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Cost Effectiveness of an Adherence-Improving Programme in Hypertensive Patients

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Abstract

Background: Non-adherence to antihypertensive drugs is high, and the economic consequences of non-adherence may be substantial. The Medication Events Monitoring System (MEMS), which is a method to improve adherence, has been shown to be a useful tool for the management of adherence problems.

Objective: To assess the cost effectiveness of the MEMS compared with usual care in a population of hypertensive patients with poor adherence. The MEMS programme consisted of provision of containers fitted with electronic caps together with adherence training if indicated.

Methods: In a randomised controlled trial, 164 hypertensive patients in the experimental strategy and 89 patients in the usual care strategy were followed for 5 months. Patients who had a systolic blood pressure (SBP) ≥160mm Hg and/or diastolic BP (DBP) ≥95mm Hg despite the use of antihypertensive drugs were eligible. Patients were recruited by a GP, and treatment took place in general practice.

In the experimental strategy, electronic monitoring of the intake of antihypertensive drugs was introduced without change of medication. Unsatisfactory adherence was defined as <85% of days with the number of doses taken as prescribed. In the usual care strategy, antihypertensive treatment was intensified by the addition or change of antihypertensive drugs, if necessary, without provision of an electronic monitor.

Outcome parameters included the proportion of patients with normalised blood pressure (NBP) at 5 months and QALYs. Costs were quantified from the healthcare and societal perspective. Non-parametric bootstrap simulations were per-

formed to quantify the uncertainty around the mean estimates and cost-effectiveness acceptability curves were presented. In addition, a number of univariate sensitivity analyses were performed on deterministic variables.

Results: At 5 months, 3.1% (95% UI [uncertainty interval] −9.7%, +15.8%) more patients had NBP, and 0.003 (95% UI −0.005, +0.010) more QALYs were generated in the experimental strategy. A statistically significant lower percentage of patients had a dose escalation in the experimental strategy. Irrespective of the ceiling ratio for cost effectiveness, the cost-effectiveness probability was between 75% and 80% for the analysis from the healthcare perspective using proportion of patients with NBP as the outcome parameter. For the analysis from the societal perspective using QALYs as the outcome parameter, this probability was between 45% and 51%.

Conclusion: For a time horizon of 5 months, a difference in both cost and effect could not be detected between an adherence-improving programme compared with usual care for hypertensive patients. The probability that the adherence-improving programme is cost effective is at best moderate. Moreover, the cost-effectiveness result is surrounded with considerable uncertainty and large-scale implementation warrants additional research into the economic consequences of this intervention. Patients may benefit from the use of a MEMS monitor in situations where BP targets are not reached because of suspected non-adherence and both patient and GP are reluctant to increase the dose or number of antihypertensive drugs.

For pharmacological treatment to be beneficial, it is of the utmost importance that patients adhere to prescribed medication. Failure to adhere to prescribed medication regimens increases the risk of illness[1] and total healthcare costs.[2] Non-adherence is common and has been identified as a major public health problem.[3] The proportion of patients that do not adhere to treatment ranges from considerable to high and depends on the class of drug. It is estimated to vary between 33% for cholesterol-lowering agents and 87% for inhaled corticosteroids.[4]

Hypertension is one of the chronic conditions where non-adherence needs attention. It has been estimated that only approximately 50–70% of patients with hypertension take their medication according to the prescribed regimen.[5,6] Because of the high prevalence of the disease, which has been estimated to be on average 44% in six European countries and 28% in North America,[7] economic consequences of non-adherence may be substantial. In The Netherlands, superfluous expenses associated with treatment non-adherence are estimated to total €234 million (year 1998 values), which is 0.7% of the total healthcare budget in 1998.[4] Development of patient management strategies that are targeted at increasing patients' own role in improving blood pressure (BP) control, may lead to cost containments and therefore deserve interest.

Several methods to monitor and improve adherence have been used, e.g. self-reported adherence, prescription renewal, counting pills, or biological markers. All these methods have their limitations,[8,9] and a number of systematic reviews have demonstrated that no single intervention has emerged as superior.[10-12] Several years ago, the Medication Event Monitoring System (MEMS; Aardex Corp., Geneva, Switzerland) became available, which is a drug container and cap equipped with a microchip that registers the date and time of each opening container.[13] It seems to be an effective tool to identify non-adherent patients.[14-21] Moreover, electronic monitoring has been shown to improve adherence in hypertensive patients,[14,15] in psychiatric patients,[22,23] in those with obstructive lung dis-

ease[24] and in women participating in a smoking cessation trial.[25] The consequences of non-adherence with pharmacotherapies have been largely neglected in the medical and health economic literature.[26] Although the cost effectiveness of a number of adherence-enhancing interventions in hypertension has been assessed,[27-31] the cost effectiveness of electronic monitoring as a tool to improve adherence remains to be elucidated.

The objective of the present study was to assess the cost effectiveness of an adherence-improving programme using the MEMS in hypertensive patients in the primary care setting, compared with usual care. Differences in healthcare and societal costs were related to the difference in effects in terms of normalised BP (NBP) and generic quality of life (QOL), respectively.

Methods

Study Design

This economic evaluation has been performed alongside TULIPA (The Utrecht Limburg Initiative on Patient adherence with Antihypertensives) study,[32] a randomised clinical trial with two parallel groups. Patients were randomly assigned to either the experimental or usual care strategies, according to a randomisation ratio of 2 **:** 1. This ratio was employed in order to allow for a reliable estimation of the proportion of poor adherers in the experimental care strategy. Randomisation was performed centrally by telephone through the Trial Coordinating Centre. For each GP a random allocation scheme was generated using computer-generated random permuted blocks with a block size of six. Both patients and the referring GPs were unaware of the randomisation sequence. Patients were followed for 5 months. The Institutional Review Board granted ethical approval for the study. A written informed consent form was obtained from each enrolled patient.

Patients and Methods

Patients were recruited by 43 GPs in the southern area of The Netherlands. Patients were eligible if they had a diagnosis of hypertension that was inadequately controlled despite the use of antihypertensive drugs. Uncontrolled BP was defined as a systolic BP (SBP) ≥160mm Hg and/or diastolic BP (DBP) ≥95mm Hg.[33] In diabetic patients, high BP was defined as ≥150mm Hg SBP and ≥85mm Hg DBP. Furthermore, there had to be an indication for treatment escalation, defined as an increase in dosage, addition or change of antihypertensive drugs. Patients were excluded when treatment was adjusted because of adverse effects of current medication, or when patients insisted on using dose organisers. Patients not eligible for the study also included those who were institutionalised and those not managing their drug intake themselves.

The power calculation was based on the proportion of patients with a normalised BP (NBP). Assuming a significance level of 5%, NBP in 50% of patients in the usual care strategy, and a randomisation ratio of 2 **:** 1, it was calculated that 167 patients were needed in the experimental care strategy and 83 patients in the usual care strategy in order to detect an increase in the proportion of patients with an NBP of 20%, with a power of 85%.

Intervention

The intervention provided to the patients in the experimental strategy consisted of adherence monitoring and adherence-improving training only for patients with unsatisfactory adherence. In the experimental strategy, antihypertensive medication was monitored for 8 weeks without medication changes. For each prescribed drug, patients received a MEMS container and cap. Patients were informed that the MEMS cap recorded the date and time of each opening of the container. After the first evaluation period of 2 months, adherence data were downloaded to a personal computer using dedicated software, and medication adherence was determined by a GP assistant. Adherence was defined as the proportion of days with the number of doses taken as prescribed, e.g. correct dosage. For all prescribed medication, patients taking ≥85% of prescribed doses were considered adherent. In patients with unsatisfactory adherence, no dose escalation or

medication adjustment took place and irrespective of their BP, electronic monitoring was continued for another 3 months. Patients with satisfactory adherence who still had uncontrolled BP after 2 months of electronic monitoring, were referred to their GP who decided whether or not adjustment of medication was indicated.

Additionally, those patients with unsatisfactory adherence received training to manage adherence, provided by a GP assistant in three sessions of 15 minutes duration. The training consisted of a review of the adherence report with the patient. The goal was to give insight into their own dosing history, to identify periods of suboptimal adherence, to explore reasons for suboptimal adherence and to define 'cues' linked to drug taking. In the usual care strategy, antihypertensive medication was intensified by addition or change of antihypertensive drugs if necessary, and regular drug containers and caps were used.

Costs

Costs were quantified from both the healthcare and societal perspectives. The healthcare perspective takes only medical costs into account (either paid for by insurance or by the patients themselves). The societal perspective incorporates medical and non-medical costs and health effects regardless of who incurs the costs and who obtains the effects.[34,35]

Data on healthcare utilisation, informal care, paid house assistance, over-the-counter medication, transportation and productivity loss were collected using cost diaries, which were prospectively completed over three separate 4-week periods; during months 1, 3 and 5. All resource use was collected, irrespective of its reason. Cost diaries have proven to be a successful means to gather information on healthcare resource use during a longer period.[36] Cost data were interpolated under the assumption that costs in month 1 were representative for costs in month 2, and costs in month 3 and 5 were representative for costs in month 4 (i.e. month 4 costs were taken as the mean of months 3 and 5). Information on the volume and the type of drugs obtained by each patient was obtained from the patient's pharmacist. We distinguished between direct healthcare costs, direct non-healthcare costs and indirect costs. Details concerning these cost categories are presented in table I.

The intervention costs consisted of costs of instruction, electronic monitoring costs and training aimed at improving adherence. These costs were determined based on the following assumptions:

- Patients were given instructions on how to use the monitor by the GP assistant during the first visit for 15 minutes.
- Relevant to the electronic monitoring costs are the costs of the MEMS container and cap, the communicator and software for reading out of the monitor, as well as personnel costs for packaging the drug in the electronic monitor and reading out of the monitors.
- Patients were assumed to have one GP consultation, during which the patient was provided with the monitor container and cap. Subsequently, the pharmacist assistant filled caps with electronic monitors for every prescribed drug.
- It was assumed that re-use of the monitor cap was allowed, but that monitor containers (standard bottle containers to which the monitor cap can be fitted) were for single use only, and that every practice was equipped with one communicator and a software programme for reading out the monitors.
- Electronic monitor caps, the communicator and the software programme were depreciated in 3 years using the annuity method, with an interest rate of 4.5%.[39]
- The costs of the communicator and software programme were calculated by dividing the total depreciation costs per year (€242) by the mean number of antihypertensive medication prescriptions for patients without adequate BP control in a usual GP practice (459 per year). The mean number of antihypertensive medication prescriptions was determined by multiplying the average number of patients without adequate BP control per usual GP practice (255)[40] by the mean number of antihypertensive medication prescriptions

Table I. Mean total costs (€, 2002 values) [SD] per patient per group

Cost category	Costs per unit (€)	Experimental strategy (n = 164)	Usual care strategy (n = 89)	Increment (95% UI)
Direct healthcare costs				
Medication	Price/drug[37]	334 (194)	374 (202)	−40 (−90, 8)
Initial instruction	6.53/instruction[a]	7 (0)	0	
Electronic monitor	15.28/monitor[a,b]	26 (16)	0	
Training	19.80/three sessions[a]	1 (4)	0	
Costs directly related to the intervention[c]		367 (198)	374 (202)	−7 (−58, 39)
GP consultation	17.60/consultation[39]	120 (57)	120 (61)	
Specialist	77.00/consultation[39]	87 (174)	91 (266)	
Physical therapist	19.25/visit[39]	47 (122)	28 (72)	
Hypertension nurse	59.85/consultation[39]	0 (0)	2 (13)	
Home care	26.65/hour[39]	47 (204)	65 (402)	
Admission	351.89/day[39]	157 (708)	247 (1263)	
Other		460 (879)	553 (1582)	−92 (−421, 192)
Total direct healthcare costs		*827 (903)*	*927 (1594)*	*−100 (−415, 189)*
Direct costs				
Informal care	8.42/hour[39]	79 (310)	47 (267)	
Paid house assistance	Price/hour[39]	26 (101)	9 (28)	
OTC medication	Price[d]	7 (37)	12 (28)	
Transportation	0.12/kilometer[39]	3 (3)	3 (3)	
Direct non-healthcare costs		115 (332)	71 (271)	44 (−23, 121)
Total direct costs		*942 (1027)*	*998 (1619)*	*−56 (−375, 247)*
Indirect costs				
Productivity loss				
paid work	Friction costs[39]	358 (1804)	257 (2014)	
unpaid work	8.42/hour[39]	268 (1827)	251 (1709)	
household work	8.42/hour[39]	5 (22)	20 (128)	
Indirect non-healthcare costs		32 (3488)	528 (3720)	104 (−794, 966)
Total costs		**1573 (3602)**	**1526 (4032)**	**47 (−873, 867)**

a The costs of training were calculated by multiplying the personnel costs per minute (€0.44) by the duration of training (15 minutes).[38]

b On average 1.8 different drugs were used.

c Resource utilisation derived from patient-completed cost diaries.

d Reported in cost diary.

OTC = over the counter; **UI** = uncertainty interval based on bootstrap replications.

per patient (1.8 per year), as observed in this study.

- The costs of the training were calculated by multiplying the personnel costs per minute (€0.44) by the mean duration of the training (three 15-minute sessions).

The most recent drug prices (25 May 2005) were obtained from an online database on medication costs[37] and included the pharmacist dispensing fee. Unit prices from the Dutch manual for cost research were used to estimate the direct costs.[39] Informal care, productivity loss of unpaid work and household work were valued using the shadow-price method.[39] Productivity loss costs for paid labour were calculated according to the friction cost method, based on a mean income of the Dutch population according to age and gender for employees.[41]

The healthcare costs per patient were calculated by combining the resource utilisation data with the

corresponding unit cost estimates and are reported in €, 2002 values (€1 = $US1.27 as at 12 June 2006 conversion rate).

Effects

The effectiveness of the adherence-improving programme was assessed in terms of the proportion of patients with NBP at 5 months and generic QOL. NBP was defined as an SBP <160mm Hg and a DBP <95mm Hg.

Generic QOL was measured using the EQ-5D[42] at baseline and at 5 months. This questionnaire contains items to measure five different dimensions of QOL: (i) mobility; (ii) self-care; (iii) daily activities; (iv) pain; and (v) anxiety/depression. Based on the scores on the items of the EQ-5D, a population health state utility estimate was calculated.[43] The obtained utility estimates were used to compute QALYs, by multiplying utility by life expectancy. The QALY is a measure of health outcome that assigns a weight ranging from 0 (worst imaginable health state) to 1 (best imaginable health state) for each period of time.[44] One year in perfect health yields one QALY. One patient could generate a maximum of 0.417 QALYs, as the time horizon in this study was 5 months. Extrapolation in time was considered not to be valid. The QALY was estimated using regression analysis adjusting for baseline utility, by equations 1 and 2.[45]

$$\text{Unadjusted QALY} = \alpha + (\beta_1 \times [\text{Utility-T}_0 - \text{Utility-mean}]) + \beta_2 \times \text{group} \quad \text{(Eq. 1)}$$

$$\text{Adjusted QALY} = \text{unadjusted QALY} - (\beta_1 \times [\text{Utility-T}_0 - \text{Utility-mean}]) \quad \text{(Eq. 2)}$$

where α = constant, β_1 = coefficient of corrected baseline utility, Utility-T_0 − Utility mean = corrected baseline utility and β_2 = coefficient of group. BP and other measurements were carried out by a research nurse in the first week, 2 months and 5 months after inclusion.

Cost Effectiveness

The cost effectiveness of electronic monitoring of medication adherence was assessed in two ways: (i) by relating the difference in healthcare costs between the two strategies to the difference in the proportion of patients with NBP; and (ii) by relating the difference in societal costs between the two strategies to the difference in QALYs. The resulting point estimates, the incremental cost-effectiveness ratios (ICERs), reflect the healthcare costs per patient with NBP and the societal costs per QALY, respectively. Results were not extrapolated beyond the 5-month follow up and therefore discounting was not relevant.[34,35]

Analysis

Data were analysed according to the intention-to-treat principle. Missing values, as a result of incompleteness, were substituted by the total group mean.[46] Statistical significance was indicated by a p-value of <0.05.

In order to get insight into the uncertainty around the incremental costs, incremental effects, and ICERs, non-parametric bootstrap simulations were conducted.[47] In a bootstrap simulation, a sample of cost and effect pairs of equal size of the original sample is selected a thousand times at random with replacement. These simulations are presented in a cost-effectiveness plane, and yield information concerning the joint distribution of the cost and effect differences. From these data 95% uncertainty intervals (UI) for cost and effect differences were calculated based on the 2.5th and 97.5th percentiles.

Within the cost-effectiveness framework, the choice for a treatment strategy depends on what society is prepared to pay for a gain in effectiveness: the so called ceiling ratio. In other words, the probability that a new treatment is cost effective varies depending on the ceiling ratio used. This can be shown in a cost-effectiveness acceptability curve (CEAC).[48] A CEAC is derived using the results from the bootstrap simulation, and the net-benefit framework,[49] for different levels of ceiling ratios. For each strategy, the net-monetary-benefit statistic is calculated by subtracting the costs valued in €

from the effect multiplied by the ceiling ratio, for a thousand simulations. Per simulation, the strategy with the highest net monetary benefit is preferred. Over all simulations for each strategy, the probability that a particular strategy has the highest net monetary benefit is calculated. This is repeated for a range of ceiling ratios, in order to construct the CEAC.

The CEAC is constructed under the assumption that the willingness to pay (WTP) for health gain is identical to the willingness to accept (WTA) compensation for health loss. However, it has been shown in economics that individuals do not consider these situations identical. The amount of saving that will be required to accept losing health is generally larger than the extra money people are prepared to pay for gaining health.[50] To take this disparity into account, a CEAC was constructed with the addition of the situation that society is not prepared to accept compensation for health loss (WTA is infinite).[51] All analyses were performed using the Statistical Package for the Social Sciences (SPSS) 12.0; the bootstrap simulations and the CEAC were generated using Microsoft Excel.

Sensitivity Analysis

One-way sensitivity analyses were conducted on deterministic variables to provide information on the robustness of the results of the economic evaluation. Costs were assumed to be fixed and therefore were not varied. In the first analysis, the electronic monitors were provided for only one drug for 3 months, instead of for each drug for a maximum of 5 months. In the second analysis it was assumed that both the cap and the container were used only once, instead of re-use of the cap and single use of the container. In the third analysis, in order to assess whether the results were robust to a change in the method of handling missing data, we conducted a complete case analysis. The sensitivity analyses were performed under the assumption that WTP and WTA are identical.

Results

In total, 258 patients were included in the study between September 2002 and March 2004. No follow-up data were available for five patients. Four patients refused to participate after inclusion (two due to illness, and two without giving a specific reason), and one patient died of stroke. Of the 253 patients (98%) with complete follow-up, 164 were randomised to the experimental strategy and 89 to the usual care strategy (figure 1). The mean age of the participants was 62 years (SD 10) in both groups; 59% were male in the experimental strategy and 49% were male in the usual care strategy. On average, 70% of the participants had paid employment and 77% were married in both groups.

Complete first, third and fifth month cost data were available for 139, 136 and 127 patients, respectively (85%, 83% and 77%) in the experimental strategy and for 84, 82 and 76 patients (94%, 92% and 85%) in the usual care strategy. There were no differences in QOL, BP, age and gender between patients with complete cost diaries and patients with missing cost data. In the experimental strategy, complete EQ-5D data were obtained from 160 patients

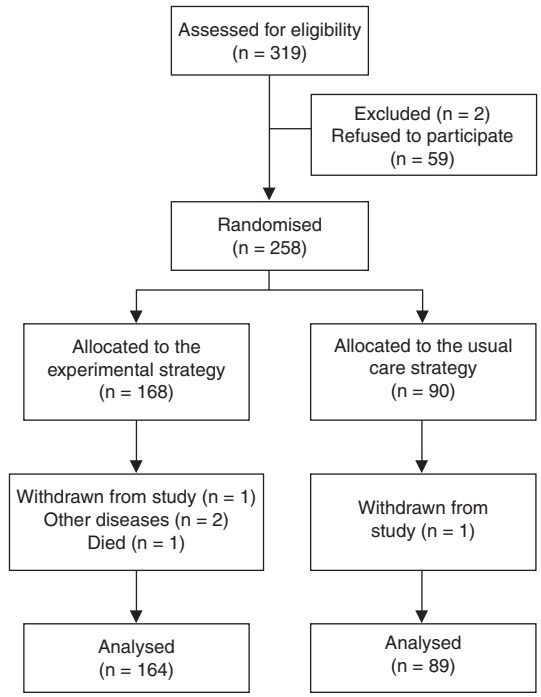

Fig. 1. CONSORT diagram summarising the progress of patients throughout the trial.

Table II. Mean outcomes (SD) of the experimental and usual care strategies

Outcome	Experimental strategy (n = 164)	Usual care strategy (n = 89)	Increment (95% UI)
Normalised BP at 5 months (% patients)	53.7	50.6	3.1 (−9.7, 15.8)
Utility			
Baseline	0.757 (0.252)	0.808 (0.184)	−0.052 (−0.103, 0.000)
5 months	0.794 (0.224)	0.813 (0.198)	−0.019 (−0.067, 0.030)
QALY[a]	0.323 (0.092)	0.338 (0.075)	−0.015 (−0.035, 0.005)
QALY, baseline utility adjustment[a]	0.330 (0.033)	0.327 (0.026)	0.003 (−0.005, 0.010)

a Range 0–0.417.

BP = blood pressure; **UI** = uncertainty interval based on bootstrap replications.

(98%) at baseline, and from 156 patients (95%) at 5 months versus 85 (95%) and 86 patients (95%), respectively, in the usual care strategy.

Costs

Electronic monitoring for 5 months led to a saving of €40 in medication costs versus usual care (95% UI −90, +8; table I). Reduction in drug costs is achieved as a result of the statistically significant ($p < 0.01$) lower percentage of patients with drug additions and/or dose escalations in the experimental care strategy. The average costs of electronic monitoring were €26 per patient. The communicator and software costs amounted to €242 per year per GP practice and €0.04 per prescription per month. The costs of the adherence improving training amounted to €19.80 per patient. In total, mean costs per patient directly related to the intervention were €367 in the experimental strategy and €374 in the usual care strategy. The mean total healthcare costs per patient amounted to €827 in the experimental strategy versus €927 in the usual care strategy (incremental costs: €100 saved; 95% UI −€415, +€189). This cost difference is mainly caused by a longer hospital stay (not related to hypertension) of patients in the usual care strategy, which resulted in higher admission costs compared with the experimental care group. The mean total 5 months societal costs per patient were slightly higher in the experimental strategy (€1573) than in the usual care strategy (€1526); incremental costs: €47 (95% UI −€873, +€867). This cost difference is mainly due to longer health-related work absenteeism in the experimental care strategy, which resulted in higher productivity loss costs for paid work compared with the usual care strategy.

Effects

At the end of the follow-up period, 53.7% of the patients in the experimental strategy achieved NBP, compared with 50.6% in the usual care strategy (table II). This resulted in an increment of 3.1% in favour of the experimental strategy (95% UI −9.7%, +15.8%).

The mean population health state utility estimate at baseline was 0.757 in the experimental strategy and 0.808 in the usual care strategy. Without adjustment for the baseline utility difference, less QALYs were generated in the experimental strategy compared with the usual care strategy. Adjusting for the baseline difference[46] 0.330 QALYs were yielded in the experimental care strategy versus 0.327 QALYs in the usual care group. As a result, the incremental QALY was 0.003 (95% UI −0.005, +0.010) in favour of the experimental care strategy.

Cost Effectiveness

From the healthcare perspective, electronic monitoring led to a cost saving of €100, and 3.1% more patients with NBP than with usual care. As a result, the ICER point estimate indicated a dominance situation for this outcome parameter. The uncertainty around this outcome is visualised in the cost-effectiveness plane in figure 2. In total, 55% of the cost-effectiveness replicates were situated in the south-east (dominance) quadrant. However, the uncertainty around the ICER was considerable and the replicates were scattered over the origin.

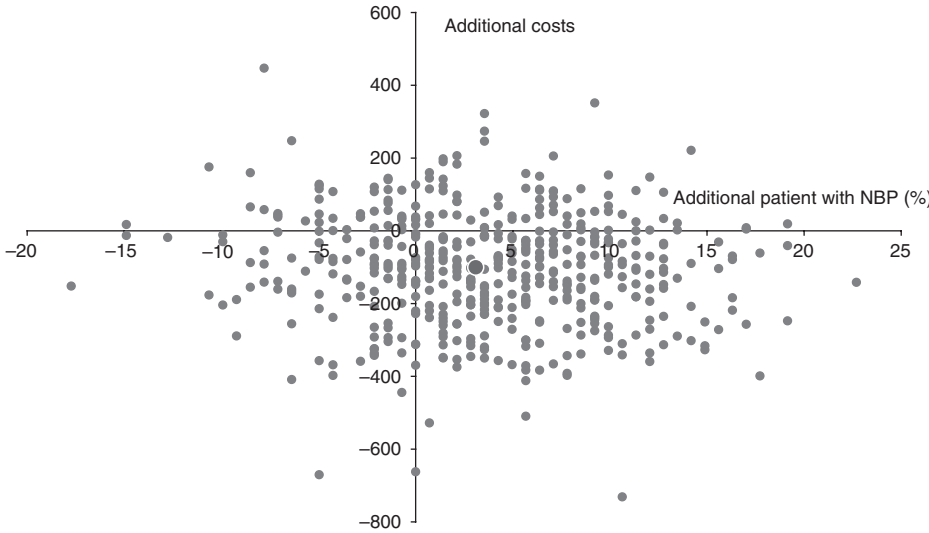

Fig. 2. Cost-effectiveness plane, constructed with 1000 bootstrap replications, showing the uncertainty around the point estimate of cost effectiveness (€, 2002 values) of the medication events monitoring system vs usual care; costs per patient with normalised blood pressure (NBP) from the healthcare perspective.

From the societal perspective, electronic monitoring resulted in extra costs of €47. This meant that electronic monitoring for a period of 5 months cost €15 667 per QALY gained. The uncertainty around the ICER point estimate showed the same pattern as for the clinical effectiveness measure (figure 3). In total, 43% of the pairs were located in the north-east quadrant, 33% in the south-east quadrant and 11% in the north-west quadrant. Again the uncertainty was considerable and the pairs covered the origin.

The acceptability curve is presented in figure 4. Concerning the healthcare costs per patient with

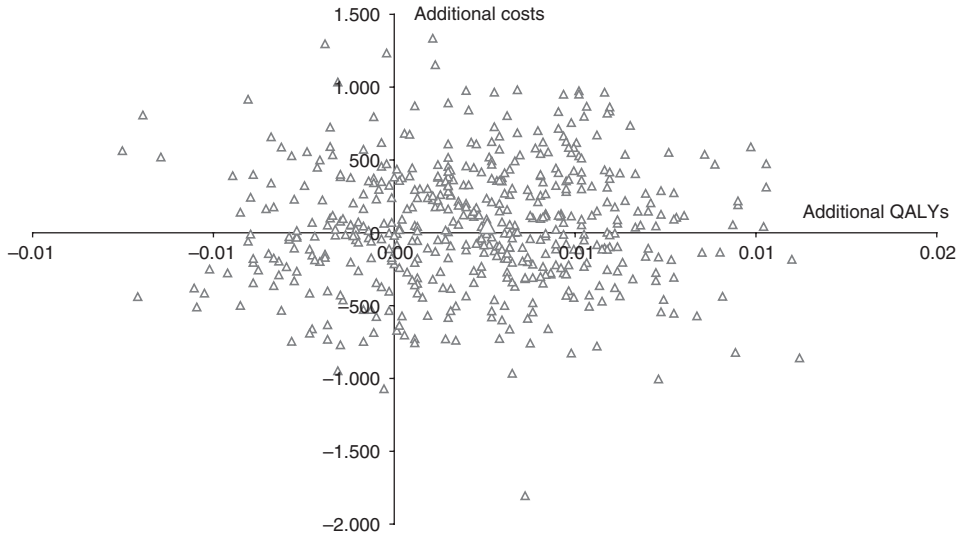

Fig. 3. Cost-effectiveness plane, constructed with 1000 bootstrap replications, showing the uncertainty around the point estimate of cost effectiveness (€, 2002 values) of the medication events monitoring system vs usual care; cost per QALY from the societal perspective.

NBP, the probability that the experimental strategy is the most cost-effective alternative ranged between 75% and 80% for all ceiling ratios, assuming WTP to be identical to WTA. When assuming that society is not willing to accept health loss, the probability ranged between 57% and 72%. For the societal costs per QALY analysis, the probability of cost effectiveness ranged from 45% to 51%, depending on the ceiling ratio and presuming WTP and WTA to be equal. This probability dropped 10% over the whole range of ceiling ratios when no compensation for health loss is accepted by society.

Sensitivity analysis

In the first sensitivity analysis it was assumed that in patients who use more than one antihypertensive drug, an electronic monitor was provided for only one drug. As this obviously results in lower costs in the experimental care group, the point estimate of the ICER remained to indicate a dominance situation (lower costs and more effects) from the healthcare perspective. From the societal perspective as a result of the decreasing costs, the extra costs decreased and the probability that electronic monitoring is cost effective was 53% at a ceiling ratio of €25 000 per QALY instead of 51%.

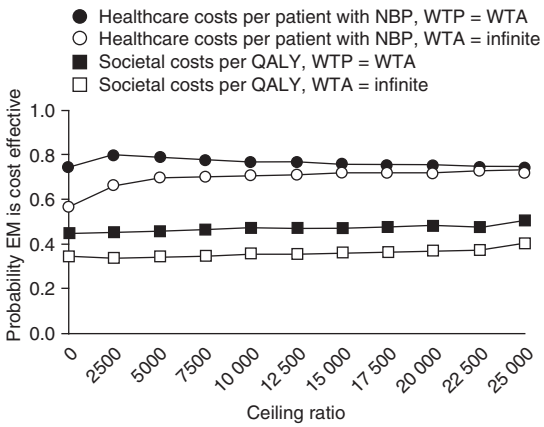

Fig. 4. Cost-effectiveness acceptability curves showing the probability that electronic monitoring (EM) is cost effective, given various thresholds for healthcare costs (€, 2002 values) per patient with normalised blood pressure (NBP) and societal costs per QALY, based on 1000 replications; data presented according to whether willingness to accept (WTA) is infinite or equivalent to willingness to pay (WTP).

In the second sensitivity analysis, it was assumed that the electronic monitor cap was not re-used. From the healthcare perspective, as a result of the increasing electronic monitoring costs, the probability that electronic monitoring is cost effective at a ceiling ratio of €25 000, decreased from 74% to 69% for the proportion of patients with NBP as the outcome parameter. From the societal perspective the probability dropped from 51% to 43% for the costs per QALY analysis at the maximum ceiling ratio.

In the third sensitivity analysis, as the effect data were virtually complete, we conducted a complete case analysis only for the mean total costs. In this analysis the incremental healthcare costs amounted to a saving of €150 (95% UI −€512, +€169). The incremental societal costs amounted to an additional €27 (95% UI −573, +597).

Discussion

The present study was the first economic evaluation of an adherence-improving programme in hypertensive patients. We demonstrated that the programme was slightly more expensive from a societal perspective than the usual care strategy but from the healthcare perspective it resulted in cost savings. However, it should be emphasised that the observed costs were not statistically significantly different between the groups, and that the uncertainty intervals of the differences were rather wide. The acceptability curve showed that the probability of cost effectiveness from the societal perspective (cost per QALY analysis) was rather low (47% irrespective of the ceiling ratio). It must be noted that inclusion of non-healthcare costs and use of generic QOL as the outcome parameter is especially appropriate in studies evaluating interventions in which these parameters are likely to be influenced. In this study on medication adherence in a population of patients with mild to moderate hypertension, this was not the case; the intervention had only a small impact on non healthcare costs and generic QOL.

In this respect, the societal perspective might not be the most appropriate perspective. Therefore, an analysis from the healthcare perspective was also

conducted. Only taking into account the healthcare costs and the proportion of patients with NBP, the probability of cost effectiveness was moderate (around 77%, irrespective of the ceiling ratio). A cost-minimisation analysis, whereby the less costly treatment is the preferred one, was not performed because Briggs and O'Brien[52] recommended focussing on the joint density of costs and effect differences, rather than separate and sequential hypothesis testing in costs and effects.

The sensitivity analyses demonstrated that the results were insensitive to the number of drugs per patient that are electronically monitored, that the costs of the electronic monitor strongly depended on re-use of the monitor cap, and that complete case analyses of costs led to similar results to mean imputation. Only when the cap can be used multiple times in different patients did the intervention appear to be a moderately cost-effective adjustment in the usual management of patients with hypertension (the probability of cost effectiveness was around 77%). In summary, the results strongly depend on the taken perspective (healthcare or societal), the outcome parameter (proportion of patient with NBP or QALY) and the re-use or single use of the electronic monitor cap.

We chose the relatively short time horizon of 5 months as we supposed that the effects of MEMS would manifest immediately (within 2 months), and the duration of the training was 3 months. Therefore, we expected to capture all relevant costs within this period of time. Moreover, since the observed effect in both outcome parameters was rather small, extension of the time horizon beyond 1 year using a modelling technique would be very difficult.

A limitation of the study may be the application of mean imputation. By imputing the group mean for missing values, the variation is reduced, and the degree of uncertainty has been underestimated. As a consequence, the uncertainty interval around the cost difference may be artificially small. It seems likely that the probability of cost effectiveness is an optimistic estimate. Thus, the cost-effectiveness probability of around 77% for healthcare costs per QALY can be regarded as a maximum. However, the conclusion that the difference in societal costs is small and not statistically significant was not altered.

In our opinion, there are no strong reasons to suppose that effectiveness of the MEMS would be different in other countries. However, it is generally known that transferability of costs to other countries is problematic.[53] For instance, the price level of medication or the costs of use of MEMS in the GP practice may differ in other countries. As a consequence, the cost-effectiveness results cannot be transferred to other healthcare delivery systems without careful consideration.

The cost effectiveness of several adherence-enhancing interventions has been assessed by others.[27-31] The majority of these studies were performed from the patient or healthcare perspective; only one trial by Eastaugh and Hatcher[27] included the societal perspective. As in our study, this study[27] related costs to the proportion of patients with BP control, whereas in the other studies a specific reduction in mm Hg[29,30] and medication adherence improvement[30] were used as outcome parameters. Because of the diversity of interventions and the use of different outcome parameters, studies in this area are difficult to compare. In the study by Friedman et al.[28] an automated telephone patient monitoring and counselling system was found to be a cost-effective tool to improve adherence compared with usual care. In the study by Logan et al. [28] a worksite hypertension programme proved to be substantially more cost effective than regular care. Cantor et al.[26] demonstrated that multiple educational intervention combinations are not more cost effective than single interventions. The results of the study by Eastaugh and Hatcher[27] showed that only in a subsample of highly depressed patients do the benefits of the triage method (consisting of clarification of the prescribed regimen, social support and increase of self confidence of the patients) outweigh its costs. Finally, Zarnke et al.[30] found that a patient-directed hypertension management strategy, in which patients measured their own BP at home, did not result in a lower frequency of physician visits or

a difference in QOL compared with office-based care.

Implementation of provision of MEMS monitors to all patients with mild to moderate hypertension in general practice who have not achieved adequate BP control could have favourable budget implications. Given a reduction in drug costs of €40 per 5 months, and assuming unchanged drug use over 1 year, a yearly reduction of €96 per patient can be obtained. As the costs directly related to electronic monitoring are relatively low (€26 per patient), this would result in a net cost reduction of €70 per patient. Taking into account that >2 million patients are prescribed antihypertensive drugs in The Netherlands,[4] and that in only 36% of these patients adequate BP control is not reached,[40] the provision of MEMS monitors to nonadherent patients could lead to a substantial cost saving.

Conclusion

The probability that the adherence-improving programme is cost effective is at best moderate. Moreover, the cost-effectiveness result is surrounded with considerable uncertainty and large-scale implementation warrants additional research into the economic consequences of this intervention.

Patients may benefit from the use of a MEMS monitor in situations where BP targets are not reached because of suspected non-adherence and both patient and GP are reluctant to increase the dose or number of antihypertensive drugs.

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