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Management of Patients with Heart Failure and Type 2 Diabetes Mellitus

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Abstract: The management of patients with cardiometabolic diseases is particularly complex and involves professionals from various disciplines. Cardiologists and diabetologists, the coordinators of this process, should cooperate in the implementation of a joint treatment and care plan. Based on these premises, a group formed by cardiologists from the Regional Association of Ambulatory Cardiologists (ARCA) and diabetologists from the Association of Diabetologists (AMD), operating in Campania, was set up to define the critical points and create shared diagnostic and therapeutic processes. We review the current evidence and gather the opinions of the group concerning the identification of patients at higher risk of diabetes and/or heart failure and the management of patients with known diagnosis of diabetes mellitus and heart failure.

Keywords: Diabetes; Heart failure; Cardiovascular risk

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1. Introduction

Patients with multimorbidity are under the care of health professionals from diverse backgrounds at different times in their natural history and with reduced likelihood of information exchange between outpatient and hospital settings. This can be a criticality in the care process, especially as a common Diagnostic and Therapeutic Care Pathway (PDTA) is not shared. Among them, patients with cardiometabolic diseases have a particularly complex diagnostic-therapeutic pathway, involving multiple professional figures: a cardiologist, an endocrinologist/diabetologist, a nephrologist, a neurologist, an emergency room doctor, a general practitioner, a nurse, a dietician, *etc*. The cardiologist and diabetologist, as coordinators of this process, must cooperate with each other to achieve a shared virtuous pathway of treatment and care. With this in mind, an improvement group consisting of cardiologists from the Regional Associations of Ambulatory Cardiologists (ARCA) and diabetologists from the Association of Diabetologists (AMD), operating in Campania, was formed to define, in the first instance, the criticalities of reality in which they operate and implement a dedicated PDTA, which considers the different clinical stages of heart failure (HF) and diabetes and proposes shared diagnostic and therapeutic processes.

2. Epidemiology and pathogenetic aspects of heart failure in a person with diabetes

HF is a chronic and disabling disease whose prevalence is about 11.8% worldwide, reaching 16.1% in individuals aged more than 80, with markedly reduced life expectancy [1]. In Italy, HF represents the leading

cause of hospitalization among those aged more than 65 and is the leading cause of death among cardiovascular diseases [2]. Concerning the association of diabetes compensation, it is estimated that about 12% of people with type 2 diabetes mellitus (T2DM) are affected by HF and 30% of those hospitalized for HF recurrences are diabetic [3]. The two diseases share several risk factors, such as age, obesity, and hypertension [4], in addition to numerous pathophysiological mechanisms, including alterations in free fatty acid metabolism, alterations in the renin-angiotensin-aldosterone system, microvascular dysfunction, hyperglycemia-mediated damage, and cardiac autonomic dysfunction [5].

3. Diagnosis and stratification

The diagnosis of HF requires the presence of symptoms and/or signs of decompensation and evidence of cardiac dysfunction [6]. Typical symptoms include dyspnea, fatigue, and marked asthenia. Clinical signs include pretibial edema, jugular vein distention, and skin and mucosal pallor due to anemia. The diagnostic tests required for the diagnostic framing of patients with suspected HF are as follows:

(i) electrocardiogram (ECG); ECG can reveal arrhythmias such as atrial fibrillation;
(ii) natriuretic peptide (NP) measurement; a plasma concentration of B-type natriuretic peptide (BNP) less than 35 pg/mL or of N-terminal (NT)-proBNP less than 125 pg/mL supports the diagnosis of HF;
(iii) echocardiography; echocardiography represents the "gold standard" for the evaluation of cardiac function and provides information on other parameters, in addition to left ventricular ejection fraction (FE), such as the chamber size, the presence of eccentric or concentric remodeling, diastolic function, regional wall motion abnormalities, the right ventricular function, and pulmonary pressure; in addition, it allows us to define the HF phenotype in relation to the ejection fraction:
    (a) heart failure with reduced ejection fraction (HFrEF; EF $\leq$ 40%);
    (b) heart failure with mildly reduced ejection fraction (HFmrEF; EF between 41% and 49%);
    (c) heart failure with preserved ejection fraction (HFpEF; FE $\geq$ 50%).

Determination of the levels of natriuretic peptides (BNP and NT-proBNP), in addition to the analysis of conventional risk factors, increases the predictive value of the latter for the occurrence of cardiovascular events. The exemption identification code 013 granted for diabetes mellitus does not entitle the patient exemption from cardiac echocolordopplergraphy and BNP and NT-proBNP assay. This limits the ability to screen diabetic patients at risk of decompensation in outpatient diabetic clinics, thus delaying their diagnosis, especially given that the echocardiographic evaluation and BNP assay of diabetic patients with suspected HF must be repeated over time.

4. Pharmacological therapy of heart failure

The combination of angiotensin-converting enzyme inhibitor (ACE-I) + beta-blocker + mineralocorticoid receptor antagonist (MRA) is recommended as a basic therapy in patients with HFrEF, unless the drugs are contraindicated or not tolerated. New drugs, which have been introduced more recently in clinical practice, including sacubitril/valsartan, an angiotensin receptor neprilysin inhibitor (ARNI), and sodium-glucose cotransporter-2 (SGLT2) inhibitors are currently considered among the drugs of choice in the treatment of HFrEF. The glyphlozines dapagliflozin and empagliflozin, in particular, added to ACE-I/ARNI-beta-blocker-MRA therapy, have been shown to reduce the risk of cardiovascular death and worsening of HF in patients with HFrEF, regardless of the presence of diabetes, a class I indication, on a level of evidence A, for reducing HF relapse hospitalizations and deaths (**Table 1**) [6]. No treatment to date has been convincingly associated with a reduction in mortality and morbidity of patients with HFpEF. In August 2021, the EMPEROR-Preserved trial showed a reduction in risk of cardiovascular death and hospitalizations for HF in patients with HFpEF treated with empagliflozin, regardless of the presence or absence of diabetes [7]. The results of this study will definitely be adequately incorporated into future

guidance on the therapy used for HFpEF.

Table 1. Treatment recommendations for heart failure patients with reduced ejection fraction (New York Heart Association Class II–IV).

Recommendations	Class	Level
ACE-Is are recommended in patients with HFrEF to reduce the risk of hospitalization for heart failure and death	I	A
Beta-blockers are recommended in patients with stable HFrEF to reduce the risk of hospitalization for heart failure and death	I	A
MRAs are recommended in patients with HFrEF to reduce the risk of hospitalization for heart failure and death	I	A
Dapagliflozin and empagliflozin are recommended in patients with HFrEF to reduce the risk of hospitalization for heart failure and death	I	A
Instead of ACE-Is, sacubitril/valsartan is recommended in patients with HFrEF to reduce the risk of hospitalization for heart failure and death	I	B

Abbreviations: ACE-Is, angiotensin-converting enzyme inhibitors; HFrEF, heart failure with reduced ejection fraction; MRAs, mineralocorticoid receptor antagonists.

5. Pharmacological therapy of diabetes in heart failure

The 2021 guidelines on the treatment of type 2 diabetes mellitus, issued by the Istituto Superiore Sanità (ISS) and developed by the panel proposed by the Italian Society of Diabetology (SID) and Association of Diabetologists (AMD), recommend the use of SGLT2 inhibitor as the drug of first choice for the long-term treatment of patients with type 2 diabetes mellitus in heart failure. Glucagon-like peptide-1 receptor agonist (GLP-1 RA) and metformin should be considered as second-choice drugs, followed by dipeptidyl peptidase 4 (DPP-4) inhibitor, acarbose, and insulin as third-choice drugs (**Figure 1**) [8].

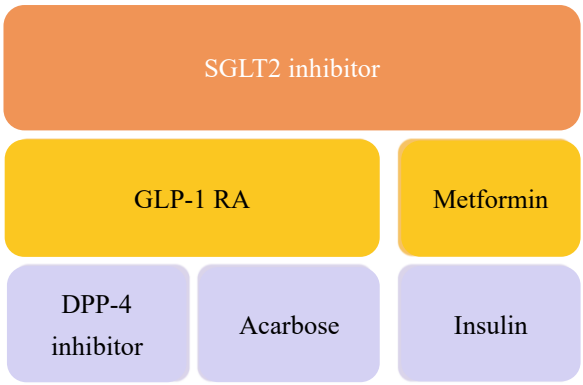

Figure 1. Long-term treatment of patients with type 2 diabetes mellitus in heart failure

6. Lifestyle

Patients with diabetes and heart failure must be encouraged to adopt a healthy lifestyle, eat a balanced diet, with moderate salt intake, control their body weight, avoid alcohol consumption, carry out regular physical activity, and stop smoking. It is also important to avoid the intake of large amounts of fluids, address sleep problems, and monitor changes in symptoms. The Mediterranean-style diet is the recommended diet. An exercise program, supervised by the physician and designed according to the patient's health status, can improve the patient's quality of life and reduce the frequency of hospitalizations for decompensated chronic HF.

7. Iron deficiency and anemia

Martial assessment should be an integral part of the management of patients with HF. Anemia (hemoglobin < 12 g/dL in women and < 13 g/dL in men) is a marker of severity of decompensation and a negative prognostic indicator. The recommendation for all patients with HF is to undergo periodic screening for anemia and iron deficiency (Class IC), with serial assessments of complete blood count, sideremia, serum ferritin, and transferrin saturation. Intravenous supplementation of iron with ferric carboxymaltose should be considered in symptomatic patients recently hospitalized for HF with ejection fraction < 50% and iron deficiency (Class IIA) [6].

8. Cardiologist-diabetologist collaboration

8.1. Identifying diabetic patients at higher risk of decompensation in outpatient diabetic clinics

Identifying diabetic patients at higher risk of HF represents an effective screening strategy for early diagnosis and institution of appropriate therapeutic measures; in addition, some hypoglycemic drugs could be useful in preventing the onset of HF and thus used in patients at higher risk. The task of a diabetologist is to recognize the signs and symptoms of HF in patients who have not been diagnosed with heart failure and, at the same time, to estimate the risk of developing heart failure in asymptomatic patients and subsequently design a personalized prevention program for follow-up.

In addition to the typical symptoms of heart failure such as dyspnea, fatigue, and ankle swelling, other manifestations may lead to the suspicion of the diagnosis, at which point appropriate laboratory and instrumental investigations shall be performed. The symptoms include asthenia, chest pain, palpitations, orthopnea, cough, swollen or painful abdomen, loss of appetite, confusion, and memory deterioration, while the signs include pretibial edema, distended jugular vein, hepatojugular reflux, tachycardia, third heart sound, tachypnea, bendopnea, basal crepitations, hepatomegaly, reduced urine output, and changes in body weight. According to the ARCA-AMD improvement group, the presence of these signs and/or symptoms in patients with diabetes mellitus indicates the prescription of echocardiography, BNP or NT-pro-BNP assay levels, and, depending on the results, a cardiology examination. In the absence of these signs and/or symptoms, observance of echocardiographic follow-up would identify patients who are already suffering from heart failure but not yet diagnosed, with positive implications for the natural history of the disease. The timing of the echocardiographic follow-up, as suggested by the ARCA-AMD improvement group, is as follows:

(i) patients with T2DM at very high cardiovascular risk (known cardiovascular disease or signs of organ damage or at least three risk factors) require echocardiography once a year;
(ii) patients with T2DM at high cardiovascular risk (onset of diabetes for more than 10 years, with no organ damage, and only one additional risk) require echocardiography once every 2 years;
(iii) patients with T2DM at moderate cardiovascular risk (younger than 50 years of age and with onset of diabetes less than 10 years, in the absence of other risk factors) require echocardiography once every 3 years.

The suggested echocardiographic follow-up can be modulated and customized according to the specific clinical features of the patient. The ARCA-AMD improvement group recommends its integration with the WATCH-DM, a risk score developed by a group of researchers at Brigham and Women's Hospital and UT Southwestern Medical Center to identify patients at high risk of developing HF over the next five years. The 10 predictors of heart failure in the WATCH-DM score are age, body mass index (BMI), systolic and diastolic blood pressure (SBP and DBP), serum creatinine (Cr), high-density lipoprotein cholesterol (HDL-c), fasting plasma glucose (FPG), QRS duration, prior myocardium infarction (MI), and prior coronary artery bypass graft (CABG) surgery (**Figure 2**) [9]. In outpatient diabetic clinics, the reassessment of these parameters and WATCH-DM score at each outpatient diabetes visit may allow the recognition of patients

at higher risk of HF to be referred for more stringent follow-up.

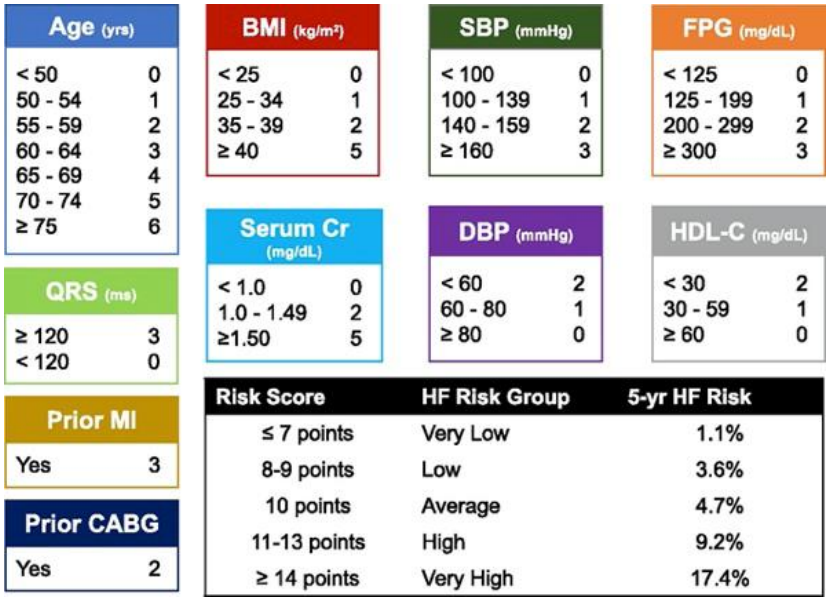

Figure 2. WATCH-DM risk score [9]

8.2. Detection of occult diabetic patients in cardiology outpatient clinics

In cardiology outpatient clinics, the detection of "occult" diabetic patients benefits from the careful application of the American Diabetes Association (ADA) 2021 guidelines, which suggest screening for diabetes or prediabetes in all individuals who have cardiovascular disease and a BMI greater than 25 kg/m^2 [10]. Specifically, the measurement of blood glucose and glycated hemoglobin (high-performance liquid chromatographic method) as a screening examination 1–2 times a year could aid the timely diagnosis of diabetes and initiation of appropriate hypoglycemic treatment, according to the flow chart in **Figure 3**.

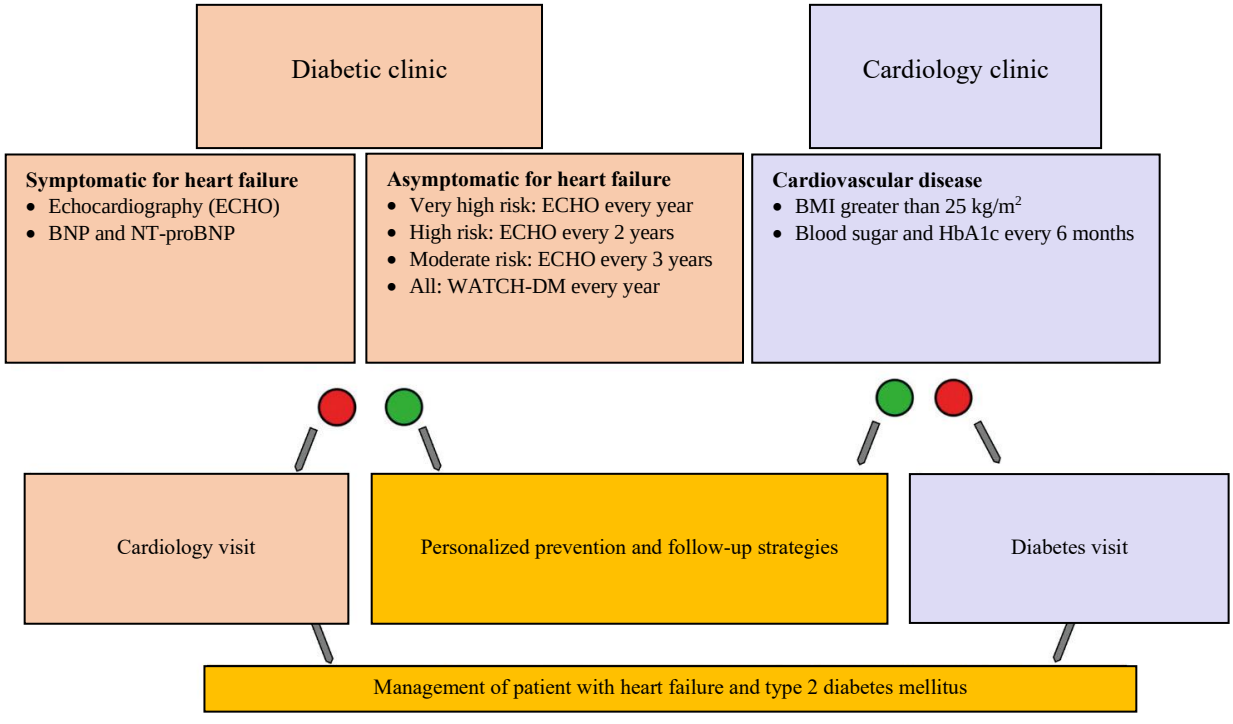

Figure 3. Diagnostic flow chart of patients diagnosed with diabetes mellitus or heart failure

8.3. In a patient with a diagnosis of heart failure and known type 2 diabetes mellitus

Based on a network meta-analysis of 53 randomized trials [11] and an individual-patient-data meta-analysis of an additional 20 studies [12], which demonstrated that the use of multidisciplinary HF management programs results in a marked reduction in HF hospitalizations and related mortality, the European Society of Cardiology (ESC) 2021 guidelines [6] have attributed a Class IA recommendation to the implementation of these strategies, emphasizing how multidisciplinary programs should include both proper diagnosis and programming intrahospital therapeutics as well as appropriate follow-up of patients at home.

Models of long-term management of patients with HF and diabetes in Campania should include cardiologist-diabetologist care pathways that are well defined (**Table 2**), based on the sharing of the following:

(i) clinical information (the use of integrated computerized medical records is preferred);
(ii) laboratory tests;
(iii) targets to be achieved;
(iv) treatment strategies.

With regard to drug treatment, the improvement group encourages the adoption of treatment strategies that adhere to the guidelines, favoring drugs that have a positive impact on the prognosis of patients with HF and discontinuing drugs that are not recommended (thiazolidinediones, saxagliptin, and metformin in NYHA class III or IV).

Table 2. Management of patients diagnosed with type 2 diabetes mellitus and heart failure

	Common examination panel (cardiometabolic)	Shared targets	Therapeutic synergy
Data sharing	CBC, serum electrolytes, blood glucose, HbAlc, total cholesterol, LDL-c, HDL-c, triglycerides, uric acid, microalbuminuria, AST, ALT, GGT, creatinine, serum protein electrophoresis and total protein, sideremia, ferritin, transferrin, urine examination	• HbAlc 6.6%–7.5% in patients treated with hypoglycemic drugs • HbAlc < 7% in patients treated with non-hypoglycemic drugs • LDL-c < 70 mg/dL (high cardiovascular risk); < 55mg/dL (very high cardiovascular risk)	• Guideline-oriented treatment • Correction of anemia and iron • Lifestyle modifications: healthy diet, physical activity, control of body weight and muscle mass, abstention from smoking

Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase; CBC, complete blood count; GGT, gamma-glutamyl transferase; HbAlc, glycosylated hemoglobin; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol.

8.4. SCODIAC experience

The ARCA-AMD collaboration has already proven the favorable effects of shared management of patients with heart failure and diabetes mellitus in the 2019–2020 biennium. In the SCODIAC I and II trials, data of 406 patients with heart failure and type 2 diabetes mellitus were retrospectively collected and analyzed; these data included clinical and laboratory parameters, duration of disease, comorbidities and complications, pathogenesis of decompensation, and therapies commonly used by ambulatory cardiologists in "real life." The patients were divided into two groups: Group A (HFpEF), consisting of 136 patients (EF > 45%) and Group B (HFrEF), consisting of 270 patients (EF ≤ 45%). All patients had periodic clinical and echocardiographic evaluations. Antidiabetic therapies were found to be modified after 1 year with increased use of GLP-1 RA, glyptins, and SGLT2 inhibitors in both groups, while cardiovascular therapies were found to be modified with greater use of sacubitril/valsartan and a reduction of ACE-I and angiotensin

receptor blocker (ARB) in HFrEF patients. In addition, analysis of diastolic and systolic functions on echocardiography showed effects of reverse cardiac remodeling in both HFpEF and HFrEF patients treated with glyflozines compared with the whole sample at the beginning and those treated with other hypoglycemic drugs. Left atrial volume index (LAVI) was reduced only in HFpEF patients at the end of the study, and ejection fraction was increased only in HFrEF patients. The SCODIAC experience testified, in the real world, that collaboration between cardiologists and territorial diabetologists, can improve the care given to patients with HF and diabetes, leading to improved cardiac performance in patients with HFrEF and diabetes and a significant increase in the number of patients treated according to guidelines at the end of the study [13,14].

9. Counseling on the prevention and treatment of heart failure in patients with diabetes

HF is a chronic disease that requires ongoing treatment with both pharmacological interventions and lifestyle changes. As in all chronic diseases, it requires ongoing work of empowerment, taking into account the ability of the patient to accept his/her disease, modify his/her lifestyle and learn to self-manage. More complex still is the case of patients with heart failure and diabetes, who must follow a considerable number of indications to maintain the compensation of the two diseases. In these cases, specific approaches and communication with the patient by the multidisciplinary team as a whole (biopsychosocial management) may be necessary. In this framework, the hypothesis of providing healthcare personnel with counseling tools represents a process of growth in the ability to care, improving the doctor-patient relationship and patient compliance to prescriptions.

10. Hospital-territory integrated approach

The integrated territorial and hospital approach, tailored to the needs of individual patient, is integral to the effective management of patients with heart failure and diabetes. Patients with stable disease may be followed-up on an outpatient basis involving general practitioners, nurses, and specialists, while more intensive care such as hospital and/or home-based integrated care is required in advanced and/or unstable stages of the disease. The hospital-territory partnership must also ensure ease of access to intensive care in cases of clinical instability.

Hospital discharge is also a crucial moment; coordination with the territory can ensure adequate continuation of care upon leaving the ward with effective management by the referring outpatient services. An inadequate hospital-territory transition plan may be reflected in the following:

(i) increase in early re-hospitalizations (rate of rehospitalization within 30 days of discharge is 14.4%–21% in diabetics versus 8.5%–13.5% in the general population);
(ii) increase in rehospitalization-associated costs (39% of the overall health care cost is related to the frequency of re-hospitalizations and thus avoidable).

Therefore, hospital discharges must take place according to a personalized program of indication of home therapy and territorial referral principals through a discharge kit that includes a detailed discharge letter with indications for the general practitioner and the territorial specialist, provision of glucometer, a plan for therapy and prescriptions, education on the use of injection drugs and dietary pattern, cardiology and diabetes follow-up scheduling, and contact with the general practitioner.

11. Future perspectives

The COVID-19 outbreak and the emergency situation that ensued have promoted a series of initiatives aimed at ensuring effective treatment process by reducing the number of outpatient and hospital admissions. In the field of diabetes, numerous centers have begun offering telemedicine visit services, and the scientific societies are working to further define the guidelines in a precise manner to integrate telemedicine into the

national health service. As for HF, a software to control devices remotely and determine the disease stage is available to date. In the near future, similar procedures will also need to be shared in patients with heart failure in class I and II of the New York Heart Association (NYHA) functional classification who do not have electronic devices, lowering the related costs, in order to optimize and rationalize the resources available for in-person visits as well as to cope with possible health emergencies. Telemedicine can be a means by which to "connect" specialists from different centers and districts, facilitating direct comparison and integrated management in patient care.

Disclosure statement

The authors declare no conflict of interest.

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