Supplementary Online Content


eAppendix. Supplementary Material

This supplementary material has been provided by the authors to give readers additional information about their work.

eAppendix

Supplementary Material

Further details about determining whether studies were active comparator or inactive comparator studies

Each study was classified as either an active comparator study or an inactive comparator study as follows: studies in which a medication or medication strategy was compared either to a placebo group or a group receiving no therapy were designated as inactive comparator studies while studies in which a medication or medication strategy was compared with at least one other active therapy were designated as active comparator studies. Studies with three or more treatment arms in which at least two arms were active treatments and one was an inactive control were also designated as active comparator studies.

Additionally, studies were counted as active comparator studies only if subjects in more than one treatment arm received active therapies that were not available to subjects in other treatment arms. For example, a hypothetical study comparing a diabetes medication with a nutritional intervention in patients with diabetes would only be considered an active comparator study if the subjects in the medication arm did not also receive the nutritional intervention. Similarly, a hypothetical study comparing optimal medication therapy for coronary artery disease with a percutaneous coronary intervention (PCI) would only be considered an active comparator study if the PCI group did not also receive optimal medication therapy. In fact, a study comparing optimal medication therapy with PCI plus optimal medication therapy would not be included in our analysis at all since the treatment under study would be PCI, not a medication.

Studies in which subjects received different medications within a class

In some observational studies and meta-analyses in this analysis, subjects in a given treatment arm received different medications within a class of medications. For example, in a hypothetical study examining the effects of statin therapy in reducing the risk of cardiovascular disease relative to a placebo, subjects might receive different statins such as atorvastatin and simvastatin. If there were direct formal comparisons (with a reported P-value) between subjects receiving different statins (e.g. between subjects receiving atorvastatin and simvastatin), the study was counted as an active comparator study. However if there were no direct formal comparisons between subjects receiving active medications, the study was counted as an inactive comparator study, even if there were individual comparisons between subjects who received specific statins such as atorvastatin and simvastatin and a placebo group.
**Further details about determining the type of active comparator studies**

As noted in the methods, for the purposes of this study, steroid injections into joints, locally active injected medications, topical medications, and oral vitamins, minerals, and compounds that are legally marketed in the U.S. as dietary supplements were considered to be non-pharmacologic therapies while studies involving intravenous vitamins and electrolytes were counted as medications. Therefore, studies comparing medications to steroid injections, locally active injected medications, topical medications, or oral vitamins, minerals, or dietary supplements were classified as active comparator studies in which medications were compared to non-pharmacologic therapies.

Studies comparing different pharmacologic strategies in which each study arm received different medications (e.g. a study comparing rate control and rhythm control for the treatment of atrial fibrillation in which the rate control group received a beta blocker and the rhythm control group received amiodarone) were classified as studies of different pharmacologic strategies.

**Further details about determining whether randomized trials reported positive results**

When two medications were compared with each other rather than a medication with an inactive control group, the more recently FDA approved medication was designated as the treatment arm and the other arm was designated as the control. Non-FDA approved medications were automatically considered to be the newer medication, and in none of the studies were two non-FDA approved medications compared. When the control arm was a non-pharmacologic therapy, the medication arm was designated as the treatment arm. And when different doses, durations of therapy, frequencies of medication administration, or different medication strategies were compared, the arm receiving more medication was designated as the treatment arm except when this was not clear; in these cases, the study was deemed ineligible for this analysis.

As noted in the methods section, trials were also considered ineligible for this analysis if there was not a pre-specified primary endpoint, or if there were three or more treatment arms because, in these cases, it was not possible to determine which two arms should be considered when determining if there was a positive result. An exception to this were trials in which different doses of a medication were compared with an inactive control group; in these cases, if any one of the medication doses was superior to the inactive control the study was deemed to have a positive result.

**Pooled randomized trials**

Pooled reports of multiple original randomized trials that were published as one article were counted as one study rather than as multiple studies. These studies were classified as randomized trials in our analysis rather than meta-analyses since these were original reports. When analyzing pooled reports of multiple original randomized trials that were published as one article, studies classifications were assigned if any trial within the analysis fulfilled a particular characteristic. For the most part, however, these pooled analyses concerned randomized trials with identical or nearly identical study characteristics.