TABLE 280-3 PRINCIPLES OF ICD IMPLANTATION FOR PRIMARY PREVENTION OF SUDDEN DEATH

Principle	Comment
Arrhythmia–sudden death mismatch	Sudden death in heart failure patients is generally due to progressive LVD, not a focal arrhythmia substrate (except in patients with post-MI HF)
Diminishing returns with advanced disease	Intervention at early stages of HF most successful since sudden death diminishes as cause of death with advanced HF
Timing of benefits	LVEF should be evaluated on optimal medical therapy or after revascularization before ICD therapy is employed; no benefit to ICD implant within 40 days of an MI (unless for secondary prevention)
Estimation of benefits and prognosis	Patients and clinicians often overestimate benefits of ICDs; an ICD discharge is not equivalent to an episode of sudden death (some ventricular arrhythmias terminate spontaneously); appropriate ICD discharges are associated with a worse near-term prognosis

Abbreviations: HF, heart failure; ICD, implantable cardioverter-defibrillator; LVD, left ventricular disease; LVEF, left ventricular ejection fraction; MI, myocardial infarction.

medical therapy alone or medical therapy plus CABG. There was no significant difference between groups with respect to the primary endpoint of death from any cause. Patients assigned to CABG had lower rates of death from cardiovascular causes and of death from any cause or hospitalization for cardiovascular causes. An ancillary study of this trial also determined that the detection of hibernation pre-revascularization did not materially influence the efficacy of this approach, nor did it help to define a population unlikely to benefit if hibernation was not detected.

Surgical ventricular restoration (SVR), a technique characterized by infarct exclusion to remodel the left ventricle by reshaping it surgically in patients with ischemic cardiomyopathy and dominant anterior left ventricular dysfunction, has been proposed. However, in a 1000-patient trial in patients with HFrEF who underwent CABG alone or CABG plus SVR, the addition of SVR to CABG had no disease-modifying effect. Cardiac symptoms and exercise tolerance improved from baseline to a similar degree in both study groups. SVR resulted in lower left ventricular volumes at 4 months after operation. However, left ventricular aneurysm surgery is still advocated in those with refractory heart failure, ventricular arrhythmias, or thromboembolism arising from an akinetic aneurysmal segment of the ventricle. Other remodeling procedures, such as use of an external mesh-like net attached around the heart to limit further enlargement, have not been shown to provide hard clinical benefits, although favorable cardiac remodeling was noted.

Mitral regurgitation (MR) occurs with varying degrees in patients with HFrEF and dilated ventricles. Annular dilatation and leaflet noncoaptation in the setting of anatomically normal papillary muscles, chordal structures, and valve leaflets characterize functional MR. In patients who are not candidates for surgical coronary revascularization, mitral valve repair remains controversial. Ischemic MR (or infarct-related MR) is typically associated with leaflet tethering and displacement related to abnormal left ventricular wall motion and geometry. No evidence to support the use of surgical or percutaneous valve correction for functional MR exists as disease-modifying therapy even though MR can be corrected.

CELLULAR AND GENE-BASED THERAPY

The cardiomyocyte is no longer considered a terminally differentiated cell and possesses regenerative capacity. Such renewal is accelerated under conditions of stress and injury, such as an ischemic event or heart failure. Investigations that use either bone marrow–derived precursor cells or autologous cardiac-derived cells have gained traction. A number of small- and moderate-scale trials of such therapy have focused on post–myocardial infarction patients and have used autologous bone marrow–derived progenitor or stem cells. These trials have had variable results, with most demonstrating modest improvements in parameters of cardiac structure and remodeling. More promising, however, are cardiac-derived stem cells. Two preliminary pilot trials delivering cells via an intracoronary approach have been reported. In one, autologous c-kit–positive cells isolated from the atria obtained from patients undergoing CABG were cultured and reinfused. In another, cardiosphere-derived cells grown from endomyocardial biopsy specimens were used. These small trials demonstrated improvements in left ventricular function but require far more work to usher in a clinical therapeutic success. The appropriate route of administration, the quantity of cells to achieve a minimal therapeutic threshold, the constitution of these cells (single source or mixed), the mechanism by which benefit accrues, and short- and long-term safety remain to be elucidated.

Targeting molecular aberrations using gene transfer therapy, mostly with an adenoviral vector, is emerging in HFrEF. Several methods of gene delivery have been developed, including direct intramyocardial injection, coronary artery or venous infusion, and injection into the pericardial space. Cellular targets under consideration include β_2-adrenergic receptors and calcium cycling proteins such as inhibitors of phospholamban. SERCA2a is deficient in patients with HFrEF and is primarily responsible for reincorporating calcium into the sarcoplasmic reticulum during diastole. A phase II randomized, double-blind, placebo-controlled trial called CUPID (Efficacy and Safety Study of Genetically Targeted Enzyme Replacement Therapy for Advanced Heart Failure) was completed. This study used coronary arterial infusion of adeno-associated virus type 1 carrying the gene for SERCA2a and demonstrated that natriuretic peptides were decreased, reverse remodeling was noted, and symptomatic improvements were forthcoming. Stromal-derived factor 1 enhances myocardial repair and facilitates "homing" of stem cells to the site of tissue injury. Strategies using intramyocardial injections to deploy this gene at sites of injury are being studied.

More advanced therapies for late-stage heart failure such as left ventricular assist devices and cardiac transplantation are covered in detail in Chap. 281.

DISEASE MANAGEMENT AND SUPPORTIVE CARE

Despite stellar outcomes with medical therapy, admission rates following heart failure hospitalization remain high, with nearly half of all patients readmitted to hospital within 6 months of discharge. Recurrent heart failure and related cardiovascular conditions account for only half of readmissions in patients with heart failure, whereas other comorbidity-related conditions account for the rest. The key to achieving enhanced outcomes must begin with the attention to transitional care at the index hospitalization with facilitated discharge through comprehensive discharge planning, patient and caregiver education, appropriate use of visiting nurses, and planned follow-up. Early postdischarge follow-up, whether by telephone or clinic-based, may be critical to ensuring stability because most heart failure–related readmissions tend to occur within the first 2 weeks after discharge. Although routinely advocated, intensive surveillance of weight and vital signs with use of telemonitoring has not decreased hospitalizations. Intrathoracic impedance measurements have been advocated for the identification of early rise in filling pressure and worsened hemodynamics so that preemptive management may be employed. However, this has not been successful and may worsen outcomes in the short term. Implantable pressure monitoring systems do tend to provide signals for early decompensation, and in patients with moderately advanced symptoms, such systems have been shown to provide information that can allow implementation of therapy to avoid hospitalizations by as much as 39% (in the CardioMEMS Heart Sensor Allows Monitoring of Pressure to Improve Outcomes in NYHA Class III Heart