

To the Editor

In the Scientific statement from the American Heart Association "Drugs that may cause or exacerbate heart failure", insulin is not listed among the drugs that may cause or worsen heart failure (HF) (1). Fluid retention caused by insulin was first reported by Gibson and Larimer in 1925, just a few years after its discovery, and is due to sodium retention at the renal tubular level, as clearly observed by De Fronzo in 1975. The onset or worsening of HF in patients treated with insulin has already been described extensively in the literature and it has been hypothesized that insulin can also cause myocardial steatosis and left ventricular diastolic dysfunction(2). Guidelines for the Treatment of Acute and Chronic Heart Failure of the European Society of Cardiology of 2016 underline how insulin in diabetic patients with HF may cause fluid retention and thus worsening HF (3). In our recent post-hoc analysis of the Valsartan Heart Failure (Val-HeFT) and of the Gruppo Italiano per lo Studio della Sopravvivenza-Heart Failure (GISSI-HF) trials, we found that insulin was associated with increased mortality (HR 1.35 [1.12-1.62] $p=0.0015$) and more frequent hospital admission for HF (HR 1.37 [1.15-1.65], $p=0.01$) compared to other anti-diabetic therapies, after adjustment for HF and diabetes severity and other co-morbidities with propensity score (4). A very recent cohort study in 469688 UK people with type 2 diabetes showed that insulin was independently associated with a 47% higher risk of all-cause mortality and a 32% higher risk of incident HF while significant better outcomes were associated to metformin, gliptins and glitazones (5)

Our recent data, associated with the analysis of the literature, show how is compelling to include insulin in the list of drugs that may exacerbate HF, also considering that about one third of patients with HF also has type 2 diabetes mellitus and that 27% of these patients are treated with insulin (GISSI-HF data).

If there are no alternatives to insulin therapy, the administration should be individualized, carefully avoiding hypoglycemia and increase in body weight.

Deborah Cosmi MD

Cardiovascular Department, S. Corona Hospital, Pietra Ligure (SV) Italy

Franco Cosmi MD

Cardiovascular and Neurological disease Department, Valdichiana Cardiology, USL Sudest Toscana, Italy

Roberto Latini MD

Department of Cardiovascular Research, IRCCS-Istituto di Ricerche Farmacologiche Mario Negri, Milan, Italy

1. Page RL II, O'Bryant CL, Cheng D, Dow TJ, Ky B, Stein CM, Spencer AP, Trupp RJ, Lindenfeld J. American Heart Association Clinical Pharmacology and Heart Failure and Transplantation Committees of the Council on Clinical Cardiology; Council on Cardiovascular Surgery and Anesthesia; Council on Cardiovascular and Stroke Nursing; and Council on Quality of Care and Outcomes Research. Drugs That May Cause or Exacerbate Heart Failure: A Scientific Statement From the American Heart Association. *Circulation*. 2016; 134: e32-e69; doi: 10.1161/CIR.0000000000000426

2. Gilbert RE, Krum H. Heart failure in diabetes: effects of anti-hyperglycaemic drug therapy. *Lancet*. 2015; 23: 2107-2017. doi: 10.1016/S0140-6736(14)61402-1

3. Ponikowski P, Voors AA, Anker SD, Bueno E, Cleland JGF, Coats AJS, Falk V, Gonzalez-JuanateyJR), Harjola VP, Jankowska EA, Jessup M), Linde C, Nihoyannopoulos P, Parissis JT, PieskeB, Riley JP, Rosano GMC , Ruilope LM, Ruschitzka F, Rutten FH, Van Der Meer P. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J*. 2016; 37:2129–2200. doi:10.1093/eurheartj/ehw128
4. Cosmi D, Barlera S, Masson S, Staszewsky L, Maggioni AP, Tavazzi L, Tognoni G, Cosmi F, Latini R. Treatment with insulin increases mortality in diabetic patients with chronic heart failure: data from the GISSI-HF trial. *Eur J Heart Fail*. 2016; 18 (Suppl.1),8-521.
5. Hippisley-Cox J, Coupland C. Diabetes treatments and risk of heart failure, cardiovascular disease, and all cause mortality: cohort study in primary care. *BMJ*. 2016; 12:354:i3477. doi: 10.1136/bmj.i3477.