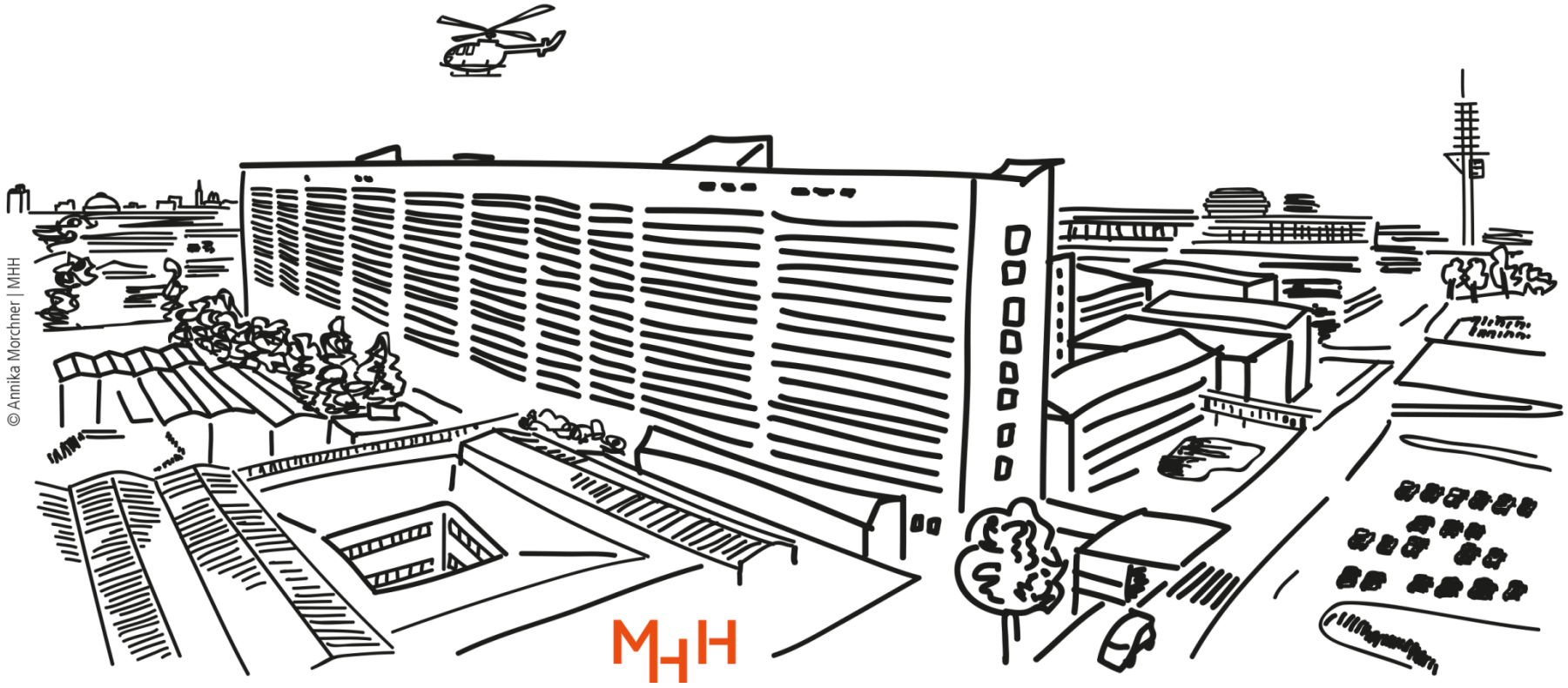
Observational vs. randomized analyses of digoxin-mortality in the DIG trial

Lukas Aguirre Dávila



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Section Biostatistics

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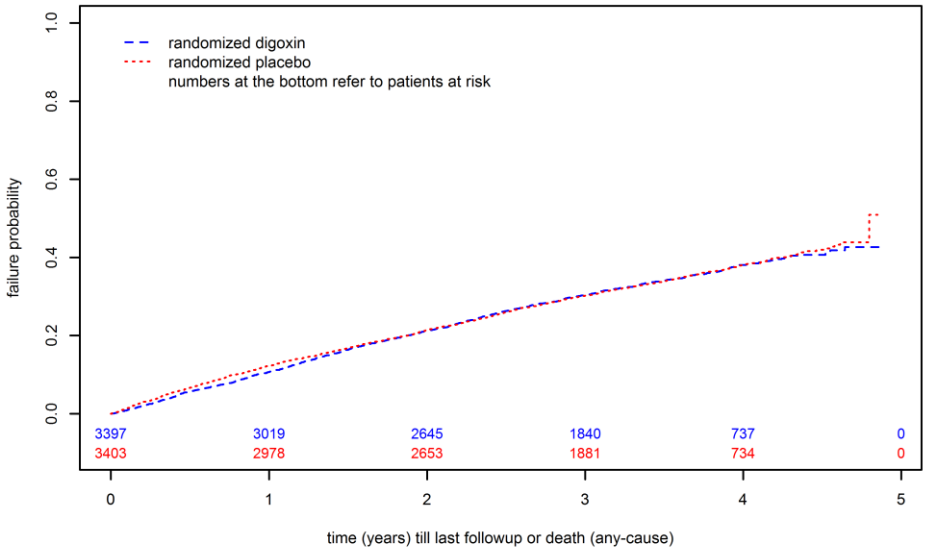
The following slides represent my personal views and do not necessarily reflect the views of the Paul-Ehrlich-Institut or any other European agency.

Digoxin – background

- Long history as treatment for congestive heart failure and arrhythmia
- > 330000 patients treated daily with digoxin or other digitalis glycosides in Germany
  (Schwabe & Paffrath 2014)
- One large randomized trial of digoxin: DIG (1997)
  (The Digitalis Investigation Group 1997)

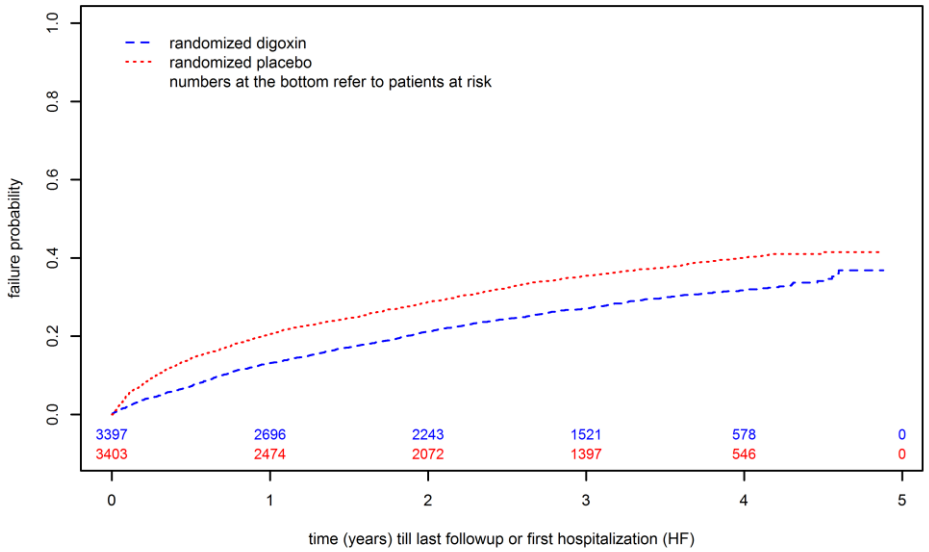


The DIG trial	Digoxin	Placebo
Deaths	1181 / 3397	1194 /3403
(any cause)	(34.8%)	(35.1%)

Hazard Ratio: 0.99, 95%-CI (0.91 – 1.07), p=0.80

Digoxin use in Heart Failure: rationale

- DIG suggested beneficial effects on secondary endpoints
  (The Digitalis Investigation Group 1997)
- Post-hoc analyses suggested association of serum levels with mortality
  (Rathore 2003)



Concerns in observational data

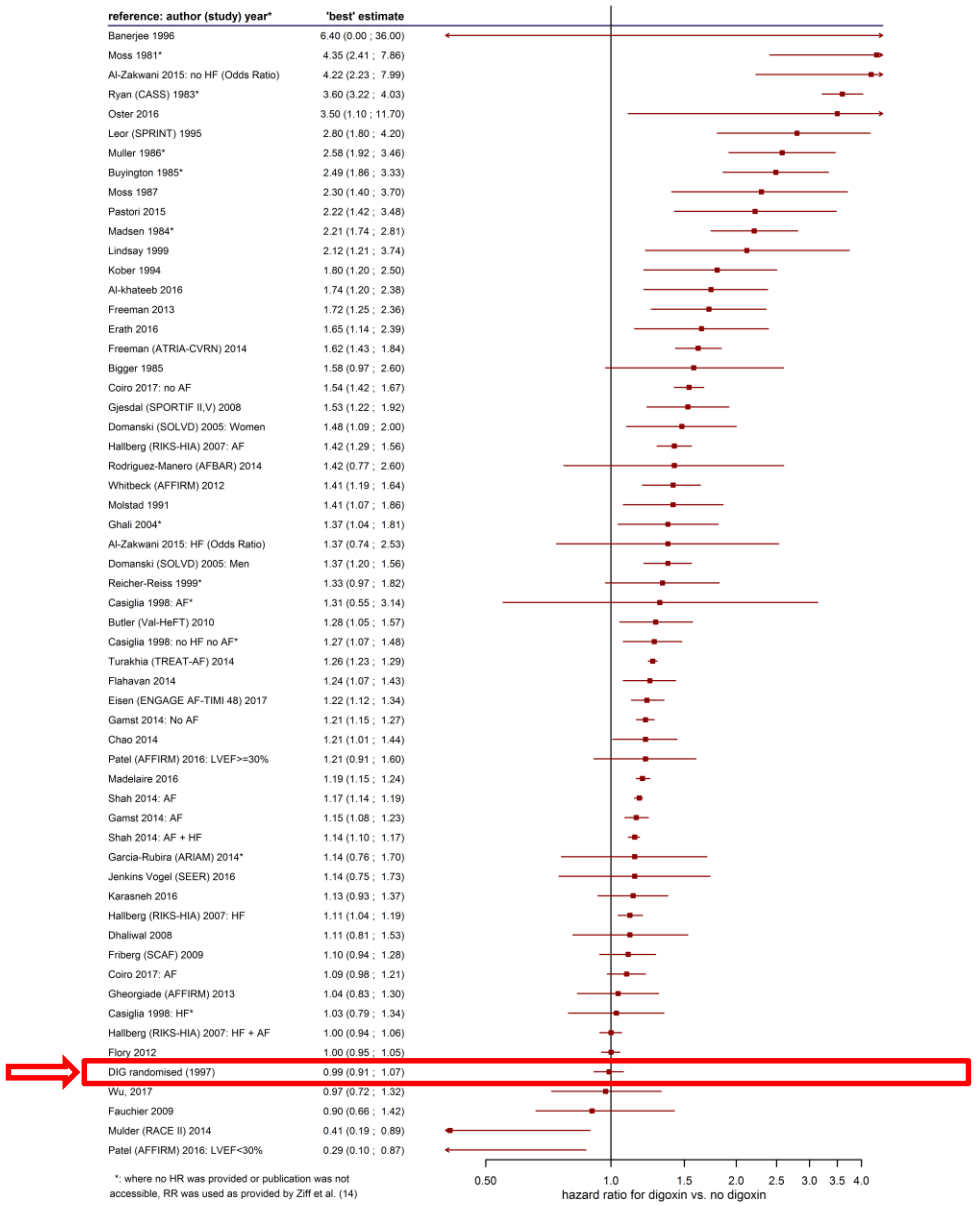
- E.g. Val-HeFT (2001): Valsartan vs. placebo in heart failure with reduced ejection fraction
- 67% of patients received digoxin at baseline
  (Cohn et al. 2001)
- Post-hoc analysis (2010) compared survival between patients on digoxin and not on digoxin
  (Butler et al. 2010)

Val-HeFT	Digoxin	No digoxin
Deaths	733 / 3374	246 / 1636
(any cause)	(21.7%)	(15.0%)

- Hazard Ratio: 1.46, 95%-CI (1.23 – 1.64), p<0.001
  Adjusted HR: 1.28, 95%-CI (1.05 – 1.57), p=0.02

Observational data: overview

- Results are heterogeneous
- Excess mortality with digoxin (even after adjustment)
- Underlying assumption: adjustment correctly accounts for population differences (no unmeasured confounding)

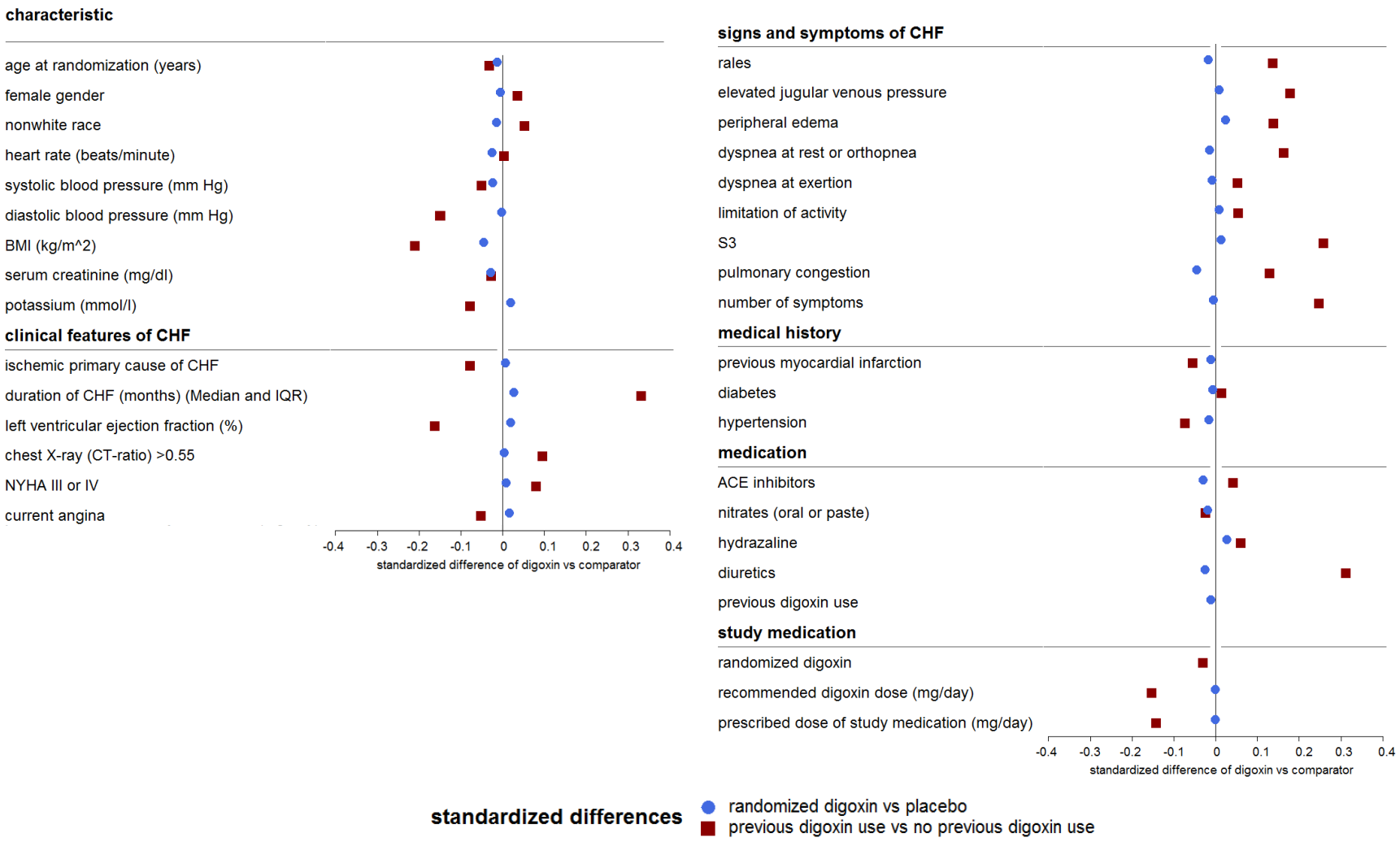


(previous) digoxin use and mortality in the DIG trial

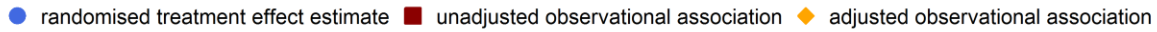
44% of the patients in the DIG trial received digoxin before randomisation

Patients	Randomized digoxin	Randomized placebo	Total
Previous digoxin use	1498	1519	3017
No previous digoxin use	1899	1884	3783
Total	3397	3403	6800

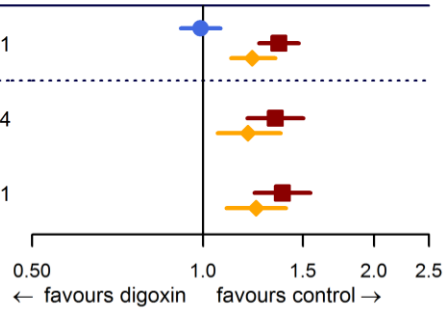
Pre-treated patients have worse prognosis



Bias remains after adjustment



	previous digoxin use	no previous digoxin use	unadjusted hazard ratio (95%-CI)	p-value	adjusted hazard ratio (95%-CI)	p-value
mortality (any-cause)						
all patients	1207 / 3017 (40.0%)	1168 / 3783 (30.9%)	1.36 (1.25; 1.47)	<.001	1.22 (1.12; 1.34)	<.001
digoxin patients only	596 / 1498 (39.8%)	585 / 1899 (30.8%)	1.34 (1.20; 1.50)	<.001	1.20 (1.06; 1.37)	0.004
placebo patients only	611 / 1519 (40.2%)	583 / 1884 (30.9%)	1.38 (1.23; 1.54)	<.001	1.24 (1.10; 1.40)	<.001



The DIG trial was designed to estimate the effect of digoxin:

- Modern trial
- Well characterized patients

→ It is not plausible to assume that other observational data allow better estimation of the effect of digoxin after adjustment

Digoxin: summary

- Observational data will not clarify the effect of digoxin
- Even in the DIG trial, a modern trial with high quality data, the assumption of no unmeasured confounding is not valid in an observational approach
- Digoxin in observational data should be interpreted as indicator for disease severity
- Another randomized trial is needed

Circumstances in the example

- (Big) observational data from different sources
- Randomized trial allows validation of mortality hypothesis

Differences in rare diseases

Rare disease trials vs. non-rare disease trials:

- fewer participants (median 29 vs. 62)
- More often open label (78.7% vs. 52.2%)
- **More often single arm (63.0% vs. 29.6%)**
- **More often non-randomised (64.5% vs. 36.1%)**

(Bell, Tudur Smith, 2014)

Final remark

If it wasnt for the DIG trial (RCT) we might have discarded digoxin already based on observational findings.

In rare diseases: Are we accepting the risk to be mislead by observational data?

Thank you

for your attention!

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