Diabetes Management Update: Individualizing Treatment

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CONTINUING MEDICAL EDUCATION

LEARNING OBJECTIVES

After reading this article, primary care providers will be able to:

- Summarize differences among glucagon-like peptide-1 receptor agonists and sodium glucose cotransporter-2 inhibitors regarding cardiovascular safety and benefits
- Initiate patient-centric pharmacotherapy in patients with type 2 diabetes mellitus and established cardiovascular disease who are inadequately controlled with metformin-based therapy consistent with current recommendations
- Implement simple strategies in clinical practice to address common unmet needs and concerns of patients with type 2 diabetes mellitus that impact treatment adherence and self-management

TARGET AUDIENCE

Family physicians and clinicians who wish to gain increased knowledge and greater competency regarding primary care management of diabetes mellitus.

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CASE SCENARIO

April is a 69-year-old African American woman diagnosed with type 2 diabetes mellitus (T2DM) 11 years ago. Initial treatment with lifestyle intervention and metformin reduced her glycated hemoglobin (A1c) from 8.4% to 6.9% and her body mass index (BMI) from 32.6 kg/m^2 to 27.9 kg/m^2, which she was able to maintain for approximately 5 years. Her A1c remained at approximately 7% during this time, but began to rise as her BMI increased. Intensified lifestyle intervention resulted in no further weight loss; her BMI stabilized at 33.8 kg/m^2. Pharmacotherapy was intensified to lower and maintain her A1C at 7.1% to 7.3% over the next several years. Over the past 3 years, her A1c has again increased and is now 7.9%. April experiences frequent symptomatic hypoglycemia, which has required treatment at the local emergency department twice in the past 4 years. April also experiences occasional symptoms of angina, which combined with her T2DM, obesity,

hypertension, and dyslipidemia, has contributed to declining treatment adherence.

April is being seen by her primary care provider following hospital discharge for a cardiovascular event. Current medications: metformin 1000 mg twice daily, pioglitazone 45 mg once daily, sitagliptin 100 mg once daily, enalapril/hydrochlorothiazide 20 mg/50 mg once daily, atorvastatin 40 mg once daily, and low-dose aspirin.

What modifications would you make to her diabetes treatment plan? Does her history of cardiovascular disease impact treatment?

CARDIOVASCULAR DISEASE IN TYPE 2 DIABETES MELLITUS

Cardiovascular (CV) disease is common in the United States, with approximately 11% of US adults having been diagnosed with heart disease and nearly 3% with stroke.[1] Type 2 diabetes mellitus is an independent risk factor for CV disease, conferring about a two-fold excess risk for CV disease.[2] Moreover, in 2016, high fasting plasma glucose was among the top 5 risk factors contributing to disability-adjusted life-years in the United States.[3]

Peripheral arterial disease is the most common initial presentation of CV disease in patients with T2DM, followed by stroke and coronary heart disease.[4] Beyond vascular events, persons with diabetes mellitus (DM) are at high risk for heart failure (HF) and HF-related death, as well as chronic kidney disease (CKD). People with T2DM have more than twice the risk of HF than those without T2DM,[5-8] while up to 40% of people with HF have diabetes.[4,7,9-13] There is a linear relationship between glycemic control and the incidence of HF with a risk ratio for HF of approximately 1.2 for each 1% increase in the A1c.[14,15] Patients with T2DM and HF have a worse prognosis than those with T2DM without HF.[16] The risk of death in persons with DM has been shown to be nearly 9 times higher for those with vs without HF.[17] Of individuals hospitalized for acute HF, those with vs without DM have a worse outcome (composite of all-cause mortality, heart transplantation, and left ventricular assist device implantation).[18] HF hospitalization is also more common in patients with T2DM.[19]

CKD also is common in patients with DM as approximately 1 in 3 US adults with DM is thought to have CKD.[20,21] Nearly half (45%) of new cases of end-stage renal disease in the United States are due to DM.[22] While the prevalence of stages 3-4 CKD has remained stable over the past decade or so,[23,24] the increasing prevalence of DM in the United States has been followed by a proportional increase in the prevalence of diabetic kidney disease (DKD).[25] Moreover, the prevalence of adults with estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 and albumin-to-creatinine ratio <30 mg/g nearly tripled from 1988-1994 to 2007-2010.[26] This was associated with a 50% increase in the mortality rate.[26] In 2015, 124,000 people in the United States started treatment for end-stage renal disease[22] and approximately 325 persons began treatment for kidney failure every day.[20,22]

THE CHANGING PARADIGM OF TYPE 2 DIABETES MANAGEMENT

Over the past decade, there have been 2 important shifts in the management of patients with T2DM as reflected in treatment guidelines such as those developed by the American Diabetes Association. The first is a focus on the importance of individualizing glycemic treatment.[27,28] This shift in focus results from the availability of several new classes of medications for T2DM with different mechanisms of glucose-lowering and very good safety profiles, particularly low incidences of hypoglycemia and weight neutrality or weight loss effects.[29] There has also been improved recognition that T2DM is a largely self-managed disease that is impacted by the patient's willingness and ability to adhere to the treatment plan.[28,30,31] To better understand these issues, a collaborative relationship between patient and provider has become essential (see below).[32]

The other shift has been a heightened concern about the CV safety of medications for T2DM following publication of several clinical trials and a meta-analysis related to the thiazolidinediones in 2005 to 2007. Results of the clinical trials indicated an increased risk for heart failure with rosiglitazone[33] and pioglitazone.[34,35] The subsequent meta-analysis of 42 clinical trials demonstrated rosiglitazone was associated with a significant increase in the risk for myocardial infarction (MI) (odds ratio [OR], 1.43; 95% confidence interval [CI], 1.03-1.98; *P*=.03) and a nonsignificant increase in the risk for CV death (OR, 1.64; 95% CI, 0.98-2.74; *P*=.06).[36] Shortly after, the Rosiglitazone Evaluated for Cardiovascular Outcomes in Oral Agent Combination Therapy for Type 2 Diabetes (RECORD) trial found no significant increase in the risk for MI with rosiglitazone, but confirmed a significant increase in risk for HF.[37,38]

CARDIOVASCULAR OUTCOME TRIALS

Regulatory requirements

In 2008, prior to publication of the final RECORD results in 2009, the US Food and Drug Administration (FDA) took steps to assure the safety of medications for T2DM. This included issuing a guidance requiring industry sponsors to conduct a clinical trial demonstrating that a new medication for T2DM is not associated with an unacceptable increase in CV risk compared to placebo as part of standard care.[39] The guid-

ance applies to the dipeptidyl peptidase-4 inhibitor (DPP-4i), glucagon-like peptide-1 receptor agonist (GLP-1RA) (except exenatide twice-daily), and sodium glucose cotransporter-2 inhibitor (SGLT-2i) classes of medications.

Key recommendations in the FDA guidance included (1) assessment of major adverse CV events (MACE), a composite of CV death, nonfatal MI, and nonfatal stroke; (2) enrollment of patients with T2DM at higher risk of CV events, eg, those with advanced CV disease, advanced age, or renal impairment; and (3) study duration of at least 2 years to allow assessment of longer-term risks.[39]

The guidance also identified that for initial FDA approval, a finding of no increase in CV risk compared to placebo as part of standard care is observed if the upper limit of the two-sided 95% confidence interval (CI) for the estimated risk ratio for MACE is less than 1.8. If the upper limit for the estimated risk ratio is found to be between 1.3 and 1.8 and the overall risk-benefit analysis is favorable, the medication is generally approved. However, a postmarketing trial is usually required to clearly demonstrate that the upper limit of the two-sided 95% CI for the estimated risk ratio is less than 1.3, in which case, a definitive finding of noninferiority regarding the CV safety of the new medication compared to placebo as part of standard care is reached. Put differently, the medication for T2DM is found to pose no increase in CV risk compared to placebo as part of standard care.

If noninferiority is demonstrated, a finding of superiority can be investigated. A finding of superiority is reached if the two-sided 95% CI for the estimated risk ratio is less than 1.0. Should this be the case, the new medication for T2DM is determined to significantly reduce CV risk compared to placebo as part of standard care and, therefore, offer a CV benefit. Medications offering a CV benefit have the potential to change the treatment paradigm for T2DM, as will be discussed below.

Results

Nearly all of the CV outcome trials required by the FDA for new medications for T2DM have been completed; note that the CV outcome trial for ertugliflozin is ongoing. Most trials have been for both primary and secondary prevention. All completed CV outcome trials have demonstrated that each new medication for T2DM poses no increased CV risk compared to placebo as part of standard care, thereby providing reassurance about the CV safety of DPP-4is, GLP-1RAs, and SGLT-2is. It is also worth noting that the CV safety of insulin glargine U-100 and insulin degludec have been assessed in clinical trials and shown to pose no increase in CV risk compared to standard care.[40,41] In addition, the FDA judged there to be no safety concern regarding CV risk for glargine U-300 compared to glargine U-100.[42]

In addition to CV safety, the CV outcome trials of the DPP-4is, GLP-1RAs, and SGLT-2is showed that some of these medications provide a CV benefit, ie, reduce the risk for MACE (the composite of CV death, nonfatal MI, and nonfatal stroke) compared to placebo as part of standard care. These include the GLP-1RAs albiglutide,[43,44] dulaglutide,[45] liraglutide,[46,47] and semaglutide,[48] and the SGLT-2is canagliflozin,[49,50] dapagliflozin,[51,52] and empagliflozin[53,54] (**TABLE**).

The results of these trials provide an opportunity to include consideration of CV risk reduction when selecting medications for T2DM. Moreover, differences among the GLP-1RAs and SGLT-2is with respect to their effects on CV events, eg, MI, stroke, HF, and renal outcomes, provide an opportunity to further individualize therapy as recommended in the 2019 ADA Standards of Medical Care (**FIGURE**).[28]

CASE SCENARIO

The rise in April's A1c to 7.9% despite treatment with optimized metformin, pioglitazone, and sitagliptin indicates the need to modify her diabetes treatment plan. Sitagliptin should be discontinued since there is no CV, HF, or CKD reduction benefit. Pioglitazone might be continued if April has established atherosclerotic cardiovascular disease (ASCVD) since there is a potential benefit, but should not be continued if April has HF or renal impairment due to fluid retention.[55] Since she has experienced a CV event, selecting a medication shown to lower CV risk is recommended.[28]

If April had experienced a MI or stroke, a GLP-1RA is preferred with the strongest evidence for liraglutide, dulaglutide, and semaglutide. Alternatively, an SGLT-2i can be considered, with the strongest evidence for empagliflozin > canagliflozin.

If April had experienced acute heart failure or had CKD, an SGLT-2i shown to reduce HF or CKD (empagliflozin, canagliflozin, dapagliflozin) is preferred. Alternatively, a GLP-1RA (liraglutide, dulaglutide, and semaglutide) can be considered if SGLT-2i therapy is not tolerated or contraindicated or if the eGFR is below the recommended threshold for SGLT-2i therapy.

In selecting therapy, other general factors to consider include hypoglycemia, weight effects, and patient affordability. In addition, prior to initiating a GLP-1RA, a history of pancreatitis, multiple endocrine neoplasia type 2, thyroid cancer, as well as the ability to tolerate transient nausea are to be considered. Prior to initiating an SGLT-2i, the patient's eGFR must be determined and treatment not initiated if the eGFR is <45 mL/min/1.73 m^2 (canagliflozin, dapagliflozin, empagliflozin) or if the eGFR is 30 to <60 mL/min/1.73 m^2 (ertugliflozin). A comprehensive foot examination should be performed with emphasis on peripheral vascular disease and a history of amputations. Other factors to consider related to SGLT-2i therapy are the risk of urinary tract infection, genital mycotic infection, and volume depletion with all

TABLE Effects on key endpoints of medications shown to offer a cardiovascular benefit vs placebo

	Hazard ratio[a] (95% CI)					
	MACE[b]	CV death	Nonfatal MI	Nonfatal stroke	Heart failure hospitalization	Renal
Glucagon-like peptide-1 receptor agonists						
Albiglutide	0.78 (0.68-0.90)	0.93 (0.73-1.19)				
Dulaglutide	0.88 (0.79-0.99) *P*=.026			0.76 (0.61-0.95) *P*=.017		0.85[c] (0.77-0.93) *P*=.0004
Liraglutide	0.87 (0.78-0.97) *P*=.01	0.78 (0.66-0.93) *P*=.007	0.88 (0.75-1.03) *P*=.11	0.89 (0.72-1.11) *P*=.30	0.87 (0.73-1.05) *P*=.14	0.78[d] (0.67-0.92) *P*=.003
Semaglutide	0.74 (0.58-0.95) *P*=.02	0.98 (0.65-1.48) *P*=.92	0.74 (0.51-1.08) *P*=.12	0.61 (0.38-0.99) *P*=.04	1.11 (0.77-1.61) *P*=.57	0.64[e] (0.46-0.88) *P*=.005
Sodium glucose cotransporter-2 inhibitors						
Canagliflozin	0.86 (0.75-0.97) *P*=.02	0.87 (0.72-1.06)	0.85 (0.69-1.05)	0.90 (0.71-1.15)	0.67 (0.52-0.87)	0.60[f] (0.47-0.77)
Dapagliflozin	0.93 (0.84-1.03) *P*=.17	0.98 (0.82-1.17)			0.73 (0.61-0.88)	0.53[g] (0.43-0.66)
Empagliflozin	0.86 (0.74-0.99) *P*=.04	0.62 (0.49-0.77) *P*<.001	0.87 (0.70-1.09) *P*=.22	1.24 (0.92-1.67) *P*=.16	0.65 (0.50-0.85) *P*=.002	0.54[h] (0.40-0.75) *P*<.001

Abbreviations: CI, confidence interval; CV, cardiovascular; eGFR, estimated glomerular filtration rate; MI, myocardial infarction.

[a]Hazard ratio of active medication vs placebo.

[b]MACE is a composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke.

[c]New macroalbuminuria, sustained decline in eGFR ≥30% or chronic renal replacement therapy.

[d]Nephropathy defined as new onset of macroalbuminuria or a doubling of the serum creatinine and an eGFR ≤45 mL/min/1.73 m^2, the need for continuous renal-replacement therapy, or death from renal disease.

[e]New or worsening nephropathy including persistent macroalbuminuria, persistent doubling of the serum creatinine and an eGFR <45 mL/min/1.73 m^2, or the need for continuous renal-replacement therapy.

[f]≥40% reduction in eGFR, renal-replacement therapy, or renal death.

[g]≥40% decrease in eGFR to <60 mL/min/1.73 m^2, end-stage renal disease, or death from renal cause.

[h]Doubling of serum creatinine accompanied by eGFR ≤45 mL/min/1.73 m^2, initiation of renal-replacement therapy, or death from renal disease.

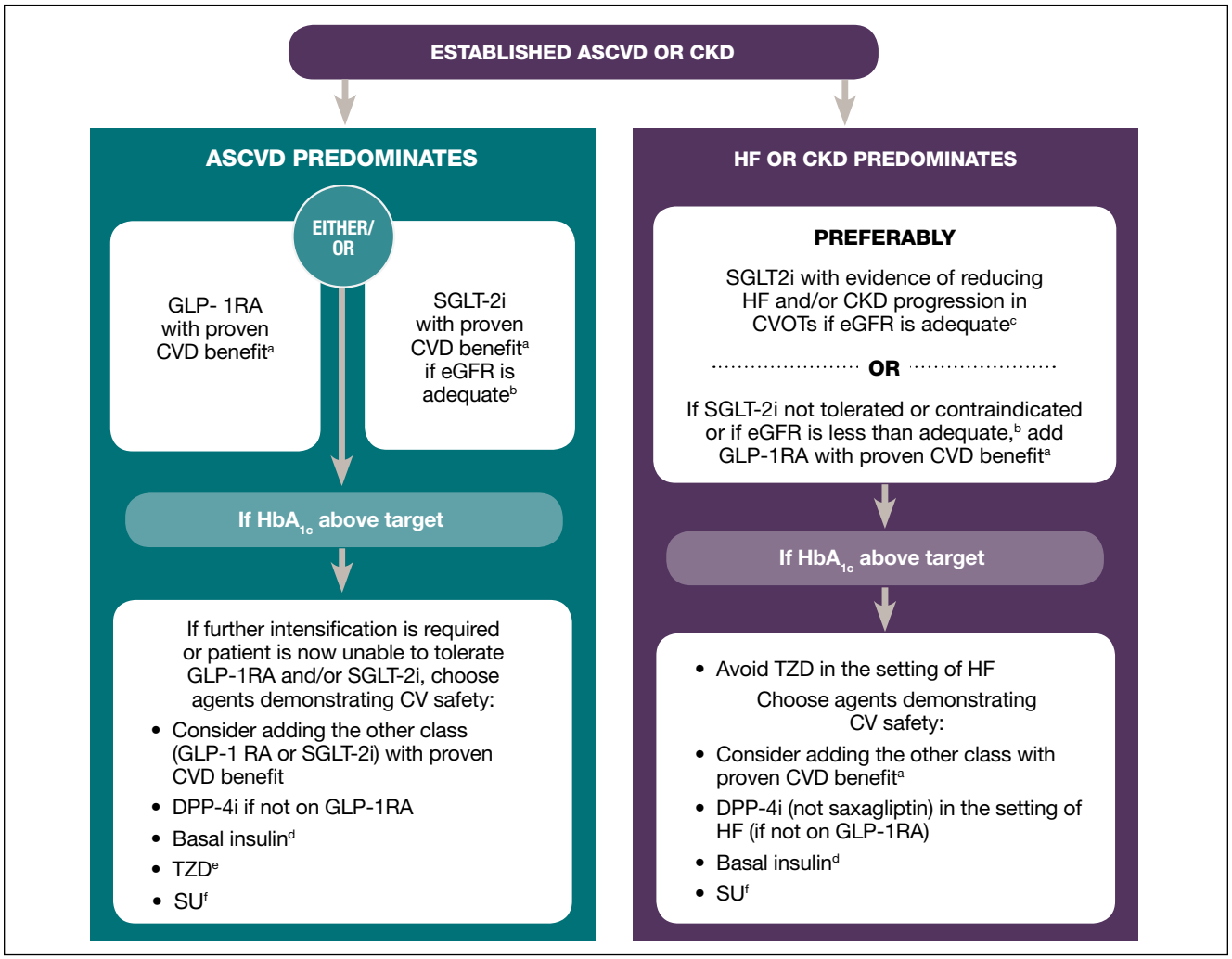
Boxes shaded in green indicate the medication significantly reduces the risk of the specified endpoint vs placebo as part of standard care.

SGLT-2is, as well as amputation (canagliflozin and ertugliflozin), bone fracture (canagliflozin), and bladder cancer (dapagliflozin).

PATIENT SELF-MANAGEMENT

As noted earlier, HF is a largely self-managed disease; thus, it is essential that the patient is willing and able to implement an individualized treatment plan. This requires a collaborative relationship between patient and provider built on effective patient-provider communication and shared decision-making.[56] A recent systematic review suggests that utilization of several techniques lead to improved patient-provider communication. These include: (1) asking open-ended questions; (2) utilizing active listening skills; (3) employing motivational interviewing techniques; (4) discussing the most important information first and using the phrase "This is important…" when discussing key points; (5) delivering simple, clear, concrete instructions supported by a written action plan that is appropriate for a patient's culture and health literacy and numeracy; and (6) asking patients to write a list of questions prior to the visit.

FIGURE Recommended therapy for patients with type 2 diabetes mellitus and established atherosclerotic cardiovascular disease, heart failure, or chronic kidney disease who have inadequate glycemic control with metformin and comprehensive lifestyle management



Abbreviations: ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; CV, cardiovascular; CVD, cardiovascular disease; CVOTs, cardiovascular outcome trials; DPP-4i, dipeptidyl peptidase-4 inhibitor; FDA, US Food and Drug Administration; eGFR, estimated glomerular filtration rate; GLP-1 RA, glucagon-like peptide-1 receptor agonist; $HbA1_c$, hemoglobin A1c; HF, heart failure; SGLT-2i, sodium glucose cotransporter-2 inhibitor; SU, sulfonylurea; TZD, thiazolidinedione.

[a] Proven CVD benefit means it has label indication of reducing CVD events. For GLP-1RA, liraglutide is FDA approved to reduce the risk of MACE in adults with type 2 diabetes and established CVD; liraglutide and dulaglutide showed superiority for MACE outcomes in large CVOTs; semaglutide showed superiority for MACE outcomes in a safety CVOT. These results were primarily in patients with known ASCVD although there was consistent benefit in the dulaglutide trial in patients with and without established ASCVD. For SGLT-2i, evidence modestly stronger for empagliflozin > canagliflozin.

[b] Be aware that SGLT-2i vary by region and individual agent with regard to indicated level of eGFR for initiation and continued use.

[c] Empagliflozin, canagliflozin, and dapagliflozin have shown reduction in HF and reduction in CKD progression in CV outcome trials.

[d] Degludec or glargine U-100 have demonstrated CV safety.

[e] Low dose may be better tolerated though less well studied for CVD effects.

[f] Choose later generation sulfonylurea with lower risk of hypoglycemia.

A shared decision-making process provides a mechanism to identify patient concerns and develop a treatment plan that addresses those concerns. To accomplish this, the Agency for Healthcare Utilization and Review has outlined the 5-step SHARE process: (1) seek your patient participation; (2) help your patient explore and compare treatment

options; (3) assess your patient's values and preferences; (4) reach a decision with your patient; and (5) evaluate your patient's decision.[32] This approach is applicable to both initiating as well as modifying treatment.

SUMMARY

The rapid evolution in medications available for the treatment of patients with T2DM allows for a more individualized approach to treatment that includes a low incidence of hypoglycemia and weight-neutral or weight-loss effects. Beyond these benefits, evidence now demonstrates that reducing CV events with some GLP-1RAs and SGLT-2is is achievable, thereby enabling greater focus on reducing CV risk as a key treatment objective. For patients with ASCVD alone, a GLP-1RA shown to reduce CV risk is preferred; an SGLT-2i can be considered. For patients with HF or CKD, an SGLT-2i shown to reduce related events is preferred; a GLP-1RA shown to reduce CV risk can be considered. This is a real paradigm shift in our approach to managing patients with T2DM. Finally, the large self-managed nature of HF underscores the importance of individualized treatment through effective communication and the use of shared decision-making. ●

REFERENCES

1. Benjamin EJ, Virani SS, Callaway CW, et al. Heart Disease and Stroke Statistics-2018 Update: A Report From the American Heart Association. *Circulation.* 2018;137:e67-e492.
2. Di Angelantonio E, Kaptoge S, Wormser D, et al. Association of cardiometabolic multimorbidity with mortality. *JAMA.* 2015;314(1):52-60.
3. Mokdad AH, Ballestros K, Echko M, et al. The state of US health, 1990-2016: burden of diseases, injuries, and risk factors among US states. *JAMA.* 2018;319(14):1444-1472.
4. Shah AD, Langenberg C, Rapsomaniki E, et al. Type 2 diabetes and incidence of cardiovascular diseases: a cohort study in 1.9 million people. *Lancet Diabetes Endocrinol.* 2015;3(2):105-113.
5. Kannel WB, Hjortland M, Castelli WP. Role of diabetes in congestive heart failure: the Framingham study. *Am J Cardiol.* 1974;34(1):29-34.
6. Thrainsdottir IS, Aspelund T, Thorgeirsson G, et al. The association between glucose abnormalities and heart failure in the population-based Reykjavik study. *Diabetes Care.* 2005;28(3):612-616.
7. Dei Cas A, Khan SS, Butler J, et al. Impact of diabetes on epidemiology, treatment, and outcomes of patients with heart failure. *JACC Heart Fail.* 2015;3(2):136-145.
8. Komanduri S, Jadhao Y, Guduru SS, Cheriyath P, Wert Y. Prevalence and risk factors of heart failure in the USA: NHANES 2013 - 2014 epidemiological follow-up study. *J Community Hosp Intern Med Perspect.* 2017;7(1):15-20.
9. McAlister FA, Teo KK, Taher M, et al. Insights into the contemporary epidemiology and outpatient management of congestive heart failure. *Am Heart J.* 1999;138(1 Pt 1):87-94.
10. Nichols GA, Hillier TA, Erbey JR, Brown JB. Congestive heart failure in type 2 diabetes: prevalence, incidence, and risk factors. *Diabetes Care.* 2001;24(9):1614-1619.
11. de Simone G, Devereux RB, Chinali M, et al. Diabetes and incident heart failure in hypertensive and normotensive participants of the Strong Heart Study. *J Hypertens.* 2010;28(2):353-360.
12. Boonman-de Winter LJ, Rutten FH, Cramer MJ, et al. High prevalence of previously unknown heart failure and left ventricular dysfunction in patients with type 2 diabetes. *Diabetologia.* 2012;55(8):2154-2162.
13. Timmermans I, Denollet J, Pedersen SS, Meine M, Versteeg H. Patient-reported causes of heart failure in a large European sample. *Int J Cardiol.* 2018;258:179-184.
14. Erqou S, Lee CT, Suffoletto M, et al. Association between glycated haemoglobin and the risk of congestive heart failure in diabetes mellitus: systematic review and meta-analysis. *Eur J Heart Fail.* 2013;15(2):185-193.
15. Nichols GA, Gullion CM, Koro CE, Ephross SA, Brown JB. The incidence of congestive heart failure in type 2 diabetes: an update. *Diabetes Care.* 2004;27(8):1879-1884.
16. MacDonald MR, Petrie MC, Varyani F, et al. Impact of diabetes on outcomes in patients with low and preserved ejection fraction heart failure: an analysis of the Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM) programme. *Eur Heart J.* 2008;29(11):1377-1385.
17. Bertoni AG, Hundley WG, Massing MW, Bonds DE, Burke GL, Goff DC, Jr. Heart failure prevalence, incidence, and mortality in the elderly with diabetes. *Diabetes Care.* 2004;27(3):699-703.
18. van den Berge JC, Constantinescu AA, Boiten HJ, van Domburg RT, Deckers JW, Akkerhuis KM. Short- and long-term prognosis of patients with acute heart failure with and without diabetes: Changes over the last three decades. *Diabetes Care.* 2018;41(1):143-149.
19. Cavender MA, Steg PG, Smith SC, Jr., et al. Impact of diabetes mellitus on hospitalization for heart failure, cardiovascular events, and death: Outcomes at 4 years from the Reduction of Atherothrombosis for Continued Health (REACH) Registry. *Circulation.* 2015;132(10):923-931.
20. Centers for Disease Control and Prevention. National chronic kidney disease fact sheet, 2017. Published 2017. https://www.cdc.gov/diabetes/pubs/pdf/kidney_factsheet.pdf. Accessed July 26, 2018.
21. Bailey RA, Wang Y, Zhu V, Rupnow MF. Chronic kidney disease in US adults with type 2 diabetes: an updated national estimate of prevalence based on Kidney Disease: Improving Global Outcomes (KDIGO) staging. *BMC Res Notes.* 2014;7:415.
22. United States Renal Data System. 2017 USRDS Annual Data Report/Volume 2-ESRD in the United States. Published 2017. https://www.usrds.org/2017/download/2017_Volume_2_ESRD_in_the_US.pdf. Accessed August 17, 2018.
23. Murphy D, McCulloch CE, Lin F, et al. Trends in prevalence of chronic kidney disease in the United States. *Ann Intern Med.* 2016;165(7):473-481.
24. Afkarian M, Zelnick LR, Hall YN, et al. Clinical manifestations of kidney disease among US adults with diabetes, 1988-2014. *JAMA.* 2016;316(6):602-610.
25. de Boer IH, Rue TC, Hall YN, Heagerty PJ, Weiss NS, Himmelfarb J. Temporal trends in the prevalence of diabetic kidney disease in the United States. *JAMA.* 2011;305(24):2532-2539.
26. Kramer H, Boucher RE, Leehey D, et al. Increasing mortality in adults with diabetes and low estimated glomerular filtration rate in the absence of albuminuria. *Diabetes Care.* 2018;41(4):775-781.
27. Nathan DM, Buse JB, Davidson MB, et al. Management of hyperglycemia in type 2 diabetes: A consensus algorithm for the initiation and adjustment of therapy: a consensus statement from the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care.* 2006;29(8):1963-1972.
28. American Diabetes Association. Standards of Medical Care in Diabetes-2019. *Diabetes Care.* 2019;42(Suppl 1):S1-S193.
29. Bolen S, Tseng E, Hutfless S, et al. AHRQ Comparative Effectiveness Reviews. In: Diabetes Medications for Adults With Type 2 Diabetes: An Update. Rockville (MD): Agency for Healthcare Research and Quality (US); 2016: https://effectivehealthcare.ahrq.gov/topics/diabetes-update-2015/research/. Accessed February 2, 2018.
30. Gordon J, McEwan P, Idris I, Evans M, Puelles J. Treatment choice, medication adherence and glycemic efficacy in people with type 2 diabetes: a UK clinical practice database study. *BMJ Open Diabetes Res Care.* 2018;6(1):e000512.
31. Wimmer BC, Cross AJ, Jokanovic N, et al. Clinical outcomes associated with medication regimen complexity in older people: A systematic review. *J Am Geriatr Soc.* 2017;65(4):747-753.
32. Agency for Healthcare Research and Quality. The SHARE approach. Essential steps of shared decisionmaking: Expanded reference guide with sample conversation starters. Published 2014. https://www.ahrq.gov/sites/default/files/wysiwyg/professionals/education/curriculum-tools/shareddecisionmaking/tools/tool-2/share-tool2.pdf. Accessed April 30, 2019.
33. Kahn SE, Haffner SM, Heise MA, et al. Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. *N Engl J Med.* 2006;355(23):2427-2443.
34. Dormandy JA, Charbonnel B, Eckland DJ, et al. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomised controlled trial. *Lancet.* 2005;366(9493):1279-1289.
35. Lincoff AM, Wolski K, Nicholls SJ, Nissen SE. Pioglitazone and risk of cardiovascular events in patients with type 2 diabetes mellitus: a meta-analysis of randomized trials. *JAMA.* 2007;298(10):1180-1188.
36. Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. *N Engl J Med.* 2007;356(24):2457-2471.
37. Home PD, Pocock SJ, Beck-Nielsen H, et al. Rosiglitazone evaluated for cardiovascular outcomes--an interim analysis. *N Engl J Med.* 2007;357(1):28-38.
38. Home PD, Pocock SJ, Beck-Nielsen H, et al. Rosiglitazone evaluated for cardiovascular outcomes in oral agent combination therapy for type 2 diabetes (RECORD): a multicentre, randomised, open-label trial. *Lancet.* 2009;373(9681):2125-2135.
39. US Food and Drug Administration. Guidance for Industry. Diabetes Mellitus- Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes. Published 2008. https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guiddances/ucm071627.pdf. Accessed February 6, 2018.
40. Gerstein HC, Bosch J, Dagenais GR, et al. Basal insulin and cardiovascular and other outcomes in dysglycemia. *N Engl J Med.* 2012;367(4):319-328.
41. Marso SP, McGuire DK, Zinman B, et al. Efficacy and safety of degludec versus glargine in type 2 diabetes. *N Engl J Med.* 2017;377(8):723-732.
42. U.S. Food and Drug Administration. Center for Drug Evaluation and Research. Application number: 206538Orig1s000. Medical review(s). http://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/206538Orig1s000MedR.pdf. Accessed May 17, 2017.
43. Hernandez AF, Green JB, Janmohamed S, et al. Albiglutide and cardiovascular outcomes in patients with type 2 diabetes and cardiovascular disease (Harmony Outcomes): a double-blind, randomised placebo-controlled trial. *Lancet.* 2018;392(10157):1519-1529.

44. Lepore JJ, Olson E, Demopoulos L, et al. Effects of the novel long-acting GLP-1 agonist, albiglutide, on cardiac function, cardiac metabolism, and exercise capacity in patients with chronic heart failure and reduced ejection fraction. *JACC Heart Fail.* 2016;4(7):559-566.
45. Gerstein HC, Colhoun HM, Dagenais GR, et al. Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial. *Lancet.* 2019;394(10193):121-130.
46. 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.
47. Mann JFE, Orsted DD, Brown-Frandsen K, et al. Liraglutide and renal outcomes in type 2 diabetes. *N Engl J Med.* 2017;377(9):839-848.
48. Marso SP, Bain SC, Consoli A, et al. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med.* 2016;375(19):1834-1844.
49. Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med.* 2017;377(7):644-657.
50. Davies MJ, Merton K, Vijapurkar U, Yee J, Qiu R. Efficacy and safety of canagliflozin in patients with type 2 diabetes based on history of cardiovascular disease or cardiovascular risk factors: a post hoc analysis of pooled data. *Cardiovasc Diabetol.* 2017;16(1):40.
51. Wiviott SD, Raz I, Bonaca MP, et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. *N Engl J Med.* 2019;380(4):347-357.
52. Heerspink HJ, Johnsson E, Gause-Nilsson I, Cain VA, Sjostrom CD. Dapagliflozin reduces albuminuria in patients with diabetes and hypertension receiving renin-angiotensin blockers. *Diabetes Obes Metab.* 2016;18(6):590-597.
53. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med.* 2015;373(22):2117-2128.
54. Wanner C, Inzucchi SE, Lachin JM, et al. Empagliflozin and progression of kidney disease in type 2 diabetes. *N Engl J Med.* 2016;375(4):323-334.
55. American Diabetes Association. 9. Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes-2019. *Diabetes Care.* 2019;42(Suppl 1):S90-S102.
56. Beverly EA, Worley MF, Court AB, Prokopakis KE, Ivanov NN. Patient-physician communication and diabetes self-care. *J Clin Outcomes Manag.* 2016; 23(11).