Diabetes and the Younger/Middle-Aged Hypertensive Subject; Obesity, Sympathetic Nerve Activity and Treatment Implications

JM Cruickshank*

Oxian Cardiovascular Consultantancy, UK

*Corresponding author:** JM Cruickshank, BM, BCH, MA (Oxford), DM (Oxford), FRCP (London), Oxian Cardiovascular Consultantancy, UK, **E-mail:** Johndtl@aol.com

Abstract

Summary and conclusion

There is an obesity/type-2 diabetes/hypertension epidemic in developed countries around the world. Central obesity is closely linked to hypertension and type-2 diabetes in young/middle-age. In this younger, probably obese, age-group diastolic hypertension is linked to increased sympathetic nerve activity (via raised plasma insulin and leptin levels acting upon the hypothalamic region), particularly in the presence of type-2 diabetes. Chronically raised sympathetic nerve activity and beta-receptor levels (in lymphocytes), independent of blood pressure, are powerful predictors of myocardial infarction in the middle-aged. This has treatment implications for the young/middle-aged hypertensive subjects, with or without type-2 diabetes.

Antihypertensive agents that increase sympathetic nerve activity e.g. dihydropyridine calcium blockers, thiazide-type diuretics, and angiotensin receptor blockers, do not reduce (and may increase) the risk of myocardial infarction in the younger/middle-aged hypertensive subject. Beta-1 blockade, effective in reversing and stabilizing coronary atheromataous plaque, is at least as good as ACE-inhibition in preventing hard cardiovascular endpoints (including myocardial infarction, and is significantly superior in preventing all-cause death). Thus, beta-1 blockade is a highly reasonable first-line treatment in young/middle-aged hypertension with or without type-2 diabetes.

Keywords: Diabetes; Hypertension; Sympathetic nerve activity

Abbreviations: BP: Blood Pressure; HT: Hypertension; DM2: type-2 diabetes; BB: Beta-blocker; ARB: Angiotensin Receptor Blocker; SNA: Sympathetic Nerve Activity; BMI: Body Mass Index; MI: Myocardial Infarction.

Introduction

In the last 30 years or so there has been a global increase in obesity [1], being particularly apparent in the USA [1,2] the UK and Australia [3,4]. Obesity tends to be less prevalent among educated wealthy individuals [2].

Weight-gain is associated with an increased risk of type-2 diabetes (DM2) [5]. DM2 is associated with a two-fold increase in cardiovascular events [6]. Weight-gain, in addition to other life-style factors such as physical inactivity, a Westernized diet and alcohol-abuse, is also responsible for about 70% of cases of essential hypertension (HT) in younger/middle-aged subjects [7,8].

This mini-review sets out to examine the inter-relationships between obesity, DM2, and HT, and to highlight the importance of raised sympathetic nerve activity (SNA) and treatment implications.

Essential Hypertension, Obesity, Sympathetic Nerve Activity, Resting Heart Rate, Plasma Renin Activity (Pra), and Prognostic Implications

The classic Framingham Study has investigated the origins of essential HT in a normal (primarily white) population [9] (Table 1). It is apparent that (1) The development of diastolic (± systolic) HT is closely associated to a younger age and an increased body mass index (BMI), and (2) The development of isolated systolic HT occurs in an older age-group, reflecting stiffening/aging of the arteries. Essential HT in the younger age-group is linked primarily to an increased cardiac output [10], while in the

elderly (say greater than 60 years old), where there is a fall in cardiac output [11,12], high BP is dependent upon an increased peripheral resistance.

Obese adolescents with HT experience a substantial fall in BP after weight-loss following bariatric surgery, with 74% becoming normotensive [13]. In younger subjects, obesity (particularly central) is linked to a significant increase in SNA in muscle [14] (Figure 1). In men, there is a powerful linear relationship between waist circumference and SNA [15] (Figure 2). Obesity-related increases in SNA are particularly apparent in the presence of HT [16], especially if DM2 is also present [17] (Figure 3). The raised SNA is associated with the release of leptin (so-called "thin hormone") from central adipose tissue; leptin acts upon the hypothalamic region of the mid-brain, resulting in increased SNA [18]. High insulin levels, associated with obesity-related insulin resistance, also act upon the hypothalamic region, resulting in heightened SNA [19,20].

High levels of SNA are associated with a poor long-term prognosis. Firstly, high norepinephrine (noradrenaline) levels are associated with the atherosclerotic process [21] and (via an increased heart rate) coronary plaque rupture [22]. Secondly, high plasma norepinephrine levels, independent of smoking and blood pressure levels, are powerful predictors of cardiovascular death and survival in young/middle-aged hypertensive subjects over a 6-7 year follow-up period [23] (Figure 4). Importantly, high intra-lymphocyte beta-receptor density (Bmax) and cyclic adenosine monophosphate (DMP) levels predict (independent of BP) future myocardial infarctions, but not stroke (which relates to BP) [23] (Figure 5).

High resting heart rates are a surrogate for increased SNA. The Framingham Study [24] has shown that in young/middle-aged hypertensive subjects, high resting heart rates (particularly over 85 bpm) have been shown to predict all-cause death and cardiovascular and coronary heart disease events for both hypertensive men- (Figure 6) and women, over a 36 year follow-up period.

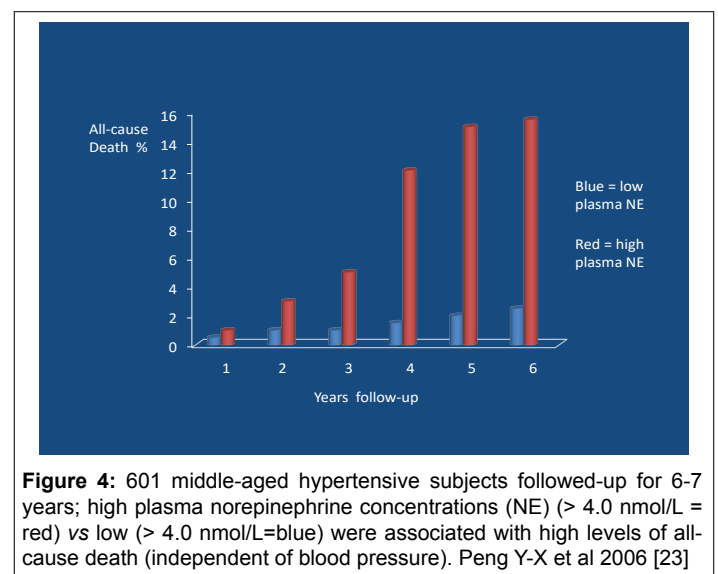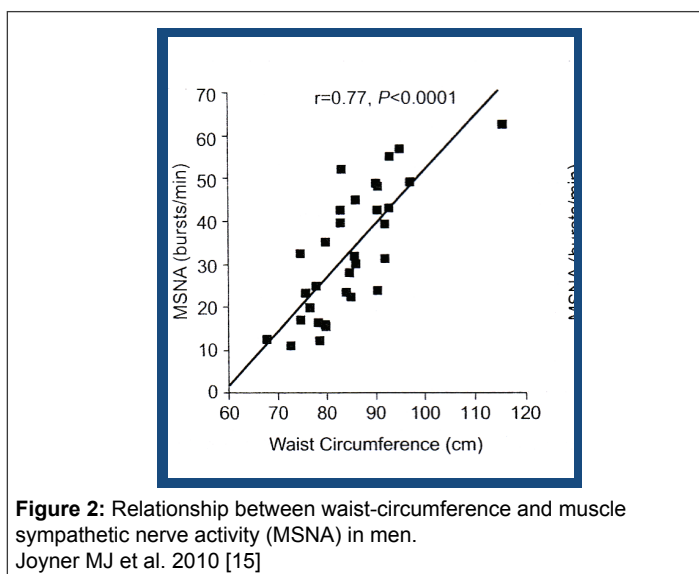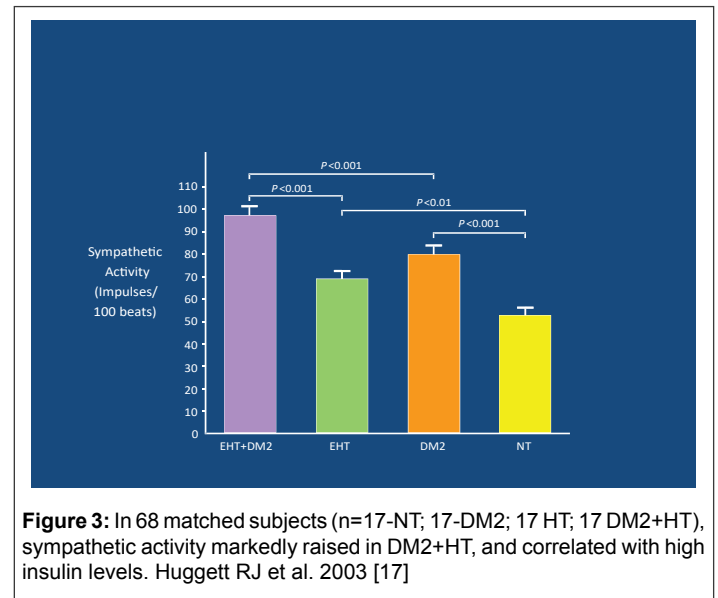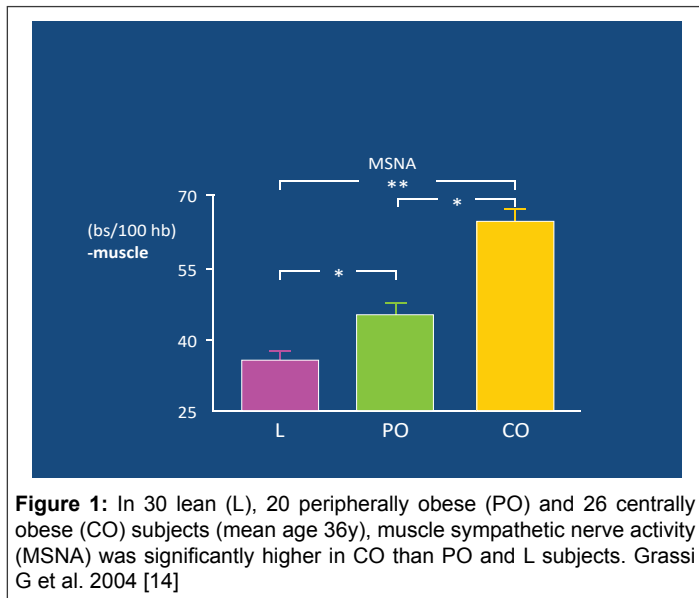Beta-1 stimulation of the renal juxtaglomerular apparatus results in the release of renin. Thus, high plasma renin activity (PRA), like high sympathetic activity [23], could be an indicator of a poor prognosis. It is note-worthy that in high PRA cases, beta-blockers have a particularly powerful anti-hypertensive effect [25].

Therapeutic Implications in Young/Middle-Aged Hypertension with or without DM2

Antihypertensive agents that increase SNA have performed poorly in terms of reducing cardiovascular events in young/middle-aged hypertensive subjects.

Predictors of Diastolic Hypertension (± Systolic Hypertension)=DBP ≥ 90 mmHg (± SBP ≥ 140 mmHg)	Predictors of Isolated Systolic Hypertension=SBP ≥ 140 mmHg+DBP<90 mmHg (wide P-P)
1. Young age	1. Older age
2. Male sex	2. Female sex
3. High BMI at baseline	3. Increased BMI during follow-up (weak)
4. Increased BMI during follow-up	4. ISH arises more commonly from normal and high normal BP, than "burned out" diastolic hypertension
5. Main mechanism of DH and SDH is raised peripheral resistance	5. Only 18% with new – onset ISH had a previous DBP ≥ 95 mmHg
	6. Main mechanism of ISH is increased arterial stiffness=aging of arteries

Table 1: Different Predictors of Diastolic Hypertension (DH) (± raised systolic–SDH) and Isolated Systolic Hypertension (ISH)–FRAMINGHAM Study [9].

Figure 1: In 30 lean (L), 20 peripherally obese (PO) and 26 centrally obese (CO) subjects (mean age 36y), muscle sympathetic nerve activity (MSNA) was significantly higher in CO than PO and L subjects. Grassi G et al. 2004 [14]

Figure 3: In 68 matched subjects (n=17-NT; 17-DM2; 17 HT; 17 DM2+HT), sympathetic activity markedly raised in DM2+HT, and correlated with high insulin levels. Huggett RJ et al. 2003 [17]

Figure 2: Relationship between waist-circumference and muscle sympathetic nerve activity (MSNA) in men. Joyner MJ et al. 2010 [15]

Figure 4: 601 middle-aged hypertensive subjects followed-up for 6-7 years; high plasma norepinephrine concentrations (NE) (> 4.0 nmol/L = red) *vs* low (> 4.0 nmol/L=blue) were associated with high levels of all-cause death (independent of blood pressure). Peng Y-X et al 2006 [23]
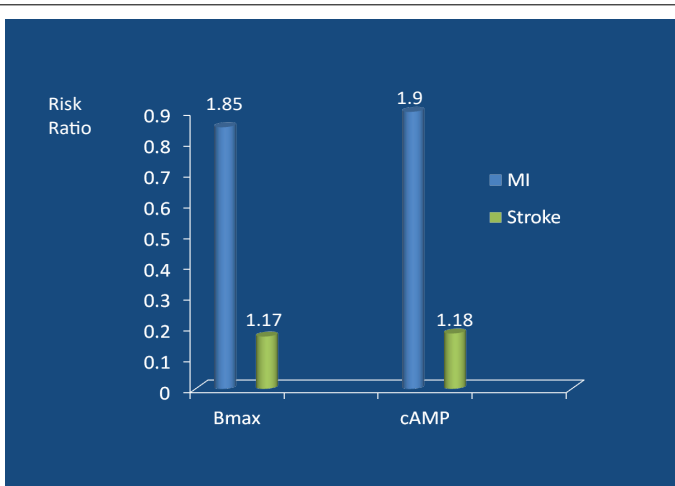
Figure 5: Beta-receptor density (Bmax) and cAMP levels (in lymphocytes) as predictors of MI and stroke in middle-aged hypertensives followed for 7 years. Peng Y-X et al 2006 [23]
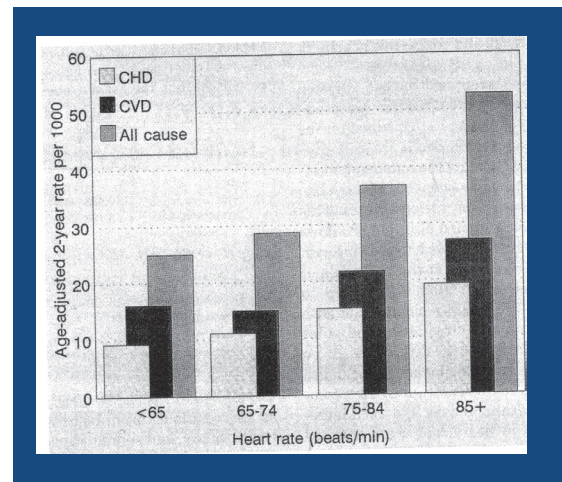

Figure 6: Framingham: Effect of resting heart rate on all-cause death, CHD and CVD events in untreated male hypertensives, followed-up for 36 years. Gillman MW et al. 1993 [24]

Thiazide-type diuretics increase SNA [26], and in 3 studies involving diuretic therapy in young/middle-aged hypertensive subjects [27-29] there was no reduction in the risk of myocardial infarction, and even a significant increase [29], versus randomised placebo/non-treatment.

Dihydropyrididne calcium blockers increase heart-rate and plasma norepinephrine levels [30], and in the ABCD study involving middle-aged hypertensive subjects with DM2 [31], the investigation was terminated prematurely due to a significant excess of myocardial infarctions in the nisoldipine, vs the enalapril, group.

Angiotensin receptor blockers (ARBs) increase SNA in younger subjects [32,33]. Meta-analyses indicate that, in contrast to ACE-inhibitors, ARBs increase the risk of myocardial infarction [34,35] (Figure 7). In two subsequent placebo-controlled studies involving hypertension [36] and pre-hypertension plus DM2 [37] (Figure 8), there was a significant excess of fatal cardiovascular events in those receiving the ARB.

ACE inhibitors reduce SNA [38], and performed well *vs* the calcium blocker nisoldipine in terms of fewer myocardial infarctions [31]. In the classic UKPDS-39 study [39], involving middle-aged hypertensive subjects with DM2, atenolol was compared to captopril in terms of reduction of 7 primary endpoints versus less-tight control (10/5 mg Hg) of BP, over a 9 year period of observation. The effects of the 2 agents upon the 7 primary endpoints (plus heart failure, a secondary endpoint), *vs* less-tight control, are shown in figure 9. It is apparent that all 8 trends favoured atenolol (over captopril). Compared to less-tight control of BP, atenolol reduced stroke-risk by about 50%, peripheral arterial disease-related endpoints by about 60%, micro-vascular (kidney and eye) endpoints by about 45%, and heart failure by about 65%. After 14.5 years long-term follow-up, the above trends persisted but now there was a significant (23%) reduction in all-cause death in favour of atenolol [40] (Figure 10).

The Beta-Blocker Story

Recent negative messages regarding the role of beta-blockers (BBs) in the treatment of HT, have arisen from meta-analyses that did not take age into account [6,41-47]. Two meta-analyses that did take age into account arrived at very different conclusions [46,47]. Compared to randomised placebo, in the younger hypertensive subject (mean age less than 60 years old) BBs were significantly superior to randomised placebo in reducing the risk of death/stroke/MI (Figure 11), with only a positive trend in the

elderly. When compared to randomised comparator antihypertensive agents, BBs were at least as effective as randomised comparator drugs in reducing the risk of death/stroke/MI in younger subjects (Figure 12), in contrast to those older than 60 years old, where BBs were significantly less effective in reducing the risk of death/stroke/MI. Thus, BBs are an effective first-line option regarding the treatment of younger/middle-aged (less than 60 years old) hypertensive subject. In the elderly hypertensive subject, first-line BBs are appropriate only if myocardial ischaemia is also present [48].

The Important Beta-Blocker/Smoking Interaction in Younger/Middle-Aged Hypertensive Subjects

In 3 major prospective, randomised, hard-endpoint studies in middle-aged hypertensive subjects, cigarette smoking played a key role in modifying the potential of the BB to reduce the risk of a cardiovascular event. The MRC-1 study [28] compared non-selective propranolol with a thiazide diuretic and placebo; the IPPPSH study [49] compared non-selective oxprenolol with placebo; the MAPHY [50] compared moderately beta-1 selective metoprolol with a thiazide diuretic.

In the case MI (about 3 times more common than stroke in the younger subject), the ability of the BB to reduce the risk of an event by 33-49% (versus randomised placebo or diuretic) in non-smokers, was not observed in smokers [28,49,50]. Indeed, in the case of non-selective propranolol and oxprenolol, the risk of MI was actually increased by 13-35% in smokers (Figure 13). A similar result relating to stroke was noted in the MRC-1 study [28].

How can these events relating to smokers be explained and avoided? Cigarette smoking is linked to a two-to-threefold increase in plasma epinephrine (adrenaline) levels [51]. Epinephrine stimulates beta-1, beta-2 and alpha-receptors, and in the presence of non-selective BBs (and to a lesser extent with only moderately beta-selective agents like metoprolol and atenolol) there is unopposed (total or partial) alpha-vasoconstriction, resulting in an increase in BP [52]. This increase in BP is about 30 mm Hg for non-selective BBs and about 9-10 mm Hg for a moderately selective agent like metoprolol, compared to no change in BP (*vs* control) with a highly beta-1 selective agent like bisoprolol (which permits full beta-2 stimulation-induced vasodilatation [53,54] (Figure 14).
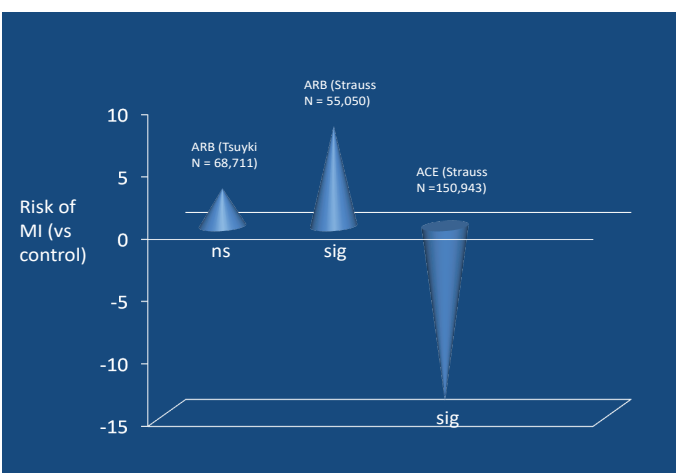
Figure 7: Relative risk of MI in meta-analyses of ARB and ACE-inhibitors. Strauss and Hall, Circulat 2007 [35]

Figure 8: ROADMAP Study; Olmesartan vs placebo (randomised) in 4447 DM2, mean age 57, mean BMI 31, BP 136/81, over 3.2 years. Haller H et al. NEJM 2011 [37]

Figure 9: UKPDS 39 – all primary end-point trends favour atenolol vs captopril when compared with less-tight BP control (BP diff 10/5 mm Hg)
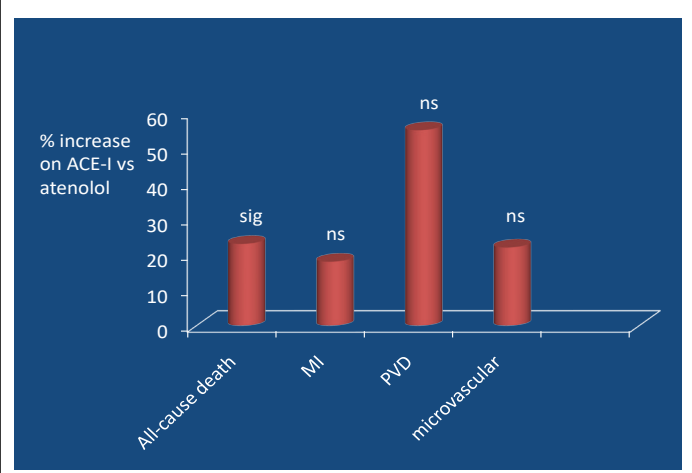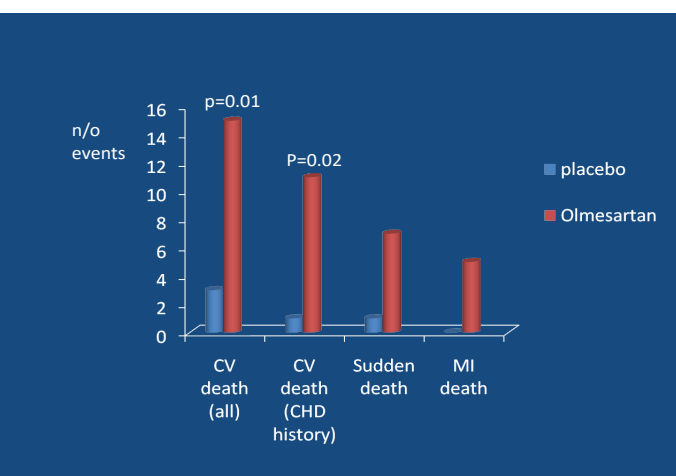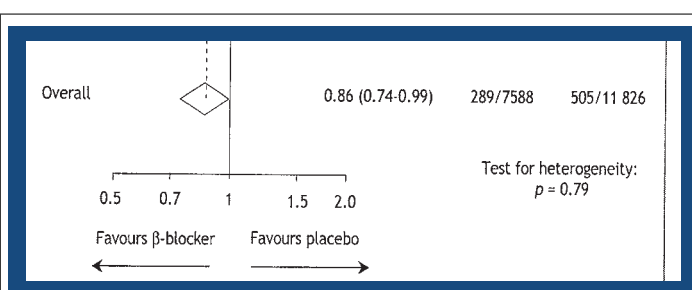

Figure 10: UKPDS study 20 year follow-up (mean 14.5 years); significant (p<0.05) increase in all-cause death on ACE-I (vs atenolol). Holman RR et al. 2008 [40]

Figure 11: A meta-analysis of 2 studies in the younger (< 60y) hypertensive subject; beta-blockers significantly superior to randomised placebo in preventing all cause death/stroke/MI. Khan and McAlister, 2006 [46]
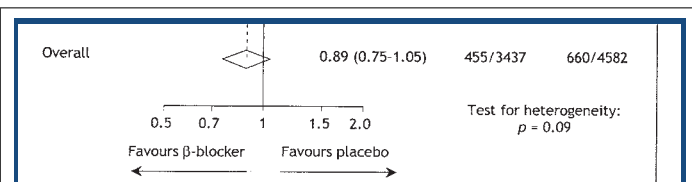

Figure 12: Meta-analysis of 5 studies in the elderly hypertensive subject (> 60y) – a strong trend favouring beta-blockers vs randomised placebo in the prevention of the composite death/stroke/MI. Khan and McAlister 2006 [46]
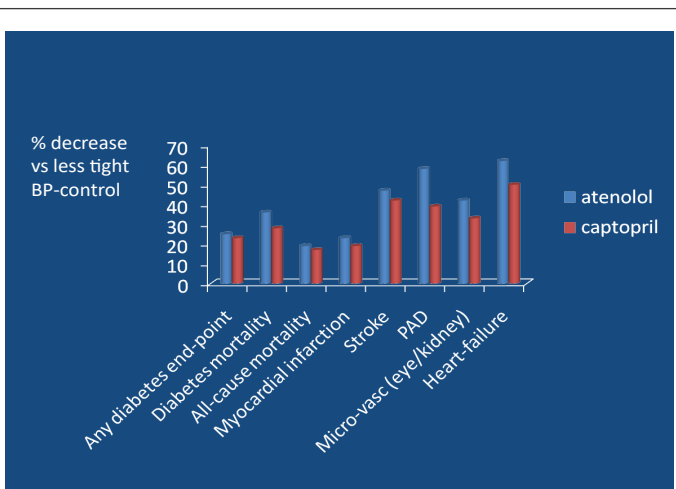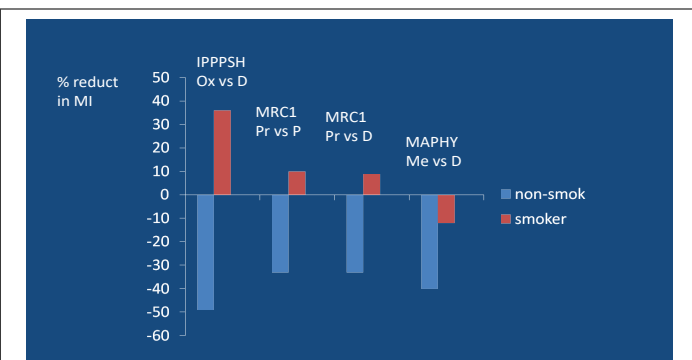

Figure 13: Beta Blocker/Smoking interaction in young/mid-age hypertensives, regarding myocardial infarction (MI); Ox=Oxprenolol, Pr=Propranolol, Me=Metoprolol, P=Placebo, D=Diuretic.
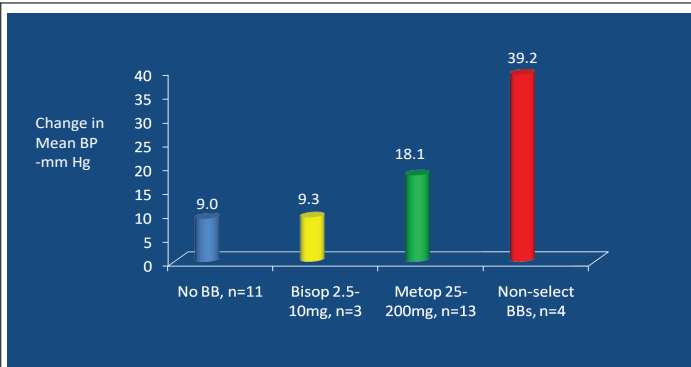
Figure 14: Peri-operative interaction between adrenaline and beta-blockers. Tarnow J and Muller R, 1991 [52]

Choice of Beta-Blocker

a) Pharmacokinetic properties

These properties have been described [55] (Table 2). As a general rule -

1. Agents with a plasma half-life of 6 hours or more may be dosed on a once daily basis

2. Liver-metabolised agents e.g. metoprolol, should be avoided in patients with hepatic dysfunction; in such cases use either a renally excreted agent like atenolol, or an agent with a balanced metabolised/renally excreted profile such as bisoprolol.

3. In patients with renal dysfunction, avoid renally excreted agents like atenolol; in such cases use either a liver-metabolised agent like metoprolol, or bisoprolol (balanced metabolism/excretion).

4. Agents that are metabolised via the hepatic cytochrome P450 system are vulnerable to genetic polymorphism. Thus, nebivolol [56] and metoprolol [57], in poor metabolisers, experience a 3 to 5 fold increase on peak blood levels, leading to loss of beta-1 selectivity and a possible increase in adverse reactions such as fatigue (metoprolol) [58]. Such poor metabolisers account for 8-10% of the UK White population [59], and possibly 30% of Chinese [60].

b) Pharmacodynamic properties

1. **Beta-1 selectivity (cardioselectivity):** Beta-1/beta-2 selectivity ratios are shown in figure 15 [53]. ICI118.551 is a pure beta-2 selective antagonist; propranolol inhibits beta-1 and beta-2 receptors equally; metoprolol, atenolol and betaxolol are only moderately beta-1 selective; bisoprolol is highly beta-1 selective. Beta-1 selectivity is diminished/lost at higher doses (eg - greater than 10 mg/day of bisoprolol [61]). Nebivolol is not beta-1 selective, as it occupies and stimulates (ISA) the beta-3 receptor (see later).

2. **Intrinsic sympathomimetic activity (ISA):** The ISA of agents like oxprenolol and pindolol acts via the beta-1 and beta-2 receptors [62], while the ISA of nebivolol acts via the beta-3 receptor [63]. Stimulation of the beta-2 [64] and beta-3 [65-67] receptor (via ISA) results in release of nitric oxide (NO) and vasodilatation. It is worth noting that BBs with ISA are less effective in treating heart failure than BB with no ISA [55]. In the failing heart, beta-3 stimulation worsens cardiac function, and in the post-myocardial infarction period, L-arginine (a substrate for nitric oxide (NO)) significantly increases mortality compared to placebo [68].

3. **Alpha-blocking properties:** Both labelalol and carvedilol are non-selective for the beta-1 and beta-2 receptors, but contain additional alpha-blocking properties. Such agents lower peripheral resistance [69], and lower heart rate less than traditional beta-blockers [70].

4. **Antihypertensive effects in young/middle-aged subjects:** Beta-2 blockade results in a rise in BP of about 7/5 mmHg [71]. Thus moderately beta-1 selective atenolol lowers BP more effectively than non-selective propranolol [72]. Atenolol in turn, is a less effective antihypertensive agent than highly beta-1 selective bisoprolol [73]. Indeed, in middle-aged hypertensive subjects bisoprolol is a more effective antihypertensive agent than amlodipine, doxazosine, lisinopril, and bendrofluazide [74] (Figure 16). Bisoprolol is also more effective at reducing BP than angiotensin receptor blockers [75], being at least as reno-protective as the latter [76]. Bisoprolol lowers BP equally in White and Black middle-aged hypertensive subjects [77,78].

5. **Adverse reactions:** Certain generalised statements are possible [55]:

   a) Lipophilic (lipid soluble) agents, e.g. propranolol and metoprolol (Table 2), readily cross the blood brain barrier, resulting in an increased risk of sleep-problems, dreaming and nightmares.

   b) High beta-1 selectivity e.g. bisoprolol, is compatible with a better "quality of life" compared to non-selective propranolol.

   c) Postural hypotension/dizziness can be troublesome with agents possessing alpha-blocking properties e.g. labetalol and carvedilol.
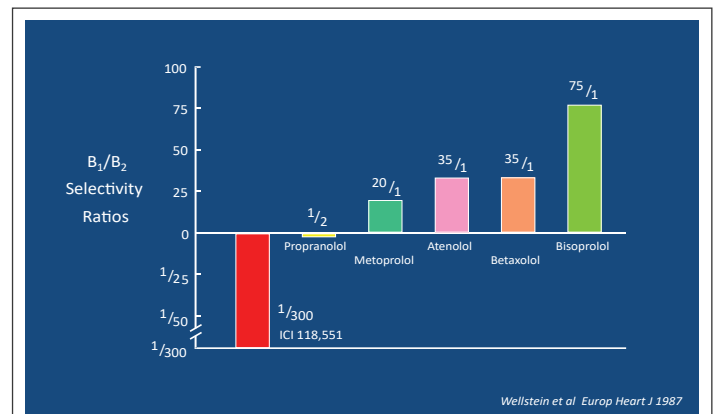

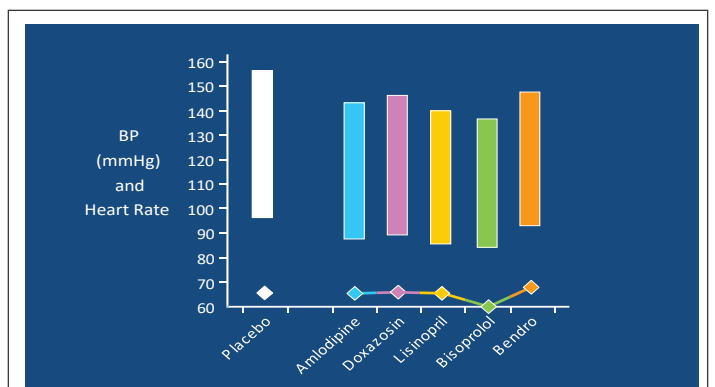**Figure 15:** Beta$_1$ and Beta$_2$ Selectivity Ratios. Wellstein A et al. 1986 [53]

Figure 16: In 34 young (28-55yrs) hypertensives, Bisoprolol 5mg was more effective than Amlodipine 5mg, Doxazosin 104mg, Bendrofluazide 2.5mg, Lisinopril 2.5-10mg (double blind, crossover, 1 month each) in controlling office and 24 hr BP. Deary AJ et al. J Hypertens 2002 [74]

β-Blocker	Lipid solubility X=water-soluble xxxx=lipid soluble	Extent Absorbed (% dose)	Time to peak blood level (hr)	Plasma half-life (hr)	First-pass (liver) elimination (%)	Systemic bioavailability (%)	Metabolized (hepatic)	Active Metabolite
Atenolol	x	40-60	2-4	6-10	0	50	No	No
Bisoprolol	xx	>90%	2-3	10-12	<10	90	Yes (50%)	No
Carvedilol	xxx	85	1.5	6-7	60-75	25	Yes	No
Labetalol	xxxx	>90	1-2	3-6	60-70	30-40	Yes	No
Metoprolol tartarate slow release succinate	xxx	>90	1-3	3-4 / 12-24	25-50	50-75	Yes	Yes (Weak)
Nebivolol	xxxx	90	1-4	13	70	12-96	Yes	Yes
Oxprenolol	xxx	90	1-1.5	1-2	25-80	20-75	Yes	No
Pindolol	xx	>90	0.5-1	2-5	20	80	Yes	No
Propanolol slow release	xxxx	>90	1-3	3-4 / 10-12	70	30	Yes	No
Sotalol	x	>90	2-3	7-15	0	>90	No	No
Timolol	xxx	>90	1-4	2-5	50-60	40-50	Yes	No

Table 2: Pharmacokinetics of commonly used beta-blockers
From: Cruickshank JM, Prichard BNC (1994) Beta-blockers in Clinical Practice. 2nd Edition. Edinburgh: Churchill Livingstone, 1119-1126 [28].

d) Fatigue/lethargy can be a problem with BBs, particularly at higher doses, or in slow metabolisers of metoprolol [58]. For patients involved in aerobic pursuits, non-selective agents should be avoided (blockade of muscle beta-2 receptors), with preference given to highly beta-1 selective agents like bisoprolol [79,80].

e) Cold peripheries can be troublesome, but are less likely with highly beta-1 selective agents or, when ISA or alpha-blocking properties are also present.

f) Renal function can be reduced by non-selective BBs, while moderately beta-1 selective atenolol was at least as reno-protective as captopril in the UKPDS-39 study [39], and bisoprolol was at least as renoprotective as the ARB losartan [76].

g) In reversible airways disease, high beta-1 selectivity is advantageous i.e. increasing airways resistance (brochospasm) is less likely, and beta-2 induced broncho-dilatation is permitted.

h) Metabolic disturbance is less likely with highly beta-1 selective agents such as bisoprolol i.e. less risk of disturbances involving blood lipids and sugar.

i) Weight-gain is less likely with highly beta-1 selective agents.

j) Sexual dysfunction (*vs* randomised placebo) is most common with agents that display combined beta-1, beta-2, and alpha blocking properties e.g. carvedilol, followed by non-selective propranolol and moderately selective atenolol, and can be avoided by high beta-1 selectivity e.g. bisoprolol.

References

1. James PA, Oparil S, Carter BL, Cushman WC, Dennison-Himmelfarb C, et al. (2014) 2014 evidence-based Guideline for the management of high blood pressure in adults. Report from the panel members appointed to the Eighth Joint National Committee (JNC 8). JAMA 311: 507-520.

2. Mancia G, De Backer G, Dominiczak A, Cifcova R, Fagard R, et al. (2007) 2007 Guidelines forthe management of arterial hypertension. The task force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). Eur Heart J 28: 1462-1536.

3. Krause T, Lovibond K, Caufield M, McCormak T, Williams B (2011) Management of hypertension: summary of NICE guidelines. BMJ 343.

4. Wu H-Y, Huang J-W, Lin H-J, Liao WC, Peng YS, et al. (2013) Comparative effectiveness of renin-angiotensin system blockers and of other antihypertensive drugs in patients with diabetes: systematic review and bayesian network meta-analysis. BMJ 347.

5. Lindholm LH, Carlberg B, Samuelsson O (2005) Should beta-blockers remain the first choice in the treatment of primary hypertension? A meta-analysis. Lancet 366: 1545-1553.

6. Thomopoulos C, Parati G, Zanchetti A (2015) Effects of blood pressure-lowering on outcome incidence in hypertension: 4. Effects of various classes of antihypertensive drugs--Overview and meta-analysis. J Hypertension 33: 195-211.

7. Lambert E, Straznicky N, Schlaich M, Esler MP, Haikerwal D, et al. (2007) Differing pattern of sympathoexcitation in normal- weight and obesity-related hypertension. Hypertension 50: 862-868.

8. Huggett RJ, Scott EM, Gilbey SG, Stoker JB, Macintosh AF, et al. (2003) Impact of type-2 diabetes on sympathetic neural mechanisms in hypertension. Circulation 108: 3097-4101.

9. Franklin SS, Pio JR, Wong ND, Larson MG, Leip EP, et al. (2005) Predictors of new-onset diastolic and systolic hypertension. The Framingham Heart Study. Circulation 111: 1121-1127.

10. Druktenis JS, Roman MJ, Fabsitz RR, Lee ET, Best LG, et al. (2007) Cardiac and systemic hemodynamic characteristics of hypertension and prehypertension in adolescents and young adults. the Strong Heart Study. Circulation 115: 221-227.

11. Palatini P, Julius S (2009) The role of cardiac autonomic function in hypertension and cardiovascular disease. Curr Hypertens Rep 11: 199-205.

12. Sowers JR, Lester M (2000) Hypertension, hormones and aging. J Lab Clin Med 135: 379-386.

13. Inge TH, Courcoulas AP, Jenkins TM, Michalski MP, Helmrath MA, et al. (2016) Weight loss and health status 3 years after bariatric surgery in adolescents. N Eng J Med 374: 113-123.

14. Grassi G, Dell Oro R, Facchini A, Quarti Trevano F, Bolla GB, et al. (2004) Effect of central and peripheral body fat distribution on sympathetic and baroreflex functionin obese normotensives. J Hypertens 22: 236-239.

15. Joyner MJ, Charkoudian N, Wallin G (2010) Sympathetic nervous system and blood pressure in humans: individualized patterns of regulation and their implications. Hypertension. 56: 10-16.

16. Lambert E, Straznicky N, Schlaich M, Esler MP, Haikerwal D, et al. (2007) Differing pattern of sympathoexcitation in normal- weight and obesity-related hypertension. Hypertension 50: 862-868.

17. Huggett RJ, Scott EM, Gilbey SG, Stoker JB, Macintosh AF, et al. (2003) Impact of type-2 diabetes on sympathetic neural mechanisms in hypertension. Circulation 108: 3097-4101.

18. Barnes MJ, McDougal DH (2014) Leptin into the rostral ventral lateral medulla (RVLM) augments renal sympathetic nerve activity and blood pressure. Front Neurosci 8: 232.

19. Coats AJS, Cruickshank JM (2014) Hypertensive subjects with type-2 diabetes, the sympathetic nervous system, and treatment implications. Int J Cardiol 174: 702-709.

20. Cruickshank JM (2014) The unholy alliance between obesity, type-2 diabetes, the sympathetic nervous system, and hypertension in young/middle-aged subjects. J Mol Genet Med S1: 016.

21. Helin P, Lorenzen I, Garbash C, Matthiessen ME (1970) Atherosclerosis in rabbit aorta induced by noradrenaline. The importance of the duration of noradrenaline action. Atherosclerosis 12: 125-132.

22. Heidland UE, Strauer BE (2001) Left ventricular muscle mass and elevated heart rate are associated with coronary plaque disruption. Circulation 104: 1477-1482.

23. Peng Y-X, Shan J, Qi XY, Qi XY, Zhang SJ, et al. (2006) The catecholamine-beta-adrenoceptor-cAMP system and prediction of cardiovascular events in hypertension. Clin Exp Pharmacol Physiol 33: 227-231.

24. Gillman MW, Kannel WB, Belanger A, D'Agostino RB (1993) Influence of heart rate on mortality among persons with hypertension: the Framingham Study. Am Heart J 125: 1148-1154.

25. Buhler FR, Laragh JH, Baer L, Vaughn ED, Brunner HR (1972) Propranolol inhibition of renin secretion. A specific approach to diagnosis and treatment of renin dependent hypertensive diseases. N Engl J Med 287: 1209-1214.

26. Menon DV, Arbique D, Wang Z, Adam-Huet B, Auchus RJ, et al. (2009) Differential effects of chlorthalidone versus spironolactone on muscle sympathetic nerve activity in hypertensive patients. J Clin Endocrin Metab 94: 1361-1366.

27. The Australian therapeutic trial in hypertension (1980) Report by the Management Committee. Lancet 1: 1261-1267.

28. Medical Research Working Party (1985) MRC trial of treatment of mild hypertension: principle results. Medical Research Council Working Party. Br Med J (Clin Res Ed). 291: 97-104.

29. Leren P, Heigeland A (1986) Coronary heart disease and treatment of hypertension. Some Oslo Study data. Am J Med 80: 3-6.

30. Fogari R, Zoppi A, Coradi L, Preti P, Malalamani GD, et al. (2000) Effects of different dihydropyridine calcium antagonists on plasma norepinephrine in essential hypertension. J Hypertension 18: 1871-1875.

31. Estacio RO, Jeffers BW, Hiatt W, Biggerstaff SL, Gifford N, et al. (1998) The effect of nisoldipine as compared with enalapril on cardiovascular outcomes in patients with non-insulin-dependent diabetes and hypertension. N Engl J Med 338: 645-652.

32. Heuser K, Vitkovsky J, Raasch W, Schmieder Re, Schobel HP (2003) Elevation of sympathetic activity by eprosartan in young male subjects. Am J Hypertens 16: 658-664.

33. Moltzer E, Mattace Raso FU, Karamermer Y, Boersma E, Webb GD, et al. (2010) Comparison of candesartan versus metoprolol for treatment of systemic hypertension after repaired aortic coarctation. Am J Cardiol 105: 217-222.

34. Strauss MH, Hall AS (2006) Angiotensin receptor blockers may increase the risk of myocardial infarction. Circulation 114: 838-854.

35. Strauss MH, Hilgers KF, Schlaich MP, Schmidt BM (2007) Renin-angiotensin system and cardiovascular talk. Lancet 369: 1208-1219.

36. Imai E, Chan JC, Ito S, Yamasaki T, Kobayashi F, et al. (2011) Effects of olmesartan on renal and cardiovascular outcomes in type-2 diabetes with overt nephropathy: a multicentre, randomised, placebo-controlled study. Diabetologia 54: 2978-2986.

37. Haller H, Ito S, Izzo JL, Januszewicz A, Katayama S, et al. (2011) Olmesartan for the delay or prevention of microalbuminuria in type-2 diabetes. N Engl J Med 364: 907-917.

38. Noll g, Wenzel RR, de Marchi S, Shaw S, Luscher TF (1997) Differential effects of captopril and nitrates on muscle sympathetic nerve activity in volunteers. Circulation 95: 2286-2292.

39. (1998) Efficacy of atenolol and captopril reducing risk of macrovascular and microvascular complications of type-2 diabetes: UKPDS 39. UK Prospective Diabetes Study Group. BMJ 317: 713-720.

40. Holman RR, Paul SK, Bethel MA, Neil HA, Matthews DR (2008) Long-term follow-up after tight control of blood pressure in type-2 diabetes. N Engl J Med 359: 1565-1576.

41. Wu H-Y, Huang J-W, Lin H-J, Liao WC, Peng YS, et al. (2013) Comparative effectiveness of renin-angiotensin system blockers and of other antihypertensive drugs in patients with diabetes: systematic review and bayesian network meta-analysis. BMJ 347: f6008.

42. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R, et al. (2002) Prospective Studies Collaboration. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data foe one million adults in 61 prospective studies. Lancet 360: 1903-1913.

43. Wiysonge CS, Opie LH (2013) β-blockers as initial therapy for hypertension. JAMA 310: 1851-1852.

44. Lindholm LH, Carlberg B, Samuelsson O (2005) Should beta-blockers remain the first choice in the treatment of primary hypertension? A meta-analysis. Lancet 366: 1545-1553.

45. Xue H, Lu Z, Tang WL, Pang LW, Wang GM, et al. (2015) First-line drugs inhibiting the renin angiotensin system versus other first-line antihypertensive drug classes for hypertension. Cochrane Database Syst Rev.

46. Khan N, McAlister FA (2006) Re-examining the efficacy of beta-blockers for the treatment of hypertension: a meta-analysis. CMAJ 174: 1737-1742.

47. Kuyper LM, Kahn NA (2014) Atenolol vs non-atenolol beta-blockers for the treatment of hypertension: a meta-analysis. Can J Cardiol 30: S47-S53.

48. Pepine CJ, Handberg EM, Cooper-DeHoff RM, Marks RG, Kowey P, et al. (2003) A calcium antagonist vs a non-calcium antagonist hypertension treatment strategy for patients with coronary artery disease. The International Verapamil-Trandolapril Study (INVEST): a randomised controlled trial. JAMA 290: 2805-2816.

49. The IPPPSH Collaborative Group (1985) Cardiovascular risk and risk factors in a randomised trial of treatment based on the beta-blocker oxprenolol: The International prospective primary prevention study in hypertension (IPPPSH). J Hypertens 3: 379-392.

50. Wikstrand J, Warnold T, Tuomilehto J, Olsson G, Barber HJ, et al. (1991) Metoprolol versus diuretics in hypertension. Morbidity results from MAPHY study. Hypertension 17: 579-588.

51. Cryer PE, Haymond MW, Satiago JV, Shar SD (1976) Norepinephrine and epinephrine release and adrenergic mediation of smoking-associated hemodynamic and metabolic events. N Eng J Med 295: 573-577.

52. Tarnow J, Muller RK (1991) Cardiovascular effects of low-dose epinephrine infusions in relation to the extent of pre-operative beta-blockade. Anaesthesiology 74: 1035-1043.

53. Wellstein A, Palm D, Belz GG (1986) Affinity and selectivity of beta-adrenoceptor antagonists *in vitro*. J Cardiovasc Pharmacol 8: S36-S40.

54. Smith C, Teitler M (1999) Beta-blocker selectivity at cloned human beta-1 and beta-2 adrenergic receptors. Carsiovasc Drugs Ther 13: 123-126.

55. Cruickshank JM (2010) The modern role of beta-blockers in cardiovascular medicine. USA, Shelton, Peoples Medical Publishing House.

56. Prisant LM (2008) Nebivolol: pharmacological profile of an ultra selective, vasodilatory beta-1 blocker. J Clin Pharmacol 48: 225-239.

57. Lennard MS, Silas JH, Freestone S, Ramsay LE, Tucker GT, et al. (1982) Oxidation phenotype – a major determinant of metoprolol metabolism and response. N Eng J Med 307: 1558-1560.

58. Bijl MJ, Visser LE, van Schaik RH, Kors JA, Witteman JC, et al. (2009) Genetic variation in the CYP2 D6 gene is associated with a lower heart rate and blood pressure in beta-blocker users. Clin Pharmacol Ther 85: 45-50.

59. Evans DA, Mahgoub A, Sloan TP, Idle JR, Smith RL (1980) A family and population study of the genetic polymorphism of debrisoquine oxidation in a white British population. J Med Genet 60: 102-105.

60. Kalow W (1982) The Upjohn Award Lecture 1981/La Conférence Upjohn 1981. The metabolism of xenobiotics in different populations. Can J Physiol Pharmacol 60: 1-12.

61. Brodde O (1997) The pharmacology of bisoprolol. Rev Contemp Pharmacother 8: 21-33.

62. Bundkirchen A, Brixius K, Block B, Nguyen Q, Schwinger RH (2003) Beta-1 adrenoceptor selectivity of nebivolol and bisoprolol. A comparison of [3H]CGP 12.177 and [125I]iodocyanopindolol binding studies. Eur J Pharmacol 460: 119-126.

63. Rozec B, Erfanian M, Laurant K, Trochu JN, Gauthier C (2009) Nebivolol, a vasodilating selective beta-1 blocker and beta-3 adrenergic agonist in the non-failing transplanted human heart. J Am Coll Cardiol 53: 1539-1542.

64. Broeders MA, Doevendans PA, Bekkers BC, Bronsaer R, van Gorsel E, et al. (2000) Nebivolol a third generation beta-blocker that augments vascular nitric oxide release. Circulation 102: 677-684.

65. Ignaro LJ (2004) Experimental evidences of nitric oxide-dependent vasodilatory activity of nebivolol, a third generation beta-blocker. Blood Press Suppl 13: 2-16.

66. Moniotte S, Kobzik L, Feron O, Trocho JN, Gauthier C, et al. (2001) Upregulation of beta-3 adrenoceptors and altered contractile response to inotropic amines in human failing myocardium. Circulation 103: 1649-1655.

67. Gauthier C, Leblais V, Kobzik L, Trochu JN, Khandoudi N, et al. (1998) The negative inotropic effect of beta-3 adreoceptor stimulation is mediated by activation of a nitric oxide synthase pathway in human ventricle. L Clin Invest 102: 1377-1384.

68. Schulman SP, Becker LC, Kass DA, Champion HC, Terrin ML, et al. (2006) L-arginine therapy in acute myocardial infarction: the Vascular Interaction With Age in Myocardial Infarction (VINTAGE MI) randomized clinical trial. JAMA 295: 58-64.

69. Prichard BNC, Thompson FO, Boakes AJ, Joekes AM (1975) Some haemodynamic effects of compound Ah 5158 compared with propranolol, propranolol plus hydralazine and diazoxide. Clin Sci Mol Med 48: S97- S100.

70. Cruickshank JM, Prichard BNC (1994) Beta-blockers in Clinical Practice. 2nd Edition. Edinburgh: Churchill Livingstone, 1119-1126.

71. Robb OJ, Petrie JC, Webster J, Harry J (1985) ICI 118,551 does not reduce blood pressure in hypertensive patients responsive to atenolol and propranolol. Br J Clin Pharmacol 19: 541-542.

72. Zacharias FJ, Cowen KJ (1977) Comparison of propranolol and atenolol in hypertension. Postgrad Med J 53: 111-113.

73. Neutel JM, Smith DH, Ram CV, Kaplan NM, Papademetriou V, et al. (1993) Application of ambulatory blood pressure monitoring in differentiating between antihypertensive agents. Am J Med 94: 181-187.

74. Deary AJ, Schumann AL, Murfeet H, Haydock SF, Foo RS, et al. (2002) Double-blind, placebo controlled crossover comparison of 5 classes of drugs. J Hypertens 20: 771-777.

75. Hiltunen TP, Suonsyrja T, Hanilla-Handelberg T, Paarvonen KJ, Miettinen HE, et al. (2007) Predictors of antihypertensive drug responses: initial data from a placebo-controlled, randomesed, cross-over study with four antihypertensive drugs (The GENRES Study). Am J Hypertens 20: 311-318.

76. Parrinello G, Paterna S, Torres D, Di Pasquale P, Mezzero M, et al. (2009) One year renal and cardiac effect of bisoprolol versus losartan in recently diagnosed hypertensive patients. Clin Drug Investig 29: 591-600.

77. Frishman WH, Burris JF, Mroczek WJ, Weir MR, Alemayehu D, et al. (1995) First-line therapy option with low-dose bisoprolol fumarate and low-dose hydrochlorthiazide in patients with stage 1 and stage 11 systemic hypertension. J Clin Pharmacol 35: 182-188.

78. Prisant LM, Mensah GA (1996) Use of beta-adrenergic receptor blockers in Blacks. J Clin Pharmacol 36: 867-873.

79. Vanhees L, Defoor JG, Scheoers D, Lijnen P, Peeters BY, et al. (2000) Effects of bisoprolol and atenolol on endurance excercise capacity in healthy men. J Hypertension 18: 35-43.

80. Brion R, Carre F, Verdier JC, Poncelet P, Douard H, et al. (2000) Comparative effects of bisoprolol and nitrendipine on exercise capacity in hypertensive patients with regular physical activity. J Cardiovasc Pharmacol 35: 78-83.