

XLIX LECCIÓN CONMEMORATIVA JIMÉNEZ DÍAZ

“Diabetes, hipertensión y enfermedad renal. La tormenta perfecta”

Jesús Egido, MD, PhD

Madrid, 18 mayo 2017

Buenos días

Querida Secretaria de Estado, queridos patronos de la Fundación Conchita Rábago, querido Director médico, queridos compañeros, queridos amigos.

En primer lugar quisiera **agradecer a** la Fundación Conchita Rábago por elegirme para impartir esta Lección Conmemorativa, **honor** en el que me han precedido **científicos ilustres** que contribuyeron al **avance de la Ciencia biomédica** en los últimos 50 años.

Pueden comprender la **emoción que me embarga** al dirigirme a Ustedes en esta **Aula Magna**, cargada de historia, una de las más bonitas del mundo, y en ésta Institución, que es **la mía desde hace 40 años**.

Antes de comenzar con la Lección, quisiera **recordar**, aunque sea brevemente, la figura del **Profesor Jiménez Díaz**, Don Carlos, dado que justamente hoy se cumplen **50 años de su fallecimiento**.



Prof. Carlos Jiménez Díaz

Maestro de la Medicina española

Madrid, 9 de Febrero de 1898; 18 de Mayo de 1967

- Docencia universitaria
- Trabajo clínico hospitalario
- Investigación al servicio de la Medicina

Instituto de Investigaciones Médicas, 1935 (ambiente prebélico)

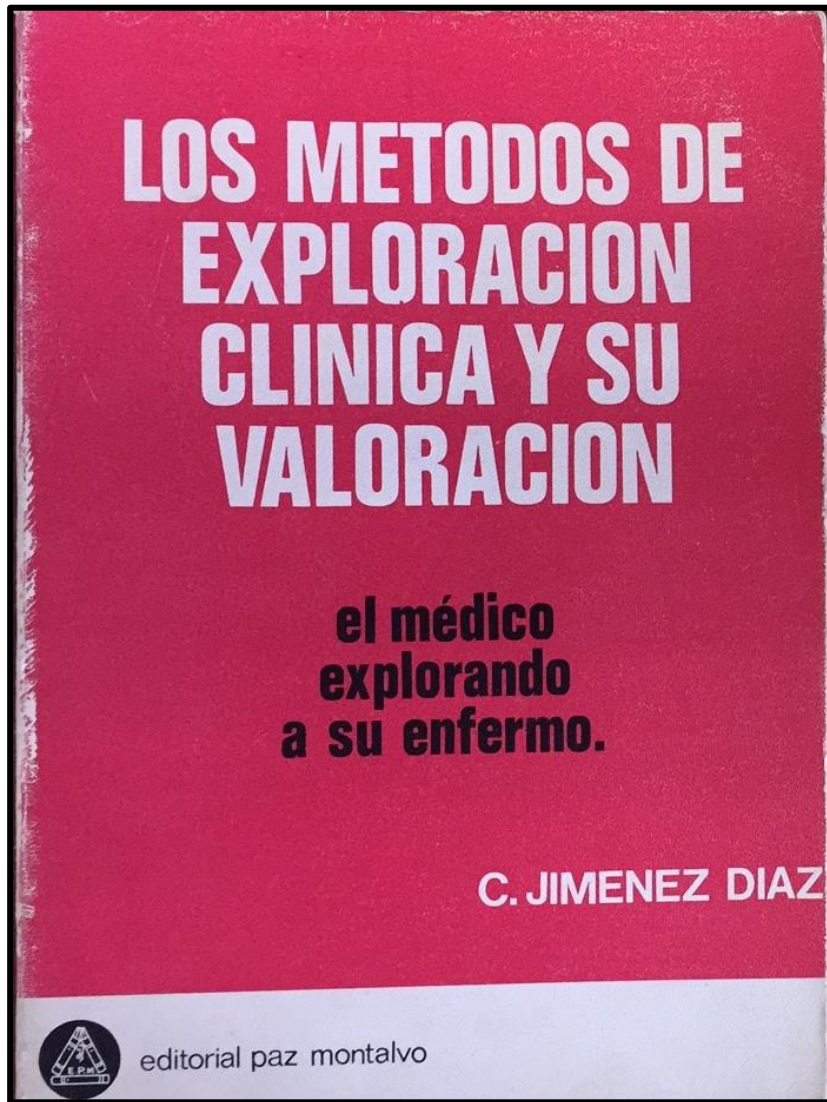
- El Instituto renace el 13 de febrero de 1940
- En 1955 se inaugura el Instituto de Investigaciones Médicas y la Clínica de la Concepción en su sede actual
- En 1962 se constituye la Fundación Jimenez Díaz
- Ingente obra médica y científica

Fundador de la Revista Clínica Española, 1940
Bulletin of the Institute for Medical Research, 1948

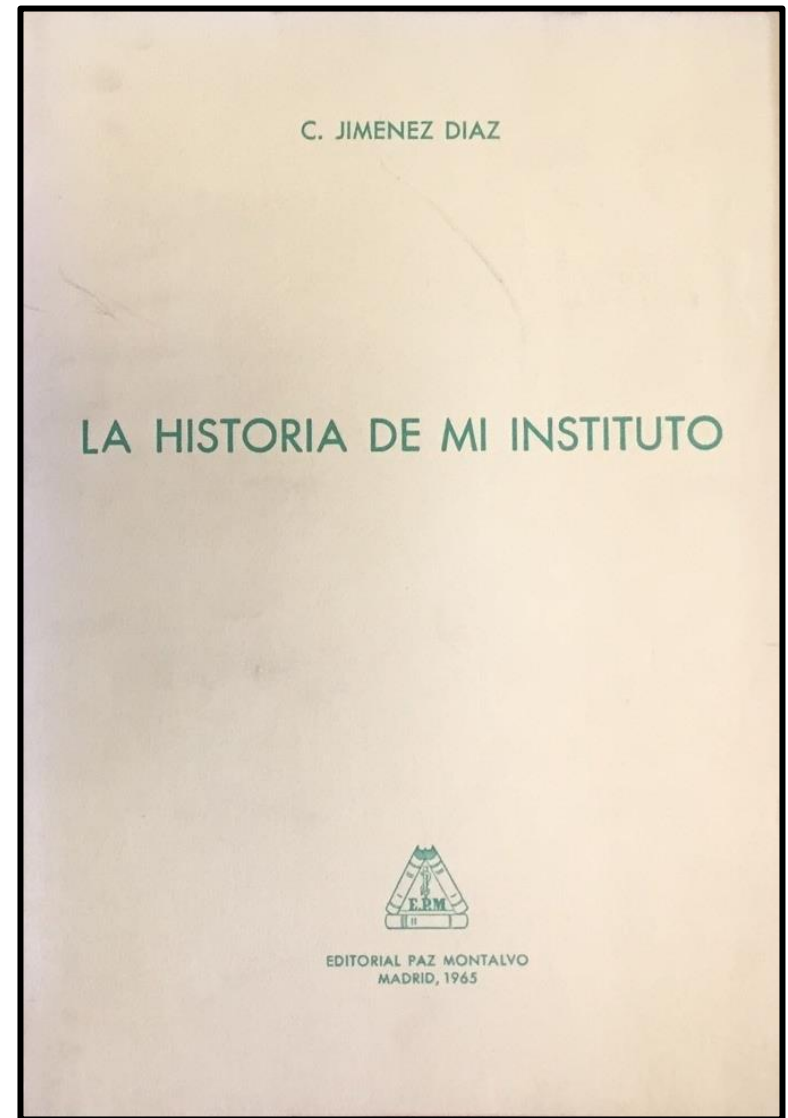


Fuente Carlos Jiménez Díaz de Juan de Ávalos y Taborda (1969) en la Plaza de Cristo Rey

Don Carlos, mi maestro

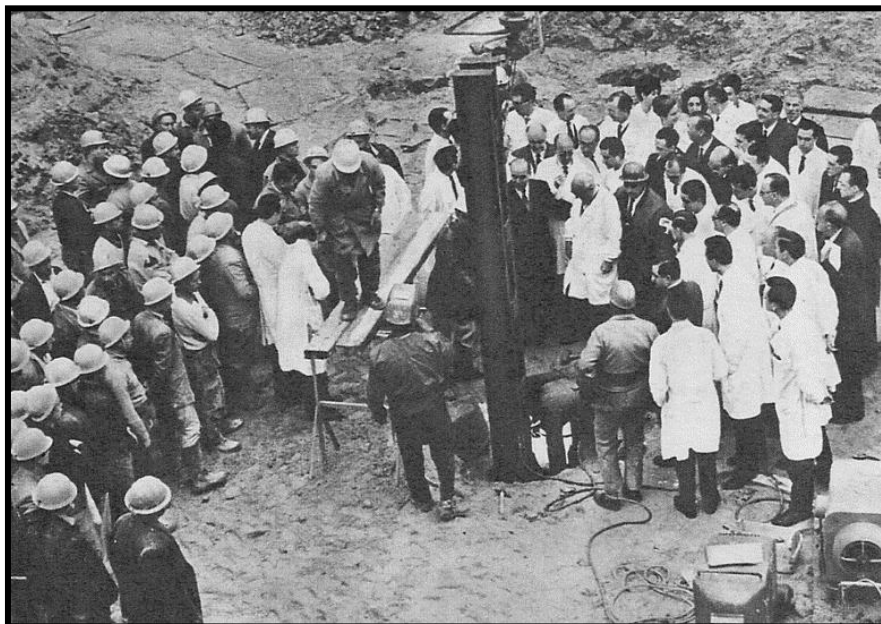
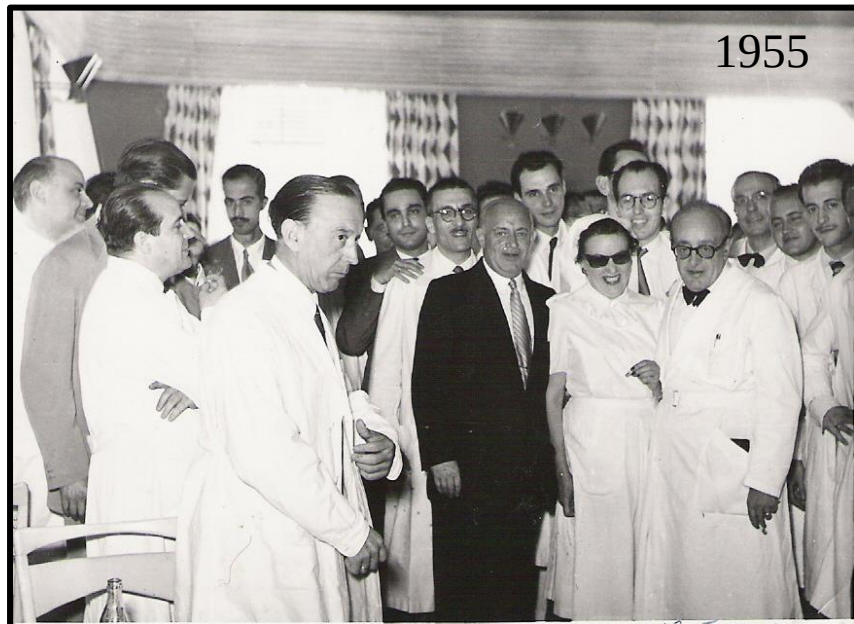


Cuidado de los enfermos

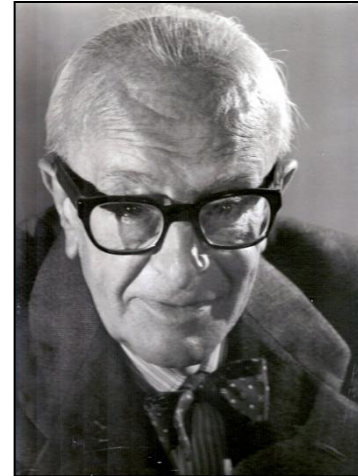
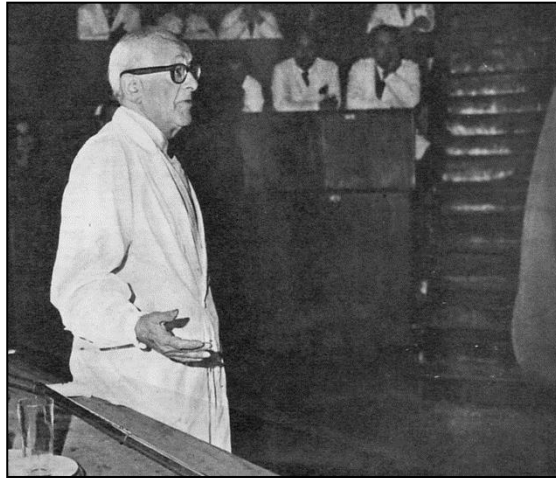
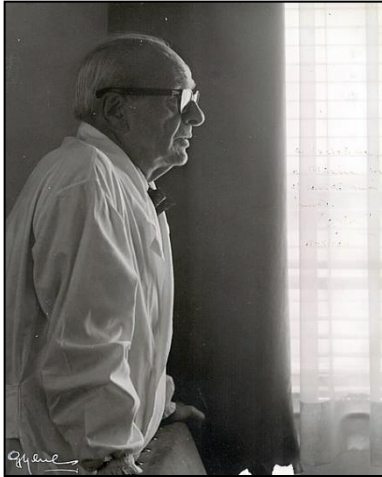


Pasión por la investigación

Inauguración en 1955 y la primera piedra de la ampliación de la Clínica de la Concepción ,1964



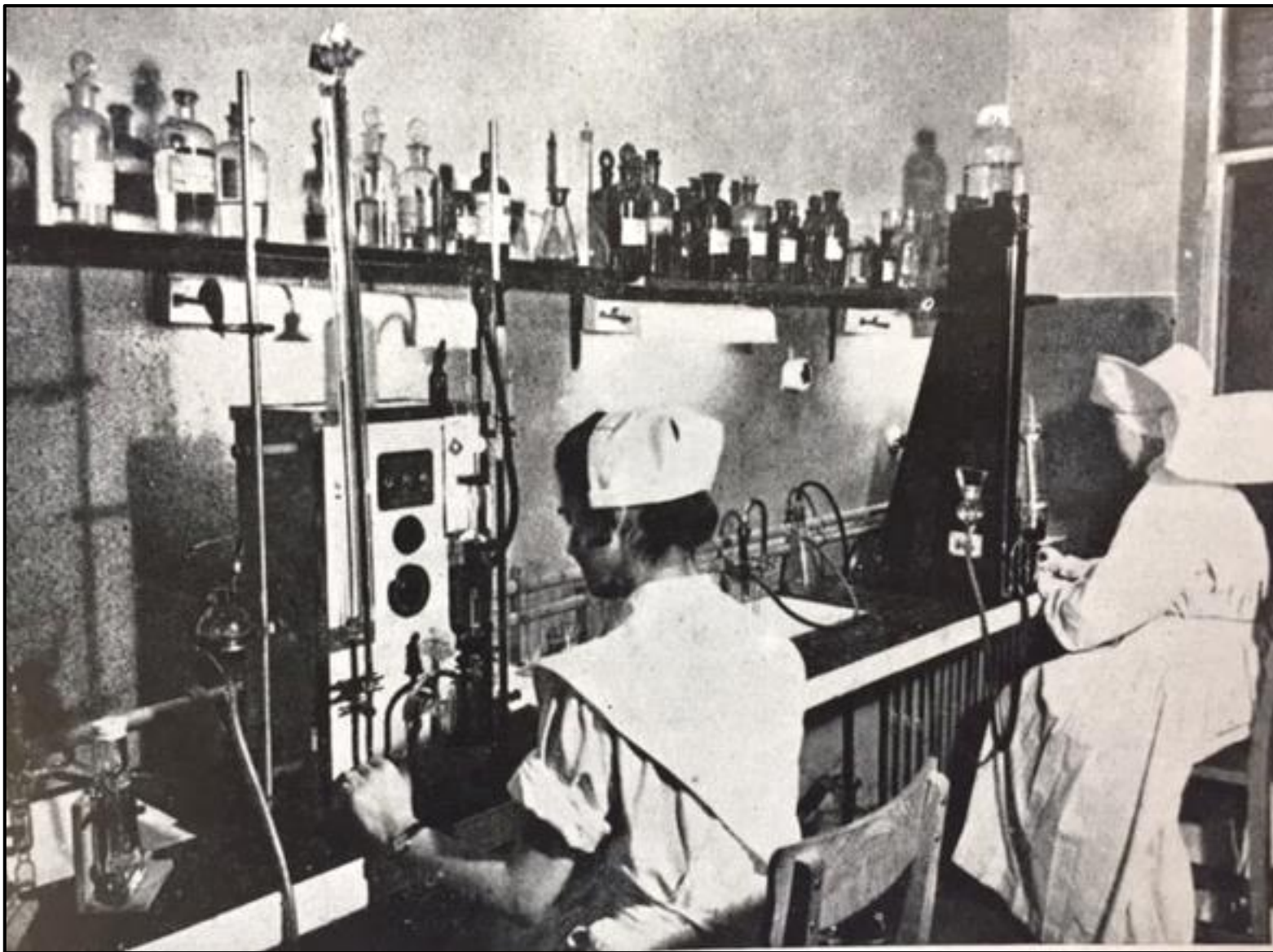
Algunas fotos de D Carlos en 1966, un año antes de su fallecimiento



En esta Aula, en la recepción de la Medalla del Trabajo



Monja at work



Don Carlos, un personaje popular en la sociedad española!!!



Recibimiento a su regreso de las conferencias pronunciadas en Latinoamérica (1943) y en las Universidades portuguesas (1952)

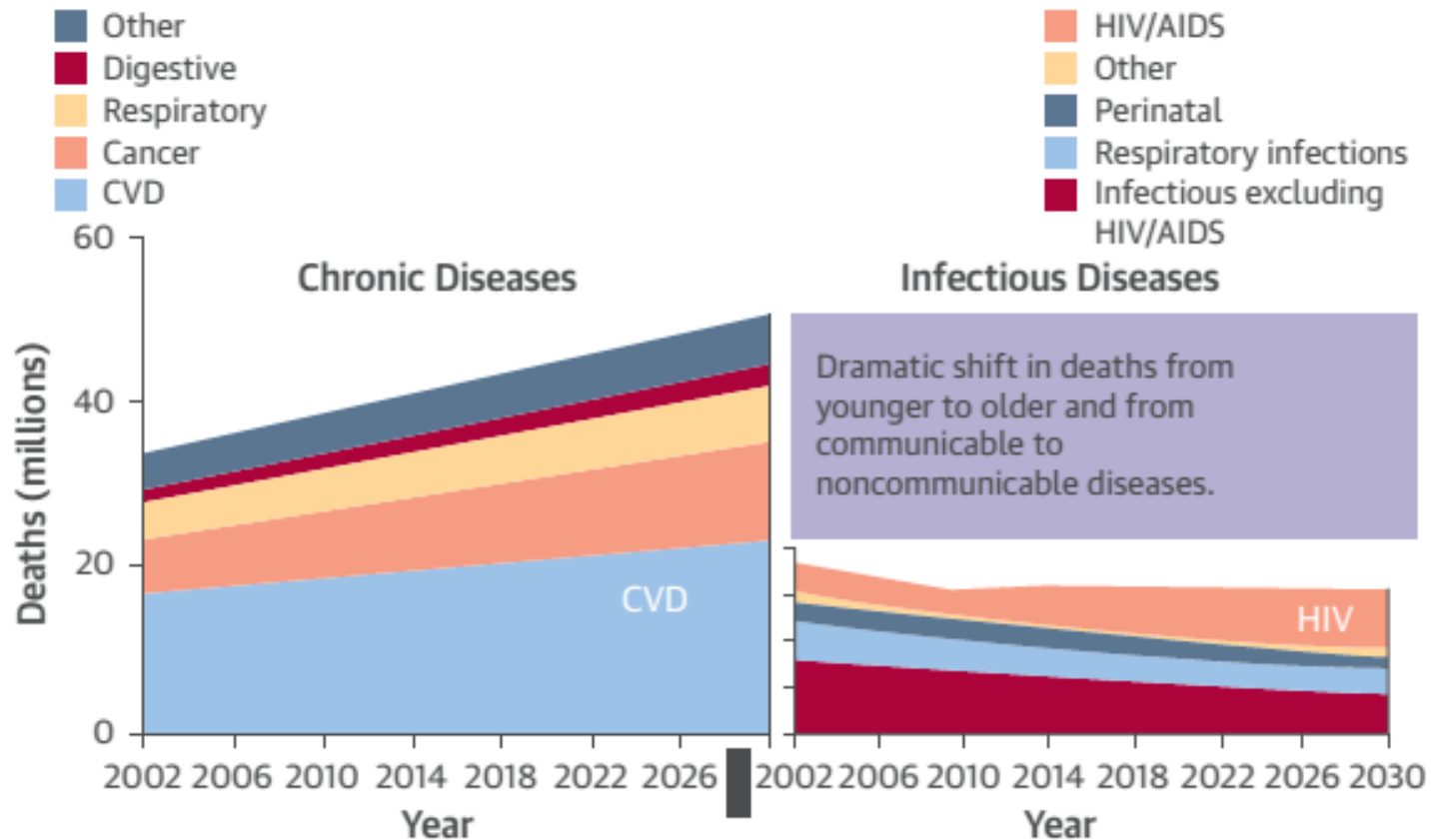
Diabetes, hipertensión y enfermedad renal

La tormenta perfecta

Jesús Egido, MD, PhD



Global Burden of Disease: Chronic and Infectious Diseases 2002 to 2030

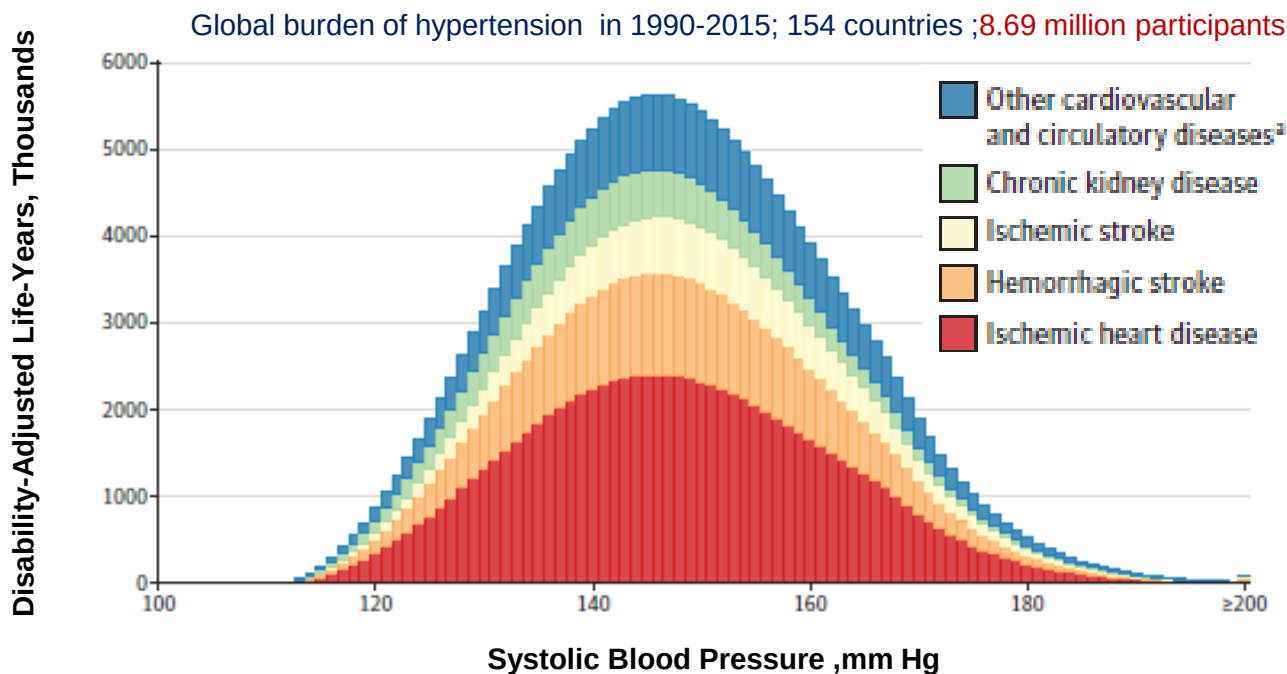


The top ten of **global risk factors for CVD** include:

- High **blood pressure**
- Obesity** and diabetes
- High **cholesterol**
- Chronic kidney disease**

Hypertension: A worldwide health problem

- Hypertension **kills** about **7.5 million people** every year worldwide.
- 1975: **594 million** adults with hypertension
2015 : **>1,100 million**, mainly **in low and middle-income countries**



A blood pressure target $\leq 140/90$ mm Hg (or $\leq 130/80$ in high risk patients) should markedly reduce cardiovascular and renal events

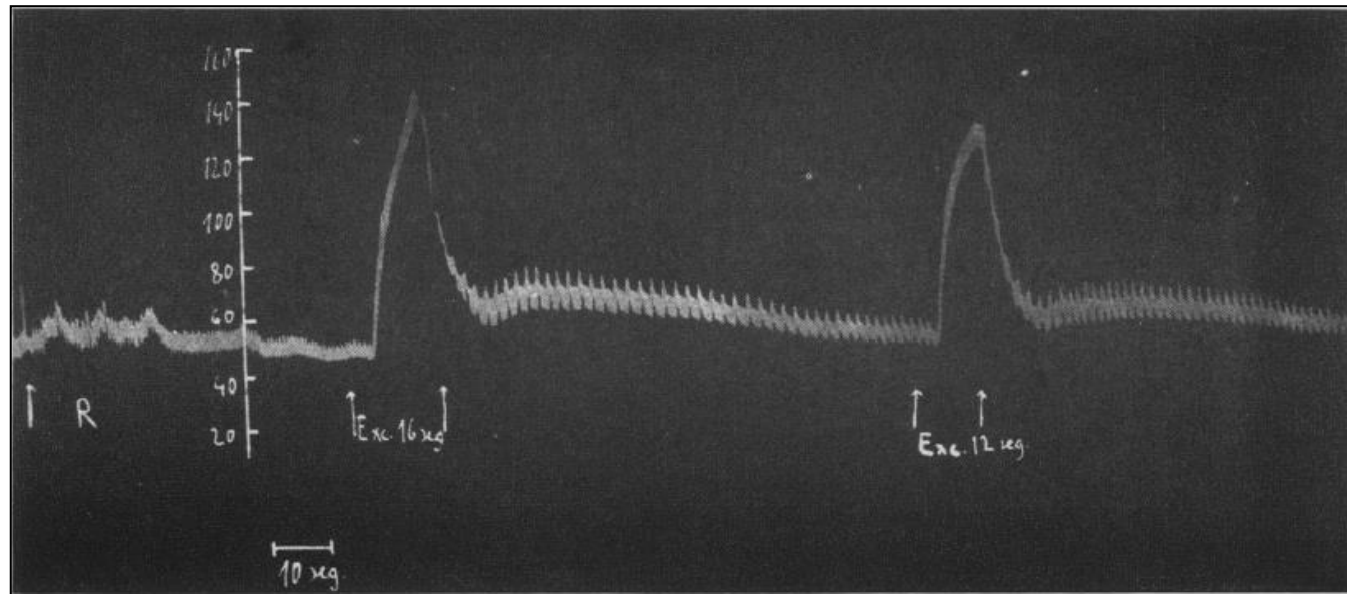
Every 10 mmHg reduction in systolic blood pressure reduces a 20% the risk of cardiovascular events!

Role of Arterial Wall Secretion in the Regulation of Blood Pressure C. JIMÉNEZ DIAZ, P. BARREDA, A. F. MOLINA and R. ALCALÁ

JIMENEZ DIAZ C, BARREDA P, MOLINA A On
the mechanism of nephrogenic hypertension.
Rev. Clin. Esp.1949 Dec 31;35:375-7.

Circulation. 1954;9:903-907
doi: 10.1161/01.CIR.9.6.903

“Tonina”



..... hypertension can be produced by the appearance of a pressor substance liberated into the circulation by the arterial wall

Nature,1980: Discovery of endothelium-dependent vasodilatation by Furchgott and Zawadzki
Nature,1988: Identified as nitric oxide by Moncada.

Nobel Prize winner: Robert Furchgott

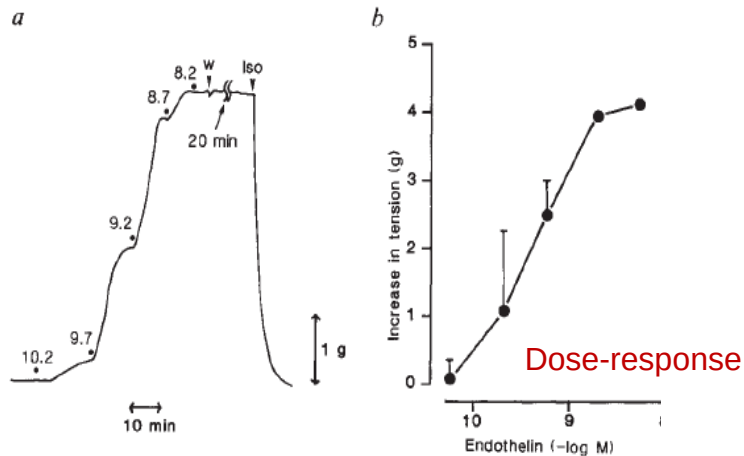
The Discovery of Endothelin

A novel potent vasoconstrictor peptide produced by vascular endothelial cells

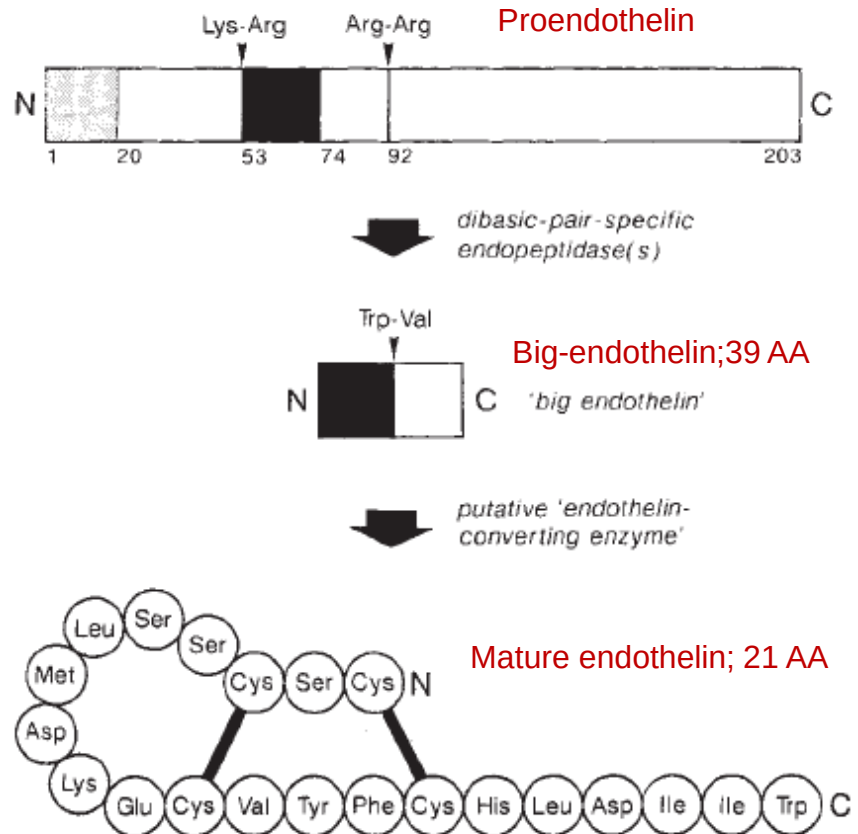
Masaki Yanagisawa and Tomoh Masaki

Nature 1988; 332:31.

Constrictive response of coronary artery strips



Pathway of Endothelin biosynthesis



The recognition of vascular endothelium as a key element in the regulation of blood pressure

Endothelin at Fundación Jiménez Díaz

Endothelin elicited :

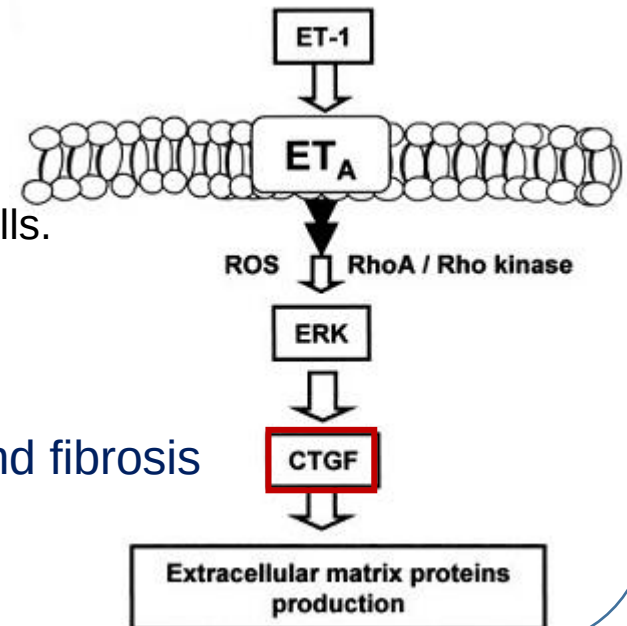
- Increase in **cytosolic calcium** in human **neutrophils**. López-Farré et al; Biochem Biophys Res Commun. 1991
- **Aggregation** of human polymorphonuclear **leukocytes**. Gómez-Garre D et al; Eur J Pharmacol. 1992
- Neutrophil **adhesion to endothelial cells** and perfused heart. López Farré A et al; Circulation. 1993

Neutrophils and endothelin in myocardial infarction

- Endothelin-1 causes **inflammation** through **NF- κ B activation**.
Gómez-Garre D. et al. Hypertension. 2001

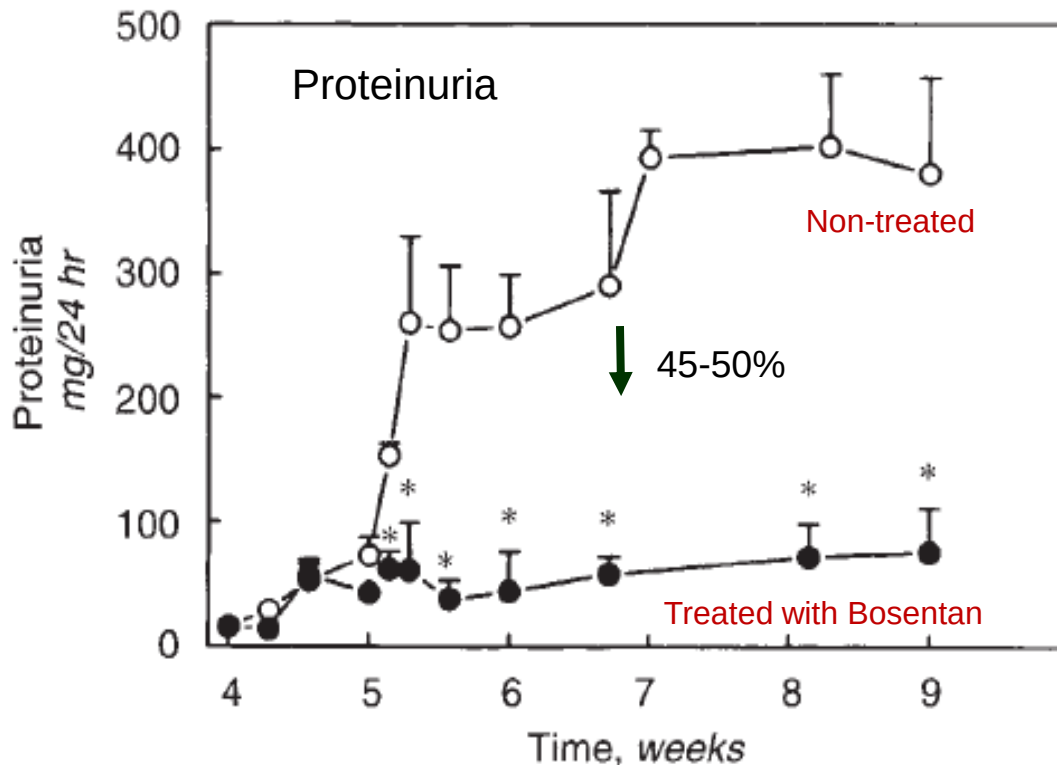
- Endothelin-1 via ETA Receptor increases **Connective Tissue Growth Factor (CTGF)** in Vascular Smooth Muscle Cells.
Rodriguez-Vita et al. Circ Res. 2005

Endothelin in cardiovascular and lung inflammation and fibrosis



An orally active ET_A/ET_B receptor antagonist ameliorates proteinuria and glomerular lesions in rats with proliferative nephritis

Gómez-Garre D et al . Kidney Int; 1996;50:962-972



Study Of diabetic Nephropathy with AtRasentan

4000 patients

Estimated Completion Date: July 2018

Abbvie Inc.

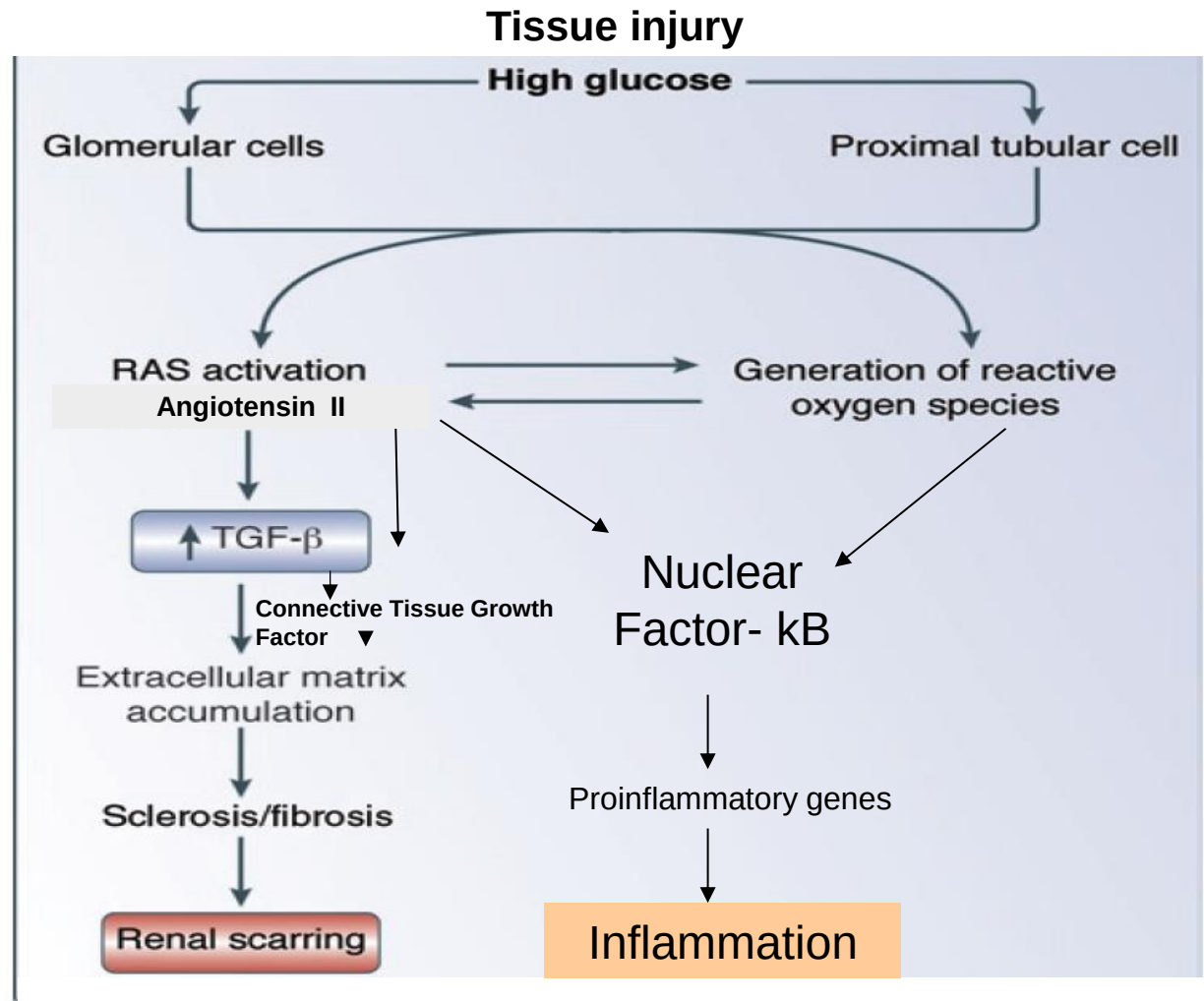
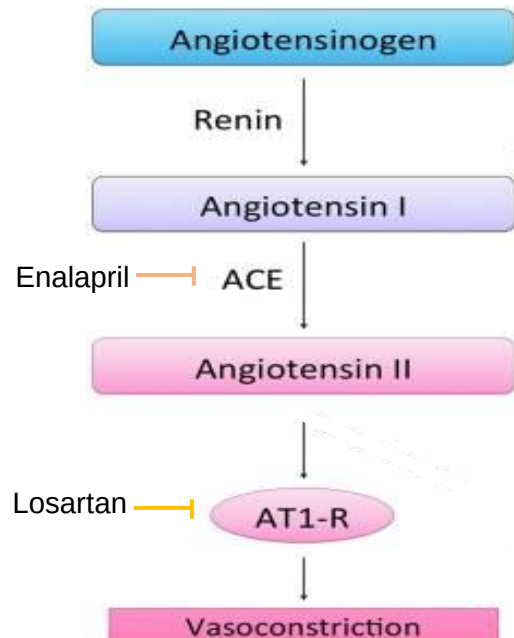
- Endothelin-1 participates in the genesis of proteinuria and glomerular injury
- The endothelin receptor antagonists could be useful in the treatment of proteinuric nephropathy



Dulcenombre Gómez-Garre

Angiotensin II and **organ damage** in renal and cardiovascular diseases.

Renin-Angiotensin System



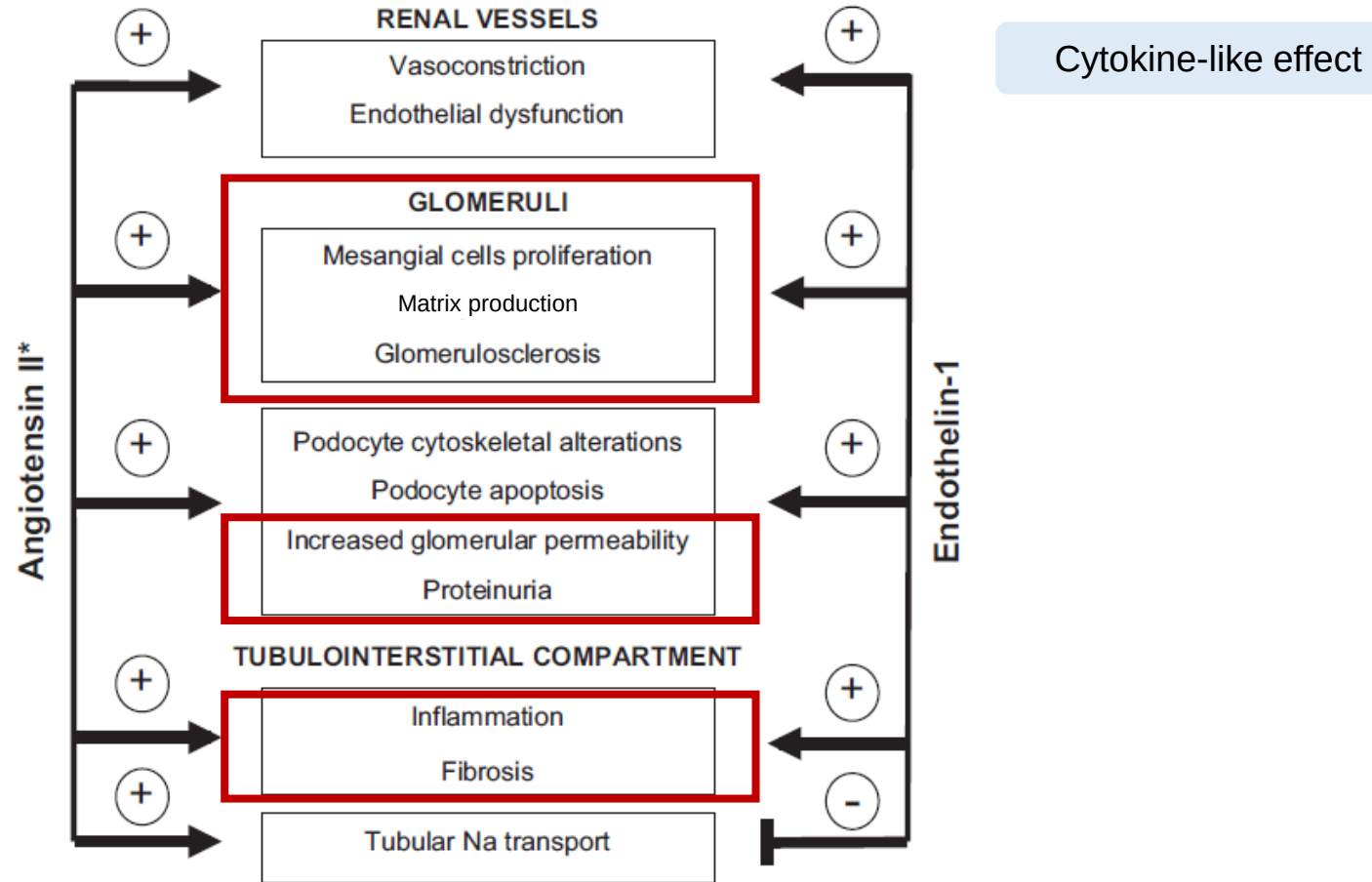
Marta Ruiz-Ortega



Cir Res 2000; Am J Pathol 2001, 2003; JASN 2004; Circulation 2003,2005. Kidney Int 2008,2010, PLoS One. 2012 ,Clin Sci (Lond). 2014 J Renin Angiotensin Aldosterone Syst. 2015 , J Am Soc Nephrol . 2017

Major similarities in physiopathological actions of angiotensin II and endothelin 1 in the kidney.

The activation magnitude and duration



The combination of drugs interfering with both Angiotensin and Endothelin may be of therapeutic interest in renal diseases with severe proteinuria

[Randomized, Double-Blind, Safety and Efficacy Study of RE-021 \(Sparsentan\) in proteinuric nephropathies](#)



Marta Ruiz-Ortega



Miguel A. Hernandez- Presa



Yusuke Suzuki



Dulcenombre Gómez-Garre

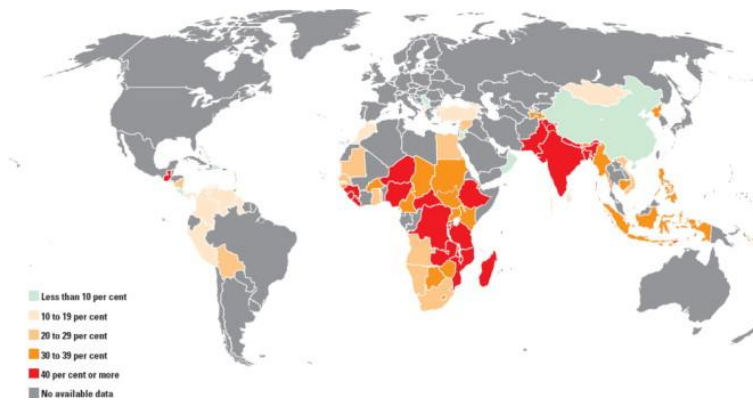


Raquel Largo- Carazo

Global Burden of Disease Study 2015

The dominant nutrition challenges on the road to 2030

-Child **undernutrition** still a major problem in sub-Saharan Africa

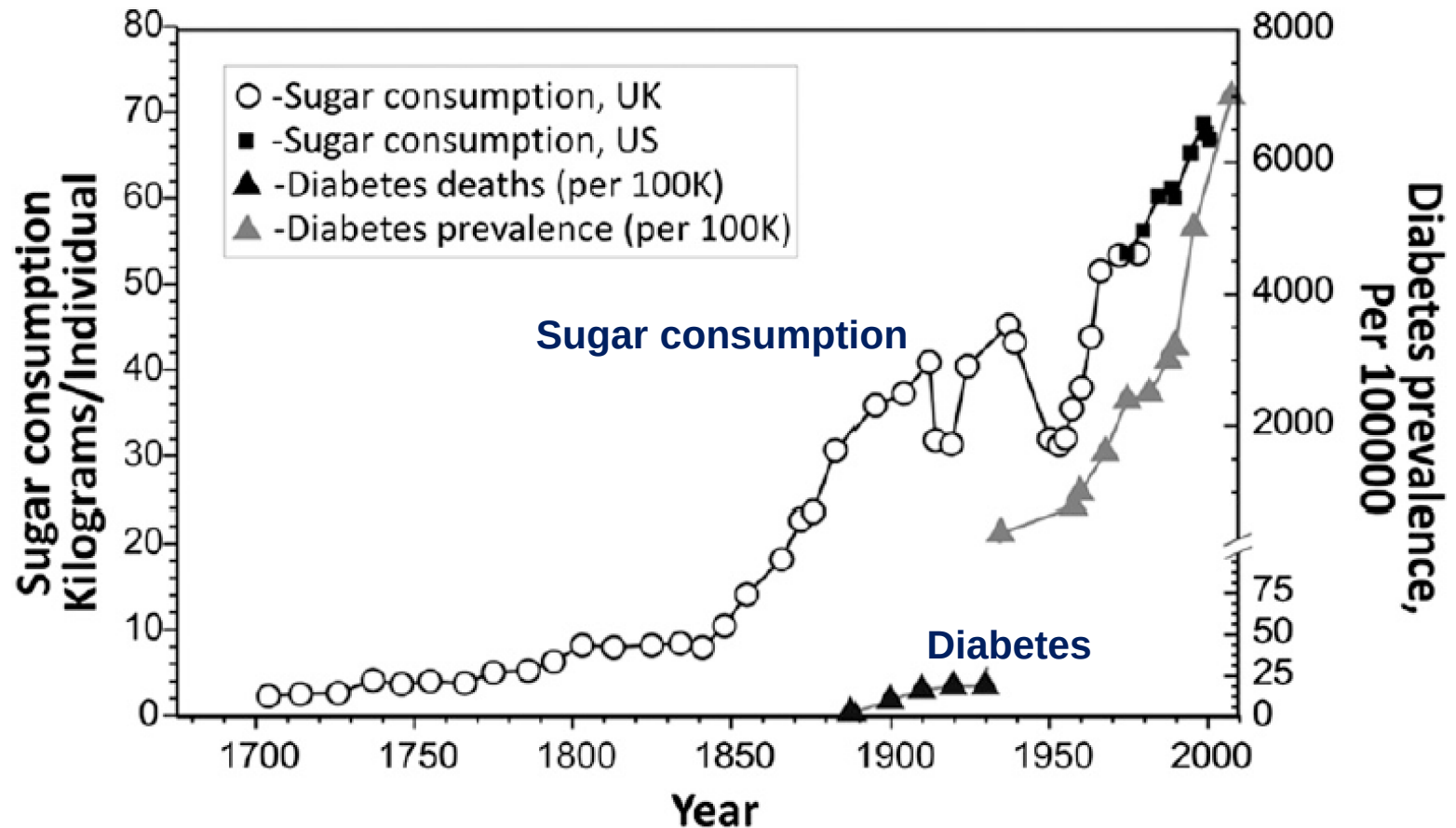


- Diet related diseases due to **overnutrition** : Obesity and Diabetes



Screen time as well as **television advertising** for soft drinks are associated to a greater **obesity** risk among children. Nightingale et al. Arch Dis Child, 2017

Rise in **sugar intake** correlates with rise in **obesity** and **diabetes** in the general population.



Saab, Johnson JASN 2015

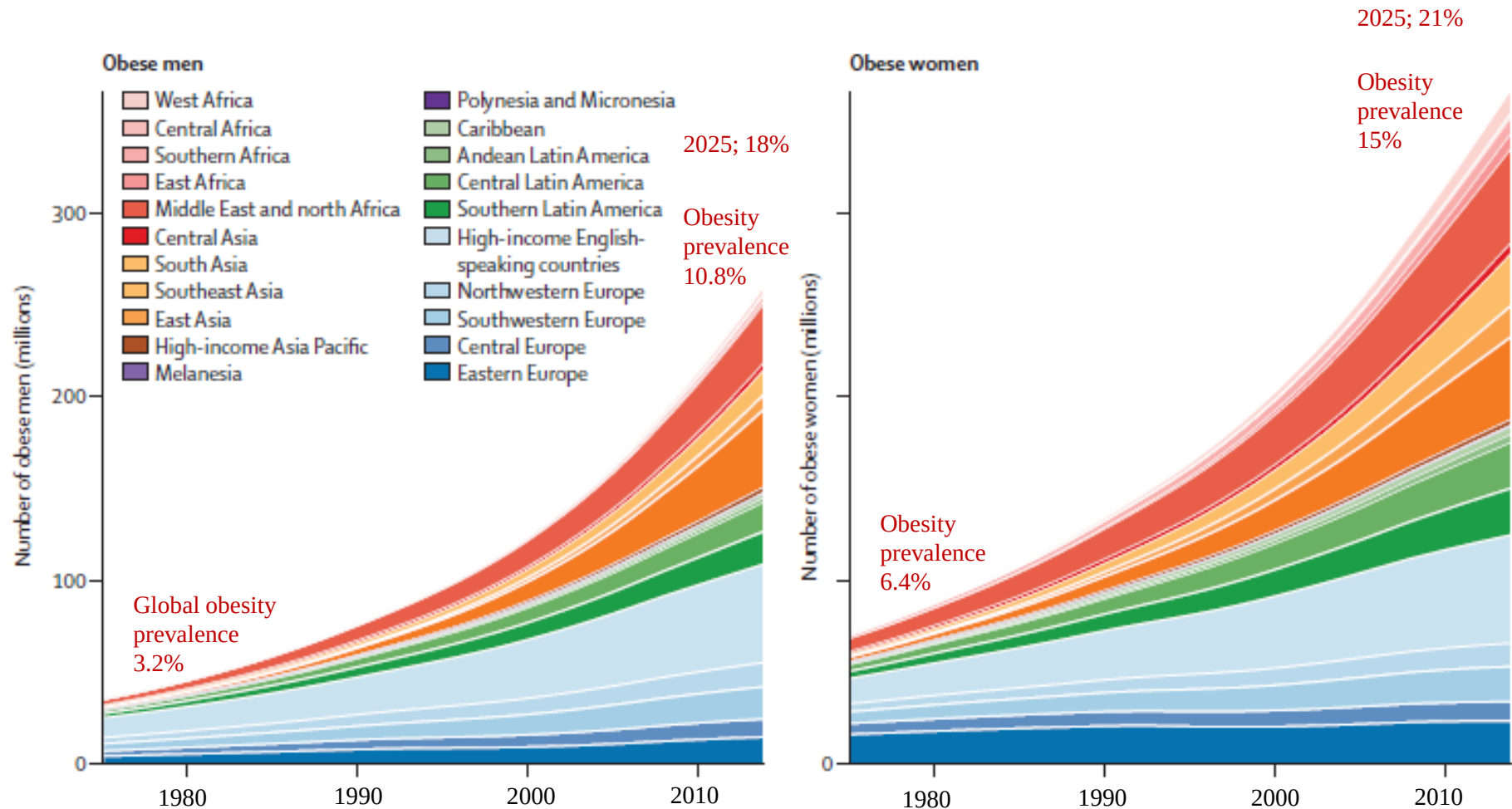
Compared to the 1970s, the average caloric intake in the United States has increased now more than 500 kcal per day (**182,500 kcal per year** !!!) ➡ 12-14 kg year

Obesity as a worldwide pandemic

Trends in adult body-mass index in 200 countries from 1975 to 2014: a pooled analysis of 1698 population-based measurement studies with 19·2 million participants

NCD Risk Factor Collaboration (NCD-RisC)*

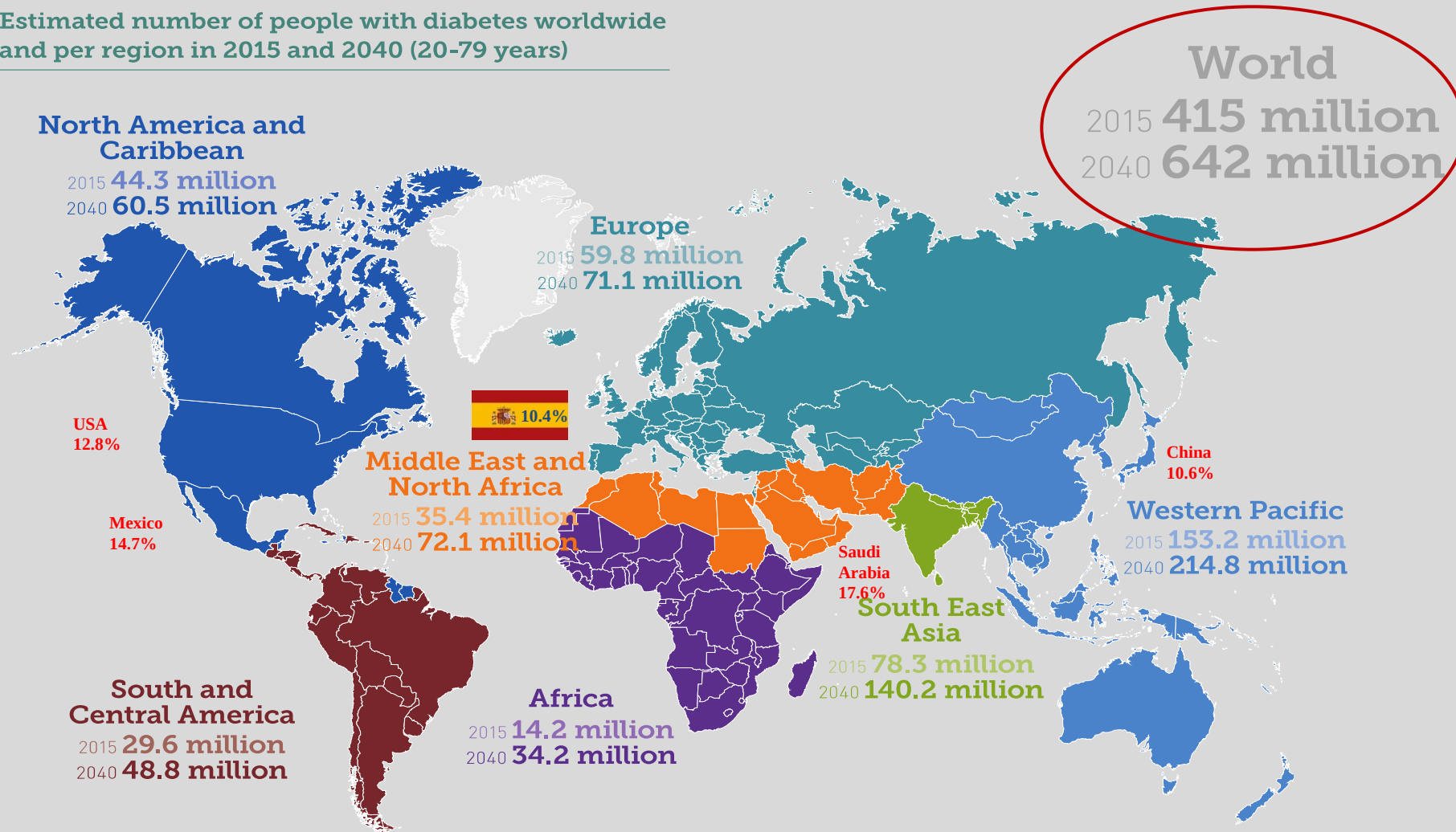
Lancet 2016; 387: 1377-96



Diabetes, a global emergency.

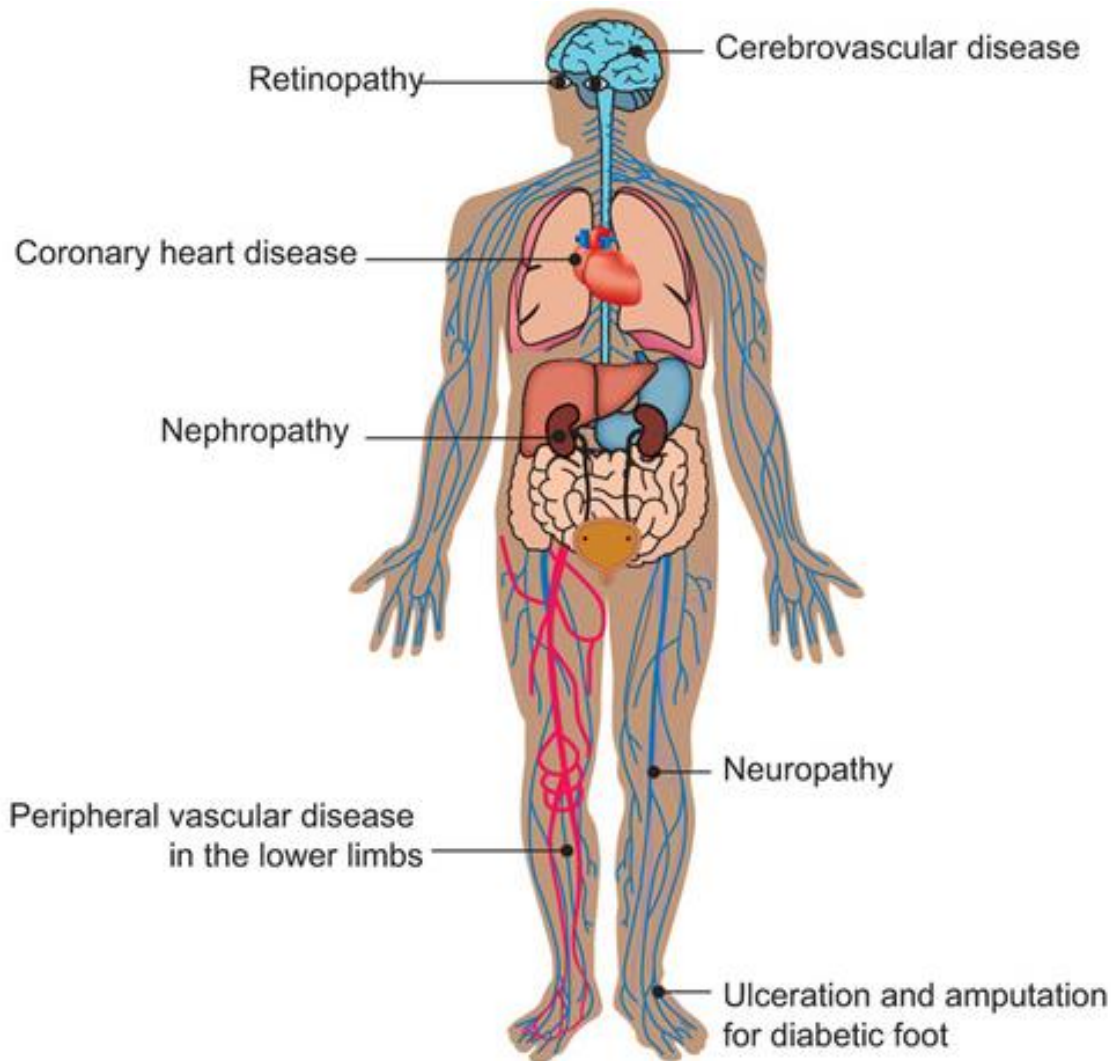
The epidemic of the 21st century

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



International
Diabetes
Federation

Diabetic complications represent a significant economic burden in all Western health systems



Diabetes Contributes to More US Deaths than Previously Thought

304,136 people from the National Health Surveys

-12% of deaths in the US

-The third-leading cause of death after heart disease and cancer.

PLOS ONE, 2017

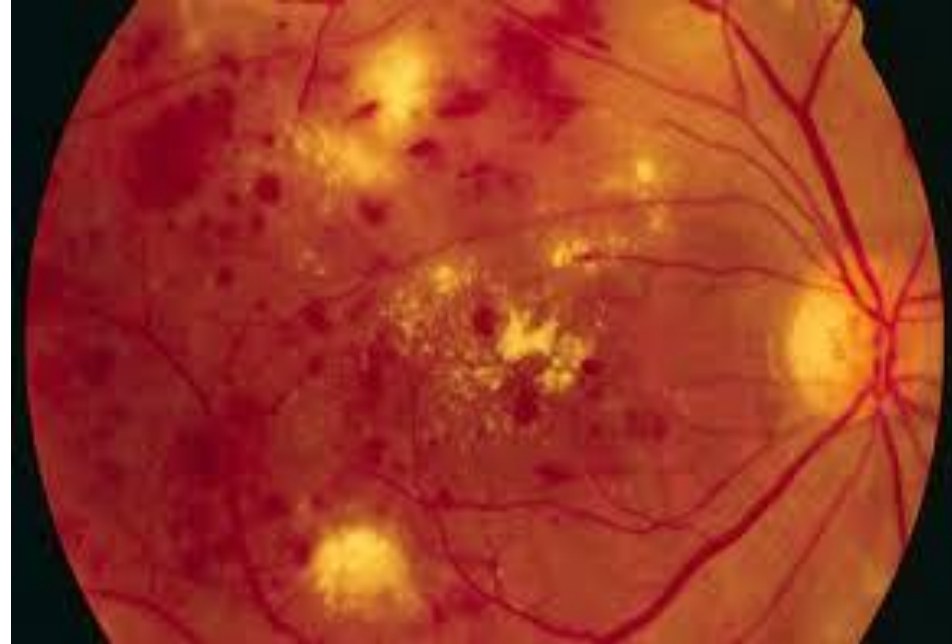
Most significant causes of death in patients with diabetes:

- cardiovascular disease (70%)
- renal failure (10%)
- infection (6%)

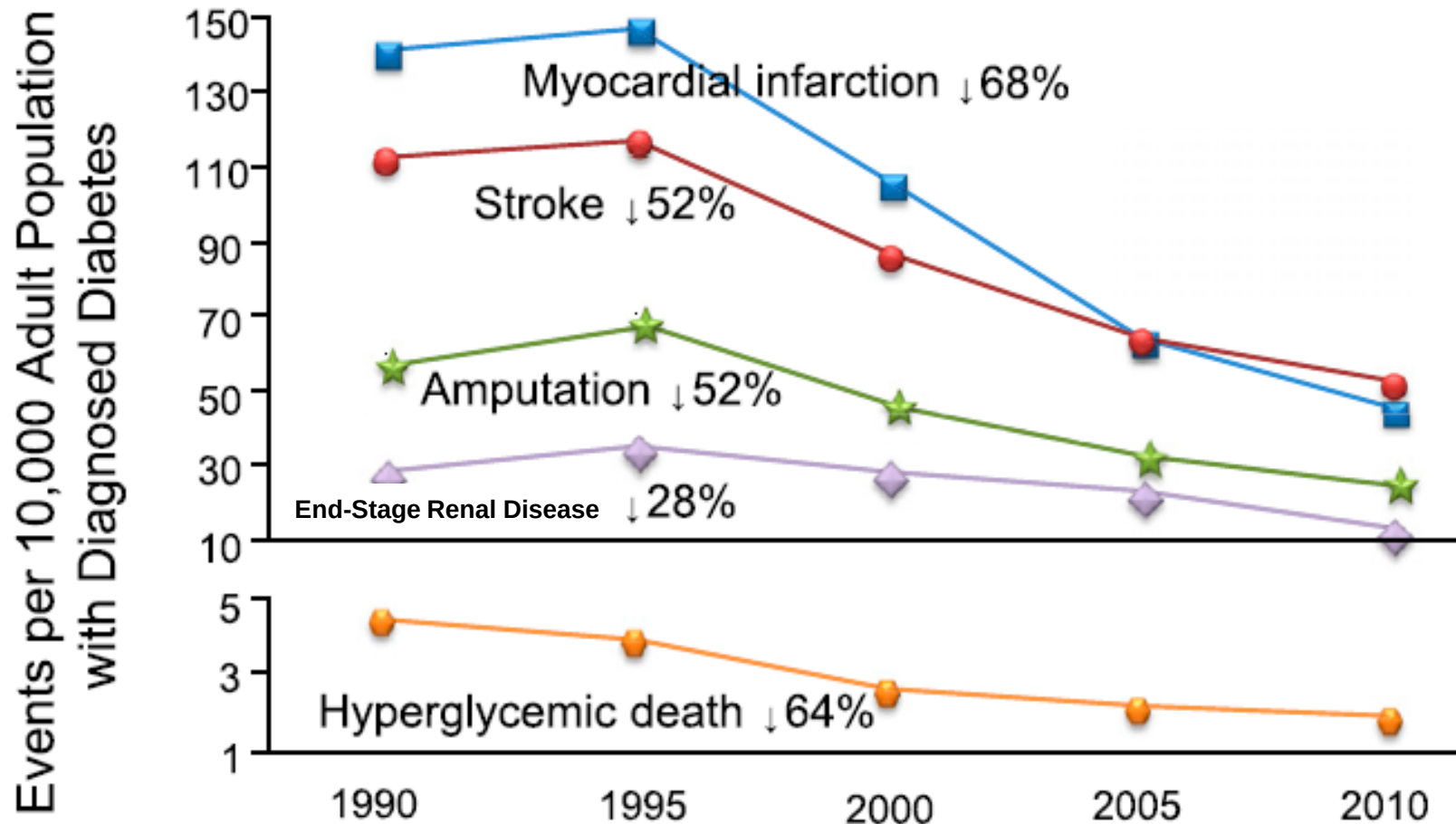
Complicaciones de la diabetes de aparición temprana no esperables !!!

Varón 50 años, obesidad grado III e hipertension arterial, diagnosticado de diabetes mellitus tipo 2 hace 5 años . HbA1c entre 5.5 - 7.30.

Nefropatía diabética, insuficiencia renal y albuminuria intensa.



Trends in the occurrence of diabetes-related complications from 1990 to 2010 in US

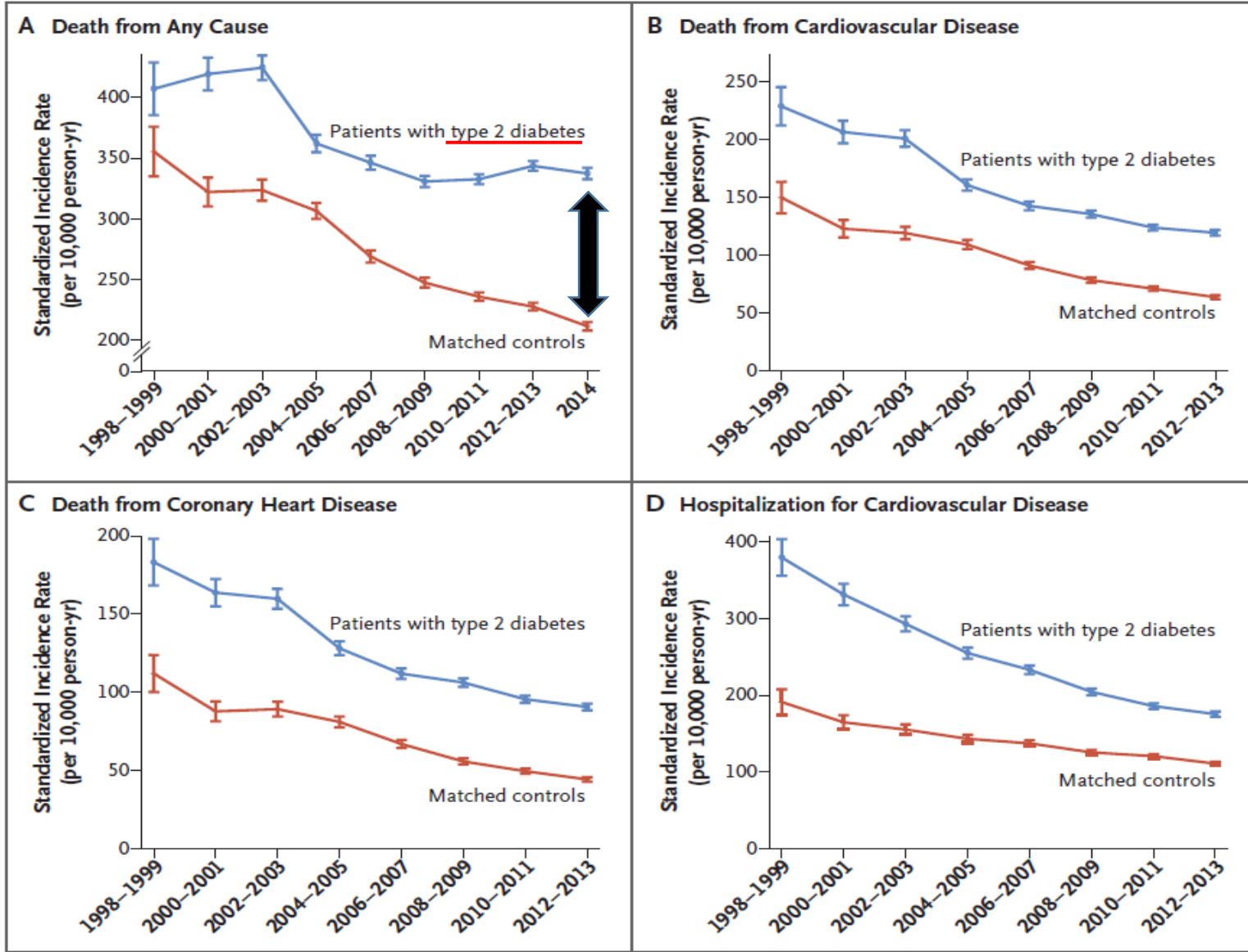


The new threats: population growth, obesity and aging

Mortality and cardiovascular disease in type 1 and type 2 diabetes

N Engl J Med . 2017; 376;15. April 13

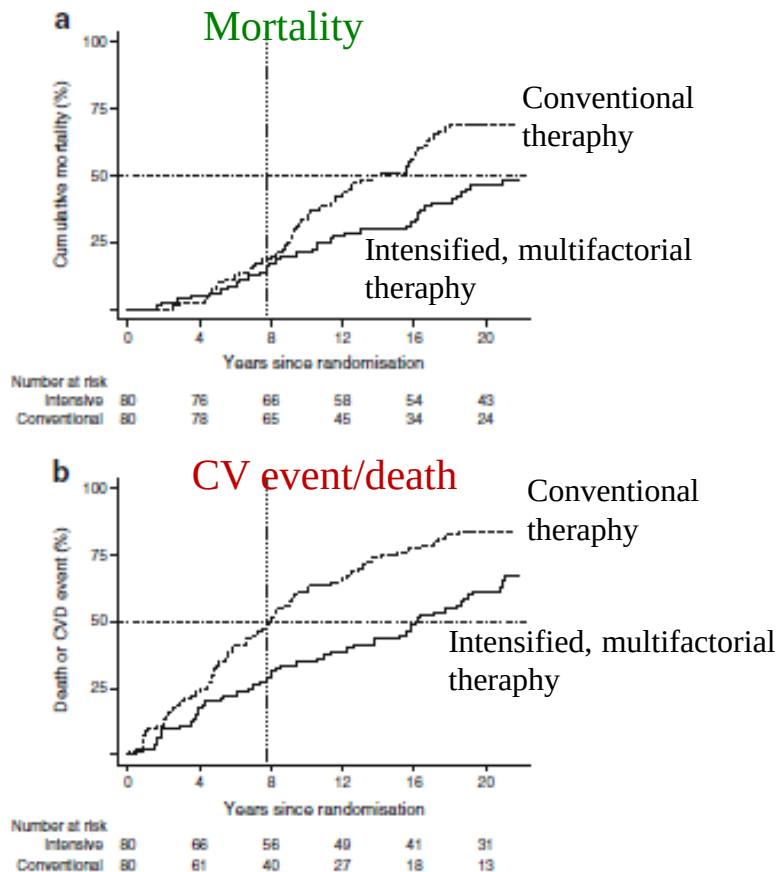
Swedish National Diabetes Register from 1998 through 2012



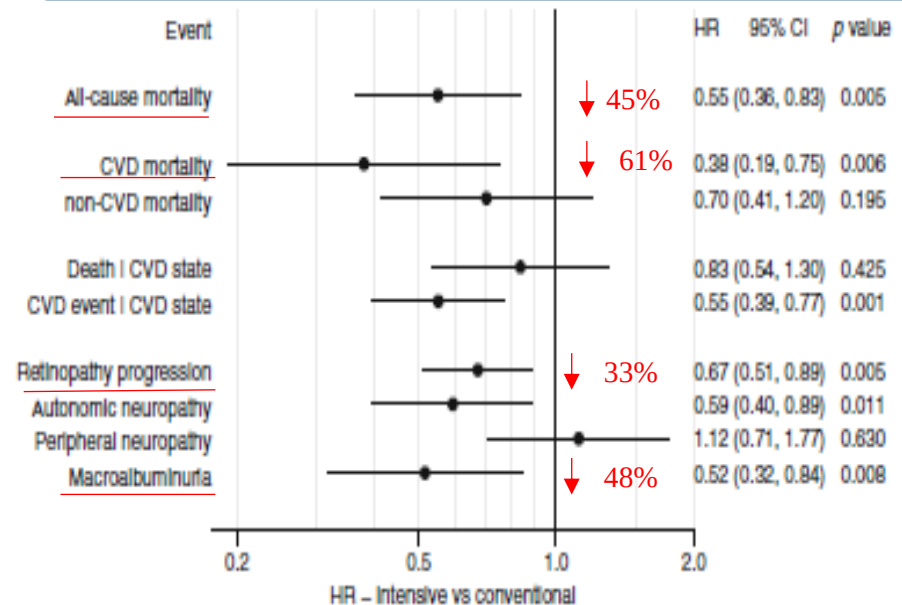
Years of life gained by multifactorial intervention in patients with type 2 diabetes mellitus and microalbuminuria: 21 years follow-up on the Steno-2 randomised trial

Gæde, P. et al. Diabetologia (2016) 59: 2298

Cumulative mortality cardiovascular or death endpoint



160 patients with type 2 diabetes with microalbuminuria 7.8 years of intensified, multifactorial treatment

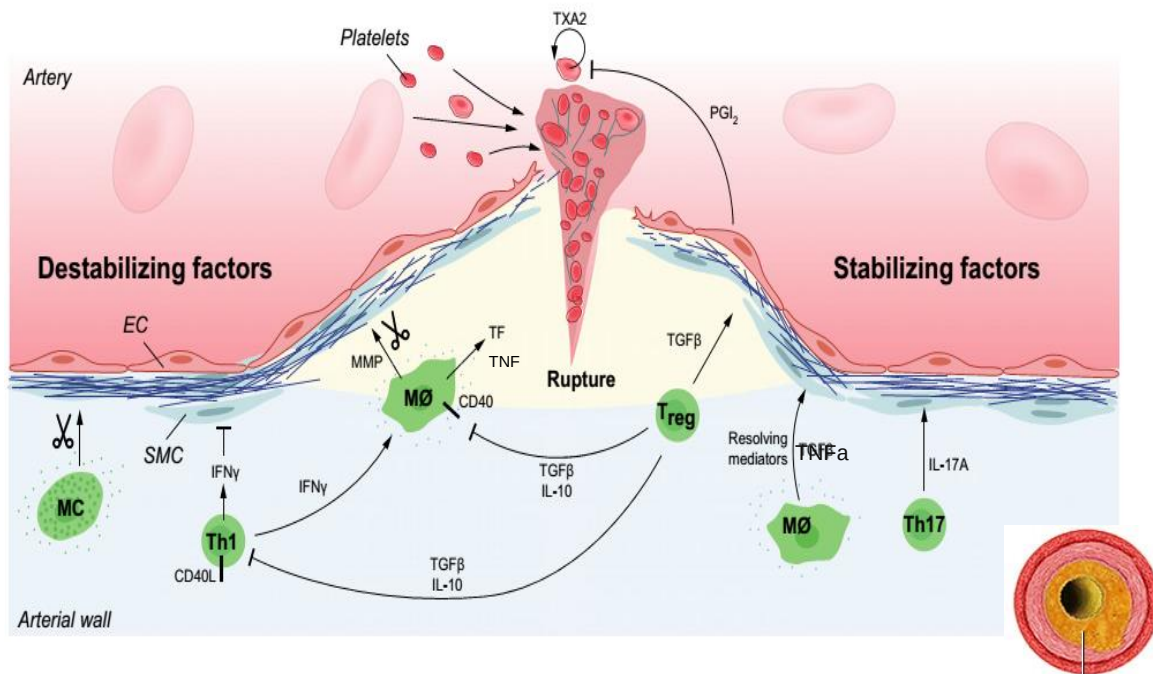


A median of 7.9 years of gain of life, mainly by a reduction of CV events

Cardiovascular disease and Cholesterol Lowering

Hurray for statins !!!

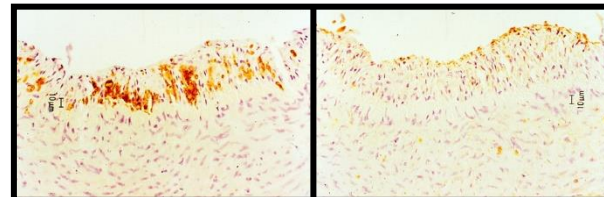
Atherosclerosis: chronic inflammation in the artery wall
Mechanisms of plaque rupture



Anti-inflammatory

CONTROL

ATORVASTATIN

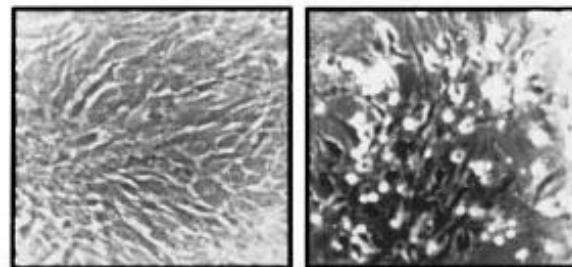


(J Am Coll Cardiol 1998;32:2057-64)

Pro-apoptotic

CONTROL

ATORVASTATIN



(Circ Res. 1998;83:490-500.)

Immunomodulators

(Circulation. 2003;108:1506-1513.)



Luis Blanco-Colio



Jose Luis Martín-Ventura

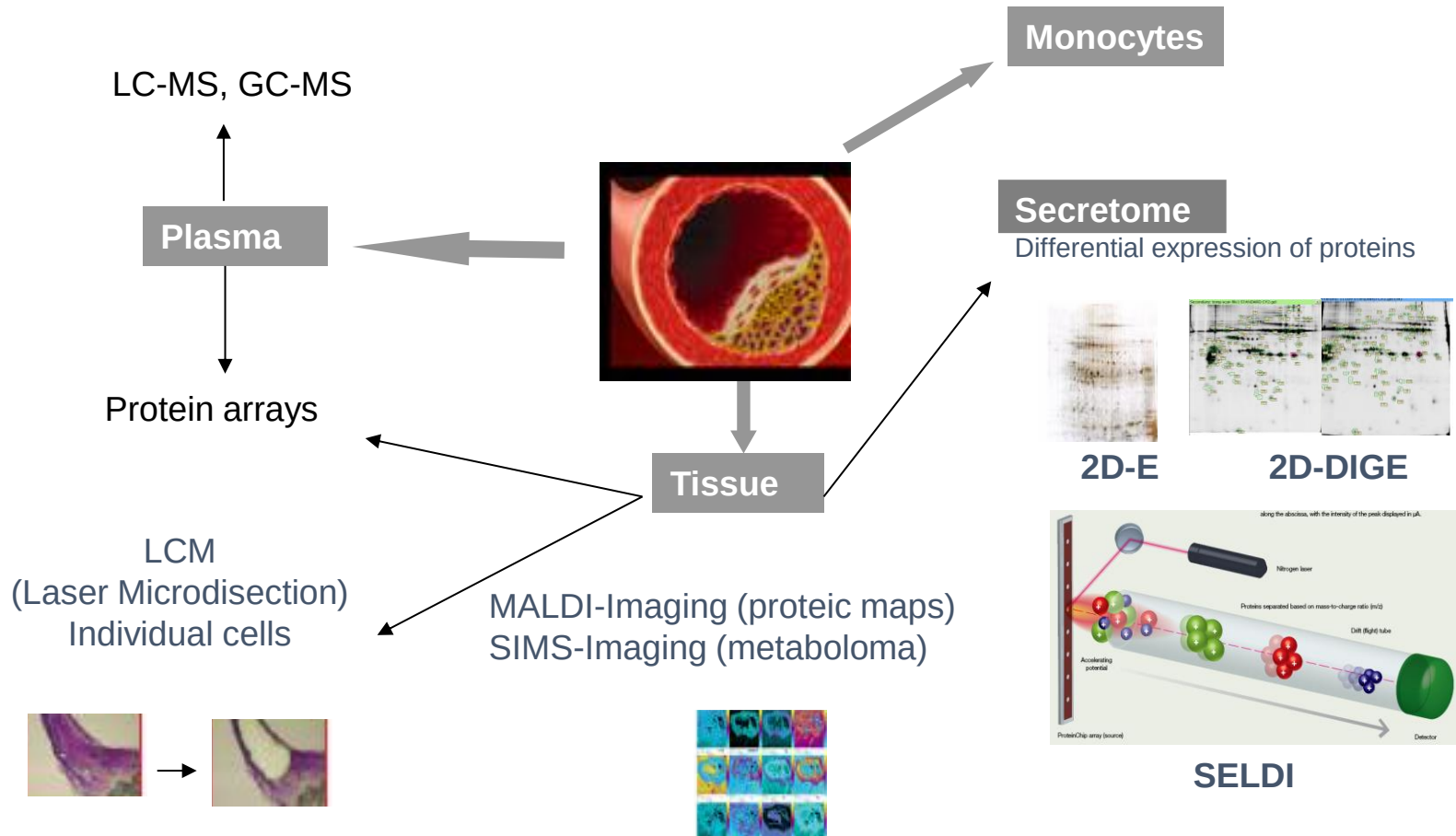


José Tüñón



Carlos Guisjarro

Searching for novel cardiovascular biomarkers at Fundación Jiménez Díaz



Luis Blanco-Colio



Cardiovascular

TWEAK (Tumor necrosis factor-like weak inducer of apoptosis)

Arterioscler Thromb Vasc Biol 2007; 2010; Clin J Soc Am Nephrol 2009; 2010; 2011; 2016; J Am Soc Nephrol. 2011
Atherosclerosis 2009; 2011; 2015; 2017; Eur J Clin Invest 2013 ; Biochim Biophys Acta. 2013; J Pathol. 2013; PLoS One.
2014; Nephrol Dial Transplant. 2014; J Cell Physiol. 2015; Kidney Int. 2016

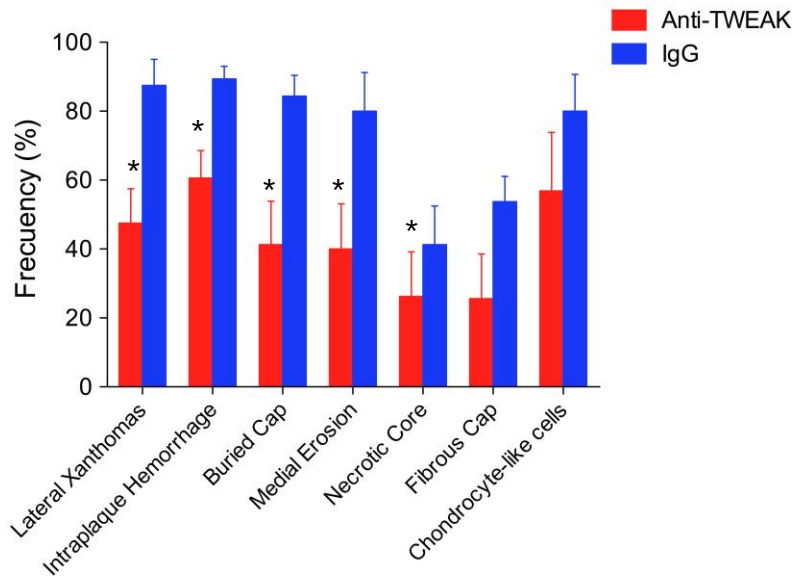
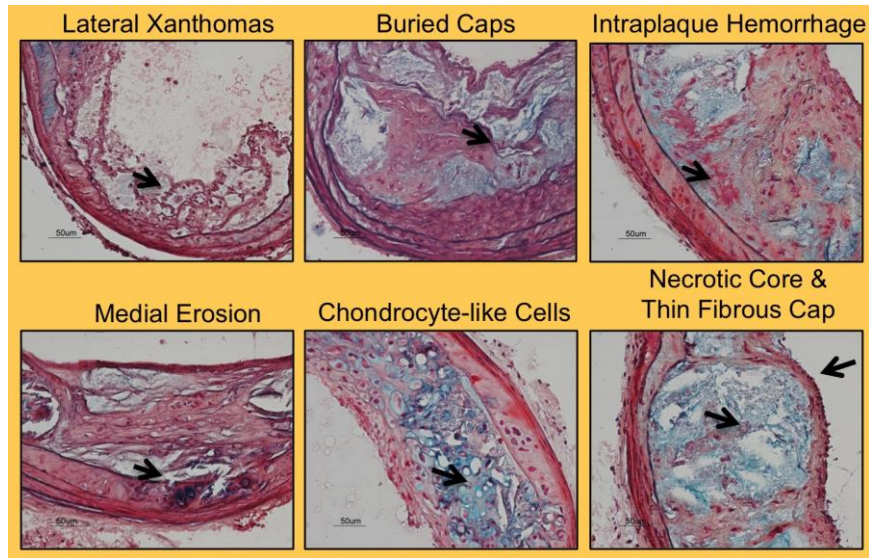
Alberto Ortíz



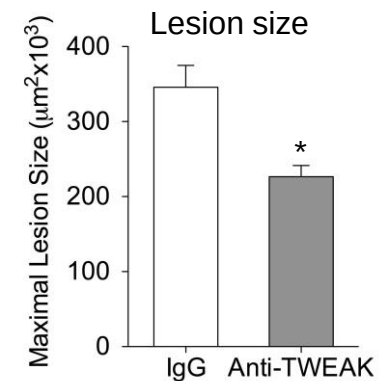
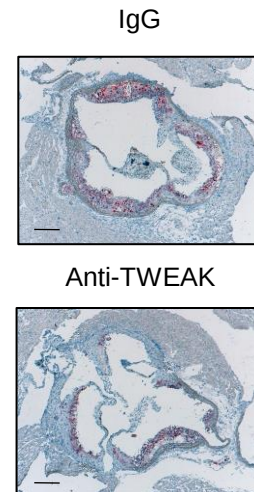
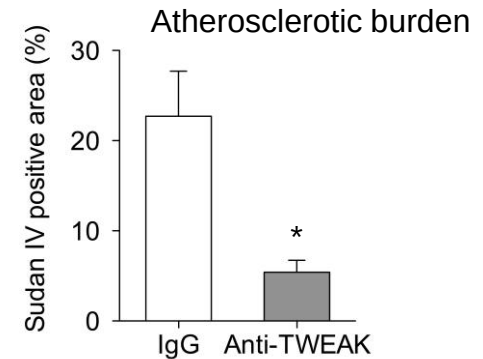
Renal

Anti-TWEAK therapy to prevent atherosclerosis development and progression

Hypercholesterolemic mice



Diabetic mice



Fernández-Laso et al. Sci Rep. 2017;7:46679

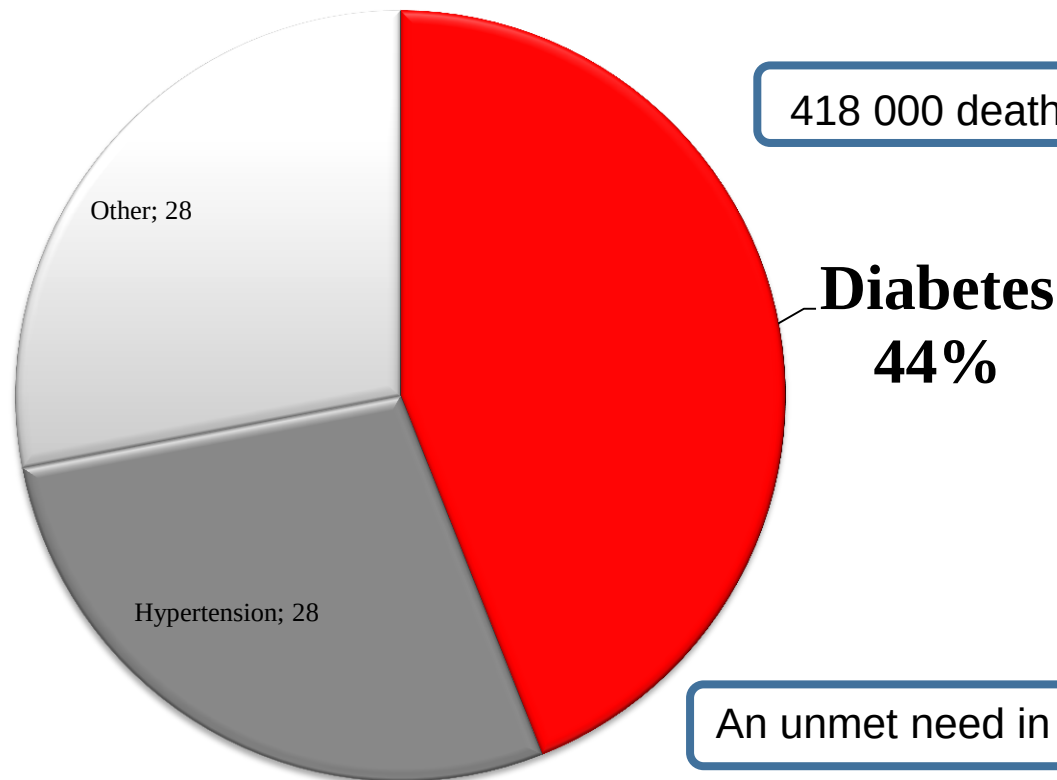
The contribution of Chronic Kidney Disease (CKD) to the global burden of major non communicable diseases

- Milder CKD affects 5–7% of the world population and higher in developing countries
- CKD occurs in 25–40% of patients with diabetes within 20 years of onset.

Diabetes is now the leading cause of end-stage kidney disease (dialysis)

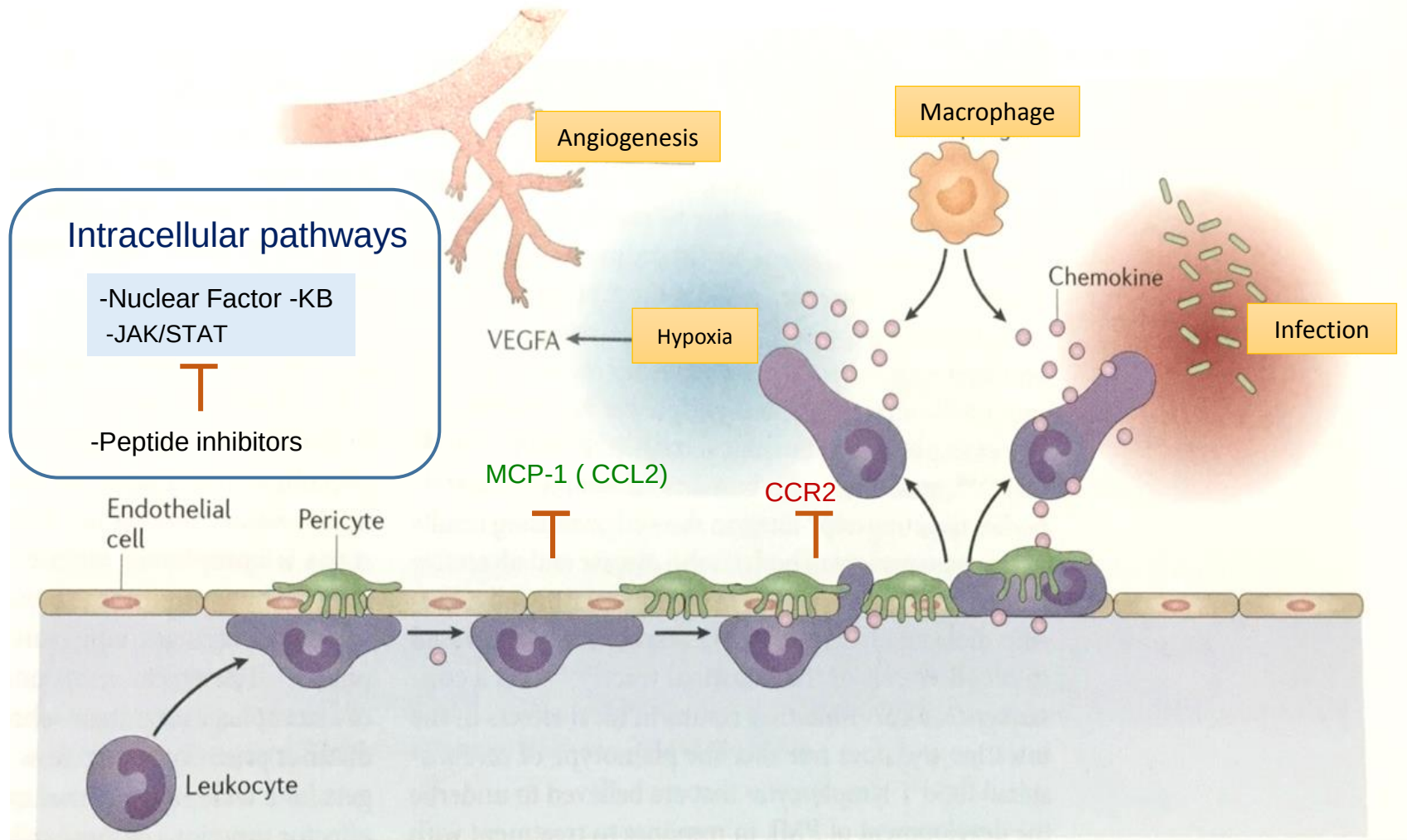
- DPP IV inhibitors
- GLP-1 agonists
- SGLT-2 inhibitors
Empagliflozin

- Mineralocorticoid receptor antagonist
Finerenone



More effective therapy for diabetic kidney diseases needed beyond the control of hyperglycemia, hypertension and high blood cholesterol

Leukocyte recruitment cascade and the potential drug target in diabetic nephropathy

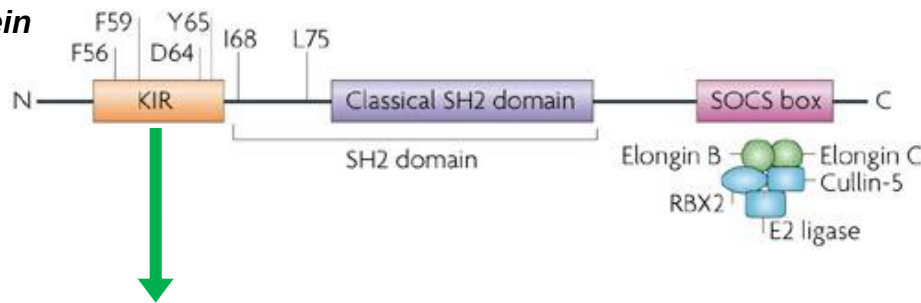


Dysregulated JAK/STAT contributes to the pathogenesis of autoimmune disease, inflammation, cancer and diabetes

SOCS1 mimetic peptide to treat diabetic complications

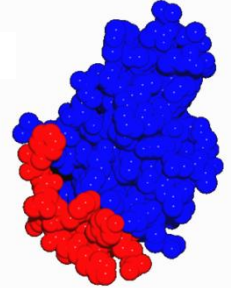
Plan of development

SOCS1 protein



Suppressor Of Cytokine Signalling, a negative regulator of JAK/STAT pathway

SOCS1



KIR: Kinase Inhibitory Region

KIR

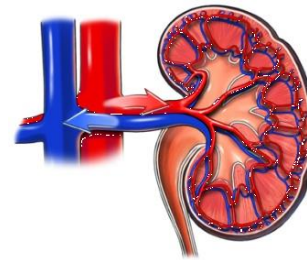
Cell-permeable SOCS1-derived peptide (S1 peptide)



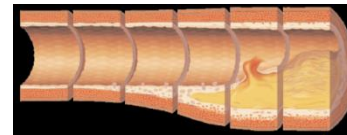
Diabetic mice



With/without hyperlipidemia



Nephropathy



Atherosclerosis



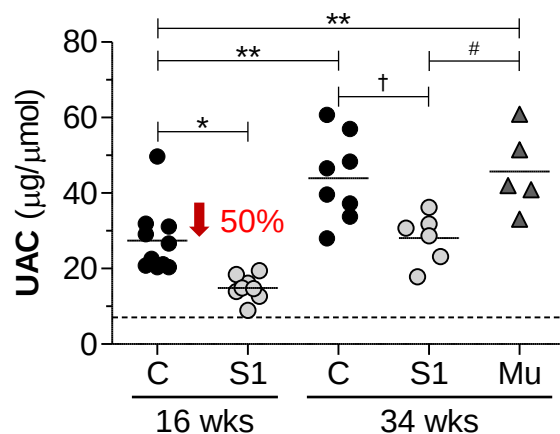
Retinopathy



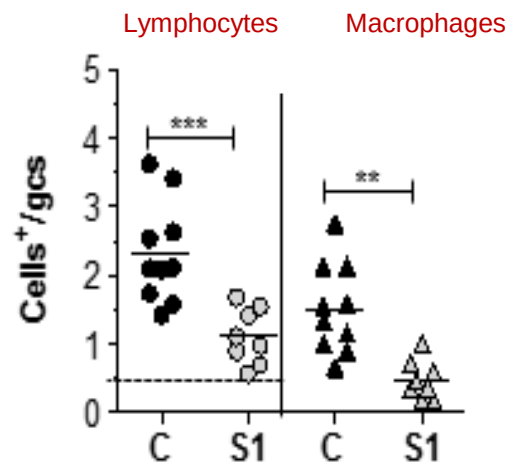
SOCS1 peptide improves renal damage in diabetic mice

SOCS peptide inhibited JAK/STAT activation

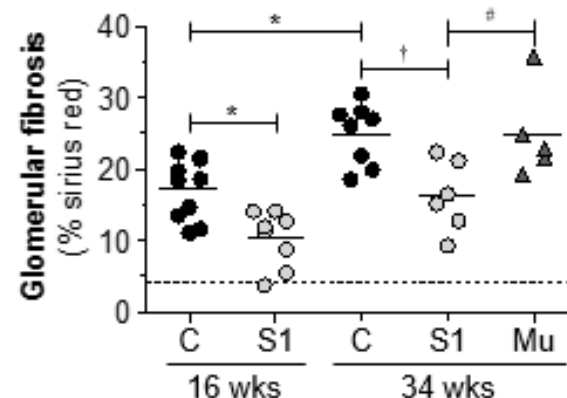
Albuminuria



Inflammation



Fibrosis

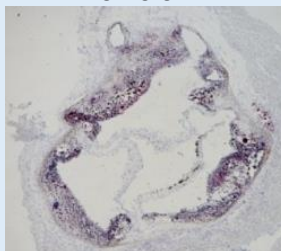


C: Control
S1: SOCS1 peptide
Mu: Mutant Peptide

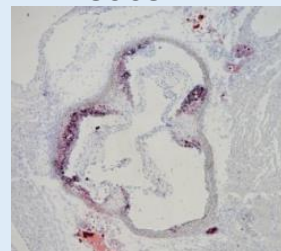
Recio et al. JASN, 2017

Vascular protection by the SOCS peptide

Vehicle



SOCS1



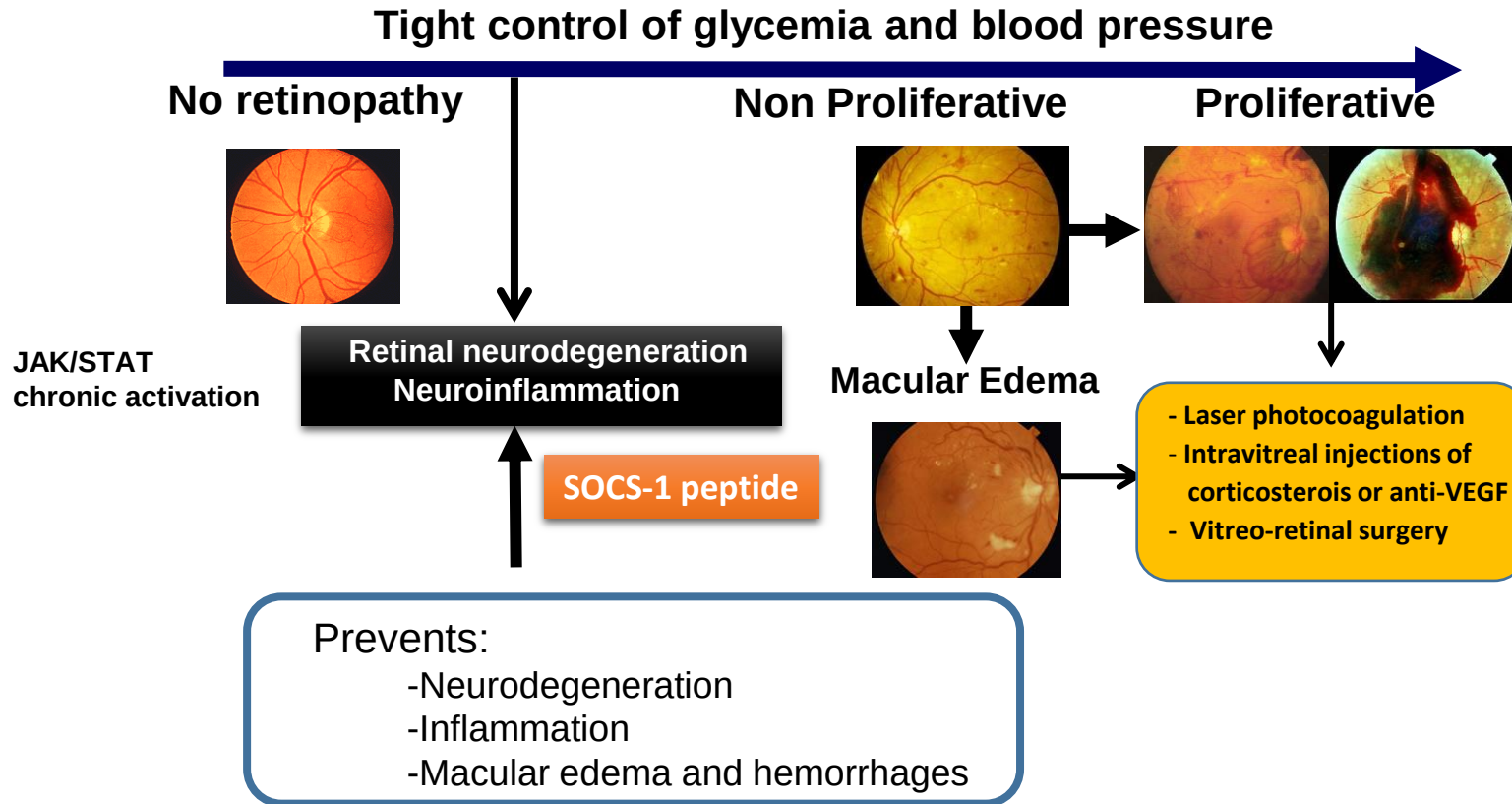
Improves plaque composition
and confers stability

Recio et al., ATVB 2014;34:1953-60.

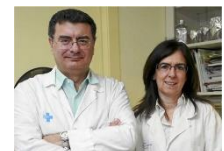


Topical administration of SOCS1 peptide in the prevention and treatment of diabetic retinopathy

Diabetic retinopathy may lead to blindness in 75% of individuals who have been diabetic for more than 20 years



- Targeting early stages
 - Easy application, self-administered
 - Absence of systemic adverse effects
 - Preclinical → Phase I-IIa → Phase III
- Patent No P201430796



Rafael Simó
Cristina Hernandez

Confronting the perfect storm

Diabetes, hypertension and chronic kidney disease are silent, invisible killers that rarely causes symptoms

Undiagnosed adults :

- Hypertension, about 40%
- Diabetes, about 50%
- Chronic kidney disease, about 90%

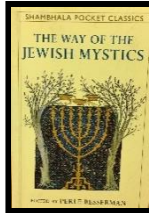
Increasing public awareness is key, as is access to early detection



The way of frugality



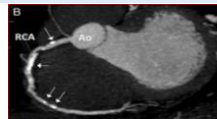
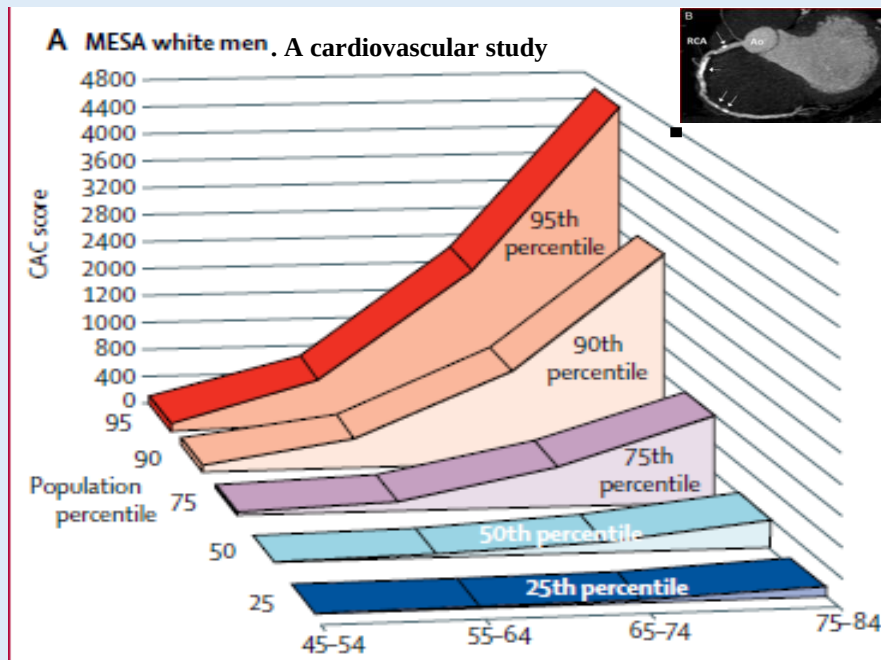
- Take only enough **food** and drink as **you require for your sustenance**
- Limit yourself to **one course only**
- Rely upon **simple food**



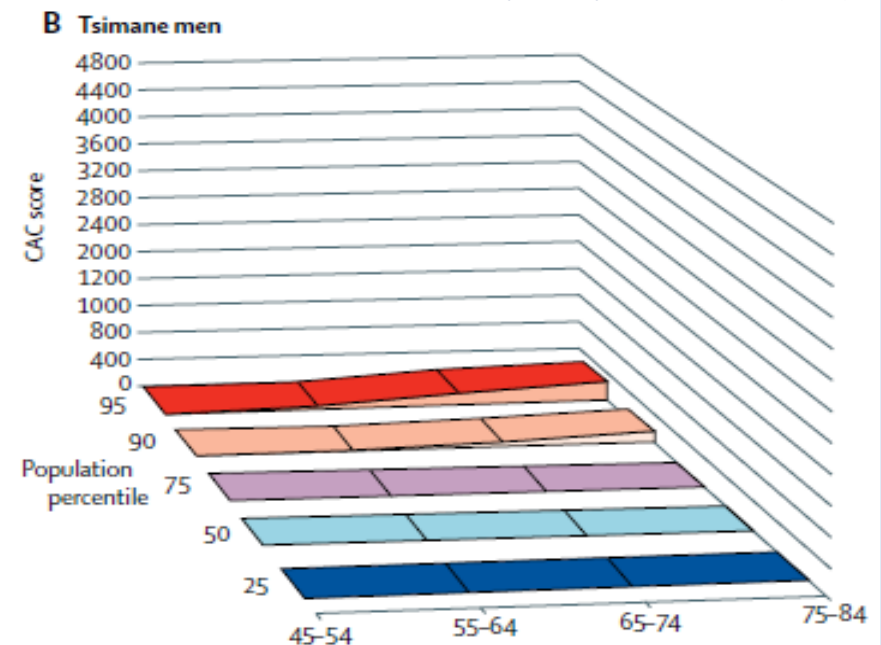
Coronary atherosclerosis in indigenous South American Tsimane: a cross-sectional cohort study

www.thelancet.com Published online March 17, 2017

The horticulturalist population of the Bolivian Amazon have the **lowest reported** levels of **coronary artery disease** recorded to date.

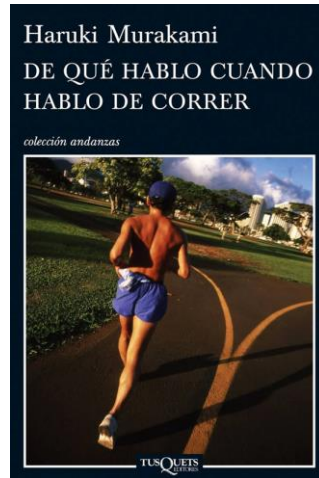
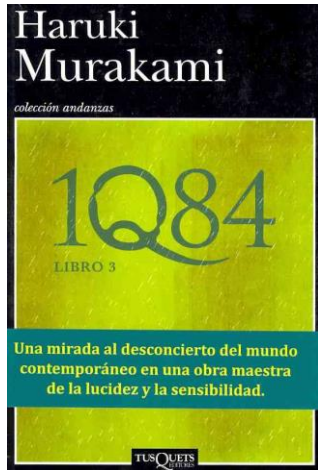


85% of 705 individuals had no Coronary Artery Calcification (CAC)



La presencia de **obesidad**, **hipertensión**, aumento de la **glucemia** y del **colesterol** fue excepcional, sugiriendo que el control de estos factores previene la enfermedad coronaria, incluso en personas mayores

Dietary and lifestyle modifications are very effective for the treatment of obesity and prevention of diabetes



EL escritor **Haruki Murakami** (Kioto, Japón, 1949) **empezó a correr** siendo ya adulto porque se veía gordo y con falta de aire.

En 6 meses **adelgazó 6 kilos** y **se sentía otra persona**. Así describe la sensación:

"Me gustaría que imaginaran que van a una carnicería, piden 6 kilos de carne y luego vuelven a casa caminando con ellos en la mano; tal vez así puedan hacerse una idea de lo que significa cargar con ese peso".

Estar motivado para cambiar y nunca es tarde para hacerlo

Early Prevention of Diabetes Complications in people with hyperglycemia in Europe: Study e-PREDICE

ePREDICE

FP7-HEALTH PROGRAM

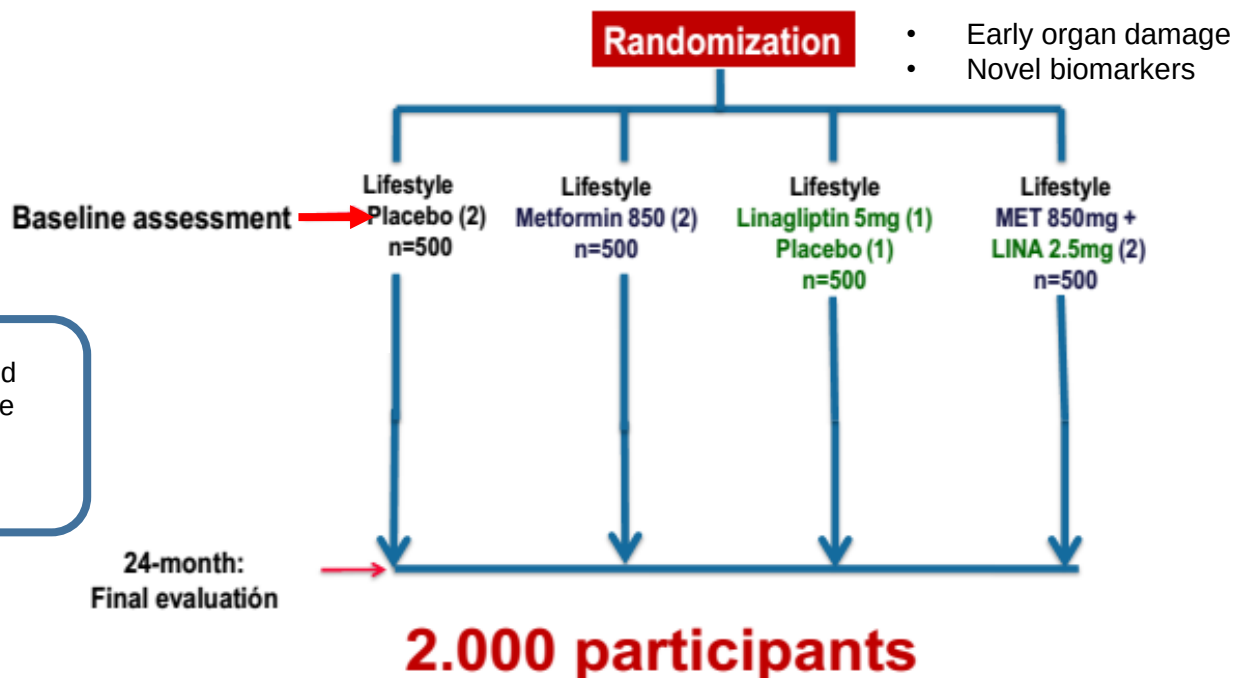
The biobank is located at FJD

The Diabetes Prevention Program

Lifestyle changes reduced the incidence of diabetes in persons at high risk .
N Engl J Med. 2002

Prediabetes and Type 2 Diabetes are Associated with Generalized Microvascular Dysfunction: The Maastricht Study
Circulation. 2016 ;134:1339-1352

STUDY DESIGN



Estimated Completion Date: End 2018

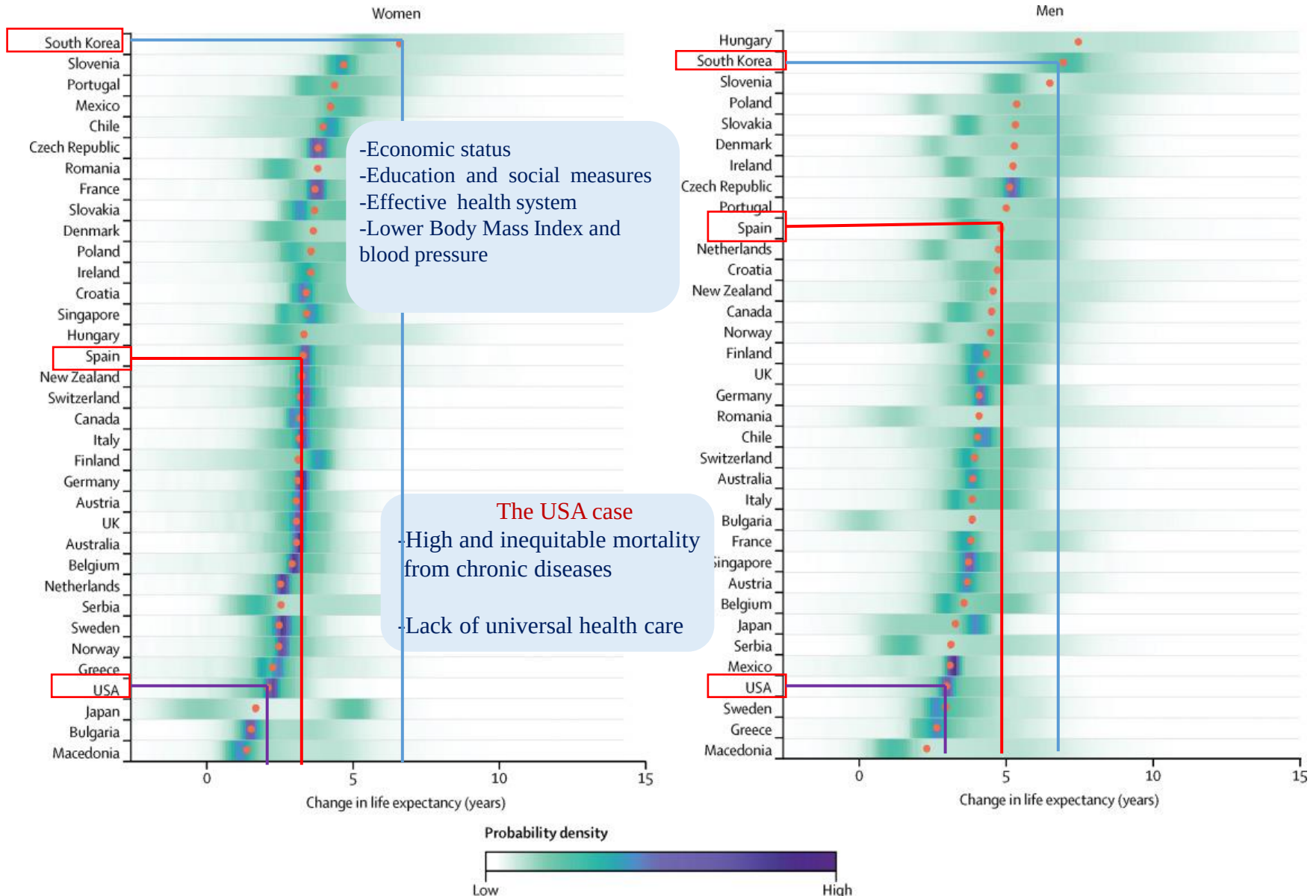
Around 7% of prediabetic subjects present lesions of diabetic retinopathy !!!

Future life expectancy in 35 industrialised countries:

Towards an aging society

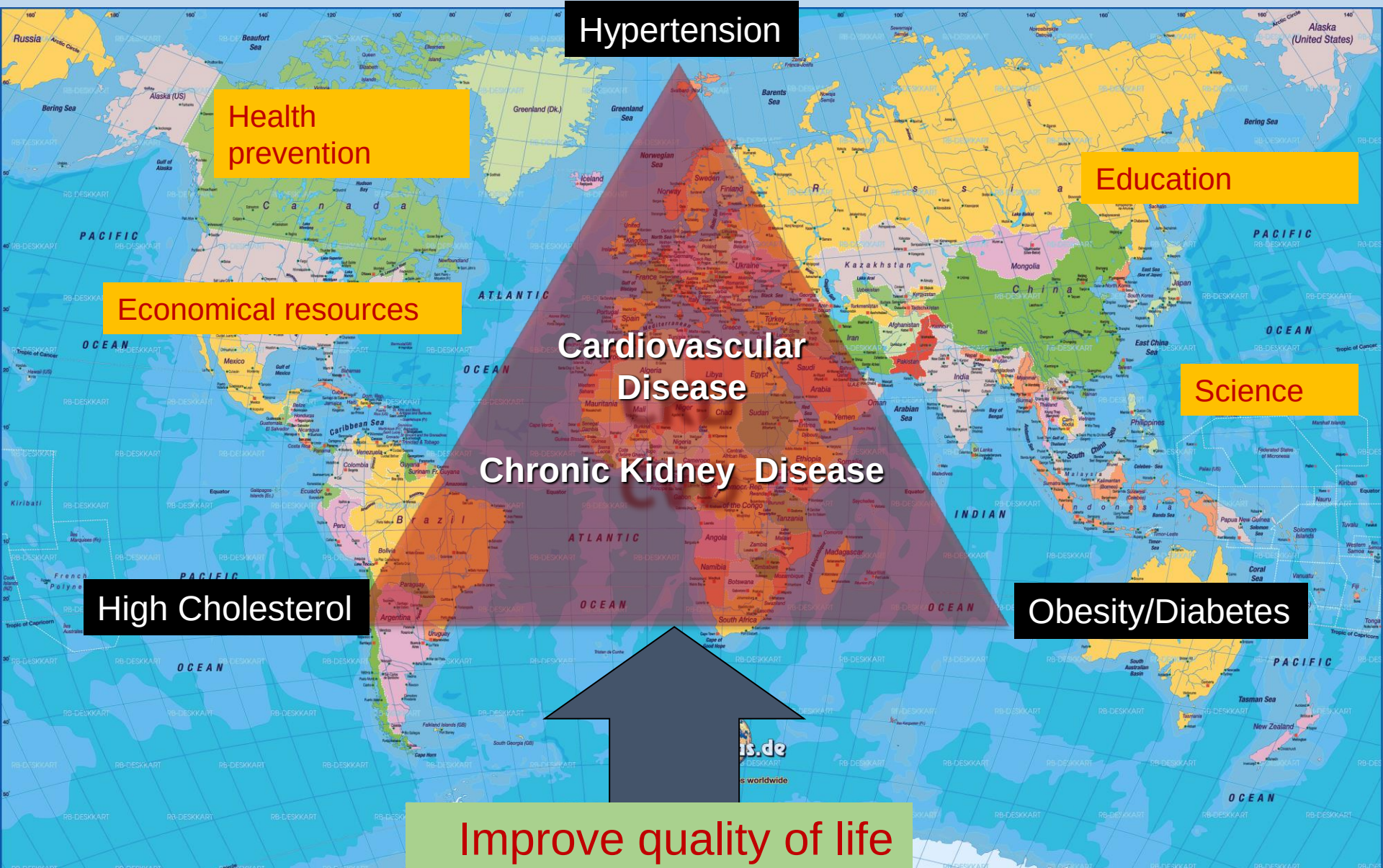
www.thelancet.com Published online February 21, 2017

Projected change in life expectancy at birth from 2010 to 2030



TOWARDS A GLOBAL HEALTHY WORLD

Over **60% of deaths** from Cardiovascular and Chronic Kidney Disease in 2010 were attributable to **3 preventable cardio-metabolic causes**



In Memoriam

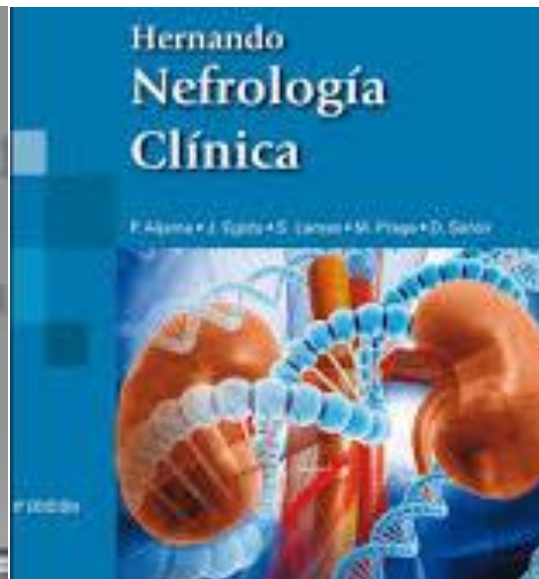
Luis Hernando Avendaño, 1926-2017

Fundador y Jefe de Servicio de Nefrología en la Fundación durante casi treinta años

Ser médico...
«y haber implantado la Nefrología en España»

L. Hernando, J. Crabbé, E.J. Ross, W.J. Reddy, A.E. Renold, D.H. Nelson

Clinical experience with a physicochemical method for estimation of aldosterone in urine. Metabolism: 6, 1957



Homenaje a la Fundación Conchita Rábago,

El alma de la Investigación en nuestra Institución



Núcleo inicial del Laboratorio:

- Margarita López-Trascasa
- Jaime Sancho
- Alberto Ortiz
- Francisco Rivera
- Luz Lozano
- José Tuñón
- Dulcenombre Gómez-Garre
- Miguel Ángel Hernández-Presa
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- Corina Lorz
- Almudena Gómez Hernández
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- Maria José Lopez Armada
- Gabriel Herrero Beaumont
- Raquel Largo
- Javier Alonso
- Jesus Gonzalez-Cabrero †
- Rosa Garcia-Hoyo †
- Carlos Caramelo †



A todos los médicos y enfermeras del Servicio de Nefrología e Hipertensión pasados y presentes por su excelente labor en el cuidado de los pacientes.

Un recuerdo particular para el Dr. Santos Casado fallecido en 2016

OF
MICE
AND
MEN

A Novel by
JOHN STEINBECK
AUTHOR OF 'TORTILLA FLAT'



A los clínicos e investigadores nacionales e internacionales con los que hemos colaborado a lo largo de los años



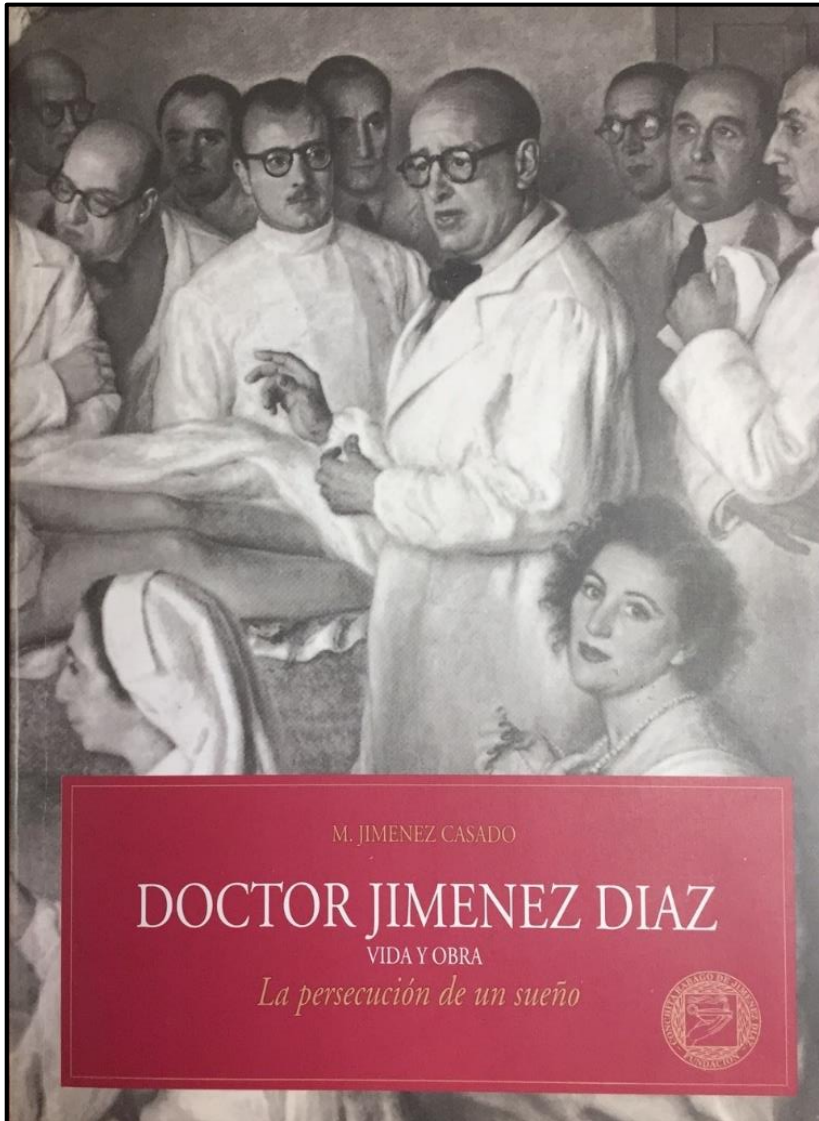
La familia en 2012



A los estudiantes, a los jóvenes médicos y a los jóvenes investigadores

La persecución de un sueño

Prof. Mariano Jiménez Casado



Sois afortunados por haber elegido esta profesión

- Sed entusiastas
- Nunca os deis por vencidos
- Seguid siempre vuestros sueños
- Intentad ser felices