SID
Società Italiana di Diabetologia

Strategie condivise
nella gestione
del paziente diabetico

VIDEOCONFERENZA
12 DICEMBRE 2020

I SESSIONE
LO STATO DELL'ARTE
Moderatori: S. Perlini, G. Perseghin

Nuove linee guida diabetologiche: è tempo per target più ambiziosi?

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Sistema Socio Sanitario
Regione Lombardia

Antonio C. Bossi - DISCLOSURES

Nell'arco degli ultimi tre anni dichiaro di aver ricevuto onorari per conferenze, collaborazioni scientifiche, lavori di ricerca clinica e documentale dalle seguenti Aziende:

- *Lilly Italia Spa*
- *Novo Nordisk Italia SpA*
- *Johnson & Johnson SpA*
- *Boehringer Ingelheim SpA*
- *Artsana SpA*
- *Takeda SpA*
- *Bayer SA*
- *Sanofi SpA*
- *Astra Zeneca SpA*
- *MSD Italia SpA*
- *Mundipharma SpA*

Se oggi sono qui in qualità di relatore è perché la SID ha contribuito alla mia formazione culturale, scientifica, clinica.

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Nuove linee guida diabetologiche: è tempo per target più ambiziosi?

Agenda

- From the «Intention to treat» trials through «CVOTs» …
- … Toward «Precision Medicine»
- To «Prevention Medicine» ?
- Un confronto con la realtà

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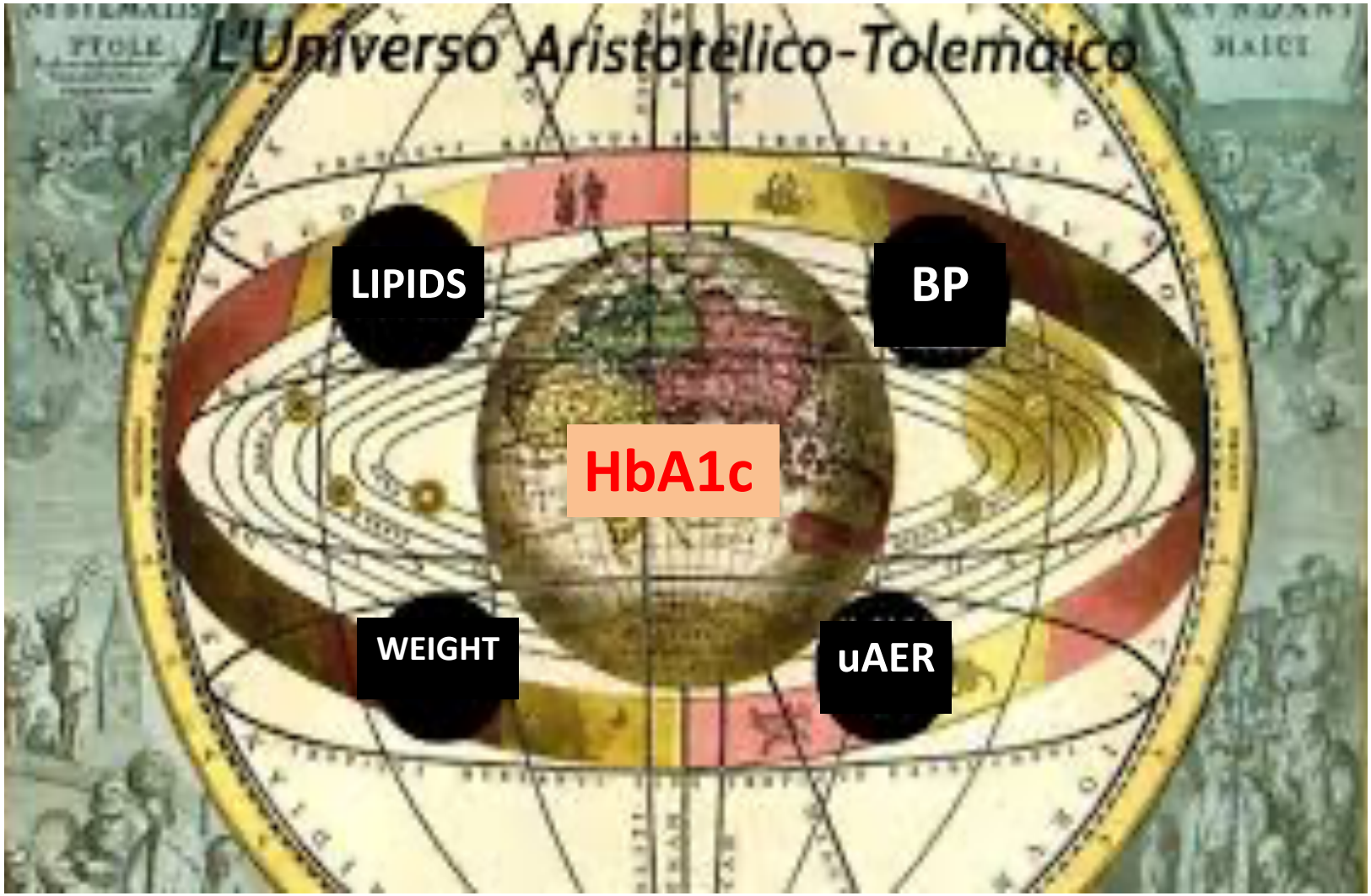
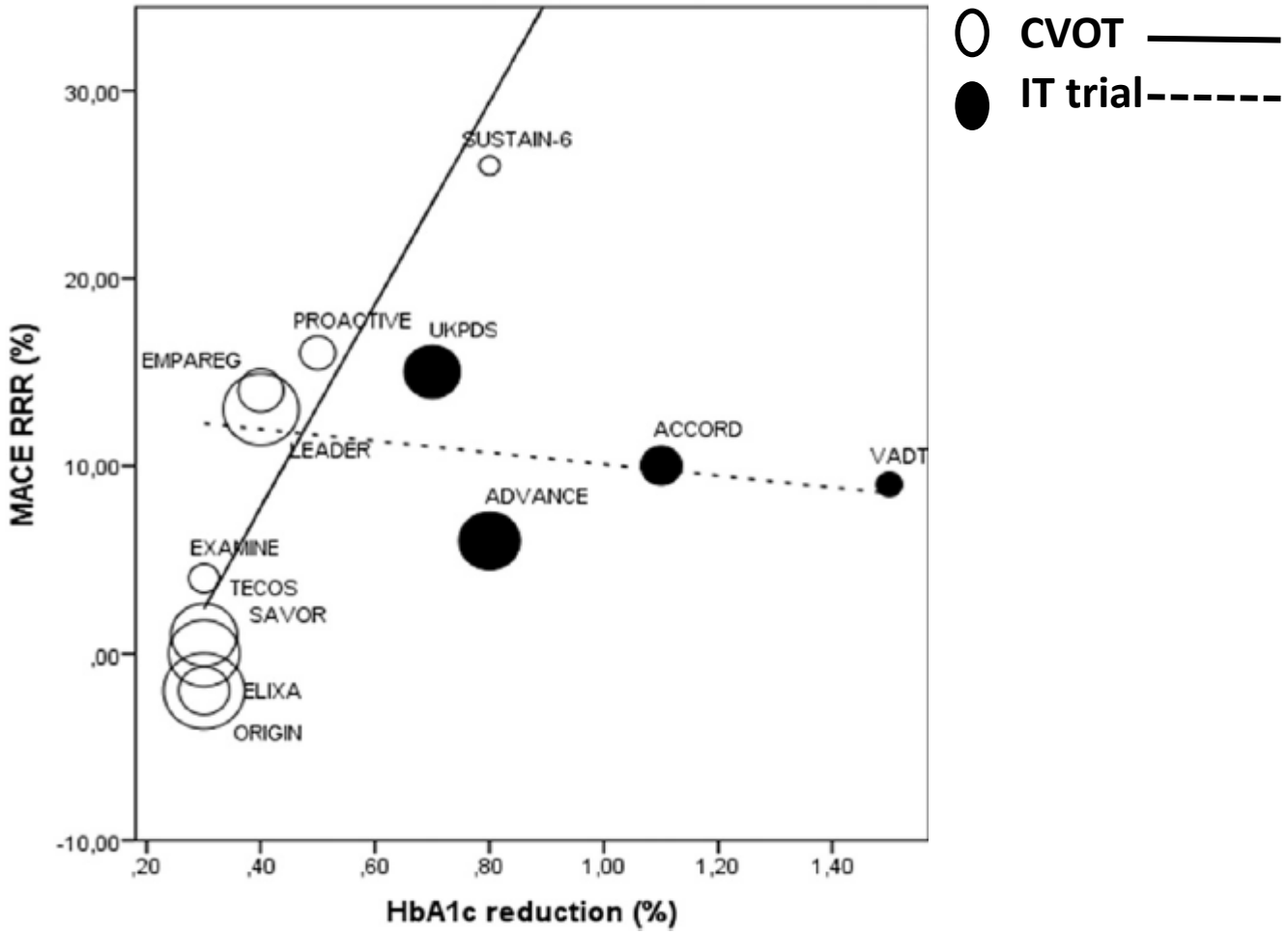
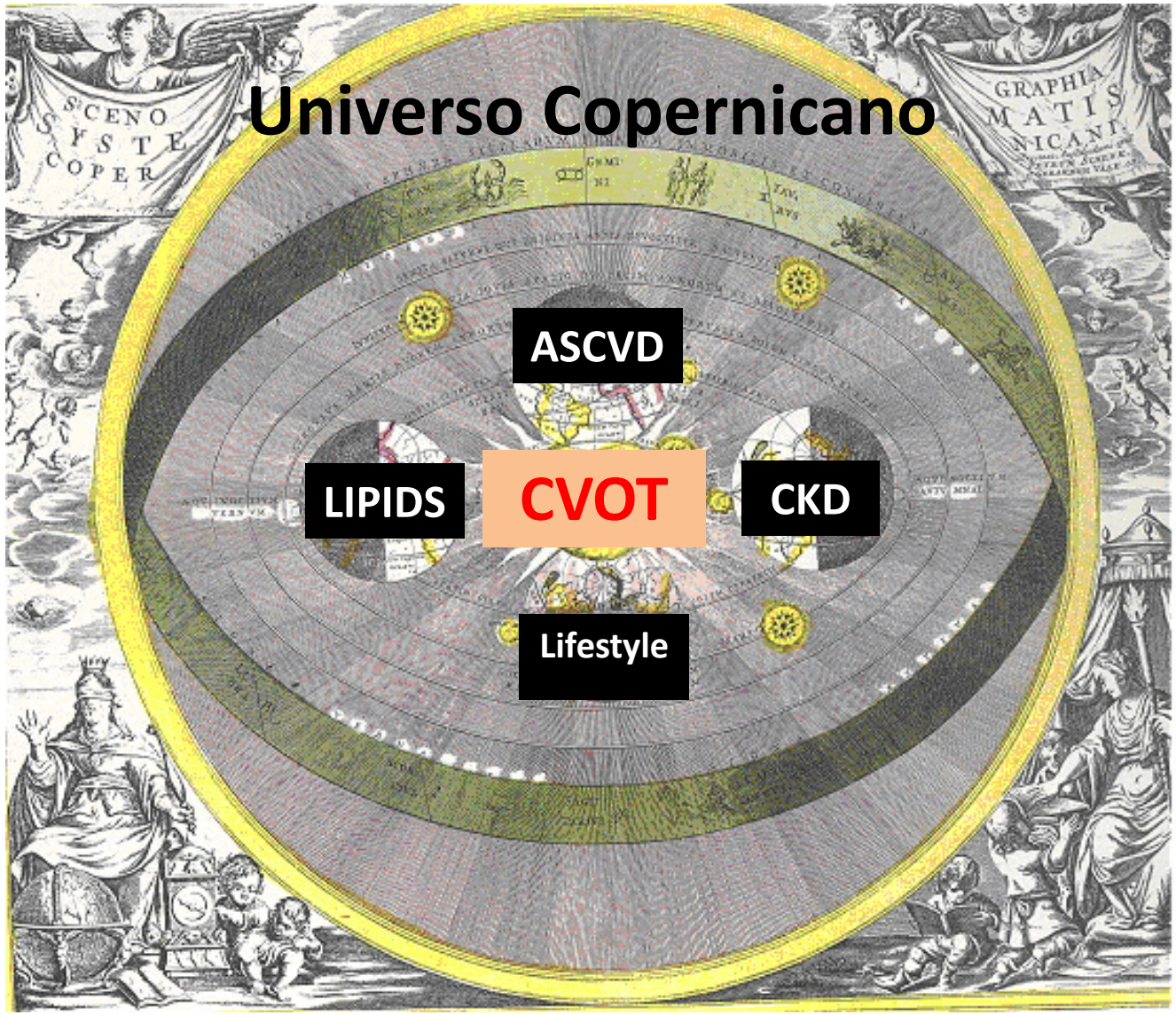

L'Universo Aristotelico-Tolemaico
LIPIDS
BP
HbA1c
WEIGHT
uAER

Back to glycemic control: An alternative look at the results of cardiovascular outcome trials in type 2 diabetes



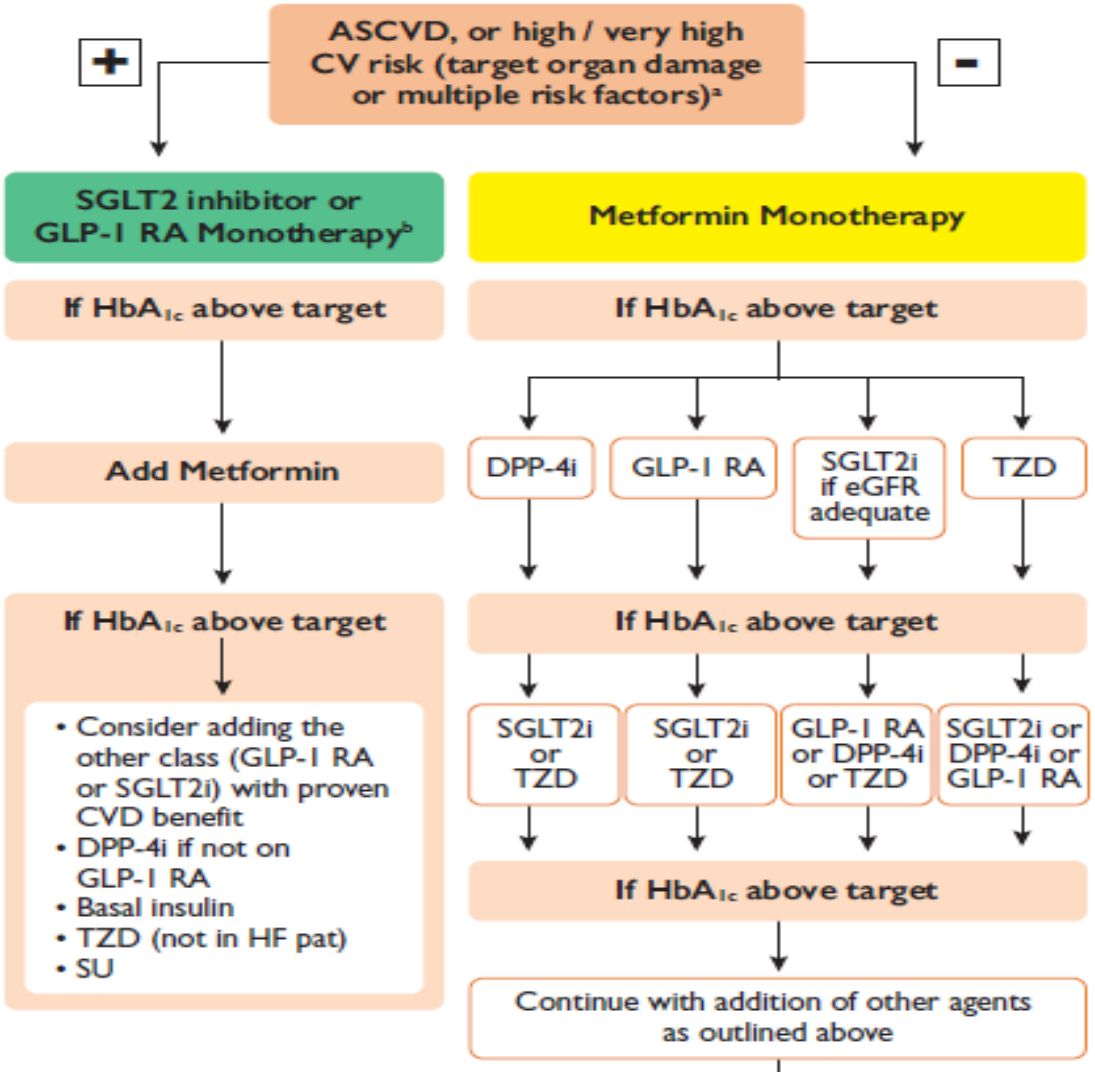
Monami M et Al. NMCD 2018
http://dx.doi.org/10.1016/j.numecd.2017.01.003

Universo Copernicano




883
HANNO UCCISO
LA METFORMINA

A Type 2 DM - Drug naïve patients



ESC European Society of Cardiology

European Heart Journal (2019) **00**, 1–69
doi:10.1093/eurheartj/ehz486

B Type 2 DM - On metformin

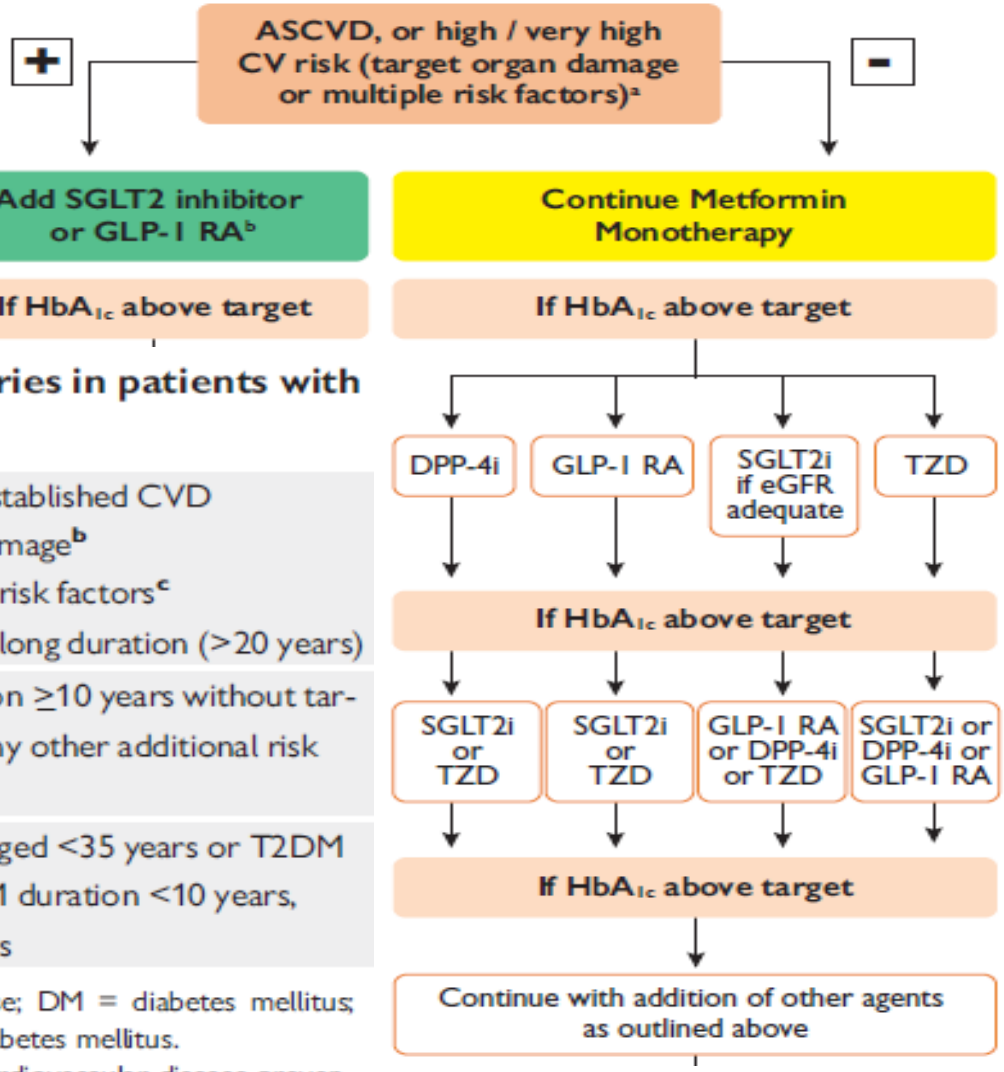


Table 7 Cardiovascular risk categories in patients with diabetes[a]

Very high risk	Patients with DM **and** established CVD **or** other target organ damage[b] **or** three or more major risk factors[c] **or** early onset T1DM of long duration (>20 years)
High risk	Patients with DM duration ≥10 years without target organ damage plus any other additional risk factor
Moderate risk	Young patients (T1DM aged <35 years or T2DM aged <50 years) with DM duration <10 years, without other risk factors

CV = cardiovascular; CVD = cardiovascular disease; DM = diabetes mellitus; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus.

[a]Modified from the 2016 European Guidelines on cardiovascular disease prevention in clinical practice.[27]

[b]Proteinuria, renal impairment defined as eGFR ≥30 mL/min/1.73 m^2, left ventricular hypertrophy, or retinopathy.

[c]Age, hypertension, dyslipidemia, smoking, obesity.

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European Heart Journal (2019) **00**, 1–69
doi:10.1093/eurheartj/ehz486

AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS
AMERICAN COLLEGE OF ENDOCRINOLOGY

AACE/ACE COMPREHENSIVE TYPE 2 DIABETES MANAGEMENT ALGORITHM

2020

 | DOI 10.4158/CS-2019-0472

ASCVD RISK FACTOR MODIFICATIONS ALGORITHM

DYSLIPIDEMIA

LIFESTYLE THERAPY (Including Medically Assisted Weight Loss)

LIPID PANEL: Assess ASCVD Risk

STATIN THERAPY
If TG >500 mg/dL, fibrates, Rx-grade OM-3 fatty acids, niacin

If statin-intolerant

Try alternate statin, lower statin dose or frequency, or add nonstatin LDL-C- lowering therapies

Repeat lipid panel; assess adequacy, tolerance of therapy

Intensify therapies to attain goals according to risk levels

RISK LEVELS	HIGH	VERY HIGH	EXTREME
	DESIRABLE LEVELS	DESIRABLE LEVELS	DESIRABLE LEVELS
LDL-C (mg/dL)	<100	<70	<55
Non-HDL-C (mg/dL)	<130	<100	<80
TG (mg/dL)	<150	<150	<150
Apo B (mg/dL)	<90	<80	<70

RISK LEVELS:
- **HIGH*:** DM but no other major risk and/or age <40
- **VERY HIGH*:** DM + major ASCVD risk(s) (HTN, Fam Hx, low HDL-C, smoking, CKD3,4)
- **EXTREME*:** DM plus established clinical CVD

If not at desirable levels:	Intensify lifestyle therapy (weight loss, physical activity, dietary changes) and glycemic control; consider additional therapy
To lower LDL-C:	Intensify statin, add ezetimibe, PCSK9i, colesevelam, or niacin
To lower Non-HDL-C, TG:	Intensify statin and/or add Rx-grade OM3 fatty acid, fibrate, and/or niacin
To lower Apo B, LDL-P:	Intensify statin and/or add ezetimibe, PCSK9i, colesevelam, and/or niacin
To lower LDL-C in FH:**	Statin + PCSK9i
If TG 135–499:	Add icosapent ethyl 4 g/day if high ASCVD risk on maximally tolerated statins

Assess adequacy & tolerance of therapy with focused laboratory evaluations and patient follow-up

* EVEN MORE INTENSIVE THERAPY MIGHT BE WARRANTED ** FAMILIAL HYPERCHOLESTEROLEMIA

HYPERTENSION

GOAL: SYSTOLIC <130, DIASTOLIC <80 mm Hg

ACEi or ARB

For initial blood pressure >150/100 mm Hg:
DUAL THERAPY

ACEi or ARB + Calcium Channel Blocker ✓ / ß-blocker ✓ / Thiazide ✓

If not at goal (2–3 months)

Add calcium channel blocker, ß-blocker or thiazide diuretic

If not at goal (2–3 months)

Add next agent from the above group, repeat

If not at goal (2–3 months)

Additional choices (α-blockers, central agents, vasodilators, aldosterone antagonist)

Achievement of target blood pressure is critical

 | DOI 10.4158/CS-2019-0472

GLYCEMIC CONTROL ALGORITHM

INDIVIDUALIZE GOALS

A1C ≤6.5% For patients without concurrent serious illness and at low hypoglycemic risk

A1C >6.5% For patients with concurrent serious illness and at risk for hypoglycemia

LIFESTYLE THERAPY AND ONGOING GLUCOSE MONITORING (CGM preferred)

INDEPENDENT OF GLYCEMIC CONTROL, IF ESTABLISHED OR HIGH ASCVD RISK AND/OR CKD, RECOMMEND SGLT2i AND/OR LA GLP1-RA

Entry A1C <7.5%

MONOTHERAPY[1,2]

- ✓ Metformin
- ✓ GLP1-RA
- ✓ SGLT2i
- ✓ DPP4i
- ⚠ TZD
- ✓ AGi
- ⚠ SU/GLN

Independent of glycemic control, if established ASCVD or high risk, CKD 3, or HFrEF, start LA GLP1-RA or SGLT2i with proven efficacy*

Entry A1C ≥7.5% - 9.0%

DUAL THERAPY[1]

- ✓ GLP1-RA
- ✓ SGLT2i
- ✓ DPP4i
- ⚠ TZD
- ⚠ SU/GLN
- ⚠ Basal Insulin
- ✓ Colesevelam
- ✓ Bromocriptine QR
- ✓ AGi

3 MONTHS[2]

TRIPLE THERAPY[1]

- ✓ GLP1-RA
- ✓ SGLT2i
- ⚠ TZD
- ⚠ SU/GLN
- ⚠ Basal Insulin
- ✓ DPP4i
- ✓ Colesevelam
- ✓ Bromocriptine QR
- ✓ AGi

3 MONTHS[2]

MET + or other agent

Entry A1C >9.0%

SYMPTOMS

NO	YES
DUAL Therapy OR TRIPLE Therapy	INSULIN ± Other Agents

ADD OR INTENSIFY INSULIN

Refer to Insulin Algorithm

LEGEND

- ✓ Few adverse events and/or possible benefits
- ⚠ Use with caution

1 Order of medications represents a suggested hierarchy of usage; length of line reflects strength of recommendation

2 If not at goal in 3 months, proceed to next level therapy

*CKD 3: canagliflozin; HFrEF: dapagliflozin

CKD 3 = stage 3 chronic kidney disease; HFrEF = heart failure with reduced ejection fraction; LA = long-acting (≥24 hour duration)

PROGRESSION OF DISEASE

ADA-EASD STANDARDS OF MEDICAL CARE IN DIABETES 2021

Diabetes Care 2021;44(Suppl. 1):S73–S84 | https://doi.org/10.2337/dc21-S006

Recommendations

6.3 Standardized, single-page glucose reports from continuous glucose monitoring (CGM) devices with visual cues, such as the ambulatory glucose profile (AGP), should be considered as a standard printout for all CGM devices. E

6.4 Time in range (TIR) is associated with the risk of microvascular complications, should be an acceptable end point for clinical trials moving forward, and can be used for assessment of glycemic control. Additionally, time below target (<70 and <54 mg/dL [3.9 and 3.0 mmol/L]) and time above target (>180 mg/dL [10.0 mmol/L]) are useful parameters for reevaluation of the treatment regimen. C

Recommendations

6.5a An A1C goal for many nonpregnant adults of <7% (53 mmol/mol) without significant hypoglycemia is appropriate. A

6.5b If using ambulatory glucose profile/glucose management indicator to assess glycemia, a parallel goal is a time in range of >70% with time below range <4% (Fig. 6.1). B

6.6 On the basis of provider judgment and patient preference, achievement of lower A1C levels than the goal of 7% may be acceptable, and even beneficial, if it can be achieved safely without significant hypoglycemia or other adverse effects of treatment. C

6.7 Less stringent A1C goals (such as <8% [64 mmol/mol]) may be appropriate for patients with limited life expectancy, or where the harms of treatment are greater than the benefits. B

ADA-EASD STANDARDS OF MEDICAL CARE IN DIABETES 2021

Diabetes Care 2021;44(Suppl. 1):S73–S84
https://doi.org/10.2337/dc21-S006

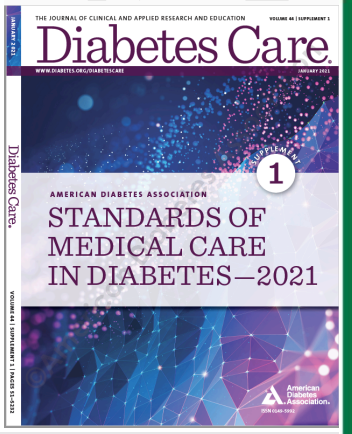
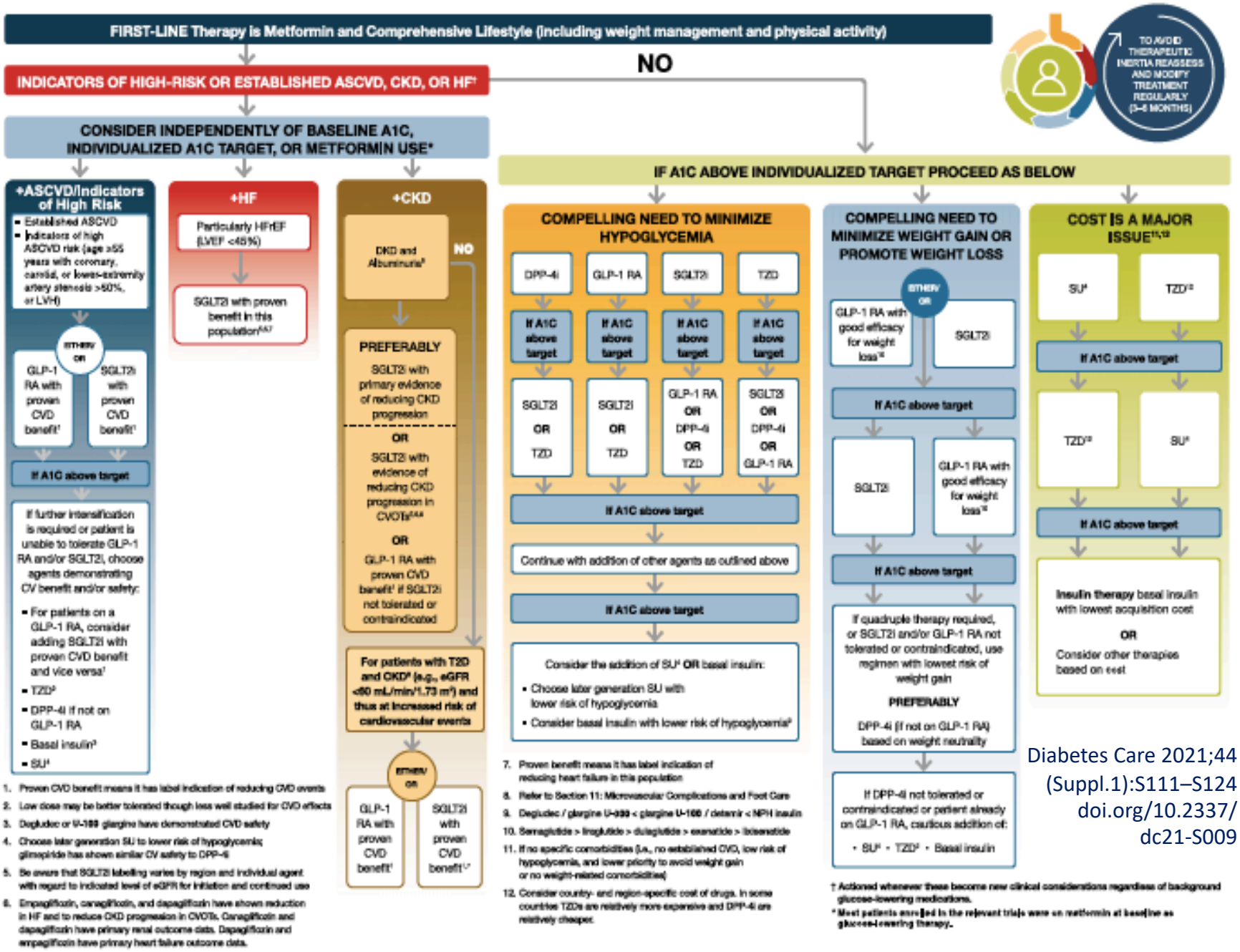


Table 6.3—Summary of glycemic recommendations for many nonpregnant adults with diabetes

A1C	<7.0% (53 mmol/mol)*#
Preprandial capillary plasma glucose	80–130 mg/dL* (4.4–7.2 mmol/L)
Peak postprandial capillary plasma glucose†	<180 mg/dL* (10.0 mmol/L)

*More or less stringent glycemic goals may be appropriate for individual patients. #CGM may be used to assess glycemic target as noted in Recommendation 6.5b and **Fig. 6.1**. Goals should be individualized based on duration of diabetes, age/life expectancy, comorbid conditions, known CVD or advanced microvascular complications, hypoglycemia unawareness, and individual patient considerations (as per **Fig. 6.2**). †Postprandial glucose may be targeted if A1C goals are not met despite reaching preprandial glucose goals. Postprandial glucose measurements should be made 1–2 h after the beginning of the meal, generally peak levels in patients with diabetes.



1. Proven CVD benefit means it has label indication of reducing CVD events
2. Low dose may be better tolerated though less well studied for CVD effects
3. Degludec or U-100 glargine have demonstrated CVD safety
4. Choose later generation SU to lower risk of hypoglycemia; glimepiride has shown similar CV safety to DPP-4i
5. Be aware that SGLT2i labelling varies by region and individual agent with regard to indicated level of eGFR for initiation and continued use
6. Empagliflozin, canagliflozin, and dapagliflozin have shown reduction in HF and to reduce CKD progression in CVOTs. Canagliflozin and dapagliflozin have primary renal outcome data. Dapagliflozin and empagliflozin have primary heart failure outcome data.
7. Proven benefit means it has label indication of reducing heart failure in this population
8. Refer to Section 11: Microvascular Complications and Foot Care
9. Degludec / glargine U-300 < glargine U-100 / detemir < NPH insulin
10. Semaglutide > lixisenatide > dulaglutide > exenatide > lixisenatide
11. If no specific comorbidities (i.e., no established CVD, low risk of hypoglycemia, and lower priority to avoid weight gain or no weight-related comorbidities)
12. Consider country- and region-specific cost of drugs. In some countries TZDs are relatively more expensive and DPP-4i are relatively cheaper.

† Actioned whenever these become new clinical considerations regardless of background glucose-lowering medications.

* Most patients enrolled in the relevant trials were on metformin at baseline as glucose-lowering therapy.

Diabetes Care 2021;44 (Suppl.1):S111–S124 doi.org/10.2337/dc21-S009

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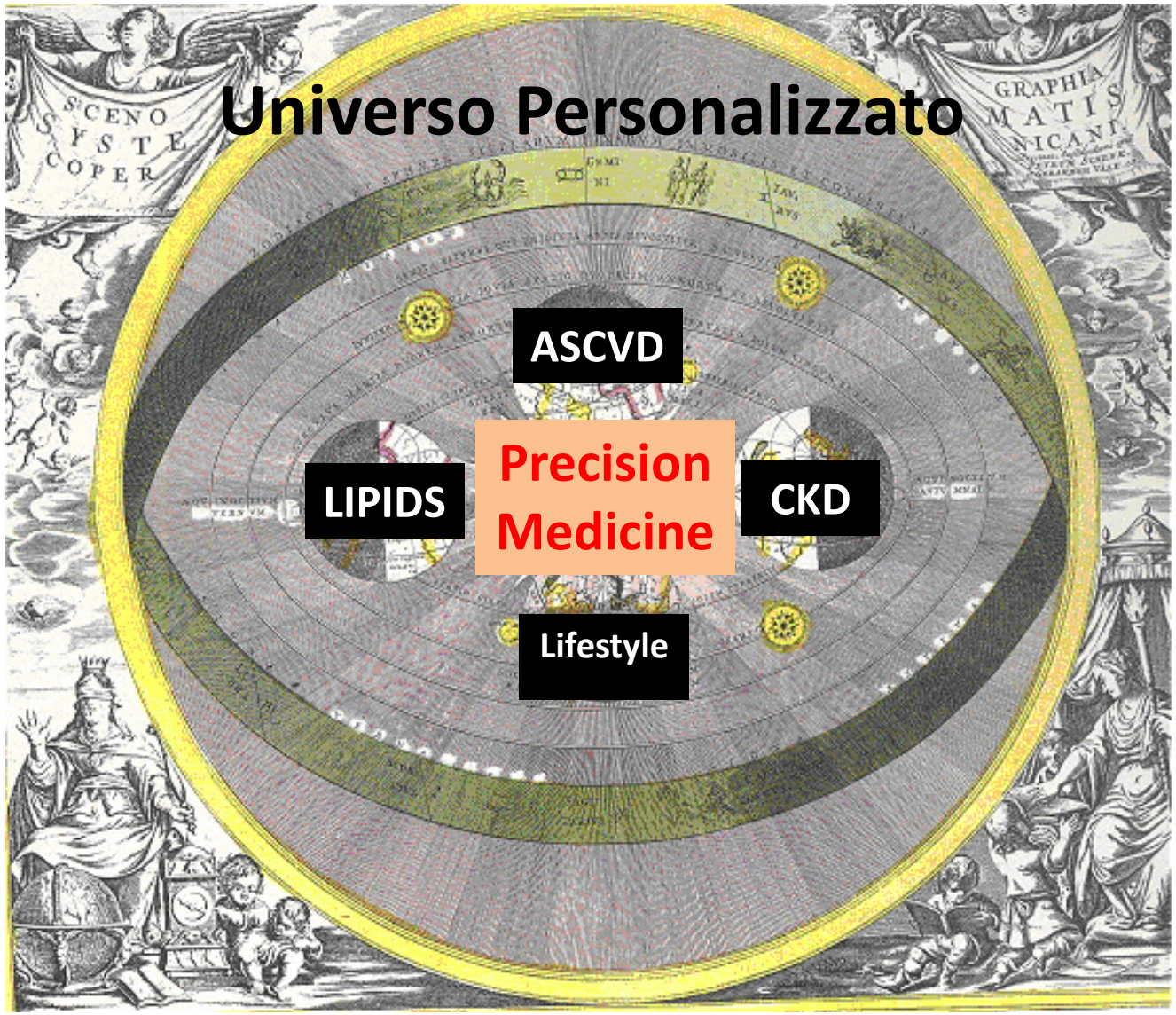
Universo Personalizzato
ASCVD
LIPIDS
Precision Medicine
CKD
Lifestyle

Precision medicine in the management of type 2 diabetes

Lancet Diabetes Endocrinol 2018
Published Online
April 23, 2018

Anna L Gloyn, Daniel J Drucker

Panel: Evolving clinical considerations underlying personalised medicine recommendations for intensification of therapy after metformin in people with type 2 diabetes*

Clinical characteristics influencing selection of glucose-lowering drugs

Older age, fragility
DPP-4 inhibitors, age-specific treatment goals

Severe or recurrent hypoglycaemia
DPP-4 inhibitors, SGLT2 inhibitors, GLP-1 receptor agonists, modern insulins

Poor, variable, or subotimal compliance
Once-weekly GLP-1 receptor agonists

Obesity
Bariatric surgery, GLP-1 receptor agonists, SGLT2 inhibitors

High HbA_{1c} failure of oral antidiabetes drugs
Bariatric surgery, insulin, GLP-1 receptor agonists

Considerations based on non-glycaemic actions of glucose-lowering therapies and the reduction in rates of complications associated with diabetes

Non-alcoholic fatty liver disease, non-alcoholic steatohepatitis
Thiazolidinediones, GLP-1 receptor agonists

Heart failure
SGLT2 inhibitors

Coronary artery disease
GLP-1 receptor agonists

Stroke
Thiazolidinediones, GLP-1 receptor agonists

Chronic kidney disease
SGLT2 inhibitors

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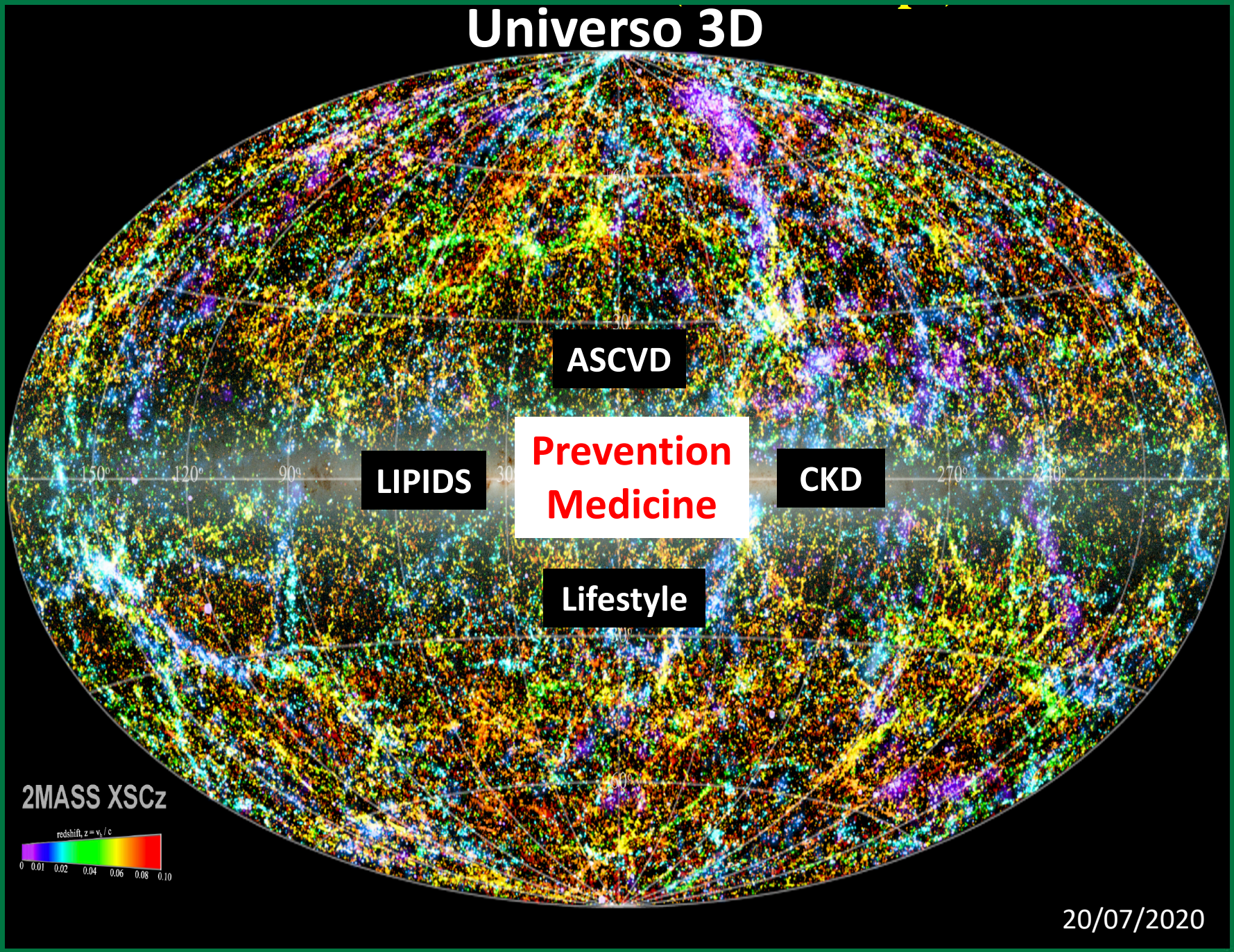
Universo 3D



20/07/2020

https://www.ebi.ac.uk/gwas/diagram

GWAS Catalog

The NHGRI-EBI Catalog of human genome-wide association studies

diabetes mellitus

Examples: breast carcinoma, rs7329174, Yao, 2q37.1, HBS1L, 6:16000000-25000000

Catalog stats

Last data release on 2020-12-02

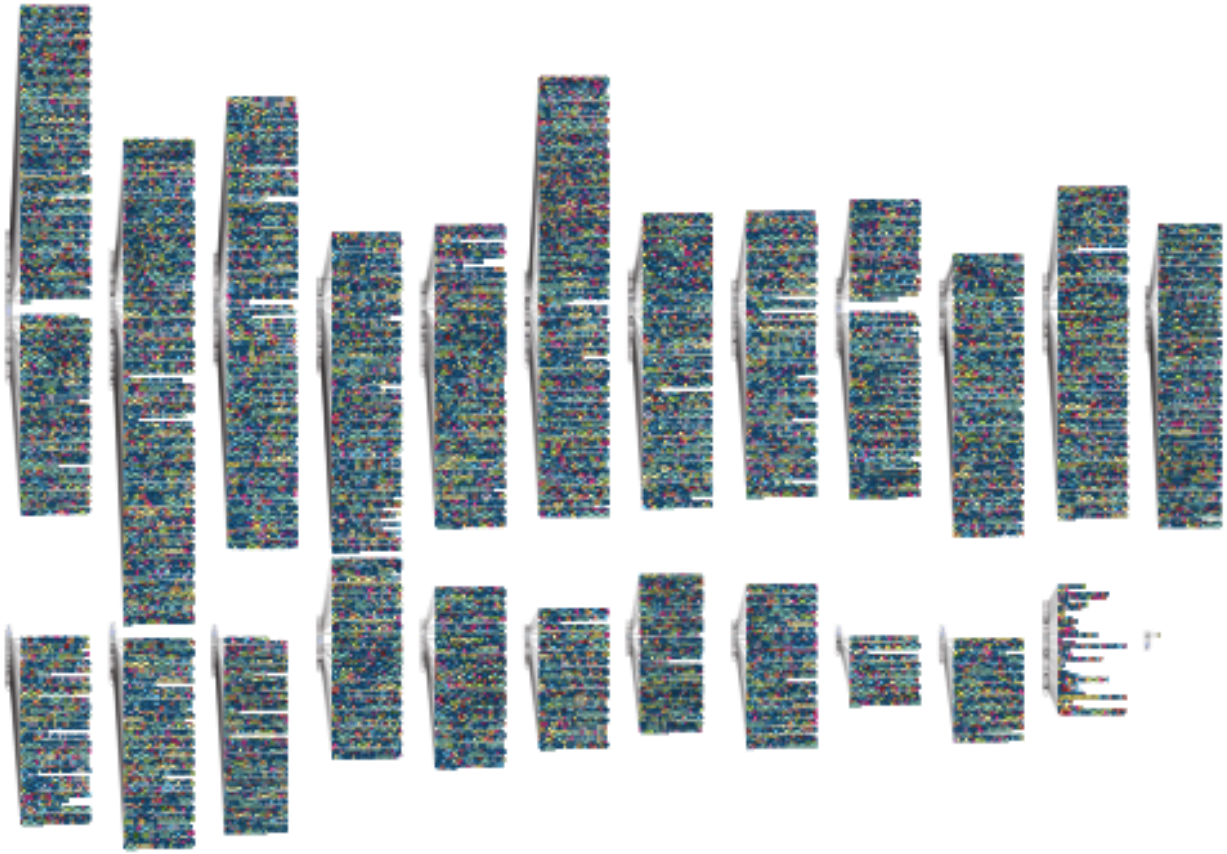
4795 publications

143758 SNPs

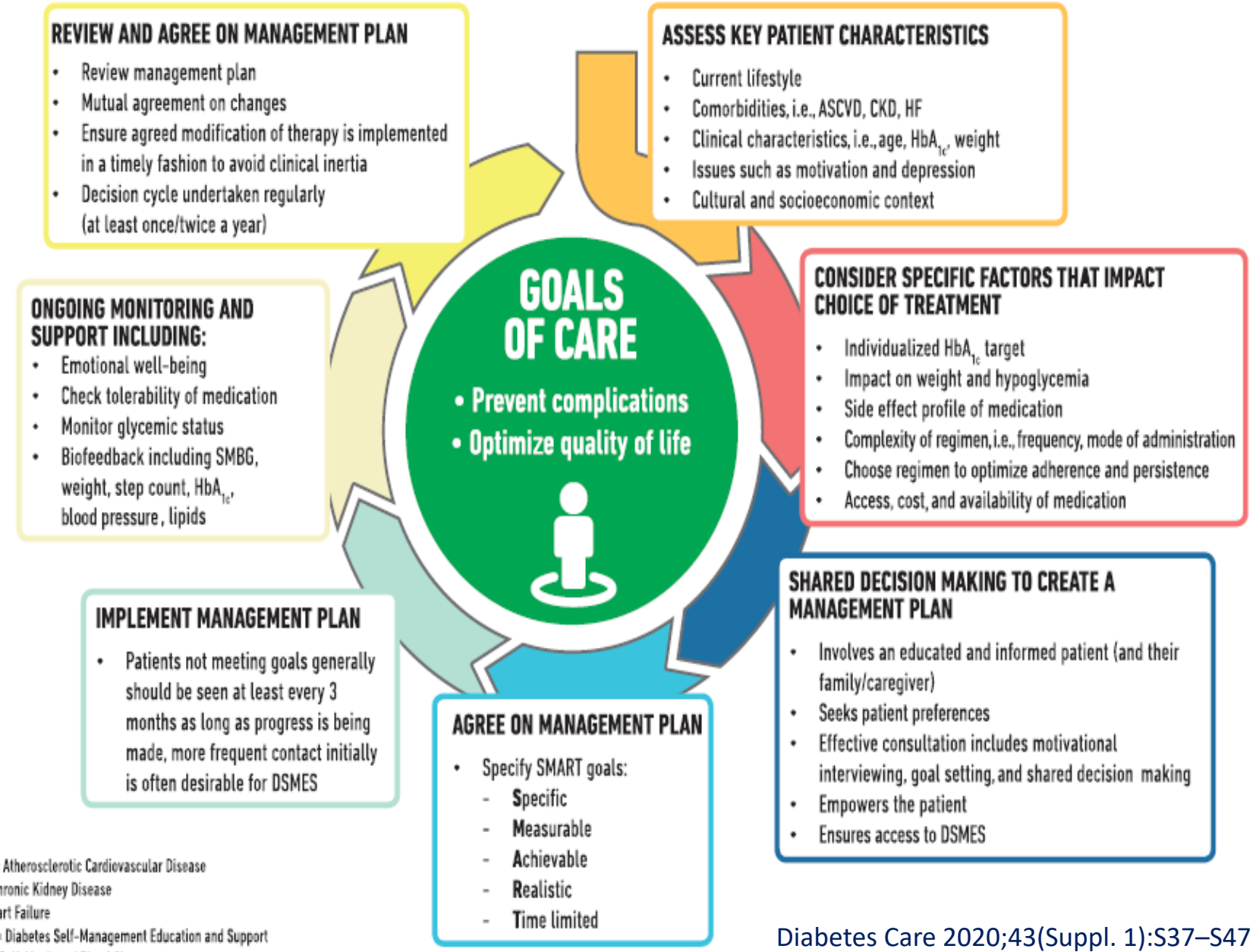
222481 associations

Genome assembly GRCh38.p13

dbSNP Build 153
Ensembl Build 100




BACK
TO THE FUTURE
OUTATIME



ASCVD = Atherosclerotic Cardiovascular Disease
CKD = Chronic Kidney Disease
HF = Heart Failure
DSMES = Diabetes Self-Management Education and Support
SMBG = Self-Monitored Blood Glucose

Diabetes Care 2020;43(Suppl. 1):S37–S47
https://doi.org/10.2337/dc20-S004

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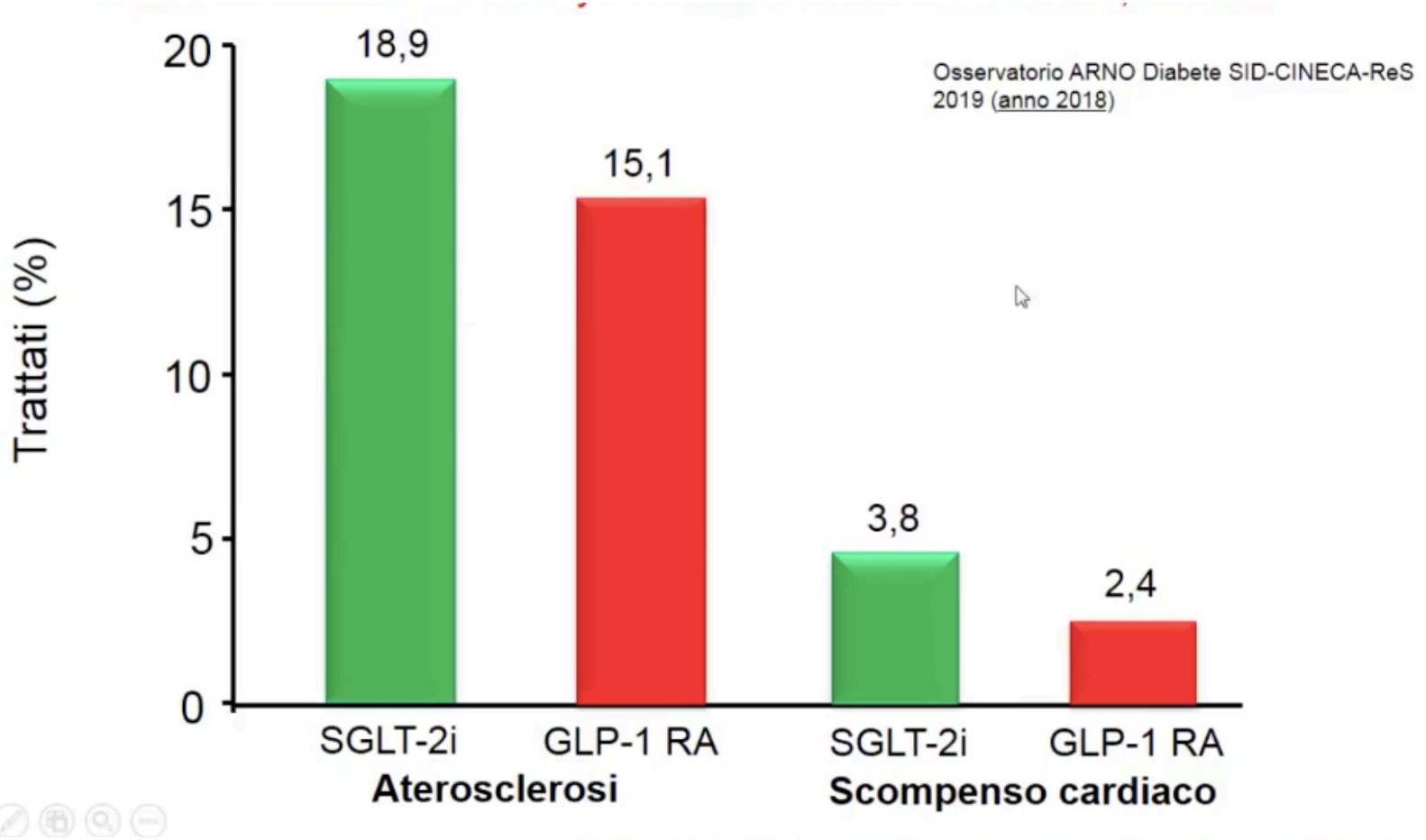
Farmaci cardioprotettori prescritti nei soggetti diabetici con CVD / ad alto rischio CVD / con scompenso cardiaco assistiti nei CAD



ARNO Diabetes Obesrvatory
Bonora E et al. NMCD 2020, 30, 1945

SID
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GRAZIE
per la Vostra Attenzione!