Hypertension in the Elderly

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Internal Medicine Grand Rounds
University of Texas Southwestern Medical Center at Dallas

February 1, 2008

This to acknowledge that Dr. Kaplan has disclosed financial interest or other relationships with commercial concerns related directly to this program. Dr. Kaplan has received honoraria and travel expenses from Boehringer-Ingelheim and Pfizer Pharmaceutical Companies. Dr. Kaplan will not be discussing off label uses in his presentation.

Copies of slides included in syllabus

CASE REPORT:

78 year old Caucasian male with these previous blood pressure measurements:

Age 45 130/80
Age 65 145/85
Age 78 180/70

No history of symptoms of hypertension and no evidence of significant target organ damage. He had been started on an antihypertensive drug regimen of hydrochlorothiazide 12.5 mg, atenolol 50 mg daily and clonidine 0.2 mg prn for home BP > 170. He has noted dizziness frequently when arising from bed and occasionally after breakfast.

This number of the elderly, defined as over age 65, will increase greatly in the next few years (Figure 1). As people are living longer, isolated systolic hypertension has become the most common form of hypertension (Franklin et al, 2001) (Figure 2). The likelihood that systolic hypertension will appear as people live longer was documented in the Framingham population (Vasan et al, 2002). When both men and women who where still normotensive at age 65 were followed for 20 years, 90% developed hypertension, in almost all isolated systolic (Figure 3). The danger from increases in systolic pressure was clearly shown in the meta-analysis of observational data from almost one million adults followed for over 10 years in 61 prospective studies (Prospective Studies Collaboration, 2002). The proportional risk of mortality from both ischemic heart disease (IHD) and stroke rose progressively with each increment of initial blood pressure in people in each decade (Figure 4), with a steeper rise in the younger than the older whose risk started at a higher level.

Lest some think that these data for those over 70 may not be clinically pertinent since there will be few people who live that long, actuarial data show that the average life expectancy for 70 year old men and women in reasonable health is 12 and 16 years respectively (Figure 5). More and more are living longer and, with that, acquiring the risk of hypertension.

The relatively greater risk of systolic hypertension in the elderly was defined in the Framingham Heart Study participants by Franklin et al (Franklin et al, 2001). The prediction of coronary heart disease was better by diastolic BP in the younger but better by systolic BP in the older, with a cross—over at 55 years (Figure 6). They further showed that 60% of the systolic pressure so commonly found in the elderly arose de novo, not as a consequence of a burn-out of previous isolated diastolic or combined systolic/ diastolic hypertension (Franklin et al, 2005).

CURRENT CONTROL

Even though hypertension remains the most common indication for visits to physicians and the overall use of prescription drugs, the control of hypertensive patients in the U.S. remains woefully inadequate even among the participants in the Framingham Heart Study (Lloyd-Jones, 2005). In particular, control rates are low in the elderly, even lower in the rapidly increasing number of elderly women (Figure 7). Moreover, control rates are inadequate among patients with other cardiovascular conditions. Only 35% of patients with a prior stroke have their hypertension under control (Wong et al, 2007).

MEASUREMENTS OF BLOOD PRESSURE

Of all the procedures done routinely in physicians' offices, measurement of blood pressure may be performed the sloppiest, even though important decisions are often based on them. Even when done well, office readings are usually higher than those obtained by home or ambulatory monitoring. As documented years ago by Tom Pickering, ambulatory monitoring can reveal both "white coat" and "masked" hypertension (Figure 8).

The presence of white coat hypertension seems relatively benign unless it gives rise to unnecessary treatment. On the other hand, masked hypertension is associated with as much an increased risk for the incidence of cardiovascular events as is sustained hypertension (Fagard et al, 2007) (Figures 9 and 10). Elderly patients with systolic hypertension are even more susceptible to the white coat effect than are younger hypertensives (Fagard et al, 2004).

The need for more widespread use of both ambulatory and home readings seems obvious but they are rarely used, even less in a setting such as Parkland.

Table 1. Blood-Pressure Patterns That Can Be Determined by Means of Ambulatory Blood-Pressure Monitoring and Other Methods.

Variable	Ambulatory Blood-Pressure Monitoring	Clinic Blood-Pressure Monitoring	Home Blood-Pressure Monitoring
True, or mean, blood pressure	Yes	Questionable	Yes
Diurnal blood-pressure rhythm	Yes	No	No
Dipping status	Yes	No	No
Morning surge	Yes	No	Questionable
Blood-pressure variability	Yes	No	Questionable
Duration of drug effects	Yes	No	Yes

Source: Pickering T et al N Engl J Med 2006;354:2368.

Systolic blood pressure always rises upon awakening and ambulating. In many, this rise is as much as 45 mmHg, an effect now referred to as the "morning surge". The need to recognize and dampen the typical morning surge of pressure has been related to the effect of the surge to destabilize atherosclerotic plaques (Marfella et al, 2007). In addition, ambulatory monitoring provides data that can not be obtained even by the best of office and home readings: the nighttime dipping status. The course of blood pressure during sleep turns out to be the best prognosticator for future cardiovascular events (Dolan et al, 2005) (Figure 11). In the future, ambulatory and home monitoring will be more widely utilized. For now, more accurate clinic readings can help.

Orthostatic Hypotension

A number of factors may complicate the management of hypertension in the elderly (Table 2). Of these, orthostatic (postural) hypotension is common and often not recognized (Figure 12). All hypertensives over age 60 should have supine and standing BP measurement, needed even more if diabetes or postural symptoms are present. Hypotension may be seen after a large breakfast from splanchnic pooling of blood. A decrease in cardiovagal baroreflex sensitivity, the most common mechanism, is closely associated with arterial stiffness (Mattace-Raso et al, 2007).

Treatment should start with non-drug therapies (Table 3) but, if those are not enough to relieve symptoms, a number of medications may help (Gupta and Lipsitz, 2007).

Table 2

Factors Complicating Treatment of Hypertension in the Elderly

FACTORS	POTENTIAL COMPLICATIONS
Diminished baroreceptor activity	Orthostatic hypotension
Impaired cerebral autoregulation	Cerebral ischemia with small falls in systolic pressure
Decreased intravascular volume	Orthostatic hypotension Volume depletion, hyponatremia
Sensitivity to hypokalemia	Arrhythmia, muscular weakness
Decreased renal and hepatic function	Drug accumulation
Polypharmacy	Drug interaction
CNS changes	Depression, confusion

Table 3

Nondrug Treatment for Orthostatic Hypotension

Withdraw offending medication
Rise slowly from supine to sitting to standing position
Avoid prolonged standing in hot weather
Isometric exercise before rising
Raise head of bed 10 to 20 degrees
Small meals and coffee in the morning
Elastic waist high stocking
Increase salt and water intake
Exercise, eg, swimming, recumbent biking

MECHANISMS OF SYSTOLIC HYPERTENSION

The belief of increasing stiffness of the large arteries with age goes back a very long time and palpation of the radial artery was long used to evaluate cardiovascular risk. But only over the past decade has it been possible to measure arterial stiffness and the other dynamic properties of the arterial tree. Much credit goes to Michael O' Rourke, Gary Mitchell, Michel Safar, and Stanley Franklin and their co-workers.

I can do no better than to quote Stanley Franklin form his syllabus provided for the American Society of Hypertension Review Course:

"An age- associated rise in systolic blood pressure (SBP), occurring as a consequence of increased arterial stiffness, was once considered an inconsequential part of the aging process; more recently, we recognized that it represents a major global pubic health problem, not only because it is extremely common, but also because isolated systolic hypertension [ISH, SBP $\geq$ 140 and diastolic blood pressure (DBP) $<$ 90 mm Hg] is an independent risk factor a variety of cardiovascular (CV) diseases.

"The central pressure waveform is produced by two major components: a forward traveling or incident wave, generated by ventricular ejection and a backward wave, reflecting off

of distal arteries at the branching origins of arterioles (Figure 13). The smooth forward going wave is influenced by intermittent ventricular ejection and by mechanical properties of the aorta and large elastic arteries which serve to buffer the pressure changes. In contrast, the reflected wave is influenced by the elastic properties of the entire arterial system, including both elastic and muscular arteries.

"In young normotensive adults, the aorta is still very distensible: peripheral amplification of the arterial pulse wave will result in considerably higher brachial artery peak SBP as compared to SBP values in the ascending aorta. In young subjects the reflected pressure waves return to the ascending aorta in diastole and serve to elevate mean DBP, thus boosting coronary artery perfusion (Figure 14). The summation of the incident pressure wave with the reflected wave in young adults produces a normal phenomenon of pressure amplification of pulse pressure and SBP. Mean arterial pressure (MAP) and DBP are relatively constant throughout the central and peripheral arteries, but SBP increases moving distally away from the aortic valve. As a consequence, brachial artery pressure in healthy young persons is some 15-25 mmHg higher than that recorded in the ascending aorta. Therefore, central and not peripheral SBP, regardless of age, determines cardiac afterload and hence cardiovascular risk (Figure 15). The changing pattern of age-related brachial artery BP components that predict CV risk results from altered peripheral resistance, aortic stiffness, and early wave reflection, all acting in concert to raise SBP, decrease DBP, and to partially abolish pressure amplification; this leads to an age-related shift form sphygmomanometric-determined diastolic hypertension (IDH) to mixed systolic/diastolic hypertension (SDH), defined as a SBP $\geq$ 140 and a DBP $\geq$ 90 mm Hg, and ultimately to elevated systolic and decreased diastolic values—wide pulse pressure ISH.

"More direct measurement of arterial stiffness and wave reflection may be of value in the improved assessment of cardiovascular risk and outcome compared to peripheral SBP and pulse pressure (Figure 16). Local stiffness in various blood vessels can be addressed by echo-tracking, ultrasound and by MRA. Generalized systemic stiffness can be measured by diastolic decay, modified Windkessel or stroke volume/pulse pressure measurements. A popular method of assessing arterial stiffness uses applanation tonometry to measure both wave reflection analysis and aortic pulse wave velocity (PWV). Analysis of the entire arterial waveform may improve risk stratification in patients with CV disease, or those at high risk of developing it by assessing augmentation index (Alx), central pulse pressure, amplification ratios, and carotid to femoral PWV (aortic PWV). Aortic pulse waves can either be assessed invasively using solid-state or fluid filled catheters, or non-invasively by pulse wave analysis. This technique relies on the use of generalized transfer functions to synthesize aortic waveforms from directly measured radial artery peripheral waveforms. The transfer function used to derive the central aortic pressures is founded on the observation that pressure wave transmission in the upper limb is remarkably consistent under different conditions. This includes the effects of aging, disease, drug therapy, and variation in heart rate, thereby allowing a generalized transfer function to be used to convert the radial to aortic pressure wave.

"Previous studies have shown that PWV is a superior predictor of increased CV mortality than brachial BP components in patients with end stage renal disease (ESRD), essential hypertension, and the elderly. The Alx, central pulse pressure and amplification ratios have predicted all cause mortality in ESRD and in patients with known coronary heart disease. Two recent studies have utilized central pulse wave analysis to measure arterial stiffness and predict CV events—the Strong Heart Study and the CAFE substudy of the ASCOT trial."

CONSEQUENCES OF ARTERIAL STIFFNESS

The literature related to arterial stiffness has rapidly expanded. Some of the most useful references are Laurent, 2006; Redfield, 2005; O'Rourke and Hashimoto, 2007; Agabiti-Rosei, 2007; Vasan, 2008, and Mitchell, 2008.

Table 4 lists clinical conditions associated with increased aortic stiffness and/or wave reflections. To these, endothelial dysfunction, as measured by flow-mediated vasodilation, has also been shown to accompany increased aortic stiffness in patients with isolated systolic hypertension (Wallace et al, 2007)

Table 4: Clinical conditions associated with increased arterial stiffness and/or wave reflections

Ageing	CV risk factors	CV diseases
Other physiological conditions	Obesity	Coronary heart disease
Low birth weight	Smoking	Congestive heart failure
Menopausal status	Hypertension	Fatal stroke
Lack of physical activity	Hypercholesterolaemia	Primarily non-CV diseases
Genetic background	Impaired glucose tolerance	ESRD
Parental history of hypertension	Metabolic syndrome	Moderate chronic kidney disease
Parental history of diabetes	Type 1 diabetes	Rheumatoid arthritis
Parental history of myocardial infarction	Type 2 diabetes	Systemic vasculitis
Genetic polymorphisms	Hyperhomocyteinaemia	Systemic lupus erythematosus
	High CRP level	

Source: Laurent et al. Eur Heart J 2006; 27:2588.

STUDIES OF CLINCIAL USEFULNESS OF MEASURING ARTERIAL STIFFNESS

As noted, two papers have been published which indicate additional clinical usefulness of the measurement of central pressure:

- The Strong Heart Study (Roman et al, 2007) measured central pressure by radial applanation tonometry with the SphygmoCor device in 3520 people. Central pressures were more strongly related to vascular hypertrophy, extent of atherosclerosis and prediction of cardiovascular events than were brachial systolic pressures. The authors conclude that "These findings support prospective examination of the use of central blood pressure as a treatment target in future trials"
- The Conduit Artery Function Evaluation (CAFE) Study (Williams et al, 2006) involved 2073 hypertensive patients enrolled in the much larger Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) (Dahlof et al, 2005). In the larger ASCOT trial, hypertensive patients were randomly chosen to take either the CCB amlodipine, followed by the ACEI perindopril, or the beta-blocker atenolol, followed by a thiazide diuretic. Those chosen for the CAFE trial were equally divided between the 2 regimens and had central pressure measured at least twice during the 3 years of the trial.

Baseline brachial blood pressure of the CAFE participants was 160/93 mm Hg. At the end of the trial, the fall in brachial BP was almost the same for both regimens: -26/-18 for atenolol-thiazide versus-27.8/-15.7 for the amlodipine-perindopril (Figure17). However, the central aortic systolic pressure was significantly lower by 4.3 mmHg with amlodipine-perindopril.

The CAFE investigators provide 2 possible reasons for the higher central systolic pressure with atenolol: 1) a shift of arterial reflection sites proximately via a relative peripheral vasoconstriction which would result in earlier wave reflection, thereby increasing central aortic systolic augmentation, or 2) the lower heart rate induced by the beta-blocker, prolonging ejection time and increasing the likelihood that pressure wave reflections will augment the outgoing pressure wave during systole.

As described in a Clinical Prospective on the CAFE study (Circulation 2006;113:1225): "In a secondary analysis using Cox proportional-hazards modeling, central aortic pulse pressure was identified as a significant determinant of a post hoc-defined composite of cardiovascular and renal outcomes. This study demonstrates that brachial blood pressure measurements do not always reflect the impact of different blood pressure-lowering treatments on central aortic pressures. This study suggests a mechanism by which different drug treatments in hypertension trials could differentially affect central aortic pressures and thus clinical outcomes beyond brachial blood pressure."

The CAFE results were published shortly after the meta-analysis by Lindholm et al, in 2005 which showed that beta-blocker based antihypertensive therapy was no better than therapy with other antihypertensives in reducing the incidence of myocardial infarction and was associated with a 16% increased incidence of stroke (Figure 18).

CAFE provided the explanation for the lesser efficacy of beta-blockers described by Lindholm et al. As a consequence, the British Hypertension Society (and many "unofficial" groups) have strongly recommended not using beta-blockers as primary therapy of hypertension except in those patients in whom a beta-blocker is indicated, e.g. post-MI, CHF, tachyarrhymias.

The implications of CAFE and the STRONG data are obvious: Central pressures should be obtained in large clinical comparative trials, in epidemiologic studies of cardiovascular risk, and in the approval process for new antihypertensive agents. At a present price over $15,000 the Syphgmo Cor device used in CAFE or other available devices to measure central pressure will not likely be used in clinical practice but that possibility may come about in the near future.

Stroke

In various observational and therapeutic trial data in the elderly, stroke is often as common or more common than myocardial infarction although heart diseases, mainly heart failure, remain the leading causes of death in the elderly (Kjeldsen et al, 2001) (Figure 19).

Nonetheless, strokes may lead to more disability. CCBs, in particular amlodipine have been found to reduce the risk of stroke more than seen with ACEIs (Verdecchia et al, 2005) (Figure 20). However, drugs which lower the circulating levels of angiotensin, e.g. ACEIs and beta-blockers have been found to protect against strokes less well than drugs which increase the level of circulating angiotensin, e.g. diuretics, CCBs, and ARBs (Boutitie et al, 2007) (Figure 21). The rationale for this hypothesis is as follows:

"In their hypothesis, proposing angiotensin II as a cerebroprotective agent, Brown and Brown (1986) suggested that the vasoconstrictive effect of angiotensin II in the proximal cerebral arteries could be the mechanism preventing the Charcot-Bouchard aneurysms from rupturing. This AT_1 receptor-mediated vasoconstrictive effect could, however, only explain the prevention of hemorrhagic strokes, but would have no effect on ischemic strokes. To explain the reduction in ischemic stroke, which is a far more prevalent complication of hypertensive cardiovascular disease, it may be hypothesized, on the basis of experimental data with acute stroke, that the activation of the non-opposed AT_2 receptor by drugs that increase angiotensin II

would facilitate the recruitment of collateral vessels or increase neuronal resistance to anoxia. (Dai et al, 1999) and (Li et al, 2005) provided some experimental evidence for a non-haemodynamic neuroprotective effect mediated by the AT_2 receptor. The investigators showed that the intracerebral administration of low doses of irbesartan (which did not interfere with the systemic effect of angiotensin II) before the induction of experimental brain ischemia in the rat improved the neurological outcome, whereas the coadministration of an AT_2 receptor blocker prevented such improvement (Figure 22). In addition, two independent teams using AT_2 gene-deleted mice showed that the neurological outcome, after a comparable ischemic insult, was more severe in these animals than in wild-type animals, and was associated with a greater reduction in the cerebral blood flow around the necrotic core (Iwai et al, 2004)."
Conginitive Decline: There is limited evidence that arterial stiffness is also associated with cognitive decline (Waldstein et al, 2008) (Figure 23). However, lowering of blood pressure has not been shown to protect against dementia in patients without prior cerebrovascular disease (McGuinness B et al, 2008).

TREATMENT OF HYPERTENSION IN THE ELDERLY
NONDRUG THERAPIES

It may be more difficult to change life-long habits but the elderly may respond as well or better to some non drug therapies.

Sodium Reduction: The elderly may respond even more to moderate reduction in dietary sodium intake than younger hypertensives because they have lower levels of renin-angiotensin to counter the antihypertensive and volume contracting effect of reduced sodium intake (Weinberger and Fineberg, 1991; Melander et al, 2007) (Figure 24). In 12 elderly patients with systolic hypertension, 4 weeks of a lower sodium intake improved compliance of the carotid artery (Gates et al, 2004). Another possible way that excess sodium may cause vascular damage is by stiffening the vascular endothelium (Oberleithner et al, 2007).

There is now suggestive evidence that a lower sodium intake may reduce long term risk of cardiovascular disease (Cook et al, 2007) (Figure 25).

Increased Dietary Fruit and Vegetables: Fewer strokes were seen in people who regularly eat 3-5 servings a day; even more benefit was seen with more than 5 servings a day (He HJ et al, 2006) (Figure 26).

Smoking Cessation: Those who smoke have greater arterial stiffness and quitting gradually diminishes stiffness (Jatoi et al, 2007).

Moderate Alcohol Consumption: Consumption of one to three usual portions of beer, wine or whiskey was associated with fewer MIs but not to cardiovascular mortality in 11,711 hypertensive men (Beulens et al, 2007). Among the 12,480 elderly women in the Nurses' Health Study, those who consumed one drink per day had a slower rate of cognitive decline than did nondrinkers (Stampfer et al, 2005).

Increased Physical Activity:

Among 51 elderly hypertensives, after 6 months of increased exercise, diastolic BP fell about 2 mmHg more than seen in regular exercisers but neither systolic BP or arterial stiffness improved (Stewart et al, 2005).

ANTIHYPERTENSIVE DRUG THERAPY

The general guidelines are shown in table 5

Table 5:

Guidelines in Treating Hypertension in the Elderly

1. Check for postural and postprandial hypotension before starting
2. Choose drugs that will help other concomitant conditions
   a. For uncomplicated patients, a thiazide diuretic + K^+ sparer
   b. If a second agent is needed, a CCB
   c. β-blockers are not appropriate unless an indication is present, e.g., coronary disease
3. Start with small doses, titrating gradually
4. Use longer acting, once daily formulations
5. Avoid drug interactions, particularly from over-the-counter medications, e.g. NSAIDs
6. Look for subtle drug-induced adverse effects, e.g. weakness, dizziness, depression, confusion
7. Monitor home blood pressures to avoid over and under treatment
8. Aim for the goal of SBP = 140-145, DBP = 80-85

A number of additional points are worth noting.

Diuretics: A significant fall in serum potassium, great than 0.2 L mEq/ L, should be avoided in order to prevent a concomitant rise in blood sugar (Zilich et al, 2006) (Figure 27). Another reason to use thiazide diuretics in the elderly is the decrease in urinary calcium excretion which reduces age-related osteoporosis and the risk for hip fracture (Schoofs et al, 2003).

Aldosterone Blockers: The most appropriate way to prevent diuretic-induced falls in potassium is to combine them with an aldosterone blocker. Spironolactone in small doses, 25 mg per day, has been repeatedly found to have a significant antihypertensive effect in patients with resistant hypertension (Chapman et al, 2007) (Figure 28). Aldosterone levels may breakthrough during long term use of ACEIs (Sato and Saruta, 2003) and even modest increases of aldosterone may increase hypertensive target organ damages (Pratt, 2008).

Caution about hyperkalemia is needed when aldosterone blockers are used, particularly in patients with renal insufficiency or taking ACEIs or ARBs (Juurlink et al, 2004).

In general, elderly patients respond better to diuretics and CCBs than to renin suppressing drugs, likely because their renin levels are low (Morgan et al, 2001) (Figure 29).

ACEIs and ARBs: Both classes lower BP similarly but there are, as yet, no comparative studies on their protection against target organ damage (Matchar et al, 2008). In the near future, results of a large comparative trial between the ACEI ramipril and the ARB telmisartan, the On-Target Trial, may provide such data.

The duration of action of even presumably long-acting ARBs may not be long enough to keep the BP down for the entire 24 hours (Fabia et al, 2007). In the absence of early morning BP

measurements, the better course might be to give the drugs at bedtime, particularly in view of the greater impact of nocturnal and early morning BPs on cardiovascular risk (Hermida et al, 2007).

Although ACEIs and ARBs are frequently combined for greater reduction in proteinuria, no additional benefit of the ARB irbesartan when added to the ACEI ramipril was seen in the largest trial on this issue (Bakris et al, 2007) (Figure 30). There are little data of an additive effect on BP.

Direct Renin Inhibitors: Aliskerin has been marketed. It clearly lowers BP and may have an additive effect to an ARB given in the maximally recommended dose, valsartan 320 mg per day (Oparil et al, 2007) Figure (31).

Nitrates: As NO providers, nitrates have a rapid and significant antihypertensive effect mediated by a decrease in the pulse wave reflection (Stokes et al, 2003) (Figure 32). Stokes has advocated the use of isosorbide for treatment of systolic hypertension but has been unable to perform a proper outcome trial since the available nitrate preparations are generic (Stokes et al, 2005).

Statins: Statins use has been associated with a 21% reduction in the incidence of stroke (Heart Protection, 2004) perhaps because they have a significant antihypertensive effect (Strazzullo et al, 2007) (Figure 33).

TREATMENT OF HYPERTENSIVES OVER AGE 80

Few data have been published on the value of antihypertensive therapy of those over age 80. Preliminary data from the largest such trial, the Hypertension in the Very Elderly Trial (HYVET) were equivocal (Figure 34) but according to a Heart Wire press release on August 7, 2007 the trial has been prematurely stopped "following significant reductions in both stroke and mortality in patients in the treatment arm." Treatment was with the diuretic indapamide and the ACEI perindopril.

THE GOAL OF TEATMENT OF HYPERTENSION IN THE ELDERLY

Uncertainty persists. Currently available data suggest that systolic pressure can be lowered to as low a level as possible as long as the (usually already low) diastolic pressure is not lowered to below 70 mmHg in hypertensives with known coronary artery disease (Messerli et al, 2006) (Figure 35) or to below 55 mmHg in those without CAD (Fagard et al, 2007).

Reference List

(1) Agabiti-Rosei E, Mancia G, O'Rourke MF et al. Central blood pressure measurements and antihypertensive therapy: a consensus document. *Hypertension* 2007 July;50(1):154-60.

(2) Bakris GL, Ruilope L, Locatelli F et al. Treatment of microalbuminuria in hypertensive subjects with elevated cardiovascular risk: results of the IMPROVE trial. *Kidney Int* 2007 October;72(7):879-85.

(3) Beulens JW, Rimm EB, Ascherio A, Spiegelman D, Hendriks HF, Mukamal KJ. Alcohol consumption and risk for coronary heart disease among men with hypertension. *Ann Intern Med* 2007 January 2;146(1):10-9.

(4) Boutitie F, Oprisiu R, Achard JM et al. Does a change in angiotensin II formation caused by antihypertensive drugs affect the risk of stroke? A meta-analysis of trials according to treatment with potentially different effects on angiotensin II. *J Hypertens* 2007 August;25(8):1543-53.

(5) Brown MJ, Brown J. Does angiotensin-II protect against strokes? *Lancet* 1986 August 23;2(8504):427-9.

(6) Chapman N, Dobson J, Wilson S et al. Effect of spironolactone on blood pressure in subjects with resistant hypertension. *Hypertension* 2007 April;49(4):839-45.

(7) Collins R, Armitage J, Parish S, Sleight P, Peto R. Effects of cholesterol-lowering with simvastatin on stroke and other major vascular events in 20536 people with cerebrovascular disease or other high-risk conditions. *Lancet* 2004 March 6;363(9411):757-67.

(8) Cook NR, Cutler JA, Obarzanek E et al. Long term effects of dietary sodium reduction on cardiovascular disease outcomes: observational follow-up of the trials of hypertension prevention (TOHP). *BMJ* 2007 April 28;334(7599):885.

(9) Dahlof B, Sever PS, Poulter NR et al. Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendroflumethiazide as required, in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA): a multicentre randomised controlled trial. *Lancet* 2005 September 10;366(9489):895-906.

(10) Dai WJ, Funk A, Herdegen T, Unger T, Culman J. Blockade of central angiotensin AT(1) receptors improves neurological outcome and reduces expression of AP-1 transcription factors after focal brain ischemia in rats. *Stroke* 1999 November;30(11):2391-8.

(11) Dolan E, Stanton A, Thijs L et al. Superiority of ambulatory over clinic blood pressure measurement in predicting mortality: the Dublin outcome study. *Hypertension* 2005 July;46(1):156-61.

(12) Fabia MJ, Abdilla N, Oltra R, Fernandez C, Redon J. Antihypertensive activity of angiotensin II AT1 receptor antagonists: a systematic review of studies with 24 h ambulatory blood pressure monitoring. *J Hypertens* 2007 July;25(7):1327-36.

(13) Fagard RH, Staessen JA, Thijs L et al. Relationship between ambulatory blood pressure and follow-up clinic blood pressure in elderly patients with systolic hypertension. *J Hypertens* 2004 January;22(1):81-7.

(14) Fagard RH, Cornelissen VA. Incidence of cardiovascular events in white-coat, masked and sustained hypertension versus true normotension: a meta-analysis. *J Hypertens* 2007 November;25(11):2193-8.

(15) Fagard RH, Staessen JA, Thijs L et al. On-treatment diastolic blood pressure and prognosis in systolic hypertension. *Arch Intern Med* 2007 September 24;167(17):1884-91.

(16) Fagard RH, Celis H, Thijs L et al. Daytime and nighttime blood pressure as predictors of death and cause-specific cardiovascular events in hypertension. *Hypertension* 2008 January;51(1):55-61.

(17) Franklin SS, Gustin W, Wong ND et al. Hemodynamic patterns of age-related changes in blood pressure. The Framingham Heart Study. *Circulation* 1997 July 1;96(1):308-15.

(18) Franklin SS, Larson MG, Khan SA et al. Does the relation of blood pressure to coronary heart disease risk change with aging? The Framingham Heart Study. *Circulation* 2001 March 6;103(9):1245-9.

(19) Franklin SS, Jacobs MJ, Wong ND, L'Italien GJ, Lapuerta P. Predominance of isolated systolic hypertension among middle-aged and elderly US hypertensives: analysis based on National Health and Nutrition Examination Survey (NHANES) III. *Hypertension* 2001 March;37(3):869-74.

(20) Franklin SS, Pio JR, Wong ND et al. Predictors of new-onset diastolic and systolic hypertension: the Framingham Heart Study. *Circulation* 2005 March 8;111(9):1121-7.

(21) Gates PE, Tanaka H, Hiatt WR, Seals DR. Dietary sodium restriction rapidly improves large elastic artery compliance in older adults with systolic hypertension. *Hypertension* 2004 July;44(1):35-41.

(22) Gupta V, Lipsitz LA. Orthostatic hypotension in the elderly: diagnosis and treatment. *Am J Med* 2007 October;120(10):841-7.

(23) He FJ, Nowson CA, MacGregor GA. Fruit and vegetable consumption and stroke: meta-analysis of cohort studies. *Lancet* 2006 January 28;367(9507):320-6.

(24) Hermida RC, Ayala DE, Fernandez JR, Calvo C. Comparison of the efficacy of morning versus evening administration of telmisartan in essential hypertension. *Hypertension* 2007 October;50(4):715-22.

(25) Iwai M, Liu HW, Chen R et al. Possible inhibition of focal cerebral ischemia by angiotensin II type 2 receptor stimulation. *Circulation* 2004 August 17;110(7):843-8.

(26) Jatoi NA, Jerrard-Dunne P, Feely J, Mahmud A. Impact of smoking and smoking cessation on arterial stiffness and aortic wave reflection in hypertension. *Hypertension* 2007 May;49(5):981-5.

(27) Juurlink DN, Mamdani MM, Lee DS et al. Rates of hyperkalemia after publication of the Randomized Aldactone Evaluation Study. *N Engl J Med* 2004 August 5;351(6):543-51.

(28) Kjeldsen SE, Julius S, Hedner T, Hansson L. Stroke is more common than myocardial infarction in hypertension: analysis based on 11 major randomized intervention trials. *Blood Press* 2001;10(4):190-2.

(29) Laurent S, Cockcroft J, Van BL et al. Expert consensus document on arterial stiffness: methodological issues and clinical applications. *Eur Heart J* 2006 November;27(21):2588-605.

(30) Lee M, Entzminger L, Lohsoonthorn V, Williams MA. Risk factors of hypertension and correlates of blood pressure and mean arterial pressure among patients receiving health exams at the Preventive Medicine Clinic, King Chulalongkorn Memorial Hospital, Thailand. *J Med Assoc Thai* 2006 August;89(8):1213-21.

(31) Lewington S, Clarke R, Qizilbash N, Peto R, Collins R. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet* 2002 December 14;360(9349):1903-13.

(32) Li J, Culman J, Hortnagl H et al. Angiotensin AT2 receptor protects against cerebral ischemia-induced neuronal injury. *FASEB J* 2005 April;19(6):617-9.

(33) Lindholm LH, Carlberg B, Samuelsson O. Should beta blockers remain first choice in the treatment of primary hypertension? A meta-analysis. *Lancet* 2005 October 29;366(9496):1545-53.

(34) Lloyd-Jones DM, Evans JC, Levy D. Hypertension in adults across the age spectrum: current outcomes and control in the community. *JAMA* 2005 July 27;294(4):466-72.

(35) Marfella R, Siniscalchi M, Portoghese M et al. Morning blood pressure surge as a destabilizing factor of atherosclerotic plaque: role of ubiquitin-proteasome activity. *Hypertension* 2007 April;49(4):784-91.

(36) Matchar DB, McCrory DC, Orlando LA et al. Systematic review: comparative effectiveness of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers for treating essential hypertension. *Ann Intern Med* 2008 January 1;148(1):16-29.

(37) Mattace-Raso FU, van den Meiracker AH, Bos WJ et al. Arterial stiffness, cardiovagal baroreflex sensitivity and postural blood pressure changes in older adults: the Rotterdam Study. *J Hypertens* 2007 July;25(7):1421-6.

(38) McGuinness B, Todd S, Passmore AP, Bullock R. Systematic review: Blood pressure lowering in patients without prior cerebrovascular disease for prevention of cognitive impairment and dementia. *J Neurol Neurosurg Psychiatry* 2008 January;79(1):4-5.

(39) Melander O, von WF, Frandsen E et al. Moderate salt restriction effectively lowers blood pressure and degree of salt sensitivity is related to baseline concentration of renin and N-terminal atrial natriuretic peptide in plasma. *J Hypertens* 2007 March;25(3):619-27.

(40) Messerli FH, Mancia G, Conti CR et al. Dogma disputed: can aggressively lowering blood pressure in hypertensive patients with coronary artery disease be dangerous? *Ann Intern Med* 2006 June 20;144(12):884-93.

(41) Mitchell GF, Conlin PR, Dunlap ME et al. Aortic diameter, wall stiffness, and wave reflection in systolic hypertension. *Hypertension* 2008 January;51(1):105-11.

(42) O'Rourke MF, Hashimoto J. Mechanical factors in arterial aging: a clinical perspective. *J Am Coll Cardiol* 2007 July 3;50(1):1-13.

(43) Oberleithner H, Riethmuller C, Schillers H, MacGregor GA, de Wardener HE, Hausberg M. Plasma sodium stiffens vascular endothelium and reduces nitric oxide release. *Proc Natl Acad Sci U S A* 2007 October 9;104(41):16281-6.

(44) Oparil S, Yarows SA, Patel S, Fang H, Zhang J, Satlin A. Efficacy and safety of combined use of aliskiren and valsartan in patients with hypertension: a randomised, double-blind trial. *Lancet* 2007 July 21;370(9583):221-9.

(45) Pickering TG, Shimbo D, Haas D. Ambulatory blood-pressure monitoring. *N Engl J Med* 2006 June 1;354(22):2368-74.

(46) Pratt JH. A not-so-modest proposal that a "modest" increase in aldosterone causes hypertension and more. *Hypertension* 2008 January;51(1):39-40.

(47) Redfield MM, Jacobsen SJ, Borlaug BA, Rodeheffer RJ, Kass DA. Age- and gender-related ventricular-vascular stiffening: a community-based study. *Circulation* 2005 October 11;112(15):2254-62.

(48) Roman MJ, Devereux RB, Kizer JR et al. Central pressure more strongly relates to vascular disease and outcome than does brachial pressure: the Strong Heart Study. *Hypertension* 2007 July;50(1):197-203.

(49) Sato A, Saruta T. Aldosterone breakthrough during angiotensin-converting enzyme inhibitor therapy. *Am J Hypertens* 2003 September;16(9 Pt 1):781-8.

(50) Schoofs MW, van der KM, Hofman A et al. Thiazide diuretics and the risk for hip fracture. *Ann Intern Med* 2003 September 16;139(6):476-82.

(51) Staessen JA, Richart T, Birkenhager WH. Less atherosclerosis and lower blood pressure for a meaningful life perspective with more brain. *Hypertension* 2007 March;49(3):389-400.

(52) Stampfer MJ, Kang JH, Chen J, Cherry R, Grodstein F. Effects of moderate alcohol consumption on cognitive function in women. *N Engl J Med* 2005 January 20;352(3):245-53.

(53) Stewart KJ, Bacher AC, Turner KL et al. Effect of exercise on blood pressure in older persons: a randomized controlled trial. *Arch Intern Med* 2005 April 11;165(7):756-62.

(54) Stokes GS, Bune AJ, Huon N, Barin ES. Long-term effectiveness of extended-release nitrate for the treatment of systolic hypertension. *Hypertension* 2005 March;45(3):380-4.

(55) Strazzullo P, Kerry SM, Barbato A, Versiero M, D'Elia L, Cappuccio FP. Do statins reduce blood pressure?: a meta-analysis of randomized, controlled trials. *Hypertension* 2007 April;49(4):792-8.

(56) Vasan RS, Beiser A, Seshadri S et al. Residual lifetime risk for developing hypertension in middle-aged women and men: The Framingham Heart Study. *JAMA* 2002 February 27;287(8):1003-10.

(57) Vasan RS. Pathogenesis of elevated peripheral pulse pressure: some reflections and thinking forward. *Hypertension* 2008 January;51(1):33-6.

(58) Verdecchia P, Reboldi G, Angeli F et al. Angiotensin-converting enzyme inhibitors and calcium channel blockers for coronary heart disease and stroke prevention. *Hypertension* 2005 August;46(2):386-92.

(59) Waldstein SR, Rice SC, Thayer JF, Najjar SS, Scuteri A, Zonderman AB. Pulse pressure and pulse wave velocity are related to cognitive decline in the Baltimore Longitudinal Study of Aging. *Hypertension* 2008 January;51(1):99-104.

(60) Wallace SM, Yasmin, McEniery CM et al. Isolated systolic hypertension is characterized by increased aortic stiffness and endothelial dysfunction. *Hypertension* 2007 July;50(1):228-33.

(61) Weinberger MH, Fineberg NS. Sodium and volume sensitivity of blood pressure. Age and pressure change over time. *Hypertension* 1991 July;18(1):67-71.

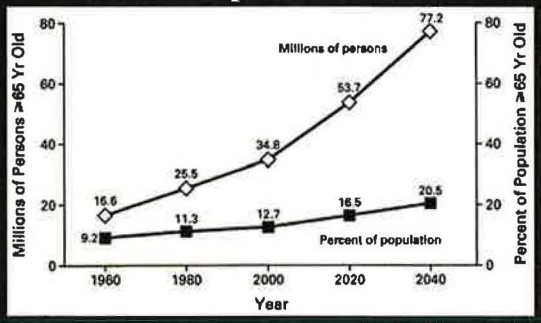
(62) Williams B, Lacy PS, Thom SM et al. Differential impact of blood pressure-lowering drugs on central aortic pressure and clinical outcomes: principal results of the Conduit Artery Function Evaluation (CAFE) study. *Circulation* 2006 March 7;113(9):1213-25.

(63) Wong ND, Lopez VA, L'Italien G, Chen R, Kline SE, Franklin SS. Inadequate control of hypertension in US adults with cardiovascular disease comorbidities in 2003-2004. *Arch Intern Med* 2007 December 10;167(22):2431-6.

(64) Zhang H, Thijs L, Staessen JA. Blood pressure lowering for primary and secondary prevention of stroke. *Hypertension* 2006 August;48(2):187-95.

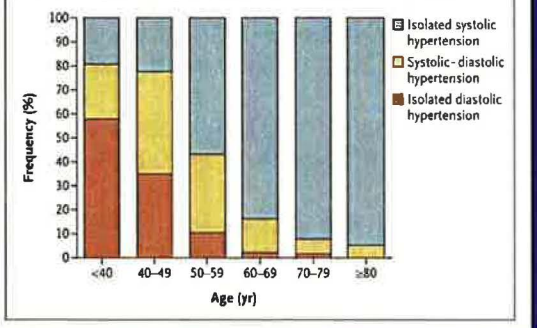
(65) Zillich AJ, Garg J, Basu S, Bakris GL, Carter BL. Thiazide diuretics, potassium, and the development of diabetes: a quantitative review. *Hypertension* 2006 August;48(2):219-24.

Projected Increases in U.S. Population >65



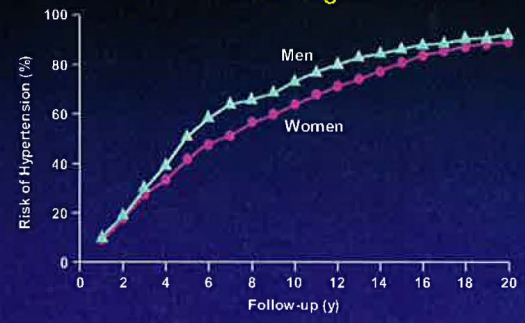
Data from U.S. Census Bureau
Redfield MM. *N Engl J Med.* 2002;347:1442-1444

Frequency of Untreated Hypertension According to Subtype and Age



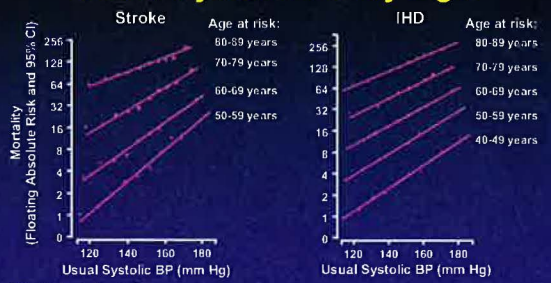
Source: Franklin et al. Hypertension 2001;37:869.

Residual Lifetime Risk of Hypertension in Women and Men Aged 65 Years



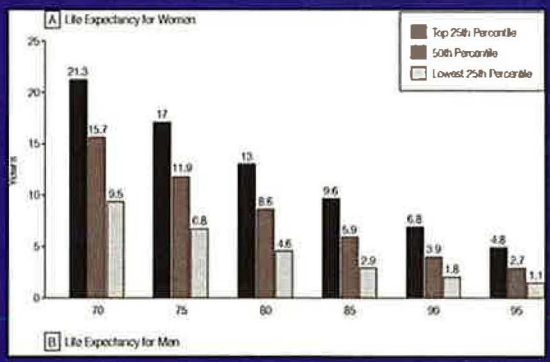
Adapted with permission from Vasan RS, et al. *JAMA.* 2002;287:1003-1010.

Stroke and IHD Mortality vs Usual Systolic BP by Age



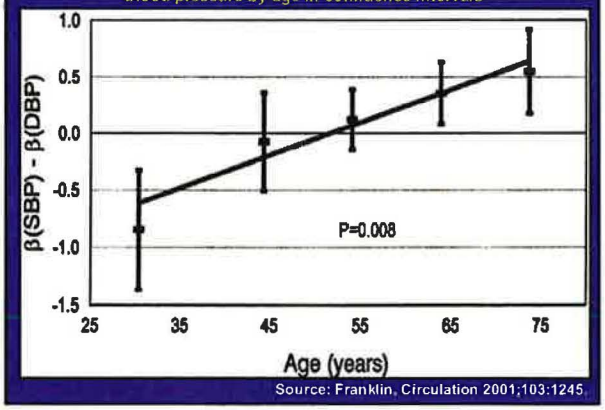
IHD = ischemic heart disease.
Reproduced with permission from Lewington S, et al; Prospective Studies Collaboration. *Lancet.* 2002;360:1903-1913.

Quartiles of Life Expectancy of Woman at Selected Ages



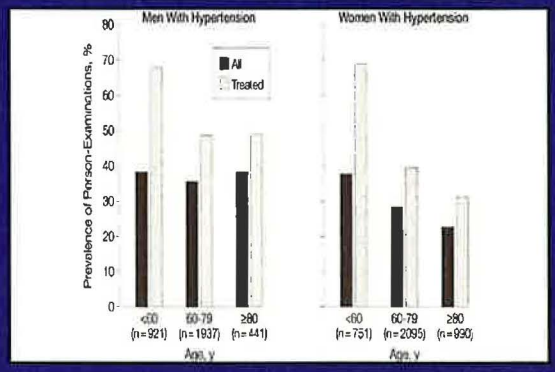
Source: Life Tables of the United States

Coronary heart disease prediction by systolic and diastolic blood pressure by age in confidence intervals



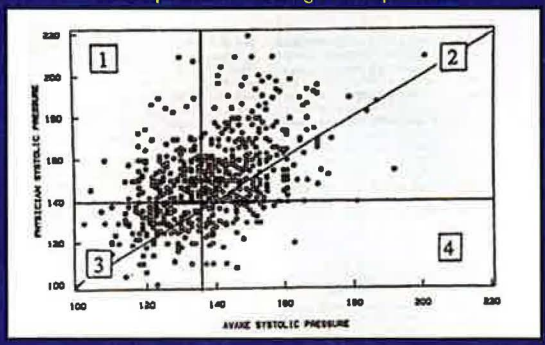
Source: Franklin, Circulation 2001;103:1245.

Prevalence of Control to Blood Pressure below 140/90



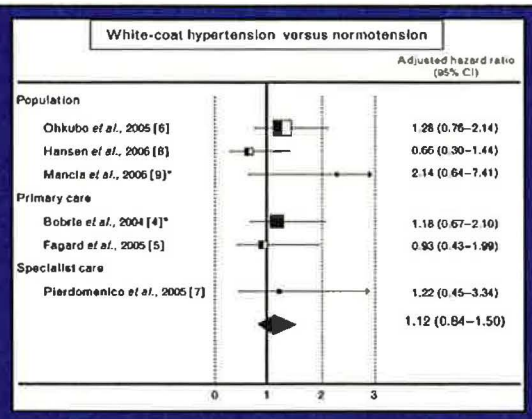
Source: Lloyd-Jones DM et al. JAMA 2005;294:466.

Plot of clinic systolic and daytime ambulatory blood pressure reading in 573 patients



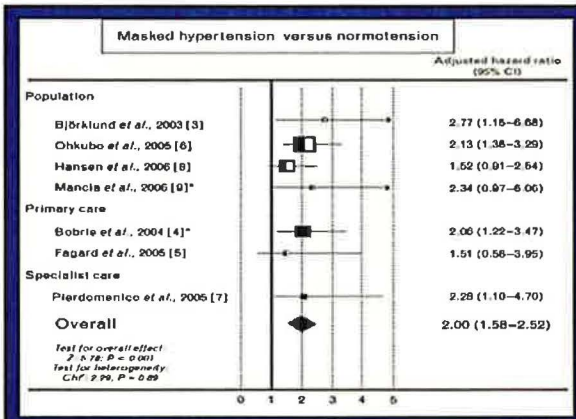
Source: Pickering. J Hypertens.1992;10:401-409

White-coat hypertension versus normotension



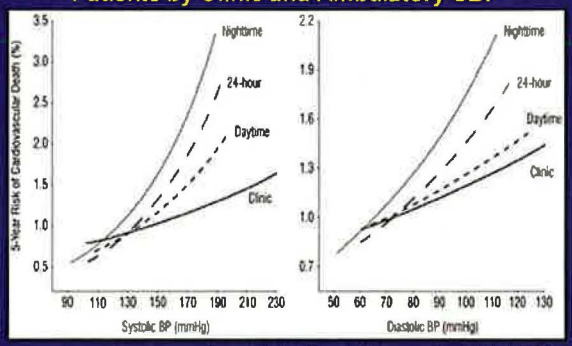
Source: Fagard et al. J Hypertension 2007;25:2193.

Masked hypertension versus normotension



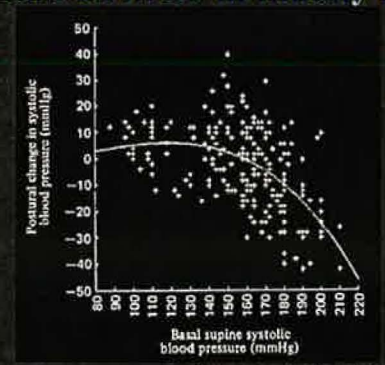
Source: Fagard et al. J Hypertension 2007;25:2193.

Adjusted 5- year Risk of CV Death in 5292 Patients by Clinic and Ambulatory SBP



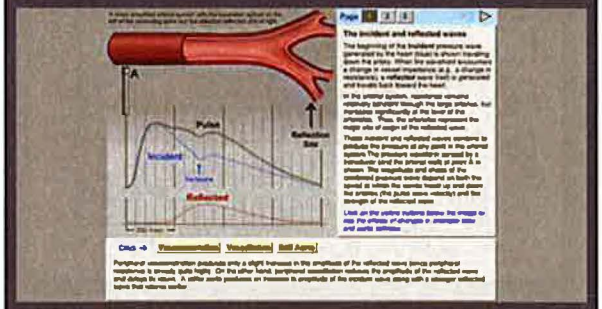
Source: Dolan E at al. Hypertension 2005; 46:156

Postural Fall in BP in Elderly People

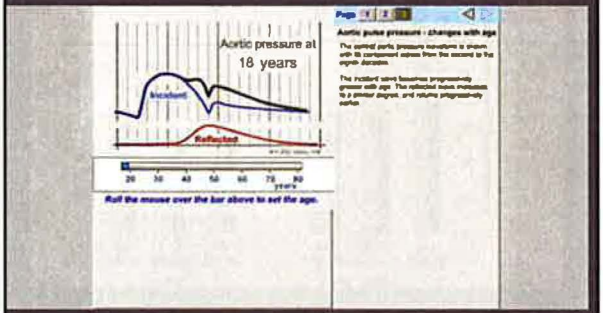


Lipsitz et al. *Clin Sci* 1985;69:337

Pressure Wave Reflection

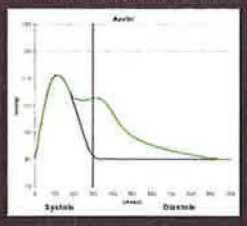


Aortic Pressure Waveform

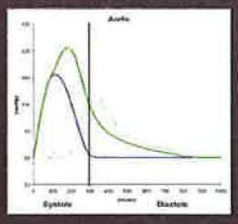


Wave Reflection and Central Blood Pressures

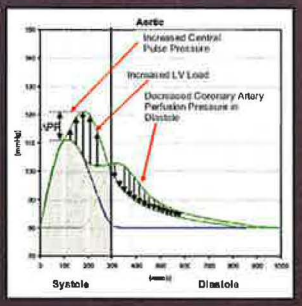
CENTRAL BP - LATE WAVE REFLECTION



CENTRAL BP - EARLY WAVE REFLECTION

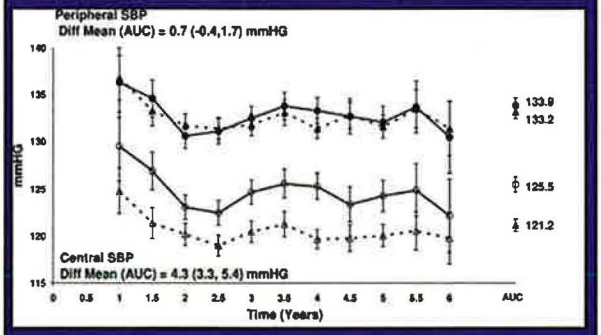


The Impact of the Early Wave Reflection



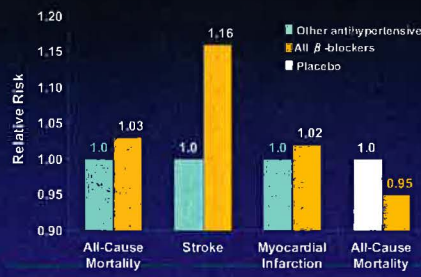
- The earlier return to the heart of the reflected pressure wave changes the central blood pressure waveform, **with 3 key clinical implications**
  - Central pulse pressure increases … **increasing risk of stroke and renal failure**
  - LV Load increases, … **increasing LV mass**, and accelerating progress towards LV hypertrophy and heart failure
  - Coronary artery perfusion pressure in diastole reduces, … **increasing risk of myocardial ischemia**

Peripheral and Central Systolic BP with Atenolol-based or Amlodipine-based (…) Therapy (CAFE study)



Source: CAFE Investigators. Circulation 2006; 113:1213

β-Blockers and Clinical Outcomes

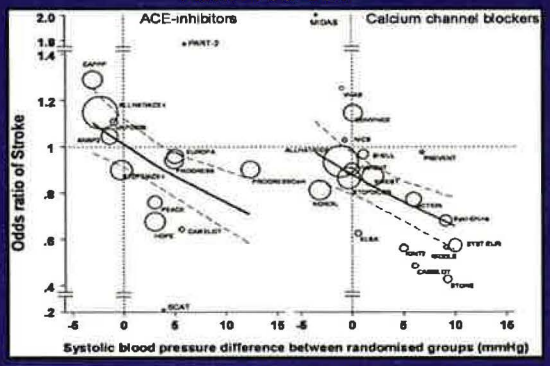


Lindholm LH, et al. *Lancet*. 2005;366:1545-1553.

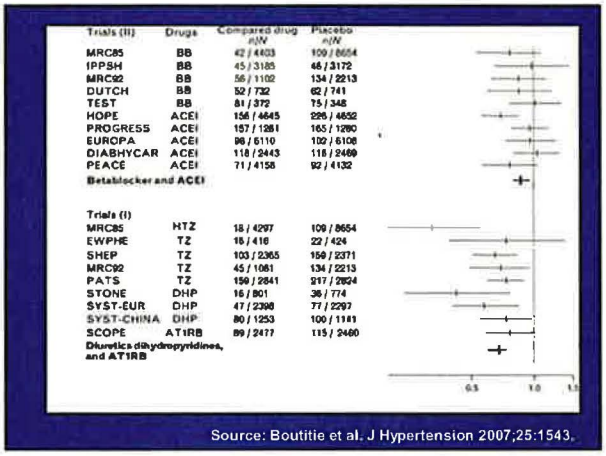
Strokes and MIs in Recent Trials

Acronym	Year Published	Average Age (yrs)	Number Patients	Number Strokes	Number MIs
STOP-1	1991	76	1,627	82	53
SHEP	1991	72	4,736	269	165
SYST-EUR	1997	70	4,695	124	78
HOT	1998	61	18,790	294	209
CAPPP	1999	53	10,985	340	327
STOP-2	1999	76	6,614	452	293
NORDIL	2000	60	10,881	355	340
INSIGHT	2000	67	6,575	141	138
			TOTAL:	2,057	1,603

Odds for Stroke by Difference in Achieved SBP

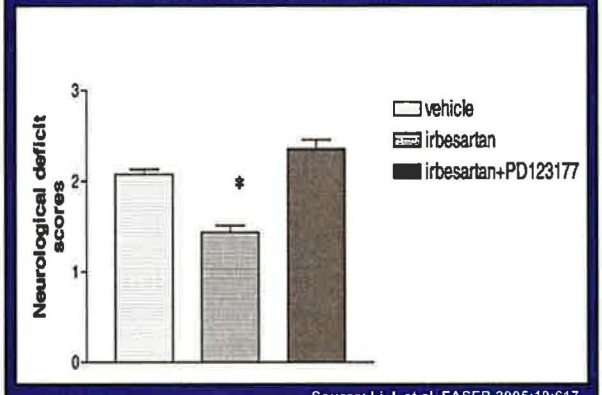


Source: Verdecchia P et al. Hypertension 2005; 46:386



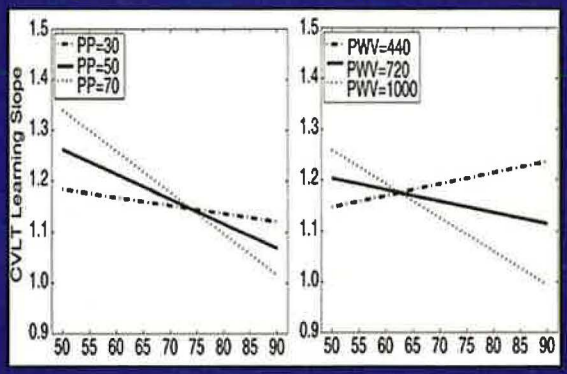
Source: Boutitie et al. J Hypertension 2007;25:1543.

Neurological Deficit after cerebral Ischemia



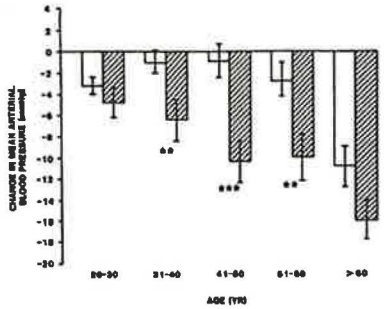
Source: Li J, et al. FASEB 2005;19:617

Changes in California Verbal Leaning Test Over 14 Years



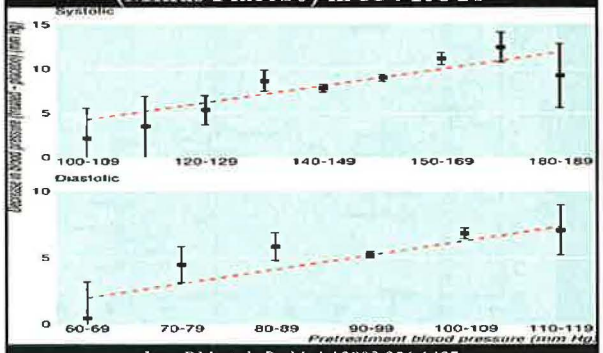
Source: Waldstein et al. Hypertension 2008;51:99.

Change in Mean BP with Acute Increases in Sodium Excretion



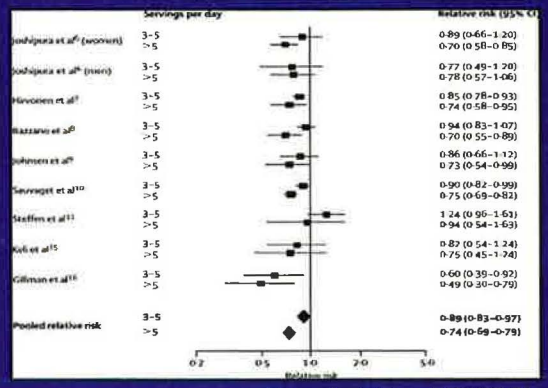
Weinberger and Fineburg, *Hypertension* 1991;18:67

Average Reduction in BP (Minus Placebo) in 354 RCTs



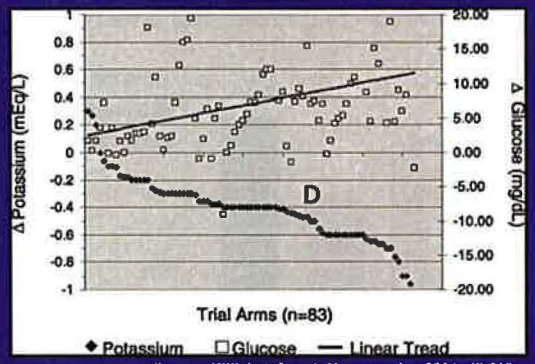
Law RM et al. *Br Med J* 2003;326:1427

Risk of Stroke with Fruit and Vegetables



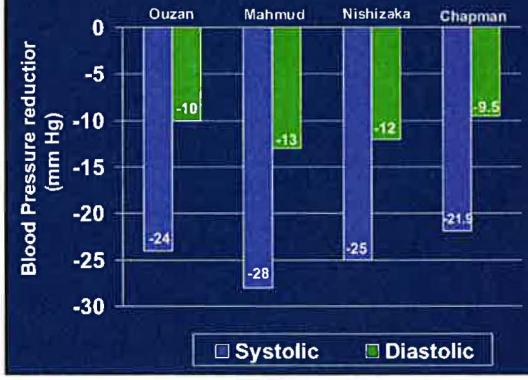
Source: He et al. Lancet 2006;367:320.

Relation between Changes in Serum Potassium and Glucose in 83 Trials

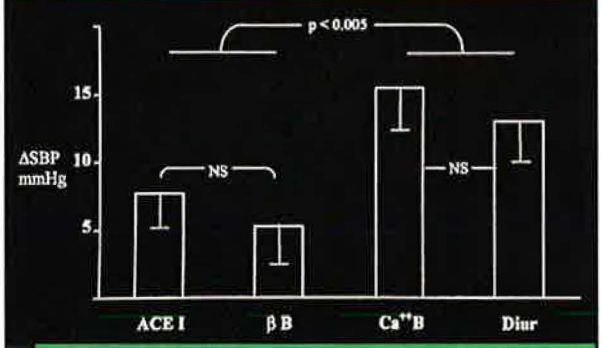


Source: Zillich A J et al. Hypertension 2006; 48:219

Spironolactone, 25-50mg/d, in Resistant Hypertensives

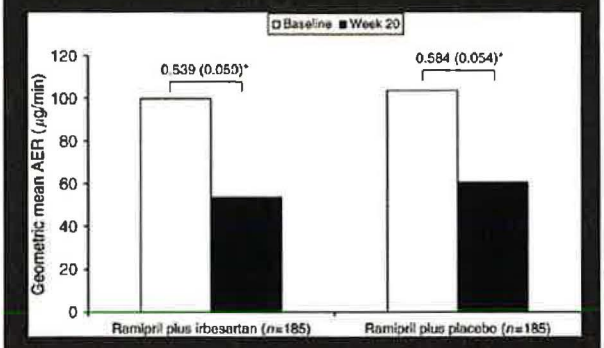


Random Therapy of Elderly with Systolic Hypertension



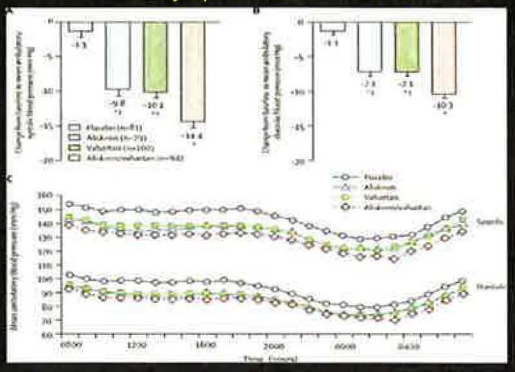
From Morgan et al.Am J Hypertension 2001;14:241

Mean albumin excretion rate from baseline to week 20



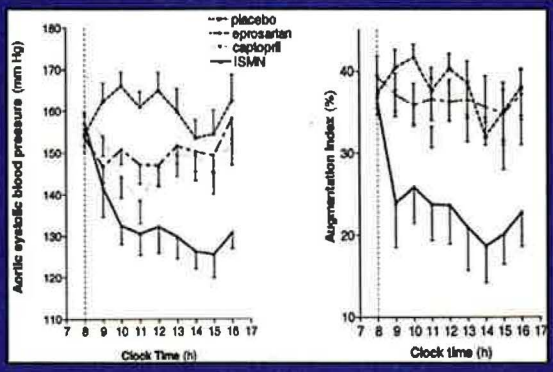
Source: Bakris GL et al. Kidney Int 2007 ;72:879

Effects of Aliskerin and Valsartan Alone of in Combination on Ambulatory Systolic and Diastolic BP



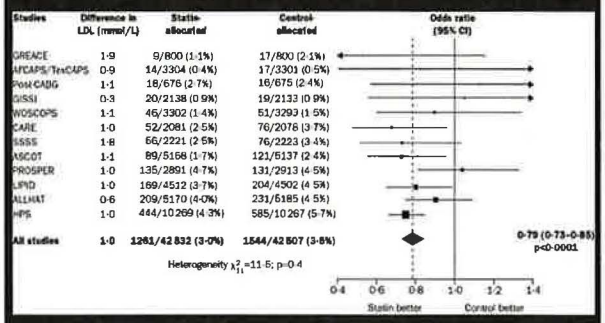
Source: Oparil S et al. Lancet 2007;370:221-229.

Effects of Drugs on Central Arterial Properties



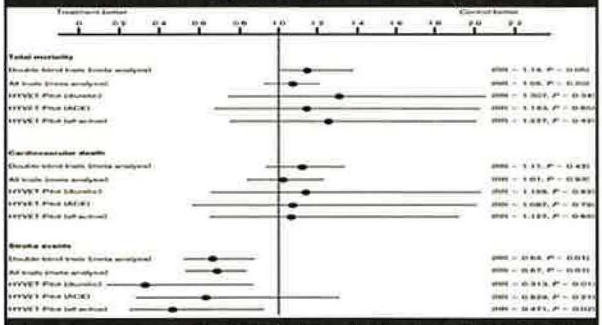
Source: Stokes et al. Hypertension 2003;41:297.

Meta-Analysis of Statins on Stroke



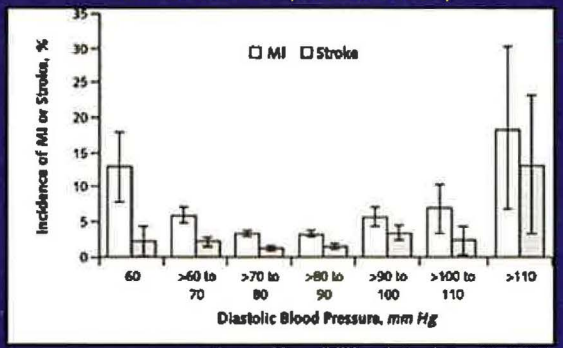
Source: Heart Protection Study Group. *Lancet* 2004;363:757

Relative Risk of Mortality and Strokes In Patients >80



From Bulpitt CJ et al. *J Hypertens* 2003;21:2409

Incidence of MI an Stroke by Average treatment BP (INVEST trial)



Source: Messerli FH et al. Ann intern Med 2006