Improving Adherence to Lipid-Lowering Therapy in a Community Pharmacy Intervention Program: A Cost-Effectiveness Analysis

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ABSTRACT

BACKGROUND: Pharmaceutical care in community pharmacies has been shown to improve adherence to chronic therapies. Long-term impact on clinical outcomes or medical cost savings, however, remains understudied.

OBJECTIVE: To estimate the cost-effectiveness of a pharmaceutical care intervention program in Dutch community pharmacies that improved patients' adherence to lipid-lowering therapy.

METHODS: An economic evaluation was performed using a time-dependent Markov model from the health care payer perspective. Participants were patients initiating lipid-lowering therapy for primary prevention (40%) or secondary prevention (60%) of cardiovascular events (CVEs). The intervention was the pharmaceutical care program MeMO (Medication Monitoring and Optimisation) in 9 community pharmacies in the Netherlands, based on continuous monitoring and optimization of lipid-lowering therapy in new patients. The follow-up period of the program was 1 year. The main outcome of the intervention program was discontinuation of lipid-lowering therapy. This outcome was extrapolated in the economic model to lifelong costs, quality of life, reductions in cardiovascular events, and incremental cost-effectiveness ratios.

RESULTS: Patients in the MeMO program had a lower risk for therapy discontinuation, RR = 0.49 (0.37 to 0.66); the effectiveness was similar in primary and secondary prevention. In a cohort of 1,000 primary and secondary prevention patients, the MeMO program resulted in a reduction of 7 nonfatal strokes, 2 fatal strokes, 16 nonfatal myocardial infarctions (MIs), 7 fatal MIs, and 16 revascularizations over patients' lifetime. Additional medication, disease management, and intervention costs in the MeMO program were €411,000; the cost savings due to reduced CVEs were €443,000. The MeMO program resulted in 84 quality-adjusted life-years (QALYs) gained and net cost savings of €32,000. Clinical benefits and cost savings were highest in the secondary prevention population.

CONCLUSION: Pharmaceutical care in community pharmacies can improve statin therapy adherence, resulting in better prevention of CVEs. The MeMO program resulted in considerable clinical benefits and net cost savings. Programs by community pharmacies targeted at improving adherence may provide good value for money, and health care insurers should consider reimbursing these activities.

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What is already known about this subject

- Cardiovascular events, such as myocardial infarction and stroke, are a main cause of death and morbidity in most developed countries.
- Lipid-lowering therapy reduces the risk for cardiovascular events; however, therapy adherence in clinical practice is low.
- Pharmaceutical care in community pharmacies has been shown to improve adherence to chronic therapies, including lipid-lowering therapy.

What this study adds

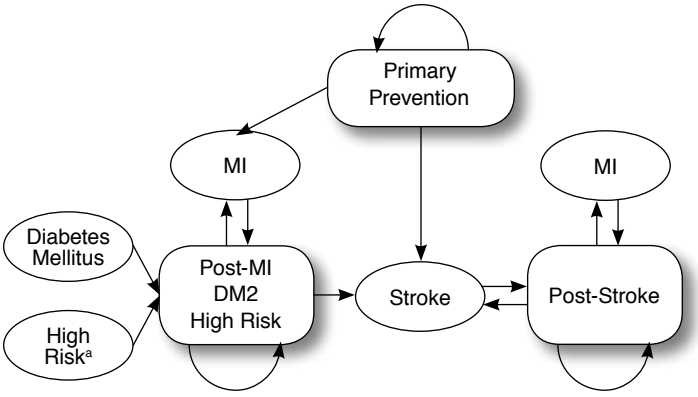
- A Dutch pharmaceutical care program in community pharmacies led to increased adherence to lipid-lowering therapy.
- The pharmaceutical care program was modeled to result in considerable clinical benefits, including reduced cardiovascular events, increased quality of life, and added life-years.
- Despite intervention costs and increased medication costs, the pharmaceutical care program led to net cost savings.

Cardiovascular events, predominantly myocardial infarction and stroke, are a main cause of death and morbidity in most developed countries.[1] Dyslipidemia is a major risk factor for cardiovascular events (CVEs). Lipid-lowering therapy, specifically statins, have become a cornerstone of treatment for dyslipidemia due to their marked lowering of low-density lipoprotein cholesterol (LDL).[2] Indeed, statins have demonstrated considerable efficacy in reducing myocardial infarction (MI), stroke, and costly revascularization procedures.[3,4] The clinical benefits of statin therapy are largest for *secondary prevention* of CVEs, that is, for patients who already experienced a CVE.[5,6] Also, as *primary prevention*, statin therapy reduces the risk for CVE, although the absolute risk reduction is smaller due to the lower baseline risk in this population.[7,8] The relative risk reduction of CVEs is around 30%, regardless of age, sex, prior history of CVEs, or other comorbid conditions, such as diabetes mellitus type 2 (DM2).[2]

Contrasting with the high therapy adherence often achieved in clinical trial settings, adherence to lipid-lowering medication in real-world settings is often suboptimal, and many patients discontinue therapy.[9,10] The promising results of clinical trials may therefore not be achieved in real-world settings.[11] Discontinuation of cardiovascular medication obviously leads to lower drug costs, but these cost savings are more than offset by increased medical costs of CVEs.[12,13] Although novel drugs may improve cardiovascular outcomes in the future, increasing therapy adherence to currently available drugs is at least equally important to optimize therapy.[14]

As a common place of interaction between patients and health care professionals, community pharmacies provide a promising setting for pharmaceutical care aimed to increase therapy adherence. In the Netherlands, the MeMO (Medication

FIGURE 1 Model Structure



[a]*High-risk patients were defined as patients with coronary disease except MI or other occlusive arterial disease.*[5]

DM2 = type 2 diabetes mellitus; MI = myocardial infarction.

TABLE 1 Model Population Characteristics

	Population Characteristics (%)
Age (mean; 95% CI)	61.3 (55.3-67.3)
Female gender	45.4 (41.0-49.8)
No CVE history or DM	40
CVE history or DM	60
DM	20
MI	40
Stroke	15
Other high risk[a]	25
Drug use	
Simvastatin	83.4
Pravastatin	3.0
Atorvastatin	7.4
Rosuvastatin	4.4
Other lipid-lowering drugs	1.8

[a]*High-risk patients were defined as patients with coronary disease except MI or other occlusive arterial disease.*[5]

CI = confidence interval; CVE = cardiovascular event; DM = diabetes milletus; MI = myocardial infarction.

Monitoring and Optimisation) program has been an ongoing pharmaceutical care program since 2006, focusing on osteoporosis, asthma/chronic obstructive pulmonary disease, cardiovascular disease, DM2, and depression.[15] In particular, the program is targeted at the monitoring and optimization of chronic therapy use. The clinical and economic benefits of MeMO have been demonstrated for bisphosphonate use in osteoporosis.[16,17] Recently, the efficacy of the MeMO program in reducing discontinuation of lipid-lowering therapy was demonstrated.[18]

In the Netherlands in 2008, large-scale and often mandatory generic substitution policies have been installed for many chronic medications, including lipid-lowering drugs. The ensuing competitive bidding strategies led to considerable price reductions of these generics. For example, the average list price for simvastatin 40 milligrams (mg; 30 pieces) dropped from 14.16 euros (€) in December 2007 to €0.99 one year later.[19] There have been concerns that generic substitution negatively influences therapy adherence.[20] The costs of improving adherence should be low because of the generics price drops. More recently, other policy reforms opened up the possibility for direct financial reimbursement of pharmaceutical care. Taken together, these 2 policy changes demonstrate the need for the study and evaluation of adherence improving programs in community pharmacies.[21] Potential reimbursement of pharmaceutical care interventions will partly depend on their clinical benefits and cost impact.

The purpose of this study was to determine whether a proactive pharmaceutical care intervention aimed to increase adherence to lipid-lowering medications (the MeMO program) offers good value for the money. To this purpose, a cost-effectiveness analysis was performed to estimate the short- and long-term costs and benefits from a Dutch health care payer perspective, taking into account all direct medical costs, including intervention costs, drug costs, medical costs, and disease management costs.

Methods

Model Structure

A cost-effectiveness model was built to evaluate the costs and benefits of lipid-lowering therapy. The following CVEs were monitored: nonfatal MI, fatal MI, nonfatal stroke, fatal stroke, and revascularization (either coronary artery bypass graft or percutaneous transluminal coronary angioplasty). Patients could die from cardiovascular or noncardiovascular causes. The key model driver was discontinuation of therapy, which influenced therapy effectiveness and thereby occurrence of CVEs. The comparators in the model were the MeMO program and usual care.

Three time-dependent Markov models were developed through which patients progressed. In the first model, patients entered without a history of CVEs ("primary prevention" model). Patients with a history of MI or other CVE,[5] patients with DM2, and patients from the primary prevention model who experienced a nonfatal MI entered the second model ("secondary prevention" model). A third model was developed for patients who had a history of stroke before entering the model or experienced a nonfatal stroke in the model ("secondary prevention after stroke" model). A simplified schematic of the Markov models is shown in Figure 1.

Patient Population

In the MeMO population, the average age was 61.3 years (95% confidence interval [CI]: 55.3 to 67.3), and 45.4% were female (95% CI: 41.0% to 49.8%).[18] Forty percent of the patients could

not be identified as having had a CVE and did not have DM; these patients entered the primary prevention model. The other 60% of patients either had DM or a history of CVE, as shown in Table 1. Patients with DM2 started in the same secondary prevention model as patients who had experienced an MI or other CVE because, with regards to lipid-lowering therapy, DM is considered a coronary disease equivalent.[22]

Statin Efficacy

Large clinical trials were used to calculate statin efficacy for patients with hypercholesterolemia but without history of CVE (WOSCOPS study[8]), patients with a history of CVE (except stroke) or DM2 (HPS study[5]), and patients with a history of stroke (SPARCL study[6]). Patients' gender or age did not influence therapy efficacy, as shown by a large meta-analysis.[7]

Incidence Rates

For patients without a history of CVEs, the incidence of a first MI was taken from a Dutch observational study.[23] No Dutch incidence rates were available for the other CVEs; therefore, these were assumed to be proportional to those measured in the WOSCOPS trial.[8] Mortality after a first MI,[24,25] first stroke,[26,27] or first revascularisation[28,29] were taken from Dutch observational data and were inserted in the model age-dependent. Revascularization as a first cardiovascular event does not significantly increase the risk of subsequent cardiovascular death, all-cause death, or stroke.[30] Therefore, patients in the primary prevention model experiencing a revascularization but no MI did not progress to the secondary prevention model. For patients with a history of CVEs, a similar approach was used. Incidence rates for MI and stroke were taken from Dutch observational data,[31] and these were supplemented with data from the HPS and SPARCL trials to estimate CVE rates in the model.[5,6]

Adverse Events and Noncardiovascular Mortality

Serious side effects of statins are rare. For the model, we used an incidence rate of rhabdomyolysis of 0.10 per 1,000 patient-years based on observational data registering 21 cases in 219,000 patient-years of statin use.[32] The average case fatality of rhabdomyolysis was 10% (96 out of 935 cases).[33] Myopathy was more common, with an incidence rate of 0.69 per 1,000 patient-years, based on 4,002 cases in 5.8 million patient-years of statin use.[34] Myopathy was not assumed to be fatal, but both myopathy and nonfatal rhabdomyolysis were associated with a loss in quality of life as will be described. Noncardiovascular mortality rates were based on Dutch overall population data and were age and sex specific.[35]

Therapy Persistence

Statin discontinuation (nonpersistence) rates were based on real-world Dutch observational data.[10] After 1 year, therapy persistence was 61.5%; after 2 years, persistence was 47.7% in primary prevention patients and 57.7% in secondary prevention patients. Persistence was assumed to remain stable thereafter, as supported by observational data with up to 10 years of follow-up.[9] Persistence in clinical trials is often higher than in the real world.[11] Indeed, persistence rates were reported to be between 80% and 90% in the clinical trials used for this model.[5,8] Statin efficacy was therefore adjusted for the difference in persistence between trial and real-world settings. For example, in primary prevention patients after year 2, persistence was 80.6% in the WOSCOPS trial[8] and 47.7% in the real world.[10] The average statin efficacy in real-life patients was assumed to directly reflect this difference in persistence, that is, to be 59.2% (=47.7/80.6×100%) of the efficacy measured in the clinical trial.

Efficacy of the Pharmaceutical Care Program

The effectiveness of the intervention to prevent discontinuation of lipid-lowering therapy was measured using the MeMo pharmaceutical care program in the Netherlands. This program was based on a continuous monitoring of therapy use in patients who initiated lipid-lowering drugs.[15,18] A detailed description of the MeMO program is provided elsewhere.[18] A total of 500 patients were included in the MeMO program, while 502 patients who received care as usual served as historical controls. One year after therapy initiation, the difference in discontinuation between the intervention and the usual care groups was significant with a hazard ratio (HR) of 0.49 (95% CI: 0.37 to 0.66).[18] In a post-hoc analysis of these data, similar efficacies were found for patients in primary prevention (HR = 0.47; 95% CI: 0.32 to 0.62) and secondary prevention (HR = 0.54; 95% CI: 0.35 to 0.73).

Costs

All direct medical costs were taken into account: intervention costs, drug costs, medical costs, and disease management costs. Time investments in the MeMO program were collected for the following activities:

1. Automatic selection of nonadherent patients and printing of medication profiles. The average duration of this action was 14 minutes per pharmacy per month.
2. Manual evaluation of medication profiles for nonadherence by pharmacists. This action took between 1 and 3 minutes per patient.
3. Contacting nonadherent patients and/or their prescribers. These actions took between 5 and 60 minutes, with an average time investment of 15 minutes per nonadherent patient.

Over a period of 3 months, in which the time investments were measured, 3,844 minutes were spent, and 418 patients were selected for intervention. These 418 patients were part of a total of 6,710 patients using lipid-lowering drugs. The average time investment per patient per year therefore was 2.3 minutes.

TABLE 2 Influence of CVEs on Work Productivity

CVE	% Return to Full-Time Work[a]	Median Time to Return (Days)	% Return to Part-Time Work[a]	Median Time to Return (Days)	Reference
MI	70	50	70	50	Perk, 2007[40]
Revascularization (no MI)	77	69	64	85	Hackett et al., 2012[41]
Stroke	82	43	82	43	Hlatky et al., 1998[42]

[a]*Refers to persons below retirement age (65 years).*
CVE = cardiovascular event; MI = myocardial infarction.

This time investment was assumed to be performed by pharmacists with an hourly rate of €61.17 The total intervention costs were €2.33 per screened patient treated with statins or, alternatively calculated, €36.80 per patient selected for intervention. Start-up costs, such as costs for training sessions, were not taken into account, since these differed between pharmacies and could not be estimated on a per-patient basis.

The average drug costs, including pharmacists' prescription fees, per defined daily dose (DDD) in the Netherlands in 2012[36] were applied to the distribution of drugs used in the MeMO program,[18] shown in Table 1. The most used lipid-lowering drug was simvastatin (83.2%). Use of nonstatin lipid-lowering drugs was rare (1.8%). Medical costs for CVEs were based on Dutch data and were inflated to 2012 prices using the Dutch consumer price index; the costs were differentiated into costs for the first year and annual costs thereafter.[37] Disease management costs included general practitioner (GP) visits at €106 per year and laboratory tests at €26 per year.[38] Similar to another cost-effectiveness study of statin therapy,[38] patients who had discontinued statin therapy did not accrue drug costs but still used 50% of GP visits and 100% of laboratory tests.

Reliable Dutch data on productivity losses after CVEs are scarce. Therefore, indirect nonmedical costs (productivity losses) could not be taken into account in the base-case analysis. Still, strong economic, clinical, and social arguments exist to support cardiac rehabilitation and returning to work for patients suffering from a CVE.[39] Some assumptions could be made on employment and return-to-work rates based on international data as summarized in Table 2.[40-42] All persons were assumed to retire at age 65. In a separate analysis, an estimate was made of the potential impact of productivity gains of the MeMO program.

Utilities

Cardiovascular disease has a large impact on patients' health-related quality of life (HRQoL). This was reflected in the model by taking into account the health-related utilities of the various health-states, ranging from 1 (perfect health) to 0 (death). Patients' utilities were assumed to decrease with age, based on results from a large United Kingdom sample interviewed with the EQ-5D questionnaire.[43] The relationship between age and utility was described as follows: utility = 1.060-0.004 × age.[44]

After a CVE, patients in the model incurred a disutility, based on data of the Dutch national burden of disease study.[45-47] After an MI or stroke, the disutility was 0.288 and 0.609, respectively. No disutility was assumed after revascularization. In case of joint health-states (such as MI in poststroke patients), only the largest of the 2 disutilities was applied.[48,49] For patients with DM2, an additional disutility of 0.198 was applied.[45-47] No disutility from taking a pill everyday was assumed in the model.[50,51] In the rare case of nonfatal rhabdomyolysis or myopathy, disutility of 0.530 was applied for 1 year.[52] Utilities and life expectancies were multiplied to calculate quality-adjusted life years (QALYs).

Cost-Effectiveness Analysis

In the cost-effectiveness analysis, the costs and clinical benefits of the MeMO program were compared with usual care. The incremental cost-effectiveness ratio (ICER) can be calculated as:

$$ICER = \frac{C_{MeMO} - C_{Usual\ care}}{E_{MeMO} - E_{Usual\ care}}$$

where C equals the costs and E the clinical benefits (in QALYs) of the MeMO and usual care groups. Cohorts of 1,000 patients entered the model. The time-horizon for analysis was lifelong years in the base-case; shorter time-horizons were used in sensitivity analyses. Costs and clinical effects were discounted at 4.0% and 1.5% per annum, respectively, following Dutch guidelines.

Sensitivity Analyses

An overview of all model parameters that were varied in sensitivity analyses is shown in Table 3. For brevity, statin effectiveness and incidence rates for the nonfatal and fatal events or for non-cardiovascular death are not shown in the table. In univariate sensitivity analyses, parameters were varied by 25% to determine the main cost-effectiveness drivers. Scenario analyses were performed varying the duration of the program, the costs of the intervention, and the baseline risk for vascular disease in patients without a history of CVEs. In probabilistic sensitivity analyses (PSA), 10,000 random samples were drawn from all parameters according to the specified distributions and confidence intervals shown in Table 3. For costs and utilities, standard errors of 10% of the mean were used, since no variances were available from

TABLE 3 Summary of Model Parameters Varied in Sensitivity Analyses

Parameter	Value	95% CI	Distribution	Reference
MeMO program effectiveness				
Primary prevention	Nonadherence: 0.47	0.32 to 0.62	Normal	Stuurman-Bieze et al., 2013[18]
Secondary prevention	Nonadherence: 0.54	0.35 to 0.73		
Drug effectiveness				
Primary prevention	MI: 0.71	0.52 to 0.89	Normal	Shepherd et al., 1995[8]
	Stroke: 0.90	0.50 to 1.30		
	Revascularization: 0.64	0.29 to 0.98		
Secondary prevention after MI, DM, or other high risk[a]	MI: 0.74	0.67 to 0.81	Normal	Heart Protection Study, 2002[5]
	Stroke: 0.75	0.64 to 0.86		
	Revascularization: 0.71	0.61 to 0.81		
Secondary prevention after stroke	MI: 0.69	0.41 to 0.96	Normal	Amarenco et al., 2006[6]
	Stroke: 0.85	0.70 to 1.01		
	Revascularization: 0.58	0.08 to 1.09		
Incidence rates in nonusers of lipid-lowering therapy (per 1,000 patient-years)				
Primary prevention	MI: 4.1	3.6 to 4.6	Binomial[b]	Shepherd et al., 1995[8]; Heintjes et al., 2009[23]
	Stroke: 0.9	0.7 to 1.1		
	Revascularization: 1.2	0.9 to 1.5		
Secondary prevention after MI, DM, or other high risk[a]	MI: 32.4	28.0 to 37.1	Binomial[b]	Heart Protection Study, 2002[5]; Klungel et al., 2002[31]
	Stroke: 9.5	7.1 to 12.1		
	Revascularization: 17.0	13.8 to 20.3		
Secondary prevention after stroke	MI: 10.7	8.8 to 12.6	Binomial[b]	Amarenco et al., 2006[6]
	Stroke: 28.8	25.6 to 32.1		
	Revascularization: 14.6	12.4 to 16.9		
Adverse event rates (per 1,000 patient-years)				
	Rhabdomyolyse: 0.10	0.05 to 0.13	Poisson[b]	Graham et al., 2004[32]
	Myopathy: 0.69	0.67 to 0.71	Binomial[b]	Molokhia et al., 2008[34]
Costs				
Intervention (per patient per year)	€2.33	€1.91 to €2.82	Lognormal	GIPdatabank[36]
Drug costs (per year)	€63	€52 to €77		
Medical costs[c]				
Fatal MI	€1,700	€1,400 to €2,100	Lognormal	Heeg et al., 2007[37]
Nonfatal MI	€14,700	€12,000 to €17,800		
Post-MI (annual)	€2,000	€1,600 to €2,400		
Fatal stroke	€3,700	€3,100 to €4,500		
Nonfatal stroke	€28,200	€23,100 to €34,100		
Poststroke (annual)	€5,200	€4,200 to €6,300		
Nonfatal MI after stroke	€23,900	€19,500 to €28,900		
Post-MI and stroke (annual)	€5,200	€4,300 to €6,300		
CABG	€11,800	€9,700 to €14,300		
PTCA	€3,500	€2,800 to €4,200		
Other mortality	€1,200	€900 to €1,400		
Disease management				
GP visits (annual	€106	€87 to €129	Lognormal	Greving et al., 2011[38]
Laboratory visits (annual)	€26	€21 to €31		
Disutilities				
Disutility per higher age (year)	0.004	0.002 to 0.006	Normal	Ward et al., 2007[44]
DM	0.198	0.161 to 0.238	Beta	National Kompas Volksgezondheid[45]; Stouthard et al., 1997[46]; van Baal et al., 2006[47]
MI	0.288	0.233 to 0.346		
Stroke	0.609	0.487 to 0.725		
Rhabdomyolysis or myopathy	0.530	0.426 to 0.633		Cham et al., 2010[52]

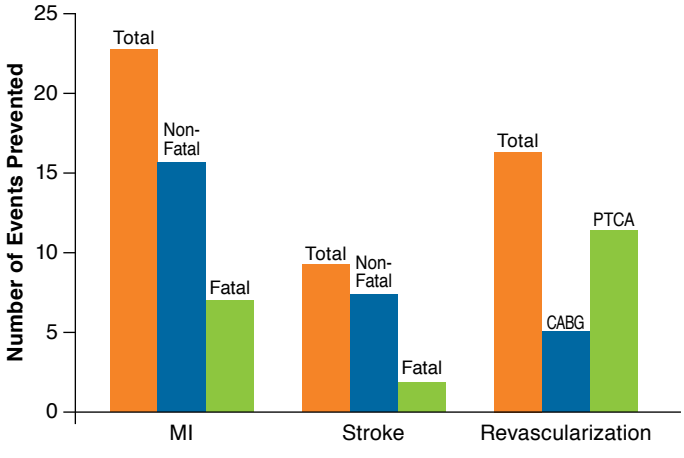
[a] *High-risk patients were defined as patients with coronary disease except MI or other occlusive arterial disease.*[5]

[b] *Sampling was performed on the actual patient numbers, not on the rates.*

[c] *Rounded to the nearest €100 for ease of presentation; unrounded figures were used in the model.*

CABG = coronary artery bypass graft; CI = confidence interval; DM = diabetes mellitus; GP = general practitioner; MeMO = Medication Monitoring and Optimisation; MI = myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty; € = euro.

FIGURE 2 CVEs Prevented in the MeMO Intervention Compared with the Control Group, As Estimated in the Model with Lifelong Time Window



CABG = coronary artery bypass graft; MI = myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty.

the literature. Using the PSA, 95% CIs around the model results and the probability of the MeMO program to be cost saving or cost-effective could be calculated.

Results

Statin Adherence

After 1 year in the model, 38.5% of the control patients discontinued statin therapy compared with 19.0% in the interventions group; after 2 years, statin discontinuation was 47.7% versus 23.3%, respectively.

CVE Occurrence

Occurrence of CVEs is summarized in Figure 2. Over the total time-period of the model, a total of 7 nonfatal strokes (95% CI: 2.8 to 14.0), 2 fatal strokes (95% CI: 0.2 to 4.4), 16 nonfatal MIs (95% CI: 8.5 to 25.6), 7 fatal MIs (95% CI: 2.9 to 12.5), and 16 revascularizations (95% CI: 8.9 to 26.5) were prevented in the intervention group compared with the control group. The average life expectancy in this cohort was 81.3 years in the control group; the increase in average life expectancy in the intervention group was 48 days (95% CI: 28 to 97).

Costs and Cost-Effectiveness

In the first 5 years of the model, the increased statin use in the intervention group led to additional drug costs of €61 per patient, spread over these 5 years. In addition, a similar increase in disease management costs was estimated of €53 per patient, spread over 5 years. The average costs required for the pharmacist intervention were €7.70 per patient, spread over the first 5 years. These additional costs were more than offset by lower medical costs due to prevented CVEs, leading to an average cost savings of €126 per patient over the first 5 years of the model.

The cost-effectiveness of the MeMO program over patients' lifetime is summarized in Table 4. Increasing statin adherence with the MeMO program was a dominating strategy in the overall patient population. The majority of cost savings were due to CVE prevention in the secondary prevention population. Still, the MeMO intervention was highly cost-effective (€4,585 per QALY gained) in primary prevention.

Sensitivity Analyses

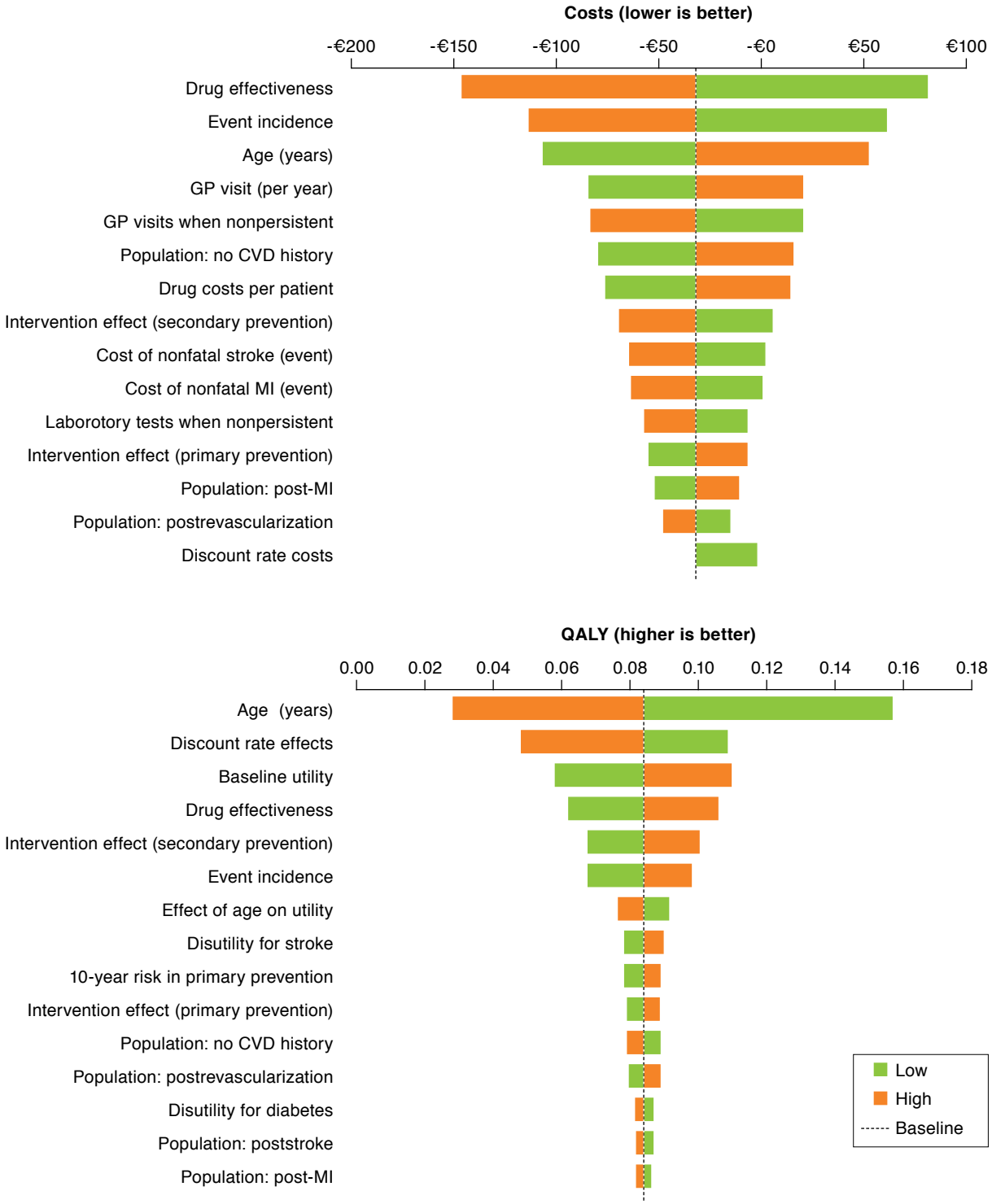
All model parameters described in Table 3 were subjected to univariate sensitivity analyses. The only parameters resulting,

TABLE 4 Cost-Effectiveness of the MeMO Intervention

	Primary Prevention Population			Secondary Prevention Population			Overall Population[a]		
	MeMO	Control	Difference	MeMO	Control	Difference	MeMO	Control	Difference
Costs									
Intervention cost (€)	22	0	22	22	0	22	22	0	22
Drug costs (€)	601	405	197	590	421	169	596	415	181
Medical costs (€)	1,931	2,059	-129	27,195	27,842	-647	17,086	17,529	-443
Management costs (€)	1,559	1,394	165	2,353	2,120	233	2,038	1,829	208
Total costs (€)	4,113	3,858	255	30,160	30,383	-223	19,741	19,773	-32
Effects									
QALYs	13.15	13.10	0.052	6.97	6.86	0.105	9.44	9.36	0.084
Life-years	17.36	17.31	0.053	15.05	14.92	0.131	15.98	15.88	0.100
Cost-effectiveness of MeMO									
Cost per QALY gained (€)		4,585			*Dominating*			*Dominating*	
Cost per life-year gained (€)		4,517			*Dominating*			*Dominating*	

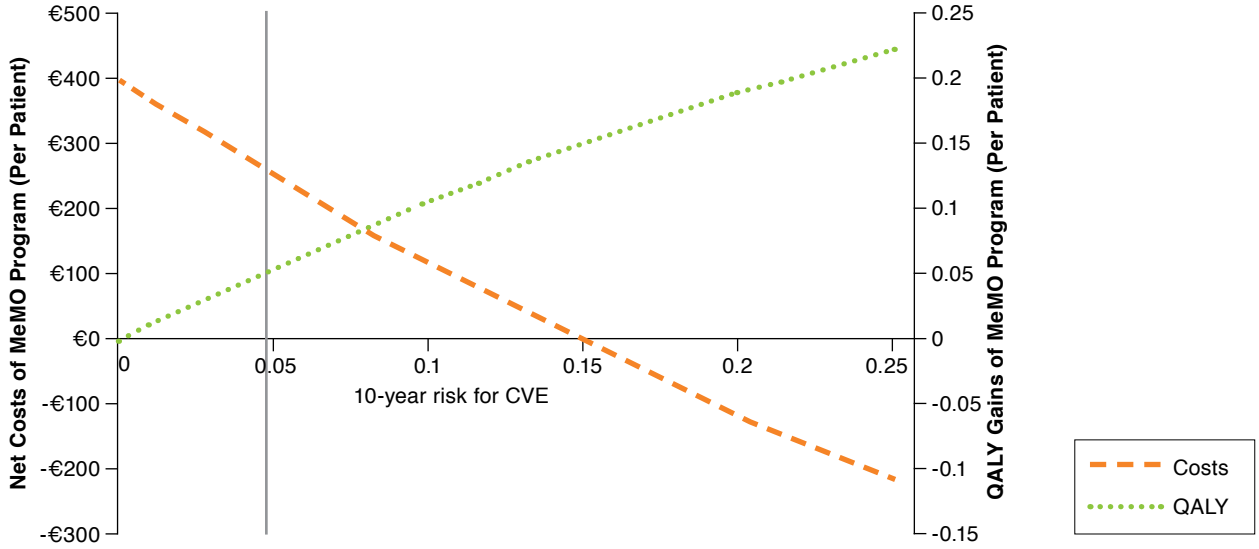
[a]*As shown in Table 1, the proportion of patients in the MeMO study in the primary and secondary prevention population was 40% and 60%.*
MeMO = Medication Monitoring and Optimisation; QALYs = quality-adjusted life years; € = euro.

FIGURE 3 Univariate Sensitivity Analysis



CVD = cardiovascular disease; GP = general practitioner; MI = myocardial infarction; € = euro.

FIGURE 4 Scenario Analysis: Influence of 10-Year CVE Risk in Primary Prevention Patients



Note: Vertical line denotes base-case 10-year CVE risk for primary prevention patients.
CVE = cardiovascular event; MeMO = Medication Monitoring and Optimisation; QALY = quality-adjusted life-years; € = euro.

when changed by 25%, in a positive ICER were a higher age (€1,866 per QALY), a lower statin effectiveness (€1,289 per QALY), or lower CVE incidence (€905 per QALY). The 15 most influential factors for net cost savings and QALY gains are shown in Figure 3.

Probabilistic sensitivity analyses showed that the probability of cost savings of the MeMo program was 60.7%. The probability of being cost-effective at the common willingness-to-pay thresholds of €20,000 or €50,000 per QALY gained was 100%. In the primary prevention population, there was a low (5.3%) probability of cost savings, but a 91.7% and 98.1% probability for cost-effectiveness at the above mentioned thresholds. In the secondary prevention population, there was a very high (94.1%) probability for net cost savings and a 100% probability of cost-effectiveness.

Scenario Analyses

The cost savings and health gains decreased with more pessimistic assumptions on the durability of the effectiveness of the intervention. Still, even if the MeMO program would have no effectiveness after the first year, there would be net cost savings and QALY gains (€10 and 0.006 QALY's per patient vs. €32 and 0.084 QALY's per patient when assuming lifelong effectiveness). The intervention cost, estimated at €2.33 per screened patient per year (equivalent to €36.80 per patient selected for intervention by the pharmacist), was a relatively minor cost driver. The program led to cost savings even if intervention costs were doubled. In the primary prevention population, the 10-year risk for CVEs was 4.8%. In patients with a higher risk for CVEs, the cost savings and clinical benefits increased, shown in Figure 4.

Work Productivity

Table 5 summarizes permanent and temporary loss of work because of CVEs in cohorts aged 40, 50, or 60 years. As all patients were assumed to retire at age 65, the productivity gains from the MeMO program were higher for younger patients than for older patients. Around 40%-45% of permanently lost jobs were full-time jobs; around 50%-60% of temporary lost jobs were full-time jobs. The average absent time for persons temporarily out of work was 50 days.

Discussion

Principal Findings

This study assessed the cost-effectiveness of a community pharmacy intervention program aimed to improve adherence to statin therapy by preventing discontinuation for both primary and secondary prevention patients. Improvements in therapy use were extrapolated to lifetime reductions in cardiovascular events, cost savings, and quality-of-life gains. Based on the model's results, the intervention was a dominating strategy (net cost savings and clinical benefits) compared

TABLE 5 Work Losses Due to CVEs

Age	Number of Persons Out of 1,000		
	MeMO	Control	Difference
40 years			
Permanent loss of work	219	232	-13
Temporary loss of work	193	214	-21
50 years			
Permanent loss of work	157	166	-9
Temporary loss of work	122	136	-14
60 years			
Permanent loss of work	68	72	-3
Temporary loss of work	44	49	-5

CVEs = cardiovascular events; MeMO = Medication Monitoring and Optimisation.

with usual care. The benefits of the intervention were largest in patients with DM2 or a history of CVEs, but the program was also cost-effective for patients receiving statins for primary prevention.

Limitations

To our knowledge, this is the first pharmacoeconomic analysis of statin therapy to model primary as well as secondary prevention patients. The model was quality checked by an author not involved in model building using a standardized checklist[53] as well as a thorough check of all model calculations. The effectiveness of the MeMO program was based on a large community pharmacy program.[18] A limitation of this program was that clinical parameters (such as LDL levels) were not measured. Several important assumptions were made in this cost-effectiveness model. An important assumption was that the effect of the intervention program would last throughout the patients' lifetime. If the duration of effectiveness of the intervention was reduced in scenario analyses, the cost savings and clinical benefits decreased accordingly. Still, even with a 1-year duration of effectiveness, the intervention was cost saving strategy albeit with fewer QALY gains. The model also assumes similar efficacy for the different lipid-lowering drugs, which may not be true.[23,54,55] Finally, the assumption was made that adherent patients could achieve the efficacy measured in clinical trials at a dose equivalent of 1 DDD (this unit is the average daily dose of a drug for its main indication in adults and is recommended by the World Health Organization). The actual DDD equivalents prescribed in the Dutch setting varied per drug but was close to 1 for the most commonly prescribed simvastatin (1.02 ± 0.39).[56]

Comparison with Other Studies

Few studies have assessed the costs and effectiveness of adherence-improving interventions for lipid-lowering drugs.[57] The most effective of these interventions were those where adherence is closely monitored, similar to the MeMO intervention. Although several studies assessed the cost-effectiveness of statin therapy, and some included the level of adherence as a model parameter,[38] none specifically assessed the cost-effectiveness of improving adherence to statin therapy.

Some health economic analyses of statins included a small but measurable disutility from taking a statin pill every day.[38,58] Other studies, however, did not[44,59] or only applied a disutility in sensitivity analyses.[60,61] The studies that included a disutility for statin use based this on assumption[58] or on analogy to models in aspirin or warfarin.[38] Long-term follow-up studies, however, have found no influence of statin use on quality of life.[50,51] Therefore, we included no disutility for chronic statin use apart from disutilities arising from possible side effects.

Implications for Pharmacists and Policymakers

The results of our study suggest that it would be cost-effective to promote and reimburse pharmacy-led interventions to improve statin therapy adherence. The costs of pharmacist intervention was low compared with standard disease management costs. This has also been reported for other adherence-improving programs.[57] Compared with these other programs, the per-patient costs of this intervention were also relatively low. This is because in the MeMO intervention patients are monitored with semiautomated procedures, and only nonadherent patients are selected for the more time-consuming personal counseling. Such targeted approaches lead to more efficient pharmaceutical care programs.[21] Scenario analyses show that apart from medical cost savings, considerable productivity gains may also be achieved by the intervention, especially in younger persons.

Future Research

As with most pharmacoeconomic analyses, several assumptions had to be made. The most important of which was the extrapolation of the short-term follow-up period of the MeMO intervention to lifelong costs and CVEs. Future research should continue to monitor adherence-improving programs and ideally directly measure the clinical benefits of such programs. However, as time constraints and costs may be prohibitive for such studies, cost-effectiveness modeling efforts such as this study should provide valuable information on the potential value of adherence-improving programs in community pharmacies.

Conclusion

Pharmaceutical care in community pharmacies can improve statin therapy adherence, resulting in more optimal prevention of CVEs. The MeMO program resulted in considerable clinical benefits and overall cost savings. Adherence-improving programs in community pharmacies may provide good value for money, and health care insurers should consider reimbursing these activities in the Netherlands.

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Concept and design for this study were contributed by Vegter, Hiddink, Stuurman-Bieze, and Postma. Van Boven, Oosterhof, Hiddink, and Stuurman-Bieze were responsible for data collection, and Vegter, Oosterhof, Hiddink, and Stuurman-Bieze interpreted the data. The manuscript was written and revised by Vegter, van Boven, and Postma.

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