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Synopsis of Most Relevant Articles on Cardiac Arrhythmias

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Clinical outcomes of cardiac resynchronization therapy with and without defibrillator in elderly patients with heart failure*

Cardiac resynchronization therapy (CRT) is well established for individuals optimized for heart failure (HF) with New York Heart Association (NYHA) functional class II, III and IV ambulatory, left ventricular ejection fraction (LVEF) ≤ 35% and prolonged duration of QRS, with several studies demonstrating the benefits of CRT in morbimortality. There is, however, still a gap between patients who should receive CRT associated with cardioverter defibrillator (ICD) for primary prevention, with most receiving more CRTD than CRTP. While elderly patients were underrepresented in studies that validated this therapy, recent literature suggests that these patients achieve similar benefits of CRT when compared to young patients in morbimortality. The study in question was performed comparing CRTD to CRTP in elderly patients since the arrhythmic mortality in this age group is overcome by non-arrhythmic death. This is a study realized in Sao Bonifacio Hospital, Winnipeg, Canada, between 2007 and 2017. All patients over 75 years old were included (new implants or exchanges). Of 170 patients, the majority (112) made a new implant, with 58 patients submitted to the exchange of the device; there was more implantation of CRTD (128) versus CRTP (42), and in the CRT group the majority (104) was by primary prevention, with a mean follow-up of 2.8 years. The mean age was 79 (IQR 77-81), with 37% having LVEF <20%. There were more men than women (141 versus 29), more pronounced in the CRTD group than CRTP (88% men versus 67% men, respectively; p <0.001). Patients in the CRTD group had more ischemic etiology (87 versus 48%, respectively, p < 0.001) and those in the CRTP group were older than those in the CRTD group (81 years versus 79 years, respectively, p <0.001). The primary outcome occurred in 47/128 (36.7%) in the CRTD group and 12 of 42 (28.6%) in the CRTP group, and the Kaplan Meier curve showed no difference in the survival curves in both prevention indications primary or secondary, after three years (p = 0.69). The 1:1 propensity score identified 27 CRTD and 27 CRTP, coinciding for age, gender, Charlson comorbidity score, the implant (primary versus secondary) indication and date of an implant. There was no difference in survival from the Kaplan Meier analysis in a 3-year follow-up between CRTD versus CRTP. In both univariate and multivariate analyses, chronic kidney disease and ischemic cardiomyopathy were predictors of higher and lower mortality, respectively, and were not predictors of mortality age, gender, Charlson score or decision to implant CRTD versus CRTP. Regarding hospitalization, the univariate predictors were ischemic cardiomyopathy (hazard ratio (HR) 0.45; 95% confidence interval (95% CI) 0.22-0.92; (HR 3.34, 95% CI 1.68-6.62, p <0.001), as well as secondary prevention (HR 2.28, 95% CI 1.09-4.77, p = 0.029), and in the multivariate analysis of chronic

kidney disease (HR 3.55, 95% CI 1.72-7.35, p <0.001) and secondary prevention (HR 3.05, 95% CI 1.36-6.84, p = 0.007) remained as independent predictors. In the ICD therapies, appropriate therapy was not a predictor of mortality (HR 0.99, 95% CI 0.40-2.42, p = 0.973). The authors conclude that there is no significant difference in mortality between patients with CRTD and CRTP and more than 75 years of HF and optimized medical therapy submitted to primary prevention and that in patients with CRTD, secondary prevention conferred a higher risk of hospitalization , individuals with chronic kidney disease have a higher risk of mortality in both CRTD and CRTP, and it is possible to evaluate CRTP in this population with significant comorbidities.

*Christie S, Hiebert B, Seifer CM, Khoo C. Clinical outcomes of cardiac resynchronization therapy with and without a defibrillator in elderly patients with heart failure. Journal of Arrhytmia. 2019;35:61-69. https://doi.org/10.1002/joa3.12131

Survival after cardiac resynchronization therapy: results from 50.084 implants*

Randomized controlled trials (RCTs) have shown that cardiac resynchronization therapy (CRT) prolongs survival and reduces morbidity in selected patients with heart failure (HF), left ventricular (LV) dysfunction and enlarged QRS complex; On this basis, CRT is accepted as a standard treatment for HF. Because RCTs express the results in terms of absolute or relative risk reduction, which quantifies the efficacy of the treatment, patients question how much survival it will have. For this, it will be considered the relative survival (RS), defined as survival observed divided by the expected survival in the general population, a concept already well developed in the field of cancer and most commonly used in cardiovascular diseases. This was a non-randomized, retrospective study exploring total mortality after the first CRT implant; the sample included patients in England between January 2009 and September 2017, both CRTP and CRTD being evaluated. The primary outcome was mortality; survival time based on observed mortality was defined as the duration between the date of the implant and that of death. The secondary outcome was expected survival, calculated according to national life expectancy tables. As for comorbidities, patients were analyzed on the history of hypertension, diabetes mellitus, chronic kidney disease or myocardial infarction prior to implantation. The Charlson comorbidity index (CCI) was used and categorized as: no comorbidity (CCI = 0), mild (CCI = 1), moderate (CCI = 2) and severe (CCI ≥ 3). Over a period of 8.8 years, 50.084 patients were submitted CRT [CRTD: 25,273 (50.5%), CRTP: 24.811 (49.5%)]. As in 2014, after a change in the CRT guidelines, there was an increase in the proportion of CRTD implants and significant statistical differences (p < 0.001) were observed in relation to the baseline characteristics. Patients with CRTD had a history of ischemic disease (67.2 versus 56.0%) and less hypertension (57.6 versus 58.8%) or chronic kidney disease (12.4 versus 15.8%) (all p < 0.001). Mean follow-up of 2.7 years (interquartile range 1.3 - 4.8 years), 14.108 (28.1%) patients died, 5.975 (23.6%, 8.2 per 100 people-years) after CRTD and 8.133 (32.8% , 11.1 per 100 people-years) after CRTP; in the Kaplan Meier curve, CRTD was more associated with lower mortality than CRTP (log rank p < 0.001). After multivariate analysis, mortality was lower after CRTD [hazard ratio adjusted (HRa) 0.85; 95% confidence interval (95% CI 0.82-0.88) after adjustment for age, gender, history of comorbidity, CCI, history of ischemic heart disease and year of implantation. In univariate analysis of age, mortality increased with age (≥ 80 years; HR 4.37; 95% CI 4.07 - 4.68 compared to < 60 years) and the majority were men (37.511 (74.9%); p <0.001] with higher mortality in men (HR 1.41, 95% CI 1.36-1.47) after univariate analysis. For etiology, in patients with ischemic heart disease, CRTD was associated with lower mortality (HRa 0.83; 95% CI 0.80-0.87) and excessive mortality (HRa 0.79; 95% CI 0.74-0.84) compared to CRTP. This was the largest study of long-term outcomes in the real world population of patients submitted to CRT, RS quantification being a unique aspect that expresses

how long a patient is expected to survive after CRT. The authors conclude that RS was higher in young patients, women, and no history of ischemic heart disease, diabetes or chronic kidney disease. CRTD was associated with higher RS than CRTP in patients with or without ischemic heart disease, and comorbidities were more associated with worse outcomes.

*Leyfa F, Zegard A, Okafor O, Bono J de, McNulty D, Ahmed A, et al. Survival after cardiac resynchronization therapy: results from 50,084 implantations. EP Europace. 2019;21(5):754-62. https://doi.org/10.1093/europace/euy267

Risk factors for atrioventricular block after transcatheter aortic valve implantation: single-center analysis including assessment of aortic calcifications and follow-up*

Transcatheter aortic valve implantation (TAVI) has emerged as an alternative to valve replacement surgery (VRS) in cases of severe aortic stenosis in patients with intermediate or high surgical risk and those who are inoperable. The occurrence of conduction disorders requiring definitive pacemaker implantation (DP) after the procedure is not uncommon, represents an important clinical event, its incidence remains high in TAVI versus VRS, the presence of aortic calcification had a greater association with atrioventricular block (AVB) and the necessity for DP as a consequence of mechanical trauma to the bundle of His. The aim of the study was, therefore, to assess the risk factors for total AVB (AVBT) after TAVI in a cohort of a single large center, using a multi-parameter approach, taking into account aortic valve calcification based on multidetector computed tomography (multidetector computed tomography – MDCT) enhanced by contrast. Retrospective procedures were performed retrospectively between July 2009 and October 2016, with severe aortic stenosis, according to international guidelines, and exclusion of bicuspid aortic valve, pure aortic regurgitation and valve ring diameter >30 mm. During this period, 707 patients were submitted to TAVI and, after exclusion of those with valvular valve procedures and previous pacemaker patients, 585 patients were eligible for the study. Due to the factors described in the study, some cases were excluded, leaving 470 patients for analysis. Most patients received expansive balloon prosthesis: Edwards SapienXT, n=157; Edwards Sapien3, n= 185; Medtronic CoreValve, n=27; Medtronic CoreValve EvolutR, n=12; Medtronic Engager, n=5; e Symetis Accurate, n = 84. To avoid bias, the analysis was performed on SapienXT and Sapien3 prostheses (n = 342). The following intraoperative and hospital outcomes were recorded: intermittent or permanent high-grade AVB (AVBT or Mobitz II); a necessity for DP; and new or worsened intraventricular conduction disturbance, including right branch block (RBB), left branch block and left anterior hemiblock. The pacemaker implant was performed in the case of symptomatic bradycardia or high-grade AVBs lasting up to seven days. Patients were classified into three groups, according to the outset of AVB (either, transient/reversible or permanent/irreversible). The study population consisted of 342 consecutive patients; of these, 14 (4%) presented transient/reversible AVB, while 26 (7.6%) had permanent/irreversible AVB. Compared to those without AVB, patients with transient AVB had a higher incidence of post-dilatation of the balloon, while those with permanent AVB had a higher incidence of percutaneous coronary intervention (PCI), RBB and Q waves on baseline electrocardiogram (EKG). Regarding calcification, the cusp with the highest amount of calcium was the non-coronary (CNC), above and below the basal plane. Univariate and multivariate analyses identified independent predictors associated with a transient and permanent high degree of AVB; RBB on baseline EKG, calcium volume below the CNC in the left ventricular outflow tract, prior PCI and excess size (overestimated) were more associated with permanent AVB. On the other side, calcium volume below the right coronary cusp and dilation of the balloon after implantation were associated with transient AVB. The mean follow-up was 21.2 ± 18 months; Transient AVB showed a trend towards lower survival in the first year after valve implantation, but without statistical significance. It was possible to interrogate the pacemakers after 12 months in 14 of the 26 patients; Of these, seven (50%) had ventricular pacing percentage > 95%, while the

other percentage <1%. The authors conclude that the preoperative assessment of valve calcification prior to prosthesis implantation may help to predict mechanical stress in the bundle of His and the subsequent risk of DP, calcification below the CNC is associated with irreversible AVB, and, finally, patients with reversible AVB should be followed up more briefly.

*Pollari F, Grobmann I, Vogt F, Klinsnik JM, Cuomo M, Schwab J, et al. Risk factors for atrioventricular block after transcatheter aortic valve implantation: a single-centre analysis including assessment of aortic calcifications and follow-up. EP Europace. 2019;21(5):787-95. https://doi.org/10.1093/europace/euy316

Antibacterial envelope to prevent infection in implantable device*

It is estimated that 1.5 million patients receive implantable electronic cardiac devices (IECDs) and, despite prevention, the infection continues as an important complication associated with the important morbidity, mortality, and costs of the health system. There is little evidence about different prophylaxis strategies other than preoperative antibiotic use. The study in question evaluated the use of an envelope (TYRX Absorbable Antibacterial Envelope, Medtronic) absorbable in nine weeks, multifilament in terms of efficacy and safety in reducing infection. The envelope has the ability to stabilize IECD in the subcutaneous space and release the antibiotics rifampicin and minocycline. The Worldwide Randomized Antibiotic Envelope Infection Prevention Trial (WRAP-IT) study was a multicenter, randomized, controlled, prospective, single-blind, post-marketing, interventionist, comparing infection incidence at 12 months in those who received the envelope versus those who did not receive it. Diverse devices (CRTP, CRTD, ICD, and pacemaker) were used and follow-up occurred every six months to a minimum of 12 months.

The study has one primary and three secondary outcomes. The primary outcome was the occurrence of infection in 12 months (superficial cellulitis in the space with incision dehiscence, erosion or purulent drainage, deep or space incision infection, persistent bacteremia or endocarditis) leading to the withdrawal of the system, invasive procedure, long therapy term with antibiotic or death. Secondary outcomes were complications related to the procedure or to the system, minor infection at 12 months and major infection regardless of when it occurred. Seven thousand and seventy-five patients were enrolled, 6.983 of whom were randomized, with 3.495 assigned to receive the envelope and 3.488 not to receive, with recruitment from January 2015 to July 2017. The characteristics of the groups were balanced, except for a higher percentage of patients on immunosuppressive therapy in the control group and with a mean age of 70.1 ± 12.5 years; 28.3% were women. Follow-up occurred for 20.7 ± 8.5 months, with 89.4% of patients completing 12 months; during this period, 181 system reviews occurred in 153 patients in the envelope group and 229 in 186 patients in the control group [annual rate 0.06 and 0.07, respectively; rate ratio 0.79; 95% confidence interval (95% CI) 0.65-0.96]. At 12 months, there were 30 major infections in 25 patients in the envelope group and 45 in 42 patients in the control group (Kaplan-Meier estimated event rate at 12 months 0.7 and 1.2%, respectively, hazard ratio 0.60, 95% CI 0.36 -0.98, p = 0.04). Regarding the first major infection in each patient, 17 were endocarditis or bacteremia and 50 were space infections; of the 36 microorganisms identified, 23 were *Staphylococcus* bacteria. The authors conclude that the use of the antibacterial envelope resulted in a 40% lower incidence of IECD infection when compared to the strategies currently used and that patients using the envelope had no further complications related to the device or procedure.

*Tarakji KG, Mittal S, Kennergren C, Corey R, Poole JE, Schloss E, et al. Antibacterial envelope to prevent cardiac implantable device infection. N Engl J Med. 2019;380:1895-1905. https://doi.org/10.1056/NEJMoa1901111

Gender differences in frequency and rhythm control for atrial fibrillation*

Atrial fibrillation (AF) is the most common sustained arrhythmia and is associated with a substantial increase in morbimortality. Several studies have shown differences in several aspects related to gender, including age at diagnosis, clinical manifestations, management, and prognosis; these differences may dictate approaches in patients and translate different outcomes as a tendency to treat women more conservatively and less aggressively than men. The article, therefore, reviews gender-related disparities in patients with AF, discusses therapeutic options, and specifically refers to differences in access to treatment, success rates, and potential treatment-related complications. FA is rare in pre-menopausal women, suggesting a protective effect of female hormones, and the BiomarCaRE study showed occurrence 10 years later when compared to men. The risk of mortality is > 3.5 times in both genders, but recent studies have shown that AF is an important risk factor for cardiovascular disease and death in women. In the Women's Health Initiative (WHI) Observational Study, a prospective observational study of 93.676 post-menopausal women (mean age 63 years) followed by 11.5 years, elevated levels of physical activity were associated with lower rates of AF and modified the association between obesity and AF. Regarding the clinical presentation, gender-related differences were compared in the Euro Observational Research Program on Atrial Fibrillation (EORP-AF) in 3.119 patients; women were more symptomatic and had more palpitations (80 versus 69%, respectively, $p < 0.0001$), as well as more symptomatic episodes of AF. In treatment, although its present more symptoms, women receive fewer interventions for rhythm control, with fewer referrals for catheter ablation, but receive, in contrast, more antiarrhythmic medications. It is therefore subject to more drug complications and is referred for ablation with older age and longer arrhythmia, which increases the arrhythmogenic substrate. Takigawa et al. reported that sinus rhythm was similarly maintained between men and women in the first intervention (56.4 versus 59.3% in men up to five years of age, $p = 0.24$), but was significantly lower in women after the last catheter ablation (76.5 versus 81.3% in men up to 5 years, $p = 0.007$) and women had more triggers outside the pulmonary veins ($p < 0.05$) versus men. As women have less participation in clinical studies on AF, future studies will be important to improve expected outcomes in this population, especially for catheter ablation. The authors conclude that low adherence, emotional stress, hormonal changes, and sleep quality may interfere with AF symptoms, but gender-specific differences have not yet been studied.

*Weberndorfer V, Beinart R, Ricciardi D, Ector J, Mahfoud M, Szeplaki G, et al. Sex differences in rate and rhythm control for atrial fibrillation. EP Europace. 2019;21(5):690-7. https://doi.org/10.1093/europace/euy295