



# **VALOR-HCM: Mavacamten as An Alternative to Surgical Septal Myectomy or Alcohol Ablation in Patients With Severely Symptomatic Obstructive Hypertrophic Cardiomyopathy**

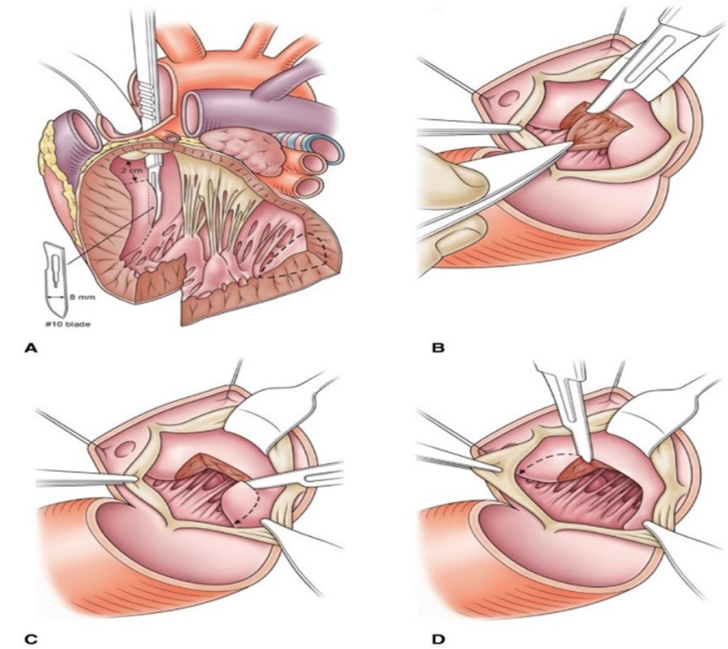
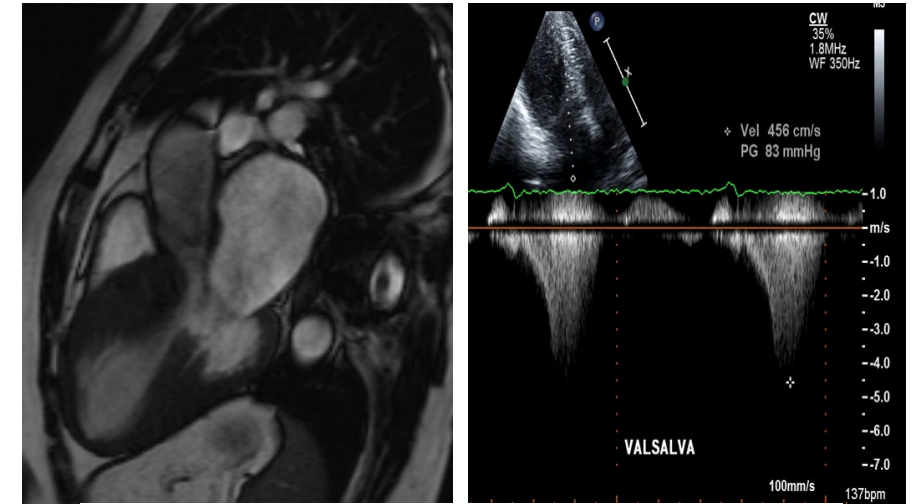
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Professor of Medicine, CCLCM  
Director, Hypertrophic Cardiomyopathy Center  
Heart, Vascular & Thoracic Institute  
Cleveland Clinic  
Cleveland, OH

On behalf of the Valor-HCM investigators

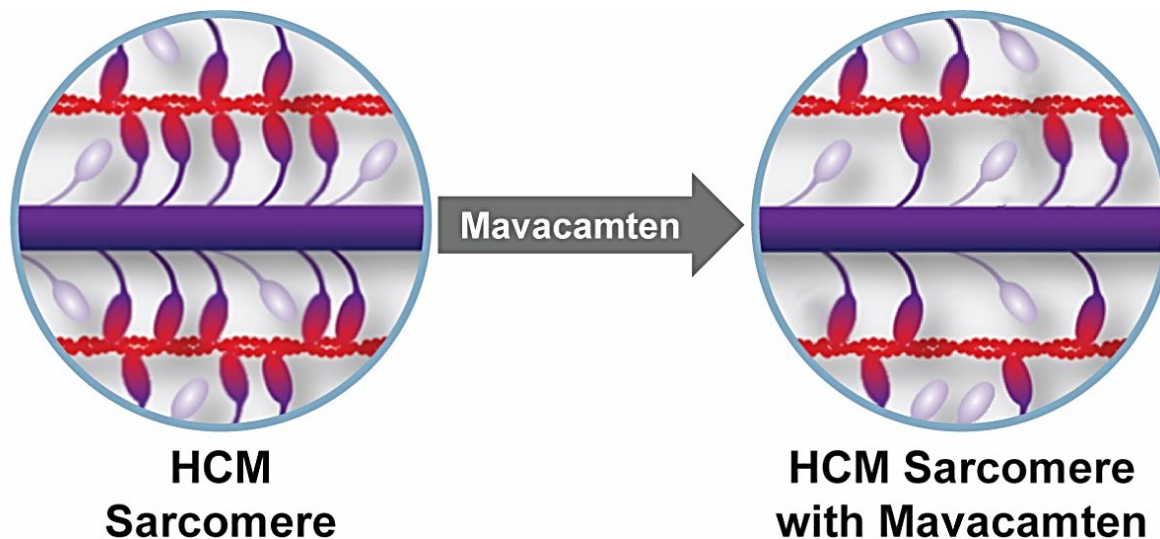
Disclosures: Dr. Desai is a consultant for Bristol Myers Squibb and Medtronic  
The VALOR-HCM study was funded by MyoKardia, Inc., a wholly owned subsidiary of Bristol Myers Squibb

# Hypertrophic Cardiomyopathy

- Hypertrophic cardiomyopathy (HCM) is a myocardial disorder characterized by primary left ventricular (LV) hypertrophy
  - Prevalence: 1:200 to 1:500, Estimated 15-20 million worldwide
    - Two-thirds of patients have obstructive HCM (oHCM)
    - Symptoms often related to LV outflow tract (LVOT) obstruction
  - Current medical therapies not developed specifically for HCM
- Septal reduction therapies (SRT), either surgical septal myectomy or alcohol ablation, are recommended for patients with intractable symptoms despite maximal medical therapy
  - Although SRT improves long-term survival, symptoms and quality of life, optimal results require specialized care not widely available
- Accordingly, there is an unmet need for noninvasive alternatives to SRT for highly symptomatic oHCM patients



# Mavacamten: Mechanism of Action

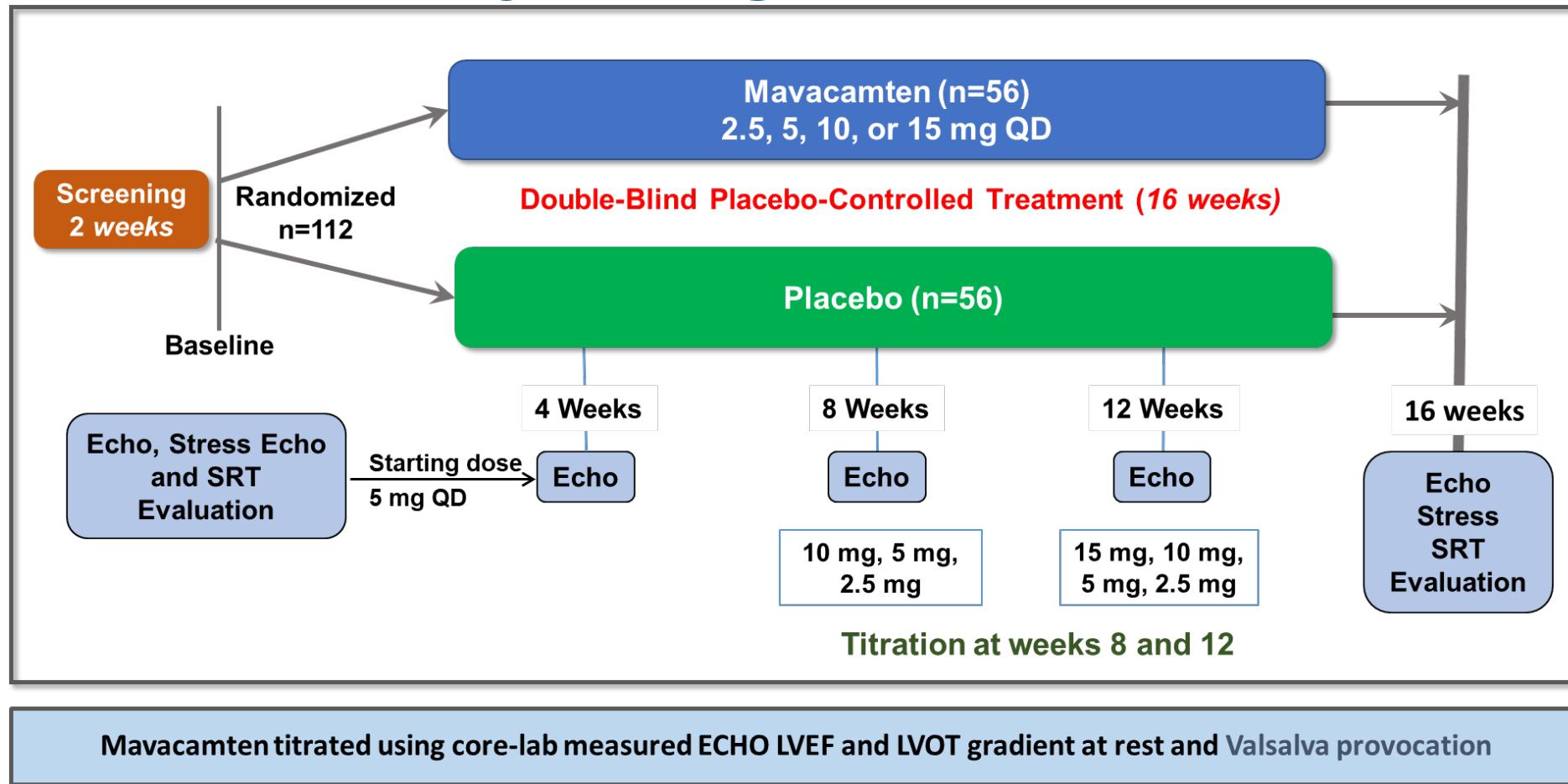


Hyper contractility  
Impaired relaxation  
Altered myocardial energetics

Reduces myosin-actin cross bridges  
To attenuate hypercontractility and  
improved compliance and energetics

Mavacamten, a targeted inhibitor of cardiac myosin, decreases the number of myosin-actin cross-bridges and reduces excessive contractility characteristic of HCM  
In oHCM, improves LVOT gradient, QOL and physical functioning

# Valor-HCM Study Design



Valor HCM sought to determine if addition of mavacamten to maximally-tolerated medical therapy would allow severely symptomatic oHCM patients to improve sufficiently that they no longer met guideline criteria for SRT or chose not to undergo SRT for 16 weeks

# Baseline Data and Primary Endpoint

	Mavacamtem (n=56)	Placebo (n=56)
Age	59.8 years	60.9 years
Female sex	48.2%	50.0%
NYHA Class III or higher	92.9%	92.9%
Medical therapy		
Beta Blocker monotherapy n(%)	26 (46.43%)	25 (44.64%)
Nondihydropyridine CCB monotherapy	7 (12.50%)	10 (17.86%)
Resting LVOT Gradient	51.2 mmHg	46.3 mmHg
Post-exercise Gradient	82.5 mmHg	85.2 mmHg

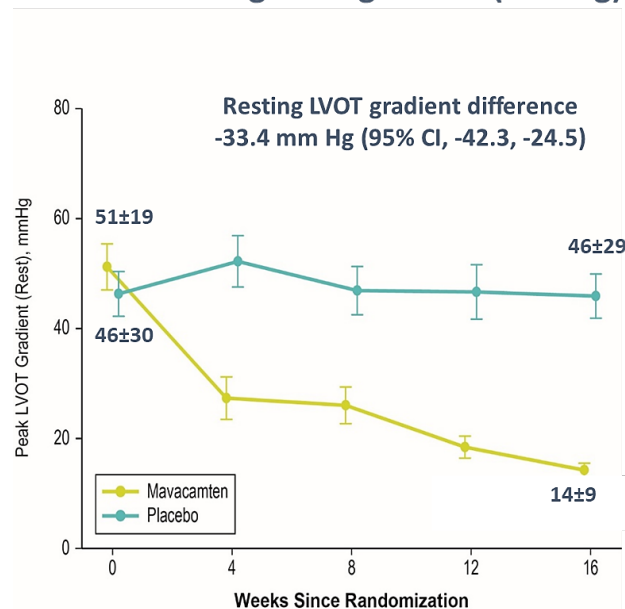
36 (32%) on combination medical therapy; 22 (20%) were on disopyramide (mono or combination therapy)

## Primary Endpoint

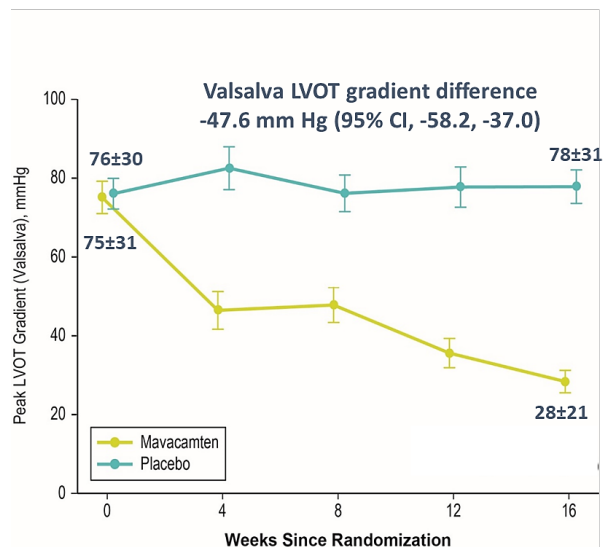
Parameters	Mavacamtem (N=56)	Placebo (N=56)	Treatment Difference (95% CI)
Composite of: Decision to proceed with SRT by Week 16 or guideline eligible at Week 16 n/N (%)	10/56 (17.9)	43/56 (76.8)	58.93 (43.99,73.87) <i>P</i> <0.0001

# Secondary Efficacy Endpoints

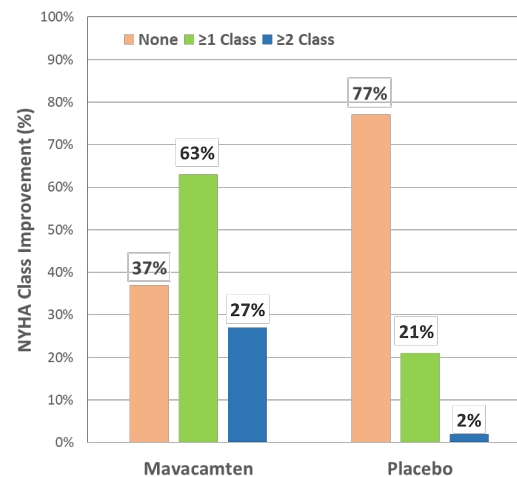
Resting LVOT gradient (mm Hg)



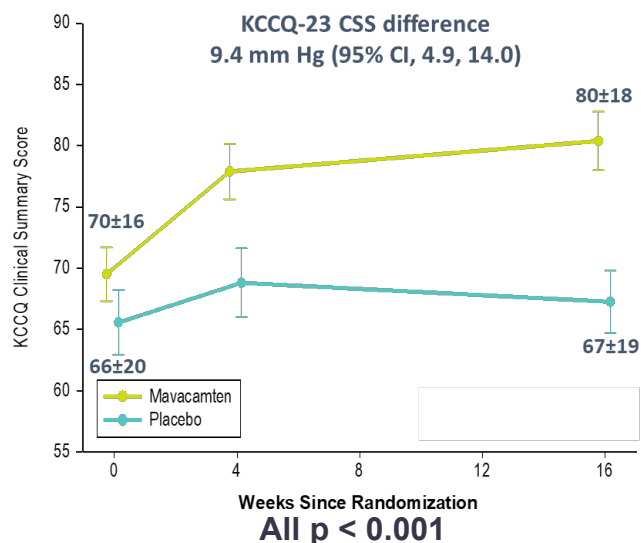
Valsalva LVOT gradient (mm Hg)



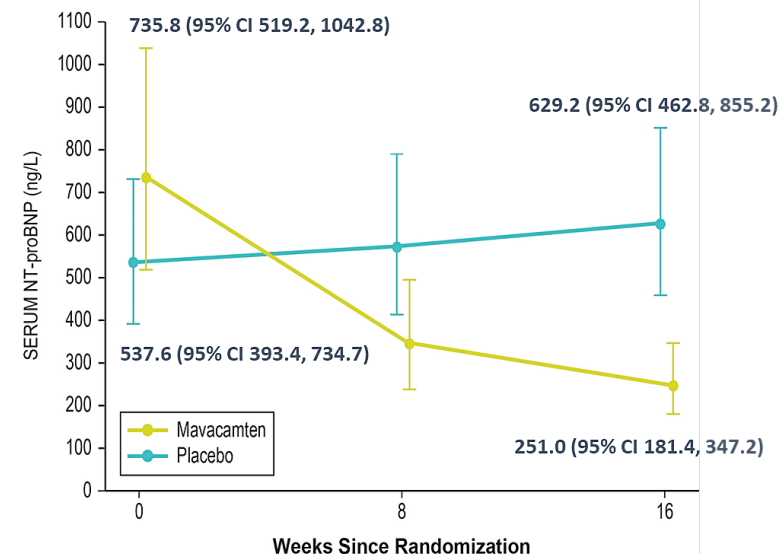
Patients Who Improved  
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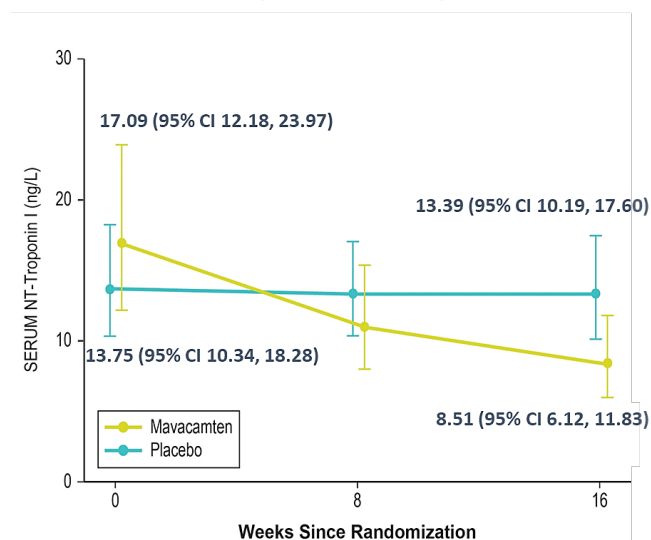
KCCQ-23 Clinical Summary Score



NT-proBNP geometric mean ratio difference  
0.33 (95% CI, 0.26, 0.45)

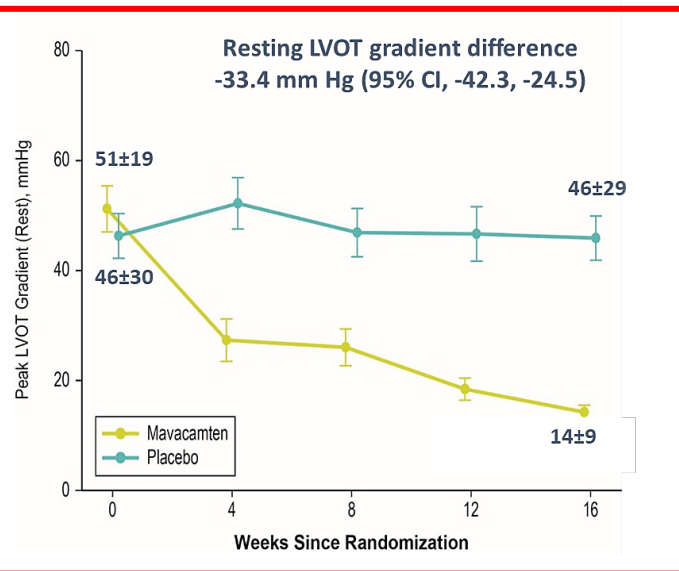


Troponin I geometric mean ratio difference  
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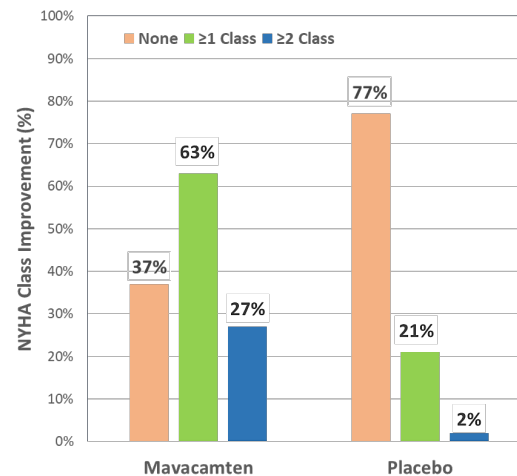


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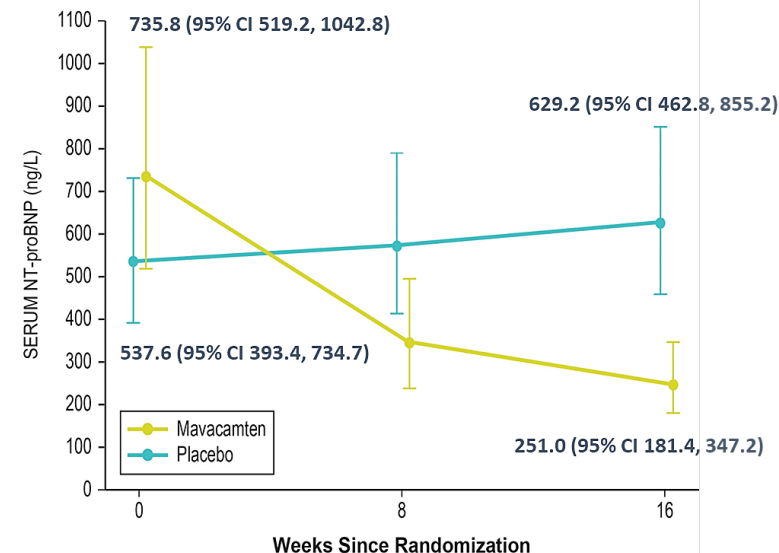
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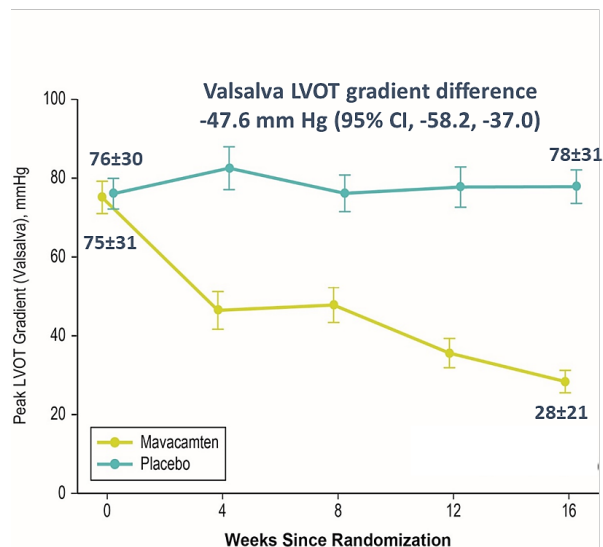
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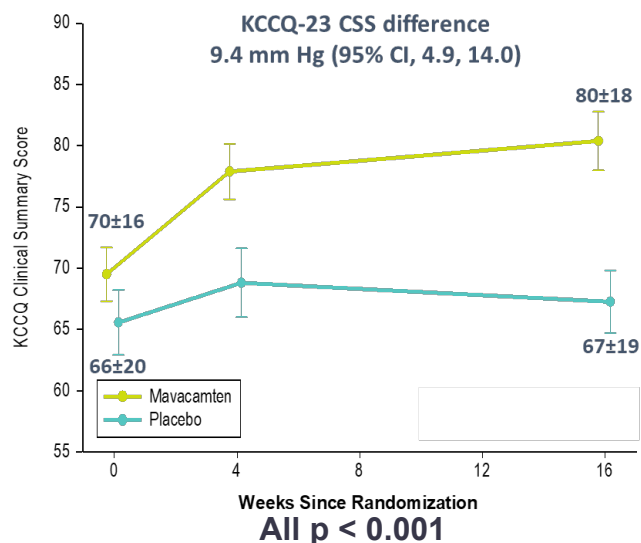
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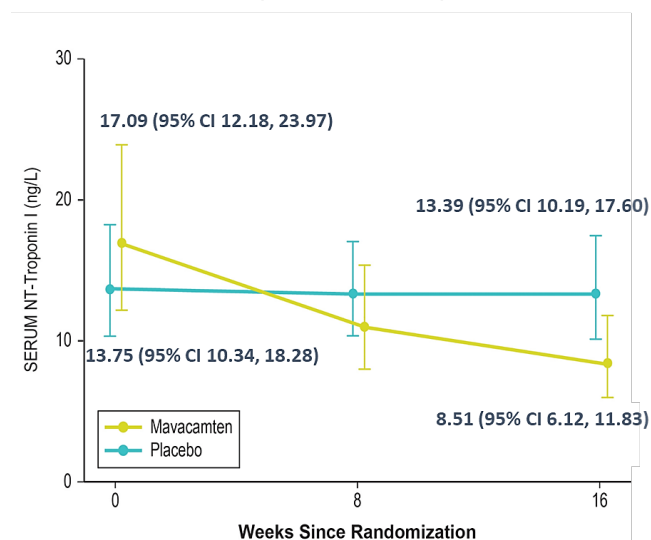
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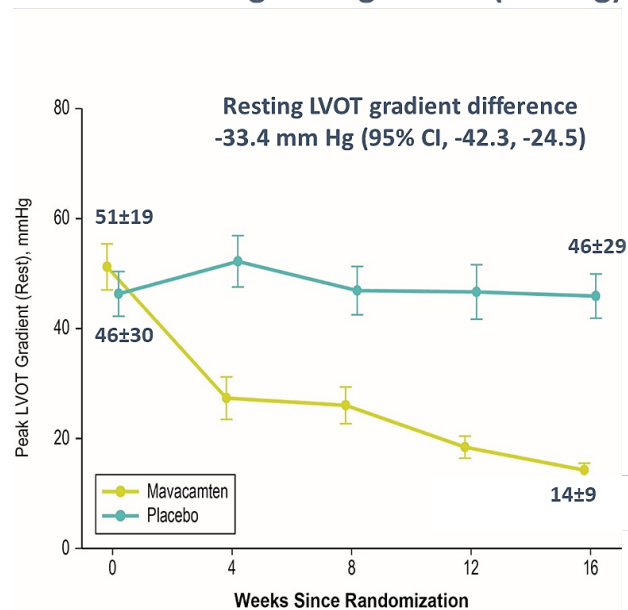


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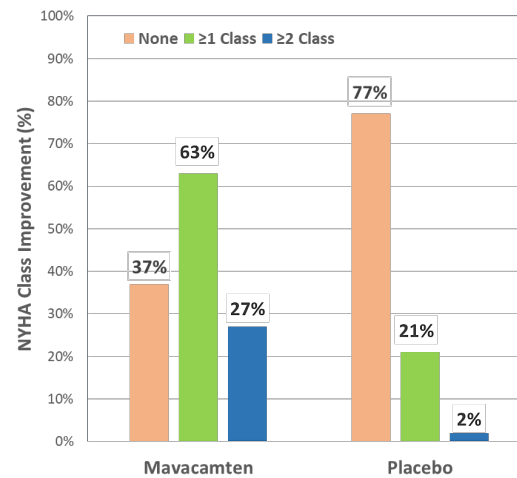


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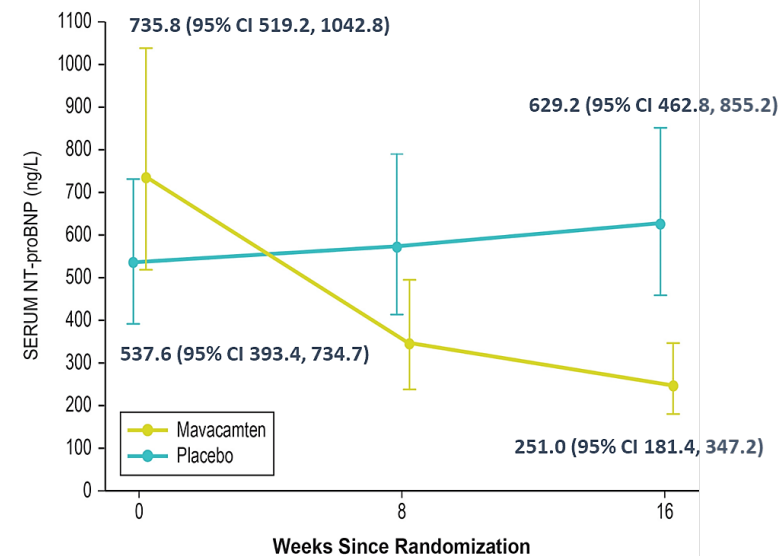
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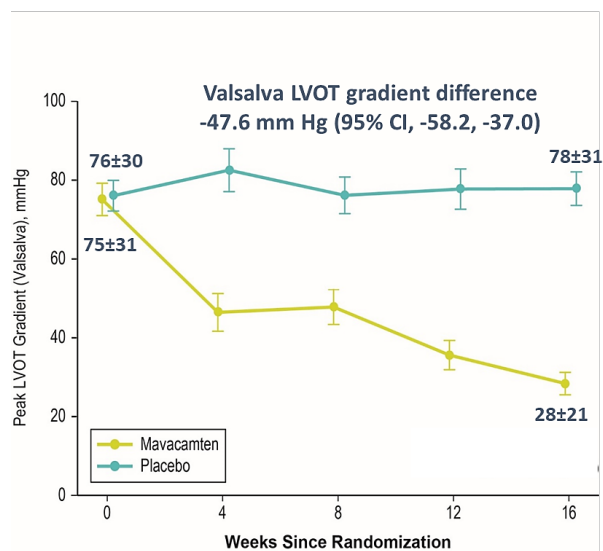
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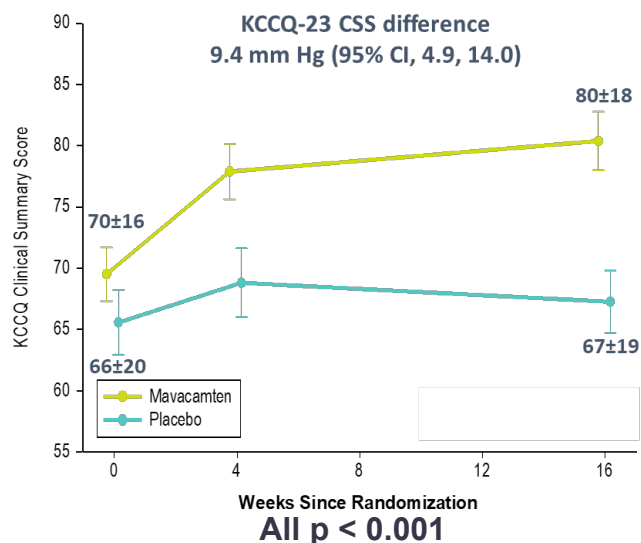
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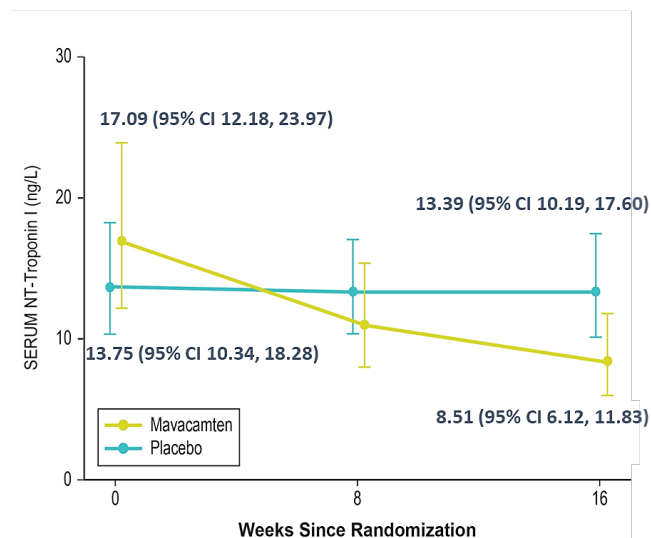
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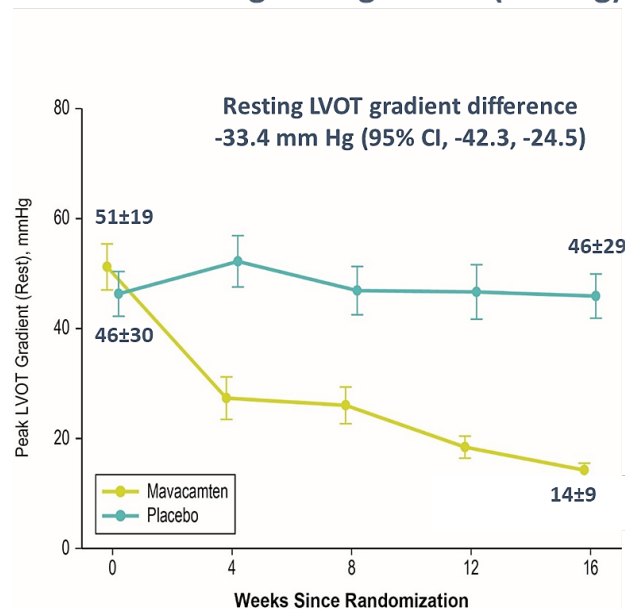


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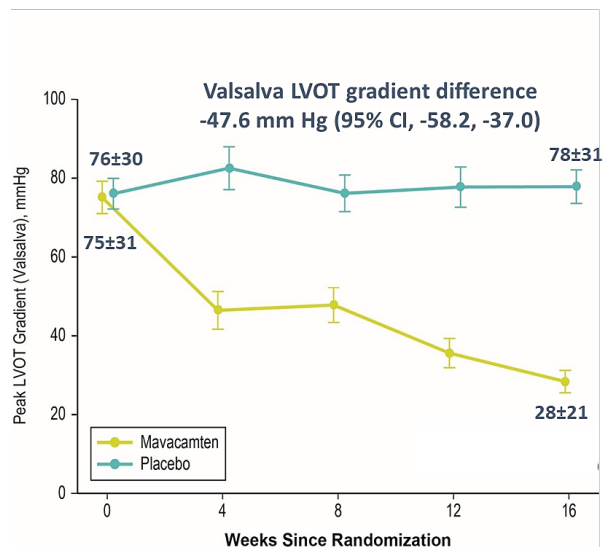


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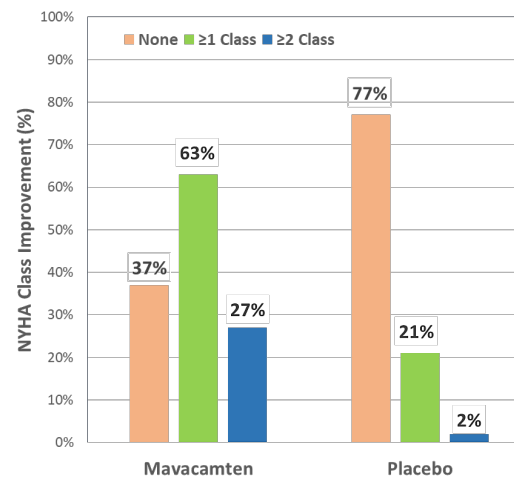
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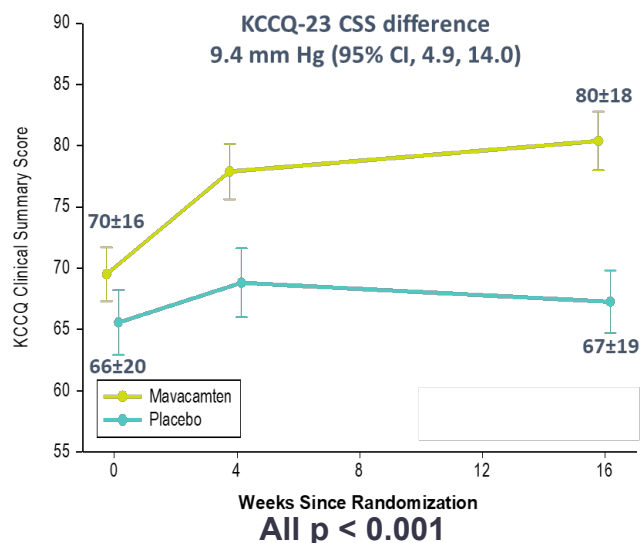
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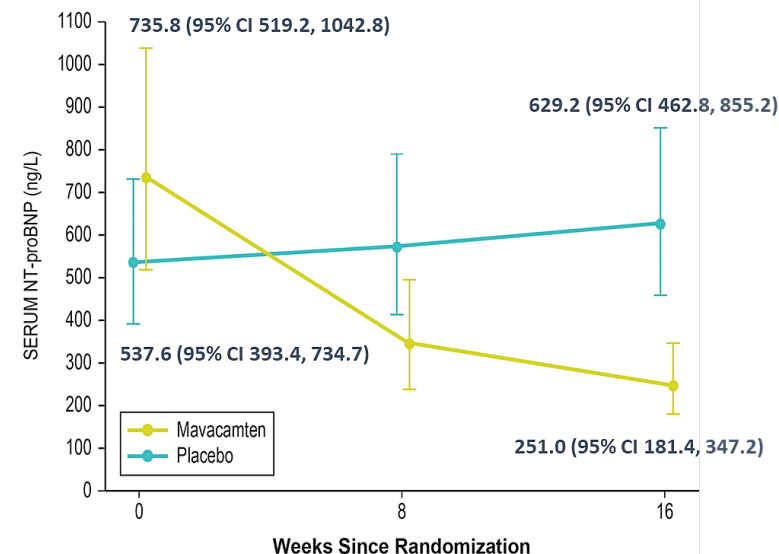
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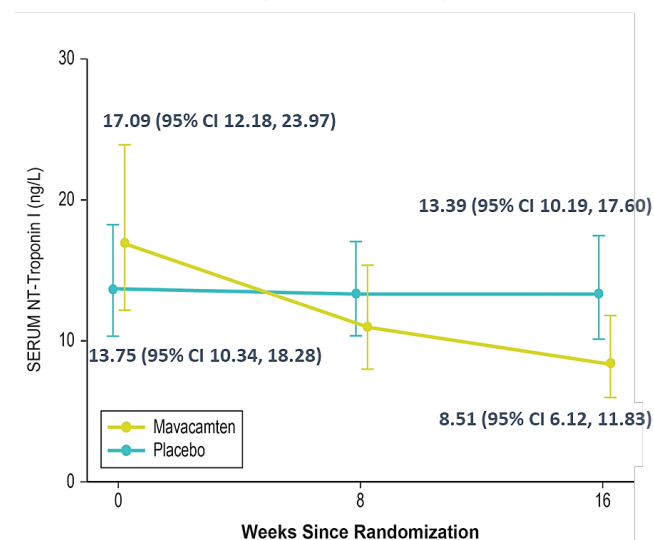
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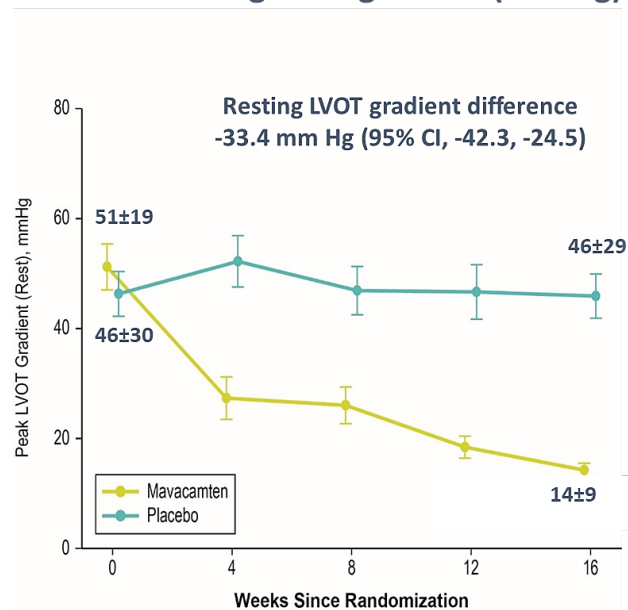


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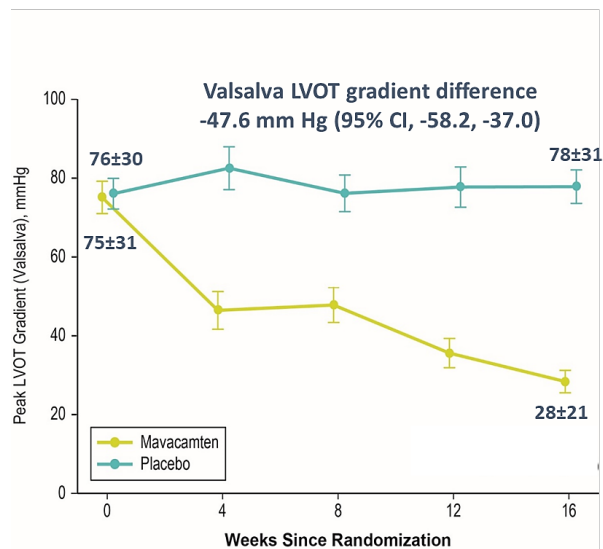


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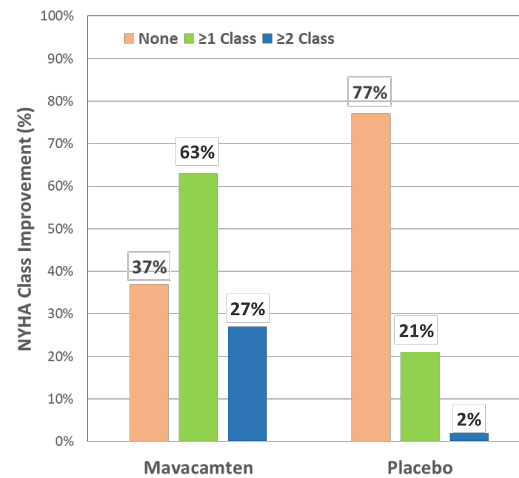
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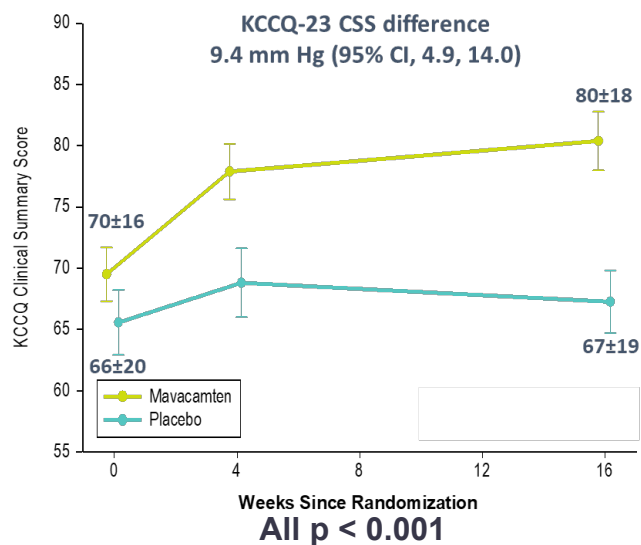
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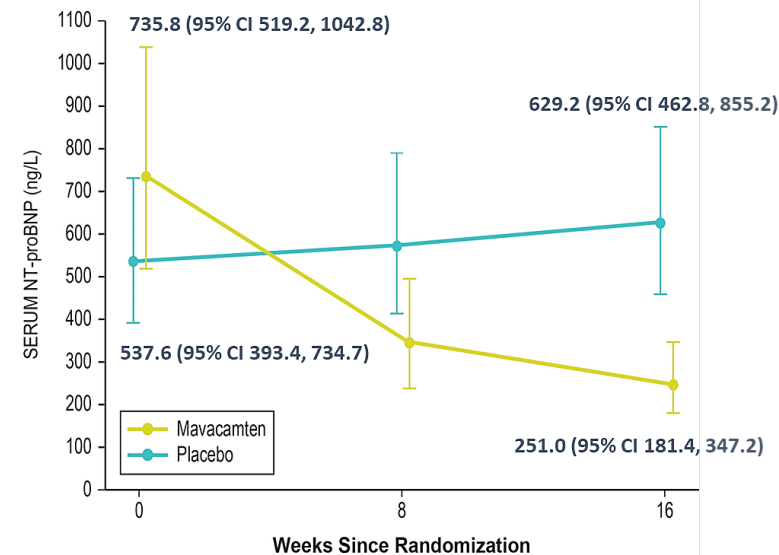
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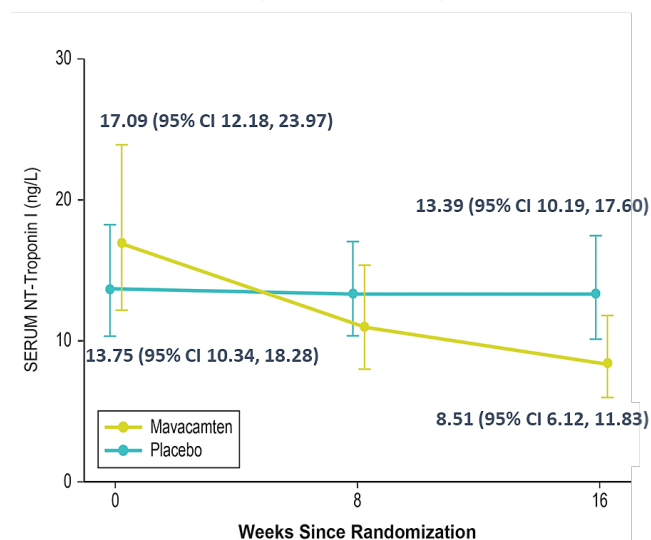
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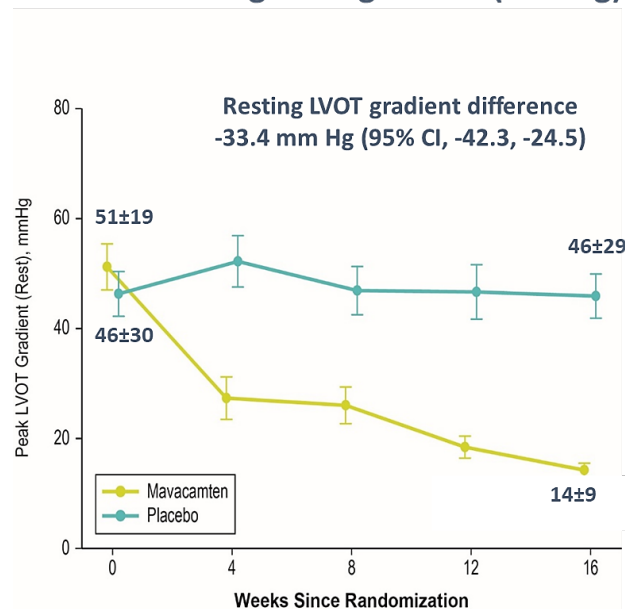


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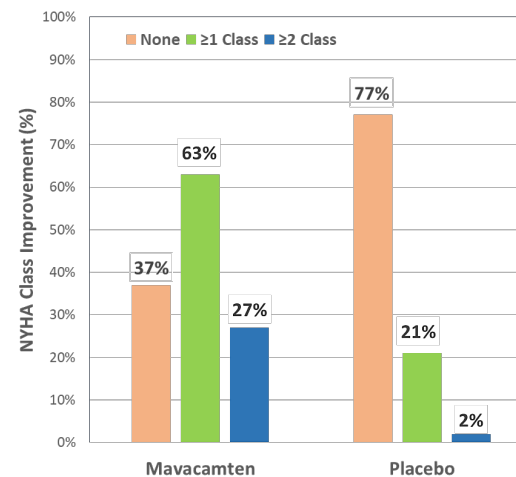


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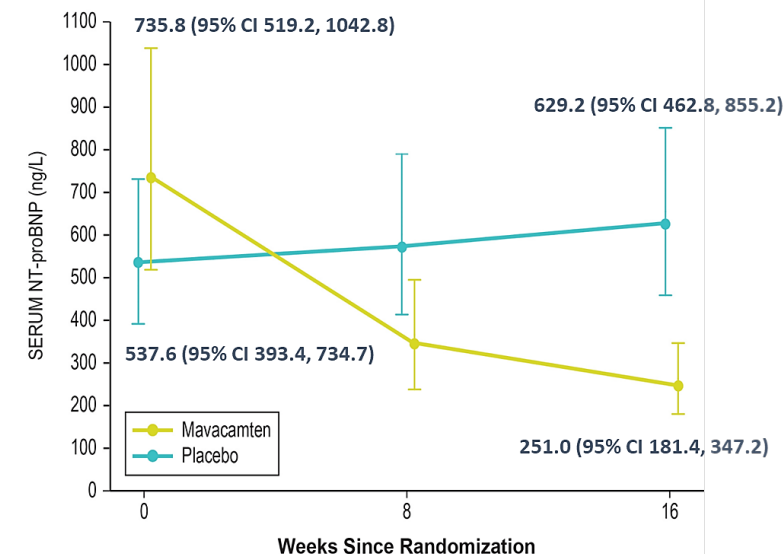
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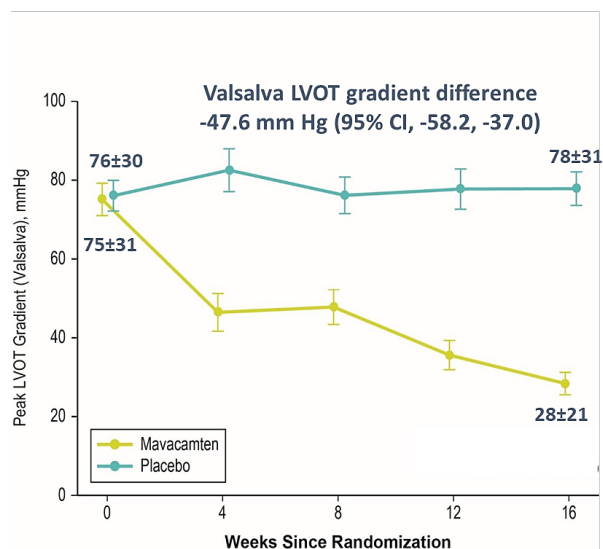
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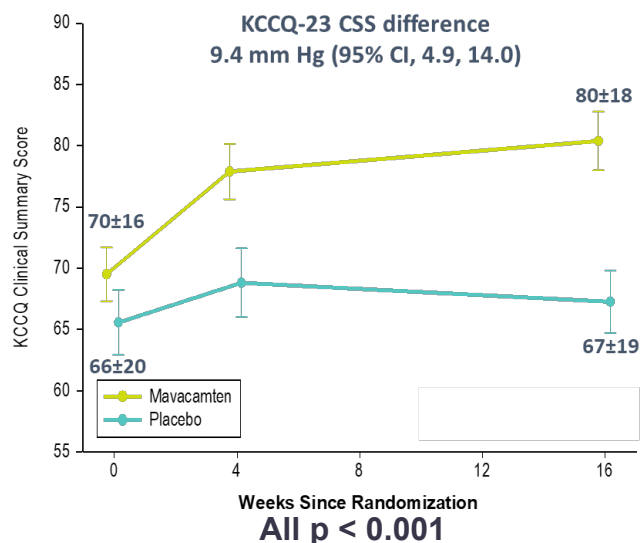
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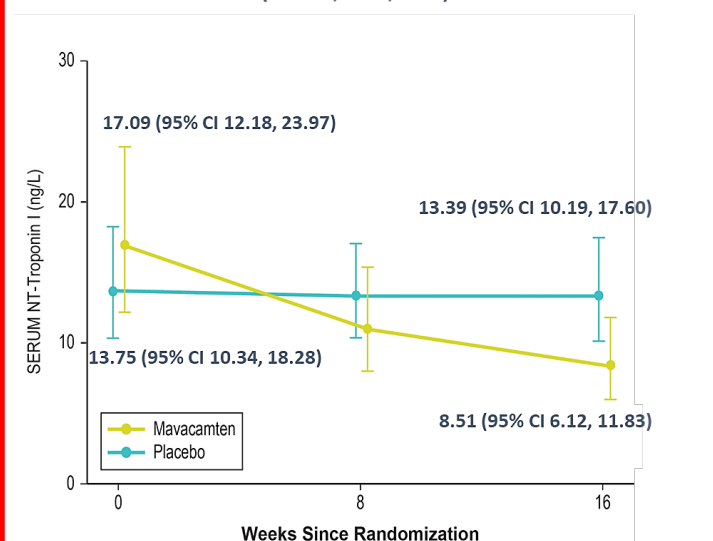
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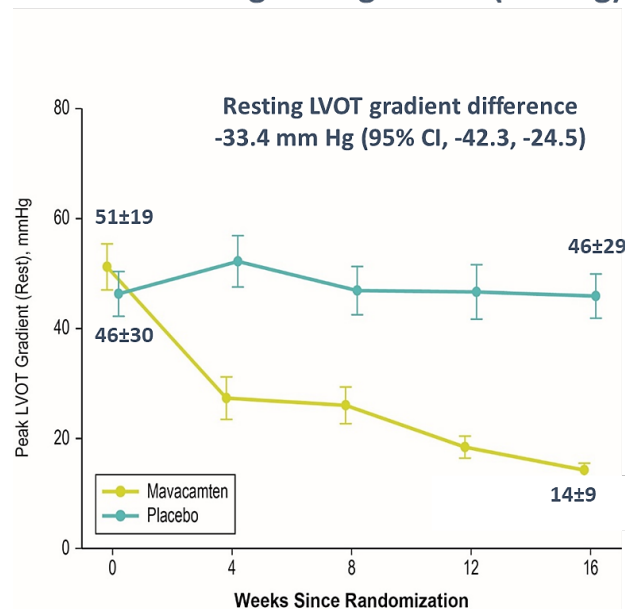


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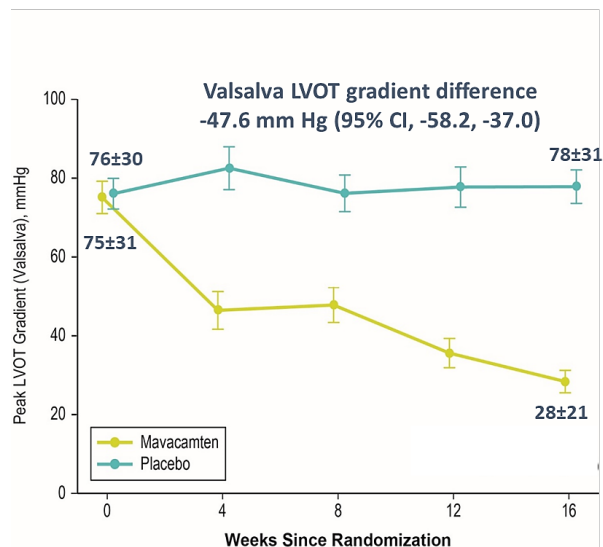


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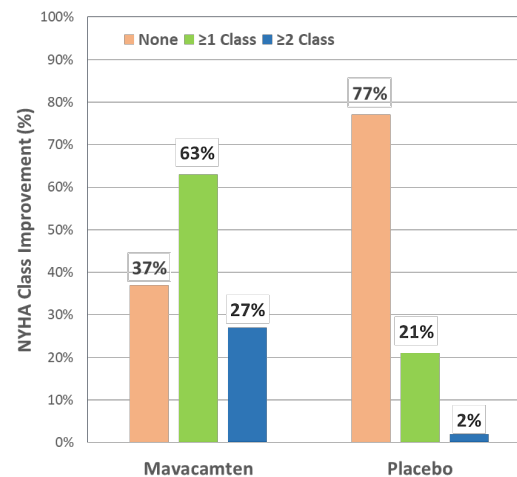
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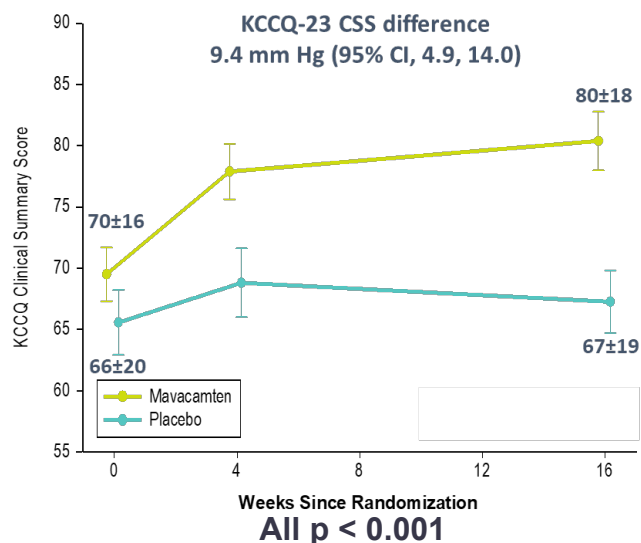
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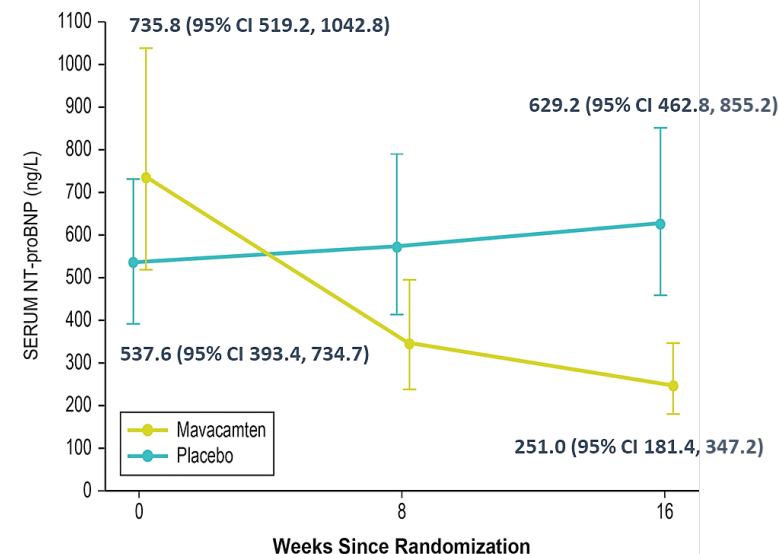
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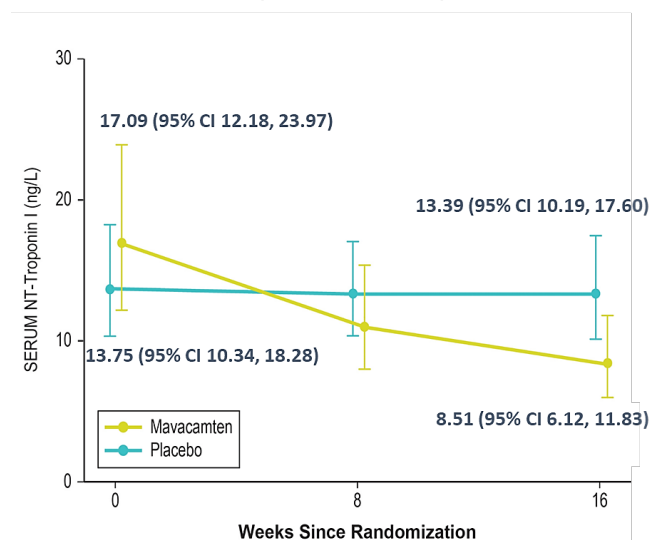
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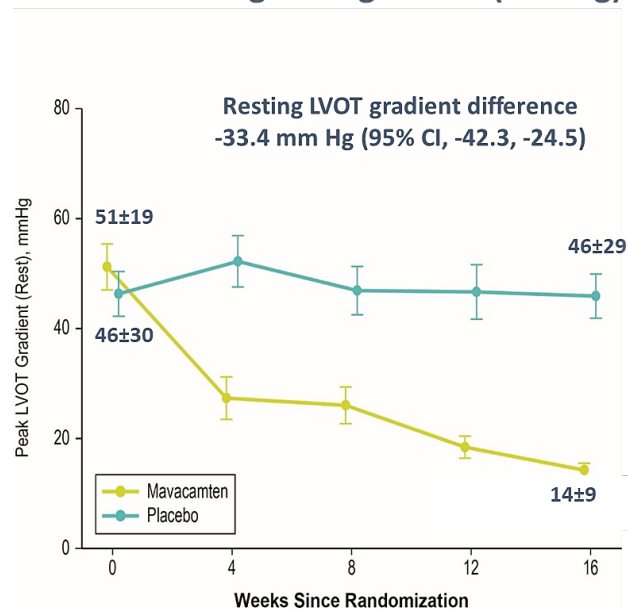


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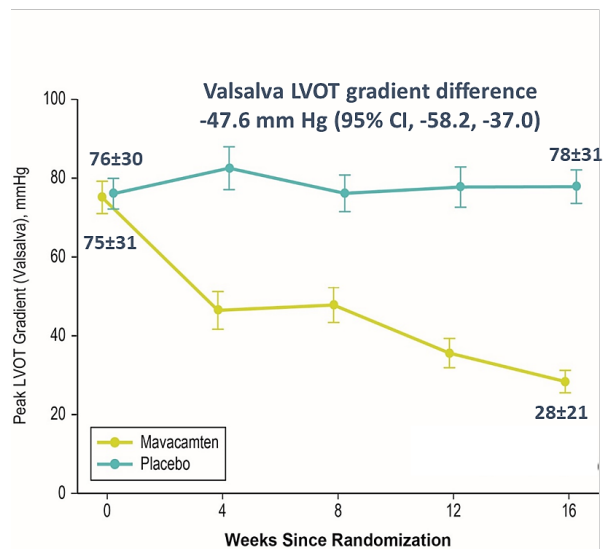


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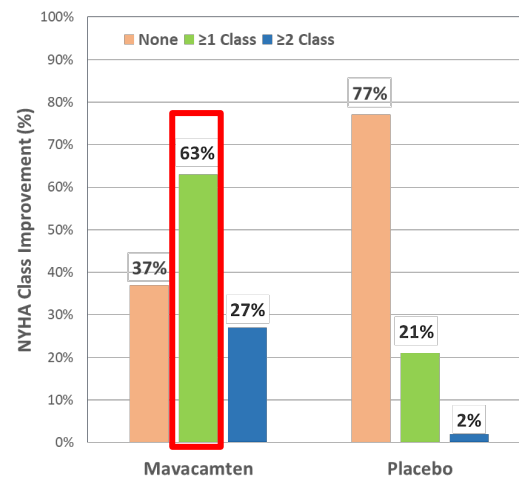
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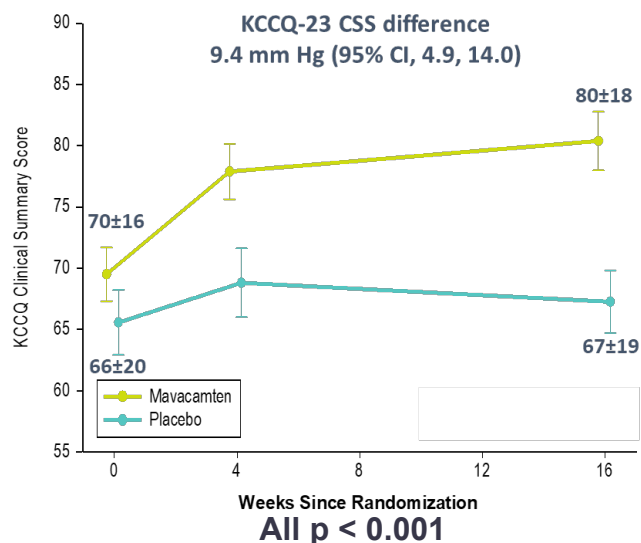
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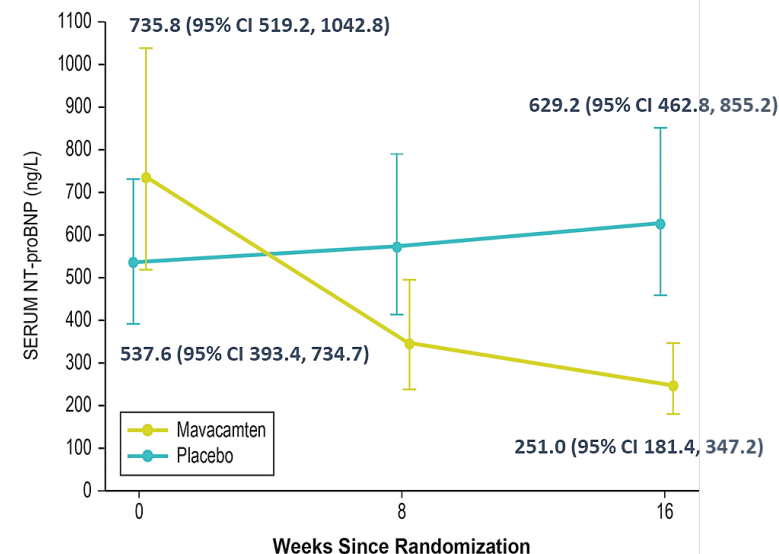
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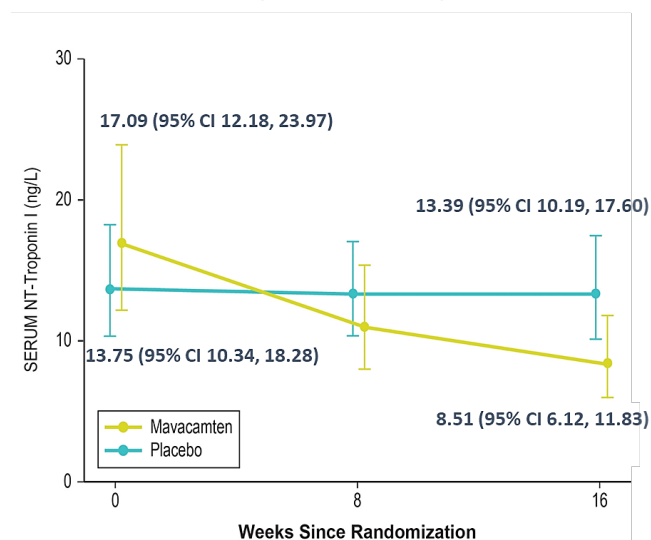
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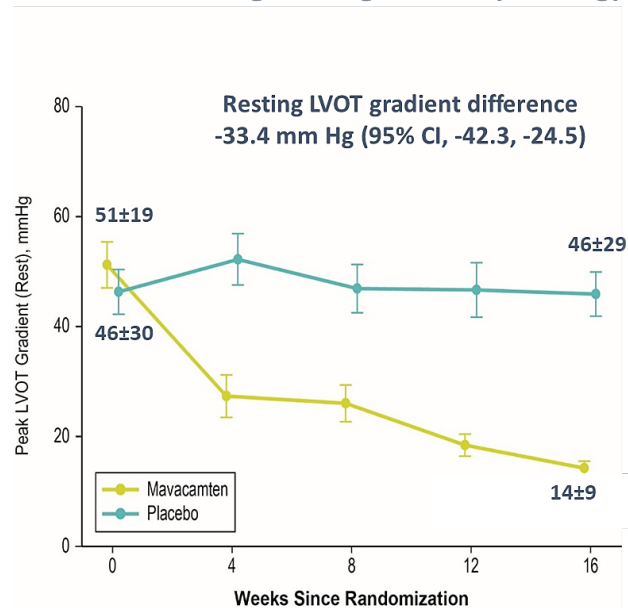


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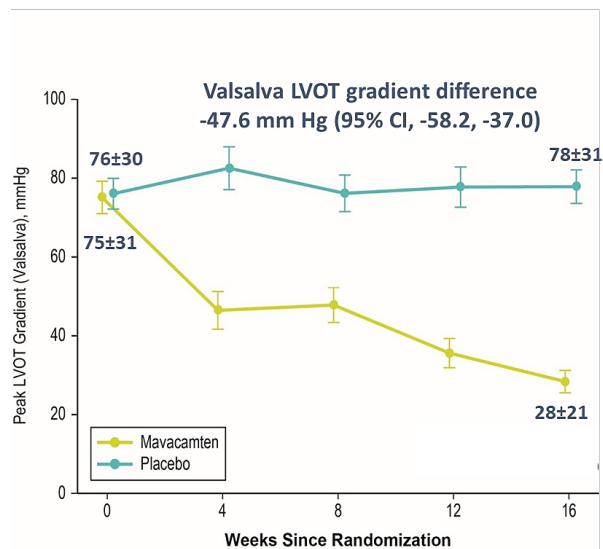


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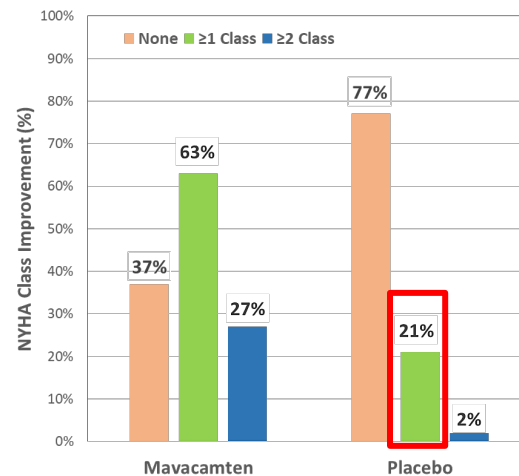
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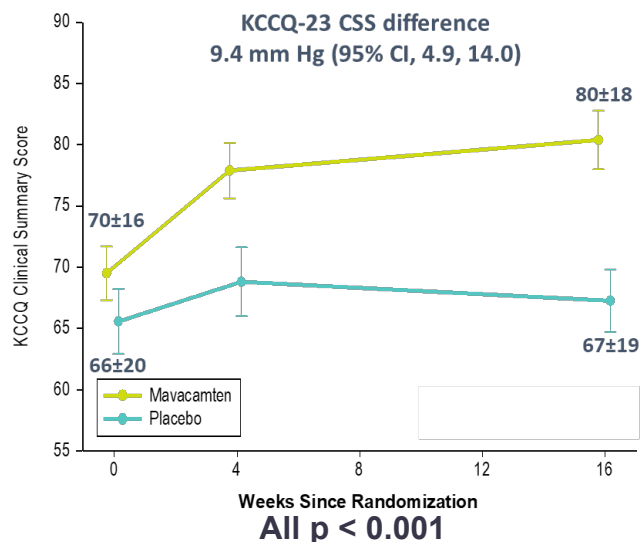
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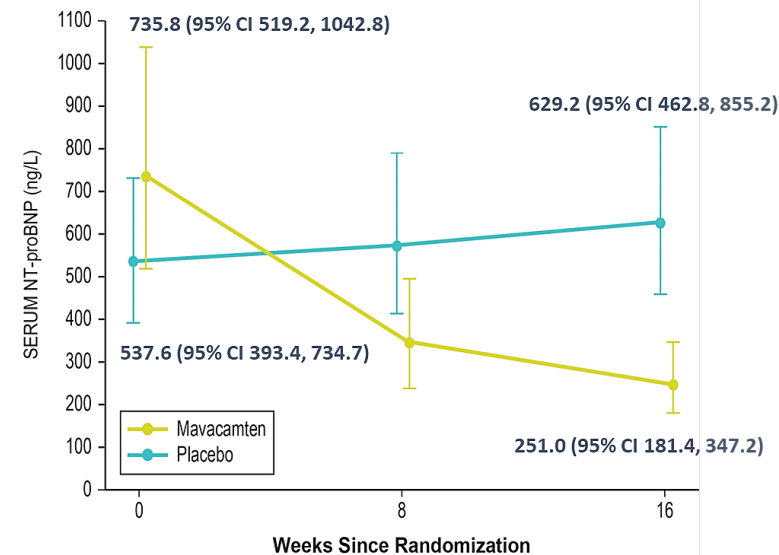
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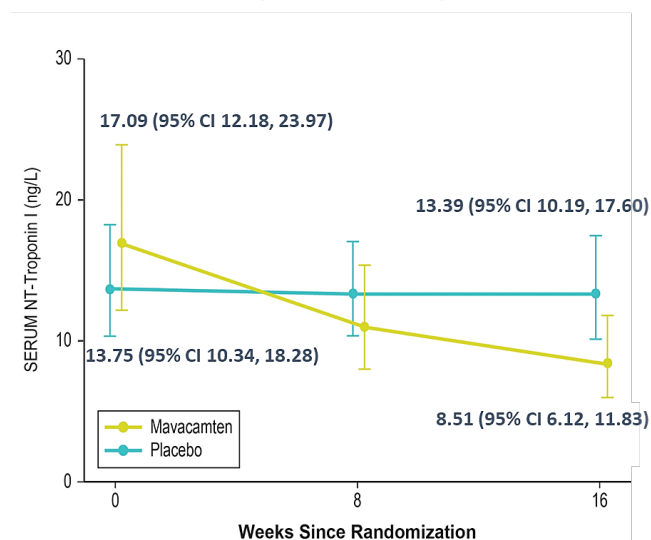
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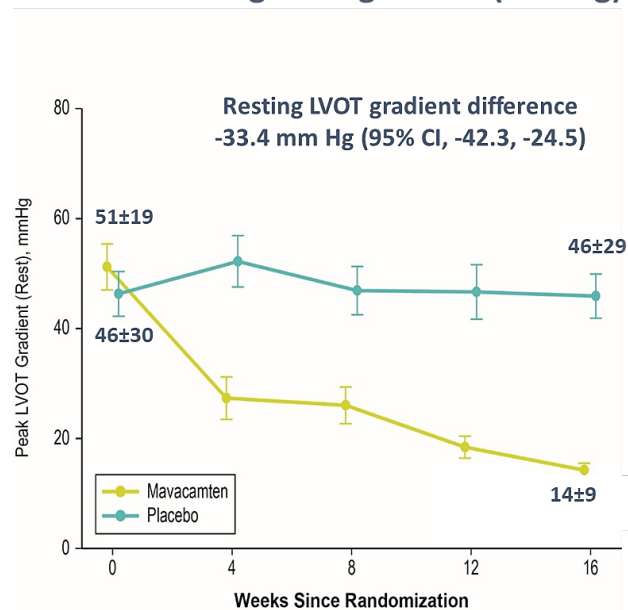


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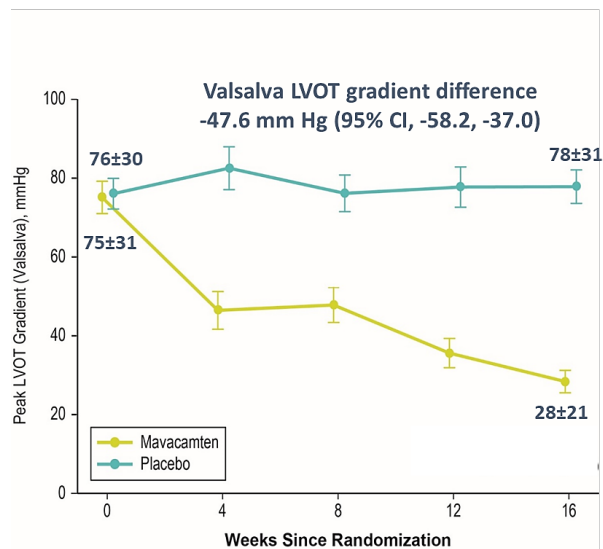


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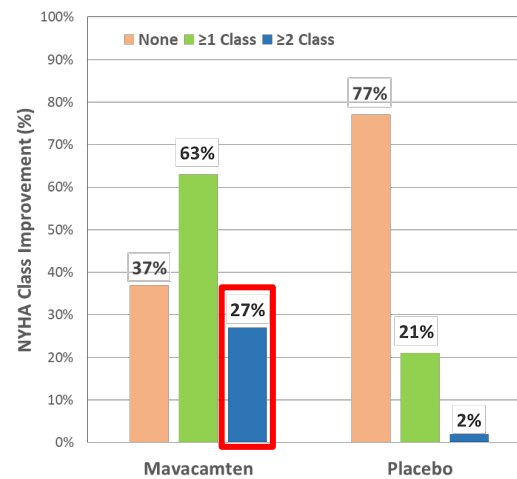
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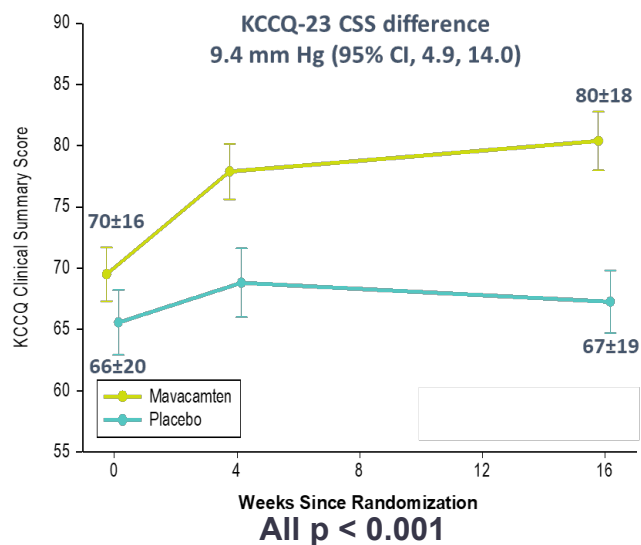
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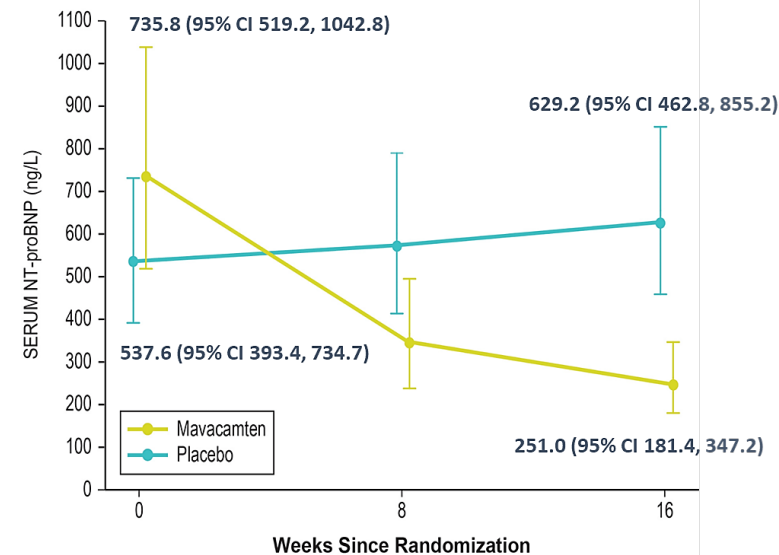
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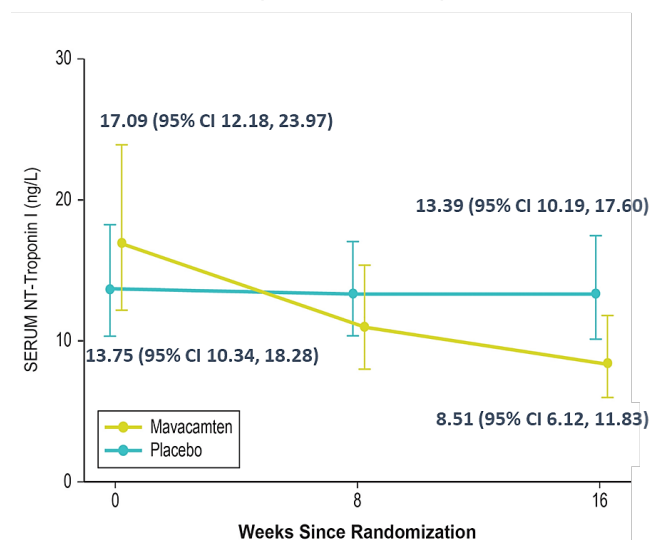
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# Conclusions and Medical Relevance

- In oHCM patients with intractable symptoms, referred for SRT, administration of mavacamten, titrated using echocardiography:
  - Safely and significantly reduced eligibility for invasive SRT procedures at 16 weeks ( $P < 0.0001$ )
  - Showed treatment benefits for all secondary endpoints, all  $P < 0.0001$ :
  - Reduction in LVOT gradient,  $\geq 1$  class improvement in NYHA Class, improvement in KCCQ-clinical summary score, reduction in NT ProBNP and troponin I
- Mavacamten may provide an alternative to SRT in severely symptomatic oHCM patients who are on maximally tolerated standard HCM therapy, including disopyramide
  - Additional data is needed to assess the durability of improvement in SRT eligibility over longer time periods