Meeting the Value Imperative in Cardiovascular Medicine: Opportunities in Hypertrophic Cardiomyopathy

Nihar R. Desai, MD, MPH
Associate Professor of Medicine, Yale School of Medicine
Vice Chief, Section of Cardiovascular Medicine
Medical Director, Value Based Programs
Investigator, Center for Outcomes Research and Evaluation

Heart Failure Landscape

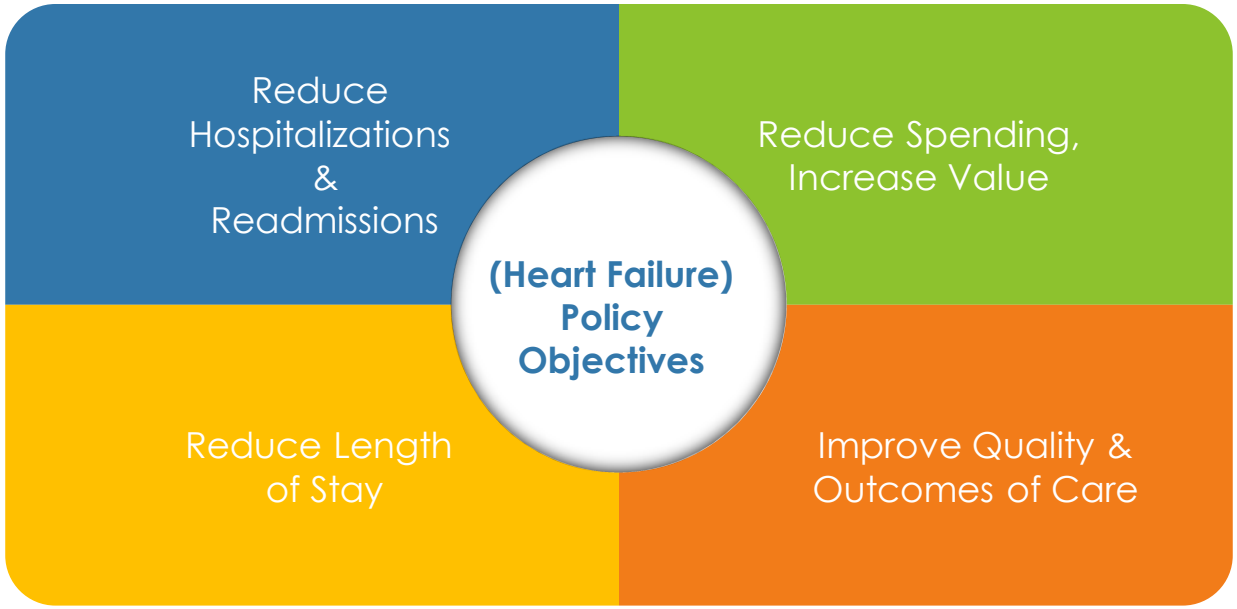
HF is a **leading cause of hospitalization and 30-day readmission**

5-year mortality rate of **≈75%** for patients hospitalized for HF

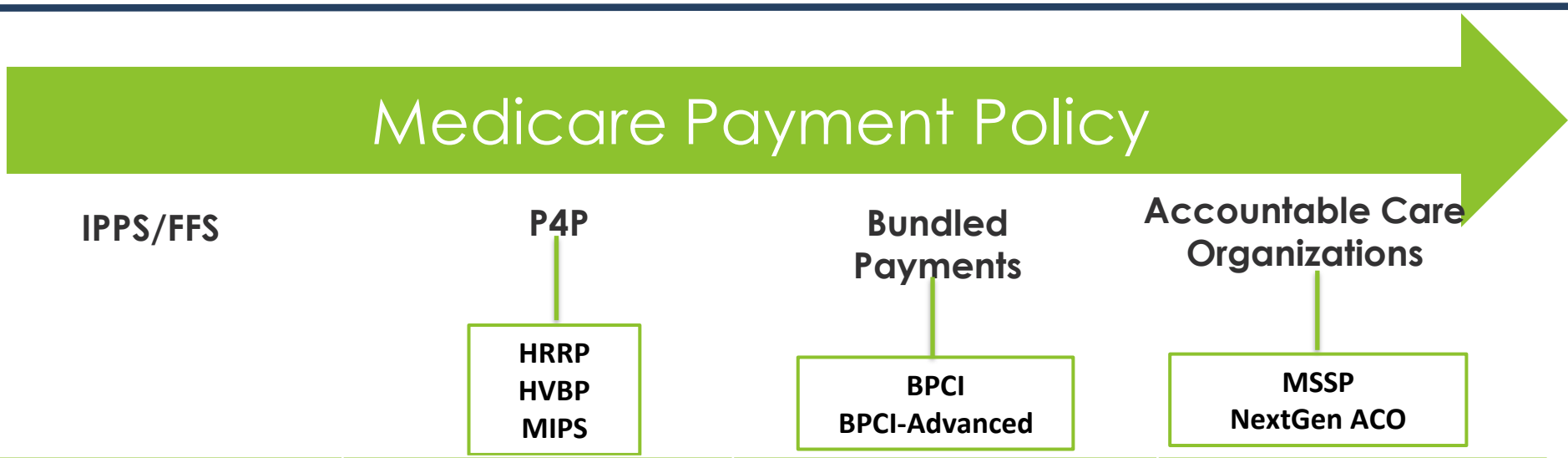
127% projected increase in the total cost of HF from 2012-2030, now nearly $80 billion

Substantial variation in quality, outcomes, and payments (Value Opportunity)

We Are In the Midst of Climate Change



Payment Models…They Are A Changin'



Alternative Payment Model	P4P (HRRP, HVBP, MIPS)	Bundled Payments	Accountable Care Organization
Overview	Focus on specific measures and specific quality domains	One payment per defined episode – movement away from simple utilization-based reimbursement	Population-based care (payment not triggered by service delivery) rewarding integration, quality, outcomes, and efficiency

Srinivasan D et al. *J Card Fail*. 2017;23:615-620; Burwell SM. *N Engl J Med*. 2015;372:897-899.

Payment Models…They Are A Changin'

Medicare Payment Policy

IPPS/FFS

P4P
- HRRP
- HVBP
- MIPS

Bundled Payments
- BPCI
- BPCI-Advanced

Accountable Care Organizations
- MSSP
- NextGen ACO

Srinivasan D et al. *J Card Fail*. 2017;23:615-620; Burwell SM. *N Engl J Med.* 2015;372:897-899.

P4P: Pay For Performance; FFS: Fee-For-Service; IPPS: Inpatient Prospective Payment System; BPCI: Bundled Payment for Care Improvement; MSSP: Medicare Shared Savings Program; ACO: Accountable Care Organization; HRRP: Hospital Readmission Reduction Program; HVBP: Hospital Value Based Purchasing Program; MIPS: Merit Based Incentive Payment System

Foundational Questions to Guide Us

- How can we continue to refine our understanding of the pathobiological and pathophysiological mechanisms that underlie HCM?
- How can we identify patients with HCM and streamline the process for evaluation and management?
- How can we characterize an individual's care journey and ascertain symptoms, QoL, and other relevant patient reported outcomes?
- How can we work as a scientific community to define evidence-based strategies and interventions?
- How can we leverage the 'learning health care system' approach to ensure the delivery of high-quality, high-value care for our patients?
- How can we best partner with patients and apply shared decision-making principles to enable them to make clinical decisions consistent with their values, preferences, and aspirations?

Lots of Progress…
Lots of Important Work Ahead…

Mavacamten for treatment of symptomatic obstructive hypertrophic cardiomyopathy (EXPLORER-HCM): a randomised, double-blind, placebo-controlled, phase 3 trial

Iacopo Olivotto, Artur Oreziak, Roberto Barriales-Villa, Theodore P Abraham, Ahmad Masri, Pablo Garcia-Pavia, Sara Saberi, Neal K Lakdawala, Matthew T Wheeler, Anjali Owens, Milos Kubanek, Wojciech Wojakowski, Morten K Jensen, Juan Gimeno-Blanes, Kia Afshar, Jonathan Myers, Sheila M Hegde, Scott D Solomon, Amy J Sehnert, David Zhang, Wanying Li, Mondira Bhattacharya, Jay M Edelberg, Cynthia Burstein Waldman, Steven J Lester, Andrew Wang, Carolyn Y Ho, Daniel Jacoby, on behalf of EXPLORER-HCM study investigators*

Summary

Background Cardiac muscle hypercontractility is a key pathophysiological abnormality in hypertrophic cardiomyopathy, and a major determinant of dynamic left ventricular outflow tract (LVOT) obstruction. Available pharmacological options for hypertrophic cardiomyopathy are inadequate or poorly tolerated and are not disease-specific. We aimed to assess the efficacy and safety of mavacamten, a first-in-class cardiac myosin inhibitor, in symptomatic obstructive hypertrophic cardiomyopathy.

Methods In this phase 3, randomised, double-blind, placebo-controlled trial (EXPLORER-HCM) in 68 clinical cardiovascular centres in 13 countries, patients with hypertrophic cardiomyopathy with an LVOT gradient of 50 mm Hg or greater and New York Heart Association (NYHA) class II–III symptoms were assigned (1:1) to receive mavacamten (starting at 5 mg) or placebo for 30 weeks. Visits for assessment of patient status occurred every 2–4 weeks. Serial evaluations included echocardiogram, electrocardiogram, and blood collection for laboratory tests and mavacamten plasma concentration. The primary endpoint was a 1·5 mL/kg per min or greater increase in peak oxygen consumption (pVO_2) and at least one NYHA class reduction or a 3·0 mL/kg per min or greater pVO_2 increase without NYHA class worsening. Secondary endpoints assessed changes in post-exercise LVOT gradient, pVO_2, NYHA class, Kansas City Cardiomyopathy Questionnaire-Clinical Summary Score (KCCQ-CSS), and Hypertrophic Cardiomyopathy Symptom Questionnaire Shortness-of-Breath subscore (HCMSQ-SoB). This study is registered with ClinicalTrials.gov, NCT03470545.

Findings Between May 30, 2018, and July 12, 2019, 429 adults were assessed for eligibility, of whom 251 (59%) were enrolled and randomly assigned to mavacamten (n=123 [49%]) or placebo (n=128 [51%]). 45 (37%) of 123 patients on mavacamten versus 22 (17%) of 128 on placebo met the primary endpoint (difference +19·4%, 95% CI 8·7 to 30·1; p=0·0005). Patients on mavacamten had greater reductions than those on placebo in post-exercise LVOT gradient (–36 mm Hg, 95% CI –43·2 to –28·1; p<0·0001), greater increase in pVO_2 (+1·4 mL/kg per min, 0·6 to 2·1; p=0·0006), and improved symptom scores (KCCQ-CSS +9·1, 5·5 to 12·7; HCMSQ-SoB –1·8, –2·4 to –1·2; p<0·0001). 34% more patients in the mavacamten group improved by at least one NYHA class (80 of 123 patients in the mavacamten group *vs* 40 of 128 patients in the placebo group; 95% CI 22·2 to 45·4; p<0·0001). Safety and tolerability were similar to placebo. Treatment-emergent adverse events were generally mild. One patient died by sudden death in the placebo group.

Interpretation Treatment with mavacamten improved exercise capacity, LVOT obstruction, NYHA functional class, and health status in patients with obstructive hypertrophic cardiomyopathy. The results of this pivotal trial highlight the benefits of disease-specific treatment for this condition.

Mavacamten for treatment of symptomatic obstructive hypertrophic cardiomyopathy (EXPLORER-HCM): health status analysis of a randomised, double-blind, placebo-controlled, phase 3 trial

John A Spertus, Jennifer T Fine, Perry Elliott, Carolyn Y Ho, Iacopo Olivotto, Sara Saberi, Wanying Li, Chantal Dolan, Matthew Reaney, Amy J Sehnert, Daniel Jacoby

Summary

Background Improving symptoms is a primary treatment goal in patients with obstructive hypertrophic cardiomyopathy. Currently available pharmacological options for hypertrophic cardiomyopathy are not disease-specific and are often inadequate or poorly tolerated. We aimed to assess the effect of mavacamten, a first-in-class cardiac myosin inhibitor, on patients' health status—ie, symptoms, physical and social function, and quality of life.

Methods We did a health status analysis of EXPLORER-HCM, a phase 3, double-blind, randomised, placebo-controlled trial. The study took place at 68 clinical cardiovascular centres in 13 countries. Adult patients (≥18 years) with symptomatic obstructive hypertrophic cardiomyopathy (gradient ≥50 mm Hg and New York Heart Association class II–III) were randomly assigned (1:1) to mavacamten or placebo for 30 weeks, followed by an 8-week washout period. Both patients and staff were masked to study treatment. The primary outcome for this secondary analysis was the Kansas City Cardiomyopathy Questionnaire (KCCQ), a well validated disease-specific measure of patients' health status. It was administered at baseline and weeks 6, 12, 18, 30 (end of treatment), and 38 (end of study). Changes from baseline to week 30 in KCCQ overall summary (OS) score and all subscales were analysed using mixed model repeated measures. This study is registered with ClinicalTrials.gov, NCT03470545.

Findings Between May 30, 2018, and July 12, 2019, 429 adults were assessed for eligibility, of whom 251 (59%) were enrolled and randomly assigned. Of 123 patients randomly assigned to mavacamten, 92 (75%) completed the KCCQ at baseline and week 30 and of the 128 patients randomly assigned to placebo 88 (69%) completed the KCCQ at baseline and week 30. At 30 weeks, the change in KCCQ-OS score was greater with mavacamten than placebo (mean score 14·9 [SD 15·8] *vs* 5·4 [13·7]; difference +9·1 [95% CI 5·5–12·8]; p<0·0001), with similar benefits across all KCCQ subscales. The proportion of patients with a very large change (KCCQ-OS ≥20 points) was 36% (33 of 92) in the mavacamten group versus 15% (13 of 88) in the placebo group, with an estimated absolute difference of 21% (95% CI 8·8–33·4) and number needed to treat of five (95% CI 3–11). These gains returned to baseline after treatment was stopped.

Interpretation Mavacamten markedly improved the health status of patients with symptomatic obstructive hypertrophic cardiomyopathy compared with placebo, with a low number needed to treat for marked improvement. Given that the primary goals of treatment are to improve symptoms, physical and social function, and quality of life, mavacamten represents a new potential strategy for achieving these goals.

Summary and A Look Ahead

- The pressure to move to a value based model of health care delivery and financing is intense and will only further intensify.
- There is an urgent need to reimagine heart failure (and HCM) care with this push to value.
- Therapies and strategies that deliver value to patients, providers, and payers (improved outcomes, better QoL, reduced costs) will thrive in this evolving ecosystem.

Meeting the Value Imperative in Cardiovascular Medicine: Opportunities in Hypertrophic Cardiomyopathy

Nihar R. Desai, MD, MPH
Associate Professor of Medicine, Yale School of Medicine
Vice Chief, Section of Cardiovascular Medicine
Medical Director, Value Based Programs
Investigator, Center for Outcomes Research and Evaluation