Selection of the Best of 2017 in Acute and Chronic Heart Failure

Selección de lo mejor del año 2017 en insuficiencia cardíaca aguda y crónica

To the Editor,

Heart failure is a leading health care problem in Spain and other countries due to its rising incidence (population aging) and prevalence (higher survival rates among patients with heart disease). While improvements have been made in both diagnosis and treatment, prognosis is still poor and the highrehospitalization rates associated with this condition place an enormous burden on the health care system.

Conceptually speaking, the latest European guidelines for the diagnosis and treatment of acute and chronic heart failure distinguish between 3 groups of heart failure based on left ventricular ejection fraction (LVEF). This distinction has therapeutic implications, as most of the current evidence is based on the treatment of heart failure with reduced LVEF (< 40%). No treatments to date have been shown to be effective or to improve prognosis in patients with preserved LVEF (> 50%). The most novel concept in the European guidelines is the inclusion of heart failure with mid-range LVEF, a move aimed at promoting research and building scientific evidence to improve the management of patients with LVEF between 40% and 49%.

Natriuretic peptides are now recognized as key biochemical markers for early heart failure screening. They are mostly used in primary care and emergency departments as an adjunct to history and physical examination. They have also proven useful as a prognostic stratification tool, although approaches based on serial measurements are not perhaps the most valid option for guided therapy (GUIDE-IT study).

None of the treatments applied to patients with acute heart failure to date have succeeded in improving prognosis. We have witnessed the failure of promising new treatments, such as recombinant serelaxin and ulitadite (TRUE-AHF trial). We are also learning that early treatment of acute heart failure, with shorter door-to-diuretic times, improves prognosis and is becoming a quality metric that should be implemented across hospitals (REALITY study).

The most notable aspect of chronic heart failure treatment is the now widespread use of angiotensin receptor nepriylin inhibitors (ARNIs) to treat symptomatic disease in patients with systolic dysfunction. ARNIs have emerged as an alternative to traditional angiotensin-converting enzyme inhibitors II (ARA II), and the latest U.S guidelines recommend their use at an earlier stage than that proposed by the European guidelines (where they are ranked at the same level as mineralocorticoid receptor antagonists).

Another interesting development is the increasing importance attached to the adequate management of comorbidities in a bid to improve quality of life, prevent disease progression, improve prognosis, and reduce heart failure hospitalizations. Intravenous iron therapy, for example, has been shown to improve functional capacity in patients with systolic dysfunction, although its effectiveness in reducing hospitalizations due to heart failure remains to be confirmed in clinical trials. Promising reductions in hospitalization rates have been reported in trials of sodium-glucose cotransporter 2 inhibitors (SLGT-2), where particularly good results have been observed for empagliflozin, although specific evidence is lacking for diabetic patients with heart failure. Finally, although sleep disorders are known to play a role in the pathophysiology and perpetuation of heart failure, no benefits have been observed for the use of specific systems to treat central sleep apnea in this setting.

Heart failure is the paradigmatic example of a chronic disease that requires new treatment approaches if there is to be a true impact on prognosis. Apart from specific therapeutic interventions, we need integrated care systems that bring together the different actors involved to form multidisciplinary teams, with carers and patients taking a leading role. Improved adherence to treatment guidelines has been found to have a favorable impact on prognosis and on heart failure hospitalizations in particular (QUALIFY study). Health care managers, professionals, and society at large must all engage in fostering a coordinated multidisciplinary strategy aimed at improving outcomes in patients with heart failure and reducing associated health care costs.

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Selection of the Best of 2017 in Pulmonary Hypertension

Selección de lo mejor del año 2017 en hipertensión pulmonar

To the Editor,

Pulmonary arterial hypertension (PAH) is characterized by pulmonary vascular remodeling and the resulting increase in pulmonary vascular resistance. This increased afterload leads to hypertrophy of the right ventricle (RV), which is initially adaptive but ultimately maladaptive, causing right-sided heart failure and death.1

The World Health Organization has classified pulmonary hypertension (PH) into 5 major groups, according to clinical, hemodynamic, and histological similarities. The most prevalent entities are PH associated with left-sided heart disease (group 2) and PH resulting from respiratory disease and hypoxia (group 3).

Despite their very low prevalence, PAH and its associated subtypes (group 1) have been the subject of considerable research. Continual advances in understanding the underlying physiopathological mechanisms in PAH and the development of new therapies have improved the survival of these patients, but their prognosis remains ominous. Current treatments are unable to reverse disease progression and available diagnostic strategies often miss early-stage PAH.

In 2017, guideline recommendations have been widely implemented regarding the latest therapeutic approaches and risk assessment; knowledge of PAH pathophysiology and genetics has improved; and treatment of inoperable chronic thromboembolic pulmonary hypertension (CTEPH) has been established.

Three new drugs have appeared on the market, targeting each of the 3 available pathophysiological pathways involved in PAH: a) macitentan, an endothelin receptor antagonist; b) riociguat, a soluble guanylate cyclase stimulator of the nitric oxide-mediated pathway; and c) selexipag, a prostacyclin receptor agonist that targets the prostacyclin pathway.

Following the AMBITION trial (initial therapy with a phosphodiesterase type 5 inhibitor [taladafil] and an endothelin receptor antagonist [ambrisentan]), initial combination therapy has been established as the most widely-therapeutic strategy for patients with newly-diagnosed PAH.1,2

The multidimensional approach to risk assessment recommended by guidelines has been validated. This type of risk assessment guides treatment decisions and determines survival by taking into consideration achievement of low-risk criteria in multiple risk markers.3

Regarding the advances in physiopathology and genetics, while vasoconstriction remains the key therapeutic target of available treatments, other mechanisms have found to be involved in the progressive obstruction of the pulmonary vascular bed characteristic of PAH. These mechanisms include cell proliferation, cell death inhibition, inflammation, immune alteration, excessive activation of signaling pathways and altered mitochondrial function and oxidative metabolism. This novel metabolic theory suggests that metabolic dysregulation goes beyond the vascular bed and is also present in the RV and skeletal muscle. In addition, immune system involvement due to bone marrow participation means that PAH is actually a systemic disease.4

This alteration of multiple metabolic pathways has a genetic component. The first gene linked to PAH was BMPR2, which encodes the morphogenetic protein receptor type 2 and regulates multiple cellular functions. Mutations in BMPR2 have been described in 75% of the hereditary forms of PAH and 25% of the idiopathic forms. These mutations show an autosomal dominant inheritance pattern with incomplete penetrance (20%), varying by sex (42% in women vs 14% in men) and expressivity. There are more than 300 known mutations in BMPR2. Recently, new genes have been found to be involved in the development HAP, such as KCNK3 (encoding for a pH-dependent potassium channel), TBX4 (encoding for the TBX4 transcription factor involved in embryonic development), and EIF2AK4, which is linked to the development of pulmonary veno-occlusive disease. The presence of a mutation guides a correct diagnosis.5 The door has been opened to genetic counselling and early diagnosis of patients’ relatives.

The treatment of choice for CTEPH (group 4) is still pulmonary endarterectomy in a CTEPH center, where the outcome is low mortality and good long-term survival. In patients who are ineligible for endarterectomy, riociguat has shown benefit and is the only drug recommended by clinical practice guidelines for the treatment of CTEPH. In addition, in 2017 it has been demonstrated that balloon pulmonary

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