Patients' role and using PED/PROs in clinical trials

Trialist perspective

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ESC European Society of Cardiology

Disclosures

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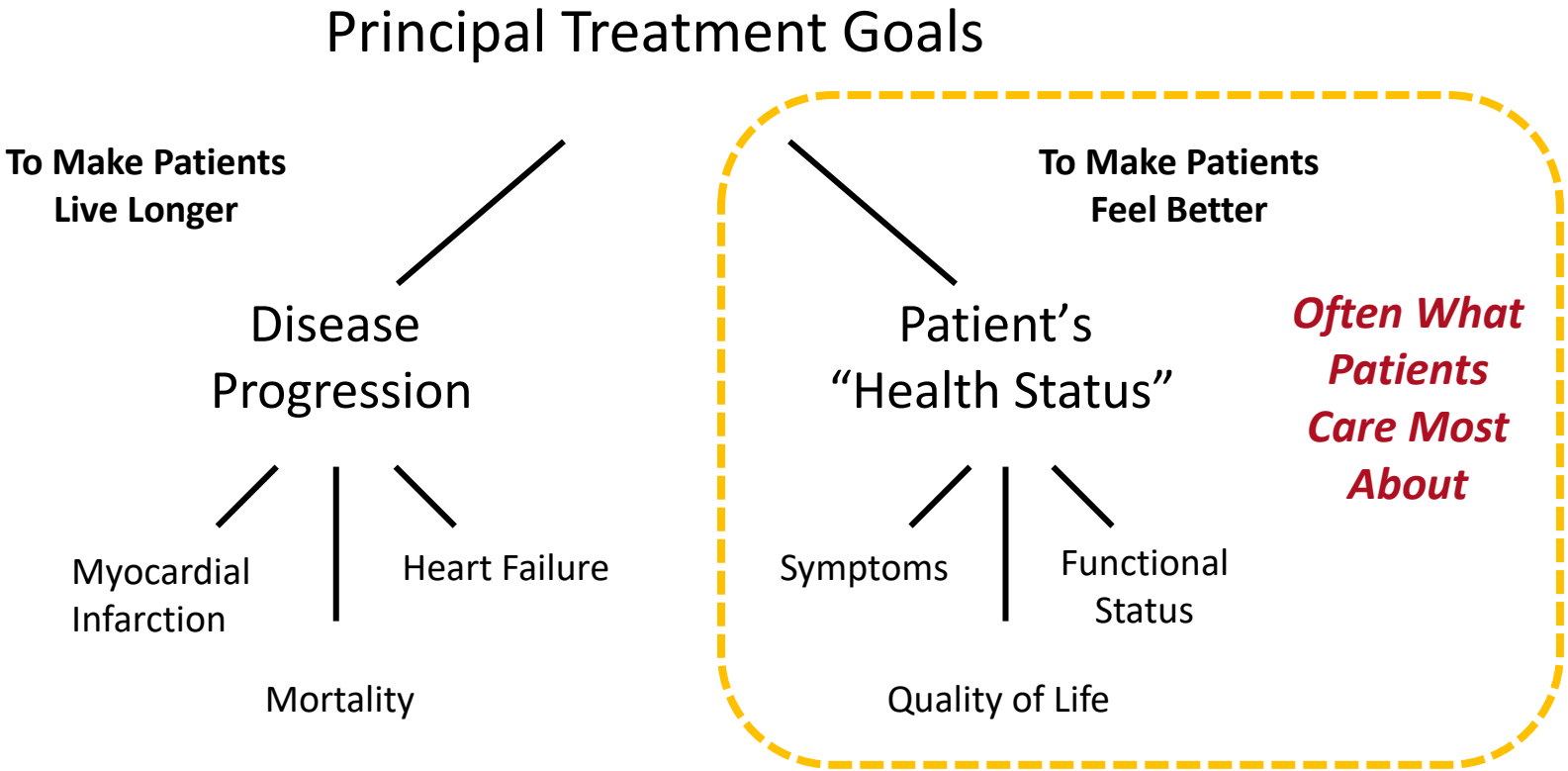
Affiliation/Financial Relationship	Company
Consultant/Advisory/Speaking Engagements:	Elixir Medical, IQVIA, Medtronic, Medscape/WebMD Global, NovoNordisk
Research Funding to Institution:	Abbott, Alleviant Medical, Beth Israel Deaconess Medical Center, Concept Medical, Cordis, CPC Clinical Research, Elixir Medical, Faraday Pharmaceuticals, Idorsia Pharmaceuticals, Janssen, MedAlliance, Mediasphere Medical, Medtronic, Novartis, Protembis GmbH, RM Global Bioaccess Fund Management, Sanofi US Services, Inc
Equity <1% in:	Elixir Medical, Stel, ControlRad (spouse)
No Fees from:	SCAI (Women in Innovations Committee Member), Faculty Cardiovascular Research Foundation (CRF), Women as One (Founding Director)
Honorarium:	AMA - JAMA Cardiology (Associate Editor), ACC (BOT Member, SC Member CTR Program)

Focusing on Treatment Goals



Benefit of PROs in Cardiovascular Medicine

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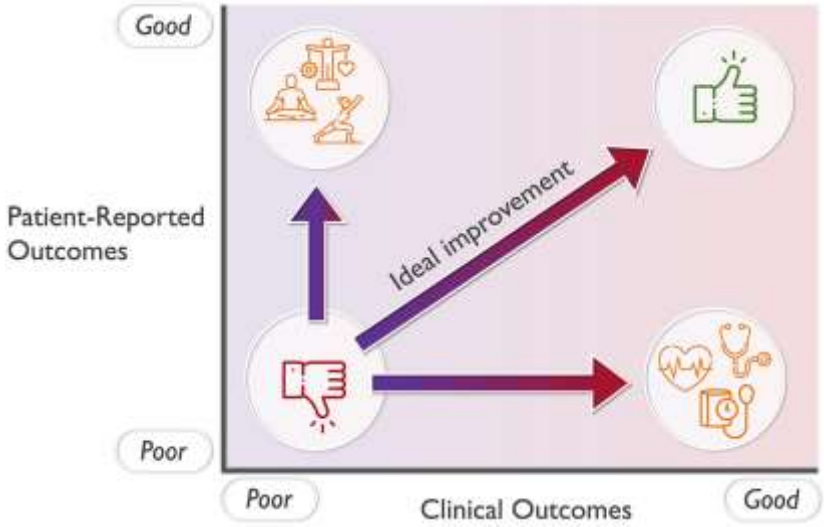
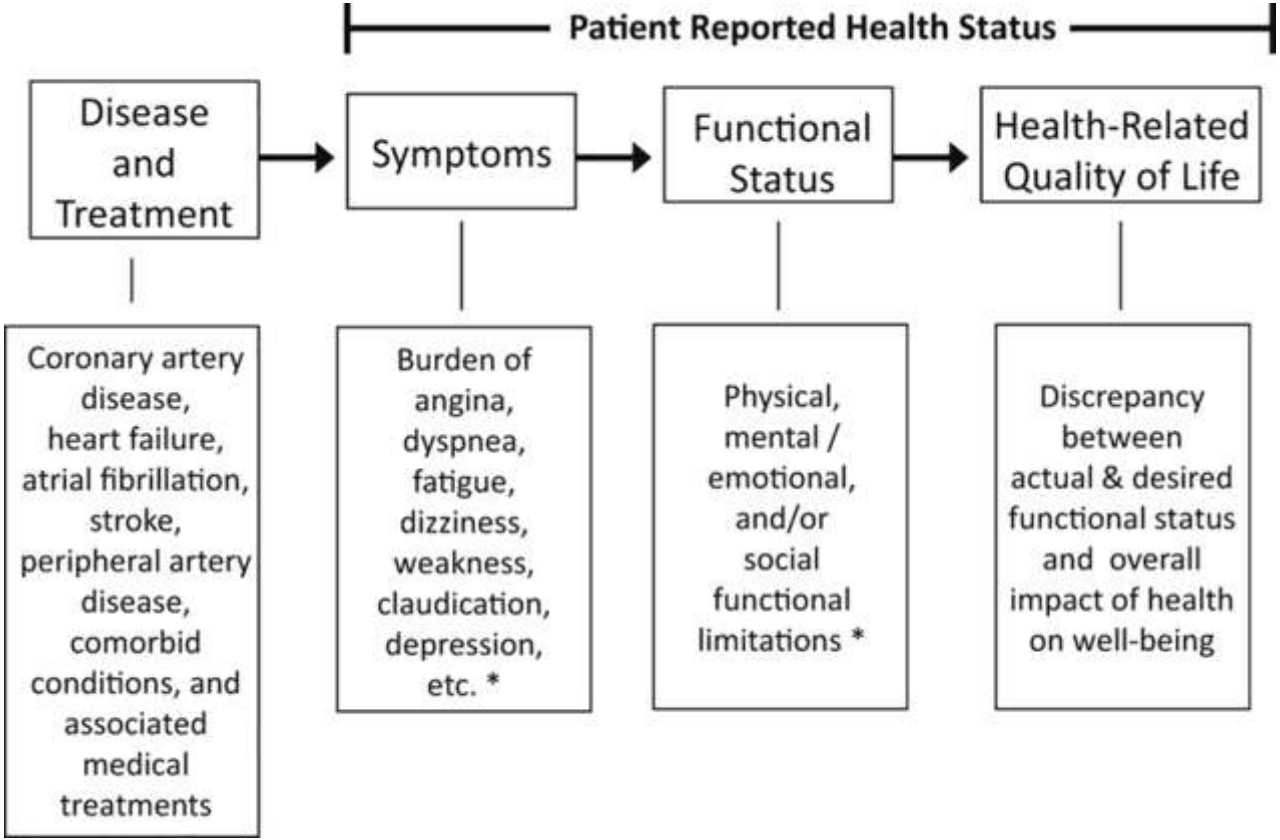


Moons et al, European Heart Journal (2023) 44, 3405–3422

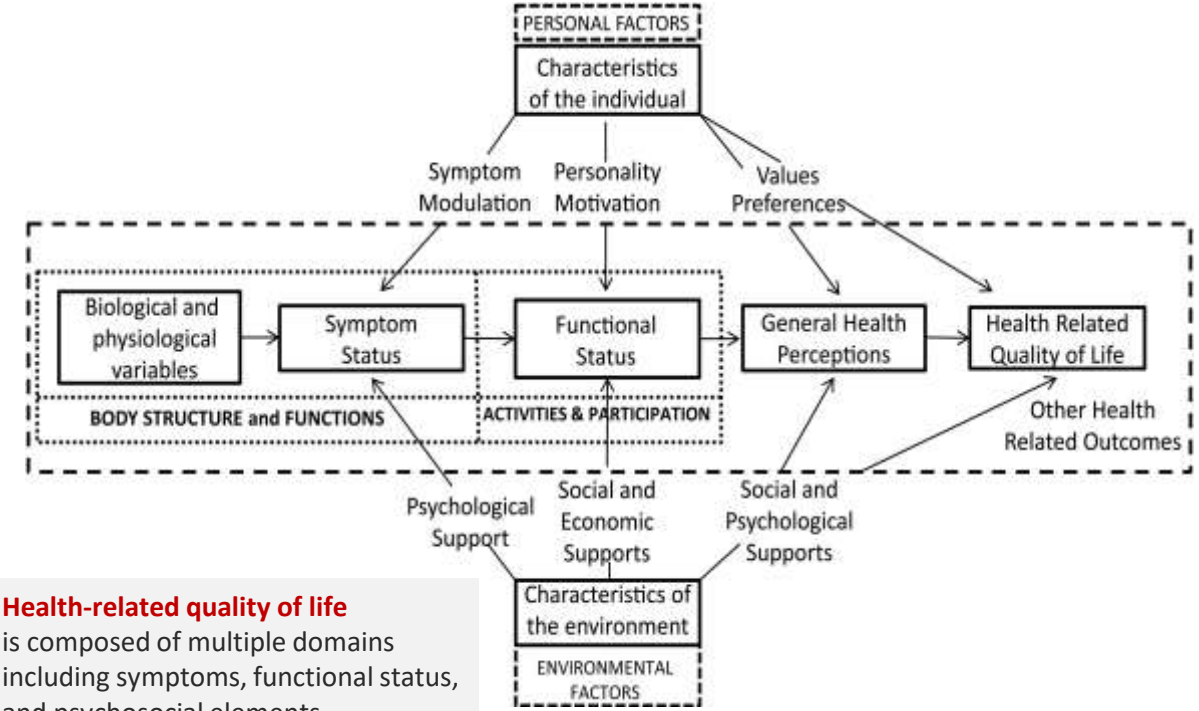
U.S. FDA Roadmap to patient-focused outcome measurement in clinical trials

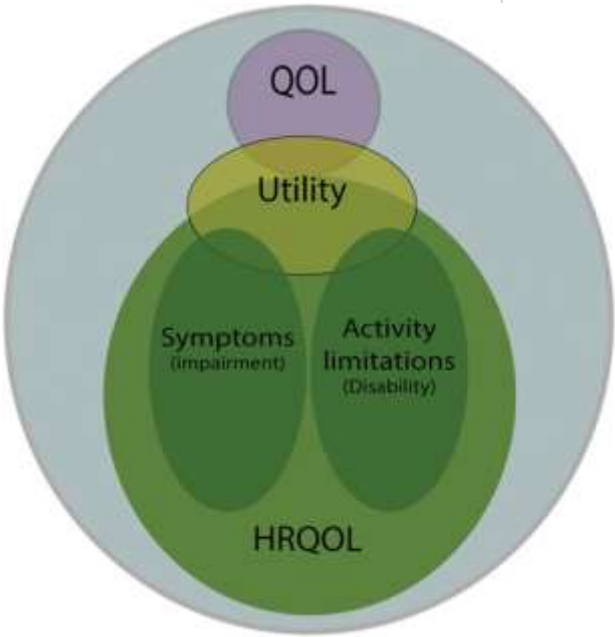
Patient related health status may look simple…



Rumsfeld JS et al, Circulation 2013

However, models for health outcomes assessment are intricate





Health-related quality of life
is composed of multiple domains including symptoms, functional status, and psychosocial elements

Anker SD et al, EHJ 2014

PROs and PED in CV clinical trials

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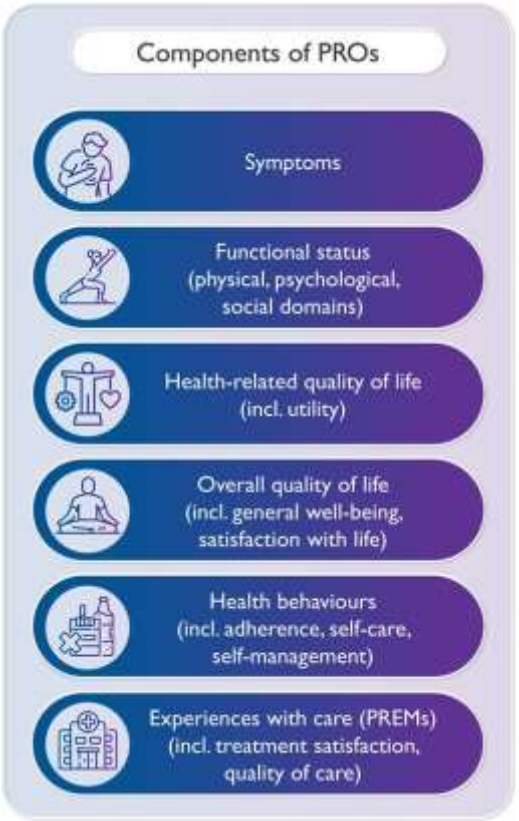
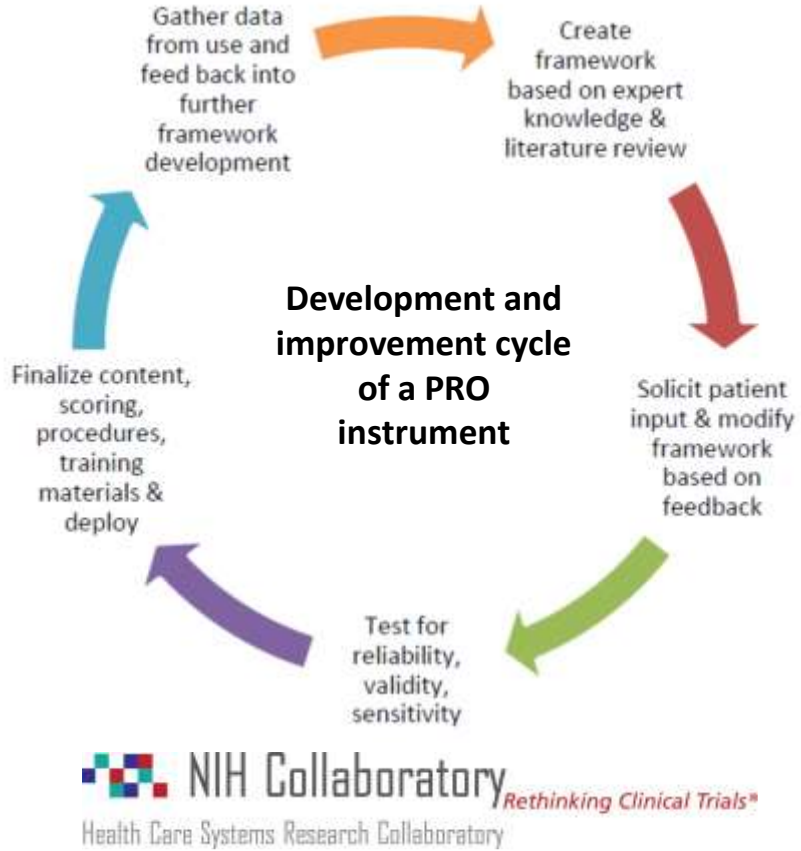
	PROs (Patient-Reported Outcomes)	PED (Patient Experience Data)
Definition	**Direct reports from patients** about their **health status**, symptoms, functional outcomes, and quality of life	**Information collected from patients on their experiences** with a disease, treatment, and participation in clinical trials.
Purpose	**To assess treatment effectiveness from the patient's perspective.**	**To understand patient perspectives on trial participation, decision-making, and healthcare interactions.**
Examples	- Symptom severity (e.g., dyspnea, chest pain, fatigue) - Health-related quality of life (HRQoL) - Physical function (e.g., walking distance, daily activities) - Psychological well-being (e.g., depression, anxiety)	- Patient satisfaction with trial participation - Reasons for treatment adherence or non-adherence - Preferences in trial design and consent process - Burden of participation (e.g., travel, time, logistics)
How It's Measured	Standardized validated tools (e.g., KCCQ, EQ-5D, SF-36, PROMIS).	Surveys, focus groups, interviews, and social media listening.
Regulatory Relevance	Increasingly used in clinical trials and regulatory approvals (FDA, EMA, HTA bodies) for demonstrating patient-centered benefits.	Helps optimize trial design, recruitment, and retention, but not typically a primary endpoint in regulatory submissions.
Application in Cardiovascular Trials	Evaluates treatment benefits beyond survival (e.g., impact of heart failure therapies on patient-reported function).	Improves patient engagement, diversity, and trial feasibility by addressing real-world barriers to participation.

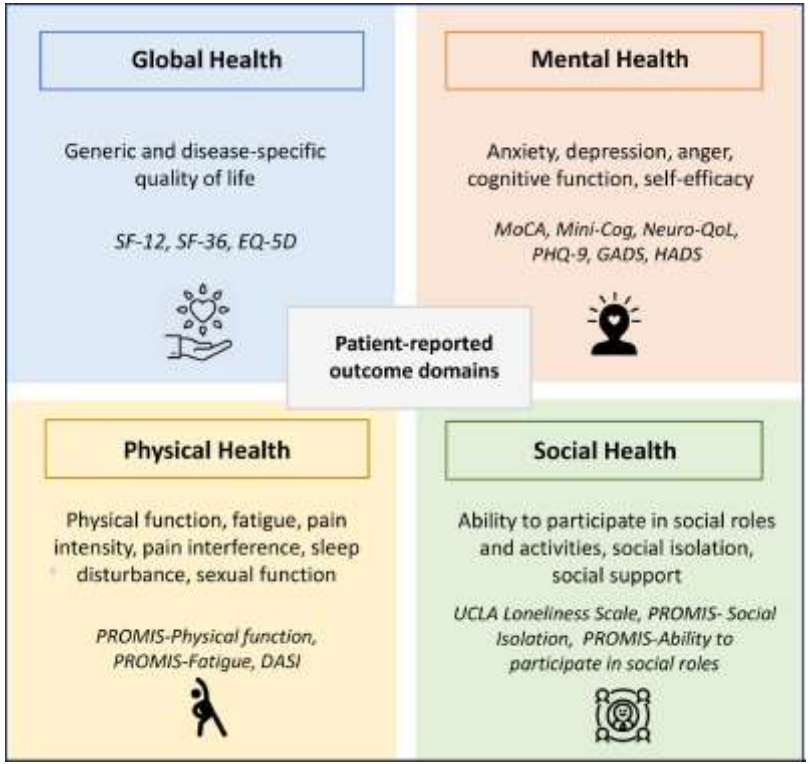
Key components of PROs

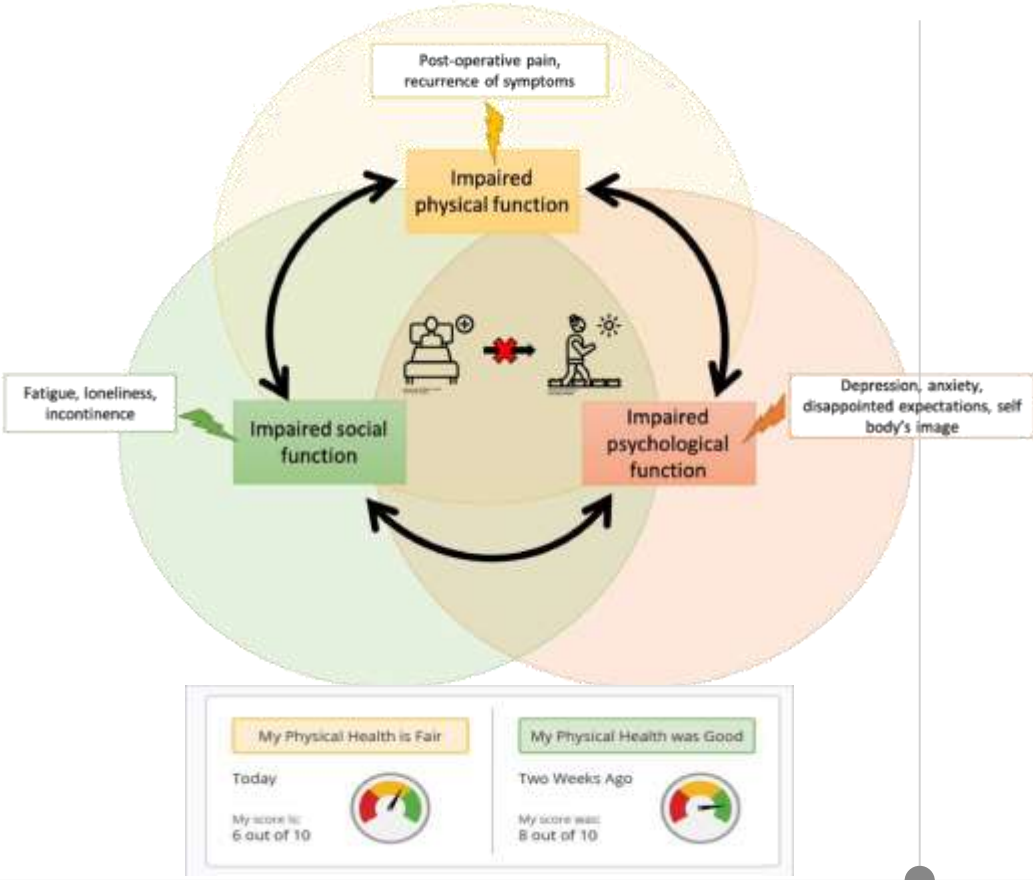




Moons et al, European Heart Journal (2023) 44, 3405–3422

What to collect: domains of PROs





Masterson Creber R, et al. Can J Cardiol. 2021

Cardiovascular Disease-specific PROs

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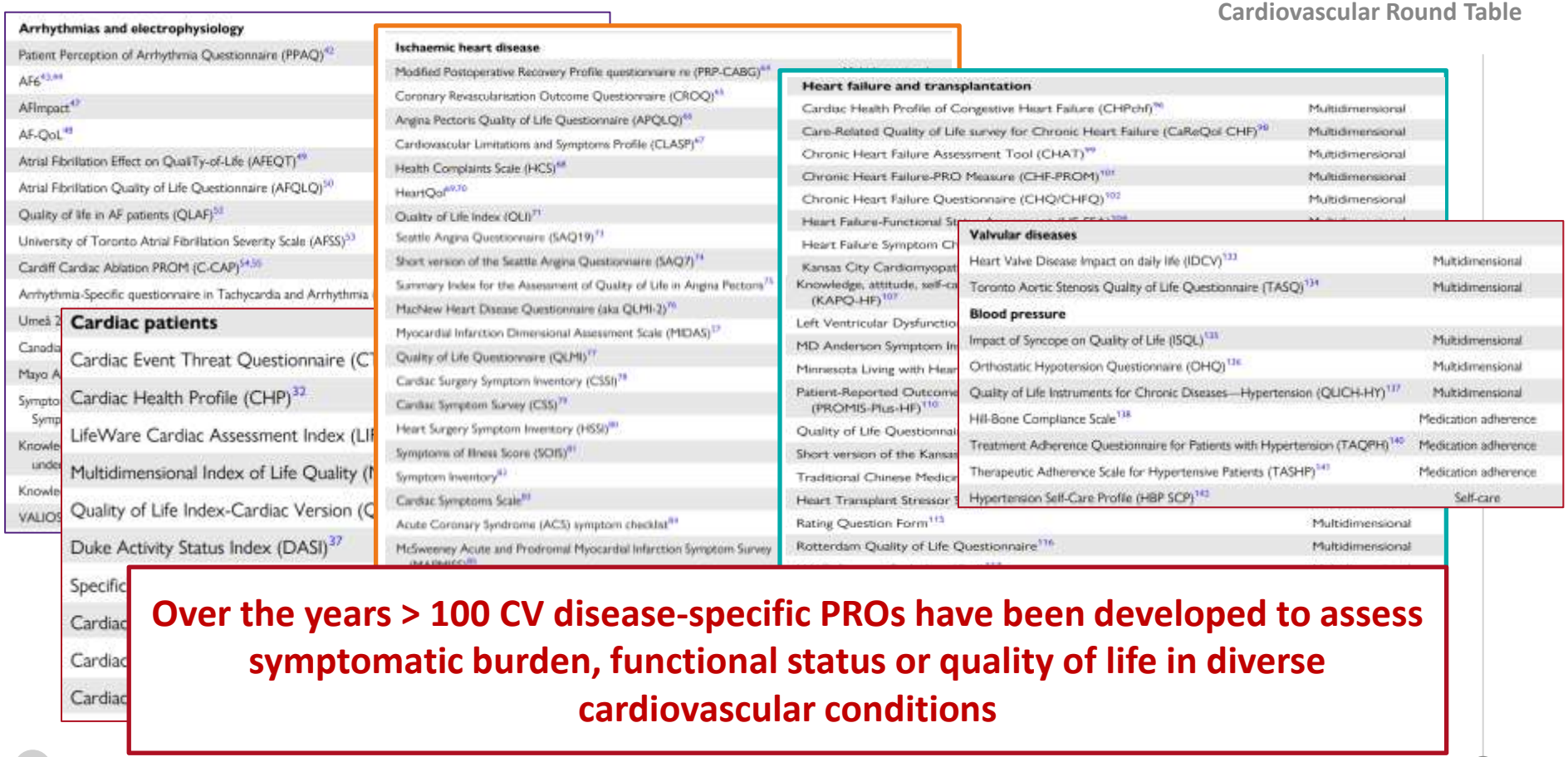

Arrhythmias and electrophysiology

- Patient Perception of Arrhythmia Questionnaire (PPAQ)[42]
- AF6[43,44]
- AFImpact[47]
- AF-QoL[48]
- Atrial Fibrillation Effect on QualiTy-of-Life (AFEQT)[49]
- Atrial Fibrillation Quality of Life Questionnaire (AFQLQ)[50]
- Quality of life in AF patients (QLAF)[52]
- University of Toronto Atrial Fibrillation Severity Scale (AFSS)[53]
- Cardiff Cardiac Ablation PROM (C-CAP)[54,55]
- Arrhythmia-Specific questionnaire in Tachycardia and Arrhythmia
- Umeå 2
- Canadia
- Mayo A
- Sympto Symp
- Knowle unde
- Knowle
- VALIO

Cardiac patients

- Cardiac Event Threat Questionnaire (C
- Cardiac Health Profile (CHP)[32]
- LifeWare Cardiac Assessment Index (LI
- Multidimensional Index of Life Quality (
- Quality of Life Index-Cardiac Version (
- Duke Activity Status Index (DASI)[37]
- Specific
- Cardiac
- Cardiac
- Cardiac

Ischaemic heart disease

- Modified Postoperative Recovery Profile questionnaire re (PRP-CABG)[64]
- Coronary Revascularisation Outcome Questionnaire (CROQ)[65]
- Angina Pectoris Quality of Life Questionnaire (APQLQ)[66]
- Cardiovascular Limitations and Symptoms Profile (CLASP)[67]
- Health Complaints Scale (HCS)[68]
- HeartQol[69,70]
- Quality of Life Index (QLI)[71]
- Seattle Angina Questionnaire (SAQ19)[73]
- Short version of the Seattle Angina Questionnaire (SAQ7)[74]
- Summary Index for the Assessment of Quality of Life in Angina Pectoris[75]
- MacNew Heart Disease Questionnaire (aka QLMI-2)[76]
- Myocardial Infarction Dimensional Assessment Scale (MIDAS)[77]
- Quality of Life Questionnaire (QLMI)[77]
- Cardiac Surgery Symptom Inventory (CSSI)[78]
- Cardiac Symptom Survey (CSS)[79]
- Heart Surgery Symptom Inventory (HSSI)[80]
- Symptoms of Illness Score (SOIS)[81]
- Symptom Inventory[82]
- Cardiac Symptoms Scale[83]
- Acute Coronary Syndrome (ACS) symptom checklist[84]
- McSweeney Acute and Prodromal Myocardial Infarction Symptom Survey

Heart failure and transplantation

Cardiac Health Profile of Congestive Heart Failure (CHPchf)[96]	Multidimensional
Care-Related Quality of Life survey for Chronic Heart Failure (CaReQol-CHF)[98]	Multidimensional
Chronic Heart Failure Assessment Tool (CHAT)[99]	Multidimensional
Chronic Heart Failure-PRO Measure (CHF-PROM)[101]	Multidimensional
Chronic Heart Failure Questionnaire (CHQ/CHFQ)[102]	Multidimensional
Heart Failure-Functional St	
Heart Failure Symptom Ch	
Kansas City Cardiomyopat	
Knowledge, attitude, self-ca (KAPQ-HF)[107]	
Left Ventricular Dysfunctio	
MD Anderson Symptom In	
Minnesota Living with Hear	
Patient-Reported Outcome (PROMIS-Plus-HF)[110]	
Quality of Life Questionnai	
Short version of the Kansa	
Traditional Chinese Medica	
Heart Transplant Stressor S	
Rating Question Form[115]	Multidimensional
Rotterdam Quality of Life Questionnaire[116]	Multidimensional

Valvular diseases

Heart Valve Disease Impact on daily life (IDCV)[133]	Multidimensional
Toronto Aortic Stenosis Quality of Life Questionnaire (TASQ)[134]	Multidimensional

Blood pressure

Impact of Syncope on Quality of Life (ISQL)[135]	Multidimensional
Orthostatic Hypotension Questionnaire (OHQ)[136]	Multidimensional
Quality of Life Instruments for Chronic Diseases—Hypertension (QUICH-HY)[137]	Multidimensional
Hill-Bone Compliance Scale[138]	Medication adherence
Treatment Adherence Questionnaire for Patients with Hypertension (TAQPH)[140]	Medication adherence
Therapeutic Adherence Scale for Hypertensive Patients (TASHP)[141]	Medication adherence
Hypertension Self-Care Profile (HBP SCP)[142]	Self-care

Over the years > 100 CV disease-specific PROs have been developed to assess symptomatic burden, functional status or quality of life in diverse cardiovascular conditions

Moons et al, European Heart Journal (2023) 44, 3405–3422

How to select the adequate PROMs

- Select PRO measuress based on validity, reliability, burden, ethics, and licensing.
- Combine different PRO measures through **generic**, **disease-specific**, and **domain-specific** instruments
- Use validated tools to find high-quality PROMs that match the intended purposes (e.g. EMPRO tools, COSMIN checklist, etc)
- Involve patients in selection
- Address ethical issues: timely PRO Alerts & adherence to ethical guidelines.
- Some PROMs have strict licensing & fees

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European Heart Journal (2023) 44, 3405–3422
https://doi.org/10.1093/eurheartj/ehad514
SPECIAL ARTICLE
Epidemiology, prevention, and health care policies

Placing patient-reported outcomes at the centre of cardiovascular clinical practice: implications for quality of care and management

A statement of the ESC Association of Cardiovascular Nursing and Allied Professions (ACNAP), the Association for Acute CardioVascular Care (ACVC), European Association of Percutaneous Cardiovascular Interventions (EAPCI), European Association of Preventive Cardiology (EAPC), Heart Failure Association (HFA), European Heart Rhythm Association (EHRA), European Association of Cardiovascular Imaging (EACVI), ESC Regulatory Affairs Committee, ESC Advocacy Committee, ESC Digital Health Committee, ESC Education Committee, and the ESC Patient Forum

PROs in clinical trials

- PRO endpoints should be decided *a priori* and included in the ethical review and the trial registration.
- Trial committees should have PRO expertise.
- Patients should be involved in selecting suitable PRO instruments.
- Guidance for the use, analysis, and interpretation of PROs in clinical trials should be developed.
- Recommendations for designing, analysing and reporting PRO findings should be used (e.g. SPIRIT-PRO; CONSORT-PRO).
- PRO Alerts are advised to capture issues that require prompt intervention.

PROs-specific recommendations for clinical trials

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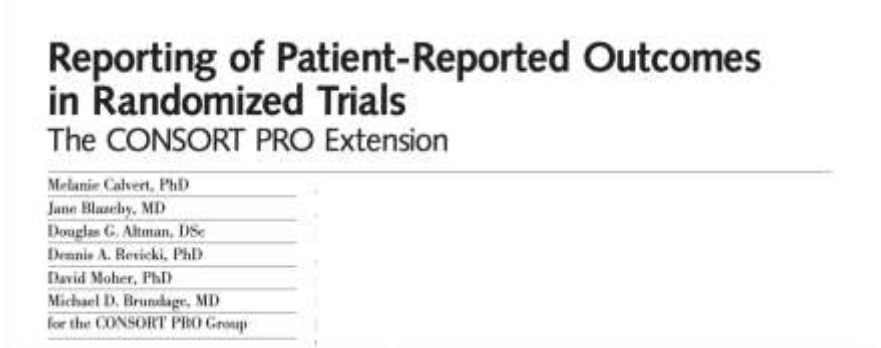
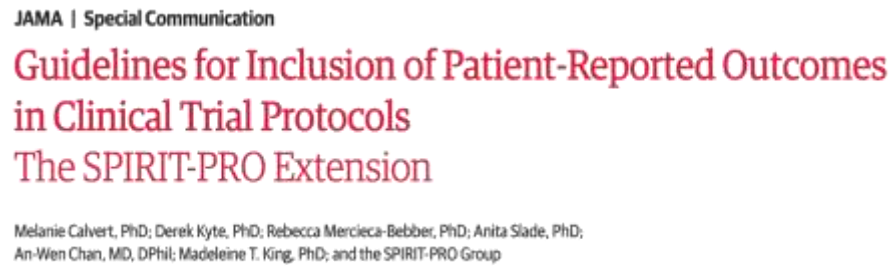

Reporting of Patient-Reported Outcomes in Randomized Trials
The CONSORT PRO Extension

Melanie Calvert, PhD
Jane Blazeby, MD
Douglas G. Altman, DSc
Dennis A. Revicki, PhD
David Moher, PhD
Michael D. Brundage, MD
for the CONSORT PRO Group


JAMA | Special Communication

Guidelines for Inclusion of Patient-Reported Outcomes in Clinical Trial Protocols
The SPIRIT-PRO Extension

Melanie Calvert, PhD; Derek Kyte, PhD; Rebecca Mercieca-Bebber, PhD; Anita Slade, PhD; An-Wen Chan, MD, DPhil; Madeleine T. King, PhD; and the SPIRIT-PRO Group

Key recommendations

- Describe PRO-specific **research questions, objectives** and **hypothesis**
- Specify any PRO-specific **eligibility criteria**
- Specify the PRO **domains** used to evaluate interventions, analysis metric and time point or period of interest
- Include the **schedule** for PRO-assessment
- When PRO is primary endpoint, justify **sample size**
- When PRO is not primary endpoint, discuss the **power**
- Justify the **PRO instrument selected**, methods and language of administration, and proxy respondent (if used)
- Specify PRO data collection and management strategies, and if PRO will be monitored
- State PRO analysis methods, including plans for statistical error and missing data mitigation

Analyzing PROs over the time

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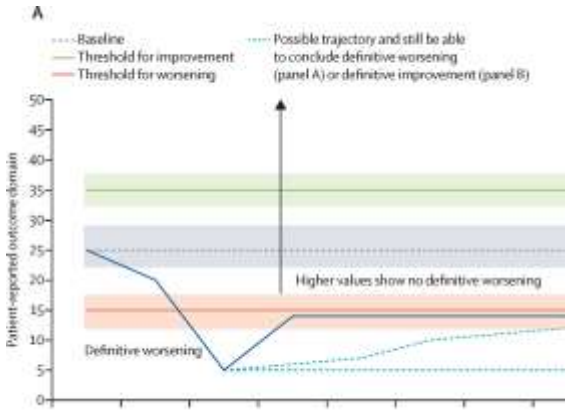
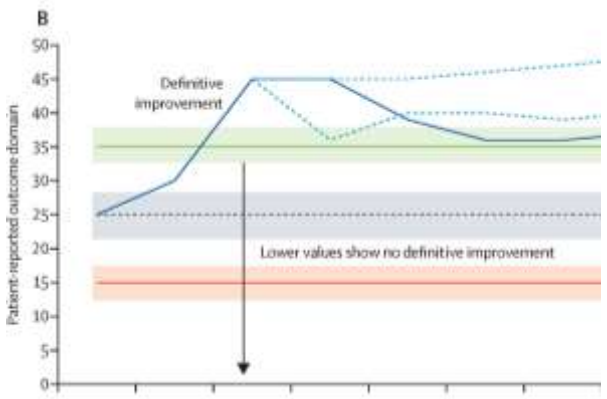
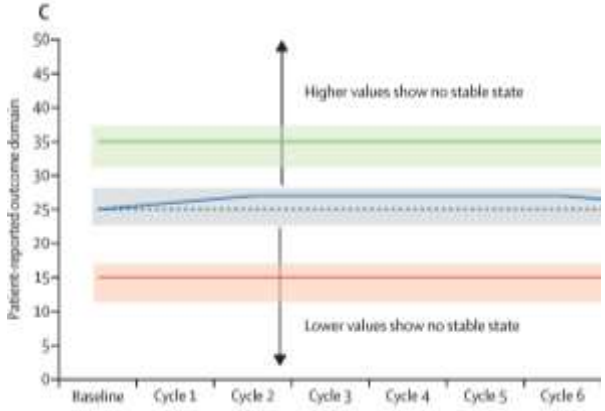
Worsening



Improvement



Stable state



How to analyze PROs over time:

- **Overall effect and magnitude of improvement / worsening**
- **Time to worsening / improvement / stable state**
- **Proportion of patients with worsening / improvement / stable state at time t**

Coens C, et al. Lancet Oncol. 2020.

Are PROs more Vulnerable to Placebo Effects?

Placebo Effect

Natural disease course

Regression towards the mean

Time effects

Patient-related Factors

Enhanced Care at Centers of Excellence

Frequent medical visits

Changes in patient behavior (e.g. medical adherence, diet, exercise, etc.)

Factors relating to trial design

Are PROs more Vulnerable to Placebo Effects?

Data come directly from patients

- Patients may know what they received

Patients' beliefs may influence their responses

- Likely more relevant to Global Impressions of Change
  - *How much better are you know than when you started the trial?*
- Less likely with modern PROs that ask concrete questions
  - *Over the past 2 weeks, how often have you had shortness of breath?*

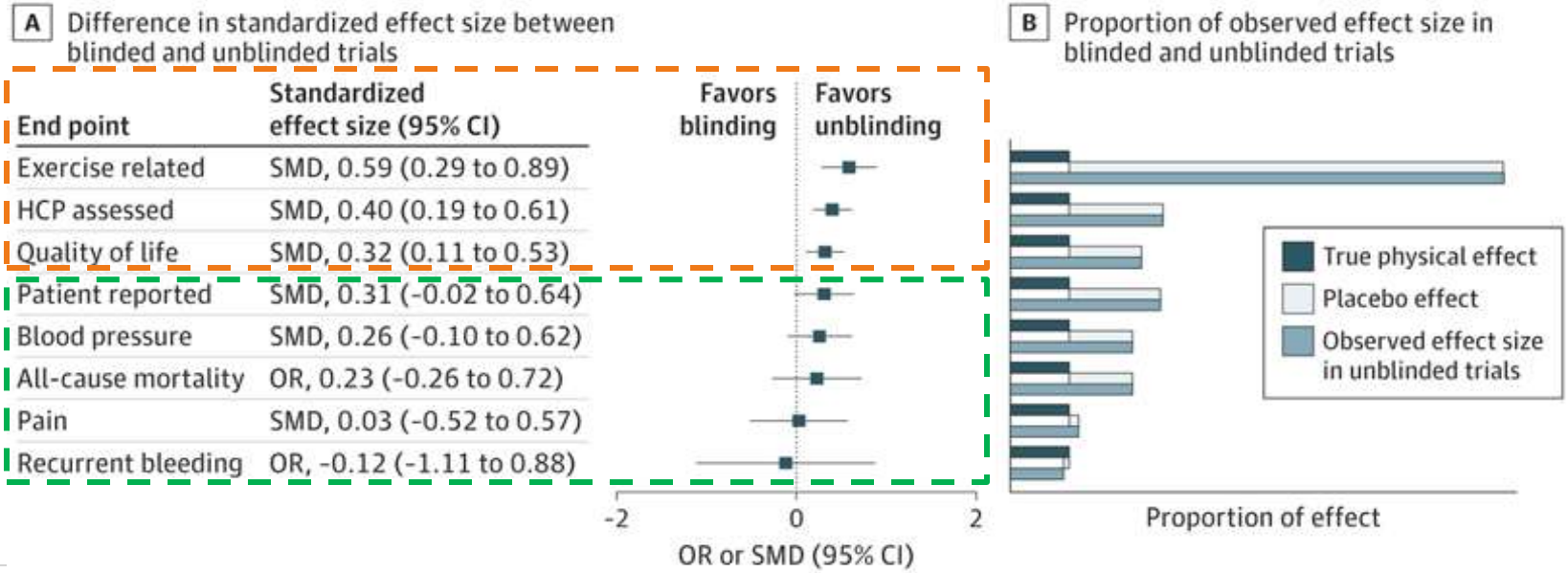
Less concern when the effects are large or sustained over time

Do the data support this concern when effect sizes are smaller?

How should we design trial? Mind placebo effect, but…

72 blinded placebo-controlled RCTs and 55 unblinded RCTs without placebo for procedural interventions (>100k pts)

- **Placebo effect** affected assessments of exercise capacity, quality of-life evaluations, and end points assessed by **health care professionals**.
- **Placebo effect did not significantly impact patient-reported end points** or end points reporting blood pressure, pain, recurrent bleeding events, or all-cause mortality.



Rajkumar C et al, JAMA Surgery 2024

A lesson from PCI trial: what is the true effect of PCI on angina?

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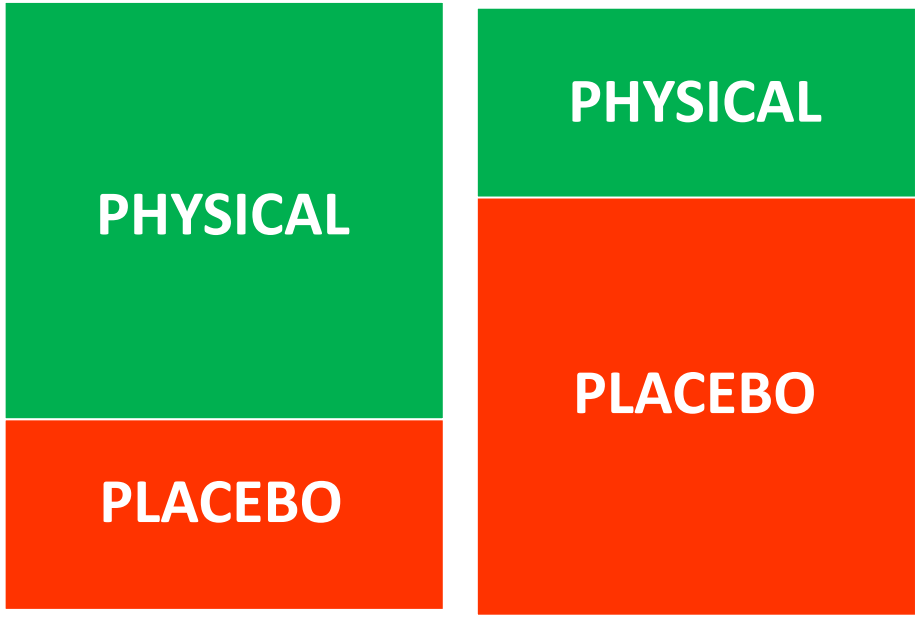
Increased efficacy of therapy

Greater burden of ischaemia

Less anti-anginal medication



Physician-patient interaction

Reassurance

Telling patient stenosis fixed

Unblinded trials

Al-Lamee R. Presented at TCT 2018

A lesson from PCI trial: what is the true effect of PCI on angina?

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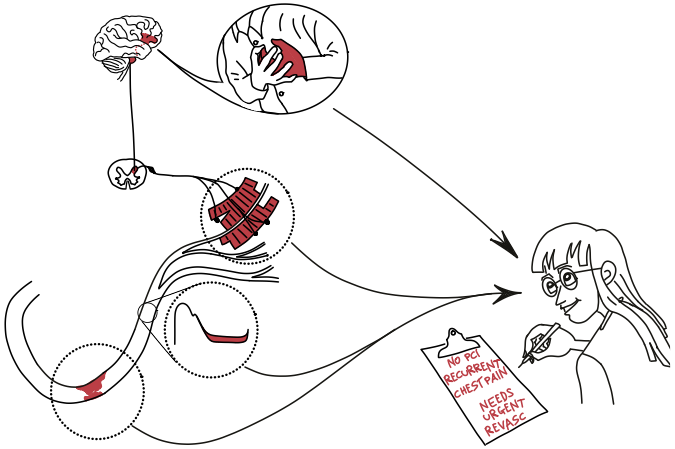
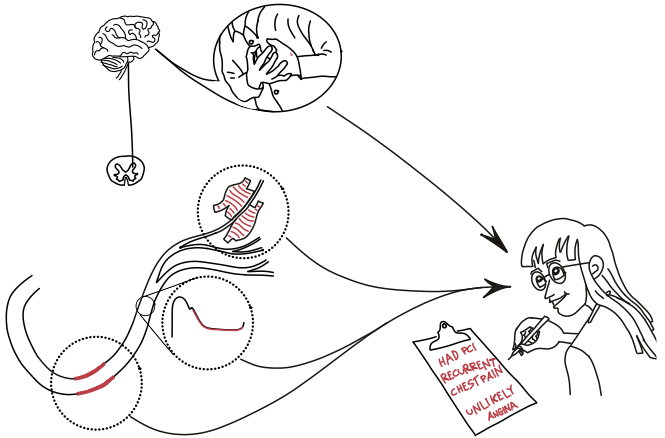
Control arm in unblinded trials



No PCI: recurrent chest pain needs revasc

PCI arm in unblinded trials



PCI: recurrent chest pain unlikely angina

Al-Lamee R. Presented at TCT 2018

ORBITA-2: what is the true effect of PCI on angina?

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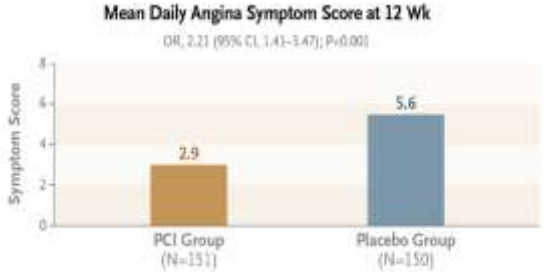
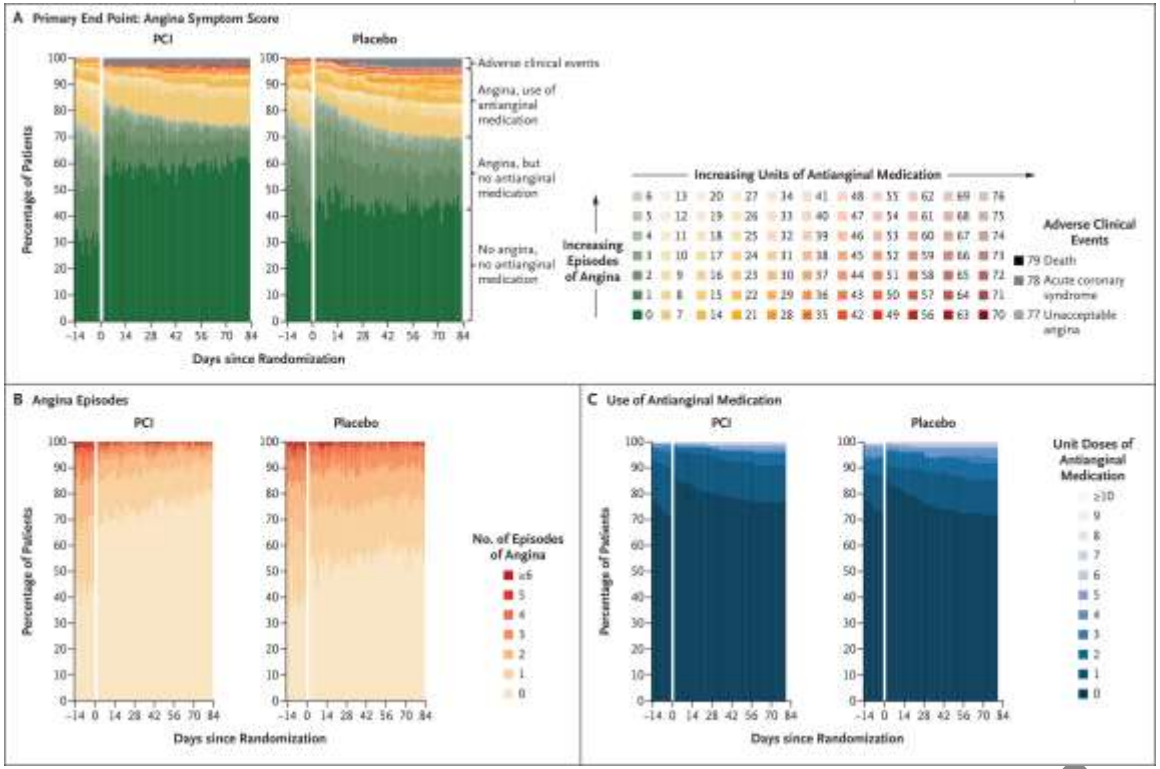
The NEW ENGLAND JOURNAL of MEDICINE

RESEARCH SUMMARY

A Placebo-Controlled Trial of Percutaneous Coronary Intervention for Stable Angina

Rajkumar CA et al. DOI: 10.1056/NEJMoa2310610





How to interpret PROs: Lessons from the Structural Trials

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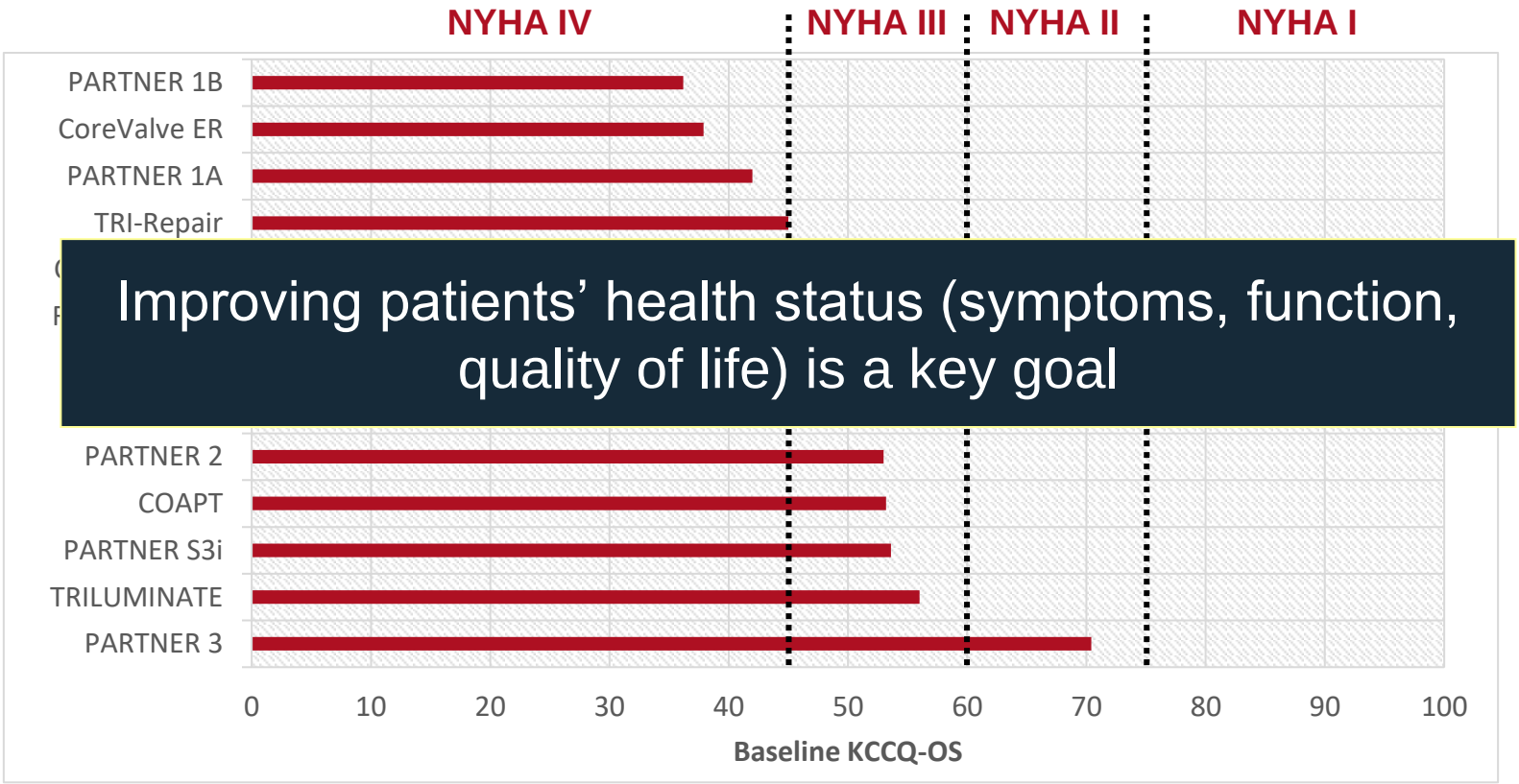

Improving patients' health status (symptoms, function, quality of life) is a key goal

Baron SJ et al. JACC 2019. Arnold SV et al. JAMA Cardiol 2017.
Arnold SV et al. JAMA Cardiol 2018. Arnold SV et al. JACC 2019. Arnold SV et al. JACC 2024. Arnold SV et al. JACC 2024

Regulatory Approval Trials in TTVI

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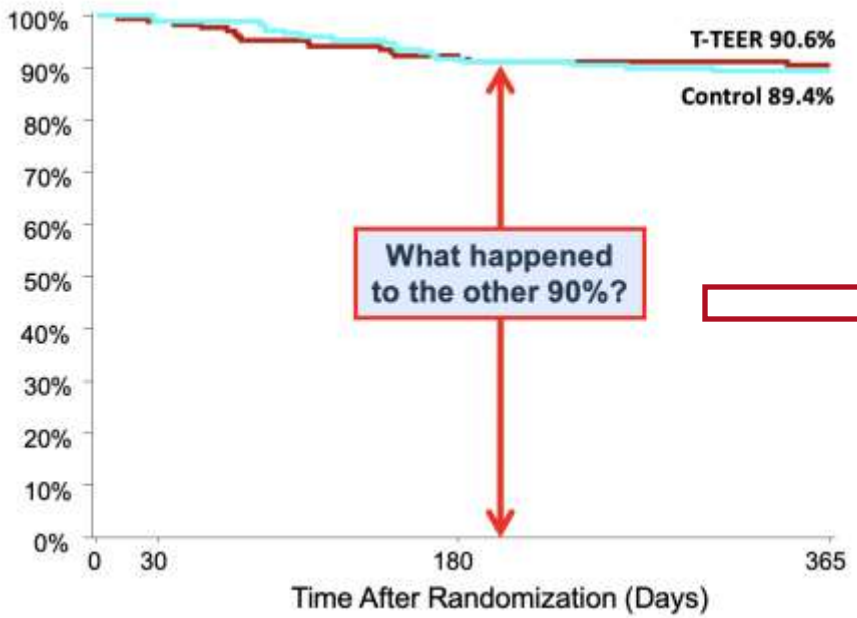
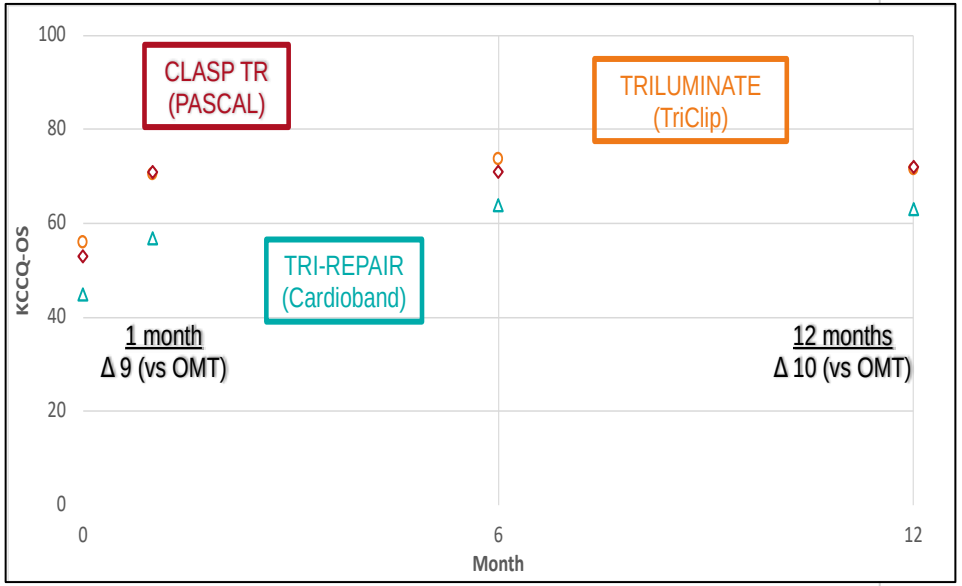
1-year Mortality TRILUMINATE trial



Health status after TTVI



Arnold SV et al. JACC 2024. Kodali SK et al. JACC 2021. Nickenig et al. Eurointervention 2021.

Regulatory Approval Trials in TTVI

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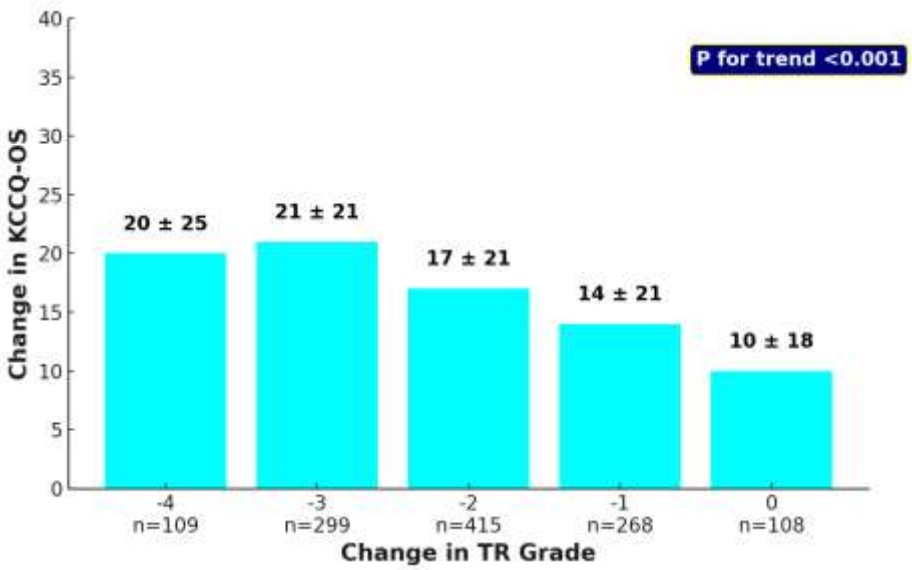
Pooled analysis of 2693 patients from 11 clinical trials of transcatheter tricuspid valve interventions (TTVI)

KCCQ improvement associated with prognosis

Outcome	Association of KCCQ-OS with end point (per 10-point decrement)[a]			
	Unadjusted HR (95% CI)	*P* value	Adjusted HR (95% CI)[c]	*P* value
Death	1.33 (1.21-1.46)	<.001	1.34 (1.22-1.47)	<.001
HFH	1.25 (1.18-1.32)	<.001	1.24 (1.17-1.31)	<.001
Death or HFH	1.27 (1.20-1.33)	<.001	1.26 (1.19-1.32)	<.001

Outcome	Association of change in KCCQ-OS with end point (per 10-point increase)[b]			
	Unadjusted HR (95% CI)[d]	*P* value	Adjusted HR (95% CI)[e]	*P* value
Death	0.78 (0.70-0.87)	<.001	0.80 (0.72-0.89)	<.001
HFH	0.82 (0.76-0.89)	<.001	0.83 (0.77-0.90)	<.001
Death or HFH	0.81 (0.77-0.87)	<.001	0.83 (0.78-0.88)	<.001

KCCQ improvement associated with TR change



Arnold SV et al. JAMA Cardiology 2024

Incorporating PROs in primary endpoint: is WIN-RATIO an option?

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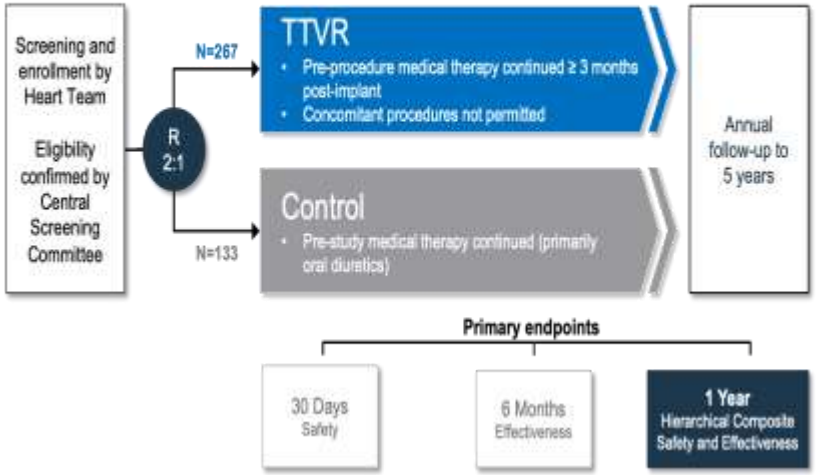
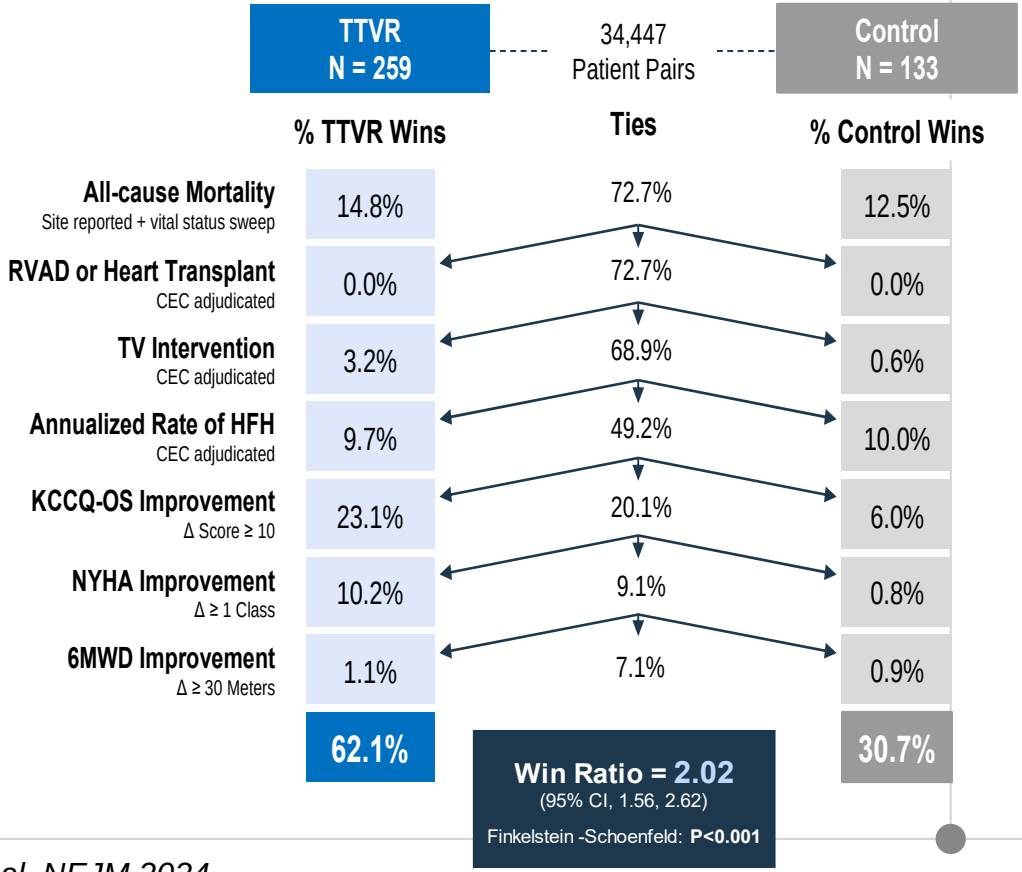
THE TRISCEND II PIVOTAL TRIAL





Hahn C et al, NEJM 2024

THANK YOU!

@Drroxmehran

Icahn School of Medicine at Mount Sinai