Journal of Diabetes and Its Complications 31 (2017) 1719–1727

Contents lists available at ScienceDirect

Journal of Diabetes and Its Complications

journal homepage: WWW.JDCJOURNAL.COM

A comprehensive review of the FDA-approved labels of diabetes drugs: Indications, safety, and emerging cardiovascular safety data

Evgenia Gourgari [a,b,*], Erin E. Wilhelm [b], Hamid Hassanzadeh [b], Vanita R. Aroda [c], Ira Shoulson [b]

[a] Division of Pediatric Endocrinology, Department of Pediatrics, Georgetown University Medical Center, Washington, DC, United States
[b] Program for Regulatory Science & Medicine, Georgetown University, Washington, DC, United States
[c] MedStar Health Research Institute, Hyattsville, MD, United States

ARTICLE INFO

Article history:
Received 20 February 2017
Received in revised form 24 July 2017
Accepted 7 August 2017
Available online 12 August 2017

Keywords:
Diabetes
Drug labels
Cardiovascular outcomes

ABSTRACT

Aims: FDA-approved drug labels are an important source of information for clinicians who prescribe medications for treatment of diabetes. We reviewed drug labels to (1) understand the landscape of classes of medications approved for type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM), (2) explore the indications and safety information and (3) examine their cardiovascular safety.
Methods: We searched four public references and reviewed all FDA-approved labels for "indication and usage," "adverse effects," "warnings and precautions," and "cardiovascular outcomes" from October 1982 to July 2016. We also reviewed FDA drug-safety communications from January 2015 to May 2017.
Results: The labels reveal 12 classes of medications approved for T2DM with only 2 classes approved for T1DM. There is emerging evidence about cardiovascular safety and risk reduction from diabetes medications which is now being incorporated in drug labels.
Conclusions: All currently available diabetes medications are approved for adults with T2DM with a remarkably limited number for adults with T1DM and children with T1DM or T2DM. The incorporation of emerging data on cardiovascular outcomes in FDA drug labels is expected to influence the way physicians treat patients with diabetes.

1. Introduction

Approximately 30 million American children and adults have type 1 or type 2 diabetes mellitus and the incidence keeps increasing (T1DM or T2DM).[1] Major complications of diabetes include hypertension, dyslipidemia, cardiovascular disease (CVD), stroke, blindness, kidney disease, and amputation.[2] In 2012 the estimated annual cost of diabetes in the U.S. was $245 billion mainly due to expenses related to management of diabetic complications.[3] Therefore, achieving optimal glycemic control in patients with diabetes is critical.[4,5] However, it is estimated that only 30% of adult patients with T1DM, 17% of adolescents with T1DM, and 50% of adults with any type of diabetes achieve optimal glycemic control with current management.[6] Therefore, there is a need for effective and safe medications that can improve the management of diabetes and decrease complications. The physicians refer to the drug labels as an important source of information to prescribe medications to improve glycemic control of diabetes.

Furthermore, in 2008, FDA published a Guidance for Industry recommending that new drug applications (NDAs) for diabetes should include evidence that the therapy does not increase the risk of cardiovascular events.[7]

Given the significant burden of diabetes and the importance of drug labels to guide physicians in the management of diabetes, we undertook this study to evaluate all FDA-approved medications for the treatment diabetes. The aims of this research were to (1) overview the different classes of medications that are FDA approved for use in patients with type 1 and type 2 diabetes, (2) examine the different indications for pediatric patients versus adults with diabetes, (3) review adverse events and warnings and precautions per class of drugs, and (4) investigate the labels for data on cardiovascular outcomes.

2. Methods

We searched the FDA public database of approved diabetic medications[8] and three other public references with information on FDA approved medications: WebMD,[9] CenterWatch[10] and Medscape[11]

* Corresponding author at: Georgetown University Hospital, Division of Pediatric Endocrinology, 4200 Wisconsin Avenue, N.W., 4th Floor, Washington, D.C. 20016, United States.
E-mail address: eg685@georgetown.edu (E. Gourgari).

https://doi.org/10.1016/j.jdiacomp.2017.08.005

to retrieve the label information for all diabetes medications from October 1982 to July 2016. Specifically, for the FDA public database we searched the medications listed under sections "Insulins and Diabetes Drugs Approved Between 2013–2016", "Insulins and Diabetes Drugs Approved Between 2000–2012" and "Insulins and Diabetes Drugs Approved Before 1999", which have information about drugs approved since October 1982.[8] We understand that information about diabetes drugs might be available on different places within the FDA website but we chose this method because in our opinion this was the most comprehensive list of diabetes drugs available at the FDA website. In addition, to capture information that has been released by the FDA but has not yet been included on the actual FDA label, we reviewed the FDA website for recent "drug safety communications"[12] and "press announcements"[13] published between January 1, 2015, and May 30th, 2017, for information relevant to diabetes drugs safety and cardiovascular disease.

For each drug, we searched the label under the "indications and usage" section to identify the class of drug as well as the indicated population(s) (i.e., pediatric or adult patients with T1DM or T2DM). We searched labels for the terms "cardiovascular" and "macrovascular" to determine what information on cardiovascular outcomes is available. Finally, we reviewed the "adverse reactions" and "warnings and precautions" sections of all labels and grouped adverse effects according to the specific class of drug.

3. Results

3.1. Overview: medications for the treatment of diabetes in adults and children

Overall, 74 medications (including generic), belonging to 12 different classes and in 19 different combinations, have been approved (between 1982 and 2015) to treat hyperglycemia in both type 1 and type 2 diabetes mellitus. The number of drugs per class is shown in Table 1; active substance names are shown in Table 2.

Of these medications, all 74 are approved for treatment of hyperglycemia in adults with T2DM. Only 10 medications (belonging to 2 classes) are approved for pediatric patients with T2DM: insulin and biguanide (metformin). We found 22 medications (belonging to only 2 classes) for adults with T1DM; of these, 20 are different types of insulin and 2 are amylin analogs. For pediatric T1DM, 10 medications (belonging to one class) are approved; all are different types of insulin.

Interestingly, the only insulin that is approved for pediatric T1DM, long-acting insulin glargine (under two brand names), is not approved for pediatric T2DM. Furthermore, metformin is the only oral medication currently approved to treat pediatric T2DM, although extended release (XR) metformin is not approved for pediatric T2DM.

For the medications approved for pediatric patients, we further investigated the information from clinical studies that are relative to their safety profile. All insulin types that have been approved for use in pediatric T2DM are based on safety data from clinical trials in pediatric patients with T1DM. The safety information about insulin use in pediatric T1DM does not have data for pediatric patients younger than 2 years or, in some cases, younger than 6 years. The safety data of metformin for use in pediatric patients with T2DM is based on data from pediatric patients ages 10–16 years with T2DM.

Of note, we found one medication in the CenterWatch reference that was approved in 2016, which we included in our review in an effort to make our list of diabetes drugs as current and comprehensive as possible, mindful that the FDA website under the "Insulins and Diabetes Drugs Approved Between 2013–2016" only displayed information up to December 16th 2015. We excluded two other medications approved for adult T1DM and T2DM because they are not indicated to treated hyperglycemia due to diabetes. One of these medications is a VEGF inhibitor, approved for diabetic retinopathy, and the other is glucagon, approved for hypoglycemia.

3.2. Recent safety updates from FDA

The FDA issues drug safety communications to the public and healthcare providers as new and relevant information becomes available. From January 2015 to May 2017, the FDA has issued a number of warnings about four classes of diabetes drugs.

For SGLT2 inhibitors, alerts were issued about the risk of decreased bone mineral density (September 2015) and leg or foot amputations (May 2016 and 2017), associated with canagliflozin, as well as the risk of ketoacidosis associated with all SGLT2 inhibitors (December 2015).

For DPP-4 inhibitors, alerts were issued about the risk of joint pain associated with sitagliptin, saxagliptin, linagliptin, and alogliptin (August 2015) and the risk of heart failure with saxagliptin and alogliptin (April 2016). The FDA also issued a complete response letter to the sponsor in regard to the use of sitagliptin and adverse cardiovascular outcomes (April 2017).

Table 1
FDA-approved medications to treat T1DM and T2DM in adults and children.

Medications (n)*	Adults w/ T1DM (n)	Adults w/ T2DM (n)	Children w/ T1DM (n)	Children w/ T2DM (n)
Alpha-glucosidase inhibitor (2)	N	Y (2)	N	N
Amylin analogs (2)	Y (2)	Y (2)	N	N
ATP-dependent K^+ channel binders (1)	N	Y (1)	N	N
Biguanide and sulfonylurea combination (2)	N	Y (2)	N	N
Biguanides (5)	N	Y (5)	N	Y (2)
Bile acid sequestrant indicated (1)	N	Y (1)	N	N
Dipeptidyl peptidase-4 (DPP-4) inhibitors (5)	N	Y (5)	N	N
Dopamine receptor agonist (1)	N	Y (1)	N	N
DPP-4 inhibitor and biguanide combination (6)	N	Y (6)	N	N
Glucagon-like peptide 1 (GLP-1) receptor agonists (7)	N	Y (7)	N	N
Insulin types (20)	Y (20)	Y (20)	Y (10)	Y (8)
Meglitinide and biguanide combination (1)	N	Y (1)	N	N
SGLT2 and DPP4 combination (1)	N	Y (1)	N	N
SGLT2 inhibitor and biguanide combination (3)	N	Y (3)	N	N
Sodium-glucose co-transporter 2 (SGLT2) inhibitors (3)	N	Y (3)	N	N
Sulfonylureas (7)	N	Y (7)	N	N
Thiazolidinedione and biguanide combination (3)	N	Y (3)	N	N
Thiazolidinedione and sulfonylurea combination (2)	N	Y (2)	N	N
Thiazolinediones (2)	N	Y (2)	N	N

* n = number of medications approved, N = not FDA approved, Y = yes FDA approved.

Table 2
Drug labels reviewed.

Class of drug	Names of drugs reviewed
Alpha-glucosidase inhibitor (2)	Miglitol
	Acarbose
Amylin analogs (2)	Pramlintide acetate
ATP-dependent K^+ channel binders (1)	Nateglinide
Biguanide and sulfonylurea combination (2)	Glyburide and metformin hydrochloride
	Glipizide/metformin HCl
Biguanides (5)	Metformin hydrochloride, extended release
	Metformin hydrochloride
Bile acid sequestrant indicated (1)	Colesevelam hydrochloride
Dipeptidyl peptidase-4 (DPP-4) inhibitors (5)	Alogliptin benzoate
	Sitagliptin and simvastatin
	Linagliptin
	Saxagliptin
	Sitagliptin phosphate
Dopamine receptor agonist (1)	Bromocriptine mesylate
DPP-4 inhibitor and biguanide combination (6)	Sitagliptin and metformin HCl extended-release
	Linagliptin plus metformin hydrochloride
	Saxagliptin/metformin hydrochloride extended-release
	Sitagliptin/metformin HCl
	Linagliptin and metformin hydrochloride
	Alogliptin and metformin hydrochloride
Glucagon-like peptide-1 (GLP-1) receptor agonists (7)	Dulaglutide
	Abliglutide
	Exenatide extended-release
	Liraglutide
	Exenatide
	Lixisenatide
	Liraglutide injection
Insulin types (20)	Insulin glargine
	Insulin degludec
	Glargline U300
	Insulin human
	Insulin detemir
	Insulin glulisine
	Insulin aspart
	70% insulin aspart protamine and 30% insulin aspart
	75% insulin lispro protamine and 25% insulin lispro
	Insulin lispro
	50% insulin lispro protamine and 50% insulin lispro
	70% NPH and 30% regular
	Insulin regular
	70% NPH and 30% regular
	NPH (N)
	Regular (R) insulin
	Regular (R) insulin (5 times concentration)
	Insulin degludec/insulin aspart
Meglitinide and biguanide combination (1)	Repaglinide/metformin hydrochloride
SGLT2 and DPP4 combination (1)	Empagliflozin/linagliptin
SGLT2 inhibitor and biguanide combination (3)	Canagliflozin/metformin hydrochloride
	Empagliflozin and metformin hydrochloride
	Dapagliflozin and metformin hydrochloride, extended release
Sodium-glucose co-transporter-2 (SGLT2) inhibitors (3)	Empagliflozin
	Dapaglifozin
	Canagliflozin
Sulfonylureas (7)	Glipizide
	Glyburide
	Glimepiride
	Chlorpropamide
	Tolbutamide
	Tolazamide
Thiazolidinedione and biguanide combination (3)	Pioglitazone hydrochloride and metformin hydrochloride
	Rosiglitazone maleate and metformin HCl
	Pioglitazone and metformin hydrochloride, extended release
Thiazolidinedione and sulfonylurea combination (2)	Pioglitazone hydrochloride and glimepiride
	Glimepiride/rosiglitazone
Thiazolinediones (2)	Rosiglitazone
	Pioglitazone

For metformin, the FDA updated the safety profile to indicate that the drug can be used in patients with mild impairment in kidney function and in some patients with moderate impairment in kidney function (April 2016). In the metformin label, under the section "Additional Information for Health Care Professionals," metformin is contraindicated in patients with an eGFR below 30 mL/min/1.73 m^2 and not recommended in patients with an eGFR between 30 and 45 mL/min/1.73 m^2.

Finally, for thiazolidinediones, an alert was issued for increased risk of bladder cancer associated with pioglitazone (December 2016).

A table summarizing the warnings and precautions for most common adverse events listed in FDA-approved labels, grouped by class of drug, for all diabetes medications is in Appendix A.

3.3. Cardiovascular outcomes information on diabetes drug labels

For all classes of drugs for diabetes, except insulin, drug labels include information about macrovascular outcomes. The labels include information about *increased* risk of cardiovascular-related mortality, such as those listed on the labels of sulfonylureas and the combination of sulfonylurea and biguanide. Warnings listed for thiazolidinediones include the potential to cause or exacerbate congestive heart failure in some patients, and data on potential risk of myocardial ischemia with rosiglitazone are inconclusive. Increased low-density lipoprotein cholesterol (LDL-C), is reported with the use of SGLT2 inhibitors, or when present in combination formulations. Warnings and precautions related to heart failure are included on the labels for alogliptin and saxagliptin.

In contrast to the standard summary statement found on most labels: "There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with this or any other antidiabetic drug," the label for empagliflozin has been recently updated to reflect recent cardiovascular outcomes data. Empagliflozin received a new indication in December 2016 to reduce the risk of cardiovascular death in adult patients with T2DM and established cardiovascular disease. Of note, an FDA Advisory Committee Meeting was held in June 2017 to discuss a proposed additional indication to the label of liraglutide as adjunct to standard treatment to reduce the risk of major adverse cardiovascular events in adults with T2DM at high risk for cardiovascular disease. The members of the FDA Advisory Committee voted in favor of this change to the label, and final decision by the FDA on including this data in the label is pending.

4. Discussion

In summary, we conducted a comprehensive overview of all current FDA-approved drugs for treatment of diabetes. We found a total of 74 medications across 12 classes, with all having approval for adults with T2DM; a remarkably limited number have been approved for adults with T1DM or children with either T1DM or T2DM. As per FDA 2008 guidance document, industry sponsors have conducted large randomized clinical trials to examine the cardiovascular safety of new diabetes drugs, data of which is now being incorporated into their labels.

4.1. Pediatric T1DM and T2DM

In our overview of the number of approved medications and indications, we noted a dearth of available approved therapies for adults with type 2 diabetes, however insulin is the only treatment approved for pediatric T1DM. Among the 20 available types of insulin that are FDA approved for use in adults, only 10 labels have data on safety and efficacy in pediatric T1DM, and none have safety information from clinical trials with pediatric T2DM. However, for years pediatric endocrinologists have used most types of available insulin formulations to treat pediatric T1DM.[14] In addition, the existing pediatric trials in T1DM that are described on the labels do not have data on the safety and efficacy in the very young, particularly those patients who are younger than 6 years old, and the safety and efficacy information on insulin labels for pediatric T2DM are derived from clinical trial data for pediatric T1DM.

For pediatric T2DM, metformin is the first treatment option when lifestyle modifications fail to control diabetes. Pediatric endocrinologists prescribe insulin to children with T2DM when glycemic control is poor and unresponsive to diet and exercise, or to metformin alone.[15] Different types of insulin are used to control pediatric T2DM when metformin has failed; however, as discussed, none of the insulin labels have information about the safety and efficacy of these products in pediatric T2DM.

Despite the combination treatment of insulin plus metformin most adolescents with T2DM remain in poor glycemic control.[15] Moreover, even when adolescents with T2DM achieve control with the combination of metformin and insulin, many fail to maintain adequate control after several months of treatment. These outcomes indicate a more aggressive course of T2DM in adolescents compared to adults with T2DM, and therefore an urgent need to optimize therapeutic options for pediatric T2DM.[16,17] Several ongoing clinical trials in pediatric patients with T2DM should provide useful safety information upon conclusion.[16,17] As of today, the lack of guidance from clinical trials on the safety of other types of medications – besides insulin and metformin – in pediatric T2DM remains an important clinical problem, given the increasing incidence of pediatric T2DM.[1]

4.2. Adult T1DM and T2DM

As in pediatric T1DM, there are a limited number of approved therapies for adults with T1DM. Several studies have been done exploring adjuvant treatments for adults with T1DM — including metformin, GLP-1, DPP-4 inhibitors, SGLT2 inhibitors and thiazolidinediones but they are not approved for use. Overall, the studies that have examined alternate treatments for adult T1DM were done in a small number of subjects and for a relatively short period of time.[18–20,21,22,19] It is unknown whether other classes of diabetes drugs can be used as adjuvant treatments to improve glycemic control in patients with T1DM. The few small studies have shown minimal improvement. More robust research is needed to better establish the safety profile of adjuvant therapy for glycemic control in adult T1DM.

Despite the number of approved and available therapies for T2DM, there is little consensus on which medication to choose as a second line treatment after metformin monotherapy to control hyperglycemia.[3] Further studies are needed to determine the appropriate second choice of therapy for patients with T2DM. The ongoing GRADE study is expected to provide some guidance to providers in the future by comparing the effects of medications from four different classes (sulfonylurea, DPP-4 inhibitor, GLP-1 agonist and insulin) as add-on to metformin.[3]

4.3. Cardiovascular outcomes in adult patients with T1DM and T2DM

The risk of macrovascular complications from T2DM remains high, despite available treatments.[23,24] Since the FDA-issued Guidance in 2008[7] more research has been undertaken to examine cardiovascular safety of new diabetes medications. A list of the studies completed at the time of this review is shown in Table 3. Ongoing studies are expected to report results in the coming months.[25]

Sulfonylureas have been widely used for the treatment of T2DM for more than 50 years perhaps due to their lower cost and the possibility of using them once daily.[26] Sulfonylureas have a warning for increased cardiovascular risk. This increased risk is based on a study done by the University Group Diabetes Program in 1970 using the drug tolbutamide. In this study, 823 patients with T2DM were randomly assigned to four different groups and tolbutamide was associated with increased cardiovascular mortality. The results of this study caused debate within the medical community.[27] The FDA includes safety warnings for other medications in the sulfonylurea class, even though only one drug in this class (tolbutamide) signaled a CVD risk.

In addition, the DPP-4 inhibitors saxagliptin and alogliptin have a warning to consider the risks and benefits of their use prior to initiating treatment in patients at risk for heart failure. This warning is based on the results from the SAVOR and the EXAMINE study respectively. In the SAVOR trial 3.5% of the patients randomized to saxagliptin (289/8280) were hospitalized for heart failure compared to 2.8% of

Table 3
Studies investigating cardiovascular safety outcomes (CVOs) in response to 2008 FDA mandate.

Name of the study (by year published)	Patient population (n)	Duration of study (median)	Medication used	Primary CVOs	Secondary CVOs	FDA label on cardiovascular safety.
SAVOR (2013)[34]	T2DM and established - or at risk for-cardiovascular disease ($n = 16{,}492$)	2.1 years	Saxagliptin or placebo	No change in the primary composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal ischemic stroke.	No change in the primary composite end point plus hospitalization for heart failure, coronary revascularization, or unstable angina. When analysed separately, more patients in the saxagliptin group than in the placebo group were hospitalized for heart failure (3.5% vs. 2.8%, according to 2-year Kaplan–Meier estimates; hazard ratio, 1.27; 95% CI, 1.07 to 1.51; $P = 0.007$).	Heart failure: consider the risks and benefits in patients who have known risk factors for heart failure. There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction.
ELIXA (2015)[35]	T2DM and established cardiovascular disease ($n = 6068$)	2.1 years	Lixisenatide or placebo	No change in the primary composite of the first occurrence of any of the following: death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for unstable angina.	No change in a composite of the primary end point or hospitalization for heart failure and a composite of the primary end point, hospitalization for heart failure, or coronary revascularization procedures.	Clinical studies have not shown macrovascular risk reduction.
EMPA REG (2015)[31]	T2DM and established cardiovascular disease ($n = 7028$)	3.1 years	Empagliflozin 10 mg or 25 mg or placebo	Lower rate of the primary composite outcome defined as death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke.	No change in a composite of the primary outcome plus hospitalization for unstable angina.	Indicated to reduce the risk of cardiovascular death in adult patients with type 2 diabetes mellitus and established cardiovascular disease.
TECOS (2015)[29]	T2DM and established cardiovascular disease ($n = 14{,}671$)	3 years	Sitagliptin or placebo	No change in primary composite outcome defined as the first event of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for unstable angina.	No change in the secondary composite cardiovascular outcome defined as the first event of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke. No change in the occurrence of the individual components of the primary composite cardiovascular outcome, fatal and nonfatal myocardial infarction, fatal and nonfatal stroke, death from any cause, and hospitalization for heart failure.	There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction.
EXAMINE (2016)[28,36]	T2DM and established cardiovascular disease ($n = 5380$)	1.5 years	Alogliptin or placebo	No change in the primary composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke.	No change in the primary composite end point with the addition of urgent revascularization due to unstable angina within 24 h after hospital admission.[36] Alogliptin had no effect on composite events of cardiovascular death and hospital admission for heart failure in the post hoc analysis (HR 1.00, 95% CI 0.82–1.21).[28]	Consider the risks and benefits prior to initiating treatment in patients at risk for heart failure. If heart failure develops, evaluate and manage according to current standards of care and consider discontinuation.
LEADER (2016)[32]	T2DM and established-or at risk for-cardiovascular disease ($n = 9340$)	3.8 years	Liraglutide or placebo	Decreased rate on the primary composite outcome of the first occurrence of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke.	Decreased risk of the expanded composite cardiovascular outcome (death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or hospitalization for unstable angina pectoris or heart failure).	There have been no studies establishing conclusive evidence of macrovascular risk reduction.

patients randomized to placebo (228/8212). In a time to-first-event analysis the risk of hospitalization for heart failure was higher in the saxagliptin group compared to placebo (HR 1.27, 95% CI 1.07–1.51). The increased risk for heart failure was observed mainly among patients with elevated levels of natriuretic peptides, prior heart failure, or chronic kidney disease. In the EXAMINE trial, 5380 patients were assigned to alogliptin or placebo and followed for a median of 1.5 years. The warning for heart failure on the FDA label for alogliptin is based on the EXAMINE study where among the patients taking alogliptin 106 (3.9%) were hospitalized for congestive heart failure versus 89 subjects (3.3%) of patients treated with placebo. The authors of the EXAMINE trial published a follow up analysis of hospital admissions for heart failure which were seen in 3.1% (85/2701) of patients taking alogliptin compared with 2.9% (79/2679) of patients taking placebo (HR 1.07, 95% CI 0.79–1.46) and found that alogliptin had no statistically significant effect on composite events of cardiovascular death and hospital admissions for heart failure in the post hoc analysis (HR 1.00, 95% CI 0.82–1.21).[28] The TECOS study showed no adverse CVOs with the use of sitagliptin. In TECOS study 14,671 patients with T2DM and established CVD were assigned to sitagliptin or placebo in addition to standard of care therapy and were followed for a median time of 3 years.[29] With the addition of sitagliptin to usual care[29] there was no increased risk detected for heart failure.[30]

With SGLT2 inhibitors, the EMPA-REG study, a large randomized controlled trial (RCT), showed decreased mortality rates from cardiovascular causes in patients with T2DM who were treated with empagliflozin.[31] Based on the results of this trial, FDA added the new indication to empagliflozin to reduce the risk of cardiovascular death in adult patients with T2DM and established cardiovascular disease.

Large studies have also examined cardiovascular safety of GLP1 agonists. In the ELIXA study, patients with T2DM and established CVD received lixisenatide (GLP1 agonist) or placebo in addition to the standard of care. The addition of lixisenatide did not significantly alter the rate of major cardiovascular events.[29] In the LEADER trial, patients with T2DM and established CVD received liraglutide (GLP1 agonist) or placebo in addition to the standard of care. The addition of liraglutide showed a significantly reduced mortality from a cardiovascular event compared to placebo.[32] As mentioned earlier, an FDA advisory committee met in June 2017 and recommended that liraglutide gets a new indication as "an adjunct to standard treatment of cardiovascular risk factors to reduce the risk of major adverse cardiovascular events in adults with T2DM and high cardiovascular risk." Final decision by the FDA on updating the label in light of these new data is pending.

Finally, it is worth mentioning that older studies such as the United Kingdom Prospective Diabetes Study (UKPDS), a large RCT with 5102 patients, showed decreased risk for myocardial infarction and death in patients with T2DM who were treated with intensive insulin therapy and metformin during 10 years follow up.[33]

4.4. Drug label information on the FDA public database

Based on our review of the cardiovascular outcomes of the diabetes drugs we found that some drugs have the potential to reduce cardiovascular risk in patients with T2DM. In addition, because these medications can have other safety risks not related to cardiovascular outcomes, FDA continues to issue drug safety communication alerts to provide clinicians with new data. We anticipate that more drug labels will be updated in the coming months and years as new information becomes available from ongoing and recently completed large clinical trials.

Another finding from our study is the absence of 27 diabetes medications from the specific section of "Insulins and Diabetes Drugs Approved" per year, on the FDA website. These include Actoplus Met XR, Fortamet, Glucophage, Glucophage XR, Glucovance, Glumetza, Kazano, Riomet, Synjardy, Xigduo and others. Information about the diabetes drugs listed above is found scattered in other places within the FDA website but it might be hard for patients and physician to retrieve that information if it is not organized in a proper way. With the increasing number of diabetes drugs approved every year, efforts should be made to keep the agency's website as current and user friendly as possible.

5. Conclusions

Based on our review of diabetes medications, we found that all are approved for adults with T2DM, while a limited number are approved for adults with T1DM and children with T1DM or T2DM. It remains to be examined whether these medications are safe and effective as adjuvant treatments for adults with T1DM and pediatric patients with T1DM or T2DM. Furthermore, after the 2008 FDA guidance to industry to include cardiovascular safety data on their clinical trials, new data have emerged not only about safety but also about cardiovascular risk reduction with certain diabetes drugs. The FDA initiative has generated important knowledge on cardiovascular safety and outcomes in high risk patients with T2DM that could influence physicians' treatment approach to patients with diabetes.

A post-marketing update of labels that includes information from large randomized controlled trials could provide treating physicians and patients with additional useful risk management information. Finally, an updated FDA online database of approved diabetes medications per year would be helpful for both patients and prescribers, ultimately leading to safer medical practice and patient care.

Acknowledgments

We thank Joseph Verbalis, MD, Georgetown University, for his helpful review and comments about the draft manuscript.

Funding

This work was supported by the Program for Regulatory Science & Medicine Fellowship in Pediatric Regulatory Science, supported by the Pharmaceutical Research and Manufacturers of America (PhRMA), Georgetown University, Washington, DC; and by Federal funds (UL1TR001409 from the National Center for Advancing Translational Sciences (NCATS), National Institutes of Health, through the Clinical and Translational Science Awards Program (CTSA), a trademark of DHHS, part of the Roadmap Initiative, "Re-Engineering the Clinical Research Enterprise (KL2 Award, Dr. Gourgari).

Disclosures

At the time of this study, Dr. Gourgari was a Georgetown University Fellow in Pediatric Regulatory Science, supported by the Pharmaceutical Research and Manufacturers of America (PhRMA). Dr. Aroda has research contracts pertaining to clinical trials with Astra Zeneca/BMS, Calibra, Eisai, Elcelyx, Janssen, Novo Nordisk, Sanofi, and Theracos, all contracts directly with employer (MedStar Health Research Institute) and consultant activities with Adocia, Astra Zeneca, Janssen, Medscape, Novo Nordisk, and Sanofi, all contracts directly with employer. Ira Shoulson, M.D., is a non-executive director of Prana Biotechnology Ltd. (Melbourne, Australia), which develops experimental treatments for neurodegenerative diseases. He is compensated by Prana as a director and consultant but does not have equity positons or other financial incentives with the company. He is also a principal of Grey Matter Technologies, a limited liability company formed in January 2017 that is developing innovative approaches for systematically capturing and analyzing verbatim patient reports for use in clinical care and research. In the past 3 years, Dr. Shoulson has received honoraria or consulting fees from Auspex Pharmaceuticals, AZTherapies Inc., Banner Health, Columbia University, Dart Neurosciences, Decibel Therapeutics, Huntington

Study Group, JAMA Neurology, Jazz Pharmaceuticals, Lysosomal Therapeutics, Michael J. Fox Foundation, Northwestern University, Partners Health Care, Sarepta Therapeutics, Teva Pharmaceuticals, the University of California Irvine, and the University of Michigan. As director of the Georgetown University Center for Regulatory Science & Medicine, Dr. Shoulson receives research and educational grants from the Food and Drug Administration (PI, Center of Excellence in Regulatory Science & Innovation, FD004319), The Pharmaceutical Research and Manufacturers of America (Regulatory Science Postdoctoral Fellowship), The Griffin Foundation, and The Michael J. Fox Foundation for Parkinson's Disease (Regulatory Science Postdoctoral Fellowship). As a co-author, Dr. Shoulson has no financial or other relevant conflicts of interest related to the preparation, content or publication of the submitted manuscript. All other authors have nothing to disclose.

References

1. Mayer-Davis EJ, Lawrence JM, Dabelea D, et al. Incidence trends of type 1 and type 2 diabetes among youths, 2002–2012. *N Engl J Med.* 2017;376:1419-29.
2. American Diabetes A. Statistics about diabetes. http://wwwdiabetesorg/diabetes-basics/statistics/2016.
3. Nathan DM, Buse JB, Kahn SE, et al. Rationale and design of the glycemia reduction approaches in diabetes: a comparative effectiveness study (GRADE). *Diabetes Care.* 2013;36:2254-61.
4. Diabetes C. Complications trial/epidemiology of diabetes I, complications study research G. Mortality in type 1 diabetes in the DCCT/EDIC versus the general population. *Diabetes Care.* 2016;39:1378-83.

Appendix A

Table 4
Warnings, precautions and adverse events per class of diabetes drug.

Warnings and precautions	Common adverse events
Alpha glucosidase inhibitors	
Hypoglycemia, loss of control of blood glucose, hepatic and renal impairment.	Abdominal pain, diarrhea, flatulence, skin rash, elevated serum transaminase levels and mild decrease in hematocrit.
Amylin analogs	
Severe hypoglycemia Slow gastric emptying Should be administered in separate injections with insulin because mixing can alter the pharmacokinetics of both products.	Nausea, vomiting, anorexia and headache
ATP-dependent K channel blockers	
Hypoglycemia, loss of control of blood glucose, hepatic impairment	Upper respiratory infections, back pain, flu symptoms, dizziness, arthropathy, diarrhea, accidental trauma, bronchitis, coughing and hypoglycemia.
Biguanides	
Vitamin B12 deficiency Lactic acidosis Temporarily discontinued in patients undergoing radiologic studies with intravascular administration of iodinated contrast materials or any surgical procedures necessitating restricted intake of food and fluids. Impaired hepatic and renal function Loss of blood glucose control Warning against excessive alcohol intake (alcohol potentiates the effect of metformin on lactate metabolism)	Hypoglycemia Diarrhea, nausea, indigestion, constipation, taste disturbance, abdominal pain, flatulence Asthenia Dizziness Headache
Bile acid sequestrant	
Hypertriglyceridemia which may lead to pancreatitis; it can decrease the absorption of fat-soluble vitamins and lead to deficiencies of vitamin A, D, E and K; it may reduce gastrointestinal absorption of some drugs and also cause constipation.	Constipation, dyspepsia and nausea.
Dopamine receptor agonist	
Hypotension, syncope, psychosis and somnolence and therefore it is advised that patients avoid situations that could lead to injury if syncope was to occur and avoid operating heavy machinery if somnolence was to occur. Because of the interaction with other dopamine antagonists and agonists concomitant use is not recommended.	Nausea, fatigue, dizziness, vomiting, and headache; postmarketing reports with higher doses of bromocriptine used for other indications include psychotic disorders, hallucinations, and fibrotic complications.
Glucagon-like peptide (GLP-1) receptor agonists	
Pancreatitis, hypoglycemia, renal impairment/kidney failure, severe gastrointestinal disease and hypersensitivity reactions. An important warning is the potential to cause thyroid C-cell Tumors (not described in exenatide and lixisenatide) based on evidence from animal models — therefore, most GLP-1 agonists are contraindicated in patients with a personal or family history of medullary thyroid cancer or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). Liraglutide has an additional warning for causing an increase in the heart rate, acute gallbladder disease and suicidal behavior and ideation.	Nausea, hypoglycemia, diarrhea, constipation, vomiting, headache, decreased appetite, dyspepsia, fatigue, dizziness, abdominal pain, urticaria, injection site reactions, cough, back pain and arthralgia, sinusitis and influenza, occasional bleeding due to increased international normalized ratio (INR) with concomitant use of warfarin.

(continued on next page)

Table 4 *(continued)*

Warnings and precautions	Common adverse events
Insulin medications	
Hypoglycemia	Hypoglycemia
Hypersensitivity reactions	Allergic reactions
Hypokalemia	Injection site reactions
Fluid retention and heart failure with concomitant use of thiazolidinediones	Lipodystrophy
Hyperglycemia due to dosing errors	Pruritus
Acute bronchospasm (inhaled insulin)	Rash
Decline in pulmonary function (inhaled insulin) inhaled insulin is contraindicated in patients with chronic lung disease such as asthma or COPD.	Edema
Diabetic ketoacidosis	Weight gain
Renal or hepatic impairment	Cough and throat pain or irritation (inhaled insulin)
Lipodystrophy	
Lung cancer (inhaled insulin)	
Swelling of hands and feet	
Vision changes	
SGLT2 inhibitors	
Impaired renal function, increased genital mycotic infections, hypoglycemia, hypotension, increased LDL-C, increased urosepsis and pyelonephritis (except dapagliflozin), ketoacidosis, hypersensitivity reactions. Bladder cancer (dapagliflozin), increased risk for bone fracture (canagliflozin) and hyperkalemia (canagliflozin). Increased risk of leg and food amputation (canagluflozin)	Urinary tract infections, female genital mycotic infections, nasopharyngitis and increased urination.
Sulfonylureas	
Increased risk of cardiovascular mortality	Hypoglycemia,
Loss of blood glucose control	GI disturbances, nausea, cholestatic jaundice, taste alterations
Hemolytic anemia	Dermatologic skin reactions, disulfiram-like reactions, Pruritus
Hypersensitivity reactions	Hematologic disorders
Hypoglycemia	Metabolic reactions, endocrine reactions
Renal and hepatic disease	Dizziness, drowsiness, and headache
	Vision effects (blurred or change in accommodation)
	Weakness, fatigue, vertigo, malaise
Thiazolinediones	
Possibly exacerbating or causing heart failure in some patients. Therefore, its use is not recommended in patients with symptomatic heart failure and it is contraindicated in patients with established New York Heart Association (NYHA) Class III or IV heart failure.	Upper respiratory tract infections
Increased risk of myocardial ischemic events in short-term trials.	Injuries
Higher risk for hypoglycemia, fractures (in female patients), macular edema, fluid retention, dose-related edema, weight gain, and anemia. Combination therapy with insulin and use in congestive heart failure may increase the risk of cardiovascular effects of thiazolinediones.	Headaches
Fatal hepatic failure	
Bladder cancer — pioglitazone is contraindicated in patients with active bladder cancer, should be used with caution in patients with prior history of bladder cancer and pioglitazone should not be given in patients that develop liver injury that can be explained otherwise.	

5. Gregg EW, Li Y, Wang J, et al. Changes in diabetes-related complications in the United States, 1990—2010. *N Engl J Med.* 2014;370:1514-23.
6. Miller KM, Foster NC, Beck RW, et al. Current state of type 1 diabetes treatment in the U.S.: updated data from the T1D exchange clinic registry. *Diabetes Care.* 2015;38:971-8.
7. FDA. *Guidance for Industry: Diabetes Mellitus — Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes. 2008.*
8. FDA. http://www.fda.gov/ForPatients/Illness/Diabetes/ucm408682.htm2016, Accessed June , 2016.
9. WebMD. Diabetes drugs. http://www.webmd.com/diabetes/diabetes-medications-02016, Accessed June , 2016.
10. CenterWatch. http://www.centerwatch.com/drug-information/fda-approved-drugs/medical-conditions/D2016, Accessed June , 2016.
11. Medscape. http://reference.medscape.com/drugs/metabolic-endocrine2016, Accessed June , 2016.
12. FDA. Drug safety communications. https://wwwfdagov/Drugs/DrugSafety/ucm199082htm2017.
13. FDA. https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/default.htm2017, Accessed May , 2017.
14. Libman IM, Miller KM, DiMeglio LA, et al. Effect of metformin added to insulin on glycemic control among overweight/obese adolescents with type 1 diabetes: a randomized clinical trial. *JAMA.* 2015;314:2241-50.
15. Flint A, Arslanian S. Treatment of type 2 diabetes in youth. *Diabetes Care.* 2011;34:S177-183.
16. Meehan C, Silverstein J. Treatment options for type 2 diabetes in youth remain limited. *J Pediatr.* 2016;170:20-7.
17. Tamborlane WV, Haymond MW, Dunger D, et al. Expanding treatment options for youth with type 2 diabetes: current problems and proposed solutions: a white paper from the NICHD Diabetes Working Group. *Diabetes Care.* 2016;39:323-9.
18. Rother KI, Spain LM, Wesley RA, et al. Effects of exenatide alone and in combination with daclizumab on beta-cell function in long-standing type 1 diabetes. *Diabetes Care.* 2009;32:2251-7.
19. Frandsen CS, Dejgaard TF, Madsbad S. Non-insulin drugs to treat hyperglycaemia in type 1 diabetes mellitus. *Lancet Diabetes Endocrinol.* 2016;4:766-80.
20. Frandsen CS, Dejgaard TF, Holst JJ, Andersen HU, Thorsteinsson B, Madsbad S. Twelve-week treatment with Liraglutide as add-on to insulin in normal-weight patients with poorly controlled type 1 diabetes: a randomized, placebo-controlled, double-blind parallel study. *Diabetes Care.* 2015;38:2250-7.

21. Henry RR, Thakkar P, Tong C, Polidori D, Alba M. Efficacy and safety of Canagliflozin, a sodium-glucose cotransporter 2 inhibitor, as add-on to insulin in patients with type 1 diabetes. *Diabetes Care.* 2015;38:2258-65.
22. Orchard TJ. The effect of rosiglitazone on overweight subjects with type 1 diabetes. *Diabetes Care.* 2006;29:746-7. [author reply 747].
23. 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;38:140-9.
24. 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;35:1364-79.
25. Schnell O, Ryden L, Standl E, Ceriello A, Group CES. Current perspectives on cardiovascular outcome trials in diabetes. *Cardiovasc Diabetol.* 2016;15:139.
26. Sola D, Rossi L, Schianca GP, et al. Sulfonylureas and their use in clinical practice. *Arch Med Sci.* 2015;11:840-8.
27. Bradley RF, Dolger H, Forsham PH, Seltzer H. Settling the UGDP controversy? *JAMA.* 1975;232:813-7.
28. Zannad F, Cannon CP, Cushman WC, et al. Heart failure and mortality outcomes in patients with type 2 diabetes taking alogliptin versus placebo in EXAMINE: a multicentre, randomised, double-blind trial. *Lancet.* 2015;385:2067-76.
29. Green JB, Bethel MA, Armstrong PW, et al. Effect of Sitagliptin on cardiovascular outcomes in type 2 diabetes. *N Engl J Med.* 2015;373:232-42.
30. Scirica BM. The safety of dipeptidyl peptidase 4 inhibitors and the risk for heart failure. *JAMA Cardiol.* 2016;1:123-5.
31. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med.* 2015;373:2117-28.
32. Marso SP, Daniels GH, Brown-Frandsen K, et al. Liraglutide and cardiovascular outcomes in type 2 diabetes. *N Engl J Med.* 2016;375:311-22.
33. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-Year follow-up of intensive glucose control in type 2 diabetes. *N Engl J Med.* 2008;359:1577-89.
34. Scirica BM, Bhatt DL, Braunwald E, et al. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. *N Engl J Med.* 2013;369:1317-26.
35. Pfeffer MA, Claggett B, Diaz R, et al. Lixisenatide in patients with type 2 diabetes and acute coronary syndrome. *N Engl J Med.* 2015;373:2247-57.
36. White WB, Cannon CP, Heller SR, et al. Alogliptin after acute coronary syndrome in patients with type 2 diabetes. *N Engl J Med.* 2013;369:1327-35.