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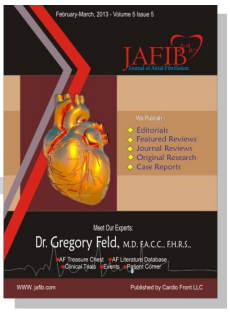

Atrial Fibrillation in Patients with Cardiac Resynchronization Therapy: Clinical Management and Outcome

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Abstract

Atrial fibrillation (AF) and heart failure (HF) are two emerging epidemics in the cardiovascular field and are strictly inter-related since may directly predispose to each other. Cardiac resynchronization therapy (CRT) has emerged as an important therapeutic option for selected HF patients with LV dysfunction and ventricular dyssynchrony. However almost all RCTs demonstrated the CRT effectiveness in patients in sinus rhythm (SR), including permanent AF among the exclusion criteria.

In patients with paroxysmal or persistent AF strategies for rhythm control can be applied, but usually with limited efficacy. Furthermore, rhythm control strategy did not result superior to rate-control in patients with heart failure. AF ablation in HF patients is usually performed only in selected centres. In patients with permanent or long-standing AF and a CRT device the option of AVN ablation offers the advantage of allowing >95% biventricular pacing.

AF implies a harmful increase in Thromboembolic Risk. Detection of AF in patients treated with a CRT device is enhanced by device diagnostic capabilities, that allow detection of episodes of atrial tachyarrythmias, including silent AF. In these cases decision making on appropriate antithrombotic prophylaxis has to consider clinical risk stratification, usually applying $CHADS_2$ and $CHA2DS_2VASc$ scores.

In summary, in order to maximise outcome, AF in patients with CRT prompts the need to appropriately decide on antithromboembolic prophylaxis (according to risk stratifications), as well as on rate and/or rhythm control strategies, with the aim to allow constant biventricular pacing. In this perspective, AVN ablation has an important role since by inducing pace-maker dependency guarantees continuous biventricular pacing.

Introduction

Atrial fibrillation (AF) and heart failure (HF) are two emerging epidemics in the cardiovascular field and are strictly inter-related since may directly predispose to each other. The prevalence of AF increases in more advanced New York Heart Association (NYHA) class; in detail it is around 4% in NYHA functional class I, 10-27% in NYHA

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Table 1 Current Indications of the European Society of Cardiology for Cardiac Resynchronization Therapy (CRT) in Heart Failure, using a Device with only Pacing Capabilities (CRT-P) or with Defibrillation Capabilities (CRT-D). Modified with Permission.[2]

Patients in NYHA Functional Class III and Ambulatory Class IV
- In patients with LBBB QRS morphology CRT-P/CRT-D is recommended in patients in sinus rhythm with a QRS duration of ≥120 ms, LBBB QRS morphology, and an EF ≤35%, who are expected to survive with good functional status for >1 year, to reduce the risk of heart failure hospitalization and the risk of premature death (class I recommendation, level of evidence A)
- In patients with non-LBBB QRS morphology CRT-P/CRT-D should be considered in patients in sinus rhythm with a QRS duration of ≥150 ms, irrespective of QRS morphology, and an EF ≤35%, who are expected to survive with good functional status for >1 year, to reduce the risk of heart failure hospitalization and the risk of premature death (class IIa recommendation, level of evidence A)
Patients in NYHA Functional Class II
- In patients with LBBB QRS morphology CRT, preferably CRT-D is recommended in patients in sinus rhythm with a QRS duration of ≥130 ms, LBBB QRS morphology, and an EF ≤30%, who are expected to survive for >1 year with good functional status, to reduce the risk of heart failure hospitalization and the risk of premature death (class I recommendation, level of evidence A)
- In patients with Non-LBBB QRS morphology CRT, preferably CRT-D should be considered in patients in sinus rhythm with a QRS duration of ≥150 ms, irrespective of QRS morphology, and an EF ≤30%, who are expected to survive for >1 year with good functional status, to reduce the risk of HF hospitalization and the risk of premature death (class IIa recommendation, level of evidence A)
Patients with Heart Failure and Permanent Atrial Fibrillation
CRT-P/CRT-D may be considered in patients in NYHA functional class III or ambulatory class IV with a QRS duration ≥120 ms and an EF ≤35%, who are expected to survive with good functional status for >1 year, to reduce the risk of heart failure worsening if:
- The patient requires pacing because of an intrinsically slow ventricular rate (class IIb recommendation, level of evidence C).
- The patient is pacemaker dependent as a result of AV nodal ablation (class IIa recommendation, level of evidence B).
- The patient's ventricular rate is ≤60 b.p.m. at rest and ≤90 b.p.m. on exercise. (class IIb recommendation, level of evidence C).
Patients with an Indication for Conventional Pacing and No Other Indication for CRT
In patients who are expected to survive with good functional status for >1 year:
- CRT should be considered in those in NYHA functional class III or IV with an EF ≤35%, irrespective of QRS duration, to reduce the risk of worsening of heart failure (class IIa recommendation, level of evidence C).
- CRT may be considered in those in NYHA functional class II with an EF ≤35%, irrespective of QRS duration, to reduce the risk of worsening of heart failure (class IIb recommendation, level of evidence C).

class II -III, and up to 50% in NYHA class IV .[1] AF may present in HF patients with different forms, with frequent evolution from paroxysmal or persistent AF to permanent AF (detectable in 10-30% of HF patients) and this is frequently associated with increased morbidity and mortality.

Cardiac resynchronization therapy (CRT) has emerged as an important therapeutic option for selected patients with left ventricular ejection fraction (EF) ≤ 35%, ventricular dyssynchrony (QRS duration ≥120 ms with NYHA class II-IV drug refractory HF and, according to more recent randomized trials, also in mild HF (NYHA II).[2]

The current indications to CRT in clinical practice are reported in Table 1.

Clinical Issues in Patients with AF and HF Treated with CRT

The spectrum of clinical issues related to AF in HF patients treated with a CRT device is wide, as summarized in Table 2. Most of these issues have not been highlighted by RCTs evaluating CRT versus control, while they appear of major relevance in daily clinical practice, since appropriate management and clinical decision making is required.

Table 2	Clinical Issues Related to AF in HF Patients Treated with CRT

- AF with Symptomatic Bradyarrhythmias as an Indication to Biventricular Pacing in Patients with HF and LV Dysfunction;
- AF-related symptoms (palpitation, syncope, light-headedness, chest pain, etc.)
- AF-related Thromboembolic Risk (need for oral anticoagulant according to $CHADS_2$ risk stratification)
- Hemorrhagic risk related to oral anticoagulants;
- Detection of "silent" AF by device diagnostics (algorithms, EGMs)
- Possibility of conversion of persistent/long-standing AF to SR secondary to CRT-related improvement in LV function);
- Worsening of HF (acute decompensation, chronic worsening) due to new onset or paroxysmal/persistent/permanent AF;
- Loss of biventricular pacing during AF: loss of CRT benefit (need for rhythm-control, including drugs or AF ablation, or rate-control, including drugs or AVN ablation);
- Electrical conversion of AF for rhythm control (by external DC shock, by delivery of a manual shock by a CRT-D device)
- Inappropriate shocks delivered by a CRT-D device (need for device reprogramming/rate control)
- Induction/worsening of myocardial ischemia (secondary to AF with high ventricular rate)
- Facilitation of ventricular tachyarrhythmias (secondary to short-long-short ventricular cycles during AF or to myocardial ischemia)

In the present review we will analyse some of the clinically relevant aspects related to use of CRT in HF patients with AF (paroxysmal, persistent and permanent) focusing on daily clinical management of CRT patients.

Efficacy and Effectiveness of CRT in HF Patients with AF

The efficacy of CRT in selected HF patients with LV dysfunction and ventricular dyssynchrony, as detected by wide QRS complex, was demonstrated by RCTs, initially focused on moderate to severe HF and more recently on mild HF (NIHA II), as shown in Table 3. However, it is noteworthy to stress that almost all RCTs on CRT included permanent AF among the exclusion criteria.

MUSTIC (MUltisiteSTimulation in Cardiomyopathies) was a randomized study dedicated to assess the response to CRT in AF patients[17] versus patients in sinus rhythm. It included 131 patients, 67 in sinus rhythm and 64 in AF, all with NYHA class III. The results showed that CRT was associated both in sinus rhythm or in AF with a similar improvement at the 6-minute walk test as compared to no CRT. The study had some limitations, since only 75 out of 131 patients completed the study till the 12-month follow up. Moreover its applicability to all HF patients with AF was low, since all patients in AF had a slow ventricular rate, due to spontaneous or induced atrioventricular (AV) block, thus allowing a high percentage of biventricular pacing, with very low or absent spontaneous ventricular activations or fusion beats.

Recently, the RAFT trial[18] enrolled patients either in sinus rhythm or in AF and the analysis showed that patients with AF who are otherwise CRT candidates appear to gain a minimal benefit from CRT-D compared standard ICD. However, the correct interpretation of this study should consider that in RAFT AV node ablation was performed in only one patient and that optimal biventricular pacing (>95%) was achieved in only one third of the patients. Therefore this randomized study does not appear to give a clinically oriented answer to the question on what is the benefit of CRT in AF, which could benefit form the meta-analysis presented below.

Management of AF in CRT and Patient Outcome

In a general view AF effects in patients with HF are linked to loss of atrial kick, irregularity of ventricular rate and fast ventricular rates (which at mid- or long-term may lead to the overt picture of "tachycardiomyopathy"). However in the specific context of a patient with HF and ventricular dyssynchrony treated with CRT AF almost inevitably leads to loss of constant biventricular pacing, unless an AV block per se reduces or blocks spontaneous ventricular response during AF (Figure 1).

Table 3 Randomized studies on CRT

Trial	Number of Enrolled Patients	NYHA class	LVEF (%) at Enrolment	SR/AF at Enrolment	QRS Width at Enrolment (ms)	CRT Device with Defibrillation Capability
MUSTIC-SR[3]	58	III	≤35	SR	≥150	No
MIRACLE[4]	453	III, IV	≤35	SR	≥130	No
MUSTIC AF[5]	43	III	≤35	AF	≥200	No
PATH CHF[6]	41	III, IV	≤35	SR	≥120	No
MIRACLE ICD[7]	369	III, IV	≤35	SR	≥130	Yes
CONTAK CD[8]	227	II, IV	≤35	SR	≥120	Yes
MIRACLE ICD II[9]	186	II	≤35	SR	≥130	Yes
PATH CHF II[10]	89	III, IV	≤35	SR	≥120	Yes/no
COMPANION[11]	1520	III, IV	≤35	SR	≥120	Yes/no
CARE HF[12]	814	III, IV	≤35	SR	≥120	No
CARE HF Extension 2006[13]	813	III,IV	≤35	SR	≥120	No
REVERSE[14]	610	I, II	≤40	SR	≥120	Yes/no
MADIT CRT[15]	1800	I, II	≤30	SR	≥130	Yes
RAFT[16]	1800	II, III	≤30	SR/AF	≥130 (> 200 if AF)	Yes

In patients who have normal rate AF, phases of effective biventricular capture alternate with phases of competing AF rhythm which causes spontaneous, fusion or pseudo-fusion beats and this suggests that the potential benefit in terms of effective resynchronization may be markedly reduced compared with atrial synchronous rhythm with a short AV interval (as is achieved during sinus rhythm) since the number of effective biventricular captured beats are reduced.

In AF patients treated with CRT there is a growing body of evidence on the necessity of reaching the highest possible percentage of biventricular pacing , >95% but possibly in the range of >98% according to recent data collected on around 37 000 patients using remote monitoring .[19, 20]

In patients with paroxysmal or persistent AF strategies for rate control or rhythm control can be applied usually with limited efficacy, particularly at the onset of an AF recurrence when the increase in adrenergic tone induces fast ventricular rates with spontaneous ventricular activation (in the absence of AV block). Substrate AF ablation in HF patients is usually performed only in selected centres. In patients with heart failure the first experience on left atrial ablation was a non-randomized study on 58 patients, published by the Haissaguerre's group.[21] The authors reported an improvement in left ventricular function at 1-year follow up both in patients with and without structural heart disease, and both in patients with and without adequate rate control, suggesting that correction of underlying tachycardiomyopathy played a major role in the improvement. A subsequent study, from MacDonald et al.[22] on patients with advanced HF randomized to rhythm control with left atrial ablation versus pharmacological rate control showed that ablation resulted in only 50% of patients in sinus rhythm at 6 month-follow up (versus 0% in control group). In this study left atrial ablation did not improve exercise capacity, quality of life or pro-BNP, while controversial results were found on left ventricular ejection fraction (improved at radionuclide angiography but not at cardiac magnetic resonance). In summary, considering that these data derive from high-volume centres, controversial data exist on the role of left atrial ablation in "real-world clinical practice", when applied to patients with advanced heart failure, such as most of the candidates to CRT.

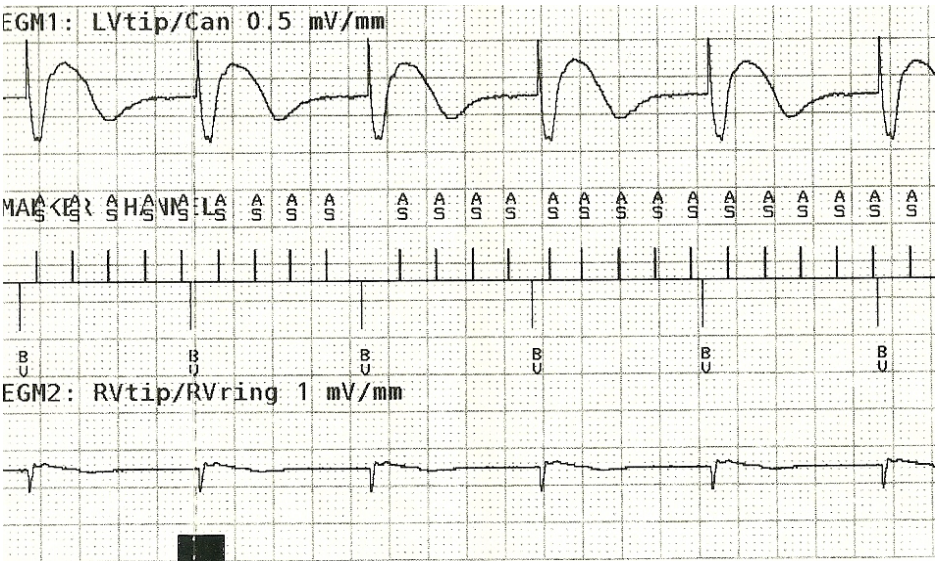
In patients with permanent or long-standing AF the decision on rhythm versus rate control should be guided by clinical considerations. In patients with AF and a CRT device the option of AVN ab-

lation offers the advantage of allowing >95-98% biventricular pacing, therefore with all the clinical advantages of CRT in terms of symptoms improvement, LV reverse remodelling, morbidity and survival.

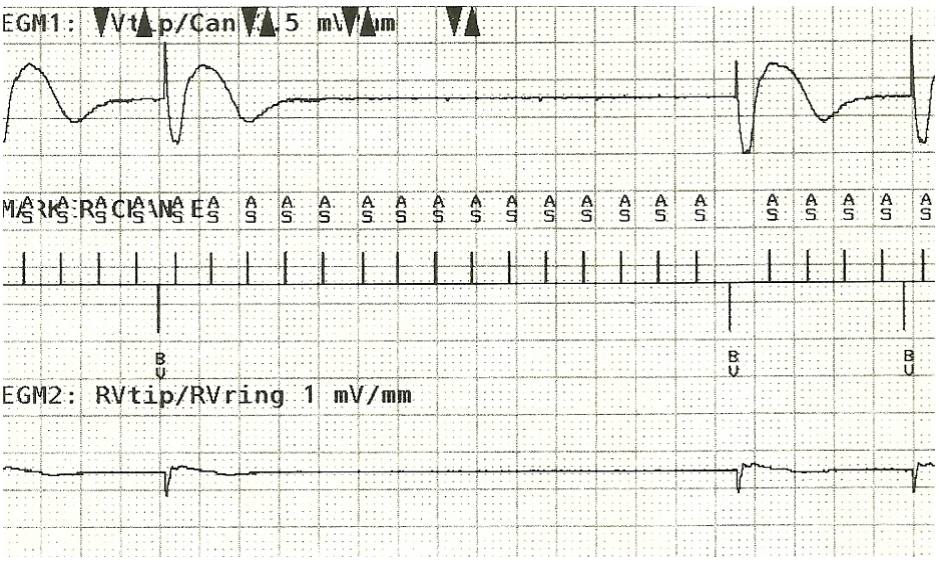
Maintenance of left atrial contribution to ventricular filling, as well as maintenance of a physiological rate responsiveness, may be good theoretical reasons for applying a rhythm control strategy but this strategy did not result superior to rate-control in patients with heart failure, selected independently on indication to CRT.[23] A rhythm control strategy based on pharmacological agents has to consider only amiodarone, since dronedarone is specifically contraindicated in heart failure patients. For left atrial ablation positive results have been reported in highly specialized centres, but the

Figure 1: CRT in AF Patients (Panel A) and AF Patients Treated with Atrioventricular Node (AVN) Ablation (Panel B)

Panel A



Panel B

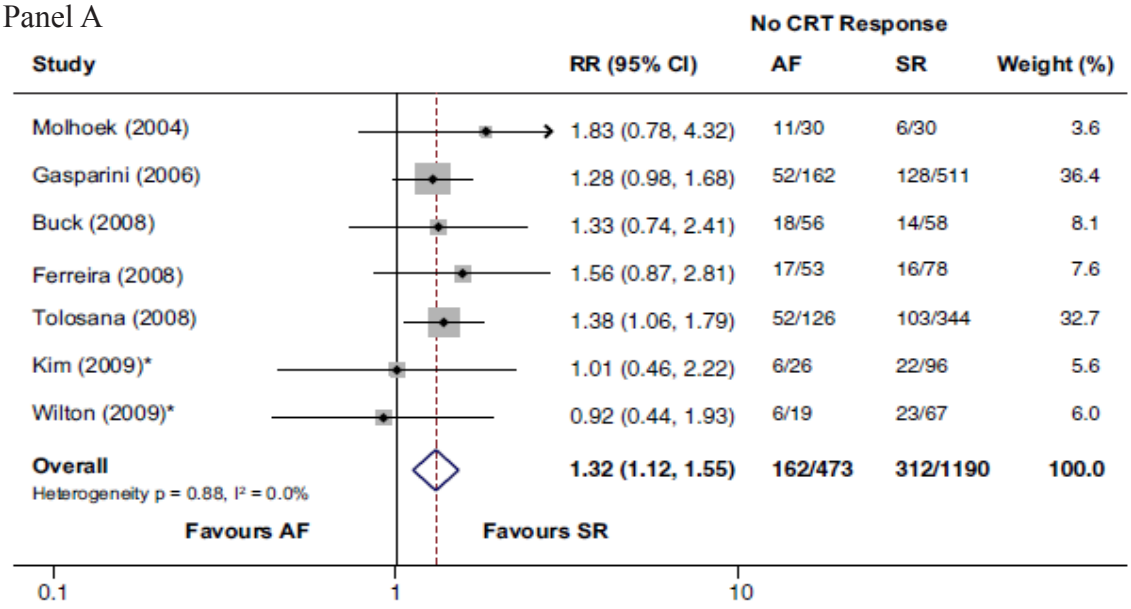


possibility to replicate these results in daily practice, for the large amount of CRT patients presenting AF, is not defined.

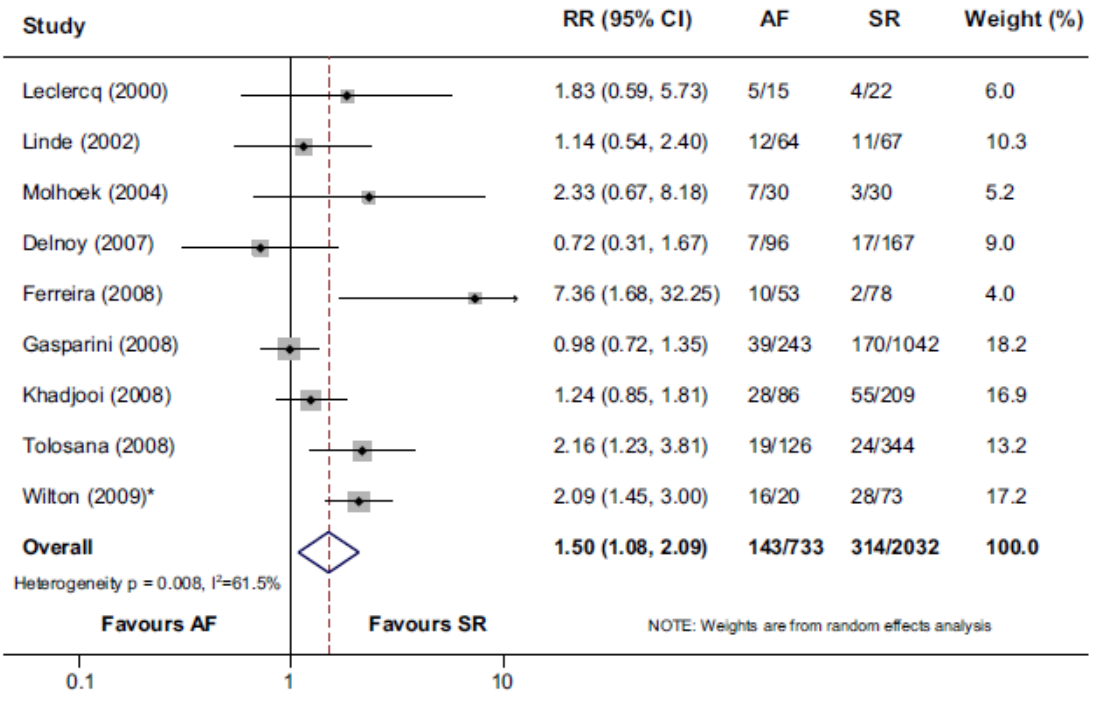
With regard to the benefit of applying AV node ablation to CRT patients there is paucity of data derived from RCTs, therefore it becomes topical to analyse data derived from observational studies. Gasparini et al.[19] reported the largest series and found that patients with AF treated with CRT had a worse outcome in comparison to comparable patients in SR (Figure 1 panel A). however, the negative prognosis associated with AF was no longer evident when AF patients treated

Figure 2: Meta-analysis of the Relative Risk (RR) of Clinical Nonresponse to Cardiac Resynchronization Therapy (CRT) over 6 to 12 months in Patients with Atrial Fibrillation (AF) Versus Sinus Rhythm (SR). P value for the Pooled RR _ 0.001. Heterogeneity P Values from the Cochran Q Statistic. CI _ Confidence Interval; I2 _ Proportion of the Variation in Relative Risk that is Due to Between-Study Heterogeneity (Panel A); Meta-Analysis of the Relative Risk (RR) of all-Cause Death in Patients with Versus those without Atrial Fibrillation (AF) Undergoing Cardiac Resynchronization Therapy. P Values for the Pooled RR in the Peer-Reviewed Articles, Abstracts, and Combined Groups are .06, .006, and .003, Respectively (Panel B).

Panel A



Panel B



with CRT and atrioventricular node (AVN) ablation were considered (Figure 1 panel B).This is in agreement with the general principle that CRT is effective and improves Patients Outcome only when the percentage of biventricular pacing is high, higher than 95% .[20, 23] This observation is also supported by some meta-analysis of all the studies performed on CRT in permanent AF. A systematic review and meta-analysis on AF, HF and CRT was recently published by Wilton et al.[24]Twenty-three observational studies were included and followed a total of 7,495 CRT recipients, 25.5% with AF, for a mean of 33 months. AF was associated with an increased risk of nonresponse to CRT (34.5% vs 26.7%; pooled relative risk [RR] 1.32; 95% confidence interval [CI] 1.12, 1.55; P = .001) and all-cause mortality (10.8% vs 7.1% per year, pooled RR 1.50, 95% CI 1.08, 2.09; P = .015). The presence of AF was also associated with less improvement in QoL, 6-minute hall walk distance, and LV end-systolic volume but not LV ejection fraction. (Figure 2, Panel A and B). With regard to role of AV node ablation a more recent meta-analysis was published in 2012 by Ganesan et al.[25]After a systematic search the authors identified 6 studies, including 768 CRT-AF patients, composed of 339 patients who underwent AV nodal ablation and 429 treated with medical therapy aimed at rate control alone. AV nodal ablation in CRT-AF patients was associated with significant reductions in all-cause mortality (risk ratio: 0.42 [95% confidence interval: 0.26 to 0.68]), cardiovascular mortality (risk ratio: 0.44 [95% confidence interval: 0.24 to 0.81]), and improvement in mean New York Heart Association functional class (risk ratio: –0.52 [95% confidence interval: –0.87 to –0.17]). AV nodal ablation was associated with a substantial reduction in all-cause mortality and cardiovascular mortality and with improvements in New York Heart Association functional class compared with medical therapy in CRT-AF patients. This meta-analysis has several limitations since primarily based on observational data, rather than randomized controlled trial data.

AF, Silent AF and Thromboembolic Risk

It is well known how AF implies a harmful increase in Thromboembolic Risk, including invalidating stroke. Detection of AF in patients treated with a CRT device is enhanced by device diagnostic capabilities, since specific device algorithm may detect episodes of atrial tachyarrythmias, including AF and store EGMs in device memory. In patients with a CRT device, device diagnostics allow to detect silent AF and recent data[26] show how device detected atrial tachyarrythmias are associated with a 2.5 fold increase in the risk of stroke. In these cases decision making on appropriate antithrombotic prophylaxis has to consider clinical risk stratification by applying $CHADS_2$ and CHA_2DS_2VASc scores.[27] These scores were not derived and validated in populations of patients implanted with a device; however, there are no specific reasons for not applying them to CRT patients for guiding the prescription of anti-thromboembolic prophylaxis. In view of the negative impact of both over- and under-treatment with oral anticoagulants,[28] we think there is strict indication to apply a guideline-based approach to oral anticoagulation, with the advantage of current availability of novel anticoagulants.[29]

Conclusions

AF and HF are two common epidemics and in view of progressive aging of the population an increase burden is expected in the next decades. In HF patients with systolic dysfunction and ventricular dyssynchrony. CRT has emerged in the last decade as a very effective treatment, with reduced morbidity and improved outcomes.

AF is common in HF patients and therefore may present in different forms (new onset, paroxysmal, persistent, permanent) at different times of the "unnatural history" of a HF patients treated with CRT, ie before or at different time after implant of a CRT-P or CRT-D device. CRT devices increase the ability to detect AF since device diagnostics allows to detect "silent" AF, with important implications for clinical decision making and patients' care.

As a matter of fact AF in patients with CRT prompts the need to appropriately decide on antithromboembolic prophylaxis (according to risk stratifications) as well as rate and/or rhythm control strategies whose aim is to allow constant biventricular pacing. In this perspective AVN ablation has an important role since by inducing pace-maker dependency guarantees continuous biventricular pacing.

Disclosures

- Giuseppe Boriani received speaker's fees from Medtronic.
- The remaining authors have no disclosures to report

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