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Adverse Effects of Diuretics

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Summary

Analysis of the available evidence indicates that diuretics do not increase coronary heart disease morbidity and mortality. The multiclinic trials supporting the cardiotoxicity hypothesis are few in number and flawed in design. The majority of the trials, including the well designed trials, indicate no excess of coronary heart disease (CHD) events in diuretic-treated patients compared with those given other drugs or placebo.

Recent studies indicate no increase in cardiac arrhythmias after diuretic treatment. Also, although depletion of intracellular potassium and magnesium occurs in patients with congestive heart failure even without diuretics, intracellular concentration of these ions is not significantly reduced by diuretics in patients with uncomplicated hypertension.

Modest elevations of serum cholesterol may occur during the first 6 to 12 months of treatment with thiazide diuretics. However, after this time these elevations fall to or below the pretreatment level. The fall may be greater in patients receiving other drugs but the differences are small and their clinical significance is questionable.

The incidences of hyperglycaemia and diabetes were only minimally increased in long term clinical trials while the importance of hyperinsulinism and insulin resistance in causing CHD remains unproven in patients. Thiazides remain, therefore, a safe and effective treatment for patients with hypertension.

Few drugs in common use today have been accused of more serious adverse effects than the thiazides and related diuretics. The allegations include increased risk of myocardial infarction and sudden death due to either associated hypokalaemia, hypomagnesaemia, hypercholesterolaemia or hyperinsulinism. Additional reactions include hyperglycaemia with aggravation of diabetes as well as the nonketotic, hyperglycaemic syndrome. Hyperuricaemia is common but seldom leads to gout. In addition, diuretics have been associated with adverse effects on quality of life including impotence, fatigue and weakness. This review assesses the validity of these alleged reactions.

1. Do Thiazide Diuretics Cause Myocardial Infarction or Sudden Death?

The multiclinic trials have shown a striking reduction in stroke but with few exceptions they have shown little benefit in preventing the complications of coronary heart disease (CHD) [table I]. It has been proposed that the difference might be due to adverse effects of the thiazides which were used as 1 treatment arm in the major clinical trials.

It is widely believed that the above hypothesis has gained support from the Multiple Risk Factor Prevention Trial (Multiple Risk Factor Intervention Trial Research Group 1985b). The patients were randomly assigned to 2 groups: the special intervention (SI) group treated in hypertension clinics in large teaching hospitals, and the usual care (UC) group who were referred to their usual community care facilities. There was no essential difference in CHD mortality in the 2 groups (table I). However, subgroup analysis of the patients who had minor baseline resting electrocardiogram (ECG) abnormalities revealed insignificantly greater CHD mortality in the SI than in the UC patients. Could this be due to thiazide treatment which was given more frequently to the SI patients?

The hypothesis seems unlikely for the following reasons: (a) another retrospective analysis from the same study (Multiple Risk Factor Intervention Trial Research Group 1985a) in patients who had abnormal baseline exercise ECGs indicated a 57% higher CHD mortality in the UC patients than in the SI group ($p = 0.002$). This was directly contradictory to the previous subgroup analysis; (b) the results of nonrandomised subgroup analysis are known to be unreliable, as was shown by these 2 opposing results; (c) the trial was not a clear comparison of diuretics versus placebo or other drugs, as only 56% of the SI group received diuretics while 33% of the UC group received similar treatment, over half of whom were given rather large doses; (d) the results were skewed in the UC group with minor resting ECG abnormalities in that they exhibited an abnormally low CHD mortality, lower than the UC group without such baseline abnormalities; (e) there were no correlations between CHD mortality and hypokalaemia or with size of the diuretic dose. Also, the more reliable total randomised trial showed no difference in CHD mortality between the SI and UC groups. The above evidence, therefore, provides no convincing support for the existence of cardiotoxicity due to thiazides.

The Metoprolol Atherosclerosis Prevention in Hypertension Study (MAPHY trial) found more CHD mortality with thiazides than with metoprolol (Wilkstrand et al. 1988). However, the MAPHY trial was a subgroup of the Heart Attack Primary Prevention in Hypertension trial (HAPPHY trial). The parent HAPPHY study reported no significant difference between the diuretic- and β-blocker-treated groups in CHD mortality (Wilhelmsen et al. 1987). The other subgroup that made up the HAPPHY trial (receiving atenolol), therefore, must have had fewer CHD deaths with thiazides than with β-blockers.

The Oslo trial (Holme et al. 1984) indicated a higher CHD death rate with thiazides, but this study was too small to draw any valid conclusions (6 deaths per 1000 patient years in thiazide recipients versus 2 in the placebo group).

These observations indicate that the evidence for diuretic-induced CHD mortality derived from only a minority of the clinical trials is weak and contains many contradictions. On the other hand, there were 9 other therapeutic trials which found quite different results (table I). The largest and one

Table I. Coronary heart disease (CHD) mortality and morbidity with thiazides versus placebo or other drugs (from Freis 1989, published with permission from the American Medical Association)

Trial	No. of patients	Diuretic and dose (mg)	All CHD events		Fatal CHD events	
			thiazide	other	thiazide	other
Trials associating thiazides with increased CHD risk						
MRFIT (Multiple Risk Factor Intervention Trial Research Group 1985b)	2 478[a]	Chlorthalidone; hydrochlorothiazide 50			29.2[b]	17.7
Oslo trial (Holme et al. 1984)	747	Hydrochlorothiazide 50	20[c]	13	6[c]	2
MAPHY (Wilkstrand et al. 1988)	3 234	Hydrochlorothiazide 50-100; bendroflumethiazide 5-10			43[d]	36
Trials indicating thiazides do not increase CHD risk						
EWPHE (Amery et al. 1985)	840	Hydrochlorothiazide 25-50; triamterene 50-100			12[c]	23
MRC (Medical Research Working Party on Mild Hypertension 1985)	17 354	Bendroflumethiazide 10	5.2[c]	5.5	2.5[c]	2.3
Veterans Administration (Veterans Administration Cooperative Study Group on Antihypertensive Agents 1970)	380	Hydrochlorothiazide 100	11[e]	13	6[e]	11
Australian trial (Report by the Management Committee 1980)	3 427	Chlorothiazide 500-1000	70[e]	88	2[e]	8
Public Health Service (Smith 1977)	785	Hydrochlorothiazide 50	8[e]	7	2[e]	2
HDFP (Williams et al. 1986)	10 940[f]	Chlorthalidone 25-100			131[d,e]	148[d]
HAPPHY (Wilhelmsen et al. 1987)	6 569	Bendroflumethiazide 5 hydrochlorothiazide 50	9.5[c]	10.6	4.1	4.4
IPPPSH[g] (The IPPPSH Collaborative Group 1985)	6 372					
MPPCD[h] (Miettiner et al. 1985)	1 203	Hydrochlorothiazide 50				

a Subgroup with baseline ECG abnormality among 12 888 total patients.
b Per 1000 patients.
c Per 1000 person-years of observation.
d Total deaths due to myocardial infarction plus other ischaemic heart disease.
e Number of events.
f Total patients. See text for analysis of subgroups with and without resting ECG abnormalities.
g Randomised to receive placebo or oxprenolol, but diuretics were soon added in 67% of the oxprenolol group and 82% of the placebo group. Numerical data were not given but no significant association found between diuretic usage and cardiovascular events.
h Coronary events tended to be accumulated in subgroups treated with β-blocking agents or clofibrate but there were few in those receiving probucol or diuretics.

Abbreviations: MRFIT = Multiple Risk Factor Intervention Trial; ECG = electrocardiogram; MAPHY = Metoprolol Atherosclerosis Prevention in Hypertension study (a subgroup of the Heart Attack Primary Prevention in Hypertension [HAPPHY] trial); EWPHE = European Working Party on High Blood Pressure in the Elderly; MRC = Medical Research Council of Great Britain; HDFP = Hypertension Detection and Follow-up Program; IPPPSH = International Prospective Primary Prevention Study in Hypertension; MPPCD = Multifactorial Primary Prevention Trial of Cardiovascular Disease in Middle-Aged Men.

of the best controlled trials was the Medical Research Council (MRC) trial of Great Britain (Medical Research Working Party on Mild Hypertension 1985). Propranolol, thiazide or placebo were randomly assigned. There was no difference in CHD events in the thiazide recipients compared with the

propranolol or placebo group. However, stroke was reduced by 69% in the thiazide group and by 27% in the propranolol-treated patients compared with the placebo group. Although a subgroup of nonsmokers showed fewer CHD deaths in the propranolol as compared with the thiazide patients, the HAPPHY trial found no such difference between β-blockers and thiazide among nonsmokers.

Another well controlled trial, the Australian trial (Report of the Management Committee 1980), noted a trend toward a lower incidence of nonfatal CHD events in the thiazide recipients as compared to those receiving placebo. The results of these 9 trials (table I) indicated no significant difference in CHD morbidity and mortality between thiazide recipients and those receiving placebo or other drugs. Therefore, the majority of the trials including those which were best controlled outweigh the contrary evidence supplied by the few flawed trials. An additional recent study, the large SHEP trial in elderly patients, with isolated systolic hypertension (SHEP Cooperative Research Group 1991) reported a smaller number of CHD events in diuretic-treated patients compared with placebo. The questions of hypokalaemia, hypomagnesaemia, elevations of cholesterol with thiazides and insulin resistance are discussed later but it seems evident that if thiazides increase CHD risk from any cause then a higher incidence of CHD events with thiazides should have been manifested in the majority of the clinical trials.

2. Thiazide Diuretics and Electrolyte Balance

2.1 Potassium

The intracellular concentration of potassium is many times greater than the extracellular content. This gradient is maintained by a Na^+,K^+-ATPase metabolic pump which actively extrudes sodium from the cells but retains potassium. Therefore, extracellular potassium concentrations bear little relation to the intracellular content. Sodium and potassium loss in the urine following continuous thiazide administration increases during the first 2 or 3 days but then comes back into balance with intake, thus preventing excessive body losses during continuous treatment (Papademetriou 1984). A review of many studies indicated that after long term administration of thiazide diuretics the reduction of intracellular potassium approximates only 5%, which is physiologically unimportant (Kassirer & Harrington 1977).

The Nernst equation expresses the electrical potential across the cell membrane. The transmembrane voltage is related to the ratio of various ions inside to outside the cell. A reduction in the ratio of potassium outside to that inside the cell (such as occurs with thiazide diuretics) increases the negativity of the resting membrane potential which stabilises or reduces its electrical excitability (Guyton 1981). Thus, predominantly extracellular hypokalaemia should reduce rather than increase cardiac arrhythmic activity.

2.2 Magnesium

Thiazide-induced magnesium deficiency had been widely considered to be a cause of cardiac arrhythmias. However, interest in this hypothesis has declined in recent years because of the following considerations.

The influence of diuretics on intracellular magnesium and potassium is controversial. Some investigators have found only negligible reductions (Araoye et al. 1978; Bergstrom et al. 1973) while others have reported a deficit of both ions (Dyckner & Webster 1979; Lim & Jacob 1972). As indicated in the previous section, biologically insignificant changes were found in intracellular potassium with thiazide treatment of patients with uncomplicated hypertension (Kassirer & Harrington 1977) and intracellular magnesium concentrations paralleled potassium concentrations (Lim & Jacob 1972). Therefore, as is the case with potassium, only small reductions in intracellular magnesium would be expected with thiazide administration. Also, thiazides should not have much influence on magnesium excretion because these diuretics act in the early distal tubules while mag-

nesium is absorbed predominantly in the loop of Henle (Ryan 1986).

The controversial findings of different investigators on reduction in potassium and magnesium is probably the result of patient selection. The studies which found deficiencies of these ions were conducted in patients who mostly had congestive heart failure or myocardial infarction complicated by heart failure (Dyckner & Webster 1979; Lim & Jacob 1972).

It has been known for many years that patients with congestive heart failure have significant deficits of intracellular potassium (and, therefore, magnesium) even in the absence of diuretics. Iseri et al. (1952) and Cort and Mathews (1954) found marked reductions in potassium in muscle tissue taken by biopsy in patients with congestive heart failure and severe myocardial infarction in the era before thiazides were available.

Treatment with magnesium- and potassium-sparing diuretics may possibly have a place in the treatment of congestive heart failure, although evidence from well controlled studies is lacking. It is also possible that the use of thiazides in combination with potassium-sparing diuretic may be helpful in elderly diabetics whose diet may be potassium poor. However, in patients with uncomplicated hypertension there does not appear to be any indication for routine replacement therapy.

3. *Effect of Thiazide Diuretics on Monitored Cardiac Arrhythmic Activity*

Early studies (Holland et al. 1981; Hollifield & Slaton 1981) indicating increased cardiac arrhythmias following thiazide diuretics have been refuted by subsequent better-designed trials. Papademetriou et al. (1983) selected 16 hypertensive patients receiving hydrochlorothiazide 50mg twice daily whose serum potassium levels averaged 2.8 mmol/L. The ECG was monitored for 24h following which hypokalaemia was normalised by appropriate treatment for 4 weeks. There were no significant ECG differences between the hypokalaemic and the normokalaemic periods, including couplets and runs of ventricular tachycardia. The lack of effect of thiazides on cardiac arrhythmias was confirmed by other investigators (Lief et al. 1984; Madias et al. 1984). Papademetriou et al. (1985) also found that thiazides caused no increase in arrhythmias in thiazide-treated patients with hypertension and left ventricular hypertrophy.

4. *Diuretics in the Presence of Acute Myocardial Infarction*

The stress of an acute myocardial infarction is often associated with increased levels of plasma catecholamines (Struthers et al. 1983). Because catecholamines reduce the levels of plasma potassium, severe myocardial infarction is often accompanied by hypokalaemia, even in the absence of thiazide diuretics. The question has been raised that thiazides may increase the risk of fatal arrhythmias by aggravating the hypokalaemia.

This hypothesis is not supported, however, by the multiclinic trials. The majority of these trials have found that the incidence of fatal myocardial infarction is no greater in thiazide recipients than in patients receiving other regimens (table I). Mortality is, however, related directly to the level of circulating catecholamines (Karlsberg et al. 1981). These results suggest that the arrhythmias are not due to the hypokalaemia *per se*, but rather to the direct arrhythmogenic effects of catecholamines on the heart in the setting of myocardial cell injury, tissue ischaemia and other factors related to the myocardial insult. Nordrehaug et al. (1985) found that catecholamines were raised in the initial period following an infarction. Plasma potassium levels were inversely related to ventricular tachycardia during this early period. However, patients receiving diuretics at this time did not show a significant increase in ventricular arrhythmias. These investigators also showed that 8 hours following the infarction, when catecholamine levels had fallen, the degree of hypokalaemia also was not related to the incidence of cardiac arrhythmias, again suggesting that other factors were the cause of the arrhythmias.

Another reason for doubting the importance of hypokalaemia in worsening the course of acute

myocardial infarction is the negative results obtained with potassium replacement therapy (Fletcher et al. 1968; Rogers et al. 1979). 'Polarizing solutions' have been used in the past which contained potassium, glucose and insulin. Intravenous infusion of these solutions in sufficient amounts to raise the plasma potassium level to normal failed to prevent ventricular arrhythmias or reduce mortality in patients with acute myocardial infarction.

5. Diuretics and Cholesterol

Numerous investigators have demonstrated an increase in serum cholesterol during the first few months of treatment with thiazide diuretics (Ames & Hill 1976; Schoenfeld & Goldberger 1964). The elevations were small, averaging less than 0.28 mmol/L.

Long term studies, usually longer than 1 year, have shown either no change in cholesterol or a slight decrease compared with baseline (table II). Other long term studies have shown a greater drop in serum cholesterol with other drugs than with thiazides (Lasser et al. 1984; Williams et al. 1986). Again, the differences were small, averaging 0.10 to 0.18 mmol/L with the other drugs as compared to thiazides and were probably clinically unimportant. It should also be noted that the various clinical trials used considerably larger doses of diuretics than are used today. Cholesterol levels may be further reduced with smaller doses during long term treatment.

6. Diuretics and Blood Glucose Control

It has been recognised for many years that thiazide diuretics may raise blood glucose but the incidence, severity and duration of the rise have been unclear. The best evidence should be found in long term clinical trials. After 5 years of diuretic treatment the MPPCD (Helsinki) trial found a mean rise 1h after a glucose load of only 0.3 mmol/L from baseline as compared to 0.7 mmol/L in the control group (Miettiner et al. 1985).

The HAPPHY trial involving approximately 6000 patients reported an incidence of diabetes over a 45-month period of 6.1 per 1000 patient-years in diuretic recipients compared with 6.9 per 1000 patient-years in those on β-blockers (Wilhelmsen et al. 1987).

In the MRC trial there were no significant changes in casual blood glucose levels, although there was a slight increase at 1 year followed by a fall after 2 years (Medical Research Working Party on Mild Hypertension 1977). On the other hand, the HDFP trial reported an incidence of 1.6% of diabetes or hyperglycaemia in chlorthalidone recipients compared with 0.1% in those receiving reserpine and none in those receiving methyldopa (Williams et al. 1986).

A 10-year controlled trial indicated that low doses of thiazides are not diabetogenic (Berglund et al. 1986). Thus, aside from HDFP and considering the natural increase of diabetes in middle-aged to elderly patients, the reported increased incidence of diabetes with thiazides is low and in some studies nonexistent (Berglund et al. 1986).

The hyperosmolar nonketotic syndrome is characterised by an acute, severe elevation of blood glucose occurring without ketosis. It is not limited to diabetic patients. It usually occurs in patients receiving diuretics (Curtis et al. 1972). These patients often develop severe dehydration and occasionally coma. The syndrome is manifested by polyuria and markedly elevated levels of blood glucose. Rapid rehydration is indicated. It is often possible to transfer the patient to a chemically different diuretic such as chlorthalidone in place of a thiazide or vice-versa without recurrence of the hyperglycaemic state.

6.1 Hyperinsulinism and Insulin Resistance

The association between hypertension and diabetes represents a major health problem affecting 2.5 million Americans (Working Party on Hypertension in Diabetes 1987). The presence of hypertension in diabetes greatly increases the risk of both CHD and nephropathy. Nephropathy but not CHD has been favourably influenced by reduction of blood pressure (Christlieb 1982; Mogensen 1989).

Table II. Changes in serum cholesterol level with short term versus long term treatment of hypertension with diuretics (from Freis 1989, published with permission from the American Medical Association)

Trial	No. of patients	Diuretic and dose (mg)	Duration of treatment	Mean change in cholesterol (mmol/L)
Trials indicating a rise in cholesterol				
Ames and Hill (1976)	74	Chlorthalidone 25-100	1-3 months	+0.28
VA-NHLBI (Goldman et al. 1980)	302	Chlorthalidone 50-100	1 year	+0.26
Grimm et al. (1981)	57	Chlorthalidone 100 *or* hydrochlorothiazide 100	1.5-3 months	+0.18
Studies indicating no change or a fall in cholesterol				
EWPHE (Amery et al. 1985)	190	Hydrochlorothiazide 25-50	2 years	−0.52
Framingham study (Kannel et al. 1977)	288	Thiazides	2 years	−0.16
MRC (Medical Research Working Party on Mild Hypertension 1985)	17 354	Bendroflumethiazide 10	3 years	+0.05[a]
MRFIT (Multiple Risk Factor Intervention Trial Research Group 1985b)	1 021[b]	Chlorthalidone or hydrochlorothiazide 50-100	6 years	−0.23
MPPCD (Miettiner et al. 1985)	1 203	Hydrochlorothiazide 50	5 years	0
Oslo trial (Holme et al. 1984)	300	Hydrochlorothiazide 50	3 years	0
HAPPHY (Wilhelmsen et al. 1987)	6 669	Bendroflumethiazide 5 *or* hydrochlorothiazide 50	1 year	0
Trials indicating an early rise followed by a fall below baseline				
VA propranolol-hydrochlorothiazide (Veterans Administration Cooperative Study Group on Antihypertensive Agents 1982a,b)	147	Hydrochlorothiazide 50-200	2 months 1 year	+0.16 −0.08
Alcazar et al. (1982)	236	Hydrochlorothiazide 50-100	1-3 months 1-2 years	>0[c] <0[c]
HDFP (Williams et al. 1986)	7 006	Chlorthalidone 50	6-12 months 2-5 years	+0.10 −0.23

a Considered essentially unchanged from baseline.

b Number of patients with special interventions who received diuretics only.

c Numerical value of changes not given ($p < 0.01$).

Abbreviations: VA = Veterans Administration; NHLBI = National Heart, Lung, and Blood Institute; EWPHE = European Working Party on High Blood Pressure in the Elderly; MRC = Medical Research Council of Great Britain; MRFIT = Multiple Risk Factor Intervention Trial; MPPCD = Multifactorial Primary Prevention Trial of Cardiovascular Disease in Middle-Aged Men; HAPPHY = Heart Attack Primary Prevention in Hypertension trial; HDFP = Hypertension Detection and Follow-up Program.

Hyperinsulinism and insulin resistance may occur in diabetes, hypertension and obesity (Ferrannini et al. 1987; Modan et al. 1985; Mogensen 1989; Reaven 1988), raising the hypothesis that hyperinsulinism may be a risk factor in CHD, although this assumption has not been convincingly demonstrated. Both hyperinsulinism and insulin resistance may be aggravated by thiazides in some patients.

Sodium retention is characteristic of diabetes (Working Party on Hypertension in Diabetes 1987), which is aggravated by the antidiuretic effects of insulin (Saudek et al. 1974). Therefore, thiazides have been commonly used alone or in combina-

tion with other drugs in hypertensive diabetics (Christlieb 1982).

Warram et al. (1991) in a retrospective study of 749 diabetic patients reported that both total and CHD mortality were significantly higher in patients receiving thiazide diuretics than in other patients. There are a number of problems, however, with this study. First and probably most important, it was a retrospective study. Secondly, drug treatment was most likely given to the more severe hypertensives who were, therefore, at higher risk of CHD. A prospective controlled trial is needed to determine the validity of this report.

While diuretics have been associated with a decrease in insulin sensitivity and an increase in hyperinsulinism, an increase in risk of CHD with diuretics has not been confirmed by the long term controlled trials (table I). Also, there was no or only a minimal increase in hyperglycaemia and diabetes in thiazide-treated patients in most of the long term treatment control trials.

7. Hyperuricaemia and Gout

While hyperuricaemia frequently occurs with thiazide treatment, the incidence of gout is only slightly more common than in patients treated with other drugs. For example, in the HAPPHY trial (Wilhelmsen et al. 1987) involving 6500 patients, gout was diagnosed in 63 patients receiving thiazides compared with 44 patients taking β-blockers. Furthermore, the hyperuricaemia and most attacks of gout are preventable with uricosuric drugs. If acute attacks of gout occur they respond rapidly to nonsteroidal anti-inflammatory drugs such as indomethacin.

8. Quality of Life - Sexual Function

Little information is available on the quality of life in patients receiving diuretics. A multicentre, randomised, controlled trial (TAIM study) [Wassertheil-Smoller et al. 1991] compared chlorthalidone 25 mg/day with atenolol 50 mg/day and with placebo in patients on different diets. They did not find any impairment of quality of life except for sexual function. Sexual performance was adversely affected in approximately 25% of patients receiving chlorthalidone. However, this problem was prevented in chlorthalidone recipients who followed a weight reduction diet. In fact, this latter group had the least sexual problems of any patients and also exhibited the most effective control of their hypertension. This finding contradicts the suggestion that impaired sexual function results from reduction of blood pressure *per se*.

Reduction of bodyweight, therefore, exerts several favourable effects when combined with diuretics. It prevents impaired sexual function, it considerably enhances the antihypertensive effectiveness of the drug and it favourably affects cardiovascular risk. As the authors suggest, weight reduction of overweight patients should be combined with drug treatment in the general management of patients on diuretic therapy.

9. Conclusions and Clinical Implications

The current opinion of the toxicity of diuretics, particularly with respect to cardiotoxicity, has been greatly exaggerated. Analysis of the long term controlled clinical trials do not indicate an excess mortality from CHD with thiazides compared with other drugs. The allegations that hypokalaemia, hypomagnesaemia, hypercholesterolaemia, hyperinsulinaemia or insulin resistance when associated with diuretics increase the risk of CHD either remain unproven or have been disproved.

The majority of the long term clinical trials have indicated no or trivial changes in blood glucose or increase in the incidence of diabetes. Only the hyperglycaemic nonketotic syndrome has been definitely associated with thiazide diuretics but this is an acute condition rapidly reversible with appropriate therapy. Also, the hyperuricaemia associated with diuretics seldom leads to gout, which can be controlled with uricosuric drugs and the early treatment of the acute attacks.

The modern trend is to use small doses of diuretics in treating hypertension, such as 12.5 or 25mg of hydrochlorothiazide daily. This is in keeping with the general principle of titration which re-

cognises that some patients respond to smaller doses more than others. However, it fails to recognise that other patients require higher doses to achieve blood pressure control. Therefore, in view of the low toxicity of the diuretics more patients will be effectively controlled if the doses are titrated to at least 50 mg/day of hydrochlorothiazide or equivalent doses of other diuretics before adding another drug. This also will result in considerable cost saving since thiazides cost only a fraction of the price of most other drugs.

These considerations pertain to the great majority of hypertensive patients who have uncomplicated hypertension. In certain patients other drugs probably should receive preference over the diuretics as primary therapy. Those include β-blockers in patients with prior myocardial infarction, converting enzyme inhibitors in the presence of congestive heart failure or nephropathy and calcium antagonists in severe gout or diabetes. In the great majority of patients who do not present such complications, diuretics would appear to be effective, safe and far less costly than most other drugs.

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