Patient-Reported Outcomes: A Critical Insight into the Impact of Therapy

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Missouri/Lauer Endowed Chair and Professor, UMKC
Saint Luke’s Mid America Heart Institute
Presentation Overview

回合 Overview of PROs and the KCCQ

◆ Applications of PROs
  – Clinical Trials and the FDA
  – Quality of Care
  – Clinical Practice

◆ A New Paradigm for Translating Clinical Trials to Clinical Care through Precision Medicine
Treatment Goals for Heart Failure

Principal Treatment Goals

To Make Patients Live Longer

Disease Progression
- Arrhythmias
- Heart Failure Admissions
- Mortality

To Make Patients Feel Better

Patient’s “Health Status”
- Symptoms
- Functional Status
- Quality of Life
Long-term ACE-inhibitor therapy in patients with heart failure or left-ventricular dysfunction: a systematic overview of data from individual patients

Marcus D Flather, Salim Yusuf, Lars Køber, Marc Pfeffer, Alistair Hall, Gordon Murray, Christian Torp-Pedersen, Stephen Ball, Janice Pogue, Lemuel Moyé, Eugene Braunwald, for the ACE-Inhibitor Myocardial Infarction Collaborative Group

Summary
Background We undertook a prospective systematic overview based on data from individual patients from five long-term randomised trials that assessed inhibitors of angiotensin-converting enzyme (ACE) in patients with left-ventricular dysfunction or heart failure.
Methods Three of the trials enrolled patients within a week

Interpretation This systematic overview shows that ACE inhibitors lower rates of mortality, myocardial infarction, and hospital admission for heart failure in patients with left-ventricular dysfunction or heart failure with or without a recent myocardial infarct. The use of ACE inhibitors should be part of routine practice in these patients.

ACE Inhibitors = Better Survival

\[ \{ p < 0.001 \} \]
Contextualizing the Benefits...

What happened to the other 75%??

\{ p<0.001 \}

<table>
<thead>
<tr>
<th>Time since randomisation (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
</tr>
<tr>
<td>0</td>
</tr>
</tbody>
</table>

Number at risk

<table>
<thead>
<tr>
<th></th>
<th>ACE-I</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 at risk</td>
<td>6391</td>
<td>6372</td>
</tr>
<tr>
<td>1 at risk</td>
<td>5378</td>
<td>5279</td>
</tr>
<tr>
<td>2 at risk</td>
<td>4204</td>
<td>4025</td>
</tr>
<tr>
<td>3 at risk</td>
<td>2457</td>
<td>2364</td>
</tr>
<tr>
<td>4 at risk</td>
<td>892</td>
<td>742</td>
</tr>
<tr>
<td>5 at risk</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Strengths/Weaknesses of Outcomes

**Potential Outcomes**
- Mortality
- All-cause readmission
- EF/Biomarkers
- PROs describing Symptoms, Function and Quality of Life

**Limitations/Benefits**
- Rare
- Mediated by other factors
- A surrogate measure
- A clinically meaningful outcome and the primary indication for many treatments (e.g. PCI)
A principal reason patients seek care is to feel better.

Patient’s health status can be measured.

- **Disease** → **Symptoms** → **Functional Limitation** → **Quality of Life**
  - Myocardial Injury
  - RAAS Activation
  - LV dysfunction
  - Fatigue
  - Dyspnea
  - Edema
  - Physical
  - Emotional
  - Social
  - Discrepancy between actual & desired health and functioning

**The Range of Health Status**
QoL is Often More Important than Survival

- Patients’ care about both their survival and their QoL

Clinical characteristics of a Heart Failure Population (n=99)

- Age (years) 52±13
- Male = 75%
- Duration of HF 6±5 years
- LVEF (%) 24±10
- NYHA class
  - Class I 7%
  - Class II 19%
  - Class III 58%
  - Class IV 16%

25% will give up over HALF of their Survival to have Perfect Health

The Golden Path to Patient Experience Being Used in FDA Approval

FDA Approval

Guidance for Industry
Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims

Office of Communications, Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave., Bldg. 51, rm. 2201
Silver Spring, MD 20993-0002
Tel: 301-796-3400; Fax: 301-547-8714; E-mail: druginfo@fda.hhs.gov

Well-designed RCTs with PRO Outcomes
Problems with the FDA Guidance

Recommendations
◆ Emphasis on Content

Limitations/Benefits
◆ pre-2009 instruments don’t

Will the FDA’s Medical Device Development Tools (MDDT) and Clinical Outcomes Assessment (COA) Qualification Programs provide a crack in the wall???

We will see…
◆ Very expensive to create new PROs
◆ Creates barriers to capturing patients’ experiences
Working with the FDA to Certify KCCQ

KCCQ Application to be a Certified Outcome Assessment

CDER

9/15/15
Submission of 52-page document supporting KCCQ psychometrics

12/21/15 – Request for Briefing Package

3/8/16
Submission of 194-page document supporting KCCQ Symptom and PL Domains only

8/11/16 – Feedback Given

9/2/16
Submission of 3,829-page document Support KCCQ Symptom and PL domains

CDRH

8/15/15
Submission of 52-page document supporting KCCQ psychometrics

9/25/15 – Accepted into MDDT Program

10/20/15 – CC

1/4/16
Submission of 60-page document supporting KCCQ

8/6/16 – Moved to Qualification Stage

9/28/16
Submission of 3,839-page document Supporting KCCQ

11/25/16 – Feedback and ?s

12/4/16 Questions Addressed

1/5/17 – Feedback and ?s

Final Analyses to be Submitted

Internal FDA Meetings

1/18/17-2/23/17

Still Awaiting Decision
The KC Cardiomyopathy Questionnaire

- 23/12 items that measure 5 clinically relevant domains
  - Physical Limitation
  - Symptoms: Frequency, Severity and Change over time
  - Social Limitation
  - Self-Efficacy
  - Quality of Life

- Represents the patient’s perspective of their HF
- Available in over 90 translations
- Established validity, reliability and responsiveness

Green et al, JACC 2000; 35:1245-55
The KCCQ-12

**Limitations in Physical Activity**

<table>
<thead>
<tr>
<th>Activity</th>
<th>Extremely limited</th>
<th>Quite a bit limited</th>
<th>Moderately limited</th>
<th>Slightly limited</th>
<th>Not at all limited</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Showering/bathing</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>b. Walking 1 block on level ground</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>c. Hurry (as if you had to)</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
</tbody>
</table>

**Frequency of Symptoms**

<table>
<thead>
<tr>
<th></th>
<th>Every morning</th>
<th>3 or more times per week but not every day</th>
<th>1-2 times per week</th>
<th>Less than once a week</th>
<th>Never over the past 2 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>2. Over the morning?</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
</tbody>
</table>

**Quality of Life**

6. Over the past 2 weeks, how much has your heart failure limited your enjoyment of life?

<table>
<thead>
<tr>
<th>How much has your heart failure limited your enjoyment of life?</th>
<th>Not at all satisfied</th>
<th>Mostly satisfied</th>
<th>Somewhat satisfied</th>
<th>Mostly dissatisfied</th>
<th>Slightly satisfied</th>
<th>Completely satisfied</th>
</tr>
</thead>
<tbody>
<tr>
<td>It has not limited my enjoyment of life at all</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>It has slightly limited my enjoyment of life</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>It has moderately limited my enjoyment of life</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>It has limited my enjoyment of life quite a bit</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>It has extremely limited my enjoyment of life</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
</tbody>
</table>

7. If you had to spend the rest of your life with your heart failure the way it is right now, how would you feel about this?

<table>
<thead>
<tr>
<th>How much would you feel about the rest of your life?</th>
<th>Not at all limited</th>
<th>Mostly satisfied</th>
<th>Somewhat satisfied</th>
<th>Mostly dissatisfied</th>
<th>Slightly satisfied</th>
<th>Completely satisfied</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not at all limited</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>Mostly satisfied</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>Somewhat satisfied</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>Mostly dissatisfied</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>Slightly satisfied</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>Completely satisfied</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
</tbody>
</table>

**Social Limitations**

<table>
<thead>
<tr>
<th>How much has your heart failure limited your participation in activities?</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Hobbies, recreational activities</td>
</tr>
<tr>
<td>b. Working or doing household chores</td>
</tr>
<tr>
<td>c. Visiting family or friends out of your home</td>
</tr>
</tbody>
</table>
Mapping the KCCQ Scales

Disease \(\rightarrow\) Symptoms \(\rightarrow\) Functional Limitation \(\rightarrow\) Quality of Life

Symptom Scales \(\rightarrow\) Physical and Social Function Scales \(\rightarrow\) Quality of Life Scale

KCCQ Clinical Summary Scale

KCCQ Overall Summary Scale
KCCQ Valid in Multiple HF Etiologies

HFrEF

Valvular Heart Disease

HFrEF

HFpEF

HOCM

Use of the Kansas City Cardiomyopathy Questionnaire for Monitoring Health Status in Patients With Aortic Stenosis

Suzanne V. Arnold, MD, MHA; John A. Spertus, MD; Adnan K. Chhatriwalla, MD; Martin B. Matthew R. Reynolds, MD, MSc; John G. David J. Cohen,

Comparative Performance of Cardiomyopathy Questionnaire Failure With Preserved and Red

Susan M. Joseph, MD; Eric Novak, MS; Suzanne V. Himad Khattak, MD; Anne E. Platts, BS; Victor G. Div, MD; John A. Spertus, MD

Background—Despite the growing epidemic of heart failure with preserved ejection fraction (HFpEF), there are few validated instruments to assess health status in this population. This study compared the Kansas City Cardiomyopathy Questionnaire (KCCQ), a questionnaire developed to assess health status in patients with heart failure with reduced ejection fraction (HFrEF), across patients with HFrEF, HFpEF, and healthy controls.

Methods and Results—The KCCQ was administered to 300 patients with HFrEF, 154 with HFpEF, and 200 healthy controls. The KCCQ scores were compared across the three groups using analysis of variance. The KCCQ was also administered to 200 patients with HFrEF and 200 with HFpEF who were followed for 1 year. The KCCQ scores were compared between the two groups using the Student t test. The KCCQ was also administered to 200 patients with HFrEF and 200 with HFpEF who were followed for 1 year. The KCCQ scores were compared between the two groups using the Student t test. The KCCQ was also administered to 200 patients with HFrEF and 200 with HFpEF who were followed for 1 year. The KCCQ scores were compared between the two groups using the Student t test.

Conclusions—the KCCQ is a valid and reliable instrument for assessing health status in patients with HFrEF and HFpEF.

Key Words: aortic stenosis, health status, KCCQ, HFpEF, HFrEF, HFpEF, HFrEF, HOCM

Correlations between physician-perceived functional status, patient-perceived health status, and cardiopulmonary exercise results in hypertrophic cardiomyopathy

Christopher M. Haff, MD; Adam T. Tarter, MD; Andrew Wang, MD

Background—Hypertrophic cardiomyopathy (HCM) is a common acquired heart disease characterized by an increased risk of sudden death. The KCCQ is a validated instrument to assess health status in patients with HCM. The purpose of this study was to assess the correlation between KCCQ scores and cardiopulmonary exercise testing (CPX) results in patients with HCM.

Methods—The KCCQ was administered to 200 patients with HCM who were followed for 1 year. The KCCQ scores were compared between the two groups using the Student t test. The KCCQ scores were also compared between the two groups using the Student t test. The KCCQ scores were also compared between the two groups using the Student t test.

Conclusions—the KCCQ is a valid and reliable instrument for assessing health status in patients with HCM.
Attributes of Health Status Measures

◆ Validity:
  
  *Does the instrument capture what is important to patients (content)?*
  
  *Does it measure what it is supposed to (criterion)?*

◆ Reliability:

  *Are the results the same when given repeatedly to stable patients?*

◆ Responsiveness:

  *Do the results reflect changes in patients’ disease status?*

◆ Interpretability:

  *What does a given score or change in score mean?*

◆ Translations:

  *Are linguistically and culturally appropriate translations available?*
Interpretation of Health Status

◆ The challenge of new metrics

– *Interpreting Scores at a Single Point in Time*
  » Translation to a clinical framework
  » Prognostic import

– *Interpreting Changes in Scores*
  » Translation to a clinical framework
  » Prognostic Import
Clinical Ranges of KCCQ Scores

KCCQ Summary Scores

NYHA VI  NYHA III  NYHA II  NYHA I

0  10  20  30  40  50  60  70  80  90  100

Very Poor-Poor  Poor-Fair  Fair-Good  Good-Excellent
Using Cross-Sectional PRO Data in RCTs

Telemonitoring in Patients with Heart Failure

Sarwat I. Chaudhry, M.D., Jennifer A. Mattera, M.P.H., Jeptha P. Curtis, M.D.,
John A. Spertus, M.D., M.P.H., Jeph Herrin, Ph.D., Zhenqiu Lin, Ph.D.,
Christopher O. Phillips, M.D., M.P.H., Beth V. Hodshon, M.P.H., J.D., R.N.,
Lawton S. Cooper, M.D., M.P.H., and Harlan M. Krumholz, M.D.
6-month KCCQ Overall Summary Scores

KCCQ>50 in 79% of TM vs. 72% UC
NNT=15

KCCQ>75 in 55% of TM vs. 51% UC
NNT=27

Mean Difference = 2.5 points
(95% CI= 0.38,4.67 p=0.02)

KCCQ>50 in 79% of TM vs. 72% UC
NNT=15
Interpretation of Health Status

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  » Prognostic Import
Scores at a Single Point in Time Predict Outcome

- Freedom from CV Mortality/hospitalization
- n=1,516 outpatients
- Scores grouped in ranges of 25 points
- Graded relationship with lower scores associated with worse outcomes

*Soto et al. Circulation 2004;110:546-51*
## Multivariable Model: 1-year CV Death/Hospitalization

<table>
<thead>
<tr>
<th>Factor</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Year CV Death/Hospitalization</td>
<td>1</td>
</tr>
<tr>
<td>KCCQ @ Wk 4 = 0-25</td>
<td>0.5</td>
</tr>
<tr>
<td>KCCQ @ Wk 4 &gt;25-50</td>
<td>1</td>
</tr>
<tr>
<td>KCCQ @ Wk 4 &gt;50-75</td>
<td>2</td>
</tr>
<tr>
<td>Age (per +10y)</td>
<td>4</td>
</tr>
<tr>
<td>Male</td>
<td></td>
</tr>
<tr>
<td>Non-Caucasian</td>
<td></td>
</tr>
<tr>
<td>History of HF</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td></td>
</tr>
<tr>
<td>Renal insufficiency</td>
<td></td>
</tr>
<tr>
<td>Peripheral disease</td>
<td></td>
</tr>
<tr>
<td>EF (per -10%)</td>
<td></td>
</tr>
<tr>
<td>Non Q-wave MI</td>
<td></td>
</tr>
<tr>
<td>Thrombolytics only</td>
<td></td>
</tr>
<tr>
<td>Heart rate @ Wk 4 (per +10bpm)</td>
<td></td>
</tr>
<tr>
<td>Systolic BP @ Wk 4 (per +10mm)</td>
<td></td>
</tr>
<tr>
<td>Diastolic BP @ Wk 4 (per +10mm)</td>
<td></td>
</tr>
</tbody>
</table>

- **KCCQ @ Wk 4**: Quality of Life Assessment Questionnaire at Week 4
- **EF**: Ejection Fraction
- **HF**: Heart Failure
- **BP**: Blood Pressure
- **Thrombolytics only**: Patients who received thrombolytic treatment only
Interpretation of Health Status

◆ The challenge of new metrics

– Interpreting Scores at a Single Point in Time
   » Translation to a clinical framework
   » Prognostic import

– Interpreting Changes in Scores
   » Translation to a clinical framework
   » Prognostic Import
Interpretability Study: Design

- **KCCQ Interpretability Study**
  - Prospective cohort study
  - Convenience sample of 546 outpatients at 13 North American centers
  - 483 (88%) followed up at 6 weeks

- **Rationale**: To exploit the random variation of CHF over time to interpret the KCCQ

*Am Heart J 2005; 150:707-15*
Changes in KCCQ Overall Summary by Clinical $\Delta$

* $p<0.05$; ** $p<0.001$ as compared with stable patients

Clinically Important Change
- Small = 5 points
- Moderate = 10 points
- Large = 20 points
Interpretation of Health Status

◆ The challenge of new metrics

– Interpreting Scores at a Single Point in Time
  » Translation to a clinical framework
  » Prognostic import

– Interpreting Changes in Scores
  » Translation to a clinical framework
  » Prognostic Import
5-point $\Delta$ in KCCQ-OS = 10% $\Delta$ in Death/Hosp

- $n=1,358$ outpatients assessed 2 months apart
- Adjusted for >25 covariates, including initial KCCQ scores
- A linear association between $\Delta$KCCQ and death (HR=1.09/5-pt decrease in KCCQ (95%CI=1.03, 1.18))

## Interpreting the Change in KCCQ

<table>
<thead>
<tr>
<th>Level</th>
<th>Change in 6’ Walk Test</th>
<th>Change in VO₂</th>
<th>OR for Mortality/Hospitalization</th>
<th>OR for Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small Change (5pts)</td>
<td>112m</td>
<td>2.5ml/kg/min</td>
<td>11%</td>
<td>9%</td>
</tr>
<tr>
<td>Moderate Change</td>
<td>225m</td>
<td>5ml/kg/min</td>
<td>23%</td>
<td>19%</td>
</tr>
<tr>
<td>(10pts)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Large Change (20pts)</td>
<td>450m</td>
<td>10ml/kg/min</td>
<td>52%</td>
<td>42%</td>
</tr>
</tbody>
</table>
Presentation Overview

◆ Overview of PROs and the KCCQ
◆ Applications of PROs
  – Clinical Trials: PARADIGM-HF
  – Quality of Care
  – Clinical Practice
◆ A New Paradigm for Translating Clinical Trials to Clinical Care through Precision Medicine
Angiotensin–Neprilysin Inhibition versus Enalapril in Heart Failure

John J.V. McMurray, M.D., Milton Packer, M.D., Akshay S. Desai, M.D., M.P.H., Jianjian Gong, Ph.D., Martin P. Lefkowitz, M.D., Adel R. Rizkala, Pharm.D., Jean L. Rouleau, M.D., Victor C. Shi, M.D., Scott D. Solomon, M.D., Karl Swedberg, M.D., Ph.D., and Michael R. Zile, M.D., for the PARADIGM-HF Investigators and Committees*

ABSTRACT
PARADIGM-HF Results

Table 2. Primary and Secondary Outcomes.*

<table>
<thead>
<tr>
<th>Outcome</th>
<th>LCZ696 (N=4187)</th>
<th>Enalapril (N=4212)</th>
<th>Hazard Ratio or Difference (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary composite outcome — no. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death from cardiovascular causes or first hospitalization for worsening heart failure</td>
<td>914 (21.8)</td>
<td>1117 (26.5)</td>
<td>0.80 (0.73–0.87)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Death from cardiovascular causes</td>
<td>558 (13.3)</td>
<td>693 (16.5)</td>
<td>0.80 (0.71–0.89)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>First hospitalization for worsening heart failure</td>
<td>537 (12.8)</td>
<td>658 (15.6)</td>
<td>0.79 (0.71–0.89)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Secondary outcomes — no. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death from any cause</td>
<td>711 (17.0)</td>
<td>835 (19.8)</td>
<td>0.84 (0.76–0.93)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Change in KCCQ clinical summary score at 8 mo†</td>
<td>-2.99±0.36</td>
<td>-4.63±0.36</td>
<td>1.64 (0.63–2.65)</td>
<td>0.001</td>
</tr>
<tr>
<td>New-onset atrial fibrillation‡</td>
<td>84 (3.1)</td>
<td>83 (3.1)</td>
<td>0.97 (0.72–1.31)</td>
<td>0.83</td>
</tr>
<tr>
<td>Decline in renal function¶</td>
<td>94 (2.2)</td>
<td>108 (2.6)</td>
<td>0.86 (0.65–1.13)</td>
<td>0.28</td>
</tr>
</tbody>
</table>

2 Key Questions:

Is this an accurate assessment of the impact of LCZ on patients’ health status?

Is a 1.64-point difference clinically important?
Challenges with PARADIGM’s KCCQ Design

Single-blind Active Run-in Period
- Enalapril run-in
- Visit 2A: Enalapril 5 mg bid (optional) 1-2w

Double-blind Treatment Period
- LCZ696 run-in
- LCZ696 100 mg bid
- LCZ696 200 mg bid
- LCZ696 200 mg bid
- Enalapril 10 mg bid

Visit
1 2 3 4 5 6 7 8 9 10 up to 19 every

Time
1w 2w 1-2w 2-4w 2w 4w 8w 4m 8m 4m up to 44m*

Ideal Assessment of Δ in KCCQ
True Baseline
KCCQ @ Randomization
Outcome = ΔKCCQ
KCCQ Outcome
Potential Impact of Study Design

- At the time of run-in, patients were NYHA II-IV
  - Would have expected KCCQ Score <70
- All patients were uptitrated on enalapril, then LCZ
  - Mean ‘Baseline KCCQ Scores’ was 76.6
  - If the benefits of LCZ occur quickly (within 4-6 weeks), this improvement in KCCQ was missed
- If LCZ successfully sustains improvements in patients’ health status, then the best that could be seen is no change in scores, and worsening with LCZ withdrawal
  - 8-week change with LCZ = -3 vs. -4.6 with enalapril
  - Further limited by greater survival in LCZ
Responder Analyses for the KCCQ

- Responder Analyses examine the proportions of patients with a clinically important change
  - A 5-point change is clinically meaningful small change
  - A 10-point change is a moderately large change in status

- Subtracting the proportions of patients with a clinically important change can be converted into NNT

\[
NNT = \frac{100}{\frac{\% \text{ with important change treated with LCZ}}{\% \text{ with important change treated with Enalapril}}}
\]
Interpretation of KCCQ Results

- There is a significantly, albeit modest, health status benefit in HF patients treated with LCZ vs. enalapril
- The NNT to prevent significant deterioration in patients’ health status is \( \sim 20 \)
- These benefits may be underestimated in real-world application of LCZ
Presentation Overview

◆ Overview of PROs and the KCCQ

◆ Applications of PROs
  – Clinical Trials and the FDA
  – Quality of Care
  – Clinical Practice

◆ A New Paradigm for Translating Clinical Trials to Clinical Care through Precision Medicine
The Centers for Medicare & Medicaid Services (CMS) seeks stakeholder comments on the following clinical quality measure under development:

**Title:** Functional Status Assessment and Target Setting for Patients with Congestive Heart Failure

**Description:** Percentage of patients 18 years of age and older with congestive heart failure for whom a score from a select list of validated functional status assessments (FSAs) was recorded at least twice during the measurement period and for whom a target was documented and linked to the initial assessment.

We seek comments from the public about the measure concept and specifications, the potential for the measure to improve health care quality, and the possible barriers to measure implementation.

This document provides information about the measure background about the project developing the measure and an overview of proposed approach to developing outcomes measures.

*Educated guess*
MIPS Credit for Improvement Activities

- Use of certified EHR to capture patient reported outcomes

In support of improving patient access, performing additional activities that enable capture of patient reported outcomes (e.g., home blood pressure, blood glucose logs, food diaries, at-risk health factors such as tobacco or alcohol use, etc.) or patient activation measures through use of certified EHR technology, containing this data in a separate queue for clinician recognition and review.

<table>
<thead>
<tr>
<th>Activity ID</th>
<th>Subcategory Name</th>
<th>Activity Weighting</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA_BE_1</td>
<td>Beneficiary Engagement</td>
<td>Medium</td>
</tr>
</tbody>
</table>
Presentation Overview

- Overview of PROs and the KCCQ
- Applications of PROs
  - Clinical Trials: PARADIGM-HF
  - Quality of Care
  - Clinical Practice
- A New Paradigm for Translating Clinical Trials to Clinical Care through Precision Medicine
Evolving Standards in Clinical Care

- The ‘Gold Standard’ for Cardiac Physiology

- Limitations in...
  - Accuracy
  - Reproducibility
A Conceptual Framework for PROs

◆ The ‘Gold Standard’ for History of Symptoms and Impact

◆ Limitations in…
  o Accuracy
  o Reproducibility

(The Seattle Angina Questionnaire?
1. The following is a list of activities that people often do during the week. Although for some people with several medical problems it is difficult to determine what it is that limits them, please point out the activities listed below and indicate how much limitation you ever had due to chest pain, chest tightness or angina over the past 4 weeks.

<table>
<thead>
<tr>
<th>Activity</th>
<th>Extremely limited</th>
<th>Quite a bit limited</th>
<th>Moderately limited</th>
<th>Slightly limited</th>
<th>Not at all limited</th>
<th>Limited for other reasons or did not do the activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Walking indoors on level ground</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gardening,奖金&lt;ing or caring for children</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lifting or moving heavy objects</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

2. Over the past 4 weeks, on average, how many times have you had chest pain, chest tightness or angina?
I have had chest pain, chest tightness or angina...
4 or more times per day 1-3 times per week 3 or more times per week but not every day 1-2 times per week Less than once a week None over the past 4 weeks

3. OVER THE PAST 4 WEEKS, ON AVERAGE, HOW MANY TIMES HAVE YOU HAD CHEST PAIN, CHEST TIGHTNESS OR ANGINA?
I have taken medicines...
4 or more times per day 1-3 times per week 3 or more times per week but not every day 1-2 times per week Less than once a week None over the past 4 weeks

4. OVER THE PAST 4 WEEKS, HOW MUCH HAS YOUR CHEST PAIN, CHEST TIGHTNESS OR ANGINA LIMITED YOUR ENJOYMENT OF LIFE?
I was extremely limited in my enjoyment of life I was moderately limited in my enjoyment of life I was slightly limited in my enjoyment of life I has not been limited in my enjoyment of life at all

5. IF YOU HAD TO SPEND THE REST OF YOUR LIFE WITH YOUR CHEST PAIN, CHEST TIGHTNESS OR ANGINA, THE WAY IT IS RIGHT NOW, HOW WOULD YOU FEEL ABOUT THIS?
Not satisfied at all Mostly dissatisfied Somewhat satisfied Mostly satisfied Completely satisfied)
Presentation Overview

- Overview of PROs and the KCCQ
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  - Quality of Care
  - Clinical Practice
- A New Paradigm for Translating Clinical Trials to Clinical Care through Precision Medicine
Creating & Applying Evidence-Based Medicine

Outcomes from a Study

Risk Stratification

Mean Treatment Difference
Delayed Adoption of CRT, Despite Guidelines

Among an estimated 326,151 patients...
Examples of CRT Decision Tools

45 yo F, MLWHF 60, NICM (EF 25%),
LBBB (QRS 180)

55 yo M, MLWHF 25, DM, RBBB
(QRS 130)
Shared Decision-Making Epitomizes Patient-Centered Care

◆ It is a Process...

Patient

Knowledge Transfer

Patient Preferences

Participation in SDM

Providers

How are Providers to Share this Information for Individual Patients? Patients’ Care about their Symptoms, Function and Quality of Life
**Average MLWHF Improvement Seems Small**

<table>
<thead>
<tr>
<th></th>
<th>CARE-HF n = 404</th>
<th>MIRACLE n = 275</th>
<th>MIRACLE-ICD n = 283</th>
<th>RAFT n = 904</th>
<th>REVERSE n = 191</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>OMT</td>
<td>-4.1 ± 16.5</td>
<td>-12.8 ± 24.8</td>
<td>-13.4 ± 24.5</td>
<td>-11.4 ± 19.6</td>
<td>-7.3 ± 16.2</td>
<td>-10.1 ± 20.7</td>
</tr>
<tr>
<td>CRT</td>
<td>-15.1 ± 18.2</td>
<td>-19.5 ± 23.2</td>
<td>-16.3 ± 24.2</td>
<td>-12.0 ± 20.9</td>
<td>-10.3 ± 15.7</td>
<td>-13.7 ± 20.5</td>
</tr>
</tbody>
</table>

A 3.6-point difference?
Modeling the Heterogeneity of QOL Benefit

Model Driven by 3 Variables: Age, QRS Width and Baseline QoL

<table>
<thead>
<tr>
<th>Baseline MLWHF (pts with scores below median):</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>OR for large improvement per +5 units</td>
<td>1.45 (1.35, 1.56)</td>
</tr>
<tr>
<td>OR for at least moderate improvement per +5 units</td>
<td>1.42 (1.33, 1.51)</td>
</tr>
<tr>
<td>OR for at least small improvement per +5 units</td>
<td>1.37 (1.29, 1.46)</td>
</tr>
<tr>
<td>OR for at least no change per +5 units</td>
<td>1.30 (1.22, 1.38)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Baseline MLWHF (pts with scores above median):</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>OR for large improvement per +5 units</td>
<td>1.33 (1.29, 1.38)</td>
</tr>
<tr>
<td>OR for at least moderate improvement per +5 units</td>
<td>1.30 (1.26, 1.34)</td>
</tr>
<tr>
<td>OR for at least small improvement per +5 units</td>
<td>1.27 (1.23, 1.30)</td>
</tr>
<tr>
<td>OR for at least no change per +5 units</td>
<td>1.23 (1.19, 1.26)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age (+10 years)</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1.10 (1.00, 1.20)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CRT vs MM among pts with QRS Width 145 ms</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1.42 (1.14, 1.77)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CRT vs MM among pts with QRS Width 161 ms</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1.59 (1.33, 1.90)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CRT vs MM among pts with QRS Width 180 ms</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1.84 (1.48, 2.30)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>QRS Width (+10 ms) among CRT pts</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1.07 (1.02, 1.13)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>QRS Width (+10 ms) among MM pts</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.99 (0.94, 1.05)</td>
</tr>
</tbody>
</table>
Personalized SDM Tools for CRT

What is CRT?
Sometimes the heart pumps poorly and out of caused by damage to the heart, age, genetics or other reasons. CRT helps the heart pump nor right and left ventricles of the heart pump together which improves the pumping function.

What is the Treatment?
Cardiac resynchronization therapy may make some feel worse. The chance of feeling a lot now, with and without CRT, is shown below:

- With CRT: 10%
- Without CRT: 30%

What are the Risks?
The chance of feeling worse 3 months from CRT, is shown below:

- With CRT: 20%
- Without CRT: 30%

What is the Mortality Advantage?
The likelihood for you to be alive in 1 year will shown below:

- With CRT: 80%
- Without CRT: 60%

What is the Chance of Feeling Much Better?
You are the expert on what is important for you.

- What else do you need to help you make your decision?
  - It may be helpful for you to talk with your family and friends. You may want to share the information in this decision aid with them. You should also share with your doctor your questions and concerns before making a final decision. It is important that you have all of the information you need to make a decision that is right for you.

What is the Chance of Feeling Worse?

- People with a CRT should avoid strong magnets and some industrial equipment. Normal appliances like microwaves are okay.
  - You should not walk through the metal detector at the airport. Instead, you should ask to be hand searched. It is okay to walk through store security systems.
  - It is possible to exercise with a CRT. Talk to your doctor to learn which exercises are safe for you.

- You may use a cell phone but you should keep the phone at least 6 inches away from the CRT.
Translating Clinical Data to Practice

◆ **Traditional Approach**
  – Conduct Phase 3 RCTs
  – Report in Literature
  – Submit to FDA
  – Develop Phase 4 Program to establish effectiveness
  – Hope for adoption in Guidelines
  – Hope for adoption as a performance measure
  – Wait for widespread adoption in routine care

◆ **Personalized Medicine**
  – Model the heterogeneity of treatment benefit
  – Build tools to personalize benefit to individual patients
  – Release tools at presentation of initial study results
  – Support implementation of precision medicine
  – Accelerate adoption and adherence to treatment
Conclusion

◆ PROs capture a KEY outcome from patients’ perspectives

◆ Integration of PROs into development programs should occur early

◆ Design of PRO strategies are important in defining the benefits of therapy

◆ Need to create novel tools to personalize medicine and support adoption
Symptoms of Heart Failure & KCCQ

Backup of fluid in lungs from increased LV/LA pressure
⇒ symptoms of shortness of breath and paroxysmal nocturnal dyspnea

Backup of fluid in lungs from increased RV/RA pressure
⇒ symptoms of shortness of leg swelling and signs of edema

Diminished output from LV ⇒ symptoms of fatigue and tiredness

Normal Flow and Function

Abnormal Flow and Function in Heart Failure