Initial Therapeutic Choices for Type 2 Diabetes in the Portuguese Sentinel Practice Network

Escolhas Terapêuticas Iniciais para a Diabetes Tipo 2 na Rede de Médicos Sentinela

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ABSTRACT

Introduction: Type 2 diabetes is a major driver of pharmaceutical spending. We aimed to determine the proportion of new patients who begin treatment with each antidiabetic medicine class, if therapy was initiated by their family physician, if family physicians alter prescriptions initiated by other physicians, and to compare prescribing patterns of family physicians and other specialists.
Material and Methods: Cohort-nested cross-sectional study within the Portuguese Sentinel Practice Network. Between 2014 and 2015, incident cases of type 2 diabetes were notified, thus reporting treatment, who made the initial prescription and if treatments initiated by other physicians were changed.
Results: A total of 415 incident cases were notified. The initial prescription was made by Sentinel Practice Network physicians in 89.4% of cases (95% CI 86.0% - 92.0%). Metformin was most often chosen as the first treatment, prescribed to 85.5% of patients (95% CI 81.8% – 88.6%). Family physicians used less dipeptidyl peptidase-4 inhibitors (4.2% *vs* 30.3%, *p* < 0.001) and insulin (0.3% *vs* 12.1%, *p* < 0.001) compared to other specialists. Prescriptions initiated by others were changed in 4.5% of cases (95% CI 0.4% - 16.0%).
Discussion: Prospective data collection is a major study strength, but few cases of treatment initiated by non-family physicians were notified. Data for disease severity was unavailable and could partly explain differences between family physicians and other specialists.
Conclusion: Metformin was most often chosen as initial therapy, in line with Portuguese guideline recommendations. Sentinel Practice Network physicians diagnosed most cases, seldom changed prescriptions initiated by others, and had a different pattern of antidiabetic medicines use compared to other specialists.
Keywords: Diabetes Mellitus, Type 2/drug therapy; Hypoglycemic Agents; Portugal; Primary Health Care; Sentinel Surveillance

RESUMO

Introdução: A diabetes tipo 2 tem um peso significativo nas despesas com medicamentos. Determinámos a proporção de novos doentes que iniciaram tratamento com cada classe de antidiabéticos, se o tratamento foi iniciado pelos médicos de família, se estes alteram as prescrições de outros médicos e comparámos padrões de prescrição de médicos de família e outros especialistas.
Material e Métodos: Estudo transversal aninhado em coorte na Rede de Médicos Sentinela. Entre 2014 e 2015 casos incidentes de diabetes tipo 2 foram notificados, reportando o tratamento, quem fez a prescrição inicial e se tratamentos iniciados por outros médicos foram alterados.
Resultados: Foram notificados 415 casos incidentes. Os Médicos Sentinela fizeram a prescrição inicial em 89,4% dos casos (IC 95% 86,0% - 92,0%). O tratamento inicial mais escolhido foi a metformina, em 85,5% dos doentes (IC 95% 81,8% - 88,6%). Os médicos de família utilizaram menos inibidores da dipeptidil peptidase-4 (4,2% *vs* 30,3%, *p* < 0,001) e insulina (0,3% *vs* 12,1%, *p* < 0,001) que outros especialistas. As prescrições iniciadas por outros foram alteradas em 4,5% dos casos (IC 95% 0,4% - 16,0%).
Discussão: A colheita prospectiva dos dados é um ponto forte, mas foram notificados poucos casos de tratamento iniciado por outros especialistas. Dados sobre a gravidade da doença não estavam disponíveis e podem explicar parte das diferenças entre médicos de família e outros especialistas.
Conclusão: A metformina foi o tratamento inicial mais escolhido, em linha com as recomendações das normas de orientação clínica Portuguesas. Os médicos da Rede Sentinela diagnosticaram a maioria dos casos, raramente alteraram prescrições iniciadas por outros e tiveram um padrão de prescrição diferente de outros especialistas.
Palavras-chave: Cuidados de Saúde Primários; Diabetes Mellitus Tipe 2/tratamento; Hipoglicemiantes; Portugal; Vigilância de Evento Sentinela

INTRODUCTION

Type 2 diabetes pharmacotherapy is one of the major drivers of pharmaceutical spending in Portugal and other developed countries.[1] Rises in expense are partly related to increased diabetes prevalence, but mainly to the greater use of newer and more expensive medicines, such as the dipeptidyl peptidase-4 (DPP-4) inhibitors and insulin glargine.[1,2]

Both international and Portuguese guidelines favour metformin as the first-line agent of choice for most patients with type 2 diabetes after lifestyle changes have been tried.[3,4] Portuguese guidelines prefer a sulfonylurea if metformin is contra-indicated or not tolerated, and recommend insulin if there is markedly symptomatic hyperglycaemia (with glycaemia above 300 mg/dL or an HbA_{1C} over 10%).[4] Starting with dual combination therapy is not recommended by Portuguese guidelines, but is considered optional for patients with HbA_{1C} over 9% by the American Diabetes Association and the European Association for the Study of

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Diabetes joint position statement.[3]

Studies regarding diabetes medicines prescribing patterns mainly focus on prevalent use,[1,2,5,6] with only a few identifying the agents used as first-line therapy.[7] Finding which agents are chosen as first-line therapy for new cases of type 2 diabetes may help determine if physicians are following guideline recommendations; and if more expensive agents are being used to initiate treatment or introduced later on (e.g., when initial therapy fails to achieve goals or causes side effects).

Although family physicians account for most diabetes prescriptions in Portugal,[1] it is unknown if new medicines are introduced by them or prescribing is induced by hospital or private practice based specialists. The influence of specialist prescribing of new medicines on primary care physicians has been shown to occur often, but not in all cases. In some studies, specialists are earlier adopters, initiating treatments with a new drug, which family physicians then continue[8-11]; while in other studies family physicians are reported to use new drugs more often.[12]

The main objective of this study was to determine the proportion of new patients with type 2 diabetes who began treatment with each antidiabetic medicine class. Secondary objectives were to determine the proportion of new patients with type 2 diabetes whose initial therapy was prescribed by their family physician, the proportion of cases where family physicians altered prescriptions initiated by other doctors, and to compare family physicians prescribing patterns with private or hospital based specialists.

MATERIAL AND METHODS
Study design and setting

The Portuguese Sentinel Practice Network is composed of volunteer family physicians working in the Portuguese National Health Service (NHS).[13] The Portuguese NHS is a single payer publicly funded system, where each citizen is registered with a family physician.[14] Therefore, each participant in the Sentinel Practice Network contributes with a cohort of their patients. This allows the network to have a reasonably stable cohort each year and to calculate the incidence of health problems in the Portuguese population. The network collects data for two different purposes: surveillance of communicable and non-communicable diseases for which specified events are systematically reported each week; and epidemiological research that comprises satellite studies, where data is collected to answer a specific question. Only observational research studies are performed within the network.

In 2013, the network agreed to expand the information being collected about incidence of diabetes mellitus for surveillance purposes, to conduct a continuous notification cross-sectional study among new cases of type 2 diabetes notified in the cohort. Data was collected from January 2014 to December 2015.

Participants

In 2014 and 2015 there were 82 active family physicians participating in the Portuguese Sentinel Practice Network, which comprised an observed population of 35 535 individuals. We asked participants to notify all incident cases of diabetes of any age. Diagnosis of diabetes was made using the nationally adopted criteria (the same as those recommended by the World Health Organization in 2006, updated in 2011 to include HbA_{1C}).[15] Only cases of type 2 diabetes were included.

Measurements

Notifications were sent using either online or paper forms. Data were collected on patient age at diagnosis, gender, type of diabetes (type 1, type 2 – only these were included, gestational, other or unknown), pharmacological treatment (the online form had a list of marketed antidiabetic medicines using the international non-proprietary name; the paper form had a free text space; up to three medicines could be entered), other treatment measures (free text), who made the initial prescription (the family physician or another doctor, who was then specified in a separate free text field), and if the initial prescription had been changed by the family physician (only for prescriptions initiated by other physicians). Free text fields were later coded by the investigators. When incomplete submissions were received, the Sentinel Practice Network coordination contacted the notifying physician to gather missing information.

Outcomes

Our main outcome was the proportion of patients who began treatment with each antidiabetic medicine class. Classes were defined using the Anatomical Therapeutic Chemical classification categories for A10B blood glucose lowering drugs excluding insulins and A10A insulins and analogues.[16]

Secondary outcomes were the proportion of patients whose diagnosis and initial therapy was prescribed by their family physician; the proportion of cases where family physicians altered prescriptions initiated by others; and the proportion of each class of antidiabetics prescribed by primary care physicians (family physicians participating in the Sentinel Practice Network or other family medicine specialists) or private and hospital based specialists.

Study size

We calculated a minimum sample size of 384 cases of type 2 diabetes needed to estimate the proportion of patients beginning treatment with each class of antidiabetic medicines with 5% precision and a 95% confidence interval, assuming as worst-case scenario that 50% of patients would begin with one class. Given the previous notification rate, we estimated that two or three years of continuous notification would be needed. To maximize the ability of the network to conduct new projects, we planned to count the number of notifications by the last trimester of the second year and only continue notifications into the third year if the desired sample size had not been achieved.

Statistical analysis

Proportions of each antidiabetic class prescribed as initial therapy were estimated with their respective 95% confidence interval (95% CI). Proportions of medicines prescribed by primary care and non-primary care physicians were compared using Fisher's exact test. A level of significance (α) of 0.01 was used as the threshold for statistical significance to account for multiple comparisons.

Ethics approval

This study was approved by the Ethics Committee of National Health Institute Dr. Ricardo Jorge (Portugal).

RESULTS

During the years 2014 and 2015, 415 incident cases of type 2 diabetes were notified to the Portuguese Sentinel Practice Network by 72 participating family physicians. Ten physicians did not contribute with any diabetes notifications, but, as they notified other health conditions under observation, their patient lists were included when calculating incidence. Having achieved the planed sample size, data collection ended by the end of the second year of the study. Type 2 diabetes incidence in the cohort was 5.8 / 1000 person-years. Median age at diagnosis was 62 (interquartile range 54 - 71) and 54.5% of patients were male. There were no differences between patients diagnosed by primary care and non-primary care physicians regarding mean age (62.7 vs 60.2 years, p = 0.25) and gender (53.7 vs 63.6% male, p = 0.28).

The diagnosis and initial prescription were made by physicians participating in the Sentinel Practice Network in 371 cases (89.4%, 95% CI 86.0% - 92.0%), other family physicians in 11 cases (2.7%, 95% CI 1.4% - 4.7%), and other specialists in 33 cases (8.0%, 95% CI 5.7% - 11.0%).

Lifestyle changes alone were introduced in 12.0% (95% CI 9.2% - 15.6%) of patients, and all were prescribed by Sentinel Practice network physicians. In total, lifestyle changes were prescribed in 65.8% (95% CI 61.1% - 70.2%) of cases.

In 81.4% (95% CI 77.4% - 84.9%) of cases patients were started on one single medicine, in 5.8% (95% CI 3.9% - 8.5%) two medicines were used and in 0.7% (95% CI 0.1% - 2.2%) three antidiabetic drugs were prescribed. Family physicians used two or more medicines less often than other specialists (4.2% vs 33.3%, p < 0.001). Fixed associations were used in 3.4% of cases, less often by primary care physicians compared to other specialists (2.4% vs 15.2%, p = 0.003).

Tables 1 and 2 show the proportion of each antidiabetic class prescribed as initial therapy by family physicians or

Table 1 – Proportion of patients prescribed each distinct combination for initial therapy (by class and type of practitioner). Antidiabetics with and without associated prescription for lifestyle changes are grouped together.

Initial therapy	Family physicians (n = 382)	Other specialists (n = 33)	Total (n = 415)
		% (95%CI)	
Lifestyle changes alone	13.1 (10.1 – 16.9)	0.0 (0.0 – 12.4)	12.0 (9.2 – 15.6)
Biguanides (metformin)	81.4 (77.2 – 85.0)	54.5 (38.0 – 70.2)	79.3 (75.1 – 82.9)
Biguanide and DPP-4-i	2.4 (1.2 – 4.5)	24.2 (12.6 – 41.2)	4.1 (2.5 – 6.5)
DPP-4-i	1.0 (0.3 – 2.8)	6.1 (0.6 – 20.6)	1.4 (0.6 – 3.2)
Biguanide and sulphonylurea	1.0 (0.3 – 2.8)	0.0 (0.0 – 12.4)	1.0 (0.3 – 2.5)
Insulin	0.0 (0.0 – 1.2)	9.1 (2.4 – 24.3)	0.7 (0.1 – 2.2)
Biguanide, sulphonylurea and DPP-4-i	0.5 (0.0 – 2.0)	0.0 (0.0 – 12.4)	0.5 (0.0 – 1.9)
Sulphonylureas	0.3 (0.0 – 1.6)	0.0 (0.0 – 12.4)	0.2 (0.0 – 1.5)
Biguanide and GLP1 agonist	0.0 (0.0 – 1.2)	3.0 (0.0 – 16.7)	0.2 (0.0 – 1.5)
Biguanide and insulin	0.0 (0.0 – 1.2)	3.0 (0.0 – 16.7)	0.2 (0.0 – 1.5)
Biguanide, DPP-4-i and insulin	0.3 (0.0 – 1.6)	0.0 (0.0 – 12.4)	0.2 (0.0 – 1.5)

DPP-4-i: dipeptidyl peptidase-4 inhibitor; GLP1: glucagon-like peptide-1: 95% CI: 95% confidence interval

Table 2 – Proportion of patients prescribed each class as part of their initial therapy (alone or in combinations)

Initial therapy	Family physicians (n = 382)	Other specialists (n = 33)	Total (n = 415)
		% (95%CI)	
Lifestyle changes	68.3 (63.5 – 72.8)	36.4 (22.1 – 53.4)	65.8 (61.1 – 70.2)
Biguanides (metformin)	85.6 (81.7 – 88.8)	84.8 (68.6 – 93.8)	85.5 (81.8 – 88.6)
DPP-4-i	4.2 (2.5 – 6.7)	30.3 (17.3 – 47.5)	6.3 (4.3 – 9.1)
Sulphonylureas	1.8 (0.8 – 3.8)	0.0 (0.0 – 12.4)	1.7 (0.8 – 3.5)
Insulin	0.3 (0.0 – 1.6)	12.1 (4.2 – 27.9)	1.2 (0.4 – 2.9)
GLP-1 agonists	0.0 (0.0 – 1.2)	3.0 (0.0 – 16.7)	0.2 (0.0 – 1.5)

other specialists grouped by distinct combinations and total class use, respectively. Metformin was used as a single agent or in combinations in 85.5% of patients (95% CI 81.8% – 88.6%), with no differences between primary care and non-primary care physicians (85.6% *vs* 84.8%, *p* = 0.801). Metformin alone was used more often by family physicians than other specialists (81.4% *vs* 54.5%, *p* = 0.01). Sulphonylureas alone or in combination were used in 1.7% of cases (95% CI 0.8% - 3.5%), with no differences between primary care physicians and other specialists (1.8% *vs* 0.0%, *p* = 1.0). The proportion of patients who began treatment with a DPP-4 inhibitor as a single agent or in combination was 6.3% (95% CI 4.3% - 9.1%), 4.2% for primary care physicians and 30.3% for other specialists (*p* < 0.001). Insulin alone or in combination was prescribed to 1.2% (95% CI 0.4% - 2.9%) of cases, by family physicians to 0.3% of patients and by other specialists to 12.1% (*p* < 0.001).

When we excluded cases treated with lifestyle changes alone, the differences between family physicians and other specialists in use of metformin alone (93.7% for family physicians *vs* 54.5% for specialists, *p* < 0.001), DPP-4 inhibitors (4.8% *vs* 30.3%, *p* < 0.001) and insulin (0.3% *vs* 12.1%, *p* < 0.001) as single agents or in combinations, and fixed combination therapy (2.7% *vs* 15.2%, *p* = 0.005) remained statistically significant. Total metformin use (as a single agent or in combinations) also achieved statistical significance (98.5% *vs* 84.5%, *p* = 0.001). There were still no differences in sulphonylurea use (2.1% *vs* 0%, *p* = 1.0).

Among the 44 cases where treatment was not initiated by physicians participating in the Sentinel Practice Network, the prescribed medicines were changed in two cases (4.5%, 95% CI 0.4% - 16.0%).

DISCUSSION
Main findings
In this study, most cases of type 2 diabetes were diagnosed by family physicians. The majority of patients began treatment with metformin as a single agent, as recommended by Portuguese and international guidelines.[3,4] This occurred more often when treatment was initiated by family physicians than when initiated by other specialists. Lifestyle changes alone were the initial strategy used by family physicians in about 13% of patients, but in none of the cases diagnosed by other specialists. When these two options are taken together, family physicians managed new cases of type 2 diabetes with lifestyle changes or metformin in 94.5% of cases, compared with 54.5% of cases diagnosed by specialists. Other specialists were more likely than family physicians to use DPP-4 inhibitors, insulin or fixed combinations as their initial choice. Despite these differences, family physicians usually didn't change prescriptions initiated by others.

Sulphonylureas and glucagon-like peptide-1 receptor agonists were seldom used as first-line agents. We observed no use of alpha glucosidase inhibitors, thiazolidinediones or sodium/glucose cotransporter 2 inhibitors as initial therapy.

Strengths and limitations
The main strength of this study is the prospective data collection about therapeutic choices among new cases of diabetes. Almost 90% of cases were reported by the prescribers themselves on the same day or a few days after the diagnosis and a therapeutic decision had been made. For the remaining 10% of cases, Sentinel Practice Network physicians gathered information from the patient or available patient records. In the Portuguese NHS, electronic prescription has been mandatory for reimbursement since August 2011.[17] Information about electronic prescriptions made elsewhere is available to family physicians through the national Health Data Platform.[18] The availability of such information would have limited patient recall bias.

There may have been some cases of type 2 diabetes diagnosed by other physicians that were not reported by participants in the Sentinel Practice Network. However, these should be rare, as the diagnosis of type 2 diabetes grants special benefits to patients in the Portuguese NHS and most would visit their family physician to be entitled to them. Also, incidence during the study period was similar to that previously reported in the cohort (since here we are only considering type 2 diabetes),[19] and to what is reported in other countries (considering these are estimates for the adult population only).[20-22]

It is possible that patients diagnosed by other specialists who were prescribed lifestyle changes alone would not come immediately to their family physician, reporting their diagnosis only when medicines are prescribed. However, when we excluded patients treated with lifestyle changes alone the differences in prescribing pattern did not disappear. Sentinel Practice Network participants could also have underreported lifestyle changes prescribed by other physicians, as patients may have not valued non-pharmacological treatment and there were no other sources of this information.

We did not collect data on disease severity or presence of contra-indications to specific medicines. Both could influence the decision of initial treatment. However, the number of variables that can be collected in the Sentinel Practice Network is limited, as the paper notification form for all studies in a given year has to fit in one sheet.

Socio-economic status may have been a confounder, as patients with more purchasing power may have been more likely not to use the NHS and also to afford more expensive medicines.

An important limitation is that family physicians participating in the Sentinel Practice Networks might sometimes have different prescribing habits than other family physicians. Participating in a research network is voluntary and could be associated with other physician or patient characteristics that influence prescribing. This has not been thoroughly studied in the Portuguese Sentinel Practice Network, but other authors have found differences to be small.[23,24]

Care must be taken when interpreting differences in use of specific drugs, as we did multiple comparisons, which make false positive results more likely, and this was not the

study's primary outcome. Therefore, our findings should be considered mostly as hypothesis generating. Nonetheless, we decided to use a lower than usual threshold for statistical significance (α = 0.01 instead of α = 0.05) to reduce false discovery rate. A formal adjustment method, such as the Bonferroni correction, was not defined in the study's methods since the number of comparisons to make would be dependent on the number of medicines classes used in our sample. Even so, most of the associations found were very unlikely to be due to chance, with a p value less than 0.001.

Interpretation of results

As expected, metformin was the most frequently prescribed first-line medicine, followed by DPP-4 inhibitors, mainly when used in a fixed association with metformin, with sulphonylureas coming in third place. This goes against recommendations in Portuguese guidelines, which favour sulphonylureas for having a better cost-benefit relationship.[4] It may, however, reflect physician perception of better safety with DPP-4 inhibitors,[25] despite their sparse data on reduction of diabetes complications.[26]

Our findings suggest family physicians prescribe more in line with guidelines than other specialists, who use more intensive pharmaceutical regimens, including newer and more expensive medicines. This may be partially explained by other specialists seeing patients with more severe disease, possibly with symptomatic hyperglycaemia – data which we were unable to collect. Since the study did not collect information on disease severity at diagnosis, we are unable to test this hypothesis. Alternatively, specialists might be more willing to use newer medicines or feel more often that their patients do not fit guideline recommendations.[10,27] However, our results are consistent with a study conducted in the Lisbon region that showed only 17.2% of initial prescriptions for new oral anticoagulant agents originated in primary care.[11]

Family physicians seem to be reluctant to change prescriptions initiated by other specialists. This might be explained by the fact that most these patients would continue to be followed by those specialists. On the other hand, family physicians might feel compelled to keep the treatment initiated by other specialists, feel they do not have all the information needed to recommend a different treatment or patients might be resistant to change.[28]

Implications for practice

When considering prevalent prescribing patterns of antidiabetic medicines, policy and decision makers should consider that most patients diagnosed with type 2 diabetes start with metformin, and probably only escalate to other treatments later in the natural history of the disease. How-

ever, more aggressive initial treatment, including more expensive agents, is more frequent when the diagnosis has not been made by family physicians. Thus, interventions to alter prescription patterns need to target hospital and private-based specialists and not only primary care doctors.

Future studies should address disease severity at diagnosis, but also when and why patients change their initially prescribed treatment as the duration of diagnosis lengthens and which agents are chosen by physicians then.

CONCLUSION

Metformin was the agent most often chosen as initial therapy, followed by lifestyle changes alone, fixed combinations of metformin and DPP-4 inhibitors and DPP-4 inhibitors. The diagnosis and initial prescription were made by Sentinel Practice Network physicians in almost 90% of cases. Family physicians changed prescriptions initiated by others in less than 5% of cases. DPP-4 inhibitors and insulin were more likely to be prescribed by other specialists.

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