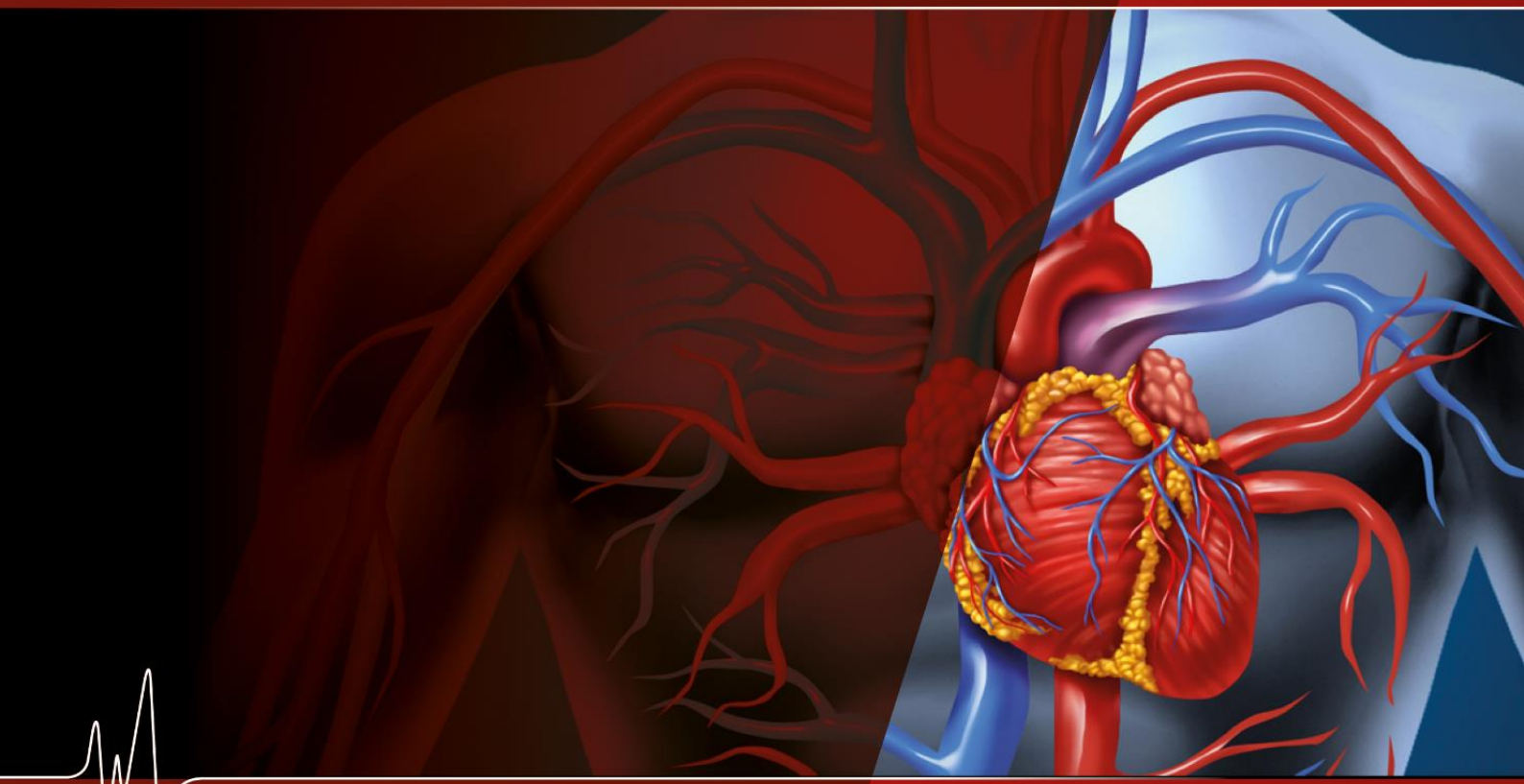
*MASTER THESIS*

# ARE COMPONENT ENDPOINTS EQUAL?

## Use of Best-Worst Scaling to Assess Patients' Perceptions Regarding the Use of Composite Endpoints in Clinical Trials.



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# Are Component Endpoints Equal? Use of Best-worst Scaling to Assess Patients' Perceptions Regarding the Use of Composite Endpoints in Clinical Trials.

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**Aims:** Modern clinical trials comparing treatments for coronary revascularization generally use composite endpoints in order to increase statistical precision and efficiency, resulting in trials becoming smaller and less costly. However, the use of composite endpoints is questioned because it assumes that all unfavourable outcomes of a treatment are equally important and therefore have equal weight to patients. We aimed to examine patients' perspectives regarding the use of composite endpoints and the utility patients put on possible unfavourable outcomes of treatment.

**Methods:** In this single-centre, prospective, observational PRECORE (PReference of COronary REvascularization) study, 176 patients with coronary artery disease (CAD), who underwent either a Percutaneous Coronary Intervention (PCI) or Coronary Artery Bypass Grafting (CABG) at the Thoraxcentrum Twente, Medisch Spectrum Twente (Enschede, the Netherlands) between May 2016 and June 2016, were invited to participate in this study. A total of 160 (response rate 91%) patients gave consent to participate in this study. A novel methodology, a survey-based best-worst scaling choice experiment was used to determine the relative importance of component endpoints to patients with CAD.

**Results:** Patients considered *repeat PCI within a year post-intervention* (odds ratio [OR]: 276.04; 95% CI, 180.78-421.48; $p< 0.001$), *minor stroke where symptoms disappear within 24 hours* (OR: 56.94; 95% CI, 38.71-83.76; $p< 0.001$), *minor MI where symptoms disappear within three months* (OR: 44.30; 95% CI, 30.21-64.97; $p<0.001$), *recurrent angina pectoris* (OR: 33.79; 95% CI, 23.25-49.12; $p<0.001$), *repeat CABG within a year post-intervention* (OR: 13.97; 95% CI, 9.81-19.89; $p<0.001$), and *major MI causing permanent disability* (OR: 3.03; 95% CI, 2.32-3.97; $p<0.001$), less severe than *death in 24 hours*, but considered *major stroke causing permanent disability* worse than *death within 24 hours* (OR: 0.698; 95% CI, 0.53-0.92; $p<0.001$). Subgroup (gender, age, revascularization procedure, prior-MI, and prior revascularization) differences can be found for the ranking of component endpoints and the relative weights attributed to *death within 24 hours* versus *major stroke causing permanent disability*.

**Conclusions:** Patients do not consider the individual component endpoints equal. The fact that patients weigh the individual components differentially has significant implications for trial statistics, and the interpretations of trial data, since they can be interpreted differently when all endpoints are considered equally important. Patient preference data should be applied more often to trial data, in order to give a better reflection of patient preference values (utilities) for treatment outcomes of revascularization procedures: leading to better patient-centred care.

**Keywords**: Best-worst scaling; Composite endpoints; Coronary artery bypass grafting (CABG); Coronary artery disease; Patient preferences; Percutaneous coronary intervention (PCI); Revascularization; Weighting procedure

**Key Points:**

- Clinical trials generally use a composite primary endpoint to increase statistical precision, improve trial efficiency, and decrease study costs.
- The use of composite endpoints is questioned because it assumes that all adverse outcomes of a treatment are equally important and therefore have equal weight to patients.
- Prior efforts to weigh composite endpoints never used patient preference data from the quantitative preference elicitation method best-worst scaling to inform the weighting of component endpoints.
- The present study demonstrated that 1) patients do not assign equal weights (relative importance) to component endpoints and 2) a vast majority of patients do not find it appropriate that component endpoints are weighted equally in clinical trials in order to measure how effective a treatment is.
- Patient preference data should be applied more often to trial data in order to give a more accurate reflection of patient preference values for treatment outcomes: leading to less misleading trial statistics and better patient-centered care.

**INTRODUCTION**

Over the past forty years, many randomized clinical trials (RCTs) used composite or combined endpoints when comparing competing (drug) therapies (1-4). The results and conclusions of these RCTs rely on their primary endpoints (PEs), and thus, it is important to choose the most appropriate PEs in the design phase of clinical research (5). These composite endpoints (CEs) combine two or more clinically relevant endpoints, also known as the component endpoints, within a single outcome variable to measure clinical benefit due to treatment. Either the time period until the occurrence of an adverse event from a given set of events is of interest (time-to-first event variables), or the occurrence of any adverse event (binary event variables) (6). A commonly used composite endpoint in cardiovascular research is *Major Adverse Cardiovascular Events* (MACE). There is no standard definition for MACE, but this composite endpoint often combines the individual endpoints of death, stroke, MI and repeat revascularization (either coronary artery bypass grafting (CABG) or percutaneous coronary interventions (PCI) (7)). Patients who have experienced any one of the component endpoint events, are considered to have experienced the composite endpoint MACE (5,8,9). In other words, a patient experiences a composite endpoint if he/she either died, experienced a MI, a stroke, or needed another revascularization procedure.

As overall medical care has significantly progressed over the past years, patients experiencing any cardiovascular event, experience a low mortality in coming years. Therefore, it is often difficult for clinical researchers to find differences in survival curves of several treatment options (6, 10). Although death is still considered the outcome of primary interest, the use of a rare event as a primary endpoint instigates the need of larger sample sizes, prolonged follow-ups, and is therefore more costly in a changed economic environment where it is yet increasingly difficult to finance clinical trials (11). By combining several adverse events in a composite endpoint, the proportion of outcome events is increased, thereby expanding the overall treatment effect, and reducing the requisite sample size and overall costs of cardiovascular trials (12, 13).

Analytic approaches to composite endpoints generally assume that component endpoints are of equal clinical severity. In practice, this assumption is seldom met, as medical interventions often have different effects on component endpoints with very different clinical importance (8,14,15). This heterogeneity of effect among component endpoints can result in too optimistic conclusions about the treatment effect, and serious misinterpretations (16-18). In some situations, the overall positive treatment effect may be related to less clinically relevant component endpoints (i.e. less important component endpoints to patients may account for the majority of events). It has been shown that component endpoints of least importance to patients, such as repeat revascularization or recurrent angina, as opposed to the most important endpoints, such as major stroke or death, typically contribute most to trial events (8, 19). A recent systematic review found that in approximately three-quarters of the trials reviewed, there were large gradients in importance to patients across component endpoints (20). Therefore, the interpretation of composite endpoints currently used in some cardiovascular trials may lead to inadequate conclusions about the true clinical value of treatments (21).

One means of adjusting for these different effects is to adjust the trial outcomes using "importance weights (i.e. (dis)utilities)" determined a-priori. Some clinical researchers have already emphasized the need to explore the relative importance patients assign to different adverse outcomes of treatment, and developed measures to weigh these component endpoints. Several different research methods have been used to determine these "importance weights": either through weighing derived completely by evaluation by an expert panel (8, 22), through weighing by use of a visual analogue scale (14), or through more quantitative methods as interviewer-administered surveys, including ranking, rating, point-allocation and trade-off exercises, or discrete choice experiments (DCE) (15, 23).

However, prior efforts to weigh composite endpoints almost never used patient preference data to inform the weighting of component endpoints. Given that, previous research has demonstrated that patients, researchers, and clinicians value individual component endpoints differently (14, 24), this would suggest that efforts to develop "weighted" composite endpoints may principally need to address patient preferences. Especially since patient preferences are of growing interest to researchers and clinicians (25): patients are considered the most important stakeholders in the design and evaluation of clinical trials, given it is their treatment that is the ultimate goal of clinical research.

The current study aimed to examine how patients with coronary artery disease (CAD), who underwent a revascularization procedure, value different adverse outcomes of treatment, by asking them whether they thought it is equally important to prevent two possible adverse events of treatment. In addition, the utilities patients put on

these adverse events associated with coronary revascularization procedures were examined by conducting the novel preference-elicitation method "case 1" best-worst scaling. To facilitate the understanding of the value of each component endpoint, we quantified the relative importance (i.e. "importance weight") of each component endpoint when compared to death. In addition, we examined whether the obtained "importance weights" differed by clinical and demographic characteristics of our study population.

**METHODS**

*Study Design*

In the single-centre, prospective, observational cohort PRECORE (PReference of COronary REvascularization) study, a custom-made questionnaire was conducted to elicit the (relative) importance patients with coronary artery disease (CAD) assign to the component endpoints associated with coronary revascularization procedures. Institutional review board approval of the protocol was obtained at the Medical Ethics Review Committee of the Medisch Spectrum Twente (MST) hospital in Enschede (the Netherlands). All patients provided written, informed consent for participation in this study.

*Patient Population*

Between May 2016 and June 2016, the PRECORE study was performed in a consecutive series of patients with CAD, who underwent revascularization procedures (either PCI or CABG), at Thoraxcentrum Twente in Enschede (the Netherlands) and agreed to participate in this study. PCI-patients were included in this study three to four hours post-intervention. CABG-patients were included on day three to four post-intervention. PCI-patients filled out the questionnaire while waiting for hospital discharge. Patients that had received a CABG procedure filled out the questionnaire while staying at the nursing departments of the MST (Enschede, the Netherlands). Patients who faced a language barrier in performing the task, or were unable to perform the task correctly, e.g. due to the cognitive burden the study posed, were excluded from participation in this study. In addition, patients who underwent aortic valve replacement (AVR) with concomitant CABG surgery were also excluded from participation. Patients included in this study represent a broad and heterogeneous patient population that reflect routine clinical practice at this tertiary hospital. Using a sample size calculated based on the number of attribute and levels, the minimum sample size recommended for this study was at least 84 patients (Orme, 2010).

*Inclusion Procedure*

A member of the treatment team (either the cardiologist, nurse practitioner or resident) assessed whether a patient could be included in the trial, prior to the treatment. Patient' demographic and clinical characteristics were collected from electronic medical files by the hospital professional who was involved in the treatment process.

*Patient Preference Questionnaire [PPQ]*

The original PPQ –of which the PRECORE study is a subpart - consisted of four different parts, each of which corresponded to the following: patient self-reported health status [7 questions]; patient preferences for health status outcomes [10 discrete choice questions]; patient preferences for unfavourable outcomes of treatment [6 best-worst scaling questions] and patient background characteristics [6 questions]. On average, it took patients one half hour to answer the complete questionnaire. Given the aim of this study to investigate how patients with CAD as a group make trade-offs between different component endpoints associated with revascularization procedures, we first had to select the "objects" (i.e. component endpoints) of interest. Through literature review and after careful consideration within the steering committee of the research team, eight component endpoints were selected for this study. The included component endpoints were expected to be relevant for all PCI or CABG patients who underwent a revascularization procedure and are the most commonly used endpoints in coronary artery disease trials. These "objects" included *major stroke causing permanent disability (difficulty moving an arm and/or a leg)*; *minor stroke where symptoms disappear within 24 hours*; *major MI causing permanent disability (tire more quickly, less physical capacity)*; *minor MI where the symptoms disappear within three months*; *recurrent angina pectoris*; *repeat CABG*; and *repeat PCI* **(Table 1)**. The decision was made to differentiate *MI*, *stroke* and *repeat revascularization* according to potential impact. There are several different types of these component endpoints according to severity, ranging from mild events to large disabling events, or more invasive events. We believe that patient preferences might differ according to event severity, and that this distribution gives a more meaningful interpretation of the relative importance of these component endpoints to patients. With the aid of the experimental design software Sawtooth 6.4.6., the most optimal design of this study was determined to be a partial-profile "case 1" BWS design with four versions, six scenario-questions per version, and four "objects" per scenario.

**Table 1.** *Objects for the "case 1" best-worst scaling tasks.*

| Treatment Outcomes ("objects" in best-worst scaling) | Description to Patients |
|---|---|
| **Minor MI** | You will experience a mild myocardial infarction of which the symptoms disappear within three months after the initial myocardial infarction. |
| **Major MI** | You will experience a large myocardial infarction causing permanent disability (i.e. tire more quickly, less physical capacity). |
| **Minor stroke** | You will experience a mild stroke of which the symptoms disappear within 24 hours after the initial mild stroke. |
| **Major stroke** | You will experience a large stroke causing permanent disability (i.e. difficulty moving an arm and/or a leg). |
| **Angina Pectoris** | You will experience recurrent angina (i.e. sensation of chest pain, pressure, or squeezing). |
| **Repeat CABG** | You need to undergo a bypass surgery within one year following your initial revascularization because of restenosis. |
| **Repeat PCI** | You need to undergo a PCI within one year following your initial revascularization because of restenosis. |
| **(all-cause) Death** | You will die within 24 hours post-intervention. |

*Format*

The patient preferences questionnaire started by asking patients to read the descriptions of the eight "objects" (i.e. component endpoints) examined in this study **(Table 1)**. After patients read the description of each "object", they were asked to answer four prepositions. In these prepositions, patients had to state whether they thought it was equally important to prevent two component endpoints (*death* versus *major stroke causing permanent disability*; *death* versus *major MI causing permanent disability*; *death* versus *repeat CABG;* and *major stroke causing permanent disability* versus *major MI causing permanent disability*). Patients could choose between four answer-options: "yes, both complications are equally unfavourable for me"; "no, the avoidance of [component endpoint X] is more important for me than the avoidance of [component endpoint Y]"; "no, the avoidance of [component endpoint Y] is more important for me than the avoidance of [component endpoint X]" or "Do not know" **(Figure 1)**. These four prepositions were included in the PPQ *to examine whether or not patients weigh component endpoints equally* [and to test whether (all-cause) death is weighted as heavily as other severe composite endpoints (i.e. major stroke, major MI, repeat CABG)]. If patients answer one of these four prepositions with "Yes, the avoidance of [component endpoint X or Y] is more important for me than the avoidance of [component endpoint Y or X]", or they answer at least one of these 4 questions with "Do not know", the relative importance of each component endpoint to patients with CAD is examined by means of six partial profile "case 1" BWS-choice questions. In each "case 1" BWS-choice question, four "objects" (i.e. component endpoints) were shown to patients

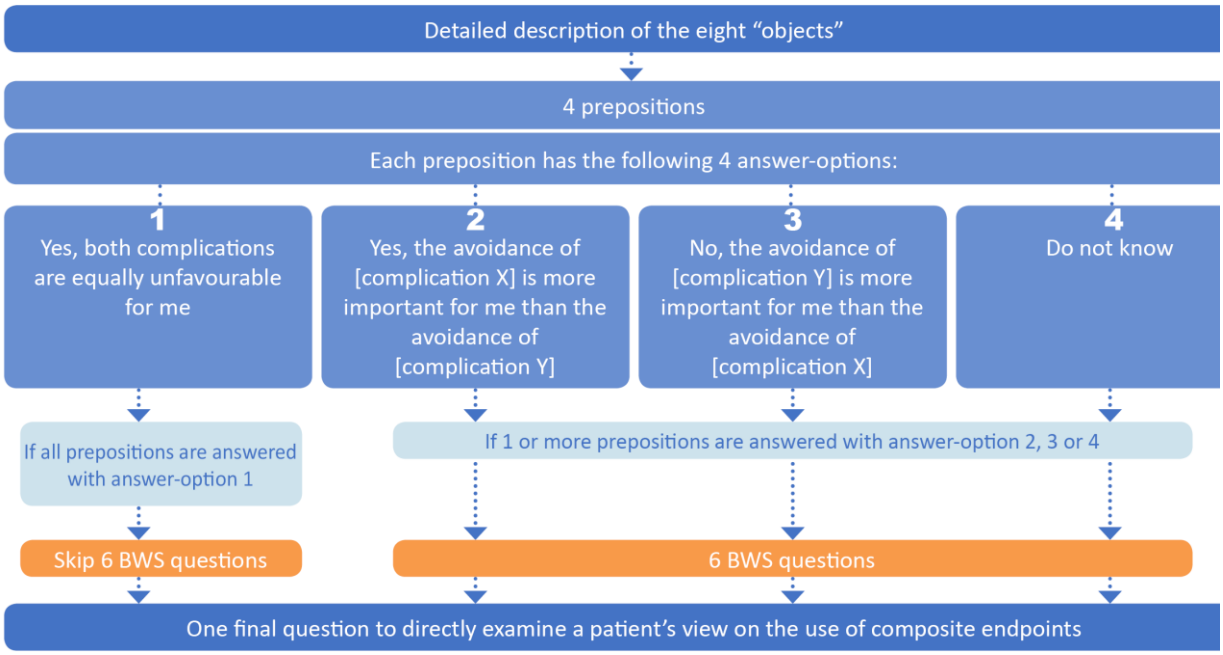


**Figure 1.** *Experimental set up. In the four prepositions, patients had to choose between death versus major stroke causing permanent disability; death versus major MI causing permanent disability; death versus repeat CABG; and major stroke causing permanent disability versus major MI causing permanent disability. BWS= "case 1" best worst scaling.* CABG= coronary artery bypass grafting; MI= myocardial infarction.


**Figure 2**. *Example of a "case 1" BWS choice question used in this study.*

and they were asked to choose the "most unfavourable complication" and the "least unfavourable complication" **(Figure 2)**. After patients completed these six "case 1" BWS questions, one final question was asked to directly examine a patient's view on the use of composite endpoints **(Figure 3)**. In addition to the preference elicitation questions, six self-rated questions on experienced health status in the week pre-intervention, and seven patient-specific questions about demographic and clinical characteristics were asked. The questionnaire was programmed on the online questionnaire application LimeSurvey (26) and was displayed to patients on IPad tablets trough a secure internet connection. In principle, it was the intention that patients self-complete the questionnaire. However, if patients indicated that they needed more explanation or assistance in completing the survey, assistance was given. A pilot test (n=7) of the questionnaire was performed to investigate which preference elicitation method patients preferred more (i.e. discrete-choice experiment or best-worst scaling), and to examine the clarity and appropriateness of the (choice)-questions.

**STATISTICAL ANALYSIS**

Data was collected and stored in the online software package LimeSurvey (26) and was processed and analysed by use of IBM SPSS Statistics 23 (SPSS Inc., Chicago, IL, USA) and StataCorp LP STATA 13.0 (StataCorp LP, College Station, TX).

*Patients' Demographic and Clinical Characteristics*

By use of SPSS Statistics 23, descriptive statistics were applied to get insights into the demographic and clinical characteristics of the study population. Frequencies of prior MI, prior CABG, prior PCI, diabetes (any), current smokers, hypertension, hypercholesterolemia, COPD and family history of cardiovascular disease were calculated. Baseline characteristics were compared between the two-revascularization patient-groups using independent T-tests for the continuous variables and Chi-Square tests for the categorical variables. Given its high distribution, the variable "Highest Education Completed" was clustered into the following categories: *Low Educational Level* (i.e. no education; Primary School; Junior Secondary Technical School; Lower General Secondary Education; and GCSE's At C level), *Intermediate Educational Level* (i.e. intermediate vocational education; GCSE's at A level; and GSE A/A2 Levels), and *High Educational Level* (i.e. University of Professional Education and University of Science). The same holds for the variable age, which was clustered in three age categories: *Younger Age Category* (30<60 years old), *Middle Age Category* (61<70 years old), and *Older Age Category* (71<100 years old). Categorical variables (i.e. nominal, ordinal or dichotomous) were reported as frequencies and percentages. Continuous variables (i.e. interval or ratio) were reported as mean ± standard deviation (SD). All statistical tests conducted in this study were two-tailed and *p* values <0.05 were considered statistically significant.

When clinical researchers want to compare two medical interventions for heart diseases with each other, they state that *a medical intervention in which 1 in 100 patients died* within 24h is as good as a *medical intervention where 1 in 100 patients experienced recurrent angina* within one year post-intervention.

Do you think it is right that clinical researchers weigh botch complications equally to measure how effective a treatment is, or should one of the two complications outweigh the other?

- ☐ **Yes**, I think it is right that both complications are weighted equally.
- ☐ **No**, I think that one of the two complications should weigh heavier than the other complication
- ☐ **Do not know.**

**Figure 3.** *Example of a "case 1" BWS choice question used in this study.*

*Analysis of Best-Worst Scaling Data*

To estimate the relative strength of preferences and the trade-offs between component endpoints, the best-worst data was analysed both by presenting best minus worst (B-W) scores and by calculating a maximum-likelihood-based model (i.e. conditional logistic regression). The design for analysis of "case 1" BWS data was made with SPSS 23.0 and the data analysis was performed with STATA 13.0. All analyses were applied on the aggregated sample level, since we were only interested in overall group preferences.

*Best Minus Worst (B-W) Counts*

Best-Minus-Worst counts were calculated to study the distribution of scores. Best and worst counts represent the number of times an attribute level was chosen as best or as worst across all choice-sets and respondents (26). By subtracting the total number of times it was chosen as worst from the total number of times it was chosen as best, an initial ranking of all eight "objects" from best (i.e. least unfavourable) to worst (i.e. most unfavourable) can be determined. To account for the number of times the "object" was available in the BWS design, average B-W counts were calculated: i.e. the B-W counts were divided by the sample size and the frequency that each "object" appeared in the design of the choice set. Average B-W counts range from -1.0 to 1.0, where higher (positive) values of average B-W counts indicate that a given "object" was chosen more often as best than worst, and were more likely to be preferred relative to the other "objects". Lower (negative) B-W counts were more often chosen as worst than best, and are less likely to be preferred when compared to other "objects" A score of "0" means that an "object" was selected as best or worst an equal number of times (26). Since it was chosen to use data on the aggregated sample level, no statistical analysis can be performed to analyse the potential significance of these B-W counts. The best and worst counts were presented in a scatter plot to evaluate the inverse relationship: it is expected that "objects" with high (positive) best counts to have minimal (negative) worst counts, and those with high (negative) worst counts, to have minimal (positive) best counts (26).

*"Importance Weights"*

To compare the relative importance of the eight "objects" to patients, "importance weights" were calculated by taking the square root after dividing the "total worst counts" by the "total best counts". The resulting coefficient models the utility (i.e. relative importance) of an "object" compared to death".

*Conditional Logistic Regression*

To verify whether the ranking obtained with the B-W method is consistent, a conditional (fixed-effects) logistic regression was performed. To facilitate the interpretation of the obtained estimates (i.e. beta coefficients), odds ratios were calculated. The resulting odds ratios measure choice probability (i.e. the utility) compared to the reference level (i.e. death within 24 hours post-intervention). An odds ratio of thirty means that, on average, patients attribute a thirty times higher rating to an object (i.e. prefer this object thirty times more), when compared with death. In addition, subgroup-analyses were performed by carrying out several conditional logit models to explore potential associations between patient characteristics (including sex, age, current revascularization procedure, prior revascularization, and prior-MI) with each of the eight BWS scores.

**RESULTS**

*Patient Inclusion*

Between May 2016 and June 2016, all patients with CAD who underwent an elective revascularization procedure, either PCI or CABG, at the Thorax-centrum Twente (Enschede, the Netherlands) were screened for their eligibility to participate in this study. Of the 176 patients who were contacted; 9 patients (5%) were excluded from participation in this study since they did not meet the predetermined inclusion criteria, 2 declined to participate (1%), and 5 were discharged early from the hospital (3%). One-hundred-sixty patients (91%) met eligibility criteria, agreed to be surveyed and were included in the study. Of the 160 patients included in this study, a total 97 patients (61%) underwent PCI and 63 (39%) were treated with CABG **(Table 2)**. The four different versions of the questionnaire were equally distributed among the patients. No significant differences were found in the distribution of questionnaire versions and current revascularization procedure (*Chi-square*= 0.53; df=3; *p*=0.913). Some patients received hands-on assistance by filling in the questionnaire (n=31, 19%) since they experienced physical constraint by filling in the questionnaire. Another six patients (4%) received additional oral information and instructions, since they indicated that they needed further assistance. Only a few patients received both hands-on assistance and additional oral information and instructions (n=9, 6%).

*Patient Characteristics*

The patients' sociodemographic and treatment-related characteristics are presented in **Table 2.** Men represented 75% (n=120) of the study population. The mean age was 67 years old (SD =

11.26) and women were on average older (70 vs. 65 years, *p*=0.015). The average self-reported health status score was 6.27 (with "0"= lowest, "10"=highest, SD=1.84). A majority of the respondents (n=84, 52.5%) had low education levels, and about a quarter (n=40, 25%) was highly educated. Eighty-six patients (53.8%) had prior MI, nine (5.6%) had prior CABG, 45 (28.1%) had prior PCI, five (3.1%) patients had prior experience with both PCI and CABG, and a total of 105 patients (65.6%) had no history of prior coronary revascularization. The PCI and the CABG patients had similar baseline profiles regarding the variables *age, educational level, hypertension, hyper-cholesterolaemia, current smokers, COPD, family history of CAD, prior CABG, prior MI and prior TIA/CVA.* However, significant differences were found between the PCI and CABG patients concerning *diabetes* (18.6% vs. 38.1%, *p*=0.006, respectively) and *prior-revascularization* (15.9% vs. 36.1%, *p*=0.005, respectively).

*Patients' Perspective Regarding CEs Differ*

A vast majority of patients (n=129, 80.63%) state that the common practice of weighting all component endpoints equally is invalid, where only a small fraction of patients report that they believe it is valid to weigh both complications equally (n=23, 14.38%). More than half of patients (n=85, 53.13%) indicate that it is more important to prevent a *major stroke causing permanent disability* to occur, as compared to *death within 24 hours post-intervention* **(Table 3).** Ninety-four patients (58.75%) state that it is more important to prevent *death within 24 hours post-intervention* versus *major MI causing permanent disability*, and 126 patients (78.75%) report that it is more important to prevent *death within 24 hours post-intention*, as compared to the need to undergo a *repeat CABG* **(Table 3)**. Only a small portion of patients state that all component endpoints mentioned (i.e. death, major stroke, major MI, and repeat CABG) are equally unfavourable (n=13, 8.13%). Eight of these

**Table 2.** *Baseline characteristics of patients participating in this study (n=160).*

| | | Revascularization Procedure | | |
|---|---|---|---|---|
| | All patients (N=160) | CABG n=63 (39.4%) | PCI n=97(60.6%) | All patients (N=160) |
| | | | | *p*-value |
| Sex | | | | 0.707 |
| Male | 120 (75.0) | 45 (71.4) | 75 (77.3) | |
| Female | 40 (25.0) | 18 (28.6) | 22 (22.7) | |
| Age† – yr. | 67 (11.3) | 68 (9.5) | 66 (12.2) | 0.300 |
| Younger Age Category (30<60 years old) | 14 (8.8) | 3 (4.8) | 11 (11.3) | |
| Middle Age Category (61<70 years old) | 82 (51.2) | 32 (50.8) | 50 (51.5) | |
| High Age Category (71<100 years old) | 64 (40.0) | 28 (44.4) | 36 (37.1) | |
| Highest level of education | | | | 0.144 |
| Low Education | 84 (52.5) | 29 (46.0) | 55 (56.7) | |
| Middle Education | 36 (22.5) | 13 (20.6) | 23 (23.7) | |
| High Education | 40 (25) | 21 (33.3) | 19 (19.6) | |
| **Risk factors** | | | | |
| Hypertension | 76 (47.5) | 33 (52.4) | 43 (44.3) | 0.319 |
| Hypercholesterolaemia | 61 (38.1) | 27 (42.9) | 34 (35.1) | 0.986 |
| Current Smoker | 36 (22.5) | 14 (22.2) | 22 (22.7) | 0.946 |
| COPD | 21 (13.1) | 9 (14.3) | 12 (12.4) | 0.726 |
| Diabetes Mellitus (any) | 42 (26.3) | 24 (38.1) | 18 (18.6) | 0.006* |
| Family history of CAD | 39 (24.4) | 13 (20.6) | 26 (26.8) | 0.375 |
| Prior MI* | 86 (53.8) | 32 (50.8) | 54 (55.7) | 0.546 |
| Prior Stroke* | 21 (13.1) | 9 (14.3) | 12 (12.4) | 0.726 |
| Prior PCI* | 45 (28.1) | 10 (15.9) | 35 (36.1) | 0.005* |
| Prior CABG* | 9 (5.6) | 2 (3.2) | 7 (7.2) | 0.278 |
| **Self-Reported Overall Health Status#** | | | | 0.721[a] |
| Fair to Poor | 106 (66.3) | 42 (66.7) | 64 (66.0) | |
| Good | 53 (33.1) | 21 (33.3) | 32 (33.0) | |
| Excellent or Very Good | 1 (0.6) | 0 (0.0) | 1 (1.0) | |

CABG= coronary artery bypass grafting; CAD= coronary artery disease; MI= myocardial infarction; PCI: percutaneous coronary intervention; SD: standard deviation. Values are means (percentages) unless indicated otherwise. †Values are means (standard errors) *A *t*-test was used for age. For categorical variables, a Pearson's chi-square test or Fisher's exact test was used, where appropriate (2-sided). # Self-reported health status ≤7.0= fair to poor; 7.1- 9.0= good; >9.0= excellent or very good. [a]=2 cells (33.3%) have expected counts less than 5.

thirteen patients (61.54%) stated that it is valid that clinical researchers weight both complications equally, where three patients stated that they had no answer (i.e. "do not know"). The remaining two patients (15.38%), made an 'illogical' choice, in that they answered all four prepositions with "both complications are equally unfavourable", however, they stated that it is not valid that clinical researchers weigh both complications equally. Perspectives regarding CEs where not significantly different for current revascularization procedure, prior-MI, age, or sex.

*Patients Did Not Consider All CEs Equal*

The two different methods used to calculate priority scores (I) best minus worst counts, and (II) conditional logistic regression were consistent and yielded the same ranking **(Table 4; Additional file 2)**. Patients with CAD did not assign equal weights (i.e. relative importance) to all component endpoints **(see Table 4)**. Patients considered the need to undergo a *repeat PCI within one-year post-intervention* the least unfavourable from this subset of component endpoints with an average B-W count of 0.82. *Minor stroke with recovery within 24 hours* was the second least unfavourable component outcome (average B-W count 0.38), followed by *minor MI with recovery in three months* (average B-W count 0.31), and *recurrent symptoms of angina* (average B-W count 0.23). Major *stroke causing permanent disability* was considered worse than *death* (average B-W count -0.76 vs. -0.69) and all other component endpoints. The third most unfavourable component endpoint was *major MI causing permanent disability* (average B-W count -0.27). The average B-W count of *re-CABG* was -0.02, indicating that patients selected this "object" as best or worst approximately an equal number of times.

The conditional (fixed-effects) logistic regression estimates showed that patients find the need to undergo a repeat *PCI* procedure within one year post-intervention, twenty times (276.037/ 13.966) less unfavourable as the need to undergo a repeat *CABG* procedure" **(Table 4).** Moreover, patients do assign different weights to component endpoints according to severity: a *major MI* is rated 15 times (44.304/ 3.032) more unfavourable than a *minor MI*, where a *minor stroke* is rated 82 times (56.938/ 0.698) less unfavourable than a *major stroke causing permanent disability*. Additionally, and in line with the B-W values, *major stroke causing permanent disability* is viewed as worse than *death* (OR=0.698 vs. 1; p=0.009) **(Figure 5).** The standard errors for the "objects" *repeat PCI* (SE=59.6), *minor stroke* (SE=11.2), and *minor MI* (SE=8.7) are the largest: indicating more heterogeneity (i.e. inter-patient variation) in indicated preferences for these "objects".

**Table 3.** *Patient perspectives regarding the four prepositions (n=160).*

| **Preposition death versus major stroke** | N=160 | 100% |
|---|---|---|
| Both complications are equally unfavourable | 42 | 26.25% |
| Avoidance of death is more important | 26 | 16.25% |
| Avoidance of major stroke is more important | 85 | 53.13% |
| Do not know | 7 | 4.38% |
| **Preposition death versus major MI** | N=160 | 100% |
| Both complications are equally unfavourable | 31 | 19.38% |
| Avoidance of death is more important | 94 | 58.75% |
| Avoidance of major MI is more important | 26 | 16.25% |
| Do not know | 9 | 5.63% |
| **Preposition death versus repeat CABG** | N=160 | 100% |
| Both complications are equally unfavourable | 21 | 13.13% |
| Avoidance of death is more important | 126 | 78.75% |
| Avoidance of repeat CABG is more important | 6 | 3.75% |
| Do not know | 7 | 4.38% |
| **Preposition major stroke versus major MI** | N=160 | 100% |
| Both complications are equally unfavourable | 38 | 23.75% |
| Avoidance of major stroke is more important | 104 | 65.00% |
| Avoidance of major MI is more important | 10 | 6.25% |
| Do not know | 8 | 5.00% |

*Inverse Relationship*

To assess whether or not there was an inverse relationship between the best and worst counts, the best and worst counts were plotted against each other in a scatter plot **(Figure 4)**. This scatter plot displays a moderate negative (not linear) association between the best and worst counts. The scatter plot indicates that patients most preferred to undergo a *repeat PCI*, and least preferred to experience a *major stroke causing permanent disability.* Two outliners could be identified in this graph (triangular figures 3 and 4); these are "objects" that are not selected frequently as best or worst (e.g. *repeat CABG* [average B-W count -0.02] or *recurrent angina* [average B-W count [0.23]). These triangles indicate component endpoints were patients attribute little value to as compared to other component endpoints.

*"Importance Weights" for CEs Differ*

If one looks at **Figure 5**, the "importance weights" for the included "objects" in this study (relative to death, which was anchored at "1") were in descending order of importance to patients: major

**Table 4.** *Estimate of subjective priority scores for "objects" (i.e. component endpoints) using two different methods (n=147).*

| | Best and Worst Counts | | | | Conditional Logit | | |
|---|---|---|---|---|---|---|---|
| **"Objects"** | Best | Worst | Count | Aver. Count [rang] | Odds Ratio [rang] | SE | *P* value |
| **Repeat PCI** | 364 | 2 | 362 | 0.82 [1] | 276.037 [1] | 59.608 | <0.001 |
| **Minor stroke** | 173 | 4 | 169 | 0.38 [2] | 56.938 [2] | 11.212 | <0.001 |
| **Minor MI** | 143 | 8 | 135 | 0.31 [3] | 44.304 [3] | 8.655 | <0.001 |
| **Angina Pectoris** | 118 | 17 | 101 | 0.23 [4] | 33.794 [4] | 6.448 | <0.001 |
| **Repeat CABG** | 74 | 81 | -7 | -0.02 [5] | 13.966 [5] | 2.519 | <0.001 |
| **Major MI** | 3 | 122 | -119 | -0.27 [6] | 3.032 [6] | 0.417 | <0.001 |
| **(all-cause) Death** | 4 | 309 | -305 | -0.69 [7] | 1 [7] | - | - |
| **Major stroke** | 3 | 339 | -336 | -0.76 [8] | 0.698 [8] | 0.097 | 0.009 |
| *Note*. SE=standard error; Aver. Score= Average B-W count (B-W count/ sample size [147] and appearance of "object" in design). Values given in square brackets are rank orders. MI= myocardial infarction; repeat CABG= repeat coronary artery bypass grafting within a year post-intervention; Repeat PCI= repeat percutaneous coronary intervention within a year post-intervention. (all-cause) death was the reference level in the conditional logistic regression. | | | | | Log pseudolikelihood<br>Pseudo $R^2$ | | -1080.5902<br>0.5072 |

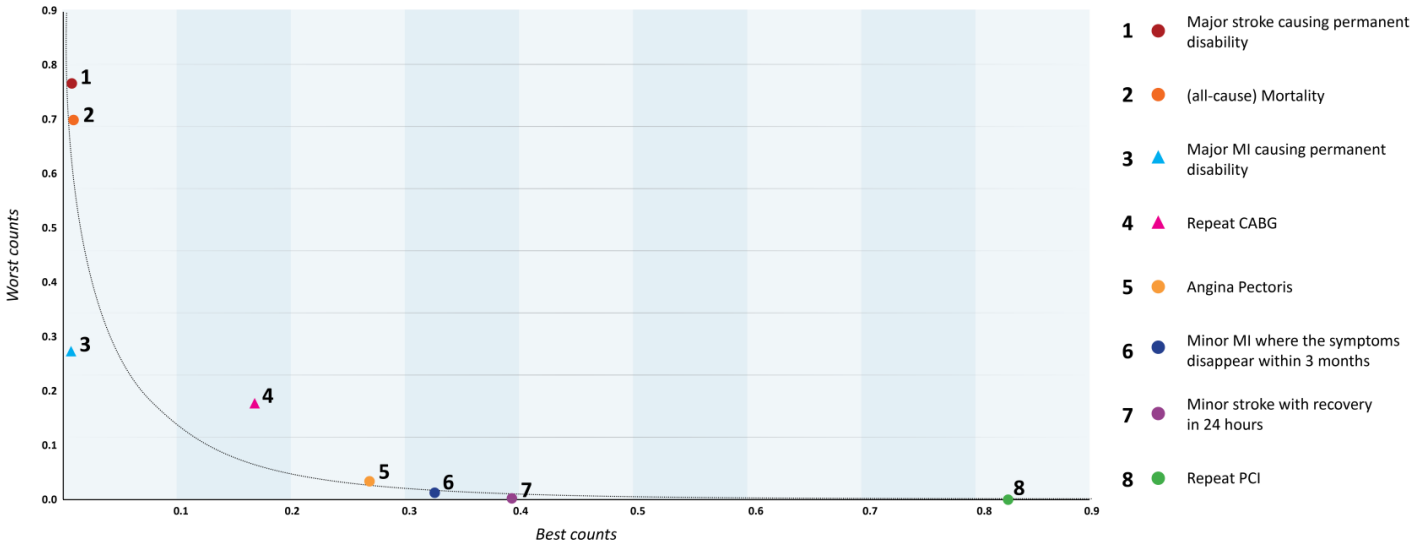


**Figure 4.** *Scatter plot of the distribution of best and worst counts. Two outliers could be identified in this graph (triangular figures 3 and 4); Major MI causing permanent disability and re-CABG. These are the component endpoints with the most preference heterogeneity (n=147).*

stroke (1.209); death (1.000); major MI (0.726); angina pectoris (0.300); repeat CABG (0.119); minor MI (0.027); minor stroke (0.017); and repeat PCI (0.008). Based on these "importance weights", approximately two patients in one arm of a RCT should have to have a repeat CABG procedure, in which one of them died following the revascularization, in order to balance one major stroke causing permanent disability.

*Patient Characteristics Had Effect on the Ranking and Mean Relative Values of Component Endpoints*

**Tables 5 to 15 (see Additional file 1, Tables 5 to 15)** show the mean odds ratios and rankings on the different component endpoints for the different patient subgroups. Patient characteristics had effect on the ranking of component endpoints. Females, patients in the highest age-category (age≥71), and patients without prior MI experience place greater emphasis on avoiding *recurrent symptoms of angina* than *minor MI*. All subgroups considered major stroke worse than death. However, no significant differences on mean scores (odds ratios) for these two adverse outcomes of treatment were found for patients who underwent a CABG procedure, both men and women, patients in all age-categories, patients without prior revascularization experience, patients with prior-MI, and patients who had never experienced a myocardial infarction. In addition, patients with prior revascularization experience "prefer" a PCI procedure 23 times (193.93/8.55) more instead of a CABG procedure, where a PCI procedure was viewed 19 times more favourable as compared to CABG for patients without prior revascularization experience. Patients with and without prior experience with MI, did not show differences in the relative value they attributed to major MI as

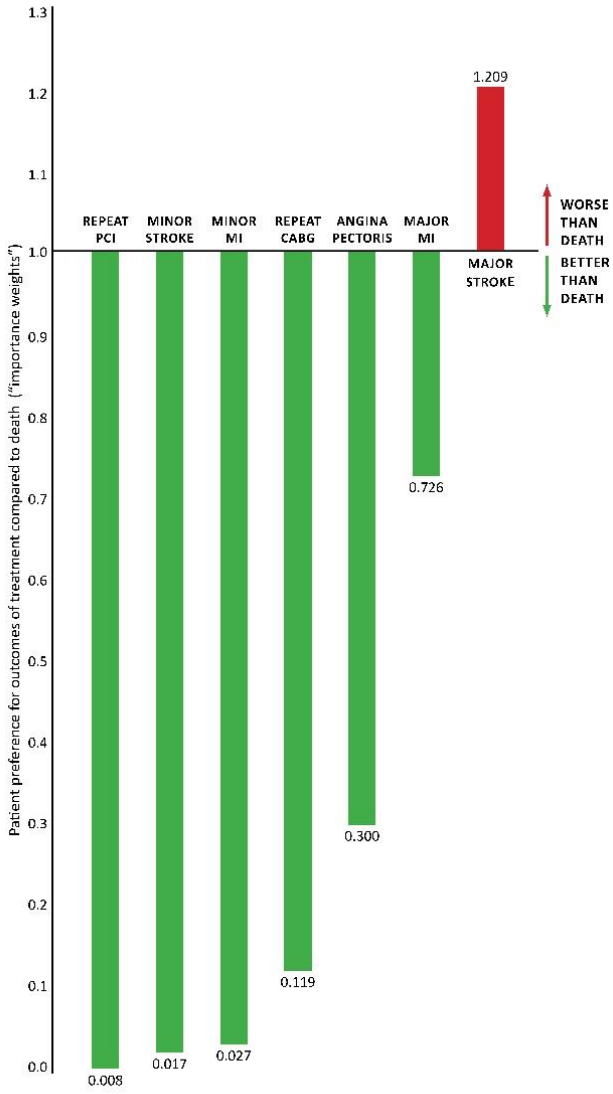


**Figure 5.** *"Importance weights" (n=147). The "importance weights" model the utility (i.e. relative importance) of a component endpoint compared to death. Weight* $_{(Component\ endpoint)} = \sqrt{\left(\frac{importance\ attributed\ to\ component\ endpoint}{importance\ attributed\ to\ death}\right)}$.
*Importance attributed to component endpoint= (Total Best counts)*$_{component\ endpoint}$*/ (Total Worst counts)*$_{component\ endpoint}$.

compared to death, that is, both patient groups "prefer" a major MI about 3 times more as compared to death.

**DISCUSSION**

The aim of this study was to examine patients' perspective regarding the use of composite endpoints and the utility patients put on possible unfavourable outcomes of treatment. The results of this study indicate that a vast majority of patients do not find it appropriate that individual component endpoints are weighed equally in clinical trials in order to measure how effective a treatment is. Despite the common practice of weighing adverse outcomes of treatment equally, our study shows that patients considered "hard" cardiovascular events *(death, major MI, major stroke*) significantly more unfavourable than "soft" events such as *repeat revascularization* (both PCI and CABG), *minor stroke*, *minor MI*, and *recurrent symptoms of angina*. In addition, more than half of the patients stated that the avoidance of a *major stroke* is more important than the avoidance of *death*.

Although the confidence intervals of the preference data showed some variability, the ranking of component endpoints was comparable across different patient characteristics (sex, age, revascularization procedure) showing the robustness of the results. Women, patients in the highest age-category, and patients who never experienced an MI, do place greater emphasis on avoiding *recurrent symptoms of angina* than *minor MI*. In addition, patients find the need to undergo a *repeat PCI* procedure twenty times less unfavourable than the need to undergo a *repeat CABG procedure*, and do assign different weights to component endpoints according to severity (major/minor event). These results are interesting since most current ongoing RCTs still do not distinguish their clinical outcomes according to severity or procedure (PCI or CABG). If one want to accomplish more patient-centred care which more closely reflect patient preferences, one might reconsider this common practice, an use component endpoints adjusted according to severity and procedure to assess the net clinical benefit of interventions.

Even though the ranking of component endpoints was the same for the two different revascularization subgroups, CABG-patients place greater emphasizes on the avoidance of *a repeat CABG procedure* than PCI patients. Perhaps knowing the full impact of this procedure (including side effects, discomfort and pain felt at the moment of survey assessment, realization of the long revalidation period ahead, and tiredness or the current dazed state brought on by the medication), instigated CABG-patients to place greater relative importance on *repeat CABG* than PCI-patients did. Alternatively, the fact that PCI procedures are more commonly known and therefore less frightening to patients, may contribute to why patients rate this procedure as less unfavourable than repeat CABG. It is known that patients' prior experiences with the component endpoints or the experiences of friends and/or family with the components affect their rating on such outcomes (27, 28). Some patients also pointed out that their rating would have been different when they would not only serve their own interests and preferences, but if they include their relatives in their (treatment) decision.

*Previous Studies*

Our results are in line with previous research, which also demonstrated a large variation in the importance of component endpoints to patients (8, 14, 29-31). For example, Ahmad and colleagues (2015) surveyed 113 patients using a structured, quantitative assessment (VAS-scale) to determine the preferences patients assign to components of the composite endpoint MACE, and found out that patients considered all endpoints worse than *death*, except *stroke* (14). This, and our result, suggests that patients fear a loss of mobility and independence above all else (20, 32). However, Tong et al. (2012) found out, by using the preference elicitation technique discrete choice experiment, that risk of *death* was most important to patients, followed by in descending order of importance: *stroke*, *potential increased* longevity and recovery time, *MI*, and *risk of repeat revascularization* (15). Thus, our data is in line with some, but not all previous research, yet demonstrating the high variability in importance of component endpoints to patients measured in different trials, highlighting the need to develop standardized "importance weights" for these component endpoints.

*Implications for Further Clinical Trials and Current Clinical Practice*

This study demonstrated that most patients had no difficulty in completing the "case 1" BWS choice-questions to indicate their preferences. Researchers who plan to elicit patient preferences may consider this approach for their future studies.

Analytic approaches to composite endpoints place equal importance on each of the individual component endpoints. This common practice to compare competing (medical) therapies is only a valid reflection of their relative value if each component endpoint is viewed as equally important to patients. The current study, and previous research in this field, suggests that this is not the case (8, 31). Therefore, it might be better to not use composite endpoint at all, or to survey a small group of patients before a clinical trial to set a sense of whether they view the component endpoints as relatively equal in importance. At least, a more nuanced and refined approach to interpretation of clinical trial data need to be developed, which acknowledges the potential heterogeneity in relative importance of these component endpoints to patients. To address this concern, some clinical researchers already emphasized the need to develop measures to weight these component endpoints, in which component endpoints are valued relative to one another (8, 14, 15, 22, 23, 33, 34). We also believe that an ideal evaluation of competing (drug) therapies should assign relative weights (i.e. "importance weights") to the endpoints being studied, such that endpoints of more clinical significance contribute to a greater extent to the final statistical comparison between competing (drug) therapies than less meaningful component endpoints. Consequently, we advise an alternative methodology that achieves this goal by assigning greater relative weight to component endpoints with greater clinical importance (a-priori decided by using a preference-elicitation technique, e.g. BWS). This way, these component endpoints contribute more to the final statistics compared to traditional component endpoints. This methodology is similar in concept to the "weighted effect measure" methodology as stated by Armstrong et al (2011), however, instead of using a modified Delphi panel of experts assigning weights to component endpoints, we suggest to make use of a more quantitative preference-elicitation technique, such as BWS, to determine the relative weights (e.g. the "importance weights" as determined in this study) attributed to the component endpoints (22)).

We believe that the most important step in more patient-centred care is to support and encourage efforts to further increase awareness of the critical role patients play in clinical research and the value that this more patient-centred research brings to the interpretation of trial data. By furthering the connection that patients have with the clinical research community, by applying patient preference data more often to trial data, e.g. by means of assigning relative weights (i.e. "importance weights") to the endpoints being studied, less misleading trial statistics which better reflect patient preferences values for treatment outcomes can be obtained. A lot more research into the values patients, but also clinical researchers, and physicians, attribute to adverse outcomes of treatment, should be done. Previous research already demonstrated that these values differ (24). Assigning equal "importance weights" to trial data evaluated by clinical researchers or physicians, will not accurately reflect the preferences of patients. More research is necessary to confirm the results of these studies and to raise awareness of possible differences in the preferences of patients, physicians, and clinical researchers. These preferences thus cannot be considered equivalent unconditionally. We recommend emphasis on reaching agreement on the most appropriate method to measure patient preferences for adverse outcomes of treatment. That way, standardized "importance weights" can be determined, and applied to trial data, creating less misleading trial statistics and better patient-centred care.

Meanwhile, existing clinical trial data should be carefully interpreted, since these "unweighted" data may be inaccurate and misleading as it can be interpreted differently when all component endpoints are considered equally important.

*Strengths and Limitations*

This study has both strengths and limitations. To the best of our knowledge, this is one of the first studies that quantified the differences patients attributed to each component endpoint by using a choice-based method and to study whether or not patients agree with the scientific practice to combine multiple component endpoints into one composite endpoint. The quantitative nature of this prospective, observational cohort study enables us to obtain insights into the distribution of preferences and the possible differences in these preferences between certain patient (sub)-groups.

The individual component endpoints in this study are differentiated according to severity and procedure (i.e. major MI/minor MI; major/minor stroke; PCI/CABG). This is done since patients can experience several different types of MI (e.g. trivial troponin rise immediately post revascularization to a large infarction), stroke (e.g. minor transient ischaemic event to major disabling insult), or revascularization procedure (e.g. minimally invasive PCI to more invasive CABG surgery). In our opinion, it was likely that patient preferences for these adverse outcomes of treatment differed according to severity/procedure. Something our results confirmed.

A number of limitations were identified in this study, for example regarding the obtained sample size. Following the rule-of-thumb as proposed by Johnson and Orme (2010), the minimum required sample size was determined to be at least 84 patients per subgroup (35, 36). Some of our subgroup analyses were small(er) in size and therefore underpowered. Consequently, the results of the subgroup analyses should be interpreted with caution. Furthermore, our data represents the "importance weights" of patients undergoing a revascularization procedure in our hospital. This data might be influenced by clinical, geographical and socioeconomic factors, and is not necessarily generalizable to other cohorts. Another possible validity issue might be that the obtained stated preferences reflect those of patients who had just undergone a PCI or CABG surgery. It is possible that post-interventional preferences differ from preferences before the intervention, as patients may be influenced by the newly acquired experience. It would be of interest for future clinical researchers to examine whether the obtained patient preferences significantly differ when measured in a larger population of patients, when measured multi-centred, and when measured pre-intervention.

The aim of this study was to determine the relative importance regarding component endpoints that are often studied in clinical trials. Therefore, after careful consideration within the steering committee of the research team, the decision was made to include the five most studied component endpoints (subdivided according to severity) in this study. We did not include more component endpoints to increase the feasibility of the study. It could be that other important adverse outcomes of treatment are missing from a patient's perspective, for example, infection, prolonged hospital stay or the need for a blood transfusion. Therefore, in future research, a qualitative study should be conducted with patients beforehand (e.g., focus groups, interviews) to ensure that the most important possible unfavourable outcomes of treatment to patients are captured in the preference elicitation task.

In the most optimal situation, the design of the choice-questions is created in such a way that it will yield as much statistical information as possible for measuring unbiased and precise preference parameters (37); therefore, four versions of the questionnaire were developed with the experimental design software Sawtooth 6.4.6. in order to avoid version-bias and to achieve a balanced design. However, the BWS design used in this study was not balanced. In a balanced design, the one-way frequencies (i.e. each "object" appeared as an option equally often) and the two-way frequencies (the "objects" co-appear with each other equally often) are nearly equivalent. In this study, the one-way frequency was 12.0 (SD= 0.0), and the two-way frequency was ± 5.1 (SD= 0.6). This means that some "objects" were underpowered and may therefore have a statistically smaller chance of being chosen in the choice sets. Although that the "objects" were not shown an equal amount of time per version of the questionnaire, they were shown an equal amount of times spread all over the versions. The possible alternative BWS design, which was balanced, consisted of fourteen partial profile choice-questions. As the PRECORE study was part of a larger study into patient preferences after revascularization, and the larger study involves another preference elicitation technique with ten discrete choice questions, for feasibility reasons, as well as to reduce the cognitive burden and potential measurement error (38), the decision was made to include not fourteen – but six- "case 1" BWS questions.

## CONCLUSIONS

The majority of patients in the PRECORE study indicated that they do not agree with the common practice of weighing clinical endpoints equally. Patients considered "hard" cardiovascular events *(death, major MI, major stroke*) significantly more unfavourable than "soft" events such as *repeat revascularization*, where one out of every two patients stated that they are more worried about permanent stroke causing disability than death, suggesting that they fear a loss of mobility and independence above death. It would be fruitful to pursue further research to confirm these results and raise awareness that patients', physicians', and clinical researchers' preferences cannot be considered equivalent unconditionally. We recommend emphasis on reaching agreement on the most appropriate method to measure patient preferences for adverse outcomes of treatment. That way, standardized "importance weights" can be determined, and applied to trial data, creating less misleading trial statistics and better patient-centred care.

## ADDITIONAL FILES

**Additional file 1:** This file contains the patient values attached to component endpoints for the different subgroup analyses.
**Additional file 2:** This file contains a comparison of estimates from the conditional logistic regression against the B-W counts.


## ACKNOWLEDGEMENTS

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## CONFLICT OF INTEREST

C. von Birgelen has been consultant to and has received lecture fees or travel expenses from Medtronic and Boston Scientific; he received lecture fees from AstraZeneca and MSD. The institution has received research grants, provided by Abbott Vascular, AstraZeneca, Biotronik, Boston Scientific, and Medtronic. All other authors reported no conflicts of interest.

## REFERENCES


1. von Birgelen C, Basalus MW, Tandjung K, van Houwelingen KG, Stoel MG, Louwerenburg JHW, et al. A randomized controlled trial in second-generation zotarolimus-eluting Resolute stents versus everolimus-eluting Xience V stents in real-world patients: the TWENTE trial. J Am Coll Cardiol. 2012;59(15):1350-61.
2. von Birgelen C, Sen H, Lam MK, Danse PW, Jessurun GA, Hautvast RW, et al. Third-generation zotarolimus-eluting and everolimus-eluting stents in all-comer patients requiring a percutaneous coronary intervention (DUTCH PEERS): a randomised, single-blind, multicentre, non-inferiority trial. The Lancet. 2014;383(9915):413-23.
3. Freemantle N, Calvert M, Wood J, Eastaugh J, Griffin C. Composite outcomes in randomized trials: greater precision but with greater uncertainty? JAMA. 2003;289(19):2554-9.
4. Lim E, Brown A, Helmy A, Mussa S, Altman DG. Composite outcomes in cardiovascular research: a survey of randomized trials. Ann Intern Med. 2008;149(9):612-7.
5. Neaton JD, Gray G, Zuckerman BD, Konstam MA. Key issues in end point selection for heart failure trials: composite end points. J Card Fail. 2005;11(8):567-75.
6. Rauch G, Rauch B, Schüler S, Kieser M. Opportunities and challenges of clinical trials in cardiology using composite primary endpoints. World J Cardiol. 2015;7(1):1.
7. Kip KE, Hollabaugh K, Marroquin OC, Williams DO. The problem with composite end points in cardiovascular studies: the story of major adverse cardiac events and percutaneous coronary intervention. J Am Coll Cardiol. 2008;51(7):701-7.
8. Ferreira-González I, Permanyer-Miralda G, Domingo-Salvany A, Busse JW, Heels-Ansdell D, Montori VM, et al. Problems with use of composite end points in cardiovascular trials: systematic review of randomised controlled trials. BMJ. 2007;334(7597):786.
9. Meinert C. Clinical Trials Dictionary: Terminology and Usage Recommendations. Baltimore, MD: The Johns Hopkins Center for Clinical Trials. 1996. ISBN 0-9646424-0-9.
10. Loscalzo J. Clinical trials in cardiovascular medicine in an era of marginal benefit, bias, and hyperbole. Circulation. 2005;112(20):3026-9.
11. Lauer MS, Topol EJ. Clinical trials—multiple treatments, multiple end points, and multiple lessons. JAMA. 2003;289(19):2575-7.
12. Detsky AS. Using economic analysis to determine the resource consequences of choices made in planning clinical trials. J Chronic Dis. 1985;38(9):753-65.
13. Kent DM, Trikalinos TA. Therapeutic innovations, diminishing returns, and control rate preservation. JAMA. 2009;302(20):2254-6.
14. Ahmad Y, Nijjer S, Cook CM, El-Harasis M, Graby J, Petraco R, et al. A new method of applying randomised control study data to the individual patient: A novel quantitative patient-centred approach to interpreting composite end points. Int J Cardiol. 2015;195:216-24.
15. Tong BC, Huber JC, Ascheim DD, Puskas JD, Ferguson TB, Blackstone EH, et al. Weighting composite endpoints in clinical trials: essential evidence for the Heart Team. The Annals of thoracic surgery. 2012;94(6):1908-13.
16. Borm GF, Teerenstra S, Zielhuis GA. Objective and perspective determine the choice of composite endpoint. J Clin Epidemiol. 2008;61(2):99-101.
17. Carneiro A. Composite outcomes in clinical trials: uses and problems. Revista portuguesa de cardiologia: orgao oficial da Sociedade Portuguesa de Cardiologia= Portuguese journal of cardiology: an official journal of the Portuguese Society of Cardiology. 2003;22(10):1253-63.

18. Chen EH, Sites F, Shofer FS, Hollander JE. Defining the outcomes of risk stratification studies of ED patients with chest pain: the marginal value of adding revascularization to the composite end point. The American journal of emergency medicine. 2005;23(7):848-51.
19. Benjamin DK, Hirschfeld S, Cunningham CK, McKinney RE. Growth as a part of the composite endpoint in paediatric antiretroviral clinical trials. J Antimicrob Chemother. 2004;54(4):701-3.
20. Cordoba G, Schwartz L, Woloshin S, Bae H, Gøtzsche PC. Definition, reporting, and interpretation of composite outcomes in clinical trials: systematic review. BMJ. 2010;341:c3920.
21. Montori VM, Devereaux P, Adhikari NK, Burns KE, Eggert CH, Briel M, et al. Randomized trials stopped early for benefit: a systematic review. JOURNAL-AMERICAN MEDICAL ASSOCIATION. 2005;294(17):2203.
22. Armstrong PW, Westerhout CM, Van de Werf F, Califf RM, Welsh RC, Wilcox RG, et al. Refining clinical trial composite outcomes: An application to the Assessment of the Safety and Efficacy of a New Thrombolytic–3 (ASSENT-3) trial. Am Heart J. 2011;161(5):848-54.
23. Stafinski T, Menon D, Nardelli A, Bakal J, Ezekowitz J, Tymchak W, et al. Incorporating patient preferences into clinical trial design: Results of the Opinions of Patients on Treatment Implications of New Studies (OPTIONS) project. Am Heart J. 2015;169(1):122-31. e22.
24. Stolker JM, Spertus JA, Cohen DJ, Jones PG, Jain KK, Bamberger E, et al. Re-Thinking Composite Endpoints in Clinical Trials: Insights from Patients and Trialists. Circulation. 2014:CIRCULATIONAHA. 113.006588.
25. Kok MM, von Birgelen C, Lam MK, Löwik MM, van Houwelingen K, Stoel MG, et al. Patient preference regarding assessment of clinical follow-up after percutaneous coronary intervention: the PAPAYA study. EuroIntervention: journal of EuroPCR in collaboration with the Working Group on Interventional Cardiology of the European Society of Cardiology. 2015;11(6).
26. Schmitz C. Lime Survey: the free & open source survey software tool. Available on: http://wwwlimesurvey.org/ Accessed: June 2016. 2012;1.
27. De Wit GA, Busschbach JJ, De Charro FT. Sensitivity and perspective in the valuation of health status: whose values count? Health Econ. 2000;9(2):109-26.
28. Ubel PA, Loewenstein G, Jepson C. Whose quality of life? A commentary exploring discrepancies between health state evaluations of patients and the general public. Qual Life Res. 2003;12(6):599-607.
29. Auger P, Devinney TM, Louviere JJ. Using best–worst scaling methodology to investigate consumer ethical beliefs across countries. Journal of Business Ethics. 2007;70(3):299-326.
30. Cozmuta R, Merkel PA, Wahl E, Fraenkel L. Variability of the impact of adverse events on physicians' decision making. BMC Med Inform Decis Mak. 2014;14(1):1.
31. Kipp R, Lehman J, Israel J, Edwards N, Becker T, Raval AN. Patient preferences for coronary artery bypass graft surgery or percutaneous intervention in multivessel coronary artery disease. Catheter Cardiovasc Interv. 2013;82(2):212-8.
32. Stevenson LW, Hellkamp AS, Leier CV, Sopko G, Koelling T, Warnica JW, et al. Changing preferences for survival after hospitalization with advanced heart failure. J Am Coll Cardiol. 2008;52(21):1702-8.
33. Montori VM, Brito JP, Murad MH. The optimal practice of evidence-based medicine: incorporating patient preferences in practice guidelines. JAMA. 2013;310(23):2503-4.
34. Wilson RF, Berger AK. Are All End Points Created Equal?: The Case for Weighting. J Am Coll Cardiol. 2011;57(5):546-8.
35. Johnson R, Orme B. Getting the most from CBC. Sequim: Sawtooth Software Research Paper Series, Sawtooth Software. 2003.
36. Orme B. Sample size issues for conjoint analysis studies. Sawthooth Software Research paper Series Squim, WA, USA: Sawthooth Software Inc. 1998.
37. Louviere JJ, Hensher DA, Swait JD. Stated choice methods: analysis and applications: Cambridge University Press; 2000.
38. Maddala T, Phillips KA, Reed Johnson F. An experiment on simplifying conjoint analysis designs for measuring preferences. Health Econ. 2003;12(12):1035-47.

**ADDITIONAL FILE**

## 1. Patient values attached to component endpoints for the different subgroup analyses.

### Current revascularization experience (CABG versus PCI)

**Tables 5 and 6** contain the results of the conditional (fixed-effects) logistic regressions for patients who underwent a CABG procedure or a PCI procedure. The ranking of the component endpoints is equal for both subgroups, and equals the overall rating of the entire study population. However, PCI patients considered the endpoint *major stroke causing permanent disability* worse than *death within 24 hours* (OR: 0.62; 95% CI, 0.44-0.89; $p$ = 0.009), where CABG patients show a nonsignificant trend toward significance (OR: 0.82; 95% CI, 0.54-1.25; $p$ = 0.354). Patients who underwent a PCI procedure find the need to undergo another PCI procedure within one year post-intervention, twenty-three times (271.36/11.81) more favourable as the need to undergo a CABG procedure, where patients who underwent a CABG surgery favour re-PCI 18 times (336.93/18.31) more than re-CABG.

**Table 5.** *Patient value attached to component endpoints as compared to (all-cause) death using logistic regression for PCI patients (n=88).*

| "Object" | Component End point | Odds Ratio | Std. Err. | z | P>\|z\| | [95% Conf. Interval] | | Rang |
|---|---|---|---|---|---|---|---|---|
| **A1** | Minor MI | 59.05 | 15.65 | 15.39 | <0.001 | 35.13 | 99.25 | 3 |
| **A2** | Major MI | 2.72 | 0.48 | 5.67 | <0.001 | 1.93 | 3.85 | 6 |
| **A3** | Minor stroke | 67.87 | 18.05 | 15.86 | <0.001 | 40.30 | 114.29 | 2 |
| **A4** | Major stroke | 0.62 | 0.11 | -2.61 | 0.009 | 0.44 | 0.89 | 7 |
| **A5** | Angina Pectoris | 38.31 | 9.81 | 14.24 | <0.001 | 23.20 | 63.26 | 4 |
| **A6** | Re-CABG | 11.81 | 2.79 | 10.46 | <0.001 | 7.44 | 18.75 | 5 |
| **A7** | Re-PCI | 271.36 | 77.15 | 19.71 | <0.001 | 155.44 | 473.75 | 1 |
| A8= (all-cause) death is reference. MI= myocardial infarction; Re-CABG= repeat coronary artery bypass grafting within a year post-intervention; Re-PCI= repeat percutaneous coronary intervention within a year post-intervention. | | | | | | Log pseudolikelihood<br>Pseudo $R^2$ | -636.10267<br>0.5152 | |

**Table 6.** *Patient value attached to component endpoints as compared to (all-cause) death using logistic regression for CABG patients (n=59).*

| "Object" | Component End point | Odds Ratio | Std. Err. | z | P>\|z\| | [95% Conf. Interval] | | Rang |
|---|---|---|---|---|---|---|---|---|
| **A1** | Minor MI | 32.37 | 9.53 | 11.81 | <0.001 | 18.18 | 57.65 | 3 |
| **A2** | Major MI | 3.59 | 0.79 | 5.79 | <0.001 | 2.33 | 5.54 | 6 |
| **A3** | Minor stroke | 49.72 | 14.90 | 13.03 | <0.001 | 27.63 | 89.47 | 2 |
| **A4** | Major stroke | 0.82 | 0.18 | -0.93 | 0.354 | 0.54 | 1.25 | 7 |
| **A5** | Angina Pectoris | 30.61 | 8.94 | 11.72 | <0.001 | 17.27 | 54.25 | 4 |
| **A6** | Re-CABG | 18.31 | 5.17 | 10.29 | <0.001 | 10.52 | 31.84 | 5 |
| **A7** | Re-PCI | 336.93 | 116.33 | 16.86 | <0.001 | 171.26 | 662.87 | 1 |
| A8= (all-cause) death is reference. MI= myocardial infarction; Re-CABG= repeat coronary artery bypass grafting within a year post-intervention; Re-PCI= repeat percutaneous coronary intervention within a year post-intervention. | | | | | | Log pseudolikelihood<br>Pseudo $R^2$ | -434.64566<br>0.5064 | |

## Gender (Male versus Female)

**Tables 7 and 8** contain the results of the conditional (fixed-effects) logistic regressions for both male and female patients who underwent a revascularization. The ranking of component endpoints for male patients equals the ranking of the overall study population, however, the rank order of component endpoints for female patients is incongruent with the ranking of the entire study population. Females consider *recurrent angina pectoris* more unfavourable than *minor MI* (OR: 70.00 vs. OR: 67.18*)*. For males, this is the other way around (OR: 27.79 vs. OR 40.22). The rest of the rating is the same as compared to the overall study population. Additionally, another deviate from the overall study results is that both males (OR: 0.74; 95% CI, 0.54-1.01; P = 0.064) and females (OR: 0.58; 95% CI, 0.33-1.01; *p* =0.053) do not consider *permanent stroke causing disability* significantly worse than *death within 24 hours,* they do show a nonsignificant trend toward significance.

**Table 7.** *Patient value attached to component endpoints as compared to (all-cause) death using logistic regression for male patients (n=109).*

| "Object" | Component End point | Odds Ratio | Std. Err. | z | P>\|z\| | [95% Conf. Interval] | | Rang |
|---|---|---|---|---|---|---|---|---|
| **A1** | Minor MI | 40.22 | 8.81 | 16.87 | <0.001 | 22.19 | 61.78 | 3 |
| **A2** | Major MI | 2.94 | 0.46 | 6.92 | <0.001 | 2.17 | 4.00 | 6 |
| **A3** | Minor stroke | 46.61 | 10.24 | 17.49 | <0.001 | 30.30 | 71.69 | 2 |
| **A4** | Major stroke | 0.74 | 0.12 | -1.87 | 0.062 | 0.54 | 1.01 | 7 |
| **A5** | Angina Pectoris | 27.79 | 5.91 | 15.65 | <0.001 | 18.32 | 42.14 | 4 |
| **A6** | Re-CABG | 13.31 | 2.69 | 12.80 | <0.001 | 8.95 | 19.78 | 5 |
| **A7** | Re-PCI | 238.44 | 58.05 | 22.48 | <0.001 | 147.95 | 384.26 | 1 |
| A8= (all-cause) death is reference. MI= myocardial infarction; Re-CABG= repeat coronary artery bypass grafting within a year post-intervention; Re-PCI= repeat percutaneous coronary intervention within a year post-intervention. | | | | | | Log pseudolikelihood<br>Pseudo $R^2$ | -823.79821<br>0.4931 | |

**Table 8.** *Patient value attached to component endpoints as compared to (all-cause) death using logistic regression for female patients (n=38).*

| "Object" | Component End point | Odds Ratio | Std. Err. | z | P>\|z\| | [95% Conf. Interval] | | Rang |
|---|---|---|---|---|---|---|---|---|
| **A1** | Minor MI | 67.18 | 29.66 | 9.53 | <0.001 | 28.28 | 159.59 | 4 |
| **A2** | Major MI | 3.41 | 1.00 | 4.17 | <0.001 | 1.91 | 6.06 | 6 |
| **A3** | Minor stroke | 120.89 | 54.42 | 10.65 | <0.001 | 50.03 | 292.10 | 2 |
| **A4** | Major stroke | 0.58 | 0.16 | -1.94 | 0.053 | 0.33 | 1.01 | 7 |
| **A5** | Angina Pectoris | 70.00 | 30.69 | 9.69 | <0.001 | 29.64 | 165.30 | 3 |
| **A6** | Re-CABG | 17.20 | 6.96 | 7.03 | <0.001 | 7.78 | 38.03 | 5 |
| **A7** | Re-PCI | 498.92 | 238.80 | 12.98 | <0.001 | 195.26 | 1274.82 | 1 |
| A8= (all-cause) death is reference. MI= myocardial infarction; Re-CABG= repeat coronary artery bypass grafting within a year post-intervention; Re-PCI= repeat percutaneous coronary intervention within a year post-intervention. | | | | | | Log pseudolikelihood<br>Pseudo $R^2$ | -251.71881<br>0.5565 | |

## Age category (1=Age≤60, 2= Age 61-70, 3=Age ≥71)

**Tables 9, 10** and **11** contain the results of the conditional (fixed-effects) logistic regressions for different age-categories. The ranking of component endpoints for patients in the low-age category (age ≤ 60) and intermediate age-category (age 61-70) equals the ranking of the overall study population, however, the rank order of component endpoints for patients in the highest age-category (age ≥71) is incongruent with the ranking of the entire study population. Patients above the age of seventy-one consider *recurrent angina pectoris* more unfavourable than *minor MI* (OR: 48.16 vs. OR: 39.38*)*. For younger patients, this is the other way around. The rest of the rating is the same as compared to the overall study population. Additionally, another deviate from the overall study results is that patients in all three age-categories do not consider *permanent stroke causing disability* significantly worse than *death within 24 hours,* they do show a nonsignificant trend toward it (1=OR: 0.897; *p* =0.673, 2=OR:0.55; p=0.060, 3=OR:0.69; *p* =0.90).

**Table 9.** *patient value attached to component endpoints as compared to (all-cause) death using logistic regression for patients in age category 1 (n=40).*

| "Object" | Component End point | Odds Ratio | Std. Err. | z | P>\|z\| | [95% Conf. Interval] | | Rang |
|---|---|---|---|---|---|---|---|---|
| **A1** | Minor MI | 44.19 | 15.21 | 11.01 | <0.001 | 22.51 | 86.74 | 3 |
| **A2** | Major MI | 3.75 | 0.97 | 5.10 | <0.001 | 2.26 | 6.23 | 6 |
| **A3** | Minor stroke | 45.54 | 15.69 | 11.09 | <0.001 | 23.19 | 89.45 | 2 |
| **A4** | Major stroke | 0.897 | 0.23 | -0.42 | 0.673 | 0.54 | 1.49 | 7 |
| **A5** | Angina Pectoris | 20.79 | 6.67 | 9.46 | <0.001 | 11.09 | 39.00 | 4 |
| **A6** | Re-CABG | 8.24 | 2.44 | 7.10 | <0.001 | 4.60 | 14.74 | 5 |
| **A7** | Re-PCI | 191.52 | 72.33 | 13.91 | <0.001 | 91.36 | 401.49 | 1 |
| A8= (all-cause) death is reference. MI= myocardial infarction; Re-CABG= repeat coronary artery bypass grafting within a year post-intervention; Re-PCI= repeat percutaneous coronary intervention within a year post-intervention. | | | | | | Log pseudolikelihood<br>Pseudo $R^2$ | -310.80625<br>0.4788 | |

**Table 10.** *patient value attached to component endpoints as compared to (all-cause) death using logistic regression for patients in age-category 2 (n=48).*

| "Object" | Component End point | Odds Ratio | Std. Err. | z | P>\|z\| | [95% Conf. Interval] | | Rang |
|---|---|---|---|---|---|---|---|---|
| **A1** | Minor MI | 72.16 | 27.94 | 11.05 | <0.001 | 33.79 | 154.14 | 3 |
| **A2** | Major MI | 4.28 | 1.15 | 5.41 | <0.001 | 2.53 | 7.24 | 6 |
| **A3** | Minor stroke | 104.54 | 40.65 | 11.96 | <0.001 | 48.79 | 223.99 | 2 |
| **A4** | Major stroke | 0.55 | 0.14 | -2.40 | 0.061 | 0.33 | 0.90 | 7 |
| **A5** | Angina Pectoris | 46.33 | 17.47 | 10.17 | <0.001 | 22.12 | 97.02 | 4 |
| **A6** | Re-CABG | 23.24 | 8.50 | 8.60 | <0.001 | 11.35 | 47.58 | 5 |
| **A7** | Re-PCI | 308.95 | 125.83 | 14.08 | <0.001 | 139.06 | 686.36 | 1 |
| A8= (all-cause) death is reference. MI= myocardial infarction; Re-CABG= repeat coronary artery bypass grafting within a year post-intervention; Re-PCI= repeat percutaneous coronary intervention within a year post-intervention. | | | | | | Log pseudolikelihood<br>Pseudo $R^2$ | -342.3083<br>0.5217 | |

**Table 11.** *Patient value attached to component endpoints as compared to (all-cause) death using logistic regression for patients in age-category 3 (n=59).*

| "Object" | Component End point | Odds Ratio | Std. Err. | z | P>\|z\| | [95% Conf. Interval] | | Rang |
|---|---|---|---|---|---|---|---|---|
| **A1** | Minor MI | 39.38 | 12.79 | 11.31 | <0.001 | 20.84 | 74.42 | 4 |
| **A2** | Major MI | 2.14 | 0.45 | 3.59 | <0.001 | 1.41 | 3.25 | 6 |
| **A3** | Minor stroke | 53.72 | 17.70 | 12.09 | <0.001 | 28.16 | 102.47 | 2 |
| **A4** | Major stroke | 0.69 | 0.15 | -1.70 | 0.090 | 0.45 | 1.06 | 7 |
| **A5** | Angina Pectoris | 48.16 | 15.74 | 11.85 | <0.001 | 25.38 | 91.39 | 3 |
| **A6** | Re-CABG | 17.10 | 5.25 | 9.24 | <0.001 | 9.37 | 31.21 | 5 |
| **A7** | Re-PCI | 487.17 | 184.99 | 16.30 | <0.001 | 231.46 | 1025.40 | 1 |
| A8= (all-cause) death is reference. MI= myocardial infarction; Re-CABG= repeat coronary artery bypass grafting within a year post-intervention; Re-PCI= repeat percutaneous coronary intervention within a year post-intervention. | | | | | | Log pseudolikelihood<br>Pseudo $R^2$ | -408.09803<br>0.5366 | |

## Prior experience with MI versus no prior experience with MI

**Tables 12 and 13** contain the results of the conditional (fixed-effects) logistic regressions for patients with and without prior experience with MI. The ranking of component endpoints for patients with prior MI experience equals the ranking of the overall study population, however, patients who do not have experience with MI assigned a different rank-order to the component endpoints. Patients who have had a myocardial infarction considered *a minor MI* more unfavourable than patients who had not experienced MI (OR: 57.34 vs. OR: 35.43*)*. Additionally, both patients with and without prior experience with MI did not value *permanent stroke causing disability* significantly worse than *death within 24 hours,* they do show a nonsignificant trend toward it (With prior MI: *p* =0.056; without prior MI: *p* =0.077).

**Table 12.** *Patient value attached to component endpoints as compared to (all-cause) death using logistic regression for patients without prior MI (n=68).*

| "Object" | Component End point | Odds Ratio | Std. Err. | z | P>\|z\| | [95% Conf. Interval] | | Rang |
|---|---|---|---|---|---|---|---|---|
| **A1** | Minor MI | 35.43 | 10.29 | 12.28 | <0.001 | 20.05 | 62.61 | 4 |
| **A2** | Major MI | 2.80 | 0.56 | 5.12 | <0.001 | 1.89 | 4.15 | 6 |
| **A3** | Minor stroke | 53.26 | 15.67 | 13.51 | <0.001 | 29.92 | 94.81 | 2 |
| **A4** | Major stroke | 0.70 | 0.14 | -1.77 | 0.077 | 0.47 | 1.04 | 7 |
| **A5** | Angina Pectoris | 45.17 | 13.20 | 13.04 | <0.001 | 25.48 | 80.09 | 3 |
| **A6** | Re-CABG | 17.43 | 4.84 | 10.30 | <0.001 | 10.12 | 30.03 | 5 |
| **A7** | Re-PCI | 315.36 | 103.33 | 17.56 | <0.001 | 165.92 | 599.38 | 1 |
| A8= (all-cause) death is reference. MI= myocardial infarction; Re-CABG= repeat coronary artery bypass grafting within a year post-intervention; Re-PCI= repeat percutaneous coronary intervention within a year post-intervention. | | | | | | Log pseudolikelihood<br>Pseudo $R^2$ | -496.92534<br>0.5103 | |

**Table 13.** *Patient value attached to component endpoints as compared to (all-cause) death using logistic regression for patients with prior MI (n=79).*

| "Object" | Component End point | Odds Ratio | Std. Err. | z | P>\|z\| | [95% Conf. Interval] | | Rang |
|---|---|---|---|---|---|---|---|---|
| **A1** | Minor MI | 57.34 | 15.40 | 15.08 | <0.001 | 33.88 | 97.05 | 3 |
| **A2** | Major MI | 3.27 | 0.62 | 6.26 | <0.001 | 2.26 | 4.74 | 6 |
| **A3** | Minor stroke | 65.07 | 17.56 | 15.47 | <0.001 | 38.34 | 110.43 | 2 |
| **A4** | Major stroke | 0.70 | 0.13 | -1.91 | 0.056 | 0.48 | 1.01 | 7 |
| **A5** | Angina Pectoris | 27.13 | 6.87 | 13.03 | <0.001 | 16.51 | 44.57 | 4 |
| **A6** | Re-CABG | 11.87 | 2.83 | 10.38 | <0.001 | 7.44 | 18.94 | 5 |
| **A7** | Re-PCI | 270.56 | 78.91 | 19.20 | <0.001 | 152.76 | 479.20 | 1 |
| A8= (all-cause) death is reference. MI= myocardial infarction; Re-CABG= repeat coronary artery bypass grafting within a year post-intervention; Re-PCI= repeat percutaneous coronary intervention within a year post-intervention. | | | | | | Log pseudolikelihood<br>Pseudo $R^2$ | -574.52448<br>0.5122 | |

## Prior revascularization experience versus no prior revascularization experience

**Tables 14 and 15** contain the results of the conditional (fixed-effects) logistic regressions for patients with and without prior revascularization experience. The ranking of the component endpoints is equal for both subgroups, and equals the overall rating of the entire study population. However, patients with prior revascularization experience considered the end point *major stroke* when compared to *death within 24 hours* significantly worse (OR: 0.45; 95% CI, 0.28-0.73; $p$ =0.001), while patients without revascularization experience do not consider *permanent stroke causing disability* significantly worse than *death within 24 hours,* they do show a nonsignificant trend toward significance (OR: 0.87; 95% CI, 0.63-1.22; $p$ =0.429).

**Table 14.** *Patient value attached to component endpoints as compared to (all-cause) death using logistic regression for patients with prior revascularization experience (n=47).*

| "Object" | Component End point | Odds Ratio | Std. Err. | z | P>\|z\| | [95% Conf. Interval] | | Rang |
|---|---|---|---|---|---|---|---|---|
| **A1** | Minor MI | 26.76 | 8.67 | 10.14 | <0.001 | 14.18 | 50.51 | 3 |
| **A2** | Major MI | 1.82 | 0.41 | 2.62 | 0.009 | 1.16 | 2.84 | 6 |
| **A3** | Minor stroke | 38.12 | 12.51 | 11.10 | <0.001 | 20.04 | 72.51 | 2 |
| **A4** | Major stroke | 0.45 | 0.11 | -3.27 | 0.001 | 0.28 | 0.73 | 7 |
| **A5** | Angina Pectoris | 23.39 | 7.42 | 9.94 | <0.001 | 12.56 | 43.54 | 4 |
| **A6** | Re-CABG | 8.55 | 2.53 | 7.26 | <0.001 | 4.79 | 15.26 | 5 |
| **A7** | Re-PCI | 193.92 | 71.58 | 14.27 | <0.001 | 94.07 | 399.77 | 1 |
| A8= (all-cause) death is reference. MI= myocardial infarction; Re-CABG= repeat coronary artery bypass grafting within a year post-intervention; Re-PCI= repeat percutaneous coronary intervention within a year post-intervention. | | | | | | Log pseudolikelihood<br>Pseudo $R^2$ | -350.44032<br>0.4999 | |

**Table 15.** *Patient value attached to component endpoints as compared to (all-cause) death using logistic regression for patients without prior revascularization experience (n=100).*

| "Object" | Component End point | Odds Ratio | Std. Err. | z | P>\|z\| | [95% Conf. Interval] | | Rang |
|---|---|---|---|---|---|---|---|---|
| **A1** | Minor MI | 58.60 | 14.44 | 16.52 | <0.001 | 36.16 | 94.97 | 3 |
| **A2** | Major MI | 3.99 | 0.70 | 7.90 | <0.001 | 2.83 | 5.62 | 6 |
| **A3** | Minor stroke | 71.67 | 17.77 | 17.23 | <0.001 | 44.08 | 116.52 | 2 |
| **A4** | Major stroke | 0.87 | 0.15 | -0.79 | 0.429 | 0.63 | 1.22 | 7 |
| **A5** | Angina Pectoris | 41.79 | 10.06 | 15.51 | <0.001 | 26.08 | 66.97 | 4 |
| **A6** | Re-CABG | 18.28 | 4.19 | 12.69 | <0.001 | 11.67 | 28.64 | 5 |
| **A7** | Re-PCI | 340.58 | 91.51 | 21.70 | <0.001 | 201.15 | 576.67 | 1 |
| A8= (all-cause) death is reference. MI= myocardial infarction; Re-CABG= repeat coronary artery bypass grafting within a year post-intervention; Re-PCI= repeat percutaneous coronary intervention within a year post-intervention. | | | | | | Log pseudolikelihood<br>Pseudo $R^2$ | -725.21127<br>0.5139 | |

**ADDITIONAL FILE**

## 2. Comparison of estimates from the conditional logistic regression against the B-W counts.

**Figure 6** contains the scores of the conditional (fixed-effect) logistic regression against the best-worst counts. This figure describes the relative difference in the individual level priority scores (i.e. utilities) obtained with these two different methods. A (positive) linear line fits these data, showing the congruency, and robustness, of the BWS data as measured with these two different methods.

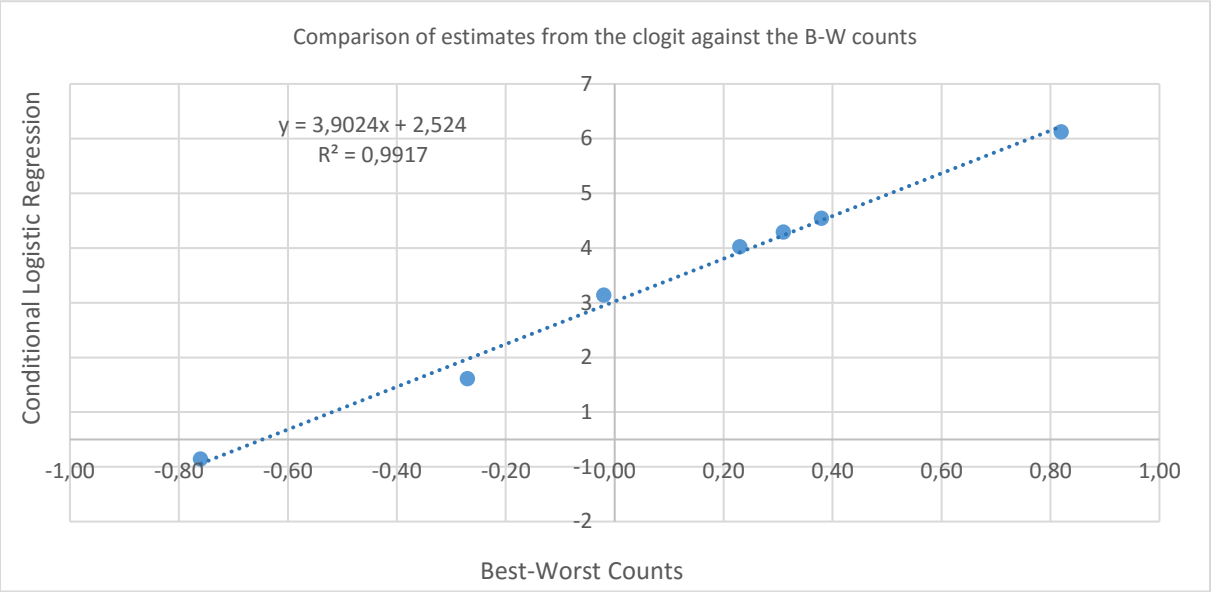


**Figure 6.** *Comparison of estimates from the conditional logistic regression against the average B-W counts.*