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Gender Disparities Among Multi-Arterial Coronary Artery Bypass Grafting

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North Carolina State University

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Abstract

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Introduction

Coronary artery bypass grafting (CABG) is the primary surgical method of intervention for advanced coronary artery disease (CAD). CAD is one of the leading causes of mortality in the USA, the need to improve this intervention is great. An emerging technique for CABG is multiple arterial grafting, or the use of multiple arteries, and is currently preformed much less frequently than single arterial despite some evidence for improved long term survival. This study set out to investigate if there was any association between multiple arterial grafting, gender, and short term/long term outcomes.

Methods

This study was a prospective case control study of 20385 Emory patients who underwent isolated CABG with 2 or more grafts. Emergent salvage patients were excluded from this analysis. Statistical methods included univariate and bivariate analysis to assess risk factors, logistic regression and Cox survival models to assess relevant outcomes, and investigations into internal study validity. Significance testing was conducted at the 95% confidence level.

Results

This study concluded that women received multiple arterial grafting half as often as men (10.83% vs 20.50%) even when controlling for PROM. Multiple arterial CABG provided improved 30-day mortality, and improved long term survival among all participants (HR=0.76) Females had significantly shorter 30-day and long-term survival than their male counterparts. Among multi-arterial patients, the difference in risk between genders was insignificant (HR_{female} =1.26, 95% CI [0.99, 1.61]).

Conclusion

This study has a three-part conclusion. First, females are at a higher risk of adverse outcomes from CABG. Second, multiple arterial grafting improves both short term and long term survival of both women and men in similar magnitude. Third, despite these improved short term and long term outcomes, females receive CABG only half as often as their equivalent male counterparts. Along with the need of awareness and shift in surgical methods, further research needs to be done into why this disparity exists, if there are other domains with similar disparities, and if more can be done to enhance the survival of female patients.

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Acknowledgments: In memory of Dr. William McClellan. He was a thoughtful and curious researcher, a caring clinician, and an incredibly supportive mentor. Dr. McClellan pushed epidemiology to be its best, to focus on how to truly improve the lives of people in the world. His teachings inspired many students and brought out their best abilities. He will be remembered.

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CHAPTER I: Multiple Arterial CABG literature review

Overview

Coronary artery bypass surgery (CABG) is the use of arteries or veins harvested from other parts of the body to circumvent sever occlusions in the coronary arteries[1]. The stenosis of these coronary arteries is known as coronary artery disease (CAD) and it is the leading cause of death in the United States for both men and women[2-4]. CAD contributes an estimated loss of over $300 million each year due to costs and loss of productivity[3]. CABG is the preferred method of treating advanced CAD and is one of the most frequently preformed procedures in the US with over 400,000 CABG operations are performed annually in the United States[1]. With such a high impact, this surgery is crucial to many lives. Current improvement discussions include multiple arterial CABG, the use of multiple arteries instead of veins to circumvent coronary plaque occlusions[5]. It is suspected that using multiple arteries will provide better long term results than using veins as bypass grafts. It is the goal of this study to investigate the association between surgery type (single or multiple arterial), PROM strata, and adverse outcomes.

Coronary artery disease

First and foremost, the decision to undergo CABG requires the diagnosis of CAD. This disease is chronic, developing asymptomatically for decades before any symptom is presented[4]. Because of this difficult detection, CAD is often diagnosed in late stages. Coronary artery disease is endemic in the United States, and causes hundreds of thousands of deaths each year[2,4]. With such a large need, and difficulty to diagnose early, the medical community has often used risk prediction to intervene as early as possible[6-9]. There are multiple known risk factors:

diabetes, smoking status, cholesterol levels, high density lipid concentration (HDL), low density lipid concentration (LDL), obesity, family history of heart disease, and hypertension that are combined to predict risk of developing CAD[4,6-9]. Development of the disease involves the buildup of atherosclerotic plaque along coronary artery walls. As the plaque builds, the arteries reshape themselves, thus not showing any signs of the disease until nearly 40% occlusion. The disease is typically not diagnosed until 50% occlusion and does not become symptomatic until 70%occlusion[4]. The development of this disease brings multiple chronic symptoms including hypertension and results in acute symptoms such as myocardial infarction or stroke with full blockage[3,4]. With these advanced stages, intervention is needed.

Because CAD diagnosis is needed for CABG decision, it is important to note the current problems in diagnosing CAD. The preliminary diagnosis has poor sensitivity for less severe cases. About 23.5% of the 3.8 million cardiac stress tests were estimated to produce false negative results[3]. Additionally, there is significant variance in the frequency of referrals based on sex and race[2,10]. CAD risk for women is often forgotten because of the higher risk for men, but CAD is still the highest cause of mortality for women in the US[2]. Women present CAD risks differently and thus may be harder to diagnose[2], this also leads to differences in risk prediction as sex is treated as an interaction term[6-9]. There is also racial disparity among frequency of referrals, this disparity is seen primarily in Africa Americans, Hispanics, and Native Americans[2]. These errors in detection ultimately influence those eligible for CABG and are thus incredibly important factors for consideration.

<u>Intervention</u>

There are two commonly used methods of intervention for CAD, percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG)[1,11]. PCI involves using a catheter and stent or balloon angioplasty to restore blood flow to the coronary arteries[11]. These two procedures are drastically different as PCI is a non-interventional treatment while CABG is incredibly invasive and involves restructuring coronary anatomy. Both methods are used in modern treatment and the decision is based off of risk factors and details about the procedures, with CABG being used in higher risk situations and more advanced conditions like triple vessel disease[1]. While medical intervention is considered for early cases, it is found to be inferior to these intervention techniques for advanced CAD[1]

PCI was first achieved by Dr. Gruentzig in Germany in 1964[12]. This procedure marked the possibility of less invasive treatment for correcting arterial defects that previously could only be treated through surgery. Doctor Gruentzig later relocated to Emory University in Atlanta to hone his technique and further explore the use of PCI as treatment for multiple arterial conditions[12]. The modern method involves an interventional cardiologist and a team of support staff who make a small incision in either the femoral artery at the groin or the radial artery[13,14]. Common practice has been to incise in the femoral artery as it is larger, but growing evidence is suggesting that the radial artery is equally feasible if not superior regarding postop complications[13]. The catheter, either outfitted with a stent or a balloon antipathy, is advanced to the coronary occlusion. There, either the stent is deployed to create a clear passage for blood, or the balloon is inflated to push away the built up plaque[12,13]. Both methods are commonly used and typically decided by the opinion of the cardiologist. This method can be applied to multiple occlusions. Common complications include bleeding, myocardial infarction, or stroke. Risk factors for these complications include age, diabetes, and several other factors and as such require a discussion by a team of cardiac focused physicians to determine the best course of action[12-15].

CABG is the use of harvested arteries or veins repurposed to bypass the coronary artery occlusions. When comparing the two main treatments of advanced CAD, PCI is shown to be less invasive and have a lower risk of stroke, CABG is shown to have lower risk of repeat procedure. CABG is thus preferred in diabetics, left ventricular disease, and advanced CAD[1,11]. The surgery involves the incision into the thoracic cavity where the patient is then put on cardiopulmonary bypass. Then two anastomoses are made on either side of the occlusion on the coronary artery, one proximal or one distal relative to the heart. Then a harvested conduit is sewn into the two anastomosis. CABG is further differentiated by procedural details. One variance not using pump bypass to divert blood flow from the heart during surgery. This method reduces heart stress and benefits higher risk patients, however it is more difficult[1,16]. Another variance in surgery is whether a vein or artery is used to circumvent an obstruction. Common practice has been single-arterial: to use one artery, often the left internal thoracic artery, and then to use vein grafts, usually the greater saphenous vein, for remaining occlusions[1,5]. However, there is an opinion that using multiple arteries to bypass the occlusions will result in better long term survival as the artery will physiologically be able to respond to blood indicators like the artery it is bypassing[5]. Common method involves the right internal mammary artery as the primary arterial graft as it is shown to have the highest success rate. After that, the left internal mammary, radial, or gastroepiploic arteries can be used[17-19]. There is no consensus on the benefits and deficits of each. This method requires further investigation as there is conflicting evidence for long term survival, both depending on the arteries used and multiple-arterial CABG itself[5,20]. General

CABG is the preferred method of treatment for multi-arterial disease and thus is the focus of this study.

As CABG is a surgery, it involves a level of risk that must be addressed. Approximately .4% of all CABG surgeries result in a major postoperative complication like sternal infection[1]. There higher risk groups among these CABG patients though, individuals with diabetes, hypertension, or old age are more likely to suffer these complications[1,16]. Stroke is also a common complication due to the possible disturbance of plaque into the blood flow[1,5,16,21]. Because of these risks, each case is carefully planned by a team of physicians including interventional cardiologist, cardiothoracic surgeon, and general physician[1]. A current opinion regarding multiple arterial CABG is that it contains a higher risk of sternal infection than single arterial, however, it is estimated to have superior long term outcomes than single-arterial[17,18]. There are numerous risk factors to be considered regarding this surgery, and because it is a frequent procedure, predictive risk models similar CAD have been produced[7,8].

Predictive risk of mortality

Predictive risk models have become increasingly useful and prevalent for a number of diseases and procedures. One of the first and most well-known predictive risk models was that for coronary artery disease developed from the Framingham heart study[8]. This study is a large coronary vessel disease research study that has collected data from the 1950s. By using multiple logistic regression physicians were able to predict risk for CAD based on known risk factors: smoking status, diabetes, serum cholesterol, left ventricular hypertrophy and systolic blood pressure[22]. The model has been improved with the addition of HDL and LDL measures. The model was further stratified by sex which was found to be a significant effect measure modifier[6-

[9]. This general model has been useful for predicting the most common disease in America and has found wide application. While the original Framingham population was lacking generalizability based on race and age, the models have been updated and found to be applicable to wider ages and many populations including blacks and Asians[9].

Like CAD precision models, the predictive risk of mortality (PROM) model was created to predict the risk involved with five common types of cardiac surgeries, one of which is CABG[23,24]. PROM is a score based variable constructed from algorithms on logistic regression models and survival analysis of 30 known risk factors for cardiac surgeries[23,24]. This model has been recognized globally as a valid method of predicting short term risk for these surgeries. It is recalibrated with updated information from STS database to maintain validity[24]. PROM has also been shown to be a valid predictor of long term mortality, with valid predictions up to 14 years' post-operation[23].

Summary

Coronary artery bypass grafting is an important surgical procedure for the most common disease in America. Because of the level of risk and the prevalence of disease, this surgical procedure is important to perfect. CABG is only a treatment for the disease, not a cure for the disease. While CAD prevalence has been decreasing, it is still crucial in today's society. The effect of multiple arterial grafts requires further study in hopes of improving the lives of patients in a long-term setting. The use of PROM will assist in adequately understanding the effects of varying surgery methods.

CHAPTER II

Gender Disparities among Multiple Arterial Coronary Bypass Grafting

By John Hunting

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Conclusion

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Gender Disparities among Multi-Arterial Coronary Artery Bypass Grafting

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Introduction

Coronary artery disease is the leading cause of mortality not just among developed countries, but among the world[3,7]. A consequence of typical human life involves the eventual buildup of plaque along artery walls, but this development is bolstered by modern, developed life styles. Factors such as inactivity, diet, and longevity have led to a high prevalence of this disease. Thus has become vital to improve the situation in every possible manner, both through preventative measures and improving treatment. The primary difficulty of preventative measures lies in the lack of clinical symptoms until approximately 50% occlusion[4,7]. This point of diagnosis is typically in middle to late life. By then, both behavioral and pathological tendencies are difficult to alter, often medial intervention will be needed to preserve life.

Medicine has developed two primary methods for intervention into coronary artery disease (CAD)[1]. Percutaneous coronary intervention (PCI) is a technique that was developed by Andreas Gruentzig in Switzerland and further improved at Emory University[25]. The procedure was intended to be a minimally invasive method to treat the targeted plaque occlusions[12,14]. Beginning with an incision into the femoral or radial artery, a catheter is advanced through the arteries up to the point of occlusion(s) in the coronary artery(ies)[13]. Once there, either a stent or balloon angioplasty can be deployed to reopen the artery and restore proper blood flow. The catheter is then withdrawn and the patient released after several hours of observation[1,14,15]. This method was sought to be a safer alternative to the pre-existing treatment of coronary artery bypass grafting surgery (CABG). PCI was hoped to be a lower risk procedure for treating advanced CAD, however CABG has been shown in the majority of patients to not be significantly different in post-operative outcomes and to have a higher patency rate, in other words there is much less instance of re-intervention[1]. CABG is currently the preferred method of treating advanced CAD.

Coronary artery bypass grafting (CABG) is a surgical intervention where veins and or arteries are harvested from various sites in the body and are sewn into the coronary arteries to provide an alternative blood flow path around the plaque occlusions[1,5]. Traditionally the right internal mammary artery is used first along with the greater saphenous vein for any subsequent grafts. Newer methods include additional arteries like the left internal mammary, radial, and gastroepiploic arteries can be used but are less common due to lower rates of patency[1,17,19]. While this surgery is open heart and carries a notable amount of risk, its benefits are well documented in many sub populations[1,5,11,21,26]. Due to the incredibly high frequency of this procedure (Emory alone preforms over 2,000 per year), intense study has gone into improving this procedure. One currently investigated method is between single and multiple arterial CABG approaches[5].

Single and multiple arterial CABG are two forms of multiple bypass grafting; they are both used to treat two or more occlusions of coronary arteries[1,17]. The difference arises in how the bypasses are done. Single arterial involves the use of one artery, usually the right internal mammary, and the greater saphenous vein, which can provide multiple graphs, to bypass the necessary occlusions. Multi arterial grafting involves at least two arterial grafts and potentially additional veins to bypass the needed occlusions. Current data is somewhat conflicting on the superior method between the two[1,18-20].

As with all surgery and disease in general, it is needed to consider risk factors for the potential threat of the disease and or procedure. The Framingham study was one of the first introductions into this process as they created a predictive risk model for coronary artery disease[6,7,9,24]. This study was conducted in the late 1950's and showed the use of developing predictive risk models to assess multiple risk factors for diseases[7]. These models can, and have been, developed in many domains, and allow consistent risk assessment in patients. Cardiothoracic surgery, a field with many procedures and substantial risk, is one of the fields to develop its own predictive risk model thanks to the lessons of Framingham. The predictive risk of mortality (PROM) model was created in the late 1990's as a method of predicting adverse outcomes of the main cardiac surgeries (bypass, aortic valve replacement, mitral valve replacement or repair, or a combination of CABG and valve repair/replacement)[24]. This was constructed from the Society of Thoracic Surgeons database, which contains data on over 5.8 million procedures. The model frequently undergoes calibration to assess the risk factors included as well as their measures of effect on 30-day mortality[23]. In coronary artery disease, the Framingham model has evolved to include gender as an interaction term, reporting risks for men separately from women[7,24]. However, the PROM model does not consider gender in this way. PROM simply combines the known risk factors in a weighted composite to provide a predictive risk for the various surgeries.

As PROM considers each type of surgery, it does not include adjustments for inner procedure variances, for example off pump (when coronary pulmonary bypass is not used) or multi-arterial grafting as they act as mediators (see figure 1). PROM allows for stratification between broad surgery types like CABG and aortic valve repair but it is possible this many not be sufficient. As CAD risk models show, gender plays an important role in the development of the disease resulting in the need for CABG[24]. It is known that gender plays a role in predicting adverse outcomes of CABG, but the role of gender between single and multi-arterial CABG is unknown. As PROM is calibrated for generalized CABG, we are currently unable to investigate potentially differential associations with gender and multi-arterial CABG while simultaneously controlling for PROM. This investigation will attempt to determine the association between gender, multi-arterial CABG, and adverse cardiac outcomes like death, stroke, and myocardial infarction.

Methods

Population and design

This data was gathered from the Society of Thoracic Surgeons (STS), a database well known for the consistency of its data. It included all patients from Emory Health System who underwent an isolated CABG procedure, which means all surgeries including valve procedure or anything besides CABG was excluded, between January 1, 2002 and January 1, 2012. All emergent salvage patients were excluded. The dataset included 20,385 patients.

This investigation was a prospective case control study as outcome is already known and the collection of data is in the past, but the exposures of gender and surgery type were determined and recorded prior to the outcome. This design helps reduce the threat of selection bias as participation contingent on the outcome was not possible.

Preliminary analysis

Preliminary analysis involved assessing univariate and bivariate preoperative risk factors. Predictive risk of mortality uses the risk factors: age, surgical status (whether it was urgent or elective), hypertension, race, ejection fraction, NYHA class, history of stroke, chronic lung disease (COPD), diabetes, hemoglobin A1C, history of myocardial infarction, cerebral vascular disease (CVD), peripheral arterial disease (PAD), serum creatinine at time of operation, smoking status, preoperative intraoperative angioplasty balloon pump, immunosuppressive therapy, and body mass index (BMI), all shown in table 1. In bivariate analysis, reporting was done through frequency within respective group and percentage of that frequency and significance testing was conducted to determine variance between groups. For binomial variables, chi squared analysis was done at the 95% significance level. For continuous variables, reports were made by the mean and standard deviation; two sample t-tests were done at the 95% significance level after verifying the necessary assumptions. All preoperative risk factors were controlled regardless of significance, both due to past literature and confounding being indefinable through significance testing.

The variables previously discussed were combined to generate predictive risk score and thus controlled in this study. Notably though, gender was a component of PROM and thus PROM itself could not be used as a proxy control variable for all the risk factors. Instead, a modified predictive risk model was created for all risk factors excluding gender and validated against traditional PROM through correlative and graphical methods. This method was previously used to investigate a similar hypothesis involving race and multi-arterial grafting[27].

Operative variables were addressed similarly to preoperative risk factors, with univariate summary and bivariate analysis. Binomial variables were addressed through Chi squared analysis and continuous variables through Mann-Whitney test as they were determined to be right skewed and the median/interquartile range was a better description. In contrast to preoperative risk factors, intra operative variables were not considered for confounding in the model as they are mediators in the causal path of exposure and disease. (see figure 1).

Outcomes were reported first as unadjusted between groups to establish a crude reference. The observed odds ratios, confidence intervals, and p-values were obtained through simple logistic regression between outcomes and exposure combinations. Adjusted values were then generated by controlling for the modified predictive risk score and the operative variables that were deemed to be meaningfully different. The outcomes investigated were all measured within 30 days after surgery. These outcomes include myocardial infarction, sternal infection, stroke, pneumonia, renal failure, death at discharge, death within the first thirty days, and major cardiac adverse events (MACE). MACE was reported a second time through polytomous logistic regression for reasons that will be discussed more fully in the bias analysis section. Polytomous logistic regression was used because it was suspected that there could be associations between exposure and multiple events. For example, females might not only be at higher risk of a single MACE, but two or three. This relationship would have been lost if only a dichotomous outcome for MACE was used. This new, multi-level MACE, was treated as a nominal variable rather than ordinal because when the proportional odds assumption for ordinal regression was tested, this multiple level variable failed. This failure is suspected to be due to the decreased sample size of three events but never the less indicates polytomous regression should be used.

Finally, survival analysis was done to further support the associations between gender, multi-arterial and outcomes in a long-term survival manner. While mortality beyond 30 days was no longer reported after January 1, 2011, a combination of prior data and 30-day mortality data was used for this analysis. An internal validation investigation was conducted to assess if this variance in time contributed had any association with the outcome, thus introducing non-independent censoring. The methods will be discussed in detail in the bias analysis section, but in summary it was found that 30-day outcomes were independent of whether the individual received surgery before or after the cut-off.

Bias assessment

MACE is a composite variable, a combined variable for death, stroke, and myocardial infarction. MACE has historically been treated as a dichotomous variable throughout past literature and contributes towards increased power. However, it was the concern of this author that this would introduce misclassification bias due to the masking effect of multiple events. An additional analysis was conducted with MACE as a multiple level categorical variable to correct for this and polytomous logistic regression was conducted to determine associations between gender, multi arterial CABG, and MACE. A multivariate bias analysis was conducted to describe the full extent of potential error due to dichotomizing MACE and the results can be seen in table 4. There were no additional findings from this analysis.

Major threats to internal study validity were assessed and it was deemed there was low risk of bias within this study. Risk factors for CABG are well documented and PROM undergoes periodic recalibration and assessment so there is low threat in this study for unmeasured confounding. In conjunction to this recalibration and data management by STS, this data set is reported by skilled surgeons and managed by an experienced data team and thus there is very little risk of measurement bias. Selection bias, as previously discussed, is assumed to be non-existent due to the prospective nature of this study and absence of loss-to-follow up as every patient receives a standard 30-days follow up.

Concerning the internal validation investigation into independent censoring, the sample was divided into two groups: those who received surgery before January 1, 2011 and those who received surgery on or after January 1, 2011. The concern was that the individuals who had long term follow up were fundamentally different from those who received only 30 days of follow up. If this were the case, the long-term data used for survival analysis would not be representative of the entire population described. To address this, the two groups would need to be compared through equal measures, and as 30-day mortality is collected for all participants, that was the comparable metric. After grouping, 30-day mortality rates were compared between both groups. To compare longer than 30-day mortality of the first group to 30-day mortality of the second would be in error. Seen below are the results of this internal validation assessment.

Table 6 shows those who died within 30 days both pre-cutoff and post-cutoff along with the person time (PT) contributed from the 30 day follow up. As shown above, the 95% confidence interval includes the null hypothesis of Incidence Density Ratio (IDR) = 1 and thus the null hypothesis that the rates are the same must be accepted. This suggests that there is no significant difference in 30-day mortality between the two groups. This allows the combination of the two methods of person time follow up.

Results

In this cohort of 20385, 3,584 (17.6%) patients underwent multi-arterial grafting procedure and 5,383 (26.4%) patients were female. Preoperative risk factors were compared between single arterial (SA-CABG) and multi-arterial CABG as well as between male and female, the results are shown in table 1. Multi-arterial patients were significantly younger (59.31 years vs 64.25 years respectively) and females were significantly older than males (65.02 years vs 62.79 years). All investigated risk factors were significantly different across groups, except for preoperative IABP, with risk factors being less prevalent among multi-arterial than single-arterial and more prevalent among women than men. STS predictive risk of mortality varied significantly among CABG types (MA-CABG: 1.25% ± 1.60%, SA-CABG: 2.00% ± 2.84% [$p<0.0001$]) and among gender (males: 1.56% ± 2.21%, females: 2.88% ± 3.53%). As gender is a component of PROM, that significance cannot be interpreted, but the modified risk score also varied significantly between gender ($p<0.0001$).

The primary endpoint was mortality within the first thirty days after surgery. In this cohort, 288 patients (1.40%) died in this period. Within SA-CABG, 260 (1.55%) of patients died as opposed to the 28 (0.78%) within MA-CABG. When comparing across gender, of the 288 deaths, 191 (1.27%) were male and 97 (1.80%) were female.

Intraoperative risk factors were assessed similarly to pre-operative factors and shown in table 2. These variables were descriptive features of the surgeries as to better characterize the study population. The most notable difference in intra-operative factors is between the two considered exposures: in this cohort, females received multi-arterial CABG almost half as often as males (10.83% vs 20.00% respectively). MA-CABG had significantly more anastomosis, longer bypass times, longer aortic cross clamp times, and higher rates of off-pump than SA-CABG. Females had significantly fewer anastomosis shorter bypass times, shorter cross clamp times, and a higher rate of off-pump procedures. These relationships were calculated while controlling for the other exposure and the modified risk score.

Figure 1 shows the suspected directed acyclic graph (DAG) of the association of interest. As shown, the two considered exposures, multi-arterial and gender, are associated with the outcomes of interest through intraoperative mediators. The pre-operative risk factors act as both an alternative path for gender and confounder for multi-arterial and so will be controlled in both cases.

After adjustment for the risk score compiled from the preoperative variables, adjusted logistic regression was used to investigate the relationship between each exposure and outcomes of interest. Each association reported is adjusted for the other exposure of interest. Interaction assessment was also conducted and found no interaction between the exposures at any outcome at the 95% confidence level.

First, between CABG types it was found that the only significant outcome was 30-day mortality. Through the logistic regression models, it was found that multiple arterial CABG presented a 39% reduced odds of 30-day mortality than single arterial. All other 30-day outcomes were found to be insignificant between multiple and single arterial grafting when controlling for all other short term risk factors.

Second, between gender and holding surgery type constant, females were found to be at an increased odds for MI ($\widehat{OR}_{\text{adj}}$ =2.54, 95%CI [1.63, 3.92]), sternal infection ($\widehat{OR}_{\text{adj}}$ =1.54, 95% CI [1.01, 2.34]), stroke ($\widehat{OR}_{\text{adj}}$ =2.08, 95%CI [1.61, 2.68], operative death ($\widehat{OR}_{\text{adj}}$ =1.47, 95% CI [1.12, 1.94]), and death within 30 days after surgery ($\widehat{OR}_{\text{adj}}$ =1.36, 95% CI [1.06, 1.75]). Pneumonia and renal failure both presented a null finding of no significant difference between groups.

As discussed previously in the methods section, the author of this paper believed a dichotomous composite variable MACE, commonly used in literature, was not solely appropriate to fully describe the relationships between the exposure variables and composite outcomes. To describe the full effect, MACE was turned into a multiple level categorical variable for polytomous logistic regression. No adverse events were set as the reference group for all ratio measures. Among surgery type, multiple arterial was shown to have an insignificant difference among all frequencies of events (($\widehat{OR}_{1\ \text{adj}}$ =0.91, 95% CI [0.70, 1.17]), ($\widehat{OR}_{2\ \text{adj}}$ =0.62, 95% CI [0.22, 1.75]), ($\widehat{OR}_{3\ \text{adj}}$ =NA, 95% CI [NA])). While these results were insignificant, the point estimates still indicate potentially meaningful implications towards the benefits of multi-arterial CABG. It is suspected that the confidence interval widths are primarily driven by insufficient sample of events, and thus may be hiding truly significant results.

When gender was considered among a multiple level MACE it was found that females had an increased chance of one event ($\widehat{OR}_{1\ \text{adj}}$ =1.87, 95% CI [1.57, 2.24]), but again insignificant odds of two and three events (($\widehat{OR}_{2\ \text{adj}}$ =1.32, 95% CI [0.68, 2.57]), ($\widehat{OR}_{3\ \text{adj}}$ =1.28, 95% CI [0.12, 14.10])). It is possible this insignificance is driven by lacking sample size and the point estimates should be considered meaningful indicators at potentially unnoticed risk. While this investigation into the potential flaws of dichotomous composite variables, it does indicate the potential for additional sources of meaningful relationships and should be considered in additional analysis.

Finally, a survival analysis was done to determine long term relationships between single/multiple arterial and death, and gender among death. National death index long term mortality was available up through January 1, 2011 and was used for this analysis. If a patient did not have that data, 30-day status was used. This analysis found, when controlling for all preoperative risk factors, that multiple arterial surgery had a protective effect on long term mortality ($\widehat{HR}$=0.76, 95% CI [0.68, 0.85], and females were again at a higher risk of mortality ($\widehat{HR}$=1.36, 95% CI [1.25, 1.49]. Figure 2 shows the respective survival curves. Interaction between the exposures was investigated and shown in table 5. A test of significant interaction was done and indicated there was no significant interaction at the 95% confidence level. Stratified hazard ratios were calculated as further support and shown in table 5. Among surgery type, there is no interaction as the point estimates are nearly identical. Among gender type there is some discrepancy but upon review of the overlapping confidence intervals, it also supports the results of no significant interaction.

Discussion

In this cohort, of coronary artery bypass grafting surgery patients, there was significant and meaningful associations between gender, multiple arterial grafting, and adverse outcomes. Gender is a known risk factor for CABG surgery, it is incorporated into PROM and factors into whether the surgery is too high risk or not. However, its relationship is not fully described within the different types of CABG surgery as PROM does not differentiate and thus the true effect is lost.

Even before discussing the differences in adverse outcome by gender, there is a discrepancy between gender in the decision of the type of surgery. Women are assigned multiple arterial bypass only half as often as men (10.83% to 20.00%). This disparity is still apparent when all known risk factors for adverse outcomes are considered. As there are potential benefits from the multiple arterial grafting technique that will be discussed later, this preliminary gender discrepancy raises questions. This association gave reason to further explore the effects (the exposure variables were found to not be collinear). Figure 3 shows the probability of receiving multiple arterial grafting surgery between gender when controlling for all factors contributing to risk of adverse outcome.

As seen in table 3, among the major adverse cardiac outcomes considered, there are few significant differences between multiple and single arterial CABG even when controlling for preoperative risk factors and gender. In fact, the only significant 30-day outcome among single and multi-arterial was 30-day mortality, which favored multi-arterial. This is an important realization as it shows, among this population, multi-arterial CABG does not convey excess short term risk of most outcomes, it even is protective regarding short term mortality.

When considering gender as an exposure presents a different meaning that multiple arterial grafting. Among females, there is an increased risk of most adverse outcomes including: MI, sternal infection, stroke, and mortality within 30 days of the operation. Renal failure and pneumonia presented null results. While gender is incorporated into the PROM risk score, the true meaning as just described would have been lost

The next point of consideration becomes how these two exposures work in relation to each other. It was already shown that females receive multiple arterial CABG far less frequently than their equivalent male counterparts. It was hypothesized there may be some association between them and the outcome to explain the surgeon's decisions. However, quite the opposite was shown to be true. Interaction between the two exposures of CABG type and gender was found to be insignificant. As the Breslow Day test can often be underpowered, stratification among the various exposure types was conducted and found comparable measures of association. Confidence intervals for stratification were wide, most likely due to insufficient sample size as females undergoing multi-arterial CABG were infrequent, but the indication of no interaction was confirmed. It remains that multiple arterial CABG seems to be incredibly beneficial to women and men regarding short term mortality.

Consider then, long term survival. This again showed both the benefits of multiple arterial CABG ($\widehat{HR}$=0.76) and the increased risk of females ($\widehat{HR}$=1.36). In suspecting a difference within the exposures and potential for violations of the proportional hazards assumption, stratified Cox models were investigated. It was found that among single arterial CABG, the hazard ratio comparing gender remained relatively unchanged ($\widehat{HR}$=1.37, 95% CI = [1.25, 1.51) from the total. However, among multiple arterial, that HR dropped to insignificance ($\widehat{HR}$=1.26, 95% CI = [0.99, 1.61). While this estimate is only on the fringe of insignificance and the confidence intervals overlap, the direction of the shift should be appreciated. These results, while not statistically significant, seem meaningful and indicate that multiple arterial CABG may improve the survival of women as compared to their male counterparts. Despite the somewhat different hazard ratios, it was determined that the proportional hazards assumption was satisfied and additionally interaction between exposures was found to be insignificant.

Limitations of the study include the rarity of the combined exposures MA-CABG and females. Females who had MA-CABG represented only 3% of the total study population. Due to the large sample size of this study, the deficits were minimized and conclusions were able to be made, but there may be associations hidden due to the lacking sample size in this sub-population. Another limitation was that long-term survival data was only available for 74% of the population. An internal validation study was conducted to determine if the two populations (before and after the cutoff date of Jan. 1, 2011) were differential. This investigation assessed the common metric of 30-day mortality and found they were similar and so this difference is determined not to have affected the results. This study was not suspected to be influenced by selection bias as there was no effect upon participation with respect to either the exposure or outcome of interest. Threat of misclassification was deemed minimal as the STS database is well known for its data management. Unmeasured confounding was also considered to be inconsequential as the risk factors for CABG are well understood.

In conclusion, women remain a higher risk patient group for CABG surgeries and risk being unrecognized as coronary heart disease intervention is often focused towards males. Multiple arterial coronary artery bypass grafting indicates a better long term survival and comparable short term outcomes. However, females receive multi-arterial CABG infrequently. Multiple arterial CABG should be further utilized in more of the population, especially among women who receive the surgery far less yet benefit equally to their male counterparts.

References

1. Alexander JH, Smith PK. Coronary-Artery Bypass Grafting. *The New England journal of medicine.* 2016;374(20):1954-1964.
2. Bullock-Palmer RP. Prevention, Detection and Management of Coronary Artery Disease in Minority Females. *Ethnicity & disease.* 2015;25(4):499-506.
3. Ladapo JA, Goldfeld KS, Douglas PS. Projected morbidity and mortality from missed diagnoses of coronary artery disease in the United States. *International journal of cardiology.* 2015;195:250-252.
4. Ambrose JA, Singh M. Pathophysiology of coronary artery disease leading to acute coronary syndromes. *F1000prime reports.* 2015;7:08.
5. Tomoaki S, Tohru A. The current status of multi-arterial off-pump coronary artery bypass grafting. *Surg Today.* 2016;46(1):1-12.
6. Aguilar JC, Martinez AH, Padial LR, et al. Assessment of cardiovascular risk in population groups. Comparison of Score system and Framingham in hypertensive patients. *Rev Clin Esp.* 2006;206(4):182-187.
7. D'Agostino RB, Sr., Vasan RS, Pencina MJ, et al. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. *Circulation.* 2008;117(6):743-753.
8. Wilson PW, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB. Prediction of coronary heart disease using risk factor categories. *Circulation.* 1998;97(18):1837-1847.
9. Anderson KM, Wilson PW, Odell PM, Kannel WB. An updated coronary risk profile. A statement for health professionals. *Circulation.* 1991;83(1):356-362.
10. Worrall-Carter L, McEvedy S, Wilson A, Rahman MA. Gender Differences in Presentation, Coronary Intervention, and Outcomes of 28,985 Acute Coronary Syndrome Patients in Victoria, Australia. *Womens Health Iss.* 2016;26(1):14-20.
11. Molstad P. Survival difference between coronary bypass surgery and percutaneous coronary intervention. *Scandinavian cardiovascular journal : SCJ.* 2015;49(4):177-182.
12. King SB, 3rd. The development of interventional cardiology. *Journal of the American College of Cardiology.* 1998;31(4 Suppl B):64b-88b.
13. Valgimigli M, Gagnor A, Calabro P, et al. Radial versus femoral access in patients with acute coronary syndromes undergoing invasive management: a randomised multicentre trial. *Lancet (London, England).* 2015;385(9986):2465-2476.
14. Clements SD, Jr., Gatlin S. Outpatient cardiac catheterization: a report of 3,000 cases. *Clinical cardiology.* 1991;14(6):477-480.
15. Shanmugam VB, Harper R, Meredith I, Malaiapan Y, Psaltis PJ. An overview of PCI in the very elderly. *Journal of geriatric cardiology : JGC.* 2015;12(2):174-184.
16. Puskas JD, Thourani VH, Kilgo P, et al. Off-Pump Coronary Artery Bypass Disproportionately Benefits High-Risk Patients. *Ann Thorac Surg.* 2009;88(4):1142-1147.
17. Al-Sabti HA, Al Kindi A, Al-Rasadi K, Banerjee Y, Al-Hashmi K, Al-Hinai A. Saphenous vein graft vs. radial artery graft searching for the best second coronary artery bypass graft. *Journal of the Saudi Heart Association.* 2013;25(4):247-254.
18. Raja SG. Bilateral internal mammary artery grafting in diabetics: outcomes, concerns and controversies. *International journal of surgery (London, England).* 2015;16(Pt B):153-157.
19. Schwann TA, Hashim SW, Badour S, et al. Equipoise between radial artery and right internal thoracic artery as the second arterial conduit in left internal thoracic artery-based coronary artery bypass graft surgery: a multi-institutional studydagger. *European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic Surgery.* 2016;49(1):188-195.

20. Deo SV, Altarabsheh SE, Shah IK, et al. Are two really always better than one? Results, concerns and controversies in the use of bilateral internal thoracic arteries for coronary artery bypass grafting in the elderly: a systematic review and meta-analysis. *International journal of surgery (London, England).* 2015;16(Pt B):163-170.
21. Ngaage DL, Hashmi I, Griffin S, Cowen ME, Cale AR, Guvendik L. To graft or not to graft? Do coronary artery characteristics influence early outcomes of coronary artery bypass surgery? Analysis of coronary anastomoses of 5171 patients. *The Journal of thoracic and cardiovascular surgery.* 2010;140(1):66-72, 72.e61.
22. Brittain E. Probability of coronary heart disease developing. *The Western journal of medicine.* 1982;136(1):86-89.
23. Puskas JD, Kilgo PD, Thourani VH, et al. The society of thoracic surgeons 30-day predicted risk of mortality score also predicts long-term survival. *The Annals of thoracic surgery.* 2012;93(1):26-33; discussion 33-25.
24. Shroyer AL, Plomondon ME, Grover FL, Edwards FH. The 1996 coronary artery bypass risk model: the Society of Thoracic Surgeons Adult Cardiac National Database. *The Annals of thoracic surgery.* 1999;67(4):1205-1208.
25. Meier B, Bachmann D, Lüscher TF. 25 years of coronary angioplasty: almost a fairy tale. *The Lancet.*361(9356):527.
26. Diodato M, Chedrawy EG. Coronary artery bypass graft surgery: the past, present, and future of myocardial revascularisation. *Surgery research and practice.* 2014;2014:726158.
27. Keeling WB, Binongo J, Halkos ME, et al. The Racial Paradox in Multiarterial Conduit Utilization for Coronary Artery Bypass Grafting. *The Annals of thoracic surgery.* 2016.

TABLES

Table 1. Study population risk factors by surgery type and gender

Pre-op characterisitics	Total (N=20385)	Single Arterial (n=16801)	Multi Arterial (n=3584)	OR* (CI)/p	Male (n=15002)	Female (n=5383)	OR** (CI)/p
Age, years, Mean±SD	63.38 (10.75)	64.25 (10.71)	59.31 (9.98)	<0.0001	62.79 (10.50)	65.02 (11.25)	<.0001
Status (Elective, n(%))	13178 (64.65%)	10846 (64.56%)	2332 (65.07%)	1.02 (0.95, 1.10)	9879 (65.85%)	3299 (61.29%)	0.82 (0.77, 0.88)
Hypertension, n(%)	29.58 (10.81)	14597 (86.88%)	2972 (82.92%)	0.73 (0.66, 0.81)	12688 (84.58%)	4881 (90.67%)	1.77 (1.60, 1.96)
White, n (%)	17569 (86.19%)	12986 (77.29%)	2779 (77.54%)	1.01 (0.93, 1.11)	12003 (80.01%	3762 (69.89%)	0.58 (0.54, 0.62)
Ejection fraction, Mean ± SD	51.41 (12.09)	51.23 (12.27)	52.27 (11.15)	<.0001	50.81 (12.11)	53.11 (11.88)	<.0001
NYHA class III or IV, n(%)	6044 (29.65%)	4787 (28.49%)	1257 (35.07%)	1.36 (1.26, 1.46)	4189 (47.22%)	1855 (55.27%)	1.36 (1.27, 1.45)
Prior stroke, n(%)	1810 (8.88%)	1572 (9.36%)	238 (6.64%)	0.69 (0.60, 0.79)	1163 (7.75%)	647 (12.02%)	1.63 (1.47, 1.80)
Chronic Lung disease				<.0001			<.0001
None, n(%)	16904 (82.92%)	13719 (81.66%)	3185 (88.87%)	1 (ref)	12620 (84.27%)	4284 (79.85%)	1 (ref)
Mild, n(%)	2054 (10.08%)	1771 (10.54%)	283 (7.90%)	0.69 (0.60, 0.78)	1404 (9.38%)	650 (12.12%)	1.36 (1.23, 1.51)
Moderate, n(%)	587 (2.88%)	545 (3.24%)	42 (1.17%)	0.33 (0.24, 0.46)	387 (2.58%)	200 (3.73%)	1.52 (1.28, 1.81)
Severe, n (%)	795 (3.90%)	729 (4.34%)	66 (1.84%)	0.39 (0.30, 0.50)	564 (3.77%)	231 (4.31%)	1.21 (1.03, 1.41)
Diabetes n(%)	8279 (40.61%)	7003 (41.68%)	1276 (35.60%)	0.77 (0.72, 0.83)	5700 (37.99%)	2579 (47.91%)	1.50 (1.41, 1.60)
Hemoglobin A1C, median (Q1, Q3)	6.64 (2.14)	6.66 (2.06)	6.59 (2.35)	0.2	6.57 (2.22)	6.83 (1.92)	<.0001
Previous myocardial infarction n(%)	5305 (26.02%)	4622 (27.51%)	683 (19.06%)	0.62 (0.57, 0.68)	3861 (25.74%)	1444 (26.83%)	1.06 (0.99, 1.14)
Cerebrovascular disease n(%)	3296 (16.17%)	2861 (17.03%)	435 (12.14%)	0.69 (0.60, 0.79)	2144 (14.29%)	1152 (21.40%)	1.63 (1.51, 1.77)
Peripheral arterial disease n(%)	3003 (14.73%)	2594 (15.44%)	409 (11.41%)	0.71 (0.63, 0.79)	2102 (14.01%)	901 (16.74%)	1.23 (1.13, 1.34)
Serum creatinine, Mean ± SD	1.23 (1.17)	1.26 (1.24)	1.10 (0.7)	<.0001	1.25 (1.13)	1.19 (1.26)	0.0013
Current smoker n(%)	3333 (16.35%)	2552 (15.19)	781 (21.79%)	1.56 (1.42, 1.70)	2515 (16.76%)	818 (15.20%)	0.89 (0.82, 0.97)
Preoperative IABP n(%)	533 (2.71%)	487 (2.9%)	66 (1.84%)	0.89 (0.63, 1.27)	420 (49.53%)	133 (48.36%)	0.95 (0.73, 1.25)
Immunosuppressive therapy n(%)	721 (3.54%)	642 (3.82%)	79 (2.20%)	0.57 (0.45, 0.72)	484 (3.23%)	237 (4.40%)	1.387 (1.18, 1.62)
Body mass index, Mean±SD	29.58 (10.81)	29.44 (10.44)	30.25 (12.37)	<.0001	29.33 (9.50)	30.29 (13.80)	<.0001
STS Predicted Risk of Mortality %, Mean±SD	1.91 (2.69)	2.05 (2.84)	1.25 (1.60)	<.0001	1.56 (2.21)	2.88 (3.53)	<.0001

*Single arterial is reference group. ** Male is reference group.

Table 2. Intraoperative risk factors by surgery type and gender

Intra-op characteristics	Total (N=20385)	Single Arterial (n=16801)	Multi Arterial (n=3584)	OR* (CI)	Male (n=15002)	Female (n=3583)	OR** (CI)
Number of anastomosies, mean (std)	3.05 (1.07)	2.95 (1.06)	3.53 (0.97)	1.74 (1.68, 1.81)	3.59 (0.96)	3.26 (0.98)	0.79 (0.76, 0.81)
Multi-Arterial, n (%)	3584 (17.54%)	NA	NA	NA	3001 (20.0%)	583 (10.83%)	0.49 (0.44, 0.53)
Cardio-pulmonary bypass time+, median (q1, q3)	88 (70, 109)	86 (69, 107)	108 (89, 128)	1.24 (1.21, 1.27)	90 (71, 111)	86 (66, 105)	0.94 (0.92, 0.95)
Aortic cross clamp time+, median (q1, q3)	59 (46, 76)	58 (45, 74)	68 (54, 86)	1.20 (1.17, 1.24)	60 (46, 77)	55 (43, 70)	0.92 (0.90, 0.94)
Offpump, n (%)	10592 (51.96%)	8007 (47.66%)	2585 (72.13%)	2.84 (2.63, 3.08)	7511 (50.07%)	3081 (57.24%)	1.34 (1.25, 1.42)

*Single arterial is reference group. ** Male is reference group.

Table 3. Adverse outcomes by Surgery Type and Gender.

Post-op variables of interest	Single Arterial (n=16801)	Multi Arterial (n=3584)	OR Crude* (CI)	OR Adjusted (CI)	Male (n=15002)	Female (n=5383)	OR Crude** (CI)	OR Adjusted (CI)
MI, n(%)	69 (0.41%)	13 (0.36%)	0.88 (0.49, 1.60)	0.91 (0.50, 1.65)	43 (0.29%)	39 (0.72%)	2.54 (1.64, 3.92)	2.53 (1.63, 3.92)
Sternal infection, n(%)	76 (0.45%)	22 (0.61%)	1.36 (0.85, 2.19)	1.57 (0.97, 2.55)	64 (0.43%)	34 (0.63%)	1.48 (0.98, 2.25)	1.54 (1.01, 2.34)
Stroke, n(%)	211 (1.26%)	40 (1.12%)	0.89 (0.63, 1.25)	1.04 (0.74, 1.47)	144 (0.96%)	107 (1.99%)	2.09 (1.63, 2.69)	2.08 (1.61, 2.68)
Pneumonia, n(%)	535 (3.18%)	124 (3.46%)	1.09 (0.89, 1.33)	1.20 (0.98, 1.46)	487 (3.25%)	172 (3.20%)	0.98 (0.82, 1.17)	0.98 (0.82, 1.17)
Renal failure, n(%)	436 (2.61%)	71 (1.98%)	0.75 (0.59, 0.97)	0.85 (0.66, 1.10)	356 (2.37%)	154 (2.86%)	1.40 (1.21, 1.63)	1.18 (0.97, 1.43)
Discharge death, n(%)	209 (1.24%)	24 (0.67%)	0.54 (0.35, 0.82)	0.66 (0.43, 1.01)	151 (1.01%)	82 (1.52%)	1.52 (1.16, 1.99)	1.47 (1.12, 1.94)
30 day death, n(%)	260 (1.55%)	28 (0.78%)	0.50 (0.34, 0.74)	0.61 (0.41, 0.91)	191 (1.27%)	97 (1.80%)	1.42 (1.11, 1.82)	1.36 (1.06, 1.75)
MACE, n(%)	568 (3.38%)	96 (2.68%)	0.79 (0.63, 0.98)	0.96 (0.77, 1.21)	405 (2.70%)	259 (4.81%)	1.82 (1.55, 2.14)	1.79 (1.52, 2.10)
More than one event	See additional table							

*Single arterial is reference group. ** Male is reference group.

Table 4. Multiple Adverse Events by Surgery Type and Gender

Event number	N (20385)		Single Arterial (n=16801)	Multi Arterial (n=3584)	OR** (95% CI)	Male (n=15002)	Female (n=5383)	OR** (95% CI)
0	19810 (97.18%)		16303 (97.04%)	3507 (97.85%)	ref	14655 (97.69%)	5155 (95.76%)	ref
1	532 (2.61%)		459 (2.73%)	73 (2.04%)	0.91 (0.70, 1.17)	318 (2.21%)	214 (3.98%)	1.87 (1.57, 2.24)
2	40 (0.20%)		36 (0.21%)	4 (0.11%)	0.62 (0.22, 1.75)	27 (0.18%)	13 (0.24%)	1.32 (0.68, 2.57)
3	3 (0.01%)		3 (0.02%)	0	NA	2 (0.01%)	1 (0.02%)	1.28 (0.12, 14.10
			ANOVA	**0.71**		**ANOVA**	**<0.0001**	

*Single arterial is reference group. ** Male is reference group.

Table 5. Survival Analysis by Surgery Type and Gender

Survival analysis	HR*	95% HR CI	p-value
Female	1.36	(1.25, 1.49)	<.0001
Where single arterial	1.37	(1.25, 1.51)	<.0001
Where multi arterial	1.26	(0.99, 1.61)	0.06
Multi arterial	0.76	(0.68, 0.85)	<.0001
Where male	0.75	(0.66, 0.85)	<.0001
Where female	0.76	(0.61, 0.96)	<.0001

* Measures of association are fully adjusted.

Table 6. Internal Validity Investigation of Follow-up Time

30 day mortality	Pre	Post
Cases	217	71
PT	445521	160547
rate	0.000487	0.000442
IDR	1.101375	
Upper CI	1.36935	
Lower CI	0.833401	

FIGURES

Figure 1. Hypothesized Association Directed Acyclic Graph

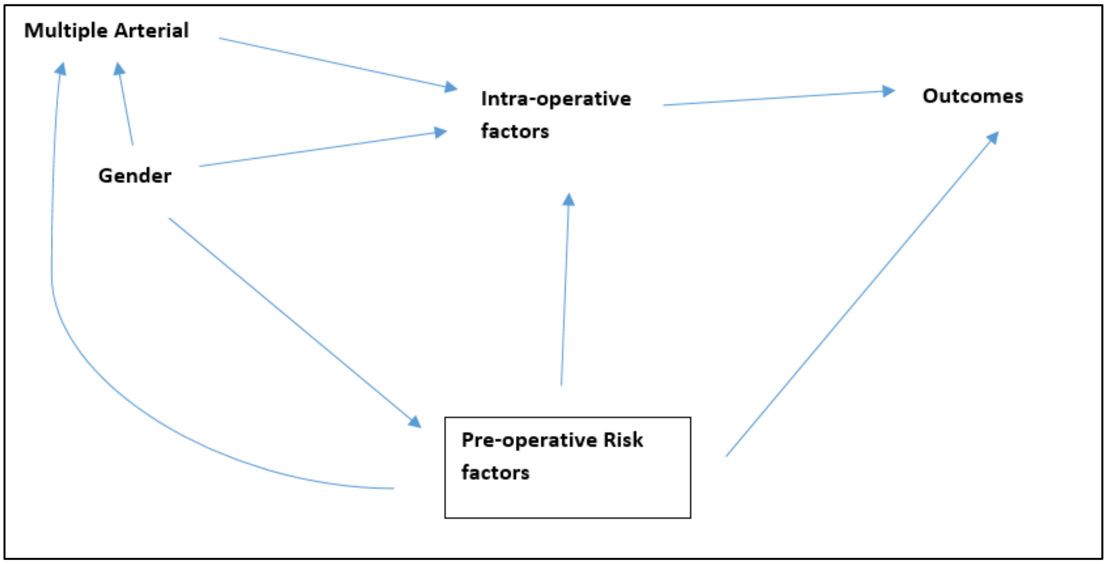
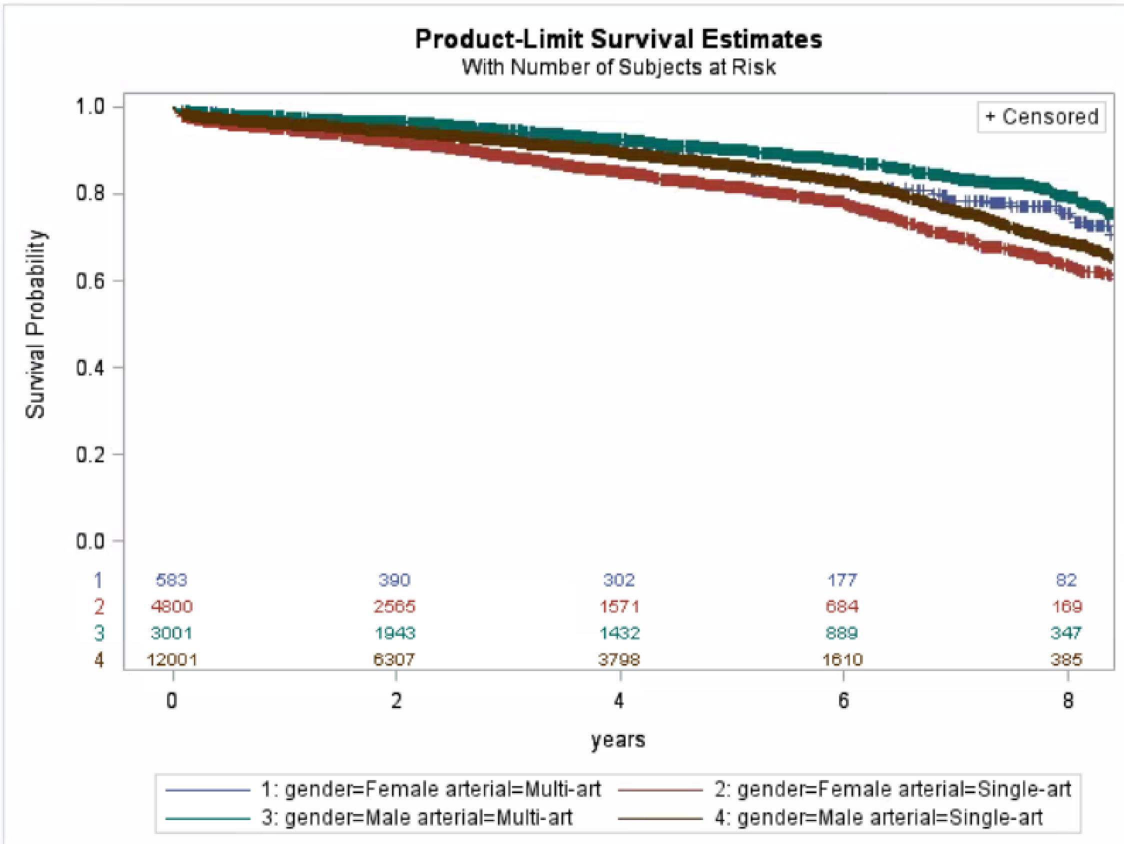


Figure 2. Kaplan Meier Curve by Surgery Type and Gender



Shown above in figure 2 are the Kaplan Meyer curves for each subset of the exposure classifications. The respective hazard ratios are shown in table 5. This plot indicates single arterial CABG females present the lowest rate of survival.

Figure 3. Probability of Multi-arterial CABG

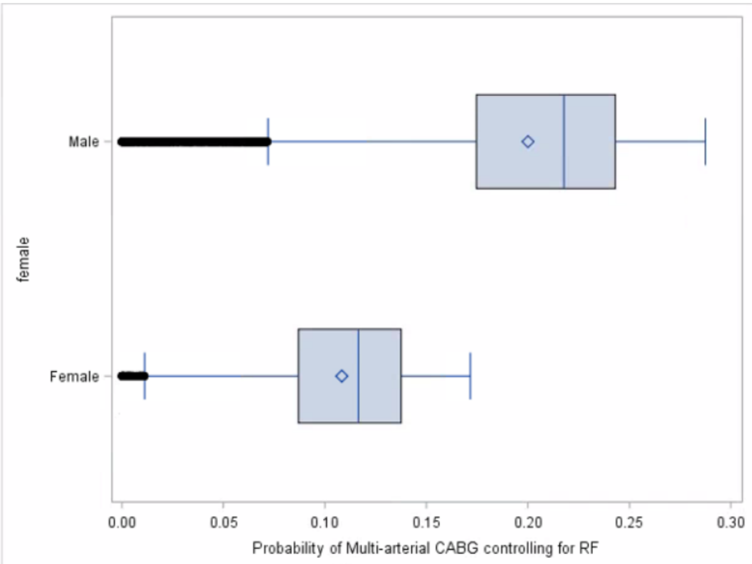


Figure 3 shows the probability of men and women receiving multi-arterial CABG even when all risk factors are held constant.

Chapter III: Future Directions/Public Health Implications

Future directions of CABG

As coronary artery disease continues to be a major driver of mortality among the modern society, it will be ever important to address the problem from multiple points. These will include learning more about preventative measures and improving the treatment/interventions needed for late stage disease. Coronary artery bypass grafting has come a long way since its inception in the 1960's, but there is still progress to be made. As with most interventions, there are new clinical methods to be developed, ways to standardize or improve existing methods, and subpopulations to better understand. All three of these improvements will require future research and investigation.

As epidemiologists and biostatisticians, I believe our work will lie in the second two improvements. The burden of developing new methods primarily falls to the clinicians, but then with a joint effort with biostatisticians to quantify and fully understand the results. It is the nature of epidemiologists to explore relationships between exposure and disease, and so they are aptly suited to investigate existing methods and to investigate them further to search for possible differential risk among patients. Coronary artery bypass grafting has been well studied and current methods have been described in detail, but it is possible new methods may uncover previously unidentified associations.

With the introduction of PROM, a composite risk score, risk factors have been merged into a single score quantifying the predicted risk of mortality. While this is incredibly useful from a clinical standpoint, there is the potential that understanding of the specific risk groups may be lost. It is further possible that true relationships are lost in the calculation. These risk factors should be individually investigated periodically and with new methods to assess whether they continue to be correct.