HOT TOPICS IN HYPERTENSION:

Too Small Babies, The Calcium Antagonist Scare, and More

Medicine Grand Rounds

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I. The fetal origins of hypertension, diabetes and coronary disease.

A. Hypertension

1. Epidemiological evidence: Although Gennser et al (1988) first published evidence that low birth weight was associated with the risk of hypertension in adult life, D.J.P. Barker and his co-workers from Southampton, UK have been the major driving force that has firmly established this connection (Barker, 1995a). As he notes; "The relation between birthweight and blood pressure has now been demonstrated in 17 studies of men, women and children, and there is a secure base for saying that impaired fetal growth is strongly linked to blood pressure at all ages except during adolescence, when the tracking of blood pressure levels which begins in early childhood is perturbed by the adolescent growth spurt." One of these 17 studies is portrayed in Table 1 (Law et al, 1993) and Figure 1 shows the amplification with increasing age.

Table 1: Mean systolic pressure (mmHg) in men and women aged 64-71 years according to birthweight

Birthweight, pounds (kg)	Men	Women
5.5 (2.50)	171 (18)	169 (9)
6.5 (2.95)	168 (53)	165 (33)
7.5 (3.41)	168 (144)	160 (68)
8.5 (3.86)	165 (111)	163 (48)
>8.5 (3.86)	163 (92)	155 (26)

In the second and third column the figures in parentheses are numbers of subjects. (From Barker et al, 1995a.)

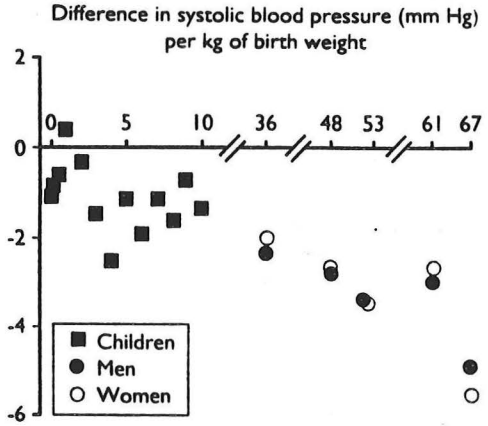


Figure 1: The degree of lower systolic blood pressure with increments of birth weight increases with age. (From Law et al, 1993.)

2. Possible mechanisms

a. *Decreased compliance* in conduit (aorta, iliac, popliteal) arteries, "the result of selective increase in peripheral vascular resistance in the fetus [with intrauterine growth retardation] leading to preferential perfusion of the brain at the expense of the trunk" (Martyn et al, 1995).

b. *Dysfunction of the placental glucocorticoid barrier* (Edwards et al, 1993). These investigators found decreased activity of the enzyme 11ß-hydroxysteroid dehydrogenase (11ß HSD) that normally inactivates the large quantities of maternal cortisol in the placentas of rats with low

birthweight. In addition, exposure of rat fetuses to exogenous glucocorticoids lead to low birthweight and subsequent hypertension. The authors conclude that "Glucocorticoids acting during critical periods of prenatal development may exert organisational effects or imprint patterns of response that persist throughout life."

This hypothesis was <u>not</u> supported by Stewart et al's (1995) failure to correlate placental weight and 11ß HSD activity to fetal weight in humans.

c. *Congenital oligonephropathy*. This hypothesis, supported by experimental work that goes back over 30 years (Winick and Noble, 1965), has been formulated and popularized by Barry Brenner (Brenner et al, 1988; MacKenzie and Brenner, 1995).

As stated by Mackenzie and Brenner (1995):

"Deficiencies in the total nephron supply, by limiting total renal excretory capacity and thereby influencing the point at which steady-state conditions between arterial pressure and sodium excretion are achieved, could profoundly affect long-term blood pressure regulation. When renal mass is greatly reduced, as in the case of extensive experimental ablation of the kidney in rodents, blood pressure increases in the systemic arterial circulation and in the glomerular capillaries, thus increasing glomerular filtration rate and promoting fluid excretion. However, sustained elevations in glomerular capillary hydraulic pressure are associated with the development of focal and segmental glomerular sclerosis leading to further loss of nephrons and a self-perpetuating vicious cycle of hypertension and progressive glomerular injury."

The reduction in nephron supply could reflect "conditions in utero. Low birth weight resulting from intrauterine growth retardation (IUGR) in humans has been shown to be associated with deficiencies in nephron number of up to 20%, even in pregnancies that went to term" (Hinchliffe et al, 1992 (Figure 2). Figure 2a shows nephron numbers in fetuses, figure 2b in infants with (x) or without (■) IUGR.

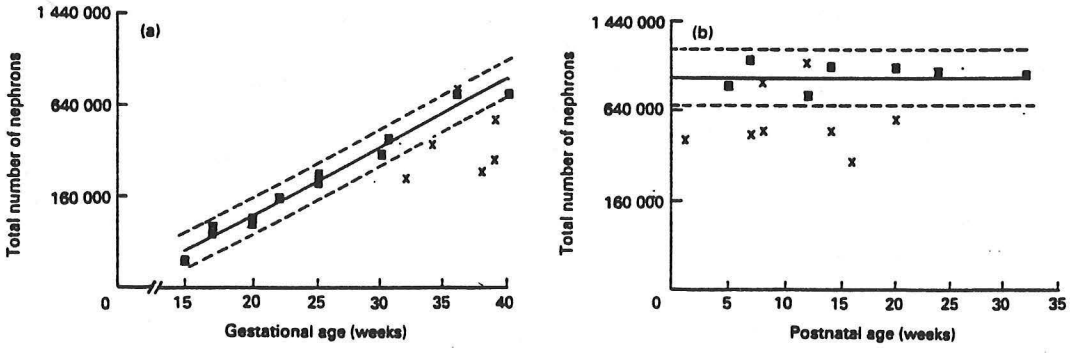


Figure 2: (a) Relation between the total glomerular i.e., nephron number, N(glom) (y-axis, square root plot), and gestational age (x-axis) for the (a) prenatal control and IUGR groups and (b) postnatal age (x-axis) for the postnatal control and IUGR groups. The regression line and 95% prediction intervals for the control group are plotted. The mean (2SD) for the control group is shown. The difference in number between control and IUGR groups was highly significant: P<0.005 (two-tailed, two-sample *t-test*). (■) = *control; (x) = IUGR. (From Hinchliffe et al, 1992.)*

Mackenzie and Brenner go on to say: "Given the association between low birth weight and fewer nephrons, it is naturally tempting to speculate that the origins of hypertension in adults who were of low birth weight lie in a deficient endowment of nephrons secondary to intrauterine growth retardation" (Figure 3).

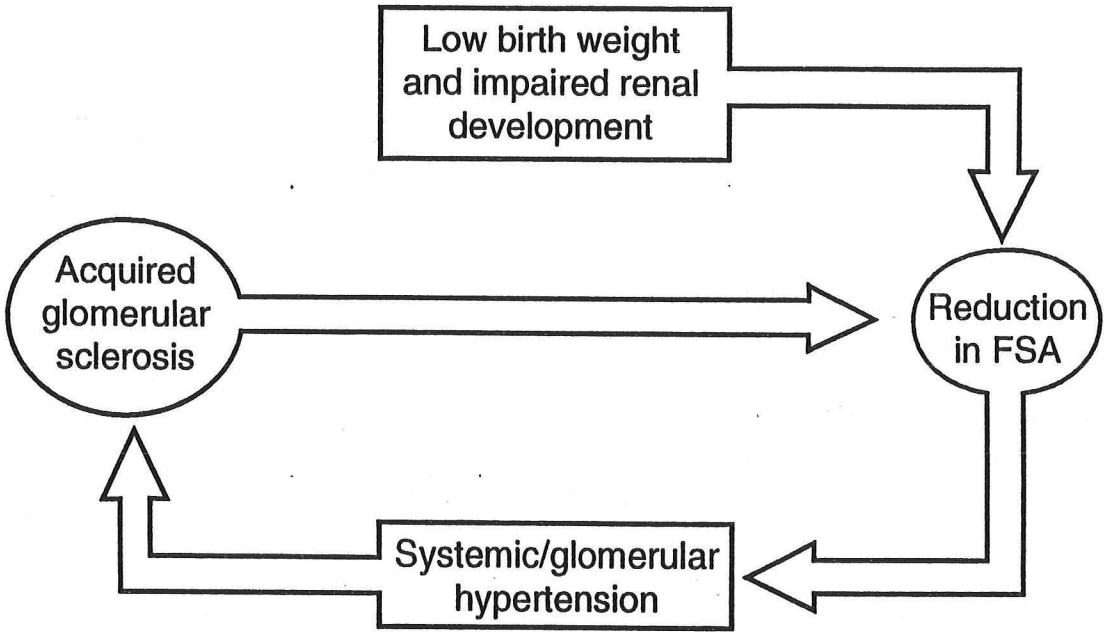


Figure 3: Hypothesis: the risks of developing essential hypertension and progressive renal injury in adult life are increased as a result of congenital oligonephropathy, an inborn deficit of filtration surface area (FSA) caused by impaired renal development. Low birth weight, caused by intrauterine growth retardation and/or prematurity, contributes to this oligonephropathy. Systemic and glomerular hypertension in later life results in progressive glomerular sclerosis, further reducing FSA and thereby perpetuating a vicious cycle, leading, in the extreme, to end-stage renal failure. (From Brenner and Chertow, 1994.)

The number of nephrons present at birth cannot increase in number and improved post-natal nutrition does not influence later blood pressure (Lucas and Morley, 1994). Twins of lower birth weight also have a more rapid rate of rise in blood pressure during infancy, further supporting the importance of intrauterine environmental factors (Levine et al, 1994). On the other hand, babies otherwise normal but delivered early can continue to generate nephrons in contrast to a loss of up to 50% of nephrons in those who experience continued intrauterine exposure to adverse circumstances after 33 weeks.

3. Implications

Low birth weight, then, may be a major precursor later to adult hypertension as shown among the 160,000 women in the Nurses Health Studies whose odds ratio (OR) for hypertension progressively fell with increasing birth weight (Curhan et al, 1996 (Table 2).

Table 2 (From Curhan et al, 1995)

NHS I (mean age 58)			NHS II (mean age 37)		
Birth wt	OR	95% CI	Birth wt	OR	95% CI
<5.0 lbs	1.39	1.29-1.50			
5.0-5.5	1.28	1.19-1.38	<5.5	1.40	1.28-1.54
5.6-7.0	1.16	1.11-1.20	5.5-6.9	1.15	1.08-1.22
7.1-8.5	1.00	referent	7.0-8.4	1.00	referent
8.6-10.0	0.91	0.86-0.97	8.5-9.9	1.02	0.90-1.15
>10.0	0.90	0.81-1.01	10+	1.07	0.86-1.34

Microalbuminuria in non-diabetics (Gould et al, 1993) and diabetics (Rossin et al, 1995) is found in those who are of shorter stature reflecting lower birth weight.

Blacks have more small babies - 13.3% compared to 6% in whites and Hispanics (Hack and Merkatz, 1995), partly because of social deprivation (Wilcox et al, 1995), inadequate nutrition (Godfrey et al, 1994), higher rates of pregnancy at younger age (Fraser et al, 1995), and shorter intervals between pregnancies (Rawlings et al, 1995) but also because of familial aggregation seen in blacks and whites for unknown reasons (Wang et al, 1995) (Table 3).

Table 3: Adjusted Odds Ratios and 95 Percent Confidence Intervals for the Combined Association of the Birth Weights of the Mother and the Youngest Child in the Family with the Risk of Low Birth Weight (LBW) among the Child's Siblings. (Modified from Wang et al, 1995.)

Variable	Group 1 Mother: Normal Infant: Normal	Group 2 Mother: Low Infant: Normal	Group 3 Mother: Normal Infant: Low	Group 4 Mother: Low Infant: Low
White				
Odds ratio	1.0	2.5	6.8	15.4
95% CI	-	1.4-4.3	4.7-9.8	9.2-25.5
Siblings with LBW/all siblings	68/1902	19/228	89/419	44/113
Black				
Odds ratio	1.0	2.6	4.7	13.9
95% CI	-	1.8-3.8	3.5-64	9.2-20.9
Siblings with LBW/all siblings	122/1530	58/305	150/483	117/205

***Odds ratios and 95 percent confidence intervals were estimated by multiple logistic-regression analysis which included the following covariates: the mother's age, parity, race, education, cigarette-smoking status, weight and height before the pregnancy, and place of birth; the year and season of the infant's birth; the interval between the sibling's birth and the birth of the index child; and the infant's sex. In group 1, neither the mother nor the index child had low birth weight (weight <2500 g); in group 2, only the mother had low birth weight; in group 3, only the index child had low birth weight; and in group 4, both the mother and the index child had low birth weight.**

Two papers in the 12/28/95 New England Journal of Medicine showed that infections of the genital tract (bacterial vaginosis) contribute up to 40% of preterm births and that appropriate antibiotic therapy reduced the rates of premature delivery (Hillier et al, 1995; Hauth et al, 1995).

Whereas maternal smoking is not associated with preterm delivery, it too causes fetal growth retardation (Peacock et al, 1995).

Obviously, the higher rate of hypertension and end-stage renal disease in African-Americans could be explained at least in part by their higher incidence of low birth weight (Lopes and Port, 1995). The potential for prevention of hypertension in the children of higher risk mothers is obvious, if pregnancies can be delayed and adequate prenatal care delivered. These goals will be even harder to reach if continued cutbacks occur in reproductive counseling, birth control, and prenatal care for the indigent.

B. Diabetes

Small babies end up with more diabetes (Barker, 1995b) and the full syndrome of obesity, insulin resistance, diabetes, dyslipidemia and hypertension (Barker 1995a; Valdez et al, 1994) (Table 4).

Table 4: Prevalence of non-insulin dependent diabetes (NIDDM) and impaired glucose tolerance (IGT) in men aged 59-70 years and for syndrome X (NIDDM, hypertension and hyperlipidemia) in men according to birthweight. (From Barker et al, 1995a.)

Birthweight, pounds (kg)	Percent with NIDDM/IGT	Odds ratio (95% confidence interval)	Percent with syndrome X	Odds ratio (95% confidence interval)
≤5.5 (2.50)	40	6.6 (1.5 to 28)	30	18 (2.6 to 118)
6.5 (2.95)	34	4.8 (1.3 to 17)	19	8.4 (1.5 to 49)
7.5 (3.41)	31	4.6 (1.4 to 16)	17	8.5 (1.5 to 46)
8.5 (3.86)	22	2.6 (0.8 to 8.9)	12	4.9 (0.9 to 27)
9.5 (4.31)	13	1.4 (0.3 to 5.6)	6	2.2 (0.3 to 14)
>9.5 (4.31)	14	1.0	6	1.0

The association has been noted to be U-shaped among Pima Indians, with more diabetes in those with either high or low birth weight (McCance et al, 1994). Hyperinsulinemia from insulin resistance has been proposed to program the fetus for later disease (Langford et al, 1994).

C. Coronary heart disease

Mortality from cardiovascular disease is increased in both men and women whose birth weight was small (Osmond et al, 1993) (Figure 4).

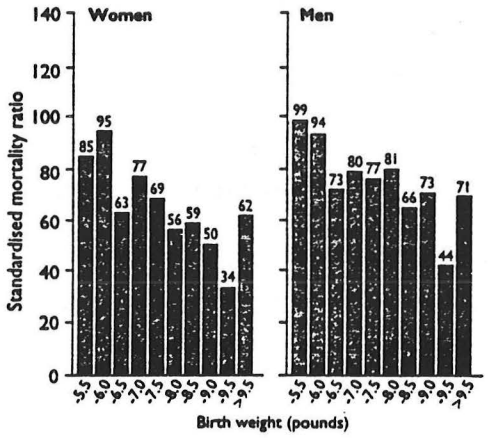


Figure 4: Standardized mortality ratios of cardiovascular disease below age of 65 according to birth weight. (From Osmond et al, 1993.)

Obviously , the increase in hypertension, dyslipidemia and diabetes seen in small babies could all contribute to the increase in coronary disease which increased further in those who become obese (Fall et al, 1995). Barker (1995b) has put all of his ideas into an overall framework linking fetal undernutrition at various trimesters of pregnancy with different outcomes (Figure 5).

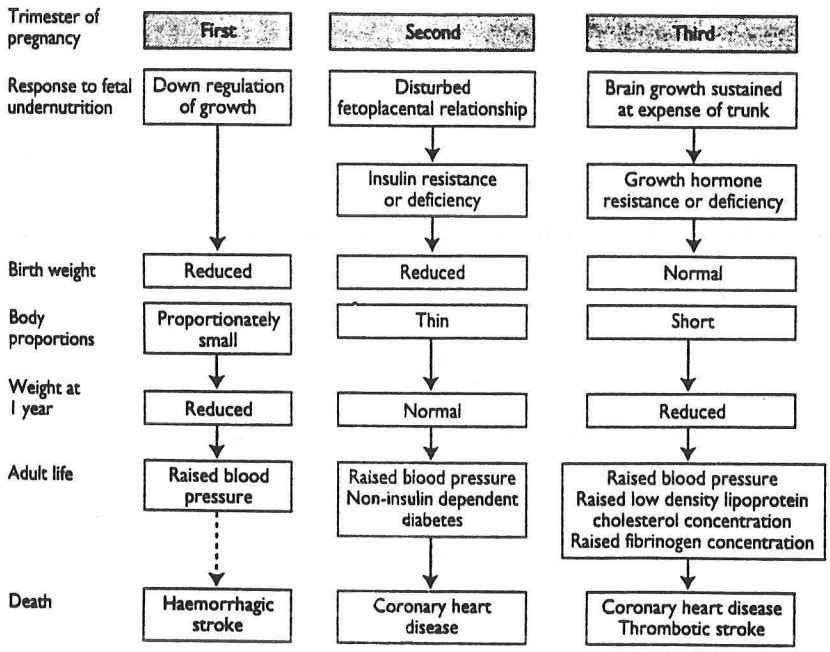


Figure 5: Framework of ideas in the fetal origins hypothesis linking fetal undernutrition during each trimester of pregnancy with later abnormalities. (From Barker DJP, 1995b.)

D. Other associations

As if these aren't enough, small babies have also been found to have lower IQ's and more attention deficit when they grow up (Breslau, 1995).

II. The role of sodium

A. Pathogenesis

The decreased number of nephrons that accompanies intrauterine growth retardation almost certainly requires interaction with environmental factors to induce hypertension. One very likely contributor is longtime exposure to excess sodium.

A large body of circumstantial evidence favors an association between excess sodium and hypertension. Perhaps the most impressive is the recent report of Denton et al (1995) of 22 normotensive chimpanzees who were living comfortably on a diet of mostly fruits and vegetables in long-established groups so that they had learned to cope with stresses. After studying the animals for a year in their natural state, half were given progressively increased amounts of sodium chloride, 5 to 15 grams per day. Seven out of 10 of the chimpanzees who ate the extra salt developed hypertension, the blood pressure rising an average of 33/10 mm Hg (Figure 6). When the high salt intake was stopped, the blood pressure returned to normal.

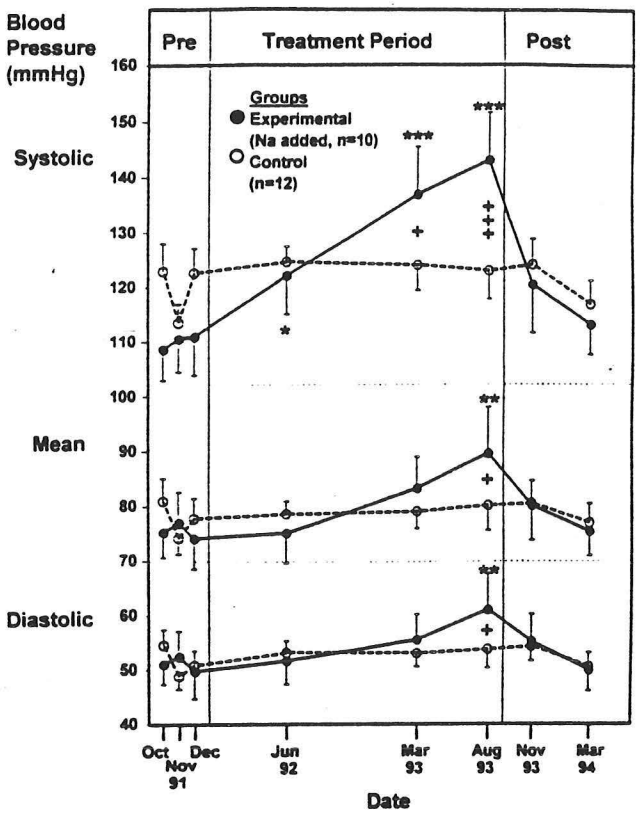


Figure 6: A group of 22 chimpanzees maintained in small long-term stable social groups and fed a vegetable-fruit diet with addition of infant formula (Cerelac, Nestlé) as a calorie, protein, calcium and vitamin supplement. Twelve control animals (○) had no change of conditions over 2.4 years and no significant change of systolic, diastolic or mean blood pressure (mean ± s.e.m.). Ten experimental animals (●) had 5 g/day of NaCl added to infant formula for 19 weeks, 10 g/day for 3 weeks, and then 15 g/day for 67 weeks. A 20-week period without salt addition followed. Increase of blood pressure relative to mean of the three baseline determinations (*P<0.05, **P<0.001), and experimental group vs control group ($^{+}$P<0.05, $^{+++}$P<0.001). (From Denton et al, 1995).

B. The effects of sodium restriction (Figure 7)

1. Lowering of blood pressure: The average fall in blood pressure in carefully controlled trials among hypertensives is only about 4/2 mm Hg (Swales, 1995). Older patients may achieve more (Weinberger and Fineberg, 1991).

2. Regression of left ventricular hypertrophy (Jula and Karanko, 1994).

3. Prevention of stroke (Antonios and MacGregor, 1995).

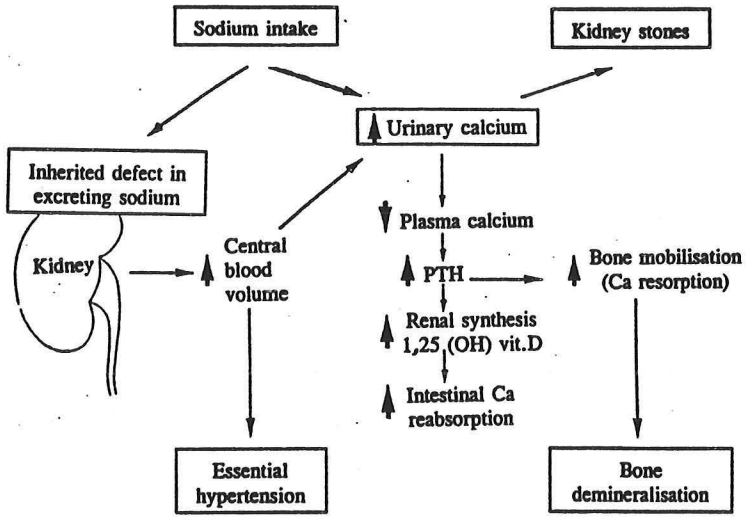


Figure 7: Possible link between the kidney, essential hypertension and bone demineralization. PTH = parathyroid hormone; 1,25 (OH) vit.D = 1,25-dihydroxyvitamin D. (From Antonios and MacGregor GA, 1995.)

4. Prevention of urinary stones and osteoporosis (Antonios and MacGregor, 1995).

5. Possible increase in myocardial infarction

A disturbing association has been reported between lower sodium intakes and myocardial infarction (Alderman et al, 1995). Among 1900 hypertensive men being treated with various antihypertensive drugs, those with 24-hour urine sodium excretion in the lower quintile (average 65 meq/day) had a 4.3 times greater relative risk of myocardial infarction than those in the upper quintile for sodium intake (average 215 meq/day) (Figure 8).

A number of features in this study, which raise questions about the validity of its findings, deserve emphasis:

- Only 46 events occurred in the entire group over a 3.8 year period.
- No association between sodium intake and myocardial infarction was found in women.
- No association between sodium intake and stroke was found in either sex.
- Only one 24-hour urine was collected in each patient, after four to five days of avoidance of high-salt foods.
- The lowest quintile must contain some patients on a very low salt intake, which may have deleterious effects.

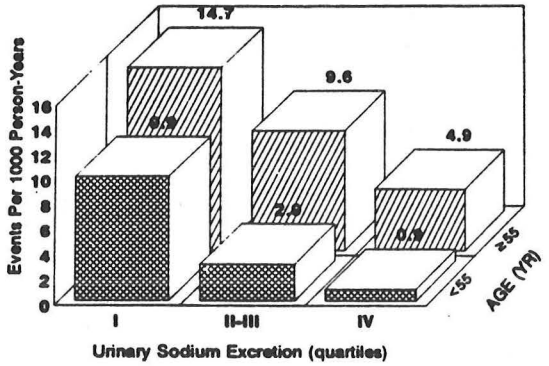


Figure 8: Bar graphs show incidence of myocardial infarction according to quartile of urinary sodium excretion and age, in men (From Alderman et al, 1995).

III. The good news about alcohol

Too much alcohol, beyond 3 usual portions per day of beer, wine or whiskey - each of which contain a little more than one ounce of alcohol - will raise the blood pressure (Vandogen and Puddey, 1994).

The right amount of alcohol, no more than one drink a day in women, two drinks a day in men will not raise blood pressure but will protect against coronary disease and mortality (Grønbæk et al, 1994; Doll et al, 1994) (Figures 9 and 10).

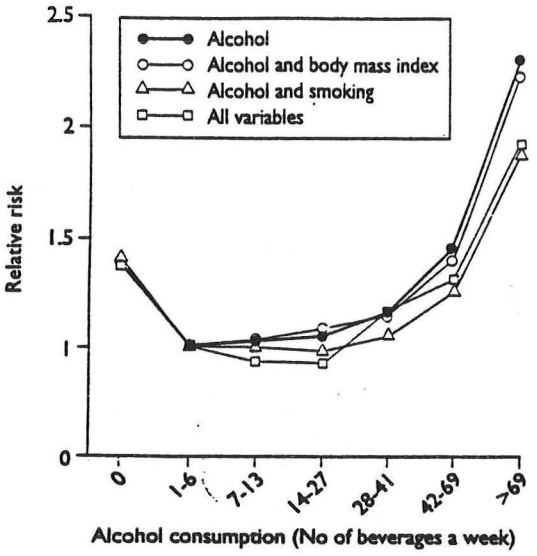


Figure 9: Relative risk of mortality in relation to alcohol intake in 14,223 men and women followed for 10-12 years after ascertainment. Curves describing estimates of different models and without covariates included. (From Grønbæk et al, 1994).

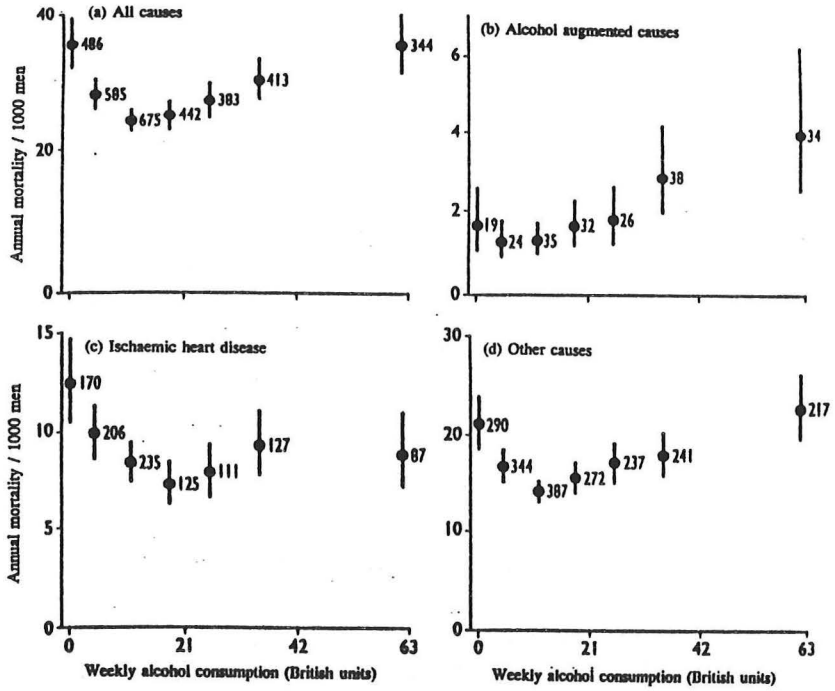


Figure 10: Annual mortality (per 1000 men) from (a) all causes (including unknown), (b) alcohol augmented causes (cancers of the liver, larynx, oesophagus, mouth, etc; cirrhosis; alcoholism; or external causes), (c) ischaemic heart disease , and (d) other known causes by alcohol consumption reported in 1978. Points are floating absolute risk and bars are 95% confidence interval standardized for exact age, smoking habit, and history of previous disease. Note different scales for events; values are numbers of deaths. (From Doll et al, 1994).

The recently promulgated U.S. Dietary Recommendations recognize, for the first time, that the drinking of such moderate amounts of alcohol provides benefit.

The mechanisms involve a rise in HDL-cholesterol (Savolainen and Kesäniemi, 1995); inhibition of platelet aggregation (Demrow et al, 1995) and increased fibrinolytic potential (Ridker et al, 1994); increased insulin sensitivity (Rimm et al, 1995); and, coronary vasodilation (Pirwitz et al, 1995).

A British cardiologist (M. J. Griffith, 1995) proposed this New Year's toast: "We have a duty to tell our patients and the wider public what lifestyle changes may be beneficial to them. The benefits of a change to a regular moderate intake of alcohol are equivalent to giving up smoking and are far greater than regular exercise or diet. The collected evidence (more than five million subject-years follow up) shows that moderate drinking is of more benefit than perhaps any other intervention in cardiology. Our advice should be 'consume one or two drinks a day, preferably with meals and perhaps red wine'. Patients already drinking at this level should be encouraged to continue, and lifetime teetotallers should be informed of the hazards of their continued abstinence. The hazards of heavy drinking should be highlighted and if necessary patients should be encouraged to cut their consumption. The timing and choice of beverage is not vital---a little of what you fancy does do you good."

Perhaps the best advice, more balanced than that of Griffith, is provided in "evidence-based guidelines... framed in terms of the absolute risks and benefits" as described by Jackson and Beaglehole (1995). They state:

"The epidemiological relation between light-to-moderate alcohol consumption (defined as up to about 3-4 standard units per day) and all-cause mortality reflects the competing risks and benefits of drinking. The risks of heavier drinking - i.e., above about 3-4 standard units per day - outweigh the benefits and are not in question. Light-to-moderate alcohol intake reduces the relative risk of coronary heart disease mortality by as much as 50%, and light drinking probably also reduces the risk of death from ischaemic stroke. Conversely, light-to-moderate alcohol intake increases mortality from hepatic cirrhosis, injury, haemorrhagic stroke, and probably from breast and large-bowel cancer."

"The relation between low levels of drinking and all-cause mortality will vary depending on a person's underlying (i.e., absolute) risk of these various causes of death. The groups most likely to benefit from drinking small amounts of alcohol are older people at high absolute risk of coronary heart disease and ischaemic stroke and at low absolute risk of injury, cirrhosis, and other alcohol-related disease, and vice versa.

"In men and women under the age of 40 years, alcohol consumption is associated with an increase in all-cause mortality even at low levels of consumption. As a group, young people have a very low absolute risk of coronary disease and a high absolute risk of injury.

"The mortality-related benefits of light-to-moderate drinking begin to outweigh the risks among men in their 40s and women in their 50s, although among women aged 50-70 years, all-cause mortality seems to be reduced only among those with at least one major coronary risk factor. As expected, the mortality-related benefits of light-to-moderate drinking continue to outweigh the risks among those over 60 years."

IV. The Calcium Antagonist (CA) Scare

A. Background

In 1963, the German physiologist, A. Fleckenstein, was asked by two pharmaceutical companies (Knoll and Hoechst) to examine two newly synthesized coronary vasodilators: prenylamine and verapamil. Fleckenstein found that they interfered with the mediator function of Ca^{++} in excitation - contraction coupling of heart and vascular smooth muscle, lowering Ca^{++}-dependent vascular tone and spasm (Fleckenstein, 1983).

Although the 3 major types of CAs act on different sites of the voltage-operated calcium channels, they all block the contraction and proliferation of various stimuli (including endothelin) but not the relaxation and antiproliferation induced by nitric oxide (Lüscher et al, 1995) (Figure 11). Nifedipine reversed endothelin-induced afferent renal vasoconstriction, maintaining renal blood flow (Kaasjager et al, 1995).

Verapamil was the first to be marketed, then diltiazem, and later a series of dihydropyridines beginning with nifedipine. The short-acting formulations of diltiazem and nifedipine were approved for both chronic stable and vasospastic angina but not for hypertension; the long-acting formulations of all three and the short-acting verapamil for both angina and hypertension. A CA but not an alpha, beta-blocker nor an ACE inhibitor completely normalized the hemodynamic abnormalities of hypertensive patients (Ting et al, 1995).

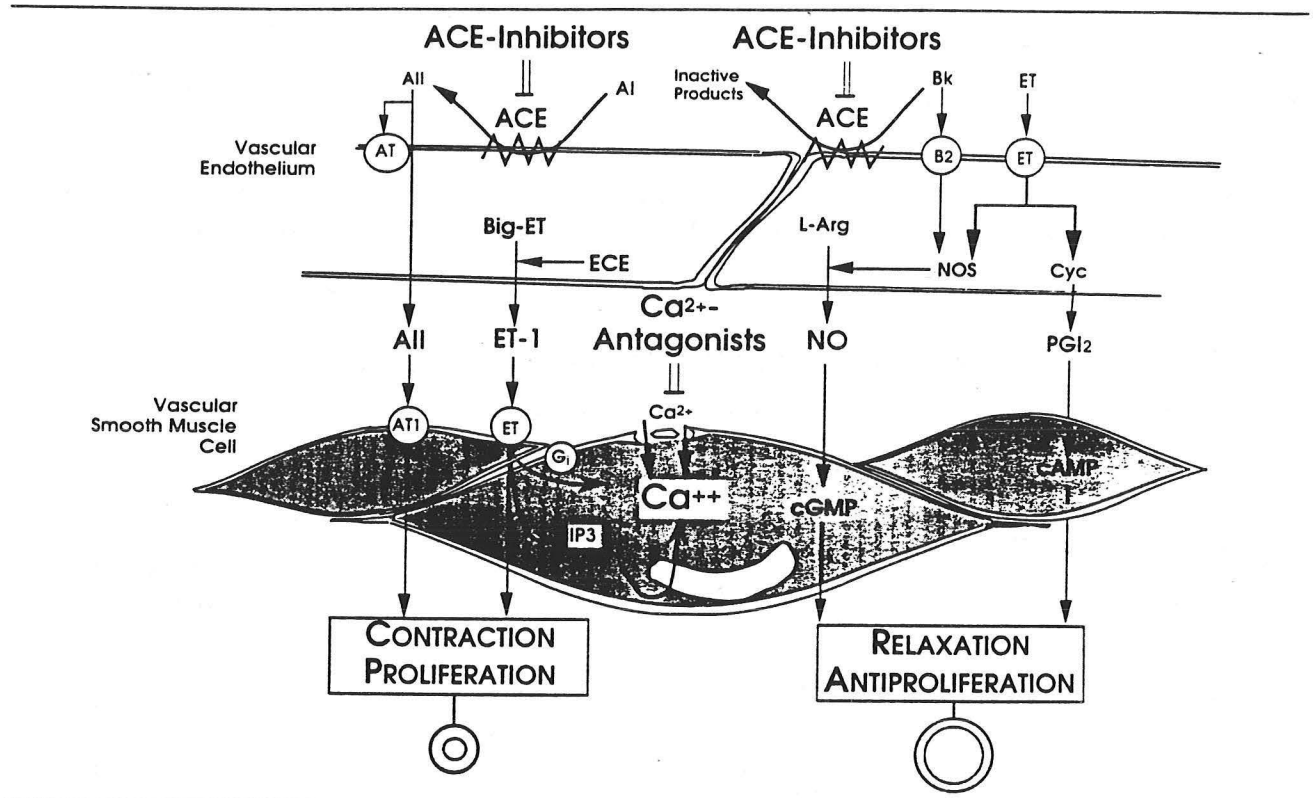


Figure 11: Local vascular effects of ACE inhibitors and calcium antagonists. While ACE inhibitors inactivate the formation of angiotensin I (AI) into angiotensin II (AII), as well as the inactivation of bradykinin (Bk) on endothelial cells, Ca^{2+} antagonists primarily interfere with Ca^{2+} influx at the level of the vascular smooth muscle. AT = angiotensin receptor; cAMP = cyclic 3',5'-adenosine monophosphate; cGMP = cyclic 3',5'-guanasine monophosphate; CYC = cyclooxygenase; ECE = endothelin converting enzyme; ET = endothelin; G_i = G_i protein; L-arg = L-arginine; NO = nitric oxide; NOS = nitric oxide synthase, PGI_2 = prostacyclin. (From Lüscher et al, 1995.)

B. Current use in hypertension

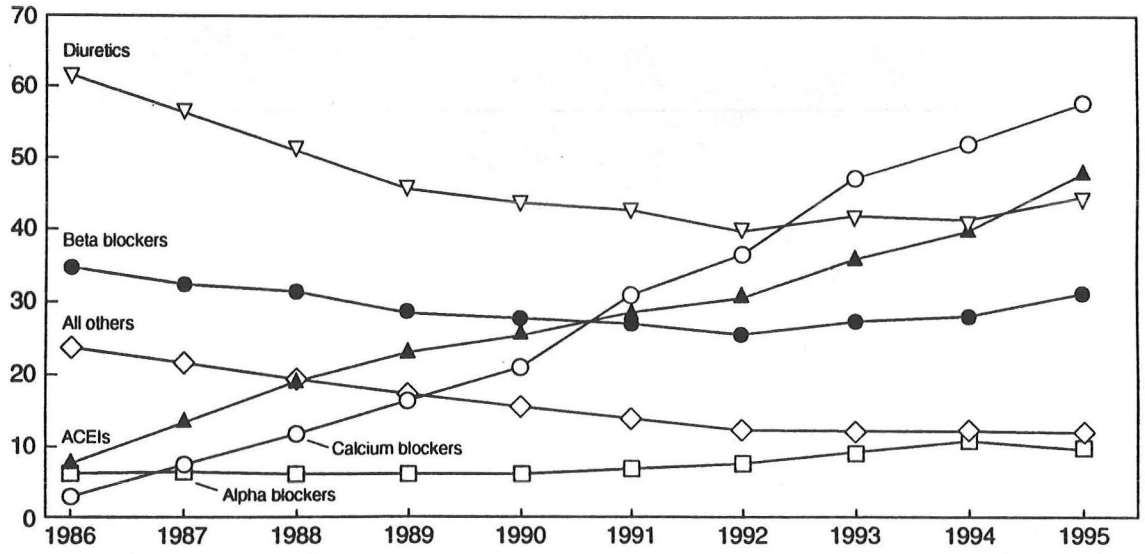
1. Efficacy: In the only two randomized, controlled trials of monotherapy with representatives of all 5 major classes of antihypertensive drugs, the CAs, diltiazem in the VA Cooperative Study (Materson et al, 1995), amlodipine in the TOMHS trial (Neaton et al, 1993), were the most effective and best tolerated (Table 5).

Table 5: Average Changes from Baseline at 48 Months in TOMHS. (Data from Neaton et al, 1993.)

	Chlorthalidone	Acebutolol	Doxazosin	Enalapril	Amlodipine	Placebo
Systolic BP	-14.6	-13.9	-13.4	-11.3	-14.1	-8.6
Diastolic BP	-11.1	-11.5	-11.2	-9.7	-12.2	-8.6
On original Rx (%)	67	78	66	68	82	58
LV mass (g)	-34	-24	-24	-26	-25	-27
HDL/TC	1.4	1.2	2.6	1.9	1.5	1.2

Since their introduction, particularly in long-acting formulations, CAs have rapidly become the most popular choice of antihypertensive therapy in the US, including at PMH, and most of the world (Kaplan, 1994).

Figure 12: U.S. ANTIHYPERTENSIVE MARKET TOTAL R_X'S (IN MILLIONS)



They work well in blacks (Skoularigis et al, 1995) and the elderly (Lacourciere et al, 1995).

2. Ancillary properties

In addition to correcting the hemodynamic alterations of hypertension (Ting et al, 1995), CAs may provide special ancillary effects.

a. Left ventricular structure and function

CAs lead to about as much regression of LV hypertrophy as other drugs (Skoularigis et al, 1995) although some report lesser regression than expected with felodipine given twice daily, presumably because of persisting sympathetic nervous overactivity (Leenen and Holliwell, 1992).

Dihydropyridines in general may not reduce the usual cardiac response to stress as well as the rate-limiting CAs. In one placebo-controlled, parallel study, one month of verapamil blunted the normal rise in functional cardiac load after stress, amlodipine did not (Nazzaro et al, 1995).

Nonetheless, even dihydropyridine CAs usually do not interfere with LV systolic performance (Skoularigis et al, 1995) and they have beneficial effects on LV diastolic filling, independent of changes in heart rate (Dohi et al, 1995).

b. Antiarrhythmic effects

Treated hypertensive patients with or without LVH have a high prevalence of complex ventricular arrhythmias (Mayet et al, 1995) which is almost certainly involved in their greater susceptibility to sudden death. Verapamil reduces ventricular ectopic activity in comparison to a diuretic (Messerli et al, 1989).

c. Antiatherosclerosis effects

In experimental animals, CAs inhibit cholesterol induced atherosclerosis (Henry and Bentley, 1981) and, in vitro, inhibit platelet-derived growth factor - induced proliferation of coronary vascular smooth muscle cells (Yang et al, 1993).

In humans, three large trials with chronic use of short-acting formulations of the dihydropyridines nifedipine or nicardipine showed that angiographic progression of coronary atherosclerosis was slowed without affecting pre-existing stenoses (Loaldi et al, 1989); Waters et al, 1990; Lichtlen et al, 1990) (Table 6). However, mortality was increased in the CA-treated half of the INTACT study (12 versus 2 on placebo), although new myocardial infarcts were not (11 versus 9 on placebo) (Lichtlen et al, 1990). These excess deaths all were seen in patients who had had a prior MI and 3 occurred in patients who had stopped nifedipine 2-4 months before.

Table 6: Progression of Minimal Lesions in Patients With at Least One Stenosis < 20% (From Waters et al, 1990.)

	Nicardipine (n=99)	Placebo (n=118)	p
Minimum Diameter Decrease ≥0.4 mm	**Progression per patient**		
None	87 (88)	90 (76)	0.035
At least one lesion	12 (12)	28 (24)	
1 Artery	12	25	
2 Arteries	0	3	0.039
Progression Per Lesion	13/178 (7.3)	33/233 (14.2)	
Percent Stenosis Increase ≥ 10%			0.046
None	84 (85)	86 (73)	
At least one lesion	15 (15)	32 (27)	
1 Artery	15	28	
2 Arteries	0	4	0.038
Progression Per Lesion	16/178 (9.0)	38/233 (16.3)	

The results of a large study comparing HCTZ to isradipine on the progression of carotid atherosclerosis (MIDAS) have been presented but never published. The data apparently show less progression on isradipine despite less antihypertensive efficacy of the CA but more morbidity with the CA (Hansson and Zanchetti, 1995). It should be noted that isradipine is a relatively short-acting agent, likely to induce sympathetic stimulation.

d. Preservation of antihypertensive efficacy with NSAIDs

All classes of antihypertensives except CAs have their efficacy blunted by concomitant intake of NSAIDs (Klassen et al, 1995; Polonia et al, 1995).

e. Preservation of antihypertensive efficacy with high sodium intake

CAs may also be unique in not having their antihypertensive efficacy blunted but rather enhanced by the usual high sodium intake of most people (Luft et al, 1991). However, despite a few negative findings, most find an additive effect of diuretics with CAs (Glasser et al, 1989; Burris et al, 1990).

f. Preservation of renal blood flow

ACE inhibitors have assumed a primary role in protection against progressive renal damage, particularly in diabetic nephropathy. In most, but not all, rat models, ACE inhibitors protect against progressive glomerulosclerosis but CAs do not (Griffin et al, 1995), presumably because the predominant afferent arteriolar vasodilation they induce leads to increased pressure transmission to the glomeruli.

In humans, dihydropyridines but not the other CAs usually increase proteinuria but all CAs maintain glomerular filtration rate and effective renal plasma flow and they may attenuate the decline in renal function (Velussi et al, 1996). The issue remains unsettled in the absence of large-scale, long-term trials. In the meantime, low doses of an ACEI and a CA may provide the best renoprotection (Fioretto et al, 1992; Bakris and Williams, 1995).

g. Other Special Indications

1) Primary pulmonary hypertension (Rich et al, 1992)

2) Severe aortic regurgitation with normal left ventricular function (Scognamiglio et al, 1994)

3) Congestive heart failure (Packer, 1995)

4) Subarachnoid hemorrhage (Fisher and Grotta, 1993)

5) Spontaneous and premature uterine contractions (Fenakel and Lurie, 1990)

C. Side effects

CAs have been better tolerated than other classes of antihypertensive drugs in the two comparative trials that have included representatives of all classes (Neaton et al, 1993; Materson et al, 1994). Long-acting formulations cause fewer of the common side-effects - constipation with verapamil, ankle edema with dihydropyridines - and overall quality of life is similar to that noted with other agents (Boissel et al, 1995).

D. Cardiac toxicity:

1. Post-myocardial infarction

a. Large doses (larger than 80 mg a day) of short-acting nifedipine may increase mortality in patents post MI or with unstable angina. In most of the trials with short-acting nifedipine there was no effect, beneficial or deleterious (Held et al, 1989). When another meta-analysis included a trial of patients with stable coronary disease (INTACT) and used 2 week but not 6 month data of the trial by Muller et al (1984), the increase in mortality became obvious (Furberg et al, 1995) (Figure 13).

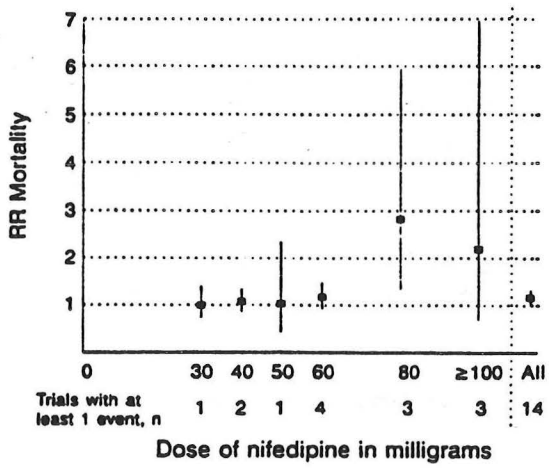


Figure 13: Graph showing risk of mortality in post-MI patients according to daily dose of nifedipine. RR indicates risk ratio. (From Furberg et al, 1995).

The principal investigators of the INTACT study noted that of the 12 deaths in the nifedipine group (versus 2 on placebo), 4 were of non-cardiac causes and 3 occurred more than 2 months after nifedipine had been discontinued (Lichtlen et al, 1995).

Opie and Messerli (1995) and Messerli (1995) recalculated the meta-analysis by Furberg et al without the INTACT data and with the 6 month data from the Muller trial. The p value and 95% confidence intervals go from 0.01 (1.05-1.43) in the Furberg analysis to 0.36 (0.91-1.28) in the corrected analysis.

b. Both verapamil and diltiazem have been found to protect post-MI patients who do not have heart failure (Weiner, 1992).

2. Hypertension

a. Psaty et al (1995) published a retrospective case-control study of the types of antihypertensive drugs prescribed to 623 patients who had an acute MI and to 2032 patients who did not. No differences were found in the use of diuretics, ß-blockers or ACE inhibitors between the 2 groups but there was a 60% increase in the use of short-acting CAs and a nondefined class of "vasodilators" among the patients who had an MI (Figure 14).

The increase in MIs with short-acting CAs were mainly with verapamil and diltiazem; the risk for users of nifedipine was less (p value = 0.22).

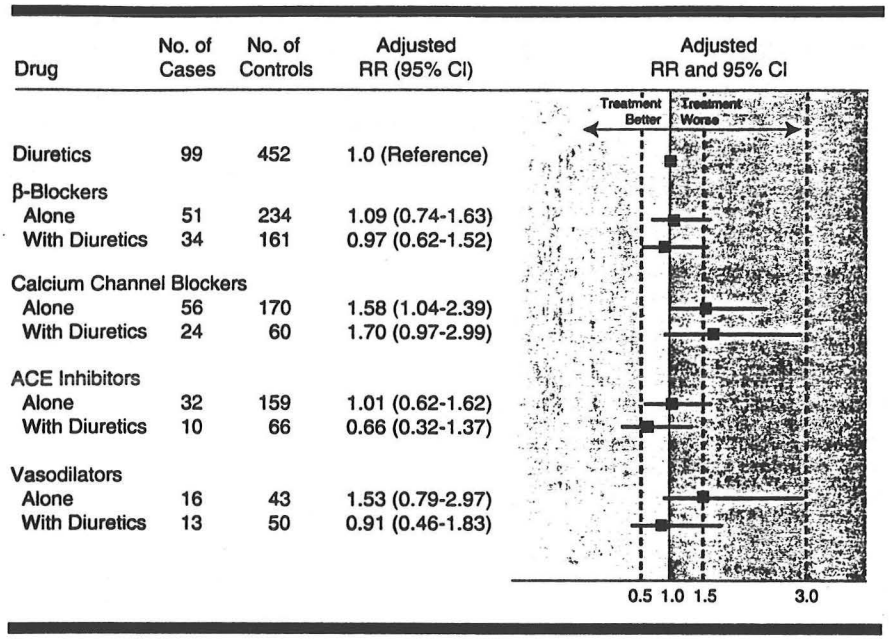


Figure 14: Association between myocardial infarction and antihypertensive drug therapies among subjects without any clinical cardiovascular disease. RR indicates risk ratio (boxes); CI, confidence interval (cross bars); ACE, angiotensin-converting enzyme. The RRs were all adjusted for age, sex, calendar year, smoking, diabetes, pretreatment systolic blood pressure, duration of hypertension, physical activity, and education. (From Psaty et al, 1995).

b. In a prospective cohort study, 906 hypertensives over age 70 were followed for up to 4 years while taking a ß-blocker, an ACE inhibitor, or one of 3 short-acting CAs (Pahor et al, 1995). The mortality rate was higher in those on nifedipine or diltiazem but they started with more coronary heart disease at baseline (Table 7).

c. On the other hand, in another case-control study, the risk for MI was *reduced by more than 50%* in those hypertensives on a long-acting CA compared to those on a diuretic or ß-blocker (Aursnes et al, 1995).

Table 7: Crude Mortality Rates per 906 Hypertensives Aged ≥ 71 Years over 4 years (Data from Pahor et al, 1995.)

	No.	CHD at Baseline	Mortality Rate/Yr	
			All-Cause	CHD
ACE inhibitors	148	21%	4.2	1.3
ß-blockers	515	32%	4.5	1.1
Verapamil	77	45%	4.6	1.0
Nifedipine (SA)	74	53%	11.8	3.9
Diltiazem	92	78%	8.0	3.2

A phenomenal amount of publicity followed the oral presentation of the Psaty data in March 1995, largely generated by a press conference given by the authors. Inflammatory headlines such as "Blood Pressure Pills Cause Heart Attacks" created (in the words of Dr. Psaty himself) "a public health hazard" with hundreds of patients discontinuing CAs and some suffering exacerbation of coronary disease and loss of control of hypertension. If nothing more, the CA scare prompted strong advice on how to avoid such fiasco's in the future (Lenfant, 1995).

The scenario duplicates one that occurred in September 1974 when three case-control studies were simultaneously published in the Lancet, all from prestigious epidemiological centers, all showing a 300% increase in breast cancer among women who took reserpine for treatment of hypertension (Boston Collaborative, 1974; Armstrong et al, 1974; Heinonen et al, 1974). The FDA considered withdrawing reserpine from the market, a major step since it was then the second most popular antihypertensive drug.

Cooler heads prevailed and a stream of prospective studies then appeared, all of which showed no association between reserpine use and breast cancer (Labarthe and O'Fallon, 1980). The false relationship claimed in the 3 case-control studies was shown to be caused by the exclusion from the controls of patients with cardiovascular disease who were likely to have taken reserpine and who had an increased risk for breast cancer (Horwitz and Feinstein, 1985).

Horwitz and Feinstein (1979) had previously documented this source of error and many more which are common to case-control and cohort studies: They reviewed 17 topics in which conflicts arose, all of which turned out to prove the case-control studies to be wrong. Table 8 shows 8 of them, including the reserpine-breast cancer error.

Table 8: Disparities in Case-Control and Cohort Studies (From Horwitz and Feinstein, 1979.)

Topic and Hypothesis	Number of Studies	
	Supportive	Nonsupportive
Normal lactation and breast cancer (protective)	2	4
Circumcision and cervical cancer (protective)	2	6
Allergy and malignancy (protective)	4	4
Appendectomy and neoplasia (causal)	3	5
Coffee drinking and bladder cancer (causal)	3	2
Tonsillectomy and Hodgkins disease (causal)	2	3
Coffee drinking & myocardial infarction (causal)	2	3
Reserpine and breast cancer (causal)	3	8

The problem was nicely described in an editorial which accompanied the Psaty paper by Buring et al (1995):

> "The greatest limitation of this and other case-control studies relates to the fact that in this design primary health care providers selected particular patients for a given antihypertensive drug regimen. This self-selection is likely to have introduced at least modest biases into the results because of differences between those who were prescribed calcium channel blockers and those who were prescribed other antihypertensive medication....Patients characteristics are important determinants of choice of antihypertensive drug therapy. Thus, in the current study, patients prescribed calcium channel blockers are likely to have been systematically different from those on other drugs, perhaps in even subtle ways that related to the severity of their illness, their prior medical history, or other factors that would independently affect their subsequent risk of myocardial infarction."

More case-control and cohort studies will likely follow those of Psaty et al and Pahor et al since CAs almost certainly have been and will continue to be selectively used in patients at higher risk of coronary disease. There will almost certainly be some with long-acting CAs as well, since they share the same indications for coronary disease and hypertension.

Another flagrant example of how misleading case-control studies can be is the paper by Hoes et al in the October 1, 1995 Annals of Internal Medicine showing that the use of ß-blockers increased the risk for sudden cardiac death by 70% over the use of other antihypertensive drugs (including CAs) (Hoes et al, 1995) (Figure 15). As richly documented by Kendall et al in the September 1, 1995 Annals, one thing is certain about ß-blockers from multiple prospectives studies: they prevent sudden cardiac death (Kendall et al, 1995) (Figure 16). For sure, patients at risk for sudden death were most likely given ß-blockers in the study by Hoes et al.

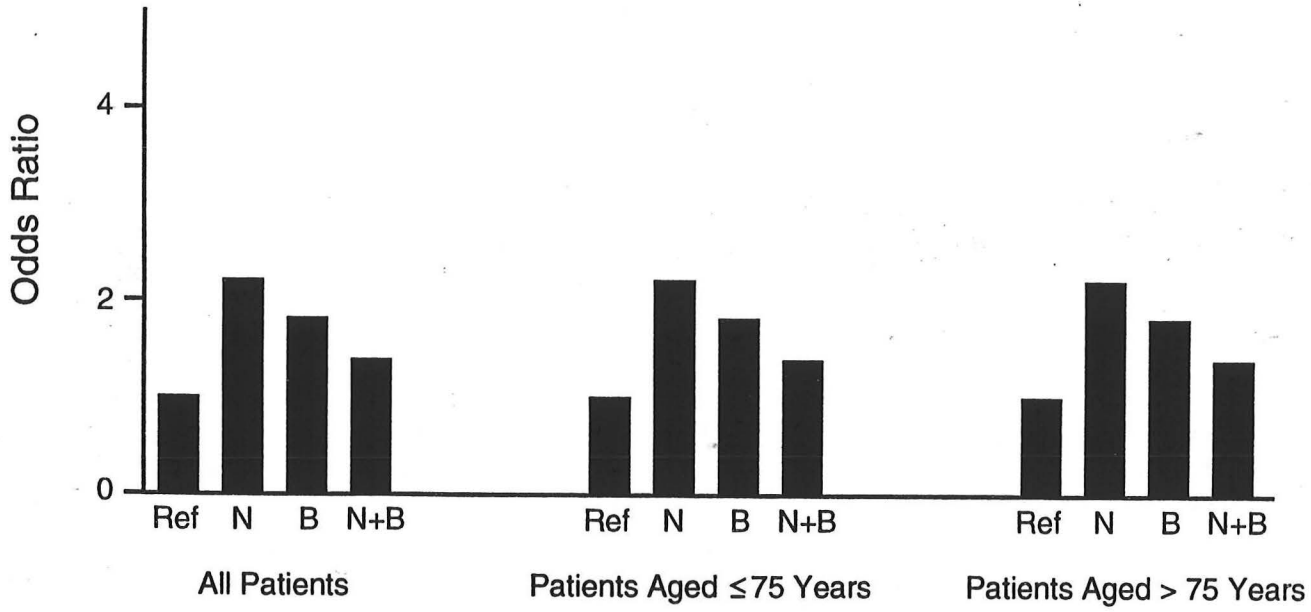


Figure 15: Antihypertensive medication and the risk for sudden cardiac death in patients aged 75 years or younger (n = 242) and those older than age 75 years (n = 272). Ref = reference group consisting of patients receiving antihypertensive drugs other than non-potassium-sparing diuretics and ß-blockers; N = patients receiving non-potassium-sparing diuretics without ß-blockers; B = patients receiving ß-blockers without non-potassium-sparing diuretics; N + B = patients receiving non-potassium-sparing diuretics and ß-blockers. (From Hoes et al, 1995).

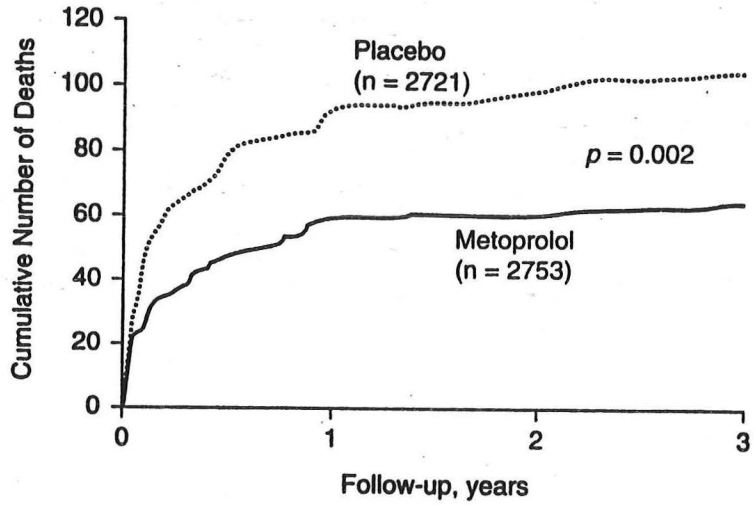


Figure 16: Cumulative number of sudden deaths reported in five postinfarction trials. (From Kendall et al, 1995.)

Why do presumably well-informed epidemiologists keep falling into this trap and why do journals keep accepting their erroneous results? Both authors and editors should go back to read G.D. Friedman's Primer of Epidemiology, page 119:

> "Case-control studies are the most readily and cheaply carried out of all analytical epidemiologic studies. For rare diseases they may be the only practical approach. Yet the problems involved in locating a representative group of cases, selecting appropriate control groups, and collecting comparable information on cases and controls are often of such magnitude that the results of case-control studies are open to a variety of legitimate questions and objections."

E. The attack on long-acting CAs

The publication of the Psaty and Furberg papers has unleashed a major attack on the use of CAs for the treatment of hypertension, an attack that is supported in a major way by a pharmaceutical company that does not market a CA but that does market major competing drugs.

The perpetrators of this attack start with the premise that the case-control studies do prove a causal connection between CAs and MI and that the inappropriate use of massive doses of short-acting nifedipine in the hemodynamically vulnerable post-MI patient incriminates the appropriate use of long-acting CAs in all patients. To justify their attack, they have marshalled evidence for 5 "plausible and potentially harmful mechanisms." I will address the evidence for these 5 mechanisms both with short-acting and long-acting CAs. I will show that only some of the claims about short-acting CAs are valid and that none of them likely apply to the long-acting agents.

1. Proischemia due to coronary steal

a. Short-acting CAs: Furberg (1995) refers to the small randomized trial by Egstrup and Anderson (1993) which showed symptomatic benefit from short-acting nifedipine in patients with angina and no collateral circulation but an increase in angina in those with collaterals, concluding that "increased ischemic activity may be due to a coronary steal phenomenon." However, as Kloner (1995) points out "No measure of coronary flow or perfusion was provided to document coronary steal."

Kloner goes on to describe 8 additional studies which "have failed to show that nifedipine causes a coronary steal phenomenon when coronary perfusion was assessed; most suggest that it has a favorable effect on coronary perfusion in humans....It is more likely that the patient who develops worsening angina with nifedipine capsules is either having a decrease in coronary perfusion pressure due to too rapid a drop in blood pressure, an increase in heart rate due to reflex tachycardia causing an increase in oxygen demand, or an increase in other sympathomimetic activities (including contractility) that could increase oxygen demand. This scenario is much less likely to develop with the slower-onset, longer-acting calcium blockers that lack large peak-to-trough fluctuations in drugs levels."

Although combined therapy with aspirin, ß-blockers and CAs is obviously the appropriate medical therapy for unstable angina, IV diltiazem was significantly better than IV glyceryl trinitrate in a randomized, double-blind trial (Göbel et al, 1995). The authors conclude "that IV diltiazem significantly reduces ischemic events and can be used safely in patients with unstable angina."

b. Long-acting CAs: As Kloner suggests, a number of controlled studies with long-acting CAs have shown reduction in myocardial ischemia, including nifedipine GITS (Parmley et al, 1992), felodipine (Trenkwalder et al, 1994) and amlodipine (Deanfield et al, 1994).

The data by Parmley et al (1992) and Deanfield et al (1994) support a particular advantage of long-acting CAs: a decrease in the incidence of early morning ischemic events.

2. Negative inotropic effect

a. Short-acting CAs: In isolated myocardial preparations, all CAs exert negative inotropic effects. In patients with decreased systolic function, first generation CAs increase the risk of developing heart failure. However, the intrinsic negative inotropic effects of dihydropyridines are greatly modified by increased ß-adrenergic tone from the activation of baroreceptors from peripheral vasodilation.

b. Long-acting CAs: The second-generation of dihydropyridines (amlodipine, felodipine) are more vascular-selective and do not have negative effects on cardiac contractility (Epstein, 1995). Furberg (1995) admits that "Treatment with amlodipine may have a different effect in patients with congestive heart failure," referring to the positive results of the PRAISE trial of patients with severe CHF. In addition, felodipine did not increase mortality in severe CHF in the V-HeFT III trial and improved those with coronary disease.

3. Proarrhythmic effects

a. Short-acting CAs: As Furberg (1995) states "Treatment with diltiazem [in the Multiple Diltiazem Postinfarction Trial] had no effect on the frequency of PVCs or unsustained ventricular tachycardia." (Where's the proarrhythmia?). But then he goes on to make an egregious misstatement: "However, it appears that CAs increase the risk of fatal cardiac rearrests in survivors of out-of-hospital ventricular fibrillation (Roine et al, 1990)." In fact, one only needs to read the summary of the placebo-controlled double-blind, randomized trial of nimodipine in 155 consecutive resuscitated patients: "Recurrent ventricular fibrillation during the treatment occurred in one patient in the nimodipine group compared with 12 patients in the placebo group." One-year cumulative survival was insignificantly improved for all patients but significantly better in the subgroup with more than a 10 minute delay in resuscitation (Figure 17).

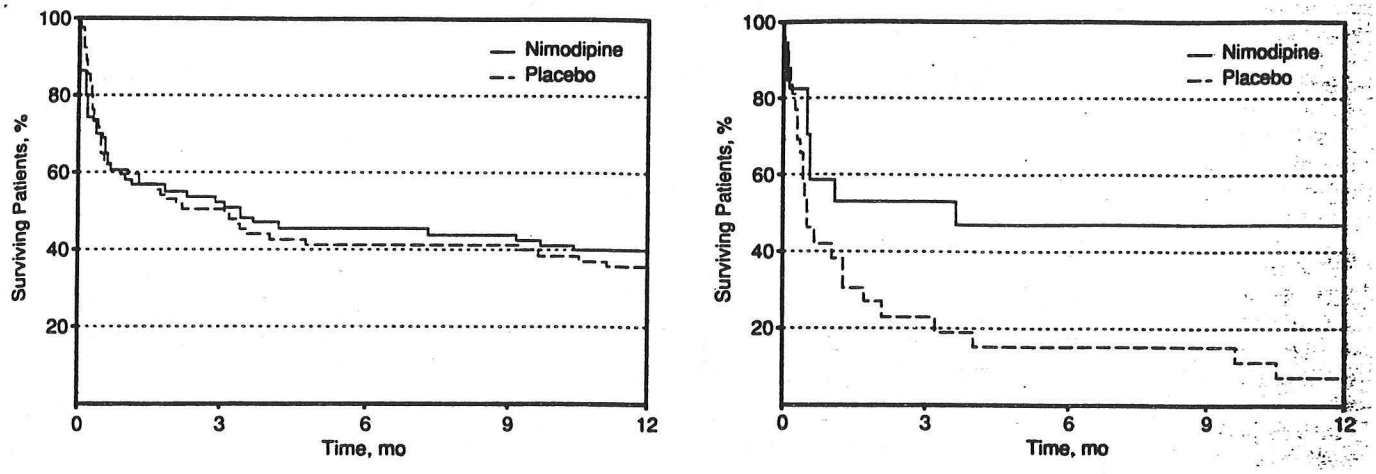


Figure 17: One-year cumulative survival in 155 patients with out-of-hospital ventricular fibrillation (left), and in the subgroup of 43 patients with advanced life support delays exceeding 10 minutes (right). (From Roine et al, 1990).

b. Long-acting CAs: Sustained-release verapamil significantly reduced ventricular ectopic activity in hypertensive patients whereas a diuretic did not (Messerli eta l, 1989). No increase in VEA was noted in the trials of nifedipine GITS (Parmley et al, 1992) or amlodipine (Deanfield et al, 1994) in patients with coronary disease.

4. Prohemorrhagic effects

Furberg (1995) states "CAs have an antiplatelet effect that theoretically might be beneficial. This action, which is much weaker than aspirin, together with peripheral vasodilation may, however, predispose selected patients to bleeding complications."

In support of this conclusion, he refers to 2 studies in which a CA was given in addition to other agents which could increase bleeding. The first revealed an increase in hemorrhagic strokes in the TIMI II trial of thrombolytics after an acute MI from 0.4% in those not receiving CAs to 1.5% in those who did (Gore et al, 1991). The second was a placebo-controlled randomized trial of nimodipine in patients undergoing cardiac valve replacement that was stopped prematurely because major bleeding (10 of 75 versus 3 of 74) and mortality (8 of 75 versus 1 of 74) were more common in those receiving the CA (Wagenknecht et al, 1995).

Furberg failed to note multiple controlled trials with the same CA that showed no increase in hemorrhagic complications while providing overall benefit, including these:

- nimodipine in the prevention of delayed ischemia after aneurysmal subarachnoid hemorrhage in 213 patients (Öhman et al, 1991)

- nimodipine in 852 severely head-injured patients (European Study Group, 1994)

- nimodipine in 4555 patients with aneurysmal subarachnoid hemorrhage (Dorsch, 1994)

- nimodipine in almost 400 patients with an acute ischemic stroke (Gelmers et al, 1988; Martinez-Vila et al, 1990)

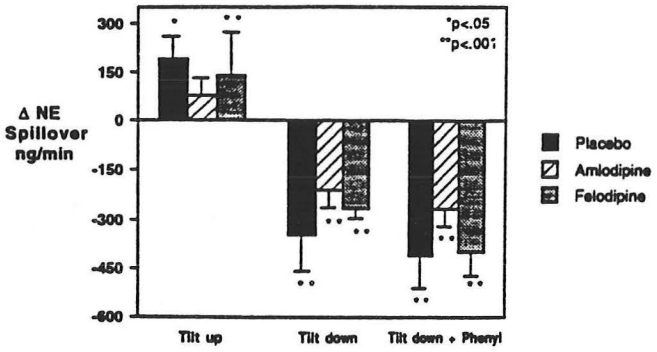
5. Marked hypotension

a. Short-acting CAs: Here, finally, Furberg is correct: short-acting nifedipine, either sublingual or swallowed, will abruptly lower blood pressure and has occasionally induced cerebral and myocardial ischemia (Yagil et al, 1982; Phillips et al, 1991). But, even here, Furberg goes too far: In referring to the study by Phillips et al, he states that "Hypoperfusion of the subendocardium and major T-wave inversions are induced in up to 25% of patients." As noted in the Summary by Phillips et al "Rapid and marked reduction of blood pressure with nifedipine is accompanied by a high incidence of asymptomatic T-wave inversions which are not accompanied by left ventricular wall motion abnormalities, suggesting that significant myocardial ischemia did not occur."

b. Long-acting CAs: Unlike the abrupt effects of short-acting CAs (which were never approved for the treatment of hypertension), long-acting formulations provide a slow onset, and a sustained antihypertensive efficacy with minimal peak-to-trough fluctuations, thereby minimizing the activation of sympathetic and renin-angiotensin systems seen with the short-acting CAs (Frohlich et al, 1991; Phillips et al, 1992).

Single doses of felodipine, 10 mg, and amlodipine, 5 mg, were shown not to alter baseline sympathetic activity or to acutely sensitize baroreceptor function (Goldsmith, 1995) (Figure 18). Furthermore, chronic administration of verapamil suppressed sympathetic activity, while no changes were seen with felodipine (Kailasman et al, 1995).

Figure 18: Changes in norepinephrine (NE), spillover between baseline and various experimental conditions (head-up tilt, and phenylephrine) after placebo, amlodipine, and felodipine. There were no statistically significant differences in the degree of any response on each of the 3 study days. (From Goldsmith SR, 1995.)



Epstein (1995) invokes these major differences in the hemodynamic and hormonal responses to short-acting CAs versus long-acting CAs to explain the inability to show regression of atherosclerosis and the occurrence of increased adverse vascular events in all of the currently available studies, all using short-acting CAs: "Medications provoking a counterregulatory response with cardioacceleration may exacerbate ischemia in patients with basal myocardial ischemia. Conversely, agents producing true steady-state levels do not evoke such unwanted counterregulatory responses, and consequently, may not promote increased adverse vascular events."

F. The Clinical Implications

If one accepts Furberg's "hypothesized relationships among drug effects, mechanism and adverse clinical effects" (Figure 19), his advice should be followed: "Clinicians have several choices. One is to dismiss the troubling data and expose patients to potentially unnecessary risks until conclusive information is available from the ongoing trials. Such as position assumes that the adverse findings for a drug or class of drugs in one population (patients with coronary disease) do *not* apply to another population (patients with hypertension). It also assumes that pharmacokinetic alterations of the rate of absorption eliminates adverse effects. Whether the new formulations differ in their effect on major disease end points remains to be seen." (Furberg disregards the major pharmacodynamic difference between short and long-acting CAs).

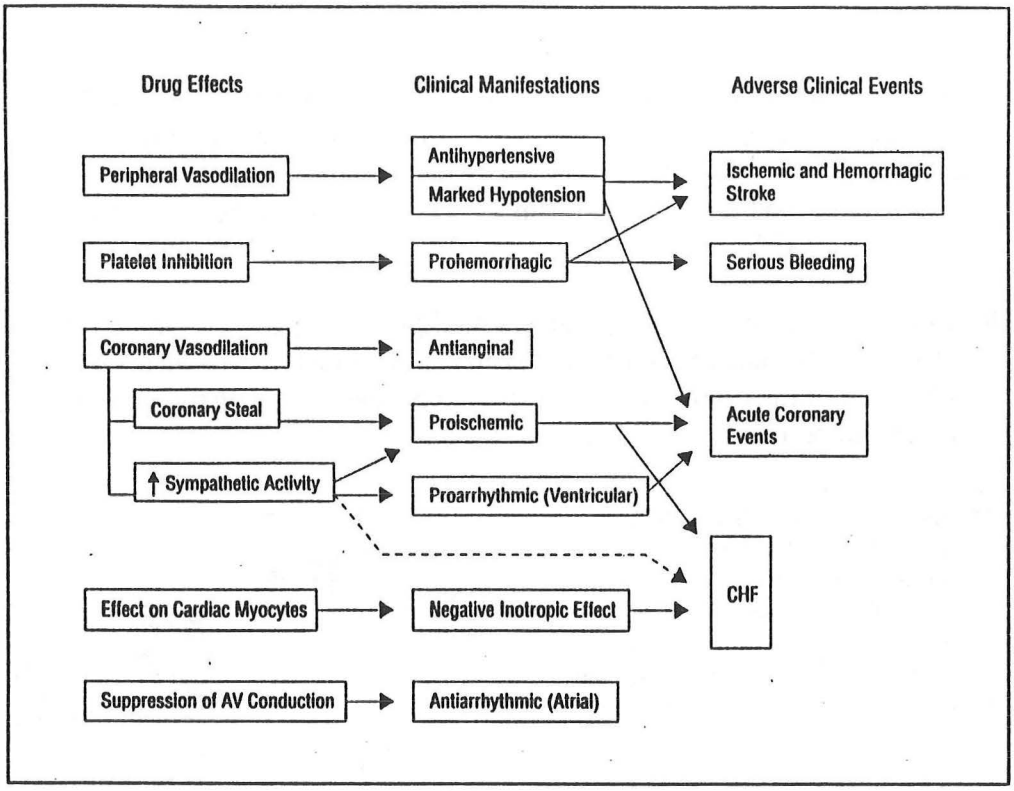


Figure 19: Hypothesized relationships among drug effects, mechanisms, and adverse clinical events. AV indicates atrioventricular; CHF, congestive heart failure. (From Furberg and Psaty, 1995).

I believe most of Furberg's arguments are biased, if not specious. On the other hand, I fully accept his warnings about the hazards of short-acting CAs. It is his assumption that these hazards also apply to long-acting formulations that I cannot accept (Table 9).

Table 9: POTENTIAL HARMFUL EFFECTS OF CALCIUM ANTAGONISTS

Effect	Short-acting Nifedipine	Long-acting Agents
Proischemic effect	**Unlikely**	**No**
Negative inotropic effect	**Yes**	**Minimal**
Effects on rhythm	**Unproven**	**No**
Prohemorrhagic effects	**Unproven**	**No**
Marked hypotension	**Yes**	**No**
Reflex increase in sympathetic activity	**Yes**	**No**

Despite Furberg's statement that "whether the new formulations differ in their effect on major disease end points remains to be seen," there are now data confirming positive effects of long-acting CAs on mortality in various conditions (Table 10). Full publications of all of these should soon appear.

Table 10: Mortality Data in Recent Trials of CCBs

			Mortality / No. Pts	
Study	**Disease**	**CCB**	**CCB**	**Placebo**
PRAISE	**CHF**	**Amlodipine**	**190/571**	**223/582**
VHeFT III	**CHF**	**Felodipine**	**31/224**	**29/227**
DEFIANT II	**Post-MI**	**Nisoldipine**	**1/271**	**7/271**
STONE	**Hypertension**	**Nifedipine**	**15/817**	**26/815**

In view of my interest in hypertension, further details about the Shanghai Trial of Nifedipine in the Elderly (STONE) are shown in Table 11.

Table 11: Shanghai Trial of Nifedipine in the Elderly (STONE)
Gong L, et al.
Seventh Meeting on Hypertension
Milan, Italy: 9-12 June, 1995

1,632 hypertensives aged 60-79: random allocation to placebo or nifedipine for up to three years.

Terminating events: death, stroke, CHF, MI, angina, severe arrhythmia, uremia, hospitalization for severe illness.

Analysis by Cox proportional hazard model: intention to treat:

	Subjects	**Events**	**CV Events**	**Mortality**
Placebo	**814**	**77**	**59**	**26**
Nifedipine	**818**	**32**	**23**	**15**

Multiple controlled trials with long-acting CAs are now in process so much more definitive evidence will soon be available.

G. Conclusion

At a time when only 21% of Americans with hypertension have their disease under adequate control (Figure 20) (Burt et al, 1995), it would be foolhardy to discard a class of drugs that are so effective and so well tolerated. As a member of JNC-5, I certainly agree with its recommendation that diuretics or beta-blockers be preferred unless special indications for alpha-blockers, ACE inhibitors, or CAs recommend their use. Currently available long-acting CAs work well, often far better than diuretics or other agents (Lacourciere et al, 1995). Therefore, when indicated (as described previously), they should be used with assurance that they are both effective and safe. That is the position recommended by the FDA Cardiorenal Advisory Committee on January 26, 1996, a position with which I wholeheartedly agree.

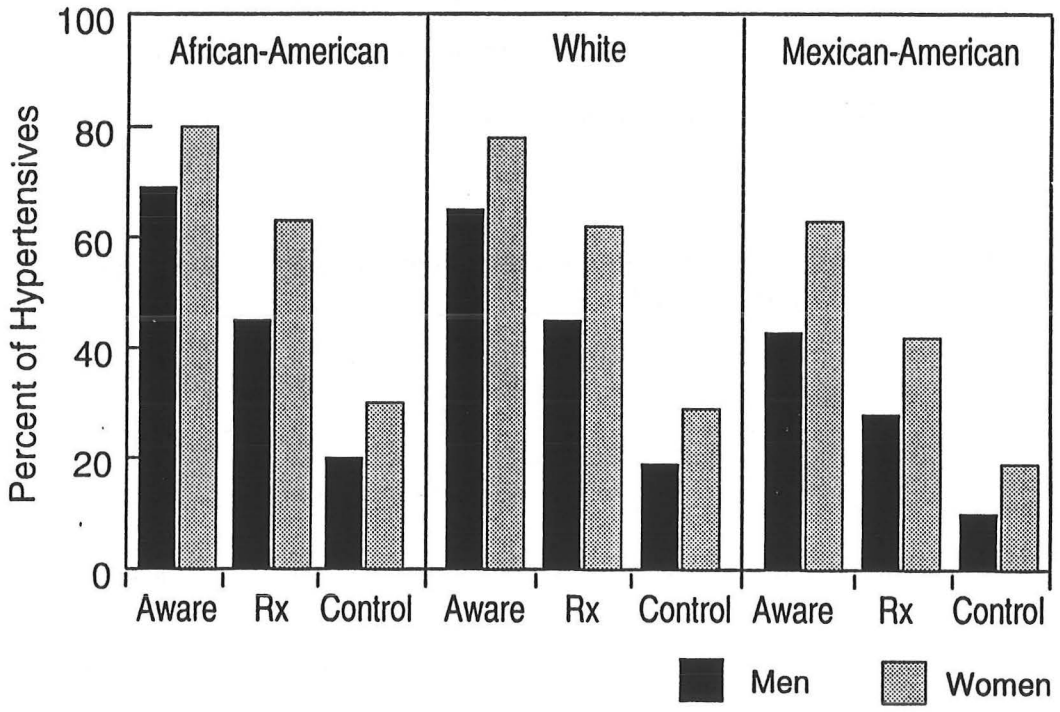


Figure 20: Data from the NHANES-III survey on hypertension awareness and control in different race/ethnic groups in the United States between 1988 and 1991. The majority of patients were aware of hypertension, but less than one-fourth achieved adequate control. (From Burt VL et al, 1995.)

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