Atrioventricular Nodal Ablation in Atrial Fibrillation: A Meta-analysis and Systematic Review

Running title: Chatterjee et al.; AV Nodal Ablation: Meta-analysis and Systematic Review

Neal A. Chatterjee MD¹; Gaurav A. Upadhyay MD¹; Kenneth A. Ellenbogen MD²;
Finlay A. McAlister, MD, MSc³; Niteesh K. Choudhry MD, PhD⁴; Jagmeet P. Singh MD, DPhil¹

¹Dept of Med and the Cardiac Arrhythmia Service, Massachusetts General Hospital, Boston, MA; ²Division of Cardiology, Virginia Commonwealth University School of Med, Richmond, VA; ³Division of Internal Med, University of Alberta Hospital, Edmonton, Canada; ⁴Dept of Medicine, Brigham & Women’s Hospital, Harvard Med School, Boston, MA

Address for Correspondence:
Jagmeet Singh MD, DPhil
Associate Professor of Medicine
Cardiac Arrhythmia Service, GRB 109
Massachusetts General Hospital Heart Center
55 Fruit Street, Boston MA 02411
Tel. (617) 726-4662
Fax (617)-726-3850
E-mail: jsingh@partners.org

Abstract:

**Background** - In the treatment of patients with refractory atrial fibrillation (AF), the safety and efficacy of atrioventricular nodal ablation (AVNA) versus pharmacotherapy alone remains unclear. Additionally, the impact of AVNA in patients with reduced systolic function is of growing interest.

**Methods and Results** - A total of 5 randomized or prospective trials were included for efficacy review (314 patients), 11 studies for effectiveness review (810 patients), and 47 studies for safety review (5,632 patients). All-cause mortality was similar between AVNA and medical therapy (3.1% vs. 3.3%, relative risk ratio: 1.05, 95% confidence interval [CI]: 0.29 to 3.85). There was no significant difference in exercise duration or ejection fraction (EF) with AVNA relative to pharmacotherapy. In subgroup analysis, patients with baseline systolic dysfunction (116 patients; mean EF 44%) showed significant relative improvement in EF following AVNA (+4% greater, 95% CI: 3.11 to 4.89). In pooled observational analysis, AVNA was also associated with significant improvement in EF only in patients with systolic dysfunction (+7.44%, 95% CI: 5.4 to 9.5). The incidence of procedure-related mortality (0.27%) and malignant arrhythmia (0.57%) was low. At mean follow-up of 26.5 months, the incidence of sudden cardiac death (SCD) following AVNA was 2.1%. There was significant heterogeneity in quality of life scales utilized; compared to pharmacotherapy, AVNA was associated with significant improvement in several symptoms (palpitations, dyspnea).

**Conclusions** - In the management of refractory AF, AVNA is associated with improvement in symptoms and quality of life, with a low incidence of procedure morbidity. In patients with reduced systolic function, AVNA demonstrates small but significantly improved echocardiographic outcomes relative to medical therapy alone.

**Key words:** atrioventricular node, ablation, pacing, fibrillation, meta-analysis
Atrial fibrillation (AF) and heart failure (HF) have been characterized as two major epidemics of contemporary cardiovascular medicine. AF, the most common clinically significant arrhythmia, affects approximately 2.2 million patients in the United States alone, while HF prevalence is estimated at 5.3 million. AF and HF are inextricably linked, as both share common risk factors and each increases the risk of the other. The prevalence of AF increases with HF severity, ranging from < 5% in functional class I patients compared to approximately 50% in class IV patients. Inversely, the life-time prevalence of HF in AF has been estimated at 42%.

Several randomized trials in AF, including those exclusive to patients with left ventricular systolic dysfunction (LVSD), have shown similar efficacy with rate versus rhythm control strategies. And though pharmacotherapy remains the first-line approach for effective rate control, ablation of the AV node with subsequent pacing is an important therapeutic option for patients with symptoms refractory to pharmacotherapy. Compared to pharmacologic therapy alone, the so-called ‘ablate and pace’ approach offers the potential for more robust control of ventricular rate as well as regularization of the R-R interval. Given the relationship between AF and HF, there may be particular benefit of such rate and interval control in patients with AF and reduced systolic function. Indeed, several observational and retrospective studies illustrate symptomatic, echocardiographic, and functional benefit following AVNA in patients with AF and LVSD.

Since comparative data are limited, we performed a meta-analysis to evaluate the efficacy of AVNA versus pharmacotherapy in patients with refractory atrial fibrillation, including subset analysis comparing patients with reduced versus normal systolic function. Additionally, we assessed the effectiveness of AVNA using pooled outcomes from observational studies, and also present a systematic review of safety outcomes from both randomized and observational data.
Methods

Search strategy We performed an electronic literature search of MEDLINE (1948 to June 2011), MEDLINE In-Process & Other Non-Indexed Citations, Cumulative Index to Nursing & Allied Health Literature, the Cochrane Database of Systematic Reviews (Fourth Quarter, 2010), the American College of Physicians Journal Club (1991 to January 2011), Database of Abstracts of Reviews of Effects, and the Cochrane Central Register of Controlled Trials. Search terms included atrial fibrillation, heart failure, ablation, and atrioventricular. The search strategy was not exclusive to patients with heart failure (see Appendix). We also hand searched the bibliographies of all review articles discussing atrial fibrillation and AVNA, published in the last 10 years.

For efficacy analysis, we included published data from randomized controlled trials (RCTs) or prospective, cohort studies with contemporaneous controls, comparing AVNA with right ventricular (RV)-only pacing versus pharmacotherapy. For effectiveness analysis we included published data from observational prospective or retrospective cohort studies; single-arm studies were included for particular end-points. For safety analysis we included randomized, prospective, and retrospective studies. We selected studies reporting mortality (all-cause and/or sudden cardiac death), adverse outcomes, echocardiographic data (e.g., ejection fraction), and/or functional outcomes (e.g., exercise stress duration, quality of life [QOL]). Arrhythmia inclusion criteria included atrial fibrillation, atrial flutter, or atrial tachycardia. Pacing inclusion criteria was RV-pacing. Reports that included heterogeneous ablation procedures (e.g. AV node modification) were excluded, as were studies with N < 20 who underwent AVNA, non-radiofrequency ablation methods (e.g. direct current), studies with heterogeneous arrhythmias (e.g. incessant sinus tachycardias, AV nodal re-entry tachycardias), studies only examining
biventricular pacing in AF with AVNA, and studies that did not represent original research data (e.g., letters, commentaries, reviews, or study design articles). Studies < 2 weeks in duration were excluded from consideration for efficacy and effectiveness analyses, but were included in safety analysis.

**Data extraction** Two investigators (N.A.C. and G.A.U.) independently extracted data on patient and study characteristics, outcomes, and study quality for each trial using a standardized protocol and reporting form. The PRISMA and MOOSE checklists were utilized for extraction of randomized controlled and observational data, respectively. Quality assessment was performed using the Jadad scale\(^\text{18}\) for randomized controlled trials and the Downs and Black checklist\(^\text{19}\) for observational studies. Disagreements were resolved by consensus.

**Data analysis** We calculated relative risks for dichotomous outcomes (e.g., mortality) using the Mantel-Haenszel random-effects model in Review Manager 5.1 (The Cochrane Collaboration, Copenhagen, Denmark). For continuous outcomes, weighted mean differences (WMD) were calculated using an inverse variance random effects model. Heterogeneity was quantified using the \(I^2\) statistic (a value of 0% indicates minimal heterogeneity).\(^\text{20}\) Study N was taken from end of protocol N to generate maximally conservative estimates of effect size. One study\(^\text{21}\) used a cross-over design with two pacing modes (DDD, VVIR). Only the VVIR group was utilized to ensure comparability across studies. For efficacy analysis, subgroup analysis was performed with studies comprised of patients with reduced systolic function. Effectiveness analysis included studies reporting all-cause mortality, echocardiographic, and functional outcomes. Single-armed studies were included for the echocardiographic and functional endpoints, but not for the all-cause mortality endpoint given that interpretation of a pooled mortality rate without contemporaneous controls was not felt to be meaningful. For safety analysis, adverse events
included sudden cardiac death (SCD), procedure-related mortality, and procedure-morbidity. Mortality and morbidity were attributed to the procedure if they occurred within 30 days of AVNA, with the exception of “lead failure” which was not time delimited. Sudden cardiac death within the first 30 days was characterized as a procedure-related mortality. An overall sudden cardiac death rate (occurring any time after AVNA) was also tabulated. 95% confidence intervals (CIs) are reported for all results.

Results

Search results The initial search yielded 2,659 results, of which (i) 5 met our inclusion criteria for efficacy analysis of AVNA and pharmacotherapy,21-25 (ii) 11 met inclusion criteria for effectiveness analysis,12, 16, 17, 26-33 and (iii) 47 met inclusion criteria for safety analysis (Figure 1, Appendix Table 1).11, 12, 14, 16, 17, 21-62 The studies comparing AVNA and pharmacotherapy included 314 patients, of whom 161 underwent AVNA and 153 received pharmacotherapy. Weighted mean follow-up was 10 months (range 6-12 months). Baseline characteristics, including weighted means and variances for each subgroup, are summarized in Table 1. Two of the efficacy studies (N=116)23, 24 were comprised of patients with reduced systolic function (weighted mean EF 44±4%). Prevalence of ACE-inhibitor use in these 2 studies was 75% and 72% in the ablation and pharmacotherapy groups, respectively. Beta-blocker use was not consistently documented. Of the other 3 efficacy studies, two22, 25 reported a mean EF (weighted mean EF 57±4%) and the authors of the third21 stated that the “majority had normal LV function at the outset”.

Four of the five efficacy studies comparing AVNA to pharmacotherapy were randomized.21-23, 25 Inclusion criteria included paroxysmal or persistent AF in 4 of 5 studies21-24
and permanent AF in one study. All studies mandated cessation of anti-arrhythmic therapy following AVNA unless medications were for a non-AF indication. Medications used in the pharmacotherapy arm were documented in 4 of 5 studies. One study allowed use of nodal agents (beta-blockade, calcium channel blockers) as well as digoxin (not explicitly quantified). Of the remaining 3 studies (pharmacotherapy subgroup N=66), most patients received anti-arrhythmics (Class I: 65%, Class III: 49%) or digoxin (47%), with a minority receiving nodal agents (beta-blockade, calcium channel blockers: 23%). All efficacy studies included a significant minority of patients with structural heart disease (Table 1), with the exception of one in which lone AF was amongst the inclusion criteria. Pacing mode differed amongst the efficacy studies: 3 of 5 used rate-adaptive VVI pacing, one used atrial-synchronous sequential pacing (DDD), and one used a cross-over strategy with both VVIR and DDR in the ablation subgroup.

Baseline characteristics for the studies included in the effectiveness and safety analyses are described in full in Appendix Table 1. Summary demographics include mean age 66±4 years, with slightly more men (58%) and a minority with ischemic heart disease (26%). Of studies reporting EF, mean was 47±8%.

**Efficacy of AV Nodal Ablation** Only two of the 5 studies comparing AVNA and pharmacotherapy had deaths during the study period; there were 10 deaths (5 AVNA; 5 pharmacotherapy) at weighted mean follow-up of 9.8 months, and all deaths occurred at least one month after AVNA or study onset (for pharmacotherapy arm). The relative risk of death was not significantly different between AVNA and pharmacotherapy (risk ratio: 1.05, 95% CI:
0.29 to 3.85), though overall numbers were low. Sudden cardiac death (SCD) accounted for 60% (3/5) of deaths in the AVNA arm and 100% (5/5) deaths in the pharmacotherapy arm.

All five studies comparing AVNA to pharmacotherapy reported changes in tolerance during exercise testing. Three studies used a treadmill test (modified Bruce protocol,\textsuperscript{24,25} and chronotropic assessment exercise protocol\textsuperscript{21}) and two used bicycle stress (linear incremental work protocol).\textsuperscript{22,23} Both ablation and pharmacotherapy groups showed modest improvement over the study period. There was an insignificant greater relative improvement in patients undergoing ablation, exercising 0.21 minutes (min) longer (95% CI: -0.70 to 1.1) with substantial heterogeneity amongst studies ($I^2=97\%$). Analysis of studies comprised of patients with reduced EF\textsuperscript{23,24} versus normal EF\textsuperscript{21,22,25} showed no difference between patients with reduced systolic function (0.40 min longer, 95% CI: -1.1 to 1.9) and patients with normal systolic function (-0.02 min longer, 95% CI: -0.62 to 0.57). There was no interaction between outcome and type of protocol utilized (treadmill vs. bicycle).

Four studies comparing AVNA to pharmacotherapy reported changes in EF during the study period.\textsuperscript{22-25} In all patients, ablation was associated with an insignificant minimal relative increase in EF (+1.0\% greater, 95\% CI: -3.7 to 5.7), with significant heterogeneity amongst studies ($I^2=97\%$). In the two studies with reduced systolic function (weighted mean EF 44±4\%), there was a modest but significant relative increase in EF following AVNA (+4\%, 95\% CI: 3.1 to 4.9) (Figure 2A), with minimal heterogeneity amongst studies ($I^2=0\%$). In contrast, efficacy studies involving patients with normal EF showed no significant relative change in EF (-2.07\%, 95\% CI: -8.0 to 3.8) and substantial heterogeneity ($I^2=95\%$) (Figure 2B).
Effectiveness of AV Nodal Ablation  Prospective single-armed studies or any retrospective studies reporting all-cause mortality, echocardiographic, and/or functional outcomes were included in the effectiveness review. Only one study (350 patients)\textsuperscript{33} included contemporaneous controls and was therefore formally included in the mortality endpoint of the effectiveness review. Similar to the analysis of RCTs, there was no difference in survival between AVNA and matched controls. In a retrospective analysis comparing AVNA versus pharmacotherapy, Ozcan and colleagues\textsuperscript{33} found no difference in mortality at a mean follow-up of 36±26 months (risk ratio for AVNA versus pharmacotherapy was 1.14, 95% CI: 0.81 to 1.60).

Observational studies reporting changes in exercise duration (study N=5; 191 patients) showed a mean increase of 1.19 minutes (95% CI: 0.52 to 1.86) following AVNA, at mean follow-up of 8.7 months (range 1-12) (Appendix Figure 1).\textsuperscript{17,26,29,30,32} Observational studies reporting change in EF (study N=10; 389 patients) showed a mean increase of 4.80% (95% CI: 2.01 to 7.58) following AVNA (weighted mean baseline EF 43%, range 26 to 53%) at a mean follow-up of 13.3 months (range 1-58).\textsuperscript{12,14,16,17,27-32} There was significant heterogeneity across studies (I\textsuperscript{2}=78%). When stratified by EF, studies with EF < 45% (study N=5; 196 patients, weighted mean EF 35%)\textsuperscript{14,16,17,30,32} showed a significant increase in EF following AVNA (+7.44%, 95% CI: 5.4 to 9.5) with minimal heterogeneity (I\textsuperscript{2}=0%) (Figure 2C). In contrast, studies with EF > 45% (study N=5; 272 patients, weighted mean EF 47%)\textsuperscript{12,27-29,31} showed no significant change in EF (+1.94%, 95% CI: -2.9 to 6.8%) with substantial heterogeneity (I\textsuperscript{2}=88%) (Figure 2D).

Safety of AV Nodal Ablation  Studies reporting procedural death, procedure morbidity, or sudden cardiac death were included in safety analysis. Thirty-seven studies reported SCD
with an overall incidence of 2.1% (range 0-11.3%) at a weighted mean follow-up of 26.5 months (range 1-46). Forty-two studies (N=4886) reported procedural mortality and/or morbidity. Most common was the need for left-sided approach after a failed right-sided ablation (6.9%), followed by the need for re-do procedures after spontaneous recurrence of AV nodal conduction (2.9%). Other notable procedure-specific morbidities included malignant arrhythmia (sustained VT or VF occurring within 30 days of AVNA; 0.57%), lead failure (0.23%), stroke (0.19%), and hematoma (0.70%) (Table 2). The incidence of procedure-related death, defined as death within 30 days of AVNA, was low (0.27%). Of the total 12 deaths recorded, 5 were reported in a single study in which the post-procedure pacing rate was less than 70 beats per minute (bpm). Post-procedure pacing rate was inconsistently recorded for several studies, though the majority reported rates greater than 70 bpm with several studies mandating an initial pacing rate of 80 bpm for at least 7 days. Other reported complications included infection, pleural effusion, pericarditis, pseudoaneurysm, RV perforation, and pneumothorax (total incidence 1.1%). In studies comparing AVNA to pharmacotherapy, there was significant heterogeneity in documentation of pharmacotherapy-related adverse events, with only one study documenting medication side effect, two documenting incidence of MI/stroke, and three recording episodes of HF/hospitalization.

**Quality of Life.** All five studies in the efficacy analysis found significant relative improvement for particular symptoms with AVNA compared to pharmacotherapy alone. Specific QOL and symptom scales utilized across efficacy studies are summarized in Appendix Figure 2. With respect to QOL, 4 of 5 efficacy studies found significant absolute improvement with AVNA.
compared to baseline, although only 3 of 5\textsuperscript{23-25} documented significant relative improvement when compared with pharmacotherapy alone (see Appendix Figure 2 with p-values for comparison). Although there was significant heterogeneity in the symptom scale utilized, there was overlap in particular symptoms surveyed. One efficacy study\textsuperscript{25} did not explicitly document specific symptoms. Of the remaining 4 efficacy studies, there was absolute significant improvement following AVNA in palpitations (4/4 studies), effort dyspnea (3/4 studies), and easy fatigue (2/3 studies), with less consistently documented absolute improvement in chest discomfort and rest dyspnea (2/4 studies each). When compared relatively to pharmacotherapy, AVNA was associated with significant improvement in palpitations (4/4 studies), effort dyspnea (3/4 studies), and easy fatigue (3/3 studies), but non-significant relative improvement in rest dyspnea (0/4 studies) and chest discomfort (1/4 studies).

Of 11 observational studies documenting QOL,\textsuperscript{11, 12, 16, 17, 29-32, 37, 54, 57} all showed statistically significant improvement of QOL and symptoms following AVNA, though none included a contemporaneous control group. There was significant heterogeneity in QOL scales utilized in observational studies which limited summative analysis.

**Discussion**

Our findings suggest that in patients with refractory atrial fibrillation, AVNA is associated with modest but non-significant improvement in functional and echocardiographic outcomes, and a significant improvement in symptoms and quality of life when compared to pharmacotherapy alone. In a subset analysis of patients with reduced systolic function, improvement in left ventricular ejection fraction after AVNA, relative to pharmacotherapy alone, did reach significance. There have been too few deaths reported (N=10) to draw conclusions
regarding the effect of AVNA versus pharmacotherapy on mortality. In safety analysis, we found a relatively common incidence of the need for redo procedures or an alternative ablation approach, although the risk of serious adverse events, including malignant arrhythmia and procedure-related death, was small.

To date, there are two reported meta-analyses of ablate and pace therapy in AF.\textsuperscript{63, 64} The report from Wood and colleagues acknowledges the inclusion of a heterogeneous mixture of non-randomized, randomized, and single-arm studies comprised of patients with both normal and reduced systolic function.\textsuperscript{64} The second report\textsuperscript{63} includes two studies\textsuperscript{36, 65} without a true pharmacotherapy-only control group. Our systemic review contributes to the evidence base by selecting a more homogenous and larger set of studies for both efficacy and safety analyses, as well as providing stratified analysis according to baseline systolic function.

The only retrospective comparison of survival in AF with LVSD found no significant difference in survival between AVNA and pharmacotherapy over a mean follow-up of 3.5 years.\textsuperscript{33} Nevertheless, retrospective analysis from the same authors found worse survival with AVNA for patients with LVEF < 40% compared to those with EF >40\%,\textsuperscript{14} and others have found the presence of systolic dysfunction and fractional shortening < 20\% to be independent predictors of mortality following AVNA.\textsuperscript{61} There is a clear need for randomized data assessing the impact of AVNA (RV or BiV pacing) versus pharmacotherapy on survival in the AF population with left ventricular systolic dysfunction.

In addition to overall survival, others have raised concern regarding the incidence of sudden cardiac death (SCD) following AVNA.\textsuperscript{40, 42} Proposed mechanisms include exaggerated repolarization abnormalities following heart rate control in patients with prior tachycardia\textsuperscript{66} and absence of an escape rhythm in the event of pacemaker failure.\textsuperscript{49, 67} The reported incidence of
SCD following AVNA has ranged between 1 and 11% in retrospective studies, with LVEF < 45%, coronary artery disease, and structural heart disease identified as independent risk factors. Of note, studies finding independent associations between systolic dysfunction and SCD were published prior to the standard use of implantable cardioverter-defibrillator as primary prophylaxis in this population. Similar to the incidence of SCD reported in the last systematic review of AVNA in AF (2.0%), our safety analysis found an overall SCD incidence of 2.1% at mean follow-up of 29.8 months. Exploratory analysis did not find any basic correlation between publication year and SCD rate. As a general comparison, the reported incidence of SCD in patients with atrial fibrillation receiving pharmacotherapy has ranged 3.1-3.8% in trials with similar duration of follow-up, including RACE (mean follow-up 27.6 months) and AFFIRM (mean follow-up 42 months).

A primary concern regarding AVNA has been the risk of procedure-related adverse events. We found a very low incidence of procedure-related death (0.27%) and malignant arrhythmia (0.57%). Indeed, given prior data suggesting that post-ablation pacing rate reduces the incidence of malignant arrhythmia and death, it is notable that nearly half of the documented procedure-related deaths (5 of 12) occurred with a post-procedure pacing rate of less than 70 bpm. The need for a left-sided approach after a failed right-sided ablation was relatively common (6.9%), as was the incidence of redo procedures (2.9%). Other significant procedure morbidities, including stroke, other thrombosis, and lead failure were rare (< 1%). As a reference, recent analysis of recipients undergoing defibrillator implantation noted an adverse event rate of 6.8% over 30 days post-procedure, including pocket hematoma (1.2%), hemothorax/pneumothorax (0.9%), and lead failure (2.2%). Documentation of medication-related adverse events was non-uniform and often not recorded in the randomized studies.
selected. As a reference, adverse events requiring cessation of therapy in the rate and rhythm control arms of the AFFIRM trial was > 30% over mean follow-up of 3.5 years, with significant cardiac, pulmonary, and GI toxicities ranging between 2.4 and 5%.\textsuperscript{8}

We found that compared to pharmacotherapy alone, AVNA was associated with a modest but statistically significant improvement in EF for patients with reduced systolic function\textsuperscript{23, 24} (+4% greater, 95% CI: 3.11 to 4.89). Pooled observational data analyzed here showed a similar association between AVNA and echocardiographic benefit in patients with systolic dysfunction, but not for patients with normal systolic function. Although our prospective findings are similar to prior observational data,\textsuperscript{11-17} interpretation of this improvement has several caveats. First, the comparative data in patients with systolic dysfunction reflect the summation of two prospective studies, one of which was non-randomized. A disproportionate percentage of the benefit in the efficacy subgroup analysis for reduced EF was derived from the non-randomized study. Second, the cardiac substrate of patients in these two studies was different; one study\textsuperscript{24} included patients with no known ischemic heart disease, whereas a significant minority of patients in the second study (38%) had ischemic heart disease.\textsuperscript{23} Third, given the influence of RV lead position on LV function in AF patients undergoing AVNA,\textsuperscript{72} the lack of data regarding RV lead location in these studies may represent an unaccounted confounding variable. Fourth, echocardiographic comparisons across studies would optimally be in the setting of a uniform, paced rate; pacemaker settings during echocardiographic follow-up were not documented in the majority of studies selected.

The optimal management of patients with refractory atrial fibrillation, and in particular those with concurrent systolic dysfunction, remains an important open question. The largest prospective study of AF with LVSD found similar benefit between pharmacologic rate versus
rhythm control,9 although a small, prospective study73 found superiority with catheter-based rhythm control (pulmonary vein isolation, PVI) compared with device-based rate control (AVNA) in AF with LV systolic dysfunction.

Taken together, available data suggest either AVNA or pharmacotherapy alone is reasonable in the treatment of refractory AF, and that there may be a modest benefit for AVNA in a subset of AF patients with systolic heart failure. These results should be interpreted cautiously, however, as particular subsets of patients with AF who may be detrimentally affected by AVNA and chronic right ventricular pacing, including those with severe mitral or tricuspid regurgitation, pulmonary hypertension, or underlying RV dysfunction, were not identified separately for comparison.17 This analysis does not address the relative benefit of different non-pharmacologic therapies for AF, including pulmonary vein isolation versus AVNA. Also not addressed by these studies is the relative impact of RV vs. BiV pacing in the AF population undergoing AVNA.36,74 On-going studies, including CASTLE-AF75 (PVI vs. pharmacotherapy), will further define the role of non-pharmacologic therapy for the growing population of patients with atrial fibrillation and systolic dysfunction.

**Limitations** These analyses have several limitations, many of which have been discussed. With respect to the efficacy analysis, several outcomes (e.g. pacing parameters during echocardiographic follow-up, exercise stress protocols) were non-standardized across studies, limiting the validity of combining them in a meta-analysis. This lack of standardization is reflected in the heterogeneity for particular outcomes (e.g. mean change in exercise stress duration). In addition, given the limited number of total studies and their small sample sizes, the power of summative calculations is limited for outcomes such as mortality. Third, lack of
consistent documentation of heart failure therapeutics, particularly in older observational studies, represents a potential confounder in the interpretation of echocardiographic benefit associated with AVNA. Finally, one of the studies included in the efficacy analysis was non-randomized.

With respect to safety analyses, because studies that did not document survival were excluded from analysis and studies recording no deaths were included, there may be a bias towards underestimating the incidence of SCD. In addition, several studies did not document complications in a systematic manner and we may therefore be underestimating the overall incidence of procedure-related morbidity. Finally, this analysis excluded patients meeting criteria for and undergoing biventricular lead implantation. As such, these safety data may not fully apply to the subset of patients undergoing AVNA, who additionally meet criteria for CRT.

**Clinical Implications** AVNA is a safe intervention that improves symptoms and quality of life in patients with drug-refractory AF. Compared to pharmacotherapy alone, AVNA may be of particular benefit to patients with baseline reduced systolic function in regards to echocardiographic improvement, although the clinical impact of this difference remains uncertain.

**Conflict of Interest Disclosures:** Drs. Chatterjee, Upadhyay, and Choudhry report no disclosures. Dr. Ellenbogen is a consultant for Biotronik, Boston Scientific, Medtronic, Sorin Group, and St. Jude Medical, receives research grants from Medtronic, Boston Science, and St. Jude, and fellowship support form Medtronic, Boston Science, and Biotronik. Dr. McAlister receives speakers’ fees from St. Jude Medical. Dr. Singh is a consultant and receives lecture fees from Biotronik, Boston Scientific, Medtronic, Sorin Group, and St. Jude Medical, and is also a consultant for CardioInsight Inc, Thoratec Inc, and Biosense Webster.

**References:**


51. Ozcan C, Jahangir A, Friedman PA, Hayes DL, Munger TM, Rea RF, Lloyd MA, Packer
DL, Hodge DO, Gersh BJ, Hammill SC, Shen WK. Sudden death after radiofrequency ablation
of the atrioventricular node in patients with atrial fibrillation. J Am Coll Cardiol. 2002;40:105-
110.

52. Piot O, Sebag C, Lavergne T, Ollitrault J, Johnson N, Dinanian S, Le Heuzey JY, Guize L,
Motte G. Initial and long-term evaluation of escape rhythm after radiofrequency ablation of the

53. Poci D, Backman L, Karlsson T, Edvardsson N. New or aggravated heart failure during long-
term right ventricular pacing after av junctional catheter ablation. Pacing Clin Electrophysiol.

Radiofrequency ablation of atrioventricular junction and pacemaker implantation versus
modulation of atrioventricular conduction in drug refractory atrial fibrillation. Am J Cardiol.
1999;83:1437-1442.

Venkatraman P, Shaheen M, Kozeluhova M, Schweikert R, Burkhardt JD, Canby R, Wazni O,
Saliba W, Natale A. Pulmonary vein antrum isolation, atrioventricular junction ablation, and
antiarrhythmic drugs combined with direct current cardioversion: Survival rates at 7 years

56. Souza O, Gursoy S, Simonis F, Steurer G, Andries E, Brugada P. Right-sided versus left-

57. Takahashi Y, Yoshito I, Takahashi A, Harada T, Mitsuhashi T, Shirot a K, Kumagai K,
Nuruki N, Shiraishi T, Nitta J, Ito H. Av nodal ablation and pacemaker implantation improves

58. Tan ES, Rienstra M, Wiesfeld AC, Schoonderwoerd BA, Hobbel HH, Van Gelder IC. Long-
term outcome of the atrioventricular node ablation and pacemaker implantation for symptomatic

59. Tops LF, Schalij MJ, Holman ER, van Erven L, van der Wall EE, Bax JJ. Right ventricular
pacing can induce ventricular dyssynchrony in patients with atrial fibrillation after

60. Victor F, Mabo P, Mansour H, Pavin D, Kabalu G, de Place C, Leclercq C, Daubert JC. A
randomized comparison of permanent septal versus apical right ventricular pacing: Short-term

radiofrequency catheter ablation of atrioventricular junction for atrial fibrillation: Clinical and

63. Bradley DJ, Shen WK. Atrioventricular junction ablation combined with either right ventricular pacing or cardiac resynchronization therapy for atrial fibrillation: The need for large-scale randomized trials. *Heart Rhythm.* 2007;4:224-232.


**Table 1.** Baseline Characteristics of Studies Included in Efficacy Analysis

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Patients</td>
<td>AVNA: 22</td>
<td>AVNA: 32</td>
<td>AVNA: 37</td>
<td>AVNA: 21</td>
<td>AVNA: 49</td>
</tr>
<tr>
<td></td>
<td>Meds: 21</td>
<td>Meds: 34</td>
<td>Meds: 19</td>
<td>Meds: 29</td>
<td>Meds: 50</td>
</tr>
<tr>
<td>Age, mean ± SD (years)</td>
<td>66 ±10</td>
<td>72 ±9</td>
<td>65 ±8</td>
<td>65 ±8</td>
<td>65 ±8</td>
</tr>
<tr>
<td></td>
<td>64 ±10</td>
<td>60 ±10</td>
<td>68 ±6</td>
<td>68 ±6</td>
<td>68 ±9</td>
</tr>
<tr>
<td>Male gender (%)</td>
<td>45</td>
<td>56</td>
<td>48.6</td>
<td>76</td>
<td>69</td>
</tr>
<tr>
<td></td>
<td>48</td>
<td>38</td>
<td>63.2</td>
<td>66</td>
<td>72</td>
</tr>
<tr>
<td>CAD (%)</td>
<td>27</td>
<td>34</td>
<td>41</td>
<td>22</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>14</td>
<td>43</td>
<td>16</td>
<td>NR</td>
<td>43</td>
</tr>
<tr>
<td>EF, mean ± SD (%)</td>
<td>58 ±11</td>
<td>43 ±12</td>
<td>44 ±15</td>
<td>45 ±6</td>
<td>55 ±16</td>
</tr>
<tr>
<td></td>
<td>60 ±10</td>
<td>44 ±15</td>
<td>NR</td>
<td>45 ±8</td>
<td>57 ±14</td>
</tr>
<tr>
<td>NYHA Class ± SD</td>
<td>2.9 ±0.7</td>
<td>2.7 ±0.7</td>
<td>2.7 ±0.6</td>
<td>2.1 ±0.7</td>
<td>2.2 ±0.6</td>
</tr>
<tr>
<td></td>
<td>5.7 ±6.9</td>
<td>2.8 ±0.7</td>
<td>NR</td>
<td>2.1 ±0.7</td>
<td>NR</td>
</tr>
<tr>
<td>AF Duration (years)</td>
<td>9 ±8</td>
<td>8 ±5</td>
<td>7.1 ±6.3</td>
<td>14 ±7</td>
<td>12 ±8</td>
</tr>
<tr>
<td></td>
<td>5.7 ±6.9</td>
<td>2.8 ±0.7</td>
<td>9.8 ±8.0</td>
<td>14 ±7</td>
<td>4.8 ±5.5</td>
</tr>
<tr>
<td></td>
<td>4.1 ±5</td>
<td>2.7 ±0.6</td>
<td>12 ±8</td>
<td>14 ±7</td>
<td>6.5 ±10.9</td>
</tr>
</tbody>
</table>

SD, standard deviation; CAD, coronary artery disease; EF, ejection fraction; NYHA, New York Heart Association; NR, not recorded.
Table 2. Procedural Performance, Morbidity and Mortality

<table>
<thead>
<tr>
<th>Procedure-related Death*</th>
<th>0.27</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Procedure Performance</strong></td>
<td></td>
</tr>
<tr>
<td>Left Sided Ablation†</td>
<td>6.9</td>
</tr>
<tr>
<td>Redo Procedure‡</td>
<td>2.9</td>
</tr>
<tr>
<td><strong>Procedure Morbidity</strong></td>
<td></td>
</tr>
<tr>
<td>Hematoma</td>
<td>0.70</td>
</tr>
<tr>
<td>Malignant Arrhythmia</td>
<td>0.57</td>
</tr>
<tr>
<td>Non-Stroke Thrombosis</td>
<td>0.27</td>
</tr>
<tr>
<td>Lead Failure</td>
<td>0.23</td>
</tr>
<tr>
<td>Stroke</td>
<td>0.19</td>
</tr>
</tbody>
</table>

*Procedure-related mortality and morbidity were limited to the first 30 days following AVNA (with the exception of “Lead Failure” which was not time delimited).
†Refers to failure to achieve AV nodal conduction blockade with an initial right-sided approach.
‡Refers to the incidence of spontaneous recurrence of AV nodal conduction following an initially successful ablation.

Figure Legends:

**Figure 1:** Study Flow. aNone of the excluded studies with N < 20 were randomized; bStudies < 2 weeks was exclusion criteria for Effectiveness analysis, but not for Safety analysis. No studies with study duration < 2 weeks were randomized.

**Figure 2:** Echocardiographic Outcomes Stratified by Baseline EF: Efficacy and Effectiveness Analyses. Panels A and B show relative change in ejection fraction (EF) following AVNA versus pharmacotherapy for studies comprised of patients with reduced and normal EF. Panels C and D show pooled estimates from single-arm observational studies reporting change in EF following AVNA for patients with reduced and normal EF.
2641 Independent References Identified in All Databases

18 References Identified in Reference Lists and Authors’ Lists

2532 Excluded Based on Screening of Titles and Abstracts Using General Criteria

127 Citations With Potential Relevance

52 Unique Articles Reporting 50 Studies That Met Inclusion Criteria

5 Included in Efficacy Review (314 patients)
4 Randomized Controlled Trials
1 Prospective, Cohort Study

12 Included in Effectiveness Review (866 patients)
7 Prospective Cohort Studies
5 Retrospective Cohort Studies

47 Included in Safety Review (5,632 patients)
7 Randomized Controlled Trials
15 Prospective Cohort Studies
25 Retrospective Cohort Studies

77 Excluded Using Specific Criteria
14 Did Not Report Primary Data (Review, Protocol, Letters)
23 Did Not Report Outcomes of Interest
20 Study N < 20
8 Heterogeneous Arrhythmias or Non-RF ablation
12 Miscellaneous (Case Reports, Studies < 2 weeks)
Atrioventricular Nodal Ablation in Atrial Fibrillation: A Meta-analysis and Systematic Review
Neal A. Chatterjee, Gaurav A. Upadhyay, Kenneth A. Ellenbogen, Finlay A. McAlister, Niteesh K. Choudhry and Jagmeet P. Singh

Circ Arrhythm Electrophysiol. published online December 20, 2011;
Circulation: Arrhythmia and Electrophysiology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2011 American Heart Association, Inc. All rights reserved.
Print ISSN: 1941-3149. Online ISSN: 1941-3084

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circcep.ahajournals.org/content/early/2011/12/20/CIRCEP.111.967810

Data Supplement (unedited) at:
http://circcep.ahajournals.org/content/suppl/2011/12/20/CIRCEP.111.967810.DC1

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation: Arrhythmia and Electrophysiology can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation: Arrhythmia and Electrophysiology is online at:
http://circep.ahajournals.org//subscriptions/
SUPPLEMENTAL MATERIAL

- Search Strategy
- Supplemental Table 1: Baseline Characteristics of Studies Utilized in Efficacy, Effectiveness, and Safety Analyses
- Supplemental Figure 1: Effectiveness Analysis: Change in Exercise Duration Following AVNA
- Supplemental Figure 2: Improvement in QOL and Reduction in Symptoms Associated with AVNA Compared to Pharmacotherapy

Search Strategy

1. atrial fibrillation and heart failure
2. atrial fibrillation and ablation
3. atrial fibrillation and atrioventricular
4. (1 or 2) and (3)
5. limit (4) to English language
6. limit (5) to humans
### Supplemental Table 1: Baseline Characteristics of Studies Utilized in Efficacy, Effectiveness, and Safety Analyses

<table>
<thead>
<tr>
<th>Study, year (REF)</th>
<th>N</th>
<th>% Male</th>
<th>Age, years (SD)</th>
<th>% CAD</th>
<th>Follow-Up, months (SD)</th>
<th>EF, % (SD)</th>
<th>NYHA (SD)</th>
<th>Duration AF, years (SD)</th>
<th>Parox/Perm</th>
<th>Efficacy</th>
<th>Effectiveness</th>
<th>Safety</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EFFICACY AND SAFETY</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brignole 1997 (20)</td>
<td>22</td>
<td>45</td>
<td>66(10)</td>
<td>27</td>
<td>6</td>
<td>58(11)</td>
<td>2.9(0.7)</td>
<td>9(8)</td>
<td>22/0</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brignole 1998 (21)</td>
<td>32</td>
<td>56</td>
<td>72(9)</td>
<td>34</td>
<td>12</td>
<td>43(12)</td>
<td>2.8(0.7)</td>
<td>5.7(6.9)</td>
<td>0/32</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Marshall 1999 (19)</td>
<td>37</td>
<td>49</td>
<td>65(8)</td>
<td>22</td>
<td>4.5</td>
<td>49(6)</td>
<td>2.1(0.7)</td>
<td>14(7)</td>
<td>37/0</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ueng 2001 (22)</td>
<td>21</td>
<td>76</td>
<td>68(6)</td>
<td>NR</td>
<td>12</td>
<td>45(6)</td>
<td>2.10(0.7)</td>
<td>14(7)</td>
<td>0/21</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weerasooorya 2003 (23)</td>
<td>49</td>
<td>72</td>
<td>68(9)</td>
<td>43</td>
<td>12</td>
<td>55(16)</td>
<td>4.8(5.5)</td>
<td>0/49</td>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>EFFECTIVENESS AND SAFETY</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brignole 1994 (24)</td>
<td>23</td>
<td>52</td>
<td>67(9)</td>
<td>39</td>
<td>3</td>
<td>46(11)</td>
<td>2.8(0.7)</td>
<td>NR</td>
<td>NR</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Edner 1995 (25)</td>
<td>29</td>
<td>66</td>
<td>65(7)</td>
<td>34</td>
<td>7.2</td>
<td>51(10)</td>
<td>1.4(0.7)</td>
<td>NR</td>
<td>NR</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hsieh 2005 (26)</td>
<td>32</td>
<td>81</td>
<td>73(5)</td>
<td>38</td>
<td>58(30)</td>
<td>51(10)</td>
<td>1.4(0.7)</td>
<td>71(18)</td>
<td>158/175</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kay 1998 (27)</td>
<td>156</td>
<td>58</td>
<td>66.1(11.5)</td>
<td>31</td>
<td>12</td>
<td>12(4)</td>
<td>3.9(4.3)</td>
<td>0/15</td>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lee 1998 (12)</td>
<td>30</td>
<td>77</td>
<td>69(9)</td>
<td>7</td>
<td>6</td>
<td>51(6)</td>
<td>2</td>
<td>6(2)</td>
<td>15/15</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morady 1993 (45)</td>
<td>20</td>
<td>35</td>
<td>63(15)</td>
<td>10</td>
<td>12(0)</td>
<td>55(14)</td>
<td>8.8(7.6)</td>
<td>11/9</td>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ozcan 2001 (31)</td>
<td>350</td>
<td>53</td>
<td>68(11)</td>
<td>45</td>
<td>36(26)</td>
<td>47(17)</td>
<td>1.3(0.7)</td>
<td>71(18)</td>
<td>158/175</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poci 2004 (43)</td>
<td>235</td>
<td>60</td>
<td>62(14)</td>
<td>20</td>
<td>14</td>
<td>58(17)</td>
<td>2.10(0.7)</td>
<td>14(7)</td>
<td>0/21</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>SAFETY</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abe 2000 (32)</td>
<td>30</td>
<td>50</td>
<td>66</td>
<td>16</td>
<td>12(8)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>7/20</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brignole 2002 (35)</td>
<td>141</td>
<td>41</td>
<td>66(11)</td>
<td>16</td>
<td>2.4</td>
<td>51(10)</td>
<td>2.5(0.5)</td>
<td>NR</td>
<td>NR</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brignole 2005 (34)</td>
<td>48</td>
<td>61</td>
<td>70(8)</td>
<td>30</td>
<td>6</td>
<td>38(1)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brignole 2011 (33)</td>
<td>106</td>
<td>64</td>
<td>67(10)</td>
<td>30</td>
<td>6</td>
<td>38(1)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Buys 1997 (36)</td>
<td>25</td>
<td>56</td>
<td>58(11)</td>
<td>24</td>
<td>7</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>0/25</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conti 1997 (37)</td>
<td>38</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>38(11)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Doshi 2005 (39)</td>
<td>106</td>
<td>64</td>
<td>67(10)</td>
<td>30</td>
<td>6</td>
<td>38(1)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fitzpatrick 1996 (11)</td>
<td>107</td>
<td>43</td>
<td>60(16)</td>
<td>30</td>
<td>6</td>
<td>38(11)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gasparini 2000 (40)</td>
<td>585</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>2.3(1)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Geelen 1997 (41)</td>
<td>235</td>
<td>60</td>
<td>62(14)</td>
<td>20</td>
<td>14</td>
<td>58(17)</td>
<td>2.10(0.7)</td>
<td>14(7)</td>
<td>0/21</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jensen 1995 (42)</td>
<td>50</td>
<td>54</td>
<td>67</td>
<td>17(4)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>23/27</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Marshall 1999 (43)</td>
<td>115</td>
<td>52</td>
<td>68(8)</td>
<td>48</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>76/39</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Menozzi 1994 (44)</td>
<td>78</td>
<td>50</td>
<td>69(10)</td>
<td>38</td>
<td>3</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>21/57</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morady 1993 (45)</td>
<td>20</td>
<td>35</td>
<td>63(15)</td>
<td>10</td>
<td>12(0)</td>
<td>55(14)</td>
<td>8.8(7.6)</td>
<td>11/9</td>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nowinski 2002 (46)</td>
<td>259</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>51(12)</td>
<td>NR</td>
<td>NR</td>
<td>54/46</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Occhetta 2007 (47)</td>
<td>163</td>
<td>44</td>
<td>71(8)</td>
<td>19</td>
<td>36</td>
<td>49(12)</td>
<td>NR</td>
<td>NR</td>
<td>20/143</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ohara 2007 (48)</td>
<td>803</td>
<td>43</td>
<td>69(12)</td>
<td>45</td>
<td>36(26)</td>
<td>51(12)</td>
<td>1.3</td>
<td>NR</td>
<td>155/179</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ozcan 2003 (14)</td>
<td>56</td>
<td>80</td>
<td>69(10)</td>
<td>64</td>
<td>40(23)</td>
<td>26(8)</td>
<td>1.7(0.8)</td>
<td>NR</td>
<td>21/35</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Petrac 2005 (60)</td>
<td>104</td>
<td>68</td>
<td>62(12)</td>
<td>29</td>
<td>20(8)</td>
<td>50(4)</td>
<td>2.1</td>
<td>NR</td>
<td>0/104</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Piot 1996 (50)</td>
<td>50</td>
<td>58</td>
<td>63(13)</td>
<td>12</td>
<td>36(16)</td>
<td>NR</td>
<td>9.2(7.5)</td>
<td>NR</td>
<td>308/277</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proclemer 1999 (52)</td>
<td>60</td>
<td>50</td>
<td>64(11)</td>
<td>27</td>
<td>7(2)</td>
<td>55(12)</td>
<td>NR</td>
<td>NR</td>
<td>103/110</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proclemer 1999 (52)</td>
<td>60</td>
<td>50</td>
<td>64(11)</td>
<td>27</td>
<td>7(2)</td>
<td>55(12)</td>
<td>NR</td>
<td>NR</td>
<td>103/110</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sonne 2009 (53)</td>
<td>101</td>
<td>67</td>
<td>69(10)</td>
<td>45</td>
<td>6(2)</td>
<td>50(11)</td>
<td>NR</td>
<td>NR</td>
<td>0/28</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Souza 1992 (54)</td>
<td>30</td>
<td>77</td>
<td>59(12)</td>
<td>3</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>25/76</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Takahishi 2003 (55)</td>
<td>38</td>
<td>50</td>
<td>69(12)</td>
<td>11</td>
<td>6</td>
<td>58(13)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tan 2008 (56)</td>
<td>121</td>
<td>49</td>
<td>65(11)</td>
<td>21</td>
<td>6</td>
<td>52(40)</td>
<td>1.8</td>
<td>8.4(6.3)</td>
<td>41/80</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tops 2006 (57)</td>
<td>55</td>
<td>49</td>
<td>61(11)</td>
<td>9</td>
<td>46(2)</td>
<td>49(2)</td>
<td>1.7(0.7)</td>
<td>7(5)</td>
<td>0/55</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Victor 2006 (58)</td>
<td>28</td>
<td>71</td>
<td>63(2)</td>
<td>11</td>
<td>18</td>
<td>46(9)</td>
<td>NR</td>
<td>NR</td>
<td>0/28</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yeung‐lai Wah 2002 (59)</td>
<td>359</td>
<td>58</td>
<td>65(11)</td>
<td>21</td>
<td>14</td>
<td>41(26)</td>
<td>33(1)</td>
<td>NR</td>
<td>5.3(4.2)</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

REF, reference number; N, number of patients; SD, standard deviation; EF, ejection fraction; NYHA, New York Heart Association Class; Parox/Perm, absolute number of patients with paroxysmal and permanent atrial fibrillation; SCD, sudden cardiac death; * Fractional Shortening.
Supplemental Figure 1: Effectiveness Analysis: Change in Exercise Duration Following AVNA. Shown is mean difference in exercise duration following AVNA from single-armed observational studies.
**Supplemental Figure 2:** Improvement in QOL and Reduction in Symptoms Associated with AVNA Compared to Pharmacotherapy

<table>
<thead>
<tr>
<th>QOL Scale</th>
<th>MLHFQ</th>
<th>PGWB</th>
<th>MHI</th>
<th>Indep Quest</th>
<th>AQoL</th>
<th>SIP</th>
<th>CAST QOL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brignole et al. 1997</td>
<td>(20)</td>
<td>Absolute ã vs. Meds b Yes No Yes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brignole et al. 1998</td>
<td>(21)</td>
<td>Absolute vs. Meds Yes (p&lt;0.05) c No No No</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Marshall et al. 1999</td>
<td>(19)</td>
<td>Absolute vs. Meds Yes No No</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ueng et al. 2001</td>
<td>(22)</td>
<td>Absolute vs. Meds Yes (p&lt;0.05) No No No</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weerasooriya et al. 2003</td>
<td>(23)</td>
<td>Absolute vs. Meds Yes Yes Yes (p=0.004) No No No</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Symptom Scale Utilized</th>
<th>SSS</th>
<th>SSS</th>
<th>VACSS</th>
<th>Indep Quest</th>
<th>N/A</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brignole et al. 1997</td>
<td>(20)</td>
<td>Absolute ã vs. Meds b Yes No Yes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brignole et al. 1998</td>
<td>(21)</td>
<td>Absolute vs. Meds Yes (p&lt;0.05) c No No No</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Marshall et al. 1999</td>
<td>(19)</td>
<td>Absolute vs. Meds Yes No No</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ueng et al. 2001</td>
<td>(22)</td>
<td>Absolute vs. Meds Yes (p&lt;0.05) No No No</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weerasooriya et al. 2003</td>
<td>(23)</td>
<td>Absolute vs. Meds Yes Yes Yes (p=0.004) No No No</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ã[Absolute] refers to whether improvement in QOL or reduction in symptom was statistically significant (p<0.05) compared to baseline in AVNA group (intra-group comparison); b[vs. Meds] refers to whether improvement in QOL or reduction in symptom was statistically significant when compared to change occurring within pharmacotherapy group (inter-group comparison); cP-value is for comparison between change with AVNA versus change with pharmacotherapy. Fields marked (¬) indicate that outcome of interest was not reported.

QOL: Quality of Life; MLHFQ: Minnesota Living with Heart Failure Questionnaire; PGWB: Psychological General Well Being Questionnaire; MHI: McMaster Health Index; Indep Quest: Independent Author-generated Questionnaire; AQoL: The Assessment of Quality of Life Questionnaire; SIP: The Sickness Impact Profile (SIP); CAST QOL: The CAST QOL Questionnaire; SSS: Specific Symptom Scale; VACSS: Visual Analog Cardiac Symptom Scale.