Improving diagnosis and risk stratification of cardiomyopathies across the ejection fraction spectrum

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IMPACT

Daily, on average 80 individuals get hospitalised, and 20 individuals die due to Heart Failure (HF) in the Netherlands. In total, around 250,000 individuals are diagnosed with HF in our country, which is accompanied by care-related costs that already exceeds 800 million euros yearly\(^1,2\). Worldwide the prevalence of HF even exceeds 38 million patients\(^3\). This prevalence is expected to increase even further during the upcoming years due to the ageing population and the growing occurrence of other HF-related risk factors (e.g., diabetes mellitus and obesity)\(^3,5\).

Sometimes major breakthroughs occur in scientific research, but usually these are small steps that provide a better understanding of e.g., the development, progression, and/or treatment of HF. Results of scientific research are generally not immediately applicable in clinical practice but rather are a little piece of the puzzle that ultimately may change the way routine clinical care is performed. Examples of such studies are presented in Part I (Chapters 2-8) of this thesis. Based on the findings of these studies, we can among others say that DCM-patients with Titin Truncating Variants (TTNtv) have more severe LA-dysfunction than DCM-patients without a TTNtv (Chapter 3), and that based on computational modelling both intrinsic left ventricular and left atrial dysfunction are likely present in DCM patients with and without a TTNtv (Chapter 3). In another study (Chapter 4), we showed that ambulant DCM patients with an inter-atrial block (IAB) or atrial fibrillation (AF) confer a similar increased risk of life-threatening arrhythmias (LTA); validation of these findings potentially results in a widely available marker for the early detection of DCM individuals at risk for LTAs.

During the performance of (registry-based) studies as presented in Part I of this thesis, a researcher faces a wide variety of logistic hurdles which often limit the number of subjects or amount of data included in these studies. These hurdles include but are not limited to the fact that routine clinical data needs to be often collected manually before it can be used for research purposes, and the fact that the follow-up of these patients and collection of additional data (e.g. to determine the quality of life, or evaluate the cost-effectiveness of certain treatments) is time-consuming. These hurdles often withhold the performance of in-depth cardiomyopathy or HF research across the entire LVEF-spectrum, which is regrettable since categorising HF based on LVEF results in an enormous oversimplification of this complex syndrome\(^6,8\).

Large scale registries with real-world data will play a pivotal role to move the current HF field forward and boost the efficacy of studies like the ones that are pre-
Presented in Part I of this thesis. These registries will form the foundation for multi-disciplinary data and hypothesis-driven (multi-omic) approaches that can challenge LVEF as the cornerstone of HF classification. HF registries including unselected subjects will provide real-world insights into clinical practice, prognosis, temporal trends, and expose novel therapeutic targets that can be subsequently challenged in (registry-based) clinical trials.

Our Maastricht Cardiomyopathy Registry team created a future proof foundation for a multidisciplinary (early) cardiomyopathy and HF registry in the past years (mCMP-registry; presented in Chapter 9 of this thesis). Logistic hurdles faced during the (registry-based) studies we performed in our centre during the past years were tackled by our team to improve the way HF registry-based research is performed. For example, the mCMP-registry uses a web-based tool (LDOT) that seamlessly integrates with the electronic case report form (eCRF, CASTOR EDC) used for this registry. This not only allows to easily create real-time insights into the logistic processes of the study but also allows to automate processes to reduce the time needed to collect study-related information significantly. For example, yearly questionnaire invitations and reminders are automatically sent by LDOT to each participant that provided informed consent for these questionaries. Due to the seamless integration with the eCRF, the questionaries are automatically filled-in in this environment by the participants. This allows us to longitudinally easily evaluate e.g. the quality of life, occurrence of events outside the hospital, and allows us to perform cost-effectiveness analysis. Since the first subjects were included in the mCMP-registry on the 19th of October of 2021, already 1031 baseline questionaries have been automatically sent (update 27-04-2022).

Another way how we significantly improved the efficacy of data collection within the mCMP-registry is by collecting routine clinical care data in standardised electronic medical record forms, which allows semi-automatic data collection within the eCRF. Such automatisations of data collection significantly reduce the workload of involved researchers and are crucial to allow the scalability of a registry like the mCMP-registry. Where it used to take ±3 minutes to e.g. manually update one echocardiogram in the eCRF of one subject, this is currently the time it takes to start the semi-automatic process to update all echocardiograms of the subjects included in the mCMP-registry irrespective of the number of subjects included.

The mCMP-registry even allows the creation of a virtual waiting room for future (interventional) studies (Figure Discussion, Chapter 11) given the seamless integration of the eCRF (CASTOR EDC) with R-studio. This integration gives among others
the unique opportunity to visualise and customise study dashboards with R-shiny\textsuperscript{11} to easily select and subsequently contact eligible subjects for future trials. The screening of eligible subjects for trials is often time-consuming reducing the efficacy of these trials. The scalability of the mCMP-registry logistics allows other centres to easily join this initiative which even allows the possibility to better study rare cardiomyopathy diseases and allow the performance of clinical trials in these patients.

The mCMP-registry closely collaborates with the Netherlands Heart Tissue Bank (NHTB) and uses its infrastructure to inform subjects about the existence of the NHTB. The NHTB aims to boost a wide range of cardiac disease-related fundamental and translational studies. The NHTB does this by strengthening the cardiovascular research infrastructure with an open-access non-profit biobank. The NHTB will include cardiac tissue and related clinical data from donors with and without known cardiovascular diseases, which will increase our understanding of cardiac diseases during early and advanced disease development.

**A critical appraisal of (logistic) hurdles faced during the conduction of (registry-based) studies should be part of every study to optimise the way these studies are performed.** This will not only allow researchers to more efficiently perform research, but will also allow researchers to unravel the complexity of the HF syndrome beyond the currently used HF nomenclature. Future HF and cardiomyopathy related research should address the challenges in early detection, prevention and management of HF and cardiomyopathies to reduce the societal, economic, and healthcare impact of this debilitating syndrome\textsuperscript{3}. In-depth characterisation of HF and cardiomyopathy patients using registry-based research will be an important asset to accomplish this.
REFERENCES