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Cost-effectiveness Analysis (CEA) for the Early Initiation of Insulin in Type 2 Diabetes Mellitus (T2DM) Patients in Malaysia Using a Discrete Event Simulation (DES) Model

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Abstract

Introduction: Type 2 diabetes mellitus is one of the most common non-communicable diseases in Malaysia. Type 2 diabetes mellitus imposes a large economic burden on the individual and national healthcare system. Ultimately, most type 2 diabetes mellitus patients will eventually need insulin therapy but misconceptions of insulin therapy being only for the end-stage of the disease often limit the early initiation of insulin therapy, even for patients who are already not being adequately controlled by oral glucose lowering drugs. The huge economic burden of type 2 diabetes mellitus can be reduced by implementing inexpensive, easy-to-use interventions such as early initiation of insulin. As such, a comprehensive study is needed to evaluate such interventions.

Objective: The objectives of this pioneer pilot study research are to utilise novel methods in type 2 diabetes mellitus modeling by using the discrete event simulation (DES) based modeling approach and to subsequestly evaluate whether early insulin initiation in patients with type 2 diabetes mellitus is more cost-effective compared to later initiation of insulin from the Ministry of Health's perspective in Malaysia.

Methodology: The analysis was performed using a DES model of people with type 2 diabetes mellitus. The model simulated a cohort of 10000 patients over a 30 year time horizon. Base-case analysis was conducted for early initiation of insulin when insulin is initiated 5 years after diagnosis of type 2 diabetes mellitus compared to late initiation of insulin when insulin is initiated 6 years after diagnosis of type 2 diabetes mellitus. Scenario analyses were conducted to evaluate the robustness of the model.

Results: For the best-case simulations, when insulin is initiated 5 years after the diagnosis of type 2 diabetes mellitus, there are 62,867 complications with a total cost of RM 83,779,605 and when insulin is initiated 6 years after the diagnosis of type 2 diabetes mellitus, there are 16,352 complications and the total cost is RM 84,248,196. For the scenario analyses, simulated patients who were started insulin 7 years after the diagnosis of type 2 diabetes mellitus had a total of 16,356 complications and a total cost of RM 84,106,407 and for the simulation where insulin is initiated 8 years after the diagnosis of type 2 diabetes mellitus, 27,970 complications were obtained with a total cost of RM 84,088,985. When comparing early initiation of insulin at 5 years after diagnosis of type 2 diabetes mellitus against late initiation of insulin when insulin is initiated 6 years after diagnosis of type 2 diabetes

mellitus, the cost for early initiation is lower where the amount saved is RM 468,591. There are also more QALYs gained for early initiation with 543.83 QALYs gain when insulin is initiated at 5 years after diagnosis of type 2 diabetes mellitus. The ICER obtained showed that initiating insulin 5 years after diagnosis of type 2 diabetes mellitus is dominant compared to initiating insulin later at 6 years after diagnosis of type 2 diabetes mellitus.

Conclusion: This pioneer pilot study research has demonstrated that DES based modeling is suitable for type 2 diabetes mellitus modeling and further research should be continued to establish this. The findings provide evidence that initiating insulin 5 years after diagnosis of type 2 diabetes mellitus is dominant compared to initiating insulin later at 6 years after diagnosis of type 2 diabetes mellitus. This evidence should encourage the Ministry of Health to continue with the recommendation that insulin should be initiated earlier for type 2 diabetes mellitus patients in Malaysia.

Declaration

This thesis contains no material which has been accepted for the award of any other degree or diploma at any university or equivalent institution and that, to the best of my knowledge and belief, this thesis contains no material previously published or written by another person, except where due reference is made in the text of the thesis.

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1.1 Disease Burden

1.1.1 Background of Type 2 Diabetes Mellitus

Diabetes mellitus is a disease characterized by elevated blood glucose levels. It is the result of defective insulin secretion or action, or both. The resulting chronic hyperglycaemia is associated with damage to and subsequent dysfunction of various organs, especially the eyes, kidneys, nerves, heart, and blood vessels.[1]

As elaborated in the International Diabetes Federation (IDF) Diabetes Atlas, the most common type of diabetes mellitus is type 2 diabetes mellitus, which accounts for around 90% of all cases of diabetes mellitus. In type 2 diabetes mellitus, hyperglycaemia is the result of an inadequate production of insulin by the pancreas and the inability of the body to respond fully to insulin which is defined as insulin resistance. During a state of insulin resistance, insulin is ineffective and therefore initially prompts an increase in insulin production by the pancreas to lower rising glucose levels but over time a state of reduce production of insulin by the pancreas will eventually develop. Type 2 diabetes mellitus is most commonly seen in older adults but it is increasingly seen in children, adolescents and younger adults due to rising levels of obesity, physical inactivity and poor diet. [2]

The signs and symptoms of type 2 diabetes mellitus include excessive thirst and dry mouth, frequent and abundant urination, lack of energy and extreme tiredness, tingling or numbness in the hands and feet, recurrent fungal infections in the skin, slow healing wounds and blurred vision.[2]

As the onset of type 2 diabetes mellitus is usually slow, the exact beginning is difficult to determine. As a consequence, there is often a long period before it is detected and as many as one-third to one-half of type 2 diabetes mellitus cases in the population may be undiagnosed as they may remain symptomless for many years. When undetected for a long time, the complications of chronic hyperglycaemia may develop. Some type 2 diabetes mellitus patients are first diagnosed only when they present with a complication due to hyperglycaemia such as foot ulcer, change in vison, renal failure or infection.[2]

Although the reasons for developing type 2 diabetes mellitus are still not known, there are several important risk factors, these include obesity, poor diet, physical inactivity, increasing age, family history of diabetes mellitus, ethnicity and poor nutrition during pregnancy affecting the developing child.[2]

1.1.2 Prevalence of Type 2 Diabetes Mellitus

Diabetes mellitus is one of the largest global health emergencies of the 21st century. Diabetes mellitus is among the top 10 causes of death globally and together with the other three major non-communicable diseases (cardiovascular disease, cancer and respiratory disease) account for over 80% of all premature deaths caused by non-communicable diseases.[2]

According to the International Diabetes Federation (IDF) Diabetes Atlas, in 2017, some 425 million people worldwide, or 8.8% of adults 20-29 years old, are estimated to have diabetes mellitus. About 79% of them live in low and middle income countries. The number of people afflicted with diabetes mellitus increases to 451 million if the age is expanded to 18-99 years old. If these trends continue, by 2045, 693 million people 18-99 years old, or 629 million people 20-79 years old, will develop diabetes mellitus. The biggest increases will be in regions of the world where countries are moving from low income to middle income economies.[2]

In the Western Pacific Region where Malaysia is located, in 2017, 9.5% of adults aged 20-79 years old are estimated to be living with diabetes mellitus which is equivalent to 158.8 million people. Over half (54%) of them are undiagnosed, 63.8% of people with diabetes mellitus live in cities and 90.2% of people with diabetes mellitus live in low or middle income countries. The Western Pacific Region is home to 37.4% of the total number of people having diabetes mellitus in the world.[2]

Globally, there are 326.5 million people in the working age group (20-64 years old) who have diabetes mellitus, and 122.8 million people 65-99 years old with diabetes mellitus. The number of people of working age with diabetes mellitus is expected to increase to 438.2 million, and the number of people with diabetes mellitus 65-99 years old will increase to 253.4 million in 2045.[2]

Roughly around 4 million people aged between 20 and 79 years old are estimated to die from diabetes mellitus in 2017. This is equivalent to one death happening every eight seconds. Diabetes mellitus accounted for 10.7% of global all-cause mortality among people in this age

group. This is higher than the total number of deaths caused by infectious diseases. About 46.1% of deaths due to diabetes mellitus among the 20-79 years old age group are in people under the age of 60 years old. For the Western Pacific Region, this estimate is 38.0% with 1.3 million deaths among adults (11% of all mortality). The Western Pacific Region has the highest number of deaths due to diabetes mellitus in the world.[2]

For Malaysia, The International Diabetes Federation (IDF) Diabetes Atlas reports that in 2017 the diabetes related deaths (20-79 years old) is 22,321 deaths.[2]

1.1.3 Economic Burden of Type 2 Diabetes Mellitus

The International Diabetes Federation (IDF) Diabetes Atlas reports that despite the human burden characterised by premature death and lower quality of life due to complications of diabetes mellitus, it imposes a significant economic impact for countries, healthcare systems, and above all, for individuals with diabetes mellitus themselves and also their families. The global healthcare expenditure for diabetes mellitus has grown enormously from USD 232 billion in 2007 to USD 727 billion in 2017 for those aged 20-79 years old. When using the expanded age group of 18-99 years old, the costs totalled a staggering USD 850 billion.[2]

The economic burden of diabetes mellitus is expected to continue to balloon to USD 776 billion by 2045 (20-79 years old) which represents a 7% growth. When using the 18-99 years old age group, the total spending for diabetes mellitus is expected to reach up to USD 958 billion.[2]

Expenditure for diabetes mellitus has a significant impact on healthcare budgets worldwide. In 2017, the spending for diabetes mellitus in the Western Pacific Region (20-79 years old) was USD 120.3 billion which corresponds to 17% of the total global spending. As for the percentage of the national health sector budget spent on diabetes mellitus, on average 10% of the total healthcare budget was allocated to diabetes mellitus in the Western Pacific Region.[2]

For Malaysia, according to the International Diabetes Federation (IDF) Diabetes Atlas, in 2017, the mean diabetes-related expenditure per person (20-79 years) with diabetes is USD 625.[2] A recently published paper estimated that the total cost of diabetes mellitus as RM 2.04 billion per year for year 2011 (both public and private sector). Of this, RM 1.40 billion per year was incurred by the government.[3]

1.1.4 Type 2 Diabetes Mellitus in Malaysia

The prevalence of type 2 diabetes mellitus in Malaysia continues to increase at an alarming rate from 1-2% in the 1960s and 1970s, 6.3% in 1986 (NHMS I), 8.2% in 1996 (NHMS II), to 14.9% in 2006 (NHMS III). More recent studies have indicated that the prevalence has risen to beyond 20%.[4] The most recent National Health and Morbidity Survey (NHMS) conducted by the Ministry of Health in 2015 has shown a prevalence of 17.5 % of the adult population.[5]

This is collaborated by estimates from the International Diabetes Federation (IDF) Diabetes Atlas which states the national prevalence for Malaysia in 2017 (20-79 years old) as 16.9%.[2]

1.1.5 Type 2 Diabetes Mellitus Complications and Economic Burden

As described by the International Diabetes Federation (IDF) Diabetes Atlas, when not well managed, diabetes mellitus can lead to a myriad of complications in many parts of the human body, resulting in frequent hospitalisations and premature death. People afflicted with diabetes mellitus have a higher risk of getting a number of serious life-threatening health problems which increases costs of medical care and lowering quality of life.[2]

Continuously high blood glucose levels cause generalised vascular damage affecting the heart, eyes, kidneys and nerves. Diabetes mellitus is one of the main causes of cardiovascular disease, blindness, kidney failure and lower-limb amputation.[2]

Complications of diabetes mellitus can be divided into acute and chronic complications. Acute complications include hypoglycaemia, diabetic ketoacidosis, hyperglycaemic hyperosmolar state, hyperglycaemic diabetic coma, seizures or loss of consciousness and infections. Chronic complications can be further divided into microvascular complications such as nephropathy, neuropathy and retinopathy and macrovascular complications such as coronary artery disease, leading to angina or myocardial infarction, peripheral artery disease contributing to stroke, diabetic encephalopathy and diabetic foot.[2]

Overall, it is estimated that every year 14 to 47 per 1,000 middle-aged people with diabetes mellitus (50-69 years old) living in high and middle income countries suffer a cardiovascular disease event. Among these, 2-26 per 1,000 are coronary artery disease events, and 2-18 per 1,000 are strokes. People afflicted with diabetes mellitus are two to three times more likely to develop cardiovascular disease than people who do not have diabetes mellitus.

Cardiovascular disease is a major reason for death and disability in people with diabetes mellitus. In middle-aged people with type 2 diabetes mellitus living in high and middle income countries, up to 27 people out of 1,000 die from cardiovascular disease every year; a third of them die from stroke, a quarter die from coronary artery disease. Cardiovascular disease takes up a significant part of diabetes resources nationally. Based on US data, 20% of all inpatient days and 15% of physician office visits are due to this chronic complication of diabetes mellitus. Moreover, cardiovascular disease related care represents the largest proportion of diabetes mellitus health spending: one out of four diabetes mellitus inpatient costs are a consequence of cardiovascular disease, and 15% of costs of physician office visits are related to cardiovascular disease. At the same time diabetes mellitus is responsible for more than a quarter of all cardiovascular disease spending. On average, people who have diabetes mellitus have medical expenditures approximately two-fold more than what expenditures would be in the absence of diabetes mellitus. For the cost categories analysed, care for people who have diabetes mellitus accounts for more than one in five healthcare dollars in the US, and more than half of that spending is directly attributable to diabetes mellitus. The situation is similar in low and middle income countries where based on a global study which included 23 low and middle income countries, it was estimated that USD 84 billion of gross domestic product (GDP) was lost due to cardiovascular disease and diabetes from 2005 to 2015.[2]

Diabetic eye disease occurs as a direct result of persistently high blood glucose levels causing damage to the capillaries of the retina, leading to leakage and blockage of the capillaries. It may lead to loss of vision and eventually blindness. The spectrum of diabetic eye disease comprises diabetic retinopathy, diabetic macular oedema, cataract, glaucoma, loss of focussing ability, and double vision. Loss of vision due to diabetic retinopathy is the main cause of vision loss in working-age adults (20-65 years old) and approximately one in three people living with diabetes mellitus have some degree of diabetic retinopathy and one in ten will develop a vision threatening form of the disease. As per the estimates of the International Association on the Prevention of Blindness (IAPB), 145 million people had some form of diabetic retinopathy and 45 million people suffered from vision threatening diabetic retinopathy in 2015. The prevalence of any retinopathy in persons with diabetes mellitus is 35% while proliferative (vision threatening) retinopathy is 7%. Diabetic eye disease has a significant impact on people's quality of life and was associated with a decrease in physical wellbeing. Globally, 64% of people with diabetic macular oedema and 58% with diabetic eye

disease have limitations on performing activities of daily living compared to 37% of those without diabetic eye disease. Besides the burden for people with diabetes, diabetic eye disease is also responsible for significant healthcare spending.[2]

Chronic kidney disease among patients with diabetes mellitus can be true diabetic nephropathy, but also can be caused indirectly by diabetes mellitus due to mostly to hypertension, but also polyneuropathic bladder dysfunction, increased incidence of relapsing urinary tract infections or macrovascular angiopathy. Worldwide data shows a range of 20% in the UK, 40% in the US and between 12% to 55% from a 54 countries pooled data of people with diabetes developing chronic kidney disease and end stage renal disease. It has also been found that the prevalence of end stage renal disease is up to 10 times higher in people with diabetes compared to those without. As with other diabetes mellitus related complications, kidney disease is associated with significant additional health spending for people with diabetes mellitus.[2]

Neuropathy is a frequently encountered complication of diabetes mellitus where the nerves are damaged by high blood glucose. Nerve damage can lead to numbness, ulceration, serious infections and amputations of the feet (diabetic foot) and also affect autonomic, motor and sensory functions throughout the body resulting in erectile dysfunction, digestive, urinary and cardiac autonomic problems. Diabetic foot is a severe chronic complication with a prevalence of between 16% to 66%. Amputation in people with diabetes mellitus is 10 to 20 times more common compared to non-diabetic people. The incidence of diabetic foot is increasing due to the increased prevalence of diabetes and the prolonged life expectancy of diabetic patients. Diabetic foot complications are among the most serious and costly complications for diabetes mellitus. In 2007, one-third of diabetes mellitus costs were estimated to be linked to foot ulcers. Compared to people with diabetes mellitus without foot ulcers, the cost of care for people with diabetes mellitus and with foot ulcers is 5.4 times higher in the year of the first episode and 2.6 times higher in the year of the second episode. Moreover, among patients with foot ulcers, costs for treating those with highest grade ulcers were eight times higher compared to treatment of the lowest grade foot ulcers.[2]

1.1.6 Rationale for Health Economic Analysis of Early Insulin Initiation

The importance of glycaemic control in reducing or delaying microvascular and other complications of type 2 diabetes mellitus is well-established. The Diabetes Control and Complications Study demonstrated that good metabolic control, resulting from intensive

insulin therapy, reduces the risk of progression or development of retinopathy, nephropathy and neuropathy in type 1 diabetes mellitus.[6] Similarly, the United Kingdom Prospective Diabetes Study (UKPDS) and other studies have shown that intensive glycaemic control in type 2 diabetes mellitus significantly reduces the risk of microvascular complications,[7,8] and may improve cardiovascular outcomes over a 14-year period.[8]

Therefore, one of the main goals of the management of type 2 diabetes mellitus is the attainment of near normoglycaemia. Consequently, the current standard goals of care for managing type 2 diabetes mellitus are quite rigorous. The American Association of Clinical Endocrinologists (AACE) recommends a target HbA1c $\leq$ 6.5% while the American Diabetes Association (ADA) recommends an HbA1c target of < 7.0%.[9,10] (< 7.0% in general and $\leq$ 6.5% in the individual patient if obtained without unacceptable side effects).

In the recent update to their 2012 joint position statement on the management of hyperglycaemia in patients with type 2 diabetes mellitus, the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) have taken into account the many antihyperglycaemic drugs currently available in the world. In this 2015 update, both organisations continue to stress on the need for personalised treatment targets and treatment strategies with emphasis on patient-centered care and shared decision making. In most patients, the management begins with lifestyle changes with metformin monotherapy added at, or soon after diagnosis. If the HbA1c target is not achieved after 3 months, one of the six treatment options in combination with metformin can be chosen - a sulfonylurea, thiazolidinedione (TZD), dipeptidyl peptidase 4 (DPP-4) inhibitor, sodium-glucose cotransporter 2 (SGLT2) inhibitor, glucagon-like peptide 1 (GLP-1) receptor agonist or basal insulin. Drug of choice is based on patient preference as well as various patient, disease, and drug characteristics, with the goal being to reduce glucose concentrations while minimising side effects, especially hypoglycaemia. If the HbA1c target is still not achieved after 3 months, triple therapy can then be considered. Insulin has the advantage of being effective where other agents may not be and should be considered as part of any combination regimen with basal insulin such as NPH, glargine, detemir and degludec being the normal basal insulins to initiate. [11]

Insulin treatment is the cornerstone of diabetes mellitus management. It is the only means of achieving glycaemic control in insulin-deficient subjects with type 1 diabetes mellitus. Insulin is also used as an intermittent or permanent therapeutic modality in subjects with type

2 diabetes mellitus. It is the only effective treatment for many subjects with type 2 diabetes mellitus when deterioration of beta cells has progressed to the point that diet, exercise and oral agents cannot achieve adequate metabolic control. Ultimately, most type 2 diabetes mellitus patients will eventually need insulin therapy but misconceptions of insulin therapy being only for the end-stage of the disease often limit the early initiation of insulin therapy, even for patients who are already not being adequately controlled by oral glucose lowering drugs. From the treating doctors perspective, there are beliefs that insulin therapy may not be effective, may result in weight gain, may increase the risk of hypoglycaemia, is inconvenient and painful to patients and will result in patient dissatisfaction. On the other hand, patients have concerns about being stigmatised, about the efficacy and safety of insulin, about weight gain about interference with activities of daily living and about the costs and access to treatment. Patients also tend to believe that insulin therapy causes late-stage diabetes complications, is an indication of imminent deterioration or death and is a punishment for their failure to take good care of themselves.[12,13]

The United Kingdom Prospective Diabetes Study (UKPDS), UKPDS 49 study estimated that >60% of type 2 diabetes mellitus patients would require insulin within 5 years of diagnosis while the UKPDS 57 study showed that 53% of type 2 diabetes mellitus patients would require insulin by 6 years. [14,15]

Two studies from the UK looking at the management of type 2 diabetes mellitus in primary care found that despite patients being not adequately controlled on oral glucose lowering drugs, the average time spent on monotherapy was 3.8 years and even after failing to achieve glycaemic control with two or more oral glucose lowering drugs the median time before commencing insulin therapy was 7.7 years from initiation of the final oral glucose lowering drug.[16,17]

Based on the above two studies in the UK, a modelling study was conducted to look at the delay in insulin initiation and the potential consequences by using a computer simulation model of long term type 2 diabetes mellitus progression. The aim of the analysis was to compare the difference in projected life-time clinical outcomes for patients immediately initiating versus delaying initiation of insulin. The results of the analysis showed that by improving glycaemic control earlier versus later leads to an increase in mean life expectancy of over 7 months.[18]

Basal insulin is the preferred insulin to be started and it is recommended by most guidelines. Most basal insulin algorithms start with 10 unit or 0.2 units/kg and titrate once or twice weekly at 1 to 2 units each time to achieve a target blood glucose between 3.9 and 7.2 mmol/L.[19]

Oral glucose lowering drugs comprise the mainstay of treatment for patients with type 2 diabetes mellitus in Malaysia. The majority of patients receiving treatment have suboptimal glycaemic control, often as a result of treatment inertia with lack of optimisation of oral medications and delay in insulin initiation. Insulin use in the management of type 2 diabetes mellitus is still seriously lacking especially in primary care. Currently, insulin therapy is used in an estimated 20% of outpatients with type 2 diabetes mellitus in the Ministry of Health facilities, noted from a survey done by the Institute of Health Management in 2008. This has increased compared to 13% in a similar survey by IHM in 2005. The National Medicines Use Survey in 2006 reported that insulin therapy contributed to only 8.2% of overall anti-diabetic drug utilisation in the country. These figures represent low rates of insulin use when compared to other countries. The National Medicines Use Survey also showed that insulin use was far greater in the public sector compared to the private sector reflecting the burden of patients seen and managed by the public sector.[3] The DiabCare Malaysia 2008 study showed that insulin prescriptions have almost doubled as compared to 2003 where insulin alone (15.4% in 2008 vs. 12.7% in 2003 and insulin + oral glucose lowering drugs (38.3% in 2008 vs. 14.4% in 2003).[20]

The increase in insulin initiation in Malaysia is expected to rise with the roll out of the Clinical Practice Guidelines by the Ministry of Health in 2009 which recommended earlier use of insulin therapy in type 2 diabetes mellitus patients with sub-optimal glycaemic control either at presentation or with failure of oral anti-diabetic agents. Subsequently, the Ministry of Health also published a Practical Guide for Insulin Therapy in 2011 to provide a clear and concise approach to all health care providers on current concepts in the use of insulin in type 2 diabetes mellitus. In 2015, the Ministry of Health updated the Clinical Practice Guidelines and continues to recommend earlier use of insulin therapy in type 2 diabetes mellitus patients.

There are numerous clinical studies conducted outside Malaysia that have provided the evidence showing that early initiation of insulin is more beneficial than adding two or more oral glucose lowering drugs in type 2 diabetes mellitus patients who are poorly controlled. Consistent with these studies, a study involving Malaysian type 2 diabetes mellitus patients

showed that initiating insulin therapy is a safe and more effective way to improve glycaemic control in patients inadequately controlled with oral monotherapy or oral combination therapy compared with optimising oral combination therapy alone.[21]

1.2 Disease Modeling

1.2.1 Health Economic Modelling in Diabetes Mellitus

The fundamental purpose of a health economic model is to evaluate the expected costs and outcomes of a decision (or a series of decisions) about the use of a pharmacotherapy compared with one or many alternatives. Decision modeling provides an excellent framework for developing estimates of these outcomes in a flexible analytic framework that allows the investigator to test many alternative assumptions and scenarios. In addition to providing an "answer" to a specific health economic decision, one of the major advantages of having a model of a particular decision is that the model can provide significant information regarding how the answer changes with different basic assumptions, or under different conditions. It is this ability to evaluate multiple "what if" scenarios that provides a substantial amount of the power of health economic modeling.[22]

In a cost-containment environment, economic evaluations are increasingly used to inform decision makers about the relative value of alternative treatment strategies.[23] Modeling techniques are especially useful to model long-term costs and outcomes such as for a chronic disease like type 2 diabetes mellitus), to forecast beyond the follow-up period of a clinical trial, or to consider other relevant endpoints or comparators.[24]

A review paper looking at the methods used in long-term cost-effectiveness models of diabetes mellitus treatment identified 17 studies for discussion. Out of the 17 studies reviewed, two studies modelled type 1 diabetes mellitus only (12%), 12 modelled type 2 diabetes mellitus populations only (71%) and three modelled both type 1 diabetes mellitus and type 2 diabetes mellitus (18%). More than half (59%) of the studies dealt with newly diagnosed patients. Almost one-third (29%) of studies modelled a prevalent population and 12% of the models had the ability to model both prevalent and incident populations. Almost three-quarters of the models (71%) allowed for the estimation of both cost-effectiveness and cost-utility analysis. The vast majority of the studies used a lifetime perspective. The type 2 diabetes mellitus models used mainly the UKPDS study as data sources for modeling type 2

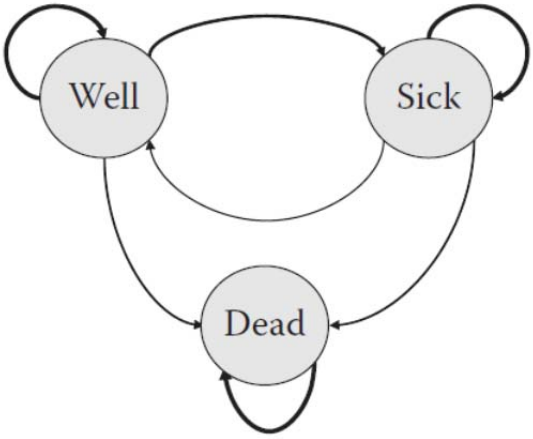
diabetes mellitus-related mortality, macrovascular complications and microvascular complications.[23]

1.2.2 Markov Models

Markov models are generally suited to model the progression of chronic diseases. The disease in question is divided into distinct states and transitions probabilities are assigned for movement between these states over a discrete time period (Figure 1). By attaching estimates of resource use and health outcomes consequence to the states and transitions in the model, and then running the model over a large number of cycles, it is possible to estimate the long term costs and outcomes associated with a disease and a particular healthcare intervention.[25]

However, despite the wide application of Markov models, an important limitation of Markov models is the property of so-called “lack of memory" property. This means that the probability of moving from one state to another does not take into account the history of the patient before he or she arrives in that state. This is also referred to as the Markovian assumption. Another limitation of Markov models is lack of the flexibility required to appropriately represent clinical reality especially in some particular diseases such as schizophrenia and diabetes mellitus. For example, as Markov model requires all aspects of a disease to be denoted by a “health state”, it forces the investigator to consider features which are naturally continuous as discrete, such as weight changes to be modeled as binary (Yes/No) rather than the actual amount of weight change, disease severity, Positive and Negative Syndrome Scale for Schizophrenia (PANSS), and so on. To account for this continuous nature of those parameters, an explosive number of health states will be needed for a Markov model to approximate reality. For instance, 40 states are required just to reflect weight changes of ±40 pounds in increments of 2 pounds. This problem is compounded if the implications of the state change over time, as each instance then generate a new state. Further, if we want to take into account for more of patients’ baseline characteristics such as age, gender and social-economic status, it will lead to an explosive number of health states. A similar proliferation is imposed if the subsequent course of the disease depends on previous history, which is usually the case for diabetes mellitus.

Figure 1: Example of Markov Model



1.2.3 Discrete Event Simulation (DES) Models

Discrete event simulation (DES) (Figure 2) is a form of computer based modeling that provides an intuitive and flexible approach to representing complex systems. It has been used in a wide range of healthcare applications ranging from analysing systems with constrained resources to identifying ways to improve healthcare delivery to conducting health technology assessments.

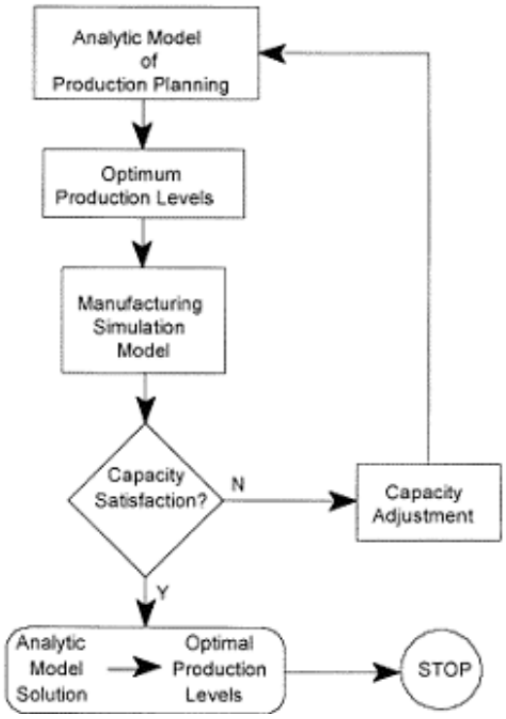
One of the problems with Markov models is that they cannot easily model the competition for resources. Therefore, although a decision analysis or a cost-effectiveness analysis might be able to determine that a particular therapeutic strategy should be adopted, these analyses cannot tell whether the resources, delivery systems, geographic constraints, or other problems allow for the optimal strategy to actually be implemented. DES provides the modeller with a set of tools that can represent queues, resource limitations, geographic distribution, and many other physical structures or limitations that constrain the implementation of a particular strategy or therapy.[22]

DES models serve as a useful technique to circumvent the aforementioned limitations as it allows individual-level modeling, capturing heterogeneity in disease progression and other outcomes.[26,27,28] DES modeling technique has been embedded within cost-effectiveness model to assist healthcare decision making in a number of disease areas such as laparoscopic surgery[29], gastric cancer[30], renal diseases[31], drug abuse[32], HIV transmission[33], early breast cancer[34,35], liver transplants[36] and diabetes mellitus[37,38] .

The advantages of discrete event simulation models are important for modeling disease outcomes as it avoids the need to oversimplify the disease by, for example, assuming patient to transition into another health state at discrete time intervals such as at 1 month and at 3 months, and thus masking the potential benefits of treatment with proliferated number of health states that might make the model overly complex and development of transition matrices impractical. The discrete event simulation modeling approach also allows for each event to be captured in a more "realistic" manner through an event-driven approach compared to traditional decision tree or Markov models which is a cycle-driven approach. By allowing individuals to be simulated, each with their own unique attributes (i.e. risk factors) that are updated throughout the simulation, discrete event simulation model not only allows for more precise projections of patient experience but is also computationally efficient because it does not need continuous processing of patients – patients are updated only when events of relevance occur.

In a systematic literature review conducted on twenty-two publications involving empirical and non-empirical studies comparing Markov models and DES models used in the cost-effectiveness analysis (CEA) of healthcare technologies, it was found that the primary advantages described for DES models over Markov models were the ability to model queuing for limited resources, capture individual patient histories, accommodate complexity and uncertainty, represent time flexibility, model competing risks, and accommodate multiple events simultaneously. The disadvantages of DES models over Markov models were the potential for model overspecification, increased data requirements, specialised expensive software, and increased model development, validation, and computational time. The authors concluded that where individual patient history is an important driver of future events an individual patient simulation technique like DES may be preferred over Markov models. Where supply shortages, subsequent queuing, and diversion of patients through other pathways in the healthcare system are likely to be drivers of cost-effectiveness, DES modeling methods may provide decision makers with more accurate information on which to base resource allocation decisions.[39]

Figure 2: Example of discrete event simulation (DES) model



The recently developed PRIME Diabetes Model for type 1 diabetes mellitus is a good example of discrete event simulation based modeling that runs as a patient-level simulation, making use of covariance matrices for cohort generation and risk factor progression, and simulating myocardial infarction, stroke, angina, heart failure, nephropathy, retinopathy, macular oedema, neuropathy, amputation, hypoglycaemia, ketoacidosis, mortality, and risk factor evolution. Several approaches novel to type 1 diabetes mellitus modeling were used, including patient characteristics and risk factor covariance, a glycated haemoglobin progression model derived from patient-level data, and model averaging approaches to evaluate complication risk.[40]

1.2.4 Cost-effectiveness Analysis

Cost-effectiveness analysis (CEA) provides a framework to compare two or more decision options by examining the ratio of the differences in costs and the differences in health effectiveness between options. The overall goal of CEA is to provide a single measure, the incremental cost-effectiveness ratio (ICER), which relates the amount of benefit derived by making an alternative treatment choice to the differential cost of that option.[22]

Cost-utility analysis (CUA) is a special case of CEA, where the numerator of the ICER is a measure of cost and the denominator is measured typically using a metric called the quality-

adjusted life year (QALY). A QALY accounts for both survival and quality of life (QoL) benefits associated with the use of a healthcare technology. The QoL component of the QALY is measured using a metric known as a health utility.[22]

Equation 1: ICER

$$ICER = \frac{(cost\ of\ option\ 1 - cost\ of\ option\ 2)}{(QALY\ of\ option\ 1 - QALY\ of\ option\ 2)}$$

1.3 Summary of Introduction

Type 2 diabetes mellitus has undoubtedly proven to be an enormous burden that imposes a significant economic impact for countries, healthcare systems, and above all, for individuals with type 2 diabetes mellitus themselves and also their families. Ultimately, most type 2 diabetes mellitus patients will eventually need insulin therapy but misconceptions of insulin therapy being only for the end-stage of the disease often limit the early initiation of insulin therapy, even for patients who are already not being adequately controlled by oral glucose lowering drugs. The huge economic burden of type 2 diabetes mellitus can be reduced by implementing inexpensive, easy-to-use interventions such as early initiation of insulin. As such, a comprehensive study is needed to evaluate such interventions. A discrete event simulation model is the most appropriate modelling method for this purpose based on the advantages discussed in section 1.2.3 above.

1.4 Aim and Objectives

1.4.1 Main Aim

This is a pioneer pilot study research with the main aim of evaluating the cost-effectiveness of the early initiation of insulin in type 2 diabetes mellitus patients in Malaysia using a discrete event simulation (DES) model.

1.4.2 Specific Objectives

The specific objectives of this pilot study are :

1. To utilise novel methods in type 2 diabetes mellitus modeling by using the discrete event simulation (DES) based modeling approach.

2. To evaluate whether early insulin initiation in patients with type 2 diabetes mellitus is more cost-effective compared to later initiation of insulin from the Ministry of Health's perspective in Malaysia.

Chapter 2 Methodology

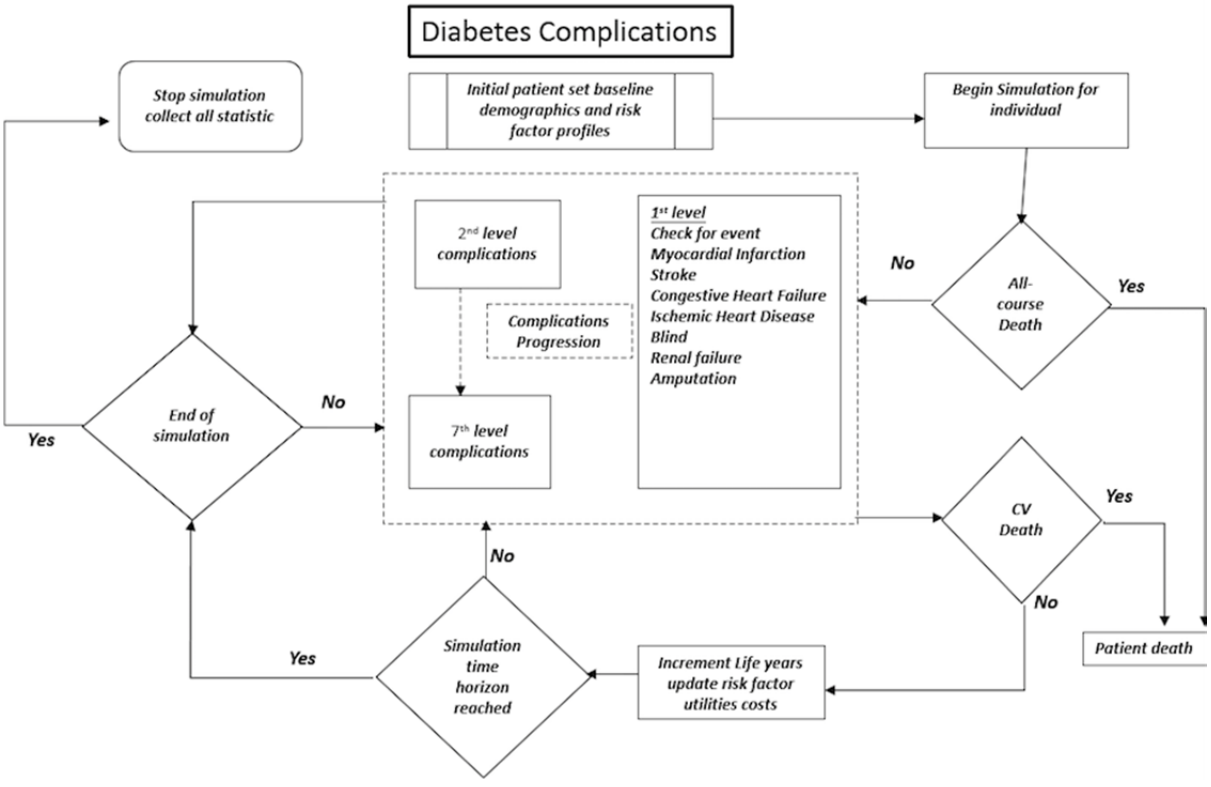
2.1 Model Structure

The purpose of this analysis is to assess the cost-effectiveness and cost-utility for the early initiation of insulin in type 2 diabetes mellitus patients in Malaysia. For the purpose of this analysis, the comparison is between initiation of insulin at year 5 and year 6 based on published data from the UKPDS studies UKPDS 49 and UKPDS 57. The UKPDS 49 study estimated that >60% of type 2 diabetes mellitus patients would require insulin within 5 years of diagnosis[16] while the UKPDS 57 study showed that 53% of type 2 diabetes mellitus patients would require insulin by 6 years.[15]

Calculations performed in this analysis will enable the assessment of cost-effectiveness from the perspective of the Ministry of Health for the early initiation of insulin for the treatment of type 2 diabetes mellitus, versus later initiation of insulin.

The analysis was performed using a discrete event simulation (DES) model of people with type 2 diabetes mellitus. The software used to generate the model is Flexsim (Flexim Software Products, Inc). The flow diagram of the model is illustrated below (Figure 3).[41]

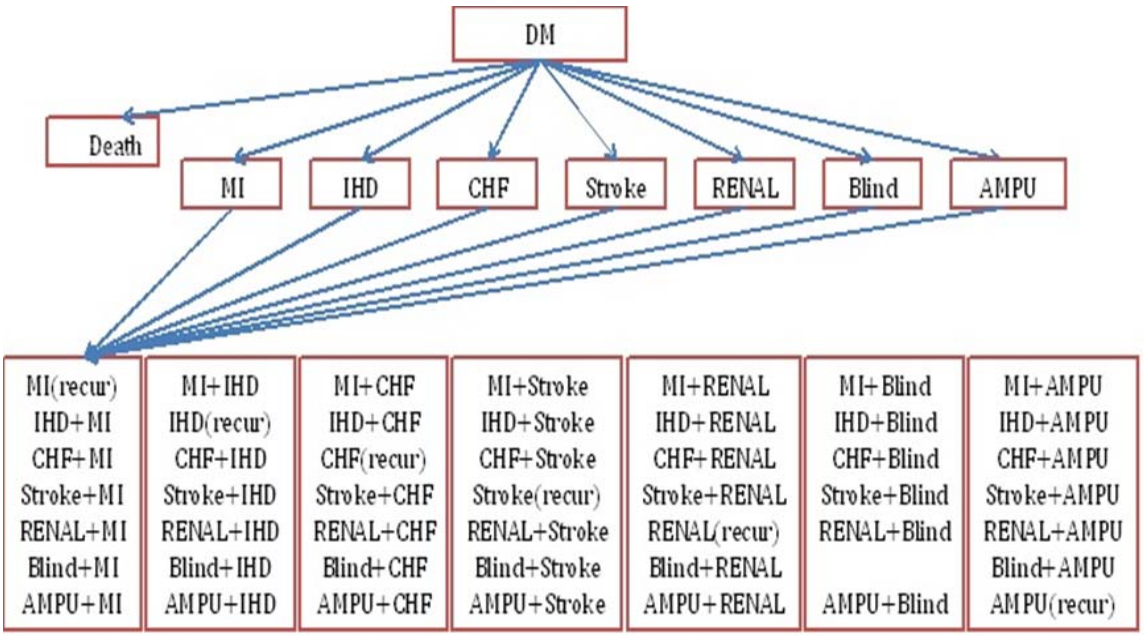
Figure 3: Flow diagram of DES model[41]



The model simulated a cohort of 10,000 patients over a 30 year time horizon. The model uses evidence from the UKPDS 68 study to simulate disease progression in type 2 diabetes mellitus patients (Figure 4). Modeling events for the type 2 diabetes mellitus component of the model is according to the UKPDS 68 outcomes model.[42]

A typical patient flow through the simulated model is based on the initial patient set data with baseline demographic and risk factor profiles. Once an individual patient is chosen for simulation, the patient will begin the journey at 'all cause death' decision box. This particular patient will either end the journey at 'patient death' or continue into the '1st level complication' depending on the baseline data set. Once past through the '1st level complication', the patient will continue into the '2nd level complication' until the '7th level complication' or end with 'complication death' at any point of time in between. Everytime the patient completes a particular level of complication and does not end with 'complication death', the patient will re-enter another level of complication if the simulation time horizon has not ended. After passing through each level of complication, the patient's life years, risk factor, utilities and cost will be updated. Simulation for the patient will end once the simulation time horizon has been reached and all statistics for the patient will be collected.

Figure 4: Progression flow of type 2 diabetes mellitus complications[41]



The time-to-event data is generated from the UKPDS 68 outcomes model utilising the event risk equation to obtain values of the seven complications in the system which are myocardial infarction (MI), ischemic heart disease (IHD), congestive heart failure (CHF), stroke

(Stroke), renal failure (RENAL), blindness (Blind) and amputation (AMPU). For each event, a pair of values, Y_i and T_i is obtained.

Equation 2: Event risk equation

$$Y_i = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_3 + \beta_4 X_4$$

Equation 3: Time to event[41]

$$T_i = \left(\frac{log(U)}{log(1-\alpha)exp(\beta' X)}\right)^{\frac{1}{v}},$$

where α = (1-mortality rate)*annual rate

X_1 = Current Age

X_2 = Proportion female

X_3 = Proportion AC

X_4 = Proportion smokers

The Y_i and T_i values for each of the seven type 2 diabetes mellitus complications were obtained using patients' characteristics generated from the DES model and applying a published methodology[43] where β is the parameter obtained from the data inputs and x= (Current Age, Proportion of females, Duration of type 2 diabetes mellitus, Height, Proportion of AC, Proportion of smokers, HbA1c, Total-Cholesterol, HDL-Cholesterol, SBP, Weight). U is a random number from a uniform distribution between 0 and 1, and it was generated when each event is generated. Once $\{Y_1,\ldots,_7\}$ and $\{T_1,\ldots,T_7\}$ are generated and the minimum of $\{T_i\}$ is found, the next path is then decided upon e.g. if T_2 is the minimum, then the patient will suffer from IHD after he had spent the amount time T_2. After deciding the path, the complication will be updated to the age of the patient, e.g. the patient's age will become his or her original age plus T_2.

The HbA1c functions used for input into the DES model follows a linear function of y=mx+b where y=HbA1c, m=annual rate of HbA1c increment or decrement, x=time (years) and b= baseline HbA1c.

For insulin started at year 5 :

$0 \leq t < 1$, HbA1c(y)=(-0.5%)t+9.9%

$1 \leq t < 5$, HbA1c(y)=(0.2%)t+9.4%

$t \geq 5$, HbA1c(y)=7%

where t = time (years)

For insulin started at year 6 :

$0 \leq t < 1$, HbA1c(y)=(-0.5%)t+9.9%

$1 \leq t < 6$, HbA1c(y)=(0.2%)t+9.4%

$t \geq 6$, HbA1c(y)=7%

where t = time (years)

For insulin started at year 7 :

$0 \leq t < 1$, HbA1c(y)=(-0.5%)t+9.9%

$1 \leq t < 7$, HbA1c(y)=(0.2%)t+9.4%

$t \geq 7$, HbA1c(y)=7%

where t = time (years)

For insulin started at year 8 :

$0 \leq t < 1$, HbA1c(y)=(-0.5%)t+9.9%

$1 \leq t < 8$, HbA1c(y)=(0.2%)t+9.4%

$t \geq 8$, HbA1c(y)=7%

where t = time (years)

2.2 Data Inputs

2.2.1 Epidemiological Data

Patient profile data was collected from two published studies – the ASEAN subgroup analyses of the A1chieve study which is part of the international A1chieve study looking at the use of insulin in type 2 diabetes mellitus patients in routine clinical practice[44] and the DiabCare Malaysia 2008 study.[20] Both studies are a good representative of the population of type 2 diabetes mellitus patients in Malaysia as both studies included patients recruited from the main Ministry of Health hospitals throughout Malaysia. Mortality data was compiled from the UKPDS 35 study.[45]

Table 1. Baseline patients' characteristics

Characteristic	Mean	SD	Source
Current age (Years)	55.3	10.8	44
Proportion female	52.5	Not available	44
Duration diabetes (Years)	7.5	5.9	44
HbA1c (%)	9.9	1.9	44
Total Cholesterol (mmol/L)	5.6	1.5	44
LDL Cholesterol (mmol/L)	3.6	1.2	44
HDL Cholesterol (mmol/L)	1.3	0.4	44
SBP (mmHg)	131.8	17.7	44
Weight (kg)	63.4	12.6	44
Smoke (%)	9	Not available	20

2.2.2 Costs data

The costs data used in the analysis were collected from published Malaysian sources[3] and clinical expert opinion obtained via face-to-face interviews.

Table 2. Costs data

Condition	Event Costs (RM)	Annual Costs (RM)	Source
Outpatient follow up	Not available	459	3
Nephropathy	Not available	42,362	3
Myocardial infarction	4,817	Not available	3
Stroke	5,345	Not available	3
Heart failure	3,880	Not available	3

Retinopathy	479	Not available	3
Amputation	5,519	Not available	3
NPH insulin	Not available	638.75	Clinical expert opinion

2.2.3 Utility data

Health-related utility values were derived from a systematic literature review that was conducted to identify studies reporting utility values for relevant type 2 diabetes mellitus complications. The methodology of each study was assessed for consistency with the NICE reference case. A suggested set of utility values applicable to type 2 diabetes mellitus modeling was derived, giving preference to studies reporting multiple complications and correcting for comorbidity.[46]

Table 3. Utility values

Condition	Utility	Source
Type 2 diabetes mellitus patients without complications	0.8255	46
Ischemic heart disease	0.7355	46
Myocardial infarction	0.7705	46
Congestive heart failure	0.7175	46
Stroke	0.6615	46
Blindness	0.7515	46
End stage kidney disease	0.6615	46
Amputation	0.5455	46

2.3 Base-case Analysis

Base-case analysis was conducted for early initiation of insulin when insulin is initiated 5 years after diagnosis of type 2 diabetes mellitus compared to late initiation of insulin when insulin is initiated 6 years after diagnosis of type 2 diabetes mellitus.

Equation 4: ICER for base-case analysis

$$ICER = \frac{(cost\ at\ Year\ 5 - cost\ at\ Year\ 6)}{(QALY\ at\ Year\ 5 - QALY\ at\ Year\ 6)}$$

2.4 Sensitivity Analysis

2.4.1 Scenario Analysis

Scenario analyses were conducted for the different scenarios below to test the robustness and reliability of the model :

1. Early initiation of insulin at 5 years after diagnosis of type 2 diabetes mellitus compared to late initiation of insulin at 7 years after diagnosis of type 2 diabetes mellitus.

Equation 5: ICER for scenario analysis 1

$$ICER = \frac{(cost\ at\ Year\ 5 - cost\ at\ Year\ 7)}{(QALY\ at\ Year\ 5 - QALY\ at\ Year\ 7)}$$

2. Early initiation of insulin at 5 years after diagnosis of type 2 diabetes mellitus compared to late initiation of insulin at 8 years after diagnosis of type 2 diabetes mellitus.

Equation 6: ICER for scenario analysis 2

$$ICER = \frac{(cost\ at\ Year\ 5 - cost\ at\ Year\ 8)}{(QALY\ at\ Year\ 5 - QALY\ at\ Year\ 8)}$$

2.5 General Assumptions Made for DES Model and CEA

The following general assumptions were made:

1. For the HbA1c functions, after starting insulin, there is a 0.5% decrease in the HbA1c level during the first year followed by a 0.2% annual increment until the eight year and then the HbA1c level remains at 7% from the eight year and beyond due to the treat-to-target insulin regimen used where the dose of insulin is adjusted to maintain the HbA1c levels within the target range set for the patients.

2. The time horizon was set to 30 years to capture all relevant long-term complications and associated costs to assess their impact on life expectancy and quality–adjusted life expectancy.

3. Major hypoglycaemia was not assessed as part of the complications as it is assumed that both arms have similar hypoglycaemia outcomes as evident by the clinical study used for the data input which found no major hypoglycaemia in the entire cohort at study end.[44]

4. Based on clinical expert opinion, Neutral Protamine Hagedorn (NPH) insulin is the basal insulin selected for insulin cost calculation as it is the main basal insulin initiated for type 2 diabetes mellitus patients treated in Ministry of Health hospitals.

5. Based on clinical expert opinion, the daily Neutral Protamine Hagedorn (NPH) insulin units used by type 2 diabetes patients is 30 units. Therefore, annual Neutral Protamine Hagedorn (NPH) insulin units used is 10,950 units per year.

6. Based on clinical expert opinion (NPH), the Ministry of Health cost for Neutral Protamine Hagedorn (NPH) insulin is RM 17.50 for a 300 unit penfill. Therefore, the annual cost of Neutral Protamine Hagedorn (NPH) insulin is RM 638.75.

7. Costs and clinical benefits are discounted according to current guidelines which is at a rate of 3%.[47]

8. The Ministry of Health perspective is taken for the analysis and therefore includes the direct cost of medications and complications.

9. All costs are inflated to 2018 values utilising the formula of cost x [2018 Consumer Price Index (CPI) / 2011 Consumer Price Index (CPI)].

Chapter 3 Results

3.1 Demographic and Clinical Characteristics of Simulated Patients

The model simulated 10,000 patients for each scenario across the four scenarios of insulin initiation at year 5, insulin initiation at year 6, insulin initiation at year 7 and insulin initiation at year 8. The final number of patients used for analysis is 8,400 due to removal of simulated patients with missing and incomplete data. The demographic and clinical characteristics of the simulated patients for each scenario are in the tables below.

Table 4: Demographic and clinical characteristics for insulin initiation at year 5

Characteristic	Frequency	Percentage (%)
Gender		
Male	3,628	43.2
Female	4,772	56.8
Age (Year)		
40 and below	0	0
41 – 50	606	7.2
51 – 60	4,950	58.9
61 – 70	2,739	32.6
71 and above	105	1.3
Complications		
Amputation	93	0.1
Blindness	395	0.6
Congestive Heart Failure	426	0.7
Ischemic Heart Disease	54,185	86.2
Myocardial Infarction	7,394	11.8
Nephropathy	57	0.1

Stroke	317	0.5

Table 4 above shows the demographic and clinical characteristics of the 8,400 simulated patients where insulin was initiated 5 years after the diagnosis of type 2 diabetes mellitus. There were more females than males in this scenario with 56.8% females compared to 43.2 % males. The majority (58.9%) were in the age group of 51-60 years old followed by 32.6% in the 61-60 years old age group. In terms of complications for this scenario (Figure 5), the total complications simulated were 62,867 complications. The most frequent complication was ischemic heart disease which was 86.2% of all complications. Myocardial infarction was a distant second with 11.8%.

Figure 5: Percentage of complications for insulin initiation at year 5

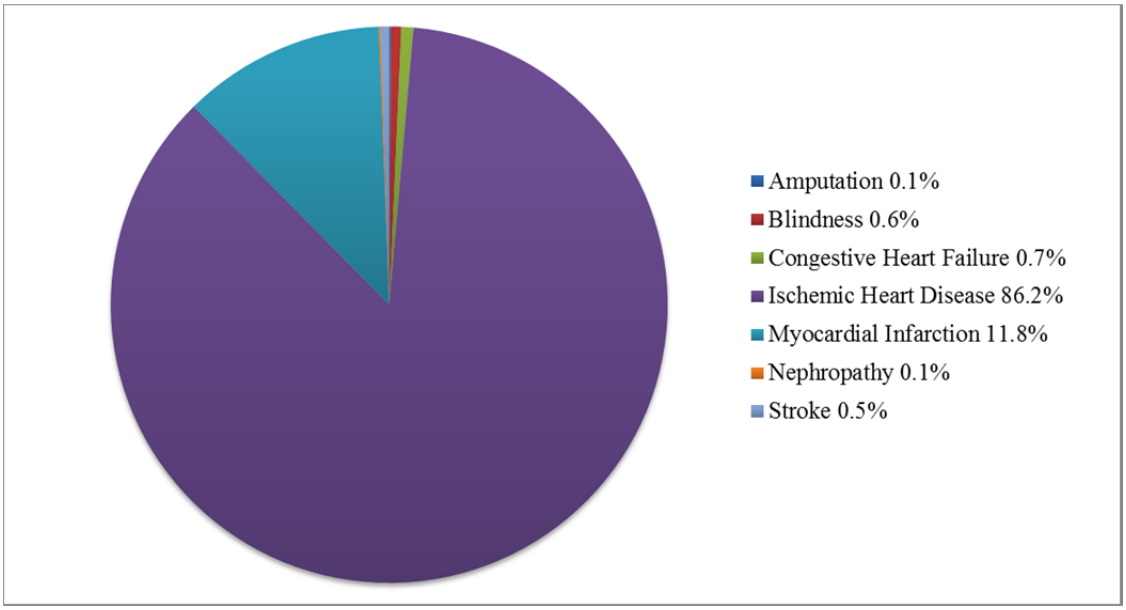


Table 5: Demographic and clinical characteristics for insulin initiation at year 6

Characteristic	Frequency	Percentage (%)
Gender		
Male	3,703	44.1
Female	4,697	55.9
Age (Year)		

40 and below	0	0
41 – 50	606	7.2
51 – 60	4,955	59.0
61 – 70	2,735	32.6
71 and above	104	1.2
Complications		
Amputation	95	0.6
Blindness	477	2.9
Congestive Heart Failure	428	2.6
Ischemic Heart Disease	7,631	46.7
Myocardial Infarction	7,380	45.1
Nephropathy	71	0.4
Stroke	270	1.7

For the scenario where insulin is initiated 6 years after the diagnosis of type 2 diabetes mellitus, Table 5 above shows a similar gender breakdown with females being more than males (55.9% vs 44.1%). The simulated patients' age spread is also similar to the previous scenario where the majority (59.0%) of simulated patients are in the 51-60 years old age group followed by 32.6% in the 61-70 years old age group. The simulated complications (Figure 6) are more evenly distributed with 46.7% ischemic heart disease and 45.1% myocardial infarction with a total of 16,352 complications.

Figure 6: Percentage of complication for insulin initiation at year 6

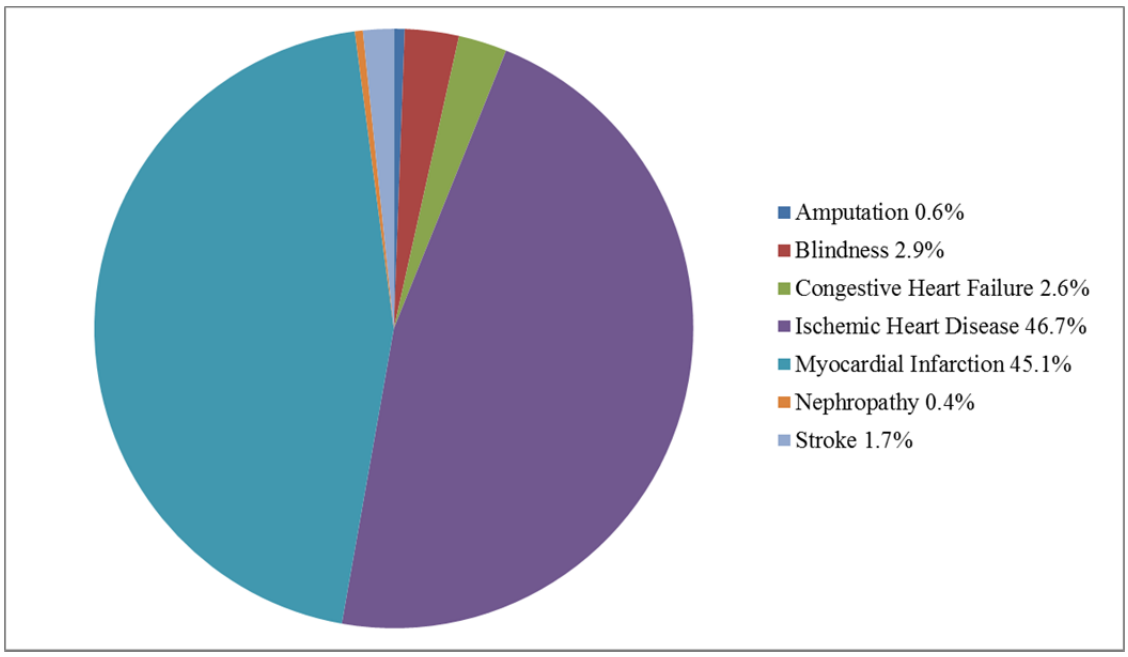


Table 6: Demographic and clinical characteristics for insulin initiation at year 7

Characteristic	**Frequency**	**Percentage (%)**
Gender		
Male	3,648	43.4
Female	4,752	56.6
Age (Year)		
40 and below	0	0
41 – 50	604	7.2
51 – 60	4,984	59.3
61 – 70	2,727	32.5
71 and above	85	1.0
Complications		
Amputation	114	0.7

Blindness	414	2.5
Congestive Heart Failure	499	3.1
Ischemic Heart Disease	7,453	45.6
Myocardial Infarction	7,464	45.6
Nephropathy	64	0.4
Stroke	348	2.1

Simulated patients with insulin started 7 years after the diagnosis of type 2 diabetes mellitus show a similar gender and age group breakdown with scenario 1 and scenario 2 as depicted by Table 6 above. Out of the total of 16,356 complications (Figure 7), both ischemic heart disease and myocardial infarction are evenly distributed at 45.6% followed by congestive heart failure (3.1%), blindness (2.5%), stroke (2.1%), amputation (0.7%) and nephropathy (0.4%).

Figure 7: Percentage of complication for insulin initiation at year 7

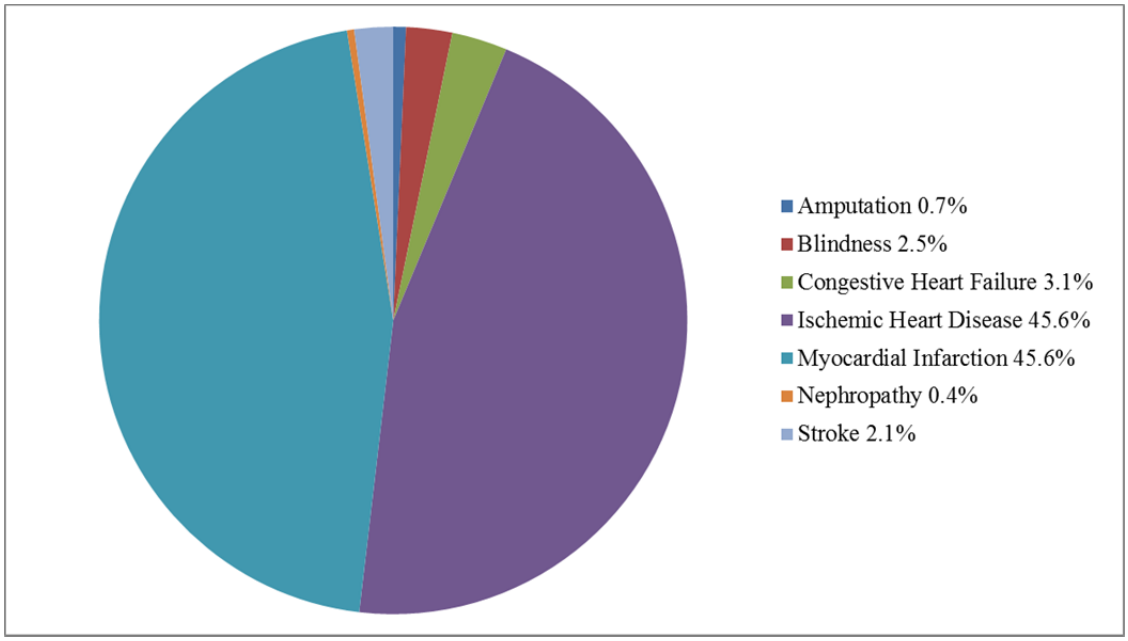


Table 7: Demographic and clinical characteristics for insulin initiation at year 8

Characteristic	**Frequency**	**Percentage (%)**
Gender		
Male	3,636	43.3
Female	4,764	56.7
Age (Year)		
40 and below	0	0
41 – 50	602	7.2
51 – 60	4,946	58.9
61 – 70	2,766	32.9
71 and above	86	1.0
Complications		
Amputation	83	0.3
Blindness	424	1.5
Congestive Heart Failure	459	1.6
Ischemic Heart Disease	19,117	68.3
Myocardial Infarction	7,460	26.7
Nephropathy	64	0.3
Stroke	363	1.3

For the 8,400 simulated patients with insulin initiated at 8 years after diagnosis of type 2 diabetes mellitus, there are 56.7% females compared to 43.3% males. The majority of simulated patients (58.9%) are in the 51-60 years old age group followed by 32.9% in the 61-70 years old age group. The breakdown of the 27,970 total complications (Figure 8) show a strong preponderance towards ischemic heart disease (68.3%) followed by myocardial

infarction (26.7%). Blindness and congestive heart failure are balance at 1.5% and 1.6% followed by stroke at 1.3%, with amputation and nephropathy both at 0.3%.

Figure 8: Percentage of complication for insulin initiation at year 8

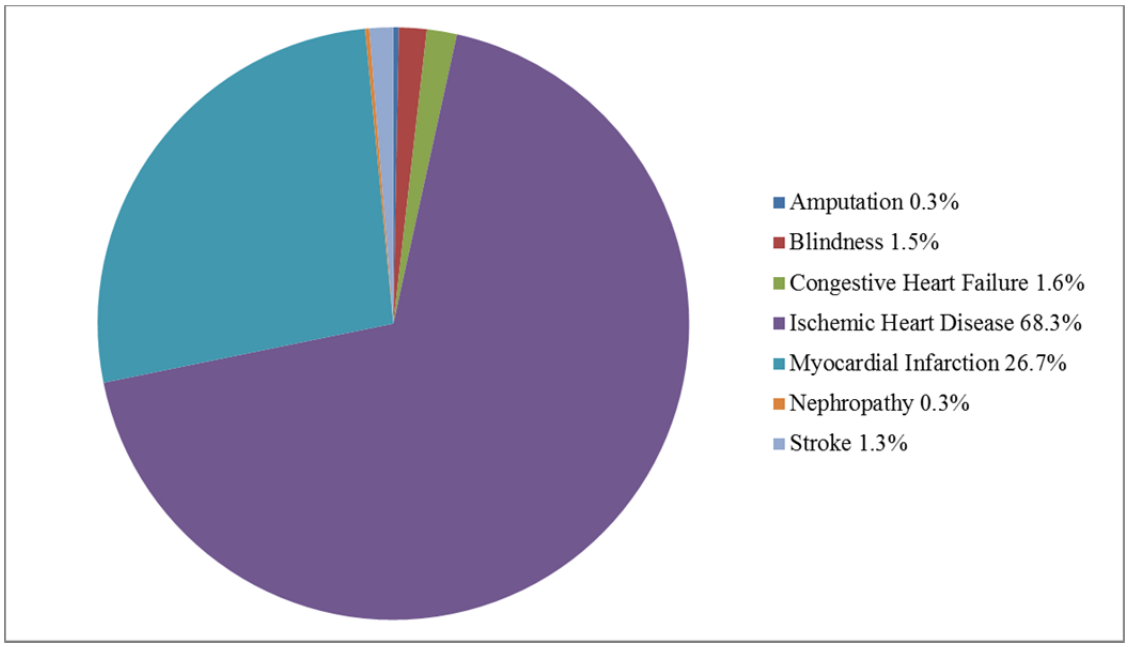


Table 8: Aggregated costs data

Scenario	Total Complications	Cost of Complications (RM)	Outpatient Cost (RM)	Insulin Cost (RM)	Total Costs (RM)
Year 5	62,867	74,558,505	3,855,600	5,365,500	83,779,605
Year 6	16,352	75,027,096	3,855,600	5,365,500	84,248,196
Year 7	16,356	74,885,307	3,855,600	5,365,500	84,106,407
Year 8	27,970	74,867,885	3,855,600	5,365,500	84,088,985

Table 8 captures the costs data obtained from the simulation of 8,400 patients for each scenario. When insulin is initiated 5 years after the diagnosis of type 2 diabetes mellitus, there are 62,867 complications costing RM 74,558,505. When added on to the cost of outpatient follow up and cost of insulin, the total costs adds up to RM 83,779,605. For

scenario 2, where insulin is initiated 6 years after the diagnosis of type 2 diabetes mellitus, the cost of complications is RM 75,027,096 which is the cost from 16,352 complications. The total costs after taking into account the outpatient follow up cost and cost of insulin is RM 84,248,196. For simulated patients who were started insulin 7 years after the diagnosis of type 2 diabetes mellitus, the total complications are 16,356 complications with a cost of RM 74,885,307. When the cost of complications, outpatient follow up cost and cost of insulin are added up, the total cost is RM 84,106,407. The simulation for scenario 4 where insulin is initiated 8 years after the diagnosis of type 2 diabetes mellitus, obtained 27,970 complications amounting to RM 74,867,885. The total cost after taking into account the outpatient follow up cost and the cost of insulin adds up to RM 84,088,985.

The total complications are highest when insulin is initiated 5 years after the diagnosis of type 2 diabetes mellitus, amounting to 62,867 complications. The next highest total complications of 27,970 are in scenario 4 where insulin is initiated 8 years after the diagnosis of type 2 diabetes mellitus. For insulin started 6 years and 7 years after the diagnosis of type 2 diabetes mellitus, the total number of complications are comparable at 16,352 and 16,356 respectively.

The total cost of RM 83,779,605 is lowest for scenario 1 when insulin is initiated at 5 years after the diagnosis of type 2 diabetes mellitus. The total costs are higher in the subsequent scenarios with the highest total cost obtained from scenario 2 where insulin is initiated 6 years after the diagnosis of type 2 diabetes mellitus at RM 84,248,196. The total costs for scenarios when insulin is initiated at year 7 and year 8 after diagnosis of type 2 diabetes mellitus are comparable at RM 84,106,407 and RM 84,088,985 respectively.

3.2 Base-case Analysis

Base case analysis was carried out to obtain the differences in cost and effectiveness for early initiation of insulin when insulin is initiated 5 years after diagnosis of type 2 diabetes mellitus compared to late initiation of insulin when insulin is initiated 6 years after diagnosis of type 2 diabetes mellitus.

Table 9: Costs, QALY and ICER for base-case

Insulin Initiation	Costs (RM)	QALYs	ICER
Year 5	83,779,605	35,416.08	
Year 6	84,248,196	34,872.25	
Difference	-468,591	543.83	Dominant

When comparing early initiation of insulin at 5 years after diagnosis of type 2 diabetes mellitus against late initiation of insulin when insulin is initiated 6 years after diagnosis of type 2 diabetes mellitus, the cost for early initiation is lower. The amount saved is RM 468,591. There are also more QALYs gained for early initiation with 543.83 QALYs gain when insulin is initiated at 5 years after diagnosis of type 2 diabetes mellitus. The ICER obtained showed that initiating insulin 5 years after diagnosis of type 2 diabetes mellitus is dominant compared to initiating insulin later at 6 years after diagnosis of type 2 diabetes mellitus.

3.3 Scenario Analysis

Scenario analyses were conducted for the different scenarios below to test the robustness and reliability of the model :

- Early initiation of insulin at 5 years after diagnosis of type 2 diabetes mellitus compared to late initiation of insulin at 7 years after diagnosis of type 2 diabetes mellitus.

Table 10: Costs, QALY and ICER for scenario analysis (Year 5 vs Year 7)

Insulin Initiation	Costs (RM)	QALYs	ICER
Year 5	83,779,605	35,416.08	
Year 7	84,106,407	36,146.27	
Difference	- 326,802	- 730.19	447.56

Scenario analysis for insulin initiated 5 years after diagnosis of type 2 diabetes mellitus compared to insulin initiated at 7 years after diagnosis of type 2 diabetes mellitus showed cost savings of RM 326,802. There is however a loss of 730.19 QALYs when insulin is initiated at year 5 compared to year 7.

- Early initiation of insulin at 5 years after diagnosis of type 2 diabetes mellitus compared to late initiation of insulin at 8 years after diagnosis of type 2 diabetes mellitus.

Table 11: Costs, QALY and ICER for scenario analysis (Year 5 vs Year 8)

Insulin Initiation	**Costs (RM)**	**QALYs**	**ICER**
Year 5	83,779,605	35,416.08	
Year 8	84,088,985	35,807.85	
Difference	- 309,380	- 391.77	789.70

Scenario analysis conducted looking at insulin initiation 5 years after diagnosis of type 2 diabetes mellitus against insulin initiation 8 years after diagnosis of type 2 diabetes mellitus also resulted in cost savings of RM 309,380. Similar to the first scenario analysis above, this scenario analysis also resulted in a QALY loss of 391.77.

Chapter 4 Discussion

4.1 Main Findings

Based on the specific objectives of this pioneer pilot study which are 1) to utilise novel methods in type 2 diabetes mellitus modeling by using the discrete event simulation (DES) based modeling approach and 2) to evaluate whether early insulin initiation in patients with type 2 diabetes mellitus is more cost-effective compared to later initiation of insulin from the Ministry of Health's perspective in Malaysia, the main findings are as discussed below.

As to utilising novel methods in type 2 diabetes mellitus modeling by using the discrete event simulation (DES) based modeling approach, the attempt has been successful in terms of generating a feasible model that is able to simulate the complex nature of type 2 diabetes mellitus. Having said this, this pioneer pilot sudy ha salso shown that more work needs to be done to improve the model and make it as robust and as realistic as possible. The next steps on what can be done to further improve the functionality of this model is elaborated below in section 3.2 Implications and Recommendations for future research.

The main findings for evaluating whether early insulin initiation in patients with type 2 diabetes mellitus is more cost-effective compared to later initiation of insulin from the Ministry of Health's perspective in Malaysia has been succesful in demonstrating that when comparing early initiation of insulin at 5 years after diagnosis of type 2 diabetes mellitus against late initiation of insulin when insulin is initiated 6 years after diagnosis of type 2 diabetes mellitus, the cost for early initiation is lower where the amount saved is RM 468,591. There are also more QALYs gained for early initiation with 543.83 QALYs gain when insulin is initiated at 5 years after diagnosis of type 2 diabetes mellitus. The ICER obtained showed that initiating insulin 5 years after diagnosis of type 2 diabetes mellitus is dominant compared to initiating insulin later at 6 years after diagnosis of type 2 diabetes mellitus. This finding is supported by the UKPDS 49 study which estimated that >60% of type 2 diabetes mellitus patients would require insulin within 5 years of diagnosis[14] and is also consistent with a study involving Malaysian type 2 diabetes mellitus patients showing that initiating insulin therapy is a safe and more effective way to improve glycaemic control in patients inadequately controlled with oral monotherapy or oral combination therapy compared with optimising oral combination therapy alone.[21]

There is however a paradox when comparing early initiation of insulin at 5 years after diagnosis of type 2 diabetes mellitus compared to late initiation of insulin at 7 years after diagnosis of type 2 diabetes mellitus and also when comparing early initiation of insulin at 5 years after diagnosis of type 2 diabetes mellitus compared to late initiation of insulin at 8 years after diagnosis of type 2 diabetes mellitus. The paradox is that there are costs savings when initiating insulin earlier at 5 years after diagnosis compared to initiating later at 7 years or 8 years but these costs savings do not come together with a gain in QALYs. The loss in QALYs when initiating insulin earlier at 5 years cannot be explained based on the disease progression of type 2 diabetes mellitus and also the current treatment algorithms that are being used to manage type 2 diabetes mellitus patients. A logical explanation can however be deduced from the simulation outcomes of the model where the spread of complications is different amongst the four scenarios simulated. The total complications are highest when insulin is initiated 5 years after the diagnosis of type 2 diabetes mellitus, amounting to 62,867 complications. There is however a big difference in total complications of the other scenarios where the total complications for scenario 4 where insulin is initiated 8 years after the diagnosis of type 2 diabetes mellitus is only 27,970. For insulin started 6 years and 7 years after the diagnosis of type 2 diabetes mellitus, the total number of complications are even lower at 16,352 and 16,356 respectively. The distribution of the various complications are also different in each scenario where for scenario 1 when insulin is started 5 years after diagnosis of type 2 diabetes mellitus, the most frequent complication was ischemic heart disease which was 86.2% of all complications. Myocardial infarction was a distant second with 11.8%. For scenario 2, where insulin is started 6 years after the diagnosis of type 2 diabetes mellitus, the simulated complications are more evenly distributed with 46.7% ischemic heart disease and 45.1% myocardial infarction. The situation is similar when insulin is initiated at 7 years after the diagnosis of type 2 diabetes mellitus where both ischemic heart disease and myocardial infarction are evenly distributed at 45.6%. The complication spread for scenario 4 where insulin is initiated 8 years after the diagnosis of type 2 diabetes mellitus again show a strong preponderance towards ischemic heart disease (68.3%) followed by myocardial infarction (26.7%).

The stark differences in the total number of complications and the distribution of various complications throughout the four scenarios simulated is believed to be the main contributor

to the QALYs loss when comparing between early initiation and later initiation of insulin in type 2 diabetes mellitus patients simulated in this model.

4.2 Implications and Recommendations for Future Research

Based on the main findings above, the implications of the findings from this pioneer pilot study is immense especially in changing the way type 2 diabetes mellitus patients are managed in Malaysia. Despite some paradoxical findings related to the loss of QALYs and also the differences in total costs and QALYs for the different scenarios simulated, the overall trend shows that costs can be saved when insulin is initiated at 5 years after diagnosis of type 2 diabetes mellitus compared to initiating insulin later at 6 years, 7 years and 8 years. This finding should add on to the many well established clinical findings that show starting insulin earlier is better for type 2 diabetes mellitus patients. For the Ministry of Health, this finding should also help to provide evidence that the Ministry of Health is on the right path starting from the roll out of the Type 2 Diabetes Mellitus Clinical Practice Guidelines in 2009 which recommended earlier use of insulin therapy in type 2 diabetes mellitus patients with sub-optimal glycaemic control either at presentation or with failure of oral anti-diabetic agents to the subsequent roll out of the Practical Guide for Insulin Therapy in 2011 to provide a clear and concise approach to all health care providers on current concepts in the use of insulin in type 2 diabetes mellitus and finally to the updated Type 2 Diabetes Mellitus Clinical Practice Guidelines in 2015 which continues to espouse earlier use of insulin therapy in type 2 diabetes mellitus patients in Malaysia.

Having said all of the above, the DES model used for this pioneer pilot study needs to undergo further research to make it an acceptable model to replicate, as close as possible, the many real life issues surrounding the very complex universe of type 2 diabetes mellitus. As with other well established and accepted type 2 diabetes mellitus health economic models in the world, further research will be needed in the following aspects :

- Comprehensive literature review and inclusive medical input from expert clinicians in the field of type 2 diabetes mellitus and also experts in the field of healthcare modeling development.[39]
- A reassessment of the DES model structure and functionality to incorporate a more holistic representation of type 2 diabetes mellitus by including as many real life Malaysian patient characteristics and parameters as possible such as comprehensive

acute and chronic complications, non-diabetes medications and other parameters associated with type 2 diabetes mellitus management such as self-monitoring of blood glucose.[39]

- A robust validation analysis to evaluate the DES model in terms of performance against real life type 2 diabetes mellitus populations including clinical outcomes and complications.[39]

4.3 Challenges and Limitations

The challenges encountered during this pioneer pilot research was the availability of local clinical and cost data in Malaysia. Malaysia has very limited and scattered cost data with respect to type 2 diabetes mellitus costs and this makes it very challenging to source for local data required to feed into the DES model. Due to the many challenges encountered in the realm of data sourcing, the following limitations have been identified for this pioneer pilot study :

- For the HbA1c functions, after starting insulin, there is a 0.5% decrease in the HbA1c level during the first year followed by a 0.2% annual increment until the eight year and then the HbA1c level remains at 7% from the eight year and beyond due to the treat-to-target insulin regimen used where the dose of insulin is adjusted to maintain the HbA1c levels within the target range set for the patients. In real life, the treat-to-target regimen may not be realistic due to the may confounding factors such as poor patient adherence and compliance to treatment and treatment inertia among healthcare professionals.

- Major hypoglycaemia was not assessed as part of the complications as it is assumed that both arms have similar hypoglycaemia outcomes as evident by the clinical study used for the data input which found no major hypoglycaemia in the entire cohort at study end.[43] Other important type 2 diabetes mellitus complications and side effects of insulin treatment were not included in this analysis such as acute complications and weight gain caused by insulin treatment.

- Costs data obtained from the most comprehensive local publication relied upon clinical pathways and estimation by clinical experts and published fee schedules. The costs estimates are a mixture of per episode costs and annual costs. For per episode costs, the costs for the complications do not involve ongoing costs and are therefore

much lower. Only nephropathy had ongoing management cost for dialysis. Other complications such as myocardial infarction, stroke, heart failure and amputation also require follow up but the costs were not available.[3]

Chapter 5 Conclusions

This pioneer pilot study was an attempt to utilise novel methods in type 2 diabetes mellitus modeling by using the discrete event simulation (DES) based modeling approach to evaluate whether early insulin initiation in patients with type 2 diabetes mellitus is more cost-effective compared to later initiation of insulin from the Ministry of Health's perspective in Malaysia.

The research outcome has demonstrated that DES based modeling is the way forward for type 2 diabetes mellitus modeling and further research should be continued to establish this.

The findings provide evidence that initiating insulin 5 years after diagnosis of type 2 diabetes mellitus is dominant compared to initiating insulin later at 6 years after diagnosis of type 2 diabetes mellitus. This evidence should encourage the Ministry of Health to continue with the recommendation that insulin should be initiated earlier for type 2 diabetes mellitus patients in Malaysia.

Chapter 6 Reference

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