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EDITORIAL

Cardiac resynchronization therapy in the real world: need to focus on implant rates, patient selection, co-morbidities, type of devices, and complications

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This editorial refers to 'Utilization and in-hospital complications of cardiac resynchronization therapy: trends in the United States from 2003 to 2013', by S.M. Hosseini *et al.*, doi:10.1093/eurheartj/ehx100.

Heart failure (HF) affects 1–2% of the population in developed countries, with a higher prevalence in patients >70 years old. These figures are likely to increase in the near future, as a result of the progressive ageing of populations.[1] It can be estimated that ~15 of 900 million Europeans and ~5.7 of 300 million US Americans will develop HF.[1,2]

Cardiac resynchronization therapy (CRT) was introduced >20 years ago as a compassionate treatment for selected patients with drug-refractory HF, and its development was based on the pioneering experiences done in France[3] Nowadays CRT is a cornerstone of HF therapy, with a positive impact on both morbidity and mortality in appropriately selected patients, according to the evidence provided by several randomized controlled trials.[1,3,4] Despite these premises, CRT implementation in the 'real world' is variable, depending on several factors, according to what has been shown by registries and surveys.[3,5]

In this issue of the journal, Hosseini *et al.* report on the trends of in-hospital CRT device implantations from 2003 to 2013 in the USA.[6] No temporal trend was recorded in the overall estimated CRT implantation rate or in the ratio between CRT pacemakers (CRTPs) and CRT defibrillators (CRTDs). In the same period, the indications for CRT widened, as reported in the consensus guidelines,[4,7] but the criteria to choose a CRTP or a CRTD device have always been a matter of debate.[1,4] This was not clarified by the COMPANION (Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure) trial, which indeed included a CRTD and a CRTP arm, as well as a medical therapy arm, but it was powered to compare device therapy with optimized medical therapy and not to compare the two device treatments directly.[7] However, the cost of CRTD devices is approximately three-fold that of CRTPs and the battery duration is significantly lower, with important financial implications. These considerations can explain, at least partially, the heterogeneity in CRT implants and particularly the proportion of CRTDs with respect to all biventricular devices. As shown in *Figure 1* (based on implant data from 2013, or 2012 if data were unavailable),[8–10] a huge heterogeneity in implantation rates for CRT devices exists across countries belonging to the European Society of Cardiology (ESC), ranging from 7 per million inhabitants in the Russian Federation to 221 per million inhabitants in Germany. Notably, in the USA the reported rate of implantations is >2-fold that of Germany. Several factors seem to influence this variability: the financial status of healthcare systems, the organization of care, demography, and cultural factors.[11] It is noteworthy that within Europe the reported variations also correspond to a 20-fold variability in the number of CRT implanting centres.[9]

Several open issues remain in patient selection for CRT, as the wide variability within the same country or even the same region clearly highlights, for implantation of both CRT devices and implantable cardioverter-defibrillators.[10,11]

The ratio between CRTDs and CRTPs, as shown in *Figure 1*, is a further source of variability between European countries and the USA. The prevalence of CRTD implants as a proportion of all CRT devices ranges between 11% in the Russian Federation and 88% in Germany, in the latter being even higher than what was reported for the USA.[9,10]

In the USA, the rate of CRTP implants nearly doubled from 2003 to 2013; this occurred in parallel with an increase in the mean age of patients implanted with a CRTP and the increasing rate of implants in older patients, often performed in the setting of an 'ablate and pace'

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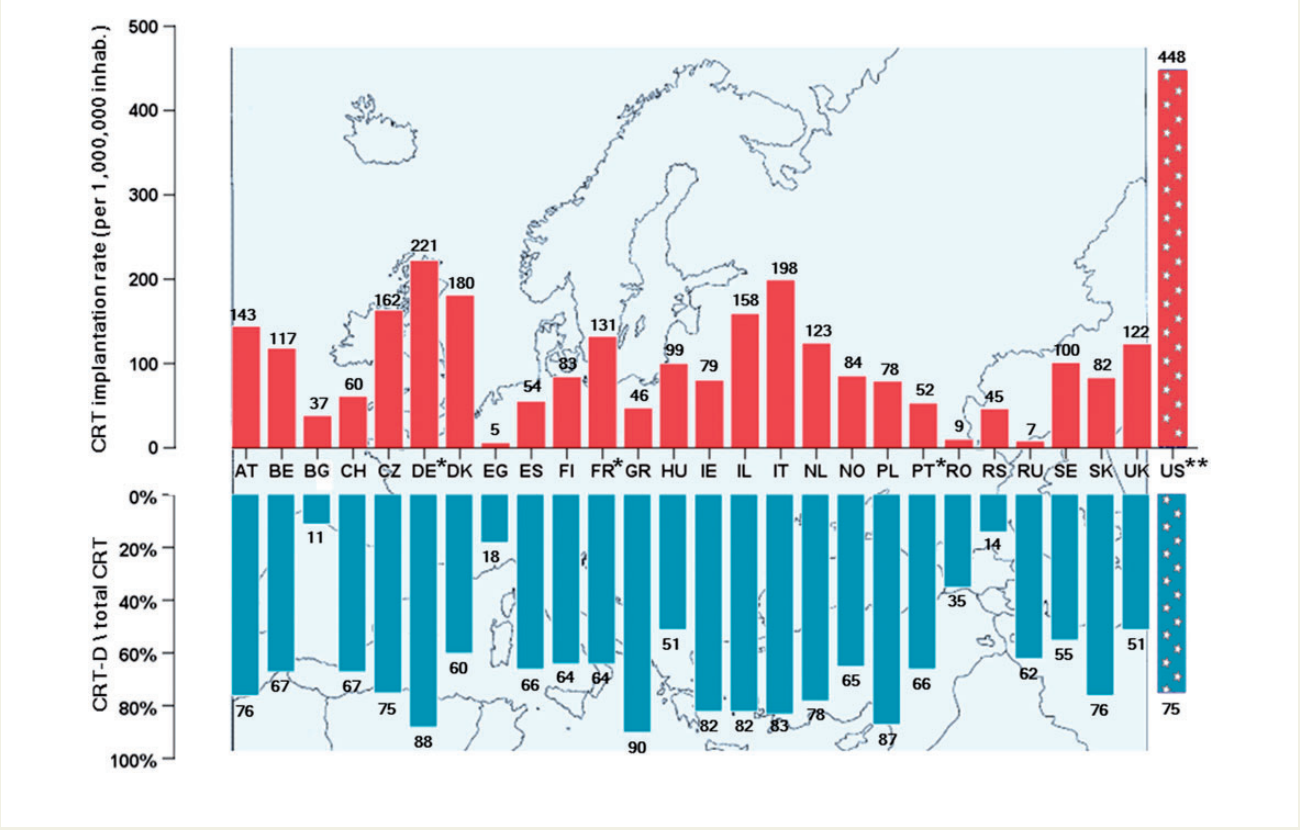

Figure 1 Implantation rates of CRT devices per million inhabitants among countries within the European Society of Cardiology during 2013 (2012 in some nations, indicated by *, when data for 2013 are missing), according to the European Heart Rhythm Association (EHRA) White Book[8,9] and according to data sets related to Medicare enrollees in the USA.[10] Only countries with ≥250 CRT implants have been included. *2012 data; **Medicare population; AT, Austria; BE, Belgium; BG, Bulgaria; CH, Switzerland; CZ, Czech Republic; DE, Germany; DK, Denmark; EG, Egypt; ES, Spain; FI, Finland; FR, France; GR, Greece; HU, Hungary; IE, Ireland; IL, Israel; inhab. inhabitant; IT, Italy; NL, The Netherlands; NO, Norway; PL, Poland; PT, Portugal; RO, Romania; RS, Serbia; RU, Russia; SE, Sweden; SK, Slovakia; UK, United Kingdom; US, United States.

strategy, which may explain this trend.[10] A more precise assessment of the outcomes of patients implanted with a CRTP is needed, through prospective registries.

In consideration of the marked increased in device implants which occurred in the last 20 years, a specific interest emerged in detecting device complications, with the aim to predict and possibly minimize their occurrence. It is noteworthy that most of these complications are associated with increased patient morbidity, healthcare costs, and possibly increased mortality.[12–15] In this regard, Hosseini *et al.* showed a significant increase in the frequency of in-hospital complications between 2003 and 2013.[6] On average, 6.1% of the procedures presented at least one complication (6.04% and 6.54% for CRTD and CRTP implants, respectively) in the study period, with a significant temporal trend (<0.01). This was associated with an increase in the frailty of CRT candidates according to the temporal trend in the Deyo–Charlson Co-morbidity Index (P = 0.002). In particular, older age, female sex, non-elective admission, and Deyo–Charlson Co-morbidity Index were independent predictors of in-hospital complications. The finding that non-elective admissions, which may be related to clinical instability and urgent admission, are associated with increased in-hospital complications integrates previous findings indicating that this patient setting is a significant determinant of adverse outcomes in the long term, in terms of mortality and hospitalizations.[16] It is noteworthy that beyond complications, co-morbidities are a major driver of outcomes. In a real-world long-term registry of ~700 CRTD patients followed for 4 years, co-morbidities (expressed by the Charlson co-morbidity index), as well as age, male gender, advanced NYHA class, and implant during unplanned, urgent hospitalization were significant independent predictors of death/cardiac transplant.[16]

Widening the perspective, co-morbidities are relevant for the management and the outcomes of all the patients with HF, also independently of CRT.[1,17] Anaemia, chronic kidney disease, chronic obstructive pulmonary disease, and diabetes are co-morbidities associated with advanced age and higher NYHA functional class, and are strongly associated with adverse outcomes and hospitalizations, that with a multidisciplinary management could be prevented or at least appropriately managed in a substantial proportion of cases.[17] According to this background, a patient's age and the most important co-morbidities, primarily advanced chronic kidney disease,[17,18] should be carefully considered in the decision between a CRTP and CRTD,[4,5] and real-world registries should be used to monitor the outcome according to specific patient characteristics, trying to improve our knowledge.

Hosseini *et al.*[6] reported a rate of acute in-hospital periprocedural complications, based on analysis of International Classification of Disease 9th Revision, Clinical Modification (ICD-9-CM) codes, of 6.1% overall which is lower than what was previously reported. In the report on data collected between 2010 and 2011 in the national clinical database on pacemaker and defibrillator implants in Denmark, Kirkfeldt *et al.*[12] showed an overall 9.5% complication rate after implant of pacemakers, defibrillators, or CRT devices. The risk of complications was higher in the presence of some patient factors (female gender, underweight), organizational issues (centres with an annual volume of <750 procedures, emergency procedure, operator with an annual volume of <50 procedures), or implanted system factors (CRTD device, system upgrade, or lead revision). These differences can easily be attributed to the method adopted for event assessment (ICD-9-CM analysis vs. prospective adjudication); however, the time window and the type of procedure are further elements to be carefully considered, especially for device infections. Several reports highlighted that complications are greatly increased in upgrade procedures (vs. first implant), with figures that can exceed 15% within 90 days.[12–15] This is particularly true for device-related infections, which are the more feared complications since they are associated with high risk of death and costs for healthcare systems.[13–15] Moreover, this type of infection commonly manifests weeks and months (even years) after discharge, especially in more frail patients, and only a careful preventive management coupled with a strict follow-up can help in controlling the spread of device infections.[13,14] Only large registries with appropriate size and design can help in improving our knowledge in this field, which is now one of the major struggles for device therapy.

In summary, improved knowledge of the rate of implantations of CRTP and CRTD devices in different geographical and organizational settings, coupled with evaluation of potential under-referral is currently needed. Moreover, a better assessment of the short- and long-term outcome of patients implanted with a CRT, of the impact of comorbidities in different settings of patients implanted with CRTP or CRTD devices, as well as better prediction and minimization of device-related complications will be crucial in order to improve patient selection according to clinical profile and to better define the type of device to be implanted (CRTD or CRTP). In this perspective, a proper evaluation of patients in the 'real world' may offer the chance to verify the impact of new models of care for HF patients, also with the contribution of innovative technologies, such as telemonitoring. Data from large data sets will be of great help, especially if coupled with proper assessment of data quality, since registries can have limitations due to selection bias and missing data. Nowadays, it is clear that there is a need for a continuous evaluation of the clinical and economic impact of current approaches to manage HF, focusing on all the treatment options that are available in appropriately selected patients, including device therapy with CRT. The involvement of different specialists, as well as of patients and caregivers, is needed, in line with the concepts of disease management and of health technology assessment.[1,5]

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