

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

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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 atheromatous 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 (\pm 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

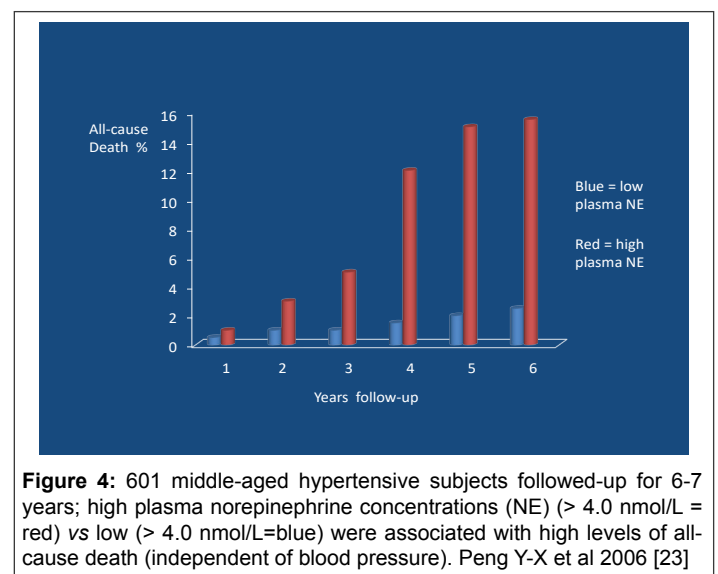
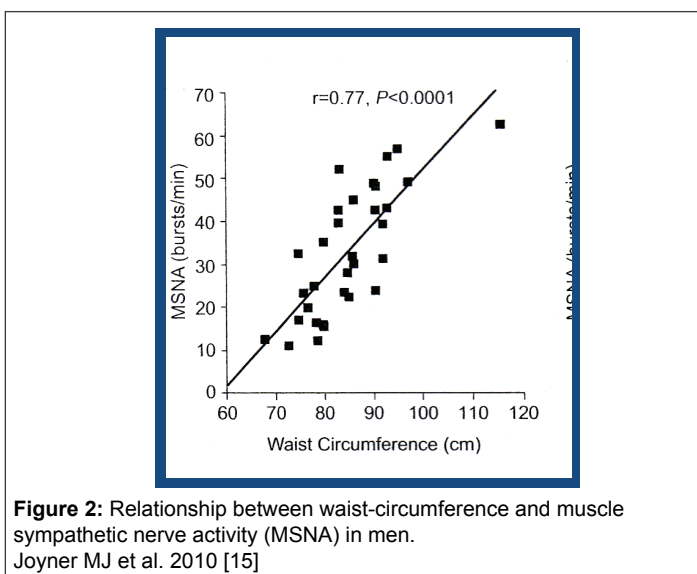
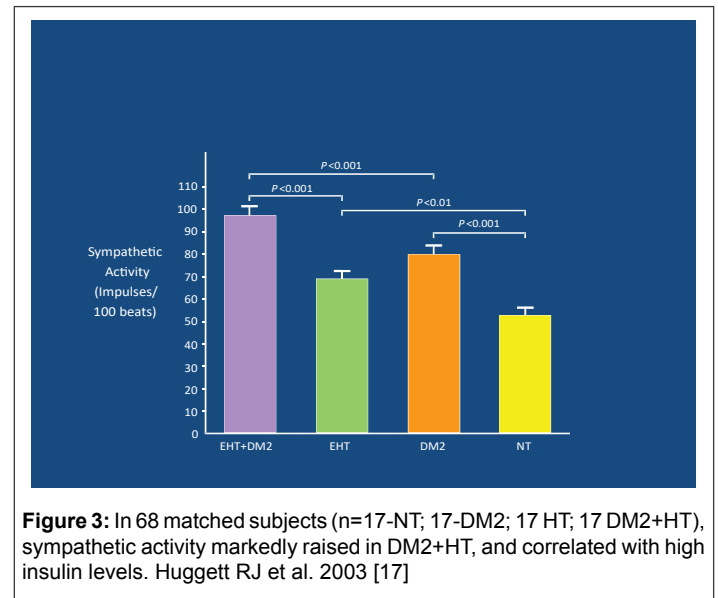
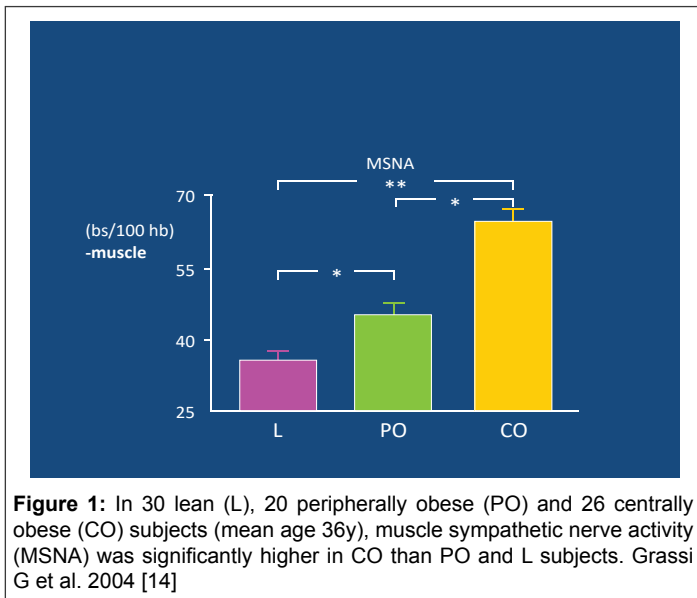
sympathetic activity [23], could be an indicator of a poor prognosis. It is note-worthy that in high PRA cases, beta-blockers have a particularly powerful anti-hypertensive effect [25].

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].



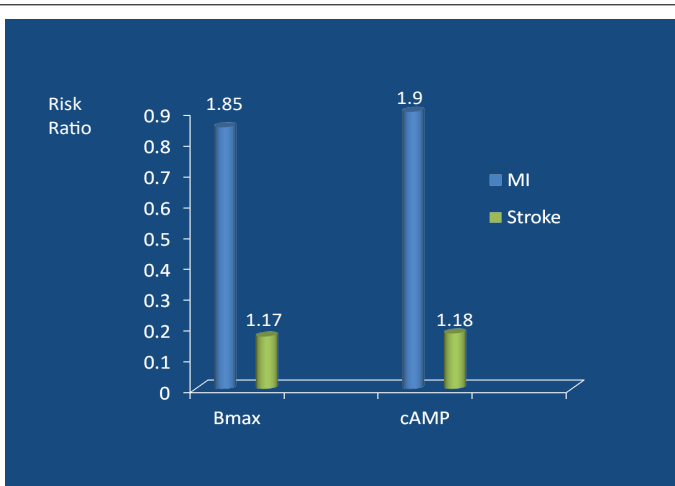


Figure 5: Beta-receptor density (Bmax) and cAMP levels (in lymphocytes) as predictors of MI and stroke in middle-aged hypertensives followed for 7 years. Peng Y-X et al 2006 [23]

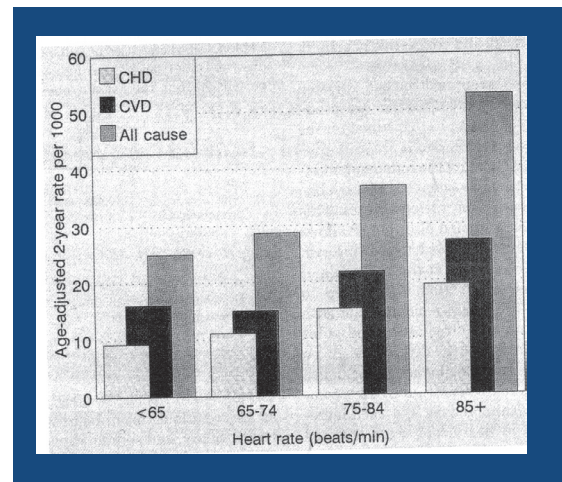


Figure 6: Framingham: Effect of resting heart rate on all-cause death, CHD and CVD events in untreated male hypertensives, followed-up for 36 years. Gillman MW et al. 1993 [24]

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.

Dihydropyridine 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).

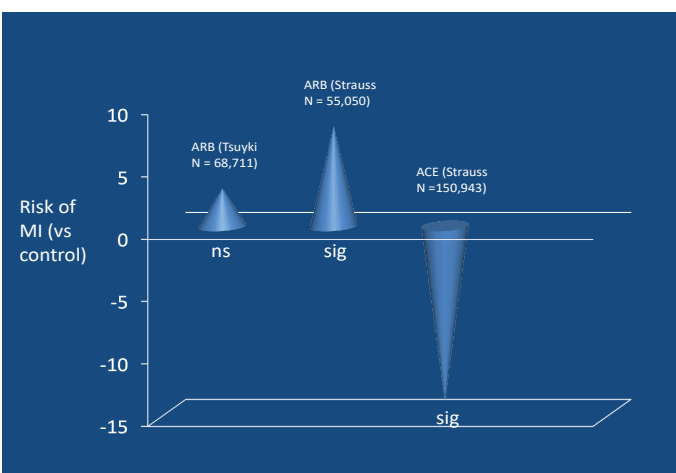


Figure 7: Relative risk of MI in meta-analyses of ARB and ACE-inhibitors. Strauss and Hall, Circulat 2007 [35]

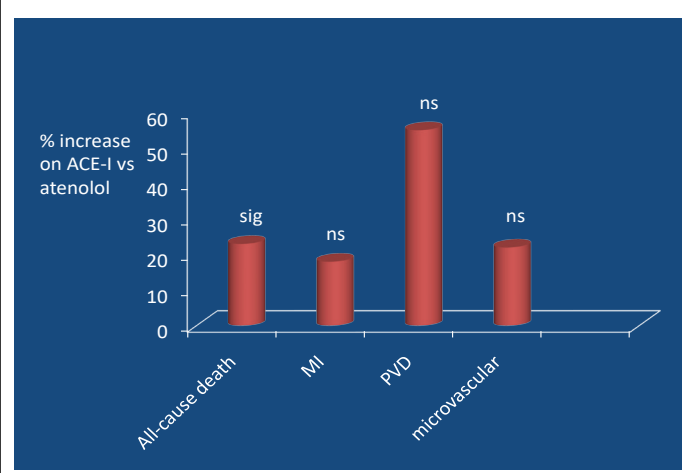


Figure 10: UKPDS study 20 year follow-up (mean 14.5 years); significant ($p < 0.05$) increase in all-cause death on ACE-I (vs atenolol). Holman RR et al. 2008 [40]

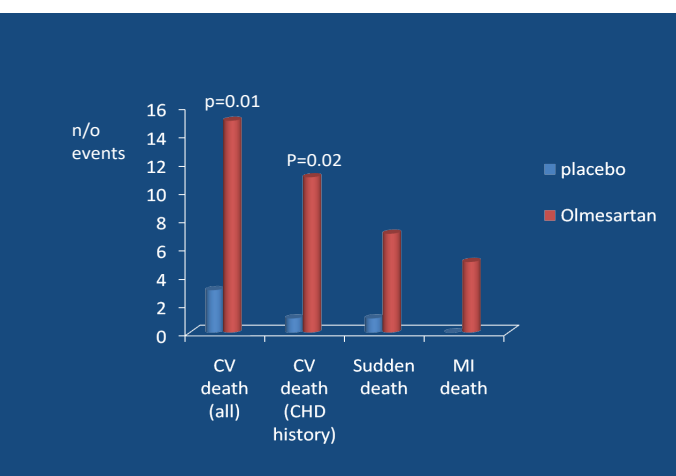


Figure 8: ROADMAP Study; Olmesartan vs placebo (randomised) in 4447 DM2, mean age 57, mean BMI 31, BP 136/81, over 3.2 years. Haller H et al. NEJM 2011 [37]

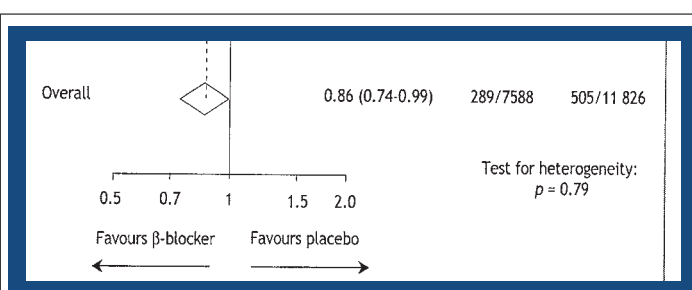


Figure 11: A meta-analysis of 2 studies in the younger ($< 60y$) hypertensive subject; beta-blockers significantly superior to randomised placebo in preventing all cause death/stroke/MI. Khan and McAlister, 2006 [46]

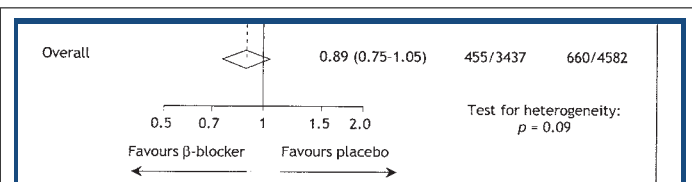


Figure 12: Meta-analysis of 5 studies in the elderly hypertensive subject ($> 60y$) – a strong trend favouring beta-blockers vs randomised placebo in the prevention of the composite death/stroke/MI. Khan and McAlister 2006 [46]

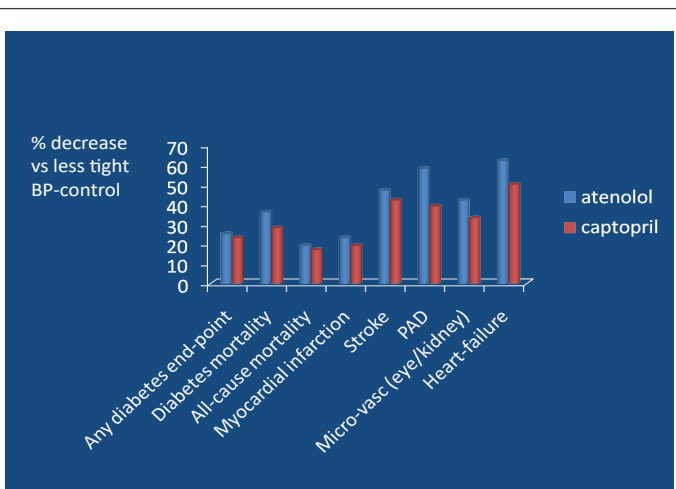


Figure 9: UKPDS 39 – all primary end-point trends favour atenolol vs captopril when compared with less-tight BP control (BP diff 10/5 mm Hg)

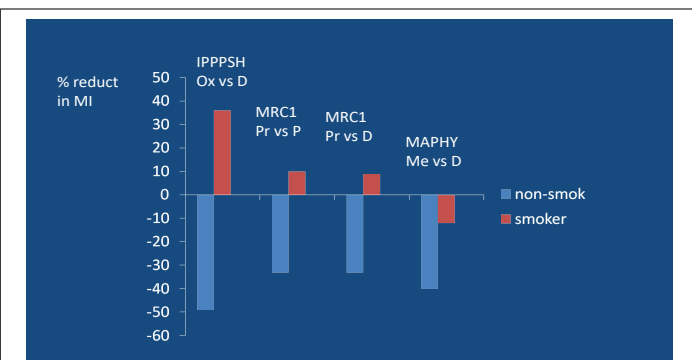


Figure 13: Beta Blocker/Smoking interaction in young/mid-age hypertensives, regarding myocardial infarction (MI); Ox=Oxprenolol, Pr=Propranolol, Me=Metoprolol, P=Placebo, D=Diuretic.

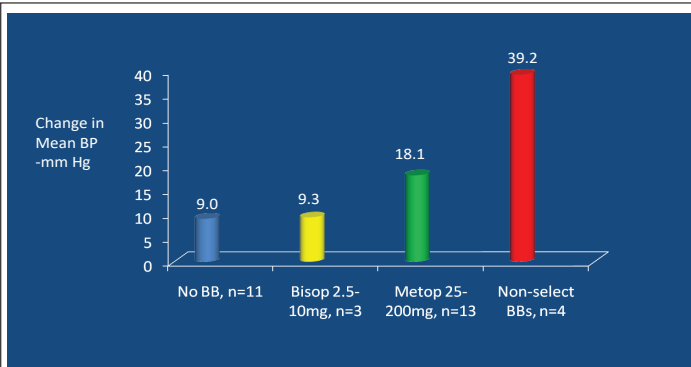


Figure 14: Peri-operative interaction between adrenaline and beta-blockers. Tarnow J and Muller R, 1991 [52]

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 labetalol 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, doxazosin, 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.

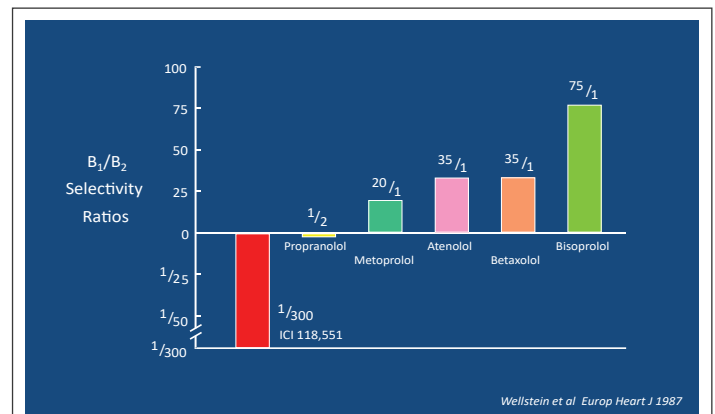


Figure 15: Beta₁ and Beta₂ Selectivity Ratios. Wellstein A et al. 1986 [53]

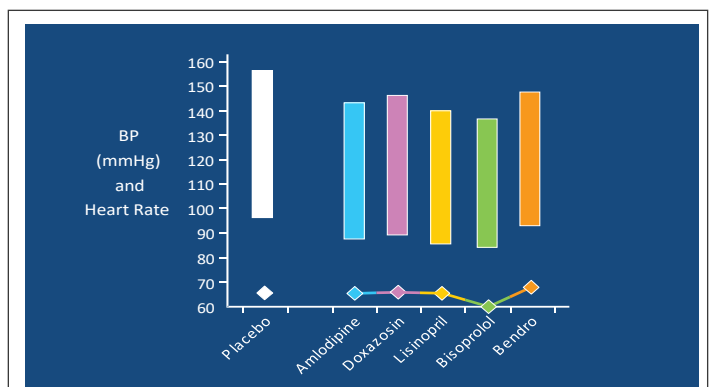


Figure 16: In 34 young (28-55yrs) hypertensives, Bisoprolol 5mg was more effective than Amlodipine 5mg, Doxazosin 104mg, Bendrofluazide 2.5mg, Lisinopril 2.5-10mg (double blind, crossover, 1 month each) in controlling office and 24 hr BP. Deary AJ et al. J Hypertens 2002 [74]

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
Propranolol 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.
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