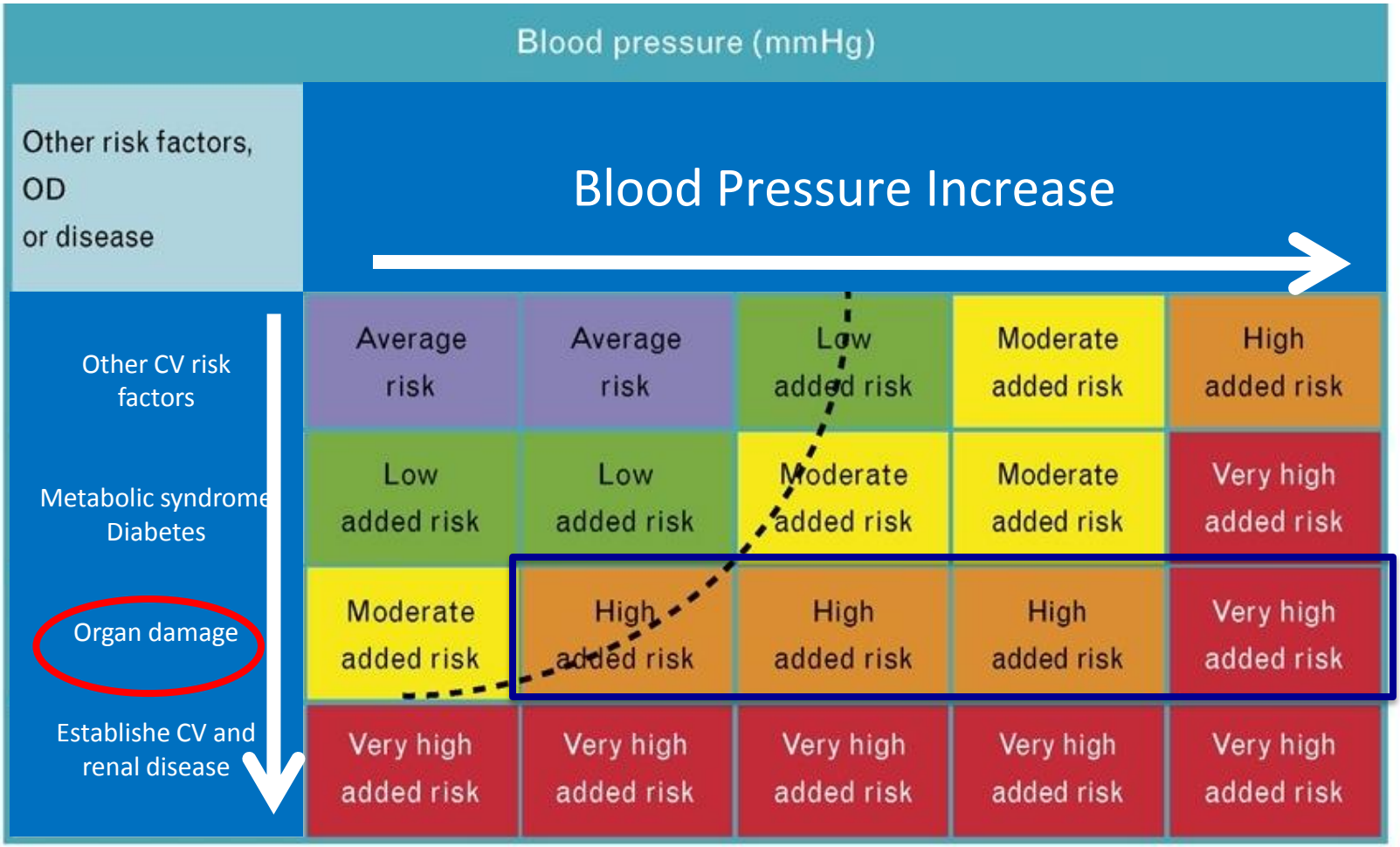
Impact of target damage in the management of hypertension: endothelium, the heart and the kidney

Stefano Taddei

Department of Clinical and Experimental Medicine

University of Pisa, Italy

Target Organ Damage in hypertension



2007 ESH-ESC Practice Guidelines for the Management of Arterial Hypertension: ESH-ESC Task Force on the Management of Arterial Hypertension

Estabilished Subclinical Organ Damage

- Electrocardiographic LVH (Sokolow-Lyon > 38 mm; Cornell > 2440 mm*ms) or:
- Echocardiographic LVH° (LVMI M ≥ 125 g/m^2, W ≥ 110 g/m^2)
- Carotid wall thickening (IMT > 0.9 mm) or plaque
- Carotid-femoral pulse wave velocity >12 m/s
- Ankle/brachial BP index < 0.9
- Slight increase in plasma creatinine:
  M: 115–133 μmol/l (1.3–1.5 mg/dl);
  W: 107–124 μmol/l (1.2–1.4 mg/dl)
- Low estimated glomerular filtration rate† (< 60 ml/min/1.73 m^2)
  or creatinine clearance◇ (< 60 ml/min)
- Microalbuminuria 30–300 mg/24 h or albumin-creatinine ratio:
  ≥ 22 (M); or ≥ 31 (W) mg/g creatinine

2007 ESH-ESC Practice Guidelines for the Management of Arterial Hypertension:
ESH-ESC Task Force on the Management of Arterial Hypertension

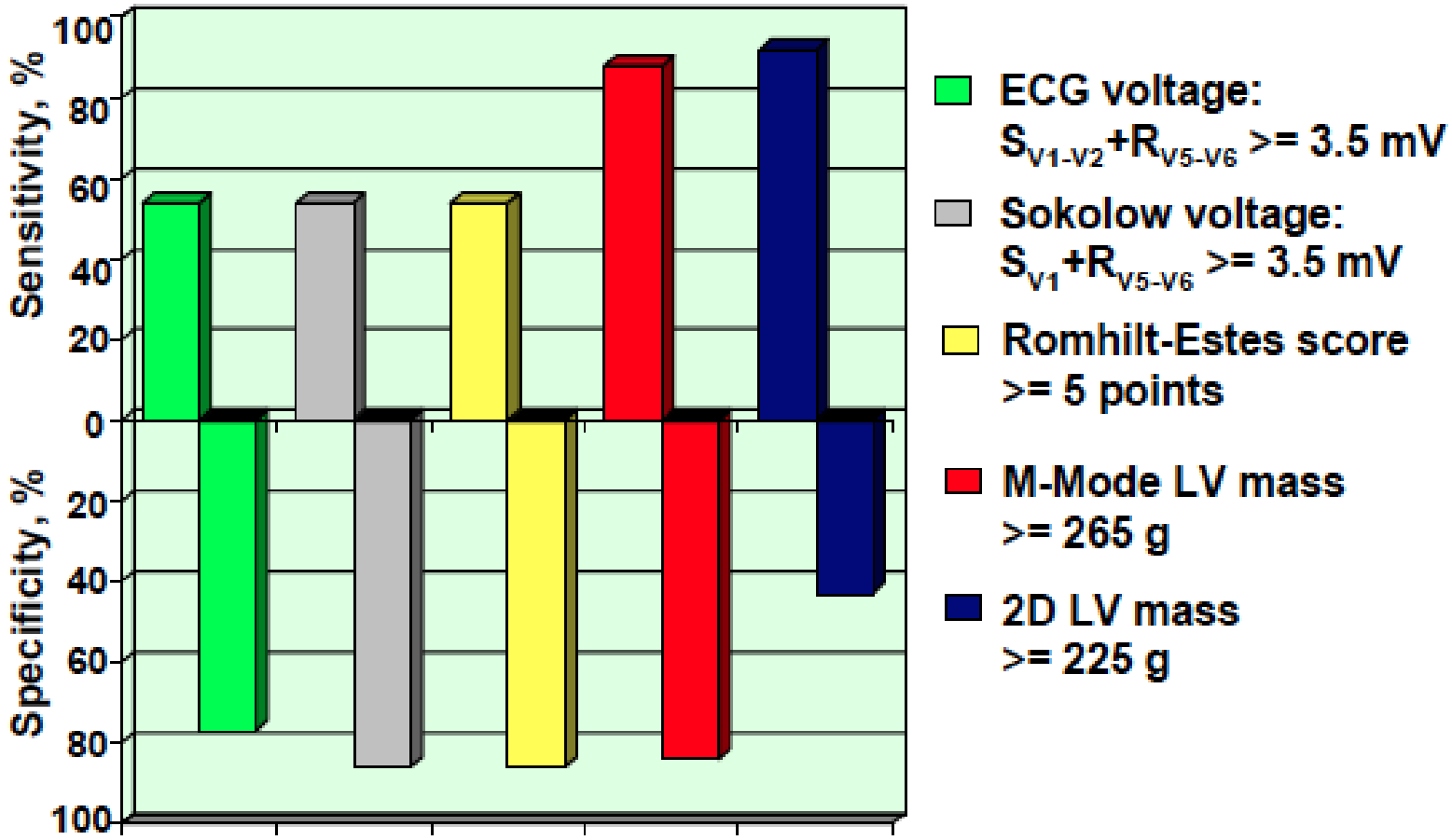
Estabilished Subclinical Organ Damage

- Electrocardiographic LVH (Sokolow-Lyon > 38 mm; Cornell > 2440 mm*ms) or:
- Echocardiographic LVH° (LVMI M ≥ 125 g/m^2, W ≥ 110 g/m^2)
- Carotid wall thickening (IMT > 0.9 mm) or plaque
- Carotid-femoral pulse wave velocity >12 m/s
- Ankle/brachial BP index < 0.9
- Slight increase in plasma creatinine:
  M: 115–133 μmol/l (1.3–1.5 mg/dl);
  W: 107–124 μmol/l (1.2–1.4 mg/dl)
- Low estimated glomerular filtration rate† (< 60 ml/min/1.73 m^2)
  or creatinine clearance◇ (< 60 ml/min)
- Microalbuminuria 30–300 mg/24 h or albumin-creatinine ratio:
  ≥ 22 (M); or ≥ 31 (W) mg/g creatinine

2007 ESH-ESC Practice Guidelines for the Management of Arterial Hypertension:
ESH-ESC Task Force on the Management of Arterial Hypertension

LVH diagnosis: sensitivity and specificity of ECG and Echo

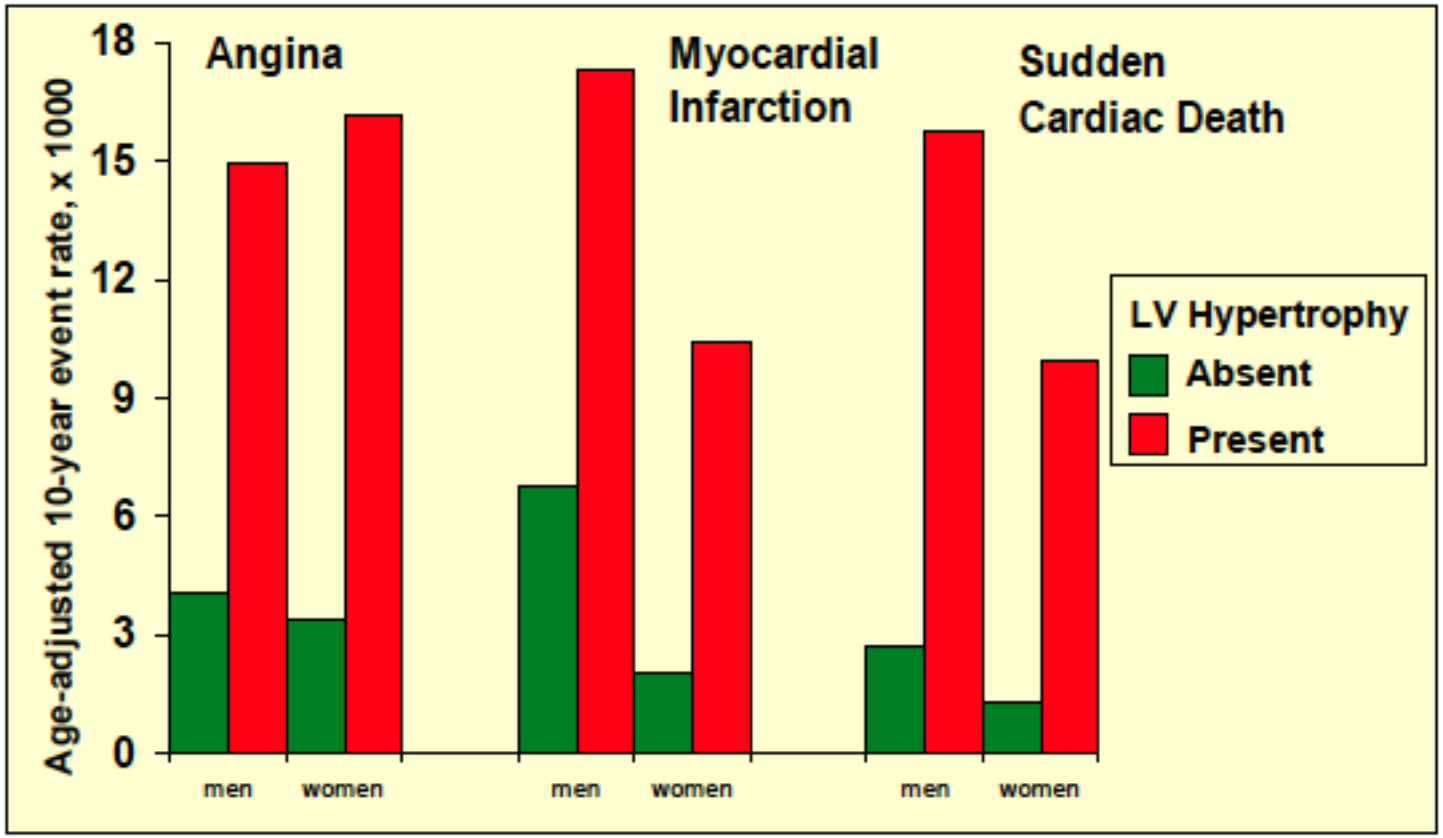
(autoptic LV mass as reference)



Woythaler JN et al. JACC 1983; 2: 305

Prognostic significance of LVH

Prognostic Value of Baseline LV Hypertrophy at ECG in the Framingham Heart Study

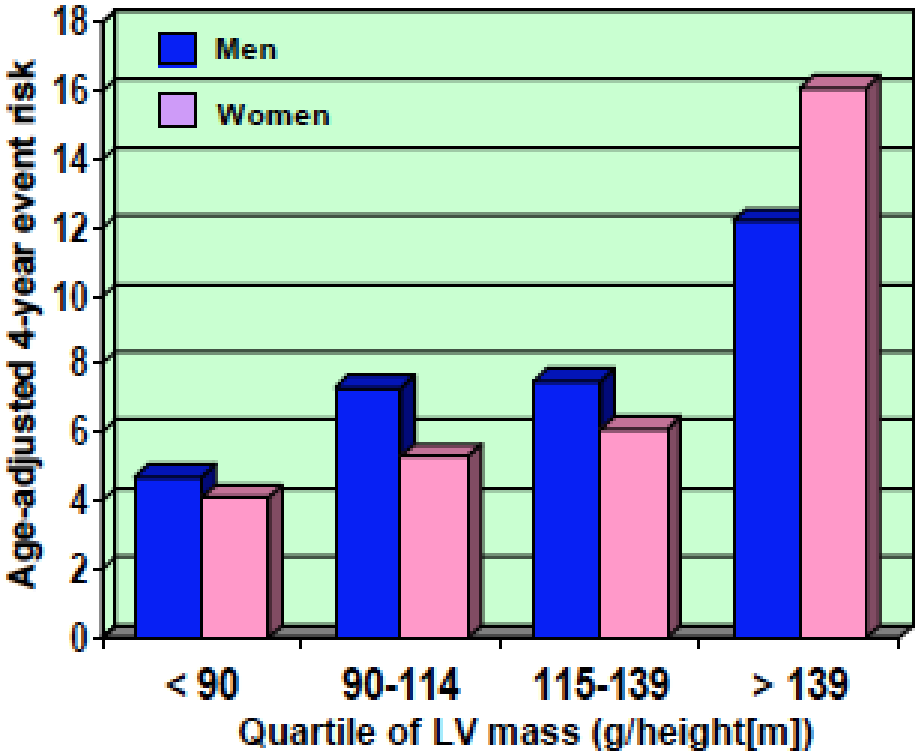


Definition of LVH: Framingham voltage + ST-T changes; Prevalence: 2.9% in men, 1.5% in women

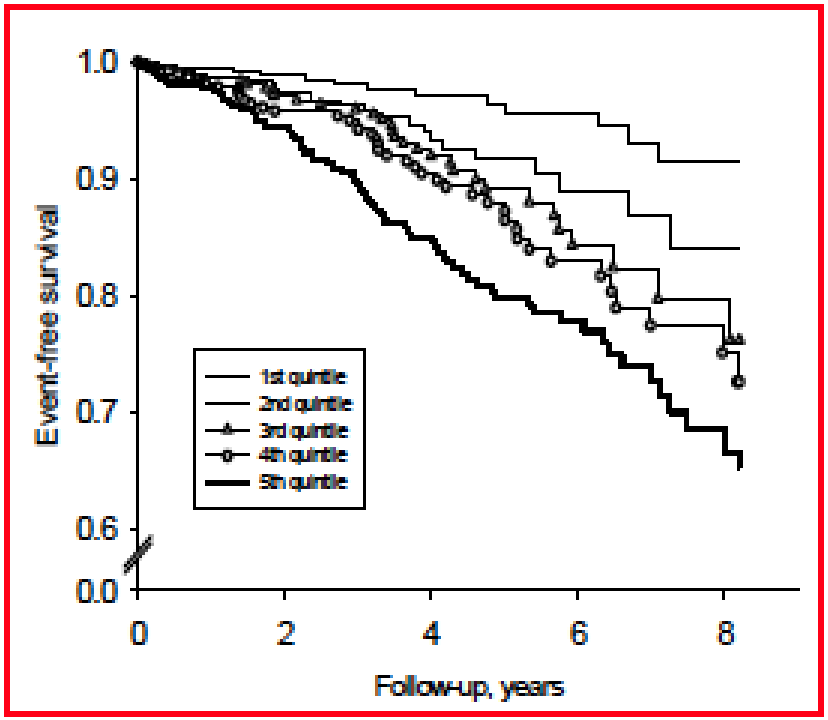
Kannel WB, Am J Med 1983;75 (suppl 3A):4-11; Levy D et al, Circulation 1990;81:815-820

LV mass by Echo predicts CV events

General Population (Framingham Heart Study)



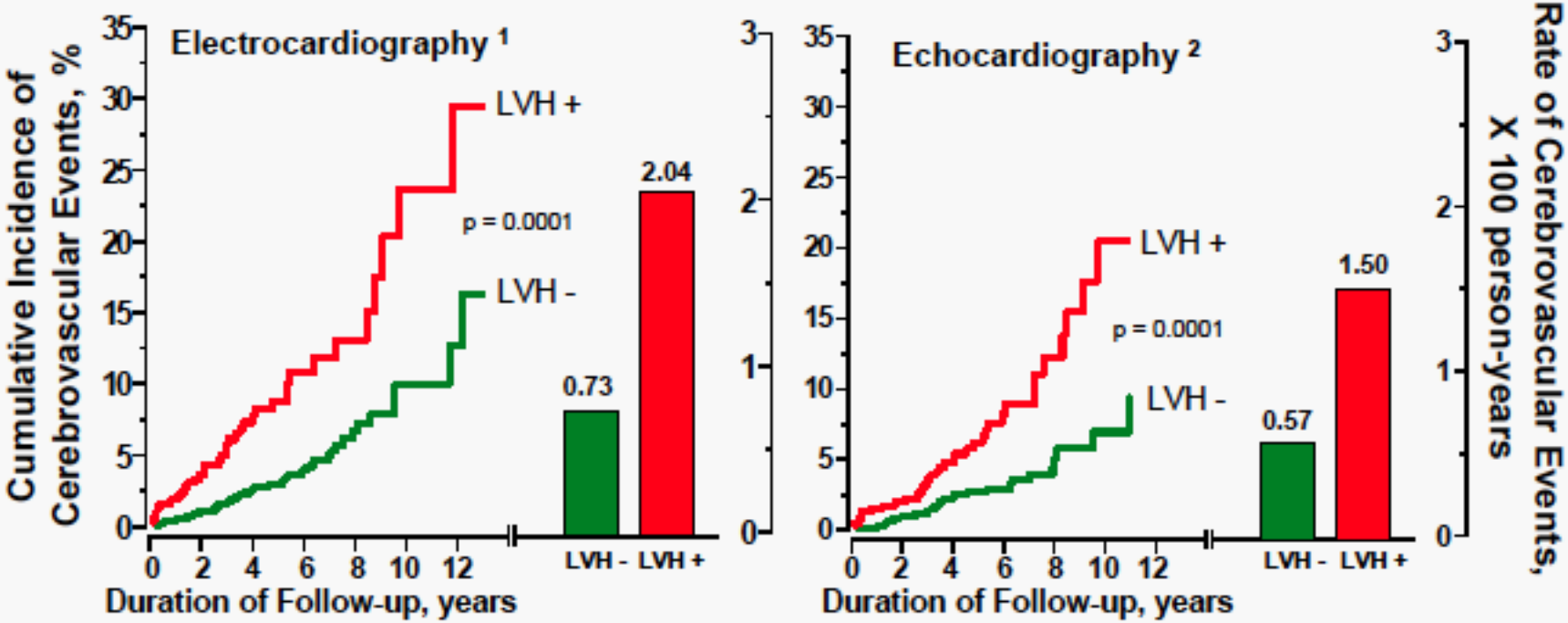
Essential Hypertension (PIUMA Study)



Levy D et al., NEJM 1990; 322: 1561-66

Schillaci G et al., Hypertension 2000; 35: 580-86

LVH at ECG or echo predicts stroke in essential hypertensive patients
The PIUMA Study



1 Perugia Score
(raVL + SV_3 > 2.0 mV (women) or 2.4 mV (men)
or presence of typical strain
or Romhilt-Estes score ≥ 5 points)

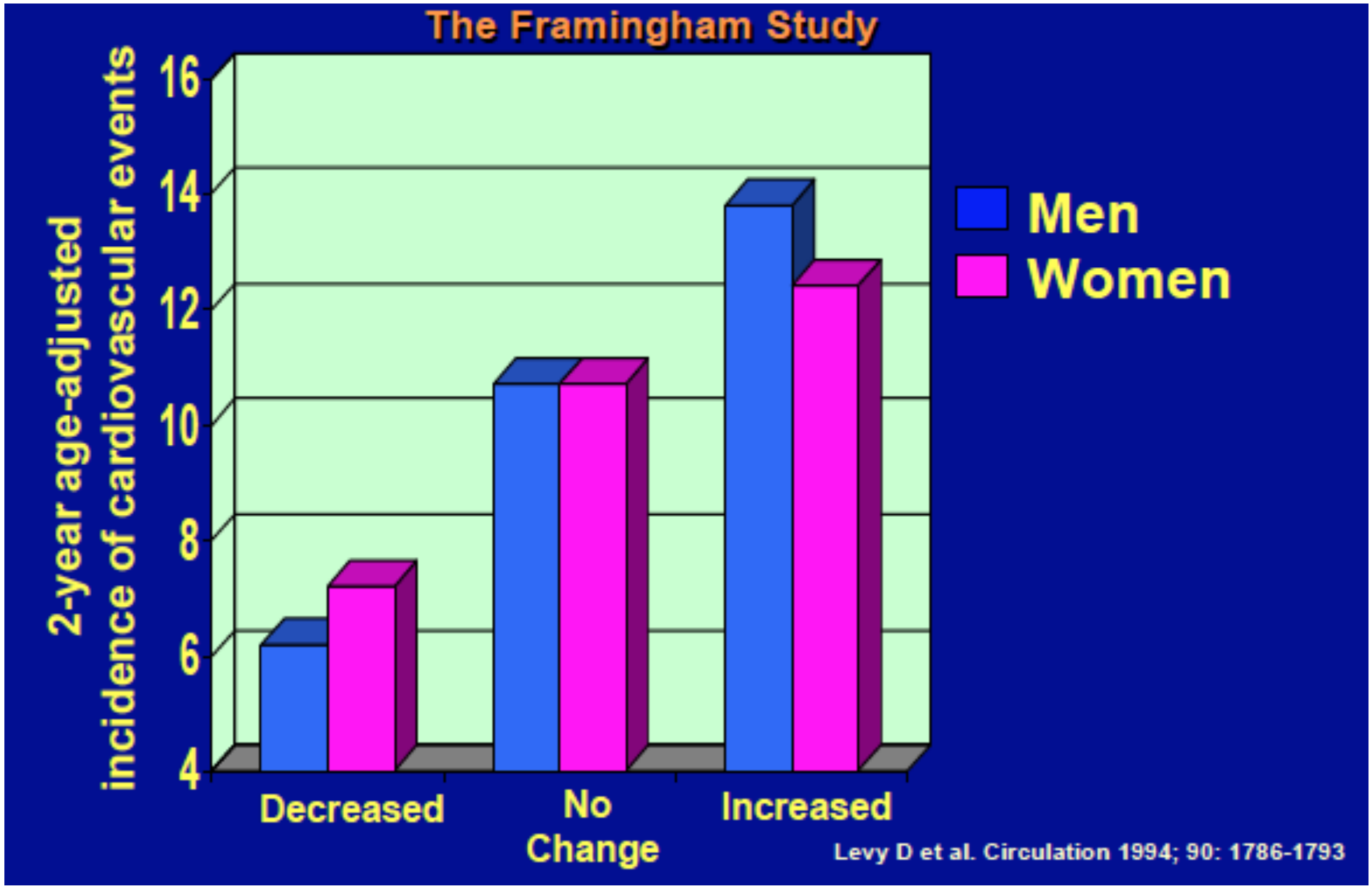
2 Left Ventricular Mass
(> 125 g/m^2 [body surface area])

N = 2363
Follow-up: 0-14 years (mean, 5)
105 Cerebrovascular Events

Verdecchia P et al. Circulation 2001; 104: 2039-44

Prognostic significance of LVH regression

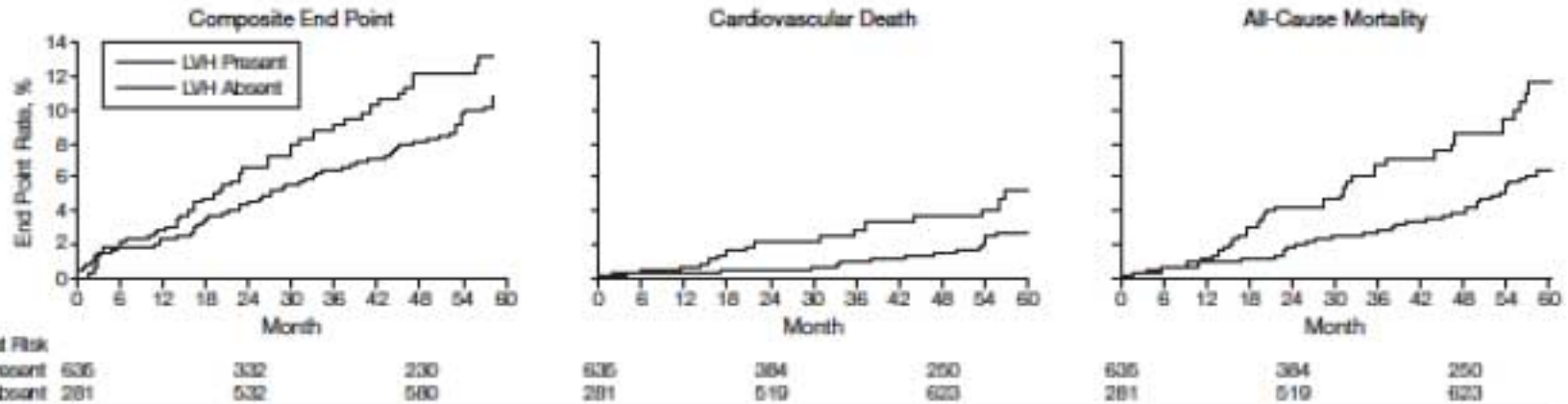
LVH regression by ECG predicts CV mortality
The Framingham study



Levy D et al., Circulation 1994; 90:1786-93

Prognostic Significance of Left Ventricular Mass Change During Treatment of Hypertension

Figure. Composite End Point, Cardiovascular Death, and All-Cause Mortality Stratified by Time-Varying Presence of Echocardiographic Left Ventricular Hypertrophy



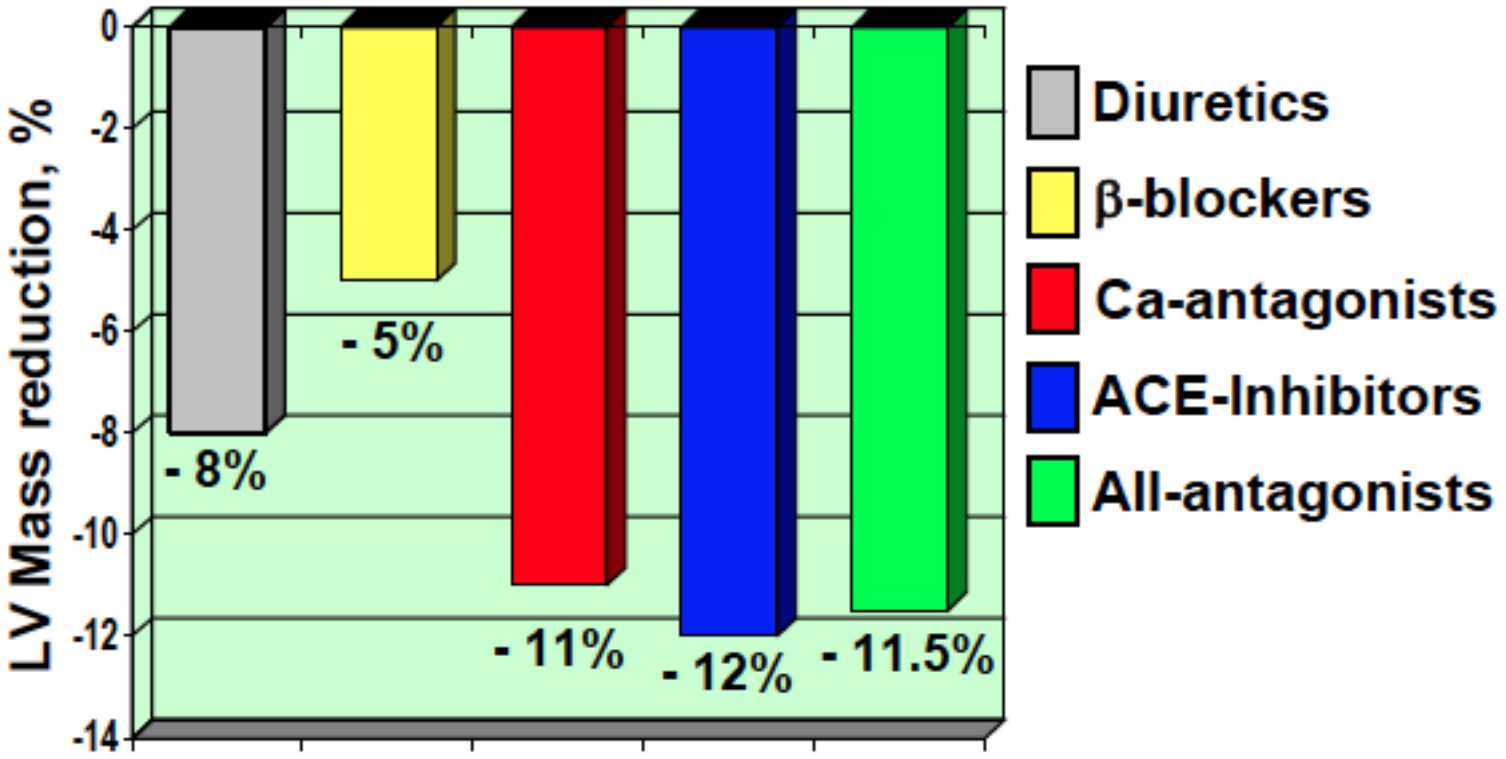
Left ventricular hypertrophy (LVH) defined as left ventricular mass index of >116.0 in men and >104.0 in women. Patients with LVH at baseline are counted in the "LVH absent" group at the time at which their LVH regresses.

Conclusion In patients with essential hypertension and baseline electrocardiographic LV hypertrophy, lower LV mass during antihypertensive treatment is associated with lower rates of clinical end points, additional to effects of blood pressure lowering and treatment modality.

JAMA. 2004;292:2350-2356 www.jama.com

LVH regression is related to antihypertensive drug class used

Meta-analysis of 80 RCTs, 4113 hypertensive patients



Klingbeil AU et al., Am J Med 2003; 115: 41-46

Estabilished Subclinical Organ Damage

- Electrocardiographic LVH (Sokolow-Lyon > 38 mm; Cornell > 2440 mm*ms) or:
- Echocardiographic LVH° (LVMI M ≥ 125 g/m^2, W ≥ 110 g/m^2)
- Carotid wall thickening (IMT > 0.9 mm) or plaque
- Carotid-femoral pulse wave velocity >12 m/s
- Ankle/brachial BP index < 0.9
- Slight increase in plasma creatinine:
  M: 115–133 μmol/l (1.3–1.5 mg/dl);
  W: 107–124 μmol/l (1.2–1.4 mg/dl)
- Low estimated glomerular filtration rate† (< 60 ml/min/1.73 m^2)
  or creatinine clearance◇ (< 60 ml/min)
- Microalbuminuria 30–300 mg/24 h or albumin-creatinine ratio:
  ≥ 22 (M); or ≥ 31 (W) mg/g creatinine

2007 ESH-ESC Practice Guidelines for the Management of Arterial Hypertension:

ESH-ESC Task Force on the Management of Arterial Hypertension

No need of 24hr urine collection for albuminuria evaluation !

AER ***(Albumin excretion rate)***
overnight o 24 ore

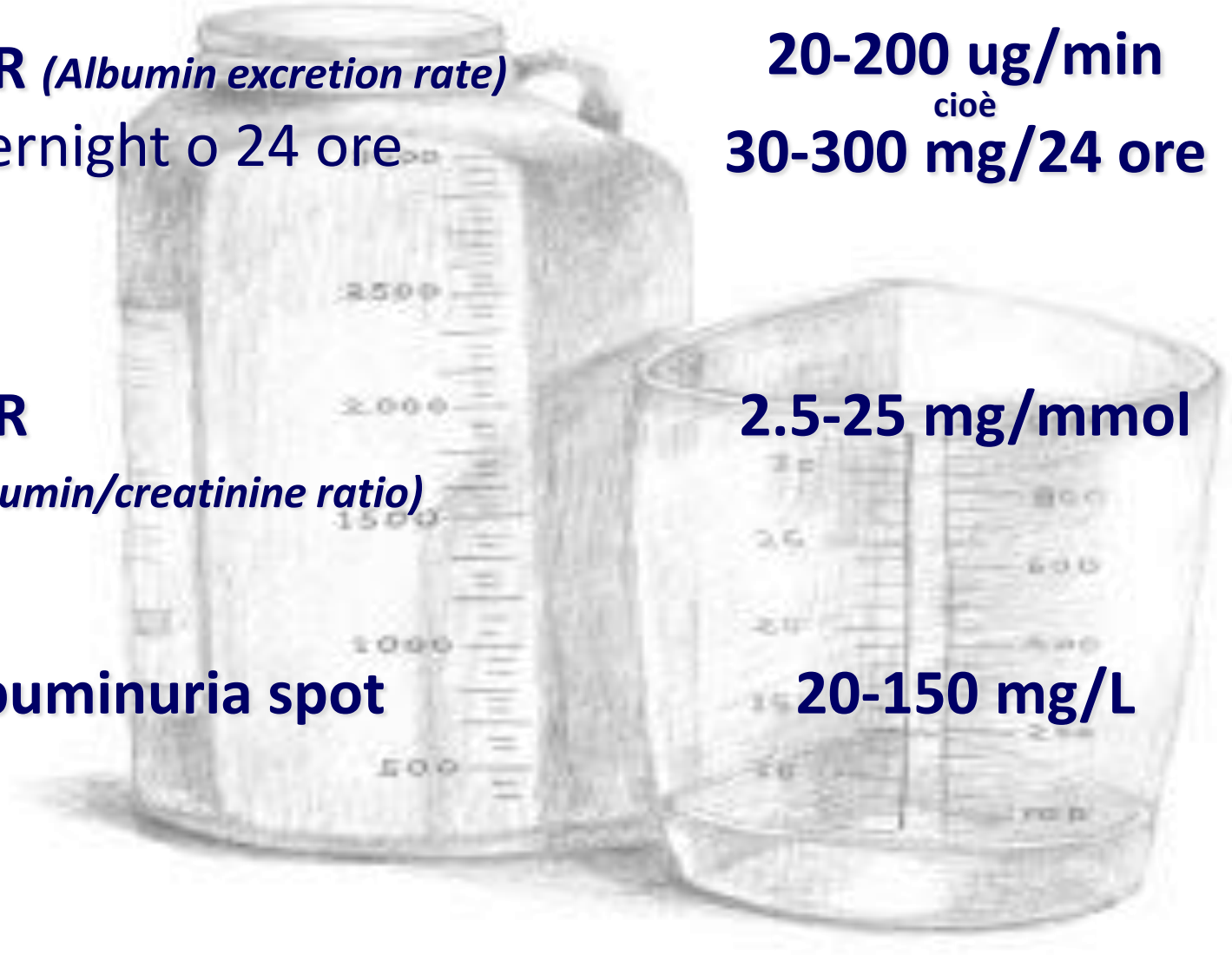
20-200 ug/min
cioè
30-300 mg/24 ore

ACR
(Albumin/creatinine ratio)

2.5-25 mg/mmol

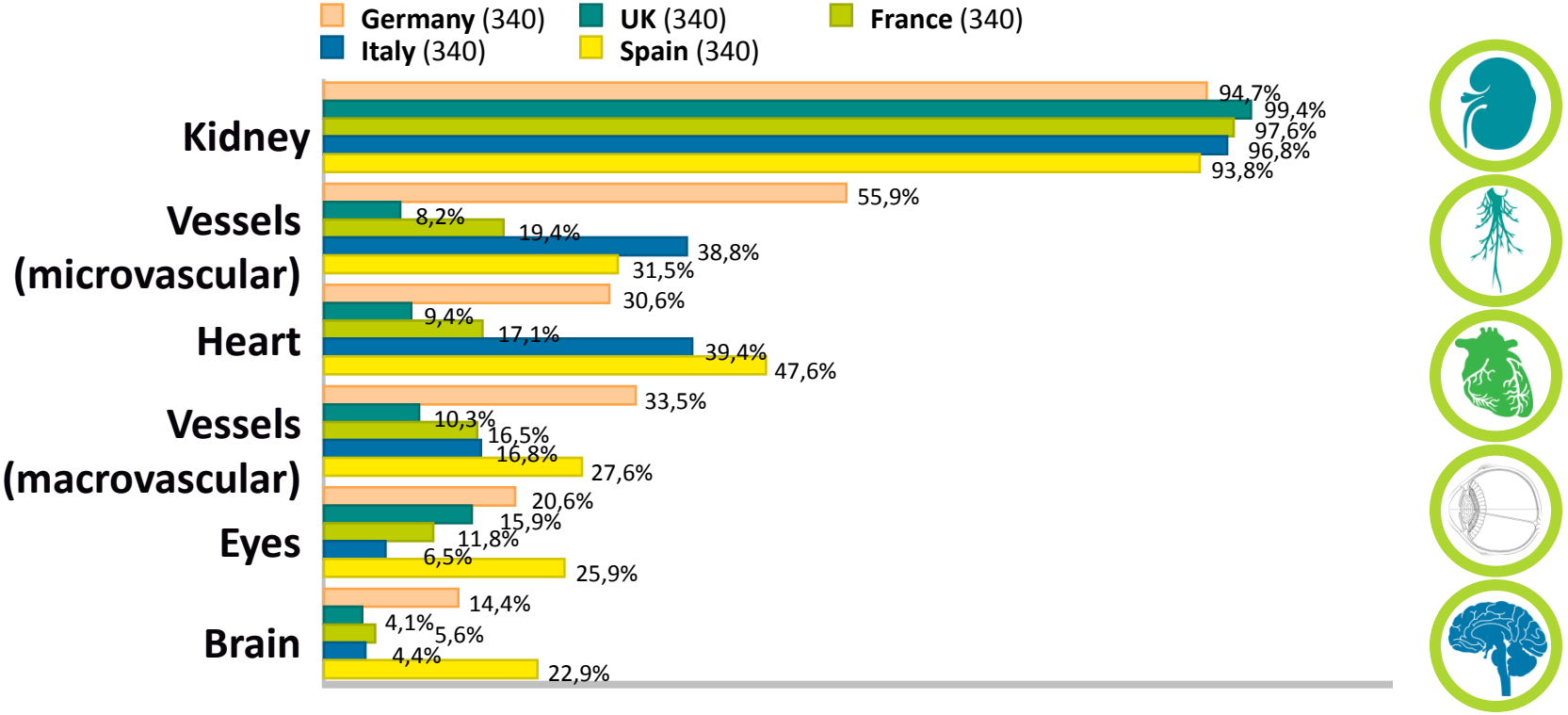
Albuminuria spot

20-150 mg/L



Prognostic significance of renal damage

The ESH survey: With which type of organ damage is Microalbuminuria associated?



Currently, only kidney damage is perceived by physicians to be associated with microalbuminuria – excluding damage to other important organs

Haller H, et al. J Hypertens. 2010;28:2204-9.

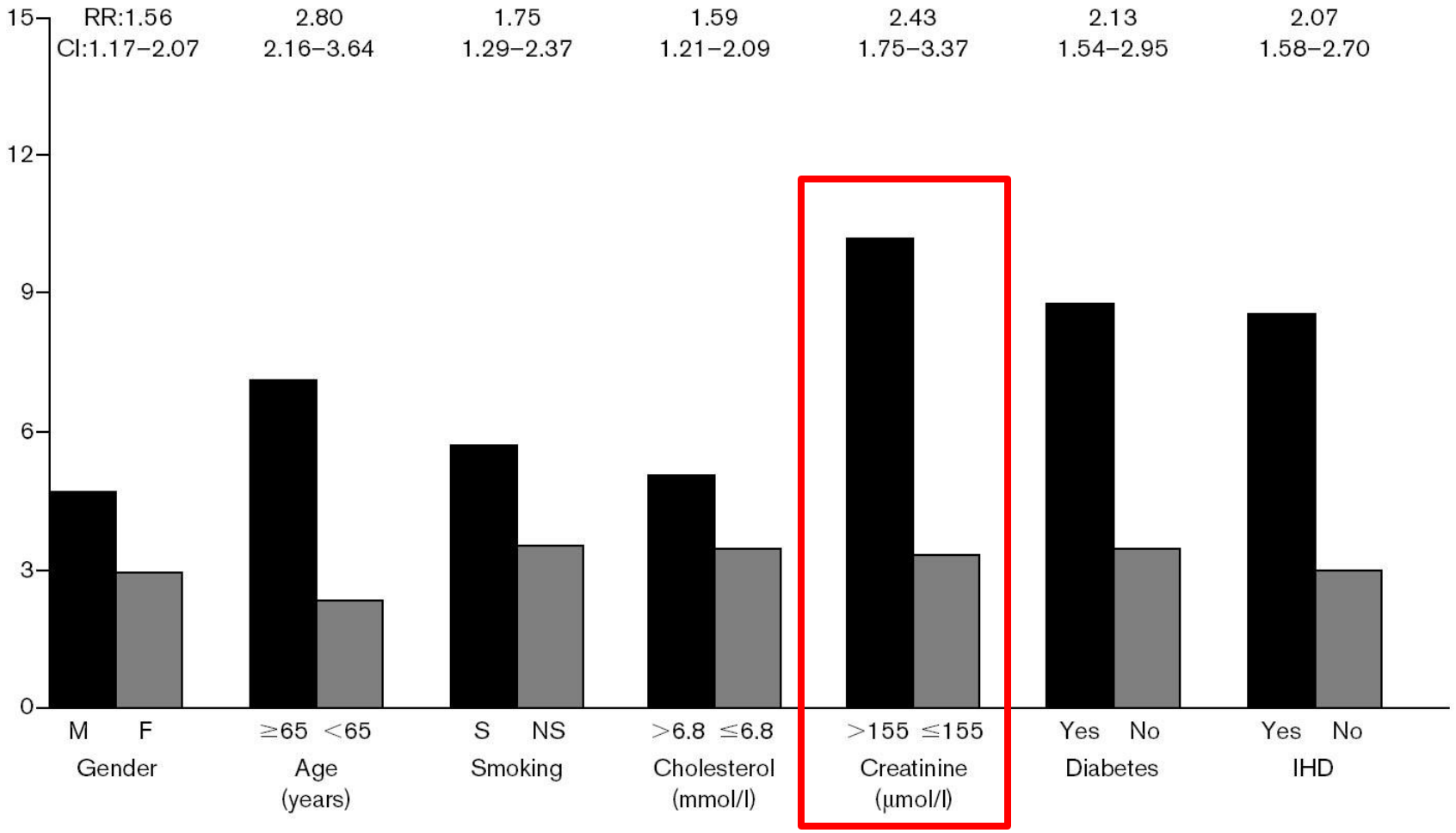
If an hypertensive patients has a slight increase in serum creatinine (or a decrease in estimated GFR) or microalbuminuria, does it mean that the patient has an increased risk to develop renal disease?

NO

It means that the patient has an increased risk of cardiovascular events.

In hypertensive patients, the kidney is a "sensitive" and "affordable" marker of cardiovascular risk!

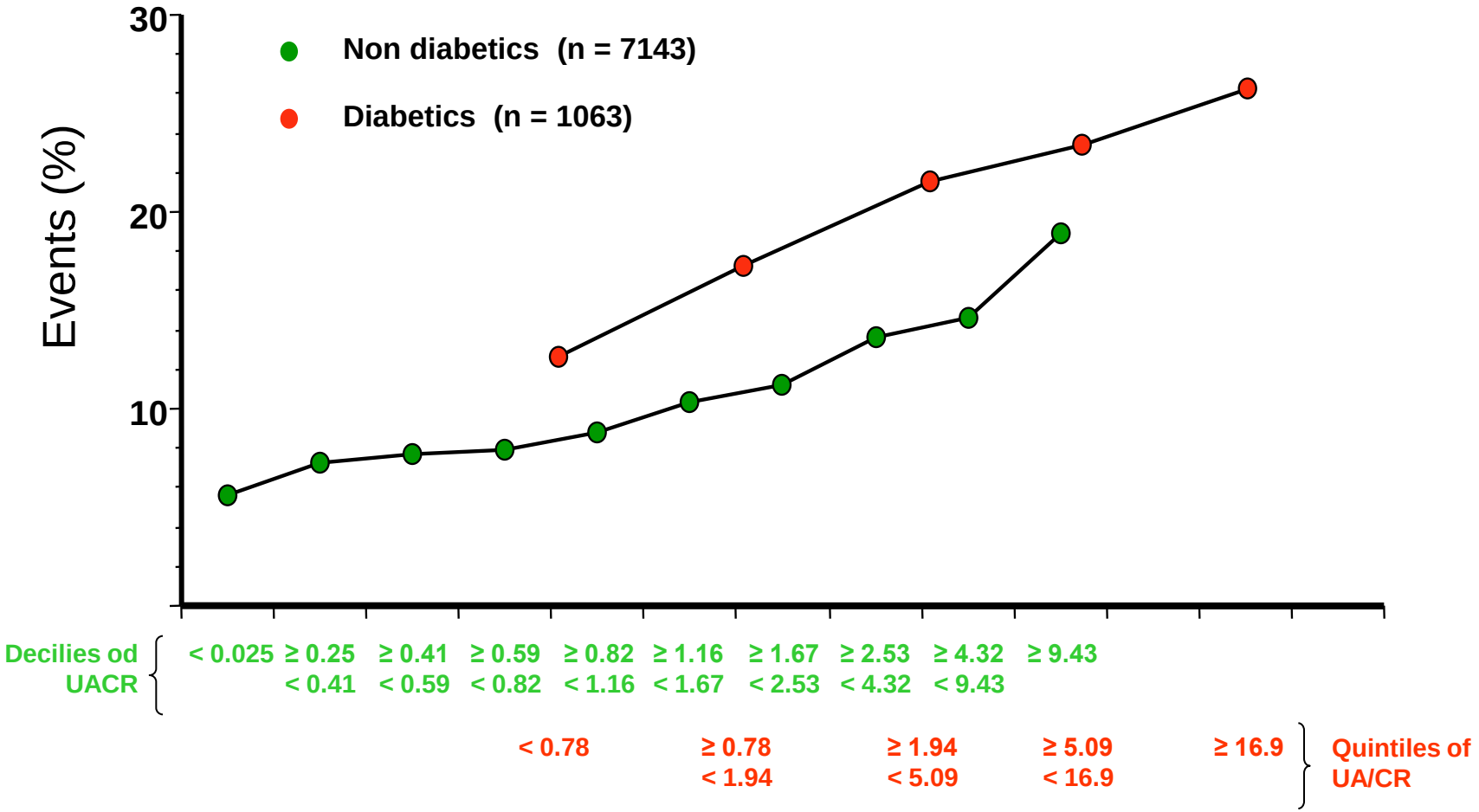
Incidence of *cardiovascular mortality* in patients with or without additional risk factors in the HOT study



RR, relative risk; CI, 95% confidence interval, adjusted for all other risk factors except the one compared.

Zanchetti A et al. *J Hypertens* 2001

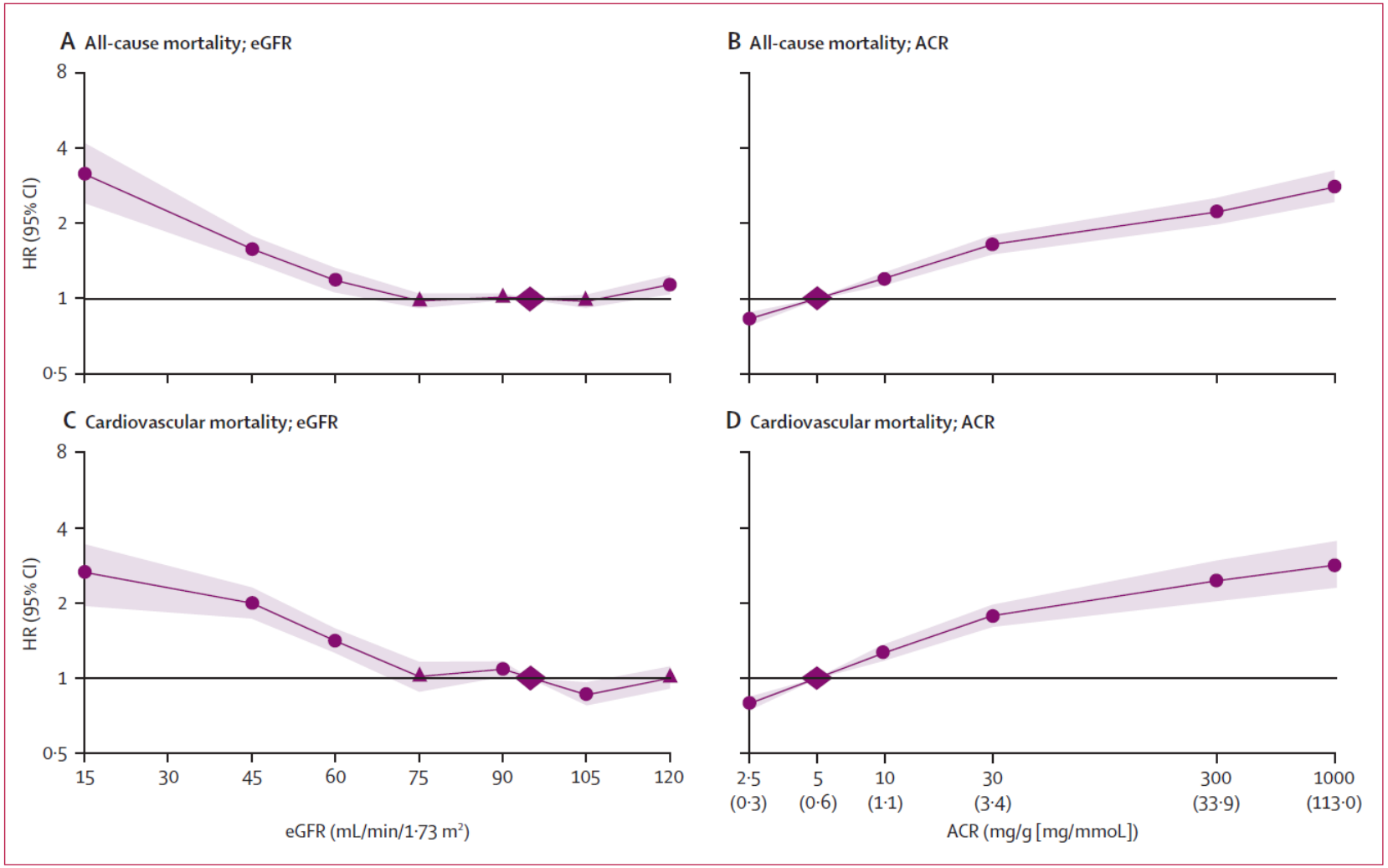
Urinary albumin-to-creatinine ratio



LIFE study; Watchell K, *Arch Int Med* 2003

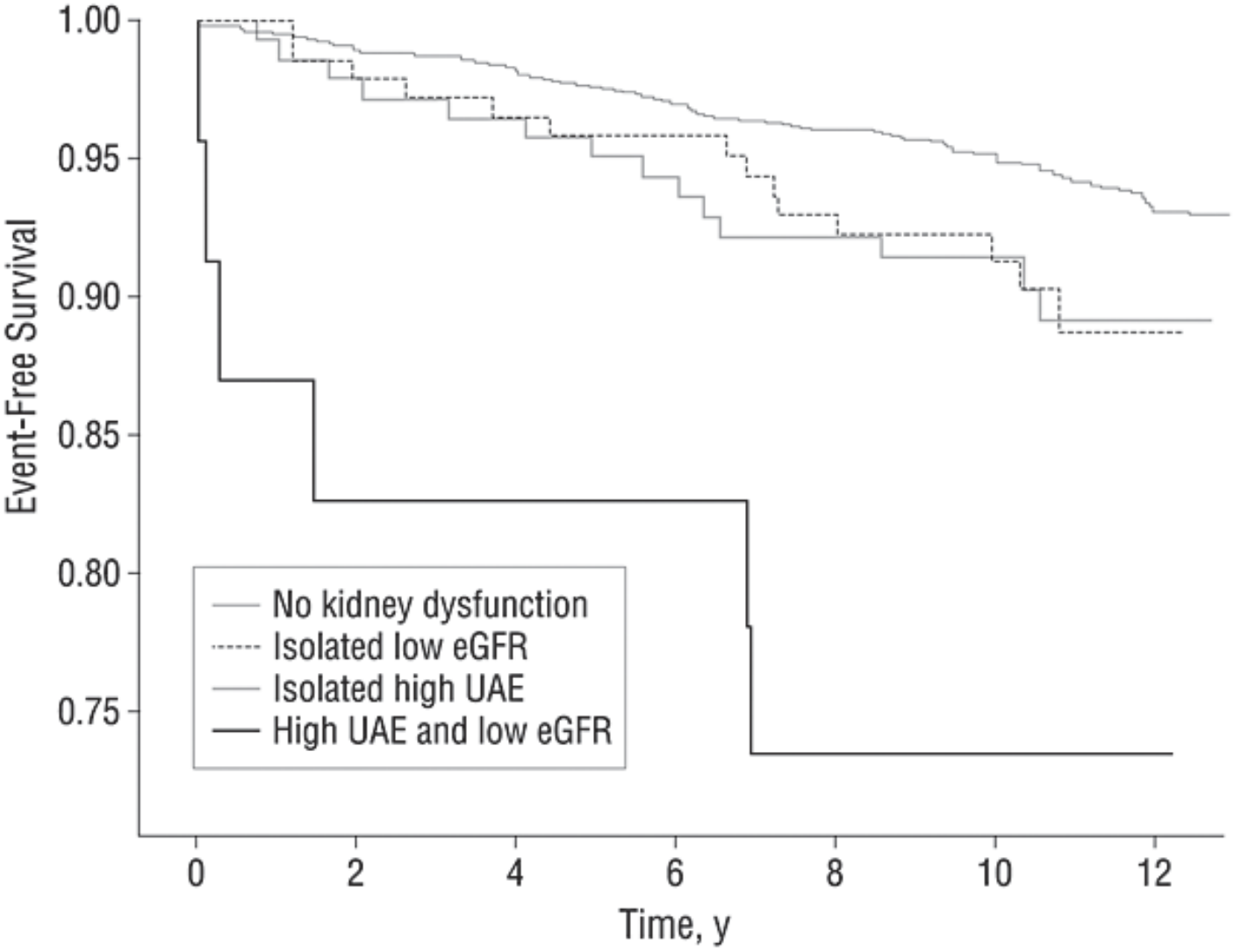
Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis

*Chronic Kidney Disease Prognosis Consortium**



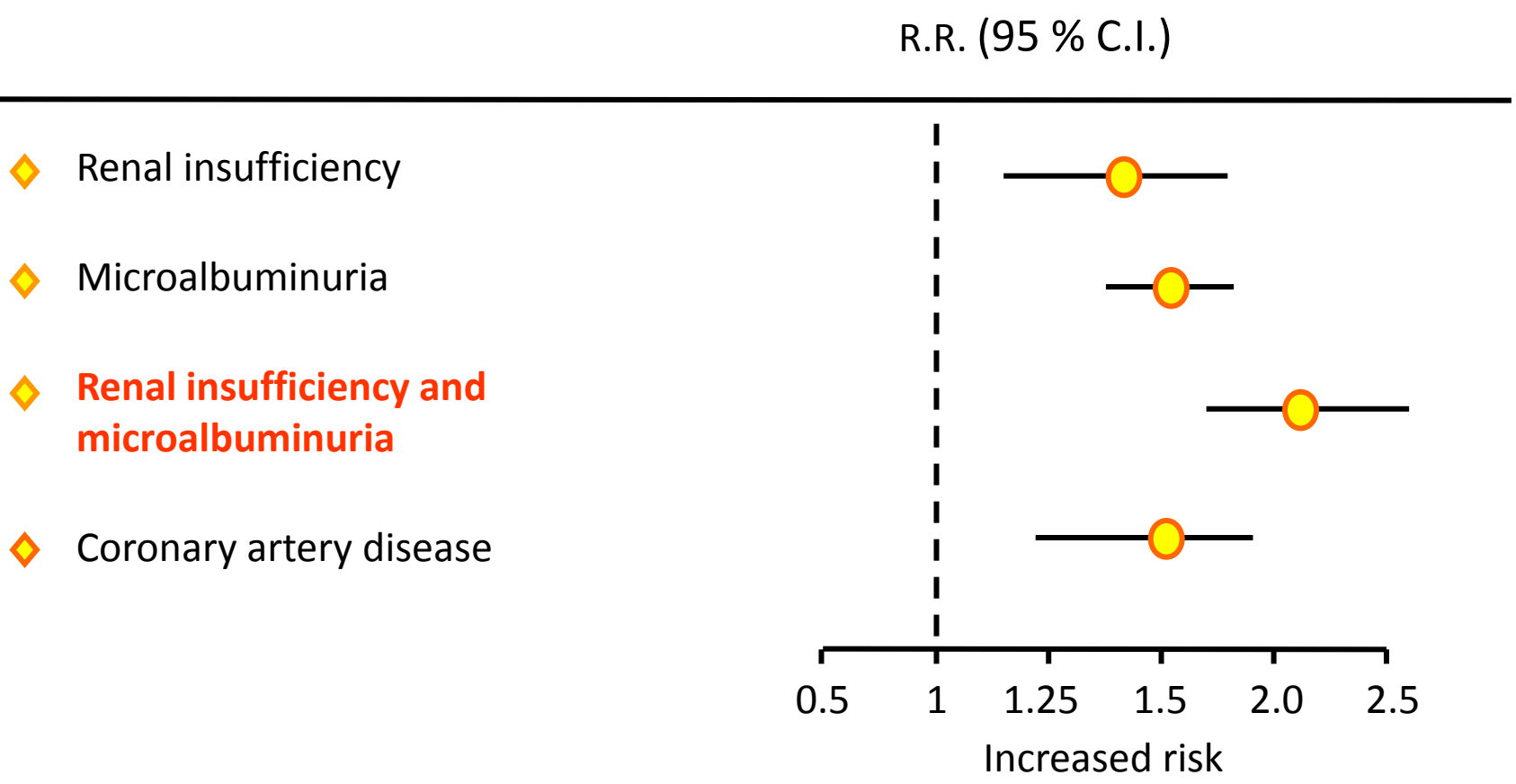
Lancet 2010; 375:2073-81

GFR & UAE



Gubbio Population Study; Cirillo M, *Arch Intern Med* 2008

Risk of cardiovascular events according to *renal* or *coronary artery disease*



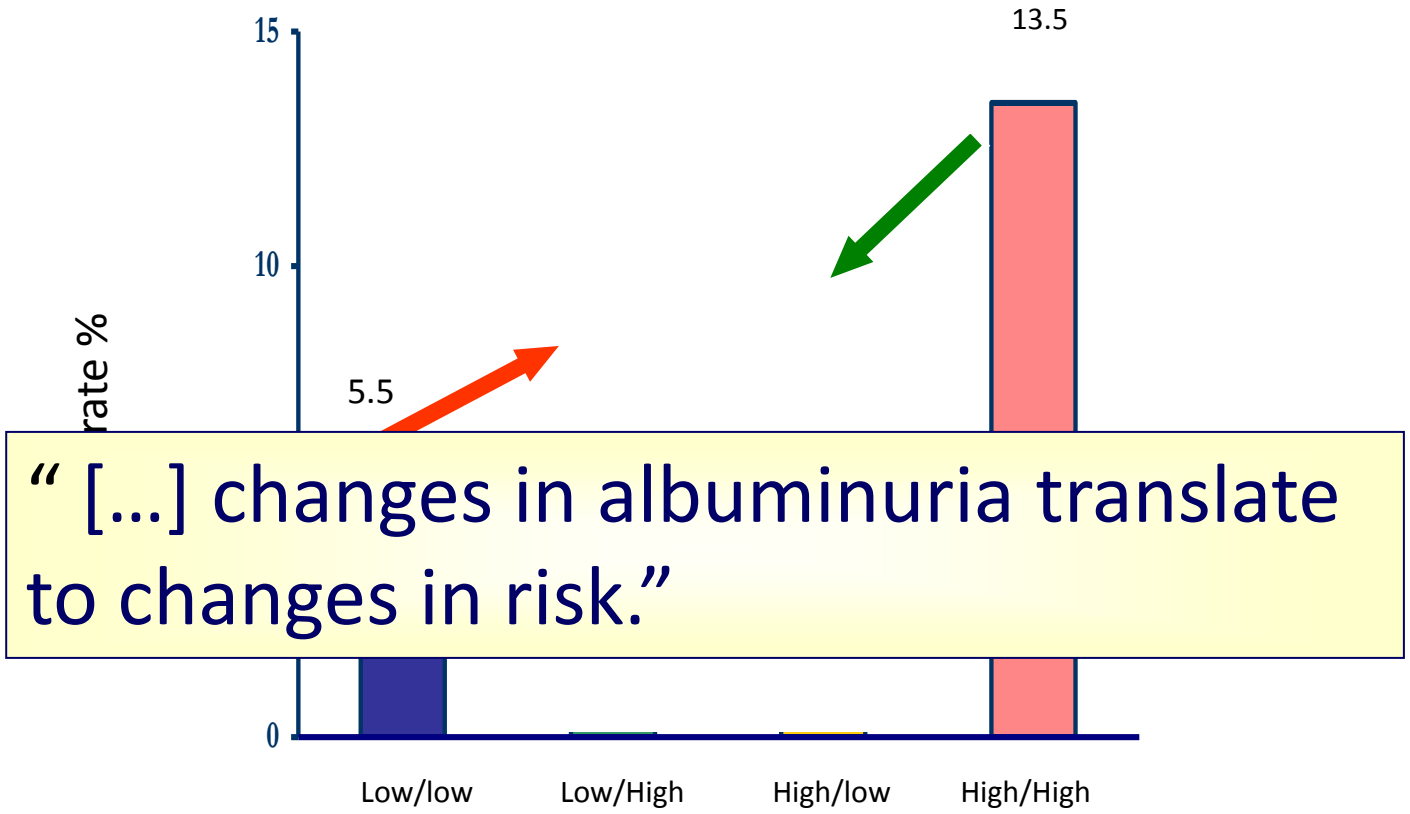
The predictive value of renal insufficiency and microalbuminuria is comparable to that of pre-existing coronary artery disease and is even superior when they are present together

Mann JF, Yusuf S et al., *Ann Int Med,* 2001

Prognostic significance of renal damage regression

Reduced albuminuria is associated with reduced CV events in patients with HTN

n=8206 pts

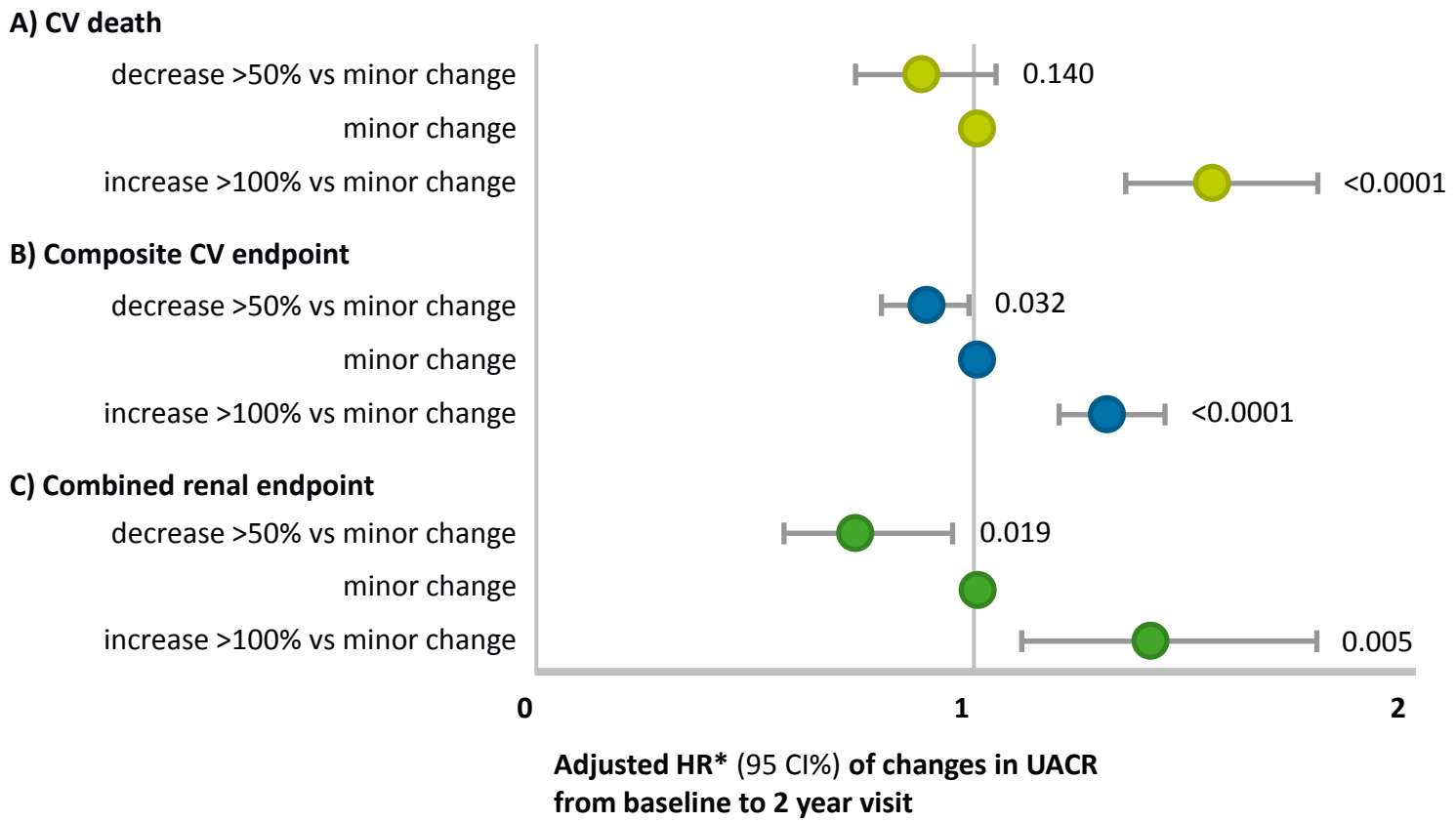


“ […] changes in albuminuria translate to changes in risk.”

Modified from Ibsen H et al., Hypertension 2005

Change in microalbuminuria as a predictor of CV and renal outcomes in patients with vascular disease

The ONTARGET/TRANSCEND study programme



Analyses were adjusted for age, gender, BMI, smoking, alcohol consumption, eGFR, plasma glucose, BP and HR at baseline, BP change within 2 years and for baseline albuminuria.

The risk of CV and renal outcomes is increased significantly if albuminuria is increased and is decreased if albuminuria is reduced

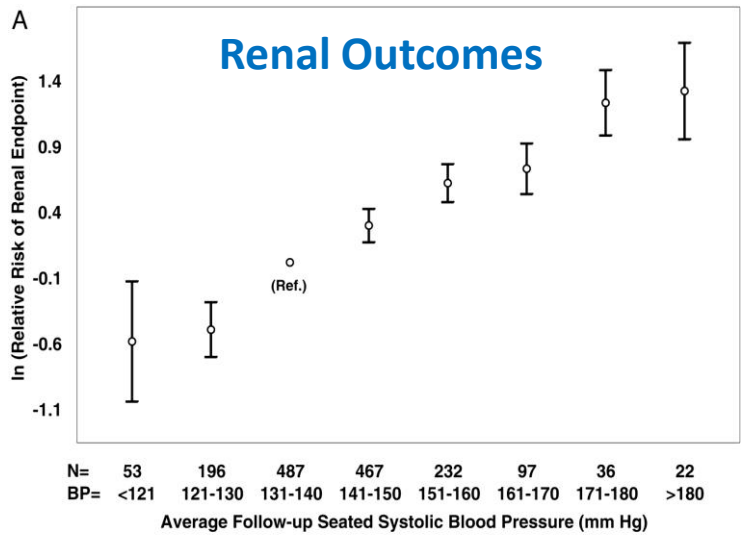
Schmieder RE, et al. JASN 2011

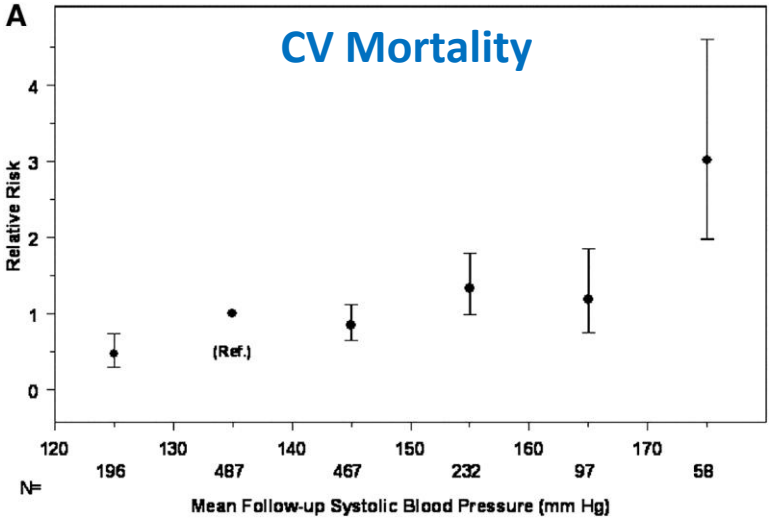
Target BP for nephroprotection in patients with renal dysfunction: < 130/80 mmHg

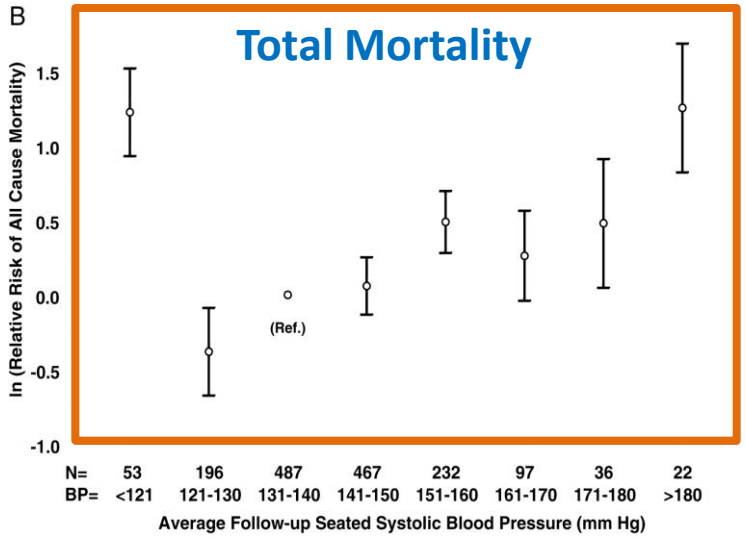
1. The JNC 7 2003
2. The 2007 ESH/ESC Guidelines and REAPPRAISAL of ESH Task Force 2009
3. K/DOQI Guidelines 2009

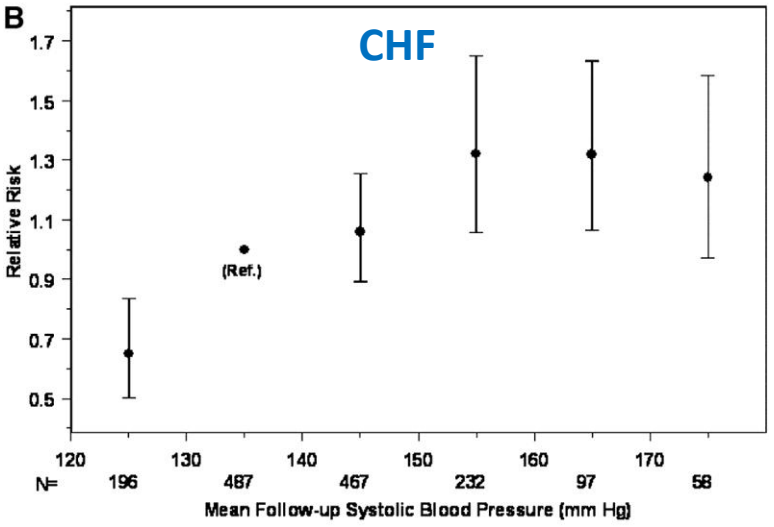
- **Diabetic nephropathy**: no randomised controlled study for BP reduction, but only retrospective and subgroup analyses
- **Non diabetic nephropathy**: 3 randomised controlled studies with contrasting results

Does the J-curve exists? Relative risk for renal and CV outcomes based on current level of systolic blood pressure in the IDNT study









Pohl MA et al JASN 2005

Berl T et al JASN 2005

ROADMAP

Table 2. Secondary Efficacy End Points during the Double-Blind Treatment Period.*

End Point	Olmesartan (N=2232)	Placebo (N=2215)	Hazard Ratio (95% CI)	P Value
	no. of patients (%)			
Composite of cardiovascular complications or death from cardiovascular causes	96 (4.3)	94 (4.2)	1.00 (0.75–1.33)	0.99
Composite of death from any cause	26 (1.2)	15 (0.7)	1.70 (0.90–3.22)	0.10
Death from cardiovascular causes	15 (0.7)	3 (0.1)		
Death not related to cardiovascular causes	8 (0.4)	10 (0.5)		
Death from unknown cause	3 (0.1)	2 (0.1)		
Composite of death from cardiovascular causes	15 (0.7)	3 (0.1)	4.94 (1.43–17.06)	0.01
Sudden cardiac death	7 (0.3)	1 (<0.1)		
Death due to fatal myocardial infarction	5 (0.2)	0		
Evidence of recent myocardial infarction on autopsy	0	0		
Death due to congestive heart failure	0	0		
Death during or after percutaneous transluminal coronary angioplasty or CABG	1 (<0.1)	0		
Death due to fatal stroke	2 (0.1)	2 (0.1)		
Composite of cardiovascular complications, excluding new-onset atrial fibrillation and transient ischemic attack	63 (2.8)	71 (3.2)	0.87 (0.62–1.22)	0.42
Composite of new-onset atrial fibrillation or transient ischemic attack	19 (0.9)	28 (1.3)	0.67 (0.37–1.19)	0.17
Composite of all cardiovascular complications	81 (3.6)	91 (4.1)	0.87 (0.65–1.18)	0.37

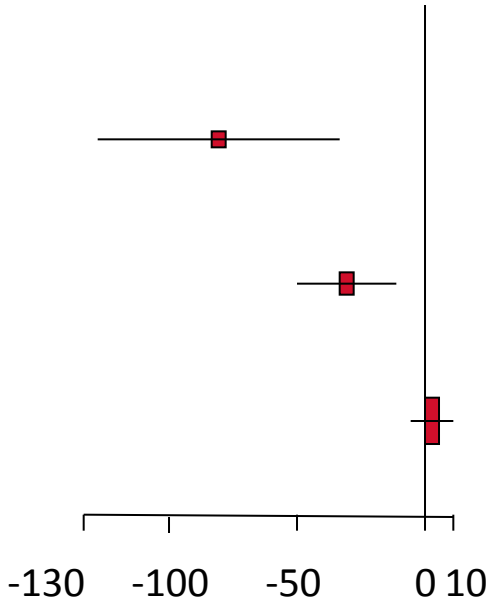
NEJM 2011

Patients with renal damage should be treated with a RAS blocker

Effect of ACEi or ARBs on renal outcomes: systematic review and meta-analysis

Degree of change of SBP and proteinuria reduction

Mean difference SBP (95%CI)	Studies (N)	Albuminuria change (mg /day)	RR (95% CI)
-7.6 (-9.8 to -5.5)	23 (1668)		-83.12 (-126.8 to -39.5)
-1.2 (-3.2 to -0.7)	15 (1734)		32.73 (-51.9 to -13.6)
3.41 (0.9 to 5.9)	17 (2312)		1.81 (-2.47 to 6.1)

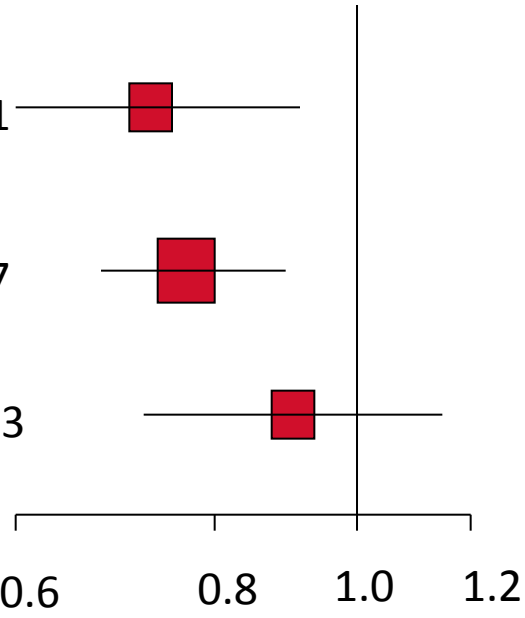


Casas P et al. Lancet 2005; 366: 2026-2033

Effect of ACEi or ARBs on renal outcomes: systematic review and meta-analysis

Degree of change of SBP and RR for ESRD

Mean difference (95%CI)	ACEi / ARB	Other drugs	RR for ESRD	RR (95% CI)
- 6.9 (- 9.1 to - 4.8)	117 / 1346	155 / 1291		0.74 (0.59-0.92)
- 1.6 (- 2.8 to - 0.4)	273 / 6344	356 / 6327		0.77 (0.67-0.89)
1.5 (0.1 to 2.9)	206 / 11049	397 / 26043		0.90 (0.72-1.12)



Casas P et al. Lancet 2005; 366: 2026-2033

The NEW ENGLAND JOURNAL of MEDICINE

Perspective

Daring to Practice Low-Cost Medicine in a High-Tech Era

Sean Palfrey, M.D.

A child with chest pain or tics, a toddler who is limping, a 12-year-old girl with abdominal pain or headaches, an infant whose fever does not respond to antibiotics — these are age-old challenges that pediatricians face. I have been teaching pediatrics to residents and medical students for more than three decades, but over the past few years, as I've watched trainees at work, sitting at their computers, and ordering and monitoring tests, I've grown worried that the practice of medicine has tipped out of balance.

Recent advances in scientific knowledge and technology have resulted in the development of a vast array of new tests, new pharmacologic agents, and new diagnostic and therapeutic procedures. These are so accessible to us in the United States that few of us can resist using them at every opportunity. By being impatient, by mistrusting our hard-earned clinical skills and knowledge, and by giving in to the pressures and opportunities to test too much and treat too aggressively, we are bankrupting our health care system. Ironically, by practicing this way, we are perpetuating serious economic and racial disparities and have built a health care system that rates in the bottom tier among all developed countries in many categories of children's health outcomes.

Most doctors are intensely risk-averse. We don't tolerate uncertainty. Not wanting anything bad to happen, we reflexively overtest and overtreat in order to protect our patients — and ourselves. We feel judged by everyone — ourselves, our colleagues, our patients, the health care system, and the lawyers. The meaning of "first do no harm" has changed for us. We feel that "doing everything" is the best practice and the way to prevent harm, and we believe that it will shelter us from blame. We order tests and treatments because they are available to us, well before their importance has been established, their safety has been determined, and their cost–benefit ratio has been calculated.

The evaluation of a child with fever and cough is a good example. There are many possible causes, and we have a huge battery of available tests that might give us potentially relevant information. But why should we no longer trust our physical exam, our knowledge of the possible causes and their usual courses,

Some comparisons of TODs

Markers	CV predictive value	Availability	Cost
Electrocardiography	++	++++	+
Echocardiography	+++	+++	++
Carotid Intima-Media Thickness	+++	+++	++
Arterial stiffness (Pulse wave velocity)	+++	+	++
Ankle-Brachial index	++	++	+
Est. Glomerular Filtration Rate or Creatinine Clearance	+++	++++	+
Microalbuminuria	+++	++++	+

2007 ESH-ESC Practice Guidelines for the Management of Arterial Hypertension:

ESH-ESC Task Force on the Management of Arterial Hypertension

Estabilished Subclinical Organ Damage

- Electrocardiographic LVH (Sokolow-Lyon > 38 mm; Cornell > 2440 mm*ms) or:
- Echocardiographic LVH° (LVMI M > 125 g/m^2, W > 110 g/m^2)
- Carotid wall thickening (IMT > 0.9 mm) or plaque
- Carotid-femoral pulse wave velocity >12 m/s
- Ankle/brachial BP index < 0.9
- Slight increase in plasma creatinine:
  M: 115–133 μmol/l (1.3–1.5 mg/dl);
  W: 107–124 μmol/l (1.2–1.4 mg/dl)
- Low estimated glomerular filtration rate† (< 60 ml/min/1.73 m^2)
  or creatinine clearance◇ (< 60 ml/min)
- Microalbuminuria 30–300 mg/24 h or albumin-creatinine ratio:
  ≥ 22 (M); or ≥ 31 (W) mg/g creatinine

2007 ESH-ESC Practice Guidelines for the Management of Arterial Hypertension:
ESH-ESC Task Force on the Management of Arterial Hypertension

Why endothelial function measurement is not included among markers of target organ damage in hypertension in ESH/ESC Guidelines?

Endothelial function

- Can be assessed by an unique method?
- Can be used to better stratify CV risk?
- Can be used to better establish the efficacy of treatment?

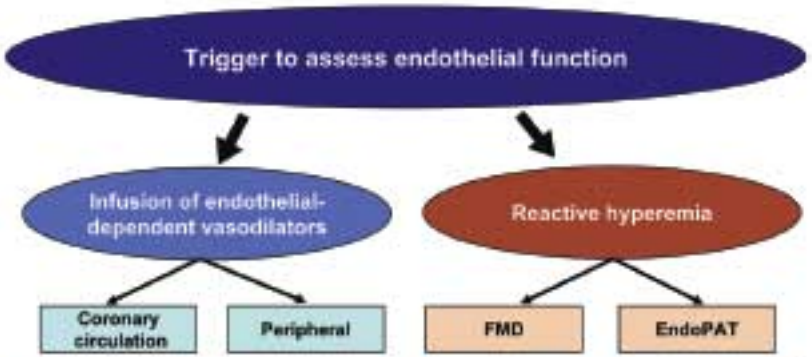
Endothelial function

- Can be assessed by an unique method?
- Can be used to better stratify CV risk?
- Can be used to better establish the efficacy of treatment?

The Assessment of Endothelial Function

From Research Into Clinical Practice

Andreas J. Flammer, MD; Todd Anderson, MD; David S. Celermajer, MD; Mark A. Creager, MD; John Deanfield, MD; Peter Ganz, MD; Naomi M. Hamburg, MD; Thomas F. Lüscher, MD; Michael Shechter, MD; Stefano Taddei, MD; Joseph A. Vita, MD; Amir Lerman, MD

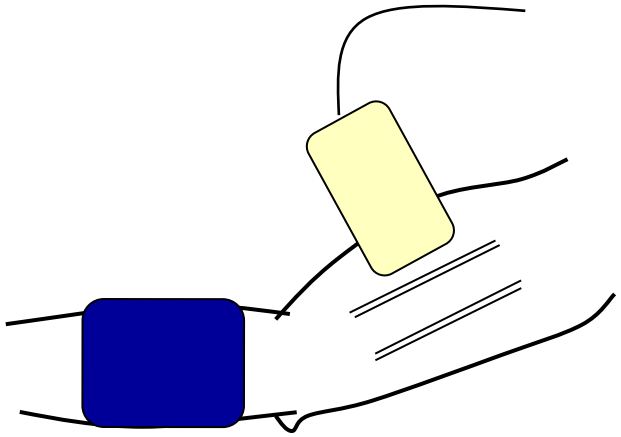


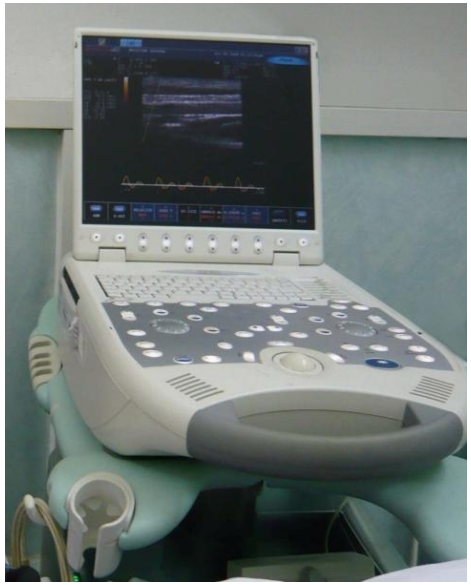
Non-Invasive	-	-	+	+
Predictive	++	++	++	+
Reversible	+	+	+	+
Control vessel	+ (control segments)	+	-	++
Not expensive	-	+	+	+/-
Low-risk	+/-	+	++	++
Operator independent	+/-	+/-	-	++
Easy to use	-	-	-	+

(*Circulation*. 2012;126:753-767.)

FLOW MEDIATED DILATION

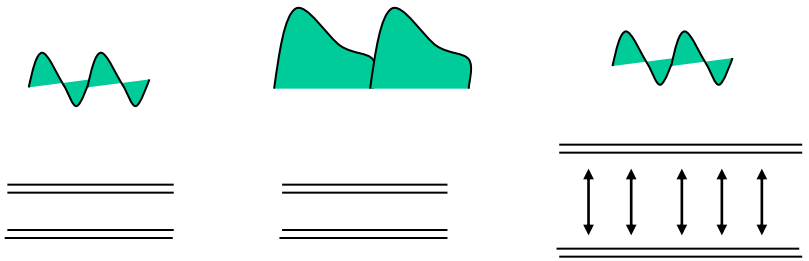
the physiological testing of endothelial function





High Resolution Ultrasound

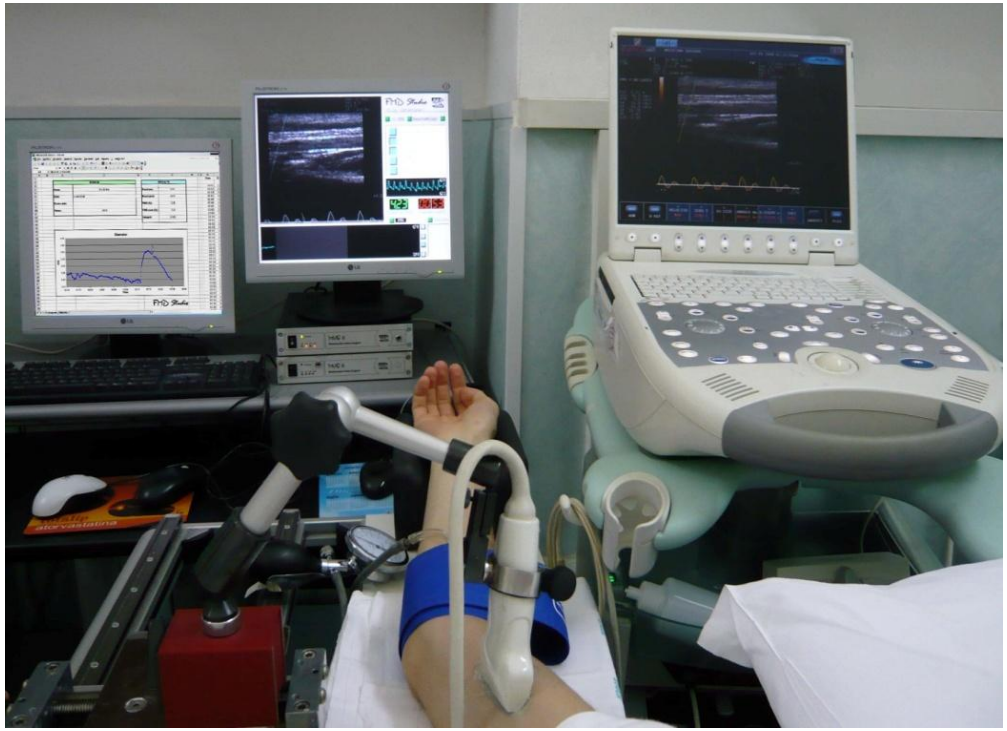
ischemia (200 mmHg, 5 minutes) to induce post-ischemic reactive hyperemia in the microcirculation and flow increase in the brachial artery



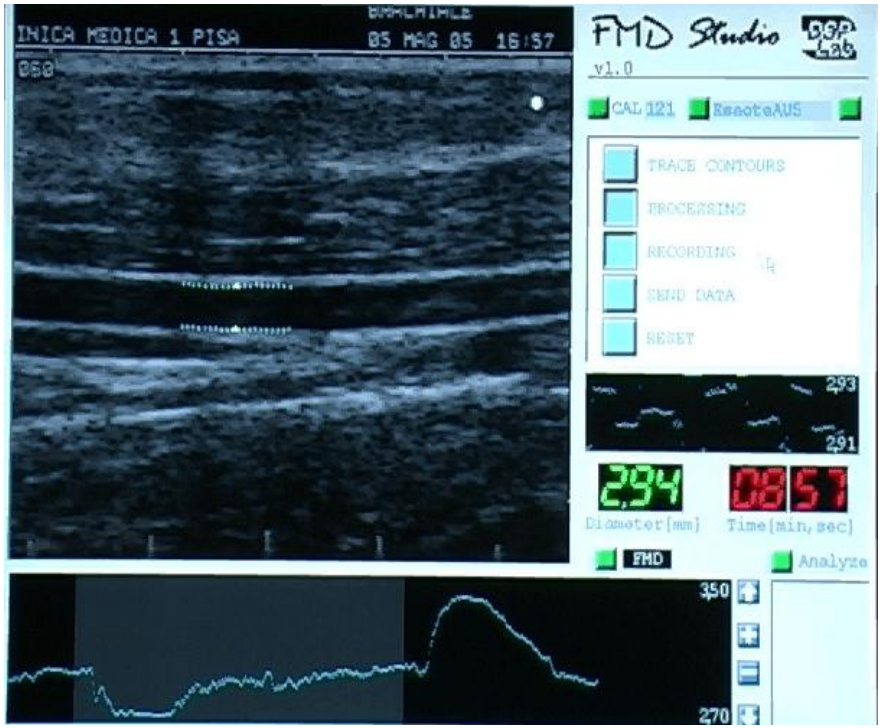
Endothelium-dependent response (FMD):
↑ diameter of the brachial artery induced by shear stress

Endothelium-independent response:
↑ diameter of the brachial artery after GTN (s.l.)

Experimental Model



Ghiadoni L al. Curr Pharm Des 2008



Gemignani V et al. Ultrasound Med & Biol 2008

Coefficients of variation (mean values and 95% intervals) for flow-mediated dilation in the different Centers.

Overall, coefficients of variation were 9.9±8.4% and 12.9±11.6% for the intra and inter-session FMD measures, respectively.

The inter-session coefficient of variation of GTN response between assessments obtained at day 1a and day 30 was 19.7±16.8%

Ghiadoni L et al. J Hypertens 2012

Endothelial function

- Can be assessed by an unique method?
- Can be used to better stratify CV risk?
- Can be used to better establish the efficacy of treatment?

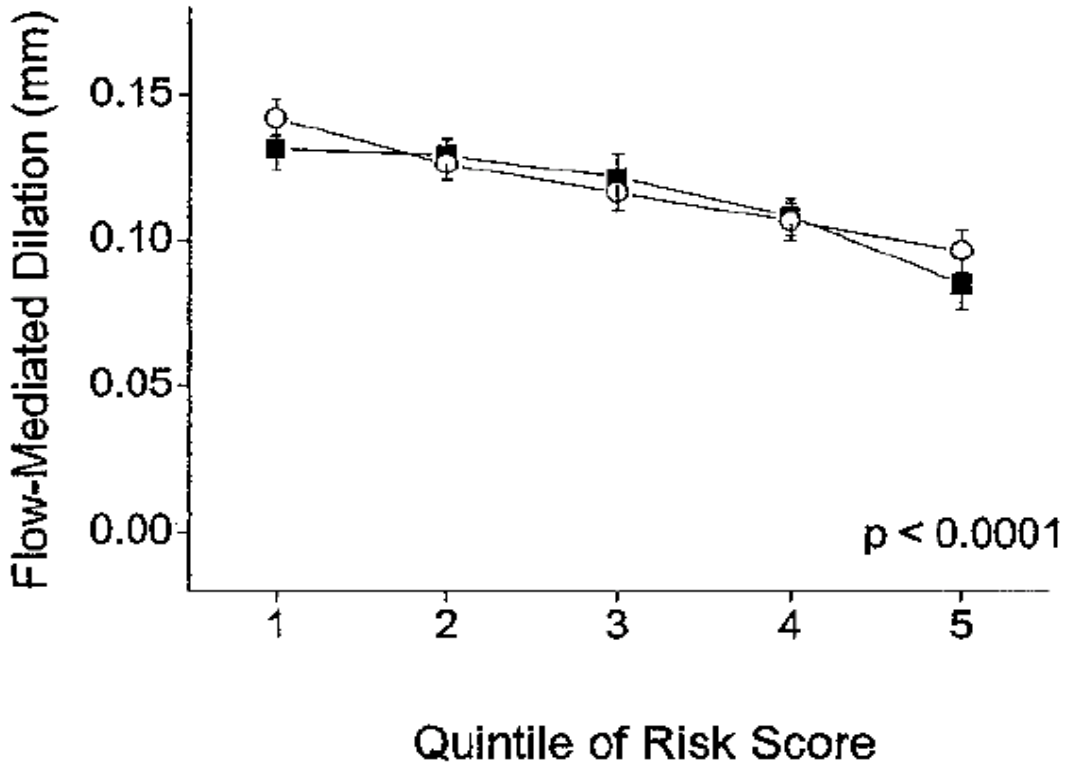
Stromg association among CV risk factors, oxidative stress and endothelial dysfunction

Cardiovascular Risk Factors	Endothelial Dysfunction	Presence of Oxidative Stress
Familial histrory of CVD	YES	YES
Age	YES	YES
Menopause	YES	YES
Hypertension	YES	YES
Hyperlipidemia	YES	YES
Diabetes Mellitus	YES	YES
Smoking	YES	YES
Hyperhomocysteinemia	YES	YES

Clinical Correlates and Heritability of Flow-Mediated Dilation in the Community

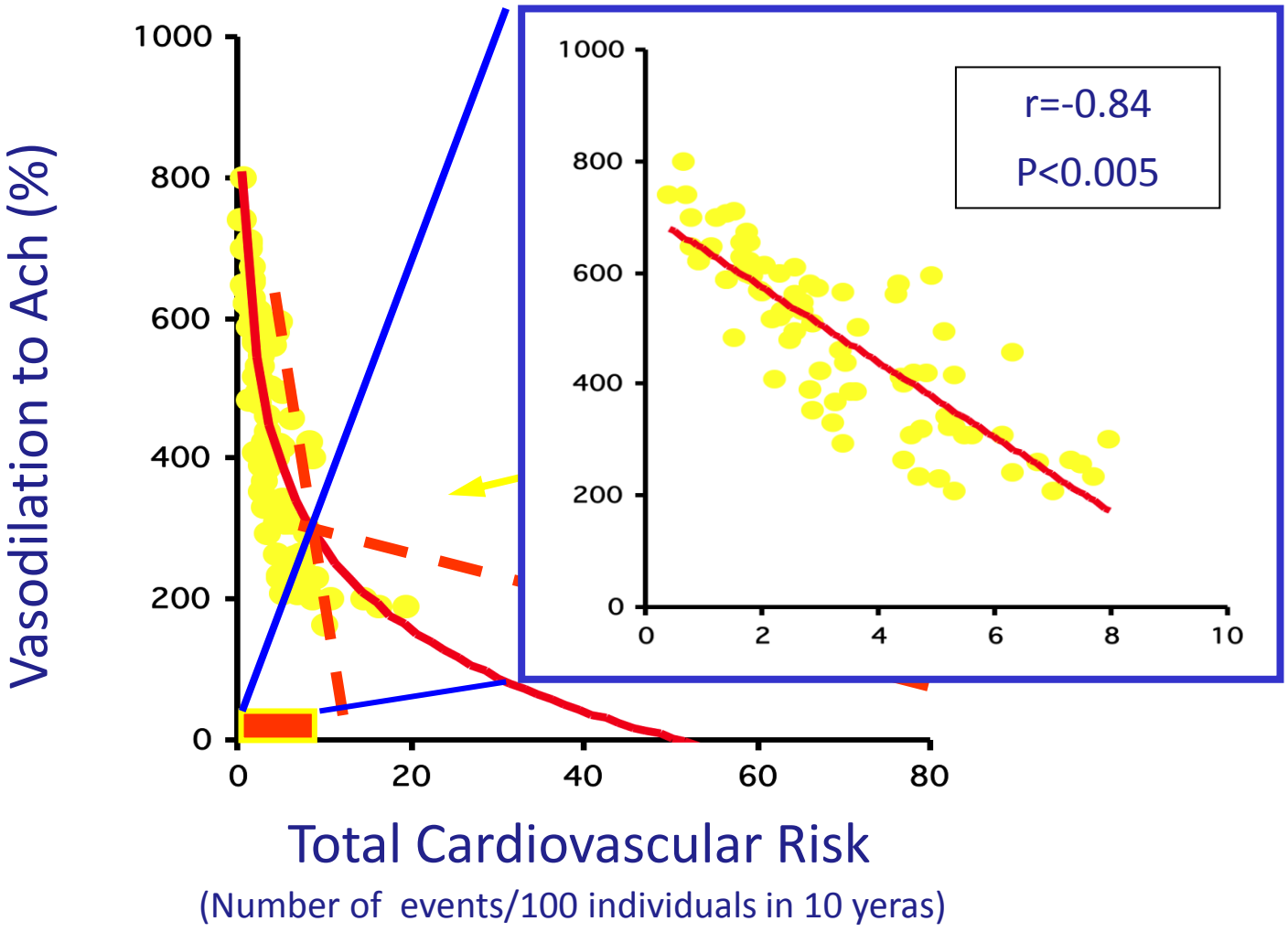
The Framingham Heart Study

2883 subjects (1526 women, 1357 men)



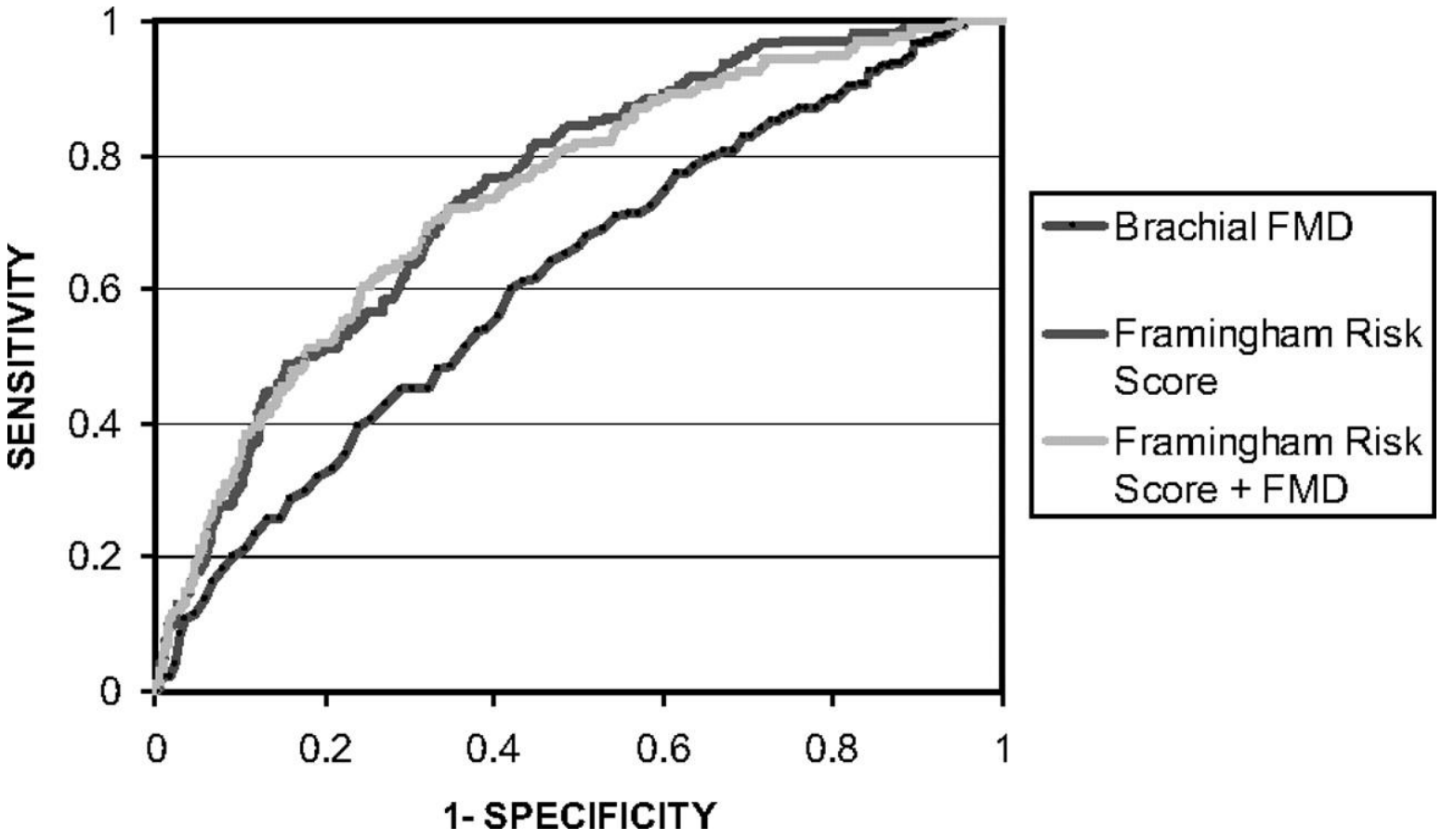
Benjamin EJ et al. Circulation 2004

Relationship between vasodilation to acetylcholine and total cardiovascular risk



Endothelial function

Receiver operating characteristic curves for FRS (AUC=0.74), brachial FMD (AUC=0.65), and FRS+FMD (AUC=0.74) to predict incident CVD events

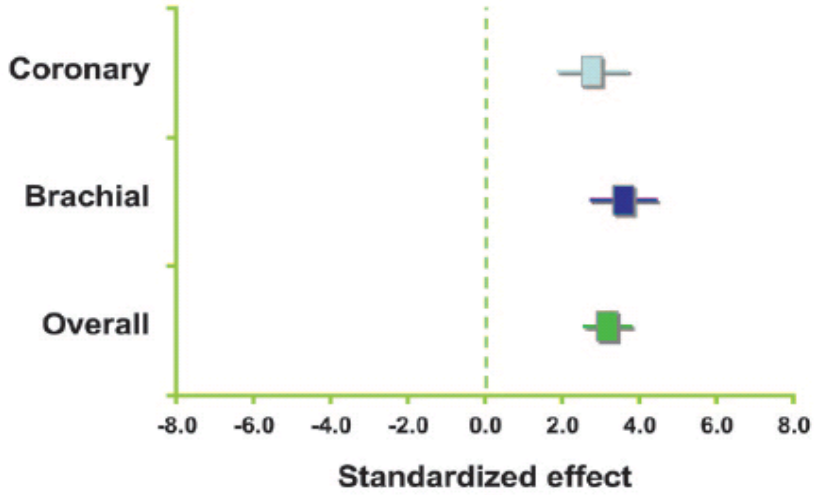


Multi-Ethnic Study of Atherosclerosis (MESA); Yeboah, J. et al. Circulation 2009

The direct relationship between endothelium-dependent relaxation and global CV risk makes unesefull the determination of endothelial function

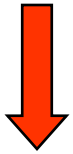
Endothelial Function Assessed by Vascular Reactivity and Cardiac Events

Multivariant analysis of hazard ratio of present studies reporting association between coronary or peripheral endothelial function and cardiovascular events



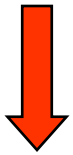
Lerman A & Zeiher A *Circulation* 2005

Association of endothelial dysfunction with CV risk profile



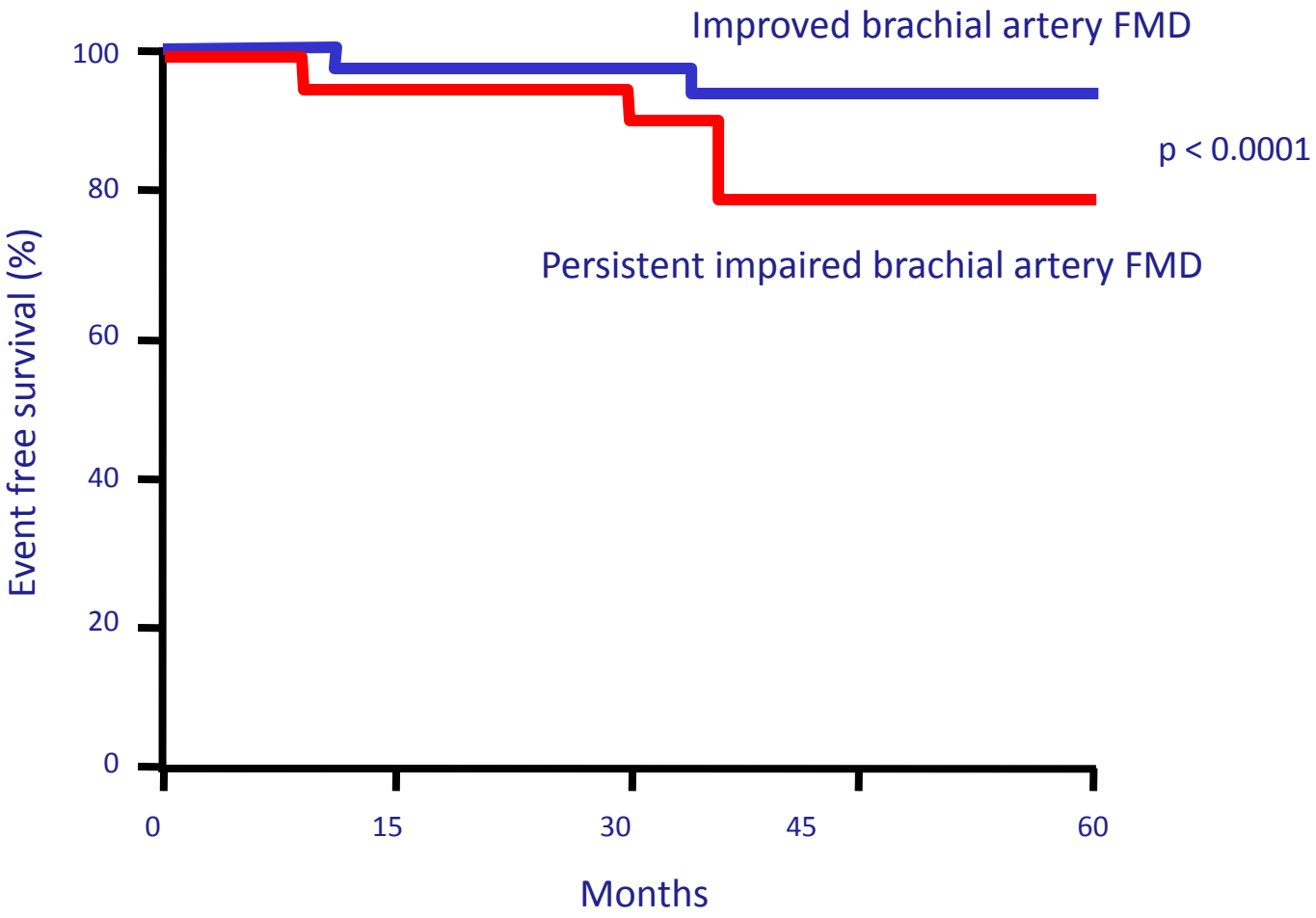
Demonstrated in untreated patients with CV risk factors

Endothelial dysfunction as independent prognostic marker of CV clinical events



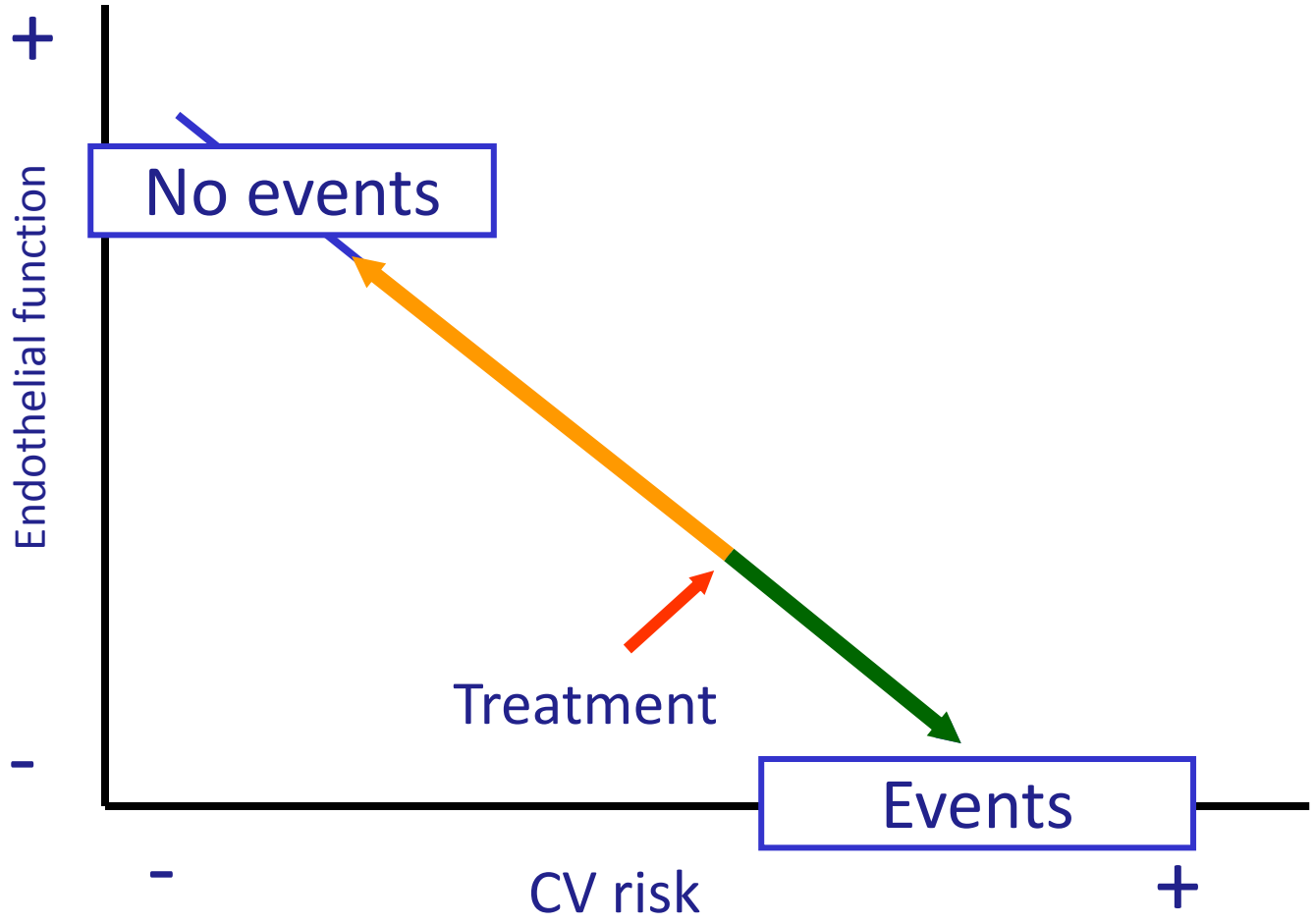
Demonstrated in high risk patients with CV disease and pharmacological treatment

Treatment of Endothelial Function and Prognosis



Modena MG et al. JACC 2002

Relationship between endothelial dysfunction and prognosis



Effect of pharmacological treatment on endothelial dysfunction

	ACE-I	AT_1-Ant	Ca-Ant	Statins
Conduit arteries				
coronary	+	+	+	+
peripheral	+	-/+	-/+	+
Subcutaneous microcirculation	+	+	+	no data
Muscle microcirculation *acetylcholine, metacholine*	-	-	+	+
bradikynin	+	no data	+	no data

Why endothelial function measurement is not included among markers of target organ damage in hypertension in ESH/ESC Guidelines?

Some comparisons of TODs

Markers	CV predictive value	Availability	Cost
Electrocardiography	++	++++	+
Echocardiography	+++	+++	++
Carotid Intima-Media Thickness	+++	+++	++
Arterial stiffness (Pulse wave velocity)	+++	+	++
Ankle-Brachial index	++	++	+
Coronary calcium content	+	+	++++
Cardiac/Vascular tissue composition	?	+	++
Circulatory collagen markers	?	+	++
Endothelial dysfunction	++	+	+++
Cerebral lacunae/White matter lesions	?	++	++++
Est. Glomerular Filtration Rate or Creatinine Clearance	+++	++++	+
Microalbuminuria	+++	++++	+

2007 ESH-ESC Practice Guidelines for the Management of Arterial Hypertension:

ESH-ESC Task Force on the Management of Arterial Hypertension

Why endothelial function measurement is not included among markers of target organ damage in hypertension in ESH/ESC Guidelines?

Because no one endothelial guy is involved in the Guidelines Task Force!!!