European Heart Journal Supplements (2019) **21** (Supplement M), M20–M24
The Heart of the Matter
doi:10.1093/eurheartj/suz219

ESC European Society of Cardiology

Physiological monitoring of the complex multimorbid heart failure patient – diabetes and monitoring glucose control

Petar M. Seferović[1,2]* and Pardeep S. Jhund[3]

[1]*University of Belgrade Faculty of Medicine, 8 Koste Todorovića, 11000 Belgrade, Serbia;*
[2]*Serbian Academy of Sciences and Arts, Belgrade, Serbia; and*
[3]*British Heart Foundation Cardiovascular Research Centre, Institute of Cardiovascular and Medical Sciences, University of Glasgow, 126 University Place, Glasgow G12 8TA, UK*

KEYWORDS
Heart failure;
Diabetes;
Therapy

Heart failure (HF) is a global epidemic, particularly affecting the elderly and/or frail patients often with comorbidities. Amongst the comorbidities, type 2 diabetes mellitus (T2DM) is highly prevalent and associated with higher morbidity and mortality. We review the detection and treatment of T2DM in HF and the need to balance the risk of hypoglycaemia and overall glycaemic control. Despite large attributable risks, T2DM is often underdiagnosed in HF. Therefore there is a need for systematic monitoring (screening) for undetected T2DM in HF patients. Given that patients with HF are at greater risk for developing T2DM compared with the general population, an emphasis also has to be placed on regular reassessment of glycaemic status during follow-up. Therefore, glucose-lowering therapies (e.g. sodium-glucose cotransporter-2 inhibitors, SGLT-2 inhibitors) with a known benefit for the prevention or delay of HF hospitalization could be considered early in the course of T2DM, to optimise treatment and reduce cardiovascular (CV) risk. Although intensive glycaemic control has been shown to effectively reduce the risk of microvascular complications in T2DM, these same trials have shown either no reduction in CV outcomes, or even an increase in mortality with tight glycaemic control (i.e. targeting HbA1c levels $<$7.0%). More lenient glycaemic targets (e.g. HbA1c levels 7.0-8.0%) may be more appropriate for HF patients with T2DM. The 2016 ESC Guidelines for the diagnosis and treatment of HF proposed metformin as the first-line therapy, given its long-standing use and low risk of hypoglycaemia. More recently, several novel glucose lowering-medications have been introduced, including dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 receptor agonists (GLP-1 RA), and SGLT-2 inhibitors. The most consistent reduction in the risk of HF hospitalisation has been shown with the three SGLT-2 inhibitors (empagliflozin, canagliflozin and dapagliflozin) which now offer improved outcomes in patients with both HF and T2DM.

Introduction

Heart failure (HF) is a global epidemic, currently affecting ~26 million patients worldwide.[1] The majority of HF population are elderly and/or frail patients that commonly have one or more associated comorbidities.[2] In addition to poorer functional status and worse outcomes, comorbidities often require more complex treatment regimens and require monitoring of treatment responses.[2,3] Amongst the comorbidities, Type 2 diabetes mellitus (T2DM) is highly prevalent (~30–40%) and associated with higher morbidity and mortality in HF patients with either preserved ejection

*Corresponding author. Tel/Fax: +381 11 361 47 38,
Email: seferovic.petar@gmail.com

fraction (HFpEF) or reduced ejection fraction (HFrEF).[4-6] In addition, treatment with several glucose-lowering medications may predispose to hypoglycaemia, which is associated with a higher risk of cardiovascular (CV) events and mortality.[7] In the present review, we will focus on the detection of undetected T2DM to ensure treatments to prevent its associated morbidity and mortality are initiated while balancing the risk of hypoglycaemia and overall glycaemic control.

Monitoring of undetected Type 2 diabetes mellitus in heart failure

The presence of T2DM nearly doubles the risk of HF independently of other clinical characteristics, and contributes to 3.1% of population-attributable risk for HF.[8] T2DM confers the largest risk amongst the modifiable risk factors (i.e. smoking, dyslipidaemia, hypertension, and obesity), suggesting that greater use of therapies for T2DM could have a large impact on the prevention of HF and the complications of T2DM.[9]

Importantly, despite large attributable risks, T2DM is often underdiagnosed in HF.[10,11] In a large pan-European Registry of ambulatory patients with HFrEF and HFpEF, 19% had previously unknown (undetected) T2DM.[12] Similarly, one-fifth of the patients in several observational studies of HFrEF, also had previously undiagnosed T2DM.[13,14] Clinical trials suggest that 21–26% and 22%, respectively, of the HFrEF and HFpEF population may have previously unknown T2DM.[10,11] Accordingly, there is a great unmet need for the systematic monitoring (screening) for undetected T2DM in the clinical assessment of patients with HF. This could be achieved by using any of the following: overnight fasting plasma glucose levels, 2-h glucose tolerance test, or glycosylated haemoglobin A1c (HbA1c) levels, in accordance with criteria proposed by current recommendations.[4,15] Given that patients with HF are at greater risk for developing T2DM compared with the general population,[16] an emphasis has to be placed on regular reassessment of glycaemic status during the long-term follow-up of HF patients. Therefore, glucose-lowering therapies (e.g. sodium-glucose cotransporter-2 inhibitors, SGLT-2 inhibitors) known to prevent or delay of HF hospitalization could be considered early in the course of T2DM, to optimize treatment and reduce CV risk, as stipulated by the European Society of Cardiology (ESC) Guidelines.[17,18]

Monitoring of hypoglycaemia

Although intensive glycaemic control has been shown to effectively reduce the risk of microvascular complications in T2DM, large clinical trials have failed to demonstrate that this strategy lowers the risk of CV events or HF.[19,20] On the contrary, these trials have shown either no improvement in CV outcomes,[19] or even an increase in mortality with tight glycaemic control (i.e. targeting HbA1c levels <7.0%).[20] All of the studies have demonstrated an increased risk of hypoglycaemic episodes with intensive glycaemic control, which in turn has been widely associated with greater mortality in observational studies.[19-21] Although the possible mechanisms by which hypoglycaemia may increase mortality are not clear, postulated mechanisms include increased sympathetic tone, abnormal cardiac repolarization (proarrhythmia), induction of cardiac and cerebral ischaemia, enhanced inflammation, and endothelial dysfunction.[22]

Hypoglycaemia is frequently associated with T2DM treatment including insulin and/or insulin secretagogues (i.e. sulphonylurea and glinides), either as monotherapy or in combination with other glucose-lowering medications.[23] The risk of hypoglycaemia (in particular, severe hypoglycaemia; i.e. plasma glucose <2.8 mmol/L), is potentiated by older age, frailty, and comorbidities frequently encountered in HF, such as chronic kidney disease (CKD) and hepatic dysfunction.[22,24] In addition, decompensated HF, worsening renal function, infection and other critical illnesses, may aggravate the risk of hypoglycaemia. In some instances, concomitant use of medications intended for the treatment of HF (e.g. beta-blockers, angiotensin converting enzyme inhibitors) or concomitant disorders (e.g. fluoroquinolone antibiotics) may exacerbate the risk of hypoglycaemia,[25] however, their benefit far outweighs the small potential risk of hypoglycaemia. In patients with HF, hypoglycaemic episodes often remain asymptomatic and undiagnosed, thus imposing a substantial risk to the affected individuals.[24]

Given the high risk of hypoglycaemia, current recommendations propose monitoring of plasma glucose levels in all critically ill patients with HF and T2DM, including decompensated HF, acute coronary events, serious infection, and in emergency settings.[15] Self-plasma glucose monitoring could also be recommended on individual basis to improve glycaemic control and the safety of T2DM treatment.[15] Dose-adjustment or even a discontinuation of a glucose-lowering agent may be required when initiating/intensifying T2DM therapy in a patient already receiving insulin/insulin secretagogues.[15] Individualized therapy goals and a multidisciplinary team management (cardiologists, diabetologists, and HF nurses) merits consideration in patients in need of complex glucose-lowering therapies (two or more drugs) to reduce the risk of hypoglycaemia.

Monitoring of glucose control

Glucose control is primarily assessed with HbA1c, which is generally reliable, except in patients with comorbidities affecting erythrocyte turnover, such as severe anaemia and end-stage CKD, which may decrease diagnostic accuracy.[15] Although higher levels of HbA_{1c} have a direct (linear) association with higher morbidity and mortality in patients with T2DM and HF, not receiving treatment with glucose-lowering drugs,[26] this relationship changes once treatments for T2DM have been introduced. A number of observational studies have reported either a U-shaped,[27,28] or an inverse relationship between HbA_{1c} levels and mortality in HF patients treated with glucose-lowering medications.[29,30] This indicates that lenient glycaemic targets (e.g. HbA1c levels 7.0–8.0%) may be more appropriate for HF patients with T2DM. This is also in line with the findings from randomized trials reporting lack of benefit (or even

higher risks) with intensive glycaemic control (typically targeting HbA1c <7.0%) patients with T2DM.[19,20]

Most of these studies have been conducted with traditional glucose-lowering medications (i.e. metformin, sulphonylurea, glinides, thiazolidinediones, and insulin). Despite efforts to understand the mechanisms linking intensive glycaemic control with higher CV risks, it is still uncertain whether the risk could only be attributed to hypoglycaemia, or whether effects beyond glycaemic control could have been involved. In addition to hypoglycaemia, renal sodium, and water retention (thiazolidinediones and insulin)[31,32] and weight gain (sulphonylureas, thiazolidinediones, and insulin)[15] have been postulated as potential contributors to a higher HF risk with several glucose-lowering drugs.[33] The 2016 ESC Guidelines for the diagnosis and treatment of HF propose that glycaemic control in patients with T2DM and HF needs to be lenient and achieved with a preferential use of medications with confirmed safety and efficacy.[18] In that respect, metformin is recommended as the first-line therapy, given its long-standing use and low risk of hypoglycaemia.[18] A substantial body of observational data suggests that metformin could be safely used in complex, multimorbid patients, including those with advanced HF and/or moderate CKD or hepatic disease.[34–36] Thiazolidinediones are not recommended due to the higher risk of HF.[18] Insulin and insulin secretagogues can be used, but should be done carefully, in particular, in patients prone to hypoglycaemia and while monitoring for fluid retention.

Recently, several novel glucose-lowering medications have been introduced, including dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 receptor agonists, and SGLT-2 inhibitors. They are all associated with a low risk of hypoglycaemia when used as monotherapy in combination with metformin. Nevertheless, when combined with insulin/secretagogues, the risk of hypoglycaemia may increase, warranting appropriate dose-adjustment and glycaemia monitoring.[15] Despite low risk of hypoglycaemia, DPP-4 inhibitors have failed to show benefit in reducing CV or HF risk, whilst saxagliptin has been associated with a statistically significant 27% increase in the risk of HF hospitalization.[37] Glucagon-like peptide-1 receptor agonists have a neutral effect on the risk of HF, but caution is advised in patients with advanced HF, based on safety concerns from small randomized trials with lixisenatide.[38,39] A consistent reduction in the risk of HF hospitalization has been shown with the three SGLT-2 inhibitors (empagliflozin, canagliflozin, and dapagliflozin).[40] It appears that the effect on HF risk reduction with SGLT-2 inhibitors is similar across the spectrum of HbA1c levels, which may provide a safety margin for patients prone to hypoglycaemia. Hence, these drugs could be recommended for the treatment of patients with T2DM to prevent or delay HF hospitalization.[41] However, monitoring of renal function and volume status in patients receiving a SGLT-2 inhibitors and in those with an estimated glomerular filtration rate $<30\,mL/min/m^2$ is necessary. The mechanism of action of the SGLT-2 inhibitors in HF remains a subject of considerable scientific interest[42,43].

Conclusions

HF and diabetes are increasingly being seen together and need to be managed in concert[44,45]. Recent and upcoming trials look set to expand our knowledge and treatment options for HF and diabetes[46].

Conflict of interest: none declared.

References

1. Ambrosy AP, Fonarow GC, Butler J, Chioncel O, Greene SJ, Vaduganathan M, Nodari S, Lam CSP, Sato N, Shah AN, Gheorghiade M. The global health and economic burden of hospitalizations for heart failure: lessons learned from hospitalized heart failure registries. *J Am Coll Cardiol* 2014;**63**:1123–1133.
2. van Deursen VM, Urso R, Laroche C, Damman K, Dahlström U, Tavazzi L, Maggioni AP, Voors AA. Co-morbidities in patients with heart failure: an analysis of the European Heart Failure Pilot Survey. *Eur J Heart Fail* 2014;**16**:103–111.
3. Damman K, Valente MA, Voors AA, O'Connor CM, van Veldhuisen DJ, Hillege HL. Renal impairment, worsening renal function, and outcome in patients with heart failure: an updated meta-analysis. *Eur Heart J* 2014;**35**:455–469.
4. Seferović PM, Petrie MC, Filippatos GS, Anker SD, Rosano G, Bauersachs J, Paulus WJ, Komajda M, Cosentino F, de Boer RA, Farmakis D, Doehner W, Lambrinou E, Lopatin Y, Piepoli MF, Theodorakis MJ, Wiggers H, Lekakis J, Mebazaa A, Mamas MA, Tschöpe C, Hoes AW, Seferović JP, Logue J, McDonagh T, Riley JP, Milinković I, Polovina M, van Veldhuisen DJ, Lainscak M, Maggioni AP, Ruschitzka F, McMurray JJV. Type 2 diabetes mellitus and heart failure: a position statement from the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail* 2018;**20**:853–872.
5. Kristensen SL, Mogensen UM, Jhund PS, Petrie MC, Preiss D, Win S, Køber L, McKelvie RS, Zile MR, Anand IS, Komajda M, Gottdiener JS, Carson PE, McMurray JJ. Clinical and echocardiographic characteristics and cardiovascular outcomes according to diabetes status in patients with heart failure and preserved ejection fraction: a report from the I-Preserve Trial (Irbesartan in Heart Failure With Preserved Ejection Fraction). *Circulation* 2017;**135**:724–735.
6. MacDonald MR, Petrie MC, Varyani F, Ostergren J, Michelson EL, Young JB, Solomon SD, Granger CB, Swedberg K, Yusuf S, Pfeffer MA, McMurray JJV. 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**:1377–1385.
7. Ukena C, Dobre D, Mahfoud F, Kindermann I, Lamiral Z, Tala S, Rossignol P, Turgonyi E, Pitt B, Böhm M, Zannad F. Hypo- and hyperglycemia predict outcome in patients with left ventricular dysfunction after acute myocardial infarction: data from EPHESUS. *J Card Fail* 2012;**18**:439–445.
8. He J, Ogden LG, Bazzano LA, Vupputuri S, Loria C, Whelton PK. Risk factors for congestive heart failure in US men and women: NHANES I epidemiologic follow-up study. *Arch Intern Med* 2001;**161**:996–1002.
9. Avery CL, Loehr LR, Baggett C, Chang PP, Kucharska-Newton AM, Matsushita K, Rosamond WD, Heiss G. The population burden of heart failure attributable to modifiable risk factors: the ARIC (Atherosclerosis Risk in Communities) study. *J Am Coll Cardiol* 2012;**60**:1640–1646.
10. Kristensen SL, Jhund PS, Lee MMY, Køber L, Solomon SD, Granger CB, Yusuf S, Pfeffer MA, Swedberg K, McMurray JJV. Prevalence of prediabetes and undiagnosed diabetes in patients with HFpEF and HFrEF and associated clinical outcomes. *Cardiovasc Drugs Ther* 2017;**31**:545–549.
11. Kristensen SL, Preiss D, Jhund PS, Squire I, Cardoso JS, Merkely B, Martinez F, Starling RC, Desai AS, Lefkowitz MP, Rizkala AR, Rouleau JL, Shi VC, Solomon SD, Swedberg K, Zile MR, McMurray JJ, Packer M; PARADIGM-HF Investigators and Committees. Risk related to pre-diabetes mellitus and diabetes mellitus in heart failure with reduced ejection fraction: insights from prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart

Failure Trial. *Circ Heart Fail* 2016;**9**. pii: e002560. doi: 10.1161/CIRCHEARTFAILURE.115.002560.
12. Dauriz M, Targher G, Laroche C, Temporelli PL, Ferrari R, Anker S, Coats A, Filippatos G, Crespo-Leiro M, Mebazaa A, Piepoli MF, Maggioni AP, Tavazzi L. Association between diabetes and 1-year adverse clinical outcomes in a multinational cohort of ambulatory patients with chronic heart failure: results from the ESC-HFA Heart Failure Long-Term Registry. *Diabetes Care* 2017;**40**:671–678.
13. Pavlovic A, Polovina M, Ristic A, Seferovic JP, Veljic I, Simeunovic D, Milinković I, Krljanac G, Ašanin M, Oštrić-Pavlović I, Seferović PM. Long-term mortality is increased in patients with undetected prediabetes and type-2 diabetes hospitalized for worsening heart failure and reduced ejection fraction. *Eur J Prev Cardiol* 2018;**26**:72–82.
14. Egstrup M, Schou M, Gustafsson I, Kistorp CN, Hildebrandt PR, Tuxen CD. Oral glucose tolerance testing in an outpatient heart failure clinic reveals a high proportion of undiagnosed diabetic patients with an adverse prognosis. *Eur J Heart Fail* 2011;**13**:319–326.
15. Davies MJ, D'Alessio DA, Fradkin J, Kernan WN, Mathieu C, Mingrone G, Rossing P, Tsapas A, Wexler DJ, Buse JB. Management of hyperglycaemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetologia* 2018;**61**:2461–2498.
16. Demant MN, Gislason GH, Kober L, Vaag A, Torp-Pedersen C, Andersson C. Association of heart failure severity with risk of diabetes: a Danish nationwide cohort study. *Diabetologia* 2014;**57**:1595–1600.
17. Authors/Task Force Members, Piepoli MF, Hoes AW, Agewall S, Albus C, Brotons C, Catapano AL, Cooney MT, Corrà U, Cosyns B, Deaton C, Graham I, Hall MS, Hobbs FD, Løchen ML, Löllgen H, Marques-Vidal P, Perk J, Prescott E, Redon J, Richter DJ, Sattar N, Smulders Y, Tiberi M, van der Worp HB, van Dis I, Verschuren WM; Additional Contributor: Binno Simone (Italy); Document Reviewers:, De Backer G, Roffi M, Aboyans V, Bachl N, Bueno H, Carerj S, Cho L, Cox J, De Sutter J, Egidi G, Fisher M, Fitzsimons D, Franco OH, Guenoun M, Jennings C, Jug B, Kirchhof P, Kotseva K, Lip GY, Mach F, Mancia G, Bermudo FM, Mezzani A, Niessner A, Ponikowski P, Rauch B, Rydén L, Stauder A, Turc G, Wiklund O, Windecker S, Zamorano JL. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: the Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts): developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). *Eur J Prev Cardiol* 2016;**23**:NP1–NP96.
18. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, Falk V, González-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GMC, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P; ESC Scientific Document Group. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J* 2016;**37**:2129–2200.
19. Gerstein HC, Bosch J, Dagenais GR, Díaz R, Jung H, Maggioni AP, Pogue J, Probstfield J, Ramachandran A, Riddle MC, Rydén LE, Yusuf S. Basal insulin and cardiovascular and other outcomes in dysglycemia. *N Engl J Med* 2012;**367**:319–328.
20. Bonds DE, Miller ME, Bergenstal RM, Buse JB, Byington RP, Cutler JA, Dudl RJ, Ismail-Beigi F, Kimel AR, Hoogwerf B, Horowitz KR, Savage PJ, Seaquist ER, Simmons DL, Sivitz WI, Speril-Hillen JM, Sweeney ME. The association between symptomatic, severe hypoglycaemia and mortality in type 2 diabetes: retrospective epidemiological analysis of the ACCORD study. *BMJ* 2010;**340**:b4909.
21. Investigators T. Does hypoglycaemia increase the risk of cardiovascular events? A report from the ORIGIN trial. *Eur Heart J* 2013;**34**:3137–3144.
22. Davis IC, Ahmadizadeh I, Randell J, Younk L, Davis SN. Understanding the impact of hypoglycemia on the cardiovascular system. *Expert Rev Endocrinol Metab* 2017;**12**:21–33.
23. Tschoepe D, Bramlage P, Binz C, Krekler M, Schneider S, Gitt AK. Hypoglycemia in patients with type-2 diabetes—incidence and prognostic significance—results of the DiaRegis 2 year follow-up. *Eur Heart J* 2013;**34(suppl_1)**. https://doi.org/10.1093/eurheartj/eht311.5924.
24. ORIGIN Trial Investigators. Predictors of nonsevere and severe hypoglycemia during glucose-lowering treatment with insulin glargine or standard drugs in the ORIGIN trial. *Diabetes Care* 2015;**38**:22–28.
25. Murad MH, Coto-Yglesias F, Wang AT, Sheidaee N, Mullan RJ, Elamin MB, Montori VM. Drug-induced hypoglycemia: a systematic review. *J Clin Endocrinol Metab* 2009;**94**:741–745.
26. Goode KM, John J, Rigby AS, Kilpatrick ES, Atkin SL, Bragadeesh T, Clark AL, Cleland JGF. Elevated glycated haemoglobin is a strong predictor of mortality in patients with left ventricular systolic dysfunction who are not receiving treatment for diabetes mellitus. *Heart* 2009;**95**:917–923.
27. Elder DHJ, Singh JSS, Levin D, Donnelly LA, Choy A-M, George J, Struthers AD, Doney ASF, Lang CC. Clinical review: Mean HbA1c and mortality in diabetic individuals with heart failure: a population cohort study. *Eur J Heart Fail* 2016;**18**:94–102.
28. Lawson CA, Jones PW, Teece L, Dunbar SB, Seferovic PM, Khunti K, Mamas M, Kadam UT. Association between type 2 diabetes and all-cause hospitalization and mortality in the UK general heart failure population: stratification by diabetic glycemic control and medication intensification. *JACC Heart Fail* 2018;**6**:18–26.
29. Eshaghian S, Horwich TB, Fonarow GC. An unexpected inverse relationship between HbA1c levels and mortality in patients with diabetes and advanced systolic heart failure. *Am Heart J* 2006;**151**:91.
30. Grembowski D, Ralston JD, Anderson ML. Hemoglobin A1c, comorbid conditions and all-cause mortality in older patients with diabetes: a retrospective 9-year cohort study. *Diabetes Res Clin Pract* 2014;**106**:373–382.
31. Skott P, Hother-Nielsen O, Bruun NE, Giese J, Nielsen MD, Beck-Nielsen H, Parving HH. Effects of insulin on kidney function and sodium excretion in healthy subjects. *Diabetologia* 1989;**32**:694–699.
32. Yang T, Soodvilai S. Renal and vascular mechanisms of thiazolidinedione-induced fluid retention. *PPAR Res* 2008;**2008**:1.
33. Maack C, Lehrke M, Backs J, Heinzel FR, Hulot J-S, Marx N, Paulus WJ, Rossignol P, Taegtmeyer H, Bauersachs J, Bayes-Genis A, Brutsaert D, Bugger H, Clarke K, Cosentino F, De Keulenaer G, Dei Cas A, González A, Huelsmann M, Iaccarino G, Lunde IG, Lyon AR, Pollesello P, Rena G, Riksen NP, Rosano G, Staels B, van Laake LW, Wanner C, Farmakis D, Filippatos G, Ruschitzka F, Seferovic P, de Boer RA, Heymans S. Heart failure and diabetes: metabolic alterations and therapeutic interventions: a state-of-the-art review from the Translational Research Committee of the Heart Failure Association-European Society of Cardiology. *Eur Heart J* 2018;**39**:4243–4254.
34. Shah DD, Fonarow GC, Horwich TB. Metformin therapy and outcomes in patients with advanced systolic heart failure and diabetes. *J Card Fail* 2010;**16**:200–206.
35. Crowley MJ, Diamantidis CJ, McDuffie JR, Cameron CB, Stanifer JW, Mock CK, Wang X, Tang S, Nagi A, Kosinski AS, Williams JW. Clinical outcomes of metformin use in populations with chronic kidney disease, congestive heart failure, or chronic liver disease: a systematic review. *Ann Intern Med* 2017;**166**:191–200.
36. Eurich DT, Weir DL, Majumdar SR, Tsuyuki RT, Johnson JA, Tjosvold L, Vanderloo SE, McAlister FA. Comparative safety and effectiveness of metformin in patients with diabetes mellitus and heart failure: systematic review of observational studies involving 34, 000 patients. *Circ Heart Fail* 2013;**6**:395–402.
37. Scirica BM, Bhatt DL, Braunwald E, Steg PG, Davidson J, Hirshberg B, Ohman P, Frederich R, Wiviott SD, Hoffman EB, Cavender MA, Udell JA, Desai NR, Mosenzon O, McGuire DK, Ray KK, Leiter LA, Raz I. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. *N Engl J Med* 2013;**369**:1317–1326.
38. Jorsal A, Kistorp C, Holmager P, Tougaard RS, Nielsen R, Hänselmann A, Nilsson B, Møller JE, Hjort J, Rasmussen J, Boesgaard TW, Schou M, Videbaek L, Gustafsson I, Flyvbjerg A, Wiggers H, Tarnow L. Effect of liraglutide, a glucagon-like peptide-1 analogue, on left ventricular function in stable chronic heart failure patients with and without diabetes (LIVE)-a multicentre, double-blind, randomised, placebo-controlled trial. *Eur J Heart Fail* 2017;**19**:69–77.
39. Margulies KB, Hernandez AF, Redfield MM, Givertz MM, Oliveira GH, Cole R, Mann DL, Whellan DJ, Kiernan MS, Felker GM, McNulty SE, Anstrom KJ, Shah MR, Braunwald E, Cappola TP. Effects of liraglutide on clinical stability among patients with advanced heart failure and reduced ejection fraction: a randomized clinical trial. *JAMA* 2016;**316**:500–508.

40. Zelniker TA, Wiviott SD, Raz I, Im K, Goodrich EL, Bonaca MP, Mosenzon O, Kato ET, Cahn A, Furtado RHM, Bhatt DL, Leiter LA, McGuire DK, Wilding JPH, Sabatine MS. 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.
41. Seferovic PM, Ponikowski P, Anker SD, Bauersachs J, Chioncel O, Cleland JGF, de Boer RA, Drexel H, Ben Gal T, Hill L, Jaarsma T, Jankowska EA, Anker MS, Lainscak M, Lewis BS, McDonagh T, Metra M, Milicic D, Mullens W, Piepoli MF, Rosano G, Ruschitzka F, Volterrani M, Voors AA, Filippatos G, Coats AJS. Clinical practice update on heart failure 2019: pharmacotherapy, procedures, devices and patient management. An expert consensus meeting report of The Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail* 2019;**21**:1169–1186.
42. Pabel S, Wagner S, Bollenberg H, Bengel P, Kovács Á, Schach C, Tirilomis P, Mustroph J, Renner A, Gummert J, Fischer T, Van Linthout S, Tschöpe C, Streckfuss-Bömeke K, Hasenfuss G, Maier LS, Hamdani N, Sossalla S. Empagliflozin directly improves diastolic function in human heart failure. *Eur J Heart Fail* 2018;**20**:1690–1700.
43. Packer M. Are the effects of drugs to prevent and to treat heart failure always concordant? The statin paradox and its implications for understanding the actions of antidiabetic medications. *Eur J Heart Fail* 2018;**20**:1100–1105.
44. Rosano GMC and Seferovic P. The management of diabetic patients with heart failure. *International Cardiovascular Forum Journal* 2017;**10**:58–62.
45. Zelniker TA, Braunwald E. Treatment of heart failure with sodium-glucose cotransporter 2 inhibitors and other anti-diabetic drugs. *Card Fail Rev* 2019;**5**:27–30.
46. Butler J, Hamo CE, Filippatos G, Pocock SJ, Bernstein RA, Brueckmann M, Cheung AK, George JT, Green JB, Januzzi JL, Kaul S, Lam CSP, Lip GYH, Marx N, McCullough PA, Mehta CR, Ponikowski P, Rosenstock J, Sattar N, Salsali A, Scirica BM, Shah SJ, Tsutsui H, Verma S, Wanner C, Woerle HJ, Zannad F, Anker SD; EMPEROR Trials Program. The potential role and rationale for treatment of heart failure with sodium-glucose co-transporter 2 inhibitors. *Eur J Heart Fail* 2017;**19**:1390–1400.