IMPACT OF INSULIN CONTAINING REGIMEN VS TRIPLE ORAL HYPOGLYCAEMIC AGENT THERAPY ON HEALTH-RELATED QUALITY OF LIFE, ECONOMIC, AND CLINICAL OUTCOMES IN POORLY CONTROLLED TYPE 2 DIABETES OUTPATIENTS IN YOGYAKARTA

By

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LIST OF ABBREVIATION

AACE	American Association of Clinical Endocrinologist
ACE	Angiotensin converting enzyme
ACER	Average cost effectiveness ratio
ADA	American Diabetes Association
ADH	Antidiuretic hormone
ADR	Adverse drug reaction
AGEs	Advanced glycation end products
ALT	Alanine aminotransferase
ANOVA	Analyses of variance
ARB	Angiotensin receptor blocker
ATP	Adult Treatment Panel
BP	Blood pressure
CAD	Coronary artery disease
CB	Cannabinoid
CCB	Calcium channel blocker
CHD	Chronic heart disease
CHF	Congestive heart failure
CODE-2	Cost of Diabetes Research in Europe – type 2
CUA	Cost-utility analysis
CV	Cardiovascular
CVD	Cardiovascular disease
DM	Diabetes mellitus
DPP	Diabetes Prevention Programme
DPP-4	Dipeptidyl peptidase-4
DQLCTQ	Diabetes Quality of Life Clinical Trial Questionnaire

DQoL	Diabetes Quality of Life
ECS	Endocannabinoid system
EDTA	Ethylenediaminetetraacetic acid
Eur IDF	European International Diabetes Federation
ESRD	End stage renal disease
FDA	Food and Drug Administration
FLP	Fasting lipid profile
FPG	Fasting plasma glucose
GFR	Glomerular filtration rate
GI	Gastrointestinal
GLP-1	Glucagon-like peptide-1
GLUT-4	Glucose transporter-4
HDL	High density lipoprotein
HIV	Human immunodeficiency virus
HRQoL	Health-related Quality of Life
IBD	Inflammatory bowel disease
ICER	Incremental cost-effectiveness ratio
IDR	Indonesia rupiah
kg	kilograms
LDL	Low density lipoprotein
mg/dL	milligram/desiliter
MNT	Management nutrition therapy
MOS	Medical outcomes study
MRFIT	Multiple risk factor intervention trial
MSE	Minor symptom evaluation
NCEP	National Cholesterol education Panel
NPH	Neutral protamine hagedorn

OHA	Oral hypoglycaemic agent
PPG	Post-prandial plasma glucose
PVD	Peripheral vascular disease
QoL	Quality of Life
RAS	Renin-angiotensin system
SCr	Serum creatinine
SD	Standard deviation
SMBG	Self-monitoring blood glucose
SPSS	Statistical package for social sciences
TZDs	Thiazolidinedione
UKPDS	United Kingdom Prospective Diabetes Study
UN	United Nation
USA	United States of America
WHO	World Health Organization

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LIST OF PUBLICATIONS AND SEMINARS

PUBLICATIONS

1. Andayani TM, Ibrahim MIM, Asdie AH. (2010). The Safety of Triple Therapy with Oral Antidiabetics versus Insulin in Type 2 diabetes. *Asian Journal of Pharmaceutical and Clinical Research.* 3(3)

2. Andayani TM, Ibrahim MIM, Asdie AH. (2010). Comparison of the glycemic control of insulin and triple oral therapy in type 2 diabetes mellitus. *Journal of Diabetes and Endocrinology*. 1(2)

3. Andayani TM, Ibrahim MIM, Asdie AH. (2010). Assessing the Impact of Complications on The Direct Medical Costs of Type 2 Diabetes Mellitus Outpatients. *International Journal of Current Pharmaceutical Research*. 2(2)

4. Andayani TM, Ibrahim MIM, Asdie AH. (2010). The Association of Diabetes-Related Factor and Quality of Life in Type 2 Diabetes Mellitus. *International Journal of Pharmacy and Pharmaceutical Sciences*. 2(1) (Jan-March 2010)

5. Andayani TM, Ibrahim MIM, Asdie AH. (2009). The Effect of Combination Therapy of Sulfonylurea, Metformin, and Acarbose in Type 2 Diabetes Mellitus Patients with Poorly Controlled Glycemia. *Indonesian Journal of Pharmacy*. 20(4):224-230

6. Andayani TM, Ibrahim MIM, Asdie AH. Quality of Life Following a Change in Therapy to Insulin for Type 2 Diabetes Mellitus Outpatients (letter to editor). (2009). *Journal of Pharmacy Practice and Research* . 39(3):249-250, September 2009

7. Andayani TM, Ibrahim MIM, Asdie AH. (2009). Health-Related Quality of Life in Type 2 Diabetes Outpatients in Dr Sardjito Yogyakarta Hospital. *Malaysian Journal of Pharmacy*. 1 Issue 7 June 2009

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4. Quality of Life Following a Change in Therapy to Insulin for Type 2 Diabetes Mellitus Outpatients. Diabetes Asia 2009 Conference (oral presentation), Kuala Lumpur, Malaysia, 7-11th October 2009

5. The Association of Diabetes-Related Factor and Quality of Life in Type 2 Diabetes Mellitus. The 9th Asean Conference on Clinical Pharmacy (oral presentation), Coex, Seoul, Korea, 26-28th September 2009

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IMPAK REGIMEN YANG MENGANDUNGI INSULIN BERBANDING TERAPI KOMBINASI ANTIDIABETIK ORAL KE ATAS HASIL AKHIR KUALITI HIDUP BERKAITAN KESIHATAN, EKONOMIK, DAN KLINIKAL DALAM PESAKIT DIABETIS JENIS 2 YANG TIDAK TERKAWAL

ABSTRAK

Penyakit Diabetes Mellitus (DM) Jenis 2 adalah progresif dan kawalan glukos darah akhirnya akan menjadi lebih buruk kerana fungsi sel-sel beta pankreatik akan menurun. Monoterapi dengan antidiabetik oral tidak akan berpanjangan dan akan disusuli dengan dua hingga tiga antidiabetik oral sebagai terapi kombinasi, dan akhirnya pesakit DM Jenis 2 akan memerlukan terapi insulin eksogenus. Kajian ini membandingkan penambahan dan penukaran terapi kepada insulin dengan terapi 3 antidiabetik oral dengan mengukur 3 parameter hasil akhir iaitu klinikal, humanistik dan ekonomi. Kajian ini menggunakan reka bentuk kajian kohort dengan melakukan pemerhatian selama 6 bulan terhadap pesakit dengan kawalan glukos darah yang buruk di Dr Sardjito Hospital, Yogyakarta, Indonesia. Subjek kajian adalah pesakit yang sanggup menukar kepada terapi insulin (Kumpulan 1) dan pesakit yang menolak cadangan menukar kepada terapi insulin dan terus menggunakan kombinasi terapi dengan sulfonylurea, metformin dan akarbos (Kumpulan 2). Keberkesanan terapi dilakukan dengan mengukur paras HbA_{1c}, glukos plasma semasa berpuasa (FPG), dan glukos plasma postprandial (PPG), tekanan darah dan profail lipid bagi setiap kumpulan terapi pada tahap awal, bulan ke tiga dan bulan ke enam. Ukuran perbezaan nilai kualiti hidup pesakit telah dilakukan dengan mengira purata nilai DQLCTQ bagi setiap kumpulan terapi. Analisis keberkesanan kos telah dilakukan daripada perspektif institusi dengan membandingkan kos perubatan langsung bagi tempoh 6 bulan dan keberkesanan terapi telah diukur berdasarkan peratus pesakit yang mencapai sasaran glisemik. Penilaian keberkesanan menunjukkan pesakit yang menukar kepada terapi insulin adalah lebih berkesan dalam mengawal paras glukos darah berbanding dengan terapi 3 antidiabetik oral. Insiden hipoglisemik adalah 36.36% bagi kumpulan 1 dan 28.57% bagi kumpulan 2. Insiden kesan sampingan gastrousus lebih tinggi bagi kumpulan 2 (67.35%) berbanding dengan kumpulan 1 (18.18%). Purata skor kualiti hidup bagi

pesakit DM Jenis 2 adalah 77.23%. Pesakit DM Jenis 2 dengan kawalan glisemik yang buruk, terapi 3 antidiabetik oral dan 2 atau lebih kombinasi mempunyai kualiti hidup yang lebih rendah berbanding dengan pesakit yang mempunyai kawalan glisemik yang baik dan pesakit dengan terapi insulin dan tanpa komplikasi. Pesakit yang menukar kepada terapi insulin menunjukkan peningkatan skor kualiti hidup yang signifikan (p=0.001) selepas 6 bulan. Manakala, bagi pesakit dengan terapi 3 antidiabetik oral, skor kualiti hidup menurun tetapi tidak signifikan secara statistic. Penambah baikan kawalan glisemik menggunakan terapi insulin akan meningkatkan kos rawatan drug berbanding dengan kepada penggunaan kombinasi sulfonylurea, metformin dan akarbos. Analisis keberkesanan kos menunjukkan hasil kumpulan insulin terapi adalah lebih berkesan dalam mengawal paras glukosa dalam darah dan meningkatkan kualiti hidup pesakit, tetapi ia memerlukan lebih tinggi kos perubatan ($ 2,959.25 setiap% tambahan 1 pesakit yang mencapai HbA_{1c} sasaran untuk 6 bulan).

IMPACT OF INSULIN CONTAINING REGIMEN VS TRIPLE ORAL HYPOGLYCAEMIC AGENT THERAPY ON HEALTH-RELATED QUALITY OF LIFE, ECONOMIC, AND CLINICAL OUTCOMES IN POORLY CONTROLLED TYPE 2 DIABETES OUTPATIENTS IN YOGYAKARTA

ABSTRACT

Type 2 Diabetes Mellitus (DM) is a progressive disease, and blood glucose control finally will get poorer because the function of pancreatic beta cells will decrease. Monotherapy with oral antidiabetics will not be effective for long so it is followed by two to three oral antidiabetics as combination therapy, and finally, type 2 DM patients will need exogenous insulin therapy. This research compared the addition and switching of therapy to insulin with triple oral therapy measuring three outcome parameters, i.e., clinical, humanistic and economic outcomes. This research applied cohort study designs by conducting six-month observations on the poor blood-glucose-control patients in Dr Sardjito Hospital, Yogyakarta, Indonesia. The research subjects were the patients who were willing to change the therapy to insulin (Group 1) and the patients who refused to use insulin and kept on using therapy combination with sulfonylurea, metformin, and acarbose (Group 2). The measurement of effectiveness was conducted by calculating the HbA_{1c}, fasting plasma glucose (FPG), and postprandial plasma glucose (PPG) levels, blood pressure and lipid profile of each therapy group at baseline, third month and sixth month. The measurement of the differences of the quality of life values of the patients was conducted by counting the average of the Diabetes Quality of Life Clinical Trial Questionnaire scores of each therapy group. Cost-effectiveness analysis was performed from the hospital perspective by comparing direct medical costs during the six month period and the effectiveness of the therapy which was measured based on the percentage

of patients who achieved the glycaemic target. The results indicates that patients who switched the therapy to insulin were more effective in controlling blood glucose levels than triple oral therapy. However, hypoglycaemic incidents were 36.36% in group 1, and 28.57% in group 2. A higher incidence of gastrointestinal side effects occurred in group 2 (67.35%) than in group 1 (18.18%). The average quality of life scores of type 2 DM patients was 77.23%. Type 2 DM patients with poor glycaemic control, triple oral therapy and two or more complications have a lower quality of life than patients with good glycaemic control, and patients with insulin therapy and without complications. Patients who switched therapy to insulin indicated a significant increase in quality of life ($p< 0.001$) after 6 months. Meanwhile, for patients with triple oral therapy, the scores of quality of life decreased although it was insignificant. The cost-effectiveness analysis shows the result that the insulin therapy group is more effective in controlling blood glucose levels and improving the patient's quality of life, but it requires higher direct medical costs ($ 2,959.25 per additional 1% of patients who achieved target HbA_{1c} for 6 months).

CHAPTER 1

GENERAL INTRODUCTION

1.1 BACKGROUND

Diabetes Mellitus (DM) is categorized as one of the burdensome and expensive chronic diseases due to its increasing prevalence annually, either in Indonesia or in many other countries in the world. The World Health Organization states that the number of the world's population suffering from diabetes in 2000 was 171 million and it is predicted that the number will increase, reaching 366 million in the year 2030 (Wild *et al*., 2004). Ten countries that have the highest prevalence of diabetes are India, China, USA, Indonesia, Japan, Pakistan, Russia, Brazil, Italy and Bangladesh. In developing countries, diabetes mellitus frequently occurs at productive ages, from the age of 35 to 64 years. Diabetes is one of the premature illnesses and cause of death in many countries, particularly due to increases of cardiovascular complications. The number of deaths due to diabetes per year is approximately 3.2 million (WHO, 2010).

Diabetes can cause many complications, both macrovascular and microvascular, and it requires comprehensive and long-term treatment and control. This causes diabetes treatment to be expensive, not only for the patient or the family, but also for the healthcare system. A study in India estimated that 25% of family income is allotted for diabetes treatment in a case of a diabetic adult in a low-income Indian family (Ramachandran *et al*., 2007). On the other hand, 10% of the family income is allotted for diabetes treatment in the case of a diabetic child in a USA family (WHO, 2010). Overall, direct healthcare cost for diabetes ranges from 2.5% to 15% of the annual healthcare

budget, depending on the diabetes prevalence in each country and the availability of existing therapies. Based on the research conducted in 25 countries in Latin America, the cost of productivity lost due to diabetes is five times bigger than its direct healthcare cost (WHO, 2010). Diabetes and its complications bring about significant economic effects on the individual, family, healthcare system and country. As an example, WHO estimates that an amount of $558 billion of China's national income is spent on heart disease, stroke and diabetes (WHO, 2010).

Based on the survey carried out by WHO, Indonesia ranks fourth with the largest number of diabetics in the world after India, China and the USA (Stephen and Murray, 2004). With the prevalence of 8.6% of the population, it was predicted that in the year 1995 there would be 4.5 millions diabetics and this number will increase to 12.4 million by 2025. Based on the data of the Ministry of Health, the number of diabetics, both the outpatients as well as hospitalized patients, ranks first among all endocrine diseases, while 4% of pregnant women suffer from gestational diabetes (WHO, 2005). Epidemiologically, it is predicted the prevalence of DM in Indonesia will reach 21.3 million people in 2003 (ADA, 2004). The results of Basic Health Research (*Riskesdas)* in 2007 indicated that the proportion of the causes of death due to DM in the age group of 45-54 years in urban areas ranks second, with a percentage of 14% (Ministry of Health Republic of Indonesia, 2009). Meanwhile, DM ranks sixth in rural areas with a percentage of 5.8%. Based on 2007 *Riskesdas* results, the national prevalence of DM obtained through blood glucose check on the population aged >15 years old in urban areas is as high as 5.7%.

In Indonesia, health expenses are increasing annually. The percentage of national expenditure in the health sector in 2005 amounted to 0.81% of the Gross Domestic Product. Despite its increase to 1.09% of GDP in 2007, it has not reached 5% of GDP, as recommended by WHO (Ministry of Health Republic of Indonesia, 2009). Similar to the health budget in 2004, a total amount of IDR 5.54 trillion was allotted to the state budget in Indonesia. This increased in 2007 to IDR 18.75 trillion, but its percentage of the entire state budget has not increased and is still around 2.6%-2.8%. Government spending for healthcare continues to rise. However, the contribution of government spending for healthcare is still small, as much as 38% of total health expenses.

The increase in medical cost is caused by the application of advanced technology, patterns of direct cash payments to health providers, patterns of chronic and degenerative diseases, as well as inflation. The increase in healthcare cost is increasingly difficult to overcome with the ability of the government and community in providing funds. The rising costs threaten the access and quality of healthcare and solutions should therefore be sought to overcome the health financing problem. Financing of public healthcare as public good becomes the responsibility of government, whereas the financing of individual healthcare is private in nature. Healthcare financing for the poor and deprived community becomes the responsibility of the government. Individual healthcare funding is administered through healthcare insurance with social insurance mechanisms (Ministry of Health Republic of Indonesia, 2009). Even though private health insurance and government programmess cover a growing portion of drug expenditure, a sizeable amount of drug costs is still paid directly by consumers. The costs of pharmaceuticals and pharmacy services have, therefore, become an important issue to patients, third-party payers, and governments alike.

Health care practitioners, regardless of practice setting, can benefit from applying the principles and methods of pharmacoeconomics to their daily practice settings. Applied pharmacoeconomics is defined as putting pharmacoeconomic principles, methods, and theories into practice to quantify the value of pharmacy products and pharmaceutical care services used in real-world environments. Today's cost-sensitive health care environment has created a competitive and challenging workplace for clinicians. Competition for diminishing resources has necessitated that the appraisal of health care goods and services extends beyond evaluations of safety and efficacy and considers the economic impact of these goods and services on the cost of health care. Selecting the most cost-effective drugs for an organizational formulary is important. However, it is equally important to determine the most appropriate way to use and prescribe these agents. Hence, developing and implementing appropriate use guidelines or policies based on sound pharmacoeconomic data can have a great impact on influencing prescribing patterns (Sanchez, 2005).

DM can cause complications in various organs such as the eyes, kidneys and nerves, thus it significantly increases morbidity and mortality. Complications, both microvascular and macrovascular, like hypertension and dyslipidemia that occur in patients with DM is a risk factor for cardiovascular disorders. These factors contribute to the increased occurrence of disease and death, which significantly becomes a burden on healthcare systems. The risk of heart failure in diabetic patients increases, with the relative risk increased by 10-15% per unit increase of HbA_{1c}. Heart failure occurs in 25%-40% of adult diabetic patients. Heart failure patients who are also diabetics usually have poor outcomes, thus increasing the number of visits to hospitals (Eurich *et al*., 2007).

The objective of therapy in diabetics is to avoid the occurrence of secondary diseases by optimizing blood glucose levels and maintaining patients' quality of life (Huang *et al*., 2006). Type 2 DM is a chronic disease that affects the general health and well being of patients. DM treatments, such as a strict diet, daily use of oral medications or insulin antidiabetics, affect the patients' health-related quality of life (HRQoL). Besides, long term complications such as nephropathy, neuropathy, heart disease and stroke will affect patients' health. Thus, they bring negative effects on patients' Quality of Live (QoL) (Redekop *et al*., 2002). The mortality rate of type 2 DM patients is about twice compared to patients without DM (Zhou *et al*., 2005).

The United Kingdom Prospective Diabetes Study (UKPDS) reported that glycaemic control would be worse. Due to this worsening glycaemic control, it is necessary to provide lifestyle intervention, monotherapy oral antidiabetics, followed by multiple therapies (Triplit *et al*., 2006). Schwartz *et al*. (2003) reported that patients not controlled with lifestyle intervention are given a single antidiabetic. A number of the 48% of the subjects of the research, who was given glibenclamide, needed additional therapy after 6 years. Based on the data from UKPDS, 8%, 42% and 24% of the subjects who were given a diet, insulin or sulfonylurea therapy can maintain their HbA_{1c} under 7% for 9 years. After 3 years of monotherapy treatment, there were around 50% of the subjects whose level of HbA_{1c} can be maintained.

UKPDS reported that many patients of type 2 DM will need exogenous insulin therapy later in their lives. The decrease of insulin secretion is caused by the decrease of pancreatic beta cells function so that oral antidiabetics cannot control blood glucose levels anymore (Raskin *et al*., 2005). Type 2 DM patients whose blood glucose control are decreasing due to oral antidiabetics can be treated by intensive insulin therapy which

can maintain glycaemia, since it can repair insulin secretion and action (Ryan *et al*., 2004). UKPDS reported that intensive therapy can reduce clinical risks and it was also reported that early addition of insulin to oral therapy can maintain HbA_{1c} at 7% in the first six years after diagnosis (Riddle *et al*., 2003).

Schwartz *et al*. (2003) reported the efficacy of basal insulin addition to patients with oral antidiabetics. Twice-daily 70/30 insulin combined with metformin indicated an equivalent decrease of HbA_{1c} (around 1.7%) with triple oral therapy (sulfonylurea, metformin, and thiazolidinedione), but only one third of the patients from each of the therapy groups reach a HbA_{1c} target $\leq$ 7%. The addition of insulin NPH, once a day, or glargine insulin on monotherapy or two combinations-oral antidiabetics can decrease HbA_{1c} levels reaching $\leq$ 7% in 60% patients, in which therapy groups with glargine showed a significant decrease of hypoglycemia nocturnal risk.

Another research conducted by Rosenstock *et al*. (2006) concluded that both the addition of glargine insulin and the maximum dose of rosiglitazone as a triple therapy regimen effectively decrease the HbA_{1c}. Groups with glargine therapy showed the decrease of fasting plasma glucose (FPG) in all patients and significant improvements in patients with high levels of HbA_{1c}. Compared to rosiglitazone, glargine insulin has more potential to initiate hypoglycemia. However, its side effects are less and does not cause edema, increase in weight, and it gives a good effect on the lipid profile with low cost therapy.

Concerning various pathophysiology of type 2 diabetes, the use of 2 to 3 oral antidiabetic combinations with different action mechanisms is the most rational measure. This regimen does not only repair glycaemic control, but also enable the decrease of the whole combination drug dose as well as the decrease of adverse drug reactions (ADR)

occurrence (Inzucchi, 2002). However, blood glucose control in the end will be worse due to decreasing function of pancreatic beta cells. Monotherapy with oral hypoglycaemic agent (OHA) will not be effective for long, thus it is continued by therapy combining 2 to 3 types of OHA (Indonesian Association of Endocrinologists, 2006). In the end, type 2 DM patients will need exogenous insulin therapy (Wright *et al*., 2002). However, the decision to switch to insulin therapy is belongs to the patients. Patients' refusal to start insulin therapy is possible due to the pain felt when the insulin is injected or the fear of hypoglycemia occurrence (Funnel, 2007). The choice of therapy for patient refusing insulin therapy is by maximizing regimens of triple oral therapy by means of increasing the dosage or usage frequency.

Polypharmacy and the increase of dosage will decrease the safety of therapy due to the increase of ADR and over dosage risks. This will effects the patients' quality of life and raise therapy costs (Cipolle *et al*., 1998). ADR can also become a potential contributing factor for patients who do not use the drugs as prescribed, which prevent the patients from obtaining optimum therapy (Krska, 2004). Drug-drug interaction can lead to hypoglycaemia and disturb patients' diabetes control as well as make the therapy less effective (Baxter, 2006).

Based on the explanations aforementioned, diabetes mellitus needs to get special attention with regard to the increasing incidence of the disease and the potential effects on the patients' quality of life as well as the large increase in medical expenses. Therefore, cost-effective therapy is needed in handling type 2 diabetes mellitus.

1.2 PROBLEM STATEMENT

Pharmacy managers, healthcare administrators, and insurers have to play a role and consider the increasing medical costs. In order to optimize the medical costs, a strategy of therapy management is required by using resources efficiently and effectively. Pharmacists encounter a challenge to provide appropriate, effective and efficient services by balancing access, costs and quality. To meet this responsibility, a related policy is required on the use of appropriate and cost-effective pharmaceuticals therapy design.

Type 2 diabetes is associated with long term complications that ultimately results in increased rate of adult blindness, renal failure, and amputation than any other disease. In addition, people with type 2 diabetes have an increased risk of stroke and myocardial infarction. Mortality rates of people with type 2 diabetes are about twice of those without diabetes. Because of the high morbidity, mortality, and costs associated with type 2 diabetes, there has been great interest in assessing the impact of medication therapy (triple oral therapy and insulin) on effectiveness, safety, quality of life, and cost.

1.3 RATIONALE OF THE STUDY

Diabetes mellitus is a chronic disorder that has been recognized by the Indonesian government as a major public health problem with far reaching consequences not just for its adverse impact on the health of Indonesians, but also for the economic burden it places on the health care system. Diabetes is ranked as the tenth leading cause of death in Indonesia. The number rises dramatically when deaths from diabetic complications are included.

Diabetes mellitus may affect patients' quality of life and have a burden on their social life. Diabetes may also cause several complications. A long-term complication encompasses retinopathy that causes loss of vision, nephropathy that causes kidney disease and peripheral neuropathy that causes amputation risks. A diabetes patient has a high risk of cardiovascular, peripheral vascular and cerebrovascular diseases. As a result, it may increase the economic burden for the diabetes patient, family, and health service system and government.

The expected achievement of DM therapy is to prevent DM-caused complications by maintaining a normal blood glucose level and improving the patient's quality of life. The blood glucose level can be controlled using diet therapy, physical exercise, oral hypoglycaemic drug or insulin. The diabetes patient whose blood glucose level has not been controlled on a monotherapy oral hypoglycaemic drug or a combination, may be given insulin therapy. However, the clinician often needs a rather long period to switch the patient from receiving an oral hypoglycaemic drug to insulin. The patient's hesitancy to switch to insulin therapy may be due to several reasons. A belief that insulin is for the person whose disease has been severe indicates the patient's failure in managing his/her disease. A belief that insulin is not effective, which may appear because a friend or family member who received insulin did not undergo any decrease in blood glucose levels, but even gained weight or hypoglycaemia event occurs more often. It may also be due to the belief that insulin causes complications, fear of pain during injection, fear of occurrence of hypoglycaemia events, and difficulties in arranging a schedule and insulin dose, hence the patient keeps using a combination of oral antidiabetic drugs.

Research on the comparison of intervention between insulin therapy and triple oral therapy on type 2 DM outpatients perceived from the clinical, humanistic and economic outcomes have not been conducted in Indonesia. Similar researches have been conducted in the United States and European countries, that is, comparing the addition of insulin and thiazolidinedione with the combination of sulfonylurea and metformin on the patients who had uncontrollable blood glucose levels. A research comparing the addition of insulin and acarbose with the combination of sulfonyurea and metformin on patients has also been conducted, but only perceived from its efficacy in controlling glycaemia. This research compared the addition and switching of therapy to insulin and triple oral therapy (sulfonylurea, metformin and acarbose) perceived from three outcome parameters, comprising clinical, humanistic and economic outcomes.

1.4 HYPOTHESIS

1.4.1 Insulin therapy, along with a combination of oral antidiabetics, is more effective and safer than triple oral therapy in a type 2 DM patient who has blood glucose level not under control.

1.4.2 Health-related quality of life in type 2 DM patient with poor glycaemic control who adds or switches the therapy to insulin is better than in the patient who keeps using triple oral therapy.

1.4.3 In terms of an institutional perspective, the addition or switching of therapy to insulin in the patient with poor glycaemic control is more cost-effective than triple oral therapy.

1.5 OBJECTIVE

1.5.1 General Aims

This study aims to compare the effectiveness and safety of two possible approaches for managing the failure of combination therapy with oral medication: 1) switching treatment to insulin and 2) combination therapy with oral medication for patients who are reluctant to initiate insulin; and 3) to estimate direct medical costs and cost-effectiveness between the two groups.

1.5.2 Specific Aims

In order to achieve the general aims, the study has the following objectives:

(i) To assess the effectiveness of the diabetes therapy which includes changes from the baseline for HbA_{1c}, fasting plasma glucose, postprandial plasma glucose, blood pressure, and lipid profiles between two groups (insulin therapy and triple oral therapy).

(ii). To assess safety parameters including general physical examination, clinical laboratory evaluations, and report adverse events and hypoglycaemic episodes between the two groups.

(iii). To compare health-related quality of life between the two groups

(iv). To compare the direct medical costs between the two groups

(v). To estimate the cost-effectiveness from the hospital perspective, of two possible approaches for managing the failure of combination therapy with oral medication (switching treatment to insulin vs combination therapy with oral medication for patients who are reluctant to initiate insulin).

1.6 CONTRIBUTION OF THE STUDY FINDINGS

The results of this research can be utilized by pharmacists or clinicians as a comparison of effectiveness and costs of type 2 DM therapy management. The data of cost-effectiveness and clinical effectiveness from the intervention of adding or giving insulin and triple oral therapy can be utilized as a reference in determining the most optimum therapy decision on type 2 DM patients.

It can be utilized also by institutions and managed care plans as a basis for determining the value of pharmaceuticals in order to achieve the expected outcomes. It can be used by policy makers as a basis in the formulary system, to put in, take out, with or without restrictions, on the related drugs with type 2 DM therapy and diabetes-related complications. The formulary system plays an important role in determining the use of an accurate drug, cost reduction and quality improvement. Formularies are mainly designed to promote the cost-effective use of safe and effective pharmaceutical products. In composing and revising the formulary, the selection criteria to choose drug alternatives are based on the clinical efficacy, effectiveness, side-effect risks and costs.

For the health service system, the research results would be useful for the development and justification of drug guidelines and disease management initiatives to promote the most appropriate use of medications for type 2 D

CHAPTER 2

LITERATURE REVIEW

Diabetes mellitus is a severe chronic disease marked by hyperglycaemia caused by disturbances in insulin secretion, insulin resistance, or both of them. The incidence of diabetes mellitus disease is increasing not only in Indonesia but all over the world. It is estimated that 300 million people will suffer from diabetes in 2025 (± 5.4% of world population). Type 2 diabetes mellitus represents 90% of all diabetes cases all over the world (Kaplan, 2004). Type 2 DM estimates will heavily affect the developing countries and will occur not only in the urban population. In the developing countries, DM disease also occurs in productive age populations such that it causes loss of human capital and productivity (Narayan and Williams, 2009).

In relation to the increasing prevalence and incidence of type 2 DM, it has been identified that the achievement of glycaemic control can decrease morbidity, and effective hyperglycaemic therapy management is the main priority. Type 2 diabetes mellitus is often related to various other health disturbances such as hypertension, dyslipidaemia, hypercoagulability, and abdominal obesity. It is often called as metabolic syndrome or insulin resistance syndrome (Carlisle *et al*., 2005; Nathan *et al*., 2009).

The target of DM therapy is to prevent and to impede the occurrence of complications, by keeping the blood glucose level in the normal range. The United Kingdom Prospective Diabetes Study (UKPDS) reported that an increase of HbA_{1c} by only 1%, can increase the risk of microvascular complications as much as 35% (Triplitt *et al*., 2005). In type 2 DM patients, more intensive treatment strategies can decrease the

occurrence of microvascular complications. An effective therapy strategy is always developed to increase the glycaemic control in DM patients for the purpose of preventing or delaying the occurrence of complications and increasing the patients' quality of life. To determine the appropriate therapy regimen in patients, the cost-effectiveness, efficacy as well as safety must be taken into consideration.

2.1 HYPERGLYCAEMIC THERAPY MANAGEMENT IN TYPE 2 DIABETES MELLITUS

Diabetes mellitus is marked by the increase in blood glucose levels caused by the metabolic abnormality of carbohydrate, fat, and protein. The diabetic condition is caused by inadequate insulin supply or inadequate tissue response toward insulin. The following is the explanation of the pathogenesis.

2.1.2 Pathogenesis of Type 2 Diabetes Mellitus

Type 2 diabetes mellitus is caused by the imbalance between the insulin sensitivity in peripheral tissues and the liver and insulin secretion from pancreatic β-cells. In non-diabetic patients, glucose homeostasis is mediated by insulin secretion stimulated from the pancreatic β-cells which will reduce the production of endogenous hepatic glucose and stimulate glucose uptake in peripheral tissues. In type 2 DM patients who are approximately 90% to 95% of diagnosed diabetes cases, resistance toward insulin in the liver and peripheral tissues occurs, and the ability of pancreatic β-cells to secrete insulin decreases. The occurrence of insulin resistance causes the pancreas to synthesize excessive insulin to metabolize the existing glucose. In the initial stages of the disease, type 2 DM patients can increase their insulin secretion. Insulin secretion

decreases more and more as time goes by, causing insufficient insulin production to maintain blood glucose. Although the pathophysiological process has not been clearly identified, the condition of hyperglycaemia has a toxic effect on the function of β-cells or causing their apoptosis without being equaled with the increase of pancreatic β-cell proliferation. The decrease of pancreatic β-cell function and relative insulin deficiency causes glucose intolerance and finally makes diabetes more serious (Bethel and Feinglos, 2005; Chitre and Burke, 2006).

Hyperglycaemia is the main cause of the occurrence of DM complications. The disturbing effect is because of the substances derived from sugar and they are known as advanced glycation end products (AGEs). AGEs are a heterogenic group of a molecule formed from a nonenzymatic reaction of reducing sugar with free amino group from protein, lipids, and nucleic acids. The early product of this reaction is called Schiff base which spontaneously rearranges itself into an Amadori product which is known as glycated haemoglobine (HbA_{1c}). The main characteristic of the precursor and these reactive AGEs is the ability to form a covalent bond between proteins which will change the function and structure as in a cellular matrix, basement membranes, and vessel-wall components. Another main characteristic is that it is able to interact with some cell surface AGE-binding receptors causing the occurrence of endocytosis and degradation or the activation of cellular, pro-oxidant, and pro-inflammatory pathways(Peppa *et al*., 2003).

2.1.3 Long-term Diabetic Complications

As the time goes by, diabetes can cause damage and dysfunction in various organ systems. Microvascular and macrovascular complications can contributes to the high rate of morbidity and mortality of diabetes.

(i) Macrovascular complications

This complication involves coronary artery, peripheral blood vessel, and cerebral blood vessel. Cardiovascular disease is the leading cause of mortality and the major cause of morbidity in patients with diabetes mellitus. The most common manifestations of cardiovascular disease are acute myocardial infarction, angina, heart failure, and sudden death. Cardiovascular disease results in a large part from the sequelae of atherosclerotic coronary artery disease (CAD) and hypertension, which are highly prevalent in patients with type 2 diabetes mellitus (Young and Chyun, 2005).

Atherosclerotic vascular disease is more common in diabetic than in nondiabetic individuals. Both pathologic studies and angiographic reports in individuals with coronary heart disease have shown that patients with diabetes have a greater number of coronary blood vessels involved with a more diffuse distribution of atherosclerotic lesions (Milicevic *et al*., 2008).

Peripheral vascular disease (PVD) affects the blood vessels outside the heart. In people with diabetes mellitus it often affects the arteries of the legs and may give rise to intermittent claudication, a cramping pain experienced on walking, due to reversible muscle ischaemia secondary to atherosclerosis. The iliac vessels can be affected, causing buttock pain and also erectile dysfunction (Hackett and Thomas, 2007).

(ii) Microvascular complications

The prevalence of retinopathy is very common in someone suffering from diabetes. After 20 years, more than 60% of type 2 DM patients will suffer retinopathy in various degrees of criticality. The incidence of diabetic retinopathy is because of the microangiopathy occurring in arteriolar retinal pre-capillary, capillary, and venula. The

damage is caused by microvascular leakage because of the decomposition of retinal barrier so that blood can enter, and the presence of microvascular block (Watkins, 2003). Glaucoma, cataract, and other disturbance in the eyes can cause retinopathy and it has to be evaluated.

Diabetic nephropathy occurs in 20-40% of the patients with diabetes and is the main cause of terminal kidney failure. Microalbuminuria (30-299 mg/24 hours) is the indication of nephropathy occurrence in type 2 DM. Patients with the microalbuminuria growing into macroalbuminuria (> 300 mg/24 hours) are likely to develop terminal kidney failure in some years (ADA, 2007). Uncontrolled blood pressure will make proteinuria more serious.

Neuropathy increases the morbidity in diabetes, mainly because of its role in the pathogenesis of diabetic ulcer (Feingold dan Funk, 2000). In addition to the improvement of blood glucose control to make hyperglycaemic damage progression slower, a specific medical treatment for the existing hyperglycaemic damage has not been available. The manifestations of diabetic autonomic neuropathy such as tachycardia in the condition of rest, orthostatic hypotension, gastroparesis, constipation, erectile dysfunction, neurovascular function disturbance, and hypoglycaemic autonomic failure (ADA, 2007).

2.1.4 Treatment Strategies in Type 2 Diabetes Mellitus

Diabetes patients have to get medical services from a well-coordinated team which includes physicians, nurse practitioners, physician assistants, nurses, dietitians, pharmacists, and mental health professionals with special skills and interests in diabetes. It really requires integrated cooperation and approach from the team to make sure that

diabetes patients participate actively in it (ADA, 2009). Patients play a very important role in the diabetes care team and they have to be trained, given skills and knowledge in preventing and handling hypoglycaemia, and also therapy adjustment based on the guideline of health care providers to reach glycaemic goals (Nathan *et al*., 2009).

The clinical route of DM disease is marked by a gradual decrease of pancreatic β-cell function, so that therapy adjustment is required (Heine *et al*., 2006). A general approach of therapy in type 2 DM begins with diet, exercise, weight control, and education. If the blood glucose level has not reached the target, a single antidiabetic can be given. The combination of two antidiabetics with different mechanism action can be given earlier if serious hyperglycemia occurs, or if monotherapy can not reach or keep glycaemic control (Bailey, 2005).

(i) Monotherapy

Giving medicine at the beginning of DM therapy is based on some factors including patient profile, early blood glucose levels, and economic considerations or formulary (Mudaliar and Henry, 2005). In determining a specific antidiabetic, it is necessary to consider its effectiveness in decreasing blood glucose levels, a extraglycaemic effect that can decrease long-term complications, safety profiles, tolerability, and cost (Nathan *et al*., 2009). Most oral antidiabetics have the same efficacy in decreasing HbA_{1c} level, except α-glucosidase inhibitor and nateglinide (Kimmel and Inzucchi, 2005).

Generally, patients with serious hyperglycaemia (> 300 mg/dL), ketonuria, ketonemia, pregnant patients, patients with acute myocardial infarction and all acute conditions have to be given insulin. In many patients, sulfonylurea or metformin can be

given as early therapy and the titration is conducted every one to two weeks according to patient response. In elderly patients with irregular eating profiles, the prescription of a short-acting secretagogue is suggested rather than sulfonylurea, because it can cause hypoglycaemia if the patients forget to eat. In predominant postprandial hyperglycaemia patients, the therapy choice is acarbose or miglitol, particularly in patients with high carbohydrate intake (Mudaliar and Henry, 2005). Dipeptidyl peptidase-4 (DPP-4) inhibitors are new oral antidiabetics which also takes effect in postprandial hyperglycaemia, but their half-life is very short (Fowler, 2007).

(ii) Combination Therapy

Diabetes is a progressive disease, and combination therapy is at times the only way to attain good glycaemic control in many patients (Inzucchi, 2006). If the second antidiabetic is added, the synergy of both antidiabetics and the possibility of medicine interaction have to be taken into consideration. Generally, antidiabetics with different action mechanisms will give bigger synergy (Nathan *et al*., 2009).

The combination of secretagogue and insulin sensitizer can work in synergy and is directed to two main pathophysiological abnormalities in diabetes. Therefore, more research has been conducted on the combination of sulfonylurea and metformin and it has been known that it can decrease additional HbA_{1c} level as high as 1.7%. Another alternative is the combination of sulfonylurea or metformin with thiazolidinedione. The combination of metformin and thiazolidinedione provides better efficacy because this combination also improves the main pathophysiological abnormality of DM. Metformin acts by decreasing hepatic glucose production, while the action of thiazolidinedione is particularly in insulin resistance in muscle and adipose tissues. The addition of acarbose

with sulfonylurea or metformin is a chosen alternative of a combination of drugs to improve glycaemic control, particularly in postprandial hyperglycaemia. If combination therapy with two oral agents does not achieve the desired goal, available options include (1) adding a third oral agent; (2) adding bed time insulin while maintaining therapy with one or both oral agents; or (3) switching the patient to a mixed-split insulin regimen (Mudaliar and Henry, 2005).

(iii) Insulin Therapy

There are some factors that need to be considered in determining an insulin regimen for individual patients. These factors can be categorized into two, namely patient factors and glycaemic factors. Before starting insulin therapy regimen, assessing patient factor needs to be conducted, that is, willingness to implement a specific insulin regimen, comfort level, ability (visual acuity, dexterity, and cognitive skills), and lifestyle factors (eating habits, physical activity, and schedule).

There are three insulin regimens that can be used to begin insulin therapy in type 2 DM patient, that is, basal insulin with oral antidiabetic, premixed insulin, or giving basal insulin with postprandial insulin. In insulin therapy regimen, therapy with basal and postprandial insulin is gold standard, but in using this regimen, the motivation of the patient must be high and enough time is needed to give support, education and follow up to the patient (Pearson and Powers, 2006).

Today, the use of background insulin with oral antidiabetic agents is a relatively common approach to initiating insulin therapy. Fasting glucose levels are targeted with background insulin and oral agents address mealtime glucose excursions. A second insulin regimen consists of premixed insulin given twice a day. This treatment approach

can include the use of insulin sensitizers (metformin, pioglitazone, rosiglitazone). A background and mealtime insulin regimen consists of a long-acting insulin as the background insulin with a rapid- or short-acting insulin taken at mealtime. This regimen most closely mimics the normal physiological insulin response to food intake (Pearson and Powers, 2006).

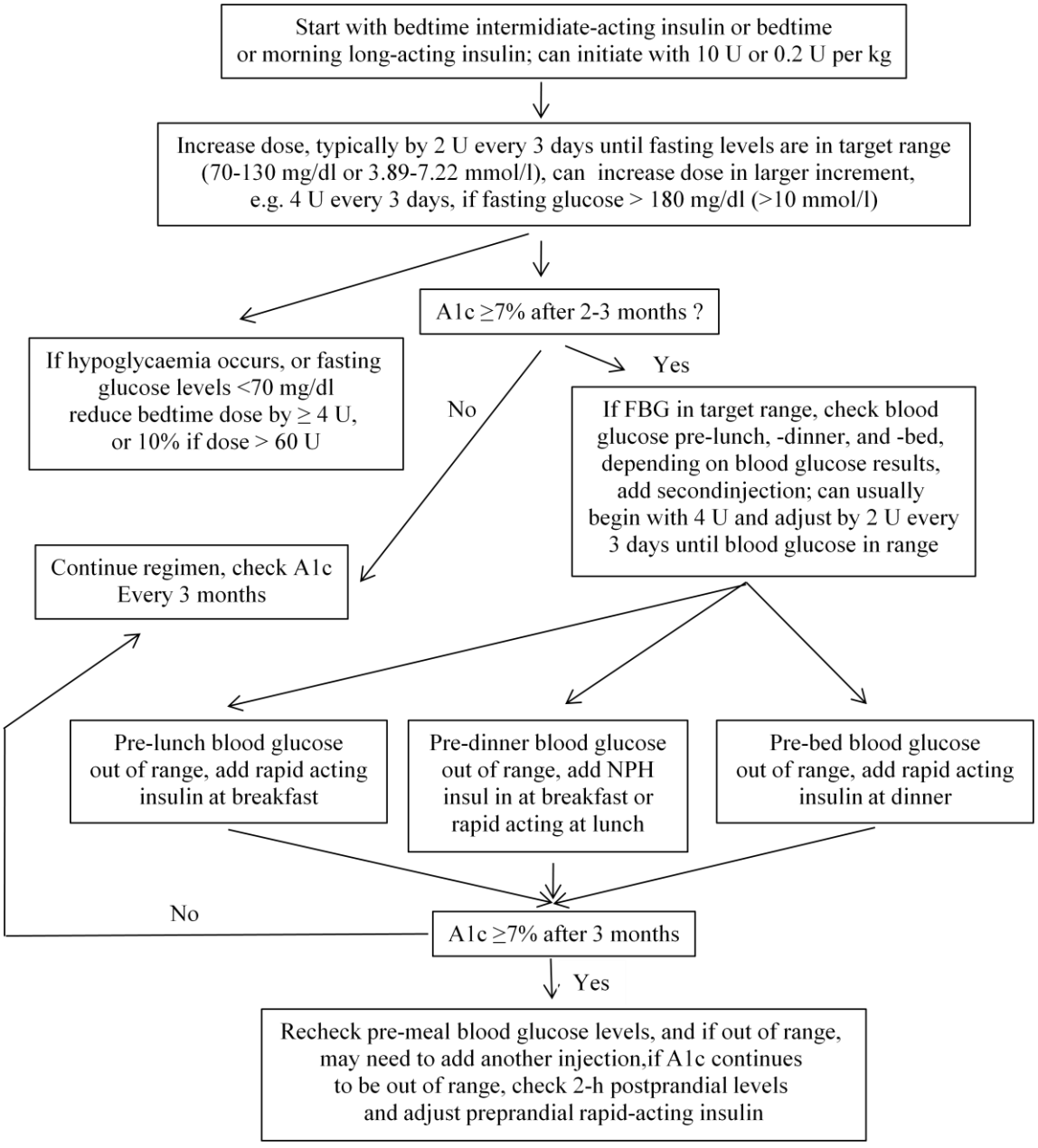

Figure 2.1 Initiation and adjustment of insulin regimens (Nathan *et al*., 2009)

The insulin initiation algorithm recommends starting with bedtime intermediate-acting insulin or bedtime or morning long-acting insulin. An initial dose could be either 10 U or 0.2 U/kg (Fig. 2.1). Table 2.1 shows the types of insulin available in Indonesia. NPH (Neutral Protamine Hagedorn) insulin more often causes nocturnal hypoglycaemia to occur than long-acting insulin. Some type 2 DM patients with HbA_{1c} value of ≤ 9% and high fasting blood glucose levels can reach HbA_{1c} value of < 7% by adding basal insulin analog. If blood glucose levels are in the target range (70 – 130 mg/dL) and HbA_{1c} value is above therapy target, the blood glucose level has to be evaluated and the patient can be given an additional second dosage of prandial insulin to reach glycaemic target. The dosage of prandial insulin can be titrated by evaluating postprandial glucose level (Blonde, 2007).

The American Diabetes Association and the European Association for the Study of Diabetes have published a consensus statement on the approach to management of hyperglycaemia in type 2 DM patients (Nathan *et al*., 2009). Figure 2.1 are the therapy algorithm recommended in the consensus.

The different types of insulin are based on onset, duration of action, source, pureness, concentration, and solubility. Table 2.1 shows the classification of insulin based on duration of action. In the past, insulin therapy for type 2 DM patients was regarded as a last choice but this paradigm begins to experience some shift as time went by. A research conducted by Ryan *et al*. (2004) shows that short-term intensive insulin therapy in newly diagnosed type 2 DM patients may increase blood glucose control for a long time.

Table 2.1. Description of onset, peak, and duration of insulins

Insulins	Onset	Peak	Duration
Short-acting insulin			
Regular (Actaprid®, Humulin®R)	30-60 minutes	30-90 minutes	3-5 hours
Analog rapid-acting insulin			
Insulin lispro (Humalog®)	5-15 minutes	30-90 minutes	3-5 hours
Insulin glulisine (Apidra®)	5-15 minutes		3-5 hours
Insulin aspart (NovoRapid®)	5-15 minutes	30-90 minutes	3-5 hours
		30-90 minutes	
Intermediate-acting insulin			
NPH (Insulatard®, Humulin®N)	2-4 hours	4-10 hours	10-16 hours
Lente	3-4 hours	4-12 hours	12-18 hours
Long-acting insulin			
Insulin glargine (Lantus®)	2-4 hours	peakless	-
Ultralente	6-10 hours	8-10 jam	-
Insulin detemir (Levemir®)	2-4 hours	peakless	-
Combinations (short- and intermediate-acting)			
70% NPH/ 30% regular (Mixtard®, Humulin®30/70)	30-60 minutes 10-20 minutes	*Dual*	10-16 hours
70% insulin aspart protamine/30% insulin aspart (NovoMix®30)	5-15 minutes	*Dual*	15-18 hours
75% insulin lispro protamine/25% insulin lispro injeksi(Humalog® Mix 25)		1-2 hours	16-18 hours

Source : Indonesian Association of Endocrinologists (2006)

The unwillingness of patients to change to insulin therapy is probably caused by many things. Common barriers among patients include beliefs that insulin is a personal failure, that insulin is not effective, that insulin causes complications or even death, or that insulin injections are painful, as well as fear of hypoglycemia, loss of independence, weight gain, and cost (Funnel, 2004 ; Meece, 2006).

(iv) Type 2 Diabetes Mellitus Treatment Algorithm

Therapy in type 2 DM patients who have just been diagnosed begins with lifestyle interventions. Lifestyle intervention can improve blood glucose level, blood pressure, lipid level, and can decrease weight or prevent weight increase. Therapy with metformin can be given together with lifestyle intervention at the time of diagnosis (Fig. 2.2). Metformin is recommended to be given as the first line therapy in non contraindicated patients because of its advantageous effect on blood glucose levels, for not causing weight increase and hypoglycaemia. Moreover, side effects seldom occur, there is a high level of acceptance, and it is relatively low cost. Metformin dosage can be titrated to effective maximum dosage every 1 to 2 months.

If lifestyle intervention and a maximal tolerated dose of metformin fail to reach a glycaemic target, other antidiabetics can be added in 2 to 3 months of early therapy, or when the HbA_{1c} level target is not reached. If in lifestyle intervention, metformin and sulfonylurea or basal insulin cannot reach a glycaemic target, the next step is giving insulin intensively. The intensification of giving insulin is conducted by adding short or rapid acting insulin given before eating to reduce the increase of postprandial blood glucose. If insulin is given, insulin secretagogue must be stopped or decreased because it does not give a synergic effect. Although the addition of a third oral antidiabetic can be considered, particularly in HbA_{1c} level of >8%, this approach is less effective in decreasing blood glucose levels and more expensive than giving therapy intensification with insulin (Nathan *et al*., 2009).

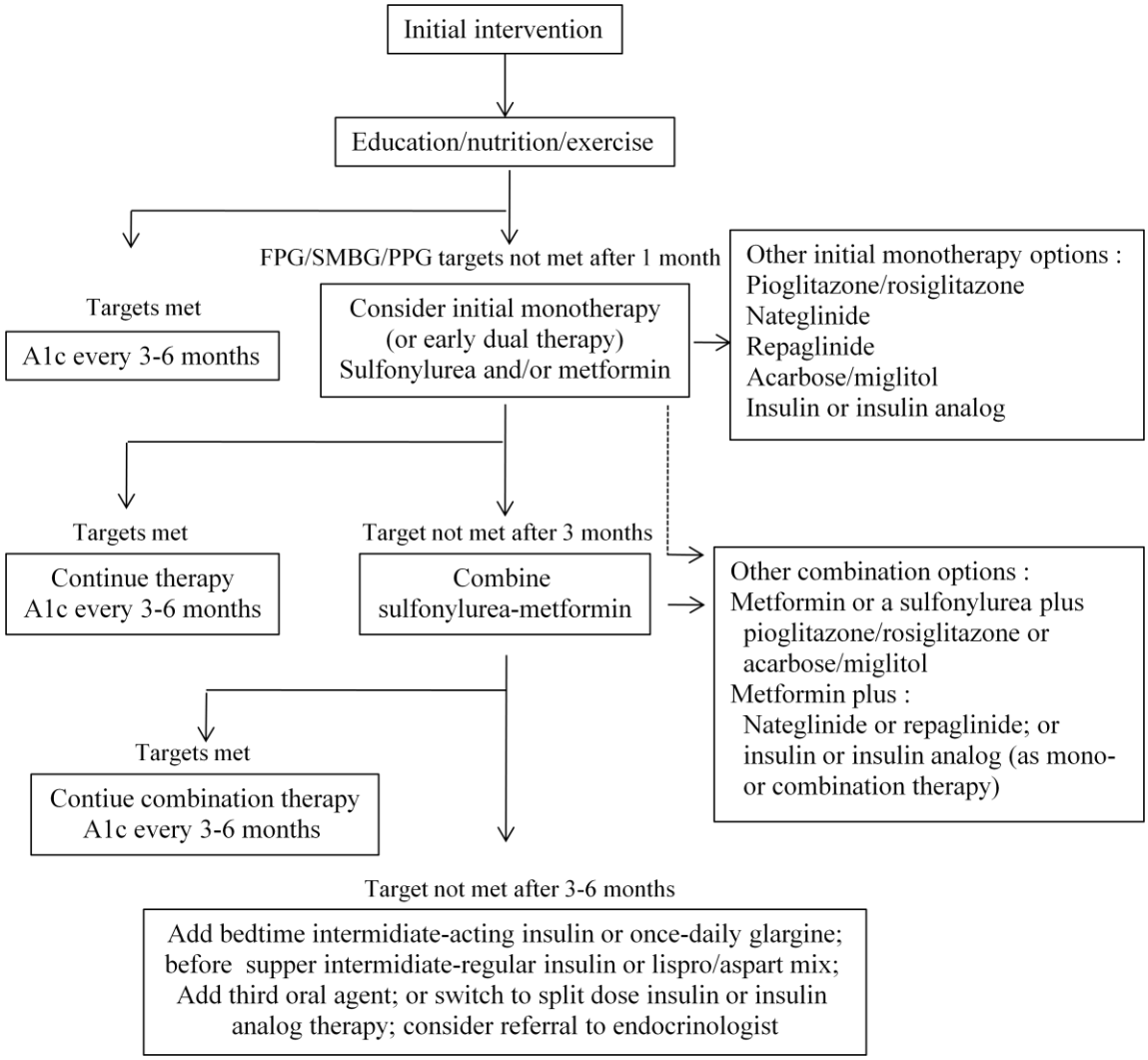

Figure 2.2 Glycaemic control algorithm for type 2 DM in children and adults (Triplitt *et al*., 2005)

2.1.5 The Effectiveness and Safety of Antidiabetics

The selection of specific antidiabetics is based on its effectiveness in decreasing blood glucose levels, extraglycaemic effects that can decrease long term complications, safety profile, tolerability, ease-of-use and expense (Nathan *et al*., 2009). Each of the antidiabetics has similarities and differences in the side effects, contraindications, and interaction with other medicines. The effects of antidiabetics can be increased by giving