COST-EFFECTIVENESS ANALYSIS APPROACHES TO COMPARE CLINICAL STRATEGIES

by

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Submitted to the Graduate Faculty of

Graduate School of Public Health in partial fulfillment

of the requirements for the degree of

Doctor of Philosophy

University of Pittsburgh

2015

UNIVERSITY OF PITTSBURGH

GRADUATE SCHOOL OF PUBLIC HEALTH

This dissertation was presented

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It was defended on

January 30, 2015

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ABSTRACT

This dissertation uses the concept of cost-effectiveness to compare interventions, procedures or treatment options in different clinical areas. This dissertation includes three manuscripts comparing specific strategies in the healthcare sector.

The first assesses the economic value of using antimicrobial-coated sutures (as compared to regular sutures) for abdominal incisions to prevent surgical site infections (SSI). We use decision tree analysis to evaluate the cost-effectiveness of antimicrobial sutures under a variety of circumstances. The results show that antimicrobial coated sutures can be a cost-effective measure for preventing SSIs if they have at least have an efficacy of preventing 10% of infections and are used for surgeries with 10% or higher SSI risk.

The second project compares the clinical outcomes, functional outcomes and costs between patients undergoing off-pump and on-pump coronary artery bypass grafting (CABG) using data from the Bypass Angioplasty Revascularization Investigation 2 Diabetes trial. The results show that the off-pump procedure is associated with significantly higher rates of major cardiovascular events (death/myocardial infarction/stroke) even though the short-term complication rate for the two types of CABG are comparable. From the hospital perspective the net health benefits (NHB) were significantly lower for the off-pump patients. From the third party payer perspective, the two strategies were comparable in terms of costs, effectiveness and

NHB. Overall, we conclude that an off-pump procedure is not the favorable strategy as compared to on-pump for patients with diabetes.

The third manuscript compares the cost-effectiveness of three pharmacotherapy switch options for treating depression (bupropion, sertraline and venlafaxine), after failure of initial treatment with citalopram, that were assessed as part of Sequenced Treatment Alternatives to Relieve Depression trial. The calculated NHBs are comparable for the three switch options. This concludes that there is no evidence that any switch option is better/worse than the other in terms of cost-effectiveness.

From a public health perspective, it is essential to determine the cost-effective strategy given the limited resources available. Identification and adoption of cost-effective options can translate to considerable costs saved per effectiveness unit across the entire nation. Also, decisions based on comparing clinical outcomes are further strengthened in cases when strategies have similar cost-effectiveness.

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ACKNOWLEDGEMENT

First and foremost, I would like to express my heartfelt gratitude towards my advisor and chair of my dissertation committee, Dr. Maria M. Brooks. I consider myself really fortunate to get the opportunity to work under her guidance and supervision. I learned a lot under her supervision. I also very sincerely would like to thank my dissertation committee members Margaret A. Potter, J.D., M.S., Ronald E. Voorhees M.D, M.P.H, Stephen R. Wisniewski, Ph.D. and Mark S. Roberts, M.D., M.P.P. for their valuable input and suggestions on the dissertation. Each of the members brought a different perspective to the projects depending on their expertise. I am really grateful to each one of them. I especially thank Dr. Wisniewski for his encouragement and support when I needed it most during my PhD program.

I would also like to thank the MIDAS (Models of Infectious Disease Agent Study) group, Dr. Bruce Lee and Ms. Sarah Bartsch for giving me the opportunity to learn about computational modeling. Also, I am grateful to the department of epidemiology for providing me the exceptional environment to carry out this multidisciplinary research.

Finally, I would like to take this opportunity to thank my friends and family. They were there to help me during my not-so-easy times and also there to share my joys and happiness. The times spent with them are most valuable to me. In particular, I would like to acknowledge my parents and younger brother for their love and support which always kept me motivated. I also

thank my husband for being supportive and immensely understanding during the most critical phase of my doctoral program.

1.0 INTRODUCTION

The World health organization (WHO) defines health as a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity[1].

In 2011, United States of America (US) spent approximately $2.7 trillion i.e. 18% of nation's gross domestic product (GDP) on healthcare[2]. These healthcare costs are predicted to increase with each passing year. The US in fact has a higher healthcare expenditure as compared to many other countries[2]. Figure 1-1 shows health expenditure in terms of GDP for many countries. Figure 1-2 further illustrates that US healthcare expenditure is higher than countries with similar GDP.

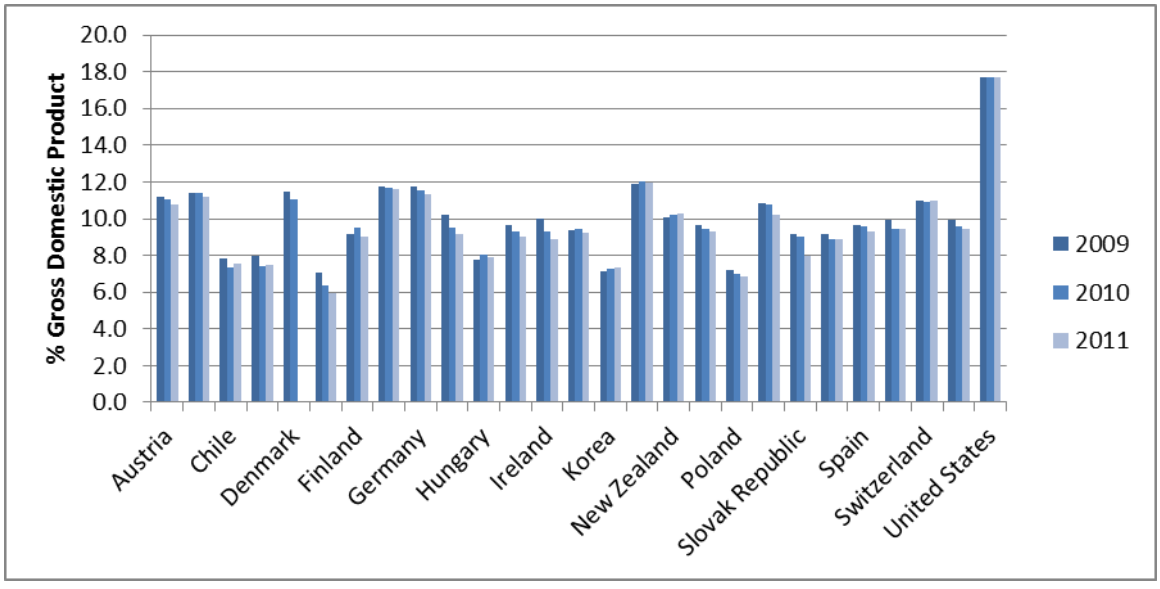

Figure 1-1: Total health expenditure as percentage GDP for years 2009 – 2011[3]

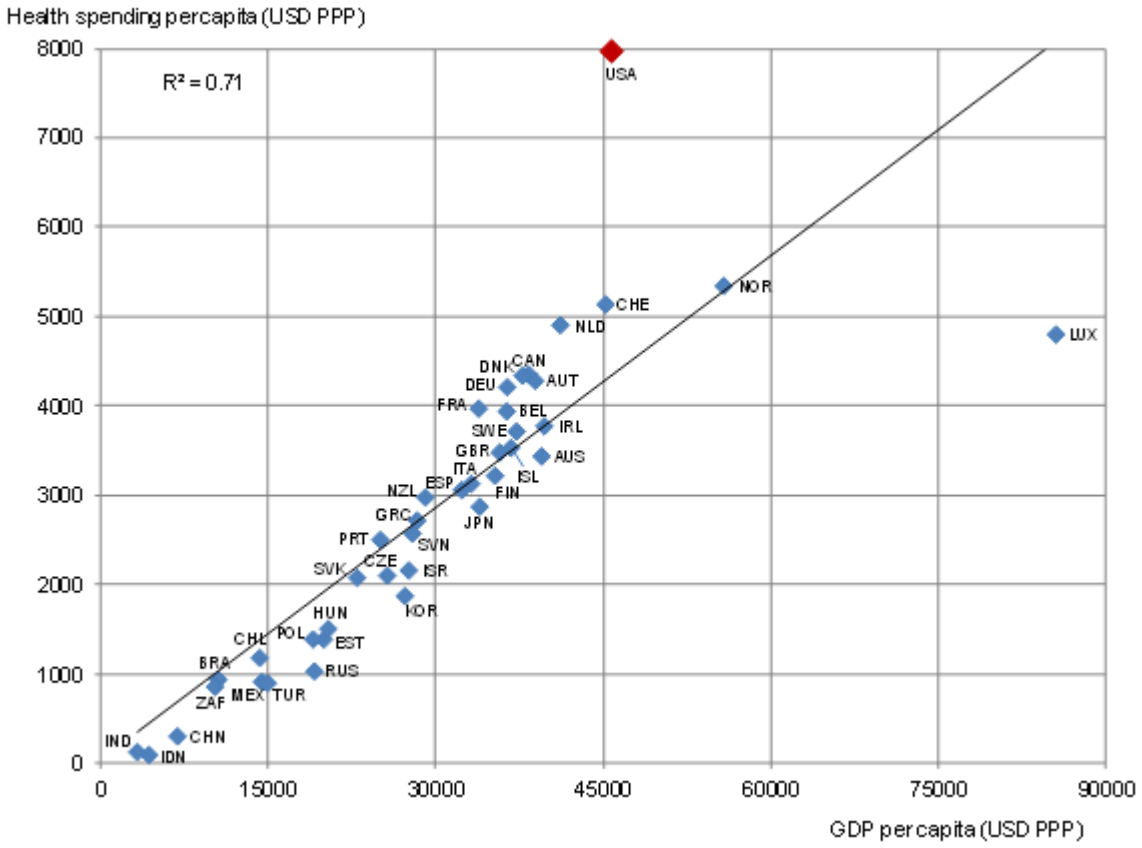

Figure 1-2: Relationship between GDP and healthcare spending per capita[4]

However, in spite of spending substantial amounts of money, US does not show better standards of care or patient satisfaction[5]. Rather, US had the third highest infant mortality rate (6.1 deaths per 1000 live births) and a life expectancy lower than the median (77.9 versus 79.7 years) among countries participating in the Organization of Economic Co-operation and Development in 2011[5, 6]. Also, the US has been shown to have the highest mortality amenable to healthcare conditions (109.7 deaths per 100,000 people) amongst industrialized countries in the past[7, 8].

Thus, newer strategies with better outcomes, higher patient-satisfaction, and lower costs are needed. A multitude of healthcare interventions, treatments and programs are already available, and many more are under development. The number of choices available increase the options that one can choose from but can also be accompanied both by anxiety and growing expectations about access to a range of interventions that may improve health and wellbeing[9]. Economic analyses in the healthcare sector can guide the decision making process and help healthcare stakeholders make informed decisions.

1.1 ECONOMIC ANALYSIS IN HEALTH CARE

1.1.1 *Rationale for economic analyses in healthcare sector*

Health and healthcare hold a prime position, not only at an individual and community level but also at the political level. National agencies have been investing substantial amounts of money towards improving individual and public health. Patient Protection and Affordable Care Act (PPACA) enacted in 2010 is a manifestation of the vested interest in nation's health. The PPACA aims to control healthcare costs, improve healthcare coverage, delivery system and establish its sustainability over the long term. Specifically, the act's comparative-effectiveness research initiative and establishment of Patient-Centered Outcomes Research Institute (PCORI) can assist patients, clinicians, purchasers, and policy-makers in making informed health decisions by advancing the quality and relevance of evidence regarding disease diagnosis, management and treatment. Although the National Institute for Health and Care Excellence (NICE) in UK recommend cost-effectiveness research, the PPACA limits the comparative

effectiveness research by precluding cost-effectiveness research[10]. The precise intent and purpose of this restriction has not been described in the law. One possible concern for this could be that cost considerations can lead to rationing of care and may support a cheaper alternative. However considering costs along with the health outcomes can lead to a more comprehensive, useful and practical decision guide[11, 12]. Especially in the environment of limited resources, comparative effectiveness research need to translate incremental costs to the "value" gained by an alternate intervention in order to be adopted into practice. The evaluation of outcomes, benefits along with side effects, and the associated heterogeneity by themselves may not be sufficient to guide decisions of choosing the appropriate therapy. Also, different stake holders may be interested in different outcomes. An economic analysis can help express results in a common denomination and hence make inferences about a strategy across perspectives. Moreover, in the absence of economic information, decision makers might default to the lower priced option irrespective of improved outcomes associated with the higher priced option. An economic analysis can in fact prevent a high price differential between various alternatives to override the associated incremental benefits, and help choose an intervention that is beneficial overall. An efficient economic analysis may also help determine if a new improved intervention is worth the incremental price given its incremental effectiveness and hence keep the rising health prices in check. Specifically, the ban on using cost-per-quality adjusted life years (QALY) thresholds in the PPACA may also be reflective of the long-standing concerns that this approach often discriminates on the basis of age and disability[13]. However QALY measures have been accepted by many panels in Britain and at the World Health Organization despite its limitations. Experts debate that populations with more impairment typically fare better in cost-effectiveness analyses in terms of QALYs gained. Also ban on cost-utility analysis would leave decision

makers with less information with which to compare the relative effects of interventions across diseases.

Decision makers including administrators, physicians, payers and patients strive to identify the best strategy among the various available choices. Decision-making entails answering numerous questions like what works, with what effectiveness, at what cost, for whom, in what circumstances, and with what impact? Economic analyses can help demonstrate value in the selected choices, and guide decisions in a setting of uncertainty and limited resources[14]. Economic analyses not only facilitate an inform dialogue on achieving affordable and high-quality healthcare but also guide payment and reimbursement policies[15]. Thus, economic information is a necessary complement to comparative clinical effectiveness information for all health care stakeholders. This information will help patients and their physicians make decisions that better reflect the needs and preferences of the patient and support the profession's commitment to a just distribution of finite resources[12].

1.1.2 *Economic evaluations*

Economic evaluations can methodologically be done as cost–minimization, cost–benefit, cost–effectiveness, or cost–utility analysis[16]. These analyses involve estimation and comparison of net or incremental costs and outcomes of two or more strategies. Cost–minimization analysis is performed when outcomes of the alternatives considered are known or can be assumed to be equal. Cost-minimization only considers costs and the least costly alternative is chosen as the most efficient strategy. However, cost-minimization is rarely used because two interventions usually cannot be assumed to have equal effectiveness. The other methods of evaluations like

cost-benefit, cost-effectiveness or cost-utility analyses can be conducted to account for the differences in outcomes. Cost-benefit analyses express both costs and benefits of an intervention in monetary units. This method directly provides an estimate of money saved or spent and can incorporate the widest range of effects across many interventions and programs. However, cost-benefit analyses remain controversial as critics argue that it is unethical to put a monetary value on health and death, and also that the willingness-to-pay may vary widely from individual to individual[17]. Cost-effectiveness is often used when the outcomes of the procedures or programs being considered vary, but their outcome can still be expressed in common health-related units like number of cases prevented, number of lives saved or disability avoided[18, 19]. Such an analysis cannot combine the associated morbidity and mortality into a single index and thus limits comparison between treatments which differ in these two dimensions. Also, it is limited in its ability to assist choices between treatments/strategies if their outcomes vary. In such cases, an extension of cost-effectiveness analysis, cost-utility analysis, is often used. Cost-utility is commonly based on quality adjusted life years (QALYs), calculated as the multiplicative product of utility of a health state and years lived in that state[20] or disability adjusted life years (DALYs).

1.1.3 *Perspectives for economic analysis*

Perspective of an analysis refers to the standpoint from which costs and outcomes (or consequences or benefits) are realized. Conclusions from economic analyses may vary depending on the considered perspective. Healthcare economic evaluations can be conducted from a patient, third-party payer, hospital, or a societal perspective[21, 22]. Each perspective caters

to a different set of decision makers involved in evaluating a new or existing intervention or strategy. The following paragraph briefly details the costs associated with each perspective.

Typically, the patient perspective includes out-of-pocket expenses for treatment and hospitalizations along with lost wages. The overall result of this type of analysis could be misleading if there are little or no out-of-pocket expenses. Third party payer's perspective includes costs paid by the insurance companies for both inpatient and outpatient treatment. Costs such as patient's out-of-pocket expenses or travel costs for treatment are not included in the third party payer's perspective. Generally, costs paid by insurance companies are believed to be good proxies in determining the value of health care products and services. Hospital perspective include the costs that hospitals have to bear due to excess attributable length of stay including intensive care unit stay, diagnostic testing, antimicrobial treatment, healthcare worker time, and isolation supplies (i.e., gloves, gowns, and masks for contact isolation or private rooms for respiratory isolation). Societal perspective is the most inclusive and accounts for all direct and indirect costs associated with a condition. The societal perspective includes all direct inpatient and outpatient medical costs as well as indirect costs such as lost wages, productivity losses due to death and mortality cost.

1.1.4 *Estimating costs*

The economic definition of cost is the value of the best opportunity forgone as a result of investing resources in an activity[23]. Costs can be expressed as average, marginal, incremental, fixed or total costs, depending on the research question of interest.

Economic evaluation of any novel intervention, strategy or program encompass a variety of costs involved in providing and accessing the healthcare services[24]. Costs can be either classified as direct or indirect depending on the way they are incurred. Direct costs comprise of resources spent to implement and provide an intervention. Direct costs can be medical or non-medical costs. Direct medical costs are those that arise directly from the treatment and include diagnosis, drug therapy, medical care, in-patient treatment costs, and direct nonmedical costs and additional resources that may be required to support the medical services such as travel cost or care services. On the other hand, indirect costs include productivity losses resulting from illness and premature death.

Productivity losses can be quantified using the human capital approach or the friction cost approach. Human capital approach calculates productivity losses based on the period-related income of the patient group concerned. If costs specific to the patient group considered are not available, then average labor costs (obtained from official database like Bureau of Labor Statistics) can be used.

Loss of productivity = (Number of days having Incapacity to work x Wage per day)

The friction cost approach assumes costs of productivity losses to be limited to a certain period called the friction period, which is until a patient is replaced by another employee and the former production level is restored. For estimating costs, the friction cost approach encompasses productivity losses in the friction period and transaction costs (searching for and training the new employee). With short-term incapacity for work (within the friction period), part of the workload might be performed by colleagues of a patient or made up for by the patient upon their return to work. Short-term productivity losses as per the friction cost approach are less than that estimated by the human capital approach (about 80 % of labor costs). However long-term losses based on

friction cost approach may or may not yield conservative estimates, depending on the long-term incapacity and mortality rate associated with the condition. Thus, there is lack of consensus on which approach is best to use[25].

1.1.5 *Estimating effects*

The choice of estimating the effect of an intervention depends on its indication as well as on the research question. The outcome parameters must be selected in advance and justified in order to avoid bias. The effects may be measured as number of cases prevented, deaths prevented, cases cured, morbidity reduced or any other physiological or biochemical end points. Effects can also be defined in terms of duration of a health condition. Some examples of time-related effects or outcomes include days spent in hospital, days of incapacity for work, healthy life years, QALY. Healthy life years indicate the number of years a person of a certain age is expected to live without disability[26]. QALYs have become a common metric of estimating effects since they allow for comparisons across different sectors of healthcare[27]. QALYs are expressed as the multiplicative product of the length of time and the health utility for a particular health state. Utility is the desirability and preference that individuals or societies give to a particular state, and is used to reflect quality of life[28]. Popular methods to assess such preferences include the visual analog scale, time trade-off or standard gamble method. Utility values range from 0 to 1[29].

1.1.6 *Adjustments for time differences*

Inflation

Inflation refers to the general increase in prices of goods and services over time. Analyses need to adjust for this increase when comparing costs through time[30]. Various indexes have been devised to measure different aspects of inflation[31]. Some commonly used are consumer price index (CPI), producer price index (PPI), employment cost index (ECI), and GDP deflator. The CPI measures inflation as experienced by consumers in their day-to-day living expenses. It reflects spending patterns for all urban consumers and wage earners, and clerical workers. The PPI measures inflation at earlier stages of the production process. The PPI measures the average change over time in selling prices, from the perspective of domestic producers of goods and services. ECI is a quarterly index measuring change in labor costs, that is, average costs per hour worked, over time. GDP Deflator measures inflation experienced by both consumers themselves as well as governments and other institutions providing goods and services to consumers. The choice of inflation index depends on the policy question and its perspective.

Discounting

Discounting accounts for the fact individuals have a time preference which determines their expenditure and consumption at a given time. It allows for the differential time preferences of costs (and benefits) between programmes by weighting all costs (and benefits) in terms of their present value[32]. Individuals prefer consumption at present over consumption in the future and expenditure in future over expenditure at present. This preference can be attributed to the general uncertainties associated with future[33]. In the case of costs, inflation might be one of the reasons for a given number of dollars having more worth earlier in time. Earlier access to costs may enable purchase of assets which would lead to further profits. Individuals may fear that

interventions might not benefit them in long course of time. Also, incomes are expected to increase over time which lowers the marginal welfare gain from an additional unit of consumption. Thus, individuals are more willing to pay (interest) to consume today rather than wait until tomorrow.

Literature shows discounting of costs is generally well-accepted, however there is less of an agreement on discounting health effects and its associated discount rates. Health, unlike money is not tradable, which generates varied opinions regarding its discounting. Equal discounting of costs and effects has been supported by many established theories like Weinstein and Stason's consistency thesis[34] and Keeler and Cretin's postponing paradox[35]. Weinstein and Stason state that a steady relation between currency and health benefits exists and discounting costs and effects at a different rate may lead to inconsistent results. Also, Keeler and Cretin illustrate that if a different rate is used to discount costs and non-monetary effects, then the results will favor postponing the health intervention to the future as it will be more profitable economically although this might not be ethical. However, critics argue that money value of health benefits such as QALYs is not stable but may change over time and infinite postponing does not seem to be a relevant option in the real world. Recently, there has been an increasing number of advocates for differential discounting, whereby health effects are discounted at a different (typically lower) rate than costs[36]. Differential discount rates can be based on distinct aspects of quantities such as the growth rates of national income and healthy life expectancy[37]. Given the current debates about discounting, guidelines recommend transparency in reporting the discounting methods used[38].

The discrete time formula for discounting is (expressed in terms of cost here):

$$Costs\ (present\ value) = \sum_{t=0}^{T} Cost/(1+r)^t$$

where *r* is the discount rate and *t* is the time period when the cost occurs. Most cost-effectiveness studies use an annual discount rate of 3 – 5%[24].

1.1.7 *Cost-effectiveness analyses*

Economic analyses can be expressed as average, marginal or incremental cost-effectiveness ratios. Average cost effectiveness ratio (ACER) is calculated by dividing the net cost of the intervention by the net change in health outcomes (e.g. total number of health outcomes prevented) due to the intervention. ACERs deal with a single intervention. ACERs can be used to compare two or more alternatives and guide resource allocation if the alternate interventions are independent and mutually compatible. However, a major limitation of ACERs is that they are unable to compare the competing health care strategies for the same medical problem. Marginal or incremental cost-effectiveness ratios (ICERs) are used to compare mutually exclusive strategies[39]. ICER compares the differences between the costs and health outcomes of two alternative interventions that are mutually exclusive. ICER is calculated as the ratio of difference in cost (ΔC) and difference in effects (ΔE) between the two interventions and describes the additional cost per additional health outcome. The incremental costs and effects can be represented visually using the incremental cost–effectiveness plane as represented in Figure 1-3.

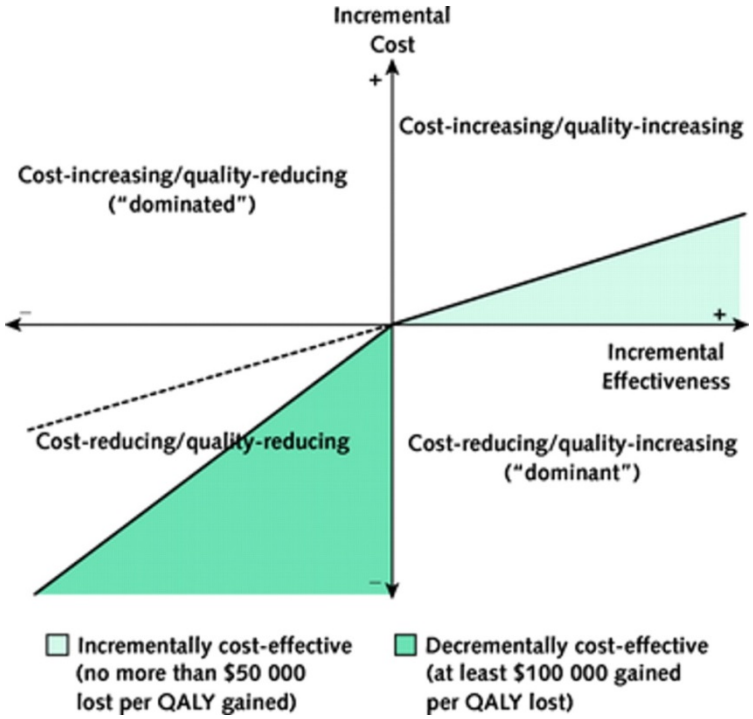

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Figure 1-3: Cost effectiveness plane to calculate the incremental cost-effectiveness ratio

The horizontal axis divides the plane according to incremental cost (positive above and negative below), and the vertical axis divides the plane according to incremental effect (positive to the right and negative to the left) resulting in four quadrants. An intervention resulting in lower costs and higher quality (dominant strategy) or in higher costs and lower quality (dominated strategy), is accepted and rejected respectively, without any controversies[40]. However, interventions that lie in the northeast and southwest quadrants involve cost-effect trade-offs and their acceptability depends on incremental costs-effectiveness ratio (ICER)[41]. The decision of a strategy being cost-effective depends on the ceiling incremental cost-effectiveness ratio.

The ICER interpretation gets ambiguous without the knowledge of incremental cost-effectiveness plane quadrants. A negative ICER can be a result of higher cost and lower quality or lower cost and higher quality, which have exactly opposite interpretations. The ICER distributions often include both negative and positive values, due to associated uncertainties that further add to the ambiguity. Moreover, in the case of multiple comparators, the ICERs along with uncertainties are associated with additional complications. Theoretically, for multiple comparators, the ICERs are calculated after removing all the dominated (more costly and less effective) and the extended dominated (more costly and less effective than a combination of two comparators). The remaining options are ordered in an increasing cost order and ICER is calculated relative to the option immediately preceding it. However, the uncertainty associated with the costs and effectiveness introduces uncertainty in the ranking of programs. A single intervention can have non-zero probabilities of being dominated, dominant, dominating its comparators, and of being ranked between each possible pair of comparators. Additionally, there could be more than one intervention which may have the ICER value less than the specified threshold. Thus, the uncertainty regarding the ranking, estimated cost-effectiveness and the cost-effectiveness of other comparator convolutes interpretation.

In response to the problems associated with the inference of ICERs, Stinnett et al proposed Net Health Benefits (NHB) method for evaluating health interventions given the uncertainties[42]. Stinnett et al define the average NHB for a treatment (T_i) is defined as:

$$NHB = \mu_{Ei} - \mu_{Ci}/\lambda$$

In this formula, and represent the mean effectiveness and the mean costs respectively, of treatment Ti; λ represent the threshold cost-effectiveness ratio. The intervention with the highest NHB is considered to be an optimal strategy.

The $50,000 per QALY threshold, which is based on renal dialysis, has been widely used in United States. This value represents the approximate cost of one year of dialysis treatment. Under Medicare rules, renal dialysis is a federal entitlement to all United States citizens, and is thus considered cost-effective by US standards[43]. This threshold, however, is surrounded by many controversies. The $50,000 limit has not been reevaluated since 1980s, and using the same value might be inappropriate. Although there are no accepted standards, studies commonly use $50,000 to $100,000 per QALY as the ceiling cost-effectiveness ratio, beyond which an intervention is no longer considered cost-effective[44]. There has been no scientific justification for any one threshold and it is more of a sociopolitical decision rather than a medical one. Moreover, the threshold is a dynamic quantity and can change over time. Changes in the optimal price of a QALY may depend on inflation as well as complex interactions between social desires to control health care costs and the rate of development of new health care technologies[43].

1.1.8 *Uncertainty in cost-effectiveness*

The uncertainty associated with cost-effectiveness studies raises concerns on the reliability and validity of its results. This uncertainty can be due to uncertainties associated with parameters, model or generalizability[24]. Uncertainty not only affects the cost and effect estimates but also the decision consequences[45] .

Parameter uncertainty can be due to sampling variation around estimates of unit costs, adherence rates, and the efficacy of an intervention or due to lack of agreement about value

judgments (e.g. discount rate) required for the cost-effectiveness analysis. Model uncertainty refers to the uncertainty around the appropriate functional form of a model used to estimate a particular parameter and the explanatory variables. This usually arises due to structural complexities when considering all joint interventions and states[24, 46]. Probabilistic and deterministic sensitivity analysis can be conducted to reflect the combined implications of uncertainty in the parameters (inputs), and to quantify the uncertainty associated with the cost-effectiveness. In probabilistic sensitivity analysis, model parameters are assigned distributions. The model parameters are sampled multiple times from the distribution, and the output is recorded for each run (using Monte Carlo method, which involves sampling at random). This results in a range of outputs which represents the uncertainty in the inputs. Parameters to which the cost-effectiveness decision is sensitive can be identified using deterministic sensitivity analysis. Deterministic sensitivity analysis sets each parameter at a plausible value, in turn and one at a time. The sensitivity of the decision is determined based on how the cost-effectiveness changes with the parameter value. Statistically, ICER confidence intervals are based on the joint density of ΔC and ΔE**.** The confidence intervals can be calculated using parametric (Fieller's method) or non-parametric (bootstrap) methods. Cost effectiveness analysis curves (CEAC) can also be used to present uncertainty. The CEAC is derived from the joint distribution of incremental costs and incremental effects. CEACs are constructed by plotting the probability that an alternative is cost-effective for a range of ceiling ratio values[47].

2.0 SPECIFIC AIMS

In this dissertation, I will compare specific interventions, procedures and medications for three separate clinical problems. The three specific aims proposed for the dissertation are as stated below.

Specific aim for manuscript 1

To assess the economic value of using antimicrobial-coated sutures (as compared to regular sutures) for abdominal incisions to prevent surgical site infections. This aim used decision tree analysis to evaluate the cost-effectiveness of antimicrobial sutures under a variety of circumstances. The input parameters for the model were obtained from previously published studies and expert opinion.

Specific aim for manuscript 2

To compare the clinical and functional outcomes between patients undergoing off-pump and on-pump coronary artery bypass grafting (CABG). This aim used data from Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI2D) trial to compare the associated clinical and functional outcomes between patients undergoing off-pump and on-pump CABG (non-randomized groups). We also performed a cost-effectiveness analysis to compare the two types of CABGs.

Specific aim for manuscript 3

To compare the cost-effectiveness of three pharmacotherapy switch options for treating depression (bupropion, sertraline and venlaflaxine), after failure of initial treatment with citalopram. This aim used data from STAR*D clinical trial to compare the pharmacotherapy switch options to which patients could be randomized after initial treatment failure with citalopram.

The following sections introduce the clinical areas for the three specific projects included in this dissertation. These sections give an epidemiological overview of the clinical area, discuss the published literature concerning with the intervention/procedure/drug of interest and identify the research gaps. Also, background of the methodologies used for the specific aims is described within each section.

3.0 BACKGROUND AND LITERATURE REVIEW

3.1 SURGICAL SITE INFECTION AND TRICLOSAN COATED SUTURE

3.1.1 *Overview of Surgical Site Infections*

Healthcare associated infections (HAIs) affect 5 to 10 percent of hospitalized patients annually, and have become a major healthcare problem[48]. In fact, HAIs are the fifth leading cause of death among hospitalized patients, accounting for almost 99,000 deaths each year[49]. HAIs can impose additional costs ranging from $28 billion to $33 billion each year[50]. Also, the Deficit Reduction Act released in 2005 does not provide reimbursements for select secondary diagnosis including some HAIs that are not present on admissions[51, 52]. Apart from these direct cost penalties, many states have enacted legislations that mandate public reporting of HAIs[53]. Such mandatory public reporting of HAIs would allow consumers to make informed choices about their health and healthcare facilities, which would impact the hospital clientele. As of December, 2009, 37 states either had passed or had pending legislations regarding public reporting of HAIs[54]. The non-reimbursements and mandatory reporting along with additional costs create even a greater impetus for hospitals to have a handle on HAIs and its prevention strategies.

Surgical Site Infections (SSIs) are the second most common HAIs after urinary tract infections[49]. SSI patients are twice as likely to die, 60% more likely to spend time in an ICU, and more than five times more likely to be readmitted[55]. On average, SSI can extend patient's length of stay by 9.7 days while increasing cost by $20,842 per admission. Nationally SSI cases would lead to an additional 406,730 hospital-days and hospital costs exceeding $900 million[56], imposing a huge burden to the hospitals and society.

SSIs usually occur within 30 days of operation can be classified into three categories depending on the anatomic site of infection: superficial incisional, deep incisional and organ/space. Superficial infections involve only the subcutaneous tissues and are characterized by pain or tenderness, localized swelling, redness or heat; or purulent drainage; or microorganisms isolated from an aseptically obtained fluid/tissues from the incision. Deep incisional SSIs involve soft tissues like the fascial and muscle layers of the incision, and have purulent drainage. Organ/space SSIs are the most severe ones and can involve any part of the anatomy (e.g., organs or spaces) opened or manipulated during the operative procedure. Specific sites are assigned to organ/space SSI to further identify the location of the infection[57].

SSI rates vary considerably with the type of the operative wound. Surgical wounds can be clean, clean-contaminated, contaminated or dirty-infected depending on the degree of intra-operative microbial contamination. Clean wounds are those with no inflammation and do not involve respiratory, alimentary, genital, or urinary tract. Clean-Contaminated involve invasion into the respiratory, alimentary, genital, or urinary tracts under controlled conditions, without any unusual contamination. Specifically, operations involving the biliary tract, appendix, vagina, and oropharynx are included in this category, provided no evidence of infection or major break in technique occurs during the procedure. Contaminated wounds are the open, fresh, accidental

wounds and that may arise from procedures having major breaks in sterile technique for surgeries like cardiac or gross spillage from the gastrointestinal tract. Incisions which have acute, nonpurulent inflammation are also included in this category. Dirty-infected are old traumatic wounds with retained devitalized tissue and those that involve existing clinical infection or perforated viscera[58].

3.1.2 *Prevention of Surgical Site Infection*

The SSIs have received much-deserved attention with many infection prevention initiatives implemented in the past. In 2002, Centers for Medicare and Medicaid Services (CMS) collaborated with CDC to implement the national Surgical Infection Prevention (SIP) project to reduce morbidity and mortality associated with post-operative infections. SIP promotes appropriate selection and timing of prophylactic antimicrobials. Specifically SIP measures include administrating the prophylactic agent within 60 minutes prior to incision, selecting a suitable, safe and narrow spectrum agent, and discontinuing the prophylactic antibiotics within 24 h after end of surgery[59]. In 2003, CMC and CDC representatives met with the VA, the American College of Surgeons, the American Society of Anesthesiologists, the Agency for Healthcare Research and Quality, the American Hospital Association and the institute for Healthcare Improvement to further refine SIP. This resulted in the emergence of Surgical Care Improvement Project (SCIP). SCIP was implemented in 2006 with a aim to achieve 25% reduction in post-operative complications by 2010[60]. SCIP measures include proper hair removal from surgery region, blood glucose control in cardiac surgery patients, and maintenance of normothermia in addition to the original SIP measures, to effectively reduce surgical site infection. Also, this initiative requires facilities to achieve 95% compliance with each of the

process measures in order to avoid penalty of 2% reduction in CMS reimbursements[61]. Studies discussing the impact and success of the SCIP project reflect mixed findings. Rosenberger et al reviewed numerous studies evaluating SCIP measures[62-64] and concluded that implementing standardized practices reduce SSI risk[60]. One other retrospective study comparing pre and post-SCIP guidelines implementation SSI rates, supported the SCIP measures. The authors observed that when their institution had low SCIP compliance (38%), their institutional superficial SSI rates were significantly higher than the national rates (13.3% vs 9.7%) with 38% SCIP compliance. However, when the SCIP measures compliance increased to 92% the SSI rates at their institution decreased to 8.3% and were comparable to the national rates[65]. Many other studies do not report significant benefits of SCIP measures. Pastor et al. reported no significant reduction of SSI rates among patients undergoing colorectal surgery even when compliance with the SCIP measures was increased from 40% to 68%[66]. Another study concluded that though adherence as a composite score of all or no SCIP measures was associated with a lower probability of developing post-operative infections, adherence to individual SCIP measures did not affect the infection rate[67]. Many others have also questioned the SCIP measures as determinants of reimbursement rates and means to reduce SSIs[68, 69]. Also, it is reported that the current evidence-based strategies are able to prevent only 55% of SSIs[70]. This cumulatively implies that existing practices might not be sufficient for preventing SSI, and thus new adjunct strategies are required to effectively prevent SSIs.

3.1.3 *Triclosan-coated Sutures to Prevent Surgical Site Infection*

The role of suture material in development of wound infection has been under speculation since many years[71]. Studies have shown that bacteria adhere to surgical sutures and

that the extent of bacterial adherence is highly dependent on the suture material. The adhered microbes form colonies and eventually a biofilm which can increase SSI risk. The bacterial biofilm is usually difficult to disrupt as it confers immunity from the antimicrobial treatment and the immune system[72]. Antimicrobial coating on sutures can prevent the microbial adherence and hence reduce SSI development. Triclosan (2, 4, 4-trichloro-2-hydroxydiphenyl ether) is a stable, synthetic, polychlorinated, aromatic hydrocarbon with broad, antimicrobial properties and an established safety profile[73]. Triclosan has also found its niche in surgical sutures. Presently, there are three commercially triclosan-coated sutures available: Monocryl Plus (poliglecaprone 25 suture), Coated Vicryl Plus Antibacterial (polyglactin 910 suture), and PDS Plus antibacterial (polydioxanone suture). In vitro studies have shown that these triclosan coated sutures are effective against common surgical site bacteria like Staphylococcus aureus, Staphylococcus epidermidis, Methicillin-resistant S aureus (MRSA), Methicillin-resistant S epidermidis (MRSE), Escherichia coli, and Klebsiella pneumonia[74-76].

There have been several clinical studies published in the past few years which evaluate the antimicrobial sutures. The published studies report varied efficacy and effectiveness of triclosan coated sutures to prevent SSI. This variation can possibly be due to differences in studies regarding the type of surgery, study design, sample size, incision closure method, SSI definition, country or other external factors. In a nonrandomized study, Justinger et al showed that using triclosan coated sutures lowered SSI rates by more than 50% for patients undergoing abdominal incisions[77]. Many other randomized clinical trials conducted across the world also support the use of these triclosan coated sutures. Rasic et al conducted a randomized un-blinded study which showed that patients undergoing elective colorectal cancer surgery had a significantly lower SSI rates (4.3% vs 13.2%) when operated using coated vicryl sutures[78].

Another double blind trial showed that using triclosan-coated PDS suture lowered the odds of developing a wound infection in abdominal surgery to 0.501 (95% confidence interval 0.3–0.9, $P < .05$)[79] . Galal et al conducted a randomized prospective multicenter study for patients undergoing any surgery and reported significant differences in SSI rates between triclosan coated and uncoated sutures (7% versus 15%)[80]. Recently, Nakumera et al conducted a randomized clinical trial showed that triclosan coated sutures are effective for preventing SSIs after colorectal surgery and also cost saving (saving upto $40,219 during the study period of 30 days). However, this estimate is based on results from just one controlled study conducted in Japan[81]. Apart from these studies demonstrating beneficial effects of triclosan coated sutures, one multicenter study did not find any beneficial effects of triclosan coated sutures[82]. The authors concluded that abdominal wall closure with looped polydiaxenine had lower SSI rates, independent of whether the suture was coated or uncoated. Triclosan coated sutures are shown to be effective even for cerebrospinal shunt and breast surgeries[70, 83, 84]. Initial results for SSI prevention among patients undergoing cardiac vascular surgeries do not indicate additional benefits of triclosan coated sutures, which could be because such surgeries have a sterile environment[85-87]. Two recent meta-analysis also support the use the triclosan coated sutures, in spite of the included studies reporting a wide range of effectiveness for the coated-sutures[88, 89].

Thus, there is clearly a growing evidence of clinical benefits of using triclosan coated sutures. However, triclosan coated sutures are almost 40% more expensive than regular sutures which may limit their adoption into practice. We aim to evaluate the cost-effectiveness of using triclosan coated sutures for abdominal incisions among adults, which is associated with a high SSI rate[90].

3.1.4 *Methods Used*

Decision analytic modeling is a systematic approach to decision making under uncertain conditions[91]. It allows comparison of expected consequences of different strategies after considering the relevant events and complication with their probabilities and accordingly weighting the outcomes and costs. A decision analytic model uses a logical mathematical framework that integrates health outcomes and costs which follow alternative courses of action. These models are often built as trees that allow visual representation of all the possible options and the consequences following each option. Decision trees are typically built from left to right, starting with a decision node (denoted by a square) to represent the decision question. Each alternative action is followed by branches representing the possible events with their respective probabilities at the chance nodes (denoted by circle). Probabilities and associated outcomes may depend on the different strategies and the patient characteristics (e.g. age). At the end of the tree each path leads to an outcome, such as symptoms, clinical score, survival, and death. The end points of each pathway are denoted by terminal nodes (triangular symbols) to which values or pay-offs, such as costs, life years, or QALYs can be assigned. For each alternative action the expected value of the clinical outcome can be calculated as a weighted average of all possible outcomes, applying the path probabilities as weights[92].

We developed a decision tree using TreeAge software to simulate the decision of choosing triclosan-coated sutures versus the standard uncoated sutures for adult patients undergoing abdominal surgeries (TreeAge software Inc, Williamstown, Massachusetts developed this software that allows visual modeling of decision trees and can support markov models, cost-effectiveness analysis, net benefits, healthcare reporting and patient-specific simulations).

Each patient in the model underwent an abdominal surgery and had a probability of developing superficial SSI, deep SSI. The probability of developing superficial or deep SSI was based on the risk of SSI and the probability of it being deep or superficial. Each type of SSI could either be mild/moderate or severe, which determined the treatment. The duration of hospitalization attributable and finally the probability of death depended on the type of SSI. Each of the pathways had the associated cost specific to each perspective. Extensive literature review and expert opinion determined the input parameters of the model. Separate analyses were carried out from hospital, third party payer, and societal perspectives to determine the economic benefits of using antimicrobial-coated sutures.

The results of any decision analytical model are influenced by random variability, uncertainty in the parameters, patient heterogeneity and structural uncertainty. These uncertainties must be handled appropriately or reflected in the results[93-95].

The individual variability in decision trees is reflected by using random numbers when determining whether an event with a given probability of occurring happens or not in any given cycle or model run. This individual patient variability is also called stochastic or first order uncertainty. A first-order Monte Carlo analysis simulates subjects one by one to determine the individual's path. Probabilities at chance nodes and random number generator result in a subject's path along the chance nodes. This path is called a random walk or a trial. This accounts for the variability due to an identical patient experiencing different outcomes. The first-order uncertainty is usually eliminated by running the model repeatedly until a stable estimate is obtained.

Secondly, there is always some uncertainty and imprecision surrounding the value of model variables such as transition probabilities, costs, and health utilities. The uncertainty about

the parameter values can be represented by probability distributions in the model. This is commonly referred as the second-order uncertainty or probabilistic sensitivity analysis (PSA). PSA involves randomly drawing a value for each parameter from its probability distribution, generating a set of values commonly referred to as a sample.

In our model, we accounted for random variability along with parameter uncertainty; we parameterized the distributions in the model representing the first-order variability by sampling each distribution per individual. Monte Carlo simulation used dynamic information from the computer's clock to initialize a sequence of pseudo-random numbers. Also, sensitivity analyses systematically varied the risk of developing an SSI (range: 5% - 20%), the cost of tricolsan coated sutures (range: $5 - $25 per inch), and the efficacy of tricolsan suture to prevent infection (range: 5% - 50%). Experts speculate that antimicrobial coated sutures will be more effective in preventing superficial SSI as compared to deep SSIs, so we also varied the efficacy of preventing superficial (range: 10% – 50%) and deep SSIs (range: 5 – 20%) differentially.

Additional method details and results are presented in the manuscript 1.

3.2 CABG SURGERY AMONG DIABETIC PATIENTS

3.2.1 *Coronary Artery Disease among Diabetics*

The prevalence of diabetes is increasing at an epidemic rate worldwide. The number of people with diabetes is projected to rise from 171 million in 2000 to 366 million in 2030[96]. Diabetes patients have many complications including amputation, lower extremity infection, gangrene, blindness, acute myocardial infarction, ischemic heart disease, stroke, and metabolic disorders[97]. Diabetes has been shown to be a major risk factor for cardiovascular disease in numerous studies. The risk of having cardiovascular disease is almost two to four times higher among individuals with diabetes as compared to those without diabetes[98-100]. This association between diabetes and cardiovascular disease persists even after adjusting for many cardiovascular risk factors like age, cholesterol level, systolic blood pressure and tobacco use. Coronary artery disease among diabetic individuals is more severe, diffused and is associated with a higher atherosclerotic burden and inadequate compensatory remodeling of the arterial wall[101-103]. Diabetes and cardiovascular disease, both, impose an enormous burden on the society[104, 105]. Many interventions like cardiovascular risk factor control, glycemic risk factor control, screening for diabetes complications, have been introduced to reduce the burden of diabetes and cardiovascular disease[99]. Never the less, the prevalence of cardiovascular disease among patients with diabetes continues to be high. As a corollary, diabetes has become disproportionately represented in patients having cardiovascular disease.

3.2.2 *Coronary artery bypass grafting: On-pump and Off-pump*

Coronary artery bypass grafting (CABG) is commonly performed for patients with severe coronary artery disease. CABG, first performed by Kolesov in 1967[106], even today, is one of the leading heart operations. According to the National Hospital Discharge Survey (NHDS), almost 232,000 patients in US underwent a total of 408,000 coronary artery bypass procedures in 2007[107]. Specifically, the percentage of patients undergoing CABG having diabetes has increased from 16.7% in 1988 - 1990 to 33.9% in 2003 - 2005[108]. CABG involves strategic placement of bypass grafts that provide an alternative route for the blood to circumvent the blockage. Arteries and veins from patient's body, which can be removed from their primary location without harming or disrupting any of the other body functionalities, are often used as bypass grafts. These blood vessels are grafted onto a blood supply source (mostly the aorta) and then in turn onto the coronary artery in a location beyond the blockage[109]. CABG can either be performed as an on-pump or off-pump strategy. On-pump CABG is often considered to be the gold standard and uses cardiopulmonary bypass (CPB) with cardioplegia arrest. Off-pump procedure is a relatively newer procedure, performed without the use of CPB.

On-pump CABG commonly results in myocardial ischemic injury, neurocognitive deficits, strokes, and activates other inflammatory pathways that may contribute to pulmonary, renal, and hematologic complications[110-112]. Advocates believe that performing the off-pump CABG may decrease the post-procedure morbidity, mortality, and costs by eliminating CPB and hence reducing the detrimental effects associated with it. Although several randomized controlled trials, prospective and observational studies have compared on-pump and off-pump CABGs, the optimal surgical strategy remains in question[113-120]. A large randomized controlled trial including patients with mixed operative risk profile compared the off-pump and on-pump CABG with respect to outcomes at 30-days and at 1 year[121]. The results of the trial showed that the composite outcome (death and complications) rate was not significantly different at 30 days, however the rate at 1 year was significantly higher for off-pump patients. A few other studies support favorable short-term outcomes with off-pump CABGs; however such beneficial effects do not persist when considering long-term outcomes[122-124]. Also, studies suggesting that off-pump CABG is comparable to on-pump in terms of complete revascularization and graft patency[125-127] have been questioned by reports of inferior graft patency and higher rates of repeat target-vessel revascularization associated with off-pump CABG[128-130]. Adverse neurologic outcome rates have also been reported to be similar between the two procedures[120, 131, 132]. The randomized controlled trials for comparison of the two types of CABGs, have been criticized for their strict patient inclusion/exclusion criteria and that the randomization process may require the surgeons and health centers to perform the assigned procedure even if they are not comfortable with it. Many observational and prospective studies, in contrary to randomized trials, show that off-pump strategy have a beneficial impact on patient mortality and morbidity[114-118]. A recent retrospective study including patients who underwent CABG between 2005 - 2010 in the Society

of Thoracic Surgeons (STS) national database, showed that off-pump procedure had significantly fewer adverse events of death, stroke, renal failure, and prolonged length of stay as compared to on-pump procedure, after adjusting for patient risk factors, center and surgeon identity[133]. Observational studies of course have the potential for confounding factors or treatment selection bias.

There is ongoing debate regarding the use of off-pump CABG over on-pump CABG. Most of the above described studies include patients with low or moderate risks of complications after CABG. Initial evidence suggests that off-pump strategy might be of maximum benefit to high risk patients[134]. Two recent trials, namely Danish On-Pump Versus Off-Pump Randomization Study (DOORS) [135] and German Off-Pump Coronary Artery Bypass Grafting in Elderly (GOPABE)[136] included only elderly patients. Elderly patients are a subgroup of people who have higher risk of adverse outcomes after surgery. Both the trials showed no significant difference in the outcomes of death, myocardial infarction or stroke between off-pump and on-pump surgeries. Although DOORS trial observed trends towards fewer strokes and more myocardial infarctions in the off-pump group, the differences were not significant. In GOPABE trial, repeat revascularization within 30 days was more common among patients undergoing off-pump CABG in comparison to those undergoing on-pump CABG; however this difference was not significant at 12 months after surgery. Another recent study, though single institution had over 5000 patients, evaluated the long-term outcomes of patients undergoing on-pump and off-pump CABG[137]. This study showed that patients undergoing off-pump procedure had a significantly higher risk of mortality as compared to those undergoing on-pump procedure.

Diabetic patients have a different cardiovascular disease profile and a higher risk of adverse events after surgery. In the studies described above, patients with diabetes form only a

fraction of the sample population. To date, there are no randomized controlled trials comparing effects of off-pump and on-pump strategies in diabetic individuals with coronary artery disease. The limited comparative data available are based on retrospective, observational, non-randomized studies and continue to be controversial. A retrospective review of STS data for diabetic patients undergoing CABG during the years 1995 to 1999 showed no significant differences in mortality (2.89% versus 3.69%, p = 0.452) between the off-pump and on-pump surgeries. However, the patients undergoing off-pump CABG had fewer complications, including decreased blood product use (34.39% versus 58.4%, p = 0.001), reduced incidence of prolonged ventilation (6.94% versus 12.10%, p = 0.005), atrial fibrillation (15.90% versus 23.26%, p = 0.002), and renal failure requiring dialysis (0.87% versus 2.75%, p = 0.036)[138]. Another retrospective analysis, which identified diabetes patients undergoing CABG during April 1997 – Sept 2002 from a cardiothoracic center, had similar conclusions as the previous STS review. The results showed that although the in-hospital mortality (2.1% versus 3.7%, p = 0.25) was not significantly different between the off-pump and on-pump groups, patients undergoing off-pump procedure had fewer post-operative complications like stroke (OR 0.15; 95% CI 0.02 - 0.96; p = 0.039) , renal failure (OR 0.38; 95% CI 0.16 - 0.94; p = 0.036) and required lesser blood transfusion (OR 0.21 ; 95% CI 0.14 – 0.32; p<0.0001) [139].

A recent retrospective study comparing off-pump and on-pump strategy among individuals with diabetes, however showed survival benefits on using the off-pump procedure[140]. In this study, patients undergoing off-pump CABG had a significantly lower mortality rate (OR = 0.11; CI 95% 0.01–0.68; *p*=0.018) as well lower odds of non-cardiac complications (including respiratory failure, renal failure, and thoracotomy compositely) (OR =0.46; CI 95% 0.35–0.91; *p*<0.001) as compared to those undergoing on-pump CABG. Cardiac complications such as

stroke, reoperation for bleeding, postoperative intra-aortic balloon pump implantation were also less frequent in the off-pump group, though the differences were not statistically significant. It should be noted that in most of the studies described above, the time to event was not clearly specified. Only one recent observational study defined time periods (30 days, 6 months and 1 year) to compare mortality rates between off-pump and on-pump procedures[141]. The study showed that off-pump CABG was associated with a significantly lower 30-day mortality rate (OR 0.09; 95% CI: 0.01 - 0.70; p = 0.021). The analyses revealed survival benefits on using off-pump strategy even at 6 months (HR 0.27 [95% CI: 0.12 to 0.61] p = 0.002) and 1 year (HR= 0.40 [95% CI: 0.22 to 0.75] p = 0.004) after surgery. The study also found off-pump CABGs to have fewer neurologic complications and less frequent hemofiltration until discharge. However, this study was limited to a single center and did not include long-term outcomes.

Overall, the current evidence is not sufficient to draw conclusions regarding the superiority of off-pump procedure among diabetic individuals. Moreover, none of the studies have compared the economic impact of using off-pump and on-pump procedures among diabetic patients. This study aims to fill the dearth of comparative data between the two procedures. The analyses will compare clinical and functional outcomes for diabetic patients undergoing off-pump and on-pump surgeries.

3.2.3 *Methods Used*

Sample Population

This aim uses data from Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI2D). BARI2D was a 2X2 factorial design clinical trial which included 2,368 patients with type 2 diabetes and angiographically documented coronary artery disease. Randomization was

stratified by the intended revascularization method (i.e. whether a patient was more suitable for CABG or percutaneous coronary intervention (PCI), determined by the individual site physicians). After stratification, the eligible patients were randomly assigned to either prompt revascularization or medical therapy within each stratum. Simultaneously, the patients were randomly assigned to either insulin sensitization or insulin provision therapy to achieve a target HbA1c < 7.0%. Trial participants were enrolled starting January 1, 2001 to March 31, 2005 from 49 sites across 6 countries including United States, Canada, Brazil, Mexico, the Czech Republic and Austria. This analysis focused on BARI2D patients who underwent a CABG procedure irrespective of their intended method revascularization and assigned treatments. In the case that a patient had more than one CABG, the index CABG within the trial was considered for all evaluations and comparisons. The surgery could either be performed as an on-pump or off-pump procedure. The decision to perform an off-pump versus an on-pump procedure in the trial was based on clinical site practice patterns, individual surgeon preference, clinical characteristics of the patient, and the perceived target quality. This aim will compare clinical and functional outcomes between patients undergoing off-pump and on-pump CABG.

Statistical Analyses

This study compares two nonrandomized groups from the BARI 2D trial, namely the off-pump and on-pump group. Summary statistics for the baseline characteristics are presented as means and standard deviation in case of continuous variables, and as numbers and percentages in case of categorical variables. The continuous variables were compared using Wilcoxon rank-sum test and categorical variables using chi-square or Fischer's exact, where appropriate.

The clinical outcomes (over the period of four years) were evaluated using Kaplan-Meier curves with log-rank statistics and multivariate Cox proportional hazard regression models. Two approaches were undertaken to evaluate the clinical outcomes of death and death/MI/stroke: 1) standard multivariate regression and 2) propensity score analysis.

Multivariable Cox Regression Model

The Cox proportional hazard regression models are commonly used for time-to-event analyses. Such analyses have an advantage of including censored data. Cox proportional hazard models provide an estimate of the ratio of hazards of two groups. The candidate variables for models for each of the two outcomes included those baseline variables that were significantly different between the off-pump and on-pump group (alpha = 0.05). The final models were determined by backward selection algorithm. We tested the proportional-hazard assumption for the cox regression model.

Propensity Score Analysis

Propensity score methodology was used to account for the imbalances between the off-pump and on-pump group that may be present due to non-randomization of the procedure. Propensity scores for each patient were calculated using multivariable logistic regression model. The propensity scores represented the conditional probability that a patient would undergo an off-pump given his/her preoperative characteristics. Three commonly used propensity scores methodology for cardiovascular research are: stratification, covariate adjustment, and matching. We used propensity score matching method to obtain a balanced sample for comparing the off-pump and on-pump group. The following text describes the propensity score techniques briefly.

Creation of Propensity Score Model:

Propensity scores are most commonly estimated using binomial logistic regression model where the treatment selected is the outcome measure. Other methods such as the probit models, classification tress, neural networks and recursive partitioning can also be used for calculating the propensity scores. The basic rule for covariate selection for any of the methods is that a liberal criterion should be used to identify the factors that lead to treatment selection choice and are related to the outcome.

Stratification based on Propensity Scores:

Stratification involves dividing individuals into groups or strata based on their propensity score values. The optimal number of strata depends on the sample size and the amount of overlap between the treatment and control groups' propensity scores. However, Rosenbaum and Rubin have demonstrated that stratifying on the quintiles of the estimated propensity score eliminates approximately 90 per cent of the bias due to the observed covariates[142]. The basic principle of stratification is that the treated and untreated subjects will have roughly similar values of the propensity score within each stratum. The average treatment effect can be estimated by a weighting average of the within-strata estimates of the effect of the exposure, with proportion of subjects who are within that stratum. Alternately, the average treatment effect among the treated can be estimated by weighting the strata by the fraction of the exposed in each strata[143, 144].

Matching based on Propensity Scores:

Matching on propensity score allows one to obtain groups of treatment and control subjects by matching individual observations which have similar distribution of measured

baseline variables. Typically, 1:1 nearest neighbor matching within a specified caliper width is used. By this method, treated subjects are randomly sorted and matched to the untreated subject with the closest propensity score within a specified range (the caliper width). If the algorithm is unable to find a match within a specified caliper width of the treated subject's propensity score, then that treated subject is left unmatched and is not used in subsequent analyses. Matching without replacement is usually employed. The propensity score–matched sample cannot be assumed to consist of independent observations, as the treated and untreated subjects within the same matched pair would be more similar than two randomly selected treated and untreated subjects. Thus any analyses within the propensity matched sample should account for the within-pair homogeneity[143, 145]. The results obtained from the propensity score matched sample estimate the average treatment effect among the treated.

Covariate Adjustment:

Propensity scores can also be used as a covariate in a regression model. The choice of regression model depends on the nature of the outcome. The treatment effect may be estimated by adjusted difference in means/odds ratio/hazard ratio depending on the outcome type. This method assumes that the relationship between the propensity score and the outcome has been correctly modeled. The average treatment effect and the average treatment effect among the treated can be estimated by evaluating the exposure effect at sample mean and the sample mean in the treated group respectively.

Propensity Score Matching Compared to Other Propensity Score Methodologies

Propensity score matching is increasingly gaining popularity for analyzing observational data. Propensity score matching allows direct comparison of the treated and untreated subject within a sample which has reduced or no baseline differences. Propensity score matching results in the elimination of a greater degree of systematic differences between treated and untreated subjects as compared to the stratification methodology. Also, when matching on propensity scores, one can check if the propensity score model has been adequately specified by confirming that the treated and untreated subjects have similar distribution of measured baseline variables. However, this is unclear when propensity scores as used as a covariate. Covariate adjustment using the propensity score is a model-based approach and thus requires the assumption that the outcomes model is correctly specified.

Propensity Assumptions

Propensity score analyses have some underlying assumptions. The first assumption is that the treatment assignment should temporally precede the effect. Secondly, every subject should have a non-zero probability to receive either treatment. Also propensity score analyses assume that the outcomes from two individuals, irrespective of their treatment assignment, are independent from each other. Finally, these analyses require that the assigned treatment is independent of the potential outcome, given the observed baseline covariates, i.e. there are no unmeasured confounders that can affect the treatment assignment or outcome.

Additional methods and results comparing the outcomes between patients undergoing off-pump and on-pump are presented in manuscript 2.

3.2.4 *Methods Used in Cost-effectiveness Addendum*

We conducted an economic analysis to compare the cost-effectiveness of off-pump and on-pump among patients who had CABG as their index procedure and had 2 years of potential follow-up data. A separate set of propensity scores was calculated to balance the baseline characteristics in this subset of patients. Analyses were conducted from hospital and third party payer perspective. We assessed cost-effectiveness in terms of the net health benefits. Non parametric bootstrap technique was used to reflect the uncertainty associated with the analyses. The bootstrap method involved estimating the sampling distribution of a statistic through a large number of simulations, based on sampling with replacement from the original data. The advantage of bootstrap technique is that it does not rely on the parametric assumptions of the distribution. Confidence intervals can be estimated using the empirical estimate of the sampling distribution[146]. The bootstrapping involved resampling the patients undergoing off-pump and on-pump separately. The cost and effects for were sampled jointly, and the mean cost and effect estimates from each of the two groups were used to calculate the required NHBs. Also, after 1000 bootstrap replications, the probability that off-pump is the optimum strategy was calculated as the percentage of iterations for which T_i is estimated to have the highest average NHB.

Additional methods and results comparing the cost-effectiveness of off-pump versus on-pump procedure are presented in manuscript 2 addendum .

3.3 MAJOR DEPRESSION DISORDER AND SECOND-LINE ANTIDEPRESSANTS

3.3.1 *Overview of Major Depressive Disorder*

The global burden of depressive disorders is continuing to increase due to population growth and higher life expectancy. Major depressive disorder (MDD) is a widespread medical illness, affecting 15 million American adults, i.e. approximately 5-8 percent of the adult population in a given year[147]. According to the Composite International Diagnostic Interview (CIDI) scores, MDD has a life time prevalence of 16.2% (95% confidence interval: 15.1-17.3), equivalent to a population projections of 32.6 to 35.1 million US adults[148]. Women are almost twice as likely to suffer from depression than males, with the lifetime prevalence ranging from 10 – 25% among females and the prevalence of 5 – 12% among males[149]. Also, MDD typically is a recurrent condition, with 50 – 85% of MDD patients suffering from a subsequent episode[150].

The common symptoms of depression include persistently sad or irritable mood, pronounced changes in sleep, appetite and energy, difficulty thinking, concentrating and remembering, physical slowing or agitation, lack of interest in leisure activities, feelings of guilt, worthlessness, hopelessness and emptiness, recurrent thoughts of death or suicide, persistent physical symptoms that do not respond to treatment, such as headaches, digestive disorders and chronic pain. MDD is in fact one of the leading cause of disability. Depressive disorders can result in 65.5 million disability adjusted life years (DALYs) and are responsible for about 4.3% of total DALYs[151]. A recent systematic review showed that MDD was the second leading cause of years lived with disability (YLD) , accounting for 8.2% of YLDs in 2010[152]. The largest proportion of YLDs from depressive disorders occurred among adults of working age. MDD also resulted in substantial disability adjusted life years (DALYs) accounting for 2.5% (1.9% - 3.2%)

global DALYs. Moreover, in their analyses MDD explained an additional 16 million DALYs and 4 million DALYs when it was considered as a risk factor for suicide and ischemic heart disease, respectively, thus increasing the overall burden of depressive disorders to 3.8% of global DALYs. Overall, MDD is associated with significant social, educational, and vocational impairment, high utilization health care services; and increased morbidity and mortality[153]. MDD can cause over $44 billion/year including direct and indirect costs. Depressed patients incur almost twice the annual health care costs of that by patients lacking depression[154].

Appropriate treatment of depression is essential. An untreated depression episode can last approximately 6 months and in 20% of cases it can even extend to 2 years or more. Also, when the major depressive episode remits without treatment, 20% to 30% of patients retain residual symptoms, which can be distressing and associated with disability.

There are many options available to treat MDD, including pharmacotherapy and psychotherapy. Pharamacotherapy aims to achieve the chemical balance between the neurotransmitters, disruption of which is often believed to be the biological cause of depression. Antidepressants usually work by increasing the availability of neurotransmitters or by changing the sensitivity of the receptors for these chemical messengers. Almost 50% to 70% of patients respond (usually defined as a ≥50% decrease in depressive symptoms) to the first choice of antidepressants[155]. However, only 50 – 70% of those who respond achieve full remission[156, 157] . Thus, a proportion of patients continue to have residual depression symptoms despite apparently adequate antidepressant therapy. Treatment-resistant depression (TRD) is defined as the failure to achieve full remission with an antidepressant used at an adequate dose and duration. TRD is associated with 40% higher costs [158]. When patients have such treatment resistant depression, they should be switched to or augmented with another treatment.

3.3.2 *Cost-effectiveness of Second-Line Antidepressants*

Though there have been studies evaluating efficacy and tolerability of antidepressant medications, data on cost-effectiveness comparing the treatments remain limited. The growing burden of depression and the range of choices available warrant an economic analysis to identify the cost-effective treatment option to treat depression[159]. Most of the existing economic evaluations for depression treatment focus on the first-line treatment options, though some do consider switch, titration and augmentation in their calculations[160]. These studies offer valuable insight, however decision on which second line treatment to choose remains ambiguous.

The literature on economic analyses of second-line treatment options for MDD remains sparse. There are two cost analyses studies which used administrative databases to compare second-line therapies for MDD. Both studies showed that the costs associated with various second-line therapies were not significantly different[161, 162], although one of them revealed differences in depression-coded expenditures between SSRI and tricyclic antidepressant therapy even after adjusting for baseline characteristics[162]. However, these were observational studies and the authors indicated that there might be differences in medication prescribing patterns for various drugs which can affect the outcomes and/or costs.

Also, two recently published studies use computational models to evaluate second-line MDD treatment options. One of the studies developed a decision analysis model to compare generic SSRIs consisting of citalopram, fluoxetine, and paroxetine; escitalopram (Lexapro); paroxetine CR (Paxil CR); sertraline (Zoloft); and venlafaxine XR (Effexor XR) [163]. The study reported generic SSRI to have the lowest cost per patient while venlafaxine was the most favorable option in terms of costs per patient achieving remission. However, this study obtained costs data from an observational study which included patients from a single prepaid health plan

and also did not consider differences in side effect profiles between various agents. Another modeling study used STAR*D clinical data to compare the cost-effects of sertraline and venlafaxine after initial failure with SSRI in Thailand settings[164]. The generalizability of both the studies is questionable. Also, none of the studies have appropriately represented the uncertainty of the cost-effective analyses. To the best of our knowledge there have been no studies simultaneously comparing the cost-effectiveness of the three switch options (Bupropion-SR, Sertraline or Venlafaxine-XR) after initial SSRI treatment failure. This aim will use STAR*D data to determine optimum switch option after initial failure with SSRI based on cost-effectiveness. The STAR*D trial design and previously published effectiveness results for the level 2 pharmacotherapy switch options are briefly described below.

3.3.3 *STAR*D Trial*

The STAR*D trial was designed to evaluate the relative efficacy and tolerability of various antidepressant treatment for outpatient with nonpsychotic major depressive disorder, who failed the initial selective serotonin –reuptake inhibitor (SSRI) or subsequent treatments.

The STAR*D trial was designed to evaluate the relative efficacy and tolerability of various antidepressant treatment for outpatients with nonpsychotic major depressive disorder, who failed the initial selective serotonin –reuptake inhibitor (SSRI) or subsequent treatments. It is a multisite, equipoise randomized, multistep clinical trial. The patients in the trial were initiated on a SSRI (citalopram) and those who failed this initial therapy entered level 2 of the trial. At Level 1 of the trial, Citalopram dosing was recommended to start at 20 mg/day, could be raised to 40 mg/day by week 4 and to 60 mg/day (final dose) by day 42 (week 6) depending

on the dose duration, symptom changes, and side effect burden. Appropriate flexibility was allowed in the regimen.

At level 2 of the trial, patients could be randomized to one of the seven different treatments including four switch options (venlafaxine, sertraline, bupropion, and cognitive therapy) and three augment options (bupropion, buspirone or cognitive therapy added to CIT). In this analysis, we focus on the patients on the patients who were switched to pharmacotherapy (venlafaxine, sertraline, bupropion) after initial failure with Citalopram.

Patient Enrollment; Inclusion and Exclusion Criteria

Patients in the trial were enrolled from primary psychiatric public and private practice settings during July 2001 – August 2004[156, 165]. The study used a broad inclusion and exclusion criteria, including patients aged 18 – 75 year who had a score greater or equal to 14 on Hamilton Rating Scale of Depression (HRSD – 17) and had single or recurrent nonpsychotic MDD by the Diagnostic and Statistical Manual of Mental Disorders, 4th edition. Patients were excluded if they had a history of bipolar disorder, schizophrenia, schizoaffective disorder, current anorexia, bulimia or primary compulsive disorder or a psychosis otherwise not specified. Patients who had a history of clear cut intolerability to, or lack of effect with, an adequate trial of at least one of the protocol medications, lack of response to 16 or more sessions of cognitive therapy 7 or more sessions of electroconvulsive therapy or if they had already been taking citalopram for more than 7 days at the time of enrollment were also not included. Other than this, only pregnant women and patients with general medical conditions that contraindicated the use of medications used in the first 2 levels of study and substance dependence requiring immediate detoxification, or those who required immediate hospitalization were excluded.

Determination of Movement to Next Level or Follow-up

The decision to move to follow-up phase or the next level depended on clinical judgment which was based on remission, intolerance and non-response. The remission and response was informed by the Quick Inventory of Depressive Symptomatology – Clinician Rating (QIDS-C16) and obtained at each treatment visit.

Remission (the absence of depressive symptoms) was defined as ≤5 on the QIDS-C16, while response without remission is a ≥ 50% reduction in baseline QIDS-C16 score but a QIDS-C16 score > 5 at exit from a treatment level (as long as exit is not due to intolerance). Intolerance was when a participant discontinued treatment within the first 4 weeks for any reason or due to intolerable side effects after that time, independent of the symptomatic status. The patient was said to be not responding if the reduction in symptom severity as measured by QIDS-C16 was <50%, at exit (except for when the exit is due to intolerance). Those without response at completion of a treatment level could move to the next treatment level, while those with remission entered the follow-up phase. Those with response but without remission could enter follow-up, but were encouraged to proceed to the next treatment level after an adequate dose and duration have been achieved. Participants with intolerance or minimal reduction in baseline symptom severity (e.g., <15% by week 6 or <25% by week 9) were encouraged to move to the next treatment level.

Clinic Visits and Research Outcome

Protocol clinic visits were required at weeks 0, 2, 4, 6, 9, and 12 at all treatment levels. The visit schedule was flexible and could be held within +/-6 days of the assigned week. Extra visits could be held if clinically needed. If a participant exhibited a response or remission only at

week 12, two additional visits may be used to determine if that status is sustained. At each clinic visit, information related to symptoms, side-effects and medications was collected in the trial.

The primary outcome of STAR*D was remission defined as a HRSD-17score of 7 or less, as assessed by treatment-blinded raters. A secondary remission outcome was a QID-SR-16 score of 5 or less. The secondary outcome of STAR*D trial was response, defined as at least a 50% reduction in the baseline QIDS-SR-16 scores at the end of the treatment. The research outcomes were assessed by Interactive Voice Response (IVR) and telephone systems. These were recorded at pretreatment, at exit from each treatment level, and at months 3, 6, 9, and 12 in follow-up. Interim research outcomes (QIDS-SR16, five-item Work and Social Adjustment Scale [WSAS], six-item Work and Productive Activity Impairment Questionnaire [WPAI], and Frequency and Intensity of Side Effects Ratings (FISER)/ Global Rating of Side Effect Burden (GRSEB) were also collected by IVR, at week 6 in each treatment level and at months 1, 2, 4, 5, 7, 8, 10, and 11 in follow-up.

*Level 2 of STAR*D Trial*

The patients entering Level 2 of the trial could be randomized to one of the seven different treatments including four switch options (venlafaxine, sertraline, bupropion, and cognitive therapy) and three augment options (bupropion, buspirone or cognitive therapy added to CIT). However, at randomization patients could choose to opt out of being randomized to select options (medication switch, medication augmentation, cognitive therapy switch, cognitive therapy augmentation). This equipoise design served several purposes, one it reflects the real life practices where in patient with mood disorders are encouraged to be involved in treatment decision making in order to empower patients, optimize treatment adherence and improve outcome; second, it increases generalizability by facilitating recruitment of a broadly

representative participant population including the population for which lack of influence over treatment decisions could have been unacceptable; and finally this design also improves patient retention. Similar to Level 1, patients with a satisfactory therapeutic response in level 2 entered the 12-month naturalistic follow-up phase and those who did not entered the subsequent level of randomization.

CIT was discontinued without a tapering or washout period at Level 2. The recommended daily doses of the three medications to which patients could be switched in Level 2 are detailed as below. These dosing regimens were however flexible and could be altered as per clinical judgment. The recommended daily dosing sustained-release (SR) bupropion was 150 mg for seven days, 200 mg from day 8 to 27, 300 mg from day 28 to 41, and 400 mg from day 42 onward. Bupropion-SR is a non-SSRI agent which can affect a number of neurotransmitters. Bupropion is a norepinephrine and dopamine reuptake inhibitor but its action mechanism is only partly understood. Sertraline was recommended to be initiated at a daily dose of 50 mg and increased to 100 mg at day 14, to 150 mg at day 28, and to 200 mg at day 63. The switch from CIT to sertraline was a within-class switch which has a higher recommended dosing regimen. For extended-release (ER) venlafaxine, the dose of 37.5 mg for 7 days was increased to 75 mg from day 8 to 14, to 150 mg from day 15 to 27 to 225 mg from day 28 to 41, to 300 mg from day 42 to 62, and to 375 mg from day 63 onward. Extended-release venlafaxine, a dual-action agent, of the serotonin-norepinephrine reuptake inhibitor (SNRI) class that inhibits the reuptake of both serotonin and norepinephrine.

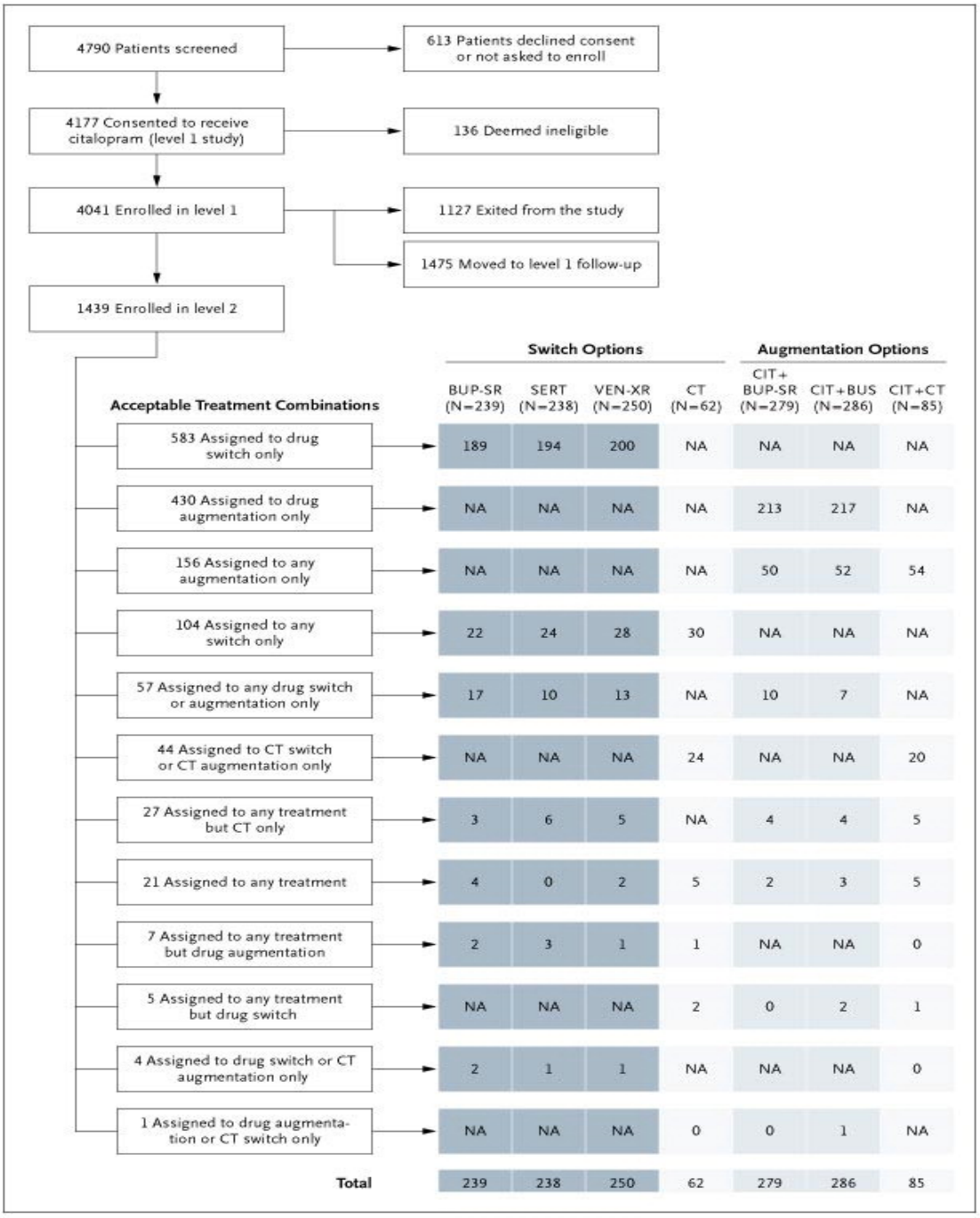
Clinical Comparison between Bupripion-SR, Sertraline and Venlafaxine-XR

Overall 21.3% of patients who were switched to an alternative therapy after failure of initial SSRI treatment achieved remission in STAR*D trial. The trial compared effectiveness of

the three pharmacotherapy switch options among patients who moved to Level 2 of the trial in terms of remission and response. Patients receiving bupropion, sertraline and venlafaxine-XR had remission rates of 21.3% (51 of 239), 17.6% (42 of 238) and 24.8% (62 of 250) respectively, that were not significantly different ($\chi 2 = 3.649$ with 2 df, $P = 0.16$). Also the treatments did not differ significantly with respect to QIDS-SR response rates, remission rates or percent reductions. The treatments were also similar with respect time to remission and time to response. The overall burden of side effects or the proportion of patients with any serious psychiatric adverse event did not differ significantly between the treatment groups, though there was a difference in the distribution of the frequency of side effects[166].

3.3.4 *Methods Used*

Using data from STAR*D trial, we will identify the cost-effective second-step pharmacological switch choice (Bupropion-SR, Sertraline, or Venlafaxine-XR) after failure of SSRIs for depression. Figure 3–1 (adopted from NEJM) shows the possible acceptable treatment combinations for patients who did not achieve an adequate response with SSRI[166]. There were a total of 727 patients switched to one of the medication switch options (Bupropion-SR, Sertraline, or Venlafaxine-XR).



Acceptable Treatment Combinations	Switch Options				Augmentation Options		
	BUP-SR (N=239)	SERT (N=238)	VEN-XR (N=250)	CT (N=62)	CIT+ BUP-SR (N=279)	CIT+BUS (N=286)	CIT+CT (N=85)
583 Assigned to drug switch only	189	194	200	NA	NA	NA	NA
430 Assigned to drug augmentation only	NA	NA	NA	NA	213	217	NA
156 Assigned to any augmentation only	NA	NA	NA	NA	50	52	54
104 Assigned to any switch only	22	24	28	30	NA	NA	NA
57 Assigned to any drug switch or augmentation only	17	10	13	NA	10	7	NA
44 Assigned to CT switch or CT augmentation only	NA	NA	NA	24	NA	NA	20
27 Assigned to any treatment but CT only	3	6	5	NA	4	4	5
21 Assigned to any treatment	4	0	2	5	2	3	5
7 Assigned to any treatment but drug augmentation	2	3	1	1	NA	NA	0
5 Assigned to any treatment but drug switch	NA	NA	NA	2	0	2	1
4 Assigned to drug switch or CT augmentation only	2	1	1	NA	NA	NA	0
1 Assigned to drug augmentation or CT switch only	NA	NA	NA	0	0	1	NA
Total	239	238	250	62	279	286	85

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Figure 3-1: Overview of STAR*D (Level 2) Study Design

Costs and effects

Calculated costs were based on three components: 1) antidepressant study medications, 2) other antidepressants and concomitant medications and 3) healthcare utilization. The prices for the medications were obtained from the Red Book Pharmacy's Fundamental Reference (Physicians' Desk Reference)[167]. The total drug costs depended on the dosage and the treatment duration. The healthcare facility utilization costs were calculated by multiplying patient-specific resource use with the corresponding unit cost. The total costs were calculated as the sum of costs related to medications and healthcare facility utilization. The effectiveness of the three switch options were in terms of remission and response (based on QIDS-SR questionnaire), as previously assessed[166].

Cost-effectiveness Analysis

The determination of cost-effective switch option based on the direct costs incurred over the duration of Level 2 of the STAR*D trial. The NHB were calculated for Bupropion–SR, Sertaline, Venlafaxine–XR from the sample data available. The treatment option with the highest NHB was designated as the optimum choice. A stochastic analysis performed using bootstrap replications, provided the confidence interval. After 1000 bootstrap replications, the probability that a given treatment (T_i) is better than others (in terms of cost-effectiveness) were calculated as the percentage of iterations for which T_i was estimated to have the highest NHB.

Additional method details and results are presented in the manuscript 3

4.0 MANUSCRIPT 1: AN ECONOMIC MODEL: VALUE OF ANTIMICROBIAL COATED SUTURES TO SOCIETY, HOSPITALS, AND THIRD PARTY PAYERS IN PREVENTING ABDOMINAL SURGICAL SITE INFECTIONS

Published
An Economic Model: Value of Antimicrobial-Coated Sutures to Society, Hospitals, and Third-Party Payers in Preventing Abdominal Surgical Site Infections

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Infection Control / Volume 35 / Issue 08 / August 2014, pp 1013 - 1020

Abstract: 240
Word Count: 2,803

Running Head: Economics Benefits of Triclosan-coated Sutures

Keywords: Triclosan-coated Sutures; Economics; Surgical Site Infection

4.1 ABSTRACT

Background: While the persistence of high surgical site infection (SSI) rates have prompted the advent of more expensive sutures that are coated with antimicrobial agents to prevent SSIs, the economic value of such sutures have yet to be determined.

Methods: Using TreeAge Pro, we developed a decision analytic model to determine the cost-effectiveness of using antimicrobial sutures in abdominal incisions from the hospital, third party payer, and societal perspectives. Sensitivity analyses systematically varied the risk of developing an SSI (range: 5% - 20%), the cost of triclosan-coated sutures (range: $5 - $25 per inch), and triclosan-coated suture efficacy in preventing infection (range: 5% - 50%) to highlight the range of costs associated with using such sutures.

Results: Triclosan-coated sutures saved $4,109 – $13,975 (hospital perspective), $4,133 – $14,297 (third party payer), and $40,127 – $53,244 (societal) per SSI prevented, when a surgery had a 15% SSI risk, depending on their efficacy. If the SSI risk was ≤5% and the efficacy in preventing SSIs was ≤10% triclosan-coated sutures resulted in extra expenditure for hospitals and third party payers (resulting in extra costs of $1,626 and $1,071 per SSI prevented for hospitals and third party payers respectively, SSI risk 5% and efficacy 10%).

Conclusion: Our results suggest that switching to triclosan-coated sutures from the uncoated sutures can both prevent SSIs and save substantial costs for hospitals, third party payers, and society, as long as efficacy in preventing SSIs is ≥10% and SSI risk is ≥10%.

4.2 INTRODUCTION

Antimicrobial surgical sutures are a relatively new intervention to prevent surgical site infections (SSIs), the second most common hospital acquired infections in the United States.[168] This intervention emerged as SSIs remain a continuing major problem despite the various existing infection measures.[66, 169] Intra-abdominal surgeries are especially associated with a high SSI rate (approximately 15%[170] depending on procedure).[171-173] Since approximately 4 million out of the 51.4 million surgeries performed annually in the United States are open abdominal surgeries,[174] preventing SSIs for such surgeries may be highly beneficial.

Since suture material may be a potential medium for infection,[175, 176] there is increasing interest in employing antibacterial sutures to lower SSI risk. Recent studies have found the efficacy of triclosan-coated sutures (Vicryl Plus, PDS Plus, and Monocryl plus) in preventing SSIs [77, 78, 82, 85, 177-184] to be variable. These mixed findings and higher cost of triclosan-coated sutures may limit their whole-scale adoption. It could be that such sutures are best used under certain circumstances. For example, triclosan-coated sutures may be particularly useful for abdominal surgeries since most involve clean-contaminated wounds, i.e., the operative procedure enters into a colonized viscus or cavity of the body, but under elective and controlled circumstances. To identify the situations for which such sutures may be appropriate, we developed a decision analytic simulation model to determine the cost and health effects of triclosan-coated absorbable sutures as compared to their uncoated counterparts for prevention of incisional infections in abdominal surgeries.

4.3 METHODS

Utilizing TreeAge Pro 2013 (Williamstown, MA), we developed a decision analytic model (illustrated in Figure 4-1) to simulate the decision of choosing triclosan-coated sutures versus the standard uncoated sutures for adult patients undergoing abdominal surgeries. Table 4-1 lists the model inputs, their values, and distributions (references listed in Table 4-2). Extensive literature review along with expert opinion determined the model inputs.

The distribution type of model inputs was based on the data's structural form and availability. The probabilities were modeled as beta distribution (the probability of severe SSI in the model was based on expert opinion and modeled as uniform distribution). The beta distribution is parameterized by two positive shape parameters, defined over an interval of [0,1]. Costs related to hospitalization, treatment and sutures were modeled as Gamma distribution (two-parameter family of continuous probability distributions, with a shape parameter k and a scale parameter θ). Triangular distribution represented the mortality costs and hourly wages. The duration of hospital stay and antibiotic treatment were modeled as gamma and uniform distribution (all intervals of the same length on the distribution's support are equally probable) respectively.

Each patient entering the model underwent an abdominal surgery and had a risk of developing an incisional SSI. The SSI could be either superficial or deep and could be either mild or severe. Superficial infections are defined as those that occur within 30 days of a procedure involving only the skin and subcutaneous tissues, whereas deep incisional infections are more severe, including those that occur within 30 or 90 days after an operative procedure involving deeper soft tissues (fascial muscles). Patients who developed an SSI had an extended attributable length-of-stay (LOS) and increased mortality rate, depending on the type of SSI. The

amount of suture used for each surgery was assumed to be four times the incision length, as recommended by previous studies.[185-187]

SSI treatment was dependent on the severity and type of SSI. Patients with a mild superficial SSI were treated with oral antibiotics, whereas severe superficial SSIs were administered intravenous (IV) antibiotics along with simple incision and drainage (I&D). All patients with a deep incisional SSI were administered IV antibiotics. Along with antibiotic treatment, deep incisional SSIs that were mild in severity received simple percutaneous I&D, whereas severe ones underwent complex I&D. Antibiotic regimens were determined using Micromedex and UptoDate (refined by expert opinion). Oral antibiotics included broad spectrum antibiotics like metronidazole (500 mg every 6-8 hours) and ciprofloxacin (500 mg every 12 hours). Intravenous antibiotics included vancomycin (15-20 mg/kg every 6-12 hours), linezolid (600 mg every 12 hours), ampicillin/sulbactam (1.5-3 mg every 6 hours), ceftriaxone (1-2 gm every 12-24 hours), or piperacillin/tazobactam (3.375 gm every 6-8 hours), depending on the causative pathogen and infection severity. Antibiotic treatment duration ranged from 7-14 days. In cases where the patient was undergoing IV antibiotic treatment and treatment duration exceeded the hospital stay, he/she switched to oral antibiotics a day prior to discharge.

Separate analyses were carried out from hospital, third-party payer, and societal perspectives to determine the economic benefits of using antimicrobial-coated sutures. The hospital perspective accounted for the suture costs and opportunity cost of lost bed-days caused by the increased LOS associated with superficial and deep SSI[188-190], which could have been filled by another patient. The third-party payer perspective included the direct hospitalization and treatment costs, along with suture costs. The societal perspective included both direct (i.e., hospitalization costs, treatment costs) and indirect costs (i.e., productivity loss due to

absenteeism and mortality, and general mortality costs that include operational costs related to death, such as transportation and burial). Productivity losses were based on median hourly and annual wages for all occupations (assuming an 8 hour work day and a 5 day work week), for the duration of hospitalization. Death resulted in the net present value of lost wages for the remainder of the person's life expectancy based on his/her age[191]. All costs were discounted to 2013 values using a 3% discount rate.

The following formula determined the cost per SSI prevented:

Cost per SSI prevented= [Cost (coated) – Costs (uncoated)]/ [Number of SSIs (coated) – Number of SSIs (uncoated)]

Each simulation run sent 1000 individuals undergoing an abdominal surgery 1000 times through the model (1,000,000 total trials). Sensitivity analyses systematically varied the risk of developing an SSI (range: 5-20%) to account for heterogeneity among different surgical techniques and the presence/absence of various pre-surgical antibiotic prophylaxis regimens. Additional analyses ranged triclosan-coated suture cost (range: $5 - $25 per inch) and efficacy (range: 5-50%). The wide range of efficacy values accounted for the debate over the true efficacy of the sutures. Experts speculate that antimicrobial coated sutures will be more effective in preventing superficial SSI as compared to deep incisional SSIs, so we also varied the efficacy of preventing superficial (range: 10-50%) and deep incisional SSIs (range: 5-20%) differentially. Monte Carlo probabilistic sensitivity analysis simultaneously varied all parameters throughout their ranges in Table 4-1. Monte Carlo simulation used dynamic information from the computer’s clock to initialize a sequence of pseudo-random numbers.

4.4 RESULTS

Hospital Perspective

Table 4-3 shows the cost per SSI prevented when triclosan-coated sutures are used for an eight inch long incision, varying the risk of SSI. Triclosan-coated sutures 5% efficacious incurred extra costs when used for surgeries having ≤10% SSI risk; resulting in an average expenditure of $46 (5% SSI risk) and $8 (10% SSI risk) per surgery. However, triclosan-coated sutures progressively saved greater costs per surgery (compared to uncoated sutures) when used for surgeries with ≥15% SSI risk, even with an efficacy as low as 5% (saved $30 per surgery, preventing 7 SSIs per 1000 surgeries at 5% efficacy which increased to $1,046 per surgery, preventing 75 SSIs per 1000 surgeries at 50% efficacy). When used for surgeries with a higher infection risk triclosan-coated sutures prevented a greater number of SSIs and consequently prevented their related costs.

A lower suture cost ($5 vs the current price, $9.93 per inch) generated even more cost-savings, leading to an additional savings ≥$150 per surgery; less expensive triclosan-coated sutures resulted in cost-savings per surgery even if only 5% efficacious, saving $186 per surgery with a 15% SSI risk. The costs-savings per abdominal surgery increased linearly with increasing efficacy. Cost-savings would decrease proportionately with higher priced sutures (Figure 4-2A). A more expensive triclosan-coated suture, costing ≥$20 per inch, resulted in cost-savings per surgery only if they had an efficacy ≥20% (saving $48 per surgery when costing $20 per inch).

The costs associated with triclosan-coated suture use for various scenarios changed, if they were assumed to prevent superficial SSIs only. Sutures that prevented only superficial SSIs for surgeries having a 15% SSI risk were not cost-effective at a 5% efficacy, incurring an extra cost of $2,885 per SSI prevented. An increase in efficacy to prevent superficial SSIs resulted in

rapid increases in costs saved per SSI prevented, as superficial SSIs are more common. Table 4-4 shows the costs saved per SSI averted when using sutures having a differential efficacy to prevent superficial and deep incisional SSIs.

Third-Party Payer Perspective

Third-party payers saved slightly more costs per SSI prevented than hospitals (Table 4-3), but followed a similar trend. For a 15% SSI risk, triclosan-coated sutures resulted in 7-14 SSIs per 1000 surgeries, while traditional uncoated sutures resulted in approximately 15 SSIs per 1000 surgeries; thus saving $4,133 (5% efficacious) to $14,297 (50% efficacious) per SSI prevented. The trend of cost saved per surgery for varied costs and efficacies of triclosan-coated sutures were also similar to the hospital perspective (Figure 4-2).

Societal Perspective

Using triclosan-coated sutures for surgeries having a 15% risk of SSI saved $40,127 to $53,244 per SSI prevented, depending on efficacy (Table 4-3). For such surgeries, triclosan-coated sutures (5% efficacy) saved $296 per surgery while preventing 0.29 deaths per 1000 surgeries; this increased to $4,001 per surgery and prevented 3.2 deaths per 1000 surgeries at an efficacy of 50%. This shows that an intervention which can reduce number of deaths, even marginally, can lead to substantial cost-savings.

Triclosan-coated sutures with a 5% efficacy, priced at $5 per inch resulted in savings of $492 per surgery. A $15 per inch triclosan-coated suture (efficacy >5%) also resulted in cost-savings per surgery. Such a triclosan-coated suture having 25% efficacy saved $1,745 per surgery while preventing 37 SSIs per 1000 surgeries. Using triclosan-coated sutures with 5% efficacy resulted in extra $34 and $171 per surgery if their costs further increased to $20 and $25 per inch, respectively. A 5% increase in triclosan-coated suture efficacy increased the cost saved

per surgery by >$300, so at efficacies ≥10% these more expensive sutures resulted in costs saved per surgery.

Triclosan-coated sutures continued to save costs per SSI prevented from the societal perspective, even if they only prevented superficial SSIs and not deep incisional SSIs. For surgeries having a 15% SSI risk, triclosan-coated sutures saved $35,116 (5% efficacious) to 48,684 (50% efficacious) per SSI prevented (Figure 4-2C). The figure shows a non-linear relationship for when efficacy of the coated suture was 20%. To further examine this, we ran a simulation experiment increasing the number of samples and trials each to 10,000. The graph obtained showed the linear trend indicating that the non-monotonic point estimate was due to variability and stochasticity (Figure 4-3).

4.5 DISCUSSION

Our analyses show that even though triclosan-coated sutures are almost 40% more expensive than the traditional uncoated sutures ($9.93 vs $7.32 per inch), the cost-savings generated by preventing abdominal SSIs offsets the extra suture costs, even when SSI risk is 15% and efficacy in preventing SSIs is as low as 5%. Depending on their efficacy, triclosan-coated sutures may in fact save more costs per SSI prevented than many of the other interventions. A study showed that collagen-gentamycin sponges for cardiothoracic surgeries save $84 per patient, preventing 45 surgical wound infections;[192] leading to $1,773 (2013 values) saved per SSI prevented. According to our model, triclosan-coated sutures when used for abdominal surgeries with 15% SSI risk saved approximately 2-8 times more costs per SSI prevented than that by collagen-gentamycin (hospital perspective). Also, as new technologies

become available (e.g., wound retractors[193] and antimicrobial abdominal meshes[194]), quantifying their potential cost-effectiveness becomes important given the limited resources available for infection prevention and control. Hospitals may want to implement strategies that minimize costs while achieving a maximal reduction in SSIs. Head to head comparison of these multiple interventions in terms of costs and benefits will guide the policy makers to determine the best strategy. Current guidelines may need to reevaluate their recommendations in light of the upcoming interventions to determine the most cost-effective strategies to prevent SSIs. Moreover, our results are not necessarily specific to triclosan as other antimicrobials such as silver, gentamycin or neomycin could be used for coating sutures.[195, 196]

There are two systematic reviews regarding the efficacy of triclosan-coated sutures; one concluded that triclosan-coated sutures do not have a beneficial effect in preventing SSIs,[72] whereas the other demonstratedsignificant SSI reduction on using triclosan-coated sutures.[89] These reviews include studies for colorectal, cardiac, breast, and shunt surgeries, which may have diverse SSI risks and risk-factors. One review performed a subgroup analysis on abdominal procedures, showing that triclosan-coated sutures significantly reduce SSI risk by 31% (relative risk 0.69, 95% CI: 0.50 – 0.97).[89] Among the studies evaluating abdominal procedures,[77, 78, 82, 177, 178, 184] two showed no effect,[82, 178] while others showed a substantial reduction in SSIs (35% to 65%). The reasons for such a wide range in results are unclear and could be due to design limitations (small sample size and limited controls), varied incision closure method, SSI definitions, incomplete data, or reporting biases.

Since the results from this analysis are sensitive to efficacy of triclosan-coated sutures, additional studies are needed to establish the efficacy of such sutures and evaluate their benefits for surgeries with varied SSI rates. While evaluating the sutures, it is important to use standard

SSI definitions, in order to allow comparisons across studies and gain more insight. Also, it will be beneficial if future studies incorporate details on SSI type; this would give a better handle on cost and health benefits, if any, obtained by using triclosan-coated sutures. If sufficiently efficacious in preventing SSIs, triclosan-coated sutures can be cost-effective even when higher-priced. The benefits obtained by using triclosan-coated sutures also depend on the SSI risk. Accurate quantification of SSI risk prior to surgery, using risk scores, may help stratify patients and consequently determine effective preventive strategies for various subgroups. National Nosocomial Infections Surveillance (NNIS) risk score is commonly used, but is often criticized for its discriminatory abilities and over-simplistic nature. Recently there have been attempts to develop alternate indices to better predict SSI rates[197, 198]. However these need to be further tested and validated.

One concern is that antimicrobial sutures may prevent only incisional SSIs and not organ space infections which are associated with a higher morbidity, mortality, and costs.[199] However, a majority of SSIs are confined to incisions,[200] hence interventions focusing on prevention of incisional SSIs could save substantial costs per SSI prevented as reflected in our results ($40,127 to $53,244 per SSI prevented, societal perspective). Another concern is that the wide use of triclosan may lead to the development of antimicrobial resistance and thus decreased suture efficacy in preventing SSIs.[201] This is a very serious concern and suggests that efficacy numbers reported in the literature may not necessarily apply in the future. Also, in-vitro studies suggest that triclosan use may further lead to the development of antibiotic resistance.[43,44] This highlights the need for more judicious and targeted use of triclosan, something that models such as ours can help guide.

It is important that policy makers consider the indirect costs along with the direct costs in order to be able to make an informed and well-rounded decision. Hospital and insurance databases typically do not capture productivity losses. When considering the societal perspective, the cost-savings per surgery were 4-13 times higher than that from the hospital or third-party payer perspectives. This shows that preventing productivity losses can save considerable costs per surgery, even when the SSIs are not associated with a high mortality rate (3.9% for superficial and 5.7% for deep incisional SSIs). Therefore, focusing on only the direct costs overlooks the impact of complicated cases that rapidly accrue costs.

Limitations

All models, by definition, are simplification of real life[202, 203] and cannot account for every possible SSI outcome. All data inputs for the model were obtained from sources of varied quality and rigor, including public databases, published literature, and expert opinion. We assumed that all pathogens had an equal probability of causing SSI in clinical settings. Our model was conservative about the potential benefits of triclosan-coated sutures, considering their efficacy to be as low as 5%. It did not consider that some severe incisional SSIs may progress to organ space infections incurring additional resources and costs. Also, for the societal perspective our productivity loss calculations assumed a 40-hour work week and did not account for decreased productivity while recovering.

4.6 CONCLUSIONS

Our results show that triclosan-coated sutures save ≥$4000 per SSI prevented for hospitals and third-party payers and ≥$23,500 per SSI prevented for society, if their efficacy is ≥10% and SSI risk is ≥10%. The high cost and risk of abdominal SSIs compensate for the cost premium of antimicrobial sutures as long as it has some efficacy in preventing SSIs. Future studies should better characterize this efficacy, but our study suggests that such sutures have the potential to save considerable costs.

Acknowledgements

This study was supported by the National Institute of General Medical Sciences Models of Infectious Disease Agent Study (MIDAS) and the Pennsylvania Department of Health. The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; or the preparation, review, or approval of the manuscript. All authors report no conflicts of interest relevant to this article.

4.7 TABLES AND FIGURES

Table 4-1: Model inputs and parameters†

Parameter	Distribution Type	Mean/Median	Standard Deviation/Range
Probabilities			
Surgical Site Infection (SSI)	-	0.15	-
Superficial SSI	β	0.697	0.305
Deep SSI	β	0.302	0.305
Severe SSI Within Each Type	U	-	0.20 – 0.30
Death due to Superficial SSI	β	0.039	0.024
Death due to Deep SSI	-	0.057	-
Durations (Days)			
Length of Hospitalization due to Superficial SSI	γ	6.22	4.25
Length of Hospitalization due to Deep SSI	γ	9.675	0.96
Antibiotic treatment	U	-	7 – 14
Costs			
Triclosan Coated Suture	γ	9.93	6.39
Regular Absorbable Suture	γ	7.32	3.175
Hospitalization due to SSI			
1-17 years	γ	12,318	1,013
18-44 years	γ	12,429	418
45-64 years	γ	15,299	443
65-84 years	γ	17,025	488
85+ years	γ	15,164	663
Simple Incision and Drainage	γ	98.32	7.63
Complex Incision and Drainage	γ	185.52	15.03
IV Insertion	-	9.53	-
Intravenous Antibiotic*	γ	51.03	70.00
Oral Antibiotics**	γ	13.65	12.81
Mortality	Δ	7,563	5,672 – 9,862
Productivity Losses due to death***	-	-	139,801 – 1,483,215
Hourly wage	Δ	9.29	20.32 – 93.42

† Sources are listed in Appendix Table 1

*IV antibiotics include vancomycin, linezolid, piperecillin/tazobactam, ceftriaxone, ampicillin and sulbactam

**Oral antibiotics include ciprofloxacin and metronidazole

***Depending on age

Table 4-2: References for Model Input Parameters

Parameter	Reference
Probabilities	
Surgical Site Infection (SSI)	Alexander JW, Rahn R, Goodman HR. Prevention of surgical site infections by an infusion of topical antibiotics in morbidly obese patients. *Surg Infect (Larchmt).* 2009;10(1):53-57
Superficial SSI	Watanabe A, Kohnoe S, Shimabukuro R, et al. Risk factors associated with surgical site infection in upper and lower gastrointestinal surgery. *Surgery Today.* 2008;38(5):404-412 Baracs J, Huszar O, Sajjadi SG, Horvath OP. Surgical site infections after abdominal closure in colorectal surgery using triclosan-coated absorbable suture (PDS Plus) vs. uncoated sutures (PDS II): a randomized multicenter study. *Surg Infect (Larchmt).* 2011;12(6):483-489. Millbourn D, Cengiz Y, Israelsson LA. Effect of stitch length on wound complications after closure of midline incisions: a randomized controlled trial. *Arch Surg.* 2009;144(11):1056-1059. Coello R, Charlett A, Wilson J, Ward V, Pearson A, Borriello P. Adverse impact of surgical site infections in English hospitals. *J Hosp Infect.* 2005;60(2):93-103.
Deep SSI	Watanabe A, Kohnoe S, Shimabukuro R, et al. Risk factors associated with surgical site infection in upper and lower gastrointestinal surgery. *Surgery Today.* 2008;38(5):404-412 Baracs J, Huszar O, Sajjadi SG, Horvath OP. Surgical site infections after abdominal closure in colorectal surgery using triclosan-coated absorbable suture (PDS Plus) vs. uncoated sutures (PDS II): a randomized multicenter study. *Surg Infect (Larchmt).* 2011;12(6):483-489. Millbourn D, Cengiz Y, Israelsson LA. Effect of stitch length on wound complications after closure of midline incisions: a randomized controlled trial. *Arch Surg.* 2009;144(11):1056-1059. Coello R, Charlett A, Wilson J, Ward V, Pearson A, Borriello P. Adverse impact of surgical site infections in English hospitals. *J Hosp Infect.* 2005;60(2):93-103.
Severe SSI Within Each Type	Expert Opinion
Death due to Superficial SSI	Coello R, Charlett A, Wilson J, Ward V, Pearson A, Borriello P. Adverse impact of surgical site infections in English hospitals. *J Hosp Infect.* 2005;60(2):93-103.

Table 4-2 Continued

	Astagneau P, Rioux C, Golliot F, Brucker G. Morbidity and mortality associated with surgical site infections: results from the 1997-1999 INCISO surveillance. *J Hosp Infect.* 2001;48(4):267-274.
Death due to Deep SSI	Astagneau P, Rioux C, Golliot F, Brucker G. Morbidity and mortality associated with surgical site infections: results from the 1997-1999 INCISO surveillance. *J Hosp Infect.* 2001;48(4):267-274.
Durations (Days)	
Length of Hospitalization due to Superficial SSI	Coello R, Charlett A, Wilson J, Ward V, Pearson A, Borriello P. Adverse impact of surgical site infections in English hospitals. *J Hosp Infect.* 2005;60(2):93-103. Fukuda H, Morikane K, Kuroki M, et al. Impact of surgical site infections after open and laparoscopic colon and rectal surgeries on postoperative resource consumption. *Infection.* 2012;40(6):649-659.
Length of Hospitalization due to Deep SSI	Fukuda H, Morikane K, Kuroki M, et al. Impact of surgical site infections after open and laparoscopic colon and rectal surgeries on postoperative resource consumption. *Infection.* 2012;40(6):649-659. Merle V, Germain JM, Chamouni P, et al. Assessment of prolonged hospital stay attributable to surgical site infections using appropriateness evaluation protocol. *Am J Infect Control.* 2000;28(2):109-115.
Antibiotic treatment	UpToDate, Micromedex, Expert Opinion
Costs	
Sutures	Medical Supply Pricings http://www.mmsmedical.com/, http://twgmedicalsupplies.com/
Hospitalization due to SSI	National and regional estimates on hospital use for all patients from the Healthcare Cost and Utilization Project (HCUP) Nationwide Inpatient Sample (NIS) 2010. http://hcupnet.ahrq.gov/. Accessed March 2013.
Incision and Drainage	American Medical Associaton. CPT Code/Relative Value Search. 2012; https://ocm.ama-assn.org/OCM/CPTRelativeValueSearch.do. Accessed February, 2013.
IV Insertion	American Medical Associaton. CPT Code/Relative Value Search. 2012; https://ocm.ama-assn.org/OCM/CPTRelativeValueSearch.do. Accessed February, 2013.
Antibiotics	Physicians Desk Reference. *Red Book Pharmacy's Fundamental Reference*. Montvale, NJ: Thompson Reuters (Healthcare); 2010.
Mortality	Gould MK, Dembitzer AD, Sanders GD, Garber AM. Low-molecular-weight heparins compared with unfractionated heparin for treatment of acute deep venous thrombosis. A cost-effectiveness analysis. *Ann Intern Med.* 1999;130(10):789-799.
Productivity Losses due to death	Human Mortality Database, http://www.mortality.org/ Accessed 2012

Table 4-2 Continued

Hourly wage	Bureau of Labor Statistics. Occupational employment statistics: May 2011 National Occupational Employment and Wage Estimates, United States. 2013; http://www.bls.gov/oes/current/oes_nat.htm#00-0000. Accessed Febraury, 2013.

Table 4-3: Costs per SSI Averted for Varied Efficacies of Antimicrobial Coated Sutures to Prevent SSI and Risk of Developing SSI for an 8 inch[204] incision from the Hospital, Third Party Payer, and Societal Perspectives

	Cost Associated with Coated Sutures per SSI prevented*			
	Risk of Surgical Site Infection (%)			
Efficacy of the Coated Sutures	5	10	15	20
	Hospital Perspective			
5	18,870	1,625	-4,019	-6,689
10	1,626	-6,685	-9,497	-11,059
15	-3,750	-9,555	-11,515	-12,378
25	-8,560	-11,650	-12,936	-13,494
50	-11,784	-13,529	-13,975	-14,309
	Third Party Perspective			
5	17,687	1,280	-4,133	-7,198
10	1,071	-6,879	-9,750	-11,242
15	-4,474	-9,821	-11,652	-12,683
25	-8,773	-12,035	-13,170	-13,730
50	-12,036	-13,740	-14,297	-14,577
	Societal Perspective			
5	-23,519	-38,198	-40,127	-46,847
10	-46,779	-46,207	-50,187	-52,187
15	-47,291	-49,151	-51,724	-52,382
25	-47,303	-50,902	-52,424	-53,698
50	-51,759	-53,160	-53,244	-54,704

*Negative costs indicate cost-savings

Table 4-4: Costs per SSI Averted from Hospital's Perspective for Differential Efficacies of Antimicrobial Coated Sutures to Prevent Superficial and Deep Incisional SSI and Associated Risk of Infection for an 8 Inches Incision

	Risk of Developing SSI (%)			
Efficacy to Prevent Deep SSI (%)	5	10	15	20
Efficacy to Prevent Superficial SSI = 10%				
0	2,558	-957	-5,131	-6,848
5	5,710	-4,491	-7,592	-9,446
Efficacy to Prevent Superficial SSI = 15%				
0	2,731	-4,751	-7,641	-9,002
5	338	-6,901	-9,216	-10,393
Efficacy to Prevent Superficial SSI = 25%				
0	-3,277	-8,333	-9,813	-10,501
5	-4,440	-9,245	-10,616	-11,227
Efficacy to Prevent Superficial SSI = 50%				
0	-8,410	-10,523	-11,442	-11,825
5	-8,539	-11,141	-11,776	-12,020

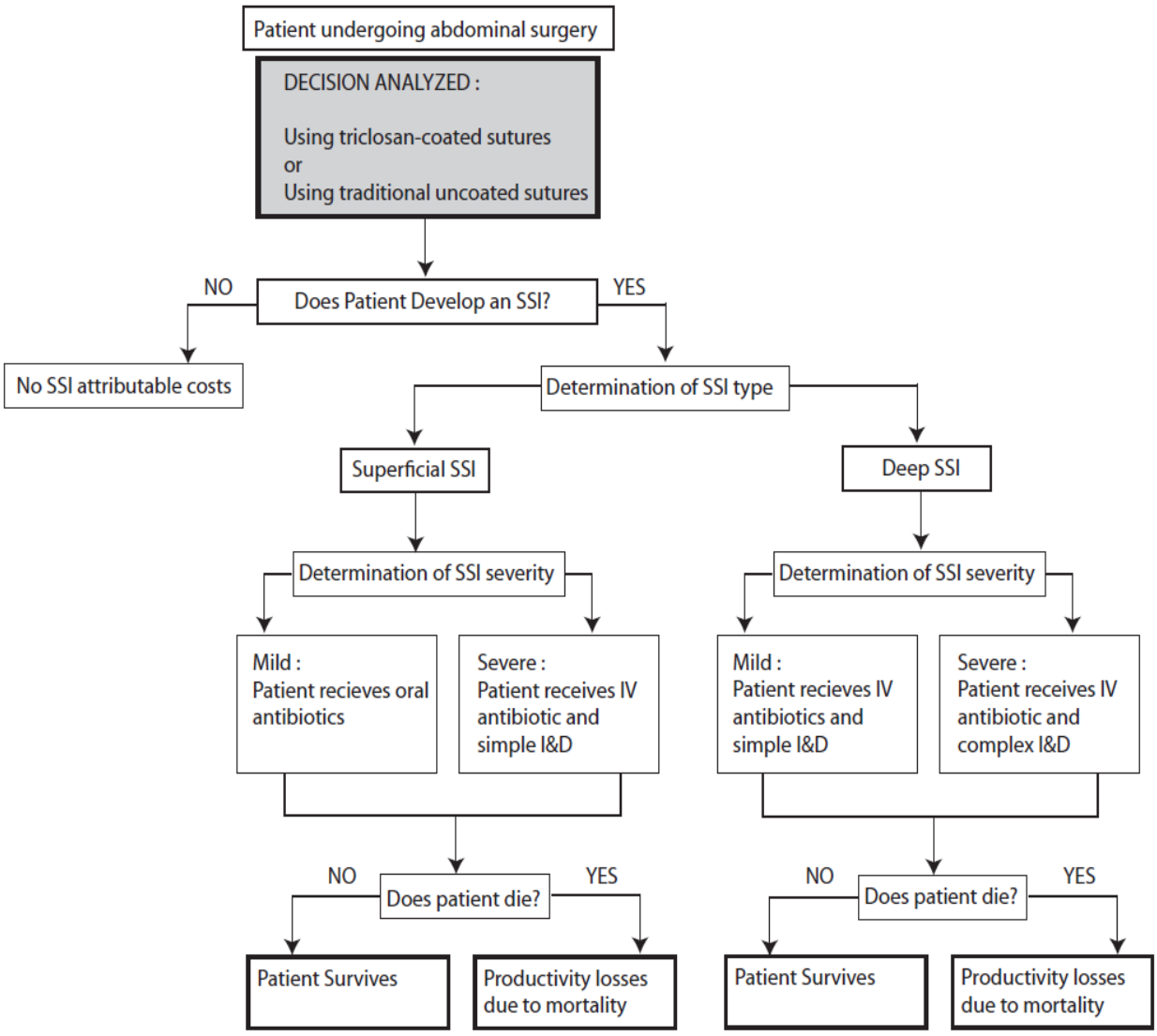

Figure 4-1: Model Outline

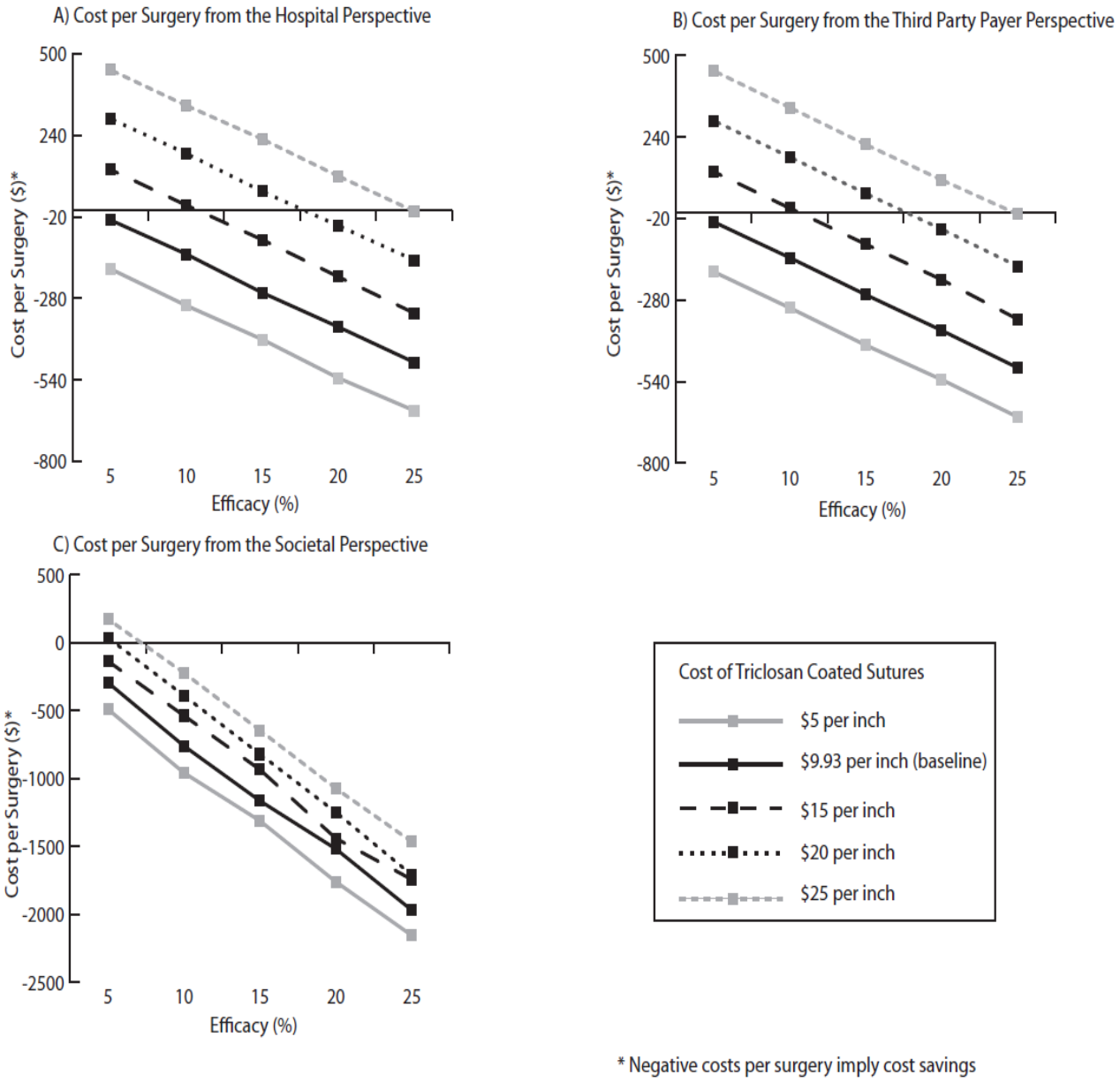

Figure 4-2: Costs Associated with Coated Sutures of varying costs and efficacies for a surgery having 15% risk of developing SSI

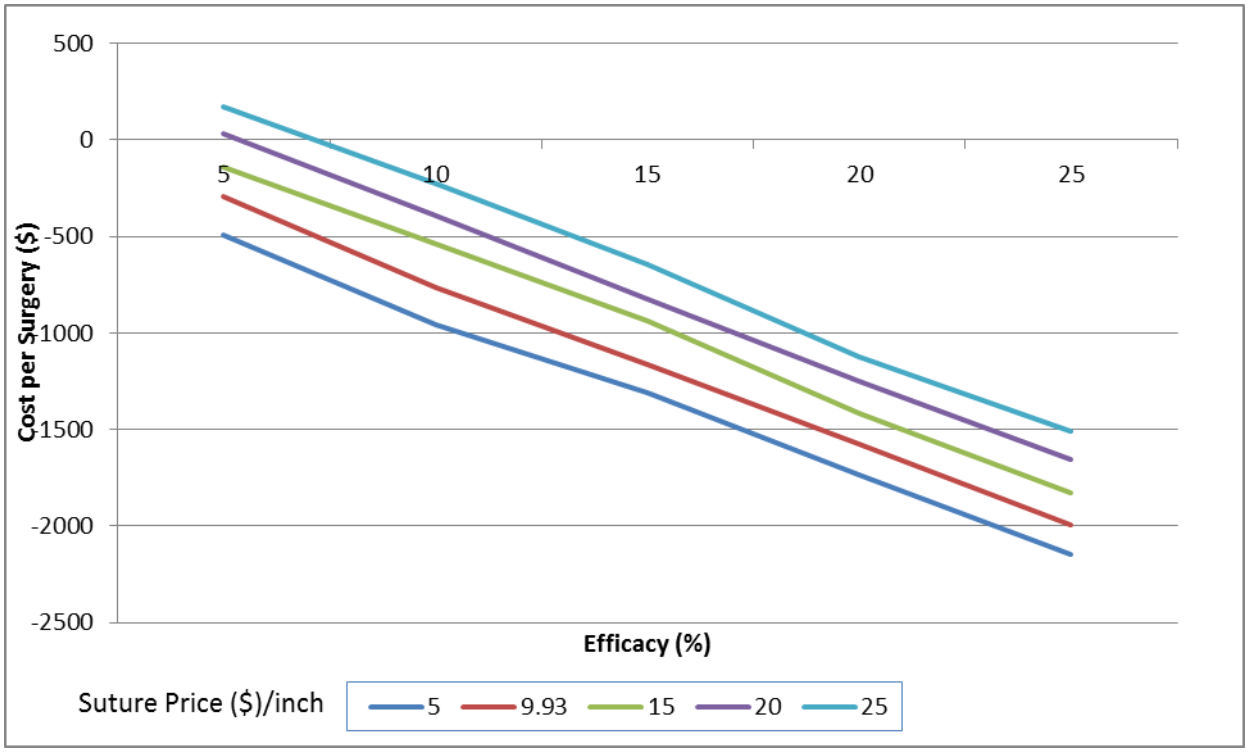

Figure 4-3: Costs Associated with Coated Sutures of varying costs and efficacies for a surgery having 15% risk of developing SSI (Societal Perspective; 10,000X10,000 runs)

5.0 MANUSCRIPT 2: ON-PUMP VERSUS OFF-PUMP CORONARY ARTERY BYPASS GRAFT SURGERY AMONG PATIENTS WITH TYPE 2 DIABETES IN THE BYPASS ANGIOPLASTY REVASCULARIZATION INVESTIGATION 2 DIABETES TRIAL

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Running Head: Off-pump versus on-pump CABG for diabetic patients

Abstract: 248; Word Count: 3,337

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5.1 ABSTRACT

Background: Conclusive evidence is lacking regarding the benefits and risks of performing off-pump versus on-pump coronary artery bypass graft (CABG) for patients with diabetes. This study aims to compare clinical outcomes after off-pump and on-pump procedures for patients with diabetes.

Methods: The Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) trial enrolled patients with type 2 diabetes and documented coronary artery disease, 615 of whom underwent CABG during the trial. The procedural complications, 30-day outcomes, long-term clinical and functional outcomes were compared between the off pump and on-pump groups overall, and within a subset of patients matched on propensity score.

Results: On-pump CABG was performed in 444 (72%) patients and off-pump CABG in 171 (28%). The unadjusted 30-day rate of death/MI/stroke was significantly higher after off-pump CABG (7.0% versus 2.9%, p = 0.02) despite fewer complications (10.3% versus 20.7%, p = 0.003). The long-term risk of death (adjusted hazard ratio (aHR): 1.41, p = 0.2197) and major cardiovascular events (death, MI or stroke) (aHR: 1.47, p = 0.1061) did not differ statistically between the off-pump and on-pump patients. Within the propensity-matched sample (153 pairs), patients who underwent off-pump CABG had a higher risk of the composite outcome of death, MI or stroke (aHR: 1.83, p = 0.046); the rates of procedural complications and death did not differ significantly, and there were no significant differences in the functional outcomes.

Conclusions: Patients with diabetes had greater risk of major cardiovascular events long term after off-pump CABG than after on-pump CABG.

5.2 INTRODUCTION

The risk of cardiovascular disease is two to four times higher among individuals with diabetes than among those without diabetes[98-100]. The BARI trial demonstrated that coronary artery bypass graft procedure (CABG) improves survival as compared with percutaneous coronary intervention in patients with diabetes and multi-vessel coronary artery disease[205]. A decade later, the BARI 2D trial established that major cardiovascular outcomes were lower with CABG as compared to medical therapy alone for patients with diabetes and stable coronary artery disease[206].

Traditionally, CABG has been performed on-pump, i.e. using the cardiopulmonary artery bypass (CPB) and cardioplegic arrest. Use of CPB has been associated with post-procedure myocardial, pulmonary, renal and cerebral complications[110-112, 207]. However, it has been suggested that off-pump CABG, which does not require CPB, may avoid many of these complications and thus result in better clinical outcomes.

The comparative effectiveness of the off-pump procedure has been controversial and few studies compared off-pump and on-pump CABG among patients with diabetes[138-141]. These studies are single-centered, retrospective, and lack long-term outcomes. Consequently, the current evidence is inadequate to make conclusions regarding the relative risks and benefits of using off-pump versus on-pump CABG for diabetic individuals.

We aim to determine the risks and benefits of off-pump CABG compared to on-pump CABG for patients with diabetes using data from the multicenter BARI 2D study.

5.3 METHODS

Study Population

The design, patient characteristics, and primary results of the BARI 2D clinical trial have been previously described in detail[206]. Briefly, BARI 2D was a 2x2 factorial design clinical trial that included 2,368 patients with type 2 diabetes and angiographically documented coronary artery disease. Participants were enrolled between January 1, 2001 to March 31, 2005 from 49 sites across the United States, Canada, Brazil, Mexico, the Czech Republic and Austria. All patients underwent informed consent prior to entry into the study, and every site had IRB approval. In addition, the Coordinating Center maintained the IRB approval for the study as a whole. Randomization was stratified by the intended revascularization method (i.e. whether a patient was more suitable for CABG or percutaneous coronary intervention (PCI), determined by the individual site physicians). The eligible patients were randomly assigned to either prompt revascularization or medical therapy within each stratum. Simultaneously, the patients were randomly assigned to treatment of hyperglycemia with either insulin sensitization or insulin provision therapy to achieve a target HbA1c < 7.0%. The trial actively managed diabetes and cardiovascular risk factors for all patients through the patient's 6 year visit or until the last annual visit prior to December 1, 2008. Clinic visits for all patients were scheduled on a monthly basis for the first 6 months and quarterly thereafter.

This analysis included BARI 2D patients who underwent a CABG procedure, irrespective of their intended method of revascularization or the assigned treatment arm. If a patient had more than one CABG, the first CABG procedure was used for all evaluations and comparisons.

Surgical Techniques

Characteristics of patients having CABG within the trial have previously been described in detail[208]. All operations in BARI 2D were performed by experienced and established surgeons certified by the trial. The decision to perform an off-pump versus an on-pump procedure was based on clinical site practice patterns, individual surgeon preference, clinical characteristics of the patient, and the perceived target vessel quality. The trial protocol called for bypassing all stenosis that were believed to contribute to a patient's clinical symptoms and ischemia; however, incomplete revascularization could be planned in cases where the morphological features did not allow bypass of all lesions. It was also strongly recommended to use at least one internal mammary conduit if possible.

Outcomes

The primary end point of BARI 2D trial was mortality, and the principal secondary end point was the composite of death, myocardial infarction (MI), and stroke. The average follow-up time in the BARI 2D trial was 5.3 years. For this analysis, we also considered a repeat revascularization outcome defined as any PCI, CABG or laser myocardial revascularization required after CABG as a secondary outcome. The peri/post-procedural complications (within-hospital) were categorized as neurological, cardiac, renal, vascular, pulmonary, bleeding, and inotrope use for > 48 hours. Neurological complications included transient cerebrovascular event, cerebrovascular accident, dementia and coma. Cardiac complications encompassed non-fatal cardiac arrest, suspected MI, congestive heart failure, pulmonary edema (cardiac), cardiogenic shock, and cardiac tamponade. Vascular complications included arterial embolism of extremity or loss of pulse requiring treatment. Renal failure requiring dialysis was categorized as a renal complication. Respiratory failure, pulmonary embolus, chest tube> 3 days post-procedure

were classified as pulmonary complications. Bleeding complications comprised of hemorrhage that required transfusion and any reoperation for bleeding.

In addition to the clinical outcomes, we assessed functional outcomes during the 4 years after surgery in the off-pump and on-pump groups. The functional outcomes included angina and Duke Activity Status Index (DASI) scores. DASI is a 12-item index (0 [worst] to 58.2 [best]) that assesses the patient's ability to perform specific physical activities. The trial collected information on angina and quality of life on a quarterly and yearly basis respectively.

Statistical Analyses

Baseline demographic and clinical characteristics were compared between patients undergoing on-pump and off-pump CABG procedures. Summary statistics for the baseline characteristics are presented as means and standard deviation in case of continuous variables, and as numbers and percentages in case of categorical variables. Continuous variables were compared using Wilcoxon rank-sum test and categorical variables using chi-square or Fischer's exact, where appropriate.

Two separate sets of analyses were conducted to compare the outcomes between off-pump and on-pump CABG. The first analysis included all patients who underwent CABG within the trial and had information regarding the use of pump during the procedure. The procedural (within-hospital) complications, short-term clinical outcomes (within 30 days of CABG), any repeat revascularizations were compared using chi-square or Fischer's test. Only unadjusted analyses were conducted for complications, repeat revascularization and short term clinical outcomes, due to small number of events. The clinical outcomes of death and major cardiovascular events (death/MI/stroke) over the follow-up period were evaluated as time-to-event outcomes using Kaplan-Meier curves, log-rank statistics and multivariate Cox proportional

hazard models. The proportional hazards assumptions between the on-pump and off-pump groups were tested. Generalized linear models, with time specified as a within-subject effect, were used to compare the functional outcomes including angina and DASI scores between patients undergoing off-pump and on-pump CABG.

The candidate variables included in multivariable models as possible confounders comprised of the baseline characteristics that were significantly different between the two CABG groups. The final sets of covariates for outcomes death and major cardiovascular events were based on stepwise backward selection model building algorithm that used an alpha = 0.10 for variable elimination, and the off-pump/on-pump variable was forced into the model after the covariates were selected. The final covariates for the functional outcomes included the baseline characteristics that were significantly different between the two groups. We tested for statistical interaction between the type of CABG and country of surgery for the clinical and functional outcomes. In addition, we tested for statistical interaction between CABG type and time for longitudinal functional outcomes.

In the second analysis, a propensity score methodology was used to control for the non-randomized treatment selection of the two groups. The propensity scores represent the probability that a patient would undergo an off-pump CABG as compared to an on-pump CABG given his/her preoperative characteristics. Propensity scores for each patient were calculated using multivariable logistic regression model. The model considered a broad set of candidate variables, baseline characteristics that were different between the off-pump and on-pump group at a significance level of 0.20 (excluding country). Backward-selection methods utilizing a liberal alpha = 0.20 for eliminating variables were used to further refine the model. Based on the calculated propensity scores, patients undergoing off-pump CABG were matched with those

undergoing on-pump (1:1 match, without replacement) using a caliper of 0.01. Regional differences were not included in the propensity score and were handled with model adjustment. Within the matched dataset, baseline characteristics were compared using Wilcoxon signed-rank test for continuous variables, McNemar's test of symmetry for categorical variables. The post-procedural complications and short-term clinical outcomes, and repeat revascularization rates were compared using McNemar tests. Cox proportional-hazards regression models adjusted for region with robust standard errors were created to determine the association between type of surgery and time to death and time to the composite of death, MI or stroke. Functional outcomes, angina and DASI scores, were compared using generalized linear model accounting for the correlations within the matched pairs and repeated observations per patient.

For all analysis, missing covariate values were imputed using the mean or the most common value so that all patients with non-missing outcome data are incorporated in the clinical and functional outcomes models. The geographic regions were categorized as US/Canada and others (Mexico, Brazil, Czech Republic and Austria). The time-to-event analyses used the date and time of the index CABG procedure as 'time zero.' The event time was calculated based on the number of days to the first event. If no event occurred, data were censored at the last available follow-up patient date for death/MI/stroke or the vital status record date (when evaluating death). All analyses were performed using SAS enterprise guide 4.3.

5.4 RESULTS

Patient Characteristics

Of the 2,368 patients enrolled in BARI 2D, 621 (26 %) underwent a CABG procedure during the trial (illustrated in Figure 5-1). Of the patients assigned revascularization procedure (i.e. they were assigned to the prompt revascularization, 347 received a CABG as their first revascularization procedure within 6 months of study entry), 76 received a CABG as their first surgical revascularization procedure but it occurred after a PCI procedure (n = 65) or more than 6 months after study entry (n = 11). Of the 1192 patients randomized to medical therapy, 198 patients received a subsequent CABG. Overall, 468 (75%) of the patients who received a CABG, were allocated prior to randomization to the CABG stratum (117 patients were those who were randomized to medical therapy and 351 patients were those who were randomized to revascularization) and the remainder to the PCI stratum. Six CABG patients had missing off-pump/on-pump use information and were excluded from the analysis. This resulted in a final sample size of 615 patients, of whom 171 (27.8%) underwent off-pump and 444 (72.2%) underwent on-pump CABG. The average (standard deviation) follow-up time for this sample of patients was 4.2 (1.7) years where the time of the CABG procedure was considered as time 0.

Patients undergoing off-pump CABG were more likely to be randomized to prompt revascularization, have CABG as their assigned index procedure, and have been allocated to the CABG intended method of revascularization stratum (Table 5-1). Patients undergoing off-pump were also younger, more likely to be female, had undergone a non-coronary vascular surgery prior to CABG, had higher glomerular filtration rate, lower serum creatinine levels, higher left

ventricular ejection fraction (LVEF), higher Hba1c, and higher energy scores. The distribution of CABG type varied significantly by country. The majority of CABGs performed in Brazil and Czech Republic/Austria were off-pump, whereas most in USA/Canada were on-pump. The two groups also differed in terms of their aspirin and diuretic medications within 48 hours prior to procedure.

Outcomes for All Patients undergoing CABG

Rates of within-hospital complications (Table 5-2) were significantly lower among patients undergoing off-pump (10.3%) as compared to those undergoing on-pump procedures (20.7%, p = 0.003). In contrast, the 30-day composite outcome of death/MI/stroke rate was significantly higher among the off-pump patients (7.0% versus 2.9%, p = 0.02). Over the long-term follow-up after CABG, 18 (10.5%) off-pump versus 33 (7.3%) on-pump patients required repeat revascularization (p = 0.21).

Unadjusted event-free rates at four years (Figure 5-2) did not differ significantly for mortality (88.0% off-pump vs 91.2% on-pump, p=0.11) or death/MI/stroke (80.0% off-pump vs 85.4% on-pump, p=0.06). Adjusted long-term risk of death among off-pump patients was 1.41 times higher than that among the on-pump patients, but this difference was not statistically significant (p = 0.22) . Similar effects were observed the outcome of death, MI or stroke (Table 3). There were no significant interactions between the procedure type and geographic region, indicating that the effect of performing off-pump CABG on death and death/MI/stroke was consistent across the regions.

At follow-up, patients undergoing off-pump CABG had less angina and higher DASI scores (Figure 5-3A, Figure 5-4A) but these differences were not significant after adjusting for the baseline characteristics (Table 5-4). The treatment effect on angina did not vary with time;

however, there was a significant interaction between treatment type and time for DASI score (p=0.002). The DASI scores tended to be higher among patients undergoing on-pump CABG one and two years after surgery but higher among patients undergoing off-pump CABG four years after surgery.

Propensity Score Analysis

The propensity score logistic regression model predicting use of off-pump CABG was well calibrated (Hosmer-Lemeshow p-value = 0.14; c-index = 0.734). The propensity scores (ranging from 0.024 – 0.910) were based on timing of the CABG (index versus subsequent), randomization arm (revascularization versus medical therapy), sex, obesity status (body mass index > 30), myocardial jeopardy score, left ventricular ejection fraction, glomerular filtration rate, and occurrence of non-coronary vascular surgery, and occurrence of chronic obstructive pulmonary disease prior to CABG. There was modest overlap in the distribution of propensity score by type of procedure (Figure 5-5). Matching resulted in 153 off-pump patients matched with 153 patients in the on-pump group. The two study groups were comparable with respect to baseline clinical characteristics (Table 5-1), ensuring a well-balanced matched dataset with the exception of regional differences that were handled through model adjustment.

Outcomes for Propensity Score Matched Subset

In the matched sample, the within-hospital complications did not differ significantly between the off-pump (11.1%) and on-pump (15.7%) patients, p = 0.25. The 30-day clinical outcomes did not differ significantly for death (1.3% on-pump versus 2.6% off-pump, p = 0.41) or death/MI/stroke (3.9% versus 7.8% patients, p = 0.16). A significantly higher proportion of patients undergoing off-pump CABG (11 %) than those undergoing on-pump CABG (2.6%) required repeat revascularization in the long-term (p = 0.005).

The long-term risks of death were not statistically different (Table 5-3), but the risk of death/MI/stroke was significantly higher (adjusted HR: 1.83, p = 0.046) among the off-pump patients. The off-pump and region interaction terms were not significant for any of the clinical outcomes.

As shown in Figure 5-3B, the proportion of patients suffering from angina within the matched sample was lower in the off-pump than the on-pump. However, the difference was not significant after adjusting for region and time after surgery (Table 5-4). The DASI scores in the matched sample were similar in the two groups (Figure 5-4B, adjusted β: -1.79, 95% CI: -4.92 to 1.34). There were no significant interactions between treatment type and time or treatment type and region for the functional outcomes in this patient set.

5.5 DISCUSSION

The use of off-pump CABG continues to be controversial with distinct advantages and disadvantages compared with on-pump CABG. In this study we found that the rates of death and major cardiovascular events (death, MI or stroke) were 40% – 80% higher after off-pump CABG, but these trends were only marginally significant because of the relatively small sample size. These patterns suggest that these trends could increase longer term. Our findings suggest that off-pump CABG should be used in patients with diabetes with caution.

One limitation of this study is that there was no randomization between the two surgical techniques. We therefore used two statistical methods to compare the off-pump and on-pump groups, enabling us to make robust inferences. Multivariable Cox regression models were used

to estimate hazard risks in the whole population, whereas the matching restricted the comparison to patients that are analogous between the two groups. The estimates obtained from multivariable regression models may not effectively account for treatment selection bias but are representative of the real world scenario where in the physicians were allowed to choose between off-pump and on-pump CABG as a means of offering their best approach to surgical revascularization. On the other hand, the estimates obtained based from matched subset of patients ensure that clinical covariates are uniformly distributed between the two groups, thus estimating the effect of off-pump CABG among those who actually receive off-pump procedures. However, unmeasured confounders that can lead to residual selection biases may exist. We did not have sufficient information regarding the off-pump to on-pump conversions which may affect our estimates. Also, details on the off-pump procedure technique (aortic manipulation, side-clamp use) were not available. Finally, since many of the revascularizations considered in this analysis were subsequent procedures, there was missing information regarding the completeness of revascularization for a large proportion of the procedures. The reasons for higher rates of adverse clinical outcomes during the course of follow-up may have been easier to decipher if this information was available.

In our analysis, we observed significant differences in the peri/post-procedural complications and short-term clinical outcomes between off-pump and on-pump patients when analyzing all patients but these were attenuated in the matched subset. The off-pump patient's marginally higher estimated risks of death that failed to reach statistical significance in both the analyses. However, the risk of death/MI/stroke which was not significantly higher among off-pump patients when considering all patients was significantly higher in the matched subset of patients. Also, a significantly larger proportion of off-pump patients in the matched subset

required repeat revascularization. These differences in results may reflect the treatment selection biases. In the BARI 2D population, patients undergoing off-pump CABG were younger, a lower proportion of them were obese, had higher glomerular filtration rate, lower serum creatinine levels, higher left ventricular ejection fraction (LVEF), higher Hba1c, higher energy scores and were more often from countries outside of the US and Canada.

A limited number of studies have compared off-pump with on-pump CABG among patients with diabetes[138-141]. Some have shown that although off-pump CABG had fewer complications, there were no survival advantages of off-pump CABG over on-pump CABG among diabetic patients[138, 139]. Other studies indicate that patients undergoing off-pump CABGs have lower complication rates as well as lower mortality[140, 141]; however, these are single center studies that did not consider long-term outcomes. The literature indicates that off-pump procedures may be associated with inferior graft patency studies and incomplete revascularization that may adversely affect in the long-term[128-130, 209]. To the best of our knowledge, there have been no multicenter observational studies or randomized trials comparing outcomes occurring more than 1 year after surgery. There has been a recent study, though single institution but with over 5,000 patients with a median follow-up of 6 years which shows a long term survival advantage with on pump surgery[19]. This is consistent with our study which includes data from multiple clinical sites, with patients having an average follow-up for more than 4 years.

There were no significant differences in angina and DASI reports after adjusting for patient characteristics at the time of surgery. Although angina rates were higher in the on-pump patients in the matched dataset, after accounting for region and repeated measures these differences were attenuated and non-significant. This indicates that the association between

surgery type and angina may have been confounded by the region where the procedure was performed.

Since the type of surgery was not randomly assigned, we performed propensity score analyses to account for the treatment selection bias. However, unmeasured confounders that can lead to residual selection biases may exist. We did not have sufficient information regarding the off-pump to on-pump conversions which may affect our estimates. Finally, many patients undergoing CABG had missing information regarding the completeness of revascularization procedure. The reasons for higher rates of adverse clinical outcomes during the course of follow-up may have been easier to decipher if this information was available.

5.6 CONCLUSIONS

In summary, our results demonstrate that in the BARI 2D trial, diabetic patients undergoing off-pump CABG had significantly higher risks of death/MI/stroke over the long term as compared to those undergoing on-pump CABG. This occurred despite having lower or comparable within-hospital complication rates. Thus, off-pump CABG is not recommended for patients with diabetes.

Acknowledgments and Disclosures

The Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) is funded by the National Heart, Lung and Blood Institute and the National Institute of Diabetes and Digestive and Kidney Diseases (U01 HL061744, U01 HL061746, U01 HL061748, U01 HL063804, R21HL121495). BARI 2D receives significant supplemental funding provided by

GlaxoSmithKline, Collegeville, PA, Lantheus Medical Imaging, Inc. (formerly Bristol-Myers Squibb Medical Imaging, Inc.), North Billerica, MA, Astellas Pharma US, Inc., Deerfield, IL, Merck & Co., Inc., Whitehouse Station, NJ, Abbott Laboratories, Inc., Abbott Park, IL, and Pfizer, Inc, New York, NY. Generous support is given by Abbott Laboratories Ltd., MediSense Products, Mississauga, Canada, Bayer Diagnostics, Tarrytown, NY, Becton, Dickinson and Company, Franklin Lakes, NJ, J. R. Carlson Labs, Arlington Hts., IL, Centocor, Inc., Malvern, PA, Eli Lilly and Company, Indianapolis, IN, LipoScience, Inc., Raleigh, NC, Merck Sante, Lyon, France, Novartis Pharmaceuticals Corporation, East Hanover, NJ, and Novo Nordisk, Inc. Princeton, NJ.

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5.7 TABLES AND FIGURES

Table 5-1: Baseline Characteristics of All Patients and Those in the Propensity Scored Matched Dataset by Type of Procedure

	All Patients undergoing CABG with type of procedure information			Patients in the Propensity Score Matched Dataset		
	On-Pump (N = 444)	**Off Pump (N = 171)**	**P-value†**	**On-Pump (N = 153)**	**Off-Pump (N = 153)**	**P-value††**
CABG Stratum	325 (73%)	139 (81%)	0.04*	121 (79%)	125 (82%)	0.17
Assigned to Revascularization (all strata)	278 (63%)	145 (85%)	<0.0001*	134 (88%)	127 (83%)	0.50
Assigned to Insulin Providing	231 (52%)	86 (50%)	0.70	73 (48%)	76 (50%)	0.74
Index CABG (all strata)	222 (50%)	125 (73%)	<0.0001*	116 (76%)	111 (73%)	0.45
Time to CABG after randomization in days, mean (standard deviation)	341 (506)	167.3 (385)	<0.0001*	206 (424)	152 (341)	0.34
Geographic Region			<0.0001*			<0.0001*
USA	253 (57%)	53 (31%)		82 (54%)	46 (30%)	
Canada	115 (26%)	8 (4.7%)		35 (23%)	8 (5.2%)	
Mexico	15 (3.4%)	21 (12%)		10 (6.5%)	18 (12%)	
Brazil	43 (9.7%)	85 (50%)		16 (11%)	78 (6.0%)	
Czech Republic/Austria	18 (4.1%)	4 (2.3%)		10 (6.5%)	3 (2.0%)	
Other Baseline Characteristics						
Age in years, mean (standard deviation)	64 (8.7)	62 (8.2)	0.03*	64 (8.8)	62 (8.04)	0.13
Male sex	340 (77%)	116 (68%)	0.03*	42 (73%)	50 (67%)	0.30
Race White non-Hispanic	305 (69%)	112 (66%)	0.45	103 (67%)	102 (67%)	0.90
Obesity (BMI >30 kg/m2) at baseline	240 (54%)	64 (38%)	0.0002*	64 (42%)	61 (40%)	0.56

Table 5-1 Continued

Number of vessels with >50% lesions, %			0.88			0.43
1 – Vessel disease, %	81 (18%)	28 (16%)		23 (15%)	22 (14%)	
2 – Vessel disease, %	174 (39%)	72 (42%)		71 (46%)	63 (41%)	
3 – Vessel disease, %	182 (41%)	69 (40%)		57 (37%)	66 (43%)	
Myocardial Jeopardy Score	60.0 (22)	56 (22)	0.10	58 (23)	59 (21)	0.89
LVEF at time of evaluation - prior to randomization	57 (12)	60.0 (9.5)	<0.001	59 (12)	60 (9.7)	0.69
Conditions Any Time Prior to CABG						
Previous MI	160(36%)	71 (42%)	0.21	52 (34%)	67 (44%)	0.09
CVA prior to CABG	45 (10%)	13 (7.6%)	0.34	9 (5.9)	12 (7.8)	0.51
COPD prior to CABG	17 (3.8)	2 (1.2)	0.09	0	2 (1.3)	-
Non-coronary vascular surgery prior to CABG	7 (1.6)	8 (4.8)	0.03*	3 (2.0)	4 (2.6)	0.71
Any CHF therapy prior to CABG	76 (17%)	21 (12%)	0.14	25 (16%)	20 (13%)	0.11
NYHA class			0.46			
Class I	34 (7.7%)	9 (5.3%)		12	7	
Class II	32 (7.2%)	6 (3.5%)		11	6	
Class III	6 (1.4%)	2 (1.2%)		0	2	
Class IV	2 (0.5%)	2 (1.2%)		2	2	
Previous percutaneous coronary intervention	112 (25%)	40 (23%)	0.64	35 (23)	34 (22.2)	0.90
Dyspnea or SOB	315 (89%)	92 (92%)	0.35	94 (85%)	85 (93%)	0.17
Conditions at the Last Visit Prior to CABG						
Hypertension at visit prior to surgery (Sitting BP > 130/80)	168 (38%)	81 (42%)	0.03*	66 (44%)	74 (49%)	0.43
Triglycerides at visit prior to surgery, mean (sd)	168 (107)	168 (81)	0.19	162 (90)	168 (79)	0.17
GFR, ml/min/1.73m^2, mean (sd)	73 (22)	80 (24)	0.01*	78 (22)	79 (24)	0.77
Serum creatinine, mg/dl, mean (sd)	1.12 (0.33)	1.03 (0.28)	0.0015*	1.04 (0.26)	1.03 (0.28)	0.48

Table 5-1 Continued

Smoking			0.5908			0.90
Current	61 (14%)	19 (11%)		17 (11.11)	17 (11.11)	
Previous	232 (55.9%)	89 (52.05%)		79 (51.63)	80 (52.29)	
Never	150 (34%)	63 (37%)		57 (37.25)	56 (36.60)	
HbA1c %	7.5 (1.5)	7.8 (1.8)	0.048*	7.5 (1.6)	7.8 (1.8)	0.43
QoL at Last Visit Prior to CABG						
Health rating	64 (20)	63 (20)	0.49	64 (21)	63 (20)	0.68
Self-rated health			0.22			0.31
Poor	49 (11%)	17 (10%)		17 (11%)	14 (9%)	
Fair	149 (34%)	65 (39%)		54 (36%)	57 (38%)	
Good	187 (43%)	75 (45%)		59 (39%)	70 (47%)	
Very good	47 (11%)	8 (4.8%)		20 (13%)	7 (4.7%)	
Excellent	7 (1.6%)	3 (1.8%)		2 (1.3%)	2 (1.3%)	
DASI (0 – 58.2)	18 (13)	16 (10)	0.25	18 (13)	16 (10)	0.31
Health distress score (0 – 100)	39 (26)	38 (24)	0.70	38 (25)	38 (24)	0.96
At Time of Surgery						
Angina status at time of surgery			0.52			0.56
Stable	358 (81%)	138 (81%)		132 (86%)	123 (80%)	
Class I	109	28		38	24	
Class II	135	75		65	67	
Class III	88	25		25	23	
Class IV	20	6		3	6	
Unstable	71 (16%)	30 (18%)		18 (12%)	27 (18%)	
Acute MI	15 (3.4%)	3 (1.8)		3 (2.0%)	3 (2.0%)	
Medication pre-procedure						
(within 48 hours), %						
Aspirin	284 (64%)	71 (42%)	<0.0001*	91 (59.48)	62 (40.52)	0.40
Beta-Blockers	388 (87%)	157 (92%)	0.12	135 (88%)	142 (93%)	0.16
ACE inhibitors	284 (64%)	102 (60%)	0.32	100 (65%)	91 (59%)	0.27
Calcium antagonists	155 (35%)	55 (32%)	0.52	49 (32%)	48 (31%)	0.90
Nitrates	249 (56%)	85 (50%1)	0.16	77 (50%)	78 (51%)	0.91
Diuretics	181 (41%)	49 (29%)	0.0054*	56 (37%)	43 (28%)	0.11
Other vasodilators	27 (6.1%)	4 (2.3%)	0.057	7 (4.6%)	4 (2.6%)	0.37
Digitalis	13 (2.9%)	3 (1.8%)	0.41	5 (3.3%)	3 (2.0%)	0.48
Clopidogrel	49 (11%)	14 (8%)	0.29	13 (8.5%)	13 (8.5%)	0.99
Antiarrythmics	12 (2.7%)	5 (2.9%)	0.88	8 (5.2%)	5 (3.3%)	0.41

Note: Baseline characteristics had no or <3% observations missing until unless indicated. The percentages are calculated based on available data and may not add to 100%

^ 45 patients missing LVEF information (43 patients in the off-pump group and 2 patients in the on-pump group)

164 patients missing Dyspnea or SOB information (93 patients in the on-pump group and 71 patients in the off-pump group)

† P-value calculated using Kruskal-Wallis test for continuous variables and using chi-square/Fischer's exact for categorical variables

†† P-value calculated using Signed rank test for continuous variables and McNemar test/test of symmetry for categorical variables

*indicates p-value < 0.05

MI=myocardial infarction, CVA= cerebrovascular accident, CHF=congestive heart failure, SOB=shortness of breath, QoL=quality of life

Table 5-2: Complications and Short-term Clinical Outcomes for Patients Undergoing CABG Surgery

	On pump (N = 444)	**Off pump (N = 171)**	**P-value***
Complications (within hospitalization)			
Peri/Post-procedure complications	90 (20.3)	17 (9.9)	0.003
Neurological	14 (3.2)	2 (1.2)	0.26
Cardiac	25 (5.6)	2 (1.2)	0.016
Renal	2 (0.45)	2 (1.17)	0.31
Vascular	0	0	-
Pulmonary	19 (4.3)	7 (4.1)	0.92
Bleeding	19 (4.3)	3 (1.8)	0.13
Inotropes >48 hours, n (%)	50 (11.4)	9 (5.3)	0.023
Short-term Clinical Outcomes (within 30 days)			
Death/MI/Stroke	13 (2.9)	12 (7.0)	0.021
Death	3 (0.68)	4 (2.3)	0.10
MI	9 (2.03)	6 (3.5)	0.29
Stroke	1 (0.23)	3 (1.8)	0.07

*P-values based on Chi-square/Fishers test

Table 5-3: Effects of Performing Off-pump Procedure on Clinical Outcomes

Outcomes for All Patients (N = 615)	**Unadjusted (Off-pump vs On-pump)**			**Adjusted (Offpump vs On-pump)**		
	HR	95% CI	P-value	HR$^{\Phi}$	95% CI	P-value
Death (events = 69)	1.49	0.91 – 2.4	0.114	1.41	0.81 – 2.45	0.220
Death/MI/Stroke (events = 103)	1.47	0.98 – 2.21	0.060	1.47	0.92 – 2.33	0.106
Outcomes for Propensity Score Matched Patients (N=306, 153 Pairs)	**Unadjusted**			**Adjusted**		
	HR	95% CI	P-value	HR*	95% CI	P-value
Death (events = 36)	1.82	0.92 – 3.16	0.090	1.55	0.71 – 3.37	0.270
Death/MI/Stroke (events = 54)	1.88	1.09 – 3.25	0.023	1.83	1.01 – 3.32	0.046

Φ Model for outcome of Death adjusted for region, age, need of diuretics pre-surgery; Model for outcome of Death/MI/Stroke adjusted for region, age, sex, blood pressure greater than 130/80, need of aspirin, diuretics pre-surgery and energy scores

*Adjusted for region (region: US/Canada versus Others)

Table 5-4: Effects of Performing Off-pump Procedure on Functional Outcomes

Effects‡	All Patients				Matched Sample			
Angina	**N = 564**				**N = 283**			
Unadjusted	**OR**	**95% CI**	**P-value**	**Type III SS P-value**	**OR**	**95% CI**	**P-value**	**Type III SS P-value**
Off-pump (Yes vs No)	0.51	0.31 – 0.81	0.005	0.002	0.47	0.26 – 0.83	0.01	0.01
Time after Surgery				0.30				0.87
Year 2 (Ref: Year 1)	1.22	0.89 – 1.69	0.21		1.12	0.69 – 1.77	0.66	
Year 3 (Ref: Year 1)	1.13	0.77 – 1.67	0.52		1.21	0.68 – 2.15	0.52	
Year 4 (Ref: Year 1)	0.86	0.55 – 1.36	0.53		0.97	0.52 – 1.94	0.94	
Adjusted	**OR‡**	**95% CI**	**P-value**	**Type III SS P-value**	**OR***	**95% CI**	**P-value**	**Type III SS P-value**
Off-pump (Yes vs No)	0.74	0.44 – 1.21	0.24	0.22	0.68	0.36 – 1.28	0.23	0.22
Time after Surgery				0.29				0.87
Year 2 (Ref: Year 1)	1.25	0.90 – 1.76	0.19		1.12	0.69 – 1.80	0.65	
Year 3 (Ref: Year 1)	1.17	0.78 – 1.77	0.45		1.21	0.68 – 2.17	0.52	
Year 4 (Ref: Year 1)	0.87	0.54 – 1.40	0.56		0.98	0.52 – 1.82	0.94	
DASI	**N = 553**				**N = 277**			
Unadjusted	**Beta‡‡**	**95% CI**	**P-value**	**Type III SS P-value**	**Beta**	**95% CI**	**P-value**	**Type III SS P-value**
Off-pump (Yes vs No)	2.52	0.61 – 4.43	0.01	0.01	0.34	-2.48 – 3.17	0.81	0.81
Time after Surgery				0.36				0.44
Year 2 (Ref: Year 1)	0.20	-0.80 – 1.21	0.69		0.28	-1.01 – 1.56	0.67	
Year 3 (Ref: Year 1)	-0.57	-1.56 – 0.43	0.26		-0.13	-1.53 – 1.28	0.86	
Year 4 (Ref: Year 1)	0.15	-0.98 – 1.27	0.80		1.05	-0.54 – 2.65	0.20	
Adjusted	**Beta‡‡**	**95% CI**	**P-value**	**Type III SS P-value**	**Beta***	**95% CI**	**P-value**	**Type III SS P-value**
Off-pump	-	-	-	-	-1.79	-4.92 – 1.34	0.26	0.27
Time after Surgery				0.044				0.44
Year 2 (Ref: Year 1)	0.25	-0.98 – 1.48	0.69		0.28	-1.01 – 1.56	0.68	
Year 3 (Ref: Year 1)	-1.22	-2.43 – -0.01	0.048		-0.15	-1.55 – 1.26	0.84	
Year 4 (Ref: Year 1)	-1.12	-2.45 – 0.21	0.10		1.03	-0.56 – 2.62	0.21	
Interaction between Procedure Type and Time				0.005	-	-	-	-
Off-Pump (Yes vs No)	-1.93	-4.42 – 0.56	0.13					

Table 5-4 Continued

at Year 1								
Off-Pump at Year 2	-2.17	-4.68 – 0.35	0.09					
Off-pump at Year 3	-0.08	-2.35– 2.19	0.95					
Off-pump at Year 4	2.04	-0.76 – 4.84	0.15					

ǂ Model adjusted for baseline characteristics that differed between off-pump and on-pump patients including region, randomization assignment, whether the surgery was performed as an index procedure, sex, age, obesity, left ventricular ejection fraction, hypertension (yes/no), glomerular filteration rate, prior pvd, hba1c level, aspirin medication prior to surgery, diuretics medication prior to surgery, energy scores in addition to time after surgery

ǂǂ Model adjusted for baseline DASI scores and characteristics that differed between off-pump and on-pump patients including region, randomization assignment, whether the surgery was performed as an index procedure, sex, age, obesity, left ventricular ejection fraction, hypertension (yes/no), glomerular filteration rate, prior pvd, hba1c level, aspirin medication prior to surgery, diuretics medication prior to surgery, energy scores, time and interaction between time and off-pump *Model adjusted for region where the procedure was performed and time after surgery

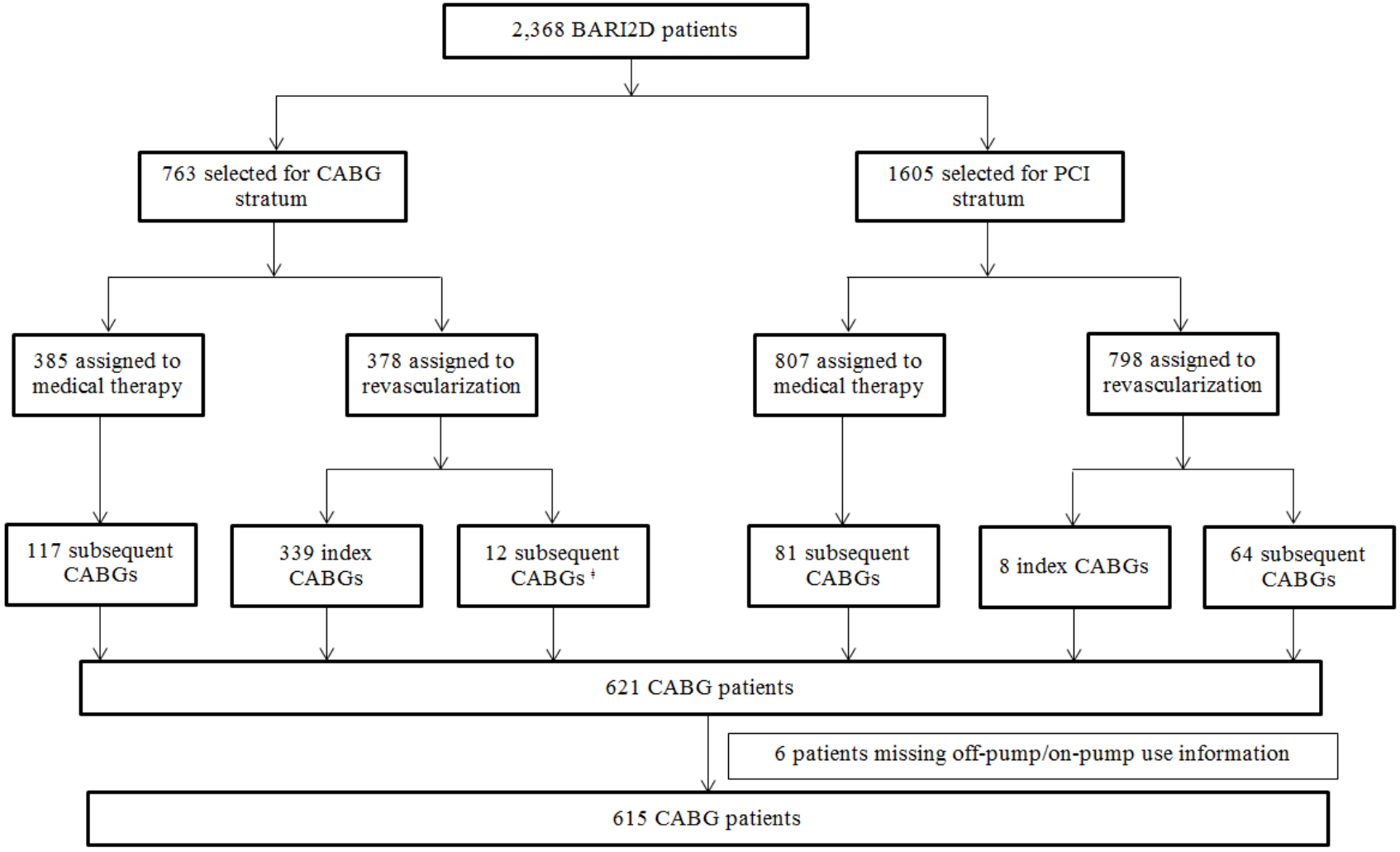
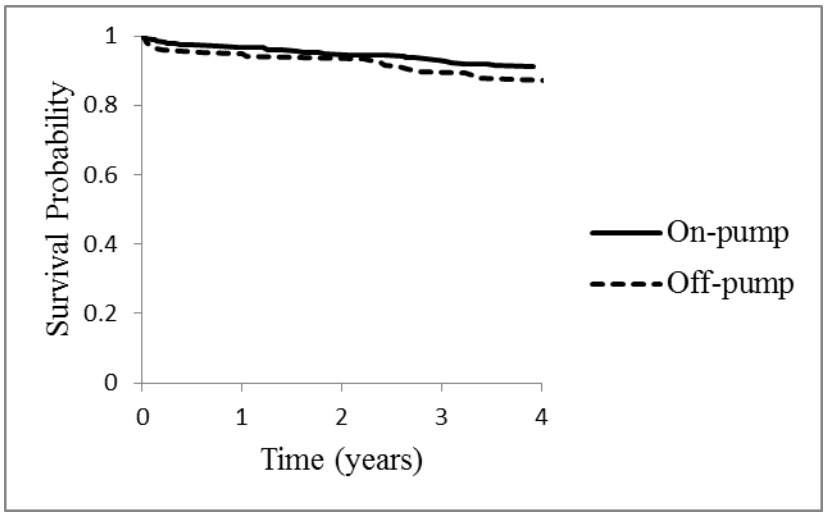
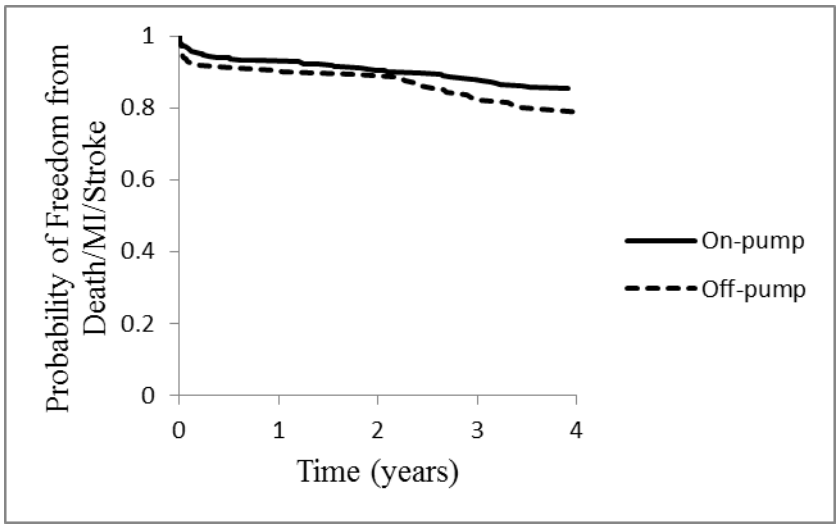


Figure 5-1: Sample Population from BARI 2D trial undergoing a CABG procedure



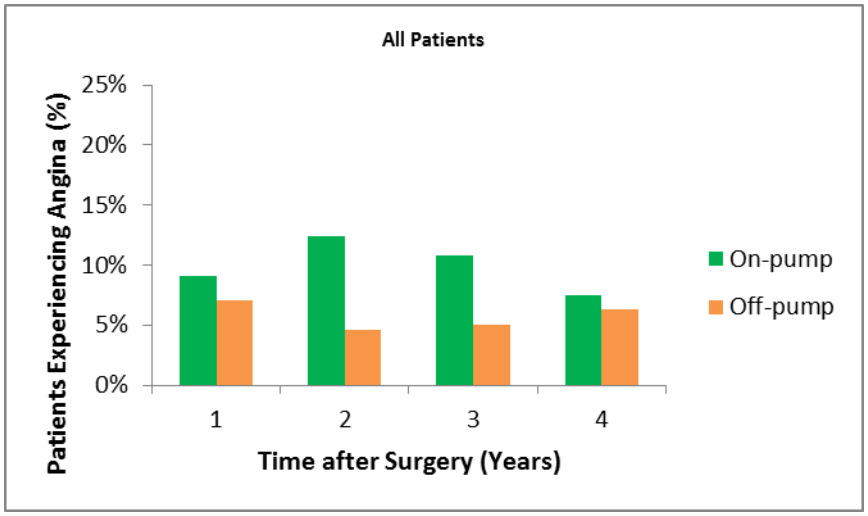
	Number of Patients at Risk at the Specified Time Points			
CABG Type	**1 year**	**2 year**	**3 year**	**4 year**
On-pump (N = 444)	418	389	350	273
Off-pump (N = 171)	161	157	145	111

Figure 5-2: Survival for Patients Undergoing Off-pump and On-pump CABG



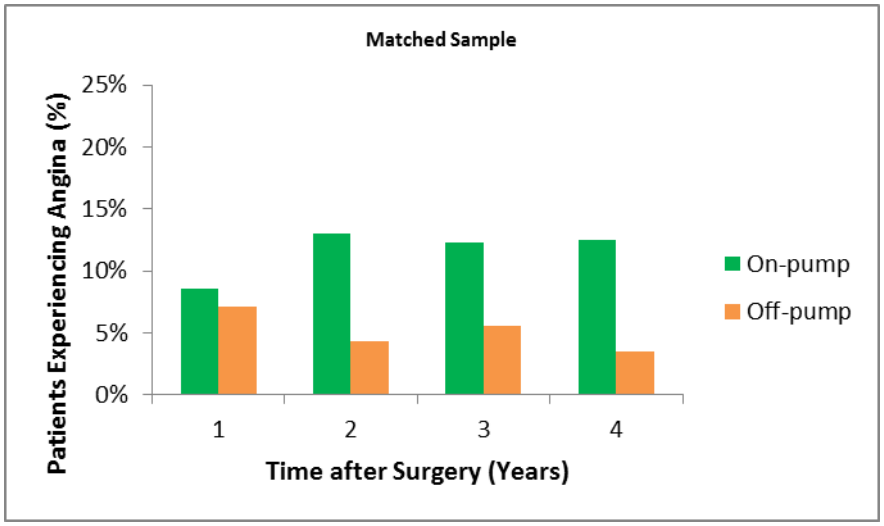
	Number of Patients at Risk at the Specified Time Points			
CABG Type	**1 year**	**2 year**	**3 year**	**4 year**
On-pump (N = 444)	379	344	287	190
Off-pump (N = 171)	150	144	115	65

Figure 5-3: Freedom from Death/MI/Stroke for Patients Undergoing Off-pump and On-pump CABG



	Number of Patients at Risk at the Specified Time Points			
CABG Type	**1 year**	**2 year**	**3 year**	**4 year**
On-pump (N = 444)	402	371	335	268
Off-pump (N = 171)	158	154	143	111

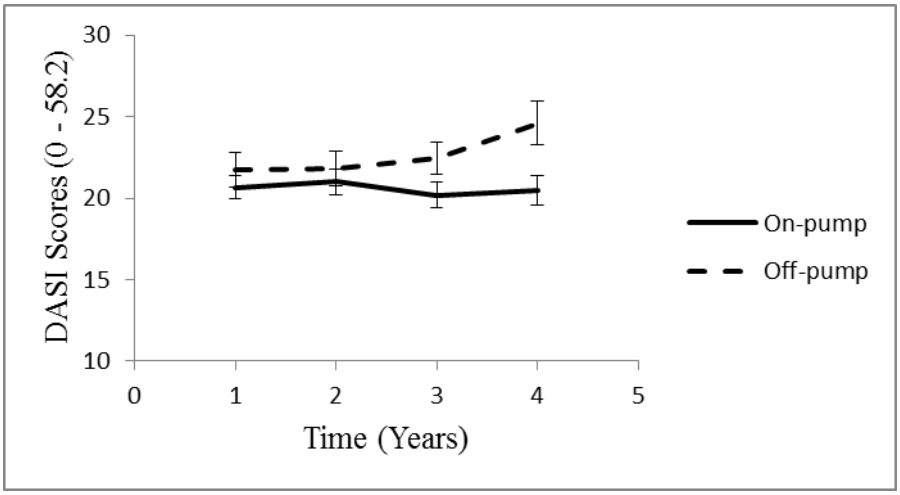
A: Patients Experiencing Angina at 1, 2, 3 and 4 Years after Surgery



	Number of Patients at Risk at the Specified Time Points			
CABG Type	**1 year**	**2 year**	**3 year**	**4 year**
On-pump (N = 153)	141	131	123	106
Off-pump (N = 153)	142	139	129	99

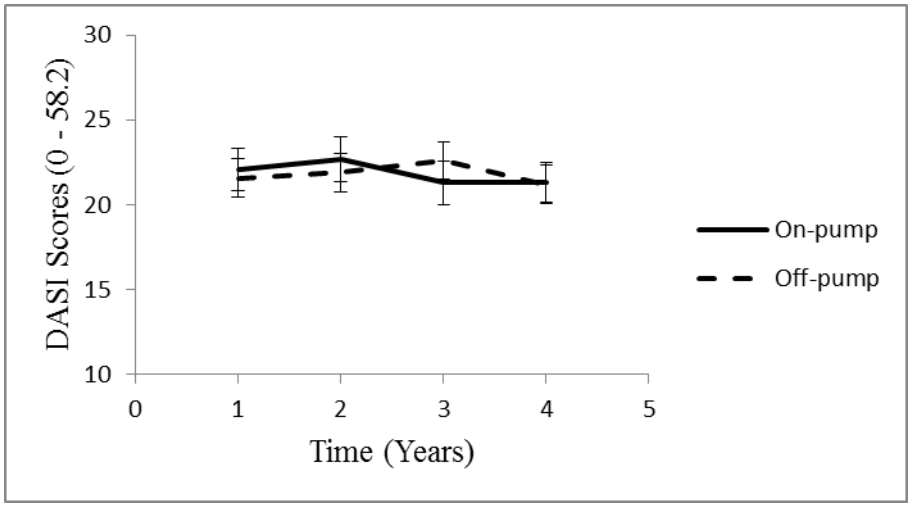
B: Patients in the Matched Sample Experiencing Angina at 1, 2, 3 and 4 Years after Surgery

Figure 5-4: Angina among Patients Undergoing Off-pump and On-pump CABG



	Number of Patients at Risk at the Specified Time Points			
CABG Type	**1 year**	**2 year**	**3 year**	**4 year**
On-pump (N = 444)	388	346	313	256
Off-pump (N = 171)	149	147	135	104

A: DASI Scores at 1, 2, 3 and 4 Years after Surgery (All Patients)



	Number of Patients at Risk at the Specified Time Points			
CABG Type	**1 year**	**2 year**	**3 year**	**4 year**
On-pump (N = 153)	135	126	118	102
Off-pump (N = 153)	134	132	121	93

B: DASI Scores at 1, 2, 3 and 4 Years after Surgery (Matched Sample)

Figure 5-5: Average DASI Scores for Patients Undergoing Off-pump and On-pump CABG

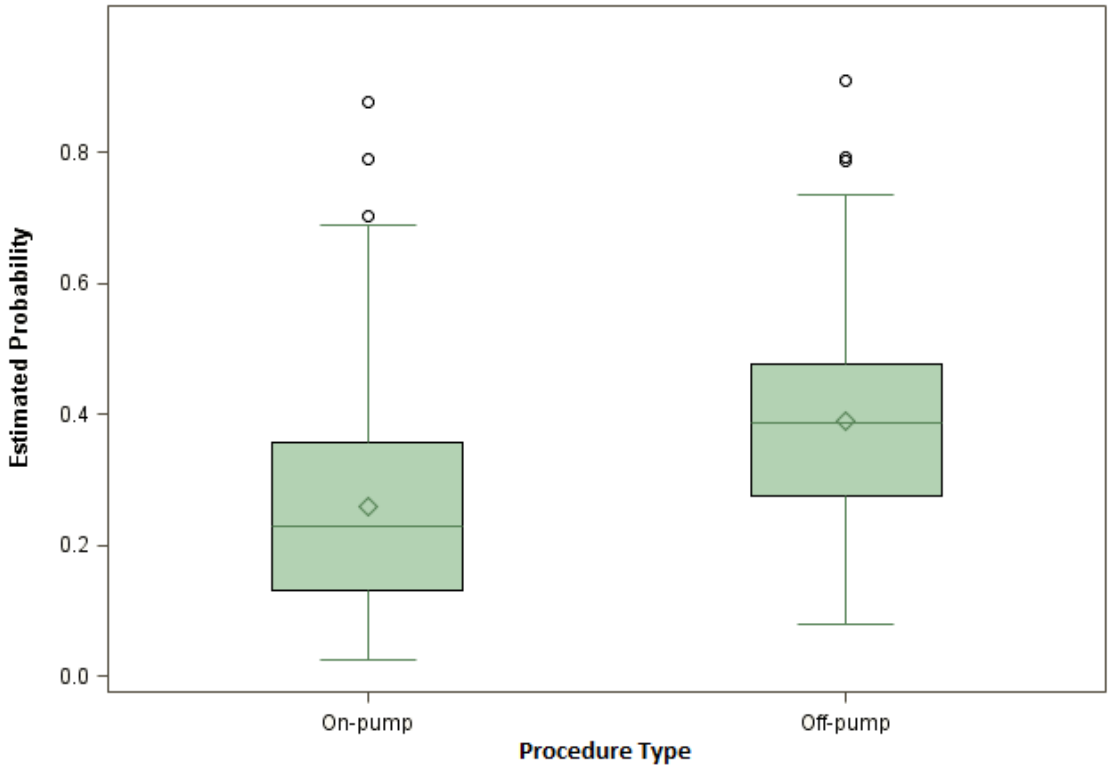


Figure 5-6: Distribution of Propensity Scores by Procedure Type

6.0 MANUSCRIPT 2 (ADDENDUM): ECONOMIC ANALYSES COMPARING OFF-PUMP AND ON-PUMP CABG

Specific Aim

To determine whether off-pump coronary artery bypass grafting (CABG) is a cost-effective strategy as compared to on-pump CABG. This aim uses data from Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI-2D) trial to identify the cost-effective strategy (comparing off-pump and on-pump CABG) at two years after surgery.

6.1 METHODS

This analysis includes a subset of patients who underwent a CABG procedure in the BARI 2D trial. The subset comprised of patients who underwent CABG as their index procedure, had at least 2 years of potential follow-up data. Of the 347 patients who underwent CABG as their index procedure, there were 269 (77.5%) patients who had at least 2 years of potential follow-up data. Of these, 2 patients had no follow-up for their quality of life assessments after surgery and hence were not included in the analyses. This resulted in a sample size of 267 patients, 159 (59.6%) of which underwent the on-pump procedure and 108 (40.4%) underwent the off-pump procedure.

In BARI 2D, an Economics Core Laboratory at Stanford University School of Medicine collected data regarding medical utilization. The patients had to consent specifically to participate in the economic research of the BARI-2D study. A core lab staff or a site designate contacted the consented patients every 3 months by telephone to document occurrence of hospital admissions, physician visits, outpatient tests and procedures, and prescription medications. The Economics core team attempted to collect records for hospital admissions to be able to verify the inpatient procedure and admissions data. They determined medical care costs for each patient by applying a standardized cost weight to each medical resource used. Hospital admissions were assigned to a Diagnosis Related Group and costs were calculated using the fiscal year weights and the national conversion factor. Physician fees from the Medicare schedule were used to determine costs for office tests and physician visits and for inpatient procedures. Prescription drugs were assigned costs based on average wholesale prices obtained from the Red Book, Pharmacy's Fundamental Reference[210].

Costs and Effectiveness

The cost-effectiveness analyses were conducted for two perspectives: hospital and third party payers. The hospitals perspective costs included the procedure costs and opportunity costs of bed-days for the duration of hospitalization. The third-party payer perspective included the costs related to the procedure, hospitalization, nursing home and rehabilitation, outpatient visits, outpatient procedures and medication.

For the hospital perspective, we obtained cost estimates of the two procedure types from the literature since the trial data did not differentiate between the off-pump and on-pump costs. The costs associated per bed-day were obtained using the Healthcare Cost and Utilization Project

(HCUP) data. The hospitalization duration (obtained from trial data) multiplied with the bed day costs determined the total bed-day costs.

For the third party perspective, the CABG procedure costs were obtained from the Physician Fee Schedule using the Healthcare Procedure Coding System Codes (33533 – 33536 along with 33517 – 33523). The costs related to hospitalization, nursing home, outpatient visits, medications and other procedures were obtained from the trial's economic core team. The costs obtained from literature and online databases were modeled as gamma distribution to reflect the variability among patients. The shape and scale parameters of the gamma distributions were approximated using means and standard deviations obtained from the HCUP and/or Physician Fee Schedule data. All costs were discounted to year 2014 using a 3% discount rate.

The associated effectiveness of each treatment was expressed as quality adjusted life-years. The quality adjusted life-years were calculated as the product of utility score of each patient and the mean survival time for the respective group. Melsop et al used a multiple linear regression model to determine the relationship between the time trade-off scale and quality of life scales, for patients with coronary disease[211]. The utility scores depended on Duke Activity State Index, self-reported health status, Canadian Cardiovascular Society class for angina, and health rating, as determined previously. Among all patients who lived for at least 2 years after surgery, 12 (4.5%) had missing angina and quality of life data. The last observations noted for the respective measures were used to impute the missing information for these patients.

Analyses

We determined the costs between all patients undergoing off-pump and on-pump CABG procedures as their initial procedure and had at least 2 years of potential follow-up data. The summary statistics for costs are presented as mean and standard deviation and compared using

the non-parametric Wilcoxon rank-sum test. Baseline demographic and clinical characteristics were compared between patients undergoing on-pump and off-pump procedure. Summary statistics for the baseline characteristics are presented as means and standard deviation in case of continuous variables, and as numbers and percentages in case of categorical variables. Continuous variables were compared using Wilcoxon rank-sum test and categorical variables using chi-square or Fischer's exact, where appropriate.

The propensity score methodology was used to control for non-randomized treatment selection of the off-pump and on-pump CABG. Two sets of propensity scores were calculated for each patient, using separate multivariable logistic regression model. The candidate variables for the first model comprised of objective baseline characteristics (demographic and clinical) which were different between the off-pump and on-pump group at a significance level of 0.10. The second model included all candidate variables used for the first model except for geographic region. Backward-selection methods utilizing an alpha = 0.20 for eliminating variables were used to further refine each model. Based on the calculated propensity scores, patients undergoing off-pump CABG were matched with those undergoing on-pump (1:1 match, without replacement) using a caliper of 0.01.

The cost-effectiveness analyses within the matched sample were carried out from the hospital and third-party payer's perspective. Bootstrapping involved resampling the costs and effects from the resulting matched sample jointly with replacement. The incremental net health benefit was calculated using this data to report the cost-effectiveness results. This process was repeated 1000 times. The 1000 bootstrap estimates of the net health benefits then provided the empirical sampling distribution, using which the percentiles were calculated. The net health benefits (NHB) framework was introduced in response to the inference issues associated with

incremental cost-effectiveness ratios, especially when the distribution of costs and effects extend to more than one quadrant[42]. NHB transforms cost and effect into a linear function, having a more comprehendible interpretation of the estimate and its uncertainty.

$$NHB = \mu_{Ei} - \mu_{Ci}/\lambda$$

Thus the incremental NHB of off-pump (T_1) compared to on-pump (T_0) was calculated as

$$(\mu_{E1} - \frac{\mu_{C1}}{\lambda}) - (\mu_{E0} - \frac{\mu_{C0}}{\lambda}) = (\mu_{E1} - \mu_{E0}) - (\mu_{C1} - \mu_{C0})/\lambda$$

Where μ_{Ei} and μ_{Ci} represent the mean effectiveness and the mean costs respectively, of treatment T_i; λ represents the threshold cost-effectiveness ratio.

The uncertainty associated with incremental NHBs was depicted using the cost-effectiveness acceptability curve. The off-pump was considered the optimum strategy if the resulting incremental health benefit was greater than 0. All costs were discounted to 2014 US dollars. As a sensitivity analyses, we examined the costs and effects for patients undergoing CABG in US/Canada within the matched sample, recognizing that costs can vary significantly by country.

6.2 RESULTS

There were 347 patients who underwent CABG as their index procedure in the BARI 2D trial. Of the 347 patients, 267 had at least 2 years of follow-up or had experienced a death. Among these, 159 (59.6%) patients had an on-pump procedure and 108 (40.4%) underwent the off-pump procedure.

Table 6-1 lists and compares cost components and effectiveness between patients undergoing the on-pump and off-pump CABG. The on-pump CABG procedure costs to the hospital are slightly higher than the off-pump CABG; but they are not significantly different. The total number of hospitalization days for patients in the off-pump group was significantly higher than the patients in the on-pump group (On-pump: 19.8 days (s.d = 22.7) ; off-pump: 24.2 days (s.d = 23.8), p = 0.0003). This translated to significantly higher bed costs incurred to the hospital. The total hospital perspective costs were significantly higher for off-pump patients. The hospitalization, outpatient, medication and other procedure costs were comparable between the off-pump and on-pump patients. Thus there were no significant differences in the total third party payer perspective costs. The mean survival time was not significantly different between the two groups. The truncated mean survival time was 1.89 (s.d. = 0.39) and 1.88 (s.d. = 0.45) years for the on-pump and off-pump patients respectively. As shown in figure 6-1, the two year survival Kaplan-Meier estimates were not significantly different between the two groups (On-pump group survival: 94.9% and 91.2%, Off-pump group survival: 94.4% and 93.5% at 1 year and 2 year respectively). However, the quality of life was significantly higher for patients in the off-pump group as compared to the patients in the on-pump group (Table 6-1).

The on-pump and off-pump groups are the not randomized in the BARI-2D clinical trial. There therefore were certain baseline differences between patients undergoing on-pump and off-pump CABG (Table 6-2). The distribution of country of origin varied significantly across the two procedure groups. In addition, patients in the off-pump group were younger, had lower serum creatinine levels and were less likely to be males, obese, have a prior history of chronic obstructive pulmonary disease. Patients undergoing off-pump and on-pump also differed in terms of medications administered prior to surgery (aspirin, diuretics, angiotensin-converting-enzyme

inhibitor**)** and self-reported quality of life measures (energy scores and health rate). Since baseline differences among patients can influence the costs, further economic analyses were based on the propensity score analyses.

Propensity Score Model 1 (including region as a candidate variable), Table 6-3

All of the baseline characteristics listed in Table 6-1 that were significantly different between the off-pump and on-pump group, and potentially affected the treatment selection decision were included as candidate variables to determine the final model for calculating propensity scores. The pre-procedural therapy (within 48 hours) was not included since it was considered part of procedural delivered rather than a predictor of treatment selection. Also, since we focused on objective measures, the self-reported quality of life assessments were not considered as candidate variables. The propensity scores model obtained from the backward selection methods included region (US/Canada versus Others) and obese (BMI greater than 30 versus less than 30). As illustrated in Figure 6-2, the distributions of the propensity scores were substantially different between the two procedure groups, with no overlap. Thus, an alternate model which did not include geographic region as a candidate variable was considered for calculating the propensity scores.

Propensity Score Model 2 (not including region as a candidate variable), Table 6-4

The second set of propensity scores were based on sex, age, obesity and prior history of chronic pulmonary obstructive disorder, as determined by the backward selection methodology. The model was further refined by including if the patient had CABG as the preferred method of revascularization to result in a more balanced off-pump and on-pump groups. There was a

modest overlap in the distribution of propensity scores between the two groups, as shown in figure 6-3. The matching resulted in 84 pairs of patients. The matched patient groups differed with respect to region, self-reported energy and rated health scores, and aspirin use within 48 hours prior to surgery. The energy and health rating scores are subjective. The medication use within 48 hours prior to surgery could be a part of the procedure protocol and hence was not adjusted for in the propensity scores. Since costs may vary with region, we did a sub-analysis for patients undergoing surgery in US/Canada. Within the matched set, the truncated mean survival time was 1.89 (s.d = 0.43) and 1.85 (s.d. = 0.50) among on-pump and off-pump patients respectively (Figure 6-4).

Economic Analyses in the Matched Set of Patients

Table 6-5 shows the costs and effectiveness measures along with the associated 2.5^{th} and 97.5^{th} percentiles for patients undergoing the on-pump and off-pump surgery obtained by bootstrapping the matched subsample. Within the matched patients, there were no significant differences in life years or quality adjusted life years. From the hospital perspective, the patients undergoing off-pump had significantly higher costs as compared to on-pump group. Combining the costs and effectiveness estimates, the net health benefits were significantly lower for patients undergoing off-pump as compared to patients undergoing on-pump CABG.

From the third party payer perspective, the two strategies are comparable in terms of costs, effectiveness and the net health benefits.

The ICER planes (Figure 6-5 and 6-6) show the variability among the bootstrap samples. The choice of the effectiveness measure (i.e. QALY or life years) also affected the decision of determining the cost-effectiveness strategy. Among the 1000 bootstrap samples, off-pump

CABG was the optimal strategy from the hospital perspective in only 0.6 – 2% of iterations when effectiveness was calculated in terms of QALY and in 0.7 - 3% when effectiveness assessed in terms of life years, the range depending on the cost-effectiveness threshold (Figure 6-7). When considering the third party payers perspective, off-pump was the optimal strategy 41 - 49% iterations with effectiveness measured in QALYs; 26 - 30% iterations showed off-pump strategy was optimal when effectiveness was measured in terms of life years.

Analyses Restricted to Patients Undergoing CABG in US or Canada

Of the 168 patients in the aforementioned matched sample, 80 patients underwent CABG in US or Canada. The on-pump CABG was more common this geographical region, 60 (75%) were performed as on-pump and only 20 (25%) as off-pump procedure. Table 6-6 lists the bootstrap mean costs and effectiveness estimate along with the 2.5^{th} and 97.5^{th} percentiles. The estimates obtained showed trends similar to what were observed within the entire matched sample, but none of the differences between the two procedures were statistically significant.

6.3 DISCUSSION

Results from this analysis further support the results obtained from comparison of clinical outcomes between the two types of procedure. The results show that from the hospital perspective, off-pump was not the favorable option as compared to on-pump patients. The net health benefits achieved by using off-pump procedures were significantly lower than that achieved by the on-pump procedure. This was mainly driven by higher costs incurred to the hospitals due to significantly greater number of inpatient days for patients in the off-pump group.

This trend was not observed for third party payers. The off-pump and on-pump strategies were very comparable from the third party perspective.

This analysis has certain limitations. First of all, the economic component of BARI-2D trial was designed to address primary randomized groups (which were revascularization and medical therapy for treatment of coronary artery disease, and insulin sensitization and insulin provision therapy for management of diabetic conditions). Due to this limitation we could not include all CABG procedures performed in the trial and had limited sample size. Also generalizability of costs particularly across geographic regions is an issue. We performed a sub-analysis on patients undergoing CABG in US and Canada patients. However, this further limited the sample size. This analysis however gives useful insight into the cost-effectiveness analysis of on-pump and off-pump CABG procedure. Off-pump procedure costs (to the hospital) by themselves might tend to be lower since for such procedures the purchase of CPB machine is avoided. However over a period of time, off-pump procedure in fact accumulates excess costs to on-pump. Also the quality of life data were well collected and document in the BARI-2D trial. Out of the 269 patients, there were only 2 patients who had no angina or quality of life assessment after surgery. Also, we did not perform the cost-effectiveness analyses from societal perspective since indirect costs were not measured in BARI-2D trial. Never the less, based on the observed worse long-term clinical outcomes along with the calculated higher/comparable short-term costs for patients in the off-pump group, it is inferable that off-pump is not an optimum CABG strategy for patients with diabetes from a societal perspective. However systematic research is required to make conclusions about the cost-effectiveness of off-pump CABG from the societal perspective.

6.4 CONCLUSIONS

Our results show that the off-pump CABG is not a cost-effective strategy as compared to the on-pump CABG from the hospital perspective. When considering cost-effectiveness from the perspective of third party payers, the two procedures are comparable. Also keeping in view the worse clinical outcomes and comparable direct costs we can deduce that off-pump procedure will not be cost-effective from the societal perspective. Thus we conclude that on-pump should be the preferred CABG type for patients with diabetes, until unless contraindicated due to clinical conditions like cannulation of the aorta and cardiopulmonary bypass

6.5 TABLES AND FIGURES

Table 6-1: Costs and Effectiveness (Mean, Standard Deviation) for Patients undergoing On-pump and Off-pump Surgery

Characteristic	Total (N=267)	On-pump CABG (N=159)	Off-pump CABG (N=108)	p-value
Costs (US $)				
CABG Procedure Costs, Hospital Perspective	15873.5, 12311.1	16292.9, 12747.3	15255.9, 11670.2	0.5199
CABG Procedure Costs, Third Party Payers Perspective	3273.7, 473.9	3272.7, 473.8	3275.1, 476.2	0.8331
Total Bed Costs, mean, SD*	52414.9, 56425.8	48144.3, 55235.8	58861.9, 57847.0	0.0003
Hospitalization Costs	50189.8, 24531.9	51363.0, 27179.4	48418.7, 19875.7	0.2845
Nursing Home/Rehabilitation Costs	268.1, 3023.3	445.7, 3892.8	0.0, 0.0	0.0445
Outpatient Visit Costs	3477.2, 1704.2	3688.9, 1825.9	3157.6, 1452.9	0.0047
Outpatient Procedure Costs	1519.9, 1176.1	1763.2, 1372.3	1152.8, 642.9	0.0002
Medication Costs	15387.0, 6539.4	15232.9, 6991.3	15619.6, 5816.0	0.4376
Total Hospital Perspective Costs	***68511.9, 57298.6***	***64505.0, 56411.2***	***74560.8, 58364.7***	***0.0029***
Total Third Party Payer Perspective Costs	***74111.7, 27791.0***	***75761.5, 31468.3***	***71621.0, 20961.6***	***0.3334***
Effectiveness				
Quality Adjusted Life Years	1.698, 0.121	1.673, 0.131	1.733, 0.096	<.0001
LIFE_YRS, mean, SD	1.890, 0.415	1.893, 0.393	1.885, 0.446	0.5472

*(Based on costs per bed-day obtained from HCUP (Mean = $2435, sd = $23) and hospitalization duration (On-pump: Mean = 19.8 days, sd = 22.7 ; Off-pump: Mean = 24.2 days, sd = 23.8, p = 0.0003)

Table 6-2: Baseline Characteristics of Patients Undergoing On-pump and Off-pump CABG (All patients and Matched Subgroup)

	All Patients			Matched Patients		
Characteristic	**On-pump (N=159)**	**Off-pump (N=108)**	**P-value**	**On-pump (N=84)**	**Off-pump (N=84)**	**P-value**
Insulin Providing Arm, %	53.5	49.1	0.4816	53.6	45.2	0.2801
CABG Strata, %	96.9	99.1	0.2299	98.8	98.8	1.0000
Male, %	79.9	64.8	0.0060*	75.0	70.2	0.4889
White non-hispanic, %	66.7	74.1	0.1963	66.7	76.2	0.1719
BMI >= 30, %	52.5	34.3	0.0033*	38.1	42.9	0.5153
SMK_STATUS, %			0.7168			0.6746
Never	34.6	38.9		38.1	35.7	
Former smoker	54.1	49.1		47.6	53.6	
Current smoker	11.3	12.0		14.3	10.7	
Computed number of vessels with lesions >=50%, %			0.6326			0.7730
1	10.7	15.7		9.5	13.1	
2	44.7	39.8		44.0	36.9	
3	44.0	43.5		45.2	48.8	
Prior PCI, %	12.6	13.0	0.9263	11.9	15.5	0.5007
Prior MI, %	30.8	35.2	0.4549	26.2	34.5	0.2402
Earlier than 90 days	40.8	57.9		63.6	55.2	
Within 90 days	59.2	42.1		36.4	44.8	
Prior CVA, %	8.8	6.5	0.4888	11.9	6.0	0.1761
Prior COPD, %	6.3	0.9	0.0305*	0.0	1.2	0.3159
Prior PVD, %	1.3	2.8	0.3686	0.0	3.6	0.0805
US/Canada, %	76.1	21.3	<.0001*	71.4	23.8	<.0001*
Patient angina status surg, %			0.1913			0.3326
Stable	91.8	89.8		92.9	89.3	
Canadian card class surgery, %						
Class I	36.6	18.9		30.3	19.2	

Table 6-2 Continued

Class II	43.7	64.2		48.7	65.8	
Class III	18.3	13.7		21.1	12.3	
Class IV	1.4	3.2		0.0	2.7	
Unstable	6.3	10.2		6.0	10.7	
Acute MI	1.9	0.0		1.2	0.0	
Prior Coronary Heart Failure, %	14.5	12.0	0.5685	7.1	11.9	0.2931
Hypertension (BP>13080), %	44.9	54.2	0.1368	42.0	56.6	0.0606
Short Breathness at Last Visit Prior Surgery, %	85.3	92.9	0.1585	85.2	93.6	0.1748
Age at date of Surgery, mean, SD	63.9, 9.0	60.9, 7.9	0.0028*	62.9, 8.9	62.5, 7.0	0.5864
Time to CABG, mean, SD	30.6, 29.8	22.9, 16.3	0.1300	33.7, 32.7	22.9, 15.9	0.1097
Serum Creatinine (mg/dl), mean, SD	1.1, 0.3	1.0, 0.3	0.0192*	1.1, 0.3	1.1, 0.3	0.4182
HbA1C, mean, SD	7.5, 1.6	7.8, 1.9	0.3273	7.3, 1.5	7.8, 1.9	0.1181
Estimated GFR, mean, SD	73.4, 19.7	77.3, 19.1	0.1493	74.5, 18.8	75.6, 19.3	0.8451
Triglyceride, mean, SD	171.9, 90.9	170.2, 74.6	0.6333	165.7, 82.5	170.3, 74.9	0.5651
Myocardial Jeopardy, mean, SD	62.5, 21.4	59.4, 21.5	0.3289	63.9, 22.4	59.6, 21.2	0.1847
LV Ejection Fraction, mean, SD	56.6, 12.7	58.9, 8.5	0.1376	56.5, 12.1	58.7, 8.8	0.1628
Health Rating (0 – 100), mean, SD	63.4, 20.6	62.6, 20.5	0.8324	62.4, 21.7	62.5, 21.5	0.9637
DASI Scores, mean, SD	16.5, 13.1	15.4, 9.3	0.7056	17.3, 14.2	14.5, 8.9	0.7586
Health Distress Score, mean, SD	39.0, 25.2	36.9, 24.5	0.5960	36.8, 24.5	34.6, 23.5	0.6350
Energy Score, mean, SD	51.8, 23.9	62.7, 22.4	0.0002*	50.9, 22.2	61.0, 23.1	0.0035
Self-rated Health, %			0.0074*			0.0995
Poor	11.5	15.0		12.0	13.3	
Fair	36.9	28.0		34.9	32.5	
Good	37.6	52.3		38.6	49.4	
Very Good	13.4	2.8		13.3	2.4	
Excellent	0.6	1.9		1.2	2.4	
Therapy Pre-Procedure, % (within 48 hours)						
Aspirin, %	56.6	35.2	0.0006*	52.4	34.5	0.0196*
Beta Blocker, %	88.1	92.6	0.2270	86.9	91.7	0.3184
Ace Inhibitor, %	70.4	60.2	0.0819*	72.6	60.7	0.1017

Table 6-2 Continued

Diuretic, %	35.2	25.0	0.0766*	31.0	27.4	0.6106
Digitalis Derivative, %	1.9	0.9	0.5259	2.4	1.2	0.5602
Ticlodipine Clop, %	6.3	2.8	0.1907	9.5	2.4	0.0504
Antiarrhythmic Agent, %	3.1	3.7	0.8038	2.4	4.8	0.4057
Vasodilator, %	3.8	2.8	0.6581	3.6	3.6	0.9999
Calcium Blocker, %	29.6	25.0	0.4139	27.4	26.2	0.8617
Nitrate,%	42.8	46.3	0.5688	33.3	46.4	0.0831

Table 6-3: Propensity Score Logistic Regression Model 1 for Undergoing an Off-pump CABG (Propensity Score Model 1, With Region in the Model)

Parameter	Estimate	Standard Error	Wald Chi-Square	Pr > ChiSq
Intercept	1.0577	0.2376	19.8101	<.0001
Bmi>30, yes/no	-0.6175	0.3051	4.0978	0.0429
region_us_can	-2.4631	0.3057	64.9160	<.0001

Table 6-4: Propensity Score Logistic Regression Model 2 for Undergoing an Off-pump CABG (Propensity Score Model 2 (without region as candidate variable)

Parameter	Estimate	Standard Error	Wald Chi-Square	Pr > ChiSq
Intercept	1.7854	1.4716	1.4718	0.2251
Male	-0.8028	0.2969	7.3111	0.0069
Prior COPD	-1.6640	1.0692	2.4219	0.1196
Bmi>30, yes/no	-0.7782	0.2710	8.2463	0.0041
Age	-0.0429	0.0156	7.5493	0.0060
CABG Strata	1.5056	1.1255	1.7895	0.1810

Table 6-5: Bootstrap Mean and Percentile Intervals of Costs and Effectiveness for Patients undergoing On-pump and Off-pump Procedure in the Matched Sample

Characteristic	On-pump (N=84)	Off- (N=84)
Total Hospital Perspective Costs (US $)	58376 (50891 – 67074)	74707 (62908 – 90078)
***Incremental Hospital Perspective Costs* (US $)**	*16331 (3607 – 31987)**	
Total Third Party Payers Perspective Costs (US $)	71904 (67912 – 76443)	72729 (67742 – 78021)
***Incremental Third Party Payers Costs* (US $)**	*824 (-5719 – 7433)*	
QALY, mean, SD	1.696 (1.665 – 1.722)	1.701 (1.680 – 1.720)
Incremental QALY	*0.005 (-0.03 – 0.044)*	
LIFE_YRS, mean, SD	1.888 (1.784 – 1.97)	1.852 (1.734 – 1.943)
Incremental LY	*-0.03 (-0.18 – 0.102)*	
Cost-effectiveness Estimates		
Hospital Perspective		
Net Heath Benefits, In terms of QALY	0.528 (0.354 – 0.684)	0.207 -0.102 – 0.446)
Incremental NHB QALY	*-0.32 (-0.644 – -0.06)**	
Net Health Benefits, In terms of Life Years	0.720 (0.533 - 0.897)	0.358 (0.004 – 0.631)
Incremental NHB LY	*-0.36 (-0.735 – -0.06)**	
Third Party Payer Perspective		
Net Heath Benefits, In terms of QALY	0.257 (0.159 – 0.349)	0.247 (0.133 – 0.352)
Incremental NHB QALY	*-0.01 (-0.16 -0.141)*	
Net Health Benefits, In terms of Life Years	0.449 (0.346 - 0.546)	0.347 (0.246 – 0.542)
Incremental NHB LY	*-0.05 (-0.23 – 0.135)*	

Table 6-6: Bootstrap Mean and Percentile Intervals of Costs and Effectiveness for Patients undergoing On-pump and Off-pump Procedure in US/Canada within the Matched Sample

Characteristic	**On-pump (N=84)**	**Off- (N=84)**
Total Hospital Perspective Costs (US $)	47150 (40208 – 54593)	53632 (42176 – 65505)
***Incremental Hospital Perspective Costs* (US $)**	6482 (-7111 – 21159)	
Total Third Party Payers Perspective Costs (US $)	73802 (68483 – 80015)	86518 (75033 – 100319)
***Incremental Third Party Payers Costs* (US $)**	12717 (-40 – 26702)	
QALY, mean, SD	1.678 (1.641 – 1.710)	1.674 (1.622 – 1.719)
Incremental QALY	-0.004 (-0.06 – 0.5110)	
LIFE_YRS, mean, SD	1.969 (1.932 – 2)	2 (2 – 2)
Incremental LY	0.031 (0 – 0.0683)	
Cost-effectiveness Estimates		
Hospital Perspective		
Net Heath Benefits, In terms of QALY	0.735 (0.5867 – 0.8839)	0.602 (0.3551 – 0.8634)
Incremental NHB QALY	-0.1338 (-0.4237- 0.1502)	
Net Health Benefits, In terms of Life Years	1.969 (1.932 – 2)	2 (2 – 2)
Incremental NHB LY	-0.0990 (-0.5643 – 0.1826)	
Third Party Payer Perspective		
Net Heath Benefits, In terms of QALY	0.202 (0.071 – 0.3212)	-0.056 (-0.335 – 0.1950)
Incremental NHB QALY	-0.2585 (-0.5643 – 0.0225)	
Net Health Benefits, In terms of Life Years	0.493 (0.364 – 0.6010)	0.269 (-0.006 – 0.4993)
Incremental NHB LY	-0.2237 (-0.5070 - 0.0276)	

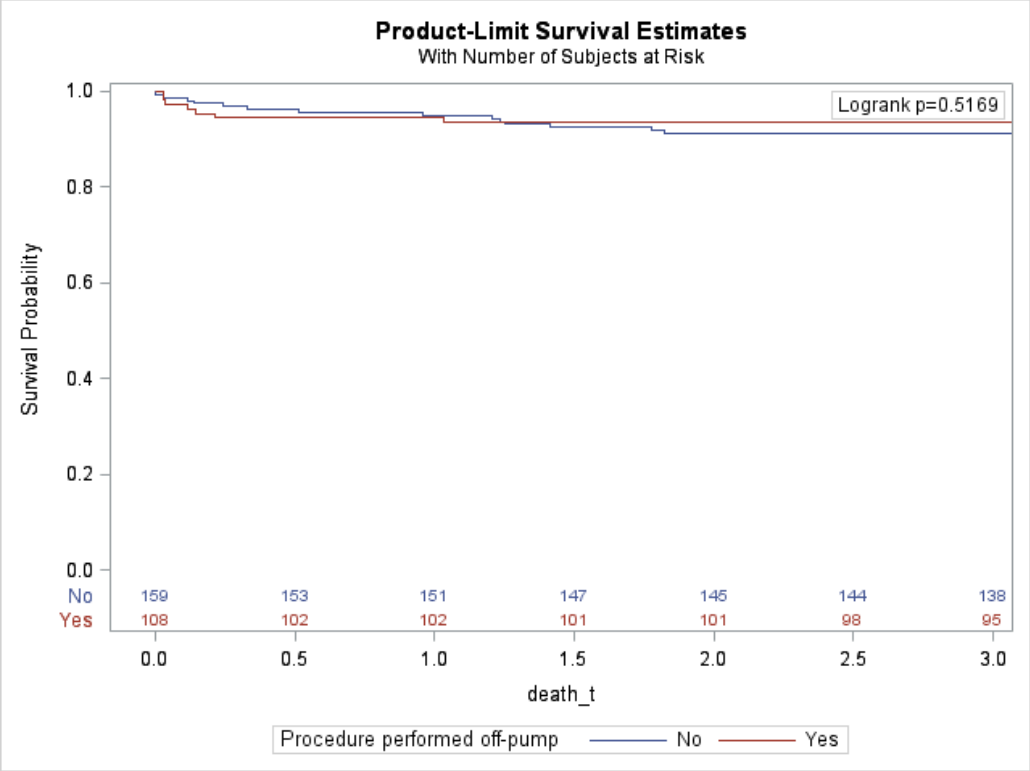


Figure 6-1: Survival for Patients Undergoing Off-pump and On-pump CABG

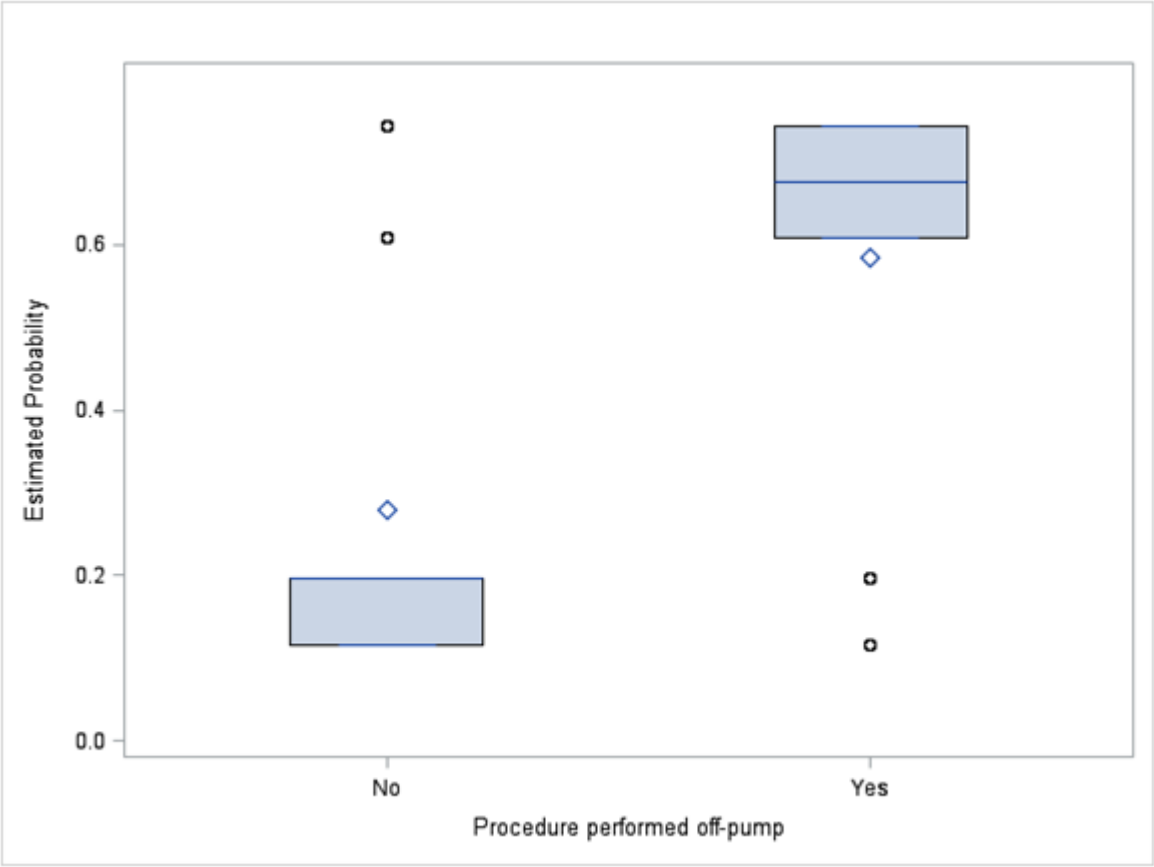


Figure 6-2: Distribution of Propensity Scores by Type of Procedure (Propensity Score Model 1: With Region in the Model)

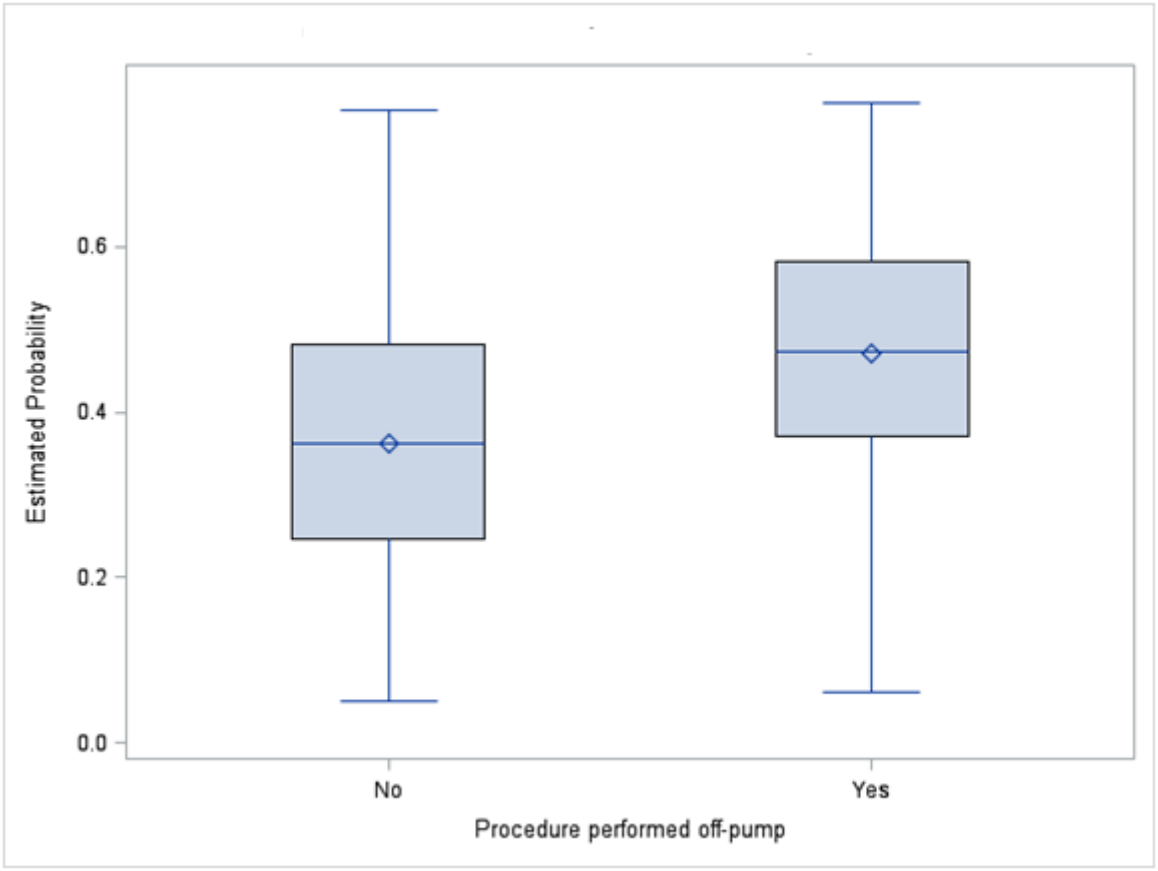


Figure 6-3: Distribution of Propensity Scores by Type of Procedure (Propensity Score Model 2: Without Region in the Model)

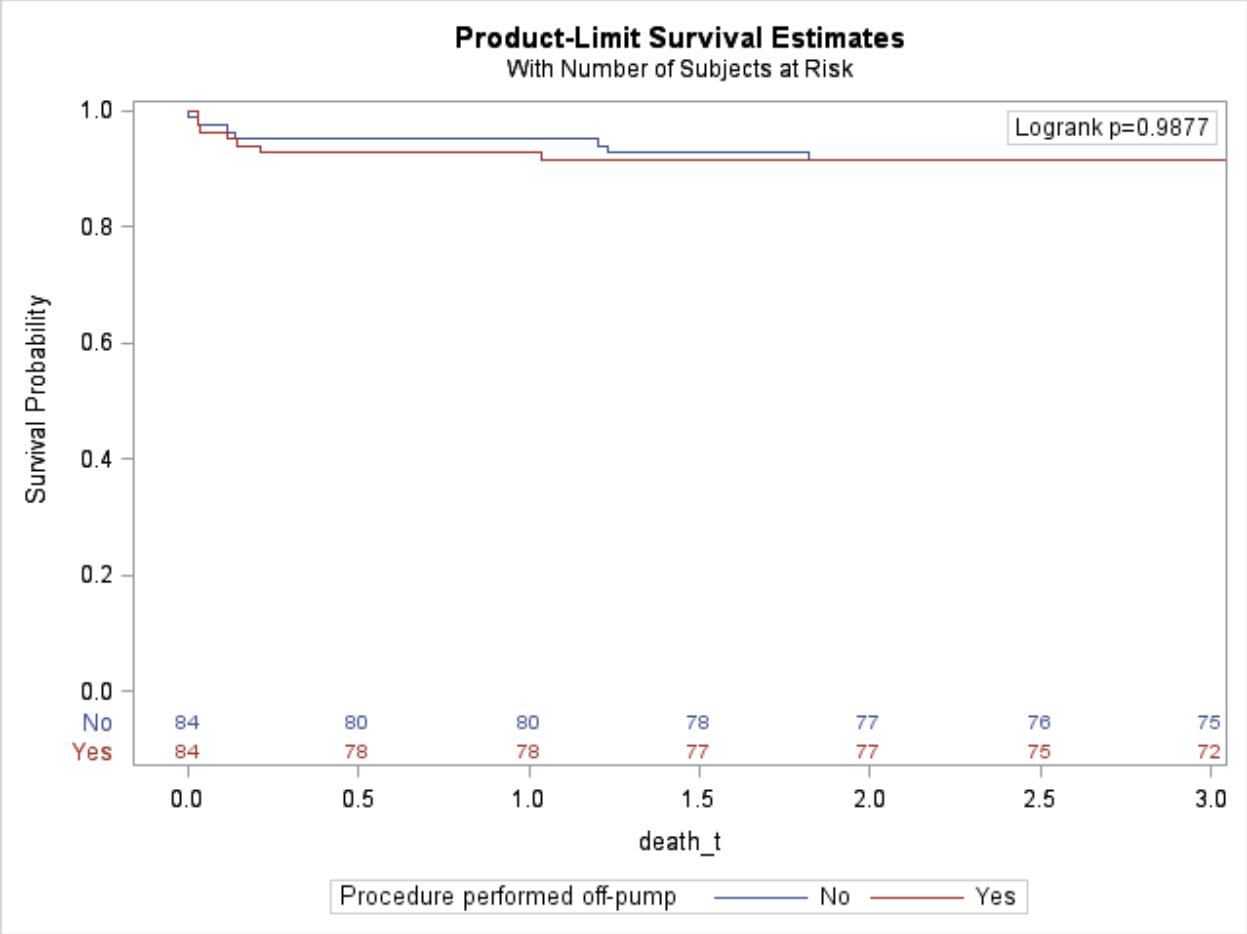
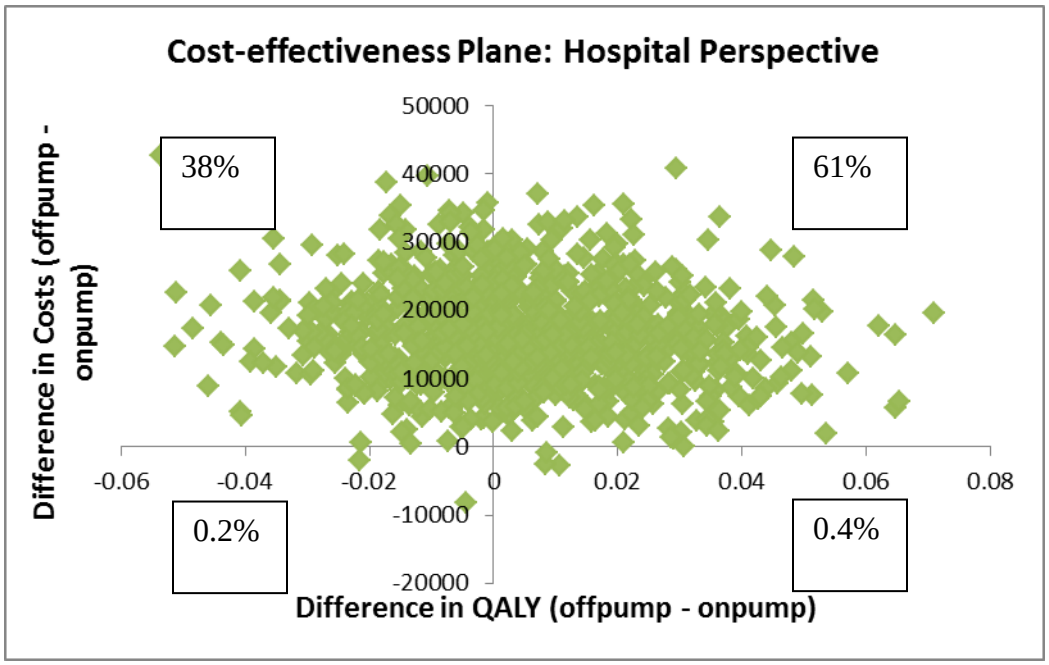
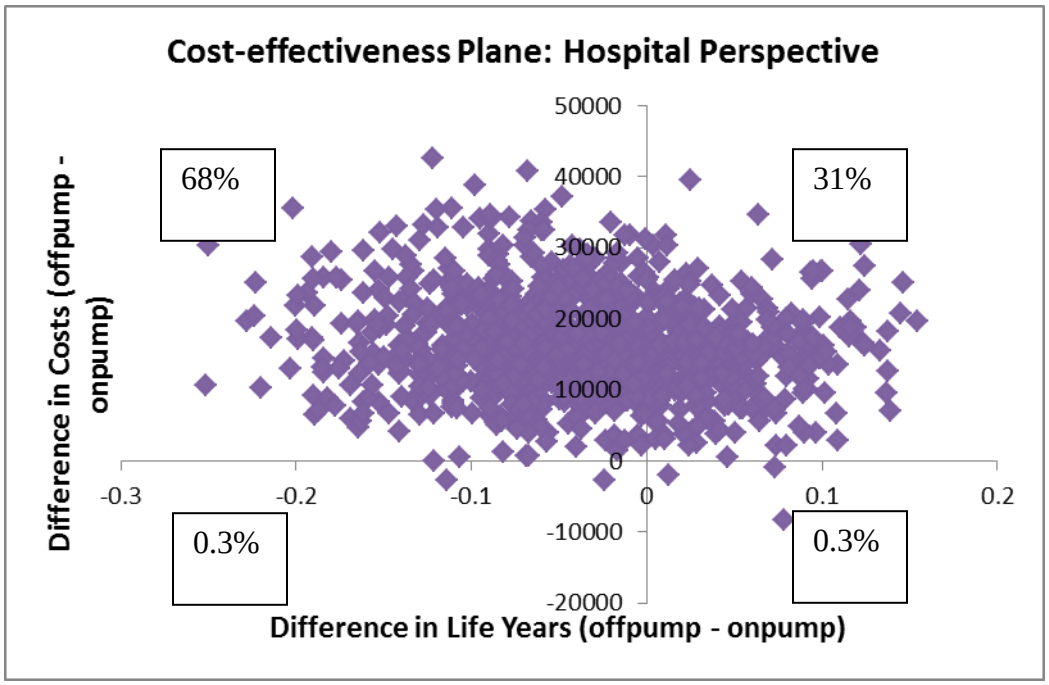


Figure 6-4: Survival for Matched Patients

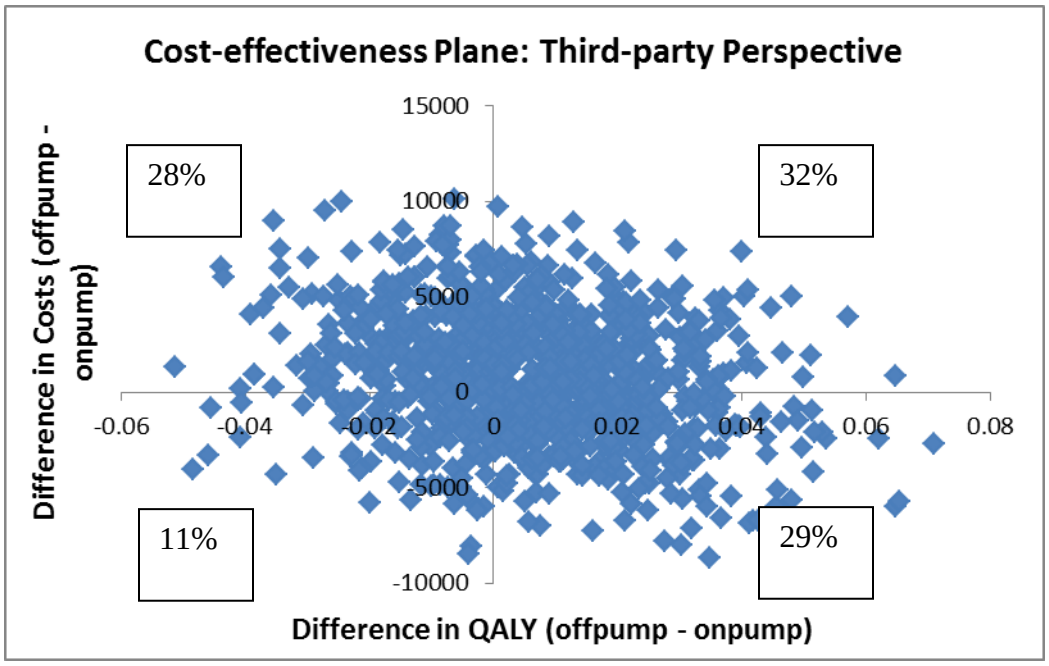


A: CE Plane when Effectiveness in terms of QALY

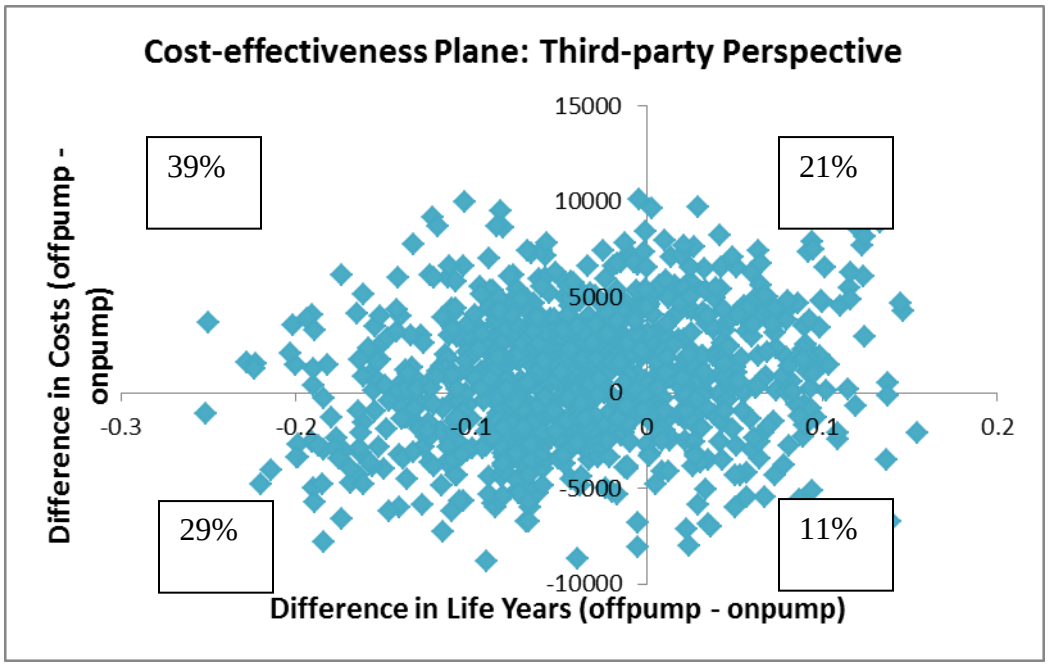


B: CE Plane when Effectiveness in terms of Life Years

Figure 6-5: Cost-effectiveness (CE) Plane from the Hospital Perspective

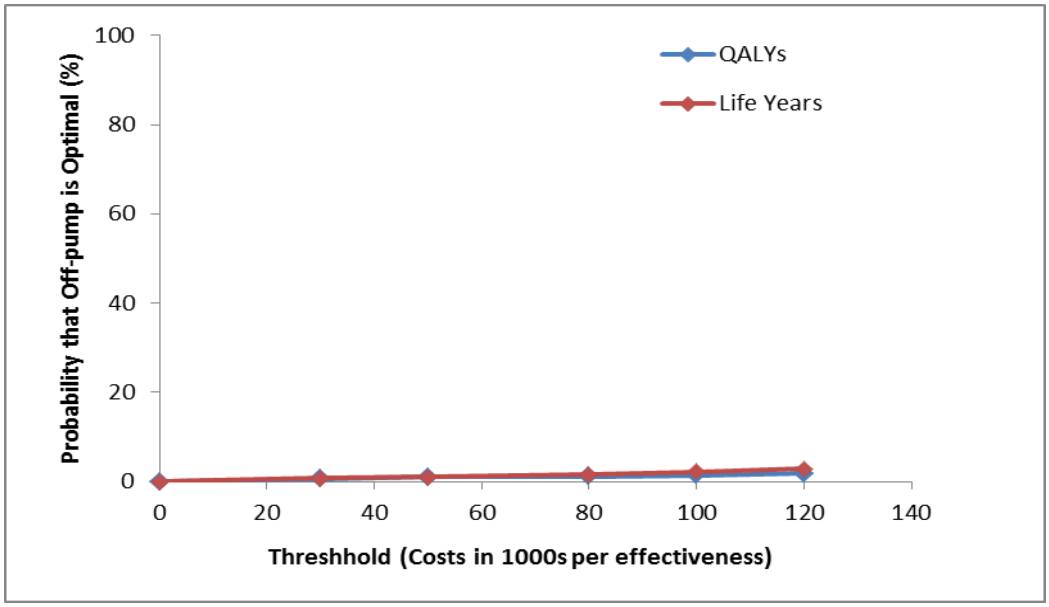


A: CE Plane when Effectiveness is in terms of QALY

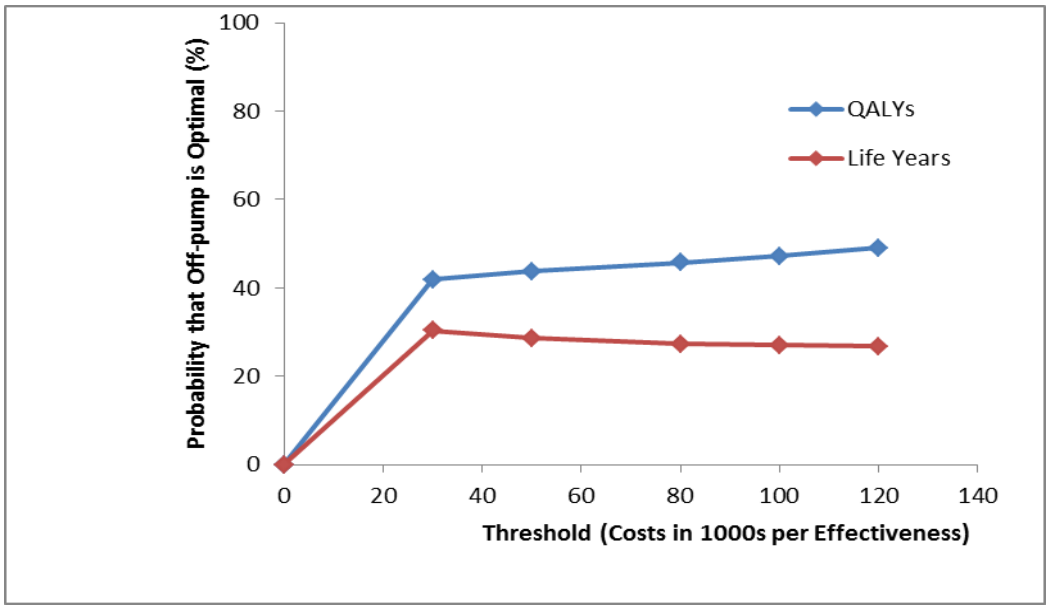


B: CE Plane when Effectiveness is in terms of Life Years

Figure 6-6: Cost-effectiveness Plane Third Party Payers Perspective



A: Cost-Effectiveness Acceptability Curve from the Hospital Perspective



B: Cost-Effectiveness Acceptability Curve from the Third Party Payers Perspective

Figure 6-7: Cost-effectiveness Acceptability Curve for Off-pump

7.0 MANUSCRIPT 3: COST-EFFECTIVE DRUG SWITCH OPTION AFTER FAILURE OF INITIAL TREATMENT WITH SSRI FOR DEPRESSION

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Abstract: 301

Word Count: 3,594

Running Head: Cost-effective Drug Switch Option for Depression Treatment

Keywords: SSRI failure, Drug switch option, Depression Treatment

7.1 ABSTRACT

Background: Majority of patients fail to respond to the initial treatment for major depressive disorder. There are multiple treatment options available after initial treatment failure. However, there are no specific guidelines for choosing one second-line therapy over another. Previous results from Sequenced Treatment Alternatives to Relieve Depression (STAR*D) project show that bupropion, sertraline and venlafaxine are comparable in terms of therapeutic effectiveness when used as a second-line after initial treatment failure with citalopram. In this study, we extend these STAR*D results to incorporate costs and determine if one option is cost-effective relative to other.

Methods: The total costs pertaining to bupropion, sertraline and venlafaxine included the costs of the second-line antidepressant (study medication), other concomitant medication and anti-depressants that patient might have used to manage side-effects and symptoms, and healthcare utilization. The missing healthcare facility utilization costs were imputed using propensity score multiple imputation method. Effectiveness was in terms of remission and response. Cost-effectiveness was assessed as net health benefits. Stochastic analysis was performed using the bootstrapping method.

Results: Over the duration of Level 2 of the trial, venlafaxine medication cost was significantly higher than bupropion and sertraline medication costs (Bupropion : $608 (sd = 464), Sertraline: $698 (sd =$ 689), Venlafaxine: $959 (sd = $915). There were no significant differences in other medications and healthcare facility utilization costs. Total costs were significantly different between the three study medications, however none of the pair-wise

differences were significant. The net health benefits were also not significantly different between the three drugs.

Conclusion: The switch options of bupropion, sertraline and venlafaxine, after initial treatment failure with citalopram, are comparable to each other in terms of cost-effectiveness. There is thus no rationale to change the clinical conclusion that states that any of the medications will provide a reasonable second-step choice for patients with depression.

7.2 INTRODUCTION

Major depressive disorder (MDD) is a common and debilitating condition, associated with poor quality of life, increased utilization of healthcare resources and high personal and societal costs[212, 213]. MDD is the most prevalent life time disorder amongst the World Mental Health Survey Initiative Version of the World Health Organization Composite International Diagnostic Interview (WMH-CIDI)/ Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) diagnoses[214]. In 2004, depressive disorders resulted in 65.5 million disability adjusted life years (DALYs) and were responsible for about 4.3% of total DALYs[151]. A recent review estimated that 2.5% (1.9% - 3.2%) global DALYs were due to major depressive disorders. Depression can cost $44 billion – 53 billion (US 1990 dollars) in a year, including direct and indirect costs[215]. Depression treatment has only been partially effective. Typically, in clinical trials (of 6 – 8 weeks duration) less than fifty percent of patients respond to initial treatment for depression, and only 30-45% patients achieve symptomatic remission. Patients who are do not tolerate treatment or do not show sufficient response to the initial treatment often require secondary treatment for depression. Moreover, patients who fail to respond after one or more adequate treatment trials add substantially to the depression costs[216].

The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) project was designed to evaluate the relative efficacy and tolerability of various antidepressant treatment for outpatients with nonpsychotic major depressive disorder and who failed the initial selective serotonin –reuptake inhibitor (SSRI) or subsequent treatments. In this trial, 47% responded and

33% remitted after a maximum of 14 weeks of treatment with Citalopram (SSRI), and 35% of the patients moved to the next level for a secondary treatment (Level 2)[217]. In the trial, patients could recieve Bupropion (Wellbutrin SR, GlaxoSmithKline), Sertraline (Zoloft, Pfizer) or Venlafaxine (Effexor XR, Wyeth-Ayerst Laboratories) at Level 2. Previously published results show that the response and remission rates are comparable between the three drug switch options [218]. However, the cost-effectiveness of treatment among these switch options has not been evaluated. Though there have been studies evaluating efficacy and tolerability of antidepressant medications, data on cost-effectiveness comparing the treatments remain limited. Most of the existing economic evaluations for depression treatment focus on the first-line treatment options, though some do consider switch, titration and augmentation in their calculations[160]. Thus decision guidelines on which second line treatment to choose remain sparse.

This study aims to estimate the costs incurred during the Level 2 of STAR*D clinical trial and then determine if any of the switch option is more cost-effective than other.

7.3 METHODS

The STAR*D trial design and protocol have been previously described in detail[156, 218]. STAR*D was a multi-level trial and the patients were moved to the next level or a 12-month naturalistic follow-up phase (wherein they continue the indicated treatment) depending on their therapeutic response assessed by Quick Inventory of Depressive Symptomatology – Clinician Rating (QIDS-C16) and side-effects. Those without response at completion of a treatment level could move to the next treatment level, while those with remission entered the follow-up phase. Those with response but without remission could enter follow-up, but were encouraged to

proceed to the next treatment level after an adequate dose and duration had been achieved. Participants with intolerance or minimal reduction in baseline symptom severity (e.g., <15% by week 6 or <25% by week 9) were encouraged to move to the next treatment level. There were 1,439 patients who moved to Level 2 of the trial after initial failure with Citalopram, of which 727 (50.5%) were randomly assigned to one of the drug switch options (Bupropion, Sertraline or Venlafaxine) for depression treatment.

We evaluated the costs of medication (depression drugs and other concomitant medications that were used to manage the known side-effects of depression) and healthcare utilizations during Level 2 for each of the three treatment options. Calculated costs were based on 3 components: 1) antidepressant medications, 2) other medications including any other antidepressant use and concomitant medications that could be used to manage treatment side-effects and 3) all healthcare utilization. The antidepressant medications included the study medications to which the patient was randomly assigned. Other medications included the antidepressants other than the assigned treatment (like citalopram or any other prescribed antidepressants) that the patient might have used while at Level 2 and concomitant medications required to manage side-effects of the antidepressants. The concomitant medications included trazodone, anxiolytics, sedatives, treatment for constipation and antiemetics, and sexual dysfunction medications. Utilization of all medication types was based on total dose intake, which depended on specific doses taken for the respective time durations. For antidepressant medications, doses were obtained from the trial data. For concomitant medications, doses were determined using the mid value of the ranges recommended in the UptoDate database[219]. The duration of use was determined using the recorded start and end dates. To accurately reflect the study medication use at level 2 of the trial, the start date was either the date of beginning of level

2 or the recorded medication start date, whichever was later. In case of missing end dates at any assessment, the medication was assumed to be continued until the start date of the subsequent record of the same medication (or same medication type in case of concomitant medications). If the end date was missing at the last observed for a patient then the study medication was assumed to be continued up until level the end of the level.

Healthcare facility utilization included the outpatient visits, emergency room visits and hospitalizations that occurred during level 2. Healthcare facility utilization data for the course of level 2 were collected using an interactive voice response (IVR) system. The IVR system was implemented using telephone and involved a script of recorded instructions followed by a set of questions. The patients responded to the questions by pressing the appropriate number on their phone keypad. The protocoled outpatient visits (post-baseline of level 2) were also considered while assessing outpatient utilization. During the course of the trial, protocol clinic visits were scheduled at weeks 0, 2, 4, 6, 9, and 12 at all treatment levels. The visit schedule was flexible and could be held within +/-6 days of the assigned week. Extra visits could be held if clinically needed. If a participant started exhibiting a response or remission at week 12, two additional visits could be used to determine if that status is sustained. The product of net utilization and unit costs estimated the associated costs.

The total costs for each of the three treatment switch arms were calculated as sum of costs of study medication, other antidepressant medications, concomitant medications and the healthcare facility utilization during the course of level 2. All medication unit costs were obtained from the Red Book, Pharmacy's Fundamental Reference[167]. The costs associated with a single outpatient and emergency room visit were obtained from the Physician Fee Schedule[220]. Hospitalization costs per day were obtained from the Healthcare Cost and Utilization Project

(HCUP)[221] database. Costs can be highly variable and typically a few patients are likely to incur high costs which commonly leads to cost data being highly skewed to the right[222]. To reflect the skewed nature, costs were modelled as gamma distribution[223]. The mean and standard deviation of costs along with source are listed in Table 7-1.

All missing cost information for healthcare facility utilization was handled using multiple imputation methods. The Markov Chain Monte Carlo Method (MCMC) method[224] was used to impute missing patient baseline scores or information. Non parametric propensity score multiple imputation method was used to impute missing cost information[225]. We used existing IVR cost information and patient characteristics of those with and without IVR data to impute missing IVR cost data. Costs were compared between the three groups using Kruskal Wallis test. As a sensitivity analysis, we also compared costs among the completers only.

Effectiveness has been previously assessed in terms of remission and response based on the Quick Inventory of Depressive Symptomatology – Self-Report Scores (QIDS-SR-16). QIDS-SR-16 remission was defined as a total score at study exit of 5 or less. QIDS-SR-16 response was defined as a reduction of 50 percent or more at level 2 exit (as compared to level 2 baseline). Both response and remission were used as effectiveness measures in this paper.

The cost-effectiveness analyses were carried out using the net health benefits (NHB) framework. The net health benefits was calculated using the following formula:

$$NHB = \mu_{Ei} - \mu_{Ci}/\lambda$$

In this formula, μE and μC are the average effectiveness and costs, respectively, for treatment *i*. λ is the willingness to pay per unit effectiveness. The treatment option with the

highest NHB is considered to be the cost-effective option. Most of the cost-effectiveness studies use willingness-to-pay per quality adjusted life years (QALY). The standard willingness-to-pay thresholds of $50,000 per QALY have been used over many years but remain controversial[43]. There are no recommendations on thresholds of willingness-to-pay based on remission from depression or response to depression treatment. For our analyses, we assume the willingness-to-pay to be $30,000 over the duration of Level 2 for remission or response achieved. Further, a sensitivity analysis varied the willingness-to-pay from $10,000 - $50,000 per effectiveness outcome (remission or response). Stochastic analysis was performed using the bootstrapping method, which involved resampling costs and effects randomly with replacement (in a joint manner) 1000 times to obtain estimates of the variability of NHB estimates for each treatment option. Using the bootstrapped sample, the average and percentile intervals (2.5%, 97.5%) for NHB were determined.

7.4 RESULTS

In STAR*D Level 2, 727 patients were randomly assigned to a switch drug treatment after initial failure with citalopram; 239 (32.9%) were randomized to bupropion, 238 (32.7%) to sertraline and 250 (34.4%) to venlafaxine. The duration of time spent in Level 2, and subsequent actions at end of Level 2 were comparable between the three groups (Table 7-2). Overall, the average time in Level 2 was 8.9 ± 5.03 weeks. At the end of level 2, 227 (31.2%) moved to level 3, 257 (35.4%) entered the follow-up phase and 243 (33.4%) terminated from the study.

Cost of Study Medications

The average dose prescribed for bupropion, sertraline, venlafaxine was 223 (sd = 61) mg/day, 94 (sd = 34) mg/day and 122 (sd = 53) mg/day within the respective assigned treatment arms. Over the duration of level 2, on an average patients in the specific treatment arms used total 16,339 (sd = 11,675) mg bupropion, 7,557 (sd = 5,193) mg sertraline and 10,730 (sd = 8,089) mg venlafaxine. Accounting for utilization and unit costs, the translated study medication costs were significantly different among the three treatment groups (Table 7-3). The bupropion and sertraline costs over the duration of level 2 were comparable (bonferroni adjusted p-value = 0.5016), however venlafaxine costs were significantly higher than each of the other two medications ($p \leq 0.0001$).

Cost of Other Medications

Besides the assigned study medication, 694 (95.4%) patients used other antidepressants to manage the disorder. All of these patients had records of citalopram use (Level 1 medication) in Level 2. These patients used citalopram for an average of 9 days and the average prescribed dose was 38mg/ day. Over the entire duration, patients used approximately 278 mg of citalopram(Patients assigned to bupropion, sertraline, venlafaxine used 184 (sd = 227) mg , 341 (sd = 484) mg, 310 (sd = 464) mg of citalopram respectively). In addition to citalopram, in the sertraline group, 2 patients used venlafaxine, 1 used bupropion and 1 patient used nortriptyline. Table 7-3 shows that patients in sertraline group had significantly higher costs, due to other antidepressants use, as compared to bupropion and sertraline.

Three hundred seventeen (43.6%) patients required at least one concomitant medication to manage the side effects of antidepressant medications. Amongst the patients requiring

concomitant medication, 124 (39.1%) used trazodone, 120 (37.8%) used sedatives, 86 (27.1%) needed anxiolytics, 35 (11.0%) needed GI medications and 47 (14.8%) used medications for erectile dysfunction. Overall, patients required a median of 2 (range: 1 – 6) concomitant medications. The proportion of patients requiring concomitant medications was not significantly different between the three treatment options. The costs incurred due to concomitant medications were similar between the three groups (Table 7-3).

Overall, the total costs related to other medications (other antidepressant and concomitant medication costs) were not significantly different between the three groups.

Cost of Healthcare Facility Utilization

Only 229 (31.5%) had complete information on healthcare facility utilization as collected by the IVR system at exit of Level 2. In this system, patients reported healthcare utilization for depression (140 of 229), mental health condition (29 of 229), and general medical conditions (90 of 229). Table 7-4 compares the characteristics between patients who completed the IVR questionnaire versus those who did not. The patients who had missing IVR data were more likely to be those who terminated from the trial, had shorter duration of time in level 2, had greater severity of depression symptoms at Level 2 baseline or had exited level 1 due to intolerance. For IVR cost imputation, the propensity score model was based on the assigned treatment, achievement of the remission and response outcome (as assessed by the QIDS at end of level 2), and characteristics that were significantly different between patients having IVR data and patients missing IVR data at alpha = 0.20 (Table 7-5).

After imputation of missing costs, the healthcare facility utilization costs were comparable among the three groups (average $1116, $1280 and $1076 for patients in the

bupropion, sertraline and venlafaxine group respectively). The costs related to healthcare facility utilization recorded by the IVR system and protocoled outpatient visits were not significantly different between the groups (Table 7-3). When considering only the IVR completers, healthcare facility utilization costs were marginally different among the bupropion, sertraline and venlafaxine (average healthcare facility utilization costs for bupropion, sertraline and venlafaxine were $910 (95% CI: $541 – $1,279), $1542 (95% CI: $439 – $2,644), and $782 (95% CI: $439 – $1,125) respectively, p-value = 0.0497).

Total Costs and Effectiveness

Figure 7-1 shows the total costs (mean, confidence interval) for each of the treatment arms. The total costs, including study medications, other medications and healthcare facility utilization, were significantly different among the three groups, with venlafaxine tending to have higher costs (Table 7-3). There however were no significant differences for any of the pairwise comparisons when adjusting for multiplicity using Bonferonni correction. Among the IVR questionnaire completers, there were no significant differences in total costs among the three groups (average $1824, $2749, $2354, p-value = 0.1131). The proportion of patients achieving remission and response were comparable among the three groups.

Cost-Effectiveness

Table 7-6 shows the net health benefits obtained if patients used the specified drug as opposed to spending the money in a marginally cost-effective treatment for a given willingness to pay. The average NHB represents the net benefit (in terms of health) that is achieved by investing resources in a given treatment as compared to the standard marginally cost-effective

program (which has a fixed willingness-to-pay). Here, the willingness-to-pay to achieve response or remission is assumed to be $30,000. The higher the NHB indicates the better the treatment option. The point estimates show that when effectiveness is expressed in terms of response, venlafaxine has a numerically higher NHB as compared to other drugs (an incremental 20% of patients would respond, if the costs associated with venlafaxine were spent instead on a marginally effective treatment that costs $30,000 to achieve response). When effectiveness is assessed in terms of remission, venlafaxine had the lowest net health benefit as compared to bupropion and sertraline. The bootstrap percentile intervals indicate however that none of these differences are statistically significant. The cost-effectiveness acceptability curves varying the willingness to pay (Figure 7-2) show that when effectiveness is expressed in terms of response, the curves are very overlapping (Figure 7-2A). When effectiveness is assessed in terms of remission, venlafaxine appears to be the dominated strategy (Figure 7-2B) due to its slightly higher costs and slightly lower proportion of patients achieving remission, but the confidence intervals for the net health benefits are overlapping.

7.5 DISCUSSION

This study shows that the three drug switch options of bupropion, sertraline and venlafaxine in Level 2 of STAR*D project are comparable in terms of cost-effectiveness, assessed using the net health benefits framework. This study extends the previously published study which showed that the effectiveness was similar between the three drug switch options. Bupropion-SR is a non-SSRI agent which does not inhibit serotonin reuptake, sertraline is within-class switch, and venlafaxine is a dual action agent that inhibits reuptake of both

serotonin and norepinephrine. Venlafaxine study medication costs are significantly higher than bupropion and sertraline. The overall costs were significantly different among the three groups. However, there were no pairwise differences in overall costs among the three drugs. This can be because of large standard deviations in costs and greater degree of freedom for the comparison of three groups. Thus overall treatment costs need to be considered rather than drug costs alone in order to make unbiased decisions.

We used the net health benefits framework proposed by Stinett et al,[42] as opposed to the incremental cost-effectiveness ratios (ICERs). Interpretation of ICERs can be ambiguous because of the nature of the ratios. A positive ICER can result from a combination of positive incremental costs and positive incremental effects or negative incremental costs and negative incremental effects when comparing interventions. Likewise, a negative ICER can result from a combination of negative incremental costs and positive incremental effects or positive incremental costs and negative incremental effects. Thus, interpretation gets complicated when considering uncertainty in cost-effectiveness results extending across different quadrants. However the NHB is a linear expression of effects and costs and has a straightforward interpretation.

Also, calculating ICERs for multiple comparators involves ranking options in an increasing order of cost after removing the dominated options from consideration. When performing a stochastic analysis (like bootstrapping method) for multiple comparators, a single intervention might have non zero probabilities of being dominated and of being ranked differently between possible comparators. This methodology can have uncertainties in the ranking of the treatments that can lead to a more complicated interpretation of stochastic analyses results.

The literature on economic analyses of second-line treatment options for depression is sparse. There are two cost analysis studies which used an administrative database to compare second-line therapies for MDD. Both studies showed that the costs associated with various second-line therapies were not significantly different.[161, 162], although one of them revealed differences in depression-coded expenditures between SSRI and tricyclic antidepressant therapy even after adjusting for baseline characteristics[162]. However, these were observational studies and medication prescribing patterns have been questioned. In contrast, STAR*D is a clinical trial in which the patients are randomized to one of the investigated medication.

Also, two recently published studies used computational models to evaluate second-line MDD treatment options. One of the studies developed a decision analysis model to compare generic SSRIs consisting of citalopram, fluoxetine, and paroxetine; escitalopram (Lexapro); paroxetine CR (Paxil CR); sertraline (Zoloft); and venlafaxine XR (Effexor XR) [163]. The study reported generic SSRI to have the lowest cost per patient while venlafaxine was the most favorable option in terms of costs per patient achieving remission. However, this study obtained costs data from an observational study which included patients from a single prepaid health plan and also did not consider differences in side effect profiles between various agents. Another modeling study used STAR*D clinical data to compare the cost-effects of sertraline and venlafaxine after initial failure with SSRI in Thailand settings[164]. The generalizability of both the studies is questionable. In our cost analyses, we use cost estimates from United States national databases like HCUP and Physician Fee Schedule. Also we included costs of concomitant medications that a patient might have used to manage the side-effects of anti-depressants. None of the studies have appropriately represented the uncertainty of the cost-effective analyses. We capture the uncertainties in analyses by incorporating the variances in costs using gamma

distributions. Also stochasticity is captured using the bootstrapping methodology. To the best of our knowledge no previous study has simultaneously compared the cost-effectiveness of the three switch options (Bupripion-SR, Sertraline or Venlafaxine-XR) after initial SSRI treatment failure.

Our study has some limitations. The information collected by the IVR system resulted in 68.5% having missing data. We however employed appropriate statistical imputations to minimize bias due to missingness. Also, our analyses focused on cost-effectiveness from a clinical trials perspective and only during the level 2 of the STAR*D study. A different perspective such as patients' or society's for the long-term effect may yield different conclusions. Willingness to pay is another factor of uncertainty in our analyses. There are no fixed standards for willingness to pay and moreover there are no recommendations for this measure when effectiveness is assessed in terms of response and remission. To overcome this limitation, we systematically varied the willingness to pay over a wide range of values. Also the dosing of the antidepressants that patients used were well characterized in the STAR*D project and were directly translated into costs. Since STAR*D included a broad population and was designed to closely reflect real practice, the cost-effectiveness results are highly generalizable.

7.6 CONCLUSION

Our results show that costs of the study medication costs differ significantly between bupropion, sertraline and venlafaxine. However, there are no significant differences in the cost-effectiveness of the three medications. Thus, we conclude that after considering costs and cost-

effectiveness there is no rationale to change the conclusions based on therapeutic effectiveness. Any of the three options is reasonable relative to one another. There might be other factors like clinician's preference, family history, or treatment of most evident cardinal symptoms that might lead to choice of one antidepressant over another.

7.7 TABLES AND FIGURES

Table 7-1: Unit Costs for Healthcare Utilization

Costs/unit	Mean (SD)	Reference
Depression Medications ($/ gm)		
Bupropion	0.03 (0.006)	Red Book, Fundamental Reference
Sertraline	0.08 (0.05)	Red Book, Fundamental Reference
Venlafaxine	0.08 (0.04)	Red Book, Fundamental Reference
Citalopram	0.21 (0.13)	Red Book, Fundamental Reference
Nortryptline	1.04 (0.95)	Red Book, Fundamental Reference
Concomitant Medications ($/day)		
Trazodone	1.9 (1.6)	Red Book, Fundamental Reference
Sedatives	5.3 (5.7)	Red Book, Fundamental Reference
Anxiolytics	8.9 (7.3)	Red Book, Fundamental Reference
GI Medications	1.7 (2.9)	Red Book, Fundamental Reference
Erectile Dysfunction Medications	19.1 (11.7)	Red Book, Fundamental Reference
Healthcare Facility		
Outpatient Visit ($/visit)	66.7 (44.5)	Physician Fee Schedule
Emergency Room ($/visit)	83.3 (62.2)	Physician Fee Schedule
Hospitalization ($/day)	1001.3 (77.0)	HCUP

Table 7-2: Treatment Characteristics at Level 2

	BUP (N = 239)	SER (N=238)	VEN (N=250)	P-value
Time in Level 2 (weeks), Mean (SD)	8.3 (5.01)	9.1 (5.0)	9.3 (5.1)	0.0584
Action at Level 2 End				0.0921
Follow-up (n = 257)	69 (28.9%)	87 (36.6%)	101 (40.4%)	
Terminate (n = 243)	87 (36.4%)	75 (31.5%)	81 (32.4%)	
Enrolled in L3 (n =227)	83 (34.7%)	76 (31.9%)	68 (27.2%)	

*Kruskal-wallis for continuous variable and chi-square for categorical variable

Table 7-3: Costs and Effectiveness for Patients who Switched to Pharmacotherapy after Initial Failure with Citalopram (All Patients)

	BUP (N=239)	SER (N=238)	VEN (N=250)	p-value
Costs ($), mean, SD				
Study Medications	607.5, 464.6	698.3, 688.9	958.9, 915.0	0.0022
Other Medications	249.7, 522.7	286.6, 526.2	372.5, 805.4	0.1019
Depression Drugs	43.5, 70.3	95.6, 359.8	76.0, 186.8	0.0028
Concomitant Medications	206.2, 507.6	191.1, 388.2	296.5, 780.8	0.8813
Healthcare Facilities	1115.9, 1470.9	1279.6, 3079.7	1076.0, 1591.7	0.7293
IVR Recorded Utilization	903.6, 1476.3	1056.4, 3063.2	846.4, 1599.5	0.3461
Protocoled Outpatient Visit	212.3, 200.6	223.2, 202.5	229.6, 211.9	0.6035
Total Costs	1973.1, 1628.0	2264.5, 3254.6	2407.4, 2133.9	0.0214
Effectiveness, N (%)				
Response based on QIDS-SR	62 (25.9%)	63 (26.6%)	70 (28.0%)	>0.05
Remission based on QIDS-SR	61 (25.5%)	63 (26.6%)	62 (24.8%)	>0.05

Table 7-4: Characteristics of Patients having IVR Response at Exit as compared to those not having IVR Response at Exit not Present

Characteristic	**Missing IVR data (N=498)**	**Not Missing IVR data (N=229)**	**p-value**
Treatment (L2), %			
BUP	33.9	30.6	0.6385
SER	32.5	33.2	
VEN	33.5	36.2	
ACTION, %			
Follow-up	26.7	54.1	<.0001*
Randomize to L3	30.1	33.6	
Terminate	43.2	12.2	
Duration of level 2 (weeks), mean, SD	7.7, 5.1	11.6, 3.7	<.0001*
Age, mean, SD	41.4, 12.8	42.8, 12.7	0.1861
Race, %			
White	76.5	74.2	0.7594
Black	17.3	18.3	
Other	6.2	7.4	
Hispanic, %			
Yes	10.2	12.7	0.3322
No	89.8	87.3	
Female sex, %			
Yes	58.6	59.0	0.9356
No	41.4	41.0	
Education (yr), mean, SD	13.3, 2.9	13.4, 3.1	0.4871
Employment, %			
Employed	53.5	53.3	0.6221
Unemployed	41.6	40.2	
Retired	4.8	6.6	
Highest degree received, %			
None	12.2	11.4	0.2100

Table 7-4 Continued

HS Diploma	43.0	37.6	
GED	9.8	9.6	
Assoc degree	11.8	18.3	
College diploma	15.5	14.4	
Masters degree	6.2	5.7	
Doc/professional degree	1.4	3.1	
Monthly household income, mean, SD	2141.6, 2808.2	1808.9, 1905.3	0.4477
Medical insurance, %			
Any private	45.7	42.2	0.6687
Public only	14.5	14.7	
None	39.9	43.1	
Marital status, %			
Never married	27.9	26.2	0.7367
Married/cohabiting	38.8	41.5	
Divorced/separated	28.9	26.6	
Widowed	4.4	5.7	
Age at first episode, mean, SD	24.9, 14.0	25.1, 13.9	0.6881
Number of MDEs, mean, SD	6.9, 12.7	7.4, 13.2	0.2973
Duration of index episode (mo), mean, SD	31.6, 73.0	25.1, 47.0	0.5705
Recurrent depression, %			
Yes	74.4	78.8	0.2288
No	25.6	21.2	
Duration of index episode 2+ years, %			
Yes	27.1	26.9	0.9555
No	72.9	73.1	
Family history of depression, %			
Yes	54.4	52.9	0.7049
No	45.6	47.1	
Prior suicide attempt, %			
Yes	17.3	17.1	0.9476
No	82.7	82.9	
CIRS Total score, mean, SD	4.8, 4.0	4.7, 3.7	0.9790
Psychiatric Care, %			

Table 7-4 Continued

Yes	61.4	57.2	0.2781
No	38.6	42.8	
Heart problems, %			
Yes	17.7	15.3	0.4252
No	82.3	84.7	
Vascular problems, %			
Yes	27.1	28.4	0.7205
No	72.9	71.6	
SF-12 Mental, mean, SD	29.2, 9.6	29.9, 10.0	0.5170
SF-12 Physical, mean, SD	45.2, 12.7	45.5, 12.5	0.7973
QLESQ, mean, SD	39.7, 16.2	42.2, 17.4	0.1415
WSAS, mean, SD	24.7, 9.4	22.9, 10.0	0.0507
HRSD-17, mean, SD	19.3, 7.2	18.0, 7.5	0.0295*
IDS-C30, mean, SD	34.8, 12.6	32.6, 13.8	0.0608
QIDS-C16, mean, SD	14.2, 4.4	13.5, 4.8	0.0640
QIDS-SR16, mean, SD	13.5, 4.9	12.7, 4.9	0.0174*
Anxious features, %			
Yes	44.2	44.9	0.8795
No	55.8	55.1	
Atypical features, %			
Yes	19.4	22.3	0.3821
No	80.6	77.7	
Duration of Level 1 (weeks), mean, SD	8.2, 4.0	7.7, 4.5	0.1827
CITLAST1, mean, SD	42.1, 17.3	40.6, 18.5	0.3153
Exited prior level due to intolerance, %			
Yes	28.7	10.9	<.0001
No	71.3	89.1	

Table 7-5: Logistic Regression Model for Calculating the Propensity of Missingness

Parameter	Estimate	Standard Error	Wald Chi-Square	P
Intercept	1.0158	0.0996	104.0142	<.0001
Assigned to Bupripion	0.0285	0.1030	0.0768	0.7817
Assigned to Sertraline	0.0298	0.1006	0.0877	0.7671
Moved to Follow-up	-0.3881	0.1509	6.6115	0.0101
Moved to Level 2	-0.3920	0.1281	9.3642	0.0022
Age	-0.0777	0.0899	0.7464	0.3876
Weeks in Level 2	-0.7430	0.1367	29.5467	<.0001
Qlesq score at Level 2 baseline	-0.0631	0.1442	0.1916	0.6616
wsas score at Level 2 baseline	0.0664	0.1419	0.2188	0.6400
Hrsd score at Level 2 baseline	0.1283	0.2328	0.3038	0.5815
ids score at Level 2 baseline	-0.0550	0.2534	0.0472	0.8281
Qids-sr score at Level 2 baseline	0.0951	0.1673	0.3232	0.5697
QIDSC score at Level 2 baseline	-0.0474	0.1517	0.0976	0.7548
Weeks in Level 1	0.2424	0.0920	6.9376	0.0084
Moved to Level 2 due to Intolerance at Level 1	-0.1088	0.1230	0.7829	0.3762
QIDSS_remission at 2	0.0603	0.1395	0.1872	0.6653
QIDSS_response at 2	-0.00589	0.1387	0.0018	0.9661

Table 7-6: Net Health Benefits for Patients who switched to Pharmacotherapy after Initial Failure with Citalopram (lambda = 30,000)

	BUP (N = 239)	SER (N = 238)	VEN (N = 250)
Point Estimates			
Effectiveness: Response	0.1940	0.1884	0.2000
Effectiveness: Remission	0.1900	0.1894	0.1680
Bootstrap Estimates, Mean (Percentile Interval)			
Effectiveness: Response	0.1931 (0.1400 – 0.2498)	0.1898 (0.1309 – 0.2491)	0.1994 (0.1444 – 0.2550)
Effectiveness: Remission	0.1896 (0.1324 – 0.2522)	0.1907 (0.1314 – 0.2509)	0.1675 (0.1167 – 0.2203)

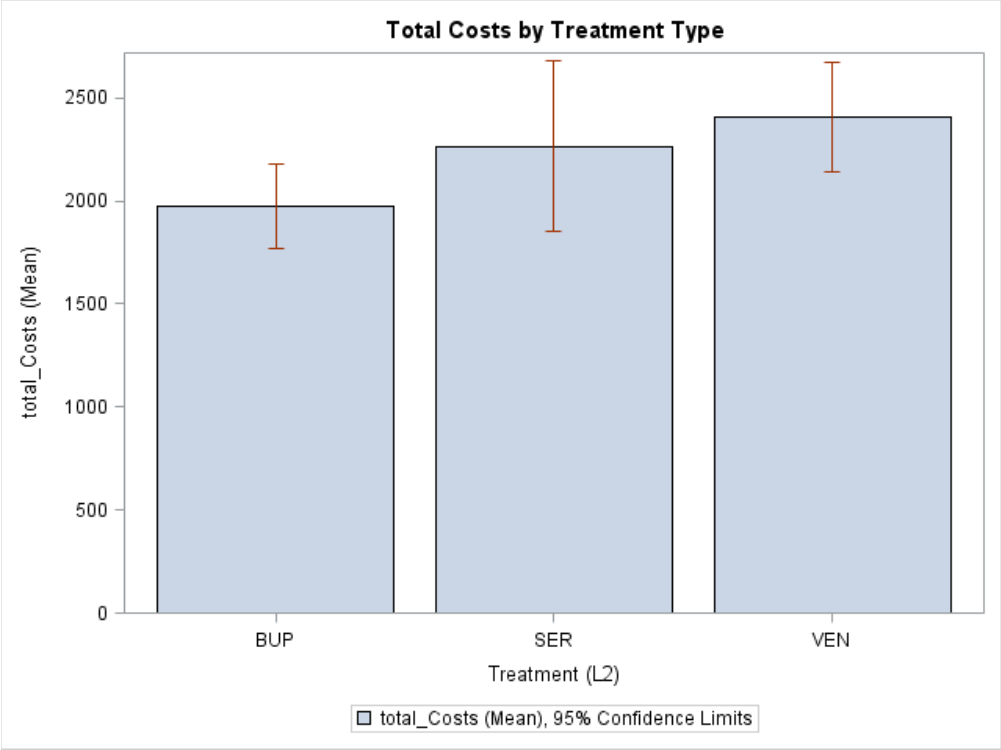
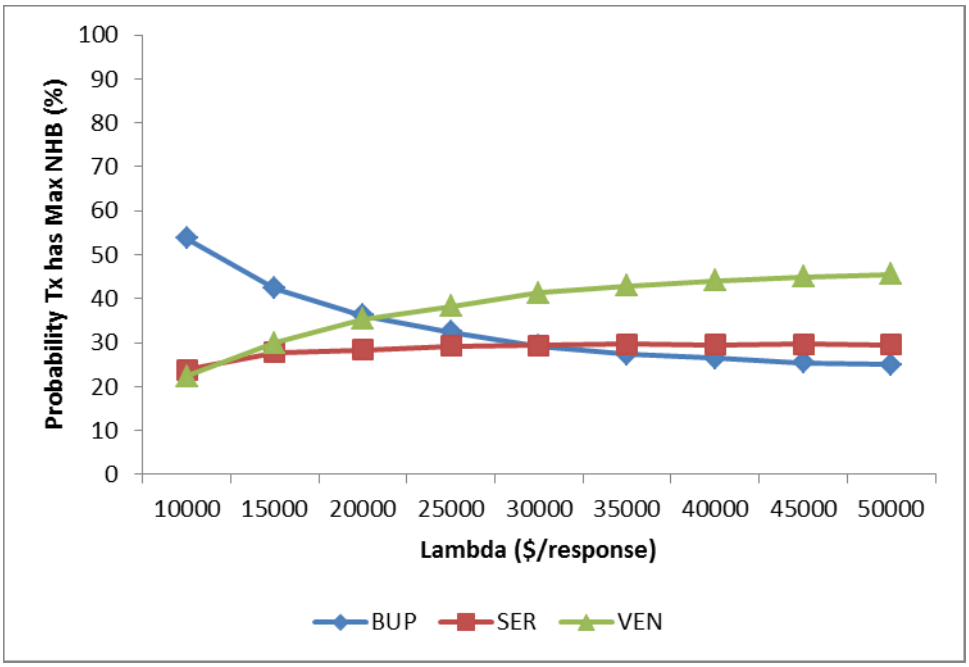
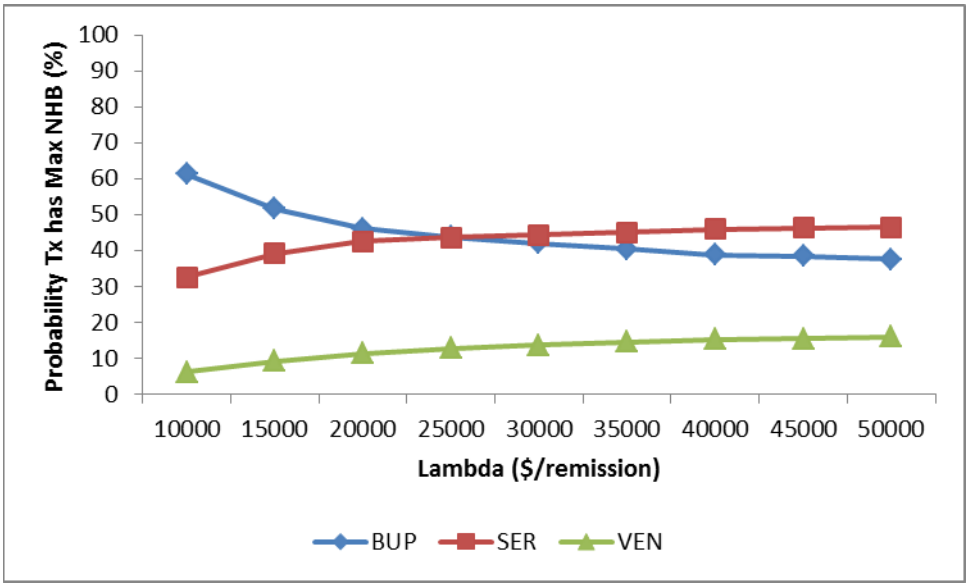


Figure 7-1: Total Costs (US Dollars) for the Treatment Arms



A: Effectiveness in terms of Response



B: Effectiveness in terms of Remission

Figure 7-2: Cost-effectiveness Acceptability Curve

8.0 PUBLIC HEALTH SIGNIFICANCE

The advancement of medical research and technologies has made a multitude of options available to consumers for almost any particular medical issue. Decisions about which option to use are of high value to the health-care systems[226]. Moreover, in an environment of limited resources available for healthcare, identifying the cost-effective strategy becomes indispensable. This not only holds true for resource-constrained countries but also for the wealthier nations which have many competing priorities. It is pertinent that the society gets the greatest value per dollar thus gaining maximum health benefits for the amount of money spent. Identification and adoption of cost-effective options translates to considerable costs saved per effectiveness unit, given the willingness to pay.

8.1 PUBLIC HEALTH SIGNIFICANCE OF USING COST-EFFECTIVE SUTURE (COATED SUTURES VERSUS UNCOATED SUTURES)

Operating room procedures account for nearly one-third of all hospitalization stays. According to the data published by the Agency for Healthcare Research and Quality (AHRQ), Center for Delivery, Organization, and Markets, Healthcare Cost and Utilization Project (HCUP), National Inpatient Sample (NIS), there were more than 28 million non-maternal and non-neonatal hospital stays in US in the year 2012, with operating room procedures performed

during 28.0 percent of these stays[227]. The data show that procedures involving the digestive system were among the most common procedures in the operating room. These surgeries included cholecystectomy (removal of the gall bladder, 406,300 stays; 129.4 stays per 100,000 population); colorectal resection (305,900 stays, 97.4 stays per 100,000 population); excision, lysis peritoneal adhesions (305,800 stays, 97.4 stays per 100,000 population); and appendectomy (removal of the appendix, 293,000 stays, 93.3 stays per 100,000 population)[227]. Overall, approximately 4 million surgeries in United States are open abdominal surgeries[174]. Moreover the abdominal incisions have a high surgical infection rate. SSI rates for abdominal surgeries vary from study to study depending on the population, facility and procedure type ranging <5% - 25%[170-173, 228]. Assuming that digestive system surgeries have a 15% SSI rate for all procedures, there will be 196,650 infections nationwide. Using a coated suture which has a 10% efficacy (that saves $9,497 per SSI prevented) can potentially save gastrointestinal departments $1.8 billion (US dollars) nationwide. Third party payers reimbursing gastrointestinal surgeries will also save similar amounts of money. From a societal perspective (that saves 50,187 per SSI prevented), almost $9.8 billion can be saved nationwide based on the point estimates of costs saved per infection prevented. The extrapolated costs were three times the above extrapolations when considering all abdominal open procedures. With greater awareness and adoption of prevention measures, certain procedures and facility types have substantially lower SSI rates. Surgeons and physicians should be cognizant to not use coated sutures for surgical procedures which have <5% SSI rate in order to avoid extra costs.

8.2 PUBLIC HEALTH SIGNIFICANCE OF USING ON-PUMP VERSUS OFF-PUMP CABG

According to the most recent data available from National Hospital Discharge Survey, there were 395,000 CABG procedures performed in the United States in 2010[229]. Off-pump CABG was introduced in the early 1990s and gained popularity over the next decade as a potential means of avoiding several of the complications and adverse effects of cardiopulmonary bypass (CPB). The data from Society of Thoracic Surgeons Adult Cardiac Surgery Database (STS ACSD) show that the relative use of off-pump CABG peaked at 23% in 2002. The rate of off-pump use has been steadily decreasing over time. In 2008, 21% of CABGs were performed as off-pump and in 2012, 17% of CABG procedures were off-pump. Over the period of 2002 – 2012, there have been 1,458,732 isolated CABG procedures. Of these, ~40% (N = 574,367) were performed on patients with diabetes mellitus. Among diabetic patients, 20% of procedures were performed off-pump and the rest were performed on-pump. Our results support the use of on-pump procedures as opposed to off-pump CABG for diabetic patients[230]. Diabetic patients undergoing off-pump procedures in the long term were almost twice as likely to experience adverse events of death/MI/stroke as compared to those undergoing on-pump. In the BARI 2D trial, 16.7% of the patients undergoing CABG suffered from major cardiovascular events (death/MI/stroke). The unadjusted rate of major cardiovascular events among off-pump and on-pump patients was 20% and 15% respectively. Extrapolating these point estimates of event rates to the STS data, we estimate that 23,723 patients may have experienced death/MI/stroke that could have been avoided. Also, from the hospital's perspective, off-pump procedure results in lower net health benefits, indicating that off-pump is not the cost-effective strategy compared to

on-pump strategy. Thus these results confirm the current trend that the on-pump procedure should continue to be used as the standard surgical treatment for diabetic patients.

8.3 PUBLIC HEALTH SIGNIFICANCE OF USING SECOND LINE SWITCH OPTIONS FOR TREATMENT OF MAJOR DEPRESSIVE DISORDER

Previous STAR*D results have shown that bupropion, sertraline and venlafaxine switch options after initial failure with citalopram for treatment of depression exhibit similar therapeutic response and remissions. The third project in this dissertation extends this comparison to incorporate cost and determine if one switch option is more cost-effective than another. The results show that even though the study medication costs are significantly different among the three groups, the net health benefits (which incorporate costs and effectiveness) are similar among the three groups. Thus, in terms of cost-effectiveness, any of these is a viable option. A survey in the past reflects that more than 50% of the professionals base their choice of antidepressants on their personal experiences with the drug and observing trends in psychiatric practices[231]. In addition, some drugs may be cheaper or more expensive for different health plans. There are no fixed guidelines for prescribing the second-line antidepressants based on either clinical effect or overall cost-effectiveness. Cardinal symptoms of depression including behavioral changes, psychosis, cognition, and mood disorder can help guide treatment selection. Other factors like family history of response and drug interactions should also be considered while administrating antidepressant options[232]. Further research is warranted to identify a well-defined prescription algorithm of second-line depressants after initial treatment failure with citalopram.

9.0 DISCUSSION

The three projects in this dissertation evaluate the economic value of a specified intervention, procedure or treatment in three different clinical areas. This dissertation document illustrates a range of methods that can be employed to estimate the cost-effectiveness of the option. Each of the three projects uses a different approach to estimate the respective costs and effectiveness measures. The first project compares antimicrobial coated sutures to regular sutures using a decision tree model; the second project compares two non-randomized CABG procedure options within BARI 2D clinical trial; and the third project compares three randomized drug switch options using data from the STAR*D trial. The methods employed have distinct advantages and disadvantages.

9.1 SIMULATION STUDY FOR COST-EFFECTIVENESS ANALYSES

Decision trees are simulation models that use mathematical relationships to define a series of possible consequences following each of the options being evaluated[233]. Simulation models are a way of representing the complexity of the real world in a simple and comprehensible form. Many studies have used simulated decision trees to compare multiple alternatives and adjudicate the decision making process. Clinical trials, although the gold standards for comparing alternatives, are limited in number of comparisons and are often

constrained in terms of range of outcome (including cost and utility information) collected[234, 235]. In contrast, the decision trees can include multiple comparators in the model and depending on the research question being analyzed can include a range of outcomes, with no or minimal impacts on to the project budget. Clinical trials have short-follow-up time and often assess effectiveness in terms of intermediate endpoints, while the final consequences of disease may take many years to manifest themselves. Economic evaluations restricted to immediate end points do not give a complete picture. Computational models with assigned probabilities can extrapolate the events into long term outcomes. Models can also be used to explore alternative scenarios which have not been studied in the key clinical trials. Moreover, models can be used to simulate experiments when true experiments are infeasible or impractical due to ethical constraints, time pressures, and political considerations. Overall, models with explicit structure and working can help gain insight into many complex questions.

9.2 CLINICAL TRIALS FOR COST-EFFECTIVENESS ANALYSES

The above listed advantages of models over clinical trials do not imply that the gold standard trials and other epidemiological studies are not needed. Since models are simplified representation of real life scenarios, the heterogeneity among patients observed in real world may or may not be accurately captured depending on the details. Certain simplifying assumptions of simulation models can result in a homogenous population that impact the economic outcome and lead to incorrect conclusions[236]. For example, a treated group in a randomized study could experience fewer as well as less severe complications manifesting in shorter lengths of stay for the same cause of admission. This, in a classic model based approach, might be ignored as a

result of assuming the same costs per complication. The variability of parameters and pay-offs should be incorporated in the model. One of the major concerns for simulation models is that the variables and their ranges included are at the discretion of analyst and have the potential to be biased. The uncertainty of parameters is commonly handled by varying the parameters individualistically as sensitivity analyses. However such analyses ignore interactions with other parameters and might yield incorrect estimates. Thus, validating a model and exploring beyond internal consistency is of prime importance. Also, a model is only as good as the data it utilizes; the source of data obtained is the existing published literature or an on-going clinical study. This further emphasizes the need of unbiased and detailed data from other observational and/or prospective studies. An estimate from a biased study will lead to an incorrectly calibrated model. For example, if in a study, the adverse events are obtained from a patient population within which there might be differences resulting in sub-populations; certain differences might remain unmeasured. Such estimates if incorporated in the model can result in misleading conclusions as it will not appropriately account for differences in characteristics that can affect the event rates. Cost-effectiveness analyses alongside clinical trials also fill in many of the limitations of computational simulation models and are increasingly being implemented. Economic evaluation alongside clinical trials can be used to estimate the covariance between costs and outcomes and can help construction and validation of models. Clinical trials are also free of structural assumptions that are present within a model which might be spurious. Clinical trials and other prospective and observational studies are required to generate reliable estimates to feed the simulation models, and in-fact provide patient-level data for reliably dealing with the heterogeneity present in real life.

9.3 OBSERVATIONAL STUDY DESIGN FOR COST-EFFECTIVENESS ANALYSES

Clinical trials primarily designed to evaluate differences between randomized branches, can also be used to compare non-randomized options. Comparing non-randomized options using clinical trials data is similar to comparing options in an observational study. Highly structured protocol from a trial though may have advantages over most observational studies regarding uniformity of care but on the flip side the trials have the disadvantage of not being reflective of the real world. However, both observational studies and comparing non-randomized options within a trial are subjected to treatment-selection bias. The treatment choice might be based on patient/disease characteristics, physician's personal preferences or site/regional practices. Treatment-selection bias should be handled using appropriate statistical methods such as propensity score methods. One should be cognizant that propensity score methods do not account for unmeasured confounders.

One issue, however, for conducting economic evaluations alongside clinical trials is the lack of agreement on study design issues like methods of efficient data collection, reliable measurement of patient outcomes and methods of extrapolation. Further research on standardization of these methods can help minimize bias and lead to more acceptable cost-effectiveness estimates. Other concerns regarding the prospective collection of cost and resource utilization data are the limited by the budget available for such studies. Also, most clinical trials have a sample size too small to be able to generalize their findings to a broader population. Electronic medical records (EMRs), which virtually have no costs after the installation and implementation, can serve as a rich alternate source to provide valuable information. The EMRs contain granular measurements of a patient's hospitalization, including detailed records of

symptoms, test measurements, data from monitoring devices, clinicians' observations and billing data. The increasing adoption of EMR system by hospitals will increase the availability of the EMR system data. However the researchers should be aware of the limitations of EMR data[237]. The set of recorded patients having EMR data is not a random sample from the population. Instead, it varies depending on the nature of particular practice, the care unit, and the geographical location of the medical institution. All analysis using EMR data should deal with the censored data if present. EMR data can be left or right censored in case the patient gets transferred too late or discharged too early resulting in a skewed distribution. Also, there can be interventions performed by the caregivers that affect the outcome and hence the associated costs. These confounding medical interventions should be incorporated and accounted for while assessing the economic value of a treatment option.

9.4 SUMMARY

Irrespective of the methodology and the data source used, the cost-effectiveness analyses need to include comprehensive information about numerous factors related to treatment effects, health-related preferences, resource use, and costs. However, most epidemiological studies focus only on establishing a product's efficacy and safety as it is the primary information required to obtain a pharmaceutical product license. This results in evidence gaps and highly imprecise estimates of resource use, costs and health utilities[226]. The uncertainties associated with parameters need to be handled appropriately. One method of handling the uncertainty is stating the data collection and study methods explicitly at the outset. However, researchers and decision makers may not share the exact same views on certain methodologies. Thus, it is preferred that

the uncertainty is internalized in the study itself. In case of decision trees, conditional probabilities, resource use consequences and utilities can be modeled as distributions. While in clinical trials these uncertainties are accounted for by heterogeneity and randomized nature of the study. The clinical trials are increasingly being used to collect economic data prospectively that help describe distributions of data and to represent uncertainty as a point estimate accompanied by a confidence interval through the use of standard statistical techniques[46].

The method of cost estimation leads to additional uncertainty. The different methods used for cost estimation vary in precision and detail. The costs can vary depending on the method of identification of cost components (gross costing versus micro-costing) and the method of validation of the components (top-down versus bottom-up)[238]. In gross-costing method, resources are defined at an aggregated level and a unit cost is attached. In micro-costing method, all relevant costs are defined at the most detailed level[239]. For example, in a gross-costing approach the number of hospital days could be measured and valued by the unit cost of a hospital day. In micro-costing, the costs like staff time spent administering a drug could be measured and valued by staff cost per hour would also be detailed out. Costs information for micro-costing methodology can be collected using either the top-down or the bottom-up approach[240]. The top-down approach separates out the relevant costs for an intervention from comprehensive sources (for example hospital or center annual budgets). The use of such readily available data from routine accounts is a low cost approach but could limit transparency and consistency. In contrast, the bottoms-up approach identifies all the resources directly employed for a patient or intervention, resulting in detailed costs. Though the bottoms-up micro-costing approach is very time consuming it provides most accurate information. Many economic evaluations combine the approaches for assessing total costs.

Thus to conclude, cost-effectiveness analyses alongside clinical trials and decision models are important and complementary components of cost-effectiveness research. These methods in isolation from each other may lead to biased decisions with high degree of errors. Both the research methods are highly influenced by uncertainties of costs and effectiveness measures. These uncertainties might defer investments in order to wait for new information. However, studies need to account and appropriately report the uncertainties when informing decisions.

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