Chapter II

Literature Review

This chapter composed of 3 main parts as follow.

Part I : Pharmaceutical expenditure and high cost drug use in Civil Servant Medical Benefit Schemes (CSMBS)

1.1 Situation of pharmaceutical expenditure

Concerning the pharmaceutical expenditure, it associated with health care delivery expenditure which has increased widely throughout many countries. In developed countries, in two recent decades the proportion of GDP spent on health increased (Table 2.1). This increase in health care expenditure was largely due to new medical technologies and the introduction of new and more expensive medications. Pharmaceuticals account for over 20 % of the total health spending in France and Italy. Expenditure of pharmaceuticals is also one of the fastest growing components of health care cost in the United States. The cost of new medications was increasing and consumes a growing percentage of the total care expenditure in many countries

Table 2.1. Health expenditure as a percentage of GDP in 1995 and 2003

Country	1987	1995	2003
France	8.5	9.9	10.1
Italy	7.4	7.7	8.4
Germany	8.7	9.6	11.1
Netherlands	8.1	8.8	9.8
United Kingdom	5.9	6.9	7.7
Canada	na	na	9.9
United States	na	na	15.0
Australia	8.4	9.6	9.3*

Source: OECD Health Data (1996) ,World Bank Reports cited in Panos Kanavos and Martin McKee, Macroeconomic constrains and Health challenges facing European health systems : 27 in Critical Health challenge in Europe,)

: OECD Health data (2003) cited in The Australian Health Care System and High Cost Medications (HCMs) :28).

* 2002

In Thailand, it was found that the proportion of drug expenditure in 1998 was 29.2 % of total health expenditure which was very high when compared with the developed countries which the proportion of drug expenditure was only 10– 22 % of total health expenditure. The growth rate of drug expenditure grew up in the same direction of the growth rate of health expenditure and economics. It was found that the highest average growth rate of pharmaceutical expenditure was 6.95% which was higher than the average of economic growth rate (6.22%). But it was lower than the average of health expenditure growth rate (9.23%) (Kulsomboon, , Tearngpitak, and Thanaviriyakul, 2002). Drug expenditure in Thailand still increased every year. The IMS showed that the wholesale drug price value in the drug market in 2005 was 63.5 billion baht which about 1.78 times of its value in 2001 (35.6 billion baht) The growth rate of pharmaceutical market in 2005 was 19%. In addition, it was showed that the hospital drug market trend to increase every year. The growth rate of hospital market was 21% whereas the growth rate of drug-store market was 16% in 2005. Moreover, IMS reported that total wholesale drug price in drug market in 2006 was also increase, 69 billion baht. Seventy five percent (52 billion baht) of all market value was in hospital channel.

1.2 Factor influencing the increasing of pharmaceutical expenditure

There were many factors influencing the increasing of pharmaceutical expenditure. For this study, three main factors were reviewed.

The expansion of aging population which was increased two times from 4.5% in 1960 to 9.3% in 2000 and expected to 15.9% in 2020 was an important factor affecting the growth of drug spending. Because disease patterns mainly found in aging group were chronic diseases which needed long term continuity of care and drug use. Concerning drug use for chronic disease treatment, high cost drugs and new drugs were also included. The experience from USA was shown that the elderly represent only about 13% of the US population. The US Senate Committee on Ageing found that they accounted for almost 35% of all prescriptions dispense in the United State. In Canada, 98% of patients were in high cost pharmaceutical users. Eighty two percent of total prescription cost were in high cost users (Kozyrskyj, Lix, Dahl et al., 2005). Besides, 54% of persistent high users were in aging group. In Thailand, it was found that high cost drug use for chronic patients were mainly use in aging gruoup (Munkratok, Kulsomboon, and Sirisinsuk., 2006).

Health insurance scheme was also an important factor affecting the increasing of pharmaceutical expenditure. It was found that drug spending of patients who enrolled in fee for service payment mechanism health insurance scheme trend to be much higher than the patients who enrolled in capped payment mechanism. In USA, Fee for Service (FFS) plan enrollees had 25% to 218% higher levels of prescription use than Medicaid Managed Care (MC) enrollees. For the average prescription cost per enrollee across six months, it was $119.89 for FFS and $33.89 for MC. The prescription costs were more than $60,000 higher in the FFS group, although the MC sample was twice as large as the FFS samples. Besides, number of prescriptions received by FFS enrollees for outpatient visit with any comorbidity were higher than MC enrollees. (Theresa, Richard, Mana et al, 2002). For Thailand, the effect of health insurance schemes on the growth of pharmaceutical spending was described in 1.4.

The increasing of high cost drug use was another important factor affected the increasing of pharmaceutical spending. Most of high cost drugs were new drugs with patent. Therefore, drug prices were very high because of monopoly characteristic. Thailand still faced with the growth of high cost drug use. IMS reported that top sale 10 pharmaceutical products in the market in 2005 were high cost drugs. Concerning drugs items sold in the market, Atorvastatin was the highest sold (1553.3 million baht). Clopidogrel, Meropenam, Human erythropoietin, and Celecoxib were the next respectively. Moreover, IMS reported that top ten wholesale drugs in hospital channel in 2006 was estimated 6,159 million baht (11.8% of total wholesale drugs in hospital channel). Moreover, 76% of sailing drug value in hospital channel was produced from multinational companies. Thus, most of drug items were high cost drugs. Most of drug items except Celecoxib and Esomeprazole were in "2004 National Essential Drug List". (Table 2.2).

Table 2.2. Top ten drug items sold in hospital channel in 2006

Order		Generic name	Trade name	Value (million baht)	Market share(%) Bangkok: Others	Growth rate (%)
2006	2005					
1	1	Atorvastatin	Lipitor	1,618	58 : 42	29
2	3	Clopidogrel	Plavix	804	56 : 44	67
3	2	Meropenem	Meronem	697	45 : 55	41
4	4	Human erythropoeitin	Eprex	567	50 : 50	24
5	10	Gabapentin	Neurontin	441	48 : 52	38
6	6	Celecoxib	Celebrex	434	45 : 55	13
7	7	Clavulonate+Amoxycillin	Augmentin	415	50 : 50	10
8	9	Imipenem+Cilastatin	Tienam	406	35 : 65	10
9	5	Sulbactam+Cefoperazone	Sulperazon	404	38 : 62	-4
10	18	Esomeprazole	Nexium	373	50 : 50	65

Source: IMS Health 2Q2006

Recent study of the expenditure of high cost drugs in a regional hospital reported that only 10 essential high cost drugs in subclass 4 contained 18-20 % of overall pharmaceutical expenditure (Munkratok, Kulsomboon, and Sirisinsuk, 2006). Because irrational drug use especially high cost drugs might affect not only high financial lose but also the accessibility to drugs in social aspects. There were many studies showed the effect of irrational high cost drug use on financial waste. In Thailand, there were some studies about irrational use of high cost drugs affected money loss. It was found that the cost of inappropriate use of Coxibs in patient at low risk of gastrointestinal effects was 2.4 million bath per year. (Phosri, Kulsomboon, and Kiatying-Angsulee, 2005). The study of drug use evaluation (DUE) in essential list class 4 in 1999 reported by regional hospitals, general hospitals, medical schools during 1st June – 31 December 2000 that the rate of inappropriate use was 21.6 for Ceftazidime inj., 37.1 for Ciprofloxacin tablet, and 62.4 for Pentoxyphylline (Akleepan, 2001 cited in Matankasombat et al , 2002). The other previous studies in 8 hospitals from 1992 – 2000 reported about economic lost from irrational drug use such as inappropriate use of Cephalosporin inj.at Taksin (Soyson, 1992 cited in Matankasombat et al, 2002) and Ramathibordhi hospitals(Akleepan, 1997 cited in Matankasombat et al, 2002) caused excess drug expense 4,801 baht/visit and 432,109 baht/year/ hospital and 676 baht/patient and 171,632 baht/5 months/hospital respectively.

1.3 Definition of High Cost Drugs

About this topic, these terms were used interchangeably; high cost drugs , high cost medications, high cost pharmaceuticals, and costly medicines.

There were different definitions of high cost drugs or high cost medications or high cost pharmaceuticals. The definitions may vary depending on the setting and perspective of the person or group of the setting and the perspective of the person or group making the decision. Those who had attempted to give a definition had identified two different kinds of high cost medications 1) "modest acquisition cost but used in high volume" 2) "very high cost medication, which even limited used might create budgetary pressure (Macintyre, Sindusake, and Rubin, 2001 and Mucklow , 2000).

In Australia, high cost medicine definitions also vary according to who made the definition and how they made it. For the Commonwealth Government, there were two kinds of high cost medications. The first one was defined by Section 100 of the PBS "Highly Specialised Drug program" criteria, which states if medications were recommended for inclusion in the program, they had to have high unit cost. Other medications like Atorvastatin, Omeprazole or Celecoxib were also considered high cost drugs because they were used in high volume. Lu also described these two types of high cost drugs when discussed access in Australia.

For states, such as New South Walses and Victoria had also provided definitions for high cost medication. In 1997 in New South Wales (NSW), high cost medications for outpatient use not funded by the Commonwealth Government were defined as: those not listed for subsidy on the PBS Section 85 or 100 of the National Health Act, and which incur an acquisition cost equivalent to, or more than A$100 per week per medication per patient and require particular expertise for management of patient care. This definition was only update in October 2004 when the acquisition cost was change to $ 500 per week per medication per patient. [The Australian Health Care System and High Cost Medications (HCMs)]

In Victoria, the Victorian Therapeutic Advisory Group (Vic TAG) defined high cost medications use in public hospital as those had acquisition cost more than A$ 1,000 per treatment episode.(Victorian Therapeutics Advisory Group, 2004)

In Canada, high cost drugs seemed to have two definitions. First, those defined as drugs in the Special Drugs Program (SDP), which covers drugs listed under Section 8, Regulation 552 of the Health Insurance Act, was restricted mainly to rare or life-

threatening conditions for which drug therapies had traditionally been costly. Among them were enzyme deficiencies, such as Gaucher's Disease (alglucrase), endogenous growth hormone deficience, thalassemia, cystic fibrosis, and HIV/AIDS. Other costly therapies adopted by the SDP include cyclosporine for patients undergoing solid organ or bone marrow transplants, erythropoietin for patients with end-state renal disease, and clozapine for treatment-resistant schizophremia. (Institute for clinical Evaluative Sciences, 2002). Another definition is those are expensive new drugs. (Institute for Clinical Evaluative Sciences, 2002)

In United Kingdom, the report of "The prescribing of costly medicine" from Royal Collage of Physicians in defined costly medicines as "one that is expensive when the overall cost of its use is compare with the overall cost of using currently recommended treatment (Prescribing of expensive medicine [Online], 2000)

In USA, high cost drugs definitions were drugs used in particular problematic therapeutic categories having high effect on the increasing of pharmaceutical expenditure. New drugs were also included.(Institute for Clinical Evaluative Sciences, 2002).

In Thailand, at the beginning of establishing national essential drug list, there was no explicit definition of high cost drugs. However, high cost drugs was found as a criteria in the National List of Essential Medicine 2004 in subclass 3 and subclass 4 (National Drug Committee, 2004). In Universal Health Insurance Policy, some high cost drugs were included in high cost care. The present of some costly drugs in the clinical guideline in high cost care were for specific services or treatment such as chemotherapy for cancer outpatients and drugs for Cryptococcus Meningitis treatment for HIV outpatients and inpatients (National Health Insurance office, 2006) In CSMBS, six non-essential drugs for cancer treatment including imatinib, rituximab, trastuzumab, bivacizumab, erlotinib, and gefitinib were defined as high cost drugs which pre-authorized are needed for reimbursement.(The Comptroller General's Department, 2006.). Recent study reported that Human erythropoietin 4000 u. inj., Atorvastatin 10 mg. tab., Meropenem 1g inj,Iimipenem/Cilastatin 500 mg/vial IV, and Cefoperazone/Salbactam 1g inj and Clopidogrel 75 mg. tab. were essential high cost drug expenditure in subclass 4 (Munkratok, Kulsomboon, and Sirilinsuk, 2006)

1.4 Effect of high cost drug use on pharmaceutical expenditure in CSMBS

In Thailand, like other countries, the patients who enrolled in CSMBS with fee for service payment mechanism trend to use medical services higher than the patients who enrolled in UC with capped payment mechanism. Concerning the medical expenditure in CSMBS, it has been continuously increased since 1980. After economic crisis, the government tried to solve this problem by implementing CSMBS System Reform policy in 2000. But total medical expenditure still increased from 17,062 million baht in 2000 to 37,004 million baht in 2006. Moreover, in the last four year (2003 – 2006) the medical spending for outpatients were higher than the medical spending for inpatients. Outpatient medical expenditure increased with the highest growth rate when compare with the growth rate of total medical expenditure and inpatient expenditure (GFMIS).

Main outpatient medical spending was for pharmaceutical use for disease treatment. According to many studies, the results showed that CSMBS consumed higher drug spending more than the patients who enrolled in Universal Coverage (UC) with capped payment mechanism. For example, the study of quality of drug use service in diabetes in UC program compare with the other health insurance scheme showed that patients who enrolled in UC program trended to got cheap drugs whereas the patients who enrolled in CSMBS trended to received medium price or expensive drugs (Charng-soong , 2003.) Consistent with this result, another study reported the total average charge for diabetes patients in a provincial hospital in 2002. It was showed that drug charge for out patient per capita in CSMBS was 5,248 baht meanwhile their values in UC and Social Security Scheme (SSS) were only 2,733 and 1,759 baht respectively. In the same study reported that the proportion of drug cost for diabetes outpatients accounted for 50% of medical cost in general hospitals and 70-80% of medical cost in central hospitals or teaching hospital (Pongchareonsuk, 2003).

CSMBS outpatients trend to overuse high cost drugs which were prescribed by the providers without following standard treatment guideline. For example, one study reported that the patients who can reimburse were prescribed COX-2 inhibitors together with Misoprostol (Pochnukul, 1999 cited in Matankasombat, Archananuparp, Suthanurak et al, 2002). Besides, it was found that the formulations were not consistent with diagnosis results and lack of systematic evaluation and

monitoring of side effect. Over standard treatment is not good for the patients because those treatments were not approved for effectiveness and receiving many drugs especially chemotherapy that might increase severe side effects in the patients and money wastes. One reason for highly prescribing high cost drugs in CSMBS at the hospitals was for cross subsidy. This was the main cause of the increasing of drug spending in CSMBS.

1.5 Controlling of high cost drug use

Since medicines were not only used to improve health and quality of life but can reduce the cost of ill-health. The use of some medicines, initially considered expensive, had led to reductions in the overall cost of managing the conditions for which they were indicated. But in the condition of limited resources, high quality care freely available to all can not be sustained without setting priorities. High cost drugs use was also an important issue to be concerned by the policy makers in every level of healthcare in order to achieve the gold of rationale drug use.

Because increasing of pharmaceutical spending was one of the major parts of the growth of health care expenditure and the scare of resources, pharmaceutical cost containment was concerned together with the quality of health care service improvement in many countries. Effective high cost drug use management can not only reducing the pressure of pharmaceutical expenditure but also increasing equity of access and quality of pharmaceutical services. High cost drug use management strategies had been implemented in many countries at various levels. Essentially, there were four strategies; controlling prices of medicines at various levels, influencing demand by implementing financial measures such as reimbursement, influencing demand by implementing professional measures such as prescribing restriction, and monitoring and evaluating processes and outcomes to control pharmaceutical expenditure which HCD spending was included.

For reimbursement measure, positive list of the medicine eligible for reimbursement, reference price systems, co-payment, generic substitution, compulsory licensing, prescription controls and limits on the duration of prescribed drug treatment were methods use.

In Thailand, many methods of reimbursement measure were used to control high cost drug use in CSMBS such as positive list, generic substitution, prescribing restriction, and prescription control. Drug use evaluation was also widely used for

antibiotic drugs. However, there was not strong monitoring process from the payers. Thus, the increasing of drug spending can not control.

Regarding positive list, it is a list of those medicines eligible for reimbursement. The existence of an approved list of reimbursable medicines was regarded as an important tool in improving the quality of care as well as in containing the costs of pharmaceutical care. Experience in many countries, both in Europe and the developing world, strongly suggests that limitation of the range of reimbursed drugs can be achieved without depriving the population of valuable therapeutic opportunities. Each country had direct responsibility for developing and adopting a list of essential drugs, according to its own policy in the field of health. The positive list should specify drugs under their generic names. The criteria for drug selection should be objective and transparent. Their application consistent and the criteria should be laid down on a law or other form of regulations. One criteria should be restrictive in reimbursement new more expensive medicines that are meant for the treatment of diseases that can already be treated with existing products. New product which were not more effective and/or encumbered with fewer side effects than well-tired older drug should not be reimbursed. Furthermore, where equally effective alternative drug treatments were available, the least costly alternatives should have preference for reimbursement purpose. Where new drugs appear to have advantages over existing drugs, a careful assessment is necessary as to whether these advantages were relevant.

For drug use monitoring and evaluating processes and outcome, the detail was in 1.6

1.6 Monitoring and evaluating processes and outcomes of high cost drug use

Monitoring process involved a regular review of the activities that make up drug management and delivery programs, and that were intended to achieve policy objectives as regards to both health and expenditure. To determine the effect of drug policies, one had to find and select suitable indicators. Indicators that prooved helpful in measuring the effect of a cost containment policy should relate variously to internal process (i.e. implementation of the policy) and to the policy's actual effects on drug management and delivery in the field as measurable in terms of health and economics.

For the evaluation, economic evaluation was an important tool for assessing the efficiency and effectiveness of pharmaceutical programs in terms of costs and

outcomes. Five types of economic evaluation use are cost containment analysis, cost-effectiveness analysis, cost-benefit analysis, cost-utility analysis, and cost-consequence analysis.

Evaluating quality of pharmaceutical care provided from prescribing through to delivery is also important. The narrowest of these was the Drug Utilization Review (DURs). DURs are used to evaluate the level and pattern of drug use. They were originally motivated by concerns about excessive or inappropriate prescribing. DURs can be used to document the association between inappropriate prescribing and its adverse clinical and/or economic consequences. Quality audit was a second common method of evaluating quality. Audit was used to determine whether an optimal quality of service was being achieved within the resources available. Finally, quality assurance provides a systematic approach to evaluating health and pharmaceutical care. Quality assurance can be used to evaluate variously outcomes depending of the focused aspects.

To monitor and to evaluate processes and outcomes of high cost drug use, drug use evaluation method would be applied.

DUE definition

Drug Use Evaluation (DUE) is defined as an authorized, structured, ongoing review of physician prescribing, pharmacist dispensing, and patient use of medication (JCHA, 1994). The purpose of a DUE is to ensure that drugs are used appropriately, safely, and effectively to improve patient health status. In addition, continual improvement in the appropriate and effective use of drugs has the potential to lower the overall cost of care

It involves a comprehensive review of patients' prescription and medication data before, during, and after dispensing to ensure appropriate medication decision making and positive patient outcomes.

Classification of DUE

DUE is classified in three categories (APhA special report, 1994):

- **Prospective DUE** : Prospective review involves evaluating a patient's planned drug therapy before a medication is dispensed. This process allows the pharmacist to identify and resolve problems before the patient has received the medication. Pharmacists routinely perform prospective reviews in their daily practice by assessing a prescription medication's dosage and directions and reviewing patient information for possible drug interactions or duplicate therapy.

Issues commonly addressed by prospective DUE are drug-disease contraindications, therapeutic interchange, generic substitution, incorrect drug dosage, inappropriate duration of drug treatment, drug-allergy interactions,clinical abuse/misuse

- **Concurrent DUE**: Concurrent review is performed during the course of treatment and involves the ongoing monitoring of drug therapy to ensure positive patient outcomes. Some refer to this as case management or health management. It presents pharmacists with the opportunity to alert prescribers to potential problems and to intervene in areas such as drug-drug interactions, duplicate therapy, over or underutilization, and excessive or insufficient dosing. This type of review allows therapy for a patient to be altered if necessary.

Issues commonly addressed by concurrent DUE are drug-drug interactions, excessive doses, high or low dosages, duplicate therapy, drug-disease interactions, over and underutilization, drug-age precautions, drug-gender precautions, drug-pregnancy precautions

- **Retrospective DUE**: A retrospective DUE is the simplest to perform since drug therapy is reviewed after the patient has received the medication. A retrospective review may detect patterns in prescribing, dispensing, or administering drugs to prevent recurrence of inappropriate use or abuse and serves as a means for developing prospective standards and target interventions. In retrospective DUE, patient medical charts or computerized records are screened to determine whether the drug therapy met approved criteria and aids prescribers in improving care for their patients, individually and within groups of patients, such as those with diabetes, asthma, or high blood pressure.

Issues Commonly Addressed by Retrospective DUE are therapeutic appropriateness, over and underutilization, appropriate generic use, therapeutic duplication, drug-disease contraindications, drug-drug interactions, incorrect drug dosage, inappropriate duration of treatment, clinical abuse/misuse

Selecting drugs for drug use evaluation

When selecting drugs for evaluation, priorities must be set to make the best use of limited resources DUEs might address drugs that are;

- Frequently prescribed

- Expensive associated with potentially serious adverse reactions or interactions with drugs, foods, or diagnostic procedures used
- Used in patient populations at high risk for adverse reactions
- Most efficacious when used in a specific manner
- Designated for formulary evaluation (e.g., deletion, addition)
- Potentially toxic
- Associated with discomfort when used at therapeutic dosage
- Designated for study by hospital infection control or quality assurance activities ([American Society of Health-System Pharmacists (ASHP),1993]

Steps in Conducting a Drug Use Evaluation

Most authors agree that the following five steps are essential when conducting any quality-related DUE program (Plumbo and Ober, 1995 and Yate and Rupp, 1991):

1. **Identify or Determine Optimal Use –**

Criteria are defined to allow for comparisons of optimal use with actual use. Criteria should focus on relevant outcomes. Good criteria can be expected to ensure improvement in patient care and outcomes. They are usable, reliable, relevant and reasonable (ASHP),1993. Usable criteria are written for readily retrievable data which clear, complete, and concise with specific measurable numerical decision points. Reliable criteria require no judgment or interpretation by the user; all users should arrive at the same decision was met. Reasonable criteria are not written with such low expectations that they encourage poor performance or with such high expectations that they are unrealistic. Reasonable criteria also reflect consideration for local practitioners and unique characteristic of the hospital. For example, if the use of a drug prescribed to treat a patient with diabetes is being evaluated, then set standards should be determined to evaluate its effectiveness, such as a decrease in blood glucose or HbA1c (glycosylated hemoglobin) levels.

2. **Measure Actual Use**

This step is where data is gathered to measure the actual use of medications. This data can be obtained from medical and prescription records or electronic claim forms.

3. **Compare**

This involves the comparison between optimal or appropriate and actual use. During this process, the evaluator determines whether findings are expected and causes for any discrepancies. In this process, patterns or aberrations can be interpreted.

4. **Intervene**

This is the step where corrective action is implemented. Action should be targeted to areas of concern such as prescribing patterns, medication misadventures, the quality of drug therapy, or economic consideration.

5. **Evaluate the DUE Program**

The last step is to assess the effectiveness of the DUE program. Efforts should be made to evaluate the outcomes and document reasons for positive and negative results. Implementing appropriate changes to the DUE program and continued observation should be undertaken.

Value of DUE Programs

DUE programs play a key role in helping policy makers and providers in health care systems understand, interpret, and improve the prescribing, administration, and use of medications. In addition the results of DUE programs can be used to foster more efficient use of scarce health care resources.

In USA, The Academy of Managed Care Pharmacy (AMCP) recognizes the value of drug use evaluation (DUE) as a means of improving the quality of patient care, enhancing therapeutic outcomes, and reducing inappropriate pharmaceutical expenditures, thus reducing overall health care costs. Managed health care systems and pharmacy benefit management companies (PBMs) have the responsibility of managing the medication use of anywhere from a few hundred thousand to millions of patients. DUE programs play a key role in helping these organizations understand, interpret, and improve the prescribing, administration, and use of medications. This is often accomplished by using DUE programs to provide physicians with feedback on their performance and prescribing behaviors as compared to pre-set criteria or treatment protocols.

DUE information also allows physicians to compare their approach to treating certain diseases with their peers. The "peer pressure" generated by these comparisons is useful in stimulating physicians to change their prescribing habits in an effort to improve care. For example, many health plans use DUE to encourage physicians to use more generic drugs and to comply with treatment guidelines established by national organizations such as the National Institutes of Health or the American Heart Association.

DUE information also assists managed health care systems and PBMs in designing educational programs that improve rational prescribing, formulary compliance, and patient compliance. These educational programs may take the form of face-to-face education of physicians and patients by clinical pharmacists, telephone calls, letters, newsletters, and educational symposia.

1.7 Role of computer programs on evaluation of drug use

In current health care service system, computer programs have been widely use for database system development, health care service evaluation ,drug use evaluation ,etc. Because many computer programs can provide information electronically in the interactive and real-time basis.

For drug use evaluation, various computer programs have been used in all drug use evaluation categories, prospective, concurrent and retrospective DUE purposes.

In some developed countries, national electronic databases are ongoing setting up process. For example, in USA, Medicare Prescribing Drug Improvement and Modernization Act of 2003 (MMA) requires DHHS to work with expert to establish national standard electronic prescriptions. The goal of these national standards is to create an infrastructure that will improve patient safety and the quality and efficiency of patient care, and in which all prescribing computer systems will be compatible and work together seamlessly (Center for Medicare & Medicaid Service, 2004). They expect that medication errors that result from unclear handwriting or other errors will be sharply reduced with the implementation of electronic prescribing. In addition, electronic prescribing is likely to be more efficient than the current paper system.

For rational drug use evaluation, software program was established and used in stead of conventional DUE using paper system. The study of epoetin alfa Drug Use

Evaluation Using A Software System conducted at 32 sites across US was an example. (Armstrong E.P., et al, 2000).

In Thailand, computer programs using in health care services systems are widely in both government and private sectors. After the implementation of UC , electronic databases especially for registration and inpatient service are national compulsory for the contacted hospitals. In pharmaceutical system, the government established drug inventory program; INV, for the government program. Now, most of hospitals use various dispensing program in dispensing process . Another departments in the hospitals mainly use computer program in their working process are patient registry parts , laboratory department, etc. There were some studies using computerized databases as data resources in Thailand, for example, the study of the expenditure of high cost drug and the difference of their use in various health insurance schemes in a regional hospital in North-Eastern part, Thailand (Munkratok , Kulsomboon, and Sirisinsukl, 2006), the study of Cost of diabetes disease in government hospitals in 2002-2003 (Pongchareonsuk, 2003) and the study of electronic database for hospital drug use analysis : Universal coverage policy evaluation instrument (Limwattananon, Pannarrunothai, 2003).

Part II : Pharmacology and Clinical Practice Guideline of high cost drugs

Regarding pharmacology and clinical practice guideline of some high cost drugs, these two high cost drugs; Atorvastatin, and Rosiglitazone were reviewed.

2.1 High blood cholesterol : Detection, Evaluation, Treatment, and Atorvastatin

According to National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) updated clinical guidelines for cholesterol testing and management identified elevated LDL cholesterol as the primary target of cholesterol –lowering therapy to reduce risk for coronary heart diseases (CHD). The relation ship between LDL cholesterol levels and CHD risk is continuous over a broad range of LDL level from low to high. Therefore, AIP III adopts the classification of LDL cholesterol levels showed in Table 3 which also shows the classification of total and HDL cholesterol level.

Table 2.3. ATP III Classification of LDL, Total, and HDL cholesterol(mg/dL)

LDL Cholesterol	
< 100	Optimal
100 - 129	Near optimal/above optimal
130 - 159	Borderline high
160 – 189	High
≥ 190	Very high
Total Cholesterol	
< 200	Desirable
200 – 239	Borderline high
≥ 240	High
HDL Cholesterol	
< 40	Low
≥ 60	High

Risk determinants in addition to LDL-cholesterol include the presence or absence of CHD, other clinical forms of atherosclerotic disease, and the major risk factors other than LDL (Table 4). (LDL is not counted among the risk factors in Table 3

because the purpose of counting those risk factors is to modify the treatment of LDL.) Based on these other risk determinants, ATP III identifies three categories of risk that modify the goals and modalities of LDL-lowering therapy. Table 5 defines these categories and shows corresponding LDL-cholesterol goals.

Table 2.4. Major Risk Factors (Exclusive of LDL Cholesterol) That Modify LDL Goals*

- Cigarette smoking
- Hypertension (BP ≥140/90 mmHg or on antihypertensive medication)
- Low HDL cholesterol (<40 mg/dL)†
- Family history of premature CHD (CHD in male first degree relative <55years; CHD in female first degree relative <65 years)
- Age (men ≥45 years; women ≥55 years)*

* In ATP III, diabetes is regarded as a CHD risk equivalent.
† HDL cholesterol ≥60 mg/dL counts as a "negative" risk factor; its presence removes one risk factor
from the total count.

Table 2.5. Three Categories of Risk that Modify LDL Cholesterol Goals

Risk Category	LDL Goal (mg/dL)
CHD and CHD risk equivalents	<100
Multiple (2+) risk factors*	<130
Zero to one risk factor	<160

* Risk factors that modify the LDL goal are listed in Table 5

- The category of highest risk consists of CHD and CHD risk equivalents.The latter carry a risk for major coronary events equal to that of established CHD, i.e., >20% per 10 years (i.e., more than 20 of 100 such individuals will develop CHD or have a recurrent CHD event within 10 years). CHD risk equivalents comprise:
- Other clinical forms of atherosclerotic disease (peripheral arterial disease, abdominal aortic aneurysm, and symptomatic carotid artery disease);
- Diabetes;
- Multiple risk factors that confer a 10-year risk for CHD >20% using Framingham scoring.

(Risk factors used in Framingham scoring include age, total cholesterol, HDL cholesterol, blood pressure and cigarette smoking.)

Primary Prevention with LDL-Lowering Therapy

Primary prevention of CHD offers the greatest opportunity for reducing the burden of CHD in the United States. The clinical approach to primary prevention is founded on the public health approach that calls for lifestyle changes, including: 1) reduced intakes of saturated fat and cholesterol, 2) increased physical activity, and 3) weight control, to lower population cholesterol levels and reduce CHD risk, but the clinical approach intensifies preventive strategies for higher risk persons. One aim of primary prevention is to reduce long-term risk (>10 years) as well as short-term risk (≤10 years). LDL goals in primary prevention depend on a person's absolute risk for CHD (i.e., the probability of having a CHD event in the short term or the long term)—the higher the risk, the lower the goal. Therapeutic lifestyle changes are the foundation of clinical primary prevention. Nonetheless, some persons at higher risk because of high or very high LDL cholesterol levels or because of multiple risk factors are candidates for LDL-lowering drugs. Recent primary prevention trials show that LDL-lowering drugs reduce risk for major coronary events and coronary death even in the short term.

Secondary Prevention With LDL-Lowering Therapy

Recent clinical trials demonstrate that LDL-lowering therapy reduces total mortality, coronary mortality, major coronary events, coronary artery procedures, and stroke in persons with established CHD. As shown in Table 4, an LDL cholesterol level of <100 mg/dL is *optimal;* therefore, ATP III specifies an LDL cholesterol <100 mg/dL as the goal of therapy in secondary prevention. This goal is supported by clinical trials with both clinical and angiographic endpoints and by prospective epidemiological studies. The same goal should apply for persons with CHD risk equivalents. When persons are hospitalized for acute coronary syndromes or coronary procedures, lipid measures should be taken on admission or within 24 hours. These values can guide the physician on initiation of LDL-lowering therapy before or at discharge. Adjustment of therapy may be needed after 12 weeks.

LDL-Lowering Therapy in Three Risk Categories

The two major modalities of LDL-lowering therapy are *therapeutic lifestyle changes* (TLC) and *drug therapy.* Both are described in more detail later. The TLC Diet stresses reductions in saturated fat and cholesterol intakes. When the metabolic syndrome or its associated lipid risk factors (elevated triglyceride or low HDL cholesterol) are present, TLC also stresses weight reduction and increased physical activity. Table 6 defines LDL cholesterol goals and cut points for initiation of TLC and for drug consideration for persons with three categories of risk: CHD and CHD risk equivalents; multiple (2+) risk factors (10-year risk 10-20% and <10%); and 0-1 risk factor.

Table 2.6: LDL Cholesterol Goals and Cutpoints for Therapeutic Lifestyle Changes (TLC) and Drug Therapy in Different Risk Categories.

Risk Category	LDL Goal	LDL Level at Which to Initiate Therapeutic Lifestyle Changes (TLC)	LDL Level at Which to Consider Drug Therapy
CHD or CHD Risk Equivalents (10-year risk >20%)	<100 mg/dL	≥100 mg/dL	≥130 mg/dL (100-129 mg/dL: drug optional)*
2 + Risk Factors (10-year risk ≤ 20%)	< 130 mg/dL	≥ 130 mg/dL	10-year risk 10-20%: ≥ 130 mg/dL 10-year risk <10%: ≥160 mg/dL
0-1 Risk Factor†	<160 mg/dL	≥ 160 mg/dL	≥190 mg/dL (160-189 mg/dL: LDL-lowering drug optional)

* Some authorities recommend use of LDL-lowering drugs in this category if an LDL cholesterol <100 mg/dL cannot be achieved by therapeutic lifestyle changes. Others prefer use of drugs that primarily modify triglycerides and HDL, e.g., nicotinic acid or fibrate. Clinical judgment also may call for deferring drug therapy in this subcategory.
† Almost all people with 0-1 risk factor have a 10-year risk <10%, thus 10-year risk assessment in people with 0-1 risk factor is not necessary.

Drug Therapy to Achieve LDL Cholesterol Goals

A portion of the population whose short-term or long-term risk for CHD is high will require LDL-lowering drugs in addition to TLC to reach the designated goal for LDL cholesterol (Table 2.6). When drugs are prescribed, attention to TLC should

always be maintained and reinforced. Currently available drugs that affect lipoprotein metabolism and their major characteristics are listed in Table 2.7.

Table 2.7. Drugs Affecting Lipoprotein Metabolism

Drug Class, Agents and Daily Doses	Lipid/Lipoprotein Effects	Side Effects	Contraindications	Clinical Trial Results
HMG CoA reductase Inhibitors (statins)*	LDL ↓18-55% HDL ↑ 5-15% TG ↓ 7-30%	Myopathy Increased liver enzymes	Absolute: -Active or chronic liver disease Relative : - Concomitant use of certain drugs†	Reduced major coronary events, CHD deaths, need for coronary procedures, stroke, and total mortality
Bile acid Sequestrants‡	LDL ↓15- 30% HDL ↑ 3- 5% TG No change or increase	Gastro intestinal distress Constipation Decreased absorbtion of other drugs	Absolute: -dysbeta lipoproteinemia - TG>400mg/dL Relative: -TG>200mg/dL	Reduced major coronary events, and CHD deaths
Nicotinic acid¥	LDL ↓ 5- 25% HDL ↑ 15- 35% TG ↓ 20-50%	Flushing Hyperglycemia Hyperuricemia (or gount) Upper GI distress Hepatotoxicity	Absolute: - Chronic liver disease - Severe gout Relative: - Diabetes - Hyperuricemia - Peptic Ulcer disease	Reduced major coronary events, and possibly total mortality
Fibric acids§	LDL ↓ 5- 20% (may be increased in patients with high TG) HDL ↑ 10- 20% TG ↓ 20-50%	Dyspepsia Gallstones Myopathyl Unexplained non-CHD deaths in WHO study	Absolute: - Severe renal disease - Severe hepatic disease	Reduced major coronary events

* Lovastatin (20-80 mg), pravastatin (20-40 mg), simvastatin (20-80 mg), fluvastatin (20-80 mg), atorvastatin (10-80 mg), cerivastatin (0.4-0.8 mg).

† Cyclosporine, macrolide antibiotics, various antifungal agents and cytochrome P-450 inhibitors (fibrates and niacin should be used with appropriate caution).

‡ Cholestyramine (4-16 g), colestipol (5-20 g), colesevelam (2.6-3.8 g).

¥ Immediate release (crystalline) nicotinic acid (1.5-3 g), extended release nicotinic acid (Niaspan ®) (1-2 g), sustained release nicotinic acid (1-2 g).

§ Gemfibrozil (600 mg BID), fenofibrate (200 mg), clofibrate (1000 mg BID).

http://www.nhlbi.nih.gov/guidelines/cholesterol/atp3xsum.pdf 22 Dec 2006

Atorvastatin

Atorvastatin is an HMG-CoA reductase inhibitor (statin) that lowers cholesterol. Statins are first-line for the treatment of hypercholesterolaemia. In patients with coronary heart disease and in others at high cardiovascular risk, statins reduce the risk of death, myocardial infarction, revascularisation or stroke.

Atorvastatin is more potent at lowering cholesterol levels on a milligram-for-milligram basis compared to either simvastatin or pravastatin (see Figure 2.1). Similar reductions in cholesterol can be achieved with equipotent doses, but across its dose range Atorvastatin reduces LDL cholesterol about 5–20% more than the reductions achieved with Simvastatin or Pravastatin.

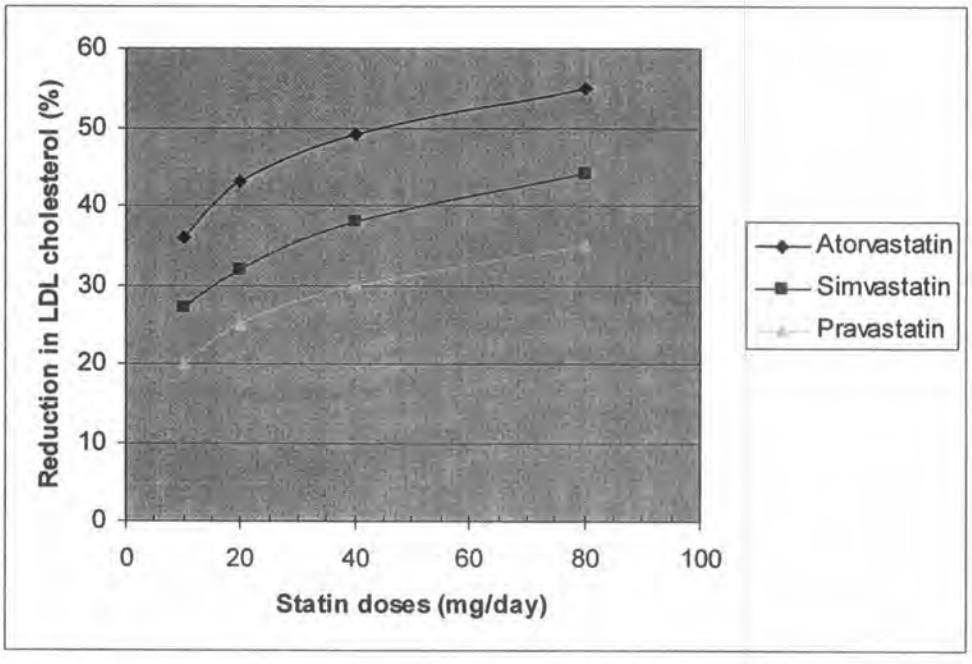

Figure 2.1: Percentage reduction in LDL cholesterol with recommended doses of atorvastatin, simvastatin and pravastatin

The dose equivalency of Atorvastatin and simvastatin was reported to be between 1:2 (Table 2. 8) Atorvastatin can reduce triglycerides more than Simvastatin, and Simvastatin elevates HDL cholesterol more than Atorvastatin. The clinical significance of these differences was unknown.

Table 2. 8 : Statin : Lowering LDL Drug Therapy : Dose Equivalency Chart

% LDL-C Reduction	HMG-CoA Reductase Inhibitor				
	Pravastatin	**Fluvastatin**	**Lovastatin**	**Simvastatin**	**Atorvastatin**
18	10mg	20mg	10mg	5mg	10mg
19					
20					
21	20mg				
22					
23		40mg	20mg	10mg	
24					
25					
26					
27		80mg			
28	40mg		40mg		
29					
30					
31	80mg			20mg	
32					
33			80mg		
34					
35					
36				40mg	20mg
37					
38					
39					
40					
41				80mg	
42					
43					
44					40mg
45					
46					
47					
48					
49					
50					
51					
52					80mg
53					
54					
55					
56					
57					
58					

Source : http://www.pec.ha.osd.mil/Contracts/Statin_Contract_Guidance.htm#MTFformulary 4 Jan 2007Guidance for the New HMG-CoA Reductase Inhibitor (Statin) Contract Department of Defense Pharmacoeconomic Center April 2003 (updated May 2006)

Atorvastatin is not a preferred choice if existing treatment with Simvastatin or Pravastatin achieves target cholesterol levels. There were no head-to-head studies comparing the effectiveness of Atorvastatin with equipotent doses of other statins for reducing the risk of cardiovascular events. The PROVE-IT trial of intensive versus moderate lipid modification in acute coronary syndromes was the only head-to-head study comparing the clinical outcomes of statins. Atorvastatin 80 mg reduced the absolute risk of death from any cause or a major cardiovascular event by 3.9% compared to pravastatin 40 mg. This was largely due to reductions in revascularisation and unstable angina.(Cannon CP. et al, 2004).

Choose Atorvastatin, Simvastatin or Pravastatin when initiating treatment with a statin. If maximum recommended doses do not achieve treatment goals, switch to a statin that is more potent at lowering cholesterol (see Figure 2.1 and Dosing Issues).

For safety issue, Atorvastatin was well tolerated and has a similar safety profile to other statins. Adverse effects include myalgia, mild gastro-intestinal symptoms, elevated transaminases and headache. Rarely, myopathy or rhabdomyolysis can occur. Atorvastatin poses a similarly low risk of myopathy and rhabdomyolysis to the other statins

Stop treatment with Atorvastatin if patients develop persistent symptoms of muscle aches, mild to severe pain, stiffness or weakness, even when creatine kinase levels were normal Symptoms are usually reversible within a few days to weeks of stopping treatment (Hamilton-Craig I, 2003). Consider restarting Atorvastatin at a lower dose after at least 4 weeks, if symptoms were mild and when creatine kinase levels had returned to normal. If the reaction reoccurs, stop Atorvastatin permanently (Australian Medicines Handbook. Adelaide: Australian Medicines Handbook, 2005)

Studies have rarely reported myopathy or rhabdomyolysis with Atorvastatin but it was strongly associated with certain risk factors. Patients most likely to develop muscle disorders, such as those with multiple co-morbidities or taking interacting drugs, were usually excluded from statin trials and thus cases with Atorvastatin may have been underreported.

Factors that increase the risk of muscle disorders with statins are as following;

1. High plasma levels of statins due to high doses
    - ≥ 40 mg daily, particularly with other co-existing risk factors
2. Concomitant drugs that may increase plasma levels of statins by inhibiting CYP3A4 hepatic or gut metabolism
    - Calcium-channel blockers (diltiazem, verapamil)
    - Macrolide antibiotics (clarithromycin, erythromycin)
    - Azole antifungals(fluconazole, ketoconazole)
    - SSRIs (fluvoxamine, fluoxetine)
    - Protease inhibitors (amprenavir, atazanavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir)
    - Others:amiodarone, cyclosporin, delavirdine, grapefruit juice
3. Concomitant drugs that may cause muscle damage
    - Cyclosporin, gemfibrozil, fenofibrate, nicotinic acid
4. Concurrent illness or disease states
    - Infection, trauma or major surgery
    - Metabolic disorder (e.g. diabetes, hypothyroidism)
    - Renal or hepatic disease
    - Previous muscle damage with a statin
5. Patient demographics
    - Older age (≥ 70 years), female gender, low body weight

The Adverse Drug Reactions Advisory Committee (ADRAC) in 2004 reported that risk factors existed in nearly half of the cases of statin-induced myalgia, myopathy or raised creatine kinase levels, and in more than 75% of cases of rhabdomyolysis. A post marketing analysis reported that Simvastatin caused more adverse effects related to

muscle than Atorvastatin, but patients taking Simvastatin on average received higher doses and more concomitant interacting drugs (Alsheikh A. et al,2005). In the A to Z trial, 9 of 2263 patients developed muscle disorders (including three cases of rhabdomyolysis) with Simvastatin 80 mg. Risk factors were evident in three cases and included renal failure, verapamil or alcohol abuse. In the TNT study, although there were no reports of elevated creatine kinase levels (> 10 times upper limit of normal) or rhabdomyolysis related to Atorvastatin 80 mg, 197 patients with adverse events (35 with myalgia) to the 10 mg dose during the run-in phase did not continue the study.

High doses of Atorvastatin increase the risk of elevated liver transaminases. Elevations in liver transaminases (ALT and/or AST) with statins were dose-dependent but uncommon and rarely develop into serious hepatic reactions (e.g. hepatitis, cholestatic jaundice). Stop atorvastatin if ALT and/or AST are persistently three or more times the upper limit of normal. Elevations usually resolve with a lower dose or alternative statin.

For dosing issue, start with a low dose of atorvastatin and titrate if necessary to achieve treatment goals (dose range 10–80 mg once daily). Measure the cholesterol level within 4 weeks of initiating Atorvastatin, or after dose titration. Higher doses (40–80 mg daily) may be required to reduce cholesterol levels by $\geq$ 50%. Atorvastatin can be taken at any time of the day, with or without food (Pfizer Australia Pty Ltd. Lipitor Product Information, 2005).

About Changing from other statins to Atorvastatin, beforere switching treatment to Atorvastatin, check that the patient has been compliant with taking their statin treatment. Monitoring the patient for adverse effects which can occur when treatments change, especially if titration Atorvastatin to a higher dose.

The use of Atorvastatin in other countries

In UK

The NICE appraisal states that statin therapy was recommended for adults with clinical evidence of cardiovascular disease (CVD). It was also recommended for the primary prevention of CVD for adults who have a 20% or greater 10-year risk of developing CVD. In addition, statin therapy should be initiated with a drug with a low acquisition cost.

Based on clinical trial evidence and cost, generic Simvastatin 20mg or 40mg daily would seem a reasonable first choice, and NICE have used this in their cost estimates. Atorvastatin 10mg daily would be a reasonable alternative. However, this was over four times more expensive than generic Simvastatin 40mg. Generic Pravastatin was an attractive alternative based on cost. However, its clinical outcome data are less convincing. Rosuvastatinq had no clinical outcome data and prescribing restrictions apply to higher doses. It seems rational to reserve this newest statin for cautious use in difficult-to-treat cases. For the secondary prevention, Simvastatin 20mg or 40mg daily would seem an appropriate first choice for patients with CV diseases. This recommendation based on the results of the 4S study and the Heart Protection Study .

Any incremental benefit of aggressive lipid lowering over standard treatment has to be considered in the context of other secondary preventative measures (e.g. smoking cessation, antiplatelet therapy, diet and exercise, beta-blockers, ACE inhibitors, blood pressure control). A recent meta-analysis of statin trials suggested that the benefits in reducing major CV events are proportional to the absolute reduction in LDL-C and the baseline CV risk, and are largely irrespective of pre-treatment lipid levels. In general, therefore, reducing the absolute LDL-C level by a significant amount, using a well-tolerated, evidence based statin dose, may be more important than aggressively chasing a specific target LDL-C level and increasing the likelihood of adverse effects and poor adherence. Based on the results of the 4S study4 and the Heart Protection Study, Simvastatin 20mg or 40mg daily would seem an appropriate first choice for patients with CV disease (MeReC Extra No 21 ,2006 published by National Prescribing Center).

In Australia

Atorvastatin was listed on the PBS as a restricted benefit for use in patients who meet the criteria set out in the General Statement for Lipid Lowering Drugs. Atorvastatin was not a preferred choice if existing treatment with maximum recommended dose of simvastatin or pravastatin achieves target cholesterol levels. (Atorvastatin (Lipitor) for the management of lipid disorders)

In USA

According to the minutes of the Department of Defense (DoD) Pharmacy and Therapeutics (P&T) Executive Council Meeting about drug class evaluations to determine clinically acceptable contracting/ formulary strategies of therapeutic interchangeability between Simvastatin and Atorvastatin, it was reported that less than 10% of patients require the magnitude of LDL-cholesterol reduction that can only be achieved by Atorvastatin. However, the Council concluded that Simvastatin and Atorvastatin have a high degree of therapeutic interchangeability.

In Thailand

Both Simvastatin and Atorvastatin were in 2004 National Essential Drug List but in the different subclass. Simvastatin (5, 10, 20,and 40 mg) was in subclass 1 (defined as list of drugs for all level of facilities). They were the standard drugs used for common prevention and health problems' solution. There were clear evidence based to support the use, enough experiences on the drug use in Thailand. It should be used as the first line drug for its indications. Atorvastatin(10 and 20 mg) was in subclass 4 which DUE was needed if prescribed. Recommended condition for Atorvastatin, it would be used if Simvastatin fail to achieve LDL-lowering goal. (National List of Essential Medicine 2004)

2.2 Diabetes and Rosiglitazone

Diabetes is a chronic condition that occurs when the pancreas does not produce enough inslulin or when the body con not effectively use the insulin it procedures. Hyperglycemia and other related disturbances in the body's metabolism can lead to serious damage to many of the body's system, especially the nerves and blood vessels.

There are two basic forms of diabetes : Type 1: people with this type of diabetes produce very little or no insulin. Type 2: people with this type of diabetes can not use insulin effectively. Most people with diabetes have type 2. A third type of diabetes, gestational diabetes mellitus (GDM), develop during some cases of pregnancy but usually disappears after pregnancy. The prevalence of diabetes for all age-groups world wide was estimated to be 2.8% in 2000 and 4.4% in 2030. The total number of people with diabetes is projected to rise from 171 million in 2000 to 366 million in 2030 the most important demographic change to diabetes prevalence across the world appears to be the increase in the proportion of people 65 years of age (Wild, Roglic, Green. et al, 2004)

Regarding glycemic gold of therapy, the most recent glycemic goal recommended by the American Diabetes Association, selected on the basis of practicality and the projected reduction in complication over time, is "in general" gglycate haemoglobin (HbA1C) level < 7%. For " the individual patient," the HbA1C should be "as close to normal ($\leq$ 6%) as possible without significant hypoglycemia." The most recent glycemic goal was consensus statement from American Diabetes Association and European Union International Diabetes Federation about the target of treatment diabetes were HbA1C less than 7% (Nathan, Buce, Devison.et al, 2006)

An important intervention that was likely to improve the probability that a patient had better long- term control of daiabetes was to make the diagnosis early, when the metabolic abnormalities of diabetes were usually less severe. Lower levels of glycemia at time of initial therapy were associated with lower HbA1C over time and decrease long-term complication.

Lifestyle interventions to control environmental factors that increase the risk of type 2 diabetes, presumably in the setting of genetic risk, are over nutrition and a secondary lifestyle, with consequent overweight and obesity. However, the limited long term success of lifestyle programs to maintain glycemic goals in patients with type 2

diabetes suggests that a large majority of patients may require the addition of medications over the course of their diabetes.

These are anti-hyperglycemic drugs available in many countries according to a consensus statement from the American Diabetes Association and the European Association for the Study of Diabetes (Nathan et al, 2006).

Metformin: Metformin is the only biguanide available in most of the world. Its major effect is to decrease hepatic glucose output and lower fasting glycemia. Typically, metformin monotherapy will lower HbA1C by ~ 1.5 percentage points. It is generally well tolerated, with the most common adverse effects being gastrointestinal. Although always a matter of concern because of its potentially fatal outcome, lactic acidosis is quite rare (1 case per 100,000 treated patients). Metformin monotherapy is usually not accompanied by hypoglycemia and has been used safely, without causing hypoglycemia, in patients with pre-diabetic hyperglycemia. The major nonglycemic effect of metformin is either weight stability or modest weight loss, in contrast to many of the other blood glucose-lowering medications.

Sulfonylureas: Sulfonylureas lower glycemia by enhancing insulin secretion. They appear to have an effect similar to metformin, and they lower HbA1C by 1.5 percentage points. The major adverse side effect is hypoglycemia, but severe episodes, characterized by need for assistance, coma, or seizure, are infrequent. However, such episodes are more frequent in elderly. Episodes can be both prolonged and life threatening, although these are very rare. Several of the newer sulfonylureas have a relatively lower risk for hypoglycemia. In addition, weight gain of 2 kg is common with the initiation of sulfonylurea therapy. This may have an adverse impact on CVD risk, although it has not been established.

Glinides: Like the sulfonylureas, the glinides stimulate insulin secretion, although they bind to a different site within the sulfonylurea receptor. They have a shorter circulating half-life than the sulfonylureas and must be administered more frequently. Of the two glinides currently available in the U.S., repaglinide is almost as effective as metformin or the sulfonylureas, decreasing HbA1C by 1.5 percentage points. Nateglinide is somewhat less effective in lowering HbA1C than repaglinide when used as monotherapy or in combination therapy. The glinides have a similar risk for weight gain as the sulfonylureas, but hypoglycemia may be less frequent, at least with nateglinide, than with some sulfonylureas.

Glucosidase inhibitors: Glucosidase inhibitiors reduce the rate of digestion of polysaccharides in the proximal small intestine, primarily lowering postprandial glucose levels without causing hypoglycemia. They are less effective in lowering glycemia than metformin or the sulfonylureas, reducing HbA1C by 0.5-0.8 percentage points. Since carbohydrate is absorbed more distally, malabsorption and weight loss do not occur; however, increased delivery of carbohydrate to the colon commonly results in increased gas production and gastrointestinal symptoms. This side effect has led to discontinuation of the glucosidase inhibitors by 25-45% of participants in clinical trials. One clinical trial examining acarbose as a means of preventing the development of diabetes in high-risk subjects with impaired glucose tolerance showed an unexpected reduction in severe CVD outcomes. This potential benefit of glucosidase inhibitors needs to be confirmed.

Thiazolidinediones: Thiazolidinediones (TZDs or glitazones) are peroxisome proliferators-activated receptor modulators; they increase the sensitivity of muscle, fat, and liver to endogenous and exogenous insulin ("insulin sensitizers"). Pioglitazone and rosiglitazone are the drugs in this group. The limited data regarding the blood glucose-lowering effectiveness of TZDs when used as monotherapy have demonstrated a 0.5-1.4% decrease in HbA1C. The most common adverse effects with TZDs are weight gain and fluid retention. There is an increase in adiposity, largely subcutaneous, with redistribution of fat from visceral deposits shown in some studies. The fluid retention usually manifests as peripheral edema, though new or worsened heart failure can occur.

Insulin: Insulin is the oldest of the currently available medications and has the most clinical experience. Although initially developed to treat the insulin deficient type 1 diabetic patient, in whom it is life saving, insulin was used early on to treat the insulin-resistant from of diabetes recognized by Himsworth and Kerr. Insulin is the most effective of diabetes medications in lowering glycemia. It can, when used in adequate doses, decrease any level of elevated HbA1C to, or close to, the therapeutic goal. Unlike the other blood glucose-lowering medications, there is no maximum dose of insulin beyond which a therapeutic effect will not occur. Relatively large dose of insulin (1 unit/kg), compared with those required to treat type 1 diabetes, may be necessary to overcome the insulin resistance of type 2 diabetes and lower HbA1C to goal. Although initial therapy is aimed at increasing basal insulin supply, usually with intermediate- or long-acting insulin, patients may also require prandial therapy with short- or rapid-

acting insulin as well. Insulin therapy has beneficial effects on triglyceride and HDL cholesterol levels but is associated with weight gain of 2-4 kg, probably proportional to the correction of glycemia and owing predominantly to the reduction of glycemia.

The use of Rosiglitazone in other countries

Global guideline set up by International diabetes federation

Thiazolidinedione will be used when glucose concentrations are not controlled to target levels, adding it to metformin as an alternative to a sulfonylurea, or to a sulfonylurea where metformin is not tolerated, or to the combination of metformin and a sulfonylurea. Be alert to the contra-indication of cardiac failure, and warn the person with diabetes of the possibility of development of significant edema.

In UK

The NICE appraisal 63 guidance limits the use of glitazone to those people with type 2 diabetes who are unable to take metformin or a sulfonylurea in combination because of intolerance or a contraindication to either metformin or sulfonylurea (National Institute for Clinical Excellence, 2003).

In Australia

For PBS listing, rosiglitazone can be used in patients with type 2 diabetes whose blood glucose concentrations are inadequately controlled, either: as dual oral therapy with metformin or a sulfonylurea is contra-indicated or not tolerated; or as triple oral therapy with maximally tolerated doses of metformin and a sulfonylurea (National Prescribing Service Limited Rational Assessment of Drugs and Research, 2005).

In Thailand

Rosiglitazone is in subclass 4 of 2004 National Essential Drug Lists which DUE is needed if prescribed. Recommended condition for rosiglitazone, it will be used in the patients who fail to use metformin or metformin contra-indicated. (National List of Essential Medicine 2004).