

Section 9: Electrophysiology Testing and the Use of Devices in Heart Failure

General Considerations

Recommendation

9.1 It is recommended that the decision to undertake electrophysiologic (EP) intervention, including implantable cardioverter defibrillator (ICD) implantation, be made in light of functional status and prognosis based on severity of underlying HF and comorbid conditions. If an ICD is considered due to left ventricular (LV) dysfunction which is of recent onset, LV function should be reassessed, ideally after 3–6 months of optimal medical therapy. (Strength of Evidence = C)

Background

Trials supporting the use of EP devices in HF for prevention of sudden cardiac death (SCD) typically have excluded patients with persistent New York Heart Association (NYHA) IV HF, patients in cardiogenic shock, those with irreversible brain damage, and those with comorbidities and an expected survival of < 1 year. Recent trials have excluded patients with a recent myocardial infarction (MI), a coronary revascularization procedure within 3 months or ongoing ischemia.¹ This allows adequate time from the index ischemic event for the appropriate application of pharmacologic therapy and for the beneficial effects of the primary therapeutic strategy to be manifest before consideration of device therapy. Patients are not good candidates for device implantation if they have significant psychiatric illness that may be aggravated by device implantation or are not expected to be compliant with systematic follow-up.

EP Testing and Evaluation of Syncope

Recommendation

9.2 Immediate evaluation is recommended in patients with HF who present with syncope. In the absence of a clear identifiable noncardiac cause, consultation with an EP specialist should be obtained. (Strength of Evidence = C)

Background

Typically, ICD implantation is accepted as first-line therapy in patients presenting with syncope of unknown origin who have hemodynamically significant sustained ventricular tachycardia (VT) induced at EP study (EPS). This

indication is supported by substantial observational data showing an annual cardiovascular mortality of approximately 20% in such patients, much of which appears to result from sudden death.^{2–5} A related indication includes patients with recurrent syncope of uncertain etiology in the presence of ventricular dysfunction when other causes of syncope are excluded. Such cases, usually associated with nonischemic dilated cardiomyopathy, may suffer a risk of SCD as high as 45%.

Few studies have been conducted in the setting of nonischemic dilated cardiomyopathy and syncope. One evaluated patients with syncope, inducible ventricular arrhythmias, and previously documented VT.⁶ ICDs proved useful in reducing arrhythmic deaths. Another study compared dilated nonischemic cardiomyopathy patients with unexplained syncope and an ICD with a group of cardiac arrest survivors with ICDs.⁷ It demonstrated that the number of appropriate ICD discharges in the syncope group were similar to those of the cardiac arrest group. Such data, although rudimentary, do provide insight into recommending strategies for clinical ICD implantation until more definitive evidence is available.

Recommendation

9.3 Routine EP testing is not recommended in patients with LV systolic dysfunction who have asymptomatic nonsustained ventricular tachycardia (VT) in the absence of prior infarction. (Strength of Evidence = B)

Background

The predictive accuracy of EP testing in nonischemic cardiomyopathy is limited.^{8–12} On the one hand, when such patients present with spontaneous ventricular arrhythmias, ventricular arrhythmias can be induced in more than two-thirds.⁹ On the other hand, EP testing is less likely to induce VT in patients with nonischemic dilated cardiomyopathy and a presentation of aborted SCD or nonsustained VT than in patients with underlying coronary artery disease.^{8,11,12} Furthermore, EP can induce ventricular arrhythmias in 10% to 40% of these patients, even in the absence of previous clinical arrhythmias.⁸ Thus EP testing is not useful for risk stratification in nonischemic cardiomyopathy. Overall, the magnitude of LV dysfunction remains the best predictor of both SCD and total mortality in this population.¹²

In the setting of ischemic cardiomyopathy and prior infarction, routine EP risk stratification is not recommended. EP testing followed by ICD implantation for inducible sustained VT can be considered for patients in whom there is concern that they are at risk for SCD, but who do not meet guidelines based on the severity of chronic LV dysfunction. This approach may be considered in patients with nonsustained VT who are more than 5 days after MI, or who have had recent revascularization, or who have LV ejection fraction (LVEF) > 0.35.^{13,14}

Prophylactic ICD Placement

Recommendations

9.4a Prophylactic ICD placement should be considered in patients with a LVEF $\leq 35\%$ and mild to moderate HF symptoms:

- Ischemic etiology (Strength of Evidence = A)
 - Non-ischemic etiology (Strength of Evidence = B)
- See Recommendation 9.1 for additional criteria.

9.4b In patients who are undergoing implantation of a biventricular pacing device according to the criteria in recommendations 9.7-9.8, use of a device that provides defibrillation should be considered. (Strength of Evidence = B)

See Recommendation 9.1 for additional criteria.

9.5 ICD placement is not recommended in chronic, severe refractory HF when there is no reasonable expectation for improvement or in patients with a life expectancy of less than 1 year. (Strength of Evidence = C)

Background

More than 80 percent of patients who experience a life-threatening ventricular tachyarrhythmia do not survive to benefit from an ICD. Thus, the concept of the ICD for primary prevention of SCD has received considerable attention. Several large trials have been conducted to address primary prevention.¹⁴⁻¹⁹ The Sudden Cardiac in Heart Failure Trial (SCD-HeFT)¹⁵ tested the hypothesis that amiodarone or an ICD would improve survival compared with placebo in patients with HF. The study enrolled 2521 patients with NYHA II or III HF and an LVEF $< 35\%$ of either ischemic or nonischemic etiology. Patients were randomly allocated to treatment with an ICD, amiodarone, or placebo. Background therapy was strong: 87% were on angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) and 78% on beta blockers at last follow-up. ICD therapy decreased mortality by 23% compared with control, with an absolute reduction in mortality of 7% over a mean follow-up of 45 months. The ICD benefit was consistent across ischemic and nonischemic etiologies of HF. Subgroup analysis found benefit in NYHA Class II, but failed to demonstrate benefit from ICDs in patients with NYHA Class III, although such subgroup findings must be interpreted cautiously. A similar subgroup differentiation between NYHA class II and III has not been observed in any other ICD trial.^{1,20} There was no benefit for amiodarone.

Trials in patients with ischemic cardiomyopathy, including patients with and without HF symptoms, but excluding Class IV HF, also support benefit of an ICD in reducing total mortality. The Multicenter Automatic Defibrillator Implantation Trial (MADIT)-I enrolled patients with a mean LVEF of 26%, a prior MI, unsustained VT, and

inducible VT at EPS. Those randomized to receive an ICD had a 54% reduction in total mortality at 27 months over those who had been given "conventional" antiarrhythmic therapy.¹⁴ The Multicenter Unsustained Tachycardia Trial (MUSTT) randomized patients with an LVEF $\leq 40\%$ and an inducible sustained VT into a group receiving beta blockers and ACE inhibitors or a group receiving these agents plus antiarrhythmics or, if they did not respond, an ICD. Over a 5-year follow-up, those receiving the ICD experienced a 27% lower risk of arrhythmic death or cardiac arrest. Total mortality was reduced by 20%.¹⁸ MADIT-II showed a significant survival benefit in patients with prior MI and LVEF $\leq 30\%$, but also a trend toward increased HF episodes in patients receiving an ICD.¹ In contrast, a study of patients undergoing coronary artery bypass (CABG) surgery who have LV dysfunction and abnormal signal-averaged electrocardiograms, but no symptomatic ventricular arrhythmias, found no benefit for prophylactic ICD implantation.¹⁶

A trial of ICDs for patients with nonischemic dilated cardiomyopathy and nonsustained VT reported a favorable trend for mortality reduction that did not reach statistical significance. A meta-analysis of trials in patients with nonischemic cardiomyopathy and the SCD-Heft trial support a survival benefit for ICDs in patients with nonischemic cardiomyopathy.^{15,21}

In evaluating these trial results, it must be remembered that numerous factors can impact ICD effectiveness, including the population tested, mode of implantation, concurrent risk of death (eg, concomitant CABG surgery and its inherent risk), background medical therapy, and the influence of ICDs on nonarrhythmic deaths. For example, only 5% of the control group in MADIT was on beta-antagonist therapy, compared with 27% in the treatment arm. It is likely that this contributed to the decrease in cardiac nonarrhythmic deaths in the ICD group.¹⁴ These trials all exclude patients with severe NYHA functional class IV HF, although the Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) trial, examining biventricular pacing with or without concomitant ICD, included some NYHA class IV patients.¹⁷ In such patients, ICD implantation is under consideration as a "bridge" to transplant.²²

Unresolved Issues

Timing of ICD Placement. Time on background therapy is a significant issue. All trials of ICDs have enrolled patients receiving stable doses of appropriate medical therapy, including beta-blockers and ACE inhibitors or ARBs. Furthermore, it is well known that treatment with these agents, particularly beta blockers, for a period of several months frequently results in reduction in LV volumes and improvement or normalization of LVEF. For these reasons, it is appropriate to delay consideration of ICD implant, particularly in the setting of newly diagnosed nonischemic dilated

cardiomyopathy, until after several months of appropriate medical therapy. Although there is no agreement regarding the ideal treatment duration prior to reevaluation of LVEF for consideration of ICD placement, data regarding the time course of reverse remodeling following institution of beta-blocker therapy support a period of 3 to 6 months. Although physicians may choose to place a prophylactic ICD in selected patients prior to such a course of therapy, studies to support such a practice are not available.

Background Therapy. Device effectiveness generally is studied in patients already on background medical therapy. Studies establishing the additional benefit of new agents change the definition of standard or optimal background medical therapy. For example, a recent study of an aldosterone antagonist showed a 15% reduction in total mortality and a 17% reduction in cardiovascular mortality on top of standard medical therapy, mainly because of a 21% reduction in SCD.²³

Significance of Arrhythmias Detected by ICDs. Trials of prophylactic ICDs have shown that the occurrence of an episode of VT or ventricular fibrillation (VF) is a marker for increased mortality and HF hospitalizations despite effective termination of VT/VF by the ICD.^{24–27} VT may be a marker for deterioration of ventricular function. When a patient experiences sustained VT detected by the ICD a careful evaluation and reassessment of HF status and therapy is warranted. The impact of therapies to reduce VT episodes is not clear, although ICD shocks reduce quality of life, and prevention is warranted.

Family History of Sudden Death. There are no systematic data to guide therapy when there is a family history of SCD. This includes patients with familial cardiomyopathy with a history of SCD in 1 or more sibling or parent. In such patients routine implantation of an ICD cannot be routinely recommended, but implantation may be considered on an individual basis after careful consideration of the circumstances.

Recommendation

9.6 ICD implantation is recommended for survivors of cardiac arrest from ventricular fibrillation or hemodynamically unstable sustained VT that is not due to a transient, potentially reversible cause, such as acute MI. (Strength of Evidence = A)

Background

Several studies have shown that ICDs reduce mortality in SCD survivors to a greater extent than antiarrhythmic drug therapy.^{28–30} The largest of these trials enrolled 1016 patients who survived cardiac arrest, sustained VT with syncope, or sustained VT in the presence of an LVEF <40% and symptoms suggesting severe hemodynamic compromise. Patients were randomized to receive

therapy with either an ICD or an antiarrhythmic drug, generally amiodarone. Survival throughout the trial was superior for patients randomized to ICD therapy. A second study randomized survivors of cardiac arrest equally among 4 treatment arms: ICD, amiodarone, metoprolol, or propafenone. The propafenone arm was terminated prematurely because of excessive mortality. The 2-year mortality was similar for patients randomized to metoprolol and amiodarone (19.6%) but significantly lower in patients randomized to ICD therapy (12.1%).

Many patients in these trials had reduced LVEF and HF. The mean LVEF in one was 39%; in another it was 32%. The survival benefit of ICD was greatest in patients with an LVEF <35%.

A meta-analysis grouping the results of these three trials indicates that therapy with ICDs resulted in a 27% reduction in total mortality.³¹ This mortality reduction is due exclusively to a reduction in arrhythmic deaths, particularly in the presence of LV dysfunction.³²

Biventricular Resynchronization Pacing

Recommendations

- 9.7 Biventricular pacing therapy is recommended for patients in sinus rhythm with a widened QRS interval (≥ 120 ms) and severe LV systolic dysfunction LVEF ($\leq 35\%$) who have persistent, moderate to severe HF (NYHA III) despite optimal medical therapy. (Strength of Evidence = A)**
- 9.8 Biventricular pacing therapy may be considered for patients with atrial fibrillation with a widened QRS interval (≥ 120 ms) and severe LV systolic dysfunction LVEF ($\leq 35\%$) who have persistent, moderate to severe HF (NYHA III) despite optimal medical therapy. (Strength of Evidence = B)**
- 9.9 Selected ambulatory NYHA IV patients in sinus rhythm with QRS ≥ 120 ms and LV systolic dysfunction may be considered for biventricular pacing therapy. (Strength of Evidence = B)**
- 9.10 Biventricular pacing therapy may be considered in patients with reduced LVEF and QRS ≥ 150 ms who have NYHA I or II HF symptoms. (Strength of Evidence = B)**
- 9.11 In patients with reduced LVEF who require chronic pacing and in whom frequent ventricular pacing is expected, biventricular pacing may be considered. (Strength of Evidence = C)**

Background

Large observational studies performed in patients with advanced HF have demonstrated that right ventricular (RV) pacing results in worsening symptoms and long-term outcome.³³ This is most likely because of the

development of RV pacing-induced left bundle branch block, resulting in intra- and interventricular dyssynchrony with resultant worsening of left and RV systolic and diastolic function. An analogous phenomenon is seen in patients with advanced HF and bundle branch block. Indeed, the majority of patients with HF have interventricular conduction delay, and up to 30% to 50% have manifest bundle branch block caused by direct pathologic involvement of specialized conduction or by scarring of the myocardium.³⁴ In those with conduction delay, pacing from the LV or simultaneously from the basal-lateral LV and RV can reduce the delay between septal and posterolateral contraction, to “resynchronize ventricular contraction.” Cardiac resynchronization therapy (CRT) seeks to normalize depolarization to improve the efficiency of ventricular contraction and ventricular septal motion, decrease atrioventricular (AV) valve regurgitation, and increase diastolic filling time.³⁵

Isolated Biventricular Pacing. The early promise of biventricular pacing^{34,35} was tested in the Multicenter InSync Clinical Study (MIRACLE),³⁶ which randomized 453 patients to activation or nonactivation of cardiac resynchronization, using a double-blind study design. Inclusion criteria were NYHA III/IV, QRS > 130 ms, LVEF < 35%, and LV end-diastolic dimension > 55 mm, as determined by echocardiography. Patients were required to be on optimal medical therapy, defined as ACE inhibitors and beta blockers, for 1 to 3 months before inclusion. Resynchronization improved symptoms, quality of life, and exercise capacity, while reducing LV dimension and improving LVEF at 6 months. Hospitalization or intravenous medications for HF treatment were both reduced by approximately 50%. There was no difference in cardiac or all-cause mortality. This study was not subjected to an intention-to-treat analysis, because randomization occurred only after successful device implantation. The Cardiac Resynchronization-Heart Failure (CARE-HF) study enrolled 813 patients with NYHA class III-IV HF resulting from LV systolic dysfunction and cardiac dyssynchrony with an LVEF ≤ 35% and a QRS duration ≥ 120 ms despite standard medical therapy.³⁷ After a follow up of just under 30 months, the CRT-treated patients showed a significant benefit in terms of the primary end point of all-cause mortality and unplanned hospitalization (HR 0.63, $P < .001$) and the secondary end point of all-cause mortality (HR 0.64, $P < .002$). Those in the CRT group also showed improved LVEF, NYHA class, end-systolic volume, mitral valve function, blood pressure, and quality-of-life indices. It should be noted that for those patients with a QRS lengthening of 120–149 ms, echocardiographic confirmation of mechanical dyssynchrony was required. This subselection criterion could have favorably influenced the outcomes by preferential enrollment of those more likely to respond to CRT. It is not known how many patients were excluded by this criterion.

Virtually all randomized trials of CRT have required subjects to be in sinus rhythm at the time of randomization. Thus few data are available to determine the benefits of

CRT in patients with atrial fibrillation. Retrospective studies and a meta-analysis suggest that patients with chronic atrial fibrillation may benefit from CRT though the benefits may be less than in patients with sinus rhythm.³⁸ Patients with previous AV nodal ablation and RV pacing may be most likely to benefit from CRT.³⁹ Prior to considering CRT in a patient with atrial fibrillation, it is important to determine if rate control is adequate to allow biventricular pacing.⁴⁰

Biventricular Pacing With ICD. Initial studies of biventricular pacing with an ICD⁴¹ led to the COMPANION trial,¹⁷ which enrolled patients with HF and NYHA Class III or IV symptoms despite maximized medical therapy. Inclusion criteria included a QRS duration ≥ 120 ms and a PR interval > 150 ms. The trial had 3 treatment arms: optimal pharmacologic therapy (OPT), optimal pharmacologic therapy plus biventricular pacing (CRT), and biventricular pacing plus backup ICD therapy (CRTD). In contrast to all others, this study was powered to evaluate a primary endpoint of combined all cause mortality and hospitalization. Data were analyzed using an “intention to treat” statistical approach. Of the 1580 patients randomized, 1080 were implanted with a CRT pacemaker or defibrillator (CRTD). As compared with patients treated with medical therapy only, there was a statistically significant event rate reduction in the primary combined endpoint of total hospitalization and total mortality at 1 year in the CRT and CRTD groups, as well as in the combined endpoint of death and hospitalization for HF. There was a trend toward reduced mortality in the CRT-alone group, although this finding did not reach statistical significance.

Asymptomatic or Mild HF symptoms. MADIT-CRT enrolled and followed 1820 patients with ischemic or nonischemic cardiomyopathy, a LVEF of 30% or less, a QRS duration of 130 msec or more, and NYHA class I or II symptoms.⁴² Patients were randomly assigned to receive CRT plus an ICD or an ICD alone. The primary end point was death from any cause or a nonfatal heart-failure event (whichever came first). The primary end point occurred in 17.2% of the CRT-ICD group and 25.3% of the ICD only group (hazard ratio in the CRT-ICD group, 0.66; 95% confidence interval [CI], 0.52 to 0.84; $P = 0.001$). The superiority of CRT was present in patients with both ischemic and non-ischemic cardiomyopathy and resulted from a 41% reduction in the risk of heart-failure events, a finding that was evident primarily in a prespecified subgroup of patients with a QRS duration of 150 msec or more. CRT was associated with a significant reduction in LV volumes and improvement in the LVEF. There was no significant difference between the two groups in the overall risk of death, with a 3% annual mortality rate in each treatment group.⁴²

Biventricular Pacing when Conventional Pacing is Indicated. There are few data concerning the use of CRT in either patients with reduced LVEF HF and a QRS ≥ 120 msec who have an additional indication for

ventricular pacing or for those who would likely have a significant burden of RV pacing following ICD implantation. However, substantial data exist to suggest that CRT rather than conventional RV pacing may be considered in these patients. The Homburg Biventricular Pacing Evaluation (HOBIPACE) prospectively randomized 30 subjects with standard indications for pacing and reduced LV function as determined by an LVEF $\leq 40\%$ or an LV end diastolic diameter ≥ 60 mm to RV or biventricular pacing.⁴³ Peak oxygen consumption, BNP levels, and LVEF were improved in the CRT group compared to the RV pacing group. In another study, patients with chronic atrial fibrillation who had AV junction ablation were randomized to either RV or biventricular pacing. At 6 months post-ablation, patients treated with cardiac resynchronization had a significant improvement in 6-minute walk distance, (31%) above baseline (82.9 \pm 94.7 m), compared to patients receiving RV pacing, (24%) above baseline (61.2 \pm 90.0 m) ($P = 0.04$). There were no significant differences in the quality-of-life parameters. At 6 months post-ablation, the LVEF in the biventricular group (0.46 \pm 0.13) was significantly greater in comparison to patients receiving RV pacing (0.41 \pm 0.13, $P = 0.03$). Patients with a LVEF $\leq 45\%$ or with NYHA Class II/III symptoms appeared to have the most benefit.⁴⁴ Other studies have demonstrated an improvement in symptoms and LVEF in patients with reduced LVEF and chronic RV pacing with an upgrade to CRT.^{45–47}

Unresolved Issues With Biventricular Pacing

The evidence supporting CRT in severe HF is compelling. However, device placement exerts a substantial “placebo” response of improved functional capacity and quality of life parameters in those randomized to the control group, and it is hampered by a significant nonresponder rate.^{48,49} Most trials of CRT have excluded patients with atrial fibrillation. Thus the benefit of biventricular pacing in these patients remains unknown.

Should resynchronization be done in isolation or must it be accompanied by an ICD device? The findings in SCD-HeFT and COMPANION suggest that CRT therapy ideally should be accompanied by ICD placement in patients with NYHA III symptoms. When considering resynchronization in patients with more severe HF, the appropriateness of ICD implantation is uncertain. A recent analysis of ambulatory NYHA class IV patients in the COMPANION trial demonstrated a benefit of CRT and CRTD, but one year mortality remained high.⁵⁰

Patients With a QRS Duration 120–150 ms. A substantial number of potential candidates for CRTs will have a QRS duration between 120 and 150 ms. Although such patients were entered in the clinical trials assessing efficacy of CRT, the average QRS duration was in the range of 160–170 ms and there are concerns that patients with moderate prolongation of the QRS interval may not derive the same benefit as those with more marked prolongation. Although CRT reduced the primary endpoint of time to death or all cause

hospitalization compared to patients randomized to optimal medical treatment by 19% ($P = .014$) in the COMPANION Trial, a significant risk reduction was seen only in patients whose QRS was > 168 ms.¹⁷ Patients whose QRS was ≤ 147 ms demonstrated essentially no benefit of treatment, whereas CRT had an intermediate effect in the patients whose QRS duration fell in between these groups. In CARE-HF, there was a benefit of CRT in subjects with a QRS duration of 120–149 msec, but to be enrolled in the study these patients had to have two of three criteria for dyssynchrony (an aortic pre-ejection delay of more than 140 msec, an interventricular mechanical delay of more than 40 msec, or delayed activation of the posterolateral LV wall).³⁷

There is no universally accepted method for measuring dyssynchrony, the methods may be operator or equipment dependent, and the strategy of using echocardiographic methods has not been tested against the well-studied strategy of using QRS duration. Therefore, caution should be applied when attempting to interpret echocardiographic measures of dyssynchrony in patients who meet standard criteria for CRT; in particular, caution should be applied when considering patients who do not meet criteria shown to benefit in randomized clinical trials (e.g. narrow QRS duration). Ongoing investigations will likely clarify use of imaging strategies for assessing dyssynchrony in the future.

Dual Chamber Pacemakers

Recommendation

9.12 The routine use of dual atrioventricular (AV) chamber pacemakers for HF in the absence of symptomatic bradycardia or high-grade AV block is not recommended. (Strength of Evidence = A)

Background

Abnormalities in AV conduction can contribute to a reduction in atrial contribution to ventricular filling and prolong the duration of mitral regurgitation into diastole. Restoration of these 2 hemodynamic phenomena provided the rationale for the potential benefits of AV synchronized pacing with optimal AV delay. Initial success showed a beneficial effect of cardiac pacing with a short AV delay in patients with HF.⁵¹ Subsequent acute^{52–54} and chronic studies^{55–60} assessing the effect of shortening the AV delay in patients with impaired ventricular function showed mixed results. Three well-designed and randomized studies failed to show any consistent improvements in HF with shortening of the programmed AV delay. Another concluded that for patients with standard indications for ICD therapy, no indication for cardiac pacing, and an LVEF of 40% or less, dual-chamber pacing offers no clinical advantage over ventricular backup pacing and may be detrimental by increasing the combined end point of death or hospitalization for HF.⁶¹

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