Pharmacotherapy in heart failure with reduced ejection fraction during the last 20 years, and the way ahead for precision medicine

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There are but a few areas in medicine, where progress has been as remarkable as in heart failure (HF) therapy over the last three decades. However, progress has been consistent only for chronic HF with reduced ejection fraction (HFREF). As a result of progress made in HFREF therapy, cumulative mortality benefit amounts to almost a three-fold decrease in death rate whether in severe or in mild-to-moderate HFREF. In acutely, decompensated HF (AHF), a 26% mortality benefit was observed whether in severe or in mild-to-moderate HFREF therapy, cumulative mortality benefit amounts to almost a two-fold decrease in death rate whether in severe or in mild-to-moderate HFREF. In acutely, decompensated HF (AHF) as well as in HF with preserved ejection fraction, despite a reasonable number of trials, none of the tested therapies so far has definitively been proved to be effective.

In chronic HFREF, it is now well established that triple therapy with angiotensin-converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARB), beta-blockers (BB), and mineralocorticoid receptor antagonists (MRA) save lives and prevent hospital readmission, and unless contraindicated, should be used in all symptomatic patients with HFREF. In asymptomatic patients, only ACEi therapy has been proved to slow the progression of the disease with mortality and morbidity benefit. No trial has tested so far the benefit–risk ratio of ARBs, BBs, or MRAs in patients with low EF and no symptoms. Further progress is announced with the premature termination for excess of benefit of the prospective comparison of ARNI with ACEi to Determine Impact on Global Mortality and morbidity in Heart Failure (PARADIGM–HF) trial, with the dual angiotensin receptor and neprilysin inhibition as an alternative to angiotensin-converting enzyme inhibition in patients with chronic systolic HF.

Still, admission for worsening HF confers a higher risk of death and/or re-admission and identifies patients with higher needs for therapy optimization. In all HFREF trials with ACEi, ARBs, BBs, and MRAs, therapy was initiated in patients with stable conditions, significantly long after discharge from an HF hospitalization, if any (one exception is the EMPHASIS-HF trial where eplerenone was initiated within 6 months, and on average after 42 days after a cardiovascular admission). However, although initiating therapy upon admission, before or short after discharge has become common practice and seems to be well tolerated for ACEi/ARBs, BBs, and MRAs; these agents are still frequently underutilized and/or prescribed at inadequate doses. For example, in chronic HF, physicians are often reluctant to aggressively titrate therapies in apparently stable patients. Data support that higher doses of RAAS inhibition result in improved outcomes compared with lower doses. Evidence-based RAAS inhibitors should be titrated to doses attained in clinical trials or to the maximally tolerated dose. Failure of initiating and/or optimizing therapy in patients with a high risk of re-admission is one major driver of high readmission rates. Therefore, therapy optimization is an area of intensive research. Observational studies and registries conducted in many regions consistently show that daily practice lags behind international evidence-based guideline recommendations. Many reasons have been described to explain the barriers to implementation. Contra-indication or safety concerns are the main factors. Frequent reports expectedly emphasize safety issues that occur more frequently in real-life daily practice than anticipated from the results of clinical trials. One major reason is the suboptimal monitoring of simple safety variables. In clinical practice, renal function and potassium levels should be monitored at least to the same extent to the manner used in clinical trials. Doses should be adjusted as frequently as mandated by pertinent changes in clinical status. This dynamic therapy optimization is frequently omitted in daily practice, which is one reason of disappointingly negative results in effectiveness registry and observational reports.

To help therapy optimization a number of ‘guided therapy’ trials are exploring several methods of personalized medicine. Basically, patients enrolled in such trials are at a high risk of re-admission after discharge from a HF admission. Because discharge natriuretic peptides (NPs) were shown to predict an outcome, a number of NP-guided therapy trials have been conducted and led to inconsistent results. A clear indication for the role of NP-guided therapy in HF still awaits definitive elucidation in an adequately powered ran-
domized trial.\textsuperscript{10,11} One such study is currently under way: the Guiding Evidence-Based Therapy Using Biomarker-Intensified Treatment (GUIDE-IT) randomized trial (ClinicalTrials.gov identifier NCT01685840), which opened to patient enrolment in December 2012 and is expected to include 1100 participants. Developing biomarker-guided therapies requires careful consideration of what patients to target, whether the target goals are correct and a number of issues relating to a trial design. One of the main limitations of these trials is the lack of a decision support system based on an agreed algorithmic expert system that integrates NP monitoring data with other patients’ critical medical data. Safety issues should be addressed. It is plausible that not all the patients may benefit from the same optimization biomarker-guided algorithm. Aggressive adjustment of indicated therapies may not benefit equally to all. Titrating to higher doses could cause harm in patients who may be more sensitive. A number of new trials and initiatives will provide important information on these questions.

Similar issues also apply to disease management programmes and device-based remote monitoring trials. Remote monitoring devices have been developed to detect early evidence of HF decompensation, with the underlying hypothesis that early detection may enable clinicians to institute therapy sooner, which may translate to fewer hospitalizations.\textsuperscript{13} Several clinical trials have tested the efficacy and safety of remote monitoring devices for improving outcomes. These trials face both the usual challenges of device trials and unique challenges since they assess therapeutic endpoints for diagnostic devices.\textsuperscript{13}

Essentially, the potential of guided therapy is not only related to the concept of tailored personalized medicine. Guided therapy allows for many more checks (potentially daily checks) of patients’ critical medical indicators than the routine practice only occasional distant encounters with the physician. Guided therapy allows for dynamic therapy optimization. So far emphasis was on dose up-titration, because of the common observation of suboptimal dosing of ACEs, ARBS, BBs, and MRAs. More frequent up and also down titration of such therapies with concomitant fine tuning of diuretic therapy might be more relevant, and could be guided by frequent checks of simple measures of potassium, renal function, and state of congestion.\textsuperscript{14} These could be allowed by simple home-based monitoring technologies. Electronic health-care tools sampling more frequent individualized information intelligently filtered at point of cares may be coupled with decision support tools that provide clinicians with options and algorithms to facilitate decisions on the basis of test results. CV remote monitoring methodology of assessment of efficacy—effectiveness and regulatory framework is to be streamlined and aligned with the faster progress of technological innovations.

Variability in drug response is another important issue, which may account to some extent to lower than anticipated efficacy or a higher than anticipated incidence or severity of adverse effects. Licensed medicines sometimes do not perform as expected in everyday clinical practice. The problem of benefit–risk is to a considerable degree a problem of variability in drug response. This includes biological and behavioural variability as well as geographical and healthcare system variability.\textsuperscript{15} Harnessing the efficacy–effectiveness gap includes ‘precision medicine’. The wider use of biomarker-guided therapy and electronic healthcare tools to improve drug prescribing, dose optimization, and patient adherence is one segment of precision medicine that is rapidly evolving in HF therapy. Another important segment is coupling established clinical—pathological indexes with state-of-the-art molecular profiling to create diagnostic, prognostic, and therapeutic strategies precisely tailored to each patient’s requirements (omics-based personalized medicines and companion diagnostics). This process has led to some successes in oncology. Cardiovascular medicine is still to deliver precision medicine success stories. Hurdles are methodological, industrial, and regulatory. But the concept is sound, especially in HF, a heterogeneous syndrome in much need to be segmented according to the contribution of the respective underlying mechanisms.\textsuperscript{16,17} Important research is on-going with the aim of clinically validating omics based biomarkers that could help mechanistic stratification of the disease. The field would then evolve, as in oncology, to prospectively further test the hypothesis that specific therapies could be used only in patients with responder profiles, most likely to benefit, and avoid exposing unnecessarily likely non responsive patients to the risk of adverse events.

For instance, large QRS, and more specifically LBBB, an excellent marker of patients most likely to benefit from cardiac resynchronization therapy, and heart rate, a simple mechanistic marker of efficacy of ivabradine\textsuperscript{18} are premises of actionable biomarkers to serve precision medicine. Great counter-examples of potentially missed opportunities because of the one-size-fits-all approach are the negative findings of trials with drugs targeting-specific mechanisms, but where all comer patients were enrolled. MOXCON might have been positive if patients were selected on the basis of high adrenergic drive. RENAISSANCE and RECOVER might have been positive if patients were selected on the basis of systemic inflammation to receive the anti-inflammatory soluble TNF-alpha enbrel. EVEREST might have been positive if patients were selected on the basis of elevated vasopressin and/or hyponatraemia.

Personalized medicine is one area identified as a priority for funding research, which would include the creation of networks among academic institutions, industry, regulatory agencies, patient representatives, and other stakeholders. Examples in HF include the European Commission Seventh Framework Programme for Research (FP7) projects such as ‘A systems BIOlogy Study to TAIlored Treatment in Chronic Heart Failure’ (BioStatCHF, www.biostatchf.eu), ‘Heart Omics in Ageing’ (HOMAGE, www.homage-hf.eu) and ‘Targeting cardiac fibrosis for heart failure treatment’ (Fibrotargets, www.fibrotargets.eu). Identifying profiles of patients more likely to benefit or more likely to not tolerate therapy optimization is the main objective of the BIOSTAT programme. The objectives of HOMAGE are to validate the association of ‘omics-based’ biomarkers with the risk of developing HF and co-morbid conditions in cross-sectional population cohorts and to investigate an innovative ‘omics biomarker-based therapeutic strategy. Fibrotargets aims to validate new anti-fibrotic strategies and develop the potential clinical scenario of targeted anti-fibrotic therapies for HF therapy.
The ‘time for action’ in personalized medicine comes in the context of defining a common strategic framework for research and innovation activities: Horizon 2020.

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