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The year in cardiology 2016 – Heart failure

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Preamble

The current year has been mainly characterized by the publication in Europe of the guidelines on the diagnosis and treatment of heart failure (HF) and in USA by an update on pharmacological treatment of HF with the praiseworthy effort to provide consistent recommendations on drug therapy (1–3). Therefore, the large majority of new evidences published at the end of 2015 and in the first quarter of 2016 are included in these publications. However, as always happens, the scientific community has been provided, more recently, with additional relevant information from new studies very relevant for the management of patients with HF.

ESC guidelines 2016: the most relevant novelties

The most important novel recommendations of the 2016 ESC guidelines on diagnosis and treatment of HF can be summarized in the following points.

1. A novel algorithm for the diagnosis of HF in the non-acute setting has been proposed considering the clinical probability of the disease (derived from medical history, physical examination and resting ECG), the measure of natriuretic peptides and transthoracic echocardiography.
   The novelty with respect to the prior 2012 guidelines (4) is the fact that, in the algorhythm of the use of natriuretic peptides (NPs), their measure is recommended as a first step in all patients with suspected HF. If at least one element among clinical history, physical examination, and ECG is abnormal, plasma NPs should be measured, if available, to identify those who need echocardiography (an echocardiogram is indicated if the NP level is above the exclusion threshold or if circulating NP levels cannot be assessed).The role of NP levels is mainly for excluding HF, due to the their very high negative predictive value.
2. Transthoracic echocardiography in patients with suspected or established HF for the assessment of myocardial structure and function along with the measure of left ventricular ejection fraction (LVEF) to stratify the patients with chronic HF in: reduced (heart failure reduced ejection fraction (HFrEF) LVEF <40%), mid-range (HFmrEF, LVEF: 40-49%) preserved ejection fraction (HFpEF, LVEF ≥50%).
   The main terminology used to describe HF is historical and is based on measurement of the LVEF: patients with normal LVEF [typically considered as ≥50%; HF with preserved EF (HFpEF)] and those with reduced LVEF [typically considered as <40%; HF with reduced EF (HFrEF)]. The novelty of the updated guidelines is the introduction of a specific consideration on the patients with an LVEF in the range of 40–49% who represent a “grey area”, which now is defined as HFmrEF. Some criticisms were raised regarding this classification mainly for two reasons: first, the EF measure done with echocardiography can have a certain degree of variability, therefore to have such a rigid separation between categories does not seem to be appropriate; second, EF can relevantly change over time without a modification of the pathophysiological model of HF. Future research is needed to understand better the clinical epidemiology of the patients of this ‘grey area’, before considering them as a real new phenotype in itself.

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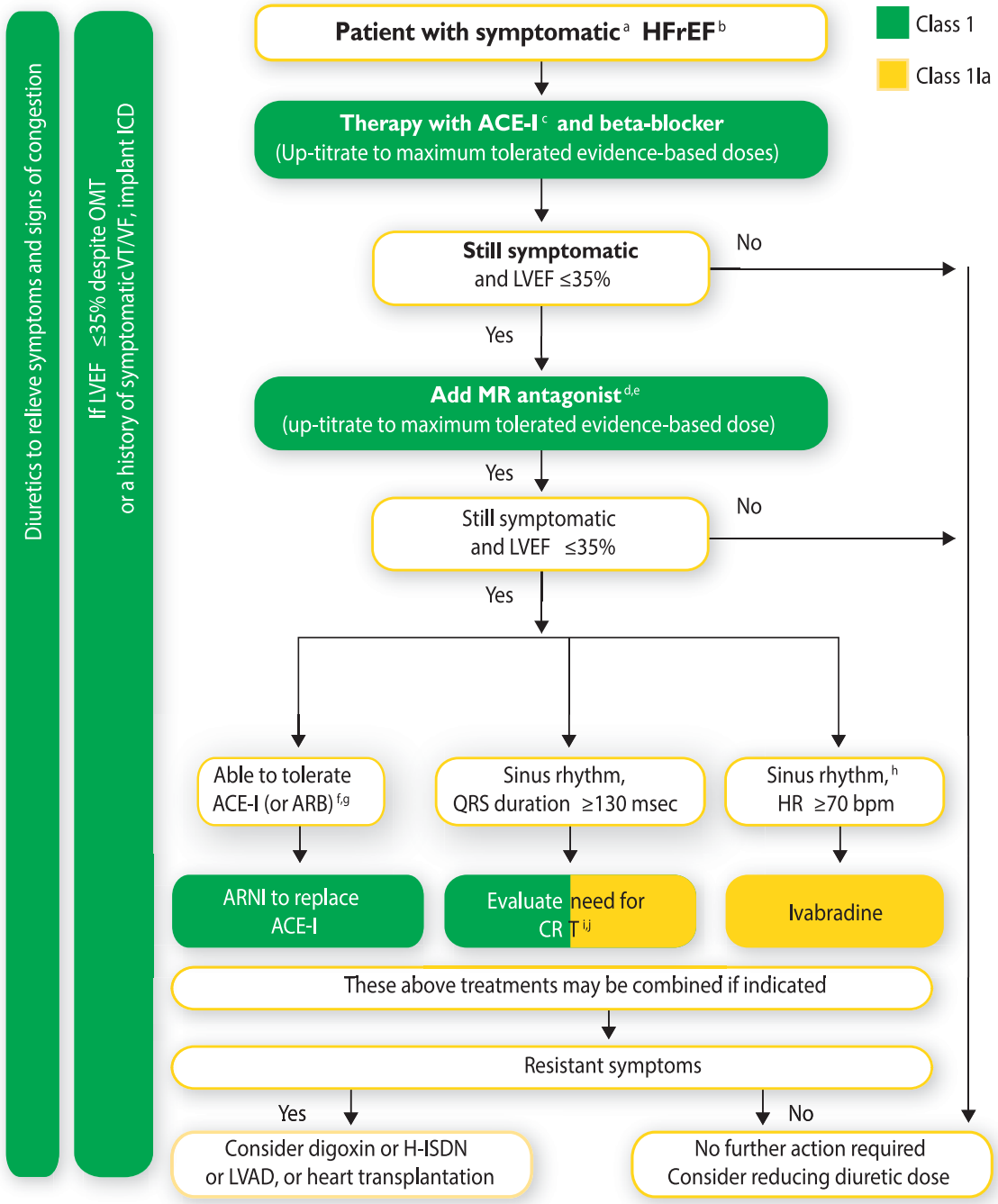

Green indicates a class I recommendation; yellow indicates a class IIa recommendation.
ACE-I: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker; ARNI: angiotensin receptor neprilysin inhibitor; BNP: B-type natriuretic peptide; CRT: cardiac resynchronization therapy; HF: heart failure; HFrEF: heart failure with reduced ejection fraction; H-ISDN: hydralazine and isosorbide dinitrate; HR: heart rate; ICD: implantable cardioverter defibrillator; LBBB: left bundle branch block; LVAD: left ventricular assist device; LVEF: left ventricular ejection fraction; MR: mineralocorticoid receptor; NT-proBNP: N-terminal pro-B type natriuretic peptide; NYHA: New York Heart Association; OMT: optimal medical therapy; VF: ventricular fibrillation; VT: ventricular tachycardia.
[a]Symptomatic: NYHA Class II-IV. bHFrEF: LVEF <40%. cIf ACE inhibitor not tolerated/contra-indicated, use ARB. dIf MR antagonist not tolerated/contra-indicated, use ARB. eWith a hospital admission for HF within the last 6 months or with elevated natriuretic peptides (BNP >250 pg/ml or NTproBNP >500 pg/ml in men and 750 pg/ml in women). f With an elevated plasma natriuretic peptide level (BNP ≥150 pg/mL or plasma NT-proBNP ≥600 pg/mL, or if HF hospitalization within recent 12 months plasma BNP ≥100 pg/mL or plasma NT-proBNP ≥400 pg/mL). gIn doses equivalent to enalapril 10 mg b.i.d. hWith a hospital admission for HF within the previous year. iCRT is recommended if QRS ≥130 msec and LBBB (in sinus rhythm). JCRT should/may be considered if QRS ≥130 msec with non-LBBB (in a sinus rhythm) or for patients in AF provided a strategy to ensure bi-ventricular capture in place (individualized decision).

FIG. 1. Therapeutic algorithm for a patient with symptomatic HFrEF (1)

3. A revised algorhytm for the treatment of patients with chronic HF has been proposed. All patients with symptomatic HFrEF should receive a combination of an Angiotensin-converting enzyme (ACE)-I [or Angiotensin receptor blocker (ARB) if ACE-I not tolerated], a β-blocker and a mineralocorticoid antagonist (MRA). If a patient still remains symptomatic sacubitril/valsartan is recommended to replace ACE-I. Use diuretics in order to improve symptoms and exercise capacity in patients with signs and/or symptoms of congestion. Updated guidelines incorporate the results of the PARADIGM-HF trial (5), published in 2014, in the new algorhythm for the treatment of patients with symptomatic HFrEF *(Figure 1)*.
4. In the management of a patient with HF, comorbidities should be taken into account. For diabetes and hyperkalaemia new treatments are available.
Metformin is safe to use in patients with HFrEF, and it should be the treatment of choice in patients with diabetes and HF, even if contraindicated in patients with severe renal or hepatic impairment. Recently, empagliflozin, an inhibitor of sodium-glucose co-transporter 2, has been shown to be able to reduce the rate of hospitalizations for HF in patients with diabetes at high-cardiovascular risk, including patients with HF (6, 7) *(Figure 2).* Waiting for the confirmation from ongoing trials testing this class of antidiabetic drugs in patients with HF, current guidelines state that the results obtained with empaglifozin cannot be considered as a proof of a class effect. In addition, there are still great uncertainties on the mechanisms underlying the favourable effect of this drug in terms of early prevention of cardiovascular death and occurrence of HF hospitalizations.

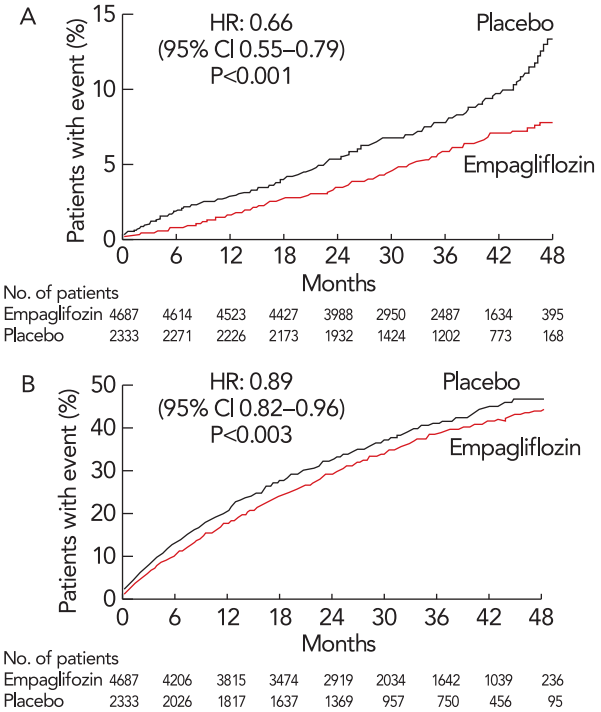

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FIG. 2. Therapeutic algorithm for a patient with symptomatic HFrEF (2)

With respect to hyperkalaemia (>6.0 mmol/L), besides the short-term cessation of potassium-retaining agents and renin angiotensin aldosterone system (RAAS) inhibitors which should be carefully reintroduced (as soon as potassium levels are under control), two new potassium binders (patiromer and sodium zirconium cyclosilicate) are currently under consideration for regulatory approval (8–10). Initial results from patients with HF are available and confirm the efficacy of these therapies in reducing serum potassium in patients with HF presenting with hyperkalaemia. Further studies are necessary to assess the role of these drugs in the prevention of recurrent hyperkalaemia in patients with HF and chronic kidney disease in the context of a treatment with RAAS inhibitors.

Some new findings on the treatment with RAS inhibitors and NEP inhibitors

Another approach to inhibit the RAS is the direct renin inhibition. The ATMOSPHERE trial tested whether combining the renin inhibitor aliskiren with the ACE inhibitor enalapril was superior to enalapril alone and whether aliskiren alone was at least non-inferior to enalapril in patients with HFrEF (11). The trial showed that the addition of aliskiren to enalapril did not result in a reduction of the risk of death from cardiovascular causes or hospitalization due to HF, as compared with enalapril alone, but did cause more hypotension, renal dysfunction, and hyperkalaemia. The ATMOSPHERE findings do not support the use of a direct renin inhibitor as an alternative to an ACE inhibitor, because also the pre-specified criterion for non-inferiority was not met in the ATMOSPHERE trial.

If the hypothesis to use a direct renin inhibitor in addition or in alternative to ACE-inhibitors/ARBs failed, some more papers have been published in 2016 reinforcing the favourable evidences on the use of sacubitril/valsartan as a replacement therapy of enalapril, defining better the population of patients who might receive a benefit from this new ARNI compound.

Specifically, several ancillary analyses evaluated if the level of EF, age, mode of death, background therapy, and level of HF risk can help in selecting patients to be switched from an ACE-inhibitor to sacubitril/valsartan (12–17).

With respect to the analysis by age (12), the most important finding was that the benefit of sacubitril/valsartan over enalapril was consistent across all the age categories studied, and also when age was

considered as a continuous variable. The same conclusion can be drawn from the analysis on EF levels (13). Sacubitril/valsartan was effective at reducing cardiovascular death (either due to sudden death or worsening HF *(Figure 3)* (14) and HF hospitalization throughout the LVEF spectrum, considering, of course, that only patients with HFrEF have been included in the trial.

Even more relevant for implementing the general conclusions of the PARADIGM-HF study in clinical practice was the evaluation of the effects of the drug according to the different levels of risk, using the MAGGIC or the EMPHASIS-HF stratification models (15). Although most PARADIGM-HF patients had mild symptoms, the benefit of sacubitril/valsartan over enalapril was apparent across the whole spectrum of risk defined by the MAGGIC and EMPHASIS-HF risk score, and even within the large subset of patients in NYHA functional II (15). Finally, a practical open question was related to the potential risk of combining the more potent sacubitril/valsartan with a MRA. The benefit of sacubitril/valsartan over enalapril was consistent for the primary composite outcome of cardiovascular death or HF hospitalization, and cardiovascular death alone, irrespective of the background therapy (16, 17). In other terms, the superiority of the new drug compared with the traditional one was present in both patients receiving or not MRAs. The whole set of ancillary analyses of PARADIGM-HF reinforces the conclusions of the trial demonstrating a very homogeneous effect of the drug in the different subgroup of patients.

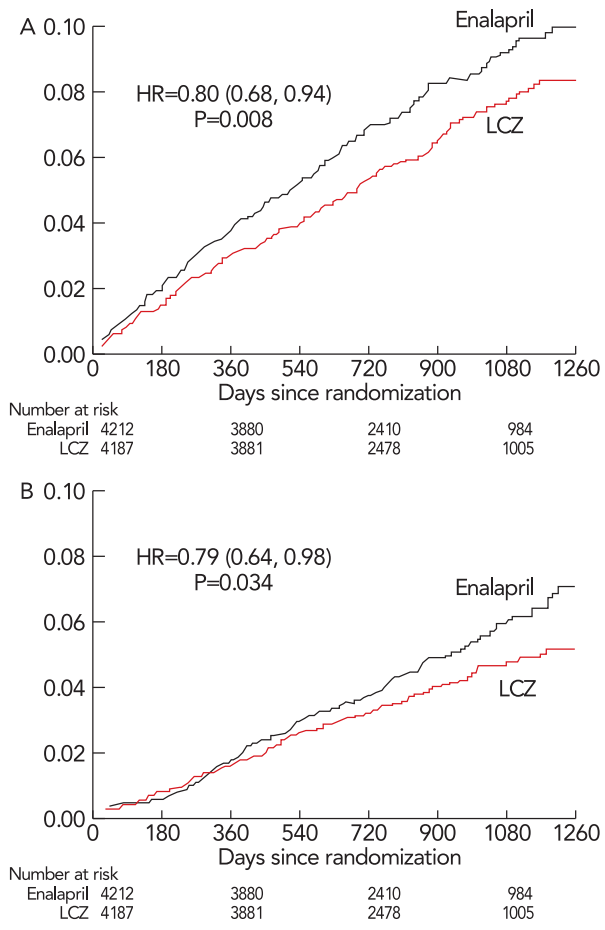

FIG. 3. PARADIGM-HF trial: Kaplan–Meier survival curve for (A) sudden death, (B) worsening heart failure, by treatment (14)

Should an ICD implanted in all patients with HFrEF?

In a randomized controlled trial, the DANISH trial (8, 19), 556 patients with symptomatic systolic HF (LVEF≤35%) not caused by coronary artery disease were assigned to receive an implantable cardioverter-defibrillator (ICD), and 560 patients were assigned to receive usual clinical care (control group). In both groups, 58% of the patients received cardiac resynchronization therapy. The primary outcome of the trial was death from any cause.

After a median follow-up period of 67.6 months, the primary outcome had occurred in 120 patients (21.6%) in the ICD group and in 131 patients (23.4%) in the control group [hazard ratio (HR), 0.87; 95% confidence interval (CI), 0.68–1.12; P=0.28]. Sudden cardiac death occurred in 24 patients (4.3%) in the ICD group and in 46 patients (8.2%) in the control group (HR, 0.50; 95% CI, 0.31–0.82; P=0.005) *(Figure 4)*. The conclusion was that ICD implantation for primary prevention in patients with HFrEF, not caused by coronary artery disease, did not reduce the rate of long-term all-cause mortality. These important findings are probably due to the fact that patients with non-ischemic HFrEF, treated at the best of contemporary pharmacological and non-pharmacological treatment, have a very low risk of sudden death. In this context, ICD implantation cannot make the difference in terms of all-cause mortality, frequently due to progression of pump failure and also, in a real-world setting, to non-cardiovascular causes. Consequently, the absolute benefit of ICDs in a well-treated population of patients with HFrEF might be not clinically significant. Due also to the high costs, it seems reasonable to better identify those at higher risk of sudden death to benefit from ICD implantation.

Prevention of HF: the role of an intensive treatment of blood pressure and some additional evidences on new anti-diabetic drugs

There is considerable evidence that the onset of HF may be delayed or prevented through interventions aimed at modifying risk factors for HF or treating asymptomatic LV systolic dysfunction.

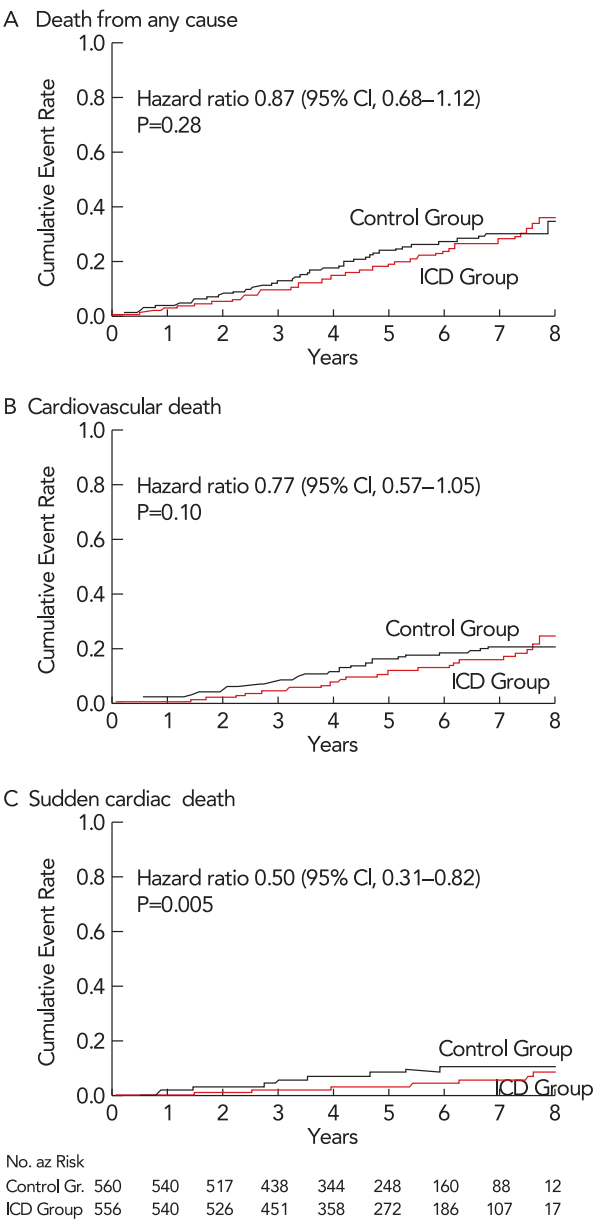

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FIG. 4. DANISH trial: time-to-event curves for death from any cause (A), cardiovascular death (B), and sudden cardiac death (C) (18)

Systolic blood pressure

Many evidences are available showing that control of hypertension will delay the onset of HF. However, it is not yet clear which is the best level of systolic blood pressure (SBP) to be reached to prevent HF and other cardiovascular events. In the SPRINT trial, 9361 subjects with a SBP of 130 mm Hg or higher and an increased cardiovascular risk, but without diabetes, had been randomly assigned to a SBP target of less than 120 mm Hg (intensive treatment) or a target of less than 140 mm Hg (standard treatment) (20). The primary composite outcome was myocardial infarction, other acute coronary syndromes, stroke, HF, or death from cardiovascular causes. The trial was stopped early after a median follow-up of 3.26 years due to a significantly lower rate of the primary composite outcome in the intensive-treatment group than in the standard-treatment group (1.65% per year vs. 2.19% per year; HR with intensive treatment, 0.75; 95% CI, 0.64–0.89; P < 0.001). Regarding, more specifically, the occurrence of HF, in patients allocated to the intensive harm, HF occurred in 62 (1.3%) cases vs. 100 (2.1%) in the usual care group (HR 0.62, 95% CI 0.45–0.84, P = 0.002). This beneficial effect was obtained in a context of an increase of serious adverse events such hypotension, syncope, electrolyte abnormalities, and acute kidney injury or failure, but not of injurious falls. Further, in just about 50% of cases the lower level of SBP (<120 mmHg) was actually achieved with the need of an increased medication costs and clinic visits.

More recently, the HOPE 3 trial randomized 12,705 patients at intermediate risk who did not have prior cardiovascular diseases to receive either candesartan at a dose of 16 mg per day plus hydrochlorothiazide at a dose of 12.5 mg per day or placebo. In this population of patients, therapy with candesartan plus hydrochlorothiazide was not associated with a lower rate of major cardiovascular events, including HF (21).

Diabetes mellitus

After some disappointing results obtained in trial testing inhibitors of dipeptidyl peptidase 4 (DPP-4) inhibitors showing an increasing risk of HF in diabetic patients treated with these drugs, some recent data are more reassuring. Besides the favourable results obtained with empaglifozin already discussed before (6, 7), two other trials showed that the treatment of diabetic patients with the glucagon-like peptide 1 (GLP-1) analogues, liraglutide and semaglutide, reduced the rate of occurrence of major cardiovascular events without significantly affecting the occurrence of HF hospitalization (22, 23). Specifically, the rate of the first occurrence of death from cardiovascular causes, non-fatal myocardial infarction, or non-fatal stroke among patients with Type 2 diabetes mellitus was lower with liraglutide than with placebo in the LEADER trial (22). The rate of hospitalization for HF, over a median follow-up period of 3.5 years, was not different among patients allocated to liraglutide vs. those in placebo.

Similarly, the SUSTAIN-6 trial showed that in patients with Type 2 diabetes at high-cardiovascular risk, the rate of cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke was significantly lower among patients receiving semaglutide than among those receiving placebo, without any significant difference in terms of hospitalization for HF (23).

Overall these evidences suggest that today we have more therapeutic options for the treatment of patients with diabetes at high-cardiovascular risk. An impro-

ved glycaemic control obtained with safer drugs could offer better opportunities of prevention of overt HF occurrence.

Influenza vaccination: an old story never appropriately implemented

Patients with HF are at increased risk of experiencing cardiovascular and respiratory-related hospitalizations compared with the general public, and for those with influenza infection these risks are substantially elevated. However, whether such risks can be reduced with influenza vaccination remains uncertain. In the absence of definite evidence from ongoing controlled studies testing the efficacy of influenza vaccination in HF, clinical practice guidelines recommend this procedure. The UK National Institute for Health and Care Excellence (NICE) (24) and the American Heart Association (AHA) (2) recommend annual influenza vaccination, as well as the recent ESC Guidelines (1). To improve the level of evidence on this topic, primary and secondary health records in England between 1990 and 2013 were used to estimate the incidence of hospitalizations in patients with HF in a year following vaccination with an adjacent vaccination-free year in the same individuals (25). Among 59,202 HF patients, influenza vaccination was associated with a lower risk of hospitalization due to cardiovascular disease (incident rate ratio (IRR) 0.73 [95% CI: 0.71–0.76]), with more modest effects for hospitalization due to respiratory infections (IRR 0.83 [95% CI: 0.77–0.90]), and all-cause hospitalizations (IRR 0.96 [95% CI: 0.95–0.98]). Authors of this observational study support the annual vaccination for patients with HF to help alleviate the burden of influenza-related admissions. Public health strategies, working closely with primary care physicians, should consider a policy of influenza vaccination in patients with HF, especially among high-risk subgroups.

TRUE-AHF – Challenging the early-intervention hypothesis in acute heart failure

TRUE-AHF (Trial of Ularitide Efficacy and Safety in Acute Heart Failure) was designed to evaluate the effect of a 48-h infusion of ularitide on the short-term clinical course of patients and the long-term risk of cardiovascular death. The study drug ularitide, a chemically synthesized analogue of urodilatin, leads to systemic and renal vasodilation, diuresis and natriuresis, inhibition of the renin-angiotensin system and exerted haemodynamic and clinical benefits in previous, though smaller trials in patients with acute HF. TRUE-AHF trial randomized 2157 patients at 156 centres and had two primary endpoints:

(i) the risk of cardiovascular death over the entire duration of the trial and
(ii) the clinical course of patients during the first 48 h, as assessed by the hierarchical clinical composite endpoint.

As compared with placebo, ularitide was accompanied by significant decreases of signs of intravascular decongestion but did not differ in degree of change in high-sensitivity-assay cardiac troponin over 48 h (26, 27). The 1069 patients receiving placebo experienced more episodes of persistent or worsening HF in the first 48 h than did the 1088 patients receiving ularitide The HR for the co-primary end point, cardiovascular mortality, for ularitide vs. placebo over a median follow-up of 27 months was 1.03 (95% CI: 0.85–1.25, P=0.75).

From a pathophysiological point of view, these results question the concept that early (and short-term) intervention with a vasodilator could reduce wall stress and myocardial injury during the critical initial period of acute HF and therefore that an early treatment is able to decrease the long-term risk of cardiovascular death (27).

A further insight on the concept of the early-injury/early intervention strategy in acute HF will be provided by the results of the ongoing RELAX-AHF2 trial with the vasodilator serelaxin in more than 6500 patients of with acute HF. The primary outcomes of cardiovascular mortality at 6 months and worsening HF through Day 5 are expected to become available during the course of the next year.

Conflict of interest

A.P.M. reports personal fees from Novartis, personal fees from Bayer, personal fees from Cardiorentis, outside the submitted work. F.R. reports grants and personal fees from SJM, personal fees from Servier, personal fees from Zoll, personal fees from AstraZeneca, personal fees from HeartWare, personal fees from Sanofi, personal fees from Cardiorentis, personal fees from Novartis, personal fees from Amgen, personal fees from BMS, outside the submitted work.

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