2021 AFS Keynote International Lecturer Paul Moayyedi

BSc (Bristol) = Bachelor of science
MB ChB (Bristol)= Bachelor of medicine
MRCP (Edinburgh) = Member of the Royal College of Physicians
Ph.D (Leeds) = Doctor of Philosophy
MPH = Masters in Public Health (Leeds)
FRCP (London) = Fellowship of the Royal College of Physicians of London
FRCPC = Fellow of the Royal College of Physicians of Canada
AGAF = Fellow of the American Gastroenterological Association
FACG = Fellow of the American College of Gastroenterology
CAGF = Canadian Association of Gastroenterology Fellow

The reality of long term PPI adverse events

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Disclosures

- None

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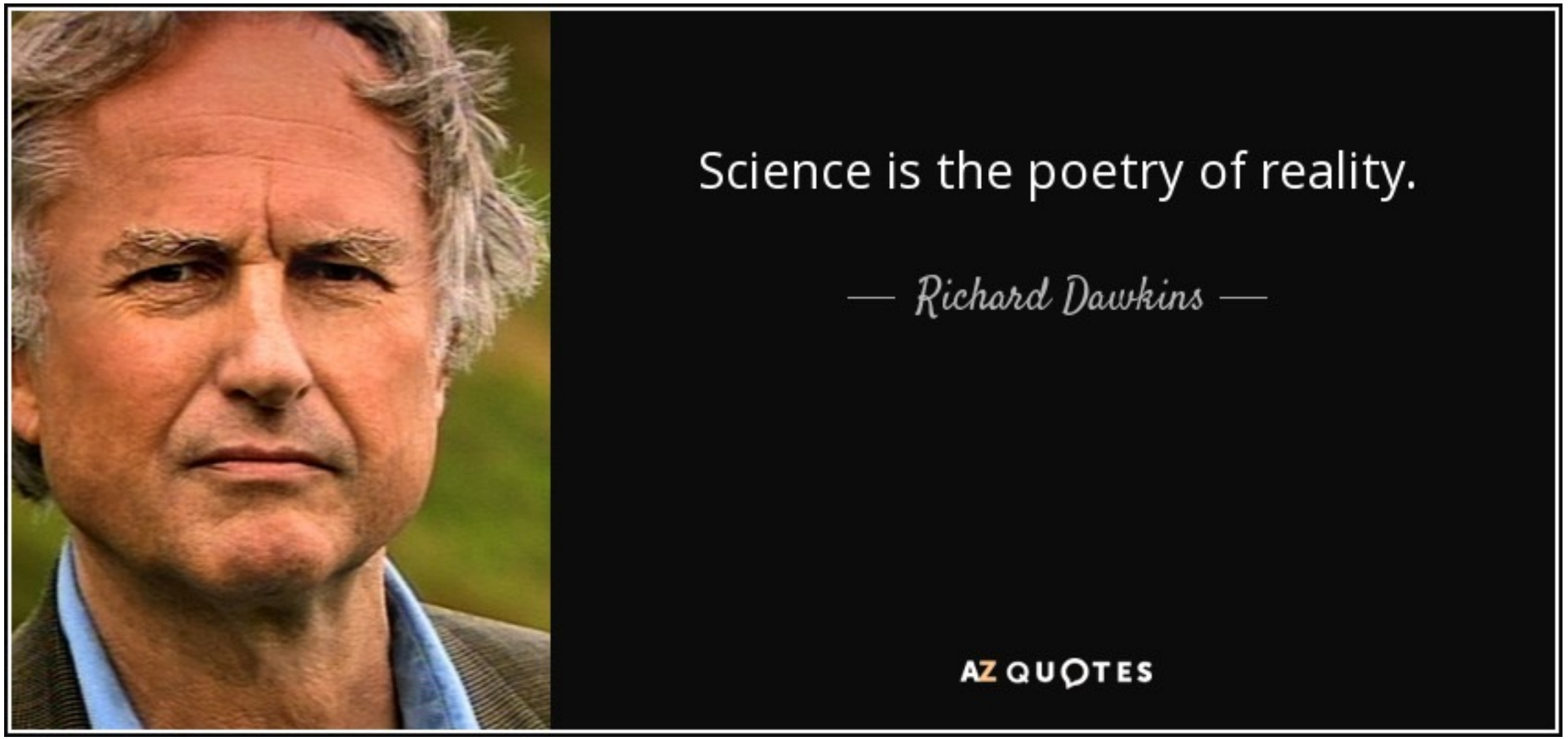
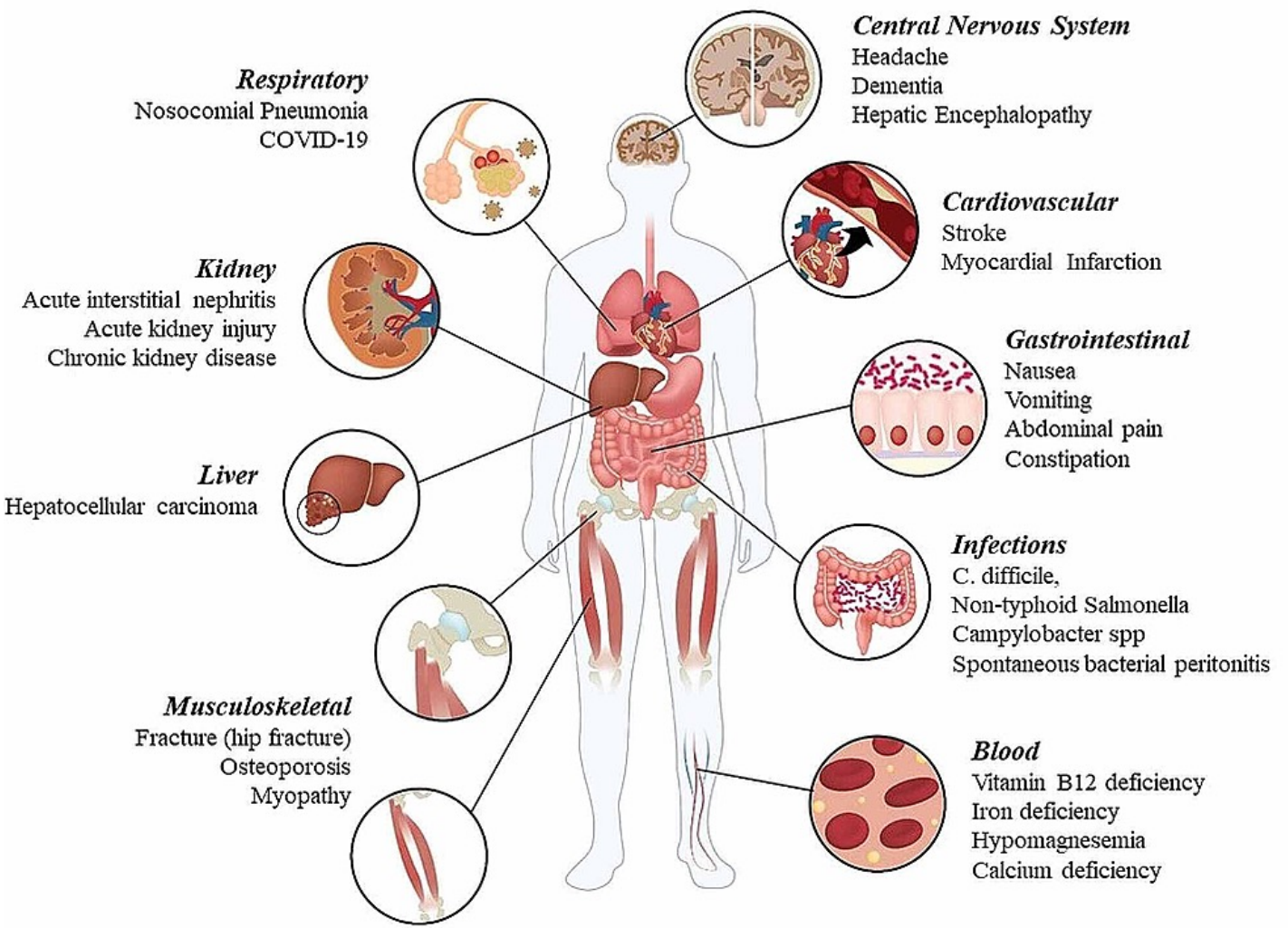


Adverse events and PPIs



Yibirin M et al. Cureus 13(1): e12759. doi:10.7759/cureus.12759

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No smoke without fire?
How can someone from McMaster criticize scientific evidence?

New Orleans April 2018

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BRITISH MEDICAL JOURNAL

LONDON SATURDAY SEPTEMBER 30 1950

SMOKING AND CARCINOMA OF THE LUNG

PRELIMINARY REPORT

BY

RICHARD DOLL, M.D., M.R.C.P.

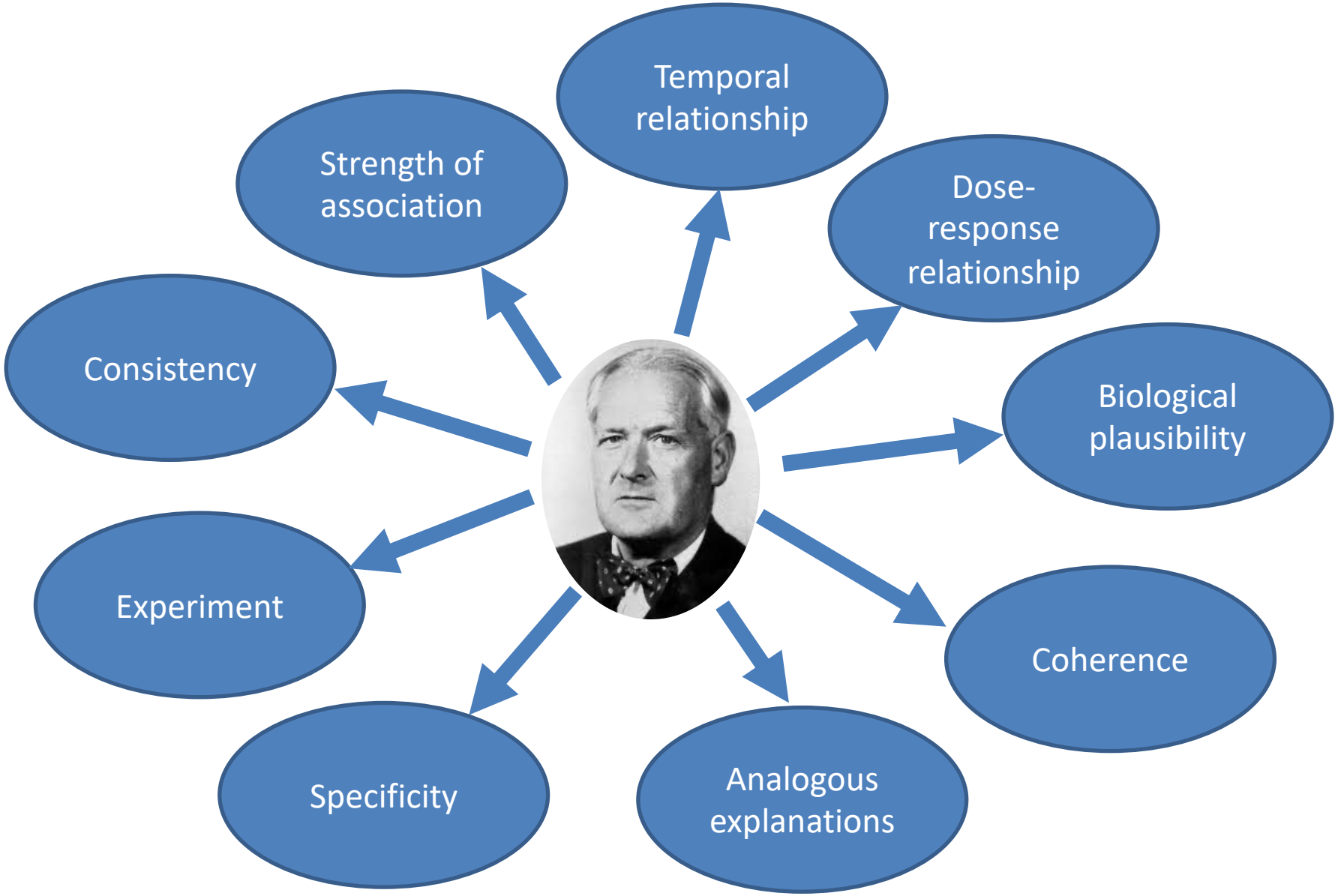
Member of the Statistical Research Unit of the Medical Research Council

AND

A. BRADFORD HILL, Ph.D., D.Sc.

Professor of Medical Statistics, London School of Hygiene and Tropical Medicine; Honorary Director of the Statistical Research Unit of the Medical Research Council

Austin Hill – issues to consider for causal inference



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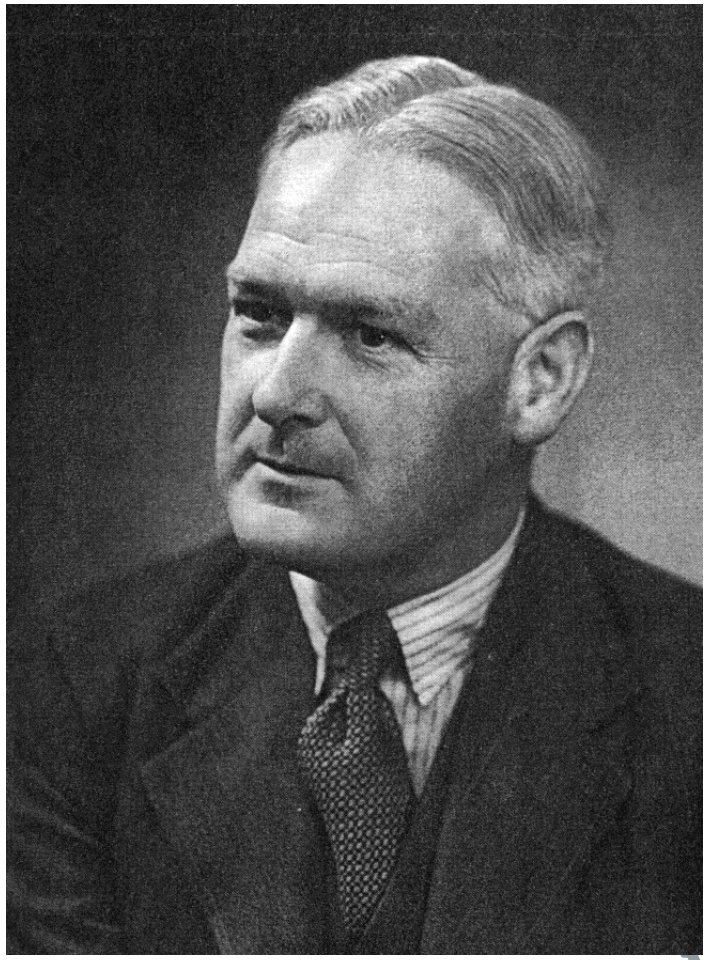
Causality in epidemiology: the Hill criteria

- Strength of association
- Consistency
- Specificity
- Temporality
- Biologic gradient?
- **Biologic plausibility**
- Coherence
- **Experimental evidence**
- Analogy



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Car pollution

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H. pylori infection influences behaviour

- Global car ownership is increasing as *H. pylori* is decreasing
- *H. pylori* induces behavioral changes in mice
- Gut bacteria can increase timidity in germ free mice
- RCT of a probiotic in humans shows this cane reduce anxiety and depression with associated fMRI changes

Bercik P et al. Am J Physiol 2009; 296: R587-94
Bercik P et al. Gastroenterology 2011; 141: 599-609
Pinto-Sanchez MI et al. Gastroenterology 2017; 153: 448-59

H. pylori and car ownership

- Leeds HELP study
- 8,289 subjects aged 40-49 years in 1994
- *H. pylori* status by ^{13}C-UBT (28% infected)
- Car ownership by questionnaire
- Other demographic variables collected

Moayyedi P et al. Am J Gastroenterol 2000;95:1448 –1455

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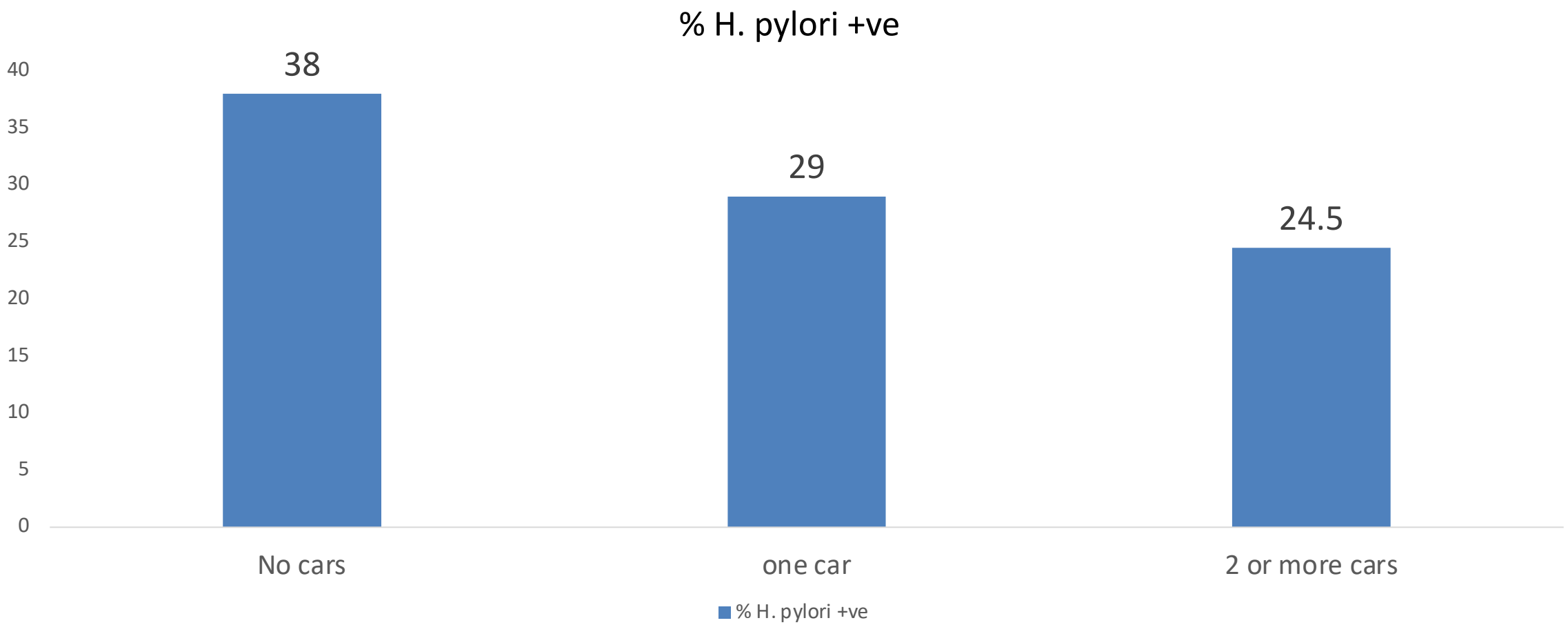
H. pylori protects against car ownership

- 885/8280 (11%) did not own a car
- 38% subjects that did not own car *H. pylori* +ve
- 26% subjects that owned car *H. pylori* +ve
- OR = 0.58 (95% CI = 0.51 to 0.68)
- *H. pylori* may protect against car ownership, reduce pollution and prevent global warming

Biologic gradient



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Adjusting for confounders

Factors Adjusted	OR (95% CI)	R squared
None	0.58 (0.51 to 0.68)	
Social class	0.73 (0.62 to 0.87)	8%
Social class, crowding, age, sex, smoking, alcohol, coffee, education, ethnicity	0.81 (0.69 to 0.95)	17%

Conclusions

- *H. pylori* reduces car ownership
- *H. pylori* mainly in childhood (before buy a car)
- Assuming association is causal
- 23 million extra cars on the road if eradicate *H. pylori* globally
- 106 million metric tons of CO_2 added to the environment per year
- Only offer *H. pylori* eradication where benefit is clear – e.g. PUD

Issues with data

- OR = 0.81 (or 1.23 if inverse OR is used)
- Large reduction in effect when adjust for known confounders
- If adjusted for more confounders effect likely to disappear
- “Biologic plausibility” post hoc
- Create impact by multiplying OR as if it is causal to world population
- *H. pylori* protects against asthma, GERD, esophageal adenocarcinoma, causes ischemic heart disease, reduced adult height

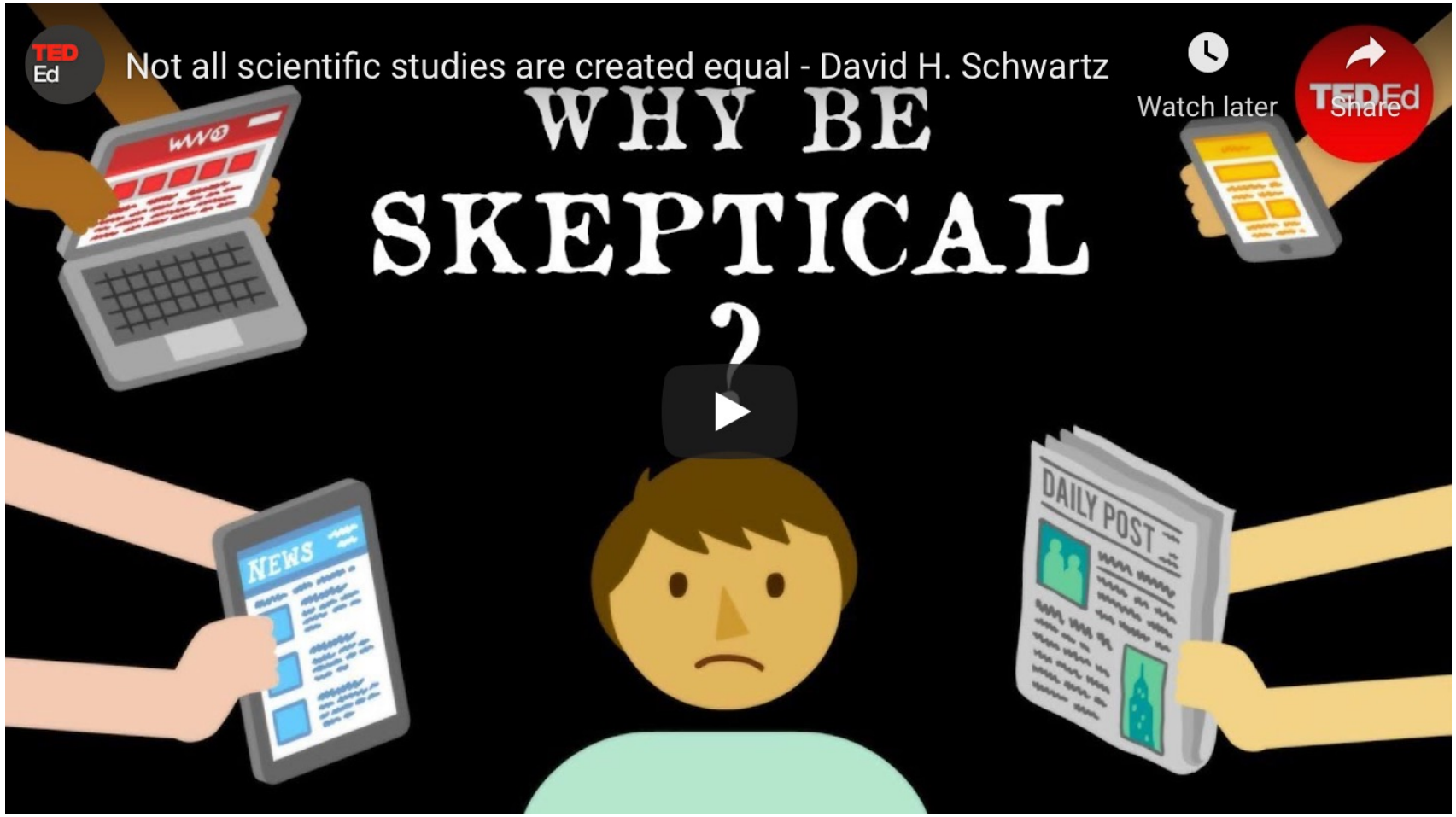
Adjusting for confounders

Factors Adjusted	OR (95% CI)	R squared
None	0.58 (0.51 to 0.68)	
Social class	0.73 (0.62 to 0.87)	8%
Social class, crowding, age, gender, smoking, alcohol, coffee, education, ethnicity	0.87 (0.78 to 0.97)	17%
20 variables (mainly related to SES)	0.97 (0.80 to 1.18)	36%

PPI and pneumonia: the impact of confounders

Study	Pneumonia with PPI	Pneumonia without PPI	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Herzig et al.	5.3%	2.0%	2.8 (2.5-3.1)	1.3 (1.1-1.4)
Sarkar et al.	4.5%	1.3%	2.1 (1.96-2.15)	1.2 (1.1-1.3)
Myles et al.	10.4%	5.7%	2.2 (1.92-2.46)	1.5 (1.4-1.8)
Gulmez et al.	10.6%	4.6%	2.4 (2.2-2.7)	1.5 (1.3-1.7)

Not all science is created equal



https://ed.ted.com/lessons/not-all-scientific-studies-are-created-equal-david-h-schwartz

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Evidence based medicine

- PPI versus placebo in patients taking aspirin and clopidogrel
- PPI versus surgery for reflux
- PPI versus placebo

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PPI with clopidogrel and aspirin

- 7 RCTs
- 5,722 patients
- Follow up 1-6 months

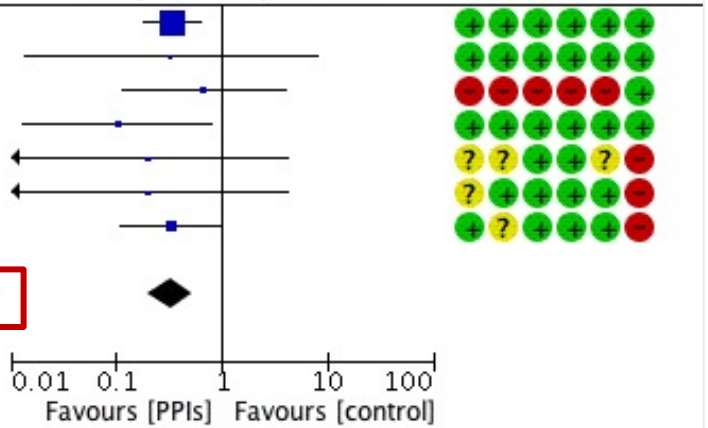
Results – Primary outcome

- **PPIs vs. placebo or famotidine for the prevention of GIB**

Study or Subgroup	PPIs Events	PPIs Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Bhatt 2010	13	1876	38	1885	60.5%	0.34 [0.18, 0.64]
Hsu 2011	0	83	1	82	2.3%	0.33 [0.01, 7.97]
Lu 2017	2	237	3	241	7.5%	0.68 [0.11, 4.02]
Ng 2012	1	163	9	151	5.6%	0.10 [0.01, 0.80]
Ren 2011	0	86	2	86	2.6%	0.20 [0.01, 4.11]
Tunggal 2011	0	84	2	84	2.6%	0.20 [0.01, 4.10]
Wu 2011	4	333	12	332	18.9%	0.33 [0.11, 1.02]
Total (95% CI)		**2862**		**2861**	**100.0%**	**0.33 [0.20, 0.53]**
Total events	20		67			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 2.12$, df = 6 (P = 0.91); $I^2 = 0\%$

Test for overall effect: Z = 4.51 (P < 0.00001)



Risk of bias legend

(**A**) Random sequence generation (selection bias)

(**B**) Allocation concealment (selection bias)

(**C**) Blinding of participants and personnel (performance bias): Upper gastrointestinal bleedings

(**D**) Blinding of outcome assessment (detection bias): Upper gastrointestinal bleedings

(**E**) Incomplete outcome data (attrition bias): Upper gastrointestinal bleedings

(**F**) Selective reporting (reporting bias)

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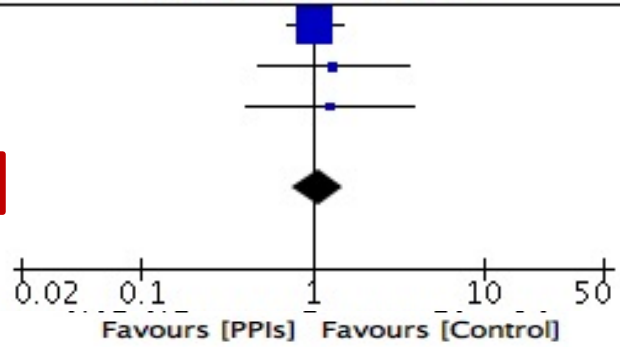
Results – Secondary outcome

- **Major adverse cardiovascular events**

Study or Subgroup	PPIs Events	PPIs Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Bhatt 2010	55	1876	54	1885	80.6%	1.02 [0.71, 1.48]
Hsu 2011	8	83	6	82	10.7%	1.32 [0.48, 3.63]
Ng 2012	7	163	5	148	8.7%	1.27 [0.41, 3.92]
Total (95% CI)		**2122**		**2115**	**100.0%**	**1.07 [0.77, 1.49]**
Total events	70		65			

Heterogeneity: Tau² = 0.00; Chi² = 0.31, df = 2 (P = 0.86); I² = 0%
Test for overall effect: Z = 0.41 (P = 0.68)



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias): Cardiovascular events
(D) Blinding of outcome assessment (detection bias): Cardiovascular events
(E) Incomplete outcome data (attrition bias): Cardiovascular events
(F) Selective reporting (reporting bias)

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PPI compared to reflux surgery

- Long term safety data of two RCTs both with 5 year follow up

Name	Countries	Surgical intervention	Conducted	Number
SPORAN	Nordic	Open anti-reflux surgery	1991-2005	298
LOTUS	11 Europe	Laparoscopic ARS	2001-2009	514

Atwood S et al. APT 2015; 41: 1162-74

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PPI versus surgery

Lab value	SPORAN				LOTUS			
	Baseline	1 year	3 year	5 year	Baseline	1 year	3 year	5 year
Hb (g/dl)								
Surgery	13.9	13.7	13.6	13.2	15.0	14.8	15.1	15.0
PPI	14.0	13.8	14.1	13.4	15.1	15.1	15.2	15.1
Ferritin (ug/l)								
Surgery	92	66	55	80	111	109	120	122
PPI	70	71	67	79	118	131	133	156
B12 (pmol/l)								
Surgery	333	309	321	308	309	297	298	289
PPI	330	323	332	321	304	320	320	317
Calcium (mmol/l)								
Surgery	2.4	2.3	2.4	2.3	2.3	2.3	2.3	2.3
PPI	2.3	2.3	2.3	2.3	2.4	2.4	2.3	2.3

Atwood S et al. APT 2015; 41: 1162-74

Other adverse events

SPORAN

SAE (preferred term) Number of patients Total number of person-years	Open ARS *n* = 144 1324	Omeprazole *n* = 154 1518
Myocardial infarction	2 (1.4)	10 (6.5)
Angina pectoris	6 (4.2)	7 (4.5)
Chest pain	3 (2.1)	7 (4.5)
Injury	3 (2.1)	6 (3.9)
Osteoarthritis	3 (2.1)	6 (3.9)
Cerebral infarction	0 (0.0)	5 (3.2)
Abdominal pain	8 (5.6)	4 (2.6)
Inguinal hernia	5 (3.5)	4 (2.6)
Cardiac failure*	4 (2.1)	4 (2.6)
Pneumonia	4 (2.8)	3 (2.0)
Transient ischaemic attack	3 (2.1)	3 (2.0)
Cholelithiasis	2 (1.4)	3 (2.0)
Appendicitis	0 (0.0)	3 (2.0)
Syncope	0 (0.0)	3 (2.0)
Gastrointestinal haemorrhage	3 (2.1)	2 (1.3)
Postoperative infection	9 (6.2)	1 (0.6)
Intervertebral disc herniation	5 (3.5)	1 (0.6)
Hernia NOS	3 (2.1)	1 (0.6)
Pancreatitis	3 (2.1)	1 (0.6)
Postoperative hernia	14 (9.7)	0 (0.0)
Anaemia	5 (3.5)	0 (0.0)
Gastric ulcer	3 (2.1)	0 (0.0)

LOTUS

SAE (preferred term) Number of patients Total number of patient-years	LARS *n* = 248 1046	Esomeprazole *n* = 266 1067
Myocardial infarction*	5 (2.0)	5 (1.9)
Noncardiac chest pain	3 (1.2)	5 (1.9)
Musculoskeletal chest pain	1 (0.4)	4 (1.5)
Pancreatic carcinoma	0	4 (1.5)
Angina pectoris	1 (0.4)	3 (1.1)
Gastroenteritis	1 (0.4)	3 (1.1)
Pneumonia	1 (0.4)	3 (1.1)
Osteoarthritis	4 (1.6)	2 (0.8)
Post-procedural complication	4 (1.6)	0
Cholelithiasis	3 (1.2)	0
Incisional hernia	3 (1.2)	0
Procedural pain	3 (1.2)	0

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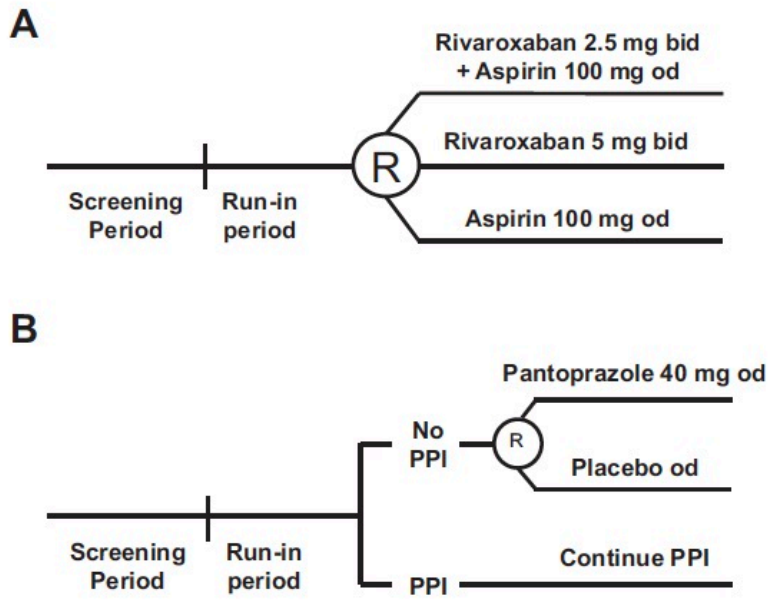
COMPASS trial

- 27,395 participants with CAD/PAD
- Partial factorial design
- 602 centers in 33 countries
- 17,598 randomized to PPI vs placebo
- Three year follow-up



Bosch J et al. Can J Cardiol 2017; 33: 1027-35

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PPI arms of COMPASS trial

- 17,598 participants enrolled March 2013 to May 2016
- 580 centres in 33 countries
- Mean follow up 2.98 years
- 52,532 patient years of follow up

Moayyedi P et al. Gastroenterology 2019; 157: 682-91

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Adverse events: CVS, cancer and all cause mortality

Outcome	Pantoprazole (N=8791)	Placebo (N=8807)	Pantoprazole versus placebo	
	No. of first events (%)	No. of first events (%)	Hazard ratio (95% CI)	P value
MI, stroke, CVS death	691 (7.9%)	668 (7.6%)	1.04 (0.93 to 1.15)	0.51
MI	252 (2.9%)	267 (3.0%)	0.94 (0.79 to 1.12)	0.51
Stroke	184 (2.1%)	159 (1.8%)	1.16 (0.94 to 1.44)	0.16
All new cancers	429 (4.9%)	435 (4.9%)	0.99 (0.87 to 1.13)	0.87
GI cancers	86 (1.0%)	83 (0.9%)	1.04 (0.77 to 1.40)	0.81
All hospitalizations	3074 (35.0%)	3000 (34.1%)	1.04 (0.99 to 1.09)	0.14
All cause mortality	630 (7.2%)	614 (7.0%)	1.03 (0.92 to 1.15)	0.63

Moayyedi P et al. Gastroenterology 2019; 157: 682-91

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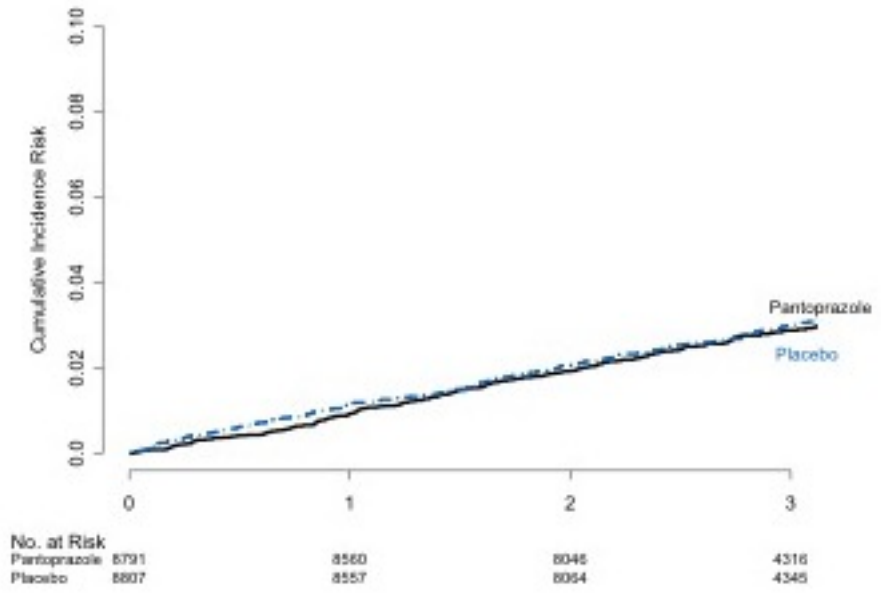
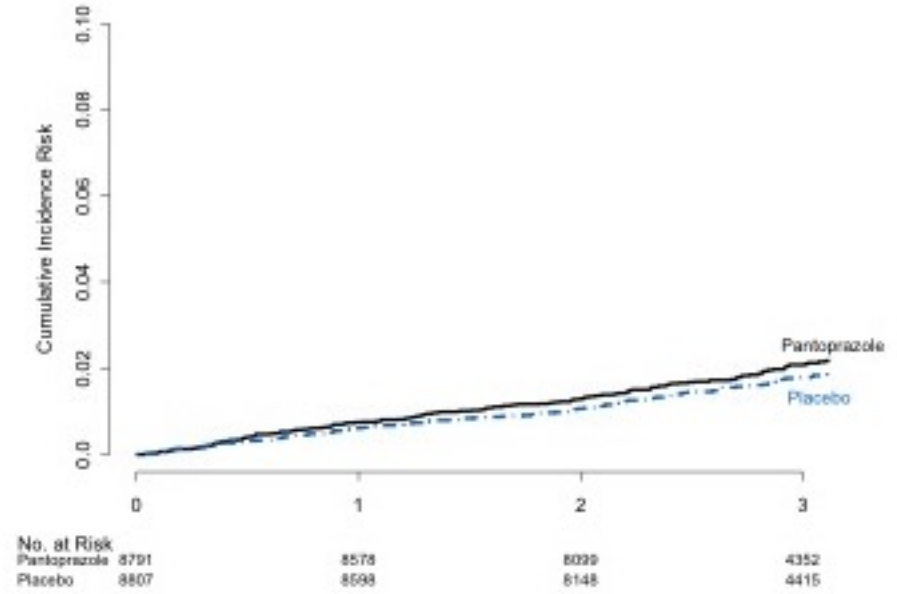
Cardiovascular outcomes

a) Myocardial infarction



b) Stroke



Moayyedi P et al. Gastroenterology 2019; 157: 682-91

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Other outcomes related to PPI randomization: ITT analysis

Outcomes	Pantoprazole 40 mg od (N=8791)	Pantoprazole placebo (N=8807)	Pantoprazole 40mg od versus placebo	
	no. of first events (%)	no. of first events (%)	Odds ratio (95% CI)	P value
Gastric atrophy	19 (0.2)	26 (0.3)	0.73 (0.05 to 1.32)	0.30
Clostridium difficile	9 (0.1)	4 (<0.1)	2.26 (0.70 to 7.34)	0.18
Other enteric infection	119 (1.4)	90 (1.0)	1.33 (1.01 to 1.75)	0.04
Chronic kidney disease	184 (2.1)	158 (1.8)	1.17 (0.94 to 1.45)	0.15
Dementia	55 (0.6)	46 (0.5)	1.20 (0.81 to 1.78)	0.36
Pneumonia	318 (3.6)	313 (3.6)	1.02 (0.87 to 1.19)	0.82
Fracture	203 (2.3)	211 (2.4)	0.96 (0.79 to 1.17)	0.71
COPD	146 (1.7)	124 (1.4)	1.18 (0.93 to 1.51)	0.17
Diabetes mellitus	513 (5.8)	532 (6.0)	0.96 (0.85 to 1.09)	0.56

NNH = 5266

NNH = 900

Moayyedi P et al. Gastroenterology 2019; 157: 682-91

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Even Scientists believe what they want to believe

Type of study (Reference)	Deaths n/N (%)	Association (95% Confidence Interval) NNH
Systematic review and meta-analysis of three observational studies [17] Median follow-up 1 year	PPI: 765/4,775 (16%) Non-PPI users: 1,794/17,652 (10%)	OR 1.68 (1.53-1.84)
US Veterans Affairs longitudinal cohort study [18] new users of PPI vs. H2RA Median follow-up 10 years	PPI: 59,771/157,625 (37.9%) H2RA: 20,287/56,842 (35.7%)	HR 1.17 (1.10-1.24) 45.20 excess deaths/1,000 (28.20-61.40)
COMPASS RCT [19] Pantoprazole 40mg/d vs. placebo Median follow-up 3 years	PPI: 630/8791 (7.2%) Placebo: 614/8807 (7.0%)	HR 1.03 (0.92-1.15)

"The COMPASS trial findings are not Inconsistent with contemporaneous findings from observational studies"

"The COMPASS RCT was unlikely to detect an increase in mortality given the trial was not powered to detect this outcome"

Ben-Eltriki M et al. Pharmacol Res Perspect 2020: e00651

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Discussion

- Insufficient power for some outcomes (e.g. *C. difficile*)
- Even in these cases number needed to harm extremely large
- Enteric infections data not adjusted for multiple comparisons
- Adverse effects may take longer than 3 years
- No dose response data

Conclusions

- PPIs unlikely to cause long term harm
- Exception may be enteric infections
- Risk related to *C. difficile* uncertain
- Important to improve patient's quality of life – give a PPI when indicated