

## Clinical Research and the Development of Medical Therapeutics

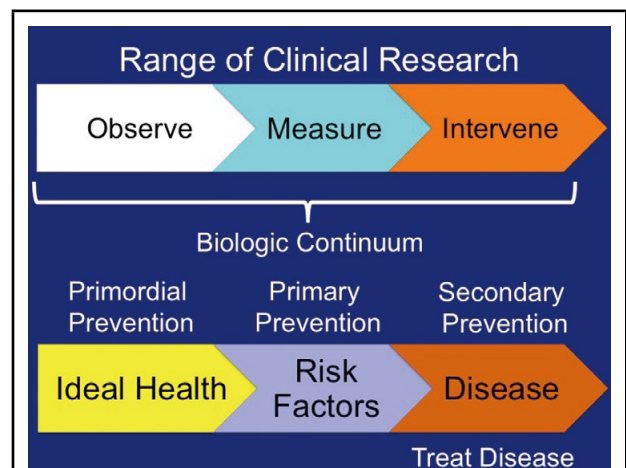
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Clinical research plays a central role in the development of medical therapeutics, but the current system is estimated to take 10–15 years from initial discovery to regulatory approval, at a cost of approximately US\$1 billion. Contrast the paths by which 2 anticoagulant options for atrial fibrillation were discovered and ultimately established as treatment options in clinical medicine. Warfarin was discovered by serendipity and compared with placebo in relatively small trials; this was associated with a low cost of development. The new oral anticoagulants were synthesized to provide highly specific, targeted inhibition of critical steps in the coagulation system. They were compared with warfarin for prevention of stroke and systemic embolic events in large, phase 3 trials; this resulted in very expensive development programs. Neither of these paths is desirable for future development of therapeutics. We need to focus on innovative approaches at the preclinical level (systems approach, greater use of inducible pluripotent stem cells, use of novel bioengineering platforms) and clinical trial level (adaptive design, greater use of new and emerging technology). Focusing on disruptive innovations for development of medical therapeutics has the potential to bring us closer to the goal of precision medicine where safer, more effective treatments are discovered in a more efficient system. (*Circ J* 2014; **78**: 1267–1271)

**Key Words:** Atrial fibrillation; Coagulation; Trials

Let us consider the range of activities in clinical research (Figure 1). We can observe our patients, make a measurement that reflects their physiologic state, or intervene to modify their condition. These activities can occur anywhere along the biologic continuum from ideal health, through the development of risk factors, and ultimately the transition to clinical disease. We refer to our efforts at preventing disease as primordial when we emphasize healthy behaviors (eg, heart healthy diet) to maintain a state of ideal health, primary when we focus on risk reduction once risk factors are observed, and secondary when we attempt to prevent subsequent occurrences of disease once it has developed for the first time. Of particular interest to us are those interventions designed to treat disease once it has occurred.

There is a range of technologies we can use to manage our patients. They fit broadly into 5 categories: drugs, devices, biologics, biomarker assays, and imaging procedures. Although there are many common principles that govern the clinical research we conduct to introduce new medical therapeutics, each of these has its unique pathway of development before introduction into practice. In this article, which is based on a lecture I delivered at the 78<sup>th</sup> Annual Scientific Meeting of the Japanese Circulation Society, I will discuss the example of how new drugs are currently developed and highlight novel approaches for us to consider. This will be done in the context of drugs to



**Figure 1.** Overview of clinical research. (Top) The range of clinical research: observation, measurement, and intervention. These aspects of clinical research can occur alone or in combination and may take place anywhere along the biologic continuum from ideal health, through the development of risk factors, and the transition to clinical disease.

Received April 17, 2014; accepted April 18, 2014; released online May 16, 2014

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ISSN-1346-9843 doi:10.1253/circj.CJ-14-0459

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treat a common cardiovascular condition.

That condition is atrial fibrillation (AF): a global problem, affecting 33.5 million persons worldwide.<sup>1</sup> There is a higher prevalence of AF among the elderly members of society.<sup>2</sup> Given the increasing percentage of the elderly in populations worldwide, the prevalence of AF is projected to increase dramatically over the next several decades.<sup>3</sup> Management of patients with AF is also associated with a high cost to healthcare systems. The most feared complication is stroke, which occurs 5-fold more frequently in persons with AF than in those who do not have that rhythm disturbance. Anticoagulation reduces the risk of embolic stroke but increases the risk of bleeding. It is of interest to compare the route by which warfarin, our standard of care, was developed and introduced into clinical medicine with the new oral anticoagulants (NOACs) that became available more recently.<sup>4</sup>

In the 1920s in the Western part of the United States, farmers reported that after their cattle ate certain batches of hay (referred to as sweet clover hay) the animals developed severe bleeding that was often fatal. It was known at the time that the natural substance coumarin was found in the shaft of the hay. In 1933, a farmer delivered to the laboratory of Dr Paul Link (an agricultural biochemist in Wisconsin) a sample of the hay that seemed to be causing a bleeding problem in his cattle. Researchers in Dr Link's laboratory discovered that when the hay became wet, a fermentation reaction occurred and 2 molecules of coumarin fused together. That was the substance that caused the bleeding in the cattle. They named it dicoumarol.<sup>5</sup> Various derivatives of dicoumarol were synthesized and derivative no. 42 was much more potent at causing prolongation of coagulation. The laboratory named it after their sponsor, the Wisconsin Alumni Research Foundation (WARF), combined that with the fact that it was a coumarin derivative, and introduced to the medical literature the name "warfarin".

Six randomized trials conducted between 1989 and 1993, collectively enrolling 2,900 subjects, studied the benefits of warfarin in preventing stroke in AF. This meta-analysis identified the dramatic 64% reduction in total stroke and 67% reduction in ischemic stroke association with warfarin treatment.<sup>6</sup> However, clinicians are well aware of the difficulties in administering warfarin in clinical practice. For example, in an analysis of the Quest Diagnostic Health Trends national database in the United States, only 50.6% of patients with AF had their INR in the target range of 2.0–3.0, 16.9% were >3.0 and 32.5% were <2.0.<sup>7</sup>

The search was on for potential replacements. The direct thrombin inhibitor, dabigatran, and specific FXa inhibitors, rivaroxaban, apixaban, and edoxaban, have all been studied and compared with warfarin in large phase 3 trials for the prevention of stroke in AF.<sup>8–11</sup>

Each of these compounds went through a typical lengthy development process<sup>12</sup> that starts with an initial drug discovery phase, followed by a preclinical phase. The various phases of clinical trials then take place. It is estimated, that on average, a typical development program takes approximately 15 years, with 10,000 compounds being screened for 1 that successfully achieves regulatory approval – all at a cost of approximately US\$1 billion.

Edoxaban was first synthesized in Japan in 1994 in the Daiichi laboratories,<sup>13</sup> and the preclinical work was also done in Japan.<sup>14</sup> After the first-in-human, proof of concept, and dose-ranging work was completed, again much of it in Japan,<sup>15</sup> there were 3 observations that suggested edoxaban was worthy of further investigation: there were very few food and drug interactions; it was available in pill form that provided a stable level of an-

ticoagulation, and several doses were identified; importantly, there was no need for monitoring the anticoagulation status of the patient.<sup>16</sup>

We enrolled 21,105 patients with AF in the ENGAGE AF-TIMI 48 study, a definitive phase 3 trial of edoxaban.<sup>11</sup> Randomization was either to warfarin with a target INR of 2–3, high-dose edoxaban (60 mg once per day), or low-dose edoxaban (30 mg once per day). If subjects had diminished creatinine clearance, a low body weight, or were simultaneously taking a drug that was a strong PGP inhibitor their edoxaban dose was reduced by 50%. The primary endpoint was total stroke or systemic embolic events (SEE). The primary safety endpoint was major bleeding.

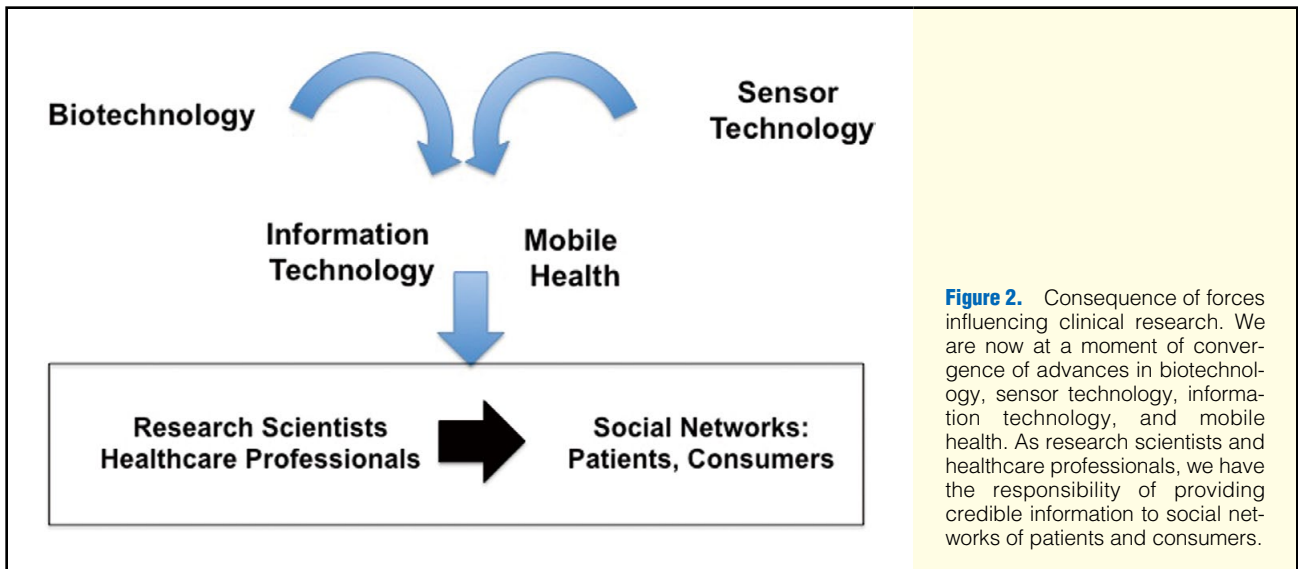
High-dose edoxaban satisfied the prespecified criteria for non-inferiority compared with warfarin for preventing stroke and SEE, when analyzed in the modified intention-to-treat cohort. It also tended to be superior to warfarin in the intention-to-treat cohort. Importantly, it was associated with a 20% reduction in major bleeding. The low dose also satisfied the criteria for noninferiority but was not as effective as the high dose compared with warfarin for preventing stroke and SEE. However, there was an even greater reduction in bleeding in the low-dose edoxaban group.

We pooled our data with the results of the 3 prior NOAC trials in a prespecified meta-analysis and had a database of 72,000 patients.<sup>17</sup> The new drugs are similar to warfarin at preventing ischemic stroke but their use was associated with a significant 50% reduction in hemorrhagic stroke. What are the important aspects of these new drugs when we consider their use in clinical practice? There is no need for laboratory monitoring; pharmacogenetics are not needed to adjust the dose; although missing a dose of warfarin is rarely a clinical problem the shorter half-life of the NOACs means that compliance with the prescribed regimen is important to avoid under-anticoagulation; specific antidotes for the new drugs are not yet available but are under development.

Let us consider the 2 broad options for anticoagulation in AF. The discovery of warfarin was by serendipity, a play of chance that a farmer delivered the spoiled hay to a laboratory that was able to solve the problem that affected the cattle; warfarin was compared with placebo in relatively small trials that resulted in a low overall cost of development.<sup>5,6</sup> Contrast that with the targeted approach to producing compounds that inhibit specific proteins in the coagulation system. Neither of these approaches is satisfactory for the development of medical therapeutics in the future. We cannot rely on serendipity alone to bring us the next breakthrough and we cannot afford to continue with the very expensive, unsustainable programs that brought us the NOACs.

We must use the scientific advances occurring in laboratories around the world to identify innovative approaches to the development of medical therapeutics. There are 2 broad categories of innovation to consider. The first is to focus on a systems-based approach, make use of inducible pluripotent stem cells (iPS) and test new drugs in novel bioengineering platforms that are producing organs on a chip. The second is to bring innovation into our clinical trials by using more adaptive designs, new research platforms, and incorporating new tools and technologies into how we organize clinical research.

In the typical population approach in classical clinical trials, we enroll a cohort of subjects that we hope is representative of the larger universe of patients with the disease we are studying.<sup>18</sup> We report our results as the average treatment effect we observe in our trial population. Often we analyze key subgroups to see if there is variation in the response to the treatments we



**Figure 2.** Consequence of forces influencing clinical research. We are now at a moment of convergence of advances in biotechnology, sensor technology, information technology, and mobile health. As research scientists and healthcare professionals, we have the responsibility of providing credible information to social networks of patients and consumers.

are studying; such efforts are best considered exploratory because we usually do not have sufficient power to make definitive statements about subgroups.<sup>19</sup> Rarely, if ever, do we actually examine the response to treatment on an individual patient level.

A systems medicine approach turns this flow around. Here, one synthesizes the network of information from investigations of genetic, molecular, cellular, and whole organ studies in individual patients to predict their personalized response to treatment.<sup>20</sup> One then extends the observations to subgroups of patients who have a similar profile, ultimately leading to a much richer picture of how a population of patients might need customized treatments for their disease.

A simple example will illustrate these points. In the classical approach, we use 1 dose of a drug for a population of patients, the so-called “one size fits all”, say 100 mg. If we study the genotype of the persons in that population, we will find that some have functional alleles, others have reduced function, and some have nonfunctional alleles. This translates to phenotypes of ultrarapid, extensive, intermediate, and poor metabolizers. These different phenotypes define the optimum dose, which ranges from 500 mg in the ultrarapid metabolizers, to 100 mg in the extensive and intermediate metabolizers, and 10 mg in the poor metabolizers.<sup>21</sup> This personalized medicine approach requires innovation in regulatory science and a number of regulatory authorities around the world are now addressing this important issue.

In 2007, Professor Yamanaka in Japan published a breakthrough paper that described how somatic cells (such as human skin fibroblasts) could be reprogrammed to become iPS.<sup>22</sup> These iPS cells can be directed to differentiate into specific cells, such as cardiomyocytes, and used to develop individualized therapy. A somatic cell is harvested from a patient with a given disease phenotype. The biopsied cells are reprogrammed to become iPS cells that then differentiate into disease-specific cells in a dish. Drug screens are performed on those cells to identify the most effective regimen for patients with a specific disease phenotype.<sup>23</sup>

Another approach of interest is a novel bioengineering platform developed by investigators at Harvard. Neonatal rat myocytes are layered on a deformable thin elastic film.<sup>24,25</sup> When the myocytes contract, they cause the film to bend. The “heart

on a chip” is placed in a microfluid test chamber, which is then sealed and drugs can be infused as well as electrical currents delivered to stimulate the cells. Dose-response curves for drugs affecting twitch stress can be established. Imagine the next phase of experiments where iPS-derived human cardiomyocytes with a specific disease phenotype are mounted on the deformable film and studied in the test chamber; this is another innovative way to screen for individual, disease-specific therapies that have an improved chance of being effective in clinical trials.

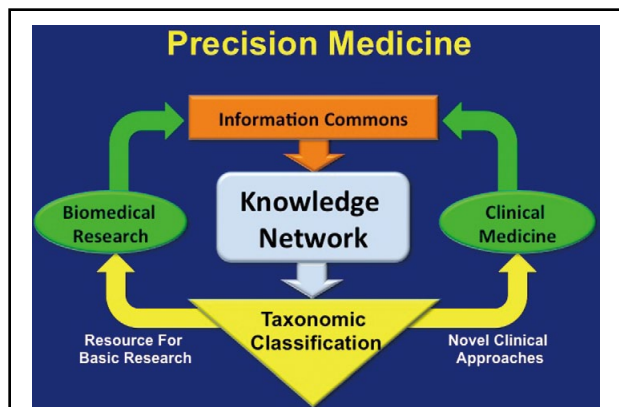
Adaptive trial designs offer the opportunity to perform more trials that have a greater likelihood of success. In the classical frequentist approach, patients fulfilling the enrolment criteria are randomized to treatment A vs. B and followed for the primary endpoint. The trial runs to completion with no modifications to its basic structure. In an adaptive design, investigators inspect the data in an interim analysis and modify the study based on the findings. The study continues, but with modifications that improve the likelihood that promising treatments are identified for the optimum profile of patients. The modifications can occur at 3 levels: enrollment criteria, the characteristics of the treatment arms, and the endpoints and analyses for the trial.<sup>12</sup>

Consider 4 different doses of an experimental treatment that are compared with a control therapy. At the interim analyses, the response to the various doses of the experimental arms is evaluated and only those that appear promising are continued, while the others are dropped. Doses that appear most promising during the dose-ranging “learning phase” of drug testing are then taken forward in a seamless fashion in a confirmatory registration pathway trial for formal evaluation against controls.

### New Technologies to Enable Clinical Research

Millions of individuals around the world currently have wearable wireless sensors that track physiologic parameters such as heart rate or calories burned every day. These wireless sensors communicate via Bluetooth to a smartphone. Once the data are on a smartphone they can be transmitted wirelessly to a research grade database on the internet where “big data” analyses can take place.

Is it possible to use such new technologies to conduct the range of clinical research activities and do so across the biological continuum from ideal health to disease? This would be a



**Figure 3.** A vision for how new data will be integrated into clinical care to provide more highly targeted therapies. The goal of precision medicine is to integrate advances in clinical medicine and biomedical research into an information commons and ultimately a knowledge network that has the potential to generate new taxonomic classifications of disease. This is anticipated to yield novel clinical approaches and serve as a resource for future basic research. (Modified from concepts in the National Research Council's *Toward Precision Medicine: Building a Knowledge Network for Biomedical Research and a New Taxonomy of Disease*.<sup>29</sup>)

very powerful novel research platform that would allow us to evaluate therapies in ways that were not available to us previously.

The Heath eHeart study based in San Francisco is doing just that.<sup>26</sup> The plan is to enroll 1 million subjects worldwide to create a distributed cohort that leverages the internet and mobile technology. Data security measures are in place to protect individual privacy. After signing an electronic consent, research subjects fill out electronic visits on the internet and can link their wireless sensors to allow real-time streaming of their physiologic measurements such as heart rate and rhythm to the database. Soon biospecimen data will be added to the study. The software interface is being written to allow linkage to electronic medical records and correlation with outcome events. The American Heart Association has a scientific collaboration with the study. We are referring subjects from our patient networks to the study and soon will be receiving data that allow us to track progress towards our goal of improving cardiovascular health. Shortly, we will be conducting randomized trials in this new research environment. The Health eHeart study is an example of a platform that is an innovative testing ground not only for new therapeutics but also disease management strategies.<sup>27</sup>

Another approach is to embed clinical research into clinical care. Every day we are faced with uncertainty about which of 2 approved treatments might be best for our patients. We now have electronic medical records, which offer an opportunity to randomize patients at the point of care and use the medical record as the case report form of the future.<sup>28</sup>

We are at a unique moment where there is a convergence of the advances in biotechnology and sensor technology with the advances in information technology and mobile health (Figure 2). These new tools are now in the hands of research scientists and healthcare professionals. We can feed credible information to social networks of patients and consumers and guide their use of the information gleaned from new and emerging technologies.

Finally, what might the future look like if we take advantage of the array of enabling technologies that are now available and others that will become available in the years to come? We could envision the emerging data from clinical medicine and biomedical research being fed into an information commons, which is used to construct a knowledge network that is likely to offer new insights into disease and even new taxonomic classifications of diseases (Figure 3). These new insights and classifications are likely to lead to novel clinical approaches and serve as a resource for basic research. This continuously updated, learning system approach holds promise for new clinical research for developing medical therapeutics and takes us closer to the goal of precision medicine for our patients.<sup>29</sup>

### Disclosures

Research grant from Daiichi Sankyo to Brigham and Women's Hospital (TIMI Study Group) to conduct a phase 3 trial with edoxaban.

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