



FEAM SPRING CONFERENCE

28th-29th May 2013

**Clinical Research with a Focus on
Cardiovascular Diseases**

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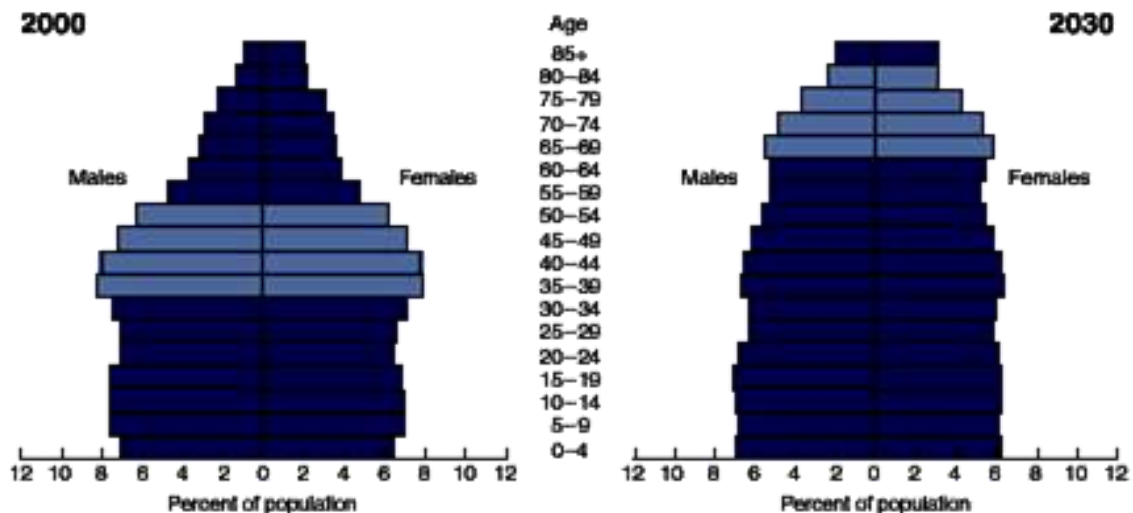
Cardiovascular diseases - A challenge for the clinician

A group of disorders of the heart and blood vessels:

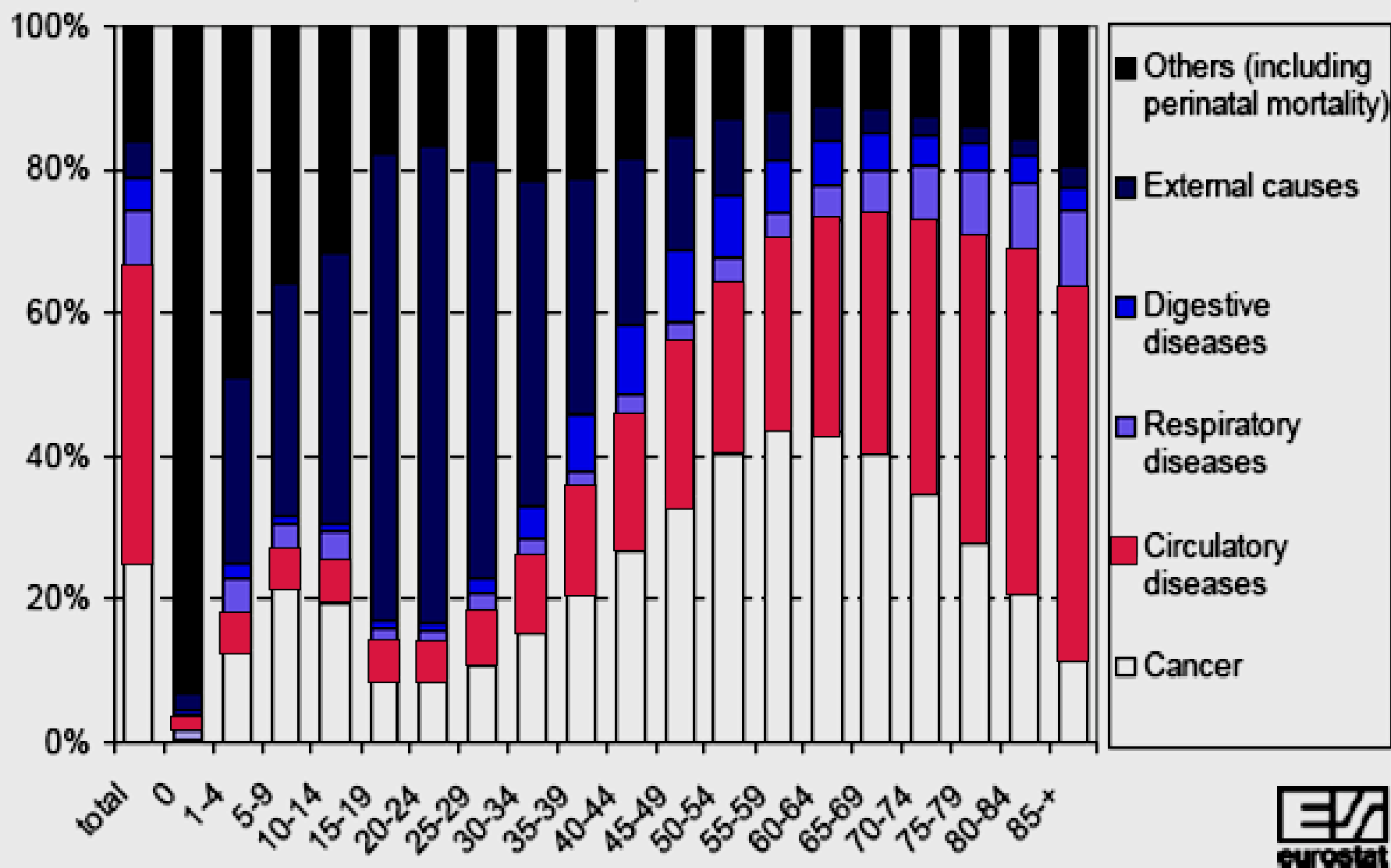
- Coronary heart disease (CHD)
 - Arterial hypertension (systemic/pulmonary)
 - Cardiac arrhythmias and sudden cardiac death
 - Diabetes mellitus
 - Congenital cardiac diseases
 - Deep venous thrombosis and pulmonary thromboembolism
- Cerebrovascular disease
 - Heart failure
 - Valvular diseases
 - Peripheral artery disease



Pluripathology and polypharmacy



Major causes of death by age group, both sexes, in the EU



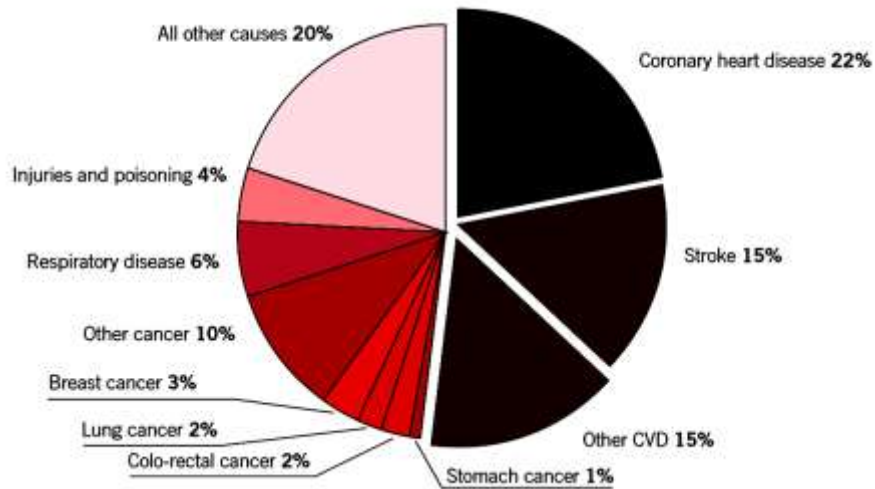
- In the 45-64 age group, cancers are responsible for 41% of all deaths
- In elderly people (> 65 y), CV diseases account for 42% of all deaths

Atherosclerotic cardiovascular diseases

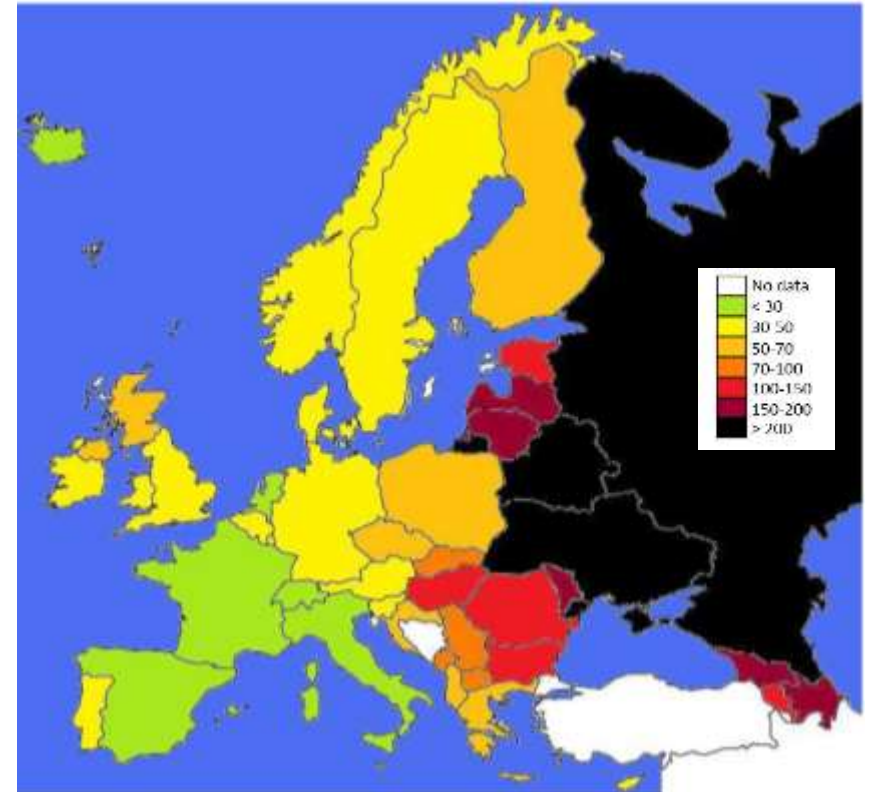
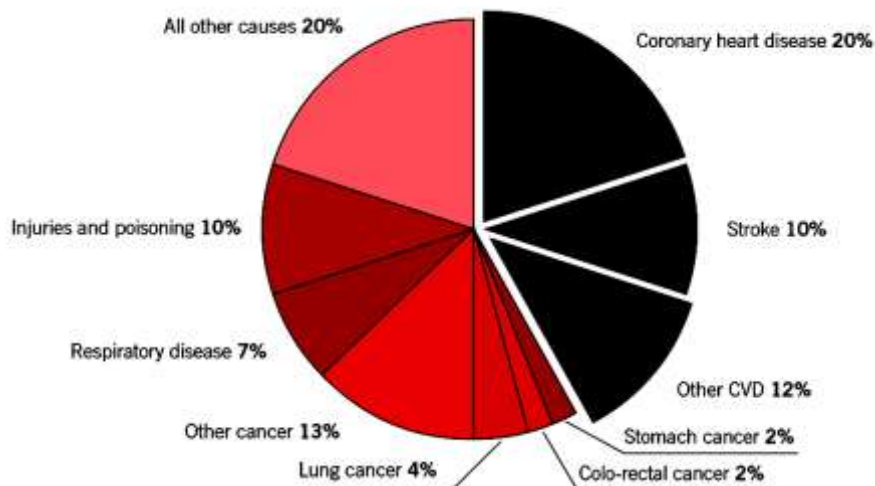
1. They are the main cause of death in Europe (47%) and in the EU (42%)
 - More than 4.3 million deaths (2 M in the EU)
 - 42% of all deaths below 75 years of age in European women and for 38% of all deaths in men
 - Major cause of death in women in all European countries
 - CHD (1.92 M deaths/y) and stroke (1.24 M deaths/y) are, and will remain, the leading cause of premature death worldwide
 - They cause mass mass disability: a loss of ~150 million DALYs in 2010

Deaths by cause, latest available year, in Europe

Women

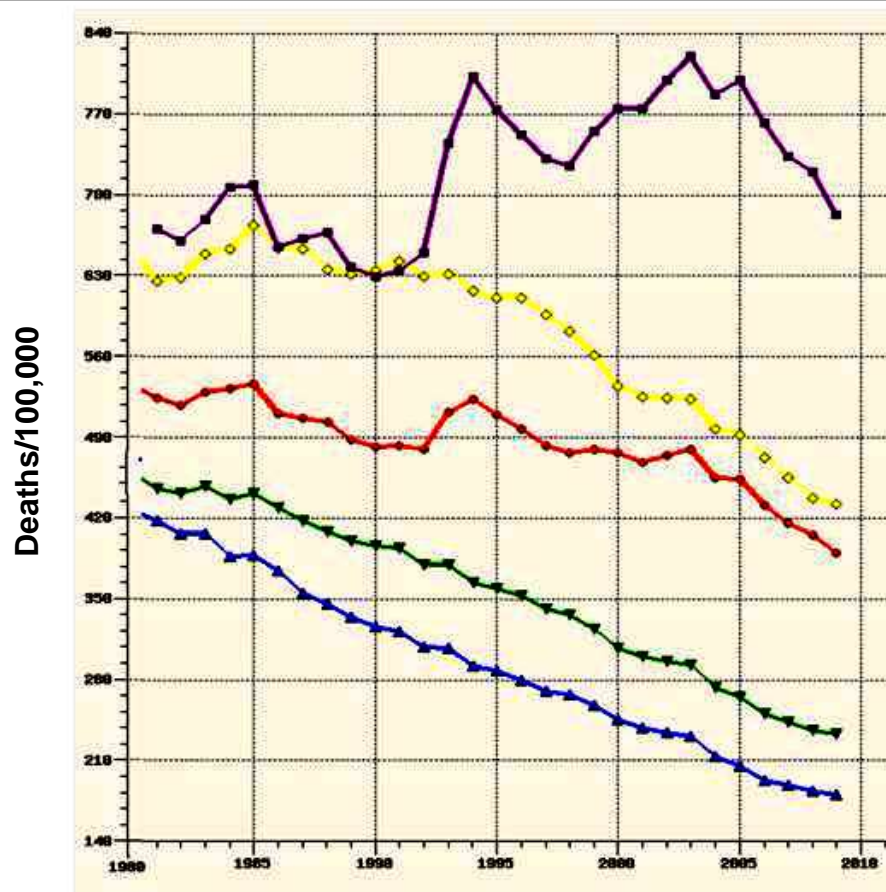


Men

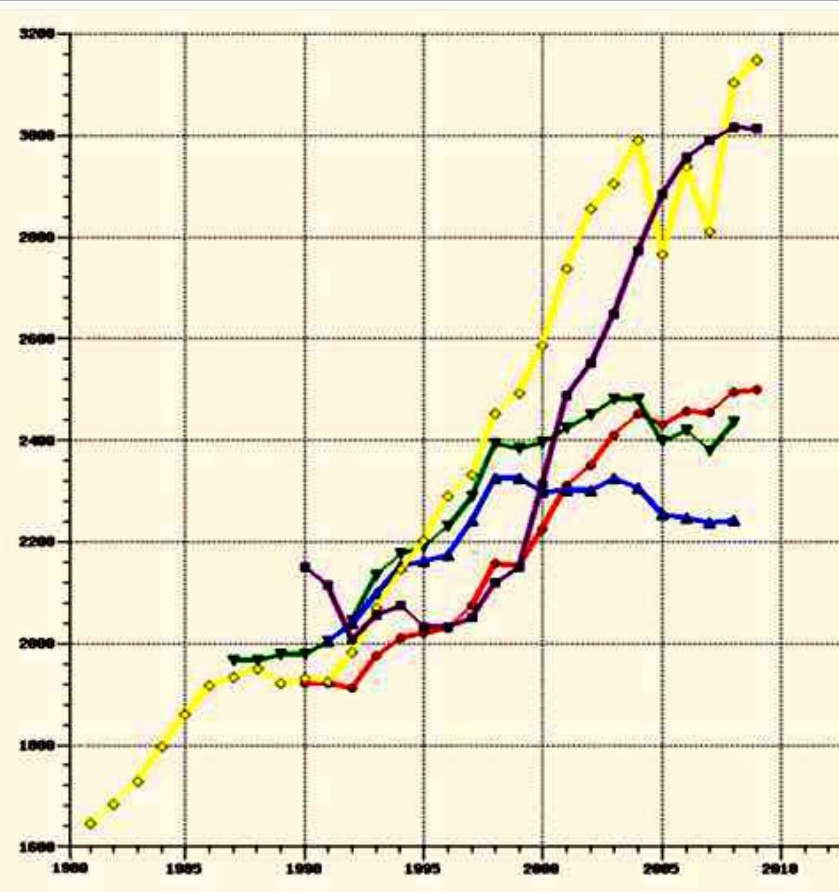


- Age standardized CHD mortality rates per 100,000 (under 65)
- Marked differences between the EU and Europe
- Death rates from CHD and stroke are higher in Central and Eastern Europe than in Northern, Southern and Western Europe

Age- and sex adjusted mortality rates (per 100,000) from CVD in Europe in the years 1980-2009

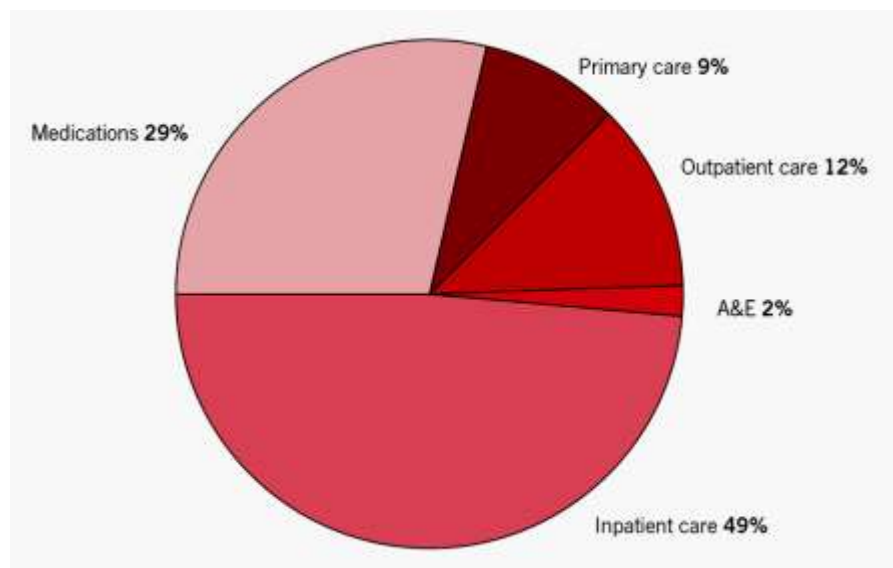


Age- and sex adjusted hospital discharge rates (per 100,000) for CVD in the years 1980-2007.



European Region
European Union
EU Members before 2004
EU Members since 2004 to 2007
The CIS countries: former Soviet Republics

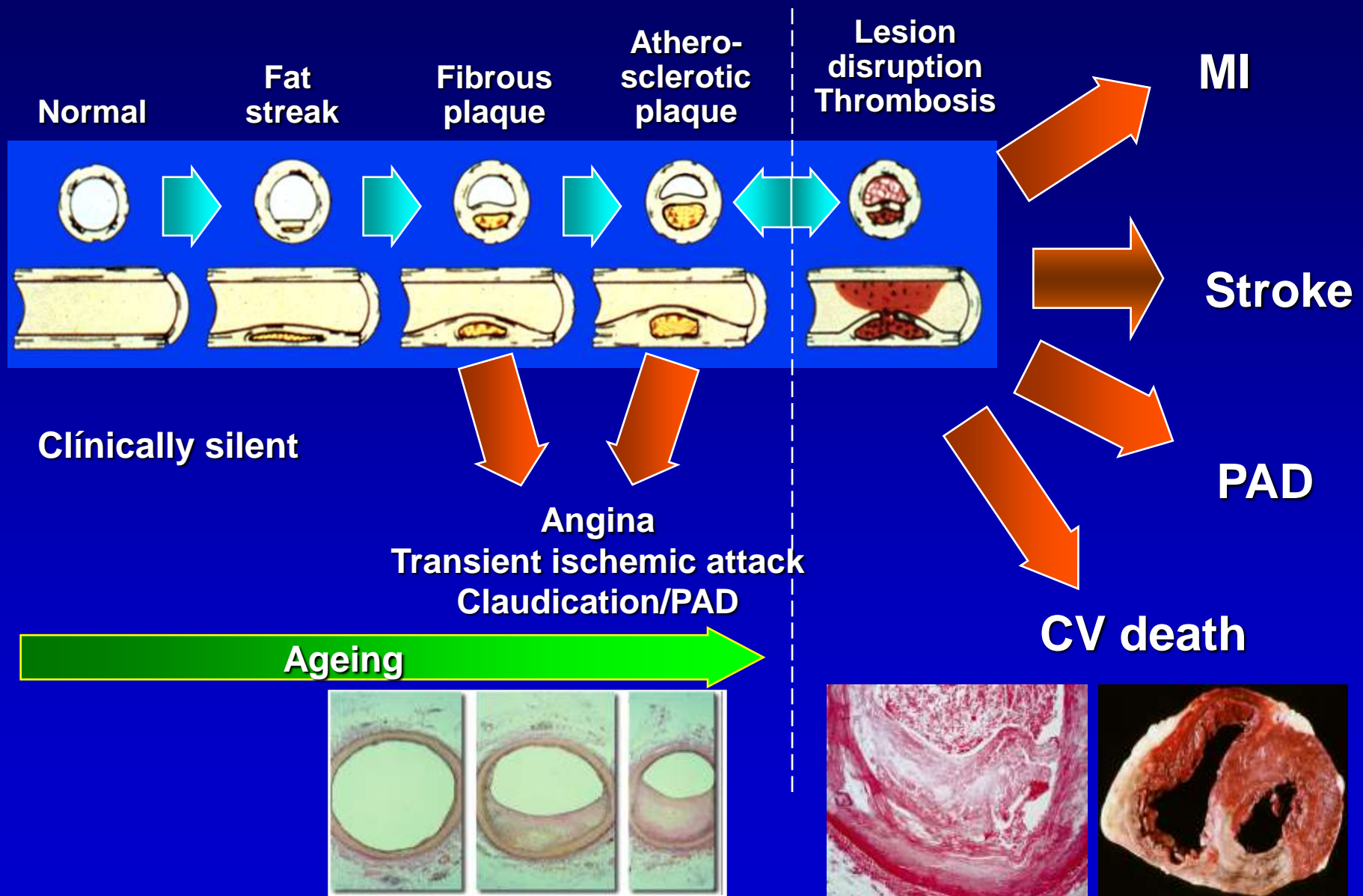
Percentage of total health expenditure on CVD in the EU (2009)



- Total CVD costs ~ €196 billion/year
- 223 €/y per capita per annum (~10-17% of the total health care costs)
- Costs will increase significantly in the next future

	CVD		CHD		Cerebrovascular disease	
	€ thousands	% of total	€ thousands	% of total	€ thousands	% of total
Direct health care costs	106,156,940	54%	19,867,875	33%	19,102,868	50%
Productivity loss due to mortality	26,963,326	14%	12,014,249	20%	4,812,409	13%
Productivity loss due to morbidity	18,873,665	10%	5,530,552	9%	3,329,282	9%
Informal care costs	43,560,202	22%	22,812,144	38%	11,115,782	29%
Total	195,554,133		60,224,820		38,360,340	

Pathogenesis of atherothrombotic events



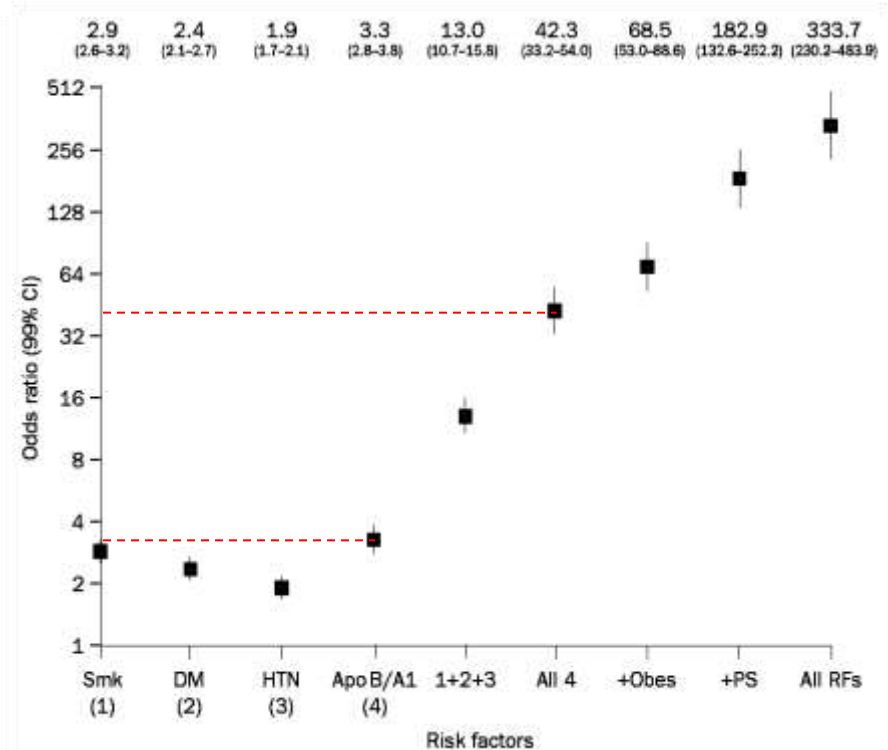
Advances in Cardiovascular Medicine

- **Advances in the treatment of atherosclerotic coronary artery disease**
 - Defining the relationship between diet, cholesterol, and atherosclerosis
 - Hypolipidemic drugs
 - Anticoagulant and antithrombotic therapy
 - Percutaneous coronary interventions and CABG surgery
- **The recognition of the importance of control of risk factors**
- **Identification and validation of diagnostic/prognostic biomarkers**
- **Cardiac catheterization, ablation and pacing**
- **Ventricular assist devices**
- **Cardiopulmonary bypass**
- **External defibrillation**
- **Heart transplantation**
- **Regenerative medicine and Cell therapy**
- **Functional genomics and pharmacogenomics**
- **Evidence-based best care (Guidelines)**
- **.....**

INTERHEART study: 9 modifiable factors account for 90% of first-MI risk worldwide

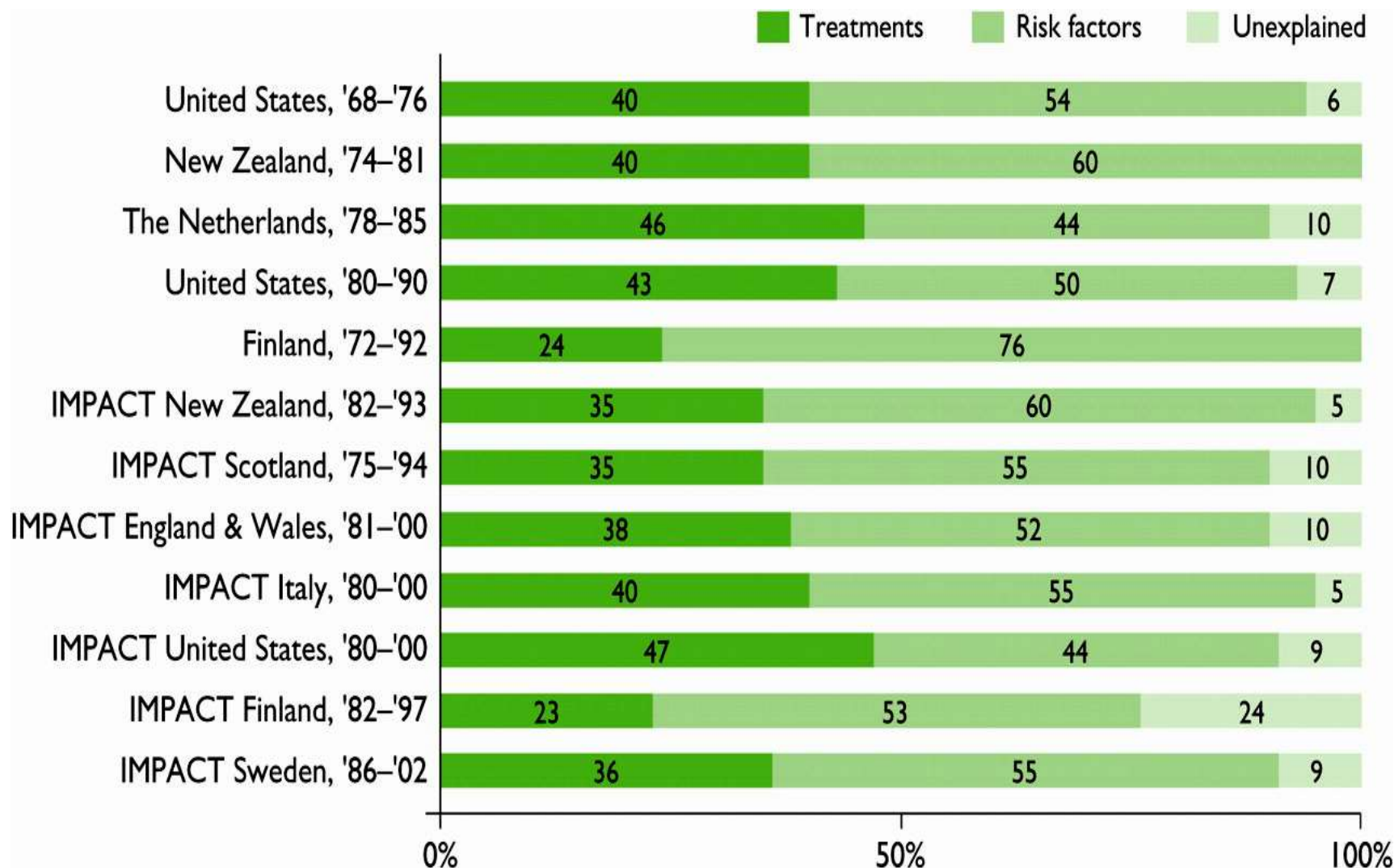
Risk factor	Population-attributable risk (%)
Diabetes mellitus	12.3
No exercise	12.5
No fruit and vegetable intake	12.9
No alcohol intake	13.9
Hypertension	23.4
Psychosocial factors*	28.8
Abdominal obesity	33.7
Current smoking	36.4
Raised Apo B:ApoA1 ratio	54.4

*Depression, perceived stress at home or work (general stress), low locus of control, and major life events. Abbreviations: Apo, apolipoprotein; MI, myocardial infarction.



- The majority of CV deaths are preventable at the population level through lifestyle and enviromental/structural change in the Society

Percentage of the decrease in deaths from CHD attributed to treatments and risk factor changes in different populations



Why is prevention of CVD needed?

1. **Prevention works: >50% of the reductions seen in CHD mortality relate to changes in risk factors-RFs (40% to improved treatments)**
 - **Efforts should be life-long, from birth (if not before) to old age**
 - **Greater healthy benefits if preventive efforts are focused on the total population**
 - **An approach limited to high-risk individual will be less effective**
 - **Population education programmes are needed**
2. **Despite gaps in understanding, there is ample evidence to justify intensive public health and individual preventive efforts**
3. **There is still substantial room for improvement in RF control, even in individuals at very high risk**

How can the burden of cardiovascular diseases be reduced?

Very cost effective interventions can be implemented even in low resource settings

Risk Factor	Treatment targets (ESC, 2012)
Life style (Education): Exercise Healthy diet	30 min 7 days per week, minimum 5 days/week Rich in fruit and vegetables, avoid foods high in fat, sugar and salt. Avoid the harmful use of alcohol
Smoking	Complete cessation mandatory No exposure to enviromental tobacco smoke
BP control	<140/90 mm Hg (<125/75 in CKD)
Diabetes management	A1c <7% (<53 mmol/mol- individualization) Fasting plasma glucose: < 6.9 mmol/L (125 mg/dL) Post-prandial: < 180 mg/dL
Lipid management	Total cholesterol: < 4.5 mmol/L (175 mg/dL) LDL <1.8 mmol/L (100 mg/dL) or <1.7 (70 mg/dL) HDL: men > 1; women > 1.2 mmol/L (40/46 mg/dL) Triglycerides: < 1.7 mmol/L (150 mg/dL)
Weight management Waist circumference	Body mass index (BMI) ≤ 25 kg/m ² Men ≤ 102 cm; women ≤ 88 cm



- People at high risk can be identified early in primary care, using simple tools (risk prediction charts)
- Intensity of intervention should be proportional to the CV risk

Guideline recommendations with established cardiovascular disease

Ample room for improvement

Guideline recommendations

Regular physical activity

Smoking cessation among smokers

BMI <25 kg/m²

Waist circumference:

- Men < 94 cm

- Women < 80 cm

BP <140/90 mmHg

T2 Diabetes:

- A1c <7%

- Fasting PG: < 180 mg/dL

Total cholesterol: < 4.5 mmol/L (175 mg/dL)

LDL-C < 2.5 mmol/L (100 mg/dl)



Improvements in patients with cardiovascular disease in EUROASPIRE III

Few adults participate in adequate levels of physical activity (less women)

Smoking has declined, but the rate of decline is slow (girls)

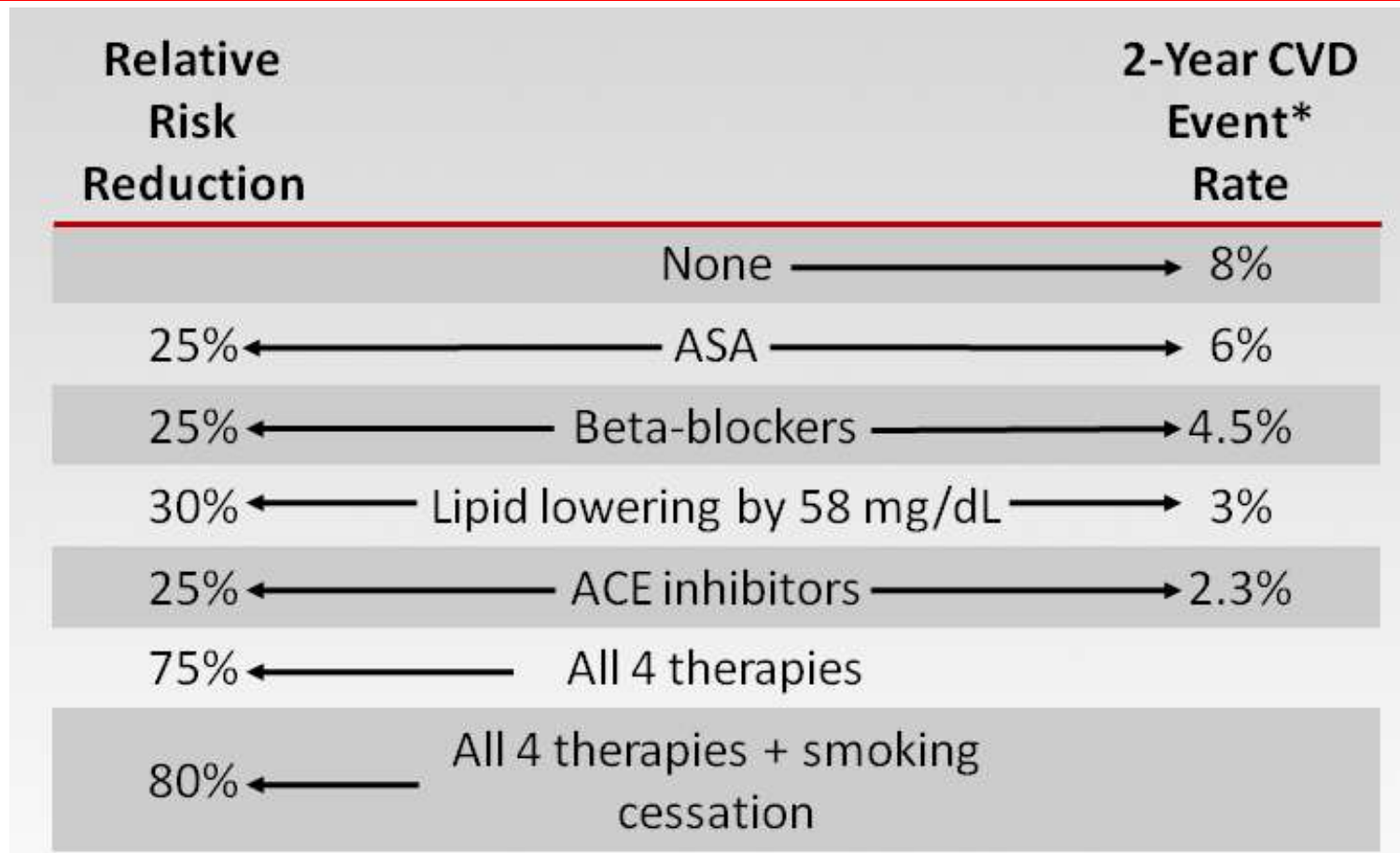
Fruit and vegetable consumption increases, while fat consumption remains stable

BP control remains unchanged, and almost 50% of patients remained above the recommended lipid targets

The prevalence of T2DM and obesity is high and continue to increase over the last 10 years

BMI: body mass index; HbA1c: glycated hemoglobin; LDL: low-density lipoprotein

Potential cumulative impact of secondary prevention treatments



It is possible to lower the risk of future events by more than four-fifths in high-risk individuals

* Cardiovascular death, MI, or stroke. ASA: acetylsalicylic acid

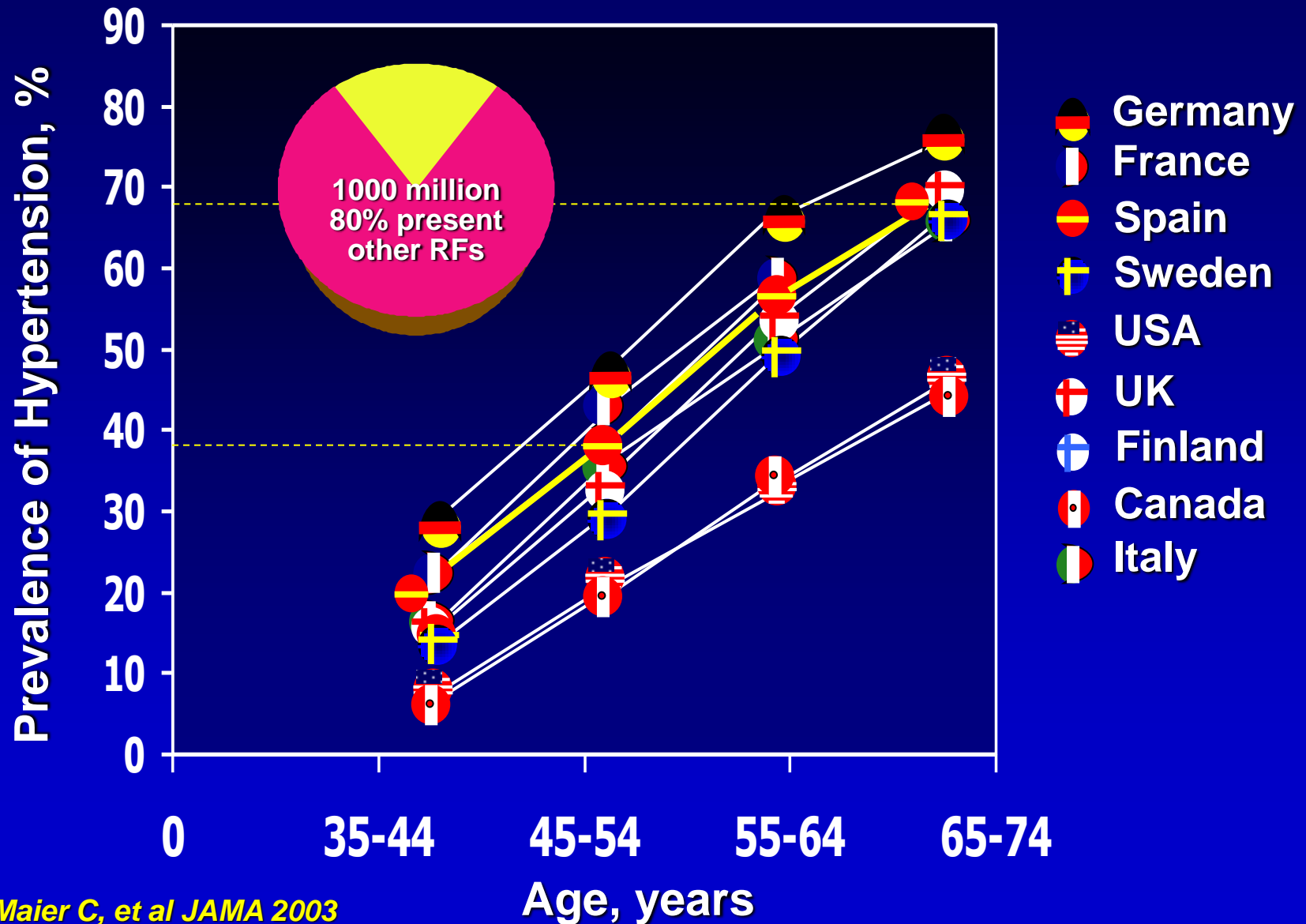
Non-adherence: A problem of Epidemic proportions

“Drugs don’t work in patients who don’t take them. C. Everett Koop”

- Non-adherence is a main cause of uncontrolled CVDs¹⁻⁵
 - 1 mo after a MI, 25-50% of patients stop at least 1 drug
 - After 1 year, < 50% of patients report persistent use of statins, antihypertensives or beta-blockers
 - 25% take less than recommended dose⁵
 - 33% did not fill the prescriptions they are given⁵
- After 1 year, hospitalizations and costs related to DM, HTN and hypercholesterolemia are significantly lower for patients with high adherence⁶
- In Europe non-adherence costs 125 billion € and contributes to 200,000 deaths per annum⁴
- Women are less likely to be prescribed pharmacotherapy

(1) Joint Guidelines on cardiovascular disease prevention in clinical practice. Eur Heart J 2012. (2) Ho et al. Circulation 2009. (3) Osterberg and Blaschke. N Engl J Med 2005. (4) http://www.talkaboutrx.org/documents/enhancing_prescription_medicine_adherence.pdf. (5) <http://www.friendsofeurope.org/Contentnavigation/Events/Eventoverview/tabid/1187/EventType/EventView/EventId/841>. (6) Sokol et al. Med Care 2005

Prevalence of Hypertension in Six European Countries, USA and Canada



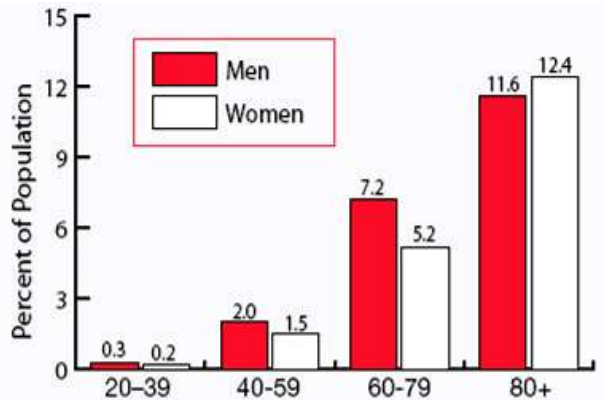
Hypertension – The triple paradox

OBJECTIVES

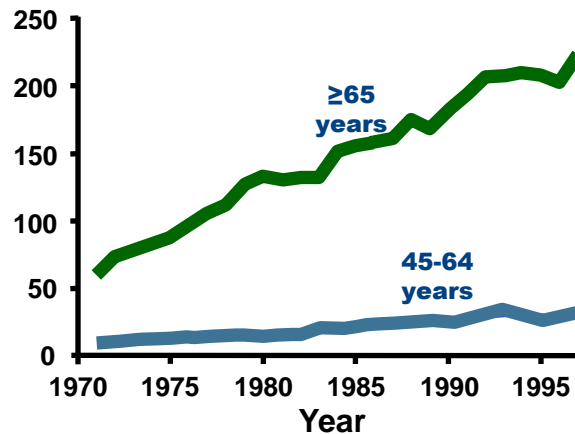
- ◆ Improve BP control (early diagnosis)
- ◆ Better understanding of the pathophysiology
- ◆ Reduce (beyond the BP control) the functional, structural and metabolic alterations
- ◆ Predict individual drug response
- ◆ Improve patients' compliance
 - It is a polygenic and polyfactorial disease
- ◆ Quite OFTEN patients did not follow the treatment (<50%)

Heart failure

Prevalence

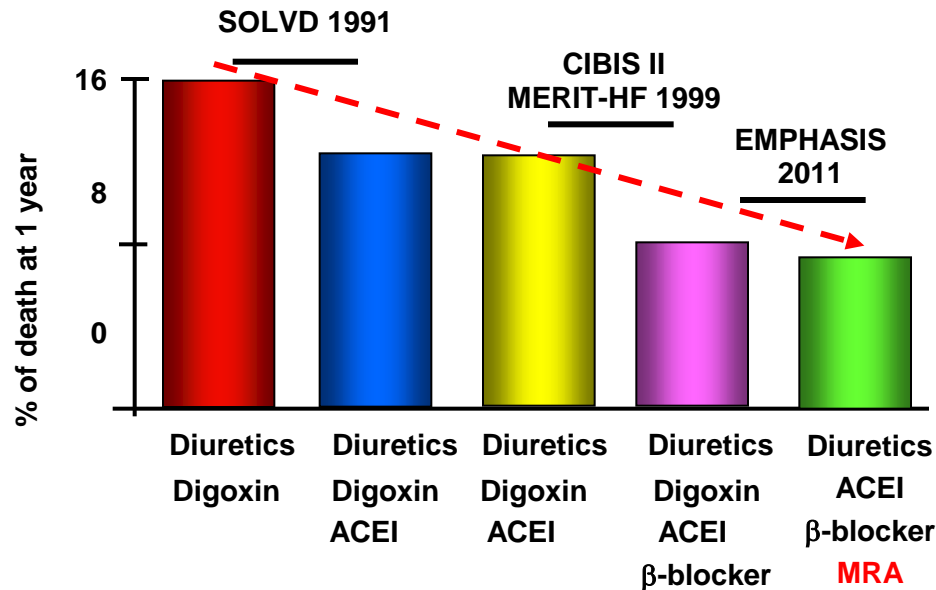


Hospitalisations/100,000 population



Poor prognosis

Disease	Survival (%)	
	1-Year	5-Year
Prostate cancer	99	99
Melanoma	98	66-92
Breast cancer	76	89
Colon cancer	82	62
Ovarian cancer	76	45
Leukemia	63	51
Heart failure	63	21
Lung cancer	42	16



2012



Acute HF: the scope of the problem

Prevalence

- >2-3% overall; 10-20% at >70y
- In ESC countries: >15 M patients

Burden

- Leading reason for hospitalization in patients > 65 years of age, tripling in last 3 decades
- Approximately 10% of patients in hospital beds
 - Hospital care represents 60-70% of all costs
- 2% of national health expenditure
- 40% of patients admitted to hospital with HF are death or readmitted within 1 year

Perspectives:

- Treatment of ADHF has not changed much over the last 25 years

Heart Failure – Pathophysiological history

60s **CONGESTIVE - Digoxin, Inotropics, Diurétiques**



70s **HEMODYNAMIC - Vasodilators**



80s **NEUROHUMORAL - ACE inhibitors,
β- Blockers, Spironolactone, ARBs**



90s **INFLAMMATION - Citokine inhibitors**



XXI **REMODELING, METABOLIC, GENETICS**

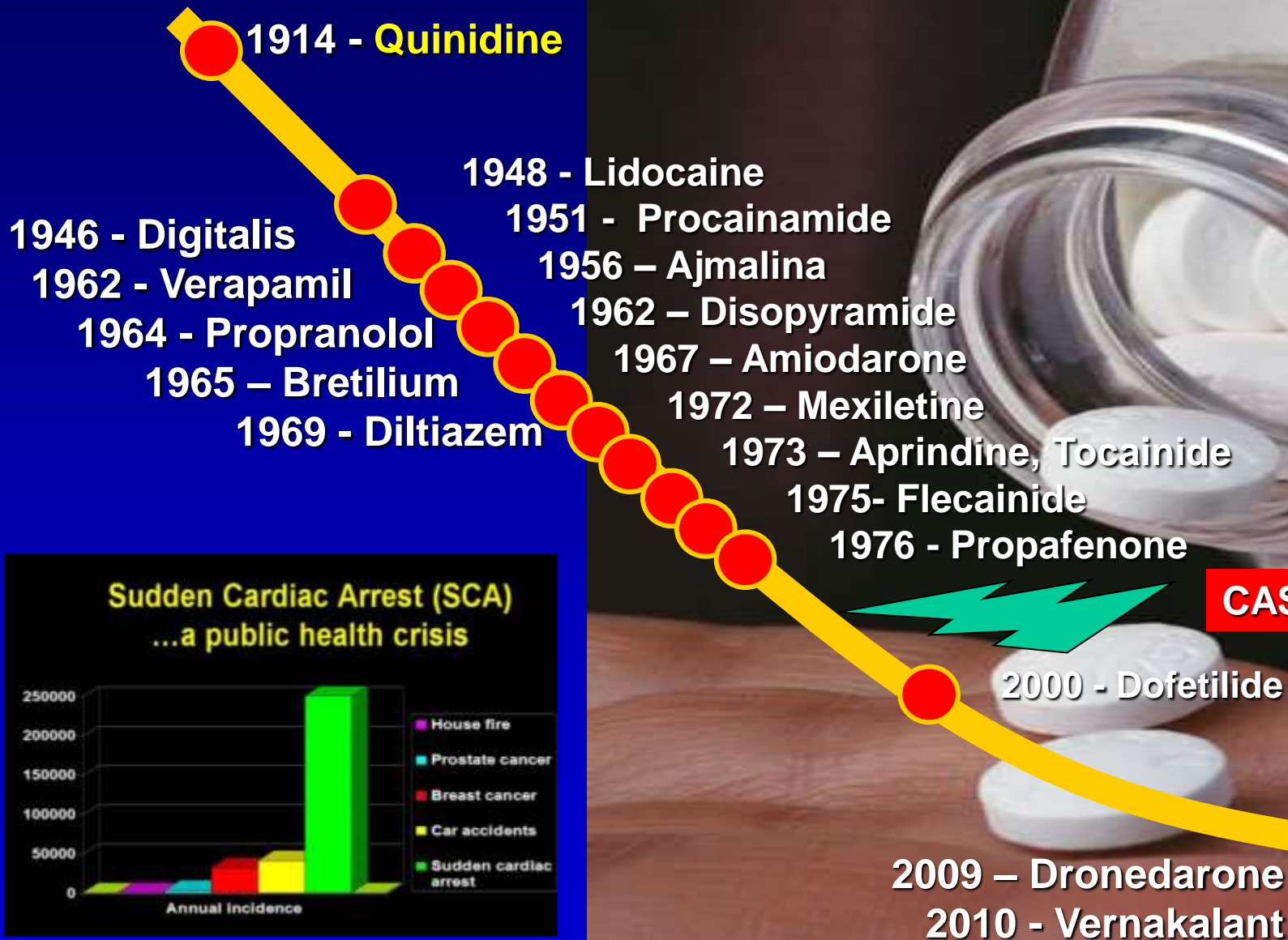


Failed targets (2000-2012)

" Failure is the opportunity to begin again with more intelligence "

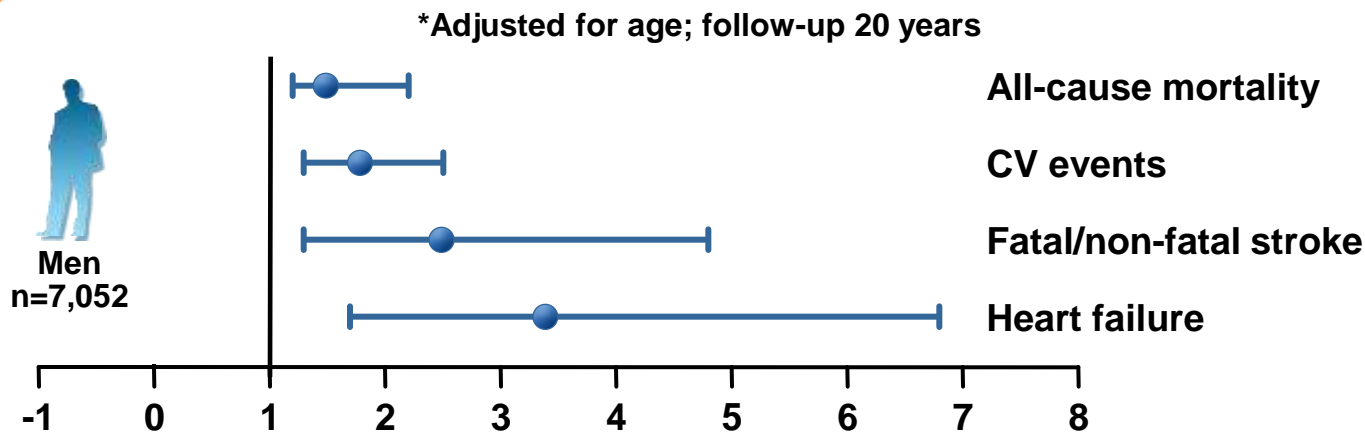
FAMILY	DRUG	RESULTS
A1-R ANTAGONISTS	Rolofillyne	NO EFFECT ON MORTALITY
NATRIURETIC PEPTIDES	Nesiritide, Ularitide, Carperitide	NO EFFECT ON MORTALITY
NOS INHIBITORS	L-NMMA	NO EFFECT ON MORTALITY
V1/V2-R ANTAGONISTS	Relcovaptan, Tolvaptan, Lixivaptan, Conivaptan	NO EFFECT ON MORTALITY
ANTIOXIDANTS	Alopurinol, oxipurinol	NO EFFECT ON MORTALITY
PROSTAGLANDIN I2	Epoprostenol	INCREASE MORTALITY
NATRIURETIC PEPTIDES	Nesiritide, Ularitide, Carperitide	NO EFFECT ON MORTALITY
TNF α INHIBITORS TGF β INHIBITORS VASOPEPTIDASE INHIBITORS	Etanercept, infliximab Pirfenidone, Tranilast Omapatrilat	INCREASE MORTALITY NO EFFECT ON MORTALITY NO EFFECT ON MORTALITY
ET-1 RECEPTOR ANTAGONISTS	A/B: bosentán, tezosentán y enrasentán ETA: darusentán	NO EFFECT ON MORTALITY ↑ transaminases, hypotension, renal failure
AGEP BREAKERS	Alagebrium	NO EFFECT ON EXERCISE TOLERANCE
HORMONES	Growth hormone, IGF-1, Testosterone 3,5-diiodothyropropionic acid (DITPA) Relaxin	NO EFFECT ON MORTALITY WORSENING OF HF REDUCE MORBIDITY
METABOLIC MODULATORS FATTY ACID OXIDATION INHIBITORS	AMPK-activating agents: Metformin Trimetazidine, Etoximir, Perhexiline	REDUCE MORTALITY NO EFFECT ON MORTALITY
RENIN INHIBITORS	Aliskiren	INEFFECTIVE
DARBEPOETIN ALFA, IRON	rHuEpo, darbopoetin- α , ferric carboxymaltose	NO EFFECT ON MORTALITY
MPP INHIBITORS	PG-116800, PG-530742, PD 166793, CP-471,474	NO EFFECT ON LV REMODELING
SYMPATHOLYTIC DRUGS	Moxonidine (I1R), Doxazosine (α -AR)	INCREASE MORTALITY
BRADYCARDIC AGENTS	Ivabradine	REDUCE MORTALITY
NEW INOTROPICS	Omecamtiv mecarbil, Istaroxime, apelin	?

Almost 25 years without new AADs!



Atrial fibrillation (AF) is the most frequent cardiac arrhythmia

1. AF affects 1/25 adults >60 years (1/10 >80 years)¹ – 4.5 M
 - The prevalence of AF may rise ≥ 2.5 fold by 2050 (in the US)²
 - Increases hospitalisations (1/3 of those for cardiac arrhythmias)³
2. AF/atrial flutter is associated with³⁻⁵:

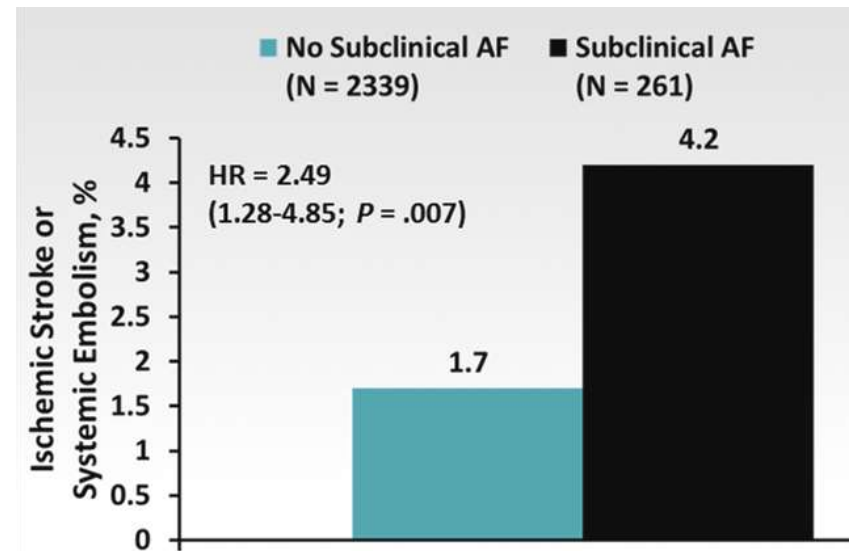
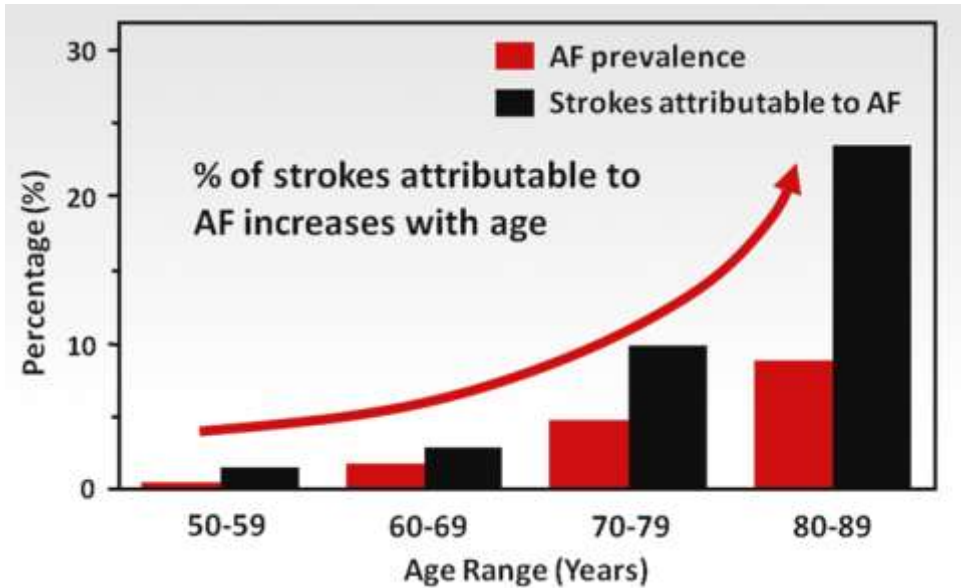


3. Substantial costs of management

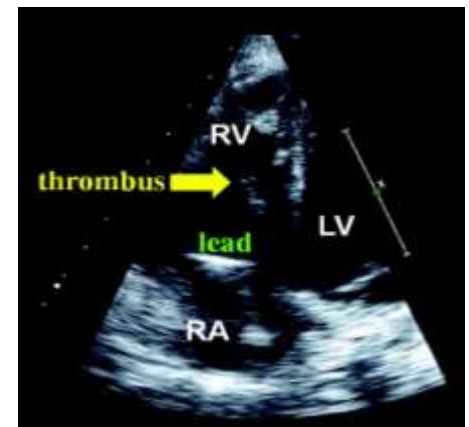
- 1-2.5% of the health care budget in 2000⁶
- 70% driven by in-patient care and interventional procedures⁷

(1) Go A et al. *JAMA* 2001;285:2370-5. (2) Benjamin E et al. *Circulation* 1998;98:946-52. (3) Fuster V et al. *Europace* 2006;8:651-745. (4) Wolf P et al. *Stroke* 1991;22:983-988. (5) Stewart S et al. *Am J Med* 2002;113:359-64. (6) Stewart S et al. *Heart* 2004;90:286-92. (7) Ringborg A, et al. *Europace* 2008;10:403-11.

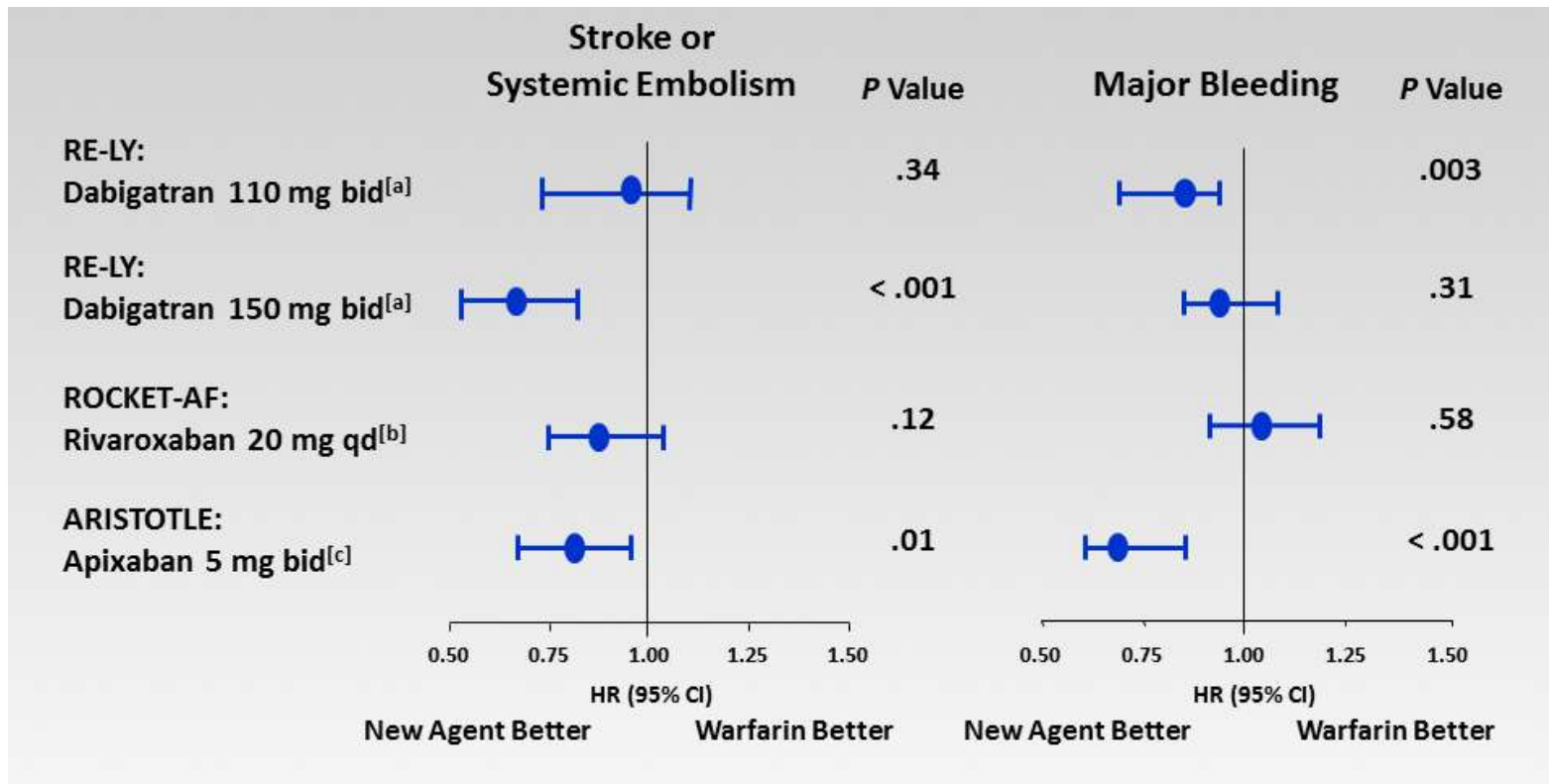
AF increases 5-fold the incidence of stroke



- AF is responsible for 15-25% of all strokes
- Ischemic strokes are often fatal, and patients who survive are left more disabled and more likely to suffer a recurrence than those with other causes of stroke
- Stroke risk persists even in asymptomatic AF
 - \approx 25-30% of stroke is cryptogenic
- The battle: Warfarin vs NOACs



New oral anticoagulantes



Direct thrombin inhibitors	Dabigatran, Vorapaxar
Factor Xa inhibitors	Apixaban, Betrixaban, Edoxaban, Rivaroxaban
Vit K inhibitors	Tecarfarin

Diabetes mellitus

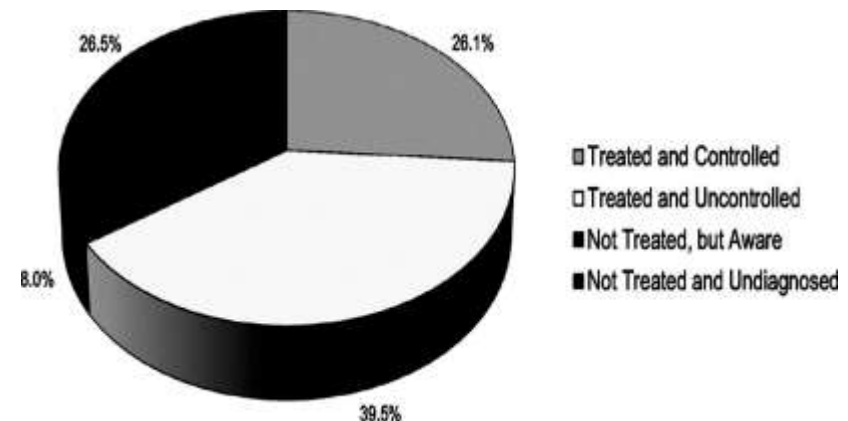
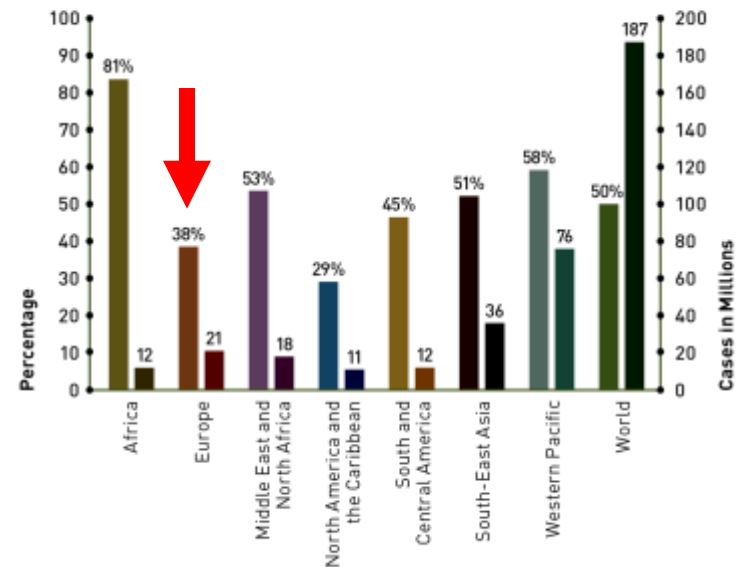
1. An independent RF for CVD

2. DM - Global burden:

- T2DM is increasing in every country
- 366 M in 2011 → 552 M by 2030
- 4.6 M deaths in 2011
- 11% of total healthcare expenditures
- 78,000 children develop T1DM annually

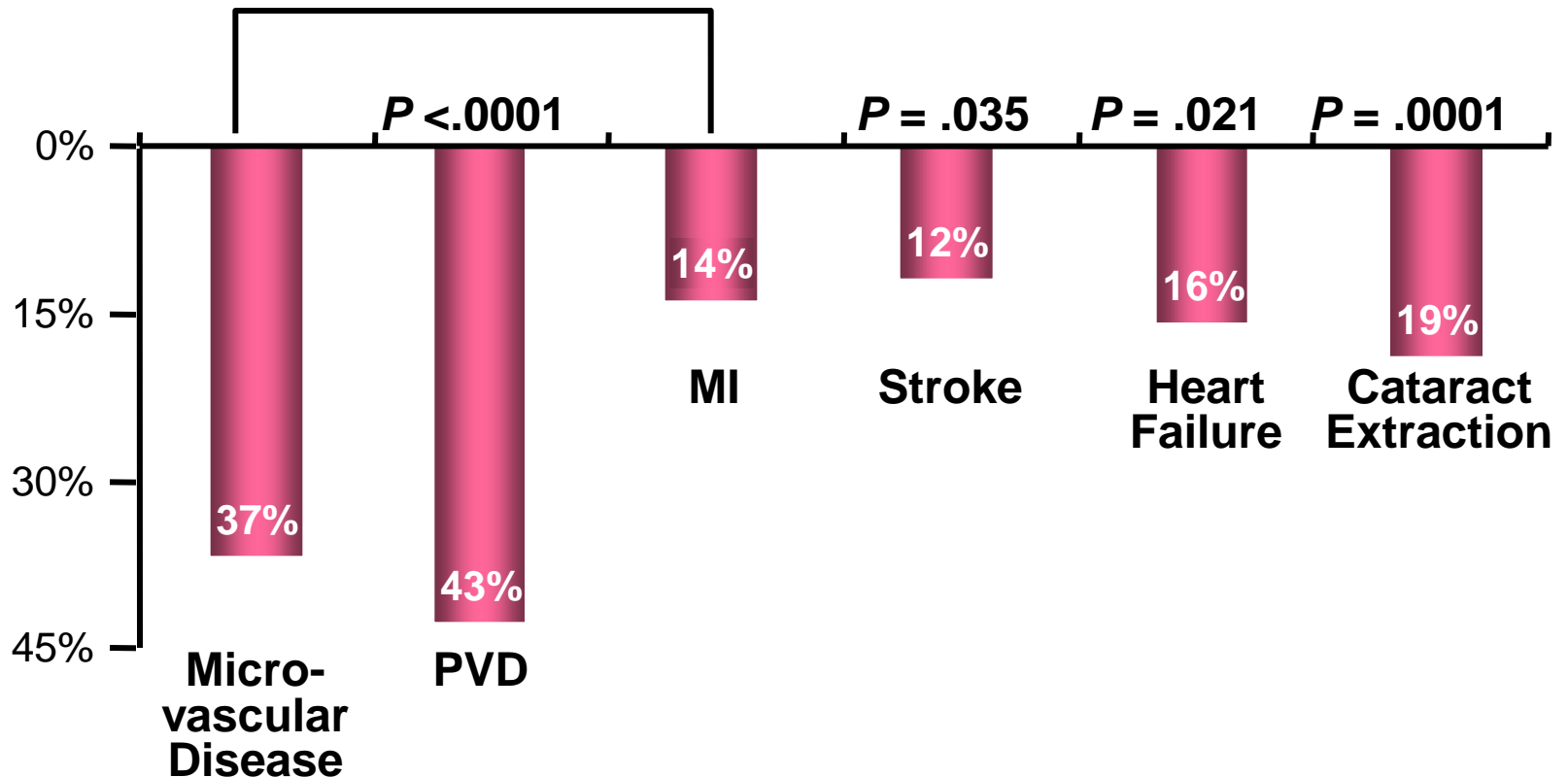
	Diabetic (%)	Nondiabetic (%)
MI	804 (9.03)	1139 (3.20)
Stroke	774 (8.69)	1345 (3.78)
Hypertension	2234 (26.2)	6002 (16.85)
End-stage renal disease	523 (5.87)	507 (1.42)
Foot ulcer	712 (7.91)	395 (1.11)
Eye disease	3940 (44.3)	1009 (2.83)

UNDIAGNOSED PERCENTAGE AND UNDIAGNOSED CASES OF DIABETES (20-79 YEARS) BY REGION



UKPDS 35: prospective observational study

RR with 1% decline in annual mean HbA1c is associated



Pharmacogenomics, Pharmacogenetics

"If it were not for the great variability among individuals, medicine might as well be a science, not an art." Sir William Osler, 1892.

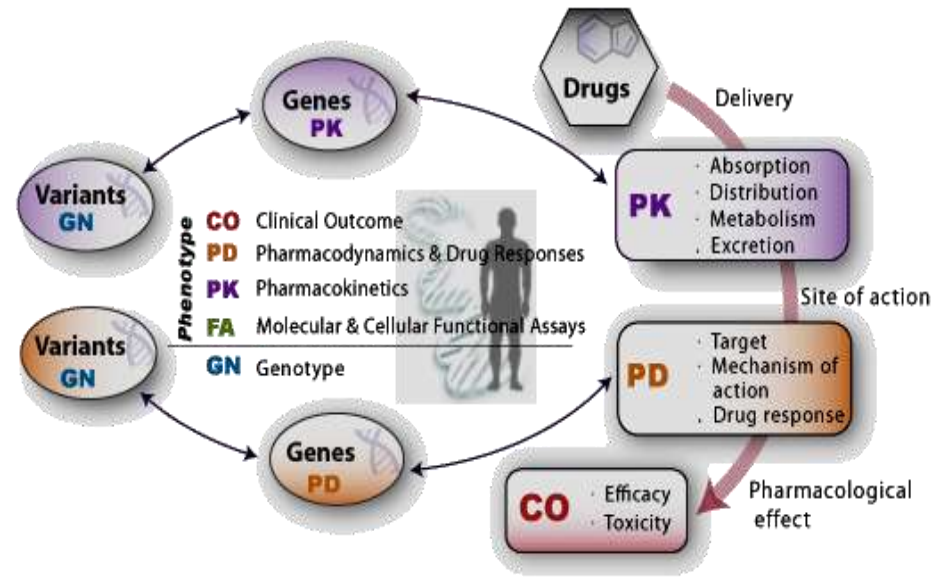
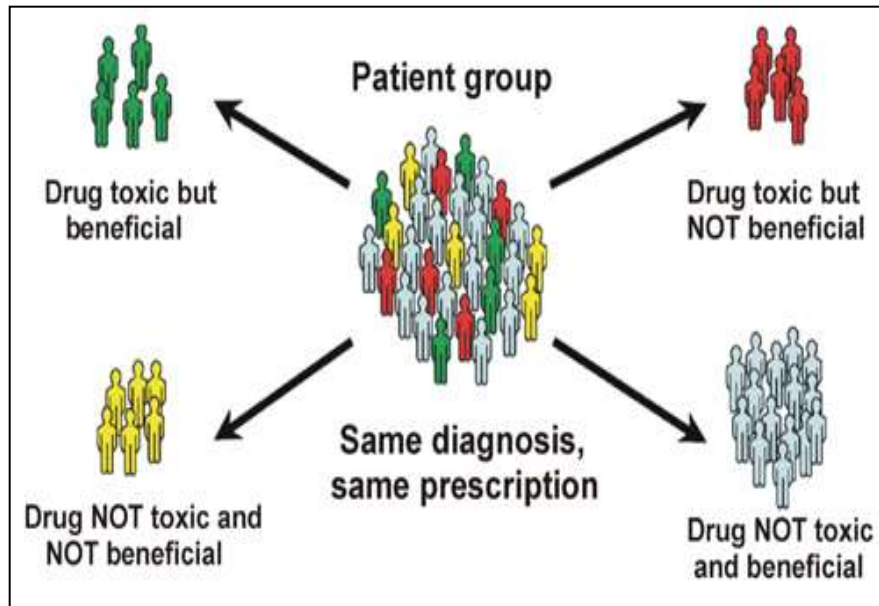


Table 1. Ranges of recommended warfarin doses (mg/day) from the US FDA drug label.

VKORC1	CYP2C9 (mg/day)					
	*1/*1	*1/*2	*1/*3	*2/*2	*2/*3	*3/*3
GG	5-7	5-7	3-4	3-4	3-4	0.5-2
AG	5-7	3-4	3-4	3-4	0.5-2	0.5-2
AA	3-4	3-4	0.5-2	0.5-2	0.5-2	0.5-2

- The **right** dose of
- The **right** drug for
- The **right** indication for
- The **right** patient at
- The **right** time

DNA polymorphisms implicated in variable outcomes of drug therapy in CV medicine



Drug	Gene	Reported Association
ACE inhibitors	ACE	Decreased response in "DD" genotype
Aldosterone antagonists	CYP11B2 gene - CC	Increased mortality and AF
Aspirin	ITGB3, VAV3, GPVI, F2R, GP1BA, PEAR1	PEAR1 - heightened platelet function
β-blockers	CYP2D6*4 (Metoprolol) ADRB1 (Ser49Gly) (Arg389Gly) ADRB2	Greater β-blockade (bradycardia: carvedilol, atenolol) ↓ Reduction in BP and HR ↓ Reduction in BP and HR, ↓ improvement in LVEF ↑ Death rate
Clopidogrel	CYP2C19 (*2, 17*) ABCB1	Less/higher platelet function ↑ Risk of MI, stroke and death
Digoxin	MDR1	Variable bioavailability and clearance
Hydrochlorothizide	α-Adducin (ADD1)	Variable stroke incidence and BP response
Losartan, irbesartan	CYP2C9	Greater BP drop with hypofunctional alleles
Procainamide	NAT2 (*5, *6, *7, *14)	Poor acetylators, higher risk for drug-induced lupus
Propafenone	CYP2D6*4	Reduced clearance, higher incidence of AEs
Statins	APOE, HMGCR SLCO1B1 CETP	↓ LDL reduction (Simvastatin) Statin-Induced Myopathy (Atrovastatin, Simvastatin) ↑ Risk of nonadherence (Atrovastatin, Simvastatin) Variable regression of atherosclerosis
Warfarin	CYP2C9 (*2, *3) VKORC1 CYP4F2	Reduction in warfarin dose requirement/risk of bleeding Reduction in warfarin dose requirement Higher warfarin dose requirements

Tamargo, Metra, Hartmann et al., 2013 (unpublished)

Ongoing and planned studies of the ESC

EURObservational Research Programme

2010	2011	2012	2013	2014	2015
				ACUTE CORONARY SYNDROMES Pilot (TBC)	ACUTE CORONARY SYNDROMES Long-Term (TBC)
				PULMONARY HYPERTENSION IN ADULTS WITH CONGENITAL HEART DISEASE	
				EUROASPIRE IV	
				ATRIAL FIBRILLATION GENERAL Pilot	ATRIAL FIBRILLATION GENERAL Long-Term
				CARDIOMYOPATHIES Pilot	CARDIOMYOPATHIES Long-Term
				CHRONIC ISCHEMIC CVD Pilot	CHRONIC ISCHEMIC CVD Long-Term
				TRANSCATHETER VALVE TREATMENT Long-Term	
				ATRIAL FIBRILLATION ABLATION Long-Term	
				PREGNANCY AND CARDIAC DISEASE (ROPAC)	
				HEART FAILURE Long-Term	
				+ PERIPARTUM CARDIOMYOPATHY (PPCM)	
2010	2011	2012	2013	2014	2015
				EUROPEAN LEAD EXTRACTION CONTROLLED (ELECTRa) Sponsored by EHRA	

To provide a better understanding of medical practice based on observational data collected with more robust methodological procedures

The final goal - To improve the CV health of all Europeans, while reducing deaths from CVDs

- 1. CVD prevalence and costs are projected to increase substantially**
 - Identify the major contributors to CVD morbidity and mortality**
 - Predict future CHD and stroke trends**
 - Identify the most effective and cost effective CVD prevention policies**
 - Increase the % of early diagnosed, treated and controlled patients**
- 2. Promote healthy “CV behaviours” throughout the lifespan**
- 3. Identify gaps, strengths, weaknesses and opportunities in CV R+D+i**
- 4. Understand CVD pathophysiology**
 - Confirm the target in RCTs**
 - Bringing innovations to clinical practice**
- 5. Better drugs, safer and more effective, than those presently available**

A vibrant landscape featuring a lush green field in the foreground, a clear blue sky with wispy clouds, and a range of green mountains in the distance. The scene is bright and sunny.

Thank you