BERTINORO ULTRASUONI

XXI CORSO NAZIONALE DI

ULTRASONOLOGIA VASCOLARE

DIAGNOSI E TERAPIA

Bertinoro,

20-22 aprile 2023

Centro Residenziale Universitario

Arteriopatia carotidea e renale del diabete: fattori di rischio e biomarcatori

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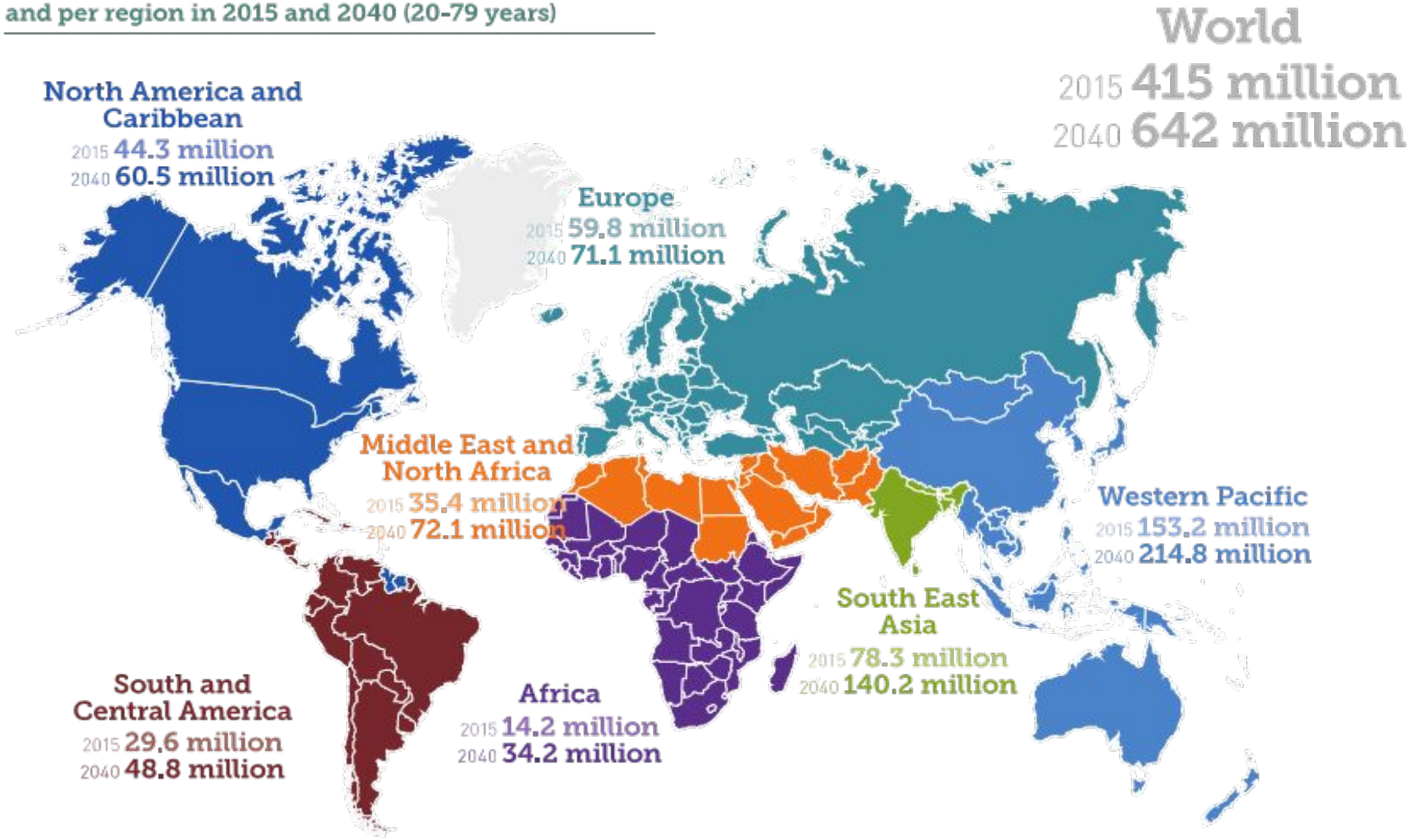
UOSD MEDICINA VASCOLARE
AST ASCOLI PICENO

Diabete nel Mondo

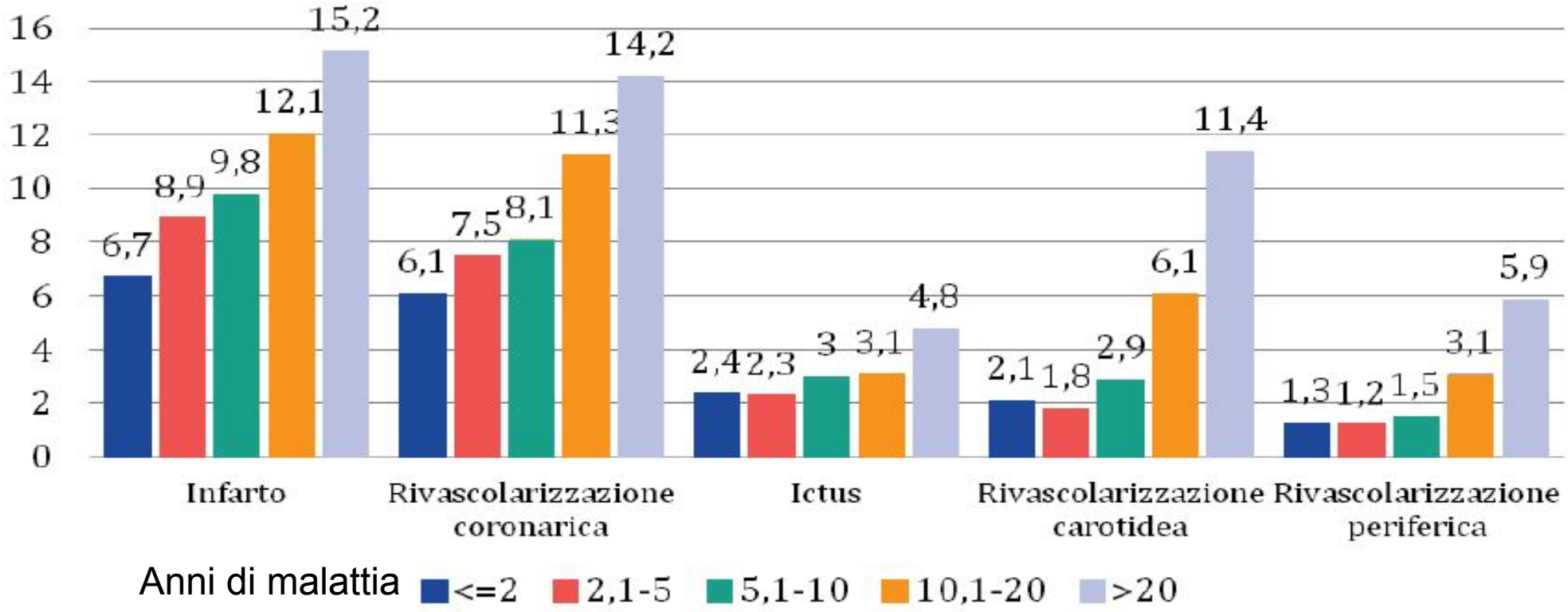
Va inoltre considerato che il **46%** dei casi di diabete non viene diagnosticato

Estimated number of people with diabetes worldwide and per region in 2015 and 2040 (20-79 years)



CVD e diabete: prevalenza delle complicanze cardiovascolari

Studio RIACE: 15773 pazienti diabetici in 19 centri diabetologici



Fra i pazienti seguiti presso i centri di diabetologia, uno su 10 (11,1%) ha avuto un infarto, uno su 10 (10%) ha avuto un intervento di riperfusione o rivascolarizzazione coronarica

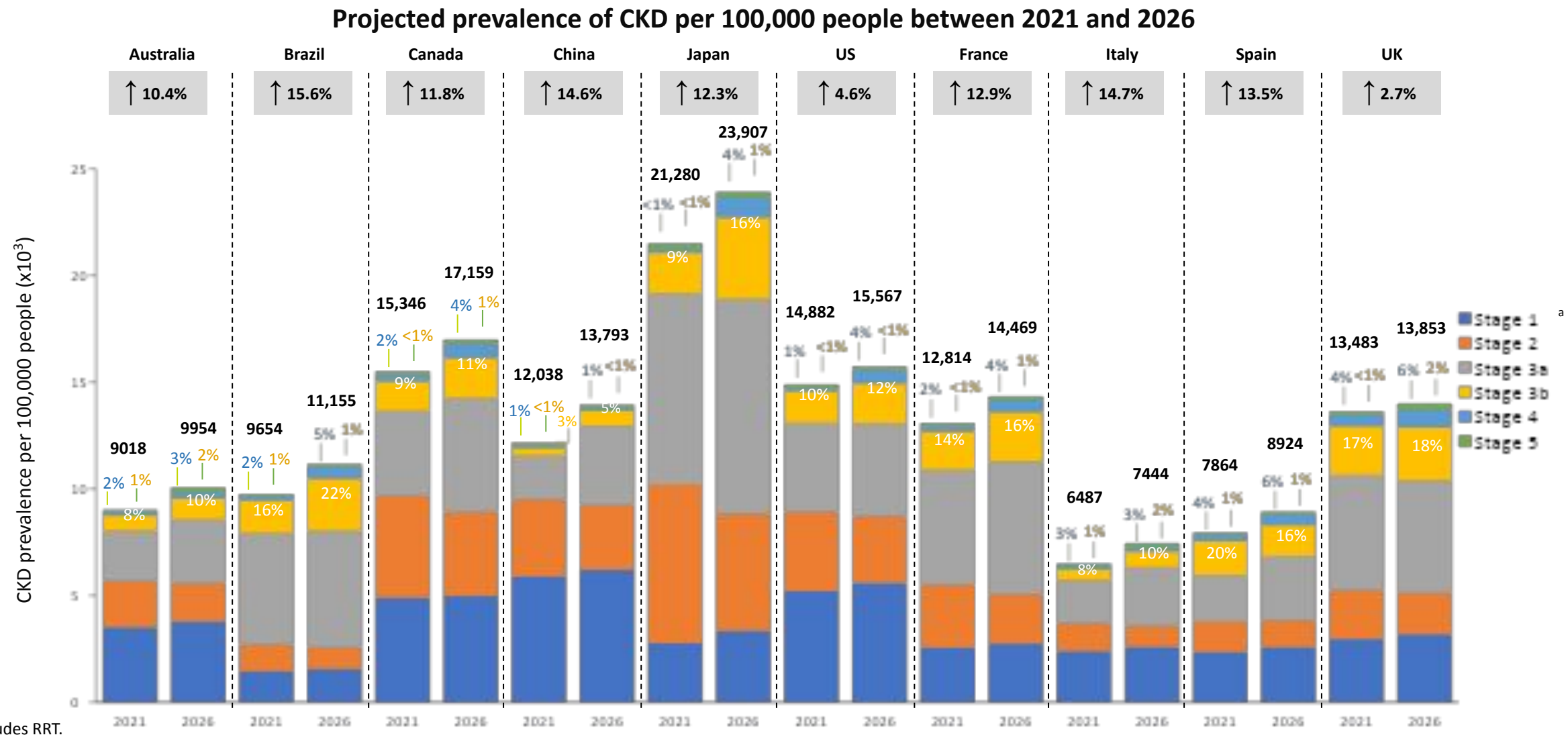
Studio RIACE

CVD e DM2: prevalenza delle complicanze cardiovascolari

	UK register	Survey internazionale
	Coorte di 148.803 pazienti con DM2 (Database dei GP)	57 studi con 4.549.481 pazienti con DM2 (46% europei)
eCVD	**35.4%**	**32.2 %**
MI	8.2 %	10 %
Angina	9.8 %	14.6 %
Stroke/TIA	9.9 %	7.6 %
Atherosclerosis	-	29.1%
PAD	18%	-
HF	5.8 %	14.9%

Lautsch D. Diabetes Ther, 2019 Einarson TR. Cardiovasc Diabetol, 2018

MALATTIA RENALE CKD NEI PAZIENTI CON DIABETE MELLITO

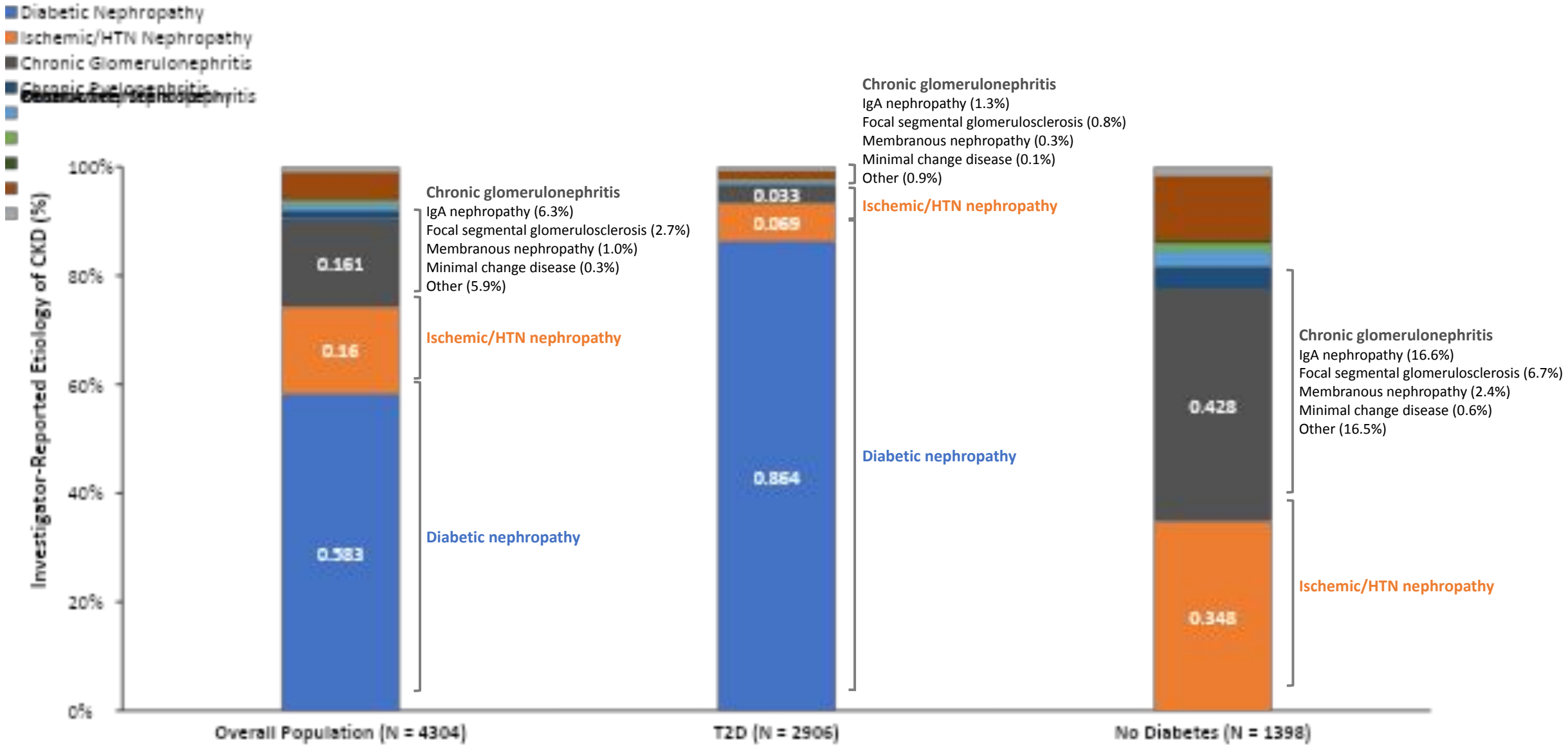


[a]Includes RRT.

CKD = chronic kidney disease; RRT = renal replacement therapy; UK = United Kingdom; US = United States.

1. Tangri N et al. Poster presented at: WCN; April 16-19, 2021; Virtual. Poster #0668; 2. Power A et al. Poster presented at: WCN; April 16-19, 2021; Virtual. Poster #0657.

ETIOLOGY OF CKD

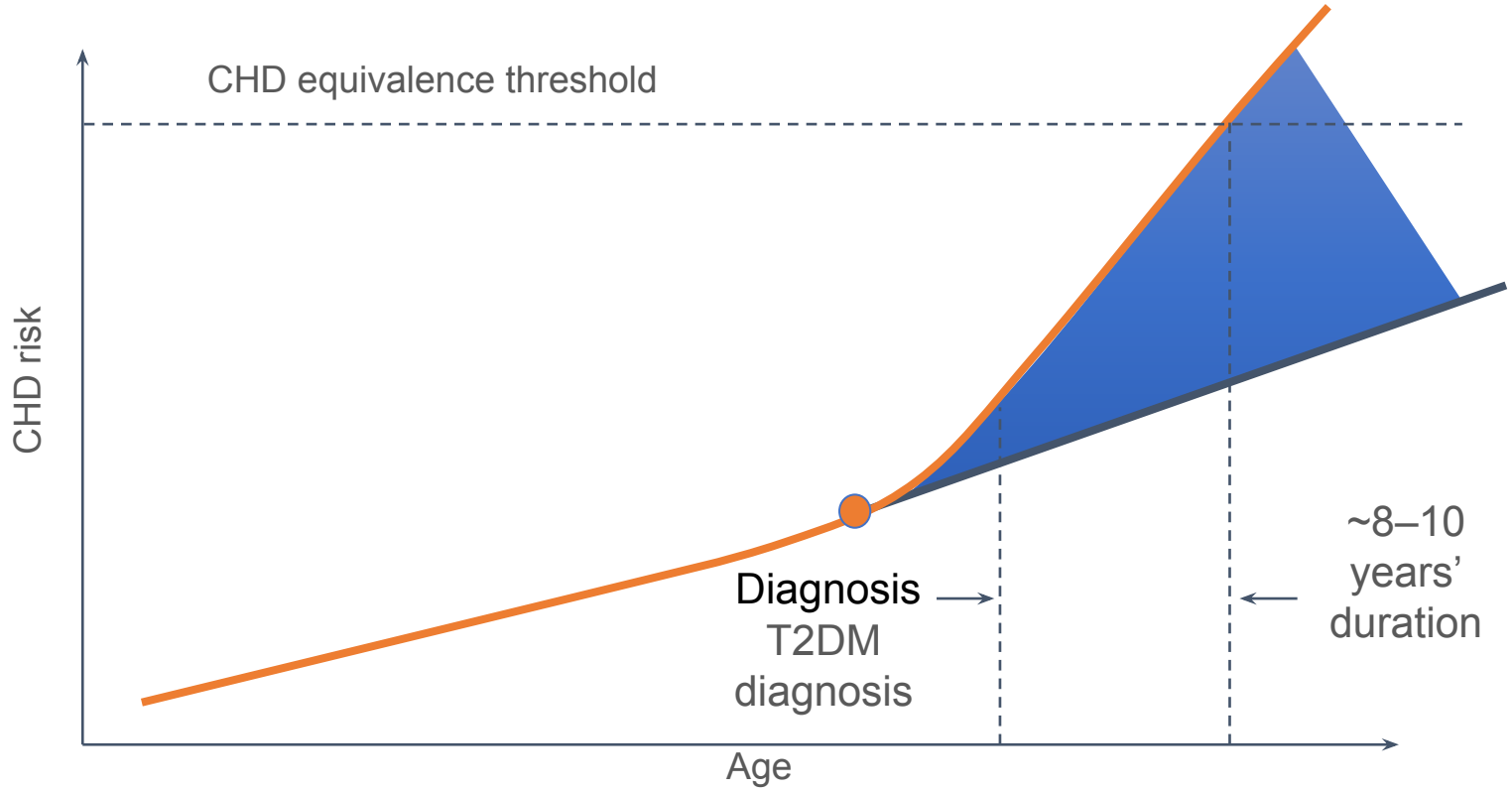


HTN = hypertensive; IgA = immunoglobulin A; T2D = type 2 diabetes.

Wheeler DC et al. *Nephrol Dial Transplant*. 2020;35:1700–1711.

T2DM INCREASES CVD RISK OVER TIME

INITIALLY CVD RISK IS LARGELY DETERMINED BY CONVENTIONAL CVD RISK FACTORS; GLUCOSE ELEVATIONS INTO THE DIABETIC RANGE INCREASE RISK GRADUALLY OVER TIME (COLORED AREA), APPROACHING CHD RISK EQUIVALENCE AFTER A DURATION OF ~10 YEARS

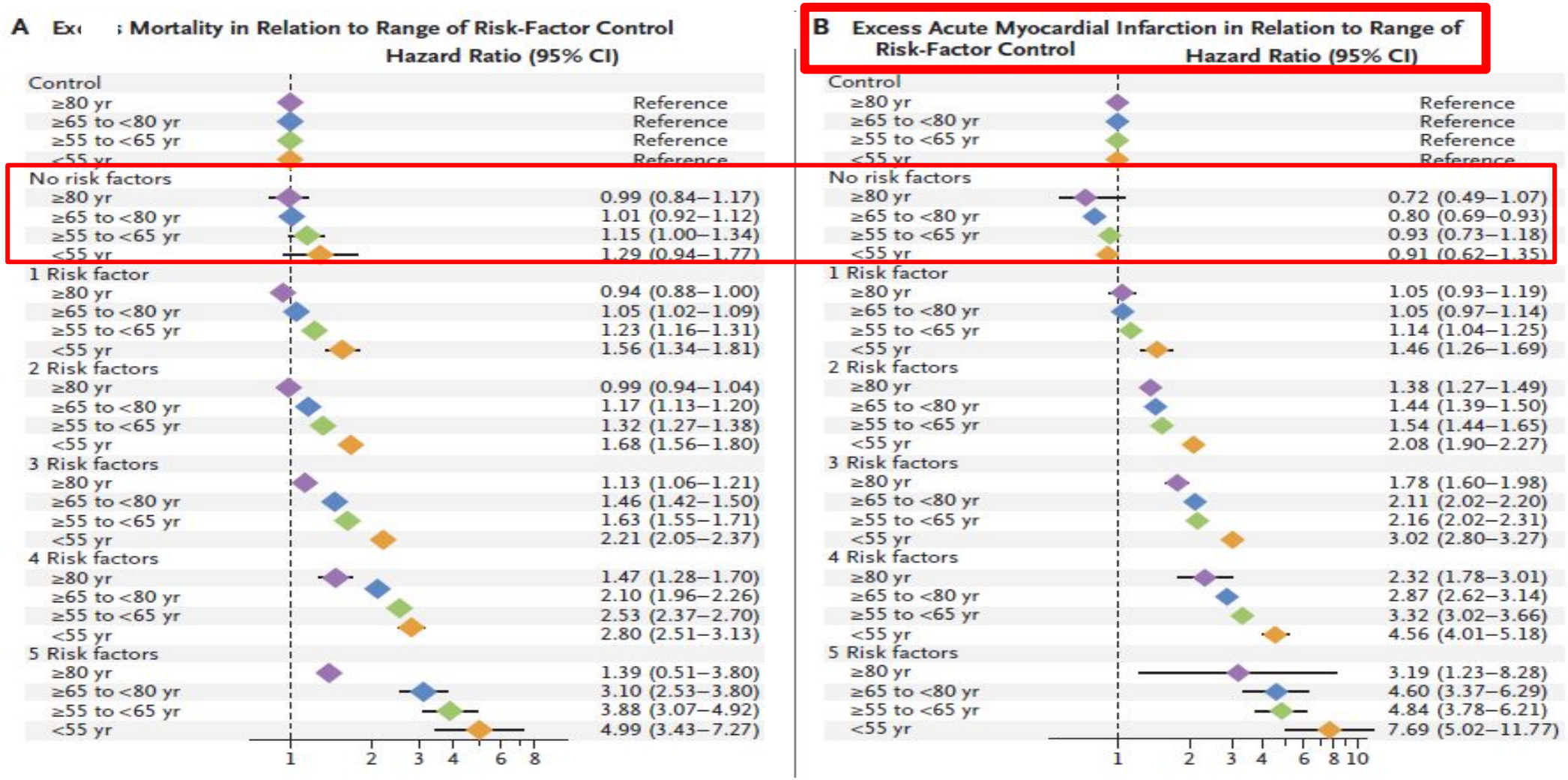


CHD = coronary heart disease; CVD = cardiovascular disease; T2DM = type 2 diabetes mellitus.
Adapted from: Sattar N. *Diabetologia*. 2013;56:686-695.

CVD e DM2: eccesso di mortalità/MI e fattori di rischio

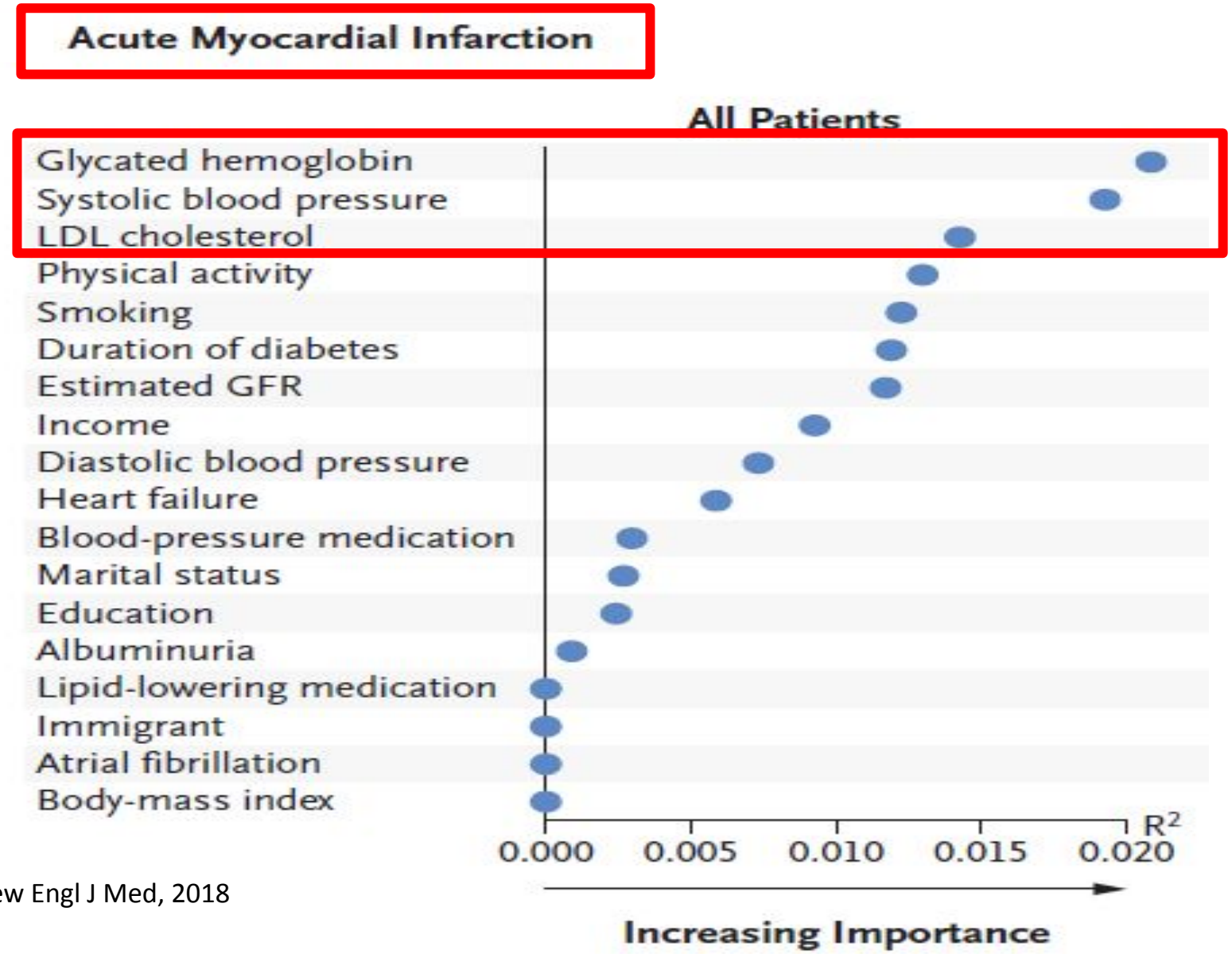
Swedish National Disease Register 271.174 pazienti con DM2 confrontati con 1.355.870 controlli

FDR: HbA1c, LDL colesterolo, albuminuria, fumo e pressione arteriosa



Rawshani A. New Engl J Med, 2018

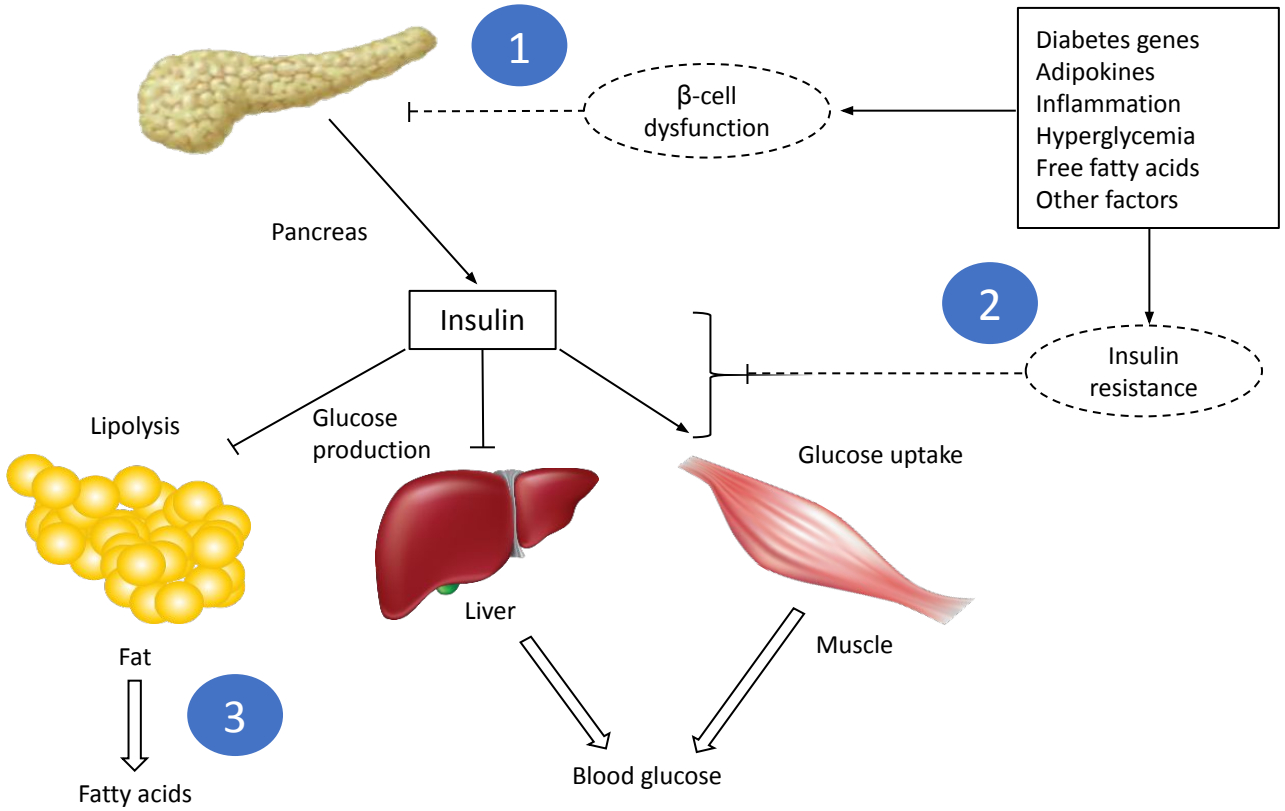
CVD e DM2: importanza relativa di ciascun fattore di rischio



Rawshani A. New Engl J Med, 2018

PATOGENESI DIABETE MELLITO II

LIFESTYLE AND GENETIC FACTORS ARE KEY TRIGGERING PATHOGENIC ELEMENTS[1]



1. In impaired glucose tolerance or T2DM, β-cell response (insulin secretion adjusting to changes in insulin action) is inadequate[1]

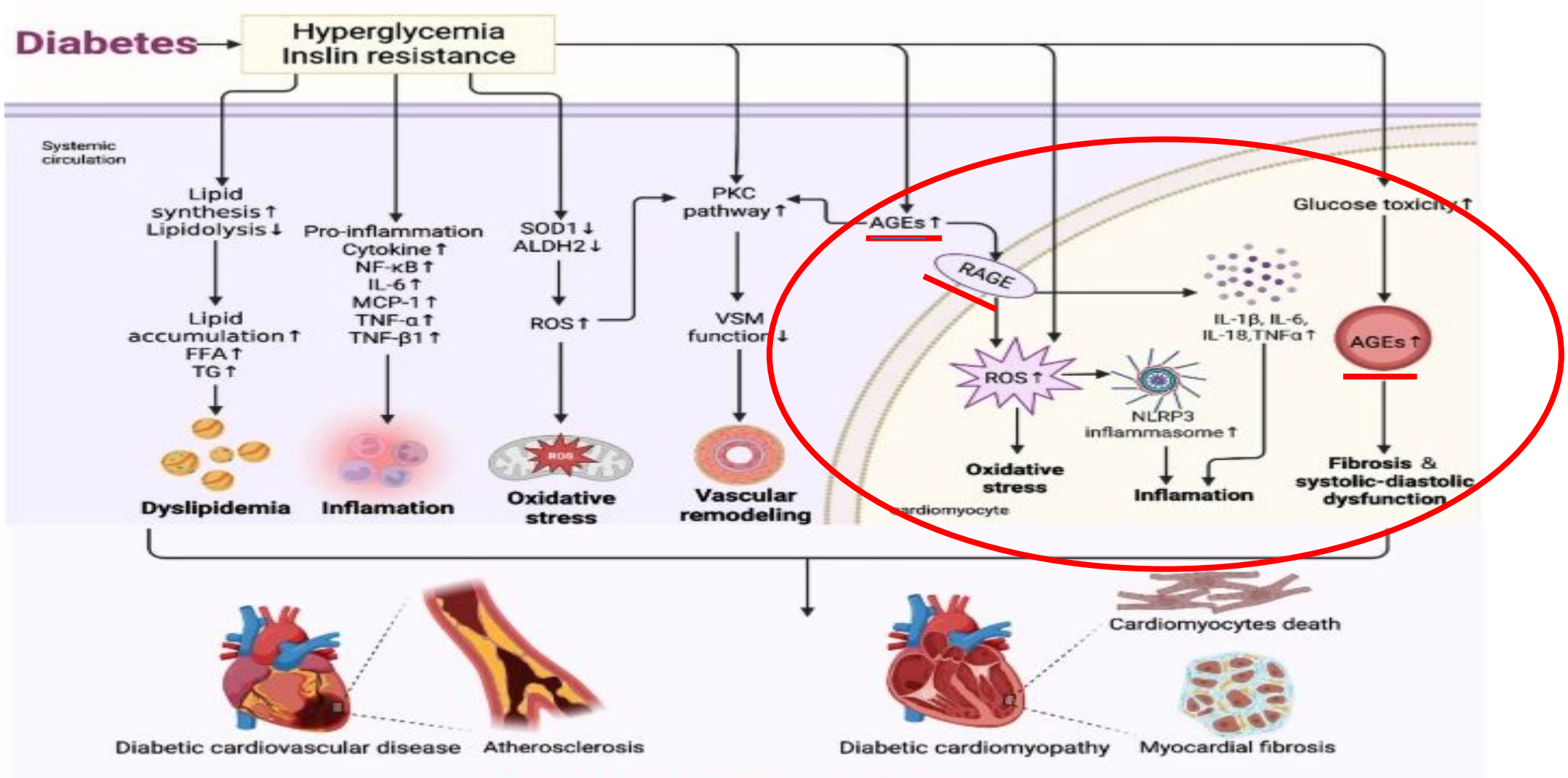
2. Insulin resistance (reduced effect of insulin in target tissues) leads to:
   - Hyperglycemia, due to reduced glucose disposal in muscle and accelerated hepatic glucose production[1]
   - Increased circulating fatty acids (released from fat tissue)[1,2]

3. Increased free fatty acid release leads to diabetic dyslipidemia[2]

T2DM = type 2 diabetes mellitus
Adapted from Stumvoll et al.[1]

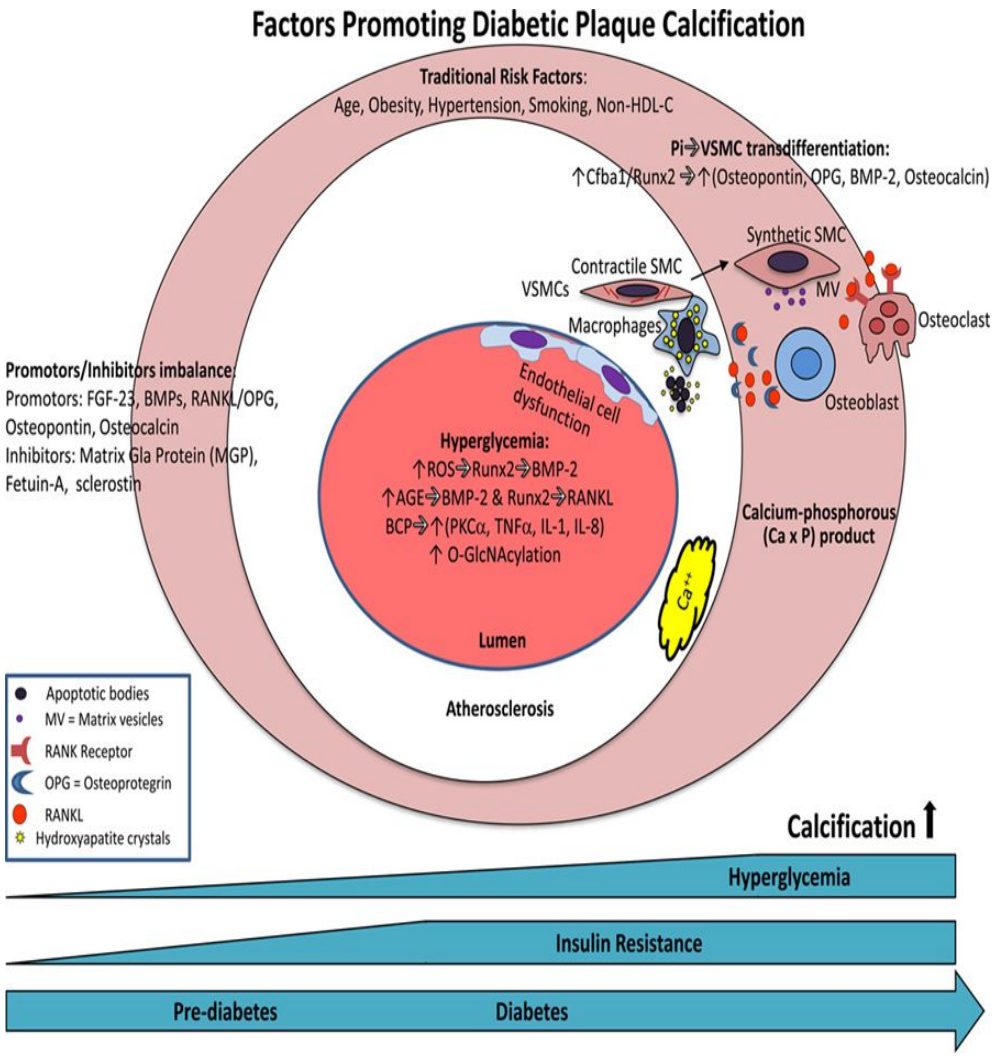
1. Stumvoll M, et al. *Lancet*. 2005;365(9467):1333-1346. 2. Mooradian AD. *Nat Clin Pract Endocrinol Metab*. 2009;5:150-159.

PATOGENESI DANNO VASCOLARE NEL DM

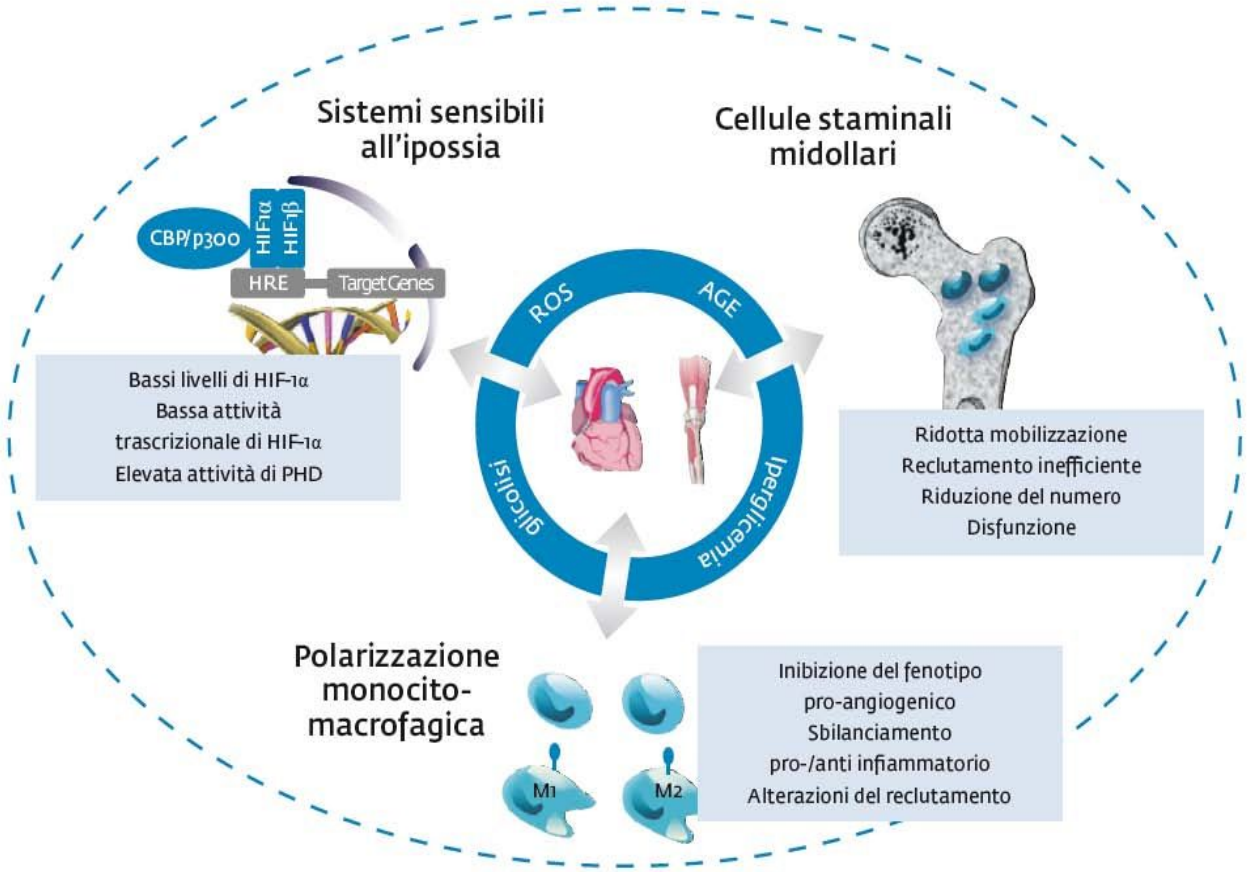


PATOGENESI DANNO VASCOLARE NEL DM

ECCESSO DI DANNO

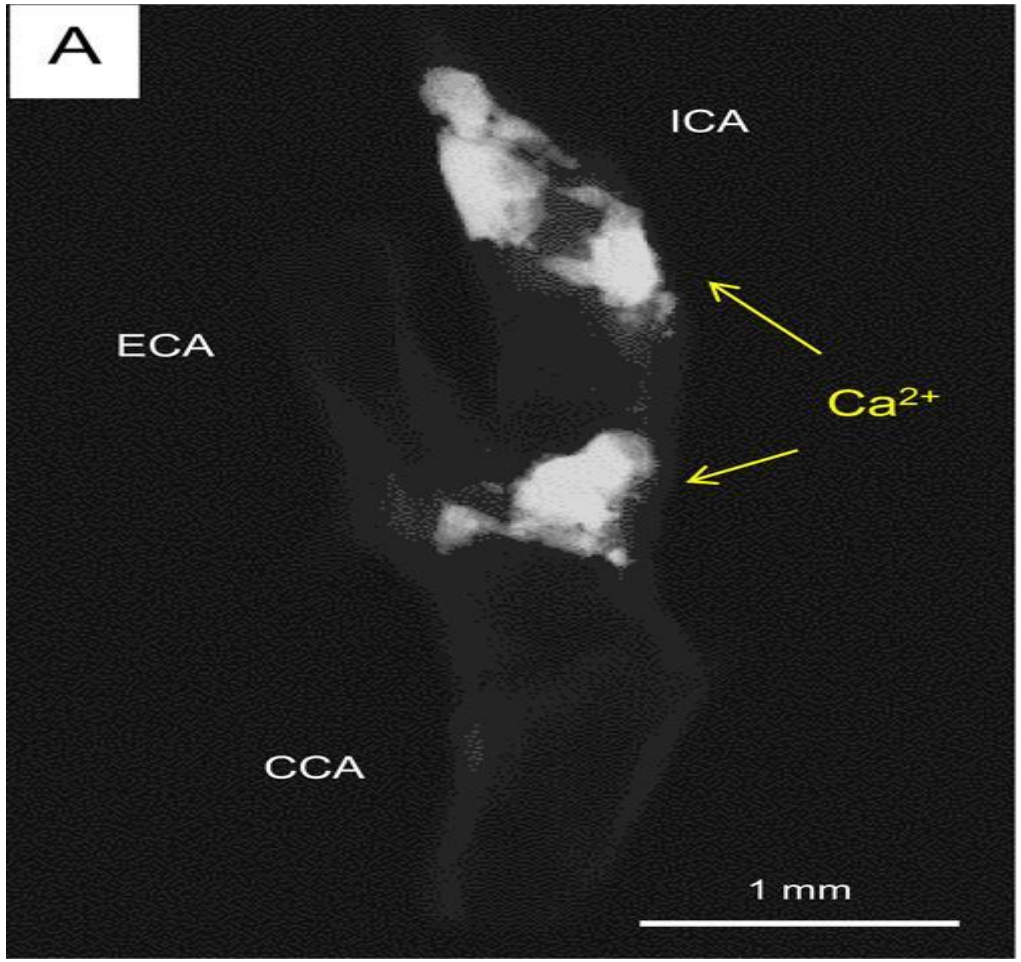


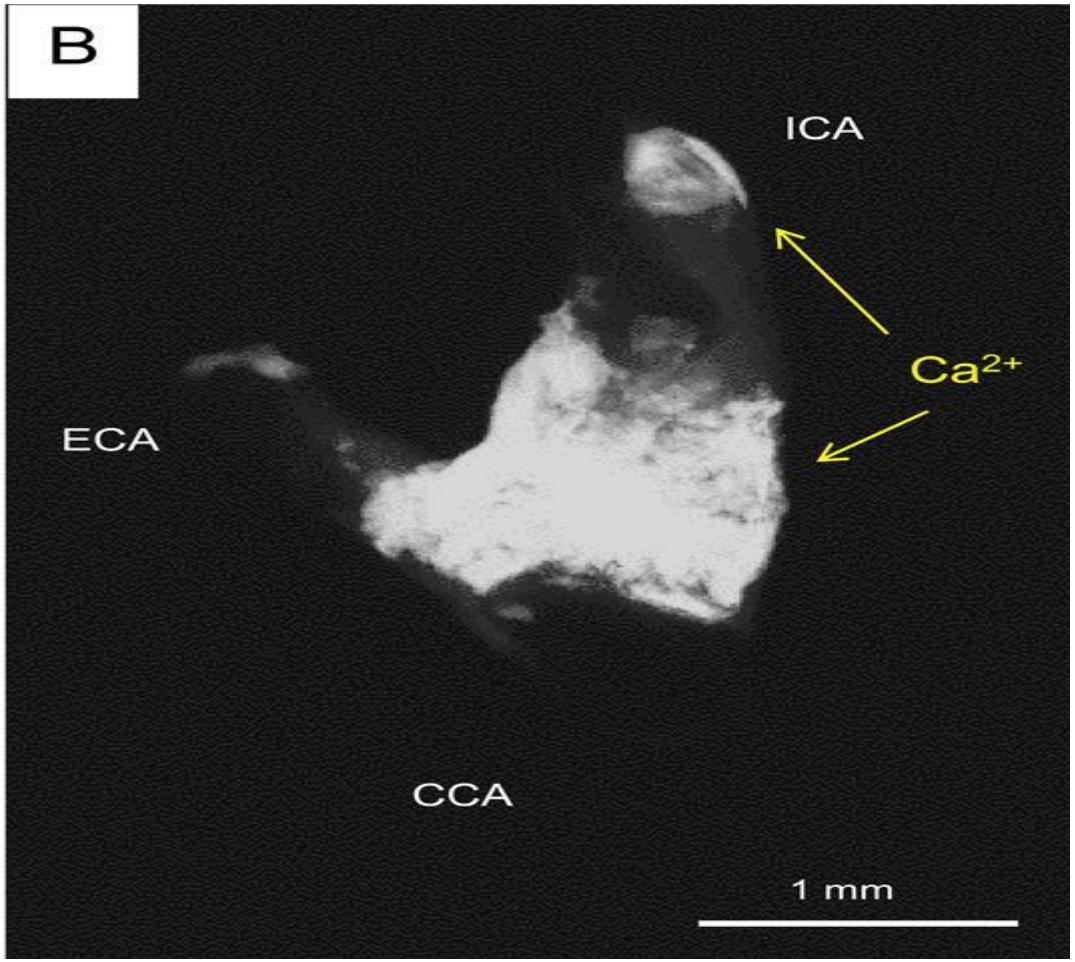
DIFETTO DI RIPARAZIONE



HIF, hypoxia inducible factor (fattore inducibile dall'ipossia). PHD, prolyl hydroxylase domain (idrossilasi dei domini in prolina). ROS, reactive oxygen species (specie reattive dell'ossigeno). AGE, advanced glycation end-products (prodotti di glicazione avanzata). Mod. da Howangyin et al. Arterioscler Thromb Vasc Biol 2014

PATOGENESI DANNO VASCOLARE NEL DM



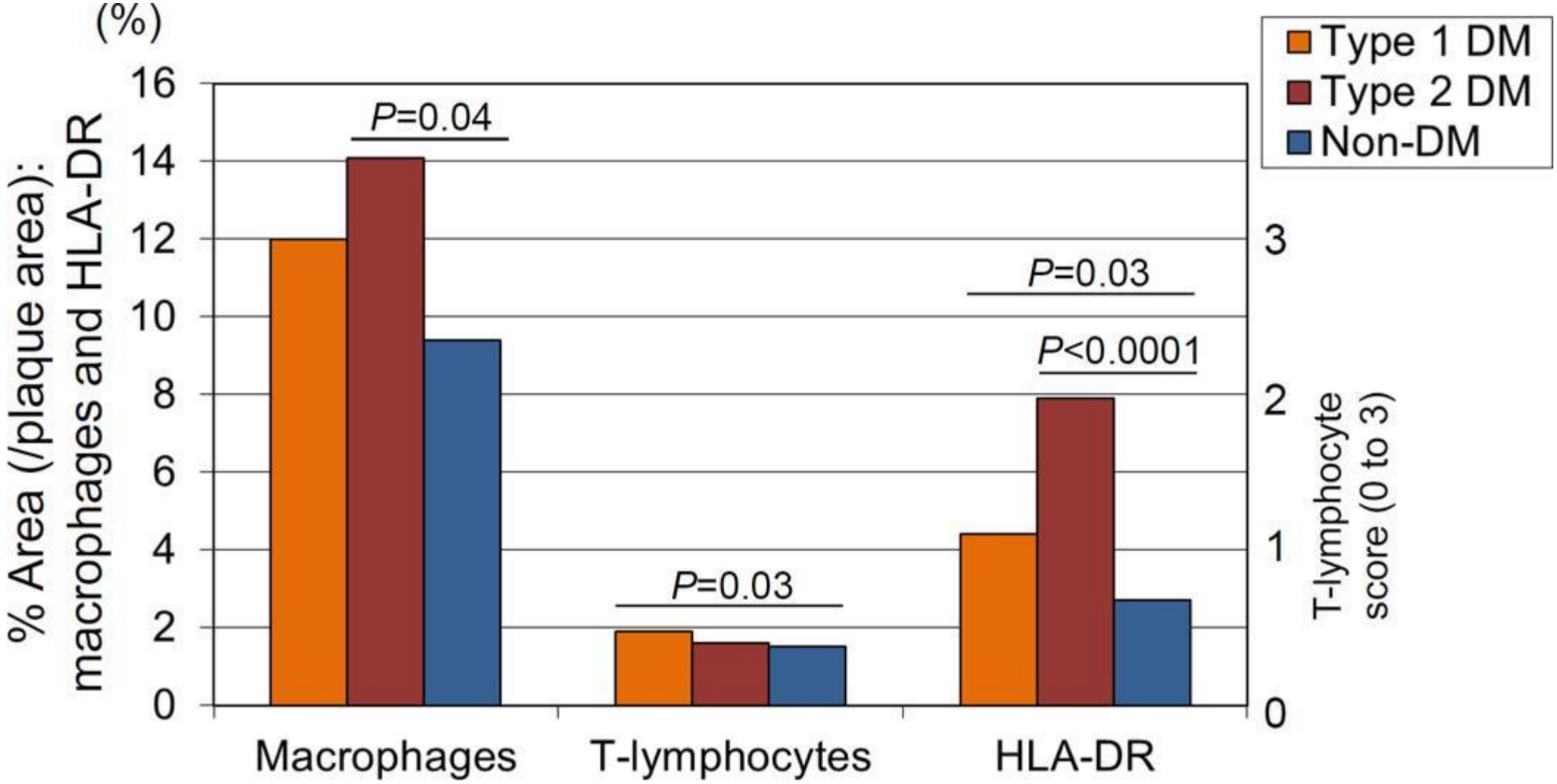


PAZ non DM
Area calcifica ICA 57,6 mm2

PAZ con DM
Area calcifica ICA 196,1 mm2

Carotid Plaque Calcification Predicts Future Cardiovascular Events in Type 2 Diabetes
Vigili de Kreutzenberg; et all *Diabetes Care* 2015;38(10):1937–1944

PATOGENESI DANNO VASCOLARE NEL DM



Pathology of Human Coronary and Carotid Artery Atherosclerosis and Vascular Calcification in Diabetes Mellitus

Kazuyuki Yahagi[1], Frank D Kolodgie[1], Christoph Lutter[1], Hiroyoshi Mori[1], Maria E Romero[1], Aloke V Finn[1], Renu Virmani[2]

ESC European Society of Cardiology
European Heart Journal (2020) 41, 748–758
doi:10.1093/eurheartj/ehz474
CLINICAL REVIEW
Imaging

ATEROSCLEROSI E DANNO ENDOTELALE

Imaging residual inflammatory cardiovascular risk

Charalambos Antoniades [1]*, Alexios S. Antonopoulos[1], and John Deanfield [2]

[1]Division of Cardiovascular Medicine, Radcliffe Department of Medicine, University of Oxford, UK; and [2]UCL Institute of Cardiovascular Science, London, UK

Received 3 December 2018; revised 13 February 2019; editorial decision 24 May 2019; accepted 24 June 2019; online publish-ahead-of-print 16 July 2019

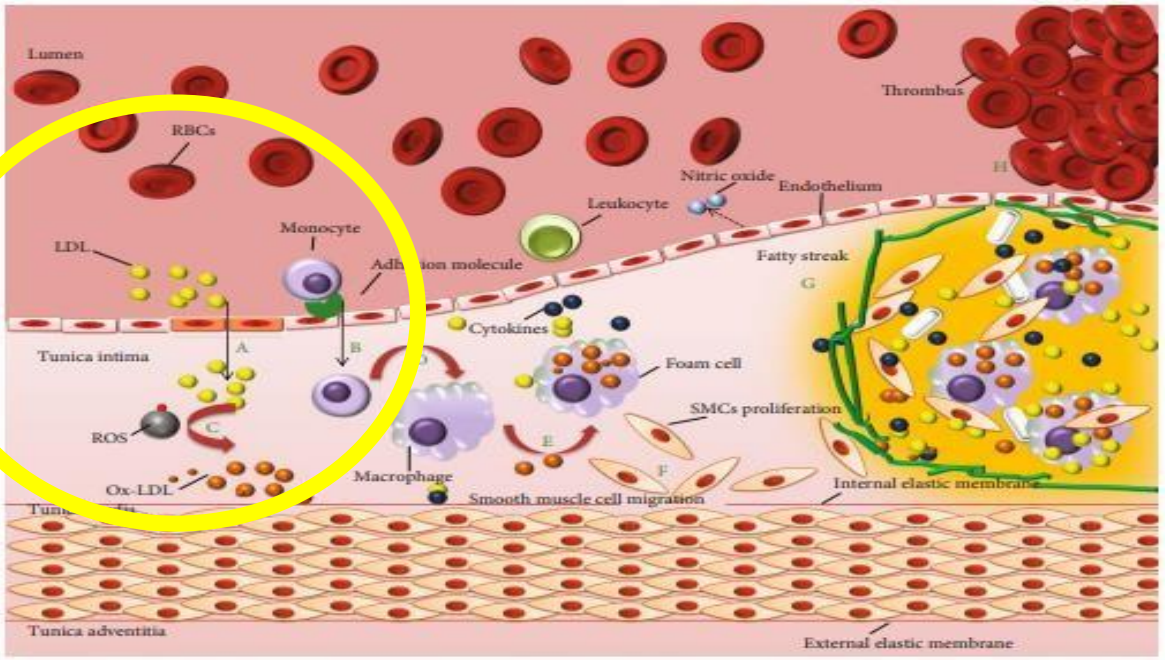
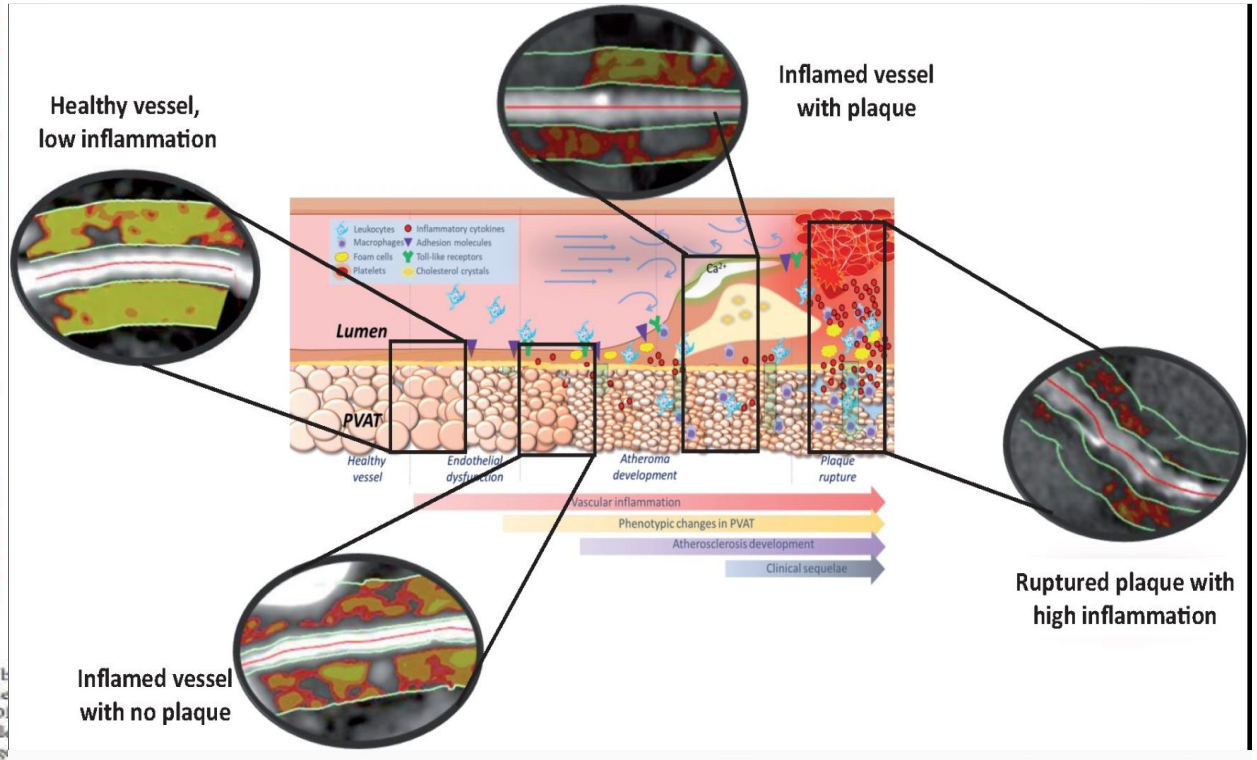
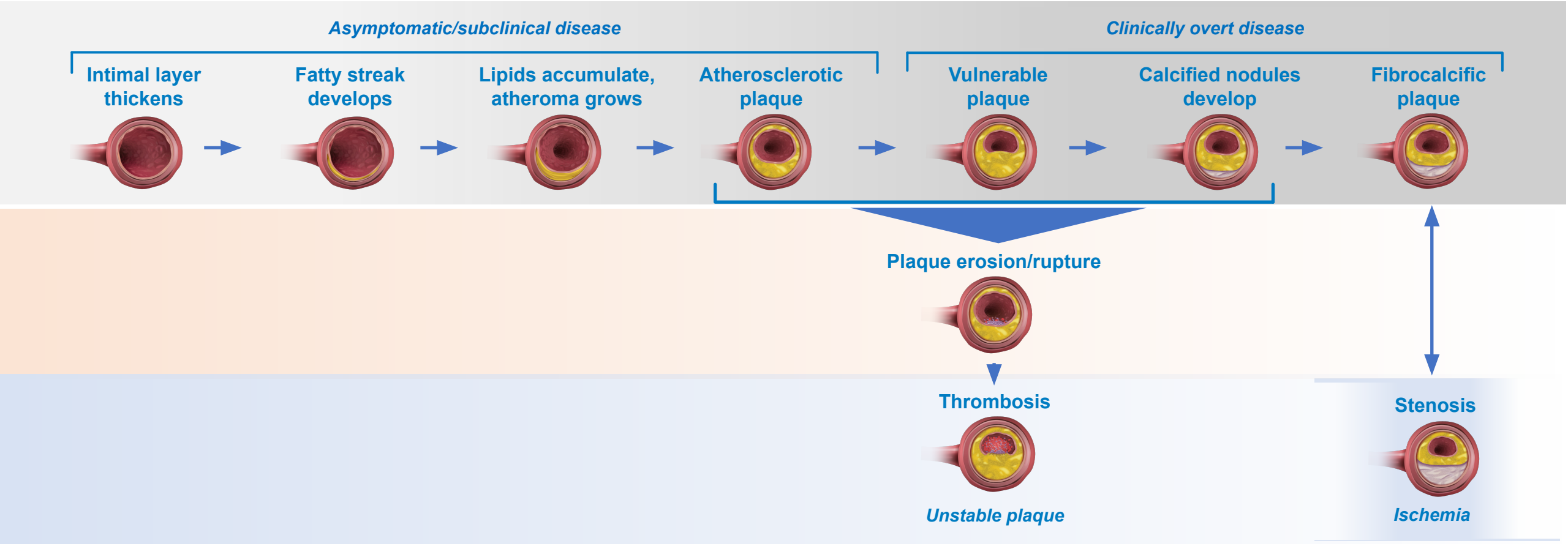


FIGURE 1: Schematic network of atherosclerosis process. The LDL in the blood stream passes through the damaged endothelium (caused b hypertension, high cholesterol, smoking, and hyperglycemia) gaining entry into tunica intima. Damaged endothelial cells being compromise express adhesion molecules that capture the monocytes. Monocytes enter into the intima producing free radicals which oxidizes the LD Oxidized LDL attracts more white blood cells (monocytes) and more immune cells to the site, macrophages engulf Ox-LDL particl becoming over laden and turning into foam cells. Foam cells die releasing its content outside that again is engulfed by other macrophag eventually building a large lesion area. Progression into this, lesion turns into plaque gradually accumulating calcium slats, smooth muscle cells (from tunica media), collagen, and the foam cells. The plaque is stable under the endothelium until the endothelium just above gets compromised. The damaged endothelium could no longer produce inhibitors for blood clotting making it more vulnerable to enter into the vessel lumen. The clot attached to the vessel wall would make a thrombus that may break causing stroke or myocardial infarction.



PROGRESSIONE DEL DANNO VASCOLARE



Le placche possono rimanere asintomatiche o diventare sufficientemente ostruttive da causare sintomatologia clinica

Le placche possono diventare vulnerabili e rompersi, provocando una trombosi acuta

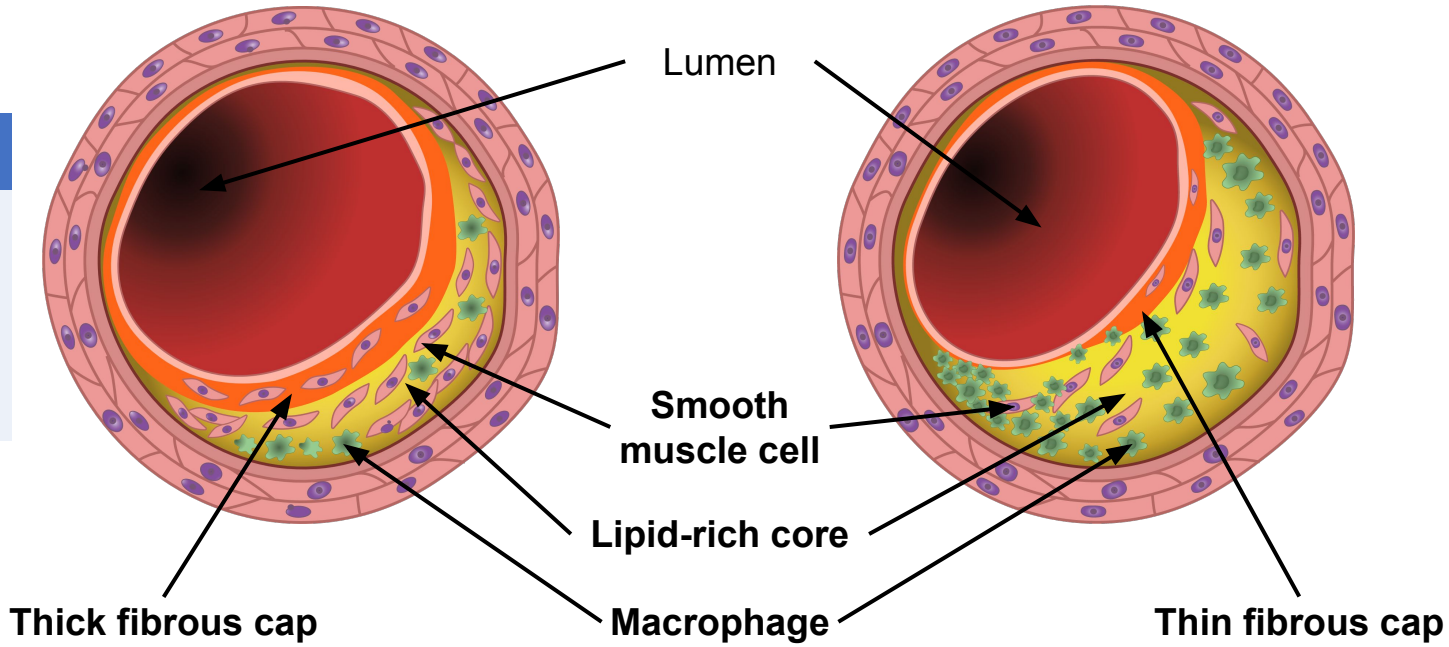
CVD, cardiovascular disease.

Sandfort V, er al. *Circ Cardiovasc Imaging.* 2015;8:e003316.

QUALI SONO LE CARATTERISTICHE PRINCIPALI DI UNA PLACCA VULNERABILE?

Stable plaque[1,2]

- Small lipid core
- Thick fibrous cap
- ⬆ Smooth muscle cells



Vulnerable plaque[1,2]

- Large lipid core
- Thin fibrous cap
- ⬆ Macrophages

Le caratteristiche della placca vulnerabile possono essere visualizzate utilizzando la tomografia a coerenza ottica (OCT)

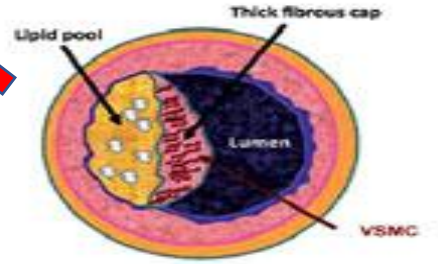
sono caratterizzate da

- **un sottile cappuccio fibroso (< 65 µm),**
- **un grande nucleo lipidico (arco lipidico > 90°)**
- **la presenza di cellule infiammatorie**

1. Virmani R, et al. *Thromb Vasc Biol*. 2000;20:1262-1275. 2. Stefanidis C, et al. *J Am Heart Assoc*. 2017;6:e005543.
3. MacNeill BD, et al. *Arterioscler Thromb Vasc Biol*. 2003;23:1333-1342.

LE PLACCHE SONO UGUALI IN TUTTI I DISTRETTI

STENOSI E > RESTENOSI POST PTA



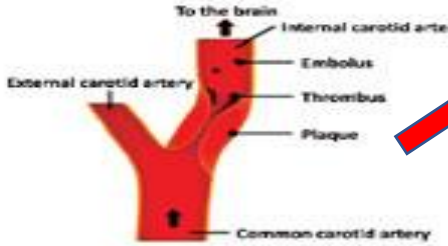
STABLE PLAQUE

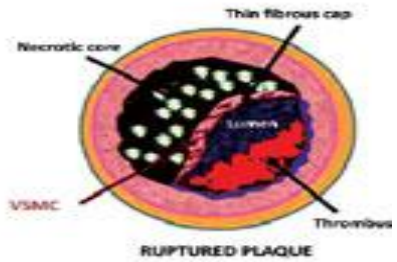
PERIPHERAL ARTERIAL PLAQUES
- **Predominant risk factors:** smoking and diabetes
- **Histological analysis:** fibroproliferative plaques with small amounts of lipids, high vascular smooth muscle cell (VSMC) content
- **Low density of vasa vasorum:** less inflammatory cells, more stable plaques
- **Plaque composition** promotes restenosis after revascularization procedures

CAROTID PLAQUES
- **Predominant risk factor:** arterial hypertension
- **Biomechanical regulation:** regions of **low shear stress, flow separation and departure from axially aligned, unidirectional flow** are prone to development of plaques
- **Histological analysis of vulnerable/rupture prone plaques:** thin fibrous cover, big lipid core, high wall stress
- **Plaque composition** leads to embolic events

Atherosclerotic lesions differ in vascular beds

EVENTI EMBOLICI





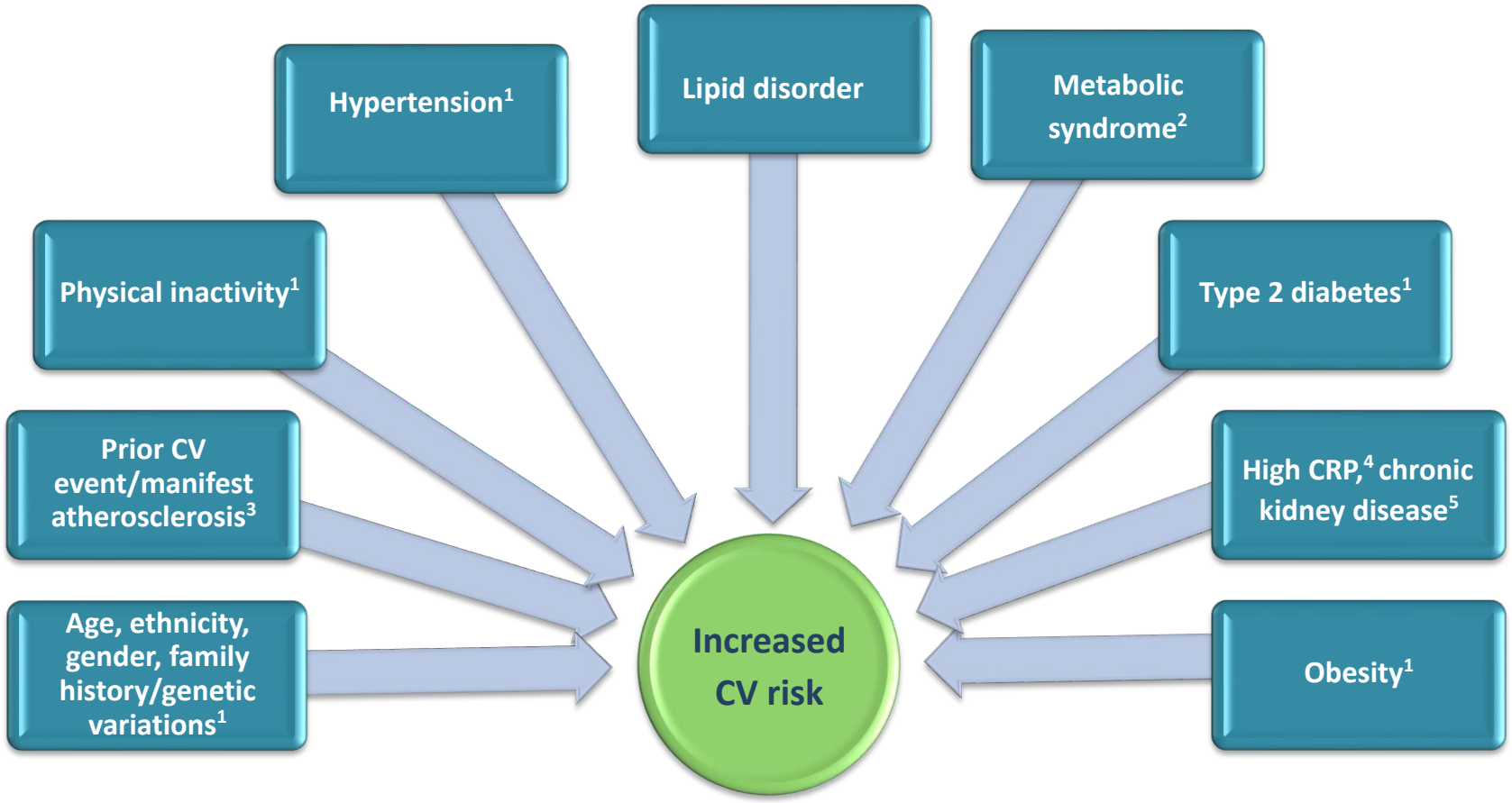
RUPTURED PLAQUE

CORONARY PLAQUES
- **Predominant risk factor:** hyperlipidaemia
- **High vasa vasorum density:** entry points for pro-inflammatory and pro-atherosclerotic components in the vessel wall
- **Histological analysis:** a large lipid core, low vascular smooth muscle cell (VSMC) content
- **Plaque composition** frequently leads to rupture and thrombotic occlusion

ROTTURA DI PLACCA E OCCLUSIONE

Pathology of Human Coronary and Carotid Artery Atherosclerosis and Vascular Calcification in Diabetes Mellitus
Kazuyuki Yahagi[1], Frank D Kolodgie[1], Christoph Lutter[1], Hiroyoshi Mori[1], Maria E Romero[1], Aloke V Finn[1], Renu Virmani[2] Arterioscler Thromb Vasc Biol. 2017 Feb;37(2):191-204.

Structure of Atherosclerotic Plaques in Different Vascular Territories: Clinical Relevance Curr Vasc Pharmacol. 2018 Jan 26;16(2):125-129

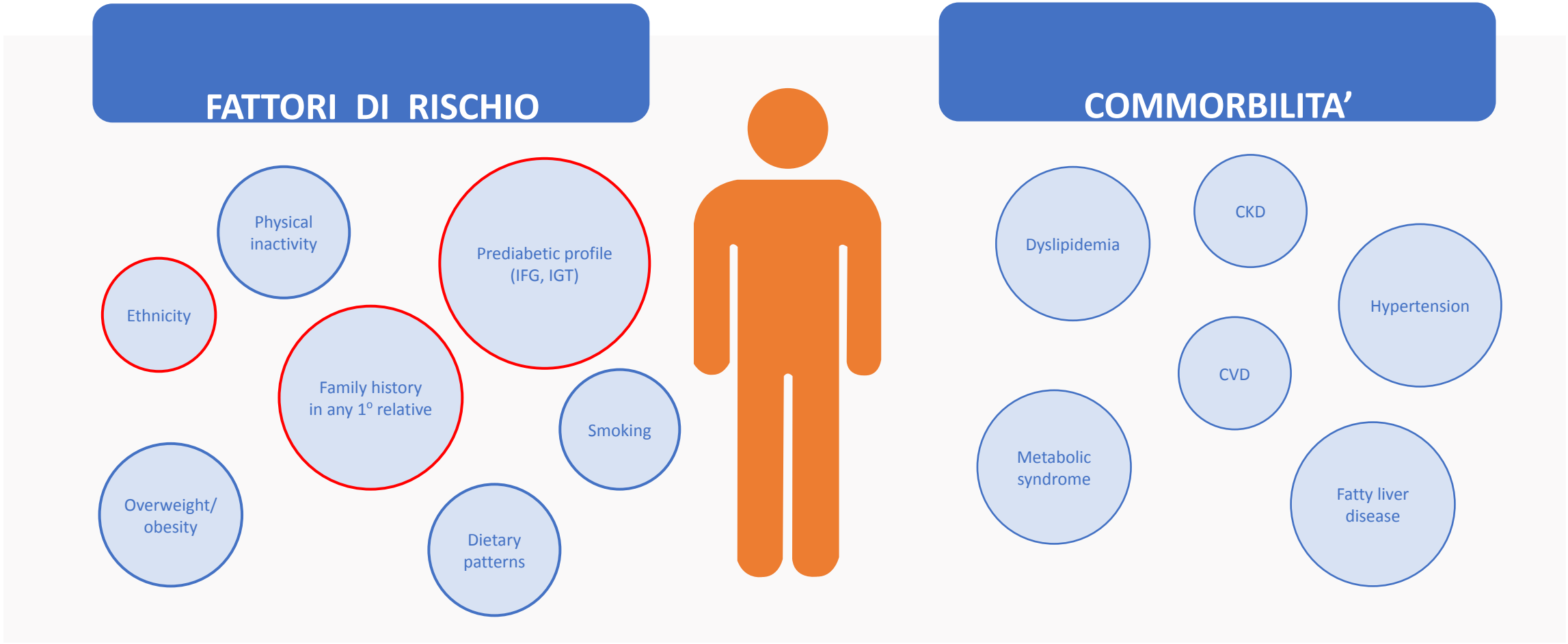


MULTIPLE FACTORS CONTRIBUTE TO INCREASED CV RISK

CRP, C-reactive protein; CV, cardiovascular; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TG, triglyceride.

1. World Heart Federation. Cardiovascular disease risk factors. www.world-heart-federation.org/cardiovascular-health/cardiovascular-disease-risk-factors. [Accessed 17 July 2015].
2. Dekker JM, et al. Circulation 2005;112:666–73.
3. Bhatt DL, et al. JAMA 2010;304:1350–7.
4. Lagrand WK, et al. Circulation 1999;100:96–102.
5. Go AS. N Engl J Med 2004;351:1296–305.

PROGRESSIONE DEL DANNO D'ORGANO DEL DM



CKD = chronic kidney disease; CVD = cardiovascular disease; IFG = impaired fasting glucose; IGT = impaired glucose tolerance; T2DM = type 2 diabetes mellitus.

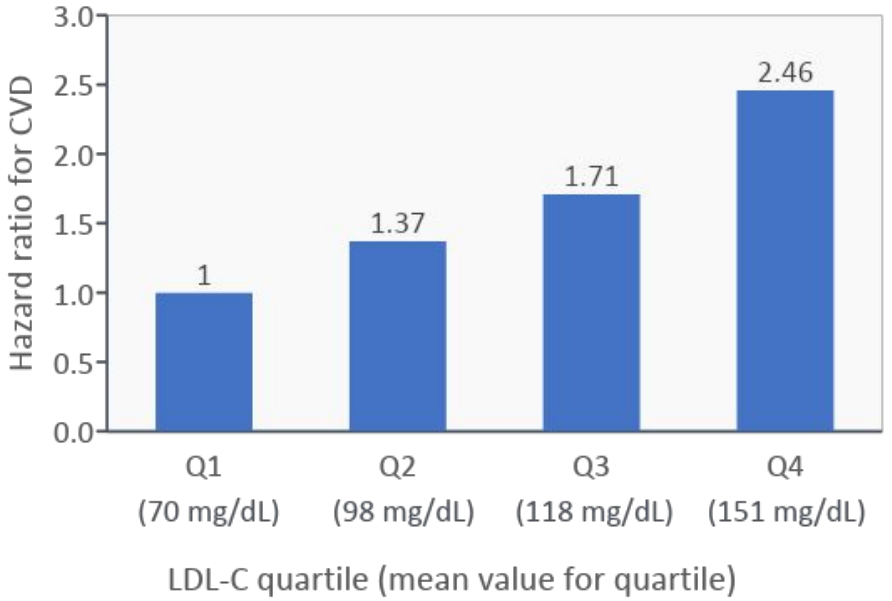
1. American Diabetes Association. *Diabetes Care*. 2017;40(Suppl 1):S11-S24. 2. Preiss D, et al. *JAMA*. 2011;305(24):2556-2564.
3. Ryden L, et al. *Eur Heart J*. 2013;34:3035-3087. 4. Handelsman Y, et al. *Endocr Pract.* 2015;21(Suppl 1):1-87.

LDL-C IS A RISK FACTOR AND INDEPENDENT PREDICTOR OF CVD IN PATIENTS WITH T2DM

LDL-C is the strongest independent predictor of CHD followed by HDL-C[1]

Variable	*P* value
LDL-C	< 0.0001
HDL-C	0.0001
HbA1c	0.0022
SBP	0.0065
Smoking	0.056

CVD risk appears to increase linearly from an LDL-C quartile average of 70 mg/dL[2]



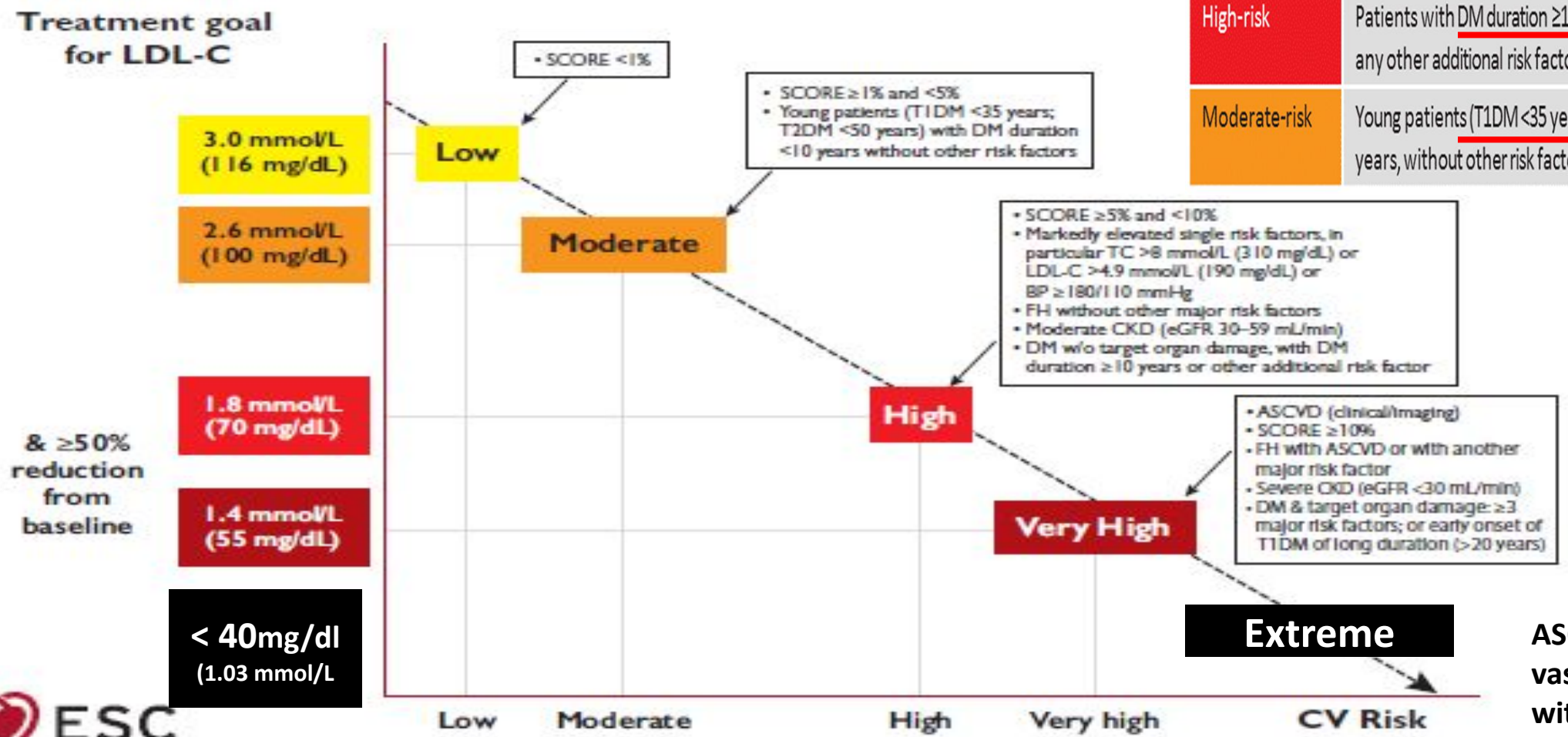
The 1998 UK Prospective Diabetes Study evaluated risk factors for CHD in 2,693 white patients with T2DM and no evidence of atheroma-related disease for a median follow-up duration of 7.9 years.[1] The Strong Heart Study published in 2000 evaluated CVD risk in 4,549 Native Americans with DM aged 45–74 years (average follow-up 4.8 years).[2]

CHD = coronary heart disease; CVD = cardiovascular disease; HbA1c = glycated hemoglobin; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; SBP = systolic blood pressure; UK = United Kingdom.

1. Turner RC, et al. *BMJ.* 1998;316:823-828. 2. Howard BV, et al. *Arterioscler Thromb Vasc Biol*. 2000;20:830-835.

MORE INTENSIFICATION OF TREATMENT GOAL ACCORDING TO CV RISK

Very high-risk	Patients with DM and established CVD or other target organ damage[a] or three or more major risk factors[b] 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 <35 years; T2DM <50 years) with DM duration <10 years, without other risk factors

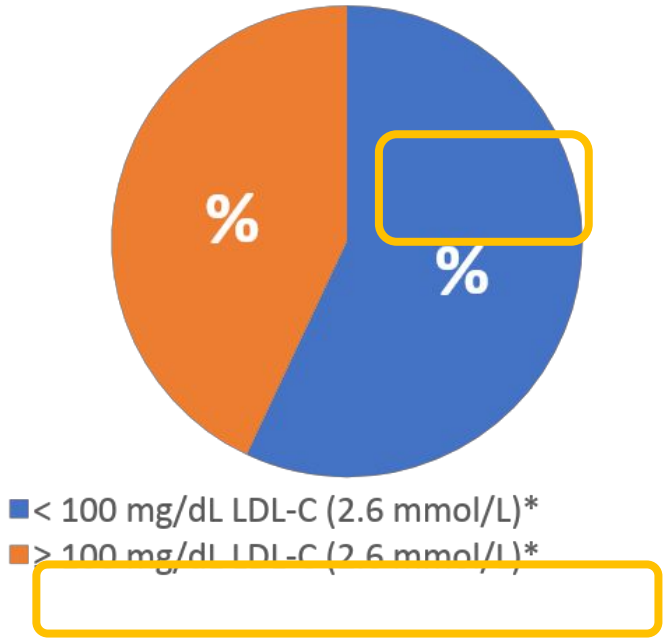


ASCVD and second vascular event within 2 years

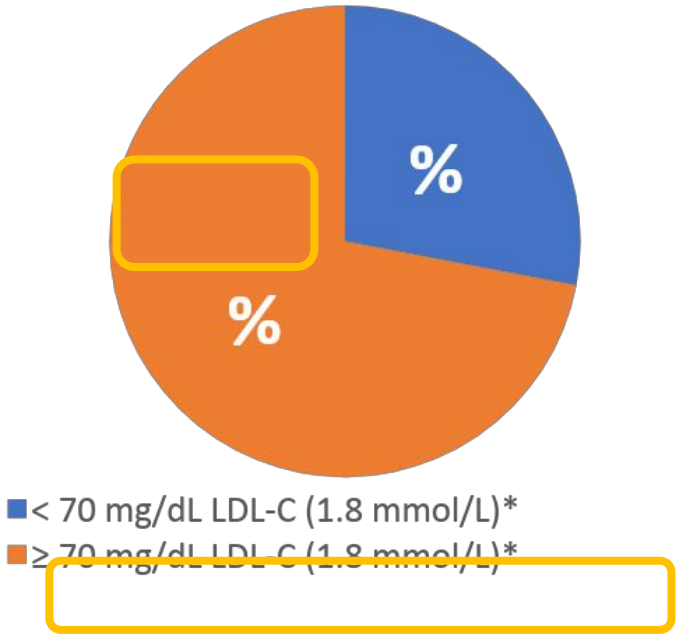
ESC
European Society of Cardiology

A SIGNIFICANT PROPORTION OF PATIENTS WITH DM MAY ALSO HAVE SUBOPTIMAL LDL-C LEVELS

PATIENTS WITH DM

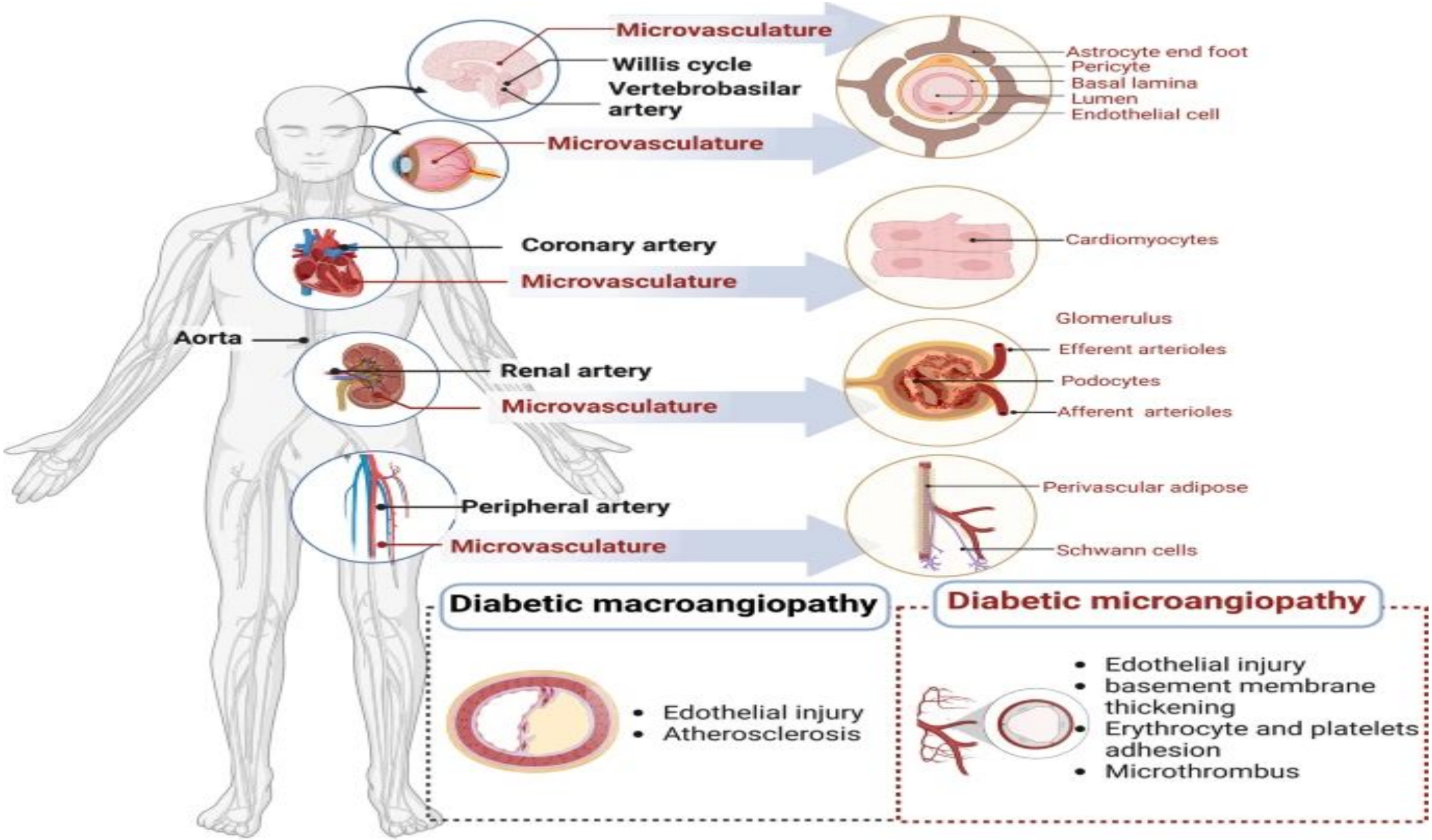


PATIENTS WITH DM AND CVD

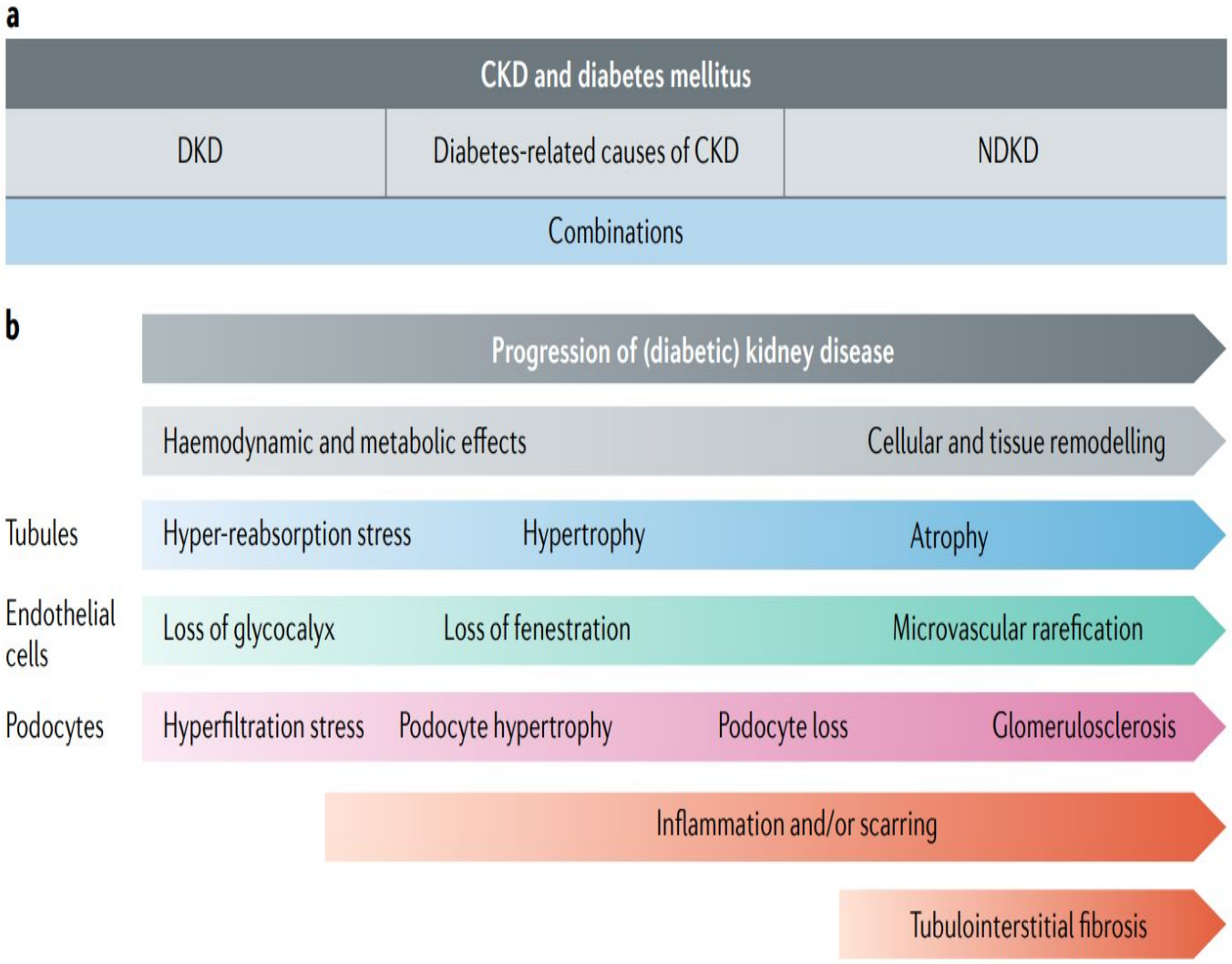


Data: 3,355 adults with a diagnosis of diabetes from a health care professional who participated in the National Health and Nutrition Examination Survey (NHANES; 2007–2010).
*LDL-C targets as defined by the American Diabetes Association; similar targets are defined by ESC[2].
CVD = cardiovascular disease; DM = diabetes mellitus; LDL-C = low-density lipoprotein cholesterol.
1. Ali MK, et al. *N Engl J Med*. 2013; 368:1613-1624. 2. Piepoli MF, et al. *Eur Heart J*. 2016;37:2315-2381.

DANNO D' ORGANO E COMPLICANZE CRONICHE DEL DM



DIABETE E PROGRESSIONE DEL DANNO RENALE

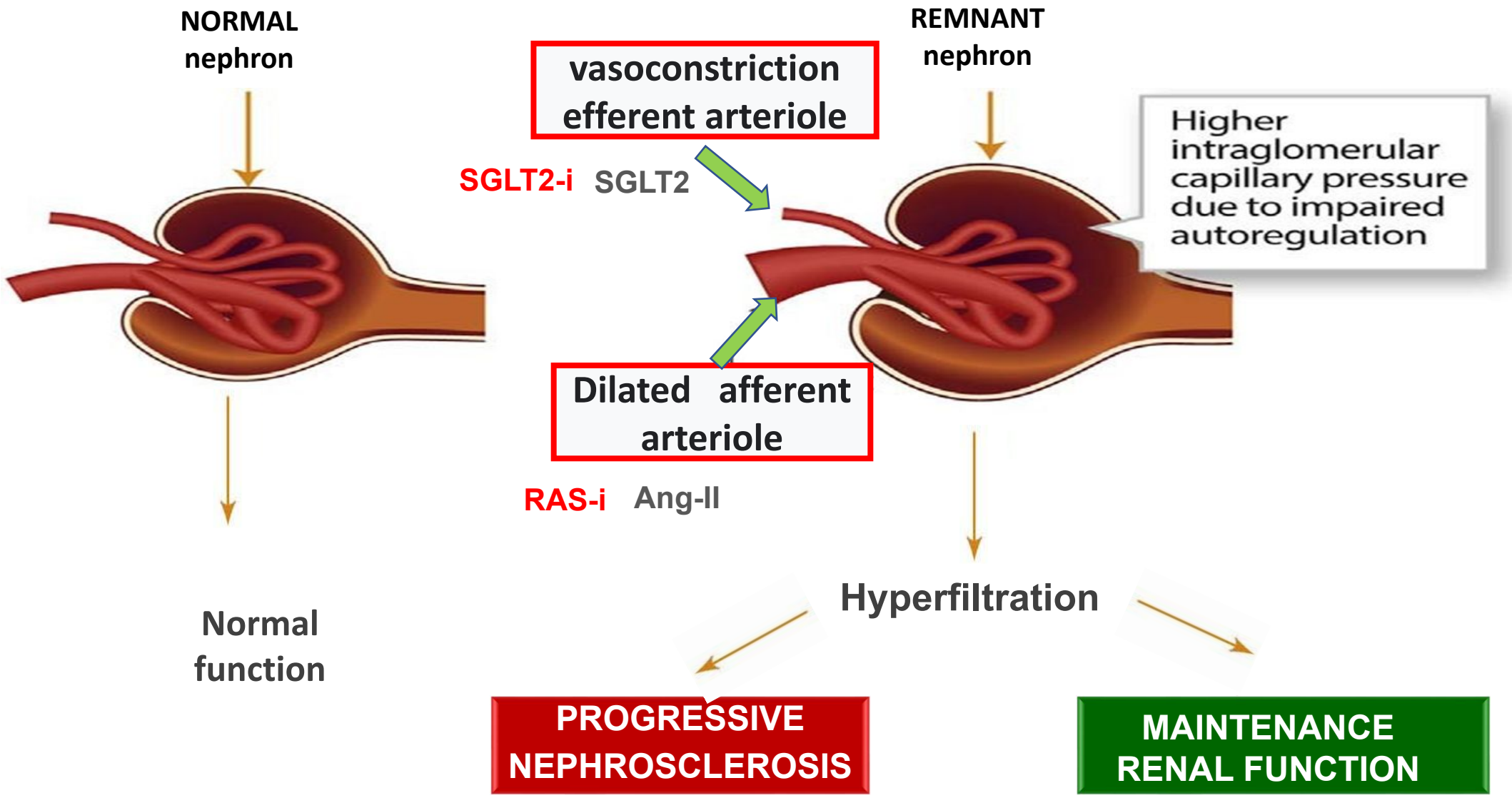


Diabetes and hypertension are responsible for more than half of all cases of CKD[1]

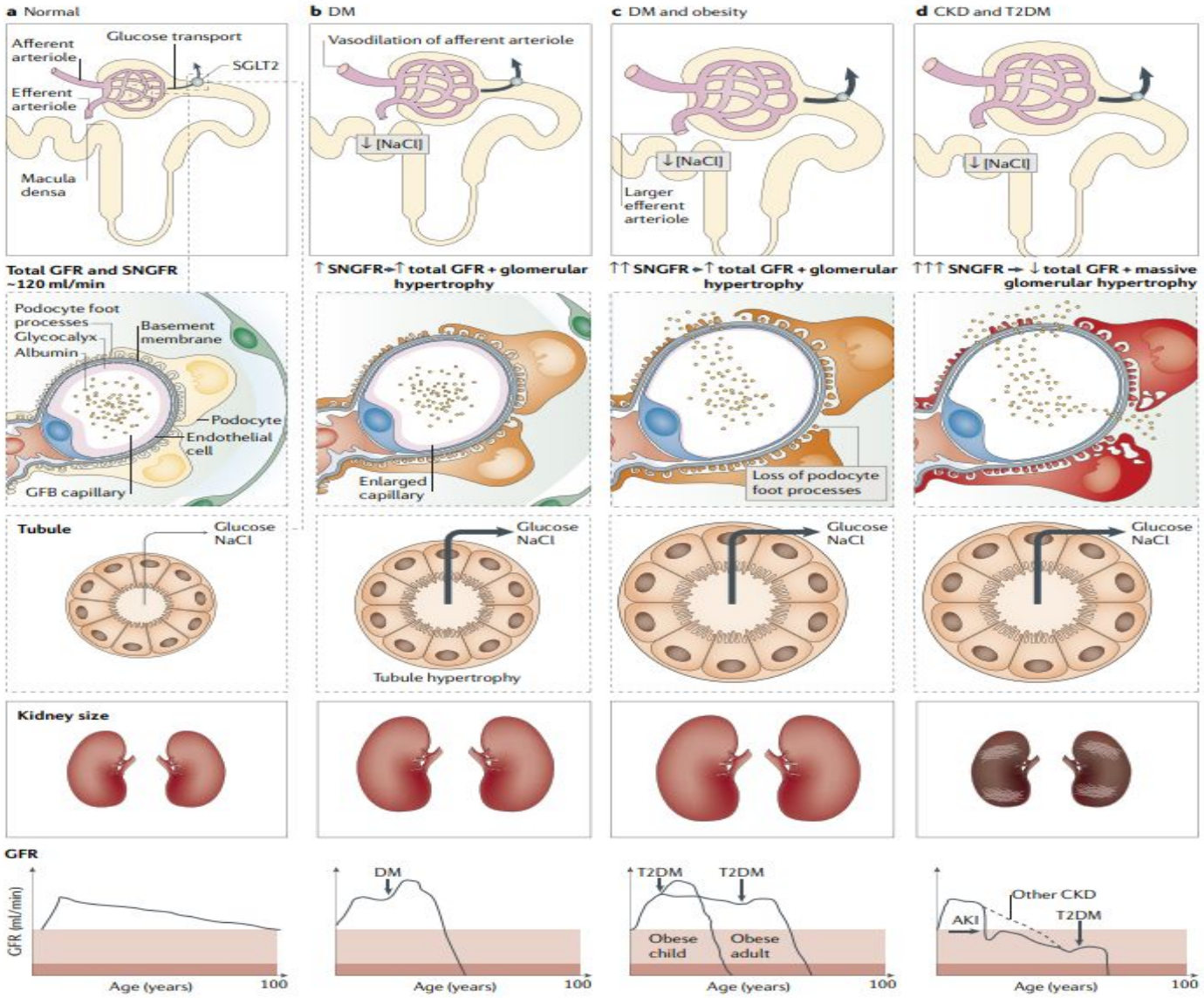
- Diabetic nephropathy[2]
- Hypertensive nephrosclerosis[3]
- IgA nephropathy[4]
- Focal segmental glomerulosclerosis[5]
- Obesity[2]
- Polycystic kidney disease[2]

1. Xie Y et al. *Kidney Int.* 2018;94:567–581; 2. Helal I et al. *Nat Rev Nephrol.* 2012;8:293–300; 3. Palatini P. *Nephrol Dial Transplant.* 2012;27:1708–1714; 4. Coppo R. *Nephrol Dial Transplant.* 2019;34:1832–1838; 5. Rosenberg AZ et al. *Clin J Am Soc Nephrol.* 2017;12:502–517.

HYPERFILTRATION: THE TWO SIDES OF THE COIN…
MICROANGIOPATHY …… SCLEROSIS

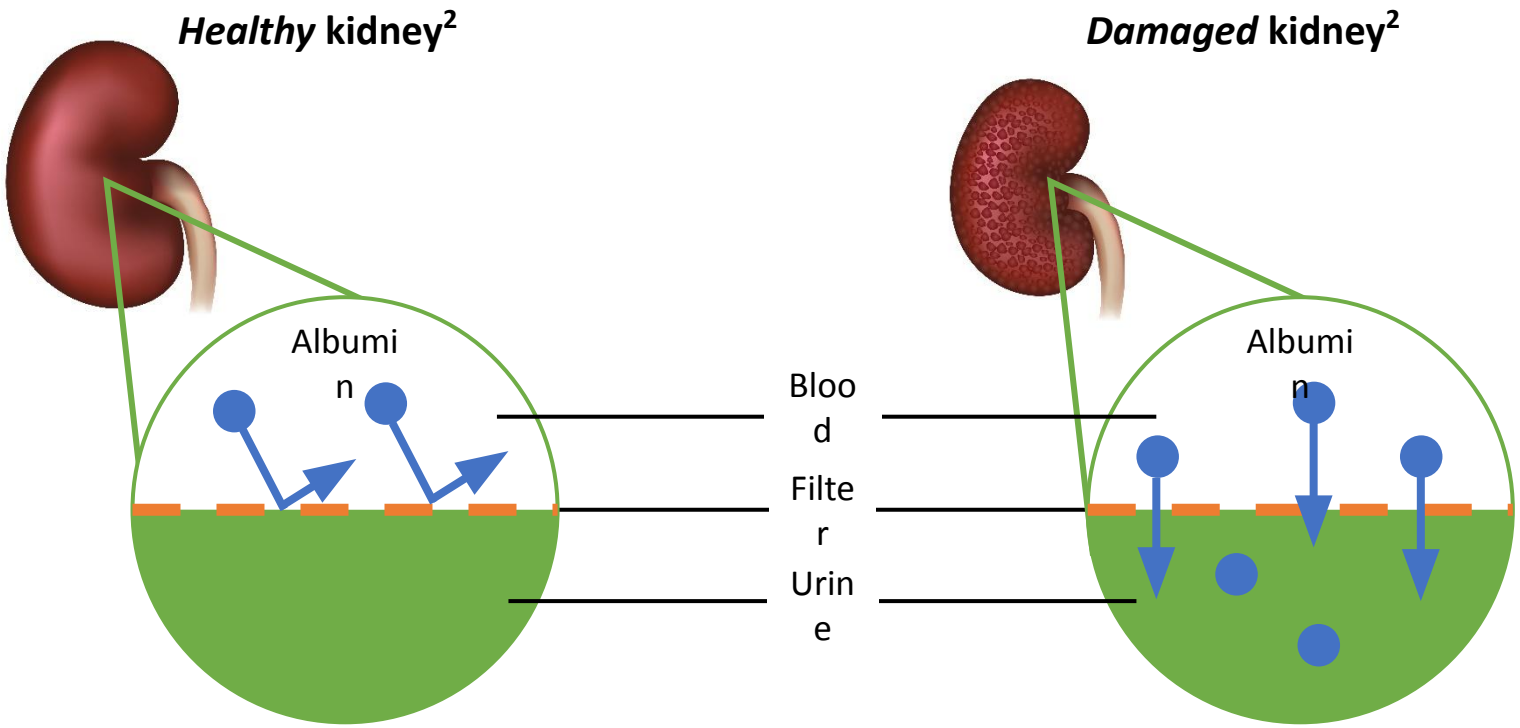


PATOGENESI DEL DANNO RENALE NEL DM



- Kidney hypertrophy
- Tubuloglomerular feedback
- Glomerular hyperfiltration
- Glomerular hypertension
- Inflammation Local expression of cytokines, adhesion molecules
- Podocyte injury and loss
- Nephron loss and CKD

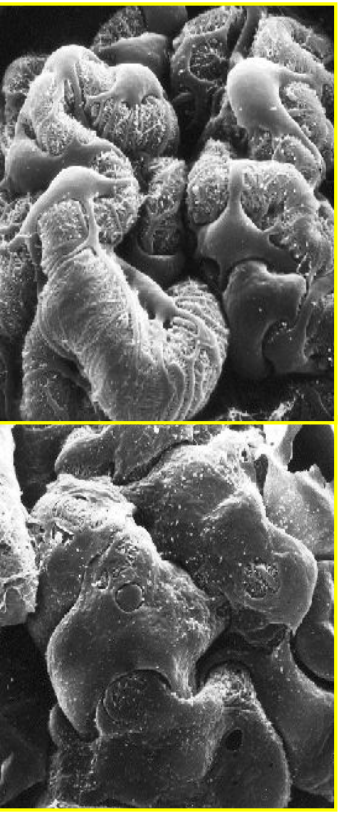
DAMAGE TO THE GLOMERULAR FILTRATION BARRIER LEADS TO DEVELOPMENT OF ALBUMINURIA

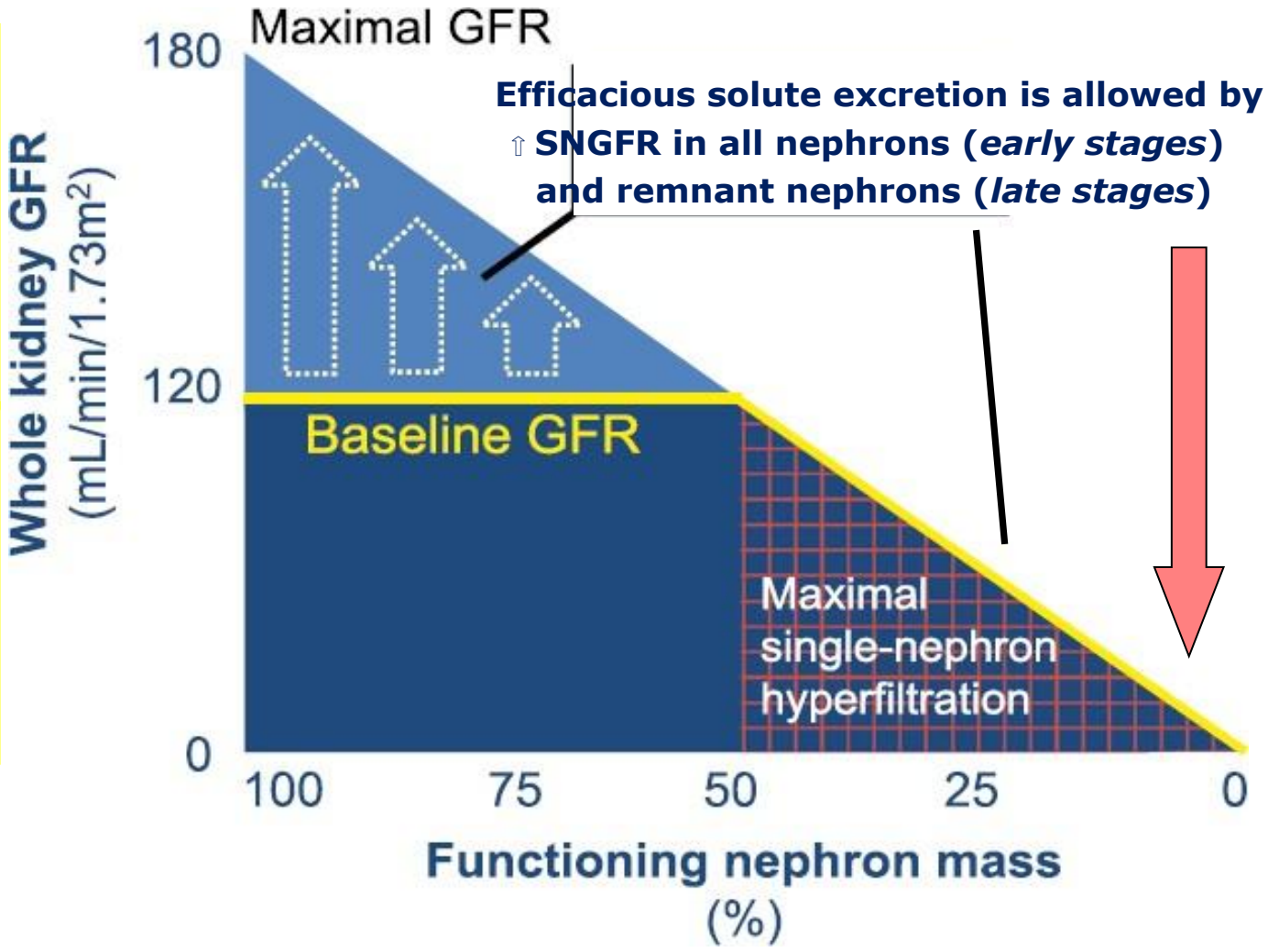


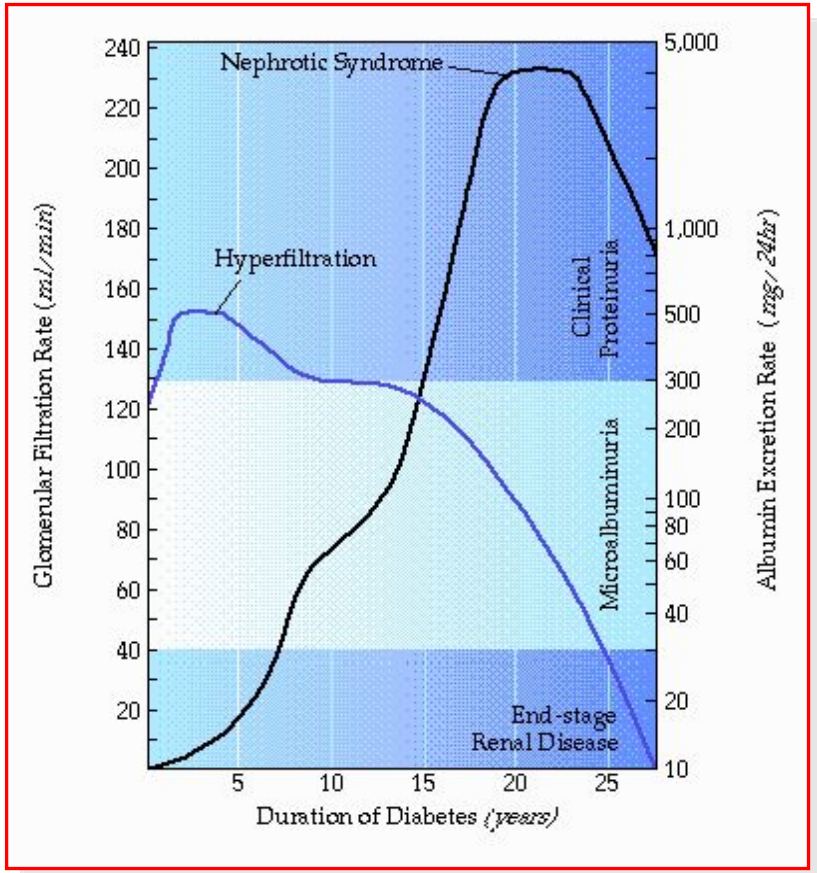
PROTEINURIA PLAYS A CRUCIAL PATHOGENIC ROLE IN THE LOSS OF KIDNEY FUNCTION AND ALSO SERVES AS A MARKER OF KIDNEY DAMAGE[3]

1. D'Amico G et al. Pathophysiology of proteinuria. *Kidney Int.* 2003;63:809–825.
2. National Institute of Diabetes and Digestive and Kidney Diseases. Albuminuria: Albumin in the urine. https://www.niddk.nih.gov/health-information/kidney-disease/chronic-kidney-disease-ckd/tests-diagnosis/albuminuria-albumin-urine. Accessed February 28, 2023.
3. Cravedi P et al. Pathophysiology of proteinuria and its value as an outcome measure in chronic kidney disease. *Br J Clin Pharmacol*. 2013;76:516–523

PROGRESSIONE DEL DANNO RENALE NEL DM





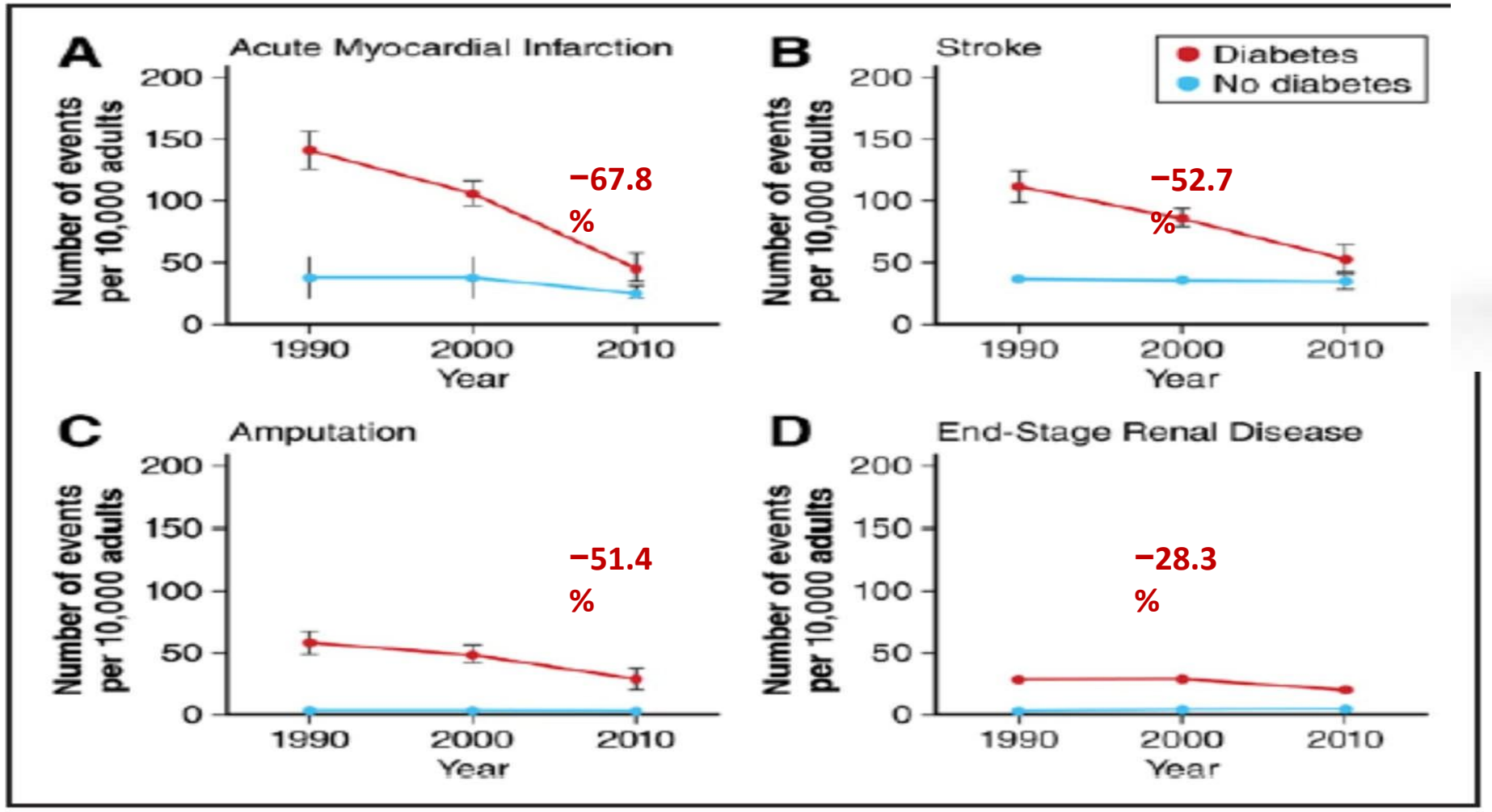


Modified from Tonneijck, JASN 2017

PROGNOSIS OF DIABETIC CKD

Changes in Diabetes-Related Complications in the United States, 1990–2010

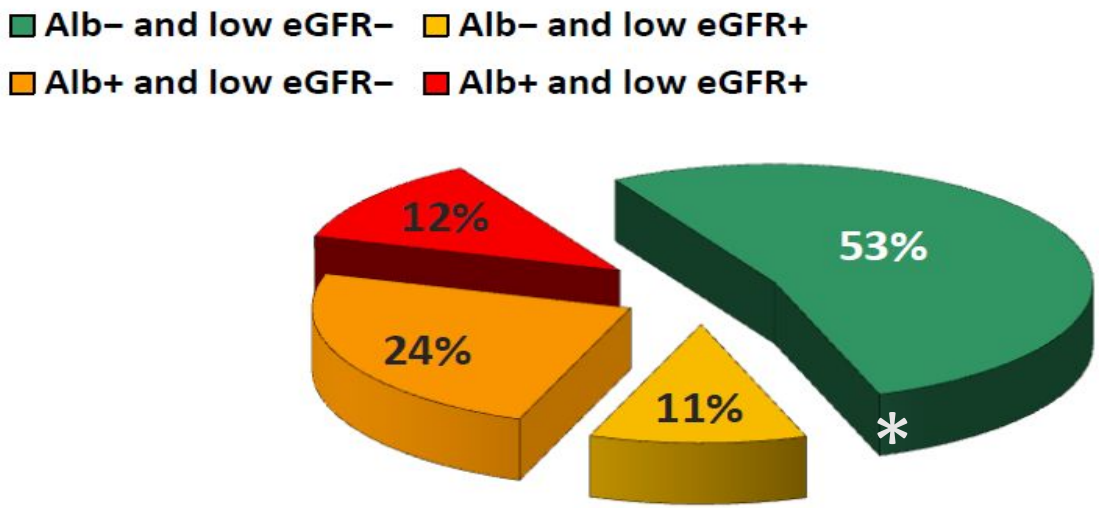
Data from the National Health Interview Survey, the National Hospital Discharge Survey, the U.S. Renal Data System, and the U.S. National Vital Statistics System



Gregg, NEJM 2014

Kidney dysfunction and related cardiovascular risk factors among patients with type 2 diabetes

Large cohort of patients (120.903) with type 2 diabetes mellitus attending 236 Italian Diabetes Clinics in 2009



Background. Kidney dysfunction is a strong predictor of end-stage renal disease and cardiovascular (CV) events. The main goal was to study the clinical correlates of diabetic kidney disease in a large cohort of patients with type 2 diabetes mellitus (T2DM) attending 236 Diabetes Clinics in Italy.
Methods. Clinical data of 120 903 patients were extracted from electronic medical records by means of an *ad hoc-developed* software. Estimated glomerular filtration rate (GFR) and increased urinary albumin excretion were considered. Factors associated with the presence of albuminuria only, GFR < 60 mL/min/1.73 m^2 only or both conditions were evaluated through multivariate analysis.

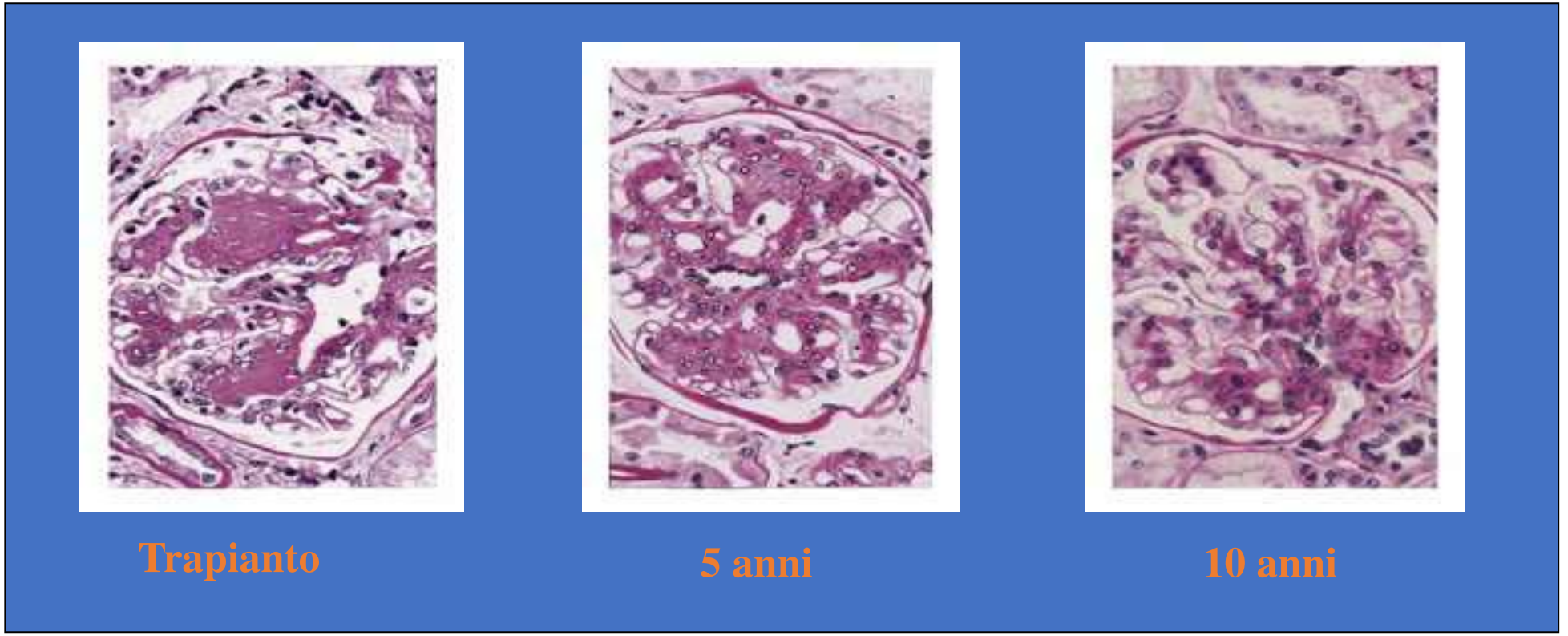
De Cosmo (RIACE) for AMD-Annals Study Group, NDT 2014

LA MALATTIA RENALE NELLE PERSONE CON DIABETE SI PRESENTA

NON SEMPRE CON A MICROALBUMINURIA COME PRIMO SEGNO

S. De Cosmo et al. for AMD-Annals Study Group, *NDT* 2014

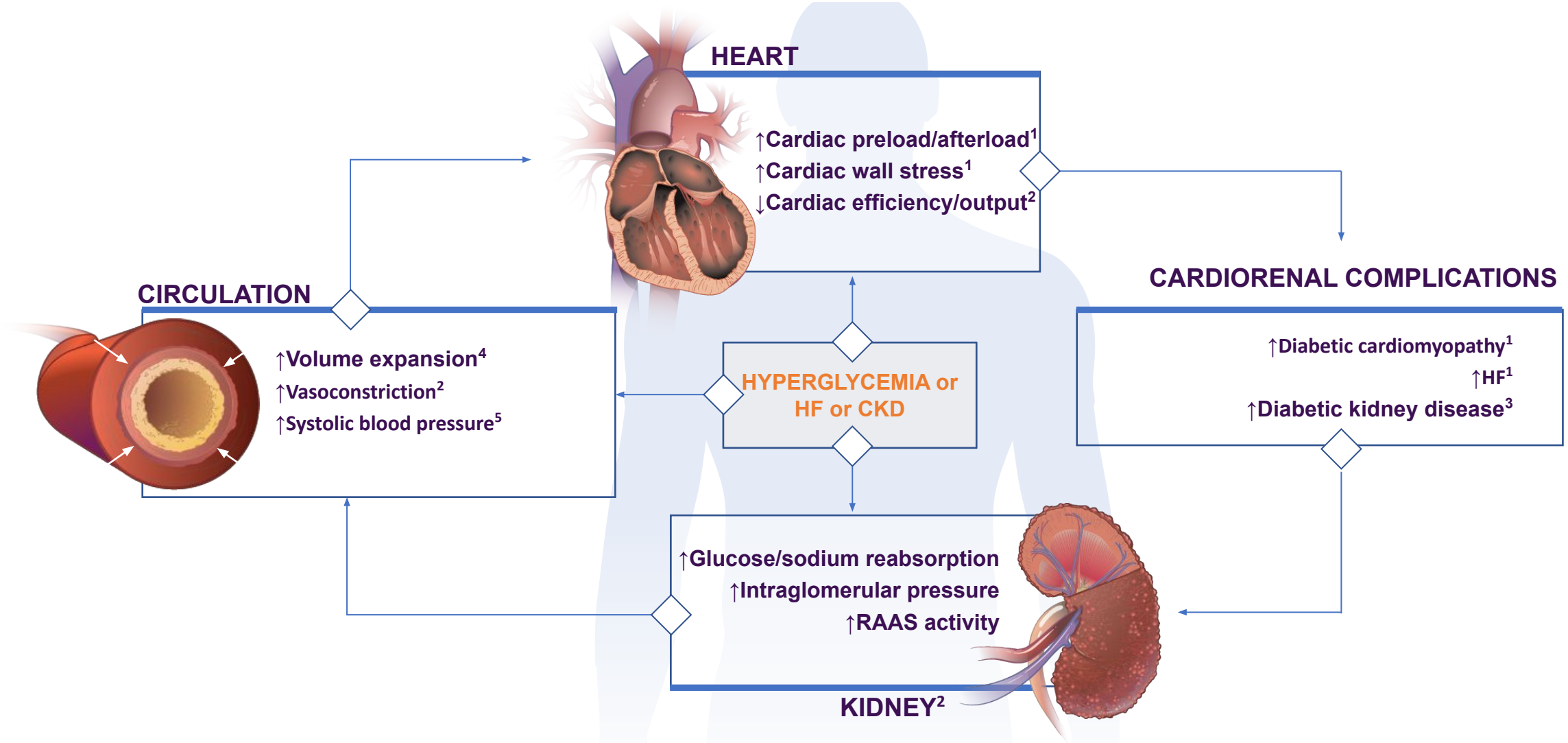
Regressione delle lesioni da nefropatia diabetica dopo trapianto di pancreas



Trapianto di pancreas per diabete mellito Pirsch]D,Andrews C, Hricik DE Commissione Rene-Pancreas della Societe Americana delle unit« di trapianto American Journal ofKidney Diseases, 1996; Vol 27 - 3 (March) , 444-450

PROGRESSIONE DEL DANNO D'ORGANO DEL DM SINDROME CARDIO –RENALE

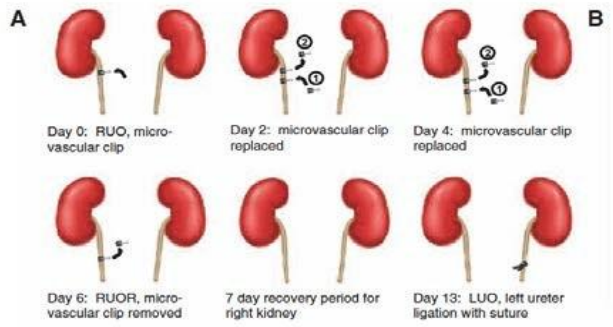
Back to Summary Slide

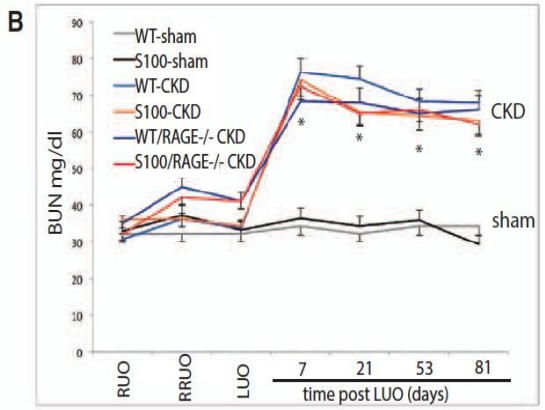


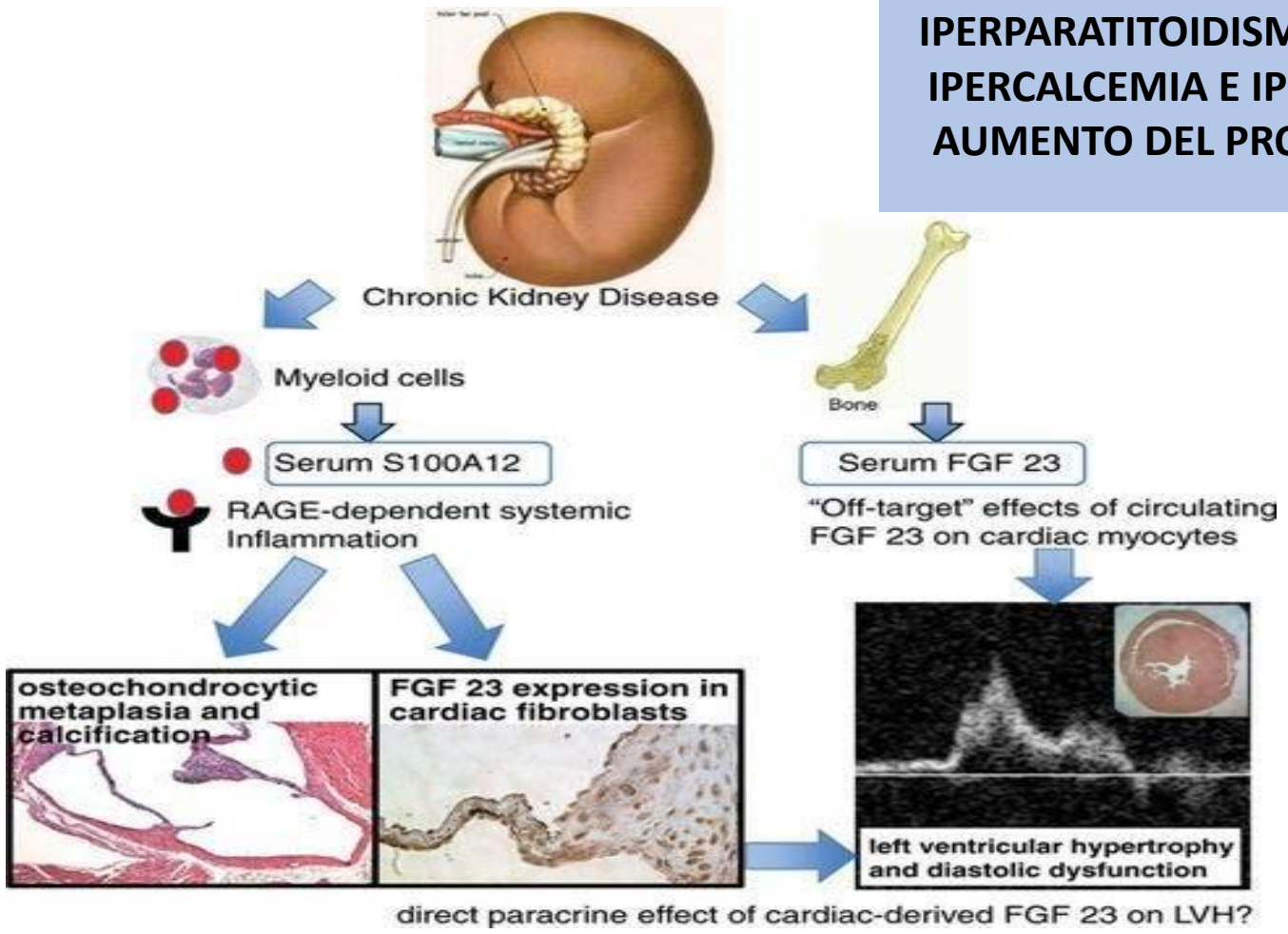
1. Muralidaran Y et al. *J Diabetes Metab.* 2015, 6:10. 2. Sattar N et al. *Diabetologia*. 2016;59(7):1333-1339. 3. Wanner C. *Am J Cardiol*. 2017;120(1S):S59-S67. 4. Sattar N et al. *Circulation*. 2018;138:7–9. 5. Mazidi M et al. *J Am Heart Assoc*. 2017;6(6):e004007.

PROGRESSIONE DELLA DKD
CALCIFICAZIONI VASCOLARI NEL DM

IPERPARATITOIDISMO SECONDARIO
IPERCALCEMIA E IPERFOSFOREMIA
AUMENTO DEL PRODOTTO Ca x P

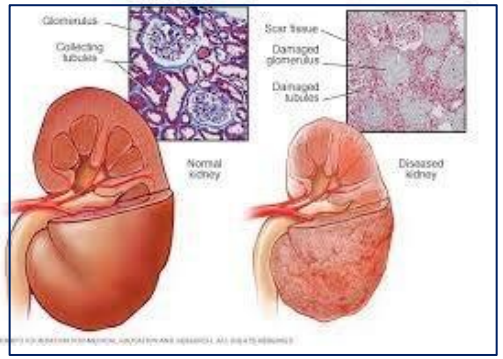




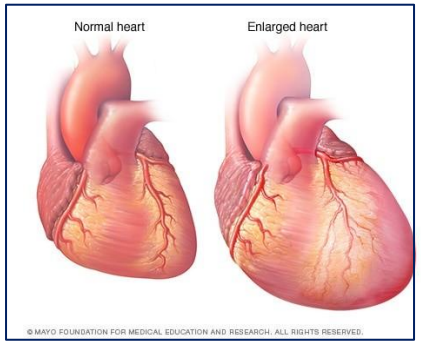


Ling Y, Arterioscler Thromb Vasc Biol. 2014;34:1399-1411

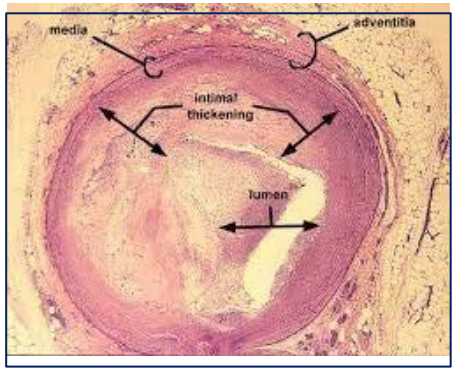
PROGRESSIONE
DELLA DKD CALCIFICAZIONI VASCOLARI



CUORE



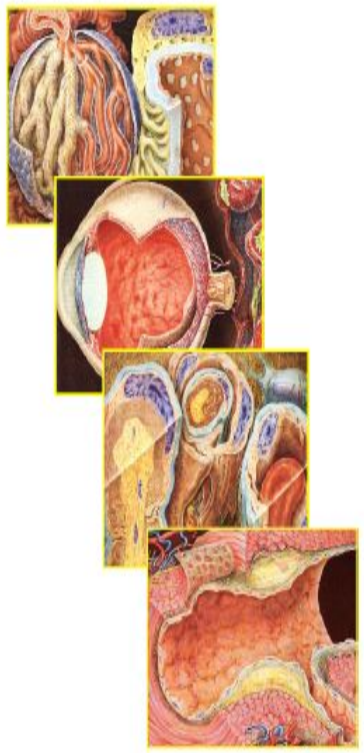
RENI

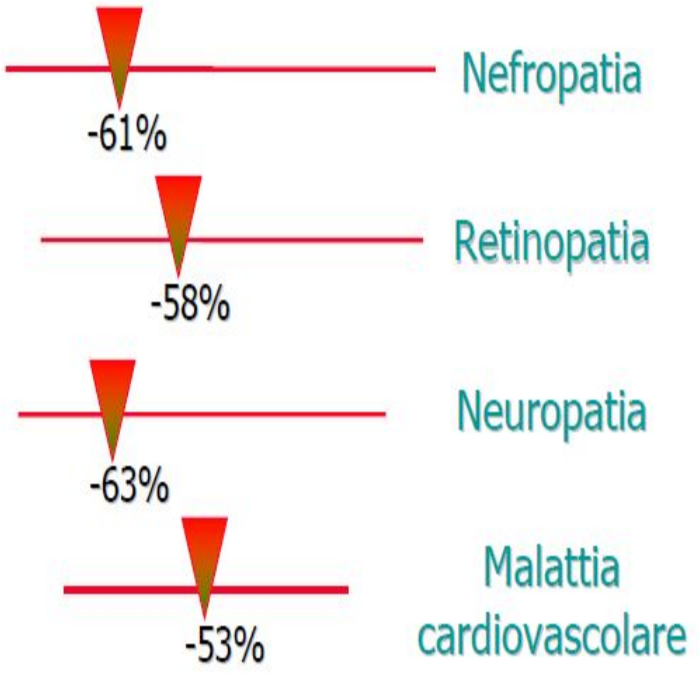


VASI

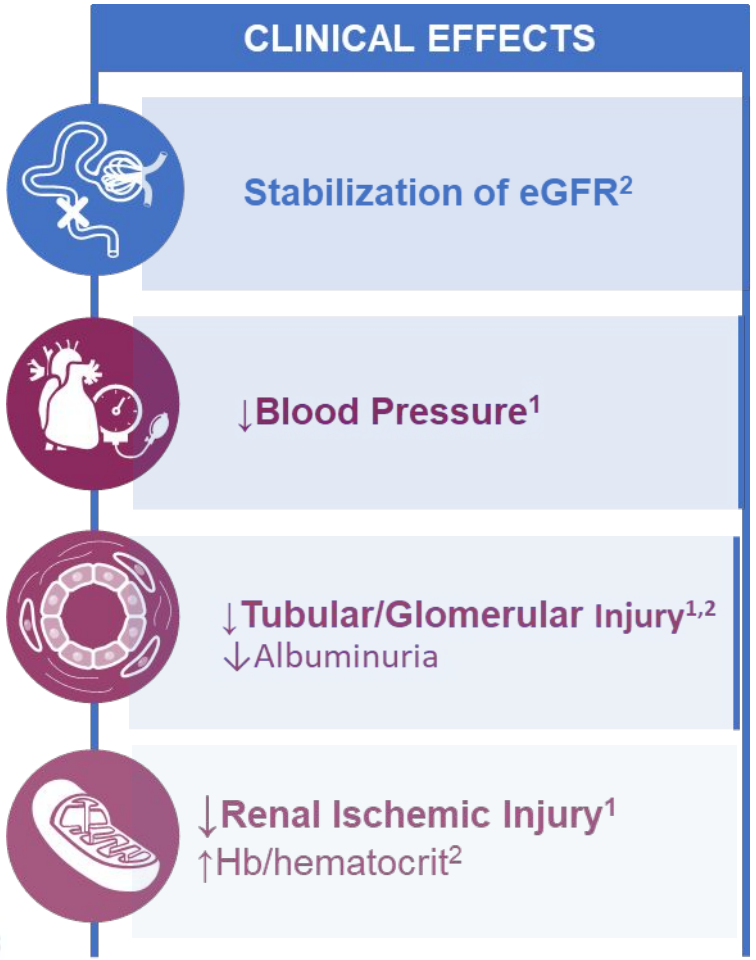
INTERVENTO MULTIFATTORIALE
COMPLICANZE DEL DIABETE

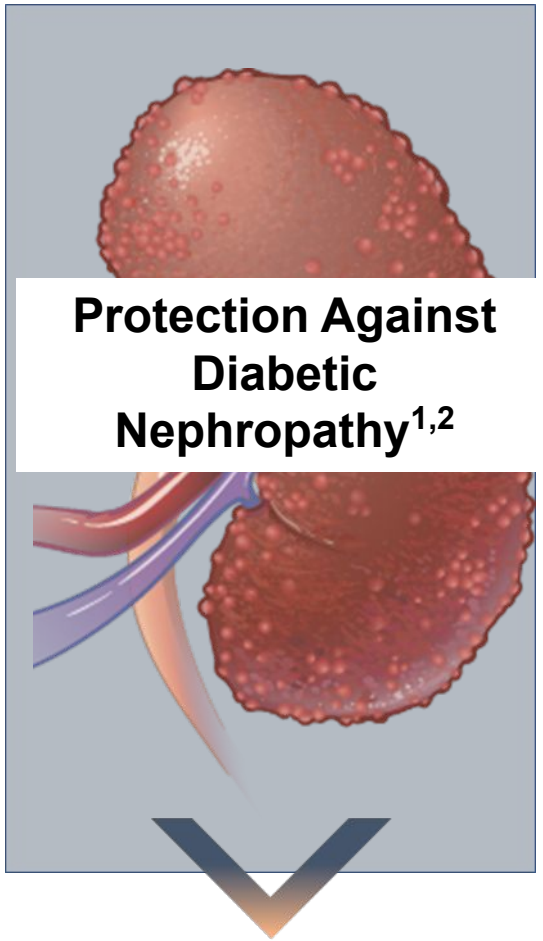
A favore della terapia intensiva: glicemia, pressione arteriosa, lipidi, aspirina



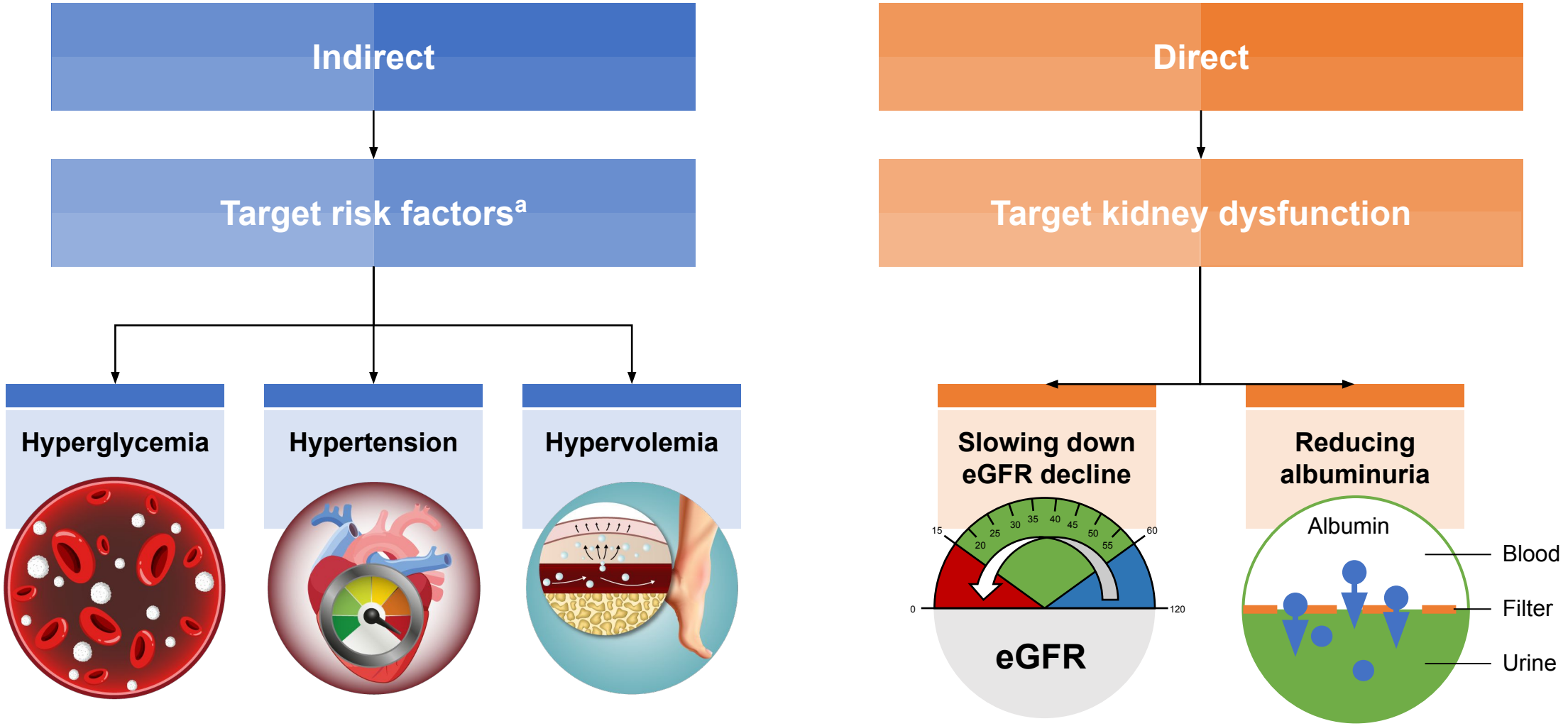


Gaede P, N Engl J Med, 348: 383-393, 2003





EFFECTIVE TREATMENT OF CKD INCLUDES BOTH DIRECT AND INDIRECT APPROACHES



[a]This is not an exhaustive list of treatable risk factors.

CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate.

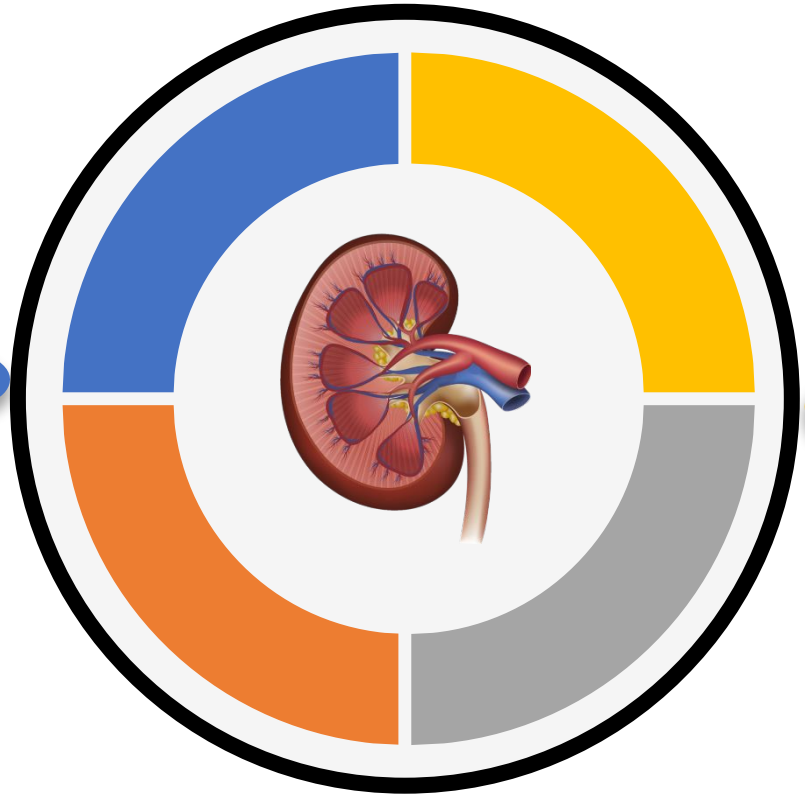
Kidney Disease: Improving Global Outcomes. *Kidney Int.* 2020;98:S1–S115.

According to the 2012 KDIGO CKD guideline, there are certain lifestyle modifications that are recommended for those with CKD

KDIGO recommend the following lifestyle modifications for those with CKD:

Protein intake

- Lower protein intake to 0.8 g/kg/day in adults with diabetes or without diabetes and eGFR <30 mL/min/1.73m^2 with appropriate education
- Avoid high protein intake (>1.3 g/kg/day) in adults with CKD at risk of progression



Lifestyle

Should be encouraged to undertake physical activity compatible with cardiovascular health and tolerance (aiming for at least 30 minutes 5 times per week), achieve a healthy weight
(BMI 20–25, according to country-specific demographics) and stop smoking

Salt intake

Lower salt intake to less than 90 mmol (<2 g) per day of sodium (corresponding to 5 g of sodium chloride) in adults, unless contraindicated

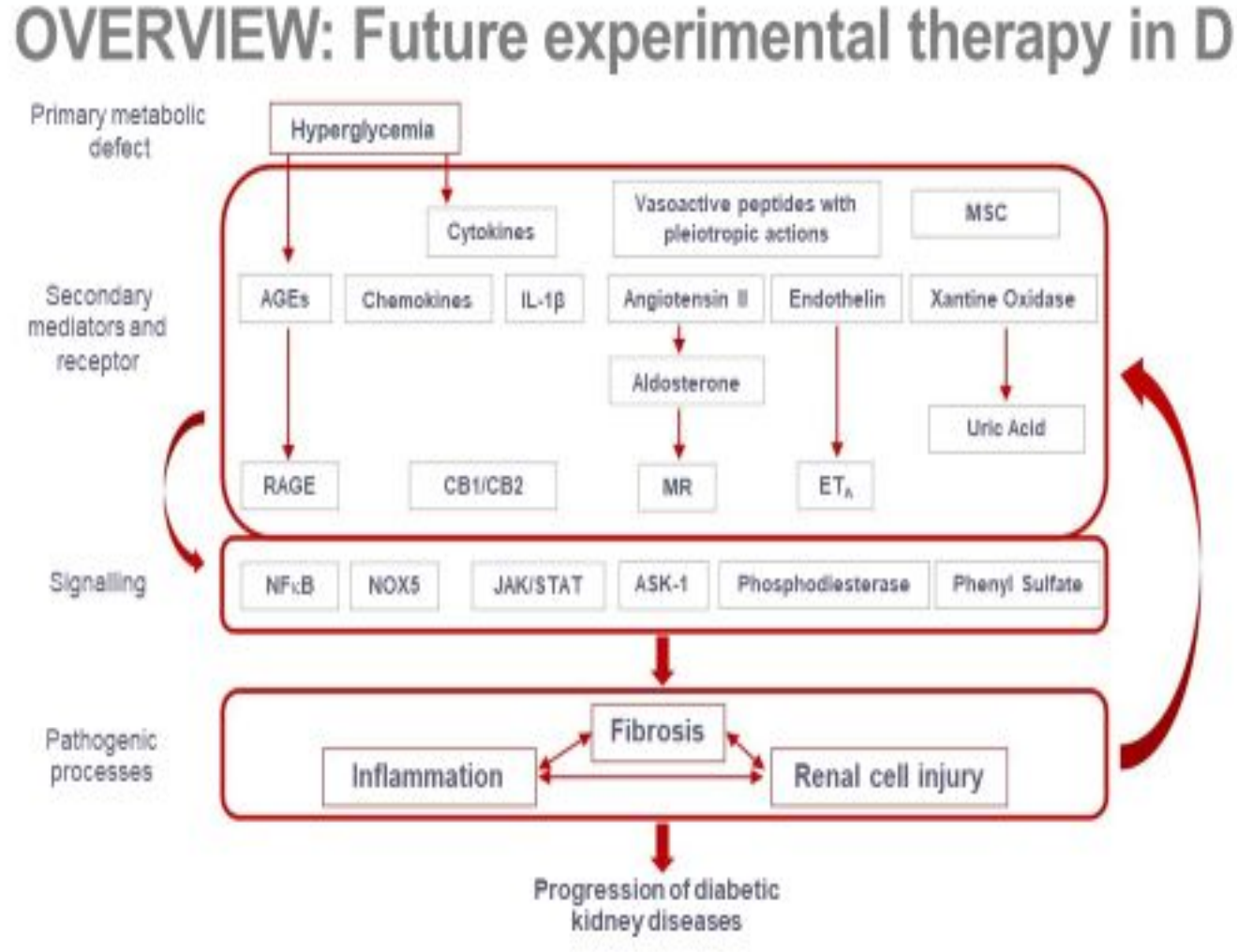
Additional dietary advice

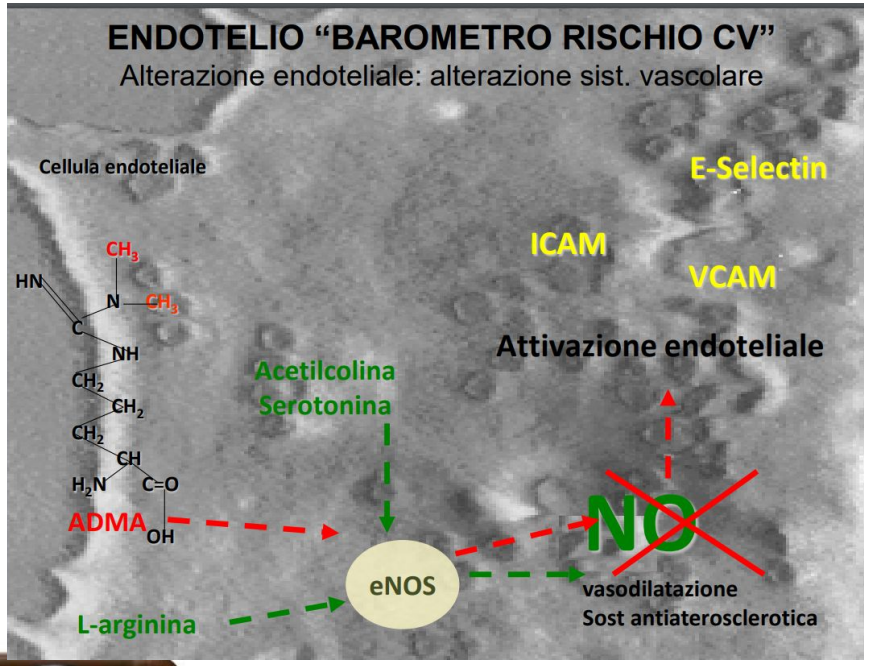
Should receive dietary advice and information in th context of an education program, tailored to severity of CKD and the need to intervene on salt, phosphate, potassium, and protein intake where indicated

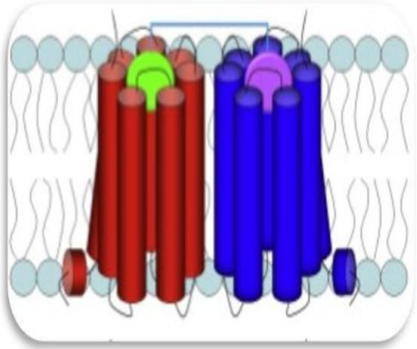
BMI = body mass index; CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; KDIGO = Kidney Disease: Improving Global Outcomes.

Kidney Disease: Improving Global Outcomes. *Kidney Int Suppl.* 2013;3:1–150.

RAGE AS POTENTIAL THERAPEUTIC TARGET?







Conclusions

Phenotype
Old, obese, G2-4
(db/db/5/6 nephrectomy)

Animal Model
DM2
Transcriptional profile

Inclusion Criteria
Baseline BG, AER, eGFR

Outcomes
Pre-specified outcomes ACR and eGFR

On top of standard TXT
Anti-DM, RASi, SGLT2i

Secondary prevention
Established DN