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My first #tweetorial - Random thoughts on digoxin

@drjohnm @ProfDFrancis #cardio

1. Large DIG RCT (n=7788) no increased mortality at 3 yrs

2. Same study -> important 28% decrease in hospitalization, major cause pt morbidity (NNT to avoid 1 hospitalization = 10–12)

3. Benefit not only to patient QoL but also society as CHF hospitalization main cost driver in the elderly

4. Neutral mortality, decreased hospitalization results confirmed in large Medicare pop (Ahmed 2014) -> external generalizability ✓

5. Double blinded RCT (n=178, RADIANCE) of digoxin withdrawal -> 5.9 times increase in CHF compared to staying on drug

6. Another small DB RCT (n=88, PROVED) also showed clinically and statistically significant deterioration with digoxin withdrawal

7. 4 other small short duration RCTs -> no increased mortality (but underpowered for meaningful conclusions)

8. Digoxin is also safe drug! What? True, get with the times. 40 years ago digoxin was a very unsafe drug but our knowledge has advanced

9. Safety improved 1) recognize lower therapeutic doses 2) appreciation of pharmacokinetics, i.e. check renal function, wt, gender & known drug interactions

10. Know more about the safety profile of digoxin than some other modern CHF meds, like Entresto

11. MDs shrug but dig = $70/year vs. $2600 for Entresto (Que prices). No formal comparisons but $70 a bargain to save for CHF hospit,

12. Against, observational studies show 76% increase death with digoxin compared to none (BMJ 2015, excellent MA)

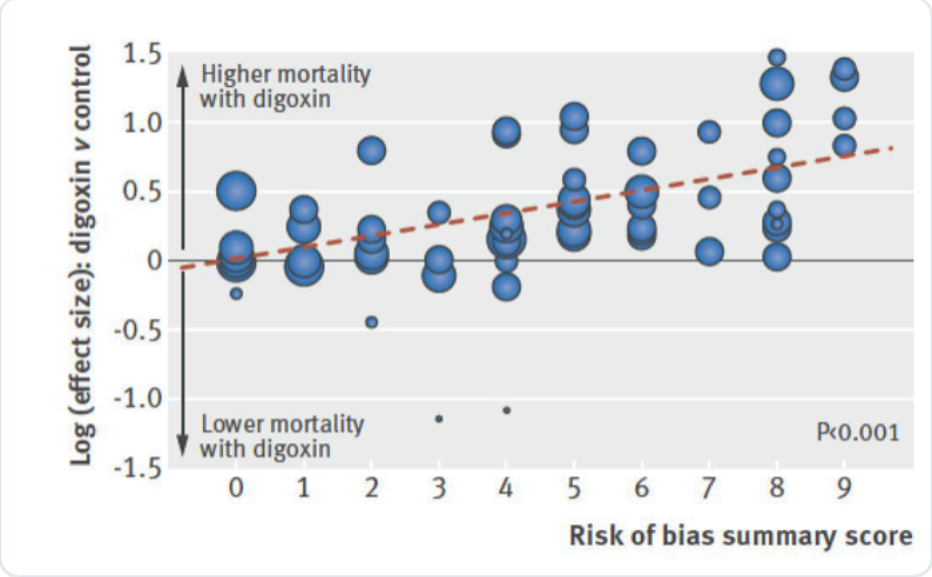
Safety and efficacy of digoxin: systematic re...
Objective To clarify the impact of digoxin on death and clinical outcomes across all observational and randomised controlled trials, accounting for study designs and methods. Data sources and study ...
https://www.bmj.com/content/351/bmj.h4...

13. But digoxin patients were older, sicker – no surprise as expect sicker patients to get drug, as MDs are not prescribing randomly

14. Adjusting for covariates -> RR decreases from 1.76 to 1.17, large change underscores imbalance between the 2 groups of dig and non-dig users in ops

15. Better confounding control with PS further decrease RR = 1.07 but, unlike RCT, problem of unmeasured confounders remains

16. In these obs studies -> higher bias greater association of digoxin with death



17. Other disincentives for an unbiased assessment of digoxin, bias of positive results and bias of sensationalizing of medical research

18. Might negative unpublished obs studies exist due to researchers' and editors' opinion that are not novel or sensational?

19. Generic drug, like digoxin, more prone to these biases. Thought exp – do obs study with Entresto -> increased mortality compared to placebo

20. Would that study be published? No!

21. Results rightly interpreted as likely bias due confounding by indication. Sicker pas get the Entresto

22. Other non-scientific reasons for non publication. Journal editors not want to antagonize advertising from on-patent manufacturers

23. KOL, industry consultants and others would also quickly rise to the Entresto defense. No such defenders for digoxin (remember cost is $.20 daily, no drug reps)

24. Don't have perfect evidence base for the use of digoxin, much space for further RCTs. In interim should be guided by the best quality study designs, not simply the most numerous ones

25. Obs studies with large sample sizes provide enhanced precision, but must cautious of being precisely wrong!

mentions