

# Recent Antihyperglycemic Prescribing Trends for U.S. Privately Insured Patients With Type 2 Diabetes

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**OBJECTIVE** — The mid-1990s witnessed the introduction of new classes of medications to treat hyperglycemia of type 2 diabetes. There is evidence that these newer classes have found a place in the therapeutic armamentarium, but details of their use patterns are not known. We sought to determine whether antihyperglycemic prescribing patterns changed concurrently with new drug introductions, and whether such changes were related to changes in the underlying patient population.

**RESEARCH DESIGN AND METHODS** — A sample of U.S. privately insured patients with suspected type 2 diabetes was identified from the MarketScan Research Database over the period of 1997–2000. Patients with type 2 diabetes were identified among those continuously enrolled in the database for at least 1 year. Drug therapy episodes were defined by sequential fulfillment of prescriptions implying a continuous supply of a particular drug (or combination) of at least 30 days duration. Univariate analyses were used to explore trends over time in drug prescriptions and patient characteristics. Multivariate logistic regressions were used to isolate the impact of year from other variables on the likelihood of receiving prescriptions for a specific therapy.

**RESULTS** — A total of 232,020 unique diabetic patients had an average of 1.91 diabetes drug therapy episodes between 1997 and 2000. Monotherapy with sulfonylureas decreased, but monotherapy with thiazolidinedione, metformin, and other oral antihyperglycemics increased over time. Combinations of sulfonylureas and metformin; sulfonylureas and thiazolidinedione; metformin and thiazolidinedione; and sulfonylureas, metformin, and thiazolidinedione each increased over the time interval. Insulin monotherapy decreased, as did insulin combination therapy with sulfonylureas. The combination of insulin and metformin increased, whereas insulin and thiazolidinedione was stable. The influence of year on prescribing patterns remained highly significant ( $P < 0.001$ ) after adjusting for patient characteristics.

**CONCLUSIONS** — Antihyperglycemic prescription patterns in the U.S. have changed in recent years in parallel with, and probably as a direct result of, the introduction of different classes of medications to the marketplace. Overall, the prescribing trend has been away from monotherapy with insulins and sulfonylureas and toward combination therapies, presumably in attempts to reduce hyperglycemic symptoms and to achieve better glucose control.

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Until the 1990s, prescribers in the U.S. had only two drug therapy classes to choose from to control hyperglycemia associated with type 2 diabetes: insulins and sulfonylureas. The introduction of metformin (a biguanide, 1995), acarbose (an  $\alpha$ -glucosidase inhibitor, 1995) and troglitazone (a thiazolidinedione, 1997) in the U.S. gave clinicians the opportunity to treat hyperglycemia in ways other than by increasing circulating insulin concentration, including ways that directly impacted the underlying pathophysiology of the disease (1). More recently, other oral agents (e.g., repaglinide), new insulin analogs (e.g., lispro insulin), and thiazolidinediones (e.g., rosiglitazone) have further expanded the therapeutic arsenal (2,3). Although prescription data indicate that these new oral drugs and insulins are being widely prescribed, it is not known through systematic study how the drugs are being used together (4,5). Of particular interest is whether clinicians are now more likely to prescribe insulin in combination with other therapies, as opposed to alone, and whether combinations of oral therapies are supplanting use of oral therapies as single agents (i.e., monotherapy).

In this study, we examined prescription and linked health care claims data from a large sample of U.S. privately insured patients to determine recent trends in drug use patterns among patients with type 2 diabetes. We sought to determine whether antihyperglycemic prescribing patterns have changed in recent years and whether any changes were related to changes in the underlying patient population.

## RESEARCH DESIGN AND METHODS

### Patient selection

A sample of U.S. privately insured patients with suspected type 2 diabetes was identified from the MarketScan Research Database over the period of 1997–2000. Approximately 40 employers (20,000–

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**Abbreviations:** HMO, health maintenance organization; OAD, oral antihyperglycemic drug; POS, point of service; PPO, preferred provider organization.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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400,000 employees each) contribute to this database, which includes enrollment and medical and prescription health claim and encounter information on current employees, retirees with Medicare supplemental insurance (so-called Medi-gap), and spouses and dependants of the primary insured.

The year 2000 MarketScan database contains information on >3.5 million commercially insured lives. Three million are <65 years of age, and 500,000 >65 years of age (nearly 2 and 5%, respectively, of the corresponding U.S. commercially insured populations). Approximately 26 and 72% of the two age cohorts (<65 and >65 years, respectively) have traditional indemnity insurance (including Medicare supplemental insurance), 46 and 27%, respectively, are enrolled in preferred provider organizations (PPO) or point-of-service (POS) plans, and the remaining 28 and 1%, respectively are enrolled in capitated health plans (e.g., health maintenance organizations [HMOs]) with insurance status unknown for ~1% of the year 2000 database. The composition of MarketScan has remained relatively stable from 1998 through 2000; however, the 1997 database included many fewer Medicare patients with complete data (inpatient, outpatient, and prescription drug claims).

Patients with type 2 diabetes were identified among those continuously en-

rolled in the database for at least 1 year (>80% of the MarketScan population). Patients with diabetes were first identified by combining patients who were given a diagnosis of diabetes (ICD 250.xx, 357.2x, 362.0x, 366.41, or 648.0) during at least one inpatient admission or outpatient visit with those who did not have such a diagnosis but who were prescribed drugs used to treat diabetes, including insulin, sulfonylureas, metformin, thiazolidinediones,  $\alpha$ -glucosidase inhibitors, and meglitinides. Patients who were more likely to have type 1 diabetes were excluded by removing those who were treated with insulin monotherapy, had no record of receiving oral antihyperglycemic drugs (OADs), and also met at least one of the following additional exclusion criteria: were either <28 years of age during the year in question (1) or had a history of diabetic ketoacidosis (ICD 250.1x) (2) or were diagnosed with insulin-dependent diabetes (ICD 250.x1, 250.x3) at some time and had neither a recorded diagnosis of non-insulin-dependent diabetes (ICD 250.x0, 250.x2) nor obesity (ICD 278.00, 278.01) (3).

**Drug use patterns**

A drug therapy episode was defined as the sequential fulfillment of prescriptions implying a continuous supply of a particular

drug (or combination) of at least 30 days in duration. A drug therapy episode was defined as continuing until a new drug was introduced (1) or a gap between the end of supply days for one fulfillment and the beginning of the next fulfillment of the same drug exceeded 90 days (2). An episode was defined as “monotherapy” when only one diabetes drug was being successively filled. An episode was defined as “combination therapy” if there were at least two successive prescription fulfillments for two or more diabetes drugs concurrently. Drug monotherapies included insulin (insulin, all formulations, doses, and chemical entities available combined), sulfonylurea (all formulations, doses, and chemical entities available combined), metformin (all doses of metformin HCl combined), and thiazolidinediones (all doses and chemical entities combined). The drug combination therapies studied were: insulin and sulfonylureas; insulin and metformin; insulin and thiazolidinediones; sulfonylureas and metformin; sulfonylureas and thiazolidinediones; metformin and thiazolidinediones; and sulfonylureas, metformin, and thiazolidinediones. Patients could have more than one drug therapy episode per year.

For each drug therapy episode, statistical analyses were applied to proportions of unique patients treated. Cochran-

**Table 1—Characteristics of patients with type 2 diabetes from the MarketScan database**

| Sample characteristic               | 1997        | 1998        | 1999        | 2000        | P*      |
|-------------------------------------|-------------|-------------|-------------|-------------|---------|
| Full year continuously enrolled (n) | 2,261,467   | 2,423,024   | 3,069,455   | 3,279,155   |         |
| Type 2 diabetes (n)                 | 81,324      | 124,203     | 161,352     | 177,718     |         |
| Female (%)                          | 48.7        | 48.4        | 48.9        | 48.9        | 0.04    |
| Mean age (SD) (years)               | 59.1 (13.7) | 63.0 (13.9) | 60.9 (13.9) | 61.2 (13.8) | <0.0001 |
| Aged <50 years (%)                  | 20.4        | 15.7        | 18.9        | 18.3        | 0.20    |
| Aged 50–64 years (%)                | 50.4        | 35.2        | 41.0        | 40.8        | <0.0001 |
| Aged >65 years (%)                  | 29.3        | 49.1        | 40.1        | 40.9        | <0.0001 |
| Insurance type (%)                  |             |             |             |             |         |
| Indemnity                           | 55.5        | 42.2        | 43.8        | 40.2        | <0.0001 |
| PPO/POS                             | 18.7        | 29.7        | 38.4        | 42.8        | <0.0001 |
| Capitation/HMO                      | 10.2        | 11.5        | 16.0        | 16.3        | <0.0001 |
| Unknown                             | 15.6        | 16.6        | 1.9         | 0.7         | <0.0001 |
| ≥1 diabetes complication (%)**      | 23.9        | 28.1        | 28.4        | 29.1        | <0.0001 |
| Retinopathy†                        | 8.5         | 10.2        | 11.4        | 11.4        | <0.0001 |
| Neuropathy‡                         | 7.0         | 8.4         | 8.0         | 8.2         | <0.0001 |
| Peripheral vascular disease§        | 8.7         | 11.4        | 10.1        | 10.4        | <0.0001 |
| Nephropathy                         | 5.9         | 6.4         | 6.9         | 7.5         | <0.0001 |

\*Cochran-Armitage test; \*\*diabetes complications include: diabetic retinopathy, neuropathy, nephropathy, and peripheral vascular disease; †retinopathy defined by ICD-9-CM codes: 250.50–250.53, 361.00–361.07, 362.01–362.02, 362.14, 362.16, 362.81–362.83, 364.42, 365.44, 366.41, or (362.01–362.02 and 369.00–369.73); ‡neuropathy defined by ICD-9-CM codes: 250.60–250.63, 337.10, 354.00–355.99, 357.20, 358.10, 536.30, or 713.50; §peripheral vascular disease defined by ICD-9-CM codes: 40.00, 250.70–250.73, 443.81, 681.00–682.90, 707.10–707.90, or 785.40; and ||nephropathy defined by ICD-9-CM codes: 250.40–250.43, 581.10, 581.81, 582.10, 583.81–583.90, 584.50–584.60, 584.70, 584.80, 586.00, 587.00, or 790.60.

Armitage tests were used to test the statistical significance of trends in prescribing from 1997 to 2000. Multivariate logistic regressions were used to isolate the impact of year (1997 vs. 2000) from other variables on the likelihood of receiving prescriptions for a specific drug therapy. Because 12% of the patient sample had measurements in both 1997 and 2000, robust standard errors were calculated (6–8) to account for the potential intercorrelation between observations. In addition, parallel analyses were conducted applying multifactorial demographic weights to adjust for differences between population samples. Explanatory variables included year (1997 vs. 2000), sex, insurance type (indemnity, PPO/POS, or HMO), age (<50, 50–64, 65+ years), and diagnosis of specific diabetes complications. Diabetes complications were identified from insurance claims and included ICD-9-CM codes for diabetic retinopathy, neuropathy, nephropathy, and peripheral vascular disease (Table 1, see footnote).

**RESULTS**— A total of 81,324 and 177,718 patients with type 2 diabetes were identified in the 1997 and 2000 samples, respectively (3.6 and 5.4% of all continuously enrolled patients, respectively). The ratios of men to women were roughly constant over this time interval, but most other characteristics of the population varied over time, with the greatest variability occurring between the 1997 sample and three other annual samples (Table 1). The reason for the differences between the 1997 sample and the other annual samples is likely explained by the much lower number of Medicare patients in the 1997 sample (see RESEARCH DESIGN AND METHODS). The 232,020 unique diabetic patients identified had an average of 1.91 diabetes drug therapy episodes between 1997 and 2000. Of these, 71% were monotherapy episodes and 29% were combination therapy episodes.

Overall, use of any insulin therapy decreased from 1997 to 2000 (by ~16%), and use of any OAD increased (by ~9%). Whereas overall OAD monotherapy remained stable over time (at ~44% of all drug therapy episodes), monotherapy with sulfonylureas decreased, and monotherapy with thiazolidinediones and metformin increased. Combinations of sulfonylureas and metformin; sulfonylureas and thiazolidinediones; metformin

and thiazolidinediones; and sulfonylureas, metformin, and thiazolidinedione each increased over the time interval; combinations that included thiazolidinediones increased relatively more (all  $P < 0.001$ ) (Table 2).

Insulin monotherapy decreased 29% ( $P < 0.001$ ) from 1997 to 2000, whereas combinations of insulin and any OAD increased 2% ( $P = 0.06$ ), and combinations of insulin and metformin increased 40% ( $P < 0.001$ ). The increase in insulin combination with metformin appeared to account for most of the increase in insulin combinations with OADs in this time interval, as insulin and thiazolidinedione was relatively stable ( $P = 0.07$ ) and insulin and sulfonylureas decreased ( $P < 0.001$ ) (Table 2). Although for most of the analyses insulin was considered a single drug class, we also determined the distribution of insulin types in 1997 and 2000 to explore whether there were changes within the insulin category. There were small reductions in use of regular- and intermediate-acting insulins, stable use of regular-intermediate insulin mixtures, and increases in use of basal (i.e., long-acting) insulin and rapid-acting insulin analog (i.e., lispro). Of these changes, the

most pronounced was the use of rapid-acting insulin. In 1997, 6.9% of patients receiving insulin were prescribed rapid-acting insulin, compared with 17% in 2000.

In logistic regression analyses of each drug category, holding the effects of patient characteristics (i.e., age, sex, insurance type, and diabetes complications) constant, the net effect of year was highly significant (Table 3) ( $P < 0.0001$  for all drug therapies tested). That is, had patients from the 2000 sample shared all of the same observable characteristics with patients from 1997, the odds of a patient being treated with a particular drug regimen would have changed. For example, the odds of being treated with insulin (alone or in combination) or sulfonylurea (alone or in combination) in 2000 would have been 27 and 18% lower, respectively, than in 1997. Similarly, the odds of being treated with insulin monotherapy decreased by 40% over this interval, whereas the odds of being treated with insulin combination therapy increased by 11% (data not shown). In contrast to the general declines in insulin and sulfonylurea prescribing over time, the odds of being treated with metformin (alone or in

**Table 2—Trends in prescription drug use (1997–2000) among patients with type 2 diabetes from the MarketScan database**

| Type 2 diabetic patients with $\geq 1$ drug therapy episode (%) | 1997 | 1998 | 1999 | 2000 | <i>P</i> * |
|---|------|------|------|------|------------|
| Any insulin therapy   | 21.6 | 20.0 | 19.2 | 18.1 | <0.0001    |
| Insulin   | 18.3 | 15.5 | 14.5 | 13.0 | <0.0001    |
| Monotherapy   |      |      |      |      |            |
| Insulin Plus Any OAD  | 5.8  | 5.8  | 5.9  | 5.9  | 0.06       |
| INS + S   | 2.1  | 1.6  | 1.5  | 1.3  | <0.0001    |
| INS + M   | 1.5  | 1.4  | 1.9  | 2.1  | <0.0001    |
| INS + T   | 2.5  | 2.9  | 2.5  | 2.6  | 0.07       |
| Any OAD therapy   | 49.2 | 52.5 | 52.0 | 53.5 | <0.0001    |
| OAD monotherapy   | 43.7 | 45.4 | 44.0 | 43.7 | <0.0001    |
| S   | 35.2 | 34.3 | 29.9 | 26.1 | <0.0001    |
| M   | 8.2  | 9.7  | 12.2 | 14.2 | <0.0001    |
| T   | 2.2  | 3.2  | 3.4  | 5.4  | <0.0001    |
| S + M   | 10.9 | 12.1 | 13.1 | 13.5 | <0.0001    |
| S + T   | 1.5  | 2.9  | 3.0  | 4.1  | <0.0001    |
| M + T   | 0.2  | 0.5  | 0.9  | 1.7  | <0.0001    |
| S + M + T   | 0.5  | 1.2  | 1.7  | 3.0  | <0.0001    |

\**P* value from Cochran–Armitage test across years 1997–2000. INS, insulin; M, metformin; S, sulfonylurea; T, thiazolidinedione. Note: “Any insulin therapy” and “Any OAD” do not sum to 100% because not all drug therapy combinations were investigated and patients could be counted under both “Any insulin therapy” and “Any OAD” (see RESEARCH DESIGN AND METHODS).

Table 3—Odds ratios for explanatory variables in logistic regressions for selected diabetes drug therapies

| Explanatory variables       | Any use of insulin      | Any use of sulfonylurea | Any use of metformin    | Any use of thiazolidinedione |
|-----------------------------|-------------------------|-------------------------|-------------------------|------------------------------|
| Year 2000 vs. 1997          | <b>0.73 (0.72–0.75)</b> | 0.82 (0.80–0.83)        | <b>1.84 (1.80–1.88)</b> | <b>2.43 (2.35–2.51)</b>      |
| Aged 50–64 vs. <50 years    | 0.85 (0.83–0.88)        | <b>1.72 (1.68–1.76)</b> | <b>1.31 (1.27–1.34)</b> | <b>1.42 (1.37–1.48)</b>      |
| Aged 65+ years              | 0.87 (0.84–0.91)        | <b>2.53 (2.46–2.60)</b> | 1.02 (1.00–1.06)        | 1.22 (1.17–1.27)             |
| Sex (Female)                | 0.91 (0.89–0.93)        | <b>1.28 (1.26–1.30)</b> | 1.05 (1.03–1.07)        | 1.06 (1.04–1.09)             |
| Neuropathy                  | <b>1.97 (1.90–2.03)</b> | 0.86 (0.84–0.89)        | 1.07 (1.04–1.11)        | <b>1.40 (1.34–1.45)</b>      |
| Retinopathy                 | <b>3.81 (3.70–3.92)</b> | 0.81 (0.79–0.83)        | 1.10 (1.07–1.14)        | <b>1.60 (1.54–1.66)</b>      |
| Nephropathy                 | <b>1.62 (1.56–1.68)</b> | <b>0.64 (0.61–0.66)</b> | <b>0.53 (0.51–0.55)</b> | 1.07 (1.02–1.12)             |
| Peripheral vascular disease | <b>1.73 (1.68–1.79)</b> | 0.89 (0.86–0.91)        | 0.93 (0.90–0.96)        | 1.18 (1.13–1.22)             |
| PPO/POS                     | 0.97 (0.94–0.99)        | 1.10 (1.08–1.12)        | 1.10 (1.07–1.12)        | 0.93 (0.91–0.96)             |
| Capitation/HMO              | 0.92 (0.89–0.96)        | <b>1.29 (1.26–1.33)</b> | <b>1.26 (1.22–1.30)</b> | 1.04 (1.00–1.08)             |

Data are OR (95% CI). Odds ratios >1.25 or <0.8 are in bold. ICD codes are listed in legend of Table 1.

combination) or thiazolidinedione (alone or in combination) in 2000 were 84 and 143% higher, respectively, than in 1997.

To further account for differences in the characteristics between years (particularly between 1997 and the other years), we undertook three additional sets of analyses. First, we weighted the data to national demographics. Next, we performed logistic regressions with interaction terms of year and age categories as additional explanatory variables. Finally, we also compared the samples from years 1998 and 2000, which were similar in characteristics, instead of those from 1997 and 2000. The results from all three additional analyses were similar to those presented above (data not shown) and do not change any of the inferences drawn from them.

**CONCLUSIONS**— We used a health care claims and encounters database representative of the privately insured U.S. population (MarketScan) to determine whether drug prescription patterns for type 2 diabetes have changed in recent years, along with the introduction of new drugs to treat this disease. Results of the study suggest that antihyperglycemic drug prescription patterns in the U.S. have changed in recent years in parallel with the introductions of different classes of medications to the marketplace. Overall, the prescribing trend is away from monotherapy with insulins and sulfonylureas and toward combination therapies, perhaps in attempts to reduce hypoglycemic symptoms and to achieve better glucose control. Further study will be needed to determine whether these trends persist

over time and whether they are associated with improved outcomes.

Before the introductions of metformin and acarbose in the U.S., the only OADs available for prescription were sulfonylureas. It is therefore not surprising that, with the introduction of other drug classes, use of sulfonylureas as monotherapy has declined. Some of this decline appears to be accounted for by an increasing use of other oral drugs as monotherapy. Perhaps the prescribing trends away from monotherapy with sulfonylureas to monotherapy with metformin or thiazolidinediones reflects an interest of clinicians to more directly address the underlying pathophysiology of type 2 diabetes and avoid hypoglycemia.

At the same time that sulfonylurea use as monotherapy was declining in this database population, its use in combination with metformin and thiazolidinediones was increasing. This suggests that sulfonylurea monotherapy has been supplanted in part by combinations of sulfonylureas with newer drugs, an hypothesis that is consistent with post-U.K. Prospective Diabetes Study treatment guidelines developed and promulgated by several diabetes advocacy organizations and governmental agencies that have called for more intensive glycemic control among patients with type 2 diabetes in the U.S. since 1999 (9). Thus, there is evidence that clinicians are beginning to accept the notion that combination therapies will be useful for achieving glycemic targets.

Similar to the declining use of monotherapy with sulfonylureas, use of insulin monotherapy declined during the study

interval. Use of insulin in combination with metformin increased, whereas other combinations with insulin either decreased (insulin and sulfonylureas) or were relatively stable (insulin and thiazolidinediones). The most likely explanation for this observation is that the combination of insulin and metformin is viewed most favorably from a benefit/risk perspective compared with the other insulin plus OAD combinations. The fact that insulin is being used less as monotherapy and more often in combination with metformin, beginning in 1999, is also consistent with the above-mentioned changes in treatment guidelines for type 2 diabetes.

Several interesting associations between drug prescriptions and disease characteristics were uncovered during this study that could serve as internal validation of our other findings. For example, there was a clear inverse relationship between nephropathy and the prescribing of metformin and sulfonylureas. It is well known that use of metformin and sulfonylureas in patients with renal insufficiency may be hazardous, increasing the risks of lactic acidosis with the former and hypoglycemia with the latter (1,2). Therefore, the apparent aversion to prescribing these drugs among patients with nephropathy would be expected. The association of insulin prescribing with retinopathy also deserves commentary. Such an association has been described repeatedly and has been confirmed in controlled clinical trials (10). The phenomenon is predominant among patients with retinopathy that preexists insulin therapy and may be related to an increase

in circulating IGF-1 levels that accompanies intensive glycemic control (10,11). While the association found here is supportive of the known causal link between intensive insulin therapy and worsening of retinopathy, the current study design does not allow determination of the temporal relationship between onset of retinopathy and insulin use in this population.

An advantage of the MarketScan database over others that only track prescription fills is that it allows identification of type of disease (from insurance claims) and can be used to determine whether certain other patient characteristics, such as age and sex, influence prescribing. Because individual patients' prescription fills are recorded, therapies prescribed concurrently (and presumably used in combination) can be ascertained, providing information on actual drug use patterns as opposed to individual drug prescription trends. The large sample size (over 3 million lives continuously enrolled in 2000) and diverse data sources provide for a representative sampling of the U.S. insured population.

Several important limitations of this study are worthy of mention. The algorithm we used to identify patients with type 2 diabetes is imperfect. It was designed to reduce the likelihood of including typical type 1 diabetic patients in the sample, so that our findings would be specific to type 2 diabetes prescribing trends. However, the algorithm likely identifies fewer patients with type 2 diabetes than actually exist within the database, as it excludes undiagnosed patients and those that did not receive a diagnosis or prescription in the period of 1997–2000. In addition, nonobese patients with type 2 diabetes who were receiving insulin monotherapy and were diagnosed as insulin dependent were also excluded. An unknown proportion of those who were classified as having type 2 diabetes and included in the analyses actually have la-

tent autoimmune diabetes of adulthood (LADA), as measurements of relevant antibodies were not available. Second, the study was retrospective and the hypotheses tested were exploratory. No definitive conclusions can be drawn. Third, reliance on ICD-9 codes to identify patients with diabetes complications is imperfect; many patients who have such complications will be missed. Finally, the MarketScan database, while likely representative of the U.S. population that is covered by employer-sponsored commercial insurance, is likely not representative of the entire U.S. population, as it excludes the unemployed, uninsured, and those receiving Medicaid and Medicare without supplemental insurance. Generalizations beyond the commercially insured population may be inappropriate.

In summary, the results of our study suggest that antihyperglycemic drug prescription patterns in the U.S. have changed in recent years in parallel with, and probably as a direct result of, the introductions of different classes of medications to the marketplace. Overall, the prescribing trend has been away from monotherapy with insulins and sulfonylureas and toward combination therapies, presumably in attempts to reduce hyperglycemic symptoms, directly impact the underlying disease pathogenesis, and achieve better glucose control.

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