A call for phase 4 studies on comparative effectiveness and safety of medicines

About HSA

Applied sciences

- We serve the administration of justice with the use of forensic medicine, forensic science and analytical chemistry testing.

Blood services

- We secure the nation's blood supply by ensuring a safe and adequate blood supply for public and private hospitals.

Health products regulation

- We regulate health products to meet standards of safety, quality and efficacy.

Agenda

- Enhancing benefit-risk ratio of medicines: a collective goal
- Promoting grant applications for trials focused on comparative effectiveness and safety of medicines
- Key considerations for prospective grant applicants

Why conduct Phase IV trials

- Hold high public health value
- Lack of Asian / local data
- Findings typically have important clinical, regulatory and health economic consequences

Why conduct Phase IV trials

- Important role in identifying real-world safety issues relating to medicines
  - Rofecoxib (NSAID) – cardiovascular events [VIGOR trial, NEJM 2000]
  - Pioglitazone (anti-diabetic) – bladder cancer [PROactive trial, Lancet 2005]
  - Rosiglitazone (anti-diabetic) – cardiovascular events [RECORD trial, Lancet 2009]
  - Febuxostat (lower blood uric acid levels) – cardiovascular events [CARES trial, NEJM 2018]
  - Tofacitinib (rheumatoid arthritis etc) – cancers, cardiovascular events [ORAL Surveillance trial, NEJM 2022]
  - Testosterone replacement – fractures / arrhythmias / AKI [TRAVERSE trial, NEJM 2023]
- Instrumental in detecting beneficial effects of drugs (anti-diabetic agents)
  - SGLT2 inhibitors / GLP1 agonists reduce cardiovascular and renal outcomes
- Useful in clarifying harms of medicines observed in real-world data

Observational data vs RCTs [Digoxin]

European Heart Journal (1994) **15**, 382–388

Is digoxin an independent risk factor for long-term mortality after acute myocardial infarction?

L. KØBER, C. TORP-PEDERSEN, N. GADSBØLL*, P. HILDEBRANDT AND P. F. HØILUND-CARLSEN*

KEY WORDS: Myocardial infarction, digoxin treatment, long-term prognosis.

The safety of treatment with digoxin in patients with acute myocardial infarction (MI) was investigated in 584 hospital survivors of MI. All patients were examined by radionuclide ventriculography, with determination of left ventricular ejection fraction (LVEF), close to the time of discharge. Clinical data were collected on admission. All patients were followed up with regard to death (median 6·2 years, range 3·9–7·8 years).

Patients treated with digoxin (N=172(29%)) were older (median 66 vs 59 years; (P<0·001), had a higher incidence of diabetes (13% vs 7%; P=0·025), and a lower LVEF (0·33 vs 0·49; P<0·001). As expected, clinical heart failure was more frequent among them (84% vs 14%; P<0·001), than in patients not receiving digoxin.

The 1- and 5-year mortality of patients treated with digoxin was 38% and 74% compared to 8% and 26% in patients not receiving digoxin (P<0·001). The increased risk associated with digoxin therapy remained statistically significant when patients were stratified according to the presence or absence of heart failure or atrial fibrillation/flutter during hospitalization, or to LVEF above or below 0·45 at discharge. In a proportional hazard model including age, LVEF, diabetes mellitus, heart failure, atrial fibrillation or flutter, ventricular fibrillation, gender, dose of furosemide at discharge and calcium antagonists and digoxin treatment as covariates, digoxin was independently associated with an increased risk of death (relative risk 1·8 (95% confidence limit 1·2–2·5)). We conclude that administration of digoxin may be harmful in hospital survivors of MI

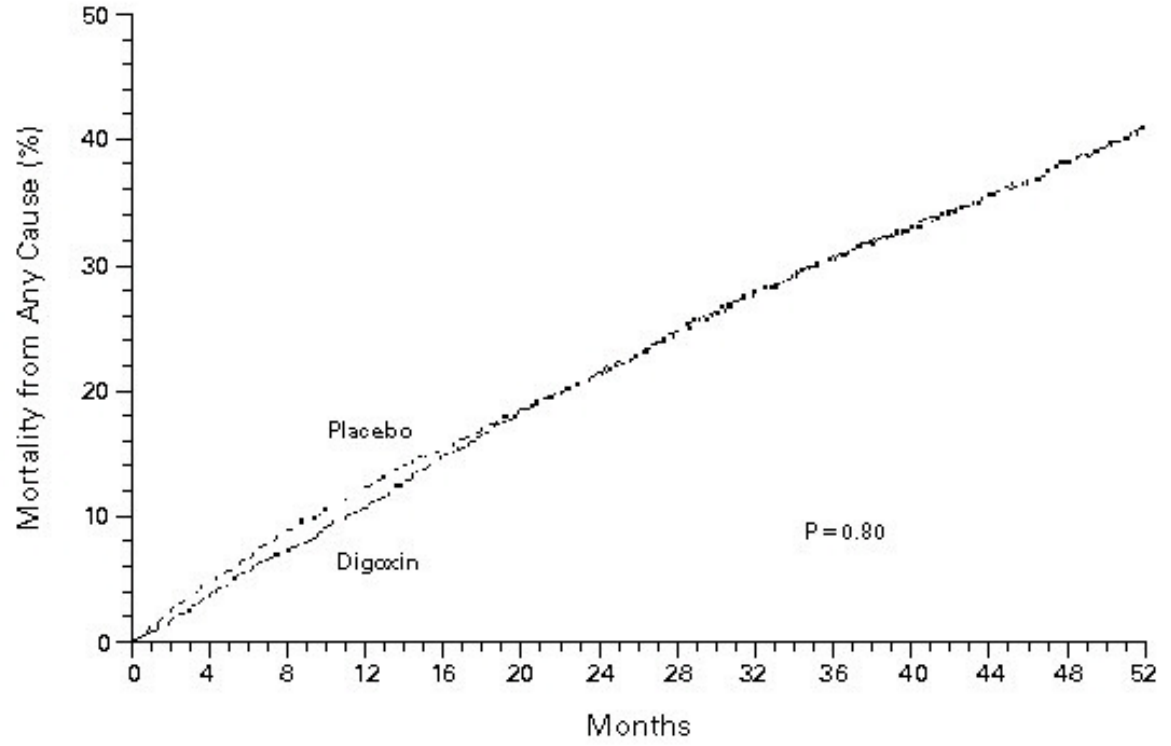
Observational data suggested that digoxin was associated with **increased mortality**

Observational data vs RCTs [Digoxin]

DIG Trial, NEJM 1997,

N= 6800 , 37 months of follow up

All cause mortality



NO. OF PATIENTS AT RISK

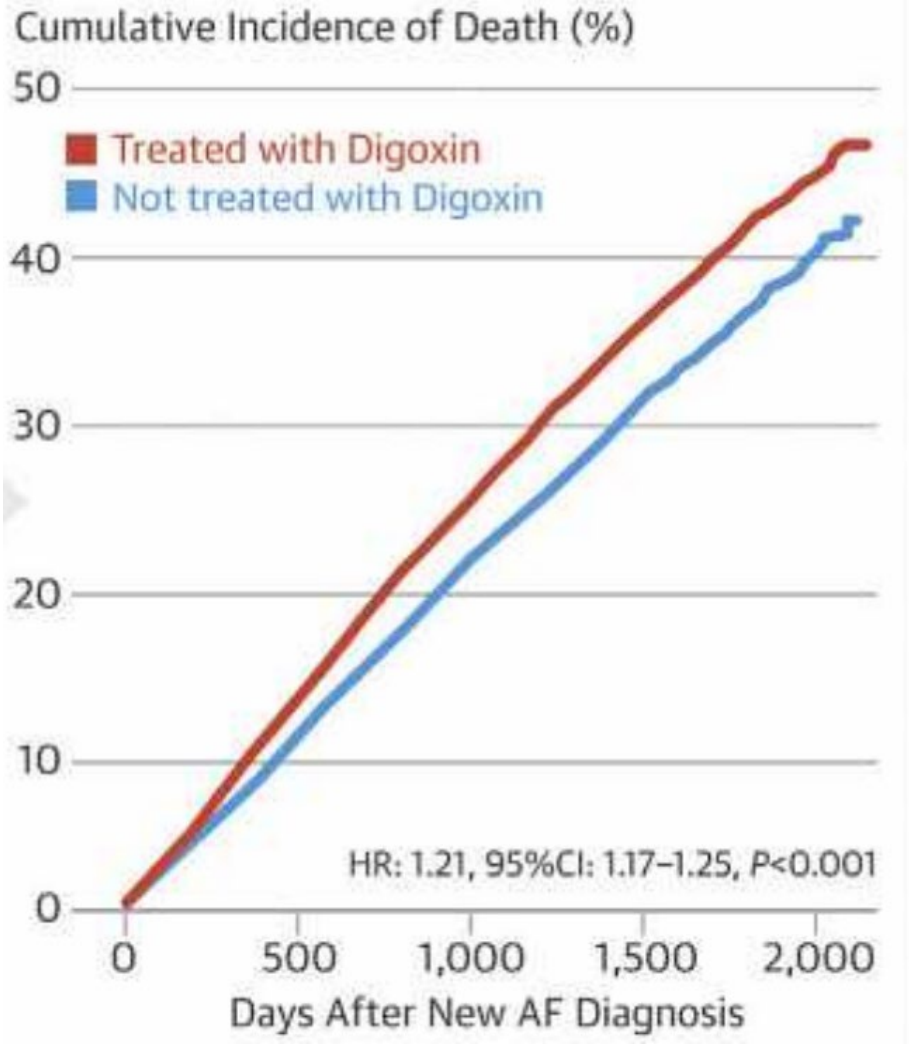
Placebo	3403	3239	3105	2976	2868	2758	2652	2551	2205	1881	1506	1168	734	339
Digoxin	3397	3269	3144	3019	2882	2759	2644	2531	2184	1840	1475	1156	737	335

However, randomized trial showed **no increased mortality risks**

Observational data vs RCTs [Digoxin]

Turakhia MA et al. JACC 2014

N =122,465 real-world analysis of outcomes



Large real world data studies subsequently continued to link digoxin with with **higher mortality risk**

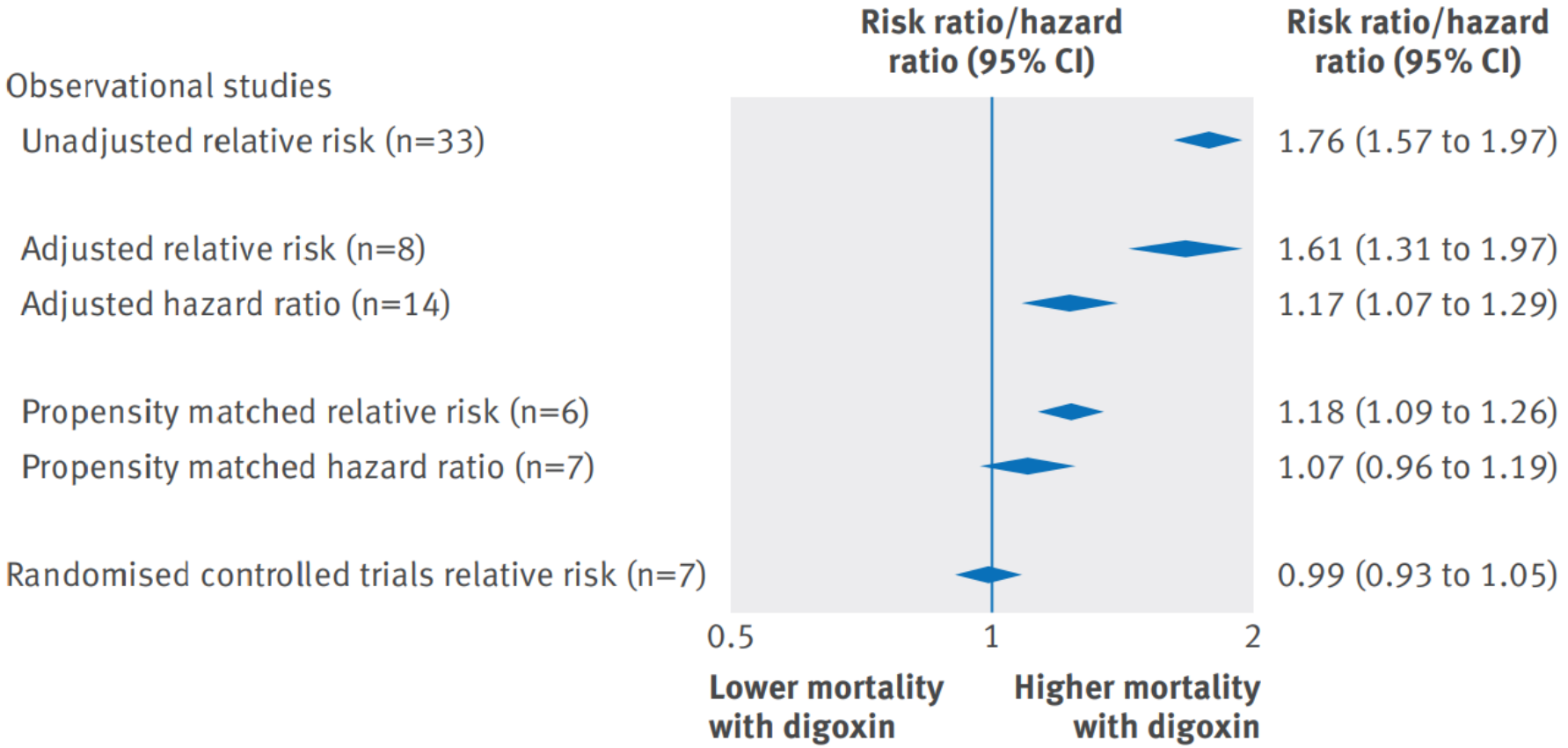
Observational data vs RCTs [Digoxin]

Research

Safety and efficacy of digoxin: systematic review and meta-analysis of observational and controlled trial data

BMJ 2015 ; 351 doi: https://doi.org/10.1136/bmj.h4451 (Published 30 August 2015)

Meta analysis of 41 Studies, 4 million patient-years of follow up



Residual confounding in observational real-world data compared to randomized controlled trials (RCTs)

Better methods for confounder control gets us closer to RCT findings

Some potential questions

Targeted therapies and health-related Quality of Life in the metastatic setting

- HR+/HER2- metastatic breast cancer:
  - Ribociclib or palbociclib + aromatase inhibitor (AI) vs AI only

Antiplatelets and blood clot prevention

- Ticagrelor vs clopidogrel in combination with aspirin post-MI

Anticoagulants and bleeding / stroke prevention

- Rivaroxaban vs apixaban in atrial fibrillation patients with high-bleed / stroke risk (e.g. chronic kidney disease)

Other crucial clinical decision areas that lack randomized evidence

- Presence of clinical equipoise
- Where observational comparisons reveal conflicting findings
- Methodological issues of RCTs potentially affecting generalizability of findings

Key considerations

- No earmarked funding for Phase IV, comparative efficacy and safety trials under current RIE 2025

- Applications will have to be considered under current grant programmes by NMRC (e.g. CTG-IIT)

- Trialists interested in Phase IV studies are encouraged to contact HSA to express your interest and discuss potential proposals

End-of-presentation

Thank you

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