

Abstracts' Service

Empirical Evaluation of Very Large Treatment Effects of Medical Interventions

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Context. Most medical interventions have modest effects, but occasionally some clinical trials may find very large effects for benefits or harms.

Objective. To evaluate the frequency and features of very large effects in medicine.

Data Sources. Cochrane Database of Systematic Reviews (CDSR, 2010, issue 7).

Study Selection. We separated all binary-outcome CDSR forest plots with comparisons of interventions according to whether the first published trial, a subsequent trial (not the first), or no trial had a nominally statistically significant ($P < .05$) very large effect (odds ratio [OR], ≥ 5). We also sampled randomly 250 topics from each group for further in-depth evaluation.

Data Extraction. We assessed the types of treatments and outcomes in trials with very large effects, examined how often large-effect trials were followed up by other trials on the same topic, and how these effects compared against the effects of the respective meta-analyses.

Results. Among 85,002 forest plots (from 3082 reviews), 8239 (9.7%) had a significant very large effect in the first published trial, 5158 (6.1%) only after the first published trial, and 71605 (84.2%) had no trials with significant very large effects. Nominally significant very large effects typically appeared in small trials with median number of events: 18 in first trials and 15 in subsequent trials. Topics with very

large effects were less likely than other topics to address mortality (3.6% in first trials, 3.2% in subsequent trials, and 11.6% in no trials with significant very large effects) and were more likely to address laboratory-defined efficacy (10% in first trials, 10.8% in subsequent, and 3.2% in no trials with significant very large effects). First trials with very large effects were as likely as trials with no very large effects to have subsequent published trials. Ninety percent and 98% of the very large effects observed in first and subsequently published trials, respectively, became smaller in meta-analyses that included other trials; the median odds ratio decreased from 11.88 to 4.20 for first trials, and from 10.02 to 2.60 for subsequent trials. For 46 of the 500 selected topics (9.2%; first and subsequent trials) with a very large-effect trial, the meta-analysis maintained very large effects with $P < .001$ when additional trials were included, but none pertained to mortality-related outcomes. Across the whole CDSR, there was only 1 intervention with large beneficial effects on mortality, $P < .001$, and no major concerns about the quality of the evidence (for a trial on extracorporeal oxygenation for severe respiratory failure in newborns).

Conclusions. Most large treatment effects emerge from small studies, and when additional trials are performed, the effect sizes become typically much smaller. Well-validated large effects are uncommon and pertain to nonfatal outcomes.

How to Use a Noninferiority Trial: Users' Guides to the Medical Literature

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Clinical investigators are increasingly testing treatments that have the primary benefit of decreased burden or harms relative to an existing standard. The goal of the resulting randomized trials—called noninferiority trials—is to establish that the novel treatment's effectiveness is not substantially less than the existing standard. Conclusions from these trials are, however, based on noninferiority thresholds specified by authors whose judgments may not coincide with those of patients and

clinicians. This article highlights issues related to validity, interpretation, and applicability of results specific to noninferiority trials. Suboptimal administration of standard treatment or exclusive reliance on the analyze-as-randomized approach that is standard for conventional superiority trials may produce misleading results in noninferiority trials. Clinicians should judge whether the novel treatment's impact on effectiveness outcomes—the prime reason for wanting to prescribe it—is

sufficiently close to that of standard treatment that they are comfortable substituting it for the existing standard. Trading off desirable and undesirable consequences is an individual decision: given the

benefits of a novel treatment, some patients may perceive the uncertainty regarding a reduction in treatment effectiveness as acceptable while others may not.

Reporting of Noninferiority and Equivalence Randomized Trials: Extension of the CONSORT 2010 Statement

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The CONSORT (Consolidated Standards of Reporting Trials) Statement, which includes a checklist and a flow diagram, is a guideline developed to help authors improve the reporting of the findings from randomized controlled trials. It was updated most recently in 2010. Its primary focus is on individually randomized trials with 2 parallel groups that assess the possible superiority of one treatment compared with another. The CONSORT Statement has been extended to other trial designs such as cluster randomization, and recommendations for noninferiority and equi-

valence trials were made in 2006. In this article, we present an updated extension of the CONSORT checklist for reporting noninferiority and equivalence trials, based on the 2010 version of the CONSORT Statement and the 2008 CONSORT Statement for the reporting of abstracts, and provide illustrative examples and explanations for those items that differ from the main 2010 CONSORT checklist. The intent is to improve reporting of noninferiority and equivalence trials, enabling readers to assess the reliability of their results and conclusions.

Association Between Use of Lung-Protective Ventilation With Lower Tidal Volumes and Clinical Outcomes Among Patients Without Acute Respiratory Distress Syndrome: A Meta-Analysis

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Context. Lung-protective mechanical ventilation with the use of lower tidal volumes has been found to improve outcomes of patients with acute respiratory distress syndrome (ARDS). It has been suggested that use of lower tidal volumes also benefits patients who do not have ARDS.

Objective. To determine whether use of lower tidal volumes is associated with improved outcomes of patients receiving ventilation who do not have ARDS.

Data Sources. MEDLINE, CINAHL, Web of Science, and Cochrane Central Register of Controlled Trials up to August 2012.

Study Selection. Eligible studies evaluated use of lower vs higher tidal volumes in patients without ARDS at onset of mechanical ventilation and reported lung injury development, overall mortality, pulmonary infection, atelectasis, and biochemical alterations.

Data Extraction. Three reviewers extracted data on study characteristics, methods, and outcomes. Disagreement was resolved by consensus.

Data Synthesis. Twenty articles (2822 participants) were included. Meta-analysis using a fixed-effects model showed a decrease in lung injury development (risk ratio [RR], 0.33; 95% CI, 0.23 to 0.47; I^2 , 0%; number needed to treat [NNT], 11), and mortality (RR, 0.64; 95% CI, 0.46 to 0.89; I^2 , 0%; NNT, 23) in patients receiving ventilation with lower tidal volumes. The results of lung injury development were similar when stratified by the type of study (randomized vs nonrandomized) and were significant only in randomized trials for pulmonary infection and only in nonrandomized trials for mortality. Meta-analysis using a random-effects model showed, in protective ventilation groups, a lower incidence of pulmonary infection (RR, 0.45; 95% CI,

0.22 to 0.92; I^2 , 32%; NNT, 26), lower mean (SD) hospital length of stay (6.91 [2.36] vs 8.87 [2.93] days, respectively; standardized mean difference [SMD], 0.51; 95% CI, 0.20 to 0.82; I^2 , 75%), higher mean (SD) PaCO₂ levels (41.05 [3.79] vs 37.90 [4.19] mm Hg, respectively; SMD, -0.51; 95% CI, -0.70 to -0.32; I^2 , 54%), and lower mean (SD) pH values (7.37 [0.03] vs 7.40 [0.04], respectively; SMD, 1.16; 95% CI, 0.31 to 2.02; I^2 , 96%) but similar mean (SD) ratios of PaO₂ to fraction of inspired oxygen (304.40 [65.7] vs 312.97

[68.13], respectively; SMD, 0.11; 95% CI, -0.06 to 0.27; I^2 , 60%). Tidal volume gradients between the 2 groups did not influence significantly the final results.

Conclusions. Among patients without ARDS, protective ventilation with lower tidal volumes was associated with better clinical outcomes. Some of the limitations of the meta-analysis were the mixed setting of mechanical ventilation (intensive care unit or operating room) and the duration of mechanical ventilation.

Multivitamins in the Prevention of Cancer in Men: The Physicians' Health Study II Randomized Controlled Trial

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Context. Multivitamin preparations are the most common dietary supplement, taken by at least one-third of all US adults. Observational studies have not provided evidence regarding associations of multivitamin use with total and site-specific cancer incidence or mortality.

Objective. To determine whether long-term multivitamin supplementation decreases the risk of total and site-specific cancer events among men.

Design, Setting, and Participants. A large-scale, randomized, double-blind, placebo-controlled trial (Physicians' Health Study II) of 14 641 male US physicians initially aged 50 years or older (mean [SD] age, 64.3 [9.2] years), including 1312 men with a history of cancer at randomization, enrolled in a common multivitamin study that began in 1997 with treatment and follow-up through June 1, 2011.

Intervention. Daily multivitamin or placebo.

Main Outcome Measures. Total cancer (excluding nonmelanoma skin cancer), with prostate, colorectal, and other site-specific cancers among the secondary end points.

Results. During a median (interquartile range) follow-up of 11.2 (10.7-13.3) years, there were 2669 men with confirmed cancer, including 1373 cases of prostate cancer and 210 cases of colorectal cancer. Compared with placebo, men taking a daily

multivitamin had a statistically significant reduction in the incidence of total cancer (multivitamin and placebo groups, 17.0 and 18.3 events, respectively, per 1000 person-years; hazard ratio [HR], 0.92; 95% CI, 0.86-0.998; $P=.04$). There was no significant effect of a daily multivitamin on prostate cancer (multivitamin and placebo groups, 9.1 and 9.2 events, respectively, per 1000 person-years; HR, 0.98; 95% CI, 0.88-1.09; $P=.76$), colorectal cancer (multivitamin and placebo groups, 1.2 and 1.4 events, respectively, per 1000 person-years; HR, 0.89; 95% CI, 0.68-1.17; $P=.39$), or other site-specific cancers. There was no significant difference in the risk of cancer mortality (multivitamin and placebo groups, 4.9 and 5.6 events, respectively, per 1000 person-years; HR, 0.88; 95% CI, 0.77-1.01; $P=.07$). Daily multivitamin use was associated with a reduction in total cancer among 1312 men with a baseline history of cancer (HR, 0.73; 95% CI, 0.56-0.96; $P=.02$), but this did not differ significantly from that among 13 329 men initially without cancer (HR, 0.94; 95% CI, 0.87-1.02; $P=.15$; P for interaction =.07).

Conclusion. In this large prevention trial of male physicians, daily multivitamin supplementation modestly but significantly reduced the risk of total cancer.

Trial Registration. clinicaltrials.gov Identifier: NCT00270647