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EDITORIAL COMMENT

Cardiac resynchronization therapy in the real world: need to upgrade outcome research

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This article refers to 'Upgrades from a previous device compared to *de novo* cardiac resynchronization therapy in the European Society of Cardiology CRT Survey II' by C.M. Linde *et al.*, published in this issue on pages 1457–1468.

Cardiac resynchronization therapy (CRT) is an effective electrical treatment for selected patients with heart failure and wide QRS interval that, following the pioneering experiences performed in France around 20 years ago, obtained full development and clinical validation, moving from a compassionate treatment used in a few cases as a 'last resort' option, to a treatment tested and validated in randomized controlled trials (RCTs), both in the setting of moderate–severe heart failure and of mild heart failure with reduced ejection fraction.[1] The implementation of CRT across Europe is variable, fluctuating considerably in implant rates within and across countries, as a result of the influence of different types of health care systems, as well as of different economic, demographic and cultural contexts.[2,3]

As a result of the RCTs performed in the last 15 years, that overall involved more than 10 000 patients,[4] CRT has been included in consensus guidelines as a treatment with proven efficacy in improving symptoms and outcomes in appropriately selected patients. The implant of a CRT system with a pacemaker (CRT-P) or a defibrillator (CRT-D) may be indicated also in patients previously implanted with a pacemaker (PM) or an implantable cardioverter-defibrillator (ICD), and this constitutes what is normally considered as an 'upgrade procedure'. Only in the last 5–6 years has an upgrade to CRT-P or CRT-D been included among the recommendations for CRT delivered by European or American societies.[1] This reflects the relative paucity of literature on upgrade to CRT and the lack of RCTs: a search on PubMed showed that in the last 5 years only 73 articles were published on CRT and upgrade, while during the same period 3350 papers were published, in general, on CRT.

In this issue of the Journal, Linde *et al.*[5] report the results of the European Society of Cardiology CRT Survey II focusing on baseline patient characteristics, details of implantation procedures and related short-term complications in patients undergoing upgrading to CRT-P or CRT-D in comparison to patients who underwent *de novo* implantation with a CRT device. The data were collected across 42 European Society of Cardiology countries between October 2015 and December 2016. Out of 11 088 patients, ~23% were upgraded from a previous PM or ICD while ~77% underwent *de novo* implantation. Although upgraded patients compared to patients with *de novo* CRT implant had older age and more advanced heart failure, CRT implantation procedures were equally successful and had similar in-hospital complication rates.

The authors are to be commended for having provided a contemporary overview of upgrading procedures to CRT across Europe. However, some considerations are needed in order to realise that such analyses are of primary importance and need to be expanded to larger cohorts with longer follow-up periods. In this CRT Survey II, the patients were discharged after a median hospital stay of 3 days and the study plan did not include follow-up data after discharge. A focus on longer follow-up periods, up to 6 months–1 year, is necessary in order to capture the occurrence of post-discharge major complications, most of which are reported in *Figure 1*, with the indication of the most vulnerable periods.[6–11]

The majority of CRT implantations (82%) were performed in either university or teaching hospitals and this may condition the rate and type of complications. Analysing the Danish National registry on cardiac implantable electronic device procedures, Kirkfeldt *et al.*[10] found that centres with <750 annual procedures and low volume operators (<50 annual procedures) had higher complication rates overall. In a series of reports, upgrade procedures appear to be associated with a higher burden of complications as compared to *de novo* implants ranging from 6.8% to 20.9%.[9]

Probably the most feared complication of upgrades to CRT is device-related infection,[9] due to the high impact on associated mortality, morbidity and costs for health care systems, and the only effective approach to manage this issue is complete removal of all the implanted hardware through percutaneous lead extraction.[12] Notably, this complication usually occurs weeks or months after the procedure and the presence of a delay in defining the correct

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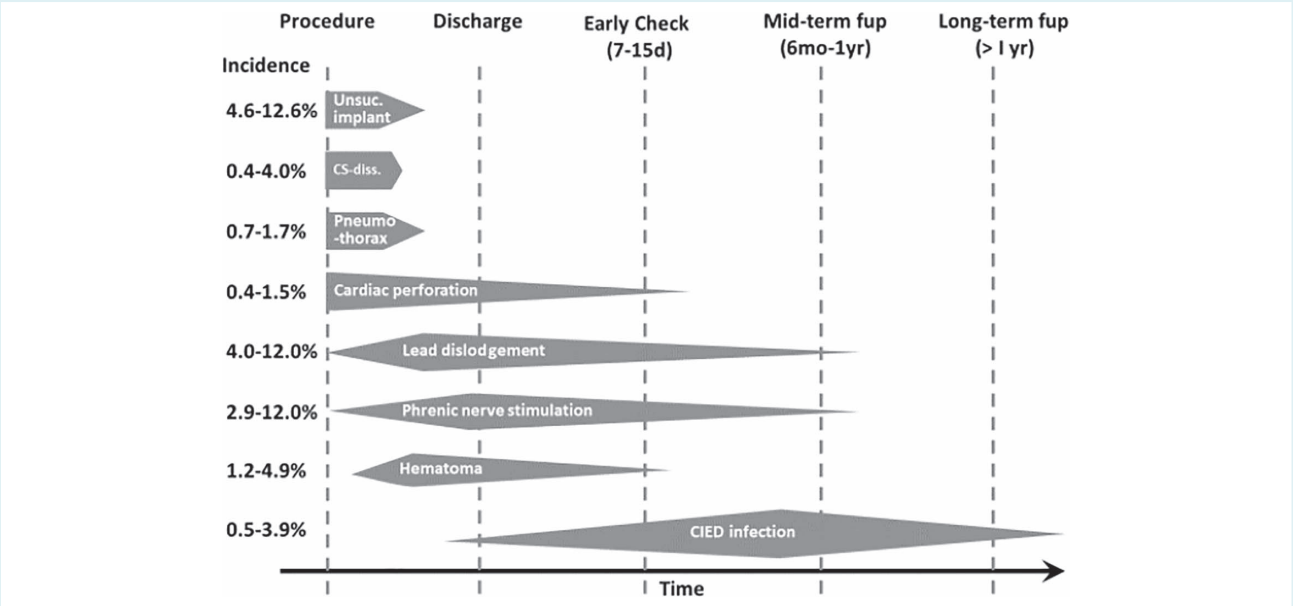

Figure 1 Incidence and usual most vulnerable periods for complications of cardiac resynchronization implants or upgrades.[6–11] CIED, cardiac implantable electronic device; CS-diss, coronary sinus dissection; d, days; fup, follow-up; mo, months; unsuc, unsuccessful; yr, years.

diagnosis is common. This means that this type of complication could not be a topic of investigation in this survey focused on pre-discharge events. However, when planning an upgrade procedure, the risk of device infection has to be considered since both the procedure type and the involved device (CRT) are independent risk factors.[8] Despite the relevant improvements in tools and techniques leading to an impressive decrease in procedure-related complications,[13] 1-year mortality ranges between 10% to 20%.[14,15] In this regard, it is relevant to note that the same risk factors for development of device infection are associated with increased risk of post-extraction mortality, leading to consideration that prevention of infection is of paramount importance by carefully evaluating upgrade procedures in high-risk patients and by adopting all the precautions including all the procedural factors.[8,16] Hopefully, the results of the ongoing WRAP-IT trial will provide important data on this relevant topic.[16]

Additional clinical points can be considered. The upgrade from a PM to a CRT-D is technically complex, and at least in non-ischaemic cardiomyopathy should occur less frequently in the future considering the mean age of patients with a previous implanted PM who are candidates for upgrade and the results of the DANISH trial.[4,17] The issue of atrioventricular node ablation in patients with atrial fibrillation who receive an upgrade to CRT is another important point, and it should be stressed that atrioventricular node ablation is crucial for achieving the full benefit of CRT (by ensuring >95% ventricular pacing) even if no RCT validated the strategy of atrioventricular node ablation combined with CRT.[18]

The data reported by Linde *et al.*[5] clearly show that patients who are candidates for upgrade to CRT have a different profile as compared to *de novo* CRT implant: they are older, with higher prevalence of coronary artery disease, valvular heart disease, chronic kidney disease, anaemia, and atrial fibrillation. Most of these factors have been found to be associated with a worse response to CRT and a worse outcome,[17,19,20] leading to an important clinical question: 'What is the long-term outcome of these patients?'. Upgrade to CRT has never been the subject of a randomized clinical study but a recent systematic review and meta-analysis identified a total of 16 reports including 489 568 CRT recipients, of whom 21 363 patients underwent an upgrade procedure. The results included both unadjusted and adjusted estimates, but in general found similar risks for all-cause mortality and heart failure hospitalizations for CRT upgrade vs. *de novo* CRT implant, also with similar improvement in functional capacity and similar degree of left ventricular reverse remodelling.[11]

Observational studies or surveys like the European CRT Survey II are extremely interesting when a procedure, like upgrades, has not been covered by RCTs, because of lack of interest from the industry. The challenge in the future will be to have follow-up data as part of the quality control that every health care system should provide, in order to upgrade outcome research in the field, in line with the virtuous circle of Health Technology Assessment.[21]

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