Persistence of initial oral antidiabetic treatment in patients with type 2 diabetes mellitus

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Summary

Background: Adequate persistence of oral antidiabetic treatment is highly important to achieve proper glycemic control in patients with type 2 diabetes. The aim of this study was to evaluate the persistence of initial treatment with metformin and/or sulphonylureas in patients with type 2 diabetes.

Material/Methods: The study was performed among diabetic patients (n=256,384) who were newly prescribed oral antidiabetic drugs (metformin and/or sulphonylureas) between 2007 and 2009. For making comparison, patients with newly prescribed statin or clopidogrel therapy (with and without percutaneous coronary intervention) were investigated. The database of the Hungarian National Health Insurance Fund Administration was used.

Results: The 1-year persistence of initial treatment with metformin, sulphonylureas or metformin/sulphonylurea combination was 47.7%, 45.4% and 55.8%, respectively, which was significantly better than the persistence of statin therapy (26.3%) but worse than that of clopidogrel therapy in patients undergoing coronary intervention (73.2%). Within the sulphonylurea group there was a tendency of better persistence of treatment with the “modified-release” tablets at 12 months compared to the conventional sulphonylureas (47.8 vs. 42.2%). The persistence of therapy using metformin 1000 mg – 60 tablets was significantly better (60.4%) at 12 months than that of other forms of metformin therapy with lower doses and smaller boxes (with fewer tablets) analyzed together (47.7%).

Conclusions: The persistence of initial treatment with metformin and/or sulphonylureas is far from optimal. Better diabetic care and continuous patient education should be encouraged to achieve higher persistence of oral antidiabetic treatment in patients with type 2 diabetes.

key words: type 2 diabetes mellitus • oral antidiabetic treatment • persistence of treatment • metformin • sulphonylureas • statin • clopidogrel

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**BACKGROUND**

Successful treatment of chronic diseases depends on a number of factors. It is understood that in order to achieve the treatment goals not only physicians and medical personnel but also the patients have to make adequate efforts.

The term “compliance”, according to the traditional approach, focuses on the activities of the physician. This concept is somewhat out-of-date now, as the work overload of doctors is a limiting factor and patients are able to obtain information about their illness from a number of other sources. It is also clear that besides external motivation (medical advice), developing internal motivation of the patient is of fundamental importance. The term “adherence” reflects the more modern, patient-oriented concept of patient cooperation that is often used in relation to a particular therapy. Adherence reflects the proportion of medications effectively taken. “Persistence”, the duration of continuous therapy from initiation to discontinuation of a particular treatment [1], is another easily measurable indicator.

Diabetes mellitus is a lifelong disease that requires appropriate lifestyle modification and drug treatment in order to achieve efficient metabolic control and to prevent late complications. Most diabetic patients have type 2 disease. This type of diabetes usually manifests in adults and in the elderly, but has recently been diagnosed in an increasing number of younger patients, too. If signs of acute metabolic deterioration cannot be detected, the treatment of patients – besides complying with lifestyle and dietary recommendations – means the use of oral antidiabetic agents. Among the oral antidiabetic drugs, according to the international and national guidelines, metformin is recommended as first-line treatment. If metformin intolerance is present or the drug is contraindicated, a sulphonylurea may be prescribed [2,3]. Because of the progressive nature of type 2 diabetes mellitus, diabetic patients might later receive combination therapy [4–6]. According to the results of a national survey conducted in Hungary (MULTI GAP), the most commonly used combination is metformin + sulphonylurea, with only a minority of patients receiving other, newer forms of combination therapy [7].

Adequate persistence of oral antidiabetic treatment of patients with type 2 diabetes mellitus is essential to achieve efficient glycemic control. Data on the persistence of oral antidiabetic treatment are not available in Hungary. In our study, using the database of the National Health Insurance Fund Administration, the persistence of the most common initial oral antidiabetic therapy – metformin and/or sulphonylureas – between 2007 and 2009 was analyzed. Our data were compared to the persistence of other widely used therapies for cardiovascular prevention (statins and clopidogrel).

**MATERIAL AND METHODS**

Patients (n=256,384) starting oral antidiabetic therapy (metformin and/or sulphonylureas) between January 1, 2007 and March 31, 2009 according to the database of the National Health Insurance Fund Administration (study license number: 44-p-82/2010) were enrolled in this study. The database was analyzed anonymously. No dispensing of oral antidiabetic drugs or insulin to the patients occurred since January 1, 2006, therefore they can be considered as receiving starting antidiabetic therapy for the first time. We excluded patients whose initial oral antidiabetic medication was other than metformin and/or sulphonylureas. More women (55%) than men (45%) were involved but this corresponds to the total population of Hungary (56% women, 44% men, total population 10,066,158 by Jan 1, 2007). The highest number of patients was in the 50–59 years age group, followed 60–69 years and >70 years (Table 1.) In the patients receiving sulphonylureas, the persistence of conventional and “modified-release” preparations were also evaluated. At that time, gliclazide MR was the only available “modified-release” sulphonylurea in Hungary. In the metformin group, the persistence of a given preparation with higher dose and larger box (Metformin® 1000 mg – 60 tablets) was determined separately. As more than 20 sulphonylurea or metformin generic drugs with different doses were available during the study period in Hungary, no other particular statistical analysis than “modified-release” sulphonylurea preparation (ie, gliclazide MR) versus all other conventional sulphonylureas or metformin with higher dose and larger box (ie, Metformin® 1000 mg – 60 tablets) versus all other metformin preparations could be carried out. For each patient, dispensing of the prescribed drugs was followed until March 31, 2010.

The persistence curves were obtained by using time-to-event analysis and the numerical value of persistence in each case was calculated by Kaplan-Meier method [8]. Patients were considered persistent if 1) the medicine was taken (dispensed) throughout the test period (continuous monotherapy), 2) a different oral antidiabetic drug or insulin was started while initial oral therapy was maintained (add-on combination therapy), or 3) if a replacement therapy had been initiated by any antidiabetic drug inclusive of insulin (discontinuation with initial oral therapy and switching to any other antidiabetic drug). Overall, this means that patients were considered to be persistent if they started their oral antidiabetic therapy with metformin and/or sulphonylureas and later continued to use (drugs were dispensed) any hypoglycemic agents (insulin included). Consequently, patients were classified as non-persistent if they started the antidiabetic therapy and then later – including the grace period – did not receive any antidiabetic medication. The grace period is the permissible time gap for the patient to resume taking the medication following a discontinuation and still be considered as persistent.

It was determined in advance for how many days the defined dosage forms of the medication would last for a patient. Based on these results it was calculated for how long the dispensed quantities would be enough for the patients. A grace period of 180 days was applied according to the ISPOR (International Society for Pharmacoeconomics and Outcomes Research) criteria often used in international literature [9]. The therapy was considered continuous if the patient still had medication (either an oral antidiabetic drug or insulin) 180 days before the end of the study period. A patient was considered non-persistent if the last dispensed amount of medication had been used up, based on the earlier dosing, and within a further 180 days no repeated dispensing occurred.

We excluded those patients who had a “negative” drug dispensing event (technical operation, correction or
included in the database in a given month, the “no data” notation appeared, as with fewer than 10 patients the protection of privacy would not have been fulfilled. Because of this the Kaplan-Meier curves could not cover the entire duration of the study. The numerical value (with 95% confidence interval [95% CI]) of persistence of the actual drug therapy (the proportion of persistent patients in the given cohort) was determined 12 months after the initiation of the medication. The statistical significance of persistence values at 12 months were compared by using the Peto-Wilcoxon test. The p<0.05 value was considered statistically significant.

### Results

During the study period 115,426 patients started metformin monotherapy; 125,362 patients initiated sulphonylurea monotherapy, whereas metformin + sulphonylurea combination therapy was begun in 15,596 patients. The persistence of drug therapy fell after 2 months to 57.4% (95% CI 57.2–57.7) in the group with sulphonylurea monotherapy, to 64.8% (95% CI 64.6–65.1) in the group with metformin monotherapy and to 68.0% (95% CI 67.3–68.7) in the group with sulphonylurea + metformin combination therapy. At the 12th month of follow-up the persistence values were as follows: sulphonylurea treatment 45.4% (95% CI 45.1–45.7), metformin therapy 47.7% (95% CI 47.4–48.0) and metformin + sulphonylurea combination therapy 55.8% (95% CI 55.1–56.6) (p<0.0001 in all comparisons).

Within the sulphonylurea group there was a significantly better persistence of treatment with the “modified-release” tablets at 12 months compared to the other conventional sulphonylureas (47.8% [95% CI 47.4–48.2] vs. 42.2% [95% CI 41.8–42.6], p<0.001).

The persistence of therapy using metformin 1000 mg – 60 tablets (Meforal®) was significantly (p<0.001) better (60.4%; 95% CI 60.1–60.7) compared to the other conventional forms at 12 months (55.1–55.7), metformin therapy 47.7% (95% CI 47.4–48.0) and metformin + sulphonylurea combination therapy 55.8% (95% CI 55.1–56.6) (p<0.0001 in all comparisons).

### Table 1. Distribution of diabetic patients (n=256,384) according to sex and age-groups.

|                | Men n (%) | Women n (%) | Total n (%) |
|----------------|-----------|-------------|-------------|
| Metformin      | 51.898 (45)| 63.528 (55) | 115.426 (100)|
| Metformin + sulphonylurea | 7.824 (50) | 7.772 (50)  | 15.596 (100)|
| Sulphonylurea  | 55.438 (44)| 69.924 (56) | 125.362 (100)|
| Total          | 115.160 (45)| 141.224 (55)| 256.384 (100)|

| Age Group | Men n (%) | Women n (%) | Total n (%) |
|-----------|-----------|-------------|-------------|
| <20 ys    | 1.196 (1) | 3.740 (3)   | 4.936 (7)   |
| 20–29 ys  | 7.340 (7) | 22.145 (27)| 29.485 (44)|
| 30–39 ys  | 5.372 (6) | 16.826 (15)| 22.198 (31)|
| 40–49 ys  | 5.192 (3) | 5.192 (3)  | 10.384 (16)|
| 50–59 ys  | 1.850 (1) | 1.850 (1)  | 3.700 (6)  |
| 60–69 ys  | 2.518 (1) | 2.518 (1)  | 5.036 (8)  |
| ≥70 ys    | 2.518 (1) | 2.518 (1)  | 5.036 (8)  |
| Total     | 2.518 (1) | 5.884 (2)  | 8.398 (13)|
considerable difference between men and women in the persistence of therapy using Meforal® 1000 mg – 60 tablets (men: 62.2%; 95% CI 61.5–62.8; women: 58.8%; 95% CI 58.2–59.5; p<0.001). The persistence of therapy using Meforal® 1000 mg – 60 tablets was the best in patients aged between 40 and 70 years (60–66%), the persistence was reduced both in patients over 70 years of age (58%) and less than 40 years of age (20–50%, mean values in respective age-groups by decades).

During the study period 20,697 patients received clopidogrel therapy after PCI, while 50,422 patients receiving clopidogrel did not undergo PCI. Statin therapy was initiated in 607,422 patients, but 158,849 (26.1%) patients were excluded from the analysis because of suspected insufficient or dual therapy. Since 41,250 (6.8%) patients were excluded due to other reasons (fully subsidized statin therapy, ezetimibe monotherapy as initial treatment), data of 407,323 patients were included in the analysis. The persistence of antidiabetic therapy was better than that of statin therapy (26.3%) but worse than that of clopidogrel therapy in patients undergoing coronary intervention (75.2%).

The 1-year persistence of oral antidiabetic therapy (metformin and/or sulphonylureas) (45.4–55.8%) proved to be surprisingly low. In addition, the rapid drop of persistence values within 2 months after initiation warrants further notice. Due to the inherent limitation of a database study, we can only speculate about the premature discontinuation of medication. Clearly, some medical conditions should be taken into account. Accordingly, uncertainties surrounding the indication for metformin prescription (polycystic ovary syndrome or type 2 diabetes) and other likely explanations for medication withdrawal (exercise, weight loss, renal impairment, adverse effects) might be present in some cases [10–12]. More likely, disregarding the importance of type 2 diabetes mellitus and the need for continuous medical treatment (lack of sufficient information, possibility of negligence) is the explanation in the majority of patients. Clearly, more effort should be made to improve persistence immediately after initiation of antidiabetic drugs in patients with type 2 diabetes. The particular impact of early and continuous intensive antihyperglycemic treatment on micro- and macrovascular complications even in the long run was documented in newly diagnosed type 2 diabetic patients by the UKPDS [13,14].

One specific dosage form of metformin (Meforal® 1000 mg – 60 tablets) was separately tested and the 1-year persistence was found to be significantly better than that of the other metformin preparations with lower doses and smaller boxes. Changes of subsidy costs cannot be ruled out as an explanation since this dosage form was supported through prescription. Due to the inherent limitation of a database study, we cannot only speculate about the premature discontinuation of medication. Clearly, some medical conditions should be taken into account. Accordingly, uncertainties surrounding the indication for metformin prescription (polycystic ovary syndrome or type 2 diabetes) and other likely explanations for medication withdrawal (exercise, weight loss, renal impairment, adverse effects) might be present in some cases [10–12]. More likely, disregarding the importance of type 2 diabetes mellitus and the need for continuous medical treatment (lack of sufficient information, possibility of negligence) is the explanation in the majority of patients. Clearly, more effort should be made to improve persistence immediately after initiation of antidiabetic drugs in patients with type 2 diabetes. The particular impact of early and continuous intensive antihyperglycemic treatment on micro- and macrovascular complications even in the long run was documented in newly diagnosed type 2 diabetic patients by the UKPDS [13,14].

Our data show that the 1-year persistence of initial treatment with metformin, sulphonylureas or with metformin/sulphonylurea combination was 47.7%, 45.4% and 55.8%, respectively, which was significantly better than the persistence of statin therapy (26.3%) but worse than that of clopidogrel therapy in patients undergoing coronary intervention (75.2%).

The 1-year persistence of oral antidiabetic therapy (metformin and/or sulphonylureas) (45.4–55.8%) proved to be
medical practitioners in Hungary have more experience with sulphonylureas than with metformin. Nevertheless, adverse effects such as hypoglycaemia and weight gain caused by sulphonylureas may play a role in poor persistence [15]. Accordingly, we found 1-year persistence was worst in the case of sulphonylurea monotherapy (45.4%). Nevertheless, the better persistence of treatment with the “modified-release” tablets compared to the conventional sulphonylureas (47.8% vs. 42.2%) is in agreement with the improved safety profile of “modified release” gliclazide [16].

The 1-year persistence data of the metformin + sulphonylurea combination therapy (55.8%) might not be considered as a good result, because sulphonylurea therapy provides a relatively short glycemic durability [17], and patients on metformin + sulphonylurea combination therapy usually need an earlier modification of the treatment.

Overall, our data on the persistence of oral antidiabetic therapy are in agreement with those reported internationally, although it is difficult to compare the data directly due to the different populations and methodology. According to a meta-analysis of 25 studies published by Rubin in 2005 [18], the adherence to oral antidiabetic therapy ranges from 65% to 85%, and the rate of adherence was found to be only 36–54% in the case of some drug preparations or forms of treatment. More recently, the 12-month persistence of initiating therapy with metformin or sulphonylurea was found to be between 56% and 65% in a population-based cohort study from Quebec [19].

The low persistence of statin therapy in our study should not be considered unusual. From Poland, a very low rate (12%) of proper level of both compliance and persistence of patients treated with statins was recently reported [20]. The persistence of clopidogrel therapy was better in patients with than without PCI. Similar to our results, a negative impact on clopidogrel adherence in patients treated with PCI but without stenting (versus PCI with stenting) was recently reported [21].

Our study has some limitations. Due to the study being a database analysis, information on reason of non-persistence to medications could not be provided. In addition, clinical database analysis, information on reason of non-persistence or sulphonylurea is far from optimal. Better diabetic care and continuous patient education should be encouraged to achieve higher persistence of oral antidiabetic treatment in patients with type 2 diabetes.

CONCLUSIONS

The persistence of initial treatment with metformin and/or sulphonylureas is far from optimal. Better diabetic care and continuous patient education should be encouraged to achieve higher persistence of oral antidiabetic treatment in patients with type 2 diabetes.

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