Effect of Ivabradine vs Atenolol on heart rate and effort tolerance in patients with mild to moderate mitral stenosis and normal sinus rhythm (IVA-MS Trial)

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Introduction

- Mild to moderate mitral stenosis frequently becomes symptomatic during episodes of exercise and increased heart rate
- Theoretically, negative chronotropic agents should be helpful in controlling tachycardia related symptoms in this individuals
- However, results from various clinical and hemodynamic studies with these agents have been conflicting
- Ivabradine has selective action on sinus node and thus is devoid of the usual side effects of beta-blockers
- We investigated the comparative efficacy of ivabradine and atenolol in patients with mild to moderate mitral stenosis and normal sinus rhythm.

Methods

- Randomized, open-label, cross over trial of ivabradine and Atenolol
- Inclusion criteria:
  - Patients with mild to moderate mitral stenosis in normal sinus rhythm
  - Age 18 – 70 years
  - Mitral valve area ≥1.0 cm² and < 2.0 cm² on echocardiography in normal sinus rhythm
  - Requiring rate controlling agents for their effort/tachycardia related symptoms
- Exclusion criteria:
  - Atrial fibrillation
  - Other significant valvular lesions
  - Inability to perform treadmill test (TMT)/Contraindication for TMT
  - Need for surgical treatment or Balloon Mitral Valvotomy
  - Presence of significant non-cardiac co-morbidities
  - Pregnancy
  - Known allergy/intolerance to study drugs
  - Known coronary artery disease.

Protocol

- Heart rate-limiting agents were stopped for 5 half-lives prior to the baseline visit
- Patients were randomized to either ivabradine (5 mg twice a day) or atenolol (50 mg once a day), according to the computer generated random number sequence
- Each drug was given for 4 weeks each and then switched over to the other drug without any washout period.
- History and clinical examination, detailed echocardiography, TMT as per Bruce protocol and 24 hour Holter monitoring was done prior to initiation of therapy and were repeated in the final week of each drug therapy i.e. in the 4th and 8th week
- Primary endpoint - Difference in total exercise time on TMT between the two treatments.
- Secondary endpoint - Difference in mean and maximum heart rate between the two treatments on Holter and TMT, respectively

Statistical analysis

We used the standard AB/BA design for analyzing crossover studies. Analysis of variance (ANOVA) for a 2x2 crossover study specifically to assess period effect and carryover effect. Point estimates (absolute difference in time [s] between atenolol and ivabradine) and their 95% confidence intervals (CI) for the three main treatment effects were calculated. We have done per protocol analysis i.e. only those patients who completed both the treatment phase were analyzed.