Editorial

The Impact of Diabetes and Comorbidities on the Outcome of Heart Failure Patients Treated With Cardiac Resynchronization Therapy

Implications for Patient Management

Giuseppe Boriani, MD, PhD

Heart failure (HF) affects 1% to 2% of the population in developed countries, with a marked rise of its prevalence in subjects aged >70 years[1]. It has been estimated that ≈15 of 900 million Europeans and ≈5.7 of 300 million US Americans may present HF.[1,2] It is worrisome to consider that the prevalence of HF is expected to further increase, as a result of the increasing aging of the population.

See Article by Echouffo-Tcheugui et al

HF is a major driver of morbidity for affected patients and of costs for healthcare systems. It has been reported that there are >1 million hospitalizations for HF annually in both the United States and Europe.[2] This burden is also related to the high risk of rehospitalization because after discharge, the 3-month rate for death and readmission is close to 17% and 32%, respectively.[3] The outcome of patients affected by HF is generally poor, with a 1-year occurrence of the combined end point of mortality or HF hospitalization of 36% for acute HF and of 14.5% for chronic HF[4]. At 5 years, the survival rate of patients with HF is close to 50%, and it is, therefore, worse than that of the most common cases of diagnosed cancer.[5] With this epidemiological profile, the consequent financial burden is impressive: the costs for HF-related care can come to ≈$40 billion each year.[2]

Comorbidities are important in the management and the outcome of patients with HF[1]. The majority of patients with HF enrolled in the EORP-HF registry (Eurobservational Research Programme–Heart Failure Pilot; 74%) had at least 1 comorbidity, the most prevalent being chronic kidney disease (CKD; 41%), anemia (29%), and diabetes mellitus (29%). Co-morbidities were independently associated with higher age, higher New York Heart Association (NYHA) functional class and underlying ischemic heart disease.[6] Diabetes mellitus is a frequent comorbidity among patients with HF because diabetes mellitus not only increases the risk of HF 2.5-fold, on average, but also accelerates its occurrence.[7] Diabetes mellitus and CKD have a similar prevalence among HF patients with preserved and reduced left ventricular ejection fraction[6] and both may contribute to poorer outcomes.[6,8]

In the present issue of the journal, Echouffo-Tcheugui et al[9] report on >18 000 patients implanted with a biventricular defibrillator (CRT-D device) using the framework of the National Cardiovascular Data Registry (NCDR). For this report, the implantable cardioverter-defibrillator (ICD) registry data were linked to Medicare claims data, thus providing a picture of patients aged ≥65 years, with a left ventricular ejection fraction ≤35% and a preimplant NYHA class predominantly III, and a QRS duration ≥120 ms, who had been hospitalized for denovo CRT-D implantation in the period 2006 to 2009[9]. At the time of device implantation, patients who were diabetic, on the basis of medical history or new clinical diagnosis, accounted for 38% of the cohort. They were more frequently male, with a higher prevalence of hypertension, as well as of ischemic heart disease and advanced CKD on dialysis. During the post-CRT implant follow-up, patients with diabetes mellitus had a higher mortality than those without diabetes mellitus, both at 1 and 3 years, in agreement with a recent meta-analysis based on 5 studies of CRT in HF[10]. However, these findings have to be analyzed in combination with the evidence derived from randomized studies that CRT is equally effective in reducing mortality versus control in diabetic when compared with nondiabetic patients.[10,11] These data from the large data set of NCDR contribute to the evaluation of CRT-D in the real world, although, as is well known, registries can have limitations because of selection bias and missing data.

Cardiac resynchronization therapy (CRT) was introduced >20 years ago for selected patients with drug refractory HF on the basis of a series of pioneering experiences performed in Europe, in France,[12] and now constitute an effective treatment for appropriately selected patients with moderate to severe and even mild HF.[1,13] The most evident and measurable effect of CRT is the reduction of left ventricular volumes, so-called left ventricular reverse remodeling.[12–14] It is noteworthy that the response to CRT in terms of reverse ventricular remodeling and improvement in functional status after CRT implantation was found to be independent from most common comorbidities (including diabetes mellitus and CKD), but diabetes mellitus and CKD had an important impact on outcome, with a 3-fold increase in mortality risk.[14]

In a real-world long-term registry of around 700 CRT-D patients followed for 4 years, Boriani et al[15] found a 3-year

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

From the Cardiology Division, Department of Diagnostics, Clinical and Public Health Medicine, University of Modena and Reggio Emilia, Policlinico di Modena, Italy.

Correspondence to Giuseppe Boriani, MD, PhD, Cardiology Division, Department of Diagnostics, Clinical and Public Health Medicine, University of Modena and Reggio Emilia, Policlinico di Modena, Via del Pozzo, 71, 41124 Modena, Italy. E-mail giuseppe.boriani@unimore.it

(*Circ Arrhythm Electrophysiol*. 2016;9:e004463. DOI: 10.1161/CIRCEP.116.004463.)

***Circ Arrhythm Electrophysiol* is available at http://circep.ahajournals.org**

DOI: 10.1161/CIRCEP.116.004463

mortality rate similar to that reported by Echouffo-Tcheugui et al.[9] Moreover, comorbidities (expressed by the Charlson comorbidity index), as well as age, male sex, advanced NYHA class and implant during unplanned, urgent hospitalization were significant independent predictors of death/cardiac transplant.[15] The impact of diabetes mellitus as a comorbidity on the risk of hospitalizations and HF-related hospitalizations after CRT-D implantation is evident in the report by Echouffo-Tcheugui et al.[9] The assessment of freedom from first rehospitalization, as done in this report, has some limitations in quantifying patient outcome. Boriani et al[15] recently investigated the overall impact of ICD/CRT-D implantation on mortality and morbidity through the composite end point of Days Alive and Out of Hospital (DAOH).[15] In patients implanted with a CRT-D device, a significant reduction of DAOH was found to be associated with multiple comorbidities, expressed by a high Charlson comorbidity index, male sex, urgent unplanned hospitalization, NYHA class III and class IV.[15] The evaluation of DAOH may provide a valuable tool for summarizing the overall absolute effect of a treatment on mortality and morbidity and for improved patient targeting, although few data are available in the literature.[15]

In the setting of HF, many studies highlighted that noncardiac comorbidities, commonly present, especially in elderly patients, are strongly associated with adverse outcomes and hospitalizations, which could be preventable in up to half of the cases.[16] The direct implications of these observations are that the model of care should be adapted to the frailty of current HF patients, with continuous vigilance as to patient status at the patient's home, and delivery of appropriate interventions at the right time, in the right setting, with integration and coordination of multispecialty teams. This chain of care along the continuum of HF, with focus on both cardiac and noncardiac problems, constitutes a paradigm shift in patient care and could benefit from remote monitoring aimed at detecting the development of complications or disease progression requiring changes in management, or targeted interventions.[1] Remote monitoring of implanted devices has been recently recommended as the standard method for the follow-up of implanted electric devices, including CRT-D systems, for monitoring the appropriate functioning of the system (device/leads), with timely detection of lead failure or pulse generator exhaustion/malfunction.[13] Extending the monitoring function to HF in patients with a CRT-D device implies a closer and more detailed monitoring of patients' conditions through integrated signals and sensors that are the subject of ongoing development, validation, and improvement.[17] A recent meta-analysis of telemonitoring in patients with HF implanted with CRT-D or ICD concluded that telemonitoring is safe and is associated with a marked reduction in planned hospital visits, with a favorable economic return, but without a significant reduction of cardiac hospitalizations.[18] The scant evidence currently available suggests that further technological evolution is probably necessary before we can gain a complete and exhaustive picture of the potential impact of telemonitoring in improving outcomes in CRT-D patients and the impact on economic efficiency.[18,19]

Patient surveillance after implant of a CRT-D device has also to consider the risk of device system infections. In the report by Echouffo-Tcheugui et al,[9] no significant difference was found between diabetic and nondiabetic patients in the occurrence of device-related mechanical complications or device-related infections within 90 days after implant, even when other patient characteristics were taken into account. These data need to be interpreted in light of the observational nature of this study, and the actual risk of device-system infection in diabetic patients probably deserves some considerations. In the literature, there is evidence that diabetes mellitus is a significant predictor of infection, a risk that is usually amplified by the association with other factors, such as device replacement, reintervention for lead dislodgement, CKD, anticoagulant drug use, corticosteroid use, postoperative hematoma, etc.[20] There are many possible approaches for assessing the impact of diabetes mellitus or of other risk factors on the risk of device infections, including retrospective studies, case–control studies, or prospective cohorts, and this may explain the partial discrepancy between the report by Echouffo-Tcheugui et al[9] and other literature data, recently the subject of a systematic review and meta-analysis.[20]

In summary, HF has a major impact on patient survival and quality of life as well as on costs for the healthcare system and the community.[2] Improved knowledge about the impact of comorbidities such as diabetes mellitus will be crucial to offer to patients with HF new models of care that could benefit from innovative technologies, such as telemonitoring, currently available in CRT-D systems. The approach to these complex issues has to be multidisciplinary, in line with the concepts of Health technology assessments, trying to offer, if possible, win–win solutions to all stakeholders.[19]

Disclosures

Dr Boriani received speaker's fees of small amount from Boston Scientific and Medtronic Inc.

References

1. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, Falk V, González-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GM, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J*. 2016;37:2129-2200. doi: 10.1093/eurheartj/ehw128.
2. Ambrosy AP, Gheorghiade M, Chioncel O, Mentz RJ, Butler J. Global perspectives in hospitalized heart failure: regional and ethnic variation in patient characteristics, management, and outcomes. *Curr Heart Fail Rep*. 2014;11:416–427. doi: 10.1007/s11897-014-0221-9.
3. Maggioni AP, Dahlström U, Filippatos G, Chioncel O, Crespo Leiro M, Drozdz J, Fruhwald F, Gullestad L, Logeart D, Fabbri G, Urso R, Metra M, Parissis J, Persson H, Ponikowski P, Rauchhaus M, Voors AA, Nielsen OW, Zannad F, Tavazzi L; Heart Failure Association of the European Society of Cardiology (HFA). EURObservational Research Programme: regional differences and 1-year follow-up results of the Heart Failure Pilot Survey (ESC-HF Pilot). *Eur J Heart Fail*. 2013;15:808–817. doi: 10.1093/eurjhf/hft050.
4. Crespo-Leiro MG, Anker SD, Maggioni AP, Coats AJ, Filippatos G, Ruschitzka F, Ferrari R, Piepoli MF, Delgado Jimenez JF, Metra M, Fonseca C, Hradec J, Amir O, Logeart D, Dahlström U, Merkely B, Drozdz J, Goncalvesova E, Hassanein M, Chioncel O, Lainscak M, Seferovic PM, Tousoulis D, Kavoliuniene A, Fruhwald F, Fazlibegovic E, Temizhan A, Gatzov P, Erglis A, Laroche C, Mebazaa A; Heart Failure Association (HFA) of the European Society of Cardiology (ESC). European Society

of Cardiology Heart Failure Long-Term Registry (ESC-HF-LT): 1-year follow-up outcomes and differences across regions. *Eur J Heart Fail*. 2016;18:613–625. doi: 10.1002/ejhf.566.
5. Stewart S, MacIntyre K, Hole DJ, Capewell S, McMurray JJ. More 'malignant' than cancer? Five-year survival following a first admission for heart failure. *Eur J Heart Fail*. 2001;3:315–322. doi: 10.1016/S1388-9842(00)00141-0.
6. van Deursen VM, Urso R, Laroche C, Damman K, Dahlström U, Tavazzi L, Maggioni AP, Voors AA. Co-morbidities in patients with heart failure: an analysis of the European Heart Failure Pilot Survey. *Eur J Heart Fail*. 2014;16:103–111. doi: 10.1002/ejhf.30.
7. Nichols GA, Gullion CM, Koro CE, Ephross SA, Brown JB. The incidence of congestive heart failure in type 2 diabetes: an update. *Diabetes Care*. 2004;27:1879–1884. doi: 10.2337/diacare.27.8.1879.
8. Boriani G, Savelieva I, Dan GA, Deharo JC, Ferro C, Israel CW, Lane DA, La Manna G, Morton J, Mitjans AM, Vos MA, Turakhia MP, Lip GY; Document reviewers. Chronic kidney disease in patients with cardiac rhythm disturbances or implantable electrical devices: clinical significance and implications for decision making-a position paper of the European Heart Rhythm Association endorsed by the Heart Rhythm Society and the Asia Pacific Heart Rhythm Society. *Europace*. 2015;17:1169–1196. doi: 10.1093/europace/euv202.
9. Echouffo-Tcheugui JB, Masoudi FA, Bao H, Spatz ES, Fonarow GC. Diabetes mellitus and outcomes of cardiac resynchronization with implantable cardioverter-defibrillator therapy in older patients with heart failure. *Circ Arrhythm Electrophysiol.* 2016;9:e004132. doi: 10.1161/CIRCEP.116.004132.
10. Sun H, Guan Y, Wang L, Zhao Y, Lv H, Bi X, Wang H, Zhang X, Liu L, Wei M, Song H, Su G. Influence of diabetes on cardiac resynchronization therapy in heart failure patients: a meta-analysis. *BMC Cardiovasc Disord*. 2015;15:25. doi: 10.1186/s12872-015-0018-0.
11. Hoppe UC, Freemantle N, Cleland JG, Marijianowski M, Erdmann E. Effect of cardiac resynchronization on morbidity and mortality of diabetic patients with severe heart failure. *Diabetes Care*. 2007;30:722–724. doi: 10.2337/dc06-2035.
12. Boriani G, Diemberger I, Biffi M, Martignani C. Cost-effectiveness of cardiac resynchronisation therapy. *Heart*. 2012;98:1828–1836. doi: 10.1136/heartjnl-2012-301845.
13. Brignole M, Auricchio A, Baron-Esquivias G, Bordachar P, Boriani G, Breithardt OA, Cleland J, Deharo JC, Delgado V, Elliott PM, Gorenek B, Israel CW, Leclercq C, Linde C, Mont L, Padeletti L, Sutton R, Vardas PE. 2013 ESC guidelines on cardiac pacing and cardiac resynchronization therapy: the task force on cardiac pacing and resynchronization therapy of the European Society of Cardiology (ESC). Developed in collaboration with the European Heart Rhythm Association (EHRA). *Europace*. 2013;15:1070–1118. doi: 10.1093/europace/eut206.
14. Verbrugge FH, Dupont M, Rivero-Ayerza M, de Vusser P, Van Herendael H, Vercammen J, Jacobs L, Verhaert D, Vandervoort P, Tang WH, Mullens W. Comorbidity significantly affects clinical outcome after cardiac resynchronization therapy regardless of ventricular remodeling. *J Card Fail*. 2012;18:845–853. doi: 10.1016/j.cardfail.2012.09.003.
15. Boriani G, Berti E, Belotti LM, Biffi M, De Palma R, Malavasi VL, Bottoni N, Rossi L, De Maria E, Mantovan R, Zardini M, Casali E, Marconi M, Bandini A, Tomasi C, Boggian G, Barbato G, Toselli T, Zennaro M, Sassone B; RERAI (Registry of Emilia Romagna on Arrhythmia Interventions) Investigators. Cardiac device therapy in patients with left ventricular dysfunction and heart failure: 'real-world' data on long-term outcomes (mortality, hospitalizations, days alive and out of hospital). *Eur J Heart Fail*. 2016;18:693–702. doi: 10.1002/ejhf.509.
16. Braunstein JB, Anderson GF, Gerstenblith G, Weller W, Niefeld M, Herbert R, Wu AW. Noncardiac comorbidity increases preventable hospitalizations and mortality among Medicare beneficiaries with chronic heart failure. *J Am Coll Cardiol*. 2003;42:1226–1233. doi: 10.1016/S0735-1097(03)00947-1.
17. Boriani G, Diemberger I, Martignani C, Biffi M, Valzania C, Bertini M, Domenichini G, Saporito D, Ziacchi M, Branzi A. Telecardiology and remote monitoring of implanted electrical devices: the potential for fresh clinical care perspectives. *J Gen Intern Med*. 2008;23(suppl 1):73–77. doi: 10.1007/s11606-007-0355-5.
18. Klersy C, Boriani G, De Silvestri A, Mairesse GH, Braunschweig F, Scotti V, Balduini A, Cowie MR, Leyva F. Effect of telemonitoring of cardiac implantable electronic devices on healthcare utilization: a meta-analysis of randomized controlled trials in patients with heart failure. *Eur J Heart Fail*. 2016;18:195–204. doi: 10.1002/ejhf.470.
19. Boriani G, Maniadakis N, Auricchio A, Müller-Riemenschneider F, Fattore G, Leyva F, Mantovani L, Siebert M, Willich SN, Vardas P, Kirchhof P. Health technology assessment in interventional electrophysiology and device therapy: a position paper of the European Heart Rhythm Association. *Eur Heart J*. 2013;34:1869–1874. doi: 10.1093/eurheartj/eht031.
20. Polyzos KA, Konstantelias AA, Falagas ME. Risk factors for cardiac implantable electronic device infection: a systematic review and meta-analysis. *Europace*. 2015;17:767–777. doi: 10.1093/europace/euv053.

KEY WORDS: Editorials ■ cardiac resynchronization therapy ■ diabetes mellitus ■ heart failure ■ renal insufficiency, chronic

Circulation
Arrhythmia and Electrophysiology

The Impact of Diabetes and Comorbidities on the Outcome of Heart Failure Patients Treated With Cardiac Resynchronization Therapy: Implications for Patient Management

Giuseppe Boriani

Circ Arrhythm Electrophysiol. 2016;9:
doi: 10.1161/CIRCEP.116.004463
Circulation: Arrhythmia and Electrophysiology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 1941-3149. Online ISSN: 1941-3084