Mendelian Randomization: A Way to Bridge Evidence Gap in the Absence of a Clinical Trial?

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Randomized controlled trials (RCTs') are considered to be the echelon of evidence-based evidence. Given the rigor and low risk of bias in well-conducted RCTs', their findings frequently dictate the guidelines and form the basis for informed decision making. There are however numerous scenarios in which it is practically impossible or very difficult to conduct a clinical trial. Moreover, RCTs' are expensive to conduct and frequently require years to complete. On the other hand, observational studies have a host of limitations that can render their conclusions difficult to generalize and are, at best, considered hypothesis generating. Mendelian randomization may be one way of overcoming a limitation of observational study without the rigor of a clinical trial [1]. A Mendelian randomized study is based on the hypothesis that alleles are randomly distributed in a population of interest. If that is the case, all the other factors that can potentially bias an observation are distributed equally. Thus, any differences in the endpoints in the population of interest are deemed to be due to the allele of interest.

For instance, based on the efficacy of statins both for primary and secondary prevention, there has been enthusiasm in the scientific community to investigate whether alternative lipid lowering therapies can generate the same net clinical benefit. This is because not all the lipid lowering therapies have been shown to confer clinical benefit. To investigate the potential impact of PCSK9 inhibition, the investigators examined the impact of variants of PCSK9 gene on cardiovascular outcomes [2]. They found that the variants associated with low LDL had a similar cardiovascular risk reduction than the variants of HMG coreductase (which is the pathway blocked by statins).

At the time of publication, these findings were hypothesis generating only. However, the subsequent publication of the FOURIER trial confirmed these findings by showing that the use of PCSK9 inhibitors is indeed associated with a reduced risk of major adverse cardiovascular events in patients despite the use of the background statin therapy [3].

Several important limitations of the Mendelian randomized studies need to be kept in perspective when using it to replace a clinical trial. First, the effect of the alleles of interest is seen after a lifelong exposure in a Mendelian randomized study, whereas the results of the drug effects depend upon the study duration. Thus, the effect size predicted by a Mendelian randomized study may be considerably higher than that seen in a clinical trial. Second, while Mendelian randomized studies are useful for hypothesis generation, drugs in clinical trials frequently have "off-target" effects that cannot be predicted based on a Mendelian randomization study. For instance, Mendelian randomization predicts that the LDL has a cumulative and causative role in atherogenesis and consequently a reduction in LDL independent of mechanism should be associated with improved cardiovascular outcomes. In RCTs', statins, PCSK9 and, to some extent, ezetimibe are the only drugs that have been shown to be beneficial whereas similar benefits have been harder to replicate with drugs of other classes.

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