



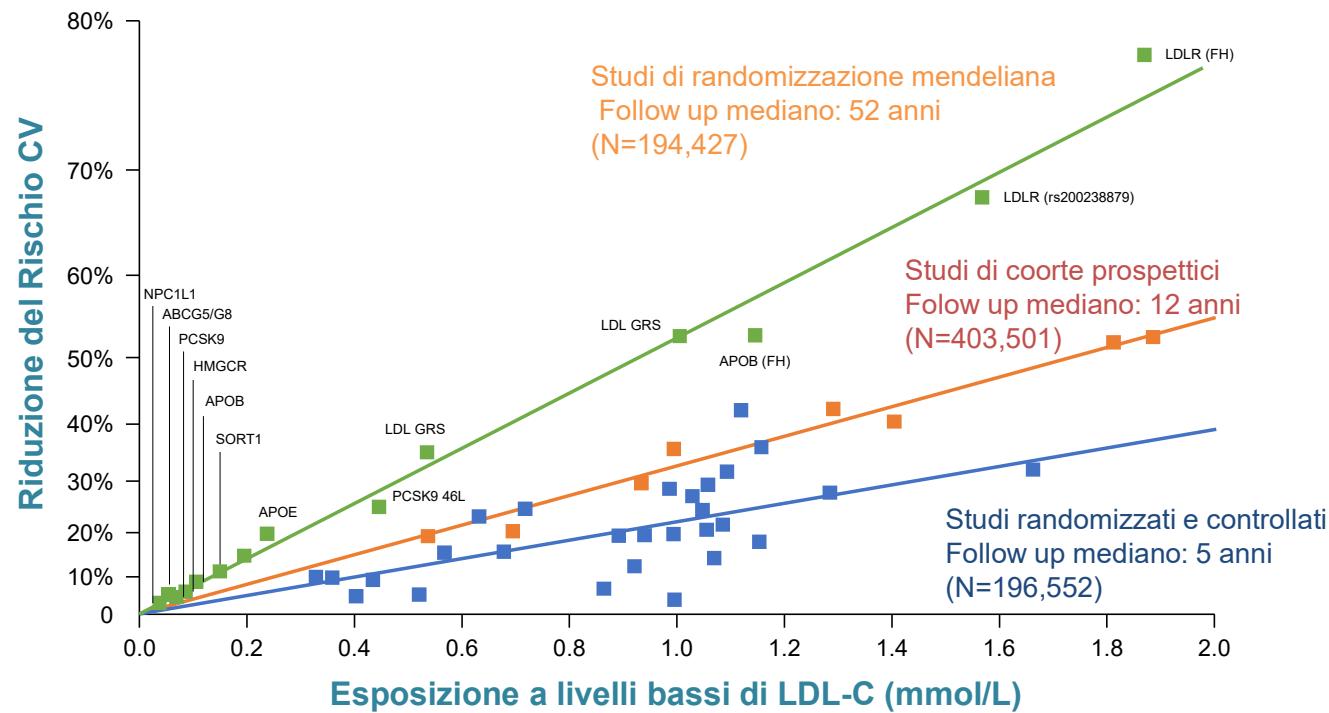
XV CONGRESSO REGIONALE AMD MOLISE

22 OTTOBRE 2022
HOTEL CENTRUM PALACE
CAMPOBASSO

TARGET LIPIDICI E PRESSORI: COME OTTENERLI

Dr Carlo Pedicino

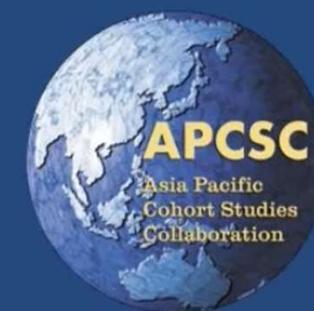
Associazione dei livelli LDL con il rischio CV



Ference BA et al. Eur Heart J. 2017.

Epidemiologically-predicted effects of reducing blood pressure and cholesterol

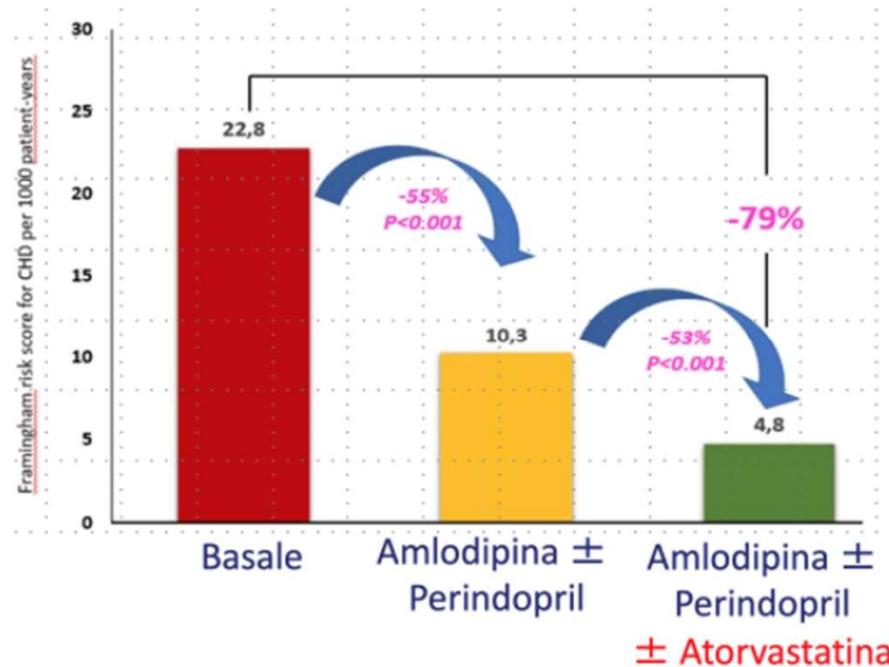
- 10 mmHg systolic (60-69 years)
 - ▶ 22% reduction in coronary disease
 - ▶ 38% reduction in stroke
- 1 mmol/l cholesterol
 - ▶ 32% reduction in coronary disease
 - ▶ 22% reduction in ischemic stroke
- Both (10 mmHg plus 1 mmol/l)
 - ▶ 47% reduction in coronary disease
 - ▶ 51% reduction in stroke



Potenziale riduzione del rischio di CAD ottenuti con la combinazione della terapia anti-ipertensiva e di quella ipocolesterolemizzante

ASCOT-BPLA e LLA

Stima della riduzione del rischio di CAD ottenuta durante il trial sulla base del rischio predetto al basale con Framingham risk score



Sever et al. Lancet 2003

ESC/EAS guidelines on the management of dyslipidemias

2019

ESC + EASD

Guidelines on diabetes, pre-diabetes, and cardiovascular diseases

CV RISK CATEGORIES

2019

Very-high-risk

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 two major epicardial arteries having >50% stenosis), or on carotid ultrasound.

DM with target organ damage,^a or at least three major risk factors, or early onset of T1DM of long duration (>20 years).

Severe CKD (eGFR <30 mL/min/1.73 m²).

A calculated SCORE ≥10% for 10-year risk of fatal CVD.

FH with ASCVD or with another major risk factor.

2016

Very high-risk

Subjects with any of the following:

- Documented cardiovascular disease (CVD), clinical or unequivocal on imaging. Documented CVD includes previous myocardial infarction (MI), acute coronary syndrome (ACS), coronary revascularisation (percutaneous coronary intervention (PCI), coronary artery bypass graft surgery (CABG)) and other arterial revascularization procedures, stroke and transient ischaemic attack (TIA), and peripheral arterial disease (PAD). Unequivocally documented CVD on imaging is what has been shown to be strongly predisposed to clinical events, such as significant plaque on coronary angiography or carotid ultrasound.
- DM with target organ damage such as proteinuria or with a major risk factor such as smoking, hypertension or dyslipidaemia.
- Severe CKD (GFR <30 mL/min/1.73 m²).
- A calculated SCORE ≥10% for 10-year risk of fatal CVD.

CV RISK CATEGORIES

2019

**Rischio
molto
alto**

il DM con danno d'organo o almeno tre fattori di rischio maggiori o DMT1 ad esordio precoce e durata maggiore di 20 aa

CV RISK CATEGORIES 2019

2019		2016	
High-risk	People with: Markedly elevated single risk factors, in particular TC $>8 \text{ mmol/L}$ ($>310 \text{ mg/dL}$), LDL-C $>4.9 \text{ mmol/L}$ ($>190 \text{ mg/dL}$), or BP $\geq 180/110 \text{ mmHg}$. Patients with FH without other major risk factors. Patients with DM without target organ damage, ^a with DM duration ≥ 10 years or another additional risk factor. Moderate CKD (eGFR 30–59 mL/min/1.73 m ²). A calculated SCORE $\geq 5\%$ and $< 10\%$ for 10-year risk of fatal CVD.	High-risk	Subjects with: <ul style="list-style-type: none">Markedly elevated single risk factors, in particular cholesterol $>8 \text{ mmol/L}$ ($>310 \text{ mg/dL}$) (e.g. in familial hypercholesterolaemia) or BP $\geq 180/110 \text{ mmHg}$.Most other people with DM (some young people with type 1 diabetes may be at low or moderate risk).Moderate CKD (GFR 30–59 mL/min/1.73 m²).A calculated SCORE $\geq 5\%$ and $< 10\%$ for 10-year risk of fatal CVD.
Moderate-risk	Young patients (T1DM < 35 years; T2DM < 50 years) with DM duration < 10 years, without other risk factors. Calculated SCORE $\geq 1\%$ and $< 5\%$ for 10-year risk of fatal CVD.	Moderate-risk	SCORE is $\geq 1\%$ and $< 5\%$ for 10-year risk of fatal CVD.
Low-risk		Low-risk	
Calculated SCORE $< 1\%$ for 10-year risk of fatal CVD.		SCORE $< 1\%$ for 10-year risk of fatal CVD.	

CV RISK CATEGORIES

2019

Rischio
alto

Giovani pazienti (DMT1 <35aa; DMT2 <50aa) con durata del DM maggiore di 10 aa senza altro fattore di rischio aggiunto

CV RISK CATEGORIES

2019

Rischio
moderato

**Paziente con DM senza danno d'organo con
durata del DM minore di 10 aa o un altro
fattore di rischio aggiunto**

Recommendations for the management of dyslipidaemia with lipid-lowering drugs (I)

Recommendations	Class	Level
<ul style="list-style-type: none">• Targets		
<ul style="list-style-type: none">• In patients with T2DM at moderate CV risk, an LDL-C target of <2.5 mmol/L (<100 mg/dL) is recommended.	• I	• A
<ul style="list-style-type: none">• In patients with T2DM at high CV risk, an LDL-C target of <1.8 mmol/L (<70 mg/dL) <u>or</u> an LDL-C reduction of at least 50% is recommended.	• I	• A
<ul style="list-style-type: none">• In patients with T2DM at very high CV risk, an LDL-C target of <1.4 mmol/L (<55 mg/dL) <u>or</u> an LDL-C reduction of at least 50% is recommended	• I	• B
<ul style="list-style-type: none">• In patients with T2DM, a secondary goal of a non-HDL-C target of <2.2 mmol/L (<85 mg/dL) in very high CV risk patients, and <2.6 mmol/L (<100 mg/dL) in high CV risk patients, is recommended.	• I	• B

Colesterolo LDL

- 55 mg/dl RISCHIO MOLTO ALTO
- 70 mg/dl RISCHIO ALTO
- 100 mg/dl RISCHIO MODERATO

Terapia di scelta

Recommendations for pharmacological low-density lipoprotein cholesterol lowering (1)



Recommendations	Class	Level
<p>It is recommended to prescribe a high-intensity statin up to the highest tolerated dose to reach the goals^c set for the specific level of risk.</p>	I	A
<p>If the goals^c are not achieved with the maximum tolerated dose of statin, combination with ezetimibe is recommended.</p>	I	B
<p>For secondary prevention, patients at very-high risk not achieving their goal^c on a maximum tolerated dose of statin and ezetimibe, a combination with a PCSK9 inhibitor is recommended.</p>	I	A

Qual è la riduzione di colesterolo LDL che possiamo ottenere con questa terapia?



Intensity of lipid lowering treatment	
Treatment	Average LDL-C reduction
Moderate intensity statin	≈ 30%
High intensity statin	≈ 50%
High intensity statin plus ezetimibe	≈ 65% (highlighted)
PCSK9 inhibitor	≈ 60%
PCSK9 inhibitor plus high intensity statin	≈ 75%
PCSK9 inhibitor plus high intensity statin plus ezetimibe	≈ 85%

... ezetimibe?

- Comment on the article “*Long-term efficacy and safety of moderate-intensity statin with ezetimibe combination therapy versus high-intensity statin monotherapy in patients with atherosclerotic cardiovascular disease (RACING): a randomized, open-label, non-inferiority trial*” published in *Lancet*; doi: 10.1016/S0140-6736(22)00916-3.

... ezetimibe?



European Heart Journal (2022) **00**, 1–2
European Society of Cardiology <https://doi.org/10.1093/eurheartj/ehac502>



Weekly Journal Scan

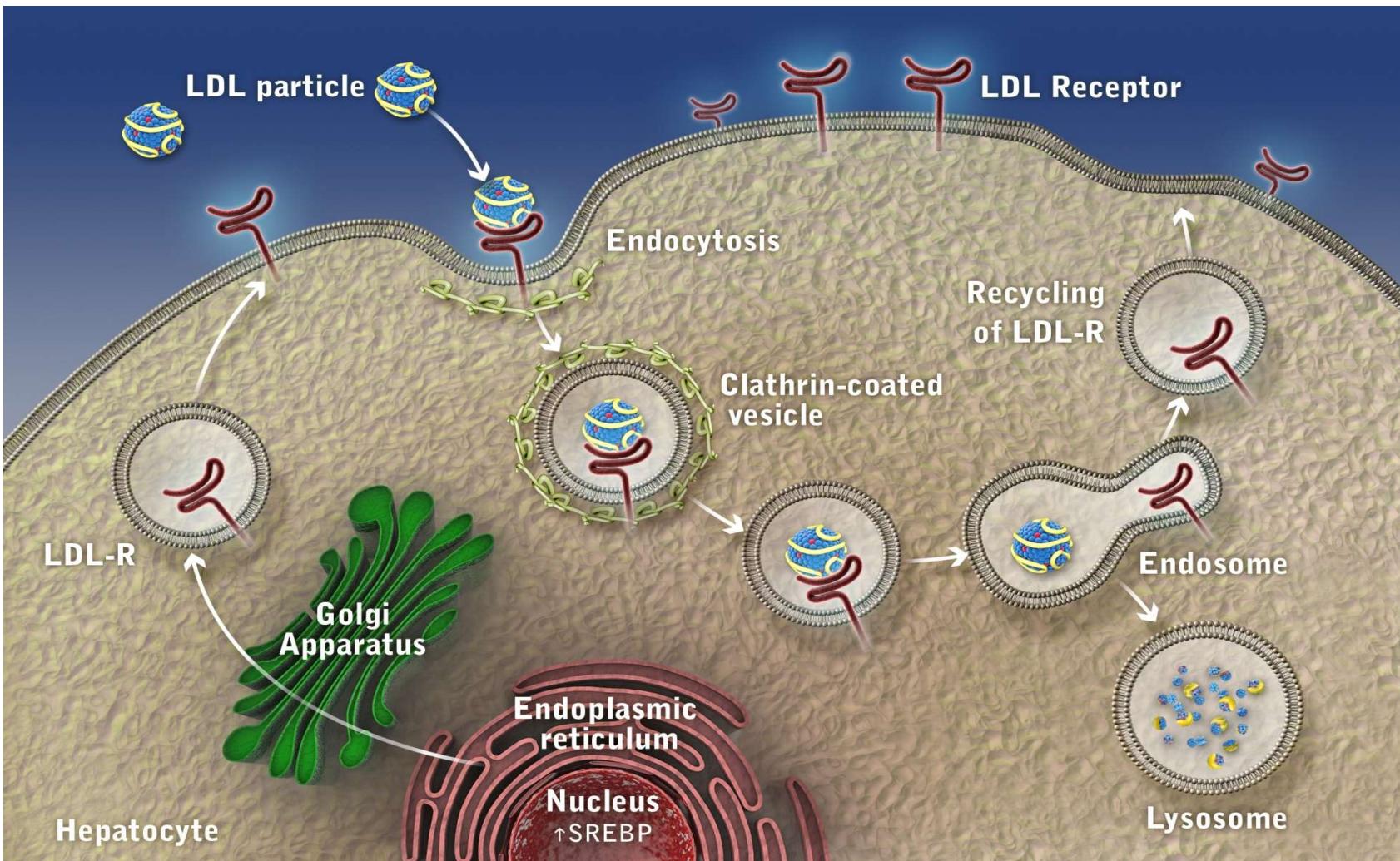
Combination of ezetimibe and moderate-intensity statin for patients with atherosclerotic cardiovascular disease: a paradigm shift in lipid management landscape

Daniela Pedicino ^{1*} and Massimo Volpe ²

¹Department of Cardiovascular Medicine, Fondazione Policlinico Universitario A. Gemelli—IRCCS, Largo A. Gemelli 8, Rome 00168, Italy; and ²Cardiology Department, Sapienza University of Rome, Sant'Andrea Hospital, Via di Grottarossa 1035-1039, Rome 00189, Italy

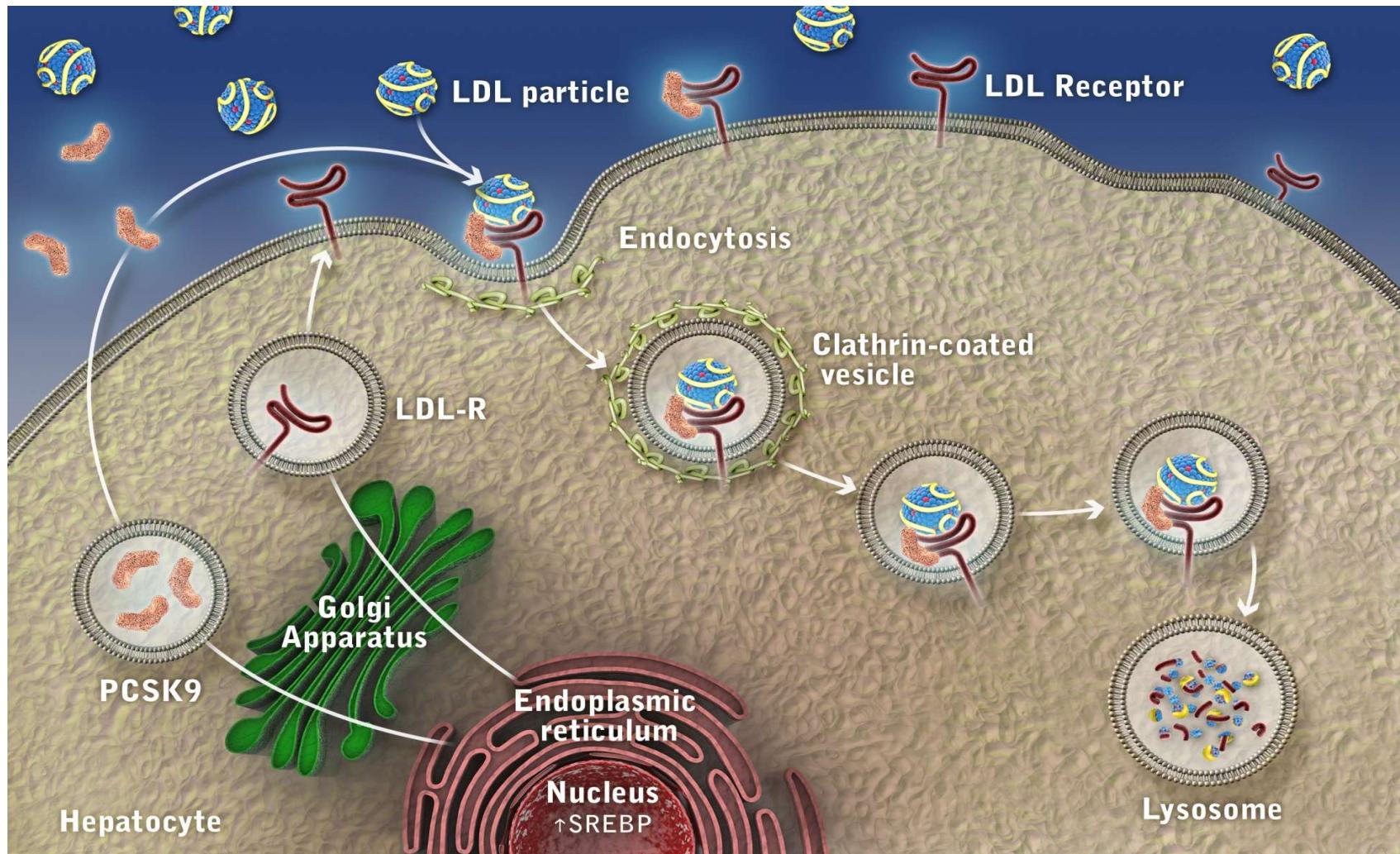
Comment on the article 'Long-term efficacy and safety of moderate-intensity statin with ezetimibe combination therapy vs. high-intensity statin monotherapy in patients with atherosclerotic cardiovascular disease (RACING): a randomized, open-label, non-inferiority trial', published in *Lancet*, [https://doi.org/10.1016/S0140-6736\(22\)00916-3](https://doi.org/10.1016/S0140-6736(22)00916-3).

LDL Receptor Function and Life Cycle



Adapted from Catapano & Papadopoulos *Atherosclerosis* 2013;228:18–28

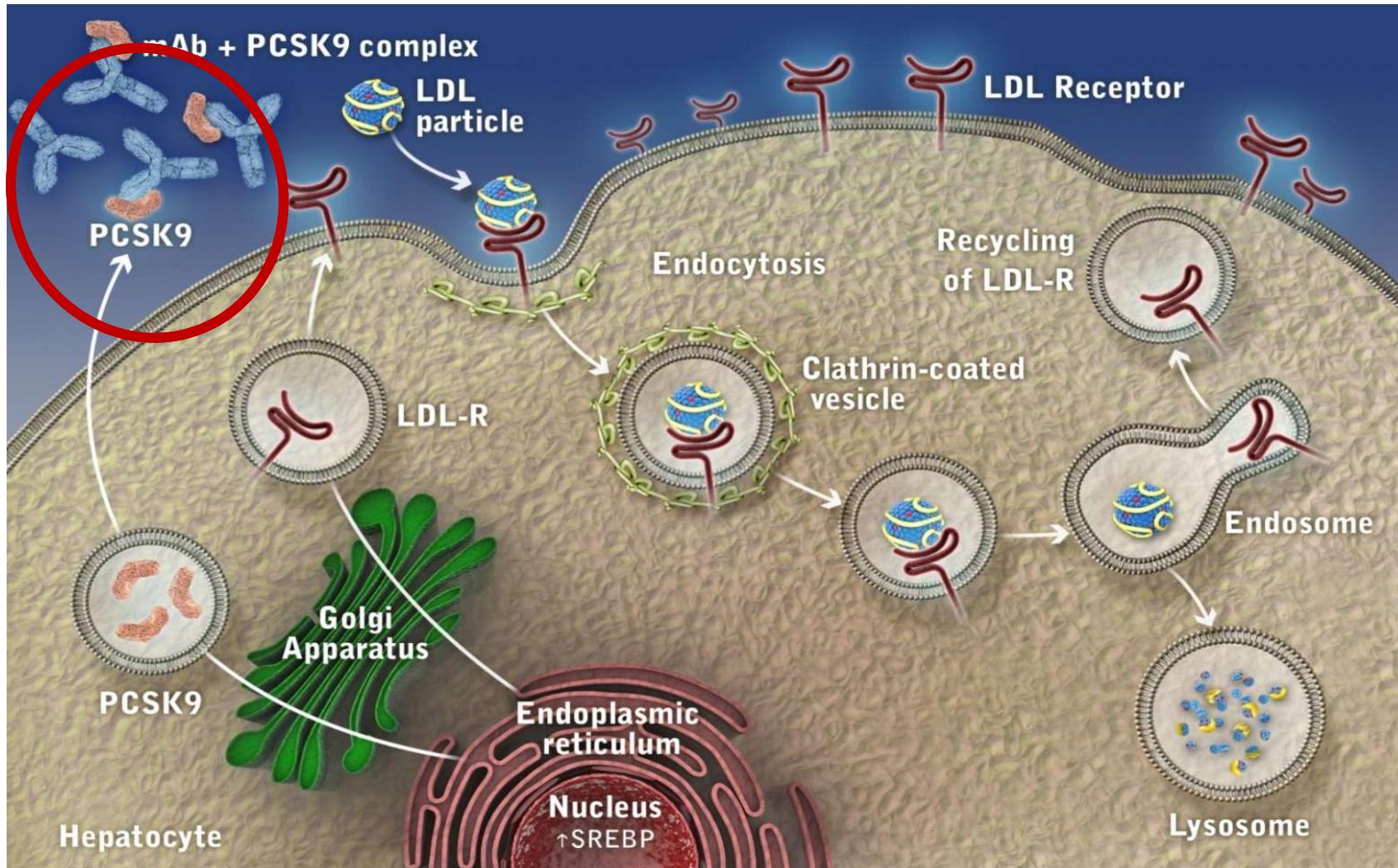
Role of PCSK9 in the Regulation of LDL Receptor Expression



1

Adapted from Catapano & Papadopoulos *Atherosclerosis* 2013;228:18-28

Impact of a PCSK9 Monoclonal Antibody on LDL Receptor Expression



Adapted from Catapano & Papadopoulos *Atherosclerosis* 2013;228:18–28

PCSK9

- **ANTICORPI MONOCLONALI** (Alirocumab Sanofi-Regeneron; Evolocumab Amgen - Anticorpo anti-PCSK9)
- **SILENZIAMENTO GENICO** (Inclisiran Alnylam Silenziamento genico mediante siRNA – studio ORION-11)
- **VACCINO** (Pfizer fase3)

DISLIPIDEMIA ATEROGENICA

- Colesterolo totale normale o alto
- Bassi valori di HDL
- Alti valori di trigliceridi

DISLIPIDEMIA ATEROGENICA

- Eccesso di particelle non LDL
- Small very LDL (VLDL)
- Intermediate density lipoprotein (IDL)
- Small and dense LDL (Id)

Colesterolo non HDL

- 85 mg/dl RISCHIO MOLTO ALTO
- 100 mg/dl RISCHIO ALTO

P.A.

Cosa cambia?

ESC/ESH 2018

Category	SBP (mmHg)		DBP (mmHg)
Office BP ^a	≥ 140	and/or	≥ 90
Ambulatory BP			
Daytime (or awake) mean	≥ 135	and/or	≥ 85
Night-time (or asleep) mean	≥ 120	and/or	≥ 70
24 h mean	≥ 130	and/or	≥ 80
Home BP mean	≥ 135	and/or	≥ 85

CLASSIFICAZIONE P.A. AMBULATORIALE

Table 3 Classification of office blood pressure^a and definitions of hypertension grade^b

Category	Systolic (mmHg)		Diastolic (mmHg)
Optimal	<120	and	<80
Normal	120–129	and/or	80–84
High normal	130–139	and/or	85–89
Grade 1 hypertension	140–159	and/or	90–99
Grade 2 hypertension	160–179	and/or	100–109
Grade 3 hypertension	≥180	and/or	≥110
Isolated systolic hypertension ^b	≥140	and	<90

BP = blood pressure; SBP = systolic blood pressure.

^aBP category is defined according to seated clinic BP and by the highest level of BP, whether systolic or diastolic.

^bIsolated systolic hypertension is graded 1, 2, or 3 according to SBP values in the ranges indicated.

The same classification is used for all ages from 16 years.

140/90 mmHg

Limite massimo da non superare in
genere e nelle rilevazioni ambulatoriali

135/85 mmHg

Automisurazione

130/80 mmHg

- Diabete mellito
- Cardiopatia ischemica
- Malattia renale cronica

> 150 mmHg
< 90 mm Hg

Ipertensione sistolica isolata
dell'anziano

120/70 nmHg

- Holter pressorio (profilo dipper)

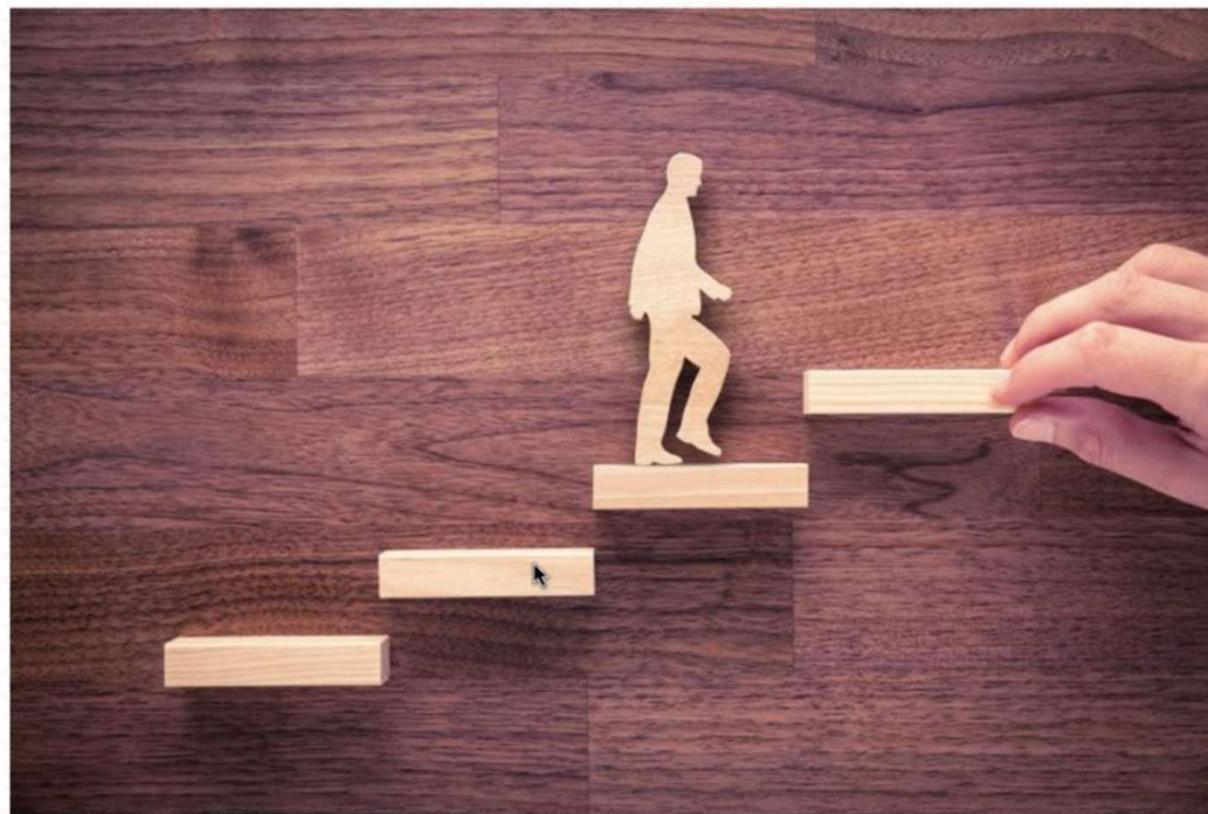
COSA CAMBIA ?

Changes in recommendations	
2013	2018
Diagnosis Office BP is recommended for screening and diagnosis of hypertension.	Diagnosis It is recommended to base the diagnosis of hypertension on: <ul style="list-style-type: none"> • Repeated office BP measurements; or • Out-of-office BP measurement with ABPM and/or HBPM if logically and economically feasible.
Treatment thresholds Highnormal BP (130–139/85–89 mmHg): Unless the necessary evidence is obtained, it is not recommended to initiate antihypertensive drug therapy at high-normal BP.	Treatment thresholds Highnormal BP (130–139/85–89 mmHg): Drug treatment may be considered when CV risk is very high due to established CVD, especially CAD.
Treatment thresholds Treatment of low-risk grade 1 hypertension: Initiation of antihypertensive drug treatment should also be considered in grade 1 hypertensive patients at low-moderate-risk, when BP is within this range at several repeated visits or elevated by ambulatory BP criteria, and remains within this range despite a reasonable period of time with lifestyle measures.	Treatment thresholds Treatment of low-risk grade 1 hypertension: In patients with grade 1 hypertension at low-moderate-risk and without evidence of HMOD, BP-lowering drug treatment is recommended if the patient remains hypertensive after a period of lifestyle intervention.
Treatment thresholds Older patients Antihypertensive drug treatment may be considered in the elderly (at least when younger than 80 years) when SBP is in the 140–159 mmHg range, provided that antihypertensive treatment is well tolerated.	Treatment thresholds Older patients BP-lowering drug treatment and lifestyle intervention is recommended in fit older patients (>65 years but not >80 years) when SBP is in the grade 1 range (140–159 mmHg), provided that treatment is well tolerated.
BP treatment targets An SBP goal of <140 mmHg is recommended.	BP treatment targets <ul style="list-style-type: none"> • It is recommended that the first objective of treatment should be to lower BP to <140/90 mmHg in all patients and, provided that the treatment is well tolerated, treated BP values should be targeted to 130/80 mmHg or lower in most patients. • In patients <65 years it is recommended that SBP should be lowered to a BP range of 120–129 mmHg in most patients.

COSA CAMBIA ?

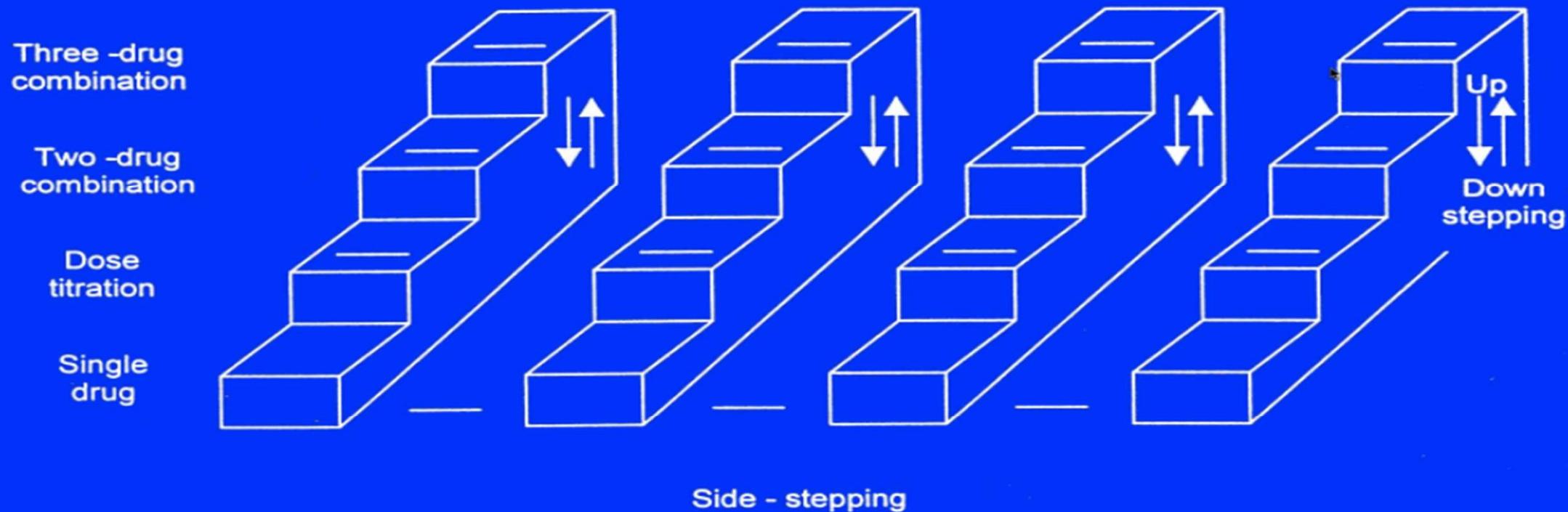
BP treatment targets in older patients (65–80 years)	BP treatment targets in older patients (65–80 years)		
An SBP target of between 140–150 mmHg is recommended for older patients (65–80 years).	In older patients (≥ 65 years), it is recommended that SBP should be targeted to a BP range of 130–139 mmHg.		
BP treatment targets in patients aged over 80 years	BP treatment targets in patients aged over 80 years		
An SBP target between 140–150 mmHg should be considered in people older than 80 years, with an initial SBP ≥ 160 mmHg, provided that they are in good physical and mental condition.	An SBP target range of 130–139 mmHg is recommended for people older than 80 years, if tolerated.		
DBP targets	DBP targets		
A DBP target of <90 mmHg is always recommended, except in patients with diabetes, in whom values <85 mmHg are recommended.	A DBP target of <80 mmHg should be considered for all hypertensive patients, independent of the level of risk and comorbidities.		
Initiation of drug treatment	Initiation of drug treatment		
Initiation of antihypertensive therapy with a two-drug combination may be considered in patients with markedly high baseline BP or at high CV risk.	It is recommended to initiate an antihypertensive treatment with a two-drug combination, preferably in a SPC. The exceptions are frail older patients and those at low risk and with grade 1 hypertension (particularly if SBP is <150 mmHg).		
Resistant hypertension	Resistant hypertension		
Mineralocorticoid receptor antagonists, amiloride, and the alpha-1 blocker doxazosin should be considered if no contraindication exists.	Recommended treatment of resistant hypertension is the addition of low-dose spironolactone to existing treatment, or the addition of further diuretic therapy if intolerant to spironolactone, with either eplerenone, amiloride, higher-dose thiazide/thiazide-like diuretic or a loop diuretic, or the addition of bisoprolol or doxazosin.		
Device-based therapy for hypertension	Device-based therapy for hypertension		
In case of ineffectiveness of drug treatment, invasive procedures such as renal denervation and baroreceptor stimulation may be considered.	Use of device-based therapies is not recommended for the routine treatment of hypertension, unless in the context of clinical studies and RCTs, until further evidence regarding their safety and efficacy becomes available.		
Recommendation Grading			
Grade I	Grade IIa	Grade IIb	Grade III

BPM = ambulatory blood pressure monitoring; BP = blood pressure; CAD = coronary artery disease; CV = cardiovascular; CVD = cardiovascular disease; DBP = diastolic blood pressure; HBPM = home blood pressure monitoring; HMOD = hypertension-mediated organ damage; RCT = randomized controlled trial; SBP = systolic blood pressure; SPC = single-pill combination.



What tools can help us in the future?

MONOTERAPIA: PERCHE'



Sequence of treatment



Initial therapy
Dual combination



Step 2
Triple combination



Step 3
Triple combination +
spironolactone or
other drug

eplerenone
amiloride

high-dose thiazide-like
loop diuretic
bisoprolol
doxazosin

ACEi or ARB + CCB or diuretic

Consider monotherapy in low-risk
grade 1 hypertension or in very old
(≥ 80 years) or frailer patients

ACEi or ARB + CCB + diuretic

Resistant hypertension
Add spironolactone (25–50 mg o.d.)
or other diuretic, alpha-blocker or beta-blocker

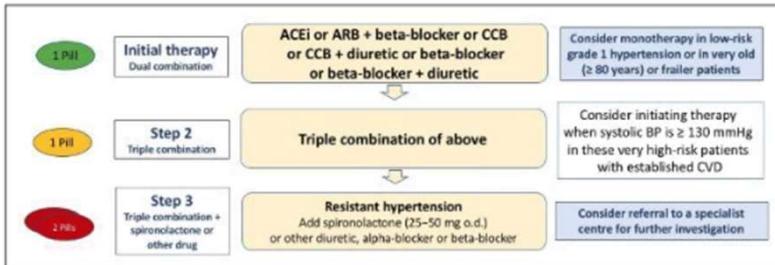
Consider referral to a specialist
centre for further investigation

Beta-blockers

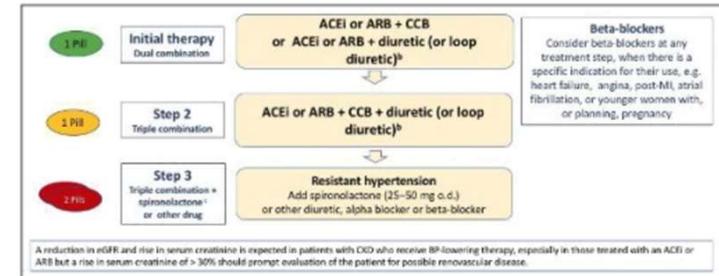
Consider beta-blockers at any treatment step, when there is a specific indication for their use, e.g. heart failure, angina, post-MI, atrial fibrillation, or younger women with, or planning, pregnancy

Drug-treatment strategies

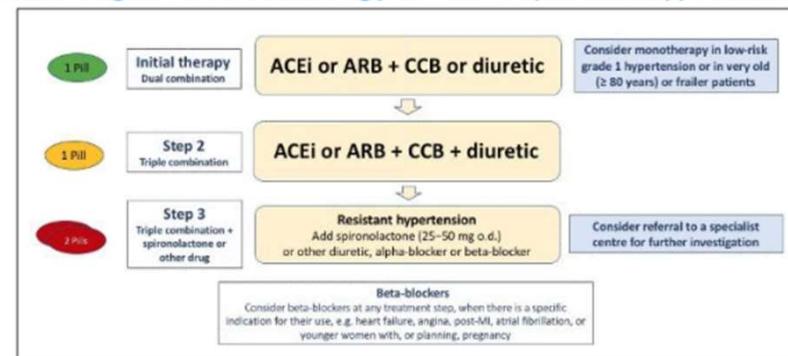
Hypertension and CAD



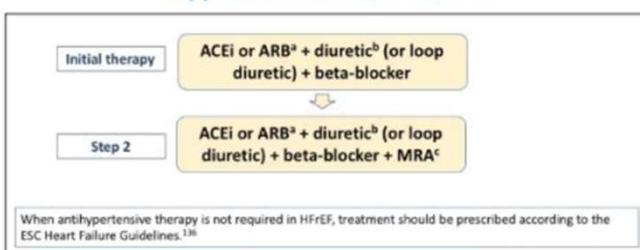
Hypertension and CKD



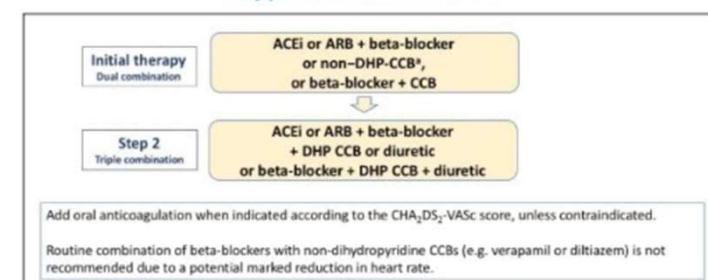
Core drug-treatment strategy for uncomplicated hypertension



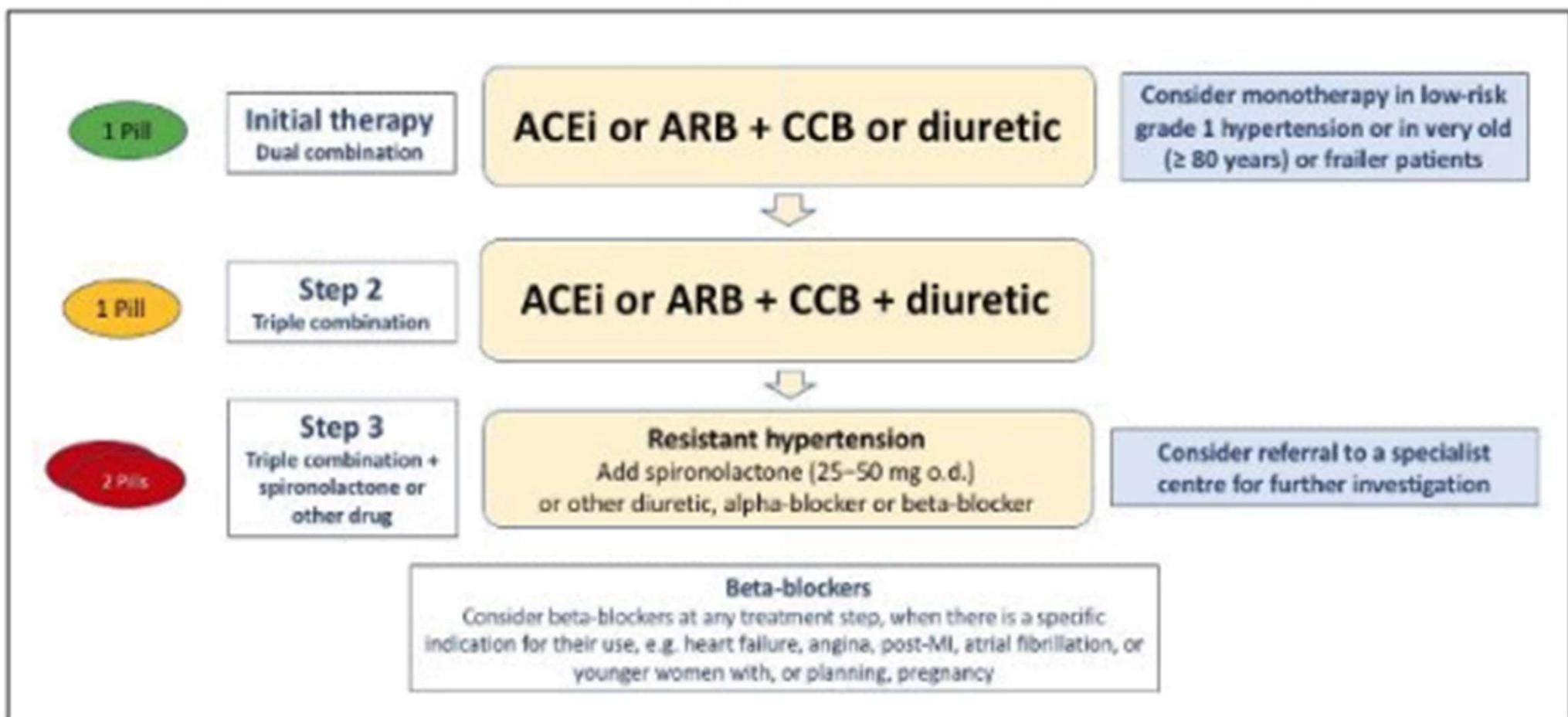
Hypertension and HRrEF



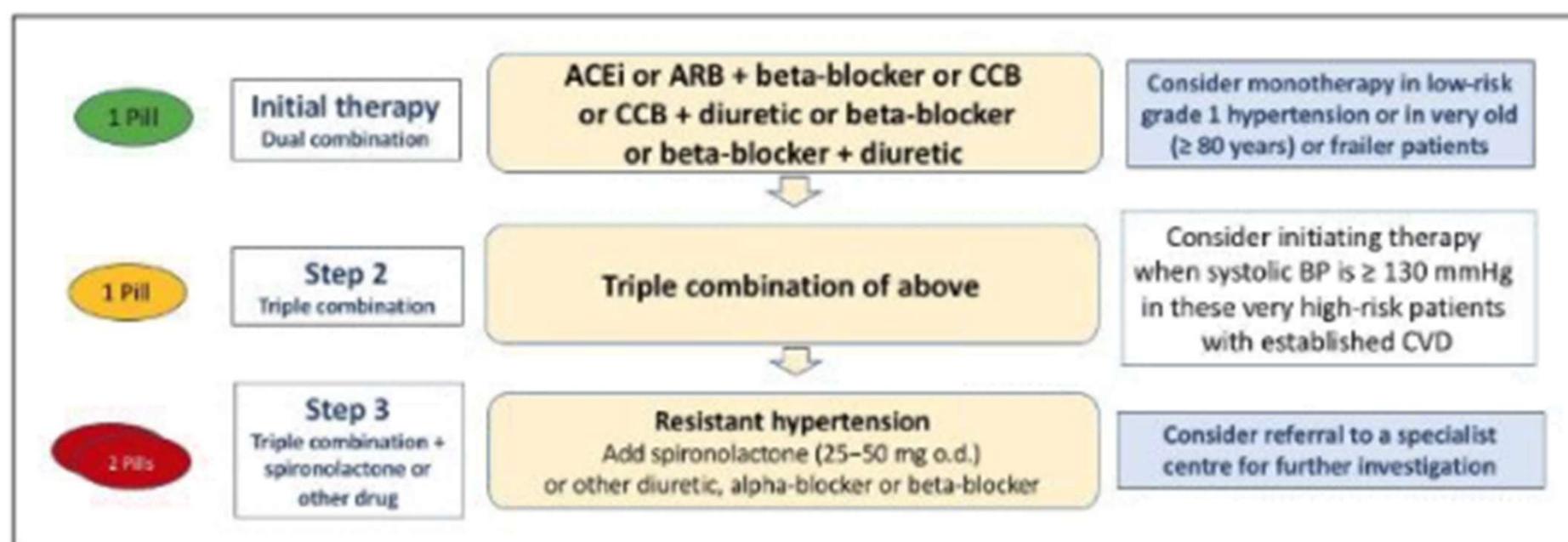
Hypertension and AF



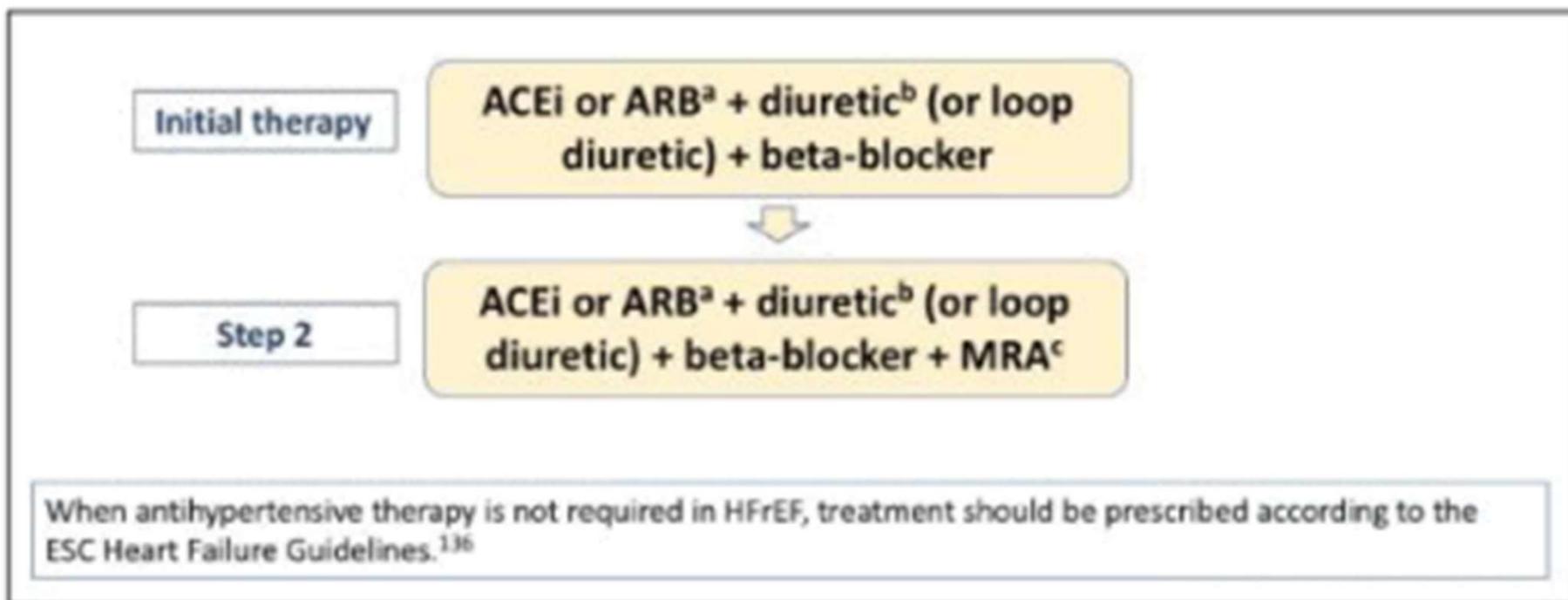
Core drug-treatment strategy for uncomplicated hypertension



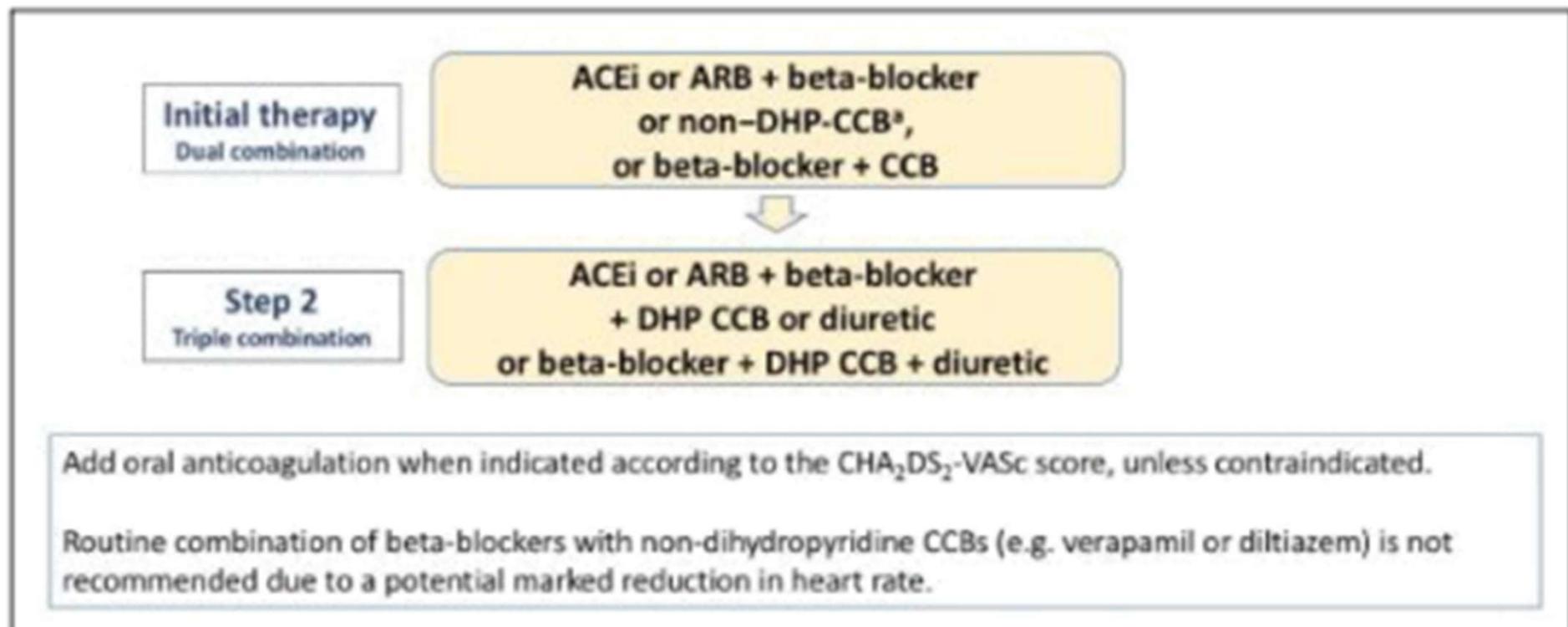
Iipertensione e CAD



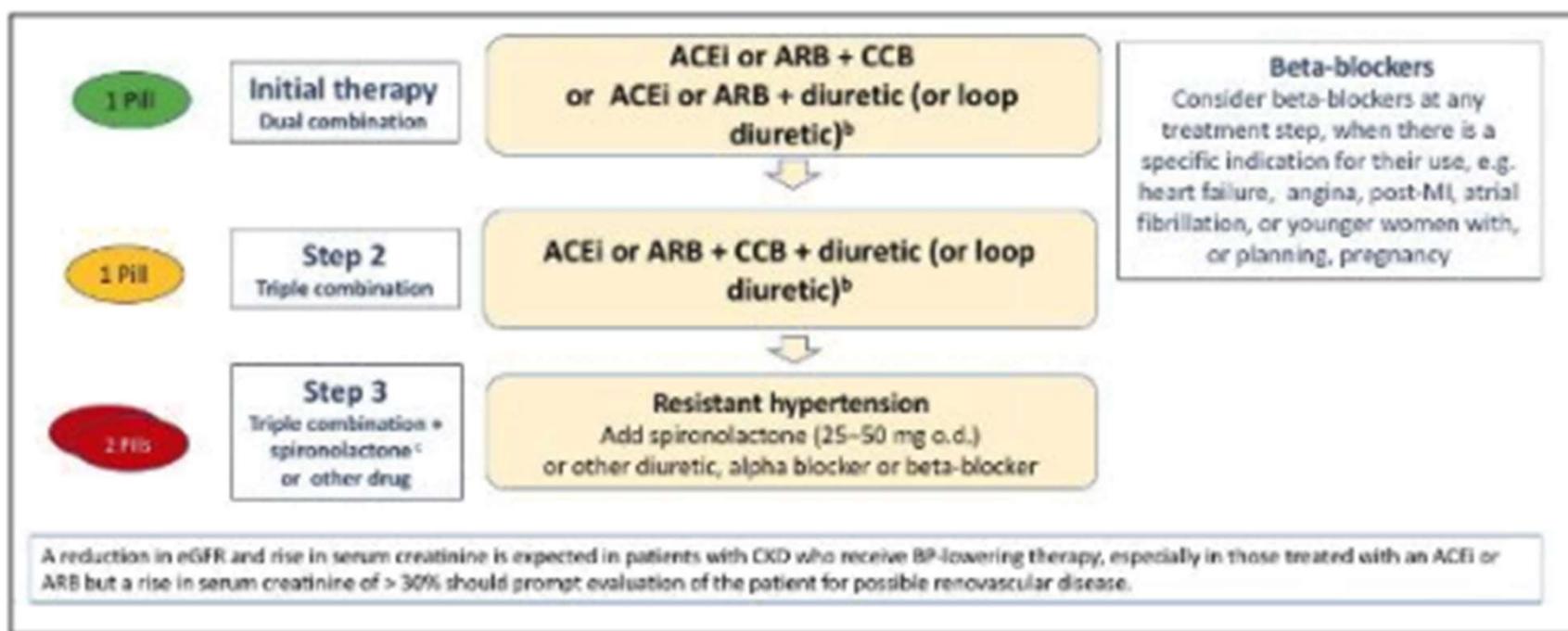
Iipertensione e HFrEF



Iipertensione e FA



Iipertensione e CKD



GRAZIE
PER
L'ATTEN-
ZIONE



Conclusioni (1):

- La metformina può essere prescritta anche in condizioni di alterata glicemia a digiuno
- La metformina NON SEMPRE rappresenta il farmaco di prima scelta nel DMT2

Conclusioni (2):

- Le sulfoniluree e le glinidi non sono raccomandate nella cura del diabete mellito
- Il pioglitazone non è raccomandato nello scompenso cardiaco e nella insufficienza renale

Conclusioni (3):

- Le glifozine (SGLT2i) sono raccomandate nella cura del diabete mellito tipo 2 con scompenso cardiaco e/o con pregressi eventi cardio-vascolari
- Le incretine (GLP1RA) sono raccomandate nella cura del diabete mellito tipo 2 con pregressi eventi cardio-vascolari