Tom MacDonald, Chris Hawkey, Ian Ford, John McMurray, James Scheiman, Jesper Hallas, Evelyn Findlay, Rick E Grobbee, Richard Hobbs, Stuart Ralston, David Reid, Matthew Walters, John Webster, Frank Ruschitzka, Lewis Ritchie, Susana Perez-Gutthann, Eugene Connolly, Nicola Greenlaw, Adam Wilson, Li Wei,
Isla S Mackenzie
On behalf of SCOT investigators

The Standard Care versus Celecoxib Outcome Trial

Declarations of interest

University of Dundee was the study sponsor.

Funding was an investigator initiated research grant from Pfizer.

TMM has provided consultancy on NSAIDs to Novartis, Pfizer, NiCox & Astra Zeneca

Background

- Selective cyclooxygenase-2 inhibitors (COX-2) and non-selective non-steroidal anti-inflammatory drugs (nsNSAIDs) have been associated with adverse cardiovascular effects.
- SCOT compared the cardiovascular safety of celecoxib with nsNSAID therapy in the setting of European healthcare systems.
- SCOT was initially an EMA commitment.

Method: Patients

- Aged ≥ 60 years with osteoarthritis or rheumatoid arthritis
- Free from established cardiovascular disease
- Taking chronic prescribed nsNSAIDs in primary care

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Pragmatic Trial

- Search Primary Care Practices
- Invite all suitable subjects
- Randomise eligible
- GPs prescribed treatment
- Usual care thereafter
- Follow up by Record-Linkage
  - Hospitalisations & Deaths

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End Points

- **Primary**
  - **Hospitalisation for non-fatal MI, non-fatal stroke or cardiovascular death**
- **Main Secondary**
  - **Hospitalisation or death from ulcer related upper gastrointestinal complications (bleeding, perforation or obstruction)**
- **Other Secondary**
  - **Heart failure, mortality, renal failure, critical limb ischaemia; pulmonary embolism.**

Power

- Powered for non-inferiority to exclude 40% increase in CV events with celecoxib v nsNSAIDs
- Required 277 events on treatment

End Point Detection & Adjudication

- By Record-Linkage to computerised hospitalisation data & deaths and/or Reported by investigators
- Original hospital & GP case records retrieved copied & abstracted
- Independent end point committees

Committees

- **Cardiovascular Endpoint Committee:**
  - **John McMurray (Chair), Pardeep Jhund, Mark Petrie, Michael MacDonald.**
- **Gastrointestinal Endpoint Committee:**
  - **James Scheiman (Chair), John Dillon, Jane Moeller, Angel Lanas.**
- **Independent Data Monitoring Committee:**
  - **Kim Fox (Chair), Gordon Murray, Frank Murray.**

Results

- >9,400 patients screened
- 7,297 patients randomised
- Mean FU ~ 3.2 years (max 6.3)
- 9 regional centers
- 706 primary care practices
- UK, Denmark & The Netherlands

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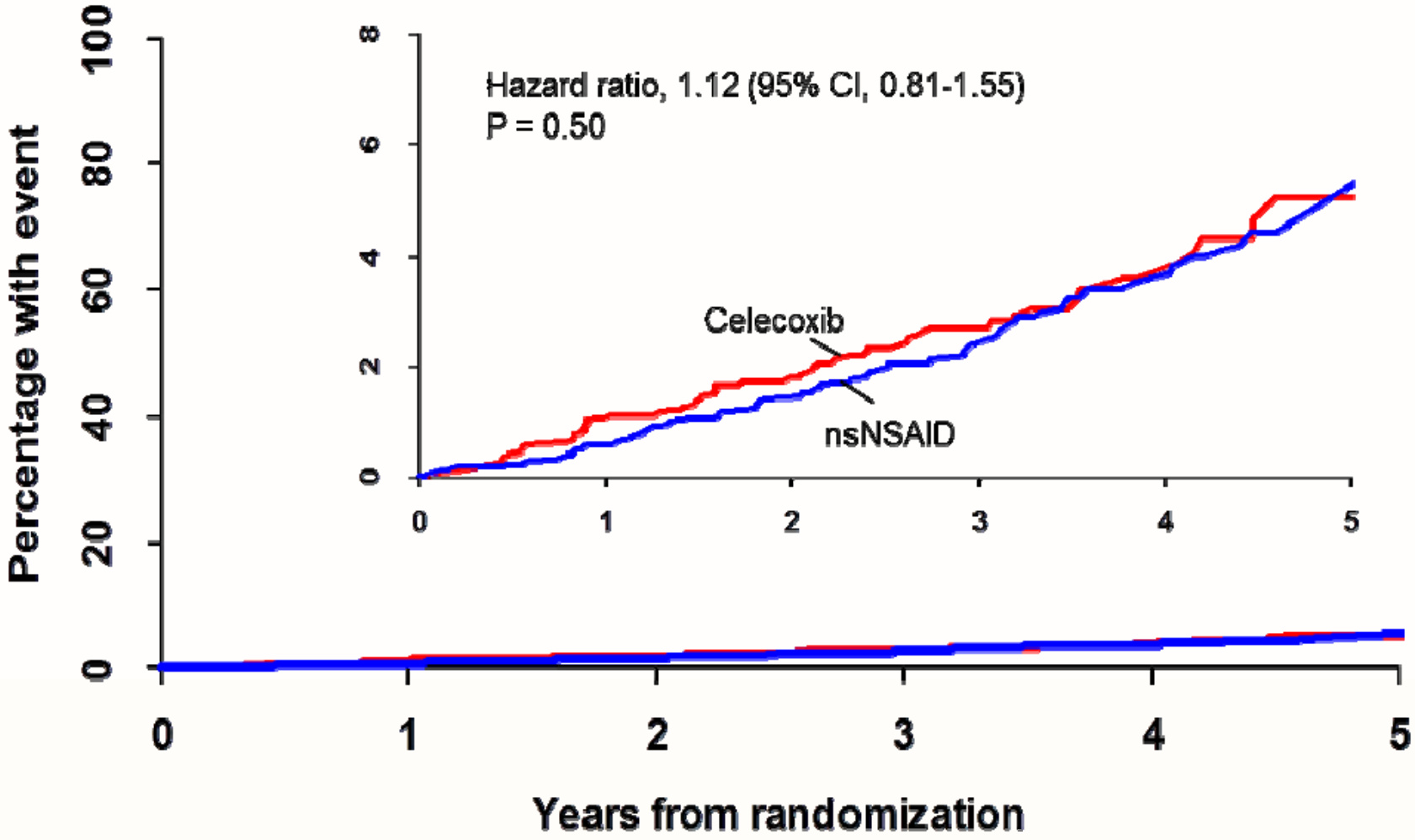
Baseline Characteristics

	Celecoxib	nsNSAIDs
Age	68.8y	68.2y
% Male	41.9%	39.2%
BMI	29.2%	29.8%
Current smoker	15.0%	16.0%
Diabetes	8.3%	7.8%
High BP	44.8%	44.0%
High Cholesterol	34.8%	33.2%
Statin Rx	21.1%	20.5%
Aspirin Rx	11.5%	11.9%
Ulcer Healing Rx	38.4%	37.2%
Peptic Ulcer History	7.0%	6.5%
Diclofenac	38.7%	38.7%
Ibuprofen	31.5%	31.6%

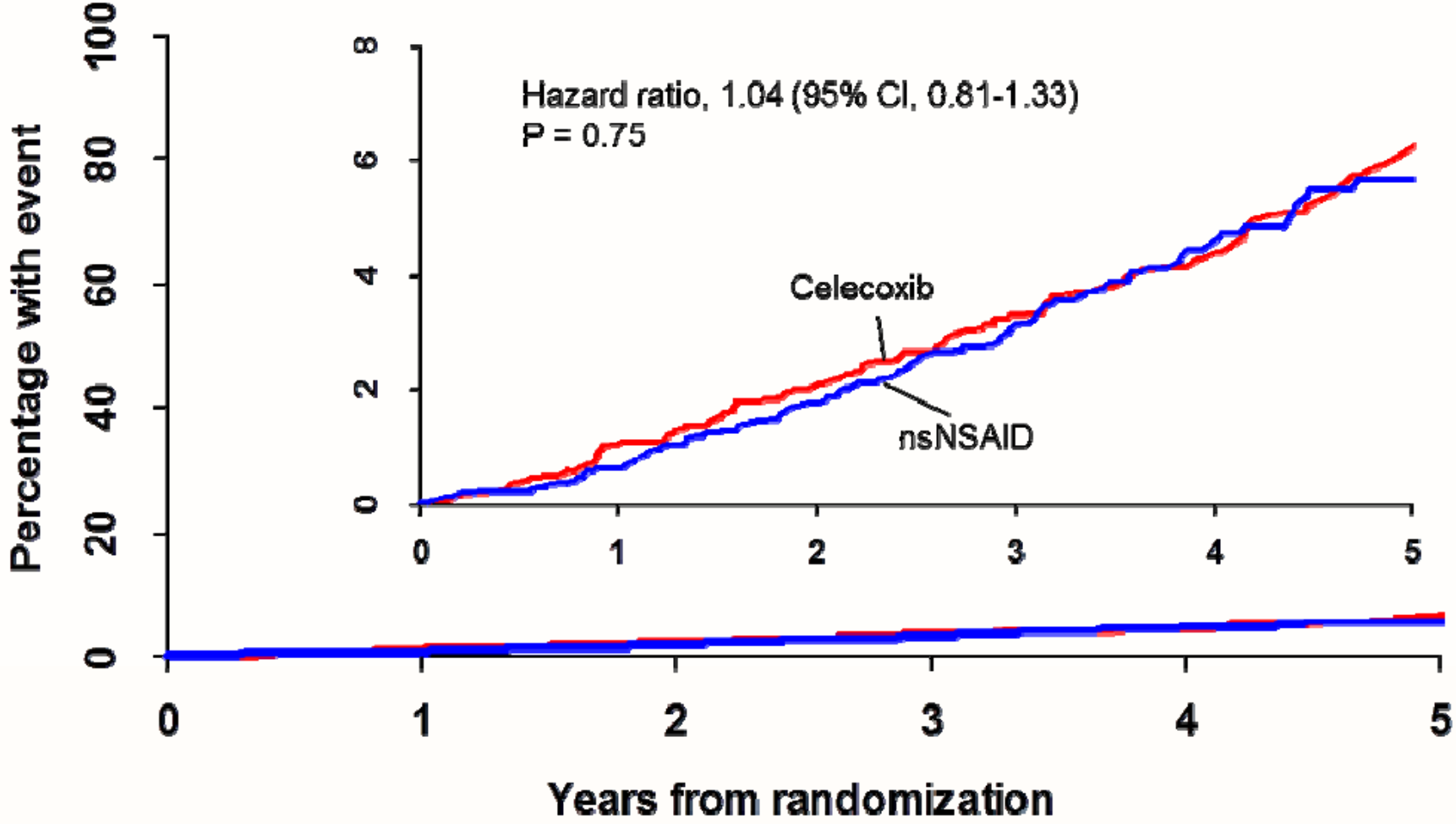
Adjudicated event Rates

- On treatment primary event rate:
  - 0.9 per 100 patient years
- Intention to Treat primary event rate:
  - 1.1 per 100 patient years
- On treatment Ulcer-related UGI Complications
  - 12 events
- ITT Ulcer-related UGI Complications
  - 15 events

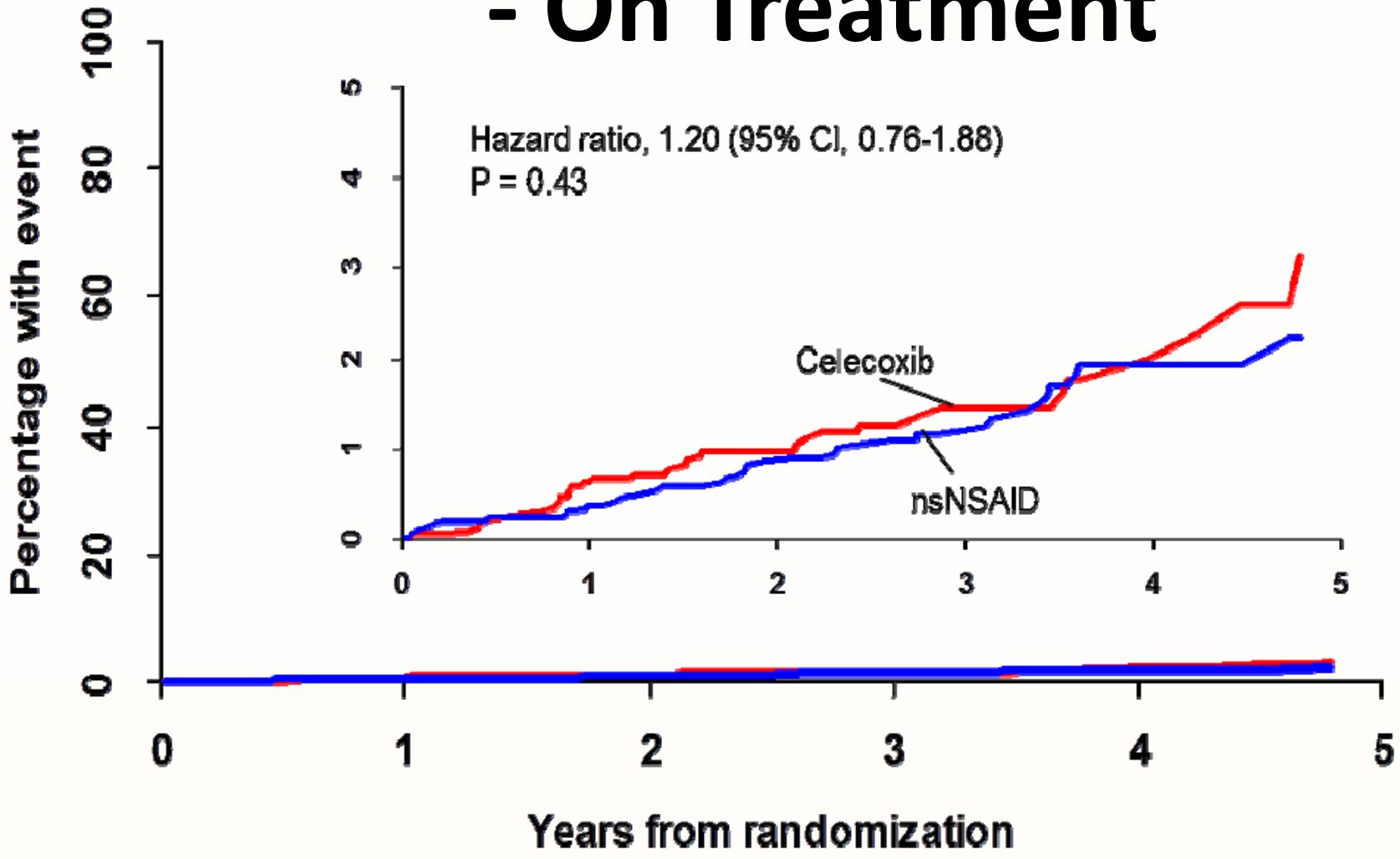
Primary Composite End Point - On Treatment



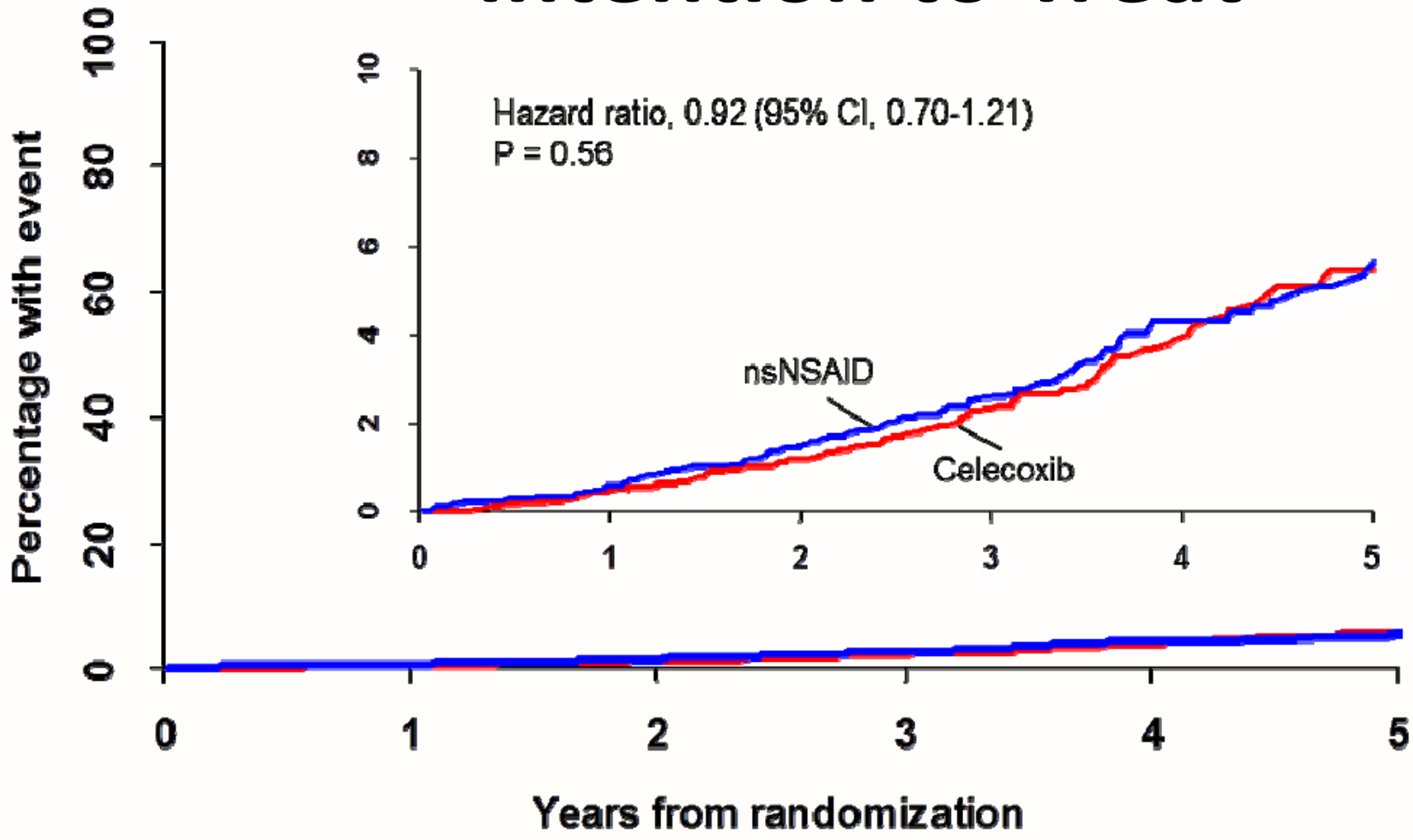
Primary Composite Endpoint - Intention to Treat



All-Cause Mortality - On Treatment

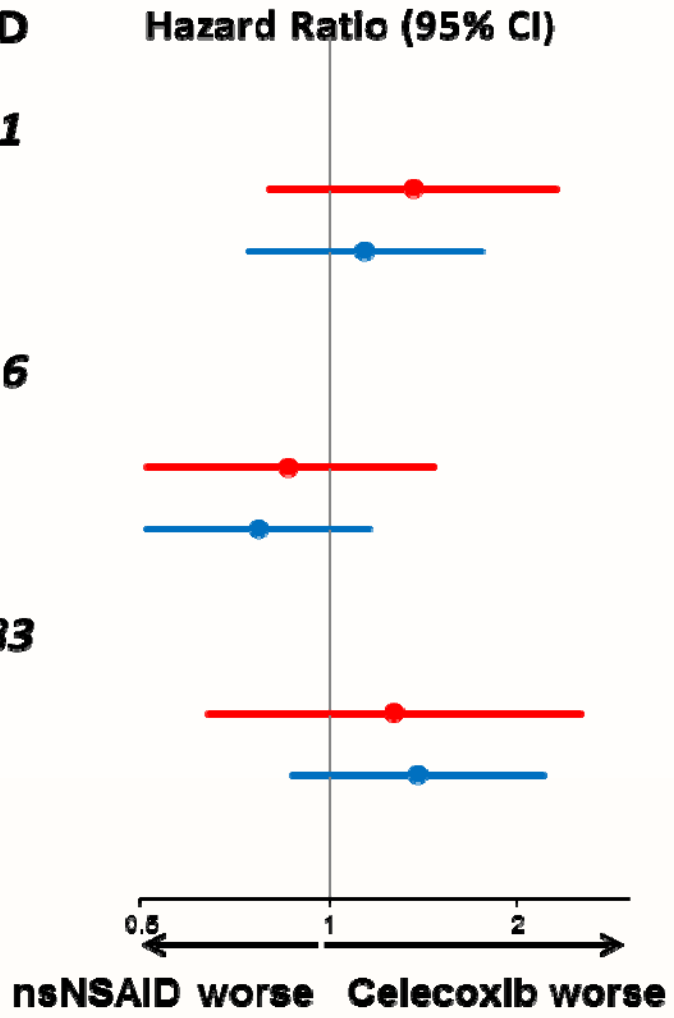


All-Cause Mortality - Intention to Treat



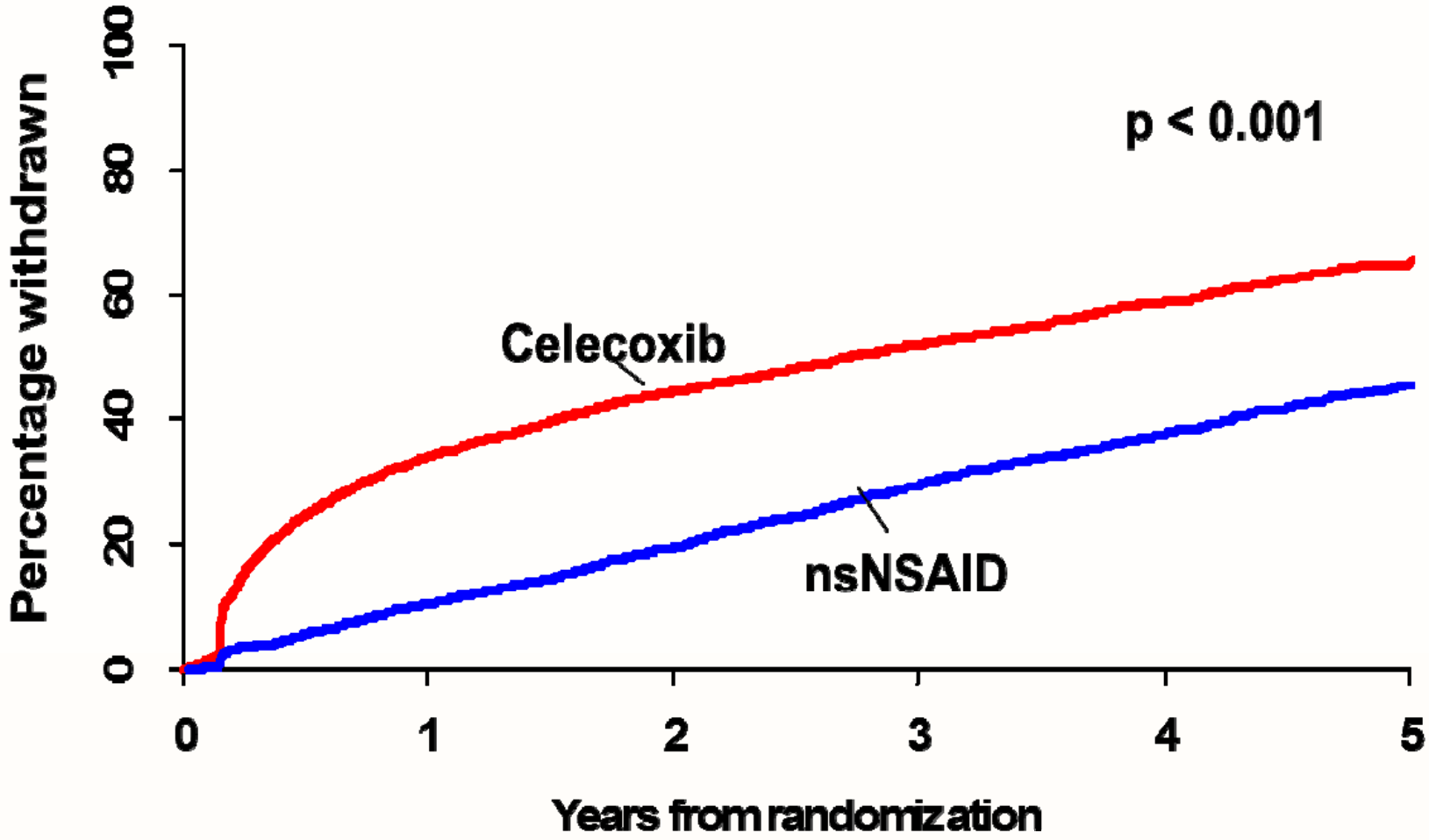
Primary Endpoint by Baseline NSAID Subgroups

Baseline NSAID	Celecoxib	nsNSAID
Ibuprofen	*1149*	*1151*
On-Treatment		
Intention-to-treat		
Diclofenac	*1410*	*1416*
On-Treatment		
Intention-to-treat		
Other nsNSAID	*1088*	*1083*
On-Treatment		
Intention-to-treat		



Withdrawal from randomized treatment group

50.9% withdrew from celecoxib vs 30.2% from any nsNSAID



% Reasons recorded in those withdrawn from randomised Rx

Reason recorded	Celecoxib	nsNSAID
Lack of efficacy	11.2%	3.0%
Switch or stopped	6.6%	8.1%
Adverse Event	8.3%	4.4%
Doctor recommended (non-AE)	4.7%	6.0%
Patient requested	6.0%	2.3%
Not tolerated	3.9%	1.2%
Serious Adverse Event	2.6%	1.9%
Protocol Violation	<0.1%	<0.1%
Other	4.6%	4.4%

Safety Outcomes

- **Serious Adverse Events:**
  - **1155 (31.7%) celecoxib**
  - **1183 (32.4%) nsNSAID**
- **Serious Adverse Reactions:**
  - **190 (5.2%) celecoxib**
  - **213 (5.8%) nsNSAID**
- **Serious gastrointestinal Adverse Reactions**
  - **38 celecoxib**
  - **66 gastrointestinal nsNSAIDs P<0.007**

Safety Outcomes

- **Adverse Reactions:**
  - **804 (22%) celecoxib**
  - **586 (16.1%) nsNSAIDs (p<0.001)**

Summary

In patients with arthritis, without known cardiovascular disease, CV event rates were low and serious ulcer-related complication rates very low, and neither outcome differed significantly between nsNSAIDs and celecoxib

Implications for patient care

- In the study population, nsNSAIDs and celecoxib both appeared acceptably safe.
- In patients who get significant symptomatic relief from these medicines the benefit / risk balance appears positive.