

FoRiSIE Winter School in Clinical Endocrinology

8-11 gennaio 2020 - Roma



BREAKING NEWS SU TERAPIE INNOVATIVE NEL DIABETE

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CASO CLINICO

F.C. - M, 64 anni, **diabete mellito tipo 2** noto da 10 anni in attuale trattamento con metformina 2,5 gr/die

Anamnesi:

- Dirigente di banca
- Fumatore attivo (15 pack/years)
- Obesità I grado
- Familiarità positiva per DMT2 (ramo materno)
- Ipertensione arteriosa dall'età di 45 anni
- Dislipidemia
- Colectomia
- Ernia discale

Screening delle complicanze:

- Eco addome: steatosi epatica di lieve entità
- Nota ateromasia non critica carotidea (stenosi massima 40%)
- ECG: alterazioni aspecifiche della ripolarizzazione; segni di IVS.
- FOO: non RD
- Microalbuminuria

Terapia :

Lansoprazolo 30 mg
Enalapril/Idroclorotiazide 20/12.5 mg
Cardioaspirin 100 mg
Rosuvastatina 20 mg

- Visita di controllo di Gennaio 2019:

Parametri	
BMI	30.1 kg/m²
PAS	140 mmHg
PAD	85 mmHg

Esami del:	21/12/2018
HbA1c	7.9% - 63 mmol/mol
Creatinina	0.9 mg/dl
eGFR	90.1 ml/min/1.73 m ²
ACR	12 mg/mmol
GOT/GPT	14/16 U/L
Colesterolo Tot	136 mg/dl
Colesterolo HDL	39 mg/dl
Trigliceridi	139 mg/dl
cLDL	69 mg/dl

Domanda 1

In considerazione del fenotipo del paziente, quale tra le seguenti strategie terapeutiche adattereste?

- a) confermare la terapia in atto e rinforzare le indicazioni su corretto stile di vita
- b) rinforzare le indicazioni su corretto stile di vita e associare analogo recettoriale del GLP-1
- c) rinforzare le indicazioni su corretto stile di vita e associare terapia con insulina basale
- d) rinforzare le indicazioni su corretto stile di vita e associare terapia con DPP4i

Domanda 1

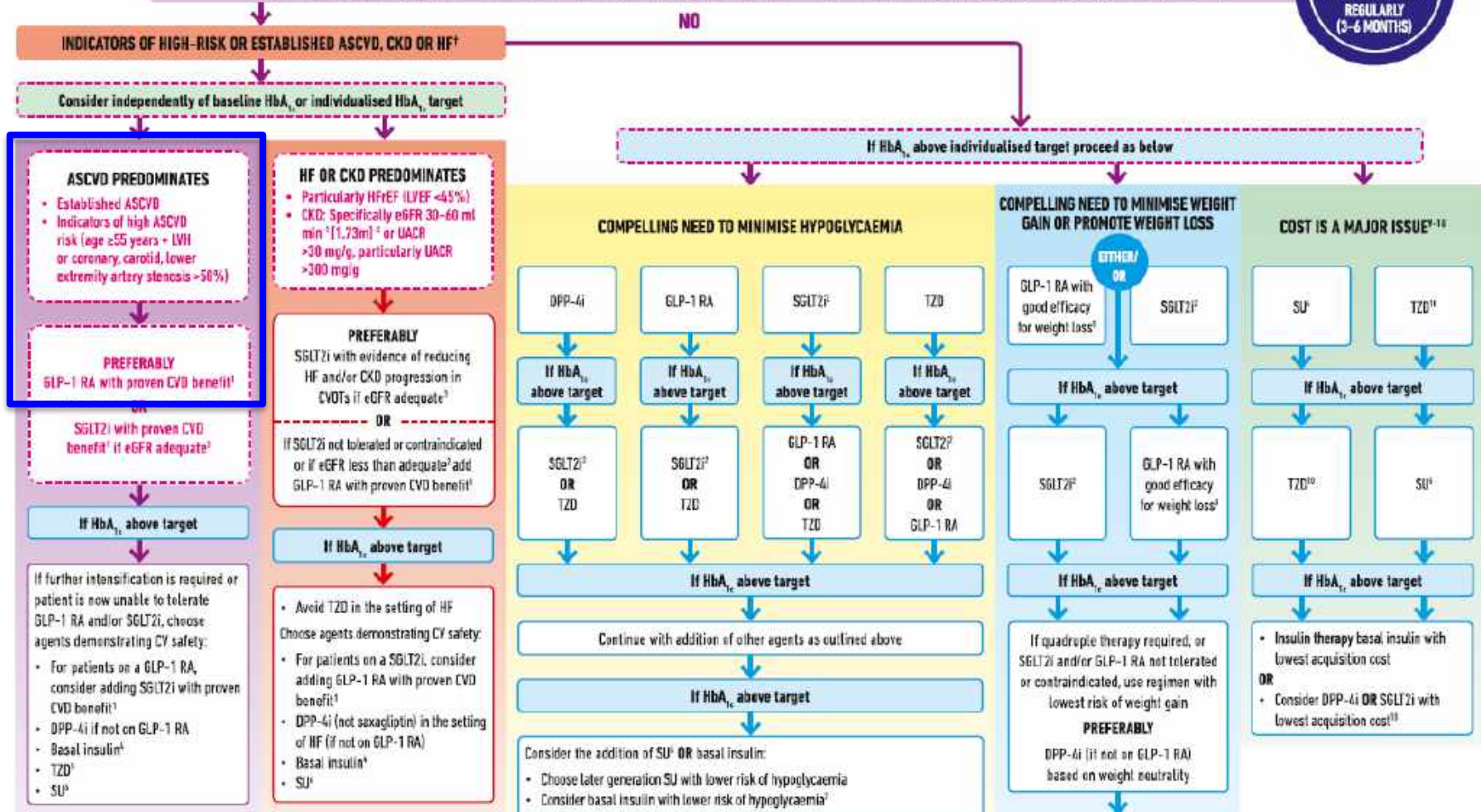
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GLUCOSE-LOWERING MEDICATION IN TYPE 2 DIABETES: OVERALL APPROACH



FIRST-LINE THERAPY IS METFORMIN AND COMPREHENSIVE LIFESTYLE (INCLUDING WEIGHT MANAGEMENT AND PHYSICAL ACTIVITY)




1. Proven CVD benefit means it has label indication of reducing CVD events.
 2. Be aware that SGLT2i labelling varies by region and individual agent with regard to indicated level of eGFR for initiation and continued use.
 3. Empagliflozin, canagliflozin and dapagliflozin have shown reduction in HF and to reduce CKD progression in CVOTs. Canagliflozin has primary renal outcome data from CRESCENDO. Dapagliflozin has primary heart failure outcome data from DAPA-HF.
 4. Degludec and U100 glargine have demonstrated CVD safety.
 5. Low dose may be better tolerated though less well studied for CVD effects.
 † Actioned wherever these become new clinical considerations regardless of background glucose-lowering medications.
 6. Choose later generation SU to lower risk of hypoglycaemia. Glimiperide has shown similar CV safety to DPP-4i.
 7. Degludec / glargine U300 / glargine U100 / detemir / NPH insulin.
 8. Semaglutide + liraglutide > dulaglutide + exenatide + lixisenatide.
 9. If no specific comorbidities (i.e. no established CVD, low risk of hypoglycaemia and lower priority to avoid weight gain or no weight-related comorbidities).
 10. Consider country- and region-specific cost of drugs. In some countries TZDs relatively more expensive and DPP-4i relatively cheaper.

LVM = Left Ventricular Hypertrophy; HFwEF = Heart Failure with reduced Ejection Fraction
 UACR = Urine Albumin-to-Creatinine Ratio; LVEF = Left Ventricular Ejection Fraction



Gennaio 2019: prescrizione del diabetologo

- Rinforzo indicazioni sullo stile di vita, in particolare interruzione del fumo
 - Raccomandazione di rivolgersi a un nutrizionista (il Servizio di Diabetologia non ha più dietista)
 - **Dulaglutide 0.75 mg s.c./settimana**, da incrementare, se tollerata, a 1.5 mg dopo un mese
- 

Maggio 2019: ricovero in Cardiologia per SCA-STEMI antero-settale e successiva angioplastica primaria su IVA media.

- **E.O.:** PA 115/70 mmHg, FC 60 R, paziente inquadrato in una **classe funzionale NYHA II**
- **ECG:** RS, FC 58 bpm, segni di pregressa necrosi in sede antero-settale
- **ECOCARDIOGRAMMA** (pre-dimissione): acinesia dell'apice in toto e del setto in sede medio-apicale; **FE 39%**.

- In corso di ricovero è stata sospesa terapia con metformina e dulaglutide ed impostato uno **schema insulinico basal-bolus**; la restante terapia farmacologica è stata modificata nel seguente modo:

Lansoprazolo 30 mg/die

Enalapril 20 mg/die

Furosemide 25 mg/die

Potassio canrenoato 25 mg/die

Metoprololo 100 mg ¼ cp x 2/die

Cardioaspirin 100 mg/die

Ticagrelor 90 mg 1cp x 2/die

Rosuvastatina 20 mg/die

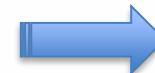
Il paziente viene rivisto in regime di post-ricovero: Giugno 2019
 Afferma di avere smesso di fumare.....

• **DIARIO GLICEMICO DOMICILIARE:**

Data	Prima di colazione	2 ore dopo colazione	Prima di pranzo	2 ore dopo pranzo	Prima di cena	2 ore dopo cena
13-05-2019			115	127		119
14-05	123		109	127	137	
15	131		120			135
16-	111	125			111	
17-	97		105	120		129
18-	102		122			
19	89		127	144	122	115
20	98	107	104			
21	95		116	126	131	97

• **Agli esami ematochimici :**

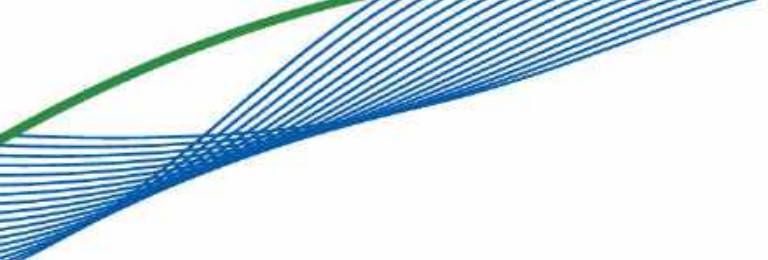

Esami del:	21/12/2018
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Creatinina	0.9 mg/dl
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Colesterolo tot	136 mg/dl
Colesterolo HDL	39 mg/dl
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cLDL	69 mg/dl



	20/05/2019
HbA1c	7.1% - 54 mmol/mol
Creatinina	1.0 mg/dl (confermata)
eGFR	80.0 ml/min/1.73 m²
ACR	10 mg/mmol
GOT/GPT	20/21 U/L
Colesterolo tot	147 mg/dl
Colesterolo HDL	38 mg/dl
Trigliceridi	145 mg/dl
cLDL	80 mg/dl



Δ=10 ml/min

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- Il paziente ha sostanzialmente raggiunto l'obiettivo glicemico, senza eventi avversi iatrogeni: è una indicazione a NON prendere in considerazione variazioni della terapia anti-iper-glicemizzante?
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Domanda 2

In considerazione del recente evento clinico, quale strategia terapeutica adotereste?

- a) mantenere terapia insulinica
- b) reintrodurre associazione con metformina e analogo recettoriale del GLP-1
- c) reintrodurre metformina sostituendo analogo recettoriale del GLP-1 con SGLT2i
- d) mantenere la sospensione di metformina e proseguire con analogo recettoriale del GLP-1

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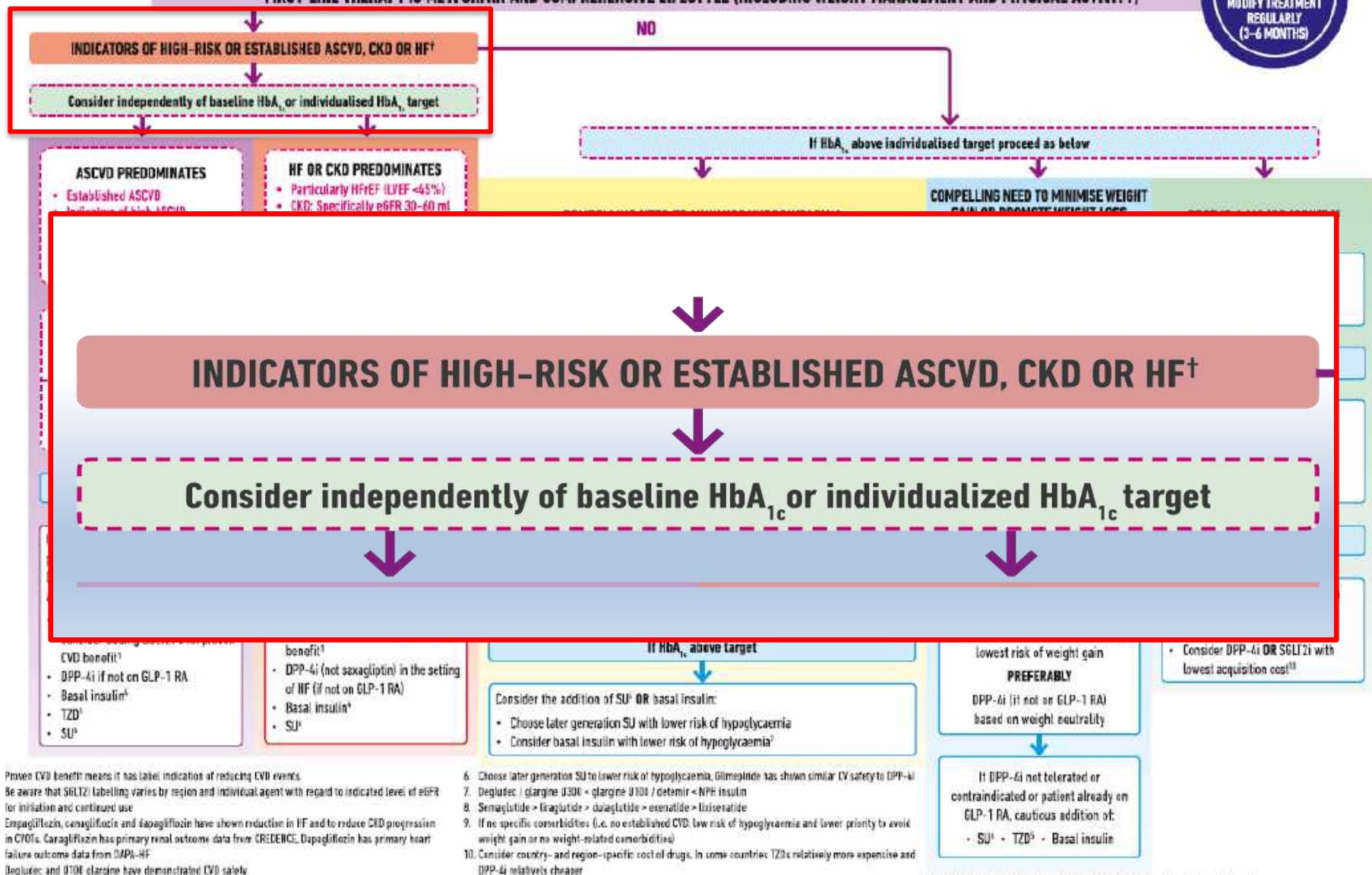
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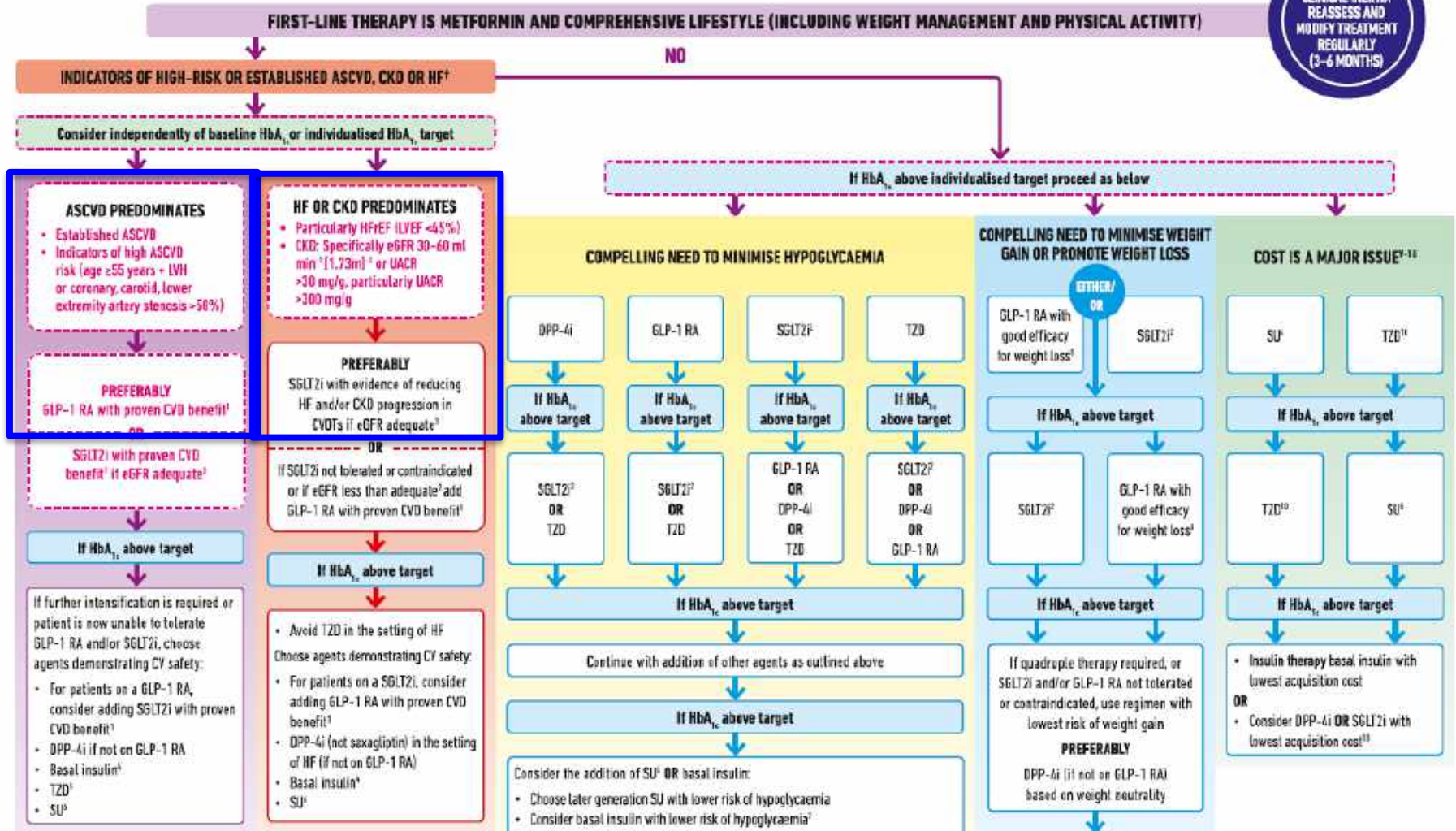


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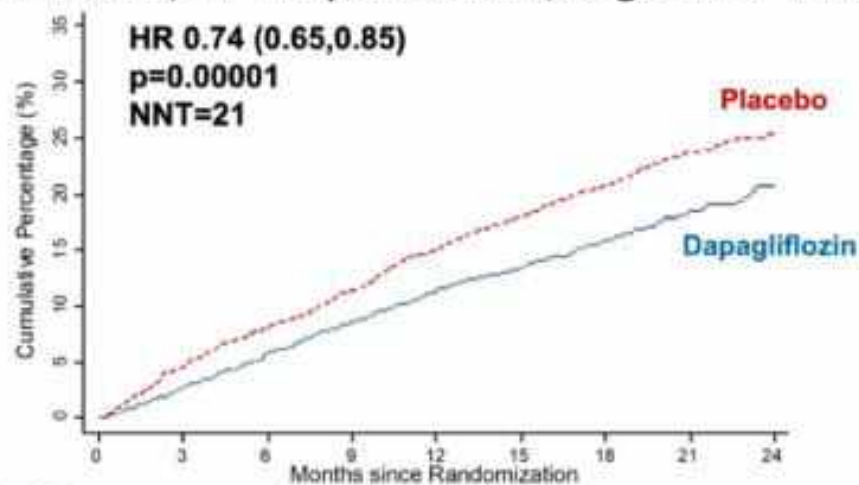
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Dapagliflozin in Patients With Heart Failure and Reduced Ejection Fraction - **DAPA-HF**

Primary composite outcome

CV Death/HF hospitalization/Urgent HF visit



Death from any cause
HR: 0.83 (0.71-0.97)
NNT: 63

Number at Risk	0	3	6	9	12	15	18	21	24
Dapagliflozin	2373	2305	2221	2147	2002	1560	1148	612	210
Placebo	2371	2298	2163	2075	1917	1478	1096	593	210

Il paziente viene rivisto in regime di post-ricovero: Giugno 2019

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- Agli esami ematochimici :

Esami del:	21/12/2018	20/05/2019
HbA1c	7.9% - 63 mmol/mol	7.1% - 54 mmol/mol
Creatinina	0.9 mg/dl	1.0 mg/dl (confermata)
eGFR	90.1 ml/min/1.73 m²	80.0 ml/min/1.73 m²
ACR	12 mg/mmol	10 mg/mmol
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Colesterolo tot	136 mg/dl	147 mg/dl
Colesterolo HDL	39 mg/dl	38 mg/dl
Trigliceridi	139 mg/dl	145 mg/dl
cLDL	69 mg/dl	80 mg/dl

Domanda 3

Quale strategia ipolipemizzante adotereste?

- a) mantenere terapia ipolipemizzante in atto
- b) potenziare terapia con introduzione di PCSK9i
- c) mantenere terapia ipolipemizzante in atto e raccomandare maggiore attenzione allo stile di vita
- d) potenziare terapia associando ezetimibe 10 mg.

Domanda 3

Quale strategia ipolipemizzante adotereste?


- a) mantenere terapia ipolipemizzante in atto
- b) potenziare terapia con introduzione di PCSK9i
- c) mantenere terapia ipolipemizzante in atto e raccomandare maggiore attenzione allo stile di vita
- d) **potenziare terapia associando ezetimibe 10 mg.**

Secondary Prevention of CV Disease

10.24 For patients with diabetes and atherosclerotic cardiovascular disease considered very high risk using specific criteria, if LDL cholesterol is ≥ 70 mg/dL on maximally tolerated statin dose, consider adding additional LDL-lowering therapy (such as ezetimibe or PCSK9 inhibitor).
A Ezetimibe may be preferred due to lower cost.



Giugno 2019: prescrizione del diabetologo

- Sospendere dulaglutide
 - Reintrodurre metformina a dose progressivamente crescente fino a 1000 mg x 2/die
 - Introdurre **dapagliflozin 10 mg 1 cp/die**
 - Introdurre **ezetimibe 10 mg 1 cp/die**
- 

- Controllo di Dicembre 2019:

Esami del:	21/12/2018	20/05/2019
HbA1c	7.9% - 63 mmol/mol	7.1% - 54 mmol/mol
creatinina	0.9 mg/dl	1.0 mg/dl
eGFR	90.1 ml/min/1.73 m ²	80.0 ml/min/1.73 m ²
ACR	12 mg/mmol	10 mg/mmol
GOT/GPT	14/16 U/L	20/21 U/L
Colesterolo tot	136 mg/dl	147 mg/dl
Colesterolo HDL	39 mg/dl	38 mg/dl
Trigliceridi	139 mg/dl	145 mg/dl
cLDL	69 mg/dl	80 mg/dl



11/12/2019
7 % - 53 mmol/mol
1.05 mg/dl
76 ml/min/1.73 m ²
10 mg/mmol
17/18 U/L
117 mg/dl
40 mg/dl
121 mg/dl
53 mg/dl

- Il paziente riferisce benessere generale e tollera bene il nuovo farmaco (**dapagliflozin 10 mg**);
- Ammette di avere ripreso a fumare, ma solo 2 sigarette al giorno (pasti principali...)
- Il compenso glicometabolico appare stabile;
- Il profilo lipidico appare migliorato con un valore di cLDL attualmente a target;
- La funzionalità renale è nella norma con microalbuminuria nota e stabile
- Ha eseguito **visita cardiologica di controllo** che mostrava stabilità del quadro clinico e buon compenso emodinamico con la terapia in atto, in esiti di cardiopatia ischemica

Grazie per l'attenzione

2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk

Very-high-risk	<p>People with any of the following: Documented ASCVD, either clinical or unequivocal on imaging. Documented ASCVD includes previous ACS (MI or unstable angina), stable angina, coronary revascularization (PCI, CABG, and other arterial revascularization procedures), stroke and TIA, and peripheral arterial disease. Unequivocally documented ASCVD on imaging includes those findings that are known to be predictive of clinical events such as significant plaque on coronary angiography or CT scan (multivessel coronary disease with major epicardial arteries having >50% stenosis on carotid ultrasound).</p> <p>DM with target organ damage,^a or at least three major risk factors, or early onset of T1DM of long duration (>20 years).</p> <p>Severe CKD (eGFR <30 mL/min/1.73 m²).</p> <p>A calculated SCORE ≥10% for 10-year risk of fatal CVD.</p> <p>FH with ASCVD or with another major risk factor.</p>
High-risk	<p>People with: Markedly elevated single risk factors, in particular TC >8 mmol/L (>310 mg/dL), LDL-C >4.9 mmol/L (>190 mg/dL), or BP ≥180/110 mmHg.</p> <p>Patients with FH without other major risk factors.</p> <p>Patients with DM without target organ damage,^a with DM duration ≥10 years or another additional risk factor.</p> <p>Moderate CKD (eGFR 30–59 mL/min/1.73 m²).</p> <p>A calculated SCORE ≥5% and <10% for 10-year risk of fatal CVD.</p>
Moderate-risk	<p>Young patients (T1DM <35 years; T2DM <50 years) with DM duration <10 years, without other risk factors. Calculated SCORE ≥1% and <5% for 10-year risk of fatal CVD.</p>
Low-risk	<p>Calculated SCORE <1% for 10-year risk of fatal CVD.</p>

Recommendations for the treatment of dyslipidaemias in diabetes mellitus

Recommendations	Class ^a	Level ^b
In patients with T2DM at very-high risk ^c , an LDL-C reduction of ≥50% from baseline and an LDL-C goal of <1.4 mmol/L (<55 mg/dL) is recommended. ^{34,418,432}	I	A
Statins are recommended in patients with T1DM who are at high or very-high risk. ⁴⁰⁷	I	A
Intensification of statin therapy should be considered before the introduction of combination therapy.	IIa	C
If the goal is not reached, statin combination with ezetimibe should be considered. ^{33,299}	IIa	B
Statin therapy is not recommended in premenopausal patients with diabetes who are considering pregnancy or are not using adequate contraception.	III	C
Statin therapy may be considered in both T1DM and T2DM patients aged ≤30 years with evidence of end organ damage and/or an LDL-C level >2.5 mmol/L, as long as pregnancy is not being planned.	IIb	C

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10. Cardiovascular Disease and Risk Management: *Standards of Medical Care in Diabetes—2020*

Recommendations

10.23 For patients of all ages with diabetes and atherosclerotic cardiovascular disease, high-intensity statin therapy should be added to lifestyle therapy. **A**

10.24 For patients with diabetes and atherosclerotic cardiovascular disease considered very high risk using specific criteria, if LDL cholesterol is ≥ 70 mg/dL on maximally tolerated statin dose, consider adding additional LDL-lowering therapy (such as ezetimibe or PCSK9 inhibitor). **A** Ezetimibe may be preferred due to lower cost.