Al cuore del diabete: un possibile PDTA cardiologo-diabetologo

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Conflict of Interest Statement

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Current Grants	Award University of Rome Sapienza, Member of CNGR at Ministry of University and Research, Italy
Speakers' Bureau	Menarini International, Daiichi-Sankyo Europe, Berlin Chemie, Bayer
Royalties/Activities	None
Consultant/Advisory Board	Novo Nordisk, Daiichi-Sankyo Europe, Menarini Int, Novartis Pharma, Amgen, Bayer
Other Activities	Reviewer ESH/ESC Hypertension Guidelines and ESC CV Prevention Guidelines Past-President of the Italian Society of Hypertension (SIIA) President of the Italian Society of Cardiovascular Prevention (SIPREC)

The burden of CVD in people with T2D is one of the most pressing public health problems of the 21st century[1]

Nadine & David Abrahams, live in South Africa;
Nadine has T1D, David has T2D

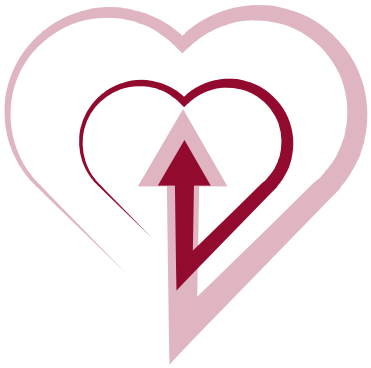
"By treating people **with type 2 diabetes** with **CV protective glucose** lowering medicines earlier, the economic burden may be reduced by **preventing cardiovascular complications**."

Dr Naresh Kanumilli, Regional Clinical Lead and Decision Maker, South Manchester Clinical Commissioning Group, UK

Abbreviations: CV, cardiovascular; CVD, cardiovascular disease; T1D, type 1 diabetes; T2D, type 2 diabetes; UK, United Kingdom.

- **References: 1.** Laakso M. Diabetes Care. 2010 Feb;33(2):442-9.

People with T2D are at increased risk of CV complications compared with those without diabetes[1]



- **53%** Increased risk of **unstable angina**
- **54%** Increased risk of **myocardial infarction**
- **56%** Increased risk of **heart failure**
- **72%** Increased risk of **stroke**

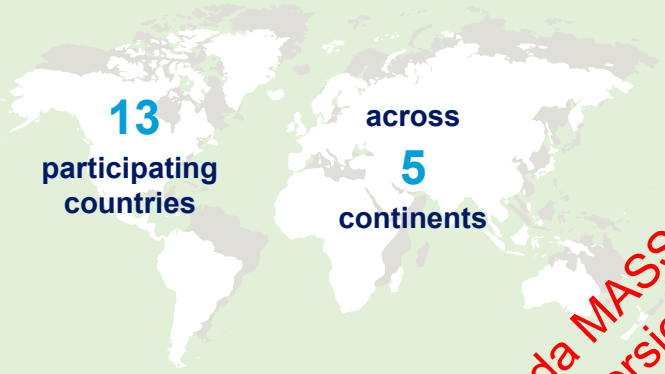
Abbreviations: CVD, cardiovascular disease; T2D, type 2 diabetes

- **Reference: 1.** Shah AD, et al. *Lancet*. 2015;3:105-13

CAPTURE: First global study prospectively captured the prevalence of CVD in people with type 2 diabetes

- A non-interventional study prospectively captured the prevalence of CVD, CV risk and its management in people living with type 2 diabetes
- Results were presented at the European Association for the Study of Diabetes 56th Annual Meeting in 2020

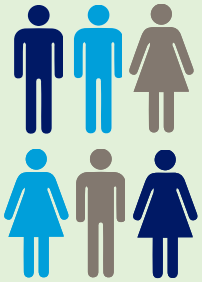
CAPTURE in numbers

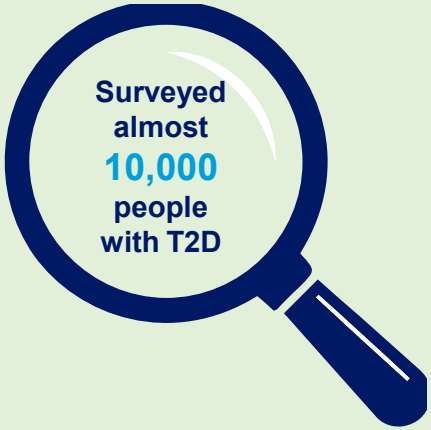


Across primary and secondary care

Spanning all ages from

18 +





CV, cardiovascular; CVD, cardiovascular disease; T2D, type 2 diabetes

1. Clinicaltrials.gov. Available at: https://clinicaltrials.gov/ct2/show/NCT03786406. Last accessed: October 2020. 2. (CAPTURE-IO). Available at: https://clinicaltrials.gov/ct2/show/NCT03811288. Last accessed: October 2020.

[5]*Mosenzon et al. Cardiovasc Diabetol 2021;20:154.*

Weighted CVD prevalence in people with T2D across the 13 countries

Region	Country (number of participants; estimated diabetes population size)	n	Prevalence estimate [95% CI], %
Australasia	**Australia** (824; 1,133,000)	332	40.1 [36.8; 43.4]
East Asia	**China** (805; 114,394,800)	273	33.9 [30.6; 37.3]
	Japan (800; 7,234,200)	298	37.3 [34.2; 40.3]
Europe	**Czech Republic** (400; 767,800)	91	22.8 [18.8; 26.7]
	France (659; 3,276,400)	220	34.2 [30.7; 37.8]
	Hungary (400; 706,800)	140	35.0 [30.3; 39.9]
	Italy (816; 3,402,300)	317	38.8 [35.5; 42.3]
Latin America	**Argentina** (834; 1,757,500)	347	41.5 [38.4; 44.7]
	Brazil (912; 12,465,800)	400	43.9 [40.9; 46.8]
	Mexico (820; 12,030,100)	302	36.9 [34.1; 39.6]
Middle East	**Israel** (869; 415,800)	454	56.5 [52.8; 60.2]
	KSA (883; 3,852,000)	158	18.0 [15.5; 20.5]
	Turkey (801; 6,694,400)	250	31.2 [28.0; 34.4]
Overall	**Overall** (9,823; 168,130,900)	3,582	34.8 [32.7; 36.8]

Adapted from Figure 1
CI, confidence interval; CVD, cardiovascular disease; KSA, Kingdom of Saudi Arabia; n, number of participants with CVD; T2D, type 2 diabetes

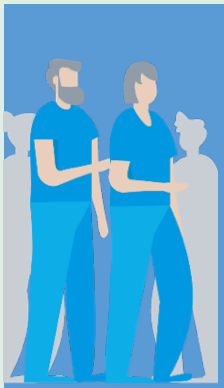
Mosenzon et al. Cardiovasc Diabetol 2021;20:154.

CAPTURE: Established CVD in T2D usually associated with ASCVD–yet few patients receive diabetes medication to reduce CV risk factors

STUDY FINDINGS[1,2]

1/3 OF ALL **PEOPLE** WITH T2D HAVE ESTABLISHED CVD

9/10 PEOPLE WITH T2D AND ESTABLISHED CVD HAVE ASCVD



2/10 PEOPLE WITH T2D ARE GETTING A GLUCOSE-LOWERING TREATMENT WITH A PROVEN CV BENEFIT

Professional cardiology and diabetes organisations/associations have recommended **GLP-1 RAs** as a preferred therapy for people **with T2D and ASCVD**

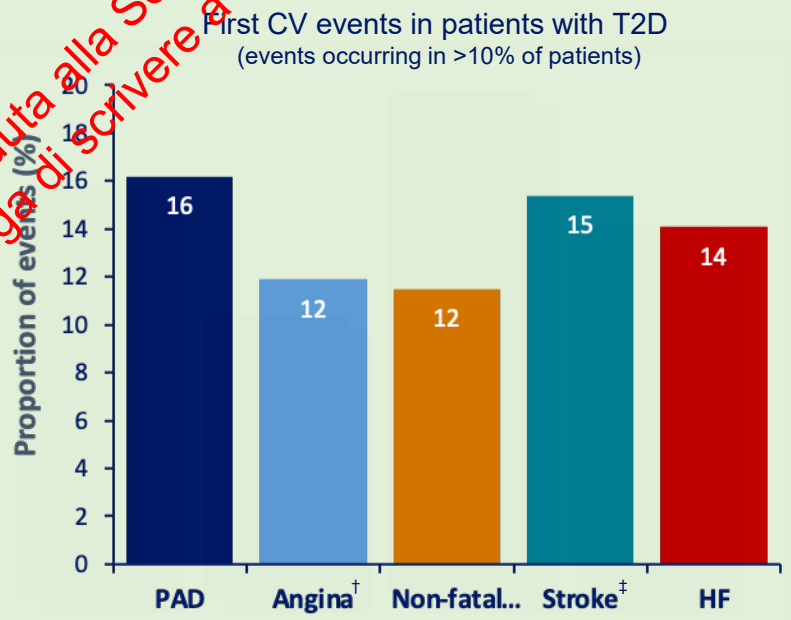
1. Mosenzon O, et al. CAPTURE. Abstract 158. Presented at the 56th Annual Meeting of the European Association of the Study of Diabetes, Macrovascular complications and beyond, 10:15 CET on 24 September 2020. PMID: 32840677 PMCID: PMC7445463 DOI: 10.1007/s00125-020-05221-52. Vencio S, et al. Abstract 945. Presented at the 56th Annual Meeting of the European Association of the Study of Diabetes, Cardiovascular complications in humans through and through, 13:15 CET on 24 September 2020. PMID: 32840677 PMCID: PMC7445463 DOI: 10.1007/s00125-020-05221-5.

[7] Mosenzon et al. Cardiovasc Diabetol 2021;20:154.

Nearly 1 in 5 people with T2D experience their first CV event within 5-6 years of diagnosis

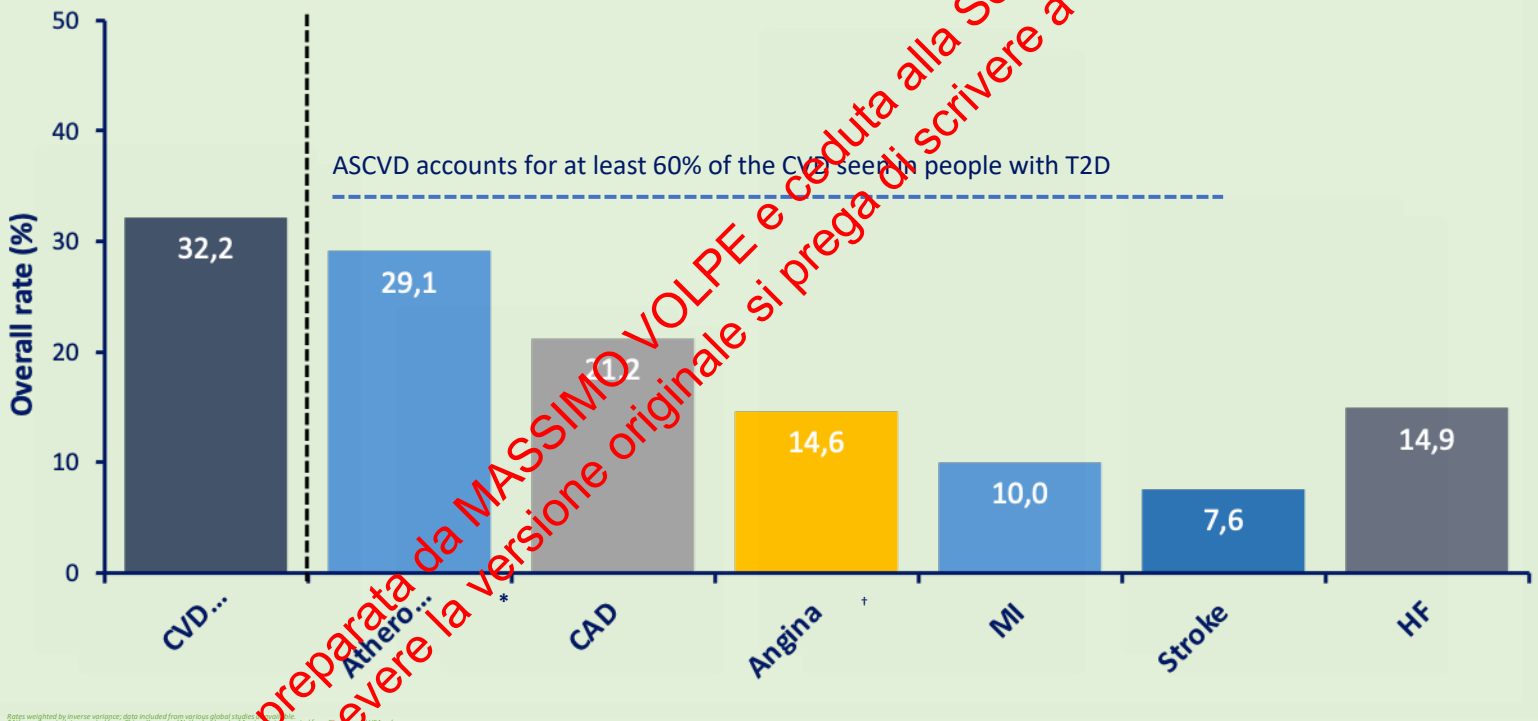
Cohort study of 34,198 patients with T2D in UK*

- Over a follow-up period of 5.5 years, **18%** of patients with T2D experienced their first CV event[1]
- T2D was associated with increased risk of PAD, stroke, angina, heart failure and non-fatal MI[1]



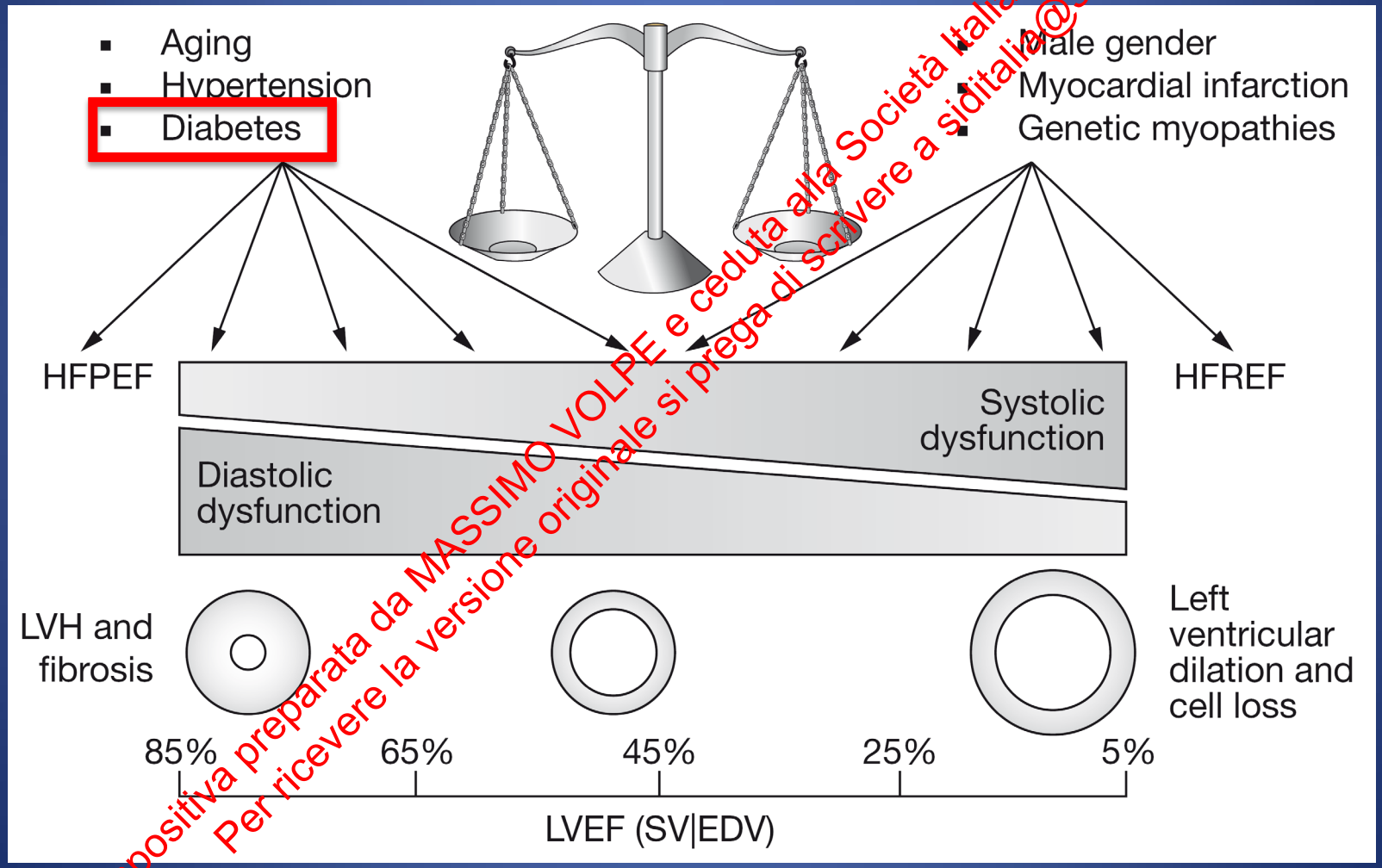
*CALIBER programme: Full cohort including non-diabetic population ~1.9 million patients; †Includes stable and unstable angina; ‡Includes ischaemic stroke and stroke not further specified
CV, cardiovascular; HF, heart failure; MI, myocardial infarction; PAD, peripheral artery disease; T2D, type 2 diabetes
Shah AD et al. Lancet Diabetes Endocrinol 2015;3:105–113.

Atherosclerotic heart diseases are the most prevalent CVD morbidities in people with T2D[1]



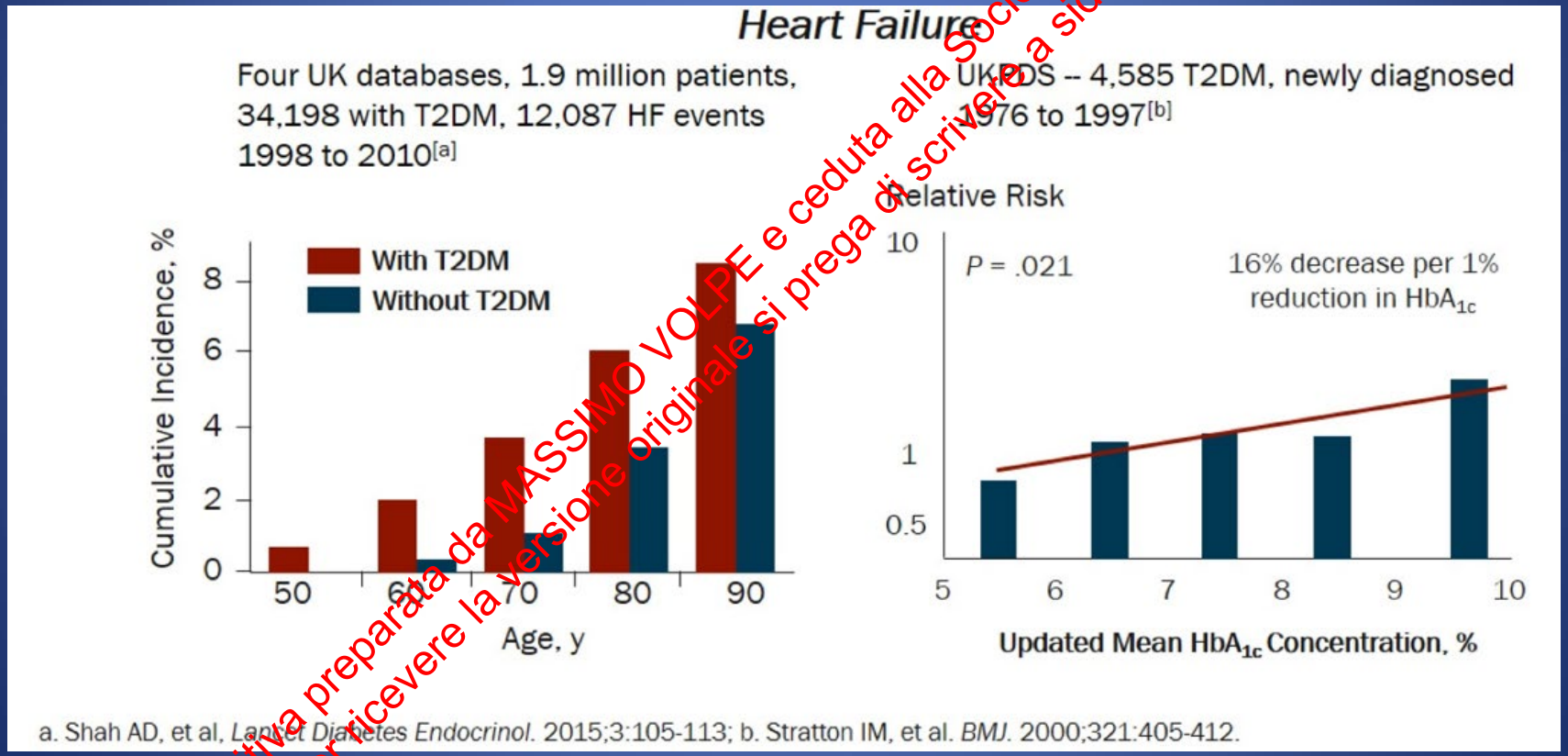
Rates weighted by inverse variance; data included from various global studies by age.
*Atherosclerosis data reported from China, Korea and Netherlands only; †Angina data reported from Korea and USA only.
ASCVD, atherosclerotic cardiovascular disease; CAD, coronary artery disease; CVD, cardiovascular disease (includes all complications); HF, heart failure; MI, myocardial infarction
Einarson et al. Cardiovasc Diabetol 2018;17:83.

The spectrum of Heart Failure from HF-PEF to HF-REF



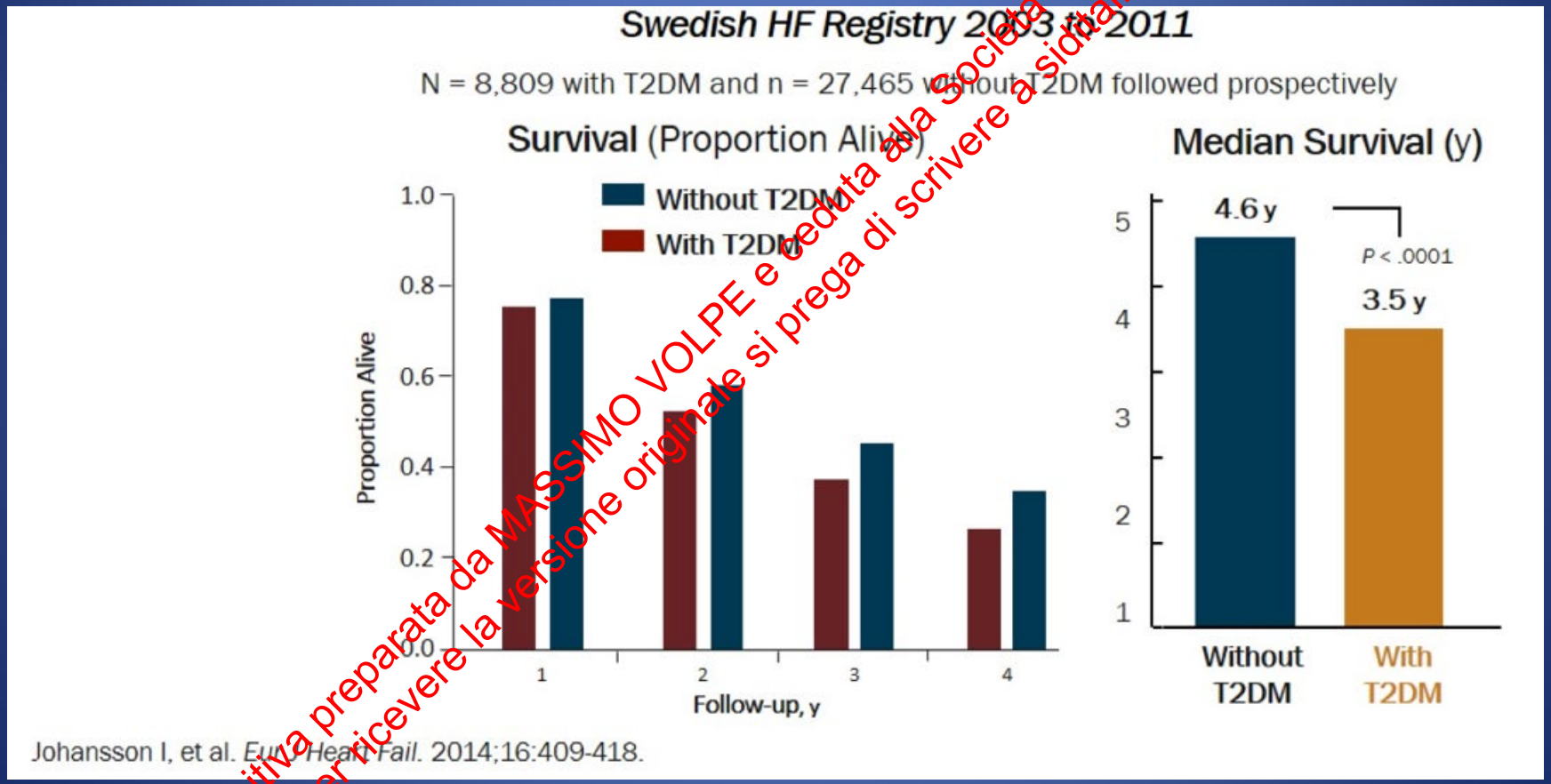
Ouzounian et al. Nat Clin Pract Cardiovasc Med 2008;5:375-86

Increased risk of HF in diabetes



a. Shah AD, et al. *Lancet Diabetes Endocrinol.* 2015;3:105-113; b. Stratton IM, et al. *BMJ.* 2000;321:405-412.

Worse prognosis for HF in diabetes



Johansson I, et al. *Eur J Heart Fail.* 2014;16:409-418.

Multifactorial treatment approach aims to reduce risk factors for ASCVD: GLP-1RAs help achieve this goal

EASD and ADA recommend that most adults with diabetes achieve the following targets:

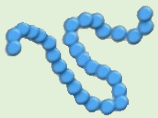
- HbA_{1c}: <7.0% (<53 mmol/mol)
- Physical activity: ≥150 mins per week*
- Blood pressure: <140/90 mmHg
- Triglycerides: <150 mg/dL (1.7 mmol/L)
- HDL-C:
  - Women ≥50 mg/dL (1.3 mmol/L)
  - Men ≥40 mg/dL (1.0 mmol/L)

Management of diabetes and its complications

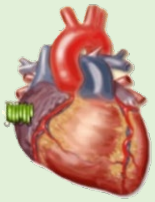
*Physical activity of moderate to vigorous intensity

ACE-I, angiotensin-converting enzyme inhibitors; ADA, American Diabetes Association; ARB, angiotensin receptor blockers; BP, blood pressure; HDL-C, high-density lipoprotein cholesterol. American Diabetes Association. Diabetes Care 2019;42(Supp1).

Preclinical effects: GLP-1 RAs reduce ASCVD risk factors

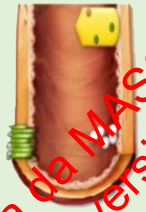


GLP-1R



- ↓ Inflammation
- ↑ Glucose uptake
- ↑ LV Function
- ↑ Heart rate
- ↓ Ischemic injury

GLP-1R



- ↓ Inflammation
- ↑ Endothelial Function
- ↑ Vasodilation
- ↑ Plaque Stability
- ↑ Blood Flow
- ↓ Platelet Aggregation
- ↓ Smooth muscle proliferation

CV, cardiovascular; GLP-1, glucagon-like peptide-1; GLP-1R, glucagon-like peptide-1 receptor; LV, left ventricle.
Drucker DJ. Cell Metab 2016;24:15–30.

GLP-1 receptor agonists have multifactorial effects beyond glycaemic control

Heart
- ↑ Contractility
- ↑ Cardiac function
- ↑ Myocyte survival
- ↑ Cardioprotection
- ↑ Glucose utilization
- ↑ Vasodilatation
- ↑ Glucose reuptake
- ↑ Left ventricle function
- ↑↓→ Blood pressure
- ↑↓→ Heart rate
- ↑ ANP production

Pancreas
- ↑ Insulin secretion
- ↑ Insulin biosynthesis
- ↓ Glucagon secretion
- ↑ Beta cell proliferation
- ↑ Beta cell survival
- ↓ Apoptosis

Bone
- ↑ Osteogenesis
- ↑ Bone mass

GI tract
- ↓ Gastric emptying
- ↓ GI motility

Kidney
- ↑ Diuresis
- ↑ Natriuresis
- ↓ Albuminuria
- ↓ Renal inflammation

Brain
- ↓ Food intake
- ↓ Water intake
- ↑ Memory and learning ability
- ↑ Neuroprotection
- ↓ Inflammation
- ↓ Rewarding behaviour
- ↓ Palatability
- ↓ Apoptosis

Liver
- ↓ Endogenous glucose production
- ↓ Steatosis

Muscle
- ↑ Insulin sensitivity
- ↑ Glucose reuptake

GLP-1RA, glucagon-like peptide-1 receptor agonist; ANP, atrial natriuretic peptid.

1. Müller TD, et al. *Mol Metab*. 2019;30:72-130; 2. Simiholidis V, et al. *Eur J Pharmacol*. 2018;818:103-109.

ESC European Society of Cardiology

Cardiovascular Research (2021) **117**, 1992–1994
doi:10.1093/cvr/cvaa334

EDITORIAL

Cardiometabolic phenotype of heart failure with preserved ejection fraction as a target of sodium-glucose co-transporter 2 inhibitors and glucagon-like peptide receptor agonists

Massimo Volpe [1,2*] **and Giovanna Gallo** [1]

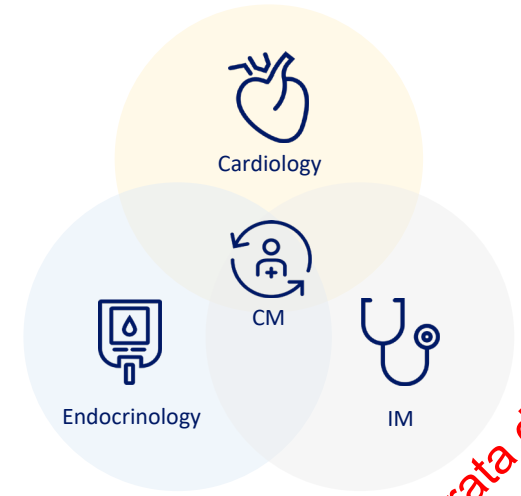
Table 1 Cardiometabolic HFpEF phenotype and potential mechanisms of action of new antidiabetic drugs

Cardiometabolic HFpEF predisposing conditions	Clinical presentations	Structural changes	Pathophysiological mechanisms	Potential mechanisms of action of SGLT2i	Potential mechanisms of action of GLP1-RA
• Obesity • Overweight • Metabolic syndrome • Diabetes mellitus • Arterial hypertension • Renal dysfunction • Advanced age • Female sex	• Increased volume overload • Lung congestion • Atrial fibrillation • Pulmonary hypertension • Chronotropic incompetence • Poor skeletal muscle function • Impaired peripheral oxygen delivery/oxygen utilization • Reduced quality of life • Reduced functional status • Reduced exercise capacity	• Concentric LVH • Left atrial hypertrophy • Preserved ejection fraction • Diastolic dysfunction • Reduced GLS • Increased end-diastolic stiffness • Increased LV filling pressure • Elevated natriuretic peptides	• Decreased NO bioavailability • Mitochondrial dysfunction • Vasoconstriction • Inflammation • Pro-thrombotic state • Endothelial dysfunction • Collagen deposition • Increased myocyte diameter • Insulin resistance	• Natriuresis • Osmotic diuresis • Interaction with RAS • Reduction of intraglomerular pressure • Improvement of renal haemodynamics • Increased myocardial energetics • Reduction in LV mass • Improved systolic and diastolic function • Increased proangiogenic progenitor cells • Increased erythropoietin • Improved endothelial function • Reduction in myocardial CaMK II activity • Improved myocardial autophagy • Inhibition of cardiac fibrosis • Increased O_2 consumption	• Improved systolic and diastolic function • Improved cardiac filling • Increased circulating proangiogenic progenitor cells • Increased myocardial energetics • Reduced arterial stiffness • Reduced inflammation • Reduced monocyte adhesion Improved endothelial function • Decreased insulin resistance • Increased lipolysis • Myocardial protection from ischaemia • Improved myocardial contractility • Increased coronary flow • Increased skeletal perfusion • Anti-atherosclerotic effect

CaMKII, Ca2+/calmodulin-dependent protein kinase II; GLP1-RA, glucagon-like peptide receptor agonists; GLS, global longitudinal strain; HFpEF, heart failure with reduced ejection fraction; LV, left ventricle; NO, nitric oxide; SGLT2i, sodium-glucose co-transporter 2 inhibitors.

Volpe M, Gallo G Cardiovasc Res 2021

Clinical focus is moving beyond T2D & CVD towards cardiometabolic care



Cardiometabolic Medicine

Cardiology	Endocrinology	IM
Myocardial infarction Stroke Heart Failure	Diabetes Obesity Thyroid	Hypertension Dyslipidaemia Screening

Cardiometabolic Medicine

Obesity – Diabetes – Hypertension – Dyslipidemia - CVD

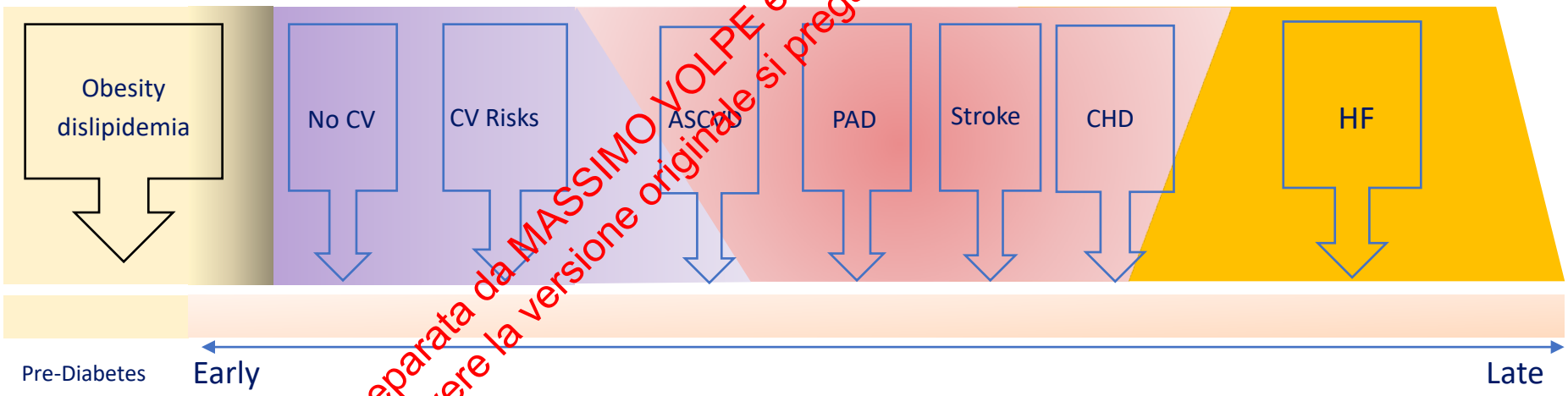
T2D = Type 2 Diabetes. CVD = Cardiovascular Disease. CM = Cardiometabolic Medicine. IM = Internal Medicine. ASCVD = Atherosclerotic Cardiovascular Disease.

Source: Cardiometabolic Medicine: A Call for a New Subspeciality Training Track in Internal Medicine, American Journal of Medicine, 2019

New Paradigm of Management of the **Cardiometabolic Continuum**

Italian Guidelines for **Diabetes** Management 2021

	T2DM patients **without** previous CV event	T2DM patients **with** previous CV event	T2DM patients with previous **CV event and HF**
1° line	Metformin	Met / GLP1RA / SGLT2i	SGLT2i
2° line	GLP1RA / SGLT2i	DPP4i / Aca / Pio / Ins	GLP1RA / Metformin*
3° line	DPP4i / Aca / Pio / Ins		DPP4i** / Aca / Ins



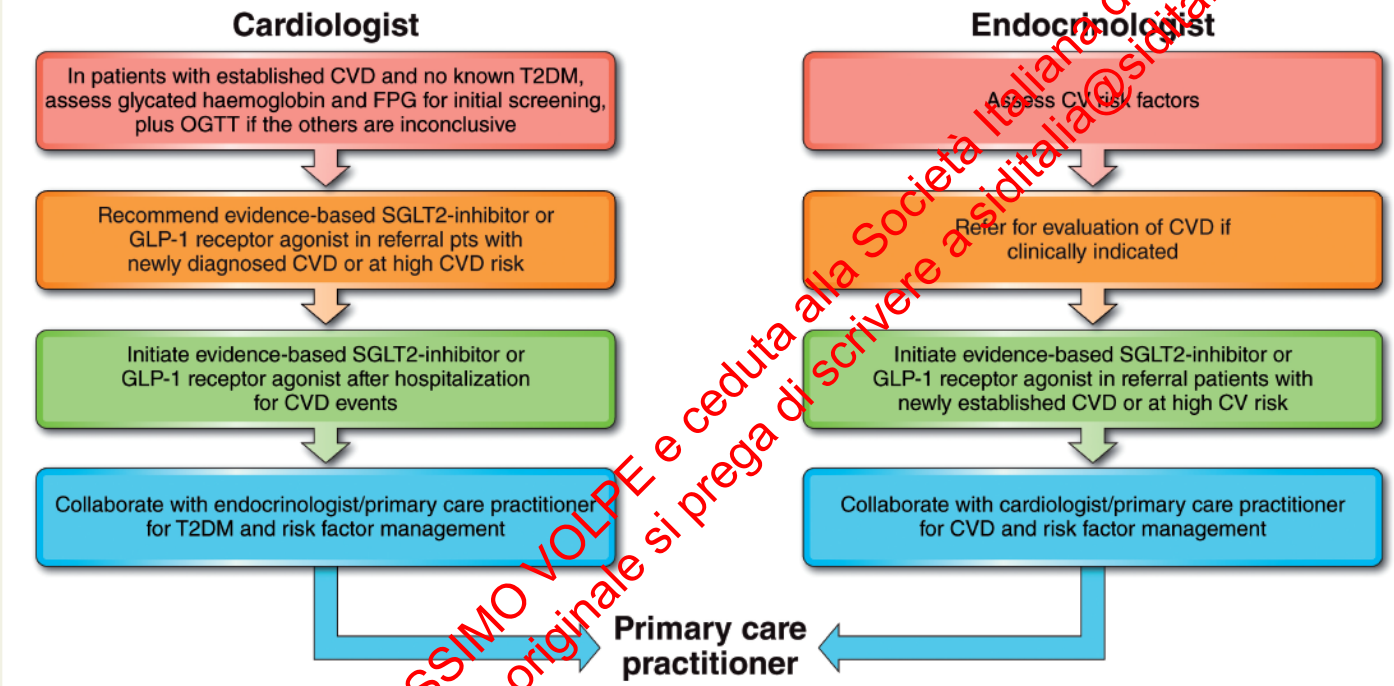


Figure 2 Individual responsibilities and opportunities for collaboration between cardiologists, endocrinologists, and primary care practitioners cardiologists and endocrinologists both have individual roles in assessing and treating cardiovascular risk in patients with Type 2 diabetes. Treatments to reduce cardiovascular risk can be initiated by either specialist, but two-way communication is essential to optimal monitoring and continuation of therapy. Primary care practitioners are involved across all stages, playing a central role and interfacing with both cardiologists and endocrinologists. ACS, acute coronary syndrome; CV, cardiovascular; CVD, cardiovascular disease; d/c, discharge; GLP-1, glucagon-like peptide 1; SGLT-2, sodium-glucose cotransporter-2; T2DM, type-2 diabetes mellitus.

Cosentino F. et al., European Heart Journal (2019) 40, 2907-2919

Progetto UNITE – Azienda Ospedaliero-Universitaria Sant'Andrea

Patient journey del paziente diabetico ricoverato in UU.OO. varie

Premessa

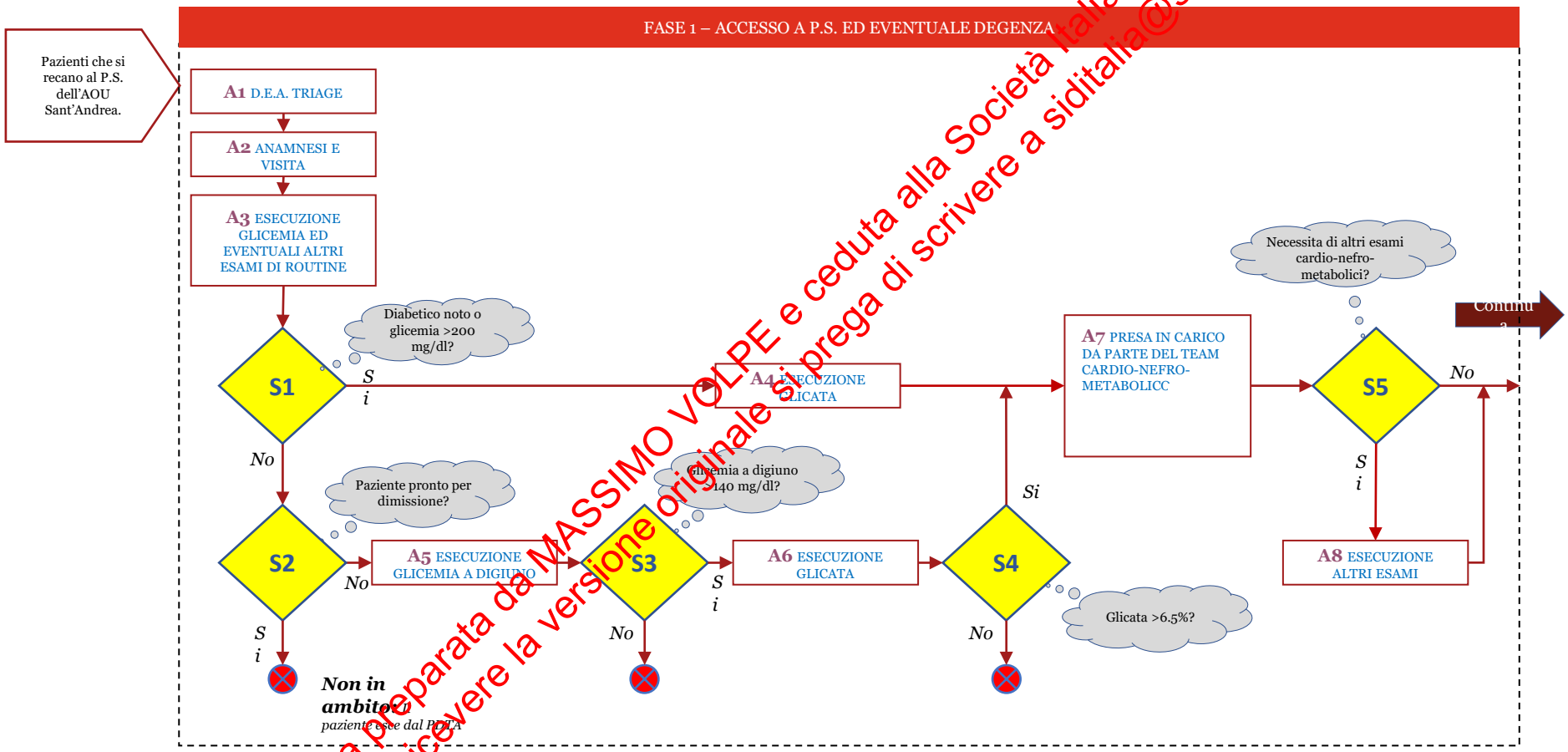
I pazienti interessati al *patient journey* descritto di seguito sono i pazienti diabetici ricoverati in unità operative appartenenti alle seguenti aree:

- ENDOCRINOLOGIA/DIABETOLOGIA;
- CARDIOLOGIA;
- MEDICINA INTERNA;
- NEFROLOGIA.

Oggetto della presente descrizione sarà quindi il percorso del paziente diabetico, dal momento in cui egli si presenta al Pronto Soccorso fino alla sua dimissione e al successivo *follow-up*.

Progetto UNITE – Azienda Ospedaliero-Universitaria Sant'Andrea

Patient journey del paziente diabetico ricoverato in UU.OO. varie



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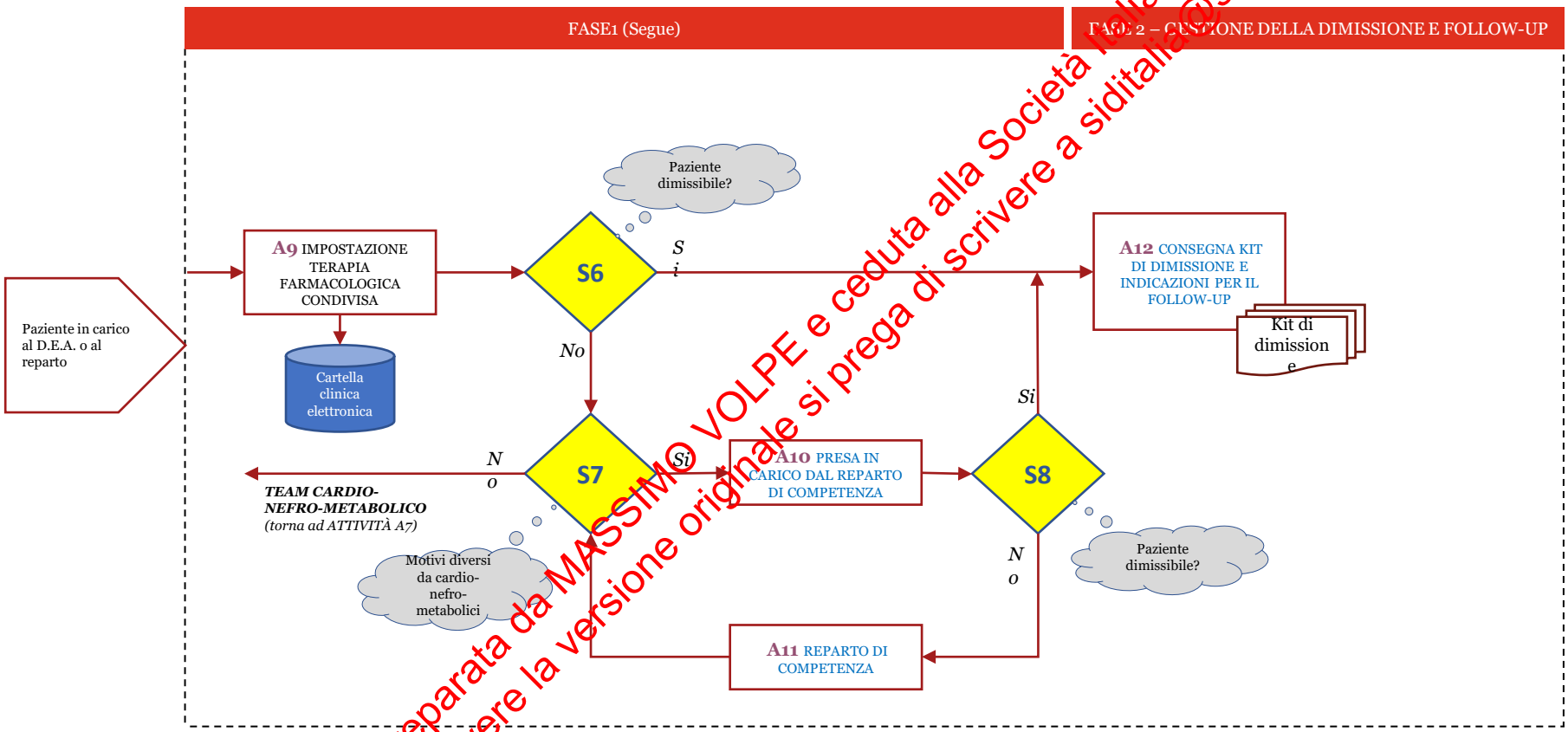
Patient journey del paziente diabetico ricoverato in UU.OO. varie



Increased focus and need for a multidisciplinary approach to patient care

As managing CV risk is increasingly prioritised in treatment guidance for type 2 diabetes, there is a **growing need for diabetologists and cardiologists to work together** to optimally treat patients, using a multi-disciplinary approach[1,2]

Specifically, there is a need for a **more integrated care and team-based approach[3]**

CV, cardiovascular;
1. Das SR et al. *J Am Coll Cardiol*. 2020 Sep, 76 (1) 1117-1145. **2.** Maranta F *et al. Int J Cardiol Heart Vasc.* 2018;21:80–86 **3.** Arnett DK *et al. Journal of the American College of Cardiology*. 2019.

La ricerca clinica di patologie cardiovascolari nel paziente diabetico di tipo 2 deve essere:

A. iniziata e proseguita dal diabetologo?
B. O è preferibile un'azione di team personalizzata alle caratteristiche del paziente?

I pazienti affetti da diabete mellito presentano un rischio di scompenso cardiaco

a) Sovrapponibile alla popolazione generale
b) Aumentato solo in relazione a HFpEF
c) Aumentato sia in relazione a HFrEF che a HFpEF

La terapia con i nuovi farmaci antidiabetici nei pazienti con alto rischio cardiovascolare o scompenso cardiaco deve essere:

A. iniziata e proseguita dal diabetologo?
B. O è preferibile un'azione di team personalizzata alle caratteristiche del paziente?