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Review

Review of heart failure treatment in type 2 diabetes patients: It's at least as effective as in non-diabetic patients!

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Abstract

Our society is currently facing an epidemic of diabetes and heart failure. Historically, certain cardiology treatments, mainly beta-blockers, have been considered 'dangerous' in diabetic patients, but the time has come for personalized medicine to be applied in the field of cardiology, especially in heart failure (HF). To determine whether HF treatment should be individualized according to diabetes status, this review of the available randomized evidence was carried out, with special emphasis on treatment-effect modification in relation to diabetes. Based on a large body of evidence in the literature, our review concludes that HF treatment should be the same for diabetic and non-diabetic patients. In concurrence, international guidelines now strongly advocate the use of HF drugs, including beta-blockers, in diabetic HF patients. The benefit of HF treatment is at least as favourable in such patients as in non-diabetic patients on a relative basis. Given the higher risk of events in diabetics, this could translate to an even greater absolute impact of HF treatment in these patients, which should further encourage caregivers to more aggressively manage HF in diabetic patients. To this end, non-cardiologists, including general practitioners and endocrinologists/diabetologists who treat diabetic HF patients, should be considered part of the HF drug optimalization process, including the referral of patients to specialized centres for possible implantable cardiac defibrillators and/or cardiac resynchronization indication assessment.

Keywords: Absolute treatment effect; Diabetes; Drug optimalization; Heart failure; Treatment

1. Introduction

Our society is currently facing an epidemic of diabetes. In parallel with this endocrinological public-health concern, cardiologists are encountering a growing number of heart failure (HF) patients with either reduced or preserved ejection fraction (EF). During the last 30 years, treatment of HF has curbed the rate of mortality in reduced EF HF patients, while the treatment of preserved EF remains mainly based on the treatment of associated risk factors [1].

Historically, certain cardiology treatments, mainly beta-blockers (BBs), were considered 'dangerous' in diabetic patients [2]. In addition, specific conditions in diabetic patients potentially translate to different management protocols for HF treatment. Personalized medicine has been applied for more than a decade in the field of oncology [3], and it is now time to apply this concept to the field of cardiology, especially in HF patients [4,5]. This raises the question: Should diabetic patients be managed differently with regards to HF?

The present review addresses whether or not HF treatment should be adapted to diabetes status.

2. Recommended treatment of HF with reduced EF

Many professional guidelines, but mainly those of the European Society of Cardiology (ESC) [1] and American

Abbreviations: ACEI, Angiotensin-converting enzyme inhibitor; ARB, Angiotensin receptor blocker; BB, Beta-blocker; MRA, Mineralocorticoid receptor antagonist.

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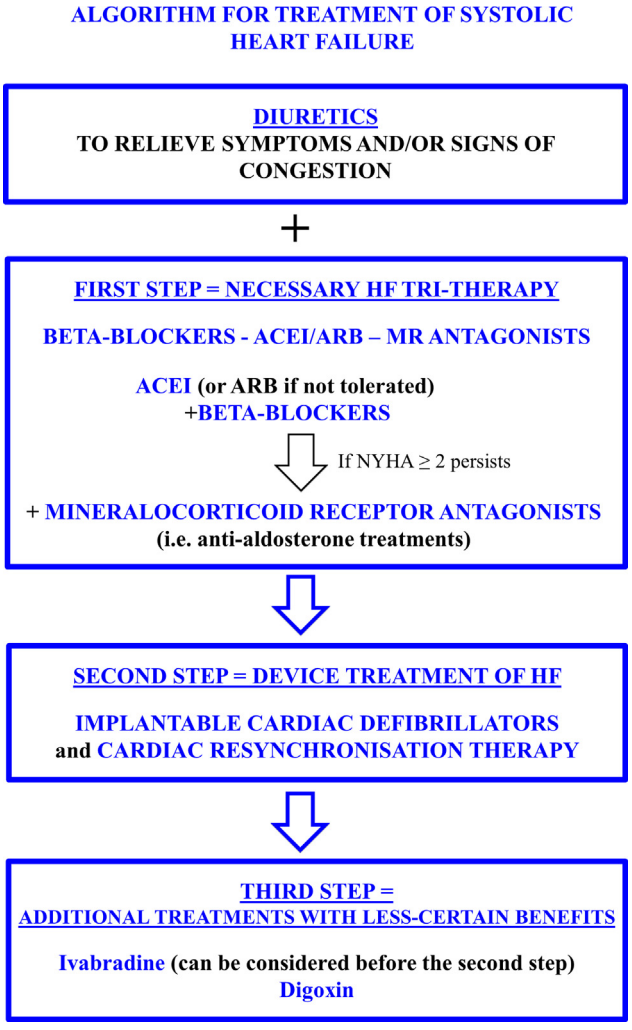

Fig. 1. Therapeutic algorithm proposed by the European Society of Cardiology (ESC) for patients with heart failure (HF) and reduced ejection fraction. Advanced HF is not mentioned in this simplified version. The "less-certain benefit" phrase referring to digoxin and ivabradine is from the original guidelines (page 1808). ACE-I/ARB: angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; MR: mineralocorticoid receptor; NYHA: New York Heart Association HF classification.
Adapted from Fig. 2 of the ESC 2012 guidelines for the diagnosis and treatment of acute and chronic heart failure.

College of Cardiology Foundation/American Heart Association (ACCF/AHA) [6], provide clear recommendations regarding the medical and interventional treatment to be used in HF patients with reduced EF. The following summarizes the therapeutic algorithm proposed by the ESC (Fig. 1).

2.1. First step of systolic HF treatment: the necessary HF drugs

In brief, for patients with signs and symptoms of HF associated with reduced EF, the first step of the algorithm recommended by the ESC [1] is a tritherapy comprising BBs, angiotensin-converting enzyme inhibitors (ACEIs), or angiotensin receptor blockers (ARBs) if ACEIs are not tolerated, and mineralocorticoid receptor antagonists (MRAs), the latter to be introduced upon persistence of symptoms. These three treatments have been proven to decrease the risk of morbidity/mortality in large-scale randomized clinical trials, and are considered mandatory in HF patients with reduced left ventricular ejection fraction (LVEF) and a recommendation of class I level of evidence A. These treatments are initiated in addition to loop diuretics, which are usually required to relieve symptoms of fluid overload. More important, BBs and ACEIs/ARBs require a progressive increase in medication dosage, which can take several months. BBs are usually increased every 10 days to 3 weeks, depending on the agent used and prescribing habits of the physician.

Upon achieving the maximum tolerated dose of each of these pharmacological agents, ivabradine can be added to the current medication in patients with a resting heart rate > 70 bpm.

2.2. Second step of systolic HF treatment: treatment devices

After the first step, which is entirely drug-based, an implantable cardiac defibrillator (ICD) and/or cardiac resynchronization therapy (CRT) should be considered in patients with persistently decreased LVEF ≤ 35% and residual symptoms of HF. The indication for CRT is mostly based on QRS width, whereas the indication for ICD, given its very high cost, is mostly based on life expectancy, with implantation contemplated only in patients with a life expectancy > 1 year. These interventional electrical treatments are also strongly recommended (class I level of evidence A).

2.3. Third step of systolic HF treatment: additional treatments with less-certain benefits

Subsequent to the previous two steps, interventions that have not been proven to reduce mortality in patients with HF may be implemented. Digoxin can be considered with or without atrial fibrillation in patients with persistently decreased LVEF and residual symptoms of HF, based on the results of the Digitalis Investigation Group (DIG) trial [7].

In end-stage HF patients, LV assist devices or heart transplantation may be considered [1].

3. Assessing differential impacts according to diabetes status

The differential impact of the above pharmacological treatments can be assessed by interaction analysis using clinical trial databases. The term 'interaction' has a specific meaning in the field of biostatistics. It refers to the impact of a given variable on the effect of another variable. For instance, our literature search was systematically made for data regarding any interaction between diabetes and the treatment effect on various considered clinical outcomes. This type of analysis is only advisable to determine whether a treatment has a differential impact in subgroups of patients—namely, patients with and without diabetes for the purposes of this review. However, some of the trials reviewed were performed/published in the late 1980s or early 1990s, when interaction was usually not assessed in primary