ABSTRACT

Aim: To describe trends in out-of-hospital utilization and to prescribe of antidiabetic drugs in Albania to use the Anatomic Therapeutic Chemical Classification/ Defined Daily Dose -(ATC/DDD methodology).

Methods: The study was retrospective, and we analyzed the prescription and consumption of these drugs classes in the primary health care in Albania during 2004-2014. All data were collected from Health Insurance Institute (HII) and analyzed reflecting the ambulatory and outpatient use for the period 2004-2014. The data about the consumption of drugs were expressed as some Defined Daily Dose (DDDs) /1000 inhabitants/day. For all the period under study 2004-2014, there were collected and analyzed the data of import and domestic production of drugs, which altogether represent the real consumption of medicines in the country. These data were subsequently included in a comparative analysis of the utilization data according to the HII.

Results: The consumption of all insulins were 1.80-5.64 DDD/1000 inhabitants/day (respectively 2004-2014). The consumption of insulin fast-acting were 0.47-2.59 DDD/1000 inhabitants/day (respectively 2004-2014). The consumption of insulin intermediate-acting were 0.38-0.70 DDD/1000 inhabitants/day (respectively 2004-2014). The consumption of insulin long-acting was 0.00-1.41 DDD/1000 inhabitants/day. The most prescribed oral antidiabetic agent was metformin 3.04-7.45 DDD/1000 inhabitants/day (respectively 2004-2014). The consumption of glibenclamide was 3.55-5.76 DDD/1000 inhabitants/day (respectively 2004-2007).

Conclusions: There is an increase in Antidiabetic drugs use from HII covering while there is a significant increase in their use of out-of-pocket expenditure during 2004-2014. There can be noted a visible discrepancy between the consumption of antidiabetic drugs and the diabetes mellitus morbidity, which indicates that only a part of patients with diabetes mellitus do benefit from the reimbursement scheme.

KEYWORDS Drug utilization DDD, antidiabetic drugs
agent selection and therapy changes as well as patient adherence to prescribed drug regimens. Drug utilization studies using administrative pharmacy claims data can provide useful insights into the prescribing patterns and patient medication-taking behavior in typical usual-care settings [4,5].

Thus, pharmacotherapy has the potential for significant clinical, economic, and humanistic impact. For these reasons takes a great importance the evaluation of drug utilization parameters associated with pharmacological management of type 1 and two diabetes among members of a large drug-insured population.

**Objective, Materials and Methods**

**Objective:**
To assess the out-of-hospital antidiabetic drugs use in Albania during the period 2004-2014.

**Materials and Methods:**
The data were obtained from the Health Insurance Institute (HII)[6]. All data were collected for the period 2004-2014 and analyzed. The analysis included the total number of prescriptions made, and quantities of drugs used. The data about the population were obtained from the Institute of Statistics (INSTAT)[7]. The data about the consumption of medicines were expressed as some Defined Daily Dose (DDDs)/1000 inhabitants/day. All drugs were classified of Anatomic Therapeutic Chemical Classification (ATC).

**Data on the levels of morbidity**
From the database of HII, there were extracted the general number of patients reported for each diagnosis, for each year. Following, there were calculated the respective levels of annual morbidity (based on the individual code-diagnoses) for 1000 inhabitants.
The total number of diabetic patients reported from the HII database is shown in the table below:

**Data on real consumption (import and domestic production)**
For all the period under study 2004-2014, there were collected and analyzed data on the import and domestic production of the drugs [8] which represent the real consumption of medicines in the country. It was noted that the increase in consumption from one year to another was small, e.g. the consumption from 2010 to 2014 (i.e. four years) was increased by only 2.98%. Consequently, to obtain an updated study, there were chosen the data of import and domestic consumption only for the last three years, 2012, 2013, 2014, and those were involved in a comparative analysis of the corresponding consumption data according to HII. To minimize the effect of variations in consumption and stock inventory balances from one year to another, it was calculated and put into analysis the average annual value of the three chosen years (on one hand that of the import and domestic consumption, and on the contrary that of HII).

**Presentation of the results and statistical elaboration**
The database of HII was modified in Microsoft Office Excel 2007, whereas the statistical discussion of the obtained results was conducted with the statistical package StatsDirect (version 2.7.2.). A descriptive statistics was used to report all data on drugs consumption and the results obtained were displayed in tabular form as well as through the histogram method. Average annual values of consumption at the country level and for each district were used as a basis to generate the overviews and the graphics that illustrate the trends of consumption for each class of drugs during the 8-years period 2004-2014. The linear regression model was used to evaluate the trends of consumption of drugs at the time. A value of $p \leq 0.05$ was considered as significant. To assess if there exists a correlation statistically significant between the level of consumption of drugs and the level of morbidity, it was applied the Spearman correlation (with a significance level of $\leq 0.05$).

### Table 1 Total number of Diabetic patients reported from HII [6] in each year of the study period.

| Years | Number of diabetic patients |
|-------|-----------------------------|
| 2004  | 32,641                      |
| 2005  | 43,504                      |
| 2006  | 41,263                      |
| 2007  | 38,473                      |
| 2008  | 42,868                      |
| 2009  | 46,606                      |
| 2010  | 55,072                      |
| 2011  | 57,727                      |
| 2012  | 62,289                      |
| 2013  | 67,858                      |
| 2014  | 71,983                      |

**Results**
The data were expressed as some defined daily doses per 1000 inhabitants/day (DDDs/1000 inhabitants/day) and as the number of prescriptions per 1000 people/month for every single drug and groups, 2004-2014. The consumption of all insulins was 1.80-5.64 DDD/1000 inhabitants/day (respectively 2004-2014). The insulins included in the reimbursement list for this period were insulin fast-acting, insulin intermediate-acting, insulin intermediate-acting combined with insulin fast-acting and insulin long-acting. The last one was involved in the scheme since 2008. The consumption of insulin fast-acting were 0.47-2.59 DDD/1000 inhabitants/day (respectively 2004-2014). The consumption of insulin intermediate-acting were 0.38-0.70 DDD/1000 inhabitants/day (respectively 2004-2014). The consumption of insulin intermediate-acting combined with insulin fast-acting was 0.95-1.18 DDD/1000 inhabitants/day. The consumption of insulin long-acting was 0.00-1.41 DDD/1000 inhabitants/day. The oral hypoglycemic agents included in the reimbursement list were glibenclamide, metformin, and repaglinide. The most prescribed agent was metformin 3.04-7.45 DDD/1000 inhabitants/day (respectively 2004-2014). The consumption of glibenclamide was 3.55-5.76 DDD/1000 inhabitants/day (respectively 2004-2007). The agent with the low values of prescription was repaglinide 0.09-0.04 DDD/1000 inhabitants/day (respec-
1). Based on this data, it results that a non-small part of persons with diabetes remain out of the treatment under the scheme. In our country, the family doctor has the right to prescribe AE insulins for diabetes type 2 patients, combined with oral antidiabetic drugs: consumption based on import (real consumption) [*] versus consumption based on HII. [*] The “Import” item includes the consumption based on import data as well as the consumption based on domestic production: this represents the real consumption.

Aiming to understand better the real situation, we have included in the analysis the import data (representing the actual consumption) of antidiabetic drugs in the three latter years 2012, 2013, 2014.

As shown in Figure 3, there is a visible difference in the use of two antidiabetic classes. In total, the use of insulins seems well-equilibrated, a fact evidencing that insulins are taken almost entirely under the reimbursement scheme. Whereas the situation in the use of oral antidiabetic is much different—a significant part of them results to be taken out of the plan, without reimbursement.

It can be noted that the real consumption based on import data approximates the morbidity data, confirming that a non-small part of the diabetes patients have no access to the reimbursement scheme.

As regards the consumption of each class of antidiabetic, by comparing the consumption based on import data with the use based on HII, there come out certain findings, which have been presented in Figure 4. The figures indicate that for rapid-acting insulins, the most used group of insulins, the consumption based on the HII is higher than the real consumption based on import data—a fact which cannot be true considering that import data include all drugs that are distributed in the primary health care service in our country. This finding can be explained with the fictive prescriptions by doctors for the most used group of insulins. Whereas, it can be noted that the real consumption of other insulins is higher compared to the figures of HII. This finding may reflect the restrictions imposed by the HII itself. The family doctor is allowed to prescribe up to 5 disposable pens/month for all types of insulin. This limitation is in contradiction with the international pharmaceutical guidelines which do not impose any restriction to the daily quantities of unities (IU) for insulin but recommend an individual dosage of insulins in direct connection with the values of glycemia for each patient.

Therapeutic guides increasingly suggest AE insulins (with prolonged action) to reach a better control over diabetes type 2. In our country, the family doctor has the right to prescribe AE insulins for diabetes type 2 patients, combined with oral antidiabetic drugs: consumption based on import (real consumption) versus consumption based on HII. [*] The “Import” item includes the consumption based on import data as well as the consumption based on domestic production: this represents the real consumption.

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Figure 4: Annual average value of consumption of Insulins in total: consumption based on import (real consumption) versus consumption based on HII (DDD/1000 inhabitants/day).

Figure 5: Annual average value of consumption of Hypoglycemics: consumption based on import (real consumption) versus consumption based on HII (DDD/1000 inhabitants/day).

Figure 6: Consumption of Insulins drugs in different regions and at the national level (DDD/1000 inhabitants/day).

Figure 7: Consumption of Oral Hypoglycemic drugs in different regions and at the national level (DDD/1000 inhabitants/day).

abtic, only for those patients that have gone through an acute myocardial infarction, cerebral insult and diabetic gangrene of the foot.

Figure 5 shows that a considerable part of the consumption of metformin falls out of the reimbursement, evidencing a low level of access to patients to the scheme and service of payment again. According to the protocol of HII, the recommended maintenance dose of metformin is 3x500 mg/day, or 2x850 mg/day; forms doses 850 mg and 1000 mg can be given only after consultation with the Endocrinology commission. Meanwhile, international therapeutic guidelines recommend 0.5 up to 1 gram, 1 to 3 times a day (maximal dose 3 gram/day) [12]. The quantitative restriction imposed by the HII is, therefore, evident. The same situation can be encountered even for glibenclamide, which, based on the protocol of the HII should be provided 2.5 mg 2-3 times a day as a maintenance dose, whereas based on the international therapeutic guidelines is recommended at 2.5 mg 3 times a day by increasing the daily dose up to 20 mg. It is to emphasize that this group alternatives offered by the scheme are only metformin and glibenclamide, whereas in the domestic pharmaceutical market there exist many other alternatives necessary for the medication of diabetes mellitus such as gliclazide, glimepiride, pioglitazone, rosiglitazone, repaglinide, acarbose, as well as the most recent options for the incretin mimetics groups such as vildagliptin and sitagliptin. 

From the Figure 6, it can be noted that the consumption of insulins in different regions represents major differences. The highest values of this consumption for all areas occurred in 2010. In the year 2004, the areas with the minimal values of consumption are Kukës (0,80 DDD/1000 inhabitants/day), Vlora (1,08 DDD/1000 inhabitants/day) and Korça (1,37 DDD/1000 inhabitants/day), while the regions with the highest values of consumption of insulins are Tirana (2,58 DDD/1000 inhabitants/day), Shkodra (2,00 DDD/1000 inhabitants/day). In 2010, the differences in the consumption of insulins vary from 1,64 DDD/1000 inhabitants/day (Kukës) and 1,79 DDD/1000 inhabitants/day (Vlora), up to the values of 4,24 DDD/1000 inhabitants/day (Durrës) and 4,63 DDD/1000 inhabitants/day (Tiranë).

Differences in the consumption of oral hypoglycemic drugs in 2004 are even more evident: Kukës (1,25 DDD/1000 inhabitants/day), Vlora (4,18 DDD/1000 inhabitants/day), Fieri (8,76 DDD/1000 inhabitants/day), Tirana (10,58 DDD/1000 inhabitants/day) (Figure 7).

These significant differences in the prescription and consumption between the different regions, especially compared to Tirana, which is considered as a reference, may reflect the differences in the professional medical level, the lack of uniformity and deficiencies is the update of professional knowledge with the recent information about useful guides and recommendations. Another significant and relevant factor may be the difference in the economic standard as well as the difference in the medical service offer in the different regions (number of doctors and primary health care service centers). Otherwise, there are no differences expected in the diabetic morbidity between the regions, such as to justify the difference in prescription and consumption.

The use of insulins at the national level (Graphic 3.2.2) is subject to a visible increase of 94% (1,80-3,49 DDD/1000 inhabitants/day, 2004-2010). Insulins with the highest consumption are A10AD insulins (combined formulations): 0,95-1,00 DDD/1000inhabitants/day, whereas insulins with the lowest value of use are A10AE insulins (with prolonged action, mainly glargine) which undergo an increase particularly in years 2008-2010 (0,01-0,34 DDD/1000inhabitants/day).
As regards the insulin glargine, a recent publication of EMA [13] which cites the results of certain recently published studies [14], suggests a possible connection between the use of insulin glargine and the increase in cancer incidence. From the analysis of these results conducted by the Committee for Medicinal Products for Human Use, it was concluded that no final conclusions can be issued at the moment. For this reason, it has been requested by the various pharmaceutical producer to conduct further studies to ensure new data [15].

The increase in consumption, especially of insulins, may reflect the better level of adherence of the doctors to the excellent guides that recommend intensification of the control to the glycemia levels [16, 17]. The increase in consumption of insulins may also be explained by the fact that the provision of insulin is necessary for a better control of diabetes type 2, in the cases where the diet and the oral hypoglycemic drugs do not result sufficiently. The consumption of oral hypoglycemic drugs has an increase (Figure 2), lower compared to the use of insulins, of 45,06% in 2004-2010. Metformin is ranked first in consumption (3,04-5,23 DDD/1000 inhabitants/day), followed by parallel but lower consumption values of glibenclamide (3,55-4,51 DDD/1000 inhabitants/day). It may be an indicator of their common prescription. The highest consumption for metformin is in line with good guides, according to which, metformin is the first choice for diabetes patients with physical overweight [16].

Glibenclamide is the most consumed out of the sulfonylureas, but with a progressive decrease in prescription (DDD%) (41,16%-34,11%) compared to the increase in prescription of metformin (35,16%-39,52%). Based on the therapeutic recommendations, the use of the drug should be avoided in patients of more than 65 years old as well as in cases of renal dysfunction [17, 18].

Regardless the decrease in the prescription trend, the values of consumption of glibenclamide remain high, ranking the second after metformin. This high consumption may have several reasons:

- The reimbursement list includes only two oral hypoglycemics since 2007. The list has not been improved, by limiting and imposing the alternatives of drugs under choice.
- Glibenclamide is one of the oldest hypoglycemics, with a duration of action of 24 hours; it achieves the strongest decrease in the level of glycemia among the sulfonylureas, and it has not a high price [19] – all of these encourage the habit of routinely prescribing it by the primary health care doctors.

Conclusions

There is an increase in Antidiabetic drugs use from HII covering while there is a significant increase in their use of out-of-pocket expenditure during 2004-2014. The consumption of insulins seems well-equilibrated, a fact evidencing that insulins are taken almost entirely under the reimbursement scheme. Whereas the situation in the use of oral antidiabetics is much different – a significant part of them results to be taken out of the scheme, without reimbursement.

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Competing Interests

The authors declare no conflict of interest.

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