measure the effect of antidepressant medication. Depression was defined as current using DSM-IV criteria for major or minor depression or dysthymia. The initial PI was cognitive behavioral therapy (CBT) with referral to a psychiatrist for SSRI (sertraline 50 mg titrated to 200 mg as necessary) if their baseline depression score was very high or there was less than a 50% improvement in depression score at 5 weeks. Primary end point was event-free survival defined as the absence of death or recurrent MI. To relate exposure to antidepressants to subsequent morbidity and mortality, the data were analyzed using a time-dependent covariate model.

Results: Mean age was 60 years. Those taking antidepressants at any time were younger, more often female, less often minorities, and more often smokers. Among patients who were depressed at enrollment, the cumulative rates of any antidepressant use in the UC and PI arms were 4.8% and 9.1% at baseline, 13.4% and 20.5% at the 6-month visit, and 20.6% and 28% by the end of follow-up. Approximately 75% of antidepressants were in the SSRI class, and median duration of use was 12 months in both groups. During a mean follow-up of 29 months, 457 fatal and nonfatal cardiovascular (CV) events occurred. The risk of death or recurrent MI was significantly lower in patients taking SSRIs (adjusted hazard ratio [HR] 0.57; 95% CI 0.38–0.84), as were the risk of all-cause mortality (adjusted HR 0.59; 95% CI 0.37–0.96) and recurrent MI (adjusted HR 0.53; 95% CI 0.32–0.90), compared with patients who did not use SSRIs. For patients taking nonselective serotonin reuptake inhibitor antidepressants, the comparable HRs (95% CIs) were 0.72 (0.44–1.18), 0.64 (0.34–1.22) and 0.73 (0.38–1.38) for risk of death or recurrent MI, all-cause mortality, or recurrent MI, respectively, compared with nonusers. There was similar reduction in CV events associated with use of SSRIs and history of depression prior to the index event.

Conclusions: Use of SSRIs in depressed patients who experience an acute MI might reduce subsequent CV morbidity and mortality. A controlled trial is needed to examine this important issue.

Perspective: Depression is a risk factor for coronary disease, and depression post-MI is a risk factor for subsequent events and mortality. It is not yet clear whether psychological depression itself or the associated neurohumoral (catecholamines, cortisol, decreased heart rate variability) and inflammatory milieu (e.g., increased IL-C and CRP) are responsible. The findings in this secondary analysis support a protective effect of the SSRIs post-MI, which may or may not be working via reducing depression. A randomized controlled trial to evaluate the effects of SSRIs post-MI on CV and overall mortality should be performed in conjunction with contemporary medical therapy. This study is not sufficient to establish the routine use of SSRIs for this indication. Melvyn Rubenfire/Kim Eagle

Contradicted and Initially Stronger Effects in Highly Cited Clinical Research

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Study Question: To understand how frequently highly cited studies are contradicted or find effects that are stronger than in other similar studies and to discern whether specific characteristics are associated with such refutation over time.

Methods: The researcher examined all original clinical research studies published in three major general clinical journals or high-impact-factor specialty journals between 1990–2003 and cited more than 1000 times in the literature. The results of highly cited articles were compared against subsequent studies of comparable or larger sample size and similar or better controlled designs. The same analysis was also performed comparatively for matched studies that were not so highly cited.

Results: Of 49 highly cited original clinical research studies, 45 claimed that the intervention was effective. Of these, 7 (16%) were contradicted by subsequent studies, 7 others (16%) had found effects that were stronger than those of subsequent studies, 20 (44%) were replicated, and 11 (24%) remained largely unchallenged. Five of 6 highly cited nonrandomized studies had been contradicted or had found stronger effects versus 9 of 39 randomized controlled trials ($p=0.008$). Among randomized trials, studies with contradicted or stronger effects were smaller ($p=0.009$) than replicated or unchallenged studies, although there was no statistically significant difference in their early or overall citation impact. Matched control studies did not have a significantly different share of refuted results than did highly cited studies, but they included more studies with "negative" results.

Conclusions: The conclusion was that contradiction and initially stronger effects are not unusual in highly cited research of clinical interventions and their outcomes.

Perspective: This innovative study suggests that contradiction and initially stronger effects are common in highly cited research. The extent to which high cited studies may provoke contradictions and vice versa needs more study. Controversies are most common with highly cited nonrandomized studies, but even the most highly cited randomized trials may be challenged and refuted over time, especially studies with modest sample size. 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. The analysis makes a strong case for transparent and thorough trial registration in order to limit premature claims for efficacy. Debabrata Mukherjee