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Physician preferences for revascularization in patients with ischemic cardiomyopathy: Defining equipoise from web-based surveys

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Abstract

Background: The optimal revascularization approach in patients with heart failure with reduced ejection fraction (HFrEF) and ischemic heart disease ("ischemic cardiomyopathy") is unknown. Physician preferences regarding clinical equipoise for mode of revascularization and their willingness to consider offering enrollment in a randomized trial to patients with ischemic cardiomyopathy have not been characterized.

Methods: We conducted two anonymous online surveys: 1) a clinical case scenario-based survey to assess willingness to offer clinical trial enrollment for a patient with ischemic cardiomyopathy (overall response rate to email invitation 0.45 %), and 2) a Delphi consensus-building survey to identify specific areas of clinical equipoise (overall response rate to email invitation 37 %).

Results: Among 304 physicians responding to the clinical case scenario-based survey, the majority were willing to offer the opportunity for clinical trial enrollment to a prototypical patient with ischemic cardiomyopathy (92 %), and felt that a finding of non-inferiority for PCI vs. CABG

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Ethical statement

Both surveys used in this study were developed by the investigators solely for use in the current study. Study conduct, data analysis, and manuscript preparation were all conducted in accord with the ethical principles as detailed on the Elsevier Publishing Ethics webpage: https://www.elsevier.com/about/policies/publishing-ethics#Authors

The surveys and research protocol were evaluated by the New York University Grossman School of Medicine Internal Review Board (IRB) and were deemed to be minimal risk and to meet criteria for exemption from further IRB review under the revised Federal Common Rule.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ahjo.2023.100263.

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would influence their clinical practice (78 %). Among 53 physicians responding to the Delphi consensus-building survey, the median appropriateness rating for CABG was significantly higher than that of PCI ($p < 0.0001$). In 17 scenarios (11.8 %), there was no difference in CABG or PCI appropriateness ratings, suggesting clinical equipoise in these settings.

Conclusions: Our findings demonstrate willingness to consider offering enrollment in a randomized clinical trial and areas of clinical equipoise, two factors that support the feasibility of a randomized trial to compare clinical outcomes after revascularization with CABG vs. PCI in selected patients with ischemic cardiomyopathy, suitable coronary anatomy and co-morbidity profile.

Keywords

Heart failure; Coronary artery disease; Ischemic cardiomyopathy; Revascularization; Clinical equipoise

Ischemic heart disease is the most common cause of heart failure in the Western world, and is associated with increased mortality when compared with non-ischemic causes of heart failure [1,2]. In patients with heart failure with reduced ejection fraction (HFrEF) attributed to ischemic heart disease, reduced coronary blood flow reserve promotes progressive left ventricular remodeling and increased mortality via a complex pathophysiological process linked to myocyte stunning, myocyte hibernation, myocyte death, and increased interstitial fibrosis [1,3]. Ischemic heart disease may be treated with lifestyle modification and medications alone or in combination with revascularization by coronary artery bypass grafts (CABG) or percutaneous coronary interventions (PCI) [4,5]. The optimal revascularization approach in patients with HFrEF attributable to ischemic heart disease ("ischemic cardiomyopathy") is unknown. The Surgical Treatment for Ischemic Heart Failure (STICH) trial demonstrated that CABG plus guideline-directed medical therapy was superior to guideline-directed medical therapy alone for long-term reduction of mortality and important secondary morbidity endpoints [6,7]. In contrast, the Study of Efficacy and Safety of Percutaneous Coronary Intervention to Improve Survival in Heart Failure (REVIVED-BCIS2) failed to show improvement in the primary outcome (death or hospitalization for heart failure) associated with PCI when compared with optimal medical therapy [8]. When considering the comparative effects of CABG vs. PCI on clinical outcomes, there were few patients with reduced ejection fraction enrolled in prior randomized clinical trials comparing CABG vs. PCI, and observational data have yielded inconsistent findings due to presence of unmeasured confounders and incremental improvements in coronary artery stent technology over time [9–13]. Recent registry data demonstrated that PCI was numerically more frequently used than CABG (57.9 % and 42.1 %, respectively) for patients with severely reduced EF undergoing revascularization [14]. Taken together, the existing evidence indicates that there may be clinical equipoise to conduct a randomized trial to determine whether PCI is non-inferior to CABG for reduction of risk of adverse clinical outcomes in patients with ischemic cardiomyopathy. However, the feasibility of a such a trial is uncertain, as specific areas of clinical equipoise and physician perceptions and attitudes regarding offering opportunity for participation in a randomized clinical trial comparing

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revascularization with CABG vs. PCI to their ischemic cardiomyopathy patients have not been previously characterized.

In order to address this important gap in knowledge, we designed two web-based surveys to assess physician preferences for CABG and PCI in patients with ischemic cardiomyopathy: 1) an anonymous case-based survey adapted from a survey used in the planning phase of the International Study of Comparative Health Effectiveness with Medical and Invasive Approaches (ISCHEMIA) study [15], and 2) an anonymous Delphi consensus-building survey adapted from the RAND corporation methodology, as previously implemented to establish Appropriate Use Criteria for cardiac imaging and coronary interventions [16]. Our objective was to use the survey results to assess physician preferences and areas of clinical equipoise to guide design for a future randomized clinical trial.

1. Methods

1.1. Study design and setting

Both surveys were evaluated by the New York University Grossman School of Medicine Internal Review Board (IRB) and were deemed to be minimal risk and to meet criteria for exemption from further IRB review under the revised Common Rule [17].

1.2. Case-based survey

For the anonymous case-based survey, we collaborated with the Heart Failure Society of America (HFSA) and the Cardiovascular Research Foundation (CRF) to send email invitations to solicit participation in the survey to their organizational subscribers. The email invitation included descriptive information about the purpose of the research survey and embedded web links to the survey that included a schematic of the proposed future study design. The overall response rate to email invitations was 0.45 %. The case-based survey data were collected and managed using REDCap (Research Electronic Data Capture) software hosted at New York University Langone Health [18,19]. The survey questions and schematic of the proposed future randomized study design were accessible online from September 15, 2020 to January 31, 2021 (see supplementary materials). The survey included an introduction with background information related to the rationale and design of a future randomized trial comparing CABG vs. PCI for patients with reduced LVEF, and a case scenario of a prototypical 70-year-old male patient with clinical features of ischemic cardiomyopathy, New York Heart Association (NYHA) Class II symptoms and objective evidence of moderate ischemia. The survey instructions asked respondents to “consider how the clinical characteristics of this patient might influence your clinical treatment approach and your willingness to enroll this patient in a randomized clinical trial.” The survey questions were composed of three sections: 1) Likert scale ratings of the perceived impact of proposed study endpoints on clinical practice; 2) Clinical factors that might influence willingness to refer patients to the proposed study; and 3) Information on respondent demographics and clinical practice setting.

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1.3. Delphi consensus-building survey

For the single-round Delphi consensus survey, we solicited participation by direct email invitations sent to investigators at the forty top-enrolling study sites of the ISCHEMIA trial, and experts in advanced heart failure, interventional cardiology, and cardiothoracic surgery who had contributed to the writing of scientific guideline documents in Europe or the United States. The email invitations provided the rationale for the research survey and instructions for activation of a unique code for survey access that would allow administrative personnel to anonymously arrange an honorarium payment for completion of the 60-minute survey. The overall response rate to email invitations was 37 %. The anonymous survey data were collected and managed using Qualtrics^{XM} software (copyright © 2021, Qualtrics, Provo, UT, USA https://www.qualtrics.com) from July 17, 2020 to December 12, 2020. The survey instructions provided information from the medical literature relevant to the rationale for the proposed future clinical trial and the Delphi consensus building method (see supplementary materials). Each survey question used the same format to allow respondents to rate appropriateness for CABG and PCI based on their clinical experience and available published data for a series of clinical scenarios based the following factors: severity of functional impairment (New York Heart Association (NYHA) class), severity of left ventricular systolic dysfunction (left ventricular ejection fraction (LVEF), presence or absence of diabetes mellitus, presence or absence of left main coronary artery obstruction, presence or absence of coronary artery chronic total occlusion, and coronary artery disease complexity based on SYNTAX score. The following appropriateness rating categories were used:

- Score 7 to 9: Appropriate procedure for that specific indication (the procedure is generally acceptable and is a reasonable approach for the combination of indicators with anticipated benefit outweighing potential harm).
- Score 4 to 6: Uncertain or possibly appropriate procedure for that specific indication (procedure may be generally acceptable and may be a reasonable approach for the combination of indicators). Uncertainty also implies that more research and/or patient information is needed to classify definitively the indication as appropriate and to update the criteria.
- Score 1 to 3: Inappropriate procedure for that specific indication (procedure is not generally acceptable and is not a reasonable approach for the combination of indicators with potential harm outweighing anticipated benefit).

1.4. Data analysis

Descriptive statistics were used to report the findings of the anonymous clinical case-based survey. The data for the RAND consensus-building survey consisted of ratings from each participating physician for a series of clinical scenarios based on SYNTAX score (3 levels), LVEF (3 levels), severity of functional impairment (mild or moderate-to-severe, 2 levels), diabetes mellitus, (absent or present, 2 levels), left main obstructive disease (absent or present, 2 levels), and chronic total occlusion (Absent, Present, 2 levels), resulting in $3 \times 3 \times 2 \times 2 \times 2 \times 2 = 144$ scenarios for rating appropriateness of PCI and CABG. The medians for all responses for each scenario and the median absolute deviation (MAD) were computed

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across respondents. The scenarios were scored as Appropriate (A) for median scores 7 to 9, Uncertain (U) for median scores 4 to 6, or Inappropriate (I) for median scores 1 to 3. To obtain an indicator for the level of agreement (+) or disagreement (−) based on the RAND criterion (see Fig. 4), two quantities are computed: (i) the inter-percentile range (*IPR*) equal to the difference between the 70th and 30th percentiles and (ii) an inter-percentile range adjusted for symmetry (*IPRAS*) defined as $IPRAS = 2.35 + 1.5 \times AI$, where $AI =$ Asymmetry Index $= |5\ IPRCP|$ and *IPRCP* is the interpercentile range central point. The scenario is classified "disagreement" (−) if the *IPR* exceeds the *IPRAS* and "agreement" (+) otherwise. A linear mixed-effects model was fit to model how the appropriateness scores depend on the procedure (CABG vs. PCI) as well as combinations of the six clinical factors considered in the scenarios. A rater-specific random effect was included in the model to account for correlations of multiple ratings from each clinician. Likelihood ratio tests were performed to assess significance of procedure type (CABG, PCI) as well as interaction effects.

The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper, and its final contents.

2. Results

2.1. Clinical case survey

Survey invitations were emailed between September to November 2020 to 4109 HFSA email subscribers (1699 (41 %) of the email messages opened, and 687 (17 %) clicks on the survey link) and 64,196 CRF email subscribers (12,415 (19 %) of the email messages opened, and 605 (0.9 %) clicks on the survey link, Fig. 1A). There were 309 total respondents (24 % of survey link clicks) of whom 304 (98 %) completed the REDCap survey. All respondents were self-identified as medical doctors (12 % female), with over 50 % self-identified as interventional cardiologists. The demographic characteristics and clinical practice settings of the respondents are summarized in Table 1. The overwhelming majority of respondents agreed that the proposed clinical trial of CABG vs. PCI in ischemic cardiomyopathy patients addresses an important gap in knowledge (96 %), and that referral to a randomized trial or CABG vs. PCI would be considered if a comparable degree of revascularization were possible (92 %). Willingness to refer to a randomized clinical trial was numerically less in patients with absence of evidence of myocardial viability, moderate frailty, more complex coronary anatomy, severely reduced EF, and co-morbid diabetes (Fig. 2). Respondent ratings of the importance of proposed clinical trial endpoints for impact on clinical practice demonstrated a preference for mortality endpoints followed closely by hospitalization, stroke, and patients' health status (Fig. 3). When asked to consider the clinical practice impact of the proposed non-inferiority study design, 78 % responded affirmatively to the following question: "If the study results demonstrated that all-cause mortality in the CABG and PCI groups differed by ≤5% over 4 years of follow-up, would this finding be sufficient to influence your clinical practice decisions regarding selection of revascularization procedures in patients with ischemic cardiomyopathy?"

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2.2. Physician Delphi consensus survey

Survey invitations were emailed to 148 individuals between June 19 and November 30, 2020, with 55 total respondents (14 respondents with <5 % completed survey data, 5 respondents with 5–35 % completed survey data, and 36 respondents with 100 % complete survey data, Fig. 1B). All respondent data with ≥5 % survey completion were used in the analysis (N = 41 respondents). Demographic and clinical practice settings of the 36 respondents with complete survey data are summarized in Table 2 (11 % female). The appropriateness ratings varied according to the complexity of the coronary artery disease and the presence of co-morbid diabetes mellitus (Fig. 4). There was strong evidence of significant two-way interaction effects between these factors as well as treatment procedure. Overall, the median appropriateness rating for CABG was significantly higher than that of PCI ($p < 0.0001$) and CABG was rated more appropriate when compared with PCI for patients 119 out of the 144 possible scenarios (83 % of the time). Fig. 5 depicts case features that were associated with preferences for CABG, PCI, or no difference in appropriateness ratings. Key features included SYNTAX score, presence of diabetes, left main disease, chronic total occlusion, and NYHA class. Seventeen of 144 possible scenarios (11.8 %) were found to have no difference in CABG or PCI appropriateness, suggesting clinical equipoise in those scenarios.

3. Discussion

In contrast to the robust evidence base available to guide clinical decision making in patients with coronary artery disease and normal left ventricular systolic function, the optimal approach to revascularization in patients with ischemic cardiomyopathy is uncertain [8,20–22]. In a web-based anonymous survey of 304 physicians with cardiovascular expertise, we found that the majority of physicians (92 %) would be willing to offer opportunity for clinical trial enrollment into a randomized trial comparing CABG with PCI for revascularization for a prototypical patient with three-vessel coronary artery disease, reduced EF, NYHA class II symptoms, and moderate ischemia. Moreover, most respondents indicated that this type of trial would address a significant gap in knowledge (96 %), and that a non-inferiority design would influence their clinical practice (78 %). In a separate Delphi consensus survey of 53 physicians, the median appropriateness rating for CABG was significantly higher than that of PCI ($p < 0.0001$) and CABG was rated more appropriate when compared to PCI for 119 out of the 144 possible scenarios (83 %).

Our findings suggest that physicians would be willing to consider offering enrollment in a randomized trial comparing CABG with PCI to selected patients with ischemic cardiomyopathy and obstructive coronary artery disease, with evidence of clinical equipoise in patients with less complex coronary artery disease anatomy. Prior randomized studies comparing CABG versus PCI for revascularization of three-vessel coronary artery disease have largely excluded patients with systolic dysfunction. In the SYNTAX and FREEDOM trials, only 2 % and 2.5 % of patients had severely reduced EF, respectively [21,22]. Observational studies have yielded varied results and are inherently limited by residual confounding and changes in PCI outcomes related to temporal improvements in stent design [13,14]. Despite evidence favoring CABG over PCI from populations with normal LVEF,

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and the results of the STICH and REVIVED studies, a clinical registry of the mode of revascularization in patients with severely reduced ejection fraction reported that PCI was numerically more frequently used than CABG (57.9 % and 42.1 % respectively) [14]. Whereas most respondents to our study clinical case scenario survey were willing to offer opportunity for clinical trial enrollment to a patient for randomization, they agreed to do so only if a comparable degree of revascularization was possible. Contrary to the viability imaging subgroup findings of the STICH study, which found no interaction between viability and survival benefit from CABG, most respondents to our clinical case scenario were less willing to offer opportunity for clinical trial enrollment to patients without evidence of myocardial viability [23]. Complex coronary anatomy substantially reduced respondents' willingness to refer to a randomized trial, and was also associated with a preference for CABG in the Delphi consensus survey results, with clinical equipoise evident in only 11.8 % of the presented scenarios. Therefore, a future trial design comparing CABG with PCI for patients with ischemic cardiomyopathy must carefully consider study entry criteria to ensure complete and comparable revascularization in both arms [13].

Our findings should be interpreted in the context of several limitations. The results are derived from a web-based survey sent via email, with a low overall response rate that may introduce selection bias. The proportion of female respondents for both surveys was consistent with the reported sex distribution of cardiovascular specialists in clinical practice [24]. Relatively few cardiothoracic surgeons responded to the surveys. The majority of questionnaire respondents were from outside of North America (63 %), which supports generalizability of our findings for enrollment at international sites. The results from the single-round Delphi consensus-building survey used for this study might differ from those results obtained from multiple survey rounds. Physician preferences recorded in response to our surveys may evolve over time in reaction to emerging information in the medical literature, changing technology, and expert consensus guidelines documents. Finally, an inherent limitation exists when asking respondents to predict future behavior. Respondent-reported willingness to offering opportunity for clinical trial enrollment may not translate to actual referrals for a future clinical trial. Patient perceptions of CABG vs. PCI are also important determinants of clinical trial feasibility, but were not assessed in this report.

In conclusion, we found that an overwhelming majority of survey respondents were willing to offer opportunity for clinical trial enrollment to the prototypical patient for randomization, agreed that this proposed clinical trial addressed an important gap in knowledge, and felt that the results of a non-inferiority trial design could change their clinical practice. These findings support the feasibility of a randomized trial to compare clinical outcomes after revascularization with PCI vs. CABG in patients with systolic left ventricular dysfunction, suitable coronary anatomy and co-morbidity profiles.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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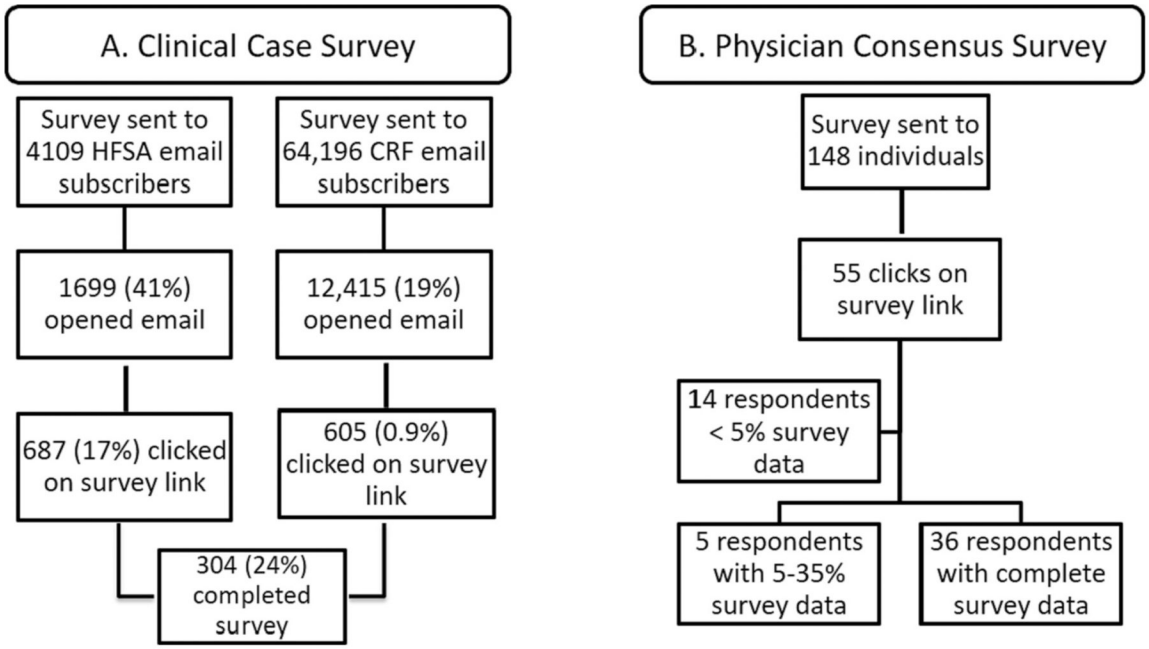

Fig. 1.
Study flow diagrams for clinical case survey (A) and physician consensus survey (B).

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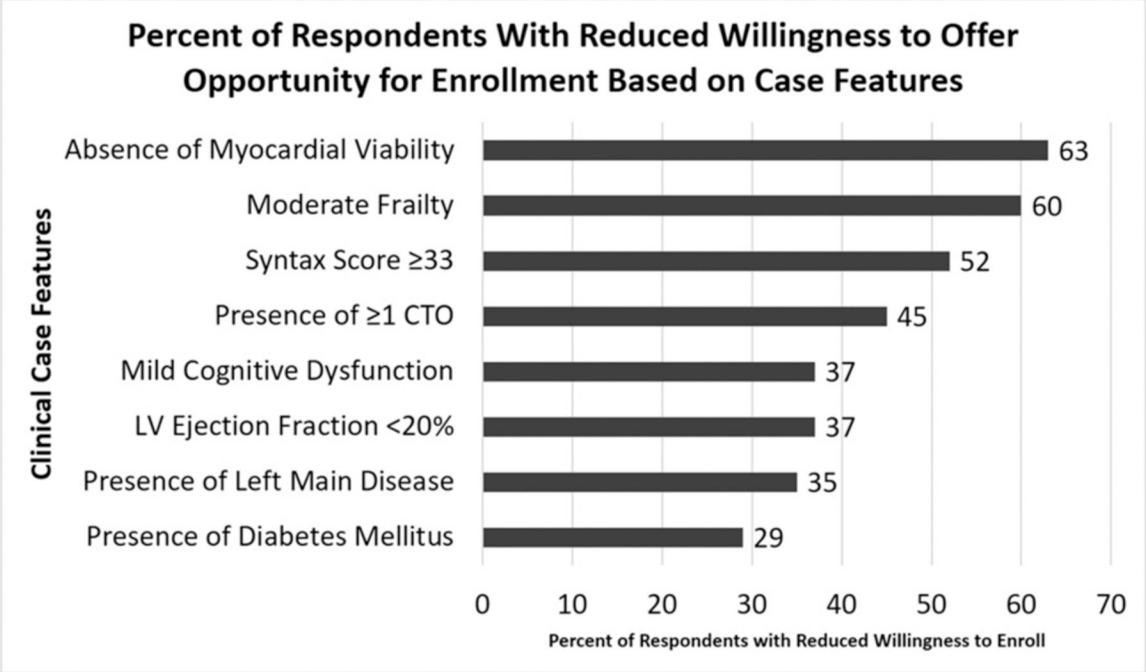

Fig. 2.

Percent of clinical case survey respondents with reduced willingness to offer patients an opportunity to enroll in a future randomized trial based on coronary anatomy, non-invasive imaging, and co-morbid conditions.

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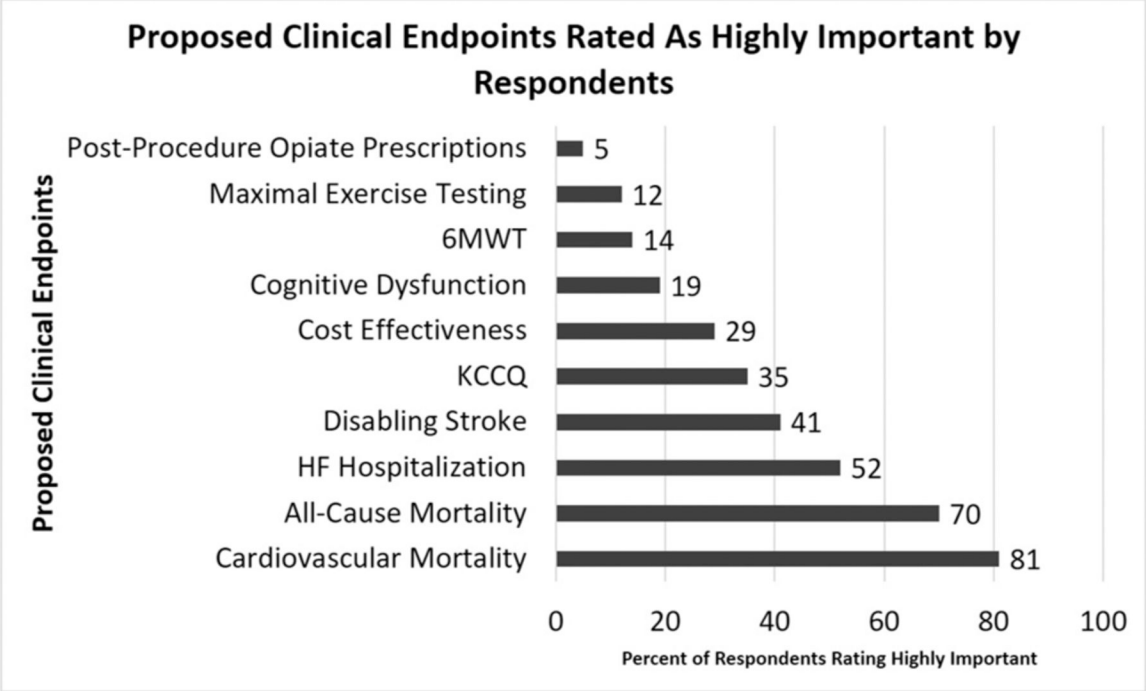

Fig. 3.

Proposed clinical endpoints rated by survey respondents as highly important for impact on future clinical practice for a future randomized trial of CABG vs. PCI in ischemic cardiomyopathy patients.

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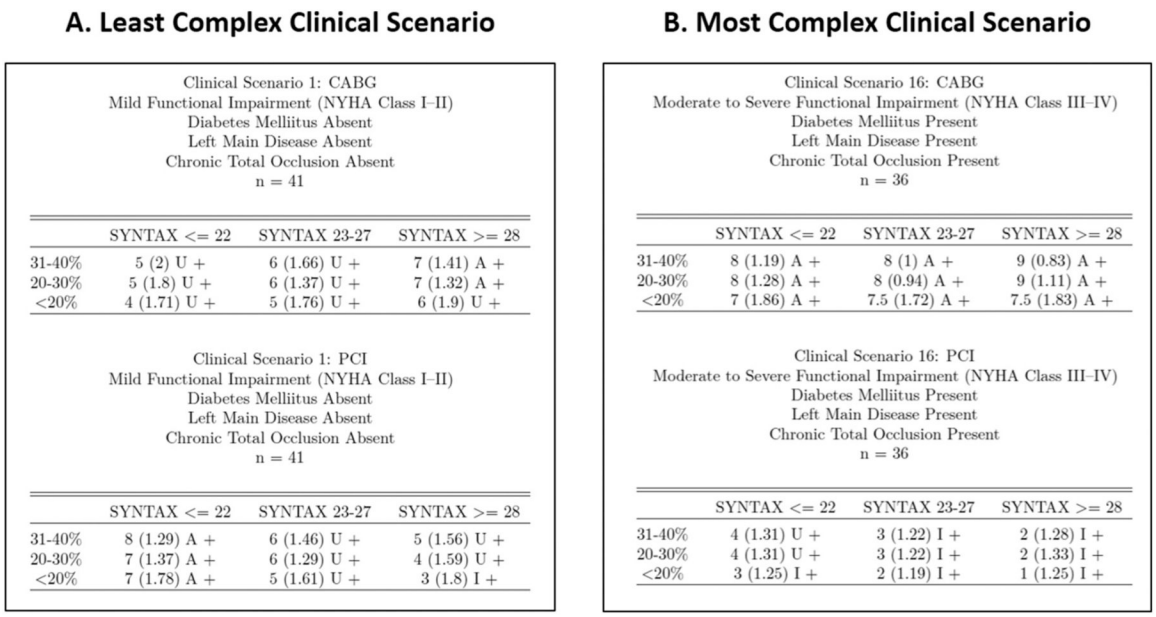

Clinical Scenario 1: CABG
Mild Functional Impairment (NYHA Class I–II)
Diabetes Melliitus Absent
Left Main Disease Absent
Chronic Total Occlusion Absent
n = 41

	SYNTAX <= 22	SYNTAX 23-27	SYNTAX >= 28
31-40%	5 (2) U +	6 (1.66) U +	7 (1.41) A +
20-30%	5 (1.8) U +	6 (1.37) U +	7 (1.32) A +
<20%	4 (1.71) U +	5 (1.76) U +	6 (1.9) U +

Clinical Scenario 1: PCI
Mild Functional Impairment (NYHA Class I–II)
Diabetes Melliitus Absent
Left Main Disease Absent
Chronic Total Occlusion Absent
n = 41

	SYNTAX <= 22	SYNTAX 23-27	SYNTAX >= 28
31-40%	8 (1.29) A +	6 (1.46) U +	5 (1.56) U +
20-30%	7 (1.37) A +	6 (1.29) U +	4 (1.59) U +
<20%	7 (1.78) A +	5 (1.61) U +	3 (1.8) I +

Clinical Scenario 16: CABG
Moderate to Severe Functional Impairment (NYHA Class III–IV)
Diabetes Melliitus Present
Left Main Disease Present
Chronic Total Occlusion Present
n = 36

	SYNTAX <= 22	SYNTAX 23-27	SYNTAX >= 28
31-40%	8 (1.19) A +	8 (1) A +	9 (0.83) A +
20-30%	8 (1.28) A +	8 (0.94) A +	9 (1.11) A +
<20%	7 (1.86) A +	7.5 (1.72) A +	7.5 (1.83) A +

Clinical Scenario 16: PCI
Moderate to Severe Functional Impairment (NYHA Class III–IV)
Diabetes Melliitus Present
Left Main Disease Present
Chronic Total Occlusion Present
n = 36

	SYNTAX <= 22	SYNTAX 23-27	SYNTAX >= 28
31-40%	4 (1.31) U +	3 (1.22) I +	2 (1.28) I +
20-30%	4 (1.31) U +	3 (1.22) I +	2 (1.33) I +
<20%	3 (1.25) I +	2 (1.19) I +	1 (1.25) I +

Fig. 4.

Example of Delphi consensus survey clinical scenarios and appropriateness ratings. Each question of the consensus survey was based on a unique combination of four clinical variables presented above each table (New York Heart Association Class, diabetes, left main disease, chronic total occlusion), and a table with 9 unique cells determined by left ventricular ejection fraction category (<20 %, 20–30 %, 31–40 %), and SYNTAX score category (≤22, 23–27, ≥28). Median values (median absolute deviation), corresponding appropriateness rating (A = Appropriate = median score 7–9, U = Uncertain = median score 4–6, I = Inappropriate = median score 1–3), and level of agreement (+) or disagreement (−) among respondents are shown for use of CABG (top table) and PCI (bottom table) based on the least complex clinical scenario (panel A) and the most complex clinical scenario (panel B). Median values for panel A demonstrate comparable appropriateness ratings for both CABG and PCI in the Uncertain range for SYNTAX Score 23–27, consistent with the presence of equipoise for randomization in this group of patients. Median values for panel B indicate divergent appropriateness ratings in favor of CABG, consistent with lack of equipoise for randomization in patients with more complex coronary artery disease and co-morbidities.

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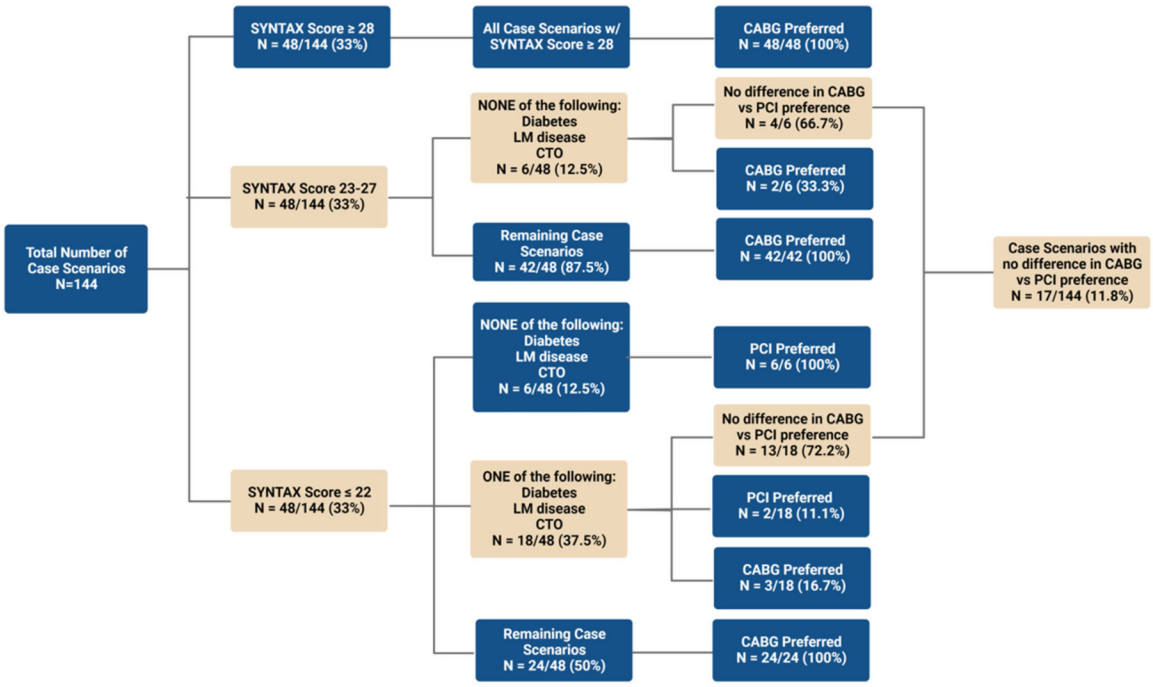

Fig. 5.

Clinical features from Delphi consensus survey associated with overall preference for CABG, PCI, or no difference. Clinical features associated with no difference in appropriateness foe CABG or PCI are colored in beige and suggest clinical equipoise. Number (%) of case scenarios with each clinical feature indicated within each box. Preference for CABG, PCI, or no difference determined using estimate of mean difference in appropriateness rating with 95 % confidence interval >0, <0, or including 0, respectively. Created with biorender.com

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Table 1

Demographic and clinical setting characteristics for 304 clinical case survey respondents by grouped by cardiovascular expertise.

	Interventional (*n* = 172)	Advanced HF (*n* = 64)	Non-invasive (*n* = 37)	CT surgeons (*n* = 31)	Combined (*n* = 304)
Age range N (%)					
<40 years	35 (20)	16 (25)	10 (27)	7 (23)	68 (22)
40–49 years	65 (28)	16 (25)	11 (30)	13 (42)	105 (35)
50–59 years	43 (25)	15 (23)	7 (19)	9 (29)	74 (24)
≥60 years	29 (17)	17 (27)	9 (24)	2 (6)	57 (19)
Sex					
Male	160 (93)	46 (72)	29 (83)	29 (97)	264 (88)
Female	12 (7)	18 (28)	6 (17)	1 (3)	37 (12)
Years in practice					
1–5 years	23 (13)	17 (27)	10 (27)	6 (19)	56 (18)
6–10 years	31 (18)	9 (14)	4 (110	8 (26)	52 (17)
11–20 years	45 (26)	9 (14)	7 (19)	9 (29)	70 (23)
>20 years	73 (42)	29 (45)	16 (43)	8 (26)	126 (41)
Location					
North America	35 (20)	58 (91)	14 (41)	4 (13)	111 (37)
Central/S. America	17 (10)	2 (3)	7 (21)	18 (58)	45 (15)
Europe	68 (40)	3 (5)	8 (24)	6 (19)	85 (28)
Asia/Australia	33 (19)	1 (2)	0	1 (3)	36 (12)
Africa/Other	19 (11)	0	5 (15)	2 (6)	26 (9)

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Table 2

Demographic and clinical setting characteristics for 36 physicians with completed Delphi consensus survey (n, (%)).

Characteristic	N (%)
Cardiovascular expertise	
Interventional cardiology	16 (44)
Advanced heart failure	2 (6)
Non-interventional cardiology	16 (44)
Cardiothoracic surgery	2 (6)
Age	
<40 years	2 (6)
40–49 years	8 (22)
50–59 years	10 (28)
≥60 years	16 (44)
Sex	
Male	32 (89)
Female	4 (11)
Years in practice	
6–10 years	2 (56)
11–20 years	8 (22)
>20 years	26 (72)
Location	
North America	13 (36)
Europe	14 (39)
South America	3 (8)
South Asia	5 (14)
Other	1 (3)