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Review

Atrioventricular node ablation and pacing for atrial tachyarrhythmias: A meta-analysis of postoperative outcomes

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ABSTRACT

Background: Atrioventricular node ablation (AVNA) and pacemaker (PM) is performed in symptomatic atrial fibrillation (AF) unresponsive to medical treatment and percutaneous ablation. This meta-analysis evaluated results after AVNA and PM.

Methods: Primary and secondary endpoints were early/late overall/cardiac-related mortality and early/late postoperative complications. Meta-regression explored mortality and preoperative characteristics relation.

Results: We selected 93 studies with 11,340 patients: 9105 right ventricular (RV)-PM, and 2235 biventricular PM (cardiac resynchronization therapy, CRT). Malignant arrhythmia (2.5%), heart failure (2.4%), and lead dislodgement (2.0%) were most common periprocedural complications. Pooled estimated 30-day mortality was 1.08% (95%CI:0.65–1.77). At 19.9 months median follow-up (IQR: 10.3–34 months), rehospitalization (0.79%/month) and heart failure (0.48%/month) were the most frequent complications. Overall mortality incidence rate (IR) was 0.43%/month (95%CI:0.36–0.51), and cardiac death IR 0.27%/month (95%CI:0.22–0.32). No mortality determinants emerged in the AVNA CRT subgroup. AVNA RV-PM subgroup univariable meta-regression showed inverse relationship between age, ejection fraction (EF), and late cardiac death (Beta = -0.0709 ± 0.0272; $p = 0.0092$ and Beta = -0.0833 ± 0.0249; $p = 0.0008$). Coronary artery disease (CAD) was directly associated to follow-up overall/cardiac mortality at univariable (Beta = 0.0550 ± 0.0136, $p < 0.0001$; Beta = 0.0540 ± 0.0130, $p < 0.0001$) and multivariable (Beta = 0.0460 ± 0.0189, $p = 0.152$; Beta = 0.0378 ± 0.0192, $p = 0.0491$) meta-regression.

Conclusions: Solid long-term evidence supporting AVNA and pace is lacking. Younger patients with reduced LVEF % have increased follow-up cardiac mortality after AVNA RV and may require CRT. Alternative strategies to maintain sinus rhythm and ventricular synchronism should be compared to AVNA to support future treatment strategies.

1. Introduction

Atrial fibrillation (AF) represents the most prevalent supraventricular arrhythmia worldwide and is associated with an increased risk of death and morbidities, including heart failure, stroke, and psychophysical debilitation [1]. AF significantly impacts the life quality and expectancy owing to frequent outpatients clinic visits and hospitalizations to manage AF and its related morbidities [2].

According to the European Society of Cardiology (ESC), the first-line management of AF starts with pharmacological therapy [3]. In patients that remain symptomatic despite optimal medical treatment of permanent AF and unsuitable for ablation, the atrioventricular node ablation (AVNA) with permanent pacemaker (PM) implantation, also known as the "Ablate and Pace" [4] procedure, should be considered (class IIa, level of evidence B), accepting that these patients will become permanently PM dependent, and will incur into the possible consequences. The chronic stimulation with a PM exposes the patient to potential long-term negative side-effects [5], without considering the additional costs and risks of permanently carrying an intracardiac lead and cardiac electronic device. Therefore, the present meta-analysis aimed to evaluate the early

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and late postoperative complications/consequences of AVNA, derive their independent determinants, and discuss management alternatives.

2. Methods

2.1. Literature search strategy

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [6] (PRISMA Checklist). The PRISMA flow diagram is presented in Supplementary Fig. 1. Pubmed MEDLINE, ScienceDirect, and Cochrane databases were searched until September 2021 for publications reporting the clinical outcome of studies regarding AVNA and pacing for AF by using combination of the keywords "atrioventricular node", "atrioventricular junction", "ablation", "His bundle", "ablate and pace", "atrial fibrillation", "atrial flutter", "atrial tachyarrhythmia". Furthermore, the references of all studies and meta-analyses were examined to identify additional articles (i.e., "backward snowballing"). Studies were independently screened for inclusion by two authors (M.B. and F.T.). In case of disagreement, a consensus was reached with the aid of a third author (S.B.).

2.2. Selection criteria

Studies were included if describing cohorts of patients undergoing AVNA for atrial tachyarrhythmia (AF, atrial flutter, ectopic atrial tachycardia) independently from the type of cardiac electronic device generator implanted and technique adopted. Only articles written in English language were included. Exclusion criteria for analysis were studies without cardiac electronic device implantation, without ablation for all included patients, lacking postoperative complications or follow-up data reporting, case reports, reviews, and comments. When the same institution published more than one study, the study period was considered and the study with the largest sample size was included in case of study period overlap.

2.3. Data extraction and critical appraisal

Microsoft Office 365 Excel software (Microsoft, Redmond, Washington, USA) was used for data extraction. Categorical variables were reported as numbers, while continuous variables were expressed as mean with standard deviation. Data on study period, study center, country, sample size, and type of pacing were retrieved. The following patient characteristics were abstracted: mean age, sex, mean body mass index (BMI), type of atrial arrhythmia, previous ablation and ablation type, previous cerebrovascular accident (CVA), diabetes, hypertension, dyslipidemia, chronic obstructive pulmonary disease (COPD), coronary artery disease (CAD), mean ejection fraction (EF), heart failure, and mean left atrial (LA) size.

The Newcastle-Ottawa Quality Assessment Scale for Cohort Studies was used for critical appraisal of the quality of included non-randomized studies [7], while the Cochrane Collaboration's tool bias risk was adopted for randomized clinical trials (RCT) [8].

2.4. Statistical analysis

The primary endpoint of the analysis was late mortality and cardiac mortality. Secondary endpoints were early and late postoperative complications including malignant arrhythmia, CVA, PM revision, cardiac perforation, cardiac tamponade, postoperative infection, PM lead dislodgement requiring revision, vein thrombosis, pulmonary embolism, heart failure, and rehospitalization. For late outcomes a Poisson regression modelling was used to account for the studies' differences in follow-up times, assuming a constant event rate. The total person-time of follow-up was calculated from the total number of events and mean follow-up time. A log transformation to model the overall incidence rate (IR) and a random effect were used. For the other outcomes, the pooled event rates (PERs) or pooled event means (PEMs) with 95% Confidence Interval [CI] were calculated.

Subgroup analyses were conducted to evaluate the late outcomes in RCTs, and differences between monoventricular (right ventricular, RV PM) and biventricular PM (cardiac resynchronization therapy [CRT]).

In all analyses, studies were weighted by the inverse of the variance of the estimate for that study, and between-study variance was estimated with DerSimonian-Laird (DL) method with random effects model. Studies with double zeros were included in meta-analysis and treatment arm continuity correction was applied in studies with zero cell frequencies.

Univariable and multivariable meta-regression was performed to explore the relation between the mortality outcomes and preoperative characteristics. The results were reported as regression coefficient (i.e., beta).

Hypothesis testing for equivalence was set at the two-tailed 0.05 level. Heterogeneity was based on the Cochran Q test, with I^2 values. In case of heterogeneity $I^2 > 50\%$, individual study inference analysis was performed through a "leave-one-out" sensitivity analysis.

Funnel plots by graphical inspection and Egger regression test were used for assessment of publication bias. In case of asymmetry positivity, visual assessment and Duval and Tweedie's trim and fill methods were used for further assessment.

All analyses were performed using R, version 4.1.0 (R Project for Statistical Computing) and RStudio version 1.4.1717, using the "meta" and "metafor" packages.

3. Results

The literature search identified 5018 potentially eligible studies. Twenty-six additional articles were identified through backward snowballing. After removal of duplicates, 2177 studies were screened. One-hundred-thirty-nine full text articles were assessed for eligibility. Ninety-three studies (Supplementary References) met our inclusion criteria (Supplementary Fig. 1) with a total of 11,340 patients, 9105 right ventricular (RV)-PM, and 2235 biventricular PM (cardiac resynchronization therapy, CRT). Publication year ranged from 1982 to 2021, and sample size ranged from 5 to 803 patients. Details of the individual studies are shown in Supplementary Table 2. Among the included studies there were 14 RCT, 11 prospective studies, and 68 retrospective studies. The demographics of the included studies are summarized in Supplementary Table 1. The pooled median follow-up was 19.9 months (interquartile range (IQR): 10.3–34 months). The critical appraisal of non-randomized and randomized included studies is shown in Supplementary Table 3 and 4.

3.1. Meta-analysis

The PER of 30-day mortality was 1.08% (95%CI: 0.65–1.77), the IR of overall mortality was 0.43%/month (95%CI: 0.36–0.51) and the IR of cardiac death was 0.27%/month (95%CI: 0.22–0.32). Malignant arrhythmia (2.5%; CI: 1.49–4.17), heart failure (2.4%; CI: 0.71–8.31), and lead dislodgement (2.0%, CI: 1.21–3.36) were the most common periprocedural complications; rehospitalization (0.79%/month; CI: 0.55–1.13) and heart failure (0.48%/month; CI: 0.32–0.71) the most frequent late complications. The postoperative and late outcomes are described in Table 1.

Leave-one-out analysis of outcomes to test for heterogeneity did not show significant change of the results (Supplementary Figs. 2-12).

At funnel plot visual inspection and Egger test, 30-day mortality and late PM revision showed significant publication bias asymmetry. The newly calculated PER of 30-day mortality was 1.70% (95%CI: 0.95–3.03) and the newly calculated IR of late PM revision was 0.57 (95%CI: 0.25–1.29). Forest and funnel plots after Duval and Tweedie's trim and fill method are depicted in Supplementary Figs. 13-14.

Table 1
Postoperative outcomes.

Postoperative outcomes					
Outcome	No. of studies	Effect	95% CI	Heterogeneity: I^2, *p*-value	Egger test p-value
Malignant arrhythmia	16	2.50%	1.49–4.17	32.7%, $p = 0.1006$	0.0760
Cerebrovascular accident	9	0.63%	0.33–1.19	0%, $p = 0.9110$	Not enough studies
PM revision	5	1.21%	0.51–2.80	8.5%, $p = 0.3582$	Not enough studies
Perforation	7	0.81%	0.30–2.13	0%, $p = 0.8501$	Not enough studies
Tamponade	9	1.20%	0.61–2.34	0%, $p = 0.7985$	Not enough studies
Infection/endocarditis	7	0.75%	0.30–1.87	0%, $p = 0.9973$	Not enough studies
Lead dislodgment	12	2.02%	1.21–3.36	0%, $p = 0.8292$	0.3464
Vein thrombosis	4	0.59%	0.24–1.48	0%, $p = 0.9997$	Not enough studies
Pulmonary embolism	5	1.29%	0.56–2.95	0%, $p = 0.8598$	Not enough studies
Heart failure	6	2.49%	0.71–8.31	56.7%, $p = 0.0414$	Not enough studies
30-day mortality	17	1.08%	0.65–1.77	6.1%, $p = 0.3825$	0.0484
Late outcomes					
Overall mortality	72	0.43% / month	0.36–0.51	85.7%, $p < 0.0001$	0.1093
Cardiac death	63	0.27% / month	0.22–0.32	74.7%, $p < 0.0001$	0.1403
Cerebrovascular accident	23	0.09% / month	0.06–0.14	62.8%, $p < 0.0001$	0.8665
Ventricular fibrillation	9	0.03% / month	0.01–0.08	58.2%, $p = 0.0142$	Not enough studies
Infection/endocarditis	11	0.10% / month	0.05–0.21	60.3%, $p = 0.0051$	0.1151
Perforation	5	0.12% / month	0.03–0.52	62.3%, $p = 0.0313$	Not enough studies
Tamponade	7	0.09% / month	0.04–0.22	25.9%, $p = 0.2311$	Not enough studies
Lead dislodgment	15	0.16% / month	0.09–0.29	74.4%, $p < 0.0001$	0.9449
PM revision	12	0.13% / month	0.06–0.27	92.3%, $p < 0.0001$	0.0448
Heart failure	33	0.48% / month	0.32–0.71	92.7%, $p < 0.0001$	0.3273
Rehospitalization	23	0.79% / month	0.55–1.13	91.6%, $p < 0.0001$	0.1739
Pocket revision	6	0.06% / month	0.03–0.16	39.1%, $p = 0.1452$	Not enough studies
Ejection fraction, (%)	47	46.70	44.56–48.95	98.8%, $p < 0.0001$	0.0649
Left atrial diameter, (AP)	11	44.34	41.82–47.03	94.8%, $p < 0.0001$	0.3031

CI = Confidence interval; PM = Pacemaker.

3.2. Analysis of the randomized clinical trials

Non-randomized trials were included in the analysis, thus adding potential risk of bias. We therefore performed a selective analysis of late outcomes of the included RCTs. The RCT data are presented in Table 2.

3.3. Meta-regression

At univariable meta-regression preprocedural patients' characteristics didn't show any significant relation with 30-day mortality. Late mortality was significantly and directly associated with COPD ($p = 0.0149$) and CAD ($p < 0.0001$). Late cardiac death was significantly and directly associated with male sex ($p = 0.0054$), CAD ($p < 0.0001$), while it was significantly and inversely associated with mean age ($p = 0.0211$) and EF ($p = 0.0018$). Univariable meta-regression outcomes are summarized in Table 3.

The preprocedural patients' characteristics didn't show any significant relation with late mortality or late cardiac death at multivariable meta-regression. Multivariable meta-regression outcomes are summarized in Table 3.

At the generator subgroup univariable meta-regression, in the monoventricular pacing (RV) subgroup CAD was significantly and directly associated to late mortality and late cardiac death ($p < 0.0001$ and $p < 0.0001$, respectively). Mean age was significantly and inversely associated to late cardiac death ($p = 0.0092$), while mean EF was significantly and inversely associated to late mortality and late cardiac death ($p = 0.0054$ and $p = 0.0008$, respectively). In the biventricular pacing subgroup (CRT), hypertension was significantly and inversely associated to late cardiac death ($p = 0.0185$). Subgroup univariable meta-regression outcomes are summarized in Table 4.

At the sub-group multivariable meta-regression, CAD was significantly and directly associated to late mortality and late cardiac death ($p = 0.0152$ and $p = 0.0491$, respectively) in the monoventricular pacing (RV) sub-group. No further determinants for late mortality and late cardiac death were found in the biventricular pacing (CRT) sub-group multivariable meta-regression. Subgroup multivariable meta-regression outcomes are summarized in Table 4.

Table 2
RCT subgroup analysis of long-term outcomes.

Outcome	No. of studies	Effect	95% CI	Heterogeneity: I^2, p-value	Subgroup difference*, p-value
Overall mortality	17	0.67% / month	0.41–1.10	84.5%, $p < 0.01$	$p = 0.0362$
Cardiac death	15	0.39% / month	0.24–0.64	65.5%, $p < 0.01$	$p = 0.0645$
Cerebrovascular accident	9	0.15% / month	0.10–0.23	0%, $p = 0.57$	$p = 0.0642$
Ventricular fibrillation	3	0.03% / month	0.01–0.12	0%, $p = 0.75$	$p = 0.7669$
Infection/endocarditis	3	0.08% / month	0.02–0.37	22.4%, $p = 0.28$	$p = 0.6840$
Perforation	3	0.15% / month	0.02–0.97	65.3%, $p = 0.06$	$p = 0.7125$
Tamponade	3	0.07% / month	0.02–0.32	9.4%, $p = 0.33$	$p = 0.8897$
Lead dislodgment	4	0.26% / month	0.06–1.16	81.2%, $p < 0.01$	$p = 0.3687$
PM revision	2	0.16% / month	0.04–0.65	55.0%, $p = 0.14$	$p = 0.7819$
Heart failure	12	0.69% / month	0.42–1.15	86.6%, $p < 0.01$	$p = 0.1058$
Rehospitalization	12	0.97% / month	0.68–1.39	75.0%, $p < 0.01$	$p = 0.2867$

CI = Confidence interval; PM = Pacemaker.
* Compared to non-RCT included studies.

Table 3
Univariable and multivariable meta-regression analysis.

Univariable meta-regression						
	30-day mortality		Late mortality		Late cardiac death	
Outcome	Beta ± SE	p-value	Beta ± SE	p-value	Beta ± SE	p-value
Age (mean)	−0.0265 ± 0.0593	0.6552	−0.0128 ± 0.0198	0.5196	−0.0494 ± 0.0214	**0.0211**
Male sex	0.0331 ± 0.0375	0.3779	0.0085 ± 0.0050	0.0891	0.0165 ± 0.0059	**0.0054**
BMI (mean)	Not enough studies		0.0961 ± 0.1786	0.5905	−0.0585 ± 0.2672	0.8267
EF (mean)	−0.0262 ± 0.0296	0.3766	−0.0224 ± 0.0117	0.0544	−0.0433 ± 0.0139	**0.0018**
COPD (%)	0.0305 ± 0.0679	0.6528	0.0435 ± 0.0179	**0.0149**	0.0246 ± 0.0168	0.1433
Diabetes (%)	0.0204 ± 0.0814	0.8023	0.0045 ± 0.0182	0.8037	0.0054 ± 0.0212	0.7973
Hypertension (%)	−0.0183 ± 0.0149	0.2196	0.0050 ± 0.0050	0.3221	−0.0020 ± 0.0053	0.7054
Renal insufficiency (%)	Not enough studies		−0.0019 ± 0.0211	0.9293	0.0047 ± 0.0099	0.6332
Coronary artery disease (%)	−0.0065 ± 0.0286	0.8198	0.0341 ± 0.0070	**<0.0001**	0.0361 ± 0.0087	**<0.0001**
Multivariable meta-regression						
Age (mean)					−0.0369 ± 0.0341	0.2790
Male sex					0.0079 ± 0.0160	0.6187
EF (mean)					−0.0383 ± 0.0231	0.0974
COPD (%)			0.0295 ± 0.0198	0.1356		
Coronary artery disease (%)			0.0374 ± 0.0213	0.0788	0.0203 ± 0.0137	0.1386

BMI = Body mass index, COPD = Chronic obstructive pulmonary disease; EF = Ejection fraction.

Table 4
– Generator subgroup univariable and multivariable meta-regression analysis.

Right Ventricular pacing	Univariable meta-regression			
	Late mortality		Late cardiac death	
Outcome	Beta ± SE	p-value	Beta ± SE	p-value
Age (mean)	−0.0405 ± 0.0257	0.1159	−0.0709 ± 0.0272	**0.0092**
Male sex	0.0110 ± 0.0083	0.1826	0.0157 ± 0.0084	0.0611
EF (mean)	−0.0632 ± 0.0227	**0.0054**	−0.0833 ± 0.0249	**0.0008**
COPD (%)	0.0300 ± 0.0217	0.1664	0.0227 ± 0.0189	0.2296
Diabetes (%)	0.0275 ± 0.0276	0.3199	0.0380 ± 0.0332	0.2513
Hypertension (%)	0.0070 ± 0.0067	0.2980	0.0082 ± 0.0072	0.2516
Renal insufficiency (%)	−0.0153 ± 0.0583	0.7927	−0.0413 ± 0.0599	0.4905
Coronary artery disease (%)	0.0550 ± 0.0136	**<0.0001**	0.0540 ± 0.0130	**<0.0001**
	Multivariable meta-regression			
Age (mean)			−0.0552 ± 0.0420	0.1889
EF (mean)	−0.0475 ± 0.0290	0.1021	−0.0555 ± 0.0343	0.1055
Coronary artery disease (%)	0.0460 ± 0.0189	**0.0152**	0.0378 ± 0.0192	**0.0491**
Bi-Ventricular pacing				
	Late mortality		*Late cardiac death*	
Outcome	Beta ± SE	p-value	Beta ± SE	p-value
Age (mean)	0.0619 ± 0.0676	0.3596	0.0731 ± 0.1200	0.5423
Male sex	−0.0242 ± 0.0159	0.1273	−0.0125 ± 0.0189	0.5095
EF (mean)	0.0329 ± 0.0226	0.1466	0.0061 ± 0.0309	0.8446
COPD (%)	−0.0095 ± 0.1537	0.9506	0.0343 ± 0.1383	0.8042
Diabetes (%)	−0.0065 ± 0.0336	0.8459	−0.0010 ± 0.1141	0.9930
Hypertension (%)	−0.0011 ± 0.0151	0.9399	−0.0234 ± 0.0099	**0.0185**
Renal insufficiency (%)	−0.0249 ± 0.0296	0.4002	Not enough studies	
Coronary artery disease (%)	−0.0096 ± 0.0155	0.5372	−0.0053 ± 0.0262	0.8390

4. Discussion

Our metanalysis of the present literature on the topic AVNA and pace has brought the following results: 1) Long-term follow-up data of ablate and pace to treat atrial fibrillation are lacking; 2) AVNA and pace still carries a not trivial burden of early and late complications; 3) Age and LVEF are inversely related to follow-up mortality; 4) CRT reduces late cardiac mortality and adds higher costs and procedural complexity.

In patients unresponsive or intolerant to intensive ventricular rate and rhythm control therapy, AVNA has been widely used to control heart rate improving quality of life by reducing symptoms and optimizing functional class [3]. The procedure, consisting of two steps (AVNA and RV-PM or CRT implantation), involves non-negligible risks in the periprocedural phase and at follow-up.

The primary goal of the present meta-analysis was to outline the estimated risks for morbidity and mortality after AVNA and pace. Malignant arrhythmias, heart failure, and lead dislodgement are among the most common complications in the periprocedural period, and rehospitalization and heart failure are the most frequent late complications. Almost no study included in our analysis has described the lead-induced tricuspid regurgitation, which is a well-known complication after RV lead placement [9]. Therefore, we cannot draw conclusions regarding this topic of potentially crucial importance.

Complications arising after AVNA and pace represent a significant burden for the patient's quality of life and the healthcare system, generating substantial additional costs. Although, to the best of our knowledge, no study has explicitly focused on the long-term economic impact of AVNA and pace, two recent European studies have investigated the complications and associated healthcare costs after transvenous permanent pacemaker implantation in France [10] and Germany [11]. They have prospected an average additional cost at three years of around €6600 and €4600 respectively to manage the cardiac electronic devices. Besides these implantable cardiac electronic device-related costs, medical expenses and rehospitalization costs may add up in those patients who develop heart failure symptoms [12].

The secondary goal of our study was to identify potential determinants for mortality (overall and cardiac) after AVNA and pace. The overall univariable meta-regression shows that age ($p = 0.0211$) and EF ($p = 0.0018$) are inversely associated to late cardiac death, meaning that younger patients and patients with reduced EF will have higher cardiac mortality rates after AVNA and pace. Our subgroup meta-regression underscores the importance of the pacing modality (RV versus CRT). Mainly in patients managed with RV PM, but not in those implanted

with CRT, age ($p = 0.0092$) and EF ($p = 0.0008$) are inversely related to late cardiac death, and CAD is directly related to late overall and cardiac death. These findings are in line with current guidelines on AF management [3] recommending the AVNA in elderly patients rather than in younger ones, and in line with guidelines on cardiac pacing [13] recommending CRT pacing in patients with reduced EF, who are candidates for AVNA, as biventricular pacing may reduce re-hospitalization rate and improve quality of life. In this context, the APAF-CRT trial has recently confirmed a drastic reduction in mortality at long-term follow-up in patients with HF and narrow QRS interval managed with AVNA and CRT, regardless of LVEF [14].

Our findings confirm that elderly patients will possibly not experience the long-term detrimental effects of RV pacing [15], as they will be exposed to it for a shorter period. In these patients, AVNA, with or without CRT, could be a reasonable option. Future studies should clarify the pros and cons of implanting a CRT after AVNA in elderly patients with already impaired LVEF%.

On the other hand, in younger patients, chronic non-physiologic RV pacing will lead to prolonged ventricular dyssynchrony that may result in HF. Consequently, implanting a CRT instead of a single RV lead will possibly improve the outcome but make the procedure more cumbersome and the budgetary burden much heavier. Furthermore, in younger patients, cardiac electronic device maintenance will be more demanding, including a higher number of battery changes through the patient lifespan and a long time of exposure to possible occurrences related to the presence of 2/3 leads within the cardiac chambers [16], like for example leads displacement and infection. These events could be underestimated in our meta-analysis, that represents the *status quo* of the scientific evidence at the present stage. It needs to be underlined that the pooled median follow-up duration was slightly longer than one year and, for this reason, there is not enough evidence to support AVNA and PM in younger patients with an extended life expectancy (Graphical abstract).

A previous meta-analysis by Wood et al. [17] evaluated quality of life after AVNA and PM. In their analysis the 30-day and 1-year mortality was 1.4% (95% CI: 0.04%–2.4%) and 6.5% (95% CI: 5.5%–7.2%), respectively. A more recent meta-analysis by Chatterjee et al. [18] focused on comparing AVNA and PM versus medical therapy, particularly quality of life after treatment. The 30-day complications rate was low, with a malignant arrhythmia rate of 0.57% and 30-day mortality below 1%. Finally, there was no specific reference to longer follow-up mortality and morbidity and determinants of outcome [18].

After discussing the limitations of AVNA and pace, some alternatives to manage patients' subgroups should be proposed and investigated in the future, possibly within the framework of prospective randomized studies. According to current guidelines, thoracoscopic procedures - including hybrid surgical ablation - should be considered (class IIa, level B) in patients who have symptomatic paroxysmal or persistent AF refractory to medical therapy and have already failed percutaneous AF ablation [3,19,20]. In this context, epicardial surgical close-chest AF ablation (with/without left atrial appendage [LAA] occlusion [21] or as a hybrid approach with epi- and *endo*-cardial ablations) should be kept into consideration before unselectively performing AVNA in all patients unresponsive to maximal medical treatment and multiple percutaneous ablations. A minimally invasive surgical approach could result particularly interesting in patients that have experienced multiple failed percutaneous ablations, and would be supported by present guidelines, as stated above. The thoracoscopic approach could allow, in addition to the pulmonary veins' isolation and during the same surgical session, the creation of a posterior left atrial box lesion, and the exclusion of the LAA.

Two recent prospective randomized trials, the CASA-AF [22] and the FAST trial [23], have compared percutaneous AF ablation with the thoracoscopic surgical approach. Although in the 12-month follow-up there seems to be no difference in freedom from AF recurrence [22], longer-term follow-up (7 years) confirms that the thoracoscopic approach allows for more consistent maintenance of sinus rhythm, with similar long-term clinical event rates [23]. A recent meta-analysis of randomized controlled studies [24] has shown that the thoracoscopic surgical approach is associated with better efficacy but a higher peri-procedural severe adverse events rate than percutaneous AF ablation. Currently, no studies have compared AVNA to the thoracoscopic surgical approach, and conclusions can only be drawn from a separate analysis of the two techniques.

There is a rationale for considering thoracoscopic AF ablation as an intermediate step before AVNA and pace. As already shown in our results, the deleterious effects of long-term RV stimulation can occur more often in younger patients that may also require a higher number of generator changes for battery exhaustion and are also exposed, for a longer time, to the risk of lead displacement and infection. In these patients, a successful attempt at surgical ablation may prevent the patient from becoming PM dependent, minimize future reoperations, and not preclude future therapeutic opportunities in the case of ablation failure. Additionally, it should be underlined that AVNA does not restore sinus rhythm. In this context, a successful surgical ablation strategy with sinus rhythm recovery would particularly benefit heart failure patients with reduced LVEF%, as recently demonstrated in the CASTLE-AF trial [25]. Furthermore, AF is associated with an increased risk of thromboembolic complications in patients with an implanted pacemaker and should be managed with strict oral anticoagulation therapy (OAT). Minimally invasive surgical ablation, leading to sinus rhythm recovery and LAA exclusion, would support OAT reduction in patients with low risk for cerebrovascular accident [3].

Future studies should also evaluate the costs of AVNA and pacing, followed by generator replacement for battery exhaustion, and compare them against the costs of epicardial surgical ablation with LAA exclusion. The technological and technical improvements of catheter ablation achieved over the years are highly impressive. The continuous implementation of new technologies has certainly contributed to make the ablation procedure faster, more effective, and most importantly also safer.

Finally, it should be emphasized that almost 70% of the AVNA and pace analyzed and presented studies are retrospective and, for this reason, should serve to generate hypotheses for further prospective investigations rather than to guide our future clinical decisions. Moreover, in the last few years, there have been tremendous technological advances in AF catheter ablation (i.e., contact force, high power, short duration ablation, and pulsed-field ablation), including technologies that are still evolving in their daily clinical application, such as conduction system pacing, and that will hopefully improve the safety and efficacy of percutaneous treatment of AF, and eventual cardiac stimulation after AVNA [26,27]. These advancements have primarily not been included in the presented studies, and future investigations led by multidisciplinary teams should evaluate, possibly in a prospective randomized fashion, the clinical and economic impact of alternative approaches for selected AF patients unresponsive to the most modern percutaneous and pharmacological management.

4.1. Conclusion

As emerging in the present meta-analysis, long-term follow-up data of AVNA and PM to treat AF are lacking. Therefore, although AVNA-pace has been considered a valid approach in highly symptomatic AF patients unresponsive or intolerant to conventional treatment, its application should be tailored to specific subgroups of patients. AVNA-pace carries a not trivial burden of early and late complications, mainly when applied to younger patients and patients with borderline or reduced LVEF%, whenever simple RV PM is used. Better outcomes are possible if a CRT is implanted instead of a sole RV lead, with additional technical and economic burdens. Results of conduction system pacing after AVNA are promising but still limited and lacking long-term verification. In any case, a cardiac electronic device with one or more endocardial leads will increase the risk of endocarditis, thrombosis,

cardiac chamber perforation with possible tamponade, tricuspid regurgitation and, in younger patients with an extended lifespan, will require multiple battery changes, with additional clinical and budgetary costs.

In particular, in younger patients with refractory symptoms, AF thoracoscopic ablation with LAA closure should be discussed after failed percutaneous ablation with the most modern percutaneous protocols and before AVNA and PM, as per guidelines [3,19] and expert consensus [20].

Availability of data and material

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Author contribution

Massimo Baudo: Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Data curation, Writing - original draft, Writing - review & editing, Visualization, Project administration; **Giuseppe D'Ancona**: Conceptualization, Validation, Writing - original draft, Writing - review & editing, Supervision, Project administration; **Francesco Trinca**: Investigation, Data curation, Visualization; **Fabrizio Rosati**: Investigation, Data curation, Visualization; **Lorenzo Di Bacco**: Formal analysis, Investigation, Data curation; **Antonio Curnis**: Writing - review & editing, Supervision; **Claudio Muneretto**: Resources, Writing review and editing, Supervision; **Marco Metra**: Writing review and editing, Supervision; **Stefano Benussi**: Conceptualization, Resources, Writing - original draft, Writing - review & editing, Supervision, Project administration.

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Declaration of Competing Interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2022.06.058.

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