Treatment Deintensification Is Uncommon in Adults With Type 2 Diabetes Mellitus
A Retrospective Cohort Study

Finlay A. McAlister, MD, MSc; Erik Youngson, MMath; Dean T. Eurich, BSP, PhD

Background—Whether treatment deintensification in Americans with diabetes mellitus varies by glycemic control, health status, and calendar year (before/after February 2008 when safety concerns about intensive glucose control were reported in the ACCORD trial [Action to Control Cardiovascular Risk in Diabetes]) is unclear.

Methods and Results—We defined deintensification as discontinuation or dosage decrease of at least 1 glycemic medication without addition of, or uptitration of, another agent in the 120 days after the index glycosylated hemoglobin (HbA1C) measurement. Of 99,694 individuals (mean age 54 years) in this retrospective cohort study being actively treated for new diabetes mellitus (50% 1 drug, 33% 2 drugs, and 17% ≥3 drugs), 12,921 (13.0%) had HbA1C <6% after 1 year, 19,670 (19.7%) had HbA1C 6.0% to 6.4%, 35,012 (35.1%) had HbA1C 6.5% to 7.5%, and 32,091 (32.2%) had HbA1C >7.5%. Glycemic therapy was deintensified in 18.3% of patients (21.2% of frail patients, 19.4% of those with multiple comorbidities, and 17.7% of otherwise healthy patients) with no gradient across glycemia levels (20.6% of those with HbA1C<6%, 17.3% of those with HbA1C 6.0%–6.4%, 17.7% of those with HbA1C 6.5%–7.5%, and 18.6% of those with HbA1C>7.5%). Similar proportions were seen even after exclusion of 26,985 patients being treated with metformin monotherapy: 23.3%, 20.4%, 20.3%, and 20% across the HbA1C strata. Therapy was deintensified in 22.5% of patients with index HbA1C <6.0% before February 2008 compared with 19.5% after (P<0.001).

Conclusions—Among frail patients or those with multiple comorbidities, over three quarters with low HbA1C did not have their glycemic therapy deintensified, even after safety concerns were raised in the ACCORD trial. (Circ Cardiovasc Qual Outcomes. 2017;10:e003514. DOI: 10.1161/CIRCOUTCOMES.116.003514.)

Key Words: comorbidity • diabetes mellitus • health status • heart failure • metformin
WHAT IS KNOWN

- The benefits of intensive glucose control are uncertain for patients with type 2 diabetes mellitus and are offset by increased risks of hypoglycemic events (and, in at least one randomized trial, of mortality), especially in individuals who are elderly or have comorbidities.
- Recent audits suggest that many individuals with type 2 diabetes mellitus may be potentially overtreated in the United States, but how often treatment deintensification is undertaken by their physicians and whether this varies by glycemic control, health status, and calendar year is unknown.

WHAT THE STUDY ADDS

- Glycemic therapy was deintensified in less than one fifth of patients.
- Disintensification rates varied only slightly by health status (21% of frail patients, 19% of those with multiple comorbidities, and 18% of otherwise healthy patients) or glycemic levels (21% of those with HbA1C <6%, 17% of those with HbA1C 6.0%–6.4%, 18% of those with HbA1C 6.5%–7.5%, and 19% of those with HbA1C >7.5%).
- Therapy was deintensified less often in more recent years, even after a randomized trial reported excess mortality with very intensive glycemic control in type 2 diabetes patients (23% of patients with index HbA1C <6.0% before compared with 20% after, \( P < 0.001 \)).

Definition of Health Status

Using previously published definitions,\(^5\) we classified patients as being relatively healthy (≤2 chronic conditions), having multiple comorbidities (≥3 chronic conditions), or frail (clinical notations of malnutrition, abnormal weight loss, difficulty walking, fecal/urinary incontinence, morbid obesity, dementia, falls, decubitus ulcer, or if they had end-stage renal disease requiring dialysis, heart failure with a most responsible HF hospitalization in the past year, chronic obstructive pulmonary disease with a most responsible chronic obstructive pulmonary disease hospitalization in the past year, or metastatic cancer). We used all visits up to and including the date that the last recorded HbA1C measurement at least 1 year of coverage (to ensure that we had sufficient data to accurately classify patients’ health status at the time of the HbA1C), to have been taking at least 1 glycemic medication in the 120 days before the index HbA1C measurement (ie, the last recorded HbA1C for each patient), and to be followed for at least 120 days after the index measurement (to ensure detection of any therapy changes in response to the HbA1C value). All patients were followed prospectively until death, termination of medical insurance, or December 31, 2010, providing a maximum follow-up of 6 years.

Definition of Diabetic Control

We defined the last recorded HbA1C for each patient as their index HbA1C, and to mirror previous publications,\(^3\) we grouped HbA1C into <6%, 6.0% to 6.4%, 6.5% to 7.5%, and >7.5%.

Covariates, Including Medications

Health status and clinical covariates were all drawn from the database up to, and including, the date of the index HbA1C measurement. We used all prescriptions in the 120 days before the index date to establish pre-HbA1C therapy. For patients with multiple prescriptions within the same drug class, only the latest prescription and dose was used. We grouped glycemic therapies into 6 drug classes (Table), and combination pills were considered as belonging to both classes.

Primary Outcome (Deintensification)

We defined deintensification as discontinuation (no refill) or dosage decrease of at least 1 glycemic medication in the 120 days after the index HbA1C measurement without addition of, or an increase in dose of, another glycemic medication. Only the first prescription after the index HbA1C measurement but within the 120-day period was considered for each drug. For insulin, as prescription records cannot define daily dose of subcutaneous insulin, deintensification was defined as switching from short- and long-acting insulins to long-acting alone or discontinuing insulin. In a sensitivity analysis, we extended the post-HbA1C period for medication changes out to 180 days. In another sensitivity analysis, we excluded patients being treated with metformin monotherapy only in the 120 days before the index HbA1C.

We compared deintensification rates for patients with index HbA1C <6.0% before February 2008 (when the National Heart Lung and Blood Institute stopped the intensive glycemic control arm of the ACCORD trial [Action to Control Cardiovascular Risk in Diabetes]\(^6\) and the American Diabetes Association issued a practice advisory highlighting the mortality increase in the intensive glucose control arm) with those having an index HbA1C <6.0% after February 2008. We also compared deintensification rates for patients who were on ≥3 glycemic agents versus those on only 1 or 2 glucose-lowering therapies.

Statistical Analysis

Patient characteristics were reported as means and SDs for continuous variables and proportions for categorical variables. ANOVA and \( \chi^2 \) tests were used to compare characteristics between HbA1C tiers. The proportion of patients with medication deintensification was summarized by HbA1C tiers and health status (relatively healthy, multiple comorbidities, or frail) and compared using \( \chi^2 \) tests. Possible interaction between health status and HbA1C was tested using a logistic regression model with medication deintensification as the dependent variable and including an interaction term in addition to health status and HbA1C main effects. All statistical analyses were conducted using SAS version 9.4 (Cary, NC).

Results

Of 191,590 individuals with diabetes mellitus and HbA1C drawn after at least 12 months of follow-up, 81,113 were excluded because they were not being actively treated with medication at the time of the HbA1C assessment, and 10,783 did not have post-HbA1C pharmacy data out to 120 days (Figure 1). Of 99,694 individuals receiving drug treatment for diabetes mellitus (median time to the index HbA1C measurement 823 [interquartile range, 513–1260] days), 12,921 (13.0%) had HbA1C <6%, 19,670 (19.7%) had HbA1C 6.0% to 6.4%, 35,012 (35.1%) had HbA1C 6.5% to 7.5%, and 32,091 (32.2%) had HbA1C >7.5%. Of note, as a result of using the last recorded HbA1C for each patient, the distribution of index dates was skewed toward more recent years with 58.2%
occurring in years 2009 to 2010, 22.3% in 2007 to 2008, and only 19.5% in 2004 to 2006. Most patients were on a single (50.2%) or 2 (32.7%) glucose-lowering medications (Table). Women, older patients, and those with lower comorbidity scores were more likely to have low HbA1C levels while patients taking multiple glycemic agents were less likely to have low HbA1C levels (Table). Most patients were relatively healthy (77.3%), but 10.6% had multiple comorbidities, and 12.0% met our definition for frailty.

Overall, 18.3% of patients had their glycemic therapy deintensified after their index HbA1C with statistically significant but small magnitude differences across HbA1C levels (20.6% of those with HbA1C <6%, 17.3% of those with HbA1C 6.0%–6.4%, 17.7% of those with HbA1C 6.5%–7.5%, and 18.6% of those with HbA1C >7.5%)—Figure 2. Deintensification was more common in patients with frailty (21.2%) or multiple comorbidities (19.4%) than those who were relatively healthy (17.7%)—both P<0.0001. There was no interaction between health status and measured HbA1C in the proportion of patients who had their therapy deintensified (P=0.6). When therapy was deintensified, the drugs most commonly discontinued or decreased in dose were gliptins, sulfonylureas, and thiazolidinediones (data available on request).

Our sensitivity analysis extending the deintensification window out to 180 days post-HbA1C found identical patterns to our primary analysis but with slightly lower proportions because some patients were started on another agent or had doses increased during the extra 60 days of follow-up: 16.0% of all patients had their therapy deintensified (15.5% of relatively healthy patients, 16.9% of those with multiple comorbidities, and 18.5% of frail patients), and 18.0% of those with HbA1C <6.0%, 15.0% of those with HbA1C 6.0% to 6.4%, 15.4% of those with HbA1C 6.5% to 7.5%, and 16.5% of those with HbA1C >7.5% had glycemic therapy deintensified.

Our sensitivity analysis excluding the 26,985 patients being treated with metformin monotherapy also found similar results (Figure 3): 20.5% of all patients being treated with agents other than metformin monotherapy had their therapy deintensified (19.8% of relatively healthy patients, 21.8% of those with multiple comorbidities, and 23.5% of frail patients; 23.3% of those with HbA1C <6.0%, 20.4% of those with

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>High (&gt;7.5%)</th>
<th>Target (6.5%–7.5%)</th>
<th>Moderately Low (6.0%–6.4%)</th>
<th>Very Low (&lt;6.0%)</th>
<th>Overall</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>N=32,091</td>
<td>N=35,012</td>
<td>N=19,670</td>
<td>N=12,921</td>
<td>N=99,694</td>
<td></td>
</tr>
<tr>
<td>Age, y; mean (SD)</td>
<td>52.4 (9.8)</td>
<td>54.8 (9.4)</td>
<td>55.2 (9.4)</td>
<td>53.3 (10.3)</td>
<td>53.9 (9.7)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Female</td>
<td>13,470 (42.0)</td>
<td>15,357 (43.9)</td>
<td>9,078 (46.2)</td>
<td>6,156 (47.6)</td>
<td>44,061 (44.2)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Johns Hopkins ACG comorbidity score, mean (SD)</td>
<td>16.3 (10.9)</td>
<td>15.3 (10.7)</td>
<td>15.0 (10.8)</td>
<td>14.8 (11.2)</td>
<td>15.5 (10.9)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>No. of glycemic medications in previous 120 d, mean (SD)</td>
<td>1.9 (0.9)</td>
<td>1.7 (0.8)</td>
<td>1.5 (0.7)</td>
<td>1.4 (0.7)</td>
<td>1.7 (0.8)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>1</td>
<td>12,861 (40.1)</td>
<td>16,924 (48.3)</td>
<td>11,715 (59.6)</td>
<td>8,537 (66.1)</td>
<td>50,037 (50.2)</td>
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</tr>
<tr>
<td>2</td>
<td>11,522 (35.9)</td>
<td>11,810 (33.7)</td>
<td>5,874 (29.9)</td>
<td>3,388 (26.2)</td>
<td>32,594 (32.7)</td>
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</tr>
<tr>
<td>3</td>
<td>6,034 (18.8)</td>
<td>5,088 (14.5)</td>
<td>1,753 (8.9)</td>
<td>878 (6.8)</td>
<td>17,753 (18.3)</td>
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<tr>
<td>≥4</td>
<td>1,674 (5.2)</td>
<td>1,190 (3.4)</td>
<td>328 (1.7)</td>
<td>118 (0.9)</td>
<td>3,310 (3.3)</td>
<td></td>
</tr>
</tbody>
</table>

Glycemic medications in previous 120 d (not mutually exclusive)

- Insulin | 11,991 (37.4) | 5,820 (16.6) | 1,572 (8.0) | 904 (7.0) | 20,287 (20.3) | <0.0001 |
- Sulfonylurea | 13,940 (43.4) | 12,579 (35.9) | 5,005 (25.4) | 2,849 (22.0) | 34,373 (34.5) | <0.0001 |
- Metformin | 20,631 (64.3) | 25,523 (72.9) | 14,745 (75.0) | 9,326 (72.2) | 70,225 (70.4) | <0.0001 |
- Metformin alone | 4,228 (13.2) | 9,561 (27.3) | 769 (39.1) | 5,005 (42.6) | 26,985 (27.1) | <0.0001 |
- Metformin plus at least one other agent | 16,403 (51.1) | 15,962 (45.6) | 7,054 (35.9) | 3,821 (29.6) | 43,240 (43.4) | <0.0001 |
- Thiazolidinedione | 7,947 (24.8) | 9,997 (28.6) | 5,559 (28.3) | 3,584 (27.7) | 27,087 (27.2) | <0.0001 |
- Gliptin | 4,004 (12.5) | 4,427 (12.6) | 2,034 (10.3) | 976 (7.6) | 11,443 (11.5) | <0.0001 |
- Other | 2,366 (7.4) | 2,320 (6.6) | 1,138 (5.8) | 784 (6.1) | 6,608 (6.6) | <0.0001 |

Health status

- Relatively healthy | 24,443 (76.2) | 27,445 (78.4) | 15,271 (77.6) | 9,927 (76.8) | 77,086 (77.3) |
- Multiple comorbidities | 3,362 (10.5) | 3,737 (10.7) | 2,166 (11.0) | 1,332 (10.3) | 10,597 (10.6) |
- Frail | 4,286 (13.4) | 3,830 (10.9) | 2,233 (11.4) | 1,662 (12.9) | 12,011 (12.0) |

Numbers are displayed as n (%) unless specified otherwise. P values calculated using χ² test (categorical or binary) or ANOVA (continuous). ACG indicates adjusted case groupings.
HbA1C 6.0%–6.4%, 20.3% of those with HbA1C 6.5%–7.5%, and 20.0% of those with HbA1C >7.5%).

Before February 2008 (and the safety signal arising from the ACCORD trial), 22.5% of patients with index HbA1C <6.0% had their therapy deintensified compared with 19.5% of patients with index HbA1C <6.0% after February 2008 (P<0.001). Deintensification rates for patients with index HbA1C <6.0% did differ by number of diabetes mellitus medications: 39.0% for patients who were on ≥3 glycemic agents at the time the HbA1C was measured versus 19.1% in those taking only 1 or 2 glucose-lowering therapies (P<0.001).

Discussion

We have shown that even in frail patients or those with multiple comorbidities, clinicians infrequently reduced their glucose-lowering therapies: over three quarters did not have any downtitration of their diabetic medications despite having HbA1C levels <6.5%. This confirms the findings from previous studies conducted in elderly patients in the Veterans’ Administration (average ages 66 and 78) or in a highly selected sample from the OptumLabs Data Warehouse (median age 58, consisting of <0.6% of all diabetic individuals in the database as only those with at least 2 consecutive HbA1C <7% who survived at least 24 months after the second HbA1C were eligible). We have not only confirmed the earlier studies’ findings in a younger and less highly selected population, but we have also extended the evidence base by demonstrating that deintensification rates did not increase after the excess mortality risks with intensive glycemic control were reported from the ACCORD trial.

Overtreatment of glycemia is not harmless: it markedly increases the risk of hypoglycemia, and treatment to achieve target HbA1C levels around 6% increased all-cause mortality in the ACCORD Study. In the United States, hypoglycemia is one of the most common causes for emergency department visits, and hospitalizations for hypoglycemia are now more frequent and have a poorer prognosis than hospitalizations for hyperglycemia among older adults. The polypharmacy usually required to achieve intensive glycemic control also places the patient at higher risk of other adverse drug events or drug–drug interactions, poorer adherence with all therapies, and poorer quality of life.

Why was treatment not deintensified more often in our cohort? A recent survey of primary care providers in the VA system found that many overestimated the benefits of intensive glycemic control in older adults and were more concerned about negative repercussions from deintensifying therapy (not meeting performance targets and medicolegal ramifications) than the potential harms of tight control. These misperceptions are not surprising given the focus in guidelines, journal publications, continuing medical education events, and

Figure 1. Derivation of cohort. DM indicates diabetes mellitus.

Figure 2. Proportion of patients with deintensification of glycemic treatment, by health status and within HbA1C strata.
performance measures on mitigating undertreatment of diabetes mellitus—in fact, only 2 of 23 performance measure initiatives in diabetes mellitus addressed hypoglycemia in a recent environmental scan. This situation is not unique to diabetes mellitus: 92% of 521 American national clinical performance measures for outpatient care focus on underuse, thereby fostering a culture of more is better and inadvertently encouraging overuse. Moreover, although pay for performance programs provide incentives for meeting treatment targets, these tend to be unidirectional, and we are not aware of any such programs that currently reward treating some patients to less stringent targets. Although increased attention to the potential hazards of overtreatment through initiatives such as the Choosing Wisely movement and the Veterans Affairs Hypoglycemia Safety Initiative will improve physician awareness of this issue, educational interventions alone will be insufficient to bring about practice change. Clinical inertia is one of the main barriers to the uptake of new interventions or treatment targets in health care and will also be a barrier to deimplementation of practices proven to be inefficient or harmful. For example, we found that patients with low HbA1C levels were not more likely to have their therapy deintensified after the excess mortality in the intensive glycemic control arm of ACCORD was reported, and others have reported that stringent glycemic control in intensive care units declined little despite publication of a randomized trial demonstrating potential harm from overtreatment.

Although our study has several strengths because of the availability of detailed clinical data in a relatively large population-based sample of patients with new diagnoses of diabetes mellitus, there are some limitations to our work. First, as the clinical records may have undercaptured some comorbidities (such as dementia, chronic pain, or depression), we may have underestimated the proportion of individuals with multiple comorbidities and thus underestimated the proportion who are potentially overtreated. Second, it should be acknowledged that there may be valid clinical reasons (including patient preferences) for treating particular patients to an intensive HbA1C goal even if they have comorbidities—thus, intensive control does not necessarily mean overtreatment in all cases. Third, although we examined deintensification rates after a single HbA1C value, the VA investigators reported that rates of deintensification were similar whether they analyzed patients with ≥2 low values or just a single low HbA1C measurement. Fourth, it should be acknowledged that rates of deintensification may be higher for patients who have been treated for longer—however, this is a testable hypothesis that has not yet, to our knowledge, been explored in the literature and the literature on clinical inertia suggests that in fact therapy changes are most likely early in treatment courses. Finally, we may have underestimated rates of deintensification because we did not know whether insulin doses had been decreased or whether patients were given the same prescriptions but told to split pills or take pills less frequently.

In conclusion, deintensification of glycemic therapy did not differ appreciably across HbA1C strata, and less than one quarter of treated adults with HbA1C levels <6.5% had their glycemic medications reduced even in the presence of frailty or multiple comorbidities. This proportion did not increase even after the National Heart Lung and Blood Institute advisory issued on February 6, 2008 about excess mortality with intensive glycemic control in the ACCORD trial. Increased attention to the potential hazards of overtreatment will improve physician awareness of this issue, but deintensification of long-term therapy is the next frontier for improving care quality.

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Disclosures
None.

References
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