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Trial participation as a determinant of clinical outcome: Differences between trial-participants and Every Day Clinical Care patients in the field of interventional cardiology

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ABSTRACT

Background: This study examines differences in clinical outcome between trial-participants and non-participants after percutaneous coronary intervention (PCI).
Methods and results: This study compromised of 11,931 consecutive patients who underwent PCI in a high volume center, during the period 2000 – 2009. Of these patients, 1787 (15%) participated in an interventional clinical trial with a follow-up period of at least six months. The maximum follow-up duration was 11.8 years, with a median of 3.8 years (IQR: 2.6 – 6.5). Baseline and procedural characteristics differed between trial-participants and non-participants. Trial-participants were more often male, were younger, had more cardiovascular risk factors and were treated more often for stable angina pectoris and single vessel disease. Overall mortality at maximum follow-up was lower for trial-participants compared to non-participants (8.1% versus 17.6%, $p < 0.001$, adjusted HR, 0.62, 95% CI: 0.52–0.74). There was no difference in the incidence of non-fatal MI and CABG. Repeat PCI was seen more often in trial-participants (18.1% versus 30.7%, $p < 0.001$, adjusted HR 1.91, 95%CI 1.73–2.10). Consequently, a higher incidence of the composite of mortality, repeat revascularization, and non-fatal MI was seen in the trail-participants (adjusted HR.1.36 95% CI 1.25 – 1.47), but this association was primarily driven by the occurrence of repeat PCI.
Conclusion: Participants in clinical trials in the field of interventional cardiology with a follow-up of at least six months differed considerably from non-participants in baseline and procedural characteristics. Trial-participants had better survival than non-participants. In contrast, a two-fold higher incidence of repeat PCI was observed in trial-participants.

1. Introduction

Randomized controlled trials (RCTs) are the gold standard by which the efficacy and safety of therapeutic strategies are evaluated [1]. Randomization results in valid estimates of treatment effect, as it minimizes bias due to differential selection and confounding [2]. However, patients who participate in these clinical trials are, often due to the strict in- and exclusion criteria, considered being a selective group of patients, questioning the external validity.

Furthermore, generalizability can be limited due to the fact that not all consecutive patients who fulfil the study criteria actually do participate. Due to a number of reasons, including willingness of patients to participate, "burden" of additional procedures (i.e. follow-up angiography), distrust in clinical research among patients and health care providers, it is observed that fewer than half of eligible patients participate in clinical trials [3,4]. Moreover, study participation is considered as hazardous by some since the therapeutic strategy under investigation may deviate from the applicable standards and guidelines. On the other hand, it is advocated that trial-participants may have a higher likelihood of beneficial outcome due to the most up-to-date treatment provided by qualified physicians embracing novel treatments [5–8].

A restriction of previous studies comparing trial-participants with non-participants is the heterogeneity of interventions and patient populations. Consequently, it remains unclear whether the observed differences reflect trial participation or differences due to heterogeneity in interventions [9]. In the current study we focus on patients with coronary artery disease (CAD) undergoing a clinically indicated percutaneous coronary intervention (PCI). The objective of this study was to evaluate the extent to which participation in a clinical trial affects clinical outcome of patients with CAD who underwent a PCI.

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2. Methods

This study was conducted in the Thoraxcenter of the Erasmus MC from January 2000 to December 2009. The Erasmus MC is a tertiary referral and teaching hospital in Rotterdam, The Netherlands, that serves a region of over 1 million inhabitants. Approximately 4000 PCIs are performed annually in the Rotterdam region (in three PCI centres), including 1600 patients in the Erasmus MC.

All consecutive patients of 18 years of age or older, who were admitted with stable angina pectoris (sAP), non ST-segment elevation acute coronary syndrome (NSTE-ACS) or ST-segment elevation myocardial infarction (STEMI) and underwent PCI in our institution were included in the analysis. In total, 15,102 PCIs in 11,931 patients were performed. In patients who underwent multiple procedures ($n = 2470$), only the initial procedure was included in this analysis.

In the context of this study we identified trial participants as those patients who were enrolled in a clinical trial, irrespective of treatment arm, with a follow-up period of at least six months. In total 1787 participants, enrolled in 76 clinical trials (including 35 randomized controlled trials with 1058 patients), were identified. In 59 out of 76 trials (78%), a repeat angiography was mandated, including 1380 patients. Non-participants ($n = 10,144$) were those who fulfilled enrolment criteria but were not included (e.g. patient or physician refusal), participated in a trial without follow-up (e.g. cross-sectional and feasibility studies) evaluating the technical safety and feasibility of a new imaging catheter, using only procedural information) or those who did not fulfil the enrolment criteria.

Patient management was in accordance with the clinical treatment guidelines of the European Society of Cardiology (ESC), which are implemented in our center. The Thoraxcenter has (since the year 2000) the policy to use one particular coronary stent as default in a given time period. The default stent between January 2000 and April 2002 was a bare metal stent (BMS), between April 2002 and March 2003 a sirolimus eluting stent (SES), between March 2003 and March 2007 a paclitaxel eluting stent (PES), and the everolimus eluting stent (EES) since March 2007. Of note, patients could be treated with another stent when participating in a clinical trial.

According to the standard data-management procedures in our department, data are collected prospectively on demographics, cardiovascular history, clinical risk factors and treatment characteristics for all patients undergoing PCI, which are stored in an electronic database. Data-elements are filled out immediately after the completion of the PCI by the interventional cardiologist and the technician who assisted during the procedure. The database, which is maintained by a dedicated IT-officer, is mainly designed for administrative purposes. A systematic evaluation of data-completion and data-integrity is implemented for all data used for research purposes.

Vital status of the entire study cohort was obtained from the municipal civil registries between April and September 2011. Subsequently, a health questionnaire was sent to all living patients with specific inquiries on rehospitalisation and cardiovascular events, including repeat PCI, coronary artery bypass graft (CABG) and non-fatal myocardial infarction (MI). For patients who reported adverse events, medical records or discharge summaries were reviewed systematically. General practitioners, referring cardiologists, and patients were contacted in case further information was required. Patients lost to follow-up were considered at risk until the date of last contact, at which point they were censored.

2.1. Endpoint definitions

The primary endpoint was all-cause mortality, evaluated at 31 days, 1 year and 4 years. The secondary endpoints included repeat revascularization, non-fatal MI, and the composite of all-cause mortality, repeat revascularization and non-fatal MI at follow-up (31 days, 1 year and 4 years). Furthermore we also evaluated all-cause mortality at maximum available duration of follow-up (approximately 10 years for the first included patients).

Repeat revascularization was defined as a repeat PCI or CABG of any lesion located in the epicardial vessels. The definition of MI was in accordance with the guidelines of the European Society of Cardiology [10].

2.2. Statistical methods

Continuous variables are presented as mean values and corresponding standard deviations (± SD), or median values with corresponding interquartile ranges (IQR). Categorical variables are expressed as numbers and percentages. Student's t tests, Chi-square tests (or Fisher's exact tests), or Mann–Whitney tests were applied to evaluate differences in baseline variables, treatment and outcome between trial-participants and non-participants.

Kaplan–Meier mortality curves were used to describe the incidence of adverse events during follow-up. Log-rank tests were applied to evaluate differences in long-term outcome between trial-participants and non-participants. Subsequently, we repeated the analysis for patients who survived the first month, thereby excluding patients who were unable to participate (i.e. not able to sign the informed consent form and/or not fulfilling study criteria) in a clinical study due to their critical illness. In addition, univariate and multivariate analysis (Cox proportional hazard) were performed to study the association in clinical variables and mortality, repeat revascularization and myocardial infarction between trial-participants and non-participants. In the multivariate analysis we adjusted for a range of potential confounders, including all variables as presented in Table 1. These variables are: age, gender, smoking, hypercholesterolemia, hypertension, diabetes, family history, renal failure, prior PCI, prior CABG, prior myocardial infarction, indication for PCI, off-hours treatment, severity of coronary artery disease, treated coronary vessel (left main, LAD, LCx, RCA, and/or graft), and use of glycoprotein (GP) IIb/IIIa Inhibitors.

For all tests, a p-value of <0.05 (two-sided) was considered statistically significant. All calculations were performed using the SPSS 20 software package (SPSS Inc. IL. USA).

Table 1
Baseline and procedural characteristics.

Variable	All	Non-participants	Trial-participants	p-value
N (%)	11,931	10,144 (85)	1787 (15)	
Mean age, yr (±SD)	62.2 (±11.8)	62.4 (±12.0)	60.8 (±10.9)	<.001
Male gender, *n* (%)	8588 (72)	7243 (71)	1345 (75)	.001
Smoking status, *n* (%)				.020
Current	3213 (27)	2688 (27)	525 (30)	
Former smoker (≥1 yr)	65 (1)	59 (1)	6 (0)	
Medical history, *n* (%)				
Hypercholesterolemia	9213 (77)	7725 (76)	1488 (83)	<.001
Hypertension	5577 (47)	4756 (47)	821 (46)	.46
Diabetes mellitus	2054 (17)	1763 (17)	291 (16)	.26
Family history of CAD	3882 (33)	3197 (32)	685 (38)	<.001
Risk factors[a] per patient, mean (±SD)	1.7 (±1.0)	1.7 (±1.0)	1.8 (±0.9)	.002
Renal failure	593 (5)	518 (5)	75 (4)	.10
Prior PCI	1411 (12)	1209 (12)	202 (11)	.46
Prior CABG	1015 (9)	895 (12)	120 (7)	.003
Prior myocardial infarction	3125 (26)	2699 (27)	426 (24)	.035
Indication for PCI, *n* (%)				<.001
sAP	4422 (37)	3631 (36)	791 (44)	
NSTE-ACS	3280 (28)	2794 (28)	486 (27)	
STEMI	4229 (35)	3719 (37)	510 (29)	
Off-hours[b], *n* (%)	2746 (23)	2404 (24)	342 (19)	<.001
Severity of CAD, *n* (%)				<.001
Single-vessel disease	5886 (49)	4871 (48)	1015 (57)	
Two-vessel disease	3565 (30)	3069 (30)	496 (28)	
Three-vessel disease	2399 (20)	2127 (21)	272 (15)	
Treated vessel, mean (±SD)	1.4 (±0.7)	1.4 (±0.7)	1.4 (±0.6)	.69
RCA, *n* (%)	4492 (38)	3819 (38)	673 (38)	.99
LAD, *n* (%)	6005 (50)	5112 (50)	893 (50)	.74
LCx, *n* (%)	3389 (28)	2887 (29)	502 (28)	.75
LM, *n* (%)	504 (4)	466 (5)	38 (2)	<.001
Graft, *n* (%)	2336 (20)	1947 (19)	389 (22)	.011
GP IIb/IIIa inhibitor, *n* (%)	1534 (13)	1345 (13)	189 (11)	.001

PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; sAP, stable Angina Pectoris; NSTE-ACS, non ST-elevation myocardial infarction; STEMI, ST-elevation myocardial infarction; CAD, coronary artery disease; RCA, right coronary artery; LAD, left anterior descending; LCx, left circumflex artery; LM, left main stem.
‡) Antithrombotic: aspirin, thienopyridines, and/or coumadin.
a) Risk factors included, smoking, diabetes, hypercholesterolemia and hypertension.
b) Off-hours, weeknights (from 06.00 PM to 08.00 AM) and weekends (from Friday 06:00 PM to Monday 08:00 AM).

2.3. Ethics

All patients participating in clinical trials provided written informed consent. All trials were approved by the Medical Ethical Committee of the Erasmus MC and were performed in accordance with the declaration of Helsinki. Patients not enrolled into clinical trials were not subject to interventions under investigation, neither was any mode of behaviour imposed, otherwise than as part of their regular treatment. Therefore, according to Dutch law, written informed consent was not required for these patients. This study was conducted according to the Privacy Policy of the Erasmus MC, and according to the Erasmus MC regulations for the appropriate use of data in patient oriented research [11].

3. Results

3.1. Baseline and procedural characteristics

Baseline and procedural characteristics of the total study sample ($n = 11,931$) are displayed in Table 1. Of these patients, 1787 (15%) participated in a clinical trial with a follow-up period of at least six months. Baseline and procedural characteristics differed considerably between trial-participants and non-participants. Trial-participants were more often men (75% versus 71%, $p = 0.001$) and on average 1.6 years younger (60.8 vs. 62.4, $p < 0.001$) as compared to non-participants. In addition, trial-participants more often had a history of hypercholesterolemia