Critical Appraisal: Cardiovascular Diseases

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Mapping Chronic Non-Communicable Disease Research Activities and their Impact
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Abbreviations

ACS	Acute Coronary Syndrome
BHF	British Heart Foundation
CEE	Central and East European
CRD	Chronic Respiratory Diseases
CVD	Cardiovascular Diseases
DALY	Disability Adjusted Life Years
DG Research	Directorate-General for Research and Innovation
DG Sante	Directorate-General for Health and Food Safety
DVT	Deep Vein Thrombosis
EAFRD	European Agricultural Fund for Rural Development
EC	European Commission
EMFF	European Maritime and Fisheries Fund
ERA	European Research Area
ERC	European Research Council
ERDF	European Regional Development Fund
ESC	European Society of Cardiology
ESF	European Social Fund
FDA	US Food and Drug Administration
FO	Funding Organization
FT	Funding Text
MD	Medical Devies
MRC	UK Medical Research Council
MS	Member States
MSCA	Marie Skłodowska-Curie-Actions
NCD	Non Communicable Diseases
NHS	National Health Service
NME	New Molecular Entities
PMA	Premarket Approval
PE	Pulmonary Embolism
RFO	Research Funding Organisation
RCT	Randomized Controlled Trial
SCI	Science Citation Index
SSCI	Social Sciences Citation Index
VTE	Venous Thromboembolism (VTE)
WOS	Web of Science

Executive Summary

❖ Eligible EU funding between 2006 and 2013 for CVD research was 413 mn €. This is a considerable share of the total CVD funding in the EU, and significantly higher than national project-based funding in any EU member state except for the UK. In addition, national research projects have been analyzed.

❖ EU funding schemes for CVD are heavily characterized by concentration effects on a regional level and across CVD research fields. Only some MS are regularly awarded with EU grants in CVD research, and this can even be broken down to a handful of institutions. Newer member states are rarely awarded with EU funds, but are confronted with high rejection rates and a high level of bureaucracy posing disincentives for institutions and researchers with limited capacities to apply. A main criticism of EU funding schemes remains the lack of evaluation routines of projects that are often coordinated amongst up to 17 project partners for 4.75 years on average. How individual projects performed and how they disseminate knowledge to the research communities or to the public remains unclear at this stage.

❖ In contrast, national RFOs focus heavily on national research agencies and grant in a majority of projects to only one single institution for a much shorter average time of 35 months. There are only few European cooperation in CVD research and research duplication effort seems very likely.

❖ Considering the European pharmaceutical sector, only 10% of all identified New Molecular Entities were CVD-relevant. Most research has been done in the area of oncology. This is contrasted by the high burden of CVDs. According to pharmaceutical companies, this is primarily due to the increasingly complex and very expensive process of drug discovery. As a result, improving the regulatory framework and establishing incentives for drug-companies to increase the variety of the pharmaceutical research agenda might improve the research output coming from this area.

❖ The Medical Devices Industry provides a mixed picture with regard to investments in CVD research. While only 5 companies with CVD-relevant products were identified by a comprehensive database research, the bibliometric data output suggests a lot more companies to engage in CVD related research.

❖ Interviews with key stakeholders in CVD research revealed valuable insights and confirmed the quantitative analysis of CVD being underfunded in the EU. Although the disease burden is persistent in a majority of EU MS, funding has falling short from cancer related funding and is not reflecting urgent needs as the raising admission rates for heart failure to German hospitals and leading cause of CVD mortality suggest. As an additional insight, the interviews as well as the bibliometric mapping revealed the pioneering role of modern European CVD research with a variety of scientists being able to publish high impact papers in prestigious journals. Hence, combining efficient funding agendas with the accumulated knowledge and the high profile of European scientists seems very promising to advance CVD research and to fight its global burden of disease.

1 European Research Programs

CVD research has become priority in most of national research agendas and is translated in a broad variety of priorities, projects and outcomes in CVD research on a European level. To shed light on some aspects of regional research and its expected outcomes, a purposive sample of CVD projects has been established. Firstly, this chapter aims to analyze the role of European funders as the European Commission (EC) and others and secondly analyzed project examples from national RFOs relevant for CVD research.

To analyze European funding a systematic search in available database offered insights in total 143 individuated CVD projects. A quantitative and qualitative analysis has been employed to this full project sample. On a national level, information had to be collected individually and are therefore limited due to varying level of details and degrees of transparency. Therefore, all identified RFOs have been targeted by website queries. This chapter is surveying grants by European sources relevant to CVD research when fulfilling three criteria: (i) grants awarded between 2006 and 2013, (ii) application to project based grants is possible for citizens in all EU member states and (iii) research is CVD relevant, including the wide range of associated research fields as basic science to specific treatment optimization programs.

(a) Research funded by European RFOs

European Research programs have seen a significant increase in budget and are received as key players for medical research. Furthermore, research in health has been categorized as priority under the latest framework programmes. Table 1 gives an overview of eligible EU funding organizations, range of provided grants, total eligible funding and their current organizational channels.

Table 1: An overview of eligible EU funding organisations

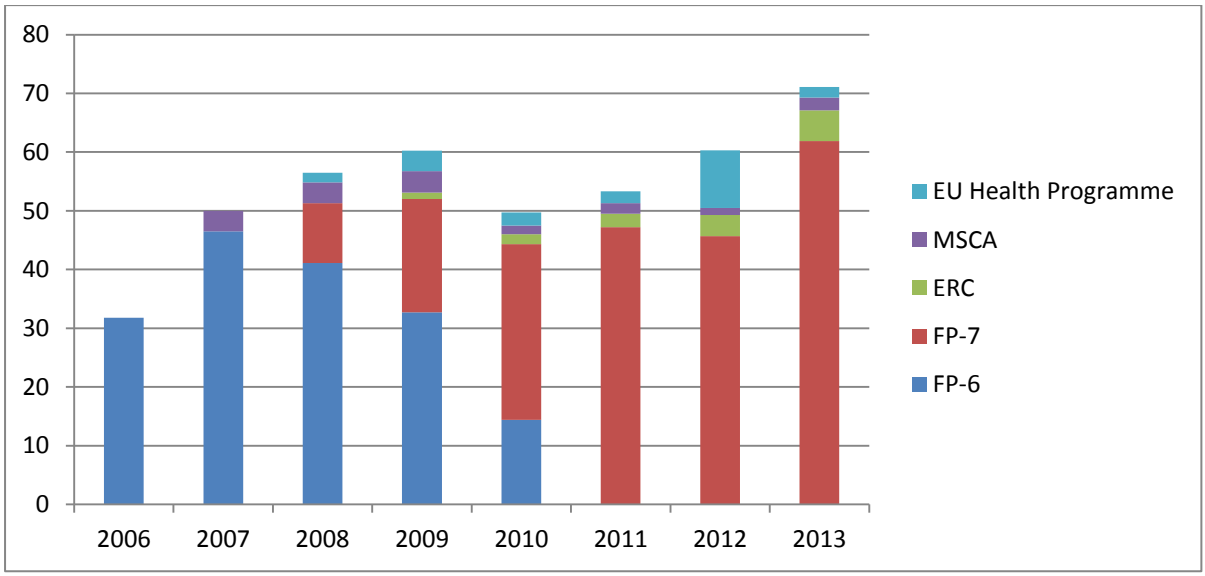
	Responsible Organisation	Name of funding programm	Valid timeframe	Awarded CVD funding (no of projects)
European Commission	DG Research & Innovation	FP-6	2002-2006	46.5 mn (28 projects)
		FP-7	2006-2013	292 mn (46 projects)
		Horizon 2020	2014-2020	
		European Research Council (ERC)	From 2007 onwards	33 mn (18 projects)
		Marie Skłodowska-Curie-Actions (MSCA)	From 2007 onwards	22.5 mn (39 projects)
	DG Health and Food Safety	Various forms		12.5 mn (4 projects)
		EU Health Programme	2007-2013	6.5 mn (8 projects)
	DG Regional and Urban Policy	European Structural and Investment Funds on Health	2007-2013	5000 mn *
	European Heart Network European Society of Cardiology			1.6 mn (2 projects)
				Total: 415 mn Eur

Source: (Commission, 2015a, CHAFEA (Consumers, 2015, European Research Council, 2015a). Notes: * funding has been omitted due to unavailability of project-based data

The EC is the most important source of funding to CVD research on a European level and does so via various channels and priorities, in total spending 413 mn € on CVD research between 2006-2013. By

far the most known funding scheme for medical research investment is run by DG Research and Innovation and managed in framework programmes (FP), here FP 6 and 7 are relevant, listing also Horizon 2020 as the successor programme since 2014. Figure 1 shows the development of CVD funding from 2006 to 2013 across the relevant funding schemes. It should be noted, that the ERC and MSCA are integrative parts of FP 7 but have been displayed individually.

Figure 1: Project Based funding by major European schemes for CVDs, 2006-2013 (in mn €)



Source: authors own compilation based on (Commission, 2015a, CHAFEA (Consumers, 2015, European Research Council, 2015a)

CVD research has seen an increase in overall EU funding from 31.8 mn € in 2006 to 71.1 mn € in 2013. Under FP-6, 28 projects have been categorized under CVD research with an average funding of 6 mn €. In 2007, 46.5 mn € were granted to CVD researchers, reaching the highest funding after the official end of the FP 6 programme in 2006. Under FP-7, CVD research has experienced an increase in funding reaching 61.9 mn in 2013. This is partly due to the prioritization of health research in the FP-7 cooperation action scheme (along with Energy, Transport and Security etc.). The European Research Council, established to implement the *Ideas* programme under FP-7, has increased steadily funding for CVD research and has gained major importance amongst research (see Chapter 3 Interviews); in 2013 5.2 mn € have been granted for CVD related topics. The Marie Skłodowska-Curie-Actions (MSCA) is part of the *People* program of FP-7 and also relevant for CVD research, although compared to other EU funding schemes of only minor importance granting in total 2.2 mn € on a project basis to CVD research in 2013. However, project based funding makes up only a small proportion of the total MSCA funding scheme, which is mainly triggering mobility for young researchers by funding exchange, networking or paying for conference participations.

The EU Health programme is another important funding scheme for CVD research and was implemented from 2003-2007 by the Public Health Programme and from 2008-2013 with the Second Health programme, mainly aiming at informed policy decisions of EU member states in the areas of: (i) improve patient's security, (ii) promote health and reduce health inequalities and (iii) generate and disseminate health information and knowledge. Reaching these aims also project based funding, called Joint Actions, have been granted to CVD research. In total, the Public Health Programme offered a total budget of 312 mn €, and 321 mn € under its succeeding programme. In total only 8 projects with a volume of 1.8 mn € in 2013 have been granted under this funding scheme for CVD related topics. In general, the EU health programme focuses much more on broader health topics as prevention of diseases, cross-border health networks, and rare diseases.

Although the increase in EU funds for CVD research seems steadily, it is not reflecting the importance of CVD for European health systems as leading cause of mortality. Table 2 shows corresponding total volumes of each funding scheme and the proportion of CVD research.

Table 2: Proportion of CVD related project funding to total EU total budgets, in % annual averages, 2006-2013

	2006	2007	2008	2009	2010	2011	2012	2013
FP-7		0	1.5	2.5	3.9	5.7	4.9	6.2
ERC		0	0	0.1	0.2	0.2	0.2	0.3
MSCA		0.8	0.8	0.7	0.3	0.2	0.1	0.2
EU Health Programme*				44.0	13.8	12.1	44.0	13.4

Source: (Research, 2013, Commission, 2011, Commission, 2012, Commission, 2013, Commission, 2015c, Union, 2012) Notes: * budget for joint actions, based on project calls

The highest proportion is reached by the EU health programme, which is broken down by the budget implemented by the joint action schemes allowing for project proposals, reaching up to 44 % of total funding for CVD research in 2012. Although this seems astonishing, only 2 projects can be fully determined to decrease CVD mortality (EUROHEART I and II respectively), the other 6 projects are for better risk management programmes across all relevant NCDs. The lowest proportions for CVD research is reached in the ERC and MSCA programmes, in both funding schemes health is not a priority per se. In 2013, CVD research accounted for 6.2 % of the FP 7 total budget, which is the highest score since 2007. Furthermore, DG Sante manages in parallel funding schemes for health related topics, which often last only one year and have an average volume of 2.5 mn. Health prevention and raising awareness towards risk factor management are of key importance for this insurance scheme. Interestingly enough, a total of 12 mn € have been categorized under CVD research for GD Sante projects.

The EU largest financing scheme, the so called Structural Funds are worth 347 bn € in the planning period of 2007-2013. In the upcoming term between 2014-2020, Structural Funds are expected to be worth 325 bn €. This impressive budget is managed by various tool as the Cohesion Fund, European Regional Development Fund (ERDF), European Social Fund (ESF), European Agricultural Fund for Rural Development (EAFRD) and European Maritime and Fisheries Fund (EMFF). Although, the link to CVD research is not that clear and direct, health has been integral part of implementing structural funds. The Cohesion Fund is deemed as the most relevant one for health programmes aiming at reducing regional and social disparities within EU member states and across member states. Member states are classified into less-developed regions, transition regions and developed regions. Each of these classifications translated into varying availability of EU structural funds for local communities and the conditionality. During the 2017-2013 period, health topics were mainly implemented by infrastructure projects, e.g. modernizing hospitals and especially so in the CEE countries(Stegemann and Kuipers, 2013). Intertwining regional project data for CVD research have been particularly difficult and are therefore omitted for this report.

It is also important to note, that medical societies on a European level, play a significant role for raising awareness campaigns and disseminate knowledge for CVD prevention. The European Sociey of Cardiology has managed two eligible projects under this report, mainly compiling patient-focused data in registries. The most prominent database is the EUROASPIRE study that is following up on patients after a fatal CVD event and monitors their individual CVD risk management since 1994. The project is financed by the ESC with 621 000 € per year (European Society of Cardiology, 2014). The European health network, also plays a role for co-managing the secretariat of the Heart Group in the European Parliament, of which 63 MP are now member and supporting public events as the Euro Health Week.

(b) **Outlook to Projects of national RFOs**

A purposive sample of CVD research projects by national RFOs should capture the variety of funding levels and expected outcomes. Smaller MSs are expected to have a small number of CVD relevant RFOs. Initially, we found over 5000 individuated CVD research projects. Given the large number of projects funded for the period 2006-2013, we considered only the projects that commenced and concluded within the time period, aiming at full project information, and representative research of a sample to 100 (N) projects for all European member states. After the retrieving of all the projects, we performed a more in depth online research to individuate the maximum level of detail possible. At this stage a mixed quantitative and qualitative analysis was performed.

Looking at the average time horizon of the projects, the average life of grant is of 35 months with a minimum time of 8 months and a maximum of 60 months per project. Projects by National RFOs are by a large share conducted by universities (n=82) or public researching bodies (n=10). In only few cases larger consortia made up from private actors and NGOs have been funded for CVD research. Typically, research has been granted to national universities or to national university research clusters by up to five universities or hospitals (n=4). Indeed, over 91% of the projects were funded within the MS of RFOs, and only 9% were developed on a European level. Interestingly enough, these rare European research projects are highlighted by highly narrowed research questions, e.g the Epidemiology of coronary heart diseases in the resident population in Luxembourg compared to the unusual high proportion of non-resident population when compared to their dietary habits in collaboration with France. On the other hand, there only few established research focused cooperation programs, as the EEA grant by Norway, Liechtenstein and Iceland funding research projects in CEE countries and Greece (n=2). The other two projects are represented by so called researching networks of the BMBF of Germany, clustering up to five universities or hospitals to competence centres for prevention of heart failure and its complications and Atrial Fibrillation, both also leading the project sample in terms of total funding of 25mn € and 18 mn € respectively.

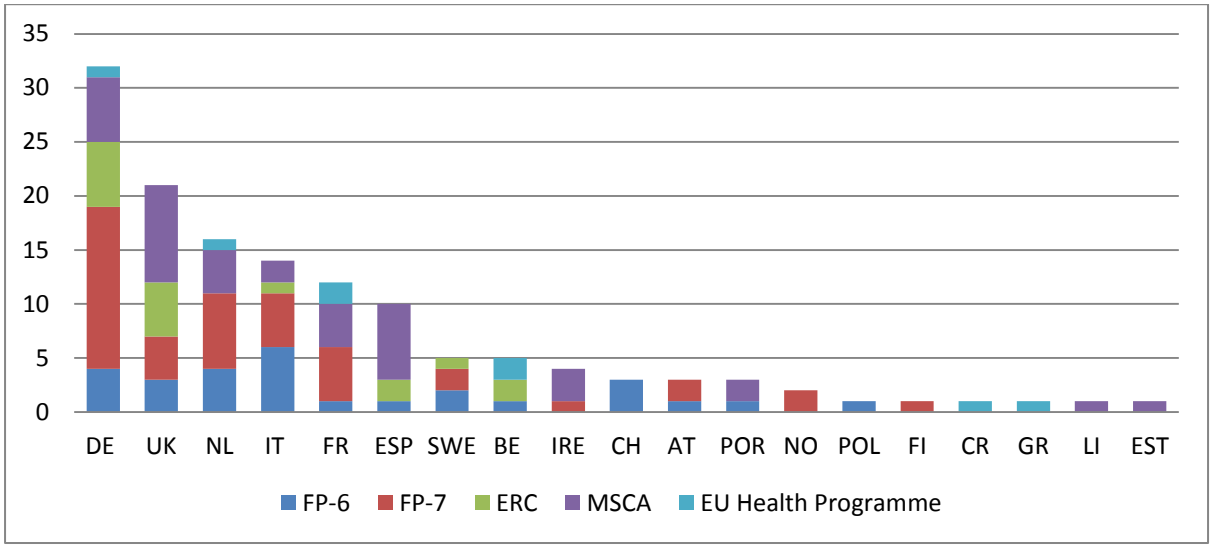
Funding volumes have increased in the project sample from 2.3 mn € in 2006 to 7.9 mn € in 2013. However, this analysis faces several limitations from the purposive sample. The projects represented in the sample has been selected for their proportional representativeness of national RFO funding projects and do not reflect on all available funding schemes by CVD relevant RFOs. Secondly, it was not possible to individuate basic from applied research projects via database queries. Often the basic research such as microbiology and fundamental chemistry is not specifically directed to a group of diseases but may be directed towards a wide range of applications. Thirdly, the website query has intrinsic limitations linked to the public availability of information. Often, RFOs do not clearly state the levels of funding for individual projects or even list the projects they are currently funded. Moreover, in some MSs, it was also not possible to individuate projects due to the lack of transparent information.

1.1 Summary of RFO Research Projects

(a) Research funded by European RFOs

It is notable, that there are dominant regional concentration effects in the eligible 143 projects funded by the EU between 2006 and 2013. Despite the transition to a new framework programme, that considerably changed priorities and funding modalities (by establishing the ERC and MSCA), EU funded projects are heavily used by only some MS in a project leading role. Figure 2 shows this regional variance over all above mentioned funding schemes in more detail.

Figure 2: Regional Variance in CVD research, sorted after project leading MS, 2006-2013



Source: (CHAFEA (Consumers, 2015, Commission, 2015a). Notes: missing two projects omitted because project leader was in non-EU country

Germany attracted the majority of EU funds, in total 32 grants, especially so under FP-7 and the ERC programme. Italy has won the majority of CVD research grants under FP-6, and almost kept their level constant under FP-7 respectively. The ERC dedicated to frontier research and excellent research clusters have been granted to only 5 MS with its 17 relevant projects. The MSCA aiming at better networking and harmonizing research efforts across member states and has been used by 10 MS in 40 projects. Poland, the Czech Republic, Lithuania and Estonia are the only representatives of the newer member states, individually awarded with 1 project each. Switzerland has not been granted any EU investment since 2007 in CVD research. It is expected, that EU structural funds would mitigate some of the regional variance, but are not fully able to balance national health infrastructural shortcomings.

The same concentration effect also holds true for awarded project coordinating institution for CVD research. Some institutions are able to concentrate several EU funds across CVD related topics: as the Chancellor, Masters and Scholars of the University of Cambridge, and the King's College in London and the Charité Hospital in Germany. Although these institutions are likely to benefit from human resources that have been trained over years in CVD research, it is likely that applications to EU funds also are handled in a more professional manner (see Chapter 3). In the forefront of drafting the Horizon 2020 programme, this regional variance was acknowledged as main barrier to the so called European Research Area (ERA), a roadmap to harmonize national research systems is not yet developed (Commission, 2015b). The impact of Horizon 2020 and the implementation of the ERA legislation are yet to be seen in terms of CVD research.

(b) Outlook to national RFOs

National RFOs target mostly research conducting agencies that are situated in the country. Therefore, regional concentration effects as with European RFOs could not be re-confirmed. However, funding volumes and frequency of granted projects vary greatly over the purposive sample of research projects. The University of Luxembourg has been granted two large CVD projects that have been based upon each other; as a consequence the university had a continuous funding for CVD epidemiology from 2007 onwards. Whereas in Bulgaria and the Czech Republic no CVD research was individuated. Therefore, national CVD research heavily depends on the particularities of national funding landscape and its embeddedness in research structures as universities.

1.2 Major European Research Programs Receiving Funding

(a) Research funded by European RFOs

CVD research has benefited from a shifted paradigm in the EC by implementing the FP-7 programme and its sub-programmes of *Ideas* (ERC) and *People* (MSCA) and stating health research as one priority. This resulted in an increase in total volumes of funding, but also in a diversification in project design and priorities. This section will shortly describe major players in CVD research by case studies and provide a sample of 10 Projects to give a rough overview of the underlying dataset of 144 projects to this report.

Case Study 1 is describing the success of the European Research Council in EU funding schemes.

Case Study 1. The European Research Council

The European Research Council (ERC) was established in 2007 as first European research organization dedicated to excellent research at the frontiers of knowledge. The council offers two kinds of funding schemes: (i) Starting Grant designated for researchers in early stages of their career and (ii) advanced grants. In 2013, Starting Grants have been added by Consolidator Grants aiming at researchers that have established already a working team. From 2007 to 2013 more than 43 000 applications have been received, of which in average terms 12 % succeeded and benefit from very special terms in the ERC funding scheme. The ERC will be crucial part of the Horizon 2020 programm and experience an upscale of its budget by 60 % to 77 bn from 2014-2020, compared to 13 bn under FP 7(European Research Council, 2015a). Applicants are open to apply for any field of research without any predetermined priorities.

(a) Researchers are awarded with grants between 1.5 -2 mn € for 5-7 years, with comparatively low bureaucratic barriers in administrating the money in early stages of their career allowing them to focus purely on research.
(b) The ERC offers a highly effective evaluation process for each application, also including a defense in Brussels with a multi-disciplinary panel (for CVD research *Life Sciences 4*) of experts assessing the expected outcome of the proposal
(c) During ERC grants, awardees are invited to benefit from a highly professionalized networking routine within similar research fields, but also across topics. Interviewees have suggested that networking actually help them most in difficult phases in their research careers and gave valuable input to drafting publications etc. ERC awardees often stay within the network far beyond their granted project timeframes.
(d) The ERC is open for EU-nonresidents when conducting their research in one of the accredited research agencies within the EU. In 2013, most of applicants have been EU residents, but 10 % were non EU residents from 29 countries. When awarded with an ERC grant, principal investigators are free to hire their research team, often up to 6 persons, also from abroad. Therefore, ERC grants are often a first step in researcher careers and contribute to teaching the next generations of researchers, across disciplines and nationalities, in the fields of Engineering, Life Sciences and Human Sciences.
(e) The ERC is dedicated to excellent frontier research and highly values publications in top academic journals and research breakthroughs, which have been awarded with 8 Nobel Prizes since 2007.The ERC has open calls without any priorities solely deciding on the quality of research. Although the excellency approach has resulted in the highest regional disparities across funding schemes, the ERC is considered as major success. Interestingly, also no gender gap can be found within ERC applications and awardees.

The ERC grants are conceptualized to have a broad focus also benefiting basic science researcher that could be very interesting in a long-run for CVD research. Eligible CVD projects under the ERC can be summarized under (i) basic science for individual genes, enzymes and cell biology (10 projects) (ii) innovation in personalized CVD therapy including imaging (4 projects), and (iii) research in cardiac regeneration and re-activate potential to reverse arteriosclerosis or heart failure (2 projects). The ERC has expanded heavily in CVD research, starting from 1.1 mn € in 2009 to 5.2 mn € in 2013. In 2015 it will operate with a total budget of 1 679 mn €, the highest amount available to the research bottom-up approach ever (European Research Council, 2015b). Across MS borders, these projects are likely to pioneer CVD management in the next years and be followed by further research team under the expanded financial means of the ERC.

(b) Outlook to national RFOs

CVD cause an immense disease burden to European population, but are in the same time highly preventable. As disease prevalence is very much diversified across Europe. On national research agendas, mitigate CVD disease burden and resulting health inequalities has been often ranked as priority. As for Germany, a competence centre for CVD has been established by 2012 unifying research networking structures that have existed before. Some national RFOs play a very important role far beyond national borders, as the British Heart Foundation being found as leading RFO in Europe. On the other side, some MS-often challenged by persistent high CVD prevalence- are not funding CVD research in sufficient scale. The average spending of the purposive sample has been 350 000 €, but CEE countries have been far more represented at the lower end of funding volume. Case study 2 gives an overview of EEA grants which aim to reduce regional diversified research capacities in newer EU member states.

Case Study 2: EEA grants

Norway, Liechtenstein and Iceland have been dedicated to reduce disparities in Europe since 1994 by providing funding to 16 country partners. In the term of 2009-2014 a total of 1 794 mn € have been distributed over a range of funding schemes to beneficiary countries as Poland, Romania, Czech Republic, the Baltic States, Hungary and Greece.

(a) Health research is only of minor importance in the bilateral cooperation, but has gained importance for all national research bodies, charities and the private sector which can apply to EEA grants. Reducing health disparities is among the top priorities of EEA health related programmes.
(b) The Norwegian Research Council channels most of the EEA funding to bilateral partners in the cooperation partners.

Table 3: Selection of Research Programs for Cardiovascular Disease, ranked to ICD categories 2006-2013

Funder	Recipient Type	Level of Collaboration (National – European - Global)	Partner Countries	Project Title	Research Area (focus)	Project Timeline (years)	Summary Description (Project aim)	Achieved/ Anticipated Outcomes	Amount of Funding
EEA Grants and Norway Grants	University, n = 3	European	Norway, Poland	Molecular Mechanisms of Tissue Fibrosis	Hypertensive Diseases, Ischemic Heart Disease	2009-2014	Fibrosis has implication for the most common diseases like hypertension, myocardial infarctions and malignant neoplasm. The objective of the project is to understand the detailed mechanism of fibrotic processes.	Identification of genes and proteins for use in early detection for prevention and treatment strategies will bring forward applications in both medicine and biotechnology.	956.094 €
Ministry of Health Slovakia	University, n = 1	National	Slovakia	Molecular genetic change after therapy by ACE inhibitors for blocking the AT 1 receptor in patients with essential hypertension	Hypertensive Diseases	2008-2010	To research in new therapy management pathways for patients with chronic hypertension	Re-evaluation of treatment by drug for chronic hypertension in long-term patient study	178.755,89 €
Ministry of Health Slovakia	University, n = 1	National	Slovakia	Oxidative stress and its role in the pathogenesis of stroke	Cerebrovascular Diseases	2008-2010	To understand better the interplay of oxidative stress to fatal stroke events	Early detection and screening management for risk patients	34.035,30 €
Swiss Heart Foundation	University, n = 1	National	Switzerland	Notch signaling in ischemic injury: Is it a bad fellow? Can we therapeutically prevent its malfunction?	Cerebrovascular Diseases				92.906,10 €

EEA Grants and Norway Grants	University, n = 2	European	Czech Republic, Poland	Treatment of Stroke and Spinal Cord Injury	Cerebrovascular Diseases	2009-2014	The primary aim of this project is to develop novel strategies for the treatment of stroke and SCI using a combination of advanced biomaterial science with stem cell therapy	Development of new treatment strategies of stroke and spinal cord injury	641.500 €
European Commission - FP7 Projects	University, Private, NGO, n = 29	European	Belgium, Denmark, Finland, France, Germany, Hungary, Italy, Netherlands, Poland, Spain, Sweden, Switzerland, UK	European Stroke Research Network www.europeanstrokenetwork.eu	Cerebrovascular Diseases	2008-2013	To develop successful strategies for brain protection and repair by working on a model and methods platform, in which relevant comorbidities, gender, age, and long-term outcomes will be investigated	Development of a research platform and the European Stroke Network	9.953.915 €
Swiss Heart Foundation	University, n = 1	National	Switzerland	The molecular switch between normal and aberrant angiogenesis by VEGF	Diseases of arteries, arterioles and capillaries				78.973,84 €
Swiss National Science Foundation	University, n = 2	National	Switzerland	Contrast enhanced ultrasound molecular imaging of vascular inflammation in atherosclerosis: development of methods for early detection of cardiovascular risk and assessment of the effect of targeted therapies	Diseases of arteries, arterioles and capillaries	2009-2012	Development of Methods for Early Detection of Cardiovascular Risk and Assessment of the Effect of Targeted Therapies	Development of Methods for Early Detection of Cardiovascular Risk and Assessment of the Effect of Targeted Therapies	650.449,07 €
Hungarian Scientific	University, n = 1	National	Hungary	Fungal siderophores function as prophylactic and protective	Diseases of arteries, arterioles and capillaries	2009-2013			122.575,59 €

Research Fund				agents against atherosclerosis and cancer and promising drugs for treatment of lead-poisoning					
European Commission - FP7 Projects	University, Private, n=15	European	France, UK, Belgium, Sweden, Germany, Spain, Denmark, Czech Republic, Netherlands, Austria, Iceland, Turkey	Fighting Aneurysmal Diseases	Arteries, Arterioles and Capillaries	2008-2012	To develop standardized clinical and biological procedures and to accelerate the acquisition of knowledge in the field of aneurysmal diseases.	Development of new diagnostic and therapeutic tools for fighting aneurysmal diseases in humans	10.998.936 €
Luxembourg Institute of Health	University, n=2	European	Luxembourg and France	The Epidemiology of Metabolic Syndrome among the Resident Population in Luxembourg and its Potential Determinants with a Focus on Dietary Habits - MSF	Coronary Heart Diseases	2011 – 2012	to investigate profoundly the potential biological and behavioral determinants of the metabolic syndrome byexploring the cross-cultural differences (Luxembourgish and Portuguese people) in dietary habits	Prevention of the metabolic syndrome by risk factor management in differing population groups in Luxembourg	373.000.00€
Federal Ministry of Research and Education of Germany	University, n=1	National	Germany	Minimally invasive implantation of heart valve prosthesis for the treatment of tricuspid regurgitation	Coronary Heart Diseases	2009-2011			209.651.00 €
European Research Council	University, n = 1	National	Netherlands	New and More Individualised Population-Based Screening for Cardiovascular Disease; From a RCT Including Self-Assessments, Primary Care and Coronary Artery Calcification Score to Modelling Risk-Benefit	Coronary Heart Diseases	2012-2017	To evaluate the health effectiveness of interventions targeting individuals with high risk of	Evaluation of early interventions in regard to their ability to reduce CHD mortality and morbidity by 15% or more within five	3.298.999 €

							developing CHD.	years	
Swiss National Science Foundation	University, Private, n = 5	European	Switzerland	Identification of miRNAs modulating the regenerative response of the heart in the zebrafish and the mouse	Coronary Heart Disease, Other Forms of Heart Disease – Heart Failure	2010-2015	The aim of this project is to systematically characterize the gene regulatory networks, which are differentially utilized in the regenerating heart of the Zebrafish as compared to the non-regenerating heart of the mouse.		871.212,70 €
Swiss National Science Foundation	University, n = 1	National	Switzerland	Modulation of regulatory genes of fatty acid oxidation in the myocardium: Role in the progression from compensated remodeling to heart failure	Other Forms of Heart Disease – Heart Failure	2005-2009	he present project is designed to elucidate causes and consequences of altered fatty acid metabolism with particular emphasis on the role of angiotensin II	Development of new therapeutic strategies for the prevention of heart failure	312.075 €
Hungarian Scientific Research Fund	University, n = 1	National	Hungary	Study of the mechanism of cardiac arrhythmias and repolarization, antiarrhythmic and proarrhythmic drug action	Other Forms of Heart Disease	2006-2009	the major goal of the project was to investigate the mechanisms involved in cardiac repolarization and in antiarrhythmic and proarrhythmic drug actions		119.404,21 €

Hungarian Scientific Research Fund	University, n = 1	National	Hungary	Analysis of interactions between inflammatory and vasoregulatory pathways in chronic heart failure: application of logical analysis of data, a novel data-mining tool	Other Forms of Heart Disease – Heart Failure	2008-2011	The aim of the current project is to introduce a data-mining tool, described in operations-research for non-medical applications, into medical research, allowing the analysis of complex interactions in chronic heart failure		171.942,07 €
Federal Ministry of Research and Education of Germany	University, n=3	National	Germany	Integrated Research and Treatment Center "prevention of heart failure and its complications"	Other Forms of Heart Disease – Heart Failure	2010-2015			25.622.581€
APVV Slovakia	University, n = 1	National	Slovakia	Protection against malignant cardiac arrhythmias and functional failure.	Other Forms of Heart Disease	2006-2008	Research into the interplay of risk-factors to develop heart failure	Development of early intervention therapy to heart failure and arrhythmias	242.216 €

1.3 Focus of Programs

(a) Research funded by European RFOs

The EC has acknowledged its key role in medical research and has changed funding priorities, volumes and targets twice over the surveyed timeframe from 2006-2013. FP-6 , worth 17 bn €, was the first EU funding scheme prioritizing health as one common challenge for European societies (Priority 1: Life Sciences, biotechnology and genomics for health awarded with 2 bn € or 13.1 % of the total FP-6 budget). Looking at CVD research, FP-6 has had a strong focus on prevention (Figure 4) and engaged neither with new therapy approaches, basic sciences as genetics nor with improving diagnostics or drug development. This is contradicting the rationale of the FP-6 priorities. In addition, FP-6 had major implementation barriers that also affect expected outcomes of CVD research.

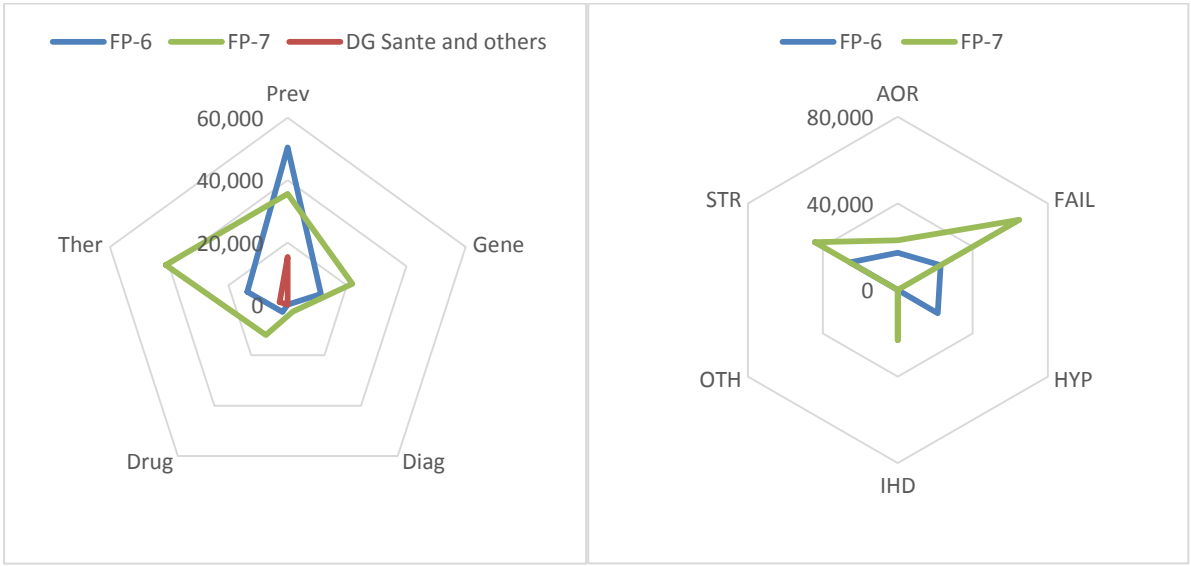
(i) FP-6 had emphasized even more regional discrepancies in awarding project leading positions to newer member states as in the preceding FP-5 programme. Partly this was driven by a high rejection rate for applications from CEE countries, adding to an overall success rate of 18 % of applications in FP-6.

(ii) FP- 6 had unclear project selection criteria, high bureaucratic barriers as an average time between receiving a project proposal and contracting of 365 days. This was contributing to the unusual spending pattern, also in CVD research, reaching its all-time high one year after the official end of FP-6.

(iii) It remains a challenge to judge on the quality of CVD projects, because data as publications etc are not made available in a systematic manner. An evaluation culture of individual FP projects is not implemented (Rietschel and Arnold, 2009)

An ex-post evaluation of FP-7 is ongoing, but an interim report of 2010 shared these points of criticism. In addition, fragmentation within FP-7 programmes and a lack of coordination between EU and MS activities was found to mitigate added value by the largest EU research programme even more. On the other side, ERC and MSCA have been surveyed as success stories, although their mandates and administrative routine have been subjects to several criticisms (Annerberg et al., 2010). In terms of CVD research, FP 7 meant an upscale of available funds and a diversification of efforts across CVD management pathways, especially expanding for treatment and genetic research.

Figure 3 and 4: CVD research classified by approach and ICD grouping, for all EU funding, 2006-13



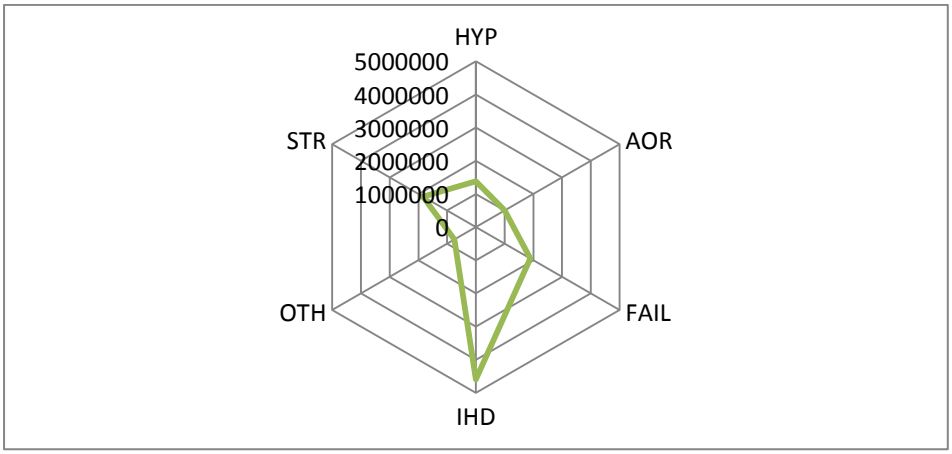
Source: authors own compilation based on (Commission, 2015a, CHAFEA (Consumers, 2015). Notes: AOR. Arterial diseases, STR: cerebrovascular diseases and stroke, FAIL: heart failure; HYP: Hypertension, CHD: Coronary heart disease, ISCH: Ischemic heart diseases and OTH: other forms not classified.

In ICD categories, FP-6 projects have been widely spread over all relevant CVD diseases, except for Ischemic Heart diseases. Under FP-7 severe concentration effect took place to Stroke and Heart failure research. Heart Failure has attracted 1.8-fold higher funding under FP-7 than under FP-6. None of the DG Sante and Health Programme projects could be classified for an ICD category, but aimed at developing prevention strategies or therapy management. Although drug and diagnosis tool development is important for overall CVD burden mitigation, it should be noted that both field are covered in cooperation with the private sector in different schemes of the FP-7 (*Joint Technology Initiatives*).

(b) Outlook to national RFOs

Analyzing the purposive project sample of national RFOs, there are different concentration effects in terms of ICD categories compared to European funding organizations. National RFOs heavily focus on Ischemic Heart Diseases and Stroke Management. A majority of projects is targeting genetic factors leading to CVD or improving therapeutic pathways for CVD patients. Especially for early detection of heart failure, biomarkers and individual genes are searched by 23 projects. On a national level, improving Diagnostics are also widespread compared to the EU level. 15 projects, spread from Slovakia to France, are targeting better imaging of CVDs. In summary, national funding programmes have a small volume of 350 000 € p.a. and aim to diversify research efforts across ICD categories and approach as Diagnostics and Therapy. Also national research benefits from a direct link to patients and national CVD treatment guidelines and thus enabled to research in pilot-projects for new treatment approaches as home-monitoring for heart failure (Switzerland).

Figure 5. CVD research classified by approach and ICD grouping national RFOs, 2006-2013



Source: authors own compilation. Notes: AOR. Arterial diseases, STR: cerebrovascular diseases and stroke, FAIL: heart failure; HYP: Hypertension, CHD: Coronary heart disease, ISCH: Ischemic heart diseases and OTH: other forms not classified

1.4 Discussion and Conclusion

Eligible EU funding between 2006 and 2013 for CVD research was 413 mn €. This is a considerable share of the total CVD funding in the EU, and significantly higher than national project-based funding in any EU member state except for the UK identified in the MAPPING NCD methodology. The broad

majority of funding is managed under the framework programmes of DG Research incorporated top-down approaches with set priorities as under the *Cooperation* projects. Additionally, several new funding tools allow for a bottom-up approach of research solely deciding on research excellency, as the ERC under the *Ideas* projects of FP 7. Additionally, the MSCA of the *People* funding scheme reaches out to young researchers increasing mobility and networking. All EU funding schemes have to be evaluated against its aims to contribute to European Research Area and Innovation Union.

CVD are the leading cause of mortality in European populations, with a striking regional variance and astonishing successes in some member states over the last years. Acknowledging this, research into CVD accounted for only 6.2 % of the total eligible FP-7 budget in 2013. Projects under the European Health Programme have incorporated up to a share of 44 % of its total eligible budget for CVD research. However, the mere funding volume does not say much about expected outcomes. Projects under the European Health Programme and other funding schemes of DG Sante aimed at raising awareness and prevention campaigns, often across NCDs. Their outcome to state if the art CVD research may be doubted. EU funding schemes for CVD are heavily characterized by concentration effects on a regional level and across CVD research fields. In fact, only some MS are regularly awarded with EU grants in CVD research, and this can be broken down even to a handful of institutions. Newer member states are often not awarded with EU funds, but are confronted with high rejection rates and a high level of bureaucracy posing disincentives for institutions and researchers with limited capacities to apply. This holds true for FP-6 and FP-7 and contradicts the rationale of building up a European Research Area. Although, FP-7 has resulted in a concentration of funding towards heart failure, coordination between projects running in parallel are not integral part of the FP-7 programme. A main criticism of EU funding schemes remains the lack of evaluation routines of projects that are often coordinated amongst up to 17 project partners for in average 4.75 years. How individual project performed and how they disseminated knowledge to the research communities or to the public remains unclear at this stage (see Chapter 4).

CVD research is of growing importance to national RFOs and captures regional particularities of disease burden and treatment pathways to patients. A majority of national research is targeting Ischemic Heart Diseases and Stroke management, compared to heart failure being lead research target under FP-7. Research in new drugs has been non-existent on the national research level, and only plays a minor role for European funding. Whereas innovation in diagnostics and treatment for CVD patients is part of national research agendas, but not that often subject of European grants.

2 Private Sector Investment in CVDs

Investments in NCD research funding originate from a variety of sources, and each of these have been documented quite well. The role of national governments, supranational sources, international organizations and charities will be also topic for further analysis. However, less is known on the industry response to NCDs in terms of research and development and cooperative role to other RFOs. This section will analyze the nature and specifics of private sector investment in CVD research.

Background: Private Sector Investment in Research and Development

The Pharmaceuticals & Biotechnology sector is one of the largest investors in R&D, claiming 18.0% share of total R&D investment for 2014 (Hernandez et al., 2014). However, the sector has a much less significant share of patents to R&D investment ratios when compared to the Electronic and Electrical Equipment sector. Today, the production of safe and effective compounds requires substantial investment over a longer period, cooperation between diverse companies across the sector, particularly bio-tech companies (Hernandez et al., 2014) and taking high barriers to market entry for each individual product.

In past, analysts lauded the contribution of industry to the advancement of science and medical technologies. Today, however, where they measure productivity in terms of the ratio of the "output" of a process to some measure of the "inputs", like rising R&D expenditures and falling or static counts of new drug approvals, they have identified a sharp decline in research productivity over the past decade (Cockburn, 2007). Old confidences in the industry and its product development pathway are fading. In the 21st century, industry analysts are concerned that the decreasing levels of productivity confronts policy makers with tough questions. Where tax-payers continue to provide significant amounts financial support to industry led R&D, analysts are now asking whether these “poor outcomes justify continued public investment at its current scale?” (Cockburn, 2007)

Mapping the Private Sector Research Pipeline

In this context, mapping private sector investment in NCD research funding becomes quite important. However, such a mapping exercise also involves unique challenges. For example, the details and strategic focus of public and third sector NCD research funding programs are readily accessible and, in many cases, a matter of public record. By contrast, the activities of the private sector are not. Governed by profit, the specifics of private sector investment in NCD research are more usually confidential or reported with significant time lag

In order to map the industry response (activity, investment and initiatives) to CVDs in terms of research investment, we describe the research pipeline for major European pharmaceutical companies in terms of Molecules in Phase I, Phase II, Phase III, Submission and Approval. Data was collected from the four most recent annual reports available at the companies’ global websites (2014-2011). Where data was not available for 2014, the range 2013-2010 was applied. Results are expressed in terms of phases of development for individual molecules, which are set out in the tables below. The tables also include the total amount of R&D expenses for the available period and the percentage of sales or revenues allocated to R&D.

Table 4 details the top 20 pharmaceutical and biotechnical companies based in the US and Europe by investment in R&D. In the sections that follow, we discuss unmet need for NCDs in both Europe and the US, mapping and analyzing the commitment of each company to CVDs in terms of their individual research pipelines.

Table 4: Top 20 European and US pharmaceutical and biotechnology companies ranked by R&D investment (2013)

Rank	World Rank	Name	Country	R&D investment (€million)
1	5	NOVARTIS	Switzerland	7173.5
2	6	ROCHE	Switzerland	7076.2
3	8	JOHNSON & JOHNSON	US	5933.6
4	12	MERCK US	US	5165.0
5	14	SANOFI-AVENTIS	France	4757.0
6	15	PFIZER	US	4750.2
7	21	GLAXOSMITHKLINE	UK	4154.3
8	23	ELI LILLY	US	4010.8
9	34	BAYER	Germany	3259.0
10	37	ASTRAZENECA	UK	3202.8
11	38	AMGEN	US	2960.6
12	39	BOEHRINGER INGELHEIM	Germany	2743.0
13	40	BRISTOL-MYERS SQUIBB	US	2705.4
14	52	ABBVIE	US	2059.3
15	65	CELGENE	US	1603.4
16	66	NOVO NORDISK	Denmark	1567.4
17	68	GILEAD SCIENCES	US	1537.1
18	70	MERCK DE	Germany	1504.3
19	95	ABBOTT LABORATORIES	US	1052.9
20	96	BIOGEN IDEC	US	1047.1

Source: (Hernandez et al., 2014)

2.1 Unmet Need for CVDs

Based on CVD literature review, conducted experts interviews and in summary to the presented data on CVD prevalence in Europe a preliminary assessment of research needs can be delivered. CVDs as the main cause of mortality challenge health systems and policy makers in their regional persistent variance across Europe.

2.1.1 Raising awareness for potential of CVD risk management targets

The immense burden of CVDs in terms of mortality, DALYs and CVD related health expenditures are striking for all EU member states. Furthermore, risk factors have been researched in plentiful detail and the ESC guidelines offer a prominent platform promoting CVD prevention. The potential of CVDs risk management is not fully exploited because a) depleting emotionality in patients to change their behavior in order to reduce CVDs risk in primary but especially in secondary prevention and b) clinicians may not find the time for comprehensive and regular risk detection screenings for coronary patients as prescribed by the ESC guidelines. High CVD risk patients may need further professional help as CVDs rehabilitation therapy to break with behavioral patterns, e.g. smoking cessation. Additionally, the persistent higher CVD prevalence in women should also be gain more attention. There is research need to find attractive solutions for the adaption of the ESC prevention guidelines to cultural variations throughout Europe.

2.1.2 Heart Failure

Even though, categories as CHD, cerebrovascular and hypertensive diseases are the main driver of CVD mortality in Europe, heart failure is increasing at a slow but steady pace since the 1990s. In Germany, heart failure was the third ranked reason of mortality, with a significant higher mortality in elderly persons and the second leading cause of hospital admission in 2012 (386 548 hospital admissions in 2012). This holds also true for other EU countries, as for the UK with 152 000 inpatient episodes in 2012/2013 contributing to the highest NHS expenditures in primary care (aggregated with CHDs) (Nichols et al., 2014). It is estimated that heart failure will pose an increasing disease burden on European health systems, asymptomatically for elderly patients (Mozaffarian et al., 2015). Chronic heart failure can be treated in only limited extend avoiding a fatal CVD event, including reduction in fluid intake and drug therapy. However, there is research need in new pharmacological tools strengthening the heart muscle.

2.2 European Pharmaceutical Sector: Research Pipeline for CVDs

The European pharmaceutical sector has five companies among the world's top ten pharmaceutical firms. And indeed, across Europe, the sector is a major investor in R&D. According to the European Federation of Pharmaceutical Industries, the European pharmaceutical sector invested an estimated €30,630 million in R&D across Europe for the year 2013 (EFPI, 2014). The industry also employs about 690,000 people and supports between three and four times than number of jobs across the EU area.

2.2.1 Roche (EUR)

ROCHE is a Swiss pharmaceutical company headquartered in Basel, Switzerland. Founded in 1896 by Fritz Hoffmann-La Roche, it is the largest European pharmaceutical company in terms of investment in R&D.ROCHE owns several important biotechnology companies, like Genentech and Ventana in the US, and Chugai Pharmaceuticals in Japan. In its early years, ROCHE gained a reputation for being the first company to mass-produce synthetic vitamin C in 1934. Today, it is a market leader in cancer research. Since 2012, ROCHE's total investment in R&D had been increasing at an average of 3.19%

Table 5: Roche (EUR) Total Research and Development Investment

Mil USD	2014		2013		2012		2011	
Total R & D Expense	Amount	% of Sales	Amount	% of Sales	Amount	% of Sales	Amount	% of Sales
	8900	18.6	8700	18.6	8500	18.6	8100	19.0
% Change	+2.30		+2.35		+4.94			

Despite being the largest pharmaceutical company in Europe, ROCHE has only three CVD relevant molecules in its research pipeline and is heavily focused on cancer related drugs. Beside of significant investments in infectious diseases and some in ophthalmology, there have been 21 out of 35 molecules over the last years accountable for cancer-related drugs. Two of the three CVD-related molecules were stopped in 2012 and 2013 respectively. One molecule against the Acute Coronary Syndrome is currently in Phase I.

Table 6: Roche (EUR) Research Pipeline: CVDs

Year	Product Name	Indication	Phase
2013	Inclacumab	ACS	I
Stopped in 2013	Aleglitazar	Metabolic diseases	III
Stopped in 2012	Dalcetrapib	Coronary heart disease	III

2.2.2 Novartis International AG (EUR)

Novartis is a Swiss based company headquartered in Basel. It was formed in 1996 through the merger of Sandoz and Ciba-Geigy. In 2003, Novartis reintroduced the Sandoz brand as a single subsidiary in which it consolidated its generic drugs businesses. Today, Novartis focuses its business on three leading divisions: pharmaceuticals (Novartis), eye care (Alcon) and generics (Sandoz). Novartis is currently expanding its presence in the emerging markets of Asia, Africa and Latin America, where there is fast-growing demand for access to high-quality medicines and healthcare.

Table 7: Novartis International AG (EUR) Total Research and Development Investment

Mil USD	2014		2013		2012		2011	
Total R & D Expense	Amount	% of Sales	Amount	% of Sales	Amount	% of Sales	Amount	% of Sales
	9900	17.1	9640	16.6	9120	16.1	9240	15.8
% Change	+2.7		+5.7		-1.3			

Since 2012, Novartis has marginally increased its commitment to R&D activities. Its research pipeline is focused on cancer drugs, similar to ROCHE. 37 molecules are currently under development or in the middle of the submission process. 24 target cancer cells. Only, 4 molecules are relevant for CVD:

E.g. Sacubitril/Valsatran, a complex drug consisting of two already approved antihypertensive drugs. A Randomized Controlled Trial (RCT) in 2014 revealed that this drug significantly reduces the risk of deaths for patients with heart failure and is superior to the commonly used drug, such as enalapril (McMurray et al., 2014).

Table 8: Novartis International AG (EUR) Research Pipeline: CVDs

Year	Product Name	Indication	Phase
2014	Valsartan, sacubitril (complex)	Heart failure, hypertension	Submission
2014	Serelaxin	Acute heart failure	III
2014	Tekturna (alisikren)	CVD death/hospitalization reduction in chronic heart failure	III
2014	Canakinumab	Secondary prevention of CV events	III

2.2.3 Sanofi-Aventis (EUR)

Sanofi-Aventis is a French pharmaceutical company currently headquartered in Paris. It was formed in 2004 when Sanofi-Synthélabo acquired Aventis via a hostile takeover. Today, the company is focused on the seven strategic growth platforms: diabetes, vaccines, consumer healthcare, rare diseases & multiple sclerosis

Table 9: Sanofi-Aventis (EUR) Total Research and Development Investment

Mil Euro	**2014**		**2013**		**2012**		**2011**	
Total R & D Expense	**Amount**	**% of Sales**	**Amount**	**% of Sales**	**Amount**	**% of Sales**	**Amount**	**% of Sales**
	4.824	14.3	4.770	14.5	4.922	14.1	4.811	14.4
% Change	+1.13		-3.09		+2.31			

Beside of research in the fields of ophthalmology, infectious and auto-immune diseases, SANOFI-AVENTIS heavily invests in Oncology: almost 60% of the research is conducted for cancer. 4 molecules (out of 35) are CVD-related – one product for the prevention of myocardial infection stopped after Phase I. The development of the drug Otamixaban was terminated in 2013 after it failed to meet the expected goals in Phase III.

Table 10: Sanofi-Aventis (EUR) Research Pipeline: CVDs

Year	Product Name	Indication	Phase
2011	SAR164653	Prevent myocardiac infarction	I
2011	SAR101099	Urotensin antagonist	Stopped
2011	Otamixaban	Acute coronary syndrome	Stopped
2012	SAR164653	Prevent myocardial infarction	I

2.2.4 GlaxoSmithKline (EUR)

GSK is a British multinational pharmaceutical company currently headquartered in Brentford. It was established in 2000 by a merger of Glaxo Wellcome and SmithKline Beecham. GSK has a portfolio of products for major disease areas such as asthma, cancer, infections, mental health, diabetes and digestive conditions.

Table 11: GlaxoSmithKline (EUR) Total Research and Development Investment

Mil GBP	2014		2013		2012		2011	
Total R & D Expense	Amount	% of Sales	Amount	% of Sales	Amount	% of Sales	Amount	% of Sales
	3100	13.5	3400	12.8	3500	13.2	4000	14.6
% Change	-8.82		-2.86		-12.5			

38 molecules have been in GSKs research pipeline over the last four years. 17 of these are relevant to Oncology and 10 to CRDs. Only 3 molecules under development for CVD could be identified. The product Losmapimod has shown antidepressant and antipsychotic effects in animals and has completed a phase II trial for the treatment of depression. Beside of that indication it is also being studied for the treatment of CVDs: A phase III trial studying the effects of the product ACS is ongoing, as well as for Darapladib.

Table 12: GlaxoSmithKline (EUR) Research Pipeline: CVDs

Year	Product Name	Indication	Phase
2014	2798745	Heart failure	I
2014	Losmapimod	Acute coronary syndrome	III
2013	Darapladib	Atherosclerosis	III

2.2.5 AstraZeneca PLC (EUR)

AstraZeneca is a British-Swedish company with its headquarters in London. Founded in 1999 by the merger of Astra AB (Swedish) and the Zeneca Group (British), AstraZeneca focusses on three areas of healthcare: CVDs, Oncology, CRDs, Inflammation and Autoimmunity. In 2012, it announced collaboration with the American company Amgen on inflammatory disease treatments. The same year, it announced a joint acquisition of the biotechnology company Amylin Pharmaceuticals with American company Bristol Myers Squibb.

Table 13: AstraZeneca PLC (EUR) Total Research and Development Investment

Mil USD	2014		2013		2012		2011	
Total R & D Expense	Amount	% of Sales	Amount	% of Sales	Amount	% of Sales	Amount	% of Sales
	5579	21.4	4821	18.8	5243	18.7	5523	16.4
% Change	+15.7		-8.0		-5.1			

Similar to other companies, the commitment of ASTRAZENECA towards the development of CVD-drugs remains moderate. Out of 52 screened molecules, only two had CVD-related targets. The superior effects of one Phase II molecule, which is designed for the treatment of atrial fibrillation (AZD2927) has been recently questioned by the scientific community (Walfridsson et al., 2014).

Table 14: AstraZeneca PLC (EUR) Research Pipeline: CVDs

Year	Product Name	Indication	Phase
2011	AZD2927	Atrial fibrilation	II
2013	MEDI6012	Acute coronary syndrome	I

2.2.6 Bayer AG (EUR)

Founded in 1863, Bayer is a German chemical and pharmaceutical company which headquarter is in Leverkusen. Today, Bayer is active in healthcare, but also has major divisions in material and crop science. The company is mainly focused on familiar over-the-counter consumer health care products and prescription medicines.

Table 15: Bayer AG (EUR) Total Research and Development Investment

Mil EURO	2014		2013		2012		2011	
Total R & D Expense	**Amount**	**% of Sales**	**Amount**	**% of Sales**	**Amount**	**% of Sales**	**Amount**	**% of Sales**
	3574	8.5	3406	8.5	3013	7.6	2932	8.0
% Change	+4.9		+13		+2.8			

*Notes:*For 2013 R&D Expenditure, there was a discrepancy between the 2014 and 2013 annual report. The table records the figure reported in 2014*

There have been 16 molecules in the research pipeline of BAYER from 2010-2014. Only 4 targeted at CVDs. One drug -Rivaroxaban- had its European approval for secondary prophylaxis for ACS in 2013. The drug revealed to have less side-effects compared to the conventional therapy. All of the other three molecules are under development, currently in the phase II trial, have chronic heart failure as their indication.

Table 16: Bayer AG (EUR) Research Pipeline: CVDs

Year	Product Name	Indication	Phase
2012	Xarelto (rivaroxaban)	Venous thromboembolism. Secondary prophylaxis for ACS	Submitted for approval
2014	Finerenone	Chronic heart failure and diabetic nephropathy	II
2014	Vericiguat	Chronic heart failure	II
2013	BAY 1067197	Chronic heart failure	II

2.2.7 Boehringer-Ingelheim (EUR)

Originally founded in 1885 by Albert Boehringer, Boehringer Ingelheim is a German pharmaceutical company headquartered in Ingelheim. Until today, Boehringer Ingelheim remains a family owned company. Its focus is on CRDs, metabolism, immunology, oncology and central nervous system diseases. The company claims a reputation for providing effective products for the treatment of COPD.

Table 17: Boehringer-Ingelheim (EUR) Total Research and Development Investment

Mil EURO	2014		2012		2011		2010	
Total R & D Expense	Amount	% of Sales	Amount	% of Sales	Amount	% of Sales	Amount	% of Sales
	2654	19.9	2743	19.5	2795	19	2516	19.1
% Change	-3.24		-1.9		11			

Boehringer-Ingelheims only CVD-related drug, Pradaxa, was approved in 2010. Although it has been significantly superior to the comparison treatment (e.g. the patent-free drug Marcumar), Pradaxa experienced some heavy debates over the last years. Over 4000 people reported heavy side-effects and the company needed to pay over 650 mn USD for people who suffered from the intake of Pradaxa. Despite this high number, the company continues the promotion of its drug. [1]

Table 18: Boehringer-Ingelheim (EUR) Research Pipeline: CVDs

Year	Product Name	Indication	Phase
2010	Pradaxa (dabigatran etexilate)	Stroke prevention in atrial fibrilation	Approved

2.2.8 Novo Nordisk (EUR)

Founded in 1989 through the merger of the smaller Danish companies Nordisk Insulin laboratorium and Novo Terapeutisk Laboratorium, Novo Nordisk is a Danish pharmaceutical company currently headquartered in Bagsvaerd. The company's major product lines address the disease areas of diabetes, hemostasis and also growth hormone therapy and hormone replacement therapy. The company manufactures pharmaceutical under various brand names, which include Levemir, NovoLog, Novolin R, NovoSeven, NovoEight and Victoza.

Table 19: Novo Nordisk (EUR) Total Research and Development Investment

Mil DKK	2014		2013		2012		2011	
Total R & D Expense	Amount	% of Sales	Amount	% of Sales	Amount	% of Sales	Amount	% of Sales
	13800	15.5	11700	14.0	10900	14.0	9300	14.5
% Change	+17.94		+7.33		+17.2			

With its focus on other disease areas, Novo Nordisk does not have any CVD relevant molecules under development. Interestingly, since 2011, the company has progressively increased its commitment to R&D.

2.2.9 UCB (EUR)

UCB was founded in 1928 and was originally a chemicals manufacturer with a separate pharmaceuticals division. In the 1950s, however, the focus of UCB had shifted to prescription medicines. In 2004, UCB acquired Celltech, the UK's leading biotechnology company, which brought expertise in antibody-based drug discovery to the company. Schwarz Pharma was acquired in 2007, bringing its own portfolio of neurology and urology products. UCB now focuses on severe diseases

[1] http://www.drugwatch.com/pradaxa/lawsuit/

within immunology and central nervous systems. The UK premises of UCB are located in Slough, Berkshire, which includes housing for around 600 of its staff.

Table 20: UCB (EUR) Total Research and Development Investment

Mil EUR	2014		2013		2012		2011	
Total R & D Expense	Amount	% of Sales	Amount	% of Sales	Amount	% of Sales	Amount	% of Sales
	928	28.0	886	28.0	861	25.0	778	24.0
% Change	+4.7		+2.9		+10.7			

UCB does not have any CVD relevant molecules under development. However, its commitment to R&D investments has increased progressively since 2011.

2.2.10 Shire (EUR)

Founded in 1986, Shire is a British pharmaceutical company (registered in Jersey) currently headquartered in Ireland. Within its first two years of operation, the company had launched a range of supplemental calcium products for patients seeking to treat or prevent osteoporosis. Soon after, innovative drug development programs were undertaken for the benefit of patients facing such challenging conditions as Alzheimer's disease and end-stage renal failure. After the turn of the millennium, with the acquisition of TKT, the company began to focus on rare diseases, which remains a strategic focus today. In 2014, Shire rejected a takeover offer by AbbVie.

Table 21: SHIRE (EUR) Total Research and Development Investment

Mil USD	2014		2013		2012		2011	
Total R & D Expense	Amount	% of Sales	Amount	% of Sales	Amount	% of Sales	Amount	% of Sales
	840.0	14,5	890.2	18,5	965.5	20,6	770.7	18,1
% Change	-5.63		-7.8		+25.2			

While its commitment to R&D experienced a large jump in 2012 it decreased again in the following years. Nevertheless, its R&D spending has increased slightly over the relevant period. Shire does have one CVD relevant, one Diabetical molecule and two drugs against mental diseases under development.

Table 22: Shire (EUR) Research Pipeline: CVDs

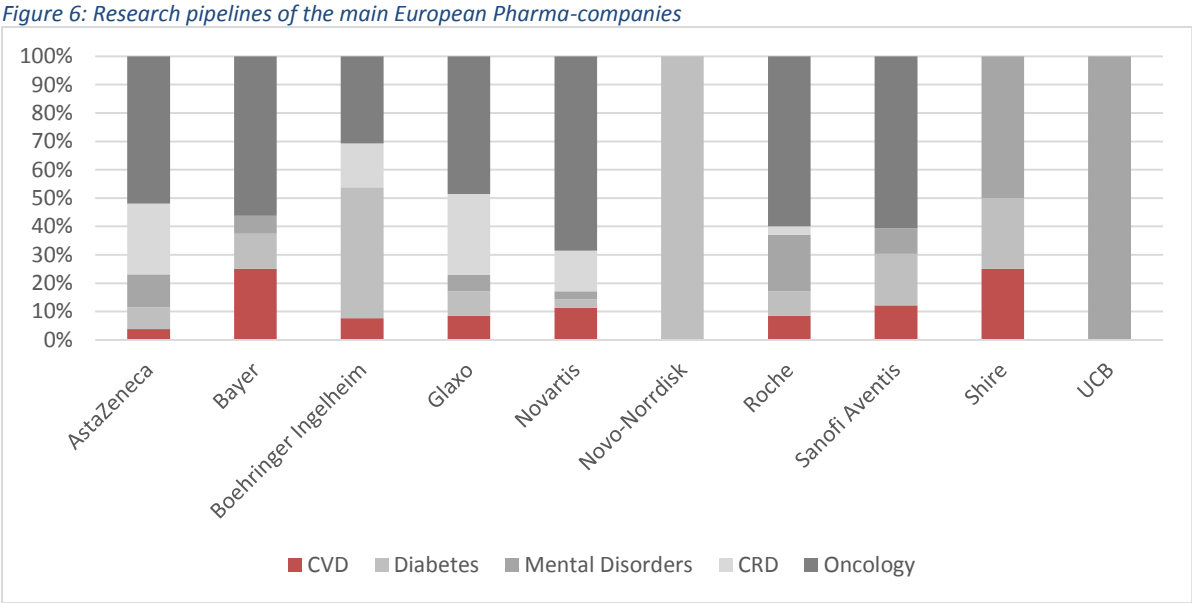
Year	Product Name	Indication	Phase
2013	SHP613	Acute Vascular Repair	II

2.3 European Pharmaceutical Sector: Short Summary

Overall, the European pharmaceutical sector has increased its commitment to R&D over the past four years. GSK is the only top 10 company which has recorded a decreasing commitment to research investment. Some companies, like AstraZeneca, have recorded a massive increase in R&D spending. But most companies have performed progressive steady increases.

While most companies have had a rather heterogeneous research pipeline (figure 5), with cancer being always the major target, two companies, UCB and Novo Nordisk, have been specialized on one NCD (Diabetes and Mental Disorders).

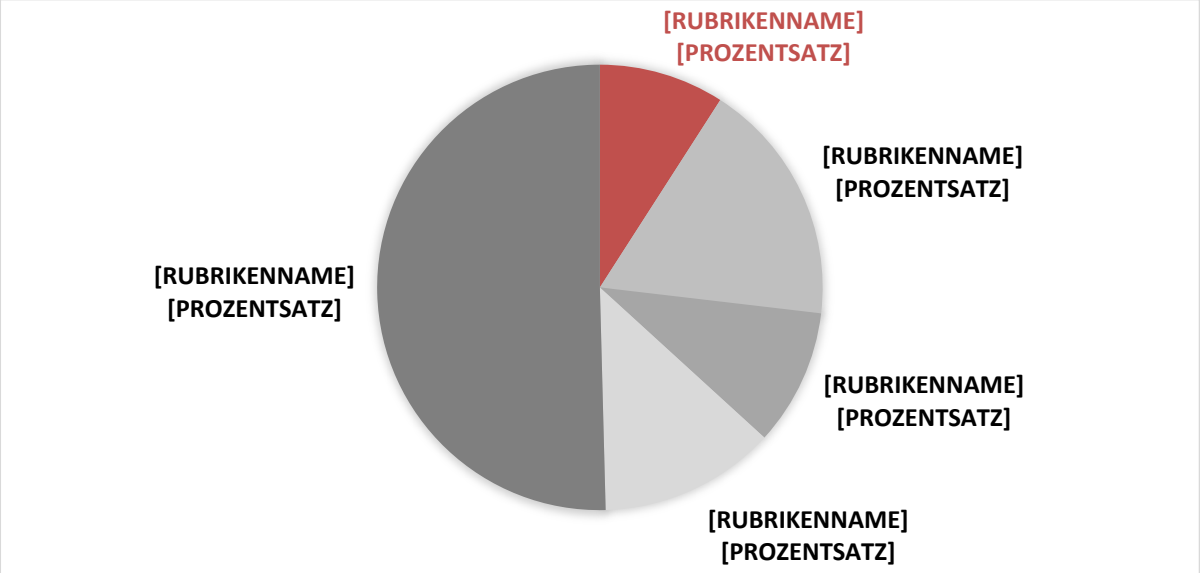
Figure 6: Research pipelines of the main European Pharma-companies



It can be summarized, that research by pharmaceutical companies in this selection for combating CVD is rather moderate. This becomes even more obvious in the figure below, which accumulates all the European pharmaceutical research pipelines and classifies them according to NCD.

Mental disorders and cardiovascular drug research plays clearly a minor role among all NCDs. Less than 10% of all R&D investments in the field of NCDs among the top10 European pharmaceutical companies has been spent on CVD research. Half of the last four years research pipeline was done for oncology-related drugs. Diabetes is on the second position with 18% of drugs. CRD and mental disorders-related drugs are on the 3rd and 4th position.

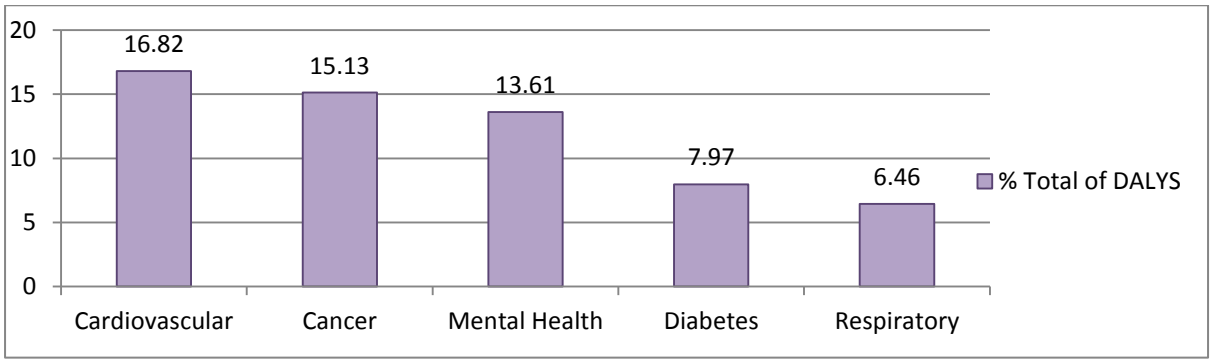
Figure 7: Last four years research pipeline of European pharmaceutical companies



2.4 US Pharmaceutical Sector: Research Pipeline for CVDs

In the United States, the burden of disease associated with CVDs is a little bit lower than that of Europe (16.82% of total lost DALYs compared to 19.53% in Europe). But remains the largest cause of lost DALYs across the country. In the US, however, there is slightly lower burden of disease associated with cancer (15.13% of total lost DALYs instead of 16.97% in Europe). The US seems to have larger problems with categories like diabetes, mental health and respiratory diseases than Europe. But overall, the levels of lost DALYs in Europe and the US are about the same.

Figure 8: NCDs in United States 2010: Percentage of Lost DALYs by Disease Category



***Sourced at: http://vizhub.healthdata.org/gbd-compare/*

Five of the world's top ten pharmaceutical companies have their headquarters in the US, which is also the world's largest market for pharmaceuticals, and a world leader for investment in R&D. U.S. firms carry out the majority of global R&D and hold the intellectual property rights on most new medicines. The US research pipeline has approximately 3,400 compounds currently under development in the United States, which is significantly more than any other region (PHRMA, 2015). The US biopharmaceutical sector is one of the most R&D-intensive sectors in the United States and around the world. In the US, the industry invests more than 10 times the amount of R&D per employee than all manufacturing industries overall (PHRMA, 2015).

2.4.1 Merck (US)

Merck US is headquartered in Kenilworth, New Jersey. The company was established in 1891 as a US subsidiary of the German company Merck, which was originally founded in 1668. During the First World War, the US government confiscated Merck and reestablished it as an independent American company. In 2013, Merck invested $7,500 million in R&D, which represents the largest amount in the sector both globally and the US. However, Merck's overall investment level in R&D has been steadily falling over the period 2010-2013, with a major fall of 22.7% in 2011.

Table 23: Merck (US) Total Research and Development Investment

(Mil USD)	2014		2013		2012		2011	
Total R & D Expense	Amount	% of Sales	Amount	% of Sales	Amount	% of Sales	Amount	% of Sales
	7180	16.9	7500	17	8200	17.4	8500	17.7
% Change	-4.30		-8.54		-3.53			

Consistent with its position as the largest US pharmaceutical company by R&D investment, Merck has the largest number of pharmaceutical technologies for CVD in its research pipeline: 3 molecules under development have been for CVDs. Two dealt with the management of lipids. The drug Anacetrapib, which is classified as a lipid management drug, is expected to gain a revenue of over 1

bn USD per year. In expectation of this high revenue, Merck has conducted a clinical trial with over 30.000 participants which has cost almost 100 mn USD (Cannon et al., 2010).

Table 24: Merck (US) Research Pipeline: CVDs

Product Name	Indication	Phase
Zontivity® (vorapaxar)	VTE	Approved
MK-0859 (anacetrapib)	Lipid management (LDL-C and HDL-C)	Phase III
Liptruzet (ezetimibe + atorvastatin)	Hyperlipidemia	EU application filed in 2014

2.4.2 Johnson & Johnson

Founded in 1886, Johnson & Johnson is a U.S. medical devices, pharmaceutical and consumer healthcare products company currently headquartered in New Brunswick, New Jersey Its medical devices division, which we consider in the next section, specializes in orthopedics, neurological disease, diabetes care, infection prevention, and cardiovascular disease. Its pharmaceutical division focuses on oncology, immunology, neuroscience, diabetes and cardiovascular diseases.

Table 25: Johnson & Johnson (US) Total Research and Development Investment

Mil USD	2014		2013		2012		2011	
Total R & D Expense	Amount	% of Sales	Amount	% of Sales	Amount	% of Sales	Amount	% of Sales
	8494	11.4	8183	11.5	7665	11.4	7548	11.6
% Change	+3.8		+6.8		+1.6			

The compound Rivaroxaban (anti-coagulant) was filed in the U.S. in 2010 for the prevention of stroke in patients with atrial fibrillation, which can lead to major physical and behavioral impairments, or death. In 2011 J&J made a partnership with Bayer Healthcare on the development and launch of this product with the commercial name of XARELTO®. In 2012, the FDA approved the expanded use of XARELTO® (rivaroxaban) to treat deep-vein thrombosis, or DVT, and pulmonary embolism, or PE and to reduce the risk of recurrent DVT and PE following initial treatment. In 2014 J&J received the third complete response from FDA after filing XARELTO® for the treatment of acute coronary syndrome and the second complete response for Stent Thrombosis for acute coronary syndrome. This drug is also for chronic heart failure and for prevention of symptomatic VTE and VTE-related death in high risk, medically ill patients.

Table 26: Johnson & Johnson (US) Research Pipeline: CVDs

Product Name	Indication	Phase
XARELTO® (rivaroxaban)	Prevention of stroke in patients with atrial fibrillation	Approved
	DVT and PE	
	Acute Coronary Syndrome	Phase III in 2014
	Chronic Heart Failure and prevention of symptomatic VTE and VTE-related death	

2.4.3 Pfizer

Founded in New York in 1849 by Charles Pfizer and Charles F. Erhart, Pfizer is an American pharmaceutical company currently headquartered in New York. Recently, Pfizer has also been the subject prosecutions for illegal and off-label marketing in relation to the arthritis drug Bextra, paying the US government multi-billion dollar settlements. Pfizer produces medicines for a wide range of disease areas, including: oncology, diabetes, cardiovascular disease and neurology. Interestingly, the company's commitment to R&D has been progressively decreasing since 2010 to the point that its levels of investment have been diminished by about a third over the relevant time period.

Table 27: Pfizer (US) Total Research and Development Investment

Mil USD	**2014**		**2013**		**2012**		**2011**	
Total R & D Expense	**Amount**	**% of Sales**	**Amount**	**% of Sales**	**Amount**	**% of Sales**	**Amount**	**% of Sales**
	8393	16.9	6678	12.9	7870	13.7	8681	14.2
% Change	+25.7		-15.1		-9.34			

Pfizer used to have a rather balanced pipeline over the last years, with a slight emphasis towards oncology (8 molecules out of 26 compounds for NCDs). Beside of the research on NCDs, Pfizer has a strong commitment towards research on acute and chronic pain. Currently, 4 compounds against CVDs are under development.

Table 28: Pfizer (US)Research Pipeline: CVDs

Product Name	**Indication**	**Phase**
Eliquis (apixaban)	VTE Prevention	Registration
	VTE Treatment	Phase III
	Prevention of stroke and Systemic embolism in patients with nonvalvular atrial fibrillation	Registration (2012)
Bococizumab (RN316) (PF-04959615)/ RN317 (PF-05335810)	Hypercholesterolemia	Phase III
PF-06282999	Acute Coronary Syndrome	Phase I
PF-03049423	Stroke recovery	Phase II

2.4.4 Eli Lilly

Eli Lilly was founded in 1877 by Eli Lilly, a pharmaceutical chemist and veteran of the American Civil War, who was company president until his death in 1898. Eli Lilly was the first pharmaceutical company to mass produce break-through drugs like insulin, polio vaccine and penicillin. Today, the company remains the largest manufacturer and distributor in the world of psychiatric medications. In 2009, Eli Lilly paid a $515 million fine in relation to the off-label marketing of the dementia drug, Zyprexa. Today, the company's focus is on the disease areas of autoimmunity, cardiovascular disease, musculoskeletal disorders, neuroscience, oncology and diabetes.

Table 29: Eli Lilly (US) Total Research and Development Investment

Mil USD	**2014**		**2013**		**2012**		**2011**	
Total R & D	**Amount**	**% of Sales**	**Amount**	**% of Sales**	**Amount**	**% of Sales**	**Amount**	**% of Sales**

Expense	4734	24.1	5531	23.9	5278	23.4	5021	20.7
% Change	-14.4		+5.0		+5.0			

Unfortunately, it has been difficult to retrieve detailed information about Eli Lillys last years research pipeline. It is only mentioned that there has been some effort by Lilly's in CV diseases investment, with products in the pipeline for the past 5 years.

2.4.5 Amgen

Founded in 1980, Amgen is a US biopharmaceutical company currently headquartered in Thousand Oaks, California. Amgen is focused on kidney disease, cancer, rheumatoid arthritis, bone disease and other serious illnesses.

Table 30: Amgen (US) Total Research and Development Investment

Mil USD	**2014**		**2013**		**2012**		**2011**	
Total R & D Expense	**Amount**	**% of Sales**	**Amount**	**% of Sales**	**Amount**	**% of Sales**	**Amount**	**% of Sales**
	4297	21.4	4100	22.5	3400	20.4	3200	20.9
% Change	+4.8		+20.6		+6.25			

Amgen has currently two products in their pipeline. Beside of the compound "Evacetrapib", which is designed against atherosclerosis and vascular diseases, they are developing a drug against high blood level of cholesterol, for patients, for whom statins do not work.

Table 31: Amgen (US) Research Pipeline: CVDs

Product Name	**Indication**	**Phase**
Evacetrapib	High risk vascular disease	Phase III
	Atherosclerosis	Phase II
PCSK9 MAb	Hypercholesterolemia	Phase II

2.4.6 Bristol-Myers Squibb

Founded in New York in 1858 by Edward R. Squibb, Bristol-Myers Squibb is a US based pharmaceutical company currently headquartered in New York City. Today, Bristol-Myers Squibb manufactures pharmaceutical products in a number of disease areas including: cancer, HIV/AIDS, cardiovascular disease, diabetes, hepatitis, rheumatoid arthritis, fibrotic diseases and psychiatric disorders

Table 32: Bristol-Myers Squibb (US) Total Research and Development Investment

Mil USD	**2014**		**2013**		**2012**		**2011**	
Total R & D Expense	**Amount**	**% of Sales**	**Amount**	**% of Sales**	**Amount**	**% of Sales**	**Amount**	**% of Sales**
	4534	28.5	3731	30.3	3904	28.6	3839	21.8
% Change	+21.5		-4.4		+1.7			

While there have been 14 NCD-related drugs in their 4 years pipeline, only one had a CVD as indication. The drug "Eliquis" is already approved for the indication Atrial fibrillation and is currently undergoing a phase III trial for stroke prevention, where it has shown to be superior to "warfarin".

Table 33: Bristol-Myers Squibb (US) Research Pipeline: CVDs

Product Name	Indication	Phase
Eliquis (apixaban)	Anticoagulant Drug	Phase III (studies AVERROES /ARISTOTLE)

2.4.7 Abbvie

Formed in 2011, Abbvie is a US biopharmaceuticals company headquartered in Chicago, Illinois. Abbvie was formed via a divestment from Abbot Laboratories. Whereas Abbott Laboratories focuses on diagnostic equipment, medical devices and consumer health care products; AbbVie operates as a research-based biopharmaceutical company. The company claims the development of two important breakthrough medications for the treatment of HIV. Today the company's research focus is on areas such as: immunology, oncology, neuroscience, kidney and disease, and women's health

Table 34: AbbVie (US) Total Research and Development Investment

Mil USD	2014		2013		2012		2011	
Total R & D Expense	Amount	% of Sales	Amount	% of Sales	Amount	% of Sales	Amount	% of Sales
	3297	16.5	2855	15.19	2778	15.11	2618	15
% Change	+15.48		+2.77		+6.11			

Focused on other areas, Abbvie does not have any CVD relevant molecules under development, but its commitment to R&D investment has been increasing since 2010.

2.4.8 Celgene

Founded in 1986, Celgene is a US based biopharmaceutical company currently headquartered in Summit, New Jersey. Celgene's research focus is on the areas of cancer, immune and inflammatory disorders. Major compounds in development concern the treatment of hematological and solid tumor cancers, together with chronic lymphocytic leukemia, non-Hodgkin's lymphoma, small cell lung cancer and prostate cancer.

Table 35: CELGENE (US) Total Research and Development Investment

Mil USD	2014		2013		2012		2011	
Total R & D Expense	Amount	% of Sales	Amount	% of Sales	Amount	% of Sales	Amount	% of Sales
	2431	32.13	2226	34.99	1724	32	1600	34.04
% Change	+9.2		+29.12		+7.75			

Focused on other areas, Celgene does have only one compound for CVDs, which is under development for the treatment of peripheral artery diseases. Beside of this indication it is also being studied for the diabetic foot ulcers.

Table 36: CELGENE (US) Research Pipeline: CVDs

Year	Product Name	Indication	Phase
	PDA-002	Peripheral artery diseases	Phase I

2.4.9 Gilead Sciences

Founded in June 1987 by the then 29 year old Michael Riordan, Gilead Sciences is US based biotechnology currently headquartered in Foster City, California. Gilead's research focus in on HIV/AIDS, liver diseases, cancer, CRDs and CVDs.

Table 37: Gilhead Sciences (US) Total Research and Development Investment

Mil USD	2014		2013		2012		2011	
Total R & D Expense	Amount	% of Sales	Amount	% of Sales	Amount	% of Sales	Amount	% of Sales
	2854	11.4	2120	19.6	1760	18.72	1230	15.19
% Change	+34.62		+20.45		+43.08			

Beside Gilhead's commitment to fight HIV infection, it has conducted also research for several NCD and currently, Gilhead has 3 compounds under development for the treatment of CVDs.

Table 38: Gilhead Sciences (US) Research Pipeline: CVDs

Product Name	Indication	Phase
Ranexa® (ranolazine)	Chest pain among chronic angina patients with type 2 diabetes	Phase IV
Ranolazine + dronedarone	Paroxysmal atrial fibrillation	Phase II
GS-6615	Ischemic heart disease and arrhythmias treatment	Phase I

2.4.10 Abbott Laboratories

Following the divestment of AbbVie in 2011, Abbott has refashioned itself as pharmaceutical company focused largely on consumer healthcare and prescription medicines. Since 2011, Abbot's investment in R&D activities has fallen substantially.

Table 39: Abbott Laboratories (US) Total Research and Development Investment

Mil USD	2014		2013		2012		2011	
Total R & D Expense	Amount	% of Sales	Amount	% of Sales	Amount	% of Sales	Amount	% of Sales
	1345	6.6	1452	6.66	1544	7.18	1512	7.06
% Change	-7.37		-5.99		+2.12			

One third of Abbots research among NCDs is conducted for the treatment of CVDs. We have identified three molecules under development; all of them at different stages and against various forms of CVDs.

Table 40: Abbott Laboratories (US) Research Pipeline: CVDs

Product Name	Indication	Phase
Levosimendan	Cardiogenic Shock	Phase II
Autologous, Unfractionated Bone Marrow Mononuclear Cells	Acute Myocardial Infarction	Phase I
ABT-335	Dyslipidemias, carotid artery disease and coronary heart disease	Phase III

2.4.11 Biogen Idec

Biogen Idec is a global biotechnology company based in Cambridge, Massachusetts, that specializes in the development of treatments for neurodegenerative, hematologic and autoimmune diseases. Founded in Geneva in 1978, Biogen became the third largest biotechnology company in the world after merging with San Diego, California-based IDEC Pharmaceuticals in 2003.

Mil USD	2014		2013		2012		2011	
Total R & D Expense	Amount	% of Sales	Amount	% of Sales	Amount	% of Sales	Amount	% of Sales
	1893	19.50	1444	20.80	1335	24.20	1220	24.2
% Change	+31.0		+8.20		+9.4			

With its focus on other disease-areas, Biogen Idec hasn't conducted any research over the last years in terms of CVDs.

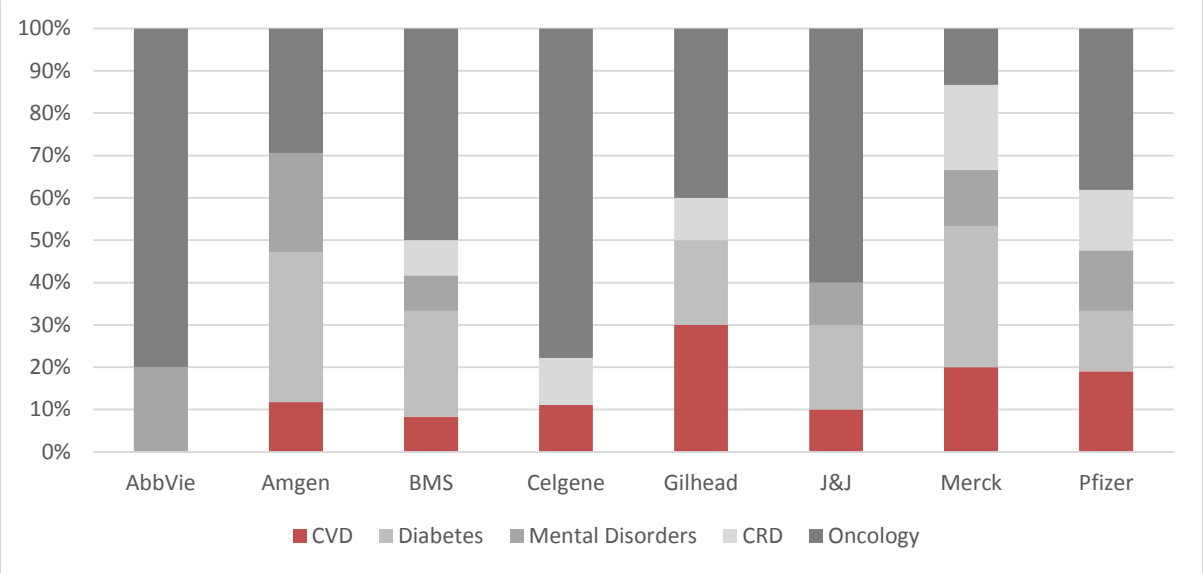
2.5 US Pharmaceutical Sector: Short Summary

US levels of investment in R&D have been very mixed over the last years. Companies at the top of the scale, like Merck and Pfizer, have steadily reduced their levels of investment. At the lower end of the scale, companies like Gilead and Celgene have massively increased their commitment.

Almost all companies have a rather heterogeneous research pipeline, with cancer being most of the time the major target. AbbVie has the least heterogeneous NCD-pipeline with a research-focus on oncology and mental health.

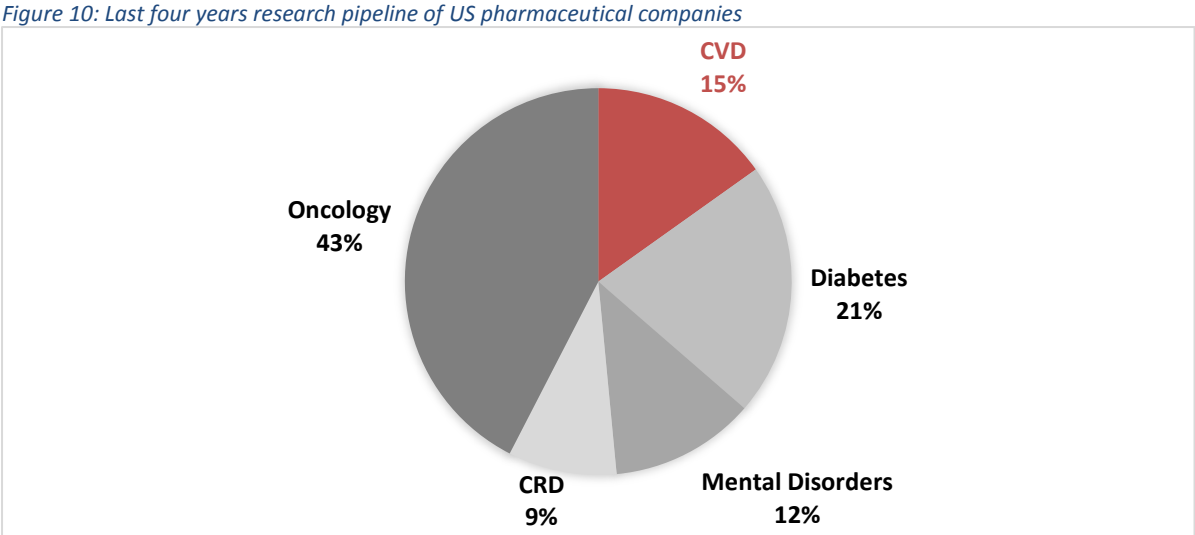
Gilhead has the highest share of NCD-related drugs with 3 compounds out of 10 being under development. In terms of the amount of NCD-related drugs, Pfizer is on position No°1, because it has conducted research on 21 different molecules over the last years. 4 of them were for CVDs.

Figure 9: Last four years research pipeline of US pharmaceutical companies



As the figure above and below clearly demonstrate: the overall research against CVDs is rather small, compared to oncology, which is the main field of interest for US pharmaceutical companies, followed by Diabetes. CVDs are on the third position and account for 15%. Mental disorders and CRD-related drugs play the smallest role among all NCDs.

Figure 10: Last four years research pipeline of US pharmaceutical companies



2.6 Pharmaceutical Research Pipelines: Discussion

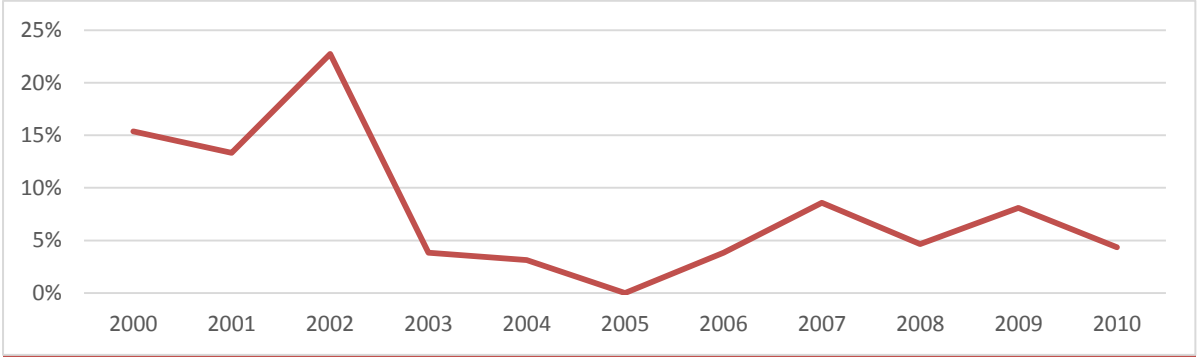
Looking at both, the North-American and the European pharmaceutical market, it becomes clear that there has been a strong focus on the development of cancer-drugs: Almost half of all observed new molecular entities (NMEs) have been developed for cancer (n=164 out of 341). All other NCD-related NMEs were almost evenly distributed – with specific market-characteristics, such as the fact that 40% of all European NMEs identified for Diabetes have been developed by Novo-Norrdisk.

The tremendously skewed research efforts towards cancer have been amplified over past years. The magazine Med Ad News compiled in 1998 a list of 200 medicines with the highest sales worldwide. In that year 12 of these 200 were cancer drugs and of the 30 drugs with sales above 1 bn USD only one was a cancer drug (Taxol). 10 years later, in 2008, 23 sales in this top 200 drugs accounted for cancer and 20 had sales over 1 bn USD. One reason for this trend is scientific motivated: recent studies have revealed the genetic changes in cells that cause cancer posing more possible targets for drug innovations (Pollack, 2009, Johnson et al., 2014). There are also financial motivations: Pharmaceutical companies seem to be focused on easy targets and are risk-averse when it comes to the development of new drugs (Spencer, 2014). This can lead to the development of a new drug, which has an expected high price and a disproportional additional benefit. One example is the drug "Tarceva", developed by Roche for the treatment of pancreatic cancer. The treatment with Tarceva costs around 3500 USD per month and prolongs the survival of patients by "only" 12 days on average (Pollack, 2009).

While almost half of the pharmaceutical research has been directed towards oncology, only 10% of NCD-related research was conducted for CVDs, approximately the same share as for mental disorders. Gilhead and Bayer have the highest share of CVD-NMEs (30%, respectively 25%), AstraZeneca the lowest with 4%. Other companies, such as Abbvie and the Diabetes-focused Novo-Nordisk haven't had any CVD-compound in their pipeline over the last years.

A look at the newly approved CVD-related NMES, approved by the FDA, shows a rather declining trend of CVD NMEs in the Pharma industry research pipelines over the last years (figure below).
Its getting more and more apparent that the commitment by the industry towards CVDs is decreasing. One reason might be the high clinical trial costs for chronic conditions, which are more prevalent among elderly patients and require a longer observation time. This is the opposite to the clinical trials of some oncology drugs (see example above).

Figure 11: Percentage of CVD-related New Molecule Entities (NMEs) to total NMEs by the FDA



Source: (FDA, IHS Global Insight)

This is contrasted by the persistent high pattern of disease burden, and DALY losses caused by CVD. European levels of investments have been, except for one company, steadily increased, while the US investments have been more mixed over the past years.

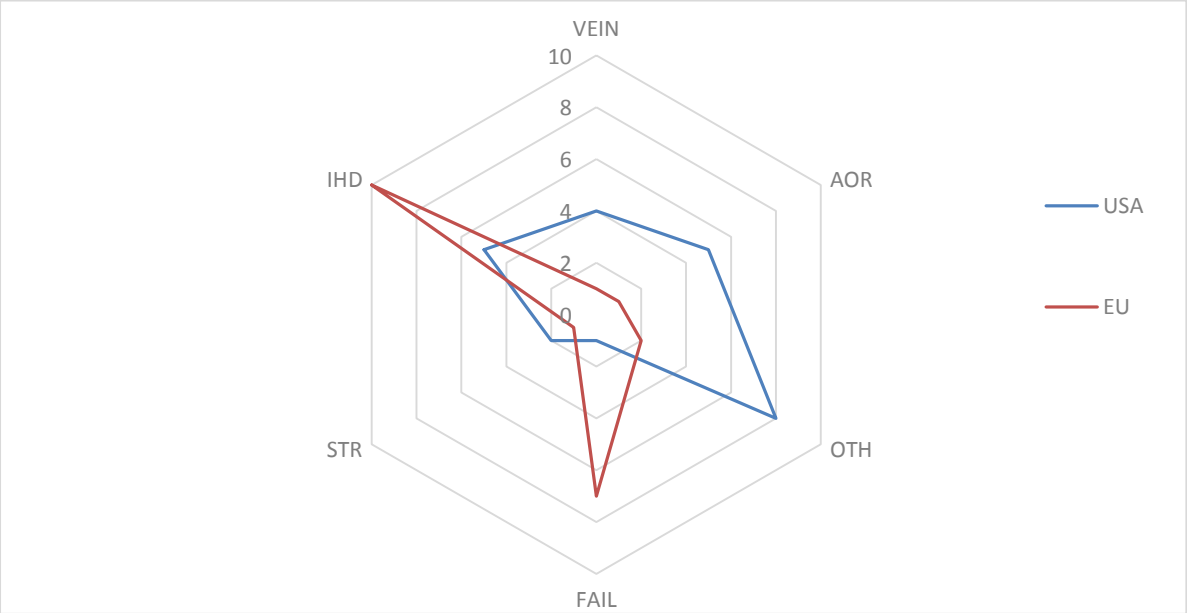
This trend is also reflected in NCD-related NMEs. The European pharmaceutical sector had in total 242 NCD related molecules under research, whereas the US market had 99.

But the numbers of NMEs or even the sales of compounds should not be the single output indicator, because it does not necessarily reflect how much the individuals and the society benefits from one NME. It rather highlights the marketing innovativeness to sell new molecules than it focuses on the clinically benefit of a new medicine.

Therefore, beside of the comparison of NMEs counts between the US and the European market, a more detailed view on the specific targets of the CVD-related compounds is shown in the figure

below. NME are classified to ICD groups – with the exception of "Heart failure", which is classified under "Other forms of Heart Diseases", but receives a special focus in our analysis, since we consider the area of heart failure as unmet need.

Figure 12: Targets of compounds under development for CVDs in the last four years research pipeline



*Heart Failure is originally classified under "Other forms of heart diseases" (VEIN: Diseases of veins, lymphatic vessels and lymph nodes; AOR: Diseases of arteries, arterioles and capillaries; OTH: Other forms of heart diseases; FAIL: Heart failure; STR: Cerebrovascular Diseases; IHD: Ischemic heart diseases)

The figure above does not show many overlaps in terms of CVD-related research between both markets. While the European companies have concentrated heavily on Ischeamic Heart Diseases and heart failure, most of the research conducted by the US companies have been directed towards diseases of arteries and veins, respectively other forms of heart diseases. Cerebrovascular Diseases have the lowest share among the represented categories and rheumatic fever as well as pulmonary and hypertensive diseases are not at all represented. The main driver of CVD prevalence Ischemic heart diseases, seems to be well-covered by the European Pharma-companies, while on the other hand fields like cerebrovascular and hypertensive diseases are heavily underrepresented by both sectors.

2.7 Medical Devices Industry: Research Pipeline for CVDs

The objective of this section is to provide a map of CVD relevant outputs of the Medical Devices (MD) Industry. In order to map MDs industry R&D investments, we identified a list of top 16 medical device manufacturers worldwide ranked by total revenue (updated to October 9, 2014). Based on website interrogations and annual reports, general information and total R&D expenses for each MD company have been collected for the period 2011 to 2014.

*Table 41:Top 16 Medical Devices Companies by Research and Development Investment (2014)**

MD Co. Rank	World Co. Rank	Company	Country	Total revenues (Bn USD)	Total R&D Investment (Mn USD)
1	34	Johnson & Johnson	United States	28.7	8,494
2	9	General Electric Co.	United States	18.1	4,233
3	249	Medtronic Inc	United States	17.1	1,477
4	54	Siemens AG	Germany	17.0	4,065
5	346	Baxter International Inc	United States	16.4	1,421
6	283	Fresenius Medical Care AG & Co. KGAA	Germany	15.2	369
7	472	Koninklijke Philips NV	Netherlands	11.8	1,635
8	327	Cardinal Health Inc.	United States	11.0	NA
9	52	Novartis AG (Alcon)	Switzerland	10.7	903
10	349	Covidien plc[2]	Ireland	10.4	546
11	719	Stryker Corp.	United States	9.3	614
12	610	Becton, Dickinson and Co.	United States	8.3	550
13	1047	Boston Scientific Corp.	United States	7.2	817
14	732	Essilor International SA	France	7.2	188
15	753	Allergan Inc. (Actavis)[3]	Ireland	6.7	1,085.9
16	957	St. Jude Medical Inc.	United States	5.6	692

*http://www.mddionline.com/article/top-40-medical-device-companies;

[2] Medtronic plc (NYSE: MDT)) has completed the acquisition of Covidien plc (NYSE: COV) in 2015
[3] Actavis plc (NYSE: ACT) has completed the acquisition of Allergan, Inc. (NYSE: AGN) in 2015

2.8 Search Methods

In order to identify new products associated with these companies, three phases have been completed.

Firstly, a database of clinical studies (i.e. clinicaltrials.gov) for recently (≥2011) closed and ongoing clinical studies funded by each MD company have been searched for companies listed above.

Secondly, the FDA premarket approval (PMA) and de novo databases have been searched for new approved products between 2011 and 2015. The 510(k) clearance has not been considered as this refers to products "substantially equivalent" to others already on the market. In this case, unlike the previous steps, the search has been performed according to indication in cancer, respiratory disease, cardiovascular disease, diabetes, mental health.

We also searched the EuroScan Database, which is an equivalent to the FDA online databases for new approved devices at the European market. EuroScan is the International Information Network on New and Emerging Health Technologies, a collaborative network of member HTA agencies for the exchange of information on important emerging new drugs, devices, procedures, programmes, and settings in health care.

All searches have been performed according to indication in the five NCD areas and Medical Devices were defined as an instrument, apparatus, appliance, material or other article, whether used alone or in combination, including the software necessary for its proper application intended by the manufacturer to be used for human beings for the purpose of:

- diagnosis, prevention, monitoring, treatment or alleviation of disease,
- diagnosis, monitoring, treatment, alleviation of or compensation for an injury or handicap,
- investigation, replacement or modification of the anatomy or of a physiological process,
- control of conception,
- and which does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its function by such means (Council Directive 93/42/EEC on Medical Devices).

2.9 Medical Devices Industry: Results

Our online search revealed 319 CV-relevant MDs by 5 different companies in terms of clinical trials, FDA premarket approval, EUDAMED or the Euroscan Database. The included companies are shown in the figure below. 11 companies needed to get excluded, because no MDs in relation to CVDs could be identified. Some companies are focused on other markets (e.g. Covidien, which has been highly involved in the development of radiofrequency ablation for the treatment of various forms of cancer), other companies developed imaging devices, such as MRI or CTs (e.g. Siemens AG or General Electric Co.), which were classified as a MD for cancer. **Medtronic PLc** was by far the company with the most MDs for CVDs. More than half of all included products (n=175) could be allocated to Medtronic. However, these data has to be interpreted with caution, since there is a selection bias how data where extracted.

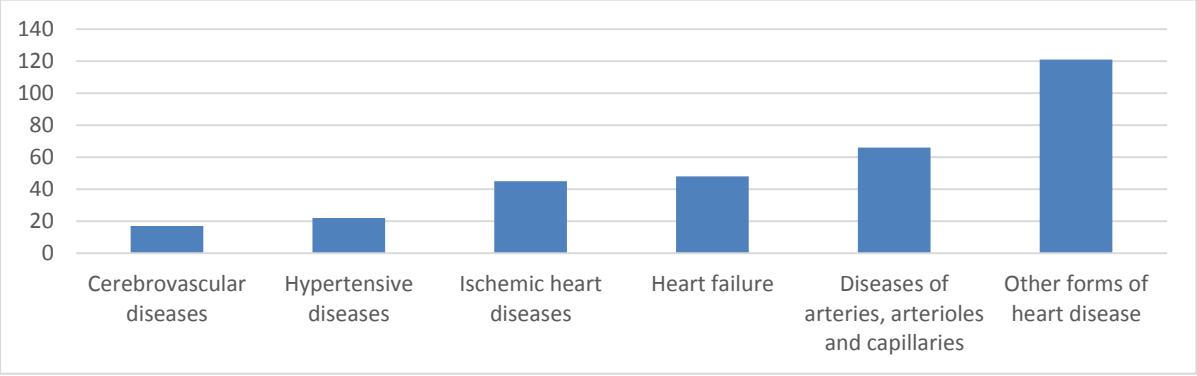
Figure 13: Companies with MD found for FDA

MD Co. Rank	World Co. Rank	Company	Country	Total revenues (Bn USD)	Total R&D Investment (Mn USD)
1	34	Johnson & Johnson	United States	28.7	8,494
3	249	Medtronic Inc	United States	17.1	1,477
11	719	Stryker Corp.	United States	9.3	614
13	1047	Boston Scientific Corp.	United States	7.2	817
16	957	St. Jude Medical Inc.	United States	5.6	692

The figure below shows all identified MDs classified according to their application. Most MDs (n=121) are categorized under "other forms of heart diseases". This is not surprising, since atrial fibrillation or arrhythmia are among this category. This includes devices such as implantable defibrillators or pacemakers.

The second highest amplitude occurs for devices against "diseases of arteries". This includes mainly products such as stents or catheters. Stents are also applied for ischemic heart diseases, for which we identified over 40 MDs. In the field of heart failure, products such as specific forms of pacemakers, defibrillators, which can be also used for the treatment of ventricular fibrillation (e.g. COGNIS CRT-D by Boston Scientific), are included.

Figure 14: Identified new medical devices at the clinical assessment stage or new approved between 2011 and 2015 classified according to ICD-10

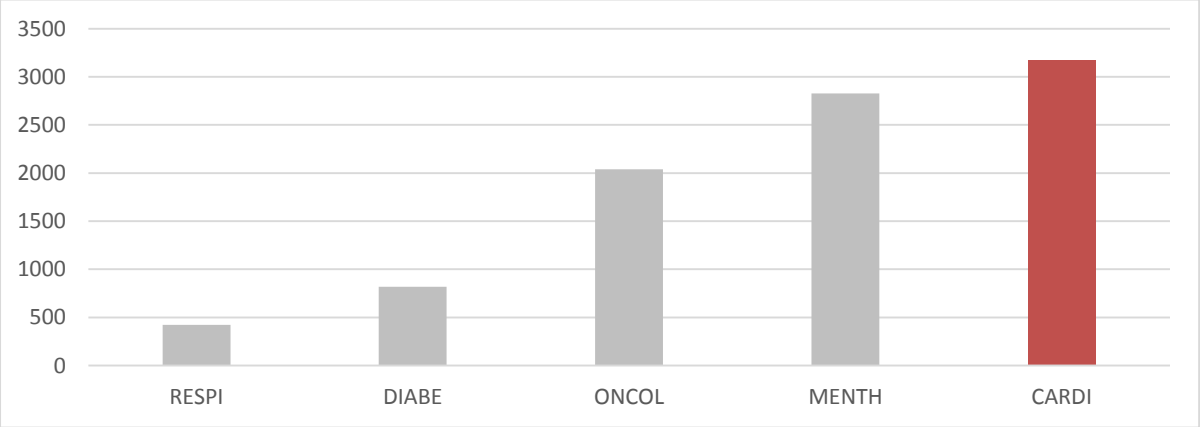


2.10 Medical Devices Industry Output Data: Bibliometric Evidence

Beside of the online databases search, we have also gathered bibliometric output data from Web of Science for the top medical device companies in the area of NCDs between 2009 and 2013. Therefore, specific search terms were used to filter the RFOs. It must be noted that the aliases/ spelling errors in naming the RFOs by WoS means that not all them may have been captured or that other organizations may have accidentally also been captured due to the simplistic terms used. In cases where a company had only generic codes, the name was searched instead of the code. It has to be noted that some of the companies also make pharmaceutical drugs and the counts of papers may include them (e.g. Johnson & Johnson). As the next figure shows, the research output for

cardiology has been the highest over the last years. With an overall share of 34% of all NCD research papers relevant to CVDs. Mental disorder and cancer are on the 2nd and 3rd place, while the fewest research papers were published in the field of respiratory diseases.

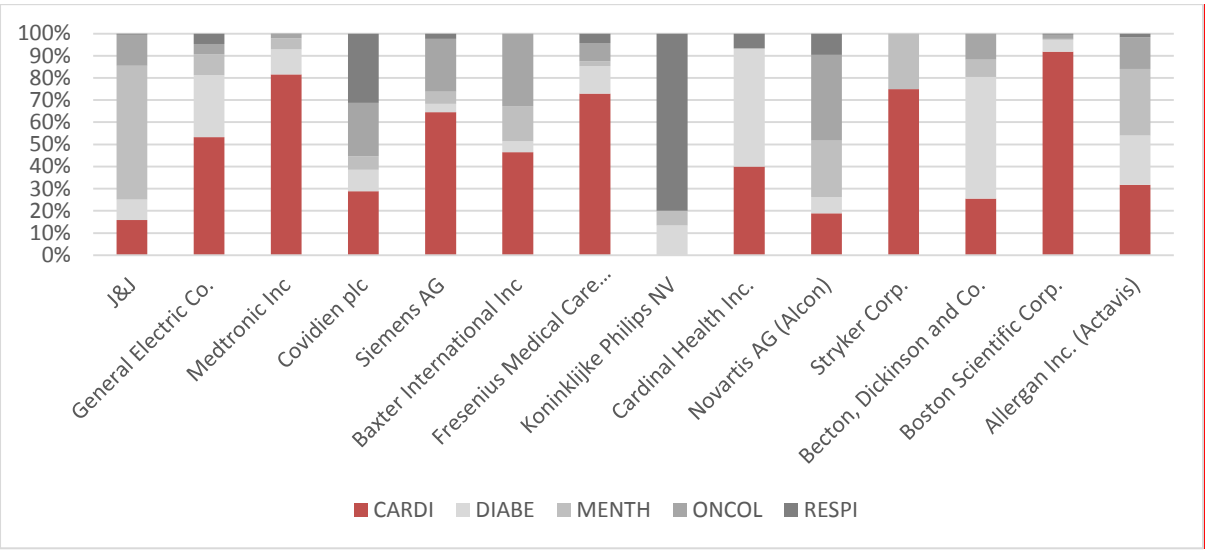
Figure 15: Aggregated research outputs of top 15 MD companies



The figure below shows the distribution of the published research papers across all companies. It clearly indicates that the publication activities of Medronic and Boston Scientific are very CVD-focused. On the other end, Koninklijke Philips NV is the only one among the MD companies without any CVD-related publication over the last years.

These bibliometric figures are highly contrasted by our previous results, where we couldn't retrieve any CVD-relevant products for most of the MD companies.

Figure 16: Bibliometric output data of MD companies



2.11 Discussion

Considering the pharmaceutical sector, most research has been done in the area of oncology. Only 10% of all identified NMEs were CVD-relevant. This is contrasted by the high burden of CVDs. This discrepancy reminds on the so called 10/90 gap, which was introduced in the end of the 1990ies and stated that only 90% of the global pharmaceutical research is conducted for 10% of the global burden of disease (Lewis, 2002, Stevens, 2004). This disparity has been significantly caused by the

high number of communicable disease-caused health problems across low and middle-income countries and the missing amount of research in this area. Although the 10/90 number can't be easily projected into the present (i.a. because of the substantially shift towards non-communicable disease in low and middle-income countries) – it is a symbol of the mismatch between needs and investments in the pharmaceutical research industry, hinting to market failure for major disease burdens. Hence, the 10/90 gap can be transferred to the current situations among the European latitudes.

Pharmaceutical companies argue with the increasing complexity of drug discovery. Nowadays, drug research is a complex and an intertwined discipline between bio-pharmacology, chemistry, nanotechnology, and computational sciences (Allarakhia and Walsh, 2011).

Also, the high R&D expenditures for developing NMEs are often used in order to explain why most pharmaceutical companies are risk-averse. The most detailed and cited study of R&D costs was written by DiMasi et al. (2003), who estimated pre-approval costs for a new drug to 802mn USD. This high number is not without controversy (Light and Warburton, 2011) and reveals the problem of asymmetric information among the pharmaceutical market: drug companies know much more about the costs and the real effectiveness of particular drugs than patients, doctors or other stakeholders. Therefore, it is important to improve the regulatory framework in order to establish incentives for drug-companies to meet the real needs of the society.

The current incentive systems seems to reward companies for developing NMEs with little advantages for a market share with high prices (e.g. Tarceva) rather than to develop clinically superior medicines (Light and Warburton, 2011).

Furthermore, there is a need for an increased forming of research consortia of pharmaceutical companies which manage and exploit the new forms of drug-discovery and should use synergy-effects for conducting large clinical trials together (Allarakhia and Walsh, 2011). The partnership between J&J and Bayer, which is described above, could play a role model for future projects.

The Medical Devices Industry provides a mixed picture in relation to investment in CVD research. On the one hand, we identified only 5 companies with CVD-relevant products but on the other hand, the bibliometric output data does not confirm this. Here, all –except of one- companies were involved in CVD-research. Siemens AG e.g. published 299 articles about CVDs, but we could not identify a single device in the searched databases. The bibliometric output data may be flawed, because some of the analyzed companies develop medical devices and pharmaceuticals (e.g. Novartis, Johnson & Johnson) and it was not possible to distinguish between papers written for pharmaceuticals or MDs. A deeper conclusion of the medical device industry is, based on this data, therefore difficult.

3 Stakeholder Interviews: CVD

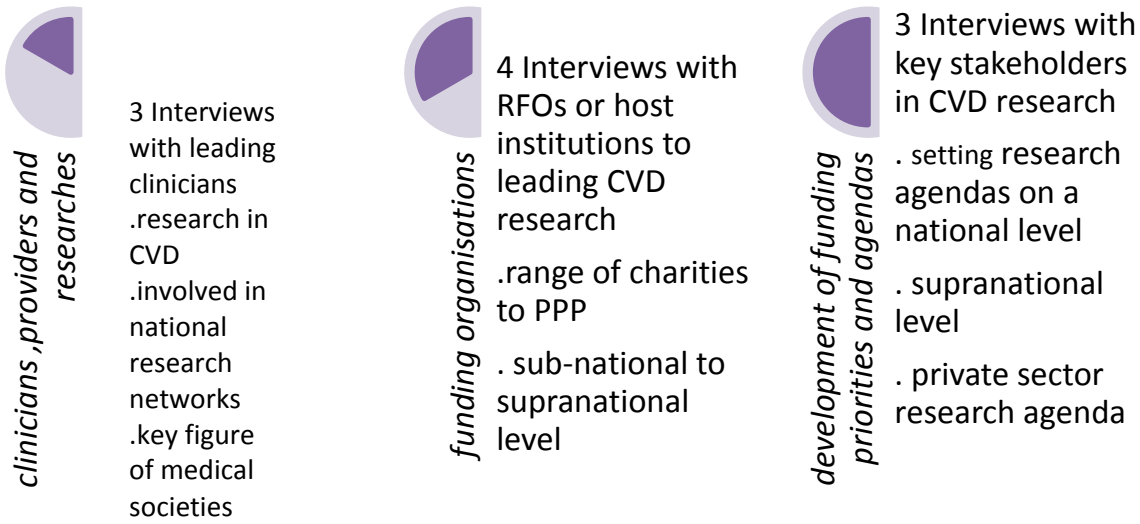
Cardiovascular diseases are the leading cause of deaths globally, with a rising gap between developed and developing countries. CVDs are the main cause of death in the EU, and causing 1.92 mn deaths, translating in 39.2 % of all deaths in the EU in 2010 (WHO, 2015). There has been a trend of steadily decreasing CVD mortality in the EU, resulting in eight countries containing CVD mortality below cancer related mortality in men. CVD remains the leading cause of death in women for all EU countries.

CVD are highly preventable and risk factors are categorized into modifiable risk factors related to lifestyle choices of patients as tobacco-use, physical inactivity, nutrition and obesity. Furthermore, main risk factors are elevated blood pressure or hypertension, elevated cholesterol levels and diabetes. Other risk factors can be classified as non-modifiable, such as age or gender or psychosocial factors as stress. It is important to note, that the individual patients risk to CVD results from the interplay of risk factors that vary over life course and can be reduced significantly in short time by breaking behavioural patterns. However, European health systems are challenged by a persistent CVD prevalence, corresponding high levels of CVD mortality and high economic and social costs. Although there has been major achievements by all EU member states in declining CVD mortality, there are regional variances in pace and depth of mortality reduction across countries.

While mapping of RFOs and their funding activities via surveys and bibliometrics can assist government in identifying the most fruitful approaches to making in NCD investments research; it stays without an analysis of unmet needs or an evaluation of research done without involving views of key stakeholder. To this end, ten interviews as a means for eliciting the preferences and opinions have been conducted.

Interviews should involve the full range of involved actors for CVD research. Possible Interviewees have been identified and contacted during an eight month period starting in January 2015. Scheduling interviews took longer than anticipated given the high work load of all interviews responsible in key positions, e.g.as head of a leading hospital university, CEO of a leading firm and coordinator of CVD relevant researching networks.

Figure 17: Overview of areas involved for Interviewee selection



Source: authors own compilation

3.1 Methods

Stakeholders were purposively selected to reflect a range of factors including: expertise in CVD research, geographic location and expertise in awarding research funding. For all stakeholders, interview questions explored (1) current threads of research; (2) future research areas; (3) types of collaborations and (4) future strategies for funding NCD research. The aim was to solicit views and experiences of people involved in both the conduct and funding of research across the EU area. In total, 10 interviews were conducted. All interviews were recorded and transcribed. Consent was gained for all interview subjects and their anonymity. Transcripts were analyzed on a thematic basis, with responses collated under the most common themes, and reported in the results section below. Examples from the analysis are included below to explain or illustrate key points. While retaining anonymity, the speakers have been identified by their order of interview in order to allow readers to distinguish different voices.

3.2 Results

Interviews with stakeholders revealed four major themes with regard to the future of research in the area of CVD. There was a generalized agreement of a current situation of underfunding for CVD in general. Other informants emphasized the importance of directing research towards tackling individual CVD as heart failure. In general, interviewees have agreed that risk factors and their interplay and the preventive potential have been well researched. In future, research will be heading towards personalized medicine, e.g. tissue engineering and towards early interventions. However, also classical research approaches as new pharmaceuticals have to be further followed. Also Interviewees agreed that there is an urgent need for a funding overview and a more transparent priority setting for the major RFOs. Although, interviewees made similar points in room for improvement in European CVD research, they have found the EU and some MS in particular in a pioneering role compared to the USA. Although a generation ago, young CVD researcher were trained by US colleagues for conducting research, the situation was found to be reversed in the last years (1,5,10). More detailed insights are enlisted in the following sections structured by the main interview themes.

3.2.1. Current threads to efficient CVD research

Interviewees agreed in a very similar fashion that there are some current circumstances threatening effective CVD research across EU MSs.

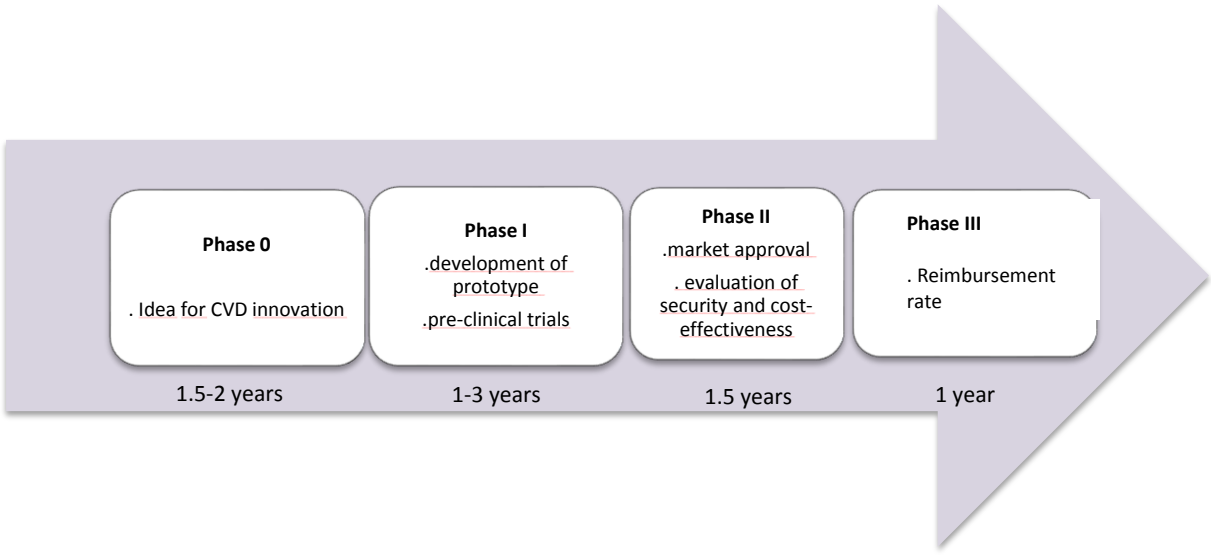
(i) Underfunding of CVD research in general and for some diseases in particular

All clinicians (1,2,3,5,6) interviewed have been worried about the continuous trend of popular crowding for some NCDs without surveying research grants against the actual disease burden or foreseeable trends in the future. CVD research suffers from an underfunding of research compared to cancer, although CVD cause the highest disease burden. Interviewees receive this as consequence for a higher emotionality of cancer in public perception (4,6). Additionally, CVD are asymmetrically affect poorer population mitigating visibility in representative councils or lobbying groups (5,8). Also CVD innovation is particular compared to other NCDs, requiring long-lasting clinical trials, high patient participation and a long cycle of evaluation. This is only possible, if researchers are early on supported by a cooperative infrastructure amongst research conducting agencies and the private sector.

(ii) Translational gap

Interviewees have pointed out to the severity of translational gaps in CVD research (1,6,9). Basic science research has made progress, but often these results are not translated into patients benefiting innovations in CVD therapy. This often needs also cooperation with other researchers to guarantee a sufficient large pool of participants for clinical trials. In the process from *bench to bedside*, there are several well-known barriers and disincentives for not completing the full research cycle. Figure 17 gives a simplified overview of all necessary steps for CVD innovations. In Phase 0, researchers have to come up with an idea and should be equipped with a supportive infrastructure and sufficient time to be compensated for possible lost income as clinicians ("kick-off funding"). When researchers are involved in basic science, their findings are of high interests and may be published pretty early in the process (driving away private sector players). The most capital intensive phase will be Phase I in developing a prototype and testing these in pre-clinical trials. Phase I can be divided into *in vitro* trials in laboratories and *in vivo* trials for different animal species. A majority of basic science innovation are not translated in this phase because of short term funding or insufficient research infrastructure. Additionally, researcher won't be able to publish each step of this phase individually (2,4,7). Funding is most probably given by national RFOs in this stage or by involvement of the private sector. In Phase II the prototype must seek for approval at the European market, and must also document its security and cost-effectiveness in small scale clinical trials. Often cooperative structures amongst hospital are needed to compile a sufficient big patient pool (in average n=100) and enough data. Funding is required to allow for such cooperative structures and to finance the clinical trials per se. It is estimated, that a majority of ideas will not make it to Phase II or failing during this phase (1). In Phase III the innovation has to be established as CVD therapy and seeks for a reimbursement rate under national financing schemes. As interviewee 2,4,7 pointed out in some trial setting its becoming more difficult to motivate patient to participation as they would prefer to be in the interventional group. All in all this research and innovation cycle may last between 7.5 and 10 years and is characterized by high volumes of required funding as well as high risk for failing in any of these phases (7,10).

Figure 18: Simplified scheme of medical device innovation for CVD



(iii) Inflexible top-down funding approaches

Interviewees 1,6,7,8 and 9 stated the inflexibility of funding tools as main threat towards successful CVD research. A set list of research priorities will disincentive researchers and often lag behind the current stand of research in CVD (4). Clinicians are in favor of pure excellency driven research

funding, as represented by the ERC and indeed, have mentioned the ERC grants as positive developments over the last years (1,2,5,3,9). Set priorities often do not correspondent to actual research needs but are vulnerable to lobbying and individual interests (8).

3.2.2 future strategies and research areas for funding NCD research

(i) *Continuity of funding and awarding good research approaches towards more visibility*

CVD research needs time for acquiring knowledge and for stakeholders to find their role. Successful research should therefore aim for the medium or the long run (8).As interviewee 3 and 8 pointed out, there is no systematic link in EU projects to publish main findings, nor a possibility to evaluate project outcomes by already established tools (as for NHS projects). It would be desirable to pressure for more visibility of research outcome by publications and online evaluation tools. There should be a European central point to evaluate research outcome and allow for tracking of funding grants within publication in a systematic manner (7). Additionally, successful projects should be awarded with ad-hoc funding to disseminate already acquired expertise, e.g. building datapool of RFOs and their funding modalities online. This would stimulate a more generic approach to research and reduce duplicating efforts.

(ii) *Minimalize formal barriers to funding*

Clinicians see a main point of CVD research in its close link to hospitals. Clinicians are often fully employed by hospitals and have to spare time for research efforts. Many research conducting agencies have reacted by establishing research manager positions or departments (4,5,10) for supporting researchers with formalities attached to research grants. Researchers are confronted with a variety of possible funding organizations, their programmes and funding modalities. Expected formal conditions for an application, expected approval rates, visibility and the flexibility of funding seem to be most important selection criteria how successful researchers apply to which grant. EU funds play an important role but are perceived as discentivising as applications have to be prepared for an in transparent, two-staged evaluation process and barriers to enter in a personal contact are high. Contracting time is unusual high (5), bureaucracy high and approval rates in the second stage low. Additionally, people normally stay in one funding scheme once they have been successful in it (6,7,8). Although, EU funds can be sorted between high formal barriers of national funding schemes and most flexible grants of sub-national level or by charities.

(i) Heart Failure

Interviewee 1,3,4 and 5 have suggested to spend more money on research to treat heart failure, whereas innovations for CVD and CHD are often not fully implemented but have contributed to decreasing CVD mortality (2,5).

3.2.3 Types of collaborations in CVD research

Interviewees shared observation of a more complex interplay of stakeholders of the last years. A majority of research projects have been motivated by close circles of researchers, who got in contact in early stages of their career or build up trust in intra-collegial networks (1,4,6,7). It is seen, that successful research is attracting a highly qualified human resource pool and is furthermore open to coorperation with the private sector or to work in public-private partnerships. Interviewee 1,2,5 pointed out, that research should be partly covered by statutory health insurance to enable for a stable financing base (2) and evaluate cost-effectiveness early on (3).

3.3 Discussion and Conclusion

Interviews with key stakeholders in the CVD research have revealed valuable insights and confirmed the quantitative analysis of CVD being underfunded in the EU. Although the disease burden is persistent in a majority of EU MS, funding has falling short from cancer related funding and is not reflecting urgent needs as the raising admission rates for heart failure to German hospitals (4,5) and leading cause of CVD mortality. However, European researchers have been able to pioneer modern CVD research in latest years, especially astonishing compared to the role of US research a decade ago. This is also reflected in the raising citation rate of EU CVD papers as shown in Chapter 4. Interviews also shed light on the immanent disincentives for researchers and other players in individual phases of a CVD innovation. Funding should therefore include a wide range starting from basic science to support innovations that have been close to market approval. CVD in particular can benefit from pharmaceutical innovations as well as medical devices. Interviewees have demanded funding that is covering a longer period of time, flexible in its spending formalities and has immanent tools of networking and disseminating findings. A majority of stakeholders are involved in a mixture of funding tools by sub-national, national and supranational players as well as the private sector. Interviewees also pointed out, that efficient project coordination is far more important than the volume of funding to guarantee its effectiveness (4,8,10).

4 Bibliometrics: Impact of CVD Research Funding

This chapter establishes the impact of funding investment in CVD by pursuing bibliometric mapping and analysis of the volume of research outputs in the EU and MSs. Bibliometrics establishes the impact of funding investments by mapping and analyzing of the volume, citations, funding sources, influence on clinical guidelines and newspaper stories of research papers and reviews in the Web of Science (WoS) published in EU MSs during the last ten years (2002-12). Where funded research produces scientific papers, funding is considered to have had 'impact'. Bibliometrics identifies specific impacts associated with individual research papers through citations in other relevant papers. Bibliometrics also checks funding acknowledgments in relevant papers. It considers the extent to which they have provided the evidence base for clinical guidelines relevant to various NCDs. And, it also considers the extent to which they are cited in stories about NCD research in newspapers and the broadcast media in MS.

Whereas the European countries suffered similarly from the disease burden caused by cancer, with the highest being the Netherlands at 19% and Latvia the smallest at 13%, there is a far greater variation in the burden from cardiovascular disease. Bulgaria suffers 37% of all its DALYs from cardiovascular diseases but France only 13%.

Given the high paper output of over 200 000 papers for CVD, this chapter remains incomplete due to the unavailability of analytic results of funding organizations and citation rate. However, it gives a systematic overview on paper output and national share on it. An analysis of research impact will be presented in the Synthesis Report for CVD.

4.1 Scientific Research Papers: CVD

A filter for CVD was developed in three rounds under major contribution of Suzanne Edwards by marking extracted papers for their fit under the used search statements. The major diagnostic categories and their share of total papers are depicted in Table 42. It shows the 13 subject areas selected, with their codes, the number of papers, and the percentage that this represented. Some of the subject areas corresponded closely to the ones used to define the disease burden, but others did not, or covered more than one such area. There are two large subject areas, stroke and arterial disease. The former is a major cause of disease burden, but the latter is not. So it appears that ischaemic heart disease including myocardial infarction is under-researched relative to its burden within CARDI, and that arterial disease is over-researched. However a large minority of the papers (43%) were not covered by any of the subject area definitions.

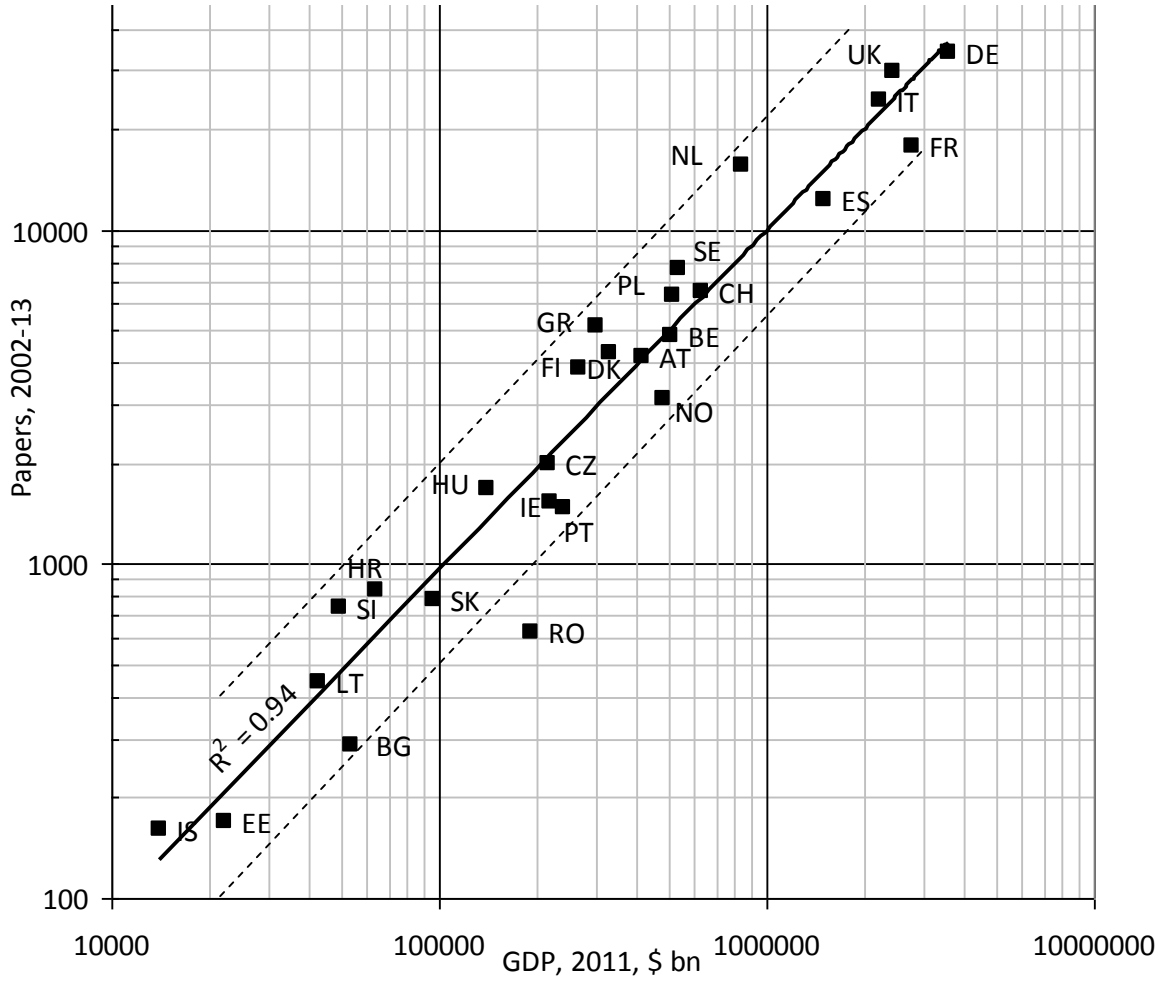
Table 42: List of 13 subject areas within CVD research, final filter, with the numbers and percentages of European CVD papers in 2002-13.

Subject area	*Code*	*DALY code*	*Papers*	*%*
cerebrovascular disease (stroke)	CER	STROK	25836	12.2
arterial disease incl. atherosclerosis & aortic aneuryms	ART	AORTA	24507	11.6
hypertension	HYP	HYPER	16251	7.7
arrhythmias, incl. atrial fibrillation	ARR	ATRFI	15129	7.2
ischaemic heart disease, including acute MI	ISC	ISCHE	12963	6.1
hypercholesterolaemia	CHO		9960	4.7
heart failure	FAI		9454	4.5

heart valve disease incl. chronic rheumatic disease	VAL	ENDOC, RHEUM	8573	4.1
cardiomyopathies	CAR	MYOCA	7588	3.6
congenital defects	GEN		5693	2.7
venous thromboembolism	VTH		2573	1.2
auto-immune vascular disease, incl. vasculitis	VAS		1344	0.6
peripheral vascular disease	PVD	PERIV	1009	0.5
not classified	none		92446	43.7

Altogether the search for paper resulted in 211 507 eligible CVD papers after employing the filters. Each filter was applied to the Web of Science for the Science Citation Index (extended) – SCI – and for the Social Sciences Citation Index(SSCI), for the twelve years 2002-13, and articles and reviews only were identified. The papers were also limited to those with at least one address in one or more of the following 31 countries – the 28 Member States of the European Union plus Iceland, Norway and Switzerland. Output of European researches has increased from 8% of the total world output in 2002 to 12 % in 2012. In total, CVD paper represent just over 8% of biomedical research output, both in the EUR31 countries and in the world overall; the percentage has declined slightly over the 12-year period of the study, whereas it increased for cancer research. The top four CVD paper producing countries have been Germany, the UK, Italy and France. There is a strong correlation of paper output to GDP of MS as shown in Figure 18.

Figure 19: Plot of CARDI paper output, 2002-13, against GDP for 27 European countries



Note: CY, LU, LV and MT omitted. Dashed lines show values x2 or x0.5 relative to power trend-line.

European CVD papers have always been more highly cited, on average, than the world mean, and that the difference is becoming larger especially so in 2013. However, CVD papers tend to receive fewer citations than ONCOL papers.

Germany had the highest overall output, but the UK had more output in hypertension (HYP), hypercholesterolaemia (CHO) and congenital defects (GEN), and Italy in the first two of these. Table 43 shows that German output in hypercholesterolaemia is in fact particularly low (relative to its overall output in CARDI). As expected, the tinted cells are mainly in the lower half of the table, where outputs are quite small, typically less than 10 papers per year, so that a few papers can make a big difference in the ratio of observed to expected numbers. However a few results stand out – Danish papers in ischemia (ISC; 583 papers with 263 expected) and Austrian output in peripheral vascular disease (PVD; 58 papers with 20 expected).

Table 43: Ratio of observed to expected outputs of papers from 31 European countries in 10 leading subfields of CARDI research, 2002-13. Values > 2.0 tinted bright green; values > 1.41 tinted pale green, values < 0.71 tinted pale yellow; values < 0.5 tinted pin

Subfield	*CER*	*ART*	*HYP*	*ARR*	*ISC*	*CHO*	*FAI*	*VAL*	*CAR*	*GEN*	*VTH*	*VAS*	*PVD*
DE	1.05	1.05	0.72	1.06	0.87	0.63	0.87	1.21	1.35	0.97	1.01	1.25	0.88
UK	1.09	0.97	0.89	0.88	0.76	0.87	0.98	0.85	0.80	1.22	0.69	0.76	1.23
IT	0.92	1.04	1.30	1.02	0.98	0.89	1.20	1.15	1.18	0.98	0.98	1.24	0.96
FR	0.91	1.02	1.11	0.94	0.86	0.88	0.84	1.34	0.88	0.84	1.40	1.58	0.86
NL	1.01	1.02	0.81	1.15	1.11	1.20	1.06	0.75	0.74	1.32	1.32	0.48	1.39
ES	1.11	0.81	1.41	0.97	1.02	1.30	1.02	1.05	1.57	0.77	1.10	0.99	1.07
SE	1.19	1.19	0.82	0.83	1.51	1.21	1.24	0.75	0.55	0.83	0.86	0.81	0.92
CH	1.04	1.03	0.85	0.88	0.65	0.80	0.76	1.06	0.83	1.19	1.65	1.21	1.40
PL	0.82	0.97	0.97	1.31	1.49	1.17	1.06	1.21	1.37	1.08	1.46	1.00	0.60
GR	0.70	1.31	1.41	1.17	0.98	1.64	1.28	0.95	0.90	0.89	0.67	1.29	1.07
BE	0.79	1.00	0.89	0.97	0.73	0.75	0.86	1.45	1.03	1.47	1.06	1.20	0.78
DK	0.82	0.72	0.88	1.34	2.22	1.14	1.24	1.12	0.48	0.65	0.94	0.34	1.21
AT	0.90	1.28	0.56	0.85	0.65	1.07	0.83	0.79	1.27	0.97	1.56	0.77	2.92
FI	1.29	1.26	1.00	0.86	1.08	1.96	0.56	0.53	0.66	0.70	0.34	0.84	0.51
NO	0.94	0.81	0.86	0.69	1.73	1.26	1.48	0.80	0.58	1.23	0.75	0.89	0.47
CZ	1.27	0.89	1.49	1.21	0.87	1.72	0.90	0.82	1.31	0.60	0.79	0.54	0.55
HU	1.19	0.87	0.98	1.10	0.94	1.38	0.43	0.65	0.79	1.01	0.28	1.06	0.33
IE	0.99	1.12	1.23	0.54	0.58	0.83	0.80	0.61	0.54	1.36	0.87	1.01	1.17
PT	1.04	0.76	1.07	0.84	1.13	0.66	1.26	1.43	1.02	1.44	1.39	1.99	0.25
HR	1.84	0.58	1.15	0.74	1.15	1.20	0.22	0.91	0.51	0.82	1.18	0.76	0.50
SK	1.22	0.59	2.13	1.12	0.71	1.44	0.29	0.32	0.61	0.63	0.34	0.52	0.00
SI	0.75	0.96	0.59	1.10	1.65	1.41	1.07	1.22	0.86	1.18	1.89	0.56	3.02
RO	0.68	0.95	1.08	1.08	0.87	1.37	1.04	1.16	0.79	0.37	1.17	0.61	1.69
LT	0.84	0.46	0.48	0.93	2.74	0.20	0.79	0.90	0.47	0.91	0.19	0.36	0.00
BG	1.03	0.93	1.69	0.70	0.55	1.70	0.33	0.42	0.22	0.49	0.57	0.29	0.00
EE	1.14	0.93	2.00	0.04	1.18	0.88	0.25	0.00	0.11	1.98	0.00	0.03	4.82
IS	0.79	0.47	1.64	1.19	1.22	1.42	0.45	0.80	0.21	0.57	1.42	0.03	0.00
CY	2.17	0.75	0.40	0.26	0.78	1.14	0.98	0.57	0.82	1.37	0.21	1.83	0.81
LU	0.94	0.52	0.39	0.15	3.66	0.73	3.22	0.51	0.47	0.15	0.00	0.50	0.46

LV	0.93	1.05	0.98	0.47	1.27	0.53	0.26	0.91	0.81	0.81	0.00	0.12	2.14
MT	0.56	1.06	1.18	0.00	2.11	0.00	0.00	1.25	1.13	4.55	0.00	0.00	0.00

4.2 Funding Sources

The funding of research is now recognised as an important source of information for its evaluation (Lewison and Devey, 1999) (Lewison et al., 2001). At its simplest, the acknowledgement of a funding source on a paper indicates that an agency, usually an external one, has reviewed the research project and judged that it is worthy of support. Multiple funding sources would indicate that the project has found favour in several places.

In the past, the recording of the funding sources on a paper was a labour-intensive task as each paper needed to be inspected individually, usually in a big library. Since the introduction of the Science Citation Index , the facilities available for searching and for retrieving data have been steadily enhanced. During 2008, Thomson Reuters started to provide details of funding for individual papers – quite likely stimulated by the earlier existence of the ROD! There are two individually searchable fields, FO = funding organization and FT = funding text. The FO field lists the names of the acknowledged funders and FT gives the full text of the acknowledgement, including recognition of individuals who have helped with the research. For some funding bodies, the FO field also lists the grant numbers, although they are often absent and have not been considered in this analysis.

Authors of papers record their funding acknowledgements in a wide variety of ways. Many papers had multiple funding acknowledgements[4]. In order to determine the funding sources for RESPI and the four other disease areas, it was therefore decided to use a coding system, with four parts:

- a trigraph (three character) code designating the individual funding body;
- a single letter code showing the form of support (no longer used);
- a digraph (two character) code designating the sector and sub-sector of the funder; and
- another digraph showing the country of the funder based on the ISO codes.

The trigraphs were designed to be easily memorable, *e.g.*, MRC = UK Medical Research Council; BHF = British Heart Foundation, although it turned out that there were so many different funders of UK research papers that many had to be given odd combinations of letters[5].

It also became apparent that some papers did not carry an acknowledgement because they had been supported internally – in a government lab (such as one supported by a research council or Government department), by a collecting charity, or by a commercial company. So the decision was made to include these "implicit" acknowledgements along with the "explicit" ones in the acknowledgement paragraph to form a composite acknowledgement[6].

In any case, most of their authors would be academics or medical personnel working in a hospital or clinic, supported by general university funds or by salary support from the health service. But such support would not be peer-reviewed, and so such papers would perhaps be of a lower standard. For these reasons, it did not seem appropriate to record this nominal support, and the ROD was set up to record such papers as "unfunded", and the hospital or university or research institute address was not given a code. However, if a specific acknowledgement appeared to a university or department,

[4] There are also acknowledgements to individuals who have provided help or advice. These are not considered further in this report.

[5] Initially, every UK research funder was given an individual trigraph in order to cater for the possibility that it would become a ROD member, although membership seldom rose above 30.

[6] Several of the ROD members maintained their own labs and also gave external research grants and this system allowed them to compare their respective outputs.

or to a hospital, then it was presumed that some system of grants was in place and the contribution of the employing organisation WAS recorded with a code.

The methodology used to extract funding information for papers whose details were downloaded from the Web of Science (WoS) was the same across the five disease areas. The basic principle used was to assign a three-part code to each funding body, with a three-letter code to identify it uniquely, a two-character code to identify the sector and sub-sector, and another two-character code to identify the ISO designation. Codes were assigned to each funding body listed in the FO = funding organisation section of the WoS, subject to redaction if they were mentioned in a conflict of interest statement only as having paid for unrelated work. Codes were also assigned where there was an acknowledgement implicit from one (or more) of the addresses - a government department or agency, the laboratory of a collecting charity, or of an industrial company.

Once codes were assigned to each funding body, they were collected and written to two thesauruses for future use. The spreadsheet of papers was then completed with the explicit and implicit codes by means of a special macro, which also combined the codes into a single column. Another macro determined the division of funders by main sector for each European country (own government including local and regional authorities; own private-non-profit (PNP), industry, international, and other). These were doubly fractionated: to allow for the fractional presence of the target country on each paper, and to allow for the total number of funders on a paper.

The commercial sector was divided up into five sub-sectors, with companies divided into three: pharmaceutical, biotech and industrial. The first and third of these were further divided into independent and subsidiary. The purpose was to distinguish between the research activities of UK subsidiaries of large multi-national companies which might be relatively independent of the parent, e.g., the Merck Neuroscience Park in Harlow, which did its own research and also gave funding to universities. However there were many takeovers of small biotech (and not so small pharma) companies and it seemed appropriate to regard the takeover as a way in which the new parent company would thereby gain the intellectual property of the new acquisition. This meant that many of the commercial codes became out-of-date. This had two consequences for the analysis of funding sources. First, the country of a company was effectively undefined, and second, the sub-sector could change when a biotech company had brought a new drug to market and had so become a pharma company.

The public sector was divided into three sub-sectors: government department (controlled by ministers), government agency (nominally independent of ministerial directives) and local authorities (including regions, counties and cities). They were given sectoral codes: GD, GA and LA, respectively. Although the latter form of support hardly exists in the UK, it is becoming increasingly common in several continental European countries (Länder in Germany, régions in France, provinces in Spain) and also in North America (provinces in Canada and states in the USA) and in Australia (states and territories).

4.3 Citations of Research Papers

Bibliometric analysis uses citation scores to measure of the impact of research papers. For most NCDs, European research was better cited than the world average, although there was much variation between countries. Interestingly, there was generally poor correlation between the burden from particular diseases and the amount of research. In this case, there may be grounds for re-balancing some national research portfolios.

These 13 subject areas varied substantially in the Research Level of the papers that contributed to them, and also in the average numbers of citations. The former is shown in chart form in Figure 19, and the latter in Figure 20. Hypercholesterolaemia papers are the most basic (but well on the clinical

side of the middle value of 2.5), and also the most cited. Their citation score is more than twice that of papers on congenital defects.

Figure 20:Chart of mean Research Level of papers and of journals in which they were published for CARDI papers in 13 subject areas. RL = 1.0 is clinical observation; RL = 4.0 is basic research.

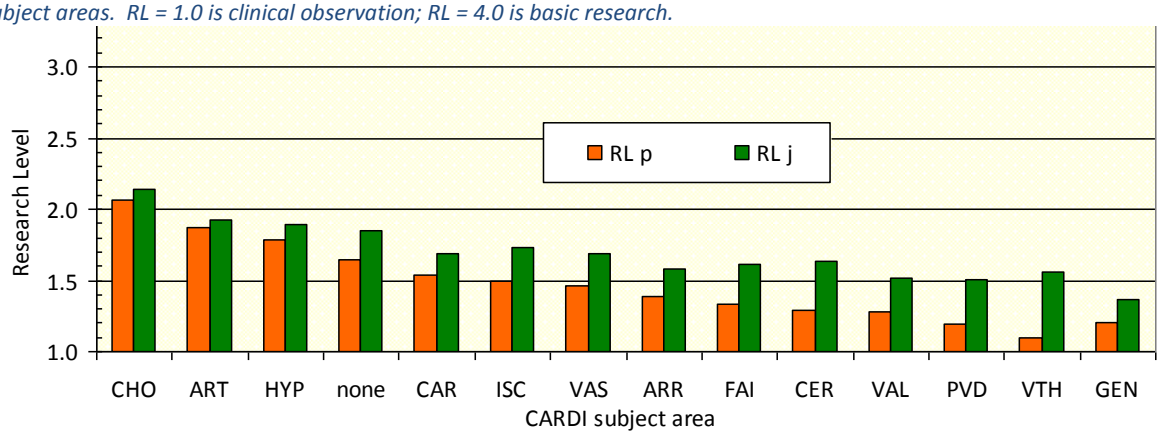
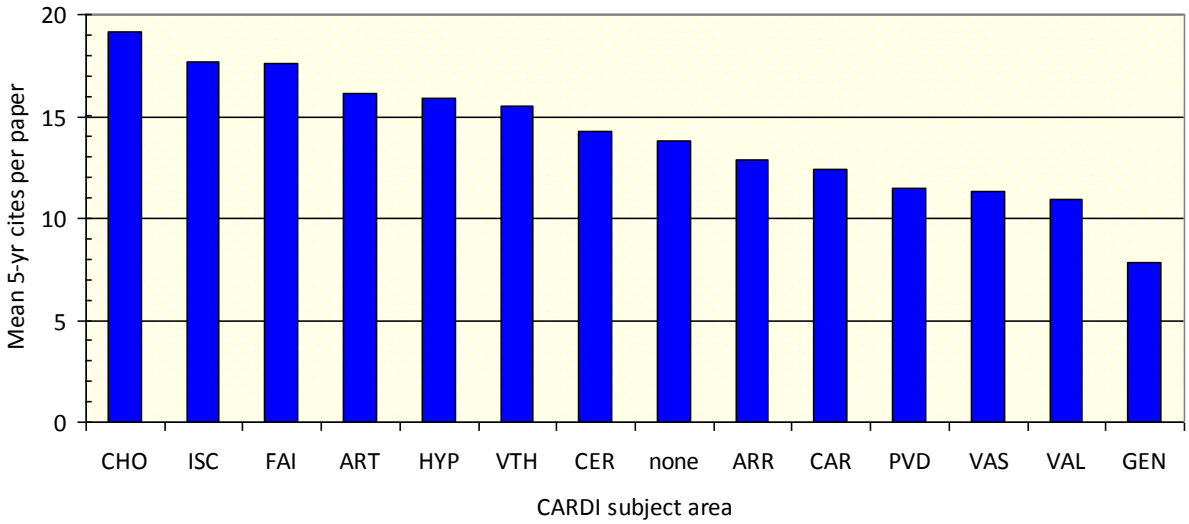


Figure 21:Chart of mean five-year cites for CARDI papers in 13 subject areas published in 2002-09.



5. Conclusion

CVDs still remain a leading cause of mortality in European populations. If there would be a direct link to share of CVD research to available funding schemes, all European funding organizations disappoint this expectation, under FP-7 only 6.2 % of total funding was dedicated to CVD research. Furthermore, the funding volume does not say much about expected outcomes. A main criticism of EU funding schemes remains the lack of evaluation routines of projects. How individual project performed and how they disseminated knowledge to the research communities or to the public remains unclear. Furthermore, funding on the EU level is heavily characterized by concentration effects on a regional level and only some MS are regularly awarded with EU grants in CVD research, and this can even be broken down to a handful of institutions. Newer member states are rarely awarded with EU funds, but are confronted with high rejection rates and a high level of bureaucracy posing disincentives for institutions and researchers with limited capacities to apply.

National RFOs are involved in CVD research in multiple ways and by applying differing research landscapes in European MS. Almost all individuated projects on a national level had a very specific target for funding, shorter funding span and very rarely cooperation across national borders. Although research outcomes cannot be assessed at this stage, the regional variance of available funds is worrisome.

Considering the pharmaceutical sector, most research has been done in the area of oncology. Only 10% of all identified NMEs were CVD-relevant. Although cancer is causing almost as much DALYs as CVDs (In Europe 16% vs 19%), it does not explain this disproportional high focus on oncology. According to the research-based pharmaceutical companies this is –inter alia- due to the increasingly complex and very expensive process of drug discovery, which make some drugs more lucrative as others. This leads to a deeper, general problem of the current pharmaceutical research landscape: Current incentives reward companies for developing new medicines of little advantages. It is estimated that 85% of new drugs are only little or no better than already existing ones (Light, 2010).
As a consequence, improving the regulatory framework and establishing a new incentive system for research-based pharmaceutical companies which is directly tied to the reduction of the global burden of disease that a new drug has, might improve the research output coming from this area (Solbakk, 2011, Pogge, 2007).

Our results have been largely confirmed in interviews with key stakeholders of CVD research. Additionally, it was demanded that funding should cover a longer period of time and should be more flexible in its spending formalities. Moreover, an improved framework for project coordinators is needed, since an efficient project management is crucial in order to guarantee the effectiveness of a project. However, despite the fact that CVD-research is underfunded, European researchers have been able to pioneer modern CVD research in latest years, which is reflected by the high citation rate of published EU CV articles. The top four CVD paper producing countries have been Germany, the UK, Italy and France.

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