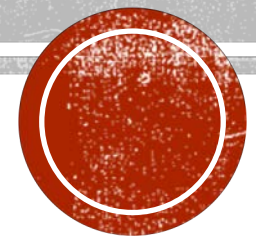
TAKING THE **BM** OUT OF **EMB**:
AN EVIDENCE YEAR IN **REVIEW**

MEDS 2019



“OUTLINE”

- BS is very fast
- Why is BS fast? → It was pushed.
- What answer would you like?
- BS is an excellent organic fertilizer
- ASA is primarily done
- That fish won’t die
- Take a CHANCE on clopidogrel
- You can’t handle the truth
- Antidepressants: Handle with care
- The reality of Pharmacogen-OH-mics
- Funny thing happened on the way to the post-marketing study
- Classy Diabetes Drugs?
- Amazing New Diabetes Drug
- Or Dog it
- K whY is this so simple?
- What!? Those water bottle people have it right!

HOUSTON, WE HAVE A PROBLEM?

RESEARCH

SOCIAL SCIENCE

The spread of true and false news online

Soroush Vosoughi,[1] Deb Roy,[1] Sinan Aral[2]*

Science 2018;359:1146–1151

THE UPHILL ROAD TO **SANE** PUBLIC HEALTH BEHAVIOUR?

Weaponized Health Communication: Twitter Bots and Russian Trolls Amplify the Vaccine Debate

David A. Broniatowski, PhD, Amelia M. Jamison, MAA, MPH, SiHua Qi, SM, Lulwah AlKulaib, SM, Tao Chen, PhD, Adrian Benton, MS, Sandra C. Quinn, PhD, and Mark Dredze, PhD

Am J Public Health. 2018;108:1378–1384.

DEFINING TERMS

- “Bots” – accounts that automate content promotion
- “Trolls” – Individuals who misrepresent their identities with intention of promoting discord
- Russian trolls and bots post content about vaccination at a higher rate than the average user
- Strategy to promote discord across a range of controversial topics
- Amplification – online disinformation strategy creates false impression of equivalence
  - Generate several tweets on the same topic with intention of flooding the discourse

THE UPHILL ROAD TO **SANE** PUBLIC HEALTH BEHAVIOUR?

EXAMPLES OF TWEETS WITH #VACCINATEUS AND CORRESPONDING THEMES: JULY 14, 2014–SEPTEMBER 26, 2017

Antivaccine theme	Example tweet
Freedom of choice/antimandatory vaccines	VaccinateUS mandatory #vaccines infringe on constitutionally protected religious freedoms
Can't trust government on vaccines	Did you know there was a secret government database of #vaccine-damaged children? #VaccinateUS
Pharmaceutical companies want vaccine profits	Pharmacy companies want to develop #vaccines to cash, not to prevent deaths #VaccinateUS
Vaccines cause bad side effects	#VaccinateUS #vaccines can cause serious and sometimes fatal side effects
Natural immunity is better	#VaccinateUS natural infection almost always causes better immunity than #vaccines
General vaccine conspiracy theories	Dont get #vaccines. Iluminati are behind it. #VaccinateUS
Vaccines cause autism	Did you know #vaccines caused autism? #VaccinateUS
Vaccine ingredients are dangerous	#VaccinateUS #vaccines contain mercury! Deadly poison!
Diseases aren't so dangerous	#VaccinateUS most diseases that #vaccines target are relatively harmless in many cases, thus making #vaccines unnecessary

Provaccine theme	Example tweet
Vaccines work	#VaccinateUS #vaccines save 2.5 million children from preventable diseases every year
Vaccines should be mandatory	Your kids are not your property! You have to #vaccinate them to protect them and all the others! #VaccinateUS
People who don't vaccinate are stupid	#VaccinateUS You can't fix stupidity. Let them die from measles, and I'm for #vaccination!
Vaccination protects herd immunity	#VaccinateUS #vaccines protect community immunity
People who don't vaccinate put me/my kids at risk	#VaccinateUS My freedom ends where another person's begins. Then children should be #vaccinated if disease is dangerous for OTHER children
Vaccines don't cause autism	#vaccines cause autism—Bye, you are not my friend anymore. And try to think with your brain next #VaccinateUS
You deserve bad things if you don't vaccinate	#vaccines are a parent's choice. Choice of a color of a little coffin #VaccinateUS
Alternative medicine doesn't work	Do you still treat your kids with leaves? No? And why don't you #vaccinate them? Its medicine! #VaccinateUS
People died without vaccines	Most parents in Victorian times lost children regularly to preventable illnesses. #vaccines can solve this problem #VaccinateUS

Am J Public Health. 2018;108:1378–1384.

WHY?

- Content Polluters – unsolicited commercial content – use post antivaccine messages more than the average twitter users
- True antivaccine sentiment ? or tactic just designed to drive up click-though rates.
- Significant proportion of antivaccine messages are organized “astroturf” – not grassroots
- Astroturf - Astroturfing is the artificial creation of a grassroots buzz for a product, service or political viewpoint. ... Astroturf marketing has a negative connotation, primarily because disreputable marketers have used deceptive tactics to build their buzz by taking advantage of the anonymity the Internet provides.

Am J Public Health. 2018;108:1378–1384.

WHY **DO WE** CARE?

8 OCTOBER 2015 | VOL 526 | NATURE | 189

Corrigendum: Many Analysts, One Data Set: Making Transparent How Variations in Analytic Choices Affect Results

67 Analysts:

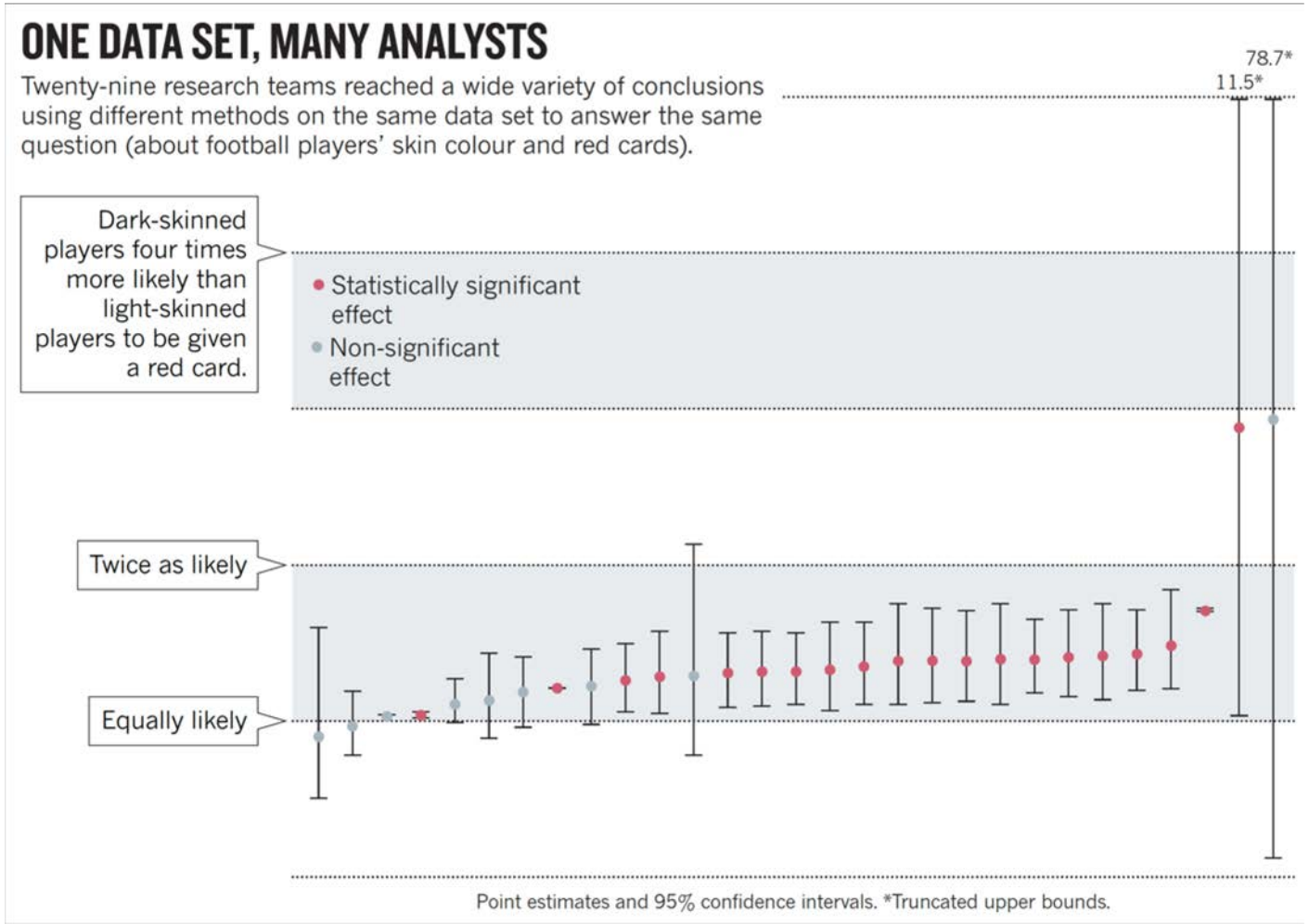
- given identical data
- research question: Soccer referees → more likely to give red cards to dark- skin toned players than light-skin toned players

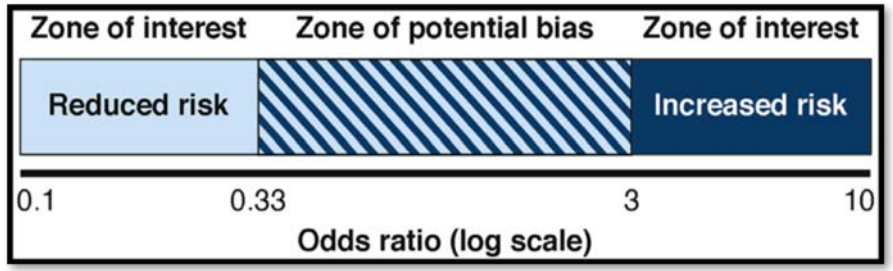
RESULTS:

- 69% of teams found a statistically significant positive effect
- 31% did not observe a statistically significant relationship
- OR ranged from 0.89 to 2.93

Adv Meth Pract Psychol Sci, 2018, 1, 337–356

WHY **DO WE** CARE?





WHY WE **DON'T** CARE?

JAMA Internal Medicine | Original Investigation

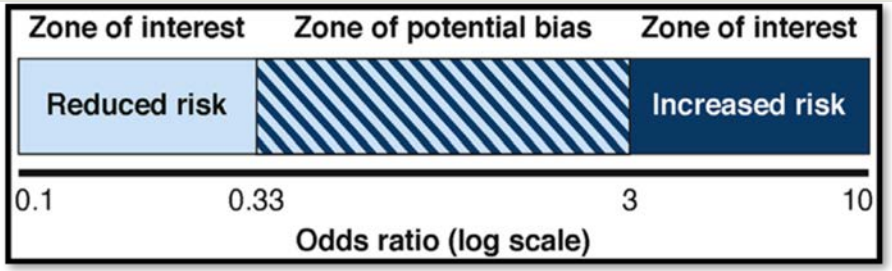
Association of Frequency of Organic Food Consumption With Cancer Risk

Findings From the NutriNet-Santé Prospective Cohort Study

Julia Baudry, PhD; Karen E. Assmann, PhD; Mathilde Touvier, PhD; Benjamin Allès, PhD; Louise Seconda, MSc; Paule Latino-Martel, PhD; Khaled Ezzedine, MD, PhD; Pilar Galan, MD, PhD; Serge Hercberg, MD, PhD; Denis Lairon, PhD; Emmanuelle Kesse-Guyot, PhD

JAMA Intern Med 2018;178(12):1597-1606

RESULTS Among 68 946 participants (78.0% female; mean [SD] age at baseline, 44.2 [14.5] years), 1340 first incident cancer cases were identified during follow-up, with the most prevalent being 459 breast cancers, 180 prostate cancers, 135 skin cancers, 99 colorectal cancers, 47 non-Hodgkin lymphomas, and 15 other lymphomas. High organic food scores were inversely associated with the overall risk of cancer (hazard ratio for quartile 4 vs quartile 1, 0.75; 95% CI, 0.63-0.88; *P* for trend = .001; absolute risk reduction, 0.6%; hazard ratio for a 5-point increase, 0.92; 95% CI, 0.88-0.96).



CAN THE **CAM**?

JAMA Oncology | Original Investigation

Complementary Medicine, Refusal of Conventional Cancer Therapy, and Survival Among Patients With Curable Cancers

Skyler B. Johnson, MD; Henry S. Park, MD, MPH; Cary P. Gross, MD; James B. Yu, MD, MHS

JAMA Oncol. doi:10.1001/jamaoncol.2018.2487
Published online July 19, 2018.

CAN THE **CAM**?

More Likely to Use CAM:

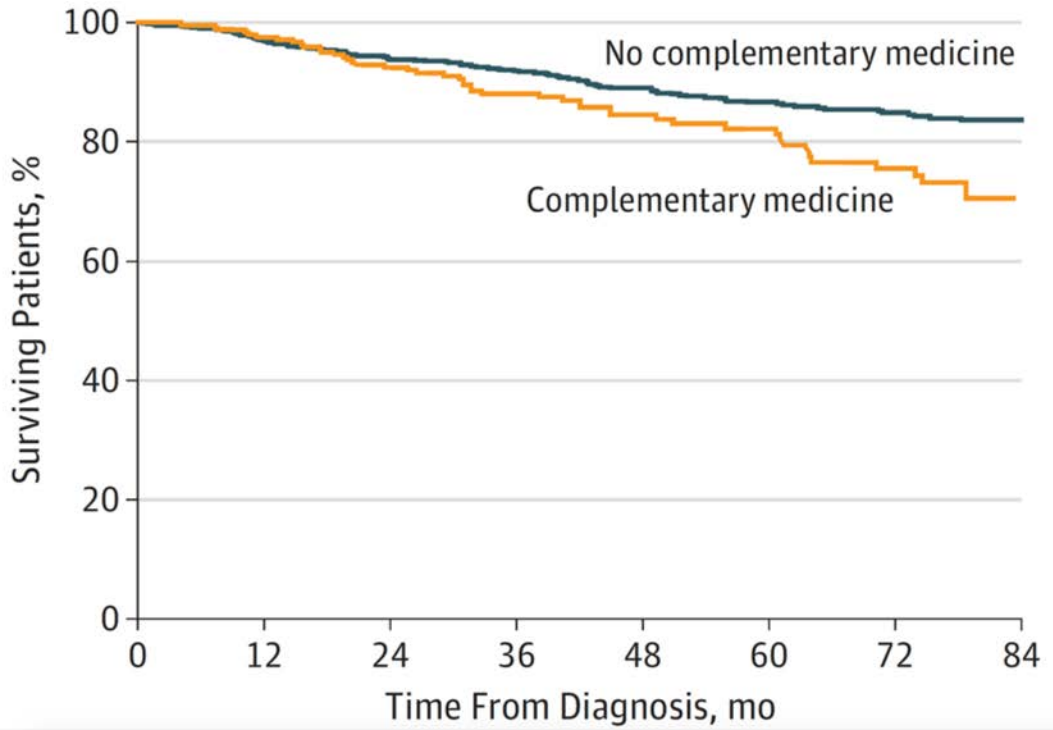
- Younger
- Female
- Higher Socio-economic status
- Higher Education

→ Poorer 5-year survival

82.2% vs. 86.6%

(p = 0.001, HR 1.70 95% CI 1.24 to 2.34)

Figure. Survival of Patients Who Used Complementary Medicine vs Those Who Used No Complementary Medicine for Breast, Prostate, Lung, and Colorectal Cancer



JAMA Oncol. doi:10.1001/jamaoncol.2018.2487
Published online July 19, 2018.

TIME WASTE?

> “I don't think this was a good year for aspirin in primary prevention.”

- Medscape, Dec 2018

I THOUGHT **WE ALREADY KNEW** THE ANSWER TO THIS…

ARRIVE (Lancet 2018; 392: 1036–46) → n=12,546 X 5 yrs

Use of aspirin to reduce risk of initial vascular events in patients at moderate risk of cardiovascular disease (ARRIVE): a randomised, double-blind, placebo-controlled trial

ASCEND (N Engl J Med 2018;379:1529-39) → n=15,480 X 7.4 yrs

Effects of Aspirin for Primary Prevention in Persons with Diabetes Mellitus

ASPREE (N Engl J Med 2018;379:1499-1528) → n=19,114 X 4.7 yrs

Effect of Aspirin on All-Cause Mortality in the Healthy Elderly

Effect of Aspirin on Cardiovascular Events and Bleeding in the Healthy Elderly

ASA 100mg vs. placebo

ASA'S **LACK OF NET BENEFIT** IN 1 SLIDE
(for primary prevention, of course)

ARRIVE (Lancet 2018; 392: 1036–46) → n=12,546 (moderate CV risk)

CV events: ⬇0.19% (NS)

Moderate bleeding: ⬆0.16% (NS)

ASCEND (N Engl J Med 2018;379:1529-39) → n=15,480 (DM2)

CV events: ⬇1.1%

Major bleeding: ⬆0.9%

Now, let us never speak of this again

ASPREE (N Engl J Med 2018;379:1499-1528) → n=19,114 (mean age = 74)

CV events: ⬇0.24% (NS)

Death: ⬆0.7%

Major bleeding: ⬆1.0%

IS SOMETHING FISHY GOING ON HERE?

Cochrane Library

CDSR 2018, Issue 11. Art. No.: CD003177

JAMA Cardiology

JAMA Cardiol 2018;3(3):225-233

n=112,059 (79 trials)

No real benefits in any major CV outcomes

n=77,917 (10 trials)

N ENGL J MED

Nov 10, 2018

VITAL

n=25,871

REDUCE-IT

n=8,179

Marine n–3 Fatty Acids and Prevention of Cardiovascular Disease and Cancer

VITAL

- WHO? >50-55 yrs of age with no history of CVD or cancer
- WHAT? 1g marine n-3 fatty acids vs placebo X 5.3 yrs
- PRIMARY ENDPOINT: CV death, nonfatal MI, or nonfatal stroke

→ RESULTS… no difference (3% vs. 3.2%)

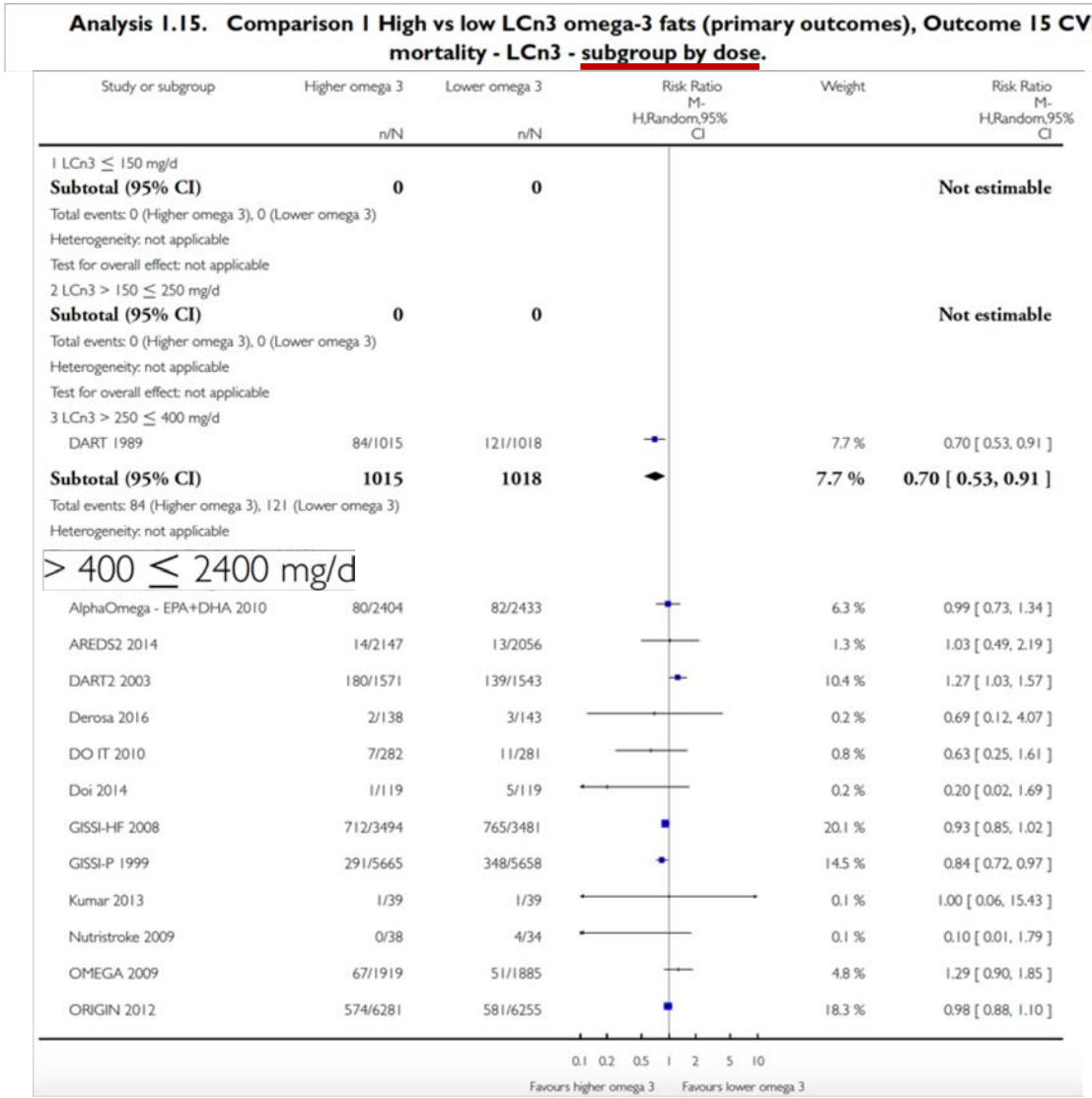
QUELLE SURPRISE!

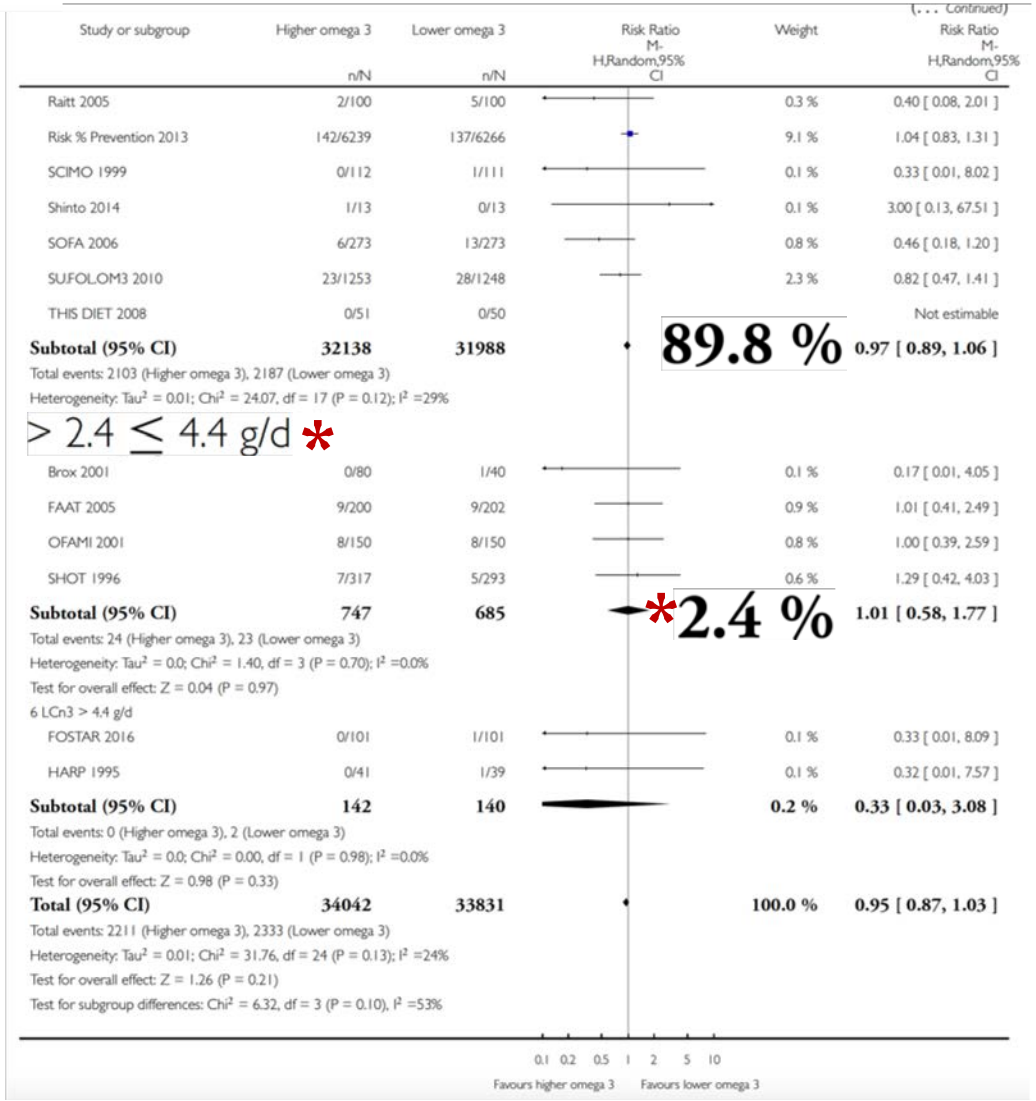
NEJM 2018;380:23-32

HOW IS **REDUCE-IT** DIFFERENT? →

1. EPA only (no DHA)
2. High dose (4g/day)

Analysis 1.15. Comparison 1 High vs low LCn3 omega-3 fats (primary outcomes), Outcome 15 CVD mortality - LCn3 - subgroup by dose.





CDSR 2018, Issue 11. Art. No.: CD003177

Cardiovascular Risk Reduction with Icosapent Ethyl for Hypertriglyceridemia

REDUCE-IT

not yet in

- WHO? → CVD (71%) or diabetes + other RF(s) (71% male)
  - → already on a statin
  - → baseline TG >1.7 (mean = 2.4)
- FOLLOW-UP = 4.9 yrs
- ENDPOINTS
  - Primary: CV death, nonfatal MI, nonfatal stroke, coronary revascularization, or unstable angina
  - * Secondary: CV death, nonfatal MI, or nonfatal stroke

NEJM 2018, Nov 10; DOI: 10.1056/NEJMoa1812792

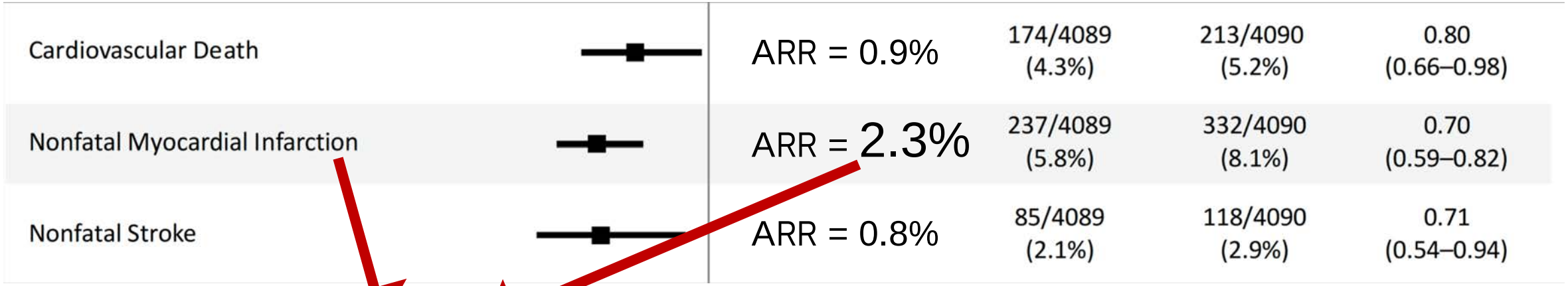
WHAT WAS REDUCED?

TAKE HOME?

- Does it need repeating? → probably? → STRENGTH trial (n=13,000 → **4g** of EPA+DHA)
- Is the net benefit big enough to give to all CAD patients on statins (when it gets to 🇨🇦)?

→ What's inside the gift basket?

SECONDARY: ARR = 3.6% (NNT=28)



Cardiovascular Death	ARR = 0.9%	174/4089 (4.3%)	213/4090 (5.2%)	0.80 (0.66–0.98)
Nonfatal Myocardial Infarction	ARR = 2.3%	237/4089 (5.8%)	332/4090 (8.1%)	0.70 (0.59–0.82)
Nonfatal Stroke	ARR = 0.8%	85/4089 (2.1%)	118/4090 (2.9%)	0.71 (0.54–0.94)

But… silent MI were included, but frequency not reported

(i.e. the most abundant gift is of questionable quality)

WHAT WAS INCREASED? → New atrial fibrillation **(ARI = 1.4%)**

IF WE CAN'T PREVENT THE 1ST, MAYBE WE CAN PREVENT THE 2ND… DAPT **POST-STROKE?**

AHA Stroke CPG 2018:

5. In patients presenting with minor stroke, treatment for 21 days with dual antiplatelet therapy (aspirin and clopidogrel) begun within 24 hours can be beneficial for early secondary stroke prevention for a period of up to 90 days from symptom onset.	**IIa**

CHANCE study

"The generalizability of this intervention in non-Asian populations remains to be established, and a large phase III multicenter trial in the US, Canada, Europe, and Australia is ongoing"

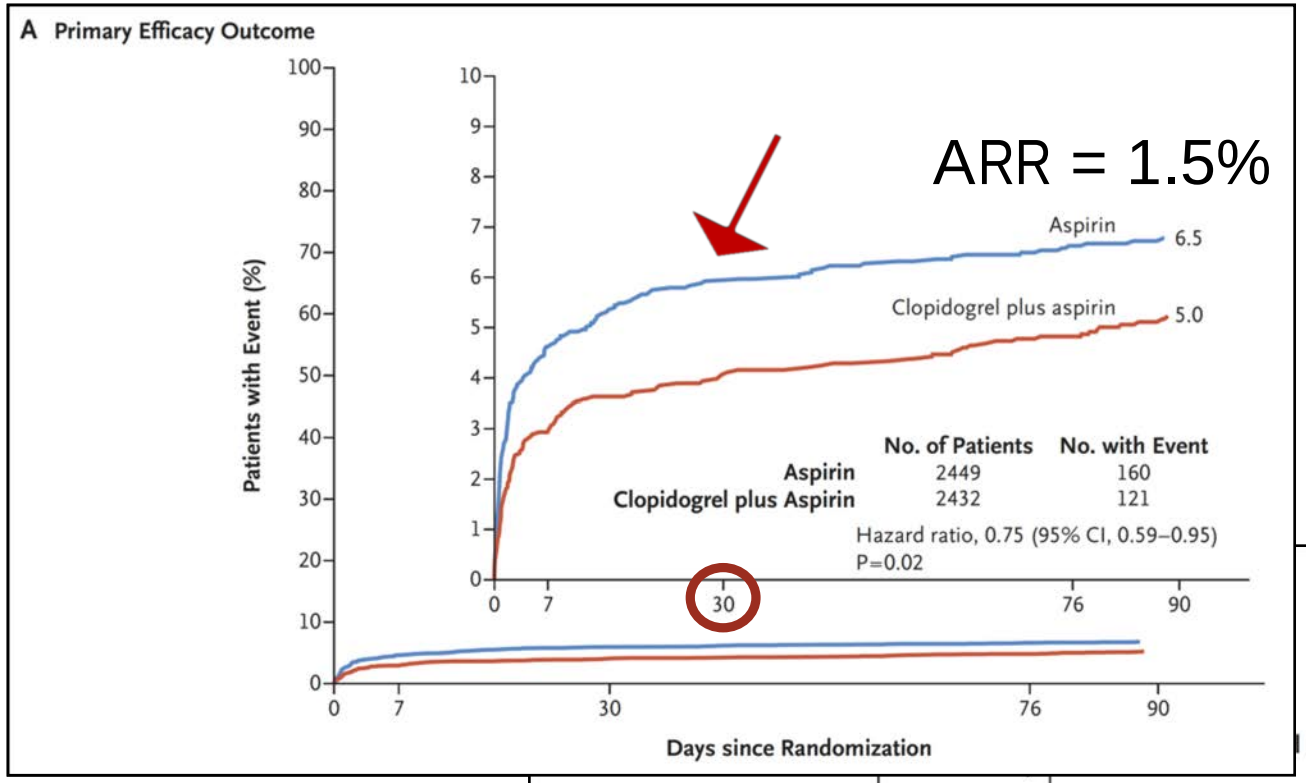
the **POINT** trial… *N Engl J Med* 2018;379:215-25

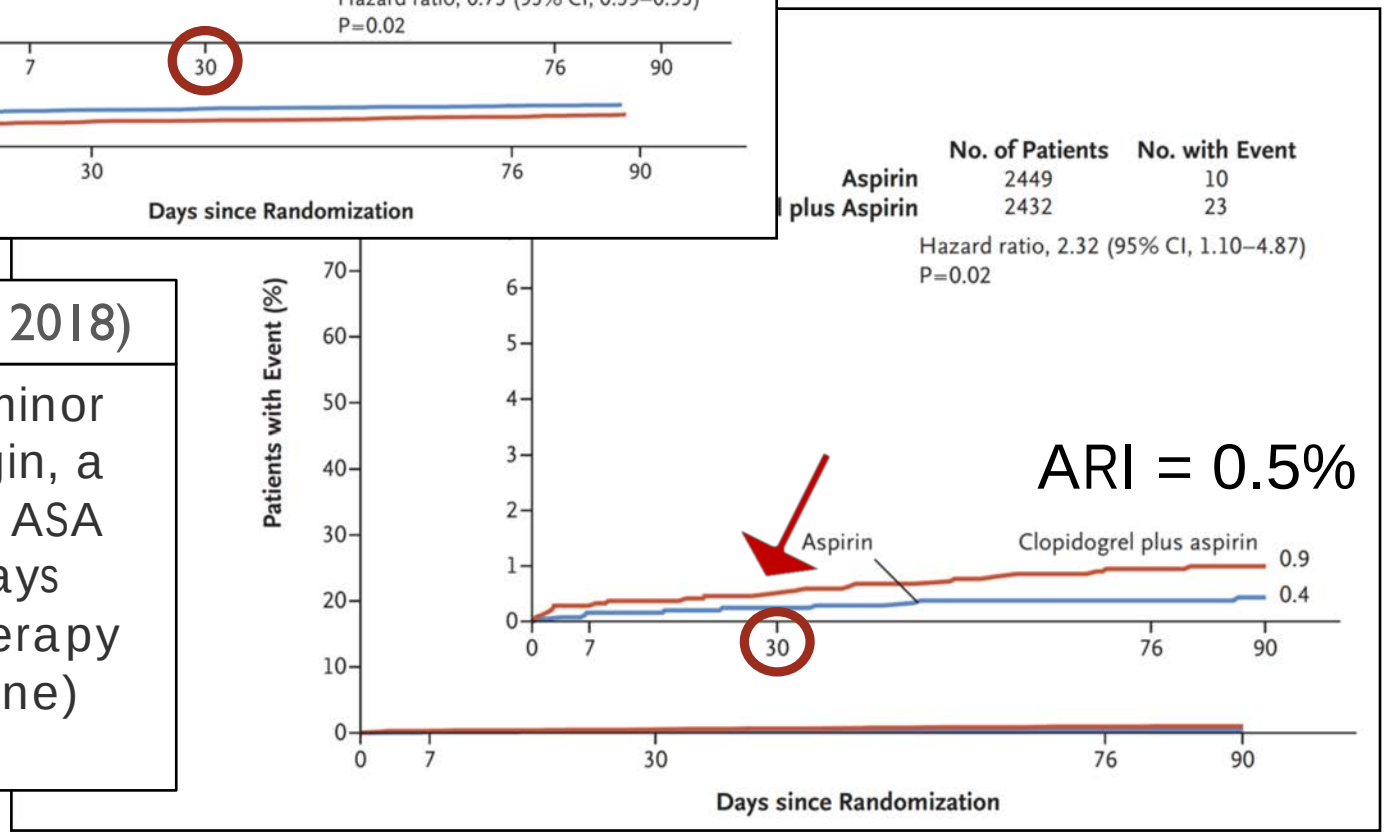
Clopidogrel and Aspirin in Acute Ischemic Stroke and High-Risk TIA

- n=4881 (83% in North America), minor ischemic stroke or high-risk TIA

→ ASA + clopidogrel *vs.* ASA alone X 90 days

THE MORE THE MERRIER AND SHORTER IS BETTER?





Canadian Stroke Best Practices (June 2018)

"In very high risk TIA patients or minor stroke of non-cardioembolic origin, a combination of clopidogrel and ASA should be given for 21 to 30 days followed by antiplatelet monotherapy (such as ASA or clopidogrel alone) [Evidence Level A]"

TRUTH CAN BE SAD… DEPRESSING

JAMA | Original Investigation

Prevalence of Prescription Medications With Depression as a Potential Adverse Effect Among Adults in the United States

Dima Mazen Qato, PharmD, MPH, PhD; Katharine Ozenberger, MS; Mark Olfson, MD, MPH

JAMA 2018;319(22):2289-2298

SUICIDE & DEPRESSION AS **ADVERSE EFFECTS**

eBox 1. List of Medications with Potential Depression Adverse Effects Identified for Inclusion in Study (N=203) [a]

A. Suicidal Symptoms (n=103) [b]

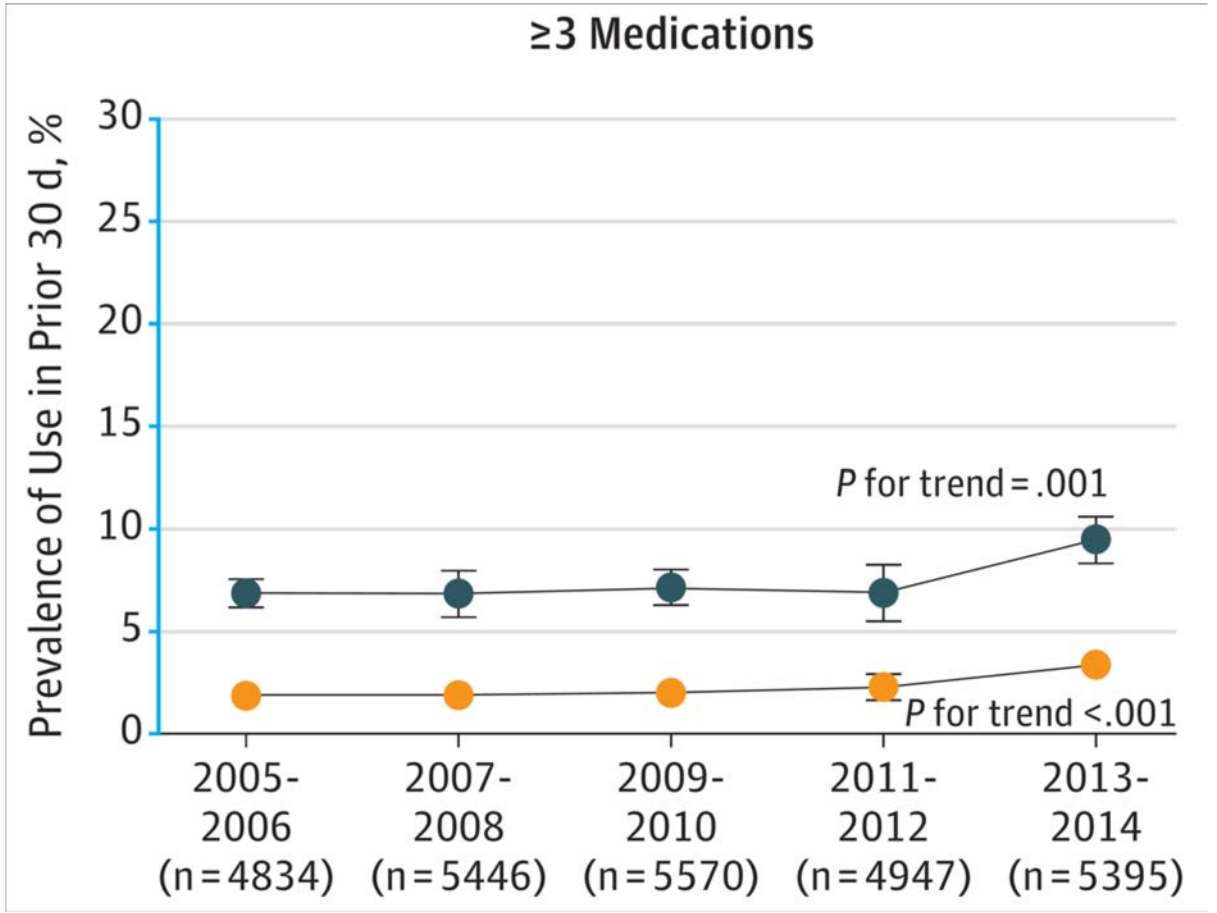
1. Analgesics (Acetaminophen/Tramadol, Hydropmorphone, Tapentadol, Tramadol)
2. Anticonvulsants (Carbamazepine, Clonazepam, Diazepam, Ethosuximide, Gabapentin, Lamotrigine, Levetiracetam, Lorazepam, Methsuximide, Oxcarbazepine, Phenytoin, Pregabalin, Topiramate, Valproic Acid, Zonisamide)
3. Antidepressants (Amitriptyline, Amitriptyline/Chlordiazepoxide, Amitriptyline/Perphenazine, Bupropion, Citalopram, Clomipramine, Desipramine, Desvenlafaxine, Doxepin, Duloxetine, Escitalopram, Fluoxetine, Fluoxetine/Olanzapine, Fluvoxamine, Imipramine, Milnacipran, Mirtazapine, Nefazodone, Nortriptyline, Paroxetine, Phenelzine, Protriptyline, Selegiline, Sertraline, Trazodone, Venlafaxine, Vilazodone)
4. Anxiolytics, Hypnotics, and Sedatives (Alprazolam, Butabarbital, Chlordiazepoxide, Clonazepam, Clorazepate, Diazepam, Doxepin, Eszopiclone, Flurazepam, Pentobarbital, Ramelteon, Triazolam, Zaleplon, Zolpidem)
5. Gastrointestinal Agents (Metoclopramide)
6. Hormones/Hormone Modifiers (Finasteride[1], Leuprolide, Levonorgestrel, Oxandrolone[2], Progesterone)
7. Respiratory Agents (Montelukast, Ribavirin, Roflumilast, Zafirlukast[3])
8. Other Therapeutic Classes (Acamprosate, Amantadine, Armodafinil, Aripiprazole, Asenapine, Atomoxetine, Carbidopa/Entacapone/Levodopa, Carbidopa/Levodopa, Ciprofloxacin, Dapsone, Efavirenz, Efavirenz/Emtricitabine/Tenofovir, Iloperidone, Interferon Beta-1a, Interferon Beta-1b, Isotretinoin, Lurasidone, Memantine, Mefloquine, Methylphenidate, Modafinil, Moxifloxacin, Naltrexone, Natalizumab, Olanzapine, Ofloxacin, Peginterferon Alfa-2a, Quetiapine, Raltegravir, Risperidone[4], Rivastigmine[5], Sibutramine, Tetrabenazine, Varenicline)

B. Depressive (Non-Suicidal) Symptoms (n=100) [c]

1. Analgesics (Cyclobenzaprine, Fentanyl, Acetaminophen/Hydrocodone, Ibuprofen, Indomethacin, Morphine, Nabumetone, Oxycodone)
2. Antihypertensives (Atenolol, Atenolol/Chlorthalidone, Betaxolol, Bendroflumethiazide/Nadolol, Brimonidine, Brimonidine/Timolol, Dorzolamide/Timolol, Enalapril, Hydrochlorothiazide/Metoprolol, Hydrocodone, Metolazone, Metoprolol, Nisoldipine, Quinapril, Telmisartan, Timolol, Trandolapril)
3. Corticosteroids (Betamethasone, Cortisone, Dexamethasone, Methylprednisolone, Prednisolone, Prednisone, Triamcinolone)
4. Gastrointestinal Agents (Atropine/Diphenoxylate, Cimetidine, Dexlansoprazole, Esomeprazole, Famotidine, Omeprazole, Ranitidine)
5. Hormones/Hormone Modifiers (Anastrozole, Bicalutamide, Cabergoline, Conjugated Estrogens, Conjugated Estrogens/Medroxyprogesterone, Desogestrel/Ethinyl Estradiol, Dienogest/Estradiol, Drospirenone/Ethinyl Estradiol, Drospirenone/Ethinyl Estradiol/Levomefolate, Esterified Estrogens, Esterified Estrogens/Methyltestosterone, Estradiol, Estradiol/Norethindrone, Estropipate, Ethinyl Estradiol/Ethynodiol, Ethinyl Estradiol/Etonogestrel, Ethinyl Estradiol/Levonorgestrel, Ethinyl Estradiol/Norethindrone, Ethinyl Estradiol/Norgestimate, Ethinyl Estradiol/Norgestrel, Etonogestrel, Exemestane, Goserelin, Hydroxyprogesterone, Medroxyprogesterone, Megestrol, Norethindrone, Tamoxifen, Testosterone)
6. Respiratory Agents (Cetirizine[6])
7. Other Therapeutic Classes (Abacavir/Lamivudine, Acebutolol, Acitretin, Amphetamine/Detroamphetamine, Baclofen, Benzphetamine, Cinacalcet, Clonidine, Cyclosporine, Dantrolene, Dexmethylphenidate, Donepezil, Dronabinol, Emtricitabine, Erlotinib, Flecainide, Fluphenazine[7], Galantamine, Haloperidol, Maraviroc, Methyldopa, Metolazone, Metronidazole, Oxybutynin[8], Phentermine[9], Pimozide, Prazosin, Propafenone, Propranolol, Rasagiline, Rotigotine, Sorafenib, Tizanidine)

TRUTH CAN BE SAD… DEPRESSING

- 37.2% use at least 1 med with depression/suicidal adverse effects
- Increasing 35.0% (2006) to 38.4% (2014)



TRUTH CAN BE SAD… DEPRESSING

Table 3. Association Between Use of Prescription Medications With Depression as a Potential Adverse Effect and Depression Among US Adults, 2005-2014[a]

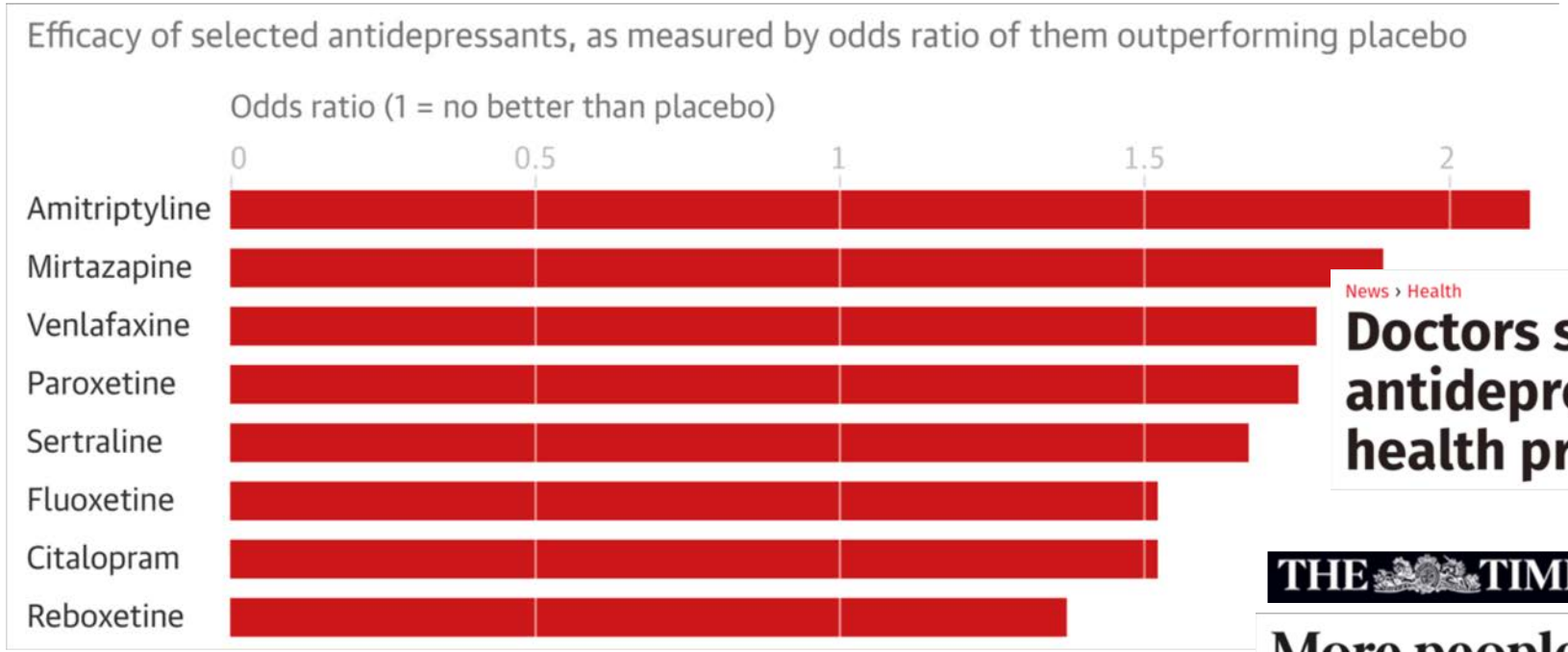
		Estimated Prevalence of Depression (PHQ-9 Score ≥10)			
			% (95% CI)[c]		
	No. of Participants[b]	Unadjusted, No. (%) [95% CI][b]	Adjusted	Adjusted Difference	*P* Value[d]
Overall	23 561	1658 (5.8) [5.3 to 6.3]	5.7 (5.2 to 6.2)	NA	
No. of Medications With Depression Adverse Effect					
0	17 039	984 (4.7) [4.2 to 5.2]	4.7 (4.1 to 5.2)	[Reference]	
1	4394	358 (6.4) [5.4 to 7.5]	6.9 (5.7 to 8.1)	2.2 (0.8 to 3.6)	.002
2	1418	176 (10.4) [8.6 to 12.4]	9.5 (7.6 to 11.5)	4.9 (2.8 to 6.9)	<.001
3 or more	710	140 (19.2) [15.7 to 23.2]	15.3 (12.0 to 18.6)	10.7 (7.2 to 14.1)	<.001
No. of Medications Without Depression Adverse Effect					
0	13 288	843 (5.2) [4.7 to 5.8]	5.5 (4.7 to 6.3)	[Reference]	
1	3613	255 (6.2) [5.3 to 7.3]	6.6 (5.5 to 7.7)	1.1 (−0.3 to 2.5)	.11
2	2171	143 (4.9) [3.8 to 6.1]	5.1 (3.8 to 6.5)	−0.3 (−1.9 to 1.3)	.67
3 or more	4489	417 (7.7) [6.8 to 8.7]	6.0 (4.8 to 7.3)	0.6 (−1.2 to 2.3)	.52

The Guardian International edition

Feb 21, 2018

The drugs do work: antidepressants are effective, study shows

Doctors hope study will put to rest doubts about the medicine, and help to address global under-treatment of depression



INDEPENDENT

News › Health

Doctors should prescribe more antidepressants for people with mental health problems, study finds

THE TIMES

More people should get pills to beat depression

Millions of sufferers would benefit, doctors told

LET'S TAKE A CLOSER LOOK…

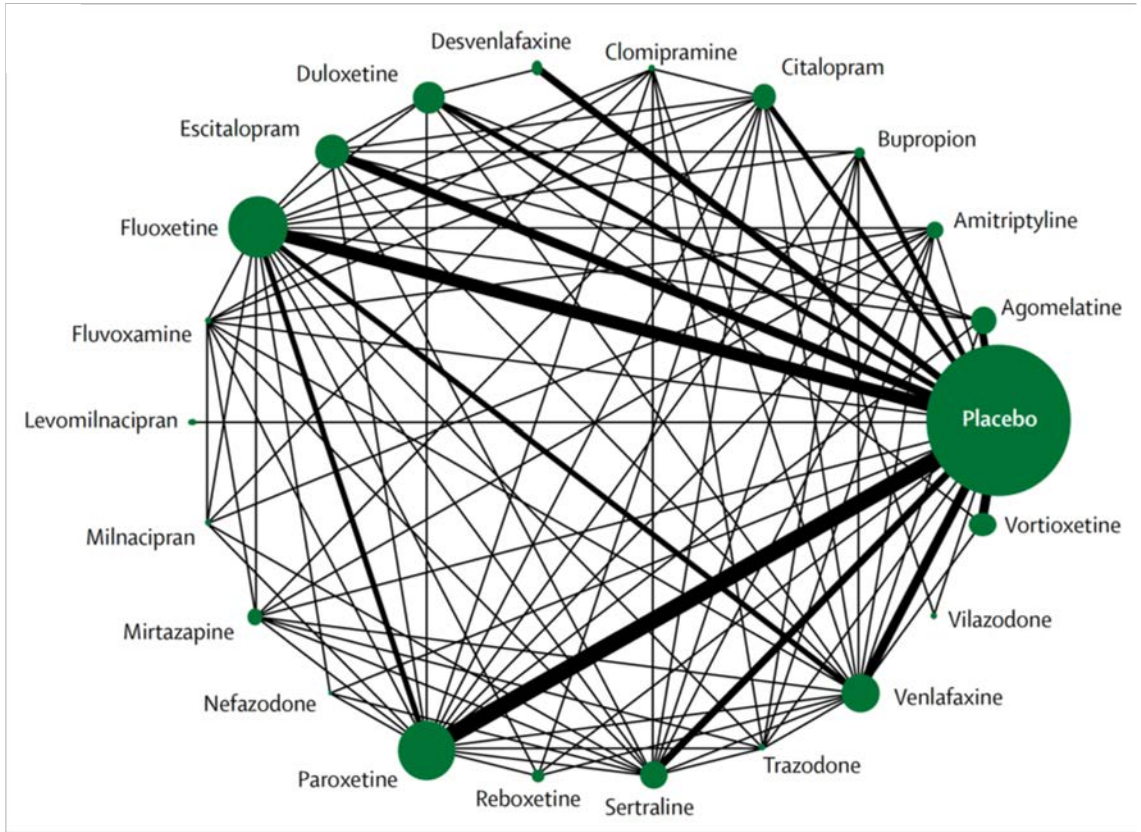
Lancet Feb 21, 2018

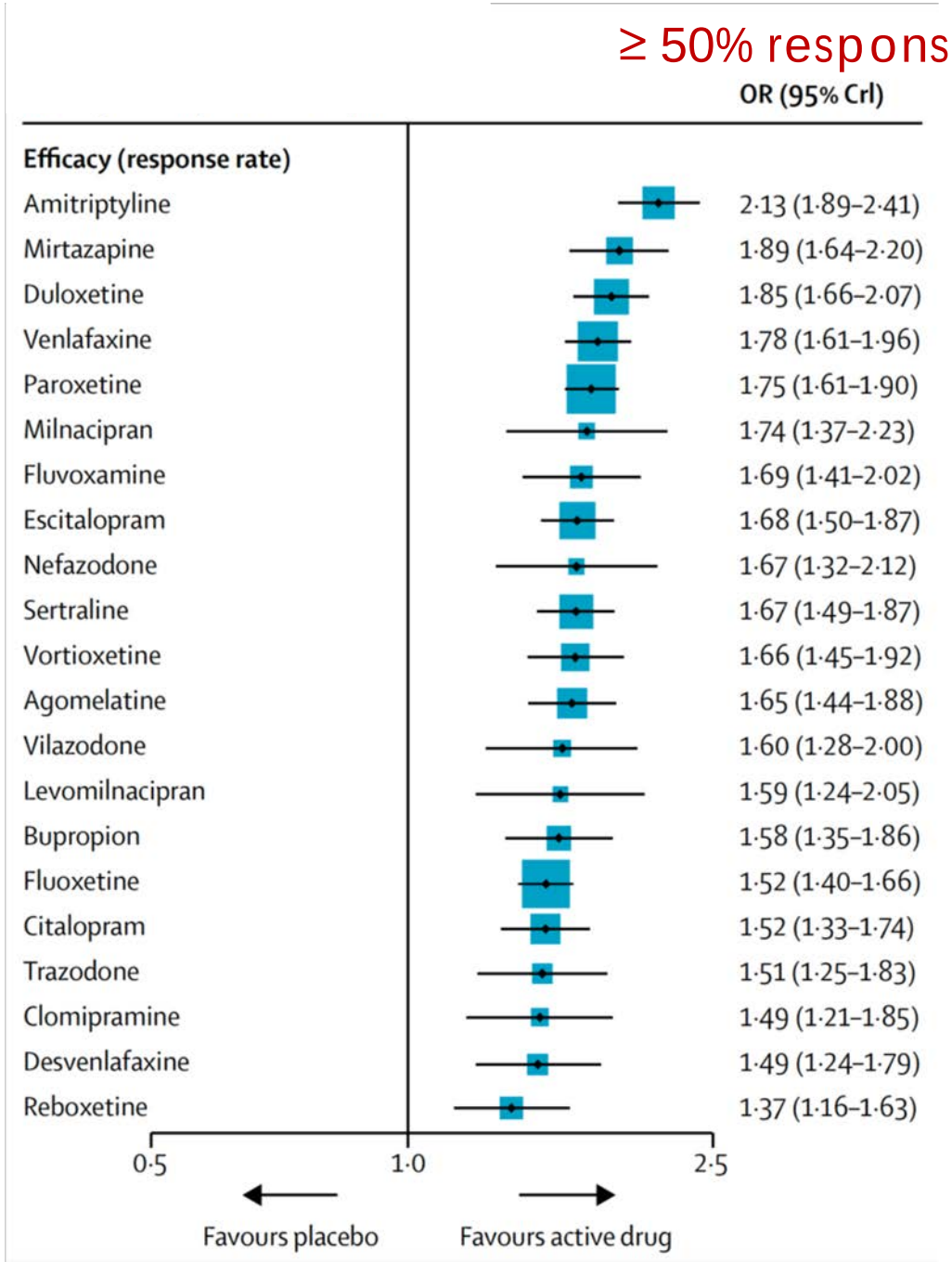
Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: a systematic review and network meta-analysis

- 522 trials of 21 antidepressants in 116,477 participants
  - How depressed were they?
    - Vast majority had moderate-to-severe major depressive disorder
    - Mean HAM-D score = 26

below 7 generally represent the absence or remission of depression
between 7-17 represent mild depression
between 18-24 represent moderate depression
25 and above represent severe depression

  - How long were they treated for?
    - Median duration = 8 weeks





WAS THE UK **MEDIA** TELLING THE TRUTH?

Some of them, SORT OF…

- But, what does the odds ratio mean?
  → it depends on the placebo response
  - If placebo response = ~40%, AND

    Odds ratio = ~1.6, THEN

    → Antidepressants add another ~12%

PUT ANOTHER WAY…

"If 10 patients with moderate to severe depression take an antidepressant for two months, five (50%) will report being "better" but in four of them the response will not be because of the drug."

Lancet Feb 21, 2018

BMJ 2018;360:k1073

Are antidepressants EFFECTIVE? → YES

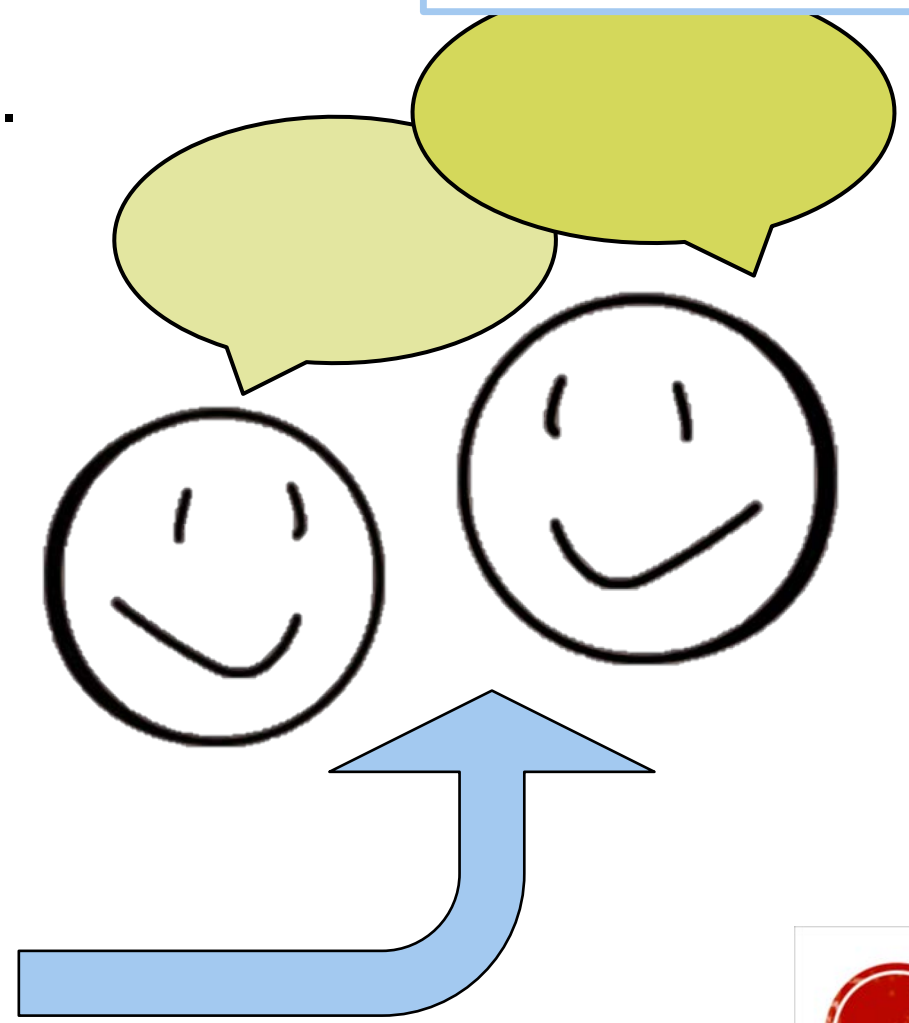
→ Are they GREATLY effective?
Yes, in some cases. No, in many cases.

What don't we know very clearly?

1. effects on MILDER forms of depression
2. effects BEYOND 8 WKS of treatment

AND, these drug are kinda DIRTY,
So, BENEFIT:HARM necessitates considerable discussion with patients

GOOD NEWS?
Another reminder to bring care back to the person in front of us



Pharmacies selling DNA tests to help patients pick best medications

Testing gene interactions with drugs is scientifically sound, but some say may not be ready for consumer use

CBC News · Posted: Oct 25, 2018 4:00 AM ET | Last Updated: October 25

GOOD

HYPE?

Medical News & Perspectives FREE

October 23/30, 2018

Companies Tout Psychiatric Pharmacogenomic Testing, But Is It Ready for a Store Near You?

Jennifer Abbasi

Article Information

JAMA. 2018;320(16):1627-1629. doi:10.1001/jama.2018.14124

In some cases, "the marketing is way out ahead of the data," Potash said. At the American Psychiatric Association annual meeting in May, Assurex Health publicized positive secondary findings in a large, double-blind, randomized clinical trial of its GeneSight Psychotropic test in major depressive disorder. However, Potash pointed out that the trial did not achieve its primary end point—a greater reduction in the 17-item Hamilton Depression Rating Scale score after 8 weeks than the treatment-as-usual group.

THIS JUST IN…

https://genesight.com/media/

Landmark GeneSight® Study Published in Peer-Reviewed Medical Journal

- n=1398 with moderate-very severe depression
  - failed anti-depressant trials (mean) = 3.5

January 14, 2019

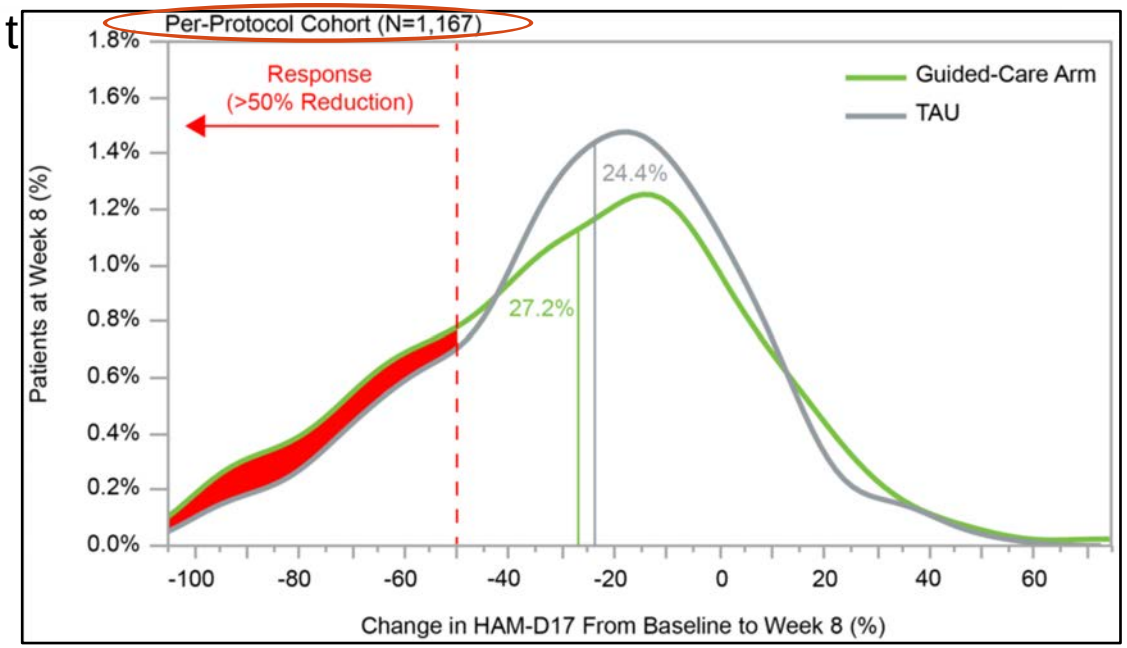
10% vs. 15% (NNT=19)

20% vs. 26% (NNT=17)

Patients 50% More Likely to Achieve Remission; 30% More Likely to Respond to Treatment

(i.e. the continually publicized secondary out

But, why did mean symptom scores (primary outcome) not differ (HAM-D score ⬇27% *vs.* 24%)



J Psych Res, Jan 2019

POST-MARKETING FUNNY BUSINESS

Postmarket studies required by the US Food and Drug Administration for new drugs and biologics approved between 2009 and 2012: cross sectional analysis

Joshua D Wallach,[1,2] Alexander C Egilman,[1,2] Sanket S Dhruva,[3,4] Margaret E McCarthy,[2] Jennifer E Miller,[5] Steven Woloshin,[6] Lisa M Schwartz,[6] Joseph S Ross[1,3,7,8]

BMJ 2018;361:k2031

→ 75% of FDA-required post-marketing clinical studies were in ClinicalTrials.gov
→ Of those with reports expected, 25% had not been reported publicly
→ Of those with result reports, 2/3 reported after deadline
→ time from FDA approval to reported results/publication of postmarket studies = 4 yrs

→ After initial approval, exploratory trial evidence suggesting the value of pregabalin for new indications often went unconfirmed for extended periods of time
→ concern: suggestion of efficacy may encourage uptake in off-label prescription and/or CPGs

JAMA Internal Medicine | Review | HEALTH CARE POLICY AND LAW

Assessment of Pregabalin Postapproval Trials and the Suggestion of Efficacy for New Indications
A Systematic Review

Carole A. Federico, MSc; Taiji Wang, MPH; Adélaïde Doussau, MD, PhD; Jeffrey S. Mogil, PhD; Dean Fergusson, PhD; Jonathan Kimmelman, PhD

JAMA Intern Med Nov 26, 2018

THE BIG **INCRETIN** PICTURE (

GOOD NEWS?
The more agents in a class that have positive results, the more confident we are that positive trials for agents in that class may be truly positive
(but confidence comes at a HEFTY price (**$115-225/month**)

	CV benefit (in a ++hig
DPP4-inhibitors	
• saxagliptin	No (+ ⬆HF
• sitagliptin	No
• alogliptin	No
• linagliptin	No
GLP-1 agonists	
• liraglutide	Yes (1.8% ARR → NNT = 211/yr)
• lixisenatide	No
• exenatide	No
• albiglutide (not marketed)	Yes (1.9% → NNT = 83/yr)
• semaglutide	Yes (2.3% → NNT = 110/yr), but
• dulaglutide (press release → CV benefit?)	2019

0/4

3/5

4/6?

	EMPA-REG (empagliflozin) (n=7,020) X3.1y NNT or NNH/yr	CANVAS (canagliflozin) (n=10,142) X3.6y NNT or NNH/yr	DECLARE (dapagliflozin) (n=17,160) X4.2y NNT or NNH/yr
CVD death, MI, stroke	192		
Mortality	120		
Amputations	NS		
Fractures	NS		
Volume depletion	NS		
Genital infections	21		

NEJM 2015;373:2117-2128 *NEJM* 2017;377(7):644-657 *NEJM* Nov 10, 2018

Is there an **SGLT2i** CLASS EFFECT?

https://www.astrazeneca.com **(Nov 12, 2018)**

(i.e. dapagliflozin)

Farxiga significantly reduced hospitalisation for heart failure or CV death in a broad patient population with type-2 diabetes in the landmark DECLARE-TIMI 58 trial

WHAT DOES THAT MEAN?

	EMPA-REG (empagliflozin) (n=7,020) X3.1y NNT or NNH/yr	CANVAS (canagliflozin) (n=10,142) X3.6y NNT or NNH/yr	DECLARE (dapagliflozin) (n=17,160) X4.2y NNT or NNH/yr
CVD death, MI, stroke	192	218	NS
Mortality	120	NS	NS
Amputations	NS	344	NS
Fractures	NS	286	NS
Volume depletion	NS	133	NS
Genital infections	21	13	NR

Is there an SGLT2i CLASS EFFECT?

What did it do?

- Adm for heart failure:
  - ⬇ 2.3 cases/1000 pts/yr
- NO ⬇ in CV death
- ⬇ those with ≥40% eGFR drop
  - ⬇ 3.1 cases/1000 pts/yr

NEJM 2015;373:2117-2128 *NEJM* 2017;377(7):644-657 *NEJM* Nov 10, 2018

BMJ 2018;363:k5207

CHRISTMAS 2018: LOOK BEFORE YOU LEAP

Key opinion leaders' guide to spinning a disappointing clinical trial result

Adam Hartley and colleagues present a playbook for commenting on trials with disappointing results

THIS JUST IN (NOV 10, 2018)…

SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials

Thomas A Zelniker, Stephen D Wiviott, Itamar Raz, Kyungah Im, Erica L Goodrich, Marc P Bonaca, Ofri Mosenzon, Eri T Kato, Avivit Cahn, Remo H M Furtado, Deepak L Bhatt, Lawrence A Leiter, Darren K McGuire, John P H Wilding, Marc S Sabatine

Implications of all the available evidence

These data suggest that SGLT2i should be considered in patients with type 2 diabetes regardless of presence of atherosclerotic cardiovascular disease or history of heart failure, given that SGLT2i safely reduce HbA_{1c} and reduce the risk of hospitalisation for heart failure and progression of renal disease across a broad spectrum of patients with type 2 diabetes. Reductions in major adverse cardiovascular events can also be expected in patients with established atherosclerotic cardiovascular disease.

Really? Based on what?

- If no CVD, ARR HF adm = 0.16% → NNT = 625/yr

What does that mean?

- ARR HF adm = 0.32% → NNT = 313/yr
- ARR renal =0.38% → NNT = 263/yr (driven by ⬇eGFR ; no diff in ESRD)

Not for dapagliflozin

For the other two:
ARR MACE = 0.61% → NNT = 164/yr

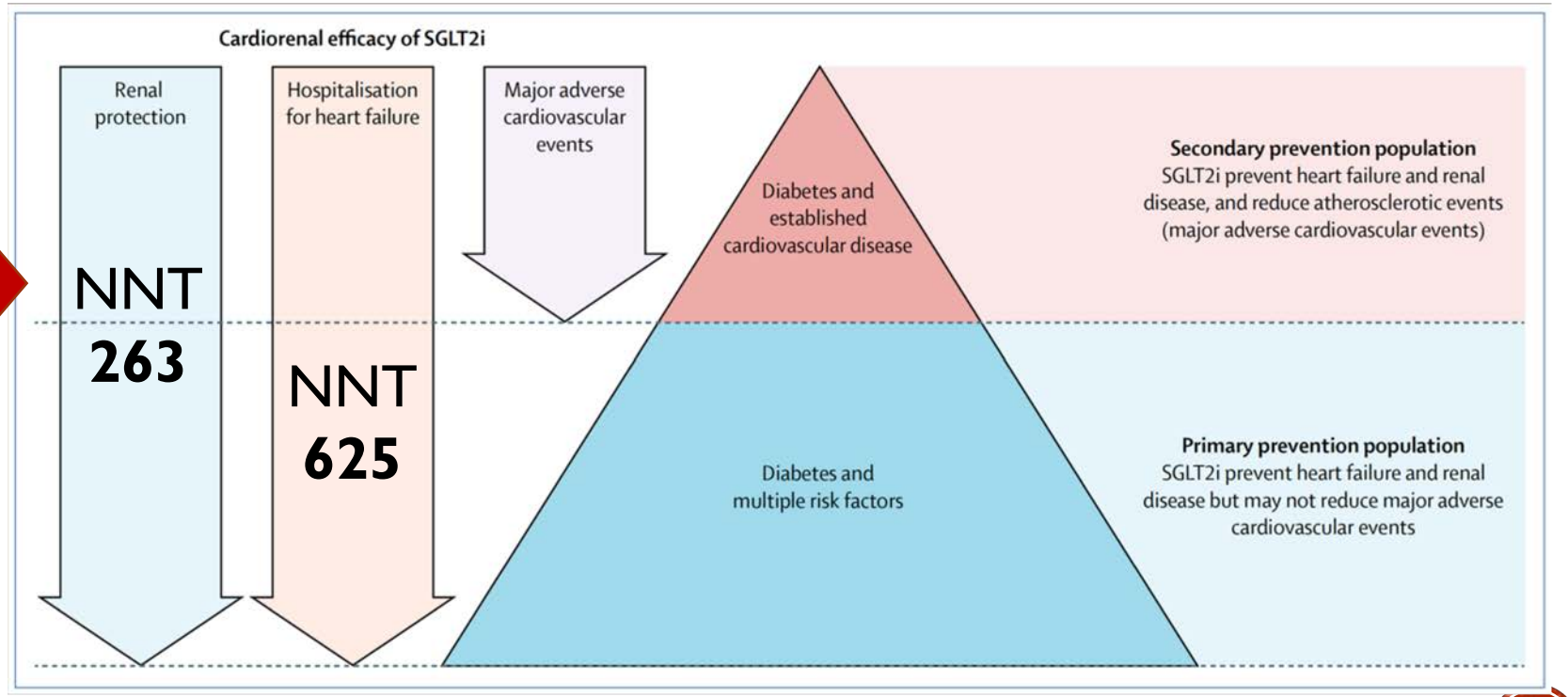
Lancet 2018 http://dx.doi.org/10.1016/S0140-6736(18)32590-X

Lancet, Nov 10 2018

Pump, pipes, and filter: do SGLT2 inhibitors cover it all?

*Subodh Verma, Peter Jüni, C David Mazer

The Commentator thinks so…



ONE OF THESE THINGS IS NOT LIKE THE OTHER

1. Should we be lumping drugs together just because they're in the same class?
2. DPP-4s can probably be lumped together and dumped together

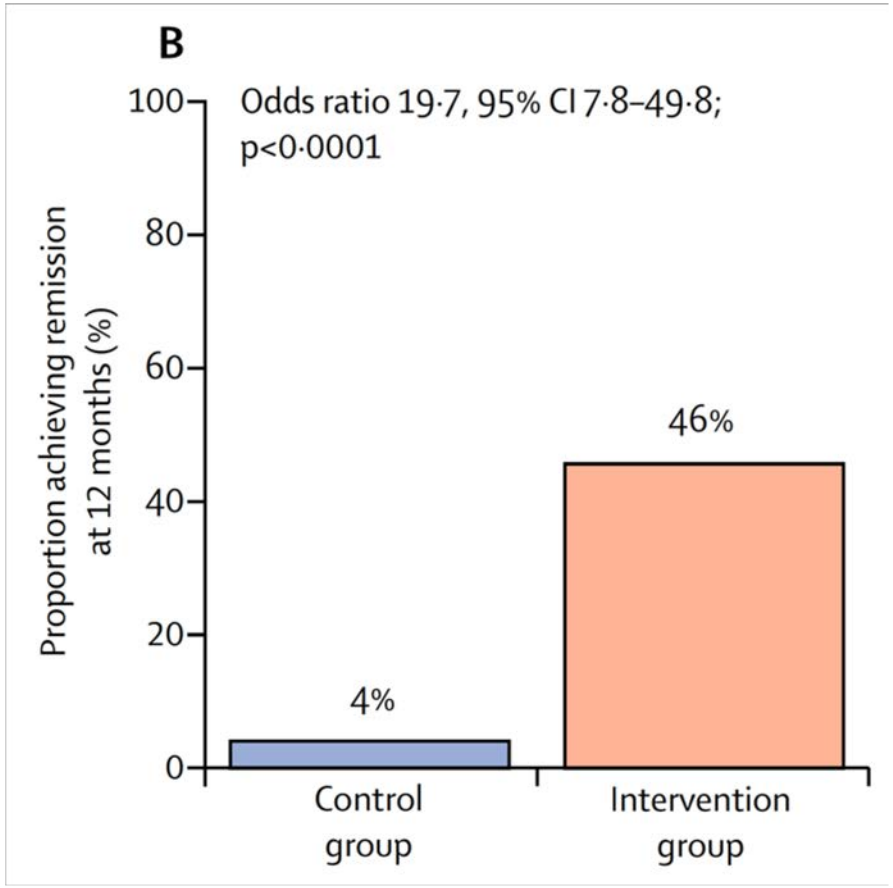
AMAZING NEW DIABETES DRUG

Cluster RCT

- Age 20-65
- Type 2 Diabetes (< 6 years)
- BMI 27-45 kg/m^2
- HbA_{1c} < 12% but > 6.0%

www.thelancet.com Vol 391 February 10, 2018

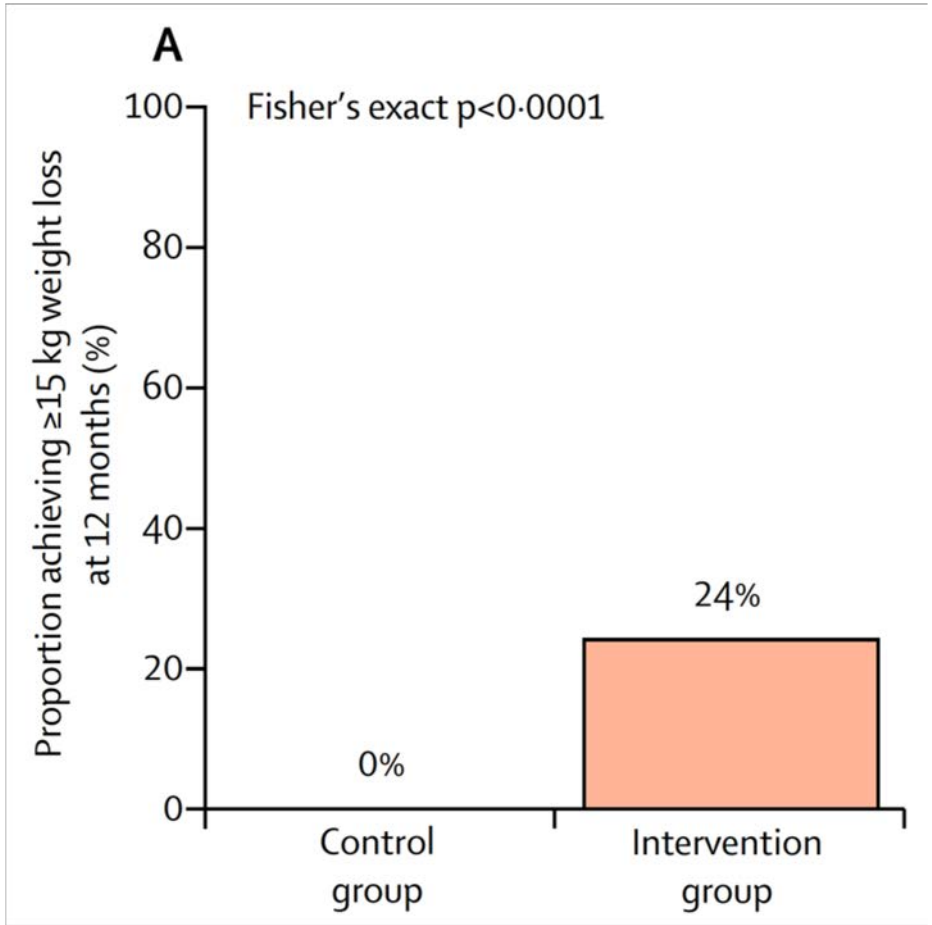
NEW DIABETES DRUG… TREMENDOUS RESULTS



- RCT data
- OR 19.7
- ARR 42% for Remission of Diabetes
- NNT = 3

www.thelancet.com Vol 391 February 10, 2018

NEW DIABETES DRUG… AND THERE IS MORE!!!!!



- Weight Loss
- > 15kg
- ARR 24%
- NNT = 5

www.thelancet.com Vol 391 February 10, 2018

OK - NEW DIABETES "DRUG"

Primary care-led weight management

Primary care-led weight management for remission of type 2 diabetes (DiRECT): an open-label, cluster-randomised trial

Michael E J Lean, Wilma S Leslie, Alison C Barnes, Naomi Brosnahan, George Thom, Louise McCombie, Carl Peters, Sviatlana Zhyzhneuskaya, Ahmad Al-Mrabeh, Kieren G Hollingsworth, Angela M Rodrigues, Lucia Rehackova, Ashley J Adamson, Falko F Sniehotta, John C Mathers, Hazel M Ross, Yvonne McIlvenna, Renae Stefanetti, Michael Trenell, Paul Welsh, Sharon Kean, Ian Ford, Alex McConnachie, Naveed Sattar, Roy Taylor**

Lancet 2018; 391: 541–51

NOT FOR **EVERYONE…**

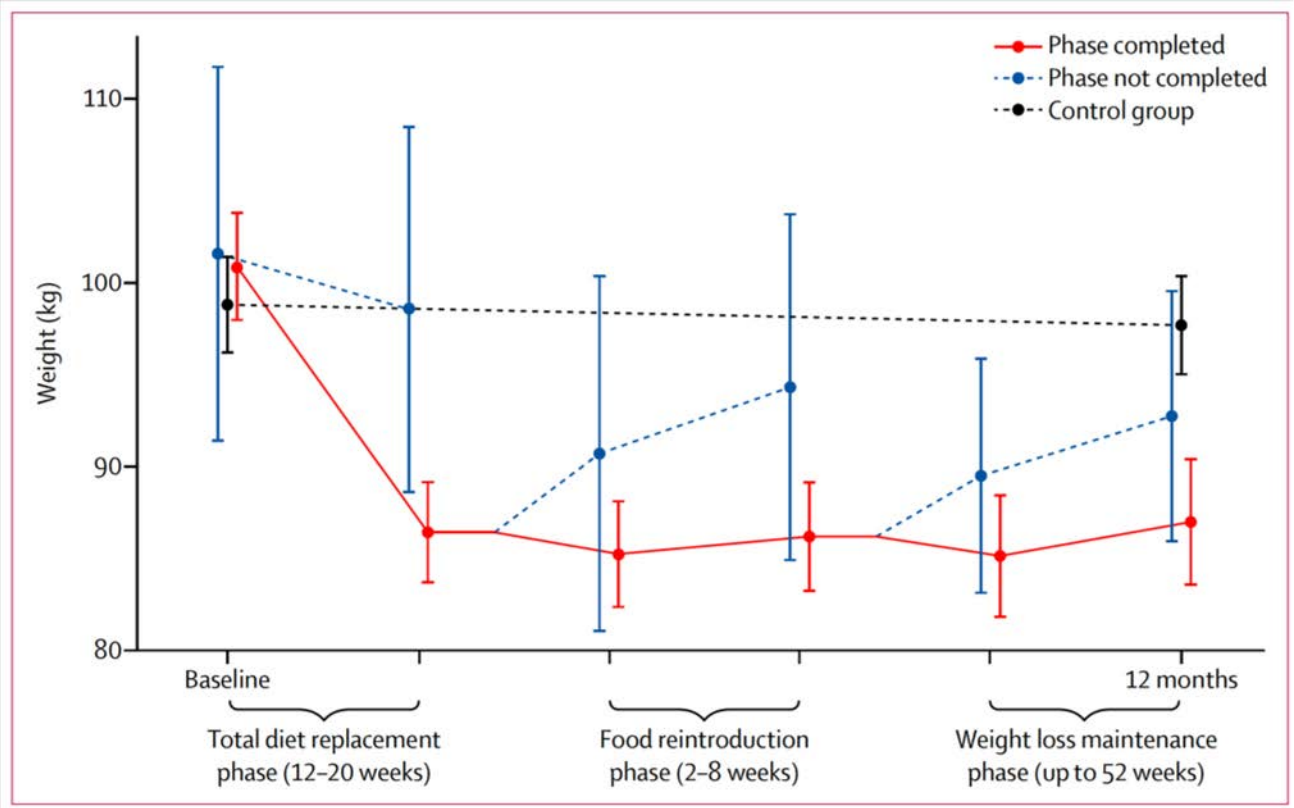
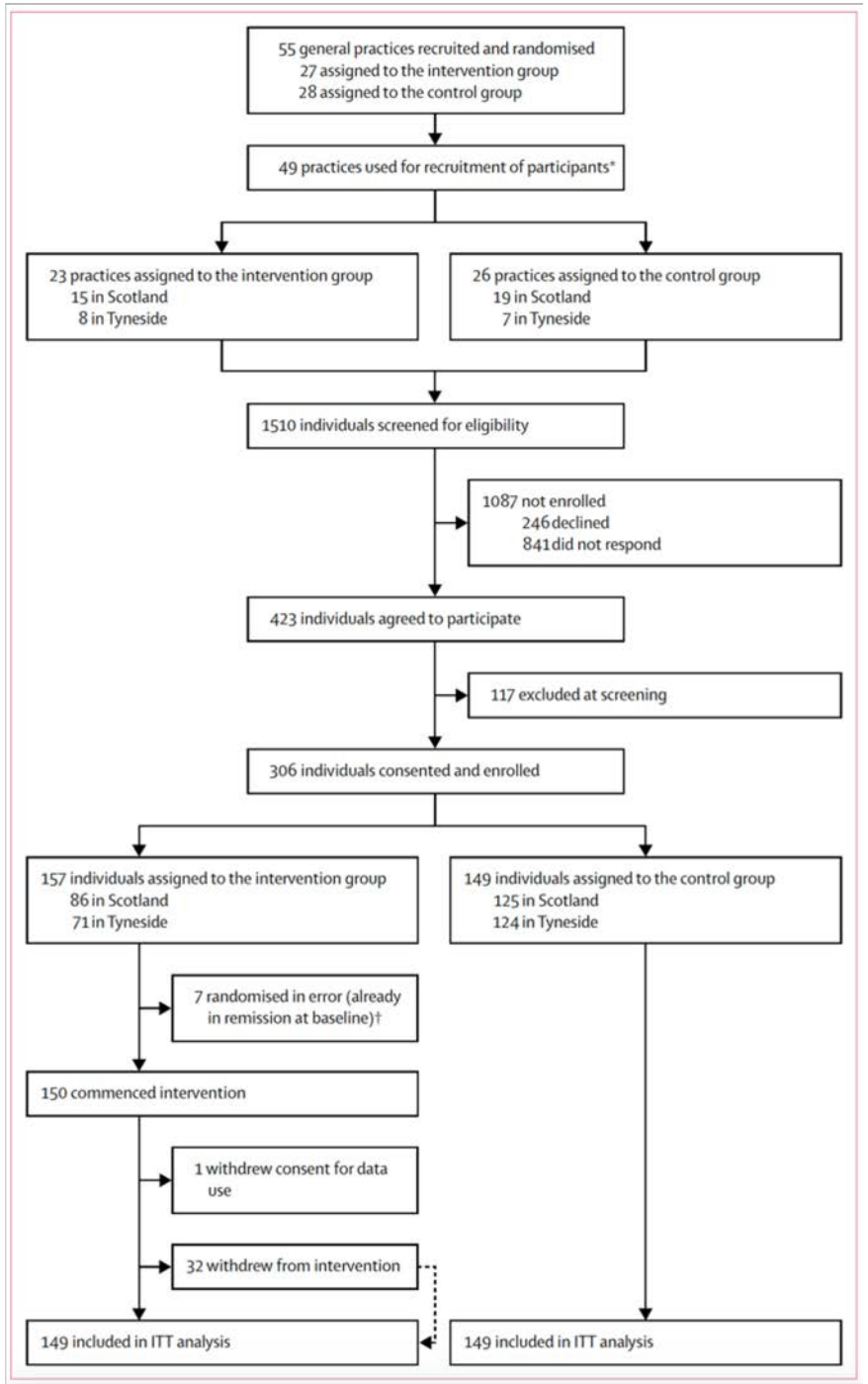
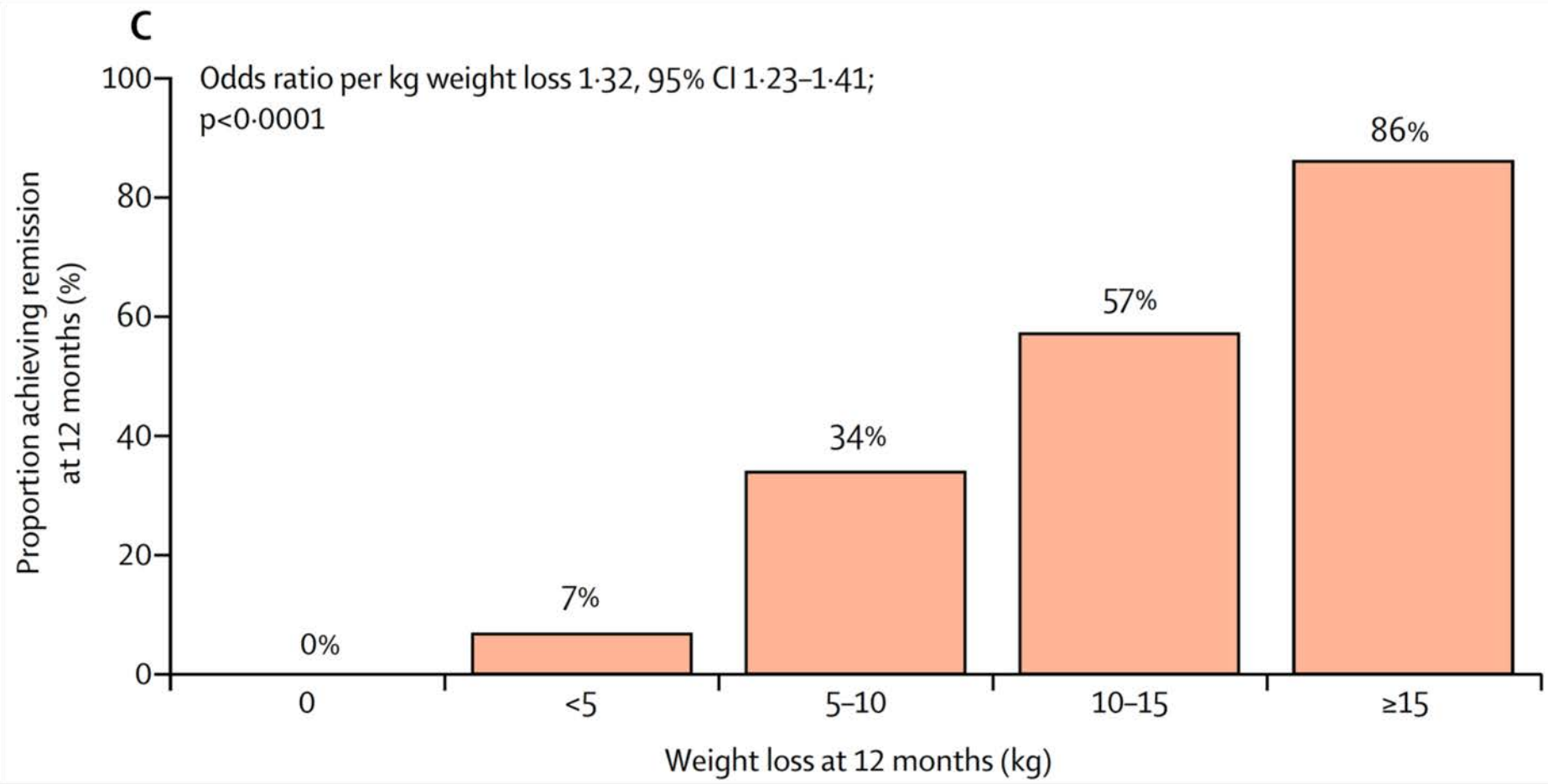


***Figure 3*: Change in weight of participants who remained in the trial and those who dropped out during each phase of the intervention**



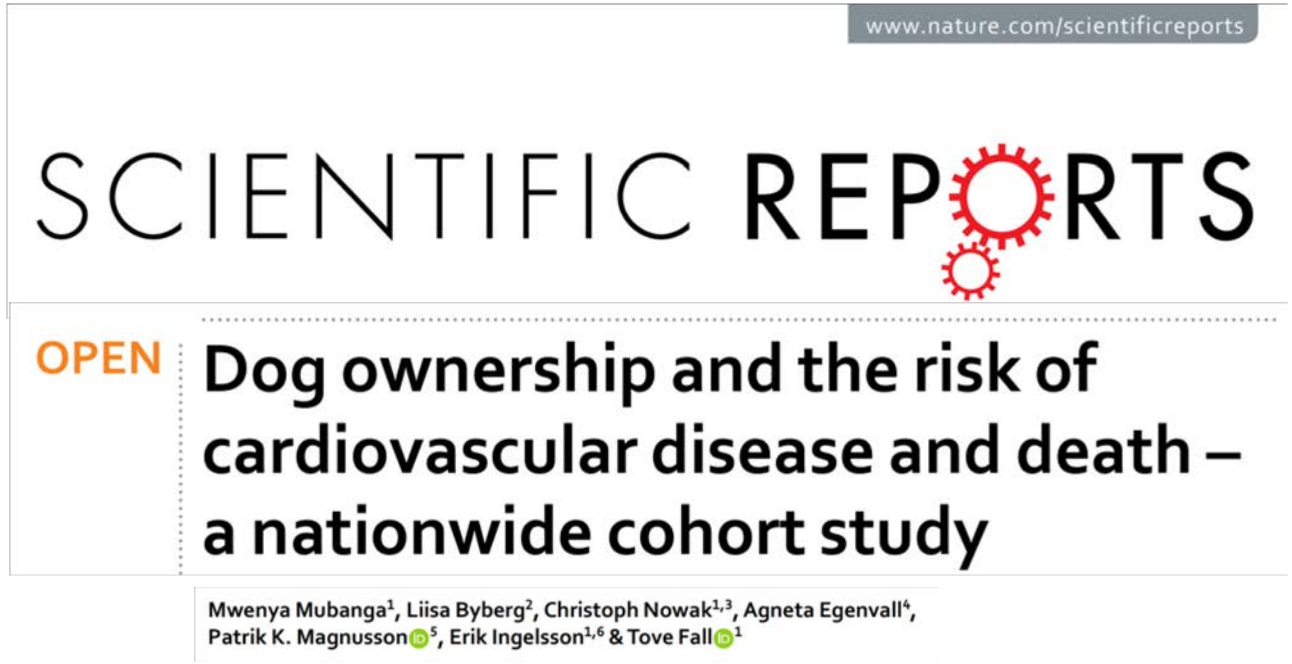
Lancet 2018; 391: 541–51

NOT FOR EVERYONE – BUT IF IT WORKS…



Lancet 2018; 391: 541–51

OR, GET A **DOG**



www.nature.com/scientificreports

SCIENTIFIC REPORTS

OPEN

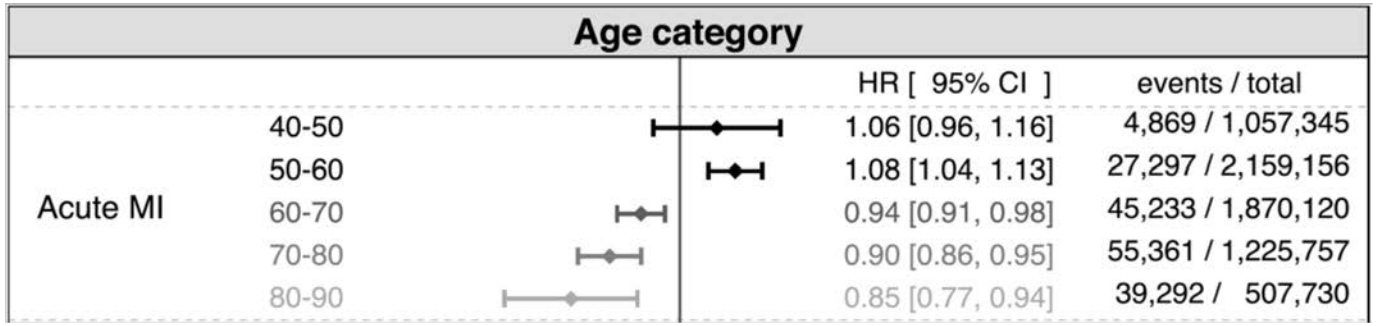
Dog ownership and the risk of cardiovascular disease and death – a nationwide cohort study

Mwenya Mubanga[1], Liisa Byberg[2], Christoph Nowak[1,3], Agneta Egenvall[4], Patrik K. Magnusson[5], Erik Ingelsson[1,6] & Tove Fall[1]

Scientific Reports 7:15821

DOG RX

Cardiovascular disease	Number of events	Person-years at risk	Crude[1] HR (95% CI)	Adjusted[2] HR (95% CI)
CVD mortality[4]	76,106	38,408,267	0.68 (0.65–0.71)	0.77 (0.73–0.80)
All–Cause mortality	502,896	38,408,267	0.72 (0.71–0.73)	0.80 (0.79–0.82)



Scientific Reports 7:15821

OPIOIDS IN **CHRONIC BACK PAIN**

Cochrane review (2013):
n= 15 trials, 5540 patients, duration = 4-12 wks

"There are no placebo-RCTs supporting the effectiveness and safety of long-term opioid therapy for treatment of CLBP."

TA-DA…

(okay, well it's not placebo-controlled, but it is 1 year long)

JAMA | Original Investigation

Effect of Opioid vs Nonopioid Medications on Pain-Related Function in Patients With Chronic Back Pain or Hip or Knee Osteoarthritis Pain

The SPACE Randomized Clinical Trial

JAMA 2018;319(9):872-882

the **SPACE** trial

DOES THIS BRING A TEAR TO YOUR EYE?

Intervention Delivery

Medication was delivered using a collaborative pain care model with demonstrated effectiveness.[9,10] In both groups, pa-

In both groups, patients received structured symptom monitoring and a treat-to-target approach to medication management delivered primarily by a single pharmacist. After randomization, the pharmacist reviewed past medications and identified individual functional goals. The initial medication regimen was determined by the assigned group and considerations such as patient preference and comorbidities.

were adjusted within the assigned group to achieve targets of improved PEG scores and progress toward individual goals. Study medications were dispensed from the VA pharmacy.

JAMA 2018;319(9):872-882

CHRONIC BACK PAIN

the **SPACE** trial

GOOD NEWS?
The drugs we're scared about are no better/a bit worse than the drugs we're less scared of

n = 240 (65% CLBP, 35% OA)

OPIOIDS:
Step 1: IR morphine, hydrocodone, oxycodone
Step 2: SR morphine, oxycodone
Step 3: fentanyl patch
} mean MEQ = 21mg/d

NON-OPIOIDS:
Step 1: acetaminophen, NSAIDS
Step 2: TCA, gabapentin
Step 3: pregabalin, duloxetine, tramadol
} NSAID > adjuncts, topicals > acetaminophen >> tramadol

Results @ 1 yr:

PAIN → a bit better with non-opioids (0.5 points (0-10))
FUNCTION → no difference
ADVERSE EVENTS → a bit more with opioids (0.9 points (0-19))
d/c med → 19% (opioids) *vs.* 8% (non-opioids)

WHO GETS A TROPHY FOR TREATING **ATROPHY**?

JAMA Internal Medicine | Original Investigation

Efficacy of Vaginal Estradiol or Vaginal Moisturizer vs Placebo for Treating Postmenopausal Vulvovaginal Symptoms

A Randomized Clinical Trial

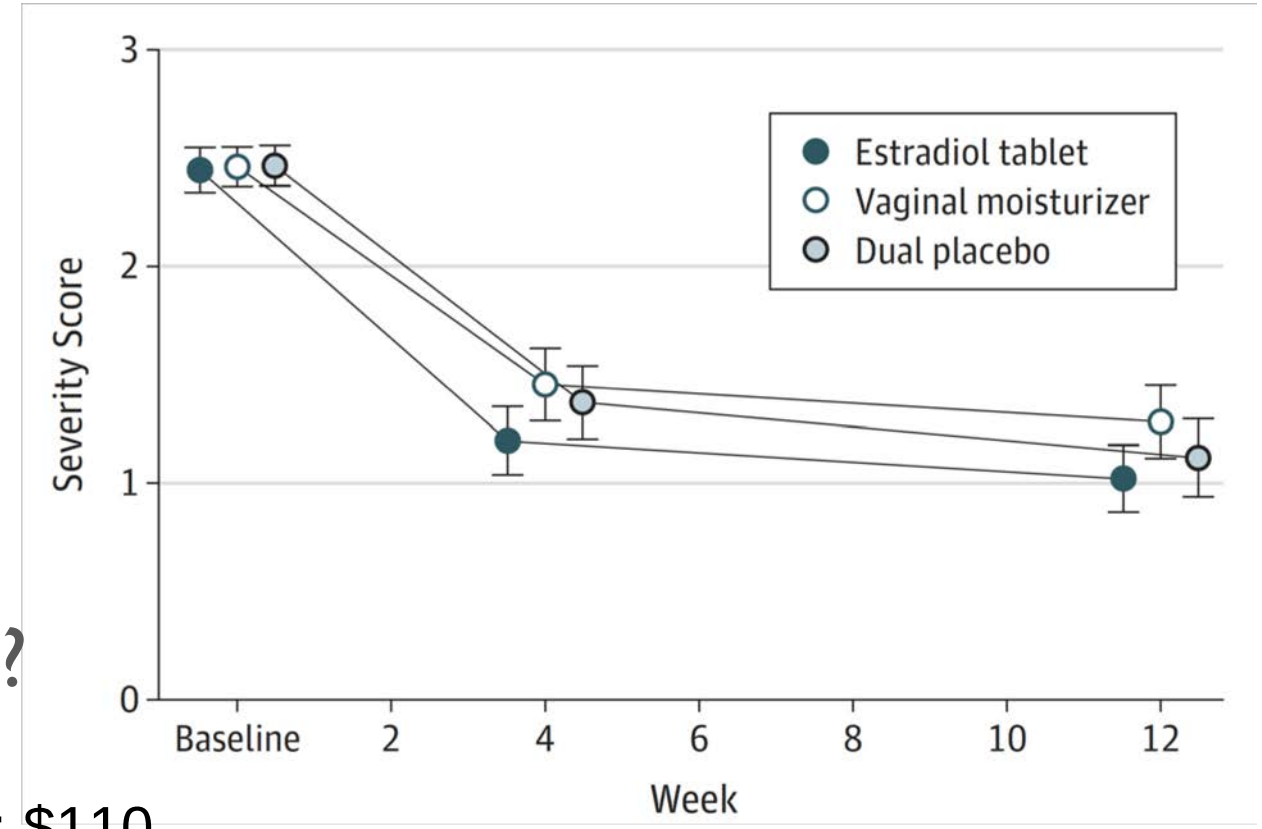
JAMA Intern Med 2018;178(5):681-690

- **WHO?** n=302, mean age = 61 with moderate to severe vulvovaginal symptoms
- Randomized to:
  - Vagifem 10-µg tablet 2X/wk + placebo vaginal gel
  - placebo vaginal tablet + Replens vaginal moisturizer 3X/wk
  - placebo vaginal tablet + placebo vaginal gel 3X/wk
- **PRIMARY OUTCOME:** Δ in severity of most bothersome symptom (MBS)
  - Severity rating → 0 - none, 1 - mild, 2 - moderate, 3 - severe

(MBS at baseline: 60% pain with penetration, 21% dryness, 18% itching, irritation, or pain)

AND THE AWARD GOES TO… WAIT, WHAT?

- Neither treatment (Vagifem or Replens) ⬇MBS severity more than placebo at 4 or 12 weeks
- ALL GROUPS had a mean ⬇ of 1.2-1.4-points (i.e. ≥ 50%) from baseline by 12 weeks



What's preferred by the patient?

- Administration/formulation
- Cost — **90 days** → Vagifem: $110
  Replens: $68
  KY Jelly: $15

JAMA Intern Med 2018;178(5):681-690

WATER: OUR MOST PRECIOUS RESOURCE

Common recommendation for recurrent UTIs:

⬆ hydration → dilution & flushing of bacteriuria is beneficial

EVIDENCE… *"sparse and unconvincing"*

JAMA Internal Medicine | Original Investigation

Effect of Increased Daily Water Intake in Premenopausal Women With Recurrent Urinary Tract Infections
A Randomized Clinical Trial

JAMA Intern Med 2018;178(11):1509-1515

JAMA Internal Medicine | Original Investigation

Effect of Increased Daily Water Intake in Premenopausal Women With Recurrent Urinary Tract Infections

A Randomized Clinical Trial

- **WHO?** n=140 mostly healthy women, mean age = 36
  - Key inclusion → ≥ 3 UTIs in past yr (mean = 3.3)
    → self-reported drinking <1.5 L of fluid/day (baseline = 1.1 L/d)
  - Exclusions → current UTI, pyelonephritis in past yr, interstitial cystitis, symptomatic vulvovaginitis, or pregnant/lactating
- **PRIMARY OUTCOME:** frequency of recurrent cystitis
- Secondary outcomes: # of antimicrobial regimens used, mean time between episodes, 24-h urinary hydration measurements

INTERVENTION…

Drink more water for 1 yr:

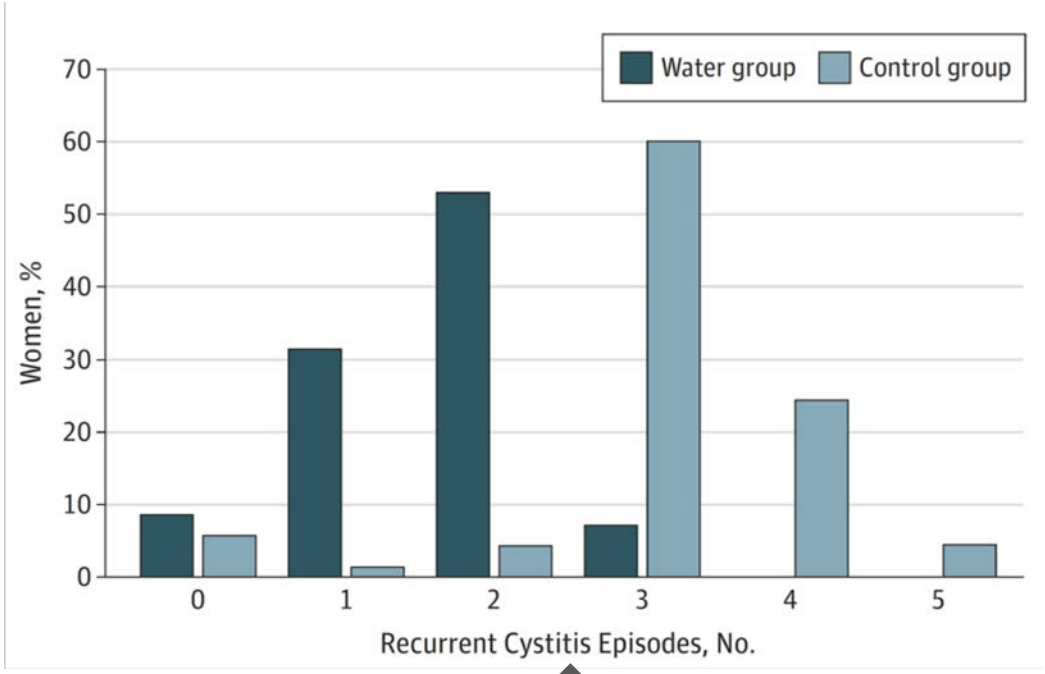
- 1.5 L of water/d in addition to usual fluid intake *vs.*
- no additional fluids (control group)

JAMA Intern Med 2018;178(11):1509-1515

RESULTS

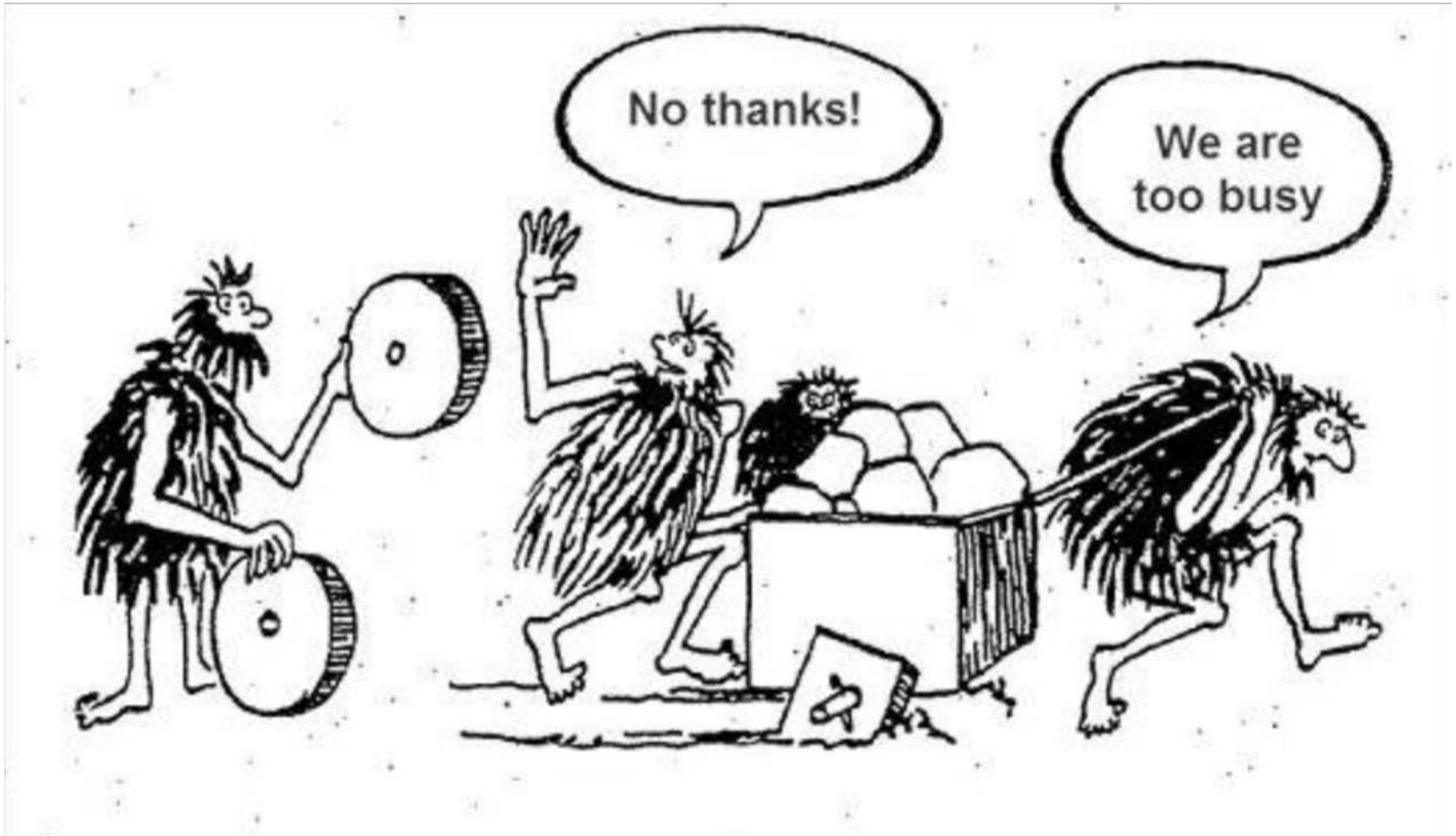
@ 1 year:

- mean fluid intake ⬆1.7 L/d & water intake ⬆ 1.15 L/d in water group (no change in control group)



- Mean cystitis episodes... 1.7 *vs.* 3.2
- Antimicrobial regimens...1.9 *vs.* 3.6
- Not surprisingly...
  - water group peed more (~2 more voids/day)
  - no adverse event differences reported

NOT TO OVER-SIMPLIFY, BUT…



“OUTLINE”

- BS is very fast
- Why is BS fast? → It was pushed.
- What answer would you like?
- BS is an excellent organic fertilizer
- ASA is primarily done
- That fish won’t die
- Take a CHANCE on clopidogrel
- You can’t handle the truth
- Antidepressants: Handle with care
- The reality of Pharmacogen-OH-mics
- Funny thing happened on the way to the post-marketing study
- Classy Diabetes Drugs?
- Amazing New Diabetes Drug
- Or Dog it
- K whY is this so simple?
- What!? Those water bottle people have it right!

QUESTIONS?

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