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# Trace analysis of therapeutic inertia and subsequent hemoglobin A1c outcomes in a 2-year cohort study

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**Abstract. – OBJECTIVE: Our understanding of therapeutic inertia in diabetes care is incomplete in terms of an assessment across a nationwide population. The key objectives of this investigation were to measure therapeutic inertia and link this phenomenon to the important surrogate outcome of hemoglobin A1c (HbA1c) control in a nationwide cohort.**

**PATIENTS AND METHODS: We performed a retrospective cohort study over 18 months. Laboratory and prescription data were collected for 41,948 patients (women: 53.1%) with diabetes who had at least two HbA1c results. The association between treatment intensity and glycemic control, using the change in HbA1c during the observation period, and whether the HbA1c outcome was greater than 9% were examined.**

**RESULTS: Among the patients who exhibited a secondary HbA1c result exceeding 9%, 8,630 (78.26%) had undergone intensified therapy at the time of the index HbA1c measurement, and among these patients, the incidence ratio of the last HbA1c outcome exceeding 9% after 6 to 18 months was 0.779-fold (95% CI 0.728 to 0.834) greater than those who had not received intensified therapy ($p < .001$).**

**CONCLUSIONS: After tracking patient data for a particular period, we found that patients with diabetes who received intensified therapy achieved surrogate outcomes of HbA1c control that were more favorable.**

*Key Words:*
Therapeutic inertia, Intensified therapy, HbA1c, Diabetes mellitus.

## Introduction

The prevalence of diabetes mellitus (DM), a chronic disease that substantially affects mortality[1], is rapidly increasing worldwide[2]. Antihyperglycemic agents (AHAs) work by lowering glucose levels in the blood. The American Diabetes Association (ADA)[3,4] recommends all people with diabetes should participate in diabetes self-management education to facilitate the knowledge, skills, and ability necessary for diabetes self-care and states that a reasonable hemoglobin A1c (HbA1c) goal for many adults is <7%. Despite strong evidence that aggressive drug therapy can mitigate or prevent the occurrence of DM-associated complications such as microalbuminuria and macroalbuminuria[5], many physicians have not prescribed appropriate drugs for disease control, particularly for managing blood glucose levels[6]. Underuse of evidence-based medications in chronic DM care by physicians and health care providers may be partly due to therapeutic inertia (also known as benign neglect or clinical inertia)[7,8]. While the studies of therapeutic inertia in DM treatment have been documented in inpatient and outpatient settings by the U.S. Department of Veterans Affairs health system[9,10], therapeutic inertia, which is defined as a failure to initiate or intensify treatment when it is clinically indicated, has been documented for patients with diabetes who received care in outpatient settings. In our previous research[11], a total of 215,679 patients

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participated in DM-P4P between 2006 to 2008. Among the 1,527,539 HbA1c test results, the proportion of patients with HbA1c levels between 7% and 8% was 48.1% (432,305 HbA1c results), and HbA1c levels between 8% and 9% were 27.8%. In addition, for 24.1% of the cohort, the HbA1c levels were over 9%. Therapeutic inertia, which is defined as a failure to initiate or intensify treatment when clinically indicated, and HbA1c over 7% have been documented for patients with diabetes who received care in outpatient settings. Based on our previous study, the therapeutic inertia rate was around 39% in Taiwan[11].

Our understanding of therapeutic inertia and glycemic control among patients with DM is still incomplete, particularly in a nationwide population. Therefore, this study's key objectives were to measure therapeutic inertia and link this phenomenon to the important surrogate outcomes of HbA1c control in a nationwide cohort.

## Patients and Methods

### Description of the Study Population

We performed a retrospective cohort study during an 18-month period from 2006 to 2008 and included all DM pay-for-performance (DM-P4P) members aged >18 and <80 years.

### Data Sources

Several administrative databases containing information about health service utilization in Taiwan were used, including the regular National Health Insurance (NHI) claims database from the period of 2006 to 2008 and the DM-P4P database. Patient and hospital characteristics were obtained from the NHI claims database. Patient outcome data, such as HbA1c values, are reported by hospitals and entered into the P4P-specific database automatically[12]. The DM-P4P program, designed by the NHI, has been the most comprehensive, mature P4P program in Taiwan[12]. It is voluntary and offers financial incentives to P4P-participating physicians to enroll their patients with DM[12].

### Identification of Study Subjects

All patients categorized according to the International Statistical Classification of Diseases and Related Health Problems code 250 and who had logged at least four outpatient visits each year from 2006 to 2008 were selected[13,14]. This selection process increased the accuracy of diagnoses by 99.16 times compared with a selection process that included patients with one or fewer outpatient visits per year[14]. Secondary data did not include changes in insulin dosage; thus, patients using insulin prior to HbA1c tests were excluded. All patients had to meet the following criteria to be considered:

1. At least one HbA1c test result in the DM-P4P database
2. At least one "P14X" code (internal code) in the NHI claims database
3. HbA1c levels between 4% and 20%
4. Complete personal information and drug-related data.

A total of 168,876 patients with DM had HbA1c levels exceeding 7.0%, but less than 11% were entered in the DM-P4P database from 2006 to 2008 (Figure 1). Each individual HbA1c result was included in our study sample. The HbA1c levels were the focus of analysis, as each was an opportunity for the clinician to assess the patient and make an informed judgment about whether or not the medication therapy should be altered.

To be included, patients must have received at least two HbA1c results during the study period. When a patient had more than two HbA1c results 6-18 months apart, the first was selected as an index visit and the last as the outcome visit. We found that 47,566 patients were ineligible as they had only one HbA1c result; 26,178 were ineligible because the interval between the two HbA1c results was less than 6 months; and 53,148 patients were ineligible due to the interval being more than 18 months (Figure 1). The final study population comprised of 41,948 patients (Figure 1).

At any single visit, not increasing pharmacological therapy might have been appropriate; therefore, according to previous researches[11,15], the interval between the index and outcome visits was required to be between 6-18 months. The correlation between whether a patient received intensified therapy at the time of the index visit and the result at their outcome visit after a period of between 6-18 months was analyzed.

### Pharmacologic Management

Data describing a patient's medical regimen at the time of each abnormal HbA1c result (exceeding 7.0% but less than 11%) were collected, and changes in therapy were also assessed. Any change in the prescription that satisfied one of the following conditions was defined as intensi-

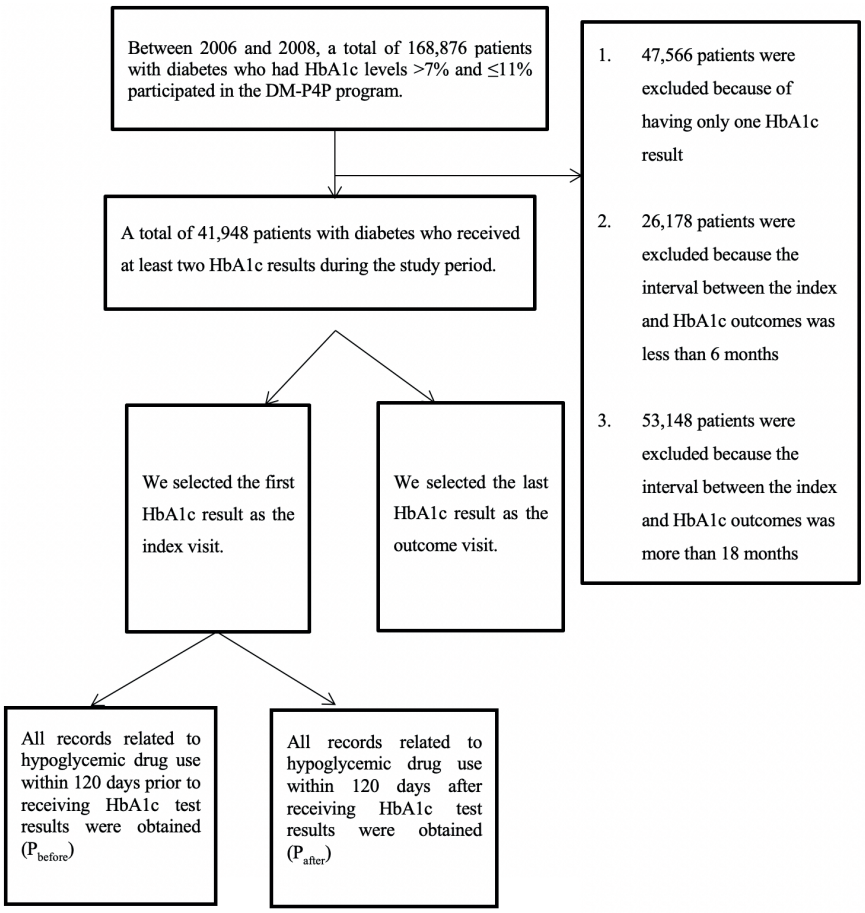


**Figure 1.** Flow chart of selected patients.

fied therapy: an increased dosage of one or more medication, a switch to another medication in a different therapeutic class, or the initiation of insulin use[11].

Because increases in medications identified in the pharmacy database may not occur on the same day as the HbA1c result, any increase within 120 days of the HbA1c result was attributed to that result; otherwise, it was assigned to the next HbA1c result[11]. A 120-day window acknowledges that physicians may order laboratory tests at one visit and subsequently contact the patient to change medications at a later time[11]. Each HbA1c result was thus classified as an antiglycemic medication "increase" or "no increase"[11]. Detailed dosage information and dose adjustments were collected for all glycemia-related medicines[11]. Glycemia-related medicines were grouped based on World Health Organization ATC codes into insulin (ATC codes: A10AB, A10AC, A10AD, A10AE) and 16 major therapeutic classes of oral antihyperglycemic agents: A10BB (sulfonamides, urea derivatives), including A10BB01 to A10BB12 (glibenclamide, chlorpropamide, tolazamide, glibenclamide, gliquidone, gliclazide, glimepiride); A10BD02 (metformin and sulfonamides); A10BA03 (buformin); A10BD03 (metformin and rosiglitazone); A10BF01 (acarbose); A10BG02 (rosiglitazone); A10BG03 (pioglitazone); A10BX01 (guar gum); A10BX02 (repaglinide); and A10BX03 (nateglinide)[16].

### Statistical Analysis

The association between treatment intensity and the two outcome measures of glycemic control was used. A linear regression model was used to explain the change in HbA1c level between the index and outcome visits where a negative regression coefficient represented a decrease or improvement in HbA1c over time, and a positive one represented an increase or worsening in HbA1c over time. In addition, a logistic regression model was used to explain the

dichotomous outcome denoted as "outcome visit HbA1c > 9%" (yes or no), adjusting for the index visit HbA1c. In both models, outcomes were adjusted for baseline patient factors, physician factors, hospital factors, age, sex, comorbidities[17], or severity/complications, as well as index HbA1c result, specialization and experience of attending physicians, and accreditation level of the medical institution[17].

The chronic illness with complexity (CIC) method was adopted to adjust for comorbidities among patients suffering from multiple chronic diseases[18]. Diabetes-related complexities were ignored because they comprised only three types of diabetes complications[12]. The diabetes complications severity index (DCSI) was used, and the number of comorbidities using CIC calculated[18,19]. All analyses were performed using SAS version 9.1.

### Ethical Committee Approval and Informed Consent

This study was approved by the Research Ethics Committee of National Taiwan University Hospital, Taiwan (no. 201203010RIC). Signed informed consent was not required because we used anonymized data and did not involve any human experimentation.

## Results

In 41,948 case studies, 6-18 months elapsed between the HbA1c index and outcome measurements, thus meeting the inclusion criteria. Most had a DCSI of 0 (91.7%, n = 38,466) and a CIC of 0 (95.4%, n = 40,005; Table I). The HbA1c outcome measurements were divided into two categories: (1) outcome HbA1c exceeding 9% or

**Table I.** Baseline characteristics of patients with poorly controlled diabetes who were tracked over an interval of 6-18 months.

| Variables | Outcome N (%) | | | | |
|---|---|---|---|---|---|
| | Total sample (n = 41,948) | HbA1c ≤ 9% (n = 30,921) | HbA1c > 9% (n = 11,027) | *p*-value | Change in HbA1c ≤ 0 (n = 21,087) |
| Age | | | | | |
| < 40 years | 1,885 (4.5%) | 1,225 (3.96%) | 660 (5.99%) | 0.000*** | 980 (4.65%) |
| 40-65 years | 25,029 (59.7%) | 17,933 (58.00%) | 7,096 (64.35%) | 0.000*** | 12,325 (58.45%) |
| 65-80 years | 15,034 (35.8%) | 11,763 (38.04%) | 3,271 (29.66%) | 0.000*** | 7,782 (36.90%) |
| Sex | | | | | |
| Male | 19,660 (46.9%) | 14,575 (47.14%) | 5,085 (25.86%) | 0.065 | 9,984 (47.35%) |
| DCSI score (DM severity) | | | | | |
| 0 | 38,466 (91.7%) | 28,429 (91.94%) | 10,037 (91.02%) | 0.003** | 19,270 (91.38%) |
| 1 | 2,107 (5.0%) | 1,521 (4.92%) | 586 (5.31%) | 0.103 | 1,094 (5.19%) |
| 2 | 1,179 (2.8%) | 836 (2.70%) | 343 (3.11%) | 0.026* | 619 (2.94%) |
| 3 | 139 (0.3%) | 98 (0.32%) | 41 (0.37%) | 0.389 | 75 (0.36%) |
| 4+ | 57 (0.1%) | 37 (0.12%) | 20 (0.18%) | 0.131 | 29 (0.14%) |
| CIC count (DM comorbidity) | | | | | |
| 0 | 40,005 (95.4%) | 29,483 (95.35%) | 10,522 (95.42%) | 0.761 | 20,079 (95.22%) |
| 1 | 1,841 (4.4%) | 1,363 (4.41%) | 478 (4.33%) | 0.747 | 945 (4.48%) |
| 2 | 95 (0.2%) | 70 (0.23%) | 25 (0.23%) | 0.995 | 59 (0.28%) |
| 3 | 6 (0.0%) | 5 (0.02%) | 1 (0.01%) | 0.592 | 4 (0.02%) |
| 4+ | 1 (0.0%) | 0 (0.00%) | 1 (0.01%) | 0.094 | 0 |
| Steroids used | 498 (1.19%) | 371 (1.20%) | 127 (1.15%) | 0.689 | 254 (1.20%) |
| Intensified therapy at the time of index HbA1c | | | | | |
| Intensified therapy | 28,306 (67.5%) | 19,676 (63.63%) | 8,630 (78.26%) | 0.000*** | 13,142 (62.32%) |
| Medications at the time of index HbA1c | | | | | |
| Monotherapy | 6,313 (15.05%) | 5,339 (17.27%) | 974 (8.83%) | 0.000*** | 3,433 (16.28%) |
| Dual therapy | 16,923 (40.34%) | 12,806 (41.42%) | 4,117 (37.34%) | 0.000*** | 8,578 (40.68%) |
| Triple therapy | 11,191 (26.68%) | 7657(24.76%) | 3,534 (32.05%) | 0.000*** | 5,394 (25.58%) |
| Add insulin | 4,055 (9.67%) | 2496 (8.07%) | 1,559 (14.14%) | 0.000*** | 955 (9.27%) |
| Metformin as monotherapy | 2,176 (5.19%) | 1,916 (6.20%) | 260 (2.36%) | 0.000*** | 1,168 (5.54%) |

HbA1c, hemoglobin A1c.

not or (2) no change or deterioration between the index and outcome levels (Table I). The mean time interval between the index and outcome levels was 12.0 ± 3.4 months. The difference between the two HbA1c levels was also measured. Control of HbA1c was improved or unchanged in 21,087 patients (50.27%).

Among those who exhibited an outcome HbA1c level exceeding 9%, 8,630 (30.49%) underwent intensified therapy at the time of the index HbA1c measurement. Among those who exhibited an outcome HbA1c level ≤ 9%, 19,676 (69.51%) underwent intensified therapy at the time of the index HbA1c measurement.

Among those who exhibited an outcome HbA1c level exceeding 9%, regarding prescriptions of hypoglycemic agents, 4,117 patients (37.34%) were prescribed a combination of two agents, whereas 3,534 (32.05%) were prescribed a combination of three agents. In addition, 1,559 patients (14.14%) received insulin therapy. In another group that exhibited a change in HbA1c, 13,142 patients (62.32%) had undergone intensified therapy at the time of the index HbA1c.

We estimated multivariate regression models to determine whether patients with therapeutic inertia at the time of the index visit were prone to poor diabetes control (HbA1c > 9%) 6-18 months later. Patients who received intensified therapy at the index HbA1c had a lower probability (approximately 22.1% less) of having an HbA1c outcome level exceeding 9% ($p < 0.001$; Table II). Furthermore, the HbA1c outcome level had significantly declined by 0.131% between the index and the outcome visit ($p < 0.001$). More intensive therapy was associated with optimal control of HbA1c. These associations between the intensity of therapy and the degree of HbA1c control remained significant after adjusting for various baseline characteristics ($p < 0.01$). Thus, with frequent HbA1c measurements, the incidence ratio of the final HbA1c level exceeding 9% was less than 1 (Table II). For each unit increase in the HbA1c level, the incidence ratio of the HbA1c level exceeding 9% increased by 2.129-fold ($p < 0.001$) after 6-18 months of observation (Table II).

After controlling for both patient and physician factors, we found that patients in medical centers had a lower probability (approximately 14%) of having an HbA1c outcome level exceeding 9% ($p < 0.001$; Table II).

## Discussion

Therapeutic inertia is defined as the recognition of a problem but the failure to act on it[6,19]. This study, the largest population-based study of the relationship between therapeutic inertia and

**Table II.** Multivariate regression models[#] relating intensity of antiglycemic medication therapy to glycemia control.

| Variables | Change in HbA1c | | Outcome HbA1c > 9% | |
|---|---|---|---|---|
| | Coefficient | *p*-value | Odds ratio (OR) | [95% CI for OR] |
| Variables of patient | | | | |
| Therapy intensification | -0.131*** | < 0.001 | 0.779*** | [0.728,0.834] |
| Frequency of HbA1c tests per person | -0.018*** | < 0.001 | 0.972*** | [0.965,0.980] |
| Mean index HbA1c (%) | -0.610*** | < 0.001 | 2.129*** | [2.073,2.186] |
| Variables of health care providers | | | | |
| Physician's seniority | | | | |
| < 10 years | -0.246 | 0.063 | 0.587 | [0.309,1.115] |
| 10-20 years | -0.261* | 0.049 | 0.549 | [0.288,1.045] |
| 21-30 years | -0.343* | 0.012 | 0.447* | [0.230,0.869] |
| > 30 years (Reference) | - | - | - | |
| Accreditation level | | | | |
| Medical center | -0.057** | 0.002 | 0.861** | [0.779,0.952] |
| Regional hospital | -0.055*** | 0.000 | 0.883** | [0.816,0.955] |
| District hospital | -0.024 | 0.146 | 0.956 | [0.874,1.046] |
| Primary care clinic (Reference) | - | - | - | |

[#]A linear model was used when modeling outcome visit HbA1c minus index HbA1c; a negative coefficient indicates improved glycemic control. A logistic model was used to predict the odds of an outcome HbA1c > 9%; an odds ratio less than 1.0 indicates better control. HbA1c, hemoglobin A1c; CI, confidence interval. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

the two measures of glycemic control to date, examined changes in HbA1c during the observation period and whether the HbA1c outcome was greater than 9%. Our results showed that patients who received intensified therapy had improved surrogate outcomes. The final HbA1c level improved by 0.131% ($p < 0.001$) in patients who received intensified therapy at the time of the index HbA1c measurement compared with those who did not.

Previous investigations[9,20] have quantified the rate of clinical inertia in several practice settings, including academic medical centers and VA hospitals. However, data are lacking on therapeutic inertia and the association with subsequent glycemic control in nationwide populations; the studies that have been conducted are relatively small in scale[21]. In this research, either the addition of another oral antidiabetic drug (OAD), an increase in the dose of an OAD, or insulin initiation was viewed as intensification. The primary strength of this analysis is that the results provide further evidence of therapeutic inertia as well as a consistency with the outcomes of previous research. We found that increases in antiglycemic medications occurred at only 66.7% of the visits despite the fact that the median HbA1c value was 8.10 ± 1.01%.

Our approach to measuring therapeutic inertia and linking this phenomenon to the surrogate outcome of HbA1c has numerous advantages over the previous efforts[9,22,23]. Most importantly, we found that improvement in HbA1c was associated with therapy intensification, a higher baseline HbA1c, a higher frequency of HbA1c tests performed per person during the observation period, physician seniority of less than 30 years, and treatment at medical centers. We found that the accreditation level of the medical institution influenced whether the patients exhibited improvement in HbA1c over time. Patients treated at medical centers or regional hospitals were more likely to exhibit improvement in HbA1c than those treated at primary clinics ($p < 0.01$). Johnston and Ponsonby[24] reported that information systems enable patients with DM to obtain more effective health care and consultations. The availability of specialized staff may help to explain why patients are more likely to receive intensified therapy at medical centers or regional hospitals than at primary clinics[25]. Although diabetes should receive attention during every visit, studies indicate that on average, only 5 minutes are spent on diabetes care in a primary care setting[25]. Overcoming clinical inertia, at least regarding DM management, can improve glycemic control in patients[25,26]. Therefore, educational interventions must be developed to teach health care practitioners the effective strategies for reducing glucose[26,27]. We have to report some limitations. First, the study population was highly selected, with a focus on the DM-P4P population rather than the entire DM population in Taiwan. Some investigations[12,28] found that patients who presented comorbidities or diseases of greater severity were more likely to be excluded from DM-P4P programs in Taiwan. Second, because we were unable to monitor changes in daily insulin doses, we could not verify whether patients already on insulin were treated adequately. Therefore, the results of this study are not applicable to such patients. Third, we did not measure patient compliance with treatment. Fourth, faulty connections between databases led to the loss of some data. Finally, this study focused on whether physicians chose to intensify therapy that involved using hypoglycemic drugs when treating a patient with poorly controlled blood sugar levels. We did not include information related to potential drug overdoses, side effects, or hypoglycemia risk.

Despite these limitations, the large patient population obtained from the independent and validated nationwide NHI claims database provided a clear clinical picture of DM control in routine practice.

## Conclusions

After tracking patients for 6-18 months, we found that those with DM who received intensified therapy achieved improved HbA1c control. Most importantly, this method of repeated HbA1c measurements correlated with favorable prognoses because patients who received intensified therapy achieved comparatively enhanced glucose control. Establishing a relationship between the process and prognostic indicators was crucial for evaluating treatment efficacy. This relationship further verified the validity of the repeated measurements of the effect of intensified therapy, as employed in this study, indicating that this research identified a critical aspect of DM management. Our results also emphasized that interventional methods for improving health care should focus on addressing therapeutic inertia.

### Conflict of Interest
The Authors declare that they have no conflict of interests.

### Acknowledgements
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### Ethical Committee
This study was approved by the Research Ethics Committee of National Taiwan University Hospital, Taiwan (no. 201203010RIC).

### Informed consent
Signed informed consent was not required because this study used anonymized data and did not involve any human experimentation.

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