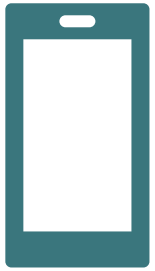
Experience of large pragmatic trials



Isla Mackenzie

Professor of Cardiovascular Medicine

Division of Cardiovascular Medicine, School of Medicine, University of Dundee, Dundee, UK

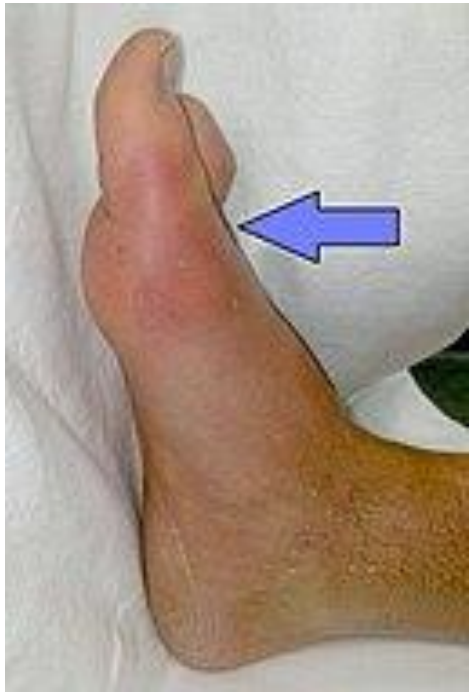
ENCePP Plenary, Amsterdam, 1st December 2025

Three examples of UK trials with pragmatic elements

- FAST (Febuxostat versus Allopurinol Streamlined Trial)
  - Funded by Menarini, sponsored by University of Dundee
- ALL-HEART (Allopurinol and cardiovascular outcomes in patients with ischaemic heart disease)
  - Funded by NIHR HTA, sponsored by University of Dundee/NHS Tayside
- TIME (Treament in the Morning vs the Evening)
  - Funded by British Heart Foundation with support from British and Irish Hypertension Society, sponsored by University of Dundee

Febuxostat versus Allopurinol Streamlined Trial (FAST)

- Cardiovascular safety of febuxostat *vs* allopurinol in patients with symptomatic hyperuricaemia / gout and at least one additional cardiovascular risk factor
- Post-licensing study - EMA
- UK, Denmark, Sweden
- 6,128 randomised participants
- **Research pharmacy**
  - **Direct to participant IMP supply (except Sweden – via local pharmacy)**
- **Record-linkage for events (hospitalisations and deaths)**
- Primary endpoint composite of non-fatal MI, non-fatal stroke or CV death



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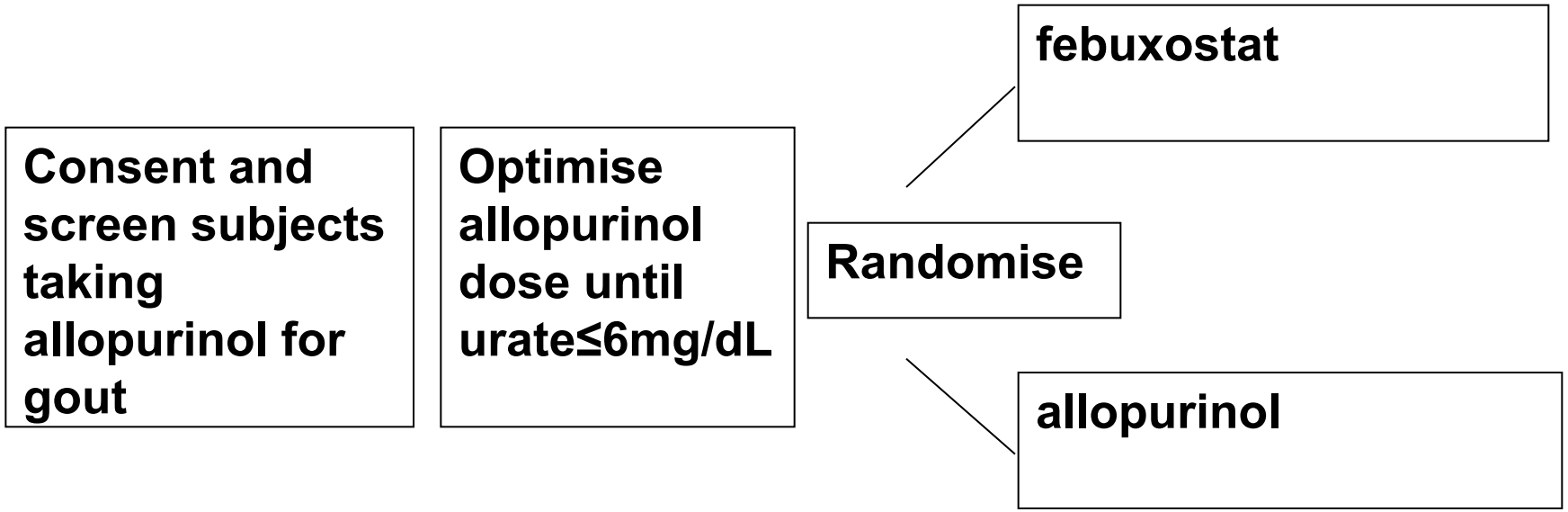
Mackenzie IS et al, Lancet 2020; 396:1745-57.

A.MENARINI

FAST

FAST



Long-term cardiovascular safety of febuxostat compared with allopurinol in patients with gout (FAST): a multicentre, prospective, randomised, open-label, non-inferiority trial

*Isla S Mackenzie, Ian Ford, George Nuki, Jesper Hallas, Christopher J Hawkey, John Webster, Stuart H Ralston, Matthew Walters, Michele Robertson, Raffaele De Caterina, Evelyn Findlay, Fernando Perez-Ruiz, John J V McMurray, Thomas M MacDonald, on behalf of the FAST Study Group**

Interpretation Febuxostat is non-inferior to allopurinol therapy with respect to the primary cardiovascular endpoint, and its long-term use is not associated with an increased risk of death or serious adverse events compared with allopurinol.

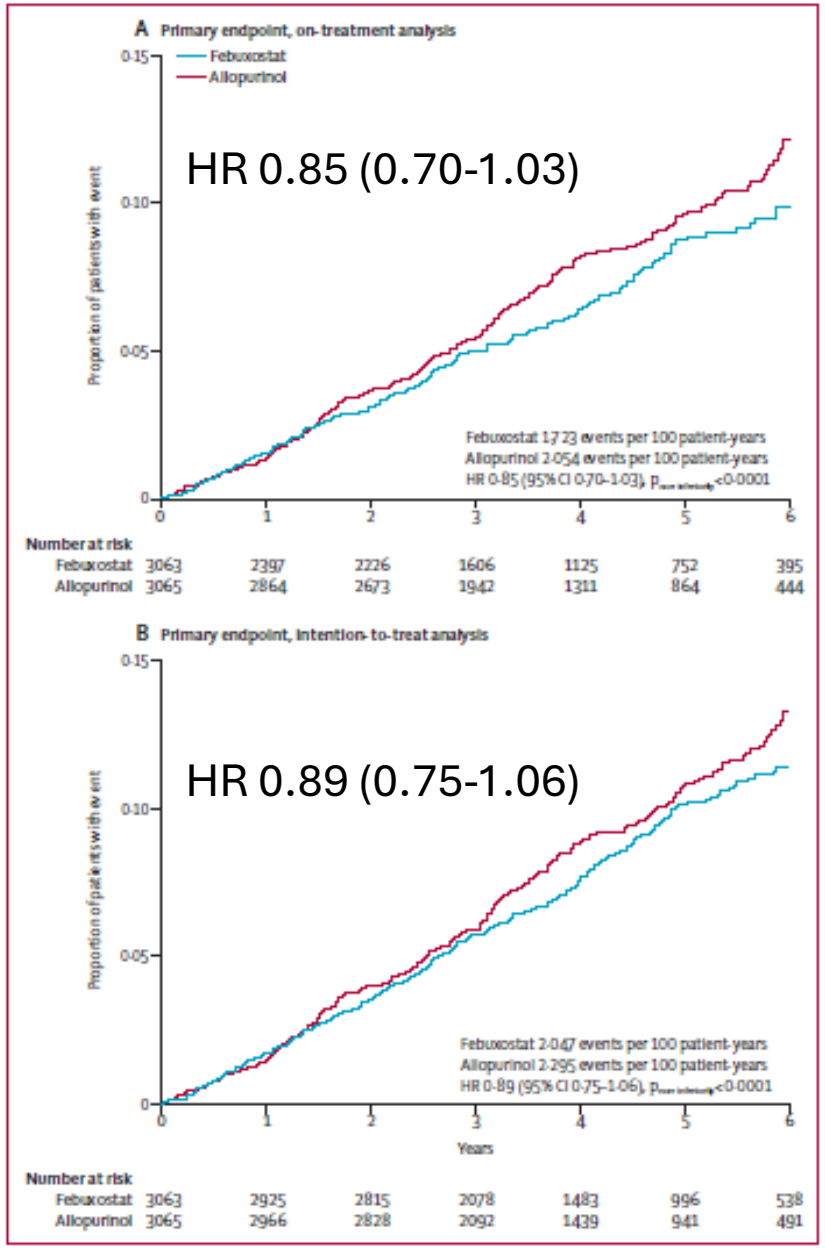


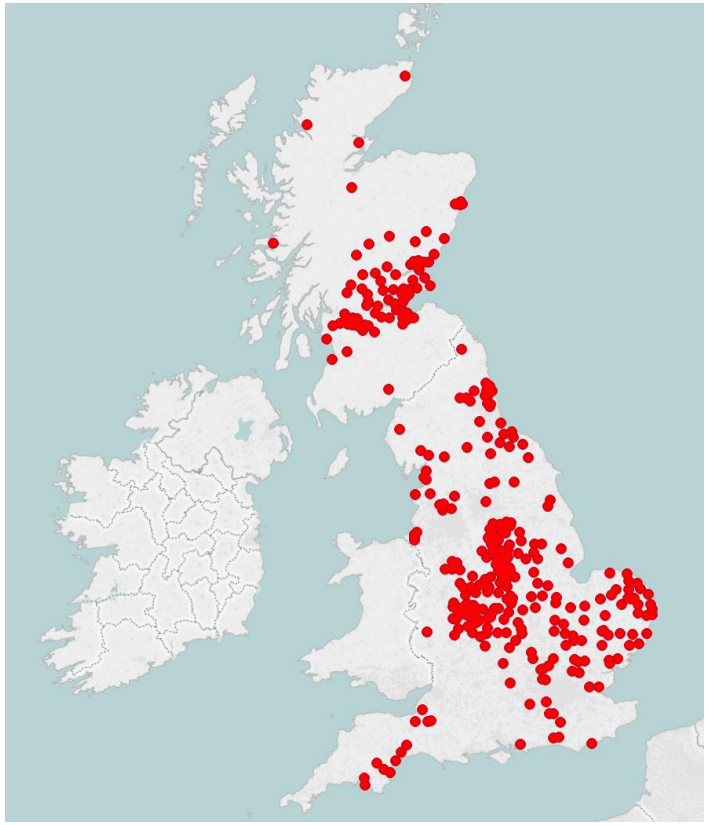
Figure 2: **Cumulative incidence functions for the primary composite endpoint (n=6128)**
The primary composite endpoint consisted of cardiovascular death, hospitalisation for non-fatal myocardial infarction or biomarker-positive acute coronary syndrome, or non-fatal stroke. Analyses were adjusted for the competing risk of deaths not included in the endpoint. (A) On-treatment analysis. (B) Intention-to-treat analysis. HR=hazard ratio.

Mackenzie IS et al, Lancet 2020; 396:1745-57.

ALL-HEART study

- Does allopurinol improve cardiovascular outcomes in patients with ischaemic heart disease?
- 5,937 patients with IHD randomised to:
  Allopurinol added to usual care vs Usual care
- PROBE design
- Primary endpoint
  - composite outcome of MI, stroke or cardiovascular death
- **Remote follow-up**
- **Record-linkage data Public Health Scotland and NHS Digital (England) for hospitalisations and deaths**

424 primary care practices



FUNDED BY
NIHR | National Institute for Health and Care Research

CI: Isla Mackenzie

Mackenzie IS et al, Lancet 2022; 400:1195-205.

Recruitment: Feb 2014 – Sept 2017

424 UK GP practices

GP Practice search:
- ≥60 years
- IHD
- No gout
- Not on urate lowering therapy
- eGFR ≥ 30ml/min/1.73m^2

Patient visit:
(i) Consent
(ii) Screening
Inclusions/Exclusions
Questionnaires

Screening bloods*

(iii) Randomisation (1:1)
Allopurinol **or** Usual care

Allopurinol arm: dose determined by screening eGFR

eGFR ≥60
100mg for 2 weeks
300mg for 2 weeks
Then 600mg daily

eGFR 30-59
100mg for 2 weeks
Then 300mg daily

Bloods* at 6 weeks

Usual care arm

Annual follow-up questionnaires:
- **Gout flares**
- **Skin rash**
- **Adverse events**
- **Compliance**
- **Quality of life**
  - EQ-5D
  - Seattle Angina Questionnaire
- **Health service usage**

Record linkage for hospitalisations and deaths

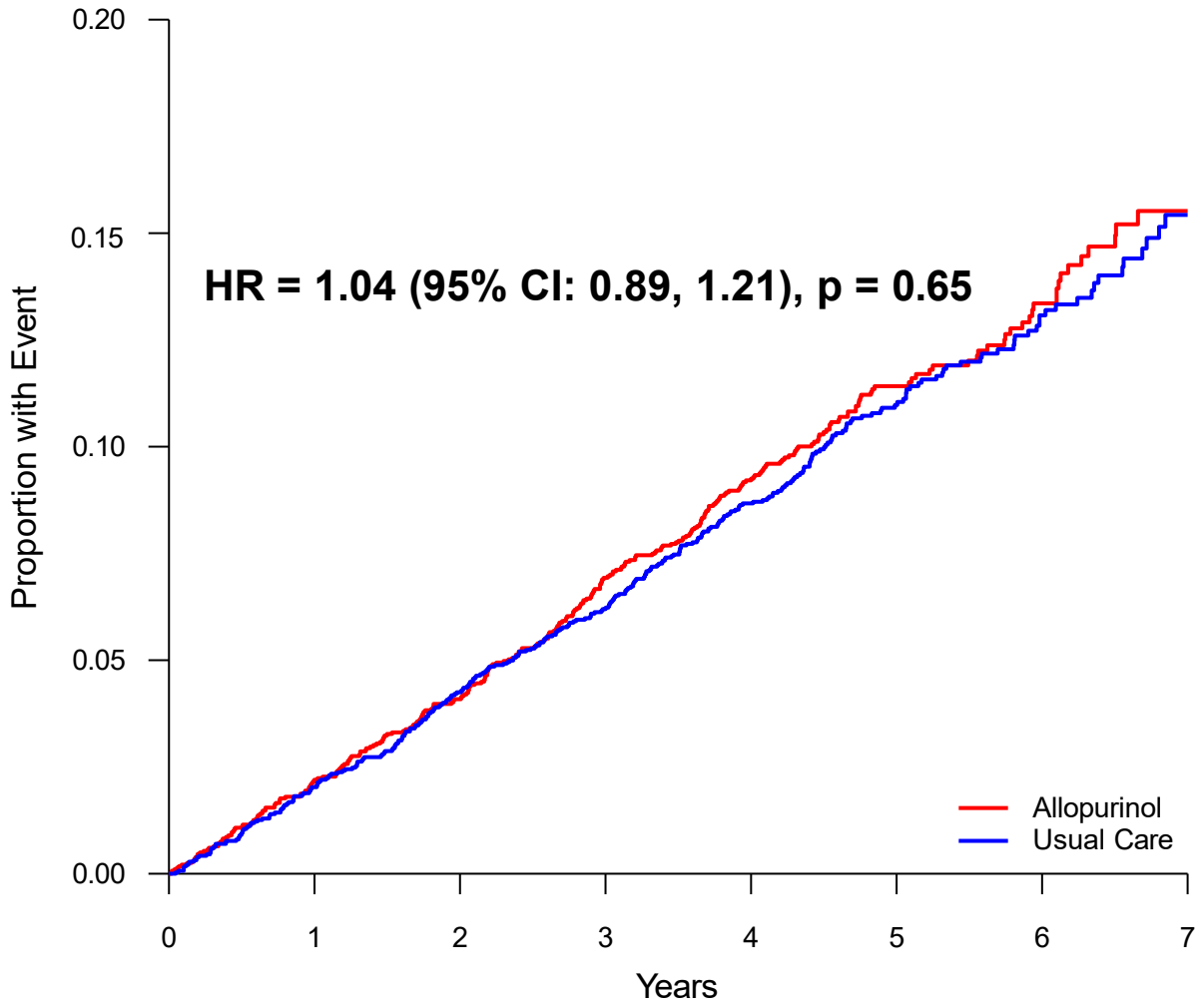
Follow-up: Ended 30 Sept 2021

***Bloods: electrolytes, urea, creatinine (eGFR), FBC, urate**

Results

- 5721 participants in the mITT analysis
- Average follow-up time was 4·8 years
- 639 first primary endpoints occurred (target 631)

Primary outcome: composite of non-fatal MI, non-fatal stroke or cardiovascular death

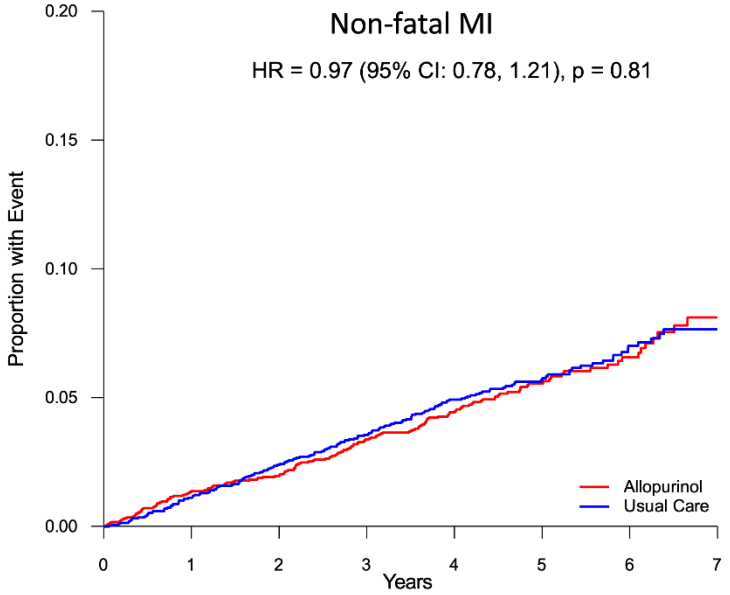


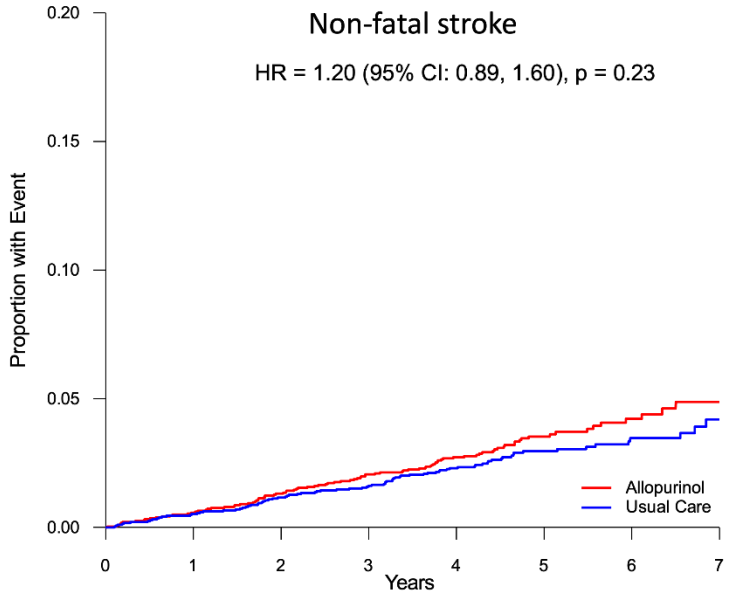
Numbers at Risk

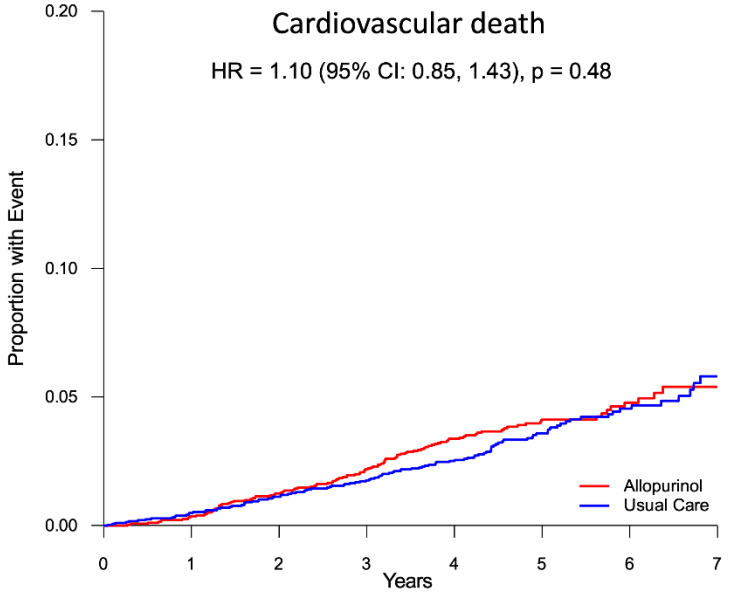
Allopurinol	2853	2681	2556	2419	2148	1140	502	151
Usual Care	2868	2790	2676	2579	2367	1280	655	210

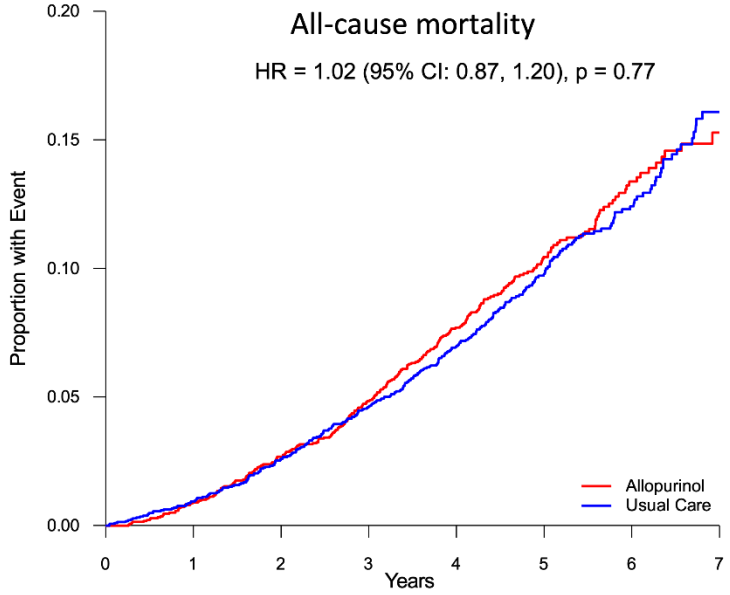
Mackenzie IS et al, Lancet 2022; 400:1195-205.

Secondary outcomes





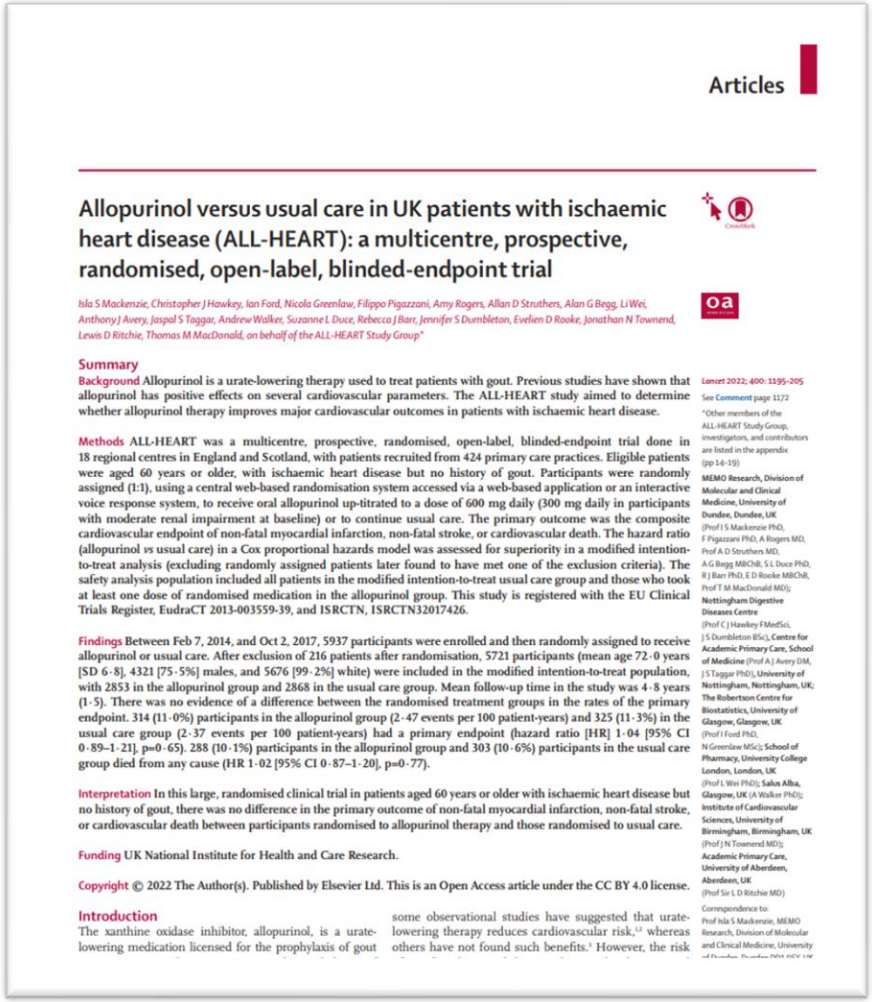




Mackenzie IS et al, Lancet 2022; 400:1195-

Conclusions from the ALL-HEART study

- Allopurinol therapy added to usual care did not improve CV outcomes in patients aged over 60 years with IHD (but no gout)
- No safety issues identified with the long term use of allopurinol



Articles

Allopurinol versus usual care in UK patients with ischaemic heart disease (ALL-HEART): a multicentre, prospective, randomised, open-label, blinded-endpoint trial

*Isla S Mackenzie, Christopher J Hawkey, Ian Ford, Nicola Greenlaw, Filippo Pigazzani, Amy Rogers, Allan D Struthers, Alan G Begg, Li Wei, Anthony J Avery, Jaspal S Taggar, Andrew Walker, Suzanne L Duce, Rebecca J Barr, Jennifer S Dumbleton, Evelien D Rooke, Jonathan N Townend, Lewis D Ritchie, Thomas M MacDonald, on behalf of the ALL-HEART Study Group**

Summary

Background Allopurinol is a urate-lowering therapy used to treat patients with gout. Previous studies have shown that allopurinol has positive effects on several cardiovascular parameters. The ALL-HEART study aimed to determine whether allopurinol therapy improves major cardiovascular outcomes in patients with ischaemic heart disease.

Methods ALL-HEART was a multicentre, prospective, randomised, open-label, blinded-endpoint trial done in 18 regional centres in England and Scotland, with patients recruited from 424 primary care practices. Eligible patients were aged 60 years or older, with ischaemic heart disease but no history of gout. Participants were randomly assigned (1:1), using a central web-based randomisation system accessed via a web-based application or an interactive voice response system, to receive oral allopurinol up-titrated to a dose of 600 mg daily (300 mg daily in participants with moderate renal impairment at baseline) or to continue usual care. The primary outcome was the composite cardiovascular endpoint of non-fatal myocardial infarction, non-fatal stroke, or cardiovascular death. The hazard ratio (allopurinol *vs* usual care) in a Cox proportional hazards model was assessed for superiority in a modified intention-to-treat analysis (excluding randomly assigned patients later found to have met one of the exclusion criteria). The safety analysis population included all patients in the modified intention-to-treat usual care group and those who took at least one dose of randomised medication in the allopurinol group. This study is registered with the EU Clinical Trials Register, EudraCT 2013-003559-39, and ISRCTN, ISRCTN32017426.

Findings Between Feb 7, 2014, and Oct 2, 2017, 5937 participants were enrolled and then randomly assigned to receive allopurinol or usual care. After exclusion of 216 patients after randomisation, 5721 participants (mean age 72·0 years [SD 6·8], 4321 [75·5%] males, and 5676 [99·2%] white) were included in the modified intention-to-treat population, with 2853 in the allopurinol group and 2868 in the usual care group. Mean follow-up time in the study was 4·8 years (1·5). There was no evidence of a difference between the randomised treatment groups in the rates of the primary endpoint. 314 (11·0%) participants in the allopurinol group (2·47 events per 100 patient-years) and 325 (11·3%) in the usual care group (2·37 events per 100 patient-years) had a primary endpoint (hazard ratio [HR] 1·04 [95% CI 0·89–1·21], p=0·65). 288 (10·1%) participants in the allopurinol group and 303 (10·6%) participants in the usual care group died from any cause (HR 1·02 [95% CI 0·87–1·20], p=0·77).

Interpretation In this large, randomised clinical trial in patients aged 60 years or older with ischaemic heart disease but no history of gout, there was no difference in the primary outcome of non-fatal myocardial infarction, non-fatal stroke, or cardiovascular death between participants randomised to allopurinol therapy and those randomised to usual care.

Funding UK National Institute for Health and Care Research.

Introduction

The xanthine oxidase inhibitor, allopurinol, is a urate-lowering medication licensed for the prophylaxis of gout some observational studies have suggested that urate-lowering therapy reduces cardiovascular risk,[1,2] whereas others have not found such benefits.[3] However, the risk

Lancet 2022; 400: 1195–205

See Comment page 1172

*Other members of the ALL-HEART Study Group, investigators, and contributors are listed in the appendix (pp 14–19)

MEMO Research, Division of Molecular and Clinical Medicine, University of Dundee, Dundee, UK (Prof I S Mackenzie PhD, F Pigazzani PhD, A Rogers MD, Prof A D Struthers MD, A G Begg MBChB, S L Duce PhD, R J Barr PhD, E D Rooke MBChB, Prof T M MacDonald MD); Nottingham Digestive Diseases Centre (Prof C J Hawkey FMedSci, J S Dumbleton BSc), Centre for Academic Primary Care, School of Medicine (Prof A J Avery DM, J S Taggar PhD), University of Nottingham, Nottingham, UK; The Robertson Centre for Biostatistics, University of Glasgow, Glasgow, UK (Prof I Ford PhD, N Greenlaw MSc); School of Pharmacy, University College London, London, UK (Prof L Wei PhD); Salus Alba, Glasgow, UK (A Walker PhD); Institute of Cardiovascular Sciences, University of Birmingham, Birmingham, UK (Prof J N Townend MD); Academic Primary Care, University of Aberdeen, Aberdeen, UK (Prof Sir L D Ritchie MD)

Correspondence to: Prof Isla S Mackenzie, MEMO Research, Division of Molecular and Clinical Medicine, University

Mackenzie IS et al, Lancet 2022; 400:1195-205.

TIME Study – Treatment in the Morning vs the Evening

- Does antihypertensive therapy taken in the evening result in improved cardiovascular outcomes compared with morning dosing?

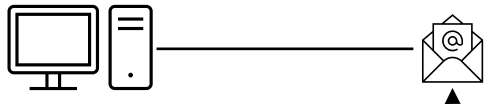
- Funded by: British Heart Foundation

- PROBE design, fully remote trial
- 21,104 randomised participants
- Primary outcome: MI, stroke or vascular death

CI: Tom MacDonald

21,104 participants

www.timestudy.co.uk



Dosing time instructions sent by email

Morning

Usual prescribed BP medications taken at assigned time

Evening

Events of interest:

Heart attack

Stroke

Cardiovascular death

average 4.5 years

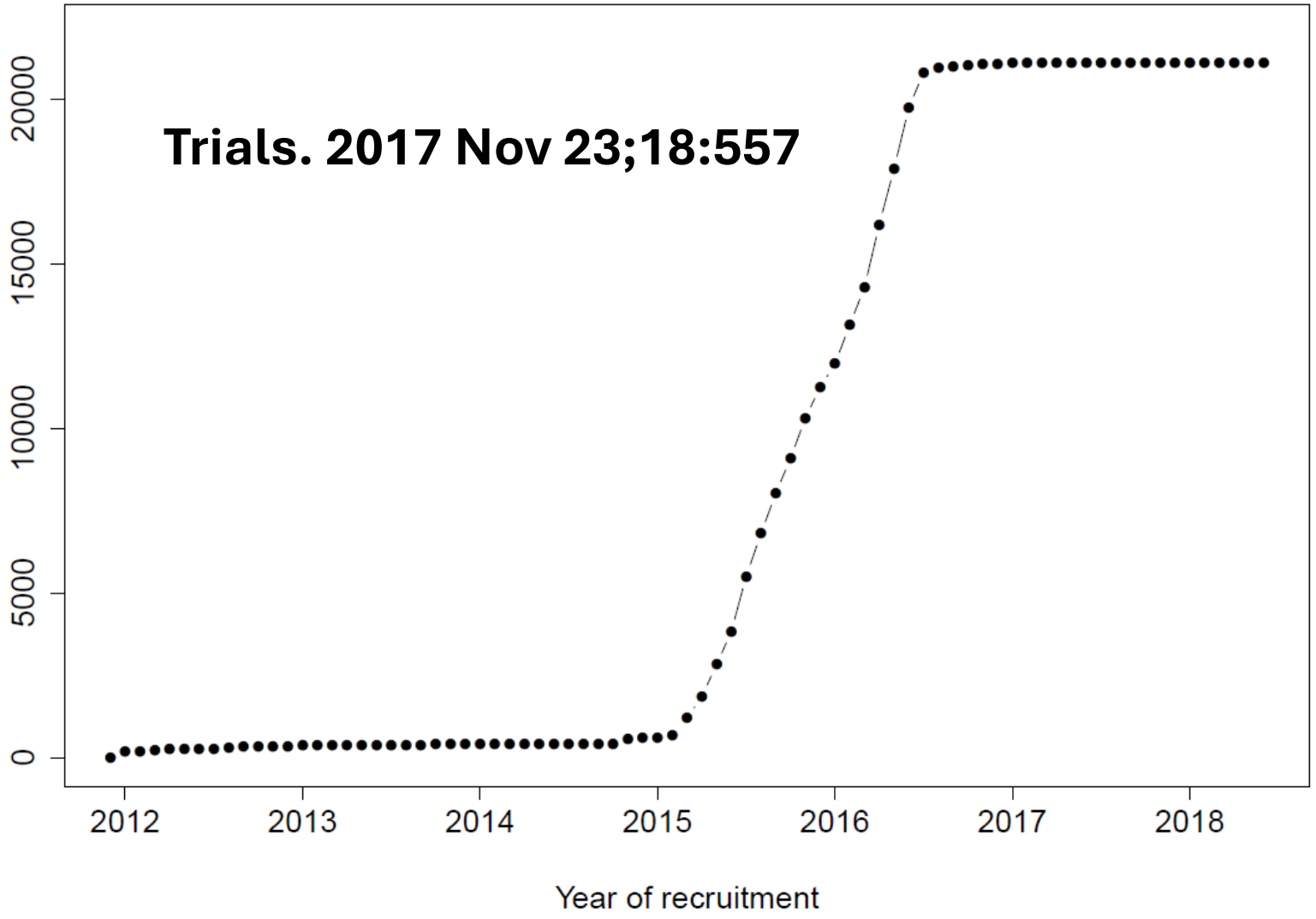
Study entry

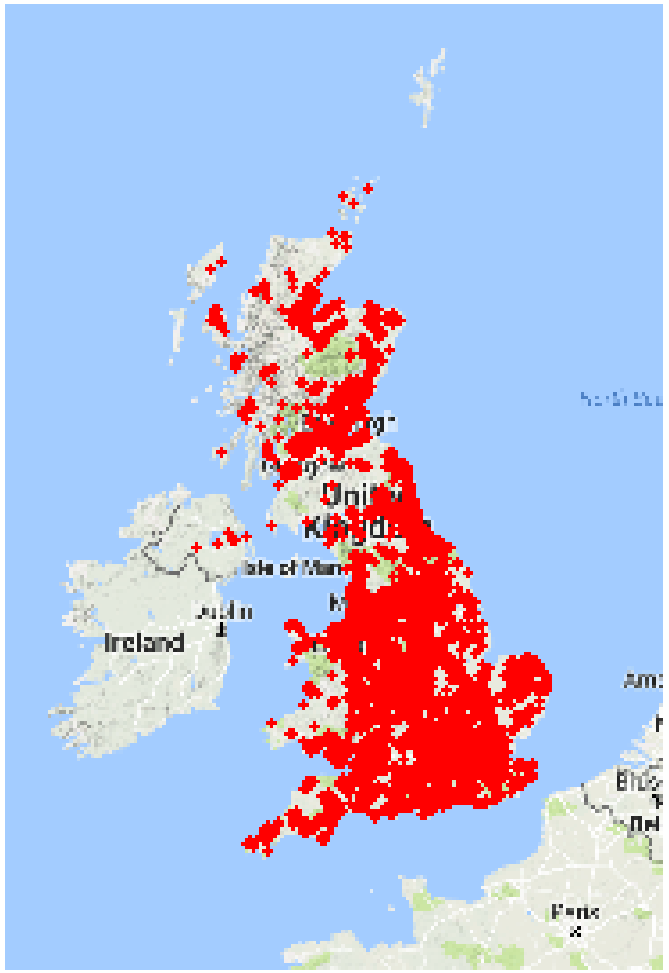
Dosing time assigned at random

Follow-up begins

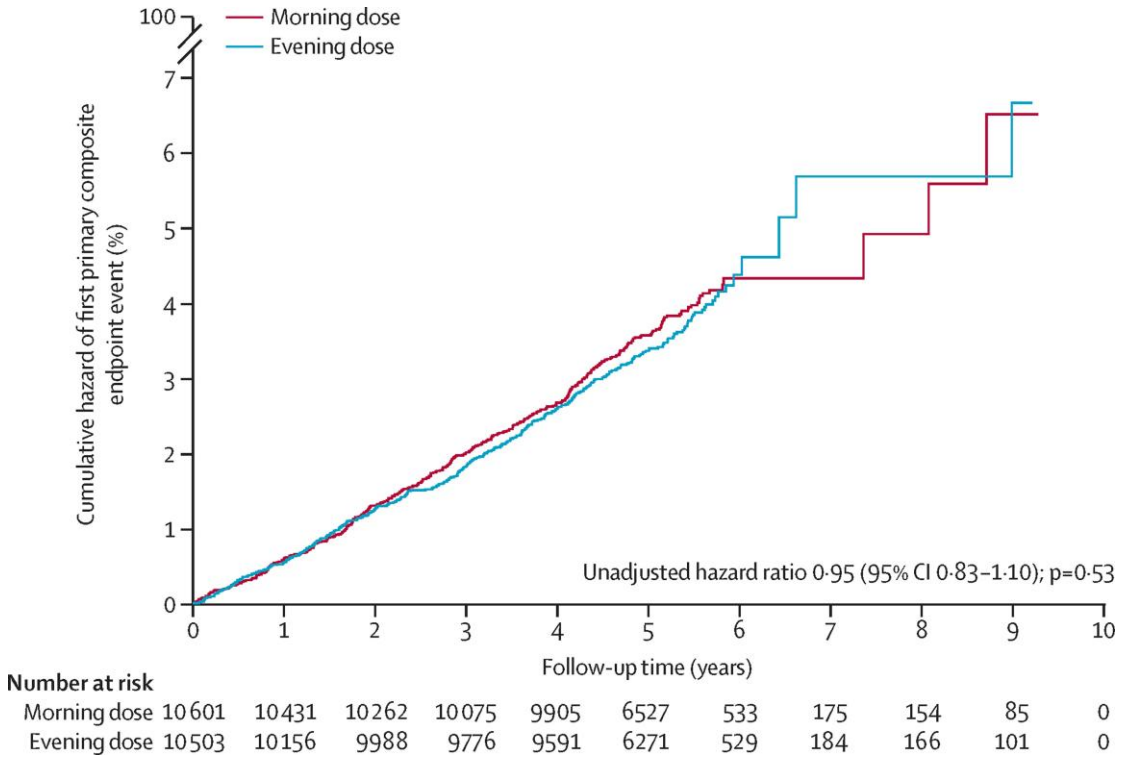
Study end

TIME study cumulative recruitment





Primary outcome: hospitalisation for non-fatal MI, non-fatal stroke or vascular death)

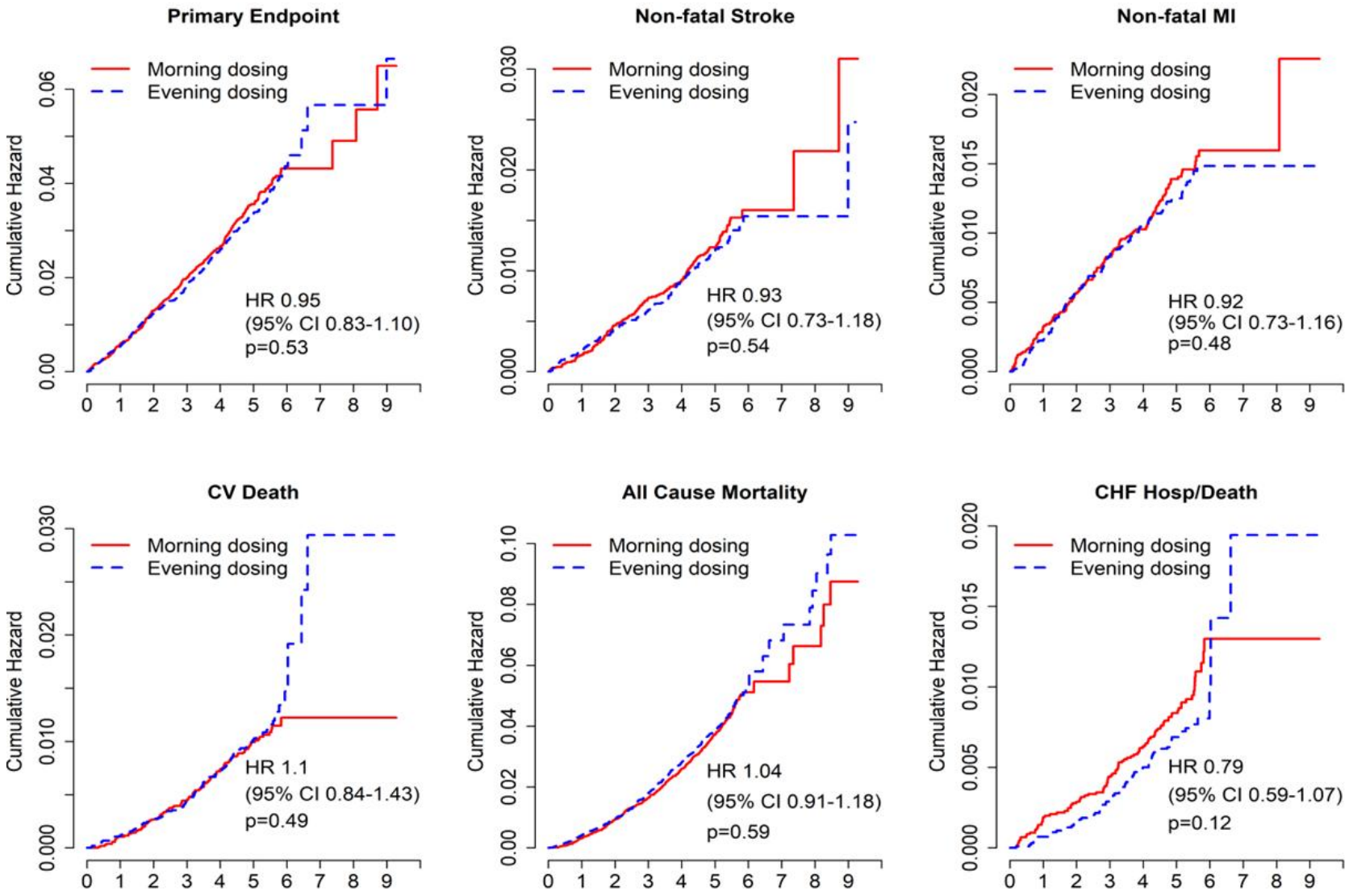


Cardiovascular outcomes in adults with hypertension with evening versus morning dosing of usual antihypertensives in the UK (TIME study): a prospective, randomised, open-label, blinded-endpoint clinical trial

*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**

Mackenzie IS et al, Lancet 2022; 400:1417-25.

Secondary outcomes



Mackenzie IS et al, Lancet 2022; 400:1417-25.

Conclusions of TIME study

- Allocation to evening dosing of usual antihypertensive medication did not improve the primary endpoint of hospitalisation for non-fatal MI, non-fatal stroke or vascular death compared to morning dosing.
- Taking medication in the evening was not harmful.
- Patients can be advised that they may take their antihypertensive medication in either the morning or evening as the timing makes no difference to cardiovascular outcomes.

Mackenzie IS et al, Lancet 2022; 400:1417-25.

THE LANCET

TIME STUDY
Antihypertensive Study

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**

- Mackenzie IS et al, Lancet 2022; 400:1417-25.

ESC European Society of Cardiology

European Heart Journal (2024) **00**, 1–107
https://doi.org/10.1093/eurheartj/ehae178

ESC GUIDELINES

2024 ESC Guidelines for the management of elevated blood pressure and hypertension

Developed by the task force on the management of elevated blood pressure and hypertension of the European Society of Cardiology (ESC) and *endorsed by the European Society of Endocrinology (ESE) and the European Stroke Organisation (ESO)*

8.3.6. Timing of blood pressure-lowering drug treatment

Current evidence does not show benefit of diurnal timing of BP-lowering drug administration on major CVD outcomes.[512] It is important that medication is taken at the most convenient time of day to improve adherence. Patients should also be encouraged to take medications at the same time each day and in a consistent setting, to help ensure adherence.[246,513]

Conclusions

- FAST, ALL-HEART, TIME
  - Three large pragmatic, decentralised/hybrid trials
  - Participants largely recruited from and followed up within their usual healthcare/home environment
- All successfully completed but many learning points along the way
- Simplicity and pragmatism important for success and generalisability of trials