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CURRENT OPINION

The continuum of personalized cardiovascular medicine: a position paper of the European Society of Cardiology

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Introduction

Personalized medicine implies a tailored approach to patients that offers more effective therapy for each individual, reduces risks and avoids unnecessary treatments or diagnostic interventions. Treatment of patients with cardiovascular diseases (CVDs) has markedly improved through the evaluation of new therapy concepts in large, controlled trials that provide evidence-based guidance. While this approach has, e.g. reduced morbidity and mortality in acute coronary artery disease and extended significantly life expectancy in chronic ischaemic heart disease and heart failure, there remains a high, and increasing, burden of CVD. Conditions such as atrial fibrillation, acute heart failure, or sudden cardiac death still cause unacceptable morbidity and mortality in the population. Furthermore, patients who survive acute cardiac events often require long-term treatment for chronic conditions. The development and implementation of a more personalized management offer potential to significantly improve outcome.

Controlled trials by nature apply the same approach and therapy to patients with the same disease entity, even if with different disease stages and manifestations. Yet clinical cardiological practice aims to take into account differences between individual patients into therapeutic decisions. Initial concepts of personalized medicine focused heavily on genetic markers, particularly in oncology, but equally in CVD where genomics was the first marker which was considered.[1,2] This has yielded interesting insights for some areas, such as unwanted drug effects,[3] but this one-sided approach has limitations and a more comprehensive strategy is needed.[4] Application of risk stratification based on clinical, biochemical, imaging, and/or genomic markers is already used to tailor therapy, but remains fragmented and research often focuses on single aspects of personalization.

Based on a workshop held by the European Society of Cardiology, this report summarizes the current state of stratified cardiovascular care and examines the available and required tools to progress towards more personalized cardiovascular medicine. Actions are proposed that are necessary to expand and implement personalized medicine in CVDs and overcome potential hurdles.

State-of-the-art in cardiovascular medicine

Evidence-based medicine provided important advances in cardiovascular care

In recent years CVD has been leading the medical field in moving away from treatment defined by individual physicians to treatment based on evidence and guidelines. Large randomized clinical trials (RCTs) and population studies have identified the benefit of novel therapies

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such as β-blockers, ACE-inhibitors, anticoagulants, PCI and stents,[5–8] defibrillators, and pacemakers.[9] The evidence-based approach has led to major reductions in mortality in acute coronary syndromes and stroke[10,11] in a time when progress in other areas has been much slower.[12] Recently, however, some limitations to the evidence-based medicine have emerged. For example, it has been recognized that this approach is driven by the enrolment criteria of the trials and may not provide results that are applicable to other subgroups of patients such as those *excluded* by the trial. For this reason, the need for different approaches to investigate efficacy of therapies in selected populations has promoted the concept of 'personalized medicine' defined as the selection of diagnostic and therapeutic strategies based on prospectively validated patient characteristics, integrating clinical parameters, biochemical, usually blood-based biomarkers, and genetic information.

The adoption of this broad definition of 'personalized medicine' is rooted in the recognition that *contemporary cardiovascular care is already using components of individualized medicine*. Assessment of an individual based on an assembly of risk factors, which is converted into risk scores (e.g. SCORE, GRACE,[13] TIMI,[14] CHA_2DS_2VASc,[15] MAGGIC[16]), is an important, first step towards individualization in current cardiology practice which requires better implementation.[17,18] The electrocardiogram is an important and immediately available 'point-of-care' diagnostic tool that provides further invaluable information, e.g. in the detection of ST elevation myocardial infarction in patients with chest pain, arrhythmias such as atrial fibrillation or ventricular tachycardias, but also information on heart rate, QRS widening, PR, or QT interval. Further individualization of care is based on biochemical markers such as elevated serum troponins which guide an invasive treatment strategy in patients with acute chest pain when clinical information is integrated.[19] On a similar line, BNP measurements can help differentiate heart failure from non-cardiac causes of breathlessness,[20] and troponin or D-dimer may be useful to further estimate risk in patients with atrial fibrillation.[21] Further individualization of therapy comes through imaging. Echocardiography has become a first line tool where, e.g. reduced left ventricular function guides therapy with, e.g. ACE-inhibitors and β-blockers, or implantation of a defibrillator.[6] In other patients, echocardiography identifies concomitant cardiac diseases that alter treatment, e.g. cardiomyopathies or valvular heart disease.[22] Advanced imaging techniques based on CT and MRI are current standard of care to guide cardiovascular interventions, e.g. fractional flow reserve to decide on stent placement,[23] or aortic valve area estimation for treatment of aortic stenosis.[24]

Unmet needs in the management of cardiovascular diseases

Yet this approach seems to have exploited much of its applications and its limitations are emerging. Implementation of guidelines and outcome studies has uncovered that the diversity in the general population precludes a 'one size fits all' approach to common clinical conditions, and that the current stratification is insufficient.[25] Examples are the need for optimizing the approach to women presenting with chest pain, specific demands of the elderly, or the variation in drug response, e.g. to anticoagulants. Possibly the best illustration of the remaining needs are the unyielding/persistent high mortality rates in patients with atrial fibrillation even when evidence-based therapy is applied.[26] While the reduction in novel drugs reaching the market has been observed in several disease areas, it is particularly salient in CVD.[27] High costs associated with the demands of large RCT to demonstrate efficacy in the global population are one of the factors that underlie the reduced investment in this market segment. Better definition of patient subpopulations through better personalized diagnosis in the framework of novel disease classifications can reduce cost and increase efficiency of clinical trials. Subsequent personalized treatments targeting those who are most likely to benefit from a novel therapy can help to reduce the risk of treatment failure and cut unnecessary expenditures. Specific markers may allow targeting new therapies to patients who would benefit most.

A distinct scope in CVD

Advanced personalization of cardiovascular medicine can be seen as a continuum as it further integrates emerging technologies, molecular markers, and genomic variants into the current practice of stratified medicine. This novel approach should be introduced in a comprehensive manner from diagnosis to risk stratification and management. One of the challenges is integrating all markers in a network analysis, as, e.g. now developed to identify key hubs for signalling pathway control.[28] Specifically in CVD functional and structural biomarkers obtained non-invasively through advanced imaging, electrocardiography, and integrated multi-parameter modelling [e.g. as done in the FP7-funded physiome project (http://www.vph-noe.eu/)] will be of major value.

Areas in need for personalized management

Identifying individuals at risk

Simple risk scores such as SCORE or CHA_2DSVA_2Sc are advocated by the ESC based on proven benefit.[29] They are easy to implement due to low cost and easy access but define broad categories and, e.g., are poor in identifying the medium-risk population. Targeting individuals at risk for primary prevention remains a goal in atherosclerosis and sudden death, but equally important are identification of patients for secondary prevention, e.g. after first ischaemic events, and of individuals needing intensified screening for early disease detection. In these areas better stratification is needed that identifies whom to treat, when to treat and the targets that represent a modifiable risk. Recent developments have used cardiac imaging, where, e.g., MRI, stress echocardiography, or CT angiogram allows to exclude relevant coronary artery disease in patients at moderate disease risk (Supplementary material online).

Improving response to existing therapy

The major road block for improving the response to existing, often life-saving therapies in CVD is the poor classification of disease entities. Typical examples are heart failure and atrial fibrillation where disease classification has not progressed beyond symptoms and poorly discriminatory clinical signs such as left ventricular function or the ECG pattern of atrial fibrillation. The recent further success

in the management of acute coronary syndromes, in contrast, was only possible due to more careful classification of patients with chest pain by troponin isoforms. There is a clear need for advanced disease classification, reflecting specific disease biology, to better guide personalized therapy.

Avoiding rare side-effects

Avoiding side-effects of therapy is another important goal in this context which is guided by integrated information. A good example illustrating the potency of integrating careful phenotyping and genomic information is the prediction of a pro-arrhythmic response to medication with action potential prolonging properties such as antibiotics. This pro-arrhythmic response is specific to only a small portion of patients who can be identified by combination of information from ECG, clinical parameters, and possibly genetic information.[30–32]

In summary, integration of biological markers for specific disease processes has the potential to identify patients at risk for first (often lethal) cardiovascular events, to allow to target therapies to patients who are most likely to benefit, and to allow better prediction of unwanted side-effects of therapy.

Existing and emerging approaches

Genomics in CVD

The genomic gold rush of the past decades has brought major insights in the spectrum of the genetic contribution to CVD. 'Classical' genetic techniques and functional assessment of the gene defect have identified arrhythmia mechanisms in the long QT syndrome and other inherited arrhythmic diseases.[33–35] These insights are now shaping 'genotype-specific therapy',[36] providing a role model for the future use of novel, genomic information in CVD management.

Large-scale GWAS studies have identified a number of relevant alleles in common chronic diseases such as coronary artery disease or atrial fibrillation.[37–44] The potential to identify new disease mechanisms and approaches for individualized therapy based on genotype has yet to be harvested. PCSK9 and PITX2 provide first examples for the potential of 'polygenic' genetic predispositions in common CVDs.

A new taxonomy: the case of heart failure and atrial fibrillation

New disease classifications are needed that better reflect known causes, as exemplified by these chronic diseases. First, imperfect attempts have been made in this direction, e.g. by distinguishing heart failure with and without reduced systolic left ventricular function,[45–47] or by more recent proposals to classify atrial fibrillation based on pathophysiology.[48] Contemporary disease classification can integrate and valorize detailed clinical, but also genetic, functional, and imaging information. A close interaction between basic scientists and clinicians is needed to allow integration of relevant pathophysiological subtypes in such a classification while retaining clinical robustness and applicability.

Imaging and functional studies to personalize management

A particular strength in CVD is the development of non-invasive imaging tools to evaluate both structure and function of heart and vessels by ultrasound, computed tomography, magnetic resonance imaging, and nuclear cardiology techniques. Several specific diagnostic tools guide therapy in ischaemic heart disease and valve replacement. Yet these are still 'stand-alone' imaging approaches. Combining advanced imaging with molecular markers can further refine taxonomy, with the potential for molecular imaging on the horizon. In atrial fibrillation imaging of fibrosis in combination with circulating markers is an example.

Blood-based biomarkers

A key problem is the extraction of information on the myocardium and the vascular wall from venous blood. Concepts are being derived from tissue sample studies, e.g. relying on mRNA and microRNA. Circulating miRNA may spill over from intercellular communication in vascular wall remodelling[g–51] and provide diagnostic and therapeutic guidance.[52,53] A search for blood-based markers for cardiac pathologies may also make use of microparticles, secreted proteins, circulating monocytes, or markers for epigenetic regulation.[54]

Inherited cardiac diseases

Several familial, monogenic heart diseases such as hypertrophic cardiomyopathy or the long QT syndromes have been well characterized. The genetic defects have been reported, and disease mechanisms have been described in suitable models. The clinical impact of the underpinning molecular defects on diagnosis, risk stratification, and management remains rather heterogeneous.[55] Despite this progress, mechanism-based or genotype-specific prevention of sudden death has yet to become clinical reality:[56] The long QT syndromes are the only example where the genetic defect can inform prognosis and hence management at present.[56] Only recently some studies have approached the field with a more integrated 'omics' view to investigate the consequences on the phenotype of polymorphisms in the coding regions of causative genes and in other regulatory gene structures as well as the role of gene–gene interaction to regulate protein expression. There is expectation that these investigations will provide insights in the identification of patients at a higher risk of life-threatening arrhythmias.

Pharmacogenomics, i.e. the use of genetic markers to identify patients at risk for adverse reactions to pharmacotherapy, has been proposed for several cardiovascular therapeutics including antithrombotic agents, antiarrhythmic drugs,[2,57] or rhabdomyolysis on statin therapy.[58] Even though the evidence for genetically conferred differences in the response, e.g., to oral anticoagulants is good, controlled trials of genotype-informed dosing did not improve therapy.[59,60] The interaction of ambient and inherited factors that often results in unexpected reactions to therapy may be easier assessed using integrated functional biomarkers, e.g., clinical profiles (as done in warfarin dosing schemes) or ECG changes,[30,61] on therapy.

Next steps towards personalized cardiovascular medicine

Collecting genomic and molecular information and their clinical context

A critical bottleneck for (pharmaco)genomic research is the limited access to DNA samples and data from RCTs. The EU can amend procedures and protocols to allow long-term follow-up of trial patients and access to biomaterials to support the identification and validation of new disease-related biomarkers in such cohorts. Such amendments should also allow using other functional information, e.g. ECG or imaging. Efforts should be supported to change public opinion on genetic testing. Good communication between patients and providers will be necessary to define and balance the 'need to know' vs. 'risk of knowledge' and this will further require education of researchers, health care providers, patients, regulators, and other stake holders.

Integrating information across platforms and technologies for a new taxonomy of CVD

To understand pathophysiology, clinical, imaging, functional, molecular, genomic, and/or epigenetic markers need to be connected, and further linked to outcomes. New disease classifications can identify patients who will benefit from existing and new interventions and guide better personalization of CVD management, as outlined above for atrial fibrillation or heart failure. The emerging phenotype/genotype-specific therapy of patients with inherited channelopathies provides first evidence for such a pathophysiologically mediated translation into new therapeutic concepts.[22,36] Such

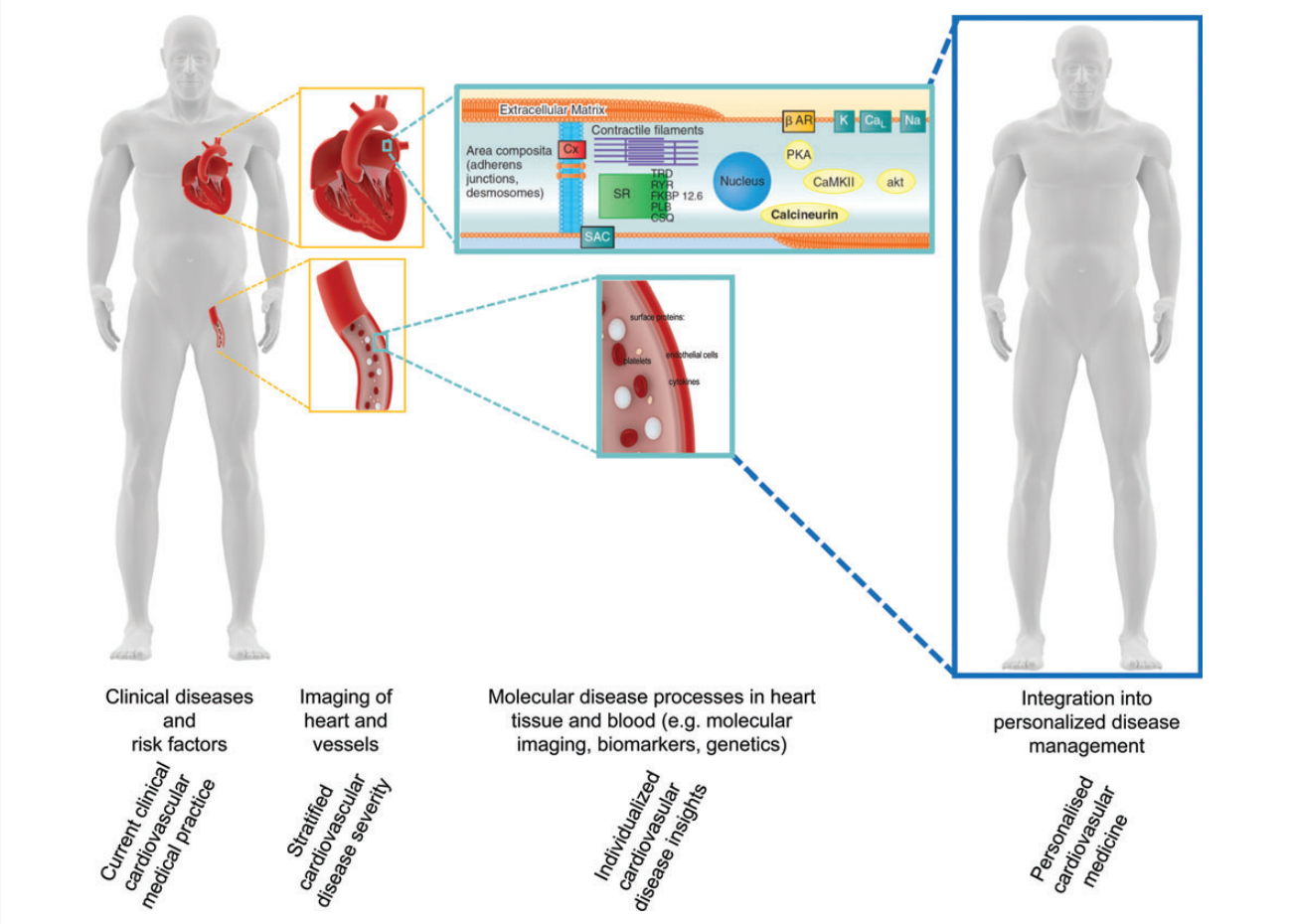

Figure 1 A roadmap from current clinical to personalized cardiovascular medicine. The left two images illustrate the current practice, namely using clinical parameters and risk factors as the basis for therapeutic decisions, recently enhanced by the use of cardiac or vascular imaging modalities. A better understanding of the molecular disease mechanisms and markers that can identify specific mechanisms in patients—especially in the common, chronic, and multifactorial cardiovascular diseases such as heart failure, atrial fibrillation, or coronary artery disease—is needed to design new and better targeted therapies to reverse disease processes. This is exemplified by the schematic of a cardiomyocyte (third image, top) and vessel wall and blood components (third image, bottom). Integrating these insights into the current practice of clinical and imaging-based cardiovascular medicine, through the application of new biological markers and new disease classifications, will allow a personalized approach to cardiovascular medicine in the near future.

integration presents a formidable challenge to data storage, management and analysis, IT capacity, and accessibility.

Adapting clinical trial design

Stratification of patients at enrolment, e.g. based on a new disease classification, or by including biological markers for disease processes in the inclusion criteria, can help to design focused, lean, and affordable trials. Innovative statistics will be needed: addressing a multiplicity of potential biomarkers, identifying reliable and valid measurements, and other issues need prospective consideration.

A sound regulatory framework and research support

The EU has an essential role in shaping a European environment that is conducive to personalized medicine, including the framework for clinical trials, access to data and human biosamples. Using existing biosample collections is an opportunity to explore personalized therapy in a *post hoc*, hypothesis-generating fashion. Continued collaboration and further implementation of a strong public–private partnership between academia and research institutes, biotech and SMEs, and large companies are essential in the development of personalized medicine, and require policy support.

Person-centred cardiovascular medicine in an era of personalization

Personalized medicine has been driven by biology and indeed will need to remain driven by biology and pathophysiology, but it is essential to consider and include the patient in his social circle. When efficacy suggests equipoise, a person-centred view that includes the patient in the process of diagnosis and therapeutic management[62,63] is at the core of personalized care. This implies considering environmental and cultural influences (e.g. gender vs. sex-dependent modulation of disease). In CVD, several examples highlight the need for inclusion of factors beyond biology, such as gender-dependent bias in diagnosis, the influence of personal care on heart failure outcome. Towards patients, information and empathy need to go together, and including patients in the development of a personalized track is essential.

Conclusions

There is strong need to develop the current stratified practice of CVD management into a better personalized cardiovascular medicine, within a broad framework of global patient care. Clinical information obtained from history and physical examination, functional and imaging studies, biochemical biomarkers, genetic/epigenetic data, and pathophysiological insights into disease-driving processes need to be integrated into a new taxonomy of CVDs to allow personalized disease management. This has the potential for major health benefits for the population suffering from cardiovascular diseases (*Figure 1*).

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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