JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
VOL. 68, NO. 7, 2016
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ISSN 0735-1097/$36.00
PUBLISHED BY ELSEVIER
http://dx.doi.org/10.1016/j.jacc.2016.07.001

GUEST EDITOR'S PAGE

The Future of Cardiovascular Medicine From the Regulatory Perspective

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For many years, the American public and the entire world have benefited from the U.S. Food and Drug Administration's (FDA) regulatory system for medical products. The field of cardiovascular medicine has been an exemplary partner with the FDA for much of this time—a period marked by advances ranging from better diet to life-saving drugs, devices, and biologics, ultimately resulting in a nearly 40% reduction in the risk of death from cardiovascular disease in the first decade of the 21st century (1). Largely due to the confluence of the FDA's standards for evidence and wise leadership within the field, cardiovascular medicine has one of the strongest evidence bases among specialties (2). Patients, physicians, and the public can have confidence in medical products used to prevent and treat cardiovascular disease because FDA standards for safety and effectiveness have been met, and also because the highly evolved approach to applying professional clinical practice guidelines in cardiovascular medicine provides important and useful clinical context for the use of medical products and behavioral interventions.

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We are now entering a new era in medicine that is characterized by dramatic accelerations in biological and information sciences and near-ubiquitous uptake of social media and personal devices. Together, these advances make possible the integration of complex measurement and decision support with traditional devices, drugs, and biologics to produce powerful interventions that can be evaluated much more rigorously and efficiently. But the potency and integrated nature of these interventions also increase the potential for harm if they are used inappropriately or if their development plans do not generate the evidence needed to guide practice, tipping the balance of risk and benefit in an unfavorable direction.

The FDA is responding to this changing world. However, we believe the needed changes must involve not only the FDA but the entire ecosystem of which the FDA is a part. As we work together to shape the future of medicine, cardiovascular specialists will play a special role.

EVIDENCE GENERATION

The cardiovascular community has been a leader in evidence-based medicine, yet only about 15% of its major practice guideline recommendations are currently supported by high-quality evidence (3,4). However, dramatic improvements in the rate, quantity, and quality of evidence generation are within reach. Almost all Americans now have electronic health records, and social media combined with wearable devices are opening new frontiers in patient- and population-level data. In addition, registries for quality and care delivery are proliferating, with efforts by the Society of Thoracic Surgeons, the American College of Cardiology, and the American Heart Association setting the standard for other

specialties. Keeping pace with rapid technological change will present a key challenge, and it will be critical for the FDA and the cardiovascular community to continue working together to create an evidence-generation system capable of guiding practice in the coming years.

PHENOTYPING

A remarkable opportunity now exists to characterize states of health and disease in human populations using intensive and continuous measurements. Cardiovascular disease is marked by complex, multifactorial phenotypes such as those presented by vascular disease and heart failure. Until recently, we were limited by our inability to measure genes and their downstream molecular products. Furthermore, the integration of molecular and physiological knowledge was thwarted by our inability to store, curate, and analyze sufficiently large quantities of data.

Those limitations are rapidly dissipating. Now is the time for cardiovascular researchers to develop approaches to using the full armamentarium of genetic, genomic, physiological, imaging, and clinical measurements to understand the interplay of factors that drive clinical outcomes and therapeutic effects. From the FDA's perspective, better phenotyping would yield much more informative early-phase clinical trials and facilitate detection of therapeutic benefit and off-target toxicities earlier in the development process.

INTEGRATIVE BIOMARKERS AND MONITORING

Despite substantial advances in biomedical knowledge, clinical decision making still relies on bedside heuristics. Unfortunately, the human brain is not well configured to integrate multiple streams of information, particularly when collected over time, into crisp decision making. Proliferating measurement methods have created a deluge of proposed biomarkers, often accompanied by unrealistic expectations and exaggerated claims of utility. However, the same methods that will drive effective phenotyping can also sort out which biomarkers have utility for particular purposes. The FDA and National Institutes of Health (NIH) are collaborating on the Biomarkers, EndpointS and other Tools (BEST) online resource (5), which will provide researchers, technology developers, and clinicians with clear definitions and other information on the development of biomarkers and outcome measures.

A critical feature within this evolving landscape is the profusion of personal electronic devices and applications that can measure heart rate and rhythm, blood pressure, and physical activity, and capture preferences and social activity using geospatial referencing. When combined with modern informatics and computing resources, this rich tapestry of information will enable a true paradigm shift, replacing the "1 biomarker at a time" approach with algorithms that integrate multiple measures to predict outcomes, diagnose and classify disease, and tailor treatment to the individual. The FDA is actively working on approaches to regulation that can both accommodate this complexity and promote useful innovation by moving to quality systems and standards-based regulation in much more transparent platforms.

TARGETED THERAPY

Major advances in cardiovascular medicine have come from broad-spectrum therapies deployed to large populations to treat such common problems as hypertension, hyperlipidemia, and glucose intolerance. Although the past year has seen even more effective therapies for hyperlipidemia and heart failure approved for market (6–8), it seems likely that many broad risk factors have underlying biological elements that will eventually guide more refined targeting of therapies.

DEVICES

Devices including physiological monitors, pacers, cardioverter/defibrillators, and stents have been an important part of cardiovascular medicine's success. The FDA has focused on developing efficient pathways across all phases of product development and throughout the product lifecycle. We now need cardiovascular specialists and major institutions with expertise to join together to create effective networks for conducting early device feasibility studies with a high degree of technical competence and attention to ethical considerations, in conjunction with FDA oversight through the investigational device exemption (IDE) regulations (9).

The later phase of cardiovascular device development is complicated by the intersection of research and payment systems. Building on the extensive availability of high-quality registries, the FDA is developing an approach that would allow existing data to be leveraged in a way that could lower the cost of premarket trials. Additional evidence can be generated with the "coverage with evidence development" (CED) system (10), in which payment is

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conditional upon participation in a study to generate needed benefit/risk information. As unique device identifiers (11) are phased in, it will be possible to measure device-related outcomes across the product lifecycle using a combination of registries, electronic health records, and claims data, as described in our plans for the National Evaluation System for healthcare Technology (NEST) (Shuren J, Califf RM, in press, July 2016).

REGENERATIVE MEDICINE

The use of human tissue and the modification of somatic genetic material are exciting technologies with the potential for an enormous impact on disease outcomes. Currently, however, much cell therapy is being administered in hospitals without the benefit of systematic frameworks such as those provided by the national quality and delivery systems in place for pharmaceuticals and devices (12,13). As the science matures, there will be many opportunities to attempt to fundamentally change the trajectory of disease, including through organ replacement, processed stem cells, and tissue scaffolding. In many cases, short-term effects may pale in comparison to long-term effects, because the regenerative process could last a lifetime.

NUTRITION AND DIET

What should we eat to optimize health and quality of life? This may be the question most commonly asked of doctors. However, the specific answer to this question is not always certain, and major miscues, including broad recommendations about intake of cholesterol and carbohydrates, have undermined public confidence and created opportunities for self-styled experts to profit from dubious advice (14). But as our capacity for generating evidence across large populations continues to improve, so will our ability to conduct quantitatively rigorous observational and experimental studies in this challenging arena. The FDA is well positioned to leverage the expertise of the Center for Food Safety and Applied Nutrition to consider these issues.

LIFECYCLE

As our knowledge continues to expand, it has become clear that we need to focus on both ends of the lifespan. Major diseases of neonates and children—which affect >1% of the population—include congenital heart defects and diseases with a primary or major secondary cardiovascular manifestation, and pose special issues, such as how to weigh the benefits and risks of broad preventive efforts in the face of uncertainty. Legislative action (15,16) has had a significant impact on the development of evidence to support the rational use of drugs in children. We now need to focus on devices, where smaller pediatric populations do not generate enough incentives for development of pediatric-specific devices despite inducements provided in the Humanitarian Device Exemption.

There is also a pressing need to better understand medications in pregnant women. Concerns about liability and risk have created a situation in which very few medicines are studied adequately for effects on pregnant women, lactating mothers, and the fetus or infant. Yet, we have a generation of women with adult congenital heart disease and other chronic cardiovascular diseases who must take medications while pregnant. The FDA and the cardiovascular community must work together to rectify this problem.

Elderly patients—particularly those >80 years of age—represent another underserved population. Although many interesting observational studies have been done, we have a real deficit in knowledge pertaining to proper dosing of therapies in elderly patients, or when invasive procedures are indicated.

DISPARITIES

Despite all the investigations of health and healthcare disparities, we continue to see enormous differences in lifespan and quality of life as a function of demographics. On a global basis, life expectancy is much shorter in low-income countries compared with wealthy countries, and an increasing component of this disparity is due to cardiovascular disease. Within the United States, similar disparities are seen according to geographic location, race, and income down to the level of individual neighborhoods (17). Although 90% of U.S. prescriptions are generic, and most essential cardiovascular medicines are inexpensive, problems with access and adherence to these medications remain, especially in underserved communities. Moreover, there is also ample evidence of similar disparities in access to surgical treatment (18). The FDA welcomes collaborative work aimed at addressing these issues.

CONCLUSIONS

The partnerships between the FDA and multiple communities of stakeholders have successfully reduced death and disability from cardiovascular disease. Now, ingenious research and technology development, combined with general advances in

biological and information technologies, will further accelerate improvement in outcomes. But if we are to harness these technologies and apply them effectively, our systems for evidence generation and healthcare delivery must continue to improve in concert with drugs, devices, and biological products.

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