Project context and main objectives

Cardiovascular disease (CVD) is the main cause of death in Europe and worldwide. CVD also leads to disability, hospital admissions and reduced ability to work and therefore affect individual patients, health care systems and societies as a whole. CVD develops slowly and from common risk factors such as high blood pressure, smoking and cholesterol levels. Not all people with these risk factors will develop severe CVD and not all people with severe CVD will have a characteristic risk factor profile. Moreover, not only the severity but also the rate of progression of CVD differ from patient to patient.

The risk of development of CVD and its progression can be estimated from traditional risk factors. However, such predictions are not accurate and may over or underestimate an individual person's risk. The EU-MASCARA project was based on the concept that more individualised risk assessment will be required in order to offer patients the best therapies to prevent and reverse CVD. The project was therefore at the forefront of a development that is now called "precision medicine" – to provide the right treatment to the right patient at the right cost.

The EU-MASCARA Consortium aimed to study if "biomarkers" can help with CVD risk assessment. Biomarkers are features that can be measured, that relate to the disease process and respond to therapeutic interventions. It should be noted that the term "biomarkers" does not only refer to circulating markers that can be measured in blood or urine but that it also includes imaging techniques and functional assessments that can all inform about a patient's cardiovascular health. The Consortium has therefore looked into a wide range of biomarkers to assess their use for diagnosis of CVD and for prediction of future CVD in the general population and in people who already have risk factors for CVD.

The EU-MASCARA project was built upon four objectives that have been addressed throughout the course of the research programme. First, as a Consortium we studied the relationship of emerging biomarkers with existing CVD. In cross-sectional studies on existing clinical cohorts, we studied people with CVD and people at early stages of CVD which were then compared to healthy control subjects. Genetic markers, proteomic markers, metabolomic markers and specific biomarkers of inflammation and cardiac remodelling were studied. Whilst all these markers have a specific role to explain specific steps in the development of CVD it is challenging to find uniform markers that apply to all forms of CVD. In a second step, the Consortium has therefore taken most of the biomarkers from the first step into studies where long-tern term follow-up was available in order to study if the biomarkers can predict the development of CVD. We focussed on heart failure

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as a model disease since this is a common endpoint of many cardiovascular conditions and is associated with significant disability and risk of death. The EU-MASCARA Consortium has developed and validated specific genetic factors (microRNAs) and proteomic factors (namely based on urinary polypeptides) that can be predictive of heart failure; the Consortium has made further developments of other biomarkers and validated them in the context of heart failure but has also studied other cardiovascular conditions including high blood pressure, coronary artery disease and renal diseases.

The third objective was to look comprehensively at all the data and find a way to bring them together in biomathematical models. This "data integration" was based on all biomarker data and also took health economic aspects into account as novel biomarkers are often very expensive to measure. We have also defined a fourth objective of developing new tests for CVD and have made the first steps in this direction, especially in the area of proteomics. For other biomarkers we have defined the most promising candidates and techniques that can inform future assay development.

Work performed since the beginning of the project and the main results achieved so far

As in previous periods the overall aim of EU-MASCARA remained the validation of biomarker candidates that improve cardiovascular risk prediction. We have already discussed in the report for Period 2 that a strict separation between such prospective/predictive studies and cross-sectional mechanistic studies is not always possible. As in Period 1 and 2 the EU-MASCARA Consortium has focussed on predictive work but used the opportunities the DoW provided, to further expand on studies that explain the relationship between novel biomarkers and cardiovascular diseases.

The plan to focus on three core cohorts continued to work well for the Consortium. The InGenious HyperCare cohort has been used to develop a model to integrate biomarker data of different dimensionality into predictive models. This is not a trivial problem as adjustments for multiple testing can be too rigid if a simple but potentially strong predictive biomarker is analysed together with a multidimensional biomarker (for example from a proteomics experiment). The Consortium has, in parallel, also developed literature mining techniques to bring data from various publications and databases together, apply appropriate weighting and then define networks and nodes than can highlight the best possible biomarker candidates.

The bioinformatics work was paralleled with experimental work into prediction of cardiovascular events in prospective study cohorts. The Consortium focussed on novel biomarkers with a sufficiently robust evidence base, but still requiring further validation in such experiments. One of the highlights is the validation of a urinary proteomic classifier to predict the development of heart failure. This work has already stimulated additional research programmes beyond the context of EU-MASCARA: further experiments in

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samples from patients with heart failure; refinement of the predictive proteomic classifier; and proteomic experiments in samples from failing and normal hearts to unravel a molecular signature of heart failure. The concept of bilateral and trilateral collaborations within the wider context of the EU-MASCARA Consortium has been extremely successful to stimulate such work and use data and infrastructure provided by the project to generate additional data and attract further funding.

The third core cohort, Generation Scotland: Scottish Family Health Study, has been used to study a wide range of biomarkers in people with prevalent and incident heart failure. For this analysis we used the pipelines that were established in the early experiments in InGenious HyperCare to study biomarkers prospectively and across most of the partners in EU-MASCARA. Logistic aspects such as coordination of measurements between INCLIVA and FIMA who shared remaining aliquots of sample, made it possible to deliver on this project despite the availability of only limited amount of plasma and urine samples.

It is a further strength of our project teams, that in addition to consortium-wide activities, all partners added a significant amount of resources and data to the knowledge generated within these 4.5 years. The infrastructure provided by this project made it possible for the partners to establish well phenotyped cohorts of patients with cardiovascular conditions. These have been used to answer specific questions within the EU-MASCARA framework but most importantly, they will also remain available to partners in the future to continue research.

Despite the significant results obtained it is clear that especially the biomarkers based on novel -omics are associated with high costs compared to their diagnostic and prognostic power. It was therefore important to study the health economic aspects of predictive biomarkers as well. In brief, our data demonstrate that at their current costs novel omics based biomarkers cannot compete with existing risk estimators that are based on clinical parameters and a limited set of routine biomarkers. However, we have worked on a modelling and given estimates of cost reductions that will be required in the future to translate novel markers into clinical practice. We are confident that such reductions are possible as with wider use of new technologies the associated costs generally tend to come down to economic levels.

As in previous periods we carried out extensive dissemination and exploitation activities. The collaborative studies between the partners produced an impressive number of publications and other scientific outputs, most of which will continue to support collaborations between the partners beyond the lifetime of the project. The final score our or peer reviewed publications has reached the 173 while presentations and posters to scientific and other events exceed the 200. Our results were presented to the scientific community and industry at an EU-MASCARA thematic workshop “BIOMARKERS OF CARDIOVASCULAR RISK: THE EU-MASCARA PROJECT” organised during the 25th European Meeting on Hypertension and Cardiovascular Protection (2015, Milan, Italy).

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With regard to exploitation the Consortium again focussed on SME partners and their specific requirements to use the results of the EU-MASCARA consortium for their future R&D strategies. Each SME had the opportunity to explore the market segments they are most familiar with and have the best potentials to seek for exploitation opportunities and identified plans to put in action. Two of them, ACS and MOS already have a promising product each in hand that is partly based on the EU-MASCARA work.

Description of the expected final results and their potential impacts and use

In the original proposal the EU-MASCARA Consortium outlined the potential impact of the work programme in four distinct areas. We will briefly summarise the achieved impact against these goals.

Complementarity to public health activities that aim to reduce the overall population risk of cardiovascular disease
EU-MASCARA has worked in concert with strategies to reduce cardiovascular risk. The project had a focus on studies in general population cohorts in order to translate results to the largest possible communities across Europe. Work within the project has addressed factors beyond molecular mechanisms of disease and studied for example the association between lifestyle factors and body weight, cardiovascular risk factors and biomarkers of CVD.

Improved cardiovascular risk prediction
A number of biomarkers that were validated and further developed within EU-MASCARA have been shown to improve cardiovascular risk prediction beyond traditional risk factors. In particular, the urinary proteomics derived biomarkers have fulfilled this goal and have already been commercialised.

Contribute to the development of personalised and predictive medicine
"Personalised medicine" or "precision medicine" feature strongly in malignant diseases and inflammatory diseases but less so in CVD. The complexity and variety of CVD with their multifactorial origins and the relatively long duration of development of CVD are reasons for the slow uptake of precision medicine in CVD. The EU-MASCARA Consortium has therefore systematically evaluated a large number of biomarkers that can contribute to better risk stratification and inform treatment decisions. The health economic analyses that were performed as part of the project provide further guidance in this respect.

Encourage SME efforts towards research and innovation with priority given to proposals demonstrating that research-intensive SMEs play a leading role.
It is evident from this report that without the expertise of SME partners the EU-MASCARA project would not have been able to deliver its results. SMEs involved in this project continue to collaborate with the knowledge partners beyond the lifetime of the project and within other international consortia.

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