Antihyperglycemic Medications: A Claims-Based Estimate of First-line Therapy Use Prior to Initialization of Second-line Medications

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OBJECTIVE

The American Diabetes Association recommends metformin as first-line therapy for type 2 diabetes. However, nonadherence to antihyperglycemic medication is common, and a clinician could confuse nonadherence with pharmacologic failure, potentially leading to premature prescribing of second-line therapies. We measured metformin use prior to second-line therapy initialization.

RESEARCH DESIGN AND METHODS

This retrospective cross-sectional study used unidentifiable member claims data from individuals covered from 2010 to 2015 by Aetna, a U.S. health benefits company. Beneficiaries with two physician claims or one hospitalization with a type 2 diabetes diagnosis were included. Recommended use of metformin was measured by the proportion of days covered over 60 days. Through sensitivity analysis, we varied estimates of the percentage of beneficiaries who used low-cost generic prescription medication programs.

RESULTS

A total of 52,544 individuals with type 2 diabetes were eligible. Of 22,956 patients given second-line treatment, only 1,875 (8.2%) had evidence of recommended use of metformin in the prior 60 days, and 6,441 (28.0%) had no prior claims evidence of having taken metformin. At the top range of sensitivity, only 49.5% patients could have had recommended use. Patients were more likely to be given an additional second-line antihyperglycemic medication or insulin if they were given their initial second-line medication without evidence of recommended use of metformin ($P < 0.001$).

CONCLUSIONS

Despite published guidelines, second-line therapy often is initiated without evidence of recommended use of first-line therapy. Apparent treatment failures, which may in fact be attributable to nonadherence to guidelines, are common. Point-of-care and population-level processes are needed to monitor and improve guideline adherence.

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The total annual cost of diabetes in the U.S. is $245 billion (1,2), including ~$21 billion for antihyperglycemic agents and diabetes supplies (2). Pharmacologic glycemic control lowers rates of microvascular complications, stroke, and myocardial infarction (3,4) and improves quality of life (5,6). The American Diabetes Association and the European Association for the Study of Diabetes recommend metformin as the most cost-effective (7) first-line therapy for type 2 diabetes, barring specific contraindications (8–10). Recent meta-analyses have supported metformin as a relatively safe and effective first-line therapy for type 2 diabetes (11,12). The 2009, 2012, and 2015 guidelines, which were in effect during the period of our study, recommend combination therapy with additional antihyperglycemic agents if monotherapy with metformin fails to achieve the specified hemoglobin A_{1c} target over 2–3 months (8–10). However, nonadherence to antihyperglycemic medication is a common reason for inadequate diabetes control (13,14) and has been linked to poor outcomes (13,15) and diminished quality of life (16). Because a clinician could confuse nonadherence with metformin failure, we explored the treatment patterns of patients who receive second-line therapy for diabetes, specifically by estimating their previous claims-based use of metformin.

RESEARCH DESIGN AND METHODS

Study Population and Data

We performed a retrospective cohort study by using unidentifiable member claims data from Aetna, a U.S. health benefits company that covers millions of beneficiaries across the country. Forty-six million unique individuals with medical claims between July 2010 and March 2015 were included in the study. Patients between 18 and 65 years old who were given a new diagnosis of and treated for type 2 diabetes between July 2010 and March 2015 were included. In the data set, each encounter was coded with up to six ICD-9 codes. Prescription drugs were reported by using the National Drug Code. We defined a washout period of 365 days to attempt to include only patients who were newly diagnosed and truly initiating antihyperglycemic medication. Therefore, we considered only those with type 2 diabetes diagnosed ≥365 days after enrollment in the insurance program. Patients were excluded if they had <180 days of follow-up after the first recorded type 2 diabetes diagnosis. The Boston Children's Hospital Institutional Review Board (Boston, MA) approved the study, granting a waiver of consent.

Case Identification

Patients were included in the study according to published and validated criteria (17). They were required to have two physician claims at least 1 day apart within 2 years or one hospitalization with the relevant diabetes ICD-9 codes (250.0x–250.7x and 250.9x, where x = 0 or 2) submitted in a claim between 1 July 2010 and 31 March 2015. To focus on patients treated for type 2 diabetes, we considered only those with claims for at least one dispensed antihyperglycemic medication for >2 weeks. Patients were excluded if they had at least one claim for pregnancy (including gestational diabetes mellitus [ICD-9 codes 640.0–679.0]) within 5 months of their first treatment claim for diabetes. Because inpatient medications are handled differently in payer claims data sets, patients with inpatient stays during the recommended use measurement periods were excluded from further analysis.

Antihyperglycemic Medications

The American Diabetes Association and European Association for the Study of Diabetes both recommend metformin as first-line pharmacologic therapy for type 2 diabetes, and all other antihyperglycemic medications are classified as second line (8–10). For each beneficiary, we defined the first-line medication as metformin and second-line medication as other antihyperglycemic agents (Supplementary Table 1). If two second-line medications were dispensed, the original and additional second-line medications were defined on the basis of the dispensed medication date. If more than one antihyperglycemic medication other than metformin was dispensed on the same day, the medication prescribed for the longer period was defined as the first second-line medication. Guideline-recommended contraindications to metformin, including heart failure, chronic obstructive pulmonary disease, liver diseases, renal diseases, and gastrointestinal adverse effects (8–10), are defined in Supplementary Table 2.

Recommended Use Measurements

We used a standard metric for adherence, proportion of days covered (PDC), defined by the Centers for Medicare & Medicaid Services as the number of days that the patient was covered by medication divided by the number of days in the measurement period (18) to assess the recommended use of first-line antihyperglycemic medication. Days of overlap between two fills counted toward the PDC but only if the two fills were of the same antihyperglycemic medication. A PDC of at least 0.80 is the accepted standard indicator of good adherence to antihyperglycemic medication (18) and has been applied in previous studies (19–21). For each individual, we calculated the PDC over a guideline-recommended 60-day period (8–10) that ended with the fill date (index date) for the first prescription of a second-line medication (PDC60) (Fig. 1). The period covered by each metformin prescription fill was defined by supply days. If patients never received metformin prior to second-line treatment or PDC60 <0.8, they were considered as having received second-line treatment without evidence of recommended use of metformin.

Because insurance claims rarely are submitted when patients obtain metformin

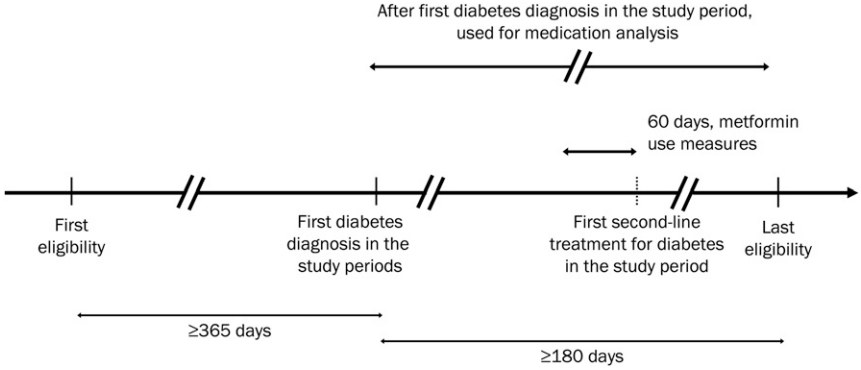

Figure 1—Study timeline showing the period used to calculate recommended use measures and medication analysis.

through a low-cost generic prescription medication program (22), we performed a sensitivity analysis across a range of usage. Among patients who received second-line treatment without evidence of recommended use of metformin, we varied the percentage of patients obtaining metformin through a low-cost generic prescription medication program and adherence to metformin prior to initialization of second-line therapy from 0 to 45% on the basis of published estimates (22), examining the effect of the possible missing claims in the claims-based medication use measurement.

Statistical Analysis

Student *t* test was used for continuous data and Pearson χ^2 test for categorical data. All statistical tests were two-sided. $P < 0.05$ was considered statistically significant. All analyses were performed by using the statistical package R version 3.2.3 (R Foundation for Statistical Computing, www.r-project.org).

RESULTS

Population Characteristics

A total of 1,500,560 individuals met the case definition of type 2 diabetes. After applying exclusion criteria, 52,544 individuals remained eligible (Fig. 2) for the retrospective cohort analysis. Of them, 3,887 (7.3%) were included on the basis of having one hospitalization with the relevant diabetes ICD-9 codes. Table 1 shows the cohort demographic characteristics. Patients who received only metformin and no other antihyperglycemic medication during the study period (29,588 [56.3%]) were older (standardized mean difference 0.123) than those who received at least one second-line antihyperglycemic medication (22,956 [43.7%]). Among patients who received at least one second-line antihyperglycemic medication, 6,441 (28.0%) had no prior claims evidence of having taken metformin.

Recommended Use of Metformin Before Receiving Second-line Medication

Of all patients given second-line medications for type 2 diabetes, only 1,875 (8.2%) had claims evidence of recommended use of metformin in the prior 60 days. Table 2 shows these patients' demographic characteristics. From 2010 to 2015, the percentage of patients with evidence of recommended use of metformin during the prior 60 days increased from 7.7 to 9.4% ($P < 0.001$). Among the 21,081 patients who received second-line medication without evidence of recommended use of metformin for the prior 60 days, 6,441 (30.6%) were not given metformin or metformin combination medications (Supplementary Fig. 1). Only a minority of these 6,441 patients had claims evidence of contraindications to metformin, including heart failure (185 [2.9%]), chronic obstructive pulmonary disease (202 [3.1%]), liver diseases (275 [4.3%]), and renal diseases (261 [4.1%]). Approximately one-third of patients (7,382 [35.0%]) received some metformin before initiation of second-line medication, but the duration of their metformin treatment prior to second-line treatment was <48 days (PDC 0.8), indicating that second-line therapy was initiated earlier than the 2 months recommended by current guidelines. Of these patients, 3,872 (52.4%) were prescribed both metformin and the second-line medication on the same day. Among patients without evidence of recommended use of metformin during the prior 60 days, only 2.6% had ICD-9 codes for metformin-related gastrointestinal adverse effects between initiating first-line and initiating second-line

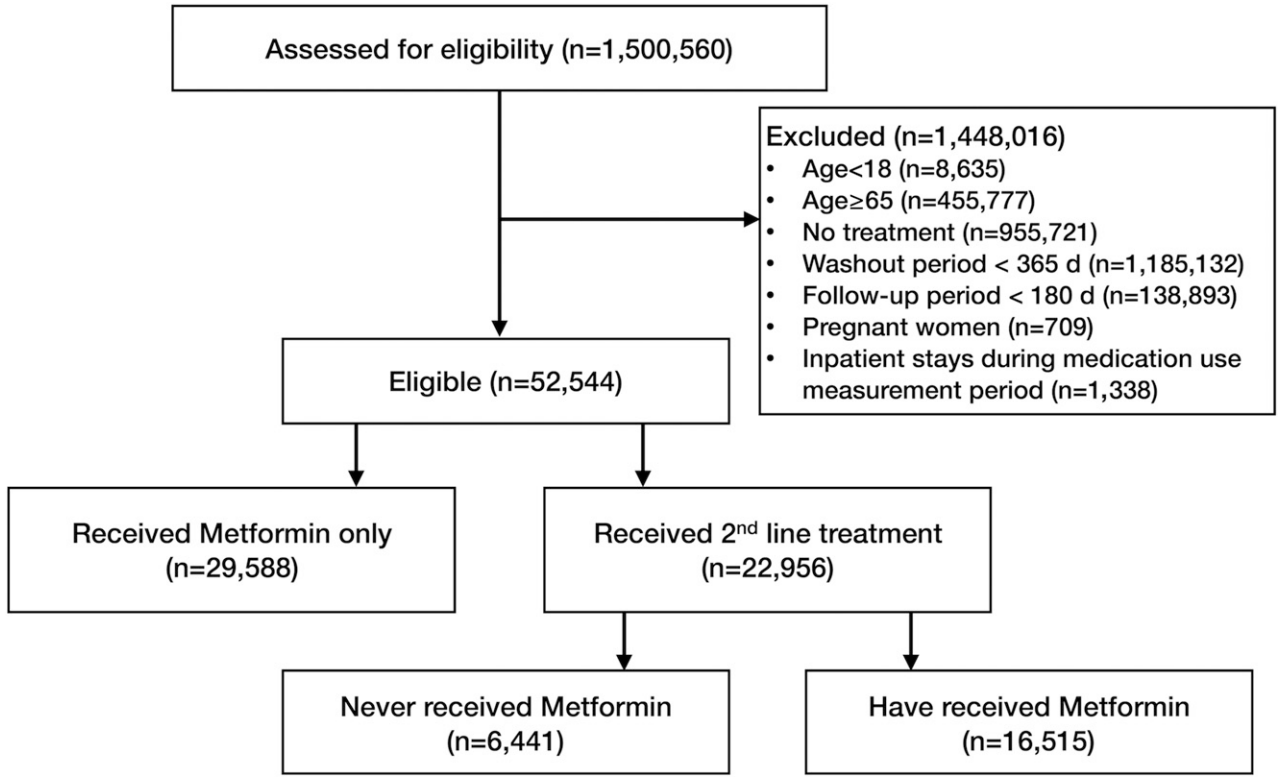

Figure 2—Study flow diagram. Exclusion criteria are not mutually exclusive. d, days.

Table 1—Demographic characteristics

	Received metformin only	Received metformin and second-line antihyperglycemic medication	Received second-line antihyperglycemic medication* only	Standardized mean difference†
Patients, *n*	29,588	16,515	6,441	
Age (years), mean (SD)	50.4 (9.2)	49.3 (9.5)	48.5 (11.5)	0.123
Male sex, *n* (%)	16,306 (55.1)	10,049 (60.8)	3,849 (59.8)	0.078
Follow-up period (days), mean (SD)	884.3 (487.7)	861.7 (494.7)	883.2 (486.1)	0.031

*Sulfonylureas, α-glucosidase inhibitors, amylin analogs, DPP-4 inhibitors, glucagon-like peptide agonists, insulin, meglitinides, sodium–glucose cotransporter 2 inhibitors, thiazolidinediones, and combination medicine. †A significance threshold of 0.1 was used to indicate differences in the mean value of the characteristic between groups.

therapy. Patients classified as nonadherers were more likely to be male ($P < 0.001$) and were dispensed additional second-line medication ($P < 0.001$).

Sensitivity Analysis

We conducted a sensitivity analysis among patients who received second-line medication for type 2 diabetes without evidence of metformin use for the guideline-recommended length of treatment of 2 months. We ranged our assumption about the percentage of patients obtaining metformin from a low-cost generic prescription medication program and having evidence of recommended use of metformin prior to initialization of second-line therapy from 0 to 45%. From the low to the high end of the range of use of low-cost generic metformin, between 8.2 and 49.5% of patients were estimated to have evidence of guideline-recommended metformin use before receiving second-line medication.

Medication Choices for Type 2 Diabetes

Beneficiaries without evidence of recommended use of metformin were more likely to be given insulin than those with evidence of recommended use (Table 2). Dipeptidyl peptidase 4 (DPP-4) inhibitors and their combination drugs were the most common branded second-line oral antihyperglycemic medications among all patient subgroups. Patients were more likely to be given an additional second-line antihyperglycemic medication or insulin (Table 2) if they were given their initial second-line antihyperglycemic medication without evidence of recommended use of metformin ($P < 0.001$).

CONCLUSIONS

A substantial fraction of patients given second-line pharmacologic treatment for type 2 diabetes did not have evidence of prior use of metformin for the guideline-recommended length of treatment of 2 months. The precise number cannot be directly measured because prescriptions filled through a low-cost generic prescription medication program are probably not represented in this data set. A previous study reported that ~30% of patients who received metformin had at least one fill through a low-cost generic prescription medication program in 2007–2011 (22). However, even at our upper estimate of 45% of patients filling prescriptions through these low-cost programs (22), less than one-half of patients started on second-line therapies have evidence of use of metformin as recommended. At the lower bound of sensitivity for use of low-cost generics, <10% have evidence of recommended use of metformin. Patients without evidence of recommended use of metformin are more likely to be male and to receive insulin or an additional second-line antihyperglycemic medication.

More than 10% of all beneficiaries starting on an antihyperglycemic medication had no claims evidence of having been prescribed metformin as a single agent or in combination with other medications. A previous study found that ~35% of patients initiating an oral antihyperglycemic medication were not started on metformin (23). Almost 15% of beneficiaries starting oral antihyperglycemic medication were

Table 2—Demographic characteristics of patients with type 2 diabetes and given second-line antihyperglycemic medication

Recommended use of metformin for 60 days*	Yes	No	*P* value
Patients, *n* (%)	1,875 (8.2)	21,081 (91.8)	
Age (years), mean (SD)	50.3 (9.2)	49.0 (10.2)	<0.001
Male sex, *n* (%)	1,064 (56.7)	12,834 (60.9)	<0.001
Follow-up period (days), mean (SD)	847.9 (490.7)	869.5 (492.5)	0.07
Dispensed additional second-line medication, *n* (%)	325 (17.3)	5,174 (24.5)	<0.001
Length of exposure of metformin prior to second-line therapy (days), mean (SD)	154.4 (104.2)	13.8 (40.2)	<0.001
Second-line agents			
Insulin, *n* (%)	161 (8.6)	5,609 (26.6)	<0.001
Generic drugs, *n* (%)	825 (44.0)	8,602 (40.8)	<0.01
Sulfonylureas, *n*	768	8,137	
Branded drugs, *n* (%)	889 (47.4)	6,870 (32.6)	<0.001
DPP-4 inhibitors, *n*	504	3,993	
Thiazolidinediones, *n*	103	1,265	
Glucagon-like peptide agonists, *n*	166	980	

*Evidence of recommended use of metformin before receiving second-line medication (sulfonylureas, α-glucosidase inhibitors, amylin analogs, DPP-4 inhibitors, glucagon-like peptide agonists, insulin, meglitinides, sodium–glucose cotransporter 2 inhibitors, thiazolidinediones, and combination medicine) defined as a PDC of at least 0.8.

initially adherent to metformin, but were started on second-line therapy prematurely (8–10). Although the guideline allows patients with a high baseline HbA_{1c} to start with a combination of two noninsulin agents ($HbA_{1c} \geq 9\%$) or with insulin (HbA_{1c} 10–12%) (9,24), prior studies have shown that 55% of newly diagnosed patients have an $HbA_{1c} < 6.5\%$ (25), yet only 13% of patients with diabetes in the U.S. have an $HbA_{1c} > 9\%$ (26). We have found a much higher proportion of patients prescribed a second-line antihyperglycemic medication than expected (24–26).

Informatics infrastructure encouraged under the Meaningful Use program for using certified health information technology should be leveraged to boost adherence (27). Data on medications recently dispensed to the patient are readily available in real time from companies that manage pharmacy benefits or execute e-prescribing transactions. Delivery of this information to population health managers or to clinicians at the point of care through electronic health record services or third-party applications (28,29) could raise awareness of nonadherence to guidelines prior to initiation of second-line therapy. A number innovative approaches from short message service messaging (30) to electronic medication packaging (31) can improve guideline adherence.

Retrospective claims-based analyses have several limitations, including the exclusion of uninsured patients, lack of detailed clinical or behavioral information, and no out-of-pocket medication cost data (23,32). Claims data include tests and treatments billed for and medications dispensed but not the motivation for testing or prescribing medications. The medication switches or choices might represent physician or patient choice. Patient-specific clinical data and nuances that might have played a substantial role in individual clinician's choices and timing of prescription medications are not included in claims data analyses. Although, gastrointestinal adverse effects related to metformin therapy might lead to guideline nonadherence and early second-line medication initiation, we did not find evidence for gastrointestinal upset in the claims data. Because we relied on claims data, diagnosis codes of gastrointestinal adverse effects and contraindications may vary in accuracy (32). Furthermore, previous studies have found that only ~5% of patients treated with metformin discontinued metformin because of an adverse event (33–35). Importantly, although claims data indicate that certain medications were dispensed and paid for, the patient may not have been actually taken them (36). Nonetheless, a substantial amount of literature supports the use of prescription fills to monitor adherence (37).

In conclusion, as few as 8% but no more than one-half of patients given second-line pharmacologic treatment for type 2 diabetes have prior evidence of use of metformin for the guideline-recommended length of treatment of 2 months. Patients without evidence of recommended use of metformin are more likely to be male and prescribed insulin or an additional second-line antihyperglycemic medication. What may be taken as evidence of treatment failure by clinicians may instead represent failure of adherence to established treatment guidelines, which in turn may lead to the use of insulin or additional second-line medications. Point-of-care decision support and population health–level approaches should focus on improving adherence to first-line therapy.

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References

1. Zhuo X, Zhang P, Kahn HS, Bardenheier BH, Li R, Gregg EW. Change in medical spending attributable to diabetes: national data from 1987 to 2011. Diabetes Care 2015;38:581–587
2. American Diabetes Association. Economic costs of diabetes in the U.S. in 2012. Diabetes Care 2013;36:1033–1046
3. Ohkubo Y, Kishikawa H, Araki E, et al. Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with non-insulin-dependent diabetes mellitus: a randomized prospective 6-year study. Diabetes Res Clin Pract 1995;28:103–117
4. Shichiri M, Kishikawa H, Ohkubo Y, Wake N. Long-term results of the Kumamoto Study on optimal diabetes control in type 2 diabetic patients. Diabetes Care 2000;23(Suppl. 2):B21–B29
5. Wake N, Hisashige A, Katayama T, et al. Cost-effectiveness of intensive insulin therapy for type 2 diabetes: a 10-year follow-up of the Kumamoto study. Diabetes Res Clin Pract 2000;48:201–210
6. Stratton IM, Adler AI, Neil HA, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. BMJ 2000;321:405–412
7. American Diabetes Association. Standards of medical care in diabetes. Diabetes Care 2011;34(Suppl. 1):S11–S61
8. Nathan DM, Buse JB, Davidson MB, et al. Medical management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 2009;32:193–203
9. Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycemia in type 2 diabetes: a patient-centered approach: position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care 2012;35:1364–1379
10. Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycemia in type 2 diabetes, 2015: a patient-centered approach: update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 2015;38:140–149
11. Maruthur NM, Tseng E, Hutfless S, et al. Diabetes medications as monotherapy or metformin-based combination therapy for type 2 diabetes: a systematic review and meta-analysis. Ann Intern Med 2016;164:740–751
12. Palmer SC, Mavridis D, Nicolucci A, et al. Comparison of clinical outcomes and adverse events associated with glucose-lowering drugs in patients with type 2 diabetes: a meta-analysis. JAMA 2016;316:313–324
13. Pladevall M, Williams LK, Potts LA, Divine G, Xi H, Lafata JE. Clinical outcomes and adherence to medications measured by claims data in patients with diabetes. Diabetes Care 2004;27:2800–2805
14. Schectman JM, Nadkarni MM, Voss JD. The association between diabetes metabolic control and drug adherence in an indigent population. Diabetes Care 2002;25:1015–1021
15. Chang P-Y, Chien L-N, Lin Y-F, Chiou H-Y, Chiu W-T. Nonadherence of oral antihyperglycemic medication will increase risk of end-stage renal disease. Medicine (Baltimore) 2015;94:e2051
16. Gusmai L de F, Novato T de S, Nogueira L de S. The influence of quality of life in treatment adherence of diabetic patients: a systematic review. Rev Esc Enferm USP 2015;49:839–846 [in Portuguese]

17. Chen G, Khan N, Walker R, Quan H. Validating ICD coding algorithms for diabetes mellitus from administrative data. Diabetes Res Clin Pract 2010; 89:189–195
18. Centers for Medicare & Medicaid Services. Quality rating system measure technical specifications [Internet], 2015. Available from https://www.cms.gov/Medicare/Quality-Initiatives-Patient-Assessment-Instruments/QualityInitiativesGenInfo/Downloads/2016-QRS-Measure-Technical-Specifications.pdf. Accessed 15 August 2017
19. Zimolzak AJ, Spettell CM, Fernandes J, et al. Early detection of poor adherers to statins: applying individualized surveillance to pay for performance. PLoS One 2013;8:e79611
20. Shore S, Ho PM, Lambert-Kerzner A, et al. Site-level variation in and practices associated with dabigatran adherence. JAMA 2015;313:1443–1450
21. Ho PM, Lambert-Kerzner A, Carey EP, et al. Multifaceted intervention to improve medication adherence and secondary prevention measures after acute coronary syndrome hospital discharge: a randomized clinical trial. JAMA Intern Med 2014;174:186–193
22. Pauly NJ, Brown JD. Prevalence of low-cost generic program use in a nationally representative cohort of privately insured adults. J Manag Care Spec Pharm 2015;21:1162–1170
23. Desai NR, Shrank WH, Fischer MA, et al. Patterns of medication initiation in newly diagnosed diabetes mellitus: quality and cost implications. Am J Med 2012;125:302.e1–302.e7
24. Simonson G, Cuddihy R, Reader D, Bergenstal R. International Diabetes Center treatment of type 2 diabetes glucose algorithm. Diabetes Manage 2011;1:175–189
25. Pajunen P, Peltonen M, Eriksson JG, et al.; Finnish Diabetes Prevention Study. HbA(1c) in diagnosing and predicting type 2 diabetes in impaired glucose tolerance: the Finnish Diabetes Prevention Study. Diabet Med 2011;28:36–42
26. Centers for Disease Control and Prevention. A1c distribution among adults with diagnosed diabetes [Internet], 2013. Available from http://web.archive.org/web/20170717004127/https://www.cdc.gov/diabetes/statistics/a1c/a1c_dist.htm. Accessed 25 August 2017
27. Cutler DM, Everett W. Thinking outside the pillbox—medication adherence as a priority for health care reform. N Engl J Med 2010;362:1553–1555
28. Mandl KD, Kohane IS. No small change for the health information economy. N Engl J Med 2009; 360:1278–1281
29. Mandl KD, Mandel JC, Kohane IS. Driving innovation in health systems through an apps-based information economy. Cell Syst 2015;1: 8–13
30. Vervloet M, van Dijk L, de Bakker DH, et al. Short- and long-term effects of real-time medication monitoring with short message service (SMS) reminders for missed doses on the refill adherence of people with type 2 diabetes: evidence from a randomized controlled trial. Diabet Med 2014;31:821–828
31. Checchi KD, Huybrechts KF, Avorn J, Kesselheim AS. Electronic medication packaging devices and medication adherence: a systematic review. JAMA 2014;312:1237–1247
32. Sickbert-Bennett EE, Weber DJ, Poole C, MacDonald PDM, Maillard JM. Utility of International Classification of Diseases, Ninth Revision, Clinical Modification codes for communicable disease surveillance. Am J Epidemiol 2010;172: 1299–1305
33. Umpierrez G, Tofé Povedano S, Pérez Manghi F, Shurzinske L, Pechtner V. Efficacy and safety of dulaglutide monotherapy versus metformin in type 2 diabetes in a randomized controlled trial (AWARD-3). Diabetes Care 2014;37:2168–2176
34. Kirpichnikov D, McFarlane SI, Sowers JR. Metformin: an update. Ann Intern Med 2002;137:25–33
35. Florez H, Luo J, Castillo-Florez S, et al. Impact of metformin-induced gastrointestinal symptoms on quality of life and adherence in patients with type 2 diabetes. Postgrad Med 2010;122:112–120
36. Haynes RB, McDonald HP, Garg AX. Helping patients follow prescribed treatment: clinical applications. JAMA 2002;288:2880–2883
37. Brennan TA, Dollear TJ, Hu M, et al. An integrated pharmacy-based program improved medication prescription and adherence rates in diabetes patients. Health Aff (Millwood) 2012; 31:120–129