

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

Paulus Kirchhof^{1,2,3*}, Karin R. Sipido⁴, Martin R. Cowie⁵, Thomas Eschenhagen⁶, Keith A.A. Fox⁷, Hugo Katus⁸, Stefan Schroeder⁹, Heribert Schunkert¹⁰, Silvia Priori¹¹, and ESC CRT R&D and European Affairs Work Shop on Personalized Medicine

¹Centre for Cardiovascular Sciences, University of Birmingham and SWBH NHS Trust, Birmingham, UK; ²Department of Cardiology and Angiology, Hospital of the University of Münster and AFNET, Münster, Germany; ³School of Clinical and Experimental Medicine, University of Birmingham and SWBH NHS Trust, City Hospital Institute of Biomedical Research, Wolfson Drive Birmingham, B15 2TT, UK; ⁴Department of Cardiovascular Sciences, KU Leuven, Leuven, Belgium; ⁵Imperial College and Royal Brompton Hospital, London, UK; ⁶Department of Pharmacology and Toxicology, University Medical Center Hamburg Eppendorf and DZHK (German Centre for Cardiovascular Research), Partner Site Hamburg/Kiel/Lübeck, Hamburg, Germany; ⁷Centre for Cardiovascular Science, University of Edinburgh, Edinburgh, UK; ⁸Department of Cardiology and Angiology, University of Heidelberg and DZHK (German Centre for Cardiovascular Research), Partner Site Heidelberg, Germany; ⁹Bayer Healthcare, Berlin, Germany; ¹⁰Department of Cardiology, German Heart Center, Technical University Munich and DZHK (German Centre for Cardiovascular Research), Partner Site Munich, Munich, Germany; and ¹¹Division of Cardiology and Molecular Cardiology, Maugeri Foundation, Department of Molecular Medicine, University of Pavia, Pavia, Italy

Received 8 January 2014; revised 22 April 2014; accepted 17 July 2014; online publish-ahead-of-print 22 August 2014

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

The opinions expressed in this article are not necessarily those of the Editors of the *European Heart Journal* or of the European Society of Cardiology.

* Corresponding author. Tel: +44 1214147042, Email: p.kirchhof@bham.ac.uk

© The Author 2014. Published by Oxford University Press on behalf of the European Society of Cardiology.

This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<http://creativecommons.org/licenses/by-nc/4.0/>), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited. For commercial re-use, please contact journals.permissions@oup.com

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 CHA₂DS₂VASc,¹⁵ MAGGIC¹⁶), 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 CHA₂DSVA₂Sc 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^{8–51} 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

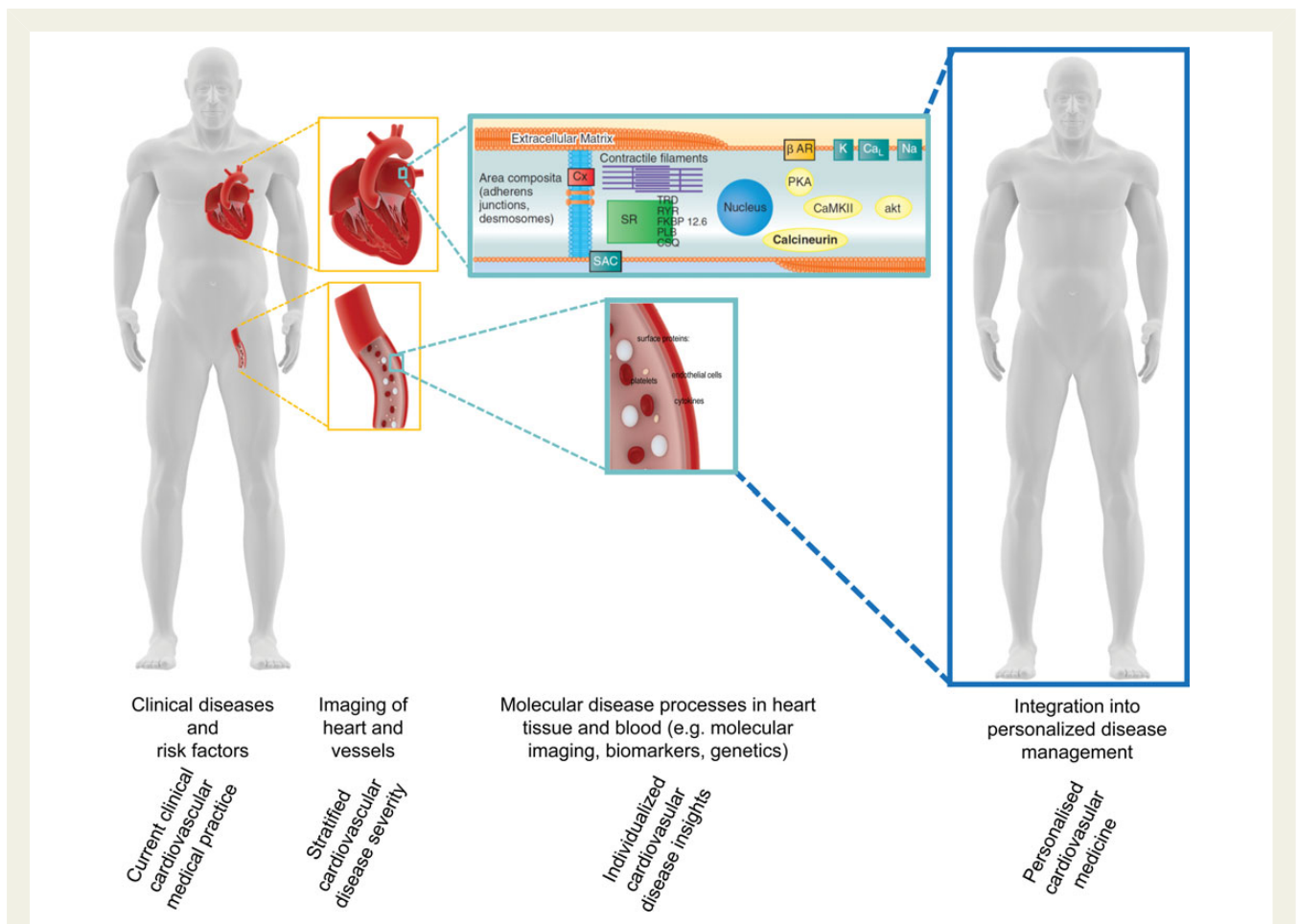


Figure 1 A roadmap from current clinical to personalized cardiovascular medicine. The left two images illustrate the current practice, namely using clinical parameters and risk factors as the basis for therapeutic decisions, recently enhanced by the use of cardiac or vascular imaging modalities. A better 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.

Acknowledgements

This paper describes the discussions held during a two-day workshop organized by the cardiovascular round table and the European Affairs Committee of the European Society of Cardiology in February 2013. All participants contributed actively to the discussions during the work shop and contributed to the content of this paper. The following persons participated in the work shop and agreed to have their name listed here: Angeles Alonso; Claire Chezeaubernard; Pieter Doevendans; Thomas Eschenhagen; Keith Fox; Hugo Katus; Yasser Khder; Paulus Kirchhof; Frank Kramer; Steen Kristensen; Anke-Hilse Maitland-Van der Zee; Sabine Oertelt-Prigione; Fausto Pinto; Stuart Pocock; Silvia G. Priori; Alfonso Sartorius; Daniela Schott; Stefan Schroeder; Heribert Schunkert; Matthias Schwab; Karin Sipido; Anders Svensson; Karl Swedberg; Lars Wallentin; Marianne Weimers; Seppo Yla Herttuala.

Funding

Funding to pay the Open Access publication charges for this article was provided by European Society of Cardiology.

Conflict of interest: none declared.

References

- O'Donnell CJ, Nabel EG. Cardiovascular genomics, personalized medicine, and the National Heart, Lung, and Blood Institute: part I: the beginning of an era. *Circ Cardiovasc Genet* 2008;**1**:51–57.
- Verschuren JJ, Trompet S, Wessels JA, Guchelaar HJ, de Maat MP, Simoons ML, Jukema JW. A systematic review on pharmacogenetics in cardiovascular disease: is it ready for clinical application? *Eur Heart J* 2012;**33**:165–175.
- Johnson JA, Cavallari LH. Pharmacogenetics and cardiovascular disease—implications for personalized medicine. *Pharmacol Rev* 2013;**65**:987–1009.
- Volzke H, Schmidt CO, Baumeister SE, Ittermann T, Fung G, Krafczyk-Korth J, Hoffmann W, Schwab M, Meyer zu Schwabedissen HE, Dorr M, Felix SB, Lieb W, Kroemer HK. Personalized cardiovascular medicine: concepts and methodological considerations. *Nat Rev Cardiol* 2013;**10**:308–316.
- Nabel EG, Braunwald E. A tale of coronary artery disease and myocardial infarction. *N Engl J Med* 2012;**366**:54–63.
- McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Bohm M, Dickstein K, Falk V, Filippatos G, Fonseca C, Gomez-Sanchez MA, Jaarsma T, Kober L, Lip GY, Maggioni AP, Parkhomenko A, Pieske BM, Popescu BA, Ronnevik PK, Rutten FH, Schwitler J, Seferovic P, Stepinska J, Trindade PT, Voors AA, Zannad F, Zeiher A, Bax JJ, Baumgartner H, Ceconi C, Dean V, Deaton C, Fagard R, Funck-Brentano C, Hasdai D, Hoes A, Kirchhof P, Knuuti J, Kolh P, McDonagh T, Moulin C, Reiner Z, Sechtem U, Sirnes PA, Tendera M, Torbicki A, Vahanian A, Windecker S, Bonet LA, Avraamides P, Ben Lamin HA, Brignole M, Coca A, Cowburn P, Dargie H, Elliott P, Flachskampf FA, Guida GF, Hardman S, Jung B, Merkely B, Mueller C, Nanas JN, Nielsen OW, Orn S, Parissis JT, Ponikowski P. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail* 2012;**14**:803–869.
- Authors/Task Force M, Mancina G, Fagard R, Narkiewicz K, Redon J, Zanchetti A, Bohm M, Christiaens T, Cifkova R, De Backer G, Dominiczak A, Galderisi M, Grobbee DE, Jaarsma T, Kirchhof P, Kjeldsen SE, Laurent S, Manolis AJ, Nilsson PM, Ruilope LM, Schmieder RE, Sirnes PA, Sleight P, Viigimaa M, Waeber B, Zannad F, Council ESHS, Redon J, Dominiczak A, Narkiewicz K, Nilsson PM, Burnier M, Viigimaa M, Ambrosioni E, Caulfield M, Coca A, Olsen MH, Schmieder RE, Tsoufis C, van de Borne P, Guidelines ESCCFP, Zamorano JL, Achenbach S, Baumgartner H, Bax JJ, Bueno H, Dean V, Deaton C, Erol C, Fagard R, Ferrari R, Hasdai D, Hoes AW, Kirchhof P, Knuuti J, Kolh P, Lancellotti P, Linhart A, Nihoyannopoulos P, Piepoli MF, Ponikowski P, Sirnes PA, Tamargo JL, Tendera M, Torbicki A, Wijns W, Windecker S, Document R, Clement DL, Coca A, Gillebert TC, Tendera M, Rosei EA, Ambrosioni E, Anker SD, Bauersachs J, Hiti J, Caulfield M, De Buyzere M, De Geest S, Derumeaux GA, Erdine S, Farsang C, Funck-Brentano C, Gerc V, Germano G, Gielen S, Haller H, Hoes AW, Jordan J, Kahan T, Komajda M, Lovic D, Mahrholdt H, Olsen MH,

- Ostergren J, Parati G, Perk J, Polonia J, Popescu BA, Reiner Z, Ryden L, Sirenko Y, Stanton A, Struijker-Boudier H, Tsoufis C, van de Borne P, Vlachopoulos C, Volpe M, Wood DA. 2013 ESH/ESC Guidelines for the management of arterial hypertension: The Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *Eur Heart J* 2013;**34**:2159–2219.
8. Camm AJ, Lip GY, De Caterina R, Savelliva I, Atar D, Hohnloser SH, Hindricks G, Kirchhof P, Bax JJ, Baumgartner H, Ceconi C, Dean V, Deaton C, Fagard R, Funck-Brentano C, Hasdai D, Hoes A, Knuuti J, Kolh P, McDonagh T, Moulin C, Popescu BA, Reiner Z, Sechtem U, Sirnes PA, Tendera M, Torbicki A, Vahanian A, Windecker S, Vardas P, Al-Attar N, Alfieri O, Angelini A, Blomstrom-Lundqvist C, Colonna P, De Sutter J, Ernst S, Goette A, Gorenek B, Hatala R, Heidbuchel H, Heldal M, Kristensen SD, Le Heuzey JY, Mavrakis H, Mont L, Filardi PP, Ponikowski P, Prendergast B, Rutten FH, Schotten U, Van Gelder IC, Verheugt FW. 2012 focused update of the ESC Guidelines for the management of atrial fibrillation: An update of the 2010 ESC Guidelines for the management of atrial fibrillation * Developed with the special contribution of the European Heart Rhythm Association. *Eur Heart J* 2012;**33**:2719–2747.
 9. Authors/Task Force M, Brignole M, Auricchio A, Baron-Esquivias G, Bordachar P, Boriani G, Breithardt OA, Cleland J, Deharo JC, Delgado V, Elliott PM, Gorenek B, Israel CW, Leclercq C, Linde C, Mont L, Padeletti L, Sutton R, Vardas PE, Guidelines ESCCP, Zamorano JL, Achenbach S, Baumgartner H, Bax JJ, Bueno H, Dean V, Deaton C, Erol C, Fagard R, Ferrari R, Hasdai D, Hoes AW, Kirchhof P, Knuuti J, Kolh P, Lancellotti P, Linhart A, Nihoyannopoulos P, Piepoli MF, Ponikowski P, Sirnes PA, Tamargo JL, Tendera M, Torbicki A, Wijns W, Windecker S, Document R, Kirchhof P, Blomstrom-Lundqvist C, Badano LP, Alyev F, Banch S, Baumgartner H, Bsata W, Buser P, Charron P, Daubert JC, Dobreanu D, Faerstrand S, Hasdai D, Hoes AW, Le Heuzey JY, Mavrakis H, McDonagh T, Merino JL, Navar MM, Nielsen JC, Pieske B, Poposka L, Ruschitzka F, Tendera M, Van Gelder IC, Wilson CM. 2013 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy: The Task Force on cardiac pacing and resynchronization therapy of the European Society of Cardiology (ESC). Developed in collaboration with the European Heart Rhythm Association (EHRA). *Eur Heart J* 2013;**34**:2281–2329.
 10. Fox KA, Steg PG, Eagle KA, Goodman SG, Anderson FA Jr, Granger CB, Flather MD, Budaj A, Quill A, Gore JM, Investigators G. Decline in rates of death and heart failure in acute coronary syndromes, 1999–2006. *JAMA* 2007;**297**:1892–1900.
 11. Schmidt M, Jacobsen JB, Lash TL, Botker HE, Sorensen HT. 25 year trends in first time hospitalisation for acute myocardial infarction, subsequent short and long term mortality, and the prognostic impact of sex and comorbidity: a Danish nationwide cohort study. *BMJ* 2012;**344**:e356.
 12. Lenfant C. Shattuck lecture—clinical research to clinical practice—lost in translation?. *N Engl J Med* 2003;**349**:868–874.
 13. Eagle KA, Lim MJ, Dabbous OH, Pieper KS, Goldberg RJ, Van de Werf F, Goodman SG, Granger CB, Steg PG, Gore JM, Budaj A, Avezum A, Flather MD, Fox KA, Investigators G. A validated prediction model for all forms of acute coronary syndrome: estimating the risk of 6-month postdischarge death in an international registry. *JAMA* 2004;**291**:2727–2733.
 14. Antman EM, Cohen M, Bernink PJ, McCabe CH, Horacek T, Papuchis G, Mautner B, Corbalan R, Radley D, Braunwald E. The TIMI risk score for unstable angina/non-ST elevation MI: a method for prognostication and therapeutic decision making. *JAMA* 2000;**284**:835–842.
 15. Lip GY, Nieuwlaar R, Pisters R, Lane DA, Crijns HJ. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. *Chest* 2010;**137**:263–272.
 16. Pocock SJ, Ariti CA, McMurray JJ, Maggioni A, Kober L, Squire IB, Swedberg K, Dobson J, Poppe KK, Whalley GA, Doughty RN, Meta-Analysis Global Group in Chronic Heart F. Predicting survival in heart failure: a risk score based on 39 372 patients from 30 studies. *Eur Heart J* 2013;**34**:1404–1413.
 17. Hamm CV, Bassand JP, Agewall S, Bax J, Boersma E, Bueno H, Caso P, Dudek D, Gielen S, Huber K, Ohman M, Petrie MC, Sonntag F, Uva MS, Storey RF, Wijns W, Zahger D, Bax JJ, Auricchio A, Baumgartner H, Ceconi C, Dean V, Deaton C, Fagard R, Funck-Brentano C, Hasdai D, Hoes A, Knuuti J, Kolh P, McDonagh T, Moulin C, Poldermans D, Popescu BA, Reiner Z, Sechtem U, Sirnes PA, Torbicki A, Vahanian A, Windecker S, Achenbach S, Badimon L, Bertrand M, Botker HE, Collet JP, Crea F, Danchin N, Falk E, Goudevenos J, Gulba D, Hambrecht R, Herrmann J, Kastrati A, Kjeldsen K, Kristensen SD, Lancellotti P, Mehilli J, Merkely B, Montalescot G, Neumann FJ, Neyses L, Perk J, Roffi M, Romeo F, Ruda M, Swahn E, Valgimigli M, Vrints CJ, Widimsky P. ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: the Task Force for the management of acute coronary syndromes (ACS) in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J* 2011;**32**:2999–3054.
 18. Writing Committee M, Jneid H, Anderson JL, Wright RS, Adams CD, Bridges CR, Casey DE Jr, Ettinger SM, Fesmire FM, Ganiats TG, Lincoff AM, Peterson ED, Philippides GJ, Theroux P, Wenger NK, Zidar JP, Anderson JL, American College of Cardiology F, American Heart Association Task Force on Practice G. 2012 ACCF/AHA focused update of the guideline for the management of patients with unstable angina/Non-ST-elevation myocardial infarction (updating the 2007 guideline and replacing the 2011 focused update): a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. *Circulation* 2012;**126**:875–910.
 19. Steg PG, FitzGerald G, Fox KA. Risk stratification in non-ST-segment elevation acute coronary syndromes: troponin alone is not enough. *Am J Med* 2009;**122**:107–108.
 20. Cowie MR, Struthers AD, Wood DA, Coats AJ, Thompson SG, Poole-Wilson PA, Sutton GC. Value of natriuretic peptides in assessment of patients with possible new heart failure in primary care. *Lancet* 1997;**350**:1349–1353.
 21. Hijazi Z, Oldgren J, Siegbahn A, Granger CB, Wallentin L. Biomarkers in atrial fibrillation: a clinical review. *Eur Heart J* 2013;**34**:1475–1480.
 22. Kirchhof P, Breithardt G, Aliot E, al Khatib S, Apostolakis S, Auricchio A, Bailleul C, Benninger G, Blomstrom Lundqvist C, Boersma L, Boriani G, Brandes A, Brown H, Brueckmann M, Calkins H, Casadei B, Clemens A, Crijns H, Derwand R, Dobrev D, Ezekowitz M, Fetsch T, Gerth A, Gillis A, Gulizia M, Hack G, Haegeli L, Hatem S, Haeusler KG, Heidbuchel H, Hernandez-Brichis S, Jais P, Kappenberger L, Kautzner J, Kim S, Kuck K, Lane D, Leute A, Lewalter T, Meyer R, Mont Girbau L, Moses G, Mueller M, Muenzel F, Naebauer M, Nielsen JC, Oeff M, Oto A, Pieske B, Pisters R, Potpara T, Rasmussen L, Ravens U, Jancus U, Rieffel J, Richard-Lordereau I, Schaefer H, Schotten U, Stegink W, Stein K, Steinbeck G, Szumowski L, Tavazzi L, Themistoclakis S, Thomitzek K, van Gelder IC, von Stritzky B, Vincent A, Werring DJ, Willems S, Lip GYH, Camm AJ. Personalised management of atrial fibrillation: Proceedings from the 4th Atrial Fibrillation competence NETWORK/European Heart Rhythm Association (AFNET/EHRA) consensus conference. *Europace* 2013;**15**:1540–1556.
 23. Tonino PA, De Bruyne B, Pijls NH, Siebert U, Ikeno F, van't Veer M, Klauss V, Manoharan G, Engstrom T, Oldroyd KG, Ver Lee PN, MacCarthy PA, Fearon WF. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. *N Engl J Med* 2009;**360**:213–224.
 24. Vahanian A, Alfieri O, Andreotti F, Antunes MJ, Baron-Esquivias G, Baumgartner H, Borger MA, Carrel TP, De Bonis M, Evangelista A, Falk V, Jung B, Lancellotti P, Pierard L, Price S, Schafers HJ, Schuler G, Stepinska J, Swedberg K, Takkenberg J, Von Oppell UO, Windecker S, Zamorano JL, Zembala M, Bax JJ, Ceconi C, Dean V, Deaton C, Fagard R, Funck-Brentano C, Hasdai D, Hoes A, Kirchhof P, Knuuti J, Kolh P, McDonagh T, Moulin C, Popescu BA, Reiner Z, Sechtem U, Sirnes PA, Tendera M, Torbicki A, Von Segesser L, Badano LP, Bunc M, Claeys MJ, Drinkovic N, Filippatos G, Habib G, Kappetein AP, Kassab R, Lip GY, Moat N, Nickenig G, Otto CM, Pepper J, Piazza N, Pieper PG, Rosenhek R, Shuka N, Schwammenthal E, Schwitler J, Mas PT, Trindade PT, Walther T. Guidelines on the management of valvular heart disease (version 2012): The Joint Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J* 2012;**33**:2451–2496.
 25. Lenfant C. Prospects of personalized medicine in cardiovascular diseases. *Metabolism* 2013; **62**(Suppl. 1):S6–10.
 26. Kirchhof P, Breithardt G, Camm AJ, Crijns HJ, Kuck KH, Vardas P, Wegscheider K. Improving outcomes in patients with atrial fibrillation: Rationale and design of the Early treatment of Atrial fibrillation for Stroke prevention Trial (EAST). *Am H J* 2013;**166**:442–448.
 27. Mullard A. 2012 FDA drug approvals. *Nat Rev Drug Discov* 2013;**12**:87–90.
 28. Barabasi AL, Gulbahce N, Loscalzo J. Network medicine: a network-based approach to human disease. *Nat Rev Genet* 2011;**12**:56–68.
 29. Fifth Joint Task Force of the European Society of C, European Association of E, European Association of Percutaneous Cardiovascular I, European Heart Rhythm A, Heart Failure A, European Association for Cardiovascular P, Rehabilitation, European Atherosclerosis S, International Society of Behavioural M, European Stroke O, European Society of H, European Association for the Study of D, European Society of General Practice/Family M, International Diabetes Federation E, European Heart N. European Guidelines on cardiovascular disease prevention in clinical practice (version 2012): the Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts). *Eur J Prev Cardiol* 2012;**19**:585–667.
 30. Kirchhof P, Franz MR, Bardai A, Wilde AM. Giant T-U waves precede torsades de pointes in long QT syndrome: a systematic electrocardiographic analysis in patients with acquired and congenital QT prolongation. *J Am Coll Cardiol* 2009;**54**:143–149.
 31. Fabritz L, Kirchhof P. Predictable and less predictable unwanted cardiac drugs effects: individual pre-disposition and transient precipitating factors. *Basic Clin Pharmacol Toxicol* 2010;**106**:263–268.

32. Kaab S, Crawford DC, Sinner MF, Behr ER, Kannankeril PJ, Wilde AA, Bezzina CR, Schulz-Bahr E, Guicheney P, Bishopric NH, Myerburg RJ, Schott JJ, Pfeufer A, Beckmann BM, Martens E, Zhang T, Stallmeyer B, Zumhagen S, Denjoy I, Bardai A, Van Gelder IC, Jamshidi Y, Dalageorgou C, Marshall V, Jeffery S, Shakir S, Camm AJ, Steinbeck G, Perz S, Lichtner P, Meitinger T, Peters A, Wichmann HE, Ingram C, Bradford Y, Carter S, Norris K, Ritchie MD, George AL Jr, Roden DM. A Large Candidate Gene Survey Identifies the KCNE1 D85N Polymorphism as a Possible Modulator of Drug-Induced Torsades de Pointes. *Circ Cardiovasc Genet* 2011;**5**:91–99.
33. Neyroud N, Tesson F, Denjoy I, Leibovici M, Donger C, Barhanin J, Faure S, Gary F, Coumel P, Petit C, Schwartz K, Guicheney P. A novel mutation in the potassium channel gene KVLQT1 causes the Jervell and Lange-Nielsen cardioauditory syndrome. *Nat Genet* 1997;**15**:186–189.
34. Chen Q, Kirsch GE, Zhang D, Brugada R, Brugada P, Potenza D, Moya A, Borggrefe M, Breithardt G, Ortiz-Lopez R, Wang Z, Antzelevitch C, O'Brien RE, Schulz-Bahr E, Keating MT, Towbin JA, Wang Q. Genetic basis and molecular mechanism for idiopathic ventricular fibrillation. *Nature* 1998;**392**:293–296.
35. Bennett PB, Yazawa K, Makita N, George AL Jr. Molecular mechanism for an inherited cardiac arrhythmia. *Nature* 1995;**376**:683–685.
36. Priori S, Wilde AA, Horie M, Cho Y, Behr E, Berul C, Blom N, Brugada J, Chiang C, Huikuri H, Kannankeril P, Krahn A, Leenhardt A, Moss A, Schwartz P, Shimizu W, Tomaselli G, Tracy C. HRS/EHRA/APHRS expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes. *Europace* 2013;**15**:1389–1406.
37. Yang J, Loos RJ, Powell JE, Medland SE, Speliotes EK, Chasman DI, Rose LM, Thorleifsson G, Steinthorsdottir V, Magi R, Waite L, Smith AV, Yerges-Armstrong LM, Monda KL, Hadley D, Mahajan A, Li G, Kapur K, Vitart V, Huffman JE, Wang SR, Palmer C, Esko T, Fischer K, Zhao JH, Demirkan A, Isaacs A, Feitosa MF, Luan J, Heard-Costa NL, White C, Jackson AU, Preuss M, Ziegler A, Eriksson J, Kutalik Z, Frau F, Nolte IM, Van Vliet-Ostapchouk JV, Hottenga JJ, Jacobs KB, Verweij N, Goel A, Medina-Gomez C, Estrada K, Bragg-Gresham JL, Sanna S, Sidore C, Tyrer J, Teumer A, Prokopenko I, Mangino M, Lindgren CM, Assimes TL, Shuldiner AR, Hui J, Beilby JP, McArdle WL, Hall P, Haritunians T, Zgaga L, Kolcic I, Polasek O, Zemunik T, Oostra BA, Junttila MJ, Gronberg H, Schreiber S, Peters A, Hicks AA, Stephens J, Foad NS, Laitinen J, Pouta A, Kaakinen M, Willemsen G, Vink JM, Wild SH, Navis G, Asselbergs FW, Homuth G, John U, Iribarren C, Harris T, Launer L, Gudnason V, O'Connell JR, Boerwinkle E, Cadby G, Palmer LJ, James AL, Musk AW, Ingelsson E, Psaty BM, Beckmann JS, Waeber G, Vollenweider P, Hayward C, Wright AF, Rudan I, Groop LC, Metspalu A, Khaw KT, van Duijn CM, Borecki IB, Province MA, Wareham NJ, Tardif JC, Huikuri HV, Cupples LA, Atwood LD, Fox CS, Boehnke M, Collins FS, Mohlke KL, Erdmann J, Schunkert H, Hengstenberg C, Stark K, Lorentzon M, Ohlsson C, Cusi D, Staessen JA, Van der Klauw MM, Pramstaller PP, Kathiresan S, Jolley JD, Ripatti S, Jarvelin MR, de Geus EJ, Boomsma DI, Penninx B, Wilson JF, Campbell H, Chanock SJ, van der Harst P, Hamsten A, Watkins H, Hofman A, Witteman JC, Zillikens MC, Uitterlinden AG, Rivadeneira F, Zillikens MC, Kiemeneij LA, Vermeulen SH, Abecasis GR, Schlessinger D, Schipf S, Stumvoll M, Tonjes A, Spector TD, North KE, Lettre G, McCarthy MI, Berndt SI, Heath AC, Madden PA, Nyholt DR, Montgomery GW, Martin NG, McKnight B, Strachan DP, Hill WG, Snieder H, Ridker PM, Thorsteinsdottir U, Stefansson K, Frayling TM, Hirschhorn JN, Goddard ME, Visscher PM. FTO genotype is associated with phenotypic variability of body mass index. *Nature* 2012;**490**:267–272.
38. Teslovich TM, Musunuru K, Smith AV, Edmondson AC, Stylianou IM, Koseki M, Pirruccello JP, Ripatti S, Chasman DI, Willer CJ, Johansen CT, Fouchier SW, Isaacs A, Peloso GM, Barbalic M, Ricketts SL, Bis JC, Aulchenko YS, Thorleifsson G, Feitosa MF, Chambers J, Orho-Melander M, Melander O, Johnson T, Li X, Guo X, Li M, Shin Cho Y, Jin Go M, Jin Kim Y, Lee JY, Park T, Kim K, Sim X, Twee-Hee Ong R, Croteau-Chonka DC, Lange LA, Smith JD, Song K, Hua Zhao J, Yuan X, Luan J, Lamina C, Ziegler A, Zhang W, Zee RY, Wright AF, Witteman JC, Wilson JF, Willemsen G, Wichmann HE, Whitfield JB, Waterworth DM, Wareham NJ, Waeber G, Vollenweider P, Voight BF, Vitart V, Uitterlinden AG, Uda M, Tuomilehto J, Thompson JR, Tanaka T, Surakka I, Stringham HM, Spector TD, Soranzo N, Smit JH, Sinisalo J, Silander K, Sijbrands EJ, Scuteri A, Scott J, Schlessinger D, Sanna S, Salomaa V, Saharinen J, Sabatti C, Ruokonen A, Rudan I, Rose LM, Roberts R, Rieder M, Psaty BM, Pramstaller PP, Pichler I, Perola M, Penninx BW, Pedersen NL, Pattaro C, Parker AN, Pare G, Oostra BA, O'Donnell CJ, Nieminen MS, Nickerson DA, Montgomery GW, Meitinger T, McPherson R, McCarthy MI, McArdle W, Masson D, Martin NG, Marroni F, Mangino M, Magnusson PK, Lucas G, Luben R, Loos RJ, Lokki ML, Lettre G, Langenberg C, Launer LJ, Lakatta EG, Laaksonen R, Kyvik KO, Kronenberg F, Konig IR, Khaw KT, Kaprio J, Kaplan LM, Johansson A, Jarvelin MR, Janssens AC, Ingelsson E, Igl W, Keees Hovingh G, Hottenga JJ, Hofman A, Hicks AA, Hengstenberg C, Heid IM, Hayward C, Havulinna AS, Hastie ND, Harris TB, Haritunians T, Hall AS, Gyllenstein U, Guiducci C, Groop LC, Gonzalez E, Gieger C, Freimer NB, Ferrucci L, Erdmann J, Elliott P, Ejebe KG, Doring A, Dominiczak AF, Demissie S, Deloukas P, de Geus EJ, de Faire U, Crawford G, Collins FS, Chen YD, Caulfield MJ, Campbell H, Burnett NP, Bonnycastle LL, Boomsma DI, Boekholdt SM, Bergman RN, Barroso I, Bandinelli S, Ballantyne CM, Assimes TL, Quertermous T, Altschuler D, Seielstad M, Wong TY, Tai ES, Feranil AB, Kuzawa CW, Adair LS, Taylor HA Jr, Borecki IB, Gabriel SB, Wilson JG, Holm H, Thorsteinsdottir U, Gudnason V, Krauss RM, Mohlke KL, Ordovas JM, Munroe PB, Kooner JS, Tall AR, Hegele RA, Kastelein JJ, Schadt EE, Rotter JJ, Boerwinkle E, Strachan DP, Mooser V, Stefansson K, Reilly MP, Samani NJ, Schunkert H, Cupples LA, Sandhu MS, Ridker PM, Rader DJ, van Duijn CM, Peltonen L, Abecasis GR, Boehnke M, Kathiresan S. Biological, clinical and population relevance of 95 loci for blood lipids. *Nature* 2010;**466**:707–713.
39. Heinig M, Petretto E, Wallace C, Bottolo L, Rotival M, Lu H, Li Y, Sarwar R, Langley SR, Bauerfeind A, Hummel O, Lee YA, Paskas S, Rintisch C, Saar K, Cooper J, Buchan R, Gray EE, Cyster JG, Cardiogenics C, Erdmann J, Hengstenberg C, Maouche S, Ouwehand WH, Rice CM, Samani NJ, Schunkert H, Goodall AH, Schulz H, Roeder HG, Vingron M, Blankenberg S, Munzel T, Zeller T, Szymczak S, Ziegler A, Tiret L, Smyth DJ, Pravenec M, Aitman TJ, Cambien F, Clayton D, Todd JA, Hubner N, Cook SA. A trans-acting locus regulates an anti-viral expression network and type 1 diabetes risk. *Nature* 2010;**467**:460–464.
40. Consortium CAD, Deloukas P, Kanoni S, Willenborg C, Farrall M, Assimes TL, Thompson JR, Ingelsson E, Saleheen D, Erdmann J, Goldstein BA, Stirrups K, Konig IR, Cazier JB, Johansson A, Hall AS, Lee JY, Willer CJ, Chambers JC, Esko T, Folkersen L, Goel A, Grundberg E, Havulinna AS, Ho WK, Hopewell JC, Eriksson N, Kleber ME, Kristiansson K, Lundmark P, Lytikainen LP, Rafelt S, Shungin D, Strawbridge RJ, Thorleifsson G, Tikkanen E, Van Zuydam N, Voight BF, Waite LL, Zhang W, Ziegler A, Absher D, Altschuler D, Balmforth AJ, Barroso I, Braund PS, Burgdorf C, Claudi-Boehm S, Cox D, Dimitriou M, Do R, Consortium D, Consortium C, Doney AS, El Mokhtari N, Eriksson S, Fischer K, Fontanillas P, Franco-Cereceda A, Gigante B, Groop L, Gustafsson S, Hager J, Hallmans G, Han BG, Hunt SE, Kang HM, Illig T, Kessler T, Knowles JW, Kolovou G, Kuusisto J, Langenberg C, Langford C, Leander K, Lokki ML, Lundmark A, McCarthy MI, Meisinger C, Melander O, Mihailov E, Maouche S, Morris AD, Muller-Nurasyid M, Mu TC, Nikus K, Peden JF, Rayner NW, Rasheed A, Rosinger S, Rubin D, Rumpf MP, Schafer A, Sivananthan M, Song C, Stewart AF, Tan ST, Thorgeirsson G, van der Schoot CE, Wagner PJ, Wellcome Trust Case Control C, Wells GA, Wild PS, Yang TP, Amouyel P, Arveiler D, Basart H, Boehnke M, Boerwinkle E, Brambilla P, Cambien F, Cupples AL, de Faire U, Dehghan A, Diemert P, Epstein SE, Evans A, Ferrario MM, Ferrieres J, Gauguier D, Go AS, Goodall AH, Gudnason V, Hazen SL, Holm H, Iribarren C, Jang Y, Kahonen M, Kee F, Kim HS, Klopp N, Koenig W, Kratzer W, Kuulasmaa K, Laakso M, Laaksonen R, Lee JY, Lind L, Ouwehand WH, Parish S, Park JE, Pedersen NL, Peters A, Quertermous T, Rader DJ, Salomaa V, Schadt E, Shah SH, Sinisalo J, Stark K, Stefansson K, Tregouet DA, Virtamo J, Wallentin L, Wareham N, Zimmermann ME, Nieminen MS, Hengstenberg C, Sandhu MS, Pastinen T, Syvanen AC, Hovingh GK, Dedoussis G, Franks PW, Lehtimäki T, Metspalu A, Zalloua PA, Siegbahn A, Schreiber S, Ripatti S, Blankenberg SS, Perola M, Clarke R, Boehm BO, O'Donnell C, Reilly MP, Marz W, Collins R, Kathiresan S, Hamsten A, Kooner JS, Thorsteinsdottir U, Danesh J, Palmer CN, Roberts R, Watkins H, Schunkert H, Samani NJ. Large-scale association analysis identifies new risk loci for coronary artery disease. *Nat Genet* 2013;**45**:25–33.
41. Gudbjartsson DF, Arnar DO, Helgadóttir A, Gretarsdóttir S, Holm H, Sigurdsson A, Jonasdóttir A, Baker A, Thorleifsson G, Kristjánsson K, Pálsson A, Blöndal T, Sulem P, Backman VM, Hardarson GA, Palsdóttir E, Helgason A, Sigurjónsdóttir R, Sverrisson JT, Kostulas K, Ng MC, Baum L, So WY, Wong KS, Chan JC, Furie KL, Greenberg SM, Sale M, Kelly P, MacRae CA, Smith EE, Rosand J, Hillert J, Ma RC, Ellinor PT, Thorgeirsson G, Gulcher JR, Kong A, Thorsteinsdóttir U, Stefansson K. Variants conferring risk of atrial fibrillation on chromosome 4q25. *Nature* 2007;**448**:353–357.
42. Ellinor PT, Lunetta KL, Albert CM, Glazer NL, Ritchie MD, Smith AV, Arking DE, Muller-Nurasyid M, Krijthe BP, Lubitz SA, Bis JC, Chung MK, Dorr M, Ozaki K, Roberts JD, Smith JG, Pfeufer A, Sinner MF, Lohman K, Ding J, Smith NL, Smith JD, Rienstra M, Rice KM, Van Wagoner DR, Magnani JW, Wakihi R, Clauss S, Rotter JJ, Steinbeck G, Launer LJ, Davies RW, Borkovich M, Harris TB, Lin H, Volker U, Volzke H, Milan DJ, Hofman A, Boerwinkle E, Chen LY, Soliman EZ, Voight BF, Li G, Chakravarti A, Kubo M, Tedrow UB, Rose LM, Ridker PM, Conon D, Tsunoda T, Furukawa T, Sotoodehnia N, Xu S, Kamatani N, Levy D, Nakamura Y, Parvez B, Mahida S, Furie KL, Rosand J, Muhammad R, Psaty BM, Meitinger T, Perz S, Wichmann HE, Witteman JC, Kao WH, Kathiresan S, Roden DM, Uitterlinden AG, Rivadeneira F, McKnight B, Sjogren M, Newman AB, Liu Y, Gollob MH, Melander O, Tanaka T, Stricker BH, Felix SB, Alonso A, Darbar D, Barnard J, Chasman DI, Heckbert SR, Benjamin EJ, Gudnason V, Kaab S. Meta-analysis identifies six new susceptibility loci for atrial fibrillation. *Nat Genet* 2012;**44**:670–675.

43. Pfeufer A, Sanna S, Arking DE, Müller M, Gateva V, Fuchsberger C, Ehret GB, Orru M, Pattaro C, Kottgen A, Perz S, Usala G, Barbalic M, Li M, Putz B, Scuteri A, Prineas RJ, Sinner MF, Gieger C, Najjar SS, Kao WH, Muhleisen TW, Dei M, Hapelle C, Mohlenkamp S, Crisponi L, Erbel R, Jockel KH, Naitza S, Steinbeck G, Marroni F, Hicks AA, Lakatta E, Müller-Myhsok B, Pramstaller PP, Wichmann HE, Schlessinger D, Boerwinkle E, Meitinger T, Uda M, Coresh J, Kaab S, Abecasis GR, Chakravarti A. Common variants at ten loci modulate the QT interval duration in the QTSCD Study. *Nat Genet* 2009;**41**:407–414.
44. Pfeufer A, van Noord C, Marcianti KD, Arking DE, Larson MG, Smith AV, Tarasov KV, Müller M, Sotoodehnia N, Sinner MF, Verwoert GC, Li M, Kao WH, Kottgen A, Coresh J, Bis JC, Psaty BM, Rice K, Rotter JJ, Rivadeneira F, Hofman A, Kors JA, Stricker BH, Uitterlinden AG, van Duijn CM, Beckmann BM, Sauter W, Gieger C, Lubitz SA, Newton-Cheh C, Wang TJ, Magnani JW, Schnabel RB, Chung MK, Barnard J, Smith JD, Van Wagener DR, Vasani RS, Aspelund T, Eiriksdottir G, Harris TB, Launer LJ, Najjar SS, Lakatta E, Schlessinger D, Uda M, Abecasis GR, Müller-Myhsok B, Ehret GB, Boerwinkle E, Chakravarti A, Soliman EZ, Lunetta KL, Perz S, Wichmann HE, Meitinger T, Levy D, Gudnason V, Ellinor PT, Sanna S, Kaab S, Witteman JC, Alonso A, Benjamin EJ, Heckbert SR. Genome-wide association study of PR interval. *Nat Genet* 2010;**42**:153–159.
45. Olsson LG, Swedberg K, Ducharme A, Granger CB, Michelson EL, McMurray JJ, Puu M, Yusuf S, Pfeffer MA. Atrial fibrillation and risk of clinical events in chronic heart failure with and without left ventricular systolic dysfunction: results from the Candesarant in Heart failure-Assessment of Reduction in Mortality and morbidity (CHARM) program. *J Am Coll Cardiol* 2006;**47**:1997–2004.
46. Granger CB, McMurray JJ, Yusuf S, Held P, Michelson EL, Olofsson B, Ostergren J, Pfeffer MA, Swedberg K. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function intolerant to angiotensin-converting-enzyme inhibitors: the CHARM-Alternative trial. *Lancet* 2003;**362**:772–776.
47. Edelmann F, Wachter R, Schmidt AG, Kraigher-Krainer E, Colantonio C, Kamke W, Duvinage A, Stahrenberg R, Durstewitz K, Löffler M, Dungen HD, Tschöpe C, Herrmann-Lingen C, Halle M, Hasenfuss G, Gelbrich G, Pieske B. Effect of spironolactone on diastolic function and exercise capacity in patients with heart failure with preserved ejection fraction: the Aldo-DHF randomized controlled trial. *JAMA* 2013;**309**:781–791.
48. Kirchhoff P, Lip GY, Van Gelder IC, Bax JJ, Hylek E, Kaab S, Schotten U, Wegscheider K, Boriani G, Ezekowitz M, Diener H, Heidbuchel H, Lane D, Mont L, Willems S, Dorian P, Vardas P, Breithardt G, Camm AJ. Comprehensive risk reduction in patients with atrial fibrillation: emerging diagnostic and therapeutic options. Executive summary of the report from the 3rd AFNET/EHRA consensus conference. *Thromb Haemost* 2011;**106**:1012–1019.
49. Boon RA, Iekushi K, Lechner S, Seeger T, Fischer A, Heydt S, Kaluza D, Treguer K, Carmona G, Bonauer A, Horrevoets AJ, Didier N, Girmatsion Z, Biliczki P, Ehrlich JR, Katus HA, Müller OJ, Potente M, Zeiher AM, Hermeking H, Dimmeler S. MicroRNA-34a regulates cardiac ageing and function. *Nature* 2013;**495**:107–110.
50. Ucar A, Vafaizadeh V, Jarry H, Fiedler J, Klemmt PA, Thum T, Groner B, Chowdhury K. miR-212 and miR-132 are required for epithelial stromal interactions necessary for mouse mammary gland development. *Nat Genet* 2010;**42**:1101–1108.
51. Thum T, Gross C, Fiedler J, Fischer T, Kissler S, Bussen M, Galuppo P, Just S, Rottbauer W, Frantz S, Castoldi M, Soutschek J, Kotliansky V, Rosenwald A, Basson MA, Licht JD, Pena JT, Rouhanifard SH, Muckenthaler MU, Tuschl T, Martin GR, Bauersachs J, Engelhardt S. MicroRNA-21 contributes to myocardial disease by stimulating MAP kinase signalling in fibroblasts. *Nature* 2008;**456**:980–984.
52. Wei Y, Nazari-Jahantigh M, Neth P, Weber C, Schober A. MicroRNA-126, -145, and -155: a therapeutic triad in atherosclerosis?. *Arterioscler Thromb Vasc Biol* 2013;**33**:449–454.
53. Dawson K, Wakili R, Ordog B, Claus S, Chen Y, Iwasaki Y, Voigt N, Qi XY, Sinner MF, Dobrev D, Kaab S, Nattel S. MicroRNA29: a mechanistic contributor and potential biomarker in atrial fibrillation. *Circulation* 2013;**127**:1466–1475. 1475e1–28.
54. Hulsmans M, Sinnaeve P, Van der Schueren B, Mathieu C, Janssens S, Holvoet P. Decreased miR-181a expression in monocytes of obese patients is associated with the occurrence of metabolic syndrome and coronary artery disease. *J Clin Endocrinol Metab* 2012;**97**:E1213–8.
55. Ackerman MJ, Priori SG, Willems S, Berul C, Brugada R, Calkins H, Camm AJ, Ellinor PT, Gollub M, Hamilton R, Hershberger RE, Judge DP, Le Marec H, McKenna WJ, Schulze-Bahr E, Semsarian C, Towbin JA, Watkins H, Wilde A, Wolpert C, Zipes DP. HRS/EHRA expert consensus statement on the state of genetic testing for the channelopathies and cardiomyopathies: this document was developed as a partnership between the Heart Rhythm Society (HRS) and the European Heart Rhythm Association (EHRA). *Europace* 2011;**13**:1077–1109.
56. Priori SG, Wilde AA, Horie M, Cho Y, Behr ER, Berul C, Blom N, Brugada J, Chiang CE, Huikuri H, Kannankeril P, Krahn A, Leenhardt A, Moss A, Schwartz PJ, Shimizu W, Tomaselli G, Tracy C, Document R, Ackerman M, Belhassen B, Estes NA 3rd, Fatkin D, Kalman J, Kaufman E, Kirchhof P, Schulze-Bahr E, Wolpert C, Vohra J, Refaat M, Etheridge SP, Campbell RM, Martin ET, Quek SC. Executive summary: HRS/EHRA/APHS expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes. *Europace* 2013;**15**:1389–1406.
57. Behr ER, Roden D. Drug-induced arrhythmia: pharmacogenomic prescribing?. *Eur Heart J* 2013;**34**:89–95.
58. Group SC, Link E, Parish S, Armitage J, Bowman L, Heath S, Matsuda F, Gut I, Lathrop M, Collins R. SLC01B1 variants and statin-induced myopathy—a genome-wide study. *N Engl J Med* 2008;**359**:789–799.
59. Pirmohamed M, Burnside G, Eriksson N, Jorgensen AL, Toh CH, Nicholson T, Kesteven P, Christerson C, Wahlstrom B, Stafberg C, Zhang JE, Leathart JB, Kohnke H, Maitland-van der Zee AH, Williamson PR, Daly AK, Avery P, Kamali F, Wadelius M, Group E-P. A randomized trial of genotype-guided dosing of warfarin. *N Engl J Med* 2013;**369**:2294–2303.
60. Kimmel SE, French B, Kasner SE, Johnson JA, Anderson JL, Gage BF, Rosenberg YD, Eby CS, Madigan RA, McBane RB, Abdel-Rahman SZ, Stevens SM, Yale S, Mohler ER 3rd, Fang MC, Shah V, Horenstein RB, Limdi NA, Muldowney JA 3rd, Gujral J, Delafontaine P, Desnick RJ, Ortel TL, Billett HH, Pendleton RC, Geller NL, Halperin JL, Goldhaber SZ, Caldwell MD, Califf RM, Ellenberg JH, Investigators C. A pharmacogenetic versus a clinical algorithm for warfarin dosing. *N Engl J Med* 2013;**369**:2283–2293.
61. Käåb S, Hinterseer M, Näbauer M, Steinbeck G. Sotalol testing unmasks altered repolarization in patients with suspected acquired long-QT-syndrome—a case-control pilot study using i.v. sotalol. *Eur Heart J* 2003;**24**:649–657.
62. Ekman I, Wolf A, Olsson LE, Taft C, Dudas K, Schaufelberger M, Swedberg K. Effects of person-centred care in patients with chronic heart failure: the PCC-HF study. *Eur Heart J* 2012;**33**:1112–1119.
63. Ekman I, Swedberg K, Taft C, Lindseth A, Norberg A, Brink E, Carlsson J, Dahlin-Ivanoff S, Johansson IL, Kjellgren K, Liden E, Ohlen J, Olsson LE, Rosen H, Rydmark M, Sunnerhagen KS. Person-centered care—ready for prime time. *Eur J Cardiovasc Nurs* 2011;**10**:248–251.