Cost-Utility of an Objective Biochemical Measure to Improve Adherence to Antihypertensive Treatment

van Schoonhoven, Alexander V; van Asselt, Antoinette D I; Tomaszewski, Maciej; Patel, Prashanth; Khunti, Kamlesh; Gupta, Pankaj; Postma, Maarten J

Published in:
Hypertension

DOI:
10.1161/HYPERTENSIONAHA.118.11227

Publication date:
2018

Cost-Utility of an Objective Biochemical Measure to Improve Adherence to Antihypertensive Treatment

Alexander V. van Schoonhoven, Antoinette D.I. van Asselt, Maciej Tomaszewski, Prashanth Patel, Kamlesh Khunti, Pankaj Gupta,* Maarten J. Postma*

See Editorial Commentary, pp 1090–1092

Abstract—Nonadherence to antihypertensive medications is known to be a major health problem. Novel biochemical analyses using liquid chromatography-tandem mass spectrometry are becoming accepted as a clinically useful objective measure to manage (non)adherence in Hypertension Clinics. Discussion of results from such analyses with patients can significantly improve adherence and blood pressure control. Our objective was to model the cost-effectiveness of performing liquid chromatography-tandem mass spectrometry-based analyses in improving adherence in patients with hypertension. Lifetime cost-utility was assessed from a UK healthcare payer perspective, using a Markov model. Efficacy was based on study findings of lowering blood pressure because of improved adherence to drug treatment. Cost and utilities were derived from literature. The base case cohort consisted of males aged 65 years. Subgroup analyses included varying population sex and age and a subgroup of patients with apparent resistant hypertension. Additionally, univariate and probabilistic sensitivity analyses were performed. Our findings are reported after the Consolidated Health Economic Evaluation Reporting Standards checklist. Per patient, screening resulted in 0.020 incremental quality-adjusted life-years and a negative incremental cost of £495, suggesting the intervention to be dominant compared with care as usual. Targeting younger patients or patients with apparent resistant hypertension would further improve these outcomes. Modeling suggested that screening prevented 518 myocardial infarctions and 305 stroke events in a cohort of 10 000 male hypertensive patients. Using liquid chromatography-tandem mass spectrometry-based biochemical analyses to improve adherence in hypertensive patients is likely to be an effective and cost-saving strategy, especially in patients with apparent resistant hypertension. **(*Hypertension*. 2018;72:1117-1124. DOI: 10.1161/HYPERTENSIONAHA.118.11227.)** ● **Online Data Supplement**

Key Words: blood pressure ■ cardiovascular diseases ■ cost-benefit analysis ■ hypertension ■ mass spectrometry ■ myocardial infarction

Hypertension is the leading cause of global disease burden and the major risk factor for mortality and cardiovascular diseases (CVD), such as angina, myocardial infarction (MI), and stroke.[1] From 2000 to 2010, the prevalence of hypertension has increased from 26.4% in men and 25.1% in women to 31.9% and 30.1%, respectively. All in all, over a billion patients suffer from the condition.[2,3]

The latest data from Euroaspire IV shows that blood pressure (BP) is optimally controlled in only half of the population.[4] Nonadherence to pharmacological therapies is a crucial reason for such poor control of BP.[5] Nonadherence in routine clinical practice has been difficult to identify as previous methods were unreliable, tedious, and not practical to use in busy clinics.[6] We and others[7–14] have developed a robust, objective clinically useful method to detect antihypertensive drugs in urine or blood using liquid chromatography-tandem mass spectrometry (LC-MS/MS). This is now becoming accepted as the standard technique to assess for nonadherence to antihypertensive medications.[15] A recent study using this technique has shown that nonadherence rates are around 30% to 40% in patients attending hypertension clinics in a large cohort of around 1350 patients from 2 European countries.[16] Furthermore, urine analysis and subsequent discussion of the results with the patient is associated with improved adherence to prescribed antihypertensive medications, resulting in improvements in BP control with average systolic BP (SBP) reductions of around 20 mm Hg.[17]

Received March 21, 2018; first decision April 3, 2018; revision accepted September 4, 2018.

From the Unit of PharmacoTherapy, -Epidemiology, and -Economics, Department of Pharmacy, University of Groningen, The Netherlands (A.V.v.S., A.D.I.v.A., M.J.P.); Department of Epidemiology (A.D.I.v.A., M.J.P.) and Department of Health Sciences (M.J.P.), University Medical Centre Groningen, University of Groningen, The Netherlands; Department of Economics, Econometrics and Finance, University of Groningen, Faculty of Economics and Business, The Netherlands (M.J.P.); Division of Cardiovascular Sciences, Faculty of Biology, Medicine, and Health, University of Manchester, United Kingdom (M.T., P.G.); Division of Medicine, Manchester University NHS Foundation Trust, Manchester Academic Health Science Centre, United Kingdom (M.T.); Department of Chemical Pathology and Metabolic Diseases, University Hospitals of Leicester NHS Trust, United Kingdom (P.P., P.G.); and Department of Cardiovascular Sciences, British Heart Foundation Cardiovascular Research Centre (P.P., P.G.) and Diabetes Research Centre (K.K.), University of Leicester, United Kingdom.

*P. Gupta and M.J. Postma share joint last authorship.

The online-only Data Supplement is available with this article at https://www.ahajournals.org/doi/suppl/10.1161/HYPERTENSIONAHA.118.11227.

Correspondence to Alexander V. van Schoonhoven, Department of Pharmacy, University of Groningen, Antonius Deusinglaan 1, Groningen 9713AV, The Netherlands. Email a.v.van.schoonhoven@gmail.com

The test is increasingly being used in routine clinical practice, however, the cost-effectiveness of implementing this technology in routine clinical practice is not known. The aim of this study was to determine the cost-effectiveness of LC-MS/MS-based urine analysis added to current practice among patients with hypertension in the United Kingdom (UK).

Methods

Data used in this study is available from the referenced literature.

Overview

To assess the cost-effectiveness of LC-MS/MS-based urine analysis as compared with current practice, a Markov model was used. The model used in this study was an adaptation of an existing model developed by the School of Health and Related Research of the University of Sheffield.[18] Based on previous research, SBP was expected to decrease by 19.5 mm Hg.[17] As per guidelines for appraisal by the National Institute of Health and Care Excellence, the findings were expressed in terms of costs, quality-adjusted life-years (QALYs), and incremental costs per QALY, over a lifetime horizon, and from a health care payer perspective. Both costs and QALYs were discounted at a discount rate of 3.5% per annum.[19] To provide a comprehensive and transparent overview of the economic evaluation performed in this article, the Consolidated Health Economic Evaluation Reporting Standards statement was used as guidance.[20] The checklist is found in the online-only Data Supplement as Table S2 in the online-only Data Supplement.

Model Construction

The model is shown in Figure 1. A cohort of 10000 hypertensive patients progresses through the model in annual cycles, up to the age of 100 years, which was assumed to sufficiently reflect the entire lifetime of the patients. As the cohort ages, the probability of cardiovascular events and death increases.

A total of 12 health states were included in the model, 3 of which represent different forms of mortality. Patients enter the model in the event-free state, where patients are treated for hypertension but have not yet experienced a cardiovascular event. They may either remain in this health state or experience a primary major adverse cardiovascular event, including stable angina, unstable angina, MI, or a stroke or a fatal event and move to the appropriate health state. The health states following nonfatal events are acute health states (the 4 health states in the gray box in Figure 1), in which patients reside for 1 cycle. The following year, patients will then either move to a chronic health state if they experience no other CVD events or move to another acute health state. These chronic health states are modeled to be associated with a higher quality of life and lower costs compared with their respective acute states because the patients had undergone treatment in the acute phase of their disease. Patients in chronic CVD event states can move the same way as patients in the acute health states.

Patients can remain in the same health state for multiple cycles except for the acute coronary artery disease event states of stable angina and unstable angina, as patients in these health states are regarded as having been diagnosed with angina and are subsequently treated. Finally, all patients faced an all-cause-mortality risk every year, which was derived from the life tables for the UK for the years 2013 to 2015.[21] The reported mortality rates were subsequently converted to yearly probabilities.

Patient Characteristics

The target population consisted of a hypothetical cohort of 10000 patients with treated hypertension (an office SBP of at least 140 mm Hg) but without history of CVD. The cohort in the base case analysis consisted of male patients with a starting age of 65, as this was assumed to adequately reflect the average hypertension patient.

Comparator

The LC-MS/MS-based urine analysis was introduced in patients with hypertension in addition to current practice. The comparative strategy consisted of current practice, that is, treating patients with antihypertensive drugs, in the absence of screening. Urine samples were collected at the general practitioner, and subsequently, the results were discussed with the patient during a later appointment. This screening strategy was repeated yearly. A detailed account on the methodology used for the LC-MS/MS-based analysis has been described previously described.[17]

Transition Probabilities

The risk for CVD in hypertensive patients was based on data from several studies.[18,22–24] From these studies, yearly probabilities for developing major adverse cardiovascular event were derived. For the screening strategy, the reduction in CVD risk as compared with current practice was modeled by using relative risks (RRs) to transform the transitions from event-free to acute health states. These RRs were derived from Lewington et al,[25] reflecting the impact of a 20 mm Hg reduction of a patient's SBP on CVD as shown in our previous data from a UK cohort who underwent adherence testing using urine LC-MS/MS and were subsequently followed up.[17] Additionally, the effect of lower or higher SBP reductions was modeled. For example, for an SBP reduction of 19.5 mm Hg, the corresponding RR was calculated by raising the reported RR to the power 19.5/20. The RRs for ages 30 to 39 were not present in the meta-analysis, and these values were estimated assuming a linear extrapolation (Table 1). In the

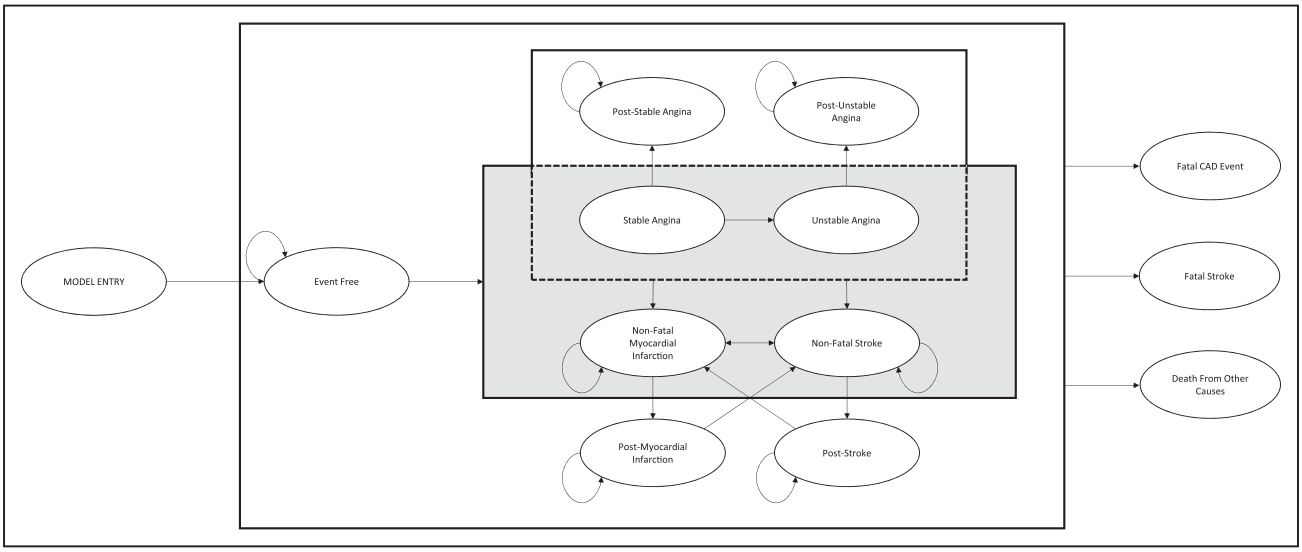

Figure 1. Markov model used for the modeling of hypertension patients. CAD indicates coronary artery disease.

Table 1. Relative Risks for all Hypertensive Patients and Patients With Resistant Hypertension for Different Patient Groups

Patient Group	Male	Female	Reference(s)
RH vs non-RH, IHE	1.24 (1.20–1.28)	1.24 (1.20–1.28)	Sim et al[26]
RH vs non-RH, CVA	1.14 (1.10–1.19)	1.14 (1.10–1.19)	Sim et al[26]
CHD 30–39	0.44 (0.32–0.58)*	0.37 (0.27–0.49)*	Assumption
CHD 40–49	0.50 (0.46–0.54)	0.40 (0.32–0.49)	Lewington et al[25]
CHD 50–59	0.50 (0.49–0.52)	0.49 (0.45–0.54)	Lewington et al[25]
CHD 60–69	0.55 (0.54–0.57)	0.50 (0.47–0.53)	Lewington et al[25]
CHD 70–79	0.62 (0.60–0.64)	0.55 (0.53–0.58)	Lewington et al[25]
CHD 80–89	0.69 (0.65–0.73)	0.64 (0.60–0.68)	Lewington et al[25]
Stroke 30–39	0.26 (0.19–0.35)*	0.37 (0.27–0.49)*	Assumption
Stroke 40–49	0.33 (0.29–0.38)	0.41 (0.34–0.49)	Lewington et al[25]
Stroke 50–59	0.34 (0.32–0.37)	0.45 (0.40–0.50)	Lewington et al[25]
Stroke 60–69	0.41 (0.39–0.44)	0.47 (0.43–0.51)	Lewington et al[25]
Stroke 70–79	0.48 (0.46–0.51)	0.53 (0.49–0.56)	Lewington et al[25]
Stroke 80–89	0.68 (0.63–0.75)	0.65 (0.60–0.71)	Lewington et al[25]

CHD indicates coronary heart disease; CVA, cerebrovascular accident; IHE, ischemic heart event; and RH, resistant hypertension.

*Assumption, no 95% CI from literature, set to 15% of the mean.

subgroup analysis for patients with apparent resistant hypertension, defined as uncontrolled hypertension, despite a 3-drug regiment, including a diuretic,[27] additional RRs were used.[26] The transition probabilities were multiplied with the appropriate RR because patients with resistant hypertension were found to have a higher risk for CVD as compared with nonresistant hypertensive patients.

Healthcare Costs

The cost-effectiveness analysis used a healthcare payer perspective in the UK, that is, the National Health Service perspective. Costs were derived from multiple sources, mostly from previous cost-effectiveness studies with a National Health Service perspective,[28–30] and are shown in Table 2. Youman et al[30] reported the costs for an acute event of stroke separated according to severity: mild, moderate, and severe. However, because this study does not distinguish between severities of stroke, a weighted mean was calculated using the distribution of severities also found in Youman et al.[30] All costs are set to 2015/2016 prices in UK pounds.[33] To account for the uncertainty around the cost estimates, an SE was used, set to 25% of the mean value.

Utilities

In this analysis, the relationship between age and baseline utility was modeled using EuroQol 5 Dimensions (EQ-5D) values from Kind et al.[31] The utilities associated with the acute event states for stable angina, unstable angina, and MI were derived from Lovibond et al,[28] while the values for their respective chronic health states were adopted from other studies.[18,34] Utilities for the acute and chronic stroke health states were based on quality of life estimates from the meta-analysis by Tengs and Lin.[32] This meta-analysis reported utilities for mild, moderate, and severe stroke at 0.87, 0.68, and 0.52, respectively. As with the stroke costs, our study did not distinguish between severities of stroke, and, therefore, a weighted mean was calculated, using the distribution of severities found in Youman et al.[30] The weighted mean for both acute and chronic stroke states was calculated as 0.63. All utility values used are shown in Table 2. To account for uncertainty in utilities, the SE was set to 5% of the mean.

Analysis

The primary outcomes of this analysis included total costs, total life-years, total QALYs, and numbers of MI and stroke events over time. Costs and QALYs were used to estimate the incremental cost-effectiveness ratio (net costs per QALY gained). Total numbers of MI and stroke cases prevented by the urine screening methodology are also reported.

Subgroup Analysis

The base case analysis covered male hypertensive patients aged 65 years. To assess the outcomes for other cohorts, we performed subgroup analyses. Female cohorts were analyzed, as well as the starting age being varied from 35 to 85 years in 10-year increments. Furthermore, the impact of limiting the screening test to those with apparent resistant hypertension was tested.

Sensitivity Analyses

To evaluate the impact of uncertainty in model parameters, univariate and multivariate (probabilistic) sensitivity analyses were performed. All parameters, utilities, costs, RRs, and transition probabilities were varied over the ranges based on their respective SE. If no SE was available, the range was calculated from a certain percentage of the mean, as mentioned above. To draw random values for the parameters in sensitivity analyses, β, γ, and log-normal distributions were used. Utilities and transition probabilities were assigned β distributions, while γ distributions were used for costs and log-normal distributions for RRs.

In the univariate analysis, costs, utilities, transition probabilities, and RRs were separately varied to test their influence on the outcomes. Furthermore, a discount rate of 1.5% for both costs and effects was also tested, as well as variations on estimated SBP reductions with an upper and lower limit of 29 and 10 mm Hg, respectively.

In the probabilistic sensitivity analysis, the model was run for 1000 iterations, in which every parameter was randomly drawn from its respective distribution. To calculate the probability of LC-MS/MS being cost-effective or even dominant, as compared with current practice, net monetary benefit was calculated, from which a cost-effectiveness acceptability curve was produced, which represents the probability of favorable cost-effectiveness for a range of willingness to pay per QALY thresholds.

Results

Base Case

In the base case cohort of males aged 65 years, the model showed that LC-MS/MS-based urine screening for hypertension was

Table 2. Cost and Utility Input Parameters Used in the Model

Costs	Value		Reference(s)
	Year 1	Years >1	
LC-MS/MS-based test	£30	£30	
Checkup	£28	£28	Lovibond et al[28]
Hypertension treatment	£237	£237	Lovibond et al[28]
Stable angina	£1636	£25	Lovibond et al[28]
Unstable angina	£11 761	£348	Lovibond et al[28]
Myocardial infarction	£19 168	£564	Lovibond et al[28]
Fatal myocardial infraction	£1472	NA	Clarke et al[29]
Stroke	£45 244	£9859	Youman et al[30]
Fatal stroke	£38 517	NA	Youman et al[30]
Utilities			
Event-free	NA	NA	Kind et al[31]
Stable angina	0.81	0.90	Lovibond et al[28] and Ward et al[18]
Unstable angina	0.77	0.88	Lovibond et al[28] and Ward et al[18]
Myocardial infarction	0.76	0.80	Lovibond et al[28] and Ward et al[18]
Stroke	0.63	0.63	Tengs and Lin[32] and Youman et al[30]

LC-MS/MS indicates liquid chromatography-tandem mass spectrometry; and NA, not applicable.

dominant, suggesting that this method of screening is likely to be both more effective and less costly, compared with current practice. Notably, the costs in the screening strategy were lower than in current practice (£69 357 versus £69 852). The modeled life expectancy was higher in the screening strategy (11.80 versus 11.78 life-years), and when adjusted for quality of life, patients obtained an incremental benefit of 0.020 QALYs (8.83 versus 8.81 QALYs) over current practice. Furthermore, the model predicted that the screening is likely to prevented 518 MI cases and 305 stroke cases over a lifetime horizon, be it fatal or nonfatal.

Subgroup and Scenario Analysis

Results for cohorts by sex and at ages 35 through to 85 years in 10-year increments are shown in Table 3. In all subgroups, costs were saved and QALYs were gained as compared with care as usual, indicating dominance of LC-MS/MS testing. Furthermore, a subgroup consisting of patients with apparent resistant hypertension was explored.[27] Finally, the influence of other cohort parameters, such as estimated SBP reduction and the discount rate on outcomes was explored in a scenario analysis (Table S1).

As was already apparent from the subgroup analyses, cost-effectiveness in older patients and women was less favorable as compared with the cohort of 65-year old males, whereas in younger patients it was more dominant. Targeting only those with apparent resistant hypertension would improve both cost savings and QALY gains. This is most probably because of worse adherence in this group,[16] which is likely to result in greater improvements in SBP. Logically, when the effect of the intervention on SBP would be different than assumed in the base case model, this would impact cost-effectiveness, where better effect would mean better cost-effectiveness and vice versa. Last, lowering the discount rate for both costs and health effects would increase the current value of future savings and QALY gains, and, therefore, this has a favorable effect on cost-effectiveness.

Univariate Sensitivity Analysis

The results of the univariate sensitivity analysis are shown in the tornado diagrams in Figure 2. Changes in utilities naturally did not influence the incremental costs, and the screening remained dominant in all analyses.

Probabilistic Sensitivity Analysis

The probabilistic sensitivity analysis performed 1000 iterations of the model. The base case incremental cost-effectiveness scatter plot of LC-MS/MS-based urine screening versus standard of care is shown in Figure 3. The screening strategy gained QALYs in 100% of iterations while being cost saving in 86.8% of iterations. Assuming a willingness to pay threshold of £20 000 per QALY, the screening test was cost-effective in 95.4% of iterations. Figure S1 shows the influence of the willingness to pay threshold on the cost-effectiveness of the LC-MS/MS-based urine screening test in the cost-effectiveness acceptability curve. It shows the screening test to be cost-effective with a probability of 86.8% with a willingness to pay threshold of £0 per QALY, and it reached 99.3% at £50 000 per QALY.

Discussion

This is the first study to model cost-effectiveness of an objective pharmacological adherence intervention in people with hypertension from a UK perspective. As in any model, results are based on assumptions that may not necessarily reflect clinical reality. Still, using the best available information, the study suggests that from the base case analysis, the screening strategy dominates over current practice, with cost savings of

Table 3. Economic and Health Outcomes of LC-MS/MS-Urine Screening as Compared With Current Practice

Sex and Age, y	Therapy	Cost (£)	LYs	QALYs	ICER (£/QALY)
Male, 35	Current practice	73 484	19.19	16.29	
	LC-MS/MS	67 171	19.22	16.32	Dominant
Male, 45	Current practice	75 262	17.37	14.15	
	LC-MS/MS	74 905	17.42	14.20	Dominant
Male, 55	Current practice	77 438	14.89	11.61	
	LC-MS/MS	76 913	14.92	11.64	Dominant
Male, 65	Current practice	69 852	11.78	8.81	
	LC-MS/MS	69 357	11.80	8.83	Dominant
Male, 75	Current practice	51 142	8.23	5.91	
	LC-MS/MS	50 873	8.24	5.92	Dominant
Male, 85	Current practice	23 710	4.91	3.41	
	LC-MS/MS	23 725	4.92	3.41	Dominant
Female, 35	Current practice	71 344	19.74	16.80	
	LC-MS/MS	64 572	19.75	16.83	Dominant
Female, 45	Current practice	72 335	18.11	14.79	
	LC-MS/MS	72 243	18.17	14.84	Dominant
Female, 55	Current practice	74 045	15.84	12.39	
	LC-MS/MS	73 802	15.88	14.42	Dominant
Female, 65	Current practice	68 897	12.84	9.62	
	LC-MS/MS	68 597	12.86	9.64	Dominant
Female, 75	Current practice	54 225	9.17	6.59	
	LC-MS/MS	54 003	9.18	6.60	Dominant
Female, 85	Current practice	28 823	5.49	3.80	
	LC-MS/MS	28 781	5.50	3.81	Dominant
Male, 65 (10 mm Hg)	Current practice	69 852	11.78	8.81	
	LC-MS/MS	69 829	11.80	8.82	Dominant
Male, 65 (29 mm Hg)	Current practice	69 852	11.78	8.81	
	LC-MS/MS	69 026	11.81	8.84	Dominant

ICER indicates Incremental cost-effectiveness ratio; LC-MS/MS, Liquid chromatography-tandem mass spectrometry; LY, Life-year; and QALY, Quality-adjusted life-year.

£495 per patient, averting 518 MIs and 305 stroke events and gaining 200 QALYs over the lifetime of the cohort of 10 000 males aged 65. To assess the influence of cohort characteristics, subgroup analyses were performed. About cohort age, a clear pattern was found in its influence on costs and effects. Performing LC-MS/MS-based urine screening in younger cohorts improved the cost savings and QALY gains while screening an older population is likely to have reduced cost savings and QALYs gained. This is because of the fact that screening at an earlier age improves the patients' SBP with reduced lifetime risk of cardiovascular events. This was supported in the probabilistic sensitivity analysis, which showed that increasing patient starting age decreases the likelihood of intervention being cost-effective. In the subgroup analysis with a female cohort, cost savings were reduced, while effects proportionally increased more. In patients with apparent resistant hypertension who underwent discussions on the basis of the urine analysis, there was an increase in the cost savings and QALY gains over the base case. The improved outcomes are a result of focusing treatment on patients with a higher probability of encountering a cardiovascular event, and the higher incidence of nonadherence in this cohort of 30% to 40%.[16] As expected, increasing the estimated SBP reduction resulted in more favorable results, as patients would be less susceptible to CVD.

A main strength of this model is the possibility for subgroup analyses, covering a wide range of possible patient ages, as well as the sex of the cohort and whether patients had apparent resistant hypertension. This model also has some limitations. First, because of a lack of hypertension-specific transition probabilities, papers reporting on the general population were used, which may underestimate the actual probabilities of hypertensive patients developing CVD. This means the cost-effectiveness may be more favorable than now reported.

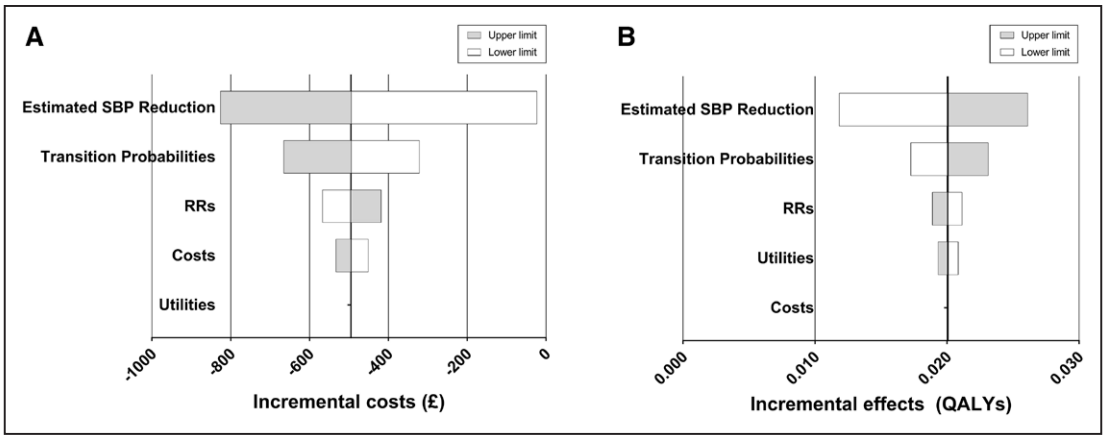

Figure 2. Tornado diagrams depicting the results of the univariate sensitivity analysis in a base case cohort on the incremental costs (**A**) and the incremental effects (**B**). QALY indicates quality-adjusted life-year; and RR, relative risk.

In addition, heart failure, end-stage renal disease, and transient ischemic attacks were not explicitly included in the model, as their impact might be slightly lower as compared with the impact of included complications. However, exclusion of these events implies an underestimation of possible cost savings and QALY gains from better BP control, reflecting a conservative approach towards cost-effectiveness. Furthermore, this study focused solely on clinical SBP measurements. International guidelines also recommend management and targets for diastolic BP. In addition, this analysis did not consider the costs savings in terms of decreased costs of referrals to select clinics and reduce cost of investigations or additional therapy, but, clearly, these would increase the cost savings and health gains of the intervention. Ideally, cost-effectiveness analysis is done using both data from randomized controlled trials next to observational data; yet, randomized controlled trials are currently ongoing. Finally, there were limitations about the estimated SBP reduction. As Gupta et al[17] mention in their limitations, bias may have been introduced from incomplete data, resulting in a more favorable SBP reduction and the inability to follow the presumable drop in sustained adherence after checkups. By administering the test yearly, adherence would be more likely to be sustained, at greater costs.

Our results are supported by a previous study by Chung et al,[35] where therapeutic drug monitoring for adherence was proven to have a potential cost-effective role. Other previous studies have also shown that interventions to improve adherence are potentially cost-effective. Chapman et al[36] performed

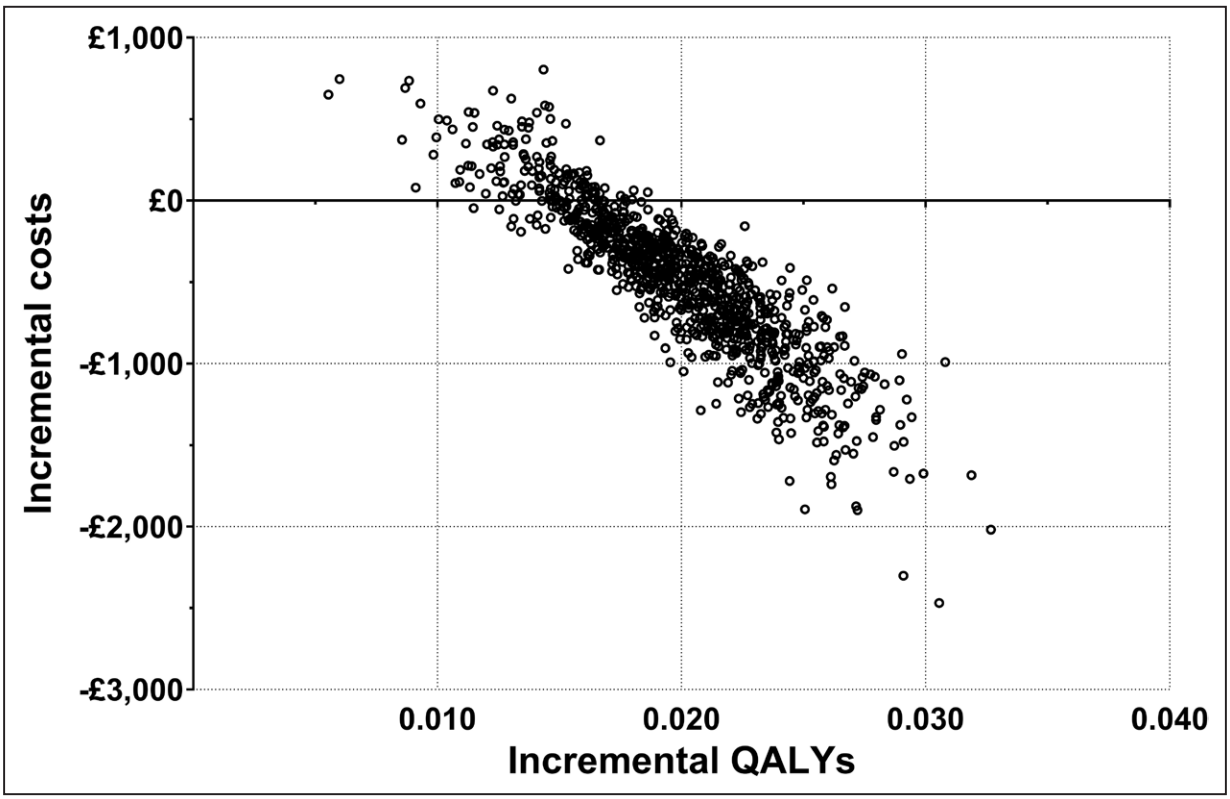

Figure 3. Cost-effectiveness plane for base case probabilistic sensitivity analysis. QALY indicates quality-adjusted life-year.

a post hoc modeling study in combination with a systematic review on the cost-effectiveness of several strategies aimed at improving adherence of lipid-lowering and antihypertensive treatment and found an incremental cost-effectiveness ratio of £4451 ($4984) per QALY gained for self-monitoring, reminders, and educational materials as compared with no adherence intervention. Pharmacist/nurse management as compared with self-monitoring, reminders, and educational materials had an incremental cost-effectiveness ratio of £5678 ($6358) per QALY gained. Depending on the willingness to pay for a QALY, both these interventions can be considered cost-effective. More recently, Vegter et al[37] studied the cost-effectiveness of a pharmaceutical care intervention program in Dutch community pharmacies that improved patients' adherence to lipid-lowering therapy. They found both QALY gains and cost savings, as in the present study.

Although some uncertainties remain, such as the exact SBP reduction and the extent of sustained adherence, it is likely that screening for nonadherence to antihypertensive medications is cost-effective. The urine analysis would prove to be the most cost-effective in younger patients and patients with apparent resistant hypertension. Additionally, it would improve the number of MI and stroke cases prevented. However, from a public health perspective, it would still be beneficial to perform this intervention strategy in all patients with hypertension with dominance remaining over all groups and ages, albeit the efficiency of resource use would be slightly lower. In addition, a more widespread use of screening could decrease the costs of performing the test, thus improving cost-effectiveness.

Perspectives

Analyses with our Markov model demonstrate that screening for nonadherence in hypertensive patients to improve adherence to antihypertensive medications in addition to current practice is likely to be a dominant intervention in preventing CVD, with both cost savings and health gains in the base case. These cost savings and health gains were robust in scenario and sensitivity analyses, although not all uncertainties could be fully addressed. In future assessments, a wider range of CVD should be accounted for, as these are frequently found in practice as well. In addition, studies about sustained adherence and true SBP reduction would further improve the accuracy of health economic assessments. Finally, the addition of this screening test could also be assessed for other countries.

Sources of Funding

M. Tomaszewski acknowledges funding from the British Heart Foundation (Clinical Study no. CS/17/3/32799). K. Khunti, P. Gupta, and P. Patel acknowledge support from the National Institute for Health Research Collaboration for Leadership in Applied Health Research and Care—East Midlands (NIHR CLAHRC—EM), and the NIHR Leicester Biomedical Research Centre.

Disclosures

K. Khunti has acted as a consultant and speaker for Novartis, Novo Nordisk, Sanofi-Aventis, Lilly, Servier, and Merck Sharp & Dohme. He has received grants in support of investigator and investigator-initiated trials from Novartis, Novo Nordisk, Sanofi-Aventis, Lilly, Pfizer, Boehringer Ingelheim, and Merck Sharp & Dohme. K. Khunti has received funds for research, honoraria for speaking at meetings and has served on advisory boards for Lilly, Sanofi-Aventis, Merck Sharp & Dohme, and Novo Nordisk. M.J. Postma reports grants and personal fees from various pharma companies, outside the submitted work. The other authors report no conflicts.

References

1. World Health Organization. *A Global Brief on Hypertension: World Health Day 2013*. Geneva, Switzerland: World Health Organization; 2013:1–40.
2. Mills KT, Bundy JD, Kelly TN, Reed JE, Kearney PM, Reynolds K, Chen J, He J. Global disparities of hypertension prevalence and control: a systematic analysis of population-based studies from 90 countries. *Circulation*. 2016;134:441–450. doi: 10.1161/CIRCULATIONAHA.115.018912
3. NCD Risk Factor Collaboration (NCD-RisC). Worldwide trends in blood pressure from 1975 to 2015: a pooled analysis of 1479 population-based measurement studies with 19·1 million participants. *Lancet*. 2017;389:37–55. doi: 10.1016/S0140-6736(16)31919-5
4. Kotseva K, Wood D, De Bacquer D, et al. EUROASPIRE IV: a European Society of Cardiology survey on the lifestyle, risk factor and therapeutic management of coronary patients from 24 European countries. *Eur J Prev Cardiol*. 2016;23:636–648. doi: 10.1177/2047487315569401
5. Kolandaivelu K, Leiden BB, O'Gara PT, Bhatt DL. Non-adherence to cardiovascular medications. *Eur Heart J*. 2014;35:3267–3276. doi: 10.1093/eurheartj/ehu364
6. Gupta P, Patel P, Horne R, Buchanan H, Williams B, Tomaszewski M. How to screen for non-adherence to antihypertensive therapy. *Curr Hypertens Rep*. 2016;18:89. doi: 10.1007/s11906-016-0697-7
7. Tomaszewski M, White C, Patel P, Masca N, Damani R, Hepworth J, Samani NJ, Gupta P, Madira W, Stanley A, Williams B. High rates of non-adherence to antihypertensive treatment revealed by high-performance liquid chromatography-tandem mass spectrometry (HP LC-MS/MS) urine analysis. *Heart*. 2014;100:855–861. doi: 10.1136/heartjnl-2013-305063
8. Jung O, Gechter JL, Wunder C, Paulke A, Bartel C, Geiger H, Toennes SW. Resistant hypertension? Assessment of adherence by toxicological urine analysis. *J Hypertens*. 2013;31:766–774. doi: 10.1097/HJH.0b013e32835e2286
9. Strauch B, Petrák O, Zelinka T, Rosa J, Somlóová Z, Indra T, Chytil L, Marešová V, Kurcová I, Holaj R, Wichterle D, Widimský J Jr. Precise assessment of noncompliance with the antihypertensive therapy in patients with resistant hypertension using toxicological serum analysis. *J Hypertens*. 2013;31:2455–2461. doi: 10.1097/HJH.0b013e3283652c61
10. Ceral J, Habrdova V, Vorisek V, Bima M, Pelouch R, Solar M. Difficult-to-control arterial hypertension or uncooperative patients? The assessment of serum antihypertensive drug levels to differentiate non-responsiveness from non-adherence to recommended therapy. *Hypertens Res*. 2011;34:87–90. doi: 10.1038/hr.2010.183
11. Brinker S, Pandey A, Ayers C, Price A, Raheja P, Arbique D, Das SR, Halm EA, Kaplan NM, Vongpatanasin W. Therapeutic drug monitoring facilitates blood pressure control in resistant hypertension. *J Am Coll Cardiol*. 2014;63:834–835. doi: 10.1016/j.jacc.2013.10.067
12. Ewen S, Meyer MR, Cremers B, Laufs U, Helfer AG, Linz D, Kindermann I, Ukena C, Burnier M, Wagenpfeil S, Maurer HH, Böhm M, Mahfoud F. Blood pressure reductions following catheter-based renal denervation are not related to improvements in adherence to antihypertensive drugs measured by urine/plasma toxicological analysis. *Clin Res Cardiol*. 2015;104:1097–1105. doi: 10.1007/s00392-015-0905-5
13. Schmieder RE, Ott C, Schmid A, Friedrich S, Kistner I, Ditting T, Veelken R, Uder M, Toennes SW. Adherence to antihypertensive medication in treatment-resistant hypertension undergoing renal denervation. *J Am Heart Assoc*. 2016;5:1–11. doi: 10.1161/JAHA.115.002343
14. Lawson AJ, Shipman KE, George S, Dasgupta I. A novel 'dilute-and-shoot' liquid chromatography-tandem mass spectrometry method for the screening of antihypertensive drugs in urine. *J Anal Toxicol*. 2016;40:17–27. doi: 10.1093/jat/bkv102
15. Berra E, Azizi M, Capron A, Høieggen A, Rabbia F, Kjeldsen SE, Staessen JA, Wallemacq P, Persu A. Evaluation of adherence should become an integral part of assessment of patients with apparently treatment-resistant hypertension. *Hypertension*. 2016;68:297–306. doi: 10.1161/HYPERTENSIONAHA.116.07464
16. Gupta P, Patel P, Štrauch B, et al. Risk factors for nonadherence to antihypertensive treatment. *Hypertension*. 2017;69:1113–1120. doi: 10.1161/HYPERTENSIONAHA.116.08729
17. Gupta P, Patel P, Štrauch B, et al. Biochemical screening for nonadherence is associated with blood pressure reduction and improvement in adherence. *Hypertension*. 2017;70:1042–1048. doi: 10.1161/HYPERTENSIONAHA.117.09631

18. Ward S, Lloyd Jones M, Pandor A, Holmes M, Ara R, Ryan A, Yeo W, Payne N. A systematic review and economic evaluation of statins for the prevention of coronary events. *Health Technol Assess*. 2007;11:1, iii-iv–160, iii-iv. doi: 10.3310/hta11140
19. National Institute for Health and Care Excellence (NICE). Guide to the Methods of Technology Appraisal 2013. https://www.nice.org.uk/process/pmg9/chapter/foreword. Accessed September 13, 2018.
20. Husereau D, Drummond M, Petrou S, Carswell C, Moher D, Greenberg D, Augustovski F, Briggs AH, Mauskopf J, Loder E; ISPOR Health Economic Evaluation Publication Guidelines-CHEERS Good Reporting Practices Task Force. Consolidated Health Economic Evaluation Reporting Standards (CHEERS)–explanation and elaboration: a report of the ISPOR Health Economic Evaluation Publication Guidelines Good Reporting Practices Task Force. *Value Health*. 2013;16:231–250. doi: 10.1016/j.jval.2013.02.002
21. National Life Tables, United Kingdom, 1980–82 to 2013–15.
22. Sutcliffe SJ, Fox KF, Wood DA, Sutcliffe A, Stock K, Wright M, Akhras F, Langford Ed. Incidence of coronary heart disease in a health authority in London: review of a community register. *BMJ*. 2003;326:20.
23. Bamford J, Sandercock P, Dennis M, Warlow C, Jones L, McPherson K, Vessey M, Fowler G, Molyneux A, Hughes T. A prospective study of acute cerebrovascular disease in the community: the Oxfordshire Community Stroke Project 1981-86. 1. Methodology, demography and incident cases of first-ever stroke. *J Neurol Neurosurg Psychiatry*. 1988;51:1373–1380.
24. Alderman MH, Davis BR, Piller LB, Ford CE, Baraniuk MS, Pressel SL, Assadi MA, Einhorn PT, Haywood LJ, Ilamathi E, Oparil S, Retta TM; ALLHAT Collaborative Research Group. Should antihypertensive treatment recommendations differ in patients with and without coronary heart disease? (from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial [ALLHAT]). *Am J Cardiol*. 2016;117:105–115. doi: 10.1016/j.amjcard.2015.10.012
25. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R; Prospective Studies Collaboration. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet*. 2002;360:1903–1913. doi: 10.1016/S0140-6736(02)11911-8
26. Sim JJ, Bhandari SK, Shi J, Reynolds K, Calhoun DA, Kalantar-Zadeh K, Jacobsen SJ. Comparative risk of renal, cardiovascular, and mortality outcomes in controlled, uncontrolled resistant, and nonresistant hypertension. *Kidney Int*. 2015;88:622–632. doi: 10.1038/ki.2015.142
27. Calhoun DA, Jones D, Textor S, Goff DC, Murphy TP, Toto RD, White A, Cushman WC, White W, Sica D, Ferdinand K, Giles TD, Falkner B, Carey RM; American Heart Association Professional Education Committee. Resistant hypertension: diagnosis, evaluation, and treatment: a scientific statement from the American Heart Association Professional Education Committee of the Council for High Blood Pressure Research. *Circulation*. 2008;117:e510–e526. doi: 10.1161/CIRCULATIONAHA.108.189141
28. Lovibond K, Jowett S, Barton P, Caulfield M, Heneghan C, Hobbs FD, Hodgkinson J, Mant J, Martin U, Williams B, Wonderling D, McManus RJ. Cost-effectiveness of options for the diagnosis of high blood pressure in primary care: a modelling study. *Lancet*. 2011;378:1219–1230. doi: 10.1016/S0140-6736(11)61184-7
29. Clarke P, Gray A, Legood R, Briggs A, Holman R. The impact of diabetes-related complications on healthcare costs: results from the United Kingdom Prospective Diabetes Study (UKPDS Study No. 65). *Diabet Med*. 2003;20:442–450.
30. Youman P, Wilson K, Harraf F, Kalra L. The economic burden of stroke in the United Kingdom. *Pharmacoeconomics*. 2003;21(suppl 1):43–50. doi: 10.1016/S0016-5085(03)81077-6
31. Kind P, Dolan P, Gudex C, Williams A. Variations in population health status: results from a United Kingdom national questionnaire survey. *BMJ*. 1998;316:736–741.
32. Tengs TO, Lin TH. A meta-analysis of quality-of-life estimates for stroke. *Pharmacoeconomics*. 2003;21:191–200.
33. Curtis L, Burns A. Unit Costs of Health and Social Care 2016. 2016. http://www.pssru.ac.uk/project-pages/unit-costs/2016/index.php. Accessed July 7, 2017.
34. Visser K, Kuntz KM, Donaldson MC, Gazelle GS, Hunink MG. Pretreatment imaging workup for patients with intermittent claudication: a cost-effectiveness analysis. *J Vasc Interv Radiol*. 2003;14:53–62.
35. Chung O, Vongpatanasin W, Bonaventura K, Lotan Y, Sohns C, Haverkamp W, Dorenkamp M. Potential cost-effectiveness of therapeutic drug monitoring in patients with resistant hypertension. *J Hypertens*. 2014;32:2411–2421; discussion 2421. doi: 10.1097/HJH.0000000000000346
36. Chapman RH, Kowal SL, Cherry SB, Ferrufino CP, Roberts CS, Chen L. The modeled lifetime cost-effectiveness of published adherence-improving interventions for antihypertensive and lipid-lowering medications. *Value Health*. 2010;13:685–694. doi: 10.1111/j.1524-4733.2010.00774.x
37. Vegter S, Oosterhof P, van Boven JF, Stuurman-Bieze AG, Hiddink EG, Postma MJ. Improving adherence to lipid-lowering therapy in a community pharmacy intervention program: a cost-effectiveness analysis. *J Manag Care Spec Pharm*. 2014;20:722–732. doi: 10.18553/jmcp.2014.20.7.722

Novelty and Significance

What Is New?

- Liquid chromatography-tandem mass spectrometry can be used for screening for (non)adherence.
- Shown to be dominant over current practice: both beneficial and cost saving.

What Is Relevant?

- Adherence to hypertensive medication is suboptimal.
- Biochemical testing and discussing results with patients can significantly improve adherence and systolic blood pressure.
- Implementing adherence screening in clinical practice could enhance the efficacy of antihypertensive treatment.

Summary

This study showed that liquid chromatography-tandem mass spectrometry-based biochemical analyses were shown to be likely dominant over current practice, as cost savings reached £495 per patient. Furthermore, in a hypothetical lifetime cohort of 10 000 males aged 65, 200 quality-adjusted life-years were gained, with 518 myocardial infarctions and 305 stroke events averted.