ANTIDIABETIC DRUG REGIMENS AND GLYCEMIC CONTROL IN TYPE 2 DIABETIC PATIENTS AT RAMATHIBODI HOSPITAL

PRIPHAGA SUWITTAYARAT

A THESIS SUBMITTED IN PARTIAL FULFILLMENT
OF THE REQUIREMENTS FOR
THE DEGREE OF MASTER OF SCIENCE IN PHARMACY
(PHARMACOLOGY)
FACULTY OF GRADUATE STUDIES
MAHIDOL UNIVERSITY
2006

ISBN 974-04-7332-6

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was submitted to the Faculty of Graduate Studies, Mahidol University
for the degree of Master of Science in Pharmacy (Pharmacology)
on
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ACKNOWLEDGEMENT

I wish to express my sincere gratitude to Associate Professor Somjai Nakornchai, my major-advisor for her guidance, support, encourage and tremendous assistance my study.

I wish to give my sincere thank to Associate Professor Dr. Petcharat Pongcharoensuk who give me a chance to conduct this work and also for her thoughtful guidance, supervision, and encouragement.

I wish to express my deep appreciation to my co-advisor: Assistant Professor Dr. Naeti Suksomboon, Dr. Usa Chaikledkaew for their criticisms and valuable device.

I wish to thank Associate Professor Dr. Supatra Srichairat, for kindness in providing suggestions for improvement, and who was the external examiner of the thesis defense.

Finally, my grate thank is directed to my parents and my brother for their love, encouragement and everything's given to me throughout my life.

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ANTIDIABETIC DRUG REGIMENS AND GLYCEMIC CONTROL IN TYPE 2 DIABETIC PATIENTS AT RAMATHIBODI HOSPITAL

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ABTRACT

Despite evidence that good glycemic control can improve medical outcomes, management of type 2 diabetes mellitus (DM) is often unsuccessful. This retrospective study was conducted at Ramathibodi hospital between July and November 2004. The antidiabetic drug regimens and glycemic control among 246 type 2 DM patients were collected from medical records started from their first diagnosis until their last visits in September 2003. Drugs used in controlling the comorbidities, hypertension and dyslipidemia are investigated as well. The majority of patients were female (64.78%). The average age was 62±11.21 years, and the mean diabetes duration was 9±6 years. A high portion of patients had also a diagnosis of hypertension, dyslipidemia or both (76.83%, 75.20%, 59.35%, respectively).

Most patients (43.50%) were receiving dual oral antidiabetic drugs (OADs) therapy. Pharmacologic management of hyperglycemia was intensified with duration of diabetes. According to the Endocrine Society of Thailand, >70% of the patients are considered as having poor glycemic controll. For the comorbidities, only 43.91% of patients achieved the target blood pressure and 28.11% of patients achieved the target lipidemia.

Only 106 patients completed information from their first DM diagnosis, 19.81% started with nondrug therapy. However, all patients finally started drug therapy. After 3 months of treatment with the first regimen, only 33.02% of patients can be considered as having good glycemic control, 66.98% of patients can be considered as having effective treatment.

HbA1c is the primary target for glycemic control. However, the test is expensive and only 158 from 246 patients (64.23%) have HbA1c data. Moreover, the correlation between HbA1c and FPG when both values coexist is not as good as expected (r=0.59).

KEY WORDS: ANTIDIABETIC / GLYCEMIC CONTROL
59 P. ISBN 974-04-7332-6

รูปแบบและผลการใช้ยาควบคุมระดับน้ำตาลในเลือดในผู้ป่วยเบาหวานชนิดที่ 2 โรงพยาบาลรามาธิบดี (ANTIDIABETIC DRUG REGIMENS AND GLYCEMIC CONTROL IN TYPE 2 DIABETIC PATIENTS AT RAMATHIBODI HOSPITAL)

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บทคัดย่อ

แม้มีหลักฐานยืนยันว่า การควบคุมระดับน้ำตาลในเลือดที่ดีทำให้ผลในการรักษา โรคเบาหวานดีขึ้น แต่การจัดการในโรคเบาหวานให้บรรลุผลมักไม่ประสบความสำเร็จ การศึกษานี้เป็นการศึกษาแบบย้อนหลัง ช่วงเวลาที่ศึกษาระหว่างเดือนกรกฎาคมถึงเดือนพฤศจิกายน 2547 ศึกษาในผู้ป่วยเบาหวานชนิดที่สองในโรงพยาบาลรามาธิบดี จำนวน 246 คน โดยเก็บข้อมูลเกี่ยวกับยาลดระดับน้ำตาลในเลือดที่ใช้ และผลการรักษาจากแฟ้มประวัติผู้ป่วย ตั้งแต่เริ่มวินิจฉัยว่า เป็นเบาหวาน ถึง กันยายน 2546 นอกจากนี้ได้เก็บข้อมูลเกี่ยวกับยาลดความดันโลหิต และยาลดไขมันในเลือดด้วย ผู้ป่วยที่ศึกษาเป็นเพศหญิงร้อยละ 64.78 อายุเฉลี่ย 62±11.21 ปี ผู้ป่วยที่ได้รับการวินิจฉัยว่ามีภาวะความดันโลหิตสูง ไขมันในเลือดสูง หรือมีทั้งสองภาวะร่วมด้วยมีสัดส่วนสูง (76.83%, 75.20%, 59.35% ตามลำดับ)

ผู้ป่วยส่วนใหญ่ (ร้อยละ 43.50) รักษาด้วยการใช้ยาลดระดับน้ำตาลในเลือดชนิดรับประทาน 2 ชนิด การใช้ยาเพิ่มขึ้นเมื่อเป็นเบาหวานนานขึ้น เมื่อพิจารณาตามเกณฑ์ของสมาคมต่อมไร้ท่อแห่งประเทศไทย มีผู้ป่วยมากกว่าร้อยละ 70 ที่ควบคุมระดับน้ำตาลในเลือดได้ไม่ดี ผู้ป่วยร้อยละ 43.91 ควบคุมความดันโลหิตได้ตามเป้า และ ผู้ป่วยร้อยละ 28.11 ควบคุมระดับไขมันในเลือดได้ตามเป้า

ผู้ป่วย 106 ราย ที่มีข้อมูลการรักษาตั้งแต่วันเริ่มวินิจฉัยว่าเป็นเบาหวาน ร้อยละ 19.81 เริ่มควบคุมระดับน้ำตาลในเลือดด้วยการไม่ใช้ยา แต่ต่อมาทุกคนล้วนต้องใช้ยา หลังจากใช้ยาสูตรแรกเป็นเวลา 3 เดือน มีเพียงร้อยละ 33.02 ที่ควบคุมระดับน้ำตาลในเลือดได้ดี และร้อยละ 66.98 มีผลการรักษาที่ดี

ค่าฮีโมโกลบินเอวันซี เป็นเป้าหมายสำคัญในการควบคุมระดับน้ำตาลในเลือดของผู้ป่วยเบาหวาน อย่างไรก็ตาม การวัดค่านี้มีค่าใช้จ่ายสูง มีผู้ป่วยเพียง 158 จาก 246 คนเท่านั้นในการศึกษานี้ที่มีค่าฮีโมโกลบินเอวันซี นอกจากนั้น ค่าสัมประสิทธิ์สหสัมพันธ์เปียร์สันระหว่างค่าระดับน้ำตาลในเลือดขณะอดอาหารกับค่าฮีโมโกลบินเอวันซี เมื่อมีข้อมูลทั้งสองร่วมกัน มีค่าไม่สูงดังคาด โดยมีค่าเพียง 0.59

59 หน้า ISBN 974-04-7332-6

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CHAPTER 1
INTRODUCTION

Type 2 diabetes mellitus (DM) is chronic and progressive, as are its underlying abnormalities and long-term complications. In most affected individuals, two defects coexist: insulin resistance and defective β-cell function that results in insulin insufficiency. Both types of abnormality have genetic origins, the effects of which may be accentuated by environment and cultural influences such as diet and lifestyle. Type 2 diabetes develops gradually, typically becoming more severe and difficult to treat over time. At the time of diagnosis, glycosylated hemoglobin (HbA_{1c}) levels close to 9% are typical, and many patients have had significant elevation of HbA_{1c} levels for years.

Initially, lifestyle modifications may be sufficient to achieve glycemic control, but long-term adherence to such changes is unusual; even patients who successfully maintain programs of diet, exercise, and weight control may experience recurrent hyperglycemia because of declining insulin secretion. Most patients require drug therapy with antihyperglycemic agents soon after type 2 diabetes is diagnosed. Monotherapy with oral agents has a high secondary failure rate, as the pathophysiologic defects become more pronounced over time; mean glucose concentrations gradually rise to initial levels in about 5 years. Furthermore, patients with fasting plasma glucose (FPG) levels well over 200 mg/dl at diagnosis may not achieve satisfactory glycemic control. Most patients, seek to avoid or postpone insulin therapy when possible. For these patients a wide range of oral antidiabetic agents with different mechanisms of action can be used to treat both defects synergistically. Such combination therapy offers the prospect of enhanced glycemic control, fewer adverse effects, and better outcomes (1).

Clinical trial findings have clearly demonstrated that intensive glycemic control results in a reduced risk of type 2 DM complications (2, 3) and are reflected by evidence-based clinical practice guidelines (4). However, many studies showed that a

substantial proportion of type 2 DM patients have unacceptable levels of glycemic control (5-7), and there is no data about glycemic control in Thai patients.

This study is a retrospective analysis to study the antidiabetic drug regimens and glycemic control in type 2 diabetic patients at Ramathibodi Hospital. Data were obtained from medical chart review. The objectives is to study the antidiabetic drug regimens and glycemic control in type 2 diabetic patients at the Ramathibodi Hospital and to evaluate the relationship between HbA_{1c} and fasting blood glucose (FPG) levels when both information exist.

Expected Outcomes and Benefits

Despite the demonstrated benefit of intensive therapy in reducing long-term complications in patients with type 2 diabetes, high percentage of patients in clinical practice did not reach therapeutic goal. The results of this study will show the pattern of antidiabetic regimens and glycemic control in DM patients at Ramathibodi Hospital. It could be a preliminary data to set any intervention to improve glycemic control in Thai type 2 diabetic patients.

CHAPTER 2
LITERATURE REVIEW

Prevalence of diabetes mellitus (DM) in adults worldwide was estimated to be 4.0% in 1995 and to rise to 5.4% by the year 2025. It is higher in developed than in developing countries. The number of adults with DM in the world will rise from 135 million in 1995 to 300 million in the year 2025. The major part of this numerical increase will occur in developing countries. There will be a 42% increase, from 51 to 72 million, in the developed countries and a 170% increase, from 84 to 228 million, in the developing countries. Thus, by the year 2025, >75% of people with DM will reside in developing countries, as compared with 62% in 1995. The countries with the largest number of people with diabetes are, and will be in the year 2025, India, China, and the U.S. In developing countries, the majority of people with diabetes are in the age range of 45-64 years. In the developed countries, the majority of people with diabetes are aged ≥65 years. This pattern will be accentuated by the year 2025. There are more women than men with diabetes, especially in developed countries. In the future, diabetes will be increasingly concentrated in urban areas (8, 9).

2.1 Pathogenesis of type 2 DM

Type 2 DM is characterized by impaired insulin secretion by pancreatic beta cells and insulin resistance in the liver and muscles, which lead to dysregulation of blood glucose (BG) levels. The resulting hyperglycemia has 2 components. Basal hyperglycemia is caused by unrestrained basal hepatic glucose output primarily a consequence of hepatic resistance to insulin action. Postprandial hyperglycemia, on the other hand, is caused by abnormal insulin secretion by beta cells in response to a meal, unregulated hepatic glucose production, and the concomitant impairment of glucose uptake by peripheral tissues, particularly muscle and adipose tissue (10, 11). Chronic hyperglycemia further impairs beta-cell secretory action and tissue sensitivity to insulin, a phenomenon called glucotoxicity, further compromising insulin secretion and action (11).

The mechanisms responsible for impaired glucose homeostasis in type 2 DM are discussed briefly to provide the foundation for discussion of currently available oral agents, including their mechanism of action, efficacy and side effects(10).

After ingestion of glucose, maintenance of normal glucose tolerance depends on three events that must occur in a tightly coordinated fashion: 1) stimulation of insulin secretion, 2) insulin-mediated suppression of endogenous (primary hepatic) glucose production by the resultant hyperinsulinemia, and 3) insulin-mediated stimulation of glucose uptake by peripheral tissues, primarily muscle. Hyperglycemia also has its own independent effect of suppressing hepatic glucose production and enhancing muscle glucose uptake, but these effects are modest compared to those of insulin (10).

In patients with type 2 DM and established fasting hyperglycemia, the rate of basal hepatic glucose production is excessive, despite plasma insulin concentrations that are increased twofold to fourfold. These findings provide unequivocal evidence for hepatic resistance to insulin, and this evidence is substantiated by an impaired ability of insulin to suppress hepatic glucose production. Accelerated gluconeogenesis is the major abnormality responsible for the increased rate of basal hepatic glucose production. The increased rate of basal hepatic glucose production is closely correlated with the increase in fasting plasma glucose level. Because the fasting plasma glucose level is the major determinant of the mean day-long blood glucose level (which clinically is reflected by the HbA_{1c} value), it follows that agents that reduce the elevated basal rate of hepatic glucose production will be especially effective in improving glycemic control (10).

Muscle tissue in patients with type 2 DM is resistant to insulin. Defects in insulin receptor function, insulin receptor-signal transduction pathway, glucose transport and phosphorylation, glycogen synthesis, and glucose oxidation contribute to muscle insulin resistance. In response to a meal, the ability of endogenously secreted insulin to augment muscle glucose uptake is markedly impaired, and muscle insulin resistance and impaired suppression of hepatic glucose production contribute approximately equally to the excessive postprandial increase in the plasma glucose level. It follows that drugs that improve muscle insulin sensitivity will be effective in decreasing the excessive increase in plasma glucose level after carbohydrate ingestion (10).

2.2 Clinical progression and complication

Although the exact etiology of type 2 DM is still unclear, the clinical progression of the disease is well understood. In many cases, metabolic and hormonal changes occur many years before clinical symptoms (ie, overt hyperglycemia [fasting plasma glucose (FPG) > 126 mg/dL or glycosylated hemoglobin (HbA_1c) >6%]) appear. Glycemic gradually deteriorates, and the progression of type 2 DM eventually leads to an increased risk for microvascular and macrovascular complications. These long-term complications account for elevated rate of morbidity and premature mortality associated with type 2 DM and drastically reduced patients quality of life (11).

An epidemiologic analysis (12) conducted by the United Kingdom Prospective Diabetes Study (UKPDS) Group estimated that for every 1% decrease in mean HbA_1c, a marker of long-term glycemic control, the incidence of clinical complications decreased significantly. Over the entire range of HbA_1c levels represented in the study (<6%-≥10%), the risk for microvascular complications was reduced by 37% for each 1% reduction in HbA_1c, the risk for any clinical event or death associated with DM was reduced by 21%, and the risk for myocardial infarction was reduced by 14% ($P<0.001$ for all relative hazards) (12). According to the recommendations of The Endocrine Society of Thailand, treatment glycemic goal for patients with type 2 DM is near normoglycemia, which includes an FPG level 80 to 120 mg/dL, a postprandial plasma glucose (PPG) level 80 to 160 mg/dL, and an HbA_1c level <7.0% (13).

Ample evidence indicates that type 2 DM follows a progressive course. Both insulin resistance (ie, supranormal insulin levels required to achieve a given physiologic effect) and beta-cell dysfunction appear to be present at the earliest detectable stages of DM (Figure 2.1). However, what determines the development of

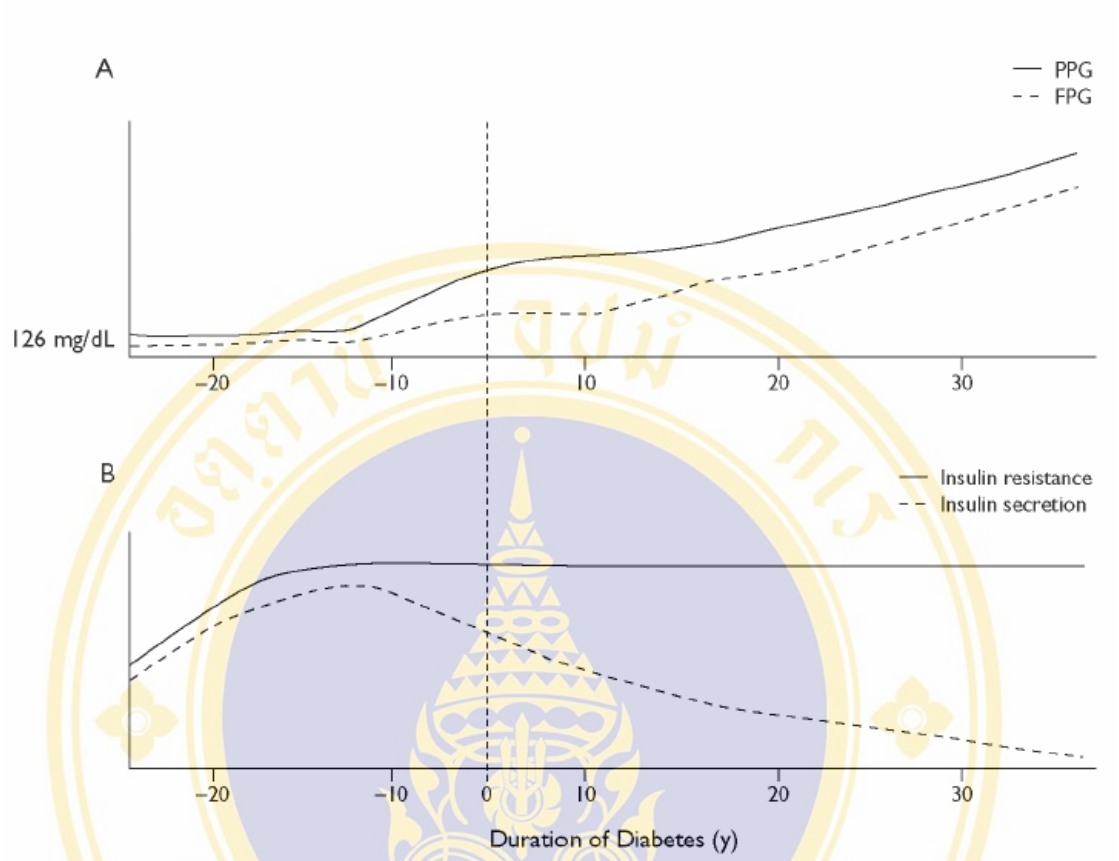


Figure-2.1 Natural progression of type 2 diabetes mellitus (DM). (A) Several years before the onset to type 2 DM, postprandial plasma glucose (PPG) and fasting plasma glucose (FPG) levels begin to increase from normal values (normal: 126 mg/dL). (B) Beta-cell function gradually decreases and patients with type 2 DM lose insulin secretory capacity. In addition, insulin resistance precedes onset of type 2 DM. Adapted with permission (11).

type 2 DM is the gradual deterioration of beta-cell function, which clearly begins years before symptomatic presentation and diagnosis. During early stages of the disease, before the onset of hyperglycemia, beta-cell function is abnormally high (although first-phase release is lost), producing enough insulin to overcome tissue resistance to insulin action. As beta-cell function decreases, however, plasma insulin levels become insufficient to maintain normoglycemia, which leads to impaired glucose tolerance and overt DM. Elevated FPG (>126 mg/dL) usually occurs at a relatively late stage in DM, when >50% of beta-cell function has already been lost. However, diabetes-related macrovascular complications may develop much earlier. Cardiovascular risk is clearly increased before the rise in FPG. In addition, the presence of microvascular

complications at diagnosis, which are clearly related to hyperglycemia, indicates that hyperglycemia often goes undetected for several years before diagnosis (Figure 2.2).

The UKPDS (15), the largest and longest (10 years) study of type 2 DM ever conducted, established that the beta-cell dysfunction is progressive, despite aggressive therapy. This large-scale (N=4209), long-term, randomized trial compared the effects of diet alone versus diet plus various intensive drug regimens in patients with newly diagnosed type 2 DM. A 6-year interim report showed an inevitable increase of hyperglycemia as insulin secretion decreased, even though patients were adhering to a strict dietary regimen and taking increasing doses of a sulfonylurea (glyburide or chlorpropramide), insulin, or metformin. During the first 6 years of the study, among patients randomized to initial long-acting insulin, nearly 25% of the patient population required the addition of short-acting insulin before meals to control hyperglycemia not curbed by increases in the dose of long-acting insulin. The final results of the UKPDS at 10 years also confirmed the progressive nature of type 2 DM, with increases in FPG and HbA_1c in all treatment groups, although intensive treatment was associated with lower median HbA_1c. Although all groups of intensively treated patients had a gradual worsening of glycemic control, intensive treatment did provide a substantial risk reduction of 25% ($P<0.010$) for microvascular complications (2). The proportion of patients with optimal glycemic control decreased from ~50% after 3 years of therapy to ~25% after 9 years of treatment with diet alone or sulfonylurea, insulin, or metformin treatment (14, 15).

These observations suggest that to limit hyperglycemia and prevent the development of acute and long-term diabetic complications, the pharmacologic management of type 2 DM needs to evolve from monotherapy to progressive dose escalation and/or the addition of other therapeutic oral hypoglycemic agents. Available oral hypoglycemic drugs generally effective in controlling glucose levels while some beta-cell function remains, but they have only limited capacity to regulate glucose metabolism as insulin secretion decreases and eventually fails. Most patients who develop type 2 DM eventually require some type of insulin treatment (2).

Recommended glycemic goals for nonpregnant individuals are shown in Table 2.1 A major limitation to the available data are that they do not identify the optimum level of control for particular patients, as there are individual differences in the risks of

hypoglycemia, weight gain, and other adverse effects. Furthermore, with multifactorial interventions, it is unclear how different components (e.g., educational interventions, glycemic targets, lifestyle changes, and pharmacological agents) contribute to the reduction of complications. There are no clinical trial data available for the effects of glycemic control in patients with advanced complications, the elderly (≥65 years of age), or young children (<13 years of age) (4). Less stringent treatment goals may be appropriate for patients with limited life expectancies, in the very young or older adults, and in individuals with comorbid conditions. Severe or frequent hypoglycemia is an indication for the modification of treatment regimens, including setting higher glycemic goals.

More stringent goals (i.e., a normal HbA_{1c}, <6%) can be considered in individual patients based on epidemiological analyses that suggest that there is no lower limit of HbA_{1c} at which further lowering does not reduce the risk of complications, at the risk of increased hypoglycemia (particularly in those with type 1 diabetes). However, the absolute risks and benefits of an HbA_{1c} goal of <6% are currently being tested in an ongoing study (ACCORD [Action to Control Cardiovascular Risk in Diabetes]) in type 2 diabetes.

By performing an HbA_{1c} test, health providers can measure a patient's average glycemia over the preceding 2-3 months and, thus, assess treatment efficacy. HbA_{1c} testing should be performed routinely in all patients with diabetes, first to document the degree of glycemic control at initial assessment and then as part of continuing care. Since the HbA_{1c} test reflects mean glycemia over the preceding 2-3 months, measurement approximately every 3 months is required to determine whether a patient's metabolic control has been reached and maintained within the target range. Thus, regular performance of the HbA_{1c} test permits detection of departures from the target (Table 2.1) in a timely fashion. For any individual patient, the frequency of HbA_{1c} testing should be dependent on the clinical situation, the treatment regimen used, and the judgment of the clinician.

Table-2.1 Summary of recommendations for adults with diabetes (16)

Glycemic control	
HbA_{1c}	<7.0%*
Preprandial capillary plasma glucose	90–130 mg/dl (5.0–7.2 mmol/l)
Peak postprandial capillary plasma glucose†	<180 mg/dl (10.0 mmol/l)
Blood pressure	<130/80 mmHg
Lipids‡	
LDL	<100 mg/dl (2.6 mmol/l)
Triglycerides	<150 mg/dl (1.7 mmol/l)
HDL	>40 mg/dl (1.1 mmol/l)§

Key concepts in setting glycemic goals:

- HbA_{1c} is the primary target for glycemic control
- Goals should be individualized
- Certain populations (children, pregnant women, and elderly) require special considerations
- Less intensive glycemic goals may be indicated in patients with severe or frequent hypoglycemia
- More stringent glycemic goals (i.e. a normal HbA_{1c}, 6%) may further reduce complications at the cost of increased risk of hypoglycemia (particularly in those with type 1 diabetes)
- Postprandial glucose may be targeted if HbA_{1c} goals are not met despite reaching preprandial glucose goals

*Referenced to a nondiabetic range of 4.0–6.0% using a DCCT-based assay. †Postprandial glucose measurements should be made 1–2 h after the beginning of the meal, generally peak levels in patients with diabetes. ‡Current NCEP/ATP III guidelines suggest that in patients with triglycerides ≥200 mg/dl, the "non-HDL cholesterol" (total cholesterol minus HDL) be used. The goal is ≤130 mg/dl. §For women, it has been suggested that the HDL goal be increased by 10 mg/dl.

Glycemic control is best judged by the combination of the results of the patient's self-monitoring of blood glucose (SMBG) testing and the current HbA_{1c} result. The HbA_{1c} should be used not only to assess the patient's control over the preceding 2-3 months but also as a check on the accuracy of the meter (or the patient's self-reported results) and the adequacy of the SMBG testing schedule. Table 2.2 contains the correlation between HbA_{1c} levels and mean plasma glucose levels based on data from the DCCT (16).

Table-2.2 Correlation between HbA_{1c} level and mean plasma glucose levels on multiple testing over 2-3 months (16)

HbA_{1c} (%)	mean plasma glucose (mg/dl)
6	135
7	170
8	205
9	240
10	275
11	310
12	345

Elevated postchallenge (2-h OGTT) glucose values have been associated with increased cardiovascular risk independent of FPG in some epidemiological studies. Postprandial plasma glucose (PPG) levels >140 mg/dl are unusual in nondiabetic individuals, although large evening meals can be followed by plasma glucose values up to 180 mg/dl. There are now pharmacological agents that primarily modify PPG and thereby reduce HbA_{1c} in parallel. Thus, in individuals who have premeal glucose values within target but who are not meeting HbA_{1c} targets, consideration of monitoring PPG 1-2 h after the start of the meal and treatment aimed at reducing PPG values <180 mg/dl may lower HbA_{1c}. However, it should be noted that the effect of these approaches on micro- or macrovascular complications has not been studied (4).

2.3 Treatment of type 2 DM

In patients with newly diagnosed type 2 diabetes in whom insulin therapy is not indicated, pharmacologic therapy with either a sulfonylurea or metformin be initiated as monotherapy, as long as no contraindications are present (Figure 2.2).

This view, which is based on proven efficacy, safety, and long-term clinical experience with oral agents, is shared by other leading authorities on diabetes (2, 3). When used as monotherapy, sulfonylureas and metformin are equally effective in decreasing plasma glucose levels. Because metformin promotes weight loss and reduces lipid levels, it is preferred in overweight patients with type 2 diabetes and dyslipidemia. In lean patients with type 2 diabetes, therapy with either a sulfonylurea

or metformin can be initiated. The dose of metformin or sulfonylureas can be increased over a 4- to 8-week period until the therapeutic goal (fasting plasma glucose <126 mg/dl and HbA_{1c} value <7%) is achieved or the maximum dose is reached.

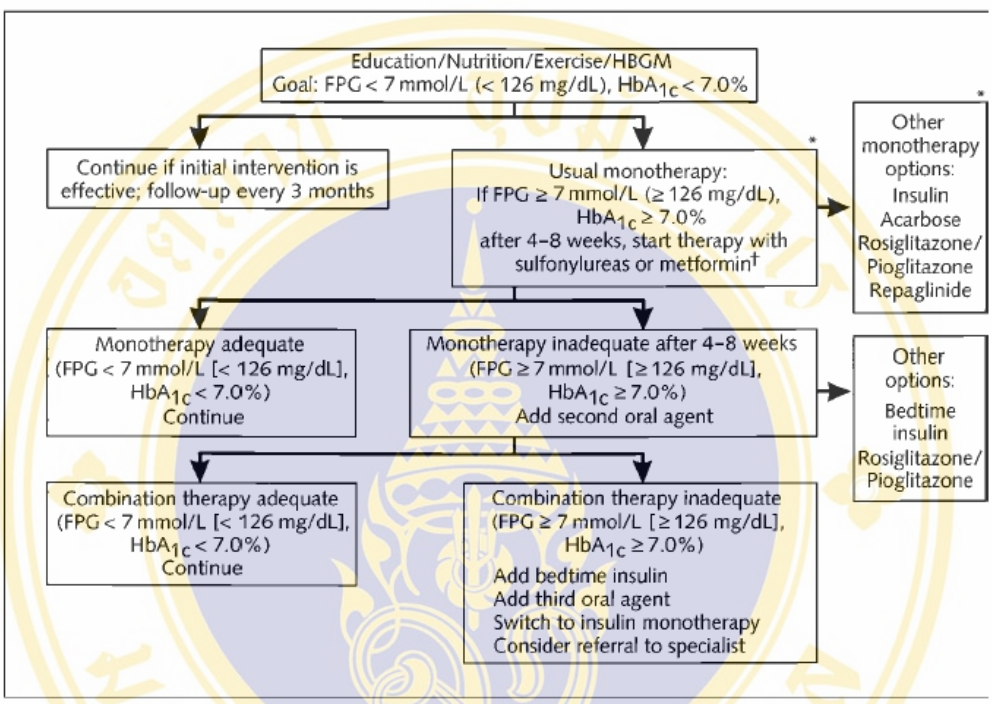


Figure-2.2 Pharmacologic algorithm for treatment of patients in whom type 2 diabetes is inadequately controlled with diet and exercise (17)**.**

FPG = fasting plasma glucose level; HbA_{1c} = hemoglobin A_{1c} value; HBGM = home blood glucose monitoring. ∗Goals and therapies must be individualized, Metformin preferred if the patient is obese or dyslipidemic.

If monotherapy with a sulfonylurea or metformin fails to achieve the desired level of glycemic control, a second oral agent should be added. If combination therapy with two oral agents does not achieve the desired goal, three options are available: 1) Add bedtime insulin while maintaining therapy with one or both oral agents, 2) switch the patient to a mixed-split (short-acting plus long-acting insulin given in 2 to 4 daily injections) insulin regimen, or 3) add a third oral agent (Figure 2.3). It is important to individualize therapy on the basis of patient and physician preferences.

Sulfonylureas and metformin appear to have a limited duration of effectiveness, with most patients requiring a change or additional medications after five years of

therapy (18). After a good initial response to sulfonylurea therapy, the secondary failure rate is about 5% to 7% per year, and after 10 years, most sulfonylurea-treated patients require a second oral agent. Secondary treatment failure is divided into patient-related factors (weight gain, lack of exercise, failure to comply with prescribed treatment regimen, or coexisting medical disorders), therapy-related factors (use of concomitant medications that antagonize insulin action or insulin secretion, β-cell desensitization secondary to long-term sulfonylurea exposure, inadequate drug dosage, or impaired sulfonylurea absorption secondary to hypoglycemia), and disease-related problems (progression of insulin resistance and increasing insulin deficiency). It is commonly stated that the high rate of secondary failure is related to the pancreas inability to maintain its augmented insulin secretory rate in response to long-term sulfonylurea stimulation. However, the UKPDS (2, 3) has cast doubt on this theory because a similar rate of secondary failure was observed with metformin therapy. Metformin, by improving insulin sensitivity and decreasing plasma insulin levels, would have been expected to preserve β-cell function (Figure 2.3). The UKPDS results suggest that once the fasting plasma glucose level exceeds a certain value (>140 to 160 mg/dl), β-cell failure inexorably progresses (10).

The proportion of patients with optimal glycemic control decreased from ~50% after 3 years of therapy to ~25% after 9 years of treatment with diet alone or sulfonylurea, insulin, or metformin treatment (14).

Although the conventional approach is to add insulin to the therapeutic regimen only after oral combination therapy is no longer effective, this practice is being reassessed to determine whether insulin therapy should be initiated earlier in the treatment scheme (11). When examined in a prospective, population-based study of over 7000 diabetic patients, this traditional stepwise approach revealed very low efficacy in maintaining normoglycemia. By the time insulin therapy was begun, the average patient would accumulate 5 years with HbA_{1c} of >8% and 10 years of HbA_{1c} > 7% (19).

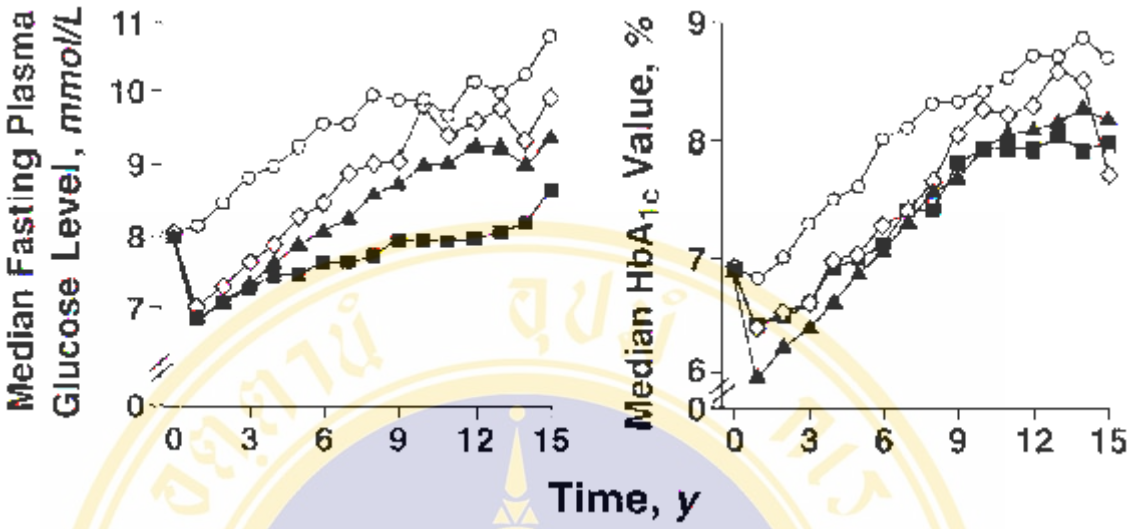


Figure-2.3 Time-related change in median fasting plasma glucose level (left) and median hemoglobin A_{1c} (HbA_{1c}) (right) in patients with type 2 diabetes treated with sulfonylureas (triangles), metformin (diamonds), insulin (squares), or conventional (diet) therapy (circles). The number of patients followed for more than 11 years drops off markedly. The curves for chlorpropamide and glibenclamide have been combined into one sulfonylurea curve for ease of presentation.

2.4 Intervention of risk factors of vascular complication

Multiple modifiable risk factors for late complications in patients with type 2 diabetes, including hyperglycemia, hypertension, and dyslipidemia, increase the risk of a poor outcome. Randomized trials that investigated the effect of intensified intervention involving a single risk factor in patients with type 2 diabetes demonstrated benefits in terms of both macrovascular and microvascular complications in kidneys, eyes, and nerves (2).

Arterial hypertension was also treated with a stepwise approach. Patients were prescribed an ACE inhibitor or an angiotensin II receptor antagonist because of the presence of microalbuminuria. If a patient had hypertension, thiazides, calcium-channel blockers, and beta-blockers were added as needed. The combination of an ACE inhibitor and an angiotensin II-receptor antagonist could also be used. Isolated instances of raised fasting serum cholesterol concentrations or combined dyslipidemia were treated with statins (atorvastatin, with a maximum of 80 mg daily, or the equivalent). Fibrates were used for isolated cases of hypertriglyceridemia, defined by a

fasting serum triglyceride concentration of more than 350 mg per deciliter, or were added to statin treatment if the fasting serum triglyceride concentration was also elevated (350 mg per deciliter) (20).

2.5 Glycemic control in DM patients

Many studies showed that glycemic control in diabetic patients are poor. The Canadian evaluation study (2002) reported mean HbA_{1c} of 7.3% and 49% of patients not at target (n = 243) (7), while the Canadian primary care physician chart audit study of 331 type 2 DM patients reported a mean HbA_{1c} of 7.9% with 74.3% not at target (5). U.S. National Health and Nutrition Examination Surveys (NHANES) (6) reported a mean HbA_{1c} of 7.7% with 74% of patients not at target (n=1215) in 1988-1994, and a mean HbA_{1c} of 7.9% with 64% of patients not at target (n=372) in 1999-2000. More detailed analyses of the NHANES 1999 to 2000 data set show that only 37% of the diabetic population had a HbA_{1c} less than 7% with 63% having a HbA_{1c} greater than 7% and 37.2% greater than 8% (6, 21). In that same survey 40.4% had a blood pressure greater than 140/90 mmHg; 51.8% had a total cholesterol greater than or equal to 200 mg/dL. Only 7.3% of the diabetic population had HbA_{1c} less than 7%, blood pressure less than 130/80 mmHg, and total cholesterol less than 200 mg/dL.

The results of Diabcare-Asia 1998 showed that majority (54%) of the analysis population was without recorded measurement of glycated haemoglobin in the form of HbA_{1c}. The mean HbA_{1c} was 8.6±2.0% for 18,211 patients. The majority (55%) had values exceeding 8%, indicative of poor glycaemic control. Of the 21,649 patients with recent blood pressure (BP) measurements, mean systolic and diastolic BP were 135±20 mmHg and 81±10 mmHg, respectively (9).

CHAPTER 3
MATERIALS AND METHODS

This study was conducted at Ramathibodi hospital. The research ethic committee approved the study protocol prior to the patient medical record recruitment.

3.1 Study design

A retrospective study by reviewing patient medical records.

3.2 Period of study

Data were reviewed and collected from patient medical records between July 1st and November 30th, 2004 (5 months)

3.3 Study population

All hospital number (HN) of subjects, were recruited from inpatients and outpatients who were treating for diabetes at Ramathibodi hospital during October 1, 2001 to September 30, 2003. Patients were identified by their primary diagnosis using ICD-9 (International Statistics Classification of Disease related health problem revision 9) or ICD-10 for outpatients, and by DRG (Diagnosis Related Group) for inpatients. Then, the researcher randomly selected 300 patients by Microsoft Excel version 2002. From the 300 patients selected, then they were recruited in the study according to the following criteria:

Inclusion criteria

Type 2 DM patients who have regular data of medical records

Exclusion criteria

Other type of DM and type 2 DM if their medical records are missing for longer than 12 months.

3.4 Sample size calculation

Sample size was estimated using the following formula.

$$N = \frac{Z^2 \times P \times (1-P)}{B^2}$$

N = sample size

Z = Z score (95% confidence interval)

= 1.96

P = estimated glycemic control from previous study

= 21%-44.3%

B = a limit of error (1%-5%)

Calculated sample size between 254.93 (P=21%, B=5%) and 9465 (P=44%, B=1%)

Thus, the number of patient's medical charts recruited in the study should be at least 255.

3.5 Instruments

Microsoft Excel version 2002.

3.6 Data collections

Data collecting forms are used to collect patient information divided into three parts.

Part 1 Demographic data

To collect demography of patient such as hospital number, birthday, gender, occupation, education, cardiovascular risk factors (smoking and alcohol consumption).

Part 2 Past medical history

To collect a history of DM such as date of diagnosis, type of diabetes, risk factors condition (date of hypertension or dyslipidemia diagnosis) and laboratory data at date of diagnosis.

Part 3 Drugs and Laboratory data

To collect medical and laboratory data every visit from date of diagnosis to September 2003.

- Medical interventions such as antidiabetic agents, antihypertensive agents, antidyslipidemia and antiplatelet agents.
- Laboratory data such as fasting plasma glucose (FPG), HbA1c, blood pressure (BP), lipid profile (Total cholesterol, LDL-c, HDL-c and triglyceride).

3.7 Data analysis

The following data were analyzed by descriptive statistical technique.

a. Characteristics of study population
   - total number of patients
   - age (mean±SD)
   - sex (percentage of male/female)
   - diabetes duration (mean±SD)
   - smoking status (percentage)
   - alcohol comsumption (percentage)
   - DM patients with concomitant hypertension
   - DM patients with concomitant dyslipidemia
   - DM patients with both hypertension and dyslipidemia

b. Therapeutic regimens (described as number and percentage)

   -antidiabetic agents
   - 1 oral antidiabetic drug (OAD)
   - 2 OADs
   - 3 OADs
   - insulin only
   - OADs + insulin

   -antihypertensive agents

   -antidyslipidemia and antiplatelet agents

c. Duration of each antidiabetic drug regimen in months (mean±SD)
   - duration from DM diagnosis to medication started
   - duration from first drug regimen to the second one
   - duration from second drug regimen to the third one
   - duration from DM diagnosis to insulin started

d. Distribution of FPG in study patients at time of diagnosis

e. Distribution of FPG in study patients at last visit classified as
   - Good control (FPG 80-120 mg/dl.)
   - Poor control

f. Glycemic control by first antidiabetic drug regimen (mean FPG, HbA_{1c} reduction in 3 months) with various drug regimens
   - monotherapy, catagorised by drug groups.
     - Sulfonylurea
     - Metformin
     - α-glucosidase inhibitor
     - insulin
   - combined OADs
   - OADs + insulin

g. Glycemic control from first to tenth year of DM (compare the mean FPG from the first year to the tenth year in patients with DM duration more than 10 years)

h. HbA_{1c}
   - Ratio of patients with data of HbA_{1c} to those without data of HbA_{1c}
   - Distribution of HbA_{1c}
   - Glycemic control based on HbA_{1c}
   - Correlation between HbA_{1c} and FPG

i. Concomitant cardiovascular risk factor (hypertension, dyslipidemia) and medical intervention. (described as number and percentage)
   - patients that blood pressure more than 130/80 mmHg and their antihypertensive regimens
   - patients with dyslipidemia and their therapeutic regimens

CHAPTER 4
RESULTS

Of 300 randomly selected diabetes patients, 246 were included in this study and 54 were excluded. Reasons for the exclusion of subjects were as follows: (a) non-type 2 DM patients (n=13); (b) loss of contact for longer than 12 months (n=41).

4.1 Characteristics of studied population

The characteristics of the patients are summarized in Table 4.1. The mean age of all patients was 62±11.21 years, with the majority (93.93%) aged between 40 and 80 years. The percentages of male and female patients were 35.22% and 64.78 % respectively. Mean diabetes duration is 9±6 years. Based on diabetes duration, there is approximately one third of patients distributed in the ≤5 years, 6-10 years and >10 years categories. Overall, 76.83% of the patients had also a diagnosis of hypertension, 75.20% had dyslipidemia and 59.35% had both hypertension and dyslipidemia.

Table 4.2 shows distribution of FPG at time of diagnosis in 112 patients. The rest of them do not have data of FPG at time of diagnosis. Forty-seven patients had FPG less than 200 mg/dl, 50 patients had FPG between 200-300 mg/dl, and 15 patients had FPG more than 300 mg/dl.

Table 4.1- Characteristics of studied population

Total number of patients	246
Age (mean±SD)	62±11.21 years
Male	87 (35.22 %)
Female	159 (64.78 %)
Diabetes duration (mean±SD)	9±6 years
≤ 5 years = 89 (36.44 %)	
6-10 years = 83 (34.01 %)	
> 10 years = 74 (29.55 %)	
Smoking status	
● never	49 (19.84 %)
● current	6 (2.43 %)
● former	21 (8.54 %)
● not known	170 (69.11 %)
Alcohol consumption	
● never	44 (17.81 %)
● current	4 (1.62 %)
● former	17 (6.83 %)
● not known	181 (73.68 %)
Comorbidity	
●hypertension	189 (76.83 %)
●dyslipidemia	185 (75.20 %)
●hypertension and dyslipidemia	146 (59.35 %)

Table 4.2- Distribution of FPG at time of diagnosis in 106 patients with complete history from diagnosis

FPG (mg/dl)	n
<200	48
200-300	47
>300	11

4.2 Therapeutic regimens

4.2.1 Glycemic management

The prescription of oral hypoglycaemic agents (as monotherapy and in combinations) and insulin at last visit are shown in Table 4.3. Most patients (107/246 [43.50%]) were receiving dual OADs therapy (74 [30.08%] glibenclamide+metformin, 23 [9.35%] glipizide+metformin, 8 [3.25%] gliclazide+metformin, 1 [0.41%] chlorpropamide+metformin, and 1 [0.41%] metformin+voglibose). Seventy-six (30.89%) patients were receiving 1 OAD. One-hundred and eighty-seven (76.02%) patients were prescribed oral diabetes medications: 76 (30.89%) were prescribed one oral agent; 107 (43.50%) were prescribed two; and 4 (1.63%) patients were prescribed three.

Table 4.3- antihyperglycemic agents prescribed in 246 patients, classified by drug regimen

Drugs		Number of patients (%)
no drug prescribed		**17 (6.91)**
1 OAD		**76 (30.89)**
-Sulfonylureas	42 (17.07)	
-Metformin	33 (13.41)	
-Acarbose	1 (0.41)	
2 OADs		**107 (43.50)**
- Sulfonylureas + Metformin	106 (43.09)	
-Metformin+Voglibose	1 (0.41)	
3 OADs		**4 (1.63)**
- Sulfonylureas + Metformin+ Acarbose/Voglibose		
Insulin alone		**23 (9.35)**
Insulin+1 OAD (metformin)		**14 (5.69)**
Insulin+2 OADs		**5 (2.03)**

Metformin, whether alone or in combination, was the most common prescribed drug (table 4.4). Forty-two (17.07%) patients were prescribed insulin, either alone

(9.35%) or combine with oral agents (7.72%). The percentage of diabetic patients who received no antidiabetic agent was 6.91%.

Table 4.4- Antihyperglycemic agents prescribed, classified by drug item (n=246)

Drugs	Monotherapy	Combination	total
Metformin	33	130	163
Sulfonylureas	42	115	157
-chlorpropamide	1	1	2
-glibenclamide	24	82	106
-gliclazide	2	8	10
-glipizide	15	24	39
Alpha glucosidase inhibitors	1	5	6
-acarbose	1	3	4
-voglibose	0	2	2
Insulin	23	19	42

Pharmacologic management of hyperglycemia was intensified with duration of diabetes as shown in figure 4.1. In the >10 years group, percentage of patients who control hyperglycemia with no drug or monotherapy are less and who need insulin or triple therapy for glycemic control are higher than other groups.

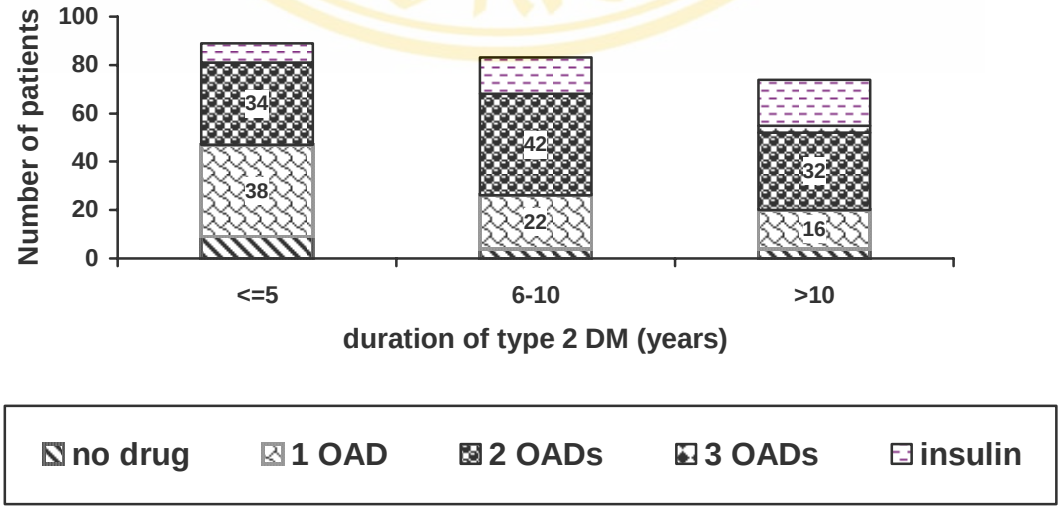


Figure 4.1- Pattern of glycemic management classified by duration of diabetes.

4.2.2 Antihypertensive agents

As regards antihypertensive drug therapy, monotherapy was prescribed in most patients. Table 4.5 shows the usage for each class of antihypertensive agent in the subgroup of patients with concomitant hypertension. In monotherapy group, patients were likely to be prescribed angiotensin converting enzyme inhibitors (ACEI).

Table 4.5- Number of antihypertensive agent prescribed in 189 DM patients with hypertension

Number of agents		Number of patients (%)
No drug		20 (10.58)
1 antihypertensive		90 (47.62)
ACEI	= 38	
Beta-blocker	= 28	
Calcium channel blocker	= 14	
Diuretic	= 8	
Angiotensin II antagonist	= 1	
Doxazosin	= 1	
2 antihypertensives		51 (26.98)
3 antihypertensives		17 (8.99)
4 antihypertensives		10 (5.29)
5 antihypertensives		1 (0.53)

Table 4.6 showed frequency of each antihypertensive drug in the monotherapy group. Enalapril was the most prescribed ACEI, atenolol was the most prescribed beta-blocker and hydrochlorothiazide (HCTZ) was the most prescribed in diuretics group.

Table 4.6- Antihypertensive agent prescribed as monotherapy

agent	n
ACE Inhibitor	
Enalapril	35
Captopril	1
Ramipril	2
Beta-blocker	
Atenolol	25
Propranolol	1
Metoprolol	1
Carvedilol	1
Calcium channel blocker	
Diltiazem	3
Amlodipine	5
Felodipine	3
Manidipine	3
Angiotensin II antagonist	
Valsartan	1
Other antihypertensive	
Doxazosin	1
Diuretic	
HCTZ	6
Amiloride+ HCTZ (Moduretic)	1
Indapamide	1

4.2.3 Antidyslipidemia and antiplatelet agents

Table 4.7 shows the usage for each class of antihyperlipidaemic agents prescribed for 114 patients with dyslipidemia. Simvastatin had highest prescribed frequency in this study.

Table 4.7- Antihyperlipidaemic agents

agent	n
Gemfibrozil	14
Atorvastatin	8
Fenofibrate	5
Simvastatin	81
Gemfibrozil+ Simvastatin	6
total	114

Antiplatelet and anticoagulants medications were prescribed in 92 (37.40%) of patients (Table 4.8). Almost all patients use aspirin as antiplatelet drugs. One patient in this study use aspirin concomitant with clopidogrel.

Table 4.8- Antiplatelet drugs and anticoagulants prescribed

drugs	n
aspirin	89
clopidogrel	1
warfarin	1
aspirin+ clopidogrel	1
total	92

4.3 Glycemic, blood pressure and lipidemic control

4.3.1 Glycemic control, based on FPG

Distribution of FPG in study patients at last visit was shown in Table 4.9. Overall, only 25.71% had FPG levels within the target range suggests by the endocrine society of Thailand (80 to 120 mg/dl). The percentage of partients with FPG levels greater than 140 mg/dl, the level suggested to focused treatment action, was 51.02%.

Table 4.9- Distribution of FPG in study patients at last visit

FBS(mg/dl)	Frequency (%)	
<60	-	
61-79	3 (1.22)	
80-120	63 (25.71)	good glycemic control
121-140	54 (22.04)	
141-200	88 (35.92)	
201-250	23 (9.39)	
251-299	9 (3.67)	
>300	5 (2.04)	
total	245 (100)	

Glycemic control in type 2 DM tends to be more difficult as the disease progress. To show this tendency, FPG of patients in the tenth year from diagnosis were collected and summarize in figure 4.2. Only 21.43% were able to maintain FPG concentrations between 80-120 mg/dl. Mean FPG was 165.42 mg/dl.

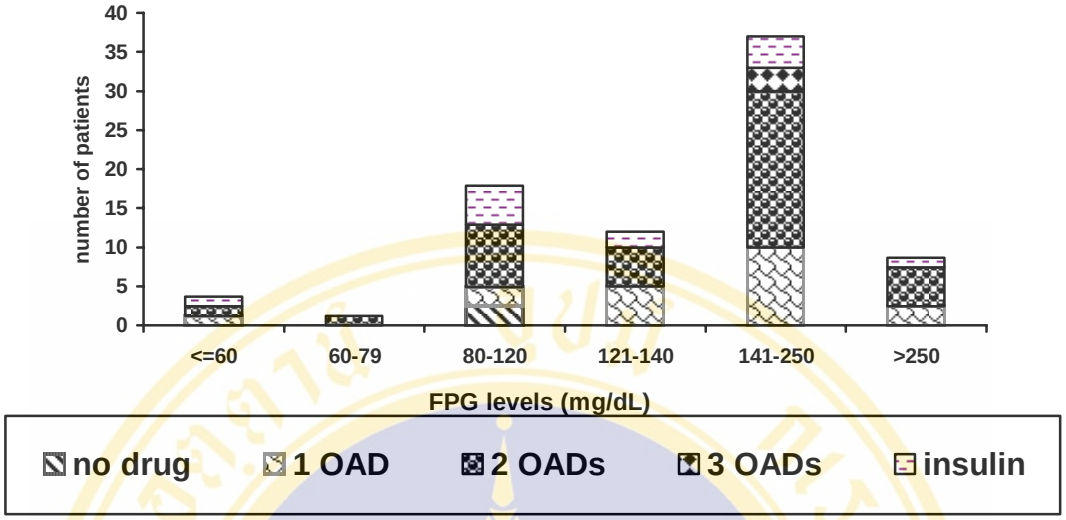


Figure 4.2- Glycemic control and management of DM patients in year tenth from diagnosis (n=78)

4.3.2 Glycemic control, based on HbA_{1c}

Only 158 from 246 patients or 64.23% have data of HbA_{1c}. The mean HbA_{1c} level from all existing data was 8.97%. To evaluate glycemic control based on HbA_{1c}, only data at last visit are shown in table 4.10. Less than half of these patients (29.23%) had HbA_{1c} levels less than 7% and 13.85% had HbA_{1c} levels greater than or equal to 10%.

Table 4.10- Distribution of HbA_1c in study patients at last visit

HbA_{1c} (%)	n (%)
≤7	19 (29.23)
7-7.9	17 (26.15)
8-8.9	14 (21.54)
9-9.9	6 (9.23)
≥10	9 (13.85)
Total	65 (100)

Figure 4.3 shows the distribution of HbA1c categorized by duration of diabetes. The proportions of patients with good control (HbA1c ≤ 7) are less as the duration of diabetes increase.

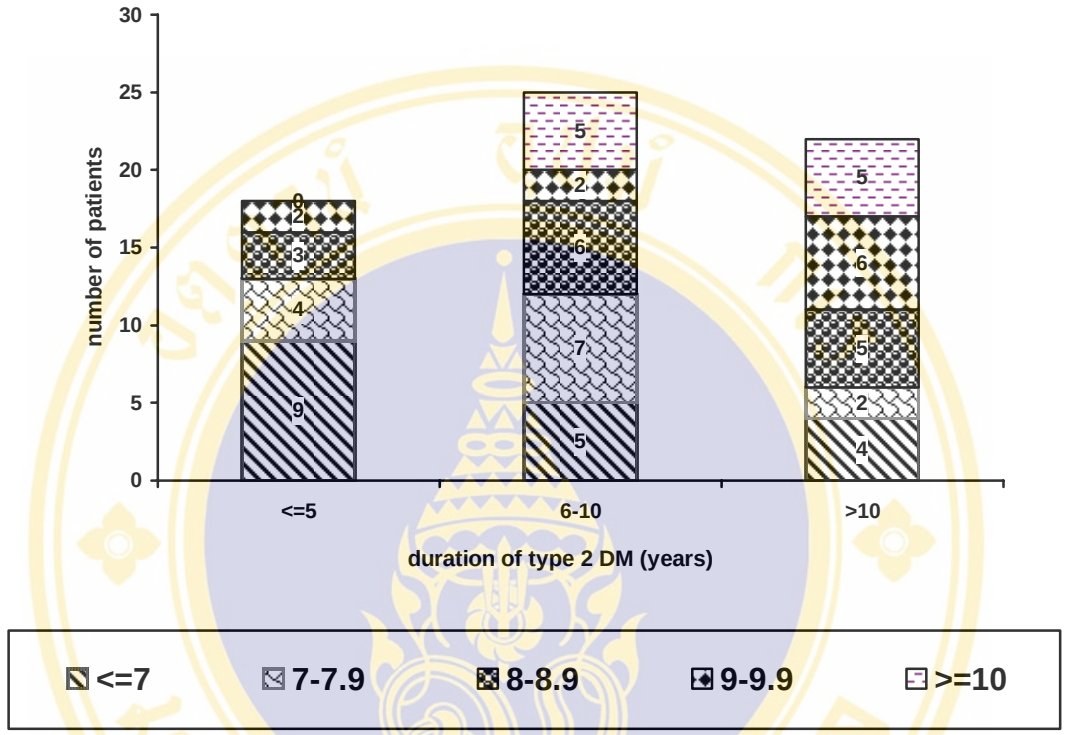


Figure 4.3- Most recent HbA_1c level categorised by duration of diabetes (n = 65)

4.3.3 Blood pressure and lipidemic control

Table 4.11 shows the percentage of patients under control for their blood pressure and lipid. The target blood pressure are <130 mmHg for systolic and <80 mmHg for diastolic. The target lipids are <100 mg/dl for LDL, <150 mg/dl for TG and HDL > 40 mg/dl (men), >50 mg/dl (women). Only 43.91% of patients achieved the target blood pressure and only 28.11% achieved the target blood lipids.

Table 4.11- Control of concomitant cardiovascular risk factor (hypertension and dyslipidemia).

	Controlled (%)	Uncontrolled (%)	n (%)
hypertension	83 (43.91)	106 (56.08)	189 (100)
dyslipidemia	52 (28.11)	133 (71.89)	185 (100)

4.4 Progression of disease

As mentioned earlier in chapter 2, type 2 DM is a progressive disease. OADs are generally effective in controlling glucose levels while some β-cell function remains. As the disease progress, patients tend to be prescribed more oral drugs and eventually require insulin treatment.

To study disease progression, patients who had medical history from their first DM diagnosis were selected and studied for the duration of each antihyperglycemic drug regimen, glycemic control and efficacy of their first drug regimen.

4.4.1 Duration of each antihyperglycemic drug regimen

Of 246 patients, only 106 patients had information from their first DM diagnosis, the others had no retrievable medical record from diagnosis. The 106 patients consist of 2 groups. The first group (21 patients), with mean FPG at time of DM diagnosis 157.40±41.37 mg/dl, started with nondrug therapy. However, all patients in this group started first regimen later. The mean number of months that elapsed until a first regimen started was 10.06±10.35 (1.61-33.2) months. The last FPG value before starting therapy was 186.15±44.21 (132-339) mg/dl. The second group (85 patients) started first antidiabetic drug regimen at time of diagnosis. Mean FPG at time of DM diagnosis of these 85 patients was 235.67±86.09 mg/dl as shown in table 4.12.

Table-4.12 Comparison of mean FPG at time of diagnosis in patients started with nondrug and with drug therapy

Patients group	n	FPG (mg/dl)
Started with non drug	21	157.40±41.37
Started with drug therapy	85	235.67±86.09

Of the 106 patients who started their first antidiabetic drug regimen, 73 changed to the second regimen. Mean duration from first drug regimen to the second one was 29.42±38.95 (3.06-286) months. Most of the patients (76.71%) changed to second regimen within 3 years.

Of the 73 patients who started their second drug regimen, 28 changed to third regimen. Mean duration from second drug regimen to the third one was 33.40±32.23 (4.11-146.94) months, 57.14% of 28 patients change to third regimen within 2 years.

For this group of 106 patients who had information from DM diagnosis, 43 patients need insulin treatment. One patient started insulin as first regimen, but most of them started insulin after 5-10 years from DM diagnosis. Duration from DM diagnosis to insulin started was 101.75±73.75 (0-312.75) months, 72.09% of 43 patients need insulin within 10 years.

Table 4.13- Duration of each antihyperglycemic drug regimen

Duration	n	mean±SD (years)
duration from first drug to the second one	73	2.45±3.25
< 1 years = 24		
1- 2 years = 22		
2-3 years = 10		
3-4 years = 2		
4-5 years = 3		
> 5 years = 12		
duration from second drug to the third one	28	2.78±2.69
< 1year = 8		
1- 2 years = 8		
2-3 years = 3		
3-4 years = 1		
4-5 years = 2		
> 5 years = 6		
duration from DM diagnosis to insulin started	43	8.48±6.15
< 5 years = 11		
5-10 years = 20		
10-15 years = 7		
>15 years = 5		

4.4.2 Glycemic control by first antihyperglycemic drug regimen

First antihyperglycemic drug regimen of the 106 patients were mostly monotherapy (83/106; 78.30%). They consisted of sulfonylurea (65; 61.32%), metformin (13; 12.26%), acarbose (4; 3.77%) and insulin (1; 0.94%). The rest 23 (21.70%) patients received combination therapy of sulfonylurea and metformin.

After 3 months of treatment with first drug regimen, only 35 (33.02%) patients can be considered to have good glycemic control (FPG <120 mg/dl) as shown in figure 4.4.

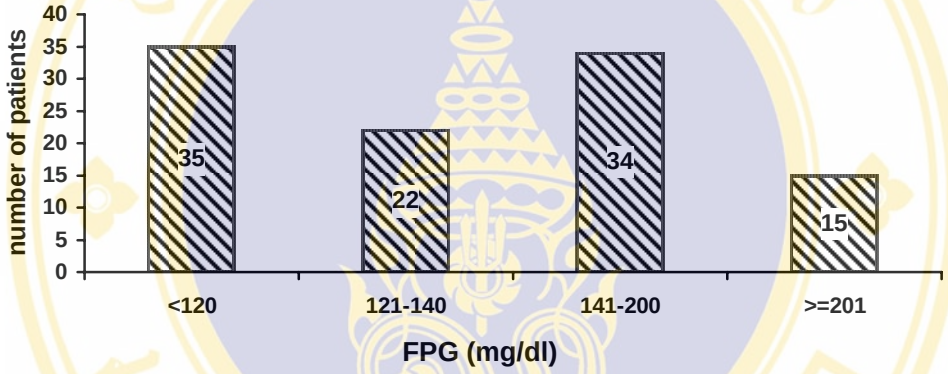


Figure 4.4- Glycemic control by first antidiabetic drug regimen after 3 months of treatment.

4.4.3 Efficacy of first antihyperglycemic drug regimen

Considering FPG decrease in individual patient, FPG decrease by first antidiabetic drug regimen after 3 months of treatment from each patient was calculated. The numbers of patients categorized by how much decrease or increase in their FPG were shown in figure 4.5. As can be seen from the figure 4.5, 71 (66.98%) patients had their FPG decrease >30 mg/dl and can be considered as effective treatment. The rest of them had so little FPG decrease or even increase.

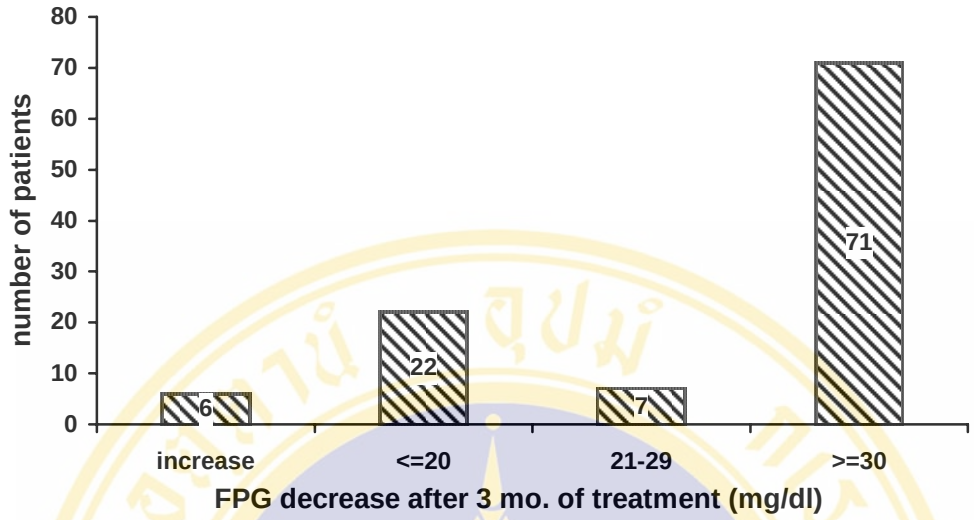


Figure 4.5- FPG decrease by first antidiabetic drug regimen

4.5 Relationship between FPG and HbA_{1c}

To evaluate the relationship between HbA1c and FPG, all the data when both values coexist were analysed. The results of linear regression analysis are summarized in Fig. 4.6. The Pearson correlation coefficient (r) was 0.59.

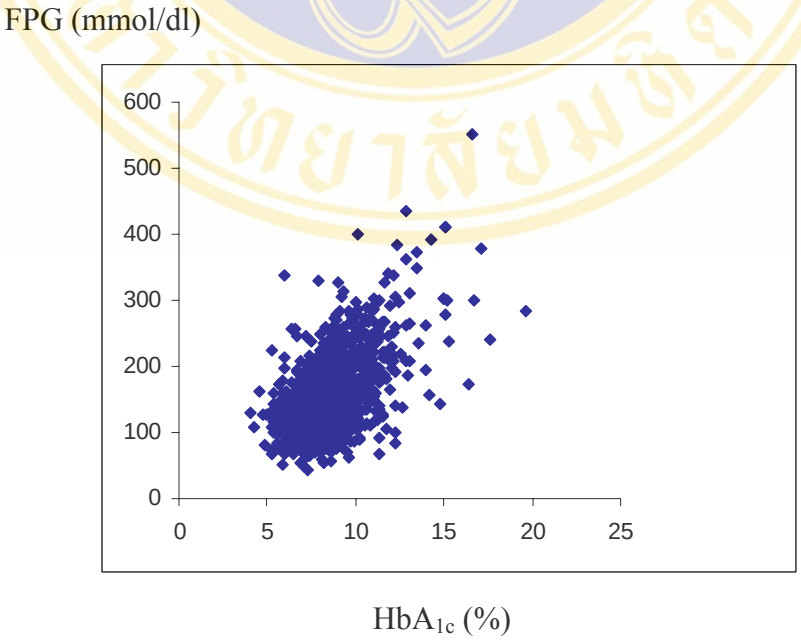


Figure 4.6- FPG versus $HbA_{1c,}$ plot of all the data when both values coexist. n= 1,127; r= 0.59.

CHAPTER 5
DISCUSSION

Type 2 DM is a heterogeneous syndrome characterized by abnormalities in carbohydrate, fat and protein metabolism. The cause of type 2 DM are multifactorial and include both genetic and environmental elements that affect β-cell function and insulin sensitivity. Although there is considerable debate as to the relative contributions of β-cell dysfunction and reduced insulin sensitivity to the pathogenesis of diabetes, it is generally agreed that both these factors play important roles, and therefore both represent logical targets for therapeutic interventions (24).

Conventional treatment strategies utilize diet and exercise, as well as pharmacological therapy with sulphonylureas, metformin and insulin, but are suboptimally effective in the clinical management of type 2 DM and generally fail to halt the long-term decline in glycaemic control and β-cell function that proceeds inexorably in most patients. Conventional stepwise approaches to clinical management generally focus on the consequences (i.e. hyperglycaemia), rather than the causes of type 2 DM. These approaches attempt to maintain blood glucose levels as near normal as possible against the background of a progressively worsening underlying disorder. This demands ever more aggressive therapy and for most patients there is an inevitable progression from diet and exercise, to pharmacotherapy with a single agent, to combination therapy and finally to insulin (14, 24).

This study use data from Ramathibodi Hospital diabetic patients to study the antidiabetic regimens and glycemic control in Thai patients.

5.1 Characteristics of studied population

Among diabetic patients in this study, there were a higher proportion of women compared to men (64.78% and 35.22%). The mean patient age was 62±11.21 years, and the mean diabetes duration was 9±6 years.

In this study, high percentage of type 2 DM patients were diagnosed hypertension, dyslipidemia or both (76.83%, 75.20 and 59.35 respectively), which are higher than previous study (Table 5.1).

Table-5.1 Comparison of comorbidity (hypertension, dyslipidemia) in patients from this study to other studies.

	Hypertension (%)	Dyslipidemia (%)	Hypertension and dyslipidemia (%)
NHANES III (21-23)	54.8	44.9	
NHANES 1999-2000 (21-23)	51.4	54.5	
Canadian evaluation study (5)	63	59	42
This study	76.83	75.20	59.35

The distribution of FPG at time of diagnosis as shown in table 4.2 reveal that more than 50% of type 2 DM patients had very high FPG even when first diagnosis, or it can be implied that there are many DM patients in population remain undiagnosed.

There are several studies about effects of alcohol consumption and smoking status on DM. However high percentage of both status (69% and 74% for smoking and alcohol consumption respectively) are not known in this study.

The meta-analysis on the relationship between alcohol consumption and the risk of type 2 DM shows a U-shaped relationship with a highly significant ~30% reduced risk of type 2 DM in alcohol consumers of 6-48 g/day compared with heavier consumers or abstainers (25). Nakanishi et al. (26) reported similar finding from a study of 2,953 Japanese male office workers aged 35-59 years. There was a U-shaped association between alcohol consumption and the incidence of impaired fasting glucose (IFG) or type 2 DM during 7 years of follow-up. Kroenke et al. (27) studied 459 associations of drinking patterns with glycemic control in U.S. female nurses, 33-50 years of age. After adjusting for age, smoking, physical activity, television watching, BMI, and several dietary factors, average alcohol intake was inversely associated with HbA_{1c} (units in percentage of HbA_{1c}): 0 g/day (reference = 5.36%), 0.1 to <5.0 g/day (-0.04%), 5.0 to <15.0 g/day (-0.09%), 15.0 to <25.0 g/day (-0.10%), and ≥25.0 g/day (-0.17%) (P value, test for trend <0.001). The studied found an

inverse association of alcohol intake and insulin, but only for women with a BMI ≥25 kg/m^2. Specifically, insulin levels were lowest for episodic drinkers consuming ≥2 drinks per day on 0-3 days per week. Consumption with meals and type of alcoholic beverage did not further influence these results.

Several prospective cohort studies suggest that smoking is associated with the development of diabetes (28). Sairenchi et al. (29) studied 192,125 Japanese subjects aged 40-79 years. They showed that current smoking was associated with a 20-40 percent increased risk of type 2 DM among men and a 40-50 percent increased risk among women. The Cancer Prevention Study I (30), a study of 434,637 women aged 30 years or more, reported a significant 20-70 percent excess risk among middle-aged women. They found a dose-response relationship between cigarettes smoked per day and the incidence of DM for both men and women. This study also found that women who had quit for ≥ 5 years and men had quit for ≥ 10 years had essentially the same incidence of DM as those who had never smoked cigarettes. Nakanishi et al. (31) studied 1266 Japanese male office workers 35 to 59 years of age who did not have impaired fasting glucose or type 2 DM and were not taking medication for hypertension. They found that the risk for impaired fasting glucose and type 2 DM increased in a dose-dependent manner as the number of cigarettes smoked per day and the number of pack-years of exposure (the long-term effect of cigarette smoking for current smokers) increased. Being a past smoker was associated with a nonsignificantly higher risk for impaired fasting glucose compared with never-smokers but was not associated with risk for type 2 DM.

5.2 Therapeutic regimens

5.2.1 Glycemic management

Three modalities of treatment are available to manage type 2 DM: lifestyle modification including appropriate diet and exercise programs, OADs, and insulin. These modalities are most commonly prescribed in a stepwise fashion, beginning with lifestyle modification and sequentially adding one or more oral agents and insulin. The general principles of stepwise treatment for type 2 DM are well established, and there are few points of contention. The physician should not delay to transition from one

treatment modality to the next if a strategy does not achieve the target blood glucose concentration within an acceptable time frame (32).

Table 5.2 showed diabetic medication regimens from this study compare with those from the Third National Health and Nutrition Examination Survey (NHANES III, conducted 1988-1994), NHANES 1999-2000 (21-23), The Canadian evaluation study (7), and the Canadian primary care physician chart audit study (5).

In this study based on data at last visit, approximately three fourth of patients were prescribed OADs. Most of the patients were prescribed OADs like the other previous studies. Duration of diabetes influence treatment intensity like the result in Canadian evaluation study (7).

Table 5.2 Comparison of medication regimen for type 2 DM from various studies

drugs	NHANES III (1988-1994) (21-23)	NHANES 1999-2000 (21-23)	Canadian primary care physician chart audit study (5)	Canadian evaluation study (7)	This study
No drug prescribed	27.4%	20.2%	17%	15%	6.91%
OADs	45.4%	52.5%	63%	73%	76.02%
1 OAD			38.43%	36%	30.89%
2 OADs			28.94%	30%	43.50%
3 OADs			0.63%	8%	1.63%
Insulin only	24.2%	16.4%	15%	6%	9.35%
OADs+insulin	3.1%	11%	5%	6%	7.72%
Antihypertensive drug¶	77%	85.2%			89.42%
Lipid-lowering agents♯	27.7%	56.1%			61.62%
Aspirin use	22.2%	22.6%			37.40%

¶Among participants who reported physician-diagnosed high blood pressure or hypertension (NHANES III: n = 692; NHANES 1999-2000: n = 244).

♯ Among participants who reported physician-diagnosed hypercholesterolemia (NHANES III: n = 365; NHANES 1999-2000: n = 178).

5.2.2 Antihypertensive agents

From NHANES use of BP medications increased (77.0% vs. 85.2%; $P = .05$). Use of BP medications could be underreported if use of renin-angiotensin system agents were attributed to nephropathy rather than to hypertension (22). From this study 169/189 (89.42%) type 2 DM patients were prescribed antihypertensive drugs. The percentage is higher than previous study (table 5.2). Most of the patients were prescribed monotherapy. ACEIs were the most prescribed drug class.

The benefits of ACEIs in diabetic nephropathy are well documented, notably reducing the incidence of diabetic nephropathy in both hypertensive and normotensive type 1 or 2 diabetic patients with microalbuminuria. In addition, they reduce the rate of mortality and the need for dialysis or a kidney transplant in patients with type 1 diabetes and nephropathy. ACEIs are thought to act within the kidneys by reducing efferent arteriolar pressure, thereby decreasing intraglomerular pressure and reducing albumin excretion. Furthermore, they act on the endothelium and decrease vascular smooth muscle growth, decrease release of endothelin, and increase fibrinolysis and release of vasodilatory substances, such as nitric oxide and prostacyclin, mediated by bradykinin. Renoprotective effects of ACEIs are a result of the suppressed generation of angiotensin II in both plasma and tissues (33).

5.2.3 Antidyslipidemia and antiplatelet agents

Percentage of type 2 DM patients who use antidyslipidemia and antiplatelet drugs in this study, comparison to data from previous study was shown in table 5.2. Medication use for high cholesterol was more than 2-fold higher in NHANES 1999-2000 (56.1%) compared with NHANES III (27.7%). Data from NHANES 1999-2000 was collected just after clinical trials demonstrated that, by lowering lipid levels, individuals with diabetes can substantially reduce the risk of developing cardiovascular disease. Moreover, in 1998, diabetes was identified as a risk factor for cardiovascular disease equivalent to having preexisting coronary artery disease. The ADA guidelines on management of lipid disorders issued in 1993 were revisited in 1998 also subsequently issued guidelines for lipid management in diabetes (22). In this study (2003) 61.62% of patients who reported physician-diagnosed dyslipidemia, the percentage is higher than previous study. The higher used of lipid-lowering agents

observed in NHANES 1999-2000 and this study occurred on the cusp of new data showing the benefits of lowering lipid levels, and further reductions in total cholesterol levels may be anticipated in the future as a result of dissemination of the new guidelines.

There was no difference in regular use of aspirin in both NHANES. In this study had higher percentage of antiplatelet agents compared with previous NHANES.

5.3 Glycemic, blood pressure and total cholesterol control

5.3.1 Glycemic control, based on FPG

In UKPDS, a continuous relationship between the risk of microvascular complications and HbA_{1c} was demonstrated. The results of UKPDS showed that risk reductions for progression of retinopathy and albuminuria were proportional to reductions in the level of HbA_{1c} (2). In this study, only 25.71% of the patients had achieved optimal control at the time of last visit. Moreover, at least 51.02% of patients require therapeutic re-evaluation (FPG more than 140 mg/dl), more intensive treatment and management in order to avoid or delay the microvascular complications. Findings suggest that a considerable proportion of type 2 DM patients are not well controlled and that the disease burden is quite high.

This study suggests that glycemic control erodes with duration of diabetes and support the UKPDS clinical findings documenting the progressive nature of type 2 DM. Canadian evaluation study examining the association between duration of disease and glucose control has also demonstrated that glucose control worsens with the duration of diabetes (7).

5.3.2 Glycemic control, based on HbA_{1c}

There are few published studies assessing glycemic control (table 5.3). HbA_{1c} was underutilized in this study. The medical records showed that 35.77% of the patients did not have HbA_{1c} assessments. The mean HbA_{1c} was (8.97%, n=65) was higher than other studies. The percentage of patients not at target is lower than those cited in Canadian primary care physician chart audit study and Diabcare-Asia 1998, but higher than the other previous studies.

Table-5.3 Percent of patients achieved target $HbA_{1c,}$ blood pressure, and percent of patients having ≥200 mg/dl total serum cholesterol from previous studies.

	HbA_{1c} less than 7% (n, mean HbA_{1c})	Blood pressure less than 130/80 mm Hg	Total cholesterol ≥200 mg/dL.
NHANES III (21-23)	44.3% (1215, 7.6)	29.0%	66.1%
NHANES 1999-2000 (21-23)	37% (372, 7.8)	35.8%	51.8%
Canadian evaluation study (7)	51% (2169, 7.3)		
Canadian primary care physician chart audit study (5)	18.5% (331, 7.9)		
Diabcare-Asia 1998 (9)	21% (18211, 8.6)		
Siriraj primary care unit (34)	38.8% (299, -)		
This study	29.23% (65, 8.97)	43.91%	

5.3.3 Blood pressure and lipidemic control

Compelling evidence from well designed, randomized clinical trials demonstrates that control of glucose levels, blood pressure, and cholesterol levels can dramatically delay or prevent the microvascular and macrovascular complications of diabetes (2, 35). Based on these data, the ADA (4) has developed guidelines for control of blood glucose levels, blood pressure, and cholesterol levels in individuals with diabetes. Despite these evidence based guidelines, only a small fraction of adults with diagnosed diabetes in the United States, Canada and Thailand are achieving the currently recommended levels of control (Table 5.3).

There was a slight increase in the percentage of patients with BP at the level currently recommended by the ADA (systolic < 130 mmHg and diastolic <80 mmHg) from NHANES III (29.0%) to NHANES 1999-2000 (35.8%) (P = .10). The proportions based on the recommended levels by the ADA in 1995 (systolic <130 mmHg and diastolic <85 mmHg) also did not change significantly from the NHANES III (1988-1994) (32.1%) to NHANES 1999-2000 (36.6%) (P = .29) (22).

Although the percentage of patients with diagnosed diabetes and diagnosed hypertension who use blood pressure medication has increased in NHANES 1999-20000, only 35.8% of individuals with diagnosed diabetes have achieved the current

ADA BP goal of less than 130/80 mmHg and only 36.6% achieved the ADA goal set in 1995 (<130/85 mmHg) (22).

Over half (51.8%) of the participants in NHANES 1999-2000 had total cholesterol levels of 200 mg/dl or greater (vs. 66.1% in NHANES III; *P*<.001) (22).

From this study, type 2 DM patients who can control hypertension to target are 43.91% and who can control their dyslipidemia (LDL < 100 mg/dl, TG < 150 mg/dl, HDL > 40 mg/dl (men), >50 mg/dl (women)) was 28.11%.

5.4 Progression of disease

5.4.1 Duration of each antihyperglycemic drug regimen

The traditional approach to the treatment of diabetes has been a stepwise introduction of nonmedication approaches followed by oral agents (figure 5.1). Insulin therapy, despite being the most potent and durable hypoglycemic intervention available, has generally been saved for last, presumably because of the need to administer it by injection. The stepwise strategy has usually been applied at a slow pace with long delays between steps. By the time patients with type 2 DM are treated with insulin, they usually have had diabetes for more than 10 to 15 years and have established complications (36).

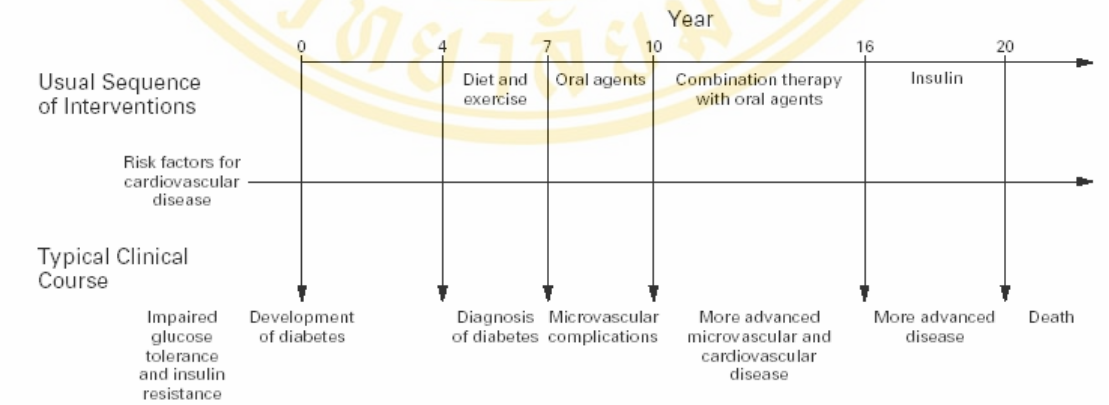


Figure-5.1 The typical clinical course of type 2 DM, including the progression of glycemia and the development of complications, and the usual sequence of interventions (36).

From this study 19.81% (21/106) of patients started with no drug prescribed. Mean FPG at time of diagnosis of patients who started with nondrug therapy were

157.40±41.37 mg/dl. All patients who started with no drug were prescribed antihyperglycemic drug eventually, 76.19% (16/21) in this group started first regimen within 1 year. Mean FPG before started first regimen in this group was 186.15±44.21 mg/dl. Approximately 81.19% (85/106) of patients started first drug regimen at time of diagnosis mean FPG at time of diagnosis was 235.67±86.09 mg/dl.

About 68.87% (73/106) of patients change to second regimen with mean duration of first drug regimen to the second one was 2.45 years, 76.71% changed to the second regimen within 3 years.

Twenty-eight patients (26.41%) need third regimen, about half of this group changes to third regimen within 2 years. Mean duration from second drug regimen to the third one was 2.78 years.

About 40.57% (43/106) of patients need insulin treatment. Most of them started insulin after 5-10 years, 72.09% of 43 patients need insulin within 10 years.

5.4.2 Glycemic control by first antihyperglycemic drug regimen

Approximately 25% of patients with type 2 DM treated with metformin or sulfonylurea monotherapy achieved a FPG level less than 140 mg/dl and should be considered complete responders (37). About 75% of patients with type 2 DM treated with a sulfonylurea will not reach the desired goal (FPG <140 mg/dl) and will require addition of a second oral agent or bedtime insulin (10).

From this study 61.32% started with sulfonylurea monotherapy, 12.26% started with metformin monotherapy. After 3 months of treatment with first drug regimen, only 33.02% patients achieved a FPG level less than 120 mg/dl.

5.4.3 Efficacy of first antihyperglycemic drug regimen

Metformin and sulfonylureas are equally effective in reducing FPG values in patients with type 2 DM and both are indicated as primary therapy. Clinical trials have documented that metformin (38, 39) and SU (10) therapy consistently decreases the FPG level by 60 to 70 mg/dl in patients with poorly controlled diabetes. Patients in whom sulfonylurea therapy fails can be subdivided into two groups. Ten percent to 20% will have a poor initial response (decrease in FPG level <20 mg/dl); these patients are considered to have primary failure. Fifty percent to 60% of patients with

type 2 diabetes have a good initial response to sulfonylurea (decrease in FPG >30 mg/dl), but they do not reach the desired treatment goal (FPG level <140 mg/dl). Such patients are considered to have partial response (10).

From this study 26.41% (28/106) of patients decrease in FPG level <20 mg/dl, 66.98% (71/106) of patients decrease in FPG more than 30 mg/dl.

5.5 Relationship between plasma glucose and HbA_{1c}

Measurement of HbA_{1c} is widely used in clinical practice to monitor glycemia in diabetic patients. HbA_{1c} serves as a key predictor of the risk of developing diabetic complications (40).

Rohlfing (16) define the relationship between HbA_{1c} and FPG levels with Pearson correlation coefficient (r) = 0.82, which imply that FPG closely correlates with HbA_{1c}.

Short-term FPG levels can fluctuate markedly. This can result in significant discrepancies when attempting to estimate HbA_{1c} based on a single FPG measurement or even a series of measurements on a single day. From this study, the Pearson correlation coefficient between HbA_{1c} and FPG (r) = 0.59, which means that FPG from this population may not reliably predict HbA_{1c} at visit time.

CHAPTER 6
CONCLUSION

This study explored the antidiabetic drug regimens and glycemic control in type 2 diabetic patients at Ramathibodi Hospital (between July 1st and November 30th, 2004). A total of 246 patient medical records were recruited into the study. The results were concluded as followed.

The ratio of female to male patients in this study was 1.8 to 1. Most patients were in the range of 40-80 years old. Mean diabetes duration is 9±6 years. Overall, 76.83% of the patients had also a diagnosis of hypertension, 75.20% had dyslipidemia and 59.35% had both hypertension and dyslipidemia. Smoking status and alcohol consumption of most patients are not known.

Most patients (43.5%) were prescribed 2 OADs, 31.3% were prescribed 1 OAD. Metformin, whether alone or in combination with glibenclamide, was the most common prescribed drug. Forty-two patients (17.07%) were prescribed insulin. 9.35% of the patients use insulin alone and 7.72% use insulin in combination with oral agents. The percentage of patients with no reported pharmacological treatment for diabetes was 6.91%. Pharmacologic management of hyperglycemia are more intensive with longer duration of diabetes.

From this study 89.42% of type 2 DM patients with hypertension were prescribed antihypertensive drugs. Most of them were prescribed monotherapy. ACEI was the most prescribed. The official recommendation of most professional organizations is to use ARB as baseline agents in type 2 diabetic patients and ACEIs in type 1 patients (41). Type 2 DM patients who use antidyslipidemia and antiplatelet drugs were 61.62% and 37.40% respectively.

About 25.71% of patients had FPG level between 80 and 120 mg/dl, and 29.23% had HbA_{1c} less than 7%, which are categorized as good diabetic control. Patients who controlled blood pressure to target were 43.91% and controlled blood lipids to target were 28.11%.

Only 106 patients had information from their first DM diagnosis. Most (80.19%) of this group started first regimen at time of diagnosis. More than half (68.87%) need changes to second regimen. More than one-third (38.36%) of patients who started their second regimen changed to third regimen. About 33.02% of patients had FPG less than 120 mg/dl, 66.98% of patients had FPG decrease more than 30 mg/dl after 3 months of first regimen.

Relationship between FPG and HbA_1c, the Pearson correlation coefficient (r) was 0.59.

Limitation of the study

1. With the nature of the retrospective study, there were some data absent, eg.
   - Smoking status, alcohol consumption
   - The time of diagnosis
2. The glycemia and antidiabetic drugs used to analyze in this study are the value at last visit. They may not represent overall glycemic control of individual patients.

Suggestion

Use HbA_{1c} to monitor glycemic control

HbA_{1c} had better precision for monitor glycemic control than FPG. There is higher advantage if had HbA_{1c} measurement at least 3 times yearly according to ADA guideline.

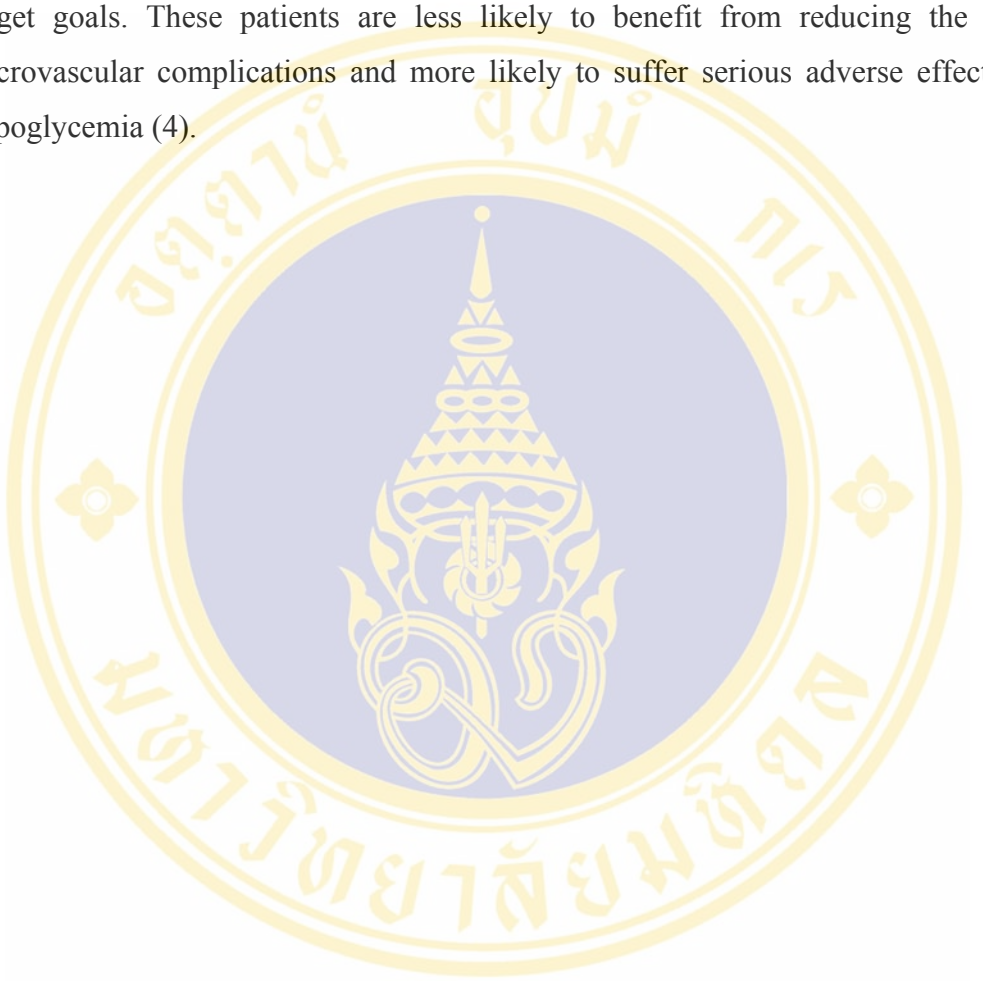
Glycemic goals and diabetes care in older individuals

The mean age of this study patient was 62±11.21 years. One hundred and eleven (45.12%) of studied population were ≥65 years old.

The care of older adults with diabetes is complicated by their clinical and functional heterogeneity. Some older individuals developed diabetes in middle age and face years of comorbidity; others who are newly diagnosed may have had years of undiagnosed comorbidity or few complications from the disease. Some older adults with diabetes are frail and have other underlying chronic conditions, substantial diabetes-related comorbidity, or limited physical or cognitive functioning, but other older adults with diabetes have little comorbidity and are active. Life expectancies are also highly variable for this population. Clinicians caring for older adults with diabetes

must take this heterogeneity into consideration when setting and prioritizing treatment goals.

For patients with advanced diabetes complications, life-limiting comorbid illness, or cognitive or functional impairment, it is reasonable to set less intensive glycemic target goals. These patients are less likely to benefit from reducing the risk of microvascular complications and more likely to suffer serious adverse effects from hypoglycemia (4).



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