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Review Article

Implementation strategies of Systems Medicine in clinical research and home care for cardiovascular disease patients

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ABSTRACT

Insights from the "-omics" science have recently emphasized the need to implement an overall strategy in medical research. Here, the development of Systems Medicine has been indicated as a potential tool for clinical translation of basic research discoveries. Systems Medicine also gives the opportunity of improving different steps in medical practice, from diagnosis to healthcare management, including clinical research. The development of Systems Medicine is still hampered however by several challenges, the main one being the development of computational tools adequate to record, analyze and share a large amount of disparate data. In addition, available informatics tools appear not yet fully suitable for the challenge because they are not standardized, not universally available, or with ethical/legal concerns. Cardiovascular diseases (CVD) are a very promising area for translating Systems Medicine into clinical practice. By developing clinically applied technologies, the collection and analysis of data may improve CV risk stratification and prediction. Standardized models for data recording and analysis can also greatly broaden data exchange, thus promoting a uniform management of CVD patients also useful for clinical research. This advance however requires a great organizational effort by both physicians and health institutions, as well as the overcoming of ethical problems. This narrative review aims at providing an update on the state-of-art knowledge in the area of Systems Medicine as applied to CVD, focusing on current critical issues, providing a road map for its practical implementation.

1. Introduction

Recent advances in experimental and computational technologies in the last decades within the framework of Systems Biology have fostered the complementary need of an implementation strategy, to provide a medical translation of such new knowledge [1]. The coupled development of biological knowledge (mainly driven by the Human Genome Project [2] and the Human Physiome Project [3]) and of technology/experimental techniques (microarrays, mass spectrometry, computational power and Internet) has indeed led to the explosion of "-omics" science [4]. Through these new tools, predictive models of physiology and disease have been developed, with new ways of thinking, including the application and development of methodologies from mathematical sciences [5]. Accordingly, and also in current wake aimed at personalized medicine there is a great need of translating this systems approach into clinical practice. Although it is easy to broadly agree with this strategy, the road map to follow is still uncertain. Systems approaches are still labeled as basic research, so that a main current challenge is to shift from the "need" of translating basic finding into clinical research toward the integration between non-clinical and clinical data. Since the usefulness of systems approach becomes clear when applied to multifactorial diseases, cardiovascular diseases (CVD) may be a potential field test for Systems Medicine. Thus, starting from these clinical needs, this narrative review, developed within the Meeting in Genoa (Italy, 19th–21st January 2014) of the Coordinated Action Systems Medicine (CASyM, the European task force appointed to design and

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update the road map for Systems Medicine in research and clinical practice) also aims at reviewing methodologies and priorities in the implementation of Systems Medicine in CV Medicine. This article is based on the material searched for and obtained via MEDLINE and PubMed up to May 2014. The searched keywords were: Systems Medicine, home-care, clinical studies, cardiovascular diseases, and -omics.

2. Definition of Systems Medicine and its role in cardiovascular diseases

A comprehensive definition of Systems Medicine has been largely debated in the last few years, considering the extremely general field of action of Systems Medicine. Ultimately, CASyM Europe has been seen as fit to communicate the basic elements underlying Systems Medicine, defined as: "*…the implementation of Systems Biology approaches in medical concepts, research and practice, through iterative and reciprocal feedback between data-driven computational and mathematical models as well as model-driven translational and clinical investigations. In essence, Systems Medicine aims at a measurable improvement of patient health through systems-based approaches and practice….*" [6]. Although this definition is widely shared, rethinking Systems Biology in the clinical context raises methodological and practical issues that need to be discussed. As already reported by Wolkenhauer and co-workers, a roadmap for systems medicine should address stronger efforts to sustain inter-disciplinary collaborations, integrating biological and computational methodologies [7]. Furthermore, systems approach applied to a clinical setting involves ethical and legal consideration that may potentially threaten its progress. Accordingly, the first action of this working group has been to include this topic within a new consensus definition of Systems Medicine, as such:

> "*An integrative approach to medical needs taking advantage and emphasizing information and tools made available by the greatest possible spectrum of scientific disciplines, aimed at improving risk prediction and individual treatment respecting ethical and legal requirements. This approach should improve medical practice by standardization, information, integration, monitoring and personalization*".

3. The "-omics" data in cardiovascular disease studies

3.1. Basic science

Considering the huge development of "-omics" science observed in the last years, it was inappropriately thought that the systems-driven problem-solving would soon potentially be useful in clinical practice. This approach progressively involved a large set of biological molecules [8], including genomics (developed immediately after the sequencing of the human genome) and epigenomics, proteomics, cytomics, ligandomics, metabolomics, and more [9]. Furthermore, this high expectation has been confirmed by the launch of several dedicated journals. The "-omics" approach has been widely applied in the field of vascular biology and CV medicine, clarifying several biological pathways underlying polygenic diseases. Gene expression analysis emphasized the role of cell-specific transcription factors in atherosclerotic plaque development and progression [10]. In addition, other overexpressed genes included chemokines and matrix degradation enzymes (cathepsin and matrix metalloproteinases) [11], but also interleukin-6, insulin growth factor binding protein and different lipoprotein components were shown to be increased within the plaque [12]. Considering arterial aneurysms, proteomic analysis of dilated aortic tissues from Marfan Syndrome patients showed an upregulation in the C-terminal fragment of filamin A (due to calpain-mediated cleavage) as compared to control patients without collagen disorders [13]. In addition, in serum from patients with abdominal aortic aneurysm after surgery, an increased thrombin generation was demonstrated by proteomic analysis in the first 6 h during the postoperative period [14]. In another study using plasma samples from patients with abdominal aortic aneurysm, the authors identified increased levels in haptoglobin, fibrinogen, α1-antitrypsin and negative association between vitamin D-binding protein (DBP) and the presence of abdominal aortic aneurysm [15]. Finally, more recent fields of interest for "-omics" that included thrombosis and hemostasis, angiogenesis and vascular remodeling [16]. The identification of a clear pathophysiological role between these biomarkers and cardiovascular diseases requires further validation in larger population-based studies.

3.2. Clinical perspectives

Following the development of genome-wide association studies (GWAS) more than 200 genetic loci were found to be associated with polygenic diseases. In the field of CVD, the best known example is represented by the studies on chromosome 9p21.3, but a potential pathophysiological role has been suggested for other loci, as reported in Table 1 [17–33]. More recently, the development of clinically-applied mass spectrometry techniques [34] has further broadened the systems approach to CVD. By screening a large amount of different potential biomarkers, both proteomics (Table 2) [35–49] and metabolomics (Table 3) [50–67] studies aimed at improving knowledge of CVD pathways. However, many factors precluded meaningful biological insights or practical prediction so that the value of these recent discoveries was currently viewed with skepticism [69]. For many biomarkers the biological function is still unknown, or even not consistent with those already known. Furthermore, by investigating single pathways, "-omics" studies potentially contributed to biological knowledge. However, their predictive power (and then their clinical feasibility) remains extremely weak. Ultimately, these evidences strongly limited the application of "-omics" science to biological knowledge, emphasizing the need of hypothesis-driven studies. In addition, we should consider that biological discoveries did not guarantee the opportunity to clinical translation because such step forward requires additional cost-effectiveness information.

4. The use of Systems Medicine paradigm to improve clinical research and management quality

The Systems Medicine approach was sometimes suggested as a future paradigm shift in the way to think medicine, aimed at reducing the gap between biological knowledge and patient care.

Accordingly, Systems Medicine might ultimately favor the transition from a traditional "reactive medicine" model to a more proactive one that is "predictive, preventive, personalized and participatory" (the 4P medicine) [70]. A critical issue in this field is to promote the convergence systems data through the digital revolution [71]. By relying on huge bidirectional transfer of information between experimental studies, epidemiology and clinical medicine, Systems-based approach requires new organizational principles and presents new challenges for advancing science and technology. Since many innovations in health care have taken years to finally become assimilated in medical practice, we might consider the use of rapid learning systems to overcome this gap to deal with large amounts of health data that will be available to doctors and medical researchers [72]. Education of health professionals and the public is one of the current priorities. Innovative training programs using information technologies' teaching strategies will be essential for a full implementation of the rapid learning model [73]. Likewise, Academic Medical Centers must play a central role in the process of developing and organizing the standards for managing these resources.

4.1. Rapid learning model

The concept of learning health systems (LHS) was first conceived as a means of rapidly converting scientific evidence into medical practice, and learn as fast as possible about what is the best treatment for each

Table 1
Clinical trials based on genomic approach in cardiovascular diseases.

Author	Year	Study design	genomics profile	Assay method	Results
Helgadottir et al. [17]	2007	Case–control (1607 patients with AMI compared with 6728 CAD patients, then replicated in other 3 cohorts)	305953 SNPs	GWAS	The identified variant on chromosome 9p21.3 (near to CDKN2A and CDKN2B genes) was significantly associated with incidence of AMI (OR for homozygous 2.02 [CI 95% 1.72–2.36]; $p < 0.05$).
McPherson et al. [18]	2007	Case–control (322 patients with CAD compared with 312 healthy controls, replicated in other 2 cohorts and then validated in 3 different cohort studies)	100000 SNPs	GWAS	The identified variant on chromosome 9p21.3 (near to CDKN2A and CDKN2B genes) was significantly associated with incidence of CAD (HR from validated cohort 1.29 [CI 95% 1.09–1.52]; $p < 0.01$).
Samani et al. [19]	2007	Case–control (1926 CAD patients and 2938 controls from WTCCC study, then replicated in a second cohort of 875 AMI patients and 1644 controls)	377875 SNPs in WTCCC and 272602 in the replicated study	GWAS	For both studies, chromosome 9p21.3 showed the strongest link in the SNPs rs1333049 ($p = 1.80 \times 10^{-14}$ and 3.40×10^{-6}, respectively).
Schunkert et al. [20]	2008	Case–control (3544 patients with AMI compared with 1101 CAD patients and 5177 controls from 7 different studies)	Single SNP rs1333049 representing the 9p21.3 locus	Linkage analysis using 416 microsatellite markers	In the pooled analysis the OR was 1.29 (CI 95% 1.22–1.37; $p < 0.001$). Furthermore, the meta-analysis including also the previous studies confirmed this association (OR 1.24 [CI 95% 1.20–1.29]; $p < 0.05$).
Samani et al. [21]	2008	Case–control (2277 patients of CAD associated with CIMT or FMD)	Single SNP rs1333049	GWAS	The identified variant on chromosome 9p21.3 failed in predict both CIMT and FMD.
Clarke et al. [22]	2009	Case–control (3145 CAD patients and 3352 control, replicated in 3 other cohort including 4846 CAD cases and 4594 controls)	48,742 SNPs in 2100 candidate genes	GWAS	Among 3 chromosomal regions found associated with risk of CAD, the Lp(a) locus had the strongest association (OR 1.70 [CI 95% 1.49–1.95]; $p < 0.05$).
Reilly et al. [23]	2011	Case–control (12393 CAD male patients compared and 7383 matched controls; 3644 CAD patients were also compared with 5783 patients with AMI)	More than 2.4 million genotyped and imputed SNPs	GWAS	Compared to controls, ADAMTS7 was found to be strongly associated with CAD ($p = 4.98 \times 10^{-13}$). The occurrence of AMI were instead associated with the glycotransferase-deficient enzyme encoding the ABO blood group O phenotype ($p = 7.62 \times 10^{-9}$).
Scheffold et al. [24]	2011	Case–control (976 ACS patients compared to controls of other published cohort)	6 SNPs representing the 9p21.3 locus	GWAS	All analyzed SNPs significantly correlated with AMI occurrence as well as family history of ACS.
Prudente et al. [25]	2011	Case–control (2015 T2DM patients from 3 CAD studies)	Single SNP rs4788102 representing the 16p11 locus	GWAS	In the pooled analysis rs4788102 containing the SH2B1 gene (encoding for SH2B1) was not associated with AMI (OR 1.21 [CI 95% 1.04–1.41]; $p = 0.016$).
Hughes et al. [26]	2012	Prospective observational (26221 men without AMI at baseline from 9 cohorts collected in the MORGAM)	11 SNPs from previous validated GWAS-analyzed cohorts	GWAS	2 models of genetic risk score were designed combining the 11 SNPs with 2 or 4 haplotypes from Lp(a). Both scores improved the prediction of Framingham score ($p = 0.001$ and 0.044, respectively)
Wauters et al. [27]	2013	Prospective observational (2099 ACS patients form GRACE UK–Belgian study)	Single SNP rs579459 located upstream of the ABO gene	GWAS	After a median follow-up of 5 years, the rs579459 variant was associated with recurrent AMI (HR 1.80 [CI 95% 1.09–2.95]; $p = 0.001$).
Holmen et al. [28]	2014	Case–control (2833 patients with AMI compared with 2938 healthy controls from 7 different studies)	80137 SNPs	GWAS	Coding variants were identified in 11 genes mainly involved in lipid metabolism. In addition, AMI was significantly associated with coding variants for 2 genes linked to TGs (OR 0.78 [CI 95% 0.66–0.92]; $p = 0.003$) and total Ch (OR 0.87 [CI 95% 0.79–0.95]; $p = 0.005$).
Abu El Maaty et al. [29]	2014	Case–control (63 CAD male patients and 31 matched controls)	SNPs rs1790349 and rs12785878 (NADSYN1/DHCR7 locus)	GWAS	Both rs1790349 and rs12785878 failed to predict CAD but in the overall population (not in the patient subgroup) they predicted the levels of 25(OH)D_3 ($p < 0.001$ for both).
Adams et al. [30]	2014	Cross-sectional (1208 T2DM patients form DHS)	50 SNPs from DHS and CHARGE	GWAS	Several SNPs showed an association with CAC, including rs599839 ($p = 0.008$), rs646776 ($p = 0.01$), and rs17398575 ($p = 0.009$). A relationship with CVD mortality was shown for COL4A2 and CXCL12 SNPs ($p < 0.05$ for both), whereas dyslipidemia was significantly related with rs3135506 ($p < 0.05$), rs651821 ($p < 0.001$) and rs13832449 ($p < 0.001$). Furthermore, SNPs associated with CAC was also related to prior CVD (OR 1.09 [CI 95% 1.02–1.34]; $p = 0.03$).
Hirokawa et al. [31]	2014	Case–control (1666 AMI patients and 3198 controls, the replicated in a cohort of 39809 Japanese subjects)	92 SNPs	GWAS	New correlations with IMA were shown for rs4618210 (codifying for PLCL2 on chromosome 3p24.3; OR 0.92 [CI 95% 0.88–0.94]; $p = 0.04$), and rs380391 (codifying for AP3D1-DOT1L-SF3A2 on chromosome 19p13.3; OR 0.89 [CI 95% 0.86–0.92]; $p = 0.06$). Among already validated markers, a strong correlation was shown for rs3782886 (OR 1.46; $p < 0.05$).
Shen et al. [32]	2014	Case–control (1423 patients CAD or AMI and 1162 control from 4 independent cohorts)	5 different SNPs within LRP8 gene	GWAS	A novel haplotype of the LRP8 gene was found to confer a significant protection in the development of familial and early-onset CAD and AMI ($p < 0.05$ for both).
Dichgans et al. [33]	2014	Meta-analysis (26929 subjects from 14 cohort studies)	SNPs associated with circulatin tPA	GWAS	3 loci were significantly associated with circulating tPA levels including rs9399599, rs3136739 and rs7301826 ($p < 0.05$ for all). However, no association was shown between these 3 SNPs and the occurrence of CAD or stroke.

AMI: Acute Myocardial Infarction; CAD: Coronary Artery Disease; SNP: Single-Nucleotide Polymorphism; GWAS: Genome-Wide Association Studies; CDKN: Cyclin-Dependent Kinase Inhibitor; OR: Odds Ratio; CI: Confidence Interval; HR: Hazard Ratio; WTCCC: Wellcome Trust Case–Control Consortium; CIMT: Carotid Intima Media Thickness; FMD: Flow-Mediated Dilatation; ADAMTS: A Disintegrin And Metalloproteinase with Thrombospondin Motifs; ACS: Acute Coronary Syndrome; T2DM: Type 2 Diabetes Mellitus; SH2B1: Src-Homology-2 (SH2) B adaptor protein 1; MORGAM: MOnica Risk, Genetics, Archiving and Monograph; GRACE: Global Registry of Acute Coronary Events; TGs: Triglycerides; Ch: Cholestrerol; 25(OH)D_3: activated vitamin D; DHS: Diabetes Heart Study; CHARGE: Cohorts for Heart and Aging Research in Genomic Epidemiology; CAC: Coronary Artery Calcification; LRP8: Low-density lipoprotein receptor-Related Protein 8; tPA: tissue Plasminogen Activator.

Table 2
Proteomics studies in cardiovascular diseases.

Author	Year	Study design	Proteomics profile	Assay method	Results
Mateos-Cáceres et al. [35]	2004	Case–control (11 AMI, 8 UA patients and a control group of 9 subjects)	Peptides matched with the 2-DE	MALDI-TOF MS	AMI group had plasma increase of apolipoprotein A1, fibrinogen and α1-antitrypsin.
Donahue et al. [36]	2006	Case–control (53 CAD and 53 healthy controls from Duke Databank for Cardiovascular Disease)	731 plasma proteins or fragments identified	Capillary LC/EI/ tandem MS	95 proteins were significantly differentially displayed among study population. They involved inflammation, growth, and coagulation.
Wilson et al. [37]	2007	Case–control (45 PAD and 43 subjects with risk factors but not PAD)	1619 protein peaks	SELDI-TOF MS	PAD was independently associated with higher levels of β2-microglobulin (OR 7.2 [CI 95% 1.6–31.3]; $p = 0.009$) and CRP (OR 1.3 [CI 95% 1.0–1.7]; $p = 0.026$).
Zimmerli et al. [38]	2008	Case–control (first analysis with 30 CAD and 20 control subjects followed by blinded analysis on 47 CAD patients and 12 controls)	15 urinary protein analysis according to the pattern found emerged from first analysis	ESI-TOF MS	The combination 15 urinary polypeptides in blinded analysis allowed the distinction between the two groups (AUC = 0.94; $p < 0.05$. Sensitivity 98%, specificity 83%).
von Zur Muhlen et al. [39]	2009	Case–control study (first analysis with 15 CAD and 14 non-CAD subjects followed by blinded analysis on 38 patients)	17 urinary proteiN analysis according to the pattern found emerged from first analysis	CE-MS	The combination 17 urinary polypeptides in blinded analysis allowed the distinction between the two groups (AUC = 0.84; $p < 0.05$. Sensitivity 81%, specificity 92%).
Gasparri et al. [40]	2010	Case–control (10 STEMI and 10 control subjects)	300 proteins	LC–tandem MS	Serum of STEMI patients was characterized by significantly higher levels of haptoglobin, α1-antitripsin, ceruloplasmin, orosomucoid-1 and vitamin d binding protein precursor ($p < 0.05$ for all).
Dardé et al. [41]	2010	Case–control (40 AMI, 10 CAD and 10 healthy controls)	1400 protein analyzed by 2-DE and 2DIGE at different time points	MALDI-TOF MS	A small group of 7 protein was long-term associated with diseases (both AMI and CAD) including α1-B-glycoprotein, tetranectin and tropomyosin 4 ($p < 0.005$ for all).
Delles et al. [42]	2010	Case–control study (first analysis with 204 CAD and 382 non-CAD subjects followed by blinded analysis on 71 CAD and 67 non-CAD patients)	238 urinary protein analysis according to the pattern found emerged from first analysis	CE–MS	The pattern of 238 urinary polypeptides in blinded analysis allowed the distinction between the two groups (AUC = 0.87; $p < 0.001$. Sensitivity 79%, specificity 88%).
Cubedo et al. [43]	2011	Case–control (39 new-onset AMI-patients and 60 healthy controls)	Proteomic analysis of lipoprotein	MALDI-TOF MS	AMI group had higher levels of apolipoprotein J/clusterin ($p < 0.001$).
Haas et al. [44]	2011	Prospective observational (30 AMI patients)	Blinded analysis using (PCA and hierarchical clustering)	MALDI-TOF MS	After 1 year follow-up, different isoforms of haptoglobin were significantly associated with HF incidence (AUC = 0.63 toward NYHA > 2).
Wykrzykowska et al. [45]	2011	Case–control (14 STEMI, 21 NSTEMI and 54 CAD)	170 biomarkers	Hierarchical clustering and PCA analyzed with microarray	78 biomarkers showed dynamic changes over time including markers of inflammation, hypercoagulability, shear stress/remodeling and cell survival.
Silbiger et al. [46]	2011	Case–control (5 first STEMI, 5 second STEMI and 7 controls subjects)	Blinded analysis of serum proteins	SELDI-TOF MS	Compared to control group, first STEMI expressed 510 different protein peaks, whereas second STEMI differed for only 76 protein peaks ($p = 0.05$ for both groups). In addition 16 protein peaks were similar between the two STEMI groups.
Gil-Dones et al. [47]	2012	Case–control (12 AS and 12 control subjects)	71 peptides analyzed by 2-DE and 2DIGE	PCA model analyzed by MALDI-TOF MS	Clustered analysis showed a correlation of AS with different classes of proteins involved in proteolysis, blood homeostasis/coagulation, inflammation and lipid metabolism.
Rezeli et al. [48]	2013	Case–control (25 STEMI and 25 non-cardiac chest pain from LUNDHEARTGENE biobank)	11 proteins associated with CVD including apolipoproteins, plasminogen, α1-antichemotrypsin and ceruloplasmin	LC–MS	Significant linear regressions were achieved for 9 of the 11 peptides. Strong direct correlation was showed between apolipoproteins and lipid subfraction, with higher levels in STEMI group.
Yin et al. [49]	2014	Case–control (135 AMI and 135 matched controls compared with 336 ASCVD case–control pairs from FHS offspring cohort)	59 markers chosen from literature review	LC–MS coupled with tandem MS	12 single markers and a cluster of 7 proteins were associated with AMI incidence improving risk prediction ($p < 0.01$ for both). In addition, 12 single proteins and a cluster of 4 proteins were associated with ASCVD incidence improving risk prediction ($p < 0.01$ for both).

AMI: Acute Myocardial Infarction; UA: Unstable Angina; 2-DE: two-Dimensional Electrophoresis; MALDI-TOF MS: Matrix-Assisted Laser-Desorption Ionization Time-Of-Flight Mass Spectrometry; CAD: Coronary Artery Disease; LC/EI/tandem MS: Liquid Chromatography–Electrospray Ionization tandem Mass Spectrometry; PAD: Peripheral Artery Disease; SELDI-TOF MS: Surface-Enhanced Laser Desorption/Ionization Time-Of-Flight Mass Spectrometry; OR: Odds Ratio; CI: Confidence Interval; CRP: C-Reactive Protein; ESI-TOF MS: Electro Spray Ionization-Time-Of-Flight Mass Spectrometry; AUC: Area Under the Curve; CE-MS: Capillary Electrophoresis Mass Spectrometry; STEMI: ST-Elevation Myocardial Infarction; LC–tandem MS: Liquid Chromatography tandem Mass Spectrometry; 2-DIGE: two-dimensional Differential Gel Electrophoresis; PCA: Principal Component Analysis; HF: Heart Failure; NYHA: New York Heart Association; NSTEMI: Non-ST-Elevation Myocardial Infarction; ASCVD: AtheroSclerotic Cardiovascular Diseases; FHS: Framingham Heart Study.

Table 3
Metabolomics studies in cardiovascular diseases.

Author	Year	Study design	Metabolomics profile	Assay method	Results
Brindle et al. [50]	2002	Cross sectional study of subjects with stenosis of one (mild, n = 28), two (moderate, n = 20) or three (severe, n = 28) major coronary arteries	CH_3 groups from fatty acid side chains in lipids, in particular LDL and VLDL	Supervised PCA and PLS-DA models analyzed with ^{1}H NMR	^{1}H NMR predicted CAD severity with a specificity >90%
Sabatine et al. [51]	2005	Case–control (18 subject with inducible ischemia and 18 control)	Lactic acid and metabolites involved in AMP catabolism	Triple quadrupole MS	Citric acid pathway metabolites significantly increased in case group ($p = 0.004$) as well as differentiated cases from controls with a high degree of accuracy ($p < 0.001$; c-statistic 0.83)
Kirschenlohr et al. [52]	2006	Cross sectional study of 322 patients with stenosis of one, two or three major coronary arteries compared with non-CAD subjects, irrespective of statin treatment	CH_3 groups from fatty acid side chains in lipids	PCA and PLS-DA models analyzed with ^{1}H NMR	Prediction of CAD by ^{1}H-NMR was therefore very weak compared with angiography (80.3% for patients not treated with statins and 61.3% for treated patients)
Lewis et al. [53]	2008	Case–control (36 patients undergoing alcohol septal ablation treatment compared to 16 elective diagnostic coronary angiography and 12 patients with MI)	Metabolites from pyrimidine, tricarboxylic acid cycle, pentose phosphate pathway	LC–MS	As early as 10 min, MI group showed a specific metabolic signature, characterized by significant higher levels of alanine, aminoisobutyric acid, hypoxanthine, isoleucine/leucine, malonic acid, threonine, and TMAO ($p < 0.05$ for all)
Mayr et al. [54]	2008	Case–control (19 sinus rhythm subjects, 18 post-operative atrial fibrillation and a group with persistent atrial fibrillation)	24 metabolites including amino acids and metabolic intermediate of tricarboxylic acid cycle	MALDI-MS ^{1}H NMR	Persistent atrial fibrillation group was characterized by an altered energy metabolism with a rise in beta-hydroxybutyrate along with an increase in ketogenic amino acids and glycine ($p < 0.05$ for all).
Teul et al. [55]	2009	Case–control (9 patients with carotid atherosclerosis and 10 healthy subjects)	Non-supervised PCA, PLS-DA and OPLS-DA	GC–MS and ^{1}H NMR	Transforming these data sets in biochemical information, 24 metabolites were found significantly ($p < 0.05$) modified in the group of atherosclerotic patients. In addition, most of the changes may be related to insulin resistance status.
Tang et al. [56]	2009	Prospective observational (1010 consecutive subjects from Cleveland Clinic GenBank study)	Higher citrulline levels remained significantly associated with both the prevalence of significantly obstructive CAD	LC–MS coupled with tandem MS	GABR and higher citrulline levels were significantly associated with both the prevalence of significantly obstructive CAD ($p < 0.001$ for both) and 3-year risk for MACE incidence ($p = 0.025$ and $p = 0.01$ respectively).
Shah et al. [57]	2009	Case–control (117 individuals from GENECARD study including CAD and non-CAD subjects)	PCA for amino acids, free fatty acids and acylcarnitine clusters	GC–MS	Premature CAD was associated with a significantly higher levels of a large amount of metabolites of different classes ($p < 0.05$).
Turer et al. [58]	2009	Cross-sectional (37 consecutive patients undergoing cardiac surgery with cardioplegic arrest categorized as CAD, LVD and controls)	63 intermediary metabolites, including conventional metabolic substrates, 12 amino acids and 45 acylcarnitine derivatives.	Tandem MS	After reperfusion, there were significantly lower extraction ratios of most substrates ($p < 0.05$) associated with increased release of acylcarnitine species ($p < 0.05$).
Huffmann et al. [59]	2009	Cross-sectional (73 sedentary, overweight to obese, dyslipidemic subjects from the STRRIDE)	75 amino acids, acylcarnitines, free fatty acids, and conventional metabolites	Tandem MS	Large neutral amino acids were inversely related to insulin sensitivity ($p < 0.001$), whereas fatty acids were inversely related to the acute insulin response to glucose ($p = 0.001$).
Shah et al. [60]	2010	Case–control groups ("initial" 174 CAD and 174 control then "replicated" with other 140 CAD and 140 control subjects from CATGHEN biorepository)	69 metabolites including acylcarnitine species, amino acids, and conventional metabolites	Tandem MS	Transforming these data sets in biochemical information, CAD was significantly related with branched-chain amino acid metabolites ($p < 0.05$) and urea cycle metabolites ($p < 0.05$). Furthermore, dicarboxylacylcarnitines predicted death/MI (HR 2.17 [CI 95% 1.23–3.84]; $p < 0.01$).
Shah et al. [61]	2012	Prospective observational (2023 patients undergoing cardiac catheterization from the Murdoc CV study and Duke CATGHEN biorepository)	45 acylcarnitines and 15 amino acids	Tandem MS	At median follow-up of 3.1 years 3 metabolites independently predicted death/MI: Short-chain dicarboxylacylcarnitines (HR 1.11 [CI 95% 1.01–1.23]; $p = 0.04$), long-chain dicarboxylacylcarnitines (HR 1.13 [CI 95% 1.04–1.22]; $p = 0.005$), and fatty acids (HR 1.18 [CI 95% 1.05–1.32]; $p = 0.004$).
Magnusson et al. [62]	2013	Nested case–control (4577 patients from the MDC-CC)	DM-AA score (including tyrosine, phenylalanine and isoleucine [68])	Triple quadrupole MS	Interquartile comparison of DM-AA score was associated with increased incidence of first CV event (OR 2.20 [CI 955 1.12–4.31]; $p = 0.001$) and cross-sectionally related to IMT (p for trend = 0.037).
Luan et al. [63]	2013	Case–control (23 HF and 23 CAD patients)	Free fatty acids, sphingolipids and amino acid derivatives	OPLS-DA model analyzed by LC–MS	Lipid molecules associated with energy metabolism and signaling pathways significantly differed between the two groups (free fatty acids, sphingolipids and amino acid derivatives).
Zheng et al. [64]	2013	Prospective observational (1744 African Americans from the ARIC study)	204 stable serum metabolites	Not specified MS	After a median follow-up of 20 years, incident heart failure was strong associated with amino acid isoform: dihydroxy docosatrienoic acid (HR 0.75 [CI 95% 0.65–0.86]; $p < 0.05$) and an isoform of either hydroxyleucine or hydroxyisoleucine (HR 1.23 [CI 95% 1.10–1.37]; $p < 0.05$)
Zheng et al. [65]	2013	Prospective observational (896 normotensive African Americans from the ARIC study)	204 stable serum metabolites	PCA models analyzed with MS	At median follow-up of 10 years, the incidence of hypertension was correlated with 4-hydroxyhippurate (adjusted HR 1.18 [CI 95% 1.08–1.29]; $p < 0.001$) as well as the sex steroids pattern (androsterone sulfate and epiandrosterone sulfate; $p < 0.001$ for both).
Stegemann et al. [66]	2014	Prospective observational (685 samples from Bruneck study)	135 lipid species from 8 different lipid classes	Triple quadrupole MS	Within the system-wide lipid network, three lipid series (TAG, CE, PE) were significant predictor ($p < 0.05$) of CVD outcome over 10-year follow-up.
Rizza et al. [67]	2014	Prospective observational (108 elderly outpatients)	different Amino acids and acylcarnitines	LC–MS coupled with tandem MS	At median follow-up of 3.5 years MACE occurrence was associated with medium- and long-chain acylcarnitines (HR 1.77 [CI 95% 1.11–2.81]; $p = 0.016$) and alanine (HR 2.18 [CI 95% 1.17–4.07]; $p = 0.014$). However only medium- and long-chain acylcarnitines improved the prediction accuracy of Framingham score.

LDL: Low Density Lipoprotein; VLDL: Very Low Density Lipoprotein; PCA: Principal Component Analysis; PLS-DA: Partial Least-Squares-Discriminant Analysis; NMR: Nuclear Magnetic Resonance; CAD: Coronary Artery Disease; AMP: Adenosine MonoPhosphate; MS: Mass Spectrometry; MI: Myocardial Infarction; LC–MS: Liquid Chromatography–Mass Spectrometry; TMAO: TriMethylAmine N-Oxide; MALDI-MS: Matrix-Assisted Laser-Desorption Ionization-Mass Spectrometry; OPLS-DA: Orthogonal Partial Least-Squares-Discriminant Analysis; GC–MS: Gas Chromatography Mass Spectrometry; GABR: Global Arginine Bioavailability Ratio (defined as arginine/[ornithine + citrulline]); MACE: Major Acute Cardiovascular Events (defined as death, myocardial infarction, stroke); LVD: Left Ventricular Dysfunction (defined as ventricular ejection fraction <45%); STRRIDE: Studies of Targeted Risk Reduction Interventions through Defined Exercise; Exercise; HR: Hazard Ratio; CI: Confidence Interval; MDC-CC: Malmö Diet and Cancer Cardiovascular Cohort; DM-AA score: Diabetes Mellitus-predictive Amino Acid score; CV event: CardioVascular event (including myocardial infarction or stroke); OR: Odds Ratio; CIMT: Carotid Intima Media Thickness; HF: Heart Failure; ARIC: Atherosclerosis Risk in Communities; TAG: TriAcylGlycerole; CE: Cholesterol Esters; PE: Phosphatidyl-Ethanolamines.

patient—and subsequently deliver such care [74]. As doctors and hospitals progressively transition away from paper medical records, these data are being increasingly collected and made available in an electronic format — the electronic health records (HER). At their core, EHR collect, store, manage, and aggregate clinical, pharmacy, laboratory, radiology, and administrative data — however, their capabilities and functionalities are constantly expanding and evolving with the introduction of new technologies. By facilitating the access to information, EHRs can support patient empowerment and decision support, increase communication and coordination between and among providers and patients, and improve the quality of care delivered [75]. Putting together large data sets of medical data and adequate tools to analyze them offers the potential to expand biomedical research capabilities. LHS is a model in which, data generated by routine clinical care and clinical research feed a set of coordinated databases which serves as an ever growing body of evidence to feed both the scientific discover engine and clinical decision support. Mining the millions of patient records collected routinely in the daily care of patients has tremendous potential to individualize care to the specific patient. Mining patient data is a multi-data-source problem. Rich clinical data are available not just from structured demographic, laboratory and drug databases but requires the extraction also from unstructured sources, such as medical images, treatment plans and various omics. There are 6 steps by which health systems learn: i) collecting data in a planned and strategic manner; ii) analyzing captured data; iii) generating evidence through retrospective analysis of existing data as well as data from prospective studies; iv) implementing new insights into subsequent clinical care; v) evaluating outcomes of changes in clinical practice; and vi) generating new hypotheses for investigation. The systems learn by doing. With the rapid advances in this field, it will be a challenge to keep health care professionals informed about the benefits, risks, limitations, and appropriate clinical applications of new tools as they become available.

4.2. Academic Medical Centers

Academic Medical Centers (AMC) are centers of education, research and patient care. The interdisciplinary nature of the AMC can be tapped to position these institutions at the epicenter of research, education, and clinical care.

By providing access to human subjects, biological specimens, and clinical data, AMC have the role of developing, integrating and adopting standards for governance and management of these resources. Such standardization might allow a relevant delivery of diagnostic information between institutions further promoting data sharing for research. The development of a network of AMCs that focuses on addressing the specific challenges described above might provide rapid and substantial advances in clinical research. By this way, new strategies to improve health and health care may be widely tested and then proposed with more authority to the health provider. Ultimately, AMC should have an educational role by keeping healthcare professionals informed about the benefits, risks, limitations, and appropriate clinical applications of new tools as they become available AMCs should be proactive in developing these skills as well as the knowledge base and clinical decision support systems for suppliers and at the same time incorporating the concept of rapid learning models in traditional models of teaching and medical school curricula. The development of innovative training programs using information technology-based teaching strategies will be an essential component for this implementation.

5. The problems of data standardization in clinical studies and medical practice targeting cardiovascular diseases

Since huge amount of information from a limited sample size may potentially lack of data consistency and reproducibility [76], the need of pooling multi-center results and of comparing them with public data repositories has increasingly emerged [77]. Unfortunately, the integration and comparison of large data sets from registries and clinical trials may be hindered by different data processing methods. The resolution of this issue requires a great effort, currently focused on developing registries and clinical trials based on electronic linkage. This need of transmitting, receiving, combining, analyzing and using shared data as information has driven the development of the U.S. National Cardiovascular Research Infrastructure (NCRI) project in 2009 [78]. Crucial task of a NCRI has been to establish a universal vocabulary of cardiovascular data elements in order to avoid ambiguous meanings. By comparing different existing data elements, the NCRI workgroup assembled a list of 353 defining words [79]. The further development of this infrastructure has been however hampered by the multiplicity of available methods for data collection, storage and transmission, generally incompatible with each other. Ultimately, the development of standard data elements compatible with electronic record system is mandatory, but still not very useful without an electronic harmonization of record systems themselves. Overall, the need of shared models for clinical trial implementation is not only a challenge for Systems Medicine development, but also a great opportunity for improving management and quality of clinical research.

In accordance with the International Conference on Harmonisation (ICH) that established the international quality standard for good clinical practice (GCP), our workgroup has highlighted the potential utility of a proper definition and use of Case Report Form (CRF). CRF are printed, optical or electronic documents designed to record all of the protocol-required information to be reported to the principal investigators and/or sponsor on each trial subject [80]. The rationale for using an electronic CRF is to ensure the timely, accurate and standardized collection of the necessary information about: i) the patient (rendered anonymous), ii) study interventions, iii) study procedures (e.g. standard operating procedure for taking a blood sample), iv) outcome of assessments/tests, and v) adverse events. Thus, the use of CRFs allows a correct data management process ensuring that clinical data are logical, medically coherent, complete and fully documented. In addition, through the CRFs the sponsor may readily oversee the progress of a clinical trial, ensuring that it is conducted, recorded, and reported in accordance with: i) protocol, ii) standard operating procedures, iii) GCP, and iv) applicable regulatory authority requirements. Unfortunately, many obstacles have so far limited the use of this tool in clinical practice [81], but a step forward in the direction of a wider adoption of CRF would be extremely cost-effective in the short term (realistically: 2–4 years), although the amount of funding requirements is difficult to estimate. Finally, it should be noted that the different laws concerning privacy in different countries may hamper this integration program.

6. The use of computational and mathematical models in clinical research and medical practice in cardiovascular diseases

Computational models of the human heart can be useful not just in studying the basic mechanisms of heart function, but also in analyzing the heart in disease states in a context of systemic medicine. One of the main objectives of Systems Medicine is to improve medical practice by: i) standardization of methods of data acquisition, ii) processing of the available information, iii) data integration and monitoring, and finally iv) personalization to the patient's needs. A sufficient understanding of patients' cardiovascular status in “a wider sense” is necessary for doctors to make the best decisions with regard to treatment; however, this is often not possible because of the limitation of clinical and instrumental measurements. In this perspective, it would be advisable to develop special approaches that can help the clinician to focus on the patient's disease in a broader view than just focusing on the target organ damage. An important field of application of Systems Medicine is heart failure (HF), because of its strong pathophysiological links with systemic disorders, including respiratory and renal diseases, and diabetes. Best practice management for patients with chronic HF includes a multidisciplinary approach implementing guidelines,

algorithm management and accessibility to information. Computational and mathematical models can be very helpful both in imaging acquisition and processing, as in echocardiography, magnetic resonance imaging, nuclear medicine, or in the development and validation of algorithms capable of providing useful information. The recent European Society of Cardiology Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure have identified as many as 57 individual markers in patients with HF, including demographic data, etiology, co-morbidities, clinical, radiological, hemodynamic, echocardiographic and biochemical parameters [82]. Indeed, multivariable analysis of clinical parameters has helped identifying the most significant predictors of survival in HF populations, enabling development and validation of several prognostic models. However, as outlined by recent HF guidelines, because treatment of HF has improved over the past 10 years, the older prognostic models need to be revalidated, and newer prognostic models should probably be developed, using multivariate analyses of predictive factors. The excessive number of variables studied increases the sample size requirements and reduces the odds ratios. New scoring systems with integrating clinical, instrumental, biochemical and pharmacological factors have been recently introduced to improve prognostic power single tools. For instance, the echocardiographic examination is useful to diagnose cardiac disorders and to stratify the risk of patients with HF, as defined by American College of Cardiology/American Heart Association (ACC/AHA) guidelines [83]. The American Society of Echocardiography and European Association of Echocardiography also provided recommendations and guidelines for the standardization of echocardiography performance and data acquisition [84,85]. The contribution of mathematical models to the design and construction of echo machines has prompted their widespread success. By capturing and storing echocardiographic images digitally, computers can process the data to enhance the quality or the interpretation of the examination. Image quality (i.e. resolution) has always been a major goal of ultrasonic examinations. A sufficient understanding of patients' cardiovascular status is necessary for doctors to make their best decisions with regard to treatment of CVD. Recent studies sought to assess whether cardiovascular function can be assessed quantitatively and for specific patients by combining echocardiographic data with computational models. In particular, these assessments utilize the measurements already in use or available in a standard echocardiogram, enhancing the clinical potential of the proposed method.

Generally, the use of conventional Doppler indices does not allow estimation of the absolute values of left ventricular filling pressures even in patients with dilated ventricles and impaired systolic function in normal sinus rhythm. To overcome the limitations of potentially confounding effects of multiple factors, combination of Doppler and echocardiographic measures in multivariable linear regression models has been proposed. Most of the regression equations (including Doppler and echocardiographic variables) have increased the accuracy for estimating pulmonary capillary wedge pressure, but many of them were not sufficiently reliable for measuring absolute values of the filling pressures. The use of multivariable equations may be useful to acquire diagnostic information based on Doppler and echocardiographic data, thus providing a cohesive guide for the estimation of important hemodynamic variables and to simulate the effects of current treatments for HF. Diagnostic flowcharts including algorithms based on multiple echocardiographic and Doppler parameters for diagnosing elevated left ventricular filling pressures require statistical validation. Among these methods, the classification and regression tree (CART) analysis may be useful to design these models. In an attempt to investigate whether a decision model based on CART analysis is valuable, a study showed that the sequential testing by CART analysis has superior sensitivity and specificity compared with standard approaches in identifying increased left ventricular filling pressures in patients with a wide range of left ventricular ejection fractions. This grading system seems particularly helpful in patients with an ejection fraction >50%, while its contribution could be less important in patients with ejection fraction ≤50%. However, we should also consider that CART analysis may provide over-complex trees, thus over-fitting the data [86]. Finally, patient-specific computational and mathematical models have been developed to predict the short-term functional improvement after cardiac resynchronization therapy in patients with left ventricular dysfunction and complete left bundle branch block.

7. Methodologies and priorities in the implementation of Systems Medicine in cardiovascular diseases

Two important Systems Medicine approaches are envisaged as a high priority for fostering knowledge in cardiovascular health and allowing affordable epidemiological and clinical research tools:

i) the development of Electronic Data Linkages;
ii) the related development of Registry-based clinical trials.

Record linkage (RL) or Data linkage is defined as the task of finding records in a data set that refer to the same entity across different data sources (e.g., data files, books, websites, databases). Record linkage is necessary when joining data sets based on entities that may or may not share a common identifier (e.g., database key, Uniform Resource Locators [URL], National identification number), as may be the case according to differences in record shape, storage location, and/or curator style or preference. A data set that has undergone RL-oriented reconciliation may be referred to as being cross-linked. In medical practice and research, RL is an important tool in creating data required for examining the health of the public and of the health care system itself. It can be used to improve data holdings, data collection, quality assessment, and the dissemination of information. Data sources can be examined to eliminate duplicate records, to identify under-reporting and missing cases (e.g., census population counts), to create person-oriented health statistics, and to generate disease registries and health surveillance systems. Some cancer registries link various data sources (e.g., hospital admissions, pathology and clinical reports, and death registrations) to generate their registries. RL is also used to create health indicators. For example, fetal and infant mortality is a general indicator of a country's socioeconomic development, public health, and maternal and child services. If infant death records are matched to birth records, it is possible to use birth variables, such as birth weight and gestational age, along with mortality data, such as cause of death, in analyzing the data. Linkages can help in follow-up studies of cohorts or other groups to determine factors such as vital status, residential status, or health outcomes. Tracing is often needed for follow-up of industrial cohorts, clinical trials, and longitudinal surveys to obtain the cause of death and/or cancer. An example of a successful and long-standing record linkage system allowing for population-based medical research is the Rochester Epidemiology Project based in Rochester, Minnesota [87]. The development of a system in which health records from various sources, e.g. hospital admissions from various hospitals, family physicians' visits, pharmacy requests, laboratory blood analyses, and death certificates, can be merged to create a comprehensive individual health (or disease) profile can be of enormous consequences for epidemiological research, and is now being implemented in several countries, such as Sweden and the United Kingdom. It is likely that such an approach will allow an unprecedented explosion of knowledge identifying risk factors and morbid associations. The development of registries, based on such a system able to track the health status of an individual after a certain diagnosis or after the implementation of a certain treatment is also likely to promote the development of a new type of clinical trials, thus becoming incredibly more affordable than through the conventional individually dedicated system of Contract Research Organizations (CRO). An example of how this can be achieved is offered by the recently completed Thrombus Aspiration in ST-Elevation Myocardial Infarction in Scandinavia (TASTE) trial [88], which was a multicentre, prospective, open-label, randomized, controlled clinical trial that used the infrastructure of a

population-based registry to facilitate patient enrolment and data collection. In this trial, the authors conducted a randomized clinical trial to evaluate the effect on hard clinical end points of thrombus aspiration in patients with ST elevation myocardial infarction (STEMI). As commented by Lauer and D'Agostino [89], to make this investigator-initiated undertaking economically and administratively feasible, the authors used national registries as online platforms for randomization, case-record forms, and follow-up data, thus conducting a registry-based randomized clinical trial [90]. The authors enrolled trial participants from the national comprehensive Swedish Coronary Angiography and Angioplasty Registry (SCAAR), which is part of the Internet-based Swedish Web System for Enhancement and Development of Evidence-based Care in Heart Disease Evaluated According to Recommended Therapies (SWEDEHEART) registry [91]. This "registry-based randomized" trial holds data on consecutive patients from all 29 Swedish and 1 Icelandic coronary intervention center, and is funded solely by national health authorities. The system provides immediate and continuous feedback on processes and quality-of-care measures. All baseline and procedural data are entered online, directly into the registry. On the background that the clinical effect of routine intracoronary thrombus aspiration before primary percutaneous coronary intervention (PCI) in patients with STEMI is uncertain, here the authors aimed at evaluating whether thrombus aspiration reduces mortality. The trial showed no effect of the tested procedure on mortality after STEMI. A most important proof of concept in the TASTE trial was however that the authors introduced a randomization module in an online, comprehensive, national clinical registry, thus combining the benefits of randomized treatment assignment with the best features of a large-scale clinical registry. In agreement with the editorial by Lauer and D'Agostino [89], we believe that advantages of this approach include broad inclusion criteria to ensure wide clinical applicability; a simplified enrolment process to maximize the commitment and compliance of the participating hospitals; a substantial reduction in the expense associated with conducting a randomized trial since the authors were able to use the established registry infrastructure; and high rates of follow-up both of patients who underwent randomization and of those who did not. Thus, the availability of national registries based on electronic data linkages offers an incredible opportunity not only to perform epidemiological studies, but also to perform trials in a substantial cost-saving fashion, particularly valuable when addressing medical questions not fundable through pharmaceutical or medical device companies, and not directly linked to a manufacturer's promise of profit.

8. Implementation of Information and Communication Technology (ICT) and robotics in home-care

Informatics platforms to design electronic patient dossier or a personal database recording information from different Hospitals or Institutes and tracking login information by the Investigator/Physician are required. Once concerns about feasibility and data protection (also considering the different privacy low in different countries) are addressed, this approach promises to reduce costs of hospitalization and improve therapeutic compliance and safety of cardiovascular patients during home care. The large amount of studies and specialized journals (such as Telemedicine Journal, e-Health as well as Telemedicine and Telecare) mirrors the expansion of this field of interest, consistent with the increased use of Internet and technological devices. The Boario Home Care Project has been the first study dating back to 1998 and still ongoing [92]. Interestingly, this project has been improved over the years through the new broadband technologies so that the economy return during 15 years (1998–2012) has been estimated at 250% [93]. Considering the positive feedback of healthcare professionals recently reported by Gund and colleagues [94] this appears to be the right way to proceed. Finally, also robotics is emerging as pivotal player in home care, especially in the area of rehabilitation programs. Focused on the elderly, this approach is more complex and also requires the support of caregivers. Thus, two ongoing European projects (the DOMEO-project [95] and the Ambient Assisted Living Joint Programme of the European Union [96]) are assessing the feasibility of this approach according to different aspects including (i) privacy, (ii) pertinence of services, (iii) possible obstacles, (iv) motivation level to use the proposed services and (v) organizational issues [97].

9. Ethical and legal issues to the use of Systems Medicine in clinical research and practice in cardiovascular diseases

The present and future development of Systems Medicine requires even more advanced informatics tools, able to merge different patterns of data (including biological, genetic, diagnostic and clinical information) to be shared among different research groups. Accordingly, collection and analysis of data from identifiable patients raise many ethical and legal questions. The main issue concerns the need of obtaining the informed consent as advocated by Good Clinical Practices (GCP) guidelines [80]. This is because Systems Medicine includes the collection of sensitive data that might represent a social burden. For instance, hesitation toward genetic screening has been previously observed by Richard and coworkers. The authors reported that many patients raised confidential concerns about a genetic screening for hypertrophic cardiomyopathy [98]. In many countries, including the U.S., genetic discriminatory practices are pursued by law [99], but also the same knowledge of one's own disease may alter social life of patients. To strengthen the law effect, many countries did not limit restrictions to a general framework, but dealt with different instances, including medical research. In Europe, the 95/46/EU Directive protects individuals with regard to personal data processing and streaming. However, it is likely that improvements on such protection systems will be needed. Ultimately, considering the increasing amount of data acquired by a Systems Medicine approach, it seems important to propose the following suggestions:

i) enhancing safety system in the field of data collection, also including a fully informed consent;
ii) organizing educational training for biological and clinical scientists in order to ensure the highest standards of quality;
iii) improving clinicians' responsibilities toward data acquired;
iv) referring to Ethics Committees and/or an Institutional Review Boards to support, improve and update a correct management of clinical data.

10. Conclusion

Despite very far from clinical translation, the significant advances of "-omics" sciences emphasized the need to implement current research strategies. However, this progress represents not only an additional set of tools, but rather appears as a radical new way of thinking and operating. Even if Systems Medicine approach will not replace the physician with a computer, health providers will have to gain confidence with the most advanced computational tools. The application of these new strategies also represents a great opportunity to improve the research, especially in the area of CVD. Accordingly to the best expectations, by overcoming the current methodological, computational and ethical challenges Systems Medicine might become actually a powerful and cost-effective approach with a wide range of application, from risk assessment/prediction to CVD rehabilitation.

Learning points

- Systems Medicine and its role in cardiovascular diseases were defined as "An integrative approach to medical needs taking advantage and emphasizing information and tools made available by the greatest possible spectrum of scientific disciplines, aimed at improving risk prediction and individual treatment respecting ethical and legal requirements. This approach should improve medical practice by standardization, information, integration, monitoring and personalization".

- The use of "-omics" data in cardiovascular disease studies is promising, but presents important limitations.
- Some problems of data standardization in clinical studies and medical practice targeting cardiovascular diseases still exist.
- The use of computational and mathematical models in clinical research and medical practice as well as the implementation of Information and Communication Technology (ICT) and robotics in home-care in cardiovascular diseases might be promising.
- Relevant ethical and legal issues remain in the use of a Systems Medicine in clinical research and practice in cardiovascular diseases.

Conflicts of interest

None.

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References

[1] Barabasi AL, Oltvai ZN. Network biology: understanding the cell's functional organization. Nat Rev Genet 2004;5:101–13.
[2] Knoppers BM. Genomics and policymaking: from static models to complex systems? Hum Genet 2009;125:375–9.
[3] Hunter PJ, Borg TK. Integration from proteins to organs: the Physiome Project. Nat Rev Mol Cell Biol 2003;4:237–43.
[4] Langley SR, Dwyer J, Drozdov I, Yin X, Mayr M. Proteomics: from single molecules to biological pathways. Cardiovasc Res 2013;97:612–22.
[5] Wolkenhauer O. Why model? Front Physiol 2014;5:21.
[6] (CASyM) CAiSM. What is Systems Medicine? https://www.casym.eu/what-is-systems-medicine/.
[7] Wolkenhauer O, Auffray C, Jaster R, Steinhoff G, Dammann O. The road from systems biology to systems medicine. Pediatr Res 2013;73:502–7.
[8] Academies IoMotN. Review of Omics-Based Tests for Predicting Patient Outcomes in Clinical Trials. http://www.iom.edu/Activities/Research/OmicsBasedTests.aspx; 2012.
[9] Weinstein JN. 'Omic' and hypothesis-driven research in the molecular pharmacology of cancer. Curr Opin Pharmacol 2002;2:361–5.
[10] Tuomisto TT, Binder BR, Yla-Herttuala S. Genetics, genomics and proteomics in atherosclerosis research. Ann Med 2005;37:323–32.
[11] Lutgens E, Faber B, Schapira K, Schapira K, Evelo CT, van Haaften R, Heeneman S, et al. Gene profiling in atherosclerosis reveals a key role for small inducible cytokines: validation using a novel monocyte chemoattractant protein monoclonal antibody. Circulation 2005;111:3443–52.
[12] Mayr M, Zampetaki A, Sidibe A, Mayr U, Yin X, De Souza AI, et al. Proteomic and metabolomic analysis of smooth muscle cells derived from the arterial media and adventitial progenitors of apolipoprotein E-deficient mice. Circ Res 2008;102:1046–56.
[13] Pilop C, Aregger F, Gorman RC, Brunisholz R, Gerrits B, Schaffner T, et al. Proteomic analysis in aortic media of patients with Marfan syndrome reveals increased activity of calpain 2 in aortic aneurysms. Circulation 2009;120:983–91.
[14] Modesti PA, Gamberi T, Bazzini C, Borro M, Romano SM, Cambi GE, et al. Response of serum proteome in patients undergoing infrarenal aortic aneurysm repair. Anesthesiology 2009;111:844–54.
[15] Gamberi T, Puglia M, Guidi F, Magherini F, Bini L, Marzocchini R, et al. A proteomic approach to identify plasma proteins in patients with abdominal aortic aneurysm. Mol Biosyst 2011;7:2855–62.
[16] Ruegg C, Tissot JD, Farmer P, Mariotti A. Omics meets hypothesis-driven research. Partnership for innovative discoveries in vascular biology and angiogenesis. Thromb Haemost 2008;100:738–46.
[17] Helgadottir A, Thorleifsson G, Manolescu A, Gretarsdottir S, Blondal T, Jonasdottir A, et al. A common variant on chromosome 9p21 affects the risk of myocardial infarction. Science 2007;316:1491–3.
[18] McPherson R, Pertsemlidis A, Kavaslar N, Stewart A, Roberts R, Cox DR, et al. A common allele on chromosome 9 associated with coronary heart disease. Science 2007;316:1488–91.
[19] Samani NJ, Erdmann J, Hall AS, Hengstenberg C, Mangino M, Mayer B, et al. Genomewide association analysis of coronary artery disease. N Engl J Med 2007;357:443–53.
[20] Schunkert H, Götz A, Braund P, McGinnis R, Tregouet DA, Mangino M, et al. Repeated replication and a prospective meta-analysis of the association between chromosome 9p21.3 and coronary artery disease. Circulation 2008;117:1675–84.
[21] Samani NJ, Raitakari OT, Sipilä K, Tobin MD, Schunkert H, Juonala M, et al. Coronary artery disease-associated locus on chromosome 9p21 and early markers of atherosclerosis. Arterioscler Thromb Vasc Biol 2008;28:1679–83.
[22] Clarke R, Peden JF, Hopewell JC, Kyriakou T, Goel A, Heath SC, et al. Genetic variants associated with Lp(a) lipoprotein level and coronary disease. N Engl J Med 2009;361:2518–28.
[23] Reilly MP, Li M, He J, Ferguson JF, Stylianou IM, Mehta NN, et al. Identification of ADAMTS7 as a novel locus for coronary atherosclerosis and association of ABO with myocardial infarction in the presence of coronary atherosclerosis: two genome-wide association studies. Lancet 2011;377:383–92.
[24] Scheffold T, Kullmann S, Huge A, Binner P, Ochs HR, Schöls W, et al. Six sequence variants on chromosome 9p21.3 are associated with a positive family history of myocardial infarction: a multicenter registry. BMC Cardiovasc Disord 2011;11:9.
[25] Prudente S, Morini E, Larmon J, Andreozzi F, Di Pietro N, Nigro A, et al. The SH2B1 obesity locus is associated with myocardial infarction in diabetic patients and with NO synthase activity in endothelial cells. Atherosclerosis 2011;219:667–72.
[26] Hughes MF, Saarela O, Stritzke J, Kee F, Silander K, Klopp N, et al. Genetic markers enhance coronary risk prediction in men: the MORGAM prospective cohorts. PLoS One 2012;7:e40922.
[27] Wauters E, Carruthers KF, Buysschaert I, Dunbar DR, Peuteman G, Belmans A, et al. Influence of 23 coronary artery disease variants on recurrent myocardial infarction or cardiac death: the GRACE Genetics Study. Eur Heart J 2013;34:993–1001.
[28] Holmen OL, Zhang H, Fan Y, Hovelson DH, Schmidt EM, Zhou W, et al. Systematic evaluation of coding variation identifies a candidate causal variant in TM6SF2 influencing total cholesterol and myocardial infarction risk. Nat Genet 2014;46:345–51.
[29] Abu El Maaty MA, Hassanein SI, Sleem HM, Gad MZ. Effect of polymorphisms in the NADSYN1/DHCR7 locus (rs12785878 and rs1790349) on plasma 25-hydroxyvitamin D levels and coronary artery disease incidence. J Nutrigenet Nutrigenomics 2014;6:327–35.
[30] Adams JN, Raffield LM, Freedman BI, Langefeld CD, Ng MC, Carr JJ, et al. Analysis of common and coding variants with cardiovascular disease in the Diabetes Heart Study. Cardiovasc Diabetol 2014;13:77.
[31] Hirokawa M, Morita H, Tajima T, Takahashi A, Ashikawa K, Miya F, et al. A genome-wide association study identifies PLCL2 and AP3D1-DOT1L-SF3A2 as new susceptibility loci for myocardial infarction in Japanese. Eur J Hum Genet 2014. http://dx.doi.org/10.1038/ejhg.2014.110 [Epub ahead of print].
[32] Shen GQ, Girelli D, Li L, Rao S, Archacki S, Olivieri O, et al. A novel molecular diagnostic marker for familial and early-onset coronary artery disease and myocardial infarction in the LRP8 gene. Circ Cardiovasc Genet 2014;7:514–20.
[33] Dichgans M, Malik R, König IR, Rosand J, Clarke R, Gretarsdottir S, et al. Shared genetic susceptibility to ischemic stroke and coronary artery disease: a genome-wide analysis of common variants. Stroke 2014;45:24–36.
[34] Roberts LD, Gerszten RE. Toward new biomarkers of cardiometabolic diseases. Cell Metab 2013;18:43–50.
[35] Mateos-Cáceres PJ, García-Méndez A, López Farré A, Macaya C, Núñez A, Gómez J, et al. Proteomic analysis of plasma from patients during an acute coronary syndrome. J Am Coll Cardiol 2004;44:1578–83.
[36] Donahue MP, Rose K, Hochstrasser D, Vonderscher J, Grass P, Chibout SD, et al. Discovery of proteins related to coronary artery disease using industrial-scale proteomics analysis of pooled plasma. Am Heart J 2006;152:478–85.
[37] Wilson AM, Kimura E, Harada RK, Nair N, Narasimhan B, Meng XY, et al. Beta2-microglobulin as a biomarker in peripheral arterial disease: proteomic profiling and clinical studies. Circulation 2007;116:1396–403.
[38] Zimmerli LU, Schiffer E, Zürbig P, Good DM, Kellmann M, Mouls L, et al. Urinary proteomic biomarkers in coronary artery disease. Mol Cell Proteomics 2008;7:290–8.
[39] von Zur Muhlen C, Schiffer E, Zuerbig P, Kellmann M, Brasse M, Meert N, et al. Evaluation of urine proteome pattern analysis for its potential to reflect coronary artery atherosclerosis in symptomatic patients. J Proteome Res 2009;8:335–45.
[40] Gasparri C, Curcio A, Torella D, Gaspari M, Celi V, Salituri F, et al. Proteomics reveals high levels of vitamin D binding protein in myocardial infarction. Front Biosci (Elite Ed) 2010;2:796–804.
[41] Darde VM, de la Cuesta F, Dones FG, Alvarez-Llamas G, Barderas MG, Vivanco F. Analysis of the plasma proteome associated with acute coronary syndrome: does a permanent protein signature exist in the plasma of ACS patients? J Proteome Res 2010;9:4420–32.
[42] Delles C, Schiffer E, von Zur Muhlen C, Peter K, Rossing P, Parving HH, et al. Urinary proteomic diagnosis of coronary artery disease: identification and clinical validation in 623 individuals. J Hypertens 2010;28:2316–22.
[43] Cubedo J, Padro T, Garcia-Moll X, Pinto X, Cinca J, Badimon L. Proteomic signature of Apolipoprotein J in the early phase of new-onset myocardial infarction. J Proteome Res 2011;10:211–20.
[44] Haas B, Serchi T, Wagner DR, Gilson G, Planchon S, Renaut J, et al. Proteomic analysis of plasma samples from patients with acute myocardial infarction identifies haptoglobin as a potential prognostic biomarker. J Proteomics 2011;75:229–36.
[45] Wykrzykowska JJ, Garcia-Garcia HM, Goedhart D, Zalewski A, Serruys PW. Differential protein biomarker expression and their time-course in patients with a spectrum of stable and unstable coronary syndromes in the Integrated Biomarker and Imaging Study-1 (IBIS-1). Int J Cardiol 2011;149:10–6.
[46] Silbiger VN, Luchessi AD, Hirata RD, Neto LG, Pastorelli CP, Ueda EK, et al. Time course proteomic profiling of human myocardial infarction plasma samples: an approach to new biomarker discovery. Clin Chim Acta 2011;412:1086–93.
[47] Gil-Dones F, Darde VM, Alonso-Orgaz S, Lopez-Almodovar LF, Mourino-Alvarez L, Padial LR, et al. Inside human aortic stenosis: a proteomic analysis of plasma. J Proteomics 2012;75:1639–53.

[48] Rezeli M, Vegvari A, Donnarumma F, Gidlof O, Smith JG, Erlinge D, et al. Development of an MRM assay panel with application to biobank samples from patients with myocardial infarction. J Proteomics 2013;87:16–25.
[49] Yin X, Subramanian S, Hwang SJ, O'Donnell CJ, Fox CS, Courchesne P, et al. Protein biomarkers of new-onset cardiovascular disease: prospective study from the systems approach to biomarker research in cardiovascular disease initiative. Arterioscler Thromb Vasc Biol 2014;34(4):939–45.
[50] Brindle JT, Antti H, Holmes E, Tranter G, Nicholson JK, Bethell HW, et al. Rapid and noninvasive diagnosis of the presence and severity of coronary heart disease using 1H-NMR-based metabonomics. Nat Med 2002;8:1439–44.
[51] Sabatine MS, Liu E, Morrow DA, Heller E, McCarroll R, Wiegand R, et al. Metabolomic identification of novel biomarkers of myocardial ischemia. Circulation 2005;112:3868–75.
[52] Kirschenlohr HL, Griffin JL, Clarke SC, Rhydwen R, Grace AA, Schofield PM, et al. Proton NMR analysis of plasma is a weak predictor of coronary artery disease. Nat Med 2006;12:705–10.
[53] Lewis GD, Wei R, Liu E, Yang E, Shi X, Martinovic M, et al. Metabolite profiling of blood from individuals undergoing planned myocardial infarction reveals early markers of myocardial injury. J Clin Invest 2008;118:3503–12.
[54] Mayr M, Yusuf S, Weir G, Chung YL, Mayr U, Yin X, et al. Combined metabolomic and proteomic analysis of human atrial fibrillation. J Am Coll Cardiol 2008;51:585–94.
[55] Teul J, Rupérez FJ, Garcia A, Vaysse J, Balayssac S, Gilard V, et al. Improving metabolite knowledge in stable atherosclerosis patients by association and correlation of GC–MS and 1H NMR fingerprints. J Proteome Res 2009;8:5580–9.
[56] Tang WH, Wang Z, Cho L, Brennan DM, Hazen SL. Diminished global arginine bioavailability and increased arginine catabolism as metabolic profile of increased cardiovascular risk. J Am Coll Cardiol 2009;53:2061–7.
[57] Shah SH, Hauser ER, Bain JR, Muehlbauer MJ, Haynes C, Stevens RD, et al. High heritability of metabolomic profiles in families burdened with premature cardiovascular disease. Mol Syst Biol 2009;5:258.
[58] Turer AT, Stevens RD, Bain JR, Muehlbauer MJ, van der Westhuizen J, Mathew JP, et al. Metabolomic profiling reveals distinct patterns of myocardial substrate use in humans with coronary artery disease or left ventricular dysfunction during surgical ischemia/reperfusion. Circulation 2009;119:1736–46.
[59] Huffman KM, Shah SH, Stevens RD, Bain JR, Muehlbauer M, Slentz CA, et al. Relationships between circulating metabolic intermediates and insulin action in overweight to obese, inactive men and women. Diabetes Care 2009;32:1678–83.
[60] Shah SH, Bain JR, Muehlbauer MJ, Stevens RD, Crosslin DR, Haynes C, et al. Association of a peripheral blood metabolic profile with coronary artery disease and risk of subsequent cardiovascular events. Circ Cardiovasc Genet 2010;3:207–14.
[61] Shah SH, Sun JL, Stevens RD, Bain JR, Muehlbauer MJ, Pieper KS, et al. Baseline metabolomic profiles predict cardiovascular events in patients at risk for coronary artery disease. Am Heart J 2012;163:844–50 [e1].
[62] Magnusson M, Lewis GD, Ericson U, Orho-Melander M, Hedblad B, Engström G, et al. A diabetes-predictive amino acid score and future cardiovascular disease. Eur Heart J 2013;34:1982–9.
[63] Luan H, Chen X, Zhong S, Yuan X, Meng N, Zhang J, et al. Serum metabolomics reveals lipid metabolism variation between coronary artery disease and congestive heart failure: a pilot study. Biomarkers 2013;18:314–21.
[64] Zheng Y, Yu B, Alexander D, Manolio TA, Aguilar D, Coresh J, et al. Associations between metabolomic compounds and incident heart failure among African Americans: the ARIC study. Am J Epidemiol 2013;178:534–42.
[65] Zheng Y, Yu B, Alexander D, Mosley TH, Heiss G, Nettleton JA, et al. Metabolomics and incident hypertension among blacks: the atherosclerosis risk in communities study. Hypertension 2013;62:398–403.
[66] Stegemann C, Pechlaner R, Willeit P, Langley SR, Mangino M, Mayr U, et al. Lipidomics profiling and risk of cardiovascular disease in the prospective population-based Bruneck study. Circulation 2014;129(18):1821–31.
[67] Rizza S, Copetti M, Rossi C, Cianfarani MA, Zucchelli M, Luzi A, et al. Metabolomics signature improves the prediction of cardiovascular events in elderly subjects. Atherosclerosis 2014;232:260–4.
[68] Wang TJ, Larson MG, Vasan RS, Cheng S, Rhee EP, McCabe E, et al. Metabolite profiles and the risk of developing diabetes. Nat Med 2011;17:448–53.
[69] Hirschhorn JN. Genomewide association studies—illuminating biologic pathways. N Engl J Med 2009;360:1699–701.
[70] Hood L, Flores M. A personal view on systems medicine and the emergence of proactive P4 medicine: predictive, preventive, personalized and participatory. N Biotechnol 2012;29:613–24.
[71] Bousquet J, Anto JM, Sterk PJ, Adcock IM, Chung KF, Roca J, et al. Systems medicine and integrated care to combat chronic noncommunicable diseases. Genome Med 2011;3:43.
[72] Embi PJ, Kaufman SE, Payne PR. Biomedical informatics and outcomes research: enabling knowledge-driven health care. Circulation 2009;120:2393–9.
[73] Etheredge LM. A rapid-learning health system. Health Aff (Millwood) 2007;26:w107–18.
[74] Grumbach K, Lucey CR, Johnston SC. Transforming from centers of learning to learning health systems: the challenge for academic health centers. JAMA 2014;311:1109–10.
[75] Friedman CP, Wong AK, Blumenthal D. Achieving a nationwide learning health system. Sci Transl Med 2010;2:57cm29.
[76] Parker LA, Gomez Saez N, Lumbreras B, Porta M, Hernandez-Aguado I. Methodological deficits in diagnostic research using '-omics' technologies: evaluation of the QUADOMICS tool and quality of recently published studies. PLoS One 2010;5:e11419.
[77] Burgun A, Bodenreider O. Accessing and integrating data and knowledge for biomedical research. Yearb Med Inform 2008:91–101.
[78] (NCRI) NCRIp. https://www.ncrinetwork.org/.
[79] Anderson HV, Weintraub WS, Radford MJ, Kremers MS, Roe MT, Shaw RE, et al. Standardized cardiovascular data for clinical research, registries, and patient care: a report from the Data Standards Workgroup of the National Cardiovascular Research Infrastructure project. J Am Coll Cardiol 2013;61:1835–46.
[80] (ICH) ICoH. http://www.ich.org/products/guidelines/efficacy/article/efficacy-guidelines.html.
[81] Ene-Iordache B, Carminati S, Antiga L, Rubis N, Ruggenenti P, Remuzzi G, et al. Developing regulatory-compliant electronic case report forms for clinical trials: experience with the demand trial. J Am Med Inform Assoc 2009;16:404–8.
[82] McMurray JJ, Adamopoulos S, Anker SD, et al. 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;14:803–69.
[83] Jessup M, Abraham WT, Casey DE, et al. 2009 focused update: ACCF/AHA Guidelines for the Diagnosis and Management of Heart Failure in Adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines: developed in collaboration with the International Society for Heart and Lung Transplantation. Circulation 2009;119:1977–2016.
[84] Quinones MA, Otto CM, Stoddard M, Waggoner A, Zoghbi WA. Recommendations for quantification of Doppler echocardiography: a report from the Doppler Quantification Task Force of the Nomenclature and Standards Committee of the American Society of Echocardiography. J Am Soc Echocardiogr 2002;15:167–84.
[85] Dini FL, Ballo P, Badano L, et al. Validation of an echo-Doppler decision model to predict left ventricular filling pressure in patients with heart failure independently of ejection fraction. Eur J Echocardiogr 2010;11:703–10.
[86] Strobl C, Malley J, Tutz G. An introduction to recursive partitioning: rationale, application, and characteristics of classification and regression trees, bagging, and random forests. Psychol Methods 2009;14:323–48.
[87] St Sauver JL, Grossardt BR, Yawn BP, Melton III LJ, Pankratz JJ, Brue SM, et al. Data resource profile: the Rochester Epidemiology Project (REP) medical records–linkage system. Int J Epidemiol 2012;41:1614–24.
[88] Frobert O, Lagerqvist B, Olivecrona GK, et al. Thrombus aspiration during ST-segment elevation myocardial infarction. N Engl J Med 2013;369:1587–97.
[89] Lauer MS, D'Agostino Sr RB. The randomized registry trial—the next disruptive technology in clinical research? N Engl J Med 2013;369:1579–81.
[90] Frobert O, Lagerqvist B, Gudnason T, Thuesen L, Svensson R, Olivecrona GK, et al. Thrombus Aspiration in ST-Elevation myocardial infarction in Scandinavia (TASTE trial). A multicenter, prospective, randomized, controlled clinical registry trial based on the Swedish angiography and angioplasty registry (SCAAR) platform. Study design and rationale. Am Heart J 2010;160:1042–8.
[91] Jernberg T, Attebring MF, Hambraeus K, et al. The Swedish Web-system for enhancement and development of evidence-based care in heart disease evaluated according to recommended therapies (SWEDEHEART). Heart 2010;96:1617–21.
[92] Scalvini S, Volterrani M, Giordano A, Glisenti F. Boario Home Care Project: an Italian telemedicine experience. Monaldi Arch Chest Dis 2003;60:254–7.
[93] Scalvini S, Volterrani M, Giordano A, Glisenti F. Boario home care project. Stud Health Technol Inform 2004;100:200–4.
[94] Gund A, Lindecrantz K, Schaufelberger M, Patel H, Sjoqvist BA. Attitudes among healthcare professionals towards ICT and home follow-up in chronic heart failure care. BMC Med Inform Decis Mak 2012;12:138.
[95] Domestic robot for elderly assistance: the DOMEO-project. http://wwwaal-domeoorg/.
[96] Ambient Assisted Living Joint Programme: AAL. http://wwwaal-europeeu/.
[97] Zsiga K, Edelmayer G, Rumeau P, Peter O, Toth A, Fazekas G. Home care robot for socially supporting the elderly: focus group studies in three European countries to screen user attitudes and requirements. Int J Rehabil Res 2013;36:375–8.
[98] Richard P, Charron P, Carrier L, et al. Hypertrophic cardiomyopathy: distribution of disease genes, spectrum of mutations, and implications for a molecular diagnosis strategy. Circulation 2003;107:2227–32.
[99] Abiola S. Recent developments in health law. The Genetic Information Nondiscrimination Act of 2008: "First major Civil Rights bill of the century" bars misuse of genetic test results. J Law Med Ethics 2008;36:856–60.