Korean Circ J. 2017 Sep;47(5):543-554
https://doi.org/10.4070/kcj.2017.0030
pISSN 1738-5520·eISSN 1738-5555

kcj
Korean Circulation Journal

Review Article

Current Drug Therapy in Chronic Heart Failure - the New Guidelines of the European Society of Cardiology (ESC)

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Received: Feb 2, 2017
Revised: Apr 3, 2017
Accepted: Apr 13, 2017

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Conflict of Interest
The authors have no financial conflicts of interest.

ABSTRACT

Congestive heart failure (HF) is a morbidity that is increasing worldwide due to the aging population and improvement in (acute) care for patients with cardiovascular diseases. The prognosis for patients with HF is very poor without treatment. Furthermore, (repeated) hospitalizations for cardiac decompensation cause an increasing economic burden. Modern drugs and the consequent implementation of therapeutic recommendations have substantially improved the morbidity and mortality of HF patients. This paper provides an overview of the current pharmacological management of HF patients, based on the 2016 guidelines of the European Society of Cardiology (ESC).

Keywords: Heart failure; Standards; Drug therapy; Angiotensin receptor-neprilysin inhibitor

INTRODUCTION

Congestive heart failure (HF) affects millions of patients worldwide; due to the aging population, the prevalence is expected to increase in the near future. HF is characterized by a very poor prognosis without therapy.[1] HF-associated mortality is higher than in most malignancies.[2] Modern drug treatments and the consequent use of established medication have substantially reduced mortality and hospitalization frequency, at least in patients with HF with reduced ejection fraction (HFrEF). Consequently, aligning patient therapies with current guidelines is critical for HF patient management. In 2016, the European Society of Cardiology (ESC) presented their new and updated guidelines on the diagnosis and therapy of HF.[3] Simultaneously, a working group of representatives from the American Heart Association (AHA), the American College of Cardiology (ACC), and the Heart Failure Society of America (HFSA) published an update to the guidelines, which focused on the pharmacological management of HF.[4]

The fundamental objectives for HF therapy are as follow[3]: symptom improvement, functional capacity improvement, enhancing quality of life, reducing the frequency of hospitalizations, and decreasing associated mortality.

Therapeutic approaches for HF differ depending on its presentation. The two well-established types are HF with reduced ejection fraction (HFrEF, left ventricular ejection

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fraction (LVEF) <40%) and HF with preserved ejection fraction (HFpEF; LVEF ≥50% and signs of diastolic dysfunction). The new guidelines introduced another form of HF, called HF with mid-range ejection fraction (HFmrEF; LVEF 40%–49% and signs of diastolic dysfunction).[3] This addition was introduced to better define the diagnostic grey area between HFpEF and HFrEF. All types of HF are characterized by decreased stroke volume and consecutively cardiac output. There is no clear recommendation for the treatment of HFmrEF patients in the current guidelines due to missing studies. However, there is evidence that patients with HFmrEF might more likely benefit from drug therapy established for HFrEF compared to patients with HFpEF.[5]

THERAPY FOR PATIENTS WITH HFrEF

The basic treatment approach for HFrEF is neurohormonal inhibition by means of angiotensin converting enzyme (ACE) inhibitors (ACEIs), mineralocorticoid receptor antagonists (MRAs), and beta-blockers. In numerous randomized trials, this therapeutic principle has been proven to be effective, leading to class IA recommendations in the current guidelines.

ACE INHIBITORS (ACEI) AND ANGIOTENSIN-II BLOCKERS (ARB)

ACEIs block the cleavage of angiotensin-I to angiotensin-II, thereby inhibiting the well-known effects of angiotensin-II, which are summarized in **Table 1**. ACEIs have been used in clinical practice for many years. Multiple trials have shown that they have beneficial effects, including reduced mortality and frequency of hospitalizations, on HFrEF patient prognoses in several clinical settings; for example, the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS)[6] and the Studies of Left Ventricular Dysfunction (SOLVD).[7] ACEI therapy in HFrEF is currently a standard. According to the ESC guidelines, every patient with HFrEF should receive an ACEI, independent of his or her symptoms.

Table 1. Effects of angiotensin-II

Hemodynamic	Vasoconstriction (preferentially coronary, renal, cerebral) - Increase in peripheral vascular resistance - Increased afterload - Left ventricular hypertrophy Inotropic/contractile (cardiomyocytes; increased cytosolic Ca^{2+})
Neurohumoral	Renin-suppression (negative feedback) Activation of the sympathetic nervous system Aldosterone release (sodium retention) ADH release (water retention) Increased endothelin secretion
Proliferative	Promotion of cell growth/growth factor stimulation - Cardiomyocyte hypertrophy - Vascular smooth muscle cell proliferation - Stimulation of vascular and myocardial fibrosis Matrix deposition
Prothrombotic/proatherogenic	Platelet aggregation Vascular smooth cell migration Increased synthesis of PAI-1

Description was modified from several references.[10][35-37]
ADH = antidiuretic hormone; PAI-1 = plasminogen activator inhibitor-1.

https://doi.org/10.4070/kcj.2017.0030

In the Assessment of Treatment with Lisinopril and Survival (ATLAS) trial,[8] a low-dose therapy with the ACEI Lisinopril was compared to a high-dose therapy in over 3,000 patients with HFrEF. Patients in the high-dose group had significantly lower risk for hospitalization and mortality. To achieve adequate inhibition of the renin-angiotensin system, up-titration of the ACEI dose to the target dose or the maximum tolerated dose is recommended. This is especially true for younger patients in whom high doses should be reached. Nevertheless, in real life, doses are frequently below the recommended level.[9]

In patients who do not tolerate ACEIs, mainly due to cough or angioedema, ARBs are an alternative therapy. The combination of ACEIs and ARBs is only recommended in exceptional cases and is contraindicated in patients with concomitant MRA treatment.

BETA-BLOCKERS

One of the earliest neurohumoral changes in HF is sympathetic activation.[10] Short period sympathetic activation improves peripheral perfusion by increasing heart rate and myocardial contractility. Ongoing activation deteriorates heart function, and these effects are shown in **Table 2**.

Multiple studies have shown the beneficial effects of a therapy with beta-blockers in HFrEF, including the Cardiac Insufficiency Bisoprolol Study II (CIBIS II),[11] Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS),[12] Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF),[13] and the Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalisation in Seniors with Heart Failure (SENIORS).[14]

Similar to ACEIs, beta-blockers should be started at a low-dose, and dosages should be increased in the clinical course. Absolute contraindications are 1) relevant bradycardia, 2) second- or third-degree heart block (without a pacemaker), and 3) bronchial asthma. Chronic

Table 2. Ongoing sympathetic activation adversely affecting cardiac myocyte and chamber contractile function leading to deterioration of heart function

Desensitization of signal transduction	Abnormal transduction of the beta-adrenergic signal - Reduced maximal functional capacity - Myocardial protection from adrenergic stimulation
Adverse biologic effects on cardiac myocytes	Alterations in gene expression leading to myocyte dysfunction - Reinduction of fetal genes - Myosin heavy chain isoform shifts Cell loss/acceleration of myocyte death - Necrosis (subendocardial ischemia, toxic effects) - Apoptosis Cell (myocyte) and chamber (left ventricular) remodeling - Myocardial hypertrophy - Fibroblast hyperplasia Induction of tachyarrhythmia Increase of heart rate/tachycardia - Subendocardial ischemia - Reduced diastolic filling time - Negative inotropic effect Altered myocardial metabolism - Increased free fatty acid uptake with decreased myocardial efficiency - Increased anaerobic glycolysis - Myofibril desensitization to calcium caused by intracellular acidosis
Others	Increased renin secretion

Description was modified from several references.[10][38-40]

https://doi.org/10.4070/kcj.2017.0030

obstructive lung disease is usually no contraindication for beta-blocker therapy. According to the current ESC guidelines, ACEIs, and beta-blockers should be started immediately after diagnosis of HFrEF.[3]

MINERALOCORTICOID RECEPTOR ANTAGONISTS (MRA), FORMERLY ALDOSTERONE ANTAGONISTS

Regulation of aldosterone synthesis is regulated by angiotensin-II and by plasma potassium. Activation of the mineralocorticoid receptor, which can also be activated by glucocorticoids, leads to several effects that can worsen cardiac function. An overview is given in **Table 3**.

After the Randomized Aldactone Evaluation Study (RALES)[15] and Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS),[16] MRA therapy for patients with HFrEF and severe symptoms (New York Heart Association [NYHA] class III and IV) has been established and implemented in the guidelines.

In the Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF) trial Zannad et al.[17] showed that patients with HFrEF and milder symptoms (NYHA class II) might benefit from a therapy with a MRA in addition to the recommended and established drug therapy. The composite endpoint (cardiovascular mortality and hospitalization for HF) was significant lower (37%) in the eplerenone group in comparison to the placebo group. Furthermore, all-cause mortality (24%), cardiovascular death (24%), all-cause hospitalizations (23%), and HF hospitalizations (42%) were all significantly reduced. The results of the EMPHASIS-HF trial have led to the recommendation that all patients with reduced left ventricular function (LVEF ≤35%) and persisting symptoms (NYHA class II–IV) despite therapy with an ACEI (alternatively ARB) and a beta-blocker should receive a MRA unless there are contraindications.[3]

The most important adverse effect of a therapy with MRA is hyperkalemia. Therefore, the treatment approaches should be used with caution in patients with existing hyperkalemia

Table 3. (Deleterious) Effects of the activation of the mineralocorticoid receptor

Sodium reabsorption and volume overload	Decrease in cardiac output
	Reduced renal flow
	- RAAS stimulation in the kidneys
	Increase in urinary potassium excretion
	- Hypokalemia
	- Electrical instability
	Hypertension
Ventricular remodeling	Myocardial hypertrophy
	Increased inflammation and upregulated expression of proinflammatory cytokines (TNF-α, IL-1β, TGF-β)
	Increased collagen synthesis by cardiac fibroblasts
	- Fibrosis of the perivascular and interstitial spaces
	- Increased ventricular diastolic stiffness
	- Electrical conduction defects
	- Malignant ventricular arrhythmia
Endothelial dysfunction and vasoconstriction	Reduced coronary blood flow
	- Recurrent ischemic events
	- Myocardial ischemia
	- Myocardial injury

Description was modified from several references.[10][41][42]
IL-1β = interleukin-1β; RAAS = renin-angiotensin-aldosterone system; TGF-β = transforming growth factor-β; TNF-α = tumor necrosis factor-α.

https://doi.org/10.4070/kcj.2017.0030

(>5.0 mmol/L) and in patients with severely impaired renal function (creatinine clearance <30 mL/min). Renal markers and electrolytes should be checked regularly in elderly patients, especially those with concomitant medications such as an ACEI or an ARB. But studies have demonstrated that older patients (≥75 years) and patients with moderately impaired renal function benefit from treatment with eplerenone.[17][18]

In addition to the established MRAs spironolactone and eplerenone, a new drug, finerenone, has been introduced and has a non-steroidal structure. Due to this different structure, finerenone treatment might be associated with fewer adverse effects;[19] however, results of ongoing studies have not yet been published.

DIURETICS

The effects of diuretics on mortality and morbidity have not been studied in randomized trials. Nevertheless, in patients with symptomatic HF (NYHA class II–IV), diuretics should be added to the drug therapy mentioned above in order to ameliorate some of the symptoms (e.g. dyspnea, edema).[3] The dose of diuretics should be as low as possible to reach and maintain euvolemia. In the course of the disease, feasible dose reductions should be checked regularly.

I_f-CHANNEL INHIBITOR

Ivabradine targets the sinu-atrial node and slows the sinus rhythm through I_f-channel inhibition. Patients with HFrEF (NYHA class II–IV, LVEF ≤35%) and in sinus rhythm (heart rate ≥70 bpm) were enrolled in the Systolic Heart Failure Treatment with I_f Inhibitor Ivabradine Trial (SHIFT). The administration of ivabradine in addition to an optimized HF medication (including beta-blocker) resulted in a significant decrease in HF hospitalizations and cardiovascular mortality (primary endpoint, relative risk reduction 18%).[20] Furthermore, left ventricular function was enhanced and quality of life improved. Due to the results of the SHIFT trial, ivabradine is recommended in patients with HFrEF (LVEF ≤35%), sinus rhythm with a heart rate ≥70 bpm, and persisting symptoms despite therapy with an ACEI (or ARB), a beta-blocker, and a MRA.[3]

In Europe, the official labeling for ivabradine to treat HF is for patients in sinus rhythm with a heart rate ≥75 bpm. These patients have been shown to notably benefit from this therapy since a subgroup analysis found a significant reduction of mortality in this cohort.[21]

ANGIOTENSIN RECEPTOR-NEPRILYSIN INHIBITOR (ARNI)

A new drug class has recently emerged in HF therapy. ARNI is a novel treatment concept in HF. The first and to this date only substance in this class is "LCZ696," which is comprised of an ARB (valsartan) and sacubitril, a neutral endopeptidase (NEP, neprilysin) inhibitor. Neprilysin plays a crucial role in the degradation of natriuretic peptides. The therapeutic concept of the ARNI is based on the established inhibition of the renin-angiotensin-aldosterone system (RAAS) and an increase in endogenous natriuretic peptides by blocking their degradation. Inhibition of neprilysin counteracts the neurohumoral activation, which leads to vasoconstriction, sodium retention, and cardiac remodeling, increasing the RAAS-blocking effects.[22]

https://doi.org/10.4070/kcj.2017.0030

The Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) trial was a large randomized phase III study to investigate the beneficial effects of this new therapeutic concept.[23] A total of 8,442 HFrEF patients were enrolled in an ambulatory setting. Important inclusion criteria were 1) symptomatic HF (NYHA class II–IV), 2) reduced left ventricular function (LVEF ≤40%, changed to ≤35% during the course of the study), 3) brain natriuretic peptide (BNP) ≥150 pg/mL or N-terminal proBNP (NT-proBNP) ≥600 pg/mL (≥100 respectively 400 pg/mL with HF hospitalization in the previous 12 months), and 4) an estimated glomerular filtration rate ≥ 30 mL/min/1.73 m^2). Therapy with sacubitril/valsartan (target dose: 400 mg/day, equivalent to 320 mg valsartan+80 mg sacubitril) was compared to a therapy with the ACEI enalapril (target dose: 20 mg/day).

The primary endpoint, composed of cardiovascular mortality and HF hospitalizations, was significantly reduced in the sacubitril/valsartan group (20%). Furthermore, significant reduction was shown for cardiovascular mortality (20%), all-cause mortality (16%), and HF hospitalization (21%). Endpoint data and adverse events are depicted in **Figure 1**.

Due to the distinct effects, therapy with sacubitril/valsartan is actually recommended in the current guidelines for all patients who meet the inclusion criteria and who remain symptomatic despite therapy with an ACEI (or ARB), a beta-blocker, and a MRA.[3)4)] When changing from an ACEI to sacubitril/valsartan, intake of the ACEI has to be stopped at least 36 hours before the first intake of sacubitril/valsartan in order to prevent angioedema.

In regard to safety, the significantly higher incidence of symptomatic hypotension under therapy with sacubitril/valsartan is important to note. Thus, patients with very low blood pressure during ACEI treatment should not be switched to ARNI.[24] Regarding sacubitril/valsartan treatment in patients with diabetes mellitus, a recent subgroup analysis found a superiority of sacubitril/valsartan compared with enalapril independent from the patient's glycemic status (normoglycemic, pre-diabetes, diabetes).[25]

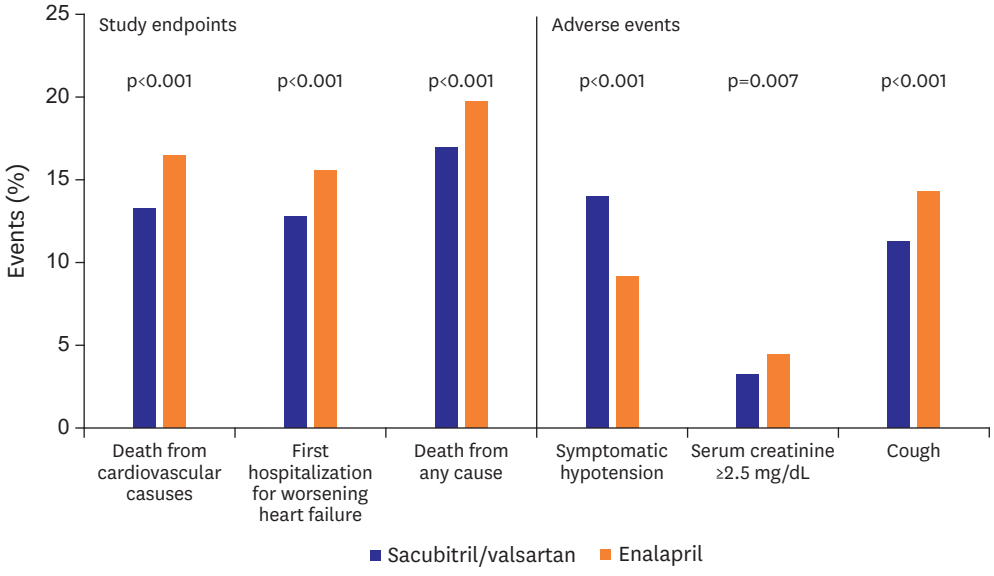

Figure 1. Main results including study endpoints and adverse events, of the PARADIGM-HF trial, comparing the ARNI sacubitril/valsartan to the ACEI enalapril (adapted from.[23])
ACEI = angiotensin converting enzyme inhibitor; ARNI: angiotensin receptor-neprilysin inhibitor; PARADIGM-HF = Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure.

https://doi.org/10.4070/kcj.2017.0030

DIGITALIS

The role and significance of cardiac glycosides in chronic HF treatment are currently unclear. One prospective randomized study with digoxin (Digitalis Investigation Group [DIG] trial) in patients with HFrEF (LVEF ≤45%, NYHA class I–IV, sinus rhythm) has been performed.[26] The DIG trial was conducted prior to the the implementation of the current HF medication; therefore, the rate of patients receiving concomitant therapy with beta-blockers and MRA was very low. The study was interpreted as neutral because digoxin did not influence total mortality, which was defined as the primary endpoint in this study, although hospitalizations for HF were reduced significantly. A recently published subgroup analysis of the DIG trial was able to show that patients with low serum levels of digoxin (0.5–0.9 ng/mL) benefited from this therapy.[27] Total mortality in this subgroup was significantly reduced, whereas patients with high serum levels of digoxin exhibited higher mortality levels. Overall, there is evidence that improvement in prognosis in patients with HF that received digoxin is not related to its inotropic effect but to a beneficial neurohumoral modulation. Especially patients with advanced HF (NYHA III–IV, LVEF <25%) seem to benefit from the therapeutic use of cardiac glycosides with regard to mortality and hospitalization rates.[28] Reports on increased mortality through cardiac glycosides in HF are limited by their retrospective and non-randomized design and therefore at best hypothesis generating.[29]

In patients with HF and atrial fibrillation (AF), randomized studies have not yet been performed to assess the impact of digoxin, and there are currently no randomized trials on the cardiac glycoside digitoxin in HF and/or AF. A large randomized study investigating the role of digitoxin in patients with HF on contemporary drug therapy is in progress: the Digitoxin to Improve Outcomes in Patients with Advanced Systolic Chronic Heart Failure (DIGIT-HF) trial (EudraCT-Nr.: 2013-005326-38).

Due to the narrow therapeutic range of cardiac glycosides, they should be used with caution, especially in women, older patients, and patients with impaired renal function.[3] Digitoxin should be used for patients with impaired renal function, rather than digoxin, as digoxin is excreted mainly by the kidneys.

TREATMENT OF PATIENTS WITH HFpEF

To date, no randomized trial has demonstrated the benefit of any drug therapy on mortality in patients with HFpEF.[3] Therefore, the primary therapeutic goal in those patients is to improve symptoms (e.g., edema, dyspnea) and subjective well-being. An adequately dosed therapy with diuretics is recommended to reach this target. In this context, it is important to note that the causes of hospitalization and mortality in HFpEF patients are frequently non-cardiovascular. Screening for comorbidities and adequately treating the comorbidities are major recommendations of the actual guidelines.

Moreover, patients in sinus rhythm benefit from treatment with nebivolol, spironolactone, or candesartan, which have been shown to reduce HF hospitalizations.[3] Similar results have not been published in patients with AF. Furthermore, sufficient management of blood pressure, preferably with renin-angiotensin system inhibitors, adequate treatment of myocardial ischemia, and acceptable heart rate control in patients with AF are major treatment targets in patients with HFpEF. The latter is complicated by the fact that no studies exist that define

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the optimal target heart rate or preferred pharmacological substances (beta-blocker, digitalis, calcium channel blockers [CCB]) for HFpEF patients.[3]

CONTRAINDICATED MEDICATION IN HF

Some treatments, which are known to cause harm in HF patients, should not be used, according to the ESC guidelines. An overview of these contraindicated drugs is given in **Table 4**.

CO-MORBIDITIES IN HF

Recently, HF patient comorbidities have received increased attention. Diagnostics and therapy of those co-morbidities interact with diagnostics and therapy of HF. Furthermore, they frequently impair prognosis and aggravate HF symptoms. Regarding drug therapy, two important co-morbidities should be mentioned.

Diabetes

Dysglycemia and diabetes are very common in HF, and co-existence of diabetes impairs the prognosis in HF. Metformin is the treatment of choice in patients with HF, whenever it is not contraindicated (e.g. severely impaired liver or kidney function).[3] Glitazones are contraindicated in HF as they provoke sodium and fluid retention and worsen HF.

Empagliflozin is a sodium-glucose cotransporter-2 (SGLT2) inhibitor (**Figure 2A**). Recently, therapy with empagliflozin has been associated with reduced hospitalization frequency for HF and overall mortality in a cohort of patients with diabetes.[30] The main results of the Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG) are shown in **Figure 2B**. A subgroup analysis revealed similar results for

Table 4. Overview of contraindicated drugs in HF patients

Substance	Potential effects
Thiazolidinediones (glitazones)	Worsening of HF
CCB (excluding amlodipine and felodipine)	Negative inotropic effect Worsening of HF Increase in hospitalizations
NSAID, COX-2 inhibitors	Sodium and water retention Worsening of kidney function Worsening of HF Increase in hospitalizations
Adding an ARB to an ACEI and a MRA	Possible worsening of kidney function Increased risk of hyperkalemia
Dronedarone (for control of frequency and rhythm in AF)	Increased risk of cardiovascular events Increased mortality
Class I antiarrhythmic agents	Increased mortality
Combination of ivabradin, ranolazine, and nicorandil	Unclear safety
Combination of nicorandil and nitrates	Missing additional effect
Moxonidin	Increased mortality
Alpha blockers	Neuro-humoral activation Water retention Worsening of HF

Description was modified from reference.[3]
ACEI = angiotensin converting enzyme inhibitor; AF = atrial fibrillation; ARB = angiotensin-II receptor blocker; CCB = calcium channel blocker; COX-2 = cyclooxygenase-2; HF = heart failure; MRA = mineralocorticoid receptor antagonist; NSAID = non-steroidal anti-inflammatory drugs.

https://doi.org/10.4070/kcj.2017.0030

patients with pre-existing HF;[31] therefore, empagliflozin is a promising substance in HF and concomitant diabetes.

Iron deficiency

Iron deficiency causes dysfunction of important proteins in the cardiac muscle and leads to anemia. Iron deficiency impairs prognosis in HFrEF, regardless of whether the patient has

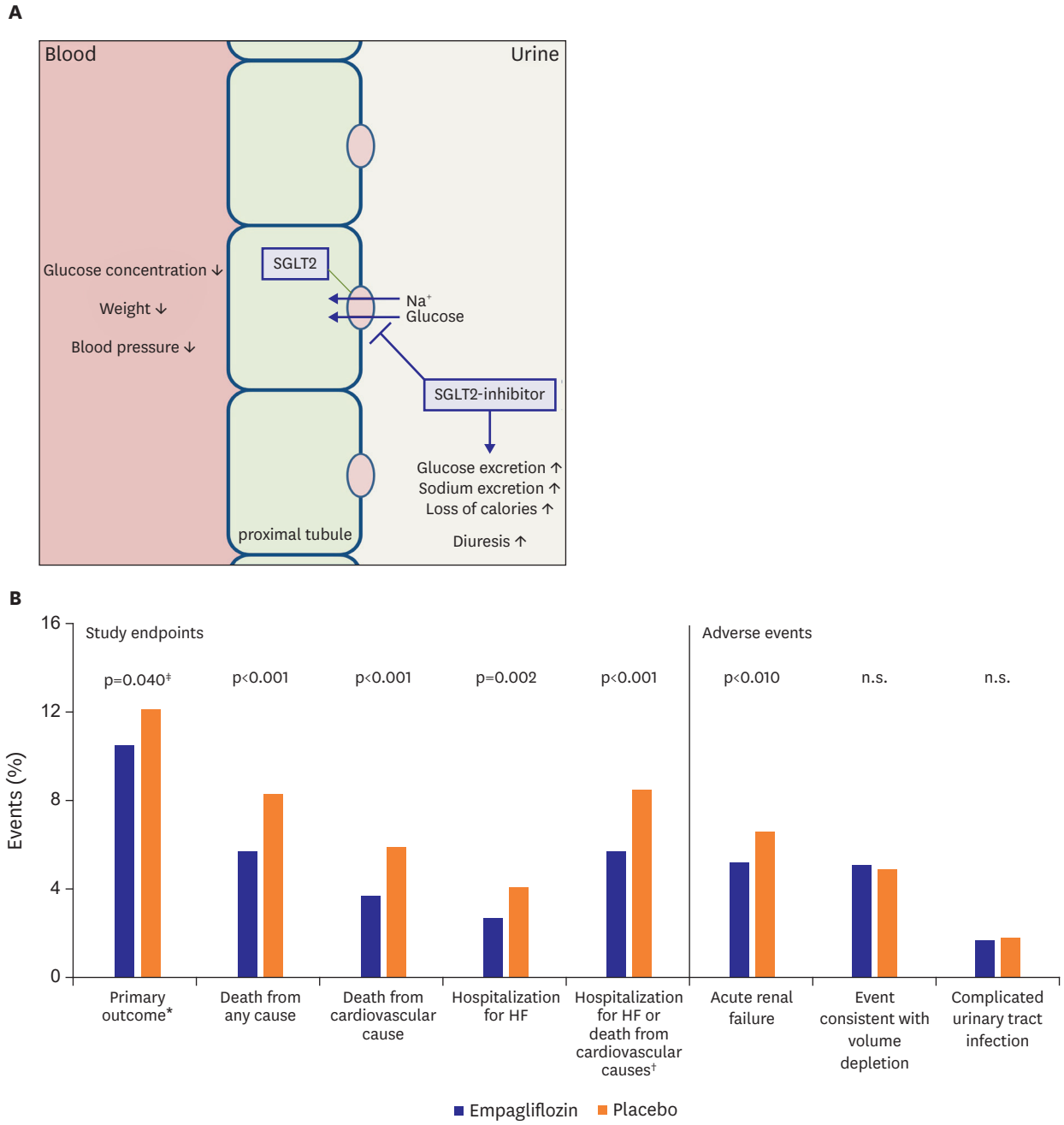

Figure 2. (A) Mode of action of empagliflozin, a SGLT2 inhibitor, in the kidneys. (B) The main results of the EMPA-REG trial on cardiovascular outcomes in patients with type 2 diabetes (adapted from[30])
EMPA-REG = Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients; HF = heart failure; n.s. = not significant; SGLT2 = sodium-glucose cotransporter-2.
*Death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke, †Excluding fatal stroke, ‡p value for test of superiority.

https://doi.org/10.4070/kcj.2017.0030

anemia.[3)32)] In the Ferric Carboxymaltose in Patients with Heart Failure and Iron Deficiency (FAIR-HF) trial,[33)] intravenous administration of iron (ferric carboxymaltose) significantly improved exercise capacity and quality of life in patients with HF (LVEF ≤40% and NYHA class II–III or LVEF ≤45% and NYHA class III) and proven iron deficiency (ferritin <100 mg/L or ferritin 100–299 μg/L and transferrin saturation <20%). The effect was independent of concomitant anemia.[33)] In a recent meta-analysis, intravenous iron substitution was shown to be associated with a lower risk of hospitalizations in HF patients.[34)] In the current guidelines, intravenous iron therapy is recommended in all HF patients with confirmed iron deficiency.[3)]

CONCLUSION

Congestive HF is a growing problem due to the increasing prevalence; HF prognosis without therapy is unfavorable. Therapeutic advances have improved the prognosis in recent years; therefore, appropriate drug therapy in adequate doses as recommended in the current guidelines is crucial for HF patients.

In addition to the established drug treatment consisting of ACEI (or ARB), betablocker, and diuretics, treatment with MRA and ivabradine have become standard in symptomatic patients with HFrEF. The ARNI sacubitril/valsartan is a promising new addition to current pharmacological treatments. The results of the PARADIGM-HF trial have been so pronounced that they have led to a class IB recommendation by the ESC for symptomatic patients despite the 'classic' HF medication.

Diagnosis and treatment of comorbidities are growing concerns in HF patients. However, in HFpEF no therapy has shown significant improvement in terms of prognosis in any trial. Therefore, treatment of comorbidities is an important approach for HFpEF patients, and additional research will be needed.

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