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

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STUDY QUESTION

What is the impact of digoxin on all cause mortality and other clinical outcomes, accounting for differences in study design and statistical methods?

SUMMARY ANSWER

Digoxin use has a neutral effect on mortality in randomised trials and reduces hospital admissions. The association of digoxin with adverse outcomes in observational studies is likely to be non-causative and a result of confounding, which cannot be mitigated by statistical adjustment. Future randomised trials of digoxin are urgently required to identify the place of this drug in the management of patients with heart failure and those with atrial fibrillation.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Recent observational studies have suggested increased mortality associated with digoxin in those with heart failure and atrial fibrillation, but findings are limited by prescription bias in which patients at highest risk receive digoxin. Our systematic review suggests that digoxin should continue to be considered as a treatment option to achieve heart rate control in those with atrial fibrillation and also to avoid hospital admissions in patients with heart failure.

Selection criteria for studies

We systematically searched Medline, Embase, and the Cochrane Library, and manually searched reference lists of relevant studies and registers of ongoing trials. We included all studies published from 1960 onwards that examined comparative outcomes with digoxin and control (placebo or no treatment), regardless of study design or population.

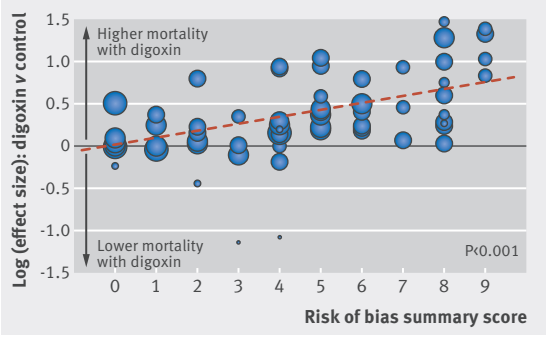
Primary outcome

The primary outcome was all cause mortality.

Main results and role of chance

Fifty two studies contributed to the systematic review, including 621 845 patients who received treatment with digoxin or control, with 2 248 775 patient years of follow-up. Forty one studies contributed to the meta-analysis of all cause mortality, including 75 separate statistical analyses. The pooled risk ratio for all cause mortality with digoxin compared with control in observational studies was 1.76 in unadjusted analyses (95% confidence interval 1.57 to 1.97), 1.61 in adjusted analyses (1.31 to 1.97), and 1.18 in propensity matched studies (1.09 to 1.26). By contrast, in randomised controlled trials digoxin use was associated with a neutral effect on all cause mortality (risk ratio 0.99, 0.93 to 1.05). Across all study types, digoxin led to a small but significant reduction in admissions to hospital (0.92, 0.89 to 0.95).

Meta-regression of all cause mortality according to risk of bias, summed across all domains



Bias, confounding, and other reasons for caution

Studies with better methods and lower risk of bias were more likely to report a neutral association of digoxin with mortality, reiterating the importance of basing treatment decisions on data from randomised controlled trials, rather than observational studies. Meta-regression of observational studies confirmed that baseline differences between digoxin and control patients had a significant impact on the mortality associated with digoxin, including characteristics such as age, diabetes, and use of diuretics (a marker of the severity of heart failure). This review is based on reported results of independent published studies; we did not have access to individual patient data and therefore had to accept the definitions of conditions and outcomes. We cannot exclude possible misclassification (particularly of heart failure and atrial fibrillation), and, as expected, there was substantial heterogeneity in non-randomised studies. The strength of our analysis was the comprehensive and systematic review of all studies relating to digoxin and clinical outcomes.

Study funding/potential competing interests

The study was internally funded with support from the Arthur Thompson Trust, University of Birmingham. DAL, PK, GYHL, and DK have received funding from various sources, not related to this work (see thebmj.com for full details).

Effect of bivalent human papillomavirus vaccination on pregnancy outcomes: long term observational follow-up in the Costa Rica HPV Vaccine Trial

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STUDY QUESTION

Is there an increased risk of miscarriage for pregnancies conceived <90 days from bivalent human papillomavirus (HPV) vaccination?

SUMMARY ANSWER

The risk of miscarriage is not increased for pregnancies conceived <90 days or any time from vaccination.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Previous studies could not rule out an effect of the bivalent vaccine on miscarriage, especially for pregnancies conceived <90 days from vaccination. An observed increased risk for miscarriages in weeks 13-20 of gestation for pregnancies conceived any time from vaccination is likely to be a random finding, but it should be further explored in existing and future studies.

Design

Observational long term follow-up of a randomised, double blinded trial combined with an independent unvaccinated population based cohort.

Participants and setting

7466 women enrolled in the trial and 2836 women in the unvaccinated cohort enrolled at the end of the randomised trial and in parallel with the observational trial component.

Relative risks of miscarriage for pregnancies conceived within 90 days of and any time since bivalent human papillomavirus (HPV) vaccination compared with all unexposed pregnancies

	Conception <90 days from HPV vaccination		Conception any time since HPV vaccination	
Analysis	Relative risk (95% CI)	P value*	Relative risk (95% CI)	P value*
Overall				
No adjustments	1.02 (0.78 to 1.34)	0.436	1.04 (0.91 to 1.17)	0.29
Adjusted for age at conception	1.03 (0.78 to 1.35)	0.422	1.03 (0.91 to 1.17)	0.306
Adjusted for calendar year	1.06 (0.79 to 1.42)	0.358	1.03 (0.91 to 1.17)	0.302
Adjusted for age at vaccination	1.15 (0.86 to 1.54)	0.17	1.06 (0.93 to 1.21)	0.198
Stratified by:				
Gestational age of miscarriage (weeks):				
0-6	0.76 (0.35 to 1.64)	NP	0.89 (0.65 to 1.22)	NP
7-12	1.04 (0.73 to 1.49)	0.411	0.98 (0.83 to 1.15)	NP
13-20	1.21 (0.67 to 2.19)	0.265	1.35 (1.02 to 1.77)	0.017
Age at conception (years):				
18-22	1.26 (0.84 to 1.88)	0.133	1.08 (0.84 to 1.39)	0.271
23-26	1.11 (0.72 to 1.70)	0.318	1.10 (0.92 to 1.31)	0.156
27-30	0.49 (0.19 to 1.28)	NP	0.94 (0.73 to 1.22)	NP
>30	0.48 (0.07 to 3.25)	NP	0.65 (0.36 to 1.20)	NP
Age at enrolment (years):				
18-22	1.11 (0.80 to 1.54)	0.266	1.07 (0.92 to 1.26)	0.19
23-26	0.92 (0.55 to 1.53)	NP	1.04 (0.83 to 1.29)	0.374
Age at vaccination (years):				
18-22	1.21 (0.83 to 1.78)	0.164	1.07 (0.90 to 1.27)	0.227
23-26	1.08 (0.70 to 1.68)	0.364	1.05 (0.84 to 1.31)	0.336

NP=not pertinent because miscarriage rate in bivalent HPV vaccine group was smaller than in the control group.
*One sided.

Primary outcomes

Risk of miscarriage (<20 weeks' gestation) among pregnancies exposed to the bivalent HPV vaccine <90 days and any time from vaccination compared with pregnancies exposed to hepatitis A vaccine and pregnancies in the unvaccinated cohort.

Main results and the role of chance

Of 3394 pregnancies conceived at any time since bivalent HPV vaccination, 381 were conceived <90 days from vaccination. A total of 2507 pregnancies conceived after hepatitis A vaccination and 720 conceived in the unvaccinated cohort were unexposed. Miscarriages occurred in 451 (13.3%) of all exposed pregnancies, in 50 (13.1%) of the pregnancies conceived <90 days from bivalent HPV vaccination, and in 414 (12.8%) of the unexposed pregnancies, of which 316 (12.6%) were in the hepatitis A vaccine group and 98 (13.6%) in the unvaccinated cohort. There was no increased risk of miscarriage for pregnancies conceived <90 days from vaccination compared with all unexposed pregnancies in unadjusted, adjusted, or stratified analyses. Among pregnancies conceived at any time from bivalent HPV vaccination, exposure was not associated with an increased risk of miscarriage overall or in subgroups, except for miscarriages at weeks 13-20 of gestation (relative risk 1.35, one sided P=0.017). This finding is likely an artifact of thorough examination of several possible scenarios.

Bias, confounding, and other reasons for caution

The post-trial crossover vaccination with either bivalent HPV or hepatitis A may have been influenced by many factors and could be subject to unmeasured confounding, as women were no longer randomised. In addition, we considered pregnancies in the hepatitis A vaccine arm and those in the unvaccinated cohort, which was ascertained outside the trial setting; sensitivity analyses show that combining the two groups did not affect our inferences.

Generalisability to other populations

The results are not directly generalisable to 11-13 year old girls who are the primary group for vaccination.

Study funding/potential competing interests

National Cancer Institute Intramural Research Program. We have no competing interests.

Trial registration numbers Clinicaltrials.gov NCT00128661 and NCT01086709.

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Diagnostic prediction models for suspected pulmonary embolism: systematic review and independent external validation in primary care

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STUDY QUESTION

Which of the diagnostic prediction models developed to rule out pulmonary embolism can be used safely and efficiently in a primary care setting?

SUMMARY ANSWER

Efficiency was comparable for all five diagnostic pulmonary embolism prediction models that are easily applicable in primary care, but the Wells rules gave the best performance in terms of lower failure rates.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Multiple diagnostic prediction models to rule out pulmonary embolism have been developed and validated in secondary care. In primary care, use of the original, modified, and simplified Wells rules, combined with a point of care D-dimer test, can exclude pulmonary embolism in about four out of 10 patients, with a failure rate of below 2%.

Selection criteria for studies

We searched the literature to identify all diagnostic prediction models developed for ruling out pulmonary embolism. Then we selected the models that are easily applicable in a primary care setting, where availability of investigations such as chest radiographs is limited. We validated the selected models in an independent cohort of 598 patients with suspected pulmonary embolism according to their general practitioner. Presence or absence of pulmonary embolism was based on a composite reference standard including all diagnostic tests performed in secondary care and three months' follow-up. Venous thromboembolism was present in 73 patients (prevalence 12%).

Primary outcome(s)

We validated the selected models in primary care by comparing the discriminative ability (C statistic). Then, we stratified patients into groups with high and low probability of pulmonary embolism according to pre-specified model cut-offs and qualitative point of care D-dimer testing. Primary outcomes were the proportion of patients classified by the model as having a low probability of pulmonary embolism (efficiency) and the proportion diagnosed as having pulmonary embolism within this low probability group (failure rate).

Main results and the role of chance

Our search identified a total of 10 diagnostic prediction models. Five of these models were validated in our primary care dataset: the original Wells, modified Wells, simplified Wells, revised Geneva, and simplified revised Geneva models. The discriminative ability of all models was good and comparable, with C statistics between 0.75 and 0.80. Efficiency of the models ranged from 43% to 48%. Differences in failure rates for the five models were largest between the simplified Wells rule and simplified revised Geneva score (1.2% (95% confidence interval 0.2% to 3.3%) *v* 3.1% (1.4% to 5.9%)), with an absolute difference of −1.98% (−3.33% to −0.74%).

Bias, confounding, and other reasons for caution

The individual patient dataset used for this study was initially designed to validate the original Wells rule in primary care. Consequently, the scores of the other models have been calculated retrospectively. Also, patient management was not directly guided by the results from the prediction models validated.

Generalisability to other populations

Our findings are generalisable to countries that have a well developed primary care structure in which general practitioners are the healthcare system's gatekeepers.

Study funding/potential competing interests

KGMM received a grant from The Netherlands Organization for Scientific Research. GJG is supported by a VENI grant from The Netherlands Organization for Scientific Research.

Efficiency and failure rates of five diagnostic prediction models, combined with point of care D-dimer testing, to rule out pulmonary embolism, validated in the primary care AMUSE-2 cohort

Measure	Efficiency (95% CI)	Failure rate (95% CI)
Original Wells ≤4	46% (41% to 50%)	1.5% (0.4% to 3.7%)
Modified Wells ≤2	45% (41% to 49%)	1.5% (0.4% to 3.8%)
Simplified Wells ≤1	43% (39% to 48%)	1.2% (0.2% to 3.3%)
Original revised Geneva ≤5	44% (40% to 48%)	2.7% (1.1% to 5.4%)
Simplified revised Geneva ≤2	48% (44% to 52%)	3.1% (1.4% to 5.9%)