NON-POTASSIUM SPARING DIURETICS

AND SUDDEN CARDIAC DEATH IN HYPERTENSIVE PATIENTS:

A PHARMACOEPIDEMIOLOGIC APPROACH

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NON-POTASSIUM SPARING DIURETICS AND SUDDEN CARDIAC DEATH IN HYPERTENSIVE PATIENTS: A PHARMACOEPIDEMIOLOGIC APPROACH

Niet-kaliumsparende diuretica
en plotselinge hartdood bij patiënten met hypertensie.
Een farmaco-epidemiologische benadering

Proefschrift

ter verkrijging van de graad van doctor
aan de Erasmus Universiteit Rotterdam
op gezag van de rector magnificus
Prof. Dr. C.J. Rijnvos
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Voor mijn ouders

Voor Carin en Tijmen

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CHAPTER 1

DO NON-POTASSIUM SPARING DIURETICS INCREASE THE RISK OF SUDDEN CARDIAC DEATH IN HYPERTENSIVE PATIENTS? - RECENT EVIDENCE

'There is a world of difference between removing a risk factor,
.....and adding an unknown one, such as a drug'

Michael F. Oliver[1]

INTRODUCTION

Case history

A 62-year-old woman was referred to the out-patient clinic because of recurring syncopes. Her medical history included hypertension and angina pectoris, for which she received chlorthalidone (Hygroton^{R}; one tablet three times a week) and prenylamine (Synadrin^{R}; 60 mg three times a day) respectively. To assess the role of arrhythmias in the development of her symptoms, a 24 hour ECG registration was performed. During the recording the patient suffered from a sudden syncope at 0.30 a.m. and was admitted to the hospital. At routine laboratory studies a severe hypokalemia (2.3 mmol/l) was established. Analysis of the 24 hour ECG recording revealed a sudden onset of polymorphous ventricular tachycardia at the time of onset of the syncope. The arrhythmia, which lasted 36 seconds, was preceded by a period of prolonged QT-interval and spontaneously developed into a regular sinus rhythm. The patient was treated with potassium suppletion and the chlorthalidone and prenylamine therapy was discontinued, resulting in a normalization of serum potassium level and the QT-interval.

The polymorphous ventricular tachycardia was identified as a 'torsade de pointes', a life threatening arrhythmia first described by Dessertenne in 1966.[2] A desynchronisation of the repolarization phase, often drug-induced, is considered to be the underlying mechanism. Drugs which have been frequently identified as potential causes of this phenomenon are non-potassium sparing diuretics and anti-arrhythmic agents. The arrhythmia which developed in the patient described above was probably initiated by the synergistic effect of the diuretic-induced hypokalemia and the anti-arrhythmic drug prenylamine.

The introduction of chlorothiazide in 1957 ushered in a new era of antihypertensive drug therapy.[3] Although electrolyte disturbances have long been recognized as an adverse effect of non-potassium sparing diuretics, i.e. thiazides and loop diuretics, the alterations in serum potassium and magnesium levels were first considered to be of minor clinical importance.[1,4-8] However, since the initial reports on the alleged arrhythmogenic properties of hypokalemia in the early nineteen eighties,[9-11] the question whether non-potassium sparing diuretics, in particular thiazides, increase the risk of sudden cardiac death in hypertensive patients has been heavily debated.[12-26] Numerous studies have attempted to shed light on the issue, but interpretation of the results varies widely among scientists, and consensus on the magnitude of the problem has not been reached. Several researchers are convinced that non-potassium sparing diuretics (NPSD) should not be considered as a drug of first choice in hypertension unless normal serum potassium levels

are ensured, preferably by concomitant use of potassium sparing diuretics or routine potassium supplements.[26-29] Others qualify the evidence of an arrhythmogenic effect of non-potassium sparing diuretics as circumstantial, and believe that three decades of experience have proven the relatively inexpensive diuretics to be efficacious, well-tolerated and safe antihypertensive drugs.[8,13,24,26] The vigour of the existing controversy is reflected by the headings of some of the published comments on the topic: "Fending of the potassium pushers", "Our national obsession with potassium" and "Our appropriate concern about hypokalemia".[13-15]

The recent publication of detailed analyses of several large-scale studies relevant to the discussion,[30-36] prompted us to undertake an updated review of the scientific evidence concerning the role of non-potassium sparing diuretics in the initiation of sudden cardiac death in hypertensive patients. Although previous reviews have addressed potassium/magnesium depletion-induced cardiac arrhythmias as the underlying etiological mechanism, a main objective of our study was to present the evidence in a format structured according to the consecutive steps of this hypothesis. Further emphasis was put on the methodological strengths and limitations of the individual studies, in view of the existing conflicting interpretation of the results.

METHODS

An extensive literature search of the current evidence was carried out. As the aim of this review was to assess the influence of non-potassium sparing diuretic therapy on sudden cardiac death in *hypertensive patients*, data concerning indications other than hypertension, e.g. congestive heart failure, were not sought. The evidence was sorted into groups representing the consecutive steps of the proposed underlying mechanism. Further, studies directly relating non-potassium sparing diuretic therapy to sudden cardiac death, irrespective of the causal pathway, were evaluated. Emphasis was put on data published since 1980 for two reasons. Firstly, extensive review papers on diuretic-induced potassium depletion[8,37] and on the association between potassium depletion and arrhythmias[13] were published around 1980. More importantly however, a tendency to prescribe lower dosages of diuretics has become apparent during the last decade. This may have had its influence on the incidence of electrolyte disturbances and arrhythmias and consequently on the potential clinical relevance. The influence of the dosages of NPSD on potassium and magnesium levels was assessed by grouping the diuretics according to the number of defined daily dosages (DDD) prescribed and by calculating mean changes in serum electrolyte levels, taking account of different sample sizes of the individual studies. Test for trends were used to evaluate the existence of a dose-response

relationship. To quantify the effect of NPSD on sudden cardiac death incidence in the published randomized trials, incidence density ratios and 95% confidence intervals were calculated.

MECHANISM

The mechanism underlying the putative relationship between non-potassium sparing diuretics and sudden cardiac death is relatively well-established. In figure 1.1 the consecutive steps of the causal pathway are depicted.

Thiazides and loop diuretics both act by blocking active sodium chloride reabsorption across the luminal membrane. An essential difference between loop diuretics and thiazides lies in the duration and strength of the diuretic effect: 4-6 hours of powerful action of loop diuretics versus a more prolonged moderate diuretic action

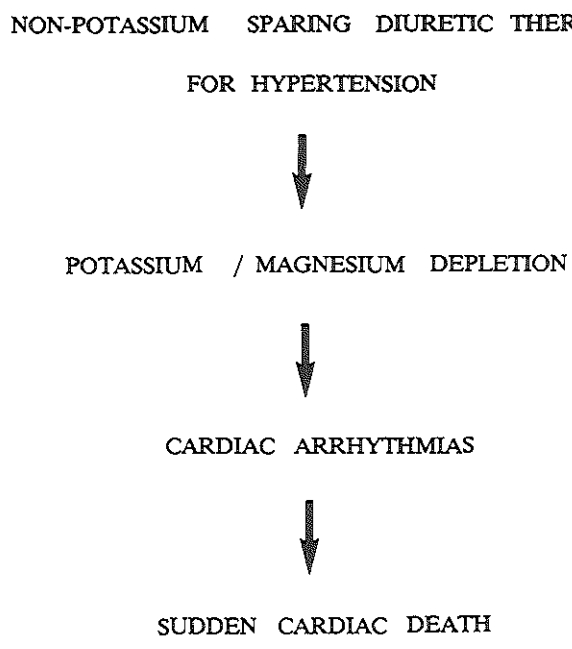

Figure 1.1
Hypothetical mechanism underlying a causal relationship between non-potassium sparing diuretic therapy for hypertension and sudden cardiac death. The evidence of the different steps of this mechanism is reviewed.

of thiazides. Loop diuretics have their major effects at the medullary part of the thick ascending loop of Henle, whereas thiazides act primarily at the cortical segment of the ascending loop and proximal part of the distal convoluted tubule. The decrease in sodium chloride reabsorption caused by non-potassium sparing diuretics leads to enhanced delivery of sodium to the more distal portions of the distal convoluted tube. Thus, active sodium/potassium exchange at this site is stimulated, resulting in increased kaliuresis and potassium depletion.[38-40] The effect of non-potassium diuretics on magnesium metabolism is more complicated. Magnesium depletion is considered to be secondary to diuretic-induced magnesuria. Administration of loop diuretics leads to a reduction of magnesium reabsorption in the ascending limb of Henle, where under normal circumstances approximately 50-60% of filtered Mg is reabsorbed. Long-term administration of thiazide diuretics induces hypocalciuria and subsequent hypercalcemia. This could stimulate magnesuria directly and reduce serum parathyroid hormone (PTH) level, which further decreases magnesium reabsorption in the limb of Henle.[41,42] Other mechanisms, notably alterations in the renin-angiotensin-aldosterone system, may also be involved in inducing magnesium depletion during diuretic treatment.[43,44]

Potassium and magnesium depletion have been repeatedly related to the development of cardiac arrhythmias. The first cases of hypokalemia-associated extrasystoles were reported by Bellet et al in 1949.[45] Hypokalemia increases resting membrane potential, action potential duration, the refractory period, and automaticity, while decreasing conductivity. All of these factors may provoke arrhythmias.[46,47] Extracellular potassium concentration has been identified as a strong predictor of rhythm disturbances, although the importance of the intra/extracellular gradient in myocardial cells has also been repeatedly stressed.[21,48-50] The electrophysiological effects of magnesium levels seem to be highly dependent of both calcium and potassium concentrations. In general, hypomagnesemia reduces intracellular free Mg^{++} in the myocardium although no clear transmembrane gradient exists.[47,51] Because magnesium activates the Na/K ATP-ase pump, magnesium loss influences active transmembranial transport of Na and K. Further, cellular calcium uptake is enhanced and calcium binding to the sarcoplasmatic reticulum is decreased, which could promote depolarization, after-potentials, and eventually arrhythmias.[51-54] Since magnesium depletion aggravates cardiac potassium loss, arrhythmogenesis may constitute an important problem during diuretic therapy, where hypokalemia and hypomagnesemia often coincide.[55,56] Cardiac arrhythmias that have been reported to relate to K and Mg depletion include ventricular premature complexes, ventricular tachycardia (e.g., "torsade de pointes"), and ventricular fibrillation.[46,57-60]

In most studies, sudden death is defined as non-violent death occurring within one

hour of onset of symptoms and is often attributed to a cardiac problem unless another cause is apparent.[61-66] Alternative time intervals, notably 24 hours, have been used. That cardiac arrhythmias, including those that have been associated with hypokalemia and/or hypomagnesemia, may cause sudden death is a well-known clinical fact, but whether the less severe arrhythmias, such as ventricular premature complexes, increase the risk of sudden death in asymptomatic men and women remains unclear.[67,68] Reports of sudden cardiac death occurring during ambulatory electrocardiographic registration have identified ventricular tachyarrhythmias to precipitate sudden death in 84% of the cases. These ventricular tachyarrhythmias were further categorized in ventricular tachycardia (75%), "torsade de pointes" (15%), and primary ventricular fibrillation (10%).[69]

Although most clinicians consider depletion of potassium and magnesium to be the most likely underlying mechanism, alternative phenomena related to diuretic use have been suggested to play a role in the development of ventricular ectopy or sudden death. Some evidence exists that a diuretic-induced increase in serum uric acid is associated with cardiac arrhythmias,[70,71] while hyperuricemia has been identified as an independent cardiovascular risk factor in several epidemiological studies.[72] Analogously, a glucose intolerance that may accompany diuretic treatment has been recognized to promote cardiovascular events.[73-76] That alterations in lipid metabolism caused by diuretics may also have an impact on the development of coronary heart disease, including sudden death, has received extensive attention.[76-78] The unfavorable increase in lipid levels changes, however, are rather small and seem to be transient, since most long-term studies have demonstrated a spontaneous normalization of the lipid levels occurring with prolonged diuretic therapy.[24,79,80] Alternative diuretic-induced phenomena that could enhance arrhythmias include alterations in zinc and calcium metabolism. If one of these alternative mechanisms were causally related to cardiac irritability, potassium and magnesium depletion could merely act as markers of diuretic usage.

EVIDENCE

Potassium- and magnesium depletion

Numerous investigators have reported potassium and/or magnesium levels in hypertensive patients treated with non-potassium sparing diuretics. The indices of potassium and magnesium metabolism that are determined differ among studies. In the majority of studies serum or plasma levels are reported, which are assumed to represent the extracellular level of these electrolytes.[50] Other indicators of electrolyte homeostasis include total body count using labelled potassium, ^{40}K and ^{42}K, and intracellular levels

Table 1.1. Characteristics and principal results of experimental studies published since 1980, reporting the effect of non-potassium sparing diuretic therapy (NPSD) on serum potassium or magnesium levels in hypertensive patients.

Study	Number of patients on NPSD	Mean age or range	% men	Diuretic and mean dosage (mgr/day)	Duration (weeks)	Serum K (mEq/l) initial	Serum K (mEq/l) change	Serum Mg (mEq/l) initial	Serum Mg (mEq/l) change
Hollifield[10,97,98]	38[f]	35-57	-	HCT/50	4	4.5	-0.3	2.10	-0.04
Holland[9]	21[§]	48	-	HCT/100	4	4.0*	-1.0	-	-
Murphy[73,99]	34	48	38	BFZ/6 (n=19) HCT/73 (n=13) CPT/0.5 (n=2)	728	4.0*	-0.3	-	-
Maronde[100]	6	38-65	50	HCT/100	8	3.8	-0.8	-	-
MRC[70]	16	45-64	-	BFZ/5-10	9-10	4.2	-0.5[◆]	-	-
MRC[101]	256	35-64	100	BFZ/10	156	4.1	-0.6[◆]	-	-
MRC[101]	229	35-64	0	BFZ/10	156	4.1	-0.6[◆]	-	-
Andersson[102]	14	31-65	-	HCT/39	12	4.1	-0.4	-	-
Caralis[103]	17	58	100	CTD/100	4-6	4.3	-0.7	1.55	-0.08
Erwteman[104]	94	46	62	CTD/25	4	3.9	-0.6	-	-
Leary[105]	9	-	-	HCT/50	22	-	-	1.54	-0.14
Lief[106]	13	-	-	HCT/100	4-26	4.0	-1.0	-	-
Madias[107]	20	52	65	HCT/100	4	4.4	-1.4	2.3	-0.2
Multicenter[108]	20	57	29	HCT/14	52	4.3	-0.2	-	-
Multicenter[108]	15	56	60	BFM/3	52	4.3	-0.2	-	-
Papademetriou[109]	18[◆]	55	-	HCT/100	4	4.2[†]	-0.8	-	-
Webb[110]	67	50	67	CTD/25	10	4.2	-0.5	-	-
Papademetriou[111,112]	44	-	100	HCT/100	4	4.1*	-0.7	-	-
Stewart[113]	10	56	70	HCT/50 (n=8) CPT/0.5 (n=2)	8	4.2*	-0.9	-	-
Verho[114]	14	47	36	PTN/6	12	4.1	-0.1	-	-
Verho[114]	12	51	67	PTN/12	12	4.1	-0.1	-	-

Table 1.1, continued.

Study	Number of patients on NPSD	Mean age or range	% men	Diuretic and mean dosage (mgr/day)	Duration (weeks)	Serum K (mEq/l) initial	Serum K (mEq/l) change	Serum Mg (mEq/l) initial	Serum Mg (mEq/l) change
Vardan[121]	13	65	-	HCT/50	52	3.9	-0.7	-	-
Leehey[122]	31	65	100	HCT/52	10	4.4	-0.4	-	-
Kohvakka[115]	26	55	19	HCT/25	12	4.1	-0.2	1.78	-0.02
Kohvakka[115]	26	55	19	HCT/50	12	4.1	-0.4	1.78	-0.08
Lumme[116]	6	28-64	33	HCT/25-50	8	4.0	-0.5	1.72	-0.10
Lumme[116]	6	28-64	33	ICN/50-100	8	3.9	-0.6	1.72	0.00
Myers[117]	41	65-80	-	HCT/42	12	4.2	-0.2	-	-
Smith[118]	443[€]	>60	37	CTD/25-50	52	4.4	-0.6[Φ]	-	-
HAPPHY[119]	3204	52	100	BFZ/5 or HCT/50	195	4.3	-0.3	-	-
Vardan[120]	60	21-69	66	CTD/15	12	4.3	-0.4[Φ]	-	-
Vardan[120]	63	21-69	66	CTD/25	12	4.3	-0.6[Φ]	-	-
McVeigh[123]	13	59	38	CPT/0.050	8	4.1	+0.2[Φ]	-	-
McVeigh[123]	15	56	33	CPT/0.125	8	4.2	-0.1[Φ]	-	-
McVeigh[123]	13	55	38	CPT/0.500	8	4.2	-0.5[Φ]	-	-
Haalboom[124]	8	33	75	CTD/50	12	4.1[*]	-0.8	1.94[f]	-0.04
Papademetriou[125]	20	54	100	HCT/100	2	4.0	-0.8	1.96	+0.11
SHEP[32]	2218[€]	72	44	CTD/12.5-25	52	4.5	-0.3[Φ]	-	-
Siegel[35]	60	35-70	100	HCT/50	9	4.3	-0.4[Φ]	1.66	+0.04[Φ]
Siegel[35]	30	35-70	100	CTD/50	9	4.4	-0.8[Φ]	1.68	0.00[Φ]

- = not reported; ∫ = the findings on the lowest dosage of the drug were included, because only a selected subgroup used increased dosages; $ = all patients had documented potassium levels below 3.5 meq/l during previous diuretic treatment; * = plasma concentration (mmol/l); Φ = change in electrolyte level adjusted for change in placebo-treated control group; ϕ = 7 patients were known with hypokalemia during previous diuretic treatment. 4 patients received K supplementation because of overt hypokalemia (≤ 2.6 mmol/l), and were excluded from the analysis; € = all participants had isolated systolic hypertension.
Abbreviations: NPSD = non-potassium sparing diuretics; K = potassium; Mg = magnesium; HCT = hydrochlorothiazide; BFZ = bendrofluazide; CPT = cyclopenthiazide; CTD = chlorthalidone; BFM = bendroflumethiazide; PTN = piretanide; ICN = indacrinone.

of both magnesium and potassium determined in erythrocytes, leukocytes, and skeletal muscle cells obtained through biopsy.[8,81-83] Given the complexity of the latter methods for routine use in clinical practice, potassium and magnesium status is usually determined by measuring serum levels, although a lack of correlation between extracellular content and total body or intracellular stores has been recognized.[41,52,83-86] To enable assessment of the influence of diuretics on electrolyte levels, measurements before and after initiation of diuretic therapy should be available in the same patients. Thus, cross-sectional studies and studies in which electrolyte levels prior to diuretic therapy were not taken into account were not included in our analysis.[44,83,87,88] In case potassium supplements were used concomitantly, the study was excluded.[89-93] Studies in which diuretic therapy was given in combination with betablocking agents were not included because of the potential influence of betablockers on diuretic-induced alterations in serum potassium and magnesium.[94,95] Ideally, changes in K and Mg during diuretic treatment should be compared with changes in a randomly allocated placebo-treated control group, in order to rule out non-diuretic associated changes in electrolyte levels occurring over time.[96]

In total, 31 studies published since 1980 were evaluated.[9,10,32,35,70,73,97-125] The impact of non-potassium sparing diuretic therapy for hypertension on blood levels of potassium and magnesium is shown in table 1.1. Large differences exist in the size of the population studied, 6 to 3204 patients, and in the duration of diuretic therapy, from 2 weeks to 14 years. A placebo-treated comparison group was included in seven studies only, and in these studies adjustments for electrolyte changes observed during placebo treatment could be made. Non-potassium sparing diuretic therapy for hypertension consistently resulted in a decrease of serum potassium levels, ranging from 0.1 to 1.4 mmol/l. Only McVeigh reported an average increase in potassium in a subgroup of 13 hypertensive patients using 0.05 mg of cyclopenthiazide. However, this extremely low dosage of one fourth of the defined daily dose (DDD) had no antihypertensive effect in contrast to the higher dosages studied.[123] In figure 1.2 the influence of the dosage on serum K^+ levels is shown for the three drugs evaluated most frequently: hydrochlorothiazide, chlorthalidone and cyclopenthiazide. A clear dose-response relationship is seen for all three medications. The for the study population size adjusted mean fall in serum potassium associated with the use of <0.5, 0.5 to 1, 1 to 2, and 2 or more DDD per day was 0.06, 0.30, 0.55, and 0.86 mEq/l, respectively (test for trend: $p<0.05$). In an analysis of the studies published before 1980, Morgan and Davidson estimated that thiazides caused an average decrease in serum potassium of 0.66 mmol/l in hypertensive patients, which would lead to hypokalemia (serum K < 3.5 mmol/l) in 50% and severe hypokalemia (< 3.0 mmol/l) in 7% of the patients.[37] Only little influence of the dosage

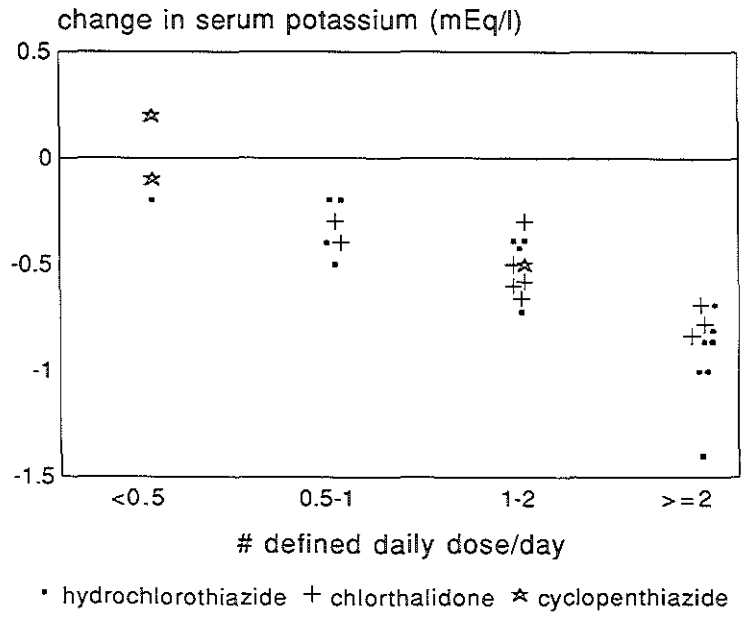

Figure 1.2
Effect of the dosage of hydrochlorothiazide, chlorthalidone, and cyclopenthiazide on serum potassium levels in hypertensive patients. Only findings in studies published since 1980 are included. The dose is expressed as the number of defined daily dosages (DDD) per day. The DDD's for hydrochlorothiazide, chlorthalidone and cyclopenthiazide are 50, 25, and 0.5 milligrams, respectively.

of the diuretic was demonstrated in that analysis. This may be partly explained by the fact that only few studies on smaller dosages were available at that time. It has been suggested from cross-sectional studies that women may respond with more pronounced decreases in potassium levels than men.[126] This could not be confirmed in the Medical Research Council trial, the only study in which separate data were reported for men and women.[101] Similarly, the fall in serum potassium observed among elderly hypertensives[32,117,118,121,122] was comparable to the changes in other age categories.[127]

Changes in serum magnesium levels were reported in nine experimental studies. In the majority of studies, a small decrease in magnesium levels was demonstrated, ranging from 0.02 to 0.20 mEq/l (table 1.1). In three studies an increase or no change in serum Mg was observed although serum K decreased as expected.[35,116,125] As depicted in figure 1.3, no clear dose-response relationship between the dosage of

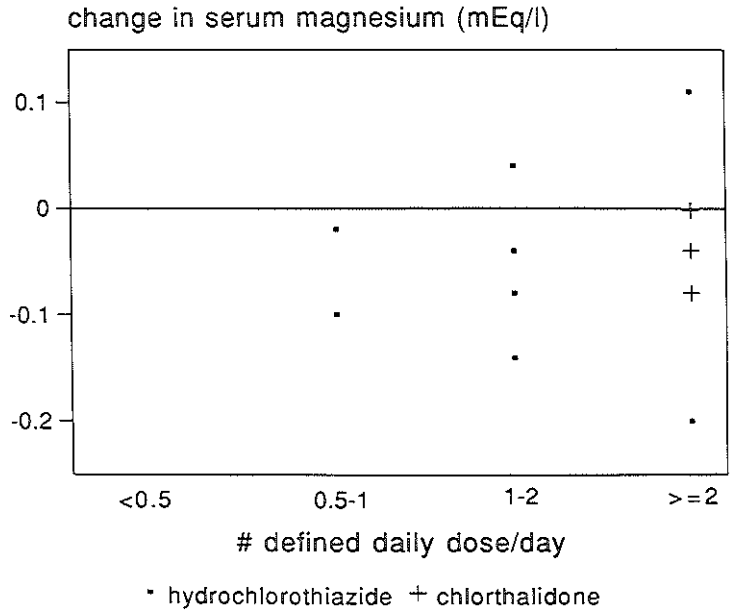

Figure 1.3
Effect of the dosage of hydrochlorothiazide and chlorthalidone on serum magnesium levels in hypertensive patients. Only findings in studies published since 1980 are included. The dosage is expressed as the number of defined daily dosages (DDD)/day. The DDD's for hydrochlorothiazide and chlorthalidone are 50 and 25 milligrams, respectively.

hydrochlorothiazide or chlorthalidone and the change in serum magnesium exists, but both the range of the dosages studied and the number of reports are limited. Diuretics have been reported to exert their action on electrolyte levels within a few hours after administration of the drug while causing the maximum fall in serum electrolyte levels within a week.[37] This is in accordance with a lack of an association between the duration of diuretic therapy and the decrease in potassium levels in our analysis (figure 1.4).

In the last decade only few experimental studies have assessed the influence of non-potassium sparing diuretics on indicators of potassium and magnesium metabolism other than serum or plasma levels in hypertensive patients.[35,103,124,128] A small decrease in total body potassium stores or intracellular potassium content of approximately 6% was reported in two studies.[103,124] This is in line with the findings from Kassirer's review of studies published before 1977 in which a small statistically non-significant reduction in total potassium stores of 200 mEq or less was demonstrated.[8,129] However, the

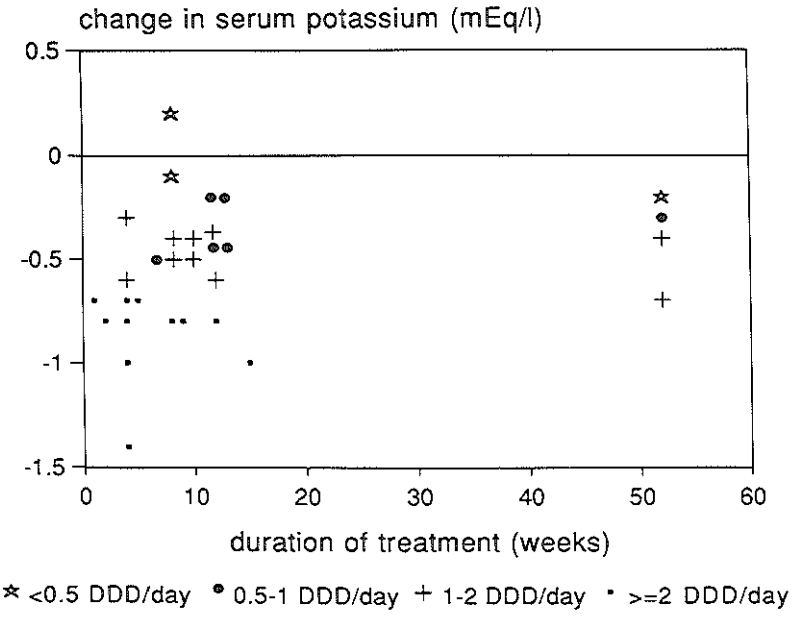

Figure 1.4
Relationship between the duration of non-potassium sparing diuretic therapy and the fall in serum potassium levels, for the different dosages of three diuretics: hydrochlorothiazide, chlorthalidone and cyclopenthiazide. Evidence from studies published since 1980.

differences in the dosages and dietary habits between studies precluded definite conclusions.[8] Furthermore, the power of these earlier studies was limited given the size of the populations, ranging from 5 to 26 patients. Surpisingly, in a very recent review based on 14 papers also included in Kassirer's review, and 9 other studies, of which only four were published after 1980, a small but highly statistically significant change in body potassium content was noted.[59] Differences in the statistical analysis are likely to be responsible for these opposite findings.

Cardiac arrhythmias

The evidence from 19 studies that determined the relationship between diuretic-induced K and Mg depletion and cardiac arrhythmias in hypertensive patients, is summarized in table 1.2.[9,10,35,70,103,106,107,111,113,116,122,124,125,130-134] Most studies were performed in middle-aged men or women. The duration of diuretic therapy was three months or less in the majority

Table 1.2. Association between the use of non-potassium sparing diuretics (NPSD) and ventricular ectopic activity (VEA) in patients with essential hypertension.

Study	Number of patients on NPSD	NPSD and mean dosage (mgr/day)	Method of ECG monitoring of VEA	Effect of NPSD on VEA	Comparison with	Association of VEA with K^+	Association of VEA with Mg^{2+}
Hypertensive patients without clinical evidence of heart disease.							
Hollifield[10,97,98]	38*	HCT/78	exercise	increase	initial VEA	yes (serum K)	yes (serum Mg)
Holland[9]	21[#]	HCT/100	24 hrs, exercise	increase[@]	initial VEA	yes (plasma K)	not reported
MRC[70]	16[§-1]	BFZ/5-10	24 hrs	no change	initial VEA, placebo	no (serum K)[%]	not reported
MRC[70]	74[§-1]	BFZ/5-10	24 hrs	increase	placebo group	no (serum K)[%]	not reported
Caralis[103]	8[$]	CTD/100	24 hrs	no change	initial VEA	no (serum or RBC K)	no (serum Mg)
Lief[106]	13	HCT/100	48 hrs	no change	initial VEA	not reported	not reported
Madias[107]	20	HCT/100	24 hrs	no change	initial VEA	no (serum K)	not reported
Lumme[116]	12	HCT or ICN	24 hrs	?[&]	initial VEA	no (serum K)	no (serum Mg)
Bause[130]	68	several[£]	exercise	increase in "simple" VEA[¥]	normotensive age-matched controls	no (K<3.7 mEq/l)	not reported
Ragnarsson[131]	42	BFM/5 or PSD[/]	24 hrs	increase	ß-blocker group	yes (serum K)	no (serum Mg)
McLenachan[132]	46	not specified	48 hrs	no difference	other antihypertensives	no (serum K)	not reported
Papademetriou[111]	44	HCT/100	48 hrs	no change	initial VEA	no (serum K)	not reported
Levy[133]	687	not specified	1 hour	increase[a]	ß-blocker and untreated hypertensives	not reported	not reported
Leehey[122]	31	HCT/52	24 hrs	no change	diltiazem group	no (serum K)	not reported
Haalboom[124]	8	CTD/50	24 hrs, exercise	no change	initial VEA	no (total or plasma K)	no (plasma Mg)
Papademetriou[125]	20	HCT/100	exercise	no change	placebo treatment	no (serum K)	no (serum Mg)
Messerli[134]	10[Ω,ß]	HCT/50-100	24 hrs	no change	initial VEA	not reported	not reported
Siegel[35]	90[ß]	HCT/50 or CTD/50	24 hrs	no change/ increase[A]	placebo treatment	yes (serum K), no (intracellular K)	no (serum Mg or intracellular Mg)

Table 1.2, continued.

Study	Number of patients on NPSD	NPSD and mean dosage (mgr/day)	Method of ECG monitoring of VEA	Effect of NPSD on VEA	Comparison with	Association of VEA with K^+	Association of VEA with Mg^{2+}
Hypertensive patients with clinical evidence of heart disease							
Caralis[103]	8[$]	CTD/100	24 hrs	increase	initial VEA	no (serum or RBC K)	no (serum Mg)
Stewart[113]	10	CTD/50 or CPT	24 hrs, exercise	increase[@]	PSD period	no (plasma K)	no (plasma Mg)

* = all patients had previous evidence of marked hypokalemia (<3.0 mEq/l or less), or had complained of palpitations or arrhythmias; # = all patients had documented potassium levels below 3.5 mEq/l during previous diuretic treatment; @ = increase only evident in 24 hours recording, not during exercise ECG monitoring; s-t = short-term substudy of the MRC-trial (9-10 weeks of BFZ treatment); l-t = long-term substudy of the MRC-trial (average 2 years of BFZ treatment); % = when data of the two studies were pooled, a small statistically significant association between serum K and VEA was present; $ = 16 hypertensive patients were divided in 8 without and 8 with clinical evidence of heart disease at baseline; & = increase in VEA in 2 patients with documented moderate VEA at baseline. In patients without VEA at baseline no increase in VEA was recorded; £ = thiazides(not specified)/50 mgr(n=38), chlorthalidone/67 mgr (n=12), frusemide/33 mgr (n=3), potassium sparing diuretic (n=15); ¥ = increase in simple premature complexes (<10% of beats in any minute). No change in more frequent or complex VEA; ƒ = all 37 patients on BFM treatment received KCl supplements 40 mmol daily, 5 patients received PSD; α = age-adjusted prevalence of ventricular premature contractions (PVC's) >9/hour higher in diuretic compared to untreated group ($p<0.05$) and prevalence of complex or frequent VPC's higher in diuretic compared to ß-blocker group ($p=0.05$); Ω = 8 of 10 patients had echocardiographic evidence of left ventricular hypertrophy; ß = all patients had baseline ECG-abnormalities; ₱= no statistically significant change in ventricular arrhythmias in the HCT or CTZ group compared to the placebo group was seen, but an increase in arrhythmias was observed among the 12 men with post treatment levels of serum K ≤ 3.0 mEq/l.

Abbreviations: NPSD = non-potassium sparing diuretics; VEA = ventricular ectopic activity; HCT = hydrochlorothiazide; BFZ = bendrofluazide; CTD = chlorthalidone; ICN = indacrinone; BFM = bendroflumethiazide; PSD = potassium sparing diuretic therapy; CPT = cyclopenthiazide; RBC = red blood cell.

of studies, although two evaluated considerably longer periods of treatment.[70,130] The prevalence of cardiac arrhythmias was usually measured during 24 hours ambulatory dual-channel electrocardiographic recordings, which have been proven to be an appropriate method with sufficient reproducibility and a higher sensitivity than monitoring during exercise testing.[135,136] Ventricular ectopic activity (VEA) is often categorized according to Lown's classification.[136] In ten studies a direct experimental comparison was made between the occurrence of ventricular ectopic activity during non-potassium sparing diuretic drug therapy with baseline arrhythmias recorded prior to drug therapy in the same hypertensive patients.[9,10,103,106,107,111,113,116,124,134] Only six experimental studies included a randomly assigned comparison group: Placebo-treated patients in four studies[35,70,125] and betablocker[131] or calcium antagonist treated patients.[122] Obviously, a lack of a proper control group increases the possibility that a spontaneous variability in the prevalence of arrhythmias, which has been known to occur frequently, is erroneously attributed to the initiation of NPSD therapy. Further, three nonexperimental studies were reported.[130,132,133]

The results of the studies performed in *hypertensive patients without clinical evidence of heart disease* are conflicting. Hollifield and Slaton[10] studied 38 hypertensive patients and an increase in VEA, recorded during exercise testing, was demonstrated after 8 weeks of hydrochlorothiazide therapy. Furthermore, the number of premature ventricular complexes (PVC's) was correlated with the diuretic-induced decrease in both serum potassium and magnesium concentrations. However, only patients with a previous episode of marked hypokalemia (3.0 mEq/l or less) on thiazide therapy, or who had complained of palpitations or arrhythmias were included.[97,98] This may explain the relatively high prevalence of PVC's at baseline (0.6/minute). Consequently, the selection of patients who are apt to develop arrhythmias may account for at least part of the increase in PVC's observed in this study. Holland et al[9] reported a hypokalemia-associated increase in VEA during 24 hour ECG-monitoring, in 7 of 21 patients after four weeks of treatment with hydrochlorothiazide. Only in two of these a similar increase in VEA during exercise testing was noted. Repletion of potassium reduced ectopic activity. The study population consisted of hypertensive patients with documented hypokalemia during prior diuretic treatment, and those with six or more PVC's at baseline were excluded. Hence, the increase in VEA reported in the remaining patients, which were prone to develop hypokalemia and had normal 24 hours ECG at baseline, may result in part from regression-to-the-mean, rather than NPSD therapy. The findings of these two earlier reports were confirmed in a placebo-controlled substudy of the Medical Research Council trial conducted in 155 patients. Ventricular extrasystoles were more frequently recorded in those receiving bendrofluazide than in the placebo group

(p=0.25). However, no 24 hours electrocardiographic monitoring was performed at the time of randomization.[70] A higher prevalence of VEA in diuretic-treated patients compared to a betablocker group was demonstrated by Ragnarsson.[131] Hypokalemia but not hypomagnesemia seemed to be related to the increased ectopic activity. Whether the detrimental effects of NPSD or cardioprotective effects of betablockers are responsible for these findings could not be clarified. Cohen and co-workers assessed the influence of diuretic use and serum potassium levels on the incidence of PVC's in the "special intervention" (SI) and "usual care" (UC) groups of the Multiple risk Factor Intervention Trial.[137] Although up to 40% of patients used potassium supplements or potassium sparing diuretics, and no extensive analysis of the hypertensive subgroup was performed, NPSD treatment was found to be related to ectopic activity in both the SC and UC group. Moreover, serum potassium concentration was associated with PVC's, also after multivariate analysis. Recently, a large study among 212 hypertensive men with baseline ECG-abnormalities, including ST-T wave changes, arrhythmias and left ventricular hypertrophy, was performed.[35] In total, 62 patients were randomized to hydrochlorothiazide, 29 to chlorthalidone and 27 to placebo treatment, while the other patients received electrolyte supplements or potassium sparing diuretics. Although serum potassium levels in the non-potassium sparing diuretic group decreased, no overall change in arrhythmias compared to the placebo group was established. However, a clear increase in ventricular arrhythmias was observed among the 12 men whose serum K level fell below 3.0 mmol/l during the study period. All of these men had been randomized to either hydrochlorothiazide or chlorthalidone. Although the randomization procedure was stratified by the presence of left ventricular hypertrophy, the authors did not provide separate results for patients with or without evidence of left ventricular hypertrophy. Further evidence of the arrhythmogenic properties of diuretics was reported in two nonexperimental studies. Bause demonstrated a higher prevalence of "simple" ventricular ectopic activity, but not of the more "complex" arrhythmias, during exercise in NPSD-treated patients relative to age-matched normotensive controls.[130] No relation with hypokalemia was established. However, other factors than diuretic therapy, such as blood pressure level and other cardiovascular risk indicators, may account for the higher prevalence of the arrhythmias. Since no attempts were made to adjust for the these factors, the possibility of incomparability of prognosis between the two comparison groups precludes from drawing conclusions.[138] In a substudy of the Framingham Heart Study, Levy et al compared the age- and sex adjusted prevalence of ectopic activity during 1-hour ECG recordings in 687 diuretic-treated hypertensive patients, with 100 betablocker treated and 1013 untreated hypertensives.[133] Diuretic-treated patients tended to experience higher rates of arrhythmias than the other two groups. The authors

recognized that other differences between the groups could not be excluded as an explanation for these findings.

An arrhythmogenic effect of non-potassium sparing diuretic therapy could not be confirmed in several other studies performed in hypertensive patients without overt heart disease. In a short-term substudy of the MRC-trial,[70] VEA was similar in patients treated with bendrofluazide for 9-10 weeks and a placebo group. In this study, baseline 24 hours ECG recordings were available. The conflicting results of the two MRC substudies may be partly related to the lack of baseline ECG recording in the long-term study. The difference in duration of diuretic treatment could be an alternative explanation. The findings of the short-term MRC substudy were supported by other studies with similar study designs.[103,106,107,111,116,122,124,125] Although diuretic-induced potassium or magnesium depletion was documented in most of these reports, no influence on the occurrence of ventricular ectopy was shown. Consequently, the lack of correlation between electrolyte depletion and arrhythmias in these studies, is not surprising. It should be stressed, however, that the sample size of most of these studies is limited. Hence, the failure to find an arrhythmogenic effect of diuretics could be the reflection of a type II error, rather than the harmlessness on NPSD. In particular the studies by Papademetriou et al,[111,125,139] have often been quoted as solid evidence against the arrhythmogenic properties of diuretics. Indeed, in a relatively large study of 44 patients no increase of ventricular ectopy could be demonstrated after 4 weeks of hydrochlorothiazide treatment, although plasma potassium levels decreased 0.7 mEq/l on average.[111] In another study, a placebo-controlled double-blind cross-over trial in 20 patients, no increase in exercise-induced arrhythmias was found after hydrochlorothiazide.[125] In an earlier report,[139] no decrease of arrhythmias, and if anything a tendency to increased VEA, was seen after correction of plasma potassium in diuretic-induced hypokalemic patients. Although this is an important finding, it cannot be concluded from the latter study that NPSD therapy does not promote arrhythmias.

Hypertensive patients with electrocardiographic or echocardiographic evidence of left ventricular hypertrophy (LVH) have been recognized to have a higher frequency of cardiac arrhythmias than hypertensive patients without LVH.[140-143] Thus it could be speculated that especially these hypertensive patients could be at risk to develop diuretic-induced arrhythmias. Several studies have assessed the influence of NPSD on arrhythmias in these patients.[111,132,134] In neither of these reports an increase in arrhythmias during diuretic therapy was shown. In the study by Papademetriou mentioned earlier,[111] no increase in the incidence of arrhythmias among NPSD-treated hypertensive patients with left ventricular hypertrophy could be demonstrated, although patients with LVH had more arrhythmias than those without LVH. A study among ten hypertensives with

baseline ECG abnormalities, of which 10 had echocardiographic evidence of LVH, reported similar findings.[134] In a nonexperimental study performed by McLenachan,[132] the prevalence of arrhythmias was similar in diuretic- and non-diuretic treated hypertensive patients with and without left ventricular hypertrophy. Again however, differences in prognosis between the two groups may partly explain the results.

Only two recent studies evaluated the influence of NPSD on arrhythmias in *hypertensive patients with clinical evidence of heart disease.* In a cross-over trial[113,144] the occurrence of VEA after 8 weeks of potassium loosing therapy was compared to VEA after 8 weeks of potassium-sparing diuretic therapy in 10 hypertensive patients with clinical evidence of typical effort angina. An increase in extrasystoles during the NPSD treatment period could be demonstrated. Moreover, evidence of electrophysiological changes and increased myocardial instability, measured by several techniques, was revealed during the potassium losing phase. No correlation of electrical instability with serum K and Mg levels was apparent, indicating that other diuretic-induced changes may be of importance. Interestingly, in the study by Caralis,[103] chlorthalidone treatment increased the prevalence of VEA in patients with clinical symptoms of heart disease, but no influence was seen in patients without symptomatic heart disease. The findings in hypertensive patients with overt cardiac disease are in accordance with the higher susceptibility to diuretic-induced electrolyte depletion demonstrated in e.g., patients with heart failure and digitalis users.[145-146] Moreover, many investigators have demonstrated the importance of hypokalemia and hypomagnesemia, sometimes irrespective of prior use of diuretics, in the development of arrhythmias in patients in the acute phase of myocardial infarction.[147-155] In general however, measurements of electrolyte content were made upon arrival in the hospital and may therefore be influenced by factors resulting from the ischemic event. Especially, an increase in adrenaline levels may cause a shift of potassium into the cell, leading to hypokalemia.[156-158] Although these studies are of limited importance to the question whether NPSD-induced hypokalemia predisposes to arrhythmias in hypertensive patients, they do indicate that any proarrhythmogenic effect of diuretic therapy could be aggravated in the presence of cardiac ischemia.

Cardiac arrhythmias and sudden cardiac death

Several cardiac arrhythmias, in particular premature ventricular contractions have been reported to increase the risk of future development of sudden cardiac death.[67,68,136,159-162] Others, such as torsade de pointes, have been known to precipitate sudden cardiac death.[69] Although no association between the use of non-potassium sparing diuretics and the length of the QTc-interval on the electrocardiogram has been demonstrated, some evidence exists that NPSD-induced hypokalemia may initiate severe cardiac arrhythmias,

Table 1.3. Characteristics of experimental studies evaluating the effect of non-potassium sparing diuretic therapy (NPSD) on the incidence of sudden cardiac death (SCD) in mild to moderate hypertensive patients.

Study	Number of participants NPSD	ctrl	Men (%)	Follow-up time (years) NPSD	ctrl	NPSD treatment and dose (mgr/day)	Control group	Cases of SCD NPSD	ctrl	SCD incidence (per 1000 py) NPSD	ctrl	Rate ratio (95% CI)
VA[165]	186	194	100	3.2	3.3	HCT/50	placebo	4	8	6.7	12.5	0.5 (0.2 - 1.8)
HSCS[166]	233	219	59	3.0	3.0	MTZ/5	placebo	2	2	2.9	3.0	1.0 (0.1 - 7.4)
USPHS[167]	193	196	80	7.0	7.0	CTZ/500	placebo	1	1	0.7	0.7	1.0 (0.1 -16.0)
VA-NHBLI[168]	508	504	81	1.5	1.5	CTD/50-100	placebo	2	0	2.6	0.0	-$^{\Omega}$
Morgan[169]	55	42	100	3.5	3.4	CTZ/500-1000	no treatment	9*	0*	4.8*	0.0*	-$^{\Omega}$
Oslo[170]	406	379	100	5.5	5.5	HCT/50	no treatment	6	2	2.7	1.0	2.7 (0.5 - 5.0)
MRFIT (ecg$^{\$}$)[16]	1233	1185	100	7.0	7.0	HCT/50-100, CTD/50-100	usual care	21	8	2.4	1.0	2.4 (1.1 - 5.4)
MRC men[30]	2238	4525	100	4.9	4.9	BFZ/10	placebo	29	41	2.6	1.8	1.4 (0.9 - 2.3)
		2285			4.9		propranolol		12		1.1	2.4 (1.2 - 4.4)
MRC women[30]	2059	4129	0	5.0	5.0	BFZ/10	placebo	4	4	0.4	0.2	2.0 (0.5 - 8.0)
		2118			5.0		propranolol		4		0.4	1.0 (0.3 - 4.0)
MAPHY[31]	1625	1609	100	5.0	5.0	HCT/46, BFZ/4	metoprolol	17	12	2.1	1.5	1.4 (0.7 - 8.5)
SHEP[32]	2365	2371	43	4.5	4.5	CTD/12.5-25	placebo	23	23	2.2	2.2	1.0 (0.6 - 1.8)

@ = The 95% CI (confidence interval) was calculated as follows: 95% CI = exp (ln (rate ratio) ± 1.96 x $\sqrt{(1/A_1 + 1/A_0)}$, where A_1 and A_0 represent the number of sudden cardiac deaths in the diuretic and the control groups, respectively; Ω=not computable because of zero cases in the denominator;*=cases of sudden cardiac death and fatal myocardial infarction combined; $=subgroup of hypertensive patients with ECG-abnormalities at baseline.

Abbreviations: NPSD = non-potassium sparing diuretic therapy; ctrl = control group; SCD = sudden cardiac death; py = person-years at risk; CI = confidence interval; VA = Veterans Administration Cooperative Study on Antihypertensive Agents (diastolic blood pressure 90-114 mm Hg); HSCS = Hypertension-Stroke Cooperative Study; USPHS = United States Public Health Service Hospitals Cooperative Study; VA-NHBLI = Veterans Administration-National Heart, Lung and Blood Institute Study; MRFIT = Multiple Risk Factor Intervention Trial; MRC = Medical Research Council trial of treatment of mild hypertension; MAPHY = Metoprolol Atherosclerosis Prevention in Hypertension trial; SHEP = Systolic Hypertension in the Elderly Program; HCT = hydrochlorothiazide; MTZ = methyclothiazide; CTZ = chlorothiazide; CTD = chlorthalidone; BFZ = bendrofluazide.

including torsade de pointes, in the presence of QTc prolongation.[59,163,164] Solid evidence for a causal relationship between diuretic-induced arrhythmias and sudden cardiac death in hypertensive patients, however, is lacking. The low incidence of sudden cardiac death, the difficulty of monitoring arrhythmias in large populations, and the short period between the onset of arrhythmias and death makes the assessment of this relationship practically impossible. Even in the large scale hypertension trials no reliable evidence in favour of or against such an association could be demonstrated.

Non-potassium diuretic therapy and sudden cardiac death: direct evidence

To answer the question whether non-potassium sparing diuretic therapy actually increases the risk of sudden cardiac death in hypertensive patients, a critical analysis of the direct evidence of an association between NPSD and sudden death is required. The underlying physiological mechanism, although essential in the assessment of causality, becomes less important when the overall relationship is evaluated. Because of the low incidence of sudden cardiac death, the larger clinical trials or epidemiological studies in hypertensive patients are most likely to provide this crucial evidence.

In table 1.3, the results of the *experimental studies* assessing the efficacy of non-potassium sparing diuretic antihypertensive therapy, and in which the incidence of sudden cardiac death was reported are summarized.[11,16,30-32,165-170] Trials not including sudden death as a separate end-point[36,171,172] and trials without a NPSD treatment arm[33,36,172] are not included in the table, but will be discussed below. As a measure of effect the rate ratio, i.e. the ratio of the incidence of sudden death in the NPSD treated group and the comparison group, was computed. Since elevated blood pressure is a well-established risk indicator of sudden cardiac death,[173,174] associated with a two- to fourfold increased risk,[175] treatment of hypertension may be expected to reduce the incidence of sudden cardiac death. As shown in figure 1.5, the expected favorable influence of NPSD on sudden cardiac death incidence was demonstrated in the Veterans Administration Cooperative study (VA) only, although the 95% confidence interval is compatible with the opposite effect (rate ratio 0.5, 95% CI 0.2-1.8).[165] In the remaining nine studies, the point estimate of the incidence of sudden death in the NPSD treated group was found to be similar to, or even higher than in the comparison group. The publication of the results of the Multiple Risk Factor Intervention Trial (MRFIT) in 1982 set about a vigorous discussion on the alleged relationship between NPSD, arrhythmias and sudden cardiac death.[11,176] In this study, 12,866 men at the upper 15% of a cardiovascular risk score were randomly allocated to either a "special intervention" (SI) strategy, including stepped-care antihypertensive drug treatment, or the "usual" sources of health care (UC) in the community. During the 7 year follow-up period the cardiovascular risk profile

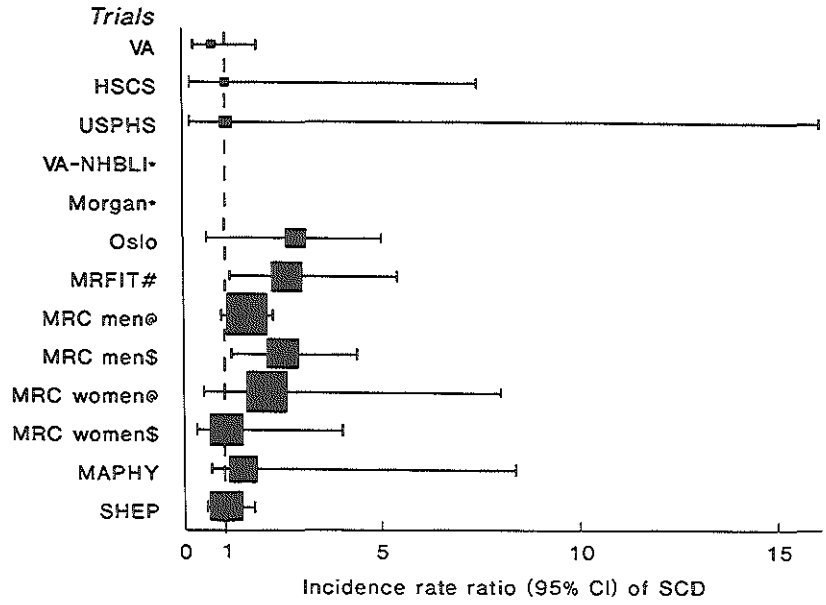

Figure 1.5
Incidence rate ratios (and 95 % confidence intervals) of sudden cardiac death in hypertensive patients on non-potassium sparing diuretic therapy compared to patients on control treatment. Results of ten trials in patients with mild to moderate hypertension. Differences in the total number of patient-years experienced in the individual trials are reflected in the areas of the squares representing the point estimates of the rate ratios.

* = not computable because of zero cases in the denominator; # = subgroup of hypertensive patients with ECG-abnormalities at baseline; @ = patients randomized to placebo treatment were considered the comparison group; $ = patients randomized to propranolol treatment were considered the comparison group. Abbreviations: SCD = sudden cardiac death; CI = confidence interval; VA = Veterans Administration Cooperative Study on Antihypertensive Agents (diastolic blood pressure 90-114 mm Hg); HSCS = Hypertension-Stroke Cooperative Study; USPHS = United States Public Health Service Hospitals Cooperative Study; VA-NHBLI = Veterans Administration-National Heart, Lung and Blood Institute Study; MRFIT = Multiple Risk Factor Intervention Trial; MRC = Medical Research Council trial of treatment of mild hypertension; MAPHY = Metoprolol Atherosclerosis Prevention in Hypertension trial; SHEP = Systolic Hypertension in the Elderly Program.

improved to a considerably larger extent in the SI group. Surprisingly however, no difference in coronary heart disease mortality between SI and UC men who were hypertensive at baseline could be demonstrated. As an explanation for these findings the authors suggested that the beneficial effect of lowering blood pressure levels were counterbalanced by a deleterious effect of NPSD treatment on coronary heart disease (CHD) mortality in hypertensive patients with baseline resting ECG abnormalities. More detailed analyses[16,177-179] showed that the excess CHD mortality in the hypertensive SI men was attributable to an increase in the incidence of sudden cardiac death within 1 hour. However, no effect of either the dose of the diuretic drug or the most recent serum potassium level on the incidence of sudden cardiac death in the SI subgroup was revealed. Throughout the years the conclusions of the MRFIT research group have been criticized.[24,180] In particular, the unexpectedly low CHD mortality reported in the usual care group with baseline ECG abnormalities, has been suggested to have led to the disturbing findings. Indeed the sudden death incidence was higher in UC patients without than in those with ECG abnormalities. However, this argument is unlikely to fully explain the findings, because the use of NPSD was associated with increased CHD mortality within the group of hypertensive SI men with baseline ECG abnormalities.[16] Although the MRFIT subanalyses should be interpreted with caution, the conclusion that NPSD treatment accounted for at least part of the increased incidence of sudden cardiac death in the SI intervention group with baseline resting ECG-abnormalities seems warranted. This conclusion was confirmed by a report from the Oslo study, using the ECG-criteria applied in the MRFIT.[181] A similar analysis of the data from the Hypertension Detection and Follow-up Program (HDFP)[182] revealed no excess risk of sudden death among "stepped care" patients with baseline ECG-abnormalities.[183] However, the results of a subsequent analysis restricted to the HDFP participants with characteristics comparable to the MRFIT participants, were remarkably similar to the MRFIT findings.[184] Crucial evidence of a relationship between NPSD treatment and sudden cardiac death was produced by the Medical Research Council (MRC) trial of treatment of mild hypertension.[185] The incidence of sudden cardiac death was found to be higher in men in the diuretic group compared to both the propranolol- and the placebo group, although only the comparison with the betablocker group reached statistical significance (rate ratio 2.4, 95% CI 1.2-4.4).[30,186] No evidence of a differential effect of bendrofluazide on patients with and without ECG-abnormalities at baseline was seen. Due to the small number of sudden cardiac deaths, the results with regard to the female participants were not conclusive.[30] In the Metoprolol Atherosclerosis Prevention in Hypertension (MAPHY) trial in middle-aged men the incidence of sudden cardiac death, defined as death occurring within 24 hours of onset of symptoms, was reported to be significantly

lower in the metoprolol group than in the group taking bendrofluazide or hydrochlorothiazide ($p=0.017$).[31] When only deaths occurring within one hour were considered, the estimated rate ratio remained the same, at the cost of loss of precision ($p>0.05$). In contrast, antihypertensive therapy including the betablocker oxprenolol did not seem to reduce the sudden death incidence compared with a therapy excluding oxprenolol in the International Prospective Primary Prevention Study in Hypertension (IPPPSH).[187] However, the results are difficult to interpret because diuretics, including potassium sparing drugs, were added in 67% of the betablocker and 82% of the non-betablocker group. In the recently published Systolic Hypertension in the Elderly Trial (SHEP) treatment with chlorthalidone (12.5 to 25 mgr) reduced the incidence of stroke and myocardial infarction in comparison with placebo treatment, in elderly patients with isolated systolic hypertension. However, the number of sudden cardiac deaths was similar in the two groups.[32] Thus, it could be argued that the reduction in cardiovascular events would have been even more impressive had NPSD therapy reduced the incidence of sudden cardiac death.

Several controlled trials not included in table 1.3 provide some additional evidence on the issue. The results of the Australian therapeutic trial in mild hypertension,[171] have often been quoted as evidence against an adverse effect of NPSD on sudden death. Indeed the incidence of fatal ischemic heart disease, the category which probably included sudden cardiac deaths, was considerably but not significantly higher in the placebo group than in the chlorothiazide treated patients. The effect of the diuretic on sudden death, however, was not determined. The European Working Party on High Blood Pressure in the Elderly trial (EWPHE) was the first trial in which the efficacy of potassium sparing diuretic therapy in the treatment of hypertension was assessed.[172] Treatment with hydrochlorothiazide/triamterene clearly reduced the incidence of myocardial infarction, but again, the effect on sudden cardiac death was not specified. Similar conclusions may be drawn from two recently published hypertension trials in the elderly which also included potassium sparing diuretic therapy. In the Swedish Trial in Old Patients with Hypertension (STOP-Hypertension),[33] treatment with atenolol or a potassium sparing diuretic combination (amiloride and hydrochlorothiazide) reduced the incidence of sudden death compared to placebo treatment in elderly hypertensives (rate ratio 0.33, 95% CI 0.08-1.10). However, the relative contribution of the individual antihypertensive drugs to the impressive results of this trial, and hence the possible role of the potassium sparing diuretic, remains unclear. In the Medical Research Council trial in older adults a potassium sparing diuretic combination (amiloride/ hydrochlorothiazide) was compared to atenolol and placebo treatment.[36] The incidence of stroke and coronary events was reduced in the diuretic treated patients only. In

contrast to the alleged cardioprotective properties of betablocking therapy in hypertensive patients, the effect of atenolol did not appreciably differ from placebo therapy. Unfortunately, no incidence rates of sudden death were reported. Although specific sudden death incidences are lacking in two of the three latter studies, the findings suggest that the addition of a potassium sparing diuretic may prevent an increased incidence of sudden death associated with non-potassium sparing diuretics.

Several *nonexperimental studies* have provided additional evidence that diuretics are related to the occurrence of sudden death. In a report after 30 years of follow-up of the Framingham cohort, antihypertensive drug therapy was associated with a twofold increased risk of sudden death among hypertensive men and women.[188] Because treated and untreated hypertensives may be expected to differ in many respects other than antihypertensive treatment, notably the level of cardiovascular risk factors, a multivariate analysis was performed to adjust for differences in prognosis. However, the possibility that certain characteristics other than drug treatment may be responsible for the reported increased risk of sudden cardiac death cannot be excluded. The interpretation of the results is further hindered by lack of information on the type of antihypertensive treatment prescribed, although the predominant antihypertensive drugs used were NPSD and reserpine. This study further illustrates the large potential of nonexperimental studies in assessing determinants of rare events: The number of sudden cardiac deaths reported (n=260) was nearly three times the number found in the largest hypertension trial.[30] In a Dutch nested case-control study of 245 sudden cardiac deaths among patients with available 24-hour ECG recordings the use of diuretics was an independent predictor of sudden cardiac death.[189] However, differences in other risk factors could have distorted the findings and the study population was not restricted to hypertensive patients. In another nonexperimental study the relative risk of myocardial infarction among hypertensive patients without prior cardiovascular event and treated with potassium losing diuretics was 3.1 (95% CI 0.7-3.1) compared to those on potassium sparing diuretics.[190] Sudden death was not considered separately and no efforts were made to adjust for differences in prognosis between the two treatment groups. Finally, in a recent 4.5 year follow-up study of 759 diabetic outpatients with severe retinopathy,[31] the highest cardiovascular mortality in patients with documented hypertension was seen among those on diuretic treatment. Again, however, the implication of the results is unclear because no data on sudden cardiac death or on the type or dosage of the diuretic used were available.

DISCUSSION

In our analysis of studies published since 1980, a clear dose-response relationship between the use of non-potassium sparing diuretics and fall in serum potassium levels in hypertensive patients, irrespective of the duration of therapy, was demonstrated. Hence, a fall in serum potassium should be expected even after the administration of the lower dosages currently prescribed (< 1 DDD/day). Unfortunately, since only a minority of studies included a randomly allocated placebo-treated control group the influence of non-diuretic related factors on the reported electrolyte changes cannot be excluded in these studies. Nevertheless, their findings seem to be in accordance with studies in which a proper control group was included. Analogous to the change in serum potassium, non-potassium sparing diuretics seem to decrease serum magnesium levels, total body potassium content and intracellular K and Mg concentrations. However, the evidence is less consistent and data are too limited to allow conclusions concerning a dose-response effect. More controlled experimental studies are needed to estimate the magnitude of the reduction of intracellular and total body stores of potassium and magnesium following diuretic therapy, in particular in the lower dosages. This is emphasized by the existence of intracellular electrolyte deficits in the absence of hypomagnesemia and hypokalemia reported in cross-sectional studies,[83-85] and the alleged role of the intra/extracellular gradient of potassium and magnesium in arrhythmogenesis.[21]

Findings are conflicting with respect to the influence of non-potassium sparing diuretic therapy on ventricular arrhythmias in hypertensive patients without clinical evidence of clinical heart disease. From numerous comments it seems that, depending on one's prior belief, the individual studies are either viewed as important evidence or severely criticized because of methodological flaws. In fact, several methodological problems, in particular the omittance of a randomly allocated control group and lack of statistical power in the experimental studies, and incomparability of prognosis in nonexperimental studies are present. However, these methodological problems are certainly not confined to the positive or the negative studies. One can only speculate on the factors that may contribute to the contrasting findings. The dosage or type of drug as well as the method applied to measure the arrhythmias, do not seem to form an explanation. Differences in selection criteria, however, are likely to play some role. The selection by Holland[9] and Hollifield[10] of patients with a higher probability to develop hypokalemia and arrhythmias, and the fact that Papademetriou included only black men[111,125] and Haalboom chose patients with a mean age of 33 years,[124] could have led to opposite findings. That inclusion of patients at higher risk for arrhythmias affects the outcome of a study is emphasized by the arrhythmogenic properties of diuretic therapy

demonstrated in the two studies performed in hypertensive patients with evidence of heart disease.[103,113] In contrast, however, in the studies among hypertensive patients with left ventricular hypertrophy an increase in arrhythmias during potassium losing diuretic therapy could not be demonstrated.[111,132,134] In several but not all of the studies in which a relationship between NPSD and arrhythmias was found, decreased serum potassium levels were associated with arrhythmias.[9,10,35,70,131] Serum magnesium was only determined in four of these studies, with opposite findings.[35,97,113,131] The failure to detect a strong correlation of hypokalemia and hypomagnesemia with VEA in our analysis of published studies, may be a reflection of the limitations of serum levels as indices of K and Mg metabolism, but could also be an indication of the involvement of other diuretic-induced phenomena in the development of ventricular arrhythmias.

Important evidence of an association between non-potassium diuretic therapy for hypertension and sudden cardiac death is provided by the published trials in mild to moderate hypertension. Although the individual studies may be criticized because of the limited number of sudden cardiac deaths reported, or the inability to allow conclusions regarding the underlying causal mechanism,[11,16,191] the consistent failure of NPSD therapy to reduce the incidence of sudden cardiac death is striking. Apparently, the reduction in sudden death incidence that could be expected because of the blood pressure lowering properties of diuretic therapy, may be offset by a deleterious effect on sudden death associated with NPSD. The identification of patients susceptible to develop sudden death during NPSD therapy deserves further study, because subgroups suggested by some studies, e.g. men with baseline ECG abnormalities,[11,182] were not confirmed to be at high risk by other studies.[30,188] The impressive reduction in the incidence in coronary events or sudden death demonstrated in the three trials in which the efficacy of potassium sparing diuretics was evaluated,[33,36,172] provides some evidence that the deleterious effect of non-potassium sparing diuretics on sudden death shown in several trials, may be avoided when potassium sparing diuretics are prescribed. Given the mechanism supposed to relate non-potassium sparing diuretics to sudden cardiac death, this certainly seems a likely conclusion. Alternatively, the findings in these studies, which were restricted to elderly hypertensives, could indicate that antihypertensive diuretic therapy is less likely to increase the risk of sudden death in older than in middle-aged hypertensive patients. Additional information from studies comparing potassium sparing to non-potassium sparing diuretic therapy among elderly and middle-aged hypertensive patients is needed to further clarify this point.

In conclusion, recent evidence from large-scale studies strongly suggests that non-potassium sparing diuretic therapy could induce sudden cardiac death in hypertensive patients. Diuretic-induced potassium and magnesium depletion, leading to arrhythmias

and subsequent sudden death is likely to be the underlying mechanism, although the importance of such an effect in hypertensive patients without clinical evidence of heart disease remains disputed. It should be stressed that the placebo-controlled trials have left little doubt as to the overall beneficial effects of non-potassium sparing diuretic therapy for hypertension.[192] In clinical practice, the impressive reduction in the incidence of cerebrovascular disease and several other complications related to elevated blood pressure, probably outweighs any propensity to induce sudden cardiac death. However, findings from several studies comparing NPSD to betablocking agents and studies assessing the efficacy of potassium sparing diuretics, indicate that the risk-benefit ratio of alternative antihypertensive drugs may be more favorable. This could at least in part be attributed to a hypokalemia-mediated excess risk of sudden death associated with non-potassium sparing diuretics. Thus, alternative antihypertensive medications, notably potassium sparing diuretics and betablockers, may be preferred as drugs of first choice in the treatment of hypertension, although the efficacy of betablocking agents in elderly hypertensive patients has recently been challenged.[36,193]

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CHAPTER 2

NON-POTASSIUM SPARING DIURETICS AND THE RISK OF SUDDEN CARDIAC DEATH - AN ESTIMATE OF THE IMPACT ON THE DUTCH HYPERTENSIVE POPULATION

INTRODUCTION

The unexpected results of the Multiple Risk Factor Intervention Trial in 1982,[1,2] suggesting that non-potassium sparing diuretic therapy could increase the risk of sudden cardiac death in hypertensive patients, initiated vigorous discussion.[3-11] Notwithstanding the favorable benefit-risk ratio of thiazides reported in hypertension trials,[12,13] the possibility that the prescription of these drugs could violate the dictum "primum non nocere" raised concern among the medical profession.[14,15] During the last decade many studies have addressed the potential causal relationship between thiazide-associated hypokalemia and hypomagnesemia, cardiac arrhythmias and sudden cardiac death. The results, however, and in particular the interpretation of the findings are conflicting.[15-24] The fact that these studies are by far outnumbered by the editorial comments on the issue indicates that even a moderately increased risk of sudden death among thiazide-treated hypertensive patients constitutes a considerable health problem. Up to the present, however, only few attempts have been made to quantify its magnitude.[14,25] The prominent role of non-potassium sparing diuretics in the treatment of hypertension, as advocated at several national consensus meetings,[26-28] further underlines the need to obtain estimates of the impact of the potential adverse effects of these drugs. Also in the Netherlands, non-potassium sparing diuretic therapy has continued to be a drug of first choice in the initial treatment of hypertension, not in the least because of its relative low cost.[29,30] The availability of detailed information on the use of different antihypertensive drugs in the Netherlands, and data on the incidence of sudden cardiac death in the Medical Research Council trial of treatment of mild hypertension (MRC-trial),[31] enabled us to quantify the potential health implications of an association between non-potassium sparing diuretic therapy and sudden death. Thus, the proportion and the absolute number of sudden cardiac deaths among treated Dutch hypertensive patients, that may be attributed to the use of non-potassium sparing diuretics could be estimated.

METHODS

To quantify the health implications of the use of non-potassium sparing diuretics (NPSD) in the treatment of hypertension, several calculations were made.

First, the *attributable proportion among the users of NPSD* (AR_{NPSD}), i.e. the proportion of the incidence of sudden cardiac death among NPSD treated hypertensive patients that is attributable to the exposure to these antihypertensive drugs, was estimated.[32] Another term frequently used for this measure is "etiologic fraction among the exposed", assuming a causal relationship between the exposure and the outcome.[33,34]

The AR_{NPSD} was calculated as follows:

$$AR_{NPSD} = \frac{Ie - Io}{Ie}$$

where Ie and Io represent incidence rates of sudden cardiac death among patients receiving NPSD for hypertension and those on other antihypertensive drugs, respectively.[32,35] Estimates of incidence rates (number of events per 1000 patient years) of sudden death were obtained from the results of the MRC-trial. The methodology of this trial has been discussed in detail elsewhere.[35] In short, the MRC-trial was a study in which men and women aged 35-64 years, with a diastolic blood pressure of 90-109 mm Hg, were randomly allocated to either a betablocking agent (propranolol), a non-potassium sparing diuretic (bendrofluazide), or placebo treatment. In total, 2285 men and 2118 women were treated with propranolol, whereas 2238 men and 2059 women were randomly allocated to bendrofluazide treatment. The mean follow-up time was five years. Sudden cardiac death was defined as death occurring within 1 hour of the onset of symptoms while autopsy did not reveal a non-cardiac cause.

Second, the *attributable proportion among the total population of treated hypertensives* (AP_{TRHT}) was calculated. Analogously, this measure could be named "etiological fraction among the total population".[34] The AP_{TRHT} is defined as the proportion of the incidence of sudden cardiac death among Dutch patients on drug treatment for hypertension, that is attributable to the use of non-potassium sparing diuretics. It is computed as follows:

$$AP_{TRHT} = \frac{It - Io}{It}, \text{ where } It = Pe \cdot Ie + (1-Pe) \cdot Io$$

It represents the (age-specific) incidence of sudden cardiac death in all patients on drug treatment for hypertension and Pe is the (age-specific) prevalence of the use of non-potassium sparing diuretics among treated hypertensives.[32] The current use of different types of antihypertensive drugs in the Netherlands was estimated from a survey among a random sample of 1300 physicians (668 general practitioners and 632 specialists) performed by the Dutch Institute of Medical Statistics (IMS). The physicians provided standard information, including drug prescription and indication, on every consultation during a period of seven days in 1988. For the purpose of our study antihypertensive drugs were categorized in two groups: non-potassium sparing diuretics (e.g. thiazides,

loop-diuretics) and a large group of other, "potassium sparing", antihypertensive drugs (potassium sparing diuretics, betablockers, ACE-inhibitors, calcium antagonists, etc.).* The incidence rate of sudden death among all treated hypertensive men aged 20 years or over (It) was estimated by applying the age-specific It from the MRC-trial, to the age-distribution of the drug-treated hypertensive population in the Netherlands. The number of inhabitants treated for hypertension was calculated by extrapolating the results of a previously published population survey (EPOZ-study),[36] to the general population in the Netherlands on January 1, 1991.[37]

Finally, the *number of sudden cardiac deaths per year attributable to the use of non-potassium sparing diuretics*, occurring among Dutch men on drug treatment for hypertension was estimated, by applying the age-specific incidence rates It and attributable proportions (AP_{TRHT}) calculated from the MRC-trial, to the hypertensive population in the Netherlands. The 95% confidence interval (CI) of the AP_{TRHT}[38,39] was computed to estimate the 95% CI of the number of attributable sudden cardiac deaths. Because of the limited number of sudden cardiac deaths (n=8) recorded among the female participants of the MRC-trial,[20] and the lack of information on age-specific sudden cardiac death incidence in treated hypertensive women from other studies, no reliable estimates of the attributable proportions among hypertensive women could be made. Thus, all calculations were performed in men only, although the possibility of generalizing the findings to the female hypertensive population are discussed.

RESULTS

The incidence rate of sudden cardiac death in hypertensive men treated with bendrofluazide in the MRC-trial was 2.7/1000 patient years, and the corresponding rate for those on propranolol treatment was 1.1/1000 patient years.[31] Hence, 59% (95% confidence interval 21 to 79%) of the sudden cardiac deaths occurring among men treated with non-potassium sparing diuretics could be attributed to the use of these drugs. As demonstrated in table 2.1, this attributable proportion (AP_{NPSD}) or etiologic fraction appears to gradually decrease with advancing age.

The different types of drugs prescribed for hypertension in the Netherlands in 1988 are shown in table 2.2. In all age groups, non-potassium sparing diuretics are more likely to be the antihypertensive drug of choice in women than in men. In total, 13.6 % of the men and 18.4% of the women on drug treatment for hypertension use non-potassium sparing diuretics. Furthermore, in both sexes the prescription of non-potassium

* Unpublished data

Table 2.1. Number of sudden cardiac deaths (n), incidence of sudden cardiac death (per 1000 patient years) in the bendrofluazide (Ie) and propranolol (Io) treatment groups, and attributable proportion among users of non-potassium sparing diuretics (AP_{NPSD}) among 4523 male participants in the Medical Research Council trial of treatment of mild hypertension.[35]

Age (years)	bendrofluazide (2238 men)		propranolol (2285 men)		AP_{NPSD}
	n	Ie	n	Io	
35-44	4	1.6	1	0.4	75 %
45-54	12	2.5	5	1.0	60 %
55-64	13	3.6	6	1.6	56 %
35-64	29	2.7	12	1.1	59 %

Table 2.2. Prescription of non-potassium sparing diuretics (Pe) and "other" antihypertensive drugs (Po)** among patients on drug treatment for hypertension in the Netherlands in 1988.*[@]

Age (years)	Men		Women	
	Pe	Po	Pe	Po
<45	6.2 %	93.8 %	11.1 %	88.9 %
45-64	13.5 %	86.5 %	16.4 %	83.6 %
>64	16.5 %	83.5 %	21.3 %	78.7 %
Total	13.6 %	86.4 %	18.4 %	81.6 %

* Non-potassium sparing diuretics include: thiazides, loop-diuretics, etc.

** "Other" antihypertensive drugs include: potassium sparing diuretics (amiloride, triamterene, spironolactone), betablocking agents, ACE-inhibitors, calcium antagonists, etc.

@ Unpublished data from the Institute of Medical Statistics (IMS).

Table 2.3. Age-specific incidence rates (per 1000 patient years) of sudden cardiac death (I_t) and proportion of sudden cardiac deaths attributable to non-potassium sparing diuretics (AP_{TRHT}) among all men on drug treatment for hypertension in the Netherlands.

Age (years)	Io	It*	AP_{TRHT}*
< 35	0.4	0.5	20 %
35-44	0.4	0.5	20 %
45-54	1.0	1.2	17 %
55-64	1.6	1.9	16 %
> 65	1.6	1.9	16 %
> 20	1.34**	1.60**	16 %

Io Incidence of sudden cardiac death among men on propranolol treatment in the MRC-trial.

* It and AP_{TRHT} are calculated with reference to the incidence rate of sudden cardiac death in the diuretic- and betablocker groups in the MRC-trial.[35] The incidence rates in the highest and lowest age categories are assumed to be equal to incidences in the 35 to 44 years, and 55 to 64 years categories, respectively.

** Estimated by applying the age-specific incidence rates of sudden cardiac death to the age distribution of men on drug treatment for hypertension in the Netherlands (table 2.5).

sparing diuretics clearly increases with age relative to other antihypertensive medication. The incidence rate of sudden cardiac death in all treated hypertensive men in the Netherlands aged 20 years or over is estimated to be 1.34/1000 patient years, as based on MRC data (table 2.3). The proportion of sudden deaths occurring among these men that could be attributed to the exposure to non-potassium sparing diuretics (AP_{TRHT}) is estimated to be 16% (95% confidence interval 3 to 29 %). This suggests that 16% of the cases of sudden cardiac death may be prevented when other antihypertensive drugs, in this case betablockers, are used. No clear differences in the attributable proportion between age categories could be demonstrated.

Of all men aged 20 years or over in the Netherlands, 7.1% is on drug treatment for hypertension, whereas the corresponding proportion in women is considerably larger: 16.7%. In both sexes a substantial increase in the prevalence of drug-treated hypertension with advancing age exists (table 2.4). The prevalences among men and women aged 65 years or over are 23.3% and 45.7%, respectively. In table 2.5 the number of sudden cardiac deaths in men treated for hypertension in the Netherlands, attributable to the use of non-potassium sparing diuretics is shown. The estimated number of attributable sudden deaths is 102 (95% CI 12 to 174) per year. The vast majority of the sudden cardiac deaths due to the usage of NPSD occurs in men aged 65 years or over.

DISCUSSION

For over a decade, the controversy regarding the possible role of non-potassium sparing diuretic therapy for hypertension in the development of sudden cardiac death has continued.[10,11,40,41] However, estimates of the health impact of this potential adverse effect of potassium wasting diuretics are few. The objective of this study was to obtain such an estimate. The proportion of sudden cardiac deaths attributable to the use of non-potassium sparing diuretics is 59% (95% CI 21 to 79%) among men using these drugs. In all men on drug treatment for hypertension in the Netherlands this attributable proportion is 16% (95% CI 3 to 29%). It is estimated that in the total population of 385,000 treated hypertensive men, 102 (95% CI 19 to 180) sudden cardiac deaths per year may be due to the prescription of non-potassium sparing diuretics, amounting to 1 case of sudden cardiac death per 3800 treated hypertensives. This indicates that theoretically one sixth of the approximately 620 cases of sudden cardiac deaths occurring among men on antihypertensive drug treatment each year, could be prevented when antihypertensive drugs other than NPSD were prescribed. Given the all-cause mortality rate of male participants in the MRC trial on placebo (8.2/1000 patient years) and bendrofluazide therapy (7.5/1000 patient years),[20] NPSD therapy compared to placebo treatment may be expected to save 270 lives per year among the 385,000 male hypertensive patients in the Netherlands. Hence, the net mortality benefit could be substantially increased when the sudden deaths attributable to NPSD treatment were avoided.

Few other estimates of the potential health impact of the causal relationship between NPSD and sudden death have been reported. The methods applied differ considerably from our study. Poole-Wilson calculated the number of sudden cardiac caused by NPSD-induced hypokalemia,[25] by assuming a prevalence of plasma potassium levels below 3.5 mmol/l of 50%, and below 3.0 mmol/l of 7% during NPSD treatment,

Table 2.4. Proportion of men and women on drug treatment for hypertension (% treated) in the Netherlands.[36]

Age (years)	Men % treated	Women % treated
20-34	1.0	2.1
35-44	2.5	6.2
45-54	7.6	17.2
55-64	13.3	27.0
>64	23.3	45.7
Total >20	7.1	16.2

Table 2.5. Estimated number of sudden cardiac deaths (SCD) per year, attributable to the use of non-potassium sparing diuretic therapy (NPSD) among men on drug treatment for hypertension in the Netherlands.

Age (years)	# men*	% treated	# treated men	It	AP_{TRHT}	attributable SCD
20-34	1,944,585	1.0	19,446	0.5	20%	2
35-44	1,210,020	2.5	30,251	0.5	20%	3
45-54	875,310	7.6	66,524	1.2	17%	14
55-64	684,451	13.3	91,032	1.9	16%	28
> 64	770,550	23.3	179,538	1.9	16%	55
> 20	5,484,916	7.1	386,791	1.6	16%	102

* Number of male inhabitants in the Netherlands on January 1st, 1991;[37] % treated = proportion of men on drug treatment for hypertension; It = incidence of sudden cardiac death among Dutch men on drug treatment for hypertension.

and a yearly incidence of life-threatening arrhythmias associated with these plasma levels of 0.1 and 0.4 percent, respectively.[42,43] Thus it was estimated that among 1,000,000 NPSD treated hypertensives in the United Kingdom, 780 cases of hypokalemia related sudden death occur each year. Using our approach, a hypothetical group op 1,000,000 hypertensive men on NPSD therapy in the Netherlands would experience twice as many (1600) NPSD-attributable sudden cardiac deaths. The different methodological approaches may be largely responsible for the differences between the studies. The estimate provided by the British study is highly dependent on the assumptions regarding the prevalence of hypokalemia and the incidence of fatal arrhythmias. This is illustrated by an earlier estimate of only 450 hypokalemia-associated deaths per year provided by the same author, but based on lower prevalences of hypokalemia and subsequent arrhythmias.[14] Obviously, our computations are influenced by other assumptions, notably the generalizibility of the incidence rates of sudden death reported in the treatment arms of the Medical Research Council trial to the Dutch hypertensive men, after adjustment for differences in age. The findings from the MRC-trial were chosen for the purpose of the present analysis for several reasons. First, it is a large randomized controlled trial in which two antihypertensive drugs, including a non-potassium sparing diuretic, were compared. Second, the time interval of one hour used in definition of sudden cardiac death is in accordance with current views. Most importantly however, it is the only trial from which detailed age-specific incidence rates of sudden cardiac death are reported. Other trials were considered less useful for our computations because sudden cardiac death was not reported as a separate end-point,[44] no direct comparison to NPSD treatment was made,[45,46] or because age-specific incidence rates were lacking.[21,47] It should be noted, however, that the choice of the betablocker treated MRC-participants as the reference group in the calculation of the attributable proportions, may have accounted for the larger health impact found in our study. Betablocking therapy in particular has been suggested to *reduce* the incidence of sudden death,[21,48] and therefore at least part of the number of NPSD-attributable sudden deaths may not be caused by non-potassium sparing diuretic therapy per se but be related to the fact that betablocking therapy was withheld, i.e. to the cardioprotective effect of betablockers. However, since non-potassium sparing diuretics and betareceptor antagonists are still considered cornerstones in the first-line treatment of hypertension,[26-29] the question whether the attributable deaths may be explained by the adverse effect of the former or the beneficial effect of the latter drugs, is of relative importance only. Furthermore, a cardioprotective effect of betablocker treatment could not be demonstrated in several recently published trials in elderly hypertensive patients.[44,46,49] For example, in the MRC-trial of treatment of hypertension in older adults atenolol did not reduce the incidence of coronary events

compared to placebo treatment, whereas potassium sparing diuretic therapy clearly did.[44]

Although the potential health consequences of non-potassium diuretic therapy for hypertension found in our analysis could be considered substantial, the findings should be interpreted with caution. As in most studies determining the magnitude of health effects, the assumptions underlying the estimates may be criticized. A major drawback of the present analysis lies in the lack of reliable estimates of the age-specific sudden death incidence among the women in the Medical Research Council trial, due to the small number of sudden cardiac deaths reported during the 5 year follow-up period (n=8). Because none of the other hypertension trials provided separate data for women on different antihypertensive drug regimes, the potential health impact of NPSD in hypertensive women could not be determined. Given the high prevalence of the NPSD treated hypertension among Dutch women, however, even a small excess risk associated with these drugs would have considerable consequences. Extrapolation of the attributable proportions for men to the female hypertensive population would lead to estimates exceeding the potential number of excess sudden cardiac deaths among men. More precise data on sudden cardiac death incidence among female hypertensive patients are needed to quantify the potential health impact. No valid estimates of the incidence of sudden cardiac deaths among elderly men on NPSD and betablockers for hypertension were available from the MRC-trial. Since the incidence of sudden death increases with age,[50] the incidence rates applied in our study could be underestimates. This, however, is not confirmed by the findings in a recent trial of systolic hypertension in the elderly (SHEP),[51] where the incidence of sudden cardiac death during chlorthalidone treatment was 2.2/1000 patient years only, but the prescribed dosages were low. As in most controlled hypertension trials, patients with overt symptoms of cardiovascular disease in the initial screening phase before randomization or with prior cardiovascular events, were excluded from the MRC-trial.[35] Consequently, the participants in the trial may be expected to have a more beneficial cardiovascular risk profile and a lower incidence of sudden cardiac death than the average hypertensive patients visiting the doctor's office. Moreover, the propensity of NPSD to induce sudden death has been demonstrated to be more pronounced among patients with symptomatic ischemic heart disease,[52,53] whereas other hypertensives and in particular betablockers, may have a beneficial effect.[48] Hence, the incidence rates of sudden cardiac death among participants on NPSD-treatment relative to those on betablocker treatment reported in the MRC-trial may be an underestimate of the relative incidence rates as they occur in daily medical practice. Our estimate of the health impact of non-potassium sparing diuretics may therefore be diluted. In contrast, the relatively high dosage of bendrofluazide used in the MRC-trial (10 mgr/day) may have led to an overestimation of the risk associated with NPSD

treatment, because the prescribed dosage of the thiazides has gradually decreased during recent years.

Although several limitations of the present analysis exist, it may be concluded that the estimate of 102 cases of sudden cardiac death attributable to NPSD-treatment for hypertension in the Netherlands each year, is most likely to be an underestimate of the true effect. As a consequence, a considerable part of the potential mortality benefit of non-potassium sparing diuretic treatment for hypertension, may be counterbalanced by an increase in sudden cardiac death incidence. This notion needs consideration, together with other pros and cons of these and alternative antihypertensive medications, in the ultimate decision to prescribe a particular drug in a patient with hypertension. Although the present calculations apply to the specific situation in the Netherlands, similar estimates of the health impact of non-potassium sparing diuretic therapy for hypertension could be made for other countries when data on the number of inhabitants, the age- and gender-specific prevalence of treated hypertension, and the prescription rate of non-potassium sparing diuretics are available. This may especially be important to countries where non-potassium sparing diuretics have continued to be a drug of first choice in the treatment of hypertension.[28,54-6]

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CHAPTER 3

DOES DRUG TREATMENT IMPROVE SURVIVAL?

RECONCILING THE TRIALS IN MILD TO MODERATE HYPERTENSION

INTRODUCTION

Practising physicians are confronted regularly with the question whether or not a particular patient with mild to moderate hypertension should be put on drug treatment. In this decision the potential benefits and hazards of drug treatment should be weighed carefully. Because blood pressure is a well-established risk factor of all-cause mortality, and of mortality from coronary heart disease and stroke, antihypertensive therapy may be expected to favorably influence survival. Especially in middle-aged patients, treatment benefit in terms of number of life-years gained could be considerable. As expected, the clinical trials in middle-aged patients with mild to moderate hypertension demonstrated an impressive reduction in fatal stroke incidence among patients randomized to antihypertensive drug therapy. However, the results regarding the effect on coronary heart disease- and all-cause mortality have been less convincing. Did the reports of the first trials indicate that treatment of even mildly raised blood pressure reduces the risk of death from all-causes and coronary heart disease,[1-5] doubts were raised again after the publication of others.[6,7] Several explanations for these disappointing results have been put forward, including the limited intervention period and the existence of a "J-shaped curve", i.e. an increase in cardiovascular events when the treated blood pressure falls below a critical level.[8] Moreover, it has been suggested that non-potassium sparing diuretics, the antihypertensive drugs evaluated in the majority of the studies, could induce premature death in certain patients by increasing the incidence of sudden cardiac death,[6,9-11] or by unfavorably influencing lipid metabolism.[12]

Fueled by these conflicting results and the limited statistical power of the individual trials, several attempts have been made to pool the results of the trials in mild to moderate hypertension.[13-18] A major limitation of the method of meta-analysis applied in these reports,[19] however, lies in the assumption that the direction of the effect is the same across subgroups of patients included in the trials, i.e. the alleged homogeneity of the study populations. Consequently, this approach does not allow an assessment of a beneficial effect in some and no or even a hazardous effect of drug treatment on survival in other patients, other than by chance variation. Yet, a distinction between subgroups of patients in whom antihypertensive therapy may do more harm than good and vice versa, seems essential to the daily management of hypertensive patients in medical practice.

To evaluate whether the published trials in mild to moderate hypertension did indeed show variability in effect on survival that could be explained by discrepancies in patient characteristics between the studies, we pooled the results of the clinical trials using a newly developed method of meta-analysis based on weighted linear regression.

Furthermore, we studied how the findings could be applied in medical practice, by identifying those middle-aged patients with mild to moderate hypertension in whom pharmacological treatment is most likely to improve survival.

METHODS

Selection of the clinical trials

To obtain information on as many clinical trials as possible, a thorough literature search was performed. A trial was included in the present analysis if the following criteria were met: (1) The trial was restricted to participants with mild to moderate hypertension, defined as a diastolic blood pressure between 90 and 114 mm Hg.[1-7,9,20-31] Trials in patients with isolated systolic hypertension were not included.[32] (2) The trial had to be performed in middle-aged or younger patients, since our scope was on mortality rather than on morbidity or quality of life, and the relative importance of the latter end-points increases with advancing age. Hence, trials confined to elderly hypertensives, i.e., above 60 years of age, were excluded.[26-31] (3) The participants had to be without antihypertensive drug treatment before entry into the trial, because the aim of our analysis was to assess the effect of initiation of drug therapy rather than of a change in antihypertensive medication. Thus, two further studies were excluded from the analysis.[23,24] In studies where separate results were given for those with and without antihypertensive drug use at entry, only the latter were used.[4,6] (4) Allocation of the participants to the intervention and the control group had to be randomized in order to ensure comparability of prognosis between the treatment arms. The two trials in which allocation of the participants to the treatment arms was not randomized, had already been excluded because of their restriction to elderly patients.[26,27] (5) The control group had to be allocated to either placebo, no treatment, or referred care, because our objective was to compare pharmacological treatment irrespective of the type of drug prescribed, to control treatment. Consequently, trials comparing different types of antihypertensive drugs were excluded.[20-22]

In total, seven trials met all five criteria.[1,2,5-7,9,25] If subgroup data of blood pressure categories or the two sexes were available,[4,6,7] these subgroups were included in the analysis as separate trials.

Effect measure

As a measure of effect of antihypertensive drug treatment on survival, we compared the all-cause mortality rate, and the incidences of fatal coronary heart disease and stroke in the intervention and control group of the individual trials. Mortality rates were calculated

as incidence densities, i.e. number of deaths per 1000 patient-years of follow-up. When the mortality rates were not given in the published reports of the trials, they were calculated by dividing the number of deaths by the product of the number of participants and the mean follow-up time.[33]

Meta-analysis

First, the incidence rates of death from all-causes, coronary heart disease and stroke in the index and the control groups of the individual trials were plotted as a scatter gram. Thus, an indication of homogeneity or heterogeneity of the effect of antihypertensive treatment in the trials could be obtained for the three mortality end-points at interest.[34] Further, a weighted linear regression model was applied to describe the death rates in the intervention groups as a function of the death rates in the comparison group in the trials. The latter incidence rate may be viewed as the baseline, or untreated, risk of the hypertensive patients included in the individual trials. Since large differences existed between the total number of patient-years in the various trials, weights for each study were calculated analogous to the weights assigned to each stratum in a stratified analysis of the incidence density ratio in a follow-up study.[35,36] The weights correspond to the inverse variance of the incidence density ratio. Trials with similar mortality rates in the intervention and control group fall on the line of identity, i.e. the line with intercept 0.0 and slope 1.0. This line represents the trials in which the beneficial and detrimental effects of antihypertensive treatment on the outcome under study are balanced. Subsequently, the weighted regression lines were compared to this "no net effect" line. A point of intersection between the regression line and the line of identity provides evidence of effect modification by the baseline mortality risk in the control groups. This indicates that whether antihypertensive treatment has a beneficial or unfavorable effect on mortality depends on this mortality risk. The influence of the inclusion of a particular trial on the findings was assessed by comparing the regression equations obtained before and after inclusion of the trial.

RESULTS

Some of the characteristics of the trials included in the meta-analysis are shown in tables 3.1 and 3.2. The trials together comprised 175,000 patient-years of follow-up. All patients randomized to intervention treatment received thiazide or thiazide-like diuretics as drug of first choice, with the exception of the participants in the propranolol arm of the Medical Research Council trial[7] and those who received hydralazine in the Veterans Administration Study.[1] In total, 1192 deaths were recorded during follow-up: 564 in the

Table 3.1. Characteristics of the randomized clinical trials in mild to moderate hypertension included in the meta-analysis.

Trial	Entry DBP (mm Hg)	Mean age (years)	Main treatment INT	Main treatment CTR	# randomized participants INT	# randomized participants CTR	Follow-up time (years) INT	Follow-up time (years) CTR
1 VA[1]	90-114	51	HCT or HDZ§	placebo	186	194	3.2	3.3
2 VA-NHBLI[25]	85-104	38	CTD	placebo	508	504	1.5	1.5
3 HDFP[2-4]	90-94	51*	CTD	referred care	1127	1120	5.0	5.0
4 HDFP[2-4]	95-99	51*	CTD	referred care	1027	992	5.0	5.0
5 HDFP[2-4]	100-104	51*	CTD	referred care	752	842	5.0	5.0
6 Oslo[9]	90-109Φ	45	HCT	no	406	379	5.5	5.5
7 ANBPS[5]	95-109	50	CTZ	placebo	1721	1706	4.1	4.0
8 MRFIT[6]	90-94	46*	HCT or CTD	usual care	1157	1181	7.0	7.0
9 MRFIT[6]	95-99	46*	HCT or CTD	usual care	830	846	7.0	7.0
10 MRFIT[6]	100-114	46*	HCT or CTD	usual care	771	739	7.0	7.0
11 MRC men[7]	90-109	51	BFZ or PRL§	placebo	4523	4525	4.9	4.9
12 MRC women[7]	90-109	53	BFZ or PRL§	placebo	4177	4129	5.0	5.0

* = mean age of all participants, subgroups combined, in the trial; Φ = or systolic blood pressure >149 mmHg and < 180 mmHg, and DBP <90 mm Hg; § = participants randomized to active treatment were combined in the analysis.
Abbreviations: DBP = diastolic blood pressure; py= patient-years; INT = in the intervention group; CTR=in the control group; VA=Veterans Administration Cooperative Study on Antihypertensive Agents; VA-NHBLI = Veterans Administration-National Heart, Lung and Blood Institute Study; HDFP=Hypertension Detection and Follow-up Program; ANBPS = Australian National Blood Pressure Study; MRFIT = Multiple Risk Factor Intervention Trial; MRC = Medical Research Council trial of mild hypertension; HCT = hydrochlorothiazide; HDZ = hydralazine; CTD = chlorthalidone; CTZ = chlorothiazide; BFZ = bendrofluazide; PRL = propranolol.

Table 3.2. Incidence rates of all-cause mortality and mortality from coronary heart disease (CHD) and stroke in the intervention and control group of the randomized trials in mild to moderate hypertensive included in the meta-analysis.

Trial	All-cause mortality rate (per 1000 patient-years)		Incidence of fatal CHD (per 1000 patient-years)		Incidence of fatal stroke (per 1000 patient-years)	
	INT	CTR	INT	CTR	INT	CTR
1 VA[1]	16.8	32.8	10.1	17.2	1.7	10.9
2 VA-NHBLI[25]	2.6	0.0	2.6	0.0	0.0	0.0
3 HDFP[2-4]	9.6	12.5	NR	NR	NR	NR
4 HDFP[2-4]	9.2	12.7	NR	NR	NR	NR
5 HDFP[2-4]	14.1	14.7	NR	NR	NR	NR
5a HDFPtotal[2-4]*			4.4	5.5	0.9	1.6
6 Oslo[9]	4.5	4.3	2.7	1.0	0.0	1.0
7 ANBPS[5]	3.6	5.1	0.7	1.6	0.4	0.9
8 MRFIT[6]	5.8	3.7	2.1	1.5	NR	NR
9 MRFIT[6]	7.4	6.6	3.3	3.2	NR	NR
10 MRFIT[6]	4.6	8.7	3.0	4.3	NR	NR
10a MRFITtotal[6]*					0.4	0.3
11 MRC men[7]	7.1	8.2	4.0	3.9	0.3	0.6
12 MRC women[7]	4.4	3.5	0.9	0.5	0.6	0.7

* = Cause-specific incidence rates were not reported in three blood pressure level subcategories of patients in the Hypertension Detection and Follow-up Program. The incidence of fatal coronary heart disease and stroke was calculated in all randomized patients, including participants on antihypertensive drugs before entry into the trial; ** = The incidence of fatal stroke was not reported in the three blood pressure level subcategories of patients in the Multiple Risk Factor Intervention Trial. The incidence of fatal stroke was calculated in all randomized hypertensive patients, including participants on antihypertensive drugs before entry into the trial.

Abbreviations: INT = in the intervention group; CTR = in the control group; CHD = coronary heart disease; NR = not reported; VA = Veterans Administration Cooperative Study on Antihypertensive Agents; VA-NHBLI= Veterans Administration-National Heart, Lung and Blood Institute Study; HDFP = Hypertension Detection and Follow-up Program; ANBPS = Australian National Blood Pressure Study; MRFIT = Multiple Risk Factor Intervention Trial; MRC = Medical Research Council trial of mild hypertension.

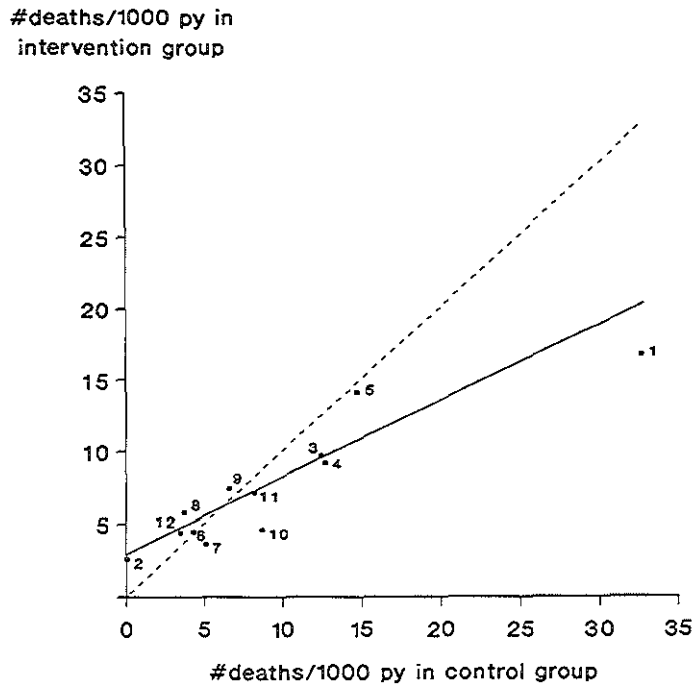

Figure 3.1
All-cause mortality rate (# deaths per 1000 patient-years) in the intervention and control group of 12 clinical trials, including subgroups, in mild to moderate hypertension. The numbers of the trials correspond to those in tables 3.1 and 3.2. The "no net effect line" (----) represents similar mortality rates in the intervention and control arms of the trials. The weighted regression line (——) describes the mortality rate in the intervention group (y) as a function of the corresponding rate in the control group (x) of the trials. The regression equation of this line is y = 2.9/1000 + 0.53 x. The 95% confidence interval of the regression coefficient is 0.33 to 0.73. The point of intersection of the regression line and line of identity is estimated to be a mortality risk in the control group of 6.1 per 1000 patient-years (py).

intervention and 628 in the control groups. The corresponding figures for coronary heart disease and stroke deaths were 544 (263 in the treatment and 281 in the control groups) and 132 (50 in the treatment and 82 in the control groups), respectively. In figure 3.1, all-cause mortality per 1000 patient-years among treated patients and controls in the individual trials are plotted as a scatter gram. In trials that fall right of the line of identity, the death rate in the intervention group was lower than in the control group, suggesting a beneficial effect of drug treatment on survival. In contrast, in trials falling

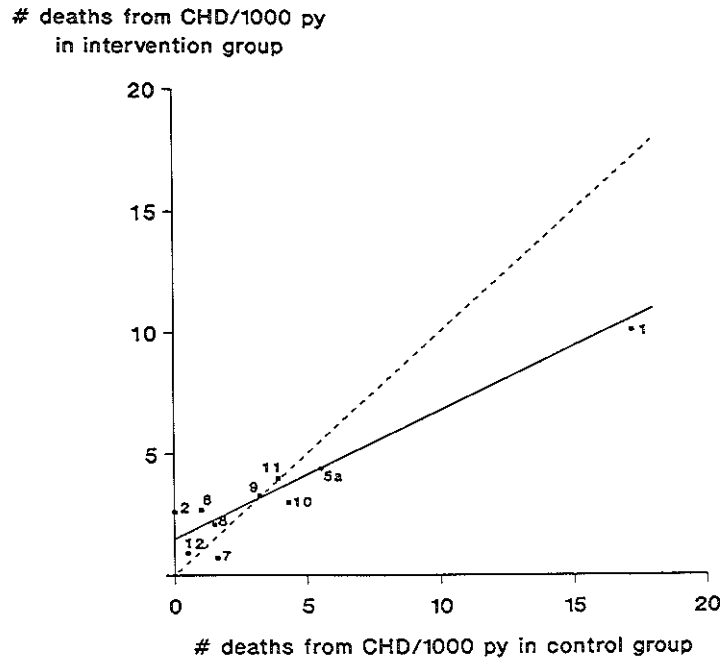

Figure 3.2
Incidence of fatal coronary heart disease (# of coronary deaths per 1000 patient-years) in the intervention and control group of 10 clinical trials, including subgroups, in mild to moderate hypertension, in which the number of fatal coronary events was reported. The numbers of the trials correspond to those in tables 3.1 and 3.2. The "no net effect line" (-----) represents similar mortality rates from coronary disease in the intervention and control arms of the trials. The weighted regression line (——) describes the coronary mortality rate in the intervention group (y) as a function of the corresponding rate in the control group (x) of the trials. The regression equation of this line is y = 1.5/1000 + 0.53 x. The 95% confidence interval of the regression coefficient is 0.39 to 0.68. The point of intersection of the regression line and line of identity is estimated to be a coronary mortality risk in the control group of 3.1 per 1000 patient-years (py).

left of the line of identity drug treatment for mild to moderate hypertension unfavorably influenced all-cause mortality. The line representing no net effect of drug treatment on survival and the regression line intersect at a point where the mortality rate in the control group is 6 per 1000 patient-years. This indicates that drug treatment for mild to moderate hypertension has no effect on, or may even increase all-cause mortality in middle-aged patients with untreated mortality risks that fall below this point. Analogously, drug treatment can be expected to prolong life, the more the baseline

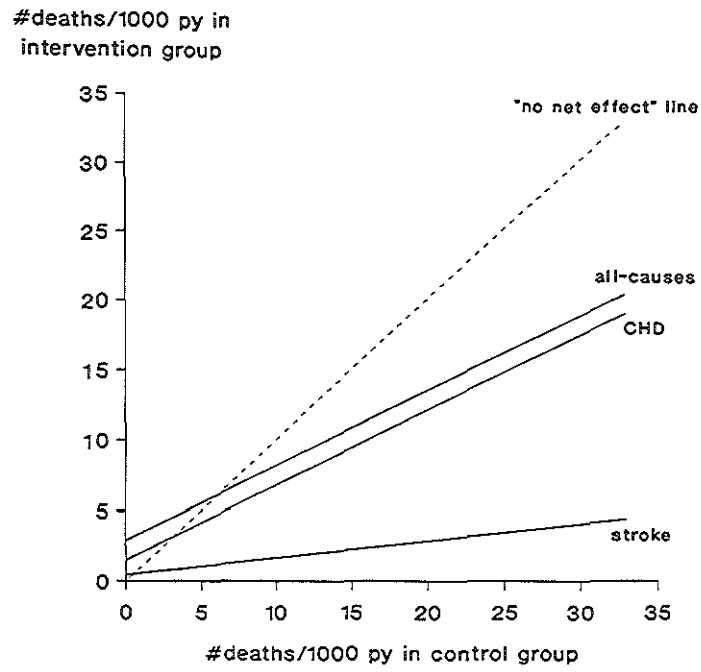

Figure 3.3
Summary of the results of the present meta-analysis of trials in mild to moderate hypetensive middle-aged patient. Clearly, heterogeneity of the effect of antihypertensive therapy according to baseline mortality risk in the control groups exists, with regard to mortality from all-causes and coronary heart disease. Hence, treatment in patients below a certain level of mortality risk may have no influence on or even increase mortality from all-causes and coronary heart disease. The effect on fatal stroke incidence seems not to be modified by the baseline risk of stroke of the participants in the trials.

mortality risk exceeds 6/1000 patient-years.

The results for mortality from coronary heart disease, by far the leading cause of death in hypertensive patients, are shown in figure 3.2. Again, in trials including hypertensive patients at a relatively high risk of coronary mortality, as indicated by the higher incidence rate in the control group, antihypertensive drug therapy reduced coronary mortality. Opposite findings were reported in trials performed among patients with more beneficial coronary risk profiles, e.g. the women in the Medical Research Council trial. The point of intersection is estimated to lie around a baseline coronary mortality risk of 3/1000 patient-years.

Initiation of antihypertensive drug treatment reduces the incidence of fatal stroke independent of the risk of stroke mortality in the control group: In one trial only,

mortality from stroke was somewhat higher in the intervention group compared to the control group. As shown in figure 3.3, the point of intersection below which antihypertensive therapy may increase stroke mortality is located very near to the origin (0.5/1000 patient-years).

DISCUSSION

In our meta-analysis of the randomized trials in middle-aged hypertensive patients, antihypertensive therapy favorably influenced life expectancy in studies in patients with mortality risks beyond 6/1000 patient-years. In trials among hypertensive patients with mortality risks below this point, drug treatment had no effect on or even decreased survival.

The benefit of drug treatment in mild to moderate hypertension remains controversial.[37-45] In recent years, in view of the apparently conflicting results of the randomized clinical trials in mild to moderate hypertension and the limited statistical power of some of the individual trials, several attempts have been made to obtain an overall quantitative measure of effectiveness of pharmacological treatment.[13-18] Our meta-analysis differs in some important respects from these previous analyses.

Firstly, in assessing the effectiveness of drug therapy, we focussed on all-cause mortality as the end-point of interest. In our view, an important aim of hypertension treatment in middle-aged patients is to prevent premature death and hence, prolong a patient's life. The rationale behind this approach is the notion that in middle age, notwithstanding the importance of the quality of life as determined for example by heart failure and other complications of hypertension, the latter is conditional on the "quantity of life". In addition, this allows to take into account the potentially fatal adverse effects of commonly prescribed antihypertensive drugs reported in some of the trials.[6,10,46] Although emphasis on a reduction in mortality as a main objective of antihypertensive treatment may be justifiable in middle-aged patients given their relatively high life expectancy, it should be realized that in the elderly, prevention of morbidity and improvement of quality of life becomes an increasingly important, if not the primary, treatment goal.[47] Hence, similar meta-analyses evaluating other end-points, for example non-fatal stroke or heart failure, may be useful in these patients.

Secondly, the meta-analyses published previously, reported pooled estimates of the net percentage of reduction achieved in the occurrence of the end-points studied. These meta-analyses share the same assumption, namely that the direction of the treatment effect is in biological fact constant across subgroups of patients. Consequently, any apparent hazardous effect of drug treatment on the incidence of the outcome in

certain trials can only be explained by random error. A non-significant statistical test of heterogeneity between the treatment effects of the trials, which is often performed in these "classical" meta-analyses, is often viewed as evidence that the underlying assumption of homogeneity of the effects does hold. It has been repeatedly shown, however, that such a test has limited power to detect differences between the trial effects.[48,49] MacMahon, in an frequently cited analysis of nine trials in mild to moderate hypertension, demonstrated that drug treatment significantly reduces all-cause mortality by 11% (95% CI 2 to 19%) and the incidence of fatal stroke by 38% (95% CI 19 to 53%). The overall reduction in coronary heart disease mortality (8%) did not reach conventional levels of statistical significance (95% CI 21% to -6%).[13] Others reported similar results although the meta-analyses were never based on the same set of trials.[14,15,17] More recently, in a joint endeavour by several authors involved in the earlier meta-analyses, a "definitive" quantitative review was published.[18] This analysis involved yet another selection of trials, including only "unconfounded trials" (referring to the fact that only randomized trials in which no multiple risk factor intervention was performed were included, which of course is no guarantee of "unconfoundedness"). The impressive reduction of 45% in the incidence of fatal stroke and a non-significant 11% reduction in fatal coronary events were in line with findings from previous meta-analyses. Furthermore, a significant reduction in all-cause mortality was mentioned by the authors, although the point estimate was not reported. Again, the conclusions were based on the homogeneity assumption, not allowing modification of the beneficial effect of antihypertensive therapy. An advantage of the regression approach to meta-analysis we developed is its potential to assess the influence of characteristics of the patients included in the trial, represented by the mortality risk in the control group, on the effect measure under study. In fact, our analysis illustrates that the assumption underlying the earlier meta-analytic approach might not hold, because it identifies mortality risk in the control arm of the trials as a strong modifier of the effect of drug treatment (figure 3.3). This could explain the opposite effect of drug treatment on all-cause mortality and fatal coronary events observed in the trials.

Our findings indicate that drug treatment for mild to moderate hypertension may not prolong life in middle-aged patients with a low all-cause-mortality risk. In hypertensive patients with higher estimated mortality rates drug treatment becomes more effective in terms of the number of life-years gained. Apparently, in hypertensive patients at a low mortality risk, the expected beneficial effect of lowering blood pressure level on survival is outweighed by the potential hazards of the pharmacological agents. The cause-specific analyses indicate that a drug-induced increase in fatal coronary events may be responsible for this phenomenon. Potential side effects include a thiazide-related increase

in sudden cardiac death incidence,[50] the existence of the J-shaped relationship between achieved blood pressure level and coronary events,[51] or a drug-related increase in blood lipid level, although any change in serum cholesterol seems small and transient.[52] In high-risk hypertensive patients any fatal side effect of drug treatment is likely to be compensated by a beneficial effect on life-expectancy related to a fall in blood pressure level.

Several limitations of our study need to be discussed. As in all meta-analyses, the results may be influenced by the inclusion- and exclusion criteria of the trials. Especially the inclusion of the Veterans Administration (VA) trial[1] may have had an important impact on the regression equation, although the sample size of this trial was limited. Indeed, after exclusion of this trial the regression quotient increased from 0.53 to 0.69. However, the change in the estimate of the point of intersection was less pronounced (from 6 to 5/1000 patient-years). Similar limited changes occurred in the regression estimates for fatal coronary heart disease after exclusion of the VA trial, but the impact on the coefficient for fatal stroke was considerable (0.12 to 0.43), although the point of intersection was not appreciably altered. Further, the inclusion of the reported subgroups according to blood pressure levels in the MRFIT and HDFP-trials as separate trials may have influenced our findings.[4,6] Yet, an analysis restricted to individual trials, and thus combining the results of the subgroups of these trials to one point in the regression analysis yielded remarkably similar results ($y=0.0031 + 0.52\ x$). A more elaborated sensitivity analysis excluding individual trials, did not identify a single trial with an dramatic effect on the regression equations.

An assumption underlying our analysis is the generalizibility of the findings in subgroups of patients, represented by the baseline risk in the control groups of the trials, to the individual hypertensive patient in medical practice. This may pose a problem when the patients developing the fatal events are not those with the highest untreated mortality risk. This however seems improbable in view of the body of evidence from nonexperimental studies. A major disadvantage of our approach to meta-analysis lies in the difficulty in deriving a precise estimate of the point of intersection of the regression line and the line of identity. The point of intersection for all-cause mortality is estimated to be an untreated mortality risk of 6.1/1000 patient-years (95% CI 3.3 to 8.8 /1000 patient-years). This, however is likely to be an overestimate of the true point of intersection because of the random error in the measurement of the x's, i.e. the mortality rate in the control groups of the trials, which may lead to spuriously lower estimates of the weighted regression coefficient.[52] Since repeated measurements of the values on the X-axis are impossible by definition, no statistical methods are available to estimate the magnitude of the correction term needed. A crude method would be to perform a

weighted regression while interchanging the dependent and independent variables y and x and then calculating the reciprocal of this line. The break-point of this computed regression line with the line of identity marks the largest possible deviation from the original point of intersection. Application of this method to our analysis of all-cause mortality yielded a regression coefficient of 0.68 and an estimated point of intersection at 4.6/1000 patient-years. The best estimate of the point of intersection would lie between the minimal and maximum option, i.e. approximately 5.4/1000 patient-years. This illustrates that any overestimation of the mortality risk marking the point of intersection between a beneficial and unfavorable effect is relatively small.

Notwithstanding the lack of precise estimates of the point of intersection, the general consequences for the management of the individual hypertensive patient in medical practice seem clear: Treat those middle-aged patients at the highest risk of mortality and refrain from potential harmful drug therapy in hypertensive patients unlikely to develop fatal complications. It should be noted that this risk is determined by an aggregate of indicators of mortality risk, including blood pressure level as well as age, gender, smoking habits, comorbidity, etcetera. This recommendation seems to be in accordance with day-to-day medical practice. A physician is more prone to initiate drug therapy in moderately hypertensive patient with a unfavorable prognosis, e.g. a man smoking 20 cigarettes per day, with a serum cholesterol level of 8 mmol/l and a family history of cardiovascular disease, than in a woman with a similar blood pressure level but without additional cardiovascular risk indicators. In applying the results to medical practice using a more quantitative approach, physicians should be able to estimate a patient's expected mortality risk and determine whether this risk exceeds the point of intersection beyond which drug treatment may be expected to improve survival. Consequently, a risk function relating a patient's risk profile, including blood pressure level as well as age, gender, smoking habits, cholesterol level and other relevant risk indicators, to all-cause or coronary mortality risk, should be available. Several useful risk functions have been published previously.[53,54] These risk functions when sufficiently applicable to the patients at issue, can be used to identify patients in whom drug treatment is most likely to increase life-expectancy and could play an important role in the decision to start drug treatment in a particular patient with mild to moderate hypertension.

In conclusion, our findings demonstrate that the clinical trials have shown that drug treatment for mild to moderate hypertension in middle-aged patients may improve survival, but that physicians should be critical in patient selection, preferably treating those at or above a certain mortality risk. In view of the estimate of the point of intersection between a favorable and a hazardous effect on survival and the possible

overestimation of its value, antihypertensive drug therapy in patients with untreated morality risks beyond 6/1000 patient-years can be expected to prolong life. Thus, this meta-analysis may contribute to answering the essential question: "Should *this* patient be treated?", which may currently be more relevant than the question answered by the earlier meta-analyses: "Should mild to moderate hypertension be treated?".

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CHAPTER 4

THE STUDY OF DRUG EFFICACY AND ADVERSE DRUG REACTIONS - STRENGTHS AND LIMITATIONS OF NONEXPERIMENTAL STUDIES

CHAPTER 4.1

SOME NOTES ON THE ABSENCE OF RANDOMIZATION IN NONEXPERIMENTAL STUDIES ASSESSING DRUG EFFICACY AND ADVERSE DRUG REACTIONS

INTRODUCTION

Random allocation of participants to treatment groups is an important concept in clinical research. One of the first formal randomized controlled trial in medicine was published in 1948.[1] In this study the efficacy of chemotherapy for tuberculosis was assessed. Patients were randomly assigned to either streptomycin treatment or bed-rest by using "statistical series based on random sampling numbers drawn up for each sex at each centre by Professor Bradford Hill".[1] Since then randomization has gradually become the accepted method of choice in the design of studies of causation, notably in the study of drug effects.

The main objective of randomization in the study of drug effects is to achieve baseline similarity of prognosis across the patient groups compared.[2] This implies that, apart from random variation, the incidence of the outcome event would have been similar had the patient groups been allocated to the same treatment regime. Similarity of prognosis is required to ensure validity of a study, i.e. to obtain an estimate of the association between the drug treatment and the outcome at interest, unconfounded by extraneous determinants.[3] Clearly, the most powerful method to achieve comparability of prognosis across treatment groups is randomization and this partly explains the widespread application of the experimental method (randomized controlled trials) in the study of drug effects. In nonexperimental studies, however, allocation to the treatment groups is nonrandomized by definition. As a consequence, these studies are often viewed as methodologically flawed.[4,5] Absence of randomization, however, does not necessarily lead to lack of comparability of prognosis. The bias resulting from nonrandom allocation to treatment groups depends on the type of drug effect studied. In this paragraph the potential consequences of the absence of randomization in nonexperimental studies assessing the effects of drug therapy will be illustrated.

NONEXPERIMENTAL STUDIES OF DRUG EFFICACY: CONFOUNDING BY INDICATION

In nonexperimental studies, as in daily medical practice, a patient is prescribed a particular drug because at a certain point in time a physician decides that a patient, with his or her particular characteristics could benefit from taking a particular medication in a certain dosage. Thus, the decision to prescribe a drug is taken *everything but* randomly, and is influenced by clinical and non-clinical factors which constitute the indication for treatment, in particular the severity of the treated

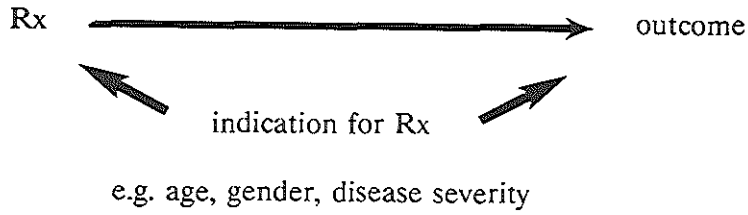

Figure 4.1.1
Nonexperimental studies of drug efficacy. Because allocation to the drug regimes compared is nonrandomized by definition, the factors comprising the indication for drug treatment (Rx), including age, gender and the severity of the condition to be treated, are confounders of the relationship between the determinant and the outcome under study. Thus, confounding by indication may occur.

condition and other prognostic factors. For instance, whether a patient with hypertension is treated pharmacologically is highly dependent on the systolic and diastolic blood pressure level, but also on the age and gender of the patient and the presence of other cardiovascular risk indicators such as prior myocardial infarction or stroke, hypercholesterolemia, smoking habits and a family history of cardiovascular disease. Evidently, other unknown factors could also influence the initiation of therapy. For research of drug effects this may cause "confounding by indication".[2]
That the indication for treatment is a confounder par excellence in nonexperimental studies of drug efficacy is illustrated in figure 4.1.1. The indication for treatment is by definition associated with the determinant under study: The prescription of the drug. Since doctors are prone to treat those patients at the highest risk of developing the outcome the drug is thought to prevent or postpone, the indication for treatment is also associated with the outcome under study. In the example of hypertension, the blood pressure level or gender of the patient is likely to be associated with both the probability of initiation of drug treatment and the risk of developing coronary heart disease or other cardiovascular complications. As a consequence, a comparison of patients on drug treatment for a certain condition with patients untreated for that condition is a comparison between two groups with different prognoses to begin with.

Table 4.1. An example of confounding by indication in the study of the efficacy of antihypertensive treatment in 793 Dutch hypertensive women followed for an average period of ten years (EPOZ-study).[6,7] *The crude and adjusted rate ratios of fatal cardiovascular disease among treated compared to untreated hypertensive women are given.*

	Rate ratio of cardiovascular death	95% confidence interval
Crude rate ratio	1.0	0.6 to 1.5
Adjusted rate ratio*	0.6	0.3 to 0.9

* adjusted for differences in age, Quetelet-index, pulse rate, smoking habits, serum cholesterol, diabetes mellitus, prior myocardial infarction and a history of stroke.

Because of confounding by indication, the treated patient group will almost certainly experience a higher incidence of the outcome event. This will result in an underestimation of the efficacy of drug treatment. Thus, because the most effective method to avoid confounding by indication is randomization, nonexperimental studies of drug efficacy are susceptible to bias and should be interpreted with caution.

An example of confounding by indication is shown in table 4.1. In a nonexperimental study in the Netherlands (EPOZ study),[6,7] 793 women with hypertension (i.e. systolic blood pressure ≥160 and/or diastolic blood pressure ≥95 mm Hg, or those on drug treatment for hypertension) were followed for an average period of 10 years. The crude incidence rate ratios of fatal cardiovascular disease in treated compared to untreated hypertensive women was 1.0 (95% confidence interval 0.6-1.5). This is in contrast with most experimental studies which have demonstrated a beneficial effect of antihypertensive treatment on cardiovascular mortality. However, after adjustment for differences in age, smoking habits, previous myocardial infarction and other factors known to influence the indication for treatment, the rate ratio was 0.6 (95% confidence interval 0.3 to 0.9). Obviously, it is impossible to adjust for unknown or unmeasurable confounders.

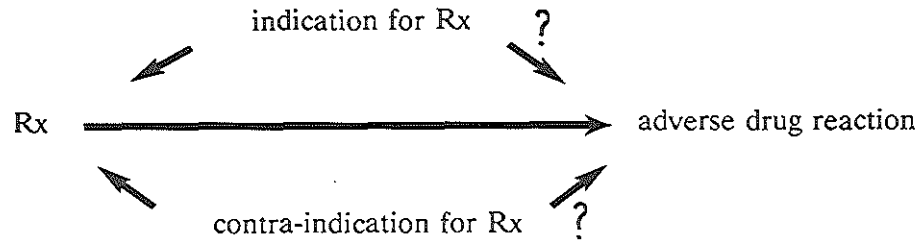

Figure 4.1.2
Nonexperimental studies of adverse drug reactions. The indication and contra-indication for the prescription of the drug (Rx) are not inherently associated with the adverse drug reaction under study. Consequently, absence of randomization does not by definition lead to the possibility of confounding by indication and contra-indication.

NONEXPERIMENTAL STUDIES OF ADVERSE DRUG REACTIONS: CONFOUNDING BY INDICATION AND CONTRA-INDICATION

In nonexperimental studies of adverse drug reactions the consequences of the lack of randomization are less straightforward than in the study of drug efficacy. This is illustrated in figure 4.1.2. Again, the indication for treatment is associated with the determinant under study: The prescription of the drug. Furthermore, contra-indications for treatment, defined as a condition of a patient known to adversely influence the beneficial effect of a drug, are inversely related to the probability of receiving the drug. However, in order to act as a confounder, the indication or contra-indication for treatment should also be associated with the outcome under study, i.e. the adverse drug reaction. This is generally not the case in the study of adverse drug reactions. An association between the indication for treatment and the risk of developing an adverse effect is unlikely, and thus the danger of confounding by indication in the study of adverse drug reactions is limited. For instance, the severity of hypertension is unlikely to be related to the risk of developing gout or impotence as a side effect of diuretic therapy. When, however, the factors known to influence the initiation of drug therapy are risk indicators for the side effect under study as

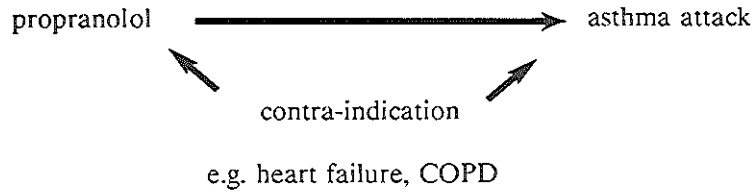

Figure 4.1.3
An example of a type A adverse drug reaction in which confounding by contra-indication is likely to occur. The contra-indication for propranolol treatment (e.g. chronic obstructive pulmonary disease (COPD)) is related to both the determinant (propranolol treatment) and the adverse drug reaction (asthma attacks) under study.

well, confounding by indication may pose a problem in the study of adverse drug reactions. As will be illustrated below, the relationship between non-potassium sparing diuretics and sudden death is likely to be an example of the latter situation.

If the contra-indication for a specific drug is associated with the side effect under study, the contra-indication for drug treatment acts as a confounding variable of the relationship between the exposure to the drug and the occurrence of the adverse drug reaction. In analogy with confounding by indication this phenomenon has been termed "confounding by contra-indication".[2] Confounding by contra-indication is most likely to occur when the adverse drug reaction studied results from the primary mode of action of the drug and is relatively common, especially at higher dosages. Thus, physicians may be expected to refrain from prescribing the particular drug in the presence of the contra-indication. These side effects are called *type A adverse drug reactions*.[8] An example of a type A side effect is shown in figure 4.1.3. If one were to study the relationship between the use of propranolol, a betablocking antihypertensive agent, and the occurrence of asthma attacks, a nonexperimental study is unlikely to find an increased risk of asthma attacks among propranolol-users, because a history of chronic obstructive pulmonary disease, a major risk indicator for future asthma attacks, is considered a contra-indication for betablocker use.

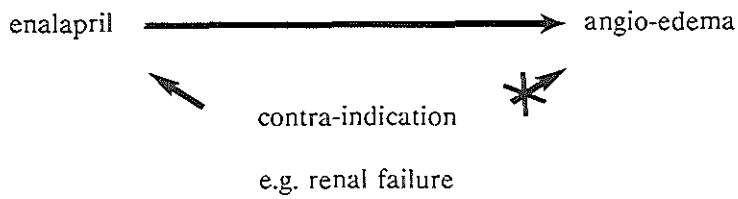

Figure 4.1.4
An example of a type B adverse drug reaction in which confounding by contra-indication is unlikely. The contra-indications for enalapril treatment (e.g. renal failure) are not related to the occurrence of the adverse drug reaction under study (angio-edema).

Consequently, those at the highest risk of the outcome event are usually prescribed alternative antihypertensive medications. Thus, confounding by contra-indication will lead to an underestimation of the "true" relationship between the drug usage and the side effect. The only exception to the rule that type A side effects may cause confounding by contra-indication occurs when the side effect is unknown, and the likelihood of developing the adverse event does not, yet, influence the decision to prescribe a specific drug therapy.

If the adverse drug reaction under study is not associated with the contra-indication of the drug, confounding by contra-indication is a nonissue. This is most likely when the adverse drug reaction does not result from the primary mode of action of the drug and is relatively uncommon. Consequently, the probability of developing the side effect cannot be predicted and the decision (not) to prescribe the drug is not influenced by it. These side effects are called *type B adverse drug reactions*.[8] In figure 4.1.4 an example of a type B side effect is shown. In the study of the relationship between the use of the antihypertensive drug enalapril, an angiotensin converting enzyme-inhibitor, and the occurrence of angio-edema,[9] confounding by contra-indication is absent. The mechanism and risk factors for angio-edema during enalapril treatment are unknown and therefore, the probability of developing angio-edema does not influence the choice of antihypertensive drug

therapy. Furthermore, the contra-indications for enalapril therapy (e.g. renal failure) are not related to angio-edema. Thus, in the study of type B side adverse drug reactions no confounding by contra-indication exists, and random allocation to the treatment regimes is not required to achieve comparability of prognosis. Other type B adverse drug reactions which have been assessed by nonexperimental studies include Reye's syndrome during aspirin use and adenocarcinoma of the vagina among daughters of mothers who used diethylstilbestrol during pregnancy.[10,11]

NON-POTASSIUM SPARING DIURETICS AND SUDDEN CARDIAC DEATH: A NONEXPERIMENTAL STUDY OF AN ADVERSE DRUG REACTION

The objective of this thesis is to determine whether patients on non-potassium sparing diuretic therapy for hypertension are at an increased risk of sudden cardiac death, compared to hypertensive patients prescribed alternative antihypertensive medications. Thus, sudden cardiac death is studied as a potential adverse drug reaction of non-potassium sparing diuretics. For reasons outlined in Chapter 5, a nonexperimental study design is chosen: A case-control study among all inhabitants of the municipality of Rotterdam who are on drug treatment for hypertension. Given the absence of randomization in this study, confounding by indication and confounding by contra-indication may be present. As a first step to limit confounding by (contra-) indication the study population was restricted to those who were on drug treatment for hypertension, excluding untreated hypertensive patients with, in general, a more favorable prognosis. This may increase the comparability of unknown factors related to the initiation of antihypertensive therapy in the study population. Nevertheless, confounding by (contra-)indication cannot be completely excluded, because (contra-) indications for different classes of antihypertensive drugs may differ. This is illustrated in figure 4.1.5.

An indication for prescribing non-potassium sparing diuretic therapy in hypertension is the concomitant presence of congestive heart failure. Because congestive heart failure is an established risk factor for sudden cardiac death, confounding by indication poses a problem in the study of the relationship between non-potassium sparing diuretics and sudden cardiac death. Furthermore, several absolute or relative contra-indications for non-potassium sparing diuretic therapy in hypertension are associated with the risk of developing sudden cardiac death. Hence, the adverse drug reaction under study is of type A and confounding by contra-indication may occur. Factors which could be considered (relative) contra-indications for prescribing non-potassium sparing diuretics, mainly because alternative

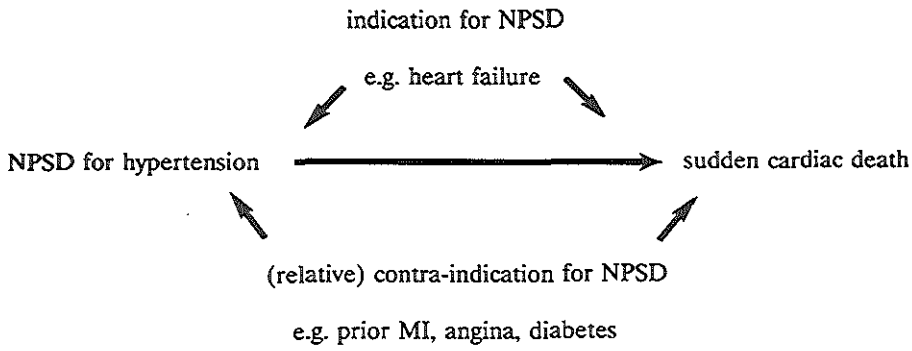

Figure 4.1.5
In the study of sudden cardiac death as an adverse drug reaction of non-potassium sparing diuretic (NPSD) therapy for hypertension, the indications (notably concomitant heart failure) and (relative) contra-indications for NPSD prescription (notably prior myocardial infarction (MI), angina pectoris and diabetes mellitus) are related to the occurrence of sudden cardiac death. Consequently, both confounding by indication and contra-indication may pose a problem in the nonexperimental study presented in this thesis.

antihypertensives are recommended as drugs of first choice, include a history of myocardial infarction or angina pectoris (where e.g. betablockers seem a more appropriate choice) and the presence of diabetes mellitus (where e.g. calcium antagonists or ACE-inhibitors may be a more rational choice). Therefore, absence of random allocation of antihypertensive drug therapy in this case-control study is likely to cause confounding by contra-indication as well.

CONCLUSION

Because in nonexperimental studies, allocation to the treatment regimes is nonrandomized by definition, nonexperimental studies of drug efficacy are susceptible to bias as a result of confounding by indication. In nonexperimental studies of adverse drug reactions absence of randomization causes confounding by indication or contra-indication only when the adverse drug reaction is associated with the indication or contra-indication of the drug, respectively. In case of a type A adverse drug reaction

confounding by contra-indication may occur. However, in the assessment of type B adverse drug reaction confounding by contra-indication is nonexistent, and the absence of randomization does not affect validity.

In the study of the relationship between the use of non-potassium sparing diuretic therapy and the occurrence of sudden cardiac death the absence of randomization may give rise to both confounding by indication and contraindication. Consequently, alternative methods should be applied to ensure similarity of prognosis across treatment groups.

In Chapter 4.2. several of these alternative methods will be discussed using the example of the published nonexperimental studies assessing the efficacy of antihypertensive treatment in the primary prevention of coronary heart disease. Furthermore, the advantages and disadvantages of a nonexperimental study design in the study of drug effects are reviewed.

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CHAPTER 4.2

PRIMARY PREVENTION IN HYPERTENSION

- VALID CONCLUSIONS FROM OBSERVATIONAL STUDIES

INTRODUCTION

The randomized trial is a paradigm for clinical research.[1-3] Several clinical trials have been published, that studied the role of drug treatment for hypertension in the primary prevention of cardiovascular disease. They clearly demonstrated that antihypertensive therapy reduces the incidence of both fatal and non-fatal stroke, even in mild to moderate hypertension, but findings on the development of first coronary events were less convincing.[4,5] Several explanations for this discrepancy have been put forward. Some suggested that the beneficial effects of lowering blood pressure were outweighed by adverse effects of certain classes of antihypertensive drugs.[6] Others postulated that reduction of blood pressure below a certain threshold might promote symptoms of coronary heart disease (CHD).[7,8] Furthermore, it has been recognized, that the published primary prevention trials may lack power to detect even considerable reductions in the incidence of CHD, because of the small number of coronary events recorded in the individual trials.[5] Perhaps most important, clinical trials may be almost by definition too short to demonstrate effects on a process as chronic atherosclerosis which may take several decades to result in symptomatic coronary artery disease. In view of this, the suitability of the clinical trial to evaluate different antihypertensive drug regimens in the primary prevention of CHD has been questioned.[3,9] Recently, several observational, i.e., nonexperimental, studies addressing the issue were reported.[10,11] The internal validity of observational studies, however, is subject to heavy debate.[2,3,9]

The objective of this paper is to discuss the advantages and disadvantages characteristic of the two main types of observational studies, follow-up and case control studies, with special reference to the role of antihypertensive drugs in the primary prevention of ischemic cardiac events. Furthermore, the available evidence from observational studies will be reviewed taking the methodological pitfalls into account.

OBSERVATIONAL STUDIES ON PRIMARY PREVENTION OF CHD IN HYPERTENSION: METHODOLOGICAL ISSUES

Study design

Epidemiological research studies a determinant or exposure and its association with the occurrence of a specific outcome or disease. Two main categories of epidemiological studies can be distinguished: experimental studies, i.e., clinical trials, and non-experimental, or observational, studies. The design of the two main types of observational studies that address the issue of primary prevention of CHD in

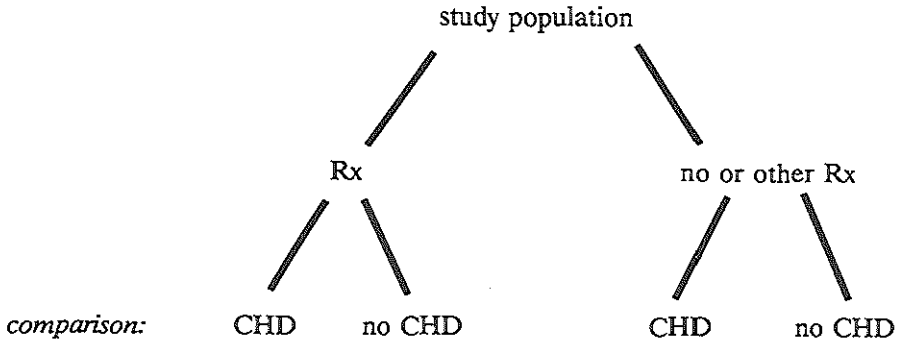

Figure 4.2.1
Design of a follow-up study assessing the efficacy of drug treatment for hypertension (Rx) in the primary prevention of coronary heart disease (CHD).

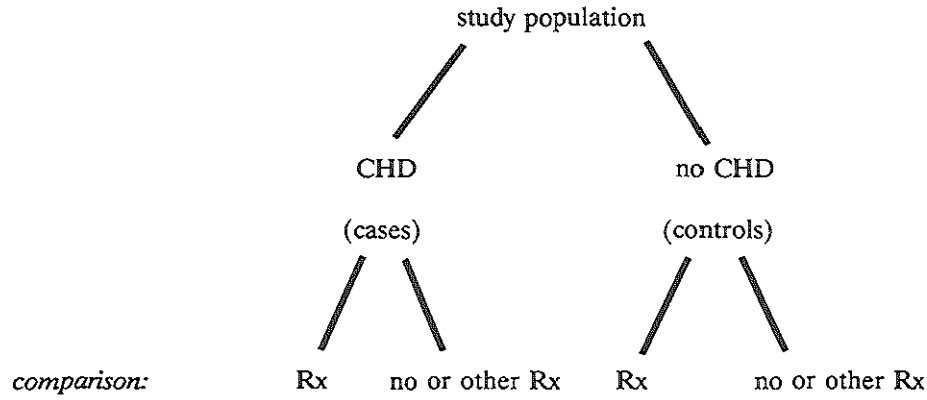

Figure 4.2.2
Design of a case-control study assessing the efficacy of drug treatment for hypertension (Rx) in the primary prevention of coronary heart disease (CHD).

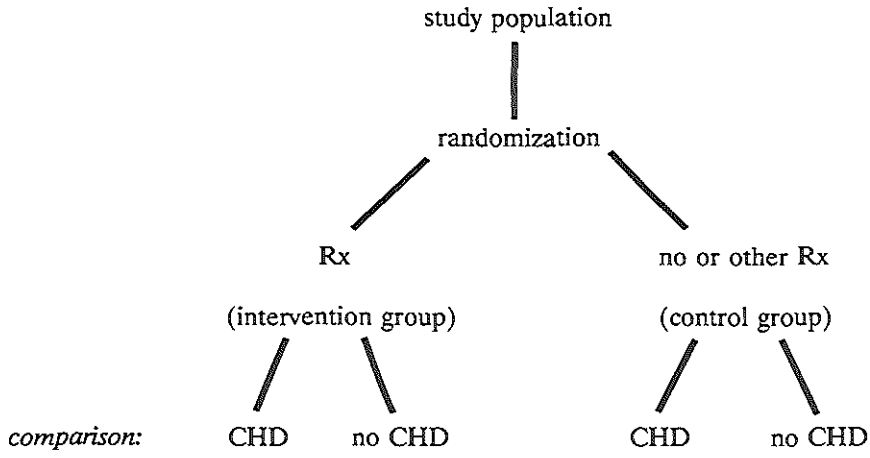

Figure 4.2.3
Design of a randomized controlled trial assessing the efficacy of drug treatment for hypertension (Rx) in the primary prevention of coronary heart disease (CHD).

hypertension is given in figures 4.2.1 and 4.2.2. For comparison the design of a clinical trial is shown in figure 4.2.3. In the research considered in this report, the exposure and disease status under study are drug treatment for hypertension and first coronary events. In follow-up studies, as in clinical trials, groups of patients are followed for a certain time period and the incidence of first coronary events in the patient groups on antihypertensive drug therapy (Rx) and a control group receiving no or other drug treatment (no or other Rx), are compared. An essential feature of clinical trials is that participants are randomly allocated to the intervention and control groups, whereas in follow-up studies no randomization takes place. In case-control studies, subjects treated for hypertension who experience a first coronary event (cases) are studied to obtain numerators of disease incidence, and a sample of the population from which the cases derive (controls or referents) is studied to obtain estimates of exposure denominators.[12] In general, these controls are free of CHD.

Internal validity

The internal validity of a study is determined by the degree to which differences in outcome between index and comparison groups may, apart from sampling error, be attributed only to the postulated effect under investigation. To ensure internal validity, the treatment groups in experimental or observational studies should be comparable with respect to "extraneous" effects, information and prognosis.[12,13]

Comparability of "extraneous" effects

"Extraneous" effects are defined as effects related to the exposure that fall outside the effect of interest. Non-exposure is not simply the absence of exposure. When emphasis is on the intrinsic effect of a pharmacologic compound, a placebo-effect is extraneous. The classical method to ensure comparability of "extraneous" effects is to use placebo treatment for comparison. Since placebo treatment cannot be achieved in observational studies, another appropriate reference category of the exposure should be sought. Antihypertensive drug therapy other than the one studied may serve as such.

Comparability of information

In follow up studies and clinical trials, outcome information in the two treatment groups should be collected independent of exposure status. Analogously, in case-control studies, information gathered on exposure status should be independent of outcome status, i.e., identical for cases and controls. Comparability of information in both experimental and observational studies may be achieved by blinding of preferably both observer and participants.

Comparability of prognosis

In the evaluation of the effect of drug therapy, baseline similarity of prognosis across treatment groups is required. This implies that the incidence of outcome events should be the same in the groups compared, had they been assigned to the same treatment. Random allocation to treatment is the generally accepted method to achieve similarity of prognosis. In observational studies assignment to the different categories of exposure is, by definition, not random. By contrast, the decision to prescribe a particular drug in clinical context is highly influenced by the severeness of the condition to be treated and by other factors affecting prognosis. This is known as "confounding by indication".[14] Consequently, methods other than randomization should be used to achieve comparability of prognosis in follow-up and case-control studies. To evaluate the relative efficacy of different antihypertensive drugs in hypertension, restriction to patients on drug therapy for hypertension, has been used to select comparable groups with regard to

severeness of hypertension. Still, within the group of patients with hypertension severe enough to require drug treatment, the use of specific drugs, e.g. betablockers and diuretics, or different dosages, could be a reflection of different indications and as such of differences in factors determining prognosis, e.g., blood pressure level, age, gender, race, smoking habits, glucose intolerance and other cardiovascular risk factors. Thus, restriction of the population to those with similar distributions for these factors may be necessary to limit discrepancies in baseline prognosis between treatment groups. Adjustments for differences in coronary risk factors between groups in the data analysis, could serve as an alternative. These methods, however, are not nearly as effective in achieving comparability of prognosis as randomization in clinical trials. Hence, confounding by indication can never be completely ruled out in observational studies.

Advantages and disadvantages of the different study designs

Some characteristics of follow-up studies, case-control studies and clinical trials, with special reference to research on the role of antihypertensive drugs in the primary prevention of ischemic cardiac events, are summarized in table 4.2.1. As mentioned earlier, a major disadvantage of observational studies is the sometimes insurmountable difficulty to ensure comparability of prognosis across different treatment groups. Yet, observational studies also offer some advantages over trials. The generalizability of study findings is considered higher because participants tend to be more representative of the hypertensive population at large than the highly selected patients included in clinical trials. This is, however, of relative importance, as generalizability is conditional on internal validity. Another advantage is that observational studies may be feasible when the incidence of the outcome is low. Very large populations may be included in observational studies, thereby increasing the power to detect small differences in effect of different treatments. Case-control studies are particularly suitable when the outcome is rare, because sampling of cases is based on the outcome, as for example in the evaluation of adverse drug reactions.[15] Further, the possibility to monitor populations for extended time periods enables the detection of differences in effect that become apparent only after years of drug use. This may be crucial when the objective is to assess the influence of antihypertensive medication on coronary atherogenesis. An advantage of a case-control design, and to a lesser degree of follow-up studies, is the possibility to compare different dosages and durations of treatment. Finally, observational studies frequently use available data and are therefore generally less expensive than experimental studies.

Table 4.2.1. Strengths (+ and + +) and limitations (-) of follow-up studies, case-control studies and clinical trials evaluating the efficacy of drug treatment for hypertension in the primary prevention of coronary events.

	follow-up study	case-control study	clinical trial
Validity			
comparability of extraneous effects	+	+	+ +
comparability of information	+	+	+ +
comparability of prognosis	-	-	+ +
Feasibility			
low incidence of outcome event	+	+ +	-
long-term effect of exposure	+	+	-
low prevalence of exposure	+	-	+ +
multiple exposure catagories	+	+ +	+
multiple outcome catagories	+ +	+	+ +
costs	+	+	-

OBSERVATIONAL STUDIES ON PRIMARY PREVENTION OF CHD IN HYPERTENSION: EVIDENCE

In total 13 observational studies on the efficacy of drug therapy for hypertension in the prevention of CHD have been found.[10,11,16-26] Several of these studies included a treatment group obtained by a non-randomized procedure and may be viewed as quasi experimental.[17,18,25] The choice of the treatment groups that are compared differs considerably between studies. Several authors compared the incidence of symptomatic CHD in treated hypertensives to the incidence in a sample of the population at large or to nationwide morbidity or mortality figures.[20-26] This method, although often applied, poses major problems in all three aspects of internal validity.[27] In particular, comparability of prognosis between the comparison groups is often illusory. The majority of the population at large is normotensive, and therefore not part of the hypertensive

domain and they may also be expected to differ with respect to the distribution of other cardiovascular risk factors. Moreover, information on outcome status will be dissimilar, in particular when the general population serves as a reference. A poor prognosis of treated hypertensives in comparison to the population at large, as reported in several studies, is not surprising and should not be attributed to failure of antihypertensive therapy to reduce CHD incidence. It is more likely to be a reflection of differences in prognosis already present *prior* to the start of drug treatment, i.e., of confounding by indication. For similar reasons, the use of historical control groups may jeopardize internal validity.[16,26] Cruickshank et al,[25] compared the incidence of fatal myocardial infarction (MI) of treated hypertensives in the Clatterbridge Hypertension Clinic, to the predicted incidence "had they not been treated". After taking a placebo effect of 5% on blood pressure into account, it was concluded from this analysis that drug treatment reduced the incidence of fatal MI by 39%. This reduction, however, merely reflects the well-known strong relationship between blood pressure level and development of MI and does not provide information on the efficacy of drug treatment. The efficacy of antihypertensive drug treatment in reducing the incidence of CHD events must be assessed by weighing all beneficial and adverse effects, and not the effect of blood pressure reduction alone. This is emphasized by reports of unfavorable effects of specific antihypertensive drugs on electrolytes, lipid metabolism and glucose intolerance.[5,6] Svärdsudd et al,[17] and Berglund et al,[18] compared the incidence of fatal and non-fatal myocardial infarction in treated hypertensives with untreated patients who were hypertensive at one screening session, but whose blood pressure level fell beyond the treatment threshold on repeat examination. The incidence of MI was significantly lower in the treated group. As the authors stated, the apparent beneficial effect of treatment should be interpreted with caution, given the possibility of incomparability of prognosis between the patient groups, even though this would have reduced the likelihood of a beneficial effect in this example.

One way to increase comparability of prognosis in observational studies, is to compare different classes of antihypertensive drugs. Three studies evaluated the efficacy of betablocking agents relative to "other" drugs.[10,11,19] Stewart compared 121 essential hypertensive patients treated with propranolol, to 48 hypertensive patients on treatment regimens excluding betablockers.[19,28,29] The incidence of first myocardial infarctions was significantly lower in patients treated with propranolol (7.5%) than in the non betablocker group (31%). No statistically significant differences were found between the prevalence of coronary risk factors in the two groups compared. However, patients receiving propranolol were younger (43.5 versus 47 years) and this may have accounted for at least part of the observed difference in effect.

In a report by Fletcher et al,[10] 2,697 treated patients from the Department of Health and Social Security Hypertension Care Computing Project were followed for an average of 4.3 years. CHD mortality was compared between groups treated with betablockers, methyldopa, and therapy excluding these two drugs (of which 70% received diuretics). In a subanalysis of patients without a history of MI and angina pectoris ("primary prevention group"), the risk of coronary death in men in the betablocker group was 0.38 (95% confidence limits(CL) 0.17 and 0.88) relative to men in the methyldopa group, and 0.54 (95% CL 0.21 and 1.36) compared to the third drug regimen. Age was found to be related to the type of drug prescribed, as men and women in the methyldopa group were older than those using other drugs. In the analysis, however, adjustments were made for differences in age and other coronary risk factors in order to increase comparability of prognosis.

The only case-control study evaluating the role of antihypertensive drugs in the prevention of CHD was conducted by Psaty et al.[11] Enrollees in a Health Maintenance Organization (HMO) receiving drug treatment for hypertension and developing angina or fatal or nonfatal MI between 1982 and 1984 (cases; n=248), were compared to a sample of patients treated with antihypertensive drugs from the same HMO remaining free of CHD during that period (controls; n=737). The investigators were blinded to the case or control status of the participants. The possibility of confounding by indication was reduced by excluding participants with a history of CHD and with known contraindications for betablocker therapy. The authors postulated that betablockers were more likely to be used in the second-line treatment of hypertension, and adjustments for differences in severity of hypertension as well as other coronary risk indicators were made through multivariate analysis. A smaller proportion of cases than controls were using betablocking agents. It should be noted that an eventual tendency to selectively prescribe betablockers to patients prone to develop coronary events, would have diluted any apparent beneficial effect of betablockade. The beneficial effect of betablockers was confined to the prevention of nonfatal MI. The relative risk of a first nonfatal MI of patients on betablockers compared to those using other antihypertensives was 0.62 (95% CL 0.39 and 0.99). Moreover, larger dosages of betablockers appeared to give greater protection.

DISCUSSION

The methodological advantages of the randomized controlled trial merit its dominant role in clinical research.[1] Its general superiority over observational studies in the evaluation of drug efficacy,[2,9,30] however, has been challenged.[3,31] Indeed, follow-up

studies and case-control studies offer some advantages compared to clinical trials, especially when disease rates are low. On the other hand, the internal validity of observational studies is often questionable. In particular the necessity of similarity in prognosis between the treatment groups poses severe problems in these studies.[12,13]

Most observational studies in which the value of antihypertensive therapy in the prevention of coronary events was evaluated suffer from a lack of internal validity as a result of the choice of the comparison groups.[16-18,20-26] Lack of internal validity precludes from drawing valid conclusions and the results of these studies should be interpreted with caution. Moreover, many studies did not exclude participants with a history of CHD. Only three observational studies have focussed entirely on the *primary* prevention of ischemic cardiac events.[10,11,19] In the design of these three studies special efforts were made to achieve comparability of prognosis, for instance by choosing different classes of antihypertensive drugs as comparison groups, and by multivariate adjustment for differences in coronary risk. Nevertheless, even in these studies, confounding by indication cannot completely be ruled out because allocation of participants to the treatment groups was not random. The available evidence from these studies suggests that betablockers might me more effective in preventing first coronary events than other antihypertensive drugs. This gives support to a beneficial effect of betablockers relative to diuretics as recently reported from the Metoprolol Atherosclerosis Prevention in Hypertensives (MAPHY) trial.[32] Interestingly, in the follow-up study by Fletcher et al,[10] the advantage of betablockers was confined to non-smoking men, a finding similar to results reported from the Medical Research Council (MRC) and International Prospective Primary Prevention Study in Hypertension (IPPPSH) trials,[33,34] but at variance with the findings from the Heart Attack Primary Prevention in Hypertension (HAPPHY) and MAPHY trials.[35,32] The results of the case-control study by Psaty et al indicated that higher dosages of betablocking agents conferred greater protection from nonfatal myocardial infarction.[11] Further evidence is needed to confirm these findings.

We conclude that observational studies could play a role in the evaluation of antihypertensive drug therapy in the primary prevention of ischemic cardiac events, when the strengths and limitations of these studies are appreciated. In view of this, follow-up and case-control studies could be useful to study the efficacy of the newer classes of antihypertensives (ACE-inhibitors, calcium channel blockers, etcetera) compared to the more "classical" drugs (diuretics, betablockers). Furthermore, case-control studies could play an important role in evaluating the effect of different dosages or durations of antihypertensive treatment on the development of coronary events.

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CHAPTER 5

DIURETICS AND SUDDEN CARDIAC DEATH IN HYPERTENSIVE PATIENTS

- A CASE-CONTROL STUDY

INTRODUCTION

The introduction in 1957 of chlorothiazide,[1] a non-potassium sparing diuretic, had a major influence on the pharmacological treatment of elevated blood pressure. Non-potassium sparing diuretics have been widely prescribed as an antihypertensive drug of first choice and many practising physicians are convinced that diuretics are efficacious in the prevention of cardiovascular complications of hypertension. The relatively low cost of the drugs has further contributed to its wide-spread use. The efficacy of diuretics, and in particular thiazides, in reducing the incidence of cardiovascular disease in hypertensive patients has been assessed in many randomized controlled trials since the early 70's. These studies produced clear evidence that diuretics reduce the incidence of fatal and non-fatal stroke.[2] In contrast, the reported impact on the occurrence of coronary heart disease was less than expected.[3] Especially the failure of the trials to demonstrate a statistically significant reduction in fatal coronary events[2] has led to much speculation on the potentially fatal adverse effects of non-potassium sparing diuretics. In particular the findings in the Multiple Risk Factor Intervention Trial indicating that non-potassium sparing diuretics may increase the risk of sudden cardiac death among hypertensive patients,[5] has repeatedly been contemplated as evidence for fatal complications related to diuretic use, although this conclusion has been challenged by others.[6] Diuretic-induced hypokalemia or hypomagnesemia leading to cardiac arrhythmias and subsequent sudden cardiac death, has been proposed as the mechanism underlying the putative association between non-potassium sparing diuretics and sudden death. In recent years, several studies addressing the topic have been performed,[7-9] but the results, and in particular their interpretation, are conflicting.[10,11] A propensity of non-potassium sparing diuretics to induce sudden cardiac death is judged to be irrelevant by some,[12] and considered a major clinical problem by others.[13] Of the alternative antihypertensive drugs, betablockers and potassium sparing diuretic therapy (usually a combination of a potassium sparing and a non-potassium sparing diuretic) have been evaluated the most extensively. In contrast to non-potassium sparing diuretics, betablockers have been reported to prevent the occurrence of sudden cardiac death.[14,15] Recently, however, the efficacy of betablocking therapy in reducing the risk of coronary heart disease in elderly hypertensives has been challenged, whereas potassium sparing diuretic therapy has been proven to reduce the risk of coronary events in the elderly.[16-18] To study the extent to which patients on non-potassium sparing diuretics for hypertension experience an excess risk of sudden cardiac death compared to patients prescribed other antihypertensive medications, we performed a population based case-control study.

METHODS

Definition of cases and controls

Eligible as cases were all residents of the municipality of Rotterdam, a town with 580,000 inhabitants, who developed sudden cardiac death between November 21, 1988 and November 21, 1990, and were on drug treatment for hypertension on the date of death. Sudden death was defined as death occurring within one hour from the onset of symptoms, or unwitnessed death.[19,20] The underlying cause was considered to be of cardiac origin unless, according to the attending physician, evidence from hospital or autopsy records suggested a non-cardiac cause.[21] Age- and gender-matched controls were also on drug treatment for hypertension on the day the corresponding case died suddenly, but were alive at that index date. The study received approval from the ethical committee of the Academic Hospital Dijkzigt/Erasmus University Medical School, Rotterdam.

Selection of cases and controls

During the two-year period information on all deaths occurring in Rotterdam in subjects aged 20 years or over (n=11,718) was provided by the municipal authorities, including a statement on the natural or unnatural cause of death and the name of the doctor who signed the death certificate. These physicians received a mailed questionnaire comprising three brief multiple choice questions asking about the time period between the onset of symptoms and the occurrence of death, the possibility of a non-cardiac cause, and the name and address of the patient's general practitioner. In case the patient met the criteria of sudden cardiac death, the general practitioner was asked by mailed questionnaire whether the patient was using antihypertensive medication on the date of death and if so, whether the indication for the prescription was hypertension, and not, as explicitly stated in the question, another condition, notably congestive heart failure and arrhythmias. In the event that the physician who signed the death certificate and the general practitioner were the same person, all five questions were asked simultaneously. Of the 11,718 inhabitants of Rotterdam aged 20 years or over who were reported to have died of natural causes in the study period, useful information from the physician who signed the death certificate was available on 10,649 patients (93%). In total 8,314 (78%) mailed questionnaires were returned, and 7,834 (74%) contained adequate information on the circumstances of death. 1,647 deaths were identified as sudden cardiac deaths and 272 (15%) of these patients were using drugs for hypertension on the date of death. The general practitioners of six cases (2%) refused to cooperate in the study. Of nine potential cases (3%) a review of the written or printed information did not reveal

evidence of antihypertensive drug treatment on the date of death and these patients were excluded from the analysis. Thus, 257 cases of sudden cardiac death were eventually identified.

As soon as a case occurred during the study period, a general practitioner practising in Rotterdam was randomly selected, and when willing to cooperate (over 95% of the general practitioners), visited at the office. The first patient of the same gender and born within a 2.5 year period from the corresponding case was selected from the alphabetically ordered patient registry (starting with the surname following the name of the case) by one of the investigators (AWH), who was unaware of any morbidity and medication history of the patient. Subsequently, the general practitioner was asked exactly the same questions answered by the case's general practitioner, regarding the use of antihypertensive medication on the index date and the indication for treatment. When the first randomly selected patient did not meet the criteria, the next age- and gender-matched patient was selected from the files until a control patient was found.

Ascertainment of the use of antihypertensive medications

A thorough examination of all written or printed information on the study subjects, available at the general practitioners office, was carried out by one of the investigators (AWH). This included the patient charts, often dating back to previous general practitioners, all referral and discharge letters and correspondence from medical specialists, laboratory results and electrocardiograms. Only printed or handwritten, and thus reproducible, information from these sources was used to assess the specific antihypertensive medication the patient was taking on the index date, and if available the duration of use and the prescribed dosage.

It was decided in advance to categorize the antihypertensive medication prescribed on the index date in four mutually exclusive medication groups:

(1) Non-potassium sparing diuretic therapy (e.g., thiazides and loop-diuretics) without betablocking agents (NPSD+/BB-).

(2) Beta-adrenoreceptor blocking agents without non-potassium sparing diuretic therapy (NPSD-/BB+).

(3) Non-potassium sparing diuretics and betablockers used concomitantly (NPSD+/BB+).

(4) Antihypertensive medication, excluding both non-potassium sparing diuretics and betablockers (NPSD-/BB-).

Thus, the latter category comprised antihypertensive drug therapy not recommended as drugs of first choice in the majority of the published national guidelines on hypertension

therapy.[22,23] In the analysis, this category served as the reference group. It mainly included potassium sparing diuretics (used by 65% of the patients in this category) and the more recently developed antihypertensive drugs, such as calcium antagonist and angiotensin converting enzyme-inhibitors. When either of these drugs was given in combination with betablockers the patient was included in group 2 or 3, and when calcium antagonists were prescribed in combination with non-potassium sparing diuretics the patient was included in group 1. The concomitant use of non-potassium sparing diuretics and potassium sparing diuretics or angiotensin converting enzyme-inhibitors was considered a potassium sparing combination and categorized in group 4.

Ascertainment of potential confounding variables

Information on several variables which were potentially associated with both the choice of antihypertensive therapy and the risk of sudden cardiac death was collected. Possible confounders considered in the study included indicators of a history of cardiovascular disease (e.g., prior evidence of myocardial infarction, stroke, angina pectoris or congestive heart failure), cardiovascular risk indicators (e.g., smoking habits, cholesterol level), the presence of important comorbidity (e.g., diabetes mellitus, chronic obstructive pulmonary disease) and indicators of the severity of hypertension (e.g., initial blood pressure level, mean blood pressure during the preceding five years). To assess the presence of these factors, again only written or printed information available at the general practitioner's office was used. A history of myocardial infarction, heart failure, angina pectoris, stroke or intermittent claudication was considered to be positive only when the diagnosis was explicitly and literary noted in the patient file. Two categories of cardiac arrhythmias were distinguished: atrial fibrillation and "other" arrhythmias (including tachycardia, bradycardia and atrioventricular blocks). As another indicator of angina, the daily use of nitrates on the index date was taken. Analogously, digitalis use was considered an indicator of the presence of either heart failure or atrial fibrillation. Of the cardiovascular risk indicators, the last serum cholesterol level, body weight and smoking habits recorded prior to the index date were obtained. A subject was considered hypercholesterolemic when the serum cholesterol level exceeded 6.5 mmol/L. In case no measurement of cholesterol or smoking habits was recorded, the patient was considered normocholesterolemic or a non-smoker. Left ventricular hypertrophy was considered present when the diagnosis was mentioned in the available information, usually based on an electrocardiogram. The presence of several comorbid conditions was assessed. Diabetes mellitus was considered to be present when the diagnosis of diabetes mellitus was explicitly mentioned in the available information, and this was usually a specialist letter. In addition, current use of insulin or oral antidiabetic drugs was used as an

indicator of diabetes. Chronic obstructive pulmonary disease was categorized in two groups: the presence of a diagnosis of asthma, chronic bronchitis or emphysema without current use of pulmonary medication, and the current use of medication for these conditions (e.g. beta-agonists, corticosteroids, theophylline). Kidney dysfunction was defined as a last measured serum creatinine level above 100 μmol/L. Several indicators of the severity of hypertension were obtained. The mean systolic blood pressure during the five years prior to the index date was calculated by using the measurements recorded by the general practitioner only. Hypertension was defined as a mean systolic blood pressure of 160 mm Hg or over and/or a diastolic blood pressure of 95 mm Hg or over. Similarly the last measured treated blood pressure level was categorized into hypertensive/non-hypertensive. When available, the initial blood pressure, that is the level of blood pressure at the time the first antihypertensive drug for hypertension was prescribed ever, was collected. Subjects were categorized as "initially severely hypertensive" when the systolic and/or diastolic blood pressure level reached or exceeded 200 or 120 mm Hg, respectively. Finally, the number of drugs prescribed for hypertension on the index date, and the total number of changes in the prescription of antihypertensive therapy since the start of drug treatment for hypertension were recorded.

Validation of data collection

Because the collection of data could not be performed blinded to the case or control status of the patient, efforts were made to obtain estimates of the potential information bias this may have caused. Firstly, the use of antihypertensive and concomitant medications on the index date as collected from the general practitioner's files was compared to the data provided by computerized pharmacy databases. For logistic reasons the collection of pharmacy data started six months after the initiation of the study. Often, information could not be obtained because the name of the patients pharmacy was unknown. In total, medication histories were available of 28% of all the cases, and of 46% of all control subjects. The main reason for these different proportions was the fact that enrollees in the mandatory collective insurance (the vast majority of the Rotterdam population) are usually deleted from the computerized databases within one to two months after their death. No large discrepancies between the findings recorded in the general practitioner's office and the pharmacy data could be demonstrated. Differences in the antihypertensive medication category obtained from the two sources were found in 11% of the cases and 4% of the controls. To further check the validity of the data collected from the patient files at the general practitioner's office, a physician (S. Tellekamp) who was unaware of the specific research question and blinded to the case

or control status of the patient, re-examined the patient files of a random sample of 10% of both the cases and the controls. No differences in the antihypertensive medication categories recorded by the two investigators were found, and only few discrepancies between the reported prevalence of the major potential confounding variables existed. Of the 51 cases and controls reviewed by the second physician, differences in the history of myocardial infarction, heart failure and angina pectoris were recorded in four, three and two patients, respectively.

Data analysis

To estimate the association between the use of antihypertensive drugs and the occurrence of sudden cardiac death, crude matched odds ratios for the three categories of antihypertensive medication (NPSD+/BB-, NPSD-/BB+, NPSD+/BB+) relative to antihypertensive medication excluding non-potassium sparing diuretics and betablockers (NPSD-/BB-) were calculated by applying conditional logistic regression.[24] Variables which were associated with both the risk of sudden cardiac death (according to a comparison between cases and controls), and the use of antihypertensive medication (according to a comparison between the four treatment categories) were included in a multivariate model, in order to adjust for potential confounding factors. All variables were entered in the conditional logistic regression analysis one by one, to evaluate the stability in the estimated odds ratios and 95% confidence intervals. When appropriate, continuous variables were included in the model as dichotomous variables or dummy variables representing three or more categories. In case of missing data on a categorized continuous variable (e.g., blood pressure level, serum cholesterol) the risk indicator was considered to be absent (and thus the patient was considered to be normotensive and normocholesterolemic). To assess the consequences of this approach, dummy variables indicating missing values were included in the model. In case the inclusion of either of the alternative indicators of a potential confounding variable (e.g., the diagnosis angina or daily use of nitrates as indicators of angina pectoris) resulted in similar point and interval estimates, the presence or absence of the diagnosis in the patient file was included in the final multivariate model.

Subgroup analyses were performed in men and women, and in those aged 75 years or less and those above 75 years of age, applying the same multivariate model as used for the entire study population. Further, multiplicative interaction terms were included in the multivariate analysis to evaluate effect modification by other variables. To study the possibility of a dose-response relationship between non-potassium sparing diuretics and sudden cardiac death, the prescribed dosage was categorized according to the number of defined daily dosages used per day.

Table 5.1. Characteristics of 257 cases of sudden cardiac death and 257 control subjects included in the study.

Characteristic	Cases		Controls	
	n	mean (SD)	n	mean (SD)
Age (years)	257	74.6 (9.8)	257	74.0 (9.2)
Men (%)	257	45.5	257	45.5
History of cardiovascular disease				
Myocardial infarction (%)	257	29.2	257	12.1
Heart failure (%)	257	25.3	257	9.7
Angina pectoris (%)	257	38.1	257	23.3
Stroke (%)	257	17.1	257	9.3
Atrial fibrillation (%)	257	12.1	257	8.6
Other arrhythmias (%)	257	12.5	257	7.4
Claudication (%)	257	16.0	257	9.3
Digitalis use (%)	257	19.5	257	12.5
Chronic nitrate use (%)	257	26.1	257	10.9
Cardiovascular risk indicators				
Cigarette smoking (%)	144	33.3	119	21.8
Last cholesterol (mmol/L)	141	6.6 (1.5)	139	6.4 (1.2)
Left ventricular hypertrophy (%)	257	11.7	257	6.6
Body weight (kgr)	185	75.2 (15.2)	169	75.2 (12.3)
Comorbidity				
Diabetes mellitus (%)	257	18.7	257	13.2
Insulin use (%)	257	3.5	257	2.7
Oral antidiabetics use (%)	257	10.9	257	6.6
COPD medication (%)	257	9.3	257	4.3
Last creatinine (μmol/L)	256	114 (77)	253	101 (51)
Severity of hypertension				
Mean systolic bp (mm Hg)	225	162 (19)	245	165 (16)
Mean diastolic bp (mm Hg)	224	91 (11)	246	93 (8)
Mean bp >160/95 (%)	257	54.5	257	68.1
Initial bp >200/120 (%)	257	14.8	257	16.7
Last systolic bp (mm Hg)	221	157 (23)	245	163 (23)
Last diastolic bp (mm Hg)	220	88 (12)	246	90 (10)
Last bp >160/95 (%)	257	47.1	257	62.6
> 1 Rx on index date (%)	257	49.0	257	37.7

n corresponds to the number of cases and controls in which the characteristics were known.
Abbreviations: SD = standard deviation; COPD = chronic obstructive pulmonary disease; bp = blood pressure; Rx = antihypertensive drug.

RESULTS

Several characteristics of the cases and controls are shown in table 5.1. The mean age of the patients included in the study was 74 years (range 42 to 93 years) and 46% was of the male gender. The prevalence of a history of cardiovascular diseases was higher in the cases than in the controls. Cases were more often cigarette smokers and had a higher prevalence of hypercholesterolemia and left ventricular hypertrophy. No differences in the last recorded body weight was found. Comorbidity was more frequently present in cases than in controls. Controls were more often hypertensive during the five years prior

*Table 5.2. Use of antihypertensive drugs (categorized in four medication groups) among the 257 cases and 257 control patients, and the matched crude and adjusted odds ratios of sudden cardiac death for the antihypertensive medication categories.**

Antihypertensive medication category	Cases n (%)	Controls n (%)	Crude odds ratio (95% CI)	Adjusted odds ratio (95% CI)
Non-potassium sparing diuretics without betablockers (NPSD+/BB-)	33 (12.8)	23 (8.9)	1.7 (0.9-3.1)	2.2 (1.1-4.6)
Betablockers without non-potassium sparing diuretics (NPSD-/BB+)	90 (35.0)	79 (30.7)	1.4 (0.9-2.0)	1.8 (1.1-2.9)
Non-potassium sparing diuretics combined with betablockers (NPSD+/BB+)	23 (8.9)	23 (8.9)	1.2 (0.6-2.3)	1.4 (0.6-3.0)
No non-potassium sparing diuretics and no betablockers (NPSD-/BB-)	111 (43.3)	132 (51.5)	1.0	1.0
Total	257 (100.0)	257 (100.0)		

* Adjusted odds ratios were obtained through multivariate conditional logistic regression analysis, including all potential confounders from the final model (table 5.4). Patients treated with antihypertensive medication other than non-potassium sparing diuretics and betablockers (NPSD-/BB-) served as the reference category. Abbreviations: CI = confidence interval; NPSD = non-potassium sparing diuretics; BB = betablocking drugs.

to the index date and at the time of initiation of antihypertensive therapy, while more cases than controls were prescribed combination therapy for hypertension.

The use of antihypertensive medication according to the four categories is shown for cases and controls in table 5.2. Cases were more often than controls on non-potassium sparing diuretic therapy without betablockers (12.8% versus 8.9%) and on betablockers without non-potassium sparing diuretics (35.0% versus 30.7%). This resulted in a crude odds ratio of 1.7 (95% confidence interval 0.9-3.1) for the use of non-potassium sparing diuretics and of 1.4 (95% confidence interval 0.9-2.0) for betablocker use.

The prevalence of the major potential confounding variables in the four distinct antihypertensive medication categories is summarized in table 5.3. The prevalence of prior myocardial infarction and angina pectoris was higher in the categories including betablocking therapy, whereas a diagnosis of heart failure or pulmonary disease was less prevalent in these medication categories. The prevalence of heart failure and digitalis use in patients prescribed non-potassium sparing diuretics (without betablockers) was somewhat higher than in the reference category.

Table 5.3. Selected characteristics of the study group (n=514), categorized according to the four distinct antihypertensive medication groups.

	Antihypertensive medication category			
	NPSD+/BB- (n=56)	NPSD-/BB+ (n=169)	NPSD+/BB+ (n=46)	NPSD-/BB- (n=243)
Characteristic	mean(SD)	mean(SD)	mean(SD)	mean(SD)
Myocardial infarction (%)	16.1	23.1	10.9	21.8
Heart failure (%)	28.6	7.7	10.9	23.0
Angina pectoris (%)	25.0	35.5	21.7	30.5
Diabetes mellitus (%)	12.5	18.3	6.5	16.9
Digitalis use (%)	23.2	8.3	10.9	20.6
COPD medication (%)	14.3	3.0	2.2	8.6
Mean systolic bp (mm Hg)	163 (20)	162 (17)	164 (17)	165 (17)
Mean diastolic bp (mm Hg)	90 (9)	92 (8)	92 (7)	93 (10)

Abbreviations: NPSD+/BB- = non-potassium sparing diuretics without betablockers; NPSD-/BB+ = betablockers without non-potassium sparing diuretics; NPSD+/BB+ = combination of non-potassium sparing diuretics and betablockers; NPSD-/BB- = antihypertensive medication other than non-potassium sparing diuretics and betablockers; SD = standard deviation; COPD = chronic obstructive pulmonary disease; bp = blood pressure.

*Table 5.4. Association between the use of different classes of antihypertensive medication and the risk of sudden cardiac death among patients treated for hypertension, adjusting for various potential confounding variables.**

Variables included in the multivariate model	Matched odds ratio (95% confidence interval) for the antihypertensive medication categories# NPSD+/BB-	NPSD-/BB+	NPSD+/BB+
Crude	1.7 (0.9-3.1)	1.4 (0.9-2.0)	1.2 (0.6-2.3)
+ myocardial infarction	2.0 (1.1-3.8)	1.4 (0.9-2.2)	1.3 (0.7-2.6)
+ heart failure	2.0 (1.0-3.9)	1.7 (1.1-2.6)	1.3 (0.6-2.7)
+ angina pectoris	2.1 (1.1-4.1)	1.7 (1.1-2.7)	1.3 (0.6-2.6)
+ stroke	2.1 (1.0-4.1)	1.7 (1.1-2.7)	1.2 (0.6-2.5)
+ arrhythmias	2.1 (1.1-4.1)	1.7 (1.1-2.8)	1.2 (0.6-2.5)
+ claudication	2.1 (1.1-4.2)	1.7 (1.1-2.8)	1.2 (0.6-2.5)
+ diabetes mellitus	2.1 (1.1-4.3)	1.7 (1.1-2.7)	1.3 (0.6-2.6)
+ COPD	2.2 (1.1-4.5)	1.8 (1.1-2.9)	1.3 (0.6-2.8)
+ kidney dysfunction	2.2 (1.1-4.6)	1.8 (1.1-2.9)	1.3 (0.6-2.7)
+ cigarette smoking	2.2 (1.1-4.4)	1.8 (1.1-2.8)	1.3 (0.6-2.7)
+ hypercholesterolemia	2.2 (1.0-4.4)	1.8 (1.1-2.9)	1.3 (0.6-2.7)
+ LVH	2.2 (1.0-4.5)	1.8 (1.1-2.9)	1.3 (0.6-2.9)
+ HT in prior 5 years	2.2 (1.1-4.5)	1.8 (1.1-2.9)	1.4 (0.6-3.0)
+ initial severe HT (final model)	**2.2 (1.1-4.6)**	**1.8 (1.1-2.9)**	**1.4 (0.6-3.0)**

* All variables were included in the multivariate model consecutively.

\# Subjects prescribed antihypertensive medication other than non-potassium sparing diuretics and betablockers (NPSD-/BB-) served as the reference category.

Abbreviations: NPSD+/BB- = non-potassium sparing diuretics without betablockers; NPSD-/BB+ = betablockers without non-potassium sparing diuretics; NPSD+/BB+ = combination of non-potassium sparing diuretics and betablockers; NPSD-/BB- = antihypertensive medication other than non-potassium sparing diuretics and betablockers; COPD = chronic obstructive pulmonary disease; LVH = left ventricular hypertrophy; HT = hypertension.

The results of the conditional logistic regression analysis are shown in table 5.4. The crude odds ratios for hypertensive patients treated with non-potassium sparing diuretics (without betablockers) and those on betablockers (without non-potassium sparing diuretics) increased after adjustment for the major potential confounding variables myocardial infarction, heart failure and angina pectoris. Subsequent adjustment for differences in the other variables did not appreciable alter the odds ratios. The estimated odds ratios of sudden cardiac death after adjustment for all measured potential confounding variables were 2.2 (95% CI 1.1-4.6) for the NPSD+/BB- category, 1.8 (95% CI 1.1-2.9) for the NPSD-/BB+ category, and 1.4 (95% CI 0.6-3.0) for the NPSD+/BB+ antihypertensive medication category, compared to antihypertensive medication excluding non-potassium sparing diuretics and betablockers. Inclusion of digitalis use, or substitution of a diagnosis of heart failure or arrhythmias by digitalis use did not influence the findings. Similarly, substitution in the multivariate model of a diagnosis of angina or diabetes by the current use of medication for these conditions had no effect on the estimates.

Subgroup analyses yielded odds ratios which were very similar for men and women. The association between non-potassium sparing diuretic therapy and sudden cardia death was more pronounced in hypertensive patients aged 75 years or less (adjusted odds ratio 4.2 (95% CI 1.1-16.0) than in those above 75 years of age (adjusted odds ratio 1.4 (95% CI 0.5-3.8). No clear discrepancies between the age categories in the estimates of the odds ratios for the other antihypertensive medication groups were found (figure 5.1).

Further subgroup analyses did not reveal a clear dose-response relationship between the number of defined daily dosages of non-potassium sparing diuretic therapy prescribed per day and the occurrence of sudden cardiac death. However, almost all patients were prescribed 1 defined daily dose or less, suggesting that the contrast in the dosages may have been too small to detect a dose-response association. Furthermore, the duration of use of non-potassium sparing diuretics seemed to influence the risk of sudden cardiac death. The adjusted odds ratio of short-term use (less than 1 year) of non-potassium sparing diuretics was 3.1 (95% CI 1.2-8.2) whereas the corresponding odds ratio for long-term use (more than 1 year) was 1.3 (95% CI 0.4-3.6), compared to the reference category. Simultaneous prescription of non-potassium sparing diuretics and digitalis was associated with a higher crude odds ratio than the use of non-potassium sparing diuretics without digitalis (odds ratios 1.9 and 1.6, respectively), but this difference disappeared after adjustment for differences in prognostic factors. Also, the multiplicative interaction term of non-potassium sparing diuretics and digitalis use did not reach conventional levels of statistical significance after inclusion in the model.

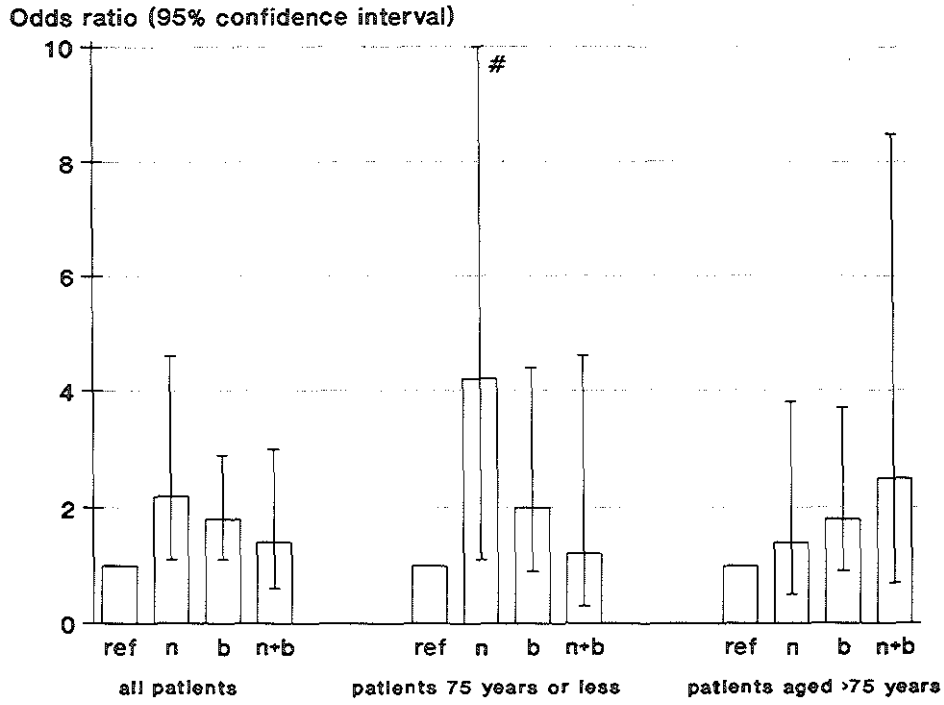

Figure 5.1
Modifying effect of age on the association between the use of different classes of antihypertensive medication and the risk of sudden cardiac death in hypertension. Treated hypertensive patients were categorized in those aged 75 ore less (n=242) and those above 75 years of age (n=272). Matched odds ratios and bars representing 95% confidence intervals resulting from the multivariate analysis including the same potential confounders as in the final model (table 5.4), are shown.

ref = NPSD-/BB- = patients on antihypertensive drugs other than non-potassium sparing diuretics and betablockers (this category served as the reference category).
n = NPSD+/BB- = patients on non-potassium sparing diuretics without betablockers.
b = NPSD-/BB+ = patients on betablockers without non-potassium sparing diuretics.
n+b = NPSD+/BB+ = patients on a combination of non-potassium sparing diuretics and betablockers.
= The value of the higher limit of the 95% confidence interval was 16.0 (not shown in the figure).

Thus, no strong evidence of effect modification by concomitant digitalis use of the risk associated with non-potassium sparing diuretics could be demonstrated. To estimate the potential influence of misclassification by the investigator, the medication findings collected from the general practitioners' patient files were substituted by the pharmacy data, when available. No change in the prevalence of the four antihypertensive medication categories among cases and controls resulted from this procedure. Only a small increase in the adjusted odds ratios occurred after substitution of the pharmacy data. The resulting odds ratios for the three medication groups compared to the reference medication were 2.3 (95% CI 1.1-5.0) for the NPSD+/BB- category, 1.9 (95% CI 1.1-3.0) for the NPSD-/BB+ category, and 1.3 (95% CI 0.6-2.8) for the NPSD+/BB+ group.

DISCUSSION

In this case-control study among treated hypertensive patients, the use of non-potassium sparing diuretics was associated with an increased risk of sudden cardiac death. These findings provide further evidence of a causal relationship between non-potassium sparing diuretics and sudden cardiac death.[13,25] Patients on betablockers for hypertension also experienced a higher incidence of sudden cardiac death in our study.

Several limitations of this study need to be discussed. A main disadvantage lies in the absence of randomization to the antihypertensive medication groups, which is inherent to the nonexperimental study design. As a consequence of specific indications for distinct classes of antihypertensive drugs, and a possible association of these indications with the risk of sudden death, confounding bias may occur. In this regard, major potential confounders are a history of myocardial infarction and heart failure which are associated with both the risk of sudden death and the preferential prescription of betablocking agents and non-potassium sparing diuretics, respectively. Several methods were applied to limit confounding by (contra-)indication in our study.[26,27] Firstly, only patients who were on drug treatment for the specific indication of hypertension were included, although it should be stressed that indications for specific antihypertensive drugs may differ considerably. Furthermore, efforts were made to assess aspects of the clinical profile of the patients believed to be related to the choice of therapy and the risk of sudden death, in order to adjust for discrepancies in these factors in the analysis. As a result of the central role of the general practitioner in the health care system in the Netherlands the information available at the general practitioner's patient files is exclusive and usually extensive. Hence, data on most confounders were available. Nevertheless, residual confounding by indication cannot completely be ruled out.

Especially concomitant mild heart failure in the hypertensive patients, not explicitly noted in the patient file, but resulting in the prescription of non-potassium sparing diuretics, may have led to a spurious relationship between non-potassium sparing diuretics and sudden death. However, the choice of the reference group, of which 65% of the patients was using potassium sparing diuretics, is likely to have resulted in a comparable prevalence of patients with mild symptoms of heart failure in the latter category. This is illustrated by the similar prevalences of an explicit diagnosis of heart failure and digitalis use in the two medication groups. Furthermore, the general practitioner was explicitly asked whether the primary indication for the antihypertensive therapy was hypertension, and not heart failure. When the primary indication was heart failure, the patient was not included in the study. The adjusted odds ratio for non-potassium sparing diuretics in patients older than 75 years was lower than in those aged 75 years or less. Because of the well-known increase in the prevalence of (mild) heart failure with advancing age, however, a bias caused by symptomatic but undiagnosed heart failure would have resulted in a higher odds ratio of non-potassium sparing diuretics in the very old. Mild anginal complaints may have led to an artificially increased risk associated with betablockade, but adjustment for current use of nitrate therapy as an indicator of angina did not alter the findings. Thus, residual confounding is unlikely to fully explain the excess risk of sudden cardiac death associated with non-potassium sparing diuretics or betablockade found in our study.

The study could not be performed blinded. This may lead to information bias if the misclassification of the use of specific antihypertensive drugs is different among cases and controls. Comparison with the findings from the pharmacy databases did not reveal any differential misclassification, and neither did the comparison with the recorded findings from the second physician who was unaware of the research question and the underlying hypothesis. The limited misclassification present appeared to be non-differential, which generally leads to dilution of the effect. This is illustrated by the slight increase in the odds ratios resulting from substitution of the antihypertensive medication recorded in the general practitioner's office by the pharmacy data, where available.

A major advantage of our study compared to previous studies, and in particular to the randomized trials, is the large number of 257 cases of sudden cardiac death collected. This is almost three times the number reported in the largest hypertension trial to date.[25,28] Furthermore, the case-control approach enables assessment of the influence of many categories of the use of antihypertensive medication (including specific drugs, dosages and the duration of use) on the risk of sudden death.

Our finding of an increased risk of sudden death among patients using non-potassium sparing diuretics for hypertension is in accordance with the reports from

several trials in mild to moderate hypertension. In the Multiple Risk Factor Intervention Trial the incidence of sudden cardiac death was higher in hypertensive patients randomized to "special intervention", including non-potassium sparing diuretic as the initial step of a stepped-care antihypertensive therapy, compared to those randomized to the "usual" sources of health care.[5,29] These findings were confirmed by a re-analyses of the data from the Oslo study and Hypertension Detection and Follow-up Program,[30,31] although in a previous analysis of the latter study no excess risk of sudden death associated with diuretics was reported.[32] In the Medical Research Council trial in mild hypertension the incidence of sudden cardiac death among men randomized to bendrofluazide was higher compared to those treated with propranolol or placebo. Only the comparison with propranolol reached statistical significance (relative risk 2.4, 95% CI 1.2-4.4).[25] Further evidence of an excess risk of sudden death associated with non-potassium sparing diuretic therapy for hypertension was reported from the Metoprolol Atherosclerosis Prevention in Hypertension trial.[14] In contrast, other randomized trials, including the recent Systolic Hypertension in the Elderly trial, could not demonstrate an increased risk of sudden death in patients on non-potassium sparing diuretic treatment.[33,34] Evidence that diuretic-induced potassium or magnesium depletion may result in sudden death, by increasing the incidence of cardiac arrhythmias, has been produced by several studies.[9,35] In other studies no association between non-potassium sparing diuretics and the occurrence of arrhythmias was found.[8,36,37] Although our case-control study was not designed to address this hypothetical mechanism, the increased risk of sudden cardiac death in patients treated with non-potassium sparing diuretics compared to those on potassium sparing diuretic therapy (included in the reference category) indicates that potassium or magnesium depletion may be involved. The relatively higher risk in recent users compared to those on non-potassium sparing diuretics for more than one year, gives further support to the view that drug-induced electrolyte depletion may be implicated. This is also illustrated by the beneficial effect on coronary heart disease incidence reported in two trials evaluating the efficacy of potassium sparing diuretic therapy in hypertension.[16,18]

The finding in our study of an increased risk of sudden death among hypertensive patient prescribed betablockers was unexpected in view of the evidence suggesting a cardioprotective effect of betablockers in the treatment of hypertension.[14,25,38] Several possible explanations for this finding should be considered. Firstly, as mentioned above, residual confounding cannot be completely ruled out in our study, although efforts were made to adjust for differences in prognosis between the antihypertensive medication groups. Further, the excess risk of sudden death during betablocker therapy in our study in relatively old hypertensive patients (mean age 74 years) could be partly explained by

the fact that these drugs may not be as efficacious in preventing coronary heart disease in the elderly as in the middle-aged.[17] This was suggested in the recently published MRC-trial in the elderly, in which treatment with atenolol was associated with an increased risk of coronary events compared to potassium-sparing diuretic therapy.[16] It also has been suggested that a sudden withdrawal from betablocking therapy may increase the instantaneous risk of coronary events,[39] possibly caused by the upregulation of the beta-adrenoreceptors during betablocking treatment.[40] Thus, certain cases of sudden cardiac death in our study may have been triggered because the patient "forgot" to take the drug the previous day, although this remains speculative because no data on day-to-day compliance were available. Future studies are needed to further establish the clinical importance and possible underlying mechanism of our finding regarding the risk of betablockers.

In conclusion, our findings indicate that at least part of the beneficial effect of non-potassium sparing diuretic therapy for hypertension is off-set by an increased risk of sudden cardiac death associated with the use of these drugs.

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CHAPTER 6

GENERAL CONCLUSIONS AND SUGGESTIONS FOR FUTURE RESEARCH

The studies described in this thesis focus on the possible relationship between the use of non-potassium sparing diuretics and the occurrence of sudden cardiac death in hypertensive patients. To study this potential adverse drug reaction several methods were applied, including estimates of population attributable proportions, a meta-analysis and, most importantly, a case-referent (case-control) study. In this chapter the main conclusions, their possible implications and suggestions for future research will be given.

The main conclusion to be drawn from this thesis, is that the use of non-potassium sparing diuretic therapy (e.g. thiazides, chlothalidone, loop-diuretics) is associated with an increased risk of sudden cardiac death in patients who are on drug treatment for hypertension. In the case-control study described in chapter 5, the odds ratio for patients using non-potassium sparing diuretics (without betablockers) was 2.2 (95% confidence interval 1.1-4.6), compared to a reference category of which the majority of patients was prescribed potassium sparing diuretics (without betablockers). The excess risk of sudden death was more pronounced in patients aged 75 years or less, than in those above 75 years of age. Moreover, short-term use (less than 1 year) of non-potassium sparing diuretics seemed to be associated with a higher risk of sudden cardiac death than long-term use. The finding of a twofold risk of sudden cardiac death during non-potassium diuretic therapy for hypertension underscores the evidence from several hypertension trials and follow-up studies, although these former studies were not specifically designed to address this issue.[1,2] The main advantage of our case-control approach is the large number of sudden cardiac deaths included in the study. The major limitation of the approach lies in the difficulty to rule out residual confounding by indication and contra-indication, although efforts were made to ensure comparability of prognosis across antihypertensive drug categories. Thus, whether the excess risk of sudden cardiac death in patients prescribed non-potassium sparing diuretics is caused by the action of the diuretic perse, or whether the use of these drugs is merely an indicator of an increased risk of sudden death, remains uncertain. Our studies were not designed to provide direct evidence concerning the hypothesis put forward to explain the association between non-potassium sparing diuretics and sudden cardiac death, notably diuretic-induced electrolyte depletion leading to cardiac arrhythmias and subsequent sudden death. However, the fact that patients on potassium sparing diuretic therapy for hypertension (included in the reference category of the case-control study) were at a lower risk of sudden cardiac death compared to the hypertensive patients prescribed potassium-loosing agents, indicates that potassium and magnesium depletion may be involved. The relatively higher risk in recent users compared to those on non-potassium sparing diuretics for more than one year, gives further support to the view that drug-induced electrolyte depletion may be

implicated. This is also illustrated by the beneficial effect on the incidence of coronary heart disease reported in the few hypertension trials that assessed the efficacy of potassium sparing diuretic therapy.[3,4]

Future studies are needed to further clarify the mechanism underlying the relationship between diuretics and sudden death. These studies should focus primarily on the relationship between the total body- and intracellular electrolyte contents and the occurrence of cardiac arrhythmias recorded during 24- or 48-hour ECG-registrations. In these studies a randomized controlled comparison between the arrhythmogenic effect of low-dose non-potassium sparing diuretic therapy and alternative antihypertensive drugs, in particular potassium sparing diuretics, betablockers, calcium antagonists and ACE-inhibitors, seems necessary. The studies should not be restricted to hypertensive patients without clinical evidence of ischemic heart disease. Especially, findings in patients with prior cardiovascular events and those with concomitant left ventricular hypertrophy are sparse.

In contrast to the increased risk of sudden death associated with non-potassium sparing diuretics, the finding of a significant 1.8-fold risk of sudden death during betablocking therapy for hypertension in our study, is not supported by a large body of evidence from earlier studies and the physiological basis is unclear. In the two trials comparing thiazides and betablockers in the treatment of uncomplicated hypertension reported so far, the incidence of sudden death in the betablocker-treated group was significantly lower than in the thiazide-treated patients.[5,6] Our findings among treated hypertensives (mean age 74 years) is in line, however, with the data from the recent Medical Research Council trial in the elderly, where the incidence of coronary heart disease in hypertensive patients on betablockers treatment was higher compared to patients randomized to potassium-sparing diuretic therapy.[4] The MRC-trial casted serious doubts on the efficacy of betablockers in the treatment of hypertensive elderly patients. Several explanations may account for this failure of betablockers to prevent coronary heart disease, including the physiological changes occurring with advancing age which could trigger a coronary event in the presence of betablockade, and the adverse effect of skipping one or more tablets which could lead to a coronary event as a result of a betablocker-induced upregulation of the betareceptors.[7,8]

In view of the limited evidence from previous studies supporting our finding of an excess risk of sudden death during betablocking therapy, and the gap in the knowledge concerning the underlying mechanism, the importance of this finding remains to be established. Apart from studies on electrolyte change and cardiac arrhythmias mentioned above, future research could focus on the effect of a temporal cessation of

betablocking therapy on 24- or 48- hour ECG-recordings. Also, the influence of different types of betablockers and the prescribed dosage and duration of use needs further attention.

An important conclusion from this thesis is that the pharmacoepidemiologic approach chosen to study sudden cardiac death as an adverse effect of non-potassium sparing diuretics was feasible. Pharmacoepidemiology is a rapidly growing discipline and is becoming increasingly important in light of the governmental guidelines for post-marketing surveillance.[9] Our case-control approach combines the strengths of the computerized pharmacy data-bases with the even more crucial advantages of the availability of unique and extensive patient information at the general practitioners office. The central role of the general practitioner in the health care system in the Netherlands offered the opportunity to perform the studies described here. Although the validity of the patient records kept by the general practitioner has been challenged, our study indicates that the study of adverse drug reactions in general practice is feasible when drug therapy for chronic conditions is studied and potential confounders may be satisfactorily identified from the printed information. Restriction of the cases and controls to patients on drug treatment for the indication hypertension undoubtedly increased the validity of the results, and, as a practical consequence, also provided for the availability of information in the patient files. The method of restricting the study population to those who are on drug treatment for the condition studied, seems a powerful method to limit confounding by indication and contra-indication in nonexperimental studies of drug effects. In view of the large number of computerized pharmacies and the increasing use of automated patient records in general practice, studies as presented in chapter 5 may become an important alternative in pharmacoepidemiologic research.

Although the work described in thesis provides evidence that non-potassium sparing drug therapy for hypertension is associated with an excess risk of sudden cardiac death, it is beyond the scope of this thesis to provide guidelines for the choice of drug therapy in hypertension, let alone strongly advice against the use of non-potassium sparing diuretics. It should be stressed that many randomized trials have proven these diuretics to be efficacious in preventing cardiovascular events, notably stroke,[10] in hypertensive patients, although the overall beneficial effect of non-potassium sparing diuretics may have been unfavorably influenced by the propensity of these drugs to induce sudden death. The estimate of 102 annual sudden cardiac deaths attributable to the use of these diuretics in the Netherlands (chapter 2) is an indication of the magnitude of this adverse effect.

However, in the choice of a particular antihypertensive drug physicians should weigh all advantages and disadvantages particular to individual drugs, and an increased risk of sudden death in some patients is but one of these. Beneficial effects of non-potassium sparing diuretics, e.g., the relatively low costs and a protective effect against fractures of the hip, should not be discarded.[11] During the last decade, the prescription of alternative antihypertensive drugs has increased. Of these drugs, only the effect of betablockers and potassium sparing diuretic therapy (usually a combination of a potassium sparing and a non-potassium sparing diuretic) on cardiovascular events has been evaluated, although not as extensively as for non-potassium sparing diuretics. The recently reported relative unfavorable effect of betablockers on coronary heart disease incidence in elderly hypertensives, also illustrated by the increased risk of sudden cardiac death in our study, is worrisome, but a beneficial effect of betablockers on the survival of post-myocardial infarction patients with hypertension seems undisputed.[12,13] Potassium sparing diuretic therapy seems to combine a lack of severe adverse events with proven efficacy in preventing cardiovascular events, in particular in the elderly.[3,4] Large studies on the effect of the newer antihypertensive agents, e.g. ACE-inhibitors and calcium antagonists, on the incidence of cardiovascular events are needed and several have been initiated. Clearly, these and future studies will learn whether the prominent role of diuretics and betablockers in the therapy of hypertension[14,15] is justifiable now that alternative antihypertensive agents are available.

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CHAPTER 7

SUMMARY

Since the introduction of chlorothiazide in 1957, diuretics have been widely used as drugs of first choice in the treatment of hypertension. Many studies have demonstrated that diuretics clearly reduce the risk of stroke in hypertensive patients, but the effect on the incidence of coronary heart disease did not come up to expectations. Several explanations for the latter finding have been put forward. In particular, the suggestion that non-potassium diuretics may increase the risk of sudden cardiac death in certain hypertensive patients has been vigorously debated. Diuretic-induced potassium or magnesium depletion leading to cardiac arrhythmias and subsequent sudden death, has often been suggested as the underlying mechanism. Up to the present, the issue remains unresolved and the possibility of a causal relationship between diuretics and sudden cardiac death is judged to be negligible by some and a major clinical problem by others. The objective of the work presented in this thesis is to determine whether non-potassium sparing diuretic therapy increases the risk of sudden cardiac death in patients who are on drug treatment for hypertension.

An extensive review of the recent scientific evidence on the association between diuretics, potassium homeostasis, arrhythmias and sudden death, is given in *Chapter 1*. A clear dose-response relationship between the use of non-potassium sparing diuretics and the fall in serum potassium levels is present. Analogously, non-potassium sparing diuretics seem to decrease serum magnesium levels and intracellular potassium and magnesium content, although data on this are too limited to allow definite conclusions. Findings on the relationship between the use of non-potassium sparing diuretics and the occurrence of ventricular arrhythmias among hypertensive patients without clinical evidence of heart disease are conflicting. This may be partly explained by methodological differences between studies. The few studies among hypertensive patients with clinical evidence of heart disease reported an increased risk of arrhythmias during non-potassium sparing diuretic therapy. No diuretic-induced increase in arrhythmias was demonstrated in the two studies in hypertensive patients with left ventricular hypertrophy. The large hypertension trials provide the strongest evidence that non-potassium sparing diuretics may induce sudden cardiac death. Although blood pressure lowering can be expected to reduce the incidence of sudden cardiac death, the incidence among non-potassium sparing diuretic-treated patients was similar to, or even higher than in the control group in nine of ten trials. Furthermore, several studies have provided evidence that, in contrast to non-potassium sparing diuretics, betablockers may reduce the risk of sudden death, although the efficacy of betablockers in elderly hypertensive patients has recently been challenged.

In *Chapter 2*, the public health consequences of a relationship between non-potassium sparing diuretics and sudden cardiac death in hypertensive patients are estimated, by using the findings from two earlier studies performed in the Netherlands, and the results of the Medical Research Council trial in mild hypertension. The proportion of sudden cardiac deaths attributable to the use of non-potassium sparing diuretics among hypertensive men treated with these drugs is 59% (95% confidence interval 21 - 79%). The proportion of sudden cardiac deaths attributable to non-potassium sparing diuretic therapy among all Dutch men on drug treatment for hypertension is 16% (95% confidence interval 3 - 29%). It is estimated that in the entire population of 385,000 treated hypertensive men in the Netherlands, 102 (95% confidence interval 19 - 180) annual cases of sudden cardiac death may be due to the use of non-potassium sparing diuretics. This suggests that one sudden cardiac death per 3800 treated hypertensive men per year may be prevented when "other" antihypertensive drugs are prescribed. Although several limitations inherent to this type of analysis exist, these findings are most likely underestimates of the true health impact in the Netherlands. No reliable estimates regarding the female hypertensive population can be made, but given the high prevalence of treated hypertension in Dutch women, a small diuretic-related excess risk of sudden cardiac death would have substantial implications.

In light of the disparate effect of diuretic therapy on fatal coronary heart disease and all-cause mortality in the published hypertension trials, a meta-analysis of these studies was performed (*Chapter 3*). Seven randomized trials in mild to moderately hypertensive middle-aged patients were included in the analysis. In the meta-analysis, a newly developed method based on weighted linear regression was used. The vast majority of the patients in the intervention groups received non-potassium sparing diuretics as drug of first choice. In trials with a high all-cause mortality rate in the control group, i.e., if the untreated risk is high, antihypertensive drug treatment increased life-expectancy. Conversely, when all-cause mortality in the control group was low, treatment had no or even an opposite effect on survival. The break-point of these two contrasting effects paralleled a mortality rate of 6 per 1000 patient-years in the control group. A similar analysis of mortality from coronary heart disease yielded comparable results, again illustrating the heterogeneity of the effect in the published trials. In contrast, drug treatment decreased stroke mortality proportionately, irrespective of the incidence of fatal stroke in the control group of the trials.

These findings demonstrate that drug treatment for mild to moderate hypertension in middle-aged patients may reduce all-cause mortality and the risk of fatal coronary events when treatment is initiated in those beyond a certain baseline mortality risk. Drug

treatment in hypertensive patients at a lower risk of fatal events has no influence on or even increases mortality, possibly as a result of fatal adverse effects of the antihypertensive drug used. Diuretic-induced hypokalemia leading to sudden cardiac death, may be one of the adverse drug reactions involved.

Several consequences of the choice of a nonexperimental study design in the assessment of drug efficacy and adverse drug reactions are described in *Chapter 4.*

First, the potential problems related to the absence of random allocation to the treatment groups are discussed (*Chapter 4.1*). Nonexperimental studies of drug efficacy are susceptible to bias as a result of confounding by indication. In nonexperimental studies of adverse drug reactions absence of randomization causes confounding by indication or contra-indication only when the adverse drug reaction is associated with the indication or contra-indication of the drug, respectively. In case of a type A adverse drug reaction confounding by contra-indication is likely to occur. However, in the study of type B adverse drug reactions confounding by contra-indication is nonexistent, and the absence of randomization does not affect validity.

In the case-control study of the relationship between non-potassium sparing diuretics and sudden cardiac death presented in this thesis (chapter 5), absence of randomization may give rise to both confounding by indication and contra-indication. Consequently, methods other than randomization should be applied in the design of nonexperimental studies to ensure similarity of prognosis across treatment groups. Several of these alternative methods are discussed using the example of the published nonexperimental studies assessing the efficacy of antihypertensive treatment in the primary prevention of coronary heart disease (*Chapter 4.2*).

To quantify the relationship between non-potassium sparing diuretic therapy and the occurrence of sudden cardiac death in treated hypertensive patients, a case-control study was performed (*Chapter 5*). During a period of two years, data on all inhabitants of the Rotterdam metropolitan area who died of sudden cardiac death (n=1,827) were collected. Eligible as cases were those who were on drug treatment for hypertension at the time of death (n=257). Age- and gender-matched controls (n=257) were alive on the date of death of the corresponding case and were also on drug treatment for hypertension. To obtain information on antihypertensive drug use and potential confounding variables, a thorough review of the patient medical file was carried out and data from computerized pharmacy databases were used. Antihypertensive medication was categorized according to four groups: Non-potassium sparing diuretic therapy without betablockers, betablocking therapy without non-potassium sparing diuretics, a

combination therapy of non-potassium sparing diuretics and betablockers, and antihypertensive therapy excluding both non-potassium sparing diuretics and betablockers. The latter category served as the reference group. The mean age of the cases and controls was 74 years and 46% was of the male sex.

The odds ratio of sudden cardiac death among patients on non-potassium sparing diuretic therapy compared to the reference group was 2.2 (95% confidence interval 1.1 - 4.6) after adjustment for confounders, notably cardiovascular history (e.g., prior myocardial infarction, heart failure), comorbidity (e.g., diabetes), and severity of hypertension. Somewhat unexpected, the corresponding odds ratio for hypertensive subjects treated with betablockers was 1.8 (95% confidence interval 1.1 - 2.9). The findings in men and women were similar, but the odds ratio of sudden death during the use of non-potassium sparing diuretics was higher in hypertensives aged 75 years or less (4.2, 95% confidence interval 1.1 - 16.0), than in those above 75 years of age (1.4, 95% confidence interval 0.5 - 3.8). Also, the risk of sudden cardiac death associated with a short duration (less than 1 year) of the use of non-potassium sparing diuretics, seemed to be higher than the risk associated with longer durations of use of these drugs.

These findings indicate that at least part of the beneficial effect of non-potassium sparing diuretic therapy for hypertension is off-set by an increased risk of sudden cardiac death associated with the use of these drugs. Furthermore, the use of betablockers may be an indicator of an increased risk of sudden death.

Finally, the general conclusions of the work described in this thesis are summarized and suggestions for future research are given (*Chapter 6*).

CHAPTER 8

SAMENVATTING

Sinds de introductie van chloorthiazide in 1957 nemen diuretica een belangrijke plaats in als bloeddrukverlagende geneesmiddelen van eerste keuze bij de behandeling van hoge bloeddruk. Onderzoekingen hebben aangetoond dat antihypertensieve behandeling met diuretica het risico op een cerebrovasculair accident doet verminderen, maar het effect op het optreden van coronaire hartziekte bleef achter bij de verwachtingen. Hiervoor worden verschillende verklaringen gegeven. Met name de mogelijkheid dat niet-kaliumsparende diuretica het risico op een plotselinge hartdood kunnen verhogen bij bepaalde personen met hypertensie heeft aanleiding gegeven tot heftige discussies. Een door diuretica veroorzaakte hypokaliëmie of hypomagnesiëmie, leidend tot aritmieën en vervolgens tot een plotselinge hartdood, wordt vaak als het onderliggend mechanisme beschouwd. Tot op heden blijven de meningen over dit onderwerp sterk verdeeld en de mogelijkheid van een causaal verband tussen niet-kaliumsparende diuretica en plotselinge dood wordt door sommigen verwaarloosbaar klein en door anderen zeer groot geacht. Het doel van de in dit proefschrift beschreven onderzoekingen is na te gaan of niet-kaliumsparende diuretica het risico op een plotselinge hartdood verhogen bij personen die medicamenteus worden behandeld wegens hypertensie.

Een uitgebreid overzicht van de recente wetenschappelijke literatuur betreffende het verband tussen diuretica, de kaliumhuishouding, aritmieën en plotselinge dood, wordt gegeven in *Hoofdstuk 1*. Er bestaat een duidelijk verband tussen de gebruikte dosis niet-kaliumsparende diuretica en de daling van het kaliumgehalte in het serum. Niet-kaliumsparende diuretica lijken ook tot een verlaging van het serummagnesium en het intracellulaire kalium en -magnesium te leiden, maar door de beperkte beschikbare gegevens zijn definitieve uitspraken hierover onmogelijk. Er zijn tegenstrijdige gegevens over het verband tussen het gebruik van niet-kaliumsparende diuretica en het optreden van ventriculaire ritmestoornissen bij hypertensieve patiënten zonder klinisch manifeste hartziekte. Dit kan mogelijk verklaard worden door methodologische verschillen tussen de studies. Bij de weinige onderzoekingen bij hypertensieve patiënten met een klinisch manifeste hartziekte is wel een toegenomen risico op aritmieën tijdens het gebruik van niet-kaliumsparende diuretica gevonden. In de twee onderzoekingen bij hypertensieve patiënten met linker ventrikelhypertrofie werd echter geen toename van aritmieën aangetoond. De belangrijkste aanwijzing dat niet-kaliumsparende diuretica een plotselinge hartdood kunnen induceren wordt geleverd door de grote hypertensie-trials. Hoewel men zou verwachten dat bloeddrukverlaging het aantal gevallen van plotselinge dood zou verlagen, blijkt de incidentie in de met niet-kaliumsparende diuretica behandelde patiëntengroep vergelijkbaar met, of zelf hoger te zijn dan in de

controlegroep, bij negen van de tien trials. Bovendien blijkt uit enkele studies dat, in tegenstelling tot niet-kaliumsparende diuretica, het gebruik van betablokkers het risico op plotselinge dood zou kunnen verlagen, hoewel de effectiviteit van betablokkers bij ouderen met hypertensie recentelijk in twijfel is getrokken.

In *Hoofdstuk 2* wordt een schatting gemaakt van de gevolgen voor de volksgezondheid van een verband tussen niet-kaliumsparende diuretica en plotselinge hartdood bij hypertensieve personen, gebruikmakend van twee eerder uitgevoerde Nederlandse onderzoekingen en de gegevens van de Medical Research Council trial bij volwassenen met een matig verhoogde bloeddruk. Van de gevallen van plotselinge hartdood bij wegens hypertensie met niet-kaliumsparende diuretica behandelde mannen, is 59% (95% betrouwbaarheidsinterval 21 - 79%) toe te schrijven is aan het gebruik van deze medicijnen. Van de gevallen van plotselinge hartdood bij alle Nederlandse mannen die met geneesmiddelen worden behandeld voor hypertensie is 16% (95% betrouwbaarheidsinterval 3 - 29%) toe te schrijven aan het gebruik van niet-kaliumsparende diuretica. Naar schatting treden er in Nederland bij de 385.000 mannen die medicamenteus worden behandeld wegens hypertensie jaarlijks 102 (95% betrouwbaarheidsinterval 19 - 180) gevallen van plotselinge hartdood op, die kunnen worden toegeschreven aan het gebruik van niet-kaliumsparende diuretica. Dit betekent dat per 3800 behandelde hypertensieve mannen één geval van plotselinge dood zou kunnen worden voorkomen indien andere antihypertensiva zouden worden voorgeschreven. Hoewel deze berekeningen enkele inherente beperkingen kennen, geven de resultaten waarschijnlijk een onderschatting van het werkelijke gezondheidseffect in Nederland. Er zijn geen betrouwbare schattingen voor de vrouwelijke hypertensieve populatie te maken, maar zelfs een gering extra risico op plotselinge dood door diuretica zou, gezien het hoge percentage Nederlandse hypertensieve vrouwen dat bloeddrukverlagende geneesmiddelen gebruikt, aanzienlijke implicaties hebben.

In het kader van de tegenstrijdige effecten van diuretica op fatale coronaire hartziekte en totale sterfte in de gepubliceerde hypertensie-trials, werd een meta-analyse van deze onderzoekingen verricht (*Hoofdstuk 3*). Zeven gerandomiseerde onderzoekingen bij personen van middelbare leeftijd met een gering tot matig verhoogde bloeddruk werden betrokken in de analyse. Bij de meta-analyse werd gebruik gemaakt van een nieuwe, op gewogen lineaire regressie gebaseerde, methode. De overgrote meerderheid van de aan de interventiegroepen toegewezen deelnemers kregen niet-kaliumsparende diuretica voorgeschreven als antihypertensivum van eerste keus. Behandeling met antihypertensiva had een gunstig effect op de levensverwachting in trials met een hoge totale sterfte in

de controlegroep, dat wil zeggen dat het onbehandelde risico hoog is. Was het sterftecijfer in de controlegroep echter laag, dan had medicamenteuze behandeling geen of zelfs een averechts effect op de overleving. Het omslagpunt van deze tegengestelde effecten lag naar schatting bij een sterftecijfer in de controlegroep van 6 per 1000 persoonsjaren. Een vergelijkbare analyse van de sterfte aan coronaire hartziekte gaf vergelijkbare resultaten. Dit wijst wederom op de heterogeniteit van de trials. Echter, antihypertensieve behandeling verminderde de kans op cerebrovasculaire sterfte proportioneel, ongeacht de cerebrovasculaire sterfte in de controlegroep van de trials.

Deze resultaten vormen een aanwijzing dat medicamenteuze behandeling van personen van middelbare leeftijd met een licht tot matig verhoogde bloeddruk het risico op overlijden en coronaire sterfte vermindert, mits die personen worden behandeld, wiens sterftekans boven een bepaalde grens ligt. Medicamenteuze behandeling van hypertensieve personen met een lager sterfterisico zal geen of zelfs een nadelig effect op de overleving sorteren, mogelijke ten gevolge van het optreden van fatale bijwerkingen van de gebruikte antihypertensieve medicatie. Door diuretica veroorzaakte hypokaliëmie leidend tot een plotselinge hartdood zou hierbij een rol kunnen spelen.

De consequenties van de keuze van een niet-experimentele onderzoeksopzet bij de bestudering van de effectiviteit of bijwerkingen van geneesmiddelen worden besproken in *Hoofdstuk 4.*

Eerst worden de problemen beschreven die kunnen ontstaan doordat de toewijzing aan de behandelingsgroepen niet gerandomiseerd gebeurt *(Hoofdstuk 4.1)*. Niet-experimentele onderzoekingen naar de effectiviteit van geneesmiddelen zijn mogelijk gebiased door "confounding by indication". Bij niet-experimentele onderzoekingen naar bijwerkingen van geneesmiddelen zal het ontbreken van randomisatie alleen dan tot "confounding by indication" of "confounding by contra-indication" leiden, indien de bijwerking geassocieerd is met respectievelijk de indicatie of contra-indicatie voor het medicament. In het geval van een type A bijwerking is "confounding by contra-indication" waarschijnlijk. Bij de bestudering van type B bijwerkingen is er echter geen sprake van "confounding by contra-indication" en zal het ontbreken van randomisatie geen nadelige gevolgen hebben voor de validiteit.

Het ontbreken van randomisatie zou in het in dit proefschrift beschreven patiënt-controle onderzoek naar het verband tussen niet-kaliumsparende diuretica en plotselinge hartdood (hoofdstuk 5), aanleiding kunnen geven tot zowel "confounding by indication" als "confounding by contra-indication". Derhalve zullen andere methoden dan randomisatie toegepast moeten worden in de opzet van niet-experimenteel onderzoek, om vergelijkbaarheid van prognose tussen de verschillende behandelingsgroepen te

garanderen. Enkele van deze alternatieve methoden worden besproken, uitgaande van het voorbeeld van de niet-experimentele onderzoekingen naar de effectiviteit van antihypertensiva bij de primaire preventie van coronaire hartziekte *(Hoofdstuk 4.2)*.

Teneinde het verband tussen niet-kaliumsparende diuretica en de kans op een plotselinge hartdood bij personen die medicamenteus worden behandeld wegens hoge bloeddruk te kwantificeren, werd een patiënt-controle onderzoek uitgevoerd (*Hoofdstuk 5*). Gedurende een periode van twee jaar werden gegevens betreffende alle aan een plotselinge hartdood overleden inwoners van Rotterdam verzameld (n=1827). Iemand die tevens medicamenteus werd behandeld wegens hypertensie op de dag van overlijden was een "case" in het onderzoek (n=257). Op leeftijd- en geslacht gematchte controlepersonen (n=257) waren in leven op de dag van het overlijden van de bijbehorende case en gebruikten ook antihypertensiva wegens hypertensie. Om informatie betreffende het gebruik van antihypertensiva en mogelijke verstorende variabelen te verkrijgen werd de medische status van de patiënt uitgebreid bestudeerd en werden gegevens van de geautomatiseerde apotheken gebruikt. De antihypertensieve medicatie werd in vier groepen onderverdeeld: niet-kaliumsparende diuretica zonder betablokkers, betablokkers zonder niet-kaliumsparende diuretica, een combinatie van niet-kaliumsparende diuretica en betablokkers, en antihypertensieve medicatie zonder niet-kaliumsparende diuretica of betablokkers. De laatstgenoemde groep gold als referentiecategorie. De gemiddelde leeftijd van de cases en controlepersonen was 74 jaar en de groep bestond voor 46% uit mannen.

De odds ratio voor plotselinge hartdood bij met niet-kaliumsparende diuretica behandelde personen, ten opzichte van de referentiecategorie, was 2,2 (95% betrouwbaarheidsinterval 1,1 - 4,6), na correctie voor verstorende variabelen, met name de cardiovasculaire voorgeschiedenis (bijv. een hartinfarct, decompensatio cordis), comorbiditeit (bijv. diabetes) en de ernst van de hypertensie. De odds ratio voor de met betablokkers behandelde personen met hypertensie was 1,8 (95% betrouwbaarheids-interval 1,1 - 2,9), hetgeen een enigszins onverwachte bevinding is. De resultaten voor mannen en vrouwen waren vergelijkbaar, maar de odds ratio voor plotselinge dood tijdens het gebruik van niet-kaliumsparende diuretica was hoger bij hypertensieve personen van 75 jaar en jonger (4,2; 95% betrouwbaarheidsinterval 1,1 - 16,0) dan bij personen ouder dan 75 jaar (1,4; 95% betrouwbaarheidsinterval 0.5 - 3,8). Verder leek het risico op een plotselinge hartdood bij een korte gebruiksduur (minder dan 1 jaar) van niet-kaliumsparende diuretica hoger te zijn dan na een langer gebruik van deze geneesmiddelen.

Deze resultaten vormen een aanwijzing dat op zijn minst een gedeelte van het

voordelige effect van behandeling van hypertensie met niet-kaliumsparende diuretica teniet wordt gedaan door een aan het gebruik van dit geneesmiddel gerelateerd verhoogd risico op een plotselinge hartdood. Bovendien lijkt in dit onderzoek ook het gebruik van betablokkers een indicator te zijn voor een verhoogde kans op een plotselinge dood.

Tenslotte worden de conclusies van de in dit proefschrift beschreven onderzoekingen beschreven en worden enkele aandachtspunten voor toekomstig onderzoek op dit gebied aangegeven (*Hoofdstuk 6*).

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About the author

Arno Hoes was born on December 9th, 1958 in Nijmegen, the Netherlands. He attended secondary school (Atheneum B) at the Titus Brandsma Lyceum in Oss and graduated in 1977. He studied at the Agricultural University in Wageningen during one year, before entering medical school at the Catholic University of Nijmegen in 1978. During his medical training he conducted a retrospective study on survival among patients with leukaemia at the Department of Haematology of the St. Radboud Hospital (head: Prof. Dr. C.A.M. Haanen). After receiving his medical degree in 1986, he was involved in a study on working methods of general practitioners at the Department of General Practice, University of Nijmegen (head: Prof. Dr. C. van Weel). In 1987 he started his training in Epidemiology at the Department of Epidemiology & Biostatistics, Erasmus University Medical School in Rotterdam (head: Prof. Dr. H.A. Valkenburg, in 1988 succeeded by Prof. Dr. A. Hofman). At that time the work described in this thesis was initiated. In 1991 he was appointed assistant professor of Clinical Epidemiology at the Department of Epidemiology & Biostatistics and assistant professor of General Practice at the Department of General Practice (head: Prof. Dr. E. van der Does) of Erasmus University. He is involved in educational programmes for medical students and has been a teacher in several postgraduate courses, including courses on clinical epidemiology, research in general practice and case-control studies. He is married to Carin Bonekamp, general practitioner in Delft.