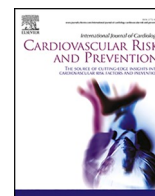




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Critical Question in Cardiovascular Risk: Can we use clinical trials to improve the outcomes of patients with hypertension?

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Can we use clinical trials to improve the outcomes of patients with hypertension? Discussion of the strengths and limitations of randomized clinical trials will serve as a basis to answer the question. Randomized clinical trials are essential in determining efficacy of pharmacologic and other interventions, are necessary for the approval by regulatory authorities and together with meta-analyses are at the apex of studies providing reliable information on these issues. Randomization and blinding of treatment allocation of the patient and the investigators (double-blind studies) are used frequently and are important in assuring the reliability of the findings. However, randomized clinical trials have important limitations that are discussed below. Statistical inference usually expressed as the p-value is difficult to ascertain because inference in general is challenging and the p-value does not adequately describe the difficulty in estimating the findings of a given trial. Also, clinical trials and the p-value do not describe the effects of an intervention throughout the life span of the participants. In addition, a statement from the American Statistical Association on p-values states that what is needed is a more nuanced approach to interpreting, communicating, and using the results of statistical methods in research.

There is a tension between internal and external validity of clinical trials. They are important in estimating their utility in practice. To avoid bias and enhance internal validity, randomized trials are conducted using strict protocols, and detailed inclusion and exclusion criteria with lack of unbalanced co-interventions, crossovers and patients lost to follow-up. However, this increase in internal validity is associated with a decrease in external validity when applied to individual patients.

In addition, the application of randomized clinical trials in practice is limited by publication bias, selection bias, where healthy persons with a given condition participate in a given clinical trial although they are not representative of the intended population as a whole, and the rather short duration (3–5 years) that may lead to incorrect projections of the lifetime benefits of the interventions (the legacy effect) where research subjects randomized to active therapy derive residual benefits after the end of the randomized phase of a study.

There is a conflict between the generalizability of the evidence (e.g.

clinical trials or meta-analyses) versus the reliable applicability of the findings to individual patients (e. g. case studies or case control studies) of different types of publication and the difficulty in applying the findings of different types of clinical research studies to individual patients [1]. Another limitation of clinical trials is the exaggerated emphasis on the p-value – a practice that is not congruent with a statement of the American Statistician. In addition, RCTs study efficacy and not effectiveness as is done in pragmatic or cohort RCTs.

Other limitations are that even perfectly conducted randomized clinical trials may lead to erroneous conclusions by chance. As is true with all diagnostic tests in medicine, some tests may, on occasion, be false positive or false negative due to the stochastic variability of tests. An example of a false negative study is the Acute Myocardial Infarction Study where aspirin did not decrease mortality in patients with history of acute myocardial infarction [2]. At present, prescribing aspirin to these patients is standard of care. Also, there may be a suspicion that on occasion the source of funding may have influenced the outcomes.

Non-inferiority studies decrease the need and associated expense of comparing the effects of an intervention in different populations or in comparing two similar interventions. However, the non-inferiority margin is set somewhat arbitrarily by the investigators. Underpowered clinical trials not indicating a benefit of an intervention may be misinterpreted as absence of benefit (Type II error). An example of Type II error is the perception that a benefit of statin therapy in women was not observed in early studies, an effect that was misinterpreted as lack of efficacy of these drugs in women. This was proven wrong as shown in a meta-analysis on the issue where statin therapy was equally effective in decreasing cardiovascular events and all-cause mortality in women as in men [3]. Finally, clinical trials may be unethical in certain instances where an increased rate of adverse events, e.g. death may occur in the active treatment group while the study is not discontinued by usual criteria such as Lan-DeMets [4].

As Hippocrates stated in the Aphorisms 2500 years ago, “Life is short, and art long, opportunity fleeting, experience misleading, and judgment difficult.” ὁ βίος βραχύς, ἡ δὲ τέχνη μακρὴ, ὁ δὲ καιρὸς ὀξύς, ἡ δὲ πείρα

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σφαλέρη, η δὲ κρίσις χαλεπή.

Answer

The above comments on clinical trials imply that you cannot live with clinical trials and you cannot live without them. The solution rests in using published clinical trials after consideration of their limitations and use structured reviews, high quality meta-analyses and “umbrella reviews”, reviews of reviews, to improve outcomes in patients with hypertension [5]. Acknowledging that without clinical trials it is difficult to report on the efficacy and effectiveness of medical interventions and considering the differences in the definition and treatment of hypertension across different countries (US vs. Europe), I propose the following. Publish and use structured reviews, high quality meta-analyses and “umbrella reviews”, to answer the question of how to improve outcomes in patients with hypertension with specific recommendations for systolic, diastolic and pulse pressure in different age groups.

The risk of patients with hypertension can be decreased by using structured reviews, high quality meta-analyses and umbrella reviews for each specific question i.e. systolic blood pressure for most patients with hypertension, and on pulse pressure, an index of arterial stiffness, that incorporates other risk factors such as heredity, comorbidities and

lifestyle.

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