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REVIEW ARTICLE

The Cardio Diabetology Era. A Concise and Illustrated Review: Four Phenotypes and Three New Evidence-Based and Practical Therapeutic Algorithms

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ABSTRACT

Type 2 diabetes mellitus (T2DM) has undergone therapeutic approaches evolving from glucocentricity towards holism, in which it is currently considered a microvascular and macrovascular risk condition determined by multiple variables beyond glucose. These include visceral adiposity, metaflammation, insulin resistance with its hemodynamic (endothelial dysfunction and hypertension) and metabolic (mixed dyslipidemia) surrogates; together with other metabolic regulation system dysfunction such as the incretin system, sodium, and glucose cotransporters at the intestinal and renal level, and the intestinal microbiota, among the most studied.

Therefore, the current treatment of this risk condition called T2DM, includes the control of all its determining factors: adiposity through a healthy diet, aerobic physical activity, and/or drugs such as glucagon-like peptide-1 receptor agonists (GLP1-RA) or bariatric surgical procedures. Inflammation remains a therapeutic target under investigation, although it has not yet been transferred to clinical practice guidelines. Insulin resistance and its hemodynamic and metabolic subrogates are the therapeutic targets of multiple pharmacological interventions, essentially insulin sensitizers, inhibitors of the renin-angiotensin-aldosterone system, facilitators of the transformation and elimination of lipoproteins with apo-B100 as omega-3 ultra-purified fatty acids, fibrates, antisense oligonucleotides (ASO) against apoC3, ASO and monoclonal antibodies (mAbs) anti-ANGPTL3, statins, ezetimibe, mAbs and small interfering RNA (siRNA) anti-PCSK9, among others.

In the last 14 years, drugs such as the dipeptidyl peptidase 4 (DPP-4) inhibitors, GLP1-RA, and, more recently, the dual GIP-GLP-1 analogs, have been incorporated to correct the dysfunction of the incretin system, as well as many others that inhibit the intestinal and renal reabsorption of sodium and glucose as sodium–glucose co-transporter-2 and 1 (SGLT2/1) inhibitors. Surprisingly, new drugs have emerged between the GLP1-RA and the SGLT2/1 inhibitors that, beyond their essential therapeutic effect (glucose control), have shown brain, cardiac, and renal protection of variable magnitude. Finally, manipulating the intestinal microbiota is a strategy under extensive investigation and incipient clinical application.

From this summary, it is clear that the current therapeutic landscape in T2DM has expanded dramatically, from a “gluco-panorama” focused on glucose control with insulin, sulfonylureas, metformin, and glitazones, to a “holo-panorama” incorporating five new therapeutic classes and at least eighteen new "anti-diabetic" drugs, in addition to a similar number of medications for hypertension and dyslipidemia control.

Objective

The objective of this concise and practical review article regarding "The Cardio-Diabetology Era" is to introduce readers to updated and cutting-edge information that allows the physician to empower and treat T2DM patients in an integral, optimal, and updated way. Thus, changing the vision of this micro and macrovascular risk factor to continue eradicating the still omnipresent "dark era", and enter the "luminous and bright era" of T2DM, which today, more than ever, is 100% feasible.

Type 2 Diabetes Mellitus therapeutic evolution. Three eras

a) Dark Era

Still, in the year 2022, in the minds of many people and even many doctors, the idea persists that T2DM is a synonym for a short life full of microvascular and macrovascular complications causing blindness, kidney failure, amputation, stroke, heart attack, and premature death. This idea, unfortunately, is still true in certain countries such as Mexico, where, in some populations with T2DM, the risks of renal, cardiac, or cerebral death are up to 31.1, 4.6, and 4.6 times greater than those of similar populations without T2DM[1], respectively. This unacceptable reality results from a delayed diagnosis and, therefore, in the treatment, coupled with a therapeutic approach focused on glucose control, insufficient and far from the control of another non-glycemic brain, cardio, renal risk factors, such as adiposity, hypertension, and mixed dyslipidemia.

This dark vision could be eradicated by applying relatively simple strategies in the diagnostic and therapeutic approach to T2DM. Specifically, a timely diagnosis and treatment with a comprehensive, optimal, or goal-guided approach. These strategies transform T2DM into a life condition that allows the patient to significantly reduce cerebrovascular, cardiovascular, and renal morbidity and mortality, which are the first causes of disability, premature mortality, and health spending in this population.

b) Luminous Era

Unlike the T2DM dark era, in the minds of few people and doctors, there is the idea that T2DM can be a life condition like that of individuals without the disease. At the beginning of this century, several authors, especially Peter Gaede et al. (Steno-2 study[2-4]), demonstrated that early, comprehensive, and optimal diagnosis and treatment of T2DM significantly compress cardiovascular morbidity and mortality and death from any cause, with reduced risks of cardiovascular disease, cardiovascular death, and total death by 54%, 59%, and 46%, respectively.

Recently, following the Steno-2 study, Aidin Rawshani et al., based on the analysis of the Swedish Diabetes Registry[5-6], confirmed that an early, comprehensive, and optimal diagnostic-therapeutic approach that includes a healthy lifestyle, eradication of smoking, low-density lipoprotein cholesterol <100 mg/dL, blood pressure <140/<80 mmHg and hemoglobin A1c <7% confer a significant reduction in death, heart attack, and stroke, matching these risks with those of the population without T2DM. In this analysis[6], T2DM patients who met these metrics, compared with their peers without T2DM, had a hazard ratio (HR) for myocardial infarction of 0.84: 0.75-0.93, for cerebral infarction of 0.95: 0.84-1.07, and for total death of 1.06: 1.0-1.12. This means that this cohort of T2DM patients had a lower risk for myocardial infarction and the same for cerebral infarction and total death compared to their peers by sex and age without T2DM. Without a doubt, a finding that broke the paradigm of dark era. Furthermore, the only risk that does not change with optimal control of "classic" cardiovascular risk factors is the risk of heart failure, which implies that the etiopathogenesis of this condition includes atherosclerotic and non-atherosclerotic risk factors, which are currently under extensive investigation. Finally, this study confirms that the greater the number and magnitude of uncontrolled cardiovascular risk factors, the greater the risk of heart attack, stroke, and death.

c) Bright Era (Cardio Diabetology Era)

As a result of the 2008 Food and Drug Administration guidance and the publication of the first thirteen Cardiovascular Outcome Trials (CVOTs) of the "golden era of T2DM", in 2018, a consensus report was published by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD)[7]. With it, a bright era began for T2DM, as perceived by patients and doctors who care for their health. Moreover, this consensus, considered universal, has been and continues to be the cornerstone for later versions of another medical societies[8-9]. Up to August 2022, twenty-six CVOTs[10-35] have been published, including 201,169 patients with 572,844 years/patient follow-up accumulated with various risk profiles for cerebrovascular, cardiovascular, and renal disease. The objectives, methods, results, conclusions, and analysis of all

those CVOTs have been deeply reviewed recently by the author[36]. Notably, some CVOTs in T2DM generated hypotheses for certain populations without T2DM, especially those with chronic kidney disease and non-diabetic heart failure.

Without a doubt, the CVOTs saga that began in June 2013 with the publication of the SAVOR and EXAMINE studies[10-11] has broadened and optimized Gaede and Rawshani' s vision. Today, as never before, there are "anti-diabetic" drugs that, beyond glucose control, reduce the risk of cardiovascular death, heart attack, stroke, hospitalization for heart failure, and progression of diabetic chronic kidney disease. The central message of this diagnosis and treatment knowledge evolution is an optimistic message whose philosophy is based on the possibility of achieving survival with quality like that of individuals without T2DM. The key is a timely diagnosis (within the first year of evolution) and treatment aimed at sustained control and goals of all cerebrovascular, cardiovascular, and renal risk factors, including the use of drugs still called "anti-diabetics," which have shown to reduce these risks beyond the "standard of care" considered until 2017 for glucose control in T2DM patients.

Four new therapeutic algorithms for T2DM

For now, identifying the four risk profiles illustrated in Figure 1 (low/intermediate risk for ASCVD, high risk for/or ASCVD, CKD or heart failure) allows us to identify our main therapeutic target: reduction of 3-MAME (triple Major Adverse Metabolic Events), 3-MACE (triple Major Adverse Cardiovascular Events), 3-MARE (triple Major Adverse Renal Events) or 2-MACE (double Major Adverse Cardiovascular Events) (Figure 2). But, most importantly, it allows us to select a therapeutic strategy that, beyond glycemic control, reduces with net benefit the incidence of the referred therapeutic targets (3-MAME, 3-MACE, 3-MARE, and 2-MACE) (Figure 3); that is the present magic of Cardio-Diabetology[36].

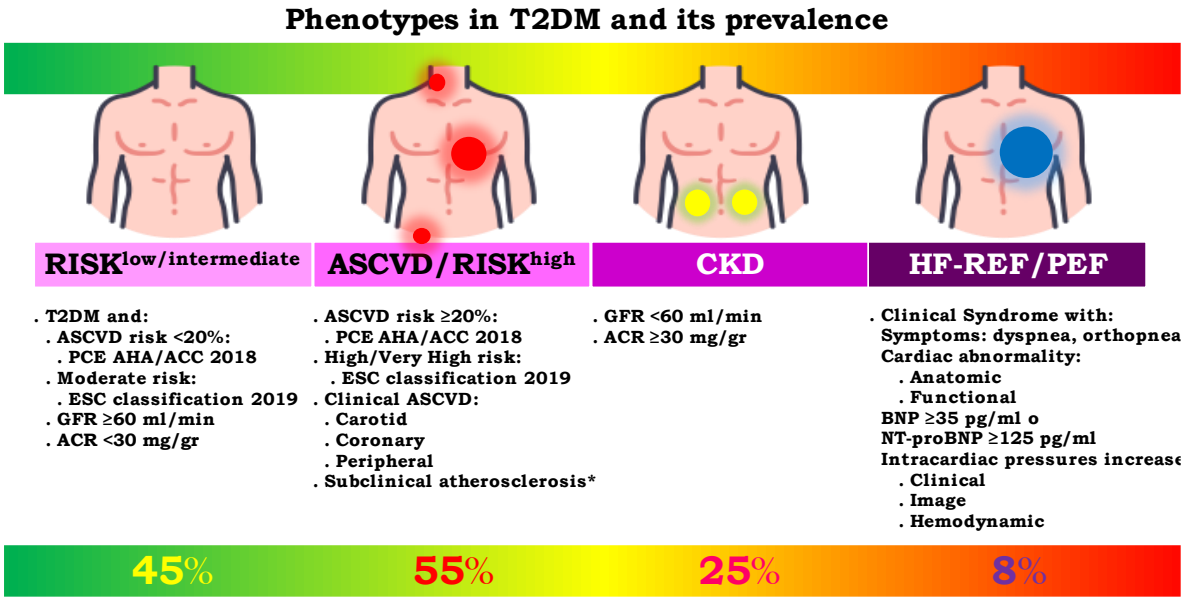

Figure 1: Phenotypes in T2DM and its prevalence

Identifying these four phenotypes is essential for optimal treatment focused on the net benefit. According to the CAPTURE study[37], on average, 45% of T2DM patients have intermediate or low atherosclerotic cardiovascular risk (<20% estimated by PCE ACC/AHA 2018[38]) or intermediate (ESC 2019 classification[39]), without CKD, ASCVD, nor the clinical syndrome of HF.

On average, 55% of T2DM patients have high risk for ASCVD (≥20% estimated by PCE AHA/ACC 2018) or high/very high (ESC 2019 classification) or ASCVD in any arterial territory. *Subclinical atherosclerosis is considered a high-risk condition according to European guidelines.

On average, 25% of T2DM patients have CKD, with a GFR <60 mL/min/1.73m^2 and/or an ACR ≥30 mg/g.

Finally, <10% of T2DM patients have clinical HF.

It is important to mention that the phenotypes of high-risk for/or ASCVD, CKD, and HF frequently overlap. Therefore, it is crucial to determine the predominant phenotype to define the therapeutic

strategy with the greatest net benefit (see Figure 3).

PCE = Pooled Cohort Equations
ACC = American College of Cardiology
AHA = American Heart Association
ESC = European Society of Cardiology
CVD = Cardiovascular Disease
GFR = Glomerular Filtration Rate
ACR = Albumin/Creatinine Ratio
ASCVD = Atherosclerotic Cardiovascular Disease
CKD = Chronic Kidney Disease
HF-REF/PEF = Heart Failure-Reduced Ejection Fraction/Preserved Ejection Fraction
BNP = Brain Natriuretic Peptide
NT-proBNP = N-terminal pro hormone BNP

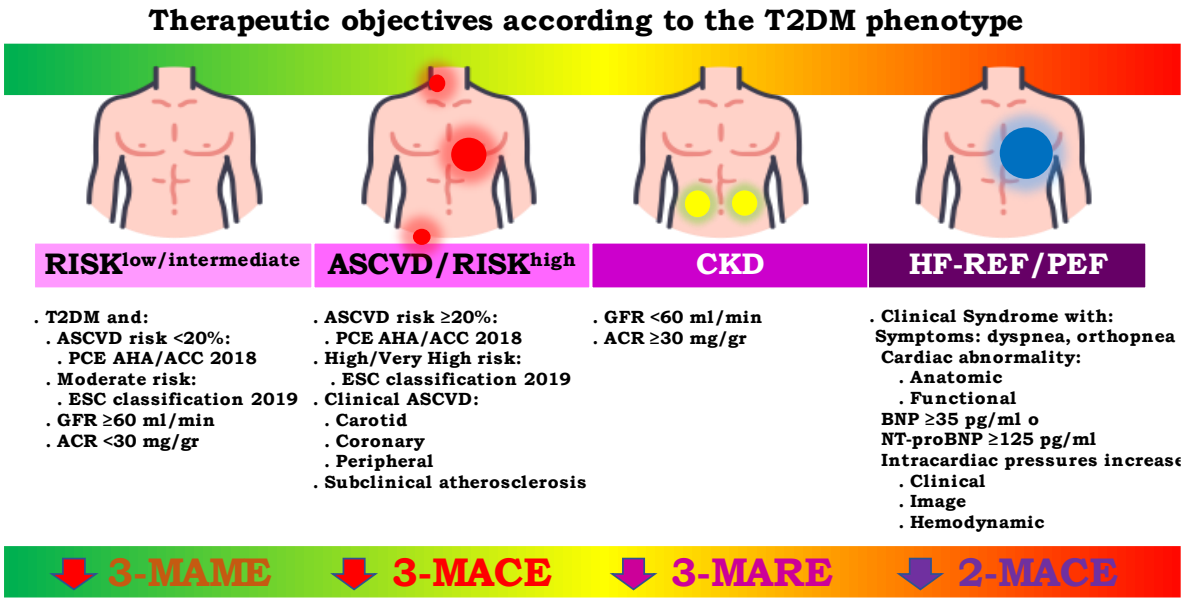

Figure 2: Therapeutic objectives according to the T2DM phenotype

Identifying these four phenotypes is essential for optimal treatment focused on the net benefit.

In the T2DM phenotype with intermediate or low risk for ASCVD (<20% estimated by PCE ACC/AHA 2018) or intermediate (ESC 2019 classification), without ASCVD, CKD, nor clinical HF, the therapeutic objective is to achieve glycemic control (HbA1c <7%) without inducing severe hypoglycemia or weight gain (triple goal), in other words, to reduce the risk of a 3-point MAME (Major Adverse Metabolic Event), a term proposed for the first time by the author in this publication.

The therapeutic objective in the phenotype with high risk for ASCVD (≥20% estimated by PCE AHA/ACC 2018) or high/very high for ASCVD (ESC 2019 classification) or ASCVD in any arterial territory is to reduce the risk of a 3-point MACE (Major Adverse Cardiovascular Event) including cardiovascular death, myocardial infarction, or stroke.

The therapeutic objective of the phenotype with CKD is to reduce the risk of a 3-point MARE (Major Adverse Renal Event), including kidney death, progression to end-stage CKD, or doubling serum creatinine.

Finally, the therapeutic objective in the phenotype with clinical HF is to reduce the risk of a 2-point MACE (cardiovascular death or hospitalization for heart failure).

If more than one phenotype coexists, it is vital to define the predominant phenotype since the therapeutic strategy may vary depending on it.

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HF-REF/PEF = Heart Failure-Reduced Ejection Fraction/Preserved Ejection Fraction
BNP = Brain Natriuretic Peptide
NT-proBNP = N-terminal pro hormone BNP
MAME = Major Adverse Metabolic Event
MACE = Major Adverse Cardiovascular Event

MARE = Major Adverse Renal Event

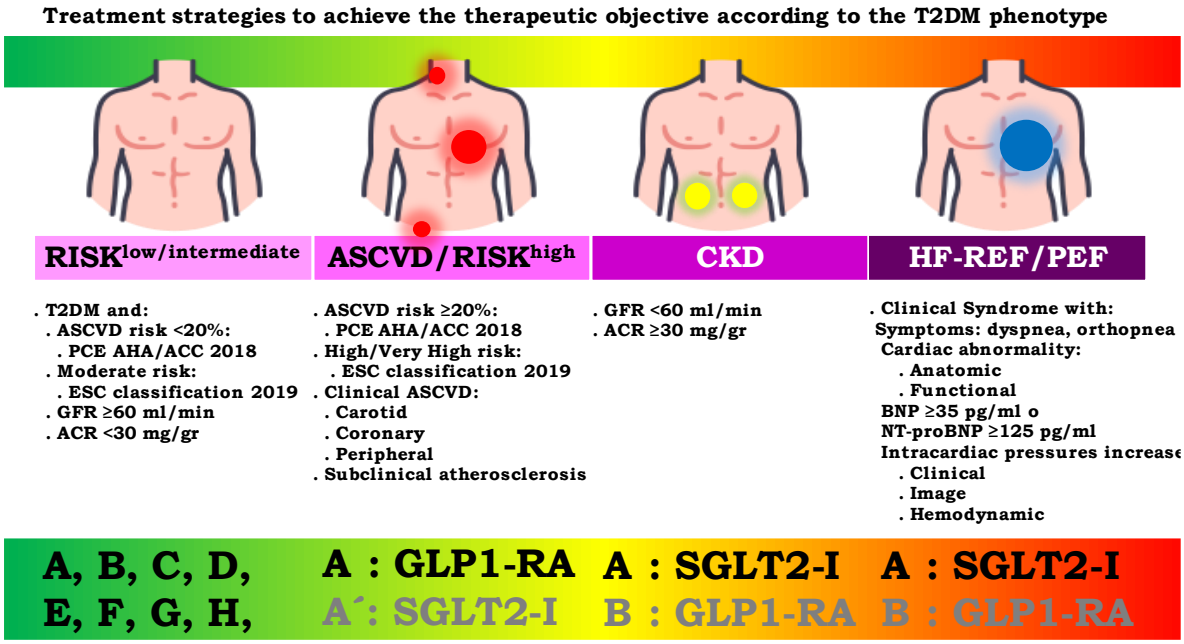

Figure 3: Treatment strategies to achieve the therapeutic objective according to the T2DM phenotype

The final purpose of identifying the four T2DM phenotypes is establishing a therapeutic strategy with net benefit (benefit > risk / saving > cost); this is possible thanks to the evidence generated in the last nine years of CVOTs publications in T2DM.

In the T2DM phenotype with intermediate or low risk for ASCVD (<20% estimated by PCE ACC/AHA 2018) or intermediate (ESC 2019 classification), without ASCVD, CKD, nor clinical HF, the strategy to achieve the therapeutic objective (reducing the risk of a 3-MAME) has metformin as a substrate and as suitable complementary therapies, the following therapeutic classes: GLP1-RA (oral), SGLT2-I, DPP-4 inhibitors, GLP1-RA (subcutaneous), combining basal insulin/GLP1-RA, pioglitazone, and third-generation sulfonylurea (A to H options in figure 3). This concept has been recently reinforced by the GRADE study.[40]

In the phenotype with high risk for ASCVD (≥20% estimated by PCE AHA/ACC 2018) or high/very high (ESC 2019 classification) or ASCVD in any arterial territory, the strategy to achieve the therapeutic objective (reducing the risk of a 3-MACE) has metformin as a substrate and the following therapeutic classes. Strategy A: subcutaneous GLP1-RA (semaglutide, liraglutide, or dulaglutide), and Strategy A´: SGLT2-I (empagliflozin, canagliflozin or dapagliflozin), one or both regardless of hemoglobin A1c result. However, if another drug is required for metabolic control, one of the other mentioned (non-redundant) therapeutic classes is recommended.

In the phenotype with CKD, the strategy to achieve the therapeutic objective (reducing the risk of a 3-MARE) has metformin (adjusted for GFR) as a substrate and the following therapeutic classes. Strategy A: SGLT2-I (dapagliflozin, empagliflozin or canagliflozin), and Strategy B: subcutaneous GLP1-RA (semaglutide, liraglutide, or dulaglutide), one or both regardless of hemoglobin A1c result. However, if another drug is required for metabolic control, one of the other mentioned (non-redundant) therapeutic classes is recommended.

Finally, in the phenotype with clinical HF, the strategy to achieve the therapeutic objective (reducing the risk of a 2-MACE) has metformin as a substrate and SGLT2-I (empagliflozin or dapagliflozin) therapy regardless of hemoglobin A1c result. However, if another drug is required for metabolic control, one of the other mentioned therapeutic classes is recommended, including subcutaneous GLP1-RA, and excluding pioglitazone and saxagliptin.

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ASCVD = Atherosclerotic Cardiovascular Disease
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BNP = Brain Natriuretic Peptide
NT-proBNP = N-terminal pro hormone BNP
MAME = Major Adverse Metabolic Event
MACE = Major Adverse Cardiovascular Event
MARE = Major Adverse Renal Event
GLP1-RA = glucagon-like peptide-1 receptor agonists
SGLT2-I = sodium–glucose co-transporter-2 inhibitor
DPP-4 inhibitors = dipeptidyl peptidase 4 inhibitors

Conclusion

This brief and illustrated review article has addressed the so-called three eras of therapeutic evolution in T2DM: dark, light, and bright. The latter, also called the Era of Cardio Diabetology, has radically changed the treatment approach and the prognosis of the T2DM patient. Going from an approach focused on glycemic control towards an approach focused on the holistic control of all cardiovascular risk factors and the use of "anti-diabetic" drugs that, beyond their effect on glucose control, add to the standard of care and significantly reduce the cerebral, cardiac, and renal risks of the T2DM patient. Thus, allowing a longer life expectancy, quantitatively and qualitatively.

Based on the same evidence, three illustrations are presented that summarize clinically and practically all the evidence accumulated in this arena in the last nine years. Algorithm 1 shows the phenotypes susceptible to net therapeutic benefit and their prevalence. Algorithm 2 illustrates therapeutic goals beyond glycemic control (reduction of 3-MAME, 3-MACE, 3-MARE, and 2-MACE). Finally, algorithm 3 shows globally agreed therapeutic strategies to achieve therapeutic goals with net benefit.

Surprisingly, the evidence generated in less than a decade has allowed us to create and put into practice diagnostic-therapeutic structures of high clinical impact, which had not been seen in almost a century since the discovery of insulin.

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