Gender differences in patients with percutaneous coronary intervention: the Armenian experience

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Abstract

Background: Coronary artery disease (CAD) is the leading cause of morbidity and mortality throughout the world. Scientists are still debating whether women benefit from invasive treatment strategy of CAD as men do. This study assessed gender differences in perioperative characteristics), 3-year event-free survival from major adverse cardiac and cerebrovascular events (MACCE) and quality of life (QoL) in patients who underwent percutaneous coronary intervention (PCI).

Methods: The study utilized an observational, retrospective cohort design. The study population included all CAD patients who underwent PCI from 2006-2008 at Nork Marash Medical Center. Data were collected from the patient medical records and patient telephone interviews.

Results: Among 485 participants included in the analysis, 419 (86%) were men. Women on average were older, more hypertensive, more obese, and had significantly higher rates of diabetes. Event-free survival from MACCE at the median follow up was 79% (95% CI 0.66 -0.87) for women and 74% (95% CI 0.69-0.78) for men. An interaction analysis revealed a differential effect of diabetes by sex 0.14 (95 % CI 0.05- 0.43). After adjustment for arrhythmia, men with diabetes had better event-free survival from MACCE (HR =0.38, 95% CI: 0.18-0.8) than men without diabetes (HR= 2.6; 95%CI: 1.1-5.9). The QoL analysis showed that women had worse mental and physical composite scores ($p < 0.05$).

Conclusion: Diabetes status and sex strongly interact with MACCE. In non diabetic population women have significantly better long-term survival than men, while the opposite was observed in diabetic population. According to the study results diabetes have significant negative impact in determining outcomes only in women patient.

1. INTRODUCTION

Coronary heart disease (CAD) is the leading cause of morbidity and mortality throughout the world. More than 7 million deaths worldwide attributed to CAD, 11.2% of all deaths in 2004 (1). Historically, CAD is considered to be a "man's disease", as it is manifested earlier in man's life (2). However, CAD remains the leading cause of death of women at all ages (2). The US Centers for Disease Control and Prevention reported that in 2008 the US death rate from CAD was almost two times higher than from cancer in women of all ages (3). Women comprise almost half of the patients with myocardial infarction (MI) (4).

Gender and sex differences exist in CAD risk factors, symptoms manifestation, management and outcome. In general, women with CAD are older and comparable incidence rates of CAD between men, and women are achieved with the interval of 10 years (2). Women generally have more existing risk factors such as obesity, hypertension, diabetes, and congestive heart failure than men (5-7). However, men have higher prevalence of smoking, previous history of MI, percutaneous coronary intervention (PCI) and coronary artery bypass surgery (CABG) compared to women in the same age group (8). Women are less likely to receive medications such as aspirin, statins, angiotensin-converting enzyme (ACE) inhibitors and β-blockers (5, 9). In addition, women have higher incidence of single-vessel disease than men (5-7, 10-11). Gender differences exist in referral rates to various treatment approaches especially invasive versus conservative strategies and between their outcomes.

Literature Review. Currently, several treatment strategies exist for CAD management including medication therapy, CABG and PCI. Researchers are still debating whether women benefit from invasive strategy as men do. Results of Framingham and Revascularization during Instability in Coronary artery disease II (FRISC II) and Randomized Intervention Trial of

unstable Angina 3 (RITA 3) randomized clinical trials (RCTs) showed that women in the invasive group (PCI and CABG) have similar or even increased rates of one-year MI or death compared to those in non invasive group (medical treatment), whereas men considerably benefited from the invasive strategy. However, Treat Angina with aggrastat and determine Cost of Therapy with Invasive or Conservative Strategy – Thrombolysis In Myocardial Infarction (TACTICS-TIMI 18) reported about a trend to odds reduction in the end points (death, MI or revascularization at 6 month) in women of the interventional group compared to women in non invasive group (12). A meta-analysis of those trials showed that women do not benefit from the early interventional approaches as opposed to conservative, and the invasive strategy should be left for men patients (13). Another meta-analysis of 8 acute coronary syndrome (ACS) trials (enrolling 3075 women and 7075 men in total), conducted by O'Donoghue, was consistent with the previous study; however after stratification by biomarkers (e.g., levels of troponin and other markers of myocardial damage), high risk (biomarker-positive) women benefited from invasive strategy, whereas in low risk (biomarker-negative) women invasive approach was associated with higher odds of mortality and morbidity (14).

Registry studies evaluating the long-term outcomes also report contradictory results. A recent study of 17 000 registry PCI patients revealed that at 3-year follow-up women experience higher overall, cardiac death rates and MI than men (15). Other studies found that differences in outcomes by sex are eliminated after long follow-up (16-20) or women gender was associated with even better outcomes (11, 21), irrespective to the fact that women had higher prevalence of diabetes and small vessel diameter. In terms of short-term morbidity and mortality, most trials reported that women tend to have worse outcomes than men (5-6, 22-23), although these

differences may be eliminated after adjusting for various confounders such as age, diabetic status, hypertension etc (24). A more detailed review of literature is presented in Appendix A.

Along with more traditional clinical outcomes in patients with CAD, health related quality of life (QoL) measured by presence of depression, anxiety and general health, differs by gender as well. Two studies reported that women with acute MI have higher level of depression, poorer psychosocial and worse general health in comparison with men (25-26). The Danish Multicenter Randomized Study on Thrombolytic Therapy versus Acute Coronary Angioplasty in Acute Myocardial Infarction (DANAMI 2) evaluated health related quality of life between genders after 12 months of PCI in patients with MI. It utilized the SF 36 validated questionnaire, which measures 8 domains of health status (physical functioning, role limitations due to physical problems, bodily pain, general health vitality, social functioning and role limitations due to emotional problems) and 2 summary scales (mental and physical composite scores) (27). The study found that women reported lower scores in all of 8 domains and in the summary scores than men (28).

Although several studies addressed the issue of gender differences in PCI, many of these studies investigated the differences as secondary research questions or as part of exploratory analyses. The 2005 American Heart Association's statement on PCI and adjunctive pharmacotherapy in women stressed the necessity to recruit more women into the studies to adequately power the studies to evaluate gender specific outcomes and differences (22).

Armenia. Armenia is a country in Southwestern Asia with about 3 million population (29). The burden of CAD in Armenia is significant as in the most of the world. In 2004 according to World Health Organization (WHO) statistics, in Armenia the proportionate mortality in adult population from CAD in women was higher than in men: 35.2% versus 37.0% (30). In 2008, the

proportionate morbidity of CAD was 32% and the proportionate mortality from CAD was 37% (31). Armenia also differs from other countries by its CAD risk profile – about 60% of men population are smokers in comparison to 2% in women, while the prevalence of overweight/obesity is higher in women than in men and comprise 42% versus 29% respectively (32).

The Nork Marash Medical Center (NMMC) is a comprehensive cardiac surgery center that serves both pediatric and adult population of Armenia. NMMC is the largest cardiac surgery center in Armenia with about 18 000 patient since its establishment in 1993. Approximately 300 patients undergo stent placement each year at NMMC, accounting for more than one-third of all patients undergoing PCI in Armenia annually. All procedures at NMMC conform to international guidelines. Its outcomes are comparable to those observed in large international cardiac centers (33). Considering the results from the past international studies and the lack of studies on gender differences in CAD treatment outcomes in Armenia, the effect of sex differences of PCI outcomes in patients in Armenia has yet to be determined. Moreover, it would be interesting to evaluate the perioperative differences and difference in the quality of life.

This study assessed gender differences in the long-term clinical and quality-of-life outcomes of PCI patients in Armenia treated at the NMMC. Specifically, the study

- Assessed sex differences in baseline characteristics upon admission;
- Assessed sex difference in average3 year event-free survival from the composite major adverse cardiac and cerebrovascular events (MACCE) which includes death, MI, repeat revascularization, stroke/transient ischemic attack (TIA)), in patients with CAD who had PCI at NMMC;

- Assessed gender differences in the quality of life (assessed by the SF-12) at 3 years of follow-up.

2. METHODS

Study design

The study utilized an observational, retrospective cohort design. The cohort included all patients who underwent PCI at NMMC from 2006-2008. Data about the MACCE was collected and compared between sexes at 3-5 years of follow-up using survival analysis. We selected such a range because short term outcomes have little clinical value and early differences in sexes disappear at long term follow-up. On the other hand one of the potential complications related to stent especially DES is late thrombosis, which mainly occurs after 1 year and more of stent placement.

Study population

Population setting was Armenia. *Target population* includes patients with CAD who underwent PCI and the *study population* was CAD patients who underwent PCI from 2006 to 2008 at NMMC. The study enrolled all PCI patients that had intervention at NMMC during the specified time period. Patients with missing contact information, missing medical records, outside of Armenia at the time of the study, those who do not speak Armenian.

Sampling frame and sampling method

The NMMC PCI patient computerized dataset for the period of time from 2006 to 2008 served as the sampling frame, with the inclusion of all patients who met the eligibility criteria.

The sample size calculation for survival analysis was conducted using the PS calculator by Dupont (34). The following assumptions were made: ratio of women to men in the sample equals to 1: 7 (3), Type 1 error (alpha) equal to 0.05, power equal to 0.8, the hazard rate of

mortality at 1-year of follow-up of women versus men equal to 0.55 (21). The calculated sample size was 703 (87 women and 616 men). Taking into account 73% response rate (35) and 90% eligibility rate, the required sample size was equal to 1070 (703/0.9*0.73) or 938 men and 132 women. Since the number of patients who had PCI during 2006 – 2008 periods in NMMC was smaller than the required sample size (n = 895, 803 mens and 92 womens), it was decided to enroll all patients who had intervention during the specified time period. Based upon that number and the prevalence of exposure variables in the sampling frame, the smallest detectable HR was 0.6 or 1.8 which was considered of statistical significance (Appendix G).

Study Variables

The dependant variables were 3 year average survival rate from MACCE, length of stay and in hospital and early operative complications and QoL. MACCE included death, MI, repeat revascularization and stroke/transient ischemic attack (TIA). A repeat revascularization was defined as a repeat (surgical or percutaneous) intervention. Operative complications were defined as all major events occurred within 30 days after the index stent placement procedure.

Independent variables were age, gender, cardiac status, ejection fraction, arrhythmia, BMI, current smoking status, family history of CAD, hypertension, hypercholesterolemia, nephropathy (by creatinine level), cerebrovascular disease, previous MIs, diabetes, previous interventions, number and type of the diseased vessels, stent type, stented vessels diameter, lesion length, as well as prescription of Aspirin, Tienopiridine derivatives, ACE inhibitors, beta blockers and statins at discharge (Appendix C).

Sources of data

Patient contact information was retrieved from the NMMC PCI dataset. A telephone survey was conducted for the evaluation of MACCE, prescribed medications, QoL, and socioeconomic status. In case of death, only the information about the date of death was asked from patient's family member. Information about the patients' perioperative characteristics was extracted retrospectively from the medical records.

Study instruments

Two instruments were developed for the study. An interviewer-administered structured questionnaire with two sections was used to collect data about patient quality of life (1^{st} section) measured by SF-12 (36) and MACCE (2^{nd} section) (Appendix D). Data from medical records was extracted to Medical Record Data Abstraction Forms (Appendix E) that included questions about demographic characteristics, cardiac status, CAD risk factors and comorbidities at admission and procedural characteristics. The name and contact information of the patients obtained for telephone interviews from NMMC dataset was registered in the specially developed Journal form (Appendix F).

Ethical Considerations

The research protocol was approved by the NMMC Administrative Board and by the Institutional Review Board/Committee on Human Research (IRB) within the College of Health Sciences at the American University of Armenia. The researcher followed the approved protocol. All participants were included into the study only after giving an oral consent (Appendix H). During the telephone interview the consent was obtained also for abstracting data

from the medical records. Although the collected data from the medical records included the information on patients' names and telephone numbers, these data were not entered into the computerized database; instead, coded patient identifiers were used. After data entry and cleaning, the paper forms containing respondent identifiers were destroyed. At this point anonymity was assured. When the patient contacted was identified as deceased by the relative, other than the date of death and permission to access patient's medical record, no further questioning was attempted and the call was ended after a condolence was expressed.

Data collection and data entry

Data collection was conducted between February 12 and April 14, 2011. Initial telephone interviews lasted on average 10 minutes. After conducting telephone interviews and receiving patient consent to access their medical records, perioperative data were extracted from the medical records. All data were entered into an SPSS 17 software package (SPSS Inc., Chicago IL) compatible data-file for analysis. Single data entry was performed. Logical and range checks were used for data cleaning. Following cleaning, a de-identified dataset was produced for the subsequent analyses.

Statistical analysis

In univariate analyses, continuous variables were presented as means and standard deviations and compared by the Student t-test; categorical variables were presented as counts and percentages and compared by the Chi-square test or by Fisher's exact test accordingly. The event-free survival rate was estimated by the Kaplan-Mayer product-limit method. Cox proportional hazard models were used to estimate unadjusted and adjusted hazard ratios of

MACCE at 3-5 year by gender. The variables with p value 0.2 - 0.25 or less were considered to be included into the model building (37). Models were adjusted for potential confounders, effect modifiers and checked for the proportionality assumption. All statistical analyses were performed using Stata10 software package (StataCorp. 2007. Stata Statistical Software: Release 10. College Station, TX: StataCorp LP).

3. RESULTS

Administrative data

Overall, 895 patients underwent PCI from 2006 to 2008 at NMMC, of whom 841 were residents of Armenia. Of those 841 patients, 314 were not possible to contact (out of the country, wrong numbers, no responders, numbers not provided, etc).

Of the 527 patient household contacted by phone, 42 patients had died, 456 completed the supplemental interview, and 23 refused to participate. Six cases were ineligible. Medical records were not found for 13 of the responders. The sample available for analysis was 485.

The difference in demographic characteristics of responders' vs non-responders were presented in Appendix B. Responders were on average 2.4 years older (($p<0.05$) from the non responders. The women to men ratio in a sample were 1:7, whereas in non responders it was 1:10. The sample over-represented responders from Yerevan versus other areas: 70% vs 30% in responders and 46% versus 54% in non responders.

After data collection and cleaning, two variables, hypercholesterolemia and acute MI type, had missing values exceeding 10 %. They were subsequently excluded from the analyses. The variable representing heart failure status was inconsistently reported in the medical records and also was excluded from the analyses.

Patient baseline and procedural characteristics

Among 485 participants included in the analysis 419 (86%) were men. Patients' baseline characteristics stratified by sex is presented in Table 1. Women on average were 5 years older than men, more hypertensive, more obese, and had significantly higher rates of diabetes. A

higher proportion of men were smokers, had a history of previous MI, PCI, and CABG. At admission, men presented with acute MI more frequently than women.

Some angiographic characteristics also differed between sexes. The average vessels diameter in women was smaller, but no differences were observed in average lesion length, in number of diseased vessel, and the types of stents implanted. In men and women, the most frequently stented vessel was the left anterior descending (LAD) artery. The average number of total stents placed was 1.1 stent per case for women and 1.3 stent per case for men ($p>0.05$).

No statistical significant differences were seen between women and men in medication at discharge including Aspirin, Tienopiridine derivatives, beta blockers, and statins. Women, however, had significantly higher rate of ACE inhibitors prescription at discharge than man.

Acute in-hospital and 30-day operative outcomes

30-day operative complications was noted in 3 women (4.52%) and in 23 men (5.5%, $p=0.7$). Overall, the following complications were observed: ventricular tachycardia/ventricular fibrillation (n=4); complete atriventricular blocks (n=2); hematoma at the intervention site (n=1), dissection (n=1), reperfusion syndrome (n=1), in stent thrombosis (n=2), TIA (n=1); acute renal failure (n=1), acute heart failure (n=1), LAD occlusion during coronary angiography (n=1) , recurrent MI (n=2), repeat revascularization (n=4). In hospital deaths occurred in 2 men. Death within 30 days after discharge occurred in 1 woman and 3 men. Hospital length of stay did not differ between genders and was on average 4.5 ±3.6 days for the total sample.

Event-free survival rates at long term follow-up

The median follow-up of the total sample was 1148 days with a range from 418 to 1917. The mean follow-up was 1267 ±321days for women and 1232± 321 days for men patients (p= 0.4). During follow up period, the total number of MACCE was 180 (Table 2). The event-free survival from MACCE at median follow was 79% (95% CI 0.66 -0.87) for women and 74% (95% CI 0.69-0.78) for men (Figure 1).

Multivariable modeling

The unadjusted predictors of long term survival (MACCE) were identified using univariate Cox proportional hazard models (Table 3). Significant predictors ($p<0.05$) of event-free survival were acute MI status, arrhythmia status, EF, number of diseased vessel and stent type.

After selecting variables that had p-value <0.25 and using backward selection method with the likelihood ratio test, the final model included arrhythmia, diabetes, and gender. A significant interaction was noted between gender and diabetes status (see Appendix I for model derivation process). From the final model (Table 3) adjusting for gender and diabetes, patients with arrhythmia had HR of 1.68 (95%CI: 1.1-2.57) for developing MACCE. Adjusting for arrhythmia, in patients with diabetes, men had better event-free survival from MACCE (HR =0.38, 95% CI: 0.18-0.8). In patients without diabetes, adjusting for arrhythmia men had HR of 2.6 (95%CI: 1.1-5.9) for developing MACCE. Men's diabetes status did not significantly affect risk of developing MACCE, but for women, being diabetic increased hazard of MACCE 6.79 times (Table 4 a,b).

Quality of life after PCI

The analysis of SF 12 questionnaire by item showed that at the end of follow up women provided significantly worse responses in 11 out of 12 items (Table 5a). Particularly, the role of physical limitations was more apparent among women. The analysis of composite scores also demonstrated statistically significant differences in both physical and mental scores, indicating worse scores for women (Table 5b).

4. DISCUSSION

This study sought to evaluate sex differences in 3 year event-free survival from MACCE in patients with CAD who had PCI at NMMC. For that purpose, an observational retrospective study was conducted.

The current study results showed that women on average were older than men, more hypertensive, more obese and had significantly higher rates of diabetes. Men were more likely to be smokers, and have a history of prior MI, PCI and CABG. These findings are consistent with many other trials (5-8). According to the literature, women receive less protocol-based medication upon discharge, such as ACE inhibitors, beta blockers, or statins (5, 9). However, the analysis showed that no genders differences existed in all but ACE inhibitor prescription rates that were more likely to be prescribed to women. This finding can be explained partially by the fact that more women had diabetes than men, and, based on the current evidence-based fuideline, ACE inhibitors are drug of choice in diabetes.

In multivariable analyses no significant differences were observed in early complication rates between genders. The studies done in contemporary PCI era also confirm that gender differences in early complication no longer exist after the adjustment for comorbidities and age (5, 20).

The sex differences in long-term outcomes became more debatable after the publication of FRISC II and Tactics TIMI 18 trials (12, 38). The debate on the validity of those findings continues. In current analysis the event-free survival at the end of follow-up was similar between genders, despite the fact that women had more risk factors than men. These results are in agreement with other studies, which showed that women gender was not an independent predictor of MACCE at long term follow up (16-18, 39), but run counter to the observations

seen in the FRISC II study. That RCT which involved unstable angina patients reported that at 1 year follow up women, unlike men, had worse outcome from invasive approach of treatment and benefited more from non invasive approach. In that study significant interaction between gender and treatment approach was reported (38). Those controversies could be as a result of difference in baseline characteristics within strata, observed in FRISC II. Thus, in FRISC II women in the conservative treatment group had more favorable risk profile (less have diabetes, previous MI, multivessel disease) than women in invasive arm. Regarding men, there were no baseline differences in risk factors between invasive and non invasive arms. More over difference in mortality rates among women between invasive and non invasive strategy was mainly attributed to CABG treatment, whereas in PCI group - difference was not observed.

A discrepancy between the current study results and a recent study done by Kovacic et al. was also observed. That large observational study demonstrated that women had inferior outcomes in terms of MI and death compared to men at 3 year follow-up (15). Such controversy may be explained by strong interaction between women gender and diabetic status, shown in the current analysis. In the study done by Kovacic et al. the proportion of diabetes among women patient comprised 47% whereas in most previous studies including our, it was 25-30%. In current study diabetic patients, the hazard of developing MACCE in women was 2.57 times higher than in men. Meanwhile, within non diabetic population, women had 2.6 less risk of developing MACCE. Similar results were shown by Mehilli at al., who evaluated the impact of gender on mortality rate after PCI in population with stable and unstable angina (21). They reported that diabetic women had almost twice hazard of mortality in comparison to diabetic men. No significant difference was observed in mortality rate by sex in the non diabetic population. In the present study diabetic status in men did not determine the outcome whereas

women with diabetes had almost 7 times higher risk of developing MACCE than those without diabetes. The negative impact of diabetes on women might be explained by its severity level among women. A study that evaluated DES effectiveness in acute coronary syndrome patients with diabetes, reported a 30:70 men to women ratio of insulin dependent diabetes and a 75:25 ratio among non insulin dependent diabetes (40). Although the present study did not evaluate whether patients had insulin dependent diabetes, this may explain the observed differences.

In contrast to other studies, age was not an independent predictor for MACCE in these findings. This lack may be explained by a small sample size or by the small proportion (< 1%) of patients over 75 years in the sample.

A previous study conducted in Armenia at NMMC in 2003, which evaluated one year survival after PCI and enrolled 160 patients, did not show any statistical differences in developing major adverse cardiac events (MACE) between sexes (35). The event-free survival from major adverse cardiac events (death /MI/ repeat revascularization) in that study at 12 months of follow-up was 92.1% (95% CI 86.5- 95.4); however, in the present study the one-year event-free survival from the MACCE lower - 87.6% (95% CI 80.9-87.4), possibly due to the inclusion of cerebrovascular events in this study.

The quality of life analysis showed that women had poorer mental and physical composite scores. Those data were inconsistent with results of another study, where the inferior QoL score for women persisted even after adjusting for age and clinical and psychosocial comorbidities (41). The significant difference between genders in QoL analysis in the present study is likely due to differential misclassification; all patients who developed stroke were men and several of them were not interviewed because of disabilities including impaired

speech function. Further analyses will be needed to compare adjusted quality of life between men and women.

One of the possible limitations of the study was that the follow up data about MACCE was collected retrospectively trough the telephone interviews, which could create recall and report biases. To minimize that bias we clarified outcome data from NMMC, if the patient he was re-hospitalized and treated there. Another source of potential bias came from the inaccuracies in medical records that, for example, did not consistently report heart failure status and blood lipid levels. About one third of the patients from the original sample were impossible to contact because of their inaccurate contact information, absence from the country, or changing addresses and phone numbers. The comparison of non-responders with the study population using NMMC patient registry information indicated that this population was on average 2 years younger ($p<0.05$) from the enrolled patients, and the difference was mainly attributed to the difference among male population, i.e in the study sample men were older, which means that predicting value of age might be diminished in the present study. The women men ratio in the current study was 1:6, whereas in overall sampling frame that was 1:9, which tell about over-representation of women population. The sample over-represents responders from Yerevan versus other areas responders, indicating that losses to follow-up were more likely for those living outside the capital. Hence the results are more applicable to the Armenia's capital city population rather than regions. On the other hand if the place of living had some impact on the event-free survival, then it might bias our results, because of over-representation of women.

Conclusions and recommendations

In this study, we assessed the difference in 3 year event free survival between sexes. Importantly, diabetes had a pronounced (HR = 6.8; 95%CI 2.5-18.4) effect on the likelihood of women suffering an adverse event, while having no effect on the men's risks. Women need heightened pre-operative assessment and post-operative follow-up, included aggressive management. Considering that the rate of PCI is lower in women and that non diabetic women show more beneficial outcomes from PCI, increasing women's appropriate and timely referral for PCI is suggested. Further research on diabetic populations, especially women, is necessary to characterize the nature, extent, and causal mechanism of this excess risk, also to expand its focus to CABG and non-invasive treatment approaches.

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Tables

Table 1. Baseline characteristics of patients

Patient characteristics*	**Men (n = 419)**	**Women (n=66)**	**P value**
Risk factors and comorbidities			
Age (years), mean±sd	58.3±9.4	63.5±8.5	<0.01
Family history of CAD	210 (53.4)	41 (65.1)	0.09
Current smoker	258 (63.9)	4 (6.2)	<0.01
Diabetes	58 (13.9)	24 (36.3)	<0.01
Hypertension	292 (69.6)	57 (86.4)	<0.01
BMI (kg/m^2), mean±sd	28.6± 4.1	30.4 ±5.3	<0.01
Stroke/TIA	33 (7.9)	8 (12.1)	0.26
Renal failure	3 (0.7)	0 (0.0)	0.49
Cardiac Status			
Acute MI	159 (37.9)	16 (24.2)	0.03
Prior MI	155 (37.2)	19 (28.7)	0.19
Unstable angina	187 (44.6)	35 (53.0)	0.20
Stable angina	56 (13.4)	16 (24.2)	0.02
Previous PCI	10 (2.4)	0 (0.0)	0.20
Previous CABG	24 (35.7)	2 (3.0)	0.36
EF, mean±sd	45.0±7.0	47.0±7.0	0.03
Arrhythmia	59 (14.2)	11 (16.7)	0.59
Angiographic characteristics			

Number of diseased vessels			
Single vessel	123 (30.2)	20 (31.8)	0.40
Double vessel	131 (39.6)	20 (31.8)	
Triple vessel	123 (30.4)	23 (36.5)	
Number of stents implanted			
One	281 (72.6)	37 (64.9)	
Two	93 (24.0)	17 (29.8)	0.40
Three	13 (3.4)	3 (5.3)	
Type of stented vessel			
LCX	130 (31.2)	19 (28.8)	0.45
LAD	221 (53.0)	45 (68.0)	0.02
RCA	125 (29.9)	18 (27.3)	0.65
Stent type			
DES	339 (81.8)	58 (87.8)	0.48
BMS	67 (16.2)	7 (10.6)	
Both	8 (1.9)	1 (1.5)	
Discharge medication			
Aspirin	384 (97.5)	63 (100.0)	0.20
Tienopiridine derivatives	382 (96.9)	62 (98.4)	0.50
Beta blockers	330 (83.7)	56 (88.9)	0.30
ACE inhibitors	259 (65.7)	50 (79.3)	0.03
Statins	340 (86.0)	52 (82.0)	0.40

**Results are presented as frequencies and percentages, unless specified otherwise.*

ACE: angiotensin converting enzyme; BMI: body mass index; BMS: bare metal stent; CABG: coronary artery bypass graft; CAD: coronary artery disease; DES: drug eluting stent; EF: ejection fraction; LAD: left anterior descending; LCX: left circumflex; MI: myocardial infarction; PCI: percutaneous coronary intervention; RCA: right coronary artery; TIA: transient ischemic attack.

Table 2. Distribution of major adverse cardiac and cerebro-vascular events between genders

Events, n (%)	Men (n=419)	Women (n=66)	P value
MI	26 (6.6)	5 (8.4)	0.8
RR (stent/CABG)	92 (23.0)	10 (16.9)	0.3
Death	31 (7.4)	7 (10.6)	0.3
Stroke/TIA	9 (2.3)	0 (0.0)	0.4
Total MACCE	158 (37.0)	22 (33.3)	0.9

CABG: coronary artery bypass graft; MACCE: major adverse cardiac and cerebro-vascular events; MI: myocardial infarction; TIA: transient ischemic attack.

Table 3. Univariate and multivariable survival analyses for MACCE

Variables	Unadjusted RR (95% CI)	p-value	Adjusted RR (95% CI)	p-value
Men gender	1.11 (0.71-1.82)	0.60	2.63 (1.2 – 5.9)	0.02
Age	0.99 (0.98-1.01)	0.70		
Family history of CAD	0.96 (0.69-1.35)	0.80		
Current smoker	0.98 (0.97-1.37)	0.90		
Diabetes	1.28 (0.85-1.93)	0.20	6.01 (2.3 – 15.9)	<0.01
Hypertension	1.17 (0.81-1.71)	0.40		
BMI	1.01 (0.96-1.04)	0.90		
Stroke/TIA	1.23 (0.72-2.11)	0.40		
Acute MI	1.58 (1.14-2.21)	<0.01		
Past MI	1.08 (0.77-1.51)	0.60		
Unstable angina	0.86 (0.62-1.19)	0.40		
Stable angina	0.78 (0.48-1.27)	0.30		
Arrhythmia	1.65 (1.08-2.52)	0.02	1.68 (1.11-2.61)	0.02
Previous PCI	1.01 (0.31-3.16)	0.90		
Previous CABG	1.16 (0.59-2.28)	0.60		
EF	0.97 (0.95-0.99)	0.02		
Number of diseased vessels				
Two vessels	1.68 (1.08-2.61)	<0.01		
Tree vessels	2.13 (1.36-3.31)	<0.01		
Number of stented placed				

Two	0.80 (0.53-1.21)	0.30		
Tree	1.08 (0.47-2.41)	0.80		
Stent type (BMS reference)				
DES	0.57 (0.39-0.84)	<0.01		
Both	0.76 (0.23-2.51)	0.6		
LCX stent	0.98 (0.69-1.41)	0.9		
LAD stent	0.76 (0.55-1.05)	0.10		
RCA stent	1.28 (0.91-1.81)	0.20		
Gender and diabetes interaction	-		0.14 (0.04-0.42)	<0.01

BMI: body mass index; BMS: bare metal stent; CABG: coronary artery bypass graft; CAD: coronary artery disease; DES: drug eluting stent; EF: ejection fraction; LAD: left anterior descending; LCX: left circumflex; MI: myocardial infarction; PCI: percutaneous coronary intervention; RCA: right coronary artery; TIA: transient ischemic attack.

Table 4a. Interaction between diabetes and sex to develop MACCE by diabetes status

Sex	Diabetes	Unadjusted HR (95%CI)	Unadjusted Interaction Term HR (95%CI)	Adjusted HR (95%CI)*	Adjusted Interaction Term HR (95% CI)
Men	Yes	0.84 (0.49- 1.44)	0 .14 (0.05 - 0.42)	0.86 (0.50-1.48)	0.14 (0.05 - 0.43)
	No	1.00		1.00	
Women	Yes	6.79 (2.50-18.43)		6.85 (2.5- 18.74)	
	No	1.00		1.00	

* Adjusted for arrhythmia

Table 4b. Interaction between diabetes and sex to develop MACCE by sex

Diabetes	Sex	Unadjusted HR (95%CI)	Unadjusted Interaction Term HR (95%CI)	Adjusted HR (95%CI)*	Adjusted Interaction Term HR (95% CI)
Yes	Men	0.38(0.18-0.80)	0 .14 (0.05 - 0.42)	0.39 (0.18-0.82)	0.14 (0.05 - 0.43)
	Women	1.00		1.00	
No	men	2.64 (1.16-6.03)		2.61 (1.14-5.96)	
	women	1.00		1.00	

* Adjusted for arrhythmia

Table 5a. SF 12 items by gender

SF 12 Domain & items	Men n (%)	Women (%)	P value
General health			
Excellent	14 (3.65)	0 (0.00)	
Very Good	37 (9.64)	1 (1.69)	
Good	220 (57.29)	29 (49.15)	0.02
Fair	94 (24.48)	20 (33.90)	
Poor	19 (4.95)	9 (15.25)	
Limitation of daily activities			
Moderate activities			
Limited a lot	79 (20.52)	24 (40.68)	
Limited a little	143 (37.14)	23 (38.98)	0.001
Not limited at all	163 (42.34)	12 (20.34)	
Climbing several flights of stairs			
Limited a lot	98 (25.45)	27 (45.76)	
Limited a little	144 (37.40)	25 (42.37)	0.001
Not limited at all	142 (36.88)	7 (11.86)	
Role of physical limitation			
Accomplished less than you would like			
All of the time	31 (8.07)	15 (25.86)	
Most of the time	41 (10.68)	14 (24.14)	< 0.001
Some of the time	72 (18.75)	8 (13.79)	
A litle of the time	80 (20.83)	8 (13.79)	
None of the time	159 (41.41)	13 (22.41)	
Were limited in the kind of work or other activities			
All of the time	30 (7.81)	14 (24.14)	
Most of the time	45 (11.72)	13 (22.41)	< 0.001
Some of the time	74 (19.27)	13 (22.41)	
A litle of the time	77 (20.05)	9 (15.52)	
None of the time	158 (41.15)	9 (15.52)	
Role of emotional limitation			
Accomplished less than you would like			
All of the time	12 (3.13)	7 (12.07)	
Most of the time	41 (10.70)	9 (15.52)	0.02
Some of the time	75 (19.58)	12 (20.69)	
A litle of the time	71 (18.54)	15 (25.86)	
None of the time	184 (48.04)	15 (25.86)	
Didn't do work or other activities as carefully as usual			
All of the time	7 (1.83)	8 (13.79)	
Most of the time	34 (8.90)	8 (13.79)	
Some of the time	57 (14.92)	11 (18.97)	< 0.001
A litle of the time	78 (20.42)	15 (25.86)	
None of the time	206 (53.93)	16 (27.59)	
Bodily pain			

Not at all	150	(39.06)	16	(27.59)	
A little bit	96	(25.00)	9	(15.52)	
Moderately	77	(20.05)	16	(27.59)	0.015
Quite a bit	48	(12.50)	11	(18.97)	
Extremely	13	(3.39)	6	(10.34)	
Vitality					
Did you have a lot of energy?					
All of the time	41	(10.70)	1	(1.72)	
Most of the time	101	(26.37)	7	(12.07)	
Some of the time	124	(32.38)	17	(29.31)	0.001
A litle of the time	81	(21.15)	24	(41.38)	
None of the time	36	(9.40)	9	(15.52)	
Mental health					
Have you felt calm and peaceful?					
All of the time	48	(12.53)	2	(3.45)	
Most of the time	111	(28.98)	17	(29.31)	
Some of the time	120	(31.33)	16	(27.59)	0.147
A litle of the time	73	(19.06)	17	(29.31)	
None of the time	31	(8.09)	6	(10.34)	
Have you felt downhearted and depressed?					
All of the time	30	(7.83)	7	(12.07)	
Most of the time	52	(13.58)	12	(20.69)	
Some of the time	111	(28.98)	23	(39.66)	
A litle of the time	133	(34.73)	12	(20.69)	0.039
None of the time	57	(14.88)	4	(6.90)	
Social functioning					
How much physical health or emotional problems interfered with your social activities?					
All of the time	19	(4.96)	14	(24.14)	
Most of the time	38	(9.92)	7	(12.07)	
Some of the time	55	(14.36)	11	(18.97)	< 0.001
A litle of the time	75	(19.58)	8	(13.79)	
None of the time	196	(51.17)	18	(31.03)	

Table 5b. QoL mental and physical composite scores

Composite scores	Men (n=419)	Women (n=66)	P value
Physical composite score	43.8± 10.7	37.0± 11.3	<0.001
Mental composite score	46.8 ± 10.6	40.8± 11.1	<0.001

**Results are presented as means ± standard deviations.*

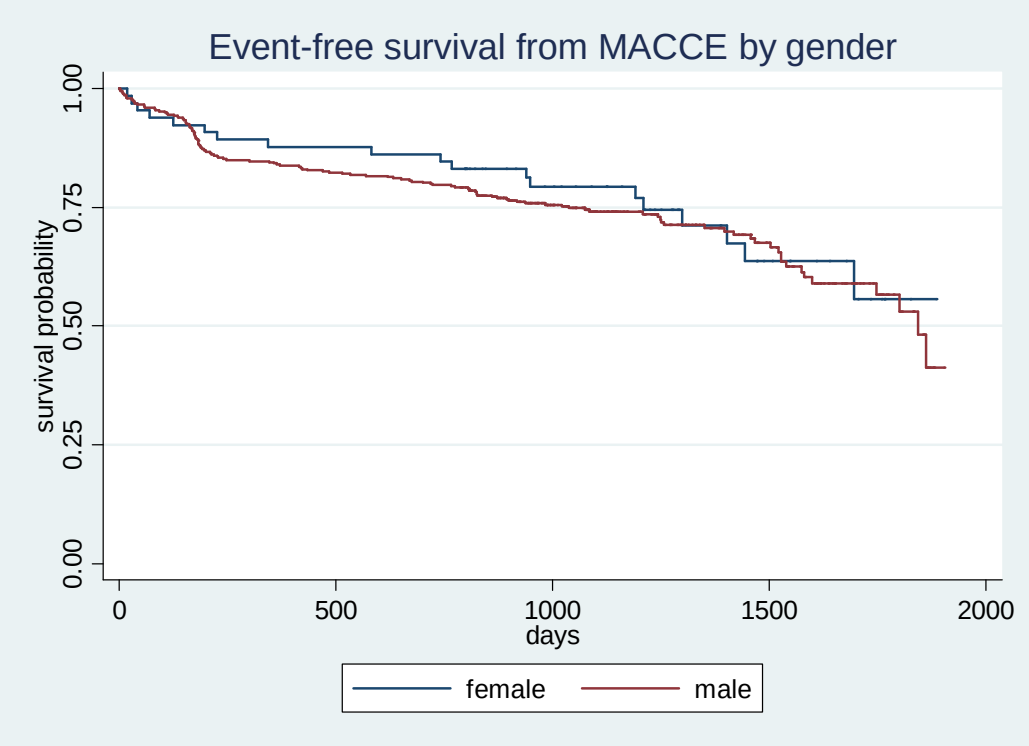
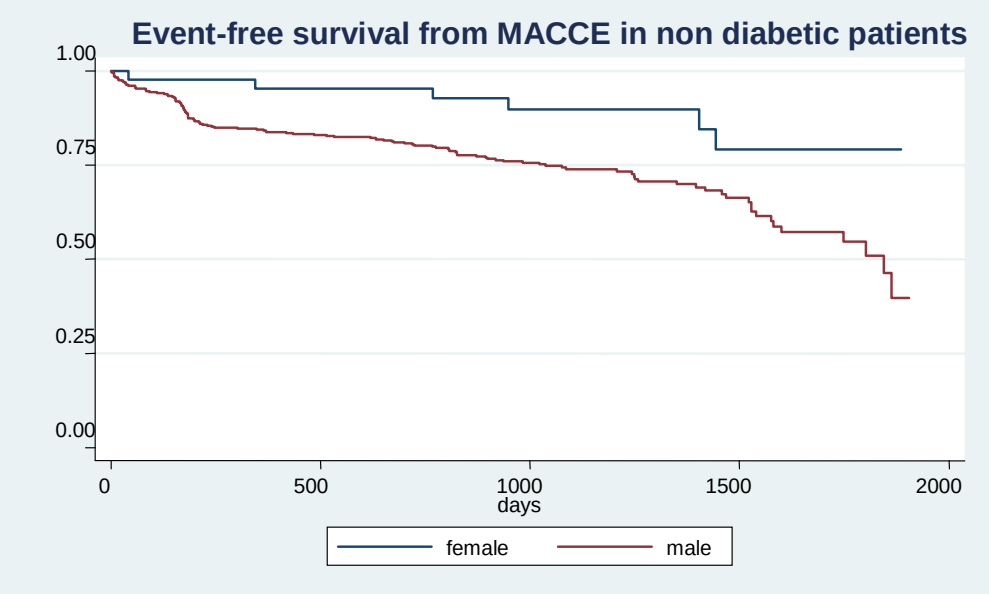
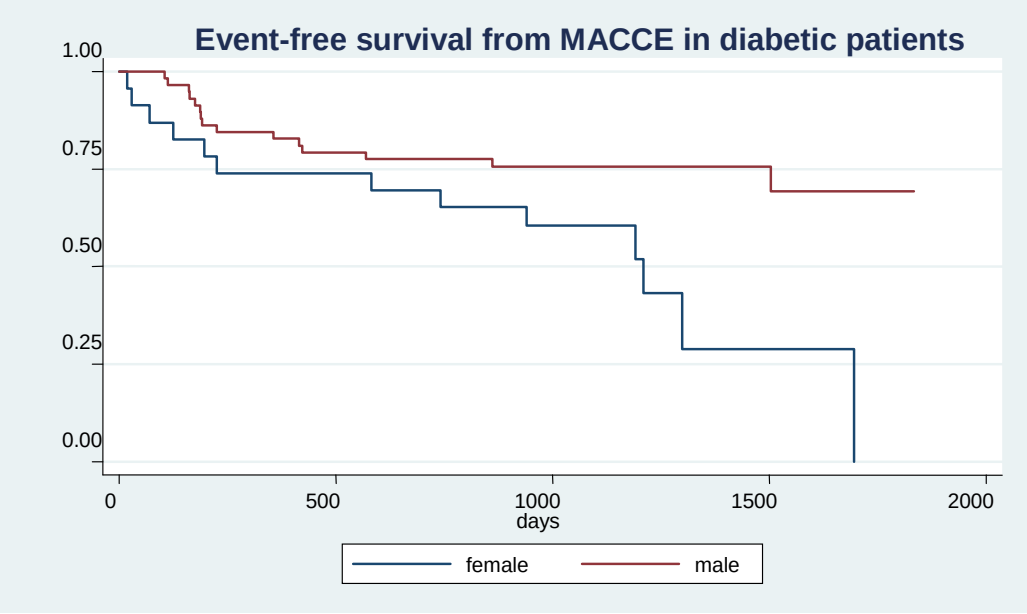


Figure 1. Event-free survival from MACCE by gender (unadjusted)

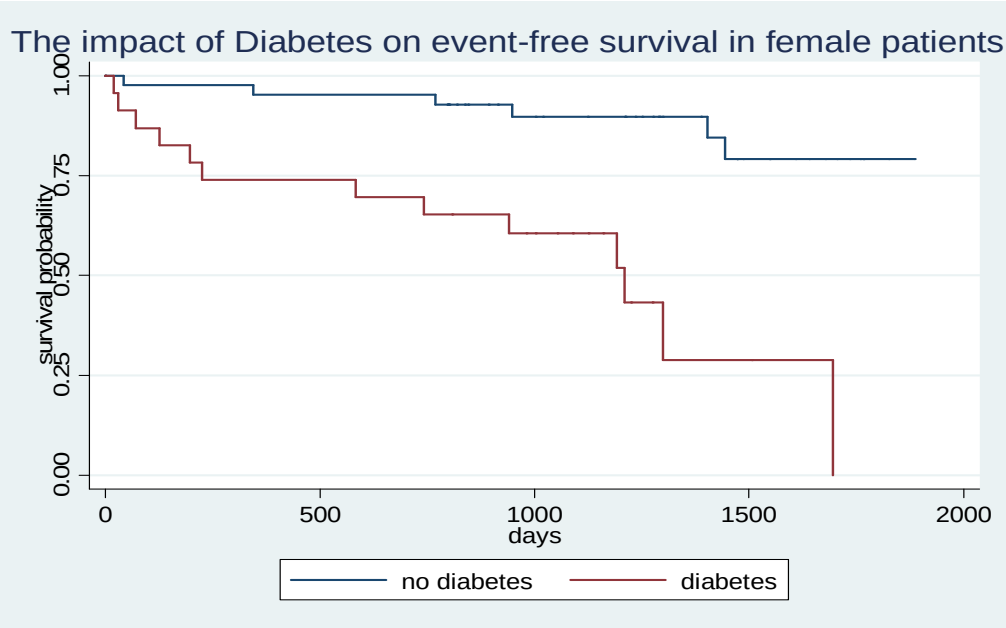


A

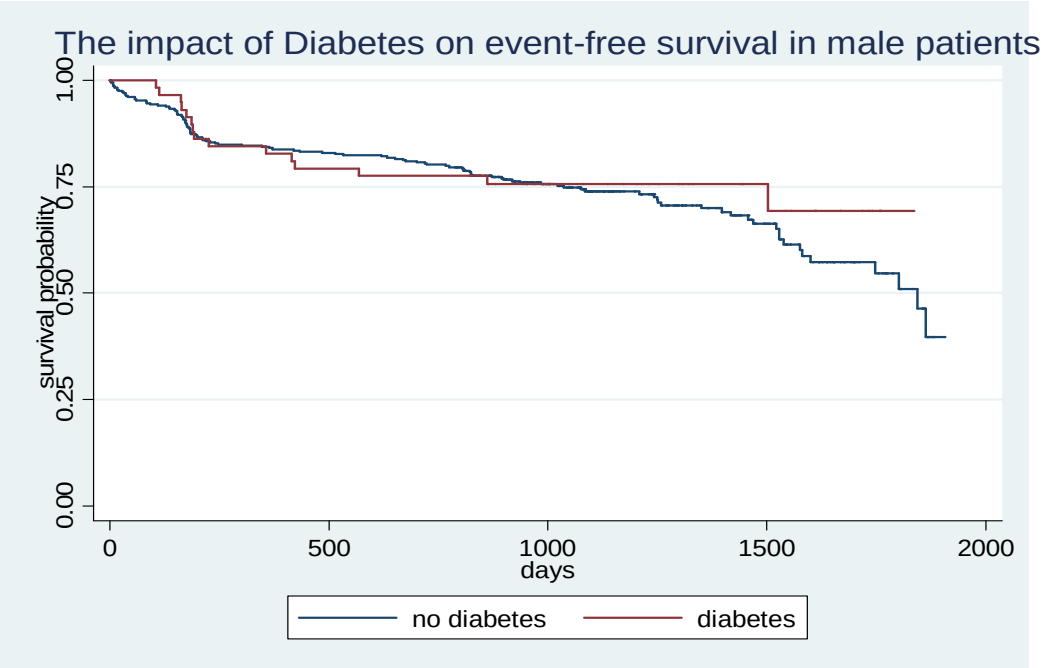


B

Figure 2. Unadjusted event-free survival from MACCE by gender for patients without (A) and with diabetes (B).



A



B

Figure 3. Unadjusted event-free survival from MACCE by diabetes status for men (A) versus women patients (B).

Appendices

Appendix A. Review of literature for PCI outcome differences by gender

Author, Year, Country	Study type	Details	Results
Lagerqvist et al, 2001, Sweden (38)	RCT : "FRISC II"	**Target population:** Patients with unstable angina **Intervention**: invasive or noninvasive treatment **Primary end points:** 1 year - death or nonfatal MI	**Primary end-points**: invasive vs. noninvasive women: 12.4% vs. 10.5%, NS men: 9.6% vs. 15.8%, $p < 0.001$. Interaction analysis: different effect of the early invasive strategy for the two genders ($p = 0.008$).
Clayton et al, 2004, UK(42)	RCT: "RITA 3"	**Target population:** Patients with NSTMI and unstable angina. **Intervention**: invasive or noninvasive treatment **Primary end points:** 1 year - death or MI	**Primary end-points:** invasive vs. noninvasive adjusted OR men 0.63, 95% CI 0.41-0.98 women 1.79, 95% CI 0.95-3.35 interaction p-value=0.007
Glaser et al, 2002 US(12)	RCT: "TACTICS-TIMI 18"	**Target population:** Patients with ACS. **Intervention**: invasive or noninvasive treatment **Primary end points:** 6 month- death, MI or revascularization	**Primary end-points:** invasive vs. noninvasive adjusted OR women 0.72; 95% CI 0.47-1.11 men 0.64; 95% CI, 0.47-0.88; P =.60 for sex interaction
Lansky et al, 2005, US (43).	RCT: "TAXUS-IV"	**Target population:** All patients with PCIs **Intervention**: BMS vs DES (n=1326). **Primary end points:** 30 day and 1 year -death, MI, TVR, TLR, MACE, stent thrombosis	**Primary end-points:** DES arm women TLR and TVR (7.6% and 10.8 %) men (3.2 and 5.7) adjusted HR 0.89, ($p = 0.76$)
Motovska et al, 2007, Czeck(44)	RCT : "PRAGUE1 and 2"	**Target population:** Patients with STEMI. **Intervention**: PCI vs. trombolysis **Primary end points:** death at 30 day	**Primary end points:** in the PCI group women 8.2% men 6.2%, $p=0.4$
Blomkalns et al. 2005, US (6)	Observational: "CRUSADE" registry	**Target population:** Patients with NSTMI. **Intervention**: PCI **Primary end points:** in	**Primary end points:** Women vs. men: unadjusted in-hospital death (5.6% vs. 4.3%), reinfarction (4.0% vs. 3.5%), heart failure (12.1% vs. 8.8%), stroke

		hospital outcomes	(1.1% vs. 0.8%), and RBC transfusion (17.2% vs. 13.2%). After adjustment, only transfusion was higher in women.
Duvernoy et al, 2010, US (5)	Observational: Prospective registry	**Target population:** all PCI patients n=22700. **Intervention**: PCI **Primary end points:** in-hospital all-cause mortality; and complications.	(**Primary end points:** OR): Vascular complication 2.82 Post procedure transfusion 2.04. GI bleeding 1.56. Infection and/or sepsis 1.46. Stroke or TIA 2.16 MACE and death N.S.
Mehilli et al, 2003, Germany(21)	Observational: prospective study	**Target population:** Patients with stable and unstable angina n= 4374. **Intervention**: PCI **Primary end points:** restenosis at 1 year	**Primary end points:** women vs. men Clinical restenosis 14.8% vs. 17.5% (*P*=0.048). Angiographic restenosis (28.9% vs. vs. 33.9%, *P*=0.01). Adjusted OR 0.77 (95% CI 0.63 to 0.93).
Peterson et al, 2001, US (23)	Observational: prospective NCN Database	**Target population:** Patient with stable angina n=109,708 **Intervention**: PCI **Primary end points:** in hospital events:	**Primary end points:** men vs. women Stroke 0.2% vs. 0.4%;adj OR 1.36 (CI 1.1, 1.7). MI 1.2% vs. 1.5%, adj OR 1.25 (CI 1.1, 1.4). Vascular complicat. 2.7% vs. 5.4% adj. OR 1.48 (CI1.3, 1.7) Repeat revascularization 4.4% vs. 4.8% adj. OR 1.13 (CI1.1, 1.2). In-hospital death 1.0% vs.1.8% adj. OR 1.07 (CI 0.9, 1.2).
Alfredsson, 2007, Sweden (11)	Observational: prospective study	**Target population:** Patients with unstable angina or NSTEMI. n= 53 781. **Intervention**: PCI **Primary end points:** in-hospital, 30-day and 1-year mortality, treatment intensity	**Primary end points:** 1 year mortality higher in men (OR 1.12; 95% CI, 1.06 to 1.19). In hospital and 30 d mort - NS
Onuma et al, 2009, Netherland (16)	Observational: retrospective cohort registry	**Target population:** Patients with PCI, n= 4936. **Intervention**: BMS vs DES **Primary end points:** 3 year – death, MI, TVR	**Primary end points** no differences between gender
Tillmanns et al, 2005, Germany (17)	Observational: prospective registry	**Target population:** Patients with STEMI, PCI n=208 **Intervention**: PTCA **Primary end points:** 30d and 4 y outcome.	**Primary end points:** women vs. men Total cumulative mortality during 4 years of follow-up was 12.5%, 14.5%, 18% and 23%, respectively, versus 9%, 10.5%, 12% and 15%, respectively. NS after adjustment.

Antoniucci et al, 2003, Italy (18)	Observational: prospective study	**Target population:** Patients with acute MI. **Intervention**: PCI **Primary end points:** Reinfarction and mortality at 6 month.	**Primary end points:** NS
Roncalli et al., 2010, France(45)	Observational: prospective study	**Target population:** Patients with PCI stent n= 9089. **Intervention**: emergency PCI vs. non emergency PCI **Primary end points:** In hospital death	**Primary end points:** Emergency PCI group men 2.2%; women 4.9% (p = 0.004) non-emergency PCI group men 0.4%; women 0.5% (p = 0.77)
Kovacic, J.C., et al., 2010 US (15)	Observational: prospective study	**Target population:** Patients with PCI stent n= 16961. **Intervention**: PCI **Primary end points:** 3y outcome	**Primary end points:** men vs. women Overall death 8.4% vs.10.3%(p = 0.0002) Cardiac death 2.3% vs.3.2% (p = 0.002) MI 0.9% vs. 1.4% (p = 0.01)

ACS- acute coronary syndrome, BMS - bare metal stents, CI – confidence interval, CRUSADE - Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes with Early Implementation, DES – drug eluting stents, FRISC II - Framingham and Revascularization during Instability in Coronary artery disease II, HR –hazard ratio, MACE – major adverse cardiac events, NCN - National Cardiovascular Network, OR – odds ratio, RBC – red blood cells, RITA - Randomized Intervention Trial of unstable Angina, STEMI – ST elevation myocardial infarction, , TACTICS-TIMI 18 - Treat angina with Aggrastat and determine Cost of Therapy with an Invasive or Conservative Strategy – Thrombolysis In Myocardial Infarction 18, TAXUS Treatment of De Novo Coronary Disease With a Single Paclitaxel-Eluting Stent, TLR – target lesion revascularization, TVR – target vessel revascularization.

Appendix B. Differences in demographic parameters between responders and non-responders

Demographics	Responders	Non responders	P value
Men :Women ratio	1:6	1:10	<0.05
Yerevan city : Other area ratio	70:30	46:54	<0.05
Age, mean ±sd	59±9.5	56±9.2	<0.05
Men	58.3±9.4	56.2±9.1	
Women	63.5±8.5	63.1±8.6	

sd: standard deviation

Appendix C. Dependent and independent study variables

Variable	Type	Measure	Source
Dependant			
MACCE	Binary	1=Yes 0= No	Telephone interview Medical records
Early complications	Binary	1=Yes 0= No	Medical records Telephone interview
LOS	Numeric (continuous)	Days	Medical records
Quality of Life General Health	Ordinal	1=Excellent 2=Very Good 3=Good 4=Fair 5=Poor	Telephone interview
Limitation of daily activities	Ordinal	1=Limited a lot 2=Limited a little 3=Not limited at all	Telephone interview
Role of physical limitation (How much of the time accomplished less than you would like/ Were limited in the kind of work or other activities)	Ordinal	1=All of the time 2=Most of the time 3=Some of the time 4=A little of the time 5=None of the time	Telephone interview
Role of emotional limitation (Accomplished less than you would like/Didn't do work or other activities as carefully as usual)	Ordinal	1=All of the time 2=Most of the time 3=Some of the time 4=A little of the time 5=None of the time	Telephone interview
Bodily pain	Ordinal	1=Not at all 2=A little bit 3=Moderately 4=Quite a bit 5=Extremely	Telephone interview
Vitality (Did you have a lot of energy?)	Ordinal	1=All of the time 2=Most of the time 3=Some of the time 4=A little of the time 5=None of the time	Telephone interview
Mental health Have you felt calm and peaceful?	Ordinal	1=All of the time 2=Most of the time 3=Some of the time	Telephone interview

		4=A little of the time 5=None of the time		
Have you felt downhearted and depressed?	Ordinal	1=All of the time 2=Most of the time 3=Some of the time 4=A little of the time 5=None of the time		Telephone interview
Social Functioning How much physical health or emotional problems interfered with your social activities?	Ordinal	1=All of the time 2=Most of the time 3=Some of the time 4=A little of the time 5=None of the time		Telephone interview
Independent				
Age	Numeric (continuous)	Years		Medical record
Sex	Binary	1=Men	0=Women	Medical record
BMI	Numeric (Continuous)	kg/m2		Medical record
EF	Numeric (Continuous)	%		Medical record
Smoking status at the time of intervention	Binary	1=Yes 0= No		Medical record
Stable angina	Binary	1=Yes 0= No		Medical record
Unstable angina	Binary	1=Yes 0= No		Medical record
Acute MI	Binary	1=Yes 0= No		Medical record
Previous MI	Binary	1=Yes 0= No		Medical record
Arrhythmia	Binary	1=Yes 0= No		Medical record
Family history	Binary	1=Yes 0= No		Medical record
Hypertension	Binary	1=Yes 0= No		Medical record
Diabetes	Binary	1=Yes 0= No		Medical record
Cerebrovascular disease	Binary	1=Yes 0= No		Medical record
Renal dysfunction	Binary	1=Yes 0= No		Medical record

Previous PCI/CABG	Binary	1=Yes 0= No	Medical record
Number of diseased vessel	Nominal	1=Single 2=Double 3=Triple	Medical record
Number of stents placed	Nominal	1=One 2=Two 3=Three	Medical record
Stent Type	Nominal	0=BMS 1= DES 2 = Both	Medical record
LAD	Binary	1=Yes 0= No	Medical record
RCA	Binary	1=Yes 0= No	Medical record
LCX	Binary	1=Yes 0= No	Medical record
Aspirin	Binary	1=Yes 0= No	Medical record
Tienopiridine derivates	Binary	1=Yes 0= No	Medical record
ACE inhibitors	Binary	1=Yes 0= No	Medical record
Beta blockers	Binary	1=Yes 0= No	Medical record
Statins	Binary	1=Yes 0= No	Medical record
Physically active days per week	Numeric	Days	Telephone interview
Duration of physical activity	Numeric (Continuous)	Minutes	Telephone interview
SES (total monthly income of household)	Ordinal	1= <30.000AMD 2=31.000– 100.000 3=101.000-250.000 4=>250.000AMD	Telephone interview

ACE: angiotensin converting enzyme; BMI: body mass index; BMS: bare metal stent; CABG: coronary artery bypass graft; CAD: coronary artery disease; DES: drug eluting stent; EF: ejection fraction; LAD: left anterior descending; LCX: left circumflex; LOS: length of in hospital stay; MACCE: major adverse cardiac and cerebrovascular events; MI: myocardial infarction; PCI: percutaneous coronary intervention; RCA: right coronary artery; TIA: transient ischemic attack, SES: socioeconomic status.

Appendix D. Patient Interview Questionnaire (English versions)

Questionnaire #_____ ID#_____ Start time of the interview (minutes) _____

Day of the interview (day/month/year) _____ End time of the interview (minutes) _____

General health (SF12)

Q#1. In general, would you say your health is?

.Excellent…..1 Very Good…..2 Good….3 Fair….4 Poor…5

Q# 2. The following items are about activities you might do during a typical day. Does <u>your health now limit you</u> in these activities? If so, how much?

		Yes, Limited A Lot	Yes, Limited A Little	No, Not Limited At All
a.	**Moderate activities**, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	1	2	3
b.	Climbing **several** flights of stairs	1	2	3

Q#3. During the <u>past 4 weeks</u>, how much of the time have you had any of the following problems with your work or other regular daily activities <u>as a result of your physical health</u>?

		All of the Time	Most of the Time	Some of the Time	A Little of the Time	None of the Time
a.	**Accomplished less** than you would like	1	2	3	4	5
b.	Were limited in the **kind** of work or other activities	1	2	3	4	5

Q#4. During the <u>past 4 weeks</u>, how much of the time have you had any of the following problems with your work or other regular daily activities <u>as a result of any emotional problems</u> (such as feeling depressed or anxious)?

		All of the Time	Most of the Time	Some of the Time	A Little of the Time	None of the Time
a.	**Accomplished less** than you would like	1	2	3	4	5
b.	Didn't do work or other activities as **carefully** as usual	1	2	3	4	5

Q#5. During the <u>past 4 weeks</u>, how much did <u>pain</u> interfere with your normal work (including both work outside the home and housework)?

Not at all….1 A little bit….. 2 Moderately…..3 Quite a bit…….4 Extremely…..5

Q#6. These questions are about how you feel and how things have been with you <u>during the past 4 weeks</u>. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the <u>past 4 weeks</u> –

		All of the Time	Most of the Time	Some of the Time	A Little of the Time	None of the Time
a.	Have you felt calm and peaceful?	1	2	3	4	5
b.	Did you have a lot of energy?	1	2	3	4	5
c.	Have you felt downhearted and depressed?	1	2	3	4	5

Q#7. During the <u>past 4 weeks</u>, how much of the time has your <u>physical health or emotional problems</u> interfered with your social activities (like visiting with friends, relatives, etc.)?

All of the time….1 Most of the time….2 Some of the time….3 A little of the time….4 None of the time….5

Q#8. Are the results from your heart stenting:

Worse than you expected….1 About what you expected…. 2 Better than you expected….3

Compliance with medications and recommendations

Q#9. After your intervention have you been prescribed Clopidogrel (PLAVIX) by your doctor?

0. NO □ 1. YES □, *if yes →Q#11a*

Q#9a. For how long?

1. 0-3 months □ 3. 6-9 months □
2. 3-6 months □ 4. 9-12 months □

9b. How long did you actually administer Clopidogrel?

1. 0-3 months □ 3. 6-9 months □
2. 3-6 months □ 4. 9-12 months □

Q#10. Are you currently smoking?

0. NO □ 1. **YES** □

if yes, how many cigarettes per day?

1. < 10 cig/ day □ 2. 10 - 20 cig/day □ 3. 20 - 30 cig/day □ 4. > 30 cig/ day □

For how long? _____years

Q#11. During the last 7 days, on how many days did you walk for at least 10 minutes at a time?

Days per week _____

Don't Know/Not Sure □

Refused □

Q#12. How much time did you usually spend walking on one of those days?

Hours per day __ __ Minutes per day __ __ __

Don't Know/Not Sure □

Refused □

Readmissions

Q#13. We want to know if after your intervention at the NMMC till now you had ANY hospital admission for:

MI	0. No□	1. Yes□	If Yes, date_YY MM_____
Repeat stenting	0. No□	1. Yes□	If Yes, date_YY MM_____
CABG	0. No□	1. Yes□	If Yes, date_YY MM_____
Stroke	0. No□	1. Yes□	If Yes, date_YY MM_____
Other reason	0. No □	1. Yes □	If Yes, date_YY MM_____

Specify the reason _____

Working status and income

Q#14. Are you currently working?

0. NO□ 1. YES □

Q#15. From the following categories which one best describes your household total monthly income in 2010?

1. < 30,000 AMD □
2. 31,000 – 100,000 AMD □
3. 101,000 -250,000 AMD □
4. > 250,000 AMD □
5. Don't know □

Q#16. Your family's general standard of living:

1. Substantially below average
2. Little below average
3. Average
4. Little above average
5. Substantially above average

Armenian Version

Հեռախոսային հարցման հարցաթերթիկ Հարցաթերթիկի #_____ ՏՀ#_____

Հարցման ամսաթիվը _____ (օր/ամիս/տարի)

Հարցման սկիզբը _____ (ժամ/րոպե) Հարցման ավարտը _____ (ժամ/րոպե)

SF12

Q#1. Ինչպե՞ս կգնահատեիք Ձեր առողջությունն ընդհանուր առմամբ:

Գերազանց – 1 Շատ լավ – 2 Լավ – 3 Ոչ այնքան լավ – 4 Վատ - 5

Q#2. Ստորև թվարկված են մի քանի առօրյա գործողություններ: Արդյո՞ք Ձեր ներկայիս առողջական վիճակը խանգարում է Ձեզ՝ կատարել այդ գործողությունները: Եթե այո, որքանո՞վ:

	ԳՈՐԾՈՂՈՒԹՅՈՒՆՆԵՐ	Այո, շատ է խանգարում	Այո, քիչ է խանգարում	Ոչ, ամենևին չի խանգարում
ա.	**Միջին ակտիվության գործողություններ**, օր՝ սեղան տեղաշարժել, փոշեծծիչով մաքրել, սեղանի թենիս խաղալ կամ պարտեզում աշխատել	1	2	3
բ.	Աստիճաններով բարձ անալ մի քանի հարկ	1	2	3

Q#3. Արդյո՞ք վերջին 4 շաբաթվա ընթացքում որքա՞ն ժամանակ եք ունեցել Ձեր աշխատանքի կամ ամենօրյա այլ գործերի հետ կապված հետևյալ դժվարություններից որևէ մեկը կամ մի քանիսը՝ Ձեր առողջական վիճակի հետևանքով:

	Ամբողջ ժամանակ	Ժամանակի մ ծ մասը	Ժամանակի որ շ մասը	Ժամանակի փոքր մասը	Ոչ մի ժամանակ
Կատարել եք ավելի քիչ, քան կցանկանայիք	1	2	3	4	5
Ի վիճակի չեք եղել կատարել **որոշակի տիպի** աշխատանք կամ այլ գործեր	1	2	3	4	5

Q#4. Արդյո՞ք վերջին 4 շաբաթվա ընթացքում որքա՞ն ժամանակ եք ունեցել Ձեր աշխատանքի կամ ամենօրյա այլ գործերի հետ կապված հետևյալ դժվարություններից որևէ մեկը կամ մի քանիսը՝ որևէ հուզական վիճակի (օրինակ՝ ընկճվածության կամ մտահոգվածության) հետևանքով:

	Ամբողջ ժամանակ	Ժամանակի մեծ մասը	Ժամանակի որոշ մասը	Ժամանակի ոքր մասը	Ոչ մի ժամանակ
Կատարել եք ավելի քիչ, քան	1	2	3	4	5

կցանկանայիք

Սովորականից պակաս **ուշադրությամբ** եք կատարել աշխատանքը կամ այլ գործեր 1 2 3 4 5

Q#5. Վերջին 4 շաբաթվա ընթացքում որքանո՞վ է ցավը խանգարել Ձեր նորմալ աշխատանքին (ինչպես տանը, այնպես էլ՝ տնից դուրս):

Ամենևին 1 Թեթևակի 2 Չափավոր 3 Բավականին 4 Չափազանց 5

Q#6. Հետևյալ հարցերը վերաբերում են Ձեր ինքնազգացողությանը վերջին 4 շաբաթվա ընթացքում: Խնդրում ենք յուրաքանչյուր հարցի համար ընտրել այն միակ պատասխանը, որն ամենից մոտ է Ձեր զգացածին:

Վերջին 4 շաբաթվա ընթացքում որքա՞ն ժամանակ եք Դուք...

	Ամբողջ ժամանակ	Ժամանակի մեծ մասը	Ժամանակի որոշ մասը	Ժամանակի փոքր մասը	Ոչ մի ժամանակ
ա. զգացել հանգիստ ու խաղաղ	1	2	3	4	5
բ. եղել շատ առույգ	1	2	3	4	5
գ. եղել սրտնեղած ու տխուր	1	2	3	4	5

Q#7.Վերջին 4 շաբաթվա ընթացքում Ձեր առողջական կամ հուզական խնդիրները որքա՞ն ժամանակ են խանգարել Ձեր շփումներին շրջապատի հետ (օրինակ՝ չեք կարողացել այցելել ընկերներին, բարեկամներին և այլն):

Ամբողջ ժամանակ 1 Ժամանակի փոքր մասը 4

Ժամանակի մեծ մասը 2 Ոչ մի ժամանակ 5

Ժամանակի որոշ մասը 3

Q#8. Ձեր ստենտավորումից հետո ստացված արդյունքները

1. Ձեր սպասվածից ավելի վատ էին ☐

2. Համարյա նույն էին ինչ Դուք սպասում էիք ☐

3. Ձեր սպասվածից ավելի լավ էին ☐

Q#9. Ձեր ստենտավորումից հետո Ձեզ բժիշկը նշանակե՞լ է "Պլավիքս" Կլոպիդոգրել դեղորայքը:

0. Ոչ……☐ 1. Այո……☐ եթե այո→ 9 a

Q#9a. Որքա՞ն ժամանակ տևողությամբ

1. 0-3 ամիս ☐ 3. 6-9 ամիս ☐

2. 3-6 ամիս s ☐ 4. 9-12 ամիս ☐

Q#9 b Որքա՞ն ժամանակ եք իրականում այն ընդունել

0-3 ամիս ☐ 3. 6-9 ամիս ☐

2. 3-6 ամիս ☐ 4. 9-12 ամիս ☐

Q#10. Դուք ներկայումս ծխում ե՞ք

0. Ոչ ☐ 1. Այո ☐ եթե այո (10a) , ապա **քանի սիգարետ օրեկան**

Q#**10a** 1. 10 քիչ …… ☐ 2. 10-20 ……☐ 3. 20-30…….☐ 4. 30 ավել ……☐

Որքան ժամանակ _____տարի

Q#11.Վերջին 7 օրվա ընթացքում քանի՞ օր եք Դուք զբոսնել/ոտքով քայլել ամենաքիչը 10 րոպեների ընթացքում:

0. _____ ___Օր շաբաթվա ընթացքում
88. _____Չգիտեմ/դժվարանում եմ պատասխանել

Q#12. Որքա՞ն ժամանակ եք Դուք ծախսել զբոսնելու/ոտքով քայլելու վրա այդ օրերին 1 օրվա ընթացքում:

__ __ __ ժամ մեկ օրում
__ __ __ Րոպե մեկ օրում
88. Չգիտեմ/դժվարանում եմ պատասխանել

Q#13. Մենք ցանկանում ենք իմանալ արդյոք Ձեր ստենտավորումից հետո ընդունվել եք հիվանդանոց հետևյալ պատճառներից որևէ մեկով

Ինֆարկտ 0 .Ոչ ☐ 1. Այո☐ եթե այո ամիս//տարի_____

Վերաստենտավորմում 0 .Ոչ ☐ 1. Այո☐ եթե այո, ամիս//տարի_____

Վիրահատման ՞շունտավորում" 0 .Ոչ ☐ 1. Այո☐ եթե այո, ամիս//տարի_____

Ինսուլտ 0 .Ոչ ☐ 1. Այո☐ եթե այո, ամիս//տարի_____

Այլ 0 .Ոչ ☐ 1. Այո☐ եթե այո, ամիս//տարի_____

Նշեք պատճառը_____

Աշխատանքային կարգավիճակ և եկամուտ

Q#14. Դուք ներկայումս աշխատում ե՞ք:

0. Ոչ ☐ 1. Այո ☐

Q#15. 2010 թվականին Ձեր ընտանիքի բոլոր անդամների կողմից ունեցած միջին տարեկան եկամուտը կազմել է՝

1. <30,000 դրամ ☐
2. 31,000-100,000 դրամ ☐
3. 101,000-250,000 դրամ ☐
4. ավելի քան 250,000 դրամ ☐
5. չգիտեմ ☐

Q#16. Ինչպես կգնահատեիք Ձեր ընտանիքի նյութական վիճակը.

1. Միջինից բավականին ցածր
2. Միջինից մի փոքր ցածր
3. Միջին
4. Միջինից մի փոքր բարձր
5. Միջինից բավականին բարձր

Շնորհակալություն Ձեր Մասնակցության Համար:

Appendix E. Medical Record Data Abstraction Form

Demographic Characteristics
1. ID#_____
2. Date of birth DD MM YY ___/____/_____ 3. Patient sex 0.□ Women 1. □ Men
4. Date of intervention DD MM YY ___/____/__ Date of hospital admission DD MM YY ___/____/__ Date of discharge DD MM YY ___/____/__
Cardiac Status
5. Stable angina 0.□ No 1.□Yes
6. Unstable angina 0.□ No 1.□Yes
7. Myocardial infarction 0.□ No 1.□Yes If Yes → 0.□ NSTM 1.□ STEMI
8. MI onset time 1. □ At the time of admission 2. □ < 3 months before intervention 3. □ 3-6 months 4. □ > 6 months
9. Heart failure 0. □No 1. □Yes If Yes → NYHA class 1. □ I 2. □II 3. □III 4. □IV
10. Ejection Fraction _____%
11. Arrhythmia 0. □No 1. □Yes If Yes, Type of arrhythmia _____
12. Cardiogenic Shock 0. □No 1. □Yes
CAD Risk Factors and Comorbidities
13. Weight (kg) _____ 14. Height (sm) _____
15. Currently smoking 0.□No 1.□Yes 20. Renal dysfunction 0.□No 1.□Yes 16. Family history of CAD 0.□No 1.□Yes 21. Cerebrovascular disease 0.□No 1.□Yes 17. Hypertension 0.□No 1.□Yes 22. Previous MI 0.□No 1.□Yes 18. Hypercholesterolemia 0.□No 1.□Yes 23. Diabetes 0.□No 1.□Yes 19. GI disease 0.□No 1.□Yes
Prior Interventions
24. Previous PCI 0. □No 1. □Yes 25. Previous CABG 0. □No 1. □Yes
26. Stented Vessel diameter_____mm Stented Lesion lenghth_____mm
27. Number of diseased vessels* 1.□Single 2.□Two 3.□Three vessel
28. Type of the diseased vessels (mark all that apply) a. □ Left main c. □ Left circumflex b. □ Left anterior descending d. □ Right coronary
29. Number of stents placed 1. □ One 2. □ Two 3. □ Three
30. Stent type 0. □BMS 1. □DES 2. □ Both

31. In hospital complications

Death	1□	GI bleeding	6□
Recurrent MI	2□	Vascular complication	7□
CABG	3□	Secondary infection/sepsis	8□
Stroke	4□	Blood transfusion	9□
TIA	5□	Other, specify _____	10□

32. Medication at discharge

Aspirin	1□	b-blockers	3□	ACE-i	5□
Clopidogrel	2□	Statins	4□	Other	_____

***** The diseased coronary vessels was defined as narrowing by ≥50% in diameter.

Appendix F. Journal form for the telephone survey

ID	Place of living	Date of stent placement	Date of contact	Result	Other

---

Option for «Result»

Complete □

Incomplete □

Absent from a country □

Refused to participate □

Impossible to contact □

Dead □ (If dead please specify the date of the death in the “Other” section)

Appendix G. Sample size calculation (PS by Dupont et al)

The following assumptions were made: ratio of women to men in the sample equal to 1: 7 (3), Type 1 error (alpha) equal to 0.05, power equal to 0.8, the hazard rate of mortality at 1-year of follow-up of women versus men equal to 0.55 (21). The calculated sample size was 703 (87 women and 616 men). Taking into account 73% response rate (35) and 90% eligibility rate, the required sample size was equal to 1070 (703/0.9*0.73) or **938 men and 132 women**.

Requested output:	**Sample size calculation (based on literature)**	**Detectable alternative (based on study data)**
Type of study	Survival analysis (hazard ratio)	Survival analysis(hazard ratio)
Alpha type I error level	0.05	0.05
Power	0.8	0.8
m1 (The median survival time on control treatment $m_1 = t \log_e(1/2)/\log_e(p)$)	12.98	4.51
Accrual period; 2006-2008)	3 years	3 years
Average follow-up)	of 3 years	3.5 years
Women vs men ratio	1:7	1:6
Sample size per group	x	66 women : 419 mens
Hazard ratio	0.55	x
Seeking value	**Sample size per group**	**Hazard ratio**
Sample size per group	87: 616	
Hazard ratio		0.6 or 1.8

Appendix H. American University of Armenia

Institutional Review Board # 1/Committee on Human Research College of Health Sciences

Subcommittee for Student Theses

Title of Research Project: Gender differences in patients with percutaneous coronary intervention: the Armenian perspective.

Hello, my name is _____. I am a physician and a graduate student in Public Health at the American University of Armenia. I am, as a member of a research team with the support of the faculty members conducting a study to investigate the 3 year outcomes of patients with PCI treated at NMMC. You have been contacted because based on NMMC records you underwent stenting during 2006-2008. Your contact information has been obtained from NMMC database. Permission to collect your contact information has been received from the NMMC Medical Board. If you are willing to participate in this study I will ask some questions concerning your health status. Your participation in the study is voluntary. You may skip any question you think is inappropriate and stop it at any moment you want with no further negative consequences. The interview will take place once at any time that is convenient for you and last no more than 15 minutes. If you don't mind I will also collect some information from your medical records regarding your health status and intervention.

There will be no monetary benefits for you if you participate in this project. The information provided by you will be very helpful for science and for other patients. There is no penalty for refusing to participate.

Whether or not you are in the study will not affect your future treatment at the NMMC. The information provided by you is fully confidential and will be used only for the study. Only aggregate data will be reported. Contact information will be destroyed upon completion of the research. If you have more questions about this study you can contact Yeva Sahakyan, the coordinator of the research team – 091 501726, Dr. Varduhi Petrosyan, the Associate Dean of the College of Health Sciences at AUA calling 512592. If you feel you have not been treated fairly or think you have been hurt by joining this study, please contact Dr. Hripsime Martirosyan, AUA Human Subjects Administrator at (374 1) 51 25 61.

If you agree to be involved in this study, could we continue?

Հայաստանի ամերիկյան համալսարան Գիտահետազոտական էթիկայի հանձնաժողով

Հանրային առողջապահության ֆակուլտետ

Բանավոր իրազեկ համաձայնագիր

Հետազոտության անվանումը. Արական և իգական սեռերի միջև տարբերությունները սրտամկանի պսակային անոթների ենթամաշկային ստենտավորումից հետո.

Հայաստանյան փորձ

Բարև Ձեզ, իմ անունը _____ է: Ես բժիշկ եմ և Հայաստանի ամերիկյան համալսարանի Հանրային առողջապահության մագիստրատուրայի վերջին կուրսի ուսանող: Ես հետազոտական խմբի անդամ եմ և մենք ՀԱՀ-ի երկու դասաղոսների ղեկավարությամբ, անց ենք կացնում հետազոտություն, որի նպատակն է գնահատել Նորք Մարաշ բժշկական կենտրոնում ստենտավորված հիվանդների առողջական վիճակը միջամտությունից հետո 3 տարվա ընթացքում: Դուք ընտրվել եք, որովհետև Նորք Մարաշ բժշկական կենտրոնում գրանցված տվյալների համաձայն Դուք ստենտավորվել եք 2006-ից 2008 տարիների ընթացքում: Ձեր տվյալները վերցվել են ՆՄԲԿ-ից՝ տնօրինության համաձայնությամբ: Եթե Դուք համաձայն եք մասնակցել այս հետազոտությանը, ապա ես Ձեզ կտամ որոշ հարցեր Ձեր առողջական վիճակի վերաբերյալ: Հարցազրույցը տեղի կունենա 1 անգամ, Ձեզ առավել հարմար ժամանակ, և կտևի ոչ ավելի քան 15 րոպե: Ձեր մասնակցությունը այս հետազոտությանը կամավոր է: Դուք իրավունք ունեք չպատասխանել այն հարցերին, որոնք Ձեզ կարող են տհաճություն պատճառել կամ դադարեցնել հարցազրույցը ցանկանած պահին՝ առանց որևէ հետագա բացասական հետևանքների: Եթե դեմ չեք, ես Ձեր առողջության վիճակի և միջամտության վերաբերյալ որոշ տվյալներ կվերցնեմ Ձեր հիվանդության քարտից: Այս հետազոտությանը Ձեր մասնակցության դեպքում որևէ դրամական խրախուսանք նախատեսված չէ: Ձեր կողմից տրամադրված տվյալները կլինեն շատ կարևոր գիտական տեսանկյունից և օգտակար կլինեն այլ հիվանդների համար: Հետազոտությանը չմասնակցելու դեպքում Ձեզ ոչ մի բացասական հետևանք չի լինի: Անկախ նրանից Դուք կմասնակցեք այս հետազոտությանը թե ոչ, ոչինչ չի ազդի Ձեր ՆՄԲԿ հետագա այցելությունների վրա: Ձեր կողմից տրամադրված ողջ տեղեկությունները գաղտնի կպահվեն և միայն ընդհանրացված արդյունքները կներկայացվեն զեկույցում: Ձեր անձնական տվյալները անմիջապես կոչնչացվեն հետազոտության ավարտից հետո: Հետազոտության հետ կապված հետագա հարցերի համար կարող եք զանգահարել Եվա Սահակյանին, հետազոտական խմբի կոորդինատորին 091501726, Հայաստանի

ամերիկյան համալսարանի Հանրային Առողջապահության մագիստրատուրայի փոխդեկանին՝ Վարդուհի Պետրոսյանին 512592, ինչպես նաև, եթե կարծում եք, որ հետազոտության ընթացքում Ձեզ հետ լավ չեն վերաբերվել և/կամ հետազոտությունը Ձեզ վնաս է հասցրել կարող եք զանգահարել Հայաստանի ամերիկյան համալսարան, Հռիփսիմե Մարտիրոսյանին – 512561 հեռախոսահամարով, նա հանդիսանում է ՀԱՀ-ի էթիկայի հանձնաժողովի ադմինիստրատորը: Եթե համաձայն եք մասնակցել, կարո՞ղ ենք սկսել:

Appendix I. Derivation of the final model

All variables which had p<0.25 in univariate analysis were included in the final model building process. Those variables were gender, acute MI status, arrhythmia, ejection fraction, DES type of stent, diabetes, number of diseased vessel, and type of stented vessel.

```
xi: stcox  q_3 q_8_1 q_11 EF50 avelength i.q_29 q_19 i.q_27 q_31_3 q_31_4
i.q_29            _Iq_29_0-2          (naturally coded; _Iq_29_0 omitted)
i.q_27            _Iq_27_1-3          (naturally coded; _Iq_27_1 omitted)
failure _d:  MACCE
 analysis time _t:  followMACCE
No. of subjects =          442                     Number of obs   =       442
No. of failures =          131
Time at risk    =       451569
                                                   LR chi2(12)     =     32.26
Log likelihood  =   -720.28825                     Prob > chi2     =    0.0013
------------------------------------------------------------------------------
          _t | Haz. Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
         sex |   .9124017   .2356257    -0.35   0.723     .5500031    1.513586
         AMI |   1.216219   .2458639     0.97   0.333     .8183471    1.807531
  arrhtyhmia |   1.698971   .3901595     2.31   0.021     1.083209    2.664771
          EF |   1.065587   .2092339     0.32   0.746     .7251884    1.565767
         DES |   .5593077   .1255693    -2.59   0.010     .3602043    .8684657
        Both |   .5531218   .4145568    -0.79   0.429     .1273086    2.403167
        diab |   1.388695   .3052786     1.49   0.135     .9025813    2.136622
    2 vessel |   1.446534   .3404193     1.57   0.117     .9120356    2.294276
    3 vessel |   1.694349    .416917     2.14   0.032     1.046053    2.744431
         LAD |   .6923319    .148571    -1.71   0.087     .4546222    1.054334
         RCA |   .8811354   .1983195    -0.56   0.574     .5668399    1.369698
------------------------------------------------------------------------------
```

The variables with p>0.25 eliminated from the model, besides gender, because of being variable of interest.

```
xi: stcox  q_3  q_11 i.q_29 q_19 i.q_27 q_31_3
i.q_29            _Iq_29_0-2          (naturally coded; _Iq_29_0 omitted)
i.q_27            _Iq_27_1-3          (naturally coded; _Iq_27_1 omitted)
failure _d:  MACCE
 analysis time _t:  followMACCE
```

```
------------------------------------------------------------------------------
          _t | Haz. Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
         sex |   .9788914   .2482936    -0.08   0.933     .5954278    1.609311
   arrhthmia |   1.660782   .3699627     2.28   0.023     1.073237    2.569981
        diab |    1.33239    .290622     1.32   0.188     .8688936    2.043131
    2 vessel |   1.527682   .3504747     1.85   0.065     .9744367    2.395037
    3 vessel |   1.858782   .4369266     2.64   0.008     1.172586    2.946541
         DES |    .535815    .109475    -3.05   0.002     .3590059    .7997017
         LAD |    .732126   .1298684    -1.76   0.079     .5171246    1.036517
```

Then interaction between gender and each variables were checked. The significant interaction was noted only between gender and diabetes status.

```
. xi: stcox q_3 q_11 q_19 q_31_3 i.q_27  i.q_29 sexdiab
i.q_27            _Iq_27_1-3          (naturally coded; _Iq_27_1 omitted)
i.q_29            _Iq_29_0-2          (naturally coded; _Iq_29_0 omitted)

        failure _d:  MACCE
  analysis time _t:  followMACCE
------------------------------------------------------------------------------
          _t | Haz. Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
         q_3 |   2.155432   .9113354     1.82   0.069      .941107    4.936621
        q_11 |   1.614863   .3590886     2.16   0.031      1.04438    2.496968
        q_19 |   5.371696    2.66714     3.39   0.001     2.029903    14.21503
      q_31_3 |   .7003087   .1251034    -1.99   0.046     .4934357    .9939133
    _Iq_27_2 |    1.56596   .3588679     1.96   0.050     .9993383    2.453855
    _Iq_27_3 |   1.951021   .4572115     2.85   0.004     1.232501    3.088422
    _Iq_29_1 |    .551081   .1131299    -2.90   0.004     .3685314    .8240552
    _Iq_29_2 |   .5501255   .4095763    -0.80   0.422     .1278586    2.366974
     sexdiab |   .1612286    .092096    -3.19   0.001     .0526289    .4939239
```

From the latest model we exclude variables with less than p=0.05 value (average length) and get

```
. xi: stcox q_3 q_11 q_19 q_31_3 i.q_27  i.q_29 sexdiab
i.q_27            _Iq_27_1-3          (naturally coded; _Iq_27_1 omitted)
i.q_29            _Iq_29_0-2          (naturally coded; _Iq_29_0 omitted)

        failure _d:  MACCE
```

```
   analysis time _t:  followMACCE
------------------------------------------------------------------------------
          _t | Haz. Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
         q_3 |   2.273056   .9589588     1.95   0.052     .9942704    5.196558
        q_11 |   1.686892   .3668212     2.40   0.016     1.101515    2.583357
        q_19 |   5.606998   2.783761     3.47   0.001     2.118976    14.83661
      q_31_3 |   .7361497   .1289269    -1.75   0.080     .5222632    1.037631
    _Iq_27_2 |   1.627741   .3703167     2.14   0.032     1.042159    2.542357
    _Iq_27_3 |   2.025337   .4713061     3.03   0.002     1.283567    3.195775
    _Iq_29_1 |   .5516484   .1114367    -2.94   0.003     .3712906    .8196167
    _Iq_29_2 |    .531206    .394448    -0.85   0.394     .1239372    2.276797
     sexdiab |   .1464185   .0833654    -3.37   0.001     .0479681    .4469301
```

We remove also variable q_31_3 because p>0.05 and then we check for proportionality assumption of our model.

```
. xi: stcox  q_3  q_11  q_19  i.q_27 i.q_29  sexdiab, nolog noshow schoenfeld(sch*)
scaledsch(sca*)
i.q_27            _Iq_27_1-3          (naturally coded; _Iq_27_1 omitted)
i.q_29            _Iq_29_0-2          (naturally coded; _Iq_29_0 omitted)

Cox regression -- Breslow method for ties

No. of subjects =          458                     Number of obs   =       458
No. of failures =          139
Time at risk    =       466833
                                                   LR chi2(9)      =     41.58
Log likelihood  =   -764.31472                     Prob > chi2     =    0.0000

------------------------------------------------------------------------------
          _t | Haz. Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
         q_3 |   2.273056   .9589588     1.95   0.052     .9942704    5.196558
        q_11 |   1.686892   .3668212     2.40   0.016     1.101515    2.583357
        q_19 |   5.606998   2.783761     3.47   0.001     2.118976    14.83661
    _Iq_27_2 |   1.627741   .3703167     2.14   0.032     1.042159    2.542357
    _Iq_27_3 |   2.025337   .4713061     3.03   0.002     1.283567    3.195775
    _Iq_29_1 |   .5516484   .1114367    -2.94   0.003     .3712906    .8196167
    _Iq_29_2 |    .531206    .394448    -0.85   0.394     .1239372    2.276797
     sexdiab |   .1464185   .0833654    -3.37   0.001     .0479681    .4469301
------------------------------------------------------------------------------
```

```
. stphtest, log detail
      Test of proportional-hazards assumption
      Time:  Log(t)
      ----------------------------------------------------------------
                  |       rho            chi2       df       Prob>chi2
      ------------+---------------------------------------------------
          q_3     |     -0.04401         0.27        1         0.6032
         q_11     |      0.10391         1.50        1         0.2207
         q_19     |     -0.01516         0.03        1         0.8596
      _Iq_27_2    |     -0.18997         5.05        1         0.0247
      _Iq_27_3    |     -0.25895         9.27        1         0.0023
      _Iq_29_1    |      0.34285        18.19        1         0.0000
      _Iq_29_2    |      0.04029         0.24        1         0.6234
        sexdiab     |      0.00914         0.01        1         0.9140
      ------------+---------------------------------------------------
      global test |                     29.58        9         0.0005
```

We find out that in some variables the hazard is not proportionate over the time, hence could not be analyzed by Cox regression analysis. We exclude those variables.

```
stcox q_3 q_19 q_11 sexdiab
failure _d:  MACCE
   analysis time _t:  followMACCE
Log likelihood  =   -801.58764                     Prob > chi2     =    0.0003

------------------------------------------------------------------------------
          _t | Haz. Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
         q_3 |   2.582527   1.084949     2.26   0.024     1.133562    5.883615
        q_19 |    6.19728   3.074149     3.68   0.000     2.344036    16.38468
        q_11 |   1.684246   .3635172     2.42   0.016     1.103284    2.571127
     sexdiab |   .1359596   .0772007    -3.51   0.000     .0446765    .4137518

 We checked HR of men diabetics versus women non diabetics and men versus women diabetics.

  stcox q_3 q_11 sexdiab if q_19==0
 failure _d:  MACCE
   analysis time _t:  followMACCE
Log likelihood  =   -623.85569                     Prob > chi2     =    0.0014

------------------------------------------------------------------------------
          _t | Haz. Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
```

```
           q_3 |   2.549456    1.07144     2.23   0.026     1.118715    5.809991
          q_11 |   1.738284   .4169239     2.31   0.021      1.08633    2.781504


stcox q_3 q_31_3 q_11 sexdiab if q_19==1
         failure _d:  MACCE
   analysis time _t:  followMACCE
Log likelihood  =   -108.28576                     Prob > chi2     =    0.0841

------------------------------------------------------------------------------
          _t | Haz. Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
             q_3 |   .3880834   .1524679    -2.41   0.016     .1796843    .8381853
            q_11 |   1.506747   .7563367     0.82   0.414     .5633335    4.030093
```