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The Role of Beta-Blockers in the Treatment of Hypertension

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Abstract

Importance

Two major guide-line committees (JNC-8 and NICE UK) have dropped beta-blockers as first-line therapy in the treatment of hypertension. Also, recent meta-analyses (that do not take age into account) have concluded that beta-blockers are inappropriate first-line agents in the treatment of hypertension. This review seeks to shed some light on the "rights and wrongs" of such actions and conclusions.

Objectives

Because the pathophysiology of primary/essential hypertension differs in elderly and younger subjects, the latter being closely linked to obesity and increased sympathetic nerve activity, the author sought to clarify the efficacy of beta-blockers in the younger/middle-aged group in reducing the risk of death, and cardiovascular end-points.

Evidence acquisition

Four searches were undertaken, utilising PubMed up to 31st Dec 2015. One search was under the terms "hypertension AND obesity AND sympathetic nerve activity". A second was "hypertension AND plasma noradrenaline/norepinephrine AND survival". A third was "beta-blockers or adrenergic beta-antagonists AND hypertension AND age AND stroke or myocardial infarction or death". A fourth was "meta-analysis of beta-blockers AND hypertension AND age AND death, stroke, myocardial infarction"

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Results

Diastolic (with or without systolic) hypertension, in contrast to isolated systolic hypertension, occurs primarily in younger subjects, and is linked to overweight/obesity and increased sympathetic nerve activity. In younger/middle-aged hypertensive subjects, high plasma norepinephrine levels are linked (independent of blood pressure) to an increased risk of future cardiovascular events and death. High resting heart rates (a surrogate for high sympathetic nerve activity) likewise predict premature all-cause death, coronary heart disease and cardiovascular events in younger hypertensive subjects. In this younger/middle-aged hypertensive group, antihypertensive agents that increase sympathetic nerve activity (diuretics, dihydropyridine calcium blockers, and angiotensin receptor blockers (ARBs)) do not decrease (and may increase) the risk of myocardial infarction, and are therefore inappropriate first-line agents in this age-group. By contrast, in younger/middle-aged hypertensive subjects (less than 60 years old), meta-analysis has shown that beta-blockers are significantly superior to randomised placebo, and at least as effective as randomised comparator agents, in reducing death/stroke/myocardial infarction. In this younger/middle-aged hypertensive group beta-blockers have been shown (vs randomised placebo or diuretics) to reduce the risk of myocardial infarction by 35–50 %, and stroke by 50–55 % (vs placebo), in non-smoker men. Atenolol was at least as effective as ACE-inhibition (captopril) in reducing all 7 cardiovascular endpoints (including stroke which was reduced by 50 %), vs less tight control of blood pressure, in obese hypertensive subjects with type-2 diabetes (UKPDS study); and after 20 years follow-up, atenolol was significantly (23 %) superior to the ACE-inhibitor in reducing the risk of all-cause death (beta-blockers have anti-cancer properties, which maybe relevant).

Conclusions and Relevance

Primary/essential hypertension in younger/middle-age is underpinned by high sympathetic nerve activity. In this age-group high resting heart rates and high plasma norepinephrine levels (independent of blood pressure) are linked to premature cardiovascular events and death. Thus, antihypertensive agents that increase sympathetic nerve activity ie diuretics, dihydropyridine calcium blockers, and ARBs, are inappropriate first-line choices in this younger age-group. Beta-blockers perform well vs randomised placebo and other antihypertensive agents regarding reduced risk of death/stroke/myocardial infarction in younger (<60 years) hypertensive subjects, and are a reasonable first-line choice of therapy (certainly in men). These facts should be reflected in the recommendations of guideline committees around the world.

Keywords

Hypertension • Age • Beta-blocker • Epinephrine • Norepinephrine • Stroke • Myocardial infarction • Smoking status

Abbreviations

BP blood pressure
BB beta-blocker

1 Introduction

There is much confusion regarding the role of beta-blockers (BB) in primary (or essential) hypertension, stemming from two main sources. Firstly there are differences among Guideline committees from the USA (James et al. 2014), Europe (Mancia et al. 2007) and UK (Krause et al. 2011), concerning the role of BBs; BBs are no longer recommended as first-line therapy for hypertension in the USA (James et al. 2014) and UK (Krause et al. 2011). Secondly, the results of 7 recent meta-analyses (Wu et al. 2013; Prospective Studies Collaboration 2002; Wiysonge and Opie 2013; Lindholm et al. 2005; Xue et al. 2015; Thomopoulos et al. 2015a, b) regarding appropriate first-line therapy for the treatment of hypertension, were not favourable to BBs (age was not taken into account).

Importantly, neither the USA-JNC-8 guidelines (James et al. 2014), nor the European guidelines (Mancia et al. 2007), take age into account (hypertension in the young/middle-aged is often associated with obesity and is underpinned by high sympathetic nerve activity, and this is a situation favourable to beta-blockade, or ACE-inhibitors which reduce sympathetic nerve activity – see later). Nevertheless, Europe views first-line beta-blockade to be similar to other classes of anti-hypertensive agents, the reduction in blood pressure (BP) being the important factor. In contrast JNC-8 no longer recommends first-line beta-blockade, primarily due to the poor results of atenolol (vs losartan) in the LIFE Study (Dahlof et al. 2002) involving elderly hypertensives. The UK NICE Committee (Krause et al. 2011) does take age into account, but gives the reason for omitting BBs as a first-line treatment of younger hypertensive patients, as 1. impaired efficacy in reducing stroke-risk. 2. a tendency to precipitate diabetes, and is therefore the least cost effective option (vs - ACE-Is and ARBs) (Williams 2007). Unlike the USA, its near neighbour Canada does (like the UK NICE Committee) take age into account and (unlike the UK NICE Committee) recommends first-line beta-blockade for hypertensive subjects less than 60 years old (Khan et al. 2009 May).

This review seeks to shed a little light upon a confused situation regarding the role of BBs in the treatment of hypertension, based on views already expressed by the author (Cruickshank 2013).

2 Methods

Involved utilisation of the PubMed Search up to December 31st, 2015, under the search terms

1. "hypertension AND obesity AND sympathetic nerve activity", where 191 studies were identified, from which 3 (Grassi et al. 2004; Lambert et al. 2007; Huggett et al. 2003) relevant, illustrative, recent (from year 2000) publications were selected by mutual agreement between the author and a medical colleague.
2. "hypertension AND plasma noradrenaline/norepinephrine AND survival", where 3 studies were identified, and one was selected (Peng et al. 2006). There was also reference to two recent reviews conducted by the author (Coats and Cruickshank 2014; Cruickshank 2014), relating to diuretics, dihydropyridine calcium channel blockers, and angiotensin receptor blockers (ARBs), and their effects on sympathetic nerve activity and the risk of myocardial infarction; this approach provided 11 references (Menon et al. 2009; No author listed 1980; Medical Research Working Party 1985; Leren and Heigeland 1986; Fogari et al. 2000; Estacio et al. 1998; Heuser et al. 2003; Moltzer et al. 2010; Strauss and Hall 2006, 2007).
3. A search was conducted under the terms "meta-analyses of beta-blockers AND hypertension AND age AND death, stroke, myocardial infarction". This search identified

5 studies, from which two were selected, being specific to BBs (Khan and McAlister 2006; Kuyper and Kahn 2014).

3 Results

1. Essential hypertension, obesity, sympathetic nervous activity, and prognostic/treatment implications.

The classic Framingham Heart Study began in 1948 with enrolment of 5209 men and women aged 28–62 years, and was enlarged in 1971 to include a further 5124 men and women who were the offspring (or their spouses) of the original participants; follow-up of subjects occurred every 2–4 years. Two of Framingham's conclusions (Franklin et al. 2005) were 1. The development of diastolic (± systolic) hypertension was closely related to a younger age and an increased body mass index (BMI), and 2. The development of isolated systolic hypertension occurred in an older age-group, reflecting a stiffening/ageing of the arteries – Table 1. Certainly from a haemodynamic view-point, primary hypertension in the young and elderly differ markedly, with the former being linked primarily to a high cardiac output (Druktenis et al. 2007); in the elderly there is a fall in cardiac output (Palatini and Julius 2009; Sowers and Lester 2000), so that high blood pressure is dependent on an increased peripheral resistance.

Obese (defined as a BMI greater than 30 kg/m2) adolescents with hypertension experience a marked fall in BP after weight-loss following bariatric surgery, with 74 % becoming normotensive (Inge et al. 2016). In younger subjects, obesity (particularly central) is linked to a significant increase in sympathetic nerve activity (Grassi et al. 2004). The obesity-related high sympathetic nerve activity may be confined to men (Kostis et al. 2015), and be apparent mainly in muscle and kidney (Brooks et al. 2015). Obesity-related increases in sympathetic nerve activity are particularly apparent in the presence of hypertension (Lambert et al. 2007)- Fig. 1, or type-2 diabetes (Huggett et al. 2003). Even high-normal blood pressure is linked to increased muscle sympathetic nerve activity (Seravalle et al. 2015). The raised sympathetic nerve activity is associated with the release of leptin (so-called "thin hormone") from adipose tissue; leptin acts upon the hypothalamic region of the mid-brain, resulting in increased sympathetic nerve activity (Barnes and McDougal 2014). High insulin levels, associated with obesity-related insulin resistance, also act upon the hypothalamic region, resulting in heightened sympathetic nerve activity (Coats and Cruickshank 2014; Cruickshank 2014). This has important prognostic implications, as high norepinephrine (noradrenaline) levels are associated with the atherosclerotic process (Helin et al. 1970) and

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

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-u	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

Franklin et al Circulat (2005)

(via an increased heart rate) coronary plaque rupture (Heidland and Strauer 2001a). It thus comes as no surprise that high plasma norepinephrine levels, independent of smoking and blood pressure levels, are powerful predictors of cardiovascular death and survival in 601 (354 men and 247 women) young/middle-aged hypertensive subjects (over a 6–7 year follow-up period (Peng et al. 2006) – Fig. 2. Importantly, high intra-lymphocyte beta-receptor density (Bmax) and cyclic adenosine monophosphate (AMP) levels predict (independent of BP) future myocardial infarctions, but not stroke (which relates to blood pressure) (Peng et al. 2006) – Fig. 3. In the Framingham Heart Study (Gillman et al. 1993), high resting heart rates, particularly over 85 bpm (a surrogate for increased sympathetic nerve activity), in young/middle-aged hypertensive subjects, have been shown to predict all-cause death and cardiovascular and coronary heart disease events for both hypertensive men – Fig. 4, and women over a 36 year follow-up period.

Though sympathetic nerve activity is increased in elderly hypertension (Yamada et al. 1989; Hart and Charkoudian 2014), this is not so within the kidney (Esler et al. 1984). There is also a marked reduction in beta-receptor

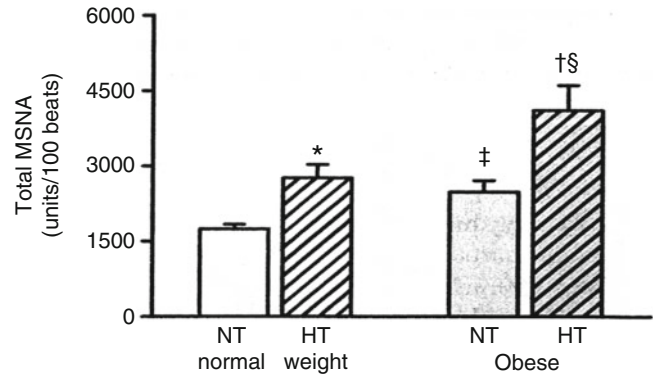

Fig. 1 Muscle sympathetic nerve activity (MSNA) in normal weight and obese, young/middle-aged normotensives (NT) and hypertensives (HT) (Lambert et al. 2007)

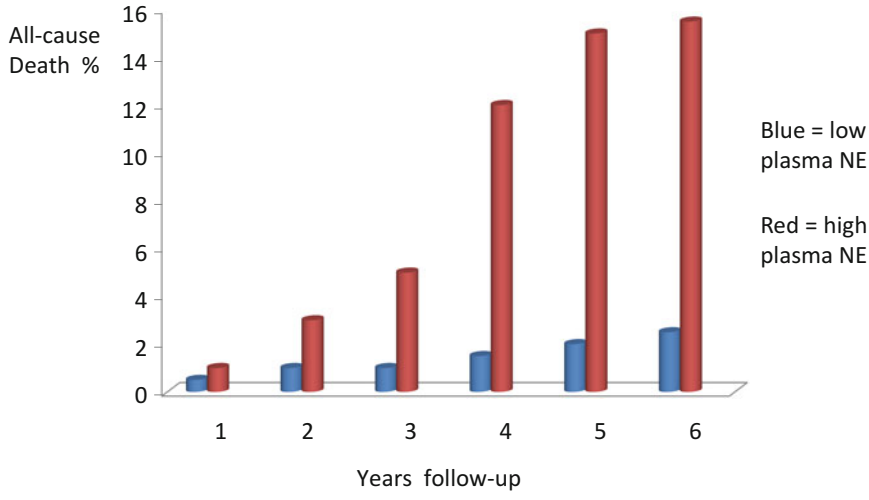

Fig. 2 601 middle-aged hypertensive subjects followed-up for 6–7 years; high plasma norepinephrine concentrations (NE) (>4.0 nmol/L = *red*) vs low (>4.0 nmol/L = *blue*) were associated with high levels of all-cause death (independent of blood pressure) (Peng et al. 2006)

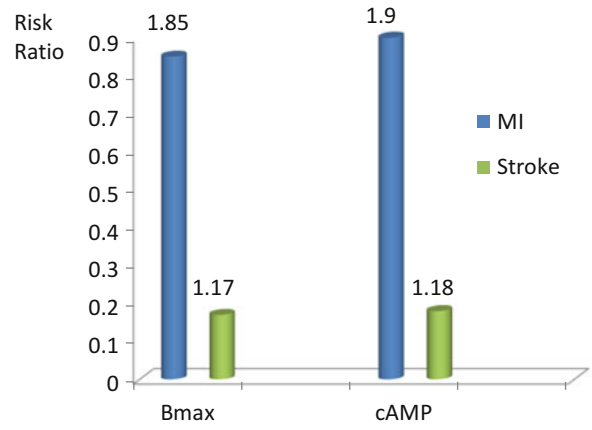

Fig. 3 Beta-receptor density (Bmax) and cAMP levels (in lymphocytes) as predictors of myocardial infarction(MI)and stroke in middle-aged hypertensives followed for 7 years (Peng et al. 2006)

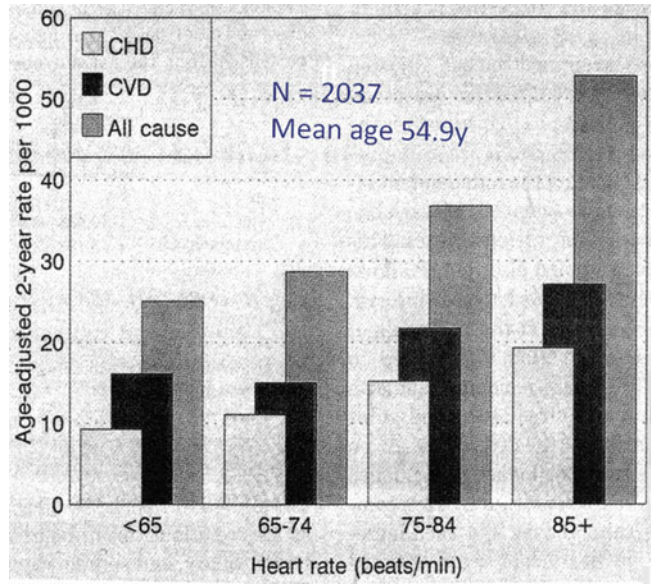

Fig. 4 Framingham: Effect of resting heart rate on all-cause death, CHD and CVD events in untreated male hypertensives, followed-up for 36 years (Gillman et al. 1993)

affinity/sensitivity in this older age-group (Feldman et al. 1984; Tenero et al. 1990), which may explain the relative lack of efficacy of beta-blockers in the elderly – (see later).

In the above context, it is notable that antihypertensive agents that increase sympathetic nerve activity in young/middle-age, perform poorly in terms of reducing cardiovascular events in this age-group. Thus, thiazide-type diuretics increase sympathetic nerve activity (Menon et al. 2009), and in 3 studies involving diuretic therapy in young/middle-aged hypertensive subjects (No author listed 1980; Medical Research Working Party 1985; Leren and Heigeland 1986) there was no reduction in the risk of myocardial infarction (No author listed 1980; Medical Research Working Party 1985), and even a significant increase (Leren and Heigeland 1986), versus randomised placebo/non-treatment. Dihydropridine calcium blockers (felodipine, amlodipine, manidipine, and lacidipine) increase heart rate and plasma norepinephrine levels (Fogari et al. 2000), and in the ABCD study (Estacio et al. 1998) the investigation was terminated prematurely due to a significant excess of myocardial infarctions in the nisoldipine, vs the enalapril, group. Likewise, angiotensin receptor blockers (ARBs) increase

sympathetic nerve activity in younger subjects (Heuser et al. 2003; Moltzer et al. 2010). Meta-analyses indicates that, in contrast to ACE-inhibitors, ARBs increase the risk of myocardial infarction (Strauss and Hall 2006; Straus and Hall 2007) Fig. 5, and in two subsequent placebo-controlled studies involving hypertension (Imai et al. 2011) and pre-hypertension plus diabetes (Haller et al. 2011), there was a significant excess if cardiovascular events in those receiving the ARB. Thus, prevention of myocardial infarction and cardiovascular events is not just about good control of BP. In contrast to ARBs, ACE-inhibition results in a reduction in sympathetic nerve activity (Noll et al. 1997) – see later.

2. The role of beta-blockers in the treatment of hypertension; the importance of age

2a. Beta-blockers and the atheromataous process

As myocardial infarction is the most common cardiovascular event in young/middle-aged essential hypertension (Medical Research Working Party 1985), it is important to note that beta-blockade is able to reverse the coronary atherosclerotic process. In a pooled analysis of four intravascular ultrasonography randomised, controlled trials in patients with coronary heart disease, over an 18–24 month time-interval, BBs (mainly atenolol and metoprolol) effected a significant ($p < 0.001$) regression of coronary artery atherosclerotic plaque (Sipahi et al. 2007). BBs also stabilise vulnerable coronary plaque. A study of 106 middle-aged patients who underwent coronary angiography twice within a 6 month period, revealed that high heart rates (>80 bpm) significantly increased, and BBs significantly decreased, the risk of atheromataous plaque disruption and rupture (a precursor to myocardial infarction) (Heidland and Strauer 2001b).

2b. Beta-blockers and control of blood pressure in the younger subject

Beta-2 blockade results in a rise in BP of about 7/5 mm Hg (Robb et al. 1985). Thus a moderately beta-1 selective agent like atenolol is more effective in lowering BP than a non-selective BB like propranolol (Zacharias and Cowen 1977). Atenolol, in turn, is less effective in lowering BP than highly beta-1 selective bisoprolol (Neutel et al. 1993). Indeed, in younger/middle-aged hypertensive subjects, bisoprolol is a more effective anti-hypertensive agent than the calcium blocker amlodipine, the alpha-blocker doxazosine, the ACE-inhibitor lisinopril, and the diuretic bendrofluozide (Deary et al. 2002), and angiotensin receptor

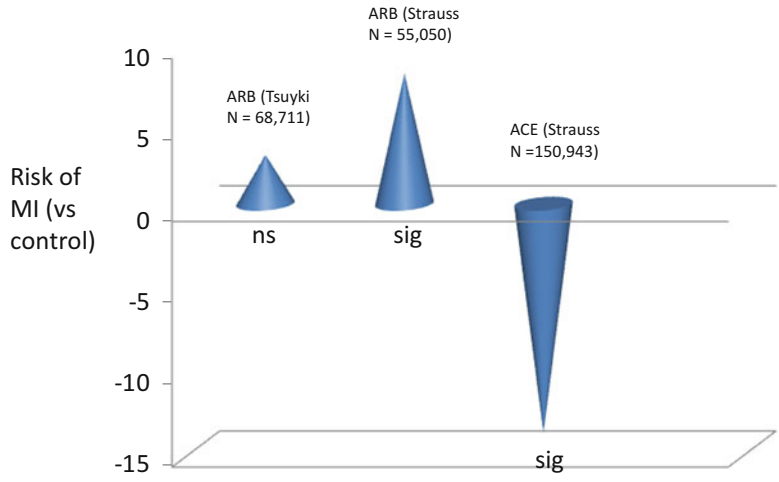

Fig. 5 Relative risk of myocardial infarction (MI) in meta-analyses of ARB and ACE-inhibitors: ARBs increase risk of MI. Strauss and Hall, Circulation 2006

blockers (ARBs) (Hiltunen et al. 2007), being at least as reno-protective as the latter (Parrinello et al. 2009).

2c. Beta-blockers and reduction of hard endpoints.

As already noted, recent meta-analyses that do not take age into account, are less than complimentary to BBs (Wu et al. 2013; Prospective Studies Collaboration 2002; Wiysonge and Opie 2013; Lindholm et al. 2005; Xue et al. 2015; Thomopoulos et al. 2015a, b; Dahlof et al. 2002). One (Wu et al. 2013) suggested that BBs increase all-cause mortality; another (Lindholm et al. 2005) indicated that first-line beta-blockade did not reduce all-cause mortality and was associated with only modest reductions in cardiovascular events (vs randomised placebo or non-treatment); another (Xue et al. 2015) suggested that BBs increase the risk of stroke; another (Thomopoulos et al. 2015a) indicated that BBs were inferior to renin-angiotensin system (RAS) inhibitors in preventing cardiovascular events and stroke; and finally 2 meta-analyses (Thomopoulos et al. 2015b; Dahlof et al. 2002) concluded that BBs were less effective than other agents in preventing stroke, and that reduction in coronary heart disease and all-cause death did not achieve statistical significance.

Two meta-analyses that do take age into account (Khan and McAlister 2006; Kuyper and Kahn 2014) arrive at very different conclusions to meta-analyses that do not. One meta-analysis (Khan and McAlister 2006) included 8 randomised placebo-controlled studies, and 9 randomised studies involving active agents (Williams 2007; Medical Research Working Party 1985; The IPPPSH Collaborative Group 1985; Coope and Warrender 1986; Dahlof et al. 1991; MRC Working Party 1992; Trial of secondary prevention with atenolol after transient ischemic attack or nondisabling stroke. The Dutch TIA Trial Study Group. Stroke 24:543–548 1993; Eriksson et al. 1995; Wilhelmsen et al. 1987; UK Prospective Diabetes Study Group 1998; Hansson et al. 1999a, b, 2000; Zanchetti et al. 2002; Pepine et al. 2003; Black et al. 2003; Dahlof et al. 2005). Compared to randomised placebo, in the younger/middle-aged hypertensive subject, with a mean age less than 60 years old, (admittedly and arbitrary cut-off point re definition of young/middle-aged) BBs were significantly superior to placebo in reducing the risk of death/stroke/MI – Fig. 6; with only a positive trend in the elderly – Fig. 7. When compared to randomised comparator antihypertensive drugs, there was a trend favouring BBs in younger hypertensive subjects Fig. 8, in contrast to those older than 60 years old, where BBs were significantly less effective in reducing the risk of death/stroke/myocardial infarction – Fig. 9. The other meta-analysis (Kuyper and Kahn 2014) involved 21 studies, comprising the same 17 studies as the first meta-analysis (Khan and McAlister 2006), plus an extra 4 studies in

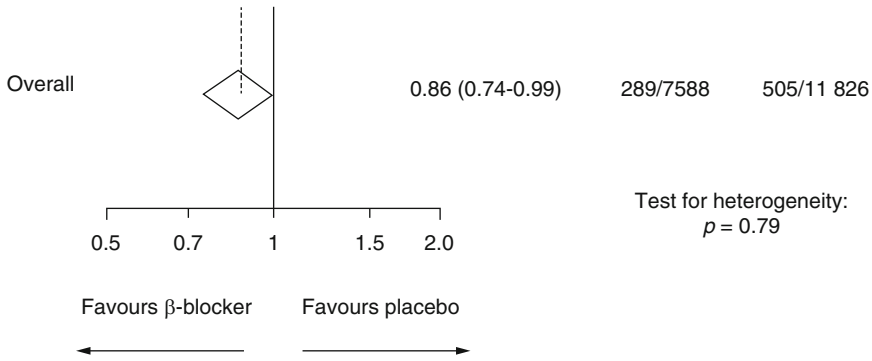

Fig. 6 A meta-analysis of 2 studies in the younger (<60y) hypertensive subject; beta-blockers significantly superior to randomised placebo in preventing all cause death/stroke/MI (Khan and McAlister 2006)

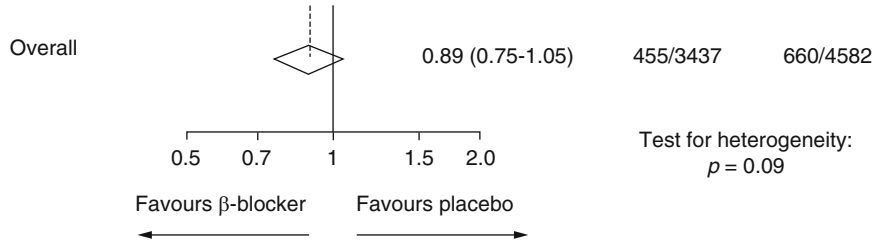

Fig. 7 Meta-analysis of 5 studies in the elderly hypertensive subject (>60y) – a strong trend favouring beta-blockers vs randomised placebo in the prevention of the composite death/stroke/MI (Khan and McAlister 2006)

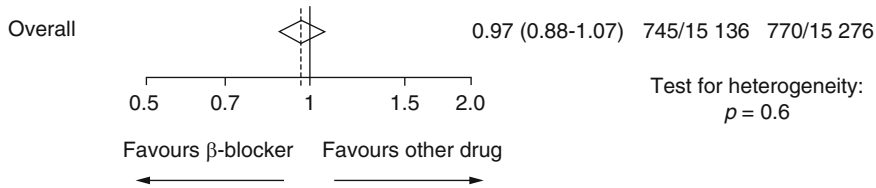

Fig. 8 A meta-analysis of 5 studies in the younger (<60y) hypertensive subject; a trend favouring beta-blockers vs. drug in preventing all cause death/stroke/MI (Khan and McAlister 2006)

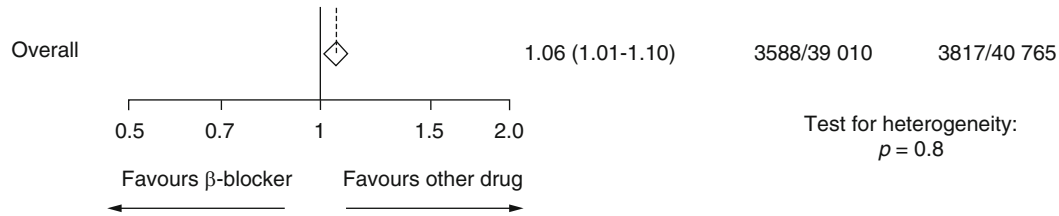

Fig. 9 A meta-analysis of 7 studies in the elderly (>60y) hypertensive subject; beta-blockers were significantly inferior to other drugs in preventing all-cause death/stroke/MI. Khan and McAlister

the younger group (3 studies compared propranolol with diuretic therapy (Veterans Administration Cooperative Study Group on Antihypertensive Agents 1982; Berglund et al. 1986; Yurenev et al. 1992), and the fourth – AASK study (Wright et al. 2002), compared metoprolol with amlodipine and ramipril in Black American hypertensive patients with renal disease). The conclusion was that in the young/middle-aged (less than 60 years old) both atenolol and non-atenolol beta-blockers were similarly effective in reducing cardiovascular endpoints, while in the elderly, atenolol (no other BBs have been studied) was associated with an increased risk of stroke. The second meta-analysis did not include the most recent results of the AASK study (Norris et al. 2006) in younger/middle-age subjects, which showed that metoprolol, amlodipine, and ramipril were similarly effective in reducing cardiovascular outcomes after 4 years of follow-up.

BBs thus have no role to play as first-line agents in the elderly hypertensive subject, unless myocardial ischemia is also present (Pepine et al. 2003), where atenolol was equivalent to the calcium blocker verapamil. The role of BBs in the elderly is as second-line therapy to either diuretics or calcium blockers, as evidenced in the MRC-elderly study (MRC Working Party 1992) and the large ALLHAT (The ALLHAT Officers

and Coordinators for the ALLHAT Collaborative Research Group 2002) and SHEP (SHEP Cooperative Research Group 1991) studies, especially in the presence of the metabolic syndrome (SHEP Cooperative Research Group 1991).

3. Beta-blockers and prevention of stroke and all-cause death in younger/middle-aged hypertensive subjects; dispelling some myths

There is a perception that BBs do not reduce all-cause mortality (Wu et al. 2013; Prospective Studies Collaboration 2002; Wiysonge and Opie 2013; Lindholm et al. 2005), and are relatively ineffective in reducing the risk of stroke (Krause et al. 2011; Xue et al. 2015; Thomopoulos et al. 2015a, b; Dahlof et al. 2002; Williams 2007; Khan et al. 2009 May), in younger/middle-aged hypertensive subjects. The UKPDS-39 (UK Prospective Diabetes Study Group 1998) and MRC-1 (Medical Research Working Party 1985) studies give no credence to these perceptions. Concerning stroke-risk reduction in MRC-1 (Medical Research Working Party 1985) in non-smoking men, both non-selective propranolol and the diuretic bendrofluazide, vs randomised placebo, reduced the risk of stroke by 54 %. In UKPDS-38 (U.K. Prospective Diabetes Study Group 1998), where smoking was not taken into account, tight control (either atenolol or captopril) of blood pressure, vs less tight control (difference 10/5 mm hg), resulted in a significant 44 % reduction in the risk of stroke. UKPDS-39 (UK Prospective Diabetes Study Group 1998) examined the effect of atenolol and captopril in reducing macrovascular and microvascular complications over a 9 year follow-up period. Figure 10 shows the effect of the 2 agents in reducing the 7 primary endpoints (plus heart failure- a secondary end point) vs less-tight control of blood pressure. It is apparent that all 8 trends favoured the BB (over the ACE-I) which reduced stroke-risk by about 50 %, peripheral arterial disease-related endpoints by about 60 %, microvascular (kidney and eye) endpoints by about 45 %, and heart failure by about 65 %. Thus, the UKPDS-39 (UK Prospective Diabetes Study Group 1998) results, like MRC-1 (Medical Research Working Party 1985), deny totally the claim that BBs are relatively ineffective in preventing stroke in young/middle-aged hypertensive subjects.

The UKPDS patients were monitored for a further 10 years, with a median total follow-up time of 14.5 years (Holman et al. 2008). The trends favouring the beta-blocker over the ACE-inhibitor tended to persist, but now, in the case of all-cause death, there was a significant 23 % reduction in favour of atenolol – Fig. 11. There is thus no truth in the claim that BBs do not reduce all cause death (Wu et al. 2013; Prospective Studies Collaboration 2002; Wiysonge and Opie 2013; Lindholm et al. 2005).

In middle-aged patients with pre/mild hypertension plus stable myocardial ischemia (von Armin and for the TIBBS Investigators 1996), randomised to either highly beta-1 selective (cardioselective) bisoprolol or nifedipine SR, at

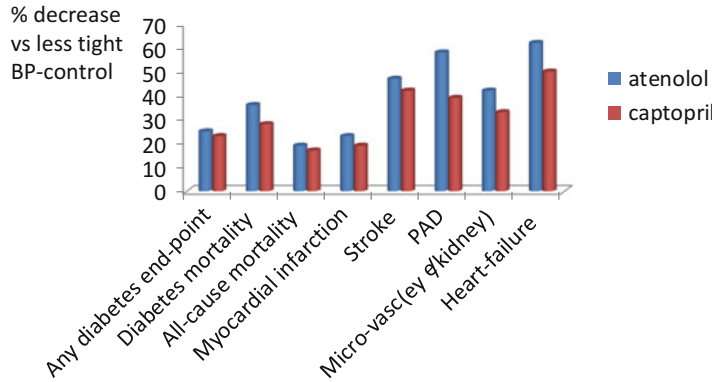

Fig. 10 UKPDS 39 – all primary end-point trends favour atenolol vs captopril when compared with less-tight BP control (BP diff 10/5 mm Hg)

1 year follow-up, event-free survival was significantly superior in those randomised to bisoprolol.

4. The possible mechanism of the reduction in all-cause death by long-term beta-blockade (in middle-age)

In UKPDS-39, apart from all-cause death, all other benefits of atenolol (relative to ACE-I) noted after the initial study (UK Prospective Diabetes Study Group 1998), tended to diminish with time (mean follow-up time 14.5 years) (Holman et al. 2008). So what other factors might be in evidence?

BBs have been observed by several authors, to modify the initiation and spread of various cancers. Certainly stress has been noted to hasten cancer-progression, probably via activation of tumour-associated beta-receptors by epinephrine and norepinephrine (Cole and Sood 2012; Fitzgerald 2012). Thus, beta-blockade has been noted to benefit 1. Breast cancer and prevent metastases (Cakir et al. 2002; Barron et al. 2011; Melhem-Bertrandt et al. 2011) 2. Colon cancer (Takezaki et al. 2001; Perrone et al. 2008) 3. Pancreatic cancer (Weddle et al. 2001; Zhang et al. 2010) 4. Melanoma (De Giorgi et al. 2012) 5. Lung cancer (Al-Wadei et al. 2012) 6. Neuroblastoma (Pasquier et al. 2013) 7. Prostate cancer (Perron et al. 2004; Grytli et al. 2013) –Table 2. This likely anti-cancer property of BBs is particularly important in the context of the increased risk of cancer in middle-aged hypertensive subjects (Harding et al. 2016).

5. The important beta-blocker/smoking interaction in younger/middle-aged hypertensive subjects

In three major prospective, randomised, hard-endpoint studies in middle-aged hypertensive subjects, cigarette smoking played a vital role in modifying the potential of the BB to reduce the risk of a cardiovascular event. The MRC-1 study (Medical Research Working Party 1985) compared non-selective propranolol with a

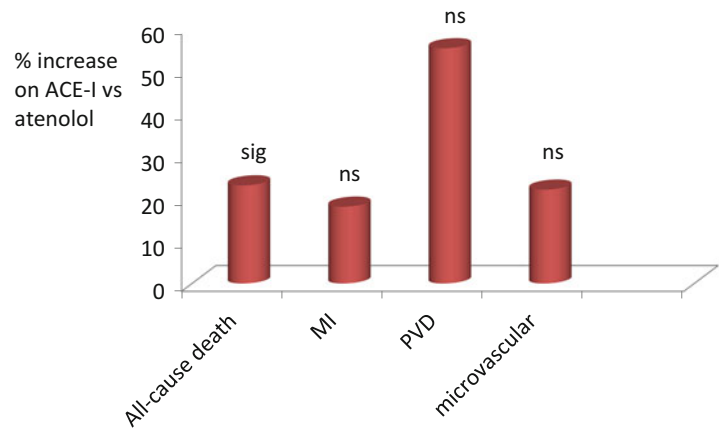

Fig. 11 UKPDS study 20 year follow-up (mean 14.5 years); significant ($p < 0.05$) 23 % increase in all-cause death on ACE-I (vs atenolol) (Holman et al. 2008)

Table 2 Cancers that may benefit from beta-blockade

Breast (Cakir et al. (2002); Barron et al. (2011); Melhem-Bertrandt et al. (2011))
Colon (Takezaki et al. (2001); Perrone et al. (2008))
Pancreas (Weddle et al. (2001); Zhang et al. (2010))
Melanoma (De Giorgi et al. (2012))
Lung (Al-Wadei et al. (2012))
Neuroblastoma (Pasquier et al. (2013))
Prostate (Perron et al. (2004); Grytli et al. (2013))

thiazide diuretic and placebo, in 17,354 subjects, of whom 30 % of men and 25 % of women were smokers, over a 5 year follow-up period. The IPPPSH study (The IPPPSH Collaborative Group 1985) compared non-selective oxprenolol with placebo, in 6357 subjects, of whom 29 % were smokers, over a 3–5 year follow-up period. The MAPPY study (Wikstrand et al. 1991) (an extension of the HAPPHY study (Wilhelmsen et al. 1987)) compared moderately selective metoprolol with a thiazide diuretic, in 3156 subjects, of whom 34 % were smokers, followed-up for 4 years.

In the case of myocardial infarction (about 3 times more common than stroke in the young/middle-aged hypertensive subject (Medical Research Working Party 1985)), the ability of the BB to reduce the risk of an event by 33–49 % (vs randomised placebo or diuretic therapy) in non-smokers, was not observed in smokers (Medical Research Working Party 1985; The IPPPSH Collaborative Group 1985; Wikstrand et al. 1991). Indeed, in the case of non-selective propranolol and oxprenolol, the risk of myocardial infarction was actually increased by 13–35 % in smokers – Fig. 12. A similar result relating to stroke was also noted in MRC-I (Medical Research Working Party 1985). In the MRC-elderly study (MRC Working Party 1992), atenolol (vs randomised placebo) increased the rate of cardiovascular events by 38 % in smokers, compared to a modest 16 % reduction in non-smokers.

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 (Cryer et al. 1976). Epinephine stimulates beta-1, beta-2, and alpha receptors, and in the presence of non-selective beta-blockers (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 blood pressure (Tarnow and Muller 1991). This increase in blood pressure 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 blood pressure (vs control) with a highly beta-1 selective beta-blocker like bisoprolol (which permits full beta-2-stimulation-induced vasodilatation) (Wellstein et al. 1986; Smith and Teitler 1999). Thus, the adverse BB/hypertensive/smoking interaction can be avoided by high beta-1 selectivity (cardioselectivity).

6. The gender debate

The proven benefit of beta-blockade in younger/middle-aged hypertensive subjects has been confined to men. In the MRC-1 trial (Medical Research Working Party 1985), the reduction in all-cause death (vs placebo) was confined to active treatment (both diuretic and beta-blocker therapy) in men only (there was an increase in women). Also in the MRC-1 trial, the 33 %

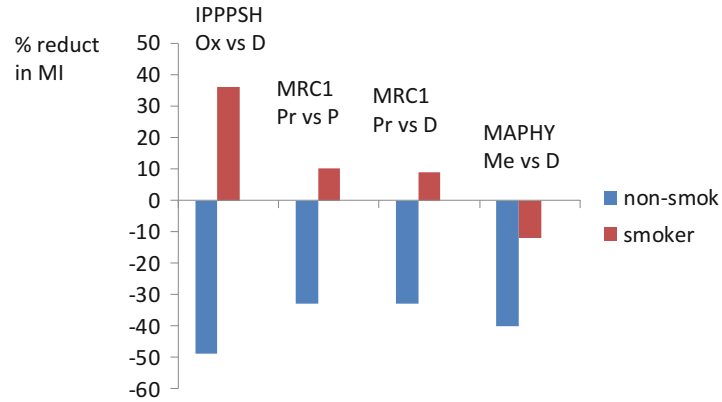

Fig. 12 BB/Smoking interaction, re reduction of myocardial infarction (MI) risk in young/mid-age hypertensives; P = placebo, D = diuretic, Ox = oxprenolol, Pr = propranolol, Me = metoprolol

reduction in coronary events in non-smoking men was confined to propranolol. Likewise in the IPPPSH study (The IPPPSH Collaborative Group 1985) involving young/middle-age hypertensive subjects, oxprenolol (vs placebo) significantly reduced cardiac events only in men, the opposite being the case for women. In the MAPHY study in male younger/middle-aged hypertensive subjects, metoprolol significantly reduced the risk of coronary events only in non-smokers. In the UKPDS-39 study (UK Prospective Diabetes Study Group 1998), 45 % were women, but the significant effects of atenolol (vs less-tight control of BP) were not analysed in terms of sexual gender.

7. Beta-blockers and Black hypertensive subjects

Black hypertensive patients usually have low plasma renin levels (Cruickshank and Prichard 1994), which were thought to account for the poor antihypertensive effect of propranolol, vs diuretics, in middle-aged Black subjects (Hammond et al. 1978). In contrast, highly beta-1 selective bisoprolol lowered BP equally in White and Black middle-aged hypertensive patients (Frishman et al. 1995; Prisant and Mensah 1996).

In the AASK Study (Norris et al. 2006), involving 1094 middle-aged African American patients with hypertension and renal dysfunction, after 4 years follow-up metoprolol, ramipril, and amlodipine all had similar effects in reducing the cumulative incidence of composite cardiovascular outcomes.

8. The importance of first-line therapy

The outcome of a drug trial is dependent on which therapy is given first-line. A classic example is the MRC-elderly study (MRC Working Party 1992). In that randomised placebo-controlled trial, there were 2 active, randomised therapy groups, namely 1. first-line diuretic, followed by (if necessary) add-on beta-blocker (atenolol), and 2. first-line beta-blocker, followed by (if necessary) add-on diuretic. Only first-line diuretic/second-line beta-blocker therapy was associated with significant risk-reduction regarding stroke, coronary events, and all cardiovascular events.

4 Summary and Recommendations

There is disagreement amongst leading Guideline Committees around the world on the role of beta-blockers in the treatment of hypertension. Unless age is taken into account, wrong conclusions will arise. Meta-analyses that do not consider age as a factor have been unfavourable to beta-blockers. By contrast, meta-analyses that include age as a factor, show that beta-blockers perform well in the younger/middle-age group (less than 60 years) in terms of preventing death/stroke/myocardial infarction (vs randomised placebo and other antihypertensive drugs).

Diastolic hypertension in younger/middle-aged subjects is closely associated with overweight/obesity and high sympathetic nerve activity. High sympathetic drive (independent of blood pressure) and high resting heart rates are linked to premature cardiovascular events and death in young/middle-aged hypertension. Antihypertensive drugs that increase sympathetic nerve activity (diuretics, dihydropyridine calcium blockers, and ARBs) are thus inappropriate first-line agents in younger/middle-aged hypertensive subjects. In this younger group, first-line beta-blockade was superior to placebo and diuretics in preventing myocardial infarction (certainly in non-smoker males). Beta-blockade was also at least as good as ACE-inhibition in reducing the risk of all 7 hard end-points (vs less-tight control of BP), including a 50 % reduction in stroke-risk, and was significantly superior in preventing all-cause death after long-term follow-up (beta-blockers have anti-cancer properties).

Thus, beta-blockade is a highly reasonable first-line choice in the treatment of the younger/middle-aged hypertensive subject (certainly in non-smoker men). There is an urgent need for leading Guide-line Committees to be aware of the importance of obesity and the sympathetic nervous system in hypertension in the young/middle-aged (and treatment implications), and for there to be a general consensus on the role of beta-blockers in the treatment of hypertension.

Conflicts of Interest The author has no conflicts of interest.

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