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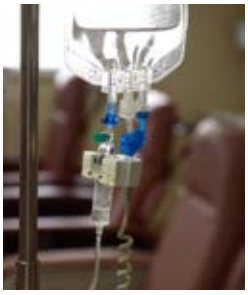
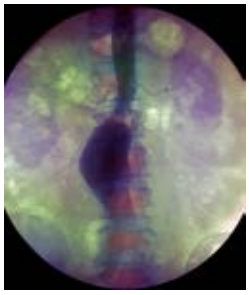
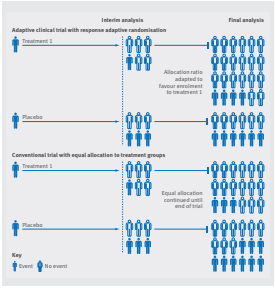


Differences exist between US cancer guidelines and FDA approvals of anticancer drugs p 395



Fluoroquinolone use associated with small increased risk of aortic aneurysm or dissection p 396

Higher vitamin D levels associated with lower risk of all cancer in an Asian population p 398



Designing adaptive clinical trials p 398

ORIGINAL RESEARCH Retrospective observational study

Frequency and level of evidence used in recommendations by the National Comprehensive Cancer Network guidelines beyond approvals of the FDA

Wagner J, Marquart J, Ruby J, et al

Cite this as: *BMJ* 2018;360:k668
Find this at: http://dx.doi.org/ doi: 10.1136/bmj.k668

Study question What differences exist between recommendations made by the National Comprehensive Cancer Network (NCCN) guidelines and US Food and Drug Administration approvals of anticancer drugs, and what evidence does the NCCN cite to justify recommendations where differences exist?

Methods The authors identified all new molecular entities approved by the FDA between 2011 and 2015. They compared all FDA approved indications (new and supplemental) against all NCCN recommendations as of 25 March 2016. When the NCCN made recommendations beyond the FDA's approvals, the authors classified the recommendation and noted the cited evidence. 21 months after their initial analysis they asked how many additional recommendations led to subsequent FDA approvals.

Study answer and limitations 39% (44/113) of identified NCCN recommendations differed from the FDA approval statement for drugs approved between 2011 and 2015, where 77% (34/44) of those recommendations were supported by citations with phase II trial design without randomisation or lower qualities of evidence. With 21 months' follow-up, 6/44 (14%) received FDA approval. Additional recommendations were assessed over time. Limitations of the study included a lack of assessment of NCCN recommendation level, not completing systematic literature reviews for independent evidence of recommendations, and performing the analysis at a locked date where future changes to the NCCN guidelines were not considered.

Cited evidence supporting additional recommendations by the National Comprehensive Cancer Network

Cited evidence	No (%) of additional recommendations (n=44)
No evidence given	16 (36)
Book chapter or review article	1 (2)
Case report or series <5 patients	2 (4)
Case series ≥5 patients	0 (0)
Phase I trial	1 (2)
Phase II trial without randomisation and <50 patients	7 (16)
Phase II trial without randomisation and ≥50 patients	6 (14)
Phase II trial with randomisation and <50 patients	1 (2)
Phase II trial with randomisation and ≥50 patients	2 (4)
Randomised, phase III trial	7 (16)
Ongoing trial	1 (2)

What study this adds These findings raise concern that the NCCN justifies the coverage of costly, toxic anticancer drugs based on weak evidence.

Funding, competing interests, data sharing The authors have declared no competing interests. Data used for analysis are available in the supplementary file on bmj.com.

Fluoroquinolones and the aorta

ORIGINAL RESEARCH Nationwide cohort study

Fluoroquinolone use and risk of aortic aneurysm and dissection

Pasternak B, Inghammar M, Svanström H

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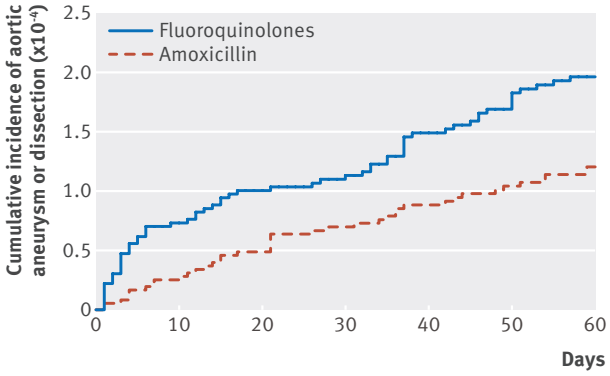
Find this at: http://dx.doi.org/10.1136/bmj.k678



Cumulative incidence of aortic aneurysm or dissection within 60 day risk period from start of study treatment

Study question Is oral fluoroquinolone use associated with an increased risk of aortic aneurysm or dissection?

Methods A nationwide historical cohort study used linked register data on patient characteristics, filled prescriptions, and cases of aortic aneurysm or dissection in Sweden, 2006-13. The cohort included 360 088 treatment episodes of fluoroquinolone use (78% ciprofloxacin), which were matched with comparator episodes of amoxicillin use (n=360 088) on a 1:1 ratio on the basis of propensity scores. Cox regression was used to estimate the hazard ratio for a first diagnosis of aortic aneurysm or dissection, defined as admission to hospital or emergency department for, or death due to, aortic aneurysm or dissection, within a 60 day period from start of treatment.

Study answer and limitations Within the 60 day risk period, the rate of aortic aneurysm or dissection was 1.2 cases per 1000 person years among fluoroquinolone users and 0.7 cases per 1000 person years among amoxicillin users. Fluoroquinolone use was associated with an increased risk of aortic aneurysm or dissection (hazard ratio 1.66;

COMMENTARY Possible link with aortic pathology but the absolute risk appears very low

Pasternak and colleagues report a significant association between outpatient treatment with fluoroquinolones (principally ciprofloxacin and norfloxacin) and aortic aneurysms and dissection.[1] Compared with patients prescribed amoxicillin, those prescribed fluoroquinolones had a 66% increase in risk of aortic aneurysm or dissection.

But do fluoroquinolones actually cause aortic pathology? It is sometimes said that observational studies cannot prove a causal association between an exposure and an outcome, but this is not entirely true (we have no randomised trials of smoking and lung cancer, for example). What is true is that imputing cause and effect from observational studies involves making a judgment, and that judgment is often hard. This is one of those times.

Bradford Hill criteria

When evaluating whether an association is causal, it is helpful to reflect on the nine criteria put forth by Austin Bradford Hill in 1965: biological plausibility, consistency, coherence, specificity, strength of association, gradient, experiment, analogy, and temporality.[4] This involves considering a pattern of information rather than following an algorithm, or tabulating a score. The various factors are not weighted equally, but the more that are fulfilled, the more likely an association is to be causal.

In this instance, biological plausibility seems fairly evident: the aorta is rich in collagen, and the ability of fluoroquinolones to alter the integrity of collagen is well known, even if the mechanisms are poorly understood.[5] The criterion of consistency is likewise met, with two related studies from other jurisdictions yielding comparable findings.[2 3] Subtly different from plausibility is the criterion of coherence, which is best understood by asking "How much of what I already know do I have to sacrifice to accept this association as causal?" To me, the idea that fluoroquinolones might cause aortic pathology seems fully compatible with existing knowledge about the drugs and their off-target effects.[5]

The criterion of specificity, which holds that one putative cause should yield one specific effect, is the least useful of the Bradford Hill criteria. (Does anyone believe that smoking causes only lung cancer?) However, a variant is sometimes useful in observational studies: falsification analysis, which can strengthen causal inference by documenting the absence of an association where none is expected. In the study by Pasternak and colleagues, the finding of no difference in all cause mortality fulfils this criterion, albeit not optimally.

Two notable criteria not met are strength of association and gradient. In some books, a hazard ratio of 1.66 barely qualifies as modest. This in itself is not an argument against causation; it is simply less compelling. Gradient (sometimes termed dose-response) was not examined.

Of the remaining criteria, the experiment criterion is not evaluable—there will never be a human trial to examine whether fluoroquinolones cause aortic pathology. By contrast, the criterion of analogy holds. Reasonably good evidence exists for a causal association between fluoroquinolones and disorders of tendons[6 7] and the retina,[8 9] both of which are rich in collagen.

Imperfect timing

Temporality is Bradford Hill's only essential criterion, and in the study by Pasternak and colleagues would seem to be met by design.

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95% confidence interval 1.12 to 2.46), with an estimated absolute difference of 82 cases of aortic aneurysm or dissection per one million treatment episodes. In a secondary analysis, the hazard ratio for the association with fluoroquinolone use was 1.90 (1.22 to 2.96) for aortic aneurysm and 0.93 (0.38 to 2.29) for aortic dissection. Most treatment episodes with fluoroquinolones in the study were with ciprofloxacin and results are therefore primarily applicable to this specific fluoroquinolone.

What this study adds Fluoroquinolone use was associated with an increased risk of aortic aneurysm or dissection. This association appeared to be largely driven by aortic aneurysm. Although the absolute risk increase was relatively small, it should be interpreted in the context of the widespread use of fluoroquinolones.

Funding, competing interest, data sharing There was no specific funding for this study, the authors have no competing interests, and there are no additional data available.

Advice remains the same: prescribe antibiotics judiciously

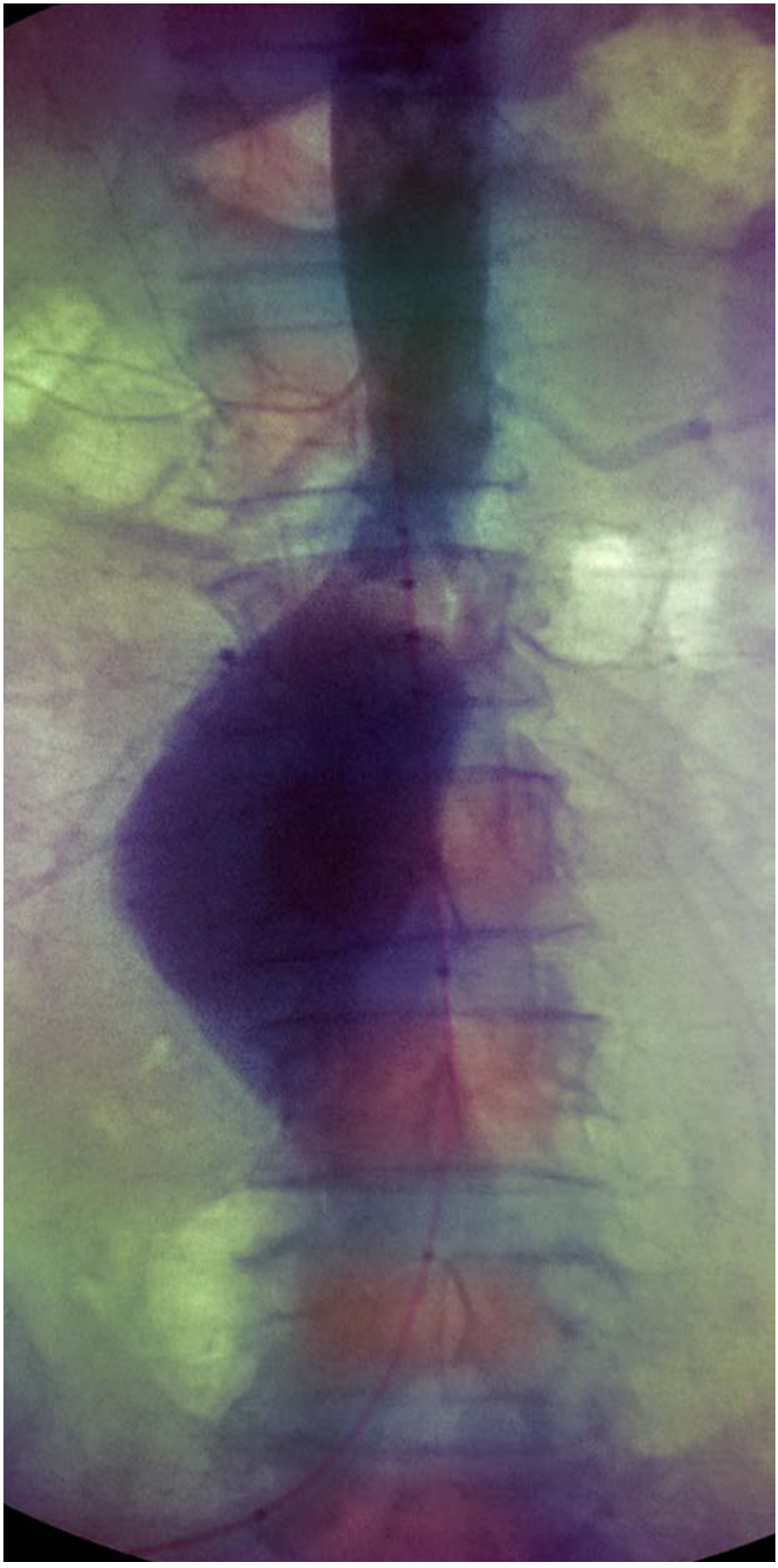
But it is curious that the survival curves for fluoroquinolones and amoxicillin diverge almost immediately. Does it seem plausible that the anatomy of the aorta could be seriously compromised by fluoroquinolones in a matter of days, as the authors postulate, or is another explanation at play?

The separation of curves is so acute that it raises the possibility of differential outcome ascertainment, as might occur if patients receiving fluoroquinolones underwent abdominal imaging more often than those receiving amoxicillin. Given that fluoroquinolones are more likely to be used in complex urinary tract infections, this seems at least possible.

On balance, this study strengthens the link between fluoroquinolones and aortic disease, but causality remains far from proved. Even if it is the case, the absolute risk is very low—at 82 extra cases of aneurysm or dissection within 60 days for every million treatment episodes—and the advice remains the same: prescribe antibiotics judiciously.

Cite this as: *BMJ* 2018;360:k988

Find the full version with references at http://dx.doi.org/10.1136/bmj.k988



SIMON FRASER/SPL

ORIGINAL RESEARCH Case-cohort study

Plasma 25-hydroxyvitamin D concentration and subsequent risk of total and site specific cancers in Japanese population

Budhathoki S, Hidaka A, Yamaji T, et al

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Find this at: http://dx.doi.org/10.1136/bmj.k671

Hazard ratios for total and site specific cancer according to quarters of plasma 25-hydroxyvitamin D

	Quarters of plasma 25-hydroxyvitamin D				
	1 (low)	2	3	4 (high)	P for trend
All cancer					
No of cases	840	792	795	874	
Hazard ratio (95% CI)*	1 (reference)	0.81 (0.70 to 0.94)	0.75 (0.65 to 0.87)	0.78 (0.67 to 0.91)	0.001
Liver cancer					
No of cases	47	43	41	34	
Hazard ratio (95% CI)*	1 (reference)	0.70 (0.44 to 1.13)	0.65 (0.40 to 1.06)	0.45 (0.26 to 0.79)	0.006

*Adjusted for age, sex, body mass index, smoking, alcohol use, physical activity, family history of cancer, and reported history of diabetes.

Study question Is pre-diagnostic circulating vitamin D concentration associated with the subsequent risk of overall and site specific cancer?

Methods This was a nested case-cohort study of 3301 incident cases of cancer and 4044 randomly selected subcohort participants within the Japan Public Health Center-based Prospective Study cohort, who resided in nine public health centre areas across Japan. Plasma concentration of 25-hydroxyvitamin D was measured by an enzyme immunoassay method. Incidence of overall or site specific cancer was evaluated across categories of 25-hydroxyvitamin D, with the lowest category as the reference.

Study answer and limitations Plasma 25-hydroxyvitamin D concentration was inversely associated with the risk of total cancer as well as liver cancer. Although the overall sample size for cancer was large, numbers of organ specific cancers were relatively small, particularly for rare cancers, and the analysis may therefore not have been sufficiently powered to capture moderate associations.

What this study adds Higher vitamin D concentration was associated with lower risk of total cancer in an Asian population.

Funding, competing interests, data sharing This study was supported by the National Cancer Center Research and Development Fund (23-A-31 [toku], 26-A-2, and 29-A-4) (since 2011), a Grant-in-Aid for Cancer Research from the Ministry of Health, Labour and Welfare of Japan (from 1989 to 2010), and the Practical Research for Innovative Cancer Control (15ck0106095h0002, 16ck0106095h0003, and 17ck0106266h001) (since 2015) from the Japan Agency for Medical Research and Development.

RESEARCH METHODS AND REPORTING Primer for clinicians

Key design considerations for adaptive clinical trials

Thorlund K, Haggstrom J, Park JJH, Mills EJ

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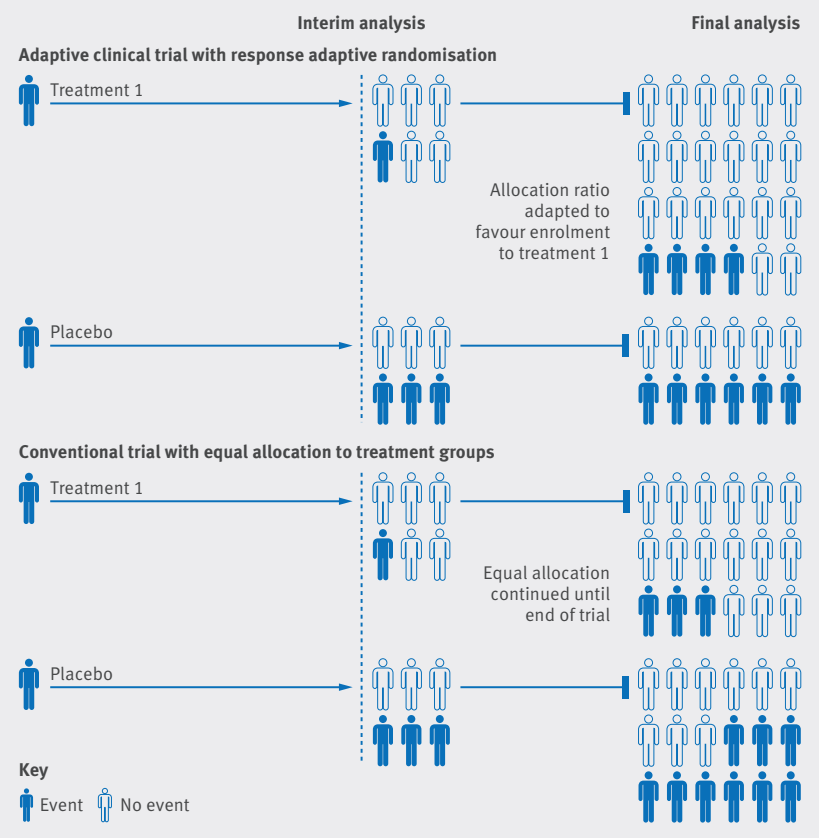
This article reviews important considerations for researchers who are designing adaptive clinical trials. These differ from conventional clinical trials because they allow and even enforce continual modifications to key components of trial design while data are being collected. This innovative approach has the potential to reduce resource use, decrease time to trial completion, limit allocation of participants to inferior interventions, and improve the likelihood that trial results will be scientifically or clinically relevant. Adaptive designs have mostly been used in trials evaluating drugs, but their use is spreading. The US Food and Drug Administration recently issued guidance on adaptive trial designs, which highlighted general principles and different types of adaptive clinical trials but did not provide concrete guidance about important considerations in designing such trials. Decisions to adapt a trial are not arbitrary; they are based on decision rules that have been rigorously examined through statistical simulations before the first trial participant is enrolled. The authors review important characteristics of adaptive trials and common types of study modifications and provide a practical guide, illustrated with a case study, to aid investigators who are planning an adaptive clinical trial.



If interim analysis shows that the treatment reduces the number of patients who have an event, the allocation ratio can be adapted so that more people receive treatment, fewer people receive placebo, and fewer people have an event, without affecting the power of the study