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MINIREVIEW

CHRONIC HEART FAILURE AND DIABETES MELLITUS: TWO UNSUITABLY MATCHED PARTNERS

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Abstract

Diabetes mellitus (DM) and heart failure (HF) are often associated and each disease independently increases the risk for the other. It is well recognized that diabetes is a risk factor for mortality among individuals with heart failure. The risk of incident HF among patients with DM increases with older age, obesity, retinopathy, hypertension, coronary artery disease, peripheral arterial disease, nephropathy, longer duration of DM and higher N-terminal pro-B-type natriuretic peptide (NT-proBNP) value. The treatment of each pathology in the presence of the other raise difficulties in the clinical practice. First-line treatment of DM in patients with HF should include metformin and SGLT2 inhibitors; conversely, saxagliptin, pioglitazone and rosiglitazone are not recommended in patients with DM and HF.

Keywords: diabetes mellitus, heart failure, HbA1c, glucose-lowering agents.

Résumé

Insuffisance cardiaque chronique et diabète sucré: deux partenaires mal assortis

Le diabète sucré (DS) et l'insuffisance cardiaque (IC) sont souvent associés et chaque maladie augmente indépendamment le risque pour l'autre. Il est bien reconnu que le diabète est un facteur de risque de mortalité chez les personnes souffrant d'insuffisance cardiaque. Le risque d'incidence de l'IC chez les patients atteints de DS augmente avec l'âge, l'obésité, la rétinopathie, l'hypertension, la maladie coronarienne, la maladie artérielle périphérique, la néphropathie, la durée plus longue de la DS et le peptide natriurétique de type N-terminal pro-B supérieur (NT-proBNP). Le traitement de chaque pathologie en présence de l'autre pose des difficultés dans la pratique clinique. Le traitement de première intention de la DS chez les patients atteints d'IC devrait inclure la metformine et les inhibiteurs de SGLT2; à l'inverse, la saxagliptine, la pioglitazone et la rosiglitazone ne sont pas recommandées chez les patients atteints de DS et d'HF.

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Mots-clés: diabète sucré, insuffisance cardiaque, HbA1c, hypoglycémiants.

Introduction

Diabetes mellitus (DM) is a progressive chronic disease and its prevalence worldwide continues to increase. DM and heart failure (HF) are often associated and each disease independently increases the risk for the other. Also, epidemiological evidence indicates a strong association between DM and HF. It is well recognized that diabetes is a risk factor for mortality among individuals with heart failure[1]. Framingham Heart Study documented a 2.4-fold increased incidence of HF in diabetic men and a 5-fold increase of HF in diabetic women[2].

The prevalence of type 2 DM has increased by 30% globally in the past 10 years, with the number of patients affected increasing from 333 million in 2005 to 435 million in 2015[3].

The Emerging Risk Factor Collaboration, a meta-analysis of 102 prospective studies, showed that DM confers a two-fold excess risk of vascular outcomes (coronary heart disease, ischemic stroke, and vascular deaths), independent of other risk factors[4].

Also, poor glycemic control is associated with a greater risk for the development of HF[5]. DM is an important predictor of the development of symptomatic HF in patients with asymptomatic left ventricular (LV) systolic dysfunction[6]. The risk of incident HF among patients with DM increases with older age, obesity, retinopathy, hypertension, coronary artery disease (CAD), peripheral arterial disease, nephropathy, longer duration of DM and higher N-terminal pro-B-type natriuretic peptide (NT-proBNP) value[7,8] These data demonstrate the high incidence, prevalence and mortality of HF in individuals with diabetes.

Antidiabetic medications increase the risk of mortality and hospitalization for HF in patients with and without pre-existing heart failure[9]. DM can contribute to the development of structural heart disease and HF via systemic, myocardial, and cellular mechanisms. The altered systemic and cardiac glucose metabolism of patients throughout the evolution of the disease goes from impaired glucose control to DM and contributes to the structural and functional abnormalities of the heart, that culminate into cardiac dysfunction. In diabetic patients, HF develops not only because of the underlying CAD, but also because of the multiple metabolic and pathophysiological abnormalities induced by altered glucose metabolism.[10]

The European Society of Cardiology Guidelines on Diabetes, Pre-Diabetes and Cardiovascular Disease recommend a HbA1c target of <7% (<53 mmol/mol) in order to reduce microvascular complications, while evidence for an HbA1c target to reduce macrovascular risk is less compelling[11]. HbA1c targets should be individualized, with more-stringent goals [6.0–6.5% (42–48 mmol/mol)] in younger patients with a short duration of DM and no evidence of cardiovascular disease (CVD), if achieved without significant hypo-glycemia. Less-stringent HbA1c goals [e.g. <8% (64 mmol/mol) or ≤9% (75 mmol/mol)] may be adequate for elderly patients with long-standing DM and limited life expectancy, and frailty with multiple comorbidities, including hypo-glycemic episodes[11].

The American Heart Association Guidelines recommend precise glycemic targets or ranges, but most agree on HbA1c thresholds ≤7.0% for most of the adults with DM and no significant comorbidities or DM complications, who do not experience severe hypoglycemia[12-15]. Older patients (particularly those with established microvascular or macrovascular complications or extensive comorbid conditions) are advised to target higher HbA1c levels, up to 8% to 8.5%, depending on the guideline[11,12]. Patients with short life expectancy, advanced microvascular or macrovascular complications, or any end-stage comorbidity should be treated to minimize symptomatic hyperglycemia and hypoglycemia, corresponding to HbA1c 8% to 9%[19].

First-line treatment of DM in HF should include Metformin and SGLT2 inhibitors. Treatment of HF encompasses pharmacological and device therapies with confirmed benefits in randomized control trials (RCTs), in which 30–40% of patients had DM[20,21]. Treatment effects are consistent, with and without DM, with the exception of Aliskiren, which is not recommended in patients with DM because of the risk of serious adverse events[17,18]. Lifestyle management should be part of the care of patients with DM and HF, because DM is linked to obesity, inactivity and poor dietary choices[22]. Also, exercise is safe and beneficial in patients with HF and DM[19]. Future research should address the risks of polypharmacy, in terms of adherence, adverse reactions and interactions, especially among vulnerable patients with HF and DM, such as elderly patients[11].

Glucose-lowering agents: new evidence from cardiovascular outcome trials

The classes of antidiabetic drugs are synthesized in Table 1. Metformin is safe in all stages of HF with

Table 1. Drugs used in DM. GLP-RAs = Glucagon-like peptide-1 receptor agonists. DPP4 = Dipeptidyl peptidase-4. SGLT2 = Sodium-glucose co-transporter-2

Insulin Senzitisers
Metformin
Pioglitazone
Insulin providers
Insulin
Sulfonylureas
Meglitinides
Incretin-based therapies
GLP1-RAs
DPP4
Gastrointestinal glucose absorption inhibitor (acarbose)
Renal glucose reuptake inhibitors
SGLT2 inhibitors

preserved or stable moderately reduced renal function (i.e. eGFR >30 mL/min), and results in a lower risk of death and HF hospitalization compared with insulin and sulfonylureas[23]. Also, metformin reduced the rate of myocardial infarction (MI) and increased survival when the study was extended for another 8–10 years of intensified therapy, including the use of other drugs[24].

Data on the effects of sulfonylureas on HF are inconsistent. Addition of a sulfonylurea to metformin was associated with a higher risk of adverse events and death, compared with the combination of metformin and a DPP4 inhibitor[25]. Since the 1960s, there has been an ongoing debate on the cardiovascular (CV) safety of sulfonylureas. Also, sulfonylureas carry the risk of hypoglycemia.

Acarbose didn't alter major adverse cardiovascular events (MACE) in patients with impaired glucose tolerance (IGT) and cardiovascular disease (CVD) during the large 5-year prospective ACE trial[26].

Thiazolidinediones are not recommended in patients with DM and symptomatic HF[11]. The PROspective pioglitazone Clinical Trial In macro vascular Events (PROactive) of pioglitazone was a neutral trial for its composite primary outcome[27,28]. Patients with type 2DM and established CVD were randomized to either pioglitazone or placebo. The primary endpoint was time to all-cause mortality, nonfatal myocardial infarction, stroke, acute coronary syndrome (ACS), endovascular or surgical intervention on the coronary or leg arteries or amputation above the ankle. Among 5238 randomized patients, there was no significant difference between pioglitazone and placebo. The main secondary endpoint of all-cause mortality, nonfatal myocardial infarction and stroke was significantly lower in the pioglitazone arm, but the number of patients with new-onset HF was greater in the pioglitazone arm than in the placebo group[27,28].

The Thiazolidinediones Or Sulfonylureas and Cardiovascular Accidents Intervention Trial (TOSCA.IT)—a large, randomized, but unblinded comparison of pioglitazone vs. sulfonylurea as add-on to metformin—was stopped prematurely because of futility. The composite endpoint and the individual components of the composite endpoint were similar in the two groups[16]. The results of this trial showed over a median observation period of almost 5 years that both sulfonylureas (mostly glimepiride and gliclazide) or pioglitazone have a similar effect as add-on to metformin on the incidence of total cardiovascular events. This finding suggests that in patients with type 2DM without CVD and with reasonable glucose control, the choice of the treatment strategy when metformin monotherapy fails might not have a major effect on CV complications. The two treatment strategies effectively controlled blood glucose in the long-term, with few clinically relevant side-effects.

In the ORIGIN trial, 12,537 people (mean age 63.5 years) at high CVD risk, with impaired fasting glucose (IFG), IGT, or DM, were randomized to long-acting insulin glargine or standard care. After a median follow-up of 6.2 years, the rates of CV outcomes were similar in the two groups[29]. Also, DEVOTE, a double-blind comparison of ultra-long-acting degludec o.d. (n=3818) with insulin glargine for 1.8 years in patients with DM at high CV risk, found no significant differences in MACE[30].

Seven CVOTs have examined the effects of GLP1-RAs on CV events in patients with DM and high CV risk. In the Evaluation of Lixisenatide in Acute Coronary Syndrome (ELIXA) trial, Lixisenatide was non-inferior to placebo, but didn't significantly affect a four-point MACE[31].

In the Exenatide Study of Cardiovascular Event Lowering (EXSCEL) study of a DM population, in whom 73% had experienced a previous CV event, Exenatide 2 mg once weekly showed non-inferiority vs. placebo and a numerical, but non-significant, 14% reduction of the primary three-point MACE[32].

The Peptide Innovation for Early Diabetes Treatment (PIONEER)-6 trial, also a phase III pre-approval Cardiovascular Outcome Trial (CVOT), examined the effect of oral Semaglutide vs. placebo on CV outcomes in patients with T2DM and high CV risk. Semaglutide significantly reduced the risk for CV death events with oral Semaglutide vs. events with placebo and all-cause death[33]. There was a significant increase in retinopathy complications, including

vitreous hemorrhage, blindness, or requirement for intravitreal agent or photocoagulation, the implications of which require further study[33].

Saxagliptin is a selective dipeptidyl peptidase-4 (DPP-4) inhibitor. The Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus–Thrombolysis in Myocardial Infarction 53 (SAVOR-TIMI 53) trial was designed to evaluate the long-term cardiovascular efficacy and safety of Saxagliptin in patients with DM at risk of cardiovascular events[34]. Over a median of 2.1 years follow-up, Saxagliptin neither increased nor decreased the risk of the primary or secondary composite endpoints. This report explores further on the observation surrounding hospitalizations for HF by examining baseline risk factors associated with an increased risk of hospitalizations, the timing of them and the risk of recurrent events. Also, it reveals the association between baseline levels of natriuretic peptides and future hospitalizations for HF events[34].

The CV benefits of SGLT2 inhibitors are mostly unrelated to the extent of glucose lowering and occur too early to be the result of weight reduction. The rapid separation of placebo and active arms in the four studies in terms of reduction in HF hospitalizations indicates that the beneficial effects achieved in these trials are more likely the result of a reduction in HF-associated events[35-38].

For the first time in the history of DM, there are data from several CVOTs that indicate CV benefits from the use of glucose-lowering drugs in patients with CVD or at very high/high CV risk. The results obtained from these trials, using both GLP1-RAs (LEADER, SUSTAIN-6, Harmony Outcomes, REWIND, and PIONEER 6) and SGLT2 inhibitors (EMPA-REG OUTCOME, CANVAS, DECLARE-TIMI 58, and CREDENCE), strongly suggest that these drugs should be recommended in patients with T2DM with prevalent CVD or very high/high CV risk, such as those with target-organ damage or several cardiovascular risk factors (CVRFs), whether they are treatment-naïve or already on metformin. In addition, based on the mortality benefits seen in LEADER and EMPA-REG OUTCOME, liraglutide is recommended in patients with prevalent CVD or very high/high CV risk, and empagliflozin is recommended in patients with prevalent CVD, to reduce the risk of death. The recommendation for empagliflozin is supported by a recent meta-analysis which found high heterogeneity between CVOTs in mortality reduction[39].

Specific cardiovascular therapies

Patients with DM treated with long-term beta-blocker have recently been evaluated by a prospective observational study, as well as a *post hoc* analysis from the ACCORD study, suggesting increased all-cause death in DM patients treated with beta-blockers[40,41]. Carvedilol and nebivolol may be preferred because of their ability to improve insulin sensitivity, with no negative effects on glycemic control[42,43].

Treatment with angiotensin-converting enzyme inhibitors (ACEIs) is recommended to prevent major CV events and HF in all patients with chronic coronary syndrome (CCS) or ACS and systolic LV dysfunction, based on a systematic review of randomized controlled trials (RCTs)[44].

Nitrates, preferably short-acting, and calcium channel blockers are indicated for relief of angina symptoms, are frequently used when beta-blockers are contraindicated or not tolerated, or in addition to beta-blockers if patients remain symptomatic, but offer no prognostic benefit[45].

Statins are safe and generally well tolerated by patients with DM. Consistent data have demonstrated the efficacy of statins in preventing CV events and reducing CV mortality in patients with DM, with no evidence for sex differences[46].

Ranolazine is a selective inhibitor of the late sodium current, effective in the treatment of chronic angina[45]. Ranolazine also has metabolic effects and may lower HbA1c levels in patients with DM[47].

Trimetazidine is an anti-ischemic metabolic modulator that improves glucose control and cardiac function in patients with DM[48,49]. These drugs should be considered as second line treatment[44].

There is no evidence to support different antiplatelet strategies in patients with ACS or CCS with vs without DM[11,50].

In the SHIFT trial (Systolic Heart Failure Treatment with the If Inhibitor Ivabradine Trial), Ivabradine significantly reduced the primary endpoint of CVD or HF hospitalization in patients with and without DM. There was also a significant reduction in HF hospitalization in both groups[51].

Conclusions

HF has a high prevalence in populations with diabetes, due to a high incidence rate. This underlines the need to focus on the prevention of HF in individuals with diabetes. Also, the coexistence of DM and HF leads to a higher risk of hospitalization for HF and all-cause death[52,53]. Prevention of HF should be a priority. First-line treatment of DM in patients with

HF should include metformin and SGLT2 inhibitors; conversely, saxagliptin, pioglitazone and rosiglitazone are not recommended in patients with DM and HF[11].

Author contributions

M.A.M. and C.C.D. conceived the original draft preparation. G.G., A.M.A.S., and O.G.B. were responsible for conception and design of the review. M.A.M. *and T.P.N. were responsible for the data acquisition.* M.A.M., G.G. *and C.C.D. were responsible for the collection and assembly of the articles/published data, and their inclusion and interpretation in this review. All authors contributed to the critical revision of the manuscript for valuable intellectual content. All authors have read and agreed to the published version of the manuscript.*

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References

1. Bell DS. Heart failure: the frequent, forgotten, and often fatal complication of diabetes. *Diabetes Care.* 2003;26:2433–2441.
2. Kannel WB, Hjortland M, Castelli WP. Role of diabetes in congestive heart failure: the Framingham study. *Am J Cardiol.* 1974;34:29-34.
3. GBD 2015. Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet.* 2016; 388:1545–1602.
4. Emerging risk factors Collaboration, Sarwar N, Gao P, Seshasai SR. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. *Lancet.* 2010;375:2215-2222.
5. Bahrami H, Bluemke DA, Kronmal R, et al. Novel metabolic risk factors for incident heart failure and their relationship with obesity: the MESA (Multi-Ethnic Study of Atherosclerosis) study. *J Am Coll Cardiol.* 2008; 51:1775–1783.
6. Cleland JG, Swedberg K, Follath F, et al. Study Group on Diagnosis of the Working Group on Heart Failure of the European Society of Cardiology. The EuroHeart Failure survey programme: a survey on the quality of care among patients with heart failure in Europe, part 1: patient characteristics and diagnosis. *Eur Heart J.* 2003; 24:442–463.
7. 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; 27:1879–1884.
8. Bibbins-Domingo K, Lin F, Vittinghoff E, et al. Predictors of heart failure among women with coronary disease. *Circulation.* 2004; 110:1424–1430.
9. Rosano GMC, Vitale C, Seferovic P. Heart failure in patients with diabetes mellitus. *Card Fail Rev.* 2017;3(1):52-55.
10. Rosano GM, Vitale C, Fragasso G. Metabolic therapy for patients with diabetes mellitus and coronary artery disease. *Am J Cardiol.* 2006;98(5A):14J–18J.
11. Cosentino F, Grant PJ, Aboyans V. 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD: The Task Force for diabetes, pre-diabetes, and cardiovascular diseases of the European Society of Cardiology (ESC) and the European Association for the Study of Diabetes (EASD). *Eur Heart J.* 2020;41(2):255-323.
12. American Diabetes Association. 6. Glycemic targets: Standards of Medical Care in Diabetes-2018. *Diabetes Care.* 2018; 41(suppl 1):S55–S64
13. Conlin PR, Colburn J, Aron D, Pries RM, Tschanz MP, Pogach L. Synopsis of the 2017 U.S. Department of Veterans Affairs/U.S. Department of Defense clinical practice guideline: management of type 2 diabetes mellitus. *Ann Intern Med.* 2017; 167:655–663. aa
14. Garber AJ, Abrahamson MJ, Barzilay JI, et al. Consensus statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the comprehensive type 2 diabetes management algorithm: 2018 executive summary. *Endocr Pract.* 2018; 24:91–120.
15. NICE. Type 2 diabetes in adults: management. National Institute for Health and Care Excellence website.Published December 2015. Updated May 2017. Available at https://www.nice.org.uk/guidance/ng28 (accessed December 1, 2017).
16. Vaccaro O, Masulli M, Nicolucci A. Thiazolidinediones or sulfonylureas cardiovascular accidents intervention trial (TOSCA.IT) study group; Italian Diabetes Society. Effects on the incidence of cardiovascular events of the addition of pioglitazone versus sulfonylureas in patients with type 2 diabetes inadequately controlled with metformin (TOSCA.IT): a randomized, multicenter trial. *Lancet Diabetes Endocrinol.* 2017;5:887-897.
17. Gheorghiade M, Bohm M, Greene SJ. ASTRONAUT Investigators and Coordinators. Effect of Aliskiren on postdischarge mortality and heart failure readmissions among patients hospitalized for heart failure: the ASTRONAUT randomized trial. JAMA. 2013;309:1125-35
18. Rosano GMC, Seferovic P, Farmakis D. Renin inhibition in heart failure and diabetes:the. Real story. *Eur J Heart Fail.* 2019;20:149-151.
19. Shannon M Dunlay, MD, MS. Type 2 Diabetes Mellitus and Heart Failure: A scientific statement from the American Heart Association and the Heart Failure Society of America: This statement does not represent an update of the 2017 ACC/AHA/HFSA heart failure guideline update. *Circulation.* 2019;140(7):e294-2324.
20. Diaconu C, Nastasa A, Zaki AR, Arsalan M. Type 2 diabetes: a driver for chronic heart failure. *The 2nd International Conference on Interdisciplinary Management of Diabetes Mellitus and its Complications – Diabetes mellitus as cardiovascular disease, INTERDIAB 2016 Proceedings,* pag. 201-210. Ed. Niculescu. Editors Cristian Serafinceanu, Octavian Negoita, Viviana Elian.
21. Dobrica EC, Gaman MA, Cozma MA, Bratu OG, Pantea Stoian A, Diaconu CC. Polypharmacy in type 2 diabetes mellitus: insights from an internal medicine department. *Medicina.* 2019;55(8), 436.

22. Gaman MA, Dobrica EC, Pascu EG, et al. Cardiometabolic risk factors for atrial fibrillation in type 2 diabetes mellitus: focus on hypertension, metabolic syndrome and obesity. *Journal of Mind and Medical Sciences*. 2019;6(1):157-161.
23. Eurich DT, Majumdar SR, McAlister FA. Improved clinical outcomes associated with metformin in patients with diabetes and heart failure. *Diabetes Care*. 2005;28:2345-2351.
24. Holman RR, Paul SK, Bethel MA. 10-year follow-up of intensive glucose control in type 2 diabetes. *N Engl J Med*. 2008;359:1577-1589.
25. Eriksson JW, Bodegard J, Nathanson D. Sulphonylurea compared to DPP-4-inhibitors in combination with metformin carries increased risk of severe hypoglycemia, cardiovascular events, and all-cause mortality. *Diabetes Res Clin Pract*. 2016;117:39-47.
26. Holman RR, Coleman RL, Chan JCN. ACE Study Group. Effects of acarbose on cardiovascular and diabetes outcomes in patients with coronary heart disease and impaired glucose tolerance (ACE): a randomized, double-blind, placebo-controlled trial. *Lancet Diabetes Endocrinol*. 2017;5:877-886.
27. American Diabetes Association. Cardiovascular disease and risk management: standards of medical care in diabetes 2018. *Diabetes Care*. 2018:41:S86-S104.
28. Dormandy JA, Charbonnel B, Eckland DJ. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study. A randomized trial. *Lancet*. 2005;366:1279-1289.
29. Gerstein HC, Bosch J, Dagenais GR. Basal insulin and cardiovascular and other outcomes in dysglycemia. *N Engl J Med*. 2012;367:319-328.
30. Marso SP, McGuire DK, Zinman B; Devote study group. Efficacy and safety of degludec versus glargine in type 2 diabetes. *N Engl J Med*. 2017;377:727-732.
31. Pfeffer MA, Claggett B, Diaz R; ELIXA Investigators. Lixisenatide in patients with type 2 diabetes and acute coronary syndrome. *New Engl J Med*. 2015;373:2247-2257.
32. Holman RR, Bethel MA, Mentz RJ. EXSCEL Study Group. Effects of once-weekly exenatide on cardiovascular outcomes in type 2 diabetes. *N Engl J Med*. 2017;377:1228-1239.
33. Husain M, Birkenfeld AL, Donsmark M. PIONEER 6 Investigators. Oral semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med*. 2019;381:841-851.
34. Scirica BM, Bhatt DL, Braunwald E, et al. The design and rationale of the saxagliptin assessment of vascular outcomes recorded in patients with diabetes mellitus-thrombolysis in myocardial infarction (SAVOR-TIMI) 53 study. *Am Heart J*. 2011;162:818–825.
35. Sattar N, McLaren J, Kristensen SL. SGLT2 inhibition and cardiovascular events: why did EMPA-REG Outcomes surprise and what were the likely mechanisms? *Diabetologia*. 2016;59:1333-1339.
36. Marx N, McGuire DK. Sodium-glucose cotransporter-2 inhibition for the reduction of cardiovascular events in high-risk patients with diabetes mellitus. *Eur Heart J*. 2016;37:3192-3200.
37. Vallon V, Thomson SC. Targeting renal glucose reabsorption to treat hyperglycemia: the pleiotropic effects of SGLT2 inhibition. *Diabetologia*. 2017;60:215-225.
38. Verma S, McMurray JJV, Cherney DZI. The metabolodiuretic promise of sodium-dependent glucose co-transporter 2 inhibition: the search for the sweet spot in heart failure. *JAMA Cardiol*. 2017:2:939-940.
39. Zelner TA, Wiviott ST, Raz I. SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. *Lancet*. 2019;393:31-39.
40. Tsujimotpo T, Sugiyama T, Shapiro MF. Risk of cardiovascular events in patients with diabetes mellitus on beta-blockers. *Hypertension*. 2017;70:103-110.
41. Tsujimoto T, Kajio H, Shapiro MF. Risk of all-cause mortality in diabetic patients taking beta-blockers. *Mayo Clin Proc*. 2018;93409-418.
42. Bakris GL, Fonseca V, Katholi RE. GEMINI Investigators. Metabolic effects of carvedilol vs metoprolol in patients with type 2 diabetes mellitus and hypertension: a randomized controlled trial. *JAMA*. 2004;292:2227-2236.
43. Ozylidiz AG, Eroglu S, Bal U. Effects of carvedilol compared to nebivolol on insulin resistance and lipid profile in patients with essential hypertension. *J Cardiovasc Pharmacol Ther*. 2016;22:65-70.
44. ACE Inhibitor Myocardial Infarction Collaborative Group. Indications for ACE inhibitors in the early treatment of acute myocardial infarction: systematic overview of individual data from 100,000 patients in randomized trials. *Circulation*. 1998;97:2202-2212.
45. Knuuti J, Wijns W, Saraste A, et al. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. *Eur Heart J*. 2020;41(3):407-477.
46. Preiss D, Seshasai SR, Welsh P. Risk of incident diabetes with intensive-dose compared with moderate-dose statin therapy: a meta-analysis. *JAMA*. 2011;305:2556-2564.
47. Gilbert BW, Sherard M, Little L. Antihyperglycemic and metabolic effects of ranolazine in patients with diabetes mellitus. *Am J Cardiol*. 2018;121:509-512.
48. Fragasso G, Piatti Md PM, Monti L. Short- and long-term beneficial effects of trimetazidine in patients with diabetes and ischemic cardiomyopathy. *Am Heart J*. 2003;146:E18.
49. Li R, Tang X, Jing Q. The effect of trimetazidine treatment in patients with type 2 diabetes undergoing percutaneous coronary intervention for AMI. *Am J Emerg Med*. 2017;35:1657-1661.
50. Ryden L, Grant PJ, Anker SD. ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD: The Task Force on diabetes, pre-diabetes, and cardiovascular diseases of the European Society of Cardiology (ESC) and developed in collaboration with the European Association for the Study of Diabetes (EASD). *Eur Heart J*. 2013;34:3035-3087.
51. Komajda M, Tavazzi L, Francq BG; on behalf of the SHIFT Investigators. Efficacy and safety of ivabradine in patients with chronic systolic heart failure and diabetes: an analysis from the SHIFT trial. *Eur J Heart Fail*. 2015; 17:1294–1301.
52. Diaconu C. Chronic heart failure: diabetes fuels a worse prognosis. *Arch Balk Med Union*. 2015;50(1):5-8.
53. Diaconu C, Balaceanu A, Bartos D. The landscape of rehospitalization in chronic heart failure patients: need for an integrated approach. *Arch Balk Med Union*. 2014;49(3):247-250.