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Drug utilization study of anti-diabetic drugs in a tertiary care hospital

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Abstract
Background: Diabetes mellitus is a major non-communicable disease and a risk factor for cardiovascular diseases. The anti-diabetic drugs used for its management constitute a significant portion of the medicines prescribed in a health care centre. The aim of our study was to analyse the utilisation pattern of anti-diabetic drugs at a tertiary care hospital in accordance with the WHO prescription indicators.
Methods: A prospective cross sectional observational study was carried out in the outpatient of General Medicine department of Shadan Institute of Medical Sciences. The prescription of the diabetic patients visiting the outpatient was monitored. From the date collected the prescription pattern of anti-diabetic drugs, and WHO prescription indicators were analysed.
Results: Among a total of 220 participants diagnosed with Type-ll diabetes mellitus 118(53.64%) were females and 102 (46.36%) were males. It was observed to be the highest 132 (60%) in the age group 40-59years followed by 66 (30%) in the age group 60-70years and above and 22 (10%) in less than 40years age group. Of the 220 participants 77(35%) had a strong family history of diabetes. It was observed that 79(36%) of participants were literates and 141(64%) were illiterates. Among the anti-diabetic drugs prescribed Metformin was most frequently prescribed (54.16%). Metformin and glibenclamide were frequently used for dual therapy. The WHO prescribing indicators as analysed from the data collected are- Average number of drugs prescribed per encounter was 5.84/prescription. Percentage of medicines prescribed by generic name was 87.35%. Percentage of medicines prescribed from essential drug list was 91.24%.
Conclusion: This study provides an overview of the anti-diabetic drug usage pattern in a tertiary care hospital. The study emphasises the need for preventive measures and effective educative measures in the population about diabetes. Medication should be prescribed taking into consideration the economic aspects; such a small negligence leads to poor patient compliance. Polypharmacy must be practised carefully taking into consideration the chances of drug interactions and adverse drugs reactions.

Keywords: Drug utilization study, diabetes mellitus, ant diabetic drugs, defined daily dose (DDD)

Introduction
Diabetes mellitus has become a common non-communicable disease spreading rapidly all over the world. It leads to high morbidity and mortality due to the disease itself and its diverse complications like coronary artery disease like hypertension, renal complications, retinal damage, and neurological disorders [1], incidence of stroke at different sites, generalised infections, etc.
According to international diabetes federation (IDF) [2], 387million people globally suffer from diabetes which is estimated to rise to 592million by 2035. The prevalence of diabetes in India in 2000was 31.7million in 2013, the prevalence has risen to 65.1million and is expected to reach 79.4 million by 2030. However current estimates revealed that there are at least 150 million people who are living with diabetes worldwide of which 2/3rd of them belong to developing countries. Appropriate management of diabetes mellitus can bring down the incidence of these conditions. With the increasing prevalence of diabetes mellitus, there is an increase in use of anti-diabetes drugs. This to a far extent can improve the quality of life and decrease the attributed morbidity and mortality. Thus, appropriate use of anti-diabetic drugs in a society, in an efficient manner is an utmost requirement. Further there is also a requirement for educating the people about diabetes and also the consequences of its inadequate management and also for implementing strategies for prevention as well.
Drug utilisation study was defined by WHO in 1977 as "the marketing, distribution, prescription, and use of drugs in a society, with special emphasis on the resulting medical, social, and economic consequences".

Prescription pattern surveys provide an insight into the drug use pattern (extent of drug use and trends in drug use) and rational use of a drug (prescription of a well- documented drug at an optimal dose, together with the correct information at an affordable price). The outcomes of this contribute to our knowledge about drug effectiveness and safety. It also provides information about cost effectiveness of the drugs. The study can be used to evaluate the extent of drug use in a particular region, and even to evaluate the extent to which the drugs are over used or under used. It can also help in the comparison of the trend in drug use with the standard guidelines [3]. The information on patterns of drug utilization can be useful for designing a drug policy and reviewing the health care budget. Hence Drug utilization studies can be used to evaluate the pattern of use of a particular group of drugs according to age, sex, morbidity at various levels of health care system which may contribute to make amendments in the drug policy of a health care system

The anatomical, therapeutic, chemical (ATC) classification system serves as an international system for classifying drugs. Defined daily dose (DDD) is an important unit of measurement in drug utilization study. DDD is the assumed average maintenance dose per day for a drug used for its main indication in adults. The main purpose of using ATC/DDD system is to compare data between countries.

This study is undertaken to analyse the different prescribing pattern in Type-II diabetes patients in Shadan Institute of Medical Sciences, Hyderabad, in respect to number of drug/drugs, dose, duration of treatment, expenditure incurred per prescription per month. Simultaneously the adverse drug reactions encountered with anti-diabetic drugs will be monitored which contributes to pharmaco- vigilance.

Aims and objectives

To analyse the current prescribing pattern in patients of type 2 diabetes mellitus with regard to drug/ drugs prescription, dose, duration of treatment and adverse drug reactions.

Study design

Patients and methods

A prospective cross sectional observational study was carried out in the Medicine outpatient department of Shadan Institute of Medical Sciences, Hyderabad. The study was started after approval from the Institutional Ethics committee and the hospital authorities.

Selection criteria of patients

Inclusion criteria

1. All new patients diagnosed with type 2 Diabetes Mellitus (T2DM) and age 18 years and above, visiting the Medicine outpatient department.
2. Patients already on anti-diabetic medications.
3. HbA1c levels between 6.5%to 9%.
4. Diabetic patients with co- morbid conditions like hypertension, obesity and dyslipidaemia.
5. Diabetic patients presenting with micro vascular complications like retinopathy, neuropathy and nephropathy.

Exclusion criteria

1. Patients less than 18 years of age.
2. Patients suffering from acute metabolic disorders like diabetic ketoacidosis or hyper osmolar coma.
3. Patients who were not willing to participate in the study.

Data collection analysis

A predesigned proforma was prepared according to the study requirements. The data was collected over a period of 3 months from the patients in the medicine outpatient department of Shadan Institute of Medical Sciences. The data included socio demographic details like age, sex, educational status, medical history, and diagnosis, other co- morbidities, number of anti-diabetic drugs prescribed and other drugs in the prescription. Adverse drug reactions were observed in the study. The WHO drug prescribing indicators were analyzed from the data.

The data collected was represented using the ATC/DDD system. The drug usage is calculated using the following formula:

Drug usage (DDD) - Defined daily dose =

Number of items used x Amount of drug per item [mg]/ WHO recommended DDD of a drug

Results

A total of 220 patients were included in the study and their prescriptions were analysed. The prescription prevalence rate was slightly higher (53.64%) in women than in men (46.36%). Maximum numbers of patients were in the age group of 40-59 years (60%), followed by 60 years and above (30.0%). (Table-1)

Prescription pattern of anti-diabetic drugs

On evaluation of individual Anti Diabetic drugs prescribed, it was found that Metformin (76.9%) was the most commonly prescribed mono therapy whereas Metformin and glibenclamide (63.5%) followed by Metformin and glimepiride (21.6%) were the most commonly prescribed dual anti diabetic drug combinations. The fixed dose combinations of anti-diabetic drugs encountered in the study were Metformin Glibenclamide (66.7%) and Metformin+Teneligliptin (33.3%) (Fig1).

According to DDD as a unit of medicine utilization, Biguanide was the most utilised class, Sulphonylureas and Dipeptidyl Peptidase-4 inhibitor (DPP-4I) ranked second and third respectively. Alpha-glucosidase inhibitors and Thiazolididiones were the least utilised class. Metformin ranked first in the drug utilisation segment followed by Glibenclamide and Glimepiride thereby making them the most utilised anti diabetic drugs in the study (Fig2).

Co-morbidities in the study population

Hypertension was the major co- morbid disease (86.1%) followed by infections (19.09%). 25.45% of patients in addition to hypertension as a co- morbid condition also suffered from one other co- morbid disease and 10.9% from two other additional co -morbid conditions.(Table-4).

Other non anti diabetic drugs prescribed

Anti hypertensive's, antibiotics, analgesics (non-steroidal anti-inflammatory drugs like Diclofenac), anti-platelet agents like Aspirin, Clopidogrel, Statins like Atorvastatin, Diuretics like Furosemide, thyroxin, multi vitamins, antacids like Pantoprazole, Ranitidine, calcium preparations, anti-depressants like Tryptomer and others.

WHO Core prescribing indicators

The values of the anti-diabetic drug utilisation indicators analysed from the data collected are

1. Average no. of drugs prescribed per encounter is equal to

5.84/prescription.
2. Average no. of anti-diabetic drugs prescribed per encounter is equal to 1.9 +/- 1.0
3. Percentage of medicines prescribed by generic name-87.35%
4. Percentage of medicines prescribed from essential drug list 91.24%.
5. Percentage of encounters with injection prescribed 18.37%
6. Percentage of drugs actually dispensed 87.94%

Discussion

Diabetes mellitus is a chronic lifelong disease affecting a large spectrum of population in the developing countries including India. In the initial stages, a single oral agent can be used to control the glucose level, but in later stages combination therapy may be needed for better glycaemic control and prevention of micro and macro vascular complications. Hence the present study aimed to evaluate the prescription trends of anti-diabetic drugs in diabetic outpatients.

A total of 220 diabetic patients were evaluated during the study period. In the present study, the maximum number of patients were from the age group of 40-59years [4]. 132(60%) of patients were from this age group and showing a slight predominance of female population 118(53.64%) over male population 102(46.36%) (Table1)

In this study, WHO core prescription indicators were analysed. The average no. of drugs prescribed per encounter was 5.84 drugs per prescription. Previous hospital based studies in India and abroad has reported 2-5 drugs per prescription. A medicine prescribed by generic name was 87.35% and a medicine prescribed from essential drug list was 91.24%. Percentage of encounters with injection prescribed was 18.37% (the injection prescribed here mostly refers to injection insulin mixtard) 87.82% of the drugs prescribed were actually dispensed at the hospital pharmacy. Rational prescribing practises are very important in the management of diabetic patients since they are likely to be on lifelong therapy.

We observed that Metformin (biguanide) was the most common individual drug to be prescribed (54.16%) which is similar to several studies followed by glibenclamide (sulfonylurea) 37.5%.A study by Johnson *et al*. [5] in Canada, similarly observed that 65% of the patients received Metformin, alone or in combination. Insulin preparation (injection mixtard 30/70 combination) accounted for 8.3% of the total anti diabetic drugs. 28% of patients in the study refused to take insulin preparations and preferred oral hypoglycaemic agents instead.

In our study maximum number of patients were on dual therapy (65.5%) followed by 21.8% patients on mono therapy. Metformin was the single most frequently prescribed anti-diabetic drug. This finding was in line with Upadhyay *et al*. [6] where Biguanide accounted for 51.2%of the total anti diabetic medications. However, in some studies conducted in India [7, 8] and abroad [9] the sulfonylurea group of anti-diabetic drugs were observed to be the most commonly prescribed drug class [10]. Advantages of Metformin that make it the preferred anti-diabetic agent include its efficacy in blood sugar reduction without risk of hypoglycaemia, greater general tolerability and relatively lower cost. Among the sulphonylureas, glibenclamide was most commonly prescribed. Apart from glibenclamide, the second generation sulphonylureas glimepiride was also used. Second generation Sulphonylureas like Glimepiride, Gliclazide, Gliclazide are preferred over Glibenclamide as they have shorter duration of action and hence less likelihood of causing hypoglycaemia [11].

The use of combination anti diabetic therapy (65.5%) was more frequent than that of monotherapy (21.8%), a finding also observed in a study by Rajeshwari *et al*. [12] in which polytherapy was used in 71.8% and monotherapy in 28.1% patients. Metformin and sulphonylureas was the most frequently used two drug combinations. Several other studies have also reported the combination of Metformin and sulphonylureas to be used most widely [13]. Insulin has been used in 15.3% of patients in combination with Metformin. The use of DPP-4 inhibitors like Teneliglptin, Alpha glucosidase inhibitors like Voglibose, glitazones like Pyoglitazone has also been used in combination with other oral hypoglycaemic agents. Pioglitazone was the least utilized anti-diabetic medicine. This could be due to the fact that it is not an essential anti-diabetic drug and moreover it is associated with cardiovascular risk factors and risk of bladder carcinoma. 2.3% of patients were on three drug therapy (mostly Metformin with Glibenclamide along with Voglibose). 10.5% of patients were using fixed drug combination (FDC) (Fig3). Similar pattern of use of newer oral hypoglycaemic agents in combination with the first line hypoglycaemic agents to achieve optimal glycemic control was observed in other studies [14].

Lifestyle modification along with anti-diabetic drug treatment has the potential to improve glycaemic control in patients with type-II diabetes mellitus.

During this study it was observed that diabetes was generally associated with hypertension (48%) followed by CVA (17%), CAD (9%), diabetic neuropathy (13%), chronic renal disease (4%), diabetic foot (6%), and susceptible infections (13%). Cerebrovascular accidents were also common in the study population (Table4). In our study hypertension was the commonest co-morbid disease. Hypertensives are more predisposed to the development of diabetes than their normotensive counterparts [15]. In people with diabetes mellitus, hypertension is associated with insulin resistance and abnormalities in both the renin-angiotensin system and sympathetic tone which results in vascular and metabolic consequences that contribute to morbidity. The hypertensive patients were mostly treated with ACE inhibitors and ARBs. It is now well established that ACE inhibitors have Reno-protective affects that may offer benefit over and above the benefits of blood pressure alone. This is in accordance with a study by Dhanraj *et al* [16]. A high incidence of hypertension co-morbid with diabetes was also seen in other studies by Rajeshwari *et al*. and Upadhyay *et al*.

Individuals with diabetes have a greater frequency and severity of infections leading to considerable morbidity and mortality in patients. The infections seen in patients included respiratory tract infections, genitor-urinary tract infections, gastrointestinal infections and fungal infections. Antibiotics and antifungal agents were prescribed in this study. The core components of diabetic care involve the prevention of hyperglycaemia, treatment of co- morbid diseases and prevention and management of macro vascular and micro vascular complications.

Conclusion

This study showed that dual therapy with Biguanide and

Sulphonylureas was the most common anti-diabetic drug pattern prescribed. Metformin was the most common anti-diabetic drug prescribed both in monotherapy as well as dual therapy. Using DDD as a unit of anti-diabetes medicine utilization, Biguanide (Metformin) had the highest share of utilization followed by Sulphonylureas (glibenclamide). In this study the utilization of anti-diabetic medicines was slightly higher in females than in males. Diabetes mellitus was predominantly seen in the age group of (40 to 59 years).

Majority of the drugs were prescribed as generic and most of them were from essential drug list. Majority of the drugs prescribed were dispensed. There was higher utilization of oral anti-diabetic agents than insulin. A significant number of patients in this study reported morbidities. Hypertension was the most common co-morbid condition associated with diabetes mellitus. Concomitant hypertension increases the risk of development of diabetes related complications like IHD, CVA, nephropathy, retinopathy and vice-versa. Hence wide spread screening and early detection of both these disorders is imperative to impede involvement and progression of end organ damage. The increasing burden of diabetes mellitus can be reduced by affective educative measures in the population about diabetes mellitus. This will not only reduce the morbidity and mortality associated with diabetes and other co-morbid conditions but also reduce the financial burden incurred by it on the society.

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Declarations

Ethical approval: The study was approved by the institutional ethics committee

Table 1: Gender and age distribution of patients receiving anti diabetic drugs.

Variables	n%
Gender	N=220
Female	118(53.64%)
Male	102(46.36%)
Age Group	N=70
<40	22(10%)
40-59	132(60%)
>=60	66(30%)

Table 2: List of ant diabetic drugs prescribed

Anti-diabetic Drugs	Drug	ATC Code	No. of units prescribed	Percentage n=220
Biguanide	Metformin	A10BA02	198	90
Sulphonylureas	Glibenclamide	A10BB01	104	47.3
	Glimepiride	A10BB12	69	31.4
Alpha Gluco- sidase inhibitor	Voglibose	A10BF03	1	0.45
DPP-4 inhibitor	Teneliglptin	A10BH1	7	3.18
Thiazolidinediones	Pyoglitazone	A10B43	2	0.9
Human insulin	Human - insulin	A10AC01	28	12.7

Drugs from National list of Essential Medicines
ATC- Anatomical Therapeutic Chemical
DPP-4 inhibitor- Dipeptidyl peptidase inhibitor

Table 3: Utilisation pattern of different Anti Diabetic drugs Prescribed

Anti-diabetic drugs	n (%)
Monotherapy	n=48
Metformin	26(54.2%)
Glibenclamide	10(20.8%)
Glimepiride	8(16.7%)
Insulin	4(8.3%)
Dual Therapy	**n=144**
Metformin, Glibenclamide	61(42.4%)
Metformin, Glimepiride	52(36.1%)
Metformin, Teneliglptin	7(4.9%)
Metformin, Pyoglitazone	2(4.5%)
Metformin, Insulin	22(15.3%)
Triple Therapy	**n=5**
Metformin, Glibenclamide, Voglibose	1(20%)
Metformin, Glibenclamide, Teneligliptin	2(40%)
Metformin, Glibenclamide, Insulin	2(40%)
Fixed Dose Combination	**n=23**
Metformin+Glibenclamide	12(52.2%)
Metformin+Glimipiride	9(39.1%)
Metformin+Teneligliptin	2(8.7%)

Table 4: Incidence of co-morbid disease

Co morbid disease	% of patients affected
Hypertension	86.1
Obesity	9.09
Infections	19.09
Stroke	8.7
Hypothyroidism	1.8
Diabetic foot	12.7
Coronary artery disease	20.9
Peptic ulcer	3.6
None	11.8

Table 5: Incidence of adverse drug reactions among patients receiving ant diabetic drugs.

ADR	No. of patients	%
Hypoglycaemia	8	4.1
Nausea	3	1.5
Gastric irritation	3	1.5
Diarrhoea	2	1.0
Abdominal discomfort	1	0.5

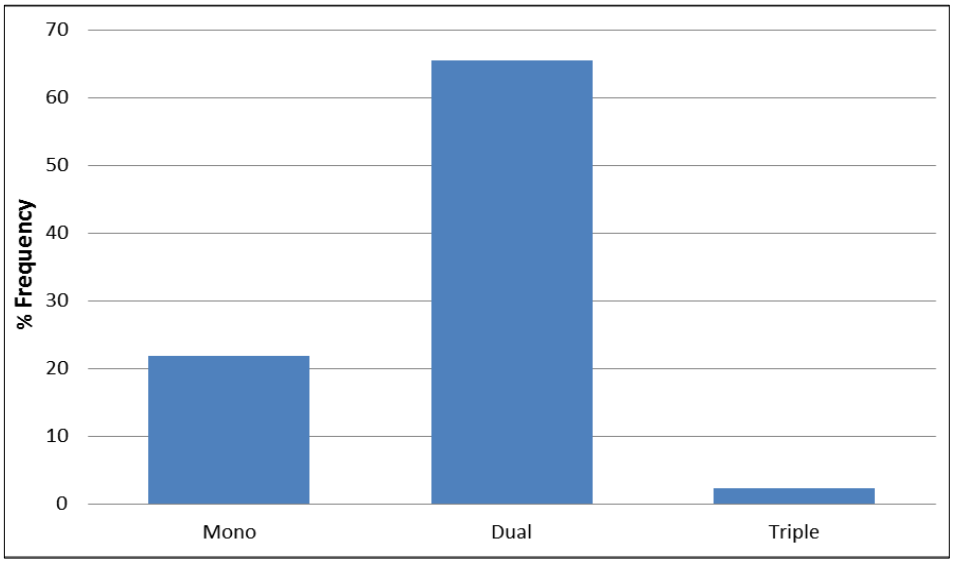
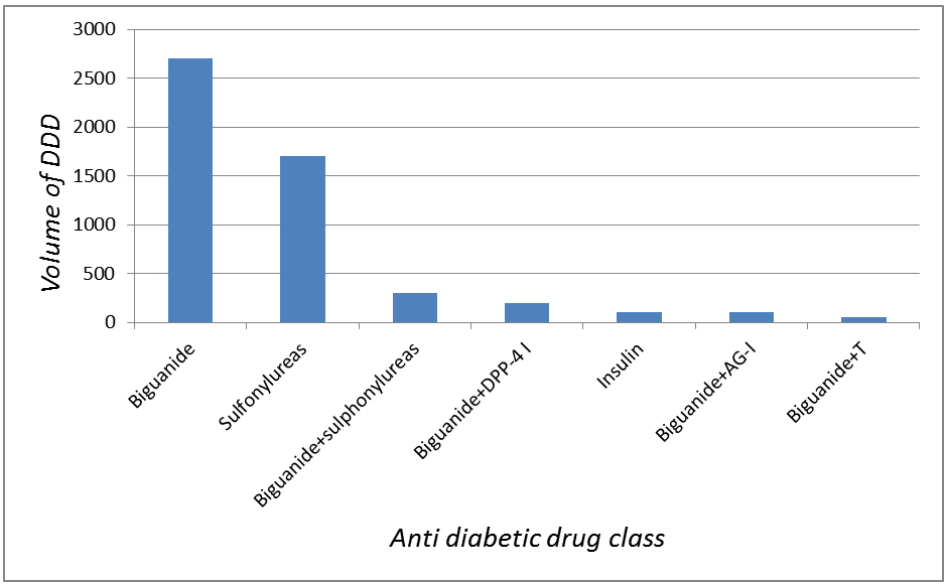
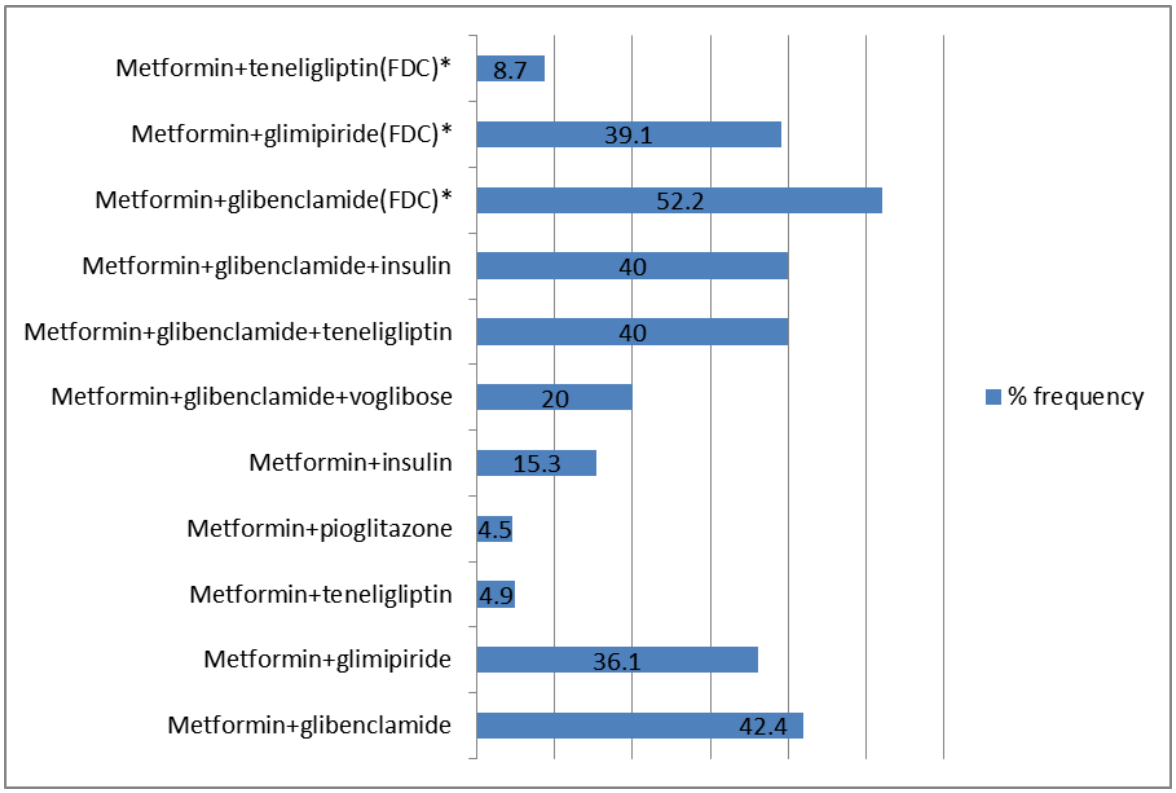


Fig 1: Overall distribution of number of anti-diabetic drugs prescribed per encounter



DPP-4 I: Dipeptidyl Peptidase 4 Inhibitor
AG I: Alpha Glucosidase Inhibitor
T: Thiazolidinediones
FDC: Fixed dose combination

Fig 2: Volume of DDD (Daily defined Dose)



***FDC: Fixed Dose Combination**

Fig 3: Relative frequency of anti-diabetic drug combinations used (n=172)

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