Alcohol

part of Western civilization for millenia

De Lorgeril, Barcelona

Adverse health effects of alcohol

- polyneuritis
- cirrhosis / hepatitis
- encephalopathy
- cardiomyopathy
- malnutrition / vitamin B1 deficiency

. . .

When I read about the evils of drinking, I decided to give up reading

Mark Twain (1835-1910)

Risks and benefits of alcohol

490,000 individuals
prospective 9 year follow-up study

Alcohol use ⇨

higher risk :

- cirrhosis
- cancer *(breast, mouth, esophagus, pharynx, larynx, liver)*
- injury *(traffic accidents etc)*

lower risk :

- cardiovascular death lower by 30-40%
- less diabetes, osteoporosis, progression of renal disease, cognitive impairment

Thun, New Engl J Med (1997) 337:1705

Which is the greater miracle ?

Wedding of Kanaan

(John 1:1-12) **–**

conversion of

water into wine

or

Which is the greater miracle ?

but :

the Kidney –

even converts wine into water

Medical use of alcohol

Hippokrates of Kos (439-377 BC)

Wine *Tranquilizer*
Analgesic
Diuretic
Antidiarrhoic
Treatment of wounds

New Testament (Luke 10; 30-37)

Treatment of wounds:
The Good Samaritan

A certain man went down from Jerusalem to Jericho and fell among thieves which stripped him of his raiment and wounded him, and departed, leaving him half dead...
a Samaritan... went to him, and bound up his wounds, pouring in oil and wine...

Luke; 10: 30-37

V. van Gogh

Medical use of alcohol

Julius Caesar *(100-44 BC)*

Troops – wine (1.5L/day) with meals to prevent gastrointestinal infections

won battles not only by strategic skill, but also by healthier defecation

Claudius Galenus,
Pergamon (130-200 AC)

Red wine → GI disease
Adstringent (tannin rich) wine → internal bleeding

Regimen Sanitatis Salernitani

Arnoldo de Villanueva

1235-1311

School of Salerno

"... during meals drink wine happily little but often..."

"...avoid harming the body - never drink between meals..."

Ursini, Ann.NY Acad Sci (2002) 957:200

Medical use of wine

Paracelsus

(Philippus Aurelius Theophrastus Bombastus von Hohenhain; 1493-1541)

”Weingeist” *(Spiritus)*

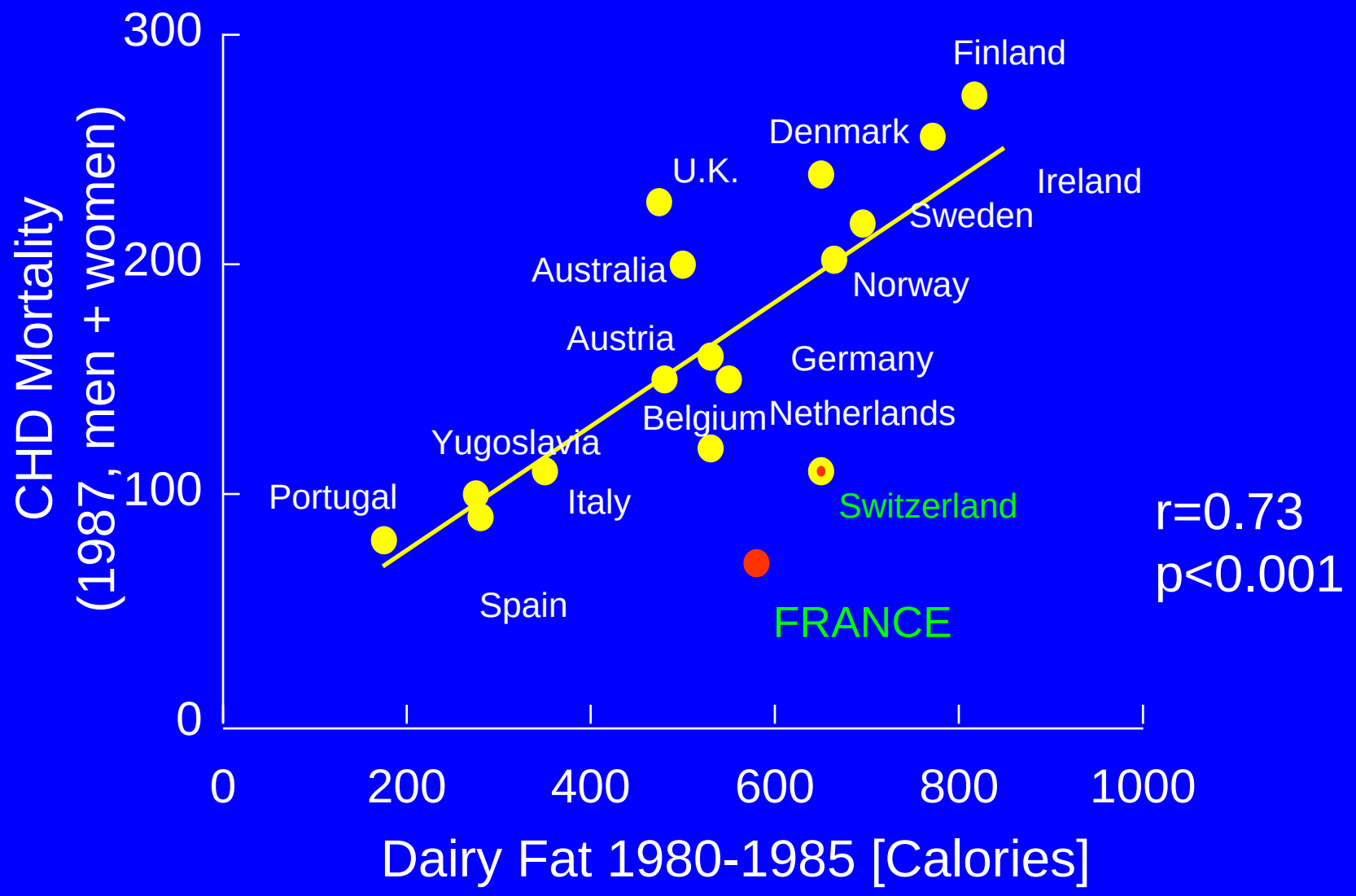
active ingredient of wine (= alcohol)

derived: spirits, Sprit

other ingredients inert contaminants

effects of wine: dosis facit venenum

French Paradox for Coronary Artery Disease



r=0.73
p<0.001

Renaud, Lancet (1992) 339: 1523

”French paradox”

- in all countries tight correlation between consumption of animal fat and coronary mortality, <u>except</u>

- in France and Switzerland:
  coronary mortality <u>low</u> in relation to consumption of animal fat

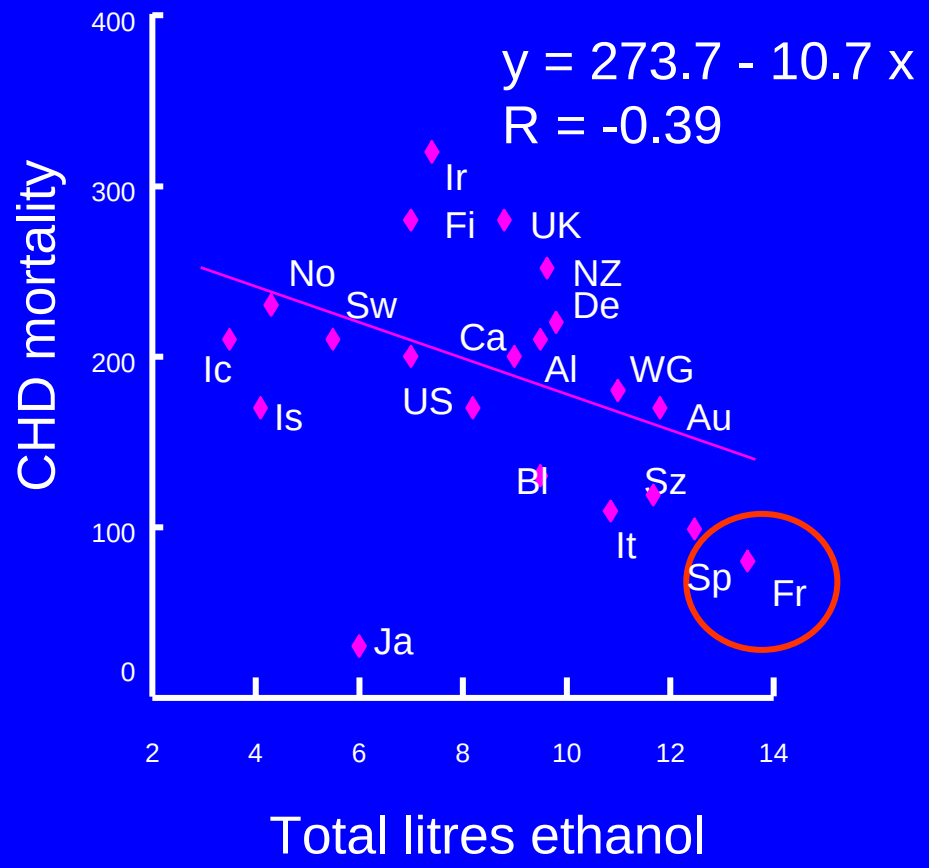
Renaud S, Lancet (1992) 339: 1523

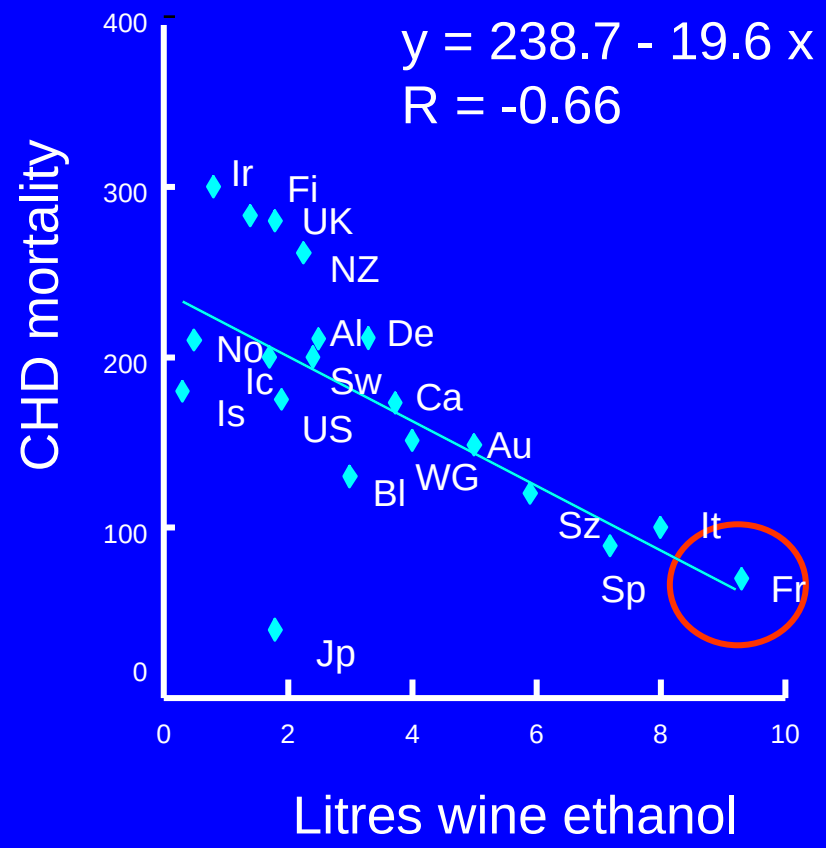
De Lorgeril, Circulation (2002) 106: 1465

<u>Hypothesis</u>

Wine antagonises adverse effects of animal fat

Ethanol and wine ethanol consumption - relation to coronary heart disease mortality

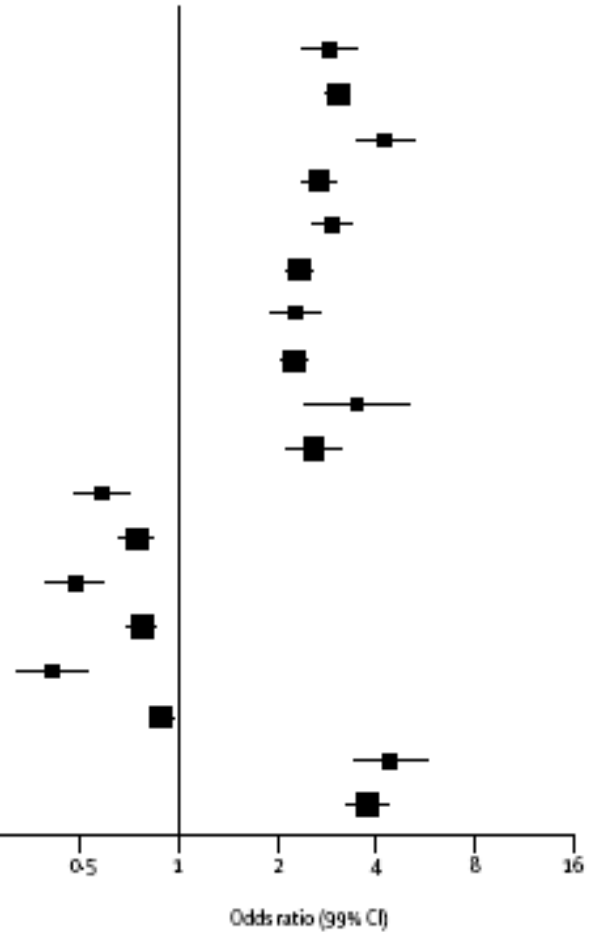




Criqui and Ringel, Lancet (1994) 344: 1719

Risk factors and myocardial infarction – *worldwide analysis*

Risk factor	Sex	Control (%)	Case (%)	Odds ratio (99% CI)	PAR (99% CI)
Current smoking	F	9·3	20·1	2·86 (2·36–3·48)	15·8% (12·9–19·3)
	M	33·0	53·1	3·05 (2·78–3·33)	44·0% (40·9–47·2)
Diabetes	F	7·9	25·5	4·26 (3·51–5·18)	19·1% (16·8–21·7)
	M	7·4	16·2	2·67 (2·36–3·02)	10·1% (8·9–11·4)
Hypertension	F	28·3	53·0	2·95 (2·57–3·39)	35·8% (32·1–39·6)
	M	19·7	34·6	2·32 (2·12–2·53)	19·5% (17·7–21·5)
Abdominal obesity	F	33·3	45·6	2·26 (1·90–2·68)	35·9% (28·9–43·6)
	M	33·3	46·5	2·24 (2·03–2·47)	32·1% (28·0–36·5)
Psychosocial index	F	–	–	3·49 (2·41–5·04)	40·0% (28·6–52·6)
	M	–	–	2·58 (2·11–3·14)	25·3% (18·2–34·0)
Fruits/veg	F	50·3	39·4	0·58 (0·48–0·71)	17·8% (12·9–24·1)
	M	39·6	34·7	0·74 (0·66–0·83)	10·3% (6·9–15·2)
Exercise	F	16·5	9·3	0·48 (0·39–0·59)	37·3% (26·1–50·0)
	M	20·3	15·8	0·77 (0·69–0·85)	22·9% (16·9–30·2)
Alcohol	F	11·2	6·3	0·41 (0·32–0·53)	46·9% (34·3–60·0)
	M	29·1	29·6	0·88 (0·81–0·96)	10·5% (6·1–17·5)
ApoB/ApoA1 ratio	F	14·1	27·0	4·42 (3·43–5·70)	52·1% (44·0–60·2)
	M	21·9	35·5	3·76 (3·23–4·38)	53·8% (48·3–59·2)



Yusuf, Lancet (2004) 364:937

Health professional follow up study

50,000 men

→ 5-30 g alcohol per day
reduction of CV mortality by ~ 25%

Rinn et al.
Wine, beer and spirits.
Are they really horses of a different colour?
Circulation (2002) 105: 2806

Alcohol consumption and cardiovascular death in hypertensive men –

Physicians' health study

14,125 / 88,882 hypertensives

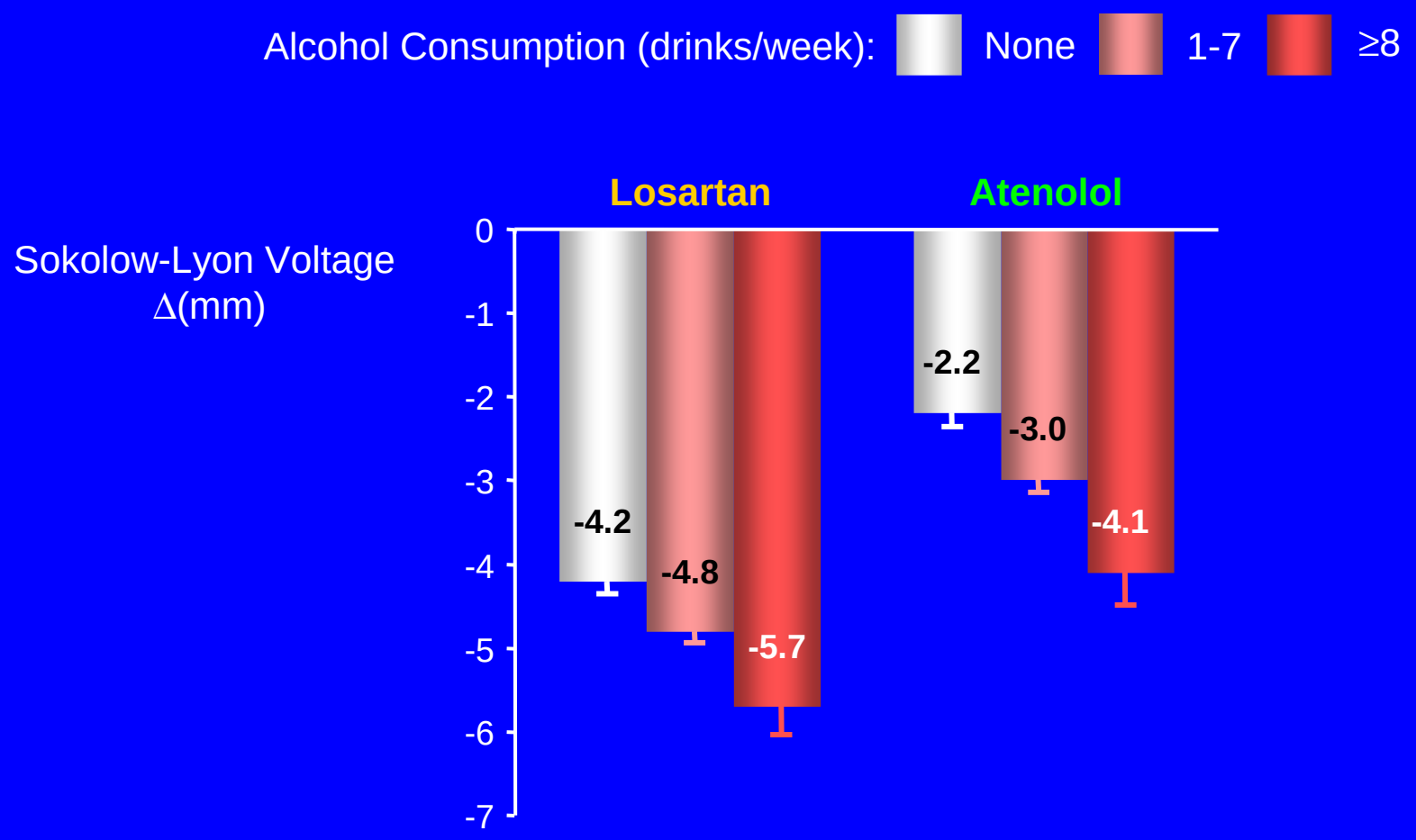
	relative risk alcohol consumption			
	never	monthly	weekly	daily
CV mortality	1.0	0.82	0.64	0.56
Overall mortality	1.0	0.86	0.72	0.73

Malinski,Arch.Int.Med (2004)164:623

LIFE study:

regression of left ventricular hypertrophy (ECG)

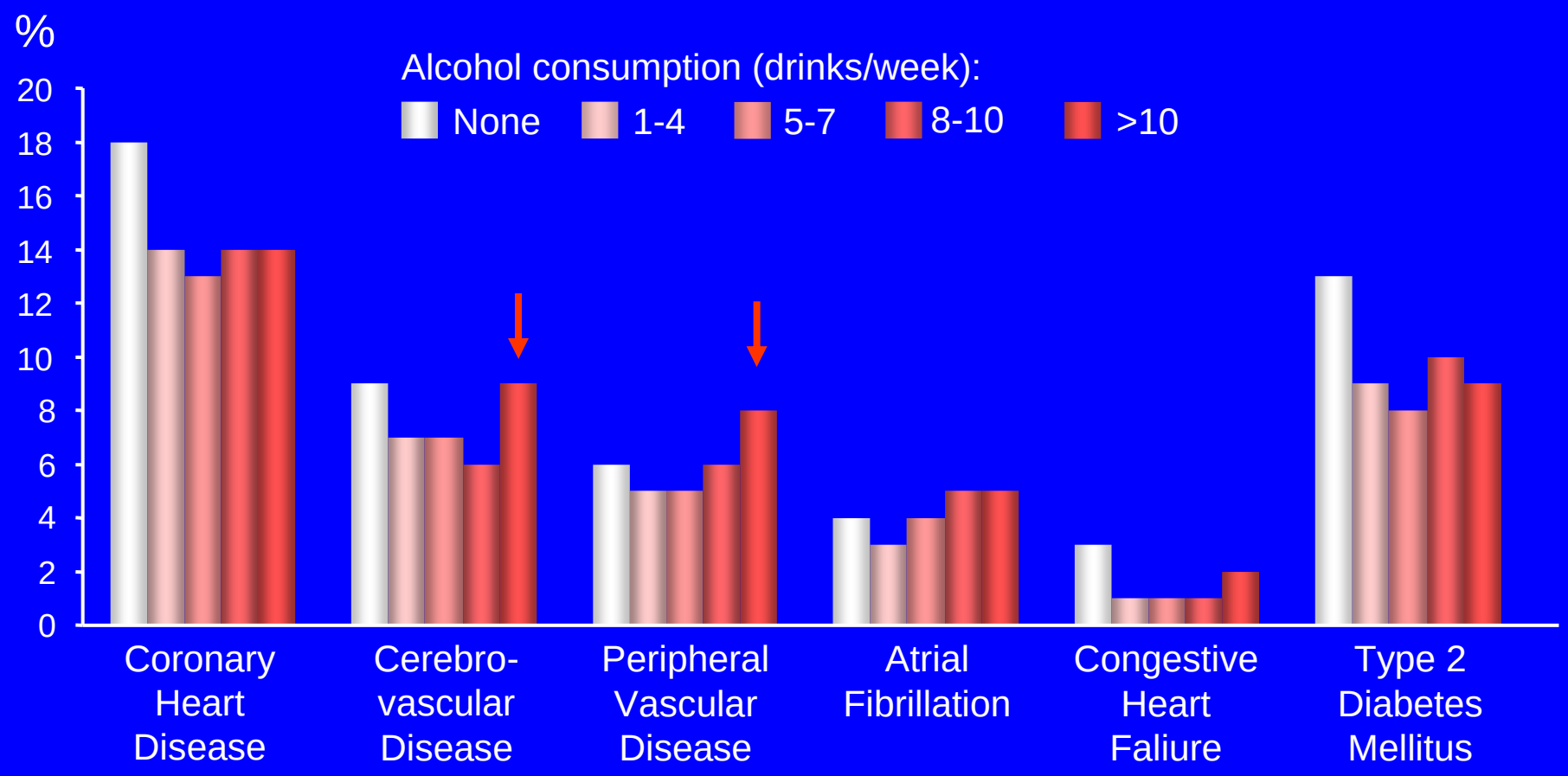
effect of treatment (Losartan or Atenolol) and of alcohol consumption



Reims. *J Hum Hypertens* (2004) 18:381

LIFE study:

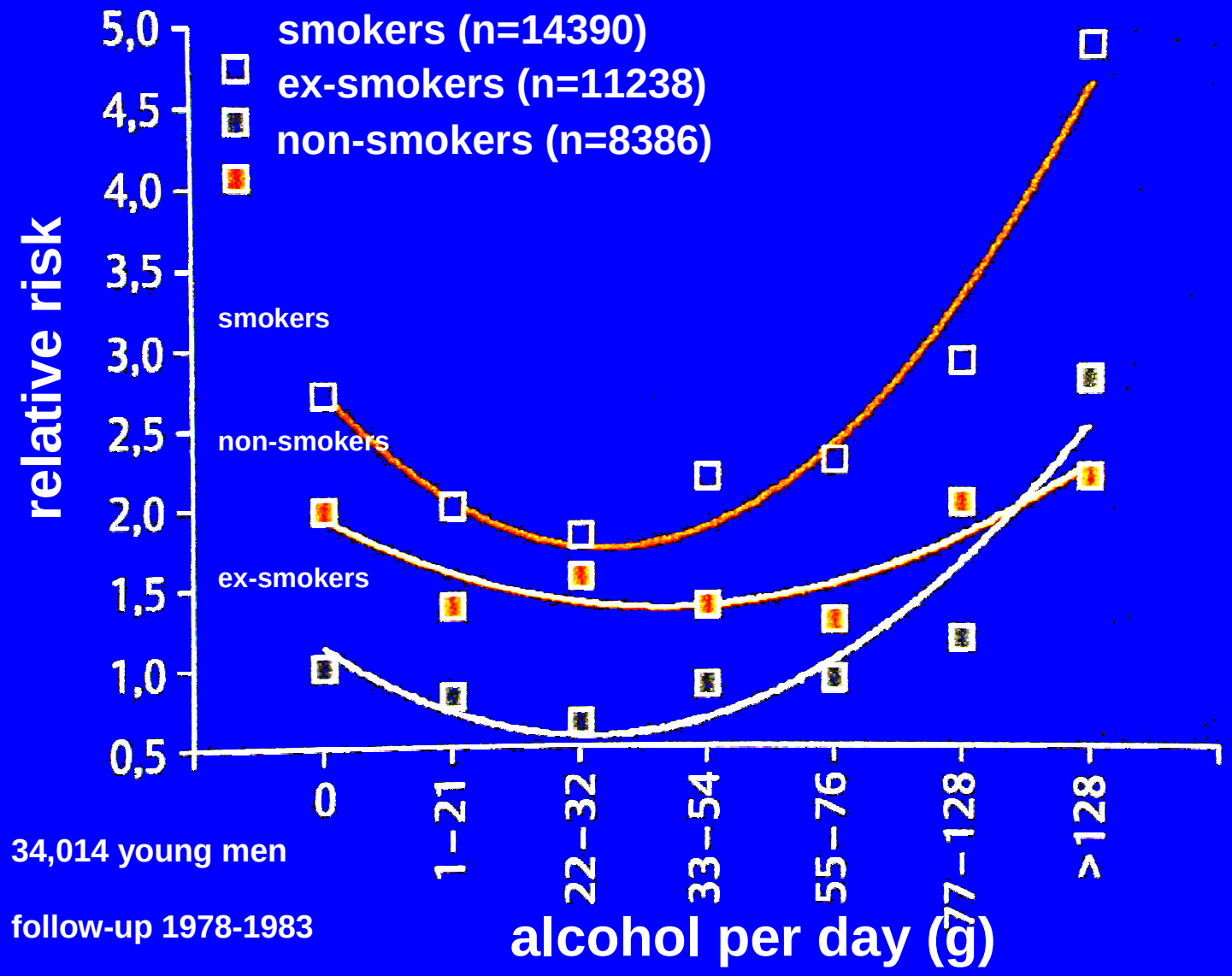
***cardiovascular events* by alcohol consumption – the U-shaped relationship**



Reims, J Hum Hypertens (2004) 18: 381

Relative risk of death in Eastern France –

both no and high alcohol consumption → adverse effects



34,014 young men

follow-up 1978-1983

Why U-shaped relationship?

Study 34014 young men in France 1978-1993

High alcohol intake

cirrhosis
colorectal, gastroesophageal carcinoma
traffic accidents

<u>but</u>,

for alcohol consumption > 50 g/day
also increased CV risk ↑

Renaud, Am J Clin Nutr (1992) 55: 1012

Copenhagen Heart Study

U-shaped relation between units of alcohol/day (30 g) and stroke

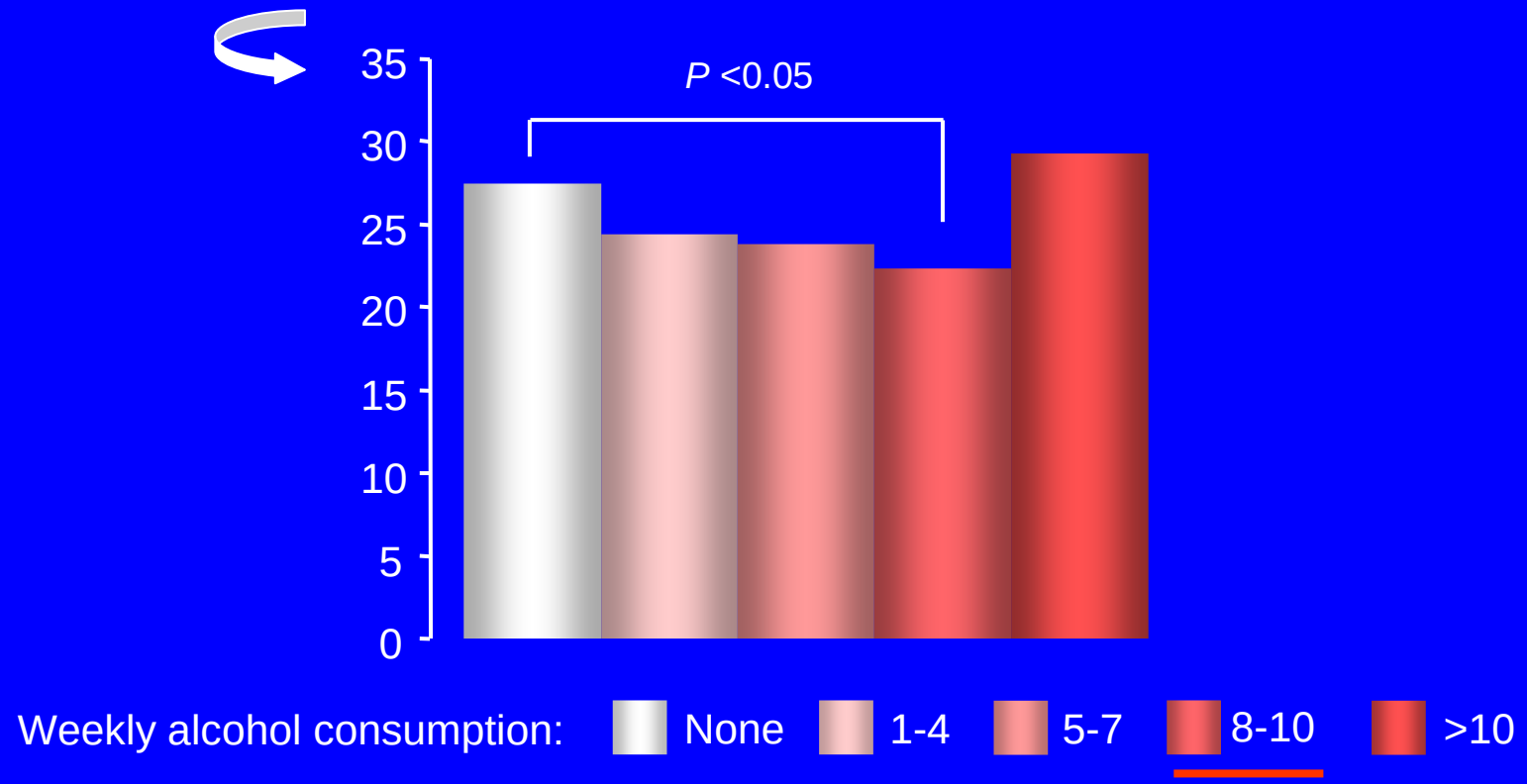
- **2 Units 40% reduction**
- **> 5 Units increased risk**

Truelsen, Stroke (1998) 29: 2467

LIFE study:

primary composite endpoint rate by alcohol consumption

Endpoint rates (1/1000 yrs) according to reported weekly alcohol consumption.



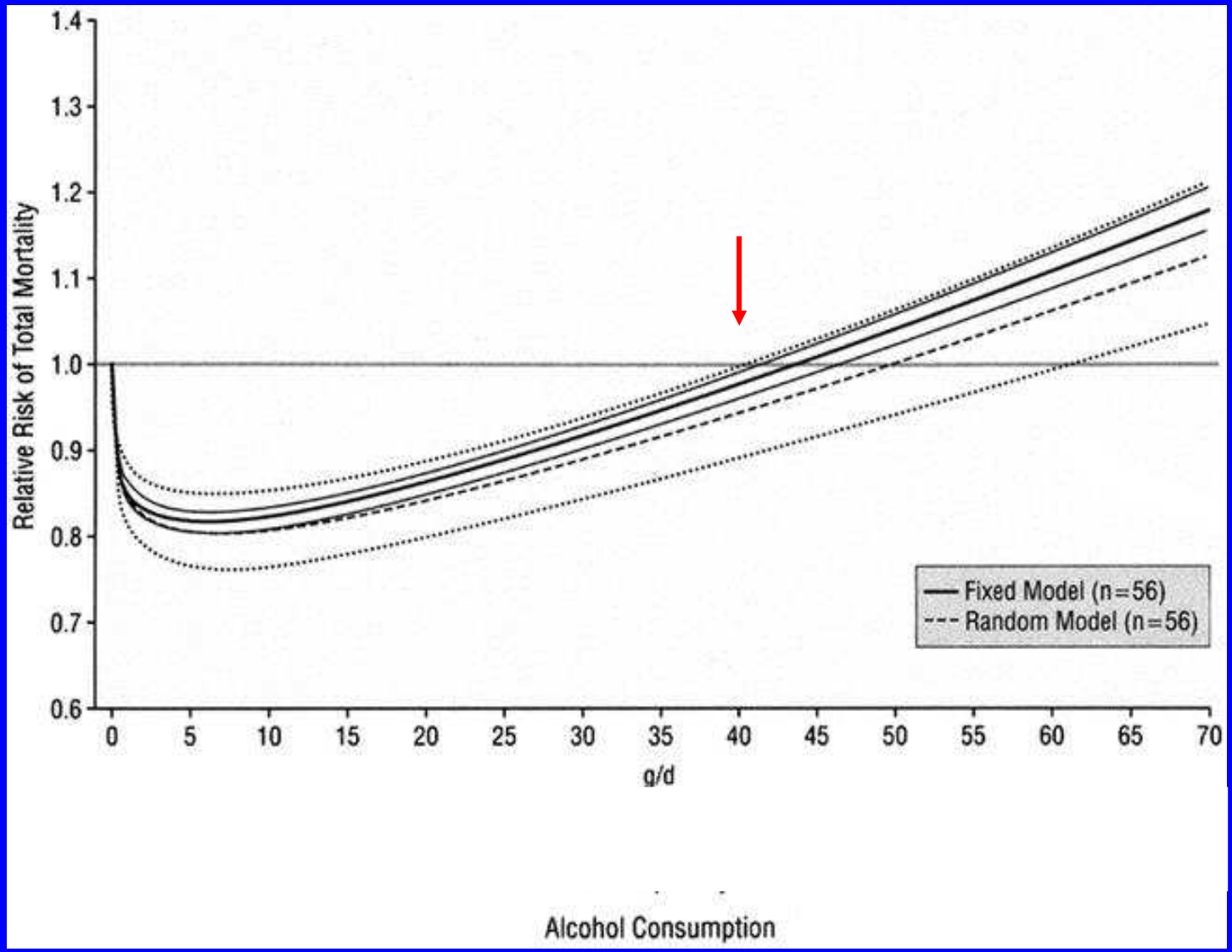
Reims, J Hum Hypertens (2004) 18: 381

Alcohol consumption and all cause mortality

R.Kloner and S.Rezkalla

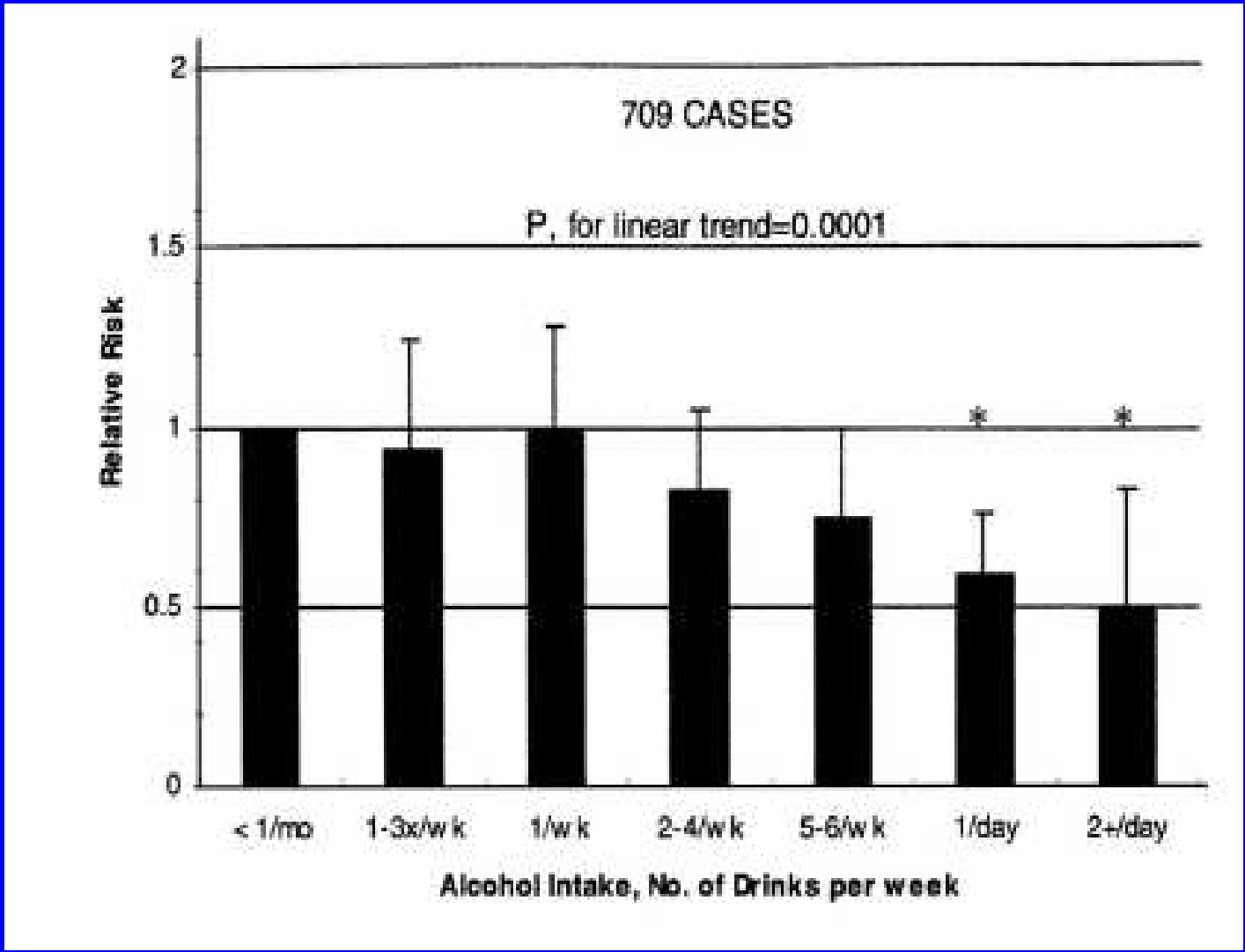
To Drink or Not to Drink? That Is the Question

Circulation (2007) 116:1306



To drink or not to drink?That is the question –

relative risk of nonfatal myocardial infarction



Kloner, Circulation (2007) 116:1306

An alcoholic can be defined as a man who drinks more than his own doctor

A.L.Barach

How often and how much ?

Alcohol Consumption and Risk of Major Coronary Event *(Patients with MI)*

Drinks per day	Days per week						
	Don't drink	Rarely	<1	1or2	3or4	5or6	Daily
Don't drink	1.00						
1 or 2 Units		1.01	0.99	0.93	0.75	0.36	1.20
3 or 4		0.65	0.44	0.91	0.56	0.46	0.87
5 to 8		0.80	1.13	1.00	0.46	0.50	0.83
≥9			0.99	2.62	1.93	2.22	2.40
Former drinker	1.06						

Case Control Study
11511 acute myocardial infarctions
6077 controls

McElduff; BMJ 1997; 314: 1159

Benefits other than cardiovascular ?

Risks and benefits of alcohol

490,000 individuals
prospective 9 year follow-up study

Alcohol use ⇨

lower risk :
cardiovascular death lower by 30-40%

- less diabetes,
- osteoporosis,
- cognitive impairment
- progression of renal disease

Thun, New Engl J Med (1997) 337:1705

Alcohol and the risk to develop type 2 diabetes

Nurses health study
84,941 nurses, follow-up 1980-1996
3,300 new cases of type 2 diabetes

Daily alcohol consumption (g)	number of cases with type 2 diabetes	relative risk
0g	1715	1.0
0.1 - 5.0g	1034	0.78 (0.72-0.84)
5.1 - 10.0g	189	0.56 (0.48-0.65)
>10g	358	0.59 (0.52-0.66)

Hu, New Engl.J.Med. (2001) 345: 790

Moderate alcohol consumption – lower risk of diabetes
(Hoorn study)

- **in 1989 alcohol intake by questionaire in 2393 subjects**

- **non-drinkers vs**
  up to 10g/day vs
  10-30 g/day vs
  > 30g/day

- **lowest mortality → up to 10 g/day**

- **risk to develop diabetes :**
  8.0% in moderate drinkers vs 12.9% for nondrinkers

de Vegt, Diabetes Res Clin Pract (2002) 57: 53

alcohol (1-2 drinks/day)

⇨lower risk of osteoporosis

higher alcohol consumption

⇨ more osteoporosis

Bainbridge, Osteoporosis Int. (2004) 15: 439

Moderate alcohol consumption – less cognitive impairment

- Nurses Health Study

  Stampfer, New Engl J Med (2005) 352:245

- Gruppo Italiano di Pharmacovigilanza nell' Anziano (GIFA)

  Carosella, Pharmacol.Res.(1999) 40: 287

- Hale Project (mediterranean diet and life style changes in the elderly)

  Knoops, JAMA (2004) 292:1433

Wein wirkt stärkend auf den Geisteszustand
den er vorfindet –
er macht die Dummen dümmer
und die Klugen klüger

(wine reinforces the state of mind which is present –
it makes the stupid one even more stupid
but the intelligent one also more intelligent)

J.W.von Goethe
1749 - 1832

IDNT study – alcohol consumption and risk of progression of diabetic nephropathy

	renal endpoint (n=462)	no renal endpoint (n=1253)
alcohol consumption: yes	23 %	28 %
p (univariate analysis)	0.02	

Lewis New Engl J Med (2001) 345:851

Alcohol and progression of renal disease

experimental data

- adriamycin model
  alcohol ⇨ less nephrotic syndrome

Tesar,Alcohol (1995) 30:47

- red wine and alcohol free red wine
  ⇨ less lipid peroxydation in kidney

Araya, Lipids (2003) 38:275

Hypothesis

kidney rich in polyunsaturated fatty acids
vulnerable to damage by reactive oxygen species (ROS)

⇨ benefit from moderate consumption of red wine via more potent antioxidant defenses

 # polyphenols → *ROS scavengers and metal chelators*
 # ethanol → *activity of antioxidant enzymes*

Rodrigo, Free Rad Biol Med (2002) 33:409

Alcohol and progression of renal disease

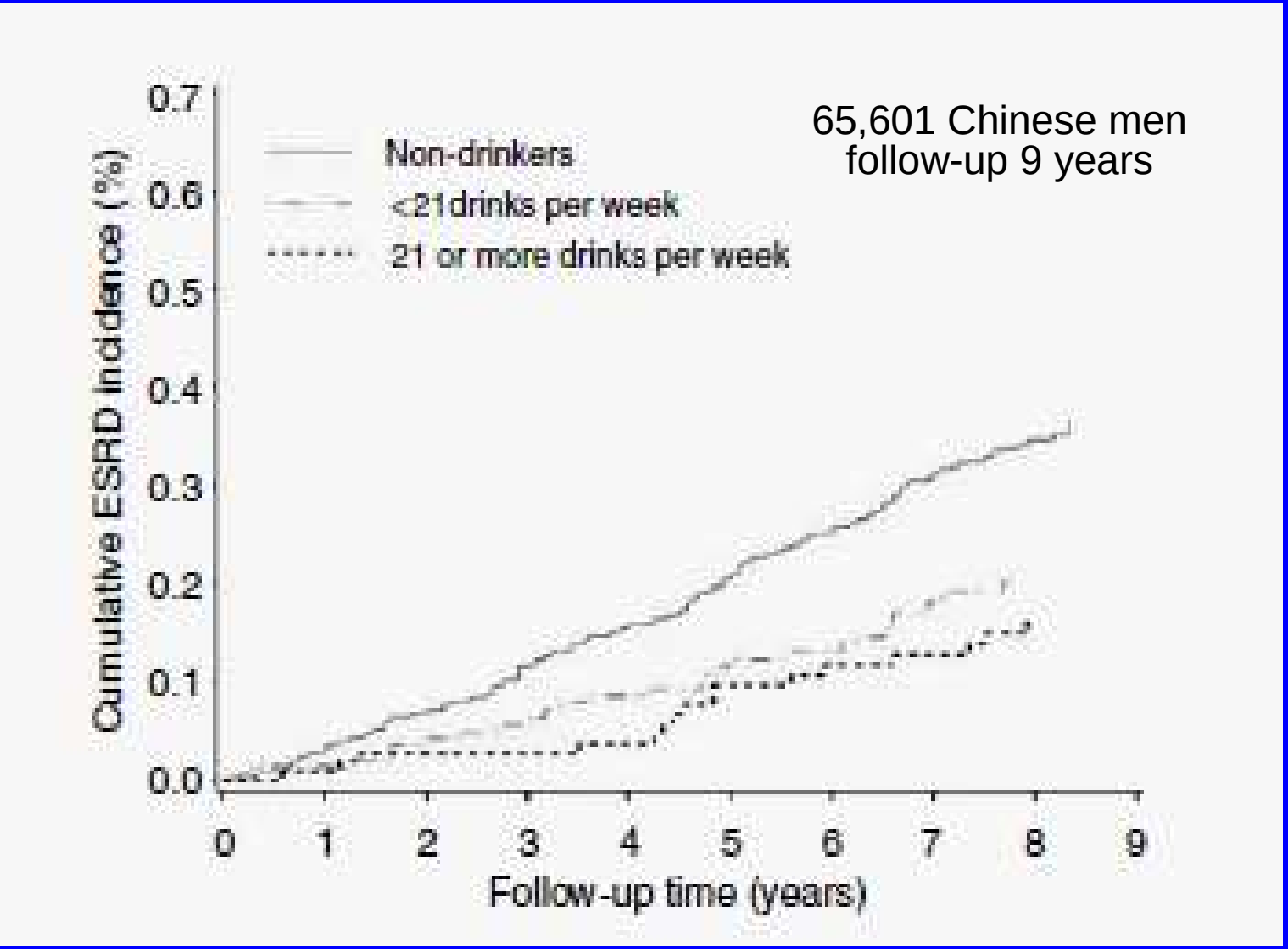
decline of renal function and alcohol
prospective 11 year study in 1658 nurses

	odds ratio > 25 % decrease GFR	
	normotensive	*hypertensive*
0 - 4.9 g/day	*0.98*	*0.98*
5 -14	*0.83*	*0.62*
15 - 60	*0.81*	*0.53*

→ **chronic kidney disease – potential benefit from alcohol**

Knight, NephrolDialTranspl (2003) 18:1549

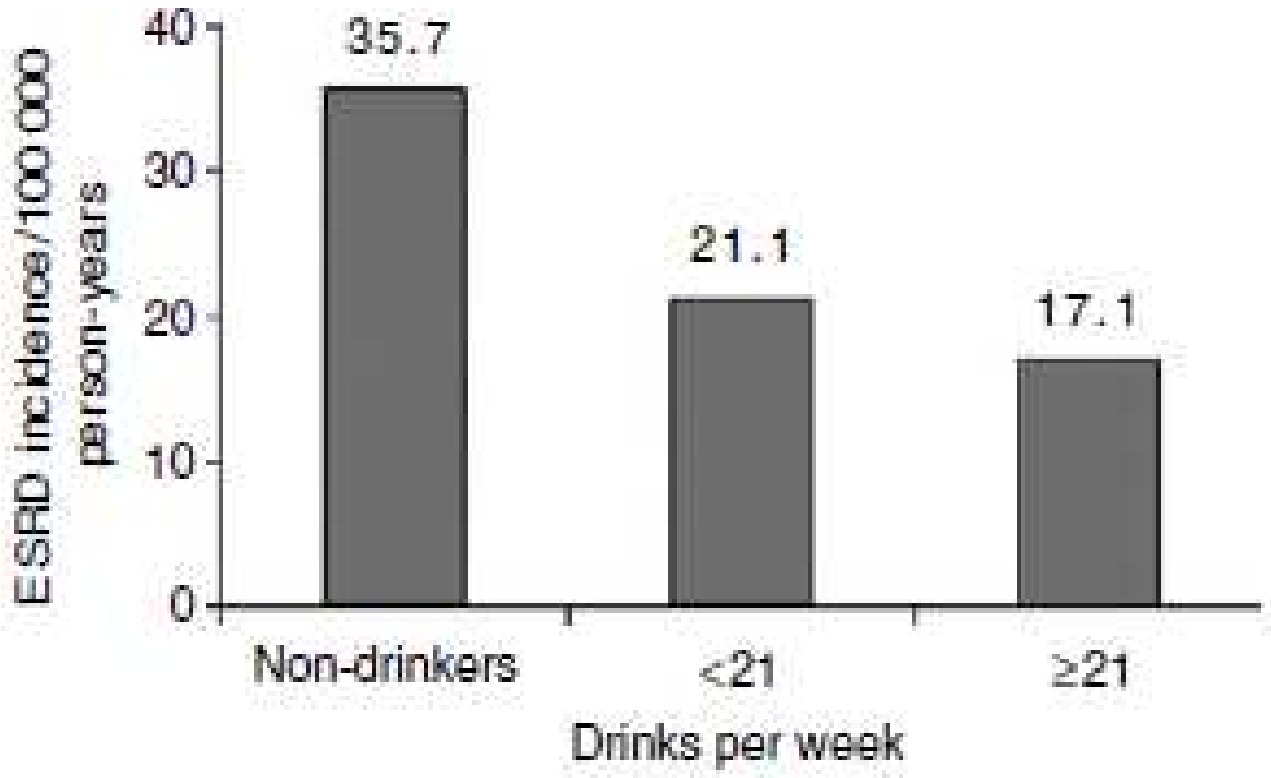
Alcohol consumption –
less endstage renal disease



Reynolds, Kid.Internat.(2008) 73:870

Incidence of all-cause endstage renal disease

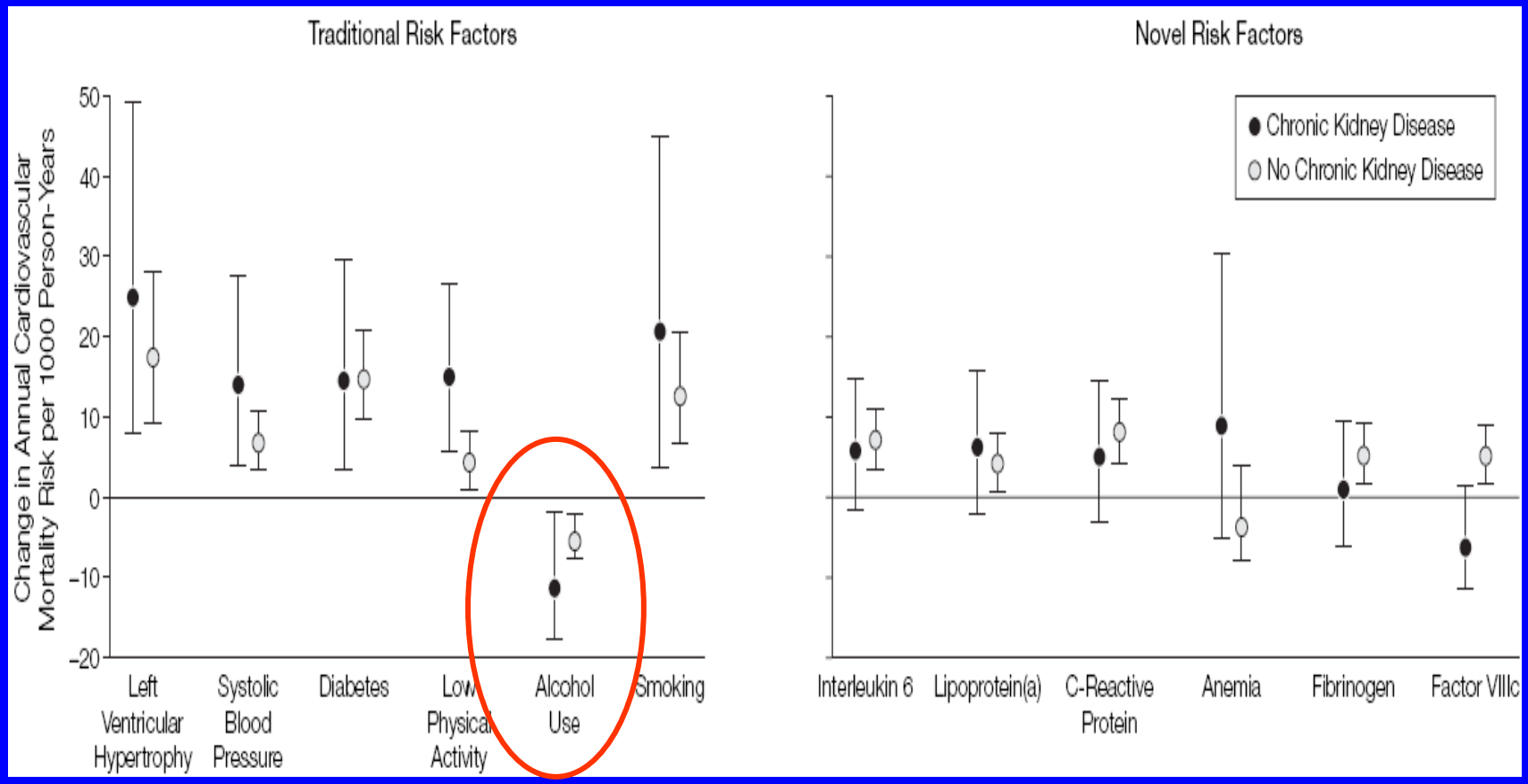
(per 100,000 person years standardized by age)



Reynolds, Kid.Internat.(2008) 73:870

Chronic Kidney Disease –

impact on risk conferred by traditional and novel CV risk factors



Shlipak, JAMA (2005) 293:1737

Alcohol increases blood pressure in Paris Gendarmes

Are all alcoholic beverages similarly beneficial with respect to coronary events?

Copenhagen Heart Study

prospective 12 year study,
6000 males, 7000 females

inverse correlation between alcohol consumption and total mortality

→ <u>only</u> for consumption of wine, not beer and spirits

Gronbaek, Brit Med J (1995) 310: 1165

Gronbaek, Ann Int Med (2000) 19: 411


in Bavaria diuresis sign of virility

Monica study –
Augsburg (Bavaria)

U-shaped relation between alcohol (including beer) consumption and total mortality in a beer drinking population

Keil, Epidemiology (1997) 8: 150

Alcohol in general vs wine:

Inverse correlation alcohol consumption and coronary mortality (r = - 0.39)

better correlation wine consumption and coronary mortality (r = 0.66)

Criqui and Ringel
Does diet or alcohol explain the French paradox?
Lancet (1994) 344: 1719

⇨ alcohol coronary protection
constituents of wine additional coronary protection

alcohol – coronary protection

wine – additional coronary protection

metaanalysis

200,000 subjects

 # beer consumption risk reduction - 20%

 # wine consumption risk reduction - 32%

Di Castelnuovo
Circulation (2002) 105: 2836

confirmed :

Klatsky
Am.J.Epidemiol (2003) 158: 585

Women and alcohol

(Nurses Health Study)

a priori:

Higher blood alcohol levels
Higher risk of mamary carcinoma
Impact on CV risk dependent on age (menopausal state)

→ **prospective study of 45,709 nurses**
alcohol:

- **CV risk increased in young women with low baseline CV risk even at low alcohol intake**
- **small decrease of CV risk only at age ≥ 50 years**

Fuchs , N Engl J Med (1995) 332: 1245

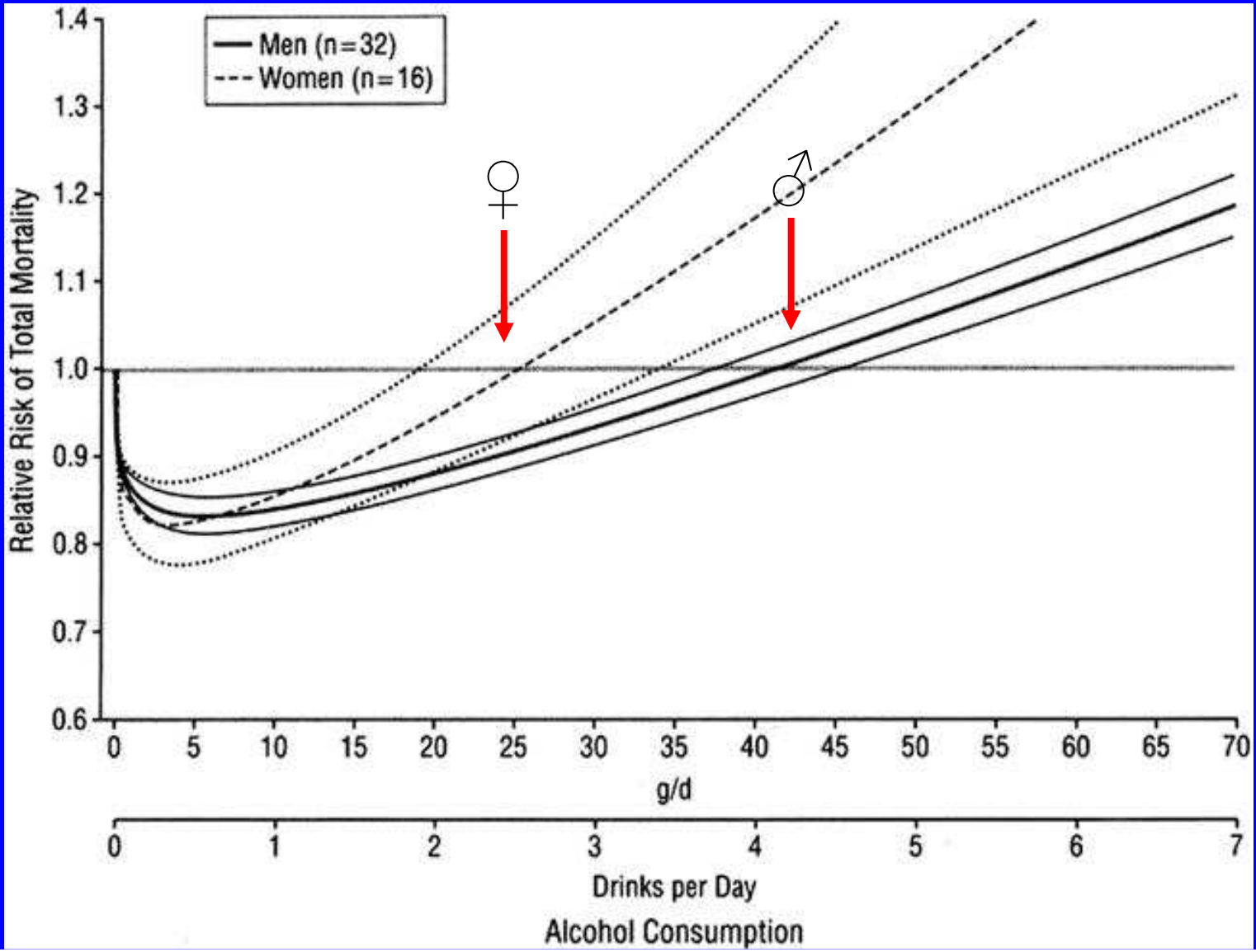
but,

even young (30 y) women at high CV risk (e.g. type 2 diabetes)
26% risk reduction with alcohol (0.1-4.9 g/day)

Salomon, Circulation (2000) 102: 494

Different CV benefit from alcohol in men and women

R.Kloner and S.Rezkalla
To Drink or Not to Drink? That Is the Question
Circulation (2007) 116:1306



Extra benefit in high risk populations ?

Risk reduction – dependent on baseline risk

→ pronounced in smokers, less in non-smokers

	RR		
	0 g alcohol	22-32 g alcohol/day	
smoker	2.8	1.9	Δ 0.9
non-smoker	1	0.7	Δ 0.3

Renaud
Am J Clin Nutr (1992) 55: 1012

History of myocardial infarction and alcohol

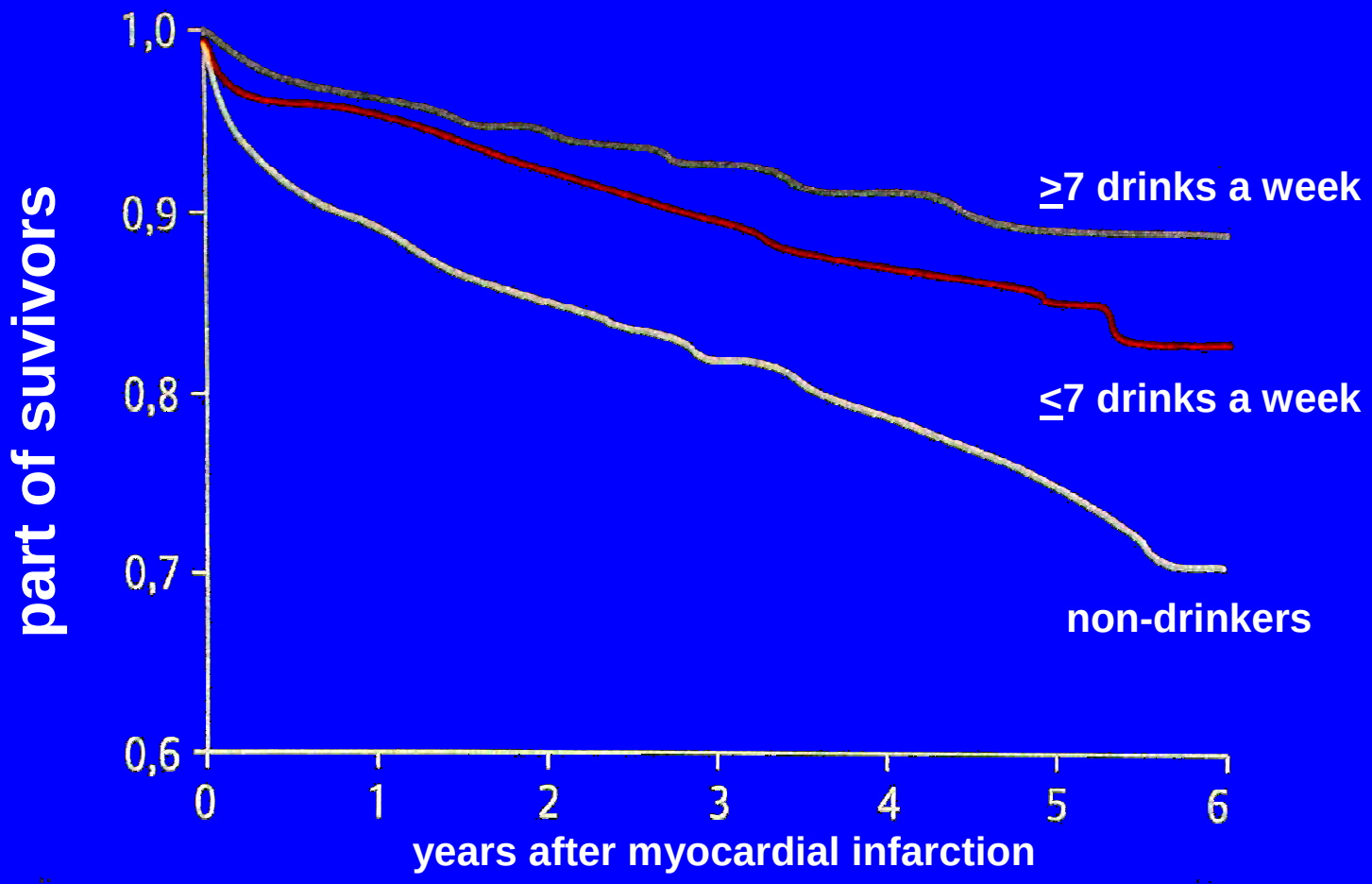
improved survival and less coronary complications with moderate alcohol intake

(no significant difference wine, beer, spirits)

De Lorgeril, Circulation (2002) 106: 1465

Mukamal, JAMA (2001) 285: 1965

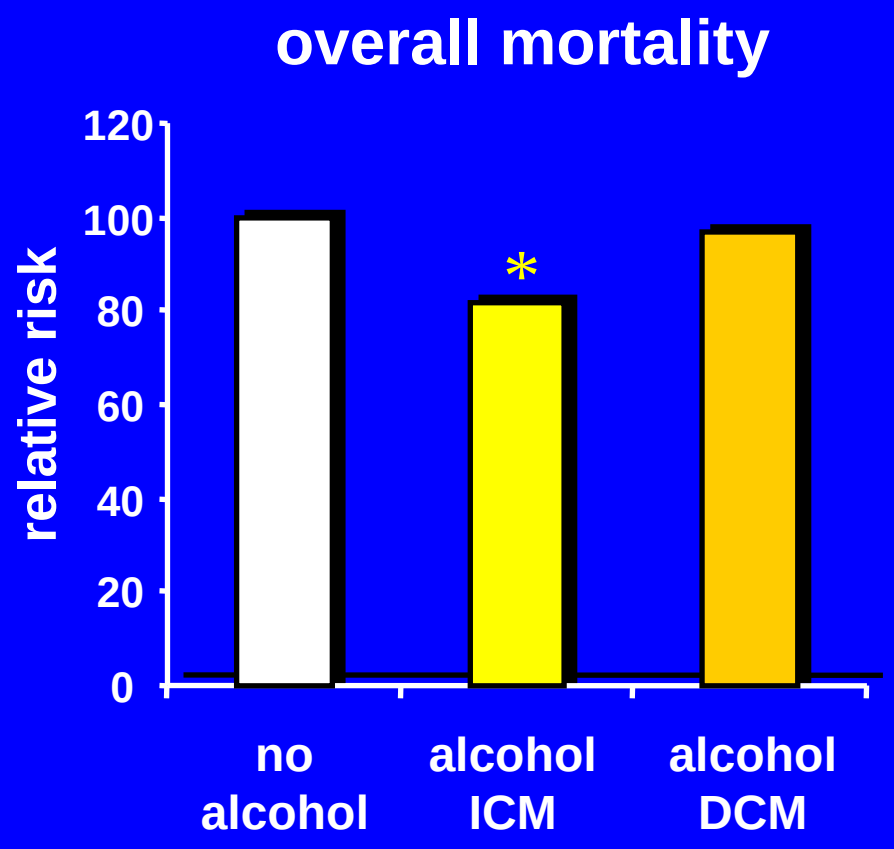
Alcohol consumption following myocardial infarction

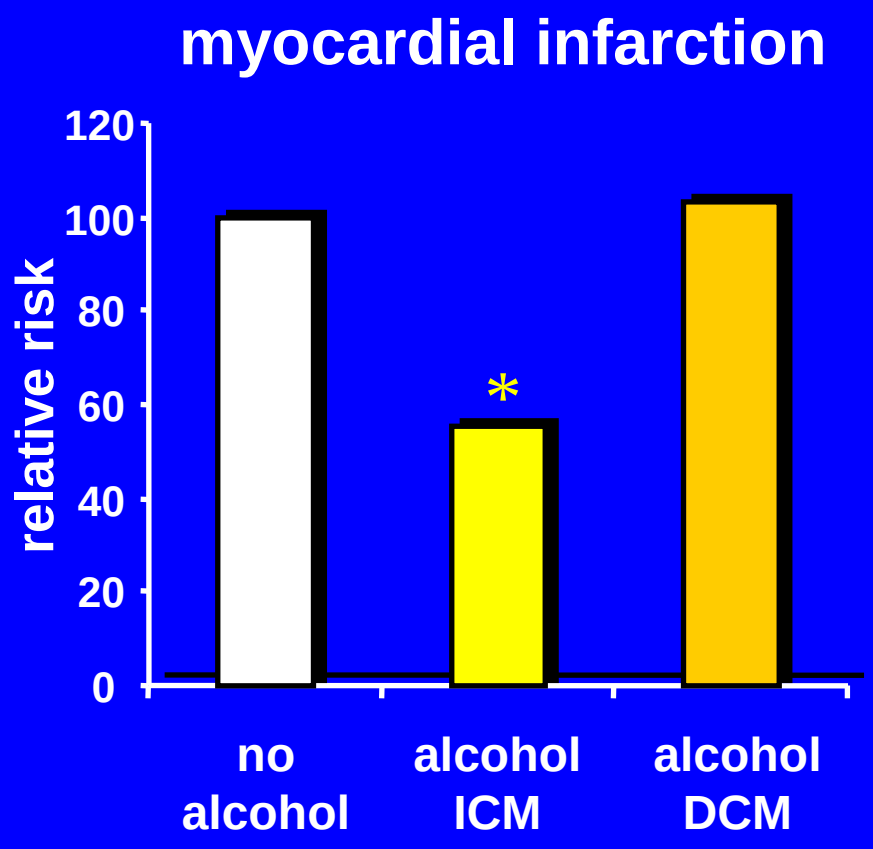


Mukamal, JAMA (2001) 285:1965

Moderate alcohol consumption and mortality in heart failure (EF < 35 %)

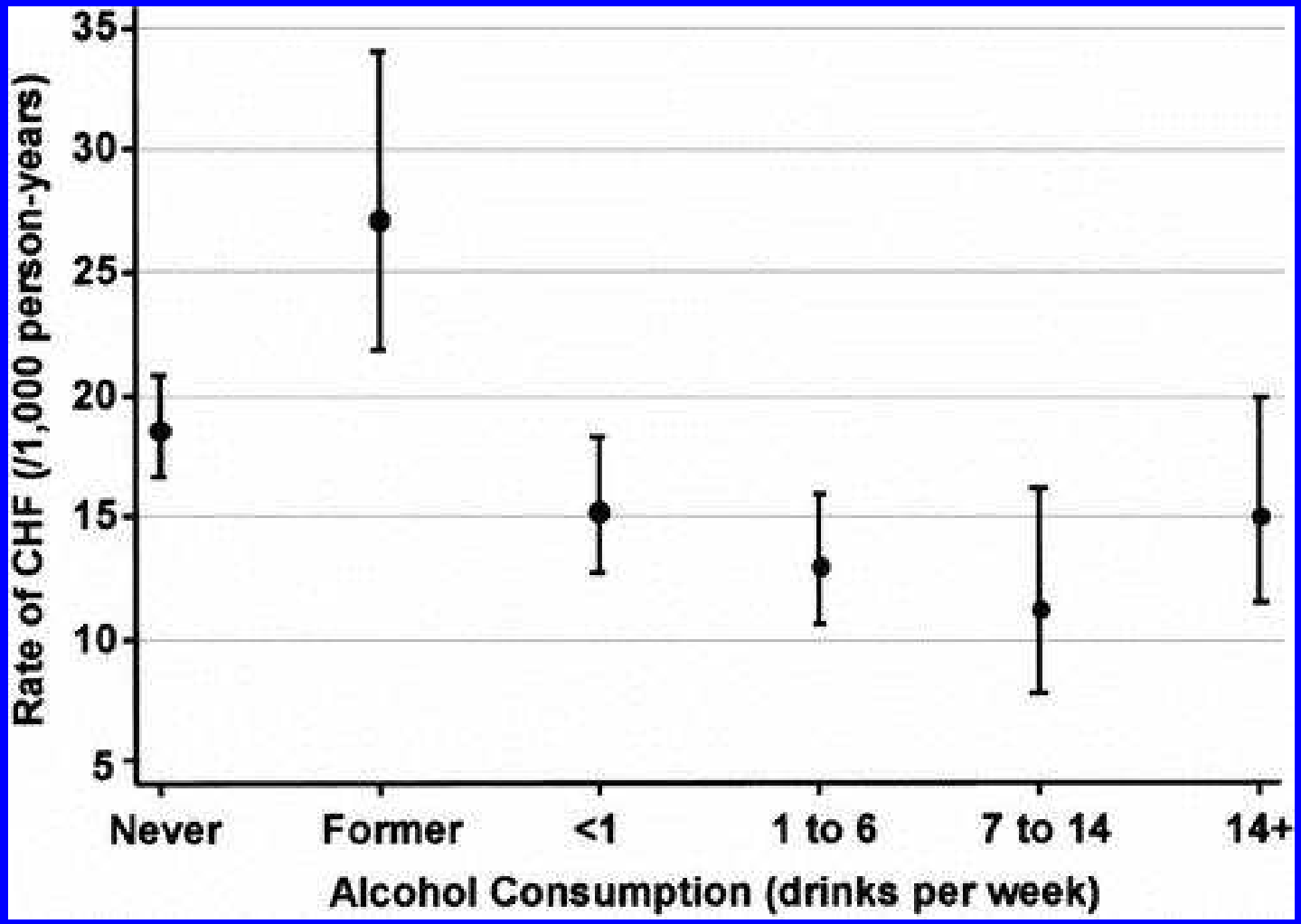
SOLVD, ~1 drink/d





J.Am.Coll.Cardiol. 2000;35:1753-9

Rate of incident heart failure by alcohol consumption
(Cardiovascular Health Study)



Bryson,J.Am.Coll.Cardiol.(2006) 48:305

Alcohol consumption reduces restenosis rate after coronary angioplasty + stent –

the Heidelberg experience

225 consecutive pat. PTCA + stent

> 50 g alcohol / week ⇨ lower :

rate of loss of lumen

1.1 ± 0.79 vs 1.45 ± 0.82 mm , p< 0.002

restenosis within stented segment

33.7 % vs 42.5 % , p<0.002

repeat angioplasty

23.3 % vs 42.5 %

→ **independent predictor**

Niroomand, Heart (2004) 90:1189

How does alcohol / wine achieve cardiovascular (and potentially other) benefit ?

Effects of alcohol potentially improving CV risk

- ***low HDL cholesterol ↑***
- ***hemostasis through reduction of platelet function and fibrinogen levels***
- ***insulin resistance ↓ .....***
- **new aspects :**

  direct protective effect on the ischemic myocardium
  Guiraud, Journal Molecular Cardiology (2004), 36:561

- **increased omega3 fatty acids, important because:**
  De Lorgeril, American Heart Journal (2008) 155:175

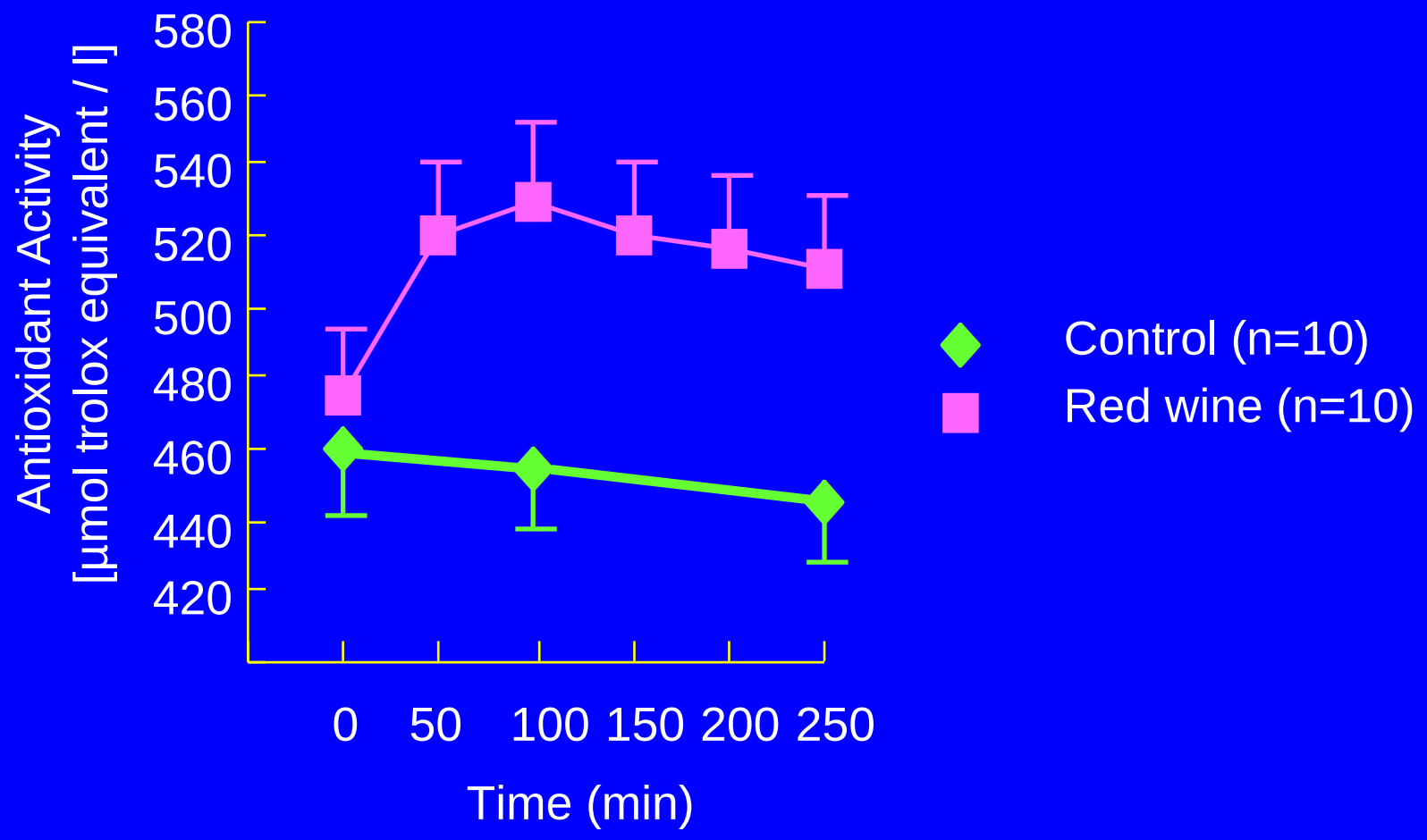
  Omega 3 fatty acids highly effective in secondary prevention
  Gissi, Lancet (1999) 354:457

Cardioprotective actions of alcohol / wine –

new aspects (ctd)

- *lowering of oxygen radicals (ROS)*
- *antithrombotic action*
- *endothelial-dependent vasodilation/NO*
- *antiproliferative effect (antagonism ANG II, PDGF)*

Impact of Red Wine on Serum Antioxidant Activity in Healthy Volunteers



Standard meal alone or with 5.7 ml Bordeaux / kg

Maxwell, Lancet 1994; 344: 193-194

Endothelial effects of wine

Red wine, but not wodka,
increases coronary flow reserve

Shimada, Lancet (1999) 354: 1002

Small amounts of alcohol increase postischemic forearm blood flow in CHD patients specifically
(nitrate as control negative)

Teragawa , Atherosclerosis (2002) 165: 145

Endothelial effects of wine

In isolated human coronary arteries:

red wine (Châteauneuf du Pape),

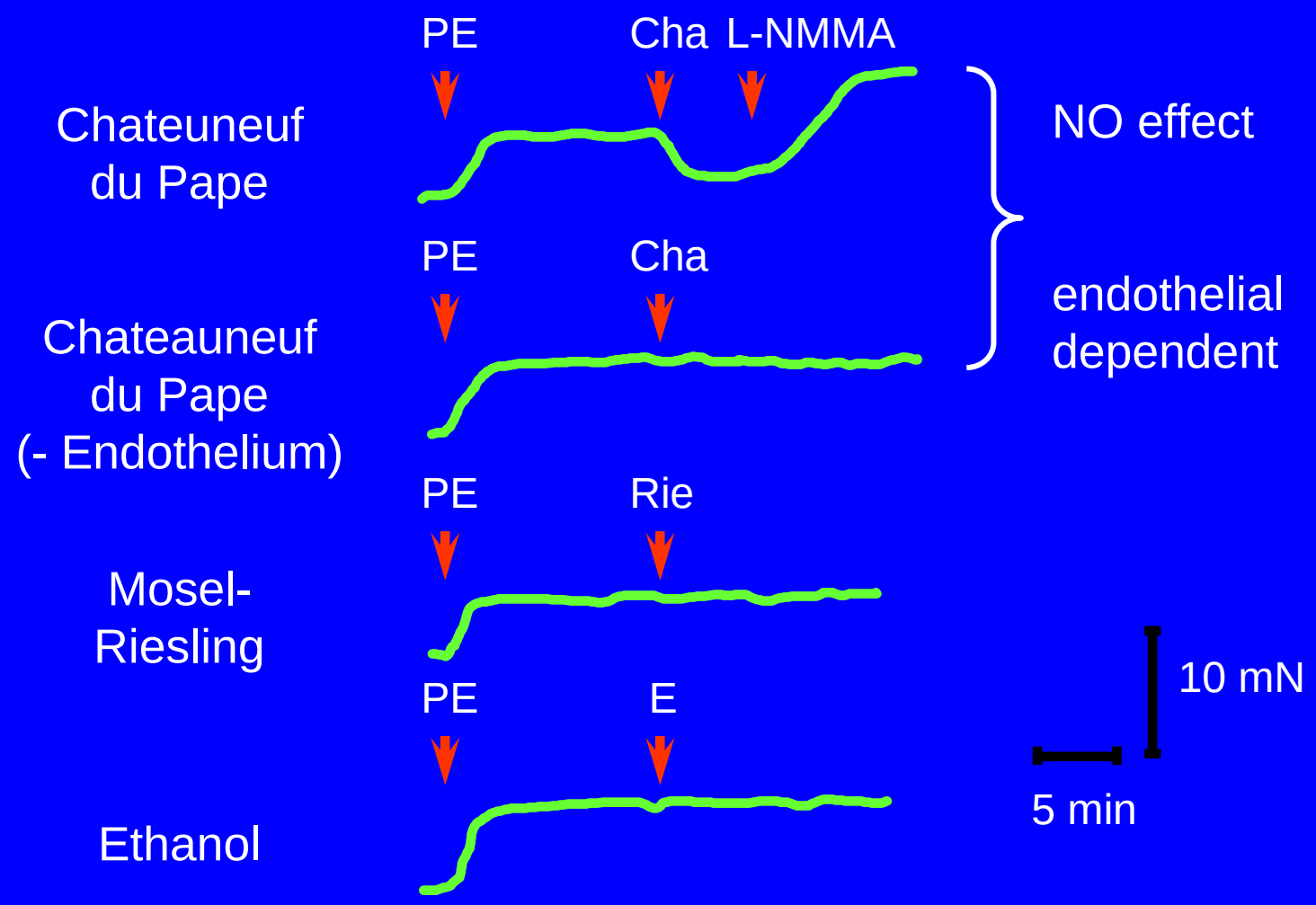
but not white wine (Mosel Riesling) or ethanol

→ ***endothelial cell dependent vasodilatation,***

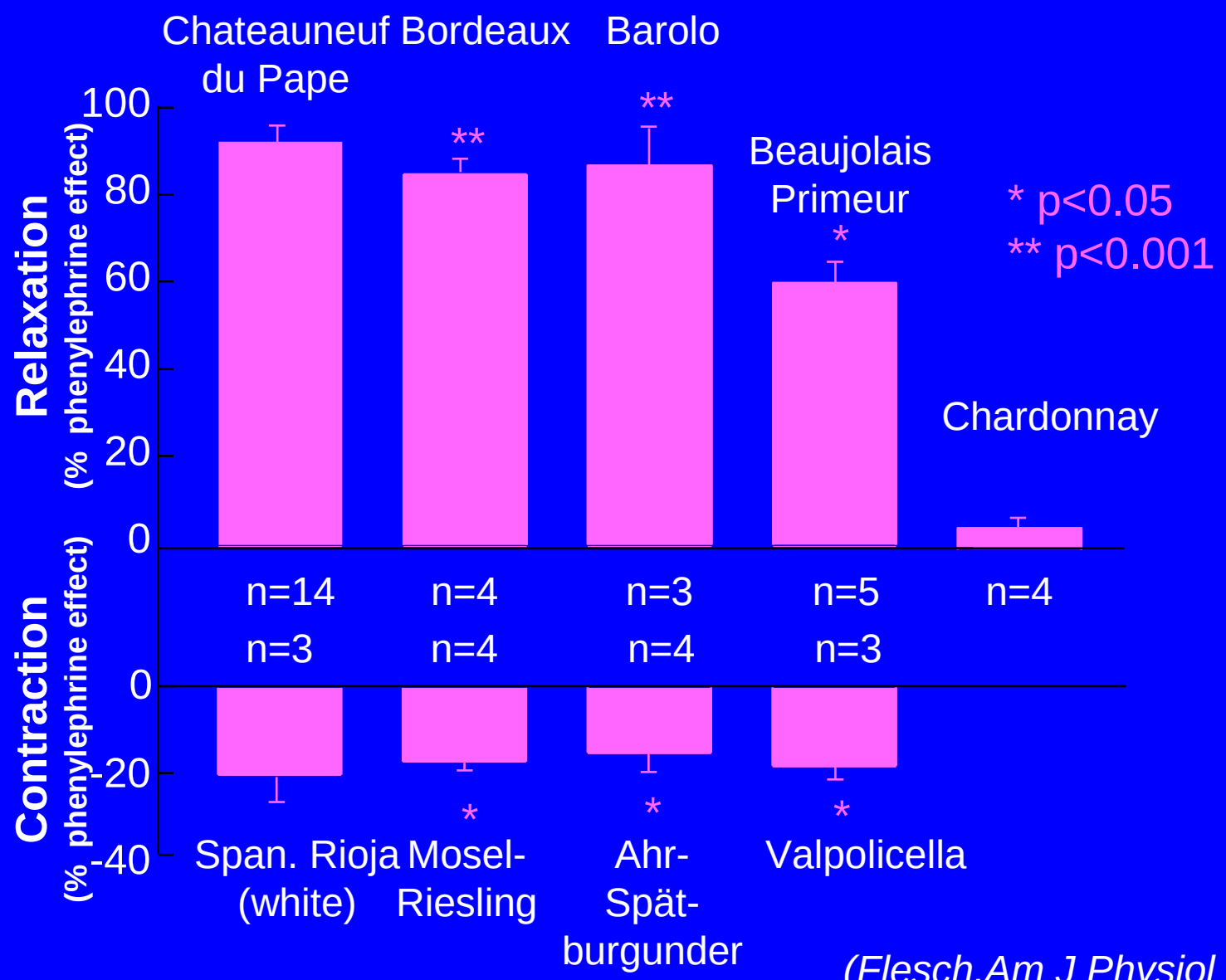
effect NO-dependent (inhibited by L-NMMA)

Flesch, Am J Physiol (1998) 275: H1183

Human Coronary Artery
Effects of Red and White Wine



Vascular Effects of Red and White Wine



(Flesch,Am J Physiol 1998)

Are all red wines created equal?

Barrique matured wines in oak vats vs

wines matured in steel tanks

→ only heavy barrique matured red wines effective,

contain higher concentrations of phenolic substances

in vitro effect reproduced by Tannin and Quercetin

Rosenkranz, FASEB J (2002) 16: 1958

Quantitative Analysis of Polyphenolics in Red Wine vs. White Wine

	Red Wine (*Chateauneuf-du-Pape*)	White Wine (*Riesling Kabinett*)	
cis-Piceid	5,1	0,0	
trans-Resveratrol	1,6	0,0	
Quercetin	0,0	0,0	
Catechin	37,3	5,2	
Epicatechin	12,0	1,6	
Procyanidin B2	9,7	0,0	
Gallic Acid	44,9	0,9	
Cafteric Acid	24,8	37,9	
Coffee Acid	7,0	16,7	
p-Coumaric Acid	23,5	6,8	
Total Polyphenolics	2113	350	[mg/l]

Virgin Mary offering the Christ child red wine

Joos van Cleve
1491-1541

Toasts pointing to wellbeing and health provided by alcohol

german	Prosit !	*to your / our wellbeing*
	zum Wohl !	
english	cheers !	
estonian	terviseks !	
finnish	terveydeksi !	
greek	για μας !	
polish	na zdrowie !	
french	santé !	*to your health*
italian	salute !	
spanish	salud !	
hungarian	egésszégére	

Antiinflammatory effect of moderate consumption of either wine or beer

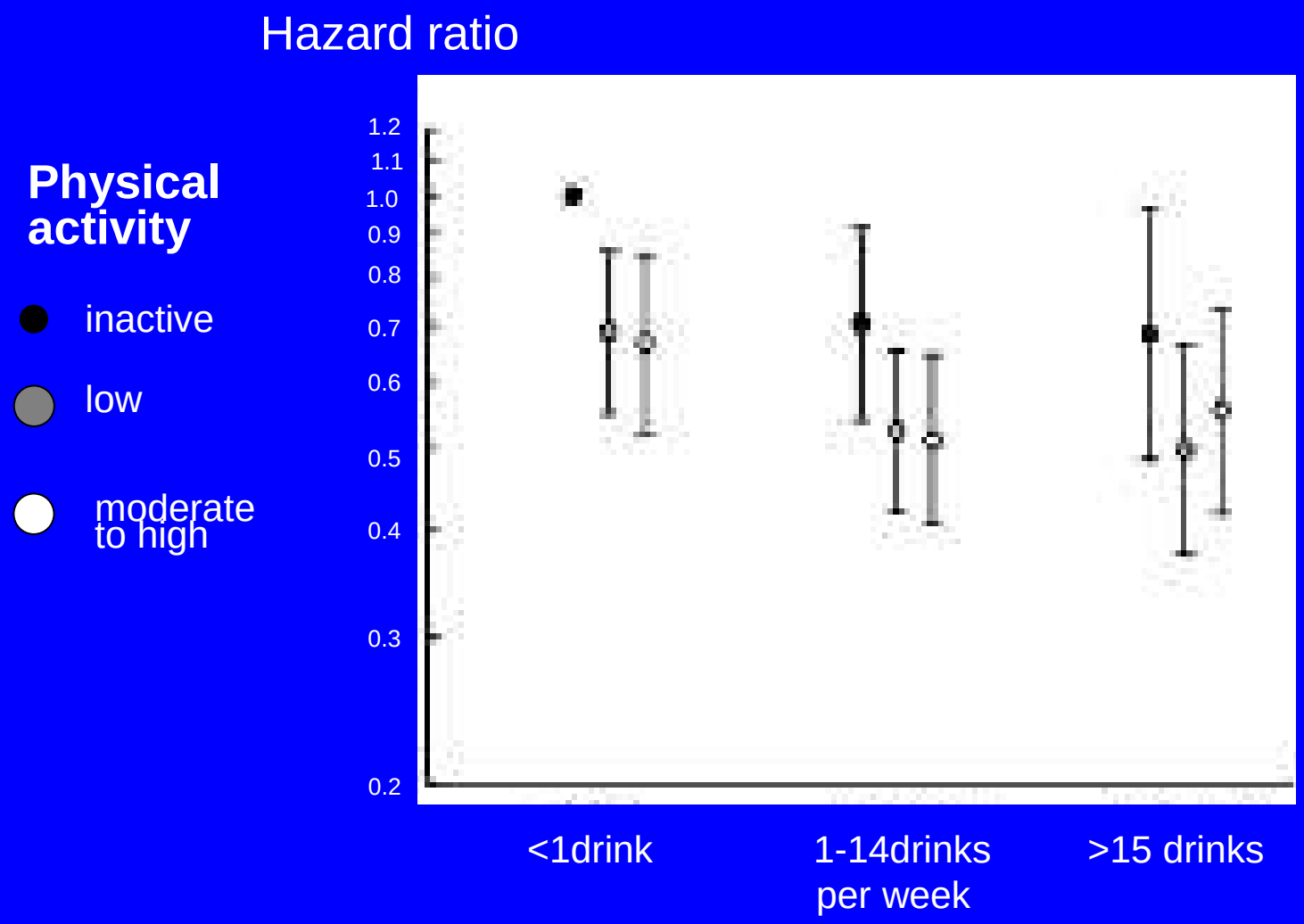
- **MONICA study (Augsburg, Glasgow, Lille)**

- ***self reported moderate (<40g/day) intake of alcohol compared to nondrinking or heavy drinking***

⇨ **lower** ***CRP***
fibrinogen
plasma viscosity
white blood cell count

Imhof, Eur.Heart J (2004) 25:2092

Alcohol consumption effect amplifies that of leisure time physical activity – *hazard of fatal ischemic heart disease*



Østergaard, Europ.J.Cardiol.(2008) 29:204

Adverse health effects of alcohol

- *polyneuritis*
- *cirrhosis / alcohol hepatitis*
- *encephalopathy*
- *cardiomyopathy*
- *malnutrition / vitamin B1 deficiency*

. . .

When I read about the evils of drinking,
I decided to give up reading

Mark Twain
(1835-1910)

Which is the greater miracle ?

Wedding of Kanaan

(John 1:1-12) **–**

conversion of

water into wine

or

Which is the greater miracle ?

Wedding of Kanaan –
conversion of water into wine

or

the Kidney –
converts wine into water

Medical use of alcohol

Hippokrates of Kos (439-377 BC)

Wine *Tranquilizer*
Analgesic
Diuretic
Antidiarrhoic
Treatment of wounds

New Testament (Luke 10; 30-37)

The Good Samaritan

A certain man went down from Jerusalem to Jericho and fell among thieves which stripped him of his raiment and wounded him, and departed, leaving him half dead...
a Samaritan... went to him, and bound up his wounds, pouring in oil and wine...

Luke; 10: 30-37

V. van Gogh

Medical use of alcohol

G. Julius Caesar (100-44 BC)

Troops – *1.5L* ***of*** *wine with meals to prevent gastrointestinal infections*

Claudius Galenus, Pergamon (130-200 AC)

GI disease →
red wine

Internal bleeding →
adstringent (tannin rich) wine

Medical use of wine

Paracelsus
(*Philippus Aurelius Theophastus Bombastus von Hohenhain; 1493-1541***)**

active volatile ingredient of wine (= alcohol) : ”Weingeist” (Spiritus)

derived: spirits, Spiritus, Sprit

effects of wine: dosis facit venenum

Medical use of alcohol

18th century

Dr. Brown (Scotland)

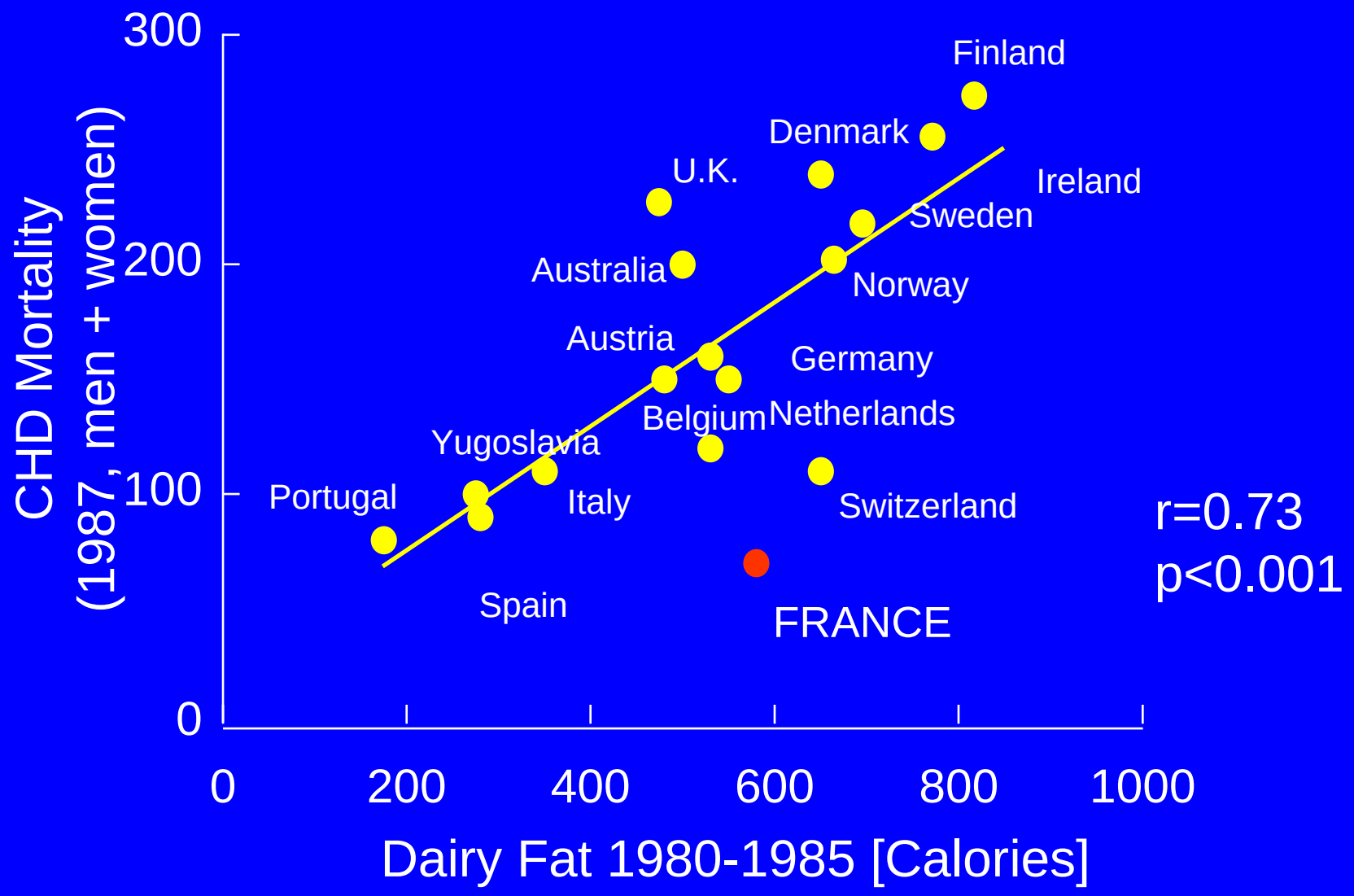
⇨ **popular cure for 32 indications**

within 4 hours:

- *2-3 bottles of red wine*
- *half a bottle of Champagne*
- *a quart of Cognac*

⇨ **exceeding the drinking capacity of all but the Scots**

French Paradox for Coronary Artery Disease



r=0.73
p<0.001

Renaud, Lancet (1992) 339: 1523

”French paradox”

- in all countries tight correlation between consumption of animal fat and coronary mortality, <u>except</u>

- in France and Switzerland:
  coronary mortality <u>low</u> despite high consumption of animal fat

Renaud , Lancet (1992) 339: 1523

De Lorgeril, Circulation (2002) 106: 1465

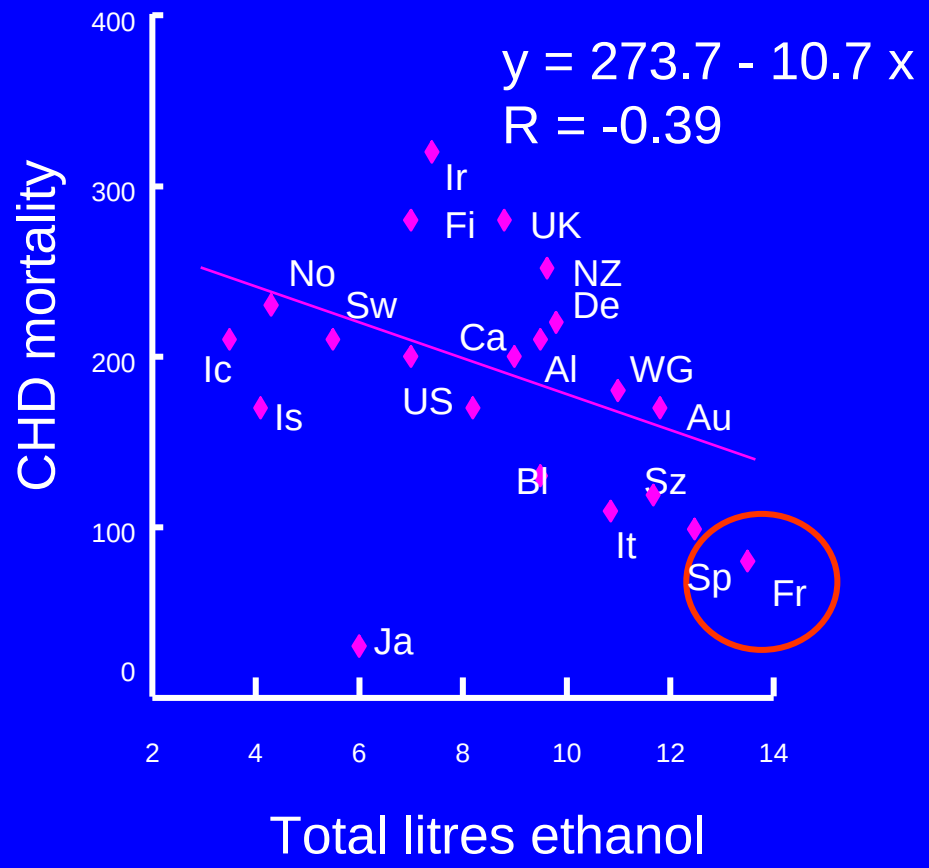
<u>Hypothesis</u>

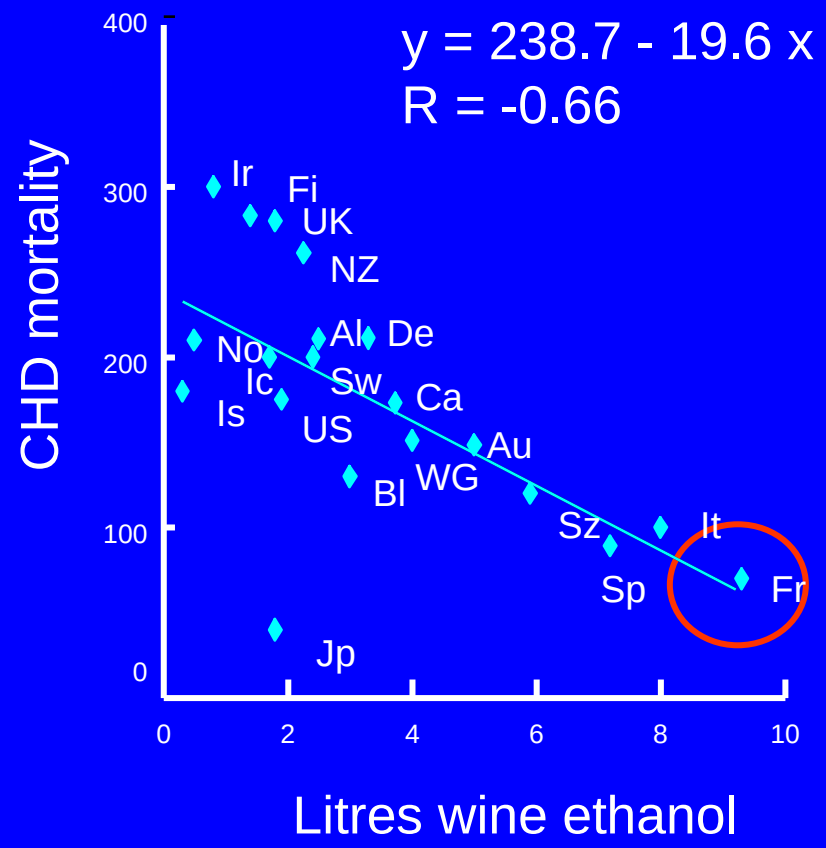
Wine antagonises adverse effects of animal fat

Alcohol and cardiovascular mortality

→ **60 retrospective and prospective epidemiological studies** *(pubmed)*

Ethanol and wine ethanol consumption - relation to coronary heart disease mortality





Criqui and Ringel, Lancet (1994) 344: 1719-1723

Health professional follow up study

50,000 men

→ 5-30 g alcohol per day
reduction of CV mortality by ~ 25%

Rinn et al.
Wine, beer and spirits.
Are they really horses of a different colour?
Circulation (2002) 105: 2806

Alcohol consumption and cardiovascular death in hypertensive men –

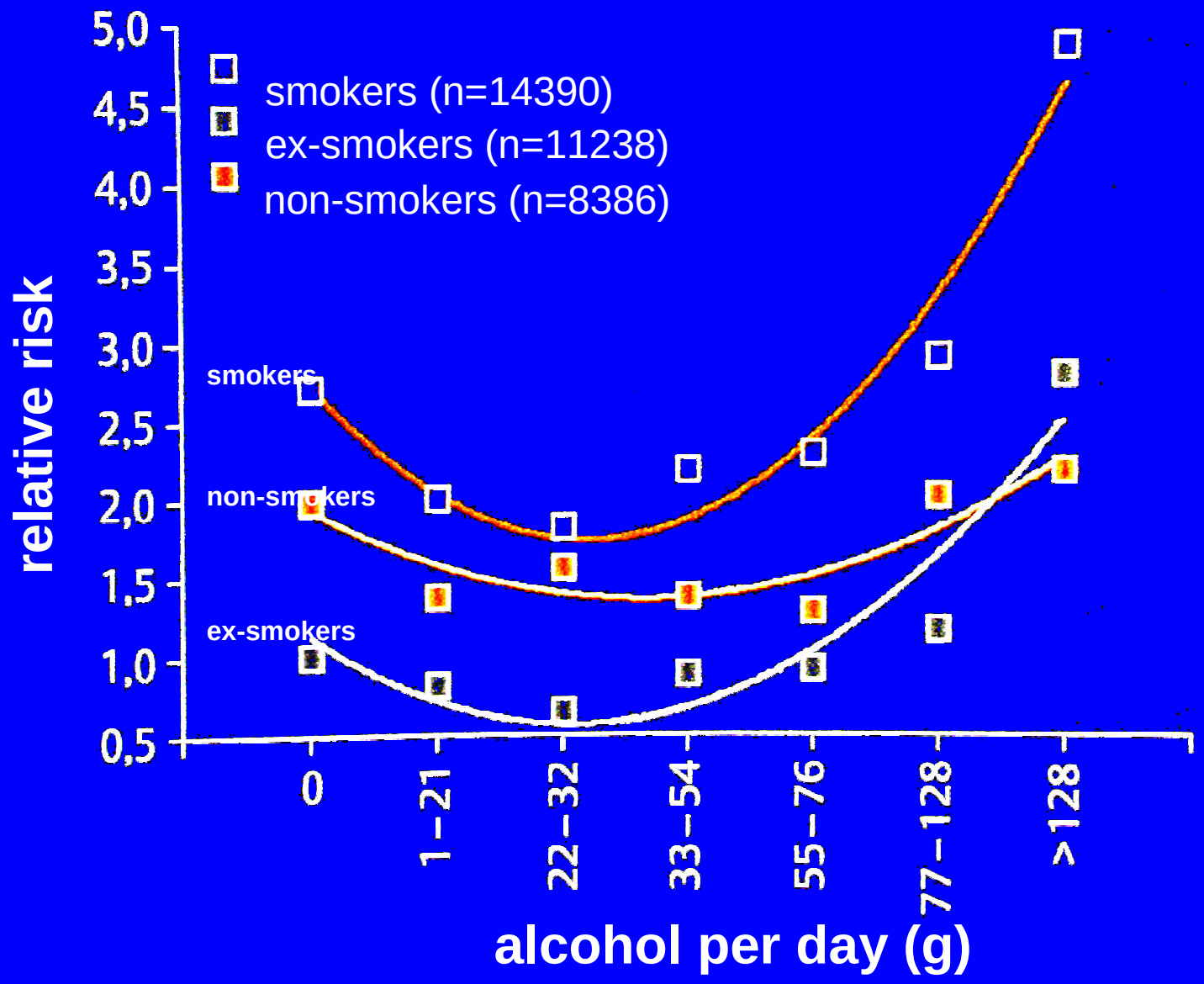
Physicians' health study

14,125 / 88,882 hypertensives

	relative risk alcohol consumption			
	never	monthly	weekly	daily
CV mortality	1.0	0.82	0.64	0.56
Overall mortality	1.0	0.86	0.72	0.73

Malinski,Arch.Int.Med (2004)164:623

Relative risk of death in Eastern France



Renaud, Am J Clin Nutr (1992) 55: 1012

Why U-shaped relationship?

Study 34014 young men in France 1978-1993

high alcohol intake →

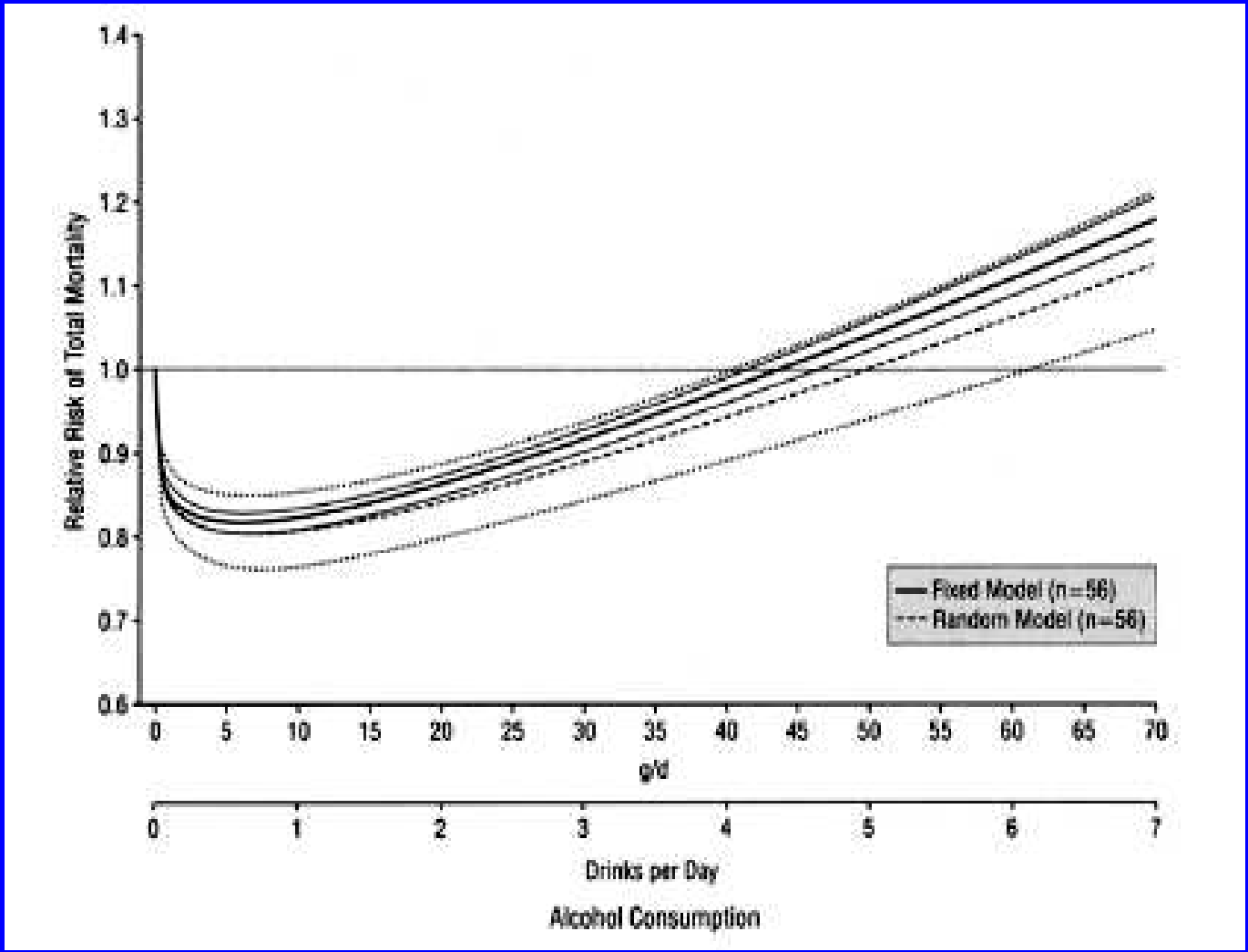
cirrhosis
colorectal, gastroesophageal carcinoma
traffic accidents

<u>but</u>,

for alcohol consumption > 50 g/day ("alcoholic")
also increased CV risk

Renaud, Am J Clin Nutr (1992) 55: 1012

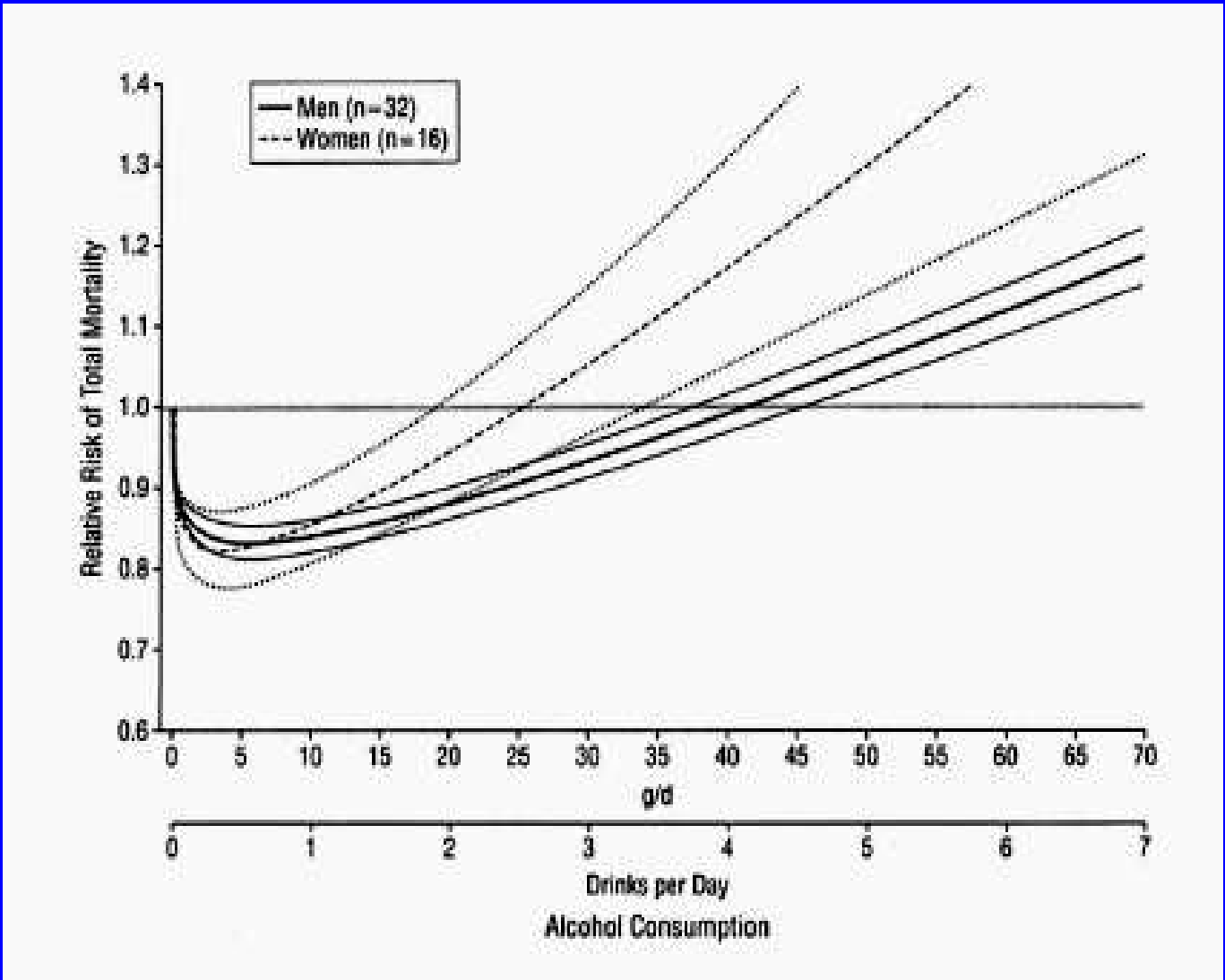
To drink or not to drink?That is the question – relative risk of total mortality



Kloner, Circulation (2007) 116:1306

To drink or not to drink?That is the question –

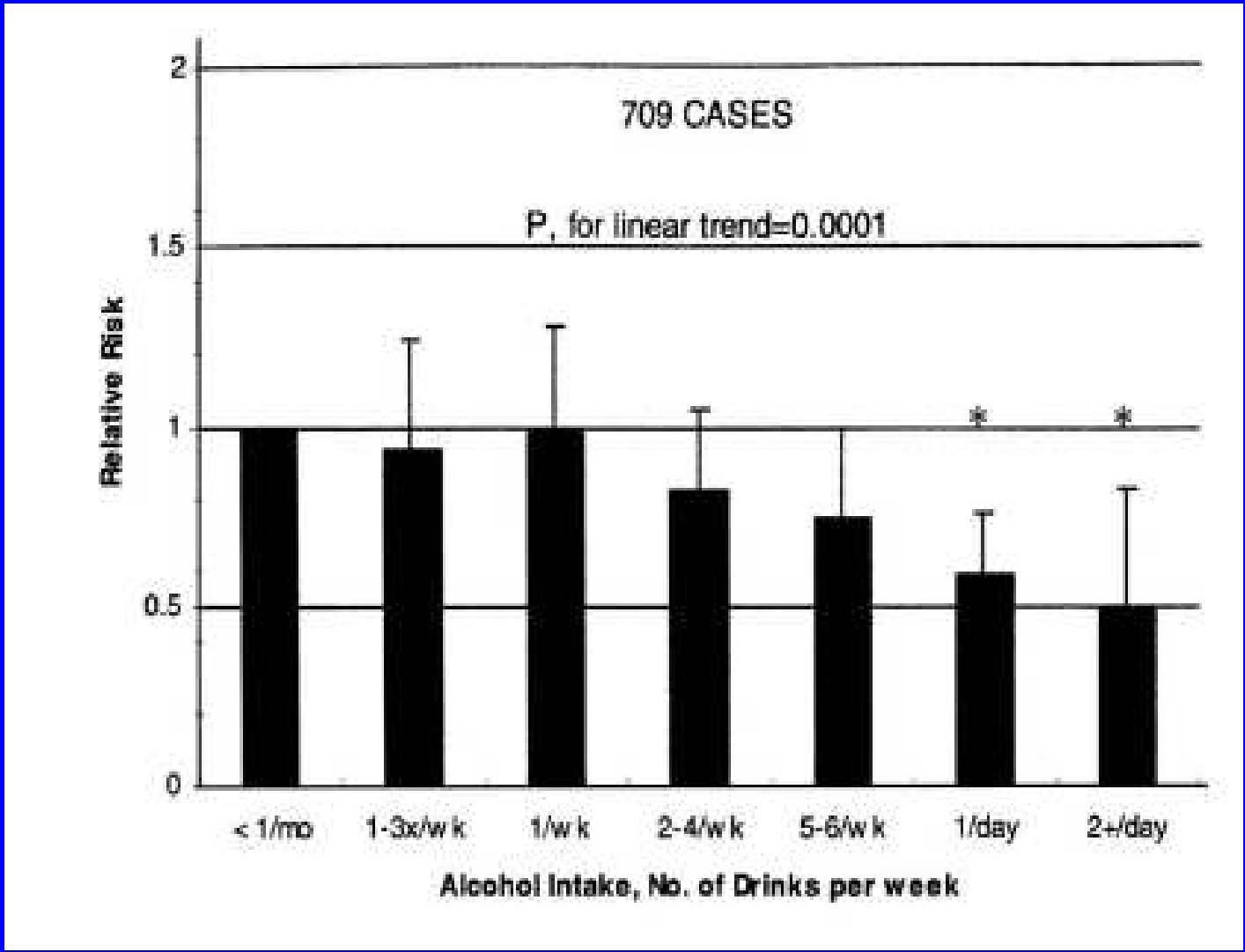
relative risk of total mortality males vs females



Kloner, Circulation (2007) 116:1306

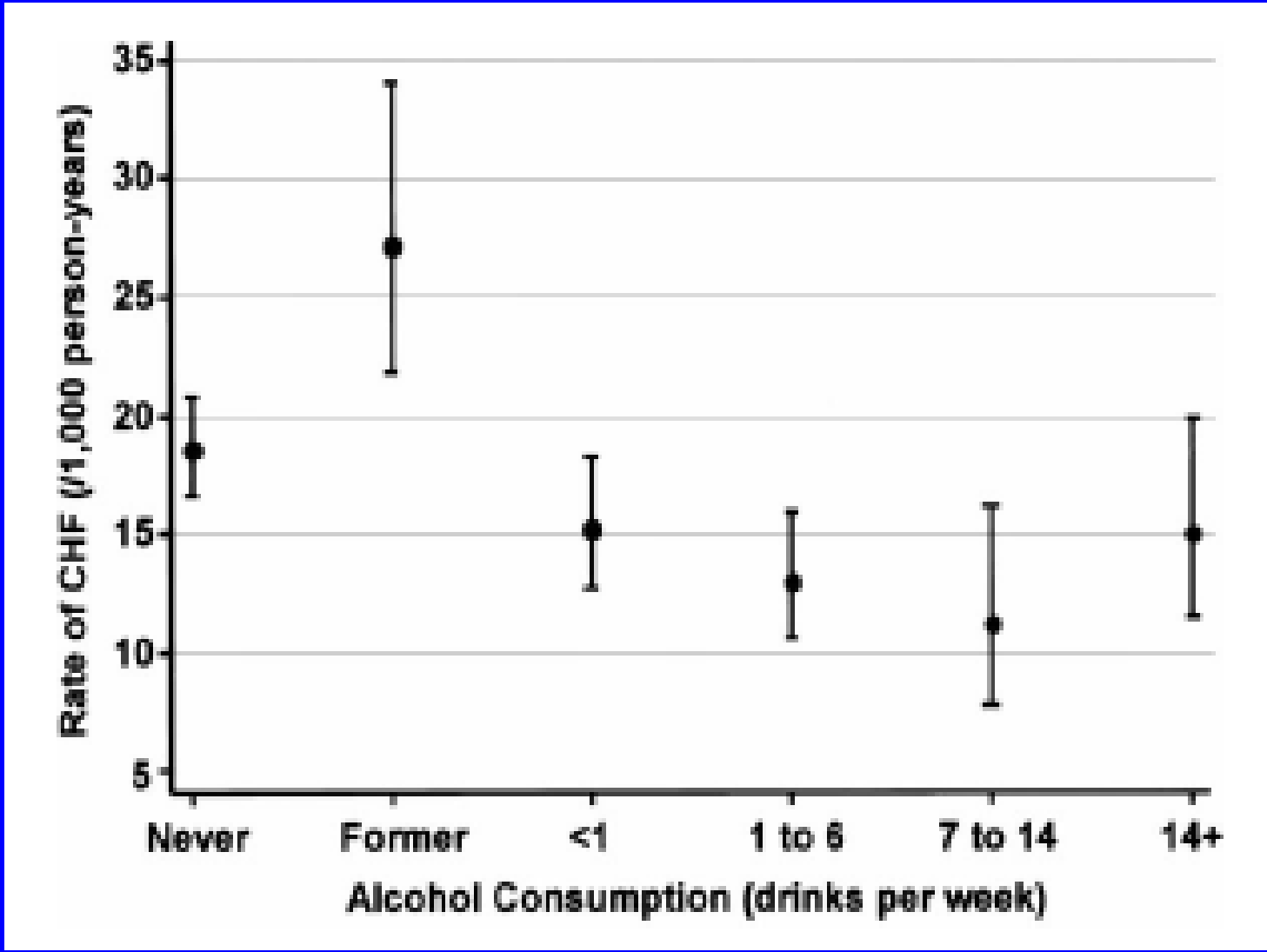
To drink or not to drink?That is the question –

relative risk of nonfatal myocardial infarction



Kloner, Circulation (2007) 116:1306

To drink or not to drink?That is the question – *relative risk of congestive heart failure*



Kloner, Circulation (2007) 116:1306

An alcoholic can be defined as a man who drinks more than his own doctor

A.L.Barach

Alcohol Consumption and Risk of Major Coronary Event

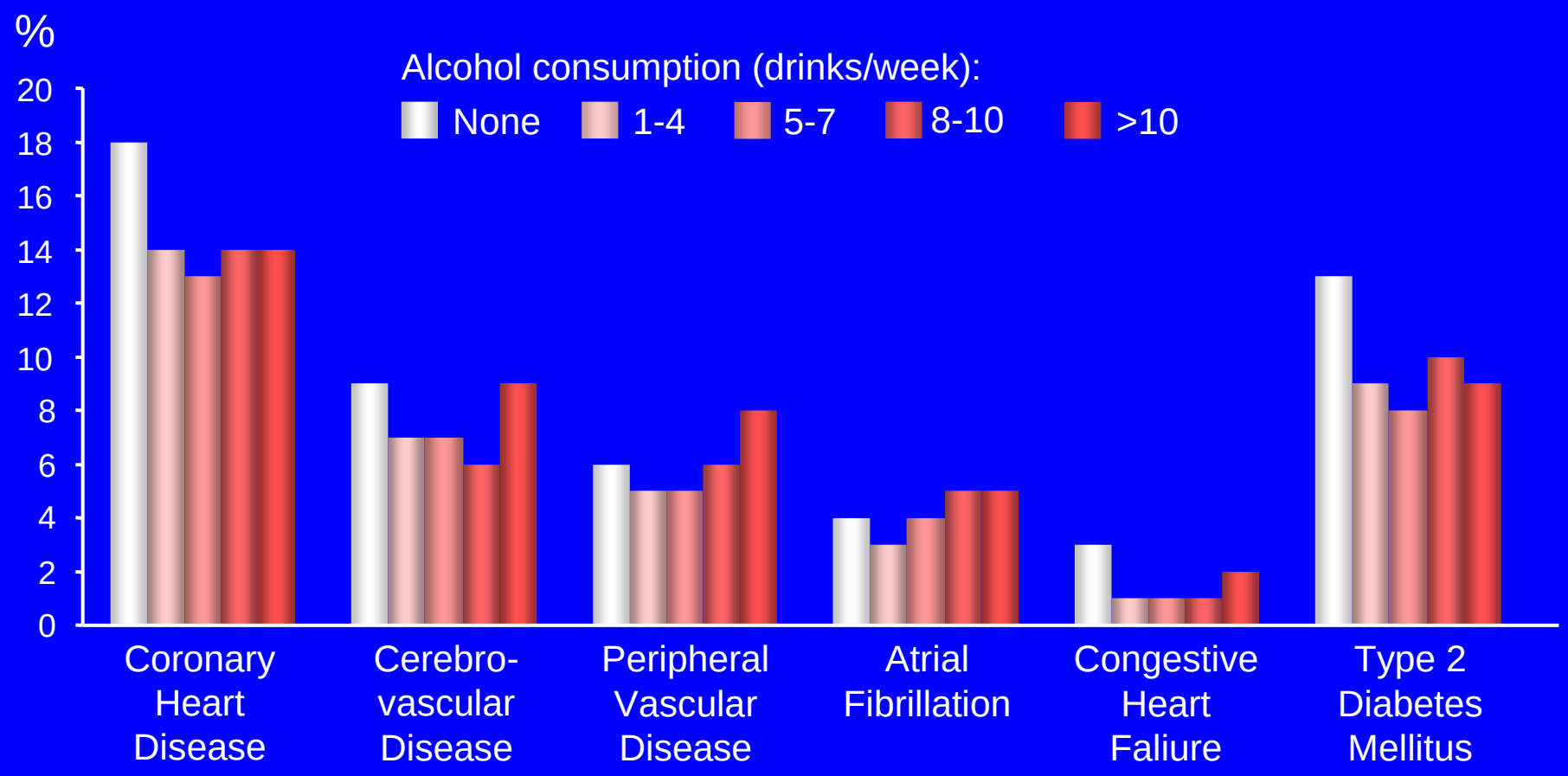
Drinks per day	Days per week						
	Don't drink	Rarely	<1	1or2	3or4	5or6	Daily
Don't drink	1.00						
1 or 2		1.01	0.99	0.93	0.75	0.36	1.20
3 or 4		0.65	0.44	0.91	0.56	0.46	0.87
5 to 8		0.80	1.13	1.00	0.46	0.50	0.83
≥9				2.62	1.93	2.22	2.40
Former drinker	1.06						

Case Control Study
11511 acute myocardial infarctions
6077 controls

McElduff; BMJ 1997; 314: 1159

LIFE study:

medical history by alcohol consumption

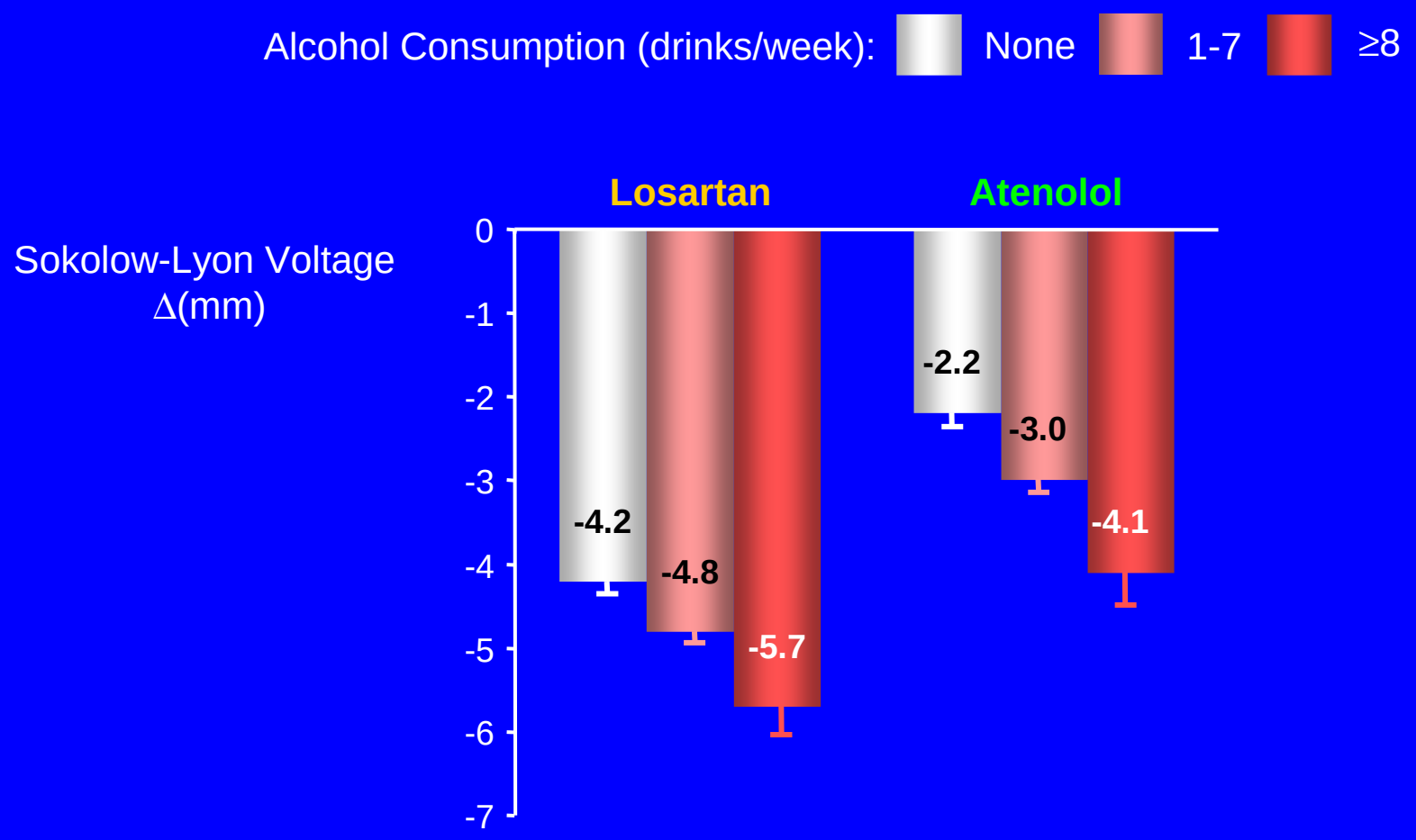


Reims, J Hum Hypertens (2004) 18: 381

LIFE study:

regression of left ventricular hypertrophy (ECG)

effect of treatment (Losartan or Atenolol) and of alcohol consumption

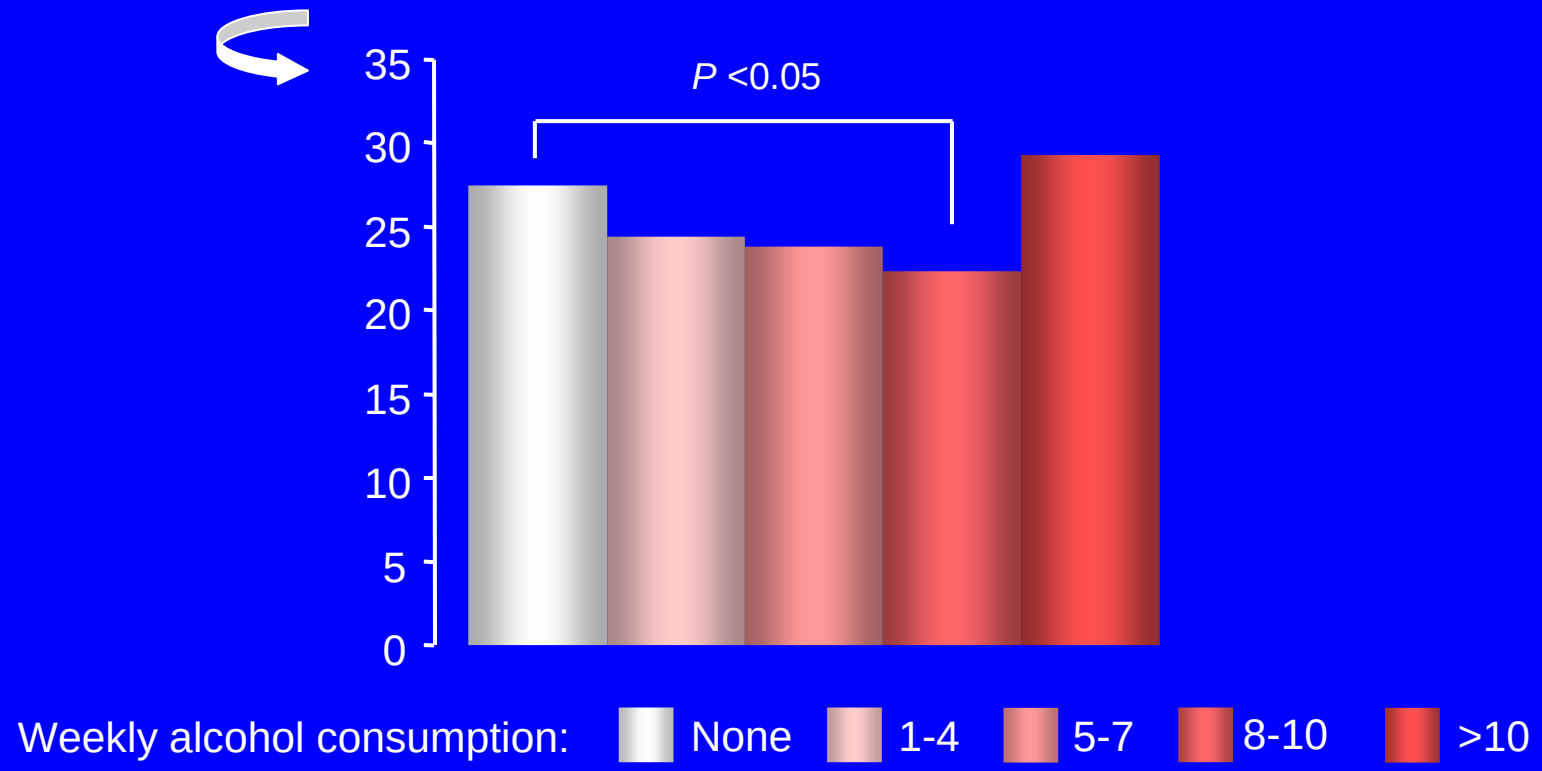


Reims. *J Hum Hypertens* (2004) 18:381

LIFE study:

primary composite endpoint rate by alcohol consumption

Endpoint rates (1/1000 yrs) according to reported weekly alcohol consumption.



Reims, J Hum Hypertens (2004) 18: 381

Copenhagen Heart Study

U-shaped relation between units of alcohol/day (30 g) and stroke

- **2 U** → *reduction by 40%*
- **> 5 U** → *progressive increase*

Truelsen, Stroke (1998) 29: 2467

Alcohol and the risk to develop type 2 diabetes

Nurses health study
84,941 nurses, follow-up 1980-1996
3,300 new cases of type 2 diabetes

Daily alcohol consumption	number of cases with type 2 diabetes	relative risk
0 g	1715	1.0
0.1 - 5.0 g	1034	0.78 (0.72-0.84)
5.1 - 10.0 g	189	0.56 (0.48-0.65)
>10 g	358	0.59 (0.52-0.66)

Hu, NEJM (2001) 345: 790

Moderate alcohol consumption – lower risk of diabetes
(Hoorn study)

- **in 1989 alcohol intake by questionaire in 2393 subjects**
- **non-drinkers vs**
  up to 10g/day vs
  10-30 g/day vs
  > 30g/day
- **lowest mortality → up to 10 g/day**
- **lowest risk to develop diabetes → up to 10 g/day**
  (8.0% vs 12.9% for nondrinkers)

de Vegt, Diabetes Res Clin Pract (2002) 57: 53

alcohol (1-2 drinks/day)

⇨*lower risk of osteoporosis*

higher alcohol consumption

⇨ *more osteoporosis*

Bainbridge, Osteoporosis Int. (2004) 15: 439

Moderate alcohol consumption – less cognitive impairment

- Nurses Health Study
  Stampfer, New Engl J Med (2005) 352:245
- Gruppo Italiano di Pharmacovigilanza nell' Anziano (GIFA)
  Carosella, Pharmacol.Res.(1999) 40: 287
- Hale Project
  (mediterranean diet and life style changes in the elderly)
  Knoops, JAMA (2004) 292:1433

Wein wirkt stärkend auf den Geisteszustand
den er vorfindet –
er macht die Dummen dümmer
und die Klugen klüger

(wine reinforces the state of mind which is present –
it makes the stupid one even more stupid
but the intelligent one also more intelligent)

J.W.von Goethe
1749 - 1832

IDNT study –
alcohol consumption and risk of progressive diabetic nephropathy

	renal endpoint (n=462)	no renal endpoint (n=1253)
alcohol consumption: yes	23 %	28%
p (univariate analysis)	*0.02*	

Lewis New Engl J Med (2001) 345:851

Alcohol –
progression of renal disease

 # animal data

- **moderate alcohol intake ⇨**
  no impact on acute or chronic thy1- glomerulonephritis

  Peters, Am.J.Physiol (2003) 284:F1105

- **adriamycin model**
  alcohol ⇨ less nephrotic syndrome

  Tesar, Alcohol (1995) 30:47

- **red wine and alcohol free red wine**
  ⇨ less lipid peroxydation in kidney

  Araya, Lipids (2003) 38:275

Hypothesis

kidney rich in polyunsaturated fatty acids →
vulnerable to damage by reactive oxygen species (ROS)

benefit from moderate consumption of red wine
►antioxidant defense ↑

 # polyphenols → *scavenge ROS and chelate metals*

 # ethanol → *activity of antioxidant enzymes ↑*

Rodrigo, Free Rad Biol Med (2002) 33:409

Alcohol and progression of renal disease

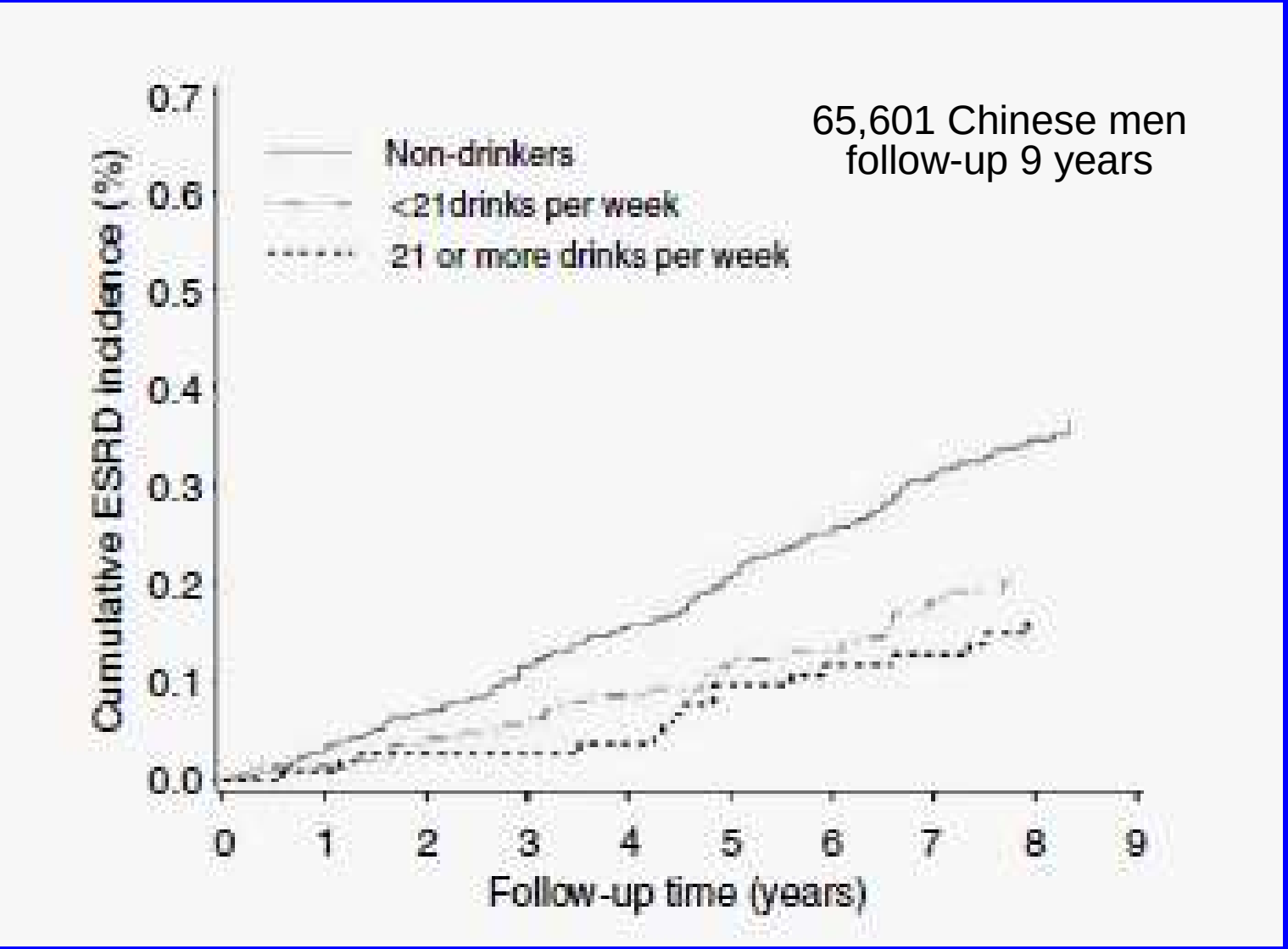
decline of renal function and alcohol
prospective 11 year study in 1658 nurses

	odds ratio > 25 % decrease GFR	
	normotensive	*hypertensive*
0 - 4.9 g/day	*0.98*	*0.98*
5 -14	*0.83*	*0.62*
15 -60	*0.81*	*0.53*

⇨ chronic kidney disease – potential benefit from alcohol

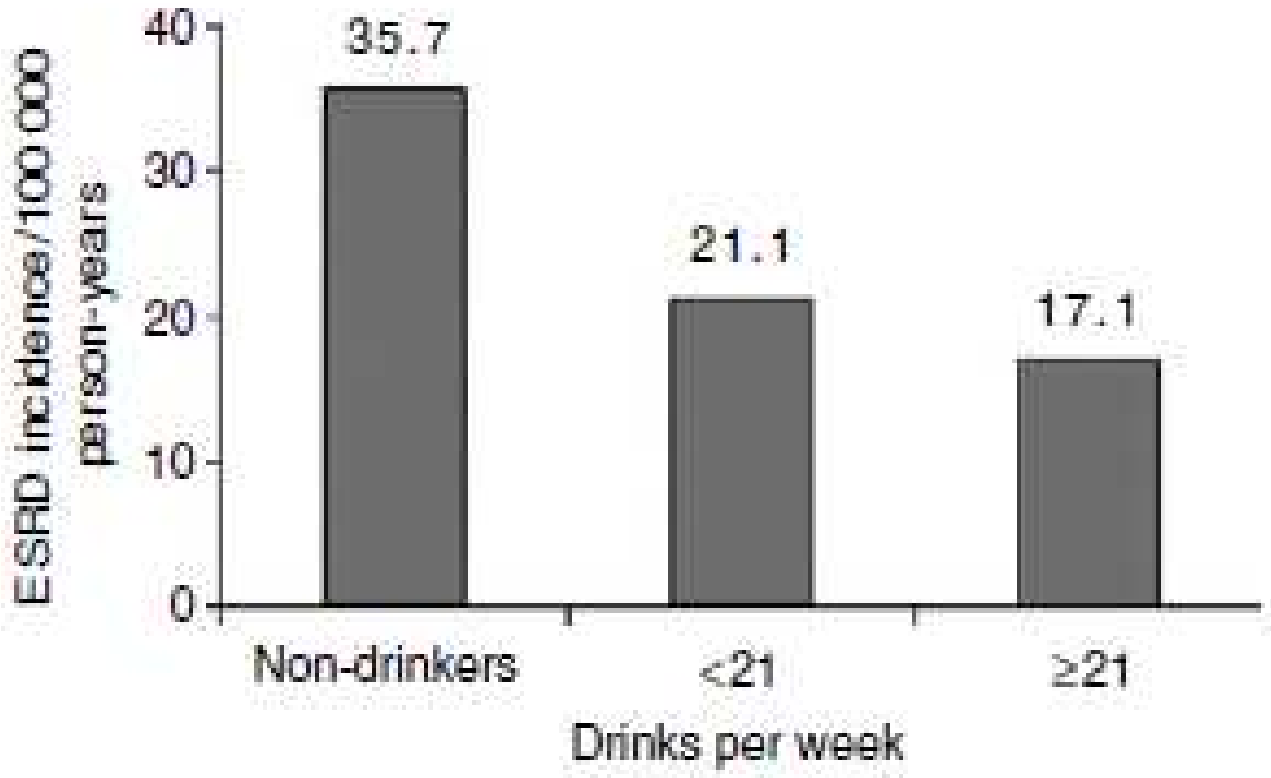
Knight, Nephrol Dial Transpl (2003) 18:1549

Alcohol consumption –
less endstage renal disease



Reynolds, Kid.Internat.(2008) 73:870

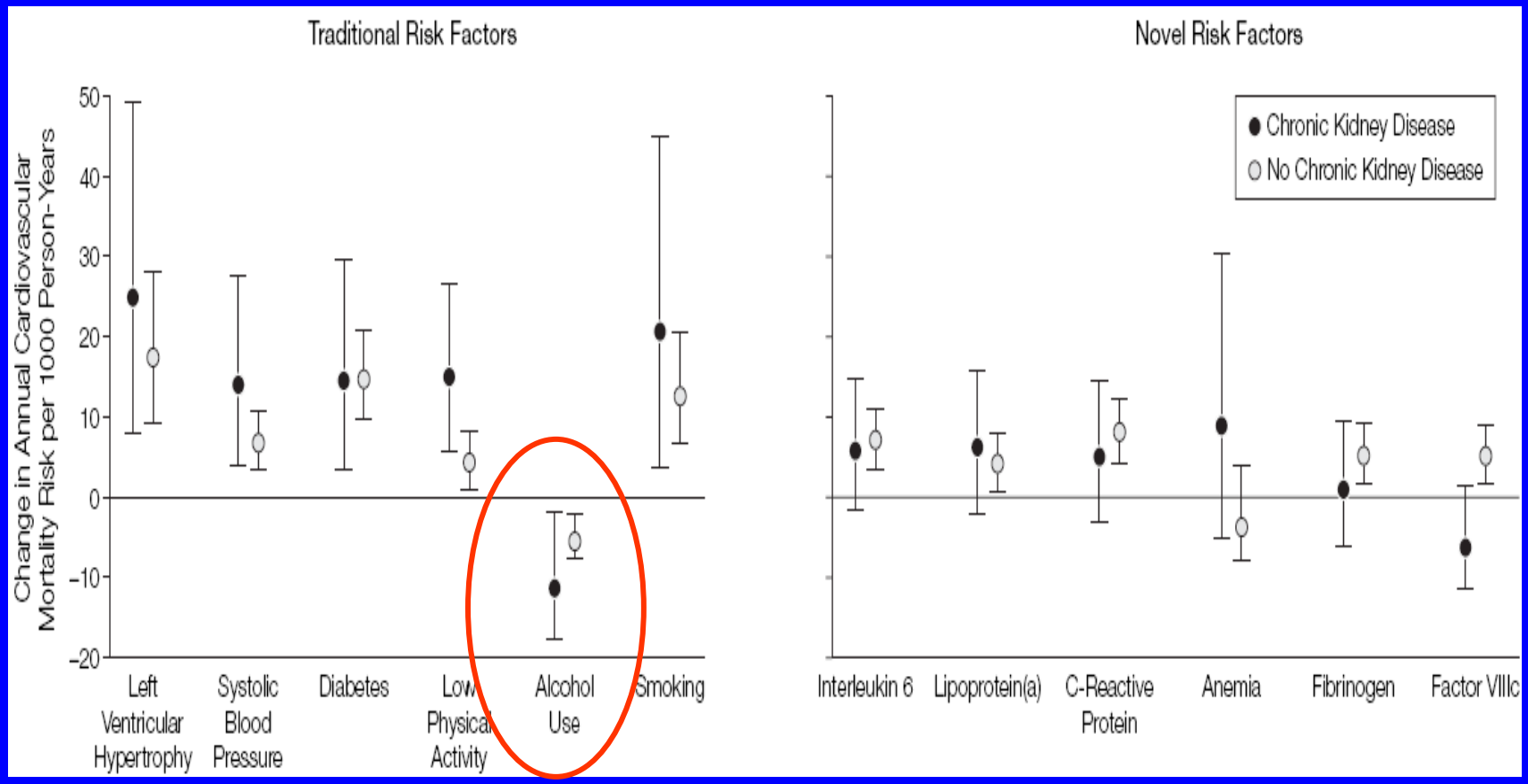
Incidence of all-cause endstage renal disease
(per 100,000 person years standardized by age)



Reynolds, Kid.Internat.(2008) 73:870

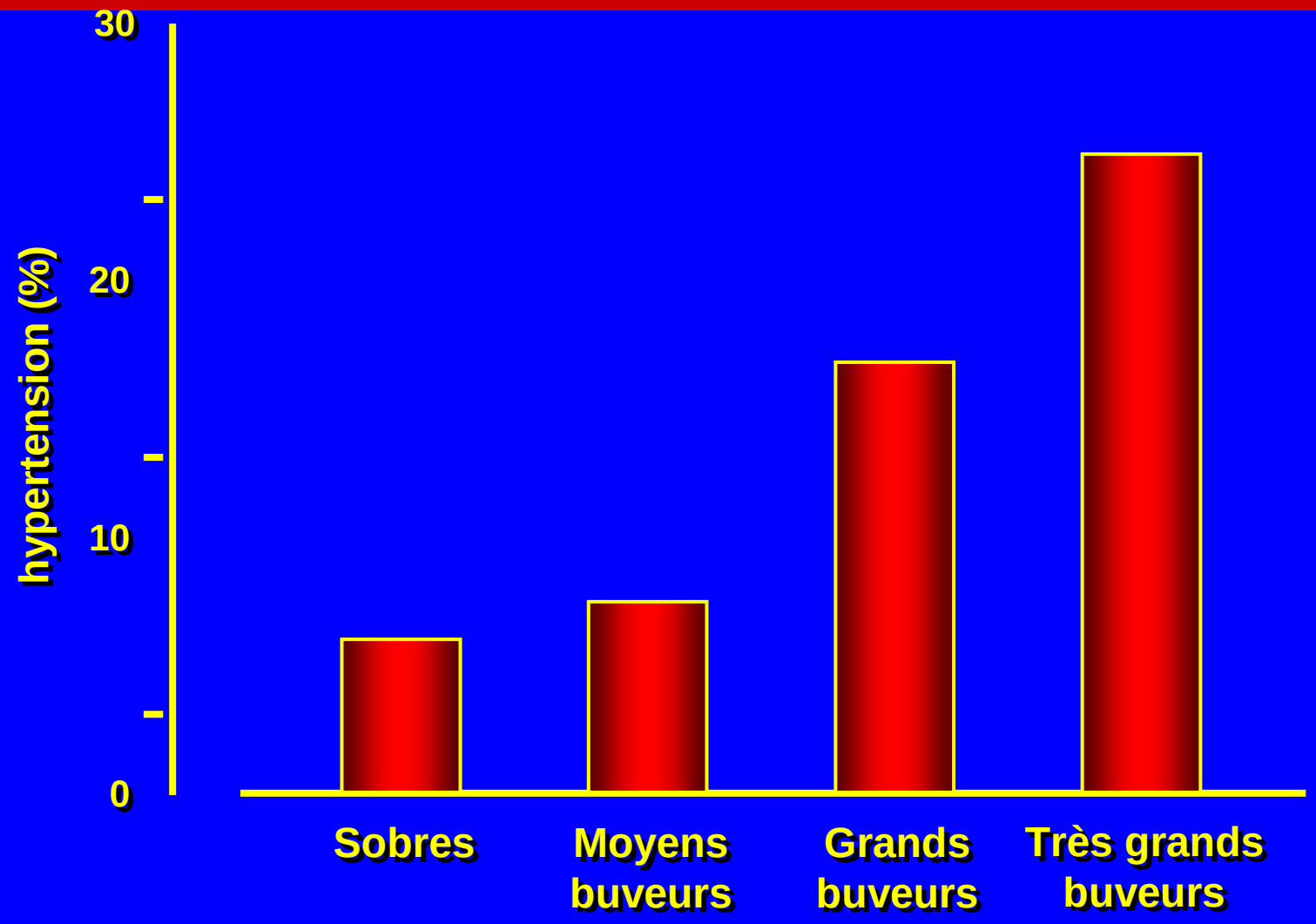
Chronic Kidney Disease –

traditional and novel CV risk factors



Shlipak, JAMA (2005) 293:1737

Cardioprotection –
although alcohol increases blood pressure
Paris Gendarmes



Are all alcoholic beverages similar with respect to benefit on coronary events?

Copenhagen Heart Study

prospective 12 year study,
6000 males, 7000 females

inverse correlation between alcohol consumption and total mortality

→ only for consumption of wine, not beer and spirits

Gronbaek, Brit Med J (1995) 310: 1165

Gronbaek, Ann Int Med (2000) 19: 411


in Bavaria diuresis sign of virility

Beer drinking and total mortality

Copenhagen Heart Study:

decreased relative risk only for wine,
but slightly increased for beer and spirits

Gronbaek, Brit Med J (1995) 310: 1165

Monica study – Augsburg (Bavaria):

U-shaped relation between alcohol (including beer) consumption and total mortality in a beer drinking population

Keil, Epidemiology (1997) 8: 150

Antiinflammatory effect of moderate consumption of either wine or beer

- MONICA study (Augsburg, Glasgow, Lille)
- self reported moderate (<40g/day) intake of alcohol compared to nondrinking or heavy drinking

⇨ **lower** ***CRP***
fibrinogen
plasma viscosity
white blood cell count

Imhof, Eur.Heart J (2004) 25:2092

Between countries:

Inverse correlation <u>alcohol</u> consumption and coronary mortality (r = - 0.39)

better correlation <u>wine</u> consumption and coronary mortality (r = 0.66)

Criqui and Ringel
Does diet or alcohol explain the French paradox?
Lancet (1994) 344: 1719

⇨ alcohol coronary protection
constituents of wine additional coronary protection

alcohol – coronary protection

wine – additional coronary protection

metaanalysis

200,000 subjects

# beer consumption	**risk reduction**	**- 20%**
# wine consumption	**risk reduction**	**- 32%**

Di Castelnuovo Circulation (2002) 105: 2836

confirmed :

Klatsky, Am.J.Epidemiol (2003) 158: 585

Women and alcohol

Higher blood alcohol levels
Higher risk of mamary carcinoma
Impact on CV risk dependent on age (menopausal state)

→ **prospective study of 45,709 nurses**
alcohol:

- **CV risk increased in young women with low baseline CV risk even at low alcohol intake**
- **small decrease of CV risk only at age ≥ 50 years**

Fuchs , N Engl J Med (1995) 332: 1245

but,

even young (30 y) women at high CV risk (e.g. type 2 diabetes)
26% risk reduction with alcohol (0.1-4.9 g/day)

Salomon, Circulation (2000) 102: 494

Risk reduction –
dependent on baseline risk

→ pronounced in smokers,

less in non-smokers

	RR	
	0 g alcohol	22-32 g alcohol/day
smoker	2.8	1.9
non-smoker	1	0.7

Renaud, Am J Clin Nutr (1992) 55: 1012

Risks and benefits of alcohol

490,000 individuals
prospective 9 year follow-up study
alcohol use ⇨

higher risk :

cirrhosis

cancer *(breast, mouth, esophagus, pharynx, larynx, liver)*

injury

lower risk :

- cardiovascular death (lower by 30-40%)
- diabetes,
- osteoporosis,
- progression of renal disease,
- cognitive impairment

Thun, New Engl J Med (1997) 337:1705

Myocardial infarction and alcohol

- **improved survival**
- **less coronary complications**

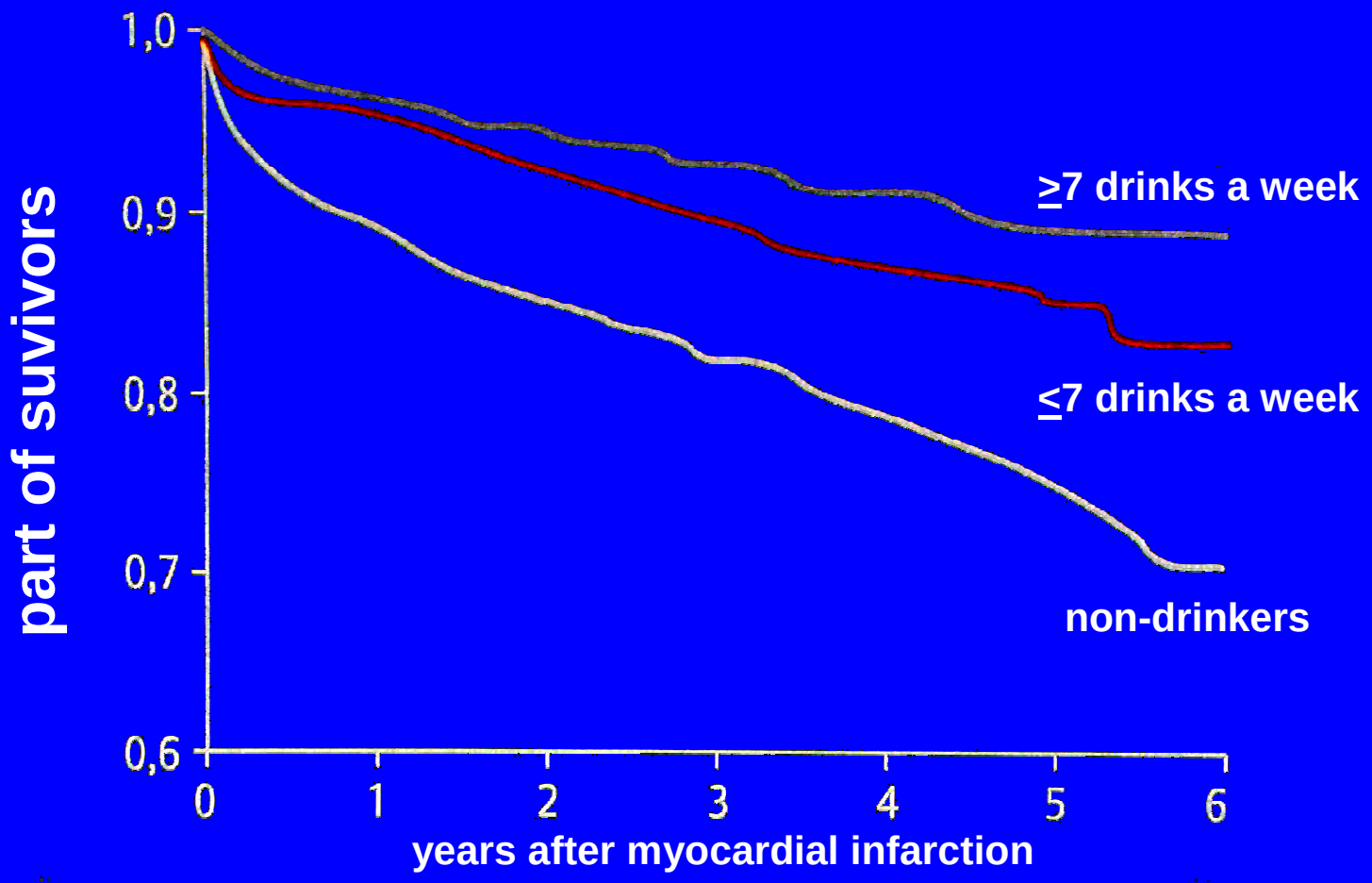
in individuals with moderate alcohol intake

(no significant difference wine, beer, spirits)

De Lorgeril, Circulation (2002) 106: 1465

Mukamal, JAMA (2001) 285: 1965

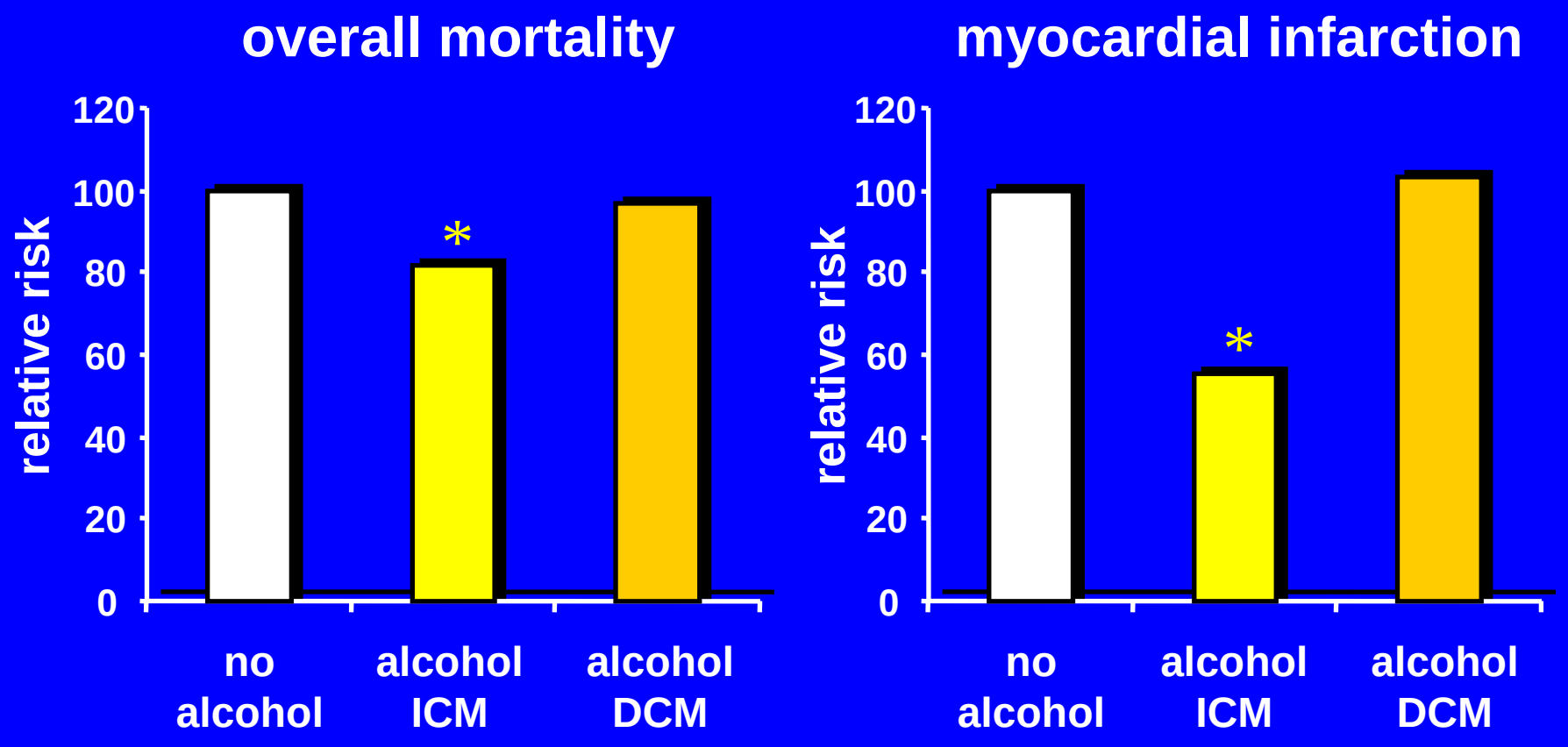
Alcohol consumption following myocardial infarction



Mukamal, JAMA (2001) 285:1965

Moderate alcohol consumption and mortality in heart failure (EF < 35 %) from ischemic cardiomyopathy

SOLVD study



J.Am.Coll.Cardiolo. 2000;35:1753

Alcohol consumption reduces restenosis rate after coronary angioplasty + stent –

the Heidelberg experience

225 consecutive pat. PTCA + stent

> 50 g alcohol / week ⇨ lower :

rate of loss of lumen	*1.1 ± 0.79 vs 1.45 ± 0.82 mm , p< 0.002*
restenosis within stented segment	*33.7 % vs 42.5 % , p<0.002*
repeat angioplasty	*23.3 % vs 42.5 %*

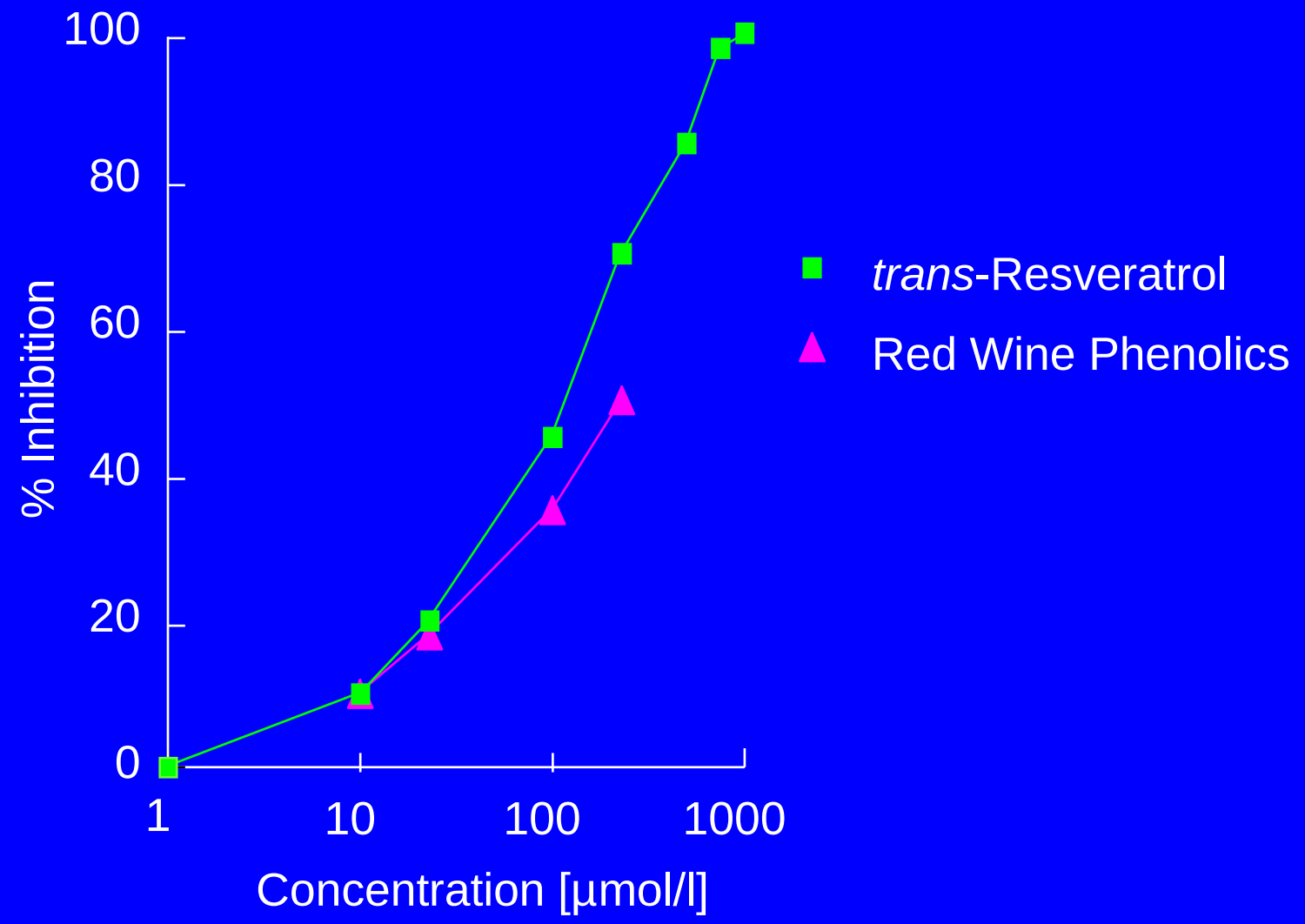
alcohol consumption → independent predictor

Niroomand, Heart (2004) 90:1189

Mechanisms of cardioprotective actions of alcohol / wine

- *serum lipid profile*
- *antithrombotic action*
- *lowering of oxygen radicals (ROS)*
- *endothelial-dependent vasodilation/NO*
- *antiproliferative effect (antagonism ANG II, PDGF)*

Inhibition of ADP-Induced Platelet Aggregation in vitro



Pace-Asciak,Clin Chem Acta 1005;235:207

Inhibition of
platelet aggregation + eicosanoid synthesis

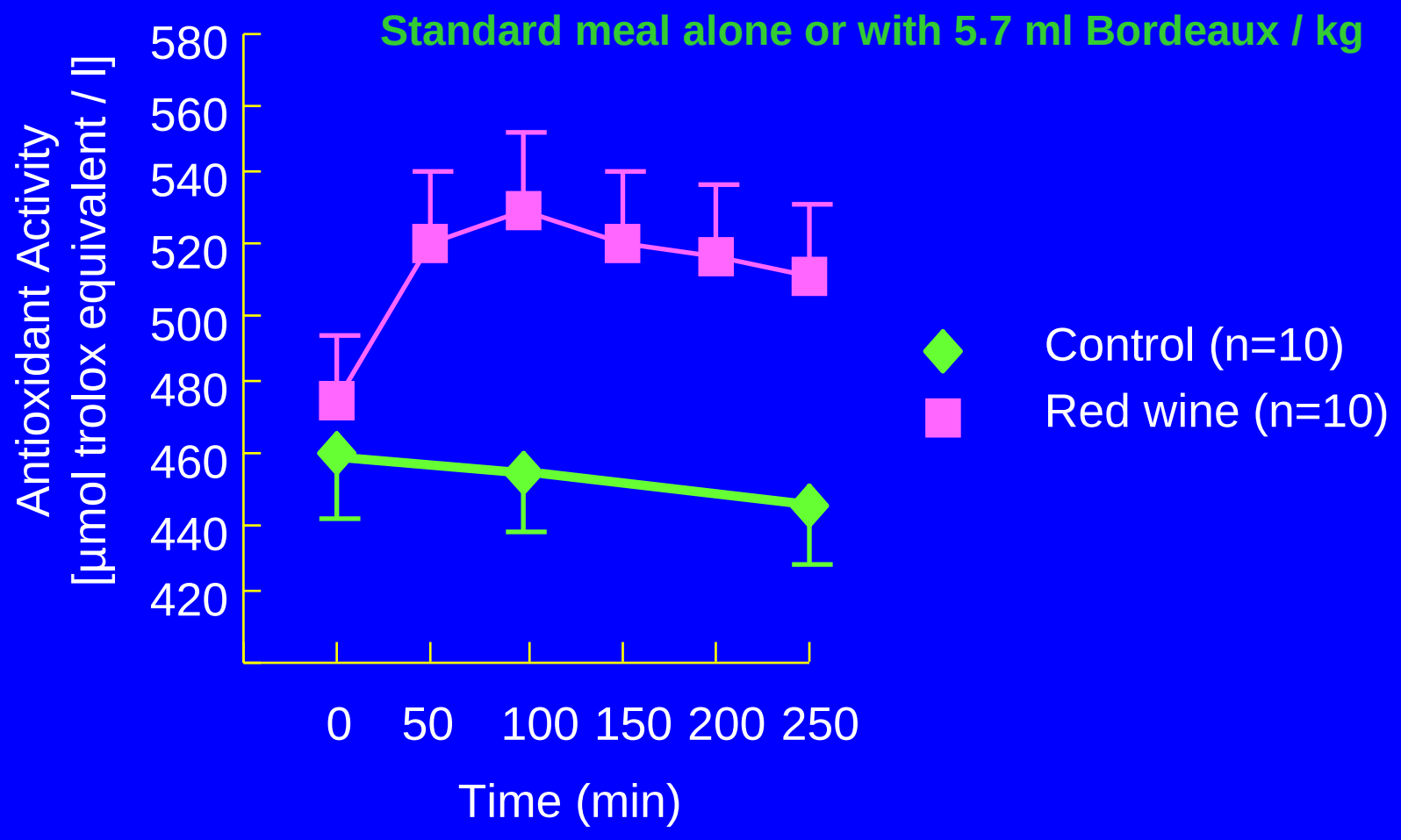
In vitro:
phenoles in red wine (trans-resveratrol, quercetin)

Pae-Asiak, Clin Chim Acta (1995) 235: 207

In vivo:
fresh grape juice,
but not orange or grape fruit juice

Keevil, J Nutr (2000) 130: 53

Impact of Red Wine on Serum Antioxidant Activity in Healthy Volunteers



Maxwell, Lancet 1994; 344: 193)

Effects of wine on endothelial cells

- *NO generation*
- *shear stress induced vasodilatation*
- *adhesion of mononuclear cells/platelets*

red wine phenols (resveratrol) increase expression and activity of endothelial NO synthase (eNOS)

Leikert, Circulation (2002) 106: 1614

Endothelial effects of wine

Red wine, but not wodka,
increases coronary flow reserve

Shimada, Lancet (1999) 354: 1002

Small amounts of alcohol specific increase of postischemic forearm blood flow in CHD patients
(nitrate as control negative)

Teragawa , Atherosclerosis (2002) 165: 145

Endothelial effects of wine

In isolated human coronary arteries

red wine (Châteauneuf du Pape),

but not white wine (Mosel Riesling) or ethanol

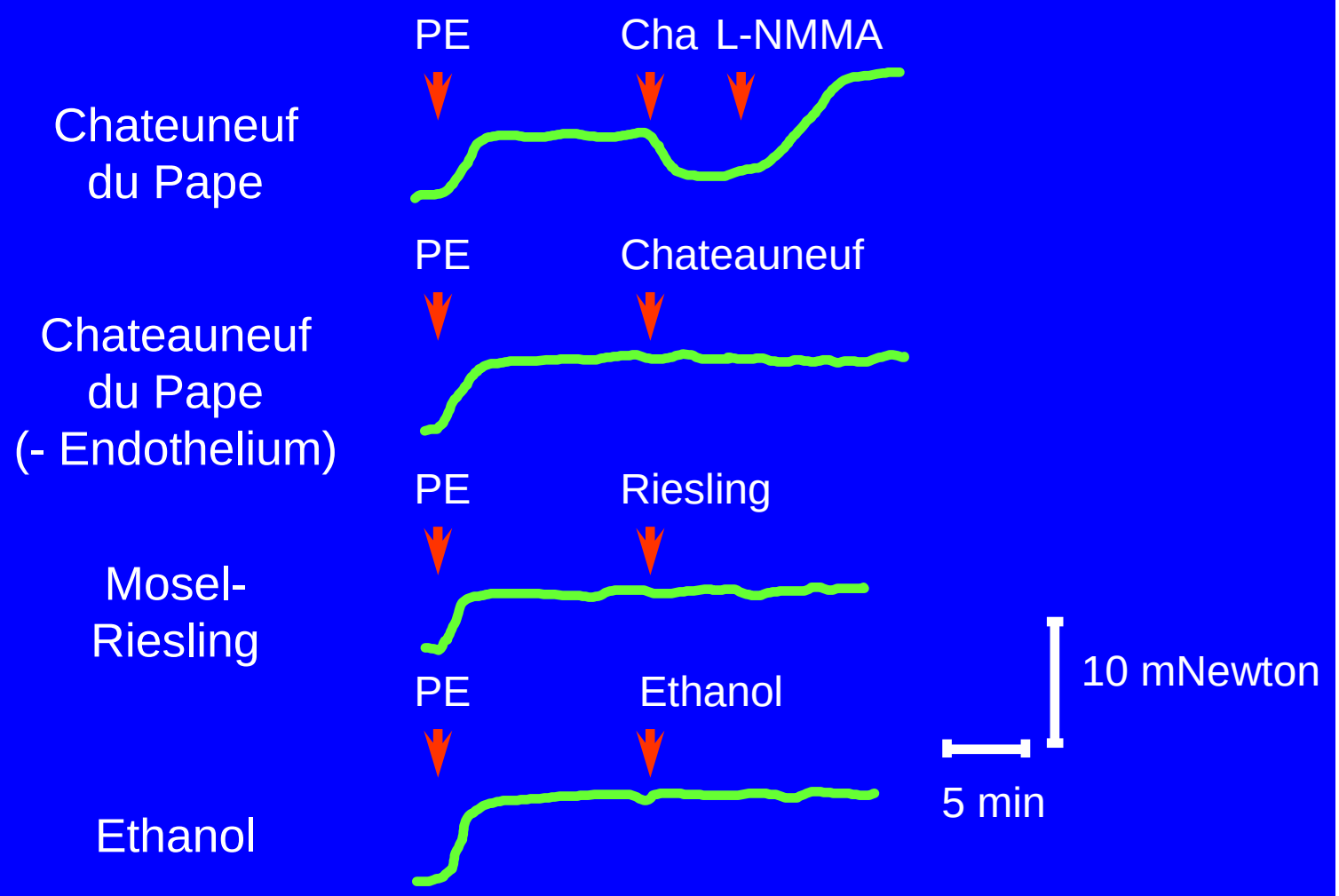
→ endothelial cell dependent vasodilatation,

effect NO-dependent

(inhibited by L-NMMA)

Flesch, Am J Physiol (1998) 275: H1183

Human Coronary Artery
Effects of Red and White Wine



Antiproliferative effect of red wine

Vascular smooth muscle cells

ANG II- and PDGF-induced proliferation inhibited by ⟶

red, but not white, wine

by quercetin and tannin

Flesch, Dtsch Med Wschr (1998) 123: 1490

inhibits ligand activated tyrosine phosphorylation of β-PDGF receptor and postreceptor signalling

Rosenkranz, FASEB J (2003) 16: 1958

Are all red wines created equal?

Barrique matured wines in oak vats vs

wines matured in steel tanks

→ **only heavy barrique matured red wines effective,**

contain higher concentrations of phenolic substances

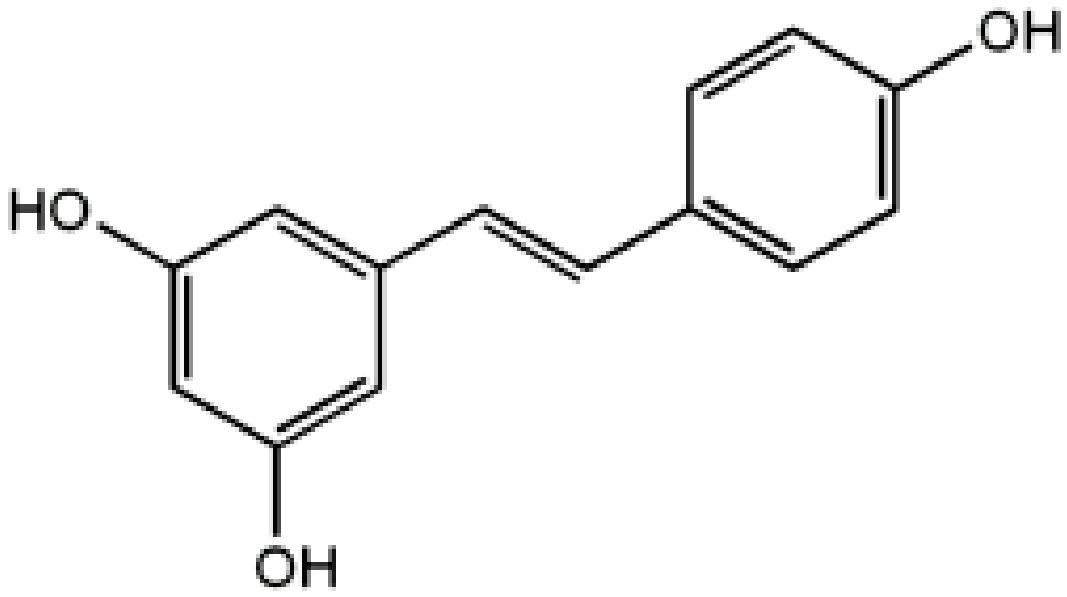
in vitro effect reproduced by Tannin and Quercetin

Rosenkranz, FASEB J (2002) 16: 1958

a phytoalexin (defense against fungi)
•grapes (skin),
•raspberries,
•mulberries,
•peanuts
fermentation (red wine with, white wine without skins)

in red wine up to 15 mg/L

polyphenols (procyanidins) in red wine more plausible candidates for French paradox (Corder, Nature(2006) 444:566

Resveratrol	
	
General	
Systematic name	5-[(E)-2-(4-hydroxyphenyl)-ethenyl]benzene-1,3-diol
	trans-3,5,4'-trihydroxystilbene

http://en.wikipedia.org/wiki/Resveratrol

Resveratrol

- ***extends lifespan in sacharomyces***

  Howitz, Nature (2003) 425:191

- ***prolongs lifespan of Caenorhabditis elegans and Drosophila melanogaster***

  Wood, Nature (2004) 430:686

- ***extends lifespan and reduces aging features in the short-lived fish Nothobranchius furzeri***

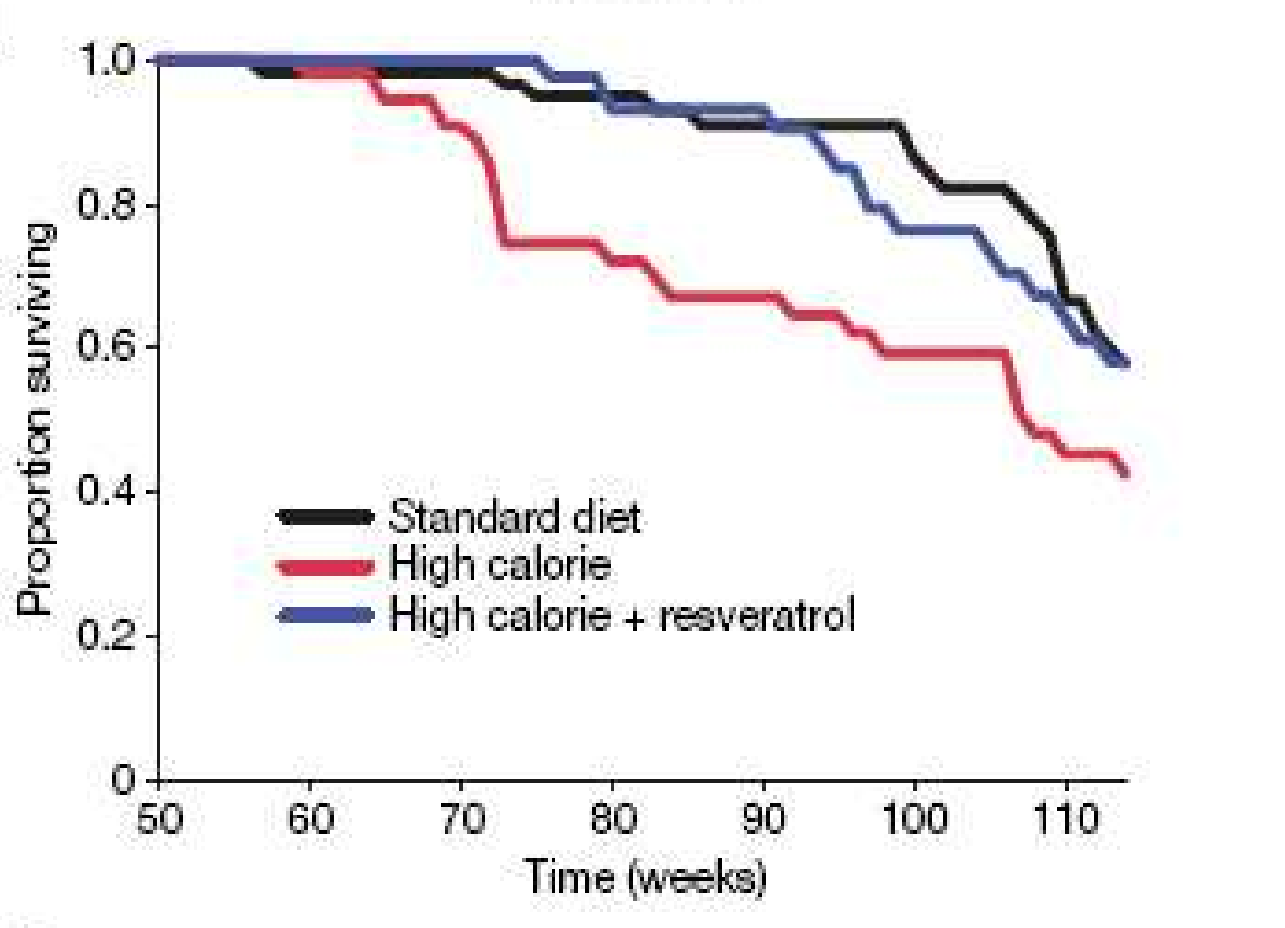
  Valenzano, Nature (2004) 430:686

- ***improves health and survival of mice on a high calorie diet acting via the histone deacetylase SIRT1***

  Baur, Nature (2006) 444:337

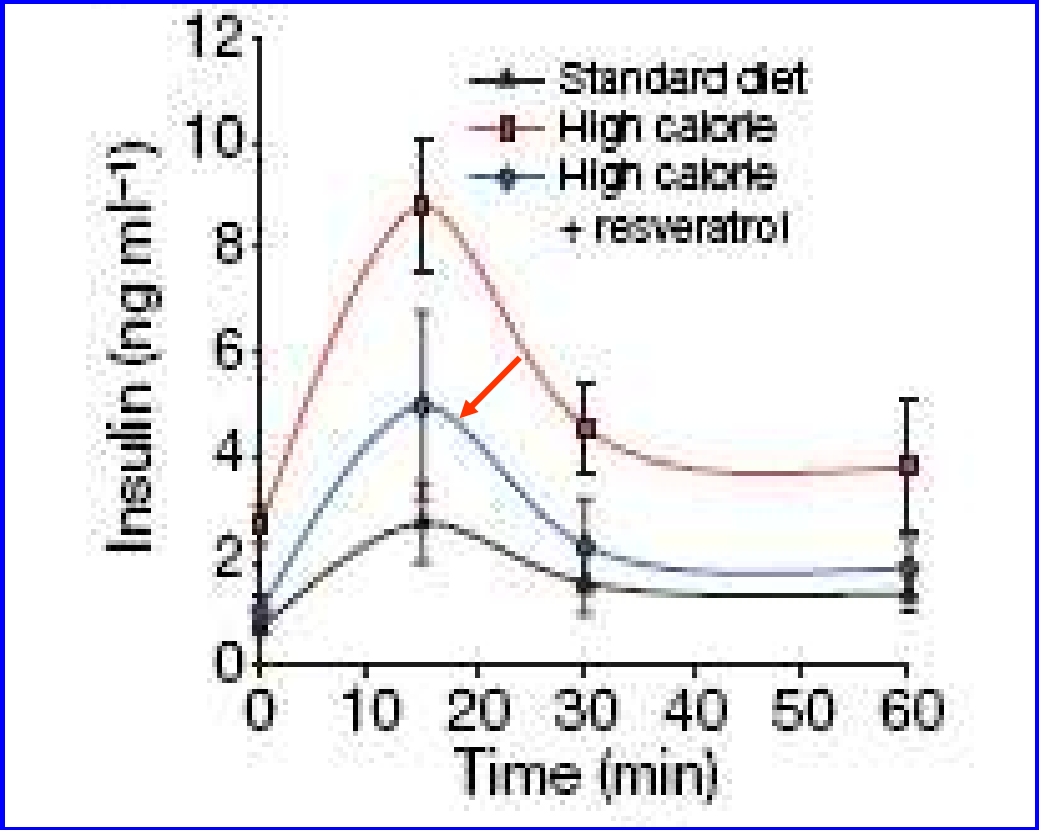
►in America marketed as a nutritional supplement

Resveratrol – effect on survival in obese mice



Baur, Nature (2006) 444:337

Resveratrol – effect on insulin in obese mice



Baur, Nature (2006) 444:337

O. FRANKEN/CORBIS

Rosy prospect? A compound found in red wine might help to protect against the health problems associated with obesity.

A votre santé: now in pill form?

Chek, Nature (2006) 444:11

Moderate drinking :

social lubricant,

major characteristic of European lifestyle *("joie de vivre")*

de Lorgeril, Europ.Heart J.,(2008) 29: 4-6

"I mix three kraters only for those who are wise.

One is for good health, which they drink first.

The second is for love and pleasure.

The third is for sleep, and when they have drunk it those who are wise wander homewards.

The fourth is no longer ours, but belongs to arrogance.

The fifth leads to shouting.

The sixth to a drunken revel.

The seventh to black eyes.

The eighth to a summons.

The ninth to bile.

The tenth to madness, in that it makes

poet Eubulos
4th century b.C.

“Semele”
(mother of Dionysos)

after how
many “glasses” ?

1. Ὑγίεια (Hygeia/health)
2. ἔρος καὶ ἡδονή (love and pleasure)
3. ὕπνος (sleep)

---

4. ὕβρις (hubris)
5. βοή (shouting)
6. κῶμος (drunken revels)
7. ὑπώπια (black eyes)
8. κλητήρ (witness)
9. χολή (anger)
10. μανία (mania)

Cook, Brit.Med.J.(2007)

Virgin Mary with the wine drinking Christ child

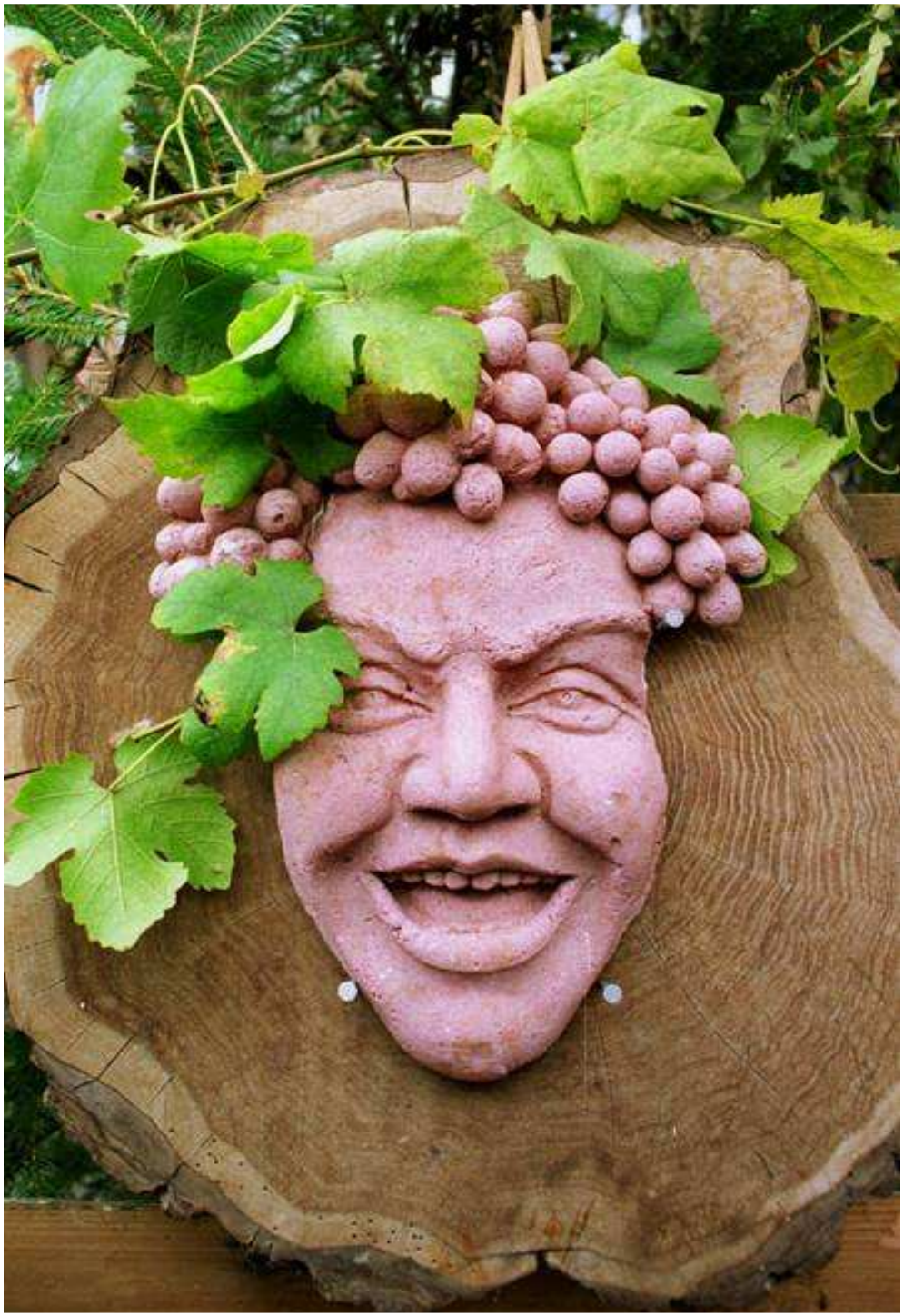
Joos van Cleve
1491-1541

Notions about benefits of alcohol

german	Prosit !	*to your / our* ***wellbeing***
	zum Wohl !	
english	cheers !	
estonian	terviseks !	
finnish	terveydeksi !	
greek	για μας !	
french	santé !	*to your* ***health***
italian	salute !	
spanish	salud !	
hungarian	egésszégére	

No one should talk longer in public
than he is prepared to make love in private

Francois La Rochefoucauld,
Prince de Marcillac
1613-1680



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Effects of Moderate Alcohol Consumption on Cognitive Function in Women

Meir J. Stampfer, M.D., Jae Hee Kang, Sc.D., Jennifer Chen, M.P.H., Rebecca Cherry, M.D., and Francine Grodstein, Sc.D.

ABSTRACT

BACKGROUND

The adverse effects of excess alcohol intake on cognitive function are well established, but the effect of moderate consumption is uncertain.

METHODS

Between 1995 and 2001, we evaluated cognitive function in 12,480 participants in the Nurses' Health Study who were 70 to 81 years old, with follow-up assessments in 11,102 two years later. The level of alcohol consumption was ascertained regularly beginning in 1980. We calculated multivariate-adjusted mean cognitive scores and multivariate-adjusted risks of cognitive impairment (defined as the lowest 10 percent of the scores) and a substantial decline in cognitive function over time (defined as a change that was in the worst 10 percent of the distribution of the decline). We also stratified analyses according to the apolipoprotein E genotype in a subgroup of women.

RESULTS

After multivariate adjustment, moderate drinkers (those who consumed less than 15.0 g of alcohol per day [about one drink]) had better mean cognitive scores than nondrinkers. Among moderate drinkers, as compared with nondrinkers, the relative risk of impairment was 0.77 on our test of general cognition (95 percent confidence interval, 0.67 to 0.88) and 0.81 on the basis of a global cognitive score combining the results of

From the Channing Laboratory, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School (M.J.S., J.H.K., J.C., F.G.); and the Departments of Epidemiology (M.J.S., F.G.) and Nutrition (M.J.S.), Harvard School of Public Health — all in Boston; and Vanderbilt Children's Hospital, Nashville (R.C.).

N Engl J Med 2005;352:245-53.

2005; 352: 245-53

Red wine polyphenols, in the absence of alcohol, reduce lipid peroxydative stress in smoking subjects

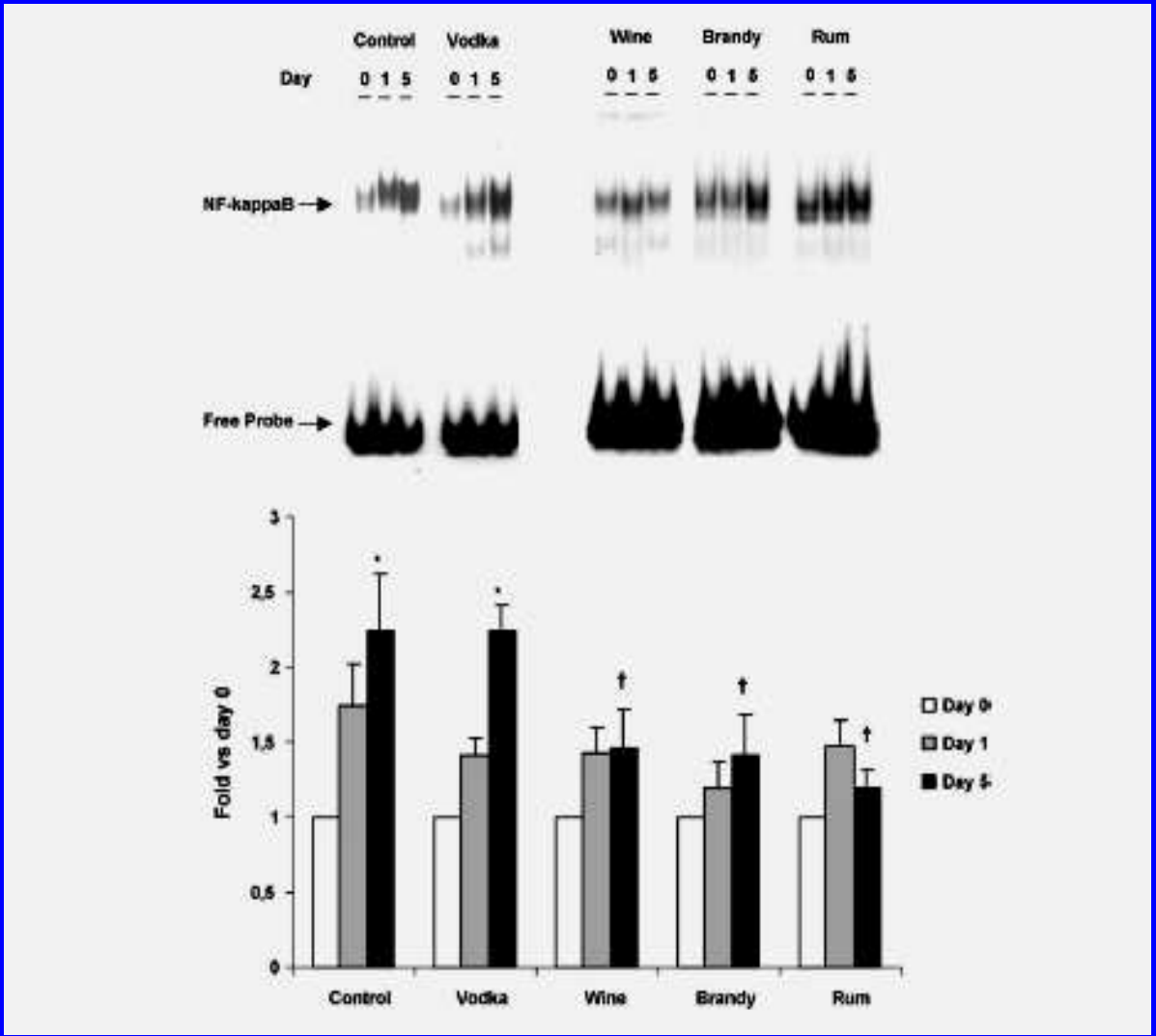
- *phenolic compounds in red wine →*
  antioxydant effect on in vitro lipoprotein oxydation
- *evidence by prospective study in smokers of in vivo antioxydant effect*

- *18 male smokers in random order red wine, white wine or dealcoholized red wine for 2 weeks*
- *read out plasma and urinary F2 isoprostane*

- *significant decrease of F2 isoprostane without any change in known antioxydants (α,γ-tocopherol, vitamin C)*

Abu-Amsha, Free Radic Biol Med (2001) 30:636

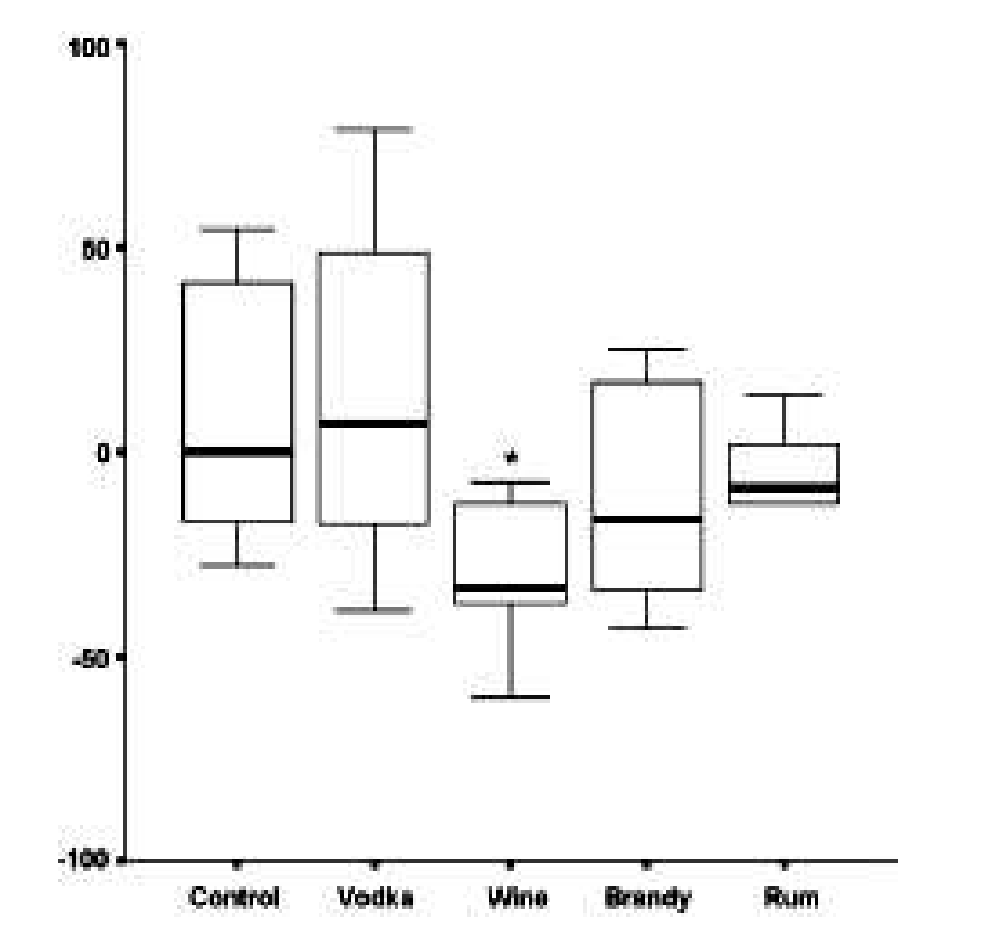
Alcohol consumption lowers $NF_{\kappa}B$ and MCP 1



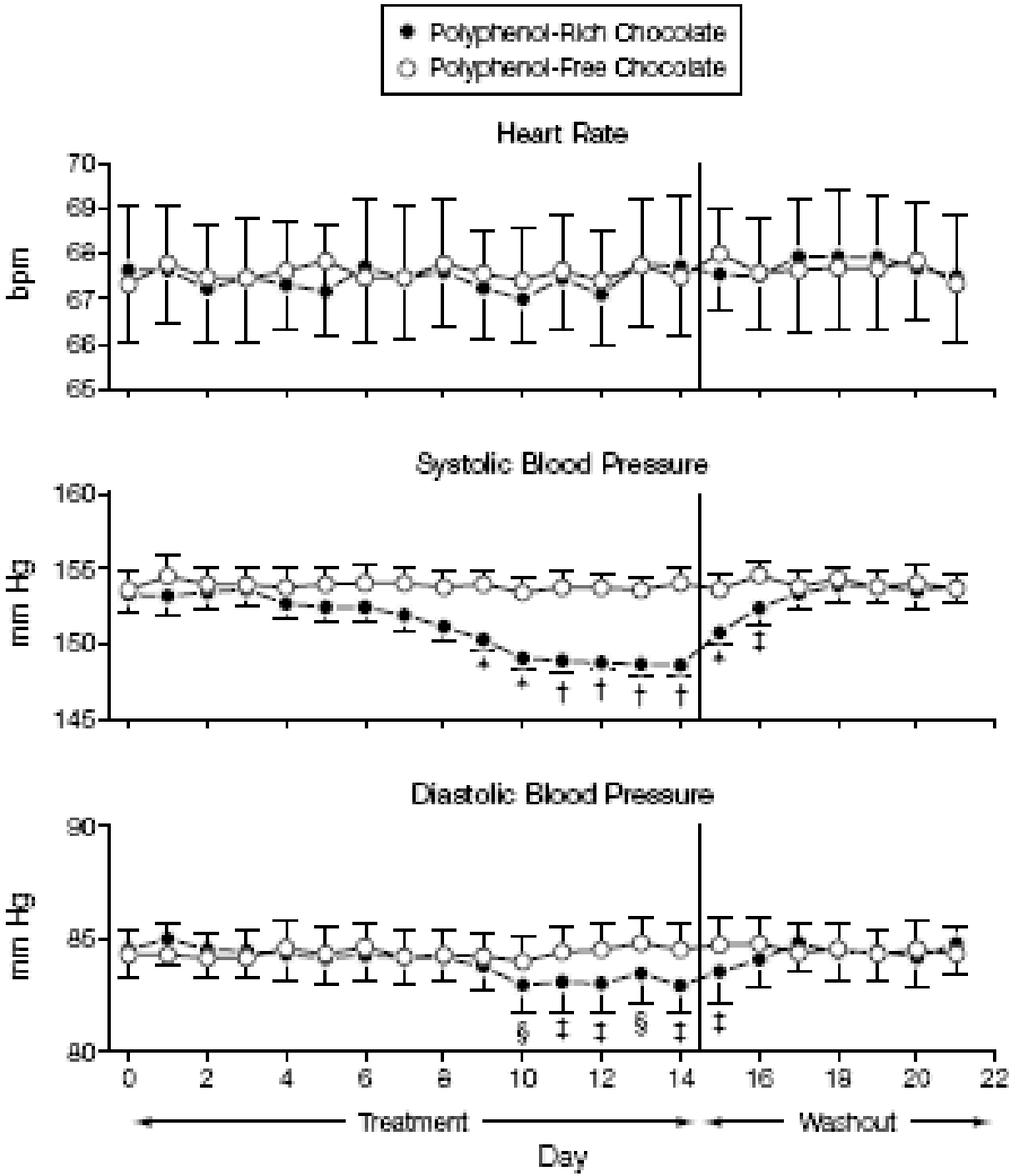
Blanco-Colio, Atherosclerosis, e-pub Sept 2006

Alcohol consumption lowers $NF_{\kappa}B$ and MCP 1

MCP1
(% change)



Blanco-Colio, Atherosclerosis, e-pub Sept 2006

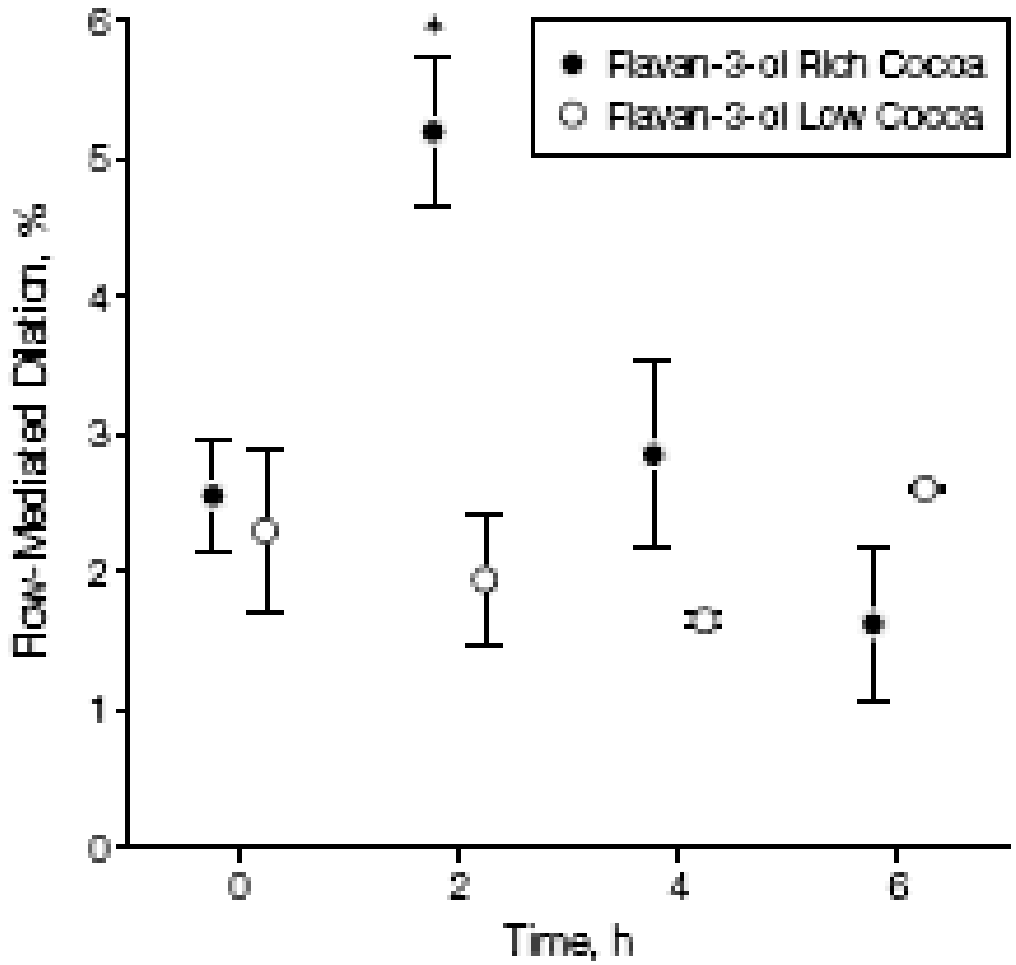


Heiss et al

Chocolate and blood pressure in elderly subjects with isolated systolic hypertension

JAMA (2003) 290:1030

Figure 1. Time Course of Flow-Mediated Dilation After Ingestion of 100 mL of Cocoa Drink Containing High (176 mg mL; n=6) or Low (<10 mg mL; n=3) Amounts of Flavan-3-ols

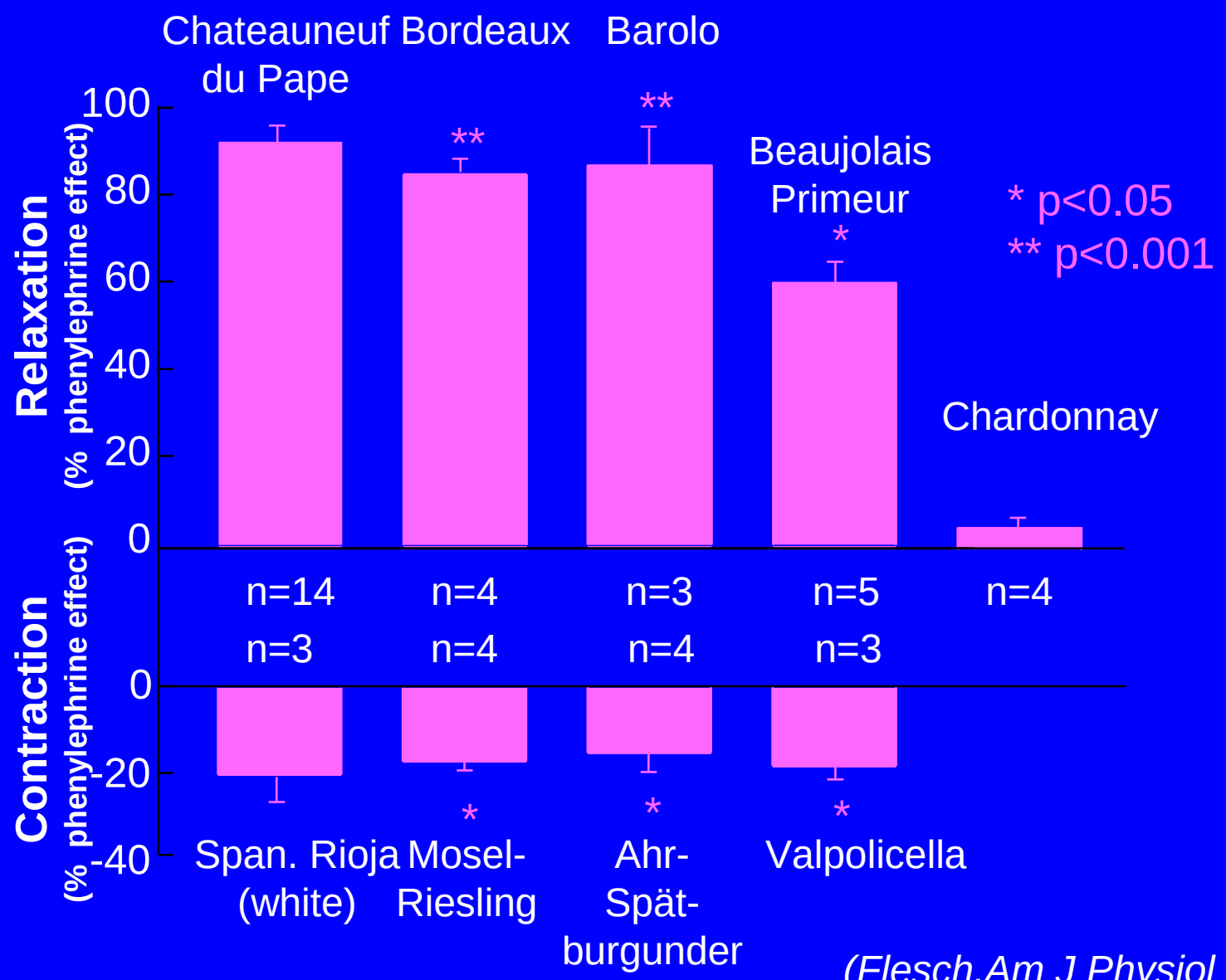


Heiss et al

Chocolate and blood pressure in elderly subjects with isolated systolic hypertension

JAMA (2003) 290:1030

Vascular Effects of Red and White Wine



(Flesch,Am J Physiol 1998)

Cost-effectiveness of BEER *versus* RED WINE *for the prevention of symptomatic coronary artery disease*

Fig. 1: The double-blind nature of the study was maintained throughout the trial. Dr. Innes is shown sitting.

Innes, CMAJ (1998) 159:1463

Quantitative Analysis of Polyphenolics in Red Wine vs. White Wine

	Red Wine (Chateauneuf-du-Pape)	White Wine (Riesling Kabinett)	
cis-Piceid	5,1	0,0	
trans-Resveratrol	1,6	0,0	
Quercetin	0,0	0,0	
Catechin	37,3	5,2	
Epicatechin	12,0	1,6	
Procyanidin B2	9,7	0,0	
Gallic Acid	44,9	0,9	
Cafteric Acid	24,8	37,9	
Coffee Acid	7,0	16,7	
p-Coumaric Acid	23,5	6,8	
Total Polyphenolics	2113	350	[mg/l]