Published in final edited form as:

J Diabetes Complications. 2020 January ; 34(1): 107477. doi:10.1016/j.jdiacomp.2019.107477.

Intensification of medical management in type 2 diabetes: a real-world look at primary care practice

Kidmealem Zekarias, MD¹, Cynthia Davey, MS¹, Elizabeth Seaquist, MD¹

¹University of Minnesota, Minneapolis, MN

Abstract

Aims: To determine which drugs were selected to be added to metformin for patients on dual anti-diabetic medication in the management of type 2 diabetes and to assess HbA1c and BMI outcomes at 6 and 12 months after the initiation of a second anti-diabetic medication.

Methods: A retrospective chart review of electronic medical record data. Second line antidiabetic medication added to metformin between 7/1/2012 to 8/31/2017 in the primary care practice in Fairview Health System in Minnesota.

Results: 3413 patients met the selection criteria of type 2 diabetes, 18 years and older, dual antidiabetes therapy with metformin being the first prescribed. The most frequently prescribed medications added to metformin were sulfonylurea and basal insulin accounting for 51% (1724/3413) and 37% (1268/3413) respectively. Mean HbA1c reductions at 6 and 12 months among 2134 patients with baseline and follow-up HbA1c data respectively were: GLP-1 agonist (−1.3, $P < 0.001$; −1.2, $P < 0.001$), sulfonylurea (−1.1, $P < 0.001$; −0.9, $P < 0.001$), basal insulin (−1.1, $P < 0.001$; −1.0, $P < 0.001$), DPP4 inhibitor (−0.7, $P = 0.223$; −0.8, $P = 0.049$).

Patients prescribed a GLP-1 agonist had a higher mean baseline BMI ($BMI = 40.3 \text{ kg/m}^2$) and this was the only group with a statistically significant BMI reduction from baseline at 6 and 12 months (−1.5, $P = 0.049$ and −1.8, $P = 0.041$).

Conclusion and Relevance: Type 2 diabetes patients treated with sulfonylurea, basal insulin and GLP-1 agonist as an add on to metformin had significant reductions in HbA1c. Patients prescribed a GLP-1 agonist had a significant BMI reduction.

Introduction

The complexity of managing type 2 diabetes (T2DM) has increased as more and more drugs have been added to the treatment armamentarium. How to best use the available drugs

Corresponding author: Kidmealem Zekarias, MD, Assistant Professor of Medicine, Division of Endocrinology and Diabetes, Department of Medicine, University of Minnesota, Mailing address: MMC 101, 420 Delaware St SE, Minneapolis, MN 55455, kzekaria@umn.edu Fax: 612 626 3133, Phone: 612 624 5150.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Declaration of interests

The authors declare that there are no conflicts of interest. Dr Elizabeth Seaquist serves as a consultant for Lilly, Sanofi, MannKind, Zucara, and WebMD. The University that employs Dr. Seaquist has accepted research funding from Lilly to support her work.

remains a topic of great interest, as indicated by the ongoing GRADE study that will determine which of four drugs leads to the best glycemic control when added to metformin. Current treatment guidelines of the American Diabetes Association and the European Association of Diabetes recommend that metformin be the first drug used in the treatment of type 2 diabetes, but recommendations for which drugs should be added if treatment with metformin alone does not optimize glycemia control have not been straight forward. Recognized guidelines have provided suggestions for the selection of second line drugs based on patient centered characteristics like cost, risk of hypoglycemia, presence of vascular or renal disease, and weight. Six possible classes of medications can be considered if metformin is inadequate in achieving optimal glycemic control: including sulfonylureas, thiazolidinediones, dipeptidyl peptidase 4 (DPP-4) inhibitors and Sodium-glucose co-transporter-2 (SGLT2) inhibitors, glucagon-like peptide-1 (GLP-1) receptor agonist or basal insulin.

In the absence of head to head comparison among these six classes of medications, observational studies are useful in providing insight to utilization and outcomes in a real-world setting. An observational study from Italy which compared liraglutide with glimepiride added on metformin showed that liraglutide is more effective in reducing HbA1c than glimepiride.¹ Similarly, a two year retrospective study that compared exenatide to long acting insulin analogues showed a significantly higher HbA1c and BMI reduction in the veterans treated with exenatide.² A study using medical records data base, which looked at T2DM patients treated with exenatide, sitagliptin or insulin reported significant weight loss and HbA1c reduction in the exenatide group.³

In this study, we used electronic medical data to determine which drugs primary care practitioners selected to be added to metformin in the management of type 2 diabetes. We also assessed HbA1c and BMI outcomes at 6 months and 12 months after the initiation of a second anti-diabetic medication for each class of second line anti-diabetic medications. We hypothesized that primary care practitioners would be more likely to select older and less expensive drugs as a second line agent to metformin and that medications which have been shown to reduce weight such as GLP like agonist would have more impact on HbA1c and BMI.

Materials and Methods

This is a retrospective chart review of electronic medical record data of patients with T2DM who were first prescribed metformin and then a second drug for the management of diabetes. The study protocol was approved by the Institutional Review Board at the University of Minnesota.

The Informatics Consulting Service of the Clinical and Translational Science Institute of the University of Minnesota identified all patients in the Fairview Health System from Minnesota aged 18 years and older with T2DM who were prescribed metformin before 7/1/12 and then prescribed a second agent between July 1, 2012 - August 31, 2017. The Fairview system serves all communities in the 12 county Minneapolis-St. Paul metro area and communities in greater Minnesota, Northern Iowa, and Western Wisconsin. The six

classes of secondary medications included in the analysis were sulfonylureas, thiazolidinediones, basal insulin, GLP-1 agonists, SGLT-2 inhibitors, and DPP-4 inhibitors. T2DM patients who were not on metformin as a first line medication, were on more than two antihyperglycemic drugs or on multiple daily injections of insulin were excluded from the analysis.

The data was provided within a Data Shelter, which is a virtual Windows server that provides researchers a secure environment in which to work with clinical data. All viewing and manipulation of the data took place within the Data Shelter. Only authorized research personnel were given permission to log in to the Shelter to view and analyze the requested data.

The data analysis for this paper was generated using SAS software, Version 9.4, copyright © 2013 SAS Institute Inc.

Patients meeting the selection criteria described above were included in the analysis for Aim 1: to determine which drugs were selected to be added to metformin for patients on dual antidiabetic medication in the management of type 2 diabetes. Patients with baseline HbA1c and BMI data in addition to one or two follow-up HbA1c and BMI were included in analysis samples for change from baseline at 6 months and 1 year post prescription of second line anti-diabetic medication. Visit windows and visit selection specifications were defined to optimize utilization of available data while maintaining the integrity of baseline, 6 month, and 1-year visits as much as possible. The baseline visit window was defined as 2 months prior to and 2 months post prescription, selecting the visit closest to prescription date; the 6 month visit window was defined as more than 2 months to and less than 7 months post prescription, selecting the visit closest to 6 months; and the 1 year visit window was defined as more than 7 months to less than 17 months post prescription, selecting the visit closest to 12 months.

A linear mixed model using restricted maximum likelihood estimation, with unstructured covariance matrices, and specifying Tukey adjustment for multiple comparisons was run for each outcome (HbA1c and BMI) to 1) estimate mean HbA1c and BMI (95% CI) at each visit for each medication, 2) estimate mean change from baseline to 6 months and from baseline to 1 year, 3) test for mean changes over time within each medication, 4) test for between medication group differences in means at each visit, and 5) test for between medication group differences in mean changes. Linear mixed models accounted for repeated measures for each patient and utilized all available data in the estimations of means and mean changes which allowed for inclusion of patients with data at only one of the two follow-up visits. Models were run with and without adjustment for age. Subgroup linear mixed models (as described above) were run limited to patients with baseline HbA1c > 9% and baseline BMI > 40 kg/m², respectively.

Results

A total of 10,550 patients registered in the Fairview EMR had a diagnosis of type 2 diabetes, were 18 years and older on 7/1/2012, and were prescribed metformin as a first line

medication before 7/1/2012. There were 82,982 patient visit records between 7/1/2012 and 8/31/2017 for these 10,661 patients. Out of these 10,550 patients, 3413 patients met the selection criteria of being on a single second line medication added to metformin between 7/1/2012 and 8/31/2017; this is the Aim 1 analysis sample. Patients prescribed SGLT-2 were not included in the Aim 2 analysis samples for HbA1c and BMI outcomes because only 18 of these patients had baseline and follow-up HbA1c data and only 4 had baseline and follow-up BMI data. The final analysis sample for HbA1c outcomes included 2134 patients (63% of the study population) with baseline HbA1c data and follow-up HbA1c at one ($n = 876$) or both ($n=1258$) 6 month and 1-year visits as described above. The analysis sample for BMI outcomes included 1134 patients (33% of the study population) with baseline BMI recorded and follow-up BMI at one ($n = 651$) or both ($n = 483$) 6 month and 1-year visits. (Figure 1)

The majority of 3413 patients meeting the selection criteria had either sulfonylurea (51%, 1724/3413) or basal insulin (37%, 1268/3413) added as a second drug to metformin between 7/1/2012 and 8/31/2017. Fewer than 6% of patients had a GLP-1 agonist, thiazolidinedione or SGLT-2 inhibitor added to metformin in the treatment of type 2 diabetes [GLP-1 agonist 5% (162/3413); thiazolidinedione 3% (89/3413); SGLT-2 inhibitor 1% (34/3413)]. (Table 1)

Baseline, 6 months, and 1 year HbA1c were significantly higher for patients who were prescribed basal insulin in addition to metformin as compared to all other classes of medications. (Table 2). Patients on sulfonylurea, basal insulin, and GLP-1 agonists had statistically significant mean reductions in HbA1c at 6 months and at 1 year; patients on DPP4 inhibitors had a significant mean decrease in HbA1c at 1 year but not at 6 months (Table 2). Mean decreases in HbA1c at 6 months and 1 year for patients on sulfonylurea, basal insulin, and GLP-1 agonists were all significantly larger than the small and non-significant HbA1c decrease for those on a thiazolidinedione (Table 2). Models for change in HbA1c adjusted for age were similar to unadjusted results; since age was missing for 6% of patients in the HbA1c analysis sample unadjusted analysis results are reported.

A subgroup analysis limited to 544 patients with baseline HbA1c $> 9\%$ was also performed. Patients prescribed DPP4 inhibitors and thiazolidinediones were not included in the subgroup analysis due to small numbers with baseline HbA1c $> 9\%$ in these groups ($n = 9$ for DPP4 inhibitors and $n = 4$ for thiazolidinediones). Similar to the full model, patients on sulfonylurea, basal insulin, and GLP-1 agonists all had significant decreases in HbA1c at 6 months and 1 year; the mean decrease from baseline for those on sulfonylurea was significantly larger than the mean decrease for those on basal insulin at both 6 months (Mean [95% CI]: $-3.7 [-4.2, -3.1]$ vs $-3.0 [-3.4, -2.5]$) and 1 year ($-3.4 [-4.0, -2.8]$ vs $-2.8 [-3.3, -2.3]$) (Table 3).

Mean BMI for patients prescribed a GLP-1 agonist was significantly higher than the mean BMI of patients prescribed other classes of medications at baseline, 6 months, and 1 year; and only these patients were noted to have a statistically significant mean decrease in BMI at 6 months and 1 year (Table 4). The mean [95% CI] BMI loss at 6 months and 1 year for those on GLP-1 agonist were $-1.5 \text{ kg/m}^2 [-2.9, -0.003]$ and $-1.8 \text{ kg/m}^2 [-3.6, -0.03]$, respectively (Table 4). Mean reductions from baseline BMI for those on GLP-1 agonists

were also significant in the model adjusted for age. However, since age was missing for 6% of the BMI analysis sample, results for the unadjusted model are reported.

A subgroup analysis limited to 217 patients with baseline BMI > 40 kg/m² was performed to address the possibility that significant mean decreases in BMI might be attributable to regression to the mean among those with higher baseline BMI. Patients who were prescribed DPP4 inhibitors and thiazolidinediones were not included in the subgroup analysis due to small numbers in these groups having baseline BMI > 40 kg/m² (n = 4 for DPP4 inhibitors and n = 1 for thiazolidinediones). Among patients with baseline BMI > 40 kg/m², those prescribed basal insulin had significant mean decreases from baseline to 6 months (−1.3 kg/m² [−2.2, −0.3]) and from baseline to 1 year (−1.8 kg/m² [−3.0, −0.6]); patients prescribed GLP-1 agonist had a significant mean decrease from baseline to 6 months (−2.2 kg/m² [−4.2, −0.2]) but not from baseline to 1 year. Patients prescribed sulfonylurea with baseline BMI > 40 kg/m² did not have a significant mean decrease in BMI at 6 months or 1 year (Table 5).

Discussion

This chart review study using electronic medical record data in a primary care clinic setting indicated that, for patients on two drug combination management of Type 2 diabetes, most patients were prescribed sulfonylureas or basal insulin as an add on to metformin. More than 50% of our cohort were on sulfonylureas added on to metformin; this finding is similar to a population-based study which assessed trends in the relative contribution of each second-line diabetes medication class between 2011–2015 where sulfonylureas were the most prescribed second line medications added to metformin.⁴ A systematic review by Ramzan et al reported 85% of patients on a dual antidiabetic treatment received a combination of metformin and sulfonylurea.⁵

There were statistically significant HbA1c reductions at 6 months and 1 year for patients on basal insulin, GLP-1 agonist, and sulfonylurea as second line diabetic medications. Patients on DPP4 inhibitor had a significant reduction in HbA1c at 1 year only. Studies have shown that non-insulin antidiabetic medications lower HbA1c by about 0.5-1.5% compared to placebo.^{6–8} Based on these observations; guidelines recommend starting basal insulin when HbA1c is > 9%⁹. Our findings from real-world practice do not support this recommendation. In analysis limited to patients with baseline HbA1c > 9%, there were significant mean decreases from baseline in HbA1c for all medications included in the subgroup analysis, including sulfonylurea, basal insulin and GLP-1 agonists. In addition, patients on sulfonylurea and GLP-1 agonists had an average mean HbA1c reduction of 3.4% or greater at both 6 months and 1 year. The mean reduction in HbA1c from baseline for those on sulfonylurea was significantly larger than the mean decrease for those on basal insulin at both 6 months and 1 year. Our study findings suggest that treatment options for those with HbA1c > 9% might not need to be limited only to insulin.

A similar finding was reported by Wilding et al¹⁰ regarding HbA1c outcome in patients treated with sulfonylurea added to metformin. Wilding et al¹⁰ compared HbA1c outcomes between different second line medications and reported greater HbA1c reduction at 6

months and 12 months in those treated with sulfonylurea and SGLT-2 inhibitors added to metformin. There have been multiple studies which have compared GLP-1 agonists with insulin that report better HbA1c outcome for those on GLP-1 agonists.^{1–3,11,12} In the study by Diamant et al, reduction in HbA1c at 26 weeks was greater in patients taking exenatide than in those taking insulin glargine.¹¹ Another study showed that liraglutide added to metformin and sulfonylurea had significant improvement in glycemic control compared to insulin glargine.¹³

Patients prescribed a GLP-1 agonist had a significantly higher mean baseline BMI (mean BMI = 40.3 kg/m²) compared to patients prescribed the other classes of medications. This was the only group with significant BMI reduction at 6 months and 1 year. In a subgroup analysis limited to patients with baseline BMI > 40 kg/m², patients prescribed basal insulin had a significant mean decrease in BMI at 6 months and 1 year whereas patients prescribed a GLP-1 agonist had a significant decrease at 6 months only. The significant decrease in BMI for those on GLP-1 in the full analysis sample may be attributable, in part, to regression to the mean. Other studies have documented weight benefit outcomes of GLP-1 agonists. In a trial that examined the impact of 3 mg of liraglutide on weight loss over a 56 weeks period of time, the mean BMI difference in the liraglutide vs placebo group was –2 kg/m² (95% CI; –2.2 to –1.9)¹⁴. The mean [95% CI] BMI reduction for patients treated with GLP-1 agonist at 1 year in our study was –1.8 kg/m² [–3.6, –0.03]. Other studies^{15–18} which compared GLP-1 agonists with other second line therapies as an add on to metformin showed greater reductions in HbA1c and weight in those treated with GLP-agonists.

In summary, we found that sulfonylurea and basal insulin were the most common second-line anti-diabetic agents prescribed after metformin for Type 2 diabetes patients in our primary care population in Minnesota. Patients who were prescribed GLP-1 agonist, sulfonylurea or basal insulin as a second line agent after metformin had significant mean decreases in HbA1c from baseline both at 6 months and 1 year. Subgroup analysis of those with baseline HbA1c > 9% indicated that the mean decrease in HbA1c from baseline for those on sulfonylurea was significantly larger than the mean decrease for those on basal insulin at both 6 months and 1 year. T2DM patients who were prescribed a GLP-1 agonist as a second medication after metformin had higher mean baseline BMI and experienced a significant mean reduction in BMI at 6 months and 1 year in this real-world practice setting. Subgroup analysis of those with BMI above 40 kg/m² indicated that this result might be attributable to regression to the mean for those who started out with a higher BMI.

Limitations of the study

Our study has multiple limitations, many of which are common to observational studies. The study was conducted using data from a primary healthcare from a single health system - Fairview Health System in Minnesota. The data on HbA1c and BMI at baseline, 6 months and 1 year were not complete which resulted in decreased sample sizes to evaluate change over time. The subset of patients with HbA1c or BMI data in the specified windows may not be representative of all patients on a specified medication. The actual duration on second line medications was unknown. Medication start dates and end dates were available in most but not all records. This study looked at intermediate outcomes rather than long term

outcomes based on implemented treatment strategies at a primary care setting. Comparison of second line medications was made in terms of HbA1c and BMI outcomes; however multiple variables that can affect these outcomes were not adjusted for due to the limitations in data extracted for the study. Generalizability of these results is limited because only 63% of patients who met the study selection criteria had sufficient HbA1c data for analysis and only 33% had sufficient BMI data for analysis.

Future directions: Future studies that use data collected from multiple health systems across a larger geographic area may extend the generalizability of our observations. Our study examined outcomes at 6 months and 1 year and future studies that examine longer term outcomes would advance the field.

Conclusion

Patients with type 2 diabetes who were treated with sulfonylurea, basal insulin or GLP-1 agonists as an add on to metformin had significant reductions in HbA1c. Subgroup analysis of those with baseline HbA1c > 9% indicated that the mean decrease in HbA1c from baseline for those on sulfonylurea was significantly larger than the mean decrease for those on basal insulin at both 6 months and 1 year. Patients prescribed a GLP-1 agonist had a higher mean baseline BMI and this was the only group with a significant BMI reduction from baseline at 6 months and 1 year. Subgroup analysis of those with BMI above 40 kg/m² indicated that this result might be partly attributable to regression to the mean for those who started out with a higher BMI.

Acknowledgment

The authors would like to thank the Informatics Consulting Service of the Clinical and Translational Science Institute of the University of Minnesota and the Fairview Health services. Funding was provided by institutional funds to Dr. Seaquist.

This research was supported by the National Institutes of Health's National Center for Advancing Translational Sciences, grant UL1TR002494. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health's National Center for Advancing Translational Sciences.

ABBREVIATIONS/DEFINITIONS

ADA	American Diabetes Association
AACE	American Association of Clinical Endocrinologists
AHC-IE	Academic Health Center Information Exchange
BMI	Body Mass Index
CDR	Clinical Data Repository
CTSI	Clinical and Translational Science Institute's
DPP-4	Dipeptidyl peptidase 4
GLP-1	glucagon-like peptide

GRADE	The Glycemia Reduction Approaches in Diabetes
HbA1c	glycated hemoglobin
SGLT-2	Sodium glucose cotransporter 2
TZD	thiazolidinedione
T2DM	Type 2 Diabetes

References

- Chiefari E, Capula C, Vero A, et al. Add-On Treatment with Liraglutide Improves Glycemic Control in Patients with Type 2 Diabetes on Metformin Therapy. *Diabetes Technol Ther.* 2015;17(7):468–474. [PubMed: 25844858]
- Bounthavong M, Tran JN, Golshan S, et al. Retrospective cohort study evaluating exenatide twice daily and long-acting insulin analogs in a Veterans Health Administration population with type 2 diabetes. *Diabetes Metab.* 2014;40(4):284–291. [PubMed: 25059703]
- Horton ES, Silberman C, Davis KL, Berria R. Weight loss, glycemic control, and changes in cardiovascular biomarkers in patients with type 2 diabetes receiving incretin therapies or insulin in a large cohort database. *Diabetes Care.* 2010;33(8):1759–1765. [PubMed: 20460445]
- Ackermann RT, Wallia A, O'Brien MJ, et al. Correlates of second-line type 2 diabetes medication selection in the USA. *BMJ Open Diabetes Res Care.* 2017;5(1):e000421.
- Ramzan S, Timmins P, Hasan SS, Babar ZU. Trends in global prescribing of antidiabetic medicines in primary care: A systematic review of literature between 2000-2018. *Prim Care Diabetes.* 2019;13(5):409–421. [PubMed: 31213359]
- Vasilakou D, Karagiannis T, Athanasiadou E, et al. Sodium-glucose cotransporter 2 inhibitors for type 2 diabetes: a systematic review and meta-analysis. *Ann Intern Med.* 2013;159(4):262–274. [PubMed: 24026259]
- Amori RE, Lau J, Pittas AG. Efficacy and safety of incretin therapy in type 2 diabetes: systematic review and meta-analysis. *JAMA.* 2007;298(2):194–206. [PubMed: 17622601]
- Bolen S, Feldman L, Vassy J, et al. Systematic review: comparative effectiveness and safety of oral medications for type 2 diabetes mellitus. *Ann Intern Med.* 2007;147(6):386–399. [PubMed: 17638715]
- American Diabetes A 8. Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes-2018. *Diabetes Care.* 2018;41(Suppl 1):S73–S85. [PubMed: 29222379]
- Wilding J, Godec T, Khunti K, et al. Changes in HbA1c and weight, and treatment persistence, over the 18 months following initiation of second-line therapy in patients with type 2 diabetes: results from the United Kingdom Clinical Practice Research Datalink. *BMC Med.* 2018;16(1):116. [PubMed: 30008267]
- Marso SP, Daniels GH, Brown-Frandsen K, et al. Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes. *N Engl J Med.* 2016;375(4):311–322. [PubMed: 27295427]
- Diamant M, Van Gaal L, Stranks S, et al. Once weekly exenatide compared with insulin glargine titrated to target in patients with type 2 diabetes (DURATION-3): an open-label randomised trial. *Lancet.* 2010;375(9733):2234–2243. [PubMed: 20609969]
- Russell-Jones D, Vaag A, Schmitz O, et al. Liraglutide vs insulin glargine and placebo in combination with metformin and sulfonylurea therapy in type 2 diabetes mellitus (LEAD-5 met +SU): a randomised controlled trial. *Diabetologia.* 2009;52(10):2046–2055.12. [PubMed: 19688338]
- Pi-Sunyer X, Astrup A, Fujioka K, et al. A Randomized, Controlled Trial of 3.0 mg of Liraglutide in Weight Management. *N Engl J Med.* 2015;373(1):11–22. [PubMed: 26132939]
- Overbeek JA, Heintjes EM, Huisman EL, et al. Clinical effectiveness of liraglutide vs basal insulin in a real-world setting: Evidence of improved glycaemic and weight control in obese people with type 2 diabetes. *Diabetes Obes Metab.* 2018;20(9):2093–2102. [PubMed: 29726082]

16. Aroda VR, Ahmann A, Cariou B, et al. Comparative efficacy, safety, and cardiovascular outcomes with once-weekly subcutaneous semaglutide in the treatment of type 2 diabetes: Insights from the SUSTAIN 1-7 trials. *Diabetes Metab.* 2019;45(5):409–418. [PubMed: 30615985]
17. Aroda VR, Bain SC, Cariou B, et al. Efficacy and safety of once-weekly semaglutide versus once-daily insulin glargine as add-on to metformin (with or without sulfonylureas) in insulin-naïve patients with type 2 diabetes (SUSTAIN 4): a randomised, open-label, parallel-group, multicentre, multinational, phase 3a trial. *Lancet Diabetes Endocrinol.* 2017;5(5):355–366. [PubMed: 28344112]
18. Rodbard HW, Bellary S, Hramiak I, et al. GREATER COMBINED REDUCTIONS IN HbA1C $\geq$ 1.0% AND WEIGHT $\geq$ 5.0% WITH SEMAGLUTIDE VERSUS COMPARATORS IN TYPE 2 DIABETES. *Endocr Pract.* 2019;25(6):589–597 [PubMed: 30865526]

Highlights

A retrospective chart review of electronic medical record data to determine which drugs were selected to be added to metformin for patients on dual anti-diabetic medication in the management of type 2 diabetes and to assess HbA1c and BMI outcomes at 6 and 12 months after the initiation of a second anti-diabetic medication in primary care practice in Fairview Health System, Minnesota. Sulfonylurea and basal insulin were the most common second-line anti-diabetic agents prescribed after metformin. Patients treated with sulfonylurea, basal insulin or GLP-1 agonists as an add on to metformin had significant reductions in HbA1c. Patients prescribed a GLP-1 agonist had a higher mean baseline BMI and this was the only group with a significant BMI reduction from baseline at 6 and 12 months.

Figure 1.
Flow diagram of study population

Table 1:

Number and percentage of patients prescribed each of six classes of antidiabetic medications after metformin

Classes of Medication	Number of patients	Percent
Sulfonylurea	1724	50.5
Basal Insulin	1268	37.1
GLP-1 agonist	162	4.8
DPP4 inhibitor	136	4.0
Thiazolidendione	89	2.6
SGLT-2 inhibitor	34	1.0
Total	3413	100

Table 2.

Mean HbA1c for second line medication classes at each visit interval and mean change in HbA1c over visit intervals and comparisons between second line medication classes in mean HbA1c and mean HbA1c changes

Second line Medication Class	Baseline HbA1c		6-month HbA1c		1 year HbA1c		Change in HbA1c Mean (95% CI) ¹ p-value ¹ for indicated change within each second line medication class	
	N	Mean (95% CI) ²	N	Mean (95% CI) ²	N	Mean (95% CI) ²	Baseline to 6 months	Baseline to 1 year
Sulfonylurea	1116	8.0 (7.8, 8.1) ^b	812	6.8 (6.8, 6.9) ^b	943	7.0 (6.9, 7.1) ^b	-1.1 (-1.3, -0.9) ^b P < 0.001	-0.9 (-1.2, -0.7) ^b P < 0.001
Basal Insulin	794	8.7 (8.6, 8.8) ^a	599	7.6 (7.5, 7.7) ^a	682	7.7 (7.6, 7.9) ^a	-1.1 (-1.4, -0.9) ^b P < 0.001	-1.0 (-1.2, -0.7) ^b P < 0.001
GLP-1 agonist	87	7.8 (7.4, 8.3) ^{bc}	72	6.5 (6.2, 6.8) ^b	67	6.6 (6.3, 7.0) ^b	-1.3 (-2.1, -0.6) ^b P < 0.001	-1.2 (-2.0, -0.4) ^b P < 0.001
DPP4 inhibitor	77	7.5 (7.0, 8.0) ^{bc}	55	6.81 (6.5, 7.1) ^b	63	6.7 (6.3, 7.0) ^b	-0.7 (-1.5, 0.1) ^{ab} P = 0.223	-0.8 (-1.7, -0.001) ^{ab} P = 0.049
TZD	60	7.0 (6.5, 7.5) ^c	45	6.7 (6.3, 7.1) ^b	54	6.7 (6.3, 7.1) ^b	-0.3 (-1.2, 0.6) ^a P = 1.00	-0.3 (-1.2, 0.6) ^a P = 1.00

¹ 95% confidence intervals and significance tests for mean changes in HbA1c adjusted for multiple comparisons with Tukey adjustment;

² Mean (95% CI) HbA1c at each time point estimated from a linear mixed model;

^{abc} Different superscript letters in each column represent significantly different means or mean changes adjusted for multiple comparisons with Tukey adjustment.

Table 3.

Subgroup analysis for baseline HbA1c > 9%. Mean HbA1c for three second line medication classes at each visit interval and mean change in HbA1c over visit intervals and comparisons between second line medication classes in mean HbA1c and mean HbA1c changes

Second line Medication Class	Baseline HbA1c		6-month HbA1c		1-year HbA1c		Change in HbA1c Mean (95% CI) ¹ p-value ¹ for indicated change within each second line medication class	
	N	Mean (95% CI) ²	N	Mean (95% CI) ²	N	Mean (95% CI) ²	Baseline to 6 months	Baseline to 1 year
Sulfonylurea	233	10.9 (10.7,11.1) ^b	185	7.2 (7.0, 7.5) ^b	177	7.5 (7.2, 7.8) ^b	-3.7 (-4.2, -3.1) ^b P < 0.001	-3.4 (-4.0, -2.8) ^b P < 0.001
Basal Insulin	294	11.4 (11.2,11.6) ^a	234	8.4 (8.2, 8.6) ^a	243	8.6 (8.4, 8.9) ^a	-3.0 (-3.4, -2.5) ^a P < 0.001	-2.8 (-3.3, -2.3) ^a P < 0.001
GLP-1 agonist	17	10.6 (9.9, 11.4) ^{ab}	17	7.1 (6.3, 8.0) ^{ab}	9	7.1 (5.8, 8.4) ^{ab}	-3.5 (-5.3, -1.6) ^{ab} P < 0.001	-3.5 (-5.9, -1.2) ^{ab} P < 0.001

¹ 95% confidence intervals and significance tests for m changes in HbA1c adjusted for multiple comparisons with Tukey adjustment;

² Mean (95% CI) HbA1c at each time point estimated from a linear mixed model;

^{ab} Different superscript letters in each column represent significantly different means or mean changes adjusted for multiple comparisons with Tukey adjustment.

Table 4.

Mean BMI for second line medication classes at each visit interval and mean change in BMI over visit intervals and comparisons between second line medication classes in mean BMI and mean BMI changes

Second line Medication Class	Baseline BMI		6-Month BMI		1-year BMI		Change in BMI Mean (95% CI) ¹ p-value ¹ for indicated change within each second line medication class	
	N	Mean (95% CI) ²	N	Mean (95% CI) ²	N	Mean (95% CI) ²	Baseline to 6 months	Baseline to 1 year
Sulfonylurea	551	33.3 (32.6, 34.0) ^b	345	33.2 (32.6, 33.9) ^b	435	33.3 (32.7, 34.0) ^b	-0.06 (-0.5, 0.4) ^b P = 1.00	0.03 (-0.4, 0.5) ^b P = 1.00
Basal Insulin	485	33.7 (33.0, 34.39) ^b	325	33.4 (32.7, 34.1) ^b	377	33.4 (32.8, 34.1) ^b	-0.3 (-0.7, 0.2) ^b P = 0.638	-0.2 (-0.7, 0.2) ^b P = 0.933
GLP-1 agonist	43	40.3 (37.9, 42.7) ^a	31	38.9 (36.5, 41.2) ^a	24	38.5 (36.1, 40.9) ^a	-1.5 (-2.9, -0.003) ^a P = 0.049	-1.8 (-3.6, -0.03) ^a P = 0.041
DPP4 inhibitor	27	32.4 (29.4, 35.37) ^b	17	31.6 (28.6, 34.6) ^b	22	30.9 (28.0, 33.9) ^b	-0.7 (-2.6, 1.2) ^{ab} P = 0.994	-1.4 (-3.4, 0.5) ^{ac} P = 0.455
TZD	28	31.0 (28.0, 33.9) ^b	17	31.0 (28.0, 33.9) ^b	24	30.9 (28.0, 33.8) ^b	0.03 (-1.9, 1.9) ^b P = 1.00	-0.05 (-2.0, 1.9) ^{bc} P = 1.00

¹ 95% confidence intervals and significance tests for mean changes in BMI adjusted for multiple comparisons with Tukey adjustment;

² Mean (95% CI) BMI at each time point estimated from a linear mixed model;

^{abc} Different superscript letters in each column represent significantly different mean BMI or mean changes in BMI adjusted for multiple comparisons with Tukey adjustment.

Table 5.

Subgroup analysis for baseline BMI > 40 kg/m². Mean BMI for three second line medication classes at each visit interval and mean change in BMI over visit intervals and comparisons between second line medication classes in mean BMI and mean BMI changes

Second line Medication Class	Baseline BMI		6-month BMI		1-year BMI		Change in BMI Mean (95% CI) ¹ p-value ¹ for indicated change within each second line medication class	
	N	Mean (95% CI) ²	N	Mean (95% CI) ²	N	Mean (95% CI) ²	Baseline to 6 months	Baseline to 1 year
Sulfonylurea	98	45.4 (44.2, 46.6)	64	44.5 (43.2, 45.8)	77	44.5 (43.2, 45.8)	−0.9 (−1.9, 0.1) P = 0.112	−0.9 (−2.1, 0.3) P = 0.318
Basal Insulin	99	47.1 (45.9, 48.3)	70	45.9 (44.6, 47.1)	79	45.3 (44.1, 46.6)	−1.3 (−2.2, −0.3) P = 0.002	−1.8 (−3.0, −0.6) P < 0.001
GLP-1 agonist	20	47.0 (44.4, 49.6)	17	44.8 (42.0, 47.6)	10	44.4 (41.4, 47.5)	−2.2 (−4.2, −0.2) P = 0.019	−2.5 (−5.8, 0.7) P = 0.269

¹ 95% confidence intervals and significance tests for mean changes in BMI adjusted for multiple comparisons with Tukey adjustment;

² Mean (95% CI) BMI at each time point estimated from a linear mixed model