Contradicted and Initially Stronger Effects in Highly Cited Clinical Research

John P. A. Ioannidis, MD

CLINICAL RESEARCH ON IMPORTANT questions about the efficacy of medical interventions is sometimes followed by subsequent studies that either reach opposite conclusions or suggest that the original claims were too strong. Such disagreements may upset clinical practice and acquire publicity in both scientific circles and in the lay press. Several empirical investigations have tried to address whether specific types of studies are more likely to be contradicted and to explain observed controversies. For example, evidence exists that small studies may sometimes be refuted by larger ones.1,2

Similarly, there is some evidence on disagreements between epidemiological studies and randomized trials.3-5 Prior investigations have focused on a variety of studies without any particular attention to their relative importance and scientific impact. Yet, most research publications have little impact while a small minority receives most attention and dominates scientific thinking and clinical practice. Impact is difficult to measure in all its dimensions. However, the number of citations received by a publication is a surrogate of the attention it has received in the scientific literature and its influence on scientific debate and progress. Citations are readily and objectively counted in established databases.6 High citation count does not necessarily mean that these studies are accepted; citations may sometimes be critical of an article. Nevertheless, citation count is a measure of how much a study has occupied the thinking of other scientists and has drawn attention—for good or bad.

It is important to evaluate the replication of clinical research studies that have the highest citation impact. How frequently are such studies eventually contradicted by other research or are found to have too strong results compared with subsequent evidence? Is this more common for specific types of studies? Answering these questions would be useful for interpreting the results of influential clinical research.

METHODS

Eligible Original Studies

Eligible original studies for this analysis included all publications that had received more than 1000 Institute for Scientific Information (ISI)—indexed6

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CONTRADICTED AND INITIALLY STRONGER EFFECTS IN HIGHLY CITED CLINICAL RESEARCH

citations; had been published between 1990 and 2003 in the 3 general medical journals with the current highest impact factor (New England Journal of Medicine, JAMA, Lancet) or in medical specialty journals with impact factor exceeding 7.0 (according to the Journal Citation Reports 2003) that are likely to publish clinical research (including in decreasing impact factor, the Journal of the National Cancer Institute, Gastroenterology, Annals of Internal Medicine, Circulation, Journal of Clinical Oncology, Archives of General Psychiatry, Blood, Hepatology, American Journal of Respiratory and Critical Care Medicine, Diabetes, Brain, Annals of Neurology, Journal of the American College of Cardiology, Diabetes Care, Journal of the American Society of Nephrology, Arthritis and Rheumatism, and the American Journal of Psychiatry); addressed the efficacy of therapeutic or preventive interventions; and pertained to primary data (excluding reviews and meta-analyses).

Citation counts for articles published between January 1, 1990, and December 31, 2003, in these journals were downloaded from ISI. Citation counts are censored on August 20, 2004. All articles with more than 1000 citations were screened further. Studies with group authorship may be cited in various ways; therefore, I summed up citations cataloged under different entries for the same article (using the first author name, group abbreviations, and anonymous entries). The total citation count does not capture the few citations for which wrong name, journal, volume, or page might have been cited. Since citations depend on the time interval since publication, a separate citation count was limited to the first 3 years after the publication year.

Other Clinical Research on the Same Questions
For each eligible original study, a search was performed to identify whether there had been any other concurrently or subsequently published clinical research addressing the same question. Other research was considered eligible, only if the sample size was close to or larger than that of the highly cited original study or if it used a theoretically better controlled design. Thus, for highly cited randomized trials, I perused all randomized trials having at least 30% of the sample size of the eligible highly cited original study. Whenever available, quantitative meta-analyses of trials were used as summaries of trial results. Whenever several pertinent meta-analyses were available, the one including the largest number of studies was preferred. For highly cited nonrandomized studies, subsequently published pertinent randomized trials and meta-analyses thereof were eligible regardless of sample size; nonrandomized evidence was also considered, if randomized trials were not available.

Concurrently or subsequently published evidence was identified in PubMed using searches that combined terms pertaining to the tested interventions, disease and outcome, and terms pertinent to the search of randomized trials and meta-analyses. Searches followed the Cochrane algorithms for finding meta-analyses and randomized trials.

Data Extraction and Classification of Studies
For each eligible original study, I recorded the study name, intervention, disease and outcomes of interest, study design, sample size, main conclusions, and citation counts. For the articles presenting or summarizing other relevant research, I recorded the study design, total sample size, and the findings as compared with those of the original highly cited study.

Highly cited studies were classified as negative (when they claimed the tested experimental intervention was ineffective, harmful, or no better from the control intervention), unchallenged (when no other clinical research of eligible design and sample size was available to validate the claimed efficacy), contradicted, initially stronger effects, or replicated effects. The classification of studies in these categories was based on the final interpretation of the results by the authors in the “Abstract” and “Discussion” sections of their original publications. Highly cited articles were classified according to whether their authors suggested that an intervention was overall effective or ineffective. When both benefits and harms or caveats were presented, I focused on the net conclusion of whether the experimental intervention merits consideration for use in clinical practice. Subsequent research was classified in the same manner. Contradiction was declared when the original highly cited study claimed the intervention to be effective, while subsequent research showed it to be ineffective. When both original and subsequent research claimed the intervention was effective, studies were compared further regarding the effect size for the major clinical outcome, the durability of the treatment effect, and the generalizability and applicability to various settings. Initially stronger effects were defined when the relative risk reduction for the main outcome in the subsequent research was half or less compared with what had been proposed by the original highly cited study (regardless of whether confidence intervals might overlap or not), or when the subsequent research showed that the originally proposed benefit was of short duration or its applicability and generalizability was limited. Classification of the studies independently by another investigator yielded a highly similar profile (weighted Cohen κ = 0.92).

Correlates of Contradicted or Initially Stronger Effects
Among original highly cited studies with efficacy claims, analyses examined whether those with contradicted or initially stronger effects differed from the replicated and unchallenged ones in study design, publication year, sample size, type of disease (heart disease vs other), journal of publication, citation count, early citation count, and average citations per year after publication. Comparisons used the Mann-Whitney U test for continuous variables and Fisher exact test for binary variables.
Comparison of Highly Cited Articles Against Less Cited Articles

To evaluate whether highly cited studies differ from other studies that are not so highly cited in their findings and potential for contradiction, a control group of articles pertaining to the assessment of interventions was also assembled. Control-group articles were 1:1 matched for journal, year of publication, and design (randomized vs nonrandomized) against each of the highly cited articles. Control articles were selected by screening chronologically the contents of the pertinent journals for each pertinent year starting July 1 (to ensure approximately similar follow-up for citations with the highly cited articles against which they were matched). Other research was searched and the control articles were categorized in a similar fashion as described for the highly cited articles above. Differences between highly cited and control articles were examined with conditional logistic regression to account for matching.

Analyses
Analyses were performed in SPSS version 12.0 (SPSS Inc, Chicago, Ill) and StatXact (Cytel Corp, Boston, Mass). P values are 2-tailed, and P<.05 was considered statistically significant.

RESULTS

Eligible Studies

One hundred fifteen articles published between 1990 and 2003 had received more than 1000 citations (major general clinical journals, n=91; specialty journals, n=24). Of those, 66 were excluded (nonsystematic reviews or editorials, n=20; meta-analyses, n=7; case-control studies of risk factors, n=12; prevalence or incidence studies, n=8; cohort studies of risk factors, n=3; recommendations, n=3; prognostic models, n=4; time-trend analysis, n=1; case series, n=1; presentations of interviews, instruments, or assays n=3, classification criteria n=4). The remaining 49 articles were eligible (TABLE 1)9-57 of which 47 had appeared in major general medical journals. They included 43 randomized trials, 4 prospective cohorts, and 2 case series. In recent years (1998 through 2003), the 3 general journals have published an almost equal number of highly cited articles (New England Journal of Medicine, n=4; JAMA, n=3; Lancet, n=3). A smaller proportion of highly cited articles published in specialty journals than those published in general journals were eligible for the analysis (2/24 vs 47/91, P<.001), because highly cited articles in specialized journals were mostly nonsystematic reviews or editorials (10/24); classification criteria (4/24); or descriptions of standardized interviews, instruments, and assays (3/24). Many diverse disciplines were represented, but the most common topic was heart disease (n=27).

Four eligible highly cited studies showed no efficacy for the tested interventions. They contradicted prior claims for potential efficacy of vitamin E, beta carotene, and retinol for lung cancer and/or coronary artery disease; and showed an increased risk of coronary artery disease with hormone therapy in postmenopausal women (TABLE 2).

Of the 45 eligible highly cited studies with efficacy claims (TABLE 2), 7 (16%) were contradicted by subsequent research, and another 7 (16%) were found to have initially stronger effects. In all these 14 cases (BOX 1), subsequent studies were either larger or better controlled (randomized vs a nonrandomized original study). The findings of 20 highly cited articles (44%) were replicated (also with a larger sample size in subsequent research compared with the original highly cited study) and 11 (24%) had remained largely unchallenged.58-78

Comparison of Contradicted or Initially Stronger vs Replicated or Unchallenged Findings

Five of 6 highly cited nonrandomized studies had been contradicted or had initially stronger effects while this was seen in only 9 of 39 highly cited randomized trials (P=.008). TABLE 3 shows that trials with contradicted or initially stronger effects had significantly smaller sample sizes and tended to be older than those with replicated or unchallenged findings. There were no significant differences on the type of disease. The proportion of contradicted or initially stronger effects did not differ significantly across journals (P=.60).

There was also no significant difference in the number of citations received in the first 3 years between these 2 groups or in the overall number of citations over time although the citations per year tended to be nonsignificantly fewer in trials with contradicted or initially stronger effects.

Comparison of Highly Cited Articles Against Less-Cited Control Articles

Of the 49 articles in the control group79-127 (with median of 157 citations, range 38-815, until 2004), the findings of 2 articles68,138 were contradicted131-137 and 8 studies* had initially stronger effects130-137 (BOX 2); 20 articles† contained “positive” findings that were replicated68,138-155 and 8 studies§ remained unchallenged, and 11 studies‖ did not have any “positive” results; in 7 articles with some “positive” finding,79,87,91,98,108,112,120 there were also other interventions evaluated that had “negative” results although this mixture of “positive” and “negative” results had not been observed in any of the highly cited articles. The control articles had a larger number of “negative” findings compared with the highly cited articles (matched odds ratio [OR], 8; 95% confidence interval [CI], 1.8-34; P=.006 for any “negative” finding; and matched OR, 3.3; 95% CI, 0.92-12.0, P=.07 for exclusively “negative” findings). The highly cited articles did not have a smaller proportion of contradicted or initially stronger effects than the control articles if anything

*References 82, 90, 92, 95, 96, 109, 110, 117.
‡References 93, 97, 98, 102, 107, 114, 115, 120.
§References 84, 85, 94, 99, 100, 105, 113, 114, 119, 120, 122.

REFERENCES

## Table 1. Eligible Highly Cited Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Type of Intervention and Disease</th>
<th>Design</th>
<th>Sample Size</th>
<th>All 3-Year No. of Citations</th>
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<td>ACTG019, 91990</td>
<td>Zidovudine in asymptomatic HIV-1 infection</td>
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<td>Brown et al., 9190</td>
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<td>146</td>
<td>1312 394</td>
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<td>Moertel et al., 9190</td>
<td>Levamisole and fluorouracil for colon cancer</td>
<td>RCT</td>
<td>246</td>
<td>1050 259</td>
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<td>V-Heft II, 9191</td>
<td>Enalapril vs hydrochloride + isosorbide for CHF</td>
<td>RCT</td>
<td>904</td>
<td>1489 386</td>
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<td>Nurses’ Health Study, 9191</td>
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<td>Cohort</td>
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<td>1356 230</td>
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<td>NASCET, 9191</td>
<td>Carotid endarterectomy in high-grade stenosis</td>
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<td>659</td>
<td>2434 347</td>
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<td>HA-1A Sepsis, 9191</td>
<td>Monoclonal antibody to endotoxin for gram-negative sepsis</td>
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<td>SOLVD, 9191</td>
<td>Enalapril in patients with LV dysfunction</td>
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<td>SAVE, 9192</td>
<td>Captopril for patients after MI</td>
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<td>PAMI, 9193</td>
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<td>Captopril Collaborative, 9193</td>
<td>Captopril for slowing disease progression in diabetic nephropathy</td>
<td>Cohort</td>
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<td>Vitamin E for CAD prevention in men</td>
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<td>Rossaint et al., 9193</td>
<td>Nitric oxide inhalation for acute respiratory distress syndrome</td>
<td>Case series</td>
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<td>1025 399</td>
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<td>DCCCT, 9193</td>
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<td>EPIC, 9194</td>
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<td>RCT</td>
<td>2099</td>
<td>1461 233</td>
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<td>ABC, 9194</td>
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<td>29 133</td>
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<td>NINDS r-PA, 9195</td>
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<td>US Carvedilol, 9196</td>
<td>Carvedilol for CHF</td>
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<td>BERET, 9196</td>
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<td>18 314</td>
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<td>Physicians’ Health, 9197</td>
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<td>ACTG320, 9197</td>
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<td>EPILLOG, 9197</td>
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<td>HIT, 9198</td>
<td>Interferon alfa-2b + ribavirin vs interferon alone for chronic hepatitis C</td>
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<td>LIPE, 9198</td>
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<td>RALEs, 9199</td>
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<td>PERI, 9196</td>
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<td>AFCAPS/TexCAPS, 9198</td>
<td>Lovastatin for primary CAD prevention with average cholesterol</td>
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<td>WHI, 2002</td>
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<td>MRC Vitamin, 9191</td>
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<td>AS, 9194</td>
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<td>CAPRI, 9196</td>
<td>Clopidogrel vs aspirin in patients at risk of ischemic events</td>
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<td>CHAOS, 9196</td>
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<td>UKPD3 34, 9198</td>
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<td>Castagna et al, 91990</td>
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<td>Tamoxifen for breast cancer prevention</td>
<td>RCT</td>
<td>13 388</td>
<td>1470 745</td>
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Abbreviations: ABC, Alpha-Tocopherol, Beta Carotene Cancer Prevention; ACAS, Asymptomatic Carotid Arteriosclerosis Study; ACTG, AIDS Clinical Trials Group; AFCAPS/TexCAPS, Air Force/Texas Coronary Atherosclerosis Prevention Study; BENESTENT, Belgian Netherlands Stent; BERET, Beta Carotene and Retinol Efficacy Trial; CAD, coronary artery disease; CAPRI, Clopidogrel vs Aspirin in Patients at Risk of Ischemic Events; CARE, Cholesterol and Recurrent Events; CHAOS, Cambridge Heart Antioxidant Study; CHF, congestive heart failure; CIBIS-II, Cardiac Insufficiency Survival Study; DCCCT, Diabetes Control and Complications Trial; EPIC, Evaluation of TE3 for the Prevention of Ischemic Complications; EPILLOG, Evaluation in PTCA to Improve Long-Term Outcome with Alocarbina Glycoprotein IIb/IIIa Blockade; HA-1H, human IgM monoclonal antibody; HERS, Heart and Estrogen/progestin Replacement Study; HIT, Hepatitis Interventional Therapy; HIV-1, human immunodeficiency virus type 1; HOPE, Heart Outcomes Prevention Evaluation; HOT, Hypertension Optimal Treatment; IHT, International Hepatitis Interventional Therapy; LIPID, Long-Term Intervention with Pravastatin in Ischemic Disease; LV, left ventricular; MI, myocardial infarction; MRC, Medical Research Council; NASCET, North American Symptomatic Carotid Endarterectomy Trial; NINDS r-PA, National Institute of Neurological Disorders and Stroke recombinant tissue-Plasminogen Activator; NSABP P-1, National Surgical Adjuvant Breast and Bowel Project P-1; PAMI, Primary Angioplasty in Myocardial Infarction; PCI, percutaneous coronary intervention; PERI, Postmenopausal Estrogen/Progestin Interventions; RALES, Randomized Alldate Evaluation Study; RCT, randomized controlled trial; SAVE, Survival and Ventricular Enlargement; SHEP, Systolic Hypertension in the Elderly Program; SOLVD, Studies of Left Ventricular Dysfunction; STRESS, Stent Restenosis Study; UKPDS 34, UK Prospective Diabetes Study 34; V-Heft II, Vasodilator-Heart Failure Trial II; WHI, Women’s Health Initiative; WOSCOPS, West of Scotland Coronary Prevention Study; 4S, Scandinavian Simvastatin Survival Study.

*Projected.

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CONTRADICTED AND INITIALLY STRONGER EFFECTS IN HIGHLY CITED CLINICAL RESEARCH

Table 2. Other Research and Current State of Knowledge

<table>
<thead>
<tr>
<th>Highly Cited Study</th>
<th>Other Research</th>
<th>No. of Participants*</th>
<th>Comment on Current State of Knowledge</th>
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<tbody>
<tr>
<td><strong>Con contradicted studies</strong></td>
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<tr>
<td>Nurses’ Health Study</td>
<td>RCT46</td>
<td>16 608</td>
<td>Estrogen/progestin do not protect from but increase CAD risk in postmenopausal women</td>
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<td>HA-1A Sepsis</td>
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<td>Contrary to initial findings, HA-1A did not improve survival in gram-negative sepsis</td>
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<td>Health Professionals</td>
<td>RCT66</td>
<td>6966</td>
<td>Contrary to initial findings, vitamin E supplementation does not reduce CAD in men</td>
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<td>Nurses’ Health12</td>
<td>RCT66</td>
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<td>Contrary to initial findings, vitamin E supplementation does not reduce CAD in women</td>
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<td>Rossaint et al.22</td>
<td>MA RCT57</td>
<td>553</td>
<td>Despite initial claims of better oxygenation, nitric oxide does not improve survival in respiratory distress syndrome</td>
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<td>PEP10 (nitrative oxide)</td>
<td>RCT15</td>
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<td>Estrogen/progestin do not protect from but increase CAD risk in postmenopausal women</td>
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<td><strong>Initially stronger effects</strong></td>
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<tr>
<td>ACTG0192</td>
<td>MA RCT58</td>
<td>5566</td>
<td>The early benefit of zidovudine against HIV-1 disease progression decreases over time</td>
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<td>PAMI16</td>
<td>MA RCT60</td>
<td>2593</td>
<td>Superiority of angioplasty over IPIA thrombolysis may be less prominent than originally proposed</td>
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<td>STRESS10</td>
<td>MA RCT50</td>
<td>9918</td>
<td>Stents reduce restenosis and need for revascularization compared with simple angioplasty, but the effect may be inflated by lack of blinding and is probably modest</td>
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<td>BENESTENT27</td>
<td>MA RCT50</td>
<td>9918</td>
<td>Stents reduce restenosis and need for revascularization compared with simple angioplasty, but the effect may be inflated by lack of blinding and is probably modest</td>
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<td>NINDS rt-PA20</td>
<td>MA RCT70</td>
<td>2775</td>
<td>rt-PA may improve outcomes in acute ischemic stroke, but benefit is limited and seen only when treatment is given very early</td>
</tr>
<tr>
<td>ACAS13</td>
<td>MA RCT75</td>
<td>2440</td>
<td>Carotid endarterectomy has a small absolute benefit in asymptomatic stenosis &gt;60%</td>
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<tr>
<td>Zulphen Elderly14</td>
<td>MA cohorts76</td>
<td>105 000</td>
<td>Flavonoids reduce the risk of CAD modestly</td>
</tr>
<tr>
<td><strong>Replicated studies</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Brown et al.19</td>
<td>MA RCT30</td>
<td>148 321</td>
<td>Cholesterol and LDL lowering achieves significant risk reductions in CAD</td>
</tr>
<tr>
<td>Moir et al.10 (lipid lowering)</td>
<td>MA RCT30</td>
<td>3902</td>
<td>Fluorouracil adjuvant therapy improves survival in colon cancer</td>
</tr>
<tr>
<td>NASCET14</td>
<td>MA RCT51</td>
<td>6092</td>
<td>Carotid endarterectomy is effective in symptomatic patients with 70%-99% stenosis</td>
</tr>
<tr>
<td>SOLVD16</td>
<td>MA RCT34</td>
<td>7105</td>
<td>ACE inhibition reduces mortality and hospitalizations in patients with CHF</td>
</tr>
<tr>
<td>SAVE17</td>
<td>MA RCT34</td>
<td>105 357</td>
<td>ACE inhibition reduces mortality after MI</td>
</tr>
<tr>
<td>EPIC12</td>
<td>MA RCT68</td>
<td>20 137</td>
<td>Glycoprotein IIb/IIIa antagonists reduce cardiovascular events in percutaneous revascularization</td>
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<tr>
<td>WOSCOPS30</td>
<td>MA RCT59</td>
<td>148 321</td>
<td>Statins achieve significant risk reductions in CAD</td>
</tr>
<tr>
<td>CARE22</td>
<td>MA RCT59</td>
<td>148 321</td>
<td>Statins achieve significant risk reductions in CAD</td>
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<tr>
<td>US Caverdilol22</td>
<td>MA RCT71</td>
<td>10 135</td>
<td>-Blockers decrease mortality in patients with CAD</td>
</tr>
<tr>
<td>ACTG32025</td>
<td>MA RCT72</td>
<td>4686</td>
<td>Protease-inhibitor-based triple therapy improves survival compared with double nucleosides in HIV-1 infection</td>
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<tr>
<td>EPLOMG35</td>
<td>MA RCT56</td>
<td>20 137</td>
<td>Glycoprotein IIb/IIIa antagonists reduce cardiovascular events in percutaneous revascularization</td>
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<tr>
<td>HIT12</td>
<td>MA RCT73</td>
<td>6585</td>
<td>Interferon alfa-2b + ribavin has better outcomes than interferon alone in chronic hepatitis C</td>
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<tr>
<td>LIPID18</td>
<td>MA RCT50</td>
<td>148 321</td>
<td>Statins achieve significant risk reductions in CAD</td>
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<tr>
<td>SHEP88</td>
<td>MA RCT50</td>
<td>15 693</td>
<td>Treatment of isolated hypertension in elderly patients reduces the risk of stroke</td>
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<tr>
<td>APEX15</td>
<td>MA RCT50</td>
<td>148 321</td>
<td>ACE inhibition reduces mortality in elderly patients</td>
</tr>
<tr>
<td>4S10</td>
<td>MA RCT50</td>
<td>148 321</td>
<td>Statins achieve significant risk reductions in CAD</td>
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<td>IHT1303</td>
<td>MA RCT57</td>
<td>6585</td>
<td>Interferon alfa-2b plus ribavin has better outcomes than interferon alone in chronic hepatitis C</td>
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<tr>
<td>CIBIS-8F</td>
<td>MA RCT71</td>
<td>10 135</td>
<td>-Blockers decrease mortality in patients with CHF</td>
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<tr>
<td>All-trans-retinoid acid26</td>
<td>MA RCT77</td>
<td>346</td>
<td>All-trans retinoid is effective for acute promyelocytic leukemia</td>
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<td>NSABP P-11*</td>
<td>MA RCT78</td>
<td>28 406</td>
<td>Tamoxifen is effective for the prevention of breast cancer</td>
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<tr>
<td><strong>Unchallenged studies</strong></td>
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<tr>
<td>V-HIFII,12</td>
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<td>ACE inhibition is superior to vasodilators for CHF</td>
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<tr>
<td>Captopril Collaborative29</td>
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<td></td>
<td>ACE inhibition slows renal disease progression in diabetes with macroproteinaemia (benefit subsequently extended to microproteinaemia and patients without diabetes)</td>
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<tr>
<td>DCCT23</td>
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<td>Intensive insulin management of type 1 diabetes reduces microvascular complications (subsequent research has addressed increasingly intensive management)</td>
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<tr>
<td>ACTG07625</td>
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<td>Zidovudine reduces the risk of perinatal HIV-1 transmission (subsequent research has addressed shorter and more convenient regimens)</td>
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<tr>
<td>Physicians’ Health34</td>
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<td>Aspirin prevents MI in patients with high levels of C-reactive protein</td>
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<tr>
<td>MRC Vitamin57</td>
<td></td>
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<td>Folate supplementation significantly reduces the risk of neural tube defects (subsequent research has addressed various doses and modes of administration of folate)</td>
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<tr>
<td>RALES30</td>
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<td></td>
<td>Spironolactone reduces morbidity and mortality in CHF (no other similar trial)</td>
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<tr>
<td>HOPE30</td>
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<td></td>
<td>Ramipril prevents CAD events in high-risk patients without left ventricular dysfunction (no other similar trial)</td>
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<tr>
<td>CAPRIE20</td>
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<td>Clopidogrel seems superior to aspirin in preventing stroke and MI in patients at risk of ischemic stroke (subsequent research has addressed the combination of clopidogrel and aspirin)</td>
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<tr>
<td>HOT24</td>
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<td></td>
<td>Intensive blood pressure lowering decreases the risk of cardiovascular events (2 much smaller trials have shown similar effects of intensive blood pressure lowering in patients with diabetes)</td>
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<tr>
<td>UKPDS 3454</td>
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<td></td>
<td>Intensive management of type 2 diabetes reduces the risk of microvascular complications</td>
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<tr>
<td><strong>Negative studies</strong></td>
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<tr>
<td>ABC</td>
<td></td>
<td></td>
<td>Neither a-tocopherol nor beta carotene prevents lung cancer</td>
</tr>
<tr>
<td>BERET33</td>
<td></td>
<td></td>
<td>Neither beta carotene nor retinol prevent lung cancer or CAD</td>
</tr>
<tr>
<td>HER233</td>
<td></td>
<td></td>
<td>Estrogen/progestin are ineffective for secondary CAD prevention in postmenopausal women</td>
</tr>
<tr>
<td>WHI24</td>
<td></td>
<td></td>
<td>Estrogen/progestin do not protect from but increase CAD risk in postmenopausal women</td>
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</table>

Abbreviations: The abbreviations of the highly cited studies correspond to the popular names listed in Table 1. ACE, angiotensin-converting enzyme; CAD, coronary artery disease; CHF, congestive heart failure; HA-1A, human IgM monoclonal antibody; HIV-1, human immunodeficiency virus type 1; LDL, low-density lipoprotein; MA, meta-analysis; RCT, randomized controlled trial; rt-PA, recombinant tissue-type plasminogen activator; IPIA, tissue plasminogen activator.

*For meta-analyses, the number of participants refers to the total sample size of all studies (large and small ones) and includes the sample size of the original highly cited study.

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there was a trend for more contradicted or initially stronger effects in the highly cited articles (matched OR, 1.6; 95% CI, 0.6-4.0; P = .35; matched OR, 6.0; 95% CI, 0.7-50; P = .10 when limited to contradicted findings).

**COMMENT**

Original highly cited articles about medical interventions are published almost exclusively in 3 general medical journals. Actually, there has been an approxi-
than a third of the top-cited randomized trials published from 1990 through 1995 have already been affected, while for more recent trials, the time frame is still early and more may be contradicted in the future. Sample size seems to be important, with smaller sample sizes in trials that have met controversy vs those that have not.

The classification of studies in this analysis involves many judgments pertaining to the complexity of studying a given research question with somewhat different populations, interventions, durations, and outcomes. However, these studies are widely known for their inferences and this is also proven by the high interrater agreement. Nevertheless, it should also be acknowledged that although the classification was performed in duplicate, the searches were performed by only 1 investigator. It is unavoidable that some other investigators may feel differently about the categorization of specific studies, especially for topics that may also have heavy debates surrounding them. However, this is unlikely to change the aggregate picture about refutation rates.

The examination of contradictions and refutations offers a fascinating look at the process of science. Four of the highly cited articles examined herein were refuting investigations with “negative” results. However, in a sense, even the other highly cited articles with “positive” results refuted prior knowledge and practice by introducing new concepts and proposing new interventions. We should acknowledge that there is no proof that the subsequent studies and meta-analyses were necessarily correct. A perfect gold standard is not possible in clinical research, so we can only interpret results of studies relative to other studies. Whenever new research fails to replicate early claims for efficacy or suggests that efficacy is more limited than previously thought, it is not necessary that the original studies were totally wrong and the newer ones are correct simply because they are larger or better controlled. Alternative explanations for these discrepancies may include differences in disease spectrum, eligibility criteria, or the use of concomitant interventions. Different studies on the same question are typically not replicas of each other. In fact discrepancies may be interesting on their own because they require careful scrutiny of the data and reappraisal of our beliefs. Thus, it is probably not surprising that the citation rate of these refuted studies did not seem to be much affected. Nevertheless, the controversy generates considerable uncertainty for clinical practice and none of the contradicted interventions is currently recommended by practice guidelines.

The mere fact that a study is highly cited suggests that there is a strong active interest in the questions addressed from a clinical or research perspective. This may increase the chances that other, larger trials may eventually be conducted. However, for most clinical questions of interest, no large trials are ever conducted and evidence is based only on small trials or nonrandomized studies. Small trials or meta-analyses thereof may often be refuted subsequently by large trials when such large trials are performed. Small studies using surrogate markers may also sometimes lead to erroneous clinical inferences. There were only 2 studies with typical surrogate markers among the highly cited studies examined herein, but both were subsequently contradicted in their clinical extrapolations about the efficacy of nitric oxide and hormone therapy. In the case of initially stronger effects, the differences in the effect sizes could often be within the range of what would be expected based on chance variability. This reinforces the notion that results from clinical studies, especially early ones, should be interpreted using not only the point estimates but also the uncertainty surrounding them. However, besides differences in effect sizes, most initially stronger effects pertained also to issues of durability, generalizability, or applicability of the proposed effects, as discussed above. Thus, clinicians should be aware that these important aspects may not be fully settled when an important treatment breakthrough is announced.

A third of the most-cited clinical research seems to have replication problems, and this seems to be as large, if not larger, than the vast majority of other, less-cited clinical research. The current analysis found that matched studies that were not so highly cited had a greater proportion of “negative” findings and similar or smaller proportions of contradicted results as the highly cited ones. Publication bias and time-lag bias favoring the rapid and prominent publication of “positive” findings may underlie some of the observed phenomena. Highly cited articles are already a selected sample with underrepresentation of “negative” findings compared with the average article on interventions published in major journals. It is possible that high-profile journals may tend to publish occasionally very striking findings and that this may lead to some difficulty in replicating some of these findings. Poynard et al evaluated the conclusions of hepatology-related articles published between 1945 and 1999 and found that, overall, 60% of these conclusions were

### Table 3. Comparison of Characteristics and Citation Counts of Randomized Trials With Contradicted or Initially Stronger Effects vs Those With Replicated or Unchallenged Findings

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Contradicted or Initially Stronger Effects (n = 9)</th>
<th>Replicated or Unchallenged (n = 30)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Published in 1990-1995</td>
<td>8</td>
<td>15</td>
<td>.06</td>
</tr>
<tr>
<td>Heart disease topic</td>
<td>4</td>
<td>13</td>
<td>1.00</td>
</tr>
<tr>
<td>Sample size, median (IQR)</td>
<td>624 (403-1500)</td>
<td>2165 (892-5201)</td>
<td>.009</td>
</tr>
<tr>
<td>All citations received, median (IQR)</td>
<td>1427 (1104-2046)</td>
<td>1542 (1255-2513)</td>
<td>.43</td>
</tr>
<tr>
<td>Citations in 3 y, median (IQR)</td>
<td>485 (421-591)</td>
<td>622 (393-825)</td>
<td>.32</td>
</tr>
<tr>
<td>Citations per year, median (IQR)</td>
<td>149 (105-215)</td>
<td>214 (146-263)</td>
<td>.07</td>
</tr>
</tbody>
</table>

Abbreviations: IQR, interquartile range.
CONTRADICTED AND INITIALLY STRONGER EFFECTS IN HIGHLY CITED CLINICAL RESEARCH

Box 2. Contradicted and Initially Stronger Effects in Control Studies

Contradicted Findings

In a prospective cohort,91 vitamin A was inversely related to breast cancer (relative risk in the highest quintile, 0.84; 95% confidence interval [CI], 0.71-0.98) and vitamin A supplementation was associated with a reduced risk (P = .03) in women at the lowest quintile group; in a randomized trial28 exploring further the retinoid-breast cancer hypothesis, fenretinide treatment of women with breast cancer for 5 years had no effect on the incidence of second breast malignancies.

A trial (n = 31) showed that cladribine significantly improved the clinical scores of patients with chronic progressive multiple sclerosis.119 In a larger trial of 199 patients, no significant treatment effects were found for cladribine in terms of changes in clinical scores.120

Initially Stronger Effects

A trial (n = 28) of aerosolized ribavirin in infants receiving mechanical ventilation for severe respiratory syncytial virus infection showed significant decreases in mechanical ventilation (4.9 vs 9.9 days) and hospital stay (13.3 vs 15.0 days). A meta-analysis of 3 trials (n = 104) showed a decrease of only 1.8 days in the duration of mechanical ventilation and a nonsignificant decrease of 1.9 days in duration of hospitalization.130

A trial (n = 406) of intermittent diazepam administered during fever to prevent recurrence of febrile seizures showed a significant 44% relative risk reduction in seizures. The effect was smaller in other trials and the overall risk reduction was no longer formally significant; moreover, the safety profile of diazepam was deemed unfavorable to recommend routine preventive use.

A case-control and cohort study evaluation showed that the increased risk of sudden infant death syndrome among infants who sleep prone is increased by use of natural-fiber mattresses, swaddling, and heating in bedrooms. Several observational studies have been done since, and they have provided inconsistent results on these interventions, in particular, they disagree on the possible role of overheating.

A trial of 54 children showed that the steroid budesonide significantly reduced the croup score by 2 points at 4 hours, and significantly decreased readmissions by 86%. A meta-analysis (n = 3736) showed a significant improvement in the Westley score at 6 hours (1.2 points), and 12 hours (1.9 points), but not at 24 hours. Fewer return visits and/or re(admissions occurred in patients treated with glucocorticoids, but the relative risk reduction was only 50% (95% CI, 24%-64%).

A trial (n = 35) showed that misoprostol was as effective as dinoprostone for termination of second-trimester pregnancy and was associated with fewer adverse effects than dinoprostone. A subsequent trial showed equal efficacy, but a higher rate of adverse effects with misoprostol (74%) than with dinoprostone (47%).

A trial (n = 30) comparing botulinum toxin vs glyceryl trinitrate for chronic anal fissure concluded that both are effective alternatives to surgery but botulinum toxin is the more effective nonsurgical treatment (1 failure vs 9 failures with nitroglycerin). In a meta-analysis of 31 trials, botulinum toxin compared with placebo showed no significant efficacy (relative risk of failure, 0.75; 95% CI, 0.32-1.77), and was also no better than glyceryl trinitrate (relative risk of failure, 0.48; 95% CI, 0.21-1.10); surgery was more effective than medical therapy in curing fissure (relative risk of failure, 0.12; 95% CI, 0.07-0.22).

A trial of acetylecysteine (n = 83) showed that it was highly effective in preventing contrast nephropathy (90% relative risk reduction). There have been many more trials and many meta-analyses on this topic. The latest meta-analysis shows a non-significant 27% relative risk reduction with acetylecysteine.

A trial of 129 stunted Jamaican children found that both nutritional supplementation and psychosocial stimulation improved the mental development of stunted children; children who got both interventions had additive benefits and achieved scores close to those of nonstunted children. With long-term follow-up, however, it was found that the benefits were small and the 2 interventions no longer had additive effects.

considered to be true in 2000 and that there was no difference between randomized and nonrandomized studies or high- vs low-quality studies. Allowing for somewhat different definitions, the higher rates of refutation and the generally worse performance of nonrandomized studies in the present analysis may stem from the fact that I focused on a selected sample of the most noticed and influential clinical research. For such highly cited studies, the turnaround of “truth” may be faster; in particular nonrandomized studies may be more likely to be probed and challenged than nonrandomized studies published in the general literature.

Finally, a certain proportion of highly cited trials may remain unchallenged. Sometimes the evidence from the original study may seem so overwhelming that further similar studies are deemed unethical to perform. The original study may be widely considered as a milestone for clinical practice and may provide the gold standard for testing new interventions. However, sometimes other, validating research may be in the works. Clinical research is time-consuming and challenging results may take several years to generate and publish. Therefore evidence from recent trials, no matter how impressive, should be interpreted with caution, when only one trial is available. It is important to know whether other similar or larger trials are still ongoing or being planned. Therefore, transparent and thorough trial registration is of paramount im-

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portance in order to limit pre-mature
claim for efficacy.

Author Contributions: Dr Ioannidis had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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