DIURETIC THERAPY: CURRENT ROLE AND EFFECTS OF WITHDRAWAL

Behandeling met diuretica: huidige inzichten en effecten van het staken van onderhoudsbehandeling

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Edmond Paul Walma
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Promotor: Prof. Dr E. van der Does

Overige leden: Prof. Dr F.W.J. Gribnau
Prof. Dr D.E. Grobbee
Prof. Dr A.J. Man in 't Veld

Co-promotor: Dr A.W. Hoes

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Manuscripts based on the studies described in this thesis

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1 Introduction

Diuretics

Diuretics are agents that stimulate the production of urine. In this definition also water is an example of a diuretic. It provokes intense diuresis if taken in sufficiently large dosages. Popular drinks such as coffee and beer have well balanced diuretic properties, caused by caffeine and ethanol.[1,2] Many other substances in our food and drinks have mild diuretic effects. For therapeutic goals however, pharmacological agents were synthesized with a much stronger diuretic action, and this thesis deals with the role of these diuretic drugs in medical practice today.

In 1920, Saxl and Heilig[3] reported the diuretic effect of the antisyphilitic drug mercaptomerin sodium. This was the first breakthrough in diuretic therapy and until the 1950's these organomercurial diuretics were used in the treatment of water and salt retention syndromes. Their toxic side effects, parenteral administration and limited efficacy precluded widespread use.

In 1957, chlorothiazide was reported to increase the excretion of Na^+, Cl^- and H_2O.[4] This was the second breakthrough in diuretic therapy, and chlorothiazide together with many of its derivates, soon categorized as thiazides, became widely used drugs. Thiazides are effective and relatively safe drugs in the treatment of many clinical disorders characterized by water and salt retention. The treatment of congestive heart failure improved tremendously by the introduction of this group of diuretics. Thiazides also have blood pressure lowering effects and until today are drugs of first choice in the treatment of hypertension.

The development of furosemide and its congener diuretics in 1963 was the third breakthrough in the field of diuretic therapy.[5,6] Their diuretic effect is considerably stronger than that of thiazides. Because of the site of action they are known as loop diuretics or, referring to their diuretic potency, high-ceiling or high-efficacy diuretics. Thiazides can elicit 5% of the ultrafiltrated Na^+ in the urine, while loop diuretics can elicit up to 20%. Furosemide and other loop diuretics are indispensable drugs in the management of heart failure.

In the same period furosemide was introduced, potassium sparing diuretics were synthesized; first the competitive antagonist of aldosterone, spironolactone, and later triamterene and amiloride, both directly acting upon the tubular epithelium. All thiazide- and furosemide-like diuretics cause loss of K^+, and thus potassium sparing diuretics constitute a welcome addition to the diuretic armamentarium, although their intrinsic diuretic effect is weak.[7,8]

New (classes of) diuretics will certainly become available. Examples of diuretics that are in the experimental phase are atrial natriuretic peptides, antivasopressins (=anti-ADH), and so called 'acquaretics', that regulate the water transport through cellular water channels.[9,10]

Indications for diuretic treatment

Hypertension and heart failure are the two main indications for diuretic therapy, each responsible for 30-40% of all diuretic prescriptions.* The remainder is prescribed for a variety of conditions accompanied by water and salt retention, such as hypostatic ankle oedema, liver cirrhosis and nephrotic syndrome.

Heart failure is characterized by insufficient blood circulation. One of the compensatory mechanisms is retention of salt and water by the kidney. Consequently, blood volume and preload (i.e. volume supply) of the heart are increased, which to a certain extent improves blood circulation. In many patients, however, fluid retention becomes too abundant and contraproductive, and worsens the symptoms of heart failure and may eventually lead to pulmonary oedema with severe dyspnoea. Diuretic therapy is very effective in these cases.[11] Several classes of drugs are available to treat heart failure, but diuretic therapy has been and still is a cornerstone in heart failure therapy since more than three decades.[12,13]

Diuretics lower blood pressure; thiazides more effectively than loop diuretics. The mechanism is not completely elucidated, but decrease of intravascular volume and presumably vasodilatation play a role. Large placebo-controlled trials have demonstrated the efficacy of diuretic treatment in hypertension.[14,15] It is beyond doubt that diuretic therapy decreases the incidence of strokes. In addition, the incidence of ischemic cardiac disease is reduced or at least postponed. Side effects are generally acceptable, albeit an increased risk of sudden cardiac death caused by

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* This thesis, chapter 7

diuretic-induced electrolyte depletion has been suggested to negatively influence the beneficial effects of diuretics on survival.[16,17]

Adverse effects of diuretics

Several overviews of the potential adverse effects of diuretics are available. For extensive literature references we refer to McInness' chapter in the authoritative textbook: Meyler's side effects of drugs.[18] An illustrative but incomplete summary is given in Table 1.1 Reported side effects range from alopecia to sudden death.

Not all side effects are harmful. A thiazide-induced reduction in renal clearance of calcium may prevent renal stone formation in hypercalciuria and the related increase in plasma calcium levels may prevent or postpone osteoporosis. Two studies demonstrated a clinically relevant decrease in the risk of hip fractures of approximately 30% in recipients of thiazides.[19,20]

Besides adverse effects, a large number of possible interactions with other drugs has been reported. The majority of patients prescribed diuretic therapy is relatively old and the clinical relevance of pharmacological interactions of diuretics is augmented by the high prevalence of polypharmacy in the elderly.

Overuse of diuretics in the elderly?

Approximately 20% of all men and women of 65 years or older, and 50% of those over 80 years of age, use diuretic medication every day, for many years in a row.[21] This illustrates that these drugs rank high in the list of most frequently prescribed drugs.[22]

It is unclear whether the long-term use of these medications on such a large scale is justified. Although heart failure and hypertension are common in the elderly, the high prevalence of these disorders cannot fully explain these high prescription rates. Several publications have questioned the rationale for this widespread use.[23] Polypharmacy in the elderly is a recognized medical problem and all prescribing physicians and patients would agree that unnecessary medication should be avoided or withdrawn. An important factor that might cause overuse of diuretics is the unwillingness of doctors and patients to stop medications that are perceived as being useful. Once started, diuretic therapy will not easily be discontinued.

Table 1.1
Adverse effects of diuretics (adapted from McInnes 1992)

Hypovolemia
Orthostatic hypotension –> falls and fractures
Mesenteric infarction
Stroke
Confusion, drowsiness
Hyponatremia
Fatigue
Encephalopathy, convulsions
Hypo/Hyperkalemia
Cardiac arrhythmia, sudden death
Hypomagnesemia
Hypo/hypercalciuria
Renal stones
Hypo/hypercalcemia
Increase of blood glucose concentration
Reduced insulin sensitivity
Hyperuricemia
Gout
Increase in serum cholesterol
Sexual impotence, decrease in libido
Dizziness, tinnitus, deafness
Visual disturbances
Thrombocytopenia, neutropenia, eosinophilia
Haemolytic anaemia
Skin rashes, urticariae, photosensitivity, chloasma
Lupus erythematodes
Alopecia
Drug fever
Allergic vasculitis
Allergic interstitial pneumonitis
Anaphylactic shock
Cholestatic jaundice
Precipitation of hepatic coma in patients with hepatic failure
Stevens-Johnson syndrome
Biliary colic
Pancreatitis
Nausea, vomiting, diarrhoea
Inappropriate antidiuretic hormone secretion syndrome
Acute urinary retention
Urine incontinence
Nephrotoxicity, interstitial nephritis
Gynaecomastia
Folic acid deficiency

The main study included in this thesis aims to assess what proportion of elderly patients on long-term diuretic therapy can be successfully withdrawn. Two earlier randomized controlled studies among hospitalized patients suggested that a major part of the elderly could be withdrawn from diuretic therapy.[24,25] Several uncontrolled studies on cessation of diuretics produced variable results,[26,27,28,29] while one uncontrolled study in the general practice setting showed a considerable risk of cardiac complications.[30] Finally, a randomized trial in general practice of withdrawing diuretics in a highly selected group of patients with non-cardiac ankle oedema (which is a dubious indication for diuretic therapy), demonstrated that 78% could stop diuretic therapy.[31]

Structure of this thesis

The central part of this thesis is formed by the description of the results of two studies on withdrawal of diuretics. The immediate cause to execute these studies was the impression that prescriptions for diuretics in elderly patients seemed to be repeated endlessly. To assess whether such long-term use of diuretics was justified, the following research questions were addressed:

1. What proportion of elderly patients on long-term diuretic therapy may be successfully withdrawn from this therapy?
2. What are the effects of withdrawal of diuretic therapy on blood pressure, heart failure symptoms, and blood parameters?
3. What are predictors for successful withdrawal?

The current role of diuretics in the therapy of heart failure and hypertension was assessed by reviewing the available national clinical guidelines on heart failure and hypertension (*Chapters 2 and 3*).

Methodological particularities of drug withdrawal studies are discussed in *Chapter 4*. A study was performed to assess the accuracy of the automatic blood pressure measuring device that was used in the diuretic withdrawal trial (*Chapter 5*).

In an uncontrolled pilot study among 15 patients receiving diuretic therapy in one general practice the logistics and the measurement instruments of the study were tested (*Chapter 6*). Subsequently a randomized, placebo-controlled, double-blind, trial assessing the effects of withdrawal from diuretics was performed in 202 patients from 8 general practices in the vicinity of Schoonhoven (*Chapter 7*).

The general discussion (*Chapter 8*) elaborates on the potential consequences for medical practice of the studies included in the thesis, and recommendations for withdrawing diuretics in general practice are given.

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2 The current role of diuretic therapy in heart failure. A critical appraisal of six national clinical guidelines

Introduction

Heart failure is a chronic disease caused by a diminished cardiac pump function. Breathlessness and fatigue, occurring at subnormal levels of exercise or even at rest are the most prominent symptoms. Insufficient blood circulation, together with dysfunctioning of compensatory mechanisms, leading to volume overload and increased sympathetic activity, generate a scala of symptoms and physical signs that form the variable clinical picture of chronic heart failure.

The number of patients with heart failure is increasing, mainly because of ageing of the population and increased survival after myocardial infarction.[1,2] The prevalence of the disease increases with age: 80% of all heart failure patients are older than 75 years and ten percent of those above 80 years of age have heart failure. In the Netherlands most of these elderly patients are diagnosed and treated by general practitioners.[3]

Since the introduction of chlorothiazide in 1957 and of furosemide in 1963, diuretics have been cornerstones in the treatment of heart failure. Early experimental studies demonstrated their efficacy.[4,5,6,7] Other drugs widely used in the treatment of heart failure are digoxin, angiotensin-converting-enzyme (ACE) -inhibitors and nitrates.

ACE-inhibitors were introduced in the Netherlands around 1983. While diuretics diminish excessive water and salt retention, ACE-inhibitors induce vasodilation and block neurohumoral (over)stimulation.[8] Their efficacy if added to existing therapy, in patients with moderate or severe heart failure, was demonstrated in several randomized trials.[9,10,11,12] The increasing evidence of the efficacy of ACE-inhibitors in the treatment of heart failure resulted in a progressively important role of these drugs. Effectiveness of ACE-inhibitors in symptomatic heart failure, however, was only demonstrated, if *added to* diuretic treatment. Before trials comparing monotherapy of diuretics with monotherapy of ACE-inhibitors become available, conclusions that ACE-inhibitors are superior to diuretics remain premature.

The classification of systolic versus diastolic left ventricular dysfunction

has recently been recognized to be important for understanding the underlying mechanisms, and for guiding therapy of heart failure. Systolic ventricular dysfunction is characterized by decreased contraction capacity of the left ventricle, and diastolic ventricular dysfunction is characterized by inadequate end-diastolic filling of the left ventricle, generally caused by decreased relaxation capability of the left ventricular muscular wall. These subtypes are functional categories (diagnosed with functional tests such as echocardiography) and should not be confused with the clinical categories of forward and backward (congestive) heart failure. Systolic and diastolic dysfunction both may produce clinical symptoms of forward and backward failure. It has been suggested that the distinction between systolic and diastolic dysfunction in heart failure patients has important therapeutic consequences. Because most patients suffer of combined systolic and diastolic dysfunction with a predominating systolic component, the label 'chronic heart failure' in this chapter refers to this group. A minority of patients predominantly suffer from diastolic dysfunction; this group is addressed in separate paragraphs on 'heart failure caused by diastolic dysfunction'.

It is not easy to keep up with all new scientific evidence pertaining to the treatment of heart failure. Many original studies, meta-analyses, reviews and editorial comments on the issue are being published yearly. The diversity of the results and, notably, of the conclusions and recommendations in these publications may pose problems for practising physicians. Under these circumstances national clinical guidelines may offer a possible solution. The general aim of such guidelines is improvement of quality of medical care by providing physicians with solid and unambiguous recommendations about, notably, diagnostic and therapeutic management of specific problems. National clinical guidelines may be considered as evidence-based, pragmatical reports with potentially a large impact on medical practice in the country of origin.

In view of the recent developments in the therapy of heart failure and by studying six available national clinical guidelines on management of heart failure we assessed the current role of diuretics in the treatment of heart failure. The three following questions were addressed in detail: (1) Are diuretics, ACE-inhibitors, or the combination of the two drugs currently recommended as treatment of first choice in chronic heart failure? (2) What types of diuretics and what dose titration schedules are recommended for the treatment of mild to moderate heart failure, and for severe heart failure with persistent edema? and (3) Do the recommendations regarding diuretic treatment differ in patients with diastolic and systolic ventricular dysfunction?

Table 2.1
Characteristics of the reviewed national guidelines on the treatment of heart failure

Guideline	Year of publication	Initiative	Medical specialty of authors (# of persons in the working party)	Target group
Sweden	1993	Medical Products Agency of the Swedish administration	Cardiology (18), General practice (2), Internal medicine (2), Clinical pharmacology (1)	All physicians
Canada	1994	Canadian Cardiovascular Society	Cardiology (27), Cardiac-surgery (3)	All physicians
Netherlands-CBO	1994	National Organization of Medical Quality Insurance (CBO)	Cardiology (6), General practice (3), Pharmacy (3), Geriatrics (2), Patients (1), Epidemiology (1), Internal medicine (1), Radiology (1)	All physicians
US-AHCPR	1994	US Department of Health and Human Services. Agency for Health Care Policy and Research	Cardiology (5), Cardiac surgery (2), Geriatrics/Internal medicine (2), Nursing (2), Patients (2), General practice (1), Pharmacy (1), Pulmonology (1)	All physicians
Netherlands-GP	1995	Dutch College of General Practitioners (NHG)	General practice (7)	General practitioners
US-ACC/AHA	1995	American College of Cardiology and the American Heart Association	Cardiology (23)	All physicians

Methods

The six available national clinical guidelines were traced by searching the Medline database 1991 to 1996 on CD-ROM, exploring references from relevant publications and by asking experts in the field. Only guidelines published in English, German, French or Dutch were sought. Although a European guideline on diagnostic procedures in heart failure patients was published, a similar guideline on therapy was not available at the time of preparation of this review.

The guidelines were scrutinized with respect to our specific questions about the current role of diuretic treatment in chronic heart failure.

Results

Characteristics of the guidelines (Table 2.1)
At the time of preparation of this manuscript six recent national guidelines on heart failure were available: two from the USA,[13,14] two from the Netherlands,[15,16] one from Canada,[17] and one from Sweden.[18] The first US guideline is one of a series of national clinical guidelines of the Agency for Health Care Policy and Research (AHCPR) of the US Department of Health and Human Services; the second is a joint publication of the American College of Cardiology and the American Heart Association (ACC/AHA). The first Dutch guideline was developed by the National Organization of Medical Quality Insurance (CBO), a fully government sponsored organization. The second Dutch guideline was produced by the Dutch College of General Practitioners (GP). The Canadian guideline is the product of the Canadian Cardiovascular Society. The Swedish Medical Products Agency, which produced the Swedish guideline, is an organization of quality insurance, comparable to the Dutch Medical Quality Insurance Organization.

The year of publication varied from 1993 to 1995. Governmental or medical professional organizations took the initiative and formed working parties of experts with the task to write a concept of the guideline. The exact way of formation of these working parties varied, as did the procedures for adjustment of the concepts, final approval and publication. A detailed description of the procedures of the development of the guidelines is summarized in the introductory sections of the guidelines,[13] in separate publications,[19] or may be obtained from the organizers[13,17,18] Most working parties were recruited from a variety of medical specialists, but two working groups were restricted to cardiologists or cardiac surgeons[13,17] and one included only general practitioners[16] (Table 2.1). All but the

Table 2.2
Combination therapy versus monotherapy with diuretics and ACE-inhibitors in the treatment of chronic heart failure

Guideline	Diuretics combined with ACE-inhibitors	Diuretics without ACE-inhibitor	ACE-inhibitor without diuretics
Sweden	Standard	Yes, mild HF with fluid retention, and EF >40%	No, generally not
Canada	Standard	Contradictory: 'Yes, but rarely' and 'ACE-inhibitors in all symptomatic patients'	Yes, patients without volume overload
Netherlands-CBO	Standard	Yes, only very old patients, for whom slight improvement of mortality counts less than morbidity	Yes, patients without volume overload
US-AHCPR	Standard	No	Yes, patients without volume overload
Netherlands-GP	Only if symptoms on ≥ 1 DDD diuretics	Yes, if asymptomatic on ≤ 1 DDD diuretics	No
US-ACC/AHA	Standard	Only in patients with predominantly diastolic HF	Yes, patients without volume overload

AHCPR = Agency for Health Care Policy and Research from the US Department of Health and Human Services, CBO = National Organization of Medical Quality Assurance, GP= General practitioners, NHG = Dutch Scientific Society of General Practitioners, ACC = American College of Cardiology, AHA = American Heart Association, EF = ejection fraction, DDD = defined daily dose, HF = heart failure

Dutch GP guideline pertain to patients in both the hospital and the primary care setting. This latter guideline was written exclusively by general practitioners, but cardiologists and internists reviewed the manuscript and were consulted during a discussion meeting. It provides recommendations for patients in general practice only.

Diuretics monotherapy versus combination therapy with diuretics and ACE-inhibitors in the treatment of chronic heart failure (Table 2.2)

All but one guideline recommend the combination of diuretics and ACE-inhibitors as standard treatment for chronic heart failure. The Dutch GP guideline recommends diuretic monotherapy for patients with mild heart failure. Addition of ACE-inhibitors is recommended only when diuretic dosages larger than 1 DDD (defined daily dose) are needed to keep patients symptom-free. In certain subgroups of patients, the Swedish, the Canadian, the Dutch CBO and the US-ACC/AHA guidelines also leave room for monotherapy with diuretics. For example, the Swedish guideline advises monotherapy with diuretics in patients with fluid retention and normal ejection fractions (>40%), and the Dutch CBO advises symptomatic treatment (e.g. diuretic monotherapy) in very old patients.

ACE-inhibitors as monotherapy in patients without symptoms of volume overload are advised by the Canadian, the US-AHCPR, the Dutch CBO, and the US-ACC/AHA guidelines. According to these guidelines, one should start with ACE-inhibitor therapy, in incident cases of heart failure without volume overload, and add diuretics only when volume overload develops. Most new heart failure patients, however, present themselves with symptoms of volume overload[20] and in these cases the generally recommended treatment sequence is to start with diuretics and add ACE-inhibitors later, with special attention to avoid underhydration, since this may cause severe hypotension when the first dose of ACE-inhibitors is administered. Up-titration of ACE-inhibitors to the average dosage used in the clinical trials is recommended in all clinical guidelines. During this up-titration of ACE-inhibitors, diuretics should be titrated down to the lowest possible dose. Most guidelines warn against the prescription of too high dosages of diuretics, because this may impair adequate up-titration of ACE-inhibitors to target dose levels.

Types and dosages of diuretic treatment in mild to moderate heart failure (Table 2.3)

All guidelines recommend thiazide diuretics in patients with mild volume overload and loop diuretics in more severe cases. In four of the guidelines thiazides are also preferred as maintenance therapy in clinically stable heart failure patients, while in the Canadian and the US-

Table 2.3
Choice of diuretic treatment in mild to moderate heart failure

Guideline	Start in mild HF of recent onset	Start in moderate to severe HF of recent onset*	Maintenance treatment in stabilized patients$	Recommendations about active titration of diuretic dose
Sweden	Thiazides@	Furosemide 20-40 mg or bumetanide 0.5-1.0 mg	Thiazides@	Aim at low dose, but preferably no complete withdrawal
Canada	Thiazides@	Loop diuretics	Thiazides@	Aim at lowest dose, or withdraw
Netherlands-CBO	Thiazides@, e.g. HCT 25-50 mg	Loop diuretics	Thiazides@	Aim at lowest dose, or withdraw
US-AHCPR	Thiazides@, e.g. HCT 25-50 mg	Loop diuretics, e.g. furosemide 10-40 mg	Thiazides@	Aim at lowest dose, or withdraw
Netherlands-GP	Thiazides@, e.g. HCT 25-50 mg	Loop diuretics, e.g. furosemide 40-120 mg	Thiazides@	Aim at low dose, but leave stable patients at 1 DDD diuretics
US-ACC/AHA	Thiazides@	Loop diuretics	Thiazides@	Aim at lowest dose, or withdraw

* Excluding the emergency management of acute heart failure, $ If insufficiently effective, thiazides should be replaced by loop diuretics, @ Not to be prescribed in case of renal insufficiency, AHCPR = Agency for Health Care Policy and Research from the U. S. Department of Health and Human Services, CBO = National Organization of Medical Quality Assurance, GP = General practitioners, NHG = Dutch Scientific Society of General Practitioners, ACC = American College of Cardiology, AHA = American Heart Association, EF = ejection fraction, DDD = defined daily dose, HF = heart failure

ACC/AHA guideline no preference for either thiazides or loop diuretics is mentioned. The guidelines mention that thiazides should be replaced by loop diuretics when the diuretic effect of thiazides becomes insufficient. Furosemide is by large the most frequently prescribed loop diuretic. The dose should be titrated individually and largely depends on the degree of heart failure and the renal response. The recommended number of gifts of furosemide per day is one or two. Only the Swedish guideline recommends four gifts per day. All guidelines recommend active titration of the dose of diuretics: up-titration when signs of volume overload persist and down titration whenever possible. The target dose is the lowest possible dose that prevents volume overload. The Canadian, American, and Dutch CBO guidelines suggest an attempt to withdraw diuretic therapy completely after establishment of therapy with ACE-inhibitors. The Dutch GP and the Swedish guideline recommend a low maintenance dose of diuretics, but complete withdrawal is not advised, not even in the absence of symptoms of volume overload. Daily assessments of body weight by patients themselves, and instructions about the dosing of diuretics or the timing of medical consultation are mentioned as essential parts of down titration strategies by the ACC/AHA and the two Dutch guidelines.

Types and dosages of diuretic treatment in severe heart failure with persistent oedema (Table 2.4)

All guidelines recommend progressively increasing dosages of loop diuretics for patients with more severe forms of heart failure with persisting oedema. Optimalization of the dose of ACE-inhibitors and the restriction of salt intake, and in more severe cases also of water intake, is generally recommended to further improve the effect of diuretic treatment. If oedema persists during treatment with high dosages of furosemide (dosages varying from 120 mg/day in the Swedish to 1000 mg/day in the Dutch CBO guideline are mentioned) addition of a diuretic of the thiazide class is generally recommended. The thiazide metozalone is considered by the Swedish and the two American guidelines as particularly potent for this purpose. Addition of spironolactone is recommended by the Swedish guideline, with replacement by a thiazide when it is not effective enough. Addition of a combination of ACE-inhibitors and spironolactone in furosemide treated heart failure patients with persistent oedema is recommended by the AHCPR and the Dutch CBO guidelines. The Canadian guideline expresses no preference for the addition of either thiazides or spironolactone in these patients. The combination of all three classes of diuretics, as an even more potent diuretic regimen, is mentioned, although not explicitly advised, in the Canadian and the Dutch GP guideline. Furthermore, the guidelines mention the usefulness of incidental intravenous administration of loop diuretics if the effect of oral

Table 2.4
Choice of diuretic treatment in severe heart failure with persistent oedema

Guideline	Consecutive steps*
Sweden	1 Dose increase of furosemide to 120 mg/day 2 Addition of spironolactone 25-50 mg/day 3 Megadoses furosemide (250-4000 mg/day) or addition of thiazides (e.g. metolazone intermittently 1-2 days/week)
Canada	1 Increased dosages of loop diuretics 2 Combination of diuretics from different classes
Netherlands-CBO	1 Dose increase of furosemide to 1000 mg/day 2 Addition of thiazides (e.g. HCT intermittently 2-3 days/week) 3 Combinations of loop diuretics and spironolactone
US-AHCPR	1 Dose increase of furosemide to 160-240 mg twice a day 2 Addition of thiazides (e.g. HCT intermittently 2-3 days/week)
Netherlands-GP	1 Dose increase of furosemide to 500 mg/day 2 Addition of thiazides 3 Addition of spironolactone
US-ACC/AHA	1 Increased dosages of loop diuretics 2 Addition of thiazides (e.g. metolazone intermittently 2-3 days/week)

* Non-pharmacological therapy such as sodium and water restriction, rest, and the avoidance of non-steroidal anti-inflammatory agents are not in this schedule, but are generally considered valuable. AHCPR = Agency for Health Care Policy and Research from the U. S. Department of Health and Human Services, CBO = National Organization of Medical Quality Assurance, NHG = Dutch Scientific Society of General Practitioners, ACC = American College of Cardiology, AHA = American Heart Association, HCT = hydrochlorothiazide

administration becomes insufficient as, through a reduction of intestinal oedema, this may subsequently cause orally administered diuretics to regain effectivity. Bumetanide is a loop diuretic with an equally maximum effect as furosemide, but its superior gastrointestinal absorption may be a relevant advantage in patients with gastrointestinal oedema. The Dutch GP guideline advises to replace furosemide by bumetanide if gifts with a larger dose than 200 mg furosemide are needed. All guidelines warn against the possible severe plasma electrolyte disturbances caused by the administration of combinations of different classes of diuretics and recommend frequent laboratory checks.

Diuretics in the treatment of heart failure caused by diastolic dysfunction (Table 2.5)

In diastolic ventricular dysfunction the filling of the heart during the diastolic phase is insufficient. This is generally caused by a decreased relaxation capability of the muscular wall of the left ventricle. Combined systolic and diastolic ventricular dysfunction is common and in elderly patients the diastolic component progressively contributes to the clinical symptoms of heart failure. It is impossible to discriminate between diastolic and systolic dysfunction on the basis of clinical symptomatology.[21,22] It is suggested that heart failure caused by diastolic dysfunction should be treated with drugs that improve relaxation of the ventricle, such as ß-blockers and calcium antagonists, while other agents such as diuretics, ACE-inhibitors and digoxin should be prescribed in case of heart failure caused by systolic dysfunction.

All guidelines except the US-AHCPR's discuss the treatment of diastolic dysfunction. Interestingly, however, the recommendations differ widely. With respect to the role of diuretics they range from 'to be avoided'[15,18] to 'first choice agent'.[13]

Other aspects

Renal insufficiency and diuretics. In case of renal insufficiency, all guidelines recommend loop diuretics instead of thiazides. A glomerular filtration rate or creatinine clearance of <30-40 ml/min is considered to be an indication for loop diuretics by most guidelines. The Dutch GP guideline recommends furosemide, whenever serum creatinine levels are above the normal range. *Adverse effects of diuretics.* Hypovolemia is considered an important potential side effect of diuretic therapy in all guidelines. Besides (postural) hypotension and renal insufficiency few specific symptoms and signs of the hypovolemic state are reported. Hyponatremia can be a serious adverse effect and is discussed in all guidelines. The Dutch GP and the Swedish guideline present a schedule for the management of hyponatremia if it occurs during diuretic treatment. Serum potassium levels below 3.5 – 4.0 mmol/l are considered to be an indication for potassium sparing diuretics. Potassium supplements are recommended in the US-AHCPR and the Canadian guidelines. ACE-inhibitors are potassium sparing, and the combination with potassium sparing diuretics may therefore lead to hyperkalemia and should be avoided. Triamterene, amiloride and spironolactone are the three available potassium sparing diuretics. No preference for one of these three agents is given in the guidelines. The dose of potassium sparing diuretics should be titrated individually. In the AHCPR guideline, maximum dosages of 100 mg twice daily for triamterene and spironolactone, and 40 mg once daily for amiloride are mentioned.[13] In contrast to the importance of hypokalemia,

Table 2.5
Diuretics in treatment of diastolic dysfunction

Guideline	Diuretics in diastolic dysfunction
Sweden	To be avoided
Canada	Can be used
Netherlands-CBO	To be avoided
US-AHCPR	Beyond scope of guideline
Netherlands-GP	Equivalent to systolic heart failure
US-ACC/AHA	First choice

AHCPR = Agency for Health Care Policy and Research from the U. S. Department of Health and Human Services, CBO = National Organization of Medical Quality Assurance, NHG = Dutch Scientific Society of General Practitioners, ACC = American College of Cardiology, AHA = American Heart Association, HF = heart failure

the relevance of hypomagnesemia as a potential adverse effect is not clear. Only the US-AHCPR advises monitoring of magnesium levels in recipients of high dosages of diuretics and oral magnesium supplementation if depletion occurs. Unfavourable influences of diuretics on blood lipids and glucose are reported in the guidelines, but the clinical relevance in heart failure patients is considered to be limited and no specific measures are recommended. *Diuretic treatment as a diagnostic test.* The two Dutch guidelines mention the use of test-treatment with furosemide if the diagnosis of heart failure is not certain. Subsequent improvement of symptoms and signs by the treatment is considered a support for the diagnosis.

Discussion

The guidelines

Carefully designed developmental procedures resulted in six clinical guidelines of high quality. The procedures varied between the guidelines, but the adequate use of scientific evidence in combination with extensive consensus meetings was the core procedure in all guidelines. In our eyes, the American AHPCR guideline reached the highest structural quality. It is extensive, very precise, developed by a multidisciplinary working party and covers almost all clinical situations. The Swedish and the Dutch CBO guidelines were also developed by multidisciplinary working parties, but their publications are less cohesive and apparent lack of consensus on some of the issues resulted in contradictory recommendations. The

Dutch GP guideline was written by general practitioners and focused exclusively on patients in the primary care setting. The ACC/AHA and the Canadian guidelines suffer from the fact that they are not multidisciplinary, but written by cardiologists exclusively.

A remark should be made about the role of specialists in the development of guidelines to be applied in general practice. Too large influence of these specialists may lead to discrepancies between their point of view, primarily based on clinical experience with patients referred to hospital and the published trials (usually restricted to these patients) and the general practitioner's point of view, based on non-hospitalized patients, representing a different spectrum of the disease. Since in many countries, such as the Netherlands, most heart failure patients are being treated by general practitioners, clinical guidelines should ideally be developed by a multidisciplinary team (including general practitioners), resulting in one national guideline for all physicians. The Dutch solution seems an appropriate alternative: guidelines for primary care are written by general practitioners and incorporate advice from specialist-experts in the field. This may have a positive influence on the acceptance and the implementation of the guideline in general practice, although the resulting existence of two different national clinical guidelines on management of the same disease (in at least in part similar patients) is certainly a major disadvantage.

Monotherapy with diuretics?

A major discrepancy between the guidelines of the Dutch general practitioners and the other guidelines is the recommendation of monotherapy with diuretics in heart failure patients who remain without symptoms on standard dosages of diuretics. All other guidelines recommend combined treatment with diuretics and ACE-inhibitors as standard treatment of heart failure. The lack of trials assessing the benefit of ACE-inhibitors in patients with mild heart failure (New York Heart Association class II) or in patients with ejection fractions >40%, and the limited beneficial effects reported in subgroups of these patients in the large trials form the scientific background for the conservative recommendations of the Dutch GP guideline.[9,10,11,12,23] Furthermore, the Dutch GP guideline mentions limitations of the generalizibility of the results of the published trials to the general practice setting, where the prevalence of relatively older patients, women, comorbidity, and relatively mild forms of heart failure is higher. A final argument for monotherapy with diuretics, as used in the Dutch GP guideline is the increasing level of diagnostic certainty during (initial) treatment with diuretics, which might help to prevent needless treatment with ACE-inhibitors of a potentially large group of patients with an uncertain diagnosis.

Types and dosages of diuretics in patients with mild to moderate heart failure

The recommendation in all guidelines to use slow and weaker acting thiazides for patients with mild heart failure instead of fast and stronger acting loop diuretics seems not in agreement with common medical practice. In the Netherlands for example, heart failure is generally treated with loop diuretics.[16] Recommendations in important pharmaceutic handbooks may contribute to this.[24] Active titration of the dose of diuretics, as recommended in all guidelines, seems important because both under- and overhydration are unwanted conditions with negative effects on cardiac function. Thus, continuous monitoring for early signs of overhydration combined with periodical down titration of diuretics in stable patients is the best strategy for optimal dosing of diuretics.

The Swedish recommendation of dosing furosemide four times a day is not endorsed by references. However, it has a sound theoretical base since the duration of the diuretic effect is approximately 6 hours. It might well be true that the peak diuresis after a dose of furosemide disappears when lower dosages are administered four times a day. Another stipulated way to avoid peak diuresis of loop diuretics is to use slow release formulations. It should be mentioned, however, that peak diuresis is not disliked by all patients. A predictable number of hours per day of strongly increased diuresis, may be well acceptable for many patients, providing them more convenience during the remaining part of the day (or night).

Types and dosages of diuretics in severe heart failure with persistent oedema

The guidelines are not unanimous about the treatment of persistent fluid retention in patients with severe heart failure. The dose level to which furosemide should be up-titrated before adding a diuretic of another class varies from 120 mg/day in the Swedish guideline to 1000 mg/day in the Dutch CBO guideline. Most guidelines recommend addition of a thiazide if furosemide alone is insufficiently effective, but the Swedish guidelines advises addition of spironolactone. Several studies have demonstrated the improvement of heart failure symptoms by additional spironolactone in patients receiving furosemide and ACE-inhibitors.[25,26,27,28] This remains to be established for the addition of thiazides. Extra monitoring is needed when combinations of diuretics are administered because of a considerable risk of hyperkalemia during loop diuretic/spironolactone therapy, and hypokalemia and hyponatremia in loop diuretic/thiazide combinations. These risks may be smaller when the additional diuretics are administered intermittently, e.g. every other day.

Diastolic dysfunction

The remarkable differences in the guidelines concerning the role of diuretic treatment in heart failure patients with predominantly diastolic dysfunction reflect the immatureness of this diagnostic entity. These patients need a relatively high preload to ensure optimal filling of the ventricle during the diastole.[21,22] Too high dosages of diuretics (and ACE-inhibitors) may lower the preload to suboptimal levels. This explains the recommendations to avoid diuretic treatment in diastolic dysfunction found in the literature and in some of the guidelines.[15,18] Clearly, one should be reluctant to prescribe diuretics in patients with diastolic dysfunction when no volume overload exists, but if volume overload (e.g. pulmonary congestion) develops, diuretics are indispensable. Careful judgement of signs of overhydration and underhydration should guide titration to optimal dosages. This is not essentially different in diastolic and systolic ventricular dysfunction. The differences between the guidelines might be explained by this duality.

Test-treatment with furosemide

Test-treatment with furosemide, as recommended in the two Dutch guidelines, is an interesting but controversial diagnostic tool. A scoring list that was used in the Framingham study also included response to diuretic treatment as one of the items.[29] The sensitivity and specificity of this test-treatment are, however, unknown. One might argue that a good response to diuretic treatment (weight loss, less breathlessness, less fatigue, more effort tolerance) pleads in favour of the diagnosis heart failure, while a negative response indicates that heart failure is absent or that heart failure with a significant forward failure component may be present. Although the use of such a test-treatment is pragmatic and based on common sense, further studies are needed to assess its diagnostic value before its use can be recommended.

Optimal guidelines?

In recent years a clear increase in the number of national clinical guidelines has occurred. They are potentially important tools with respect to quality improvement in medical care. International guidelines such as the guideline for the diagnosis of heart failure of the European Society of Cardiology[30] have several disadvantages. Differences for example in culture, tradition and economical standards between the home countries of the members of the working parties may be obstacles in reaching consensus and often results in insufficiently detailed guidelines. In addition, implementation may be less successful than for national guidelines. Another problem is the multiplicity of national guidelines per country; e.g. one by a governmental initiative, one by a professional organization of specialists and one by the national scientific organization of general prac-

titioners. This clearly is an undesirable situation. It is enough to worry about discrepancies between guidelines of different countries, but discrepancies between guidelines within one country will certainly undermine the authority and the success of the guidelines. Another vulnerable aspect is the updating of existing guidelines; the needed frequency of updates critically depends on new developments in the field. Obviously, national clinical guidelines are very important instruments to improve the quality of medical care, but more than one guideline per country and outdated guidelines should be prevented.

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3 The current role of diuretic therapy in the treatment of mild to moderate, essential hypertension. A critical appraisal of five national clinical guidelines

Introduction

Hypertension is an important risk factor for cardiovascular disease.[1,2,3] The relationship between both systolic and diastolic blood pressure level and risk of cardiovascular disease exists at all blood pressure levels.[4,5] Pharmacological treatment of hypertension became common medical practice from the beginning of the seventies after the publication of the results of the first randomized trials. A substantial number of trials followed, and the reduction of cardiovascular morbidity and mortality following blood pressure lowering medication became increasingly evident.[6,7,8,9,10,11,12,13,14,15,16,17,18,19,20,21,22,23,24,25,26,27] A reduction of 30–40% in the occurrence of strokes and of 10–20% in the incidence of coronary heart disease has consistently and convincingly been demonstrated. The main antihypertensive treatment included in these trials were diuretics or ß-blockers. Remarkably, no results from trials assessing the effect on cardiovascular morbidity and mortality of the newer classes of antihypertensive drugs, such as ACE-inhibitors and calcium antagonists, are available. Thus, it seems rather surprising that the newer classes of antihypertensive drugs are being prescribed on such a large scale. Recent surveys in the USA and the Netherlands show that of every 100 hypertension patients on blood pressure lowering medication, approximately 25 receive diuretics, 20 ß-blockers, 25 ACE-inhibitors, 20 calcium antagonists, and 10 other drugs. (Table 3.1)[28] Even angiotensine II antagonists, that were introduced only very recently, are presently being prescribed at fast increasing rates, without any empirical evidence of their capacity to eventually reduce the risk of cardiovascular disease.

Apparently, empirical scientific evidence does not have the impact on medical practice it deserves. This may be partly attributable to confusion about the drugs of first choice in hypertensive patients, generated by numerous, often contradictory, comments continuously appearing in (often non-peer reviewed, and drug industry sponsored) periodicals, widely distributed among practising physicians. Under these circumstances national clinical guidelines, developed by independent expert committees, may offer a solution by providing solid and unambiguous recommendations about diagnostic and therapeutic management to practising physicians. The general aim of such guidelines is improve

Table 3.1
Proportion of different classes of blood pressure lowering drugs prescribed in hypertensive patients in the USA in 1993 (Manolio 95) and in the Netherlands in 1995*

Class of antihypertensive drugs	Proportion (%)	
	USA	Netherlands
Diuretics	27	20
ß-blockers	14	28
ACE-inhibitors	24	28
Calcium antagonists	24	15
Other	10	9

* Medische Index Nederland (MIN), Instituut voor Medische Statistiek (IMS) te Den Haag, Nederland BV, personal communication 1996.

ment in quality of medical care, based on available scientific evidence.

We studied five currently available national clinical guidelines to review the current role of diuretics in the treatment of hypertension. Special emphasis was put on the following questions: (1) Are diuretics still recommended as drugs of first choice in the treatment of hypertension? (2) What types and dosages of diuretics are recommended? (3) When are potassium sparing diuretics indicated? (4) Is the role of diuretics in the treatment of hypertension different in older patients, and (5) What is the role of diuretics in hypertension with coexisting disease?

Methods

By searching the Medline database on CD-ROM, exploring references from relevant publications and by asking experts in the field five national clinical guidelines were traced. Only guidelines published in English, German, French or Dutch were sought. We selected only those guidelines published in 1990 or later. Although a European guideline[29] on hypertension was published, we did not include international guidelines in this study. The available guidelines were scrutinized with respect to our specified research questions about the role of diuretics in the treatment of hypertension.

Results

The guidelines (Table 3.2)
Five national guidelines on hypertension were studied: two from the Netherlands,[30,31] one from Canada,[32] one from Great Britain,[33] and one from the USA.[34] The first Dutch guideline was developed by the National Organization of Medical Quality Insurance (CBO), a fully-government sponsored organization. The second Dutch guideline was produced by the Dutch College of General Practitioners (GP). The Dutch guidelines were published in 1990 and 1991, and thus the results of three major trials that came available in 1991 and 1992 could not be taken into account.[24,25,27] The US guideline was the 1993 report of The Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure, from the National Heart, Lung, and Blood Institute. The Canadian guideline was the 1993 report by the Canadian Hypertension Society and the British guideline was produced by the British Hypertension Society in the same year. The Canadian, British, and American guidelines were revisions of formerly published versions.

In all guidelines, governmental or medical professional organizations took the initiative to form a working party of experts with the task to write a concept of the guideline. The way these working parties were formed varied between the guidelines, as did the procedures for adjustment, approval, publication and implementation of the text. All but one of the committees that prepared the guidelines were multidisciplinary. (Table 3.2) Only the Dutch-GP guideline was exclusively written by general practitioners, although cardiologists and internists reviewed the manuscript and were consulted during a discussion meeting. General practitioners were not represented in the committee that prepared the British guideline.

Diuretics as drugs of first choice in hypertensive patients (Table 3.3)
All guidelines recommend diuretics as drugs of first choice in the treatment of mild to moderate, essential hypertension. Four of the guidelines recommend either diuretics or ß-blockers as initial drug therapy. Three of the guidelines explicitly state that in contrast to ß-blockers, diuretics are also effective in black hypertensive patients. Only the oldest guideline (Netherland-CBO 1990) includes the possible choice of other classes of antihypertensive drugs as initial treatment.

If target blood pressure levels are not achieved by the initial therapy, three possibilities for additional treatment are generally mentioned: dose increment, combination with a drug from another class or monotherapy with a drug from another class. The American, the two Dutch and the

Table 3.2
Characteristics of the five reviewed national guidelines on treatment of mild to moderate hypertension

Guideline	Year of publication	Initiative	Medical background of authors (# of persons in the working party)	Target group
Netherlands-CBO (CBO 90)	1990	National Organization of Medical Quality Insurance (CBO)	Internal medicine (9), General practice (3), Cardiology (2), Epidemiology (2), Gynaecology (2), Geriatrics (1), Paediatrics (1), Pharmacy (1), Public health (1)	All physicians
Netherlands-GP (NHG 91)	1991	Dutch College of General Practitioners (NHG)	General practice (7)	General practitioners
Canada (Can 93)	1993	Canadian Hypertension Society	Internal medicine (5), Cardiology (1)	All physicians
Great Britain (Seever 93)	1993	British Hypertension Society	Internal medicine (5), Clinical pharmacology (1), Epidemiology (1)	All physicians
USA (JNC V 93)	1993	Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure. Subcommittee on Pharmacological Treatment	Internal medicine (10), General practice (1), Pharmacy (1)	All physicians

Table 3.3
Recommendations about the drug of first choice for patients with mild to moderate hypertension

Guideline	First choice treatment	Additional treatment to reach target blood pressure
Netherlands-CBO	Diuretic, ß-blocker, ACE-inhibitor or calcium antagonist	Increase drug dose, substitute with another drug, or combine drugs
Netherlands-GP	Diuretic or ß-blocker	Increase drug dose, substitute with another drug, or combine drugs
Canada	≥ 60 y: Diuretic < 60 y: Diuretic or ß-blocker	≥ 60 y, consecutive steps: 1) ß-blocker 2) Combination diuretic and ß-blocker < 60 y, consecutive steps: 1) Substitute with other first choice drug 2) Combination of first choice drugs or monotherapy with another class of drugs 3) Other combinations
Great Britain	Diuretic or ß-blocker	No recommendations in the guideline
USA	Diuretic or ß-blocker	Increase drug dose, substitute with another drug, or combine drugs

British guidelines consider these three possibilities to be equally effective, while the Canadian guideline recommends to first interchange diuretics and ß-blockers, then combine these two classes, and finally prescribe monotherapy with a drug from another class.

Type and dose of diuretics (Table 3.4)

The most widely recommended diuretics are hydrochlorothiazide and chlorthalidone. The American, Canadian and two Dutch guidelines all recommend hydrochlorothiazide or chlorthalidone. The British guideline does not mention any of the thiazides in particular. Other thiazides mentioned in at least one of the guidelines include chlorothiazide, bendroflumethiazide, indapamide and metolazone. Daily dosages of 12.5 to 50 mg hydrochlorothiazide or chlorthalidone are uniformly recommended, usually in one gift per day. In hypertensive patients with renal insufficiency loop diuretics instead of thiazides are recommended in the US

Table 3.4
Recommendations about type and dose of diuretic in the treatment of mild to moderate hypertension

Guideline	Type of diuretic	Daily dose (mg)	# of gifts per day
Netherlands-CBO	Hydrochlorothiazide, chlorthalidone, chlorothiazide or other thiazide	12.5-50 25-50 250-500	1 or 2 1 1 or 2
Netherlands-GP	Hydrochlorothiazide, chlorothiazide or bendroflumethiazide	12.5-25 not stated 2.5-5	1 not stated 1
Canada	Hydrochlorothiazide, chlorthalidone, indapamide or metolazone	12.5-50 12.5-25 2.5 2.5-5	1 1 or EOD not stated not stated
Great Britain	Thiazides, not specified	not stated	not stated
USA	Hydrochlorothiazide, chlorthalidone or other thiazide	12.5-50 12.5-50	1 1

EOD = Every other day

guideline and the Dutch-CBO guideline. The other guidelines do not mention loop diuretics, implying that ß-blockers or one of the newer antihypertensive agents are indicated when contraindications for thiazides exist.

Potassium sparing diuretics

None of the guidelines recommend potassium sparing diuretics or combinations of potassium sparing diuretics and non-potassium sparing diuretics as initial therapy in hypertension. Nevertheless, all guidelines advise to add potassium sparing diuretics in case of potassium depletion, and the American and Canadian guidelines mention potassium suppletion as an alternative. Remarkably, however, recommendations for laboratory checks and cut-off levels of acceptable plasma potassium are not given. The British and the Canadian guidelines consider potassium sparing combinations a possible first choice therapy in elderly hypertensive patients. Further, the Canadian guideline recommends potassium sparing combinations if dosages larger than 25 mg/day hydrochlorothiazide (or the equivalent of another thiazide) are required. In the Dutch-GP guideline

increased risk of arrhythmias (i.e. patients with coronary artery disease, cardiomegaly, heart failure, or digoxin treatment) is considered an indication for potassium sparing diuretic combinations. No recommendations about the type and dose of potassium sparing diuretics are given in the guidelines, with one exception: the Dutch-GP guideline prefers triamterene.

Antihypertensive therapy in the elderly

Some of the guidelines express strong preferences of diuretics over alternative antihypertensives, and notably ß-blockers, in elderly patients. The Canadian guideline states that diuretics are the only drugs of first choice in the elderly, and the British guideline mentions a clear preference of diuretics over ß-blockers. Potassium sparing diuretic combinations are recommended more explicitly for the elderly in the British and the Canadian guidelines. Finally, all five guidelines suggest the use of lower initial dosages in older patients.

Diuretic antihypertensive therapy and coexisting disease

All guidelines include specific therapeutic advices for hypertensive patients with coexisting diseases. In patients with congestive heart failure, most guidelines prefer diuretics (and ACE-inhibitors). In case of diabetes mellitus, four of the five guidelines recommend to avoid diuretics as drugs of first choice, and 'if'. diuretics have to be added, to closely monitor blood glucose levels. Hyperuricemia is not considered a contraindication for thiazides by any of the guidelines, unless symptoms of (recurrent) gout are present. The recommendations for patients with dyslipidemia are more contradictory. The American, British and Dutch-CBO guidelines recommend avoidance of diuretics in these patients, whereas the Canadian and Dutch-GP guidelines explicitly state that dyslipidemia is no reason to follow a different treatment policy.

Discussion

The guidelines

Carefully designed procedures for development resulted in guidelines of high quality. The various steps of the procedures were different, but the adequate use of scientific evidence in combination with extensive consensus procedures was the core element in all countries. The most extensive and precise recommendations were provided by the American and Canadian guidelines.

International guidelines such as the Hypertension Guideline of the World Health Organization and the International Society of Hypertension[29]

have several disadvantages. Differences for example in culture, tradition and economical standards between the home countries of the members of the working parties may be obstacles in reaching consensus and often results in insufficiently detailed guidelines. In addition, implementation may be less successful than for national guidelines.

Because most hypertension patients are treated in general practice, involvement of GPs in the development of hypertension guidelines is essential. One national guideline for all physicians written by a broad multidisciplinary working party, including general practitioners, seems the most desirable option. As in the heart failure guidelines discrepancies between the characteristics of patients treated by specialists and GPs may generate unsurmountable differences in opinion. Nevertheless, the growing tendency to consider the entire spectrum of hypertensive patients by both specialist and GP-experts in hypertension in the Netherlands is reflected by a recent proposal for adjustments of the guidelines.[35] It seems only a matter of time until the undesirable situation of two national hypertension guidelines in one country will cease to exist.

Thiazide diuretics are first choice

All guidelines recommend thiazides as drugs of first choice in the treatment of hypertension, unless specific conditions require other antihypertensive medications. Beta-blockers are usually considered an equally effective alternative for diuretics: second in line in elderly patients and when heart failure is present, but first in line when cardiac protection against ischemic events is indicated (e.g. in those with a history of myocardial infarction or angina).

Remarkably, the fifth edition of the American guideline[34] recommends either diuretics or ß-blockers, whereas in the preceding edition ACE-inhibitors, calcium antagonists and α-blockers were also included as first choice antihypertensive medications. This is not surprising in view of the evidence from clinical trials. The main antihypertensive drug in eighteen of the 22 available randomized controlled trials was a thiazide diuretic. The overwhelming body of evidence that antihypertensive treatment is beneficial, is largely based on studies with diuretics. The current lack of long-term studies of the newer classes of antihypertensive drugs is striking. Several large trials with ACE-inhibitors and calcium antagonists are underway. The recent commotion about the safety of nifedipine in hypertension illustrates the need to be cautious with drugs until results from large trials are available.[36,37]

Potassium sparing diuretics?

In all guidelines information and recommendations on indications for

potassium-sparing diuretics is scarce. Three important trials with potassium sparing diuretics as main treatment in elderly hypertensives showed impressive reduction in the incidence of stroke and coronary heart disease.[19,25,27] Furthermore, two recent case-control studies demonstrated an increased incidence of sudden cardiac death in patients treated with non-potassium sparing diuretics compared to potassium sparing diuretic combinations.[38,39] Based on this scientific evidence, one could argue that beside monotherapy with thiazides, a combination of a thiazide and a potassium-sparing diuretic should be considered therapy of first choice in hypertensive elderly patients. Non-potassium-sparing diuretics remain preferable in patients with renal insufficiency, concomitant treatment with ACE-inhibitors, or demonstrated hyperkalemia.

Diuretics in dyslipidemia and diabetes mellitus

The guidelines differ considerably concerning the rated value of diuretics in dyslipidemic patients. The Dutch-GP guideline and the Canadian guideline do not advise against thiazide therapy in these patients, in contrast to the other three guidelines. Thiazide therapy increases cholesterol level by approximately 3%, and this seems not to be a transient phenomenon.[40] Although this small increase may not seem clinically relevant in individual patients, it is not neglectable at the population level. Nevertheless, it should be stressed that the trials have demonstrated the benefits of thiazides, even when cholesterol levels may have offset a small part of this favourable effect.

The role of thiazides in patients with diabetes mellitus, remains controversial. Randomized trials assessing the long-term effect of diuretics or other medications in diabetic hypertensive patients on cardiovascular disease are not available, whereas several studies reported disadvantageous effects of thiazides on parameters of lipid and glucose metabolism, and advantageous effects of ACE-inhibitors on several relevant intermediate outcomes, such as renal function.[41,42,43,44,45] In view of this evidence, the predominant recommendations in the guidelines to initially prescribe a non-diuretic drug, such as ACE-inhibitors or calcium antagonists, and to monitor glucose levels in case diuretics are required in diabetic patients, is understandable.

Conclusions

In the current national clinical guidelines thiazide diuretics are recommended as drugs of first choice in the treatment of hypertension. In middle-aged patients ß-blockers are an equivalent alternative. The fact that despite strong recommendations in all guidelines to prescribe thiazides

or ß-blockers, prescriptions of ACE-inhibitors, calcium antagonists and other agents constitute approximately 50% of all current prescriptions in hypertension is remarkable and regrettable. The impact of national guidelines can obviously be further improved.

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4 Studies on withdrawal of medication: methodological aspects

Introduction

Many patients receive long-term drug therapy. Heart failure and hypertension are examples of conditions that may lead to drug use over prolonged periods. In clinically stable asymptomatic patients on drug treatment, withdrawal of therapy could be considered. Criteria to guide withdrawal of long-term medication in selected patients should not only be based on clinical experience, but also on knowledge about prognostic implications of withdrawal, provided by solid experimental studies. Attempts to decrease the number of patients who are on unnecessary long-term drug treatment will probably be encouraged by the availability of results from clinical trials. It is laudable that in recent years the number of reports of studies assessing the possibility of withdrawal of medication is increasing. They have been published in a variety of medical fields: for example nursing-home medicine,[1,2,3] cardiology,[4,5,6] and general practice.[7,8,9,10,11] Some of these studies are uncontrolled or non-randomized, while others are randomized controlled trials (RCTs). The latter are universally accepted as the paradigm to assess treatment efficacy and one of the questions to be addressed in this paper is whether drug withdrawal studies need to be designed as randomized, controlled, double-blind trials, or whether methodologically less stringent study designs are reasonable alternatives.

Very few literature references on the methodology of drug withdrawal trials are currently available. De Jonge describes some methodological issues in his thesis and Pocock pays attention to the methodology of so-called 'negative trials', one of the features of withdrawal studies.[12,13] It may be anticipated that more drug withdrawal studies will be conducted in the forthcoming years and in our view more attention should be payed to the specific methodological aspects of drug withdrawal studies. The aim of this paper is to highlight a number of these methodological issues, with special emphasis on the aim/research question, design and data analysis.

Aim and research question

Drug withdrawal studies aim at assessing the possibility and effects of reducing unnecessary drug therapies. Typically, the main research questions addressed in these studies are: (1) What proportion of patients can be successfully withdrawn from treatment, (2) What are the (short- and long-term) effects of drug withdrawal, and (3) What are predictors for successful withdrawal? Thus, the principle outcome in drug withdrawal studies is the proportion of long-term drug users that can be successfully withdrawn from treatment. 'Successfully' should be strictly defined by criteria that were determined in advance and typically implies: without worsening of clinical condition or prognosis.

Drug efficacy in withdrawal studies?

Sometimes a tendency occurs to use results from drug withdrawal studies to draw conclusions regarding a drug's efficacy. In other words: harmful clinical effects of withdrawal of a drug are interpreted as proof of potential beneficial effects of the same drug when initiated in previously untreated patients. An interesting example of an early drug withdrawal study is The Sixty Plus Trial.[14] In this study postmyocardial infarction patients on long-term therapy with coumarin were randomly allocated to a withdrawal group and a control group in which therapy was continued. The incidence of myocardial infarction was lower in patients that continued coumarin therapy and the authors concluded that (1) the harmful effect of withdrawing coumarines was demonstrated, and that (2) extrapolations regarding the efficacy of the treatment per se were not possible. Nevertheless, the trial results were generally seen as an endorsement of the efficacy of coumarins in secondary prevention of myocardial infarction. We believe (with the authors) that the latter conclusion is unjustified, mainly because, inherent to all drug withdrawal studies, patients who did not initially respond to the treatment or who developed side effects during treatment are very unlikely to have become chronic users and thus to be included in the study. In addition, potential rebound effects preclude extrapolation of results from withdrawal studies to drug efficacy. An extreme example of the latter is morphine: unsuccessful withdrawal for sure does not allow conclusions concerning the efficacy of morphine. Although most drugs have less profound rebound effects, complete absence of rebound phenomena can never be excluded.

Drug withdrawal studies are sometimes specifically designed to study the efficacy of a drug. In such studies, the medication is initially given to all eligible patients. This run-in phase on active medication is used to titrate the dose of the medication to optimal levels and identify non-compliers. After randomization one arm has its treatment withdrawn, while the

other patients continue to receive the drug. It is important to realize that the intervention in these trials is not the withdrawal of a drug as such, but that successive initiation and withdrawal of the drug are one composed intervention. In this design, the problem of preselecting good responders and patients with no major side effects is made somewhat more controllable by the availability of these data for all eligible patients. The biological problem of unknown rebound effects however, is not prevented and conclusions on drug efficacy remain illusive. Such study designs are used by certain research groups as an alternative for regular RCTs, and were first described by Amery and Dony in 1975.[15] The number of published reports of drug withdrawal studies with an efficacy aim is increasing. Remarkably, many are being performed in the field of cardiology, mainly studying the effects of withdrawal of drugs from patients with heart failure.[16,17,18,19]

Study design

The paradigm of drug efficacy studies is the randomized, double-blind trial. It is therefore remarkable that in studies assessing the effects of withdrawal of medications often less stringent designs are applied.

Nonexperimental (i.e. observational) studies to assess effects of drug withdrawal are theoretically possible, although, as in nonexperimental efficacy studies, there are major methodological limitations. One could think of retrospective queries or explorations of medical files of patients who had their medication withdrawn by physicians trying to cut down overmedication. To our knowledge, however, no such observational studies have been published.

Studies with an *experimental* design are less prone to biases. The most unpretentious are withdrawal studies with uncontrolled patient series, which can be efficient eye openers. Many of such studies have been published and some examples are in the list of references.[7,8,9,20,21] Interestingly, and understandably, the conclusion of these studies is always similar: 'a larger and controlled trial is needed to verify the results'. A *comparison group* in experimental designs is needed to discriminate the net result of an intervention from effects such as natural course of disease or regression to the mean.

Further, *random allocation* of patients to two (or more) trial arms is a mandatory procedure to ensure comparability of prognosis between the intervention group and the control group. This holds in drug withdrawal studies as well as in other experimental studies.

One could argue whether the use of *placebo* medication in the withdrawal group is a necessary feature of drug withdrawal studies. The purpose of placebo is elimination of the influence of extraneous effects (the placebo effect). In drug efficacy trials, prior belief of patients or doctors in beneficial effects of a new treatment may result in positive (but non-pharmacological) treatment effects; the so called placebo effect. Analogously, prior belief of patients in harmful effects (of drug withdrawal) may result in so-called nocebo effects. Nocebo refers to unpleasant in contrast to placebo which refers to pleasant.[22,23]

In an open design, extraneous effects can only partly be eliminated. Effects, such as getting used to the study setting, coinciding interventions, and extra attention of doctors are more or less controlled for by the availability of a control group, but prior expectations of the effects of cessation of therapy by both patients and doctors, may easily result in additional effects.

When the purpose is to assess the effect of withdrawal of the pharmacological substrate, all other effects are considered extraneous and thus blinding of patients and doctors is required. This can be achieved in drug withdrawal studies when patients in the control group are maintained on active drugs (=verum), whereas the withdrawal group is treated with placebo. These studies actually are not placebo-controlled but verum-controlled. Another major advantage of placebo medication is the possibility of *blinding* with, consequently, avoidance of potential information bias at measuring trial outcomes.

One could take a more pragmatic approach and not study the isolated pharmacological effect of drug withdrawal as the intervention of interest, but the effect of the procedure of withdrawing the drug as a whole. Then, the possible additional effects mentioned above are not considered extraneous. Some suggest this would be more in line with every day medical practice in which the gross success rate of withdrawal of medication is more important, and the underlying cause (withdrawal of pharmacologic substance or extraneous effect) is relatively irrelevant. In those cases an open design is feasible. A major disadvantage is the above mentioned possibility of information bias, notably in measurements of outcome parameters prone to subjective interpretation. The use of harder outcomes may, however, limit this problem.

Several additional arguments in favour of a blinded design should be mentioned. First, the availability of data about the isolated pharmacologic effect provides more insight in the nature of the events occurring after drug withdrawal than data that mix up pharmacological effects with

extraneous effects. This is important because patients on long-term medication often have gradually evolved the belief that taking the drug is an essential part of their health promoting behaviour and as a consequence withdrawing their tablets may easily result in reinitiation of therapy, which, however, may be largely caused by their fear to have their tablets withdrawn. It seems preferable to first assess the isolated pharmacological effects of drug withdrawal, preferably by blinding procedures and including placebo therapy. Subsequently, open studies on the effect of the procedure of cessation of therapy may provide important additional information.

Blinding is technically more complicated in drug withdrawal studies then in RCTs because of two reasons. First, blind down titration of the dose, generally mandatory to avoid or diminish rebound effects, is not as simple as blind up-titration in efficacy RCTs. In the latter case the boxes of study medication contain either the active drug or placebo and up-titration can simply be effectuated by increasing the dose of 'study medication', no matter if it is active or placebo. An analogous procedure for down titration in a drug withdrawal trial would result in dose reductions in the control group and sudden withdrawal in the index group, which of course is undesirable. To solve this problem, separate 'dose reduction' boxes should be added to the study medication package. Combinations of low dose tablets of active and placebo preparations can be used to realize the desired down titration schedules. Second, extra effort should be put in assuring complete similarity of active and placebo study medication (form, colour, taste, consistency), because there is an increased probability of recognition of the character of the tablets in combined sets with consequently breaking of the randomization code. Moreover, a patient's acquaintance of the drug effect can impair the success of the blinding procedure, because the patient has been using the drug for a prolonged period. For these reasons challenging the effectiveness of the blinding procedure during the course of the trial is more essential in drug withdrawal studies then in efficacy studies. This may be done by asking the patients (and the investigators) during the follow-up examinations to guess the nature of the study medication and to present these results in the report of the trial.

Study population

Knowledge of the characteristics of the study population included in a trial is important for the generalisability of the study results. Drug withdrawal studies differ from efficacy RCTs with respect to the composition of the patient population. Long-term drug use, the main inclusion crite-

rium, may lead to a considerable level of diagnostic heterogeneity of the patient population, because medication may have been prescribed for different initial diagnoses and retrospective data about the indications of initiation of therapy are usually difficult to obtain. High blood pressure is an example of a condition in which long-term drug treatment is not always justified by an adequate diagnosis. Premature start of treatment might easily explain a relative high proportion of successful withdrawals, while on the other hand contamination of the study population with patients with heart failure may have an opposite effect.

Generally, chronic medication will be prescribed at regular intervals by the treating physicians, and thus patient recruitment may take place during these consultations. Alternatively, potentially eligible patients may be actively approached. In the Netherlands this is generally possible because of the availability of a file of patient names of long-term drug users in registries of pharmacies or general practitioners. The advantage of using pharmacy registries is that initial recruitment is relatively independent from the treating physicians. This may limit selectivity of inclusion and increase generalisability of the trial results.

Refusal of patients to cooperate is another factor that may negatively influence the success of patient recruitment and limit generalisibility of the results. In withdrawal studies patients may readily perceive the suggested intervention as possibly harmful, especially if not proposed by their own treating physician, who in most cases initiated and continued the long-term medication. For this reason an active approach of patients by investigators may provoke unwillingness to cooperate and careful back up by treating physicians is essential. In our studies on withdrawal of diuretic treatment in elderly patients, potentially eligible patients (preselected with the aid of pharmacy registries) were first approached by their general practitioner and the rate of patient refusal was low (15%).

Finally, in drug withdrawal studies the stable clinical baseline condition (without symptoms) of eligible patients may result in a higher number of refusals by patients or vetos by treating physicians in comparison to efficacy trials, where eligible patients generally are in need of a treatment.

Duration of follow-up period

A specific feature of drug withdrawal studies is that no difference in outcome between the patients withdrawn from therapy and those who continue to receive medication is anticipated. In other words, the prior hypothesis is that the drug under study might be withdrawn in a large pro-

portion of patients without unfavourable clinical effects. At this point it is essential to introduce the term 'negative trial'.[13] Negative trials are trials with a prior expectance of 'no-difference' between the comparison groups. Drug withdrawal studies are an example of such negative trials. Another example are trials that aim to demonstrate equal efficacy (with fewer adverse drug reactions) of newly developed drugs and 'classical drugs'. This feature of drug withdrawal studies has consequences for the length of the follow-up period as well as for the required trial size. If a specific effect shortly after the intervention is expected, e.g. change of blood pressure after initiation or cessation of antihypertensives, one could decide to keep the follow-up period short. But if no effect is anticipated, as generally in withdrawal studies, a relevant follow-up period after which one could conclude that 'successful withdrawal' has been achieved should be chosen. Thus, in negative trials the length of the follow-up period is an essential part of the definition of the principle outcome 'successful withdrawal'. Another reason to include relatively long follow-up periods in drug withdrawal studies is the occurrence of rebound effects[10] or long lasting effects (e.g. slow return of hypertension after withdrawal of thiazides). In drug withdrawal studies the tendency exists to plan follow-up periods that are shorter than desirable. The follow-up period in randomized, controlled, blinded withdrawal studies published until now ranges from 3 to 24 months, which seems rather short, both in comparison to drug efficacy studies and in view of potential rebound effects and long-term unfavourable effects of cessation of therapy.

Trial size

A false positive statistical test is called a type I error, whereas a false negative test is called a type II error. In drug efficacy RCTs type I errors are more serious than type II errors, because the former may cause more patients to be exposed to useless, and possibly harmful, treatment. Type II errors generally have less important implications: a potentially beneficial treatment might be missed but the principle 'primam non nocere' is anyhow respected. This is why in RCTs it is more important to avoid type I than type II errors, which is reflected by the commonly chosen magnitude of the statistical parameters α and ß of 0.05 and 0.1, respectively. In drug withdrawal studies one hopes to demonstrate that withdrawal of a drug has 'no' effect and thus the anticipated outcome is: no difference between the intervention and the control group. Type I errors in these trials lead to an erroneous conclusion of the existence of a difference between the studied groups with equally important clinical consequences as type I errors in efficacy RCTs, namely unjustified (continued) use of

long-term medication. Type II errors in drug withdrawal studies lead to an erroneous confirmation of 'no difference', and may possibly have even more serious clinical consequences (unjustified drug withdrawal in many patients) then type I errors. Thus, the avoidance of type II errors in drug withdrawal trials is more important than in efficacy RCTs and consequently the value of ß should be larger in drug withdrawal studies. The magnitudes of α and ß depend on clinical judgements about the risks of withdrawing effective medication or continuing unnecessary, possibly harmful medication. The choice of smaller values of ß together with an unaltered value of α will result in larger sizes of drug withdrawal studies compared to efficacy trials.

As mentioned earlier, drug withdrawal trials are negative trials and for negative trials an adapted method to determine trial sizes has been described.[13,24] In this case the reasoning is based on predefining the size of the 100x(1-α)% confidence interval of the difference in percentage success (or risk) between the two treatments and predefining the acceptability of the chance (ß) that this CI will be exceeded. The choice of the magnitudes of both α and ß is again based on the acceptability of the clinical consequences of erroneously interpreted trial results and again, drug withdrawal trials appear to be in need of larger trial sizes, no essential difference between this method and the one described in the foregoing paragraph.

The smaller the clinical effect one wishes to exclude, the larger the trial size needed. The decision about acceptable clinical effect sizes will be influenced by the fact that drug withdrawal trials include patients in a stable clinical condition, and thus not much harm will be acceptable. Thus, smaller effects usually are of interest than in efficacy RCTs, which deal with patients whose condition need treatment or at least a preventive action. As a consequence, this is another reason why drug withdrawal trials generally require larger trial sizes, apart from the influence of the choice of α and ß.

Data analysis

When many patients drop-out during the follow-up period of a RCT, loss of comparability of prognosis between the trial arms becomes a realistic problem. Intention-to-treat analysis is the most widespread method, applied to neutralize potential bias by selective drop-out of patients. The motives for intention-to-treat analysis of the principle outcome do not differ between drug withdrawal studies or efficacy RCTs. However, the choice of the principle outcome may lead to a rather different situation

in drug withdrawal studies. Unsuccessful withdrawal of treatment in itself may very well be the major reason for drop-out, but it is at the same time the principle outcome. This simplifies the matter indeed, intention-to-treat analysis for the principle outcome becomes easier because the number of unwanted drop-outs is substantially decreased.

Also for secondary outcomes (e.g. change in blood pressure after withdrawal of antihypertensive therapy) analysis according to the intention-to-treat principle is preferable. Patients who satisfy the criteria for the principle outcome of the study, however, will generally have resumed their original treatment and including data in the analysis, after reinitiation of the treatment (e.g. blood pressure after resuming antihypertensive therapy) would lead to irrelevant conclusions, certainly if large numbers of patients resumed therapy as is often the case in withdrawal studies. To describe the changes in secondary outcomes (such as blood pressure) during the follow-up of the trial two analytic techniques may be applied as alternatives to the intention-to-treat analysis: 1) carry-forward analysis, in which the last available data (before treatment had been resumed) are carried forward until the end of the study follow-up period, and 2) separate analysis of patients who were successfully withdrawn from treatment and those who were not.

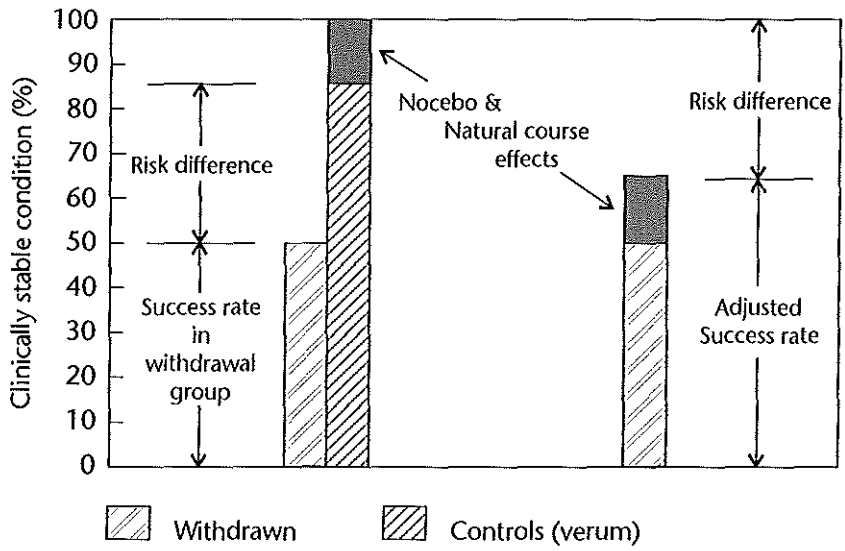
Choice of effect measure

In RCTs risk ratios and -differences are the most frequently used effect measures. Statistically, ratios are preferable when the magnitude of an outcome is proportionally related to its baseline value and differences if such a relation does not exist.[13] In this respect efficacy RCTs and withdrawal studies are similar. However, the magnitude of effects in withdrawal studies tends to be larger, which leads to a less frequent occurrence of the proportionality of relations between outcome magnitudes and their baseline values, and consequently to a more frequent use of differences instead of ratios as effect measures in drug withdrawal trials.

Risk difference and risk ratio address 'risk' (of disease), whereas essentially the interest of withdrawal studies is 'success' (of withdrawal of therapy). To more directly denominate the proportion of patients that may be successfully withdrawn from medication, an effect measure of 'success' would be preferable. In uncontrolled, but also in several controlled withdrawal studies, the proportion of patients in the withdrawal group that is successfully withdrawn is often considered the 'success rate'. This rate, however, does not take into account the proportion of withdrawn patients, in which reinitiation of therapy is not attributable to withdrawal

of the pharmacon, but to natural history of the underlying disease or nocebo effects. This latter proportion can only be assessed in placebo-controlled withdrawal trials, (Figure 4.1) and is equivalent to the proportion of patients in the control (=verum) group that requires intervention because of worsening of their clinical condition. Thus, an 'adjusted success rate', i.e. the sum of this proportion and the 'success rate' in the withdrawal group, can be calculated. This effect measure is equivalent to 'one minus the risk difference', where risk difference is the difference in risk of clinical deterioration in the two comparison groups. The clinical meaning of this effect measure is the proportion of patients in which withdrawal of the pharmacon per se, has no adverse effect on the patient's clinical condition.

Figure 4.1



Adjusted success rate as a measure of successful withdrawal of long-term medication.

In Table 4.1 the 'adjusted success rates' from seven controlled studies on withdrawal of diuretics are calculated and compared to the, usually reported, success rate in the withdrawal group. Comparison of these 2 measures provides additional insight in the clinical consequences of withdrawal of a pharmacon.

Table 4.1
Adjusted success rate, calculated from the results of randomized controlled trials of withdrawal of diuretic therapy.

Author/ group	Control group Success on active treatment (%)	Withdrawal group Success on placebo (%)	Adjusted success rate* (%)
Elderly patients on long-term diuretic therapy			
Burr[1]	92	76	84
Myers[2]	79	71	92
Walma[$]	87	51	64
Hypertension			
Veterans[25]	96	15	19
Maland(HDFP)[4]	84	58	74
MRC[5]	80	50	70
Freis(Veterans)[26]	73	31	58

* Adjusted success rate = (1 – Risk difference)
$ This thesis, chapter 7

Conclusions

Drug withdrawal studies should be designed as carefully as any other study on drug effects (e.g. drug efficacy studies) and the methodological demands are equally rigorous. Patient populations in drug withdrawal studies are less homogeneic and difficulties with inference to larger populations may occur. The outcome of interest is the proportion of patients which can be successfully withdrawn from treatment. Conclusions about efficacy of a drug, by extrapolation and reversal of withdrawal effects, however, are not possible. Criteria for successful withdrawal should be carefully defined in advance. Follow-up periods tend to be too short in published drug withdrawal trials, although relatively long follow-up periods are required to assess rebound effects and long-term effects of withdrawal. The need for placebo treatment and blinding is influenced by the decision whether other effects than cessation of administration of the pharmacon are considered extraneous and the possibility of information

bias. Trial sizes need to be larger, mainly because of the importance of avoiding both type I and type II errors. Intention-to-treat analysis may be substituted by carry forward analysis or separate group analysis in the study of secondary outcomes. Effect measures of 'success' may provide better insights in the clinical relevance of the results of withdrawal trials than 'risk' effect measures .

Double-blind, (verum-)controlled, randomized drug withdrawal trials are feasible, and if well designed they may be an important tool to learn when overmedication can be curtailed.

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5 Accuracy of an oscillometric automatic blood pressure device: the Omron HEM403C

Introduction

The mercury manometer is generally accepted as the standard instrument to measure blood pressure in medical practice. Automatic blood pressure measurement devices are frequently used by patients for self-measurement at home. The simplicity of the measurement procedure is an advantage of the automatic devices over mercury manometers. This makes them more suitable for self-measurement. The elimination of observer-related sources of error, such as expectancy bias, terminal digit preference and parallax is another attractive feature of these devices and is the main reason for the frequent use of automatic devices in clinical trials.

The current automatic devices generally apply the oscillometric method. Pressure oscillations in the air cuff of the device, which arise from the expansion of the arm by the blood pressure increase at each heart beat, are recorded by a pressure sensor and systolic blood pressure (SBP) and diastolic blood pressure (DBP) are calculated from the oscillation pattern by a microprocessor that uses a specifically developed software protocol.[1] The method is relatively insensitive to disturbing noises compared with the auscultatory method. A fundamental difference with the conventional auscultatory method is that the auscultatory method is based on the detection of Korotkoff sounds and the oscillometric method on the analysis of a pressure oscillation pattern. This has given rise to questions about the agreement of both methods in individual patients. One should recognize that agreement between blood pressure devices can be quite acceptable at average in large patient groups, and at the same time be inferior in subgroups of patients or in individual patients, notably when the measurement principles of the devices are fundamentally different. This underlines the need for a carefully designed validation procedure.

The Omron HEM403C is (in 1993) by far the most frequently used automatic blood pressure device in general practice in the Netherlands. Thus, an assessment of its accuracy is warranted. We are currently using the Omron HEM403C in the setting of a randomized clinical trial, which further urged us to determine its accuracy.

The objective of our study was to assess the accuracy of the Omron

HEM403C automatic blood pressure device and to study whether this accuracy was affected by subject-related factors such as blood pressure level, age, sex, arm circumference and pulse rate.

Patients and methods

The design of our study adhered as much as possible to the 1990 version of the protocol for validation of automatic blood pressure devices of the British Hypertension Society (BHS). The protocol of the American Association for the Advancement of Medical Instrumentation served as an additional guideline. We have made some adaptations and neither of the published protocols was followed in full.

Terminology

Terminology such as accuracy, reproducibility, agreement, validity and bias can be quite confusing. We defined accuracy as the broadest and most general term. Reproducibility was defined as the extent to which a device provides equal measurement recordings under equal conditions. Agreement is the extent to which measurements with one device agree with another device. Validity and bias are terms that we avoided because they refer to an absolute gold standard, whereas in blood pressure measurement only a relative gold standard with its own inaccuracies is available.

Description of the meters

The Omron HEM403C is a fully automatic oscillometric blood pressure device. It is the basic model of a series of models; other models are provided with extra facilities such as automatic inflation and a printer unit. The deflation rate of the cuff pressure is approximately 3 mmHg per second. The Hawksley random zero meter is a mercury column sphygmomanometer with a technical facility that enables a variable zero position of the mercury column.[2] The zero position can only be determined after the measurement and must be subtracted from the observed SBP and DBP. This 'blinding for expected values' during the measurement limits observation bias.

Blood pressure measurement

Accurate auscultatory measurements are possible at a deflation rate of 3 mmHg per second. This enabled us to choose the method of simultaneous single arm measurements, which is more precise than the method of sequential measurements. The cuff of the Omron HEM403C was used during all measurements. Its air tubing was tapped with a T-connector to the Hawksley random zero meter. The SBP of the random zero meter was

taken at the appearance of the first Korotkoff sound and the diastolic pressure at the fifth Korotkoff phase (absence of sounds). The automatic meter's display was blinded until the mercury measurement was completed.

Observers

Two of the three observers were experienced general practitioners and the third observer was a junior doctor with extensive experience in measuring blood pressure. All three observers underwent an audiographic test and no hearing deficit was observed. They refreshed their theoretical knowledge about blood pressure measuring by studying the 'Recommendations on blood pressure measuring' as published by Petrie et al.[3] Their inter-observer variation was assessed by simultaneously measuring blood pressure 10 times in each of five subjects. One cuff, which was fitted around a subject's arm, was connected to 3 mercury meters and one multi-aural stethoscope was used. One of the observers who successfully interpreted 95% of the test-sequence of the blood pressures of the British Hypertension Society video tape[4] was considered the expert-observer. The expert-observer placed the head of the stethoscope over the brachial artery, inflated the arm-cuff to about 30 mmHg above the SBP and deflated the cuff at a rate of approximately 3 mmHg per second or per heart beat. More than 90% of the measurements between the expert-observer and each of the other observers and more than 85% of the measurements between these two observers were less than 5 mmHg apart.[5]

Test-phases and study subjects

Calibration of three Omron HEM403C devices was accomplished by fitting the air cuff around a solid round object and connecting it by means of a T-connector to a new mercury meter. Pressure readings of both meters were compared throughout the 300 – 20 mmHg range. At least 20 measurements were performed for the individual instruments. This calibration procedure was repeated after three months.

The assessment of agreement with the mercury sphygmomanometer was performed in a population of 225 subjects. They were recruited at three different locations. One hundred four patients were asked to cooperate after a regular medical consultation in general practice, 98 blood donors were asked during their yearly routine physical examination and 23 colleagues from the university department of general practice volunteered. No attempt was made to recruit subjects of any particular age range or blood pressure level and no attempt was made to include patients with or without antihypertensive therapy. Every subject's blood pressure was measured two times. Thirteen subjects were excluded from the analysis because of an irregular pulse and in 23 patients the second of the two consecutive measurements was not performed. Arm circumference was mea-

sured with a measuring tape midway on the upper arm. Pulse rate and regularity were assessed by palpation of the pulse during 30 seconds.

The estimation of the reproducibility of the device was based on data from the same study population. The variability of the differences between the consecutive duplicate measurements in every subject was used to compare the reproducibility of the test device and the reference device.

Data analysis

Calibration was considered accurate when 95% of the readings of the test device were within 3 mmHg or 2%, whichever greatest, of the readings of the mercury meter,[5,6]

To assess the agreement between the Omron and the random zero meter, the proportions of the Omron HEM403C measurements that differed from the mercury meter measurements by ≤ 5, 10 and 15 mmHg were calculated and tabulated. Duplicate readings were not pooled but analyzed separately. Subsequently the device was graded according to the criteria of the British Hypertension Society (Table 5.1). The mean and the standard deviation of the differences between the test device and the mercury standard were calculated to classify the device according to the criteria of the American Association of Advancement of Medical Instrumentation (AAMI). To pass these criteria, the difference between the test device and the standard must be ≤ 5 mmHg and the standard deviation of the difference ≤ 8 mmHg.

Table 5.1
British hypertension society grading criteria for simultaneous measurements[5]

Difference between standard and test device			
Grade	*≤ 5 mmHg (%)*	*≤ 10 mmHg (%)*	*≤ 15 mmHg (%)*
A	80	90	95
B	65	85	95
C	45	75	90
D	< 45	< 75	< 90

The blood pressure device is graded according to the proportion of the readings that are within 5, 10 or 15 mmHg of the concomitant readings with the standard measurement procedure. To reach a particular grade, all three proportions should exceed the tabulated values

The variability between duplicate measurements, adjusted for the physiological fall in blood pressure at the second measurement was used to estimate reproducibility. This estimate was calculated as the absolute value of the difference between the two duplicate measurements after subtracting the mean blood pressure fall from this difference. The logarithm of this absolute value was compared between the two devices by using the Wilcoxon test for matched pairs. The variance of duplicate measurements can be estimated as the sum over all patients of the squared differences adjusted for the mean blood pressure fall, divided by twice the number of patients. The standard deviation of duplicate measurements is the square root of this variance. A multiple linear regression analysis was performed to assess whether a patient's blood pressure level, age, sex, arm circumference and pulse rate were independently related to the systolic and diastolic blood pressure differences between the meters.

Results

A summary of the characteristics of the 212 subjects in the agreement study is shown in Table 5.2.

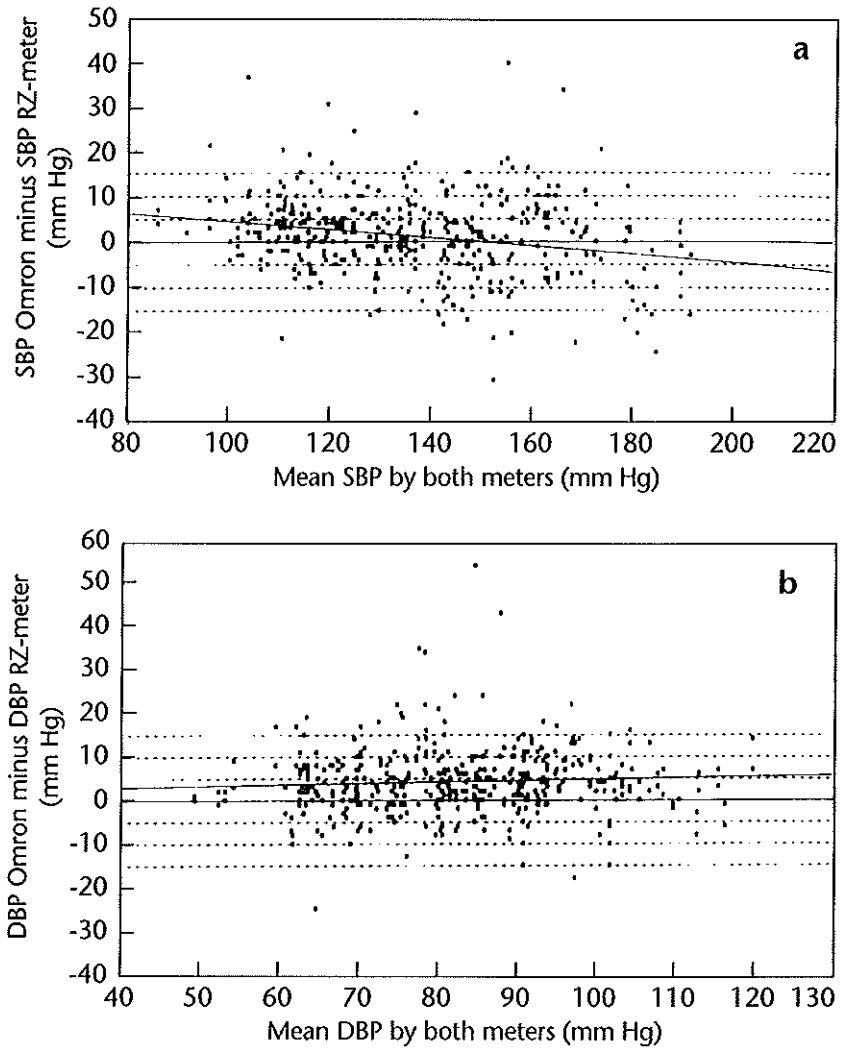
Table 5.2
Characteristics of the subjects studied (n = 212)

	mean (sd, range) or proportion	
Women (%)	54	
Age (years)	48	(17, 16-88)
Arm circumference (cm)	28	(2, 23-37)
Pulse rate (beats/min)	74	(14, 47-117)
SBP (mmHg)(%)	136	(23, 86-191)
SBP < 100	3	
100 ≤ SBP < 140	54	
140 ≤ SBP < 180	39	
180 ≤ SBP < 220	4	
SBP ≥ 220	0	
DBP (mmHg)(%)	81	(14, 49-119)
DBP < 60	3	
60 ≤ DBP < 80	44	
80 ≤ DBP < 100	44	
100 ≤ DBP < 120	10	
DBP ≥ 120	0	

n: number of patients, sd: standard deviation, SBP: systolic blood pressure, DBP: diastolic blood pressure

All three tested Omron HEM403C instruments passed the calibration criteria at the start of the study and after three months.

Figure 5.1a and Figure 5.1b



Differences between the systolic blood pressure (Figure 5.1a) and diastolic blood pressure measurements (Figure 5.1b) of the Omron HEM403C and the random zero meter. Every dot represents the difference in one pair of simultaneous readings. Duplicate readings are not pooled but plotted separately. Dotted lines are drawn at the levels of a difference of 5, 10 and 15 mmHg between the two meters. Crude regression lines are plotted in the Figures. SBP=systolic blood pressure, DBP=diastolic blood pressure, RZ=random zero

A total of 413 systolic and 414 diastolic measurements in the 212 subjects were available for the agreement analysis. In Figure 5.1, the blood pressure differences between the Omron HEM403C and the random zero meter are plotted by blood pressure level. Systolic and diastolic readings with the Omron HEM403C were on average 1 mmHg (sd 9, 95% CI 0.3-2.0) and 4 mmHg (sd 8, 95% CI 3.7-5.2), respectively, higher than those with the random zero meter. The quantification of the level of agreement (Table 5.3) shows that the Omron HEM403C was graded C for both SBP and DBP according to the BHS grading system. The Omron HEM403C marginally failed the AAMI criteria for SBP and passed these criteria for DBP.

Table 5.3
Omron HEM403C blood pressure device compared with the Hawksley random zero meter

					Readings(%)			*Grading*	
Device	*n*	*Mean* ± *sd*	*Difference* ± *sd*	*95% CI*	*≤5 mmHg*	*≤10 mmHg*	*≤15 mmHg*	*BHS*	*AAMI*
SBP									
403C	212	137 ± 23							
			1 ± 9	0.4-2.2	53	80	92	C	Fail
RZ		136 ± 25							
DBP									
403C	212	84 ± 15							
			4 ± 8	3.6-5.1	55	85	94	C	Pass
RZ		84 ± 15							

n: number of patients, sd: standard deviation, CI: confidence interval, BHS: British Hypertension Society, AAMI: Association for the Advancement of Medical Instrumentation, SPB: systolic blood pressure, DBP: diastolic blood pressure, 403C: Omron HEM403C, RZ: Hawksley random zero meter

The mean systolic difference between the Omron HEM403C and the random zero meter was related to the SBP level ($p<0.001$). The crude regression equation for the difference in SBP between the Omron and the random zero meter was: $y = 13.7 - 0.09(SBP)$ mmHg and is plotted against the mean SBP level in Figure 5.1. The Omron HEM403C overestimated the SBP at SBP levels under 152 mmHg and underestimated the SBP at higher SBP levels. Multivariate linear regression analysis showed that the SBP level and not age, sex, arm circumference and pulse rate was independently related to the systolic difference between the two meters (Table 5.4). The mean diastolic difference between the two meters was not associated with

the level of the DBP. The crude regression equation, which is plotted against the mean DBP level in Figure 5.1, was: y = 1.8 + 0.03(DBP) mmHg. The Omron HEM403C overestimated the DBP at all DBP levels. Multivariate linear regression analysis demonstrated that DBP level, age, sex, arm circumference and pulse rate were not related to the diastolic difference between the two meters (Table 5.4)

Table 5.4
Multiple linear regression analysis of the influence of blood pressure level, arm circumference, age, sex and pulse rate on the blood pressure difference between the Omron HEM403C and the random zero meter (n=212)

Variable	*SBP difference*			*DBP difference*		
	Coefficient	*s.e.*	*P value*	*Coefficient*	*s.e.*	*P value*
SBP level (mmHg)	-0.102	0.022	0.0000			
DBP level (mmHg)				0.005	0.030	0.9
Arm circumference (cm)	0.173	0.181	0.3	0.257	0.155	0.1
Age (years)	0.008	0.029	0.9	0.026	0.022	0.2
Sex (men = 0, women =1)	-0.831	1.035	0.4	-0.991	0.907	0.3
Pulse rate (beats/min)	0.018	0.033	0.6	-0.005	0.029	0.9
Constant term	9.318			-3.704		

SBP difference: systolic blood pressure difference between Omron HEM403C and random zero meter, DBP = Diastolic blood pressure difference between Omron HEM403C and random zero meter, s.e.: standard error, SBP level: mean systolic blood pressure of both the meters, DBP level: mean diastolic blood pressure of both the meters

The standard deviations of the systolic differences between the first and second measurement in the 202 subjects were 9.8 and 11.5 mmHg for the Omron HEM403C and the random zero meter, respectively. The standard deviations of the diastolic differences were 7.6 and 8.5 mmHg, respectively. These differences were statistically significant, which means that the reproducibility of the Omron HEM403C was better than that of the random zero meter.

Discussion

Assessment of the accuracy of blood pressure measurement devices is a rather complicated and time consuming activity. However, in view of the potential implications of a diagnosis of high blood pressure, it is clear that no device should be used without being adequately tested. Two different protocols exist that provide comprehensive guidelines for the com-

plete procedure of accuracy testing. *The National Standard for Electronic or Automated Sphygmomanometers* was published in 1987 by the American Association for the Advancement of Medical Instrumentation and the protocol from the British Hypertension Society was published three years later.[5,6] Updates of both the British and the American protocol appeared in 1993 but were not available at the time of data collection of the present study.[7,8] The best way to allow comparison between test reports of different devices is by adhering closely to these protocols.

In our study among 212 subjects, the Omron HEM403C measured the SBP on average 1 mmHg and the DBP 4 mmHg higher than the random zero mercury meter. The reproducibility of the Omron HEM403C was better than that of the random zero meter. The agreement between both meters was marginally acceptable, according to the requirements of the BHS and the AAMI.

Several limitations of our study should be mentioned. We have chosen the Hawksley random zero meter as the reference meter because it has been recognized for many years as the standard for 'bias free' sphygmomanometric blood pressure measuring. It has been used in numerous epidemiological studies. In accuracy studies, other investigators generally used standard sphygmomanometers instead of a random zero meter. It has been reported that the random zero meter systematically underestimates SBP as well as DBP by 4 and 7 mmHg, respectively, and produces less reproducible results compared with the standard mercury manometers.[9] If one would adjusted our results for those random zero meter inaccuracies, the overestimations of the Omron HEM403C that we have found would be reversed to underestimations of 3 mmHg for both SBP and DBP. Furthermore, one should recognize that the individual variation of the level of agreement in this study is negatively influenced by the lower reproducibility of the random zero meter in compared with a standard mercury meter. If these factors are taken into account, this would lead to a better classification of the Omron HEM403C blood pressure device in both the British and American classification systems. The subject selection in this study did not completely satisfy the distribution of ages and blood pressures requested by the BHS or AAMI protocol; especially, patients with a SBP over 200 mmHg were not available in our population. This leads to a restriction of our conclusions to patients with a SBP < 200 mmHg.

In every blood pressure measurement configuration for accuracy testing purposes, with meters connected to one cuff, the T-connected air tubes of the oscillometric device and the random zero manometer hold a larger air volume than the automatic oscillometer in a stand-alone situation. To

exclude the possibility that the larger air volume affects the accuracy of the oscillometric device we performed ten measurements in one subject with the experimental measurement configuration on one arm and a stand-alone oscillometric device on the other arm. Blood pressure was measured simultaneously on both arms of the subject with an adjustment for left to right arm blood pressure difference. We found no influence of the slightly enhanced volume of the air tubes in the measurement configuration that we used on the measurement accuracy of the Omron HEM403C.

The influence of blood pressure level on the accuracy of the measurements has been reported earlier.[10] This phenomenon can only be explained by a deficiency in the software protocol of the oscillometric device. In principle, the software protocols that are used in oscillometric devices should be able to adjust for this kind of systematic inaccuracy that is linearly dependent of the blood pressure level. Our results show a mean underestimation of the SBP of 1 mmHg at a SBP level of 160 mmHg and a mean overestimation of 5 mmHg at a DBP level of 95 mmHg. These blood pressure levels are crucial for the decision about the treatment of patients. In view of that the systolic inaccuracy that we found is acceptable, but the diastolic inaccuracy is quite large.

To our knowledge, only one earlier accuracy study of the Omron HEM403C was published.[11] This study showed a mean systolic underestimation of 5 (sd 9) mmHg and a correct diastolic estimation (sd 5) of the Omron HEM403C compared with a standard mercury manometer; the device was classified as B/C according to the BHS grading criteria and it fulfilled the AAMI criteria for DBP and failed these criteria for SBP. This earlier study, however, may be criticized because of its small number of subjects (n=17) and the methods applied to assess agreement.

Only few oscillometric blood pressure meters receive 'A or B' grades in the BHS classification system. In comparison to other recently tested automatic blood pressure devices the Omron HEM403C is reasonably accurate.[12] One should keep in mind that we used a random zero meter as the reference meter, which certainly caused some overestimation of the inaccuracy of the Omron HEM403C.

The general performance of the device was good; its construction was solid and working with it was practically without hindrances. The patients did not encounter much discomfort during the measurements. The number of invalid readings by external disturbing factors was small and no technical failures occurred during the test period.

The technicians of the manufacturing companies potentially may change the software protocols of electronic devices at any moment during the production. For this reason it is necessary to assess the accuracy of every new series of electronic devices that is produced. Even then one cannot completely trust the uniformity of the cut-off points within one series of a meter of the same type. These uncertainties are a consequence of the 'black box' character of automatic devices and must be considered a disadvantage of automatic devices that does not apply to mercury manometers. Mercury meters do not have factory-set, software determined, cut-off points.

In the cases that patients use automatic devices for self-measurements at home, we agree with the remark of James et al, that it would be preferable to test the agreement of a blood pressure device every time it is fitted to a particular patient.[13] This can easily be done by performing some, for example 10, blood pressure measurements with the automatic device and a reference mercury meter, both connected to one cuff that is fitted around the arm of the patient. The device should at least achieve C grades in the BHS grading system. This implies that >45% of the measured differences should not outreach 5 mmHg, >75% should not outreach 10 mmHg and >90% should not outreach 15 mmHg. The result of such a mini test is of course only applicable to the particular patient-meter combination that was tested, and the results hold only at blood pressure levels that approximate the level during the mini-test. The requirements for such a mini test are 10 cm of air tube, a T- or Y-connector and 10 min of time investment of the doctor.

We conclude that the Omron HEM403C is accurate enough to be recommended for those clinical and research purposes that require automatic measurements.

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Validation of blood pressure measuring devices

After publication of our results on the accuracy of the automatic oscillometric blood pressure measuring device Omron HEM403C in the Journal of Human Hypertension, the authors of the British Hypertension Society (BHS) Protocol for the evaluation of blood pressure measuring devices, O'Brien and Atkins, wrote a critical letter to the editor. This letter was published, together with a comment of our group in one of the later issues of the Journal of Human Hypertension. The letter of O'Brien and Atkins and our reply are reproduced in full underneath.

Accuracy of an oscillometric automatic blood pressure device: the Omron HEM403C (letter of O'Brien et al. J Hum Hypertens 1995;9: 781-2)

Walma and colleagues, having performed a validation study on the Omron HEM403C, conclude: 'According to the criteria of the British Hypertension Society (BHS) the Omron HEM403C is accurate enough to be recommended for those clinical and research purposes that are in need of automatic measurements'.[1] This conclusion is invalid for a number of reasons, foremost among which is the fact that, contrary to what the authors state, the OmronHEM403C does not achieve the acceptable levels of accuracy now recommended in the revised BHS protocol,[2] nor does it fulfil the criteria for accuracy of the Association for the Advancement of Medical Instrumentation (AAMI).[3,4] However, if the results were valid, critical discussion would only need to focus on the topic of what constitutes an acceptable level of accuracy in clinical practice, but these results are not valid because the study did not adhere to the requirements of the first BHS protocol,[5] which the authors claim to have followed, and this raises other important issues.

Firstly, the failure to comply with the protocol requirements merits consideration: the BHS protocol stipulates that 85 subjects must be recruited carefully to provide clearly defined levels of blood pressure (BP) that will test the device across the pressure range seen in clinical practice.[5] In the Walma study, subjects were recruited from a population that could not have yielded the BP range demanded by the protocol; and most BPs were in the range 105/60 to 150/95 mm Hg, namely the normotensive range. Serious though this may be, the main protocol violation was substitution of the Hawksley random zero sphygmomanometer recommended in all protocols.[2-5] This was done with the laudable intention of reducing observer bias but the Hawksley, as the authors acknowledge, has been shown to underestimate BP[6] and the effects this may have on validation studies has been discussed in detail by us.[7] In a further study we combined a database of paired BP measurements using the Hawksley random

zero sphygmomanometer and a standard mercury sphygmomanometer and a database of paired measurements made on a SpaceLabs 90202 ambulatory recorder to determine how the SpaceLabs 90202 would have been fared if it had been assessed against the Hawksley sphygmomanometer instead of a standard sphygmomanometer. The effect of replacing the standard instrument with a Hawksley sphygmomanometer was to reverse the direction of the average measurement error found and to demote the SpaceLabs 90202 from BHS grades C and B, for systolic and diastolic accuracy, respectively, to grade D – overall the lowest rating of accuracy in the BHS grading system.[8] Therefore, the conclusions of validation studies using the Hawksley sphygmomanometer as to the accuracy or inaccuracy of the device being validated must be regarded at very least as being questionable. Moreover, it is quite unacceptable to apply an correction factor, as the authors do, because the error in the Hawksley is not systematic.

However untenable all this may be in terms of adhering to protocol requirements, the authors then compound their disregard for procedure by publishing their erroneously derived results as satisfying protocol requirements and therefore permitting the recommendation that the device is acceptable for clinical use. The Omron HEM403C achieved a C/C grading according to the BHS protocol and failed the AAMI criteria of accuracy for systolic pressure while barely satisfying the accuracy criteria for diastolic pressure which should lead to the recommendation that the device not be used in clinical practice.

This is not, however, the end of the debacle. The Omron HEM403C may well be an accurate device and experience with another closely related model would suggest that this might well be so if the algorithms in the two models are similar.[9] But, on the basis of this study, no statement as to the accuracy or inaccuracy of the Omron HEM403C is possible.

Finally, a concluding statement may be devoted to expressing a degree of scientific disquiet. The British Hypertension Society has taken the trouble to constitute a Working Party which published a protocol for validation of BP measuring devices in 1990[5] which was revised in 1993.[2] The Association for the Advancement of Medical Instrumentation likewise published its protocol in 1986[3] and this was revised in 1993.[4] That it has been necessary to write six letters in the past year to alert researchers and potential purchasers of BP measuring devices that papers published in peer reviewed journals by failing to comply with protocol requirements were, therefore, questionable or invalid, is a cause for concern, particularly as such letters inevitably fail to influence the statement of the original paper.[10-15]

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Accuracy of an oscillometric automatic blood pressure device: the Omron HEM403C (reply of Walma et al. J H Hum Hypertens 1995;9: 781-2)

We thank Drs O'Brien and Atkins, both recognized authorities in the field of validation of blood pressure devices, for taking the trouble of criticizing our publication: 'Accuracy of an oscillometric automatic blood pressure device: the Omron HEM403C'.

Our conclusion that the Omron HEM 403C is accurate enough to be recommended for those clinical and research purposes that are in need of automatic measurements does not meet with the approval of O'Brien and Atkins. Their arguments, however, are not very convincing.

In our eyes, it is not correct to apply the grading criteria of the 1993 version of the protocol of the British Hypertension Society (BHS) to a study conducted according to the 1990 version of the BHS protocol, as O'Brien and Atkins suggest. Procedures and grading criteria were significantly altered, for example the method of simultaneous same-arm measurements was abandoned. Importantly, the revised 1993 protocol came available after the completion of our data collection and the 1990 protocol does not provide clinical inferences of the A,B,C and D grading system. Until recently, devices with A grades did not exist at all, B grades were rare and D grades were very frequently encountered in validation studies of automatic blood pressure devices. Our conclusion that a C graded device was acceptable seems adequate. The Omron HEM403C satisfied the criteria of the American Association for the Advancement of Medical Instrumentation (AAMI) for diastolic blood pressure (DBP) values and marginally failed to satisfy these criteria for systolic blood pressure (SBP).

If we would have used a standard mercury sphygmomanometer instead of the Hawksley random zero meter, as advised in the AAMI protocol, the Omron HEM403C would certainly have satisfied the AAMI criteria for SBP, as we will explain.

The subject selection in our study did not completely satisfy the distribution of BP levels as requested by the BHS protocol. Patients with SBP levels > 180 mmHg and DBPs > 100 mmHg were not sufficiently available in our population. To enable assessment of the accuracy of the device at these high BP levels we explicitly presented the relation between BP level and the accuracy of the Omron device. The substantially larger number of patients in our study than requested in the BHS protocol made this feasible. Crude regression lines were drawn in Bland and Altman plots and the results of a multiple linear regression analysis were presented in a separate Table. Indeed, the inaccuracy of the SBP of the test device increased at very low and very high BP levels. Consequently, we clearly mentioned in the discussion paragraph that our conclusions about the validity of the test device are restricted to patients with a SBP < 200 mmHg.

Another point of criticism was the use of the Hawksley random zero meter (RZ meter) as the reference device in our study. The BHS protocols prescribe the use of a standard mercury sphygmomanometer. The RZ meter is technically nothing else than an open mercury manometer and therefore, if properly used, it should produce results identical to any standard mercury manometer. The randomly variable zero point of the RZ meter has to be recorded immediately after each BP measurement by the observer and too rapid recording of the zero point level can introduce bias because of the slow return of the mercury column to the zero point. Also some expectation bias may still exist at those readings that were highly elevated by the zero-muddler. These two biases work in the same direction.[2,3,4] The use of standard sphygmomanometers, however, induces more expectation bias and terminal digit preference. Duplicate and triplicate measurements, as dictated in the 1990 BHS protocol, are most susceptible for expectation bias. This artificially diminishes the variance of the differences between the test device and the reference device. On the other hand, the variance of the RZ measurements is increased as RZ measurements are the result of two measurements, namely the BP value and the zero point value. All this explains why the Omron HEM403C would certainly have satisfied the AAMI criteria if a standard mercury sphygmomanometer would have been used.

The O'Brien group published data on the magnitude of the differences between RZ meters and standard sphygmomanometers[5,6] and we have taken these data into account in the inference of the C grade of the

Omron HEM403C to the acceptability for clinical practice and research purposes. In contrast to the statement of O'Brien and Atkins we did not use a correction factor to adjust for these differences.

Finally, a concluding statement may be devoted to the exceptional complexity of the BHS protocols and the unrestrained criticism of O'Brien and Atkins, both members of the Working Party on Blood Pressure Measurements of the British Hypertension Society, on investigators who permit themselves some deviations from the BHS protocols. The simple fact that O'Brien et al. felt obliged to write six letters to various peer reviewed journals in the past year about protocol deviations illustrates the difficulties in adhering precisely to the BHS protocols. We do underwrite the usefulness of uniform and carefully designed validation procedures for BP devices, but extreme complexity of protocols, rapid revision and venomous criticism by the members of the working party of researchers deviating from the protocol, discourages other groups to follow these protocols. Until now, the majority of validation studies of BP devices came from the Dublin laboratory, but from a scientific point of view it is desirable that this work can be reproduced by other laboratories. It is inevitable that protocolized validation studies of BP devices are more or less cooking-book exercises, but some deviations and the addition of supplementary flavours by researchers should be tolerated.

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6 Withdrawing long-term diuretic therapy in the elderly: a study in general practice in the Netherlands.

Introduction

Polypharmacy and long-term drug use increase with age, as do the number of adverse reactions due to side effects and pharmacological interactions.[1,2,3,4,5,6] Diuretics rank high on lists of most prescribed drugs for the elderly and are frequently responsible for adverse side effects.[7,8,9,10] Recent surveys demonstrated that approximately 20% of the elderly population uses diuretics.[11,12,13]

The most common indications for prescribing diuretics are hypertension, congestive heart failure, and orthostatic ankle edema caused by insufficiency of the venous system of the legs.[14] Edema caused by renal or hepatic diseases, hypercalciuria, and glaucoma are infrequent indications for diuretic therapy.

Hospital based studies have shown that, under certain circumstances, diuretics can be stopped successfully.[15,16,17,18,19,20] In these studies the proportion of patients that were successfully withdrawn from diuretic therapy ranged from 71% to 89%. There are few similar studies in outpatient general practice settings.[21] Patients in hospital geriatric wards or nursing homes have special characteristics, and conclusions drawn from research on these patients do not necessarily apply to the elderly diuretic-user in general practice. Further, the monitoring possibilities during drug withdrawal are less optimal in general practice than in the hospital, where more clinical tests to monitor the condition of the patient are readily available. Therefore, other inclusion and monitoring procedures are needed in the general practice setting to limit the risk of developing heart failure or severe hypertension after withdrawal of the diuretic. To protect patient safety, we designed inclusion/exclusion criteria and monitoring procedures applicable to general practice.

We conducted a general practice study to assess what proportion of long-term diuretic-users could discontinue their diuretic therapy without negative clinical consequences. Also evaluated were the influence of diuretic withdrawal on blood pressure, heart failure score, peripheral edema, body weight and subjective complaints of the patient. The study reported

here is a pilot study for a large multicentered randomized controlled trial of diuretic withdrawal in general practice.

Methods

Subjects for this pilot study were drawn from one general practice of approximately 2,000 patients in Schoonhoven, a small town (population 11,000) located 20 miles east of Rotterdam in The Netherlands. We reviewed the medical records of all patients in the practice who were aged 65 or older (N=280) to identify those who were currently using diuretics, and had been using them for six months or longer. We identified 52 such patients, and then excluded those who met one or more of the following criteria.

First, we excluded patients who had hypertension for less than one year, even if it was treated and well-controlled. Second, we excluded those with unsatisfactorily regulated hypertension, defined as more than one measurement over 165/95 mmHg, either recorded in the medical file during the last year, or as determined at baseline measurements for this study. The mean of two consecutive blood pressure recordings was taken at baseline and all follow-up visits. Blood pressure was measured in sitting position using an automated digital device, type: Yamasu YSE 320, which had been shown to be reliable and accurate.[22] Korotkoff V sounds determined the diastolic cut-off level. Third, we excluded patients who had a documented medical history of one or more episodes of acute left-sided congestive heart failure, occurring at any time in the past, or any symptoms of congestive heart failure occurring within the preceding three months. To identify patients with a history or symptoms of heart failure, all files were examined thoroughly by two general practitioners. Symptoms of heart failure were defined as increasing dyspnea or ankle edema. Fourth, we excluded patients with heart failure scores over three points (Table 6.1). We used a heart failure score list based on anamnesis and physical examination, adapted from a scoring system reported by Gheorghiade et al.[23]

Fifth, we excluded patients with edema caused by renal or hepatic disease, hypercalciuria or glaucoma. Finally, we excluded patients who, according to the general practitioner, were unable to adequately answer simple questions about his/her health status.

Table 6.1

Heart failure score	*points*
– Paroxysmal nocturnal dyspnea (in preceding three months)	3
– Dyspnea on exertion (in preceding three months)	2
– Elevated jugular venous pressure (>R-4)	2
– Tachycardia (> 100/min)	1
– Hepatojugular reflux	1
– Lower pulmonary crepitations	1
– S3 galop-rhythm	1
– Two-sided pitting edema of the legs	1
– Hepatomegaly	1

The heart failure score varies from 0-13 points.

This heart failure score is a modification from a similar list developed by Gheorghiade and Beller.[23] It was developed as a quantification of the clinical symptoms and signs of congestive heart failure that could be obtained at home with the patient. The weights of the items are based on clinical judgement

Basically, these exclusions were chosen to avoid withdrawing diuretics from patients who had clear indications for diuretic treatment and to thereby reduce the risk of inducing acute left-sided heart failure upon diuretic withdrawal.

The protocol of the study was approved by the medical ethics committee of the Academic Hospital Dijkzigt in Rotterdam. The patients were visited at home by their family doctor to explain the purposes and the procedures of the study and to ask for their willingness to cooperate. All but one patient cooperated and signed written informed consents.

Diuretic withdrawal

Diuretics were withdrawn according to the following schedule. Thiazides and furosemide in daily dosages of <40 mgs were stopped at once, while daily dosages of 40 mgs of furosemide were halved during one week before complete withdrawal. All patients were visited eight times at home by their family physician: one week and one day before withdrawal, and two days, one week, two weeks, one month, three months, and six months after withdrawal of diuretics. Heart failure scores were recorded and blood pressures were measured as described above. Body weight was measured with a digital balance (Tefal type, on which calibration was performed every three months to a variability of less than 100 grams). Ankle edema was quantified by measuring the ankle circum-

ference with a measuring tape just above the malleoli at the slimmest point. The reproducibility of this method was determined by measurements (N=93) at the same ankle of the same person at three different days. A standard deviation of 0.07 cm with a mean circumference of 21.5 cm was found.

During the six-month follow-up period, diuretics were resumed if the subject developed:
(a) Heart failure score >4, (b) Systolic blood pressure >180 mmHg and/or diastolic blood pressure >95 mmHg at more than one occasion, or (c) Upon request of the subject.

The Student-t test for paired observations and the Wilcoxon rank-sign test were used to evaluate the clinical consequences of withdrawing diuretic therapy.

Results

Of all 280 patients of 65 years or older in this one general practice, 20% of the women and 16% of the men had been using diuretics for six months or longer, for a total of 52 subjects (19%). The prevalence of diuretic therapy increased with age from 17% in women aged 65-69 to 46% in women of 85 years or older. The corresponding percentages in men were 3% and 73%, respectively. The median duration of diuretic use was two years and three months. Ten percent of the patients had been on diuretic therapy for a period of 10 years or longer.

Initial indications for diuretic therapy in the subjects who participated in this study were congestive heart failure (17), hypertension (21), ankle edema (six), and hypercalciuria (one). In 13 patients no indication could be found. The prescribing physician was the general practitioner in 35 cases and a specialist in 16 cases; in one case the prescribing physician could not be determined.

Of the 52 patients on long-term diuretic therapy, 11 patients died before the actual withdrawal of their diuretics; in three patients, the diuretic had already been withdrawn. We excluded 22 patients from the remaining group of 38 users because of hypertension in the preceding year (12), symptoms of overt congestive heart failure in the preceding 3 months (five), mental deterioration (four), and hypercalciuria (one). In addition, one patient refused to participate in the study.

Table 6.2
Effect of withdrawal of diuretics in 15 patients aged 65 and older in general practice

#	M/F	Age	Diuretic	Dose (mgs per day)	Start indication	Duration of use (m)	Resumed after	Reason to resume	Before withdrawal*					After withdrawal$				
									HF-score	Body weight	SBP (mmHg)	DBP (mmHg)	ankle circum (mm)	HF-score	Body weight	SBP (mmHg)	DBP (mmHg)	ankle circum (mm)
Successful withdrawn from diuretic treatment																		
1	F	74	fu	40	unknown	30			2	66	115	67	279	4	67	133	71	285
2	M	89	et	4/50	HF	23			2	54	131	80	191	0	55	123	68	194
3	F	89	fu	40	HF	67			0	46	134	61	210	0	47	142	62	217
4	F	87	fu	40	HF	87			3	86	143	65	240	2	87	145	66	245
5	M	67	et	4/50	HT	94			0	69	159	81	217	2	70	133	78	223
6	F	78	fu/tri	20/50	HF	>168			1	74	129	91	264	4	76	146	88	271
Diuretic treatment resumed within six months																		
7		90	fu	20	oedema	95	5.5m	HF	2	61	139	82	220	9	62	149	82	220
8	F	67	chl	25	HT	40	2m	HT	1	61	153	88	246	3	62	171	89	259
9	M	79	fu/et	40/4/50	unknown	32	2d	HT	1	62	165	63	238	3	65	202	65	240
10	F	73	fu	40	HF/HT	21	<1d@	HT	3	74	167	87	208	3	74	184	90	215
11	M	74	fu	40	HF	56	1w	Asthma	2	70	178	55	213	7	70	170	40	213
12	F	82	fu	20	HF	29	2w	Oedema	3	71	166	75	239	2	74	163	71	253
13	F	84	fu	40	HF	45	4m	Oedema	2	82	148	70	235	2	85	154	81	243
14	F	71	fu	11.4	unknown	37	2m	Subj.c.	0	83	150	74	225	2	82	157	69	227
15	F	69	chl	25	unknown	51	2w	Subj.c.	2	81	169	69	217	3	82	174	74	220

* All values are the mean of two duplicate measurements per patient at week –1 and day –1, $ All values are the mean of all measurements after withdrawal of diuretic treatment, ranging from 1 duplicate measurement at day +2 in patients who resumed early, to six duplicate measurements in patients who were successfully withdrawn from diuretics. @ resumal uring dose reduction week

F = Female, M = Male, fu = furosemide, et = epitizide/triamterene 4/50 mg, tri = triamterene, chl = chlortalidone, HF = heart failure, HT = hypertension, m = months, d = days, w = weeks, , subj.c. = subjective complaints

After excluding ineligible subjects, the pilot study of diuretic withdrawal involved 15 patients, 11 women and four men. The mean age was 78 (range: 67 to 90). The mean duration of diuretic therapy in this group was five years and indications for treatment were: heart failure (seven), hypertension (two), heart failure plus hypertension (one), ankle edema (one) and unknown (four). More detailed information about those patients is summarized in Table 6.2.

Six months after the withdrawal of diuretic therapy six of 15 patients were still not taking diuretics. In nine patients diuretic therapy was resumed. The reasons for resuming diuretic therapy were hypertension (three), symptoms of congestive heart failure (one), or asthma (one), subjective complaints of the patient (two,) and ankle edema (two). The one patient in whom congestive heart failure developed experienced the problem following surgical therapy of a hip fracture that occurred five and a half months after withdrawal of the diuretics. One patient developed a severe, persistent episode of bronchial asthma. The sudden occurrence of bronchial asthma in this patient after the withdrawal of diuretics prompted us to resume diuretic therapy and even to double the dose. On recurrence, this bronchial asthma was only manageable by adding high doses of sodium cromoglycate to the already extensive pulmonary medication of this patient. In two cases, diuretics were restarted following the patient's request based on subjective complaints such as atypical chest pain, dizziness, increased fatigue, and shortness of breath during exercise. Finally, troublesome ankle edema was the reason for resuming diuretics in another two patients.

Withdrawal of diuretics influenced blood pressure, heart failure scores, body weight, and ankle edema. Systolic blood pressure increased on average 6 mmHg ($0.05<p<0.1$), but no changes in diastolic blood pressure were found. The heart failure score rose 1.5 points ($0.01<p<0.05$), attributable to an increased prevalence of dyspnea during exercise. The withdrawal of diuretics caused a mean rise of body weight of 1.2 kgs ($p<0.001$), predominantly in the first two weeks after withdrawal. Ankle circumference increased 0.6 cm ($p< 0.001$).

Discussion

In our pilot study for a randomised clinical trial in general practice, six out of 15 patients (40%) were successfully withdrawn from their diuretic therapy. This proportion is lower than has been reported in the literature. Hospital-based studies reported that 71 to 89% of patients could be successfully withdrawn from diuretic therapy.[16,18,19,20] A recent Norwegian

study in general practice showed successful withdrawal in 18 of 33 elderly patients (55%).[21] The difference between our results and others may be explained partly by differences in inclusion and exclusion criteria and partly by the small sample size in our study. Differences between hospital-based patient populations and a general practice population may account for the different results as well. Finally, the less optimal monitoring conditions in the general practice setting, in comparison to hospital-based studies might have caused us to adopt a low threshold for restarting diuretics. The fact that diuretics were restarted in four of 9 cases for reasons other than hypertension or heart failure supports this notion.

Eleven of our 52 patients died before we even started the withdrawal attempt.
This high death rate among diuretic-users reflected the poor prognosis of the very old with cardiovascular disease among our patients (mean age of the deceased patients was 85 years). Note also that there was a time-delay of approximately one year between the identification of our study population and the actual start of the withdrawal study.

The mean increase in systolic blood pressure following diuretic withdrawal was 6 mmHg, which was in accordance with other reports.[16,19] The rise in the heart failure score is partly explained by an increase in shortness of breath in two patients, one with congestive heart failure after surgery for a hip fracture and another with bronchial asthma. Because of the small number of patients in our pilot study, changes in heart failure score of even a few subjects affected the overall group's mean heart failure score. An increase in body weight, almost certainly caused by water and salt retention, occurred in our subjects, mostly in the first two weeks after withdrawal. This emphasizes the need for careful monitoring for congestive heart failure signs during the early period, following the withdrawal, although alertness seems warranted beyond that period. Thorough instruction of the patient about changes in symptoms of shortness of breath is mandatory. Changes in body weight reported in the literature are of a smaller magnitude than in our study, which could be a reflection of the susceptibility for heart failure of our population.[17,18,19] A mean increase of the ankle circumference of 0.6 cm is equivalent to an increase of the skin thickness of 0.1 cms. Such a slight increase may be noted by the patient but will generally not be perceived as troublesome. Both an increase and a decrease of ankle edema after withdrawal of diuretics have been reported by others.[16,18,20]

A limitation of this study is the absence of a control group. Thus, changes after withdrawal of diuretics may also have been caused by factors other than the actual withdrawal of the drug. A randomized controlled trial

would be the method of first choice to exclude this possibility. Secondly, the sample size in our study was small, limiting conclusions that can be drawn from our data. As a result of this pilot study, however, we are currently conducting a multicenter randomized controlled trial of diuretic withdrawal in 200 patients in general practice.

We conclude that long-term diuretic medication in elderly patients in general practice may be safely withdrawn from up to 40% of patients without recent symptoms of hypertension or congestive heart failure. However, careful medical monitoring after diuretic withdrawal is mandatory. A regular evaluation by general practitioners of the need for long-term diuretic therapy may be useful in reducing polypharmacy and overmedication.

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7 Withdrawal of long-term diuretic medication in elderly patients: a double-blind randomized trial.

Introduction

Diuretics are among the most frequently prescribed drugs in westernized societies with approximately 20% of all elderly patients using diuretics as long-term therapy.[1,2,3,4,5] Approximately one third of these patients use diuretics because of heart failure, one third because of hypertension and one third because of the much weaker indication non-cardiac ankle oedema.[5]

Unnecessary use of diuretics should be minimized because of potentially serious side effects such as hypokalemia, hyponatriemia and dehydration.[6,7,8,9] Based on results of randomized trials, several national guidelines for treatment of hypertension recommend attempts of dose reduction and eventually cessation of antihypertensive therapy if blood pressure levels remain acceptable during one to two years of treatment.[10,11,12,13] The possibility of withdrawing diuretic therapy in heart failure patients has never been studied in a randomized trial and recommendations about dose reductions or cessation of diuretic therapy are currently not available.

Primary care physicians account for the majority of diuretic prescriptions.[2,5] We therefore performed a double-blind randomized trial among elderly patients in general practice to assess what proportion of elderly patients may be successfully withdrawn from diuretic therapy.

Methods

Patients

Patients of 65 years or older who had been on diuretic treatment for at least 6 months, and were without overt heart failure or hypertension were eligible for the trial. By scanning the pharmacy registers of eight general practices a total of 470 patients receiving long-term diuretic therapy was identified, of whom 268 were excluded because of the following reasons: (1) a history of acute heart failure, defined as hospitalization or requirement of intravenous diuretic therapy (n=27); (2) symptoms of heart failure during the last 3 months (n=21); (3) manifest heart failure, defined as

a heart failure score (see below) exceeding 4 points (n=39); (4) present use of furosemide dosages exceeding 80 mgs/day (n=26); (5) mean of three blood pressure values (two measured at successive home visits and one obtained from the medical file) > 180/100 mmHg (n=21); (6) hypercalciuria, nephrotic syndrome and glaucoma as indication for diuretic therapy (n=2); (7) use of fixed combinations of diuretics with beta-blockers or ACE-inhibitors (n=25); (8) combination therapy of beta-blockers, diuretics and vasodilators for hypertension (n=2); (9) use of a diuretic for which no placebo was available (n=40); and (10) non-compliance during the run-in phase (n=1). In addition, 57 patients or their general practitioners refused to cooperate and seven eligible patients could not be enroled in the trial because of logistic reasons. Each general practitioner filled out a questionnaire to assess the current indications for diuretic treatment in the patients included in the trial.

Study protocol

During the study period, participants were visited eight times at their homes by one of two study physicians (EPW, CvD). The run-in phase of 4 weeks included two home visits to collect the baseline data, to monitor the run-in phase and to perform the randomization. At the first home visit all diuretic medication was handed over to the research doctor and replaced by active run-in medication of the corresponding diuretic. At the second home visit, at the end of the run-in phase, patients were randomly assigned to placebo (the withdrawal group) or to continuation of diuretic therapy (the control group), after stratification by age (65 to 79 and ≥80 years) and type of diuretic. Matching placebo was available for the five diuretics or fixed diuretic combinations most often prescribed in our region: furosemide, chlorthalidone, hydrochlorothiazide/triamterene, epitizide/triamterene and triamterene, covering 90% of all diuretic use. Patients with furosemide dosages of 40 or 80 mgs daily went through a dose-halving regimen of 1 and 2 weeks, respectively, to prevent severe rebound effects. Dose-halving was started immediately after randomization and was performed double-blind.

The six follow-up visits took place 2 days, 1 and 2 weeks and 1, 3 and 6 months after randomization. Heart failure score, body weight, ankle oedema and blood pressure were assessed at baseline and at all follow-up visits. Heart failure symptoms were quantified by means of a standardized scoring list. This is a modification of the list used by Gheorghiade et al., compromising symptoms and signs that may be collected at the patient's home.[14] These included: paroxysmal nocturnal dyspnea in the preceding week (3 points); dyspnea on exertion in the preceding week (2 points); distention of the jugular vein above R –4 cm (2 points); heart rate > 100 beats/min (1 point); presence of hepatojugular reflux (1 point); lower pul-

monary crepitations (1 point); S3 gallop-rhythm (1 point); two-sided pitting ankle oedema (1 point) and hepatomegaly (1 point). This symptom score list appeared a valid instrument in previous studies.[5, 15]

Dyspnea on exertion was assessed at baseline and 1 and 6 months after randomization by means of a questionnaire, and by subtracting respiration frequency at rest from the frequency recorded immediately after the patient redressed following the physical examination. Body weight was measured with a digital balance and calibration was performed every 3 months. Ankle edema was quantified by measuring the smallest ankle circumference with a measuring tape. During the study, duplicate blood pressure readings were taken with an Omron HEM403C oscillometric, automatic device with the patient in a sitting position.[16] The arm with the highest blood pressure level was determined at the first session and taken throughout the study for further measurements. An ECG was recorded at baseline and one month after randomization. Blood samples were taken at baseline and at 6 months after randomization. Serum sodium, potassium, glucose, uric acid, cholesterol, HDL-cholesterol and creatinine levels were determined using routine procedures in the regional clinical laboratory. Drug compliance was checked by counting tablets at every follow-up contact and by assessment of serum diuretic levels in blood samples at the start and the end of the study. High pressure liquid chromatography and UV fluorescence methods were applied to determine serum levels of chlorthalidone, triamterene and furosemide. The blinding procedure of this study was tested at 1 month after randomization by asking both the patient and the trial doctors their opinion about the content of the trial medication: placebo or verum.

The protocol was approved by the Medical Ethics Committee of Erasmus University/Academic Hospital Dijkzigt Rotterdam, and written informed consent was obtained from all patients.

Outcome variables

The primary outcome variable of the study was successful withdrawal from diuretic therapy. Patients who still were on blinded study medication at the end of the 6 months follow-up period were considered successfully withdrawn. Those patients who did meet one of the predefined criteria for requiring diuretic therapy within the 6 months follow-up period were considered to be unsuccessfully withdrawn. Criteria for requiring diuretic therapy were: (1) heart failure score exceeding 4 points, and (2) mean of three duplicate systolic or diastolic blood pressure measurements at separate occasions >180 or >100 mmHg, respectively. Further, patients in whom diuretic therapy was reinitiated by their physician for other reasons, e.g. increase in ankle circumference or subjective symptoms,

were considered to be unsuccessfully withdrawn. An additional combined outcome was constructed as 'any increase in heart failure score and/or systolic blood pressure level exceeding 160 mmHg or diastolic blood pressure level exceeding 90 mmHg'.

Table 7.1
Baseline characteristics of the participants

Characteristic	Withdrawal group (n=102)	Control group (n=100)
Age (years)	76 ± 1	76 ± 1
Women (%)	79	70
Current indication for diuretic therapy (%)		
Heart failure	45	38
Hypertension	41	46
Oedema	13	15
Other/Unknown	1	1
Heart Failure score (0 to 13)	1.4 ± 0.1	1.5 ± 0.1
NYHA classification of all patients (%)		
1 (no limitation of physical activity)	80	77
2 (some limitation of physical activity)	16	19
3 (marked limitation of physical activity)	3	4
4 (severe limitation of physical activity)	1	0
Increase of respiration rate after redressing (#/minute) (n=62, 67)	3.4 ± 0.5	4.1 ± 0.6
Systolic blood pressure (mmHg)	147 ± 2	147 ± 2
Diastolic blood pressure (mmHg)	81 ± 1	81 ± 1
Body weight (kg)	76 ± 1.2	75 ± 1.1
Ankle circumference (cm)	22.6 ± 0.2	22.3 ± 0.2
Irregular pulse (%)	26	28
Previous myocardial infarction (%)	11	14
Diuretic therapy (%)		
Furosemide (including combinations with other diuretics)	30	33
Thiazide (including combinations with triamterene)	65	65
Triamterene mono-therapy	5	2
Diuretic dose (%)		
< 1 DDD	27	35
= 1 DDD	66	55
> 1 DDD	7	10
Duration of diuretic therapy (years)	7.2 ± 0.5	7.6 ± 0.6

Characteristic	Withdrawal group (n=102)	Control group (n=100)
Co-medication (%)		
Digoxin	9	12
Beta-blocker	27	23
ACE-inhibitor	10	8
Calcium antagonist	13	16
Nitrates (daily use)	13	9
COPD medication	13	11
ECG (%)		
Left ventricular hypertrophy	3	1
Atrial fibrillation	5	5
Infarction	14	15
Ventricular premature complexes	6	9
Blood/serum parameters (mmol/l)		
Sodium (n=93, 99)	141 ± 0.3	141 ± 0.3
Potassium (n=93, 98)	4.1 ± 0.04	4.1 ± 0.04
Glucose (n=93, 99)	5.1 ± 0.3	4.9 ± 0.2
Uric acid (n=93, 99)	0.38 ± 0.01	0.37 ± 0.01
Cholesterol (n=93, 99)	6.4 ± 0.1	6.3 ± 0.1
HDL-cholesterol (n=93, 99)	1.31 ± 0.04	1.27 ± 0.04
Creatinine (micromol/l) (n=93, 98)	97 ± 2.8	95 ± 2.4

DDD = Defined Daily Dose. Values are means ±SE, or proportions

Secondary outcome variables were changes in heart failure symptoms, systolic and diastolic blood pressure level, increase in respiration rate after exercise, ankle circumference and body weight, and alterations in serum lipid, electrolyte, creatinine, uric acid and blood glucose levels. All outcomes were assessed in a double-blind way in all but six patients, whose diuretic therapy was restarted by their treating physician and the measurements in these patients were accomplished after breaking the code of the trial medication.

Statistical analysis

The frequency of fulfilling one of the criteria for requiring diuretic treatment, and the incidence of the combined outcome between the withdrawal and the control group were compared by calculating risk differences with 95% confidence intervals and, in case of survival analysis, by log-rank tests. Effects on secondary outcome variables were assessed by calculating differences (with 95% confidence intervals) between the mean changes in these variables in the withdrawal and the control group. Mean

changes in variables were calculated by subtracting the baseline value from the last available value after randomization. Analyses were carried out by the intention-to-treat principle. Patients who fulfilled one of the criteria for requiring diuretic treatment during the trial had their last double-blind measurement of the secondary outcome variables carried forward to subsequent time points (carry-forward principle).[17] T-tests were used for continuous variables. A two sided P-value of less than 0.05 was considered statistically significant. It was decided in advance to perform subgroup analyses according to age (65 to 79 and ≥80 years), sex, and current indication of diuretic therapy (heart failure, hypertension and non-cardiac ankle oedema). Interaction tests were applied to compare subgroups.[18]

Results

From October 1991 until June 1993, 202 patients (53 men and 149 women) were included in the trial. The indications for diuretic therapy at the time of entry into the trial were heart failure (42%), hypertension (43%) and non-cardiac ankle oedema (14%). The mean age of the patients was 76 years. Furosemide was used by 32% of the patients, thiazides (alone or in combination with triamterene) by 66% and triamterene alone in 2%. The mean duration that patients had been on diuretic therapy was 7.4 years. Of the 202 patients, 102 were randomly assigned to the withdrawal group and 100 to the control group. The two groups were similar with respect to all relevant baseline characteristics (Table 7.1).

Effect on primary outcome variable

During the 6 months follow-up period, diuretic therapy was required in 50 patients in the withdrawal group and in 13 patients in the control group (risk difference (RD) 36%; 95% confidence interval (CI) 22 to 50%). Development of symptoms of heart failure was the most frequent reason to require diuretic therapy: 25 patients in the withdrawal group and 4 in the control group (Table 7.2). The probability of requiring diuretic therapy in the two groups was highest during the first 4 weeks after withdrawal of diuretic therapy (Figure 7.1). The combined outcome 'increase in heart failure symptoms and/or increase in blood pressure to a level higher than 160/90 mmHg' occurred in 83% of patients withdrawn from diuretic treatment, compared to 42% in the control group (RD 41%; 95%CI 27-55%). During the study period, none of the patients died or had to be admitted to hospital.

Table 7.2
Occurrence of conditions requiring diuretic treatment after withdrawal of diuretic therapy in elderly patients

Criterium	Withdrawal group (n=102)	Control group (n=100)	Risk difference (95% CI)
All	50	13	36% (22 to 50)
Heart failure*	25	4	21% (11 to 31)
Hypertension*	9	5	4% (– 3 to 11)
Subjective shortness of breath	6	0	6% (1 to 11)
Non-cardiac ankleoedema	4	1	3% (– 1 to 8)
Miscellaneous clinical conditions	3	1	2% (– 2 to 6)
Other	3	2	1% (– 3 to 5)

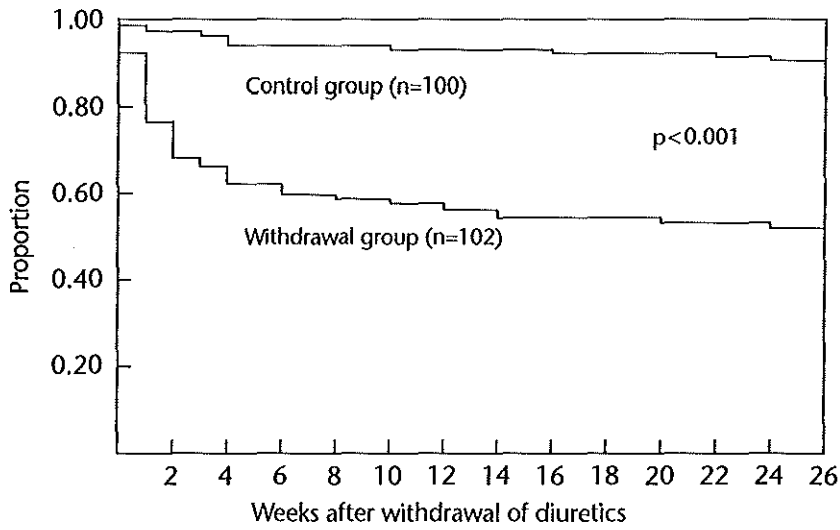
* The reason for reinitiating was classified as heart failure if patients had heart failure scores > 4 points, and as hypertension if the mean value of 3 consecutive systolic or diastolic blood pressure measurements at different occasions was >180 and/or 100 mmHg, respectively

Effect on secondary outcome variables

During the six months follow-up period a mean increase in the heart failure score of 1.4 points (95% CI 1.1 to 1.7) was found in the withdrawal group compared to the control group (Figure 7.2a). This increase was reached at 1 month and was stable during the remaining period. Similarly, the respiration rate after exercise and ankle oedema increased after withdrawal of diuretics (Figures 7.2b, 2c). An increase in body weight was observed after withdrawal with evidence of a rebound effect during the first month (Figure 7.2d).

In comparison to the control group, the mean systolic and diastolic blood pressure levels gradually increased after withdrawal of diuretics by respectively 13.5 mmHg (95% CI 9.2 to 17.8) and 4.6 mmHg (95% CI 1.9 to 7.3) (Figures 7.2e, 7.2f).

Figuur 7.1



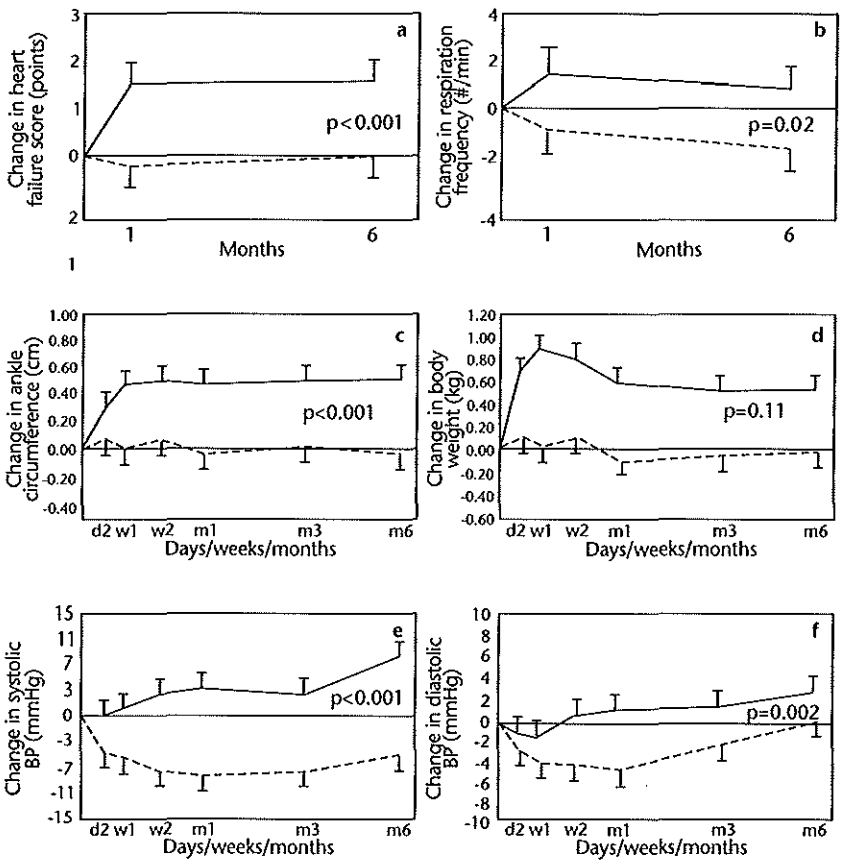
Kaplan-Meier analysis of the cumulative probability of successful withdrawal of elderly patients from diuretic therapy. Patients in the control group continued their diuretic medication, whereas this was replaced by placebo, in a double-blind way, in the withdrawal group. Patients who did not meet one of the predefined criteria for requiring diuretic therapy within the 6 months follow-up period are considered to be successfully withdrawn. Patients who fulfilled one of the criteria for requiring diuretic therapy during the dose-halving regimen (after randomization but before complete withdrawal of therapy) or during the 6 months follow-up period are also considered to be unsuccessfully withdrawn

Serum cholesterol fell after cessation of diuretic therapy (– 0.22 mmol/l; 95%CI –0.39 to –0.05), while HDL-cholesterol remained unchanged. The largest decrease in cholesterol levels (– 0.41 mmol/l; 95%CI –0.74 to –0.08) occurred in patients withdrawn from thiazides. Further, a statistically significant increase in serum sodium (1.2 mmol/l) and potassium (0.14 mmol/l) and a decrease in blood glucose (0.61) and uric acid (0.042 mmol/l) levels was observed. Renal function improved as reflected by a decrease in serum creatinine (6.5 micromol/l) (Table 7.3).

Subgroup analyses (Table 7.4)

Women more often required diuretic therapy after cessation of diuretic therapy (RD 40%; 95%CI 25 to 55) than men (RD 26%; 95%CI 1 to 51). After withdrawal of diuretics the heart failure score increased more in women (1.6 points; 95%CI 1.0 to 2.2) than in men (0.7 points; 95%CI –5 to 1.9). Similarly, the relative increase in systolic and diastolic blood pressure was more prominent in women (16.3/5.9 mmHg) than in men (5.3/-1.3 mmHg) (Interaction tests: p=0.03 and p=0.04). Patients who used diuretics be-

Figuur 7.2



Effect of withdrawal of diuretic therapy in the withdrawal group (drawn line) compared with the control group (dotted line) on heart failure score (Figure 7.2a), increase of respiration rate after exercise (Figure 7.2b), ankle circumference (Figure 7.2c), body weight (Figure 7.2d), systolic blood pressure (Figure 7.2e) and diastolic blood pressure (Figure 7.2f). The bars represent 95% confidence intervals. Follow-up data from patients who required diuretic therapy during the follow-up period had their last double-blind measurement carried forward to subsequent time points (carry-forward analysis)

cause of heart failure required diuretic therapy more often than those with the current indication hypertension or non-cardiac ankle oedema; the risk differences were 57% (95%CI 36 to 78), 21% (95%CI 2 to 40) and 10% (95%CI –11 to 31), respectively. No marked differences were found in subgroup analyses according to age or duration of use of diuretic medication, apart from a larger increase in ankle oedema in the oldest age group.

Table 7.3
Comparison of changes in serum/blood parameters after randomization in patients withdrawn from diuretic therapy (withdrawal group) and patients who continued diuretic therapy (control group)*

	Change from baseline				
	Withdrawal group (n=102)		Control group (n=100)		Mean difference between withdrawal and control group
	Mean change ±SD	n	Mean change ±SD	n	(95% CI)
Serum sodium (mmol/l)	0.5 ± 2.3	57	−0.7 ± 2.1	89	1.2 (0.4 to 2.0)
Serum potassium (mmol/l)	0.17 ± 0.39	56	0.03 ± 0.38	87	0.14 (0.01 to 0.27)
Serum creatinine (micromol/l)	−5.3 ± 13.3	57	1.2 ± 7.8	88	−6.5 (−10.4 to −2.6)
Serum uric acid (mmol/l)	−0.045 ± 0.046	57	−0.003 ± 0.035	89	−0.042 (−0.056 to −0.028)
Serum cholesterol (mmol/l)	−0.19 ± 0.48	57	0.03 ± 0.51	89	−0.22 (−0.39 to −0.05)
Serum HDL-cholesterol (mmol/l)	−0.006 ± 0.153	57	−0.008 ± 0.152	88	0.002 (−0.050 to 0.054)
Blood glucose (mmol/l)	−0.36 ± 2.26	57	0.25 ± 1.39	89	−0.61 (−1.26 to 0.07)

* In patients who were withdrawn from the study because of the development of heart failure symptoms, an 'end-of-study' blood sample was not taken before reinitiation of diuretics, since the clinical condition of the patient often did not allow the time needed for such an assessment. Those patients were excluded from the analysis

Blinding procedure and drug compliance

The patients correctly guessed whether they were allocated to the withdrawal or the control group in 62% of the cases, while their physicians guessed correctly in 65% of the patients. Patients on thiazides and furosemide guessed correctly 56% and 74% of the time, respectively. The corresponding proportions for the trial doctors were 66% and 65%. On basis of the serum levels of chlorthalidone, triamterene and furosemide at baseline and at completion of the trial, drug compliance of the patients during the trial was estimated to be 100% in the withdrawal group and 90% in the control group.

Table 7.4
Effects of withdrawal of diuretics in subgroups of patients by sex, and current indication for diuretic therapy.

	Sex		Indication for diuretic therapy		
	Men	Women	Heart failure	Hyper-tension	Non-cardiac ankle oedema
	(n=51)	(n=151)	(n=84)	(n=88)	(n=28)
	Diff. (95% CI)	Diff. (95% CI)	Diff. (95% CI)	Diff. (95% CI)	Diff. (95% CI)
Diuretics reinitiated (%)	26 (1 to 51)	40 (25 to 55)	57 (36 to 78)	21 (2 to 40)	10 (– 11 to 31)
Diuretics required because of HF (%)	12 (– 6 to 30)	23 (11 to 35)	39 (21 to 57)	5 – 7 to 17)	1 (– 18 to 20)
Change in heart failure score (points)*	0.7 (– 0.5 to 1.9)	1.6 (1.0 to 2.2)	2.3 (1.5 to 3.1)	0.6(– 0.2 to 0.9)	0.8 (– 0.7 to 2.3)
Change in systolic blood pressure (mmHg)*	5.3 (– 3 to 16)	16.3 (11to 21)	12.1 (6 to 18)	14.8 (8 to 22)	15.8 (4 to 28)
Change in diastolic blood pressure (mmHg)*	–1.3 (– 8 to 5)	5.9 (3 to 9)	3.2 (– 1 to 8)	5.2 (1 to 9)	4.8 (– 3 to 13)
Change in ankle circumference (cm)*	0.4 (0.0 to 0.8)	0.5 (0.3 to 0.7)	0.5 (0.2 to 0.8)	0.4 (0.2 to 0.6)	0.4 (– 0.1 to 0.9)

* Carry-foreward analysis
Diff. = difference between the withdrawal group and the control group

Discussion

Our findings indicate that withdrawal of long-term diuretic therapy in elderly patients without manifest heart failure or hypertension is often accompanied by occurrence of symptoms of heart failure or a rise in blood pressure level. The predefined criteria to restart diuretic treatment were fulfilled in 49% of patients withdrawn from diuretics and in 13% of those continuing diuretic therapy (RD 36%; 95%CI 22 to 50). This risk difference was most pronounced in those prescribed diuretics for the indication heart failure.

The vast majority of clinical conditions requiring reinitiation of diuretic therapy occurred during the first 4 weeks after withdrawal. This indicates that our withdrawal regimen might have been to brusque and a certain degree of rebound fluid retention cannot be ruled out. A more prudent weaning-off procedure could have produced a higher rate of successful withdrawal from diuretic therapy.

In our study, withdrawal compared to continuation of diuretic medication of diuretics led to a considerable increase in systolic and diastolic blood pressure levels. A marked decrease in blood pressure levels in the control group constitutes a substantial part of this blood pressure effect. This phenomenon could be explained by the fact that blood pressure measurements were performed at the patient's homes, and patients progressively got used to the procedures during follow-up visits. This stresses the indispensability of a control group. The blood pressure effects in this study are similar to those reported in four earlier double-blind randomized trials of withdrawing therapy in treated normotensive hypertension patients.[19,20,21,22] It is difficult to draw conclusions about the harm or benefit of the average rise in blood pressure levels we observed in patients that were successfully withdrawn from diuretic treatment. In this population of patients with a mean age of 76 years and mean baseline blood pressure levels of 147/81 mmHg, the observed increase in blood pressure level may be considered an unwanted effect leading to an increased risk of cardiovascular disease, or may reflect a beneficial correction of relative dehydration.

We found a remarkable sex difference in the effect of withdrawal of diuretic therapy on blood pressure level and on the probability of developing heart failure symptoms. Because, as far as we know, only marginal sex differences of the effect of thiazides on blood pressure levels and no difference on diuresis were reported in the literature, no clear explanation for this finding exists.[23,24]

Withdrawal of diuretics caused an average decrease in serum cholesterol at the end of the 6 months follow-up period of 0.22 mmol/l (= 3.4%) and was most pronounced after discontinuation of thiazides (0.41 mmol = 6.4%). This is an interesting finding since it has been postulated that any cholesterol rising effect of diuretics would disappear after extended use of the drug and the mean duration of diuretic usage prior to inclusion into this trial was 7 years.[20,25,26,27] The effect of cessation of diuretic therapy on serum parameters could only be determined in participants whose diuretic therapy had not to be restarted because of manifest heart failure during the trial period. The worsened clinical condition of these patients left no time to organize blood sampling before restarting diuretic therapy. It is unlikely that this selection had an important influence on our findings, because similar distributions of the baseline electrolyte and cholesterol concentrations existed in the 46 patients with only baseline measurements and in the 146 patients with additional measurements after withdrawal.

This study included patients that used diuretics for heart failure, hypertension or non-cardiac ankle oedema. The reason for studying such a heterogenic group was implicit to our research objective: to assess the proportion of all diuretic-treated elderly patients who could successfully be withdrawn from their diuretic therapy. As expected, subgroup analyses demonstrated that after withdrawal of diuretic therapy development of symptomatic heart failure most frequently occurred among patients prescribed diuretics for the indication heart failure (RD 57%). Analogously, hypertension was the most common reason for requiring diuretic therapy after withdrawal in patients using diuretics for hypertension. Interestingly, however, increase in heart failure symptoms and blood pressure levels occurred in all three indication groups, including patients with non-cardiac ankle oedema as current indication for diuretic therapy. (Table 7.4). Hypertension is a major risk factor for heart failure and apparently many of the patients on diuretic treatment for hypertension had gradually developed asymptomatic heart failure. In addition, some patients who received diuretics because of non-cardiac ankle oedema may have been suffering from (asymptomatic) heart failure.

The absence of chest X-rays and echocardiography were limitations in the assessment and classification of heart failure. Since the aim of our pragmatic study was to assess which proportion of patients receiving long-term diuretic therapy could be withdrawn from their medication in a non-hospital setting, only diagnostic procedures applicable at the general practitioner's surgery or at the home of the patients were applied. Moreover, a substantial number (>30%) of the patients in this study were over 80 years of age and others were disabled and home-bound and we

felt that hospital-based diagnostic procedures would severely impair the willingness of patients to cooperate, and thus affect the generalisability of our results. In addition, the heart failure symptom score list that we used appeared a valid and feasible instrument in a recent validation study. (see previous footnote)

Many earlier studies on withdrawal of diuretics did not include a comparison group, and of the controlled trials only a minority included placebo treatment.[21,28,29] The need of a control group to take into account the natural history of the conditions studied, is clearly illustrated by the results of our trial.[30] Although 83 % of the patients in the withdrawal group developed heart failure symptoms or hypertension after withdrawal, this proportion was as high as 42% among the patients in the control group who continued to receive diuretic therapy. A placebo-controlled design in drug withdrawal studies, as in drug efficacy trials, is necessary to isolate the pharmaceutical effect from the placebo-effect and to exclude observation bias. If our study would not have been placebo-controlled it would have suggested a too high failure rate. In fact, 'verum-controlled trials' would be a more appropriate classification of such studies, because patients assigned to the verum arm act as the reference group. Although appropriate methods were used to ensure a double-blind conduct of the trial, a potential problem in drug withdrawal studies is that both patients and doctors are aware of the effects of the medication, and may recognize the trial arm to which the patient was randomized. In our study completely effective blinding could not be achieved (for example 62% of the patients correctly guessed the trial arm they were in), but this is unlikely to have induced important bias.

The analysis of data of secondary outcomes, e.g. heart failure symptoms and blood pressure levels, was carried out according to the carry-forward principle. Patients who were withdrawn from the study had their last double-blind measurements carried forward to subsequent time points. This technique most closely approaches a formal intention-to-treat analysis. We realize that carrying forward of the last available measurements introduces virtual data. The alternative, however, is on-treatment analysis which is more likely to introduce bias. Nevertheless, we did perform such an analysis, and it disclosed similar results. Formal intention-to-treat analysis would have been useless because of large dilution effects caused by reinitiating diuretic therapy in a considerable proportion of the study population.

The proportion of patients that could be successfully withdrawn from diuretic treatment in our study was not as large as reported in previous studies. Two earlier controlled randomized trials of withdrawal of diuretic

therapy in the elderly were performed, one in 106 patients in geriatric hospital wards and one in 77 patients in geriatric institutions and the follow-up periods in these studies were 3 and 12 months.[28,29] The proportions of patients that could be successfully withdrawn from diuretic treatment were 76 and 71%, respectively, compared to 49% in our study. The risk differences of 'clinical need for reinitiating diuretic therapy' between the placebo- and the control group in these studies were only 16% (95% CI 2 to 30) and 8% (95% CI –12 to 28), while we found a larger difference of 36% (95% CI 22 to 50). The difference between these two earlier trials and the present one are most probably explained by the selection of the institutionalized patients in the former studies. Different clinical criteria to restart diuretics may be an alternative explanation for the difference.

Inappropriate medication use represents important quality of care problems in the elderly.[31] The potential adverse effects and interactions of diuretics in elderly patients justify regular evaluation of the possibility of cessation of diuretic medication. Our study, however, shows that withdrawal of long-term diuretic treatment in elderly patients leads to the occurrence of symptoms of heart failure or an increase in blood pressure levels to hypertensive values in the majority of cases. In selected patients, withdrawal may be successful, but careful monitoring is needed, notably during the initial four weeks. In patients with a history or signs and symptoms of heart failure cessation of diuretic therapy should generally not be tried. If in hypertensive patients, blood pressure is well regulated during at least one year, withdrawal is warranted. Patients with non-cardiac oedema should preferably not be treated with diuretics, and thus withdrawn. However, a relatively small but realistic risk of manifest heart failure after withdrawal of diuretic therapy in these patients as in hypertensive patients exists, because ventricular dysfunction could have been masked by diuretic therapy. This implies close monitoring for possible heart failure signs and patients should be instructed to perform body weight measurements every morning before breakfast, notably in the first month after down titration or withdrawal of diuretics. An increase of more than two kilograms, or increasing dyspnea are indications for a physician's assessment of the clinical condition of the patient on the same day.

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8 General discussion and implications for medical practice

The main studies in this thesis focus on the possibility to withdraw long-term diuretic therapy in elderly patients in the general practice setting. These studies were initiated because it seemed that, in the elderly, diuretic prescriptions are often repeated unnecessarily, for many years. Further, the available national clinical guidelines on the management of 'heart failure' and 'hypertension' are described in this thesis, to assess the current role of diuretic therapy. By critically reviewing the current role of diuretics and exploring the possibilities to withdraw long-term diuretic medication, these studies aim to contribute to rational and appropriate prescribing of diuretic therapy. In this chapter, the conclusions from the studies included in this thesis and the implications for medical practice will be discussed.

Conclusions from the randomized withdrawal study

Patients in and around Schoonhoven, over 65 years of age, and receiving long-term diuretic therapy were enroled in a randomized trial to study the possibility of withdrawal of diuretic therapy. Patients with clear indications to continue diuretic therapy (manifest heart failure or hypertension) were excluded. In 52 of 102 patients in the withdrawal group, withdrawal succeeded. The other 50 patients required resuming of diuretic therapy (which in 25 cases was attributable to the occurrence of symptoms of heart failure), while in the control group (those who continued their diuretic therapy), only 13 of 100 patients required additional diuretics (four because of symptoms of heart failure). This amounted to a risk difference (RD) of events leading to requirement of diuretic therapy of 36%. These findings may lead to two, rather opposite conclusions. At the one hand, 50% of the patients were successfully withdrawn from diuretic therapy, an argument in favour of regular assessment of the possibility of cessation of diuretic therapy in medical practice. At the other hand, the risk of withdrawal appeared to be substantial: 25% of the patients developed symptoms of heart failure, a potentially dangerous clinical situation. Thus, the trial demonstrates that long-term diuretic therapy is unnecessary in 50% of the patients, but that withdrawal of long-term diuretic therapy is a riskful medical intervention requiring careful monitoring of patients. Before the trial was initiated, it was anticipated that

more patients could be withdrawn without negative clinical effects. For example, withdrawal from diuretic therapy caused a relatively large mean increase in systolic and diastolic blood pressure of 13.5 and 4.6 mmHg, respectively, which was remarkably more pronounced in women than in men (16.3/5.9 versus 5.3/-1.3, interaction test: $p<0.05$). For this gender difference no satisfactory explanation exists. Large hypertension trials did not show a difference in the blood pressure lowering effect or efficacy of diuretics between the sexes.[1,2]

As expected, the risk of heart failure was largest in patients with a history of heart failure, but remarkably, also patients with hypertension or non-cardiac ankle oedema as the indication for diuretic therapy, were at risk of heart failure after withdrawing diuretic therapy. A not always recognized heart failure component may have played a role in these patients. Further, slowly developing heart failure may have been masked by long-term diuretic treatment.

Methodological limitations of the trial

The randomized, placebo-controlled, double-blind, design of our trial assured a high level of internal validity. Nevertheless, several remarks about methodological limitations should be made. First, the high number of patients developing heart failure during the very first weeks after withdrawal, together with the course of the mean body weight in this period (Figure 7.2d), indicates that rebound effects may have been rather strong. Perhaps, our dose down titration was not prudent enough, and apparently was not capable to prevent such rebound effects. If cessation of therapy had been carried out over a more prolonged period, we might have reached a higher success rate of withdrawal.

Because the aim of the trial was to assess the possibility of reducing long-term diuretic therapy, patients on long-term diuretic treatment were recruited regardless of the indication for treatment. This resulted in a heterogenic patient population of hypertension patients, heart failure patients and patients with non-cardiac oedema. The diagnosis at the start of the treatment could not always be reliably retrieved from the medical files and the current indication of treatment, based on information provided by the general practitioners was taken as the criterium for the subgroup analyses. Although this information is expected to be accurate, no further diagnostic tests, e.g echocardiography, were carried out to verify the indications reported by the general practitioners. This may have introduced some inaccuracy in the analyses in subgroups of indication for diuretic therapy.

It is impossible to obtain complete blinding with a fast and strong acting drug such as furosemide. As expected, patients on furosemide correctly guessed the content of their study medication more frequently (78%) than expected by chance. We believe, however, that even a partially effective blinding remains a useful tool to diminish extraneous (non-pharmacological) effects of the withdrawal procedure and to limit observer bias.

The external validity of our study was positively influenced by two important factors. First, we were able to trace all patients on long-term diuretic treatment in a coherent geographic area covered by eight general practices. Second, a number of characteristics of 130 eligible, but not included patients was assessed and compared to the patients included in the trial. These patients could not be included because of the following reasons: no informed consent (41), physician's veto (16), no placebo available (40), fixed drug combinations (25), other (8). This group appeared to be somewhat older, and used their diuretic medication somewhat longer than the patients included in the trial. Importantly, the diagnoses heart failure and hypertension, and the proportion of females were essentially the same. These results indicate that generalisability of the trial was not affected by non-inclusion of a number of eligible patients. External validity is also determined by the representativeness of our study population. Considering the characteristics of the patient population, the numbers of patients on diuretic therapy, and the indications for diuretic therapy in our study, the study population seems representative of the general practice population at large.

When conclusions are drawn about the proportion of patients that can be withdrawn from diuretic therapy, it should be kept in mind that of 470 patients on long-term diuretic therapy, we excluded 117 patients because of heart failure and 21 because of poorly regulated hypertension. These 29% were considered to require diuretic therapy and the results of the trial should not be extrapolated to this type of patients.

The guidelines

Evidence based medicine is a key word in modern medical practice. The increasing availability of a scientific basis for diagnostic and therapeutic procedures is a laudable development as such, but sometimes the amount of new information may be confusing to practising physicians. Comments and editorials in authoritative, high quality journals are helpful in summarizing and interpreting important new research findings, but they can be very contradictory. National clinical guidelines, based on

scientific evidence and consensus among doctors seem the best way to bridge scientific evidence and medical practice, and hopefully the role of national clinical guidelines in medicine will increase during the coming years.

The development of nearly sixty national clinical guidelines in many different fields of medicine, during the last 7 years by the Dutch College of General Practitioners (NHG) is a tremendous achievement. These guidelines are exclusively developed by, and intended for general practitioners. When on a certain topic a multidisciplinary national guideline already existed, this has inevitably led to the existence of more than one national guideline in the country. Also in the U.S.A. more than one national guideline on certain issues exist, for instance in heart failure. The existence of more than one national guideline on a certain clinical topic per country, with often contrasting recommendations, is undesirable and prone to create confusion instead of solving it. The policy of the Dutch College of General Practitioners (NHG) has been to develop their guidelines separate from medical specialists. Presently the quality of their guidelines is broadly recognized and the time seems ripe for more cooperation with specialists, resulting in 'transmural guidelines'. This would overcome the major problem of the existence of multiple national guidelines.

Role of diuretic therapy in heart failure guidelines

From the six national clinical guidelines studied it may be concluded that diuretics remain the basis of drug therapy in the treatment of symptomatic heart failure, and the addition of ACE-inhibitors to diuretic treatment may further improve the condition and the prognosis of the patient. It remains unclear whether elderly patients with mild forms of heart failure (NYHA II), who, on low dosages of diuretics, are free of symptoms, should be treated with monotherapy of diuretics, monotherapy of ACE-inhibitors, or a combination of diuretics and ACE-inhibitors. A randomized trial, preferably in the general practice setting, is needed to solve this question.

Role of diuretics in hypertension guidelines

Most of the evidence from randomized controlled trials about the reduction of the risk of cardiovascular morbidity and mortality by antihypertensive treatment is based on treatment with diuretics. The same magnitude of efficacy has been demonstrated of ß-blockers, albeit in a smaller

number of trials. Evidence from randomized controlled trials about the efficacy of other classes of antihypertensive drugs, such as calcium antagonists, ACE-inhibitors, α-blockers, or angiotensine-II antagonists does not exist. For this reason diuretics or ß-blockers are the drugs of first choice in the treatment of hypertension.

In this context it is surprising, that the prescription pattern in medical practice does neither fit with the results of the large trials, nor with the recommendations of the national clinical guidelines,[3,4] and that notwithstanding the lack of trials assessing their influence on cardiovascular morbidity and mortality, several newer classes of antihypertensive drugs have become increasingly popular. In the case of calcium antagonists, this happened despite suggestions of harmful effects.[5,6,7,8,9,10,11,12] Several recent studies produced additional evidence of an increased risk of severe side effects in hypertensive patients receiving short-acting dihydropyridines[13,14,15,16,17] although the methodology of these studies has been criticized. In principle, these newer classes of antihypertensive drugs should not be prescribed as drugs of first choice in the treatment of hypertension, until proper evidence of long-term studies demonstrating their superiority or equality to diuretics and ß-blockers becomes available.

Potential factors that might explain the relatively high prescribing rates of those newer antihypertensive agents, are the erroneous idea that lowering blood pressure will always lead to reduced cardiovascular morbidity and mortality, and the idea that newer drugs, with new mechanisms of action, are better than older ones. Also the much higher costs of the newer (patented) drugs did not prevent their fast and thorough penetration into the market. Most probably the commercial activities of pharmaceutical industries largely influenced prescription behaviour of many physicians, whereas the impact of independent national clinical guidelines is not large enough. Possible solutions of this problem have many political aspects and are not to be discussed here. Others have elaborated on it more extensively.[18,19,20,21,22,23]

Drug withdrawal studies

Because of the potentially important clinical consequences of drug withdrawal, studies assessing the effects of withdrawal need to meet the same methodological requirements as studies assessing the efficacy of new drugs. Uncontrolled withdrawal studies are inadequate to study the effects of drug cessation, in the same way as uncontrolled studies generate insufficient evidence about drug efficacy. Isolation of the pharmacological effect of drugs from natural course effects, extraneous effects and ob-

server bias is as important in drug withdrawal studies as it is in efficacy trials. It is undesirable that natural course or extraneous effects may lead to the erroneous conclusion that a pharmacon cannot be discontinued, while, pharmacologically, the withdrawal is safe. Unnecessary continuation of long-term drug therapy would be the consequence.

In reports of randomized trials of drug withdrawal, the tendency exists to express the proportion of successful withdrawal, as the proportion of successful withdrawal in the withdrawal group alone (as if no control group was available). This is rather odd, because one would never express the efficacy of a new intervention, as studied in an efficacy RCT, without correcting for extraneous effects (through comparison with the control group). Thus, analogously to efficacy RCTs, when reporting the proportion of successful withdrawal of treatment, the control group of withdrawal studies should not be forgotten. In chapter 4 of this thesis, an alternative effect measure for withdrawal studies is proposed: the adjusted success rate. This rate takes into account, the proportion of unsuccessful withdrawal, attributable to natural course or extraneous effects, which can be estimated by including a verum-treated control group.

In our trial, this adjusted success rate is 64%. The meaning of this figure is that in 64% of the patients diuretics may be withdrawn, without unfavourable effects attributable to the mere absence of the pharmacon. Or, in other words, this proportion of successful withdrawal would have been reached if natural course/extraneous effects were absent. This figure is considerably higher and more encouraging than 51% successful withdrawal observed in the withdrawal group alone.

Withdrawing patients from diuretics in medical practice

To prevent overmedication and polypharmacy, the need for continued drug treatment should be evaluated regularly. For this purpose, the following checklist[24] could be applied:

- Was the indication at the start of the treatment correct?
- Is the indication still present?
- Did a contra-indication evolve?
- Are adverse effects present?
- Are interactions possible?
- Do the advantages of continued treatment outweigh the disadvantages?
- Are the risks of withdrawal acceptable?

The withdrawal of diuretic treatment needs extra attention, because it is a relatively riskful procedure. Heart failure, is the most dangerous potential complication (see Table 7.4 for the magnitude of risks in subgroups of patients). In the trial presented in this thesis predicting factors for development of symptomatic heart failure after cessation of diuretic therapy were a history or symptoms of heart failure, female sex, and old age. By applying multiple logistic regression analysis it can be estimated that a man, 65 years of age, receiving diuretic therapy because of hypertension, and no history or symptoms of heart failure has a risk to develop heart failure after withdrawal of only 2.6%, whereas a woman, 84 years of age, receiving diuretic treatment because of heart failure, with minor symptoms or signs of heart failure has a risk of 84% to develop heart failure after withdrawal. This demonstrates the enormous difference in individual risk of heart failure after withdrawing diuretic medication and the importance of careful consideration of a patient's characteristics before the decision to withdraw diuretics is made.

Recommendations for medical practice

In patients with a history, signs or symptoms of *heart failure* withdrawal should generally not be tried. However, periodical down titration of the dose to avoid underhydration may be undertaken, albeit under strict monitoring of possible signs of heart failure. Patients should be instructed to perform body weight measurements every morning before breakfast, at least in the first month after down titration or withdrawal of diuretics. Notably, an increase of more than two kilograms, or increasing dyspnea indicates an enhanced risk of developing manifest heart failure, and is an indication for a physician's assessment of the clinical condition of the patient on the same day.

If in *hypertensive* patients blood pressure has been well regulated during at least a 1 year, withdrawal may be tried. In cases of long-term treatment, latent heart failure may be masked by diuretic therapy and manifest heart failure may develop after withdrawal of therapy. In many patients strict monitoring is recommended, according to the same criteria as in heart failure patients. Women will generally show larger increases in blood pressure than men, and a higher risk of developing heart failure. All patients remain at risk of an increase in blood pressure levels to hypertensive values and regular blood pressure monitoring, initially every 3 months, and later every 6 to 12 months, should be continued for years.

Patients with *non-cardiac oedema* should preferably not be treated with diuretics, and thus withdrawn. A small but realistic risk of heart failure

after withdrawal of diuretic therapy in these patients, however, implies a need for close monitoring for possible heart failure signs. Also in this group of patients, masking (by the diuretic therapy) of latent heart failure that may have developed gradually over the years, is the most likely explanation for the observed risk of heart failure after drug cessation in these patients. The need of daily body weight measurements depends of clinical judgement of the risk of heart failure.

Final conclusion

A.D. 1997, diuretics are still drugs of first choice in the treatment of heart failure and hypertension. Since diuretics are widely prescribed, especially in elderly patients, unnecessary use of diuretics is not a rare phenomenon. This merits a critical assessment of the possibility to discontinue prolonged diuretic therapy in individual patients. Cessation of diuretic therapy in heart failure patients should not be encouraged because of the risk of development of manifest heart failure, although active dose titration is useful. The possibility of withdrawal in patients receiving diuretic therapy for the indications hypertension and non-cardiac ankle oedema should regularly be evaluated. However, the risk of the occurrence of heart failure after withdrawal of diuretic treatment in patients with hypertension or non-cardiac oedema cannot be ruled out. Thus, careful monitoring after withdrawal is warranted, especially during the first month.

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9 SUMMARY

Diuretics stimulate urine production by the kidney, and are very useful drugs to evacuate excess water and salt from the body. After the introduction of chlorothiazide in 1957, diuretics rapidly became one of the most frequently prescribed classes of drugs. Approximately 20% of all men and women of 65 years or older, and 50% of those over 80 years of age, use long-term diuretic medication. Diuretics are usually divided in 3 classes: thiazides, loop diuretics and potassium sparing diuretics. Heart failure and hypertension are the major indication for diuretics. Although, heart failure and hypertension are conditions with a high prevalence in elderly people, prescriptions for diuretics often seem to be repeated without evaluation of the need for prolonged treatment. Although relatively safe drugs, potentially dangerous adverse effects of diuretics have been reported. Unnecessary therapies should always be avoided and diuretic therapy is no exception to this rule. The objective of the main study presented in this thesis, is to determine the proportion of elderly patients on long-term diuretic therapy that may be successfully withdrawn from this therapy. Further, the current role of diuretics in the treatment of heart failure and hypertension was studied.

In *Chapter 2*, six recently published national clinical guidelines, one from Sweden, one from Canada, two from the USA, and two from the Netherlands, were reviewed to assess the current role of diuretics in the treatment of chronic heart failure. In all guidelines diuretics play a key role in the treatment of heart failure. In five guidelines combined therapy with diuretics and ACE-inhibitors is recommended. The guideline of the Dutch general practitioners (NHG-Standaard) takes an exceptional position by recommending monotherapy with diuretics as a first step in the therapy of patients with mild heart failure (NYHA II). All guidelines recommend thiazide therapy in patients with mild heart failure, which should be replaced by furosemide when stronger diuretic effects are needed. Active down titration of diuretics in clinically stable patients and up-titration in case of symptoms of volume overload is advised in all guidelines. Combination of thiazides and furosemide, and in some cases spironolactone are recommended, for patients with persistent oedema, in all guidelines. Recommendations for diuretic treatment of heart failure patients with predominantly diastolic ventricular dysfunction differ remarkably in the various guidelines: ranging from 'first choice' to 'to be

avoided'. In conclusion, major differences between the six guidelines exist regarding the role of monotherapy with diuretics and treatment of patients with heart failure with predominantly diastolic ventricular dysfunction. These contrasting recommendations are attributable to differences in interpretation of the results of the published trials, and, in the case of diastolic dysfunction, of often premature and contradicting scientific evidence.

In *Chapter 3*, five recently published national clinical guidelines from the Netherlands, Canada, Great Britain and the USA were reviewed to assess the current role of diuretics in the treatment of mild to moderate hypertension. The Dutch GP, American, British and Canadian guidelines recommend to prescribe diuretics or ß-blockers as first choice drugs. Because of the lack of randomized trials assessing the efficacy of newer classes of drugs, such as ACE-inhibitors and calcium antagonists, these antihypertensives are not recommended as drugs of first choice. The Canadian and British guidelines prefer thiazides over ß-blockers in elderly patients. Hypercholesterolemia is not considered an argument against thiazide therapy and the minor increase of plasma cholesterol following thiazide administration is perceived as clinically irrelevant. In diabetes patients diuretics are not considered to be absolutely contraindicated, but because of the negative influence of diuretics on glucose metabolism, most guidelines recommend other antihypertensive drugs as first choice agents. Combinations of thiazides and potassium sparing diuretics are not generally advised as first choice agents, but the Canadian and British guidelines mention them as possible first choice therapy in elderly patients. In the light of recent scientific evidence their role seems to be somewhat undervalued in the guidelines. For elderly hypertension patients, there is substantial evidence that potassium sparing combinations are at least equally effective as thiazides.

In *Chapter 4* several methodological aspects of 'drug withdrawal trials' are discussed. The typical aim of these studies is to determine potential possibilities for reducing unnecessary and possibly harmful medication. A major pitfall is drawing conclusions about drug efficacy by extrapolation and reversal of the effects of drug withdrawal. We have claimed that the randomized controlled trial design is equally desirable in drug withdrawal studies as in any drug efficacy study. The index group is formed by patients on placebo medication, whereas the control group is formed by patients on active medication; by this reversal in comparison to efficacy trials, it is better to speak of 'verum'- controlled instead of placebo-controlled trials. Blinding of patients and doctors is required, when the purpose is to assess the effect of withdrawal of the pharmacological substrate. Alternative effect measures, that take 'success' instead of 'risk' as

a starting point, may be helpful tools to estimate the clinical relevance of the results of withdrawal trials. Finally, the equal, clinical importance of avoiding of type I and type II errors, and the consequences for trial sizes of withdrawal studies is discussed. Drug withdrawal studies are an important tool to learn in what cases overmedication can be curtailed, but they should be well designed.

In *Chapter 5* the accuracy of the Omron HEM403C blood pressure device was assessed. A comparison was made with a Hawksley random zero sphygmomanometer. Blood pressure was measured with both meters connected to one arm-cuff by means of a T-connector. To assess the level of agreement of the Omron HEM403C with the random zero meter, blood pressure was measured in 212 subjects. Systolic and diastolic readings with the Omron HEM403C were on average respectively 1 mmHg (sd 9, 95% CI 0.4-2.2) and 4 mmHg (sd 8, 95% CI 3.6-5.1) higher than those with the random zero meter. According to the criteria of the British Hypertension Society the Omron HEM403C is (marginally) accurate enough to be recommended for those clinical and research purposes that are in need of automatic measurements.

An uncontrolled study *(Chapter 6)* in the practice of the author preceding the execution of a large randomized trial (Chapter 7) was performed to assess the feasibility of a study on the cessation of diuretic therapy and to estimate the proportion of patients that could successfully be withdrawn. The effects of withdrawal on blood pressure, heart failure (HF) score, edema, body weight and subjective complaints were monitored during the 6-months follow-up period. Approximately 20 % of all people of 65 years or older were on maintenance therapy with diuretics. From 38 available patients 22 were excluded, mainly because of symptoms of heart failure or hypertension. One patient refused to participate. Thus, in 15 patients the diuretic medication was withdrawn under careful medical monitoring conditions. After 6 months, 6 patients were still without diuretic therapy. Diuretic therapy had to be resumed in 9 cases, because of congestive heart failure (n=1), hypertension (n=3), bronchial asthma (n=1), increased ankle edema (n=2) and subjective complaints (n=2). The withdrawal of diuretics caused an increase in mean systolic blood pressure, HF-score, body weight and ankle edema. We concluded that maintenance diuretic therapy in elderly patients in general practice could be successfully withdrawn in selected cases.

Consequently, we performed a double-blind randomized trial to assess the effects of withdrawal from long-term diuretic therapy in the elderly *(Chapter 7)*. Of 470 patients on long-term diuretic treatment, identified in eight general practices, 268 were excluded, mainly because of symp-

toms of heart failure or hypertensive blood pressure levels. In total, 202 patients from eight general practices were randomly allocated to either placebo (withdrawal group) or continuation of their diuretic treatment (control group) during a 6 months period. Occurrence of clinical conditions requiring diuretic therapy based on fixed criteria, was the main outcome of the trial. During the 6 months follow-up period, resuming of diuretic therapy was required in 50 patients in the withdrawal group while additional diuretics were required in 13 patients in the control group (risk difference (RD) 36%; 95%CI 22 to 50%). The risk of requiring diuretics was most prominent in patients who used diuretics for the indication heart failure (RD 57%). Cessation of diuretic therapy caused a mean increase in systolic and diastolic blood pressure of 13.5 (95%CI 9.2 to 17.8) and 4.6 mmHg (95%CI 1.9 to 7.3), respectively. Cessation of diuretic medication further lowered serum cholesterol, creatinine and uric acid levels and increased serum sodium and potassium levels. These results indicate that withdrawal of long-term diuretic treatment in elderly patients leads to symptoms of heart failure or increase in blood pressure levels to hypertensive values in the majority of cases. In selected patients, in particular those with hypertension or non-cardiac oedema as the indication for diuretic therapy, withdrawal may be successful, but careful monitoring is needed, notably during the initial four weeks.

The general discussion *(Chapter 8)* elaborates on a number of topics described in this thesis, for example the importance of national guidelines, the discrepancies between the recommendations in national guidelines for hypertension and the actual prescription pattern, and the potential implications for general practice of the results of the withdrawal studies included in this thesis. Finally, recommendations to guide decisions to withdraw long-term diuretic medication in medical practice, including suggestions concerning monitoring requirements after withdrawal, are given.

10 Samenvatting

Diuretica stimuleren de nieren tot urineproductie en zijn nuttige geneesmiddelen wanneer de uitscheiding van overtollig water en zout uit het lichaam moet worden bevorderd. Na de introductie van chloorthiazide in 1957 behoorden diuretica al spoedig tot de groep meest voorgeschreven geneesmiddelen. Ongeveer 20% van alle mensen van 65 jaar en ouder en 50% van die van 80 jaar en ouder gebruikt langdurig diuretica. De diuretica worden in drie klassen ingedeeld: thiazides, lisdiuretica en kaliumsparende diuretica. Hartfalen en hoge bloeddruk vormen de belangrijkste indicaties voor deze middelen. Hoewel hartfalen en hypertensie een hoge prevalentie hebben, krijgt men de indruk dat het grootschalige diureticagebruik deels te wijten is aan het voortdurend herhalen van recepten zonder zorgvuldige evaluatie van de noodzaak daarvan. Hoewel diuretica betrekkelijk veilige geneesmiddelen zijn, zijn er toch potentieel gevaarlijke bijwerkingen bekend. Onnodige therapieën dienen altijd te worden vermeden en diuretica vormen hierop geen uitzondering. Het doel van de belangrijkste in dit proefschrift beschreven onderzoekingen, is vast te stellen welk deel van de oudere patiënten die onderhoudsmedicatie diuretica gebruiken, kan stoppen zonder nadelige invloed op hun gezondheid. Tevens werd door middel van literatuurstudies de huidige rol van diuretica bij de behandeling van hartfalen en hypertensie onderzocht.

Aan de hand van zes recent gepubliceerde nationale richtlijnen voor de behandeling van chronisch hartfalen afkomstig uit Zweden, Canada, Verenigde Staten (2x) en Nederland (2x) wordt in *hoofdstuk 2* de huidige rol van diuretica bij dit ziektebeeld beschreven. In elk van deze richtlijnen spelen diuretica een sleutelrol bij de therapie van hartfalen. Vijf van deze zes rapporten adviseren de combinatie van diuretica en ACE-remmers als standaardtherapie. Alleen de richtlijn van het Nederlands Huisartsen Genootschap (NHG-Standaard) neemt een uitzonderingspositie in door monotherapie met diuretica te adviseren als eerste stap in de behandeling van lichte vormen van hartfalen. Alle richtlijnen adviseren bij een normale nierfunctie in eerste instantie thiazide diuretica te kiezen en die pas door furosemide te vervangen wanneer een sterker diuretisch effect gewenst is. Het verlagen van de diureticadosis bij klinisch stabiele patiënten zonder tekenen van vochtretentie en het opnieuw verhogen van de dosis in geval van symptomen van vochtretentie, wordt in alle richtlijnen aangeraden. Voor patiënten met hardnekkige vochtretentie ondanks

aanzienlijke doses furosemide, wordt het combineren van furosemide met een thiazide of met spironolacton aanbevolen. Opvallend zijn de verschillen in de aanbevelingen over diuretische behandeling van patiënten met diastolische linker ventrikel dysfunctie. In sommige van de richtlijnen zijn diuretica eerste keus, terwijl andere ze als gecontra-indiceerd beschouwen. De contrasterende aanbevelingen zijn in het geval van de rol van monotherapie met diuretica terug te voeren op verschillen in interpretatie van de resultaten van de grote trials, en in het geval van de rol van diuretica bij diastolische linker ventrikel dysfunctie op prematuriteit van deze diagnose als klinische entiteit.

In *hoofdstuk 3* wordt de huidige rol van diuretica bij de behandeling van hypertensie besproken aan de hand van vijf recent gepubliceerde nationale richtlijnen uit Nederland (2x), Canada, Engeland en de Verenigde Staten. De Canadese, de Amerikaanse, de Engelse en de Nederlandse NHG richtlijnen adviseren allemaal diuretica of ß-blockers als eerste keuze geneesmiddelen bij hypertensie voor te schrijven. Nieuwere geneesmiddelengroepen voor de behandeling van hypertensie, zoals ACE-remmers en calciumantagonisten worden hierbij niet als eerste keuze beschouwd, vanwege het ontbreken van gerandomiseerd onderzoek naar de effectiviteit van deze middelen op de morbiditeit en de mortaliteit. De Canadese en de Engelse richtlijnen spreken hun voorkeur uit voor thiazide diuretica boven ß-blokkers bij oudere patiënten. Hypercholesterolaemie wordt niet beschouwd als reden om af te zien van het voorschrijven van thiazides, omdat de kleine stijging van de cholesterolconcentratie in het bloed die door deze middelen wordt veroorzaakt, als klinisch weinig relevant wordt beschouwd. Thiazide diuretica worden bij diabetes patiënten niet als absoluut gecontra-indiceerd beschouwd maar vanwege de ongunstige invloed op het glucosemetabolisme wordt in de richtlijnen over het algemeen geadviseerd om diuretica bij diabeten niet als eerste keus voor te schrijven. Combinatietherapie met thiazides en kaliumsparende diuretica wordt niet aanbevolen als standaardbehandeling maar de Canadese en Engelse richtlijnen noemen deze combinatie wel als een mogelijke eerste keus bij oudere patiënten. In het licht van nieuwe onderzoeksresultaten lijkt de rol van kaliumsparende combinaties enigszins ondergewaardeerd. Met name voor de oudere hypertensiepatiënten is in grote gerandomiseerde trials overduidelijk aangetoond dat kaliumsparende combinaties minstens zo effectief morbiditeit en mortaliteit verminderen als thiazides.

In *hoofdstuk 4* wordt een aantal methodologische aspecten besproken van onderzoekingen naar de effecten van het staken van langdurig gebruikte medicatie. Het inherente doel van dit soort onderzoekingen is het bepalen van de proportie patiënten bij wie onnodig geneesmiddelgebruik kan worden verminderd. Een valkuil bij dit soort onderzoek is het trekken van

conclusies over effectiviteit van het geneesmiddel, door het omkeren van effecten die optreden bij het staken. Er wordt gesteld dat het belang van de gerandomiseerde, gecontroleerde opzet bij dit soort studies even groot is als bij elk ander geneesmiddelonderzoek. In deze zogenoemde geneesmiddel-stop-studies wordt de interventiegroep dan gevormd door patiënten op placebomedicatie terwijl de controlegroep juist bestaat uit patiënten op actieve medicatie. Door deze omkering ten opzichte van gebruikelijke geneesmiddelenonderzoeken is het beter te spreken van verum-gecontroleerd in plaats van placebo-gecontroleerd onderzoek. Blinderen van patiënten en behandelaars is nodig wanneer het doel van het onderzoek de bestudering van de effecten van staken van het farmacologisch substraat behelst en niet wanneer de effecten van de stopprocedure als geheel onderwerp van studie zijn. Effectmaten die 'succes' in plaats van 'risico' als uitgangspunt hebben, kunnen nuttig zijn om het inzicht in de betekenis van de resultaten van geneesmiddel-stop-studies te vergroten. Tenslotte wordt in dit hoofdstuk besproken dat het vermijden van statistische type I en type II fouten bij stop-studies even belangrijk is en dat op grond hiervan het aantal benodigde patiënten in dergelijk onderzoek vergeleken met een effectiviteitsonderzoek groter zal zijn. De conclusie luidt dat geneesmiddel-stop-studies een belangrijk instrument kunnen zijn om op rationele wijze (dreigende) overmedicatie te bestrijden, maar de opzet dient dan wel methodologisch juist te zijn.

Hoofdstuk 5 beschrijft een onderzoek naar de overeenstemming van een automatische oscillometrische bloeddrukmeter (Omron HEM403C) met een kwikmanometer (Hawksley random-zero meter). Hierbij werd gebruik gemaakt van simultaan-metingen aan één arm. De luchtslangen van beide meters waren met een T-stukje verbonden aan één en dezelfde armmanchet. Om de mate van overeenstemming van de twee meters vast te stellen werden bij 212 personen bloeddrukmetingen verricht. De systolische en diastolische bloeddrukwaarden waren met de Omron meter gemiddeld respectievelijk 1 (sd 9, 95%BI 0,4 tot 2,2) en 4 mmHg (sd 8, 95%BI 3,6 tot 5,1) hoger dan met de kwikmanometer. Naar de maatstaven van de British Hypertension Society bleek de Omron HEM403C (marginaal) voldoende nauwkeurig om aanbevolen te worden voor die klinische en research toepassingen waarvoor automatische metingen de voorkeur genieten.

Een ongecontroleerde 'pilot'–studie *(hoofdstuk 6)* in de eigen praktijk van de auteur van dit proefschrift ging vooraf aan de uitvoering van een groter gerandomiseerd onderzoek (hoofdstuk 7). Dit werd gedaan om de haalbaarheid van de studieopzet te testen en om een schatting te maken van het aantal patiënten dat met diuretica kon stoppen. De effecten van

het stoppen van diuretica op de bloeddruk, een hartfalen-symptoomscore, enkeloedeem, lichaamsgewicht en subjectief klachtenpatroon werden gedurende zes maanden na het stoppen van het diureticum regelmatig gemeten. Ongeveer 20% van alle patiënten van 65 jaar en ouder bleek onderhoudsmedicatie met diuretica te gebruiken. Van 38 opgespoorde patiënten werden er 22 van het onderzoek uitgesloten, voornamelijk wegens manifest hartfalen of hoge bloeddruk. Eén patiënt weigerde deelname. Vervolgens werd onder intensieve medische controle bij 15 patiënten de diuretische medicatie gestaakt. Na zes maanden waren zes patiënten nog zonder diuretica; in negen gevallen was de behandeling met diuretica hervat wegens hartfalen (n=1), hypertensie (n=3), bronchiaal astma (n=1), toegenomen enkeloedeem (n=2) en subjectieve klachten (n=2). Het stoppen met diuretica veroorzaakte een stijging van de systolische bloeddruk, de hartfalen-score, het lichaamsgewicht en enkeloedeem. De conclusie luidde dat onderhoudsbehandeling met diuretica in geselecteerde gevallen bij oudere patiënten in de huisartspraktijk kan worden gestaakt.

In aansluiting op de 'pilot'– studie werd een gerandomiseerde, dubbelblinde trial uitgevoerd naar de effecten van het stoppen van onderhoudsmedicatie diuretica bij ouderen *(hoofdstuk 7)*. Van 470, in acht huisartspraktijken opgespoorde patiënten die langdurig diuretica gebruikten, werden er 268 uitgesloten, wederom voornamelijk wegens hartfalen of hypertensie. De overige 202 patiënten werden willekeurig toegewezen aan hetzij de placebogroep (stop-groep), hetzij de groep die doorging met de onderhoudsmedicatie diuretica (controlegroep). Het optreden van klinische verschijnselen waarvoor diuretische therapie nodig is – gedefinieerd volgens tevoren vastgelegde criteria – was de belangrijkste uitkomstparameter van het onderzoek. Gedurende een follow-up periode van zes maanden bleek hervatting van diuretische therapie nodig bij 50 patiënten in de stop-groep, terwijl in de controlegroep slechts bij 13 patiënten additionele diuretica nodig waren (risicoverschil 36%, 95%BI 20 tot 50%). De meest voorkomende reden voor hervatten van de diuretica was het optreden van symptomen van hartfalen (25 van de 50 patiënten). Het stoppen van de diuretica veroorzaakte een gemiddelde stijging van de systolische en diastolische bloeddruk van respectievelijk 13,5 (95%BI 9,2 tot 17,8) en 4,6 (95%BI 1,9 tot 7,3) mmHg. De kans dat na het staken van diuretica een klinische conditie ontstond die (additionele) therapie met diuretica noodzakelijk maakte was het meest uitgesproken bij patiënten die onderhoudsmedicatie diuretica gebruikten voor de indicatie hartfalen (risicoverschil 57%). Gunstige effecten van het stoppen van diuretica waren een verlaging van de gemiddelde serumconcentraties van cholesterol, kreatinine en urinezuur. Ook natrium- en kaliumconcentraties gaven een gemiddelde stijging te zien. De resultaten van dit onderzoek wijzen erop dat het stoppen van onderhoudsmedicatie met diuretica bij oudere patiënten

in de meerderheid van de gevallen leidt tot het ontstaan van symptomen van hartfalen of hypertensieve bloeddrukwaarden. In een geselecteerde groep patiënten, met hypertensie of niet-cardiaal oedeem als indicatie voor de diuretische therapie, kan het staken succesvol zijn, maar ook in deze groepen zijn intensieve medische controles onontbeerlijk wegens de verhoogde kans op hartfalen. Dat risico is het grootst gedurende de eerste vier weken na het stoppen van de medicatie.

In de algemene discussie *(hoofdstuk 8)* wordt uitgewijd over een aantal onderwerpen die in dit proefschrift zijn beschreven, bijvoorbeeld het belang van nationale richtlijnen voor de behandeling van veel voorkomende aandoeningen als hypertensie en hartfalen, en de discrepantie tussen het voorschrijfgedrag van artsen bij hypertensie en de aanbevelingen in de hypertensie-richtlijnen. Tenslotte worden de potentiële implicaties van de in het proefschrift beschreven diuretica stop-studies voor de huisartspraktijk besproken. Enkele aanbevelingen omtrent de beslissing om onderhoudsmedicatie met diuretica al dan niet voort te zetten en suggesties voor het controlebeleid na het staken van diuretica worden genoemd in de slotparagraaf.

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hun patiëntenadministraties, om bij een aantal van hun patiënten de door hen voorgeschreven diuretica te stoppen, én om vervolgens als bemoeizuchtige collega hun patiënten een half jaar te blijven controleren. Han Goutier, Herman Groothuis, Frans van Eijk, Govert de Kool, Hans van Ewijk, Rob van Bekkum, Joost Berg, Herman Brandsen en Huub Reiners, zeer veel dank voor het in mij gestelde vertrouwen en voor jullie uiterst collegiale medewerking. Piet Lanser, via jouw apotheekcomputer zijn heel wat lijsten uitgedraaid. Bedankt voor de wijze waarop je altijd je volle medewerking hebt gegeven. Zonder uitzondering hebben ook de specialisten van het Groene Hart Ziekenhuis in Gouda (en in een enkel geval van elders) zeer loyaal hun volle medewerking gegeven. Een patiënt kon door ons pas worden ingesloten in de trial als ook de behandelende specialist accoord was en jullie spraken gelukkig slechts zelden je veto uit. Verder wil ik graag noemen Dr P. J. Roos, Drs I. C. de Graaf en Dr J. W. Meilink, die mij gastvrijheid boden in de apotheek van het Academisch Ziekenhuis Dijkzigt te Rotterdam, waar we duizenden pillen hebben geteld, omgepakt en geëtiketteerd, en waar de randomisatielijsten zijn gemaakt en geadministreerd. Professor F. A. de Wolf, dr L. M. S. Stolk en Mw. L. S. Chandi van de afdelingen Humane Toxicologie en Farmacie van het Academisch Medisch Centrum Amsterdam hebben vele serumdiureticaspiegels bepaald. Marc Götte, assistent in opleiding tot cardioloog, destijds in onze praktijk werkzaam als huisarts in opleiding, heeft in zijn vrije uren en tijdens diensten geheel belangeloos 350 ECG's beoordeeld, waarvoor dank. Verder ben ik iedereen die conceptteksten heeft becommentarieerd, inclusief de promotiecommissie, hiervoor erkentelijk.

De secretaresses Ingrid van Heugten en Pien Schubert in Rotterdam, en de doktersassistentes Marijke Bodenstaff en Leny Blomaard in Schoonhoven wil ik tenslotte bedanken voor hun bijdragen, zonder welke onze toch wel omvangrijke 'Schoonhoven trial', met zijn vele schriftelijke en telefonische contacten met patiënten en collega's nooit zo goed gelukt zou zijn.

Curriculum vitae

Edmond Walma werd geboren op 20 oktober 1953 te Den Haag. Hij doorliep de HBS-B aan de Christelijke Scholengemeenschap Groen van Prinsterercollege te Den Haag. Van 1970 tot 1977 studeerde hij geneeskunde in Rotterdam. Tot medio 1978 werkte hij als arts-assistent achtereenvolgens op de afdeling Interne Geneeskunde van het Van Dam ziekenhuis in Rotterdam en op de afdeling Intensive Care van het ziekenhuis Leijenburg te Den Haag. Van 1978 tot 1981 was hij werkzaam aan het Radiobiologisch Instituut van TNO te Rijswijk onder leiding van Professor D.W. van Bekkum, waar hij onderzoek verrichtte op het terrein van de oncovirologie en van de beenmergtransplantatie. In 1981/1982 volgde hij de beroepsopleiding tot huisarts aan het Rotterdams Huisartsen Instituut. Na gedurende twee jaar te hebben waargenomen in diverse huisartsenpraktijken vestigde hij zich in 1984 in Schoonhoven. Een associatie, met zijn echtgenote Froukje Boukes, met een 50/50 werkverdeling in de eigen praktijk opende de mogelijkheid voor een 50% dienstverband bij de Nederlandse Organisatie voor Wetenschappelijk Onderzoek (NWO-stimuleringsprogramma Huisartsgeneeskunde). In dat kader was hij van 1988 tot 1993 als wetenschappelijk onderzoeker verbonden aan het Rotterdams Huisartsen Instituut en werd dit proefschrift voorbereid.