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Hypertension management – An Asian perspective

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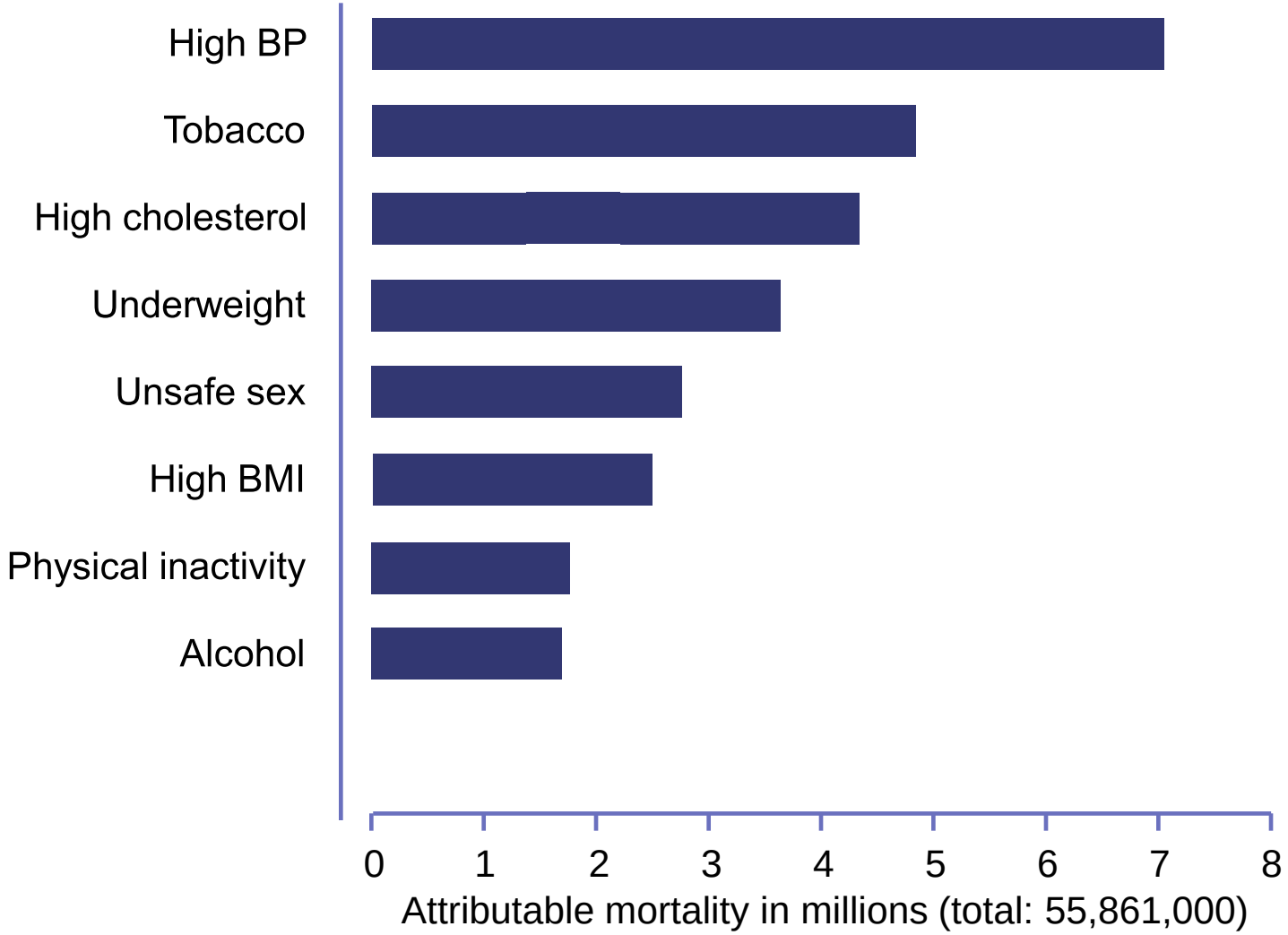
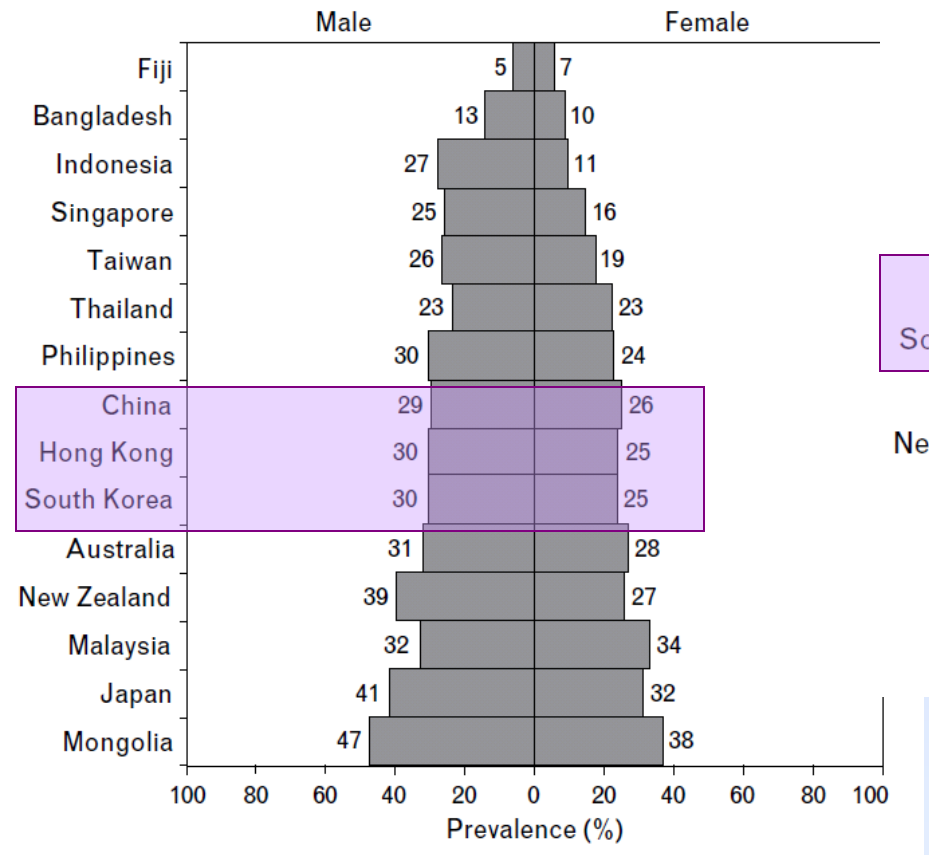
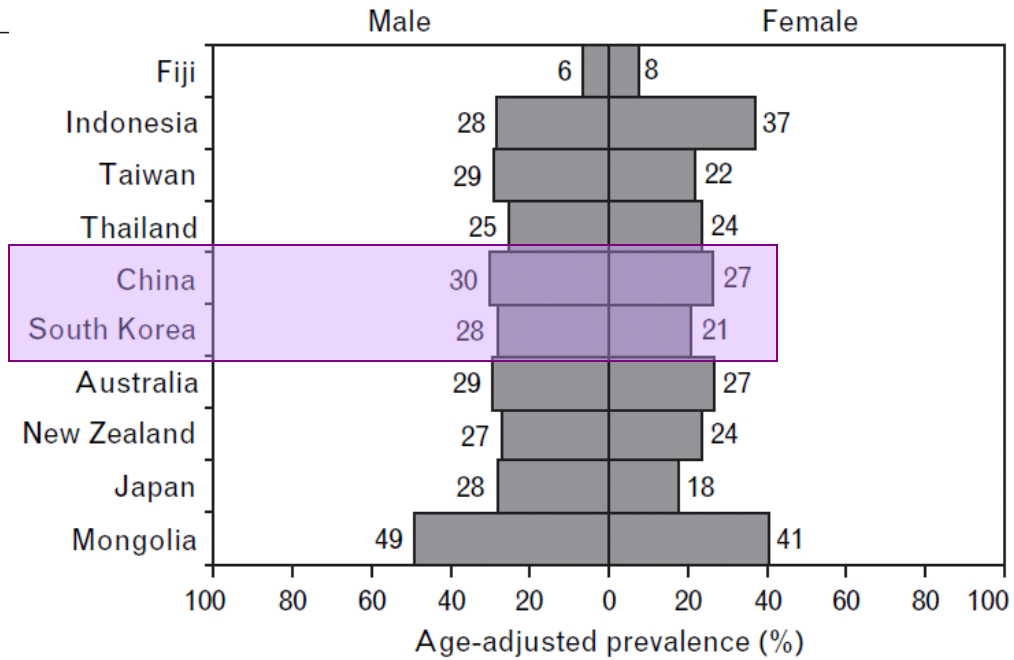
Hypertension is the Number One Risk Factor for Global Mortality



Ezzati et al. Lancet 2002;360:1347–60

Prevalence of hypertension in the Asia-Pacific region

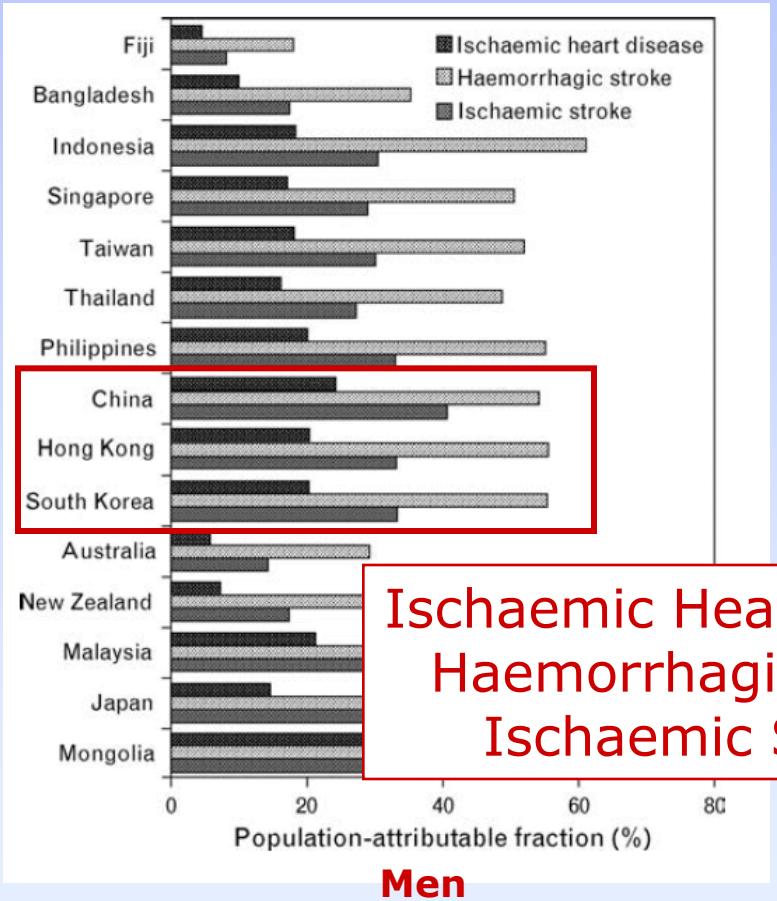




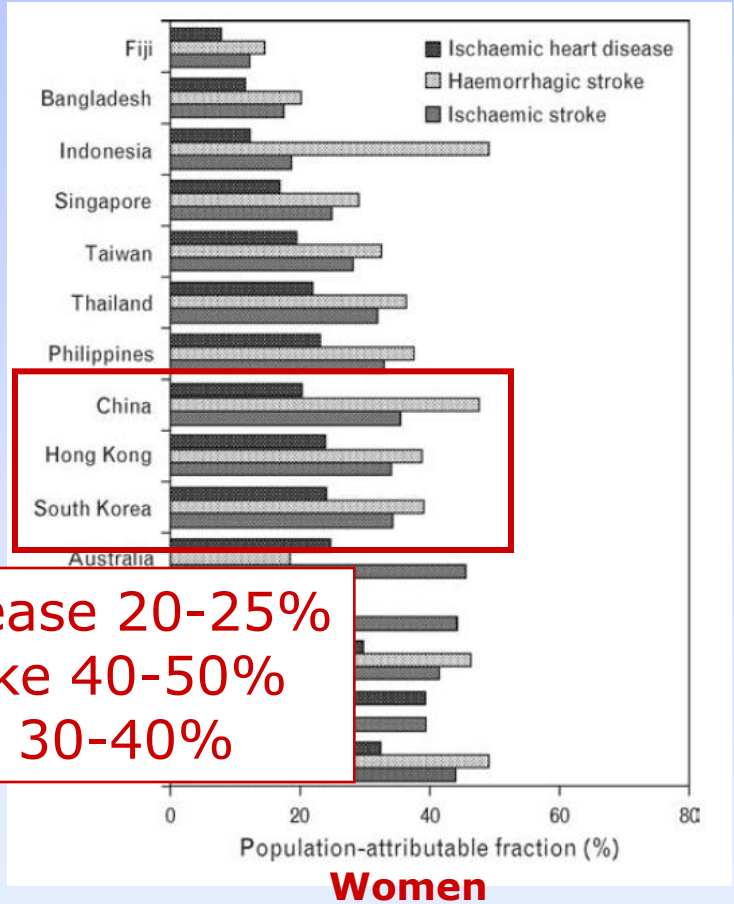
Crude prevalence of hypertension by sex – 1996-2004

Martiniuk ALC, for the Asia-Pacific Cohort Studies Collaboration, J Hypertens 2007; 25:73–79.

Population-attributable fractions for cardiovascular disease deaths due to hypertension in the Asia-Pacific region



Men

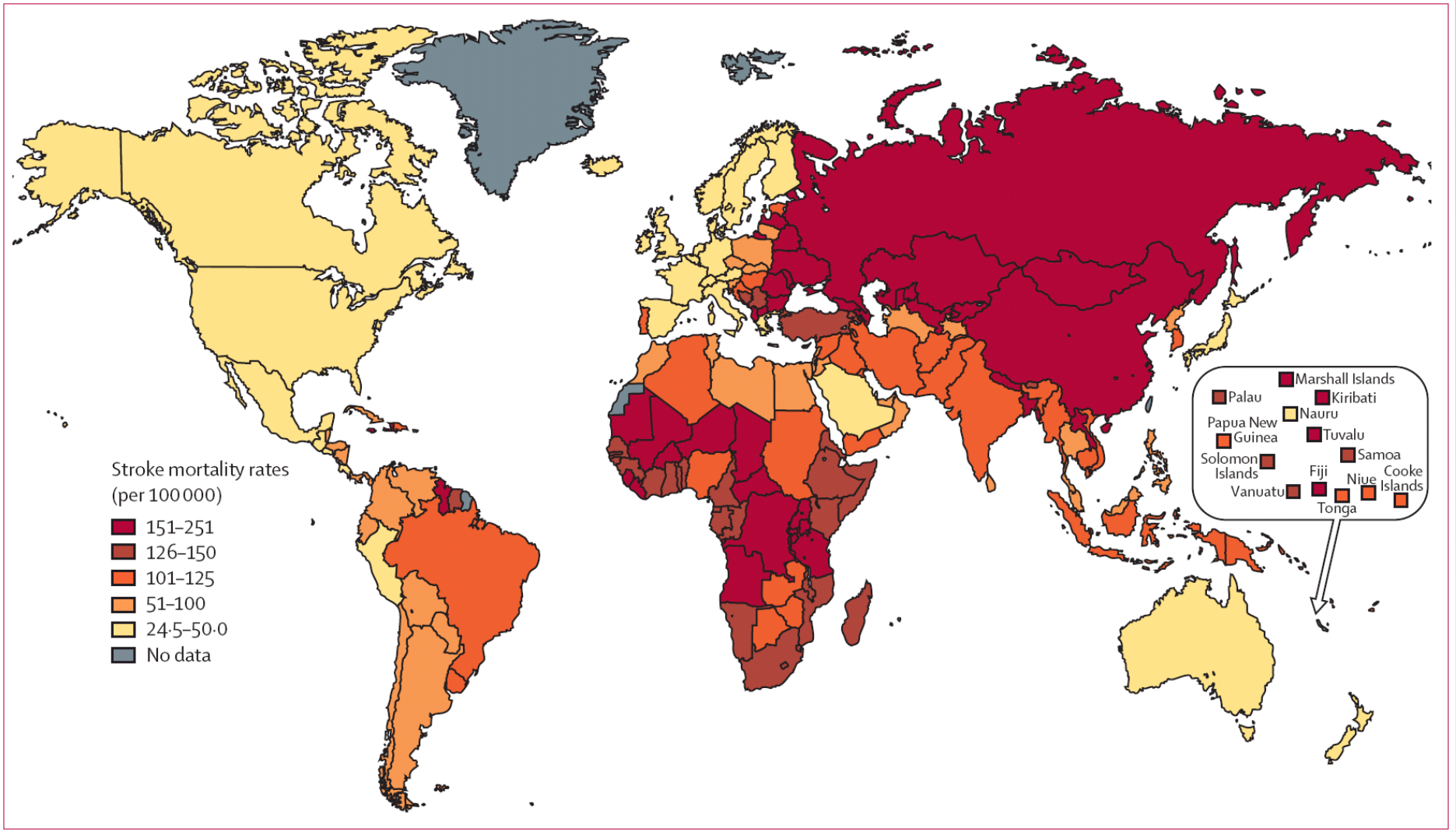


Women

Ischaemic Heart Disease 20-25%
Haemorrhagic Stroke 40-50%
Ischaemic Stroke 30-40%

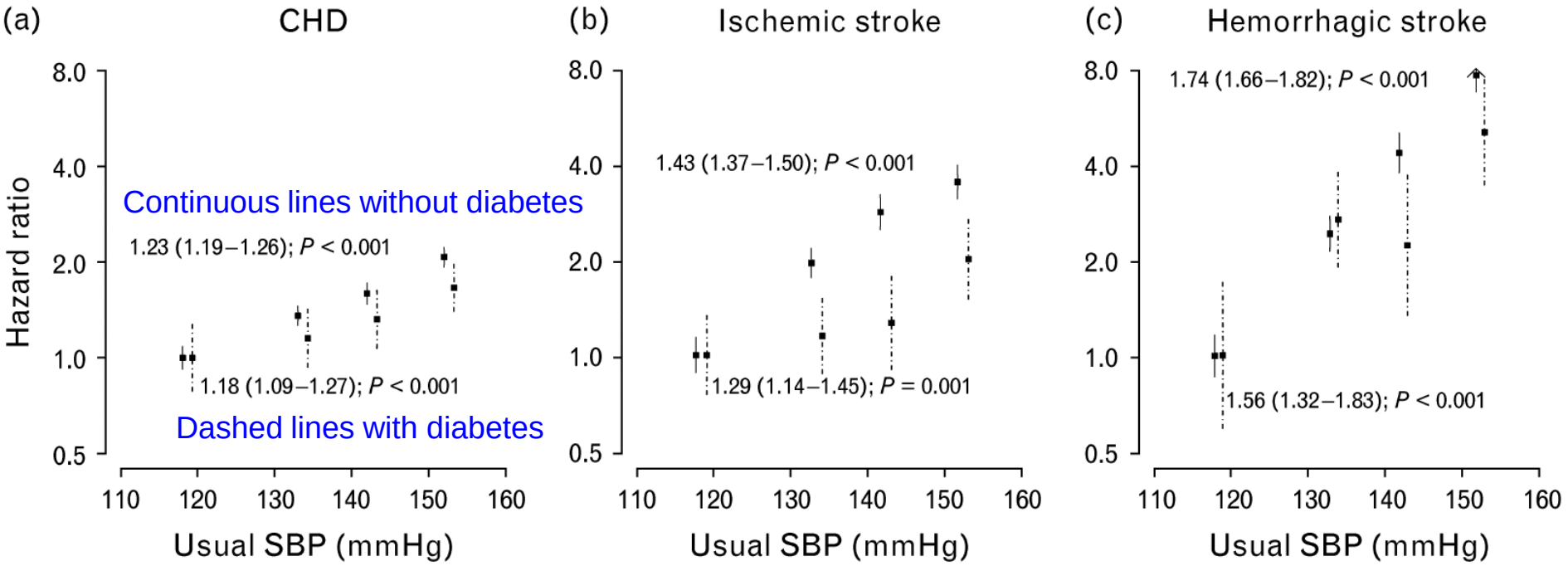
Martiniuk ALC, for the Asia-Pacific Cohort Studies Collaboration, J Hypertens 2007; 25:73–79.

Age-adjusted and sex-adjusted stroke mortality rates



Johnston SC et al, Lancet Neurol 2009; 8: 345–54.

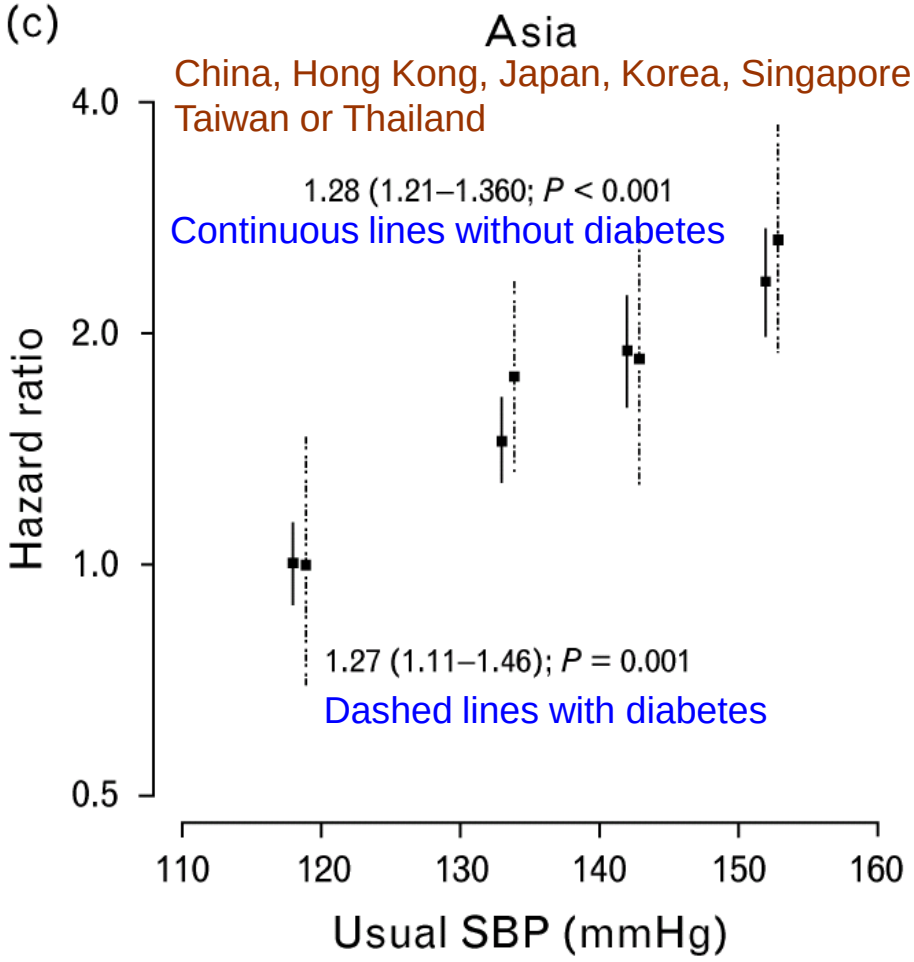
Systolic BP, diabetes and the risk of cardiovascular diseases in the Asia–Pacific region

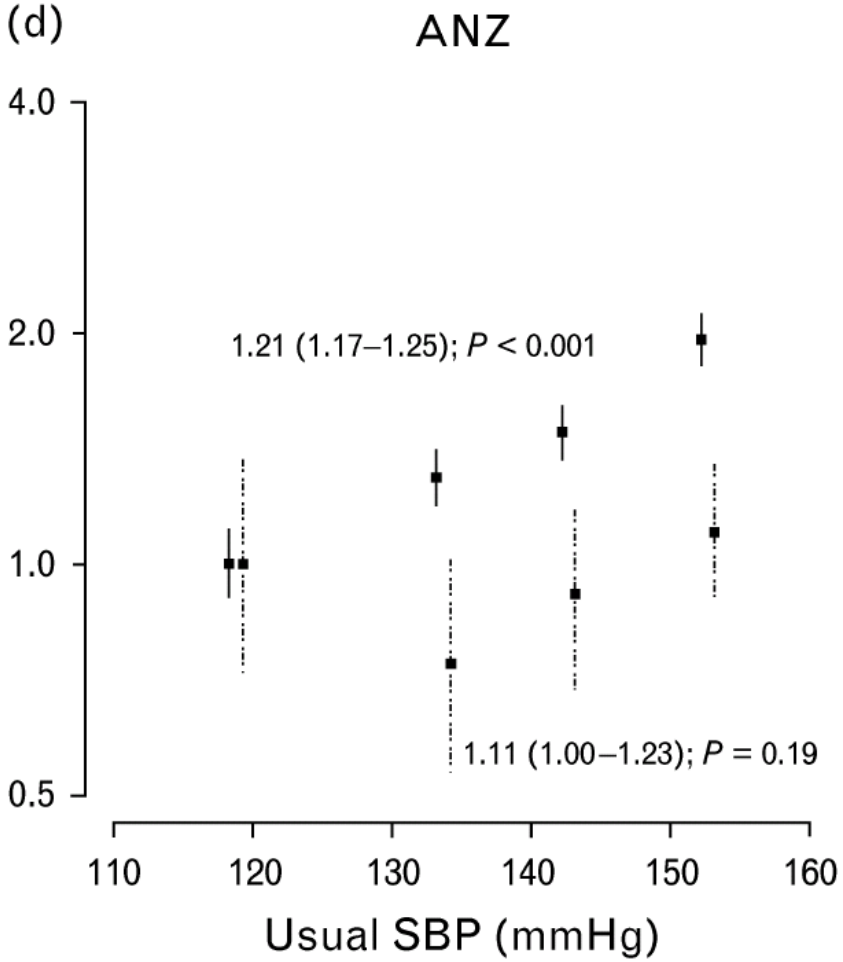


Hazard ratio (95% CI) for a 10mmHg higher level of SBP with the lower fourth of SBP fixed at 1.0, separately for those with and without diabetes. Analyses are adjusted by age and stratified by study and sex for those with and without diabetes. P value for linear trend

Asia-Pacific Cohort Studies Collaboration, J Hypertens 2007; 25:1205–1213.

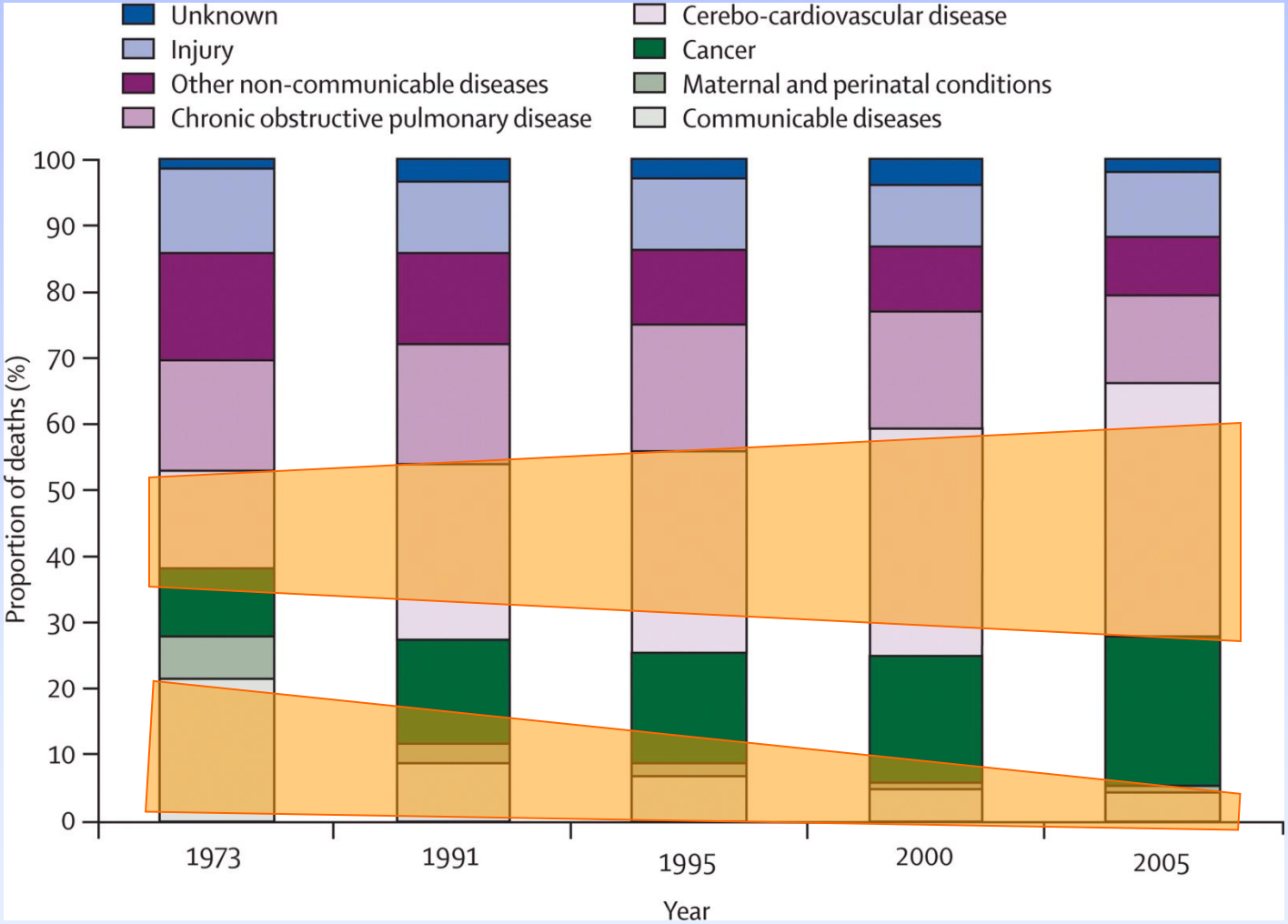
Systolic BP, diabetes and the risk of cardiovascular diseases in the Asia–Pacific region





Asia-Pacific Cohort Studies Collaboration, J Hypertens 2007; 25:1205–1213.

Distribution of causes of death in China between 1973 and 2005



Cerebro-cardiovascular disease

Communicable diseases

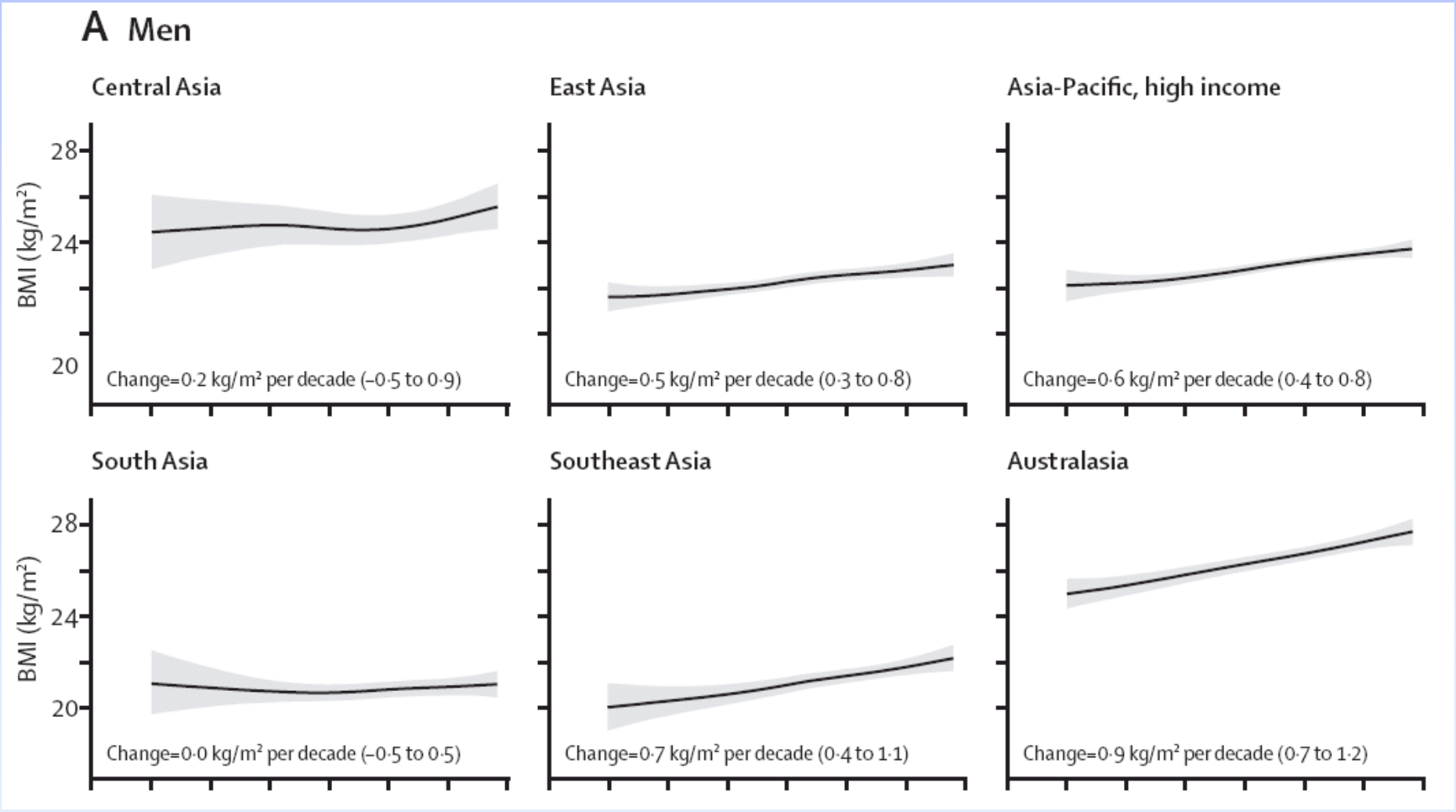
Yang G, et al. Lancet 2008; 372:1697-1705

Distribution of causes of death in China between 1973 and 2005

- Prevalence of hypertension in China has risen rapidly during the last 30 years.
- In 2002, nearly 18% of Chinese adults ≥15 years had hypertension ≡ 177 million people
- High salt intake is one causative factor
  - average daily salt intake for adult man in 2002 = 12 g/day ~ twice that recommended
  - In some rural areas, average intake as high as 14·7 g/day

Yang G, et al. Lancet 2008; 372:1697-1705

National, regional, and global trends in body-mass index since 1980



Finucane MM, et al, Lancet; Published Online Feb 2011.

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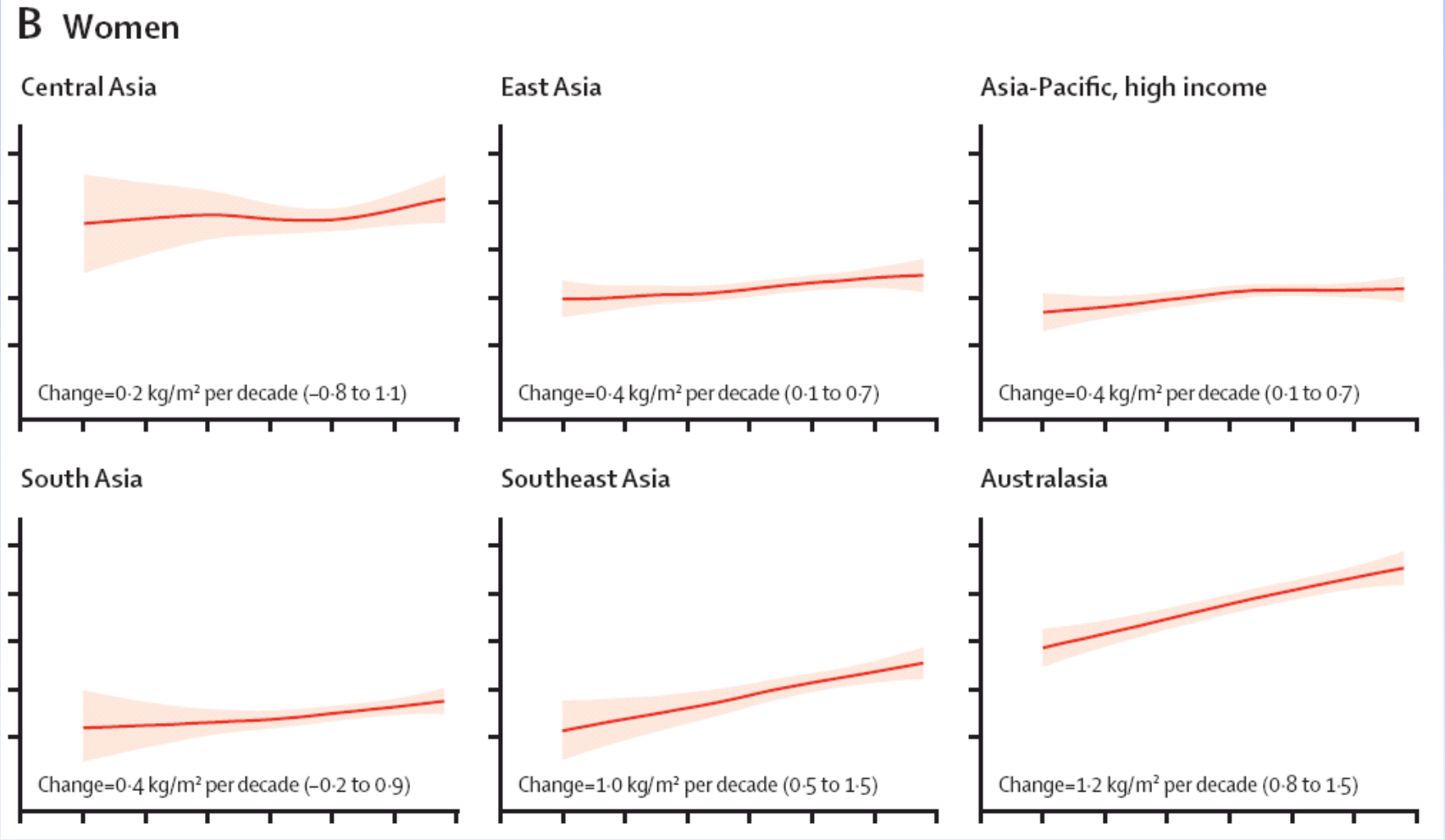
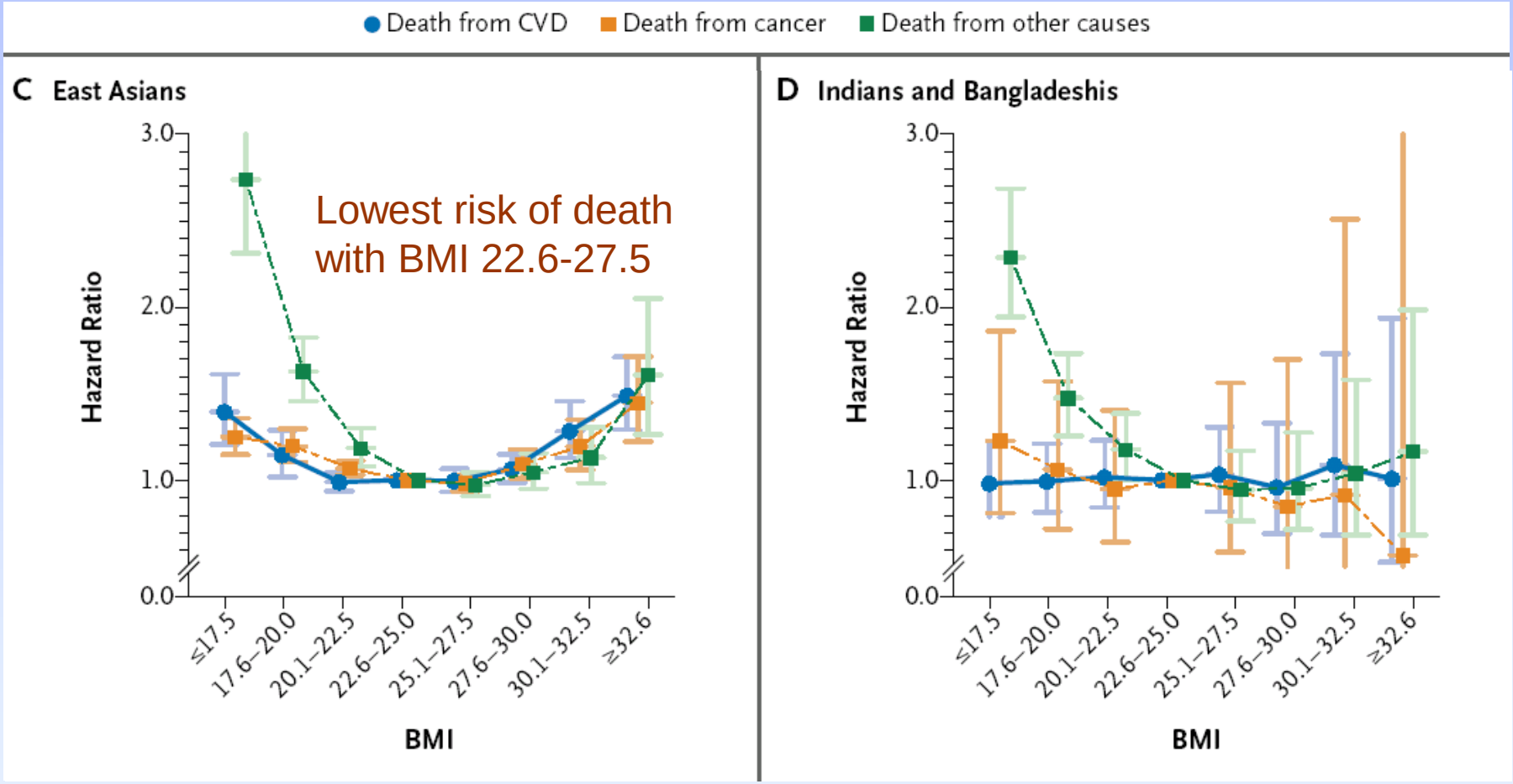


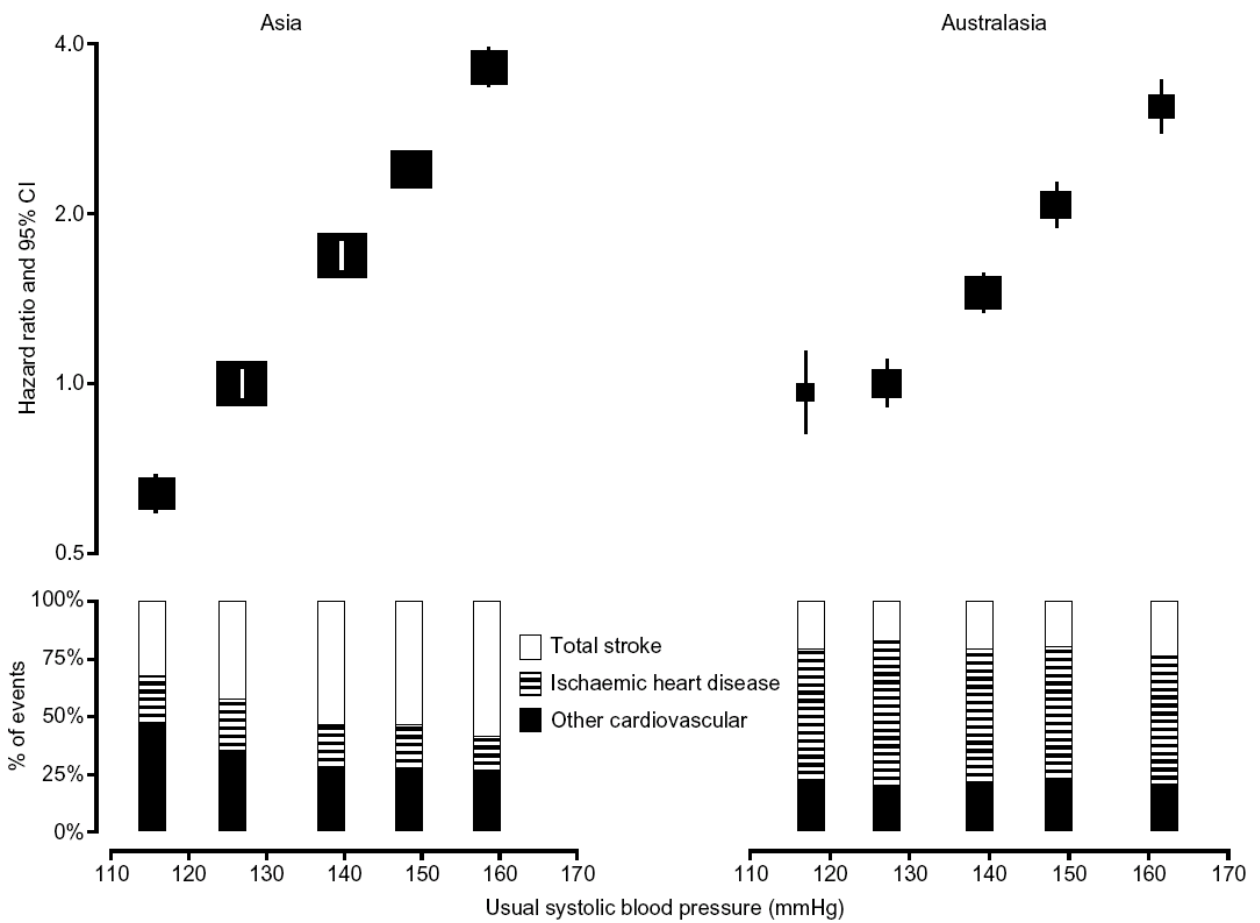
Finucane MM, et al, Lancet; Published Online Feb 2011.

Association between Body-Mass Index and Risk of Cause-Specific Death in Two Asian Populations.



Zheng W et al, N Engl J Med 2011;364:719-29.

Usual systolic blood pressure and risks of cardiovascular death in Asia and Australasia



A 10 mmHg lower SBP was associated with

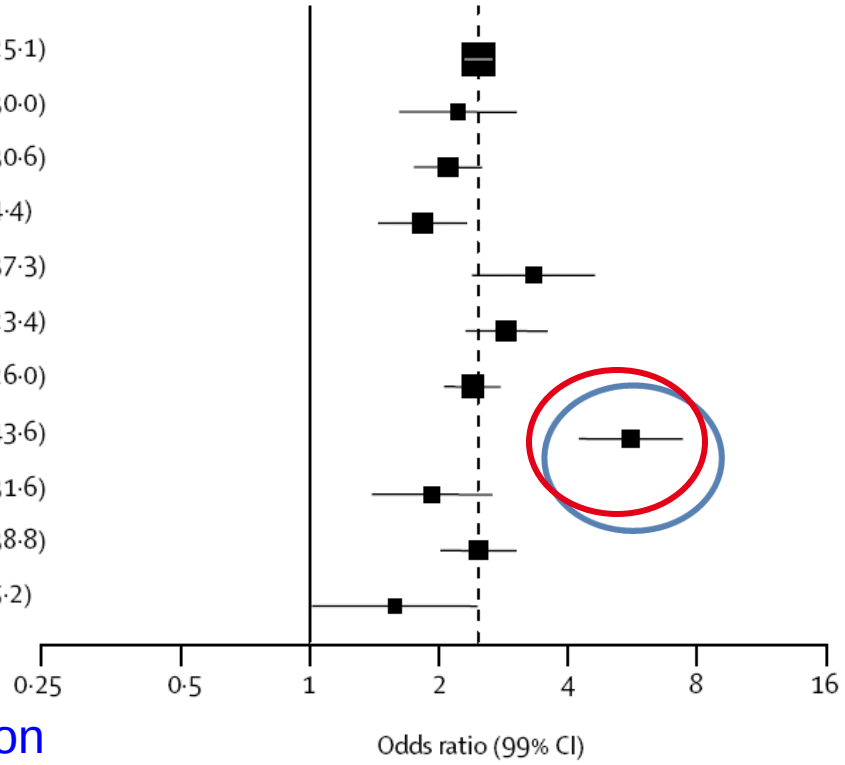
41% (95% CI, 40–42%) lower stroke risk in Asia compared to a

30% (22–37%) lower stroke risk in Australasia (P = 0.003)

Lawes CM for Asia Pacific Cohort Studies Collaboration, J Hypertens 2003;21(4):707-716.

INTERHEART study

Region	n	Control (%)	Case (%)	Odds ratio (99% CI)	PAR (99% CI)
Overall	26916	22·3	38·6	2·48 (2·30–2·68)	23·4% (21·7–25·1)
W Eur	1425	16·4	33·0	2·22 (1·62–3·05)	21·9% (15·6–30·0)
CE Eur	3636	32·7	46·0	2·11 (1·76–2·53)	24·5% (19·2–30·6)
MEC	3404	20·2	25·9	1·84 (1·45–2·33)	9·2% (5·7–14·4)
Afr	1355	21·6	43·4	3·34 (2·40–4·65)	29·6% (22·8–37·3)
S Asia	3881	13·8	31·1	2·89 (2·31–3·60)	19·3% (15·7–23·4)
China/HK	6075	21·1	37·3	2·41 (2·06–2·80)	22·1% (18·7–26·0)
SE Asia	2141	15·3	46·8	5·63 (4·26–7·45)	38·4% (33·3–43·6)
ANZ	1269	22·0	37·8	1·94 (1·40–2·68)	22·6% (15·6–31·6)
S Am	3100	27·7	49·3	2·48 (2·03–3·04)	32·7% (27·2–38·8)
N Am	630	28·6	38·8	1·58(1·01–2·47)	19·0% (9·2–35·2)



Risk of acute MI with self-reported hypertension

The risk of acute MI with self-reported hypertension was particularly high in SE Asian populations (OR 5·6, 99% CI 4·3–7·5) compared with South Asians, China/ Hong Kong or the overall world population (OR 2·5, 99% CI 2·3–2·7).

Yusuf S et al, Lancet 2004; 364: 937–52.

Question 1

Concerning the epidemiology and cardiovascular risks associated with hypertension in Asian countries, which of the following statements is correct?

A. **The prevalence of hypertension has decreased in most Asian countries in recent years**
B. **The risk of acute myocardial infarction with self-reported hypertension is lowest in Southeast Asia**
C. **Hypertension contributes a greater population-attributable fraction to ischaemic heart disease than to haemorrhagic stroke**
D. **A 10 mmHg lower systolic blood pressure was associated with a greater reduction in stroke risk in Asia compared to in Australasia**
E. **Higher levels of BMI increase the risk for cardiovascular disease mortality in India in Bangladesh**

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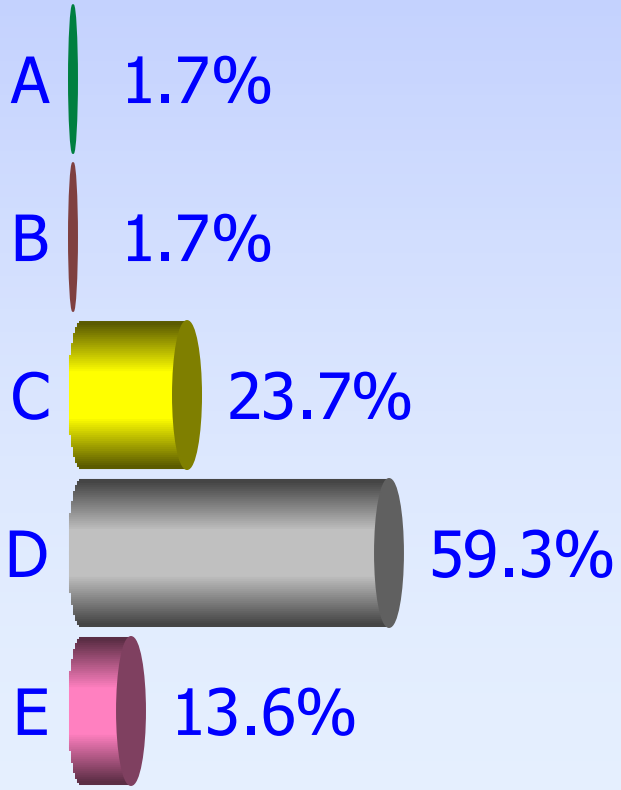


Hypertension management in Asia

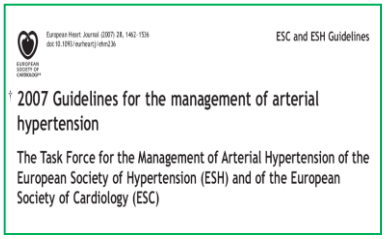
- The most obvious difference between Asians and Caucasians in the response to antihypertensive drugs is the higher rate of cough with ACEIs in some Asian countries, which probably has a genetic basis.
- Genetic factors may also be important in the blood pressure response to some antihypertensive agents.
- The high frequency of the intermediate metaboliser genotype of cytochrome P450 (CYP) 2D6 in East Asian countries increases the variability of the phamacokinetics and probably the blood pressure response to metoprolol and some other beta-blockers

Guidelines acknowledge that most patients need combination therapy to achieve BP goals

JNC VII

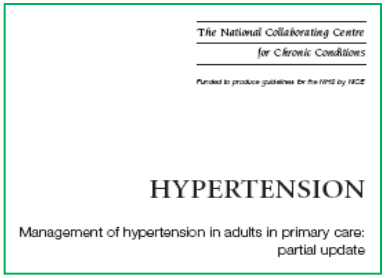
- **Most patients with hypertension will require two or more antihypertensive medications to achieve their BP goals**
  - When BP is > 20/10 mmHg above goal, consideration should be given to initiating therapy with two drugs

ESH/ESC



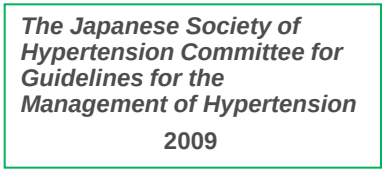
- **Combination treatment should be considered as first choice when there is high CV risk**
  - i.e., in individuals in whom BP is markedly above the hypertension threshold (> 20/10 mmHg), or associated with multiple risk factors sub-clinical organ damage, diabetes, renal or CV disease

NICE



- **Many patients will require more than one drug to achieve adequate BP control**
  - Pathophysiological reasoning suggests that adding an ACE-I/ARB to a CCB or a diuretic (or vice versa in the younger group) are logical combinations

JSH



- **The use of two or three drugs in combination is often necessary to achieve the target BP control**
  - A low dose of a diuretic should be included in this combination

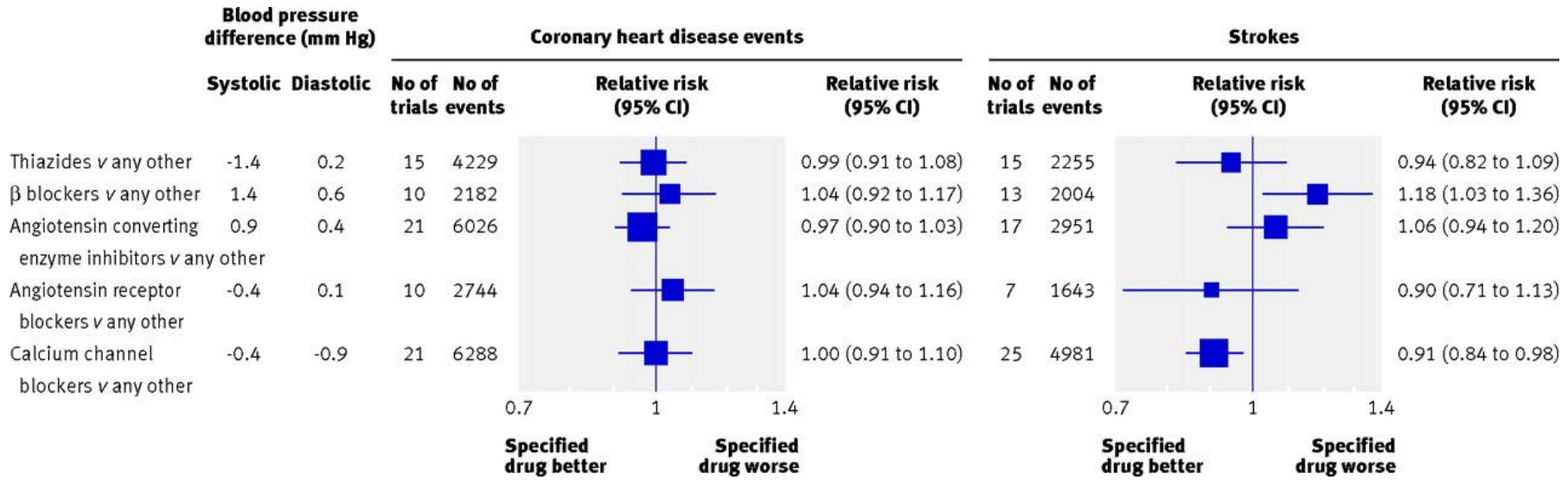
Chobanian et al. *JAMA.* 2003;289:2560–2572; Mancia et al. *Eur Heart J.* 2007;28:1462–1536; http://www.nice.org.uk/download.aspx?o=CG034fullguideline (accessed January 2010); Ogihara et al. *Hypertens Res.* 2009;32:3–107.

Reappraisal of European guidelines on hypertension management 2009

- Choice of antihypertensive drugs:
  - Large-scale meta-analyses confirm that 5 major antihypertensive drug classes, including diuretics, ACEI , calcium antagonists, angiotensin receptor antagonists, and beta-blockers do not differ significantly for their overall ability to reduce BP in hypertension
  - All 5 drug classes can be considered suitable for initiation and maintenance of antihypertensive treatment
- "However, once it is agreed
  1. that the major mechanism of the benefits of antihypertensive therapy is BP lowering ***per se***,
  2. the effects on cause-specific outcomes of the various agents are similar or differ by a minor degree,
  3. the type of outcome to occur in a given patient is unpredictable, and
  4. all classes of antihypertensive agents have their pros and cons,
- it is obvious that any all-purpose ranking of drugs for general antihypertensive usage is unnecessary and probably deceiving."

Mancia G et al. J Hypertens 2009; 27: 2121-58.

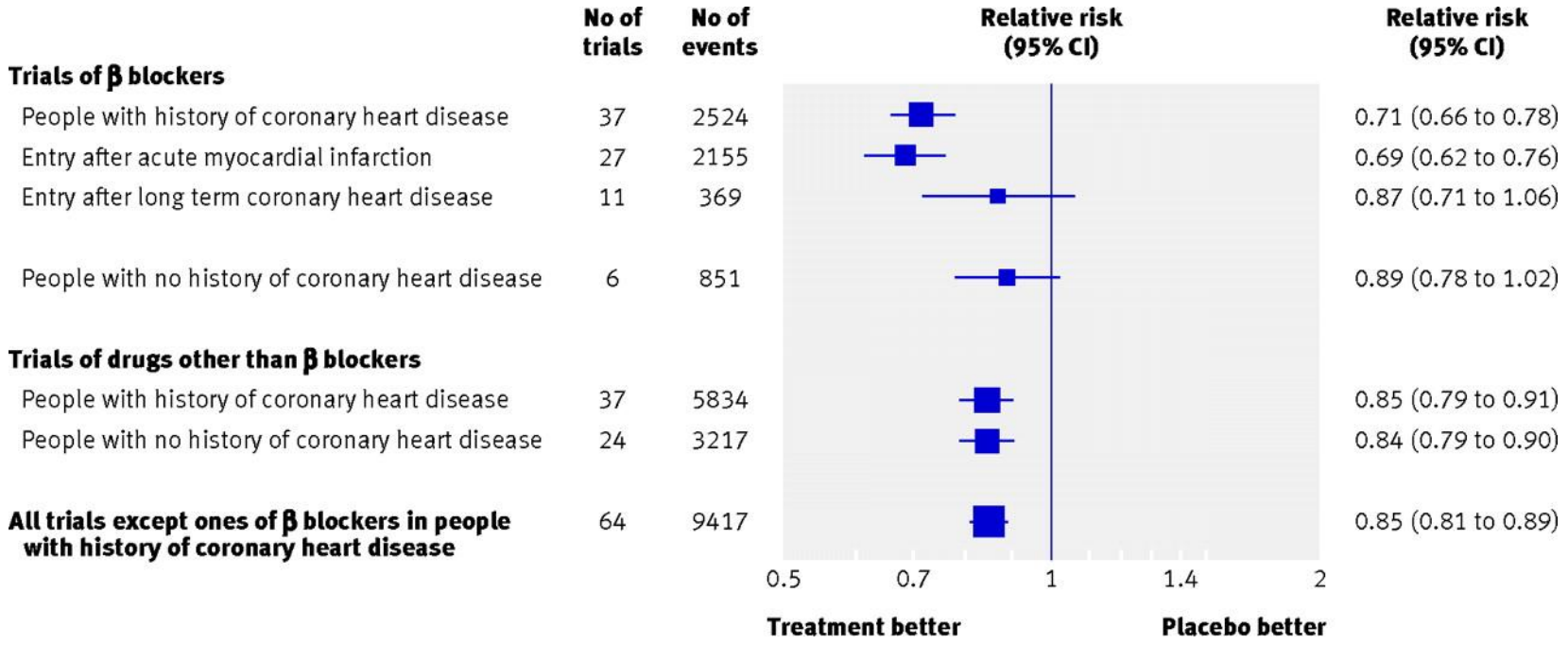
Use of BP-lowering drugs in preventing CVD: A meta-analysis



- Relative risk estimates of CHD events and stroke in 46 drug comparison trials comparing each of the 5 classes of BP-lowering drug with any other class of drug
- 5 main classes of BP-lowering drugs were similarly effective in reducing BP and preventing CHD events and strokes

Law MR et al, BMJ. 2009; 338: b1665.

Use of BP-lowering drugs in preventing CVD: A meta-analysis



- Relative risk estimates of CHD events in single drug blood pressure difference trials according to drug
- β-blockers were shown to exert effects beyond BP lowering:
  - secondary prevention of coronary artery disease (CAD)
  - Protective effect when administered after myocardial infarction (MI)

Law MR et al, BMJ. 2009; 338: b1665.

Key recommendations from Asian guidelines

Guidelines	Recommendations
Chinese Expert Consensus 2009[27]	β-Blockers are recommended as first line treatment, for long-term treatment, as monotherapy and in combination β-Blockers are recommended for ACS with hypertensive emergencies and severe uncontrolled chest pain
Indian Society of Hypertension Guidelines[28]	Adapted from JNC 7, ESH/ESC guidelines Any of the 5 drug classes are recommended as first-line treatment Use of compelling indication Target BP <140/90 mmHg or <130/80 mmHg in diabetic patients or those with kidney disease
Indonesian Society of Hypertension Consensus 2007[29]	Refer to JNC 7 All antihypertensive drug classes are recognized as a first-line option Use of compelling indications Combination therapy for BP ≥160/100 mmHg Target BP of <140/90 mmHg or <130/80 mmHg in diabetic patients and patients with renal failure
Korean Society of Hypertension Guidelines 2004[30]	Similar to JNC 7, ESH/ESC guidelines β-Blockers are considered as first-line option hypertension
Malaysian Clinical Practice Guideline on Hypertension 2008[31]	Four classes of antihypertensive agents except β-blockers are recommended as first-line in newly diagnosed, uncomplicated hypertensives with no compelling indication Combination therapy for systolic BP ≥ 160 and/or diastolic BP ≥ 100 mmHg Target BP on therapy <140/90 mmHg for all and <130/80 mmHg for diabetics Drug of choice for compelling indications listed
Philippine Society of Hypertension[32,33]	Initiate medical treatment if hypertensive (regardless of risk classification) Focus on BP control All antihypertensive drug classes recognized
Singapore MOH Guidelines 2005[34]	All 5 drug classes recognized as first-line option Use compelling indications, contraindications Combination therapy for BP ≥160/100 mmHg Target BP <140/90 mmHg Lower BP target of <130/80 mmHg for diabetics and renal failure No prehypertension classification

Tomlinson B et al, Current Medical Research & Opinion 2011

Question 2

In the meta-analysis of randomised trials of blood pressure lowering drugs recording CHD events and strokes by MR Law et al. BMJ 2009, which group of drugs had a special effect over and above that due to blood pressure reduction in preventing recurrent CHD events in people with a history of CHD or recent myocardial infarction?

A. **Thiazides**

B. **β-blockers**

C. **Angiotensin converting enzyme inhibitors**

D. **Angiotensin receptor blockers**

E. **Calcium channel blockers**

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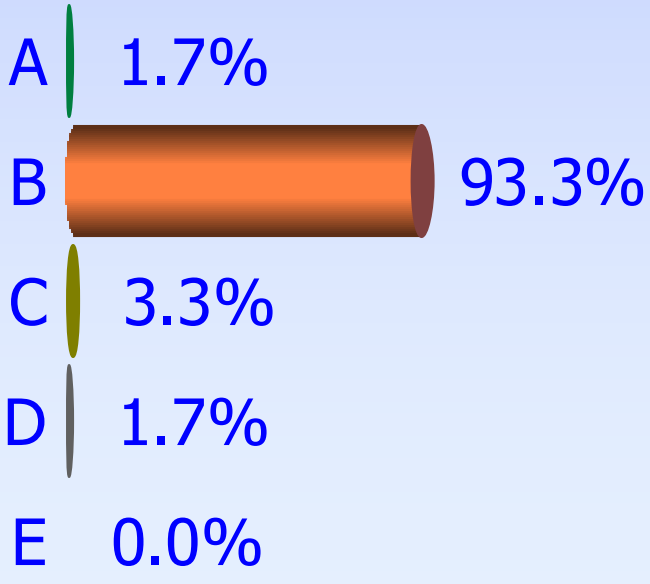
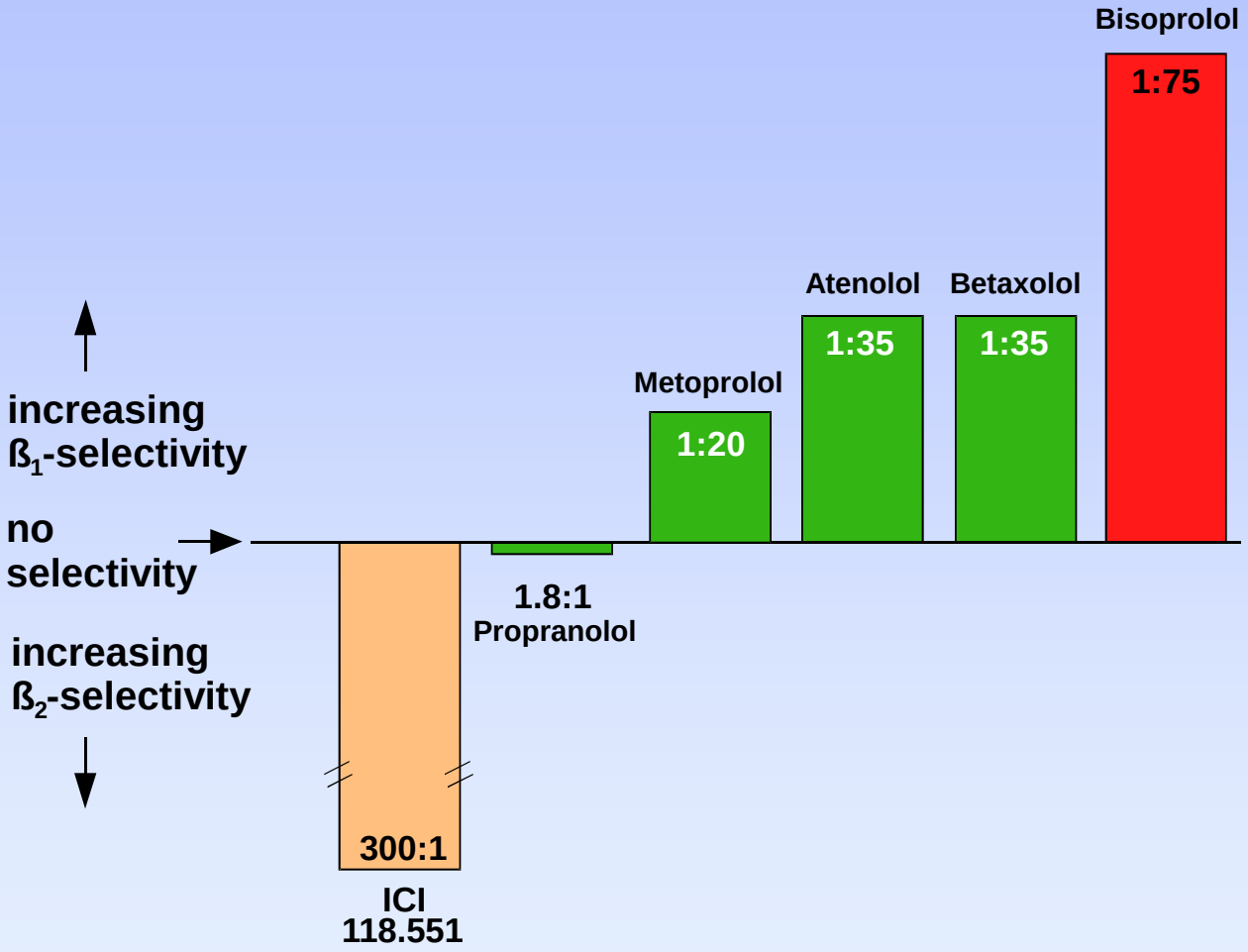


Beta$_1$-selectivity of various beta-blockers

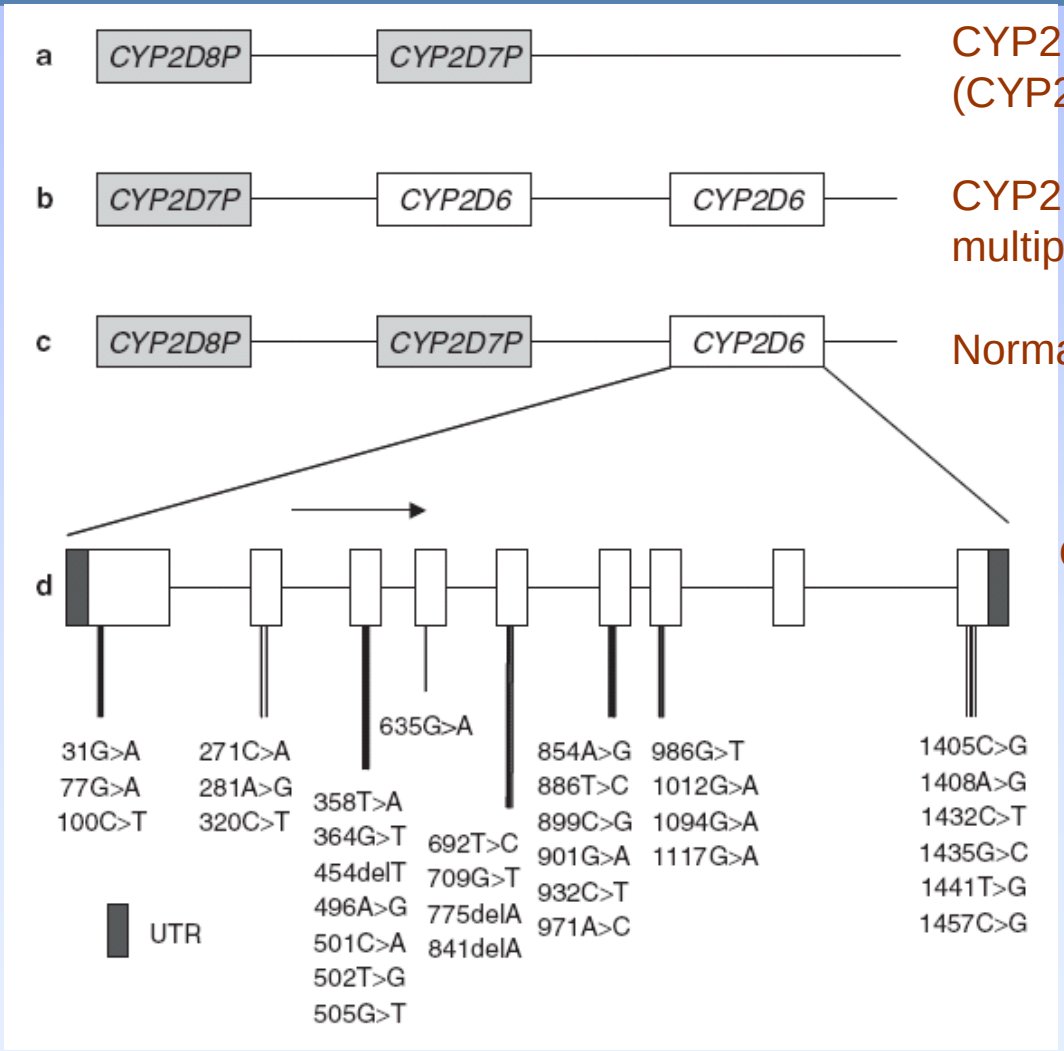


Wellstein A et al. J Cardiovasc Pharmacol 1986; 8 (Suppl. 11): 36-40
Wellstein A et al. Eur Heart J 1987; 8 (Suppl. M): 3–8

Beta-blockers in Hypertension in Asian patients

- Can the effects be predicted?

The human CYP2D gene cluster and common SNPs



CYP2D6 gene deletion (CYP2D6*5)

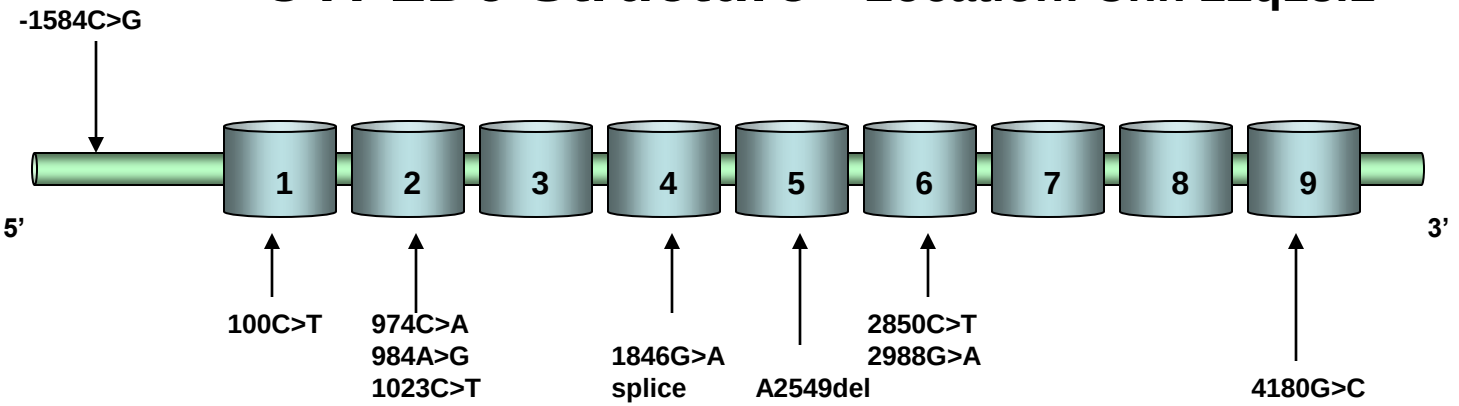
CYP2D6 duplication or multiplication

Normal CYP2D locus

Common SNPs

Zhou SF. Clin Pharmacokin 2009;48(11):689-723.

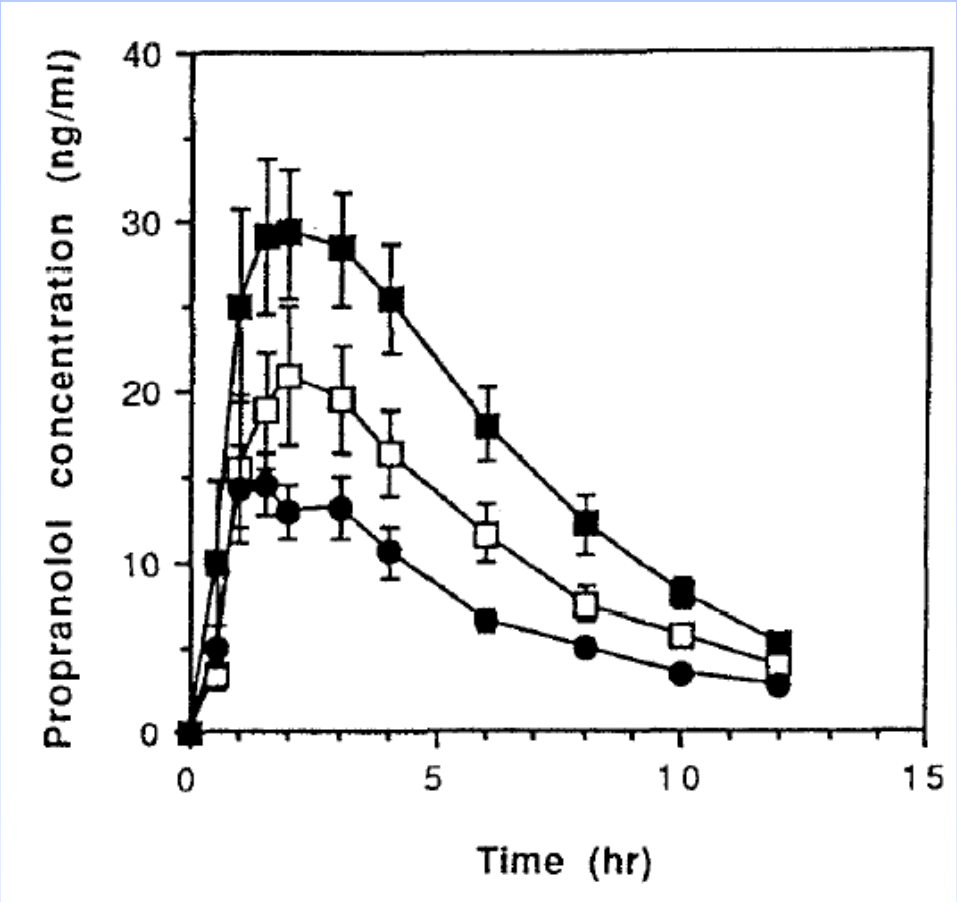
CYP2D6 Structure Location: Chr. 22q13.1



Allele	Enzyme Activity	Frequency distribution		
		Whites	Blacks	Asians
*1 wild-type	Normal	33.4-83.8%	27.8-90.4%	22.7-49.0%
*2 (-1584C>G, 2850C>T, 4180G>C)	Normal	32.4-35.3%	9.9-40.0%	8.0-13.4%
*3 (A2549del)	Inactive	0.0-2.5%%	0.0-1.0%	0.0%
*4 (100C>T, 974C>A, 984A>G, 1846G>A splice, 4180G>C)	Inactive	11.3-28.6%	0.9-9.3%	0.2-0.8%
*5 gene deletion	No Activity	0.6-7.3%	3.3-9.0%	1.2-6.2%
*10 (100C>T, 4180G>C)	Decreased	1.4-6.1%	1.0-8.6%	38.1-70.0%
*17 (1023C>T, 2850C>T, 4180G>C)	Decreased	0.0-1.1%	9.0-34.0%	0.0%
*41 (-1584C>G, 2850C>T, 2988G>A, 4180G>C)	Decreased	10-20%	-	

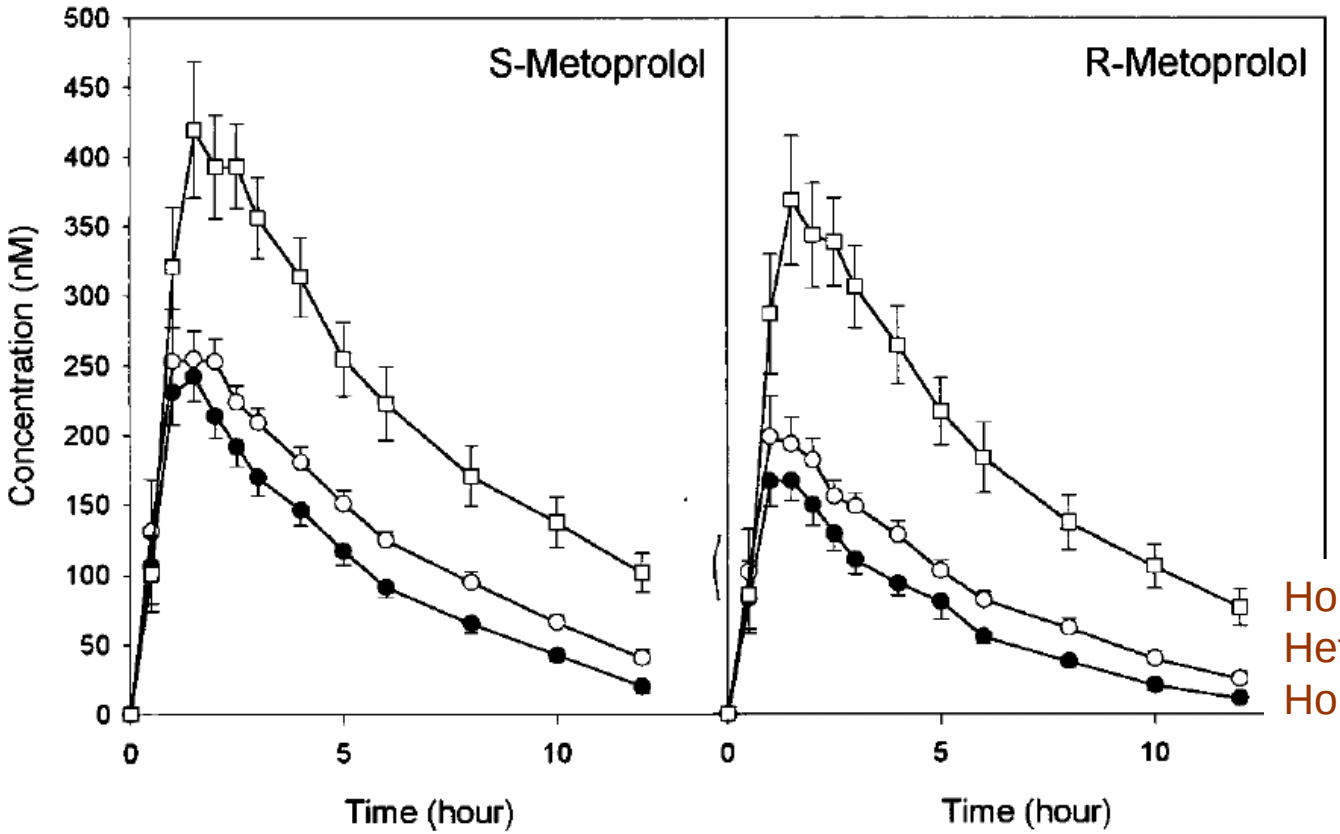
Refs: Cascorbi 2003, Xie 2001, Zanger UM 2004

Propranolol disposition in Chinese subjects of different CYP2D6 genotypes: 188C>T



Lai ML, et al. Clin Pharmacol Ther. 1995; 58(3): 264-8.

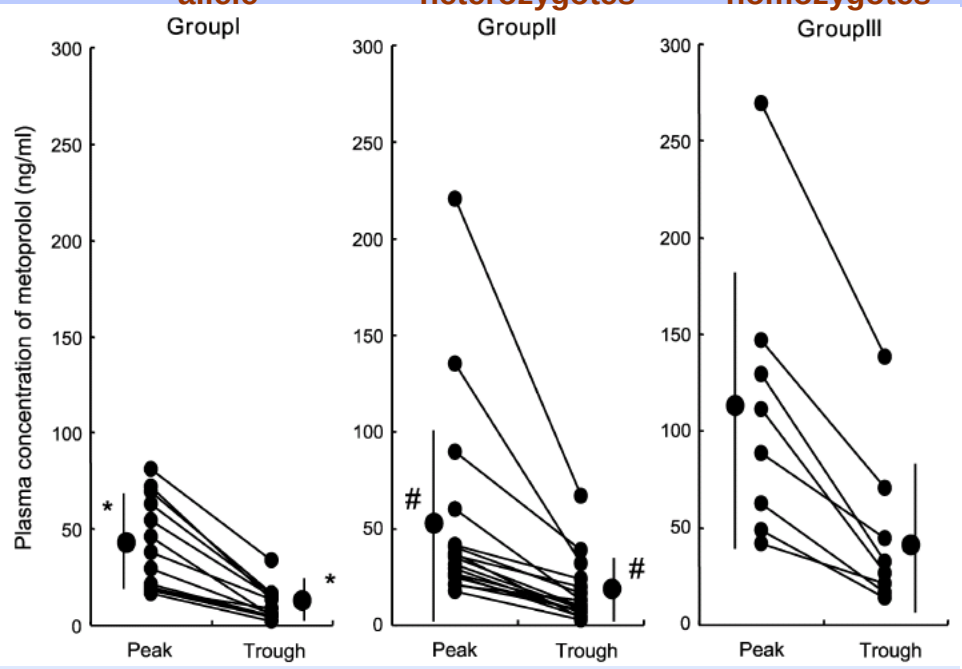
Metoprolol pharmacokinetics according to CYP2D6*10 genotypes

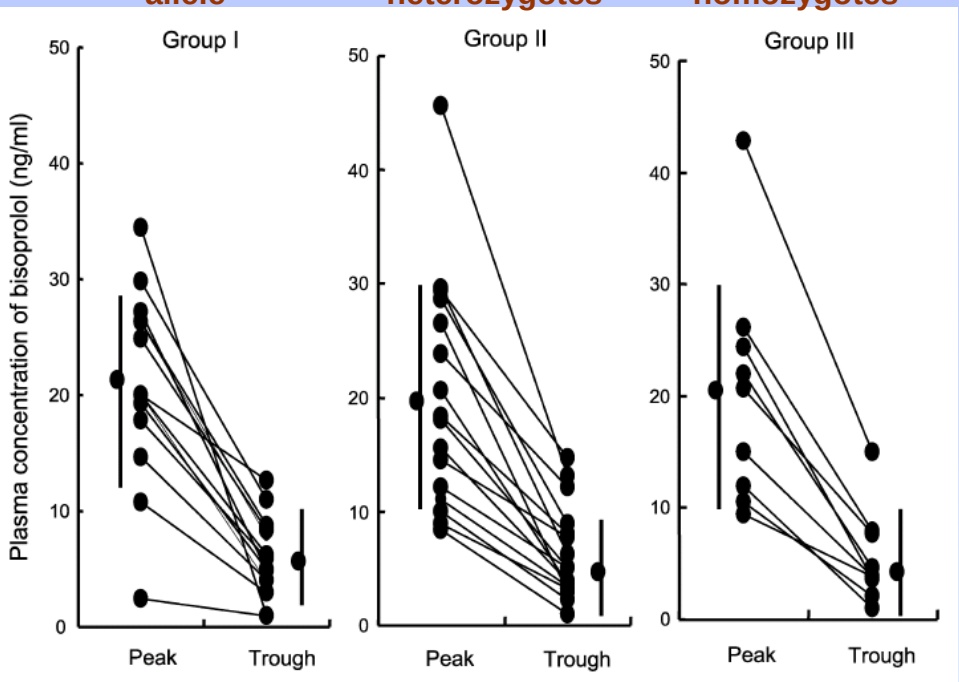


Homozygous T188 (n = 12)
Heterozygous C/T188 (n = 12)
Homozygous C188 (n = 16)

Huang JD et al. Clin Pharmacol Ther 1999;65:402-7.

Influence of CYP2D6 genotype on metoprolol concentration and beta-blockade

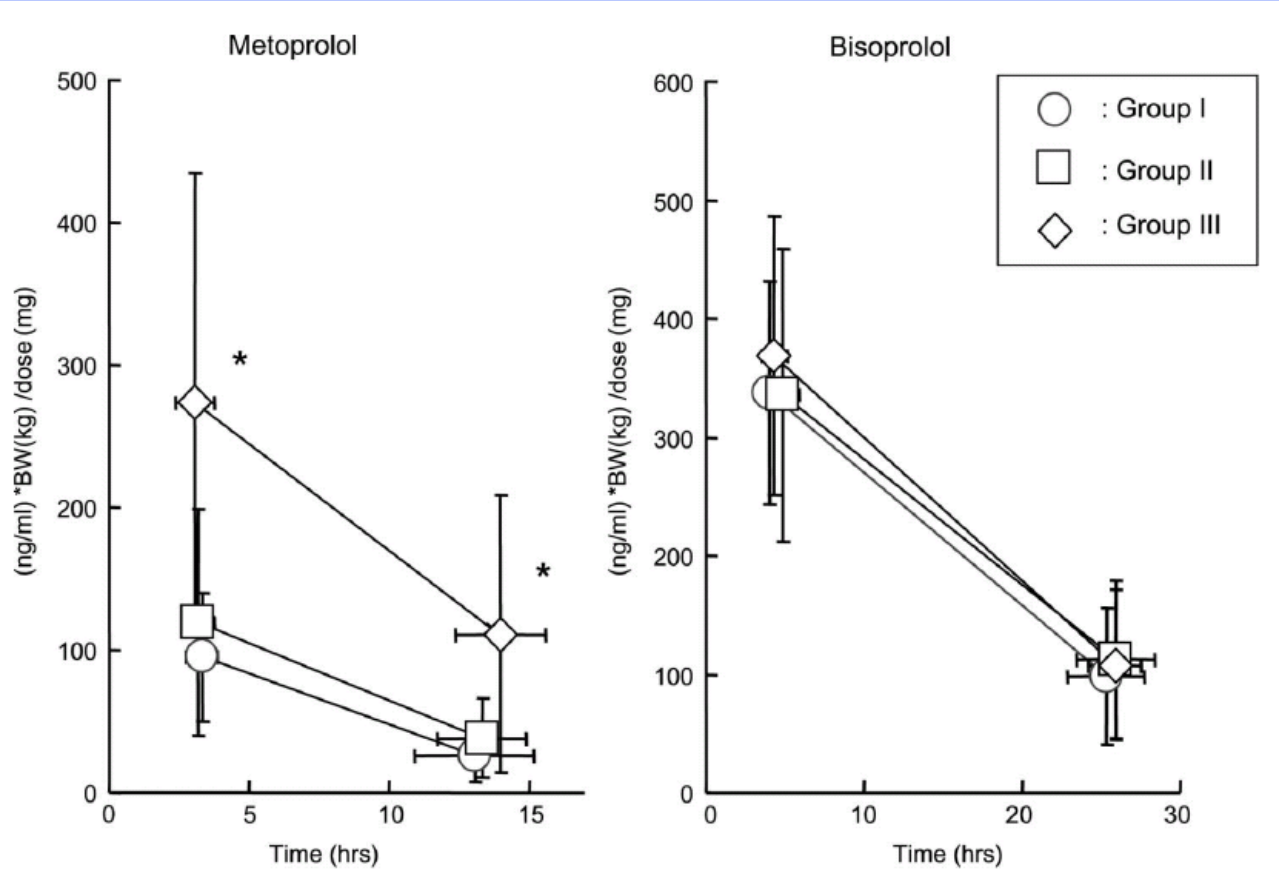




Patients routinely treated with metoprolol 2 or 3 x/day studied at peak and trough concentrations and compared with patients treated with bisoprolol once daily.

Nozawa T et al. J Cardiovasc Pharmacol 2005;46(5):713-720.

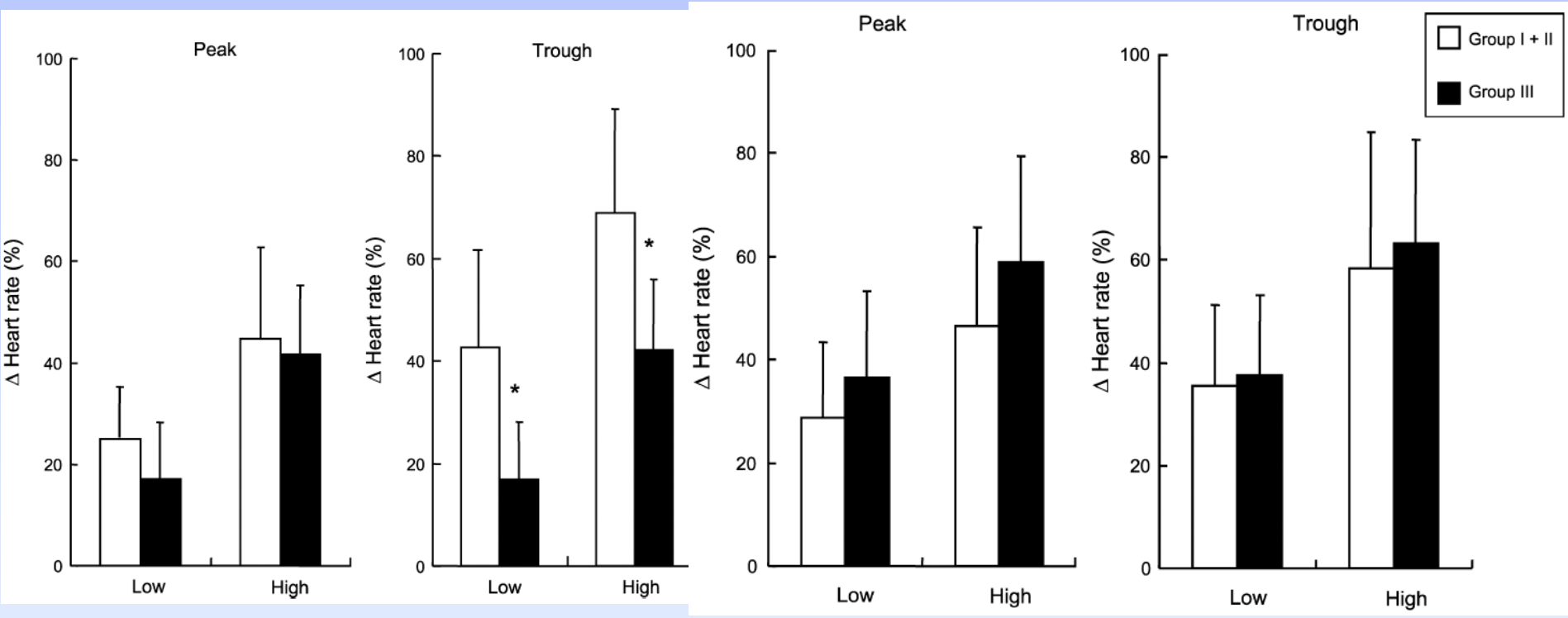
Influence of CYP2D6 genotype on metoprolol concentration and beta-blockade



CYP2D6*10 homozygotes show higher peak and trough plasma concentrations of metoprolol but not bisoprolol (concentrations normalized for dose/body weight)

Nozawa T et al. J Cardiovasc Pharmacol 2005;46(5):713-720.

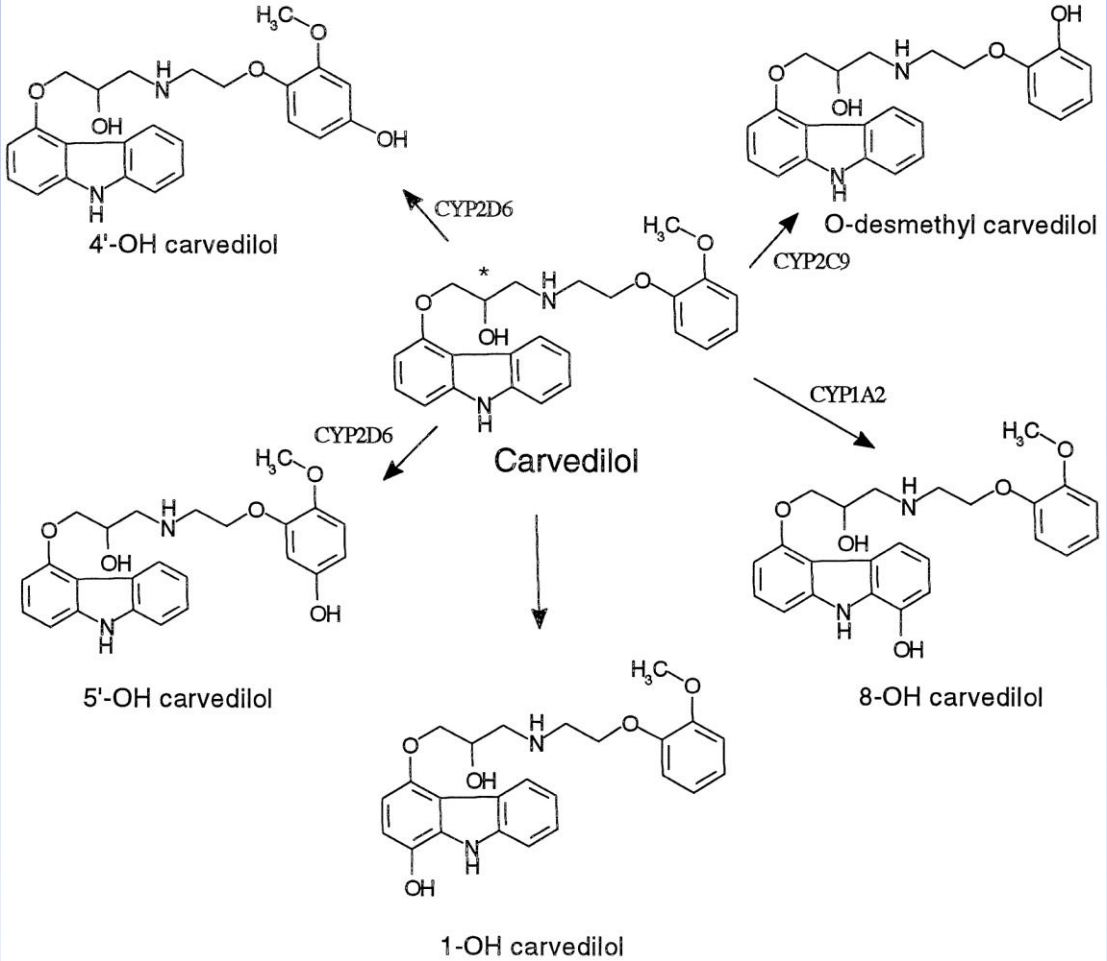
Influence of CYP2D6 genotype on metoprolol concentration and beta-blockade



Isoprenaline-induced % increases in heart rate were less in CYP2D6*10 homozygotes than in other patients at the trough, but not at peak for metoprolol but not for bisoprolol.

Nozawa T et al. J Cardiovasc Pharmacol 2005;46(5):713-720.

Structure of carvedilol and its metabolites



Oldham HG, Clarke SE. Drug Metab Dispos 1997;25(8):970-977.

Alpha-blocking effect of carvedilol

Drugs 36 (Suppl. 6): 37-47 (1988)
0012-6667/88/0600-0037/$5.50/0

Vasodilating Mechanism and Response to Physiological Pressor Stimuli of Acute Doses of Carvedilol Compared with Labetalol, Propranolol and Hydralazine

Brian Tomlinson, Francois Bompart, Barrie R. Graham, Jun-Bao Liu and *Brian N.C. Prichard*

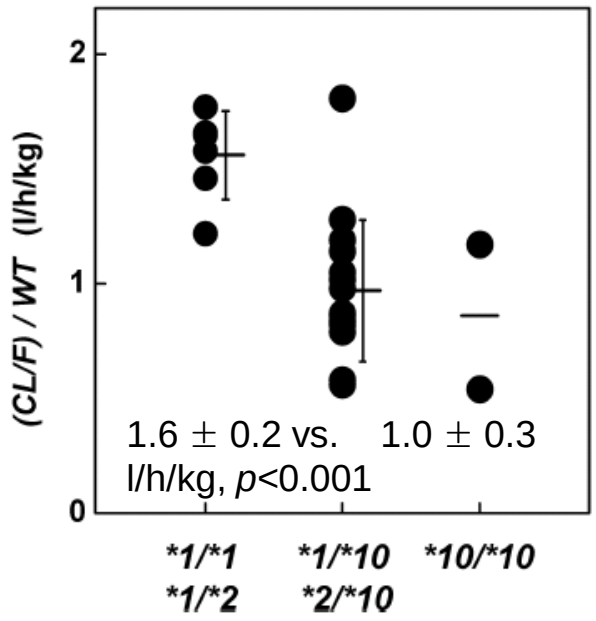
Department of Clinical Pharmacology, University College and Middlesex School of Medicine, University College London, London, United Kingdom

Tomlinson B et al. Drugs1988;36(Suppl 6):37-47.

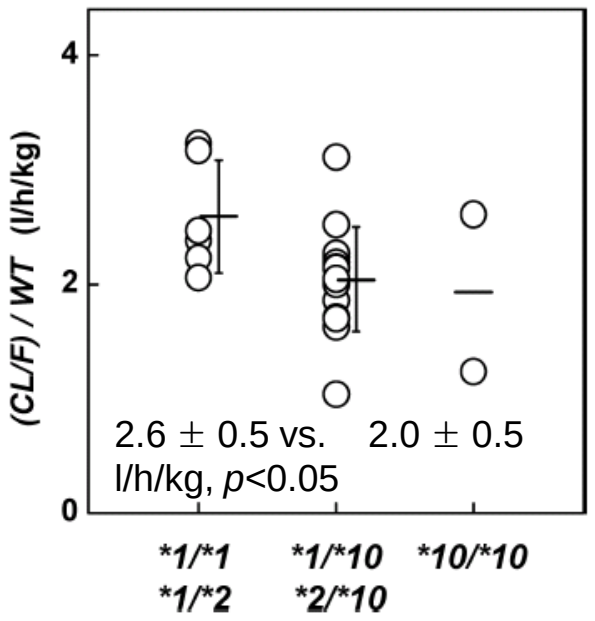
Effect of CYP2D6*10 on the pharmacokinetics of R- and S-Carvedilol

Values for weight-corrected oral clearance: (CL/F)/WT

R-Carvedilol



S-Carvedilol



Honda M et al, Biol Pharm Bull 2005;28(8):1476-1479.

Plasma concentrations of D- and L-nebivolol after 5 mg daily for 4 weeks in CYP2D6 poor (PM) or extensive (EM) metabolizers

	Peak (3 h post-dose)		Trough (24 h post-dose)	
	EMs	PMs	EMs	PMs
D-nebivolol	0.74 (0.62)	3.76 (1.76)**	0.19 (0.20)	1.87 (1.31)**
L-nebivolol	0.66 (0.58)	10.16 (4.56)**	0.64 (0.45)	6.49 (3.71)**

** $P<0.0001$

Absolute bioavailability of a single 5-mg dose of nebivolol has been reported to vary from 12% in EMs to 96% in PMs.
Nebivolol shows stereoselective metabolism.
The beta-blocking activity of nebivolol has been ascribed mainly to the D-enantiomer and the vasodilatory activity to the L-enantiomer.

Lefebvre J et al. Br J Clin Pharmacol 2007;63(5):575-582.

Question 3

Which of the following beta-blockers is not metabolized by CYP2D6 to a significant extent?

A. Propranolol

B. Metoprolol

C. Carvedilol

D. Nebivolol

E. Bisoprolol

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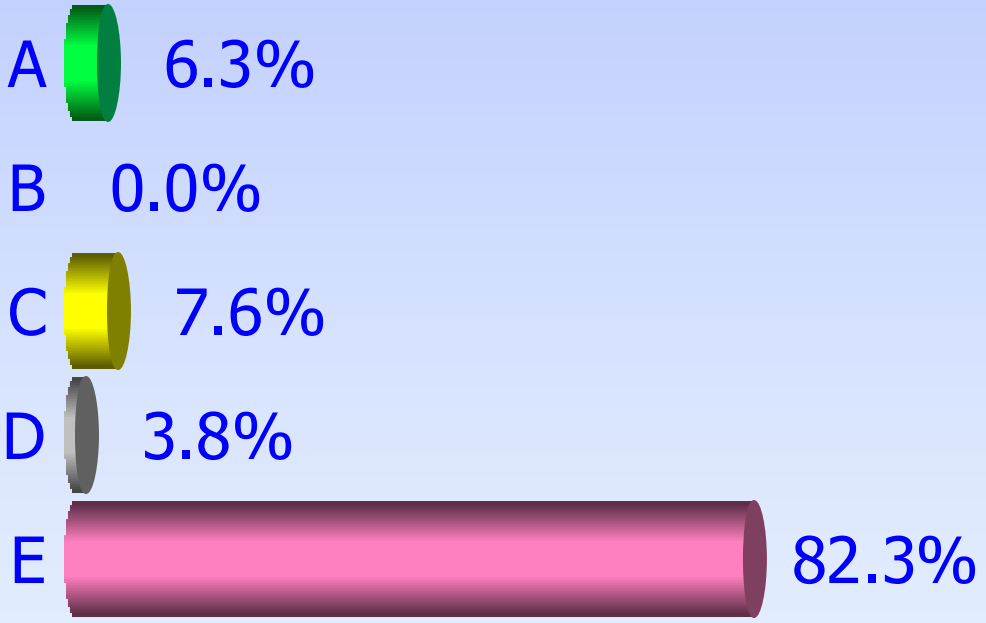


Beta-blockers in Hypertension in Asian patients

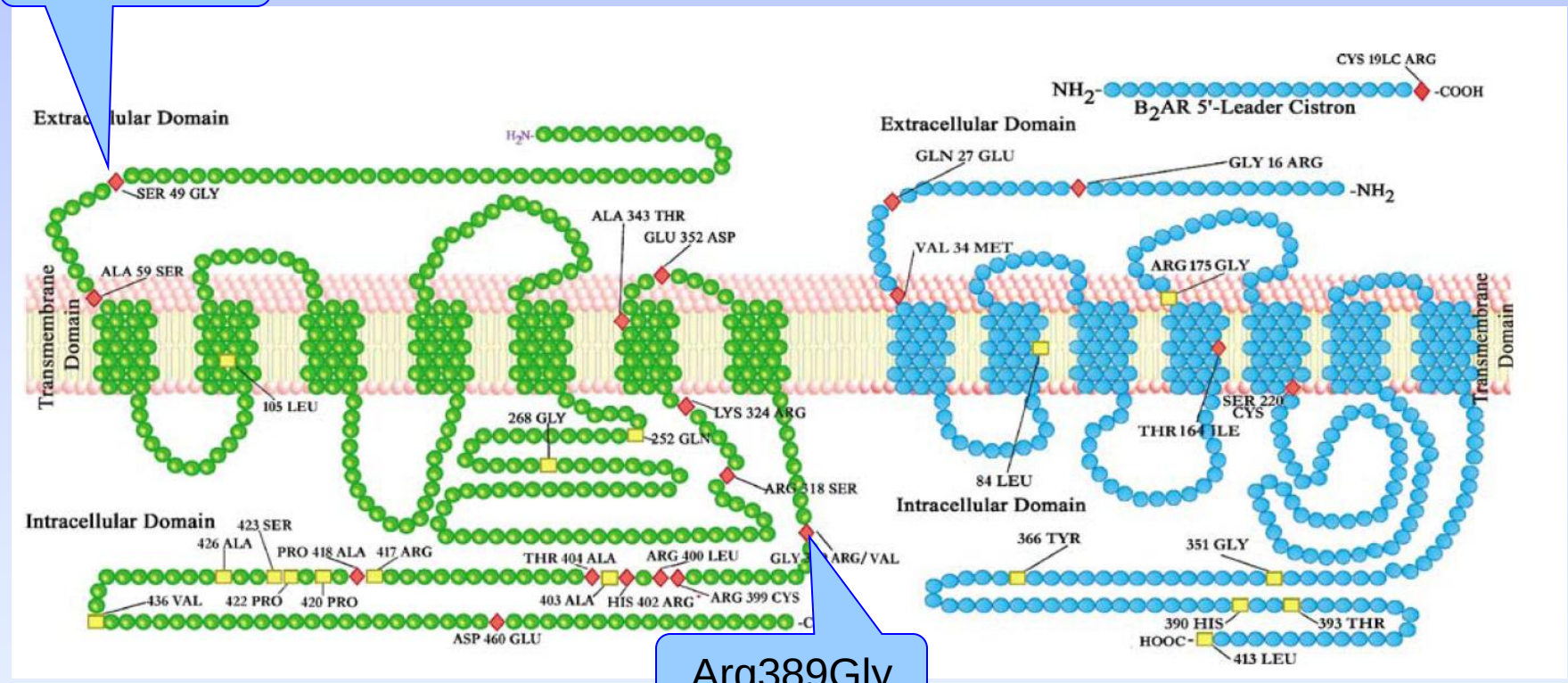
- Can the effects be predicted?
- Metoprolol and some other beta-blockers show wide variation in pharmacokinetics according to CYP2D6*10 genotypes – common in Chinese populations

Pharmacogenetics of the human beta-adrenergic receptors

Ser49Gly

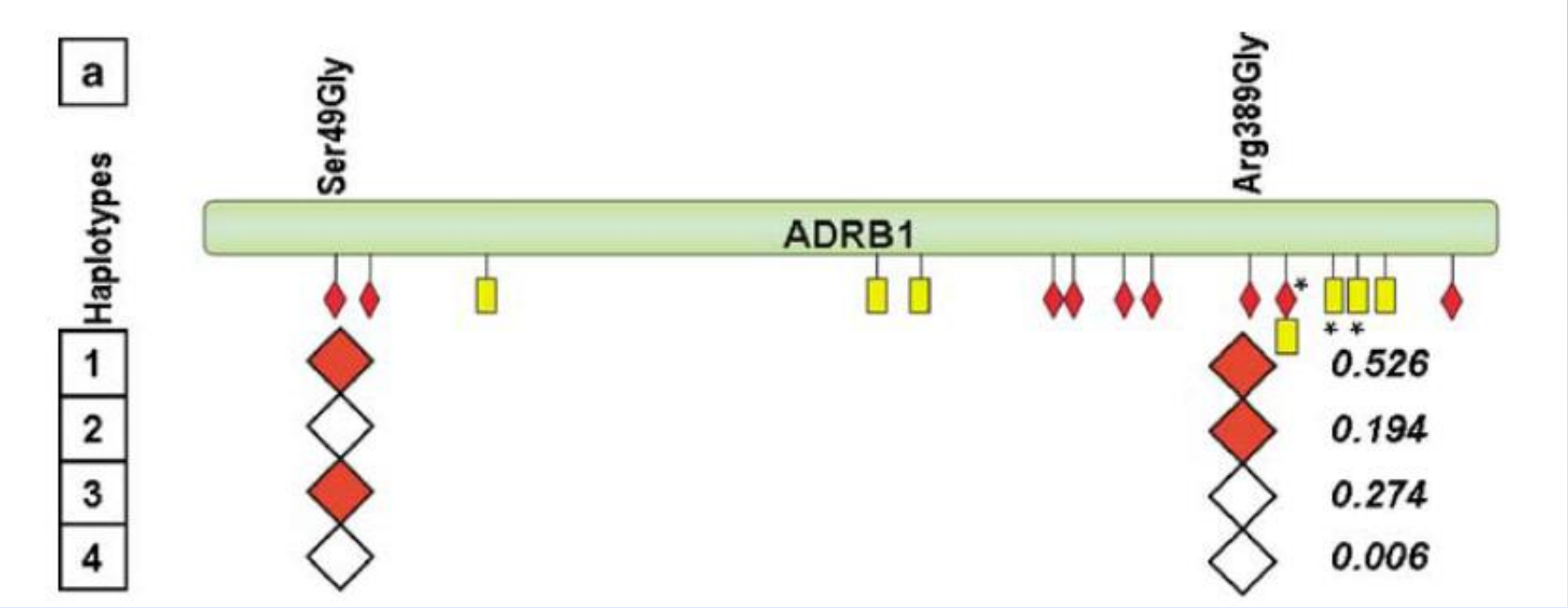
ADRB1

ADRB2



Taylor MRG. The Pharmacogenomics Journal 2007; 7: 29–37.

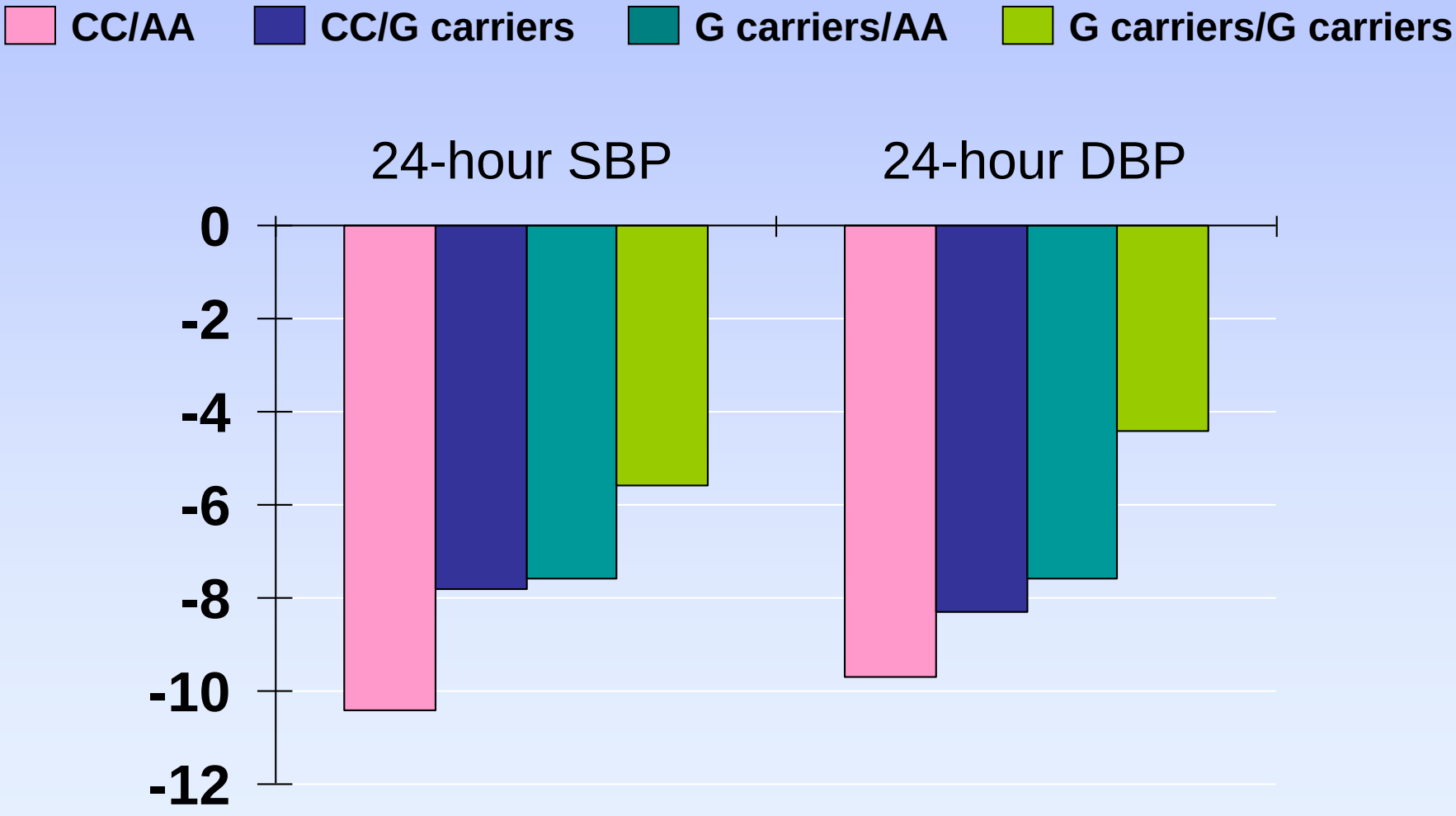
Haplotypes of the beta-adrenergic receptor



Missense (red diamonds) and silent (yellow squares) polymorphisms for ADRB1. Haplotypes indicated by red (common allele) or white (rare allele) shading of the missense polymorphisms and haplotype frequencies

Taylor MRG. The Pharmacogenomics Journal 2007; 7: 29–37.

Arg389Gly(C→G)-Ser49Gly(A→G) haplotypes
% reduction in 24-hour BP from baseline



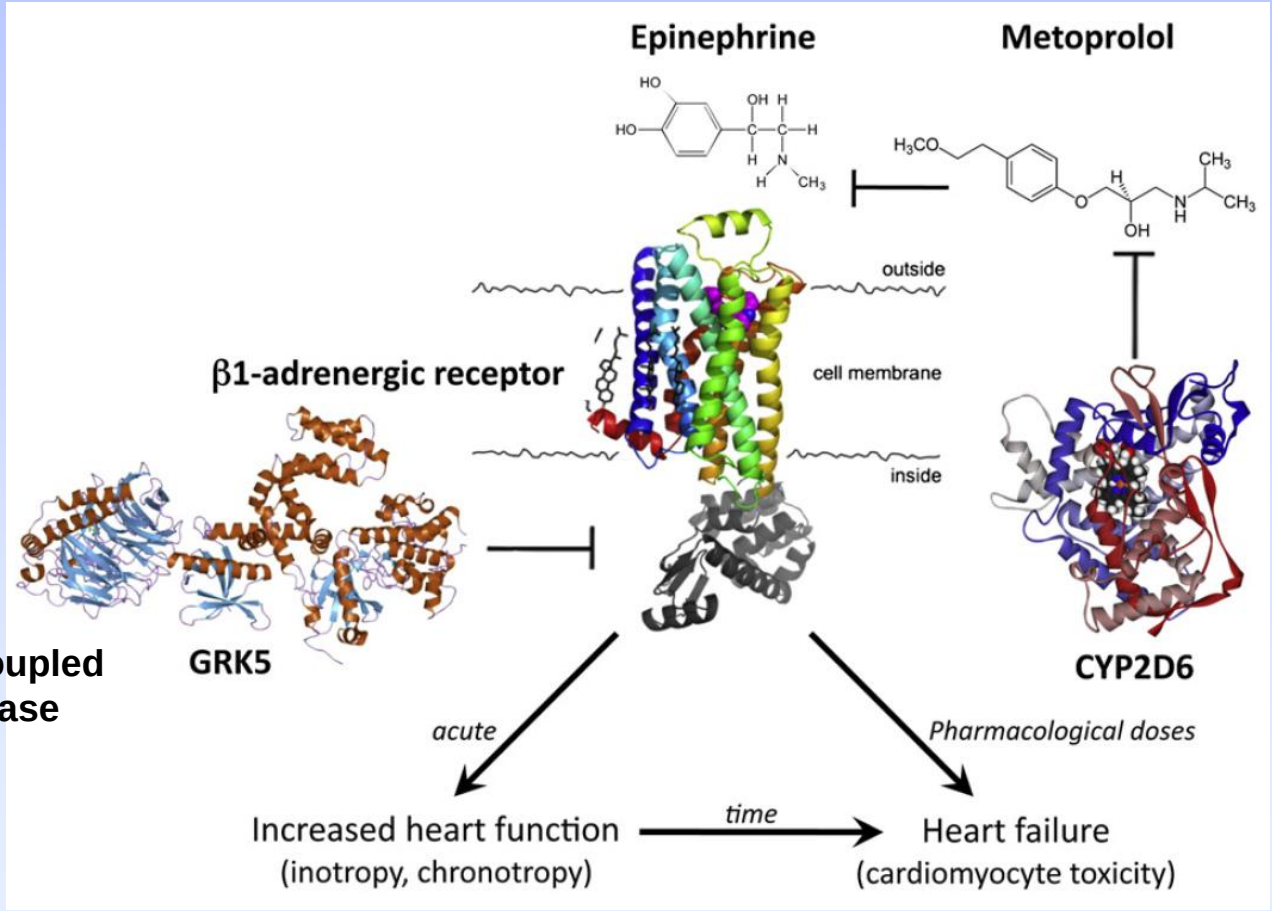
***All P* > 0.05**

Deng HB, Tomlinson B. unpublished data

Beta-blockers in Hypertension in Asian patients

- Can the effects be predicted?
- Metoprolol and some other beta-blockers show wide variation in pharmacokinetics according to CYP2D6*10 genotypes – common in Chinese populations
- The beta1-AR Arg389Gly (C1165G) polymorphism results in diminished agonist-stimulated signaling and less susceptibility to inhibition by beta-blockers
- The beta1-AR Ser49Gly (A145G) polymorphism results in more susceptibility to agonist-promoted down-regulation
- Different variants or combinations (haplotypes) may result in different responses

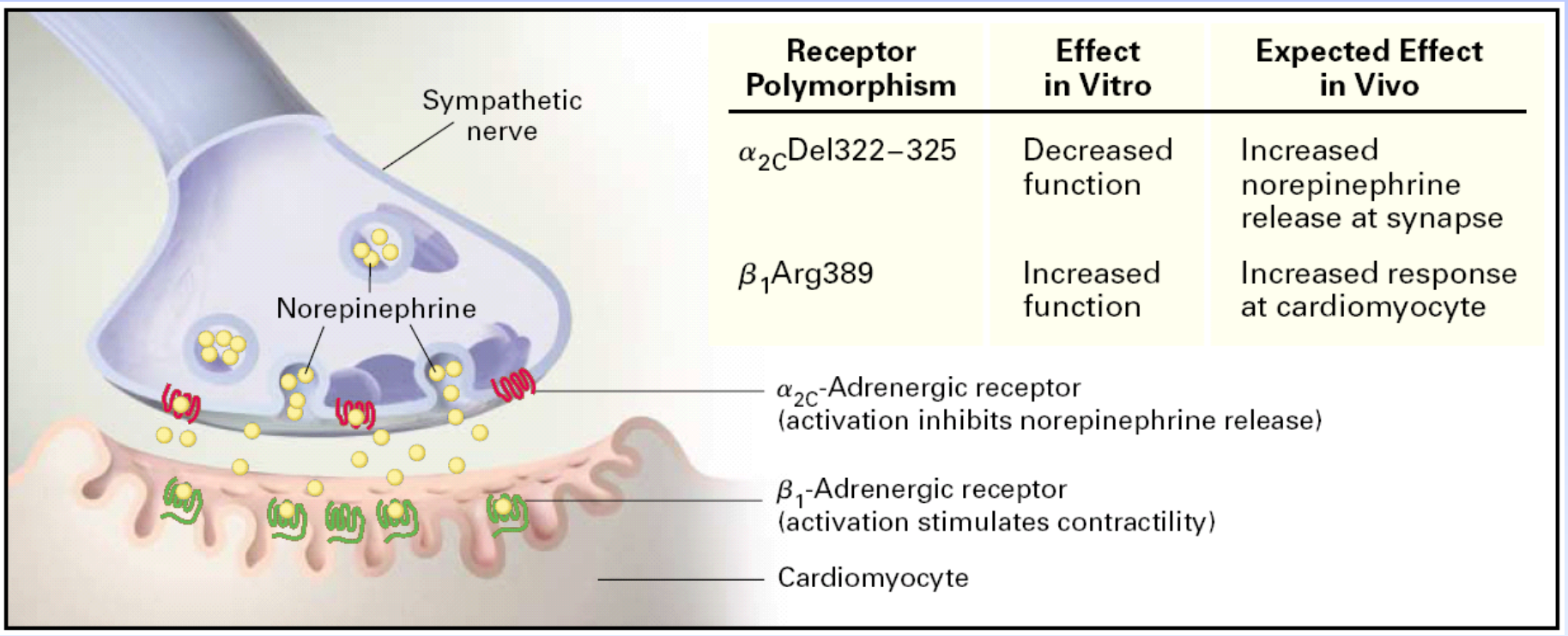
Pharmacogenetic profiling in the treatment of heart disease



G-protein coupled receptor kinase

Dorn GW, II. Transl Res. 2009; 154(6): 295-302.

Synergistic polymorphisms of the β_1- and α_{2C}-adrenergic receptors



Receptor Polymorphism	Effect in Vitro	Expected Effect in Vivo
α_{2C}Del322–325	Decreased function	Increased norepinephrine release at synapse
β_1Arg389	Increased function	Increased response at cardiomyocyte

Small KM et al, N Engl J Med 2002;347:1135-42.

Beta-blockers in Hypertension in Asian patients

- Don't throw out the baby with the bathwater!
- Das Kind mit dem Bade ausschütten
- The earliest record of this phrase is in 1512, in Narrenbeschwörng (Appeal to Fools) by Thomas Murner

Conclusions

- Hypertension is a major risk factor for coronary heart disease and particularly for stroke in most Asian countries
- The risks related to hypertension are similar or greater in Asian countries than in western countries
- ACE inhibitors cause cough more frequently in Asian patients and other treatments have to be substituted
- Some beta-blockers show wide variation in pharmacokinetics according to CYP2D6*10 genotypes which are common in East Asian populations and this may produce variations in response