Editorial

Does Computer Simulation Help Facilitate Personalized Precision Medicine for the Use of Warfarin?

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In this issue of *Circulation: Cardiovascular Genetics*, Ravvaz et al[1] presented an interesting report on the evaluation of warfarin dosing protocols among patients with atrial fibrillation with various different clinical backgrounds. This article is unique in reporting a new method using a computer simulation–based approach.

See Article by Ravvaz et al

To date, anticoagulation effects of warfarin are monitored by prothrombin time international normalized ratio (PT-INR).[2] The appropriate warfarin dose to achieve the target PT-INR is affected by various factors, including age, sex, comorbidity, concomitant drug,[3] and genetic polymorphisms of specific enzymes related to warfarin metabolism, such as vitamin K epoxide reductase complex and *CYP2C9*.[4] After clarification of warfarin metabolism, the impact of genetics on the PT-INR control with warfarin was of particular interest. Conflicting results have been published to date on the improvement of PT-INR control using genotype-guided warfarin dosing.[5–8] Despite speculated impacts of the 2 enzymes directly related to warfarin metabolism, prediction of appropriate warfarin dose in individual patients using genotype information had less impact than expected. Furthermore, the impact of genotype-guided warfarin dose adjustment strategy on the clinical outcome rather than achieving target PT-INR is difficult to prove because clinical outcomes are influenced by multiple factors including those that could not be monitored by PT-INR control. Randomized clinical trials give us strong scientific evidences but require substantial numbers of real patients who agree to participate into the trials. Constructive logic from personalized genome information to clinical practice is still underway. New methods to reduce numbers of real patients without losing the ability to test clinical efficacies in specific patient populations were awaited.

Virtual Clinical Trials With Computer-Generated Avatars

In this issue of *Circulation: Cardiovascular Genetics*, Ravvaz et al[1] showed us an interesting approach to reduce the numbers of real patients for clinical trials. They have developed a computer simulator that could generate avatars with specific warfarin pharmacokinetics/pharmacodynamics. The generated avatars are not real patients but can simulate the warfarin pharmacokinetics/pharmacodynamics characteristics using a statistical model. The model is based on Bayesian network and was trained and validated with large registry data.[9] By using this model, unlimited numbers of individual avatars with distinct clinical characteristics of warfarin pharmacokinetics/pharmacodynamics calculated based on specific age, sex, comorbidity, concomitant drugs, and genotype could be generated by the use of computers. With the avatars, theoretically unlimited numbers of clinical hypothesis could be tested without participation of real patients. How close these virtual clinical trials are to the real clinical trials?

Testing Multiple Hypothesis With Virtual Large Clinical Trials

All previously published clinical trials testing the validity of genotype-guided warfarin dose adjustment were conducted with general patient population of atrial fibrillation, posthip/knee replacement, etc. Even when the trials did not show superiority of theoretically superior genotype-guided dose adjustment, there might be subpopulation of patients who gain benefit by this protocol. To date, the best way to find patient population gain real benefit is to conduct multiple clinical trials with different patient populations as shown in Figure A. Subgroup analysis within 1 clinical trial may also be helpful but often face confounders. If our understanding of human body become more accurate and quantitative, we might be able to predict outcome after drug intake with constructive logic by calculating from genomes to organ function through cell functions as shown in the Figure B. The method proposed by Ravvaz et al[1] is in between Figure A and B. They created a mathematical model of patients by training with inductive approach using a real-world cohort composed from substantially large numbers of real patients. The model can produce unlimited numbers of avatars with various clinical parameters mimicking the distribution of other parameters in the real-world as shown in the Figure C. If someone wants to know if there is a difference in the efficacy of genotype-guided approach by age, they can run independent virtual clinical trials with distinct avatar groups without recruiting real patients. For example, they can run virtual randomized clinical trial in 1 group only including avatars with age >65 years and the other only including avatars <65 years.

The method proposed in this article by Ravvaz et al[1] could serve as a bridge between current gold standard of large-scale

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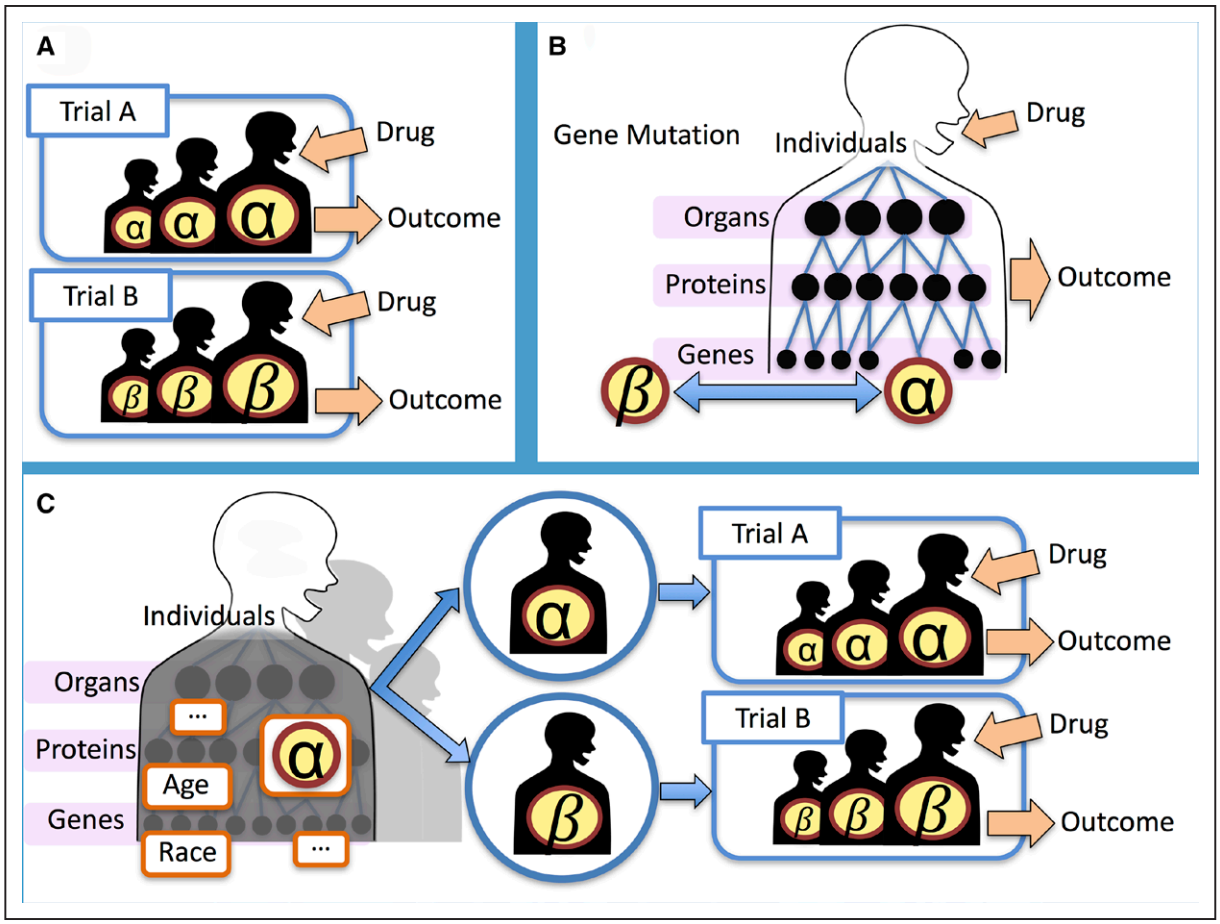

Figure. Method to bridge real randomized clinical trial to constructive precision medicine. Schematic illustration for establishing new drug interventions in patients with different backgrounds, such as young vs old, male vs female, diabetes mellitus (DM) and non-DM. To elucidate the effect in population with 2 distinct background factor of interest (α and β in this figure), the approach with the current evidence based medicine method (**A**) requires 2 independent clinical trials with large real patient recruitment to achieve balanced distribution of other potential contributing factors. The approach with constructive logic (**B**) could predict outcomes by calculating all the associated process after simply changing the factor of interest (**B**). However, this approach requires all the logic from drug intake to the outcome. One drug may influence the structure and function of target protein(s). Molecular dynamic calculation with huge computer resource is required. Indeed, all the factors influenced by the drug intake has not been clarified. Thus, precise prediction from genetic differences to the variation of drug effects is still to be elucidated. The method proposed by Ravvaz et al[1] (**C**) creates a mathematical model of patient. The model is trained by using inductive approach with a real-world cohort. By doing so, the effect of drug when the factor of interest is changed could be predicted without explicitly modeling the molecular interactions. This allows us to create avatars mimicking real patients with different background for the factors of interest. Thus, we can test hypothesis without preparing large numbers of cohorts by running virtual clinical trials using these avatars.

randomized clinical trial results–based medicine (evidence-based medicine) and the future expected pure precision medicine based on the constructive logic. The method Ravvaz et al[1] has proposed creates a simulation model based on pharmacodynamics and pharmacokinetics from an existing cohort composed of real patients. This model allows calculation of outcomes from parameters, such as age, sex, race, genetic information, etc., and can produce avatars that mimic the actual patients. Thus, the model allows us to prepare as many participants in virtual clinical trials as we need and allows us to perform enormous numbers of virtual clinical trials testing multiple clinical hypothesis.

However, the model proposed by Ravvaz et al[1] currently includes only simple parameters. There are many other factor potentially influencing PT-INR control, such as rarely used drug intake, bacterial infection, etc. Furthermore, the calculation of outcomes from warfarin intakes is greatly simplified in this model. Both PT-INR and clinical outcome should be influenced by complicated cell-based coagulation,[10] which was not implemented in this model. The method Ravvaz et al[1] reported in this article is interesting but just the simple beginning. Future expansion of research in this area is expected.

Disclosures

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