Is it time to start with device-based prognosticators?

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This editorial refers to ‘Device diagnostics and long-term clinical outcome in patients receiving cardiac resynchronization therapy’ by J.P. Singh et al., 2009;11(12), 1647–53.

Do we really need to look into device-based prognostic indicators of mortality of heart failure patients? After all, numerous studies demonstrated the predictive importance of a large number of parameters including natriuretic peptides, inflammatory markers, and electrocardiographic parameters, not to mention innumerable demographic and readily available blood tests. Thus, one could view the excellent study by Singh et al.1 in this issue of the journal as an academic exercise in prognostication of the outcome of heart failure patients. Indeed, we already have models and scores aiming at a better prognostic performance across the heart failure spectrum, i.e. the Heart Failure Survival Score, the Seattle Heart Failure Model, the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure predictive schemes, the Acute Decompensated Heart Failure National Registry tree discrimination, just to mention some of them. However, the study by Singh et al.1 provides more reasons to care about prognostic indicators in general and, in this case, based on device diagnostics. Indeed, currently available models and scores are imperfect for predicting major events, such as implantation of left ventricular assist device, heart transplantation, and mortality. The authors used a rather simple dynamic predictive model based on device diagnostic data in risk stratification of out-patient heart failure patients treated with cardiac resynchronization therapy (CRT). They showed, e.g., that higher heart rate variability measured by Standard Deviation of the averages of intrinsic R-R intervals (SDANN) at two points in time (2 weeks and 3 months after CRT implantation), and relative large increase from 2 weeks value to 3 months value were associated with a decreased risk of death.

Although the study by Singh et al.1 have several methodological (retrospective analysis, limited number of patients included, limited number of demographic and laboratory data, unadjusted models, death as only outcome, limited follow-up time) and technical limitations (due to device programming and modality of data collection for both heart rate variability and footprint analysis), the study may be considered as a first attempt to create a dynamic risk model for predicting outcome. All currently available risk stratification scores and model for prediction of outcome in heart failure patients have been built on static analysis strategies in which the time between measurement of a qualifying parameter (e.g. left ventricular ejection fraction) in relation to some other parameters and outcome was maintained fixed. Moreover, there was no attempt for repeated measures of any parameter over time. The same applies to measures of autonomic function no matter whether they have been measured with the traditional ECG or have been recorded by an implanted device.1–3 The static nature of this approach does not take into account that a disease is a dynamic process with changes over time that may influence the presence and stability of risk markers.

The concept of dynamic risk profiling has been recently summarized1 and is intended to take into account for time-dependent changes in both the presence and the power of risk markers. Device-based diagnostics are ideally designed for such an approach as they permit to move from discrete, temporally well-defined samples, to continuous, virtually indefinite sampling. Recently, there have been attempts to analyse sequential changes of device-based data.1,4 Heart rate variability, mean heart rate, and patient’s physical activity as examined by Singh et al.1 are just few of the many currently available device-based diagnostics. These and many other device sensors (e.g. pulmonary artery pressure, left atrial pressure, or intrathoracic impedance) and diagnostics give unprecedented access to important physiological information which may be very relevant for understanding the mechanisms related to acute events. Tracing the continuous changes of a combination of device-based parameters may be the key to predict risk for sudden death or impending ventricular failure requiring hospitalization or implantation of left ventricular assist device/heart transplantation. A key question is which combination of parameters offer the highest accuracy to predict each of these events. In the long run, both remote monitoring and the
development of novel, sophisticated mathematical algorithms to model outcome will play an irreplaceable role in patient profiling and personalized healthcare prescription.

Although we are now in a device-based era for treating and monitoring heart failure patients, it is very unfortunate that the authors of the study have not collected and integrated other clinical prognostic parameters which are already well validated and frequently used in prediction of outcome of heart failure patients. Hopefully, ongoing studies like the ‘Program to Assess and Review Trending Information and Evaluate Correlation to Symptoms in Patients with Heart Failure (PARTNERS HF)’ or the ‘Diagnostic Outcome Trial in Heart Failure (DOT-HF)’ which are prospectively collecting device diagnostic information may help in better defining the role of device-based diagnostic information and the added value of device-based information compared with more traditional parameters included in currently available risk models.

There are several questions which need to be answered before moving into device-based prognosticators. For reasons we do not understand, prognostic factors in virtually all cardiovascular diseases have differential association with outcome in whites versus blacks. Thus, despite controlling for multiple factors (including risk factors, symptoms, demographic variables, and comorbidities) in regression models, many studies have shown an unexplained impact of ethnicity. Whether this is the expression of a different environmental or biological basis is beyond the scope of this discussion but it does underscore the fact that data generated in one group may not be simply extrapolated in another. The study by Singh et al. does not report about race, thus it is unknown the value of device-based prognosticators in this specific setting. Another interesting finding of the study by Singh et al. is the trend toward higher proportion of females in the medium and high-risk group compared with the low-risk group. It has become increasingly apparent in recent years that there are important differences in the presentation and clinical course of many cardiovascular disorders in men and women. These gender differences extend to clinical cardiac electrophysiology, with respect to basic electrophysiology as well as the presentation and clinical course of many arrhythmias. Although this notion contrasted with the finding that men and women appear to derive equal survival from implantable cardioverter-defibrillator, it is, however, in line with a recent finding in the MADIT-CRT trial. Indeed in the MADIT-CRT study, the hazard ratio for death or non-fatal heart failure (whichever came first) was much lower in female gender. Finally and more importantly, unknown is whether device-based prognosticators are different in males and females.

The study by Singh et al. provides additional scientific evidence for the possible use of device-based information as an objective measurement of response to CRT. Over the last years, significant resources have been allocated towards the characterization of so-called ‘non-responder’ patients to CRT and there is still little agreement on definition of responder to CRT. Volume changes after CRT (or reverse remodelling) have been the most frequently used parameter for evaluating response to CRT because it fulfilled several requirements: widely available, easy to measure with good accuracy and linked to survival (surrogate endpoint of mortality). Many of the device-based parameters also present these characteristics, are not operator dependent, are based on well-described technique, are easy to be implemented, and are minimally influenced, if ever, by confounding factors. Both changes in volume and heart rate variability are surrogate endpoints of mortality, thus it would be very useful to evaluate which of these two parameters best predict major cardiovascular events and/or hospitalization for heart failure.

In conclusion, prediction of clinical events is imperfect and requires significantly more investigational efforts: device-based prognosticators are a new research area which deserves more attention and resources. However, before using device-based strategy to risk stratify patients with CRT, or eventually with any implantable devices, more evidence from prospective, randomized controlled studies is needed.

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References