POSITION STATEMENT ON ACE-INTEGRANCE (December 2002)

Approximately 8-10% of patients will not be able to tolerate ACE-inhibitors due to the development of intractable cough, hyperkalemia, renal dysfunction and/or angioedema. Angiotension II type I receptor blockers (ARBs) and vasodilating drugs (hydralazine and isosorbide dinitrate) are possible alternatives for the ACE-intolerant patient.

The Evaluation of Losartan in the Elderly (ELITE) trial\(^1\) was designed to determine whether the efficacy and safety of an ARB (losartan) are superior to those of an ACE-inhibitor (captopril) in older patients with moderate heart failure. ELITE investigators randomized 733 patients at least 65 years of age with NYHA Class II to IV heart failure and ejection fraction ≤ 40% to 48 weeks of treatment with either losartan (target dose 50 mg qd) or captopril (target dose 50 mg tid). None of the participants in the double-blind study had been previously treated with an ACE-inhibitor. The primary trial end point was renal dysfunction. The secondary end point was death and/or hospitalization for CHF, and the tertiary end points were hypotension, hyperkalemia, and cough. The incidence of the primary end point, renal dysfunction, as well as the tertiary end points of hyperkalemia and hypotension were comparable between patients randomized to captopril and those assigned to losartan. However, the incidence of death and/or hospitalization for heart failure at 48 weeks was only 9.4% in the losartan group, as compared with 13.2% in their captopril-treated counterparts. This 32% risk reduction stemmed primarily from a striking 46% reduction in all-cause mortality, from 8.7% with captopril to 4.8% with losartan (P = 0.035). Losartan was significantly better tolerated than captopril, with only 12.2% of the patients discontinuing therapy because of adverse effects, as compared with 20.8% of captopril-treated patients (p = 0.002). The difference in discontinuation rate was primarily due to a 7% withdrawal rate related to cough (3.8%), rash, angioedema, taste disturbances or reduced appetite in patients assigned to captopril. None of the losartan-treated patients stopped study drug because of cough.

Since overall mortality was not the primary end point of the ELITE trial and since the absolute number of deaths in the study was small, the larger scale ELITE II trial was conducted\(^2\). Patients (n = 3152) who were at least 60 years of age with NYHA Class II to IV heart failure and LV ejection fraction ≤ 40% were again randomly assigned to either losartan (target dose 50 mg qd) or captopril (target dose 50 mg tid). Candidates for the study were required to be ACE inhibitor/ARB-naive or to have received no more than 7 days of treatment with these agents within the three months prior to randomization. The duration of the study was event-driven, with treatment continued until 510 deaths had occurred. The ELITE II population was 69% male with a mean age of 71.5 years and a mean LV ejection fraction of 31%. Heart failure was of ischemic origin in 80% of enrollees. Most of the participants had mild to moderate heart failure (NYHA Class II: 48%, Class III: 45%, Class IV: 6%). More than 75% of ELITE II enrollees were receiving diuretic therapy, 50% were on digitalis, and nearly 25% were taking a beta-blocker. Unlike ELITE I, no significant differences were observed between the two treatment arms with respect to the primary end point of all cause mortality or with respect to the composite secondary end point of all cause mortality and hospitalization. In fact, survival rates tended to favor patients assigned to captopril (280 deaths in the losartan group vs. 250 deaths in the captopril group) despite a greater withdrawal rate from study drug (captopril: 15% vs. losartan: 10%). Thus, the superiority of losartan over captopril observed in ELITE I was not borne out by the large scale ELITE II trial. Moreover, the ELITE trial program did not include a placebo group; the impact of losartan on survival in patients with mild to moderate heart failure can only be surmised from these studies.
In the Randomized Trial of the Angiotensin-Receptor Blocker Valsartan in Chronic Heart Failure\textsuperscript{3} (Val-HeFT, see attached summary), patients (n = 5010) with NYHA Class II-IV heart failure, LVEF ≤ 40\%, were randomly assigned to receive either valsartan (target dose: 160 mg BID) or placebo in addition to conventional therapy for heart failure. Patients were stratified according to whether or not they were receiving beta-blocker therapy to ensure equal distribution. Mean duration of follow-up was 23 months. Valsartan-treated patients were less likely (27.5\% reduction) to be hospitalized for heart failure. No differences in total mortality were observed between the two groups. While valsartan had a favorable impact on combined morbidity and mortality in patients treated with either an ACE-inhibitor or a beta-blocker, an increase in mortality was observed in the group of patients treated with all 3 agents (ARB, ACE-I, beta-blocker). Of the 5010 patients evaluated, 366 (7.3\%) were not treated with ACE-inhibitors at baseline\textsuperscript{4}. In this small group of patients, all cause mortality and combined mortality and morbidity were significantly reduced in the valsartan group compared to placebo group (17.3\% versus 27\%, P = 0.017 and 24.9\% versus 42.9\%, p < 0.001, respectively).

Combined vasodilator therapy with hydralazine and isosorbide dinitrate is another alternative treatment which can be considered in the ACE-intolerant patient. The first Veterans Administration Cooperative Vasodilator – Heart Failure Trial (V-HeFT I)\textsuperscript{5} randomly assigned 642 patients with stable symptomatic heart failure (mean LVEF 30\%) to receive, in addition to digoxin and diuretics, either the alpha-adrenergic blocker prazosin or the combination of hydralazine (target dose: 75 mg QID) and isosorbide dinitrate (ISDN: target dose 40 mg q 6 hrs, except for hs), or placebo. The combination of hydralazine and ISDN significantly reduced two-year mortality by 34\% and three-year mortality by 36\%, relative to placebo. In contrast, prazosin had no impact on survival. Unlike placebo or prazosin, the hydralazine – ISDN combination significantly improved ejection fraction by 2.9\% at eight weeks and by 4.2\% at one year.

The aim of the second VA Cooperative Vasodilator – Heart Failure Trial (V-HeFT II)\textsuperscript{6} was to compare the efficacy of direct-acting, nonspecific vasodilator therapy with drug therapy embodying the dual mechanisms of vasodilation and neurohormonal blockade. To this end, the V-HeFT II investigators randomly assigned 804 men to receive either the combination of hydralazine, 75 mg QID, plus ISDN, 40 mg QID, or the ACE-inhibitor enalapril 10 mg BID. More than 90\% of the participants were in NYHA functional classes II-III and more than 50\% had coronary artery disease as the underlying etiology for their heart failure. Patients assigned to enalapril had significantly improved survival as compared with those randomized to hydralazine – ISDN. Enalapril reduced one-year mortality by 33.6\% and two-year mortality by 28.2\% (P = 0.016). Thus, the V-HeFT II results suggested that blockade of the renin-angiotensin system more successfully prolongs life in heart failure patients than does nonspecific vasodilation. Of interest, although both regimens significantly increased LV ejection fractions, the rise was significantly greater with hydralazine-ISDN than with the ACE-inhibitor. Likewise, the direct-acting vasodilator combination significantly enhanced exercise tolerance in this study whereas enalapril did not.

Based on the results of these trials, we advocate the following in ACE-intolerant patients:

1. Patients unable to tolerate ACE-inhibitor therapy due to rash, intractable cough, angioedema or taste disturbances should be placed on valsartan. Valsartan should be initiated at 40 mg BID and titrated upwards every two weeks as tolerated until the target dose of 160 mg BID is achieved. Valsartan is the preferred ARB as it is the only drug in its class to have FDA approval in the ACE-intolerant patient with heart failure due to LV systolic dysfunction (Val-HeFT).
While valsartan has not been compared to combination vasodilator therapy (hydralazine – ISDN) in a randomized trial, to prove superiority, patients are likely to be more compliant with valsartan due to ease of administration and a better side effect profile.

2. Combination vasodilator therapy (hydralazine, ISDN) is recommended in patients unable to tolerate an ACE-inhibitor due to renal insufficiency or hyperkalemia. The development of renal insufficiency or hyperkalemia on ACE-inhibitors is not an indication for conversion to an angiotensin II receptor antagonist; these agents have comparable rates for the development of renal insufficiency and hyperkalemia. The target dose for hydralazine is 75 mg QID and for ISDN is 40 mg every 6 hours except at bedtime.

References:


