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Review

Are we misunderstanding beta-blockers

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Abstract

In myocardial ischaemia and heart failure, beta-blockers with intrinsic sympathomimetic activity (ISA) e.g. pindolol, xamoterol, bucindolol, nebivolol, have performed poorly in reducing morbidity and mortality. In both indications beta-1 blockade is the vital active ingredient. Beta-1 blockade (bisoprolol) is now an alternative first-line choice to Ace-inhibition in the treatment of heart failure. The therapeutic role of beta-blockers in hypertension is less well understood, particularly since the new recommendations in the UK from the NICE committee stating that: 1. beta-blockers are no longer preferred as a routine initial therapy, 2. the combination with diuretics is discouraged due to the risk of induced diabetes, and 3. in younger patients first-choice initial therapy should be an ACE-inhibitor. Recent data from the Framingham Heart Study and other epidemiological studies have indicated that the development of diastolic hypertension in younger subjects is closely linked to weight-increase and an increase in peripheral resistance; such subjects have a high adrenergic drive and cardiac output. In contrast, elderly systolic hypertension mostly arises de novo via poor vascular compliance. Thus in younger, probably overweight, hypertensives (including diabetics) first-line beta-blockade has performed well in preventing myocardial infarction (a fact hidden by meta-analyses that do not take age into account). Conversely, in elderly hypertensives first-line beta-blockade (atenolol) has performed poorly in reducing cardiovascular risk (due to partial beta-2 blockade atenolol evokes metabolic disturbance and does not improve vascular compliance, or effectively lower central aortic pressure or reverse left ventricular hypertrophy). Thus beta-blockers like atenolol are ill-equipped for first-line therapy in elderly hypertension. Some beta-blockers, e.g. bisoprolol (up to 10 mg/day is highly beta-1 selective) and nebivolol (beta-2/3 intrinsic sympathomimetic activity), do improve vascular compliance and cause no metabolic disturbance. Beta-blockers as second-line to low-dose diuretics (which, by improving vascular compliance and increasing sympathetic nerve activity, create an optimal environment for beta-blockade) in elderly hypertension (including diabetics) have performed well in reducing cardiovascular events (this combination has the added bonus of reducing the risk of bone fracture by about 30%). Meta-analyses which include studies where it is unclear whether a diuretic or beta-blocker was a first-line therapy will dilute the benefit stemming from first-line diuretic/second-line beta-blockade. Hypertensives (of all ages) with ischaemia are well suited to beta-blockade.

Keywords: Beta-blocker; Hypertension; Ischaemic heart disease; Heart failure; Type-2 diabetes; Vascular compliance

About 45, 40 and 30 years ago the anti-ischaemic, anti-hypertensive and anti-heart failure properties (respectively) of beta-blockers were discovered. Today, the anti-ischaemic role remains unchallenged, the anti-heart failure role goes from strength to strength, while the anti-hypertensive role is being questioned.

1. Non-controversial areas (almost)

1.1. Patients with ischaemic heart disease

1.1.1. Post-myocardial infarction

1.1.1.1. a) Early beta-blockade (intra-venous followed orally within 12 h after onset of pain). The prospective-randomised MIAMI study [1] with metoprolol and ISIS-1 study [2] with atenolol showed that in-hospital cardiovascular mortality was significantly reduced by 13–15%. However the situation where thrombolytic agents had already been given prior to

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beta-blockade was unclear until the large COMMIT trial [3] involving 45,852 acute cases of myocardial infarction randomised to placebo or I.V., followed by oral, metoprolol for one month. In that study there was no reduction in death, but there was a significant 18% reduction in reinfarction and 17% reduction in ventricular fibrillation; however these reductions were counterbalanced by a 30% increase in cardiogenic shock mainly during days 0–1 after admission. Thus beta-blockade should be started only in those who are haemodynamically stable.

1.1.1.2. b) Late Intervention (oral, a few days post-myocardial infarction, and continued for several years). Yusuf [4] reviewed the area and concluded that agents without intrinsic sympathomimetic activity, reduced mortality by about 30%, compared to about 10% with agents containing significant intrinsic sympathomimetic activity. Benefit was directly related to the fall in resting heart rate [5].

1.1.1.3. c) Likely mechanism(s) of benefit. These have been extensively discussed [6] and stem from beta-1 blockade. Likely factors include: i) reduction of myocardial oxygen requirements by a decrease in heart rate, systolic pressure and ventricular contractility, ii) bradycardia prolongs coronary diastolic filling period, iii) reduction in arrhythmogenic free fatty acids, iv) redistribution of coronary flow to vulnerable sub-endocardial regions, v) reduction of platelet stickiness, vi) increase in the threshold to ventricular fibrillation, vii) reduction in infarct size, viii) reduction in risk of cardiac rupture, and ix) reduction in rate of reinfarction.

The diminished benefit observed with agents containing intrinsic sympathomimetic activity is linked not only with lesser beta-1 blockade but also by the negative inotropic effect of beta-3 stimulation [7] operating through the nitric oxide (NO) synthase pathway. L-arginine is a substrate for nitric oxide synthase and has been shown to cause a significant increase in mortality (v placebo) when administered in the acute post-infarction period [8]. Thus nitric oxide, while being vasculo-protective, can be injurious to the myocardium.

1.1.2. Chronic ischaemia

1.1.2.1. a) Symptoms. The anti-angingal properties of beta-blockers are now taken for granted. Less well known is their (atenolol) ability to reduce symptoms of syndrome X more effectively than nitrates or amlodipine [9].

1.1.2.2. b) Reduction of hard cardiovascular end-points. Atenolol has proved superior to placebo in this area [10], unlike long-acting nifedipine [11]. Bisoprolol in the TIBBS study has proved superior to long-acting nifedipine as an anti-ischaemic agent [12] and improving event-free survival [13]. Amlodipine has fared better than nifedipine: it proved superior to placebo and enalapril in reducing cardiovascular events [14].

Verapamil was equal to metoprolol in reducing combined cardiovascular events [15] and was likewise equal to atenolol in reducing primary and secondary outcomes in the large INVEST study [16], except in patients with left ventricular dysfunction at baseline where atenolol was superior.

1.1.2.3. c) High-risk patients and non-cardiac surgery. A review on the topic [17] revealed that atenolol, bisoprolol, labetalol and oxprenolol, started pre-surgery and continued post-surgery for up to 3 years, significantly improved event-free survival. The same benefits may also accrue in CABG surgery patients [18]. Sudden withdrawal of beta-blockers post-surgery can precipitate a cardiovascular event [19].

1.1.2.4. d) Mechanism of action. Beneficial actions include most of the factors outlined above concerning post-myocardial infarction and are expressed through beta-1 blockade [6]. In addition the atheromatous process is slowed [20] and the risk of plaque rupture is lessened [21,22].

1.2. Partly controversial area

1.2.1. Heart failure

It is counter-intuitive that beta-blockers should be beneficial to patients with heart failure, because even very low-doses of propranolol were known to sometimes precipitate severe heart failure in elderly patients with ischaemia [23].

1.2.1.1. a) Not all beta-blockers are equal. Six different types of beta-blocker have been tested in large, prospective, randomised, controlled heart failure studies, on a background of ACE-inhibition, where all-cause death was the primary end-point — Table 1. It would appear that the absence of intrinsic sympathomimetic activity is the vital component for optimal results.

1.2.1.2. b) The good results. Carvedilol [24], bisoprolol [25] and metoprolol [26], which lack intrinsic sympathomimetic

Table 1
Beta-blockers (BB) and heart failure — Intrinsic Sympathomimetic Activity (ISA) impairs efficacy

Beta-blockers with ISA		Beta-blockers without ISA	
Type of BB	Comment	Type of BB	Comment
Xamoterol (43% beta-1 ISA) [30]	Actually increased mortality by 250% in moderate/severe heart failure	Carvedilol [24]	All 3 BBs decrease mortality by about 35%.
Bucindolol (25% ISA; also a powerful sympatholytic) [32]	A non-significant 10% reduction in mortality (worse if LV dysfunction severe)	Bisoprolol [25]	
Nebivolol (contains both beta-2 and beta-3 ISA) [43]	A non-significant 12% reduction in mortality in elderly patients	Metoprolol (succinate) [26]	

activity, all effected an approximate 35% reduction in all-cause mortality. Another study with carvedilol in post-myocardial infarction patients with a low ejection fraction [27] showed a 25% reduction in all-cause mortality.

The most recent prospective, randomised study in patients with chronic heart failure, CIBIS III [28], has compared first-line bisoprolol with first-line enalapril. Bisoprolol was not inferior to enalapril, indeed there were strong trends favouring the beta-blocker in terms of fewer deaths. It may thus be as safe and efficacious to initiate treatment for heart failure with bisoprolol as with an ACE-inhibitor.

1.2.1.3. c) The poor results. Xamoterol — Xamoterol is a beta-1 selective agent with about 43% intrinsic sympathomimetic activity [29]. In a placebo-controlled study in patients with moderate–severe heart failure, there was a significant increase in death rate [30]. Xamoterol was accordingly withdrawn from the market-place.

Bucindolol — Bucindolol is a non-selective agent with weak alpha-blocking properties and about 25% intrinsic sympathomimetic activity[31]. The BEST placebo-controlled trial [32] in patients with moderate to severe heart failure was stopped prematurely due to a non-significant 10% reduction in death rate.

Various explanations have been forwarded to explain the poor BEST study results. i) The high proportion of Black patients cannot be the reason as equal benefit accrued to White and Black patients in the first carvedilol heart failure study [33] and with metoprolol in the MERIT study [34]. ii) The presence of intrinsic sympathomimetic activity seems a reasonable explanation as the modest fall in heart rate of only 8 bpm compared poorly with the 13–14 bpm with carvedilol and metoprolol [35]. iii) Bucindolol effects a marked sympatholytic effect (probably via blockade of pre-synaptic beta-2 receptors), whereby noradrenaline levels were markedly reduced in the BEST study [36]; those with the greatest fall in noradrenaline concentration had the highest mortality — presumably severe myocardial dysfunction was critically dependent in adrenergic support.

Nebivolol — This agent, based on hamster studies, has been described as highly beta-1 selective [37]. However when compared to bisoprolol in human myocardial tissue nebivolol was barely selective – 3–4 fold, compared to bisoprolol – 16–20 fold [38]. The much lauded effects of nebivolol upon endothelial nitric oxide (NO) release is in fact the result of intrinsic sympathomimetic activity acting through the beta-2 [39] or beta-3 [40] receptors, properties that are shared by other agents possessing intrinsic sympathomimetic activity e.g. bopindolol [41] and celiprolol [42].

The disappointing results of nebivolol in the SENIORS study [43], a just significant 14% reduction in the primary outcome (all-cause mortality plus cardiovascular hospital admissions) and a non-significant 12% fall in all-cause mortality, is quite possibly due to intrinsic sympathomimetic activity as the fall in heart rate was only a modest 9 bpm. The high age of the participants is unlikely to be relevant as a meta-analysis involving all the major heart failure studies [44] indicated that elderly and non-elderly patients benefited equally from the beta-blocker therapy lacking intrinsic sympathomimetic activity. However, a non-pre-specified, retrospective sub-analysis on the 684 patients who were similar (in age and ejection fraction) to patients participating in the more impressive carvedilol [24], bisoprolol [25] and metoprolol [26] studies, indicated a benefit from nebivolol not dissimilar to that derived from the above 3 beta-blockers.

1.2.1.4. d) Mechanism of benefit of beta-blockers in heart failure. As already noted benefit results from beta-1 blockade. Likely mechanisms of beta-1 blockade benefit include: i) bradycardia, leading to increased diastolic coronary filling time (particularly relevant to ischaemic heart failure), ii) reduction in oxygen requirement, iii) anti-arrhythmic activity, iv) up regulation of beta-1 receptors, v) inhibition of the renin/angiotensin system, vi) increase in atrial and brain naturetic protein(BNP), and vii) inhibition of catecholamine-induced necrosis. With regard to the last important mechanism, in-vivo studies have shown that sympathomimetic agents can induce skeletal and cardiac myotoxicity [44a,b] while in-vitro data have shown that myocardial necrosis/apoptosis results from beta-1 stimulation (a c-AMP process) while beta-2 stimulation (via a Gi-coupled pathway) inhibits apoptosis [45]. The implication is that beta-1 blockade would inhibit, and beta-2 blockade might exacerbate, such a harmful process.

While the detrimental effect of intrinsic sympathomimetic activity is likely to be due to a minimising of the effects of beta-1 blockade, another factor may also be relevant i.e. the fact that beta-3 receptors are up-regulated in heart failure [46] and that stimulation of these receptors (e.g. via nebivolol) has a negative inotropic effect [47]. Indeed it has been suggested that beta-3 blockade could benefit patients with heart failure [47].

2. Controversial

2.1. Hypertension

Worries about beta-blockers (and indeed diuretics) stem from drug-induced metabolic changes [48–51] and atenolol's inability to reverse left ventricular hypertrophy [52] and reduce cardiovascular events (see later) in the elderly. Such concerns are not unreasonable. However more modern beta-blockers do not induce metabolic disturbances and are far more suited to the elderly hypertensive (see later).

The whole issue has been brought to a head in the UK by the new recommendations from the National Institute for Health and Clinical Excellence (NICE), working in collaboration with the British Hypertension Society, entitled "Hypertension: management of hypertension in adults in primary care" [53,54]. The new recommendations state that a) beta-blockers are no longer preferred as a routine initial therapy, b) that the combination of a beta-blocker and a diuretic is discouraged

due to the increased risk of the patient developing diabetes, and c) in patients aged 55 years or less, the first-choice for initial therapy should be an ACE-inhibitor (or angiotensin II receptor antagonist if an ACE-inhibitor is not tolerated).

The author of this review strongly disagrees with these guidelines [55].

2.1.1. 1) *The young/middle-aged hypertensive*

2.1.1.1. a) The development of hypertension. New light is being shed on the development and nature of so called "essential hypertension". A classic study from the Framingham Group [56] followed-up 3915 normal, untreated subjects for 10 years. Their conclusions are shown in Table 2. It is clear that the development of diastolic (± systolic) hypertension in the young, particularly in men, is closely linked to a high baseline body mass index and an increase in weight during follow-up, and the diastolic hypertension is the result of high peripheral resistance. In contrast the development of systolic hypertension in older subjects was linked only weakly to increasing weight, and arose de novo (in about 80% of cases) from normal or high normal, blood pressure i.e. not "burned-out" diastolic hypertension. This process, particularly in women, was the result of ageing, non-compliant arteries.

Two other large studies have confirmed these Framingham observations. In the Bogolusa Heart Study [57] where 3255 young subjects, starting at 4 years old and followed-up for 26 years (up to 42 years old), there was a close relationship between obesity and the development of hypertension. Another study involving 36,424 young subjects followed-up for 8 years, showed that body mass index was the strongest predictor of pre-hypertension [58].

Another large study in normotensive subjects showed that over an 8 year period about 25% developed hypertension and was closely linked to high levels of markers of inflammation (C-reactive protein) [59]. Obesity is an important cause of high C-reactive protein levels [60].

Table 2
The Framingham Heart Study [56] — different predictors of diastolic hypertension (± systolic hypertension) and isolated systolic hypertension

Predictors of IDH (± systolic hypertension)=DBP >90 mm Hg (± SBP >140 mm Hg)	Predictors of ISH=SBP >140 mm Hg+DBP <90 mm Hg
1) Young age	1) Older age
2) Male sex	2) Female sex
3) High BMI at baseline	3) Increasing BMI during follow-up (but weaker than in young)
4) Increasing BMI during follow-up	4) ISH arises more commonly from normal and high normal BP, than "burned out" diastolic hypertension
5) Main mechanism of IDH is raised peripheral resistance	5) Only 18% with new-onset ISH had a previous DBP >95 mm Hg
	6) Main mechanism of ISH is increased arterial stiffness (poor compliance)

N=3915 untreated normal subjects, mean age 48.5 years, followed-up for 10 years.
IDH = isolated diastolic hypertension; ISH = isolated systolic hypertension; BMI = body mass index.

2.1.1.2. b) The metabolic and haemodynamic profile of younger/middle-aged, probably overweight/obese, hypertensives. The adipocyte, particularly if centrally/abdominally located, produces several vasculo-toxic adipokinins e.g. TNF-alpha and IL-6 [61,62]. Leptin, the so called "thin" hormone, is also produced and acts centrally to stimulate sympathetic nerve activity [63]. The adipokinins induce an endothelial inflammatory response resulting in impaired nitric oxide release, increased superoxides, endothelial dysfunction and insulin-resistance [62,63]. Insulin-resistance is accompanied by increased insulin-secretion which, like leptin, acts centrally to stimulate sympathetic over-activity [64] and thus renin release [65]. Resulting high angiotensin II levels act centrally to further stimulate sympathetic activity [66], thus setting up a vicious cycle.

There is however a school of thought that proposes that sympathetic stimulation precedes obesity [67,68] rather than the reverse. The high sympathetic drive leads to a down-regulation/desensitisation of beta-receptors leading to reduced thermogenesis and thus an increased propensity to gain weight.

Chronic sympathetic stimulation is injurious to the cardiovascular system as evidenced by cardiac necrosis/apoptosis [69], increased risk of ventricular fibrillation [70], an increased rate of atheroma formation [71–73] and left ventricular hypertrophy [74], all conditions that are benefited by beta-1 blockade. There are data that strongly indicate that hypertension in the young occurs in those with sympathetic predominance [75]. Younger hypertensives do indeed have an approximate 2-fold increase in sympathetic activity compared to normotensive controls [76], closely linked to obesity and the biochemical changes associated with the metabolic syndrome [57,77]. All these metabolic changes can be reversed by weight-loss [78].

The high adrenergic drive of overweight subjects results in an increase in stroke volume and cardiac output of about 20% [79] plus an increase in heart rate. A persistently high heart rate (>85 bpm) has been shown to predict the development of diastolic hypertension in the young [79a,b] as well as decreasing arterial compliance [79c]. High blood pressure results from an increased peripheral resistance due to inadequate compensatory (to a high cardiac output) vasodilation, presumably due to endothelial dysfunction [80].

2.1.1.3. c) How do beta-blockers lower blood pressure in the younger, probably overweight, hypertensive? Beta-blockers without, and with, intrinsic sympathomimetic activity lower blood pressure by different mechanisms. For agents without intrinsic sympathomimetic activity plasma renin activity is probably important, either as a marker (for high sympathetic activity) or as a direct agent. Thus an agent like atenolol effectively reduces plasma renin activity and

lowers blood pressure markedly in high and normal plasma renin activity cases but poorly in low renin situations, the very opposite to diuretic response [81]. The actual fall in blood pressure is effected by a fall in heart rate and cardiac output, while vascular resistance tends, if anything, to be slightly raised as do plasma noradrenaline levels [82].

Beta-blockers with intrinsic sympathomimetic activity, e.g. pindolol, lower blood pressure by a fall in vascular resistance via beta-2 stimulation; there is also a fall in plasma noradrenaline, but little effect on plasma renin activity, heart rate or cardiac output [82]. The effect of intrinsic sympathomimetic activity upon peripheral resistance undoubtedly occurs via direct effects upon the endothelium resulting in nitric oxide (NO) release, as shown in the case of bopindolol [83] and celiprolol [84]. Nebivilol also acts in this fashion either via beta-2 [85] or beta-3 [86–88] intrinsic sympathomimetic activity.

2.1.1.4. d) Are all beta-blockers equally effective in lowering blood pressure? The answer is no. The possession of beta-1 intrinsic sympathomimetic activity does lessen anti-hypertensive action [89]. Thus, xamoterol, with very high beta-1 intrinsic sympathomimetic activity, actually increases resting blood pressure [90]. Beta-2 blockade, by blocking beta-2 vasodilatory receptors, diminishes anti-hypertensive activity; indeed a highly selective beta-2 blocking agent actually increases blood pressure by about 7/5 mm Hg [91]. Thus non-selective agents like propranolol and nadolol are less effective than atenolol in lowering blood pressure [92]. The lesser efficacy of non-selective agents is particularly apparent in cigarette smokers; nicotine stimulates adrenaline release [93] and beta-1 plus beta-2 blockade permits an unbridled alpha-constriction to cause a marked pressor response [94].

Atenolol is only moderately beta-1 selective and at 100 mg blocks about 80% of beta-1 receptors and 25% of beta-2 receptors in contrast to the virtual zero-occupancy of beta-2 receptors of bisoprolol 5–10 mg [95]. Thus the latter agent does not differ from an ACE-inhibitor in its effect on local vascular resistance [96] and lowers blood pressure more effectively than atenolol [97] and indeed other anti-hypertensive agents in the young [98] — Table 3.

Table 3
Beta-blockade (bisoprolol) is superior to other anti-hypertensive therapies in the younger hypertensive [98]

Drug	Number of times as "best" treatment	Mean age (y)	24 hour mean BP (mm Hg)
Amlodipine	5	49	144/95
Doxazosin	4	46	154/102
Lisinopril	10	47	136/89
Bisoprolol	13	43	135/86
Bendrofluazide	2	52	148/99

24 hour blood pressures on "best" treatment in younger hypertensives; randomised, double-blind, crossover design.

2.1.1.5. e) 24-hour control of blood pressure. Nocturnal blood pressure may be the best predictor of cardiovascular events [99]. Thus control of blood pressure throughout 24 h is important, particularly the early morning "vulnerable" period where blood pressure peaks. Hence a small, or absent, difference in blood pressure control during the day, can conceal large differences at night and early morning. Once daily atenolol, with a plasma half-life of 6–7 h and a peak: trough blood pressure control ratio over 24 h of only 31% is inferior to bisoprolol with a half-life of 10–12 h and a peak: trough ratio of 78%, in controlling 24 hour blood pressure, particularly at the vulnerable early morning peak [97].

2.1.1.6. f) Left ventricular hypertrophy. In middle-aged hypertensives followed-up for 20 years, both body mass index and plasma noradrenaline levels predicted left ventricular mass, with the noradrenaline action being independent of both body mass index and systolic blood pressure [100].

In the Framingham study [101], left ventricular hypertrophy by ECG was the most potent of all coronary risk factors. In younger/middle-aged hypertensives, atenolol was highly effective in reversing ECG-left ventricular hypertrophy over a 5 year period [102].

When left ventricular hypertrophy was assessed by echocardiogram beta-blockers, as a class, were somewhat less effective than ACE-inhibitors in reducing left ventricular mass [103]. However, high beta-1 selectivity (bisoprolol) rendered the beta-blocker at least as effective as ACE-inhibition in reducing left ventricular mass [104].

2.1.1.7. g) Beta-blocker-induced metabolic changes. Metabolic disturbances, involving blood sugar, HbA1-c, insulin-sensitivity, free fatty acids, plasma triglycerides, VLDL and HDL, are closely associated with beta-2 blockade [105]. Thus non-selective agents like propranolol, timolol and nadolol will be the worst offenders, followed by partially beta-1 selective agents such as metoprolol and atenolol. Highly beta-1 selective agents, e.g. bisoprolol 5–10 mg, will be essentially free of metabolic disturbances involving blood sugar, insulin-sensitivity and lipids [106,107], as will agents containing alpha-blockade e.g. carvedilol [108,109] or beta-2 intrinsic sympathomimetic activity, e.g. nebivolol [110].

As a result of the obesity epidemic affecting Westernised and many developing countries there has been much interest recently in the beta-3 receptor and its association with obesity and diabetes ("diabesity"). Beta-3 receptors are expressed in human white as well as brown adipose tissue and in skeletal muscle [111]. Agonists of the beta-3 receptor increase lipolysis, fat oxidation, energy expenditure and insulin-sensitivity, leading to the hope that beta-3 stimulants might become useful in the battle against "diabesity" [112]. Conversely, beta-3 (as well as beta-2) blockade by non-selective beta-blockers may possibly be playing a role in the weight-increase and metabolic changes observed with such agents [105].

Table 4
First-line beta-blockers prevent coronary events in younger hypertensives (narrow pulse-pressure)

Trial	Beta-blocker	Mean age (y)	Initial BP (mm Hg)	Pulse-pressure (mm Hg)	Result
IPPPSH [113]	Oxprenolol (v diuretic)	52	173/108	65	Fewer coronary events in men (non-smokers) with oxprenolol
MRC mild hypertension [114]	Propranolol (v placebo v diuretic)	51	161/98	63	As above (see Table 5) but diuretics superior in stroke prevention
MAPHY [115]	Metoprolol (v diuretic)	52	167/108	59	Metoprolol superior to diuretic in coronary event prevention
UKPDS (all diabetics) [116]	Atenolol (v captopril)	56	159/94	65	No overall difference but trends in reducing all 7 primary end-points favoured atenolol (see Table 11)

First-line beta-blockade (in randomised, controlled studies) and the prevention of hard cardiovascular end-points in younger/middle-aged hypertensives (see "Search/selection criteria" at end of paper).

2.1.1.8. h) First-line beta-blockade and the prevention of hard cardiovascular end-points in younger/middle-aged hypertensives. The selection criteria for relevant studies are set out after the section Summary and Conclusions.

Table 4 illustrates the type of patient in the 4 randomised, controlled, hard-end-point studies in younger/middle-aged, overweight hypertensives, involving beta-blockers as first-line therapy [113–116].

Noteworthy, in all 4 studies, were the relative youth and narrow pulse-pressures at baseline, indicating relatively elastic, compliant arteries. Broadly speaking beta-blockade was superior to placebo and diuretics (albeit dosed higher than today's recommendations) in preventing coronary events. This is important, as coronary events far out-number stroke events in younger hypertensives [114]. Table 5 shows that in the MRC mild hypertension study involving overweight (mean BMI=27) hypertensives propranolol was superior to both placebo and diuretics in preventing heart attacks [117], in spite of treated systolic blood pressure being lower in the diuretic treated group (strongly indicating that factors other than blood pressure control are important in preventing coronary events). The pooled results of the MRC and IPPPSH (also involving overweight subjects — mean BMI approximately 27) studies for men showed that beta-blockade, compared to diuretic-based therapy, was associated with a significant 21% reduction in the risk of a coronary event [118]. However the coronary-prevention for non-selective propranolol and oxprenolol was confined to non-smokers [113,114] (see earlier comments on smoking [93,94]). In the MRC mild hypertension study propranolol (vs placebo) reduced the frequency of myocardial infarction by a significant 33% and the frequency of stroke by 47% in non-smokers. By contrast in the MAPHY study moderately beta-1 selective metoprolol prevented coronary events in smokers [119]. The UKPDS-39 study [116] will be referred to later.

2.1.1.9. i) Mechanism of beta-1 blocking benefit in the younger/middle-aged hypertensive. As for other anti-hypertensive agents, i.e. diuretics, lowering blood pressure per se will result in a lessening of the risk of stroke. However, unlike diuretics beta-blockers reduce the risk of myocardial infarction. The likely reason for this latter benefit is the ability of beta-1 blockade to inhibit the cardiovascular-toxic affects of chronically increased sympathetic nerve activation. Thus, as already outlined in the section on ischaemia [6], the work of the heart is reduced, coronary diastolic filling time is prolonged, the threshold to ventricular fibrillation is reduced, atheromatous progression is slowed [20], the risk of plaque rupture is reduced [21] and left ventricular hypertrophy is effectively reversed [104].

2.1.2. 2) The elderly isolated systolic hypertensive

2.1.2.1. a) As patients become elderly should beta-blockers be stopped? As patients pass from middle-age to elderly (say 55–60 years) there should be no reason to change therapy, as a diastolic-hypertensive invariably remains a diastolic-hypertensive [56] with impaired endothelial function of the resistance arteries [120]. Indeed there are data to suggest that an appropriate anti-hypertensive agent should be chosen not by age but by non-invasive haemodynamics [121,122]. If there is concern regarding long-term metabolic disturbance, switch to a proven beta-blocker that causes no potentially harmful metabolic changes (and improves vascular compliance) e.g. bisoprolol 5–10 mg [123,124] or nebivolol [140].

2.1.2.2. b) The metabolic and haemodynamic profile of an elderly, possibly overweight, isolated systolic hypertensive. There is an age-related fall in plasma renin activity, the fall being steeper in hypertensives [125]. The increase in

Table 5
MRC Mild Hypertension Study [117] — propranolol superior to placebo and diuretic in prevention of myocardial infarction

	Bendrofluazide	Propranolol	Placebo
Sex	MI rate	MI rate	MI rate
Men	23.2*†	17.8	19.0
Women	22.2††	15.7**	20.8
Total	22.7*†††	16.8*	19.8

The effects of propranolol, diuretics and placebo upon transmural myocardial infarction (MI) — rates per 1000 person-years of observation.
Rate differs significantly from control group, ** $P<0.01$, * $P<0.05$.
Rate differs significantly from propranolol group, ††† $P<0.0001$, †† $P<0.001$, † $P<0.05$.

noradrenaline seen in normotensives is less obvious in the elderly hypertensive [126]. Beta-receptor sensitivity and affinity are reduced in the elderly [127].

Cardiac output decreases and vascular resistance (poor vascular compliance [56]) increases [128] with age. The inelastic "pipe-stem" arteries result in a widened pulse-pressure and the peripheral organs are no longer cushioned from the effects of pulsatile pressures. There is general agreement that pulse-wave reflection is speeded up in ageing stiff arteries resulting in an augmented reflected wave arriving earlier in the central aorta i.e. during systole instead of diastole, with the result that coronary artery filling pressure is reduced and the augmented central systolic pressure increases the risk of left ventricular hypertrophy. The poor vascular compliance in the elderly will contain both a functional (endothelial dysfunction) and structural (collagen) component. Poor compliance, the increase in pulse-wave velocity and the augmented central aortic systolic pressure are strong predictors of cardiovascular events [129].

2.1.2.3. c) Beta-blockers, blood pressure and vascular compliance in the elderly. The effect of various anti-hypertensive agents upon arterial compliance is very important, as arterial stiffness is an independent predictor of total and cardiovascular mortality, coronary morbidity/mortality and fatal stroke in patients with hypertension [129–133].

Commensurate with the falling plasma renin activity levels and beta-receptor insensitivity with increasing age, traditional beta-blockers(e.g. propranolol and atenolol) tend to exert a decreasing anti-hypertensive action [134]. Certainly in the MRC mild hypertension study propranolol exerted a lesser anti-hypertensive action in older compared to younger patients [114]. Equally, if not more, important is the effect of beta-blockers upon vascular elasticity/compliance.

Beta-blockers, depending on beta-1 selectivity, intrinsic sympathomimetic activity and alpha-blocking properties, vary in their effect on vascular compliance — Table 6. A non-selective agent like propranolol tends to actually worsen compliance [135], a moderately beta-1 selective agent like atenolol is neutral [136] and is relatively ineffective in lowering central aortic systolic pressure [137]. It is noteworthy that in the CAFÉ study [138], a sub-study of the large ASCOT study, atenolol-based therapy was significantly less effective than amlodipine/perindopril-based therapy in lowering aortic systolic and pulse-pressure (not reflected in peripheral values). Others [139] have noted that while atenolol significantly lowers mean systolic peripheral blood pressure there is a relative absence of effect upon central systolic blood pressure compared to an ACE-inhibitor/diuretic combination which, by its action of slowing pulse-wave velocity and reducing the magnitude of wave reflection from periphery to aorta, markedly lowers central systolic blood pressure. Agents with beta-2/3 intrinsic sympathomimetic activity, such as nebivolol [140], pindolol [141] and celiprolol [142] improve compliance, as does labelolol [143] with additional alpha-blocking properties, and highly beta-1 selective bisoprolol [144]. The beta-blocker differences become more comprehensible when it is appreciated that beta-2 stimulation causes vasodilatation, benefits arterial elasticity and lowers central aortic pressure (augmentation index) [145,146]; beta-2 blockade would antagonise this potentially beneficial process. Calcium antagonists, ACE-inhibitors and angiotensin receptor blockers improve compliance [147]. So do diuretics [148] and are at least as good as calcium antagonists, and better than ACE-inhibitors and beta-blockers, in reducing central aortic pressure in the elderly [168]. Certainly diuretics alone, or combined with a beta-blocker, are superior to calcium blockers and ACE-inhibitors at reducing pulse-pressure [149].

2.1.2.4. d) Beta-blockers and Left Ventricular Hypertrophy in Elderly Hypertension. The raised central systolic pressure, which is closely linked to arterial stiffening, increases ventricular load thereby inducing left ventricular hypertrophy [150]. A wide pulse-pressure (also associated to arterial stiffening) is also a powerful predictor of left ventricular hypertrophy [151]. Thus one might predict than anti-hypertensive agents that do not improve arterial compliance, e.g. atenolol, would be ineffective in reversing

Table 6
Some beta-blockers improve arterial compliance

Non-desirable properties for improving compliance		Desirable properties for improving compliance		
Beta-2 blockade		Alpha-blockade	Beta-2 ISA	Absence of beta-2 blockade i.e. high beta-1 selectivity
Strong	Weak			
e.g. Propranolol (tends to actually decrease compliance i.e. stiffens arterial wall)	e.g. Atenolol (tends to be neutral in its effect on compliance; at dose 100 mg a day approximately 25% of beta-2 receptors are blocked)	e.g. Labetalol (but problems with postural hypotension and skin vasodilatation).	e.g. Pindolol, Bopindolol, Celiprolol, Nebivolol (but high ISA a)can cause tremor and palpitations b) diminishes benefits of beta-1 blockade i.e. in heart failure and coronary heart disease)	e.g. Bisoprolol (at doses up to 10 mg, 0–5% of beta-2 receptors blocked)

ISA = Intrinsic sympathomimetic activity.

Table 7
First-line beta-blockers (atenolol) perform poorly in elderly hypertension (wide pulse-pressure)

Trial	Beta-blocker	Mean-age (y)	Initial BP (mm Hg)	Pulse-pressure (mm Hg)	Result
MRC Elderly [157]	Atenolol (vs placebo vs diuretic)	70	185/91	94	Only diuretics differed from placebo in stroke prevention; diuretic superior to atenolol in reducing coronary events
HEP [158]	Atenolol (vs non-treatment)	69	196/99	97	Significant reduction in stoke but no effect on coronary events by atenolol
LIFE [155]	Atenolol (vs losartan)	67	174/98	76	Losartan superior to atenolol in reducing cardiovascular mortality and non-fatal and fatal stroke
ASCOT [159]	Atenolol±Diuretic (vs amlodipine±perindopril)	63	164/94	70	Amlodipine±perindopril was superior to atenolol±diuretic in reducing all-cause mortality and all coronary and stroke end-points

First-line atenolol (in randomised, controlled studies) and the prevention of hard cardiovascular end-points in elderly hypertensives (see "Search/selection criteria" at end of paper).

left ventricular hypertrophy in elderly subjects with isolated systolic hypertension.

In elderly isolated systolic hypertensives, atenolol in contrast to verapamil, had zero effect on left ventricular hypertrophy reversal [152]. Similarly, in contrast to perindopril that reversed hypertrophy and improved coronary flow reserve, atenolol had no effect [153], as was the case versus irbesartan [154]. In the LIFE study losartan was more effective than atenolol in reversing ECG-left ventricular hypertrophy [155] and echo cardiographic left ventricular hypertrophy [156].

2.1.2.5. e) First-line beta-blockade (atenolol) and the prevention of hard cardiovascular end-points in the elderly hypertensive. The selection criteria for relevant studies are displayed after the section Summary and Conclusions.

Table 7 illustrates the type of patient and the results in the 4 prospective, randomised, controlled studies in elderly hypertensives involving beta-blockers (atenolol) as first-line therapy [155,157–159]. Notable is that the baseline pulse-pressure is now wide (70–97 mm Hg), denoting non-compliant arteries. In all 4 studies first-line atenolol fared relatively badly against placebo [157], non-treatment [158], diuretics [157], losartan [155] and amlodipine [159] in reducing the risk of cardiovascular events. In the LIFE study the worst results for atenolol occurred in patients with the widest pulse-pressure [160].

Why did atenolol perform so badly? — Table 8. Firstly it is totally inappropriate that a classic beta-blocker like atenolol should be first-line therapy for an elderly hypertensive characterised by low plasma renin activity [125,134], low beta-receptor sensitivity [127] and non-compliant arteries [56]. Secondly atenolol does not improve compliance [136], hence lowers augmented central aortic systolic pressure inadequately [137,138] and is thus ineffective in reversing left ventricular hypertrophy [152–156]. Atenolol once daily, with a plasma half of 6–7 h controls 24 hour blood pressure inadequately [97] — possibly relevant in the ASCOT study where atenolol's add-on therapy, bendroflumethiazide, also has a short half-life of about 4 h, in contrast to the comparator drugs amlodipine/perindopril both of which have long plasma half-lives over 30 h.

Meta-analyses of first-line beta-blocker (mainly atenolol) studies in hypertension that lump together studies in younger and elderly patients [161] will inevitably draw wrong conclusions, as will accompanying editorials [162], as pointed out by the present author [163] i.e. the benefits of beta-blockade in younger patients will be missed.

One is left to speculate as to what results might have been forthcoming had an agent which improved vascular compliance and had a good 24 hour blood pressure-lowering profile, been used as the sample beta-blocker in studies on the elderly.

2.1.2.6. f) Second-line beta-blockade and the prevention of cardiovascular events in the elderly hypertensive. Most clinicians would agree that first-line therapy for the elderly hypertensive should be a low-dose diuretic [164] or possibly a calcium antagonist [165]. Diuretics [166] and dihydropyridine calcium antagonists [167] increase sympathetic nerve activity and improve vascular compliance [147,168], giving rise to a haemodynamic scenario not disimilar to that occurring in younger overweight hypertensives; they thus create an environment conducive to added second-line beta-blockade (certainly for an agent like atenolol which does not improve vascular compliance [136–138]. Witness the success of a

Table 8
What are the possible reasons for the poor performance of first-line atenolol in the treatment of the elderly hypertensive?

1. Unlike the case of younger diastolic-hypertensives it is inappropriate that a classic beta-blocker like atenolol should be first-line therapy for the elderly systolic hypertensive (with low plasma renin activity and desensitised beta-receptors) — diuretics or calcium antagonists are the natural first-line choice; beta-blockers should be as given second-line to first-line low-dose diuretic (or calcium antagonist) therapy.
2. Atenolol partially blocks beta-2 receptors and thus does not improve vascular compliance; beta-blockers like bisoprolol (high beta-1 selectivity), labetalol (alpha-blockade) and nebivolol (beta-2 ISA) do improve compliance.
3. Thus atenolol is relatively ineffective in lowering augmented central aortic systolic pressure.
4. Thus left ventricular hypertrophy is poorly, or not, reversed.
5. Atenolol dosed once daily, with a plasma half-life of only 6-7 h and a 24 hour blood pressure-lowering peak/trough ratio of only 30%, controls 24 hour blood pressure inadequately.

Table 9
Reducing the rate of stroke and coronary events (vs placebo) in elderly hypertensives with the combination of diuretic and atenolol when atenolol is first-line therapy [157] and second-line therapy [157,170]

Placebo-controlled studies involving atenolol as first or second-line therapy		Reduction in coronary events (%) vs placebo	Reduction in stroke events (%) vs placebo
Atenolol as first-line (diuretic second-line) therapy	MRC Elderly [157]	0 (NS)	17 (NS)
Atenolol as second-line (diuretic first-line) therapy	MRC Elderly [157]	44 (sig)	31 (sig)
	SHEP [170]	27 (sig)	36 (sig)

first-line diuretic/second-line atenolol combination in the massive ALLHAT study [169] and SHEP study [170] in reducing cardiovascular events. In contrast one must conclude that the presence of a first-line beta-blocker like atenolol (that does not improve vascular compliance) prevents or limits the beneficial action of a diuretic upon vascular compliance and central systolic blood pressure from occurring. A mega-meta-analysis [171] has confirmed that a diuretic/beta-blocker combination compares well with calcium antagonist or ACE-inhibitor-based therapies in terms of reducing the risk of both coronary and stroke events. However, a recent review [172] has concluded that a diuretic/beta-blocker combination (old drugs) is less effective than more modern anti-hypertensive agents in reducing the risk of stroke (important because in the elderly, in contrast to younger/middle-aged hypertensives, the frequency of strokes almost achieves parity with the frequency of coronary events [157]). It is however vitally important which agent, a diuretic or a beta-blocker, is given first-line (important for a classic beta-blocker like atenolol which does not improve vascular compliance) — Table 9. It is apparent that in the MRC Elderly study [157] when atenolol is given first-line and diuretic second-line, in spite of blood pressure control as good as in the first-line diuretic/second-line beta-blocker group, there is no significant reduction in the frequency of coronary and stroke events vs placebo (thus factors other than blood pressure control are important). In dramatic contrast, when atenolol is given second-line to a first-line diuretic in the MRC Elderly study (also noted in the SHEP study [170]) the reduction in coronary and stroke events is highly significant vs placebo, the reduction being at least as great as that observed with more modern calcium antagonist-based therapy [169]. Thus reviews/meta-analyses [172] which lump together studies where it is either clear or unclear whether a diuretic or beta-blocker was first-line, will underrate the benefit of the first-line diuretic/second-line beta-blocker combination compared to more modern therapies.

Incidentally, an added bonus for the diuretic/beta-blocker combination in the elderly is that it reduces the risk of bone fracture by about 30% [173].

2.1.3. 3) Type-2 diabetes

Obesity is assuming epidemic proportions in the USA [174] and other Westernised countries. Hand in hand with the obesity epidemic is an increase in the frequency of the metabolic syndrome and type-2 diabetes. Diabetes increases the risk of coronary heart disease more than 14 fold in women [175].

2.1.3.1. a) The metabolic syndrome, type-2 diabetes, central obesity and the sympathetic nervous system. The metabolic and haemodynamic profile of the overweight younger hypertensive have been described earlier. In such cases the sympathetic nervous system is markedly stimulated and undoubtedly plays a central role in the development of hypertension [176]. In hypertensives with type-2 diabetes [177] – Table 10 – or the metabolic syndrome [178], sympathetic nerve activity is almost twice that of normotensive subjects. High adrenergic drive and heart rates are closely linked to the early morning peak in ischaemic events [179], a pattern abolished by beta-blockade [180,181]. Central obesity appears to be the vital factor for the increased adrenergic tone [182] — Table 10.

Appropriate life-style adjustments can prevent the appearance of new type-2 diabetes [183,184].

2.1.3.2. b) Beta-blockers and the diabetic hypertensive? In the prospective, randomised, controlled UKPDS study [185] involving middle-aged overweight/obese hypertensives with type-2 diabetes, tight control of blood pressure with either atenolol or captopril-based therapy (diuretic as second-line therapy) significantly reduced cardiovascular events related to diabetes — Table 11. In the part of the UKPDS study directly comparing the effects of atenolol and captopril [116] the expected superiority of captopril was not observed. In spite of atenolol-induced increases in HbA1-c no overall significant difference in primary end-points was noted: indeed the trends in all 7 primary end-points over a 9 year follow-up period favoured atenolol — Table 11, indicating that the prime contributor to the significant superiority of tight over light control of blood pressure was atenolol and not captopril.

Table 10
High sympathetic nerve activity is associated with central obesity, hypertension and/or type-2 diabetes

Type of subject	MSNA (bs/100 hb)	Plasma Norepinephrine concentration (pg/ml)
Lean	36	215
Peripheral obesity	45 (*, vs lean)	320 (*, vs lean)
Central obesity	65 (**, vs lean)	330 (*, vs lean)
Normotensives	52	–
Hypertensives	68 (**, vs normotension)	–
Type-2 diabetes	80 (***, vs normotension)	–
Hypertension+ type-2 diabetes	97 (***, vs normotension)	–

Muscle sympathetic nerve activity (MSNA), corrected for heart rate (bs per 100 hb) in subjects with different types of obesity [182] and patients with hypertension and/or type-2 diabetes [177].
*=$P<0.05$, **=$P<0.01$, ***=$P<0.001$.

Table 11
Beta-1 blockade is at least as good as ACE-inhibition in the prevention of hard primary end-points in obese, young/middle-aged hypertensives with type-2 diabetes — UKPDS Study [116,185]

	Tight v less tight control of BP		Captopril v atenolol	
Primary clinical end-point	Relative risk for tight control (95% CI)	*P*-value	Relative risk for captopril (95% CI)	*P*-value
Any diabetes-related end-point	0.76 (0.62–0.92)	0.005	1.10 (0.86–1.41)	0.43
Deaths related to diabetes	0.68 (0.49–0.94)	0.019	1.27 (0.82–1.97)	0.28
All-cause mortality	0.82 (0.63–1.08)	0.17	1.14 (0.81–1.161)	0.44
Myocardial infarction	0.79 (0.59–1.07)	0.13	1.20 (0.82–1.76)	0.35
Stroke	0.56 (0.35–0.89)	0.013	1.12 (0.59–2.12)	0.74
Peripheral vascular disease	0.51 (0.1–1.37)	0.17	1.48 (0.35–6.19)	0.59
Micro vascular disease	0.63 (0.44–0.89)	0.009	1.29 (0.80–2.10)	0.30

UKPDS Studies 38/39 [116,185] — effect of tight (captopril or atenolol-based) versus less-tight control of blood pressure; and captopril vs atenolol-based therapy, upon the 7 primary end-points.

2.1.3.3. c) Are anti-hypertensive drug-induced changes in blood sugar/HbA1-c/insulin-resistance, dangerous to the patient? Two long-term observational studies [48,51] have indicated that increases in blood sugar, as a result of anti-hypertensive therapy, were associated with an increased risk of cardiovascular events. These observations have not however been supported by data from long-term follow-up of prospective, randomised controlled studies. Experience with studies assessing the possible benefits of hormone replacement therapy or anti-oxidant vitamin preparations have taught the medical profession that apparent facts derived from observational studies are frequently not confirmed when the ensuing appropriate prospective, randomised, controlled studies are performed.

In the UKPDS study [116] atenolol-based therapy was associated with an increase in HbA1-c concentration but after 9 years follow-up the Kaplan–Meier plots of patients who died of cardiovascular deaths related to diabetes were separating at 5–6 years in favour of atenolol over captopril.

Perhaps even more revealing were the results of the long-term follow-up (14.3 years) of the SHEP study [170] where 4732 elderly patients with isolated systolic hypertension were randomised to either placebo or low-dose diuretic (± atenolol) therapy — Table 12. In the placebo group, type-2 diabetes at baseline (vs no diabetes) was associated with a significant 63% excess cardiovascular mortality. Patients with type-2 diabetes at baseline in the group treated with diuretic ± atenolol (v placebo) experienced a significant 31% fall in cardiovascular mortality. Diabetes developing in the course of placebo (v not developing diabetes) was associated with a significant 56% increase in cardiovascular mortality. By contrast diabetes developing during diuretic ± atenolol therapy (v not developing diabetes) was not associated with an increase in cardiovascular mortality.

Thus drug-induced diabetes, unlike naturally occurring type-2 diabetes which is linked to central obesity, may not be harmful in the long-term. However, if in doubt, use a class of beta-blocker that does not increase blood sugar/HbA1 or increase insulin-resistance.

2.1.3.4. d) Mechanism of benefit of beta-1 blockade in the hypertensive diabetic. The mechanisms already outlined in the section relating to the younger, probably overweight hypertensive will be relevant, but even more so to the hypertensive, overweight/obese diabetic with extremely increased sympathetic nerve activity.

2.1.4. 4) Hypertensives with myocardial ischaemia

2.1.4.1. a) Beta-blocker v calcium antagonist. The large (n=22,576) INVEST study [16] included hypertensive elderly (mean age 66 years), overweight (mean body mass index was 29.1 kg/m2) patients with coronary artery disease. After 2.6 years follow-up there was no difference in morbidity and mortality in patients randomised to either atenolol/diuretic or verapamil/ACE-inhibitor therapy, though patients with poor left ventricular function at baseline fared better on atenolol/diuretic-based therapy. The high C-reactive protein levels associated with ischaemic heart disease are not observed in the presence of beta-blockade [186].

2.1.4.2. b) Beta-blocker v ACE-inhibitor. There have been no prospective, randomised comparisons between beta-blockers and ACE-inhibitors (though the INVEST study

Table 12
Drug-induced diabetes, in contrast to spontaneously occurring type-2 diabetes, may not be dangerous to the patient [170]

Population sub-set	Effect upon CV mortality
DM2 at baseline in placebo group (vs no DM2)	+63% (sig)
DM2 at baseline treated with diuretic ± atenolol (vs placebo)	−31% (sig)
DM2 developing on placebo (vs no DM2)	+56% (sig)
DM2 developing on diuretic ± atenolol (vs no DM2)	+4% (n s)

SHEP study (n=4732; mean age −72 years) — long-term follow-up (14.3 years); effect of diuretic-based (± atenolol) therapy, vs placebo, on cardiovascular death rate in patients with isolated systolic hypertension with, or without, type-2 diabetes = DM2 [170].

Table 13
Excessive lowering of diastolic blood pressure in hypertensive patients with ischaemic heart disease, may increase the risk of myocardial infarction [191]

Group	Target DBP (mm Hg)	*n*	Events/1000 pat. years	
			MI	Stroke
Non-IDH	<90	5245	4.7	3.0
	<85	5228	4.1	4.1
	<80	5237	3.9	3.5
With IHD	<90	1019	9.3	9.3
	<85	1036	6.8	7.9
	<80	1125	8.3	5.3

HOT study result [191] — myocardial infarction (MI) and stroke events in hypertensive patients with, and without, ischaemic heart disease (IHD), according to randomised goal diastolic blood pressure (DBP).

[16] contained an ACE-inhibitor as second-line therapy), but suffice it to say that large, randomised, controlled studies (HOPE, EUROPA, PEACE) in stable coronary heart disease involving ACE-inhibitors have resulted in a significant 14% reduction in mortality in patients receiving ACE-inhibitors [187].

2.1.4.3. c) Can excessive lowering of diastolic blood pressure harm hypertensives with coronary artery disease (impaired coronary flow reserve)? The above INVEST study examined, in a post-hoc analysis, whether induced low diastolic blood pressure could be associated with excess mortality and morbidity in an ischaemic hypertensive population [188]. They concluded that the risk of all-cause death and myocardial infarction, but not stroke, progressively increased with low diastolic blood pressure and that excessive reduction in diastolic blood pressure should be avoided in patients with coronary artery disease who are being treated for hypertension.

However the 25 year-old J-curve debate has been dogged by a "chicken and egg" dilemma. In other words, is the J-curve relationship between diastolic blood pressure and coronary events due to over treatment leading to a low diastolic pressure, coronary hypo-perfusion and thus an increased risk of a coronary event, or is the J-curve due to reverse-causality whereby established disease leads to a low diastolic blood pressure plus increased risk [189]. Only a prospective, randomised study addressing the issue "up front" is appropriate. Such a study was the HOT study [190], whose initial conclusion was that lowering diastolic blood pressure to below 82 mm Hg produced no further benefit but was safe. However information on the 3080 patients with myocardial ischaemia was sparse, but finally came to light in a published J-curve debate [191] – Table 13. Aiming to lower diastolic pressure to less than 80 mm Hg, compared to 85 mm Hg, was associated with a 22% increase in the risk of myocardial infarction. No such J-shaped relationship existed for diastolic blood pressure and stroke. For the non-ischaemic subjects no J-curve relationship existed for diastolic blood pressure and myocardial infarction.

Thus with hypertensives, in the presence of myocardial ischaemia, don't be over-zealous in lowering diastolic blood pressure.

3. Summary and conclusions

1. For the ischaemic patient, be it early or late intervention post-myocardial infarction, or chronic ischaemia in non-surgical and surgical patients, the significant benefits from beta-blockers in reducing cardiovascular end-points stem from beta-1 blockade; the main mechanisms being a) a reduction in the work of the heart via a decrease in heart rate, systolic blood pressure and ventricular contractility, b) a prolongation of coronary diastolic filling time, c) an increase in the threshold to ventricular fibrillation, d) a retardation of atheromatous plaque formation, e) a reduction in the risk of plaque rupture i.e. plaque stabilization, f) a reduced risk of cardiac rupture, g) a reduction in infarct size, and h) a reduced rate of reinfarction. Intrinsic sympathomimetic activity detracts from efficacy.
2. Likewise for the heart failure patient, on a background of ACE-inhibition, beta-1 blockade (the common property of carvedilol, metoprolol and bisoprolol) is responsible for the 35% reduction in all-cause mortality. New data (CIBIS 3) has shown that first-line beta-blockade (bisoprolol) is at least as efficacious as first-line ACE-inhibition in reducing the morbidity/mortality of moderate/severe heart failure. The mechanism of benefit includes the above factors that reduce ischaemia but one extremely important new factor applies, and that is the inhibition of beta-1 catecholamine-induced necrosis/apoptosis. Intrinsic sympathomimetic activity (with xamoterol, bucindolol and nebivolol) markedly reduces efficacy, though the sympatholytic effect of bucindolol may be important. More prospective data on the effect of nebivolol in younger patients with systolic heart failure would be useful in determining the efficacy of this agent in the treatment of heat failure.
3. The role of beta-blockers in the treatment of hypertension has been thrown into confusion in the UK (and elsewhere) by the new recommendations from the National Institute of Clinical Excellence (NICE) working in collaboration with the British Hypertension Society, which state that beta-blockers are no longer preferred as a routine initial therapy for the treatment of hypertension (Ace-inhibitors are recommended as first-line therapy for the younger hypertensive) and in particular the combination of beta-blocker and diuretic is discouraged due to the increased risk of diabetes. The author of this review strongly disagrees with these recommendations and sets out his reasons for so doing.
4. New data from the Framingham Heart Study and other large epidemiological surveys indicate that the development of diastolic (± systolic) hypertension in

younger subjects is closely linked to weight-increase/obesity and increased peripheral resistance. In contrast elderly systolic hypertension mainly arises de novo from ageing, non-compliant arteries and not from "burned-out" diastolic hypertension.

5. Central obesity in younger subjects is linked to endothelial inflammation and dysfunction, insulin-resistance, markedly increased sympathetic nerve activity and increased cardiac output, heart rate and blood pressure — a haemodynamic scenario ideal for beta-1 blockade. As noted above, prolonged increased sympathetic nerve activity is extremely injurious to the cardiovascular system.
6. Beta-1 blockade lowers blood pressure by decreasing cardiac output (maybe renin is important). Beta-2 blockade and beta-1 intrinsic sympathomimetic activity detract from anti-hypertensive efficacy. Beta-2 intrinsic sympathomimetic activity lowers blood pressure by decreasing peripheral resistance.
7. In younger hypertensives beta-blockers reverse both ECG – and echocardiographic – left ventricular hypertrophy. High beta-1 selectivity (atenolol is only moderately selective) ensures reversibility of echocardiographic left ventricular hypertrophy at least as great as the action of ACE-inhibitors.
8. Beta-blocker-induced metabolic disturbance (lipids, blood sugar and insulin-resistance) stems from beta-2 blockade (and possibly beta-3 blockade). Such disturbances are avoided by high beta-1 selectivity (e.g. bisoprolol), beta-2/3 intrinsic sympathomimetic activity (e.g. nebivolol) or alpha blockade (e.g. labetalol).
9. In trials involving younger/middle-aged overweight hypertensives (MRC mild Hypertension, IPPPSH, MAPHY, UKPDS), with relatively narrow pulse-pressures (59–65 mm Hg), first-line beta-blockade has been more effective than placebo and diuretics, and at least as good as ACE-inhibitors, in preventing coronary events (coronary events far exceed stroke events in the younger hypertensive). The benefit of non-selective agents such as propranolol and oxprenolol is restricted to non-smokers (due to an interaction between smoking-induced adrenalaemia and beta-2 blockade leading to a pressor response).
10. The mechanism of the beta-blocker benefit in the younger, probably overweight hypertensive is, like diuretics, via blood pressure-lowering resulting in a reduced risk of stroke; but (vitally) unlike diuretics, the reduction in the risk of myocardial infarction is undoubtedly linked to the inhibition of the cardiovascular-toxic effects of chronically increased sympathetic activity by beta-1 blockade.
11. Meta-analyses that include all prospective, randomised, beta-blocker studies in hypertension (i.e. studies that involve only younger/middle-aged hypertensives and studies that involve only elderly hypertensives (see later)) will miss the beta-blocker-induced benefits gained by younger patients due to the dilution-effect of the large number of poor results in the elderly.
12. Elderly systolic hypertensives tend to have low plasma renin activity, insensitive beta-receptors, low/normal cardiac output and non-compliant arteries (wide pulse-pressure). Such a haemodynamic scenario is unsuited to certain first-line beta-blockers e.g. atenolol and propranolol.
13. Beta-2 stimulation increases, and beta-2 blockade decreases, vascular compliance. Thus non-selective propranolol worsens compliance, atenolol (only moderately beta-1 selective) is neutral but agents with high beta-1 selectivity (e.g. bisoprolol), beta-2/3 intrinsic sympathomimetic activity (e.g. nebivolol) or alpha-blocking properties (e.g. labetalol) improve compliance.
14. Atenolol, which has a limited 24 hour action, induces metabolic disturbance, does not improve vascular compliance (thus lowers central systolic pressure inadequately, hence does not reverse left ventricular hypertrophy in the elderly), would be a poor choice as first-line agent for the elderly systolic hypertensive.
15. Unfortunately atenolol was the selected first-line beta-blocker in all 4 prospective, randomised, controlled, hard-end-point studies in the elderly hypertensive. In the MRC Elderly, HEP, LIFE and ASCOT studies, where pulse-pressure was between 70–100 mm Hg, atenolol-based therapy compared poorly against placebo, diuretics, angiotensin-1 receptor blockers and calcium channel blockers in reducing the risk of cardiovascular events.
16. First-line low-dose diuretic therapy (which increases plasma renin and sympathetic nerve activity and is highly effective in reducing pulse-pressure/improving vascular compliance, thus creating a haemodynamic scenario which is not disimilar to that in younger hypertensives and hence compatible with beta-blockade), with second-line beta-blocker therapy, has a track record at least as good as other combination therapies in reducing cardiovascular events in the elderly hypertensive, with the added bonus of a 30% reduction in the risk of bone fractures.
17. Meta-analyses that include studies where it is unclear whether a diuretic or beta-blocker is first-line therapy will inevitably dilute the cardiovascular benefits derived from first-line diuretic/second-line beta-blocker therapy in the elderly.
18. Central obesity, the metabolic syndrome and type-2 diabetes are all associated with high adrenergic drive and high cardiac output. High sympathetic nerve activity is closely linked to myocardial and vascular damage, left ventricular hypertrophy and an increased risk of ischaemic episodes. Such an environment favours beta-1 blockade, and undoubtedly accounts for the good result of atenolol in young/middle-aged, overweight, diabetic hypertensives in the UKPDS study (in spite of induced increases in HbA1-c).

Though observational studies have suggested that drug-induced increases in blood sugar/HbA1-c are dangerous, long-term follow-up in the prospective, randomised, controlled UKPDS study (9 years) and SHEP study (14.3 years) indicate otherwise. If in doubt, use a beta-blocker that does not induce metabolic disturbance.

19. It has been wrongly supposed, by some, that due to the small beta-blocker-induced weight-increase (1–2 kg) overweight/obesity is a relative contra-indication to beta-blockade. Quite the reverse is the case; a fact of considerable importance in view of the obesity epidemic and that most younger/middle-aged hypertensives are overweight/obese. Thus overweight/obesity in the younger/middle-aged hypertensive, and its accompanying increased sympathetic nerve activity, is a positive indication for beta-1 blockade and not a relative contra-indication.
20. The large INVEST study in hypertensives with coronary artery disease indicated that atenolol/diuretic-based therapy was as good as verapamil/ACE-inhibitor-based therapy in preventing cardiovascular events, and was superior if left ventricular dysfunction was present at baseline. Excessive lowering of diastolic BP in ischaemic hypertensives may increase the risk of myocardial infarction.
21. So what is the current role of beta-blockers in cardiovascular medicine? In acute and chronic ischaemia beta-1 blockade remains the main first-line option. In heart failure beta-1 blockade has been a mandatory second-line therapy after ACE-inhibition but has now become a first-line option.

But what is the role of beta-blockers in hypertension? Certainly not that recommended by the NICE committee/British Hypertension Society. Based on the results of randomised, controlled studies in younger, probably overweight/obese, hypertensives ± diabetes (pulse-pressure <70 mm Hg) first-line beta-1 blockade would be a highly reasonable choice for the prevention of myocardial infarction. Avoidance of beta-2 blockade would remove the problem of a troublesome cigarette smoking interaction and also the risk of induced type-2 diabetes (not to mention a virtual absence of induced bronchoconstriction and/or impotence). Second-line therapy could be a low-dose diuretic or dihydropyridine calcium antagonist. An alternative first-line choice would be an ACE-inhibitor. For the elderly hypertensive (pulse-pressure >70 mm Hg, reflecting poor vascular compliance) first-line diuretic therapy or a dihydropyridine calcium antagonist would be a sensible choice, with a beta-blocker(or ACE-inhibitor) as second-line therapy. The choice of a beta-blocker that improves vascular compliance and does not induce metabolic disturbance might be sensible. In the presence of myocardial ischaemia a beta-blocker given as first-line therapy, irrespective of age or pulse-pressure, would be appropriate.

4. Search strategy and selection criteria

References up until 1994 were heavily drawn upon from the 2nd Edition of "Beta-blockers in Clinical Practice" by Cruickshank JM and Prichard BNP [192]. More recent references were obtained from 1. comprehensive reading of the main cardiovascular and general medical journals, and 2. Searches of PUBMED, using key words (usually linked by AND) "beta-blockers (and individual names)", "ischaemic heart disease", "myocardial infarction", "heart failure", "hypertension", "sympathetic nervous system", "metabolic effects", "haemodynamic effects", "left ventricular hypertrophy", "vascular compliance", "obesity", "diabetes", and "metabolic syndrome".

Selection of studies involved judgment. Thus when there were many references on a topic, usually the most recent were chosen. In the vital area of large, randomised, hard-end-point studies involving first-line beta-blockade, where it was unclear whether a beta-blocker or diuretic was first-line (i.e. CAPP [193], STOP [194], STOP-2 [195], NORDIL [196], CONVINCE [197]) the studies were omitted (because first-line diuretic therapy in younger hypertensives has performed badly vs placebo in the prevention of coronary events [114,117,198] in contrast to first-line diuretic therapy in the elderly hypertensive which has been proved highly effective vs placebo [157,170] or active treatment [169] in reducing the frequency of cardiovascular events; the reverse holds true for beta-blockers in younger [113–115] and elderly hypertensives [155,157–159]. Likewise inappropriate dosing was a reason for omission (i.e. The Dutch T1A Trial [199] in mild/moderate hypertensives used a top dose of atenolol of 50 mg once daily resulting in a meagre fall in BP of only 5.8/2.9 mm Hg).

Finally the HAPPHY Study [200] was omitted due to its apparent "flawed" nature whereby atenolol's poor performance (relative to metoprolol) was accounted for by the lower total and coronary mortality in the diuretic group randomised against atenolol compared to the high coronary and total mortality in the diuretic group randomised against metoprolol [201,202].

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