Are Observational Studies More Informative Than Randomized Controlled Trials in Hypertension?

Con Side of the Argument

Giuseppe Schillaci, Francesca Battista, Giacomo Pucci

The very first rigorously designed, randomized controlled trial (RCT) in the history of modern medicine was published in 1948. The study, designed and carried out by the Streptomycin in Tuberculosis Trials Committee of the Medical Research Council, demonstrated the efficacy of streptomycin in treating pulmonary tuberculosis on top of bed rest, which was the best available treatment at that time. In the field of hypertension treatment and cardiovascular prevention, the history of event-based RCTs began in 1967, when the cardiovascular benefits and risks of antihypertensive drug treatment were evaluated in the setting of the Veterans Administration Cooperative Study in Hypertension. In that trial, 143 patients with severe hypertension were randomized to receive blood pressure (BP)-lowering drug treatment or matched placebo for 11 months. A major morbid or fatal event was observed in 26 of 70 patients who received placebo (37%) and in only 1 of 73 patients under active treatment (1%). The amazing results of this landmark trial established beyond any doubt the striking cardiovascular benefits of antihypertensive drug treatment of hypertension at a time when controversy still persisted regarding the supposedly deleterious effects of BP reduction on organ perfusion.

Ever since, RCTs have represented a formidable tool for evaluating risks and benefits of hypertension treatment. Over the past 50 years, the remarkable progress in treatment and control of high BP, one of the most outstanding achievements of modern medicine, has been driven by the results of many large, event-based RCTs. The influential position of RCTs in clinical and therapeutic research as opposed to real-world observational studies (surveys, registries, and retrospective analyses of existing databases) originates from their high internal validity (ie, the power to address clinical questions with a low level of internal bias). A list of strengths and weaknesses of RCTs and observational studies is given in Table 1. The present review examines values and limitations of RCTs and observational studies, with a focus on the problems arising when evidence from observational studies is used to inform decisions in the clinical practice, in the absence of less biased sources of evidence.

Internal Versus External Validity

In studies of disease risk, dependable results derive from the minimization of both random errors (imprecision) and systematic errors (biases). Because random errors are inversely proportional to the number of individuals developing the disease during follow-up, the first key determinant of the internal validity of a clinical study is represented by the numbers of observed events. This is of particular concern when effects of plausibly moderate size are to be detected. This requirement has led to the conception of RCTs with many hundreds or even thousands of incident cardiovascular events (mega-trials). Other studies that also tend to minimize random errors are meta-analyses, which combine the results of multiple individual studies using appropriate statistical methods, and observational studies drawn from large databases based on routinely collected data.

The second key determinant of the internal validity of a clinical study is to what extent the results of the research may be affected by systematic errors or biases. Minimization of systematic error is necessary to establish cause-and-effect
Table 1. Strengths and Weaknesses of Randomized Controlled Trials and Observational Studies

<table>
<thead>
<tr>
<th>Feature of the Study</th>
<th>Randomized Controlled Trials</th>
<th>Observational Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Are groups well matched?</td>
<td>Yes*</td>
<td>Generally not†‡</td>
</tr>
<tr>
<td>Is interpretation exposed to the effects of confounding factors?</td>
<td>No/little*</td>
<td>Yes†</td>
</tr>
<tr>
<td>Are methodological rules well established?</td>
<td>Yes*</td>
<td>Less well established†</td>
</tr>
<tr>
<td>Is previous registration required?</td>
<td>Usually yes*</td>
<td>Generally not†</td>
</tr>
<tr>
<td>Is selective reporting a concern?</td>
<td>No*</td>
<td>Yes†</td>
</tr>
<tr>
<td>Cost</td>
<td>Higher†</td>
<td>Lower*</td>
</tr>
<tr>
<td>Time needed for carrying out the study</td>
<td>Longer†</td>
<td>Shorter*</td>
</tr>
<tr>
<td>Number of participants</td>
<td>Lower†</td>
<td>Greater*</td>
</tr>
<tr>
<td>Does protocol reflect clinical care?</td>
<td>Usually not†</td>
<td>Usually yes*</td>
</tr>
<tr>
<td>Duration of observation</td>
<td>Shorter†</td>
<td>May be longer*</td>
</tr>
</tbody>
</table>

*Strength. †Weakness. ‡Adjustment for propensity to receive a particular treatment (propensity score matching) may increase the comparability of study groups.

relationships between a given intervention (or independent variable) and its outcome (dependent variable). The pure experiment in the form of a randomized controlled longitudinal study, also referred to as an RCT, is often regarded as the gold standard, and is believed to yield the lowest chance of bias. Nonrandomized studies, also referred to as quasi-experimental, observational, or correlation studies, are considered as having a lower internal validity. A graphic representation of the pyramidal hierarchy of the different types of studies based on their internal validity is given in the Figure.

The internal validity of a given study has little relation with its external validity, or generalizability. For instance, an RCT has a high internal validity, but may be less suited to generalization, which restricts its practical usability. Nonrandomized longitudinal studies, however, have a lower internal validity, but can nevertheless be very useful for management practice. In clinical practice, an answer to the question “How much does this treatment work?” is sometimes less relevant than the response to questions like “In what circumstances does it work or for whom does it work?”. A study design is never strong or weak in itself: it all depends on the question(s) to be addressed (Table 2).

Figure. Levels of evidence for various research designs, based on their internal validity. RCTs indicates randomized controlled trials.

Table 2. Suitability of Various Study Designs to Address Different Clinical Research Questions

<table>
<thead>
<tr>
<th>Domain</th>
<th>Research Question</th>
<th>Randomized Controlled Trials</th>
<th>Observational Longitudinal Studies</th>
<th>Cross-Sectional Surveys</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effectiveness</td>
<td>Does it work? Does it work better than other treatments?</td>
<td>++</td>
<td>+</td>
<td>−</td>
</tr>
<tr>
<td>Safety</td>
<td>Will it do more good than harm?</td>
<td>+</td>
<td>+</td>
<td>−</td>
</tr>
<tr>
<td>Context</td>
<td>In what circumstances does it work, for whom?</td>
<td>−</td>
<td>−</td>
<td>+</td>
</tr>
<tr>
<td>Acceptability</td>
<td>Will the target group accept the intervention?</td>
<td>−</td>
<td>−</td>
<td>+</td>
</tr>
<tr>
<td>Prevalence</td>
<td>How often is this intervention applied?</td>
<td>−</td>
<td>−</td>
<td>+</td>
</tr>
<tr>
<td>Appropriateness</td>
<td>Is this the right intervention for this target group?</td>
<td>−</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Explanation</td>
<td>How does it work, why does it work?</td>
<td>−</td>
<td>−</td>
<td>+</td>
</tr>
</tbody>
</table>

++ indicates very good; +, good; −, fair; and −−, poor.

Cause-and-Effect Relationship: Misinformation Resulting From Observational Studies

As shown in Table 2, observational studies can be very informative when addressing issues like the acceptability and appropriateness of a given intervention for a certain target group. However, because of the presence of a high degree of bias, their findings should be taken with greater caution or can even be misleading when they are used to establish cause-and-effect relationships. Although estimates of treatment effects are often similar in observational studies and in RCTs, this may not always be the case. We discuss a number of clinically relevant conclusions drawn from real-world observational studies in the field of hypertension treatment and cardiovascular prevention, which have subsequently shown to be false (Table 3).

Does Antihypertensive Treatment Prevent Ischemic Heart Disease?

Observational studies have reported increased risks of coronary heart disease in patients treated with antihypertensive drugs. In a population-based cohort study of elderly Swedish men, myocardial infarction or death because of chronic ischemic cardiac disease were more frequent over a 10-year follow-up in those subjects who were taking antihypertensive drugs than in those who were not, and this rate was reduced but still raised after adjustment for potential confounders, such as smoking habits, BP, dyslipidemia, diabetes mellitus, obesity, and serum creatinine concentration. Similarly, in a large Norwegian nationwide screening of 21,314 men aged 35 to 49 years, BP-lowering treatment was associated with increased mortality from all causes, coronary heart disease, and noncardiovascular causes. Again, these associations remained significant after controlling for pretreatment BP, cholesterol, age, smoking, and body mass index.

These data have been overturned by a large number of RCTs, which have uniformly and unequivocally demonstrated...
Table 3. A List of Conclusions Derived From Observational Studies, Which Have Been Eventually Confuted by Properly Designed Randomized Controlled Trials

<table>
<thead>
<tr>
<th>Conclusion</th>
<th>Observational Studies</th>
<th>Randomized Controlled Trials and Their Meta-Analyses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antihypertensive drug treatment increases the risk of ischemic heart disease</td>
<td>6, 7</td>
<td>8, 9</td>
</tr>
<tr>
<td>Aspirin use increases the risk of coronary heart disease</td>
<td>10, 11</td>
<td>12</td>
</tr>
<tr>
<td>Calcium-channel blockers increase the risk of myocardial infarction in hypertension</td>
<td>15, 16</td>
<td>18–20</td>
</tr>
<tr>
<td>Postmenopausal estrogen replacement reduces cardiovascular morbidity and mortality</td>
<td>23–25</td>
<td>26, 27</td>
</tr>
<tr>
<td>Achieved blood pressure values well lower than the usual goal of below 140/90 mm Hg carry substantial benefits (the lower, the better)</td>
<td>28, 29</td>
<td>34–37</td>
</tr>
</tbody>
</table>

that the same treatments produce a marked reduction in stroke and coronary events, as well as in cardiovascular and all-cause mortality, both in systolic–diastolic and in isolated systolic hypertension.6,7

Does Aspirin Increase the Risk of Ischemic Heart Disease?

In some observational studies, regular aspirin use has been associated with an increased incidence of coronary heart disease. In a cohort of 13,987 elderly US subjects without a reported history of angina, myocardial infarction, or stroke who were followed up for 6.5 years, the risk of incident ischemic heart disease was increased by 70% to 90% in those who took aspirin daily compared with nonusers.10 Similarly, in the Swedish National Diabetes Register, a population-based cohort study of 18,646 patients with type 2 diabetes mellitus free from cardiovascular disease followed up for 3.9 years, there was a >19% risk of incident coronary heart disease in subjects treated with aspirin. This difference remained significant after adjustment for several baseline risk factors and characteristics by stratification with a propensity score.11 The authors’ conclusions10,11 that the daily use of aspirin increases the risk of ischemic heart disease were refuted later. Indeed, aspirin has clearly been shown in carefully conducted RCTs to reduce the risks of myocardial infarction and coronary heart disease in people without prevalent cardiovascular disease, without any difference in proportional benefits in diabetic versus nondiabetic individuals.12 Also, given the absence of large trials specifically conducted in diabetic subjects, 2 current large placebo-controlled trials are specifically testing the effects of aspirin in adults with diabetes mellitus but no known vascular disease.13,14

Do Calcium-Channel Blockers Increase the Risk of Myocardial Infarction?

In 1995, the publication of 2 studies reporting adverse coronary events with calcium-channel blockers15,16 generated enduring concern in the scientific and lay communities.17 In a population-based case-control study of hypertensive patients carried out among enrollees of the Group Health Cooperative of Puget Sound, Psaty et al13 reported a 60% increase in the risk of myocardial infarction for calcium-channel blockers compared with other BP-lowering drug classes. Soon after, Pahor et al16 published the data from the hypertensive subset of a large European cohort, which documented higher mortality and coronary events for calcium-channel blockers than for β-blockers.

Over the ensuing years, the circumstantial evidence for the potentially dangerous side effects of calcium-channel blockers15,16 was contradicted when put to the test of double-blind RCTs. A number of large, active-controlled RCTs failed to show any association between the use of calcium-channel blockers and increased coronary or cardiovascular morbidity.18–20 Subsequent meta-analyses confirmed, with a greater statistical power, that the benefits of a treatment based on calcium-channel blockers are similar to or only slightly different from that based on other drug classes, with the possible exception of a somewhat better protection against stroke afforded by calcium-channel blockers.6,7

How can we explain these discrepant findings between observational studies and RCTs? Observational studies evaluating drug effects are affected by the problem of confounding by indication.21 In the observational design, treatment allocation is not under the control of the investigator, but at the discretion of the prescribing physician. Because the physician’s choice of the drug of interest depends on a number of patient characteristics, exposed and unexposed subjects will be fundamentally different. Such differences may affect the study outcome, and the design of observational studies does not allow controlling completely for this effect. In the case of calcium-channel blockers, these drugs might have been more frequently prescribed to patients with higher comorbidities, also in the light of the fact that they are approved by the Food and Drug Administration for the treatment of stable angina pectoris. The same applies to the above-reported effects of antithypertensive drug treatment6,7 and aspirin10,11 when evaluated within a nonrandomized database. Techniques to adjust for these dissimilarities are generally incomplete: the totality of clinical characteristics driving treatment selection is almost never fully measured and may, in fact, never be fully measurable.21,22 As a consequence, it is difficult to attribute a given effect to the drug rather than to the clinical characteristics that prompted its use.

However, negative results of RCTs may also be influenced by their design. First, a substantial proportion of patients in these trials withdrew from their assigned treatment (drop-out effect). Because the main results of the RCTs are reported according to the intention-to-treat analysis, this may tend to dampen any true differences. Second, combination treatment is more the rule than the exception in hypertension management and in event-based RCTs. In most trials involving calcium-channel blockers, although the randomized comparison was between single-drug classes, most patients were receiving >1 drug during the study (add-on effect). This means that the comparison is not among given drugs but among regimens based on given drugs (or drug classes). This would similarly blunt any differences among drug classes. In
summary, long-term, event-based active-controlled RCTs may generally tend to overestimate the similarity among different drug classes, although this does not diminish the reliability of the observed differences.

**Does Postmenopausal Estrogen Replacement Reduce Cardiovascular Morbidity and Mortality?**

Another classic example of the superiority of RCTs over observational studies in establishing cause-and-effect links is represented by the controversies about the cardiovascular benefits of postmenopausal estrogen replacement. Case-control studies and longitudinal investigations of large population-based cohorts with several hundreds or even thousands of major incident cardiovascular events uniformly indicated that postmenopausal women who have elected to use hormone-replacement therapy develop coronary morbidity and mortality at only about half the rate of other postmenopausal women. On the contrary, treatment with estrogen plus progestin did not reduce the overall rate of coronary heart disease events in postmenopausal women with established coronary disease in the randomized, blinded, placebo-controlled Heart and Estrogen/progestin Replacement Study. These data were confirmed and extended by the Women’s Health Initiative, a randomized, placebo-controlled trial of estrogen plus progestin in >16,000 generally healthy postmenopausal women, in which estrogen plus progestin actually increased the risk of coronary heart disease. Of course, incidence of myocardial infarction in long-term users of combined hormone therapy may not be well gauged by randomized trials in which hormone use does not extend beyond several years—the Women’s Health Initiative was stopped after 5.2 years for risk excess in the estrogen/progestin group, instead of a planned duration of 8.5 years. These trials also leave several questions open on the multiple pharmacological actions of combined hormone therapy, which bear on the risk of myocardial infarction. Nevertheless, only these RCTs were able to provide the straightforward, undisputed conclusion that, “estrogen plus progestin therapy should not be initiated or continued for the prevention of cardiovascular disease.”

**BP Treatment Goals: The Lower, The Better?**

Observational studies clearly show that BP has a direct linear relationship with cardiovascular events as low as 115 to 110 mm Hg systolic and 75 to 70 mm Hg diastolic, without indication of a J-curve phenomenon within this BP range. It should be kept in mind that this evidence has profoundly influenced clinical practice and expert recommendations. It has indeed been one of the main arguments in favor of the repeated suggestion, in several authoritative guidelines, to pursue BP values lower than the usual target values of <140 mm Hg systolic and <90 mm Hg diastolic, if tolerated. Examples of such guidelines include the ones prepared by the World Health Organization/International Society of Hypertension Liaison Committee in 1999, and those issued by the European Society of Hypertension and the European Society of Cardiology in 2003 and 2007. Extrapolation of the above data to people at higher cardiovascular risk has also formed the basis for the American Heart Association recommendation to aim at achieving a BP of <130/80 mm Hg in hypertensive subjects with diabetes mellitus, coronary heart disease, or without coronary disease but at risk of developing it (such as those with abnormal carotid ultrasound, peripheral arterial disease, abdominal aortic aneurysm, and an estimated 10-year Framingham risk score of ≥10%). Unfortunately, the expectations that BP reduction to values lower than the goal of <140/90 mm Hg carries substantial additional benefits in hypertensive patients could not be fully met in specifically designed RCTs. In the Hypertension Optimal Treatment study, the first randomized study aimed at comparing the cardiovascular outcomes of different BP targets, lower treatment goals (<80 mm Hg or <85 mm Hg diastolic) were not associated with lower rates of major cardiovascular events than the standard goal of <90 mm Hg in the whole population, as well as in individuals with overt coronary heart disease. Subsequent post hoc subgroup analyses of the Hypertension Optimal Treatment study suggested that more intensive diastolic BP lowering was actually associated with increased risk of cardiovascular events among smokers, whereas significant benefits could not be demonstrated in any of the other subgroups, with the possible exception of diabetic patients. In the Action to Control CardiOvascular Risk in Diabetes, 4733 patients with type 2 diabetes mellitus, mostly treated hypertension, high cardiovascular risk, and without overt nephropathy were randomized to achieve and maintain a systolic BP <120 mm Hg, or a systolic BP <140 mm Hg. Over a 4.7-year follow-up period, the primary composite end point of myocardial infarction, stroke, or cardiovascular death was not different in the arm randomized at achieving intensive BP control (systolic BP <120 mm Hg; average in-treatment BP 119/64 mm Hg) versus standard BP control (systolic BP <140 mm Hg; average in-treatment BP 133/70 mm Hg). Stroke was the only prespecified end point for which a significant reduction was observed in the intensive BP control group. Subsequent meta-analyses suggested that aiming at lower BP goals may lead to barely significant reductions in major cardiovascular events and myocardial infarction and a significant reduction in stroke. However, these meta-analyses combine studies that compared groups in which a variety of different BP targets were pursued, thus no definite recommendations can be directly obtained as to the optimal target BP values.

Thus, at variance with observational studies, evidence from RCTs supporting the incremental benefits and safety of a lower BP goal is scanty in most categories of hypertensive individuals. In the light of the abovementioned limitations of observational studies and in the absence of a clear-cut demonstration of the benefits and harms of such treatment strategy, a BP target of <140/90 mm Hg remains an appropriate goal for the majority of hypertensive subjects, including most of the individuals at high risk of developing coronary artery disease, as more recently acknowledged in a reappraisal of the European guidelines on hypertension management.

**Putting Randomized Versus Nonrandomized Research Into Context**

The applicability of an RCT to everyday clinical practice is necessarily limited because of its very nature and goal. An RCT is designed with the precise aim of eliminating, where possible, those effects that are on the contrary very important in
clinical practice, such as the placebo effect, the physician-patient relationship, and patient preference. Although placebo control, blinded treatment allocations, and exclusion of patients with strong treatment preferences increase the internal validity of a trial, they also separate the world of RCTs and their results from the real world and its expectations. To be enrolled in an RCT, a patient needs to be selected to meet the trial protocol’s requirements. Going back to the landmark Veterans Administration Cooperative Study in Hypertension, exclusion criteria comprised “patients who wished to return to care of their private physicians, those who for geographical or other reasons would be unable to attend clinic regularly, and patients of dubious reliability such as alcoholics, vagrants and poorly motivated patients.” In the Systolic Hypertension in the Elderly Program, which demonstrated the benefits of BP-lowering treatment in elderly subjects with isolated systolic hypertension, >400,000 subjects were screened, but as few as 4736 were eventually randomized. Although this selection process increases internal validity by creating comparable groups, it also limits the generalizability of the otherwise compelling conclusions of RCTs, which cannot be necessarily regarded as general principles valid for all subjects.

RCTs are not only a source of data obtained in a rigorously controlled experimental setting. They can also be used to obtain a number of additional findings, besides those for which they have been designed primarily. In this context, subgroup analyses are widely used. Although such analyses may generate new hypotheses, they can also falsely indicate that treatment is beneficial in a particular subgroup when the trial shows no overall benefit, or that there is no treatment effect in a particular subgroup when the trial shows benefit overall. Subgroup analyses must be predefined, carefully justified, limited to a few clinically important questions, and performed and reported following formal rules. Another post hoc extrapolation of a trial’s findings is to compare the occurrence of the study outcomes among groups based on in-treatment characteristics irrespective of treatment allocations, an approach that is typically fraught with bias. For example, in the guidelines issued by the European Society of Hypertension and the European Society of Cardiology in 2003, the recommendation for a lower BP goal was supported by a post hoc analysis of the Hypertension Optimal Trial, indicating the lowest event incidence to be at in-treatment BP values $\approx 138/83$ mm Hg. One should be aware that, irrespective of its statistical significance, any post hoc analysis of a given trial has to be considered with skepticism.

Of course, it is impractical to conduct separate large RCTs to study the effect of every treatment or treatment combination or every dose of a specific treatment, neither can a given intervention be evaluated with high statistical power in patients in every possible subgroup considered individually. In this regard, nonrandomized treatment comparisons based on routinely collected data have generally a greater external validity than RCTs because they include all patients, are performed in the real world, and include the effects of the doctor–patient relationship and patient preference. Although adjustment for between-group differences can be performed with appropriate techniques, it is impossible to be confident that the bias inherent in observational research will be corrected. Rothwell has acutely pointed out that “routinely collected data are useful where RCTs are impractical, such as in evaluating rare adverse events, but are an adjunct rather than an alternative.”

**Conclusions**

We do not believe that dependable clinical evidence only comes from RCTs. The practice of medicine cannot and should not be reduced to the hierarchy of evidence-based medicine (Figure). If RCTs were required for proof of efficacy of a given treatment, the practice of clinical medicine would indeed be reduced to a relatively few verified treatments. The process of clinical thinking involves interpretation and synthesis of relevant evidence from all sources and extrapolation to the clinical situation. This complex method is at risk of oversimplification in the approach advocated in evidence-based medicine. Having said that, there is no question that RCTs and their systematic reviews provide the most reliable source of evidence on the effects of treatment. To our knowledge, in no case the main conclusions of a large RCT in hypertension have been frankly misleading, or eventually confounded by observational studies. RCTs (and their meta-analyses) provide direct, trustworthy answers to simple, straightforward clinical questions, and establish cause-and-effect relationships. In this field, they provide unique information, which cannot be obtained in a different way with the same degree of confidence.

However, RCTs are not able to address more complex questions (eg, the role of treatment in a real-world setting in which various combinations of medications are used in a wide variety of clinical, social, and economic conditions). Observational studies and real-world data (surveys, registries, and retrospective analyses of existing databases) can, and should, be used to explore these more complex domains, although their findings should be taken with due caution. There is a need for a more integrated approach to clinical research in the field of hypertension, which includes both RCTs and observational studies.

Despite their limitations, RCTs remain a cornerstone of sound, dependable clinical research. The evidence pyramid has been built on a good foundation, and is still standing.

**Disclosures**

None.

**References**


We appreciate the defense of randomized controlled trials (RCTs) by Schillaci et al. However, their message that observational studies inevitably carry a high degree of bias is an oversimplification. It may be true when investigators use data repositories of clinical records and take selected patients to be included in a given registry. However, it is less prominent in large registries specifically designed to collect information from unselected and largely consecutive patients in a given context or disease. This is facilitated by the widespread use of electronic databases of clinical records.

We are now aware of the problems listed in Table 1 and will take steps to account for them. As touched on in their review, in large all-inclusive registries, reliable case-control matching is actually possible using propensity scores. Also the methodology of data collection and management can be substantially improved using advanced informatic tools, including cloud repositories. In our opinion, registration should be compulsory for data repositories and registries, as recently suggested.

Schillaci et al also state that it is impossible to compare treatments within observational studies. They report a number of anecdotal examples. We agree that allocation to a specific treatment in observational studies is determined by the physician’s attitude and the clinical condition of patients. However, the inconsistencies reported by Schillaci et al have often been caused by overestimation of small effects reported in many observational studies. Although the measures of risk are in general adjusted for potential confounders, statistical adjustment is not a panacea. If the odds ratios or hazard ratios in observational studies are small to moderate (ie, between 0.6 and 1.6 for a binary predictor), the observed effects could largely be because of residual confounding. This is the case in many of the reported anecdotal examples. The reader needs to be aware that in observational studies the effects have to be reported as odds ratios or hazard ratios, and need to be twice, ideally, or ≥60% (or lower) than the control, to be fully reliable. Thus, special attention should be paid to the statistics used in observational studies.

Every inconsistency between observational studies and RCTs should be carefully evaluated before drawing conclusions about the unreliability of carefully designed observational studies. We still believe that RCTs should be in the middle of a process of acquiring knowledge in which data repositories and registries can promote the need for particular RCTs to be conducted. At the same time, data repositories and registries can be used to externally validate RCT results. There are circumstances in which the evidence provided by observational studies is ironclad, and we think that medical action may take place even in the absence of confirming RCTs. The Parachute paradox should constantly be taken into account.

References
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