Translation of Cardiovascular Animal Models to Human Randomized Trials

An important paradigm in biomedical research is that the results of preclinical animal models should predict the outcome of subsequent human randomized trials. In 2006, we reported that 37% of highly cited animal studies (across all domains) translated at the level of human randomized trials.[1] No such estimate is available exclusively for cardiovascular medicine.

All data are available from the authors upon request. We searched MEDLINE (Supplementary Table 1) to identify cardiovascular animal models studying the efficacy of any intervention for any cardiovascular condition and published in the year 2010 (to allow for 10 years of subsequent translation to human trials). To be eligible, each animal study had to show evidence of benefit for an intervention for cardiovascular disease. For each animal study, we conducted a separate literature search to identify analogous human randomized trials in MEDLINE, EMBASE, Cochrane Library, NIH Clinical Trials, and Web of Science. If at least one positive trial was available, translation was deemed "positive."

Our literature search identified a total of 121 animal studies published in 78 different journals (Supplementary Figure). The median length of follow-up for animal experiments was 21 days (interquartile range 2 to 56). The median number of experimental animals used was 29 (interquartile range 19 to 53). Most studies had major methodological deficiencies including lack of randomization, lack of blinding and failure to report sample size calculations (Figure 1). Overall, translation was positive for 25 studies (20.7%; Supplementary Table 2). Neurovascular disease models were predictive of a lack of translation (odds ratio 0.08, 95% confidence interval 0.01 to 0.59).

In summary, 21% of positive cardiovascular animal studies were replicated in subsequent human randomized trials. Although lower than the estimate reported for highly cited animal studies across all domains, if the intent of preclinical research is to identify potentially effective candidate therapies for subsequent testing in humans, this proportion still reflects a substantial level of translation. Moreover, animal research may have other purposes, including delineation of disease pathways and assessment of therapeutic toxicity prior to human testing. Lack of success in replicating neurovascular models in humans has been previously reported and remains problematic.[2]

Disclosures

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2020.10.027.

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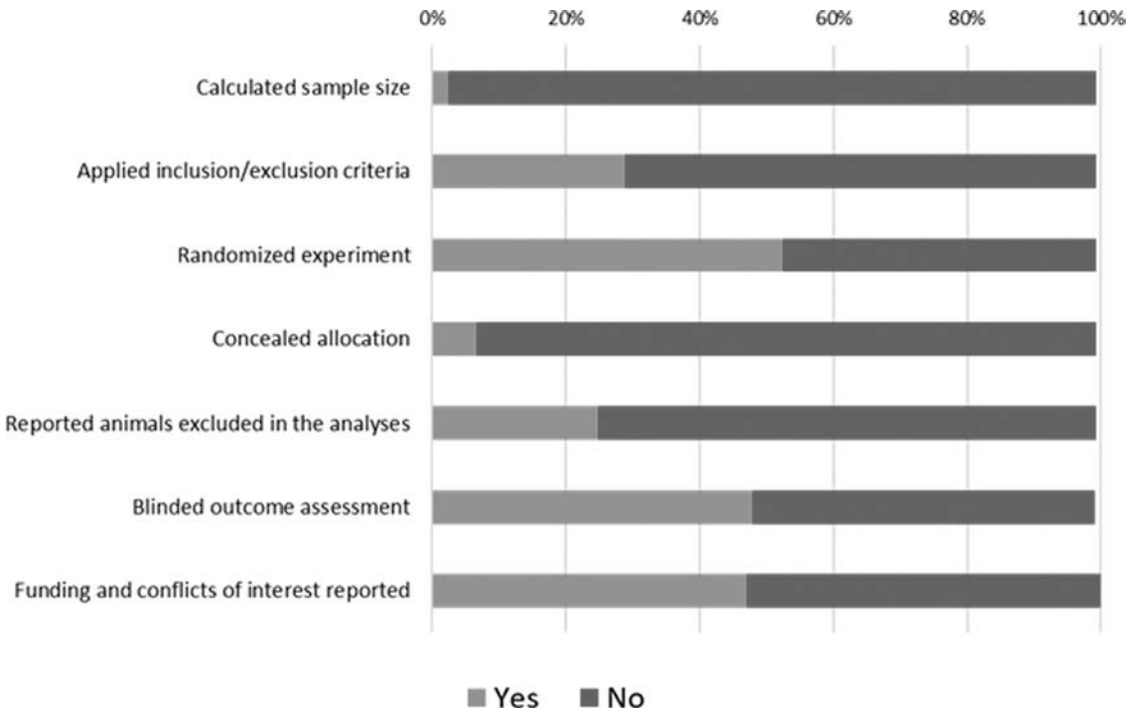

Figure 1. Methodological quality indicators in cardiovascular animal studies (n = 121).