Therapeutic inertia and intensified treatment in diabetes mellitus prescription patterns: A nationwide population-based study in Taiwan

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Abstract

Objective: To measure therapeutic inertia by characterizing prescription patterns using secondary data obtained from the nationwide diabetes mellitus pay-for-performance (DM-P4P) programme in Taiwan.

Methods: Using reimbursement claims from Taiwan's National Health Insurance Research Database, a nationwide retrospective cohort study was undertaken of patients with diabetes mellitus who participated in the DM-P4P programme from 2006–2008. Glycosylated haemoglobin results were used to evaluate modifications in therapy in response to poor diabetes control. Prescription patterns were used to assign patients to either a therapeutic inertia group or an intensified treatment group. Therapeutic inertia was defined as the failure to act on a known problem.

Results: The research sample comprised of 168 876 patients with diabetes mellitus who had undergone 899 135 tests. Of these, 37.4% (336 615 visits) of prescriptions were for a combination of two types of drug and 27.7% (248 788 visits) were for a combination of three types of drug.

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The proportion of patients in the intensified therapy group who were prescribed more than two types of drug was considerably higher than that in the therapeutic inertia group.

Conclusion: In many cases in the therapeutic inertia group only a single type of hypoglycaemic drug was prescribed or the dosage remained unchanged.

Introduction

It has been reported that more than 387 million people worldwide suffer from diabetes mellitus, and that this figure is expected to increase to over 438 million by 2030.[1,2] Diabetes mellitus is a major challenge to Asian countries, including Taiwan.[3] Despite guidelines that emphasize the importance of glycaemic control among patients with diabetes mellitus, many patients have glycosylated haemoglobin (HbA$_{1c}$) levels outside the recommended range.[4–6] Therapeutic inertia is defined as when a physician does not begin or intensify treatment when this is deemed necessary according to current clinical practice guidelines.[7–9] Previous studies have shown that patients enrolled in the diabetes mellitus pay-for-performance (DM-P4P) programme in Taiwan are more likely to undergo guideline-recommended tests and examinations.[10–13] Because the DM-P4P programme is a physician-level incentive strategy aimed at improving care quality, profiling and comparing the quality of care provided by various physician groups is a valuable strategy to facilitate this improvement.[14] Our previous study found that 38.5% of the patients were subject to therapeutic inertia.[6] Furthermore, patients at medical centres were shown to be more likely to be prescribed with intensified treatment than patients in primary clinics.[6] The primary goal of this study was to investigate differences between diabetes prescription patterns for patients subject to therapeutic inertia and those with intensified treatment.

Patients and methods

Description of the study population

In this retrospective cohort study, all patients who were categorized according to the International Statistical Classification of Diseases and Related Health Problems as code 250,[15] and who had made at least four outpatient visits each year from 1 January 2006 to 31 December 2008 were enrolled.[16] This selection process has been reported to increase the accuracy of the diagnosis by 99.16 times compared with a selection process that included patients with one or fewer outpatient visits per year.[16] HbA$_{1c}$ results were used to evaluate the therapy modifications adopted in response to poor diabetes control (i.e., HbA$_{1c}$ values were 7%–11%). Secondary data did not include changes in insulin dosage, and therefore the patients using insulin prior to the HbA$_{1c}$ tests were excluded. The influence of comorbidities on time to intensification was evaluated using the chronic illness with complexity (CIC) score.[17] A diabetes comorbidity severity index (DCSI) score was calculated for diabetes-related comorbid disease conditions.[18]

Data sources

The study used several administrative databases detailing health service usage in

Taiwan, including the National Health Insurance (NHI) Research Database (NHIRD) and the virtual private network of the DM-P4P database. The DM-P4P programme was designed by the NHI Bureau in Taiwan, and it is the most comprehensive and mature P4P programme in Taiwan.[12] Participation in the programme was voluntary, and the DM-P4P database was constructed to supplement regular NHI claims data. DM-P4P patient outcome data such as HbA_{1c} values were reported by the hospitals and entered into the P4P-specific database automatically.[12] This study was approved by the Research Ethics Committee of National Taiwan University Hospital, Taiwan (no. 201203010RIC). Signed informed consent was not required because this study used anonymized data and did not involve any human experimentation.

Pharmacological management

In this study, pharmacological therapy was defined as prescriptions filled 120 days before and after receiving HbA_{1c} test results. Antihyperglycaemic agents were evaluated according to the Anatomical Therapeutical Chemical Classification Defined Daily Dose (ATC/DDD) system developed by the World Health Organization.[19] Antihyperglycaemic agents were categorized as insulin (ATC codes: A10AB, A10AC, A10AD, A10AE) and the following 17 major classes of oral antihyperglycaemic agent (ATC codes are listed outside parentheses): A10BB (sulfonamides, urea derivatives), including A10BB01 to A10BB12 (i.e., glibenclamide, chlorpropamide, tolazamideglibenclamide, gliquidone, gliclazide, glimepiride); A10BD02 (metformin and sulfonamides); A10BA02 (metformin); A10BA03 (buformin); A10BD03 (metformin and rosiglitazone); A10BF01 (acarbose); A10BG02 (rosiglitazone); A10BG03 (pioglitazone); A10BX01 (guar

gum); A10BX02 (repaglinide); and A10BX03 (nateglinide).[19]

Analysis

Medications were quantified by assigning DDD units to each item from the NHIRD based on the index of the ATC classification system.[19] When used for the identification of changes in prescription (P_{after}–P_{before}), the prescribed total DDD was generally comprised of the 17 major classes. When prescription medications from more than one class were considered, any increase in the dosage among any of the drugs was considered as intensified therapy.

Measurements

In this study, the following prescription changes that occurred following HbA_{1c} measurements were classified into four mutually exclusive groups: group 1, the addition of one or more new classes of drug; group 2, an increase in the dosage of the same drugs used prior to HbA_{1c} measurements; group 3, no change in the drug class or a decrease in the dosage (DDD); group 4, discontinuation of drug therapy.

Definition of intensified therapy

Any change in prescription according to the following conditions was defined as intensified therapy: the prescription of new oral antihyperglycaemic agents, increasing the dosage of any current medication, switching to another medication in a different therapeutic class, or the initiation of insulin use. The study did not treat switches to medications in the same therapeutic class as therapy modification unless the DDD of the new agent was more than that of the previous agent, because switching medications could be a response to side effects rather than intensifying the therapy.

Statistical analyses

All statistical analyses were performed using the Statistical Analysis System (SAS) version 9.3. (SAS Institute, Cary, NC, USA). Descriptive statistical analyses were used to examine modifications in therapy to identify therapeutic inertia. χ^2-test for categorical variables were used to compare groups (intensified therapy and therapeutic inertia) on key variables obtained from the NHIRD data set. A P-value < 0.05 was considered statistically significant.

Results

Following the exclusion of ineligible patients, the research sample comprised of data from 168 876 patients with diabetes mellitus. Among the 899 135 tests that revealed HbA_{1c} levels ranging from 7% to 11%, 61.65% of the patients (554 320 visits) had their therapy intensified, compared with 38.35% (344 815 visits) who did not.[6] The mean $\pm$ SD age of the patients was 60.5 ± 10.8 years. The proportion of patients with HbA1c levels between 7% and 8% was 48.1% (432 305 visits) (Table 1). This study identified the following clinical characteristics that were significantly different between the intensified therapy group and the therapeutic inertia group: age, HbA_{1c} levels, DCSI scores, and CIC count ($P < 0.001$ for all four characteristics).

Patients were prescribed new drugs in 42.0% (377 675 visits) of all case visits, and 19.5% (175 239 visits) of the case visits involved an increase in dosage of the same drug class. Among the therapeutic inertia group, 72.5% (250 077 visits) of the prescriptions were for the same medication despite abnormal HbA_{1c} results. Regarding the pattern analysis of antihyperglycaemic agents, 37.4% (336 615 visits) of the studied prescriptions were for a combination of two types of drug, 27.7% (248 788 visits) were for a combination of three types of drug, and 13.3% (119 424 visits) were for a

monotherapy regimen (Table 2). Among the monotherapy prescriptions, sulfonamides were the most frequently prescribed types of medication (64.4%; 76 937 visits), and insulin monotherapy accounted for only 7.3% (8672 visits) of the prescriptions (Table 2). Sulfonamides and biguanides were the most frequently prescribed drugs for polytherapy involving two types of drug, accounting for 78.9% (265 563 visits) of all dual-drug prescriptions.

Among the polytherapy prescriptions involving three types of drug (248 788 of 899 135 visits; 27.7%), sulfonamide, biguanide, and thiazolidinedione (109 680 of 248 788 visits; 44.1%) were the most frequently prescribed combination (Table 2). An additional 8.3% (20 597 of 248 788 visits) of the prescriptions were for a combination of oral antihyperglycaemic agents and insulin.

The proportion of patients in the intensified therapy group prescribed more than two types of drug was considerably higher than that in the therapeutic inertia group. For example, 70.7 % (175 989 of 248 788 visits) of the cases in the intensified therapy group were prescribed a combination of three types of drug, whereas only 29.3% (72 799 of 248 788 visits) of the patients in the therapeutic inertia group were prescribed such a combination (Table 2). In addition, 38.3% (45 694 of 119 424 visits) of the patients in the intensified therapy group received monotherapy, among whom 8672 single drug prescriptions (of 45 694 visits; 19.0%) were for insulin. However, 61.7% (73 730 of 119 424 visits) of the patients in the therapeutic inertia group received monotherapy (Table 2).

Discussion

Therapeutic inertia is defined as a lack of treatment intensification despite a suboptimal outcome with the current diabetes management strategy.[9] In the present study in a real-world Taiwanese population, based

Table 1. Baseline demographic and clinical characteristics of patients with diabetes mellitus ($n = 168\,876$) who provided prescription data ($n = 899\,135$) for this study as part of the diabetes mellitus pay-for-performance (DM-P4P) programme in Taiwan.

Characteristics	Total prescriptions 899 135 (100.00%)	Intensified therapy group 554 320 (61.65%)	Therapeutic inertia group 344 815 (38.35%)	Statistical significance[a]
Age				$P < 0.001$
<40 years	29 059 (3.23%)	19 754 (3.56%)	9305 (2.70%)	
$\geq$40 and <65 years	522 397 (58.10%)	322 236 (58.13%)	200 161 (58.05%)	
$\geq$65 and <80 years	347 679 (38.67%)	212 330 (38.30%)	135 349 (39.25%)	
Sex				NS
Male	412 143 (45.84%)	254 156 (45.85%)	157 987 (45.82%)	
HbA$_{1c}$ levels				$P < 0.001$
$7 < HbA_{1c} \leq 8$	432 305 (48.08%)	234 619 (42.33%)	197 686 (57.33%)	
$8 < HbA_{1c} \leq 9$	250 293 (27.84%)	161 507 (29.14%)	88 786 (25.75%)	
$9 < HbA_{1c} \leq 10$	139 336 (15.50%)	98 775 (17.82%)	40 561 (11.76%)	
$10 < HbA_{1c} \leq 11$	77 201 (8.59%)	59 419 (10.72%)	17 782 (5.16%)	
DCSI score (DM severity)				$P < 0.001$
0	813 345 (90.46%)	496 194 (89.51%)	317 151 (91.98%)	
1	49 508 (5.51%)	32 390 (5.84%)	17 118 (4.96%)	
2	30 330 (3.37%)	21 219 (3.83%)	9111 (2.64%)	
3	4033 (0.45%)	2989 (0.54%)	1044 (0.30%)	
4+	1919 (0.21%)	1528 (0.28%)	391 (0.11%)	
CIC count (DM comorbidity)				$P < 0.001$
0	848 499 (94.37%)	521 024 (93.99%)	327 475 (94.97%)	
1	48 088 (5.35%)	31 415 (5.67%)	16 673 (4.84%)	
2	2349 (0.26%)	1750 (0.32%)	599 (0.17%)	
3	180 (0.02%)	116 (0.02%)	64 (0.02%)	
4+	19 (0.00%)	15 (0.00%)	4 (0.00%)	

Data presented as *n* of visits (%).
[a]χ^2-test was used to compare groups (intensified therapy and therapeutic inertia) on key variables obtained from the National Health Insurance Research Database data set.
HbA$_{1c}$, glycosylated haemoglobin; DCSI, diabetes comorbidity severity index; DM, diabetes mellitus; CIC, chronic illness with complexity; NS, no significant between-group difference ($P \geq 0.05$).

on data from more than 899 000 visits, the following patient characteristics were significantly different between the intensified therapy group and the therapeutic inertia group: age, HbA$_{1c}$ levels, DCSI scores, and CIC count. Treatment of type 2 diabetes mellitus typically begins with lifestyle adjustments and oral antidiabetic drugs.[20–23] When blood glucose can no longer be controlled merely through lifestyle changes, metformin is typically prescribed as a first-line medication, particularly for patients who are also overweight.[21–24] However, because diabetes is a progressive disease, blood glucose concentration worsens with time, and most patients with diabetes eventually need at least two types of oral medication or insulin to reach or maintain the required blood glucose level.[22,23] Current treatment guidelines differ in terms of what second-line medication should be prescribed in cases where blood glucose can no longer be controlled through metformin alone.[21,22] Some recommend supplementing metformin

Table 2. Prescribing patterns in patients ($n = 168\ 876$) with diabetes mellitus who underwent intensified therapy or therapeutic inertia and who provided prescription data ($n = 899\ 135$) for this study as part of the diabetes mellitus pay-for-performance (DM-P4P) programme in Taiwan.

Drug classes	Total prescriptions $n = 899\ 135$	Intensified therapy group $n = 554\ 320$	Therapeutic inertia group $n = 344\ 815$
Monotherapy	119 424 (13.3%)	45 694 (8.2%)	73 730 (21.4%)
A10BB Sulfonamides	76 937 (64.4%)	26 539 (58.1%)	50 398 (68.4%)
A10BA Biguanides	26 018 (21.8%)	9102 (19.9%)	16 916 (22.9%)
Insulin	8672 (7.3%)	8672 (19.0%)	0 (0.0%)
A10BG Thiazolidinediones	942 (0.8%)	333 (0.7%)	609 (0.8%)
Others	6 855 (5.7%)	1048 (2.3%)	5807 (7.9%)
Two oral drug combinations	336 615 (37.4%)	178 901 (32.3%)	157 714 (45.7%)
Sulfonamides + Biguanides	265 563 (78.9%)	147 372 (82.4%)	118 191 (74.9%)
Sulfonamides + TZD	26 778 (8.0%)	12 648 (7.1%)	14 130 (9.0%)
Others + Insulin	2907 (0.9%)	2907 (1.6%)	0 (0.0%)
Others	41 367 (12.3%)	15 974 (8.9%)	25 393 (16.1%)
Three oral drug combinations	248 788 (27.7%)	175 989 (31.7%)	72 799 (21.1%)
Sulfonamides + Biguanides + TZD	109 680 (44.1%)	72 857 (41.4%)	36 823 (50.6%)
Sulfonamides + Biguanides + Others	75 613 (30.4%)	58 868 (33.4%)	16 745 (23.0%)
Sulfonamides + Others + TZD	13 146 (5.3%)	9273 (5.3%)	3873 (5.3%)
Biguanides + Others + TZD	6956 (2.8%)	4313 (2.5%)	2643 (3.6%)
Sulfonamides + Biguanides + Insulin	20 597 (8.3%)	20597 (11.7%)	0 (0.0%)
Others	22 796 (9.2%)	10 081 (5.7%)	12 715 (17.5%)
Four or more drugs	152 554 (17.0%)	144 928 (26.1%)	7626 (2.2%)
No drugs	41 754 (4.6%)	8808 (1.6%)	32 946 (9.6%)

Data presented as *n* of visits (%).
Others, A10BX02 repaglinide, A10BF01 acarbose and A10BX03 nateglinide; TZD, thiazolidinedione.

with sulfonylurea or gradually adding other types of drug. For example, compared with the UK, Canada, and Australia,[23,24] the NHI regulations in Taiwan are not as strict and do not differentiate between first- and second-line drugs, which allowed physicians to freely choose what drug or combination of drugs they prescribed as first-line medication before May 2016.[25] Most single-drug prescriptions in Taiwan are for sulfonamide rather than metformin. In this present study, the most frequently prescribed monotherapy drug was sulfonylurea, and metformin combined with sulfonylurea for polytherapy. In addition, this present study found that of the drug prescriptions for patients, 37.4% (336 615 visits) were for two types of drug, 27.7% (248 788 visits) were for three types of drug, and 13.3% (119 424 visits) were for monotherapy. This present study also observed that in the intensified therapy group, the percentage of patients who were prescribed more than two types of drug was considerably higher than that in the therapeutic inertia group. For example, for the three oral drug combination group, 70.7% of the prescriptions were from patients in the intensified therapy group. In the therapeutic inertia group, however, the present study observed that in many cases only a single type of hypoglycaemic drug was prescribed, or that the dosage remained unchanged. Few studies have discussed switching drug types in intensified therapy. A retrospective

cohort study involving 253 238 patients was undertaken to assess the number of cases where drug treatment had been modified in the previous 6 months because of a failure to properly control one or more types of chronic disease.[26] The authors reported that 66% of the patients with poorly controlled HbA_{1c} levels had their prescription medication changed.[26] Most changes involved prescribing other types of drug (70% to 84% of cases) or increasing the prescribed dosage (15% to 40% of cases).[26] Similar to the results reported by research conducted in Taiwan,[6] this present research group previously found that 61.5% of prescriptions were modified before and after a test result of HbA_{1c} >7%.[6] New types of drug were added in 42.0% of cases (377 675 prescriptions), and dosages were increased in 19.5% of cases (175 239 prescriptions). The unique aspect of this present study is that the prescriptions of patients who had undergone intensified therapy were compared with those who had not. Most of the patients in the intensified therapy group were prescribed a combination of two types (178 901 of 554 320 visits; 32.3%) or three types (175 989 of 554 320 visits; 31.7%) of drug. However, in the therapeutic inertia group, during 67.1% (231 444 of 344 815 visits) of the visits the patients were prescribed with one or two types of medication. Academic studies or treatment guidelines for chronic diseases such as high blood pressure, dyslipidaemia, and diabetes mellitus, indicate that complications can be prevented or delayed if the disease is adequately controlled.[27] According to the treatment recommendations for type 2 diabetes from the Taiwan Diabetes Society,[28] prescribing a low-dose combination of drugs rather than a high dose of a single type of drug is more effective in lowering blood glucose and alleviating the side-effects of the medications.

This present study had several limitations. First, the study population was highly specific, focusing on the DM-P4P population rather than the entire population of patients with diabetes mellitus in Taiwan.[6] A previous study reported that patients who present with comorbidities or severe diseases are more likely to be excluded from DM-P4P programmes.[12] Secondly, the study was unable to collect data on patient adherence to the prescribed therapy. Thirdly, the study concentrated on whether physicians chose to intensify treatment for poorly controlled blood glucose levels through the use of hypoglycaemic drugs. Other measures of health care such as the risk of hypoglycaemia, type of drugs selected, increase in dosage, dietary habits of patients, and referral to care teams were not considered in this study.[6] Nevertheless, the large patient population in the validated nationwide database should be considered as a representative sample, and should thus provide a reliable clinical representation of diabetes care in routine practice in Taiwan.

In conclusion, this is the first study in Taiwan that has linked HbA_{1c} results to antidiabetic drug prescribing patterns. By analysing changes in prescriptions before and after HbA_{1c} test results, this present study sought to determine whether physicians modified prescriptions within 120 days of receiving abnormal HbA_{1c} results (i.e., >7%). These findings suggest that changes in drug prescriptions for patients with poorly controlled blood glucose levels could be used as an indicator of health care quality. For patients with HbA_{1c} over 7%, a high proportion of those in the intensified therapy group were prescribed a combination of drugs, indicating that these patients were receiving adequate clinical care. In the therapeutic inertia group, however, the study observed that in many cases only a single type of hypoglycaemic drug was prescribed or the dosage remained unchanged. Further studies are necessary to clarify the relationship between

therapeutic inertia and efforts to maintain glycaemic control.

Author contributions

The conception and design of the study, or acquisition of data, or analysis and interpretation of the data were performed by L.Y.H., W.Y.S., M.C.Y., H.L.Y., S.S., and M.S.L.

Declaration of conflicting interests

The authors declare that there are no conflicts of interest.

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