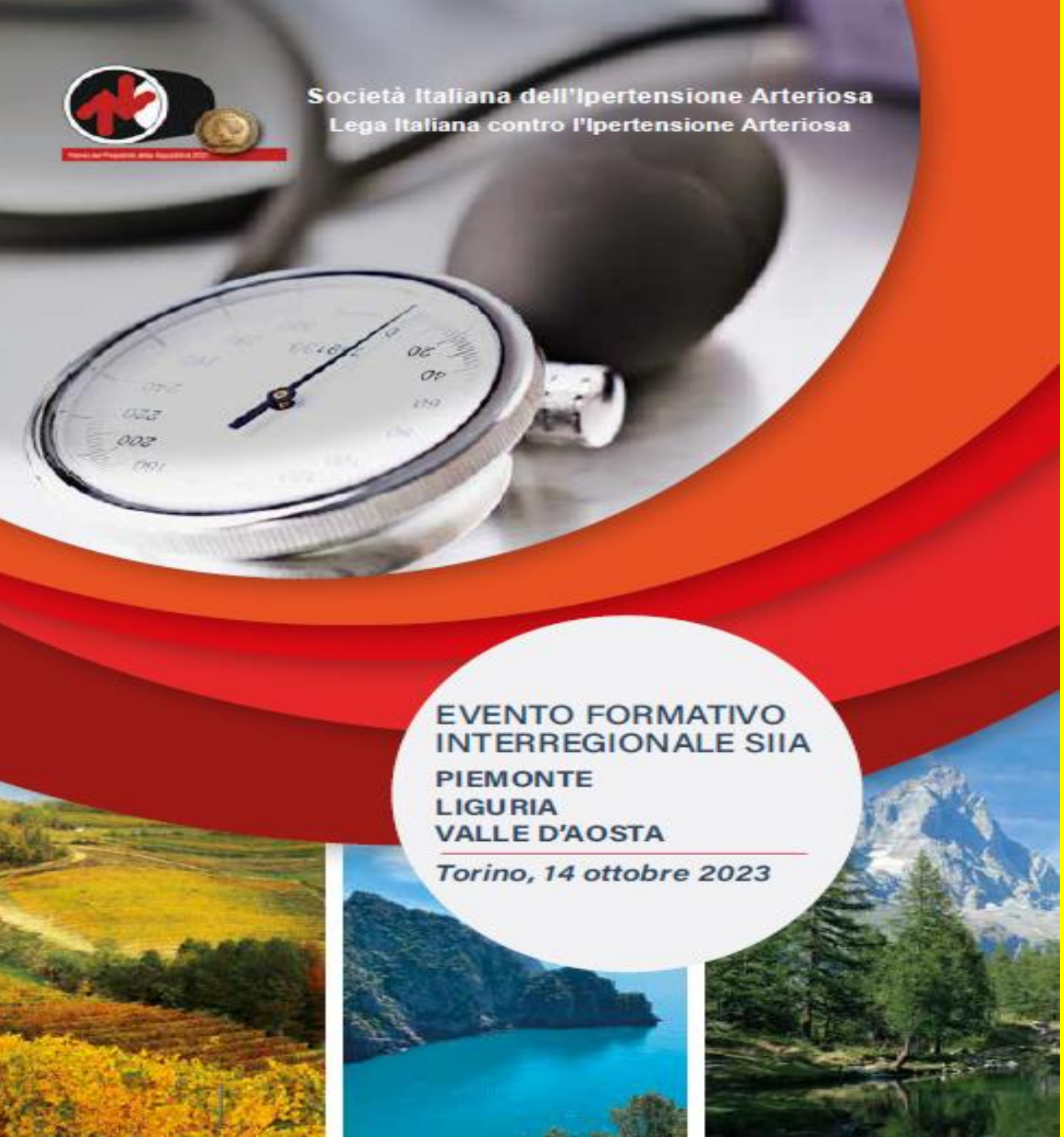


Protezione renale nell'iperteso nefropatico

Alessandro Domenico Quercia

MD, PhD
Nefrologia e Dialisi
ASLCN1
Segretario GdP AKI e Terapie Extracorporee in Area critica
Società Italiana Nefrologia

A.S.L. CN1

Febbraio 2021

Sig. Stefano - 64 anni

Anamnesi familiare

Familiarità per ipertensione arteriosa (padre) e obesità (padre, fratello)
Nega familiarità per diabete mellito

Anamnesi fisiologica

Pensionato
Tabagista (~ 20 sig/die), nega consumo di alcolici
Stile di vita sedentario
Dieta libera, graduale incremento ponderale

Anamnesi patologica remota

Ipertensione arteriosa in trattamento farmacologico (~8 anni)
Dislipidemia in trattamento farmacologico (~8 anni)
Steatosi epatica
Malattia da reflusso gastroesofageo
Non precedenti CV

Pantoprazolo 20 mg
Metformina 1,5 gr
Simvastatina 20 mg
Nebivololo 5 mg
Furosemide 25 mg ½ cp

Anamnesi patologica prossima

Diabetico da ~8 anni, riscontro occasionale
Pressione arteriosa scarsamente controllata al domicilio
Peggioramento compenso glicometabolico
Spesso glicemie >200 mg/dl

Febbraio 2021

Esame obiettivo
Peso: 101 kg
Altezza: 176 cm
BMI: circa 32.6 kg/m²
Circonferenza vita: 102 cm
PA: 160/90 mmHg
FC: 73 bpm

Hb glic	8,3%
HgT	188 mg/dl
Crs	1,68 mg/dl
eGFR	58 ml/min
colest tot	202 mg/dl
colest LDL	137 mg/dl
TGD	135 mg/dl
HDL	38 mg/dl
microalbuminuria spot	135 mg/dl
……	

Complicanze?

Febbraio 2021

Stage of CKD	eGFR result	What it means
Stage 1	90 or higher	- Mild kidney damage - Kidneys work as well as normal
Stage 2	60-89	- Mild kidney damage - Kidneys still work well
Stage 3a	45-59	- Mild to moderate kidney damage - Kidneys don't work as well as they should
Stage 3b	30-44	- Moderate to severe damage - Kidneys don't work as well as they should
Stage 4	15-29	- Severe kidney damage - Kidneys are close to not working at all
Stage 5	less than 15	- Most severe kidney damage - Kidneys are very close to not working or have stopped working (failed)

Hb glic	8,3%
HgT	188 mg/dl
Crs	1,68 mg/dl
eGFR	58 ml/min
colest tot	202 mg/dl
colest LDL	137 mg/dl
TGD	135 mg/dl
HDL	38 mg/dl
microalbuminuria spot	135 mg/dl
……	

L 'American Diabetes Association raccomanda lo screening per microalbuminuria:

- **entro 5 anni dalla diagnosi e poi annualmente nel DM1**
- **al momento della diagnosi e poi annualmente nel DM2**

Microalbuminuria as a manifestation of diffuse endothelial cell injury

Systemic Vasculature

Interstitial Albumin Leak

Injured Endothelium

Microalbuminuria

A risk marker for:

- Hypertension progression
- Cardiovascular disease
- Chronic kidney disease

Renal Vasculature

Microalbuminuria

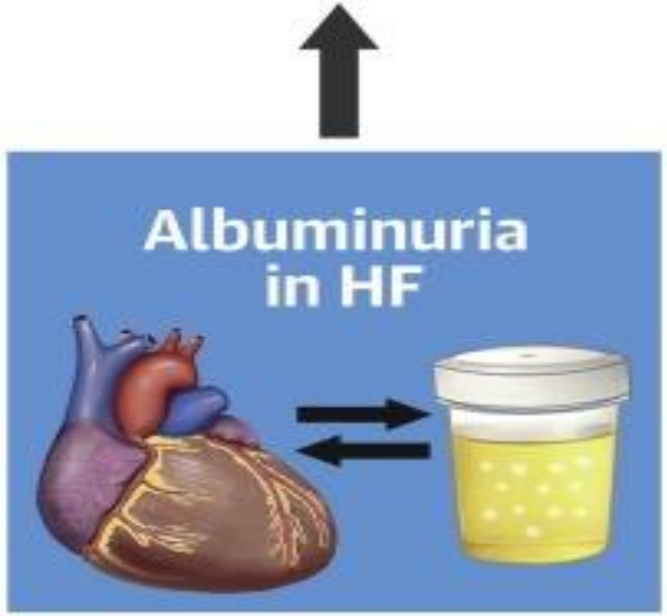
Albuminuria as a risk marker for heart failure

Albuminuria as a Risk Marker for HF

- Progressive continuous relationship with HF
- Prediction power outperforms creatinine based eGFR in HF
- Enhances HF risk prediction models
- Regression of albuminuria associated with reduced risk of HF
- Marker of early kidney damage
- Cost-effective metric to denote CV risk profile

Albuminuria in Progression of HF

- **SOLVD Trial**
  - ↑Albuminuria → ↑1.8 x risk of HHF
- **CHARM Trial**
  - ↑Albuminuria → ↑30-70% risk of HHF
- **GISSI-HF and CHARM Trials**
  - Strong independent predictor of adverse prognosis in HF irrespective of HTN or T2DM



Albuminuria Predicts Risk of Incident HF

- **RENAAL Trial**
  - ↑Albuminuria → ↑2.7 x risk of incident HF
- **FHS Study**
  - ↑Albuminuria → ↑1.7 x risk of incident HF
- **MESA Study**
  - ↑Albuminuria → ↑2.7 x risk of incident HF
- **ARIC Study**
  - ↑Albuminuria → ↑2.5 x risk of incident HF

Khan MS, et al. J Am Coll Cardiol. 2023;81(3):270-282.

Management of albuminuria as a surrogate marker in patients with diabetes

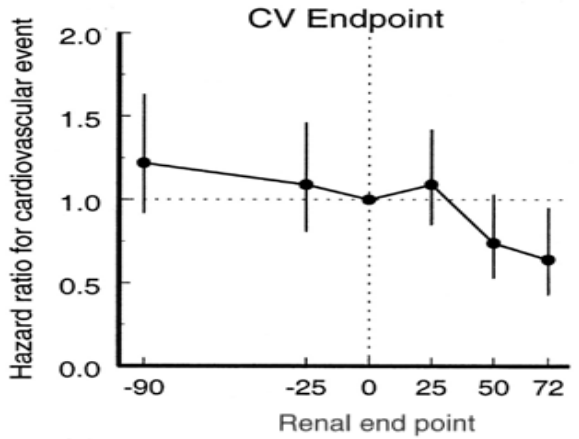
Treatments that lower urinary albumin excretion may slow progression of diabetic kidney disease (DKD) and improve clinical outcomes, even in the absence of hypertension. However, most people with diabetes and albuminuria have hypertension

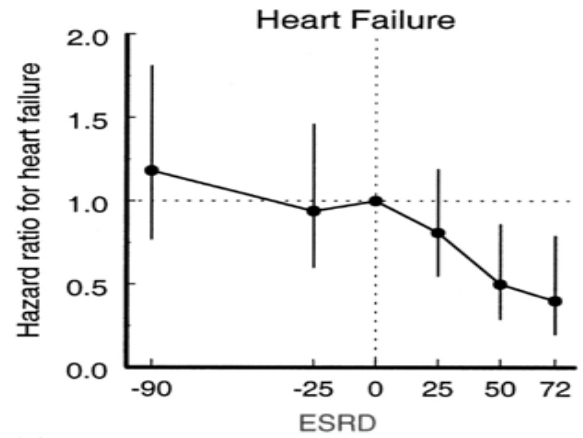
1.1 Normotensive people with diabetes and macroalbuminuria should be treated with an ACE inhibitor or an ARB. (C)
1.2 Treatment with an ACE inhibitor or an ARB may be considered in normotensive people with diabetes and microalbuminuria. (C)
1.3 Albuminuria reduction may be considered a treatment target in DKD. (C)

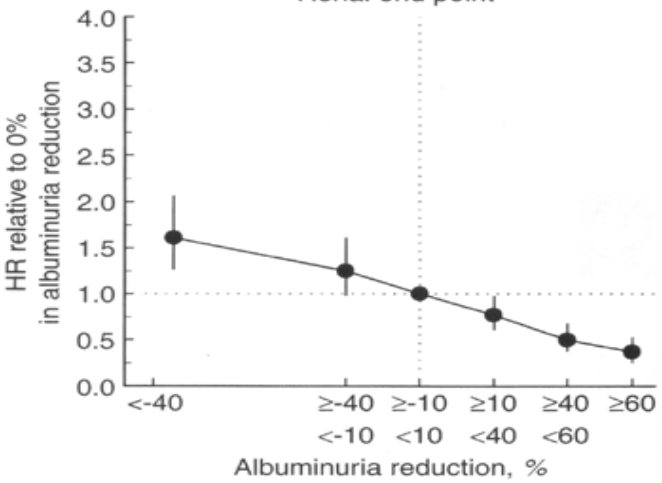
Table 44. Effect of ACE Inhibitors on Mortality, CVD, Kidney Function, Albuminuria, and Miscellaneous Outcomes in Type 2 Diabetes

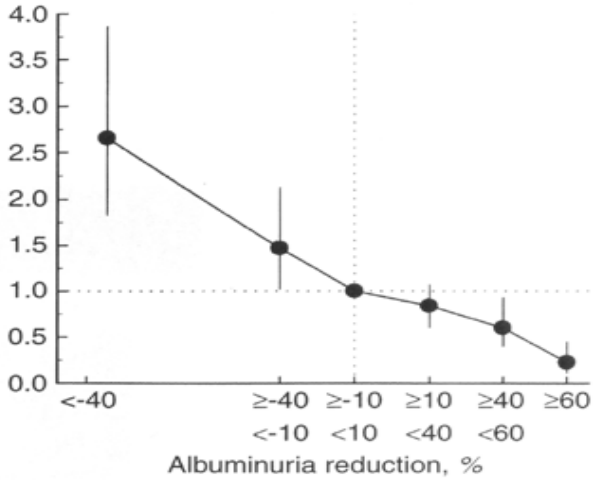
Author, Year	Mean Study Duration (y)	N	Mean GFR	Albuminuria	Applic-ability	Treatment (qd)[a]	Comparator	Outcome	Baseline Value[b]	Net Effect	P	Quality
Mortality												
Marre, 2004 [485] DIABHYCAR	4	4,912	SCr 1.0	MacroAlb 26% MicroAlb 74%	↑↑↑	Ramipril 1.25 mg	Placebo	All cause mortality	—	HR 1.04	NS	●
UKPDS 39, 1998 [486]	9	758	nd	MacroAlb 2% MicroAlb 18%	↑↑↑	Captopril 100 mg	Atenolol 100 mg	All cause mortality	—	RR 1.14	NS	○
								Diabetes-related death	—	RR 1.27	NS	
Composite Clinical Outcome												
Marre, 2004 [485] DIABHYCAR	4	4,912	SCr 1.0	MacroAlb 26% MicroAlb 74%	↑↑↑	Ramipril 1.25 mg	Placebo	CVD death, CVD event, CKD Stage 5	—	HR 1.03	NS	●
HOPE, 2000 [104]	4.5	3,577	SCr 1.1	MicroAlb 32%	↑↑↑	Ramipril 10 mg	Placebo	MI, Stroke or CVD death	—	RR 0.75	.0004	○
Cardiovascular Disease												
Marre, 2004 [485] DIABHYCAR	4	4,912	SCr 1.0	MacroAlb 26% MicroAlb 74%	↑↑↑	Ramipril 1.25 mg	Placebo	MI	—	HR 0.79	NS	●
UKPDS 39, 1998 [486]	9	758	nd	MacroAlb 2% MicroAlb 18%	↑↑↑	Captopril 100 mg	Atenolol 100 mg	Stroke	—	RR 1.12	NS	○
								PVD	—	RR 1.48	NS	
Kidney Function												
Marre, 2004 [485] DIABHYCAR	4	4,912	SCr 1.0	MacroAlb 26% MicroAlb 74%	↑↑↑	Ramipril 1.25 mg	Placebo	CKD Stage 5	—	HR 0.93	NS	●
								SCr doubling	—	HR 0.81	NS	
Ahmad, 1997 [487]	5	103	124	MicroAlb 100%	↑↑	Enalapril 10 mg	Placebo	Δ GFR	124	None	NS	○
Albuminuria												
Marre, 2004 [485] DIABHYCAR	4	1,868	SCr 1.0	MacroAlb 26% MicroAlb 74%	↑↑↑	Ramipril 1.25 mg	Placebo	Regression of albuminuria	—	RR 0.86	.07	●
Capes, 2000[c] [488] SOLVD	2	970	nd	MacroAlb/MicroAlb 0%	↑↑	Enalapril 20 mg	Placebo	New proteinuria	—	RR 0.39	.01	●
HOPE, 2000 [104]	4.5	3,577	SCr 1.1	MicroAlb 32%	↑↑↑	Ramipril 10 mg	Placebo	Macroalbuminuria	—	RR 0.76	.03	○
								Microalbuminuria	—	RR 0.91	NS	
Ahmad, 1997 [487]	5	103	124	MicroAlb 100%	↑↑	Enalapril 10 mg	Placebo	Macroalbuminuria	—	ARR 0.84[d]	<.001	○
								Δ AER (μg/min)	55 (53)	-67	<.05	
Miscellaneous Outcomes												
UKPDS 39, 1998 [486]	9	758	nd	MacroAlb 2% MicroAlb 18%	↑↑↑	Captopril 100 mg	Atenolol 100 mg	Microvascular disease	—	RR 1.29	NS	○

a Maximum daily dose.
b Baseline value of outcomes in the treatment (comparator) arm.
c Types 1 and 2 diabetes.
d Absolute risk reduction over 5-year period.









Multifaceted approach to intervention in diabetes and chronic kidney disease

Multiple risk factors are managed concurrently in patients with diabetes and CKD, and the incremental effects of treating each of these risk factors appear to add up to substantial clinical benefits.

2.1 The care of people with diabetes and CKD should incorporate a multifaceted approach to intervention that includes instruction in healthy behaviors and treatments to reduce risk factors. (C)
2.2 Target BMI for people with diabetes and CKD should be within the normal range (18.5-24.9 kg/m^2). (C)

Treatment Goals

Systolic blood pressure < 130 mm Hg

Diastolic blood pressure < 80 mm Hg

Glycosylated hemoglobin < 6.5%

Total cholesterol < 175 mg/dL

Triglycerides < 150 mg/dL

ACE inhibitor or ARB irrespective of blood pressure

Aspirin irrespective of prevalent vascular disease

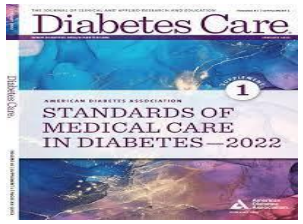
Smoking cessation

Vitamin/mineral supplement

- **Adeguata idratazione**

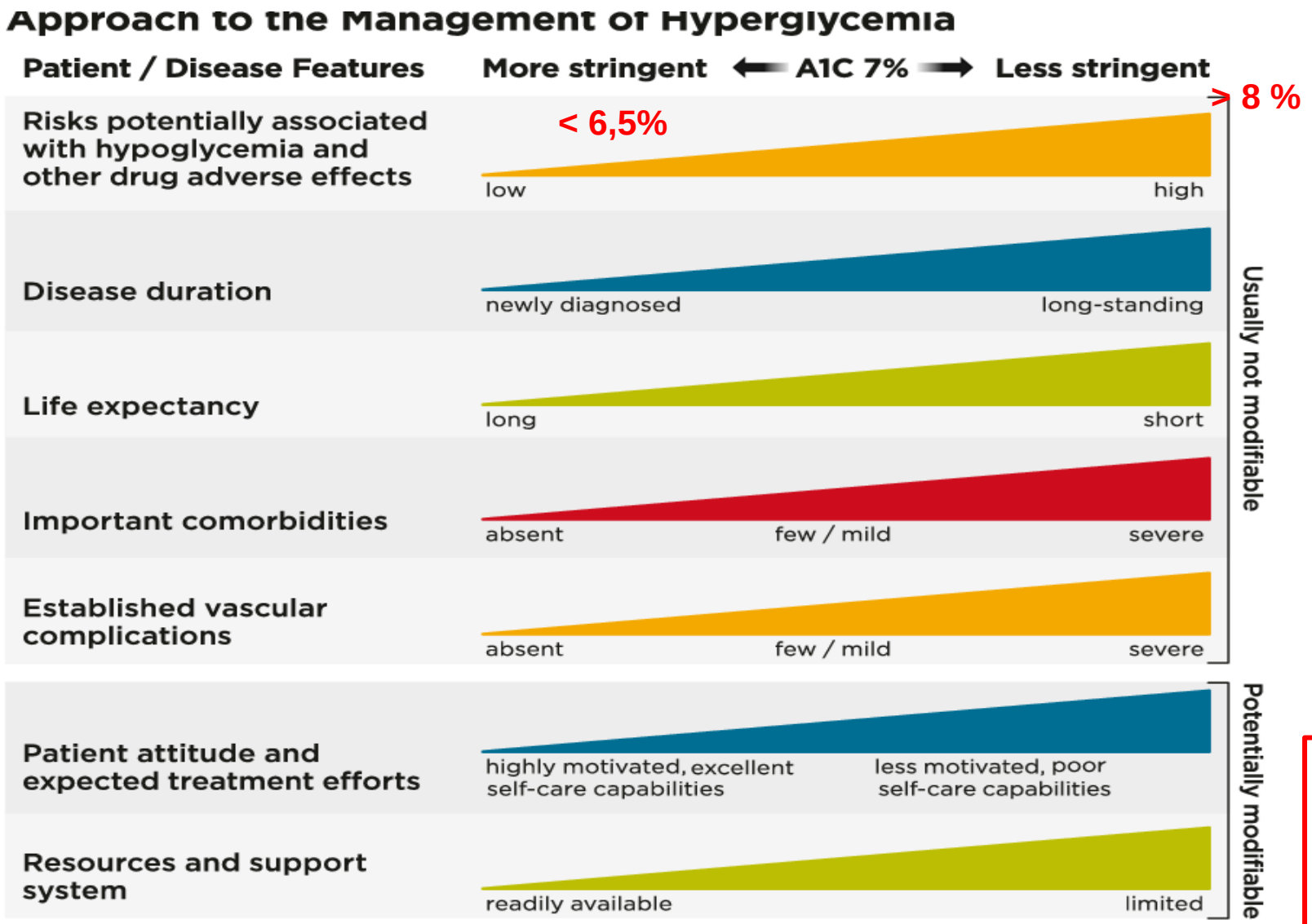
SE eGFR < 50 ml/min

- **Astensione da FANS**
- **Dieta a ridotto regime proteico**
- **Adeguata nefroprotezione se utilizzo di esami con mdc iodato**



Target glicemico e pressorio

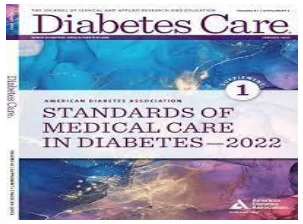
Glycemic targets



BP targets

Standard di cura SID – AMD 2018	ADA 2018
• < 140/90 mmHg • **< 130/80 mmHg** giovani, ad alto rischio, albuminurici • < 150/90 mmHg anziani	• < 140/90 mmHg • **< 130/80 mmHg** giovani, ad alto rischio , albuminurici

Intensive glycemic control with the goal of achieving near- normoglycemia has been shown in large prospective randomized studies to delay the onset and progression of albuminuria and reduced eGFR in patients with type 1 diabetes and type 2 diabetes



Algoritmo di terapia nel DM2

DIAGNOSI

Iperglicemia

Metformina

Metformina +

DPP4i | Pio | SGLT2i | GLP1RA

Metformina +

DPP4i: AGI, Pio, SGLT2i, SU

Pio: AGI, DPP4i, SGLT2i, GLP1RA, SU

SGLT2i: AGI, DPP4i, Pio, GLP1RA, SU

GLP1RA: AGI, Pio, SGLT2i, SU

Insulina

Metformina

DPP4i

Pio

SGLT2i

GLP1RA

Metformina 1,5 gr/die

\+ Liraglutide 1,2 Mg

Hb glic	8,3%
HgT	188 mg/dl
eGFR	58 ml/min
BMI	34 Kg/m2

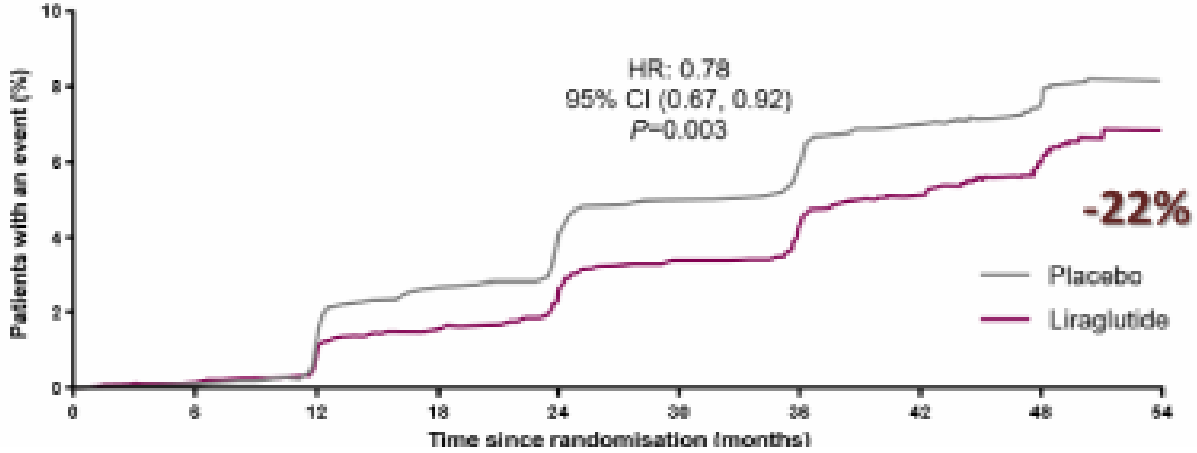
SGLT2 -I eGFR > 60 ml/min

Liraglutide and Renal Outcomes in Type 2 Diabetes

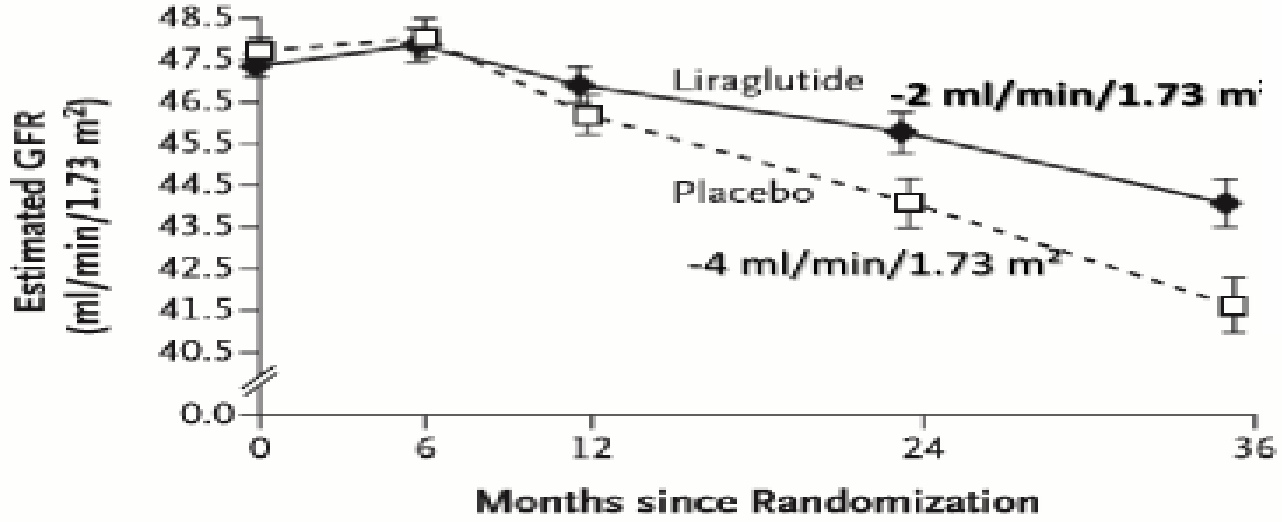
The NEW ENGLAND JOURNAL of MEDICINE

Johannes F.E. Mann, M.D., David D. Ørsted, M.D., Ph.D.,

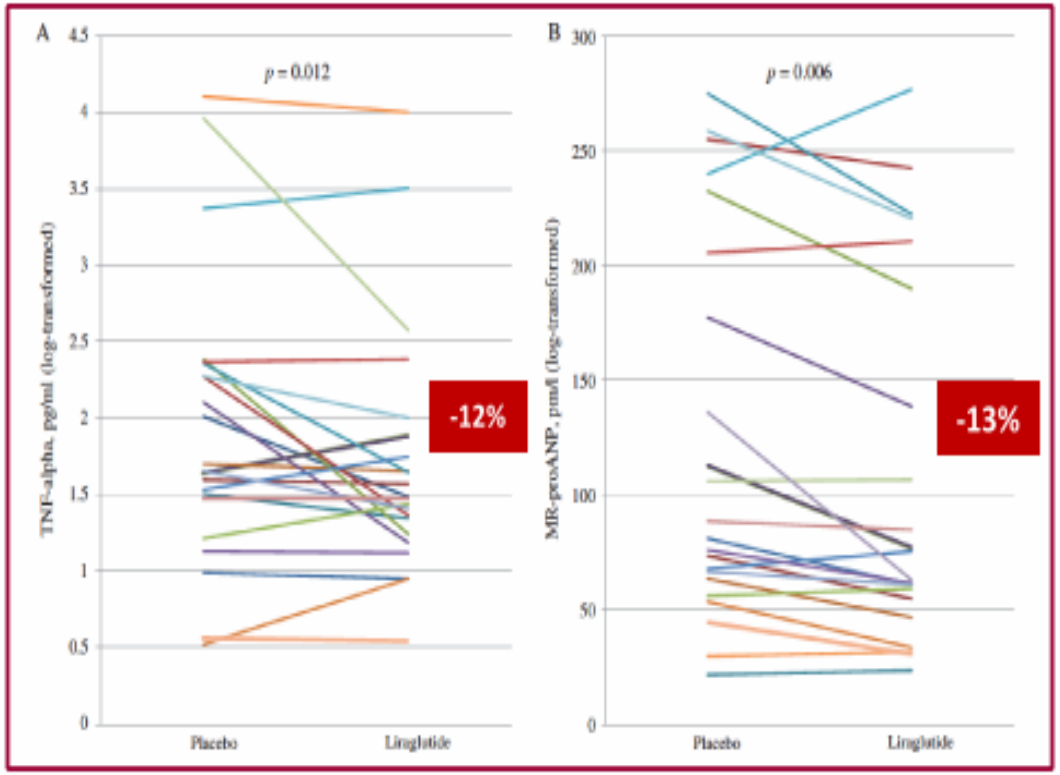
Macroalbuminuria, doubling of serum creatinine, ESRD, renal death



C Estimated GFR 30–59 ml/min/1.73 m²



Individual effects of 12 weeks of liraglutide treatment



Reduced Oxidative stress
Reduced Inflammation

Ipertensione e nefropatia diabetica

Pazienti con micro/macroalbuminuria devono essere trattati con ACE-I o ARB a prescindere dai livelli pressori

Nei pazienti con DM2 normotesi e microalbuminurici, gli ACE-I riducono il rischio CV

Nei pazienti con DM2 ipertesi e microalbuminurici sia ACE-I che ARB rallentano progressione a macroalbuminuria

Nei pazienti con DM2 ipertesi e macroalbuminurici e con insufficienza renale (eGFR < 60 ml/min) ARB rallentano progressione della nefropatia

Pantoprazolo 20 mg
Metformina 1 gr
Simvastatina 20 mg
Liraglutide 1,2 Mg
Nebivololo 5 mg
Furosemide 25 mg ½ cp
Ramipril 5 mg

Settembre 2021

Esame obiettivo
Peso: 95 kg
Altezza: 176 cm
BMI: circa 29 kg/m²
Circonferenza vita: 95 cm
PA: 135/80 mmHg
FC: 80 bpm

Hb glic	**7,5%**
HgT	**128 mg/dl**
Crs	**1,31 mg/dl**
eGFR	**73 ml/min**
colest tot	**165 mg/dl**
colest LDL	**94 mg/dl**
TGD	**110 mg/dl**
HDL	**49 mg/dl**
microalbuminuria spot	**48 mg/dl**
……	

Complicanze

- **ECG:** *ritmo sinusale, 92 bpm, asse elettrico orizzontale, turbe di conduzione destra*
- **EcoTSA** : *Ispessimento miointimale diffuso bilaterale in assenza di stenosi emodinamicamente significative*
- **Fundus oculi:** *Retinopatia ipertensiva II stadio, no RD*

Ambulatorio multidisciplinare ASLCN1

Paziente diabetico

PATOLOGIA CV
CAD ischemica con IMA
Aritmia
Ipertensione arteriosa
Stroke
Difetto di macrocircolo

DISMETABOLISMO
Difetto del microcircolo
BMI elevato
Glicemie non a target

PATOLOGIA RENALE
CKD in progressione
ESRD
Episodio di AKI

Aumento di comorbidità, tasso di ospedalizzazioni e di mortalità

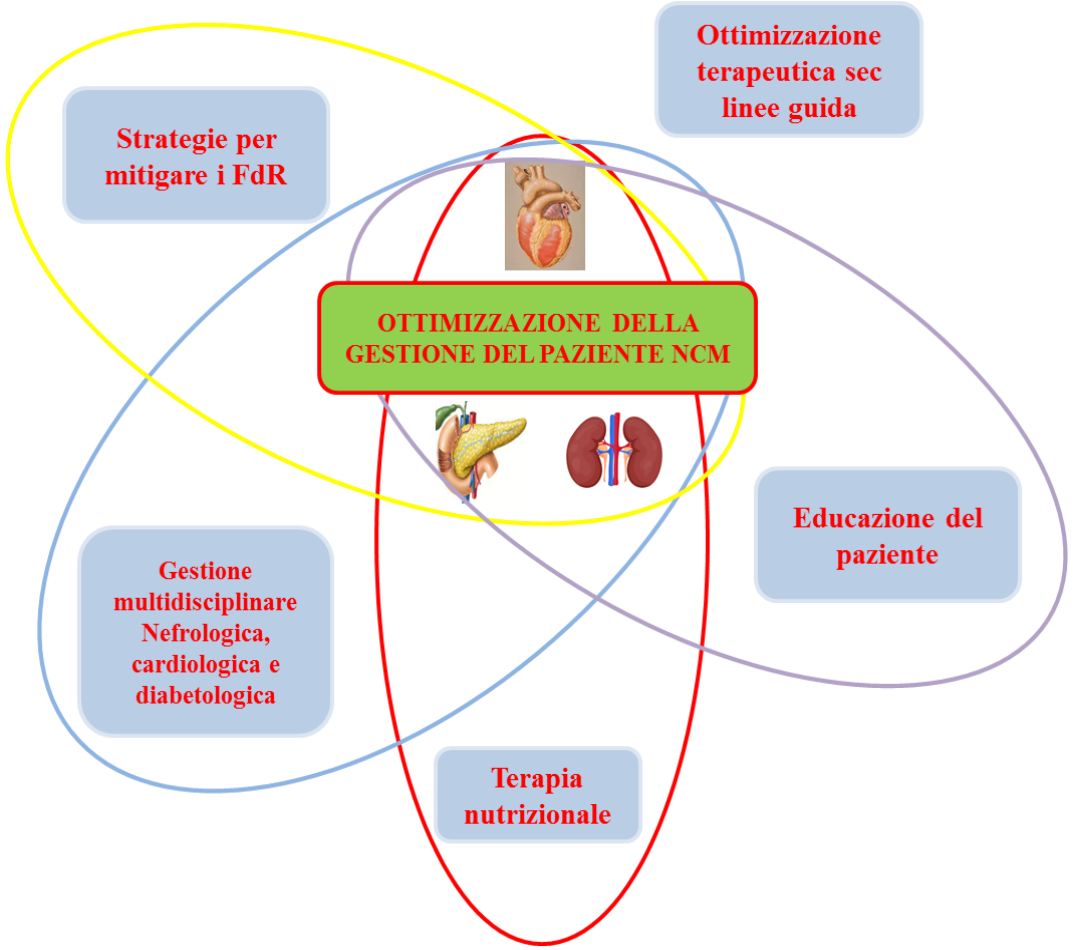
GESTIONE IN AMBULATORIO NCD

Educazione al controllo dei principali FdR (fumo, potus, compenso glicemico / lipidico, controllo pressorio, esercizio, BMI)
Visita dietista per dieta congrua al grado di CKD e al DM
ACEi/ARB
Canrenone
Diuretici
SGLT2i / GLP1RA

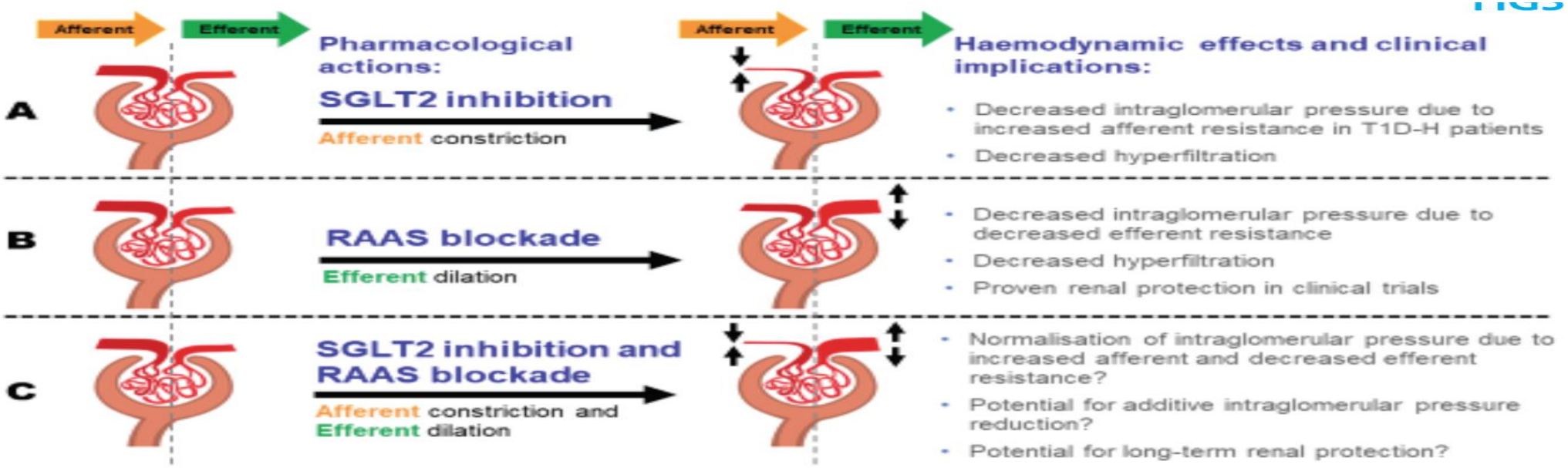
diabete.com

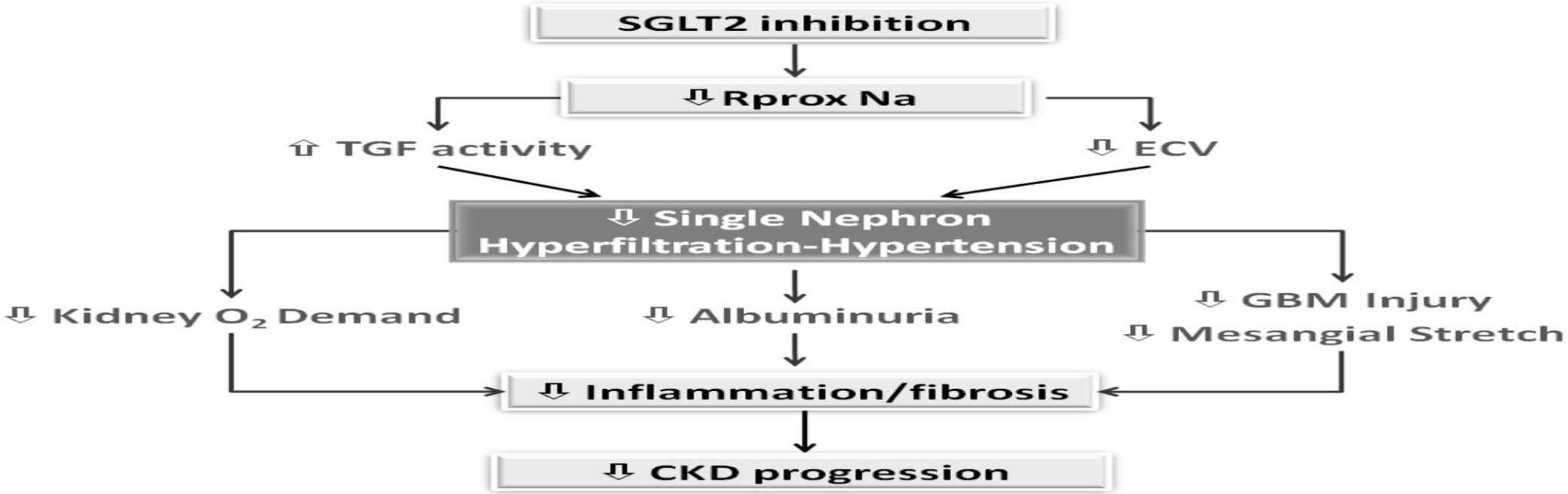
HOME SPECIALI DIABETE STILE DI VITA CO

All'Ospedale di Mondovì (CN) un Ambulatorio plurispecialistico per pazienti con diabete tipo 2 avanzato

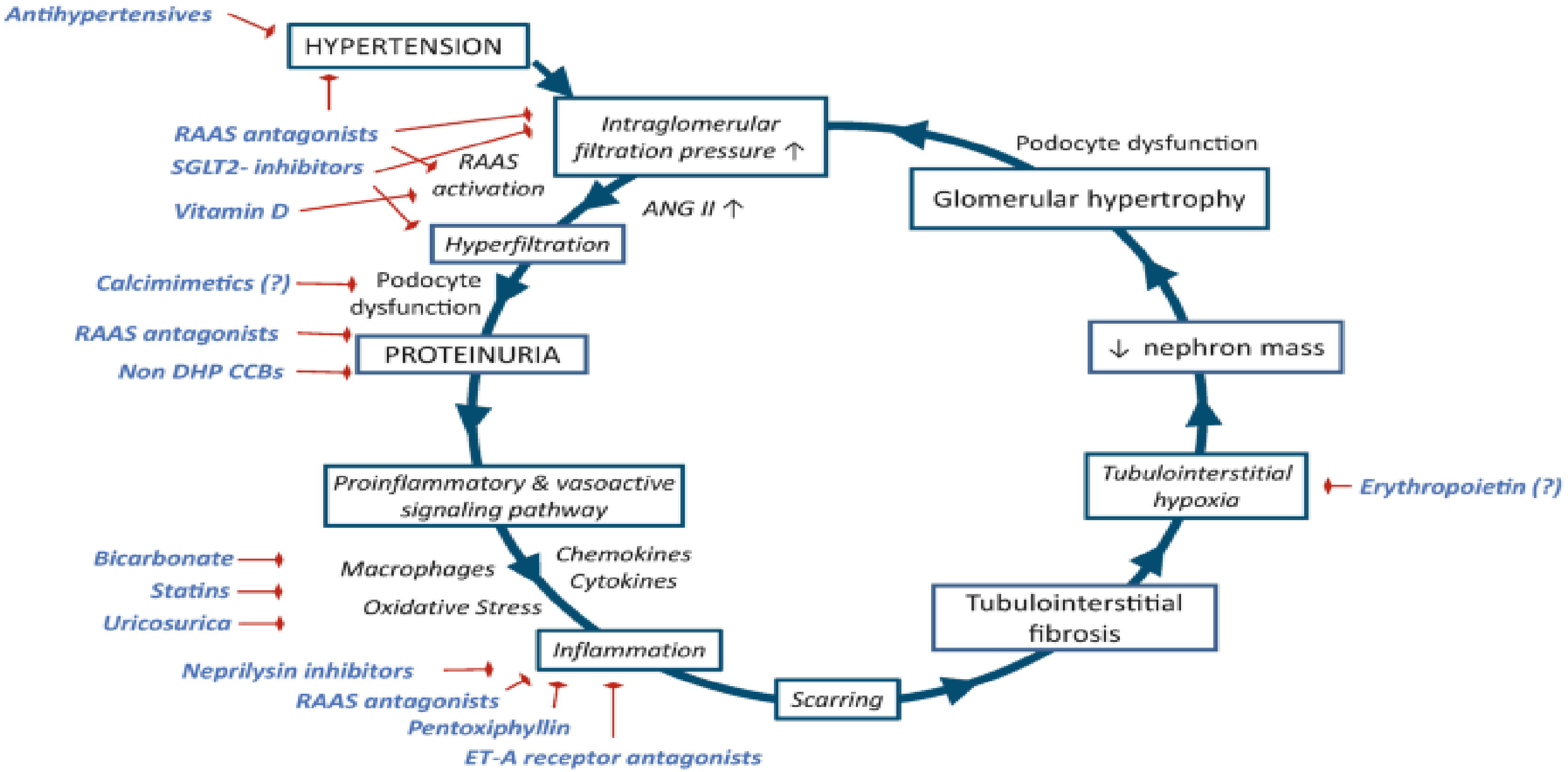


Meccanismi nefroprotettivi





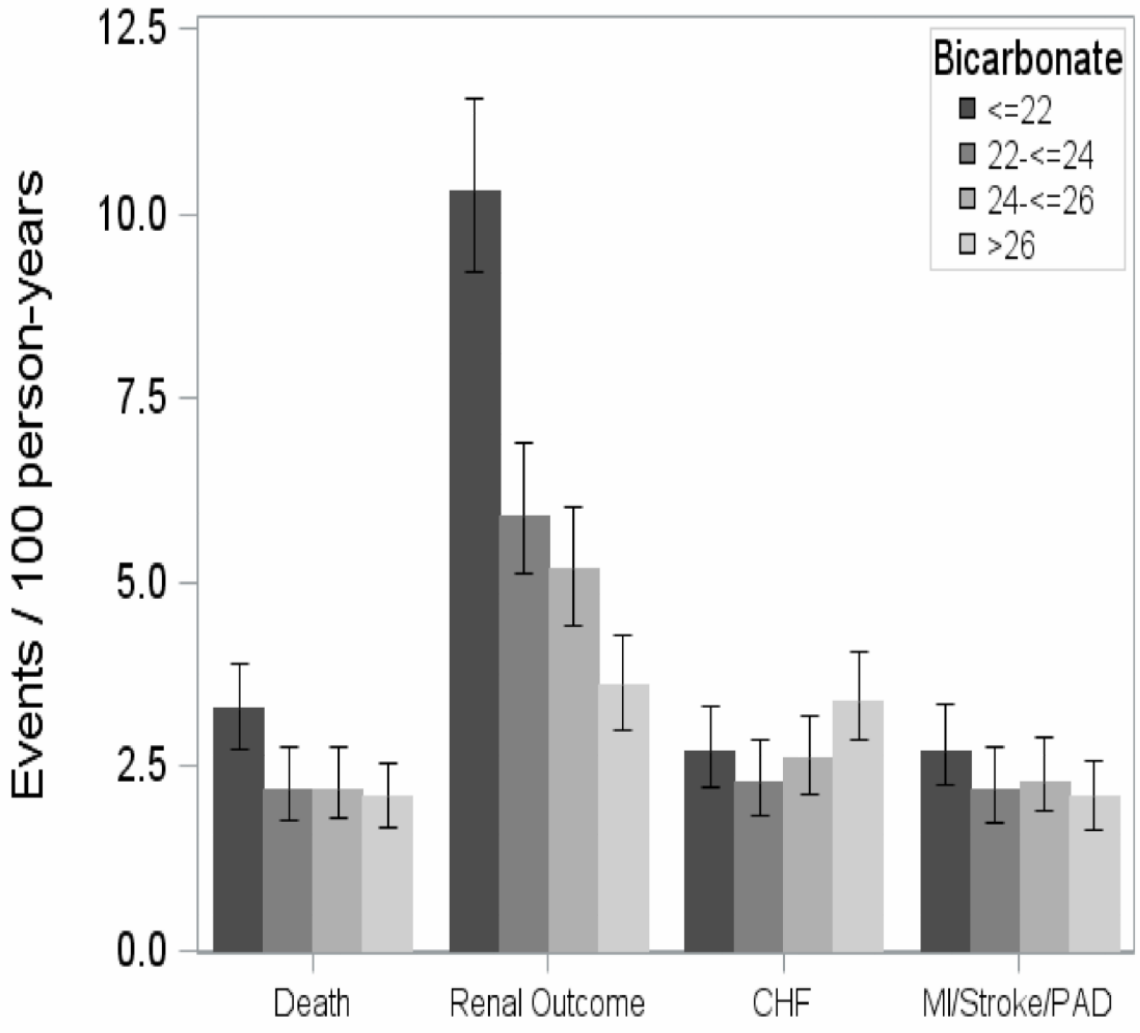
Meccanismi nefroprotettivi



Meccanismi nefroprotettivi

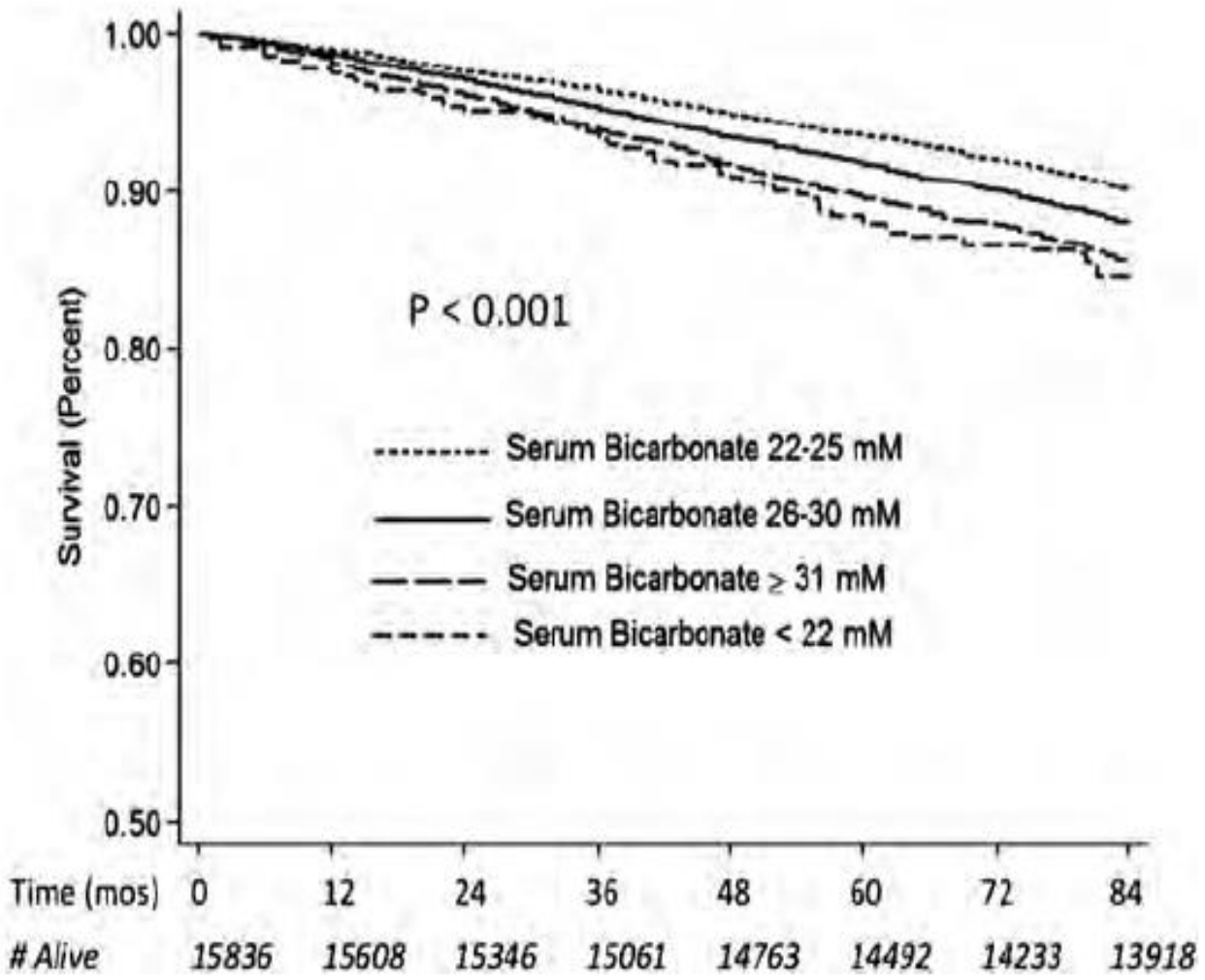
Association of Serum Bicarbonate With Risk of Renal and Cardiovascular Outcomes in CKD: A Report From the Chronic Renal Insufficiency Cohort (CRIC) Study

Mirela Dobre, MD, MPH[1,2,3], Wei Yang, PhD[4], Jing Chen, MD, MSc[5], Paul Drawz, MD, MHS[6],



Serum bicarbonate and mortality in adults in NHANES III

Kalani L. Raphael[1,2],
Yingying Zhang[2],



Conclusioni

Aprile 2023

Hb glic	7,2%
HgT	131 mg/dl
Crs	1,27 mg/dl
eGFR	70 ml/min
colest tot	191 mg/dl
colest LDL	88 mg/dl
TGD	112 mg/dl
HDL	48 mg/dl
microalbuminuria spot	55 mg/dl

Esame obiettivo

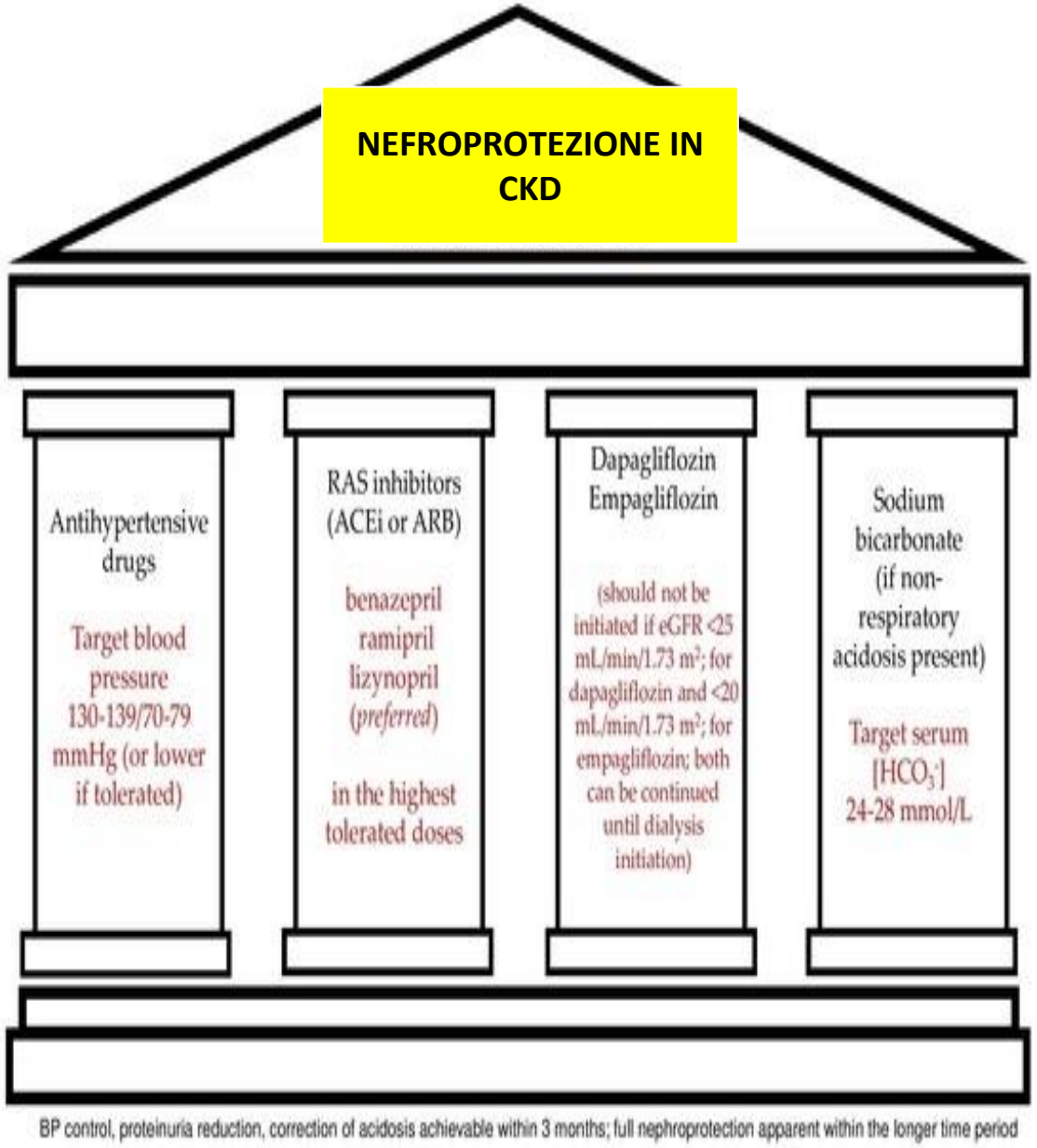
Peso: 94 kg

Altezza: 176 cm

BMI: circa 29 kg/m²

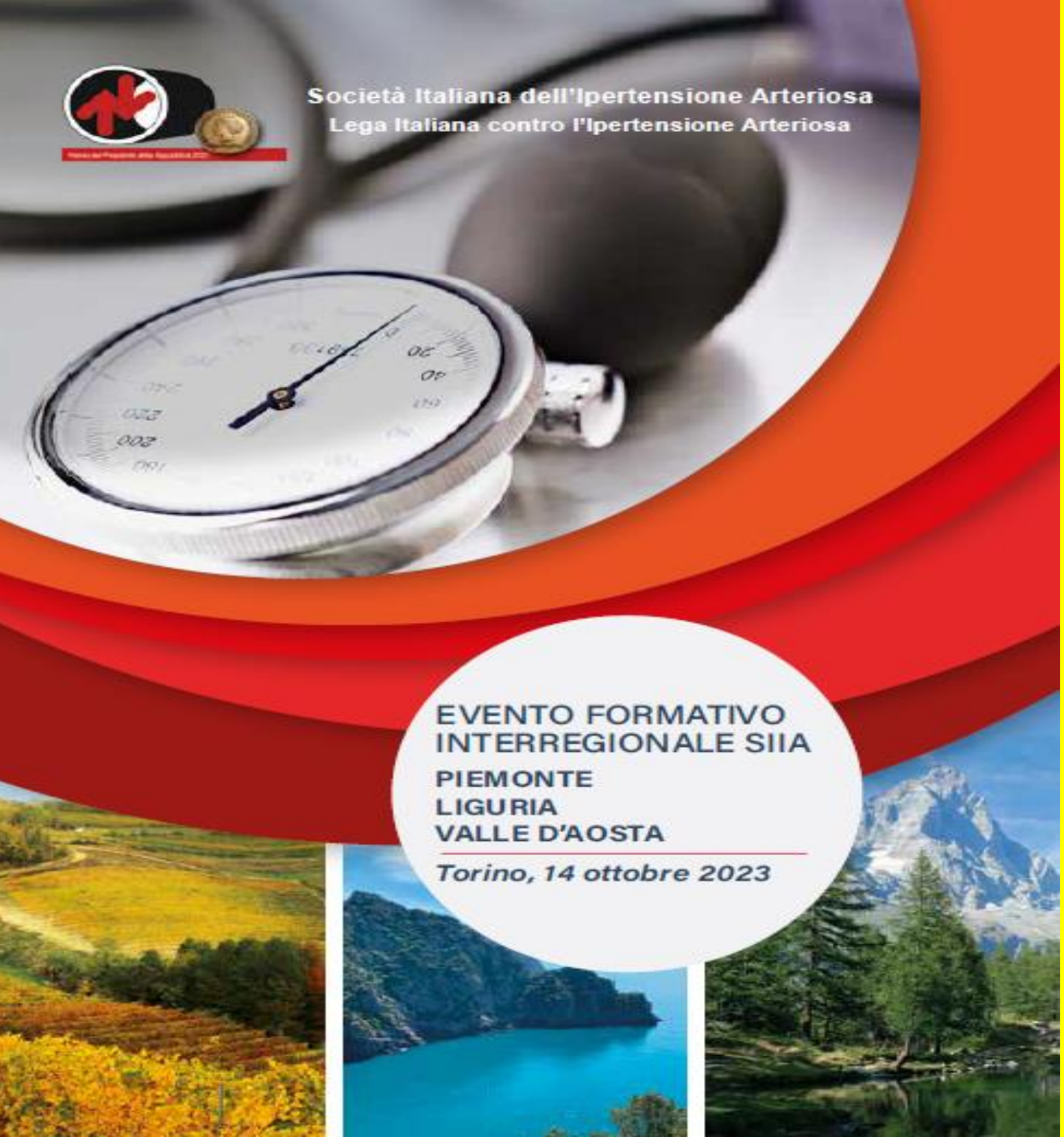
PA: 130/80 mmHg

FC: 80 bpm



La maggior parte dei pazienti con IRC necessita di un approccio nefroprotettivo universale e dovrebbe basare il proprio trattamento sui quattro pilastri seguenti: trattamento efficace dell'ipertensione, uso di ACEi o ARB e, in pazienti selezionati, spironolattone, inibitore SGLT2 (ad oggi, dapagliflozin ed empagliflozin sono formalmente registrati in tale indicazione oltre al diabete) e bicarbonato di sodio in pazienti con bicarbonato sierico inferiore a 24 mmol/L.

Gli obiettivi pressori, la riduzione significativa di albuminuria/proteinuria e la correzione dell'acidosi metabolica dovrebbero essere raggiunti entro tre mesi; certamente, è necessario un periodo più lungo per rallentare il tasso di perdita del GFR.



Grazie a tutti……!!!

A.S.L. CN1