UPDATES IN CARDIOLOGY

Causes of death analysis of patients with cardiac resynchronization theraphy: an analysis of the CeRtiTuDe cohort study

Over the last decade cardiac resynchronization therapy (CRT) and implantable cardioverter defibrilators (ICDs) have significantly improved the prognosis of heart failure(HF) patients, prolonging the survival over and above that conferred by medical therapy alone. Despite some degree of overlap, the therapeutic rationales for these two forms of device-based therapies are distinct: where ICDs abort arrhythmic death and CRT devices improve cardiac function.

According to the current guidelines, patient who are candidates for CRT will have a LVEF ≤35% and this automatically makes them candidates for an ICD. If only ICDs were totally benign and an inexpensive add-on, this difference might not be that significant, but as with most invasive therapies, there must be a constant quest to minimize harm while enhancing the value of the care being delivered. It is well known that inappropriate shock therapy from ICDs is associated with higher mortality and therefore the benefit of adding defibrillator therapy to CRT, particularly in patients whose highest risk of dying is from pump failure, has become a more and more frequently asked question.

Because the use of CRT-P or CRT-D in clinical practice has significant implications in terms of costs as well as device-related complications, it raised the concept of "cause of death analysis" among these two categories of device- treated patients in order to have a novel approach to this never ending problem: which device to choose. Using a large, multicenter study with prospective follow-up there were evaluated the characteristics of CRT-P vs. CRT-D patients and it wasanalyzed to what extent CRT-P subjects, as currently chosen in clinical practice, would have potentially additionally benefited from the presence of a back-up defibrillator.

CeRtiTuDe is a 2-year, prospective, multicenter registry analyzing cause of death in CRT therapy. The 41 medical centers participating in this study enrolled consecutive patients who, between 1 January 2008 and 31 December 2010 had undergone CRT device implantation- the criteria for CRT implantation was guided according to the guidelines of the European Society of *Cardiology and European Heart Rhythm Association*. Each patient was enrolled in a specific follow-up programme with clinical, ECG, echocardiographic and device interrogation, data collected every 6 month over the following 2 years up to the 1st of January of 2013. A standardized form was used to record major clinical events and vital status was ascertained through use of national registries.

There were pre-specified causes of death and there was defined the concept of sudden cardiac death (SCD) as death occurring within 1 hour of symptoms in the absence of cardiac deterioration, unexpected death during sleep, or unexpectedly dying within 24 hours of last being seen alive. Interestingly, fatal arrhythmias associated with end-stage heart failure were classified as non-sudden deaths. Other cardiovascular deaths (myocardial infarction, HF, acute aortic syndrome, stroke, pulmonary embolism) or non-cardiovascular deaths (cancer, infectious disease, renal failure, respiratory failure) were all included and reported in this study.

At 2-year follow-up of the 1705 patients enrolled in the study (94.5% of subjects completed it), 267 patients died, giving an overall annual mortality rate of 83.8% per 1000 person-years, with a higher rate among the CRT-P group compared to CRT-D patients (130.8 vs 65.1 per 1000 year, respectively, RR 2.01, 95% CI 1.56-2.58, p <0.0001). The incidence of SCD was not statistically higher in the CRT-P group compared with CRT-D (RR 1.57, 95% CI, 0.71-3.46, p=0.42) and the rate of hospitalization for HF was not different between the CRT-D vs CRT-P groups. (19.6 vs 22%, p=0.28). However, when considering the specific cause-of-death analysis, the increased mortality among CRT-P patients was not related to that in SCD, though SCD incidence was higher in the CRT-P group: 11.8 per 1000 among CRT-P vs 7.5 per 1000 among CRT-D recipients (p= 0.26). The main reason for the almost twice-higher risk of death in the CRT-P group were an increase in non-SCD cardiovascular mortality, mainly comprising progressive HF, as well as other cardiovascular mortality. Of note, CRT-P patients were older, had a higher proportion on women, higher rates of non-ischemic cardiomyopathy, wider QRS, more severe NYHA functional class, more atrial fibrillation, and higher rates of renal insufficiency. Overall, 95% of the excess mortality among CRT-P patients was not related to SCD- and this is the main idea that must be

acknowledged from this study. It should come as no surprise that CRT-P patients demonstrated two-fold increased all-cause mortality, as the excess of mortality in this cohort of CRT was driven by heart failures, other cardiovascular deaths and non-cardiovascular deaths.

The authors concluded that since the sudden death rates were comparable, the excess was driven by non-sudden causes and therefore CRT-D may not provide incremental benefit for that subset of patients receiving CRT-P. Still, it is unknown how many of these lives in the CRT-P cohort could have been saved- or perhaps prolonged beyond the 2-year cut-off mark of this study if they had a defibrillator.

Understanding the mode of death is important to deciding which patient might benefit most from which type of device: CRT-P vs CRT-D. This study shows that aging and worsening of heart failure are associated with higher preponderance of non- arrhythmic and non-cardiac causes of death. Above this, ICD may be associated with inappropriate therapies, which can add to the morbidity and emotional distress while worsening clinical outcomes. The results indicate that CRT-P patients, as selected in routine clinical practice, would potentially not benefit from addition of a defibrillator, emphasizing that there is still considerable room for CRT-P in the present day HF treatment. On the other hand the study suggests the need for an individualized patient-centric decision- making model.

Marjion E et al. Causes-of-death analysis of patients with cardiac resynchronization therapy: an analysis of the CeRtiTuDe cohort study. European Heart Journal (2015) 36, 2767–2776 (MI)

Ventricular arrhythmias after cardiac resyncronization therapy: does reverse remodeling reverse risk?

Cardiac resynchronization therapy (CRT) is already a standard therapy (according the guidelines) in selected patients which fulfill the right criteria: left ventricular systolic dysfunction (LVSD), symptomatic heart failure and electrical dyssyncrony. Resynchronization of the failing heart leads to favorable reverse remodeling characterized by reduced LV volumes and improved LVEF, translating to significant reduction in morbidity and mortality. Because the criteria for implanting CRT (LVEF ≤35%) coincide with the criteria for implanting an ICD, many patients will therefore undergo the implantation of an CRT-D given its efficacy in the prevention of sudden cardiac death (SCD) in patients with systolic heart failure.

Given the major effect of CRT on LV function and the relationship between risk of ventricular tachyarrhythmia (VTA) and LVEF, there has been significant interest regarding the impact of CRT- induced improvement in LV function and risk of VTA. The impact of CRT and LVEF improvement on VTA risk has important clinical and cost-effectiveness implications: identification of patients likely to experience CRT-related improvement LVEF and possibly attenuated future risk for VTA may further impact the selection of CRT-P vs CRT-D.

Today there are no prospective, randomized studies assessing the efficacy of ICD implantation in responders, so this is the reason why there was conducted a meta-analysis of cohort studies focusing on patients with left ventricular reverse remodeling after CRT-D; the main purpose was to determine the rate of ICD detected VTA after CRT-D in responders- defined by improvement in LVEF.

They pooled six retrospective cohort studies including 1740 heart failure (HF) patients with wide QRS and LVEF ≤35% before CRT and who had follow-up of LVEF. This group had an average LVEF of 20-29%. There was an increase of LVEF ≥35% in 63% of patients and an increase of LVEF ≥45% in 10% after CRT-D implant. The major findings were that patient with LVEF recovery had significantly lower rates of ICD therapy for VTA compared with patients without LVEF recovery. ($p < 0.001$). Above all, patients with recovery of LVEF ≥45% after CRT and those with CRT-D for primary prevention had very low rates of VTA (0.4-0.8/100 person-years).

There are also some limitations of the study: the lack of standardized interval for LVEF determination after CRT (ranging from 4 to 20 months), different definitions of LV recovery (LVEF ≥35% and LVEF ≥45% and assessment of LV recovery limited to LVEF measurements. This is why the authors of this meta-analysis affirmed that prospective randomized trials of long-term duration are needed to determine whether ICD therapy must be included indefinitely in responders and super-responders.

The effect of CRT on LV reverse remodeling is of particular interest since the precise mechanism remain unclear and CRT response has been variable and the myocardial substrate appears to play an important role. Factors that may influence remodeling like ischemia, infarction, fibrosis, inflammation influence the composition of myocardial substrate and may be considered irreversible or reversible and this interplay

is quite complex. That's why the response to CRT is widely variable, ranging from no LV reverse remodeling- in 30-50% of patients- the so-called non-responders, to near normalization of LV function in 10-20%- the so-called super-responders. Intense investigation continue to advance understanding of CRT response and arrhythmia risk, including means to differentiate myocardial substrate with reversible vs irreversible LV dysfunction.

It is important to know that the current classification in responders and non-responders is lying on the LVEF and the current standard for assessing LVEF is Simpson Biplane; to be noticed that reproducibility of LVEF will be improved in the future by 3D imaging. Even so, LVEF is imperfect for determining risk of VTA. Interestingly, most victims of SCD had LVEF which exceeded current primary prevention guidelines for ICD implantation. Surprisingly it was reported that appropriate ICD intervention for VTA were documented in 11% of CRT-D patients who were super-responders (LVEF ≥50% after CRT-D implant). This information is disorienting, but strong enough not to downgrade a CRT-D to CRT-P at the time of generator exchange in a responder, as the risk of ventricular arrhythmias appear to remain. Answering the title question: reverse remodeling does not reverse risk. The report also highlights the fact that advances in cardiac imaging (CMR imaging, meta-iodobenzylguanide imaging etc.) promise to refine determination of the risk of VTA after CRT and aid in clinical decisions for device therapy beyond LVEF.

Chatterjee NA et al. Reduced appropriate implantable cardioverter-defibrillator therapy after cardiac resynchronization therapy-induced left ventricular function recovery: a meta-analysis and systematic review. European Heart Journal (2015) 36, 2780–2789 (MI)

A new paradigm of heart failure therapy

The benefits of inhibiting neprilysin (NEP) (neutral endopeptidase that degrades numerous endogenous vasoactive peptides, including natriuretic peptides, angiotensin I and II, adrenomedulin and bradykinin) have been the subject of intense debates over the last two decades. Since 2002, when omapatrilat (the first NEP inhibitor with associated angiotensin converting enzyme inhibitor properties) failed to prove its superiority over enalapril in systolic heart failure, the development of NEP inhibitors lost its fans. But interest in this field revived in 2014, when the PARADIGM-HF (*Prospective Comparison of ARNI* [*Angiotensin Receptor–Neprilysin Inhibitor*] with ACEI [*Angiotensin-Converting–Enzyme Inhibitor*] *to Determine Impact on Global Mortality and Morbidity in Heart Failure Trial*) randomised controled trial ascertained the superiority of LCZ696 (a combination between valsartan and NEP inhibitor sacubitril) over enalapril, with regard to all-cause mortality, cardiovascular mortality and hospitalisations due to heart failure. After more than ten years of trials with various other molecules, that have proven inefficient in influencing the prognosis of systolic heart failure patients, the success of this study elicits promise for the treatment of heart failure (HF) with reduced ejection fraction. The recent approval of LCZ696 by the *Food and Drug Administration* (FDA) has not only caused critical acclaim from clinicians, but has also brought up several questions with regard to this new molecule, for instance, what category of patients will benefit most from this new drug? Under what conditions and in what dosage is the use of LCZ696 safe? Are biomarkers such as the plasma value of NE or its catalytic activity appropriate markers for selecting the patients or for titrating doses? Which groups of patients are at high risk of adverse effects when using this new drug?

The last issue of the *Journal of the American College of Cardiology* includes a post-hoc analysis of the PARADIGM-HF trial*, which presents the risk spectrum of the patients enrolled in the study, along with the effect of LCZ696 across this spectrum. In order to evaluate the risk, the investigators have used two scores that have already been validated in connexion to mortality and hospitalisation in heart failure patients, namely the MAGGIC (*Meta Analysis Global Group in Chronic Heart Failure*) and the EMPHASIS-HF (*Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure*) scores. Both of them were applied using baseline characteristics of patients. The MAGGIC score assesses all-cause mortality using 13 variables including age, sex, body mass index, tobacco use, left ventricle ejection fraction and systolic blood pressure. The EMPHASIS-HF score estimates cardiovascular mortality and hospitalisations due to heart failure in NYHA II functional category patients, by use of 10 variables, among which age, sex, systolic blood pressure, glomerular filtration rate, a history of myocardial infarction and heart rate, to name a few.

The MAGGIC score has been applied to 8375 patients included in the PARADIGM-HF trial, while the EMPHASIS-HF has been used to evaluate 6112 patients of the same trial. Based on the two scores, a stratification of the cardiovascular risk has been undertaken. Thus, the MAGGIC score allocates patients to quintiles of risk, whereas the EMPHASIS-HF score

distributes the risk into quartiles. By using the scores as continuous variables, the escalation by one point of the value of each of the scores is associated with an elevation of 6% in the risk of cardiovascular mortality and hospitalisation for HF and 7% in the risk of cardiovascular mortality, respectively. In addition, by use of the scores as ordinal variables, the beneficial effect of LCZ696 compared to enalapril has been significantly greater in all the MAGGIC risk quintiles and all the EMPHASIS-HF risk quartiles. Thus, the absolute effect of the LCZ696 treatment has been greater in high risk patients. For example, by applying the overall proportional risk reduction (using LCZ696 over enalapril) in the last quintile of the MAGGIC score leads to 8 fewer patients per 100 treated within a two-year timespan, as compared to a reduction of only 4 events in the first quintile. Taking this into consideration, the investigators concluded that there is a group of patients, namely those at high risk, who will benefit significantly from using LCZ 696 thus far, on a relatively short timespan.

Although the results of this post-hoc analysis are both impressive and also promising (as are the results of the PARADIGM-HF trial), there are several limitations that come arise, as well as numerous uncertainties and concerns. In the editorial dedicated to the article, Dr. William Dec pinpoints a few of the above mentioned. First of all, this is a post-hoc study that had not been pre-specified in the design of PARADIGM-HF, which accounts tor limitations and sources of error. Secondly, as is customary for most randomised clinical trials, the patients enrolled in the PARADIGM-HF trial have different characteristics as opposed to the typical patients: they are both younger (mean age is 64 years), have better controlled hypertension and lower incidences of renal dysfunction. In addition, none of the two scores includes natriuretic peptides among the analysed variables, considering that they are independent predictors of mortality in heart failure.

The promising results of the PARADIGM-HF study have led to the recent description of quantitative methods for analysing the level of serum neprilysin (sNEP) and its catalytic activity. These two new biomarkers have been validated as predictors of prognosis in acute heart failure, independently of NT-pro-BNP. Moreover, an interaction between the catalytic activity of NEP and elevated levels of BNP and NT-pro-BNP (the latter two inhibiting the former) has been documented. This discovery raises the question of whether inhibiting NEP would still be efficient in patients with severe heart failure, who characteristically exhibit elevated levels of natriuretic peptides, nonetheless. Furthermore, these new biomarkers (serum NEP and its catalytic activity, respectively) could prove useful in the choice of patients with the greatest benefit from the administration of LCZ696, as well as in the titration of the drug.

Additionally, there are a few concerns with respect to the safety of administration of LCZ696. Angiooedema has occurred in slightly higher incidences in the group taking LCZ696, although this tendency has not achieved statistical significance. A further matter of apprehension is represented by the probability of LCZ696 triggering a cognitive deficit, specifically Alzheimer's disease. The cause of this particular event could be explained by the lack of degradation of beta-amyloid, once neprilysin is inhibited (neprilysin physiologically breaks down beta-amyloid).

Having considered all the above, a further question for the clinical cardiologist arises: in which patients with chronic heart failure should the current treatment with inhibitors of the renin-angiotensin-aldosterone system be replaced with the new LCZ696? This, as well as the additional questions addressed at the beginning of this review will probably find suitable answers shortly. The good news is that a new drug with a major potential benefit in the treatment of chronic heart failure with reduced ejection fraction has been discovered.

Simpson J et al. Comparing LCZ696 with Enalapril According to Baseline Risk Using the MAGGIC and EMPHASIS-HF Risk Scores. An Analysis of Mortality and Morbidity in PARADIGM-HF, J Am Coll Cardiol 2015; 66: 2059-71. (AP)

Prediction of thrombo-embolic risk in patientswith hypertrophic cardiomyopathy

One new interesting article recently published in the march this year in the *European Journal of Heart Failure* is an article that talks about the prediction of thrombo-embolic risk in patients with hypertrophic cardiomyopathy under the supervision of Perry Elliot.

The authors started from the idea that atrial fibrillation (AF) and thrombo-embolism (TE) are two conditions associated with reduced survival in hypertrophic cardiomyopathy (HCM), but the absolute risk of TE in patients with and without AF is unclear, and tried to derive and validate a model for estimating the risk of thrombo-embolism in HCM. They also performed various analyses in order todetermine predictors of TE, the performance of the CHA_2DS_2-VASc score, and outcome with vitamin K antagonists (VKAs).

The authors performed a multicentre retrospectivelongitudinal study which took place in 7 European centres, which included adult patients (≥16 years of age) with left ventricle hypertrophy (≥15mm) unexplained by loading conditions. The patients were reviewed 6-12 months or earlier if change in symptoms, and were followed for a period of 10 years. The exclusion criteria for this study were: patients with metabolic diseases or syndromic causes, prior history of AF or TE to first evaluation.

They studied various variables like: sex, age, class NYHA at the first evaluation, greatest left ventricle thickness, shortening fraction, maximum LVOT gradient but also the presence of cardiovascular disease risk factors like: hypertension, diabetes, or the presence of heart failure or vascular disease.

The primary outcome for the studied patients was the development of TE no matter the form: cerebrovascular accident (CVA), transient ischemic accident (TIA), orsystemic peripheral embolus.

During 1986-2008, a number of 4821 patients were evaluated, from which 172 patients (3.6%) developed TE within 10 years (105 CVA, 53TIA, 14 peripheral emboli) and107 patients (2.2%) within5 years.

The authors calculated the CHA_2DS_2-VASc risk score for every patient, and for that studied group, 27.5% of patients had CHA_2DS_2-VASc score of 0, and 9.8% of patients with CHA_2DS_2-VASc score of 0 developed TE during follow-up so they concluded that CHA_2DS2-VASc risck score has a low predictive accuracy in patients with HCM mainly due to the lower prevalence of vascular risk factors.

Based on the variables studied the authors tried to find out what variables correlate better with an increased risk of thromboembolism.

After the statistical analysis, they discovered that patients that developed TE were older (55.0 years vs. 47.5 years; difference in means=7.5 years; 95% CI 4.60–10.42), had a larger LA diameter (46.0 mm vs. 43.0 mm; difference in means=3.0 mm; 95% CI1.7–4.32), were more symptomatic (NYHA III, IV) (14.4% vs.9.0%; difference in proportions=0.054; 95% CI 0.0099–0.1181) and had a higher percentage of vascular disease (5.7% vs 2.0%; difference in proportions=0.037; 95% CI 0.0074-0.0812).

They also tried to propose a novel model to estimate the risk at 5 years for patients to develop TE, a model that included the risk factors that they found out to have a statistical importance: advanced age, heart failure symptoms, LA diameter and presence af vascular disease, and they commpared this novel model for TE risk to the CHADS-VASc risk model. They found out that the novel model estimates better the risk of TE in patients with HCM.

Another interesting thing discovered by the author was a relative risk reduction for TE of 54.8% in patients taking oral anticoagulants. But when starting oral anticoagulants one should consider also the risk of adverse reactions, and the fact that not all the patients with HCM benefit from oral anticoagulation. Patients in sinus rhythm with high risk of TE don't benefit from oral anticoagulation priorto development of AF. These patients should be evaluated periodically with ambulatory ECG monitoring especially if they have LA enlargement, and anticoagulation started if they present AF on Holter monitoring. All patients with a non-valvular AF and CHADS-VASC score >1 should receive oral anticoagulant, antiagregants aren't an option. A LA dimension more than 50 mm increases the risk of development of TE exponentially.

The risk of TE in patients with HCM can beidentified using a small number of clinical features, with one of the most important variable that we should consider is LA size.

Another important take home message is that: theCHA_2DS_2-VASc does not correlate well with clinical outcome and should not be used toassess TE risk in patients with HCM.

A prospective external validation in a different cohort of patients would be ideal, in order to validate the novel risk model for TE in patients with HCM.

Guttmann OP et al. Prediction of thrombo-embolic risk in patients with hypertrophic cardiomyopathy (HCM Risk-CVA). European Journal of Heart Failure (2015) 17, 837–845 (AM)

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