Innovation in cardiovascular disease in Europe with focus on arrhythmias: current status, opportunities, roadblocks and the role of multiple stakeholders.

A report of the Innovation Forum organised by the European Heart Rhythm Association at Weissach, Germany in February 2016.

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Abstract

The European Heart Rhythm Association (EHRA) held an Innovation Forum in February 2016, to consider issues around innovation. The objective of the forum was to extend the innovation debate outside of the narrow world of arrhythmia specialists and cardiology in general, and seek input from all stakeholders including regulators, strategists, technologists, industry, academia, health providers, medical societies, payers, and patients.

Innovation is indispensable for a continuing improvement in health care, preferably at higher efficacy and lower costs. It requires people who have been trained in a good scientific environment, high quality research for achieving ground breaking inventions and the certainty of return on innovation investments. In the context of cardiovascular disease, innovation can imply better risk assessment and stratification, device technology, drug development and process design.

Several areas of promising developments were identified as well as several roadblocks to innovation. To drive innovation forward all stakeholders need to play a significant role. In a globalised and extremely competitive world, the leading role of Europe in medical innovation can only be achieved through a combined and well-coordinated effort from all involved parties.

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Introduction

The complexity surrounding true innovation in cardiovascular medicine is increasing, yet the need is more urgent than ever. Cardiovascular disease (CVD) remains a major challenge in healthcare, exacerbated by the impact of an ageing population, a dramatic rise in cardiometabolic conditions, and poor lifestyle [1]. Against a background of spiralling healthcare costs, there is strong demand for new and innovative solutions that will improve diagnosis, treatment, and outcomes for CVD patients while, at the same time, enhance the quality and efficiency of care [2]. Apart from the medical benefits, innovation may play an important role for the European nations as a motor of economic development (http://ec.europa.eu/growth/industry/innovation, accessed 3 July 2016).

To consider the issues around innovation, its characteristics and, particularly, the barriers to successful innovation, the European Heart Rhythm Association (EHRA) held an Innovation Forum in Weissach, Germany, on 11 and 12 February 2016. The objective of the forum was to extend the innovation debate to outside of the narrow world of arrhythmia specialists and cardiology in general, and seek input from all stakeholders including regulators, strategists, technologists, industry, academia, health providers, medical societies, payers, and patients.

Innovation – definition and characteristics

While there is no single definition of innovation, broad agreement exists on the elements that spark it; a recognised need, original and competent people, and funding that allows to try and test several options. Commercialisation is challenging; indeed, it is an area in which innovation may play a major role. In the context of cardiovascular disease, innovation can take many forms including risk assessment and stratification, device technology, drug development and process

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design. Each is important because clear and measurable patient outcomes are important drivers in an otherwise complex landscape.

Examples of device technologies that are considered innovative include for instance novel ECG and mapping tools for arrhythmias, ablation catheters and leadless pacemakers.

Historically, innovation has mostly been stepwise, building upon the experience of existing products as for instance during the development from the Ford Model T to a contemporary Formula 1 racing car. However, such stepwise innovation may no longer be seen as providing adequate advances of existing treatments relative to its cost. On the other hand, innovation can be disruptive [3]. At its core there will be a technology, algorithm, compound, or process which, when applied, can transform the way in which patients are managed, perhaps because it increases patient performance and independence, speeds-up diagnosis and recovery, lowers cost, improves efficiency, or reduces hospitalisation. The challenge is to rapidly identify at an early stage when innovation can be disruptive and ensure that it receives full support to overcome many potential hurdles.

Current status of medical innovation in Europe

In 2015, the number of European patent filings grew to an all-time high and medical technology was the fastest growing category for new patent activity via the European Patent Office with over 12,400 applications (http://www.epo.org/news-issues/press/releases/archive/2016/20160303.html, accessed 2 July 2016). Patents are contracts that, in exchange for full disclosure, ensure that exclusive exploitation rights are conferred on the inventor for a limited time. Patents are integral to innovation and greatly influence willingness to invest. The development of new patents is often costly and therefore requires sufficient funding. On the other hand, whether patents indeed lead to newly marketed products

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is strongly dependent on the costs of research required for safety and efficacy, especially if large clinical trials are required (see below). Also, not all patents lead to actual new therapies, because companies use patents to delay market access by the competition with products based on the same original invention ("secondary patents") or competing products ("defensive patenting") and as strategic tool to negotiate settlement payments with competitors.

EU funding of innovation

Through its Horizon 2020 programme, the EU provides funding support for innovation addressing specifically research needs in the fields of personalised medicine, promotion of healthy ageing, and human biomonitoring. Funding is allocated to projects that demonstrate research excellence, make a genuine impact, and provide added value. The Societal Challenges (SC1) Health category of Horizon 2020 has a total budget of €7.2 billion and establishes the research priorities in the sector of health sciences research. A further €24 billion is allocated to the Excellent Science category. As part of the EU funding programme, the Innovative Medicines Initiative is a collaboration between the EU and the pharmaceutical industry with a budget of €3.2 billion [4]. One of the aims is provision of support for small-to-medium enterprises to bridge the gap between Research & Development and commercialisation. With this aim Horizon 2020 is biased towards applied research and industrial developments. This may be disappointing to researchers, who compare EU funding with that of the National Institutes of Health (NIH) and other national health organizations, but is the consequence of the difference in mission of those organizations.

Promising areas in health care innovation

Innovation is a broad term and does not only apply strictly to medical science but to the broader field of health care. Significant research programmes are underway across the innovation continuum to identify new ways to treat patients and deliver improved outcomes, which are summarized in the left column of figure 1. Examples include:

- **Genetics:** The impact of genetics on the clinical management of cardiac arrhythmias is growing rapidly with major interest focusing in the areas of gene-therapy, gene-specific therapy, and the role of modifier genes [5] [6]. In many countries in Europe genetic information is already being gathered in a systemic manner, albeit for research. In some cases, however, genotypic data might already be integrated with patients' electronic records within the next decade and could transform the way medicine is practiced, possibly creating a paradigm shift towards prevention, early detection and personalized pharmacological treatment (see below). One major facilitator of this development is the dramatic fall in the costs for genetic profiling. Genome sequencing will most probably provide novel insight into medicine, and screening may enable specific interventions once complex ethical issues are addressed.

- **Big Data:** Big Data is an increasingly used term to describe the exploitation of the massive processing capabilities of fully connected, fully integrated IT networks. These networks may contain both medical and non-medical data (up to internet surfing history), which explains why large IT companies like Google and IBM are now also operational in the field. It is envisioned that combination of all this data may not only lead to better anamnesis and diagnosis but also earlier detection of disease and better follow-up of therapeutic effects. Given the information management and analysis requirements of healthcare, Big Data is seen as a future enabler and one of the major progress initiators in the field of health research [7]. Data driven innovation may enhance well-being and simultaneously increase productivity and lead to positive

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financial results (http://www.keepeek.com/Digital-Asset-Management/oecd/science-and-technology/data-driven-innovation_9789264229358-en, accessed 4 July 2016).

- **Computer modelling:** Computer models may contain a multitude of properties of the heart and circulation (structure, mechanical and electrophysiological). Available models range from relatively simple lumped parameter to complicated finite element models, electrophysiology being simulated by eikonal diffusion, monodomain or bidomain models. By integration of all available information, models can unravel novel information out of clinical measurements and simulate different scenarios, thereby aiding diagnosis and prediction of the benefit of specific therapies [8] [9] [10]. Even model-based clinical trials appear feasible in the near future [11]. This development will lead to more focused, personalized treatment and less patients required for clinical trials.

- **Personalised medicine:** This is a topic of fast-growing interest focusing on the specific requirements of the individual patient as determined by a combination of modalities [12]. The concept exploits four essential tools; genomics, a new taxonomy of diseases, imaging and functional studies, and personalised devices. The goal is to enable tailored treatment for the individual patient, leading to better outcomes, lower costs and lower exposure of patients to risks. Also here, computer models can play an important role by facilitating integration of multi-modality diagnostic information along physical and physiological principles. Moreover, drugs might first be tested in a better targeted patient cohort, which will increase probability of success. The smaller size of the required study population would reduce developmental costs for the industry, but it may take much longer to show efficacy in a large patient population, thereby lowering the return in investment. This approach would need longer patents, so that further investment also garantees return in investment

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- **Patient engagement:** This concept describes the mindset change from the traditional paternalistic relationship between physician and patient to a partnership based on good information, common decision making and patients being responsible for their own health. It will make prevention and treatments more impactful. Also in clinical research, initiatives of patient engagement should speed up access to innovative treatments, make study results more meaningful and decrease cost of development.

Roadblocks to innovation

As outlined, there are multiple areas with promising perspectives for health care innovation. However, this is not a smooth process. At the same time, the innovation process is hampered by numerous roadblocks, summarized in the right column of figure 1. Growing regulatory and administrative burdens restrict Europe's ability to develop new drugs, devices and arrhythmia related technologies. It is expected that by 2025 there will be very few companies, perhaps less than 10, that will be willing to take the financial risk associated with launching new devices and arrhythmia-related technologies in Europe. These obstacles may lead to a relocation of development and innovation in this sector to non-European regions. Such a development would have major negative implications for the implementation of new technologies in clinical practice, for the role Europe as innovation leader as well as having financial consequences for the European population. Removing the roadblocks is therefore a high priority. Areas of concern include:

- **Basic science prioritisation:** Basic science is fundamental because it frequently is the basis for major clinical developments and is thus in many cases the fuel of innovation. There are major discrepancies between the quantity of "landmark" scientific discoveries in journals and follow-up papers confirming initial laboratory findings by industrial laboratories [13]. There are

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many explanations for this phenomenon including the pressure to publish, the eagerness of major scientific journal to publish "sensational" findings and some degree of self-deception on the scientists' part [14] [15]. Whilst research methodology in the clinical and genetics arenas has evolved and refined considerably in the last 50 years, this has scarcely been the case in "basic" science, leaving the door open to bias [16]. Investment in education leading to a widespread understanding of the principles of research methodology together with a shift in the attitude of funders and scientific journals would be needed to redress these important obstacles to true innovation.

- **Reduced commitment to clinical science:** The number of people that is willing to be strongly involved in high-quality clinical (patient-oriented) research and is also suitably qualified for this, is small. Reasons for this shortage is the long time needed for post-graduate training of physicians, the limited number of training positions in academic medical centers, the existence of attractive career choices that bypass the academic route, and the relative paucity of funding for clinical research. The latter is especially true if there are no obvious commercial benefits for industries. One way to overcome this is that health care payers support studies that may reduce costs in health care while maintaining care at the same level. The environment itself is also challenging because hospitals may prioritise patients' treatment over clinical investigation, well-equipped research facilities may not be available or financially sustainable, and for various reasons patients may not be willing to participate in clinical studies. Furthermore, the bureaucracy of initiating and realizing a study (ranging from contracts with various partners to hospital administration, ethical committees and drug administration) is often difficult to navigate, contributing to the escalating costs of clinical research. Here lies the need to cooperate with the regulators and an opportunity to develop public/private partnerships.

- **Patents:** Although patents and other intellectual property play in general a positive role for innovation as they protect the innovators' rights and make the invention worthwhile to invest

in by industry, treatment methods as well as software and algorithms are not readily patentable. In this field patents can only be created if the software is coupled to a specific application, such as analysis of a specific type of images. One example is the software used to determine deformation of the myocardium out of echocardiographic images ("speckle tracking"). Patents can also be expensive to obtain and time consuming; the patent process can take several years. These obstacles may deter industry and start-up companies in particular.

- **Big Data:** Although the use of Big Data seems very promising with regard to initiation of innovative processes, this promise will not be realised until major concerns about issues such as privacy, confidentiality, access rights, and ownership of the data are addressed by regulators [17]. There is at the moment a vague legal framework that renders the large-scale exploitation of the Big Data potentially problematic.

- **Clinical trials:** The current regulatory framework has made clinical trials more costly and administratively cumbersome. Requirements for designing clinical trials are also becoming more stringent. Poor design may derive from too many exclusion criteria, too many extra-investigation/substudies/visits and poor arrangements with the clinical trial research organization and may lead to significant problems with recruitment and retention. Poor design may also lead to gender and demographic imbalance limiting the generalizability of the findings. Issues pertaining to clinical trials have also recently been addressed by the ESC [18] [19].

- **Market access:** Both pharmaceutical and device industries are beset by the high cost and risks associated with the end-to-end regulatory approval. This deters investment decisions even when there is a compelling need for new therapies. In the cardiovascular field the pipeline of new compounds is drying up. Increasing development costs are a significant part of the problem [20]. The typical cost for bringing one new drug to the market has been estimated at between 4 to 12 billion euros [21], a number largely driven by late stage attrition. With a stronger focus on disruptive

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innovation in Research & Development the late stage attrition rate is likely to increase, further driving up developmental costs. This has substantial financial consequences due to the preceding investment for the earlier stages of the process. Moreover, traditional conditions for market access, like efficacy, safety and quality, are now compounded by value-for-money considerations through health technology assessments. While these represent legitimate societal concerns, they further slow time-to-market and increase uncertainty of investments.

- **Lack of ways for timely investment:** Entrepreneurs and small start-up companies will often incubate disruptive innovation. Long regulatory delays along with, on occasions, lack of timely patent grants, can strain cash flow and shift the point at which significant investment is attracted. The consequence is that, at best, development slows or the start-up company moves out of Europe, and at worse the incentive to innovate disappears, the company ceases trading, and the innovation is lost.

- **Reimbursement:** Before they can be fully adopted, new treatments, devices, and drugs have to be accepted by reimbursement systems used by European countries. There are substantial delays in the process granting reimbursement codes. In many countries the cost calculations performed can discriminate against innovation because they often use the cost per procedure/treatment rather than taking into account the outcome.

- **Regulatory landscape:** There is a difference in regulatory regulations between pharmaceutical compounds and devices. For devices Europe's regulatory landscape is probably not a major roadblock to innovation. Time-to-market for devices can be faster than in the USA because the requirement for demonstration of clinical efficacy may be less stringent, which allows earlier access but also carries some increased risks [22]. One of the challenges for physicians is that the risk/benefit trade-off of using a new device is difficult to quantify, because too little information is publicly available from the current approval processes and because post-market

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surveillance is the responsibility of the manufacturer and its results are not usually disclosed in detail. Lack of coordination between regulatory approval and health technology assessment means that clinical data are often re-evaluated, and this can significantly delay reimbursement code approval. [19]

Role of the stakeholders

There are many stakeholders within the healthcare systems whose views on innovation should be considered. While all of them agree that the spiralling cost of healthcare in Europe is unsustainable, opinions can differ on where innovation efforts are most needed and how innovation is best exploited. It requires a mindset and behavioural change which is pushing health care providers and policy makers out of their comfort zone. (e.g. patient engagement, quality controls in hospitals, hypothesis myopia, private public partnerships, innovative trial designs, law on tenders), As discussed above, innovation can take many forms beyond the traditional focus on scientific Research & Development. Process-related, organisational, and cultural innovation can yield profound benefits in cardiovascular healthcare through initiatives such as patient engagement and quality management systems. A major challenge is to align all different perspectives and efforts so that physicians, scientific societies, academia, industry, regulators, payers, and hospitals share common ground, and that the conditions are established for all types of innovation to flourish. Stakeholder perspectives include the following:

- **Academia**: Academic institutions must by their nature play the role of cradle for innovative ideas. Most importantly they may promote by the education they provide to young scientists an innovative approach and an openness for testing new ways and disruptive innovative

processes. This culture of openness to new ideas is of paramount importance for the creation of an environment allowing innovative ideas to leave the stage of theory and begin being realized.

- **Industry:** The longstanding tradition of partnership between industry and clinicians in pursuit of innovation in medical technology becomes even more indispensable in the future: clinicians cannot create new therapeutic tools ready to be used and industry cannot have all needed expertise in house. The cardiovascular world has seen the launch of many devices over the years, representing state-of-the-art performance and technology that can be very well described as innovative. In the device area there are major developments with regards to reducing invasiveness and size, but often at the expense of increasing costs. This is driven by the complexity of developing implantable sensors, quantification of those signals, and their conversion into electrical energy for capture and analysis, which is the fundamental requirement for all devices and a major undertaking. The future priority for large industry players is to balance three imperatives: to maintain therapy innovation, a global footprint and market access, and to demonstrate economic value of their products.

- **Scientific societies:** Scientific societies have a major role to play by identifying areas with the most urgent needs for innovative approaches and, by creating the networks that may act as facilitators of innovative actions. In this respect, scientific societies may provide important support for academia and carry the ideas born in academic institutions further. Importantly, they may cooperate with the regulatory authorities and help funders to identify priorities in healthcare-related innovation.

- **Hospitals:** Hospitals do not usually rush to adopt the latest treatments, and have often difficulties to differentiate something truly innovative from something simply new. The main priority of hospitals is usually to offer state-of-the-art facilities rather than to engage in the pursuit of innovative healthcare solutions. They focus on providing safe treatments, doing no harm, and

delivering good services and value-for-money. It is difficult for a hospital to judge when to embrace technological innovation, especially because of past failures, and instead balance the investment decision against the gains from process and organisational innovation as a way of improving outcomes. Innovation can be stimulated by creating centers of excellence. Such a development requires a behavioral change, because not every hospital then offers every treatment.

- **Insurance companies:** The payers – including medical insurance companies – strive to achieve a balance between the benefits of innovation and financial viability. They prioritise improved processes, outcomes, and quality of life while considering at the same time health economics and operational efficiency. Introducing new treatments into standard care can be problematic because of long evaluation times and the need, sometimes, for statute change. Public health insurance companies in Germany for instance participate in an innovation fund with the goal to incentivise innovative developments with an expected impact on patients' health care. An example of practical ways for promoting innovation is the adoption of the Surgical Process Manager software which tracks and measures every aspect of certain surgical procedures. Results show that major efficiency improvements can be achieved by focusing on process flow and management. Payers see the combination of standardisation and big data as central to higher healthcare quality with acceptable costs. (http://sp-institute.com/)

Actions for facilitation of innovation

Based on the discussions mentioned above, the following conclusions were drawn regarding requirements for better facilitation of innovation, ultimately leading to a culture-change on multiple levels, including:

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- A change in the traditional parameters is required by which academia measures scientific achievement, so that methodological rigour, reproducibility, and impact on society, training or healthcare weigh more than metrics such as number of publications, citations, or cumulative impact factors for obtaining faculty positions or grants.
- A systematic investment on high-quality education in research methodology.
- Greater investment in projects with a high innovation potential. These are often regarded as “high risk” when compared to proposals that pursue incremental findings, and as such they are less likely to be funded.
- Active engagement in a debate to improve the public understanding of the benefits that may be accrued by “Big Data” research (e.g., using medical records or genetic data) and the establishment of a proportionate legal and ethical framework that would enable full exploitation of its potential.
- Addressing the issue of overregulation as a major obstacle for driving forward innovative ideas by the regulatory authorities. The challenge will be to retain a well-structured and –ordered regulatory framework whilst avoiding an excess of requirements that hampers innovation. A delicate balance is needed between allowing early access for new products and technologies and the associated risks.
- Standardising regulatory approvals at an international level in order to facilitate international collaboration and generate synergies that would speed-up the implementation of innovative strategies. This is a difficult task because it requires cooperation from authorities of different parts of the world.
- Patenting innovative ideas, and more generally, empowerment of patenting culture should be enhanced between young researchers and clinical practitioners. The whole patenting

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process in Europe, should also be less complex and expensive, as at the moment, in many European countries, many individuals are discouraged to patent the innovative ideas.

Innovation is more than technology: it is how technology serves the entire (health care) society best. To drive this innovation forward, all stakeholders need to contribute. In a globalised and extremely competitive world, the leading role of Europe in medical innovation can only be achieved through well-coordinated efforts from all parties involved.

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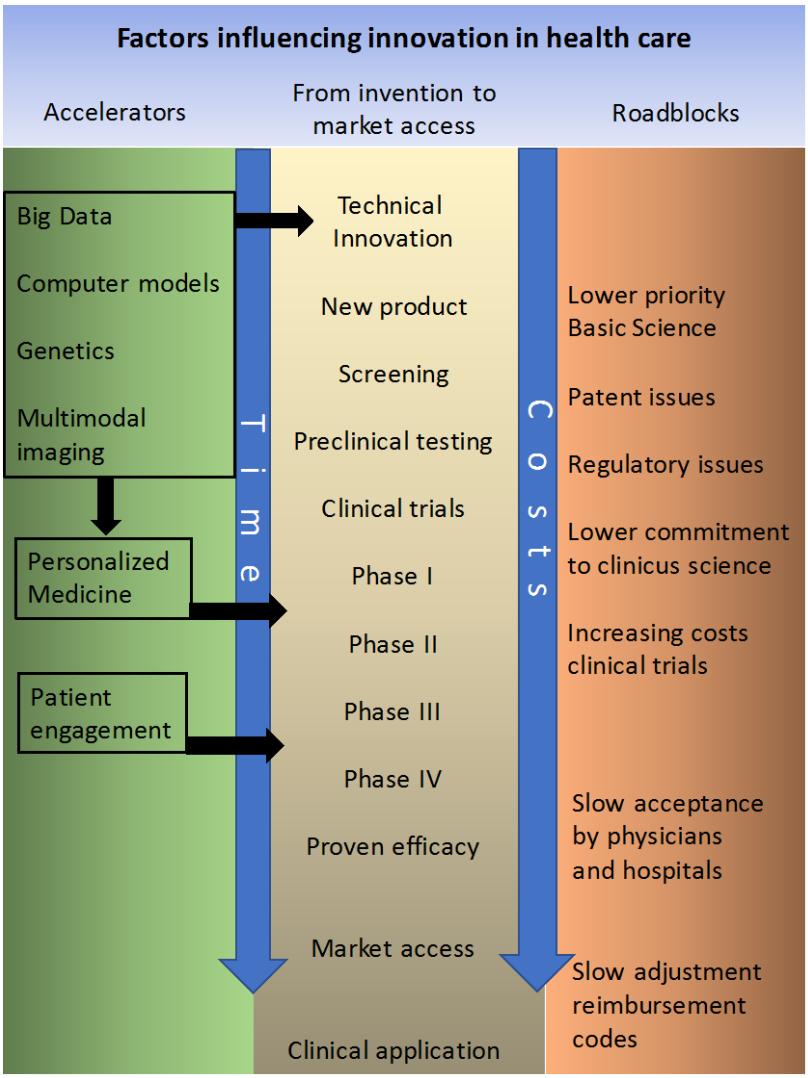

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