Perspective Article

Targeted Mono-Therapy for Newly Diagnosed Dilated Cardiomyopathy

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In patients with stage C heart failure with reduced ejection fraction (HFrEF), guidelines recommend initiating combined therapy with angiotensin-converting enzyme inhibition (ACEI) or angiotensin receptor blockade (ARB) and specific beta-adrenergic receptor blockade (BARB).[1] However, mono-therapy with BARB may be preferable to combined ACEI/ARB and BARB therapy in a subset of patients with newly diagnosed dilated cardiomyopathy.

Renin-Angiotensin-Aldosterone System Modulation

Long-term ACEI was the first pharmacologic intervention to lower mortality in patients with HFrEF, and ACEI, is well tolerated in patients with fluid overload, in contrast to BARB. Accordingly, routine management of HFrEF includes combined ACEI-BARB therapy with first starting ACEI followed by BARB. The beneficial effect of enalapril on clinical outcomes correlates with the severity of HFrEF symptoms. Enalapril decreased mortality by 27% in the Cooperative North−Scandinavian Enalapril Survival Study (CONSENSUS) that enrolled patients with HFrEF and functional class (FC) IV symptoms.[2] Enalapril reduced mortality by 16% in the treatment arm of the Studies of Left Ventricular Dysfunction (SOLVD) that mostly enrolled patients with HFrEF and FC II-III symptoms.[3] The reduction in mortality did not reach statistical significance in asymptomatic patients with HFrEF enrolled in the SOLVD prevention arm.[4] Enalapril extended life expectancy by an average of 12 months in CONSENSUS patients and by an average of 9.2 months in SOLVD treatment arm patients.[5] Symptomatic patients with HFrEF experience sudden cardiac death and have a limited life expectancy despite long-term ACEI.[2,3,5] Long-term ACEI lessens cardiac loading conditions and thereby increases left ventricular ejection fraction (LVEF) in patients with HFrEF. However, long-term ACEI does not reverse left ventricular (LV) remodeling as LVEF returns to pretreatment values within 15 days of ACEI discontinuation.[6]

The use of ARB is recommended in patients with HFrEF who are intolerant to ACEI.[1] The Candesartan in Heart failure Assessment of Reduction in Mortality and morbidity (CHARM)-Added and CHARM-Alternative trials evaluated addition and substitution of candesartan to ACEI in patients with HFrEF. Both trials showed a reduction in cardiovascular mortality and heart failure (HF) hospitalizations, which was more pronounced with substitution than with addition of candesartan (30% vs 15%). Of note, only 50% of the CHARM patients were receiving BARB.[7,8] Long-term ARB alone or in combination with ACEI has not been studied in asymptomatic patients with HFrEF.

The Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF) evaluated mineralocorticoid receptor blockade with eplerenone in patients with mild HFrEF (FC class I).[9] Eplerenone reduced death from cardiovascular causes and HF hospitalizations by 37%. In contrast to the findings of the Randomized Aldactone Evaluation Study (RALES) with spironolactone, eplerenone did not reduce sudden cardiac death.[10] However, only 10% of RALES patients were receiving BARB.

In summary, long-term renin-angiotensin-aldosterone system (RAAS) modulation extends life expectancy in symptomatic HFrEF patients but does not reverse LV remodeling or prevent sudden cardiac death in mild or asymptomatic patients with HFrEF. The survival benefit of ACEI is overall modest in HFrEF and mainly experienced by patients with FC III-IV symptoms. Prevention of fluid retention in asymptomatic or mildly symptomatic patients is best achieved by loop diuretics than by ACEI alone.

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Sympathetic Nervous System Activity Modulation

The steady deterioration of LV function triggers compensatory activation of the sympathetic nervous system (SNS) in patients with HFrEF.[11] Long-term administration of specific BARB reduces mortality by 35% in patients with HFrEF who are already receiving ACEI.[12] Long-term BARB therapy alleviates the detrimental effects of increased SNS activity on intracellular calcium transport and myocyte necrosis.[12] Waagstein et al[13] uncovered a reversal of LV remodeling during long-term metoprolol tartrate administration: the increase in LVEF persisted after discontinuation of metoprolol tartrate. The transition from HFrEF to heart failure with preserved ejection fraction (HFpEF) is more likely to occur when patients are treated with long-term BARB. Of note, patients receiving long-term ACEI do not transition from HFrEF to HFpEF.[14]

The long-lasting effect of BARB on LV size and function may contribute to its protracted effect on survival.[15]

Long-term SNS modulation reverses LV remodeling and improves survival in asymptomatic patients with LV systolic dysfunction (LVSD). The Reversal of Ventricular Remodeling with Toprol-XL (REVERT) Trial randomized asymptomatic patients with LVSD who were already receiving ACEI or ARB to 200 mg of metoprolol succinate versus placebo. After a follow-up of 12 months, metoprolol succinate increased LVEF by 6±1% ($P < .05$) compared with placebo.[16] Half of the 1959 patients enrolled in the Carvedilol Post-Infarct Survival Control in Left Ventricular Dysfunction (CAPRICORN) placebo-controlled randomized study, were asymptomatic for HF. During an average follow-up of 15 months, carvedilol reduced mortality risk by 23% ($P = .031$).[17]

In summary, long-term BARB therapy is the most reliable pharmacologic intervention to improve LV systolic function and reduce LV size in asymptomatic patients with LVSD. In the absence of head-to-head comparison, one can only speculate that BARB prolongs life expectancy to a greater extent than ACEI in HFrEF.

Angiotensin Receptor-Neprilysin Inhibition

The 2017 American College of Cardiology/American Heart Association guideline update recommends substituting ACEI/ARB with angiotensin receptor-neprilysin inhibition (ARNI) in patients who remain symptomatic (FC II-III).[18] Angiotensin receptor blockade was added to neprilysin inhibition to lessen RAAS activation and enhance the natriuretic peptide system activity.[19] The clinical effectiveness of ARNI was compared with that of ACEI with enalapril in 8339 patients with HFrEF with FC II-IV symptoms and plasma BNP >150 pg/mL or BNP >100 pg/mL when they had been hospitalized over the past 12 months. Sacubitril-Valsartan reduced cardiovascular mortality or HF hospitalization by 20% over a median duration of 27 months. Symptomatic hypotension occurred more often with sacubitril-valsartan than with enalapril.[20] In patients who were all previously receiving ACEI/ARB, ARNI increased LVEF by 4% likely from improved loading conditions.[21]

In summary, ARNI therapy is more beneficial than ACEI in symptomatic patients with HFrEF. However, unlike BARB therapy, ARNI therapy does not appear to reverse LV remodeling or prevent sudden cardiac death.

Mono-Therapy for 6 Months Before Combined Therapy

Three prospective studies of mono-therapy with ACEI or BARB for 3−6 months followed by combined ACEI-BARB therapy do not support the initiation of HFrEF therapy with BARB alone.[22−24] However, patients in these 3 studies, especially in CIBIS III, were not appropriate candidates for mono-therapy with BARB. Patients in CIBIS III were old, diagnosed with HFrEF 18 months before enrollment, and receiving diuretic therapy for FCII-III symptoms.[24] Further, 68.2% of CIBIS III patients were male and 62.4% had history of myocardial infarction.[24]

Candidates for Mono-Therapy

Long-term BARB is most likely to reverse LV remodeling in young patients with newly diagnosed dilated cardiomyopathy, normal QRS and no diabetes.[25−27] In a meta-analysis of 12 large therapeutic trials in patients with LVSD, asymptomatic women did not derive mortality benefit from long-term ACEI.[28] Last, symptomatic women with LVSD have been shown to derive greater survival benefit from long-term BARB than their male counterparts.[29] Thus, a therapeutic trial of mono-therapy with BARB in HFrEF may focus on asymptomatic, non-diabetic women with newly diagnosed dilated cardiomyopathy and normal QRS duration. The study parameters would include LV function and dimensions at baseline, 3 and 6 months with reversal of LV remodeling as a primary endpoint.

Comments

Initiation of combined ACEI/ARNI-BARB therapy with ACEI or ARNI first decreases the likelihood of achieving target doses of BARB as ACEI/ARNI reduces blood pressure (BP) margin for BARB.[30,31] In the PARADIGM-HF trial, the reduction in systolic BP was 4−6 mm Hg greater with ARNI and symptomatic hypotension occurred more frequently in patients receiving ARNI than enalapril.[32] In contrast, initiation of combined therapy with BARB first increases the likelihood to reach the dose of BARBs shown to lower mortality in randomized therapeutic trials.[33] Long-term ACEI is not likely to enhance an already normal functional capacity and increase the life expectancy of an asymptomatic patient. Long-term BARB therapy is the only intervention that reverses LV remodeling in an asymptomatic patient with normal QRS duration.[16] Long-term BARB is more effective for prevention of sudden cardiac death than long-term ACEI. To the contrary, combined ACEI-

BARB therapy may lessen adherence to medical regimen and lower the likelihood of reaching the maximally recommended carvedilol daily dose of 100 mg in a patient with body weight >187 lb (85 kg). The primary therapeutic goals in patients with HFrEF are to improve LVEF, prevent sudden cardiac death, and pump failure.

We recommend a stepwise approach to the management of asymptomatic or mildly symptomatic (FC I) patients with HFrEF with the introduction of BARB therapy and uptitration to maximally recommended doses followed by ACEI if LVEF remains low or worsening FC.

Conclusion

Mono-therapy with BARB may enhance adherence to the only medication that reverses LV remodeling. Combined ACEI-BARB/ARNI-BARB therapy lessens the likelihood of attaining effective doses of BARB and is of questionable benefit in asymptomatic or mildly symptomatic patients with dilated cardiomyopathy, especially among females. A patient-centered approach to HF guideline may be preferable to a chronological approach.

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