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Model-based and Population-based Optimization of Abdominal Aortic Aneurysm Surveillance and Surgery Protocols

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Model-based and Population-based Optimization of Abdominal Aortic Aneurysm Surveillance and Surgery Protocols

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ABSTRACT

Abdominal aortic aneurysm (AAA) is indicated when the diameter of the abdominal aorta is larger than 30 mm. The primary risk associated with AAA is an increased risk of aortic rupture, which is fatal in 68-90% of cases. Once a patient is diagnosed with AAA, the AAA is monitored via abdominal ultrasound. The rationale for the regular surveillance is that the risk of rupture is low for AAA, less than 55 mm in size, but increases dramatically in diameter larger than 55 mm. Early surgery on patients with smaller AAA diameters (lower risk of rupture) has a higher mortality rate than taking no action. Despite numerous researches done about prediction of AAA size, there is a lack of a design that quantifies the risk of surgery and rates of rupture and mortality at surveillances and integrates it with the process of decision making. This research addresses the necessity of integrating the rupture rate in different time periods.

A Monte-Carlo simulation technique was applied to a growth model based on Bayesian Analysis to simulate 10,000 and 1,000,000 hypothetical patients. To ensure that the generated data correlated to the original data, the Cholesky decomposition was determined from the patient cohort data and applied to generation of characteristics of the hypothetical patients. The probability of each possible growth trajectory and cumulative risk of rupture is computed by Bayesian Analysis for each patient. Mortality and rupture rates are calculated individually, applying the Monte-Carlo simulation on meta-analysis paper and National Vital

Statistics System data for 2014. The risk of rupture increases in patients with increase in the size and the mortality rate increases with the time.

Different protocols regarding the surgical intervention threshold, risk of surgery, and observation time limits were designed, and the effects of life expectancy simulated. Simulating all 10,000 and 1,000,000 hypothetical patients and comparing the results for different designed protocols and current available protocols in different countries, gave us a unique opportunity to analyze the effect of the surveillance and surgery decisions on patients' mortality.

DEDICATION

To Mom, Dad, Vahid, Zahra, Farzaneh, and Ayda.

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CHAPTER 1

BACKGROUND ON ABDOMINAL AORTIC ANEURYSM AND RESEARCH OBJECTIVES

1.1 Background on Abdominal Aortic Aneurysm (AAA)

Abdominal aortic aneurysm (AAA) is indicated when the diameter of the abdominal aorta is larger than 30 mm [1]. The primary risk associated with AAA is aortic rupture, which is fatal in 68-90% of cases [2-3]. AAA is generally asymptomatic, so most AAA diagnoses are from non-related abdominal ultrasounds or x-rays. Given that the prevalence of AAA is 2-8% in men over the age of 65 years old, [4-6] Britain, Australia, and the United States have implemented AAA screening programs at least for high-risk patients (patients with AAA size larger than 30 mm).

Once a patient is diagnosed with AAA, the AAA growth in size is monitored via abdominal ultrasound with recommended surveillance every 3 - 60 months. The rationale for the regular surveillance of AAA size is that the risk of rupture is low (less than 3.2% per 1,000 person-years) for AAA less than 55 mm in size but increases rapidly once the diameter is larger than 55 mm [7]. Therefore, the surveillance provides information about the current AAA diameter and the associated risk of rupture.

1.1.1 Risk of AAA Prevalence and Rupture

To understand the risk of AAA rupture, recent research has focused on the growth, rupture, and incidence of AAA [8]. Men over the age of 65 years are at highest risk for AAA.

Therefore, going under a screening/surveillance program is beneficiary and preventive. For example, the UK Multicentre Aneurysm Screening Study (MASS) took a single ultrasound screening scan from 70,000 random patients between 65-74 years old and after 13 years they observed a 42% reduction in mortality related to AAA rupture [9]. This result supports the theory that screening for AAA reduces mortality.

One could ask then why patients do not go under surgery before the diameter gets large and the risk of rupture gets high. Several trials have been conducted to determine if early repair is more preventive in comparison to going under surveillance; the result show no significant difference between the two groups [2 and 10-13]. The mortality rate for surgical repair of un-ruptured AAA is less than 3% [13] but this is still better than the risk of rupture for small AAA (less than 3.2% per 1,000 person-years).

1.1.2 Screening Protocols to Reduce AAA Mortality

There are different obstacles regarding screening protocols and its frequency. One is patients' compliance with surveillance protocols. While implementing AAA screening programs reduces the mortality rate of screening participants, the participation rates are not 100% and can vary: there was 80% participation rate in the Multicentre Aneurysm Screening Study (MASS) [14], 45% in Northern Ireland [15] and 85% in central part of Sweden [16]. There are two types of factors that lead to the low rate of participation of patients: patient and organization factors. Patient factors, such as younger age, female sex, being married, higher level of education, greater income and shorter distance from the screening center [17-22] are associated with increased rates of screening. The organization of screening, the type of invitation, and the ability to reschedule [23] are also associated with rates of screening.

Another difficulty in recommending AAA surveillance, which is considered in this dissertation, is that the growth of AAA has a large amount of inter-patient variability. That is, the AAA in one patient may expand rapidly (and require more regular surveillance and more immediate surgical intervention) while the AAA in some patients may grow slowly and require years, or decades, before surgery is needed. There are several models that predict the growth rate using data gathered from patients in different places. The lack of a model that gives the patient an individual overview about the outcomes of the surveillance, the risks, and the benefits can be a vital reason in the low participation of the people in screening programs.

1.1.3 AAA Management

Life-style related factors and their contribution to AAA incidence, AAA size, and growth rate were investigated and confirmed in different studies. A population-based study based on a prospective cohort of 14,249 male participants diagnosed with AAA in Sweden focused on several modifiable life style factors such as smoking, dietary consumption, physical activity, other comorbidities, alcohol consumption, and obesity [24]. Results of that research revealed that smoking, higher body mass index (BMI), and cardiovascular diseases were associated with an increase in mean AAA size as well as a higher chance of AAA risk [24-26]. Forsdahl *et al.* also confirmed the association of smoking with the occurrence of AAA. They found that the odds of AAA were nearly 14 times higher in people who smoked more than 20 cigarettes per day compared to those who never smoked [27]. Continued smoking has been shown to increase the AAA growth rate by 20% to 25% by Powell *et al.* [28]. Smoking has been proven to be a significant factor in both increasing the incidence of AAA and higher growth rate of AAA size [25, 28].

Interestingly, alcohol consumption (more than a glass of alcohol per day) and diabetes mellitus were shown to have an inverse effect on mean AAA size. Walking or bicycling for more than 40 minutes per day was associated with a 41% lower AAA hazard compared to never bicycling or walking [24]. The effects of using antibiotics in the management of AAA has been studied by Vammen *et al.* [29]. Comparing patients taking roxithromycin antibiotic with patients under placebo therapy, they found a decrease in the mean annual expansion rate of AAA aneurysms in the former group. However, given the known harms of using antibiotics in long term, more data is needed on this approach [30].

There are several approaches regarding management of AAA patients including participating in a surveillance protocol, medical therapy (with beta-blockers), surgery and endovascular stenting. Some studies have shown that in patients with small to medium AAA sizes who have not undergone surgical intervention, medical therapy may be helpful [31].

Despite the fact that there is no clear evidence to support the idea of treating cardiovascular diseases in order to lower the risk of AAA incident, growth rate, or rupture; Patients with previous experience of undergoing AAA repair observed a decrease in all-cause mortalities after using statin in long term [32]. Also, according to 2005 ACC/AHA guidelines it is recommended that AAA patients control their blood pressure and lipids in the same manner that atherosclerotic disease patients are recommended to [33].

Repair methods consist of surgical repair or endovascular repair (insertion of an endograft into the lumen). Endovascular repair is preferred over open surgical repair in terms of risk and cost. Endovascular repair has 83% to more than 95% short term technical success [34-36] with mortality rate of 2.7% to 5.8% in major randomized trials [10, 13, and 37]. The number of endovascular surgeries performed at hospital and expertise of the surgeon has

shown to impact the mortality rate after the surgery [38-39]. Patients will have a faster recovery, shorter hospital stay, less blood loss, and return to baseline functional capacity after endovascular repair [30].

1.1.4 Modeling the Growth of AAA

Although there has been research done about prediction of AAA size and rupture, there is a lack of a design that quantifies the risk of surgery and rates of rupture and mortality at surveillances and integrates it with the process of decision making. An accurate model that can predict the risks of rupture for each interval can help patients to make a better decision about whether, and when, to have a surgical intervention. Given an overview about the risks in every single interval, there would be no need for patients with different growth rates to participate in broad screening programs.

The objective of this project is to simulate the effect of surveillance protocols – using a model that has been fit to patient data [1] – to identify the most preventive surveillance intervals based on the AAA growth characteristics of individual patients.

1.2 Study Objectives

AAA surveillance reduces AAA mortality due to rupture by monitoring AAA size and recommending surgery once the risk of surgery is less than the risk of rupture. Due to the high level of inter-patient variability in AAA growth, the appropriate intervals of surveillance, the risks for an individual patient, and the AAA size at which an individual patient should go under surgery are unknown. Altering each one of these factors will change the whole treatment schedule. For example, one patient may need to get monitored every 6 months while another one can wait for 2 years without any risk of rupture. Predicting the risks of the rupture and surgery -if it takes place at any time- based on AAA size and other

patients' characteristics increases the accuracy of recommendation whether it is surveillance in future or it is surgical intervention. Given these facts, I proposed optimizing the AAA surveillance intervals for individual patients based on patient characteristics associated with AAA growth: age, surveillance history of AAA size measurement, D-dimer level, and diabetes status.

The objectives of this research are separated into two major segments: model-based and population-based. In the model-based phase my goal was to examine all possible combinations of variables (risk of rupture, surgical intervention threshold, and surveillance frequency) to find the optimum surveillance protocol and surgical intervention recommendation. Whereas in the population-based phase, I extracted the optimum designed protocol from step one and compared it with currently available protocols that are being applied in different countries.

In both approaches, the ultimate goals were:

1) To determine the surveillance protocol that provides the greatest benefits (higher life expectancy, less surveillance, and fewer numbers of fatalities).
2) To determine the AAA size at which surgical intervention provides the greatest benefits.

1.2.1 Objective #1: The Optimum Designed Protocol (Model-based)

There are models that capture the growth rate of AAA in patients [5-8]. Monitoring the AAA diameter in patients is essential to develop a descriptive model of AAA growth rate. Such models can then be used in simulations to predict the preventative effect of potential AAA surveillance [5-8]. But it is unknown how often the intervals of the screening should be, what the risk of rupture for an individual patient is, and at what size an individual patient should go under surgery. This is because patients with different risks, characteristics,

and financial power will not choose the same way of surveillance and treatment. Therefore, identifying the most preventive surveillance intervals based on the characteristics of an individual patient is strongly needed.

New surveillance protocols were designed and new surgical intervention thresholds were tested by changing different decisive factors in simulation. These new protocols integrated the size of AAA with the risk of rupture assigned to that size and then compared it to different risks of surgery. Risk of surgery was tested for 1% to 10% (1% increments), and then based on sensitivity analysis, was narrowed down to 0.5% to 5%. Surveillance period limit of 1, 2, 3, 5, 7.5, and 10 years were also tested on all different protocols. Surgical intervention threshold was considered to be 50 mm, 55 mm, and 60 mm in order to ensure a better insight of which can be more preventive. Simulating diverse protocols by applying different risks of rupture, risks of surgical intervention fatality, surveillance period limits, and surgical intervention thresholds enabled me to examine all possible combinations to reach the most optimum protocol.

Different studies suggest 55 millimeters as the size threshold for surgical intervention for patients with AAA and do not recommend earlier surgical intervention [8-9]. Due to the lack of postmortem studies to check the size in which the rupture happened, and the small number of cohorts who went under current surveillance protocols, it is unclear whether smaller or larger threshold sizes for surgery is more efficient. Efficient here means having a higher life expectancy in comparison with no treatment case with respect to having less number of surveillances. The ideal outcome for each protocol is to recommend surgery right before rupture happens, but is this possible with setting 55 millimeters as the threshold of surgery? Or can we have a higher number of on-time surgeries with a smaller size threshold?

Suggesting two different sizes (50 and 60 millimeters) and simulating the behavior of all generated hypothetical patients in different protocols is required to answer this vital question. This is another important factor in the efficiency of the suggested protocol.

I proposed using a model of AAA growth that has been fit to AAA growth data [1] to simulate the growth rate of AAA and predict the number of surveillances and benefits of different potential surveillance protocols. Simulations helped us to find variable non-dominated solutions for different patients. According to the solutions, we could find the optimal surveillance program that provides the lowest number of surveillances with the most effectiveness (increase in life expectancy and decrease in the number of surveillances). In addition, these simulations could support patients with different characteristics that were not available in the previous study cohort. This designed protocol can help patients to know which protocol can prevent them from fatal surgeries after rupture.

1.2.2 Objective #2: Current AAA Surveillance Protocols (Population-based)

Observed size of AAA in the surveillance is the only decisive parameter in the recommendation of next surveillance interval in the current available surveillance protocols in different countries, such as the United States, United Kingdom, Norway, Sweden, New Zealand, Australia, and Italy [7]. There is significant inter-patient variability in the AAA growth rate, which makes these protocols less accurate in predicting the most efficient interval for next surveillance or surgery. For instance, surveillance protocol in the United States suggests patients with sizes between 30 and 35 millimeters to return for surveillance after 3 years, while the same patients return for surveillance on a yearly basis in Britain (see Table 1.1).

Table 1.1: AAA surveillance intervals by country [7].

Country	Diameter (mm)	Surveillance Interval (month)
Western Australia	30-55	6-12
Britain	30-44	12
	45-54	3
New Zealand	30-55	12
Norway	25-29	60
	30-40	24
	40-45	12
	45-55	3-6
Sweden	25-29	60
	30-39	24
	40-44	12
	45-50	6
	50-55	3
United States	25-29	60
	30-34	36
	35-44	12
	45-54	6
Italy	30-55	6

If there are two patients with an AAA size of 34 millimeters, say patient A with a very fast growth rate and patient B with a constant or negative growth rate, will they have the same outcome if they follow the same protocol that is being followed in the United States? Patient A may reach the threshold size and even have a rupture before passing 3 years, while patient B will show the same or smaller size as previous surveillance. On the other hand, following the protocol that is being enforced in Britain, patient B will spend time and money on surveillances every year that he does not need. This is not the only problem with these protocols. Since having a large cohort of patients going under these surveillance protocols in a long period of time is needed to analyze and compare the outcomes, one cannot be

confident that which protocol is more preventive and efficient. Simulating these protocols with an accurate growth model, using a vast cohort of generated hypothetical patients and different surgical intervention thresholds gave us the opportunity to compare the outcomes. Additionally, according to the optimum results of the model-based approach, we created a protocol with surveillance recommendations solely based on size and compared it to different countries' protocols.

CHAPTER 2

METHODOLOGY OF SIMULATION STEPS

To accomplish the research aims of determining the most beneficiary surveillance protocol and the optimum AAA size for surgical intervention, I utilized Monte Carlo simulations to quantify the effects of varying the surveillance intervals and AAA size threshold for surgical intervention and integrate the risk of rupture in the process of recommending surveillances.

There are four major phases to performing the Monte Carlo simulations (see Figure 2.1):

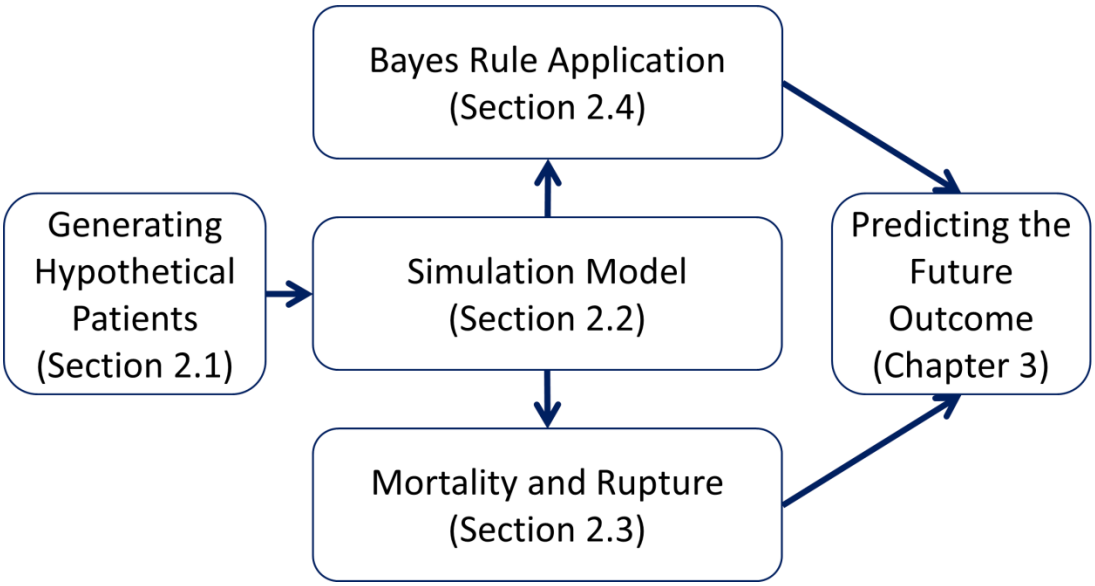

Figure 2.1: Overall flow-chart for methodology.

- "Generating Hypothetical Patients" phase (Section 2.1) generates characteristics and covariate effects for hypothetical patients that mimic those observed in a clinical cohort. These characteristics and covariate effects are inputs for the AAA growth model.
- In the second phase, the hypothetical data is used in a model of AAA growth to calculate the size of the abdominal aorta at different time intervals in the future (AAA Growth Simulation Model – Section 2.2). While all of the patients are 65 years old and above (the model is based on a cohort of screened patients with an inclusion criteria of 65 years), there are fair possibilities of natural death and sudden rupture (before reaching the rupture threshold) during the time of surveillances.
- Therefore, the third phase is to simulate the natural death and sudden rupture outcomes for each individual (Post Screening AAA Growth, AAA Rupture, and All-Cause Mortality – Section 2.3).
- In the fourth phase, Bayes' theorem is applied to calculate the probabilities of different outcomes that can occur for an individual patient. Bayes' theorem modifies the probability of an outcome at present time by the observations that have been done in the past (Section 2.4).

2.1 Hypothetical Patients' Data Generation

2.1.1 Generating the Patient Characteristics of Baseline AAA Size Diabetes Status, D-Dimer Protein Level, and Age

The distributions of hypothetical patient characteristics were generated to mimic those of the clinical cohort. Three different characteristics were associated with AAA growth parameters in the clinical cohort: baseline AAA size, status of diabetes mellitus, and level of D-dimer protein. In addition, age is associated with patient mortality so this was included as

a fourth parameter. To expand the data that mimics the original cohort, I followed these steps:

- Finding the correlation coefficients among four different characteristics

I used the pre-built correlation function in "R", which is called "cor". This function gets two vectors as input and returns the correlation coefficient between them. All of the characteristics of the original cohort (299 patients) are vectors, so using the "cor" function for each two characteristics gives us the following results.

Table 2.1 shows a weak correlation between different characteristics. The largest correlation is between the level of D-dimer protein and the baseline size, and we can say there is no correlation between the age and baseline size.

Table 2.1: Correlation coefficients of the original cohort's characteristics.

	Baseline Size	**Diabetes Mellitus**	**D-dimer Level**	**Age**
Baseline Size	1.0000	0.0461	0.2798	-0.0075
Diabetes Mellitus	0.0461	1.0000	-0.0896	-0.0980
D-dimer Level	0.2798	-0.0896	1.0000	0.1540
Age	-0.0075	-0.0980	0.1540	1.0000

- Building Cholesky decomposition matrix based on the correlation coefficients

The Cholesky decomposition matrix can be used to transform independent random variables to non-independent random variable. I used the Cholesky decomposition matrix to impose the correlations observed in the clinical data onto the hypothetical patients. The first step in this process was to calculate the Cholesky decomposition matrix for the correlation matrix of the clinical data.

The Cholesky decomposition matrix is a square matrix, which is built based on the coefficients matrix. Pre-built function of the Cholesky decomposition matrix is available in the "R" library; therefore, I used it to calculate the Cholesky decomposition matrix based on my coefficients from the previous part. This function is called "chol". It gets the square matrix of correlation coefficients and returns the Cholesky matrix result (which is a square matrix too).

- Generating four random values from the normal distribution (rnorm function in R)

  At this step four independent, normally distributed random variables are generated. This function is called "rnorm" in "R" and its inputs are number of normally distributed numbers desired, mean, and standard deviation. The output is the normally distributed random numbers generated. It is noticeable that mean is zero and standard deviation is one in default settings of "R". For example, the "rnorm(2)" command in R gives two normally distributed random numbers with a mean equal to zero and standard deviation equal to one.

- Multiplying preceding four normally distributed random numbers in Cholesky decomposition matrix

  I then had a vector of four normally distributed random numbers and the Cholesky decomposition matrix, which is a square matrix. The length of the vector is the same as the dimensions of the Cholesky decomposition matrix. Since it is a vector, I transposed the Cholesky decomposition matrix in order to perform the multiplication. The transpose of a matrix can be formed in "R" using a function called "t", which gets a matrix and returns transpose of it. The importance of this step is about the Cholesky decomposition matrix. When you generate a vector consisted of normally distributed random numbers and multiply it by the Cholesky decomposition matrix, the result vector mimics the original data that was

built that the correlation coefficients are based on. In other words, different columns in the product matrix have the same correlation between them as the original data.

- Finding Cumulative Density Function (pnorm function in R)

  To go back to the original cohort characteristics data and read the assigned data to each of the numbers in the matrix that I made in the previous part, I needed to do one more step. Elements in the vector of the previous part gave me the height of the probability density function. Since I had the cumulative density function of my characteristics, I needed to change the previous part's output into probabilities. I applied a function that calculates the probability of a normally distributed random number to be less than the given number. This function is called "pnorm" in "R". Input in this function is the vector of quantiles, mean, and the standard deviation, and the output is the cumulative density function.

- Call back the data from each row in the original cohort (quantile function in R)

  All of the previous steps were needed to be done, so I can go back to the original cohort's data and recall the characteristics for a hypothetical patient. These are called hypothetical patients because I built their characteristics by generating random numbers and then transforming them through the explained process so that they act like the original cohort. There is the original cohort's data, consisting of different columns of four characteristics of the patients, and there is a vector of probabilities with the same number of columns. It is important that columns of the probabilities' vector are consistent with the original cohort's data in all of the steps. For instance, the first column in the original data represents baseline size in the original cohort. Therefore, the first column in the probability vector should demonstrate the baseline size's probability. If I go through each column of the original data using these probabilities, I can return the desired characteristic for that patient.

"Quantile" function in "R" has two inputs. One is the vector that you want to extract data from it and the other one is its related probability. It returns the value of the characteristic from the data based on the probability that you give. Therefore, I was able to recall all four characteristics for a patient.

Repeating these steps 10,000 times generated four characteristics for 10,000 patients, knowing that their behavior is just similar to the original cohort. I tested the previous statement by plotting and comparing both the original and the generated data's cumulative distribution functions (see Figures 2.2 through 2.4). The upper plots are for the original cohort and the lower plots show the generated hypothetical data. Table 2.2 shows the similarity between generated hypothetical data and the original cohort's data. The only difference is the number of patients that I increased to have a more reliable analysis.

Table 2.2: Median (q1, q3) of characteristics of original cohort and generated hypothetical data.

	Original Cohort (N=299)	**Hypothetical Patients (N=10,000)**
Median Baseline Size, mm (q1, q3)	32.7 (30.80, 36)	32.50 (30.80, 35.8)
Diabetes Mellitus, N (%)	42 (14%)	1402 (14%)
D-dimer Level (q1, q3)	2.51 (2.15, 2.89)	2.50 (2.15, 2.89)
Median Age, year (q1, q3)	72 (69, 75)	72 (69, 75)

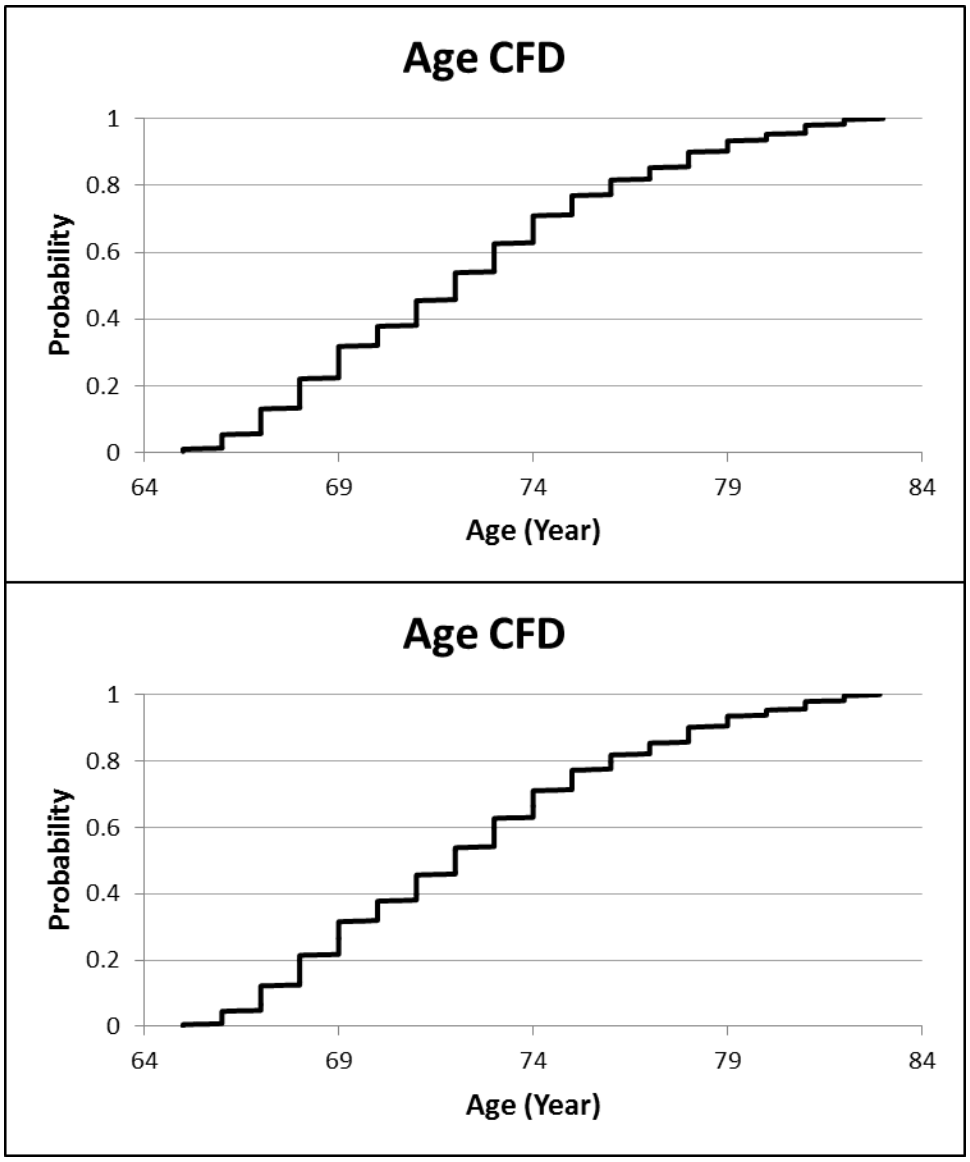

Figure 2.2: Age cumulative distribution function for (top) 299 AAA subjects from Western Australia and (bottom) hypothetical patients.

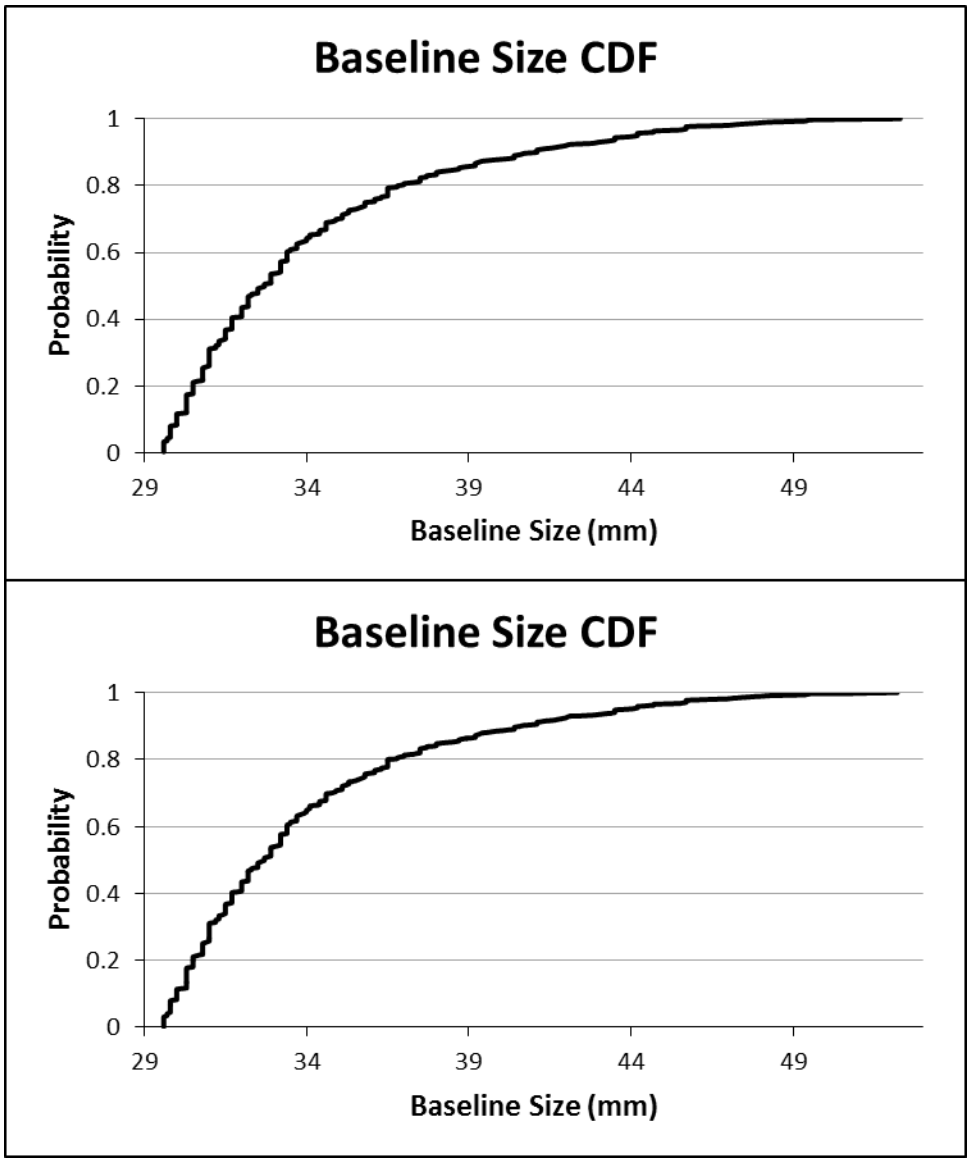

Figure 2.3: Baseline size cumulative distribution function for (top) 299 AAA subjects from Western Australia and (bottom) hypothetical patients.

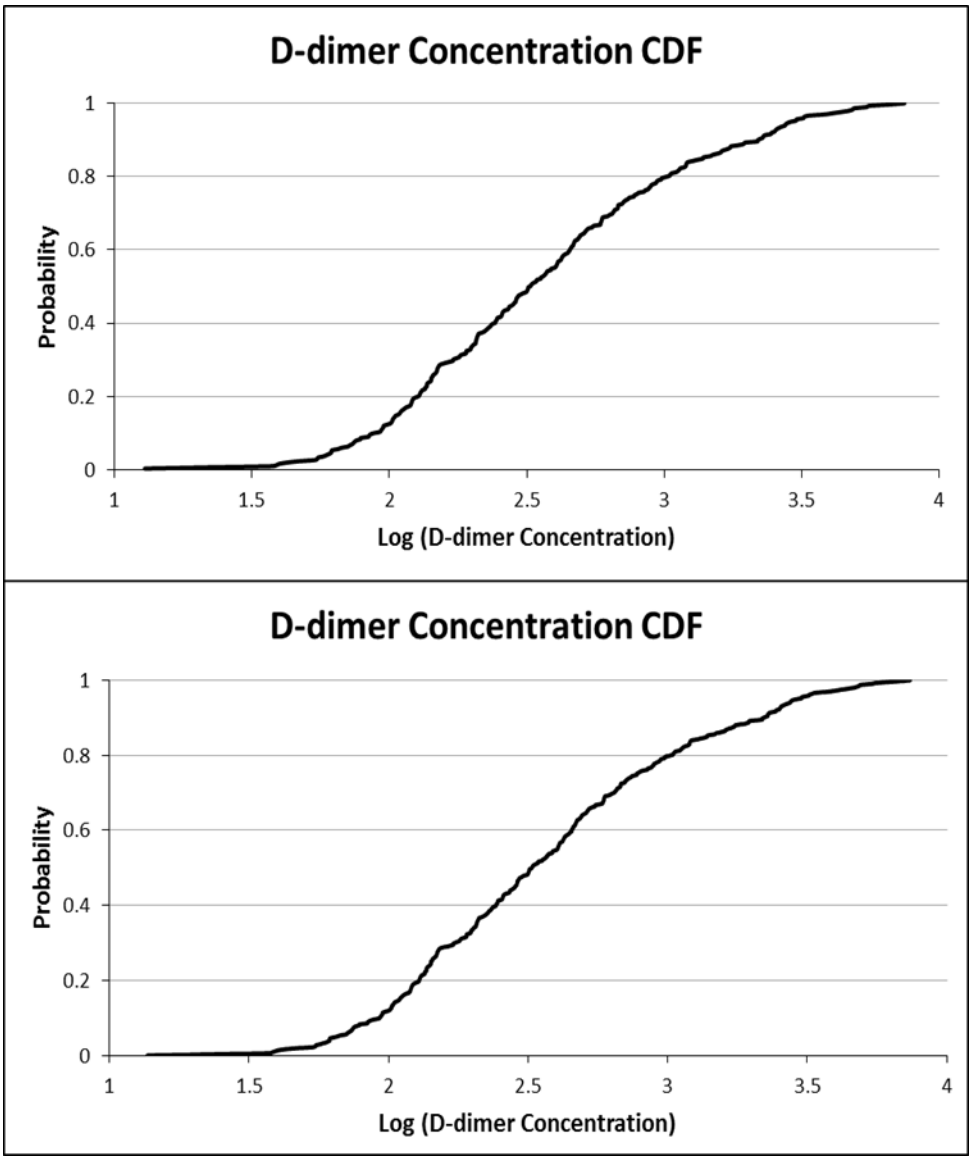

Figure 2.4: D-dimer level cumulative distribution for (top) 299 AAA subjects from Western Australia and (bottom) hypothetical patients.

2.1.2 Generating Covariates for Hypothetical Patients

The growth model that I used [1] to predict the future AAA sizes has model parameters with covariate effects based on a patient's characteristics. So it needs the patient characteristics of an individual to predict the growth rates of this individual patient. Given the posterior matrix of covariate effect values from the WinBUGS fit of the prediction model

to the data (5,000 sets of covariate values), I was able to implement the same approach as I did for characteristics. The rationale behind this part is that I wanted to be able to have a growth trajectory (based on hypothetical characteristics and hypothetical covariates) assumed as actual trajectory for each individual (described in Section 2.3.1).

- Finding the correlation coefficients among eight different characteristics

  I applied the pre-built function called "cor" in "R" again for this part. This time my input was an 8 in 5,000 matrix; including seven covariates, which are used in the predicting model (explained later), and a deviation variable, which shows the effect of the noise of surveillance.

- Building the Cholesky decomposition matrix based on the correlation coefficients

  Because I wanted to generate new hypothetical covariates for the hypothetical patients, I needed to use the Cholesky decomposition matrix again to be reliable on the original output of the model based on real patients. The "chol" function in "R" was built based on the correlation matrix given by the previous step.

- Generating 8 random values from the normal distribution (rnorm in R)

  There were seven different covariates in the data set plus one deviation factor; therefore, I needed to generate eight random values. The "rnorm" function in "R" is used to do so as. This function is completely explained in the Section 2.1.1.

- Multiplying preceding 8 normally distributed random numbers in the Cholesky decomposition matrix

  Again, it was a vector of eight normally distributed random numbers that I wanted to multiply in the Cholesky decomposition matrix. I used "t" function to make it possible for the vector and the matrix to be multipliable.

- Finding Cumulative Density Function (pnorm in R)

  I used "pnorm" function in "R" to change the height of the probability density function to the cumulative density function to be able to use the original data set (posterior) to call back the generated data.

- Call back the data from each row in the original data set (quantile function in R)

  All the previous steps made it possible to go to the posterior matrix of covariates that I had from the output of WinBUGS and recall the assigned parameter to each hypothetical patient.

  Implementing these steps 10,000 times results in having a matrix of correlated posterior values, which includes the required covariates needed to calculate the parameters in the growth model and the deviation factor used in observations.

  These parameter values for k^{th} Markov chain Monte Carlo iteration, and the i^{th} hypothetical patient are $\beta_{0,k}^{(i)}$ for baseline AAA size, $\beta_{1,k}^{(i)}$ for baseline AAA growth rate, and $\beta_{2,k}^{(i)}$ for constant first derivative of AAA growth rate with size. I used these formulas to calculate the covariates for each individual in my data set:

$$\beta_{0,k}^{(i)} = \beta_{0,k}^{(Y(0))} \frac{Y_i(0)}{\text{median}\,(Y(0))}, \qquad \text{Eq. 2.1}$$

$$\beta_{1,k}^{(i)} = \beta_{1,k}^{(0)} + \beta_{1,k}^{(Y(0))} \frac{Y_i(0)}{\text{median}\,(Y(0))} + \beta_{1,k}^{(C^{(D-dimer)})} \frac{\log_{10}(C^{(D-dimer)})}{\text{median}(\,log_{10}(C^{(D-dimer)}))}, \qquad \text{Eq. 2.2}$$

$$\beta_{2,k}^{(i)} = \beta_{2,k}^{(0)} + \beta_{2,k}^{(Y(0))} \frac{Y_i(0)}{\text{median}\left(Y(0)\right)} + \beta_{2,k}^{(C^{(D-dimer)})} \frac{log_{10}\left(C^{(D-dimer)}\right)}{\text{median}\left(log_{10}(C^{(D-dimer)})\right)} + \beta_{2,k}^{(Diabetes)}\text{Diabetes}, \quad \text{Eq. 2.3}$$

where $Y_i(0)$ is the baseline AAA size measurement, $C^{(D-dimer)}$ is plasma D-dimer concentration, and Diabetes is the diabetes status for the i^{th} patient. In the posterior matrix, and consequently, in the correlated posterior matrix, $\beta_{1,k}^{(0)}$, $\beta_{2,k}^{(0)}$, $\beta_{1,k}^{(C^{(D-dimer)})}$, $\beta_{2,k}^{(C^{(D-dimer)})}$, $\beta_{1,k}^{(0)}$, $\beta_{2,k}^{(Y(0))}$, and $\beta_{2,k}^{(Diabetes)}$ are available and $\beta_{0,k}^{(Y(0))}$ is the baseline AAA size of the patient, which is provided in the characteristics data. Therefore, I could use the hypothetical covariates to calculate the hypothetical parameters in the growth model. Table 2.3 shows the median values (Q1, Q3) of final model's fixed parameters and the median values (Q1, Q3) of generated hypothetical covariates and its similarity to the original data. Table 2.4 shows the median values (Q1, Q3) of the covariance matrix form the original study [1].

Table 2.3: Median values (q1, q3) of the final model's fixed parameters and generated hypothetical parameters.

Fixed Parameters	Value (Original)	Value (Hypothetical)
$\boldsymbol{\beta_0^{(\hat{Y}(0))}}$ **denotes covariate effect of baseline AAA size measurement on baseline AAA size model parameter**	32.6 (32.5, 32.7)	32.6 (32.5, 32.7)
$\boldsymbol{\beta_1^{(0)}}$ **denotes offset from covariate effects for baseline AAA growth rate model parameter**	-1.61 mm/year (-3.08, -0.30)	-1.47 mm/year (-2.72, -0.33)
$\boldsymbol{\beta_1^{(\hat{Y}(0))}}$ **denotes covariate effect of baseline AAA size measurement on baseline AAA growth rate model parameter**	2.03 mm/year (0.87, 3.40)	1.94 mm/year (0.93, 3.07)
$\boldsymbol{\beta_1^{(\hat{C}^{(\mathrm{D-dimer})})}}$ **denotes covariate effect of plasma D-dimer concentration on baseline AAA growth rate model parameter**	0.90 mm/year (0.11, 1.64)	0.86 mm/year (0.17, 1.55)
$\boldsymbol{\beta_2^{(0)}}$ **denotes offset from covariate effect of baseline AAA size measurement on first derivative of AAA growth rate with size model**	-1.05/year (-1.52, -0.53)	-1.07/year (-1.53, -0.59)
$\boldsymbol{\beta_2^{(\hat{Y}(0))}}$ **denotes covariate effect of baseline AAA size measurement on first derivative of AAA growth rate with size model parameter**	0.59/year (0.11, 1.03)	0.61/year (0.16, 0.99)
$\boldsymbol{\beta_2^{(\hat{C}^{(\mathrm{D-dimer})})}}$ **denotes covariate effect of plasma D-dimer concentration of first derivative of AAA growth rate with size model**	0.37/year (0.13, 0.62)	0.38/year (0.15, 0.62)
$\boldsymbol{\beta_2^{(\mathrm{Diabetes})}}$ **denotes covariate effect of diabetes status on first derivative of AAA growth rate with size model parameter**	-0.32/year (-0.45, -0.18)	-0.31/year (-0.45, -0.18)

Table 2.4: Median values (q1, q3) of the final model's fixed parameters covariance matrix.

Fixed Parameters	Value
$\sigma^2_{\beta_0} = \sum_{1,1}$ **denotes variance of baseline AAA size model parameter**	0.19 mm^2 (0.13, 0.28)
$\sigma^2_{\beta_1} = \sum_{2,2}$ **denotes variance of baseline AAA growth rate model parameter**	1.11 $mm^2/year^2$ (0.86, 1.42)
$\sigma^2_{\beta_0} = \sum_{3,3}$ **denotes variance of first derivative of AAA growth rate with size model parameter**	0.10/$year^2$ (0.07, 0.13)
$\sigma^2_{\beta_0,\beta_1} = \sum_{1,2}$ **denotes covariance between baseline AAA size and baseline AAA growth rate model parameter**	0.30 mm^2/year (0.20, 0.41)
$\sigma^2_{\beta_0,\beta_2} = \sum_{1,3}$ **denotes covariance between baseline AAA size and first derivative of AAA growth rate with size model parameters**	-0.06 mm/year (-0.09, -0.03)
$\sigma^2_{\beta_1,\beta_2} = \sum_{2,3}$ **denotes covariance between baseline AAA growth rate and first derivative of AAA growth rate with size model**	0.59/year (0.11, 1.03)

2.2 AAA Growth Simulation Model

The AAA growth simulation model used in this research is based on the output of a Bayesian analysis on the growth of screen-detected AAA in men by Sherer *et al.,* 2012 [1]. Out of 875 men diagnosed with AAA (above 30 mm) in a Western Australia screening, 299 were followed with serial AAA diameter measurements. This model is based on this 299 patient cohort who were followed for a median of 5.5 years and provided a median of 6 AAA size measurements per patient. Table 2.5 shows the characteristics that are used in the model and will be used in this study. The explanation of the growth model, characteristics, and covariates effects are included in the previous section (Section 2.1).

Table 2.5: Characteristics of patients included in the simulation model [1].

Characteristic	Value
Number of men	299
AAA diameter at baseline, median (q1, q3)	32.7 mm (30.8, 36.0)
Duration of follow-up, median (q1, q3)	5.5 years (5, 6)
AAA measurements per patient, median (q1, q3)	6 (6, 7)
Age, median (q1, q3)	72 years (69, 75)
Diabetes, *N* (%)	42 (14%)
D-dimer protein, median (q1, q3)	326 ng/ml (142,785)

2.2 Post-Screening AAA Growth, AAA Rupture, and All-Cause Mortality

2.2.1 Simulation of AAA Growth for Individual Patients

It is very important to know how an AAA grows in the upcoming years. Does it grow fast? Does it have a constant growth rate? Does it have a negative growth rate? All of these possibilities are vital for making a decision in the future of the patient. If the AAA is a fast grower, it will reach the threshold of surgery and rupture faster than a AAA that has a small or negative growth rate. Now that both characteristics and covariates were generated, I could generate the parameters for all the patients. Giving different values to *t*, provided us the size of the abdominal aorta in the future time (Section 1.1.3).

I separated the growth model outputs into two different categories; one is what I assumed as actual growth trajectory, in which I used the generated hypothetical patients' characteristics and correlated covariates. The other category which is modeled growth trajectory was also based on hypothetical patients' characteristics, but this time I used WinBUGS posterior distribution from the clinical data as covariates. In this case we could have one actual trajectory for each hypothetical patient and 5,000 modeled trajectories that

we could compare and analyze the differences in size in future. Figure 2.5 shows the actual growth trajectory for one patient in grey, with modelled growth trajectories in black. A dense area of modelled growth trajectories can be seen when the number of modelled trajectories increase.

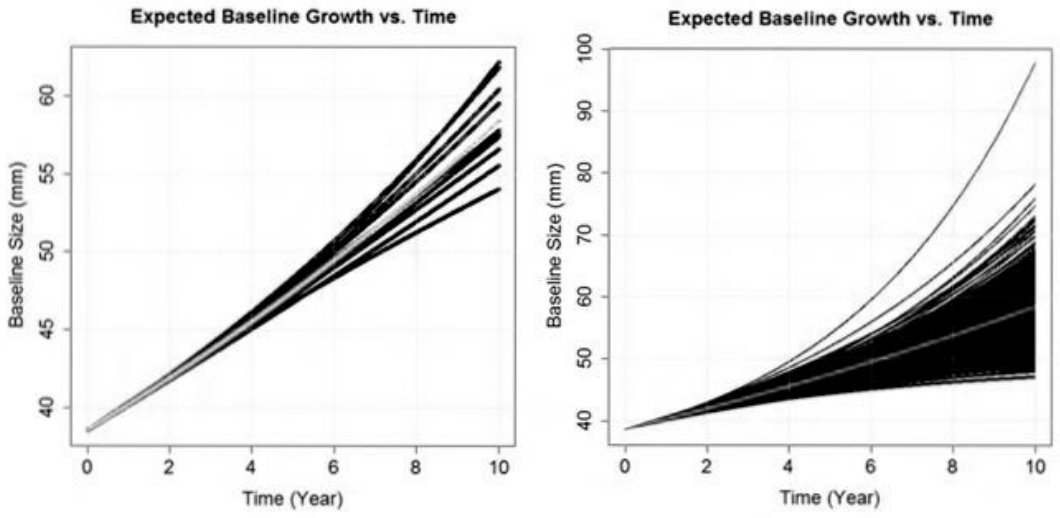

Figure 2.5: AAA size versus time for 10 and 5,000 growth trajectories (actual growth trajectory: grey, modelled growth trajectory: black).

2.2.2 Simulation of the Age of AAA Rupture for an Individual Patient

For patients diagnosed with abdominal aortic aneurysm, even if their aorta diameter is less than the threshold for elective surgery, having a rupture is possible [10-12]. Therefore, I had to consider rupture as an outcome in the future of the patients. According to numerous researches in the past 30 years, I have found that the risk of rupture is highly related to the size of aorta. The largest cohort was for the Rescan 2013 meta-analysis by Bown *et al.* 2013 [7], which showed a clear relationship between the baseline size and the rate of rupture. Because I have had a growth model that predicts the size in different time intervals, I was

able to predict the time of rupture using the assigned risk of rupture to each size and use the Monte Carlo simulation to select when the AAA will rupture for each hypothetical patient.

I used the Monte Carlo simulation to estimate the age at which a patient's AAA will rupture. In the Monte Carlo simulation, we can determine the interval of quiescence (the time period in which nothing happens – which is the time until rupture here) based on the known state of system (AAA size) at the current time [40]. To know the state of system at the current time, we could use the AAA growth rate to predict the AAA size at any future time. Then to find the interval of quiescent, we needed the transition rates; a transition rate is a function of state that describes the occurrence that we were looking for, which is AAA rupture in this case. As I mentioned before, multiple studies during the past 30 years have shown that the size of abdominal aorta is the most effective factor in the risk of rupture [7]. The Rescan 2013 meta-analysis by Bown *et al.* 2013 [7] with a cohort of 15,471 patients quantified the relationship between the baseline sizes of abdominal aorta and the rupture rate. I adopted the data from their paper (for specific baseline sizes; 30 mm, 35 mm, 40 mm, 45 mm, and 50mm) and fit the data in the most accurate way possible in Microsoft Excel (see Figure 2.6). The reason for fitting to data is because size is a continuous parameter and the size of the aorta can be any real number, and not only the exact numbers that I adopted from the Rescan study. Data was best fit using a fourth degree polynomial with R-squared value of 1. The largest baseline size related to a rupture rate available in this study was 50 mm (because surgery is generally recommended around this size), but it is possible for abdominal aorta to grow more than 50 mm without rupture and surgical intervention. Despite the fact that extrapolating can be risky in predicting the behavior of a function at unknown points due to fluctuations and possible different behavior of functions, I had to use this function for

unknown points, too, to be able to calculate the age of rupture for those patients who will have abdominal aorta larger than 50 mm without having rupture. I extrapolated this fourth degree polynomial up to 100 mm in size to check if it has any undesired behavior, such as fluctuations, but the function is monotonically increasing, which is fairly a good estimate since the risk of rupture increases with size in the available data.

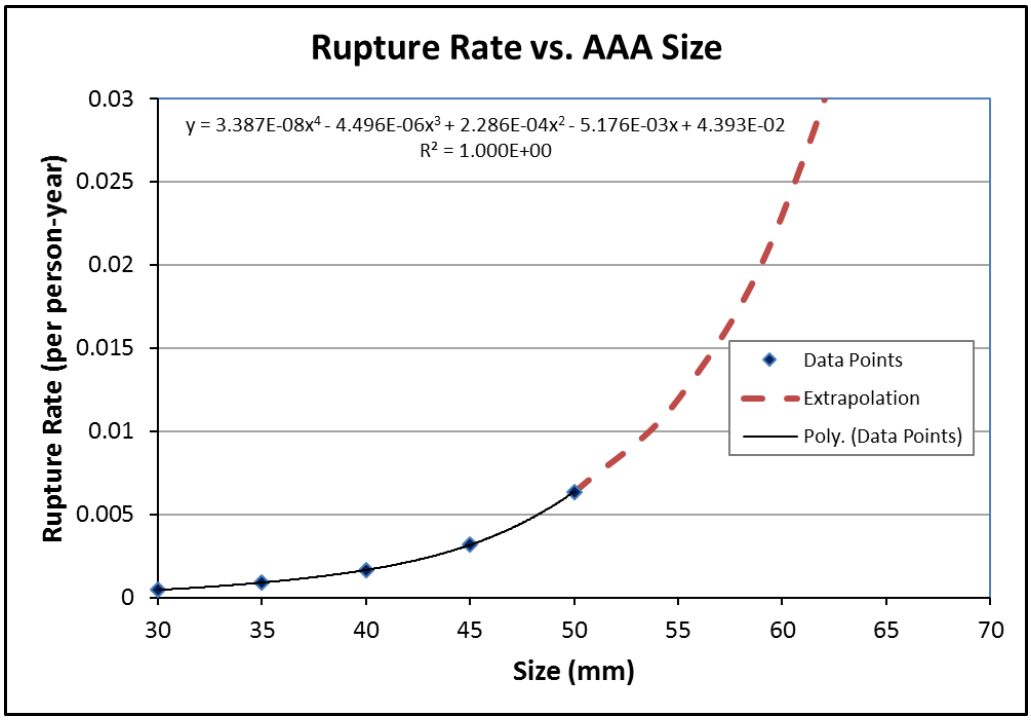

Figure 2.6: Rupture rate versus size.

Determining the transition rate (rupture rate versus the abdominal aorta's size) provided the quiescent interval as a function of the status of the patient (AAA size). The rupture age is the desired variable, but the transition rate function gives the rupture rate versus size. At this point we utilized the growth model function once again to relate the size to the time (age). In every step of the process we could use the growth model to find the size related to the age. If we consider τ as the current time and take a step equal to $d\tau$ in time, we can say that the interval of quiescence is greater than $\tau + d\tau$ since the event did not occur in

the period of $(\tau\ , \tau + d\tau)$. The shortest period of time that was recommended to a patient for surveillance is one year; therefore, I decided to choose $d\tau$ equal to three months to be fairly accurate and avoid further errors. In mathematical terms:

$$P(\tau + d\tau|x_t) = P(\tau|x_t)[1 - b(x(t + \tau,\ x_t,\ t))], \quad \text{Eq. 2.4}$$

where b is the transition rate (i.e., rupture rate) and x is the AAA size which is a function of the growth rate which is dependent to the size at current point and time. Rearranging terms and dividing by $d\tau$, letting $d\tau \to 0$:

$$\frac{d}{d\tau}P(\tau|x_t) = -P(\tau|x_t)[b(x(t + \tau,\ x_t,\ t)]. \quad \text{Eq. 2.5}$$

We know the fact that quiescence interval is greater than 0, so:

$$P(0|x_t) = 1, \quad \text{Eq. 2.6}$$

and

$$P(\tau|x_t) = \exp\left[-\int_0^\tau b(x(t + \tau',\ x_t,\ t)\ d\tau'\right]. \quad \text{Eq. 2.7}$$

Giving the cumulative distribution function for the quiescence interval:

$$F(\tau|x_t) = 1 - \exp\left[-\int_0^\tau b(x(t + \tau', x_0, t)\ d\tau'\right]. \quad \text{Eq. 2.8}$$

Randomly selecting a uniformly distributed random variable R on the cumulative distribution function, a sample value of the quiescence interval T is then found from:

$$R = 1 - \exp\left[-\int_0^T b\big(x(t + \tau, x_0, t)\big)\ d\tau\right], \quad \text{Eq. 2.9}$$

$$R - 1 = -\exp\left[-\int_0^T b\big(x(t + \tau, x_0, t)\big)\ d\tau\right], \quad \text{Eq. 2.10}$$

$$\ln(1 - R) = -\int_0^T b\big(x(t + \tau, x_0, t)\big)\ d\tau, \quad \text{Eq. 2.11}$$

$$-\ln(1-R) = \int_0^T b\big(x(t+\tau, x_0, t)\big)\, d\tau. \qquad \text{Eq. 2.12}$$

I generated a uniformly distributed random variable, R for each patient, and solved this equation to find the age of rupture, T. To solve this equation I had to use bisection method for root finding. I wrote the code in R with error precision of seven decimal points (Appendix B). For the ranges in bisection method I used the current age as lower limit and 120 years as the upper limit, which is fairly rational since there are not many people who live past this age. This formula starts from time zero to time T, when the incident happens. With a little modification I can start from the current age (λ_1) to the age when the AAA will rupture (λ_2):

$$-\ln(1-R) = \int_{\lambda_1}^{\lambda_2} b\big(x(\tau, x_0)\big)\, d\tau. \qquad \text{Eq. 2.13}$$

In the programming and calculations, I used trapezoid rule for small intervals to calculate the integrations for each step. The transition rate function is a fourth degree polynomial and with the function's behavior in the desired interval, trapezoid rule could be an accurate method.

2.2.3 Simulation of the Age of Non-AAA Related Mortality of a Patient

Another likely occurrence that may happen to the patients in the study cohort is death by all non-AAA related causes. All the patients are above 65 years old, so non-AAA related death is a likely outcome. To calculate the age when patients die by non-AAA related causes, I had an easier approach. Using the Monte Carlo simulation this time, as I have had the mortality rate versus age given by National Vital Statistics System in 2014 [41], needed less effort because I did not have to call back age by size using an additional function.

To find the transition rate for death by natural causes, I used the data from National Vital Statistics System data of 2014 [41]. This data set gives the death rate per 10,000 populations for specific ages. I first converted the death rates form per 100,000 populations to per person and applied an interpolating polynomial to the data with the most accurate function, because age is a continuous function. I adopted data for 50 to 90 years old men with 5 years intervals and fitted the data with sixth degree polynomial with R-squared value equal to 1 (see Figure 2.7).

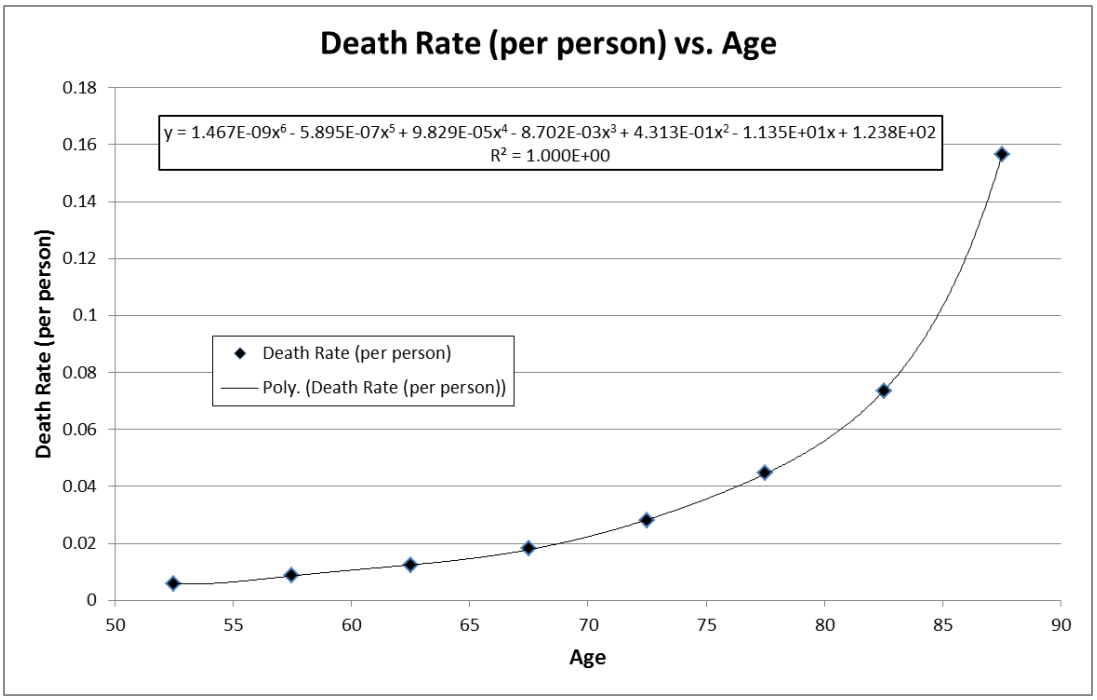

Figure 2.7: Death rate versus age.

Equation (2.13) can be easily modified for natural cause death. The only differences are that the transition rate is the mortality rate (rather than the AAA rupture rate) and the mortality rate is a function of age, which increases uniformly with time (so the growth model function does not need to transform size into age):

$$-\ln(1-R) = \int_{\lambda_1}^{\lambda_2} b\big(x(\tau, x_0)\big)\, d\tau, \qquad \text{Eq. 2.14}$$

Where λ_1 is current age of the patient, λ_2 is natural death age, b is the transition rate (i.e., mortality rate), and x is the age at current time. Again, I generated 10,000 uniformly distributed random variables for each patient and used trapezoid rule and bisection method to solve the equation and fine the natural death age.

After this section, I had the data of natural cause death and the age of rupture for each one of 10,000 patients in my data set, which gave me an overview about their future.

2.3 Application of Bayes' Rule to Predict AAA Size with Age of an Individual Patient

At the beginning of predicting the future of AAA size in a patient based on the patient characteristics, there are many potential growth paths dependent on the set of covariates that we used in the growth model. As mentioned before, I assumed the growth trajectory of a patient to be the actual growth trajectory if the generated characteristics and generated covariates are used in the growth model. The modelled growth trajectory is when the generated characteristics of a patient are used with the covariates from posterior matrix (WinBUGS posterior distribution from clinical data). Because there are 10,000 sets of characteristics and 10,000 sets of covariates generated, there are 10,000 different actual trajectories for each one of the hypothetical patients. It is important to note that this is just an assumption for further calculations and all other trajectories can be the actual trajectory for a specific patient. For each patient, using generated characteristics and 5,000 different covariates from posterior matrix, there were 5,000 different modelled growth trajectories. I used these trajectories to compare with the one which is assumed to be the actual growth trajectory. At the initial time for each patient, all of the 5,000 different trajectories are

equally likely to happen. As time passes and observations determine the actual size of abdominal aorta (the size which is read from the actual growth trajectory of the patient) the likelihood of other possible trajectories (modelled growth trajectories) can be computed. Trajectories with sizes more similar to the actual trajectory are more likely to happen and those with sizes far from the actual observation are less likely to be the actual trajectory of the patient. At the beginning, the probability of each trajectory was $\frac{1}{5000}$, but after each observation, I could update this probability based on our observation, using the Bayes' rule. According to the Bayes', rule we can write:

$$p(\mathrm{j}_i|\mathbf{x}) = \frac{p(\mathbf{x}|\mathrm{j}_i)\, p(\mathrm{j}_i)}{\sum_{\mathrm{i}} p(\mathbf{x}|\mathrm{j}_i)\, p(\mathrm{j}_i)}. \qquad \text{Eq. 2.15}$$

Where $\mathbf{x}$ is vector of size measurements and j_i is the i^{th} growth trajectory. This equation states that the probability of the i^{th} trajectory ($p(\mathrm{j}_i|\mathbf{sizes})$), given a specific size (observed size), is equal to the probability of that size, given the i^{th} trajectory ($p(\mathbf{sizes}|\mathrm{j}_i)$) multiplied by the current probability of the i^{th} trajectory ($p(\mathrm{j}_i)$) over the sum of probabilities based on previous quantities. For example, in the first observation, the probability of each trajectory is $\frac{1}{5000}$. This number keeps getting updated during later observations and that is how the probability of trajectories close to the actual trajectory gets larger and the probability of the trajectories far from the actual observations gets smaller. To perform these updates I used "R" software. First, I had to determine the actual size based on the actual growth trajectory. For this purpose, once again, I used "rnorm" function. This time I did not want to generate randomly distributed numbers. I generated this number based on the distribution over that specific time on the actual growth trajectory. As input, I set the number of observations as one and the data set as actual growth trajectory and the deviation from the

correlated posterior matrix. When I explained the formation of the correlated posterior matrix, I mentioned a column consisting of deviation (noise) in observations. Here is where we use the deviation to have the effect of noise in our calculations. The feedback of this function is the actual size at that specific time, centered on the actual growth trajectory. The next step was to compare this actual size in a specific time with other modelled growth trajectories to find the likelihood. In this step, I used "dnorm" function and set the actual size found in the previous step, and the size of the desired trajectory, to find the likelihood. Output of this function is the likelihood between the observation and the size in a modelled trajectory. Finally, I multiplied the previous probabilities in the likelihood of the modelled trajectory based on new observations and divide it by the sum. I repeated this approach each time I needed to do an observation and kept updating the probabilities of different trajectories. Another use of this approach in my research is calculating the cumulative risk of rupture. In Chapter 2.3, I explained how I found a function to relate the size in abdominal aorta to the risk of rupture. When the probability of each modeled growth trajectory is known at different observations, we can find the cumulative risk of rupture by multiplying the probabilities' of different trajectories in the assigned risk of rupture for that specific size. We define the cumulative risk of rupture as:

$$\text{Cumulative Risk of Rupture} = \sum_i p(\mathrm{j}_i|\mathbf{x})\ \mathrm{Risk}_i. \qquad \text{Eq. 2.16}$$

By this calculation, I have an estimate about the risk of rupture in a patient based on 5,000 different possible trajectories. This data is also updated based on actual observation, which makes it more precise and more reliable on the patient's actual size.

CHAPTER 3

EXPERIMENTAL PROTOCOLS AND ANALYZING PARAMETERS

The methods described in Chapter 2 can be used to generate actual growth trajectories, rupture ages and sizes, and non-AAA related mortality ages for hypothetical patients in addition to predict the likelihood of rupture for an individual patient. In this chapter, I describe how I used this simulation model to address the questions about when patients should receive surgery and how often they should receive AAA surveillance.

One of the objectives of this study was to identify the most effective surveillance protocol by integrating the effect of risk of rupture at each interval to recommend the next surveillance (Section 3.1). On the other hand, current surveillance protocols in different countries are solely based on the AAA size. These protocols recommend patients to return for another surveillance based only on the size that is observed at current observation. After extracting the most optimum surveillance protocol from the first phase (Section 3.1) we were able to compare it to current available protocols in different countries in the second phase (Section 3.2).

In this section I will explain the procedure of simulation and decision making in both designed protocols and current available protocols. In the last section I will discuss the parameters that quantified these assessments.

3.1 Designed Protocols – Proposed Protocols by Integrating Risk of Rupture in Surveillance Intervals

As The ultimate purpose of designed protocol is to integrate the risk of rupture in the process of decision making about surveillance intervals. Figure 3.1 shows the overall procedure of simulation by referring to each section in the methods. The smallest interval for surveillance, due to current protocols, is three months and, in medical terms, having surveillance in less than three months rarely happens. Therefore, the minimum time step in this procedure is three months. The simulation will stop if the patient reaches the end time, which is defined as the time he dies by natural causes (Section 2.3.3) or has a sudden rupture (Section 2.3.2). The other case that stops the simulation is when surgery happens: when the patient passes the AAA size threshold for surgery (50, 55, or 60 mm based on different simulations). After taking a step in time through the growth model, the cumulative risk of rupture (Section 2.4) is compared with the risk of surgery. If the risk of rupture is more than the risk of surgery, or if we reach the time limit without risk of rupture passing the risk of surgery, the patient should go for a surveillance which updates the probabilities (Section 2.4). The size, in which patients go for surveillance, and the time of the intervals, were also recorded for further comparison with current protocols.

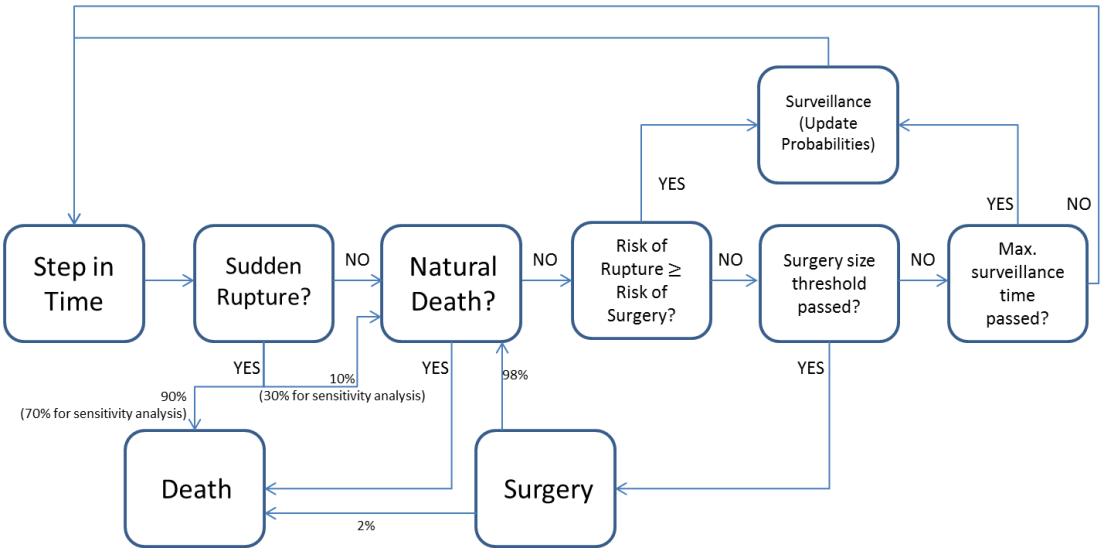

Figure 3.1: Flow-chart of designed protocols (model-based).

This procedure was implemented on 10,000 hypothetical patients, each having 5,000 modeled trajectories with different risks of surgery and time limits for surveillance to check the effect of each of these two parameters on the results. Primary simulations have been conducted for 1% to 10%, with the increment of 1%. The highest variability in the results was associated to the smallest risks. Therefore, the simulations were narrowed down to 0.5%, 1%, 1.5%, 2%, 2.5%, 3%, 4%, and 5%. Time limits for the cases that the risk of rupture does not pass the risk of surgery are 1, 2, 3, 5, 7.5, and 10 years. Considering three different thresholds for surgery (50, 55, and 60 mm) gives us 144 different protocols for simulation.

3.2 Available Protocols – AAA Surveillance Protocols in Different Countries

As mentioned in Chapter 1, because there is not a vast cohort of patients who have been under surveillance by these protocols, one cannot say which protocol has fewer deaths due to sudden rupture or which protocol results in higher number of surveillances. Therefore,

by using the accurate growth model that is available, as well as data of generated hypothetical patients, I simulated these protocols in the long term on a much larger population. I used the baseline AAA size in the hypothetical generated data as the first observation, and, according to the protocol, set the next observation. In this approach I only used the actual growth trajectory for each patient, because I did not have to calculate the cumulative risk of rupture based on modeled trajectories. I also set the threshold for surgery as 55 mm, so the patient will be recommended to go under surgery if he reaches the threshold during the observations (Figure 3.2). Doing this simulation on 1,000,000 hypothetical patients by applying different protocols (see Table 1.1), provided me with the number of surveillances, number of surgeries, number of deaths caused by natural causes, and number of sudden ruptures. All these results can show how the outcome of these protocols are different and which one is the most preventive. Additionally, I did the simulation again by setting the surgical intervention threshold as 50 mm, to be able to answer my hypothesis on the credibility of the threshold for surgery. Setting surgical intervention threshold at 60 mm was not applied in this simulation. According to the preliminary results, 60 mm did not lead to any benefit to patient's life expectancy, surveillances, or number of ruptures (Section 4.1).

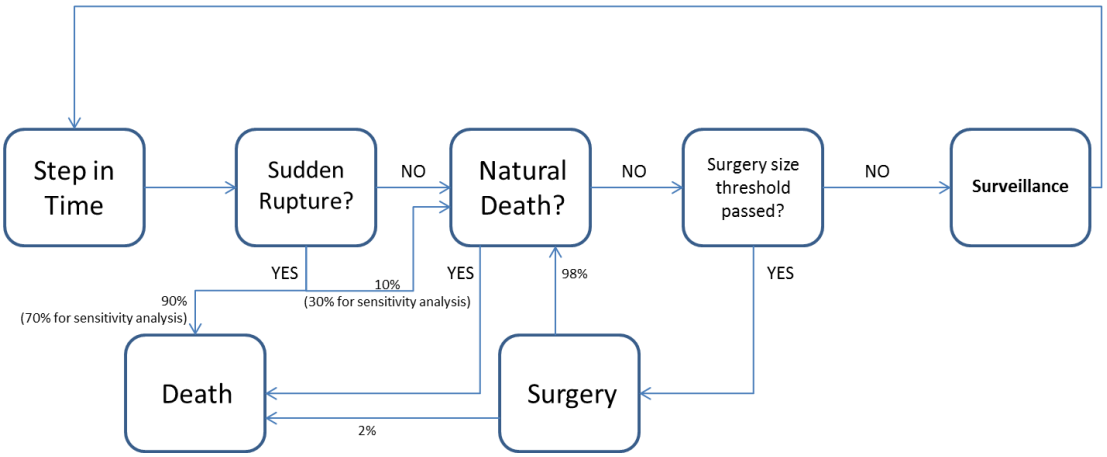

Figure 3.2: Flow-chart of current protocols (population-based).

To make a fair comparison between the optimum designed protocol from the model-based simulations with the current available protocols in different countries, I needed to modify the designed protocol in a way that its basis is similar to current available protocols in different countries. In the designed protocols, the decision of when to do another surveillance on the patient is made by integrating risk of rupture and comparing it to the risk of surgery. However, in population-based simulations (and in reality) timing of next surveillance is based on the patients' AAA size at current observation. Using records from the model-based simulations, I created a protocol like the ones that are being used in different countries. By analyzing the timing and the size in which patients went for surveillance in the most optimum outcome of model-based simulations, I categorized surveillances based on different AAA size slots. This enabled me to create surveillance intervals only based on AAA size for the most optimum outcome of the model-based simulations.

3.3 Analysis Parameters

3.3.1 Outcome #1: Life Expectancy

To point out the difference among protocols for surveillance in long term, I defined a parameter that compares the effectiveness of these protocols on the life expectancy of the patients. In this parameter, I compared the estimated lifetime of the patient with and without treatment. I had two different approaches toward fatality of sudden rupture;

- worst-case scenario which assumed that 90% of those who experience sudden rupture die and 10% will survive (Figure 3.1)
- and best-case scenario which considers fatality rate at 70% [1].

Also 2% of those who go under surgery are assumed to die [13]. In no treatment scenario, I only used data from Section 3.2 and 3.3 to estimate the age that patients will die by natural causes or will have sudden rupture. Data regarding each patient going under surveillance protocols were also available in the designed protocols, so the change in lifetime could be calculated in this case too:

$$\begin{aligned}\text{Change in Life Expectancy}(\text{Patient}_i) \\ = \text{Lifetime}_{\text{treatment}}(\text{Patient}_i) \\ - \text{Lifetime}_{\text{no treatment}}(\text{Patient}_i).\end{aligned} \qquad \text{Eq. 3.1}$$

3.3.2 Outcome #2: Number of Surveillances

Change in life Expectancy by itself is not a complete metric for the comparison of different protocols. For example, a patient may go under surveillance every 3 months and go under surgery right before the time of sudden rupture. Excessive number of surveillances is not desired because it is not possible for patients due to economic issues and patients' inconvenience. Number of surveillances is looked into in this study as a measure of

efficiency in each protocol. By focusing on this parameter, it is possible to compare two protocols more accurately. The most preventive protocol is considered to be the one with highest increase in life expectancy and fewer number of surveillances at the same time.

3.3.3 Outcome #3: Number of Ruptures

Sudden rupture, if happens before natural death or elective surgery, is the least desired outcome of the simulation because it is highly fatal [2-3]. A higher ratio of the number of surgeries to the number of sudden ruptures is preferred, because it recommends patients to go under surgery before the rupture happens. In other words, in the timeline of the events, the most preventive protocol suggests elective surgery right before the rupture happens. However, it is really important to note that in population-based simulation this parameter (number of sudden ruptures) loses its value. This is because when surgery is being recommended solely based on size and not the calculated risk of rupture, number of sudden ruptures are independent from simulation.

3.4 Analysis on the Results

3.4.1 Primary Analysis: Pareto Fronts

Increased life expectancy is the most important goal of the treatment protocols. Patients spend time and money on surveillances and take the risk of surgery in order to increase their life expectancy but there are always constraints that should be considered. Keeping an eye on increase in life expectancy in a protocol, the efficiency of that protocol should be examined too. Having surveillances too often can obviously leads into an increase in life expectancy but it comes with expense of time and money for unnecessary surveillances that could have been avoided. An effective model should be efficient at the same time to be practical. Efficiency of a surveillance can be measured by the number of

surveillances that each patient goes through (defined in Section 3.3.2). This factor gives us an idea if a protocol is increasing its effectiveness by increasing the number of surveillances unnecessarily (which is not desired). The last parameter (number of sudden ruptures) also is a valuable measure to evaluate a designed protocol. This parameter is useful in designed protocol analysis, because cumulative risk of surgery was calculated in different periods. However, in current protocols (population-based analysis) this factor is not decisive since decision making for surveillance or surgery is only based on AAA size and not a comparison risk of rupture and surgery.

To evaluate protocols both in model-based and population-based simulations, I used a series of two-dimensional plots with the combination of three analyzing parameters; change in life expectancy, number of surveillances, and number of sudden ruptures. In each of three plots, I distinguished the protocols that reside on the Pareto Fronts. These are protocols that are non-dominated by others with respect to analyzing parameters. For example, in the plot of increase in life expectancy versus number of surveillances, protocols that have higher increase in life expectancy while keeping the number of surveillances fewer are considered non-dominated. Protocols that were available in all Pareto Fronts (model-based) and on two (population-based) were considered to be the most optimum protocols regarding decisive factors.

3.4.2 Secondary Analysis: Patient Categories

Categorizing patients based on their characteristics (age, AAA size, and diabetes mellitus status) and then observing how they benefited from a treatment protocol give significant insight about the effectiveness of each protocol. For instance, if patients with smaller sizes benefit less from protocol, or if older patients benefit more. Results from

simulation on all protocols were combined and then divided into different groups based on specific criteria. This analysis was implemented both on model-based and population-based results.

CHAPTER 4

SIMULATION RESULTS

Results of this research are separated into two phases. The first phase is model-based simulations performed on 10,000 hypothetical patients to identify optimum surveillance protocol. The second phase is a population-based analysis, which applies the optimum protocol of the model-based analysis to a larger population. Simulations were performed on 10,000 hypothetical patients through designed protocols and for 1,000,000 hypothetical patients through the most optimum outcome (protocol) as well as current protocols followed in seven different countries. For each category of simulation, the timing and number of surveillances, ruptures, surgeries, and deaths by natural causes were measured. Based on these measurements, I analyzed which surveillance protocol leads to the highest life expectancy while keeping the number of surveillances and sudden ruptures as low as possible. In the designed protocols, the AAA size at each recommended observation and the time interval between observations, were recorded for each hypothetical patient. These data provided us the opportunity to address the objectives of this research on identifying the surveillance protocol and surgical intervention threshold that provides the greatest benefits (higher life expectancy, fewer surveillances, and fewer number of fatalities).

In the first section of this chapter (Section 4.1), results of the model-based analysis, (Section 3.4.1) are shown. Due to the large number of designed protocols, only three result

tables (including the best protocol) are reported here in Section 4.1.1 and the results of the rest of the protocols can be found in appendix A.

The second section of this chapter (Section 4.2) is assigned to the population-based analysis which using the methods of Section 3.4.2, was performed on the most optimum protocol from the model-based simulation and protocols that are currently being enforced in different countries. The results of the second analysis on the designed protocols are available in Section 4.2.1.

4.1 Model-based Analysis Results

4.1.1 Designed Protocols

All analysis parameters explained in Section 3.3 (increase in life expectancy, number of surveillances, and number of sudden ruptures) are summarized in tables for all 144 designed protocols. This gives a better look on how different designed protocols led to different outcomes in term of increase in life expectancy, number of surveillances, and number of ruptures.

Tables 4.1 to 4.3 show the results for varying the AAA size threshold of surgery of 50, 55, and 60 mm, respectively for 7.5 years time limit. Results for 7.5 years time limit were chosen because it includes the optimum protocol. Each surgery size threshold was tested as part of eight different protocols varying the estimated risk of surgery. The minimum time limit between observations was varied from 1 year to 10 years. Detailed results of all other protocols are available in Appendix A.

Table 4.1: Simulation results for effects of varying the surgical intervention risk for 7.5 years observation time limit and 50 mm surgery threshold.

Risk of Surgery	0.5%	1%	1.5%	2%	2.5%	3%	4%	5%
Number of Ruptures	167	184	202	173	207	189	239	268
Number of Surgeries	2898	2796	2706	2628	2589	2521	2449	2347
Number of Natural Deaths	6935	7020	7092	7199	7204	7290	7312	7385
Sum of Life Expectancies	6993	6911	6657	6394	6510	6492	6258	6140

Table 4.2: Simulation results for effects of varying the surgical intervention risk for 7.5 years observation time limit and 55 mm surgery threshold.

Risk of Surgery	0.5%	1%	1.5%	2%	2.5%	3%	4%	5%
Number of Ruptures	216	248	248	224	222	244	269	280
Number of Surgeries	2334	2190	2210	2181	2142	2101	2025	1980
Number of Natural Deaths	7450	7562	7542	7595	7636	7655	7706	7740
Sum of Life Expectancies	6644	6611	6588	6441	6450	6287	6387	5907

Table 4.3: Simulation results for effects of varying the surgical intervention risk for 7.5 years observation time limit and 60 mm surgery threshold.

Risk of Surgery	0.5%	1%	1.5%	2%	2.5%	3%	4%	5%
Number of Ruptures	271	298	305	310	316	323	316	346
Number of Surgeries	1901	1814	1762	1760	1707	1726	1712	1664
Number of Natural Deaths	7828	7888	7933	7930	7977	7951	7972	7990
Sum of Life Expectancies	6263	6041	5716	5932	5987	5807	5865	5779

Figures 4.1 through 4.3 show the simulation outcomes of all 144 designed protocols for life expectancy versus number of surveillances, life expectancy versus number of ruptures, and number of surveillances versus number of ruptures, respectively. Figures 4.1 through 4.3 are based on aggressive approach in analysis, in which, fatality rate of sudden rupture was assumed to be 90%. This will be discussed in more details in sensitivity analysis section.

Data points on each Pareto front were distinguished by size (Figure 4.1), filling (Figure 4.2), and diamond shape (Figure 4.3). There is one protocol which is available on all three Pareto fronts (large filled diamond data point). This unique protocol suggests 50 mm as the threshold for surgery, 7.5 years as the threshold for surveillance, and 0.5% as the decisive risk of rupture for surveillance compared to size-relative risk of rupture.

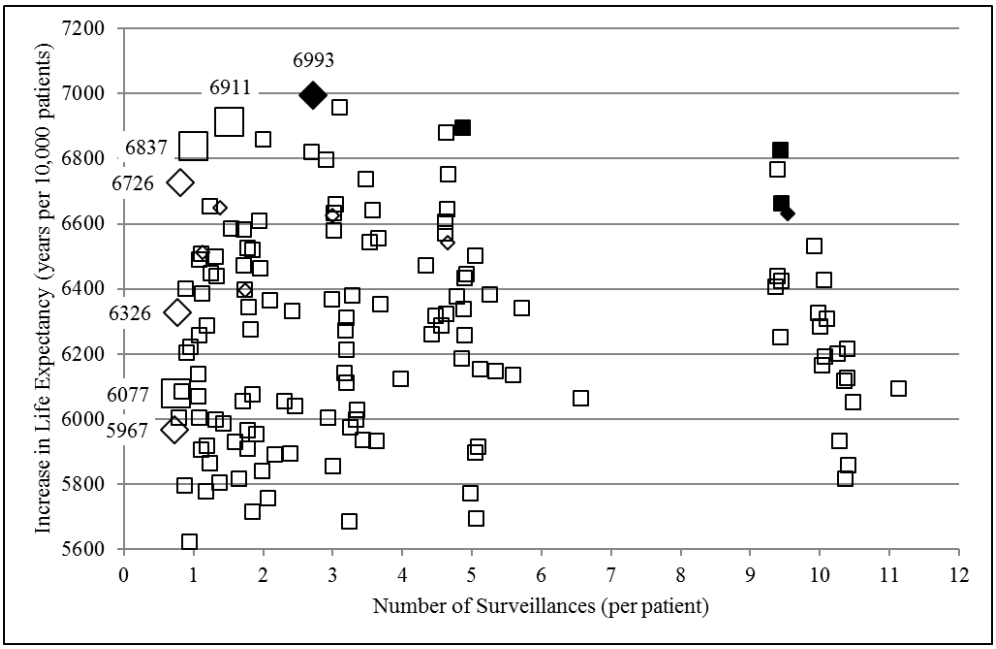

Figure 4.1: Increase in life expectancy versus number of surveillances for 90% rate of fatality after AAA rupture (larger data points are non-dominated).

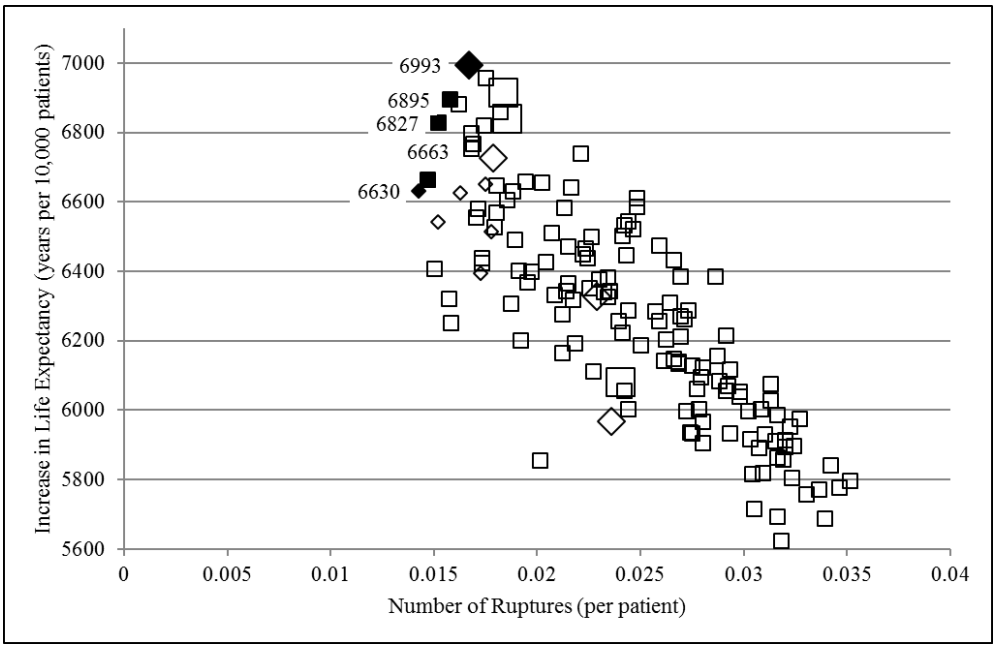

Figure 4.2: Increase in life expectancy versus number of ruptures for 90% rate of fatality after AAA rupture (filled data points are non-dominated).

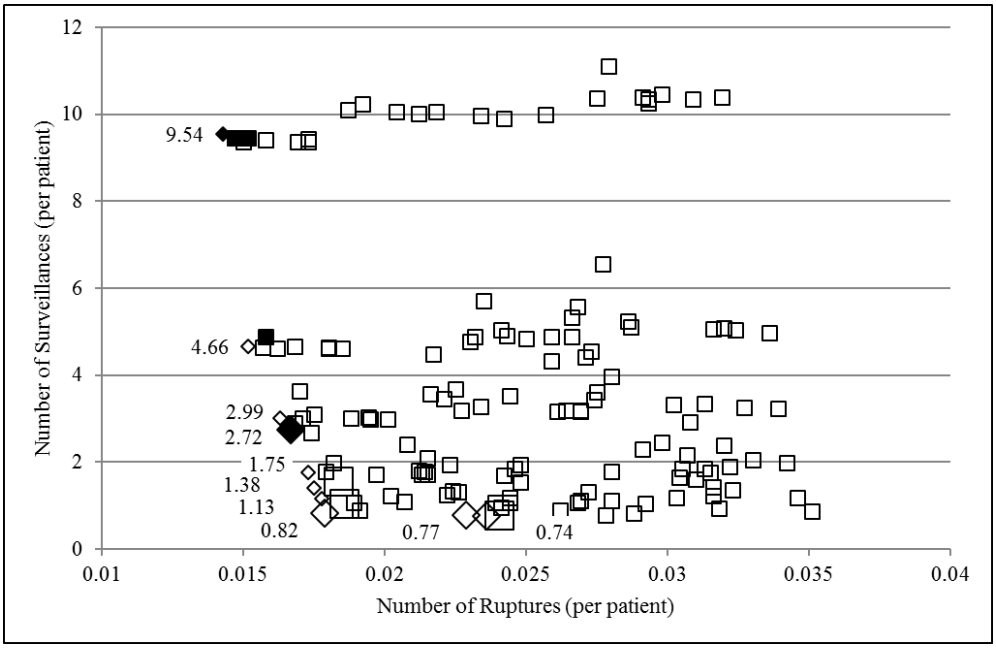

Figure 4.3: Number of surveillances versus number of ruptures for 90% rate of fatality after AAA rupture (diamond shaped data points are non-dominated).

The features of protocols that are non-dominated in at least two of the three outcomes (e.g. appear on the Pareto front in at least two of the Figures 4.1 to 4.3 are listed in Table 4.4. All the protocols available on the Pareto fronts apply the 50 mm as the threshold for surgery. Therefore, these protocols provide higher life expectancy, fewer number of surveillances, and fewer numbers of ruptures if the patients with AAA size above 50 mm go under elective surgery.

Table 4.4: Optimum protocols available on at least two pareto fronts in figures 4.1 through 4.3.

Surgery Threshold	Surveillance Time Limit	Decisive Risk	Increase in Life Expectancy per 10,000 patients	Number of Surveillances per Patients	Ruptures per Patients	Figure 4.1 Pareto front	Figure 4.2 Pareto front	Figure 4.3 Pareto front
50 mm	7.5 years	0.5%	6,993 years	2.72	0.0167	✓	✓	✓
50 mm	10 years	2.5%	6,726 years	0.82	0.0179	✓		✓
50 mm	10 years	3%	6,326 years	0.77	0.0229	✓		✓
50 mm	10 years	5%	5,967 years	0.74	0.0236	✓		✓
50 mm	1 years	0.5%	6,630 years	9.54	0.0143		✓	✓

Increasing surgery threshold to 55 mm in the optimum protocol results in 5% decrease in life expectancy, 31% increase in number of surveillances, and 29% increase in number of ruptures. For 60 mm the differences are even greater (10% decrease in life expectancy, 60% increase in number of surveillances, and 62% increase in number of ruptures).

The surveillance time limit of 7.5 years gives the most beneficial outcome. The surveillance time limit of 10 years for the optimum protocol may result in slightly less surveillances (-1%) and fewer ruptures (-4%), but it causes decrease in life expectancy (-2.5%). The scenario is different for shorter surveillance time limits. Such protocols increase the number of surveillances and the number of ruptures while lowering the life expectancy, leading to a no-win situation. For instance, the life expectancy drops by 3% for 5 years, 6% for 3 years, 1% for 2 years, and 5% for 1 year surveillance time limits in the optimum

protocol, while the numbers of surveillances rises by 6% for 5 years, 33% for 3 years, 79% for 2 years, and 250% for 1 year. The numbers of ruptures are also higher in the protocols with shorter surveillance time limits (1% for 5 years, 2% for 3 years, 5% for 2 years, and 15% for 1 year).

4.1.2 Sensitivity Analysis: Lower Rate of Fatality after AAA Rupture

In a sensitivity analysis, the life expectancy versus number of surveillances (Figure 4.4) and life expectancy versus number of ruptures (Figure 4.5) are plotted for the conservative approach, in which the fatality rate of rupture was considered to be 70%. The number of ruptures versus number of surveillances plot remain the same in both analyses, since these outcomes are independent from the fatality rate of rupture (Figure 4.4 and 4.5). Increase in life expectancy declined for all protocols. However, the order of protocols in term of increase in life expectancy and consequently optimum protocol did not change.

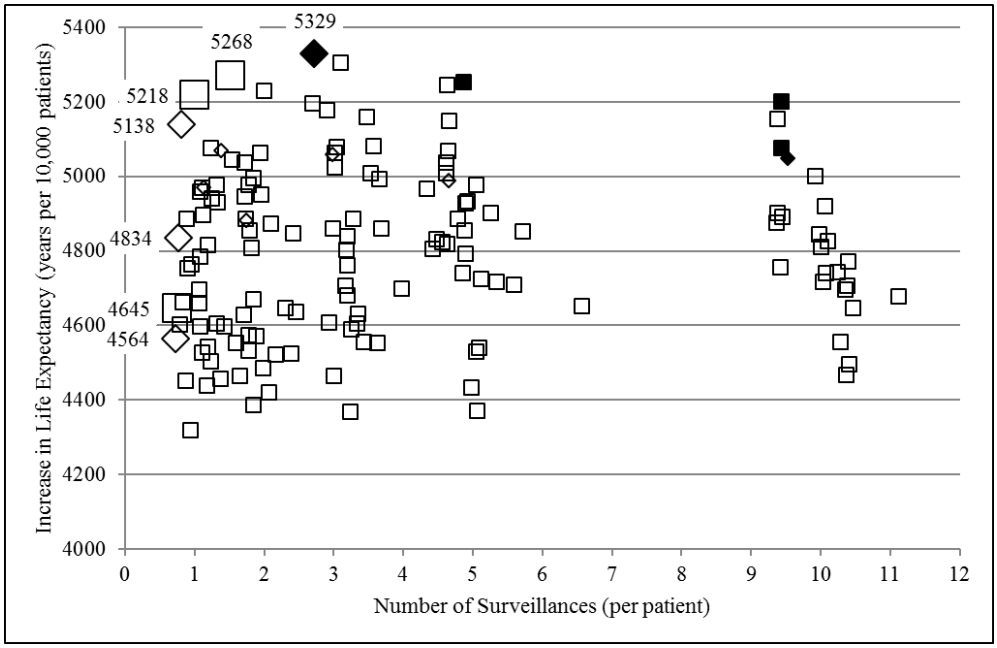

Figure 4.4: Increase in life expectancy versus number of surveillances for 70% rate of fatality after AAA rupture (larger data points are non-dominated).

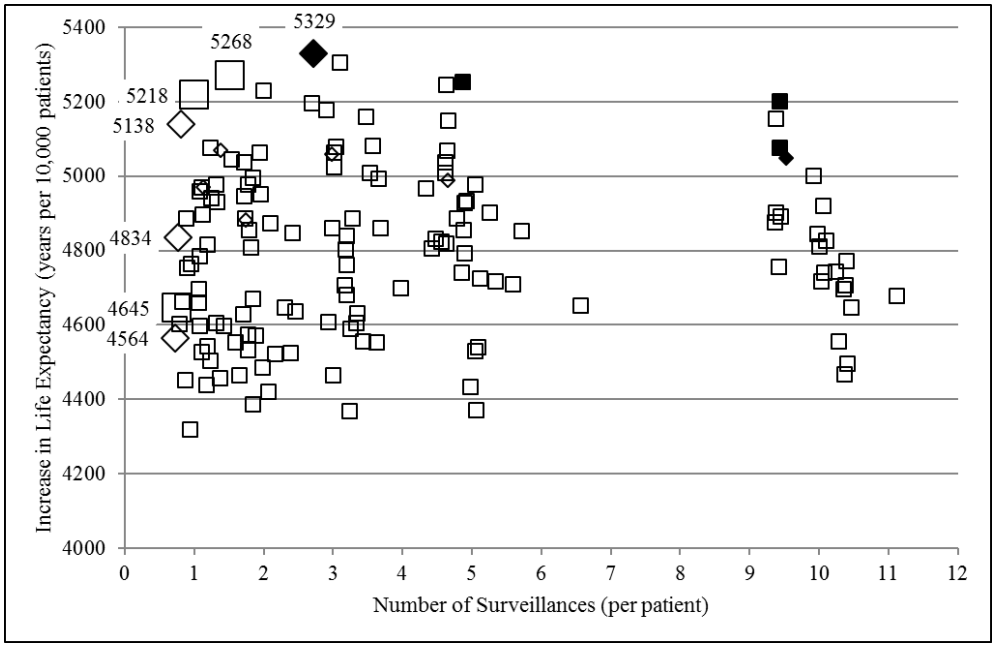

Figure 4.5: Number of surveillances versus number of ruptures for 70% Fatality after AAA rupture (filled data points are non-dominated).

4.1.3 Patient Benefits by AAA Baseline Size

Categorizing patients based on different criteria gives a stronger understanding of which patients benefit more from the optimum protocols (Table 4.1). Patients with baseline size of 45 mm or higher experienced 4.97 years increase in their life expectancy in average under the optimum protocol. This number is 42% lower in patients with baseline size between 40 and 45 mm (2.89 years), 81% lower in patients with baseline size between 35 and 40 mm (0.95 year), and 98% lower in patients with baseline size less than 35 mm (0.09 year). This is due to the fact that in patients with smaller AAA size, it takes longer to reach surgical intervention threshold or rupture. Therefore, in patients with smaller AAA size, the difference in life expectancy with or without following surveillance and surgical protocol is less than the patients with larger AAA sizes (Figure 4.6).

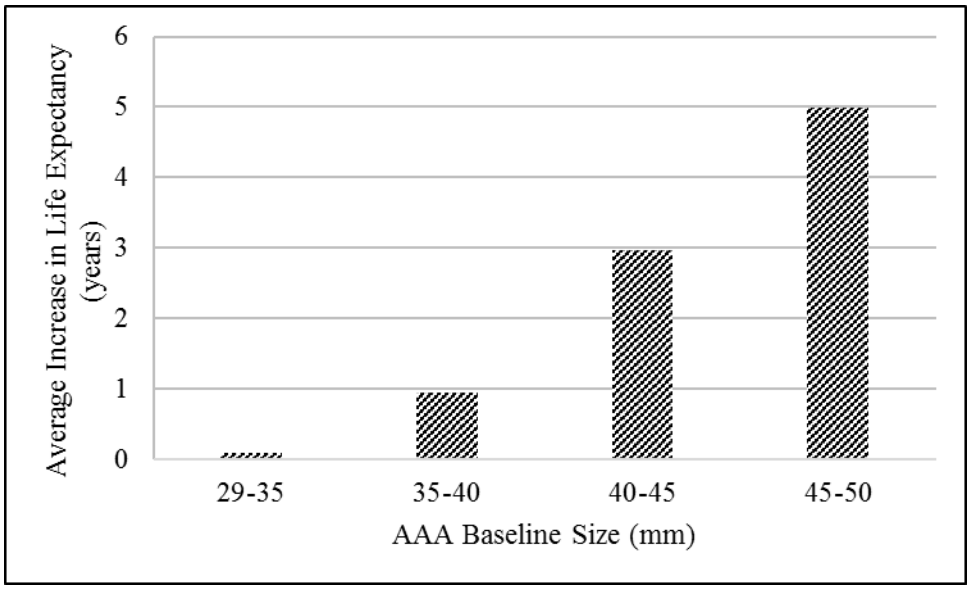

Figure 4.6: Average increase in life expectancy based on AAA baseline size (all scenarios).

Regarding the number of surveillances, patients with baseline size of 45 mm or higher went under 1.03 surveillances on average. Patients with baseline size of 40-45 mm went under 74% extra surveillances (1.8 surveillances). This number is 160% more for patients with baseline size of 35-40 mm (2.68 surveillances), and 211% higher for patients with baseline size less than 35 mm (3.21 surveillances). Other outputs (number of ruptures, surgical interventions and number of deaths due to natural cause) are also in favor of the patients with larger baseline size (Figure 4.7).

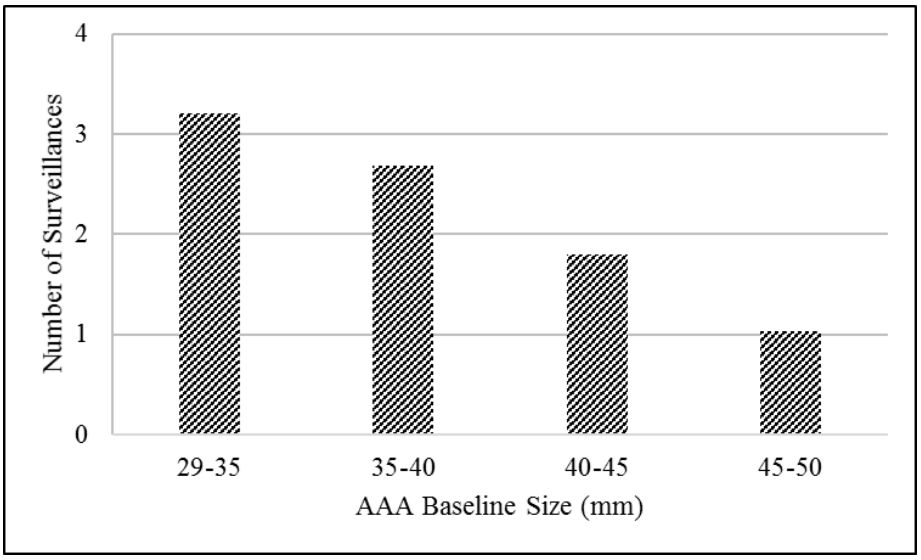

Figure 4.7: Average number of surveillances based on AAA baseline size (all scenarios).

4.1.4 Patient Benefits by Age

There was a greater increase in life expectancy for patients who are diagnosed at younger ages (Figure 4.8). Patients younger than 70 years old averaged 0.98 year increase in life expectancy while older patients took less advantage of the optimum protocols (increase of 0.57 years for 70-75 years old, 0.27 years for 75-80 years old, and 0.10 years for >80 years old).

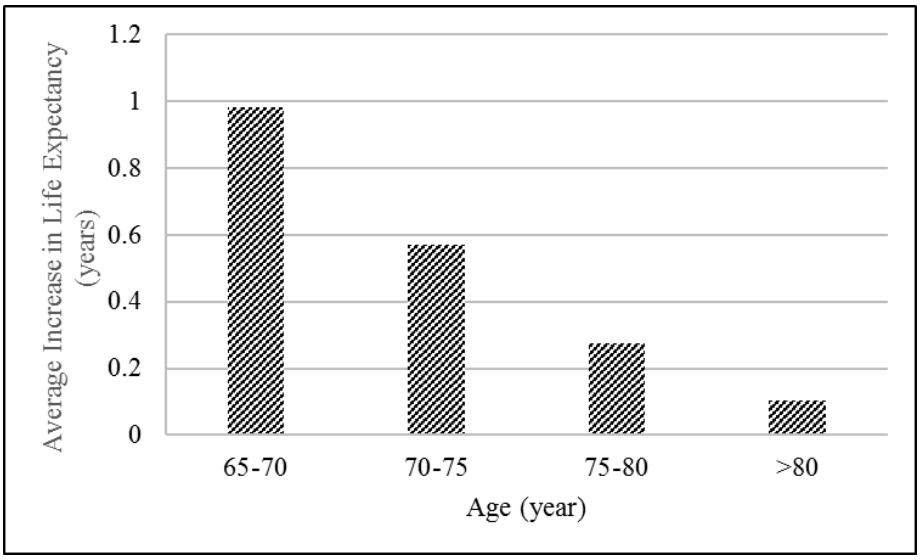

Figure 4.8: Average increase in life expectancy based on age (all scenarios).

Younger patients experience a greater number of surveillances since they live longer. Patients below 70 years of age averaged 3.53 surveillances. This number is 2.82 for patients between 70 to 75, 2.15 for 75 to 80, and 1.63 for patients older than 80 years old (Figure 4.9).

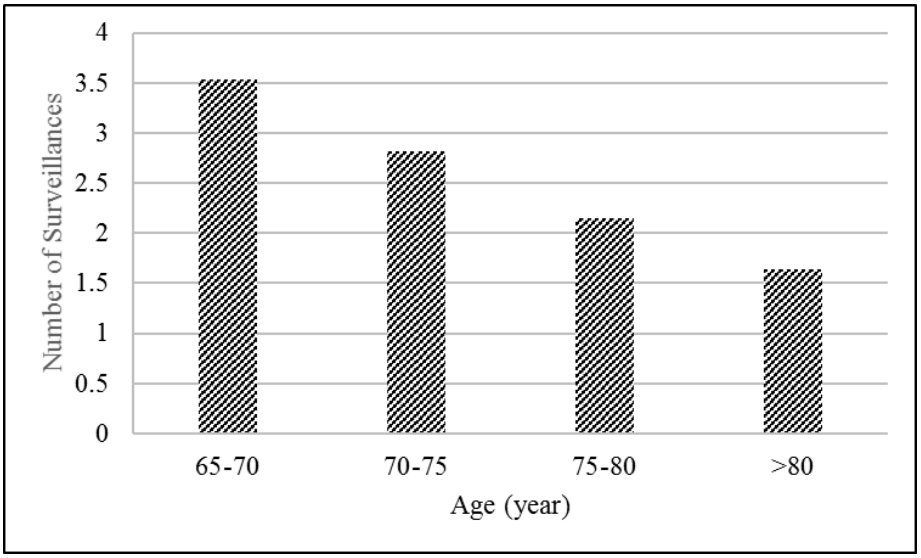

Figure 4.9: Average number of surveillances based on age (all scenarios).

Another criterion that was analyzed was the diabetes status of the patients; the average increase in life expectancy is 0.79 years for non-diabetic patients versus 0.12 years for diabetic patients.

4.2 Population-based Analysis Results

4.2.1 Optimum Designed Protocol versus Current Protocols

The average time for a patient to go under surgery in the most optimum designed protocol (Table 4.1) is 6.95 years. Surveillance recommendations based on AAA diameter size is every 6.02 (SD 1.07) years for less than 35 mm, 3.73 (SD 0.80) years for 35-40 mm, 2.09 (SD 0.45) years for 40-45 mm, and 1.16 (SD 0.24) years for 45-50 mm. Recommended timeline for surveillance based on AAA size in different countries can be seen in Table 1.1.

Figures 4.10 through 4.12 illustrate the results of population-based simulation on the optimum designed protocol and protocols that are currently being enforced in 7 different countries; United States, New Zealand, Britain, Sweden, Norway, Italy, and Australia. Life expectancy versus number of surveillances, life expectancy versus number of ruptures, and number of surveillances versus number of ruptures are plotted in three two-dimensional plots. In this simulation 50 mm and 55 mm has been applied as the threshold for surgical intervention. Results from previous simulations proved that sizes larger than 55 (i.e. 60 mm) as the threshold for surgery do not provide a more preventive treatment.

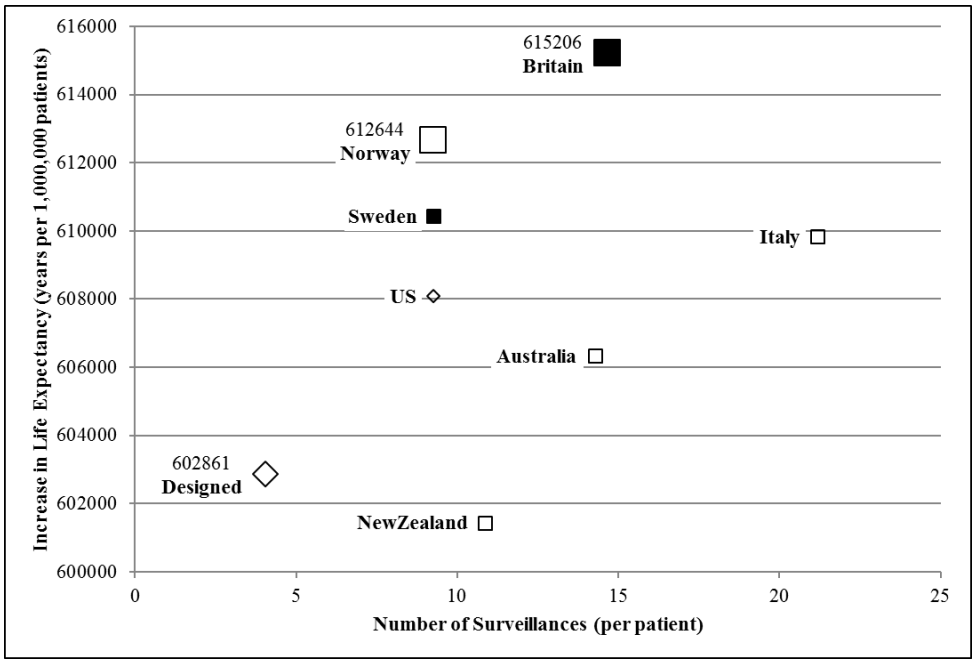

Figure 4.10: Increase in life expectancy versus number of surveillances for 7 countries (larger data points are non-dominated).

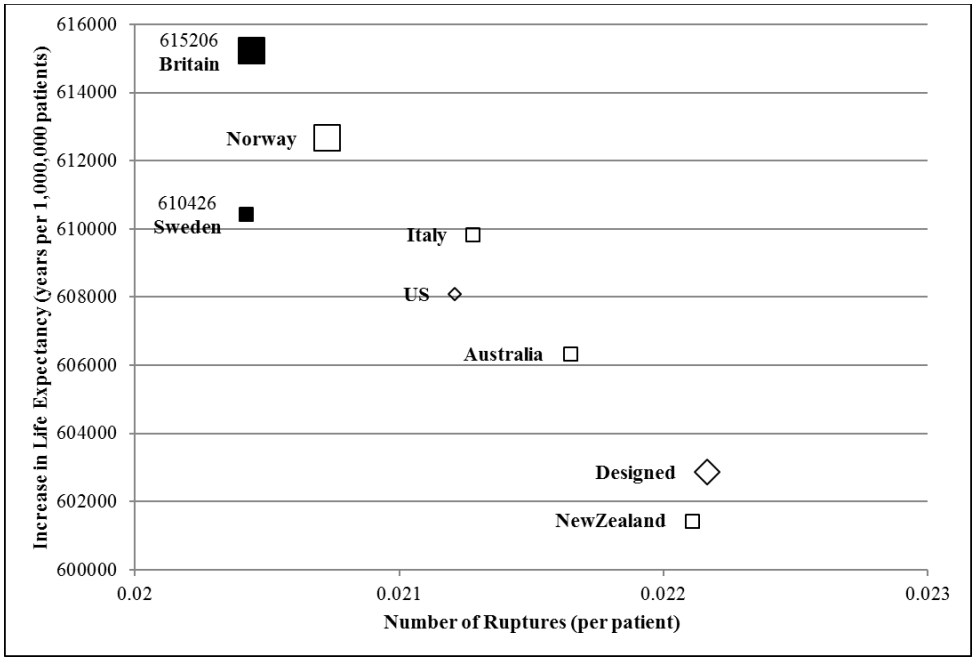

Figure 4.11: Increase in life expectancy versus number of ruptures for 7 countries (filled data points are non-dominated).

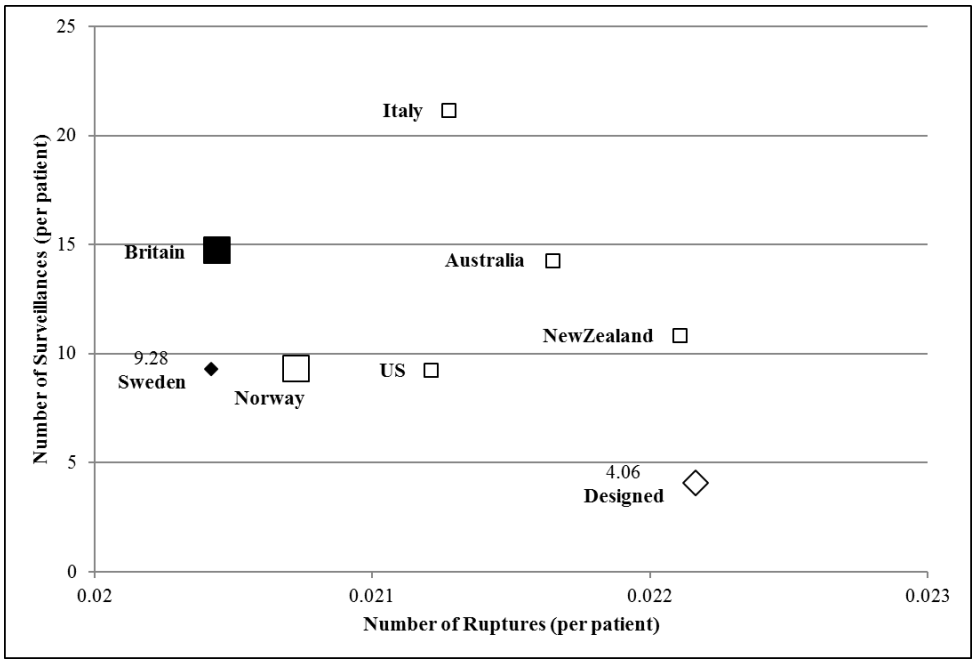

Figure 4.12: Number of surveillances versus number of ruptures for 7 countries (diamond shaped data points are non-dominated).

Results of the population-based simulation that was based on the optimum designed protocol and 7 protocols from different countries, along with their availability on Pareto fronts of Figures 4.10 through 4.12 are summarized in Table 4.5. With a closer attention to the number of ruptures it is obvious that this is irrelevant from the type of protocol that patients go under because the patient's probability of rupture is essentially insensitive to their surveillance protocol. Focusing on the two factors that actually rely on the surveillance protocol (increase in life expectancy and number of surveillances) leaves us with three protocols: the optimum designed protocol from model-based simulation, the surveillance protocol enforced in Britain, and the surveillance protocol followed by patients in Norway.

Table 4.5: Detailed results of population-based simulation.

Protocol	Increase in Life Expectancy per 1000,000 patients (years)	Number of Surveillances per Patients	Ruptures per Patients	Figure 4.10 Pareto front	Figure 4.11 Pareto front	Figure 4.12 Pareto front
Designed	602,861	4.06	0.0222	✓		✓
Britain	615,206	14.69	0.0204	✓	✓	
Sweden	610,426	9.28	0.0204		✓	✓
Australia	606,341	14.29	0.0216		✓	
Norway	612,644	9.28	0.0207	✓		
New Zealand	601,444	10.85	0.0221			
Italy	609,832	21.18	0.0213			
US	608,078	9.27	0.0212			

4.2.2 Patient Benefits by AAA Baseline Size

As it was done for model-based simulation, hypothetical patients were again divided into different groups based on their AAA baseline size, in order to have a greater understanding of which group benefits the most from surveillance protocols (Figure 4.13). Patients with baseline size of 45 mm or higher experienced 4.68 years increase in their life expectancy in average. This number is 2.84 years in patients with baseline size between 40 and 45 mm (39% lower), 0.89 in patients with baseline size between 35 and 40 mm (81% lower), and 0.09 in patients with baseline size less than 35 mm (98% lower). The rationale behind this significant difference has been discussed in section 4.1.3.

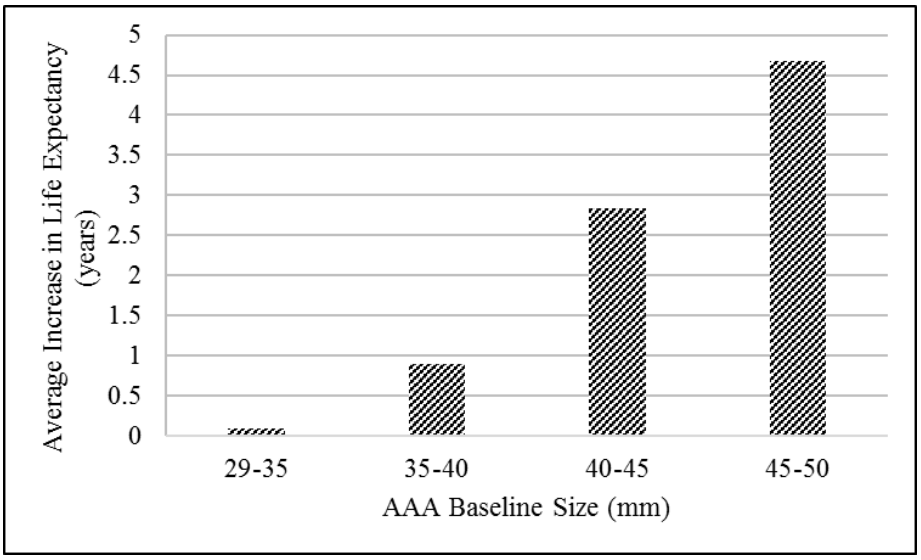

Figure 4.13: Average increase in life expectancy based on AAA baseline size for 7 countries (all scenarios).

The same analysis on number of surveillances was performed with respect to patient's AAA baseline size (Figure 4.14). Patients with baseline size of 45 mm or higher went under 2.55 surveillances on average. Patients with baseline size of 40-45 mm went under 5.54 surveillances (117% higher). This number is 9.62 for patients with baseline size of 35-40 mm (277% higher), and 11.37 for patients with baseline size less than 35 mm (345% higher).

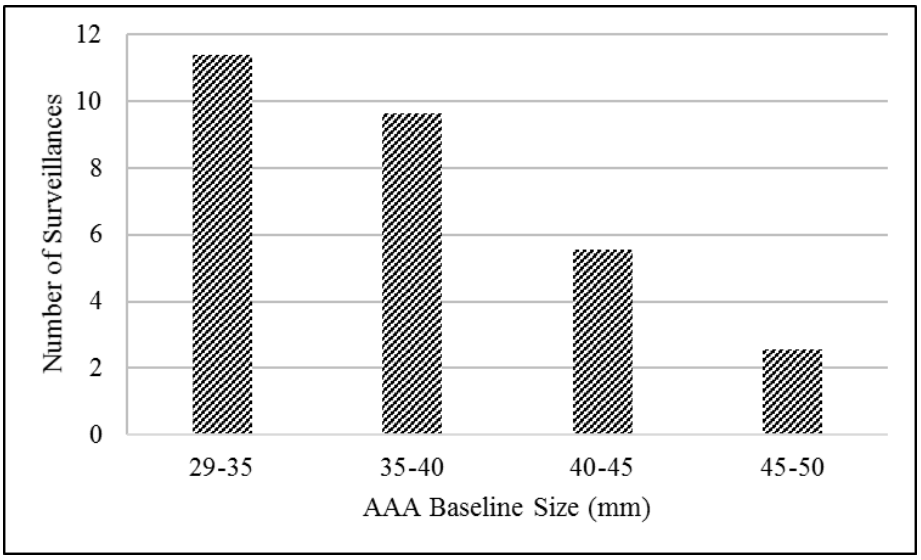

Figure 4.14: Average number of surveillances based on AAA baseline size for 7 countries (all scenarios).

4.2.3 Patient Benefits by Age

Categorizing the results with respect to age in this phase was consistent to model-based simulation. Younger patients benefited more from going under surveillance compared to older patients (Figure 4.15). Average increase in life expectancy for patients younger than 70 years old is 1.02 year. This number is 0.61 for those between 70 and 75, 0.29 for those between 75 and 80, and 0.11 for patients older than 80 years old.

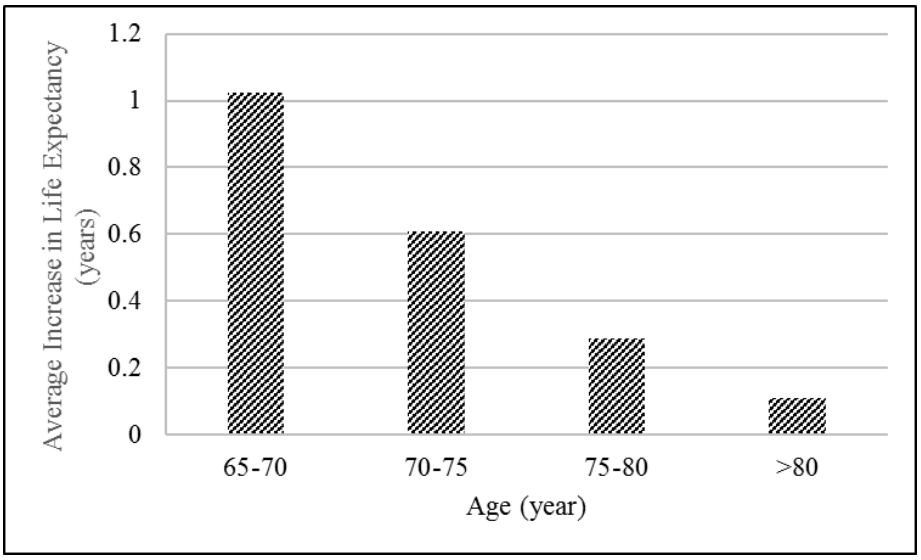

Figure 4.15: Average increase in life expectancy based on age for 7 countries (all scenarios).

Due to time limit, older patients go through fewer number of surveillances. Average number of surveillances is 12.52 for patients under 70, 10.11 for ones between 70 and 75, 6.62 for ones between 75 to 80, and 4.04 for older than 80 (Figure 4.16).

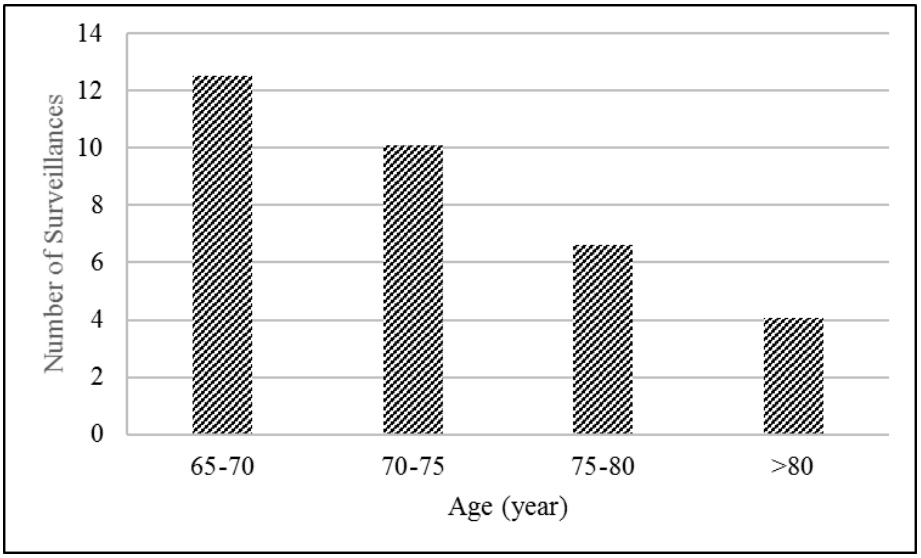

Figure 4.16: Average number of surveillances based on age for 7 countries (all scenarios).

CHAPTER 5

CONCLUSIONS, DISCUSSION, AND FUTURE WORK

5.1 Conclusions

According to the results from model-based simulations (Section 4.1) and population-based simulations (Section 4.2) going under surgery when the AAA diameter measures at least 50 mm increases life expectancy and reduces both the number of surveillances and the number of sudden ruptures. The 50 mm surgical threshold is smaller than the currently recommended threshold of 55 mm in the surveillance polices available in different countries [42]. In the study by Zarins et al. no rupture was seen in the group of patients with AAA size less than 50 mm with the survival of 89% at 5 years while it was 3% of rupture and 73% of survival in patients with AAA size from 50 to 59 mm [43]. Additionally, in a population-based study, Nevitt et al. reported patients with AAA size smaller than 50mm free of rupture in the 5 year follow up despite the 5% annual risk of rupture for patients with AAA size larger than 50mm [44]. Even 3% of rupture is too high because of the high fatality rate upon rupture; waiting for surgery until the AAA is 55 mm increase the overall mortality rate. They also showed that in AAA sizes smaller than 50 mm there are fewer AAA-related deaths, surgical interventions, and secondary interventions. The fewer secondary interventions means that, if there is surgery at 55 mm, a patient is more likely to need a second surgery, but patients who undergo surgery before reaching 50 mm are less likely to need a second

surgery. Another significant factor weighing in for elective surgery (EVAR) in the earlier stage of the surveillance is that surgery was shown to have a better outcome in patients with smaller diameter compared to those with larger diameter [45-46].

The approach should not be either surgery for every patient with AAAs, nor a late surgical intervention which increases the risk of rupture in the patient. Different randomized trials have been conducted to identify the difference between early repair (open surgery or EVAR) and surveillance for patients diagnosed with abdominal aortic aneurysms. However, no significant difference in the outcome was observed [15, 47, and 48]. These studies show that the majority of patients in the surveillance group will go under surgery eventually (61.6% in Laderle et al., 60.9% in Powell et al., and 47.7% after 2 years in Cao et al.). Brewster et al. reported that "early surgery is comparable to surveillance with later surgery, so that patient preference is important, especially for AAA 4.5 cm to 5.5 cm in diameter" [42]. Finding a balance between frequency of the surveillances and the risk of rupture is the key to increase life expectancy while minimizing the number of surveillances. For example, in a recent study based on all AAA patients admitted to hospitals in Sweden in a 4-year period, Zommorodi et al. revealed the deficiency of current surveillance policies in comparison with non-diagnosed patients and recommended more individualized protocols based on patients [49]. We optimized the surveillance policies by quantifying the risk of rupture with respect to size and recommend the surveillance for patients based on patient's unique growth trajectory. We found that the average number of surveillances per patient in the most optimum protocol is 2.72 which show that the increase in the life expectancy of the patients did not increase by redundant surveillances.

5.2 Discussion

This study focused on integrating risk of rupture in decision making for surveillances to overcome the inter-patient variability in AAA growth that is neglected in current protocols offered in different countries. It also has generated a huge population of hypothetical patients to effectively analyze the outcomes like sudden rupture -that cannot be researched on with a large cohort because of ethical and logistical issues- or the correct size for surgical intervention threshold. Despite these efforts, there are always limitations that should be considered.

Using the meta-analysis for our estimate of risk of rupture [7] might be one. Due to the lack of data for patients with AAA size above 50 mm, we used extrapolation to predict the risk associated with larger sizes. Numerous studies confirm the increase in risk of rupture with respect to increase in the AAA size, but assuming a lower rate of increase or even a flat rate from 50 to 60 mm may result in improved outcomes of larger AAA sizes to be considered the surgery threshold [13].

The growth model that was used in this study was limited to a group of patients in Australia [13]. The growth model for Western-Australia in the meta-analysis fits fairly close to the consensus of the whole study cohort, which confirms the credibility of the model and utilization of the rupture risk from the same analysis.

The post-surgery outcomes were simulated with respect to a few assumptions in this study. We assumed that patients are completely cured after the elective surgery and their quality of life has not been affected. This can be a reasonable assumption since Zarins et al. showed higher survival, no rupture, and fewer secondary interventions in patients with AAA sizes above 50 mm [42].

Given the fact of high fatality in AAA ruptures, risking on postponing the repair does not seem to be reasonable. On the other hand, studies showed that early surgical intervention is not preventive. Therefore, a practical surveillance plan with a smaller recommended threshold for surgery and longer surveillance intervals (7 years, 6 years, 3.5 years, 2 years, and 1 year) is less risky and more preventive.

5.3 Future Work

Cost-effective analysis is a potential research that can be conducted on the results of this study. In different sections of this study there are a couple of optimum solutions (protocols) on the Pareto front that one cannot be differentiated as the best protocol, because one is higher in one parameter (i.e. increase in life expectancy), and the other one is more beneficial in another parameter (i.e. number of surveillance). Considering the costs of surveillances in different times of a patient's life, and the cost of surgical intervention, will enable comparing different protocols by their cost, which is an important factor in a patient's decision making.

APPENDIX A

DETAILED TABLE OF RESULTS FOR ALL DESIGNED PROTOCOL

Table A.1: Simulation results for effects of varying the surgical intervention risk for 1 year observation time limit and 50 mm surgery threshold.

Risk of Surgery	0.5%	1%	1.5%	2%	2.5%	3%	4%	5%
Number of Ruptures	143	173	147	169	150	158	173	152
Number of Surgeries	2912	2851	2840	2871	2881	2860	2880	2879
Number of Natural Deaths	6945	6976	7013	6960	6969	6982	6947	6969
Sum of Life Expectancies	6630	6440	6663	6769	6408	6252	6426	6827

Table A.2: Simulation results for effects of varying the surgical intervention risk for 1 year observation time limit and 55 mm surgery threshold.

Risk of Surgery	0.5%	1%	1.5%	2%	2.5%	3%	4%	5%
Number of Ruptures	192	242	187	257	218	212	204	234
Number of Surgeries	2261	2237	2230	2235	2181	2203	2266	2227
Number of Natural Deaths	7547	7521	7583	7508	7601	7585	7530	7539
Sum of Life Expectancies	62012	6533	6309	6286	6195	6166	6429	6329

Table A.3: Simulation results for effects of varying the surgical intervention risk for 1 year observation time limit and 60 mm surgery threshold.

Risk of Surgery	0.5%	1%	1.5%	2%	2.5%	3%	4%	5%
Number of Ruptures	279	298	291	309	293	319	293	275
Number of Surgeries	1872	1836	1786	1776	1776	1761	1763	1794
Number of Natural Deaths	7849	7866	7923	7915	7931	7920	7944	7931
Sum of Life Expectancies	6096	6055	6217	5819	6118	5859	5934	6129

Table A.4: Simulation results for effects of varying the surgical intervention risk for 2 years observation time limit and 50 mm surgery threshold.

Risk of Surgery	0.5%	1%	1.5%	2%	2.5%	3%	4%	5%
Number of Ruptures	158	162	168	152	180	157	180	185
Number of Surgeries	2864	2794	2785	2738	2727	2759	2763	2751
Number of Natural Deaths	6978	7044	7047	7110	7093	7084	7057	7064
Sum of Life Expectancies	6895	6882	6754	6541	6647	6323	6571	6607

Table A.5: Simulation results for effects of varying the surgical intervention risk for 2 years observation time limit and 55 mm surgery threshold.

Risk of Surgery	0.5%	1%	1.5%	2%	2.5%	3%	4%	5%
Number of Ruptures	235	241	243	259	232	266	230	250
Number of Surgeries	2232	2254	2213	2145	2146	2130	2079	2115
Number of Natural Deaths	7533	7505	7544	7596	7622	7604	7691	7635
Sum of Life Expectancies	6344	6503	6446	6529	6340	6434	6378	6188

Table A.6: Simulation results for effects of varying the surgical intervention risk for 2 years observation time limit and 60 mm surgery threshold.

Risk of Surgery	0.5%	1%	1.5%	2%	2.5%	3%	4%	5%
Number of Ruptures	277	268	286	287	320	316	324	336
Number of Surgeries	1841	1866	1833	1810	1769	1730	1678	1701
Number of Natural Deaths	7882	7866	7881	7903	7911	7954	7998	7963
Sum of Life Expectancies	6064	6136	6385	6156	5915	5695	5898	5773

Table A.7: Simulation results for effects of varying the surgical intervention risk for 3 years observation time limit and 50 mm surgery threshold.

Risk of Surgery	0.5%	1%	1.5%	2%	2.5%	3%	4%	5%
Number of Ruptures	170	175	194	163	171	188	195	201
Number of Surgeries	2886	2805	2723	2664	2635	2608	2608	2637
Number of Natural Deaths	6944	7020	7083	7173	7194	7204	7197	7162
Sum of Life Expectancies	6557	6958	6660	6625	6582	6633	6370	6857

Table A.8: Simulation results for effects of varying the surgical intervention risk for 3 years observation time limit and 55 mm surgery threshold.

Risk of Surgery	0.5%	1%	1.5%	2%	2.5%	3%	4%	5%
Number of Ruptures	217	244	234	269	227	269	261	264
Number of Surgeries	2289	2276	2151	2098	2121	2070	2077	2020
Number of Natural Deaths	7494	7480	7615	7633	7652	7661	7662	7716
Sum of Life Expectancies	6319	6545	6382	6272	6114	6215	6144	6312

Table A.9: Simulation results for effects of varying the surgical intervention risk for 3 years observation time limit and 60 mm surgery threshold.

Risk of Surgery	0.5%	1%	1.5%	2%	2.5%	3%	4%	5%
Number of Ruptures	266	280	275	274	302	313	327	339
Number of Surgeries	1857	1848	1771	1773	1793	1748	1669	1702
Number of Natural Deaths	7877	7872	7954	7953	7915	7939	8004	7959
Sum of Life Expectancies	6150	6124	5934	5936	5999	6030	5976	5688

Table A.10: Simulation results for effects of varying the surgical intervention risk for 5 years observation time limit and 50 mm surgery threshold.

Risk of Surgery	0.5%	1%	1.5%	2%	2.5%	3%	4%	5%
Number of Ruptures	168	182	179	173	197	215	242	213
Number of Surgeries	2898	2794	2701	2628	2577	2488	2424	2425
Number of Natural Deaths	6934	7024	7120	7199	7226	7297	7334	7362
Sum of Life Expectancies	6798	6860	6527	6394	6400	6474	6057	6585

Table A.11: Simulation results for effects of varying the surgical intervention risk for 5 years observation time limit and 55 mm surgery threshold.

Risk of Surgery	0.5%	1%	1.5%	2%	2.5%	3%	4%	5%
Number of Ruptures	225	208	215	223	246	212	280	315
Number of Surgeries	2267	2222	2208	2198	2109	2109	2005	1956
Number of Natural Deaths	7508	7570	7577	7579	7645	7679	7715	7729
Sum of Life Expectancies	6354	6334	6356	6466	6522	6277	5968	5912

Table A.12: Simulation results for effects of varying the surgical intervention risk for 5 years observation time limit and 60 mm surgery threshold.

Risk of Surgery	0.5%	1%	1.5%	2%	2.5%	3%	4%	5%
Number of Ruptures	273	308	320	307	330	342	322	313
Number of Surgeries	1894	1822	1768	1758	1754	1714	1731	1684
Number of Natural Deaths	7833	7870	7912	7935	7916	7944	7947	8003
Sum of Life Expectancies	6288	6004	5895	5893	5758	5842	5955	6077

Table A.13: Simulation results for effects of varying the surgical intervention risk for 10 years observation time limit and 50 mm surgery threshold.

Risk of Surgery	0.5%	1%	1.5%	2%	2.5%	3%	4%	5%
Number of Ruptures	174	175	186	191	179	229	241	236
Number of Surgeries	2906	2781	2652	2632	2618	2488	2446	2292
Number of Natural Deaths	6920	7044	7162	7177	7203	7283	7313	7472
Sum of Life Expectancies	5198	5068	5218	4886	5138	4834	4645	4564

Table A.14: Simulation results for effects of varying the surgical intervention risk for 10 years observation time limit and 55 mm surgery threshold.

Risk of Surgery	0.5%	1%	1.5%	2%	2.5%	3%	4%	5%
Number of Ruptures	221	214	226	244	241	262	288	278
Number of Surgeries	2232	2262	2177	2137	2139	2106	2082	1956
Number of Natural Deaths	7547	7524	7597	7619	7620	7632	7630	7766
Sum of Life Expectancies	5160	4856	4979	4597	4766	4754	4664	4604

Table A.15: Simulation results for effects of varying the surgical intervention risk for 10 years observation time limit and 60 mm surgery threshold.

Risk of Surgery	0.5%	1%	1.5%	2%	2.5%	3%	4%	5%
Number of Ruptures	259	291	304	272	303	292	318	351
Number of Surgeries	1894	1819	1797	1791	1784	1770	1701	1700
Number of Natural Deaths	7847	7890	7899	7937	7913	7938	7981	7949
Sum of Life Expectancies	4969	4648	4465	4607	4545	4662	4321	4453

APPENDIX B

R CODES

```
*** This code calculates correlation between elements of square
matrix "x" with size "r" ***

f.correlation <- function(x,r){
    cormatrix <- matrix(nrow=r,ncol=r)
    for (i in 1:r){
        for (j in 1:r) {
            cormatrix [i,j] <- cor(x[,i],x[,j])
        }
    }
    return(cormatrix)
}
```

```
*** This code recalls patients characteristics from original
cohort based on uniformly distributed random numbers ***

f.generate.bdda <- function(x,r,n){
    q <- matrix(ncol=r, nrow=n, 0)
    bdda <- matrix(ncol=r, nrow=n, 0)
    for (i in 1:n) {
                b <- rnorm(r)
            q[i,] <- t(chol(f.correlation(x,r))) %*% b
            q[i,] <- pnorm(q[i,])

        bdda[i,1] <- quantile(x[,1],q[i,1])
        if (q[i,2] < sum(cohort[,2])/299) {
            bdda[i,2] = 1
        }   else {
            bdda[i,2]=0
            }
        bdda[i,3] <- quantile(x[,3],q[i,3])
        bdda[i,4] <- quantile(x[,4],q[i,4])
}
        return(bdda)
}
```

```
*** This code calculates the actual AAA size of the patient ***

f.actual.size <- function(x,m,y,time){
    beta0k = 32.6*x[m,1]/median(x[,1])
    beta1k = y[m,2] + y[m,6]* x[m,1]/median(x[,1]) + y[m,4]*
x[m,3]/median(x[,3])
    beta2k = y[m,3] + y[m,7]* x[m,1]/median(x[,1]) + y[m,5]*
x[m,3]/median(x[,3]) + y[m,8]*x[m,2]
    actual.size = (beta0k+ (beta1k-beta2k*beta0k)/beta2k)*
exp(beta2k*time) - (beta1k-beta2k*beta0k)/beta2k
return(actual.size)
}
```

```
*** This code calculates the modelled AAA size of the patient
***

f.model.size <- function(x,m,y,n,time){
    model.size <- matrix(ncol=n, nrow=1)
    for (i in 1:n){
        beta0k = 32.6*x[m,1]/median(x[,1])
        beta1k = y[i,2] + y[i,6]* x[m,1]/median(x[,1]) + y[i,4]*
x[m,3]/median(x[,3])
        beta2k = y[i,3] + y[i,7]* x[m,1]/median(x[,1]) + y[i,5]*
x[m,3]/median(x[,3]) + y[i,8]*x[m,2]

        model.size[1,i] = (beta0k+ (beta1k-
beta2k*beta0k)/beta2k)* exp(beta2k*time) - (beta1k-
beta2k*beta0k)/beta2k
    }
return(model.size)
}
```

```
*** This code estimates the natural death age of patients based
on their age ***

f.mortality <- function(x,m){
    p <- runif(1)
    n <- 0
    x_0 <- x[m,4]
    x_l <- x[m,4]
    x_u <- 120
    x_m <- (x_l + x_u)/2
    error <- 4.13*10^-7
    epsilon <- 1
    x_m2 <- 0
    f_x_0 <- 1.4672444435E-09*(x_0)^7/7 - 5.8952338424E-
07*(x_0)^6/6 + 9.8293291496E-05*(x_0)^5/5 - 8.7017968341E-
03*(x_0)^4/4 + 4.3130650033E-01*(x_0)^3/3 -
1.1346490352E+01*(x_0)^2/2 + 1.2376134495E+02*(x_0)

    while (epsilon > error)
    {
        f_x_l <- 1.4672444435E-09*(x_l)^7/7 - 5.8952338424E-
07*(x_l)^6/6 + 9.8293291496E-05*(x_l)^5/5 - 8.7017968341E-
03*(x_l)^4/4 + 4.3130650033E-01*(x_l)^3/3 -
1.1346490352E+01*(x_l)^2/2 + 1.2376134495E+02*(x_l) + log(1-p) -
f_x_0
        f_x_u <- 1.4672444435E-09*(x_u)^7/7 - 5.8952338424E-
07*(x_u)^6/6 + 9.8293291496E-05*(x_u)^5/5 - 8.7017968341E-
03*(x_u)^4/4 + 4.3130650033E-01*(x_u)^3/3 -
1.1346490352E+01*(x_u)^2/2 + 1.2376134495E+02*(x_u) + log(1-p) -
f_x_0
        f_x_m <- 1.4672444435E-09*(x_m)^7/7 - 5.8952338424E-
07*(x_m)^6/6 + 9.8293291496E-05*(x_m)^5/5 - 8.7017968341E-
03*(x_m)^4/4 + 4.3130650033E-01*(x_m)^3/3 -
1.1346490352E+01*(x_m)^2/2 + 1.2376134495E+02*(x_m) + log(1-p) -
f_x_0

        if (f_x_m * f_x_l > 0)
            {   x_l <- x_m
            }
        if (f_x_m * f_x_u > 0)
            {   x_u <- x_m
            }

        x_m2 <- (x_l + x_u)/2
        epsilon <- abs((x_m2-x_m)/x_m2)
        x_m <- x_m2
    n <- n+1
```

```
}
mortality.age <- x_m
return(mortality.age)}
```

```
*** This code estimates the age when patients will have rupture
based on their AAA size ***


f.rupture.age <- function(x,y,m){

    p <- runif(1)
    left_side <- -log(1-p)
    beta0k = 32.6*x[m,1]/median(x[,1])
    beta1k = y[m,2] + y[m,6]* x[m,1]/median(x[,1]) + y[m,4]*
x[m,3]/median(x[,3])
    beta2k = y[m,3] + y[m,7]* x[m,1]/median(x[,1]) + y[m,5]*
x[m,3]/median(x[,3]) + y[m,8]*x[m,2]
    dtau <- 1/365
    tau <- 0
    age <- x[m,4]
    right_side <- 0

        while(left_side>right_side & tau <55){
            size_old <- (beta0k + (beta1k-beta2k*beta0k)/beta2k)
* exp(beta2k*tau) - (beta1k-beta2k*beta0k)/beta2k
            rupture_rate_old <- 3.3866666667E-08*(size_old)^4 -
4.4960000000E-06*(size_old)^3 + 2.2863333333E-04*(size_old)^2 -
5.1762000000E-03*(size_old)^1 + 4.3930000000E-02
            tau <- tau + dtau
            size_new <- (beta0k+ (beta1k-beta2k*beta0k)/beta2k)*
exp(beta2k*tau) - (beta1k-beta2k*beta0k)/beta2k
            rupture_rate_new <- 3.3866666667E-08*(size_new)^4 -
4.4960000000E-06*(size_new)^3 + 2.2863333333E-04*(size_new)^2 -
5.1762000000E-03*(size_new)^1 + 4.3930000000E-02
            right_side <- right_side + dtau * (rupture_rate_old
+ rupture_rate_new) / 2
}
    T <- tau - dtau/2
    rupture.age <- x[m,4] + T
    return(rupture.age)
}
```

```
*** This code runs the overall simulation for population-based
protocols and returns results ***

for (i in 1:patients){

    time <- 0
    age <- cohort1[i,4]
    death.age <- f.mortality(cohort1,i)
    rupture.age <- f.rupture.age(cohort1,corposterior,i)
    end.time <- min(death.age,rupture.age)
    actual.x <- cohort1[i,1]
    surveillance <- 0
    d <- 1
    actual.x <- cohort[i,1]

        while (age + time < end.time & actual.x < 55) {

            tau <- 0

            if (actual.x >= 25 & actual.x < 30){
                tau <- 5
            } else if(actual.x >= 30 & actual.x < 35){
                tau <- 3
            } else if(actual.x >= 35 & actual.x < 45){
                tau <- 1
            } else {
                tau <- 0.5
            }

        time <- time + tau
        surveillance <- surveillance + 1

        actual.size <-f.actual.size(cohort1,i,corposterior,time)
        actual.x <- rnorm(1,actual.size,corposterior[i,1])

        surveillance_time[i,d] <- time

        if (age + time < end.time) {
            surveillance_size[i,d] <- actual.x
        }
        d <- d+1

    }
    result[i,1] <- age
    result[i,2] <- death.age
    result[i,3] <- rupture.age
    result[i,4] <- age + time
```

```
    result[i,5] <- surveillance
    result[i,6] <- cohort1[i,1]
}
write.table(result, file="result_timeprotocol_55.csv",
sep=",",row.names= FALSE, col.names=TRUE)
write.table(surveillance_time,
file="surveillance_t_timeprotocol_55.csv", sep=",", row.names=
FALSE, col.names=TRUE)
write.table(surveillance_size,
file="surveillance_s_timeprotocol_55.csv", sep=",", row.names=
FALSE, col.names=TRUE)
```

```
*** This code runs the overall simulation for model-based
protocols and returns results ***

for (i in 1:patients){

    d <- 1
    x_1_i <- x_1[i]
    x_2_i <- x_2[i]
    x_3_i <- x_3[i]
    probability <- matrix(ncol=5000, nrow=1, 1/5000)
    time <- 0
    age <- cohort1[i,4]
    death.age <- f.mortality(cohort1,i)
    rupture.age <- f.rupture.age(cohort1,corposterior,i)
    end.time <- min(death.age,rupture.age)
    actual.x <- cohort1[i,1]
    surveillance <- 0

    while (age + time < end.time & actual.x <55){

        cumulative.risk <- 0
        tau <- 0
        dtau <- 1/4
        integral <- matrix(ncol=5000, nrow=1, 0)

        while (cumulative.risk < 0.005 & tau < 35) {
            cumulative.risk <- 0
            for (j in 1:5000){
                beta0k = 32.6*x_1_i/median_x_1
                beta1k = y_2[j] + y_6[j]* x_1_i/median_x_1 +
y_4[j]* x_3_i/median_x_3
                beta2k = y_3[j] + y_7[j]* x_1_i/median_x_1 +
y_5[j]* x_3_i/median_x_3 + y_8[j]*x_2_i

                size_old <- (beta0k + (beta1k-
beta2k*beta0k)/beta2k) * exp(beta2k*(time + tau)) - (beta1k-
beta2k*beta0k)/beta2k
                rupture_rate_old <- 3.3866666667E-
08*(size_old)^4 - 4.4960000000E-06*(size_old)^3 + 2.2863333333E-
04*(size_old)^2 - 5.1762000000E-03*(size_old)^1 + 4.3930000000E-
02

                size_new <- (beta0k+ (beta1k-
beta2k*beta0k)/beta2k)* exp(beta2k*(time + tau + dtau)) -
(beta1k-beta2k*beta0k)/beta2k
                rupture_rate_new <- 3.3866666667E-
08*(size_new)^4 - 4.4960000000E-06*(size_new)^3 + 2.2863333333E-
```

```
04*(size_new)^2 - 5.1762000000E-03*(size_new)^1 + 4.3930000000E-
02

                integral[j] <- integral[j] + dtau *
(rupture_rate_old + rupture_rate_new) / 2
                cumulative.risk <- cumulative.risk +
probability[j] * ( 1 - exp(-integral[j]))
            }
            tau <- tau + dtau
        }
        time <- time + tau


        surveillance <- surveillance + 1

        actual.size <-
f.actual.size(cohort1,i,corposterior,time)
        model.size <-
f.model.size(cohort1,i,posterior,5000,time)
        actual.x <- rnorm(1, actual.size, corposterior[i,1])
        numerator <- matrix(ncol=5000, nrow=1, 0)
        for (k in 1:5000){
            likelihood <- dnorm(actual.x, model.size[1,k],
posterior[k,1])
            numerator[k] <- likelihood * probability[k]
        }
        denominator <- sum(numerator)
        probability <- numerator/denominator


        surveillance_time[i,d] <- time
        if (age + time < end.time) {
            surveillance_size[i,d] <- actual.x
        }
        d <- d+1

    }

    result[i,1] <- age
    result[i,2] <- death.age
    result[i,3] <- rupture.age
    result[i,4] <- age + time
    result[i,5] <- surveillance
    result[i,6] <- cohort1[i,1]
    result[i,7] <- corposterior[i,2] + corposterior[i,6]*
x_1_i/median_x_1 + corposterior[i,4]* x_3_i/median_x_3
```

```
    result[i,8] <- corposterior[i,3] + corposterior[i,7]*
x_1_i/median_x_1 + corposterior[i,5]* x_3_i/median_x_3 +
corposterior[i,8]*x_2_i


}

write.table(result, file="result_0.005_1_10000_risk.csv",
sep=",",row.names= FALSE, col.names=TRUE)
write.table(surveillance_time,
file="surveillance_t_0.005_1_10000_risk.csv", sep=",",
row.names= FALSE, col.names=TRUE)
write.table(surveillance_size,
file="surveillance_s_0.005_1_10000_risk.csv", sep=",",
row.names= FALSE, col.names=TRUE)
```

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