anticoagulants. To improve access to these drugs, the Spanish Society of Cardiology and other scientific societies, including those related to primary care, recently proposed a series of amendments to the Health Ministry's policy in this area.[6]

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Selection of the Best of 2016 in Clinical Cardiology: Therapeutic Novelties

Selección de lo mejor del año 2016 en cardiología clínica. Novedades terapéuticas

To the Editor,

The results of important clinical trials were published in 2016 with far-reaching implications for clinical cardiology practice.

The PARADIGM-HF trial[1] compared the effects of valsartan/sacubitril (LCZ696) 200 mg twice daily vs enalapril 10 mg twice daily added to standard therapy in about 8500 patients with symptomatic heart failure (HF), New York Heart Association functional class II-IV, and ejection fraction $\leq$ 40%. The primary outcome was a composite of death from cardiovascular causes or HF hospitalization. The trial was stopped early after a median follow-up of 27 months due to the strength of the positive results achieved with valsartan/sacubitril. LCZ696 was associated with a 20% reduction in the risk of the primary outcome and a 16% reduction in death from any cause. In addition, LCZ696 reduced HF symptoms and improved functional class.[1] These results have led the new European guidelines[2] to recommend the use of valsartan/sacubitril instead of angiotensin-converting enzyme inhibitors to reduce the risk of HF hospitalization and death in ambulatory patients with HF and reduced ejection fraction who remain symptomatic despite optimal treatment (IB recommendation). It has also recently been shown that valsartan/sacubitril therapy can be cost-effective in this context.[3]

Diabetes mellitus is one of the major epidemics of the 21st century. As is well known, diabetes increases the risk of both microvascular and macrovascular complications. Glycemic control through antidiabetic therapy effectively reduces microvascular complications and even macrovascular complications in patients with less advanced disease. However, intensive lipid-lowering therapy can be harmful in patients with more advanced diabetes. Since 2008, due to doubts about the cardiovascular safety of some drugs, all antidiabetic drugs must demonstrate cardiovascular safety in specific clinical trials, in addition to reducing glycated hemoglobin levels, before they can be approved for use in clinical practice. In this context, the cardiovascular safety of dipeptidyl peptidase-4 inhibitors (saxagliptin, alogliptin, and sitagliptin) has been shown, although doubts have been raised about the risk of HF hospitalization with some of them.

The EMPA-REG OUTCOME trial was published in the past year. This study showed that empagliflozin, a sodium-glucose cotransporter 2 (SGLT2) inhibitor, reduces the risk of the primary composite outcome of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke vs placebo in patients with type 2 diabetes and established cardiovascular disease.[4] The recent guidelines for HF specify that empagliflozin should be considered for patients with type 2 diabetes to prevent or delay the onset of HF and prolong life; this is the first time that an antidiabetic drug has received a recommendation of this type.[2] More recently, in the LEADER trial,[5] liraglutide, a glucagon-like peptide-1 (GLP-1) analog, reduced the risk of the same primary composite outcome vs placebo in patients with type 2 diabetes at high cardiovascular risk. The results of these studies are discussed in greater detail in another scientific letter on the same topic.

One of the other therapeutic innovations of this year concerns PCSK9 inhibitors. Generally, previous studies performed with these antibodies have achieved considerable reductions in low-density lipoprotein-cholesterol (LDL-C), both in monotherapy and in combination with other lipid-lowering agents, as well as a good safety profile, at least during 1-year follow-up. Although the results on morbidity and mortality from large clinical trials are required, the currently available data indicate that their use might also be associated with a significant reduction in cardiovascular events. Additionally, because these drugs are injected every 2 to 4 weeks, they might lead to better therapeutic adherence than

other lipid-lowering agents such as statins and ezetimibe that need to be taken every day. Finally, although these agents might not seem cost-effective in some health care systems due to their current price, they might be the only therapeutic alternative for certain patient groups to attain the recommended target LDL-C levels.[6]

We conclude with the polypill, which is a therapeutic approach of considerable interest for clinical cardiology, particularly in patients with treatment adherence problems. The advantages of these compounds are discussed in greater detail in another scientific letter.

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Selection of the Best of 2016 in Diabetes and Heart

Selección de lo mejor del año 2016 en diabetes y corazón

To the Editor,

Recent data published by the World Health Organization confirm that the prevalence of diabetes mellitus (DM) continues to increase, from 4.7% in 1980 to 8.5% in 2014.[1] DM caused more than 1.5 million deaths in 2012, with most of them occurring in individuals older than 70 years. In addition, a recent study of a large population of patients with DM2 showed that, despite acceptable preventive treatment, cardiovascular (CV) deaths were 33% more frequent in patients with DM2 than in controls, and that CV conditions were the most frequent cause of death in patients with DM.[2] These figures, along with the fact that at least one third of patients seen in cardiology departments have DM, should make clinical cardiologists aware of the importance of diabetic treatments for patients with cardiac disease, particularly given the reduction in the rate of CV events that can be achieved with some hypoglycemic agents. We also know, however, that hypoglycemic agents can be harmful to patients with cardiac disease because part of our job when attending these patients involves discontinuing potentially harmful treatments that may increase the risk of heart failure or even mortality in certain patient subgroups (Table). Three trials have recently been published and their results should be disseminated to maximize the benefit to patients with CV disease and DM2.

The EMPA-REG OUTCOMES study[3] reported that, after a mean follow-up of 3.1 years, empaglifozin reduced the primary outcome (composite of nonfatal myocardial infarction, nonfatal stroke, and CV death) by 14% in 7020 patients with DM2 and CV disease. This reduction was driven mainly by a 38% decrease in CV deaths. Empaglifozin also reduced hospitalization for heart failure by 35% and overall mortality by 32%. The number of patients needed to treat to avoid 1 admission for heart failure or CV death was 35 in 3 years. Of note, the reduction in the risk of admission for heart failure occurred both in patients with a history of heart failure and in those without. Possible mechanisms to explain these benefits include decreases in blood pressure, body weight

Table
Effects of the Hypoglycemic Therapeutic Groups on Cardiovascular Mortality and Admissions for Heart Failure

Therapeutic group	Cardiovascular mortality	Admissions for heart failure
Insulin	Neutral	Neutral (harmful)
Metformin	Neutral (beneficial)	Neutral
Sulfonylureas	Neutral (harmful)	Neutral (harmful)
Glitazones	Neutral	Harmful
SGLT2 inhibitors	Empaglifozin, beneficial	Empaglifozin, beneficial
DPP4 inhibitors	Neutral	Neutral; saxagliptin, harmful
GLP-1 agonist	Lixisenatide and semaglutide, neutral; liraglutide, beneficial	Neutral

Data from small studies and registries are shown in parentheses.