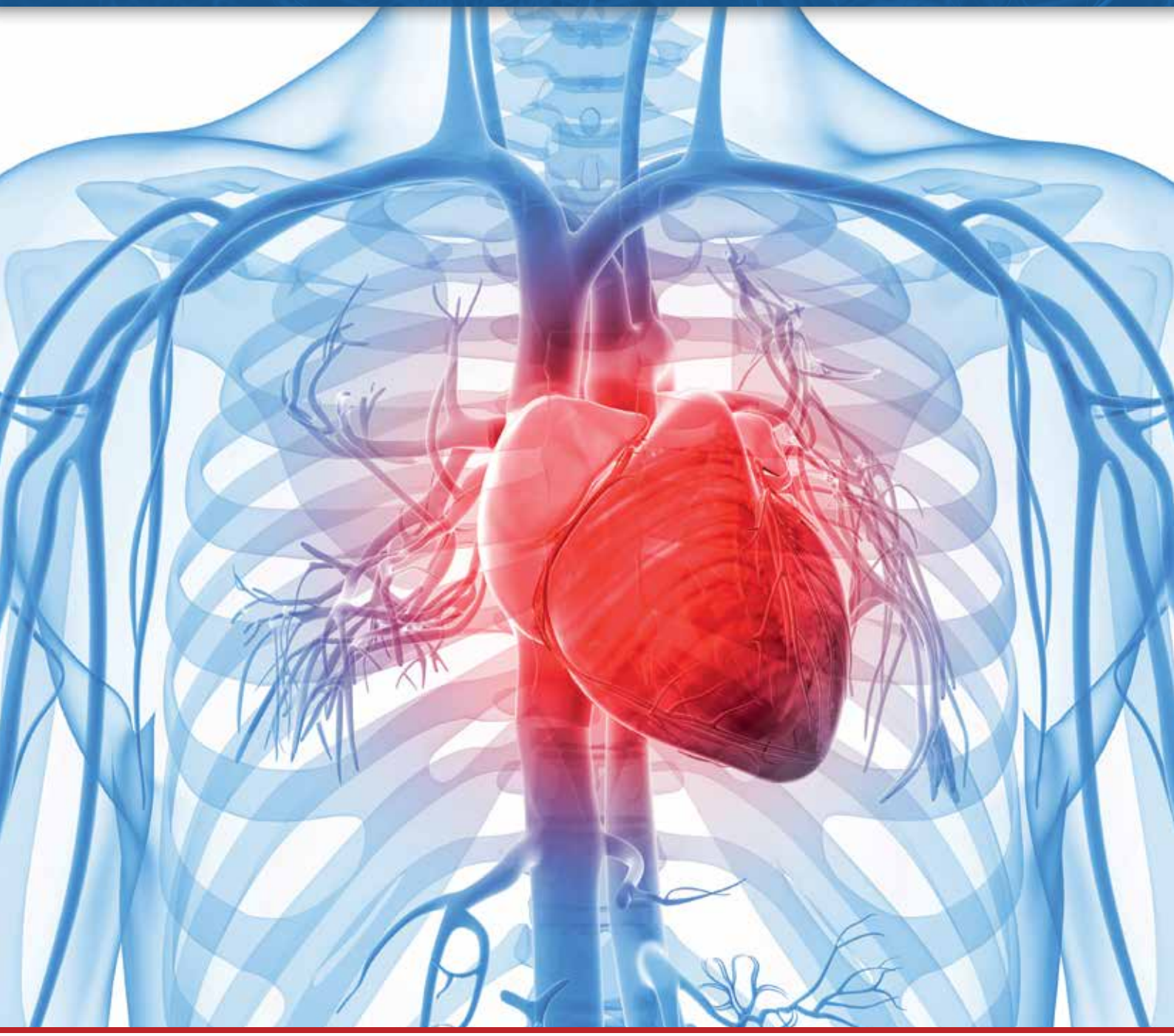
Challenges and Opportunities for Cardiovascular Disease Research

Strategic Research Agenda for Cardiovascular Diseases (SRA-CVD)



ehn fighting heart disease and stroke european heart network

ESC European Society of Cardiology

ERA CVD

Imprint

EU Grant

ERA-CVD is a European Research Area Network (ERA-Net) comprising 24 partners from 19 countries/regions that has been granted for funding through the current EU Framework Programme for Research and Innovation 'Horizon 2020' under grant agreement no **[680969].**

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Foreword

ERA-CVD is a European Research Area Network (ERA-NET) focusing on cardiovascular disease (CVD) research and comprising currently of 24 partners from 19 countries. The project is supported by the EU Framework Program for Research and Innovation 'Horizon 2020' and runs from 2015 until 2020. The goal of ERA-CVD is to contribute to a European Research Area in which cardiovascular research is conducted and funded across countries through themed calls for CVD research proposals. ERA-CVD implemented one Joint Transnational Call (JTC) with additional financial support from the European Commission (EC, co-fund call) in 2016 followed by further JTCs in the years 2017, 2018 and 2019 (non- co-fund calls).

In addition to funding cardiovascular research, ERA-CVD is tasked with developing a Strategic Research Agenda (SRA). This agenda is presented here and provides recommendations to guide the priorities of research funders and deliverers of healthcare as they tackle and seek to reverse the growing burden caused by cardiovascular diseases. For the generation of this document, ERA-CVD has been supported by their External Advisory Board (EAB). In addition, the European Society of Cardiology (ESC), the European Heart Network (EHN) and numerous specialists in cardiovascular research have strongly contributed to the SRA for Cardiovascular Diseases (SRA-CVD).

Executive Summary

There is false optimism that cardiovascular disease (CVD) is no longer a public health problem. Despite a period of decline in CVD mortality due to introduction of new treatments and prevention measures, we are facing an era where CVD, though in a different guise, is still the leading cause of death and a major burden to society. Disparities in Europe are prominent but even in the most affluent countries CVD remains a major health threat. Likewise, the perception that CVD is fully preventable by adherence to a healthy diet and lifestyle is wrong. Genetic risk factors, co-morbidities and novel causes, such as cardiotoxicity of anticancer drugs, require different approaches; implementation of prevention is less simple than it seems (Chapter 1).

The presentation of CVD and the challenges for health care have changed. However, compared to other major diseases, there is limited innovation in terms of novel products and major concern about insufficient investment. The development pipeline is stronger in the USA, clinical trials are moving out of Europe and China has a fast-growing share in cardiovascular research and development. Europe as a whole still has a competitive research output and capacity, supported by research networks, partnerships and European infrastructure but will need to become more effective in translating science into clinical solutions and products (Chapter 2).

The present document identifies areas of high medical need and opportunities for progress. These include: improving prevention and its implementation; optimising risk detection and recognition of early disease; developing more efficient treatment that is targeted and personalised; balancing cost-effectiveness and improving delivery of healthcare; taking advantage of the potential for discovery through big data mining and digital innovation; building on new discoveries in genetic editing and pathways for regeneration of heart and vessels (Chapter 3).

Overarching recommendations include a call for an increased advocacy to enhance the awareness of the urgency of the problem that the increased burden of CVD presents. A strategic plan must ensure that the pipeline

from scientific discovery to patient benefit is secure, at all stages, and address the hurdles that prevent efficient translation and implementation. Research should be reproducible and validated, using improved disease models, providing high quality data that can be shared and re-used, and thereby support faster development in biotech and industry. Clinical research, drug and device development require a supportive regulatory framework and smart thinking in novel trial design. Training and education must support a next-generation research and health care workforce that will optimally use available resources. Transnational, multidisciplinary and cross-sectoral collaboration, involvement of patients and public in research strategies, will enhance impact. Modernising the funding landscape is required (Chapter 4). Finally, ERA-CVD and its partners propose key areas for research to address the CVD epidemic (Chapter 5):

- New ways to sustain a healthy lifestyle in the long term
- The earlier recognition of cardiovascular disease
- Better assessment of the personal risk of cardiovascular disease
- Personalised treatment and management of cardiovascular disease
- Effective treatment of stroke
- Improved treatment of heart failure and atrial fibrillation
- Improved application of implantable devices
- The interaction between CVD and other disorders
- Repair of the heart and blood vessels
- Cardiovascular disease in segmented, yet under represented populations
- Cognitive dysfunction as a result of cardiovascular disease
- Living with a congenital heart defect
- Communication and collaboration between healthcare professionals and patients and citizens
- Psychosocial wellbeing in patients with cardiovascular disease
- Better guidance and care at the end of life phase of cardiovascular disease patients.

Within budgetary constraints and for a multi-annual planning, further prioritisation will be helpful. To this effect, ERA-CVD has launched a survey among a broad range of stakeholders, including citizens and patients, health care providers and scientists. The link and further information for the SRA-CVD survey will be available on the ERA-CVD webpage until May 31st 2019 under: https://www.era-cvd.eu/396.php. The results of this online survey will be incorporated in the final document.

In conclusion, implementation of the proposed research agenda will require action from ministries, funding agencies, health care administrators and the private sector, at EU and national level. ERA-CVD urges the responsible ministries and funding agencies to take the lead in advancing this agenda at European level, for the benefit of the patients and citizens.

Beyond the research agenda presented here, public and private decision makers providing health care must develop novel models for care, ensure equal access to treatment and implement digital health that will in turn support research for better cardiovascular health.

CHAPTER 1

The urgent need to reduce the burden of cardiovascular diseases

Cardiovascular diseases (CVD) cover a broad range of conditions affecting the heart and blood vessels. Highly prevalent diseases include not only ischemic heart disease leading to heart attack, but also stroke, heart valve disease, peripheral arterial disease and vascular dementia. In addition, there is a series of less common, but devastating, cardiovascular conditions such as congenital heart disease, inheritable cardiomyopathies (where the heart's structure is damaged) and arrhythmias (where the heart beat is irregular), any of which can lead to sudden and unexpected death – often in young people.

In the last decades preventive strategies, including lifestyle recommendations and new medicines, notably blood pressure lowering drugs and statins to lower cholesterol levels in the blood, have reduced the incidence of heart attack and stroke. Hugely improved acute treatments for myocardial infarction, initially clot-busting drugs but now notably arterial stents, and better acute treatment for stroke have saved many more lives. However this has led to increasing numbers of people living with the chronic consequences of CVD. Chronic diseases make up the largest proportion of all diseases and this is expected to increase as a result of an ageing society putting pressure on the sustainability of health care systems ***(1).*** Legal restriction of exposure to tobacco smoke has further reduced heart attacks and stroke. Nonetheless our understanding of and our ability to prevent or treat the less common forms of CVD are still very limited. Sectors such as those directly affecting lifestyle and behaviour, education, food industry, and public transportation are known to greatly impact population health, particularly cardiovascular health, and this requires to be tackled by coordinated policy action.

As shown in Figure 1, CVD are the largest cause of death in Europe and the leading cause of the overall disease burden in Europe that is projected to remain so over the next 20 years ***(2)*** (Figures 1 and 2 a/b/c). Moreover, the main causes of premature death in Europe are ischaemic heart disease and stroke (together accounting for over 700,000 cases in 2016), followed by trachea/bronchus/lung cancers (around 219,000 cases) ***(3).***

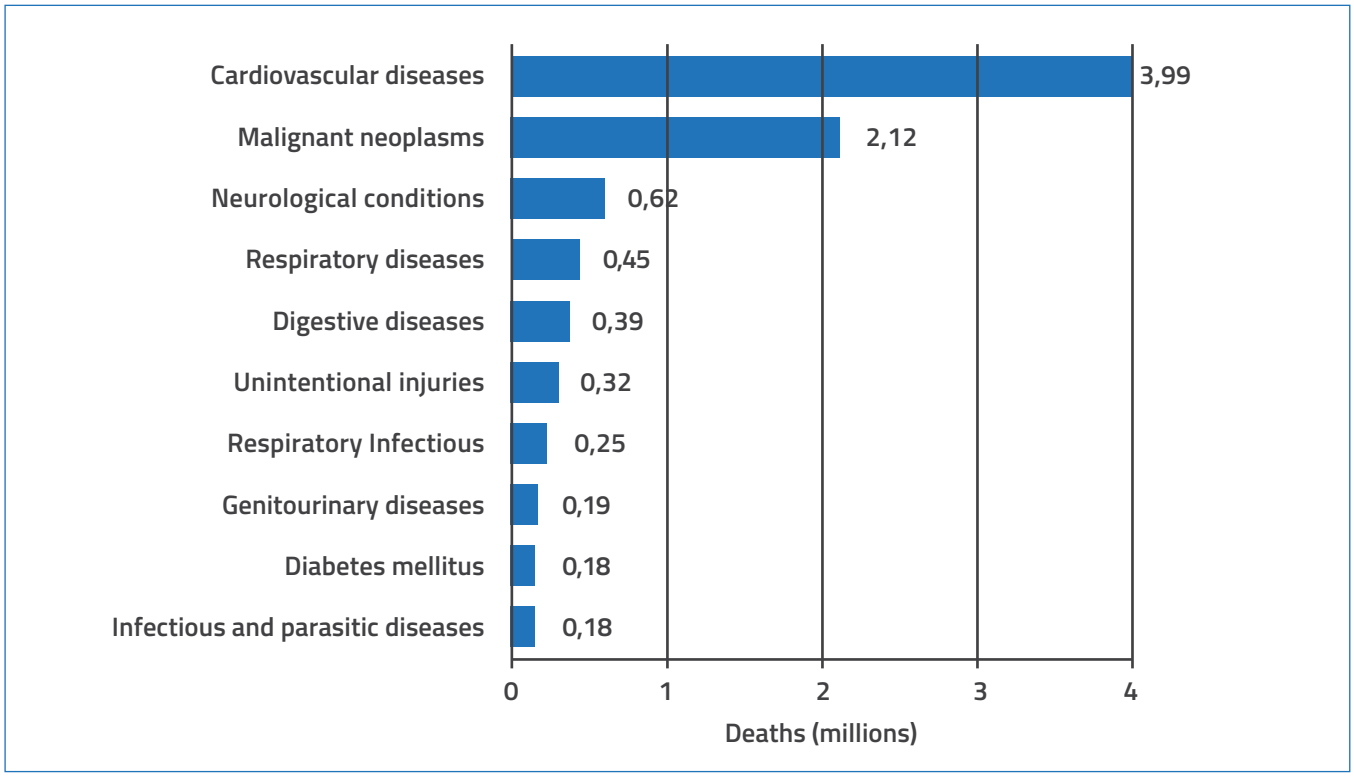

Figure 1: *Major causes of death (men and women) in 2016, European region* ***(3).***

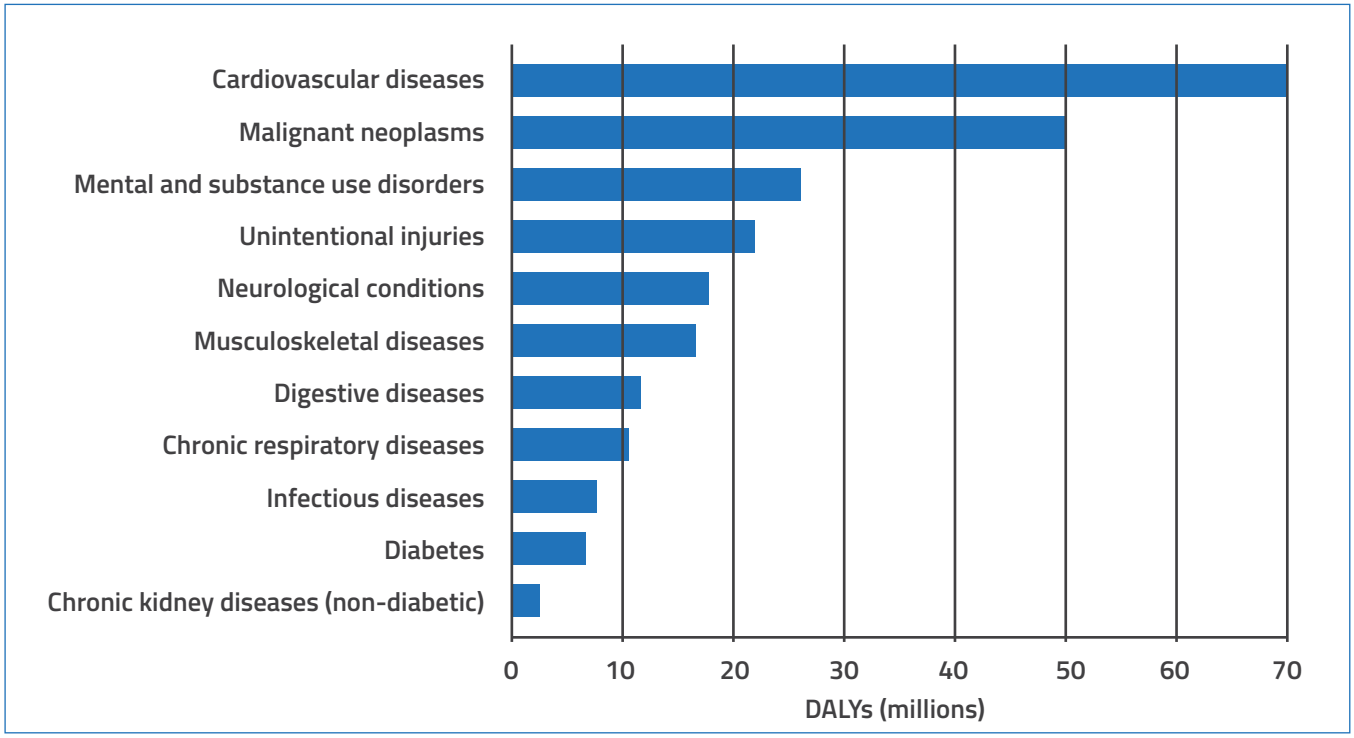

Figure 2 a: *Major causes of Disability-adjusted life years lost (DALYs) in 2016, European region* ***(3)****. One DALY indicates one year of healthy life lost.*

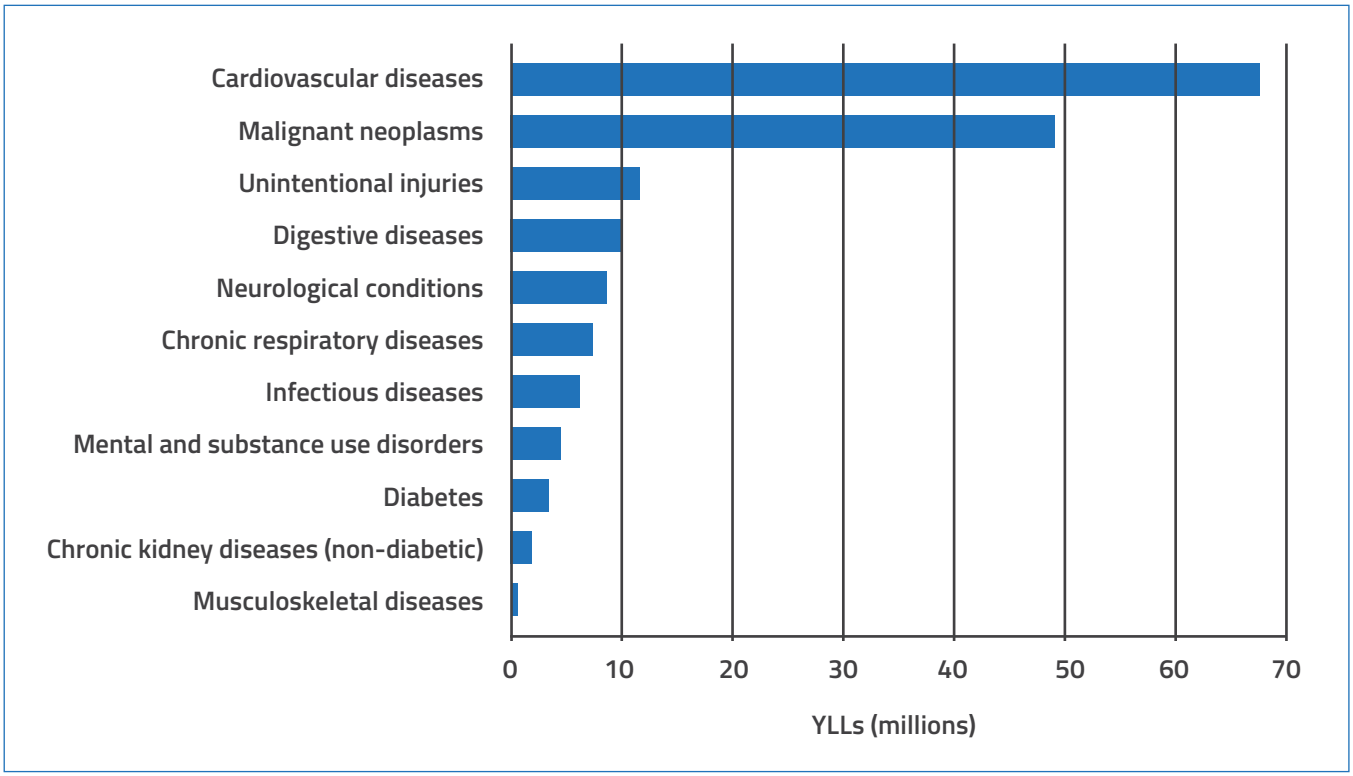

Figure 2 b: *Major causes of Years of Life Lost (YLLs) due to premature mortality (according to the WHO definition of YLL: www.healthdata.org/gbd/faq) in the population in 2016, European region* ***(3).***

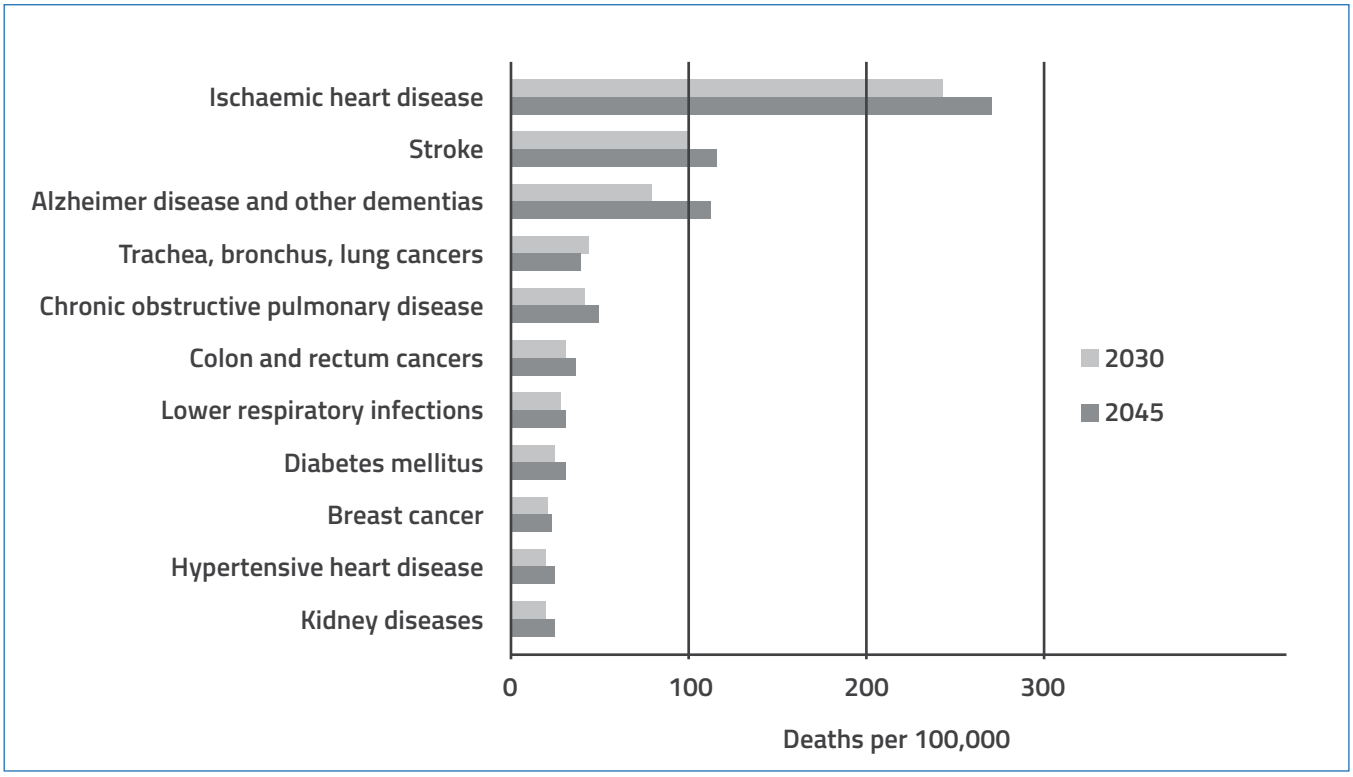

Figure 2 c: *Projections of death rates by major cause, European region* ***(3).***

Of particular concern is the changing profile of CVD. Improved initial survival from heart attack and stroke has led to an increasing population with incapacitating chronic diseases such as heart failure, peripheral arterial disease and vascular dementia. In this aging population CVD commonly co-exist with other diseases, leading to multi-morbidity – a further challenge when seeking to assess and treat patients. In addition, despite societal recognition of the need for a healthier lifestyle, major risk factors for CVD including obesity and diabetes are now increasing ***(4).*** Thus CVD are still the largest cause of burden of disease in Europe ***(4).***

Taken together, the evidence indicates that deaths from CVD will not decrease without better preventive measures and new treatments, and the societal cost of CVD, in Europe currently 210 billion Euros annually ***(5),*** is predicted to rise rapidly. This societal cost is substantially higher compared to cancer, yet CVD research funding lags well behind other areas, such as cancer research (see also Chapter 2). This challenge requires action from many sectors of society, including citizens, researchers, national healthcare systems and EU and national policy makers. There is a necessity to prioritise basic and translational clinical research in order to progress beyond the state-of-the-art, and to identify and test new strategies to further decrease CVD morbidity and mortality.

Put simply, the priority remains for CVD research and implementation of its findings to provide better patient care and prevention. The outcomes must be recognised and acted on urgently if we are to reduce the major societal burden these diseases cause.

CHAPTER 2

Current cardiovascular research in Europe

Europe has a history of strong biomedical discovery research and impactful clinical and population studies in cardiovascular diseases. Within this chapter, there is a focus on the outputs and inputs of cardiovascular research to identify strengths and weaknesses as well as the necessary actions for research policy in Europe to face the challenge posed by CVD.

A. A globally competitive research publication output

The most recent review of cardiovascular research publications noted that while the USA remains the leading national source the combined output from the EU member states is higher ***(6).*** In terms of global competition, though still substantially fewer as the number of publications from China is rapidly increasing. The impact of research, measured in terms of citations, is comparable in EU and USA and markedly higher than the world average ***(6).***

Within Europe, there is substantial variation in output between countries. This is related to country size, differences in research capacity and national investment in biomedical and CVD research, which in turn correlates with Gross Domestic Product (GDP, see Section C below). Countries with a small number of publications can nevertheless achieve high impact. There is good evidence that CVD publications with multinational authorship achieve higher scientific impact ***(6).*** Mapping these collaborations shows the growth over time and the European and worldwide networks, with the USA linking to the EU, in particular to the UK and Germany (Figure 3).

However, a benchmarking of publication output in CVD in relation to the health problem of CVD compared to other diseases indicates that the field may still be underperforming ***(7).*** While the global burden of disease of CVD was estimated being twice as high as for cancer, in line with the data for Europe shown in chapter 1, at 23% oncology has the largest share in health and biomedical publication output, compared to the 10% share of CVD publication output, and suggesting lower research activity in the area of CVD (Figure 4). This underperformance of the field in relation to disease burden aligns with underperformance in innovation and therapeutic development (see also Section D).

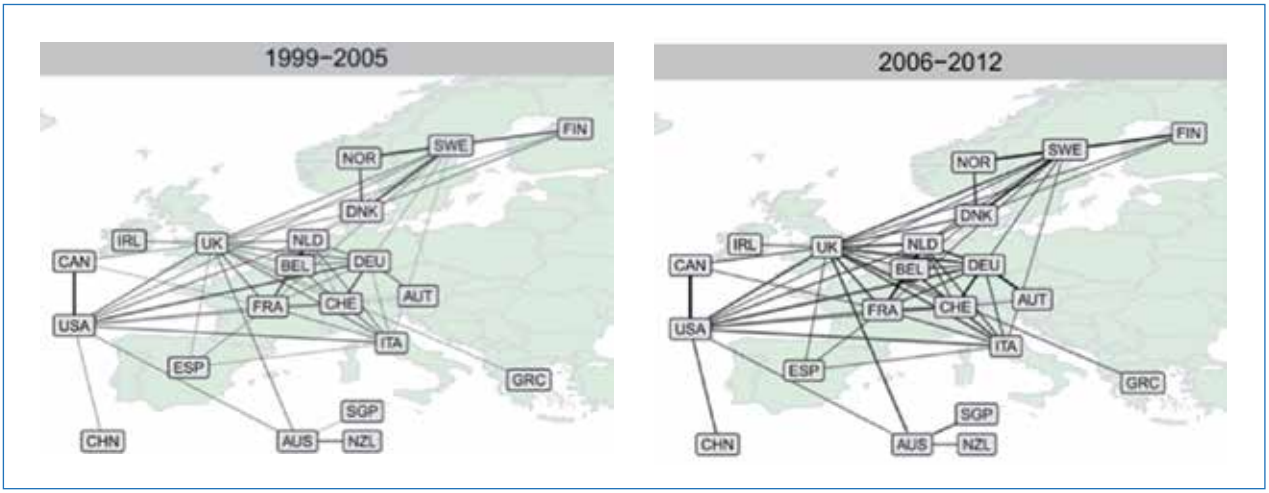

Figure 3: International collaborative networks within Europe and beyond, as derived from joint publication output, have grown substantially – illustrated by more intense lines on the right hand chart. (reproduced from 6 under CC-BY license).

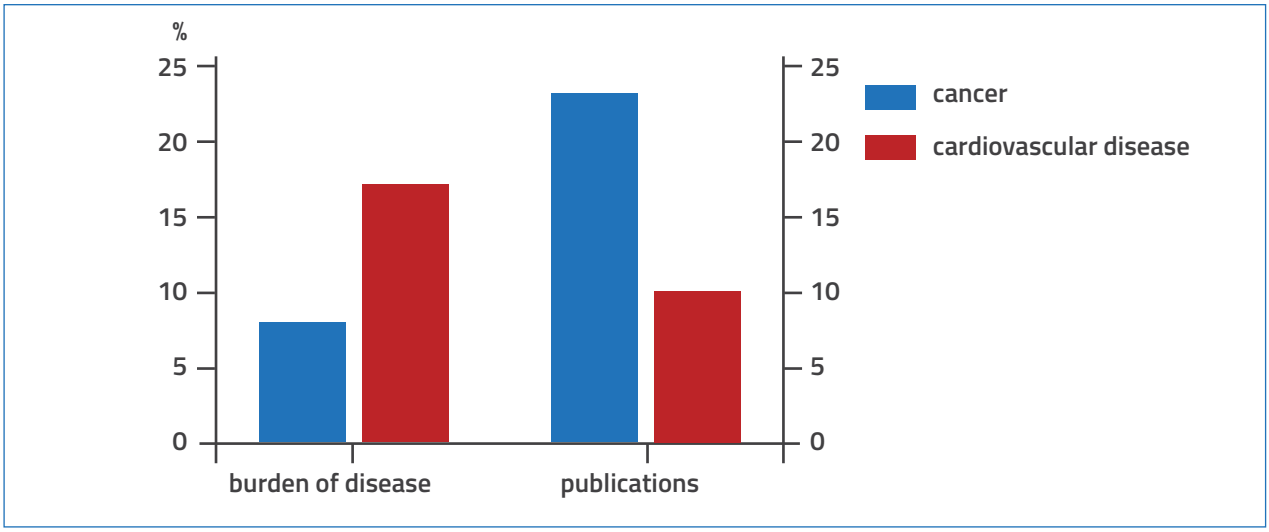

Figure 4: The share in % represents the fraction of total global publication output and share of global burden of disease (modified from 7).

Scientific output in Europe as a whole equals that of the USA and achieves high impact through international collaborations within the EU and beyond. However, scientific activity is not on a par with the burden of disease.

B. Research capacity

Universities and university hospitals are major sites for biomedical discovery research in Europe. Dedicated research institutes, collaborative public-private partnerships, and investments in infrastructure from private means strengthen the research capacity of universities. Many of these are world leading, such as the Francis Crick and Wellcome Sanger institutes in the UK, the Fraunhofer and Max Planck institutes in Germany, the CNRS and Inserm in France. The ability to translate research towards clinical benefit is enhanced by the increasing number of fully integrated medical research partnerships between universities and hospitals in major cities.

The European Commission (EC) has recognised the importance of capitalising internationally on the high quality of academic research with the formation of the European Strategy Forum on Research Infrastructures (ESFRI), the Bio-banking and BioMolecular Research Infrastructure consortium (BBMRI), the European Clinical Research Network (ECRIN) and ELIXIR for pan-European integration of bioinformatic resources.

Beyond discovery research, the translational research capacity through the biotech sector however performs less well in the EU than in the USA, notwithstanding successful examples in the area of CVD. Europe has a rich portfolio of biotech companies, often clustered in hubs associated with academic research campuses, but growth and expansion are not as strong as in the USA, despite programs at European level to incentivise Small and Medium Enterprises (SME) development.

With regard to clinical research, mapping of ongoing clinical trials as available through clinicaltrials.gov indicates that there is a global shift with many CVD trials being performed outside of the EU. Complexity in regulation and fragmentation of the European market may put the EU at a disadvantage in the clinical research field. There are further concerns that the workforce for biomedical and clinical research is under pressure through restrictions in career paths, training that is not adapted to the new demands of multidisciplinary research and a high clinical workload threatening the physician-scientist model.

Taken together, Europe has a strong infrastructural foundation to maintain and increase the quality and impact of European biomedical research. There are national examples of centres of excellence in CVD research, including the DZHK (German Centre for Cardiovascular Research), CNIC (Centro National de Investigaciones Cardiovasculares, Madrid), DCVA (Dutch CardioVascular Alliance) and the BHF (British Heart Foundation) Centers of Research Excellence.

Europe has a large research capacity for CVD linked to a strong system of higher education, infrastructures and partnerships. Yet the translational and clinical CVD research performance could be significantly enhanced.

C. Research funding

The CardioScape database, an EU funded project under the leadership of the European Society of Cardiology, is populated with over 2400 academic-led cardiovascular research projects funded over the period, as well as a compilation of funding sources across all EU28 countries during 2010–2012 ***(8).*** ERA-CVD is supporting CardioScape to update the project data, providing a new snapshot and allowing analysis of funding trends: the project is due to report in 2019.

Over €1 billion was awarded to academic CVD research in the EU28 in the years from 2010 and 2012. Governmental and public funding accounted for 53% of total spend of which EU funding under FP7 is the majority, contributing 37% of the total, while charity/private agencies provided 47%. The CardioScape findings indicate that few research programmes were at a large scale: the large majority of projects (70%) had an average grant level of €100,000 or less per year. The highest funding level is in the UK, followed by Germany: the level of funding is correlated with national Gross Domestic Product (GDP), while CVD mortality is higher in low GDP countries (Figure 5).

CardioScape also shows that the distribution of CVD research funding between basic, clinical and epidemiology/public health research is very different in various countries. However, overall it is highest for clinical research and lowest for epidemiology/population/public health research. EU funding was predominantly for clinical research. There are also substantial differences in funding source between countries (Figure 6). In a few (e.g. UK and The Netherlands), non-governmental organisations are the majority funders, reflecting a large philanthropic/charity contribution to biomedical research, but in most countries governmental funding predominates.

Cardioscape reports publicly available data of CVD research funding by governments and charities, but does not include data from private investments. Accurate figures for the level of CVD research and development (R&D) spent directly by Pharma and Medtech industry in Europe are not available, but across all fields, the investment by industry exceeds that of the public sector, and relates to the cost of final product-

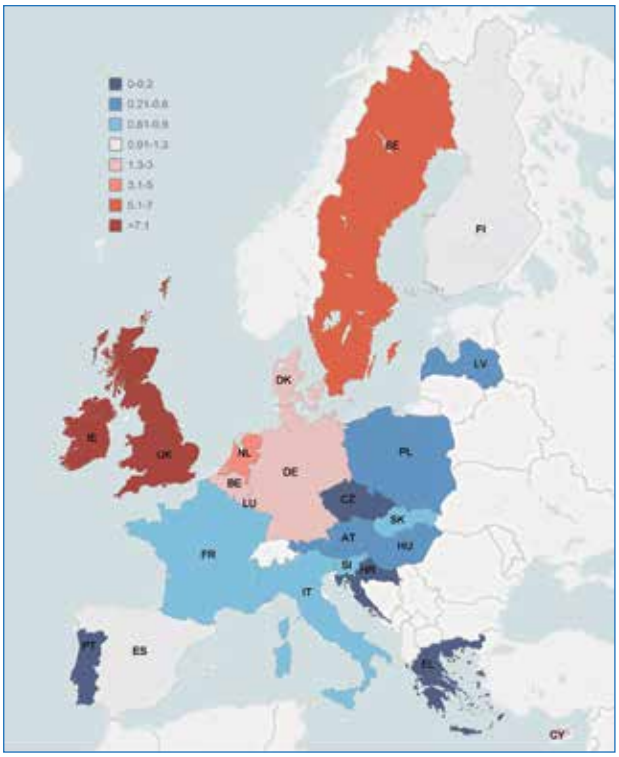

Figure 5: *CVD research funding per capita and year across Europe (2010–2012, 8).*

to-market development. A significant source of funding for CVD research is through project-linked partnership between academia and industry. In particular, all large multi-center Phase III trials involve a huge investment. However, investment by major companies in CVD research and development across Europe has declined significantly in the last decade, with the loss of some major players. At the same time, though Europe remains the largest hub for clinical trials globally, the increasing positioning of major trials in China is eroding this position.

The funding landscape for cardiovascular research in Europe is rich but fragmented. Disparities in research investments across European countries align with disparities in research outputs in CVD.

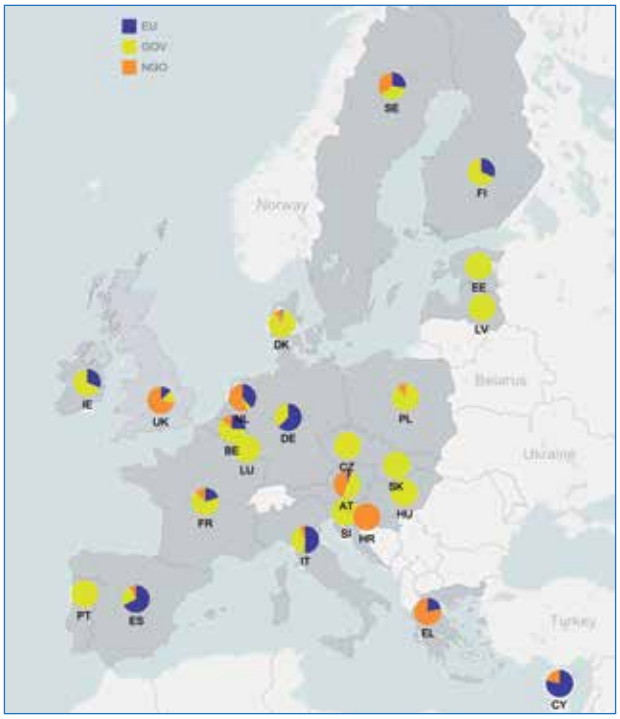

Figure 6: Proportion of governmental, private and EU funding across Europe (2010–2012, 8).

D. European innovation in cardiovascular medicine

Globally, translation of CVD research to clinical benefit has declined for more than a decade in terms of new drugs coming to market, in relation to the large increase in research and development cost per success, while at the same time there has been an increase in new anticancer drugs ***(9).*** This trend was recently confirmed in data from the USA ***(10)*** and is equally apparent in the records of the European Medicines Agency (Figure 7).

The relative failure of CVD drug development has in the majority of cases been due to poor efficacy, demonstrable only after large scale and lengthy expensive clinical

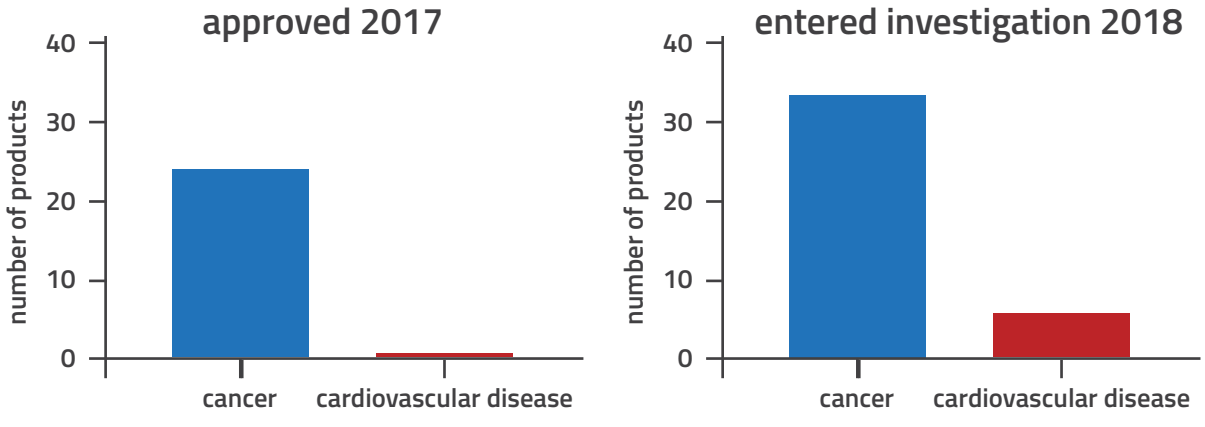

Figure 7: New products approved and under investigation. Data based on 2017 Annual Report, and the 2018 monthly reports of the European Medicines Agency (EMA, www.ema.europa.eu/en).

trials. Even so, the vast majority of recently filed patents in the cardiovascular field originate from the USA. The number of patents filed since 2014 by Germany, France, Italy and the UK altogether is only 35% of the number of patents filed by the USA ***(11).***

CVD treatment has benefited substantially in recent years from device and technology development: implantable therapeutic devices, diagnostics, and imaging devices. The roots of several market leaders are in Europe (e.g. Philips, Siemens) and together with Small and Medium Enterprises (SMEs) Europe has contributed to major developments, for example in the field of cardiac imaging. Here in particular, automated analysis and self-learning algorithms have introduced Artificial Intelligence technology (AI) to CVD research ***(12).***

Development of 'Big Data' platforms and AI (see below) has however largely taken place in the private sector and outside Europe (e.g. Google, Dr. Watson). Nevertheless, the organisation of health care in Europe and access to patient e-records creates substantial opportunities for CVD research that have not yet been fully exploited. Notable success stories include the burgeoning data analysis from the SwedeHeart registry, UK Biobank, and the Estonian National Institute for Health Development. However, much more can and should be achieved.

CVD is lagging behind in new treatments. Europe contributes significantly to innovation but less than could be expected in relation to its discovery research. A large potential exists for stimulation of innovation and better use of health data.

In addition to the introduction of novel products, clinical and population research impacts on cardiovascular outcomes by defining optimal diagnostic and treatment regimens, detecting early disease and identifying modifiable risk factors. The growth in output of clinical research contributes to a large production in clinical guidelines. The European Society of Cardiology (ESC) releases, on average, five clinical practice guidelines per year. However, one of the challenges resulting from this productivity is the implementation and adherence of these new guidelines. This too was one of the conclusions of the analysis in the USA ***(10).***

E. Building a CVD research strategy for Europe

The findings outlined in this chapter demonstrate the need for a more coherent strategy behind the investments in CVD research. At the EU level, chronic diseases have remained within the overall health agenda but without a specific CVD focus except for ERA-CVD.

The major public research investment still rests with member states and there are specific initiatives in member states that aim to boost CVD translation and innovation through collaborative research, as noted in section **B** above. The most comprehensive approach to devise a national CVD strategy in Europe is in the Netherlands, where government, the Dutch Heart Foundation (charity), industry partners, as well as patients and the general public have collaborated to set out a series of strategic research priorities and goals encompassed in the Dutch Cardiovascular Alliance ***(13).***

Overall, a comprehensive health research policy or agenda across Europe is lacking ***(14)*** and for CVD in particular. In the following chapters, we summarise the unmet needs and opportunities in CVD research, provide a set of specific areas for investment and novel research strategies, and detail the recommended research domain. These form the basis for a strategic research agenda for CVD in Europe.

A strategic research effort for CVD at European level should address fragmentation, exploit and expand the existing research capacity and bring investment to match the medical needs.

CHAPTER 3

Unmet needs and opportunities in CVD research

A. Promoting Health – Better prevention and risk detection

Prevention research and public health

For the most common CVD, we know of many important biological risk factors such as age, heart rate, blood pressure, cholesterol levels and the significant influence of lifestyle and other environmental factors, e.g. dietary habits, smoking, sedentary lifestyle. Efforts to reduce risk by improving lifestyle and the external environment are not working well enough. The solutions to these problems lie in behaviour change and a healthier environment, which are outside the remit of pure biomedical research, but there is a growing understanding of the need for large scale and rigorous transdisciplinary prevention research programmes where the outcomes can inform government policy at global, national or regional levels. Such programmes will address multiple health problems and will not normally be disease-specific, but there is an urgent need to ensure that they do include cardiovascular health outcomes. They also need involvement of end users and citizens from the outset. The starting point for prevention programmes is the need for up to date and detailed registries of population health. Several ongoing European consortia curate and update CVD incidence patterns and uptake of medicines or other interventions ***(15):*** it is essential that these initiatives continue to receive adequate funding.

Early diagnosis

Most CVD have their origin in early life, but often are only diagnosed later when common risk factors are measured or clinical events occur. The development of CVD during the life course is often substantially affected by environmental influences (e.g. air pollution, ***16***) and we still only partially recognise or act on these. A significant area of unmet need is therefore to detect signs of CVD risk early in life, and to adapt the health system to be able to use these to manage individual risk more effectively.

Further research is needed to understand whether novel early risk biomarkers will have a strong predictive value additional to current conventional later life measures of risk, such as adult high blood cholesterol levels (hyperlipidemia) or hypertension. As noted in section D below, recent advances in biotechnology and artificial intelligence now provide unprecedented research opportunities to transform this field.

B. New Concepts for better treatment and personalised medicine

Heart attacks, stroke and heart failure

Several new treatment strategies for CVD have been evaluated during the last decade. However, large trials, requiring many thousands of participants and a total investment of billions of Euros, designed to reduce mortality and morbidity from heart attack or stroke by novel lipid lowering or anticoagulant drugs have mostly shown little benefit beyond current treatments.

This has emphasised the need for further preclinical and clinical research to identify new drug targets and medicines directed at these targets. One of the clear success stories for heart disease, particularly in patients with genetically determined hypercholesterolemia, is the targeting of the metabolic enzyme PCSK9 to lower cholesterol beyond levels achievable with statins ***(17).*** One of the few truly novel findings, however, comes from the CANTOS trial, which showed that reducing inflammation with an antibody that blocks a specific cellular inflammation pathway also reduced cardiovascular event rates beyond that achieved with statins ***(18).*** Both of these new approaches included strong contributions from research and therapeutic development in Europe.

In heart failure, several trials with drugs targeting new candidate pathways have failed. Biologicals, including gene and cellular regenerative therapies, also have yet to show positive clinical benefit, but important lessons have been learned. Amongst others, biologic product

standardisation and improved delivery methods are important challenges that need addressing.

Other vascular diseases

Two further major causes of CVD death and disability are currently poorly treated. The mechanisms leading to abdominal aortic aneurysm (AAA) are not understood, so that surgery, often immediately after a near fatal rupture of the blood vessel, remains the only treatment. Further research to enable asymptomatic AAA detected by screening to be stabilised or reversed by medical treatment is urgently needed. Similarly, in critical limb ischemia, despite known strong links to smoking and diabetes, there are only weakly effective interventional treatments and the condition is the major cause of lower limb amputation.

Personalised medicine

The CANTOS trial by itself is unlikely to change clinical practice because of the high cost of the drug and the small absolute benefit. However, it points to several important ways forward. First, there is a need to understand whether a cheaper anti-inflammatory drug could have similar benefit. Second, there is a need to improve the design of CVD clinical trials. Current costs of large industry-led trials, such as CANTOS, are prohibitive (hundreds of millions of dollars). The availability of routinely collected primary care CVD health data offers huge opportunities for patient recruitment and follow-up at much lower costs, particularly if combined with simplification and revision of the present over-complex systems of trial governance and reporting. Further improvement is possible by focussing on a particular subset of patients who may obtain greater benefit from the treatment. With informed use of biomarkers, including those discovered using the innovative strategies described in section D below, careful patient selection can lead to the smarter design of more cost-effective trials and the consequent application of the outcome to defined patient groups – i.e. stratified or personalised medicine. There are other new areas of clinical trial design that need to be considered for CVD, such as adaptive trials where interim data analysis can be legitimately used to alter the trial protocol going forward, potentially saving money and time.

The underrepresentation of women in CVD trials is a particular concern, as the symptoms and pathophysiology of disease may be different from men. Furthermore, there is also need for increased investment in CVD research to understand and reduce the consequences of cancer therapy on the heart – a growing problem that has led to the creation of cardio-oncology as a new medical specialty.

A significant area of unmet need is to detect CVD in individuals earlier in life, and to prevent the occurrence of an acute CV event with concomitant irreversible damage.

C. Addressing health care costs through better management

The annual economic burden of CVD in Europe (***2, 4,*** see also Chapter 1) can be differentiated into three separate figures:

- €111 billion (53%) is due to direct health care costs
- €54 billion (26%) is related to productivity loss due to morbidity and mortality
- €45 billion (21%) is due to informal care cost supported by carers

To alleviate this financial health budget, new therapies are needed to target patient populations with the highest risk of developing recurrent cardiovascular events, namely patients with associated co-morbidities. Strategic planning and analysis are required to define where the maximum health and economic benefits can be gained by improved prevention and treatment of CVD, thus enabling prioritisation of research resources with a

The diminishing pipeline of new CVD treatments and the increasing expense of clinical trials need to be tackled by a greater emphasis on matching discovery science to unmet clinical needs and by radical changes in clinical trial methodology.

full understanding of the long-term financial and societal gains that will result from the research endeavour.

In parallel the modes of care delivery need to evolve to match the changing scale and pattern of CVD. Implementation research is needed to identify and understand how to overcome barriers in the delivery of the best possible treatment and care for CVD patients: these barriers may include skills shortages in health provision, organisational changes required to allow more efficient and effective patient journeys between communities, primary and specialised care, and financial barriers restricting access to state-of-the-art treatment.

Furthermore, the increasing burden of multi-morbidity necessitates better integrated care pathways across disease boundaries. The involvement of patients from the outset in the improved design of healthcare delivery is critical, and this needs to be enhanced.

Healthcare delivery needs to evolve to match the changing scale and pattern of CVD, particularly with the increased level of multi-morbidity.

D. Opportunities for early disease detection, better treatment and care

Big data and biomarker discovery

Rapid advances in biotechnology have enabled new ways to discover previously undetectable biomarkers. These include the ability to obtain every individual's complete DNA sequence (the genome) and study how variation in this predicts disease susceptibility. Further sophistication of related technologies, collectively termed "-omics", enables detailed quantification of the molecular content of cells and tissues, including proteins and small molecules.

Advances in bio-imaging technology (such as Magnetic Resonance Imaging, MRI and Computerised Tomography, CT) are providing ever more detailed understanding of the anatomy and physiology of internal organs and blood vessels, including non-invasive beat by beat characterisation of heart structure and function and accurate quantification of changes that occur in disease.

Taken together, "-omics" and imaging technologies produce huge amounts of data (terabytes) defining the unique biology of an individual. In principle these can be linked to a wealth of other information about the individual, including health and social care records and indicators of socio-economic status.

This unprecedented volume of data – commonly termed 'Big Data' – is thus the source material to discover new algorithms for early detection of CVD. Thanks to associated advances in computational analysis like machine learning, artificial intelligence, the combined datasets from large numbers of individuals can be mined to detect entirely new biomarkers (in connection with "-omics" and imaging technologies) that will be tested for their value either as indicators of new and unexpected disease mechanisms, or can be used to personalise patient treatment.

Big data and machine learning have the potential to enhance and personalise cardiovascular health by early detection of disease.

There is an urgent need to adopt these technologies to improve the diagnosis of CVD. Some early examples of their application exist, such as the large transformative project "One Brave Idea" led by Dr Calum MacRae in Harvard to detect novel early biomarkers of CVD and use these to stratify risk and treatment options.

Machine learning applied to cardiac MRI images has been used to define the normal range of cardiac anatomies and to detect anomalies the UK Biobank cohort ***(19),*** and in addition to demonstrate previously undetectable abnormalities in non-symptomatic people carrying mutations predisposing to cardiomyopathy. However, these projects are only the beginning of a much wider use of these technologies to improve the detection and treatment of CVD patients. Cross-disciplinary and transnational consortia are needed to maximise their potential.

A further benefit from the availability of big data, to date exploited particularly in CVD and with significant promise, is the ability to carry out "virtual trials": by correlating the level of a biomarker for CVD risk with the experimentally measured effect of population-level natural gene variations on the level of the biomarker (Mendelian randomisation) it can be determined whether the risk factor does or does not lie on a pathway that causes disease and thus whether the pathway is or is not a candidate for drug targeting. Being able to rule out a causal link saves many millions of Euros from being wasted on drug development and trials for an irrelevant target: sadly there are examples where failure to take advantage of genomic data has led this to happen.

The potential gains in healthcare from the ability to analyse big datasets are enormous, but this can only take place in the context of regulations that ensure the appropriate ethical and legal use of personal data – a topic of great importance that is being intensively investigated but beyond the scope of the agenda presented here.

Reparative and regenerative medicine

The much vaunted hope that stem cell therapy could overcome the inability of a heart to repair after damage by a heart attack or cardiomyopathy, inspired by promising experiments in small animals, has led to a series of expensive clinical trials that to date have not shown significant patient benefit. It has become clear that the initial premise – transformation of injected stem cells into beating heart cells – does not occur. Nonetheless, this field is making rapid progress towards clinical application by an alternative approach, made possible by the discovery that adult tissue cells (e.g. from skin biopsies) can be reprogrammed in culture to form induced pluripotent stem cells (iPSC) that can be expanded and differentiated into heart or blood vessel cell types. Bioengineered patches or grafts containing iPSC-derived cells from patients have already been tested in animal models, not only to repair adult hearts, but also to form living grafts for children needing surgery to repair structural abnormalities in congenital heart disease. Other cell types, such as multipotent umbilical cord cells, standardised as "off-the-shelf" investigational medical products are being tested in current clinical trials.

Genetic diseases and gene editing

The ability to generate iPSC-derived heart cells from patients with inherited or acquired arrhythmias or cardiomyopathies has initiated two major research areas that need further development. In the first, the patient's cells are used to define the existing genetic and molecular alterations, and to develop high throughput assays in culture to screen for candidate drugs to correct cell function. Even more provocatively, but now demonstrated in animal experiments, the advent of new biotechnology (e.g. CRISPR/Cas9) that can specifically repair the DNA mutation causing an inherited heart condition offers the promise that at least in some cases these diseases could be cured.

Devices

Significant CVD disease burden and premature mortality are caused by heart valve diseases. Their biology is poorly understood and treatment is primarily by mechanical repair or replacement. The field is rapidly advancing due to continued development of more sophisticated techniques to deliver interventions by catheters introduced into peripheral arteries, removing the need for open heart surgery. At the same time, there are advances in the generation of bioengineered valves that have the potential to be safer and more effective than mechanical valves.

In parallel, technological advances are miniaturising and improving the lifespan and efficiency of implanted cardiac devices to control heart rhythm or improve pumping, including wireless technology to eliminate the need for electrical leads from outside the body.

Wearables

We are at the beginning of a revolution in the ability of patients' CVD risk biomarkers (e.g. heart rate, blood glucose, blood pressure) to be continually monitored non-invasively by simple wearable devices. The datasets generated can be computationally analysed within the device or be transmitted wirelessly to health care providers, in order to automatically detect abnormalities signalling the need for altered medication, which is relayed back to the patient or medical consultant. For chronic non-communicable diseases including CVD this

e-health technology, provided it ensures maximum data protection, has the potential for huge patient benefit, and substantial implications for the organisation of health care delivery systems.

Developing novel therapies and wearables needs to take place in parallel with improving strategies to support people to achieve healthier lifestyles.

E. The framework for future CVD research

Figure 8 illustrates the central role of CVD research in the translational space between the major challenges for cardiovascular health and the implementation of improved cardiovascular health in the population. It summarises the types of research needs and opportunities arising from the challenges, and notes how a series of elements of the healthcare system need to be ready to translate the results from the research into patient benefit. Overarching recommendations to reduce barriers to progress within this framework are discussed in the next chapter.

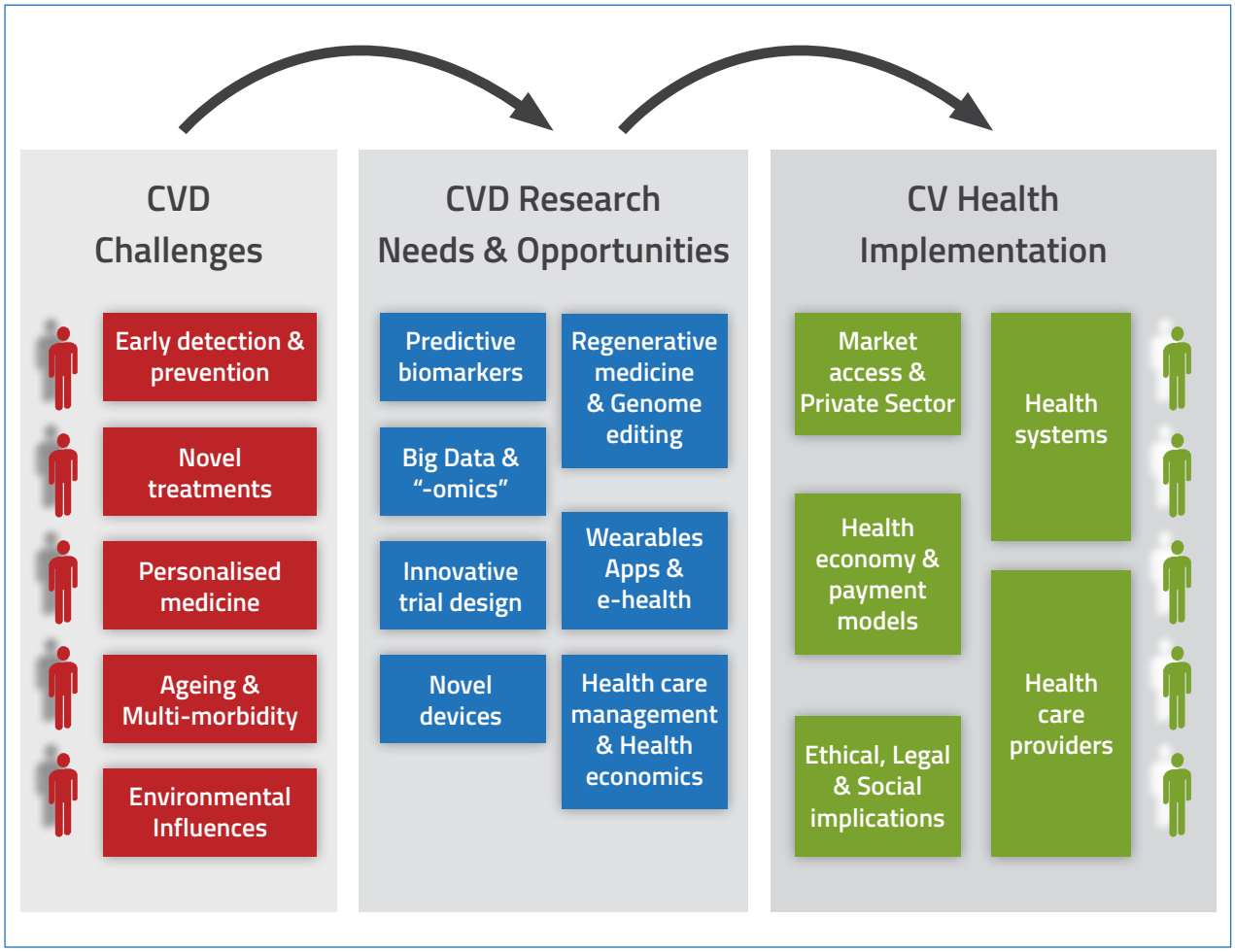

Figure 8: Schematic overview of how challenges, needs and opportunities of CVD research are connected to implementation within health systems

CHAPTER 4

Future challenges for cardiovascular research: Overarching recommendations

The preceding chapters have summarised the current state of CVD research in Europe and identified unmet needs and opportunities to tackle them. Here we provide a roadmap to meet these challenges.

A. Recognising the urgency of the problem

As noted in Chapter 1, the health and socio-economic burden of CVD in Europe and worldwide is greater than for cancer or any other disease. However, research funding is disproportionally low at a national and EU level across Europe. CVD and its risk factors feature very little in the call descriptions for Horizon 2020 funding, and the number of projects funded related to CVD is far fewer than those related to cancer for example. Recognising that many of the overall themes in Horizon 2020 are relevant to CVD research – such as chronic disease management, biomarkers and risk-based screening, the application of machine learning and artificial intelligence to health data or environmental effects on chronic diseases – the lack of funded CVD projects is a major concern. As the next framework programme, Horizon Europe is developed, cardiovascular policy makers, healthcare professionals, patients and researchers must advocate strongly to influence the shape of the final programme and to take greater advantage of the funding opportunities it presents.

B. Seizing the opportunities that new technologies bring

Detailed unique personal description of human physiology and pathology is now possible using "-omics" technologies (see also Chapter 3). Together with environmental, health and social care records these generate big data with high potential for biomarker discovery and personalised medicine. CVD research must significantly increase in this space to deliver better cardiovascular health.

C. Ensuring the pipeline from scientific discovery to patient benefit is secure

New discoveries in fundamental biology are increasingly driven by novel technology, ranging from visualising the distribution of specific molecules in real time in single cells to the ability to permanently repair a faulty gene in relevant tissues with exquisite accuracy. With few new CVD drugs in development, basic research is vital to understand disease mechanisms and to define new targets. In addition, novel bioengineering strategies promise a new generation of living grafts to repair damaged hearts or blood vessels. CVD research funders must not lose sight of the imperative to continue to support basic science: without discoveries there will be no future pipeline towards patient benefit. In addition, the benefit of new CVD drugs should not be unnecessarily lost in the clinical development phase due to the financial burden of trials and market launches, policies regarding competition between generics and branded products, and reimbursement rules at national level.

D. Accelerating the timeline to delivery of patient benefit

Faster delivery of benefit to CVD patients requires tackling several different aspects of the research ecosystem, each of which needs improvement.

Quality and availability of biomedical research data

Biomedical research should be reproducible and validated, using improved disease models, providing high quality data that can be shared and re-used, and thereby support fast development in biotech and industry. Negative data from biomedical and clinical research, should likewise be easily accessible.

Building research capacity and career development

The best research requires talented and skilled researchers. Particularly in cardiovascular medicine, and even more so in areas with significant unmet research needs such as vascular surgery or paediatric cardiology, the ability to combine clinical care with a research career is challenging. To achieve the scale and diversity of research talent needed to tackle CVD research there is an urgent need for national health systems to have the flexibility to allow research talent

to flourish and for research funders to continue to provide personal fellowship awards to enable clinician scientists to build their careers and develop leadership qualities. Both early career scientists and their mentors need to acquire improved skills in navigating the regulatory and commercial environment to ensure the route to translation of their research programmes is understood from the outset, otherwise research money is wasted. Specific effort should be made to develop innovation centres bringing together basic scientists, clinicians, intellectual property and patent valorisation offices to foster an entrepreneurial culture of scientific translation across Europe. Availability of non-dilutive funding (e.g. loans or grants) might also create a competitive advantage for EU start-ups.

Enhancing prevention research and implementation

As noted in chapter 1, while many modifiable risk factors for CVD are understood there is still patchy uptake of measures to improve population cardiovascular health. Rigorous prevention research studies with results that have national significance are needed to understand the best ways to create a society with better cardiovascular health ***(20).*** These will require multi-disciplinary approaches engaging expertise from far beyond cardiovascular medicine, such as social science and environmental planning. Many patients are still not receiving treatment and care according to best practice guidelines nor the care that may improve their health-related quality of life; this requires implementation research to identify barriers in the health system to delivery, and barriers to compliance in patients.

Smart thinking in clinical study design

The cost and complexity of event-driven clinical trials in CVD are becoming prohibitive. Radical approaches are needed to overcome this problem. These include more refined inclusion criteria using personal biomarker and genomic data to select individuals most likely to show benefit, the ability to collect outcome data simply and electronically as well as digital health data thus minimising the need for expensive face-to-face patient/clinician appointments, and consideration of adaptive trial designs. Underpinning this is the urgent need to be able to access and integrate large inter-operable health data sets combined from different sources and interrogate them; realising ambitions to create transnational cardiovascular health data science centres will greatly enhance the pace and scope of research while reducing costs. The reduction of pharmaceutical companies leading clinical trials in the field of CVD needs to be compensated by increasing the number, funding and relevance of academically-driven clinical trials.

E. The need for transnational and multidisciplinary collaboration

There is good evidence that multinational collaboration in CVD research leads to higher impact. Research on the more common CVD needs large scale investment to enhance discovery and yield significant patient benefit. For less common CVD the need for multinational collaboration is just as great, so that patient numbers are sufficient to reach valid conclusions.

A further clear signal is that optimisation of CVD research needs increasing collaboration with expertise well outside the specialty, such as computational scientists, bioengineers, social scientists and health economists. This is in addition to continued tight linkage with medicinal chemistry and drug and device development, mainly taking place in the private sector – whether at the level of biotech SMEs or big pharma. The changing nature of the CVD patient, often older and with co-morbidities has implications for the breadth of clinical expertise needed in trial design.

Underpinning all this is the need to involve patients and the public meaningfully at all stages of clinical research, from the design of a study to analysis and commentary on its outcomes, and in the prioritisation of unmet need. This is not specific to CVD research, but the contribution of patients can make needs a significant improvement and research funders can play an important role.

F. Modernising the funding landscape

The majority of European CVD research funding is national, and often fragmented within one country. This inevitably leads to duplication of effort and is also likely to generate results that have limited international impact. Going forward there is a need to map the portfolio of CVD research across Europe accurately and dynamically using mechanisms such as CardioScape and other European platforms. These will support priority setting by funders, together with an expansion of multinational funding partnerships including the private sector. While Horizon 2020 projects and its associated early career Marie Skłodowska-Curie fellowships are exemplars of this approach, as noted above the funding of CVD research in Horizon 2020 is relatively low and there is opportunity for other European CVD research funders to work together for mutual benefit. This could lead to a dedicated multinational CVD research fund, promoting long-term support of productive consortia, acting as a focal point to attract private finance.

Bringing together multiple CVD funders from different nations, as has been achieved with the current ERA-NET CVD award, has been an important first step on this journey. It has also provided the collective resource to enable the production of this Strategic Research Agenda.

CHAPTER 5

Tackling challenges for cardiovascular research: Topic driven recommendations

In Chapter 4, we identified important overarching strategies to improve innovative cardiovascular research across Europe. In this chapter, we focus on more specific topics that are either on the rise and will become major societal problems in future European health care or topics that, despite major efforts, are still facing significant unmet needs. Scientific breakthroughs and translation into clinical implementation will have major impact on society and individual well-being. The topics are divided over three research areas:

- **Prevention Strategies**
- **Treatment and Management**
- **Living with chronic Cardiovascular Diseases**

15 research domains in three areas are listed below as perceived priority challenges for CVD research as well as the health systems.

A. Cardiovascular disease prevention strategies

Several risk factors for CVD have been known for decades that are modifiable: for example blood pressure, obesity, smoking, physical inactivity, stress, environmental pollution; or non-modifiable such as age, gender, genetic background, ethnic group. Public health policy measures to reduce CVD incidence and morbidity such as the ban of cigarette smoking in public places, the promotion of healthy diet and exercise are not effective enough. New technologies to monitor lifestyle and groups at risk so far have failed to succeed in robust assessment tests. Therefore, several research domains should be supported that can impact CVD morbidity in the next decade.

1 – New ways to sustain a healthy lifestyle in the long term

Maintaining a healthy lifestyle appears to be difficult for an increasing majority of the population despite the general acknowledgement of the benefit of keeping risk factors for cardiovascular disease as low as possible. This not only applies to young people – for whom cardiovascular disease will often not develop for some time – but also to patients who, after a period of intensive rehabilitation have difficulties maintaining the healthy lifestyle by themselves. So far research has not delivered any effective strategy to improve healthy lifestyle maintenance. Research in this area will have to explore whether optimal use of new technologies like intelligent wearables will offer personalised innovative and effective solutions to this problem. Collaboration with public health authorities, press and media representatives, nurses, pharmacists, school teachers, sport centre trainers, urban planning bodies, food industry and patient associations will be an essential part of the future strategy.

2 – The earlier recognition of cardiovascular disease

Myocardial infarction, cardiac arrest and stroke strike often suddenly and without warning. Current treatment of these acute events is triggered by the onset of symptoms when first irreversible damage starts to develop. Research should make it possible to recognise disease days to weeks before the onset of the acute event and, in this way, enable personalised treatment to effectively prevent irreversible damage. The benefit of this strategy should lead to a reduction of the large and growing number of patients with chronic cardiovascular disease. Examples of early diagnostic strategies include integrative approach of the use of non-invasive imaging techniques and measuring circulating biomarkers. Integration of these data with the increasing number of personal "-omics" data of patients will require the use of artificial intelligence and machine learning techniques. Furthermore, the use of patient generated data through the assistance of wearables may be of help in early recognition of imminent acute events. Research can also help to make the correct diagnosis quickly in people whose complaints may not necessarily be

suggestive of cardiovascular disease in the first instance. Adequate therapy should be in place or in development. Setting up these systems using personalised data on line will be a challenge within the ethical and privacy boundaries as defined across Europe at the moment.

3 – Better assessment of the personal risk of cardiovascular disease

Current models for assessing personal risk for developing a cardiovascular event in the next ten years do not take into account issues such as genetic predisposition or, for example, stress and socioeconomic background. In addition, the current recommendations on healthy diet and sufficient exercise are very general. Research in this field should provide insight into the individual risk of cardiovascular disease by making optimal use of all personal medical, environmental and social data available. It will have to generate the possibility to give tailor-made advice: both with respect to life-style and preventive treatment. Furthermore, it will create the ability to monitor changes in risk and adherence to life-style behaviour and preventive treatment.

B. Cardiovascular disease treatment and management

Despite the multiplicity of randomised clinical trials in patients with cardiovascular disease, the additional benefit generated from the use of novel drugs remains very modest. Therefore, advances in therapeutic management are stagnating. One important reason for that stagnation is the focus on the optimisation of therapies that pursue already treated pathophysiological processes, leading (at best) to incremental improvement in outcome, and the limited number of studies that test newly discovered, non-redundant and critical disease-causing or aggravating pathways. Moreover, clinical trials addressing the relevance of pathways common to co-morbidities and cardiovascular disease are almost non-existent. In general, future research should focus on discovering new pathophysiological pathways in disease with high societal impact such as chronic cardiovascular disease in the growing elderly population. The following recommendations identify research topics that should be addressed by collaborating researchers, health care professionals, patients and industry across Europe. Together these consortia have to generate solutions related to the topic. National and European funding should be directed at the level of these consortia.

4 – Personalised treatment and management of cardiovascular disease

Future research should provide insight into which medications are best for whom. How are the effects and side effects from medications influenced by other factors such as diet, nutritional supplements, genetic predisposition and other diseases that the patient has? Research helps to tailor treatment to the individuals' circumstances and co-morbidities. In this respect, technical solutions continuously monitoring surrogate readouts may be of individual help. They can be also of importance to achieve optimal adherence to treatments, one of the biggest challenges in modern pharmacotherapy. In addition, strategies for improving drug adherence need to be designed, especially for example in patients with high blood pressure.

5 – Effective treatment of stroke

Acute management of stroke has reached the point that there are innovative strategies developed to effectively remove thrombus from cranial arteries. There is now urgent need to have early diagnostics available to differentiate between cerebral haemorrhages versus infarct. Furthermore, it should be investigated whether additional pharmacological treatment may generate better clinical outcome and which secondary preventive treatments have to be initiated. The field of vascular neurology is about to change dramatically, comparable to the big change in cardiology in the last two decades of the previous century when invasive treatment for the treatment of myocardial infarction was introduced. Lessons learned in that era should be taken into consideration when further optimising acute treatment of stroke. In this regard organisation of acute care facilities will be as important as the development of the treatment itself.

6 – Treatment of chronic heart failure and atrial fibrillation

Over the last three decades cardiovascular research has generated effective strategies to treat acute myocardial infarction, one-year mortality decreased from 30% in the beginning of the eighties to less than 3% at present. Cardiovascular disease has become chronic in nature. This, in combination with aging of the population across Europe and occurrence of co-morbidity factors, will result in an increase in the prevalence of heart failure and atrial fibrillation. Research in this area should result in treatment strategies that can reverse the pathophysiology responsible for these diseases. Special attention should be given to heart failure with preserved ejection fraction. Results of this research will contribute to healthy ageing of present and future populations.

7 – Improved application of implantable devices

Implantable devices are an important part of the treatment of cardiovascular disease. In some areas, technical solutions have proven to be more effective when compared to pharmacological strategies. However, critical evaluation of effectiveness between devices is often lacking. Research in this field should continue to develop innovative technical solutions for treatment of cardiovascular disease but should also develop new methodology to assess objectively the cost-benefit of these newly developed devices. In parallel, technological advances are miniaturising and improving the lifespan and efficiency of implanted cardiac devices to control heart rhythm or improve pumping, including wireless technology to eliminate the need for electrical leads from outside the body. This development will enable earlier detection of disease deterioration and/or personalised monitoring of treatment effects. EU-based common and shared databases of implanted devices need to be implemented and readily available to physicians and researchers.

8 – The interaction between CVD and other disorders

Cardiovascular diseases often co-exist with other diseases or organ dysfunctions. Given the already identified change of cardiovascular disease from an acute to a chronic disease, the interaction of chronic cardiovascular disease on other morbidities (and the reverse) is increasingly important. Research in this field should generate new insights how these interactions may be translated into combined treatment of both disorders. Important is the potential interaction of cardiovascular disease and cancer or cardiovascular disease and diabetes/obesity. This is not only important at the level of drug related interaction for these diseases, but certainly also for the interaction in the pathophysiology of both diseases. Spin-off from this research will be the increased coordinated multidisciplinary approach for patients and will be key in designing an effective strategy for healthy aging.

9 – Repair of the heart and blood vessels

Regenerative medicine has introduced the prospect that repair of damaged organs may be possible. However, the results of clinical studies performed in various cardiovascular disorders have been very disappointing despite the presence of positive experimental data. Given the present situation, a step back to the bench seems logical. Lessons from cell-based therapies indicate that, rather than transplanting cells that directly engraft and differentiate/proliferate in the host tissue, delivering factors released by these cells may be sufficient to activate repair mechanisms. This hypothesis has opened new avenues for cell-free therapies in cardiac regenerative medicine. Current efforts are also trying to identify clinically useful factors or molecules that can regenerate the damaged heart and/or to pre-condition therapeutic cells. An alternative approach is made possible by the discovery that adult tissue cells can be reprogrammed in culture to form induced pluripotent stem cells that can be expanded and differentiated into heart or blood vessel cell types. Of note, bioengineered patches or grafts containing stem cells from different origins have already been tested in animal models. A complete understanding of molecular and cellular mechanisms governing cardiovascular development and physiological and pathological signalling will also likely open the way for new therapeutic avenues.

10 – Cardiovascular disease in segmented, yet underrepresented populations

Many diagnostic and therapeutic methods are based on research performed in Caucasian men. The question is whether they can also be applied to women, other

ethnic groups or other groups not represented in the study data available. Repeating the original studies including all under represented patients is not cost effective and not feasible. Research in this field will have to provide new methodology to address this question in future studies. Insight into differences in pathophysiology over the whole spectrum of diverse populations is an important approach, but addressing the social end of improving treatment may be equally interesting. Accruing evidence highlights that women and men experience cardiovascular disease differently and suggests the need for further work to clarify the biological, behavioural, or social mechanisms involved.

C. Living with chronic cardiovascular diseases

Psychosocial aspects of CVD must be taken into account in order to reduce the burden of disease and negative impact on disease treatment and other disorders. Therefore collaboration with public health authorities, press and media representatives, nurses, pharmacists, school teachers, sport trainers, urban planning bodies, food industry and patient associations will be an essential part of a future strategy.

11 – Cognitive dysfunction as a result of cardiovascular disease

Cardiovascular risk factors including diabetes, hypertension and obesity, smoking and physical inactivity are key determinants of cognitive dysfunction. In an aging population with increasing prevalence of chronic CVD across Europe new insights are urgently needed to develop multiple optimal strategies targeting the cardiovascular compartment in at risk elderly patients. Tailored interventions to the individual risk profile in some optimal time windows such as intensive blood pressure treatment, diet and vascular health intervention may counteract cognitive decline. Research in this field should provide understanding into the intrinsic crosstalk between cognitive problems and co-morbid lifestyle diseases including cardiac as well as large and small vessel dysfunction.

12 – Living with a congenital heart defect

Young patients with a congenital heart defect increasingly experience a hand off in care between the paediatric and adult care environments as their survivability increases. With this transition a significant change in the supports they are provided with may come, depending on their specific context and care environments. Preparation for this transition may be less than optimal in many cases and these individuals can be affected by many different problems such as work restrictions, and over time other cardiovascular disease. Patients require support beyond their immediate needs relative to their physical wellbeing. Survivorship results in a much greater range of considerations for condition management as patient potential life courses develop. Paediatric cardiologists and adult cardiologists should also work together to better inform patients about their increased risk of further CVD. Research on women's health is expanding knowledge as to the cardiovascular implications of pregnancy, both in the immediate state as well as potential long terms risks. However, much is yet to be further understood particularly with respect to specific patient sub-populations such as women with congenital heart disease. Similarly, occupational health, safety research and labour legislation principally focus at a population level, and thus provide fewer insights with respect to this same sub-population. Hence, future research should be focused to provide better care and guidance that best suits the patient's personal situation.

13 – Communication and collaboration between healthcare professionals, patients and citizens

Treatment is more successful if both parties, health care professionals and the patient, are well informed and together decide on the disease management program. For example, this is particularly relevant for the growing community of people with congenital heart disease.

Informed consent, while a principle of practice, takes on a more nuanced characteristic as patients' care requirements become more complex and decision implications may be multifactorial. Multiple contextual factors also play a role with respect to transmitting information. Language, vocabulary and health literacy are relatively specific with respect to development and understanding of complex issues. While two persons with differing linguistic backgrounds may be able to develop a shared vocabulary around a new diagnostic concept, other important aspects of decision-making (with respect to emotions, religious belief, etc.) may

not be easily communicated between the physician and the patient. Sex as a biological variable and gender as a social expression are also known to have profound impacts on the care proposed and outcomes achieved. Research in this field should tackle important questions such as accessibility and communication of medical information to the patients, their transition across care settings and the consideration by the physician of age, sex/gender and cultural background. Overall, this research effort will help health professionals and patients to achieve the optimal management together, which meets the needs and wishes of the patient.

14 – Psychosocial wellbeing in patients with cardiovascular disease

Cardiovascular diseases are a condition with a lengthy development and become increasingly a chronic condition to be managed across the life course. As a result of improvements in management of acute cardiovascular disease, survivors may face significant changes to their lives in order to manage with disease. Patients with manifest disease may live many years following diagnosis and many patients with cardiovascular disease are anxious of recurrent symptoms, suffer from depression as a result of their illness, or feel extremely tired. Psychological problems such as anxiety and depression can hamper patients and their partner/family, for example, in work and social activities. There is a significant need for knowledge that supports the mental well-being of persons with cardiovascular disease, and for rehabilitative programs to which patients are able to adhere long term. Outcomes can rely heavily on behavioural changes, which are notoriously difficult for patients to maintain long term without ongoing support to find their way in daily life.

15 – Guidance and care at the end of life phase of cardiovascular disease patients.

Over 10,000 patients die of cardiovascular disease in Europe every day. Some die suddenly, however many are sick over a long period of time. Indeed, as management and treatment of cardiovascular disease has advanced, the burden of disease is concentrating in the elderly population, who has many co-morbidities. As an example, heart failure is theorised by some as perhaps one expression of the general process of ageing. How it is linked to other expressions of disease and how ageing leads to frailty are not well understood. Health systems are not optimally organised to respect the wishes of aging patients for minimal interventions as death approaches. Issues arise with respect to ethical, legal practices and requirements for practitioners in respecting the wishes of patients no longer able to confirm consent to withdraw care. Norms and practices may tend toward major intervention for elderly persons when their wishes would be to see their life end peacefully and with appropriate comfort supports. Serious consideration will need to be taken in future to consider the manner in which care is provided to persons nearing the end of their lives. Research provides insight into what patients and their caregivers need and expect from doctors and other health care providers in the last phase of life. It also shines light onto whether or not current health care practice takes this into account.

Conclusion

An ageing population, improved survival of heart attacks and congenital disease, and a growing incidence of cardiovascular complications of other disease, such as diabetes, cancer, and kidney disease, combine into an emerging epidemic of cardiovascular disease with a different presentation from 40 years ago. Chronic disease, disability and co-morbidities challenge the health care system and require increased efforts for research and innovation at all levels. A strategic investment in cardiovascular research, including regional development, networking within Europe and beyond, and expanding cross-sectoral partnerships, is needed to improve translation, innovation and patient care, and increase cardiovascular health. A large body of guidelines for prevention and better treatment exists but lacks full implementation and evaluation of efficacy. Europe has the capacity for generating large population-based data and needs to invest in proper studies for evaluation of outcome and optimisation of prevention and treatment.

Implementation of existing knowledge is essential but not sufficient. Approaches for early disease detection should take advantage from large data sets at population and cohort level, as well as insights into disease mechanisms generated in basic discovery research. New treatments are needed. Interactive and cross-sector research programs must complement the traditional bench-to-bedside development cycle. The previous chapters have identified areas where increased investment is needed, based on insights from the research and healthcare professional community, from funders and different stakeholder organisations. These areas for investment match the evolution and novel presentation of cardiovascular disease.

Several guiding principles for implementation were identified:

- Collaborative and transnational research can enhance impact at all levels from discovery to implementation and outcome studies.
- Partnerships, multidisciplinary efforts and co-design of research with patients and citizens are essential for success.
- A supportive regulatory framework will facilitate innovation and economic wealth within Europe.
- Inequality within Europe in cardiovascular health requires dedicated, research-guided programs.

Setting a strategic agenda implies choices for priority investment, as presented here. Yet, innovation relies on bright ideas. Therefore, bottom-up, discovery research must be supported and should be part of strategic efforts and funding. Implementation of the proposed agenda will require action from ministries, funding bodies, health care administrators and the private sector, at EU and national level.

Furthermore beyond the research agenda presented here, public and private decision makers providing health care must develop novel models for care, ensure equal access to treatment and implement digital health that will in turn support research for better cardiovascular health.

ANNEXES

Annex A: Development Process of the SRA-CVD

ERA-CVD established an External Advisory Board (EAB) to develop the strategic research agenda (SRA-CVD) with the support of the ESC, the EHN and all ERA-CVD partners. See also Figure 9: Schematic overview of how the SRA-CVD has been developed.

- A first ERA-CVD workshop was held in April 2017, Rome to identify the major needs and challenges in CVD research across Europe and beyond. There were 33 participants including members of the ERA-CVD External Advisory Board (EAB), invited external experts and ERA-CVD partners.
- A second ERA-CVD SRA workshop was organised in May 2018, Rome where the EAB and invited experts defined a list of CVD research topics to tackle the needs and challenges previously identified.
- A group of experts from the EAB (writing group) further developed, together with DLR and ANR, the SRA-CVD draft. This document was shared with the ESC Research Committee for feedback.
- The next step was a consultation process with selected stakeholders to collect comments on the SRA-CVD draft. Consulted stakeholders were identified in cooperation with the writing group, ESC, EHN and all ERA-CVD partners.

- ***Pending further action:*** Prioritisation of the 15 CVD research domains in the SRA via an online survey. The results will be collected and analysed to be finally presented as an annex to this SRA-CVD. The link to the survey and further information will be available on the ERA-CVD webpage until May 31st 2019 under: https://www.era-cvd.eu/396.php

Annex B: Contributors

Members of the ERA-CVD External Advisory Board (EAB) that were part of the coordination and management as well as the writing group are highlighted in **bold:**

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Figure 9: Schematic overview of how the SRA-CVD has been developed

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Annex C: References and Links

(1) Beard JR, Bloom DE. Towards a comprehensive public health response to population ageing. Lancet. 2015 February; 385(9968):658-661.

(2) European Cardiovascular Disease Statistics 2017: http://www.ehnheart.org/cvd-statistics/cvd-statistics-2017.html

(3) World Health Organisation Health statistics and information systems: https://www.who.int/healthinfo/global_burden_disease/en/

(4) European Society of Cardiology: Cardiovascular Disease Statistics 2017, Adam Timmis, Nick Townsend, Chris Gale et al. European Heart Journal. 2018 February; 39(7):508-579.

(5) Wilkins E, Wilson L, Wickramasinghe K, Bhatnagar P, Leal J, Luengo-Fernandez R, Burns R, Rayner M, Townsend N (2017). European Cardiovascular Disease Statistics 2017. European Heart Network, Brussels. http://www.ehnheart.org/images/CVD-statistics-report-August-2017.pdf

(6) Gal D et al. Mapping cross-border collaboration and communication in cardiovascular research from 1992 to 2012. European Heart Journal. 2017 April; 38:1249-1258.

(7) I Ràfols, A Yegros. Is Research Responding to Health Needs? September 2017. Available at : https://ssrn.com/abstract=3106713).

(8) CardioScape Report: see http://www.cardioscape.eu/ and Pries et al. European Heart Journal 2018; 34:2423-2430.

(9) Hwang T et al. Temporal Trends and Factors Associated With Cardiovascular Drug Development, 1990 to 2012. Journal of the American College of Cardiology, Basic to Translational Science 2016 August; 1(5):301-308.

(10) McClellan M et al. Call to Action: Urgent Challenges in Cardiovascular Disease. Circulation. 2019 January; 139(9):e44-e54.
(11) World Intellectual Property Organisation. Patentscope database: https://patentscope.wipo.int/search/fr/search.jsf
(12) Krittanawong et al. Artificial intelligence in Precision Cardiovascular Medicine. J Am Coll Cardiol. 2017 May; 69(21):2657-2664.
(13) Dutch Cardiovascular Alliance website: https://dcvalliance.nl
(14) Sipido K et al. Scientific Panel for Health: better research for better health. Lancet. 2016 August; 388 (10047):865-6.
(15) The EURObservational Research Programme (EORP) of the European Society for Cardiology: https://www.escardio.org/Research/Registries-&-surveys/Observational-research-programme
(16) Nieuwenhuijsen MJ. Influence of urban and transport planning and the city environment on cardiovascular disease. Nat Rev Cardiol. 2018 July; 15(7):432-438.
(17) Sabatine M. PCSK9 inhibitors: clinical evidence and implementation. Nat Rev Cardiol. 2018 March; 16(3):155-165.
(18) Ridker PM et al. Anti-inflammatory Therapy with Canakinumab for Atherosclerotic Disease. N Engl J Med. 2017 September; 377(12):1119-1131.
(19) Petersen SE et al. Reference ranges for cardiac structure and function using cardiovascular magnetic resonance (CMR) in Caucasians from the UK Biobank population cohort. J Cardiovasc Magn Reson. 2017 February 19(1);18.
(20) Volpe M et al. Consensus document and recommendations for the prevention of cardiovascular disease in Italy. G It Cardiol. 2018 February; 19(2):1S-95S.

Annex D: Abbreviations and Acronyms

AI	Artificial Intelligence
CVD	Cardiovascular Disease(s)
EATRIS	European Advanced Translational Research Infrastructure in Medicine
EC	European Commission
ECRIN	European Clinical Research Infrastructure Network
e-health	Electronic Health
EHN	European Heart Network
ELIXIR	ELIXIR is an intergovernmental organisation that brings together life science resources from across Europe. These incl. data-bases, software tools, training materials, cloud storage and supercomputers
ERA-CVD	European Research Area Network on Cardiovascular Diseases
ESC	European Society of Cardiology
ESFRI	European Strategy Forum on Research Infrastructures
EU	European Union
FP7	7th Framework Program for Research and Technological Development from the European Commission
GDP	Gross Domestic Product
Horizon 2020	8th Framework Program for Research and Technological Development from the European Commission
Horizon Europe	9th Framework Program for Research and Technological Development from the European Commission
iPSC	Induced Pluripotent Stem Cells
SRA-CVD	Strategic Research Agenda for Cardiovascular Diseases

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