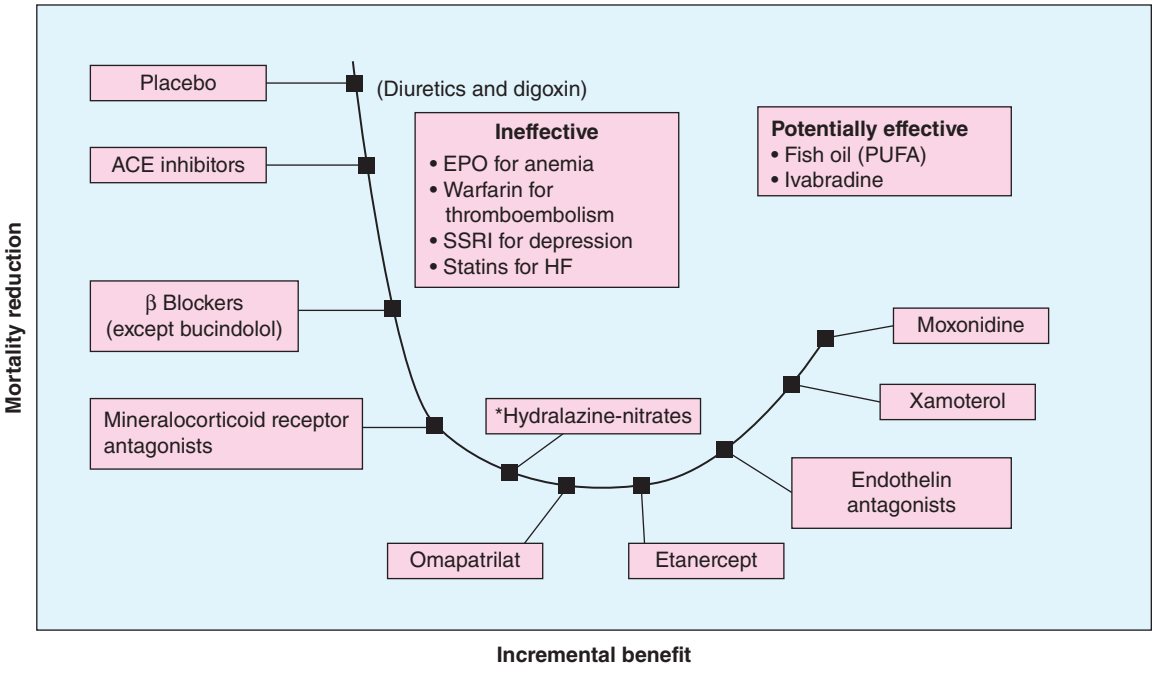

FIGURE 280-3 **Progressive decline in mortality** with angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs), beta blockers, mineralocorticoid receptor antagonists, and balanced vasodilators (*selected populations such as African Americans); further stack-on neurohormonal therapy is ineffective or results in worse outcome; management of comorbidity is of unclear efficacy. EPO, erythropoietin; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; PUFA, polyunsaturated fatty acid; SSRI, selective serotonin reuptake inhibitor.

(digoxin, inotropic therapy) ushered in the era of disease-modifying therapy with neurohormonal antagonism. In this regard, ACEIs and beta blockers form the cornerstone of pharmacotherapy and lead to attenuation of decline and improvement in cardiac structure and function with consequent reduction in symptoms, improvement in quality of life, decreased burden of hospitalizations, and a decline in mortality from both pump failure and arrhythmic deaths (Fig. 280-3).

NEUROHORMONAL ANTAGONISM

Meta-analyses suggest a 23% reduction in mortality and a 35% reduction in the combination endpoint of mortality and hospitalizations for heart failure in patients treated with ACEIs. Patients treated with beta blockers provide a further 35% reduction in mortality on top of the benefit provided by ACEIs alone. Increased experience with both agents in a broad range of patients with HFrEF has demonstrated the safety of ACEIs in treating patients with mild renal insufficiency and the tolerability of beta blockers in patients with moderately controlled diabetes, asthma, and obstructive lung disease. The benefits of ACEIs and beta blockers extend to advanced symptoms of disease (NYHA class IIIb–IV). However, a substantial number of patients with advanced heart failure may not be able to achieve optimal doses of neurohormonal inhibitors and require cautious reduction in dose exposure to maintain clinical stability. Such individuals with lower exposure to ACEIs and beta blockers represent a high-risk cohort with poor prognosis.

Class Effect and Sequence of Administration ACEIs exert their beneficial effects in HFrEF as a class; however, the beneficial effects of beta blockers are thought to be limited to specific drugs. Beta blockers with intrinsic sympathomimetic activity (xamoterol) and other agents, including bucindolol, have not demonstrated a survival benefit. On the basis of investigations, beta blocker use in HFrEF should be restricted to carvedilol, bisoprolol, and metoprolol succinate—agents tested and proven to improve survival in clinical trials. Whether beta blockers or ACEIs should be started first was answered by the Cardiac Insufficiency Bisoprolol Study (CIBIS) III, in which outcomes did not vary when either agent was initiated first. Thus, it matters little which agent is initiated first; what does matter is that optimally titrated doses of both ACEIs and beta blockers be established in a timely manner.

Dose and Outcome A trial has indicated that higher tolerated doses of ACEIs achieve greater reduction in hospitalizations without materially improving survival. Beta blockers demonstrate a dose-dependent improvement in cardiac function and reductions in mortality and hospitalizations. Clinical experience suggests that, in the absence of symptoms to suggest hypotension (fatigue and dizziness), pharmacotherapy may be up-titrated every 2 weeks in hemodynamically stable and euvolemic ambulatory patients as tolerated.

MINERALOCORTICOID ANTAGONISTS

Aldosterone antagonism is associated with a reduction in mortality in all stages of symptomatic NYHA class II to IV HFrEF. Elevated aldosterone levels in HFrEF promote sodium retention, electrolyte imbalance, and endothelial dysfunction and may directly contribute to myocardial fibrosis. The selective agent eplerenone (tested in NYHA class II and post–myocardial infarction heart failure) and the nonselective antagonist spironolactone (tested in NYHA class III and IV heart failure) reduce mortality and hospitalizations, with significant reductions in sudden cardiac death (SCD). Hyperkalemia and worsening renal function are concerns, especially in patients with underlying chronic kidney disease, and renal function and serum potassium levels must be closely monitored.

RAAS THERAPY AND NEUROHORMONAL "ESCAPE"

Neurohormonal "escape" has been witnessed in patients with HFrEF by the finding that circulating levels of angiotensin II return to pretreatment levels with long-term ACEI therapy. ARBs blunt this phenomenon by binding competitively to the AT_1 receptor. A large meta-analysis of 24 randomized trials showed the superiority of ARBs to placebo in patients with intolerable adverse effects with ACEIs and their noninferiority in all-cause mortality or hospitalizations when compared with ACEIs. The Valsartan Heart Failure Trial (Val-HeFT) suggested that addition of valsartan in patients already receiving treatment with ACEIs and beta blockers was associated with a trend toward worse outcomes. Similarly, adding valsartan to captopril in patients with heart failure after myocardial infarction who were receiving background beta blocker therapy was associated with an increase in adverse events without any added benefit compared with