Personalized Medicine in Cardiovascular Diseases

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Personalized medicine is a novel medical model with all decisions and practices being tailored to individual patients in whatever ways possible. In the era of genomics, personalized medicine combines the genetic information for additional benefit in preventive and therapeutic strategies. Personalized medicine may allow the physician to provide a better therapy for patients in terms of efficiency, safety and treatment length to reduce the associated costs. There was a remarkable growth in scientific publication on personalized medicine within the past few years in the cardiovascular field. However, so far, only very few cardiologists in the USA are incorporating personalized medicine into clinical treatment. We review the concepts, strengths, limitations and challenges of personalized medicine with a particular focus on cardiovascular diseases (CVDs). There are many challenges from both scientific and policy perspectives to personalized medicine, which can overcome them by comprehensive concept and understanding, clinical application, and evidence based practices. Individualized medicine serves a pivotal role in the evolution of national and global healthcare reform, especially, in the CVDs fields. Ultimately, personalized medicine will affect the entire landscape of health care system in the near future. (Korean Circ J 2012;42:583-591)

KEY WORDS: Personalized medicine; Cardiovascular diseases; Genomics.

There has been a remarkable progress of personalized medicine in the scientific basis and clinical applications on cardiovascular diseases (CVDs) after its introduction in the late 1990s. However, CVDs still remains the leading cause of death in the United States. Moreover, there will be needs on the education to doctors and patients for the improvement of knowledge, awareness and attitude on incorporating such method into clinical applications. Personalized medicine will contribute to the evolution of the management practice for CVDs. This article reviews the concepts, the strength, limitations and challenges, and future direction of personalized medicine with a particular focus on CVDs.

Background

Cardiovascular disease remains one of the leading causes of death worldwide, and therefore, it is a main focus of research and treatment. In medical practice, it is important to treat not only the disease, but also the patient, who by all accounts should be included in the decision-making process psycho-socio-economically. To improve the outcomes and reduce health care costs, we must first decrease the disease-specific variation in care for the populations of patients. Next, we must add back variation to individuals, based upon their specific genetics and environmental exposures, which determine one’s disease susceptibility, course, and treatment response.1

Hippocrates once stated a thousand years ago that "It's far more important to know what person the disease has than what disease the person has." Later Sir William Osler (1849–1919) noted that "If it were not for the great variability among individuals, medicine might well have been a science and not an art".

Interestingly, if drugs are not accounted for inter-individual differences, they are either 'ineffective' or 'not completely effective' in 30-60% of patients. One tends to scotomize that on average, a drug on the market works for only 50 percent of the people who take it. The use of personalized medicine may allow the physician to provide a better therapy for patients in terms of efficiency, safe-
Personalized medicine needs a multidisciplinary team approach, with different disciplines that must work together (Fig. 1). It is an approach that may help to solve medical challenges faced in the 21st century. For example, current healthcare model is expensive, reactive, inefficient, and focuses largely on “one-size-fits-all” treatments for events of late stage diseases. With personalized, individualized, tailored, predictive, preventive, and participatory medicine and etc.

There may be many benefits of personalized medicine; making better medication choices (100000 Americans die from adverse reactions to medications); select optimal therapy (on average, only 50% of people respond, 30% in hypertension); safer dosing options
(one size does not fit all); improvements in drug development (focused drug testing); decrease health care costs; decrease ADRs (Avoiding ADRs the fourth leading of cause of death according to FDA); potential to improve patient safety; reduce inappropriate testing and procedures; increased patient empowerment and awareness.

Cardiovascular diseases is the most common cause of death worldwide. Today CVDs accounts for 30% of deaths worldwide, including nearly 40% in high-income countries and about 28% in low- and middle-income countries. CVDs increases the global health burden and total cost of medical care. Such situation of health care demands the evidence, optimum quality and cost. Moreover, research funding challenge will grow after. After the Human Genome Project, many technologies aiming to use genome-wide predisposition markers, pharmacogenetics, and genomic signatures in complex CVDs have been developed. Monogenic cardiac diseases have provided insight into pathophysiological mechanisms and the genetic underpinnings of a growing number of complex cardiovascular disorders that are caused by interactions between multiple genes and environmental factors. Examples of monogenic CVDs are the long QT syndrome (LQTS), hypertrophic cardiomyopathy, factor V Leiden, and familial dyslipidemias.

In understanding the CVDs continuum, we can identify the unmet medical needs of personalized medicine along this continuum (patient engagement for disease risk and lifestyle change, tailoring prevention, improved diagnostic decisions, tailored therapy).

**Scope of Personalized Medicine & Integration of Medicine**

The ultimate goal of personalized medicine is to supply optimized medical care and outcomes for each individual. There are several important intervention time points at which genomic applications along the continuum from health to disease. Bristow described the goal of pharmacogenetic therapy to improve the probability of response and to reduce response heterogeneity, to increase the magnitude of response, to decrease the probability of adverse effects and/ or serious adverse effects, to improve the success rate of drug development, to reduce the cost of medical care and to provide additional marketing exclusivity.

Firstly, we can classify personalized medicine into comprehensive personalized medicine (e.g., family history checking, classic risk factor assessment, laboratory testing, tailored medicine) and more detailed clinical personalized medicine as a narrow meaning (e.g., only drug therapies through genetic testing), conceptually. Secondly, we
can classify from genomics to proteomics, by the expression path of genes (e.g., genomics, transcriptomics, proteomics, metabolomics). Thirdly, we can divide the structural {e.g., intima-media thickness (IMT), intravascular ultrasound, optical coherence tomography} and functional personalized medicine (e.g., endothelial function, exercise testing, heart rate variability etc.). Lastly, we can classify personalized medicine according to clinical objectives, applications, and therapies. In comprehensive concept, the assessment of risk factors like Framingham risk score, Prospective Cardiovascular Münster Heart Study, and European Society of Cardiology score, especially behavioral risk, is crucial for the comprehensive public health strategies, for chronic disease prevention and health promotion.20

Ruben21 introduced practical application of personalized medicine, proposed four parameters; the individual patients intrinsic susceptibility, intrinsic morbidity, extrinsic susceptibility, and extrinsic morbidity. Intrinsic susceptibility included genetic makeup, family history, and genetic information. Morbidity considers the effect of the disease on the individual. The susceptibility for disease is exacerbated by several extrinsic factors that include smoking and air pollution. Extrinsicly, for people who suffer from a disease, morbidity of from another disease is increased due to inadequate medical care, poverty, and other factors. Chan and Ginsburg9 proposed a framework that includes family history; assessment on a family health history would help identify high risk persons for disease (e.g., by family), enabling preventive and therapeutic interventions. The assessment of chronic disease risk, clinical decision support systems, and genome-based health assays can be used to predict risk, screen for carriers, establish clinical diagnosis and prognoses for individual, and direct clinical management.9

Genetic Contributors in Cardiovascular Diseases

Many studies reported that the variation in chronic CVDs depend on heritable factors, subclinical CVDs, and its risk factors. Examples are a familial predisposition of myocardial infarction,21 atrial fibrillation,33 atrial fibrillation, and congestive heart failure.36 Moderate heritability conditions include coronary artery calcification,37 carotid IMT,38 blood pressure, total cholesterol, and body mass index.39 The American Heart Association40 reviewed genomic epidemiology by three categories of cardiovascular condition: atherosclerosis and myocardial infarction, elevated cholesterol and other lipid disorders, and blood pressure and hypertension. The National Heart, Lung, and Blood Institute41 of USA summarized possible genetic contributors related to risk of coronary heart disease. Many kinds of gene considered mostly likely to potentially contribute toward an increased risk of coronary heart disease.42 More than genomic variants underlie the variation of CVDs. Single nucleotide polymorphisms (SNPs) are the most common sources of genetic variations. SNPs occur in about every 1000 base pairs, in approximately 3 billion base pairs comprising the human genome sequence. In human genome, there are likely >1000000 SNPs.43 Even a greater number of SNPs determine the variation of a population. Advanced technologies facilitated genotyping of SNPs. As of May 2011, over 800 GWASs have been published on 150 human diseases and traits, reporting over 2400 SNPs with statistically significant association.44 identified more than 100 variants that may contribute to coronary artery diseases risk.44–48

Personalized Medicine in Cardiovascular Diseases by Human Genome Level From Gene to Metabolite, & Pharmacogenomics

Genomics can be defined by the use of the genetic information to guide medical decision-making. Chan and Ginsburg9 proposed a human genome toolbox; human genomes sequence (genomics), gene expression profiles (transcriptomics), proteome (proteomics), and metabolome (metabolomics). Genomics is the study on human genomes sequences, and generated from whole-genome sequences, SNPs, and CNVs (~10–15 million). Transcriptomics refers to the genome-wide study of RNA expression (~25000 transcripts), and includes a spectrum of molecules from messenger-ribonucleic acid (RNA) to noncoding RNAs (small interfering RNA, and microRNAs). However, analysis of miRNA can be difficult due to their lack of specificity.49 RNA sequencing is used in transcriptome analysis. Proteomics is the study of proteins, where the proteome refers to the full complement of proteins and their various derivatives. It continues to be a priority area for biomarker and molecular medicine. Biomarkers have been defined as indicators of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention that can be objectively measured.43 They can take many forms – genes, proteins, carbohydrates, radioactively labeled molecules, cells, or physiologic measurements.51 Biomarkers can be used in the screening, diagnosis, treatment of disease, and drug development. Stable isotope approaches, DNA, RNA, and metabolic profiling, mass spectros-copy technology are used in proteomics. Metabolomics refer to the study of measure changes in the nonprotein small molecules related to a biological or physiological state. The number of human metabolome is estimated 5000 (~10000–100000) discrete small molecule metabolites. Metabolite profiles for ischemia and CAD was investigated in cardiovascular field.9

Pharmacogenomic is the study of changes in DNA sequence, chromosomal aberrations, and epigenetic alteration of the chromatin and DNA (i.e., changes that don’t affect DNA sequence). Pharmacogenetic approaches aim to identify the genetic determinants of
interindividual variability in response to drugs, and improve the efficacy and safety for a specific drug. Pharmacogenetics is the study of how genetic differences in a single gene influence the variability in drug response (i.e., efficacy and toxicity), but pharmacogenomics is the study of how genetic (genome) differences in multiple genes influence the variability in drug response. \(^{53}\) Examples of clinical genomic markers are shown in Table 1. LQTS is used for risk prediction, clinically. LQTS is an autosomal dominant disease, and variation in disease phenotype is found to be associated with mutations in 12 different LQTS susceptibility genes, warranting genetically testing of patients for these mutations. \(^{53}\) Beta-blockers are an effective treatment for patients with LQTS1 \((KCNQ1)\), but not for patients with LQTS2 \((KCNH2)\) or LQTS3 \((SCN5A)\). \(^{35}\) Meta-bolomics and proteomics applied to distinguish between the acute coronary syndrome state of acute myocardial infarction and unstable angina. \(^{30,46}\) Platelet proteome in patients with and without non-ST segment elevation showed differences in platelet activation, especially, elevated levels of the secreted protein acidic and rich in cysteine protein. \(^{57}\) Corus™ CAD test severity on based evidence that peripheral blood gene expression has been associated with CAD

| Biomarkers/Tests | Indications |
|-----------------|-------------|
| **Cytochrome P450 2C9 genotype (CYP2C9)** | Affect the metabolism of warfarin in the liver, Increased bleeding risk for patients carrying either the CYP2C9*2 or CYP2C9*3 alleles |
| **Vitamine K epoxide reductase complex genotype (VKORC1)** | Associated with lower dose requirements for warfarin through leading to differential rates of vitamin K recycling |
| **Cytochrome P450 2C19 genotype (CYP2C19)** | Loss-of-function alleles result in diminished conversion of clopidogrel to its active metabolite, Increasing the risk for major CV events and coronary stent thrombosis |
| **Familion® 5-gene profile** | Guides prevention and drug selection for patients with inherited cardiac channelopathies such as Long QT Syndrome (LQTS), which can lead to cardiac rhythm abnormalities |
| **Potassium channel KCNQ1 and KCNH2 genes** | Cause long QT1 syndrome and long QT2 syndrome, respectively, with different eliciting factors and treatment recommendations |
| **Sodium channel SCN5A gene** | Lead to long QT3 syndrome, Brugada syndrome, or both through defects in cardiac sodium ion channels |
| **Protein C or its cofactor, protein S deficiencies** | Associated with tissue necrosis following warfarin administration |
| **Phyziotype SINM** | Predicts risk of statin-induced neuromyopathy, based on a patient’s combinatorial genotype for 50 genes |
| **LDLR** | Doses should be individualized according to the recommended goal of therapy, Homozygous Familial hypercholesteremia (10-80 mg/day) and Heterozygous (10-20 mg/day) |
| **Factor V Leiden (F5) and prothrombin (F2) genes** | Polymorphisms R506Q and 20210G>A, respectively, in these coagulation factors result in an inherited hypercoagulable state, Testing for factor V Leiden is indicated for venous thrombosis in any individual younger than 50 years or in unusual sites |
| **9p21 region** | Associated with CAD and MI as well as intracranial and aortic aneurysms |
| **4q25 region** | Associated with atrial fibrillation |
| **Corus™ CAD** | Use it for screening and diagnosing CAD |
| **TnI, BNP, CRP** | Use it for prognosing ACS |
| **SLCO 1B1** | Use it for pharmacogenomics clinical decision on statins drug or dose |
| **Platelet aggregation assay, Paraoxonase I (PONI) genotype** | Use it for aspirin dose, clopidogrel dose, or need for combination antiplatelet therapy |
| **Bradykinin type I (B1) receptor Haplotype, Angiotensin II (AT-II) type I receptor haplotype** | Have treatment benefit of angiotensin converting enzyme (ACE) inhibitor |
| **Apolipoprotein A5 (ApoA5) genotype** | Have benefit of fenofibrate |
| **Niemann-Pick Cl Like I (NPC1L1) haplotype** | Have benefit of ezetimibe |
| **KIF6 Gene** | Have greater benefit from Statins |
| **AlloMap® gene profile** | Use it for monitoring transplant rejection |
Peripheral blood mononuclear cell gene expression profiling is used to monitor the status of graft after solid organ transplantation, like cardiac transplantation. This test is commercially available as AlloMap® (XDx; Brisbane, CA, USA).

A study by Degoma et al. reviewed and classified four major pharmacotherapeutic drugs within vascular medicine; antiplatelet therapy (platelet aggregation assay (VerifyNow® PRA-100), cytochrome P450 2C19 genotype, paraoxonase I genotype), antihypertensive therapy (plasma rennin activity, bradykinin type I receptor haplotype, angiotensin II type I receptor haplotype), lipid-lowering therapy (solute carrier organic anion transporter family, member 1B1 genotype, apolipoprotein A5 genotype, Niemann-Pick C1 Like 1 haplotype), and antithrombotic therapy (cytochrome P450 2C9 (CYP2C9) genotype, vitamin K epoxide reductase complex genotype).

In fact, warfarin therapy is an important traditional example of pharmacogenomics. Warfarin is an anticoagulant widely used to prevent blood clots, which has a narrow range between efficacy and toxicity, and a large variation in the dose (up to 10-fold) is required to achieve therapeutic anticoagulation. CYP2C9 is the enzyme responsible for the metabolism of warfarin, and SNPs in the CYP2C9 gene decrease the activity of the CYP2C9 metabolizing enzyme. It is complicated by genetic variations in a drug metabolizing enzyme (CYP2C9) and a vitamin K activating enzyme (VKORC1). Frequency of variant poor-metabolism phenotype was approximately 3% in England (those homozygous for the 2 and 3 alleles).

Dosing is typically adjusted for the individual patient through multiple rounds of trial and error, throughout the first year of treatment, during which time the patient may be at risk for excessive bleeding or further blood clots. The need to get warfarin dosing right the first time to avoid adverse effects led the FDA to recommend genotyping for all patients before receiving treatment with warfarin in 2007.

Nevertheless, despite the strong association between the CYP2C9 genotype and warfarin dose, CYP2C9 genotype accounts for only a small portion of the total variability in warfarin doses (~10–20%). Thus, there is a need to determine other genetic and non-genetic factors, which contribute to the interindividual variability in warfarin doses.

Functional Aspect of Personalized Medicine in Cardiovascular Disease

As mentioned previously, functional aspects provide a different perspective to structural aspect, like imaging measurements. However, it is very difficulty to define the range of functional values in personalized medicine. Examples of functional factors include endothelial function, exercise testing, and heart rate variability. This section will focus on endothelial function. The endothelium regulates vascular tone through releasing several vasoactive substances, like nitric oxide (NO). NO mediates the protection of the endothelium by limiting the vascular inflammation, vascular smooth muscle proliferation, platelet aggregation, and tissue factor production.

Endothelial function can be tested by flow-mediated dilation (FMD) in the brachial artery. The treatment of coronary heart disease reverses endothelial dysfunction, including drugs that modify lipids and reduce blood pressure, along with smoking cessation, physical exercise, and dietary intervention. Due to the inconsistent study results, standardization of the FMD method and development of alternative methods for measuring endothelial function is requested. Among them, noninvasive peripheral arterial tonometry that examine the endothelial dysfunction can predict late CV events. Reactive hyperaemia (RH) response with peripheral arterial tonometry as detected by the RH index has been shown to be related to multiple traditional and metabolic risk factors. Also, PAT-derived measures of arterial stiffness (augmentation index, AI) had strong repeatability.

Challenges & Infrastructure of Personalized Medicine in Cardiovascular Disease

Basically, the nature of personalized medicine is multidisciplinary approach to science. Its wide spread adoption will require the harmonization of many components; advances in technology; changes in health care infrastructure and medical practice convention; improvement in the efficiency and quality of healthcare delivery; diagnostic and therapeutic business models for genetically designed markets; attempts by government and private players to justify a new genre of tests and drugs; a different approach to regulatory oversight; and, of course, the ethical and legal issues that go along with the extensive use of genetic information in medical records.

The realization of personalized medicine relies on the input and contributions of a broad community of stakeholders, all working together toward a shared goal of harnessing breakthroughs in science and technology to improve patient care. Kramer and Croswell showed that the true value of cancer screening tests is clouded by four kinds of bias; lead time bias, healthy voluntary bias, length biased sampling, and overdiagnosis. Personalized medicine of CVDs faces similar challenges. CVDs are developed by complicated interactions between multiple genes and environmental factors, and epidemiological issues exist whether or not genetic/genomic factors are the confounder or independent factors.

Personalized medicine is already being practiced in the clinic, and the use of genomic tools, particularly in cardiology, has enhanced patient care. The integration of genomic research into the clinic...
needs to be standardized and streamlined. But there are limitations of personalized medicine. Multiple studies were performed, but the results of literature is discrepant and inconclusive in some instances. Genetics accounts for an insufficient percentage of response variability for a given case or drug. This might be due to inadequately powered studies, studying the different drug response phenotypes or patient populations (differences in allele frequencies), problems precisely measuring the phenotype, subtlety of functional effects of polymorphisms, focus on single SNPs instead of haplotypes, and failure to consider the complexity of drug response. Nevertheless, few studies documenting genotype-guided therapy are better than the "usual care" approach, and few "point-of-care" tests available to determine a person's genetic make-up or protein expression.

The promise and final goals of personalized medicine, for which tangible evidence already exists, includes the ability to shift emphasis in medicine from reaction to prevention, enable the selection of optimal therapy and reduce trial-and-error prescribing, make the use of drugs safer by avoiding ADRs, increase patient compliance with treatment, reduce the time and cost of clinical trials, revive drugs that are failing in clinical trials or were withdrawn from the market, and reduce the overall cost of healthcare. The Personalized Medicine Coalition required a substantial effort on the alignment of laws, regulatory and insurance reimbursement policies, healthcare information technology, medical education, and research investment.

For personalized medicine to be successful, Califf and Ginsburg emphasized the need to enhance infrastructure in terms of laboratory (i.e., biobanking; coordinated efforts, operational and informatics support, standards: genomic technologies; core laboratories, economies of scale) and bioinformatical infrastructures (informatics; reliable, interoperable EHRs; integration of research, clinical, molecular data: decision support; biostatistics; critical shortage must be addressed, physician training in quantitative skills: decision making; understanding of human decision making, biological, psychological and social factors, education of health care professionals).

Other important issues are the economic and legal systems, along with the education on the personalized medicine. Further integration of personalized medicine into the clinical workflow requires overcoming several barriers in education, accessibility, regulation, and reimbursement.

Lewin highlighted socioeconomic/regulatory and ethical issues related to personalized medicine, which differs from the traditional models of payment and regulation. Currently, tests are not covered by public or private payers, and are financially viable for only a select patient population. There will be need to defined roles of professional societies, regulatory agencies and congress in promoting personalized medicine.

Most of the commentators on personalized medicine describe urgent needs for education, for both doctors and patients to promote knowledge, perception, and awareness, related to personalized medicine. More than half of cardiologists do not feel confident in their understanding of personalized medicine, and education/educational opportunities are insufficient. In his report, the primary driver of short-term skepticism is that the three out of four cardiologists believe that a lack of patient outcome data is the primary challenge to the implementation of personalized medicine in their practice. Additionally, there are reimbursement concerns for these tests (68%), lack of formal physician education, such as CME on the topic (66%), and lack of guidance from professional societies/associations (55%) on personalized medicine. In Canada, a strong majority of medical doctor respondents agreed that genetic testing and personalized medicine can have a positive impact on their practice; however, only 51% agreed that there is sufficient evidence to order such tests. Canadian physicians recognize the benefits of genetic testing and personalized medicine, but lack the education, information and support needed to effectively practice in this area.

In the next five years, 73% of cardiologists indicate that personalized medicine will have some measurable impact on patient treatment. Within the next 10 years, more than 9 out of 10 cardiologists believe that personalized medicine will have a larger role in cardiovascular therapy.

Cardiologists report that 6% of patients are asking about personalized medicine. We should raise the awareness to patients on personalized medicine. A 2009 PricewaterhouseCoopers report found that 20-75% of patients respond to the drugs they are taking, but with genetic testing that response rate could improve "dramatically".

Conclusion

Personalized medicine provides the means to predict, prevent, treat and cure diseases, enabling targeted diagnostics, prognostics and therapies to promote longitudinal wellness and advance health care for individuals and populations. There are many challenges from both perspectives of scientific and policy to personalized medicine. Individualized medicine serves a pivotal role in the evolution of national and global healthcare reform. Personalized medicine can overcome many challenges by comprehensive concept and understanding, clinical application, and evidence based practices.

Individualized medicine contributes to the evolution of health management practice, especially in CVDs fields. Ultimately, it will affect the entire landscape of healthcare system. The overall outcome is the well-being of each individual through the continuum.
of life, transforming the future of personalized health care.

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