zijn er 7 voor HCT en slechts 1 voor chloortalidon. Daarbij zijn

mechanisme achter dit vaatverwijdende effect is vooralsnog onopgehelderd.[2] Hoewel nog niet zeker, is het wel aannemelijk dat ook het vaatverwijdende effect van chloortalidon langer aanhoudt dan dat van HCT, wellicht door de lange halfwaardetijd.

Waarschijnlijk vertalen de verschillen in farmacokinetische eigenschappen zich in een stabieler effect van chloortalidon op zowel natriurese als vaatverwijding.

NED TIJDSCHR GENEESKD. 2010;154:A1608

- Based on the available information, the patient could have been started on a **low dose combination of ARB with a CCB**.
- the above 4 points would become mute and there would be little if any need for “follow-up … electrolyte measurements in 3 to 4 weeks”

Messerli et al. Hypertension, June 2018

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

# Effect of Salt Substitution on Cardiovascular Events and Death

B. Neal, Y. Wu, X. Feng, R. Zhang, Y. Zhang, J. Shi,* J. Zhang, M. Tian, L. Huang, Z. Li, Y. Yu, Y. Zhao, B. Zhou, J. Sun, Y. Liu, X. Yin, Z. Hao, J. Yu, K.-C. Li, X. Zhang, P. Duan, F. Wang, B. Ma, W. Shi, G.L. Di Tanna, S. Stepien, S. Shan, S.-A. Pearson, N. Li, L.L. Yan, D. Labarthe, and P. Elliott

## ABSTRACT

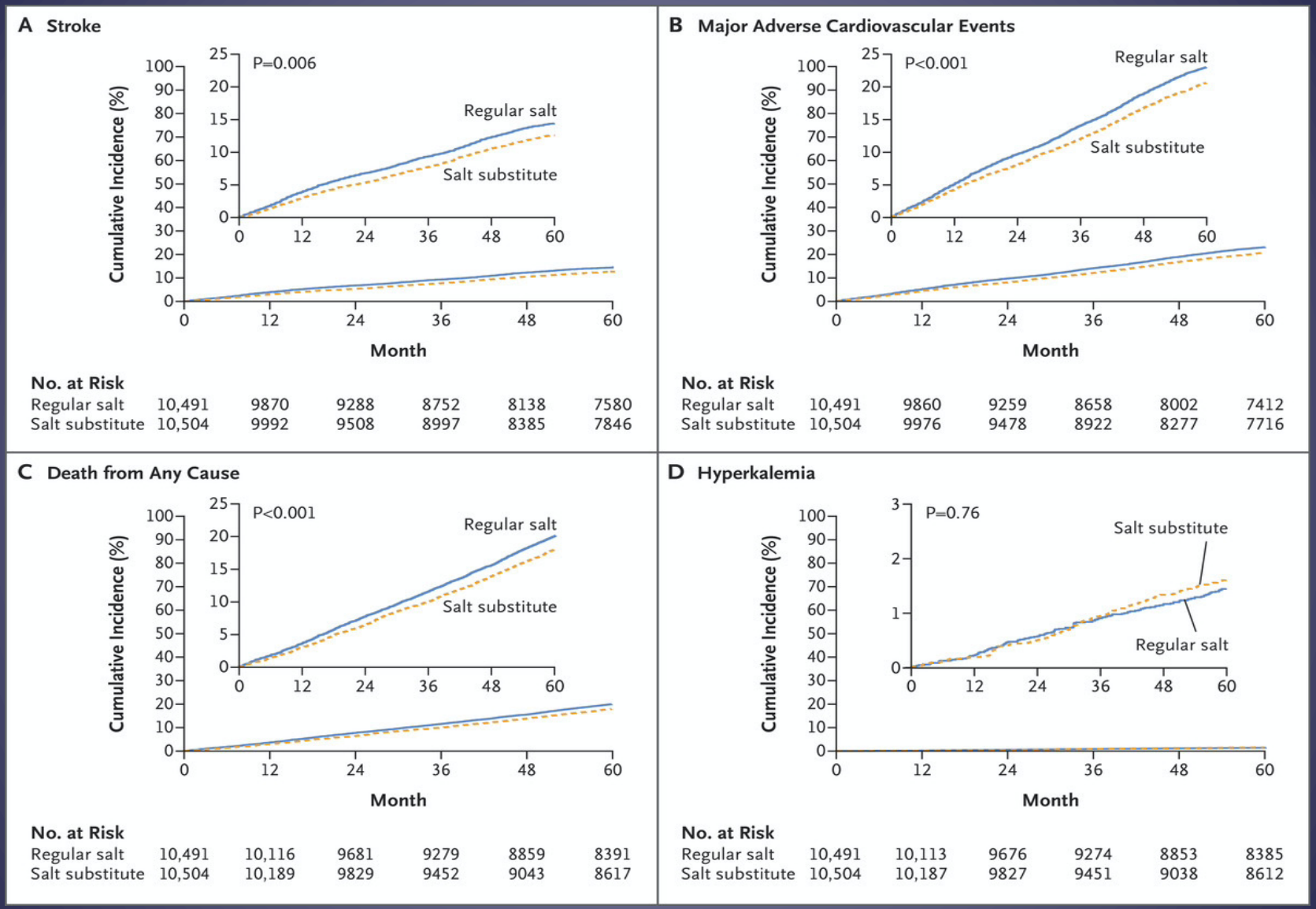
**BACKGROUND**

Salt substitutes with reduced sodium levels and increased potassium levels have been shown to lower blood pressure, but their effects on cardiovascular and safety outcomes are uncertain.

- Participants with prior stroke or risk for stroke were randomized to a salt substitute (n = 10,504) versus regular salt (n = 10,491).
- Total number of enrollees: 20,995
- Duration of follow-up: 4.74 years
- Mean patient age: 65 years

Neal et al. N Engl J Med 2021. September 16th.

# Effects of Salt Substitution on Trial Outcomes.




B Neal et al. N Engl J Med 2021. DOI: 10.1056/NEJMoa2105675

The NEW ENGLAND JOURNAL of MEDICINE

**Table 1. Effects of Salt Substitution on Cardiovascular Outcomes and Death.***

| Outcome | Salt Substitute | Regular Salt | Rate Ratio (95% CI) |
|---|---|---|---|
| | *no. of events per 1000 person-years* | | |
| Stroke | 29.14 | 33.65 | 0.86 (0.77–0.96) |
| Fatal | 6.78 | 8.79 | 0.77 (0.65–0.91) |
| Nonfatal | 22.36 | 24.86 | 0.90 (0.80–1.01) |
| Ischemic | 21.36 | 22.90 | 0.93 (0.82–1.05) |
| Hemorrhagic | 4.37 | 6.30 | 0.69 (0.56–0.85) |
| Undetermined | 3.41 | 4.45 | 0.76 (0.61–0.96) |

Neal et al. N Engl J Med 2021. DOI: 10.1056/NEJMoa2105675

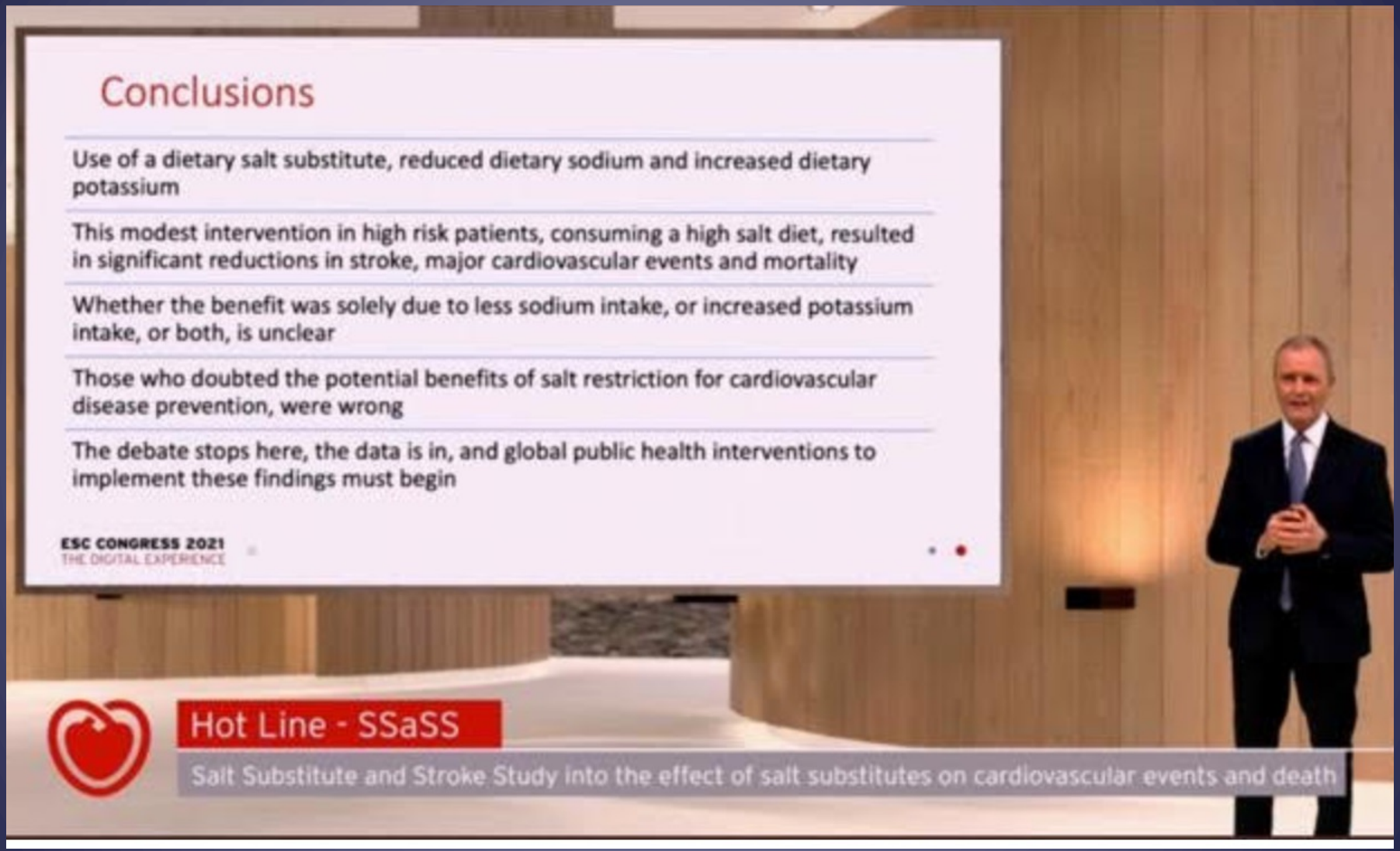
## CONCLUSIONS

- Among persons who had a history of stroke or were 60 years of age or older and had high blood pressure, the rates of stroke, major cardiovascular events, and death from any cause were lower with the salt substitute than with regular salt

Neal et al. N Engl J Med 2021. DOI: 10.1056/NEJMoa2105675

- “Our data also provide reassurance about the efficacy and safety of sodium-intake reduction for the prevention of cardiovascular events and death.”

Neal et al. N Engl J Med 2021. September 16th.


Conclusions
Use of a dietary salt substitute, reduced dietary sodium and increased dietary potassium
This modest intervention in high risk patients, consuming a high salt diet, resulted in significant reductions in stroke, major cardiovascular events and mortality
Whether the benefit was solely due to less sodium intake, or increased potassium intake, or both, is unclear
Those who doubted the potential benefits of salt restriction for cardiovascular disease prevention, were wrong
The debate stops here, the data is in, and global public health interventions to implement these findings must begin
ESC CONGRESS 2021
THE DIGITAL EXPERIENCE
Hot Line - SSaSS
Salt Substitute and Stroke Study into the effect of salt substitutes on cardiovascular events and death

The New York Times

- **“Cutting Out Even a Little Salt Can Have Big Health Benefits”**

Oct. 11, 2021, Jane Brody

# Effect of Salt Substitution on 24-hour Na and K excretion*

* Data from Neat B. et al. NEJM, August 29, 2021

| | sodium | potassium |
|---|---|---|
| Global mean intake | 3.94g/day (2) | 1.7 g to 3.7 g/day (3) |
| 24-hour urinary excretion at baseline | 4.3 g (187 mmol) | 1.4 g (36 mmol) |
| | | |
| | | |

Messerli, O'Donnell, Mente, Yusuf; Eur. Heart J. 2022

CLINICAL KIDNEY JOURNAL

ckj OXFORD era edta LEADING EUROPEAN NEPHROLOGY

*Clinical Kidney Journal*, 2020, vol. 13, no. 6, 952–968

doi: 10.1093/ckj/sfaa157
Advance Access Publication Date: 2 September 2020
CKJ Review

CKJ REVIEW

# Dietary potassium and the kidney: lifesaving physiology

Kuang-Yu Wei[1,2], Martin Gritter[1], Liffert Vogt[3], Martin H. de Borst[4], Joris I. Rotmans[5] and Ewout J. Hoorn [1]

[1]Department of Internal Medicine, Division of Nephrology and Transplantation, Erasmus MC, University Medical Center Rotterdam, Rotterdam, The Netherlands, [2]Department of Internal Medicine, Division of Nephrology, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan, [3]Department of Internal Medicine, Division of Nephrology, Amsterdam University Medical Center, Amsterdam, The

# recommended levels of K intake: 3.5 -4.7 g

- “a long-term low K diet can cause chronic Na reabsorption by upregulating NCC (Na/Cl co-transporter) with subsequent plasma volume expansion and hypertension.
- low K diet-induced Na reabsorption through NCC may be a key driver in the pathogenesis of salt-sensitive hypertension

Wey KY et al. Clin Kidney J. 2020 Sep 2;13(6):952-968

# Effect of Salt Substitution on 24-hour Na and K excretion*

* Data from Neat B. et al. NEJM, August 29, 2021

| | sodium | potassium |
|---|---|---|
| NHANES | 3.61 g/ day | 2.16 g/ day (9) |
| Switzerland | 3.63 g/ day | 2.57 g/ day (15) |
| 24-hour urinary excretion at baseline | 4.3 g (187 mmol) | 1.4 g (36 mmol) |
| Effect of Intervention (salt substitute) | –0.35 g (15.21 mmol) | +0.8 g (20.64 mmol) |
| Change from baseline % | 8.1 % | 57.3 % |

Messerli, O'Donnell, Mente, Yusuf; Eur. Heart J. 2022

- “Our data also provide reassurance about the efficacy and safety of sodium-intake reduction for the prevention of cardiovascular events and death.”

?

Neal et al. N Engl J Med 2021. DOI: 10.1056/NEJMoa2105675

- "Our data also provide reassurance about the **efficacy and safety of sodium-intake reduction** for the prevention of cardiovascular events and death."

?

Neal et al. N Engl J Med 2021. Sept 16

- The SSaSS trial provides novel information on the **efficacy and safety of increasing potassium intake** for the prevention of cardiovascular events and death in a population with very low potassium intake and persisting high sodium intake

Messerli, O'Donnell, Mente, Yusuf; Eur. Heart J. 2022

# recommended levels of K intake: 3.5 -4.7 g

- “increasing dietary K intake to recommended levels (3.5 -4.7 g) could be an effective public health strategy to reduce hypertension and cardiovascular disease”

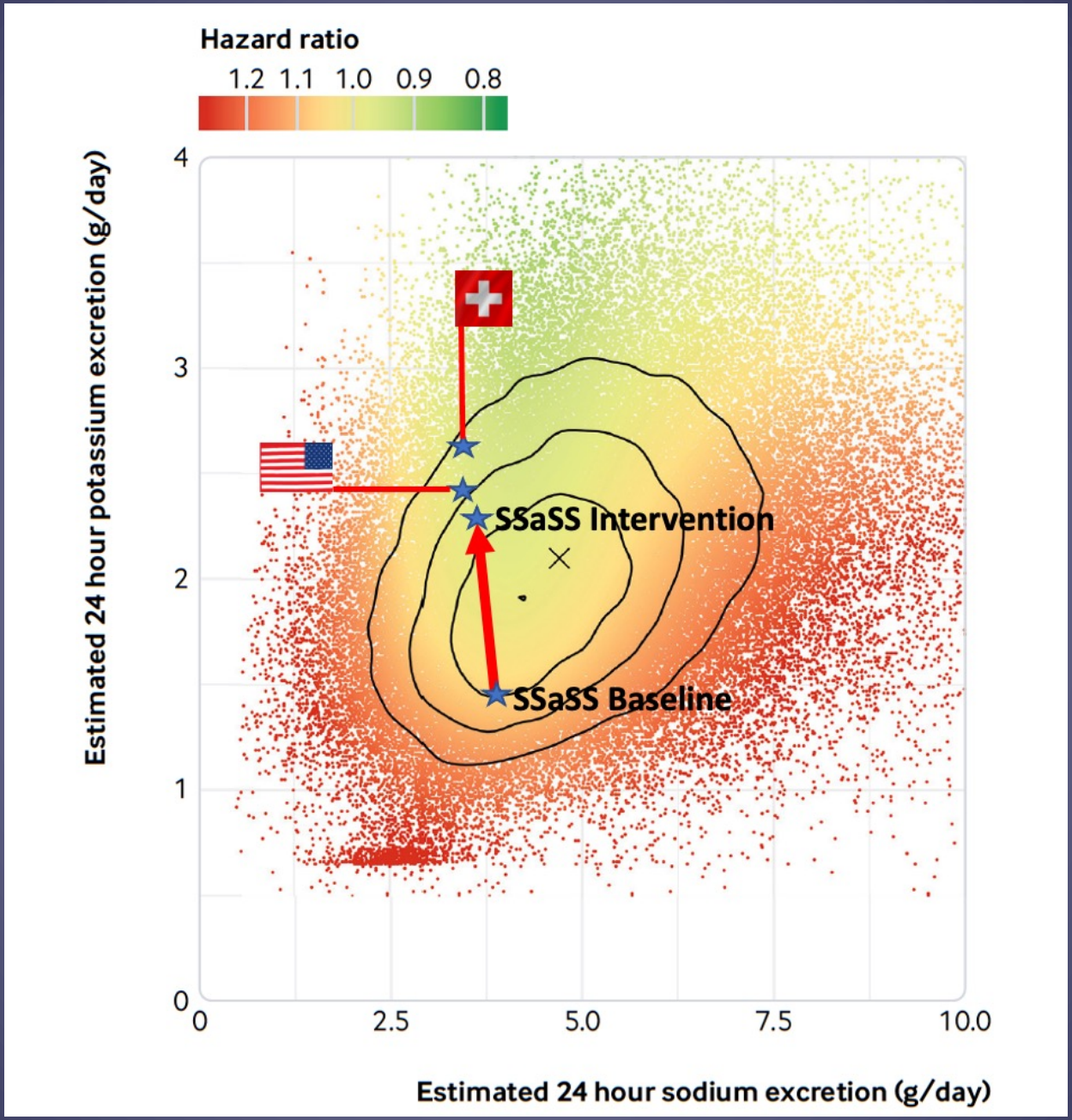
Wey KY et al. Clin Kidney J. 2020 Sep 2;13(6):952-968

# sodium and potassium excretion, effect on cardiovascular events and mortality



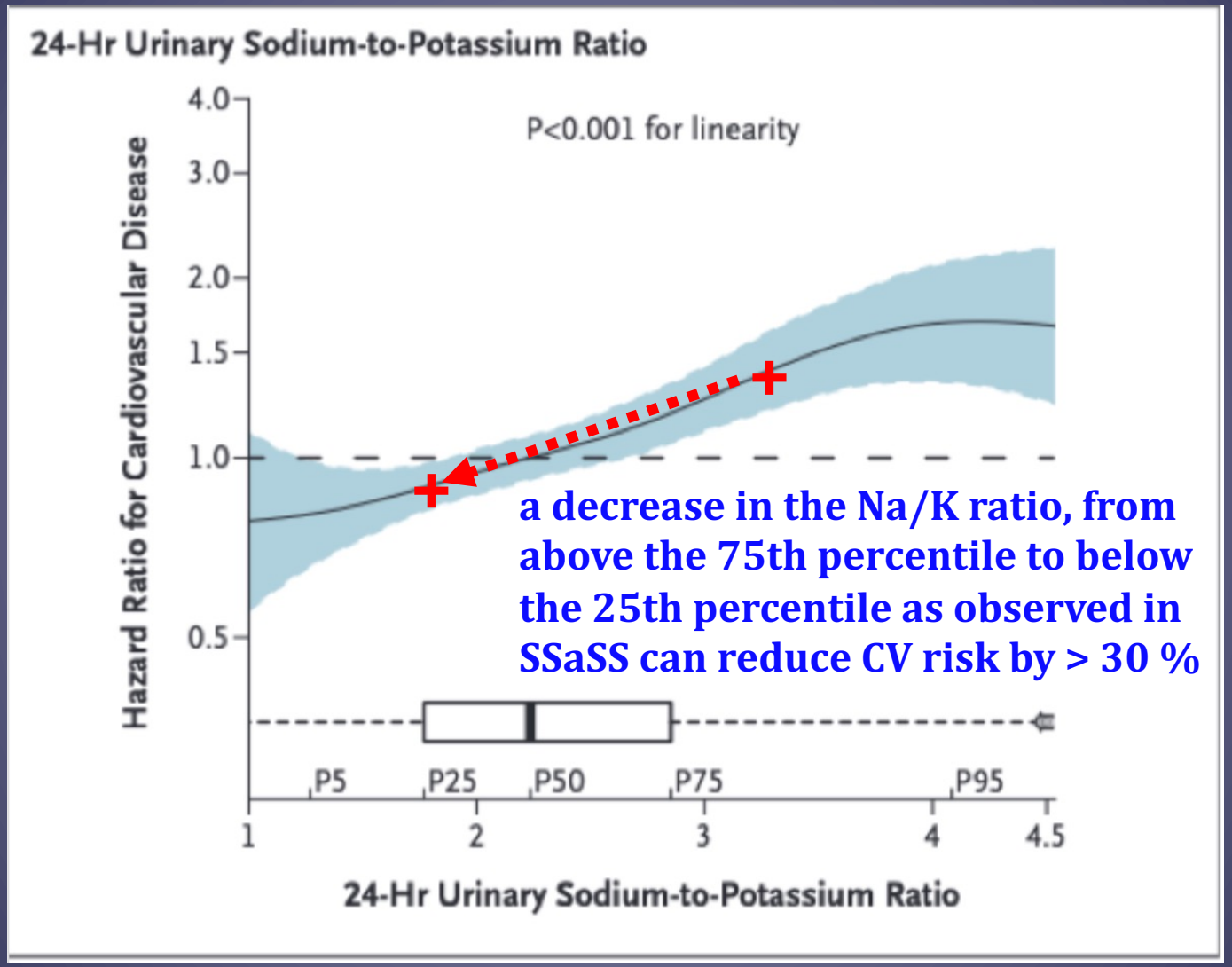



O'Donell et al. European Heart Journal (2020)41, 3363–3373

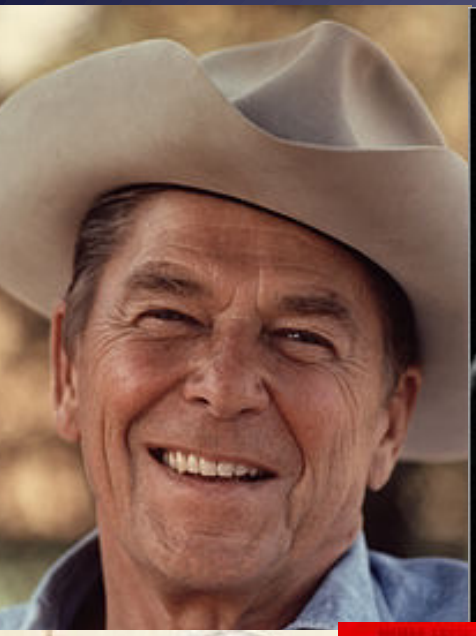



Messerli, O'Donnell, Mente, Yusuf; Eur. Heart J. 2022

# 24-Hour Urinary Sodium and Potassium Excretion and Cardiovascular Risk.




Ma et al. N Engl J Med. Nov. 13, 2021




TIME
The Weekly Newsmagazine
HENRY FORD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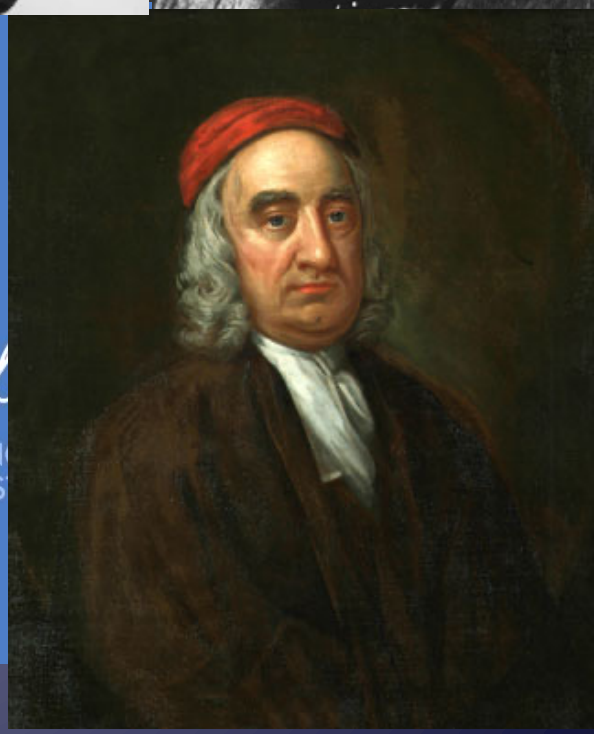


## What do the following people have in common?

- Ronald Reagan (U.S. President)
- Winston Churchill (Prime minister)
- Frank Sinatra (singer)
- Henry Ford (car mogul)
- Jonathan Swift (author)
- Aaron Copeland (composer)
- Willem DeKooning (painter)
- Rita Hayworth (actress)

**They all died with Dementia of the Alzheimer type.**

1952

1981


Whatever happened to our sexual relations?
I don't know. I don't even think we got a Christmas card from them this year.
parodyville.com

Hypertension
JOURNAL OF THE AMERICAN HEART ASSOCIATION


# Benefits in Cognitive Function, Blood Pressure, and Insulin Resistance Through Cocoa Flavanol Consumption in Elderly Subjects With Mild Cognitive Impairment : The Cocoa, Cognition, and Aging (CoCoA) Study

Giovambattista Desideri, Catherine Kwik-Uribe, Davide Grassi, Stefano Necozione, Lorenzo Ghiadoni, Daniela Mastroiacovo, Angelo Raffaele, Livia Ferri, Raffaella Bocale, Maria Carmela Lechiara, Carmine Marini and Claudio Ferri

*Hypertension*. 2012;60:794-801; originally published online August 14, 2012;
doi: 10.1161/HYPERTENSIONAHA.112.193060
*Hypertension* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0194-911X. Online ISSN: 1524-4563

# Conclusion

- “Regular consumption of cocoa flavanols might be effective in improving cognitive function in elderly subjects with mild cognitive impairment”.

Desideri et al., Hypertension. 2012; 60: 794-80

- “We found a significant inverse relationship between flavonoid intake and dementia in a 5-year follow- up study of a cohort of 1367 elderly subjects”.

Commenges et al., European Journal of Epidemiology 16: 357, 2000

Bisson JF, Nejdi A, Rozan P, Hidalgo S, Lalonde R, Messaoudi M.

# Effects of long-term administration of a cocoa polyphenolic extract (Acticoa powder) on cognitive performances in aged rats.

Br J Nutr. 2008 Jul;100(1):94-101.

The Journal of Experimental Biology



RESEARCH ARTICLE

Expand

# A flavonol present in cocoa [(−)epicatechin] enhances snail memory

Lee Fruson, Sarah Dalesman and Ken Lukowiak*

Author Affiliations

* Author for correspondence (lukowiak@ucalgary.ca)

Received January 16, 2012.
Accepted July 2, 2012.


## SUMMARY

Dietary consumption of flavonoids (plant phytochemicals) may improve memory and neuro-cognitive performance, though the mechanism is poorly

Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

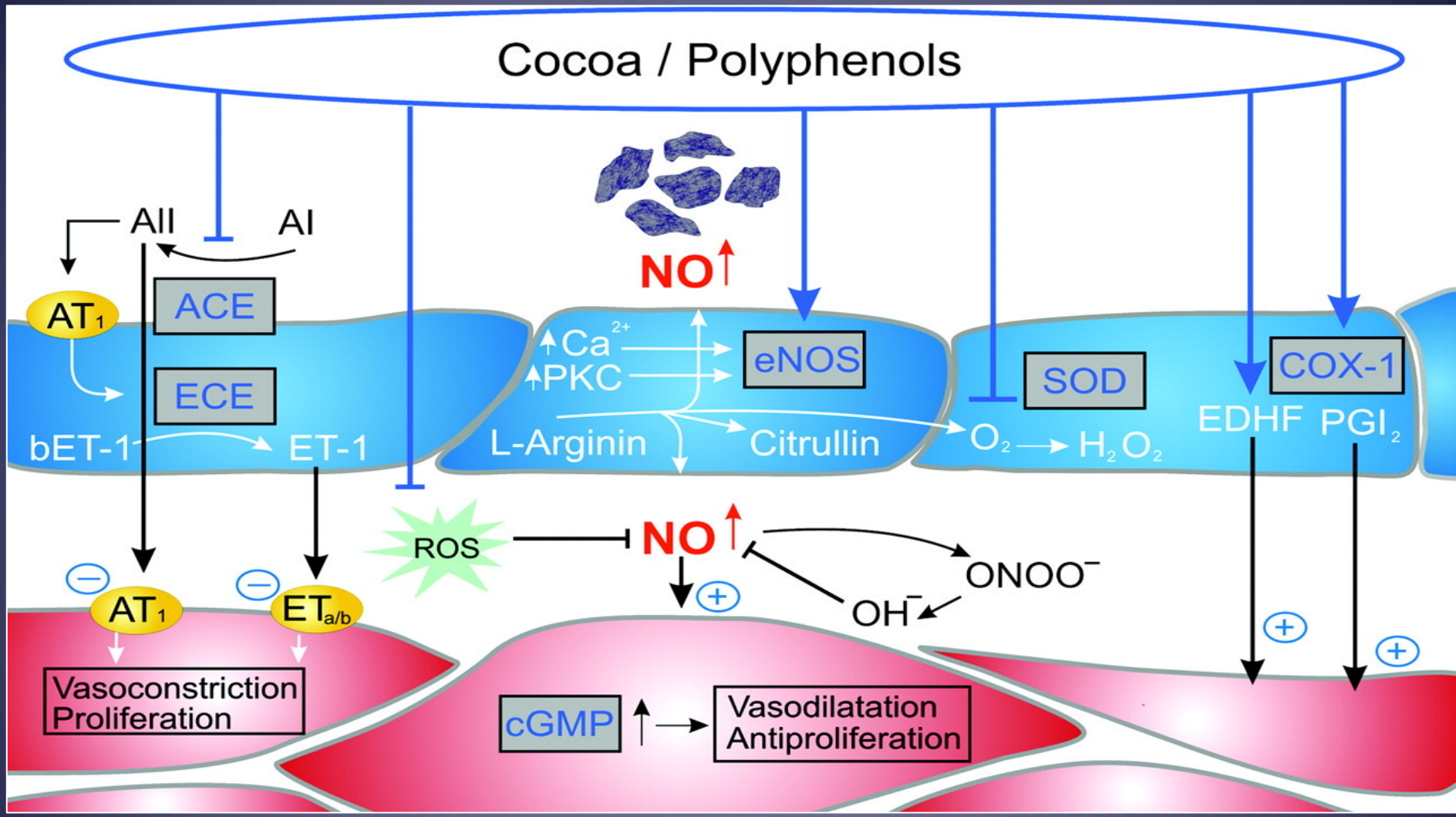
American Heart Association.

# Cocoa and Cardiovascular Health

Roberto Corti, Andreas J. Flammer, Norman K. Hollenberg and Thomas F. Lüscher

*Circulation*. 2009;119:1433-1441
doi: 10.1161/CIRCULATIONAHA.108.827022
*Circulation* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0009-7322. Online ISSN: 1524-4539




**SOD, superoxide dismutase**
**ECE, endothelin-converting enzyme**

**Corti R et al. Circulation 2009;119:1433**

"The beneficial effects of cacao are most likely due to an increased bioavailability of NO. This may explain the improvement in endothelial function, the reduction in platelet function, and the potentially beneficial effects on blood pressure, insulin resistance, and blood lipids".

**Corti R et al. Circulation 2009;119:1433**

Circulation 2007; 116: 2360-2362

Editorial

# Is It the Dark in Dark Chocolate?

Norman K. Hollenberg, MD, PhD; Naomi D.L. Fisher, MD

When we first entered this scientific area about 10 years ago, we did not fully appreciate the emotional content of discussions involving chocolate. Contacts between medical scientists and the lay press tend to be sporadic. When chocolate is the issue, however, the lay press interest becomes intense and widespread. We have participated in many dozens, probably hundreds, of interviews about our research into the vascular effects of cocoa. Two questions inevitably emerge. The first is, "Is there some way of identifying which chocolate available for purchase is especially good for you?" The second is, "Does this mean that chocolate is a health food?" Reporters have been, almost without exception, rather

One relatively underreported effect of alkalization is, in fact, darkening of cocoa, so that a very dark chocolate might be essentially devoid of flavanols.

If the industry wants us to use chocolate as a health food, then they will have to change their behavior. Specifically, what the world needs is a label on each package that describes the flavanol content of the chocolate. It should be obvious that the percent of cocoa, like the color of chocolate, does not represent a measure of flavanols at all. The medical community should encourage the industry to participate. Probably the most effective mechanism is for the lay press to stop

Circulation 2007; 116: 2360-2362

erg, MD, PhD; Naomi D.L. Fisher, MD

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One relatively underreported effect of alkalization is, in fact, darkening of cocoa, so that a very dark chocolate might be essentially devoid of flavanols.

If the industry wants us to use chocolate as a health food, then they will have to change their behavior. Specifically, what the world needs is a label on each package that describes the flavanol content of the chocolate. It should be obvious that the percent of cocoa, like the color of chocolate, does not represent a measure of flavanols at all. The medical community should encourage the industry to participate. Probably the most effective mechanism is for the lay press to stop

# Effect of cocoa on blood pressure (Review)

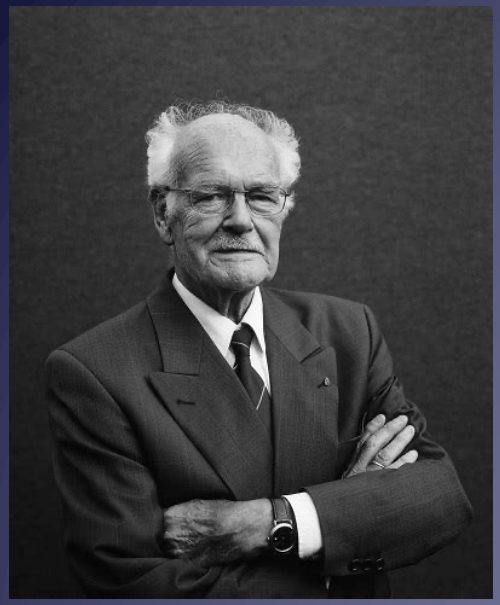
Ried K, Sullivan TR, Fakler P, Frank OR, Stocks NP

THE COCHRANE COLLABORATION®

Published Online: 15 AUG 2012

- Meta-analysis of 20 studies involving 856mainly healthy participants revealed a small but statistically significant blood pressure reducing effect of **-2.8 mm Hg systolic** and **-2.2 mm Hg diastolic.**

Ried K, Sullivan TR, Fakler P, Frank OR, Stocks NP.
Effect of cocoa on blood pressure.
*Cochrane Database of Systematic Reviews 2012,*

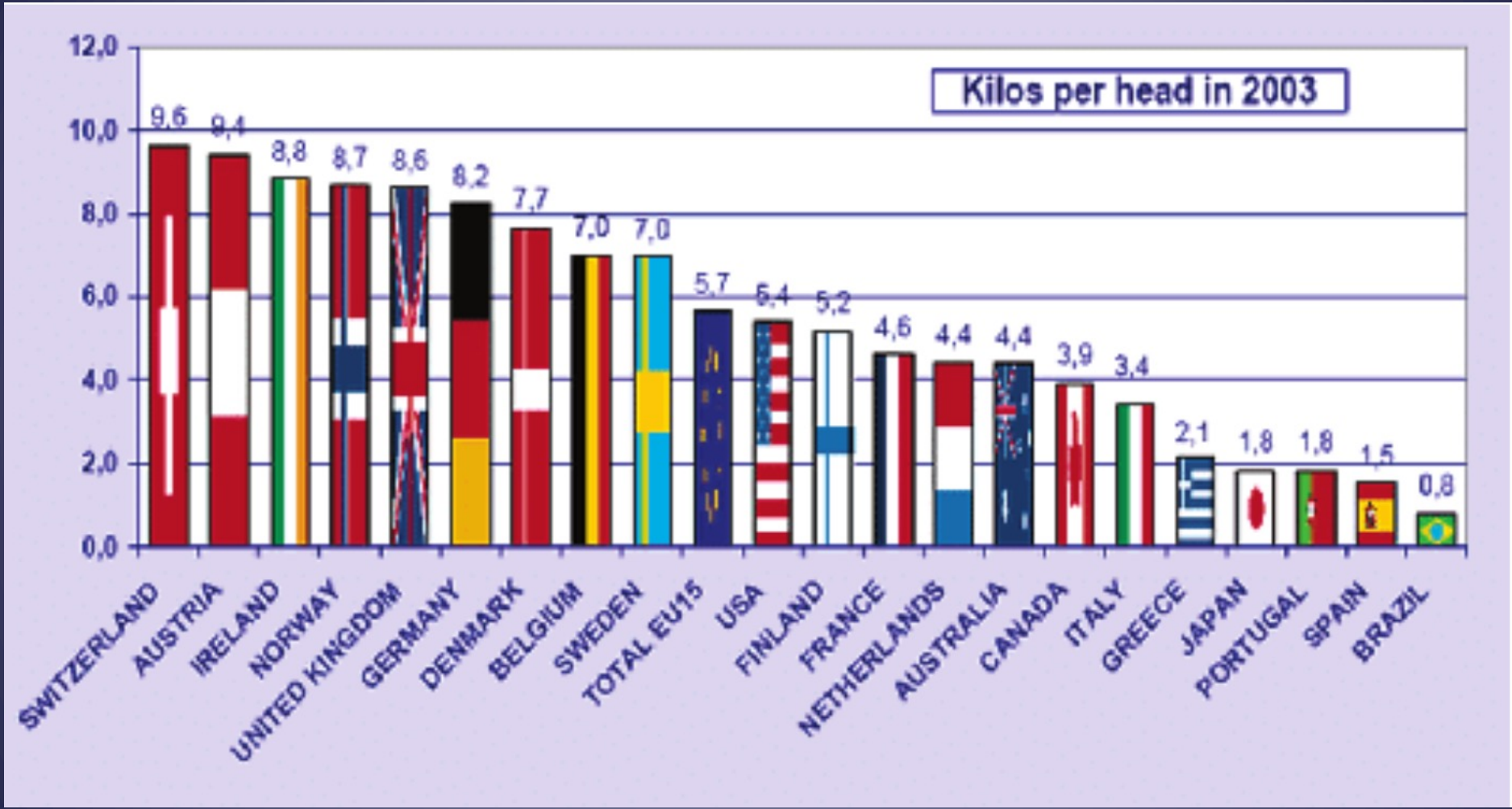


# BP and Dementia

- The temporal relationships may be obscured because of the observation that BP tends to fall in the face of imminent Alzheimer disease.
- A low BP in this phase of life could be equally harmful as hypertension in the preceding period.

Birkenhager and Staessen. Prog Cardiovasc Dis Jul-Aug 2006;49(1):1-10

# Chocolate Consumption per Capita per Country



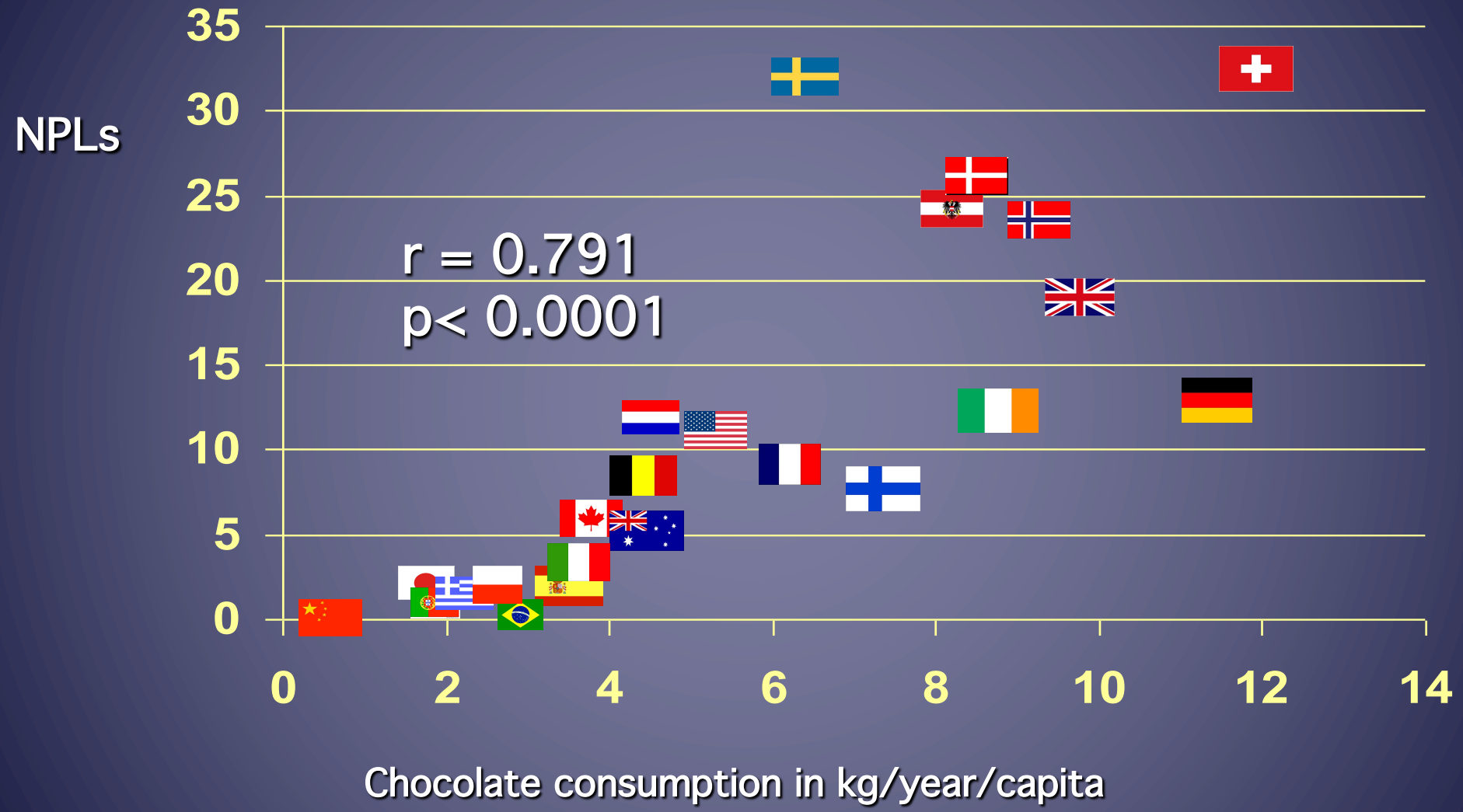
# Hypothesis:

Since chocolate consumption could improve cognitive function not only individually but possibly in the general population, a correlation might be expected between chocolate consumption and cognitive function among various countries..

Conceivably the total number of Nobel Prize Laureates (NPLs) per capita could give us some measure of the overall cognitive function of a given country…

| Rank | Country | Nobel laureates[1] | Population (2011)[2] | Laureates/ 10 million |
|---|---|---|---|---|
| — | *Faroe Islands* | 1 | 49,267 | 202.976 |
| 1 | Saint Lucia | 2 | 161,557 | 123.795 |
| 2 | Luxembourg | 2 | 503,302 | 39.738 |
| 3 | Switzerland | 25 | 7,639,961 | 32.723 |
| 4 | Iceland | 1 | 311,058 | 32.148 |
| 5 | Sweden | 29 | 9,088,728 | 31.908 |
| 6 | Denmark | 14 | 5,529,888 | 25.317 |
| 7 | Austria | 20 | 8,217,280 | 24.339 |
| 8 | Norway | 11 | 4,691,849 | 23.445 |
| 9 | United Kingdom | 118 | 62,698,362 | 18.820 |
| 10 | Timor-Leste | 2 | 1,177,834 | 16.980 |
| 11 | Israel | 10 | 7,473,052 | 13.381 |
| 12 | Ireland | 6 | 4,670,976 | 12.845 |
| 13 | Germany | 103 | 81,471,834 | 12.642 |
| 14 | Netherlands | 19 | 16,653,734 | 11.409 |
| 15 | United States | 332 | 311,050,977 | 9.369 |
| 16 | Hungary | 9 | 9,976,062 | 9.022 |
| 17 | Cyprus | 1 | 1,120,489 | 8.925 |
| — | *European Union* | 448 | 502,748,173 | 8.911 |

# Chocolate and the Nobel Prize



- editorial@nejm.org
  via manuscriptcentral.com
- Sep 19. 2012
- Dear Dr. Messerli,

  Thank you for submitting your article on chocolate consumption, cognitive function, and Nobel laureates to the Journal. We greatly enjoyed it and would like to publish it as an Occasional Note -- in fact, our hope is to publish it in early October, to coincide with the announcements of this year's Nobel Prizes…

The NEW ENGLAND JOURNAL of MEDICINE

EMBARGOED until October 10. 2012, at 10.00 AM

OCCASIONAL NOTES

# Chocolate Consumption, Cognitive Function, and Nobel Laureates

Franz H. Messerli, M.D.

Dietary flavonoids, abundant in plant-based foods, have been shown to improve cognitive function. Specifically, a reduction in the risk of dementia, enhanced performance on some cognitive tests, and improved cognitive function in elderly patients with mild impairment have been associated with a regular intake of flavonoids.[1,2] A subclass of flavonoids called flavanols, which are widely present in cocoa, green tea, red wine, and some

Thus, the numbers must be read as the number of Nobel laureates for every 10 million persons in a given country.

All Nobel Prizes that were awarded through October 10, 2011, were included. Data on per capita yearly chocolate consumption in 22 countries was obtained from Chocosuisse (http://www.chocosuisse.ch/web/chocosuisse/en/instruction_material.html),{Q1} Theobroma-cacao{Q2} (http://

October 10, 2012

“With a per capita chocolate consumption of 6.4 kg/year Sweden should have produced a total of about 14 NPLs, yet we observe 32.

The observed exceeds the expected more than twofold, meaning that either the Nobel Committee in Stockholm has some inherent patriotic bias…or, perhaps, that the Swedes are particularly sensitive to chocolate and even minuscule amounts greatly enhance their cognition”.

# Chocolate and the Nobel Prize

Rolf Zinkernagel, MD received the 1996 Nobel Prize in Medicine for the discovery of how the immune system recognizes virus-infected cells. With this he became the 24th Swiss Nobel laureate

Dear Franz,

I seem to be your outlier because my yearly consumption is  less than 500 g - Sorry!

I shall let you know when I am in NYC next time.

All the best

Rolf

# Chocolate Consumption

Switzerland

11.9 kg or 119 bars/year

Professor Zinkernagel

< 500 g or 5 bars/year

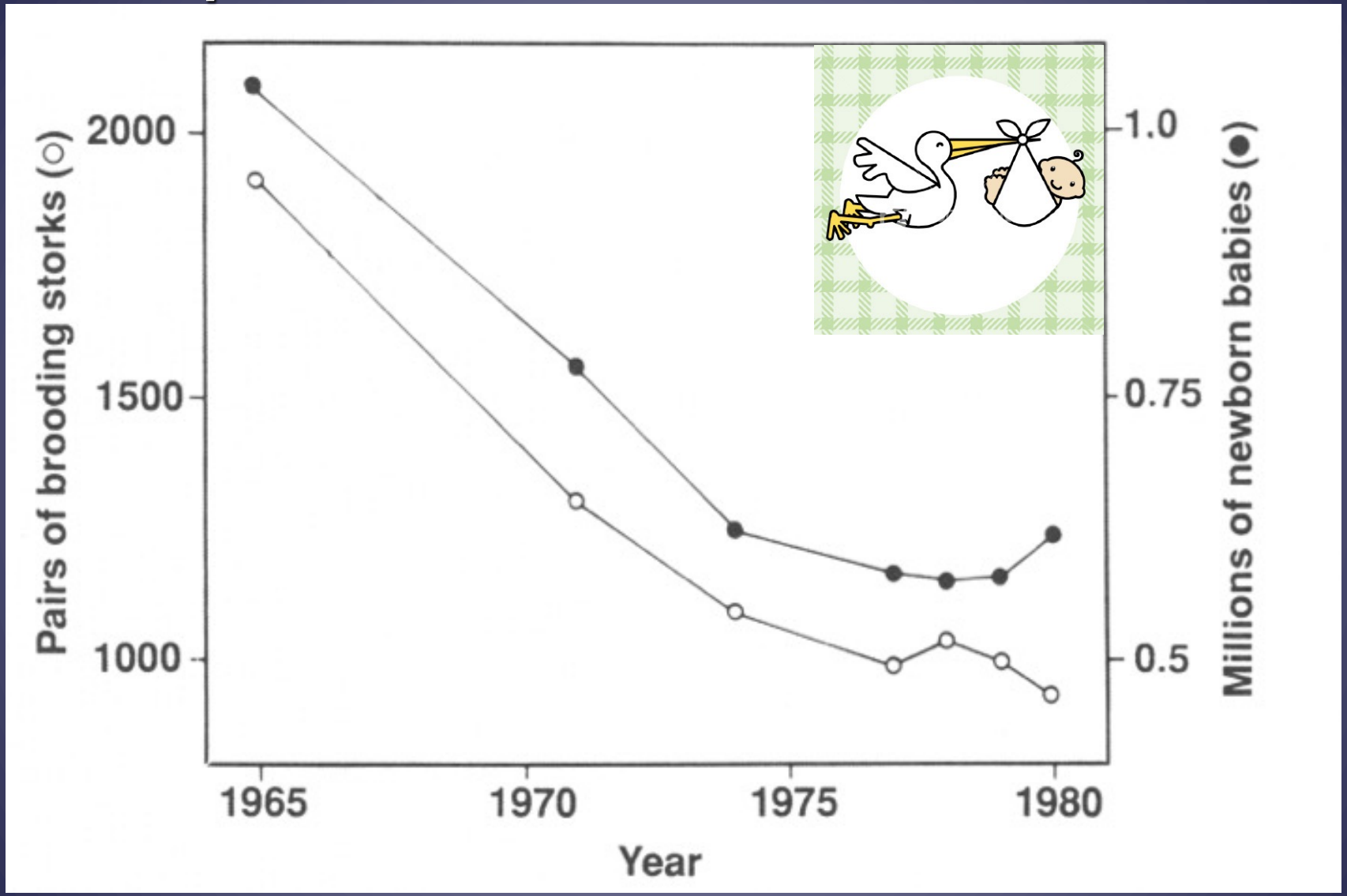
For synthesizing the first Bose–Einstein condensate in 1995, Cornell, Wieman, and Ketterle shared the Nobel Prize in Physics in 2001

""I attribute all my success to the very large amount of chocolate that I consume. Personally I feel that milk chocolate makes you stupid. .. It's one thing if you want like a medicine or chemistry Nobel Prize, but if you want a physics Nobel Prize it pretty much has got to be dark chocolate".


Eric Cornell, American physicist, Nobel Laureate in 2001 interviewed by Frederic Joelving, Reuters. October 05.2012

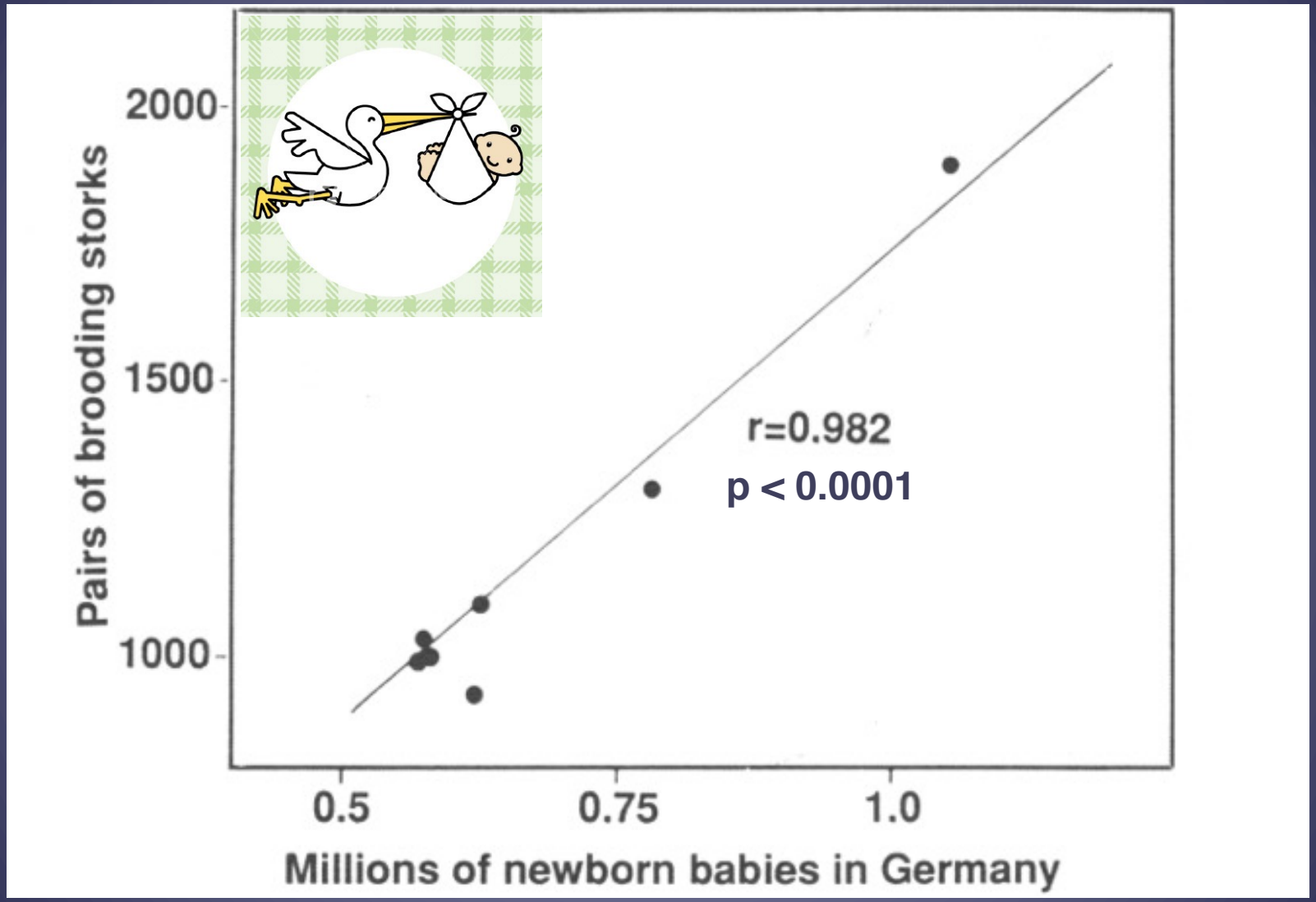
$p < 0.0001$

# Stork Population and Newborn Babies in Germany




Sies, H. Nature 1988, 332, 495

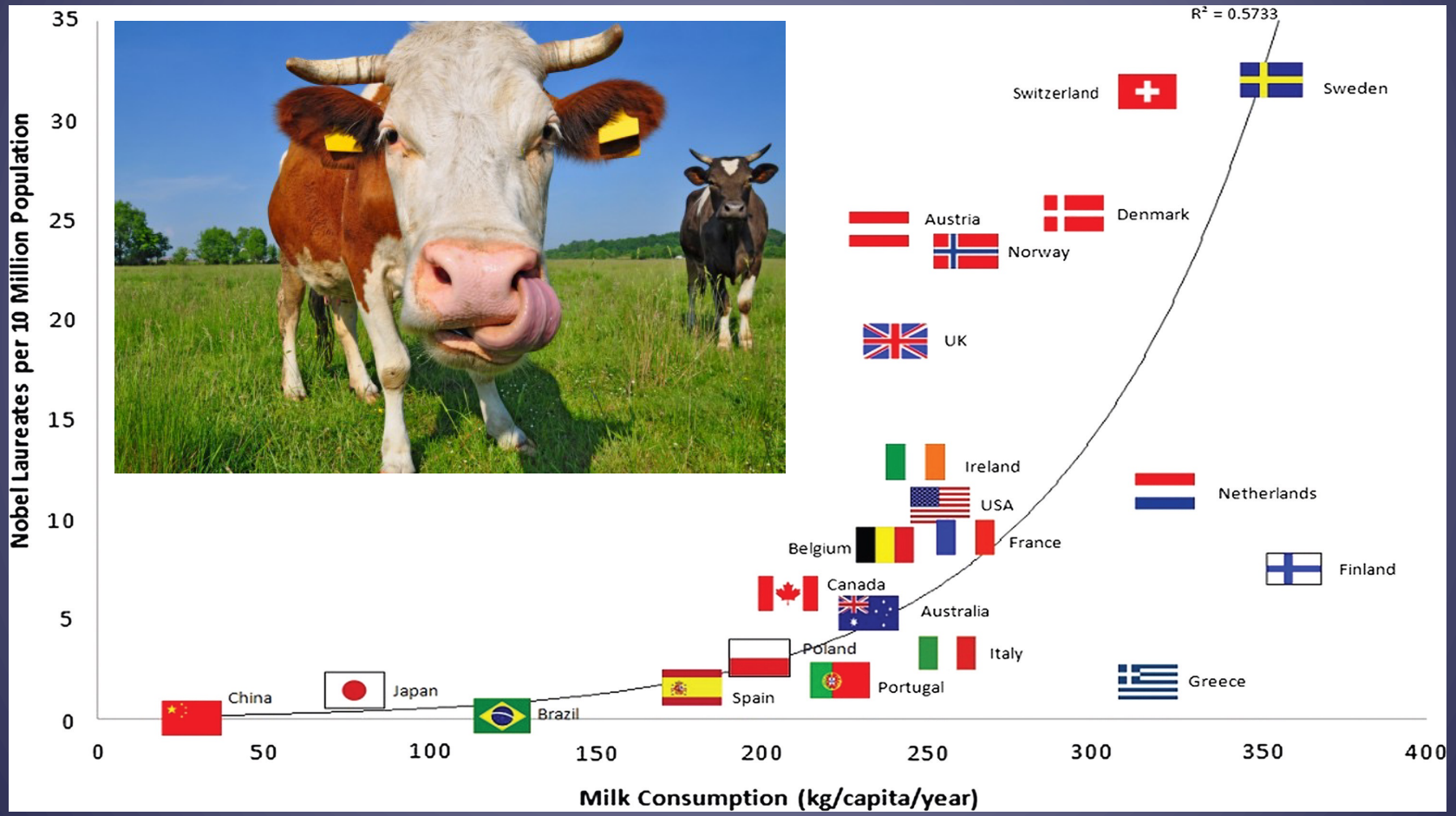
# Stork Population and Newborn Babies in Germany




Sies, H. Nature 1988, 332, 495


The common denominator between dwindling in birth rates and in brooding storks is excessive urbanisation and construction...

# Correlation between countries' annual per capita milk consumption and number of Nobel laureates per capita




Linthwaite S, Fuller GN. Pract Neurol 2013;13:63.

**“the correlation with milk does not find Sweden an outlier, absolving the Nobel Committee from Dr. Messerli’s suggestion of patriotic bias”.**

Linthwaite S, Fuller GN. Pract Neurol 2013;13:63.

# Wanna go to Stockholm?
# Eat your Chocolate!

# THE PERSON LEAST LIKELY TO HAVE A HEART ATTACK

He is an effeminate municipal worker or embalmer, completely lacking in physical and mental alertness.
He has no drive, ambition or competitive spirit. He never has attempted to meet a deadline.

# THE PERSON LEAST LIKELY TO HAVE A HEART ATTACK

He is low in income, blood pressure, blood sugar, uric acid and cholesterol. He has been on nicotine acid, *Lindt*-*Chocolate* and long term anticoagulant therapy ever since his prophylactic castration.

Irvine Page, 1960