Cardiology – Latest Evidence Update

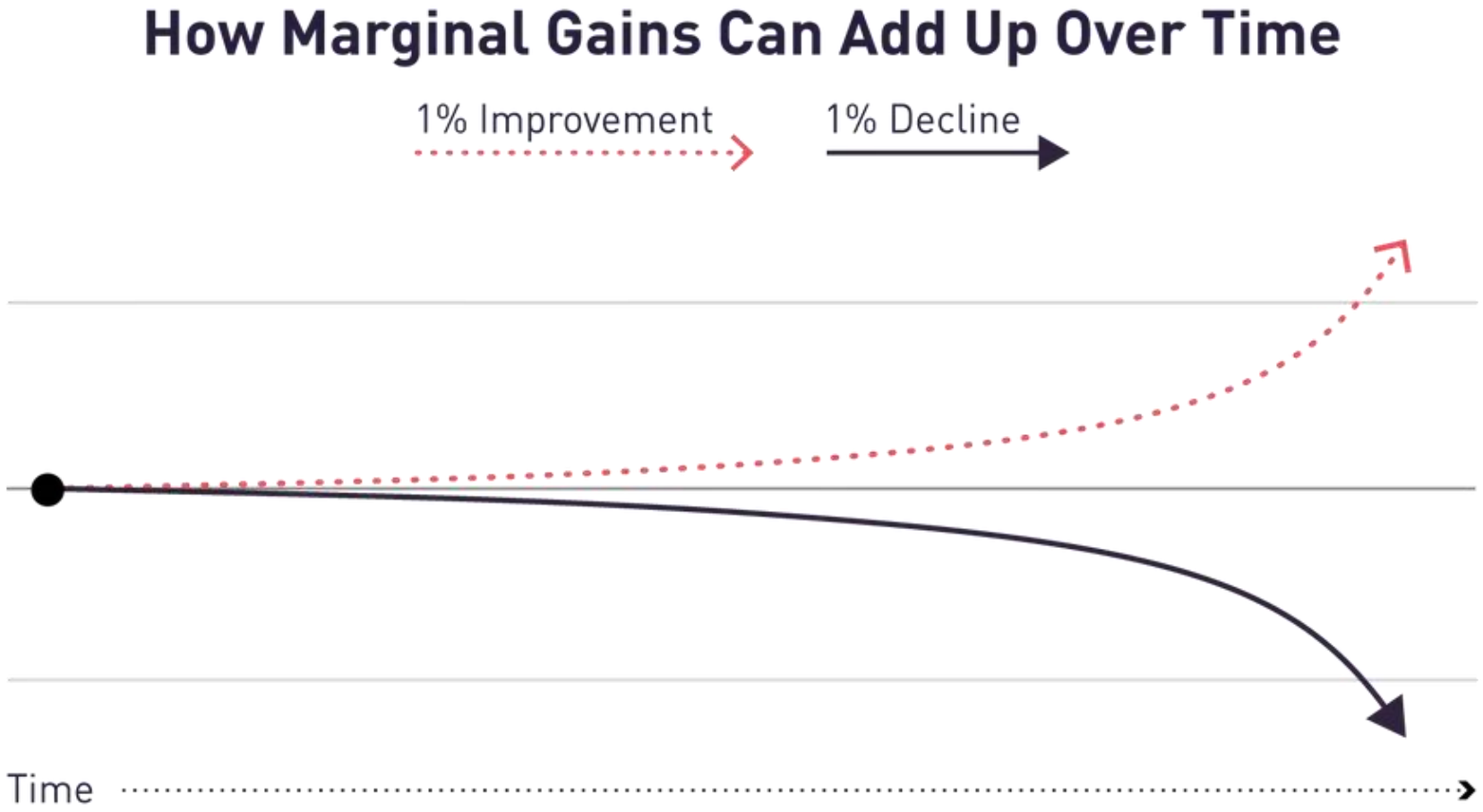
22/11/2022

Dr Mark Dayer

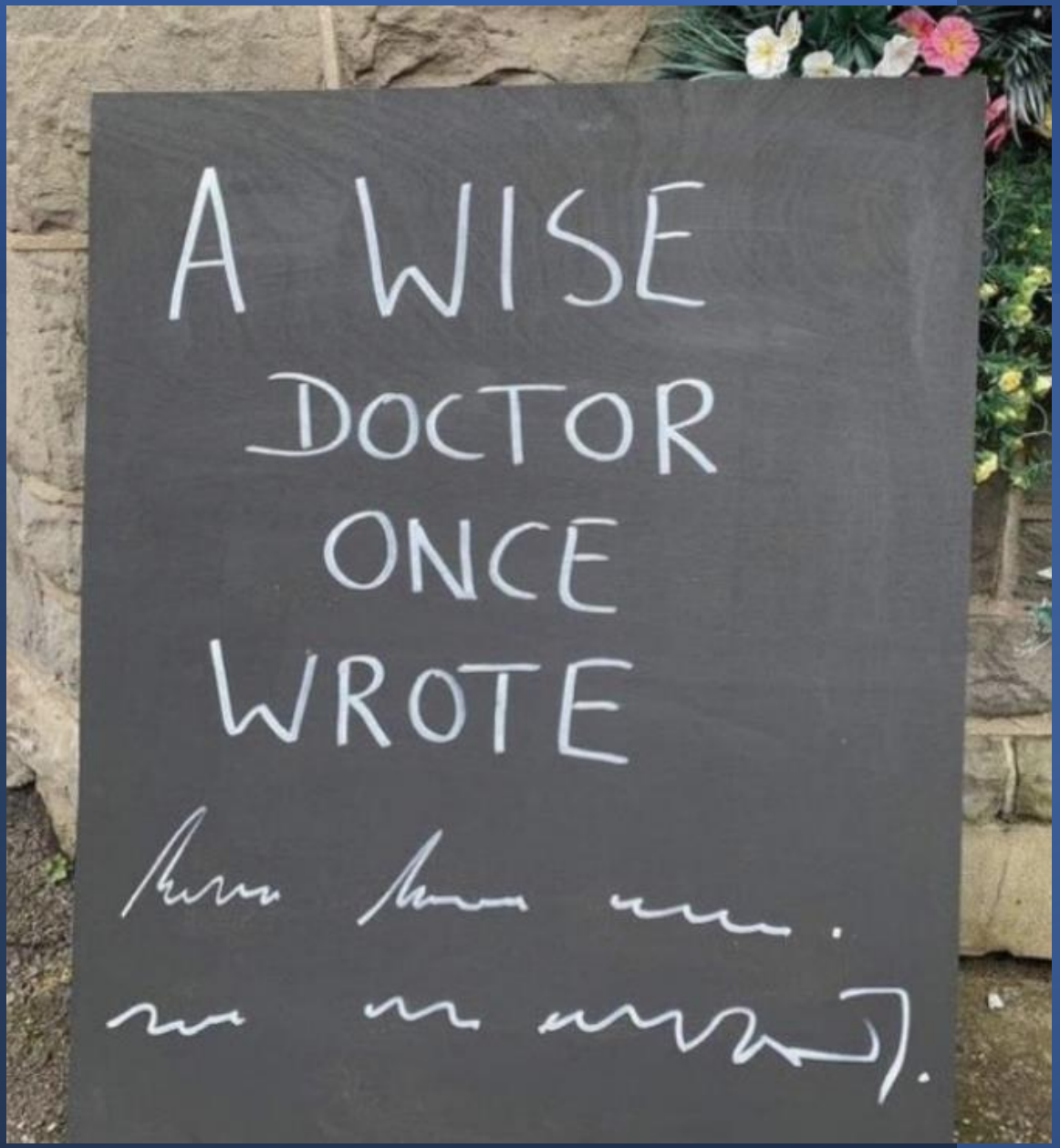
Consultant Cardiologist, Somerset NHS Foundation Trust

Structure

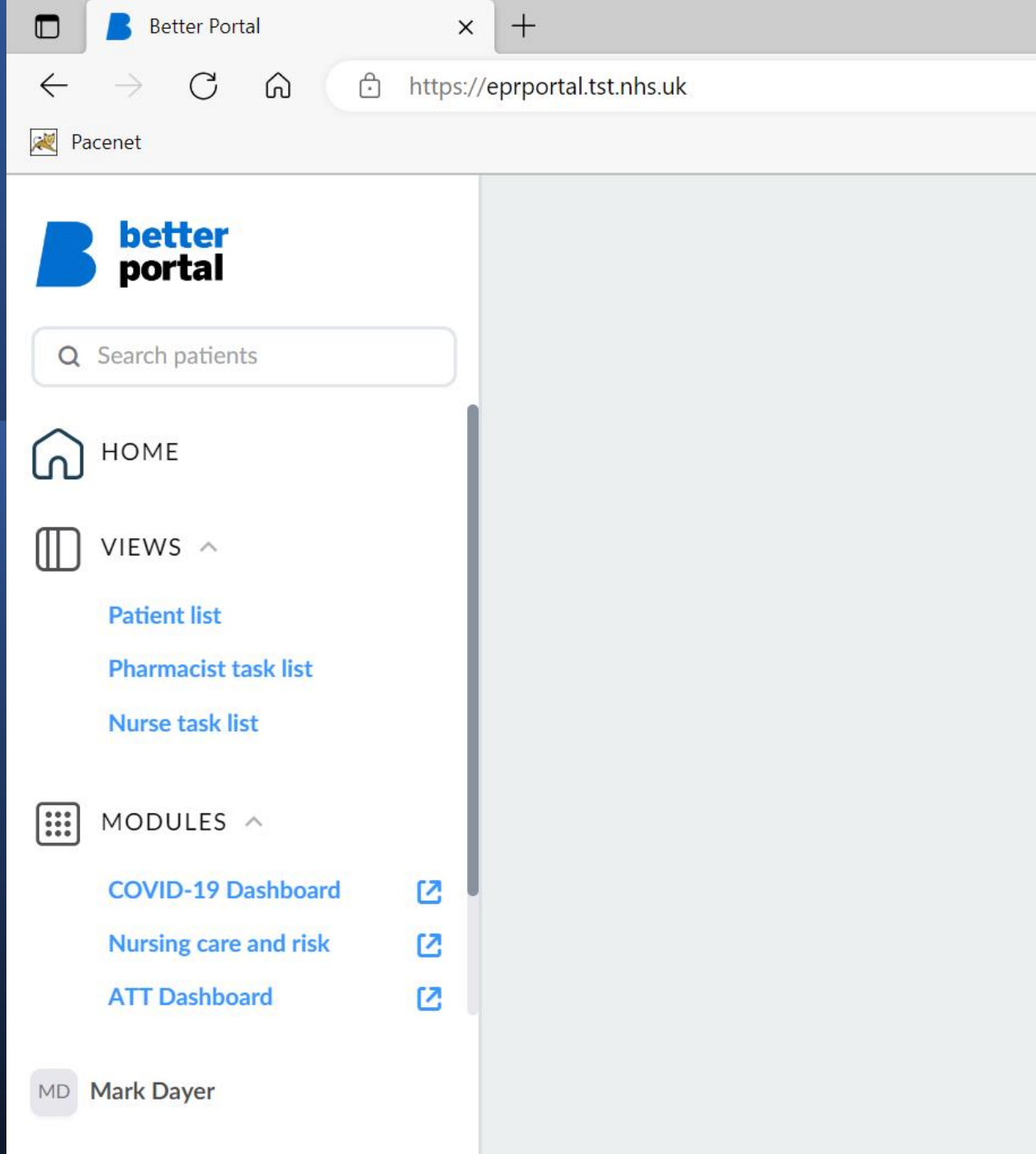
- EPMA
- Heart Failure
  - Reduced ejection fraction
  - Preserved ejection fraction
- Weight
- Coronary artery disease
- Lipids
- Atrial fibrillation
- Hypertension
- Genetics



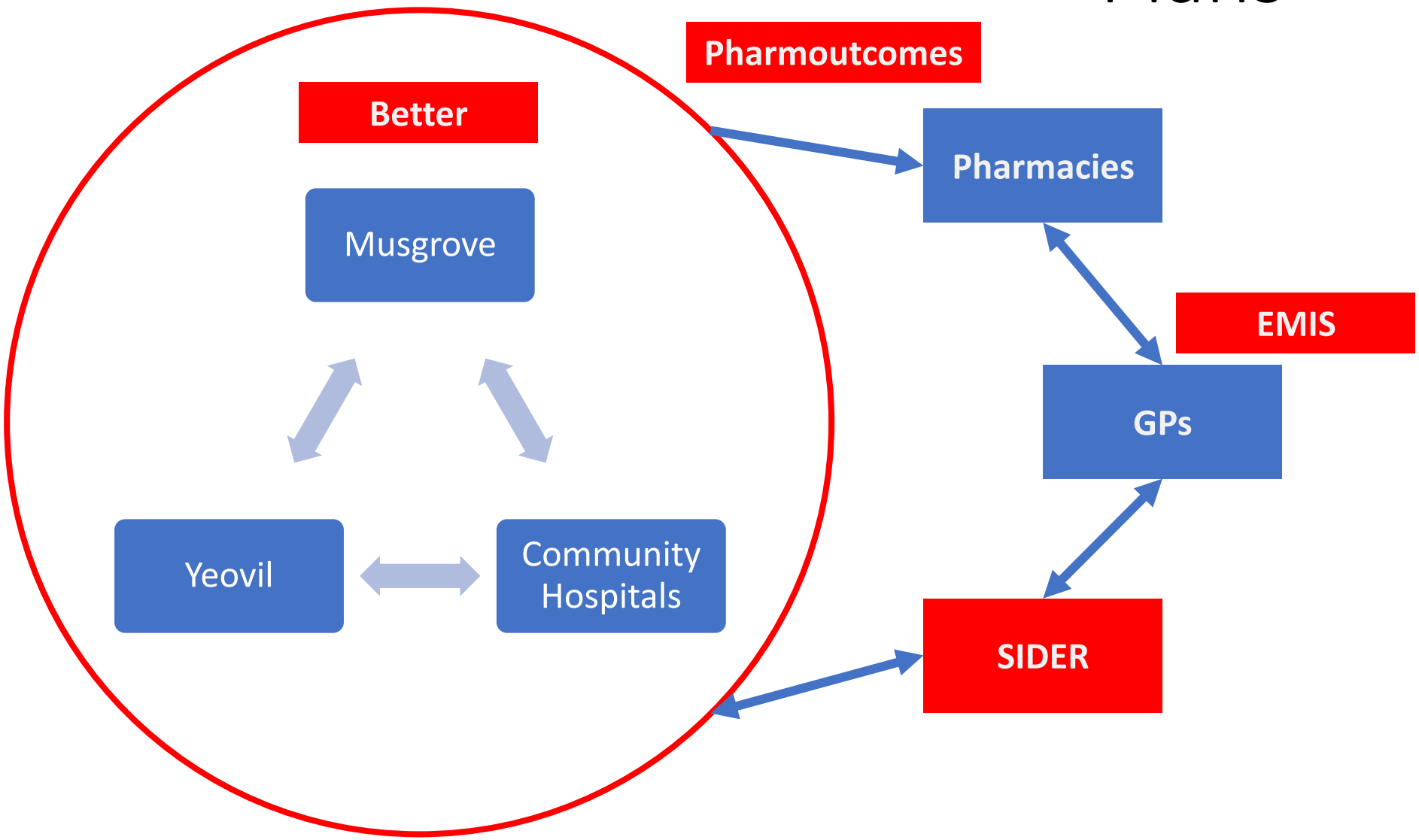
Cardiology is all about marginal gains now

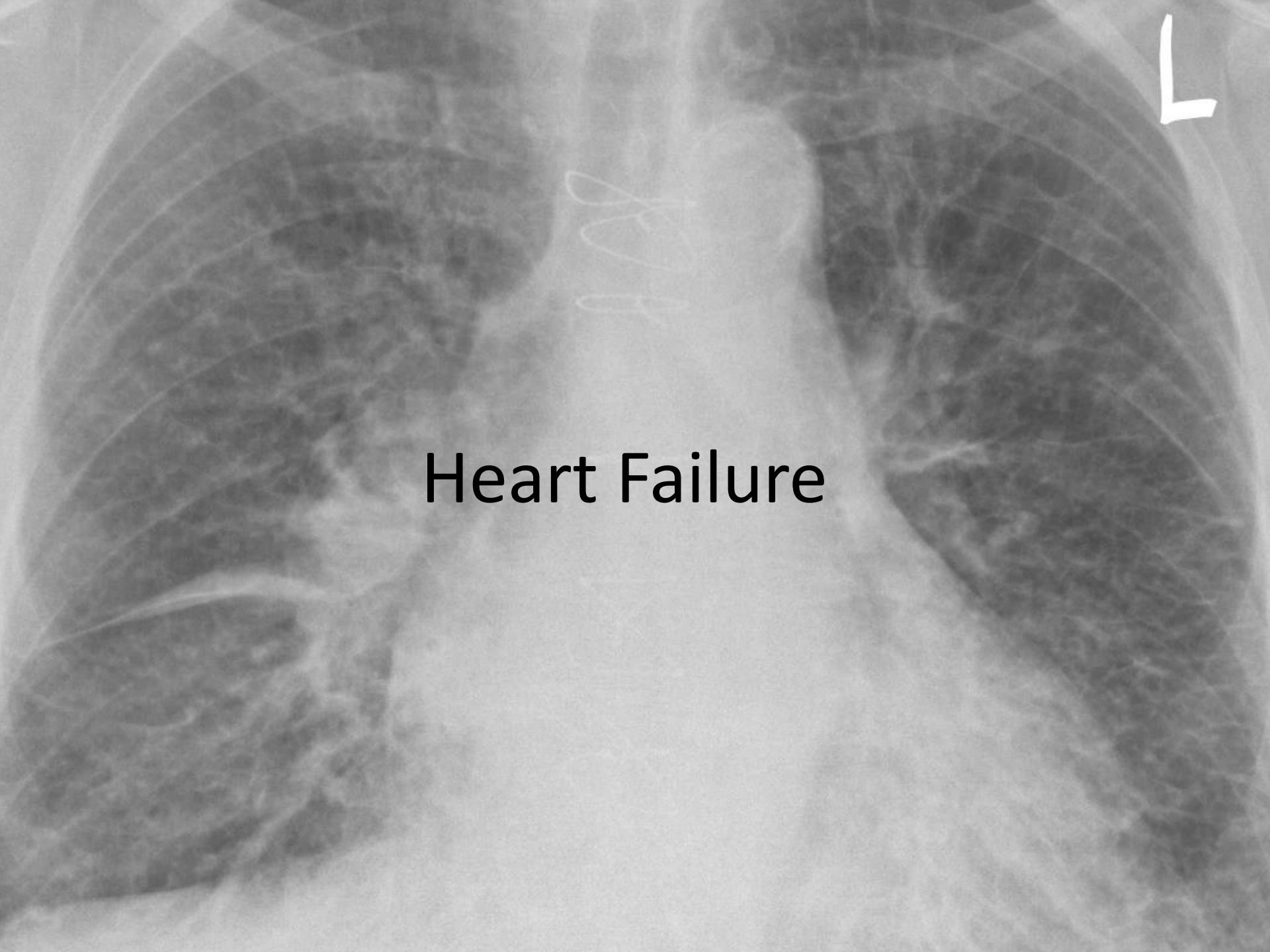

A WISE
DOCTOR
ONCE
WROTE

Which is why we have E-prescribing



Plans


Pharmoutcomes
Better
Pharmacies
Musgrove
EMIS
GPs
Yeovil
Community Hospitals
SIDER



Heart Failure

Heart Failure

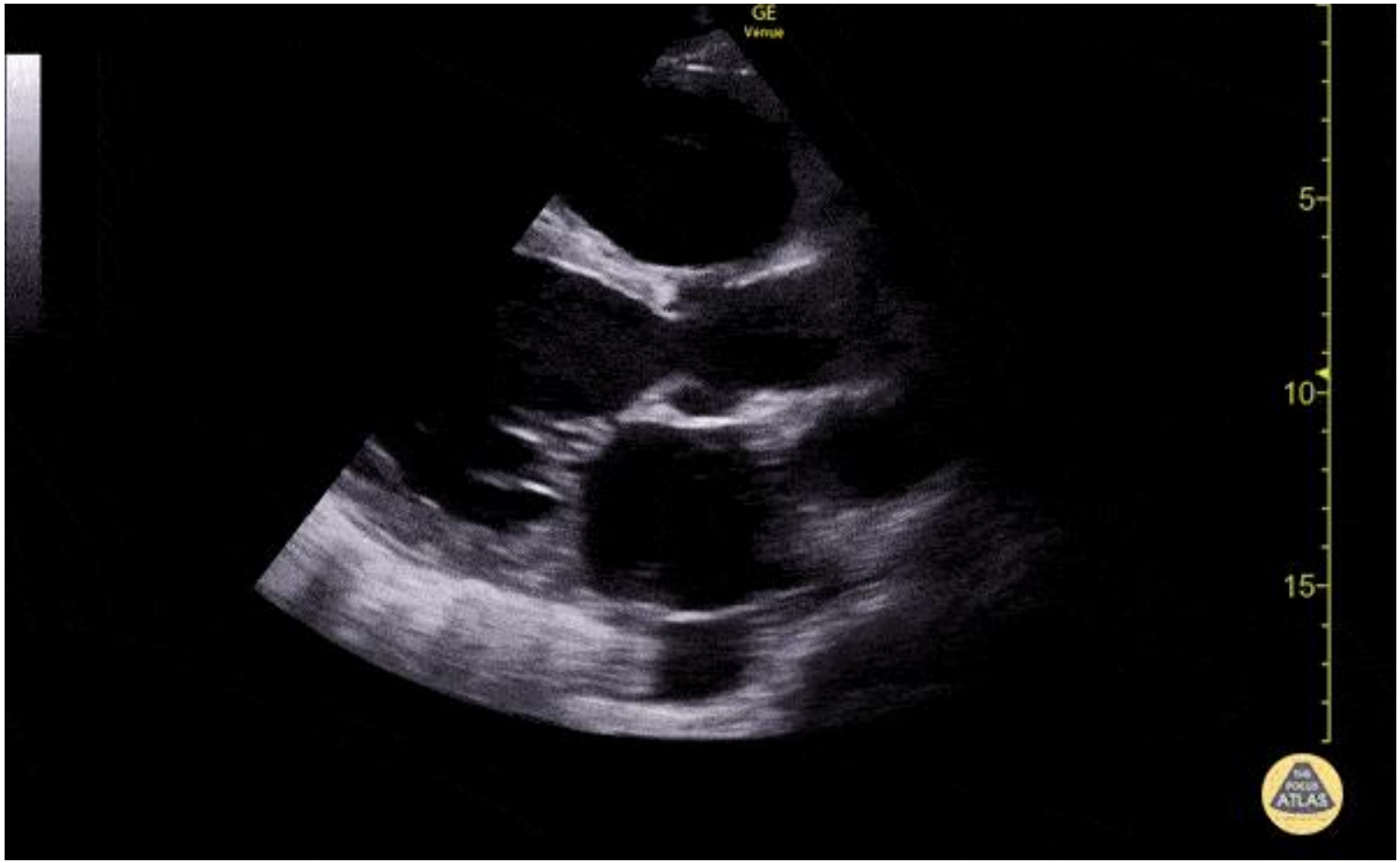
"Heart failure is a clinical syndrome with typical symptoms (breathlessness, ankle swelling, and fatigue) and signs (elevated jugular venous pressure, basal crepitations, and peripheral oedema). Heart failure is caused by a structural and/or functional abnormality that produces raised intracardiac pressures and/or inadequate cardiac output at rest and/or at exercise."

(NICE, September 2022, https://cks.nice.org.uk/topics/heart-failure-chronic/background-information/definition/)

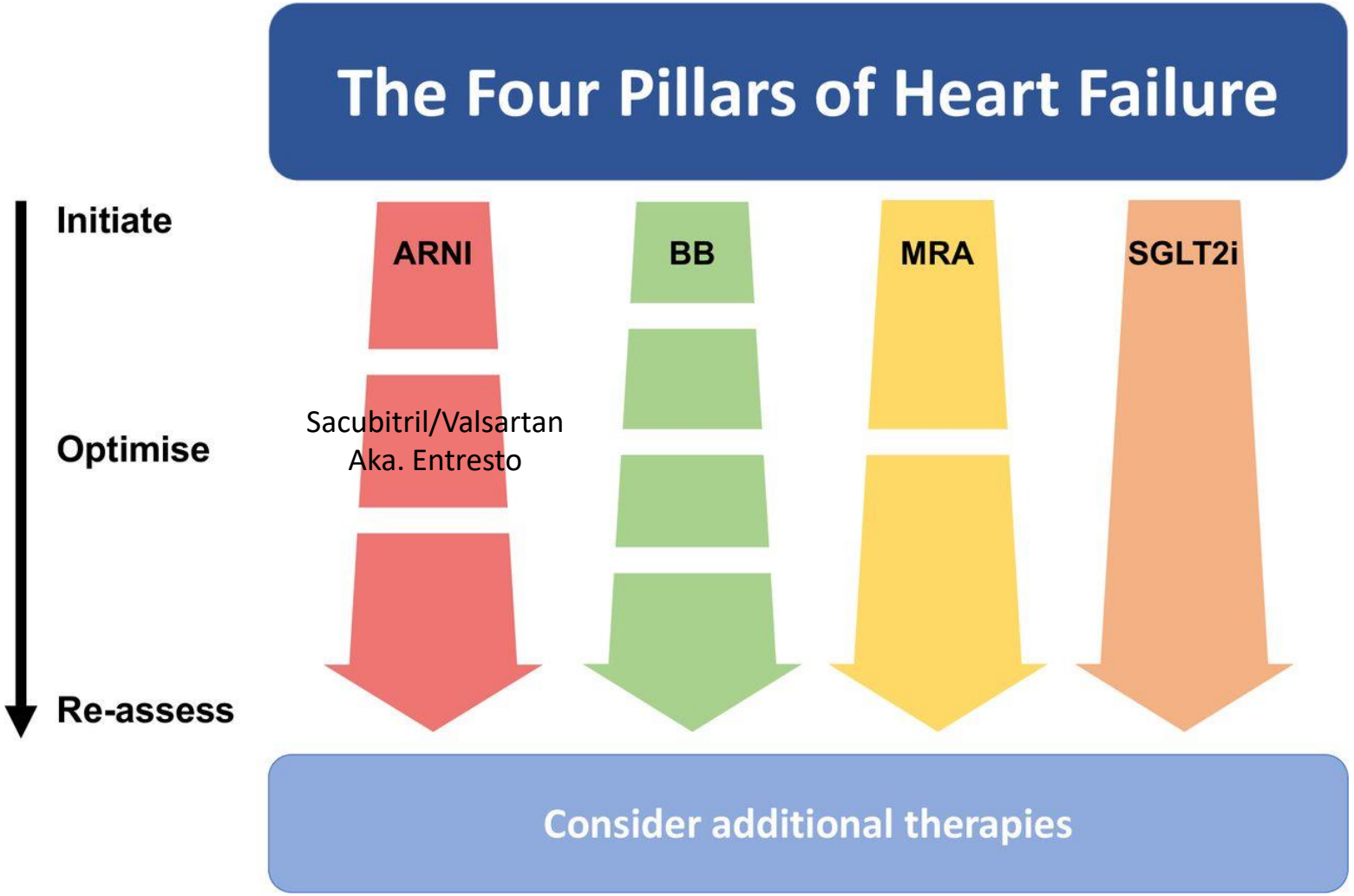
Heart Failure

Further Definitions	Abbreviation	EF
Heart failure with a *normal/preserved* ejection fraction	HFnEF HFpEF	≥50%
Heart failure with a *mid-range* ejection fraction	HFmrEF	41-49%
Heart failure with a *reduced* ejection fraction	HFrEF	≤40%

Heart Failure with a Reduced Ejection Fraction



Initiation and optimisation of the Four Pillars of Heart Failure (HFrEF)



Sam Straw et al. Open Heart 2021;8:e001585

openheart

Beta-Blockers

- Bisoprolol: 1.25mg od – 10mg od
- Carvedilol: 3.25mg bd – 25mg bd
- Nebivolol: 1.25mg od – 10mg od

People with asthma who are young and who have had ITU admissions are not suitable for beta-blockers.

Older people on inhalers – fine.

Gulea et al. Respir Res (2021) 22:64
https://doi.org/10.1186/s12931-021-01661-8

Respiratory Research

REVIEW Open Access

Beta-blocker therapy in patients with COPD: a systematic literature review and meta-analysis with multiple treatment comparison

Claudia Gulea[1,2*], Rosita Zakeri[3], Vanessa Alderman[4], Alexander Morgan[5], Jack Ross[6] and Jennifer K. Quint[1,2,7]

Abstract

Background: Beta-blockers are associated with reduced mortality in patients with cardiovascular disease but are often under prescribed in those with concomitant COPD, due to concerns regarding respiratory side-effects. We investigated the effects of beta-blockers on outcomes in patients with COPD and explored within-class differences between different agents.

Methods: We searched the Cochrane Central Register of Controlled Trials, Embase, Cumulative Index to Nursing and Allied Health Literature (CINAHL) and Medline for observational studies and randomized controlled trials (RCTs) investigating the effects of beta-blocker exposure versus no exposure or placebo, in patients with COPD, with and without cardiovascular indications. A meta-analysis was performed to assess the association of beta-blocker therapy with acute exacerbations of COPD (AECOPD), and a network meta-analysis was conducted to investigate the effects of individual beta-blockers on FEV1. Mortality, all-cause hospitalization, and quality of life outcomes were narratively synthesized.

Results: We included 23 observational studies and 14 RCTs. In pooled observational data, beta-blocker therapy was associated with an overall reduced risk of AECOPD versus no therapy (HR 0.77, 95%CI 0.70 to 0.85). Among individual beta-blockers, only propranolol was associated with a relative reduction in FEV1 versus placebo, among 199 patients evaluated in RCTs. Narrative syntheses on mortality, all-cause hospitalization and quality of life outcomes indicated a high degree of heterogeneity in study design and patient characteristics but suggested no detrimental effects of beta-blocker therapy on these outcomes.

Conclusion: The class effect of beta-blockers remains generally positive in patients with COPD. Reduced rates of AECOPD, mortality, and improved quality of life were identified in observational studies, while propranolol was the only agent associated with a deterioration of lung function in RCTs.

Keywords: COPD, Beta-blockers, Network meta-analysis

Background

COPD and cardiovascular disease (CVD) often co-occur, in an interaction characterized by complex biological mechanisms and risk factors such as smoking. Beta-blockers are recommended in treatment regimens of people with heart failure (HF), following myocardial infarction (MI), angina or hypertension, due to proven mortality benefits [1–4]. Seventeen years after the publication of the first robust meta-analysis demonstrating that beta-blockers do not impair lung function in patients with COPD [5], prescription rates remain lower than for people without COPD, among those with an indication for treatment. This treatment gap is thought

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Full list of author information is available at the end of the article

"The class effect of beta-blockers remains generally positive in patients with COPD (not propranolol)"

MRAs Mineralocorticoid receptor antagonists

- Spironolactone
  - Note breast swelling
- Eplerenone
  - No breast swelling
  - More expensive
- 25-50mg
- Avoid if: K+ >5.0, Cr >200
- Patiromer, Lokelma
  - Potassium binders
  - Increasing use
  - https://bjcardio.co.uk/2021/04/novel-potassium-binders-a-clinical-update/

The Atlas Trial

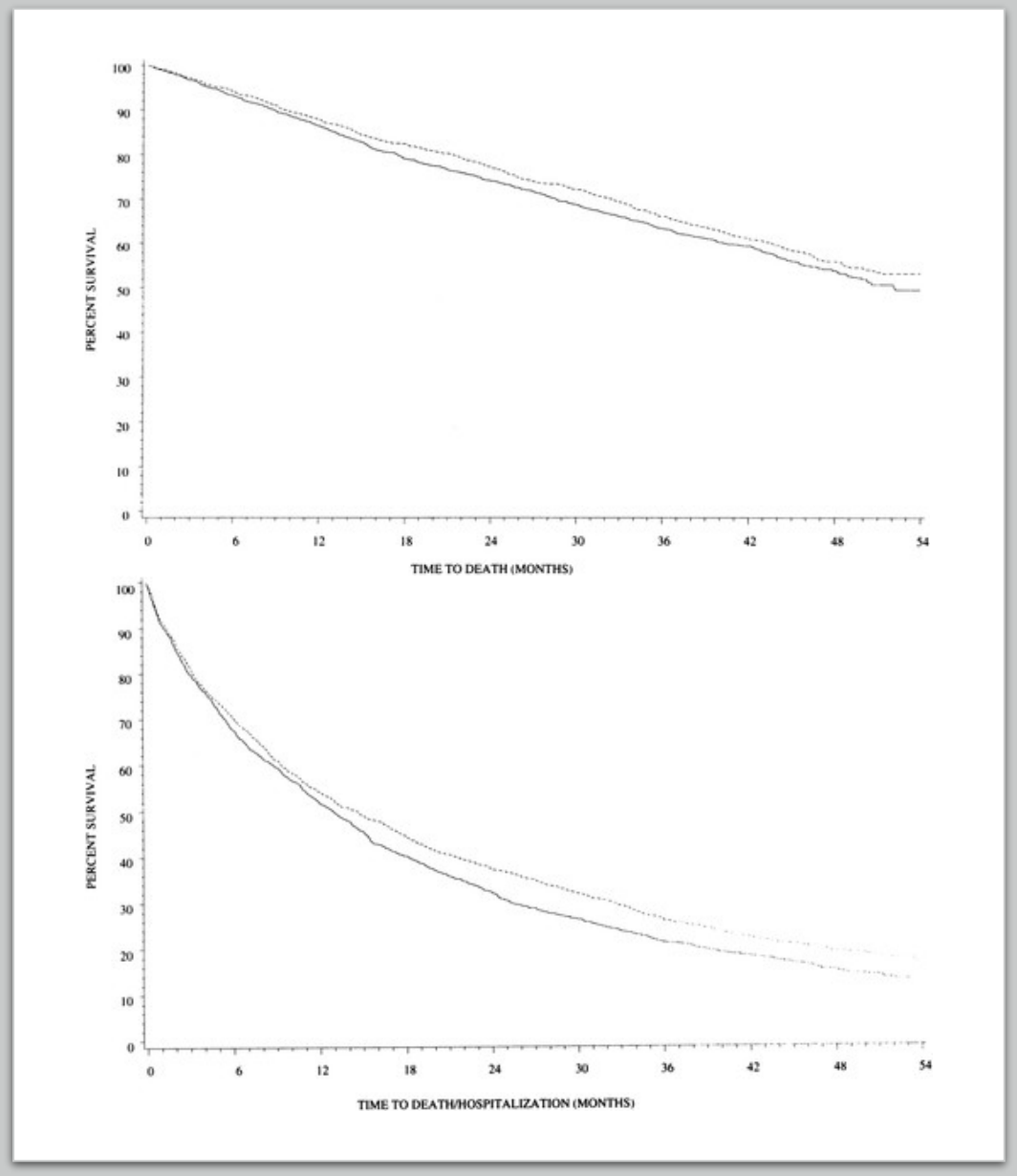
2.5-5mg Lisinopril vs. 32.5-35mg Lisinopril

Packer et al. Circulation. 1999;100:2312–2318

The Atlas Trial

Comparative Effects of Low and High Doses of the Angiotensin-Converting Enzyme Inhibitor, Lisinopril, on Morbidity and Mortality in Chronic Heart Failure.

Packer et al. Circulation. 1999;100:2312-2318.



Entresto (Saubitril / Valsartan) Notes

Allow at least a 36-hour washout period when switching from an ACEI before starting sacubitril/valsartan

Patients must be able to tolerate an ACEI or an ARB before being started on sacubitril/valsartan; BP > 110mmHg in trials

24/26mg bd

49/51mg bd

- recommended starting dose

97/103mg bd

SGLT2 Inhibitors in Heart Failure

(Irrespective of diabetes status)

Mechanism of Action

- Glycosuria and natriuresis

Drugs

- Dapagliflozin
- Empagliflozin
- Sotagliflozin
- Canagliflozin

Side effects

- UTI
- Genital yeast infections

SGLT2 Inhibitors

Benefits of Taking Sodium-Glucose Cotransporter 2 Inhibitors in Patients With Type 2 Diabetes Mellitus and Cardiovascular Disease: A Systematic Review. Cureus 14(9): e29069. DOI 10.7759/cureus.29069

- SGLT2 inhibitors
  - Significantly reduce weight and blood pressure due to their natriuretic effects.
  - Improve heart failure symptoms and reduce hospitalizations.

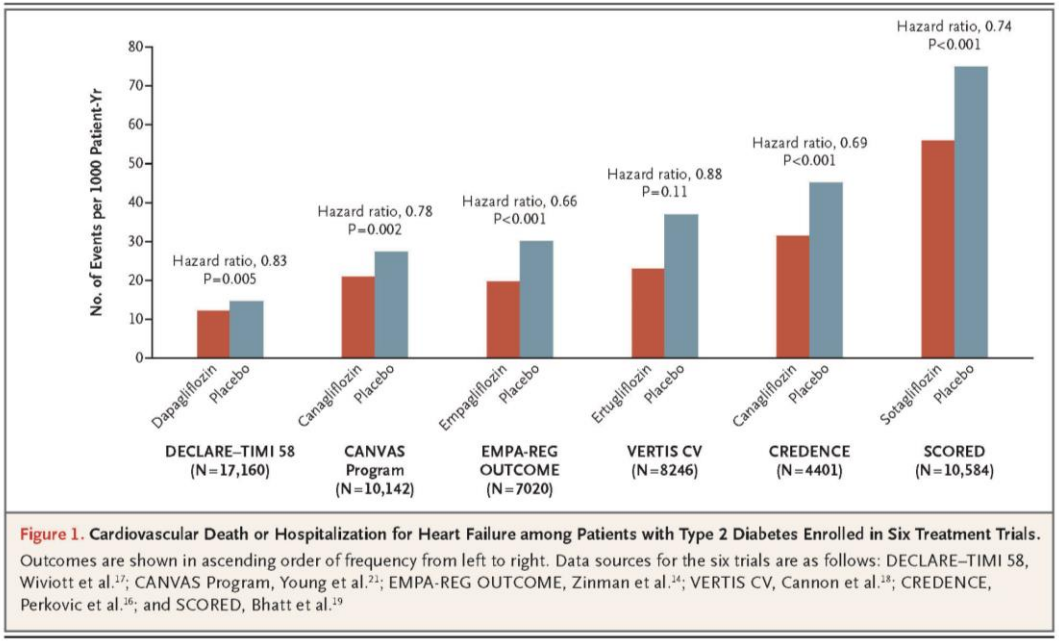


Figure 1. Cardiovascular Death or Hospitalization for Heart Failure among Patients with Type 2 Diabetes Enrolled in Six Treatment Trials.

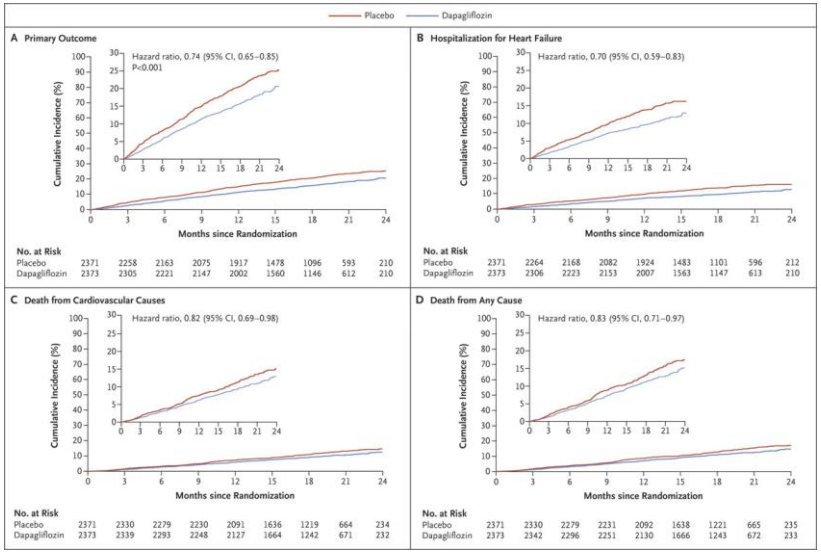
Outcomes are shown in ascending order of frequency from left to right. Data sources for the six trials are as follows: DECLARE–TIMI 58, Wiviott et al.[17]; CANVAS Program, Young et al.[21]; EMPA-REG OUTCOME, Zinman et al.[14]; VERTIS CV, Cannon et al.[18]; CREDENCE, Perkovic et al.[16]; and SCORED, Bhatt et al.[19]

SGLT2 Inhibitors in Heart Failure

(Irrespective of diabetes status)

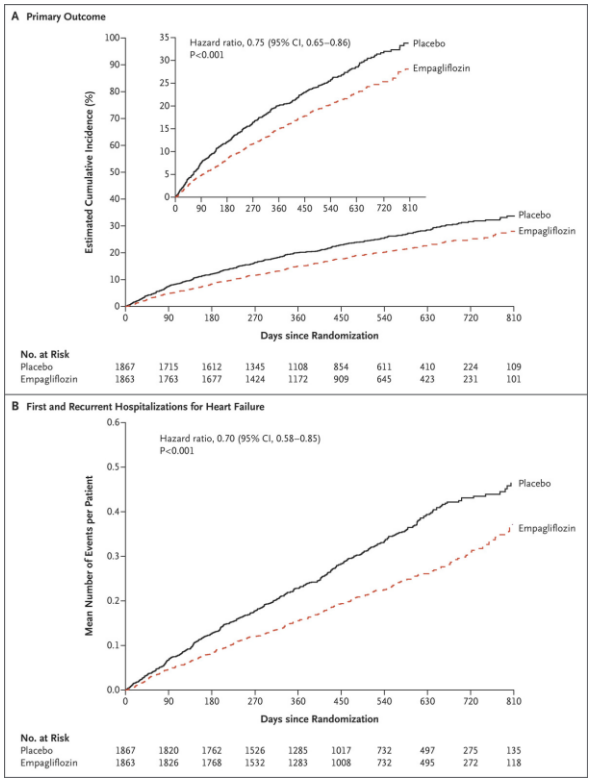
Dapagliflozin

JJ McMurray et al. N Engl J Med 2019;381:1995-2008



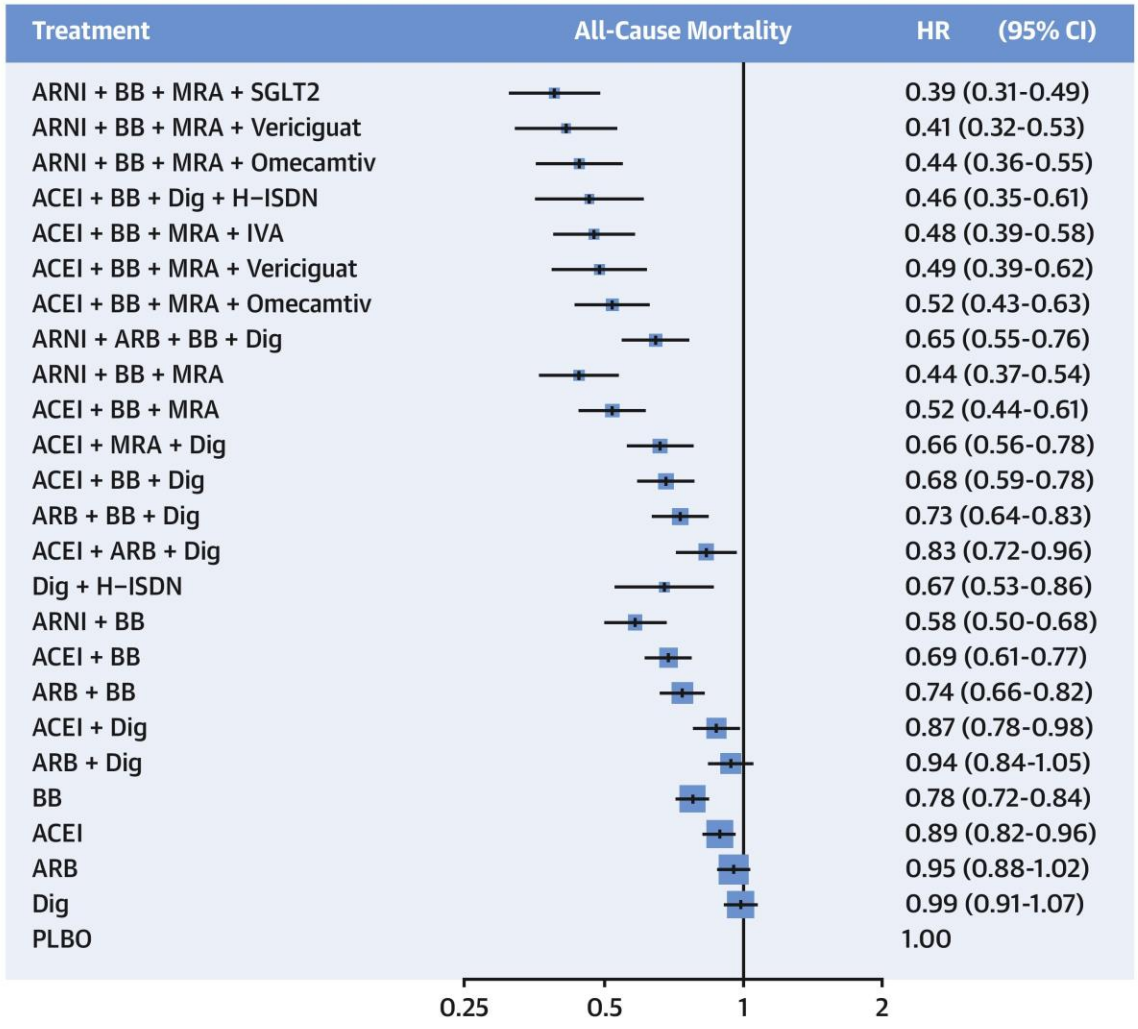
Empagliflozin

M Packer et al. N Engl J Med 2020;383:1413-1424

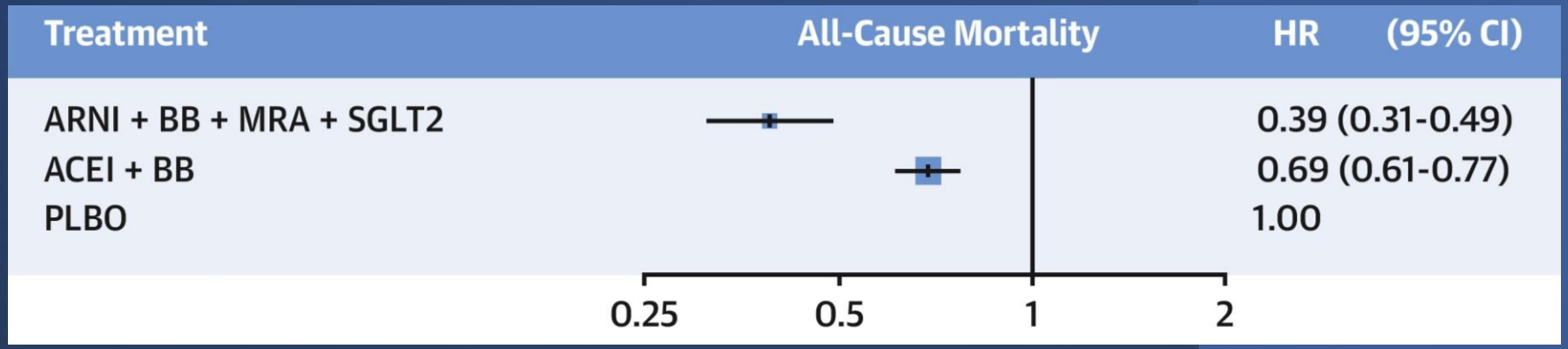


CENTRAL ILLUSTRATION: Relative Risk Reduction of Different Pharmacological Treatment Combinations for Heart Failure

A



Tromp, J. et al. J Am Coll Cardiol HF. 2022;10(2):73-84.


Treatment
All-Cause Mortality
HR (95% CI)
ARNI + BB + MRA + SGLT2
0.39 (0.31-0.49)
ACEI + BB
0.69 (0.61-0.77)
PLBO
1.00
0.25
0.5
1
2

HFpEF

Heart Failure with a Preserved Ejection Fraction

Multiple aetiologies, often co-existing

- Hypertension
- Infiltration – amyloid/sarcoid
- Coronary artery disease
- Valve disease
- Obesity
- Deconditioning/aging
- COPD/other lung diseases
- Atrial fibrillation
- Anaemia
- Myopathy
- Neuropathy
- Depression/Motivation
- Distorted expectation

Therefore, the concept that one treatment will restore exercise capacity is naive

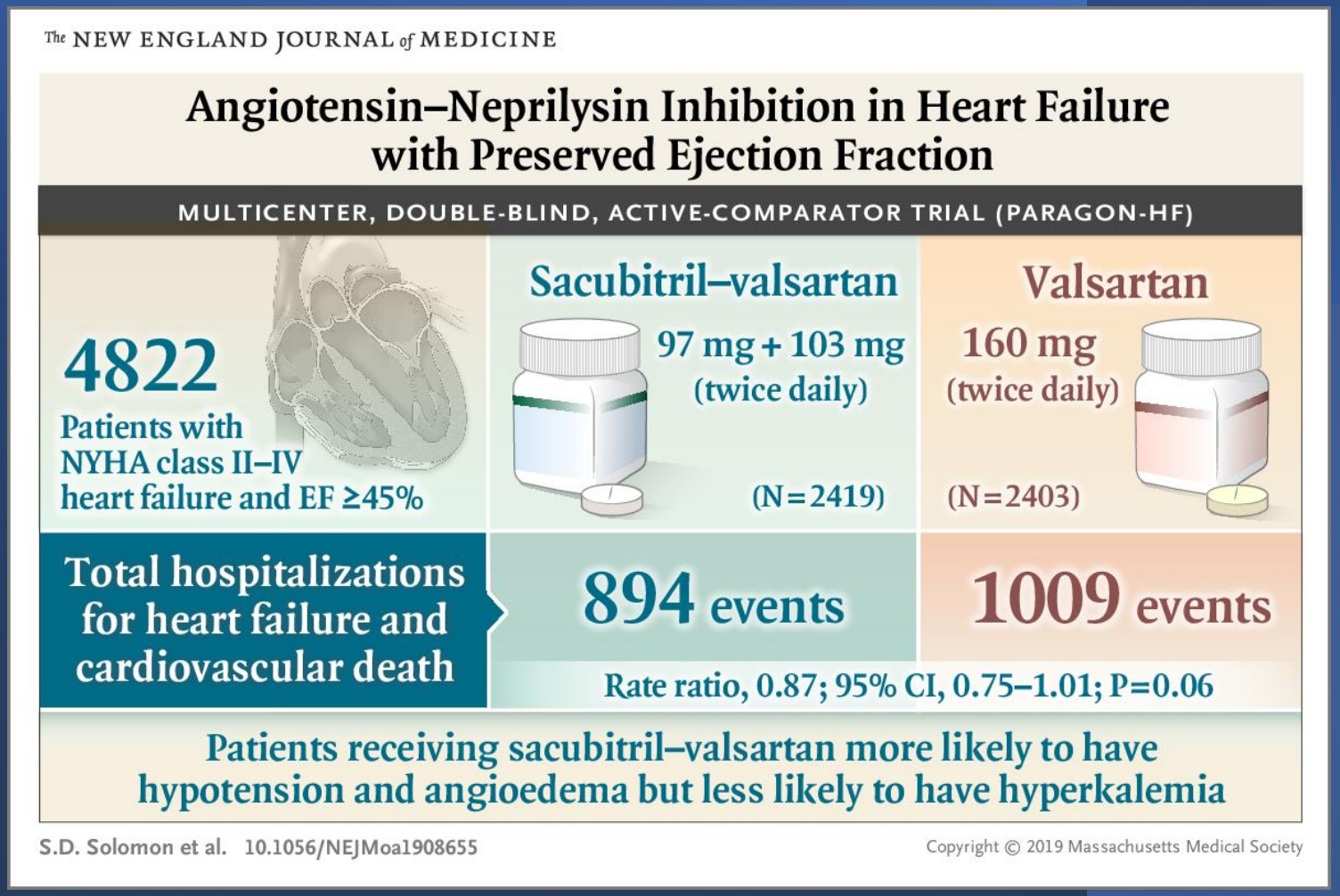
Multifactorial approach needed, often with exercise and weight loss as the core components

The Efficacy of Various Pharmacological Agents on Long-Term Outcomes in Patients With Heart Failure With Preserved Ejection Fraction: A Meta-Analysis of Randomized Control Trials

Faisal et al. 2022. DOI: 10.7759/cureus.28145

"As per our meta-analysis of RCTs in patients with HFpEF, **beta-blockers** were found to decrease cardiovascular mortality and all-cause mortality.

However, **no significant effect** of angiotensin receptor blockers, aldosterone receptor blockers and ACE inhibitors on cardiovascular and all-cause mortality was reported."



Sacubitril–valsartan **did not** result in a significantly lower rate of total hospitalizations for heart failure and death from cardiovascular causes among patients with heart failure and an ejection fraction of 45% or higher.

Original Article

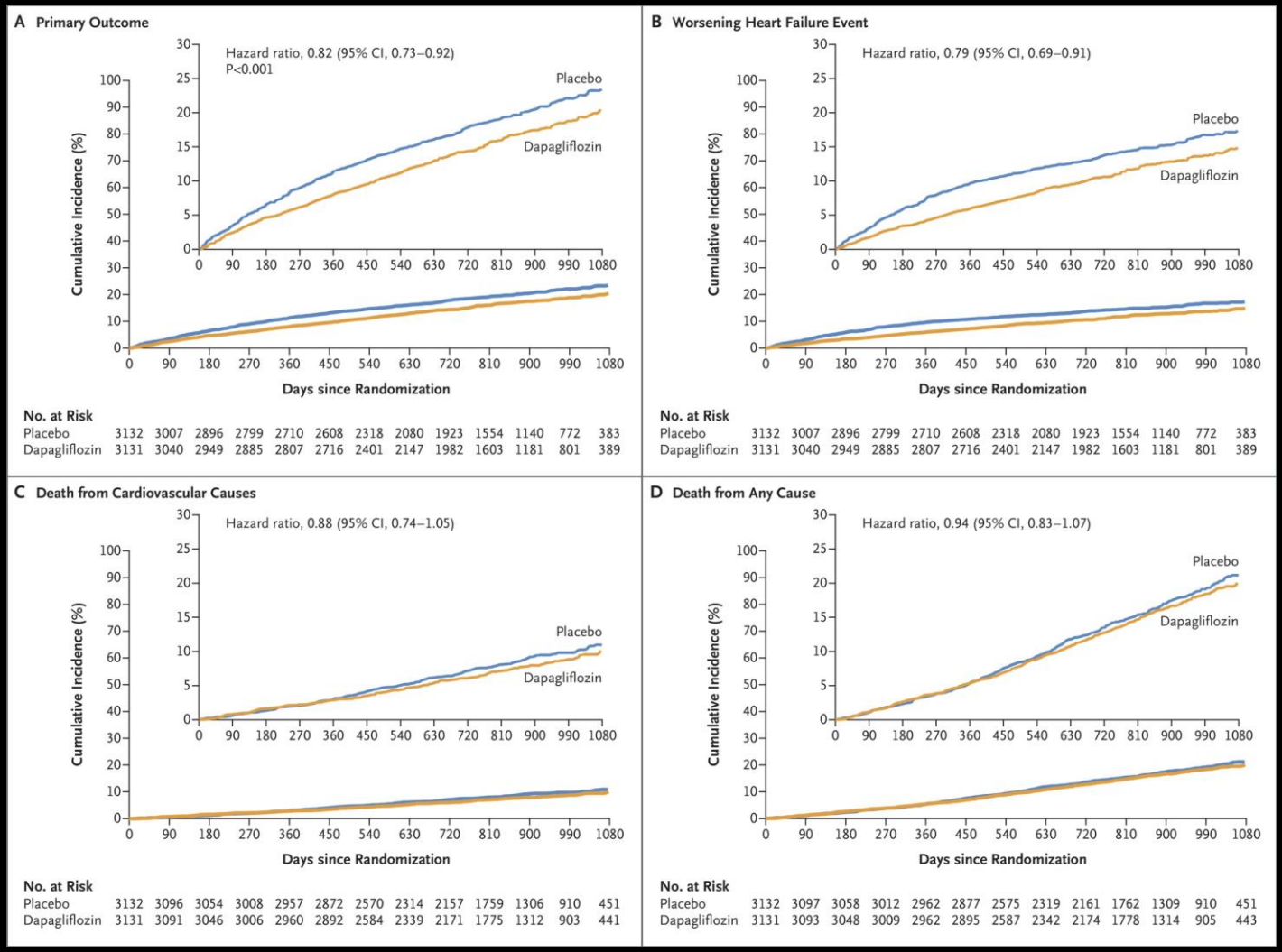
Dapagliflozin in Heart Failure with Mildly Reduced or Preserved Ejection Fraction

Scott D. Solomon, M.D., John J.V. McMurray, M.D., Brian Claggett, Ph.D., Rudolf A. de Boer, M.D., David DeMets, Ph.D., Adrian F. Hernandez, M.D., Silvio E. Inzucchi, M.D., Mikhail N. Kosiborod, M.D., Carolyn S.P. Lam, M.D., Felipe Martinez, M.D., Sanjiv J. Shah, M.D., Akshay S. Desai, M.D., Pardeep S. Jhund, M.B., Ch.B., Ph.D., Jan Belohlavek, M.D., Chern-En Chiang, M.D., C. Jan Willem Borleffs, M.D., Josep Comin-Colet, M.D., Ph.D., Dan Dobreanu, M.D., Jaroslaw Drozdz, M.D., Ph.D., James C. Fang, M.D., Marco Antonio Alcocer-Gamba, M.D., Waleed Al Habeeb, M.D., Yaling Han, M.D., Jose Walter Cabrera Honorio, M.D., Stefan P. Janssens, M.D., Tzvetana Katova, M.D., Masafumi Kitakaze, M.D., Béla Merkely, M.D., Ph.D., Eileen O'Meara, M.D., Jose Francisco Kerr Saraiva, M.D., Ph.D., Sergey N. Tereshchenko, M.D., Jorge Thierer, M.D., Muthiah Vaduganathan, M.D., M.P.H., Orly Vardeny, Pharm.D., Subodh Verma, M.D., Vinh Nguyen Pham, M.D., Ulrica Wilderäng, Ph.D., Natalia Zaozerska, M.D., Ph.D., Erasmus Bachus, M.D., Ph.D., Daniel Lindholm, M.D., Ph.D., Magnus Petersson, M.D., Ph.D., Anna Maria Langkilde, M.D., Ph.D., for the DELIVER Trial Committees and Investigators

N Engl J Med
Volume 387(12):1089-1098
September 22, 2022

The NEW ENGLAND JOURNAL of MEDICINE

Efficacy Outcomes in the Overall Population.



Solomon SD et al. N Engl J Med2022;387:1089-1098

The NEW ENGLAND JOURNAL of MEDICINE

Original Article

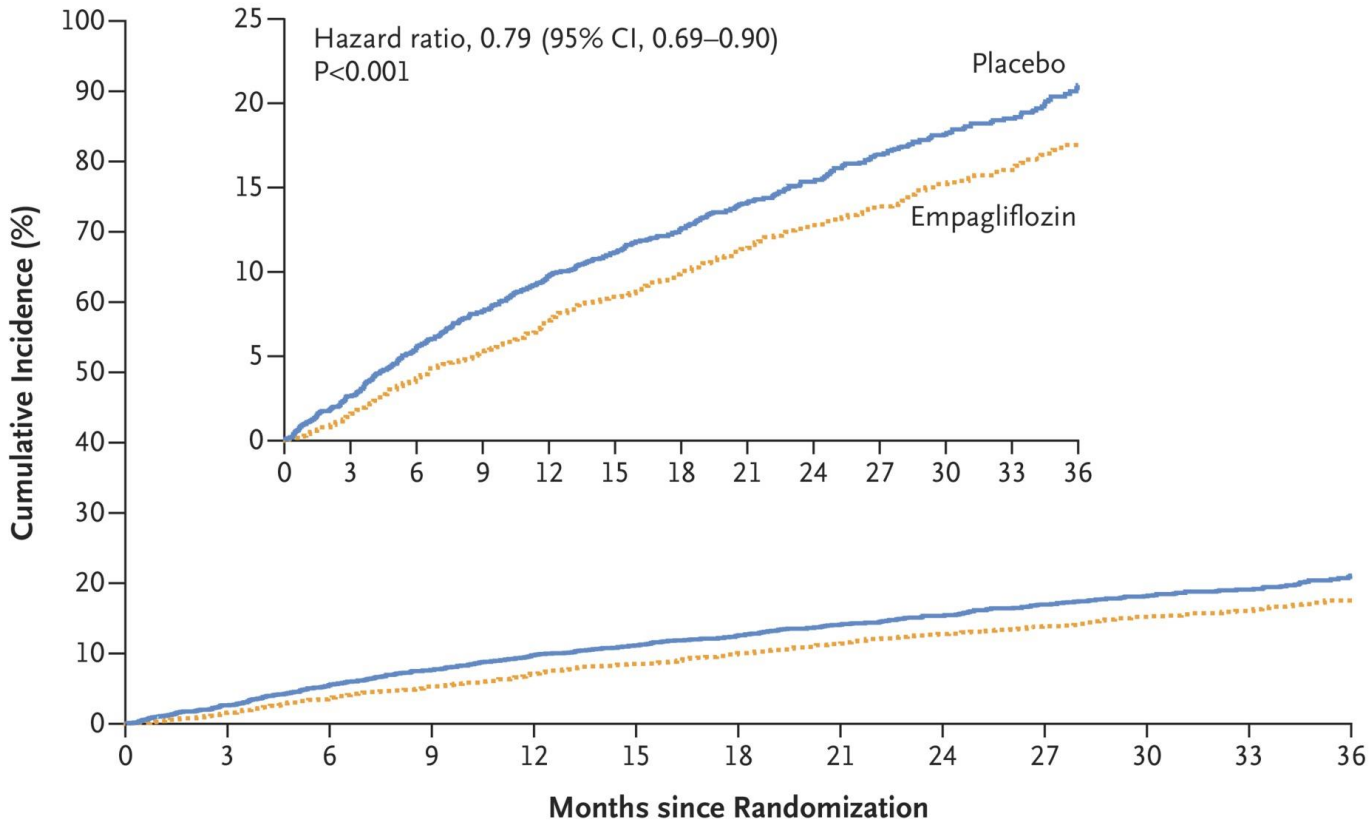
Empagliflozin in Heart Failure with a Preserved Ejection Fraction

Stefan D. Anker, M.D., Ph.D., Javed Butler, M.D., Gerasimos Filippatos, M.D., Ph.D., João P. Ferreira, M.D., Edimar Bocchi, M.D., Michael Böhm, M.D., Ph.D., Hans-Peter Brunner–La Rocca, M.D., Dong-Ju Choi, M.D., Vijay Chopra, M.D., Eduardo Chuquiure-Valenzuela, M.D., Nadia Giannetti, M.D., Juan Esteban Gomez-Mesa, M.D., Stefan Janssens, M.D., Ph.D., James L. Januzzi, M.D., Jose R. Gonzalez-Juanatey, M.D., Bela Merkely, M.D., Stephen J. Nicholls, M.D., Sergio V. Perrone, M.D., Ileana L. Piña, M.D., Piotr Ponikowski, M.D., Michele Senni, M.D., David Sim, M.D., Jindrich Spinar, M.D., Iain Squire, M.D., Stefano Taddei, M.D., Hiroyuki Tsutsui, M.D., Subodh Verma, M.D., Dragos Vinereanu, M.D., Jian Zhang, M.D., Ph.D., Peter Carson, M.D., Carolyn Su Ping Lam, M.D., Nikolaus Marx, M.D., Cordula Zeller, Dipl.Math., Naveed Sattar, M.D., Waheed Jamal, M.D., Sven Schnaidt, M.Sc., Janet M. Schnee, M.D., Martina Brueckmann, M.D., Stuart J. Pocock, Ph.D., Faiez Zannad, M.D., Ph.D., Milton Packer, M.D., for the EMPEROR-Preserved Trial Investigators

N Engl J Med
Volume 385(16):1451-1461
October 14, 2021

The NEW ENGLAND JOURNAL of MEDICINE

Primary Outcome, a Composite of Cardiovascular Death or Hospitalisation for Heart Failure



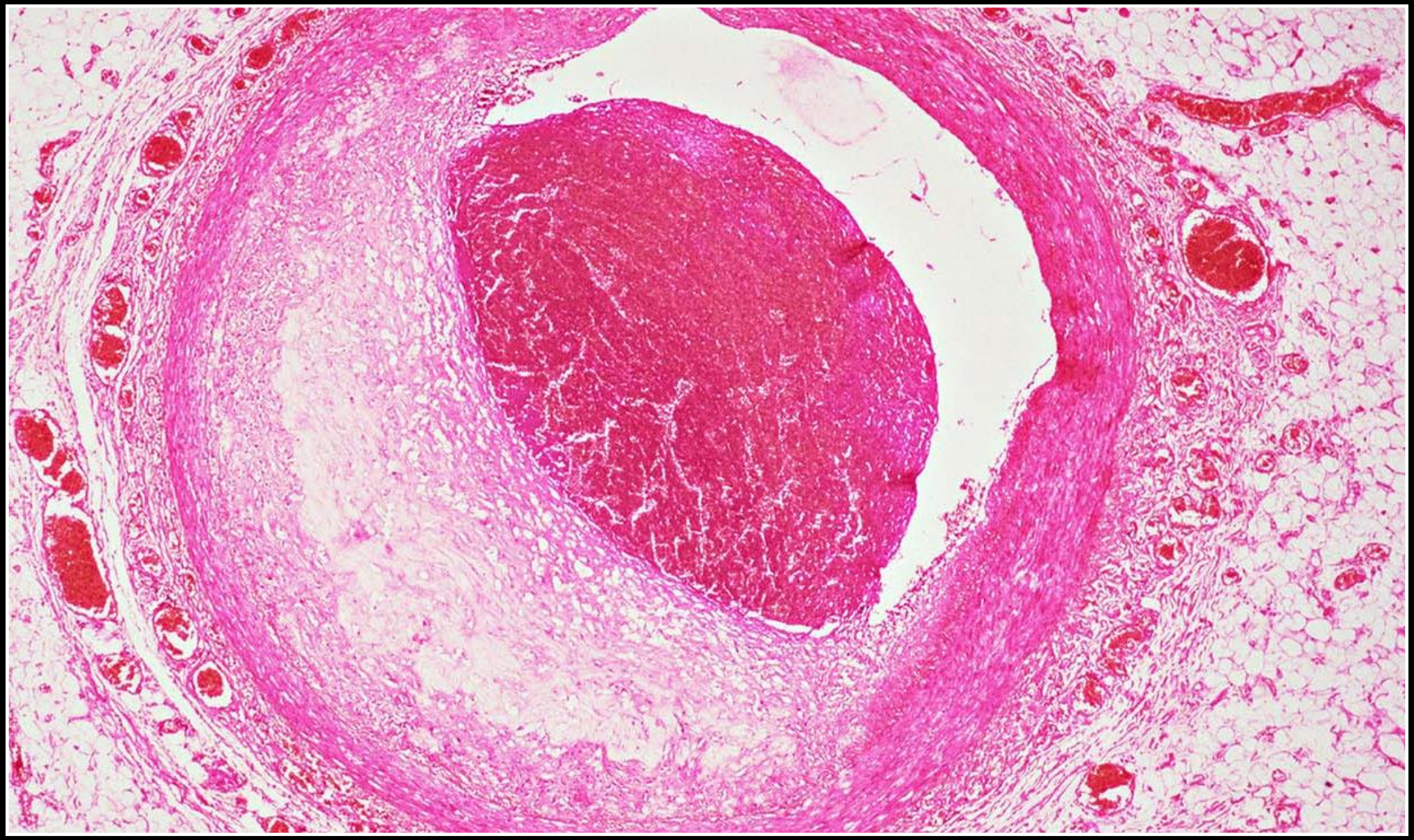
No. at Risk													
Placebo	2991	2888	2786	2706	2627	2424	2066	1821	1534	1278	961	681	400
Empagliflozin	2997	2928	2843	2780	2708	2491	2134	1858	1578	1332	1005	709	402

Anker SD et al. N Engl J Med 2021;385:1451-1461

The NEW ENGLAND JOURNAL of MEDICINE

HFpEF

- Beta-blockers
- Dapagliflozin / Empagliflozin
- Diuretics
- Focus on **all** the underlying conditions

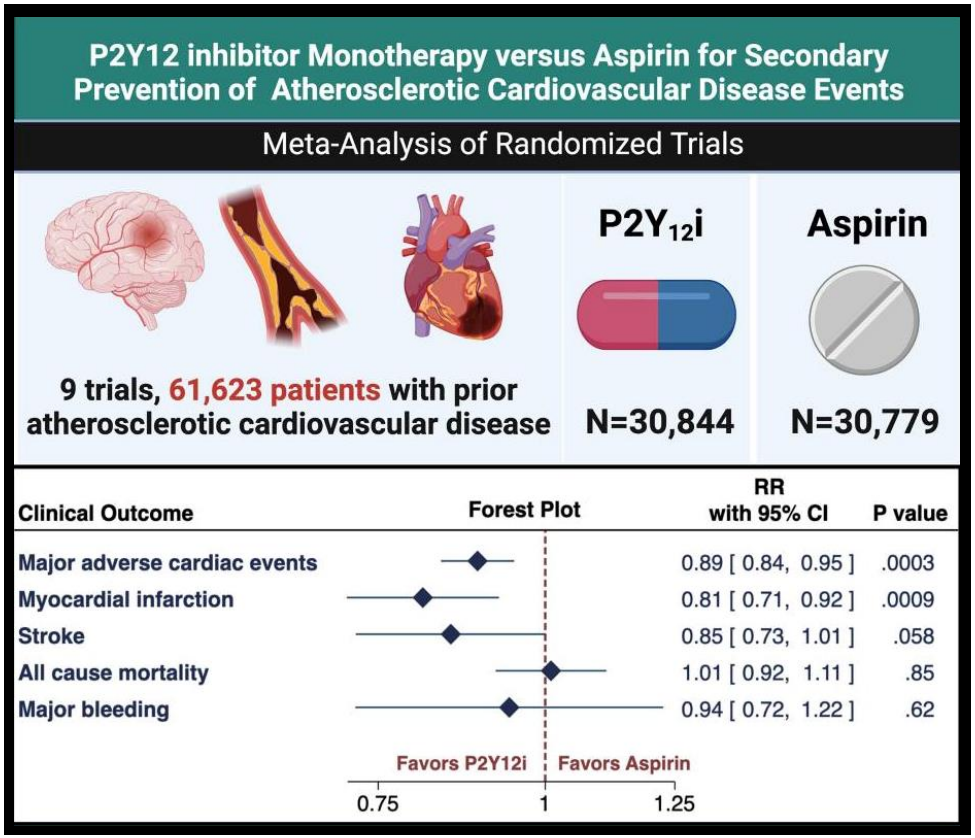


Coronary Artery Disease

PANTHER

$P2Y_{12}$ inhibitor versus aspirin monotherapy for secondary prevention of cardiovascular events: meta-analysis of randomized trials

- $P2Y_{12}$ inhibitors
  - Clopidogrel
  - Praugrel
  - Ticagrelor
- 9 trials
- 61,623 patients
- Safer than aspirin
- Note – no change in all-cause mortality



frontiers in Pharmacology

SYSTEMATIC REVIEW
published: 02 August 2021
doi: 10.3389/fphar.2021.694698

Check for updates

Clinical Outcomes of Concomitant Use of Proton Pump Inhibitors and Dual Antiplatelet Therapy: A Systematic Review and Meta-Analysis

*Hongzhou Guo, Zhishuai Ye and Rongchong Huang**

Cardiac Center/Division of Cardiovascular Diseases, Beijing Friendship Hospital, Capital Medical University, Beijing, China

Background: The safety and efficacy associated with the use of proton pump inhibitors (PPIs) by patients with coronary artery disease receiving dual antiplatelet therapy (DAPT) remain unclear.

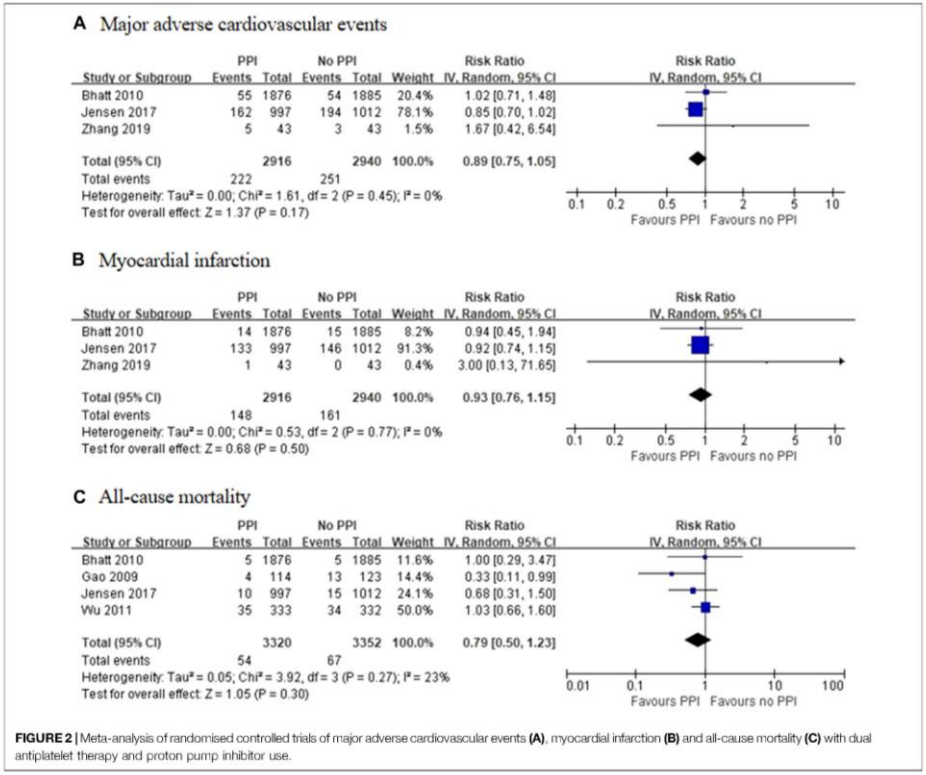


FIGURE 2 | Meta-analysis of randomised controlled trials of major adverse cardiovascular events **(A)**, myocardial infarction **(B)** and all-cause mortality **(C)** with dual antiplatelet therapy and proton pump inhibitor use.

MACE and DAPT and PPI

RCTs

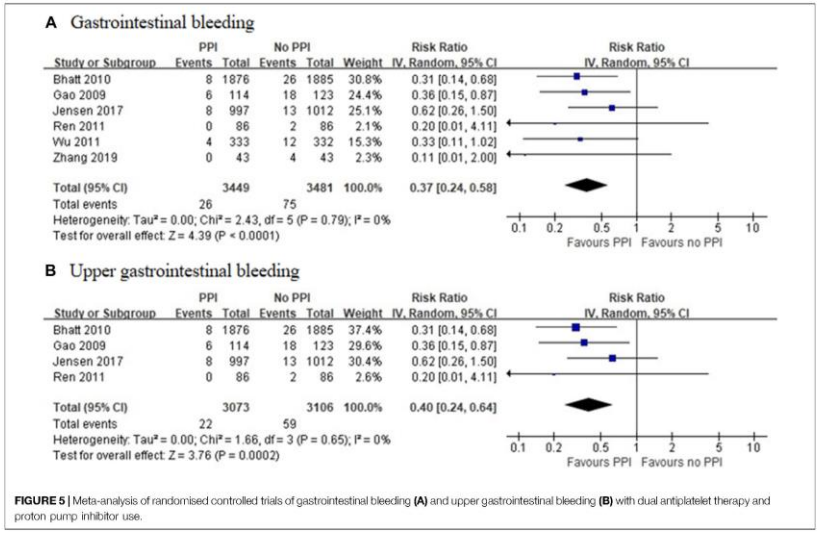


FIGURE 5 | Meta-analysis of randomised controlled trials of gastrointestinal bleeding **(A)** and upper gastrointestinal bleeding **(B)** with dual antiplatelet therapy and proton pump inhibitor use.

GI Bleeding and DAPT and PPIs

RCTs

NICE Guidelines – Lipid Lowering Therapy

- **Inclisiran for treating primary hypercholesterolaemia or mixed dyslipidaemia (TA733)**
  - Published: 6 October 2021
- **Bempedoic acid with ezetimibe for treating primary hypercholesterolaemia or mixed dyslipidaemia (TA694)**
  - Published: 28 April 2021
- **Familial hypercholesterolaemia: identification and management (CG71)**
  - Last updated: 4 October 2019
- **Cardiovascular disease: risk assessment and reduction, including lipid modification(CG181)**
  - Last updated: 27 September 2016
- **Alirocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia (TA393)**
  - Published: 22 June 2016
- **Evolocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia (TA394)**
  - Published: 22 June 2016
- **Ezetimibe for treating primary heterozygous-familial and non-familial hypercholesterolaemia (TA385)**
  - Published: 24 February 2016
- **Icosapent ethyl with statin therapy for reducing the risk of cardiovascular events in people with raised triglycerides (TA805)**
  - Published: 13 July 2022

Cardiovascular disease: risk assessment and reduction, including lipid modification

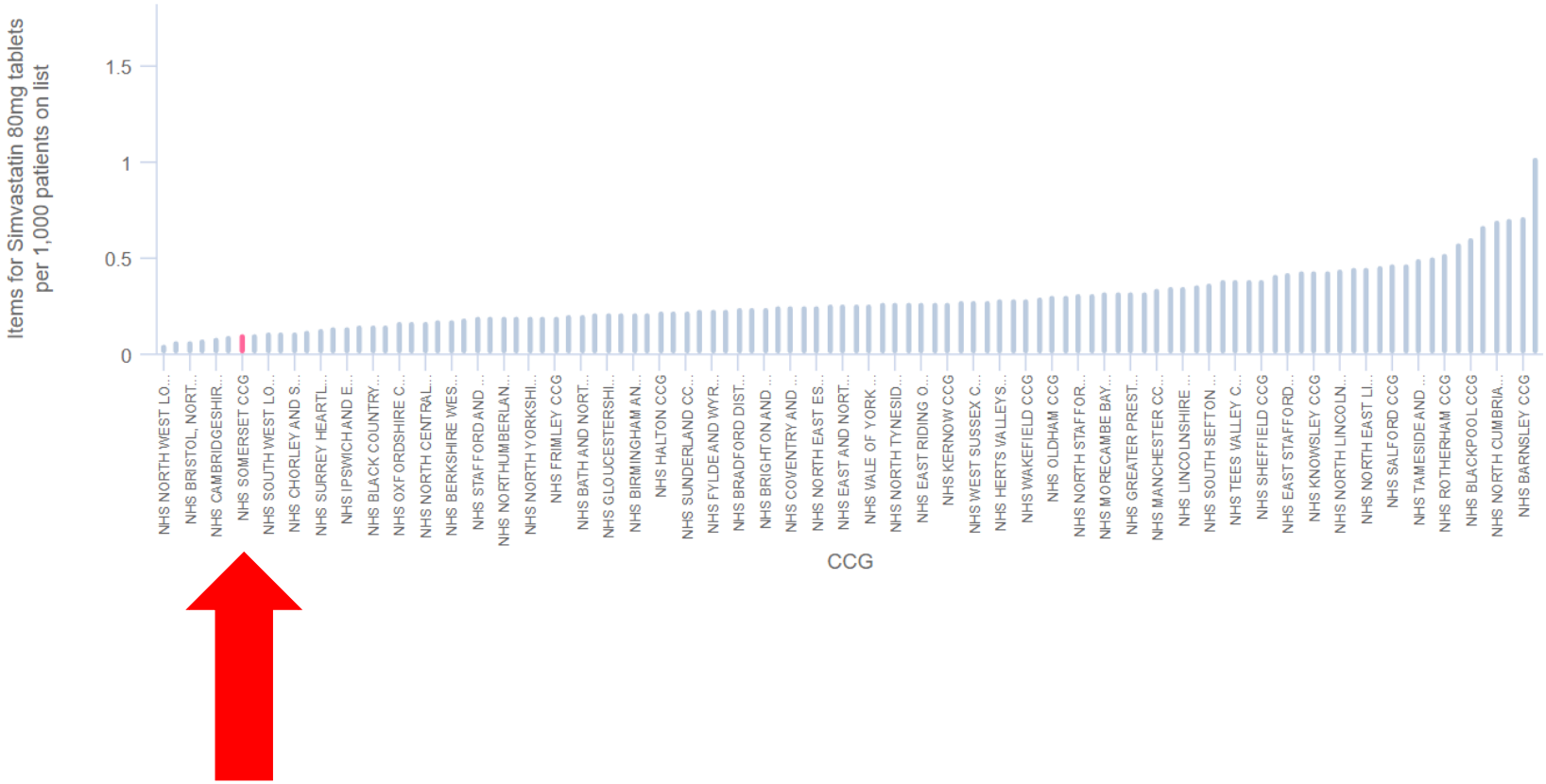
In development [GID-NG10178] Expected publication date: 10 May 2023

Statins and Lipid Lowering

	Reduction in LDL Cholesterol				
Dose (mg/day)	**5**	**10**	**20**	**40**	**80**
Fluvastatin	-	-	21	27	33
Pravastatin	-	20	24	29	-
Simvastatin	-	27	32	37	-
Atorvastatin	-	37	43	49	55
Rosuvastatin	38	43	48	53	-

Lipid Lowering	Shading	Intensity
20-30%		Low
31-40%		Medium
>40%		High

Simvastatin 80mg Prescribing in Somerset Compared with Other CCGs



Statin Use

QRISK3 ≥20% not taking statins*:	38,907
QRISK3 15-19% not taking statins*:	20,902
QRISK3 10-14% not taking statins*:	34,417
CVD patients not taking statins*:	7,176

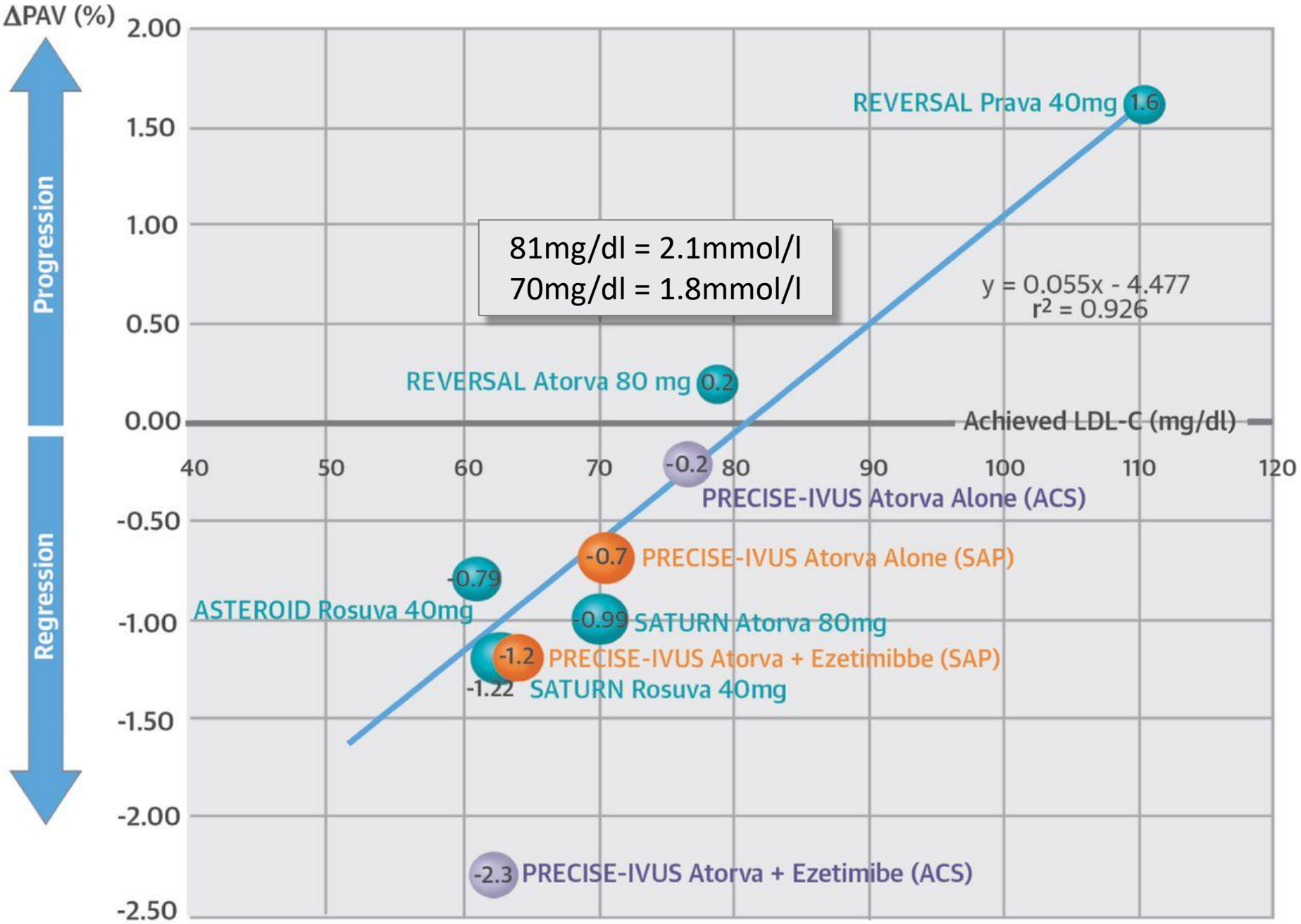
*Excluding: statin not tolerated, statin declined, statin contra-indicated, statin allergy, statin not indicated

Effect of statin therapy on muscle symptoms: an individual participant data meta-analysis of large-scale, randomised, double-blind trials.

CTT Collaboration.

The Lancet 400, P832-845, SEPTEMBER 2022

- 19 double-blind trials of statin versus placebo (n=123 940) and
- 4 double-blind trials of a more intensive versus a less intensive statin regimen (n=30 724)
- During year 1, statin therapy produced a 7% relative increase in muscle pain or weakness (1·07; 1·04–1·10)
- An absolute excess rate of 11 (6–16) events per 1000 person-years
- only **one in 15** ([1·07–1·00]/1·07) of muscle-related reports by participants allocated to statin therapy were actually due to the statin
- After year 1, there was no significant excess in first reports of muscle pain or weakness (0·99; 0·96–1·02)

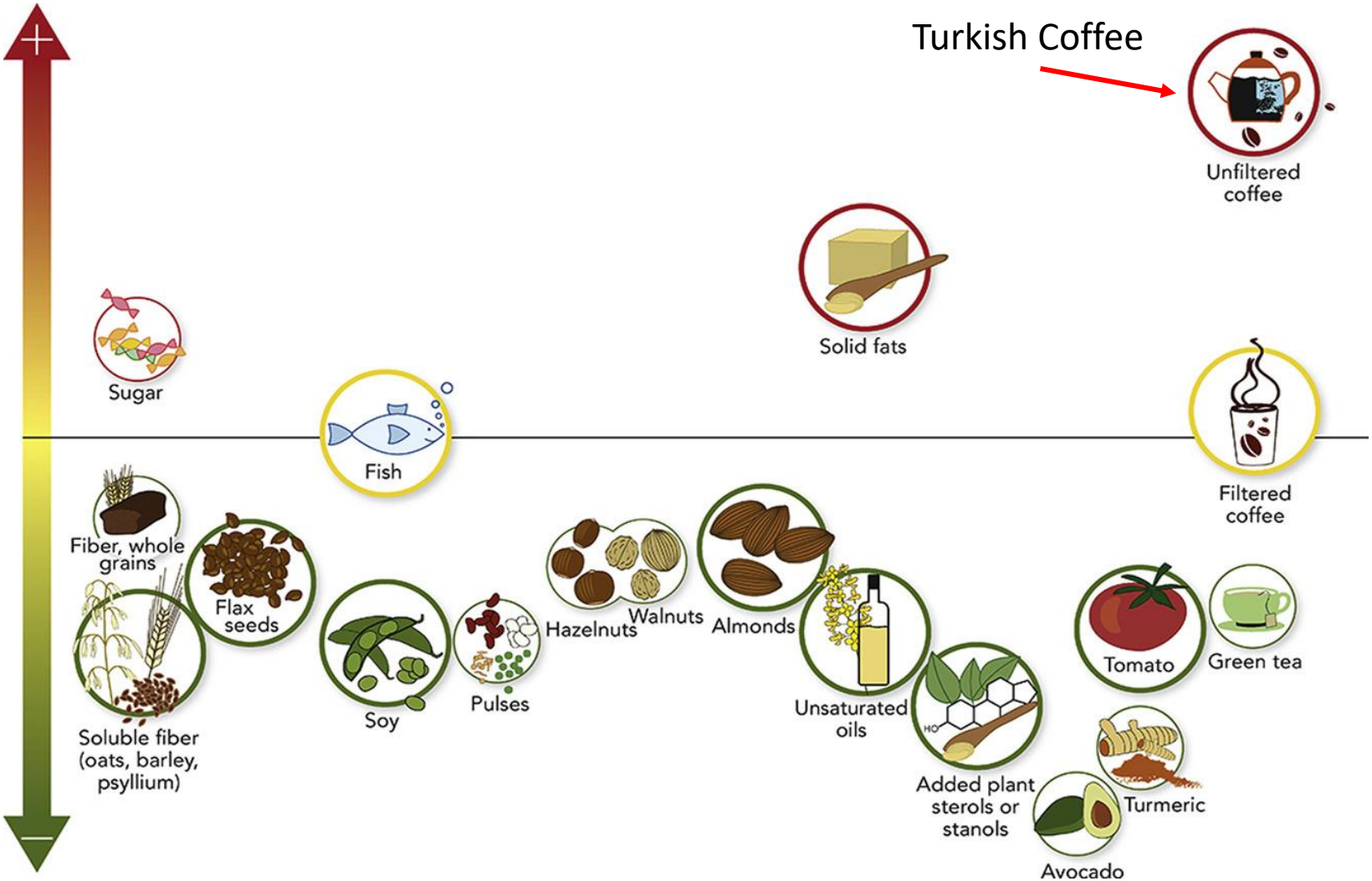


Tsujita, K. et al. J Am Coll Cardiol. 2015; 66(5):495–507.

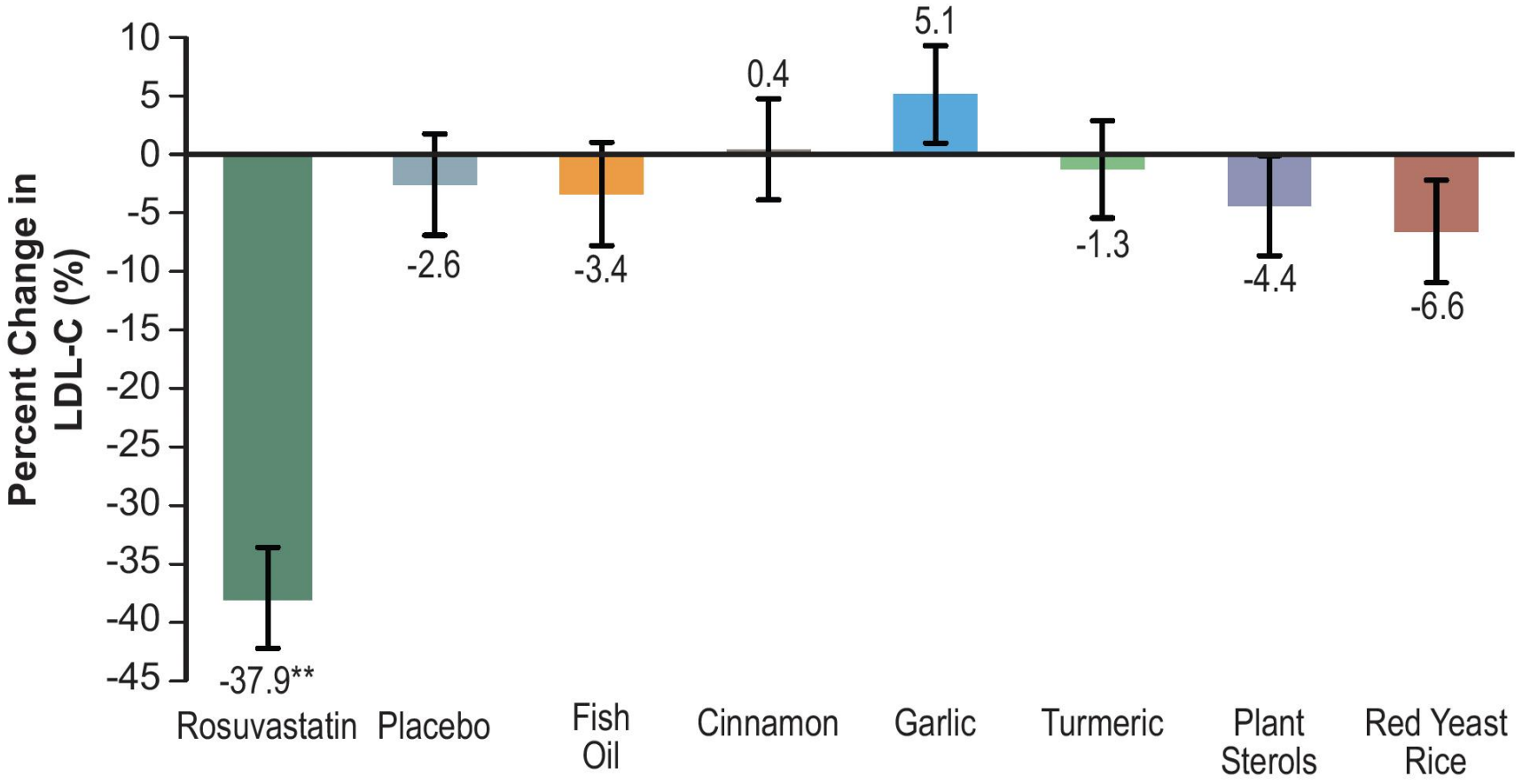
9-12 month follow-up

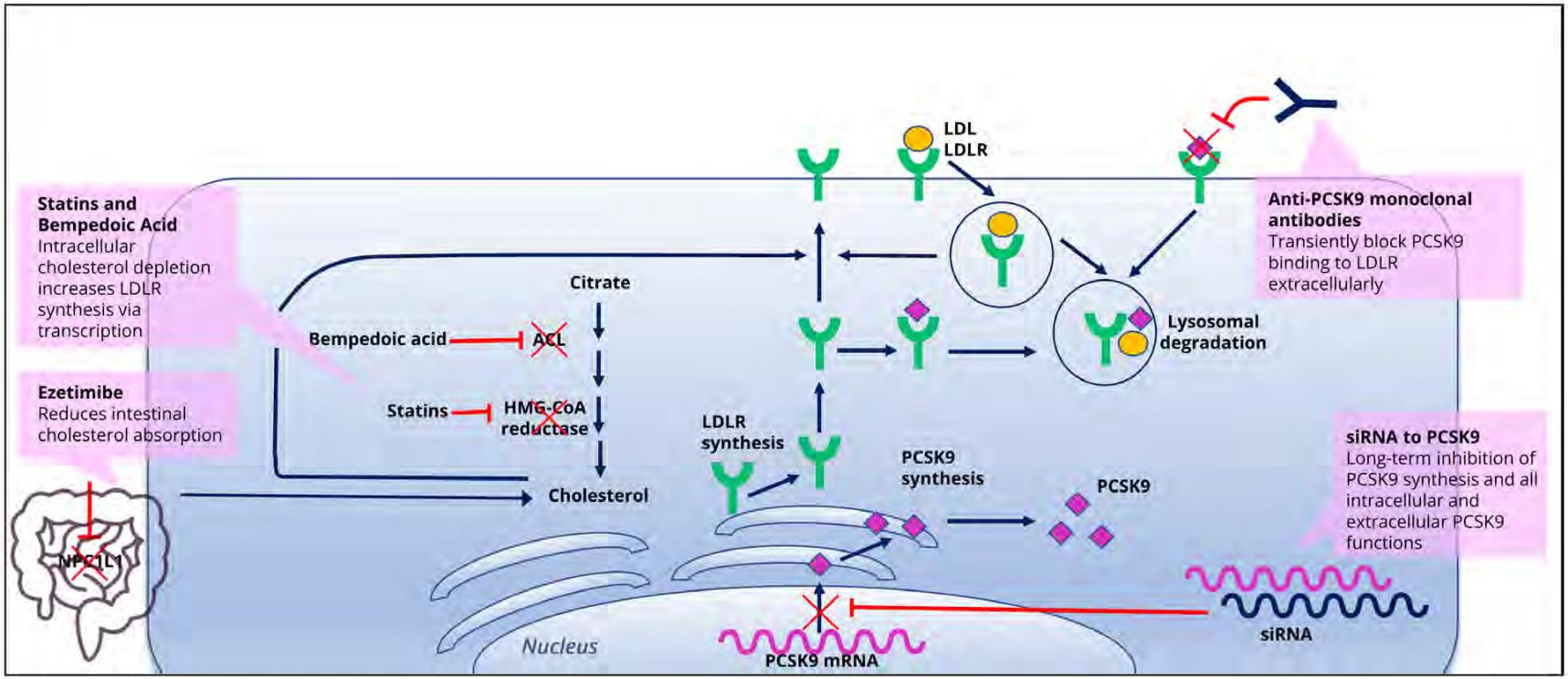
The effects of foods on LDL cholesterol levels: A systematic review of the accumulated evidence from systematic reviews and meta-analyses of randomized controlled trials

Malin Schoeneck, David Iggman. Nutrition, Metabolism and Cardiovascular Diseases Volume 31 Issue 5 Pages 1325-1338 (May 2021) DOI: 10.1016/j.numecd.2020.12.032.



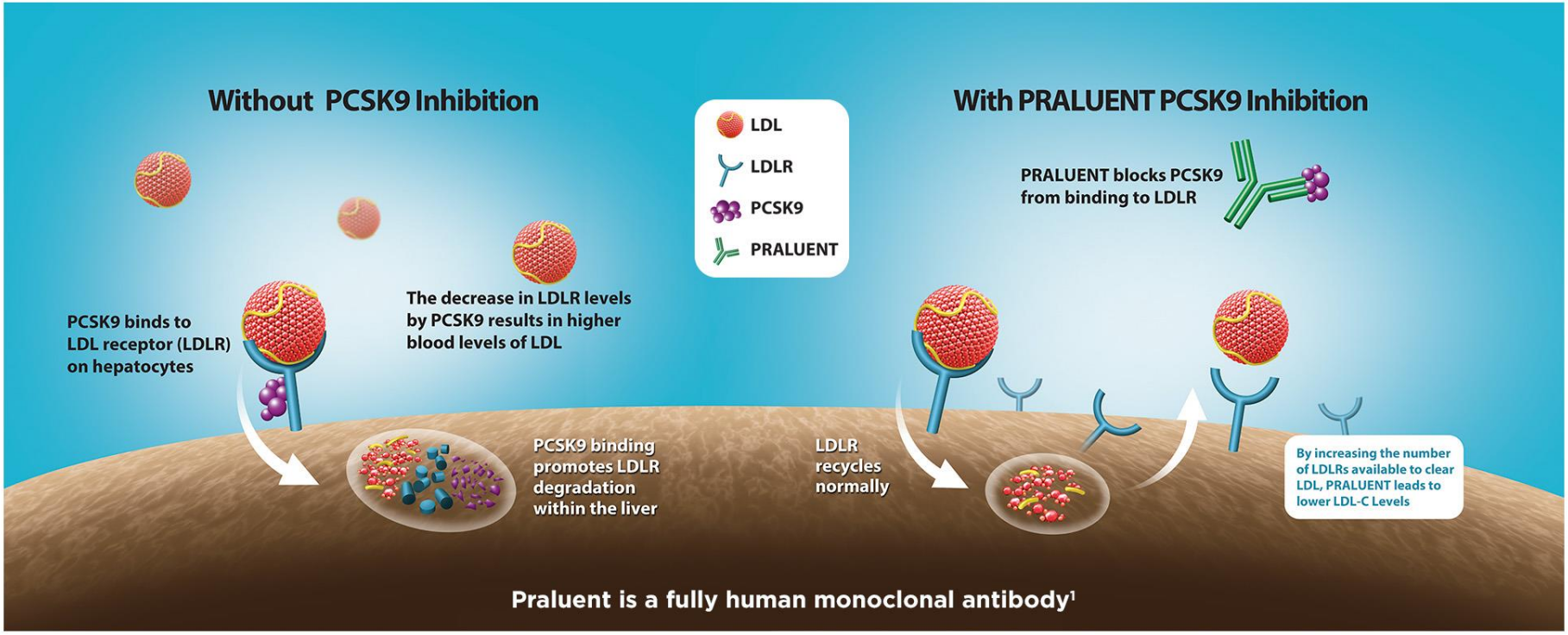
Supplements, Placebo, or Rosuvastatin (5mg od) Study (SPORT)
Laffin et al. 2022 https://doi.org/10.1016/j.jacc.2022.10.013




Statins and Bempedoic Acid
Intracellular cholesterol depletion increases LDLR synthesis via transcription
Ezetimibe
Reduces intestinal cholesterol absorption
NPC1L1
Citrate
Bempedoic acid
ACL
Statins
HMG-CoA reductase
Cholesterol
LDL
LDLR
Anti-PCSK9 monoclonal antibodies
Transiently block PCSK9 binding to LDLR extracellularly
Lysosomal degradation
LDLR synthesis
PCSK9 synthesis
PCSK9
siRNA to PCSK9
Long-term inhibition of PCSK9 synthesis and all intracellular and extracellular PCSK9 functions
Nucleus
PCSK9 mRNA
siRNA

PCSK9 Inhibition

Alirocumab (Praluent) & Evolocumab (Repatha)



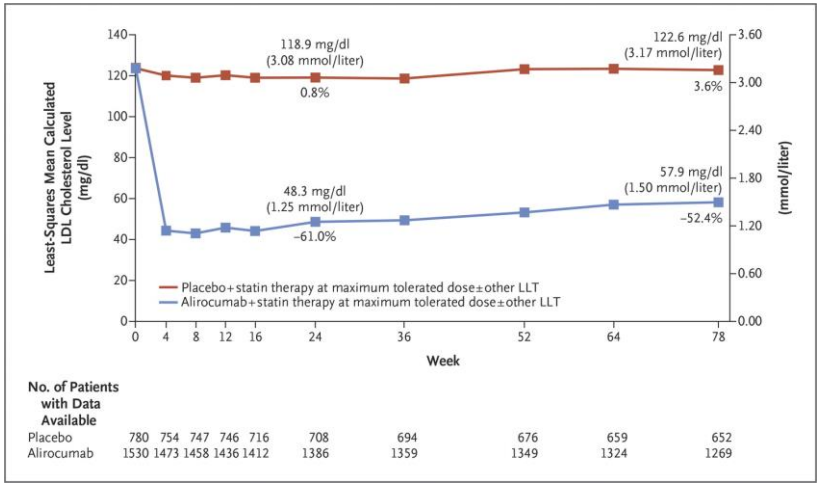
Subcutaneous injection 2-4 weekly

PCSK9 Inhibition

Alirocumab (Praluent) & Evolocumab (Repatha)

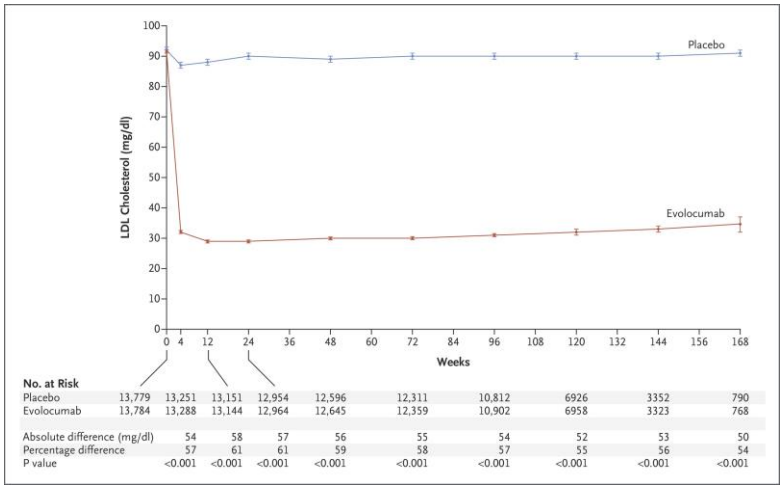
Alirocumab

Robinson JG et al. N Engl J Med 2015;372:1489-1499



Evolocumab

Sabatine MS et al. N Engl J Med 2017;376:1713-1722



Low-density lipoprotein cholesterol concentrations above which alirocumab is recommended

	Without CVD	**With CVD**	
		High risk of CVD [1]	**Very high risk of CVD** [2]
Primary non-familial hypercholesterolaemia or mixed dyslipidaemia	Not recommended at any LDL-C concentration	Recommended only if LDL-C concentration is persistently above 4.0 mmol/l	Recommended only if LDL-C concentration is persistently above 3.5 mmol/l
Primary heterozygous-familial hypercholesterolaemia	Recommended only if LDL-C concentration is persistently above 5.0 mmol/l	Recommended only if LDL-C concentration is persistently above 3.5 mmol/l	

[1]High risk of cardiovascular disease is defined as a history of any of the following: acute coronary syndrome (such as myocardial infarction or unstable angina requiring hospitalisation), coronary or other arterial revascularisation procedures, coronary heart disease, ischaemic stroke, peripheral arterial disease.
[2]Very high risk of cardiovascular disease is defined as recurrent cardiovascular events or cardiovascular events in more than 1 vascular bed (that is, polyvascular disease).
Abbreviations: CVD, cardiovascular disease; LDL-C, low-density lipoprotein cholesterol.

https://www.nice.org.uk/guidance/ta393/chapter/1-Recommendations

Low-density lipoprotein cholesterol concentrations above which evolocumab is recommended

	Without CVD	With CVD	
		High risk of CVD [1]	**Very high risk of CVD** [2]
Primary non-familial hypercholesterolaemia or mixed dyslipidaemia	Not recommended at any LDL-C concentration	Recommended only if LDL-C concentration is persistently above 4.0 mmol/litre	Recommended only if LDL-C concentration is persistently above 3.5 mmol/litre
Primary heterozygous-familial hypercholesterolaemia	Recommended only if LDL-C concentration is persistently above 5.0 mmol/litre	Recommended only if LDL-C concentration is persistently above 3.5 mmol/litre	

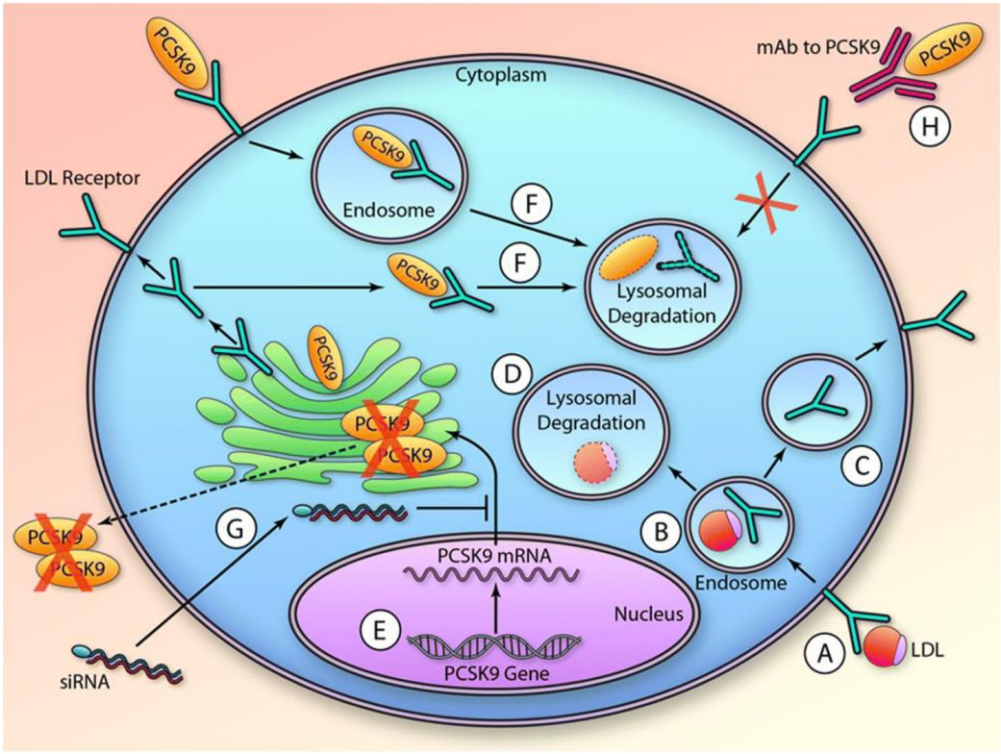
[1] High risk of CVD is defined as a history of any of the following: acute coronary syndrome (such as myocardial infarction or unstable angina needing hospitalisation); coronary or other arterial revascularisation procedures; coronary heart disease; ischaemic stroke; peripheral arterial disease.
[2] Very high risk of CVD is defined as recurrent cardiovascular events or cardiovascular events in more than 1 vascular bed (that is, polyvascular disease).
Abbreviations: CVD, cardiovascular disease; LDL-C, low-density lipoprotein cholesterol.

https://www.nice.org.uk/guidance/ta394/chapter/1-Recommendations

NOW AMBER DRUGS

Monoclonal antibodies prevent PCSK9 binding with LDL receptors.

Silencing RNAs (siRNAs) prevent production of PCSK9



The NEW ENGLAND JOURNAL of MEDICINE

Inclisiran in Patients with Elevated LDL Cholesterol

TWO PHASE 3, DOUBLE-BLIND, RANDOMIZED, CONTROLLED TRIALS

ORION-10
(U.S.)

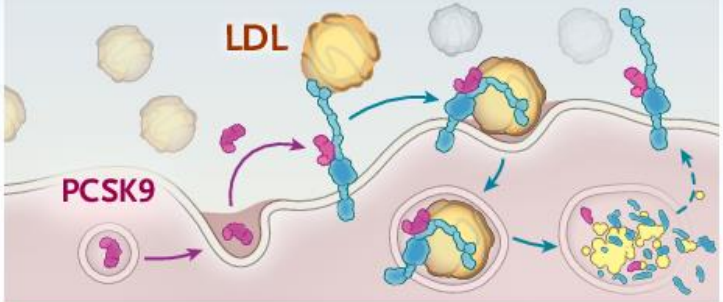
(N=1561)

–51.3% with Inclisiran

Difference, –52.3%
(95% CI, –55.7 to –48.8; P<0.001)

+1% with Placebo

Adults with CVD and elevated LDL



Percentage change in LDL cholesterol at 510 days

ORION-11
(Europe and South Africa)

(N=1617)

–45.8% with Inclisiran

Difference, –49.9%
(95% CI, –53.1 to –46.6; P<0.001)

+4% with Placebo

K.K. Ray et al. 10.1056/NEJMoa1912387

Inclisiran – Recommendations

https://www.nice.org.uk/guidance/ta733/chapter/1-Recommendations

Inclisiran is recommended as an option for treating primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia as an adjunct to diet in adults. It is recommended only if:

- **there is a history of any of the following cardiovascular events:**
  - acute coronary syndrome (such as MI or unstable angina needing hospitalisation)
  - coronary or other arterial revascularisation procedures
  - coronary heart disease
  - ischaemic stroke or
  - peripheral arterial disease, **and**
- LDL concentrations are persistently 2.6 mmol/l or more, despite max tolerated lipid-lowering therapy, that is:
  - maximum tolerated statins with or without other lipid-lowering therapies or,
  - other lipid-lowering therapies when statins are not tolerated or are contraindicated, and
  - the company provides inclisiran according to the commercial arrangement

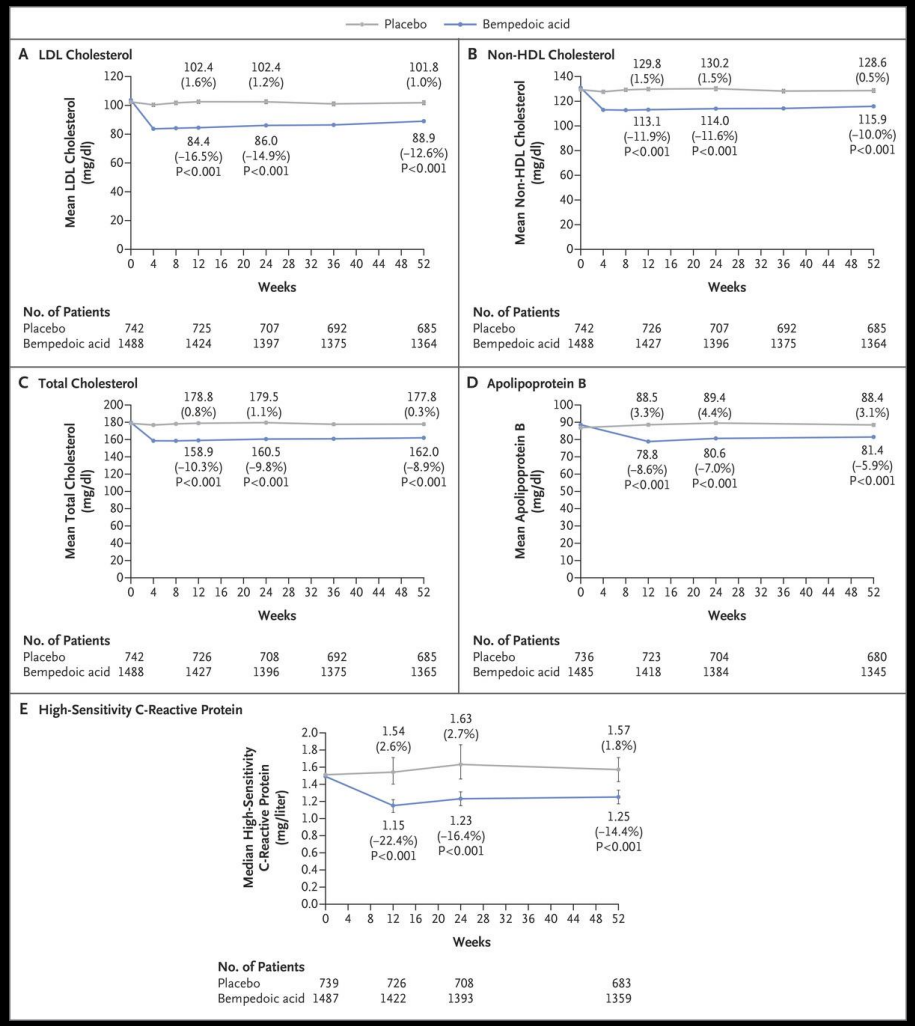
Inclisiran is recommended only in research for treating primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia in adults who have no history of cardiovascular events. This research is in the form of a clinical trial currently in development.

NOW GREEN DRUG

Bempedoic Acid + Ezetemibe Nustendi (180mg/10mg)

- Statins contra-indicated or not tolerated
- Ezetemibe alone does not reduce LDL cholesterol adequately
- Bempedoic acid reduced LDL cholesterol by 16.5% (https://www.nejm.org/doi/full/10.1056/NEJMoa1803917)
- Ezetemibe reduced LDL cholesterol by 23% (https://www.nejm.org/doi/full/10.1056/nejmoa1410489)
- Technology appraisal guidance [TA694]

Efficacy Measures over the 52-Week Trial (Intention-to-Treat Population)



KK Ray et al. N Engl J Med 2019;380:1022-1032.

The NEW ENGLAND JOURNAL of MEDICINE

Bempedoic Acid – Recommendations

https://www.nice.org.uk/guidance/ta694/chapter/1-Recommendations

Bempedoic acid **with ezetimibe** is recommended as an option for treating primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia as an adjunct to diet in adults. It is recommended only if:

- statins are contraindicated or not tolerated
- ezetimibe alone does not control low-density lipoprotein cholesterol well enough and
- the company provides bempedoic acid and bempedoic acid with ezetimibe according to the commercial arrangement.

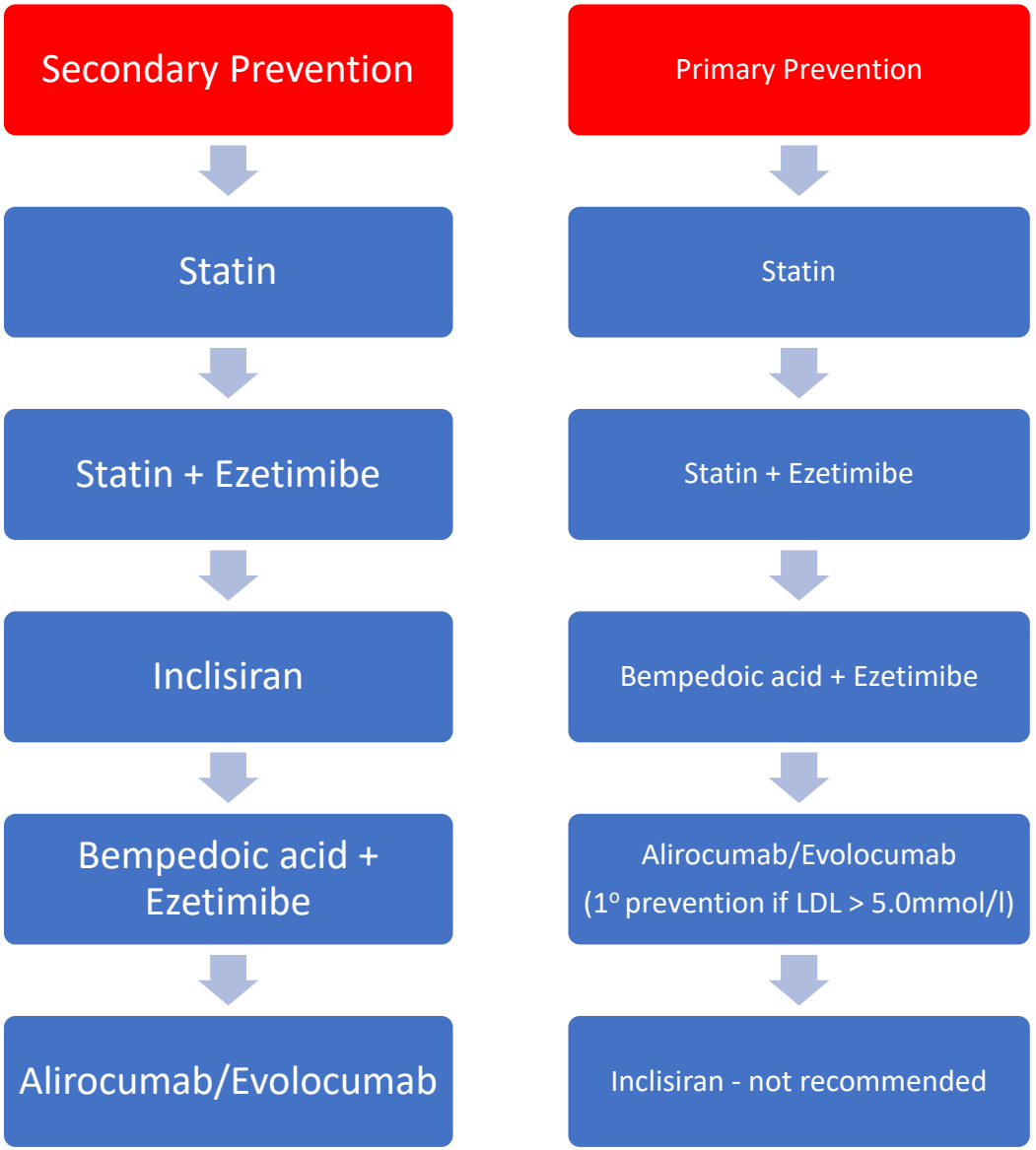
Bempedoic acid with ezetimibe can be used as separate tablets or a fixed-dose combination.

This recommendation is not intended to affect treatment with bempedoic acid with ezetimibe that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop.

NOW AMBER DRUG

Statins – Order of use?

NB. Alex Bickerton



One more thing:

Icosapent Ethyl / Vazkepa

- Omega 3 Fatty Acid
- Indication: Elevated triglycerides, in conjunction with a statin
- REDUCE-IT Trial
- N Engl J Med 2019; 380:11-22, DOI: 10.1056/NEJMoa1812792

"Among patients with elevated triglyceride levels despite the use of statins, the risk of ischemic events, including cardiovascular death, was significantly lower among those who received 2 g of icosapent ethyl twice daily than among those who received placebo"

Icosapent ethyl with statin therapy for reducing the risk of cardiovascular events in people with raised triglycerides.

Technology appraisal guidance [TA805] Published: 13 July 2022

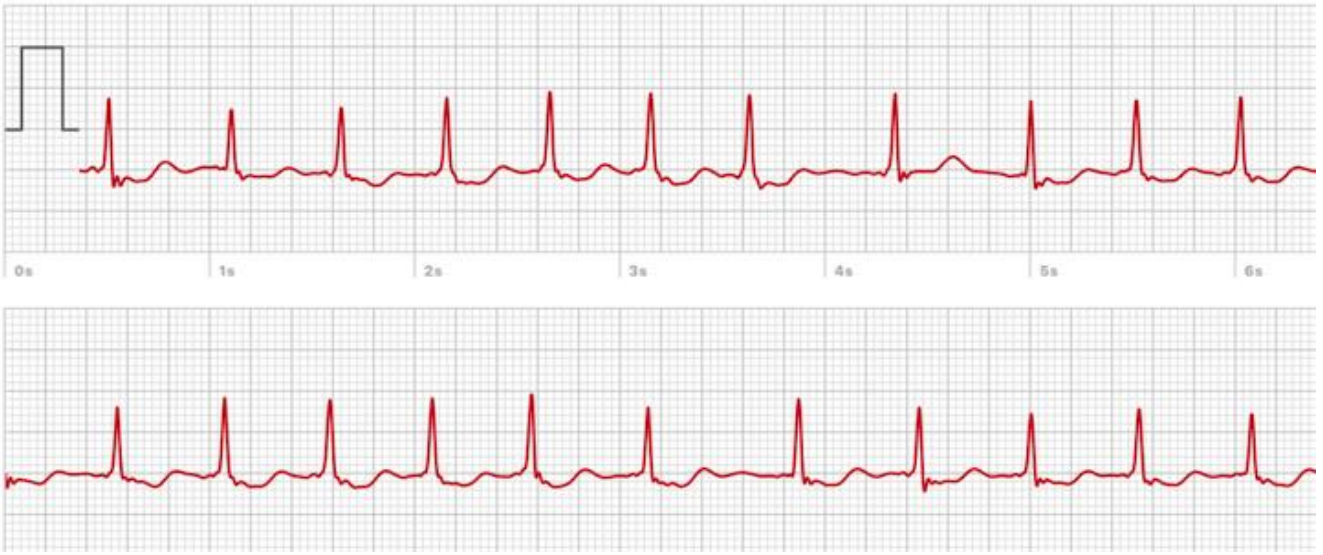
Icosapent ethyl is recommended … if they have a … raised fasting triglycerides (1.7 mmol/litre or above) **and are taking statins**, but only if they have:

- established cardiovascular disease (**secondary prevention**), defined as a history of any of the following:
  - acute coronary syndrome (such as myocardial infarction or unstable angina needing hospitalisation)
  - coronary or other arterial revascularisation procedures
  - coronary heart disease
  - ischaemic stroke
  - peripheral arterial disease, **and**
- low-density lipoprotein cholesterol (LDL-C) levels above 1.04 mmol/litre and below or equal to 2.60 mmol/litre.

Atrial Fibrillation — ♥ 103 BPM
Average

This ECG shows signs of AFib.

If this is an unexpected result, you should talk to your doctor.



Atrial fibrillation

Very common

Annals of Internal Medicine ORIGINAL RESEARCH

Comparative Effectiveness and Safety Between Apixaban, Dabigatran, Edoxaban, and Rivaroxaban Among Patients With Atrial Fibrillation

A Multinational Population-Based Cohort Study

Wallis C.Y. Lau, PhD*; Carmen Olga Torre, MSc*; Kenneth K.C. Man, PhD; Henry Morgan Stewart, PhD; Sarah Seager, BA; Mui Van Zandt, BSc; Christian Reich, MD; Jing Li, MS; Jack Brewster, PhD; Gregory Y.H. Lip, MD; Aroon D. Hingorani, PhD; Li Wei, PhD; and Ian C.K. Wong, PhD

Background: Current guidelines recommend using direct oral anticoagulants (DOACs) over warfarin in patients with atrial fibrillation (AF), but head-to-head trial data do not exist to guide the choice of DOAC.

Objective: To do a large-scale comparison between all DOACs (apixaban, dabigatran, edoxaban, and rivaroxaban) in routine clinical practice.

Design: Multinational population-based cohort study.

Setting: Five standardized electronic health care databases, which covered 221 million people in France, Germany, the United Kingdom, and the United States.

Participants: Patients who were newly diagnosed with AF from 2010 through 2019 and received a new DOAC prescription.

Measurements: Database-specific hazard ratios (HRs) of ischemic stroke or systemic embolism, intracranial hemorrhage (ICH), gastrointestinal bleeding (GIB), and all-cause mortality between DOACs were estimated using a Cox regression model stratified by propensity score and pooled using a random-effects model.

Results: A total of 527 226 new DOAC users met the inclusion criteria (apixaban, n = 281 320; dabigatran, n = 61 008; edoxaban, n = 12 722; and rivaroxaban, n = 172 176). Apixaban use was associated with lower risk for GIB than use of dabigatran (HR, 0.81 [95% CI, 0.70 to 0.94]), edoxaban (HR, 0.77 [CI, 0.66 to 0.91]), or rivaroxaban (HR, 0.72 [CI, 0.66 to 0.79]). No substantial differences were observed for other outcomes or DOAC–DOAC comparisons. The results were consistent for patients aged 80 years or older. Consistent associations between lower GIB risk and apixaban versus rivaroxaban were observed among patients receiving the standard dose (HR, 0.72 [CI, 0.64 to 0.82]), those receiving a reduced dose (HR, 0.68 [CI, 0.61 to 0.77]), and those with chronic kidney disease (HR, 0.68 [CI, 0.59 to 0.77]).

Limitation: Residual confounding is possible.

Conclusion: Among patients with AF, apixaban use was associated with lower risk for GIB and similar rates of ischemic stroke or systemic embolism, ICH, and all-cause mortality compared with dabigatran, edoxaban, and rivaroxaban. This finding was consistent for patients aged 80 years or older and those with chronic kidney disease, who are often underrepresented in clinical trials.

Primary Funding Source: None.

Ann Intern Med. doi:10.7326/M22-0511 **Annals.org**
For author, article, and disclosure information, see end of text.
This article was published at Annals.org on 1 November 2022.
* Dr. Lau and Ms. Torre are co-first authors.

"Among patients with AF, apixaban use was associated with a **lower risk for gastro-intestinal bleeding** and similar rates of ischemic stroke or systemic embolism, intracranial haemorrhage, and all-cause mortality compared with dabigatran, edoxaban, and rivaroxaban."

DOACs and Heart Valves

Can you?

- I keep getting asked this question
- On-X valve
- Less warfarin required – INR 1.5-2.0
- PROACT Xa Trial
- Apixaban vs. Warfarin

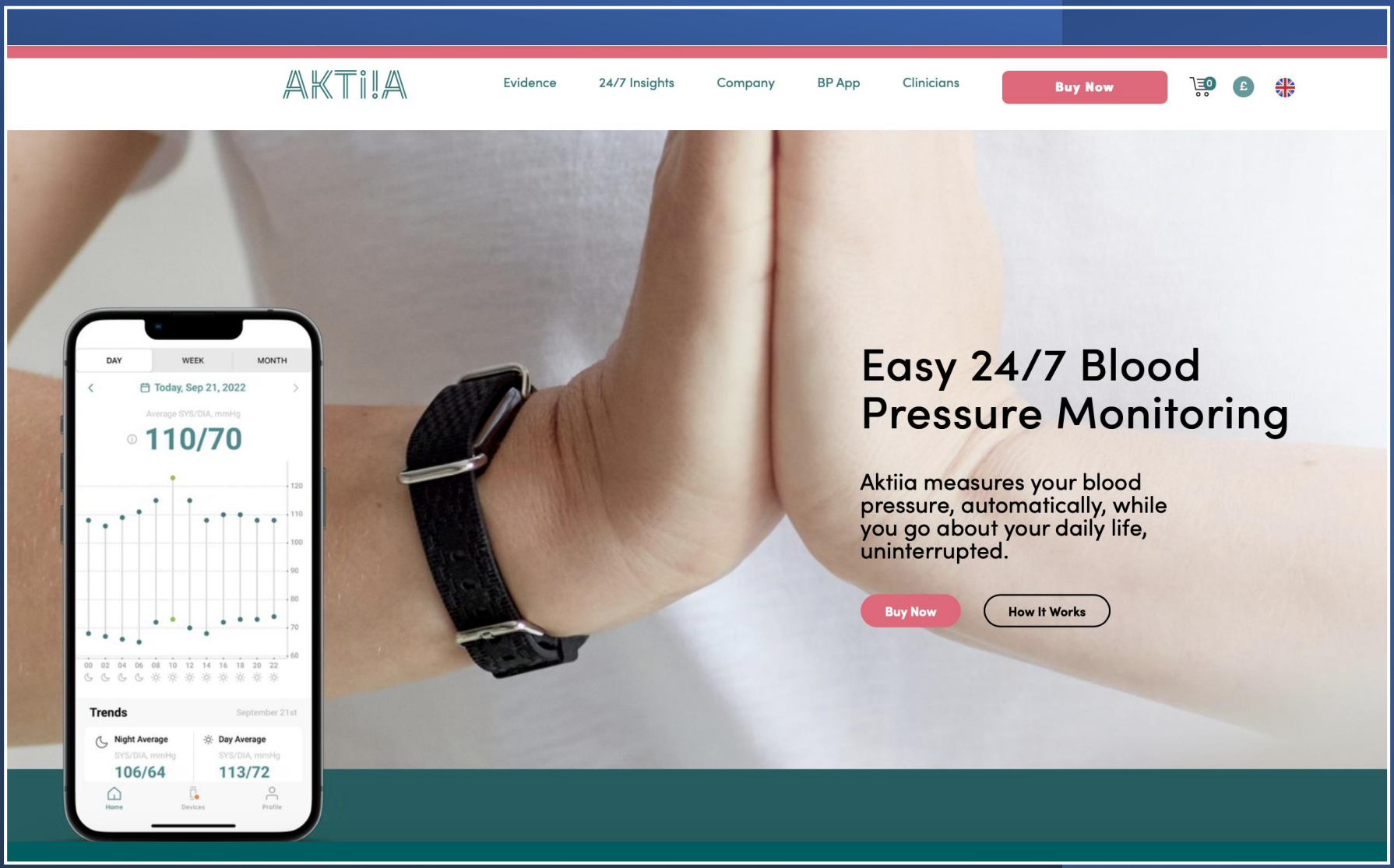
On-X Valve

DOACs and Heart Valves

Can you?

"The DSMB found that blood clots, resulting in stroke, **occurred more frequently in patients receiving apixaban** and that continuing the trial was unlikely to achieve the primary endpoint while possibly exposing patients to increased risk"

On-X Valve



https://aktiia.com/uk/

Cardiovascular outcomes in adults with hypertension with evening versus morning dosing of usual antihypertensives in the UK (TIME study): a prospective, randomised, open-label, blinded-endpoint clinical trial

*Isla S Mackenzie, Amy Rogers, Neil R Poulter, Bryan Williams, Morris J Brown, David J Webb, Ian Ford, David A Rorie, Greg Guthrie, J W Kerr Grieve, Filippo Pigazzani, Peter M Rothwell, Robin Young, Alex McConnachie, Allan D Struthers, Chim C Lang, Thomas M MacDonald, on behalf of the TIME Study Group**

Summary

Background Studies have suggested that evening dosing with antihypertensive therapy might have better outcomes than morning dosing. The Treatment in Morning versus Evening (TIME) study aimed to investigate whether evening dosing of usual antihypertensive medication improves major cardiovascular outcomes compared with morning dosing in patients with hypertension.

Methods The TIME study is a prospective, pragmatic, decentralised, parallel-group study in the UK, that recruited adults (aged ≥18 years) with hypertension and taking at least one antihypertensive medication. Eligible participants were randomly assigned (1:1), without restriction, stratification, or minimisation, to take all of their usual antihypertensive medications in either the morning (0600–1000 h) or in the evening (2000–0000 h). Participants were followed up for the composite primary endpoint of vascular death or hospitalisation for non-fatal myocardial infarction or non-fatal stroke. Endpoints were identified by participant report or record linkage to National Health Service datasets and were adjudicated by a committee masked to treatment allocation. The primary endpoint was assessed as the time to first occurrence of an event in the intention-to-treat population (ie, all participants randomly assigned to a treatment group). Safety was assessed in all participants who submitted at least one follow-up questionnaire. The study is registered with EudraCT (2011-001968-21) and ISRCTN (18157641), and is now complete.

Findings Between Dec 17, 2011, and June 5, 2018, 24 610 individuals were screened and 21 104 were randomly assigned to evening (n=10 503) or morning (n=10 601) dosing groups. Mean age at study entry was 65·1 years (SD 9·3); 12 136 (57·5%) participants were men; 8968 (42·5%) were women; 19 101 (90·5%) were White; 98 (0·5%) were Black, African, Caribbean, or Black British (ethnicity was not reported by 1637 [7·8%] participants); and 2725 (13·0%) had a previous cardiovascular disease. By the end of study follow-up (March 31, 2021), median follow-up was 5·2 years (IQR 4·9–5·7), and 529 (5·0%) of 10 503 participants assigned to evening treatment and 318 (3·0%) of 10 601 assigned to morning treatment had withdrawn from all follow-up. A primary endpoint event occurred in 362 (3·4%) participants assigned to evening treatment (0·69 events [95% CI 0·62–0·76] per 100 patient-years) and 390 (3·7%) assigned to morning treatment (0·72 events [95% CI 0·65–0·79] per 100 patient-years; unadjusted hazard ratio 0·95 [95% CI 0·83–1·10]; p=0·53). No safety concerns were identified.

Interpretation Evening dosing of usual antihypertensive medication was not different from morning dosing in terms of major cardiovascular outcomes. Patients can be advised that they can take their regular antihypertensive medications at a convenient time that minimises any undesirable effects.

Funding British Heart Foundation.

Introduction

Hypertension, or high blood pressure, is a key risk factor for cardiovascular disease worldwide.[1] Adequately controlling blood pressure reduces the risk of major cardiovascular events, including stroke, ischaemic heart disease, and cardiovascular death.[2] Clinical trials supporting the cardiovascular benefits of antihypertensive therapy primarily use conventional morning dosing. When measured using 24 h ambulatory monitoring, normal blood pressure exhibits a diurnal rhythm, with lower pressures during night-time sleep (referred to as dipping), followed by a morning increase or surge in blood pressure. The risk of adverse cardiovascular outcomes is increased in people whose blood pressure does not have the typical diurnal variation, such as reduced, reversed, or extreme dipping

Lancet 2022; 400: 1417–25

Published Online October 11, 2022 https://doi.org/10.1016/S0140-6736(22)01786-X

See **Comment** page 1383

*Other members of the TIME Study Group and contributors are listed in the appendix (p 17)

MEMO Research (Prof I S Mackenzie PhD, A Rogers MD, D A Rorie PhD, G Guthrie MBChB, F Pigazzani PhD, Prof T M MacDonald MD), **Division of Molecular and Clinical Medicine** (Prof A D Struthers FMedSci, Prof C C Lang MD), **Ninewells Hospital and Medical School, University of Dundee, Dundee, UK; School of Public Health, Imperial College London, London, UK** (Prof N R Poulter FMedSci); **NIHR University College London Hospitals Biomedical Research Centre and University College London, London, UK** (Prof B Williams FMedSci); **Queen Mary University of London, London, UK** (Prof M J Brown PhD); **British Heart Foundation/University Centre for Cardiovascular Science, University of Edinburgh, Edinburgh, UK** (Prof D J Webb DSc); **The Robertson Centre for Biostatistics, University of Glasgow, Glasgow, UK** (Prof I Ford PhD, R Young PhD, Prof A McConnachie PhD); **Department of Neurology, Aberdeen Royal Infirmary, Aberdeen, UK** (J W Kerr Grieve MD); **Wolfson Centre for Prevention of Stroke and Dementia, Nuffield Department of Clinical Neurosciences, University of Oxford, Oxford, UK** (Prof P M Rothwell FMedSci)

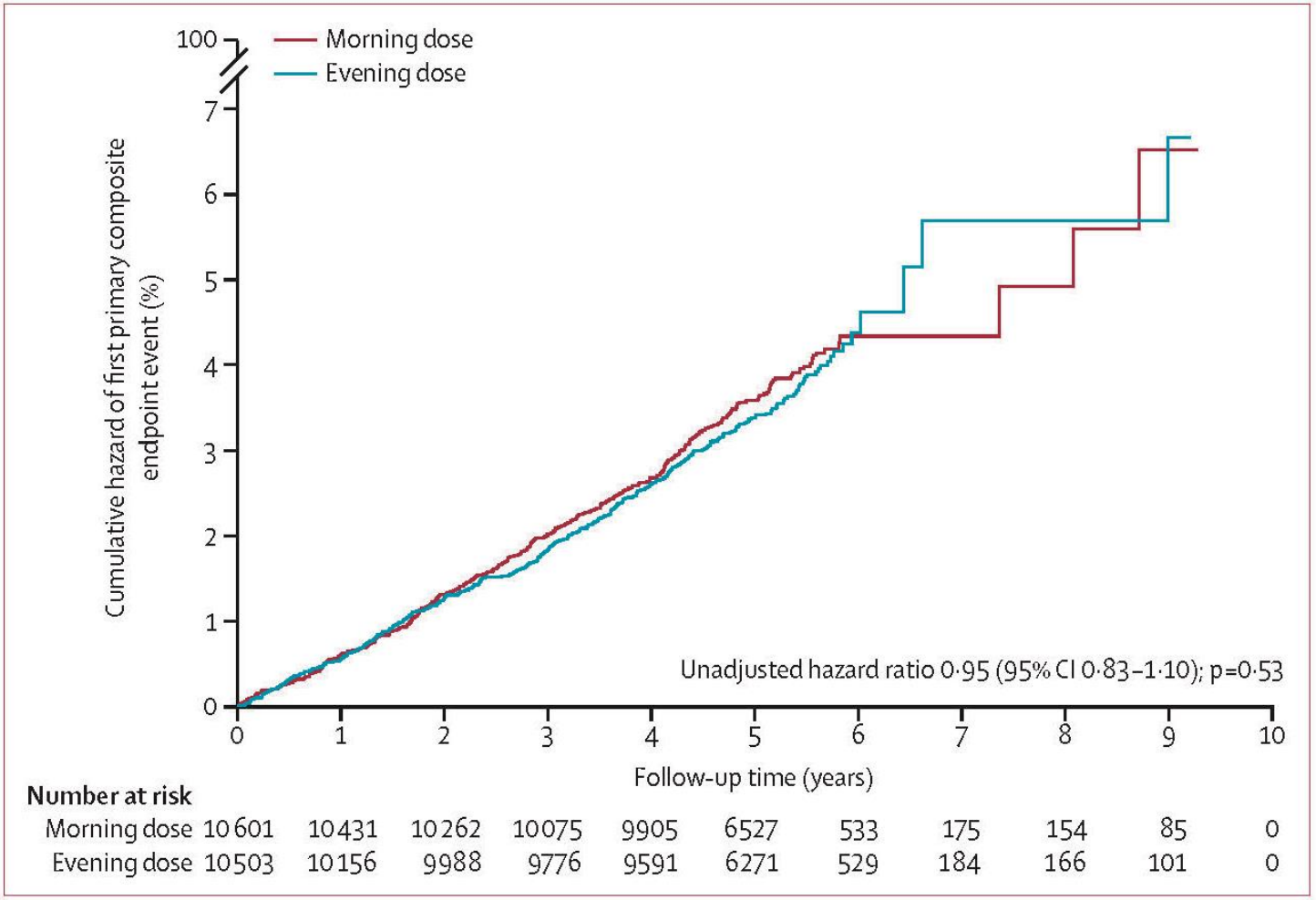


Figure 2: **Cumulative hazard of the first primary composite endpoint event, accounting for the competing risk of deaths not included in the endpoint (intention-to-treat population; n=21 104)**

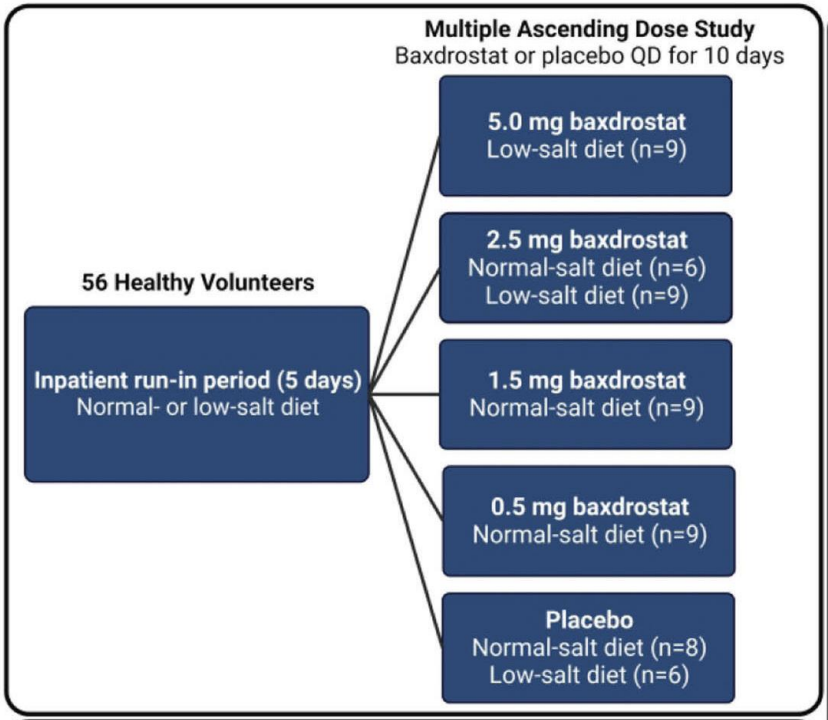
The primary composite endpoint was vascular death or hospitalisation for non-fatal myocardial infarction or non-fatal stroke.

Baxdrostat

- Selective inhibition of aldosterone synthase
- Difficult to achieve, because cortisol synthesis also affected (reduced) due to similarity of aldosterone synthase to cortisol synthase
- Baxdrostat does **not** reduce cortisol significantly

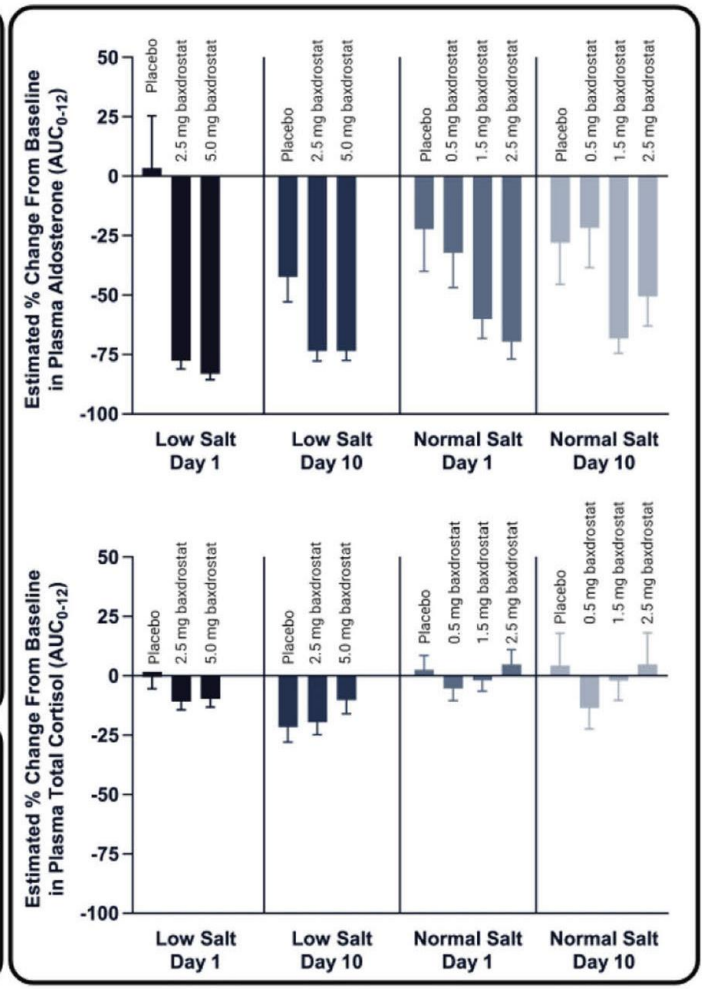
Graphical Abstract

This multiple ascending dose study of the selective aldosterone synthase inhibitor baxdrostat demonstrated a dose-dependent reduction in plasma aldosterone with no meaningful effect on plasma cortisol. There were no deaths or serious adverse events, and all treatment-emergent adverse events in subjects receiving baxdrostat were mild in severity.



Key Study Outcomes

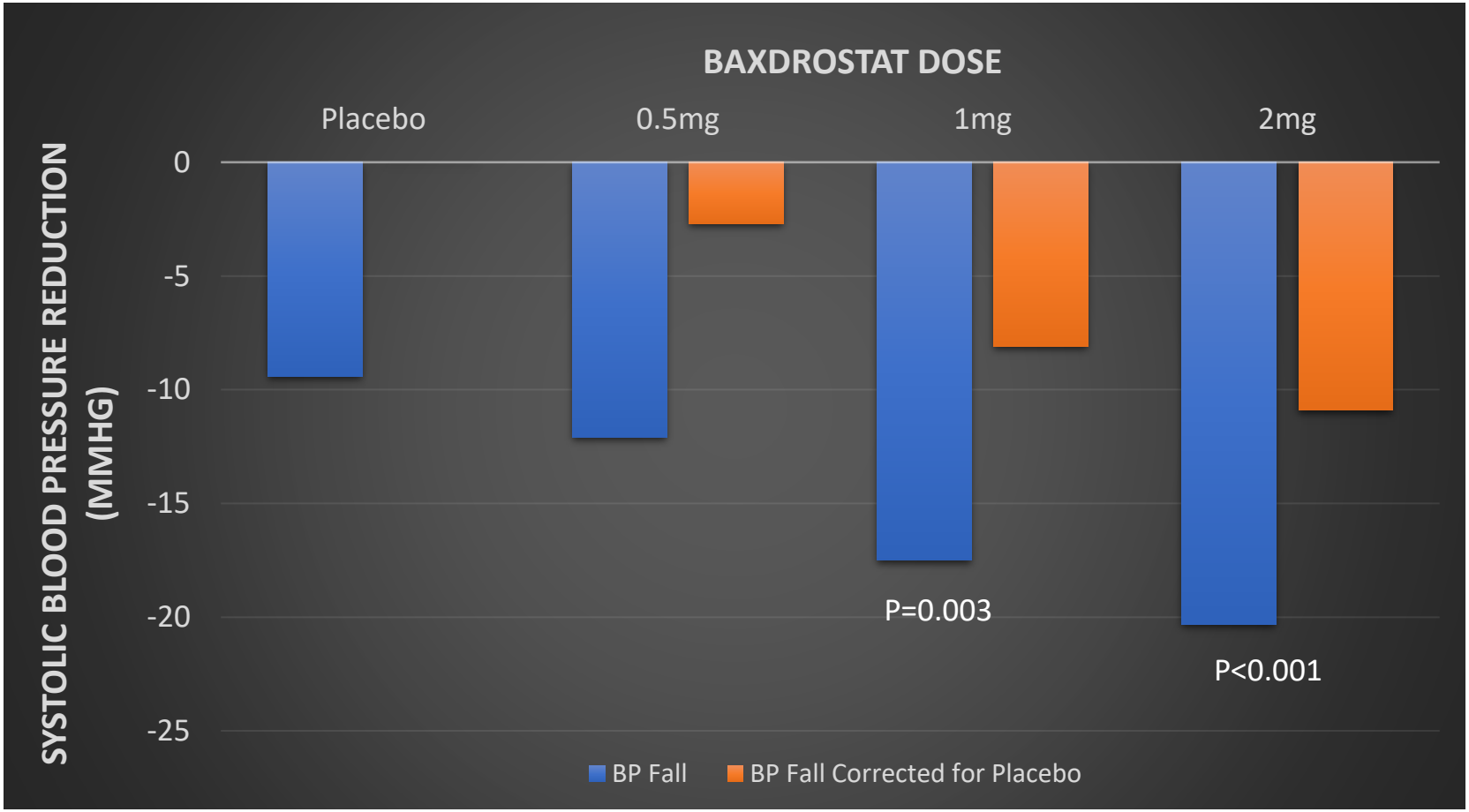
- Plasma levels of baxdrostat increase proportionally with ascending doses
- Baxdrostat reduces plasma aldosterone concentrations in a dose-dependent manner
- Baxdrostat does not have a meaningful effect on plasma total cortisol levels
- Baxdrostat is safe and well tolerated



Hypertension Research; Mason W. Freeman, MD

Phase 2 Trial of Baxdrostat for Treatment-Resistant Hypertension

NEJM November 7, 2022. DOI: 10.1056/NEJMoa2213169



ACE Inhibitors -8mmHg; DHP Ca++ channel blockers -9-13mmHg; HCTZ (50mg) -11mHg

Genetics

Oxford nanopore MinION device

Specifications

Compare products | Download brochure

MinION Mk1C | MinION

Read length

Nanopores read the length of DNA or RNA presented to them — from short to ultra-long (longest >4 Mb)

Suitable applications include

- Whole genomes/exomes
- Metagenomics
- Targeted sequencing
- Whole transcriptome (cDNA)
- Smaller transcriptomes (direct RNA)
- Multiplexing for smaller samples

Dimensions

- Size: W 140 mm, H 30 mm, D114
- Weight: 450 g

High yields

Up to 50 Gb per MinION Flow Cell / 2.8 Gb per Flongle Flow Cell*

* Theoretical max output when system is run for 72 hours (or 16 hours for Flongle) at 420 bases / second. Outputs may vary according to library type, run conditions, etc.

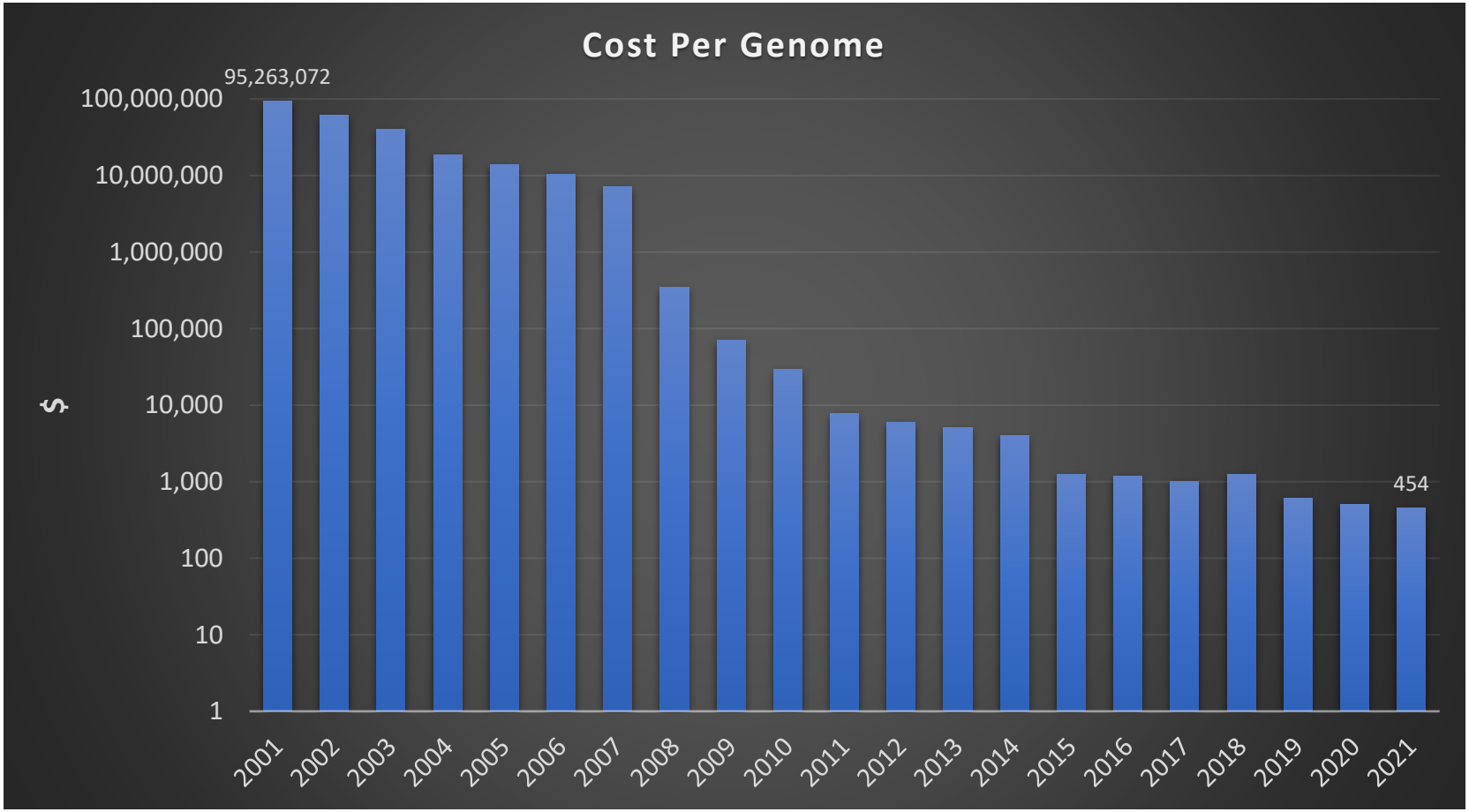
All-in-one device

- High-resolution touchscreen — simple device control and visualisation of results
- Complete connectivity — LAN and Wi-Fi enabled
- Integrated, powerful compute — pre-installed basecalling and analysis software

Low cost

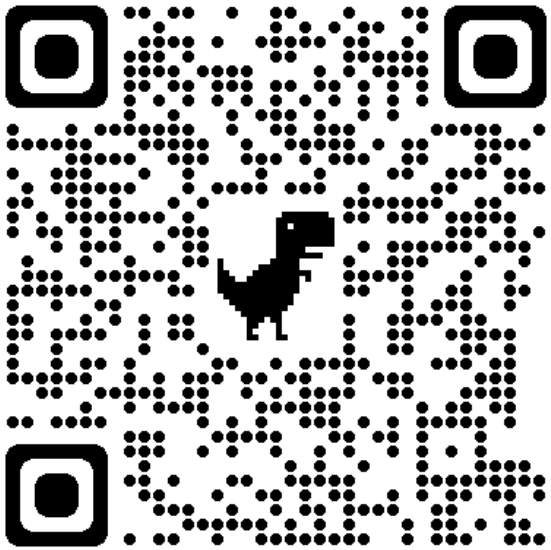
- Starter Packs from $4,900, including consumables
- Compatible with Flongle Flow Cells for smaller tests and analyses
- Multiplexing kits for higher sample throughput

Sequencing Costs



Genetics is Coming to GP Practices

- Pharmacogenomics
  - Precision medicine
  - The study of how your genetics affects your response to drugs
- Mainstreaming
  - Direct requesting of appropriate genomic testing (using the “National Genomic Test Directory”
  - https://www.england.nhs.uk/publication/national-genomic-test-directories/



Where is it coming first?

- Familial hypercholesterolaemia
  - Wales already has a world-leading service

- Pilot pharmacogenomic testing for patients taking:
  - Statins
  - Antidepressants
  - PPIs
  - Clopidogrel
  - The Pharmaceutical Journal, October 2022, Vol 309, No 7966. DOI:10.1211/PJ.2022.1.161533


THANK
YOU


Questions?