Cost-effectiveness of intracoronary flow velocity measurements and myocardial perfusion scintigraphy for management of intermediate coronary lesions

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Background. Coronary flow velocity reserve (CFVR) is an alternative for myocardial perfusion scintigraphy (SPECT) in assessing functional severity of coronary lesions. For the acceptance of CFVR in daily clinical decision-making, cost-effectiveness must be proven.
Aim. Economic evaluation of different diagnostic management strategies using CFVR compared with SPECT for making decisions regarding use of PTCA of an intermediate coronary lesion in patients with multivessel disease.
Methods. The incremental cost-effectiveness analysis was based on data from a prospective multicentre study in 201 patients with multivessel coronary artery disease. Four management strategies, assuming performance of angioplasty after positive test result(s), were compared: SPECT alone, CFVR alone (cut-off value of 2.0), and combined strategies of SPECT and CFVR with one ('extensive') or two ('restrictive') positive test(s). Probabilistic sensitivity analyses were performed using Monte Carlo simulation. Primary outcome was the probability of a cardiac event-free first year with respect to the intermediate lesion.
Results. A 10% event rate was observed, which was predominantly associated with ischaemia-driven revascularisations. A strategy based on CFVR was most effective. The restrictive strategy had the lowest costs and was most cost-effective; with increasing willingness-to-pay values (above €20,000) a CFVR-alone strategy became equally cost-effective.
Conclusion. It is mandatory to measure CFVR to decide upon angioplasty of the intermediate lesion in patients with multivessel coronary artery disease. This decision can be based on the restrictive strategy (i.e. performance of PTCA in case of abnormal test results of both SPECT and CFVR) or solely on CFVR, depending on society's willingness-to-pay to prevent cardiac events. (*Neth Heart J* 2005;6:214-23.)

Key words: coronary artery disease, cost-effectiveness, coronary flow velocity reserve, diagnosis, myocardial perfusion, scintigraphy

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On behalf of the Intermediate Lesions: Intracoronary flow Assessment versus 99mTc-MIBI SPECT (ILIAS) investigators

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Coronary artery disease is the leading cause of morbidity and mortality in the Western world. Antianginal medication is the treatment of choice for patients with chest pain (on effort) due to coronary artery disease. A revascularisation procedure can be considered if angina persists despite an optimal medical strategy. In Europe, 617,176 percutaneous transluminal coronary angioplasty (PTCA) procedures were performed in the year 2001.[1] Over the last years there has been an increase in procedures of approximately 20% a year. The majority (50-70%) of patients eligible for PTCA have multivessel coronary artery disease. About one third of these patients have an intermediate (40-70% diameter stenosis) coronary lesion. In 2001, multivessel interventions in one session were performed in 18% of patients.[1]

Intermediate lesions can be treated in the same procedure as the elective percutaneous transluminal coronary angioplasty (PTCA) of a severe coronary narrowing (>70% diameter stenosis). Extending the procedure to prevent the intermediate lesion from causing new events is feasible and will probably save costs in the end, although this has not yet been investigated.

Table 1. Clinical outcome of the ILIAS study with respect to the intermediate lesion (n=191).

SPECT	CFVR	PTCA performed?	n	Event rate at one year
Negative	Negative	No	124	8 (6%)
Negative	Positive	No	37	9 (24%)
Positive	Negative	No	21	1 (5%)
Positive	Positive	Yes	9	1 (11%)

SPECT=single photon emission computed tomography, CFVR=coronary flow velocity reserve (positive if CFVR<2.0), PTCA=percutaneous transluminal coronary angioplasty.

Objective evidence of functional severity is mandatory before an accurate decision can be made to treat the intermediate lesion. The standard diagnostic approach is noninvasive stress testing, for instance by single photon emission computed tomography (SPECT).[2-4] Recently, intracoronary measurement of haemodynamic parameters during the cardiac catheterisation has been introduced to selectively determine functional severity.[5-7] The Intermediate Lesions: Intracoronary flow Assessment versus ^{99m}Tc-MIBI SPECT (ILIAS) study showed that intracoronary-derived flow velocity reserve (CFVR) was a better predictor than SPECT for the occurrence of cardiac events (predominantly ischaemia-driven target vessel revascularisations).[8]

For the acceptance of CFVR in daily clinical decision-making, proof of cost-effectiveness is, next to its clinical value, mandatory. In this paper, three diagnostic management strategies with CFVR for deciding on whether or not to perform PTCA of an intermediate coronary lesion in patients with multivessel disease are evaluated on economic grounds in comparison with a reference strategy based on SPECT alone.

Methods

The ILIAS study: patient population, protocol, and clinical outcomes

The details of the ILIAS study have been described previously.[8] In brief, 191 patients with one intermediate coronary narrowing in the presence of multivessel coronary artery disease were enrolled in six centres in the Netherlands. All patients were referred for PTCA of a severe narrowing in another coronary artery. SPECT and CFVR were compared regarding making decisions on PTCA of the intermediate lesion. The protocol was approved by the Institutional Review Board at each clinical site; patients gave written informed consent.

All patients underwent both SPECT and CFVR within one week. A PTCA of the intermediate lesion was only performed if both test results were positive, i.e. a reversible perfusion defect in the area of interest on SPECT and a CFVR <2.0. Otherwise, the intermediate lesion was left untreated. Patients were followed for one year to document the occurrence of major cardiac events (death, myocardial infarction or 'ischaemia-driven' target lesion revascularisation), related to the intermediate lesion. The primary outcome was the occurrence of major cardiac events related to the intermediate lesion after an expectative policy.

The main results are summarised in table 1. Based on the test results, a PTCA of the intermediate lesion was deferred in 182 patients. In total, 19 events related to the intermediate lesion occurred: no cardiac deaths, three CABGs, three myocardial infarctions and 13 PTCA procedures. Measurement of CFVR (cut-off value 2.0) was a significantly better predictor of the primary outcome than SPECT in the first year following diagnosis and related to the intermediate lesion (relative risk for CFVR 3.9, 95% CI 1.7-9.2; and for SPECT 0.5, 95% CI 0.1-3.2, $p<0.05$). Multivariate analysis revealed CFVR as the only significant predictor of cardiac events.[8] Of note, both tests (SPECT, CFVR) were unable to predict the occurrence of the three myocardial infarctions. Therefore, the predicted cardiac events only included the ischaemia-driven target vessel revascularisation procedures.

Economic modelling of diagnostic strategies

A decision tree model including data on health effects and costs was applied to investigate whether CFVR could serve as a diagnostic tool – either to supplement or to replace SPECT – for the diagnosis and treatment of the intermediate lesion in multivessel disease (figure 1). CFVR was considered positive if its value was below the cut-off of 2.0. Four management strategies were defined:

- SPECT, i.e. management based on SPECT alone; hence, a PTCA is performed if a reversible perfusion defect is detected (reference strategy);
- CFVR, i.e. management based on CFVR alone; hence, a PTCA is performed if CFVR<2.0;
- Extensive, i.e. a combined strategy starting with SPECT, only followed by CFVR if SPECT is negative; a PTCA is performed if SPECT or CFVR is positive ('believe-the-positive');
- Restrictive, i.e. a combined strategy starting with SPECT, only followed by CFVR if SPECT is positive; a PTCA is performed if SPECT and CFVR are positive ('believe-the-negative').

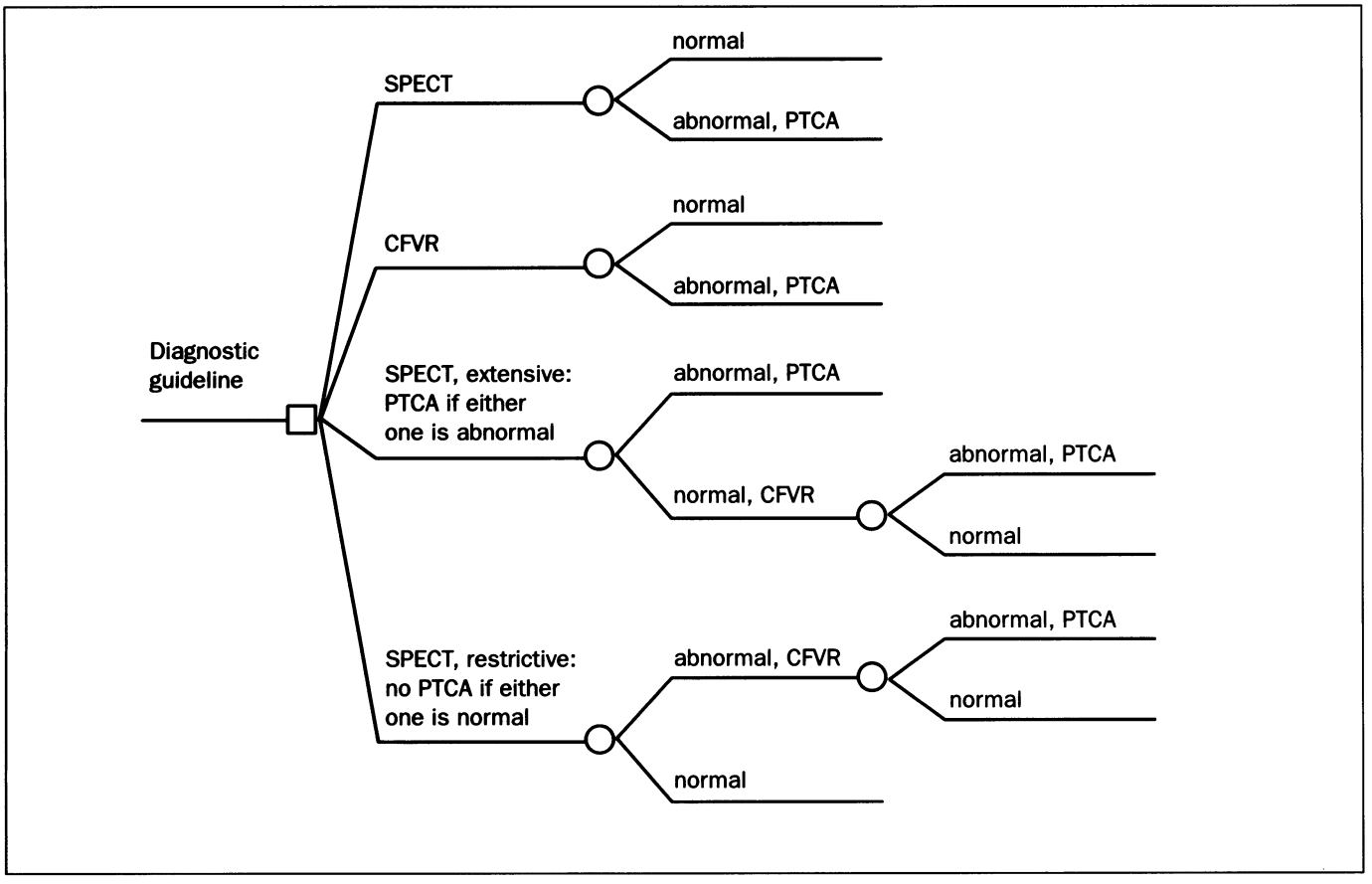

Figure 1. Decision tree for economic assessment of management of the intermediate lesion in patients with multivessel disease. The four strategies are decision-making using the results of: SPECT alone (1), CFVR alone (2), SPECT conditionally followed by CFVR measurement; PTCA is performed depending on the test results, i.e. an 'extensive' policy (3) with patients receiving PTCA treatment if at least one test is positive, or a 'restrictive' policy (4) with patients receiving PTCA treatment if both test results are positive.

Diagnostic test results, health effects and costs associated with these strategies were determined alongside the ILIAS study.

Diagnostic test results and health effects

In this economic evaluation, health effects and costs associated with the four management strategies are

Table 2. Overview of probabilities used for decision modelling, as derived from the ILIAS study.

Probability (p) on	Value	95% CI
Positive SPECT	0.157	0.111-0.218
Positive CFVR	0.241	0.183-0.309
Positive CFVR, conditional on negative SPECT	0.230	0.169-0.304
Positive CFVR, conditional on positive SPECT	0.300	0.154-0.496
Event, after PTCA*	0.209	0.155-0.275
Event, if CFVR is negative	0.0621	0.031-0.118
Event, if SPECT is negative	0.106	0.0650-0.166
Event, if both SPECT and CFVR are negative	0.0645	0.024-0.096
Event, if CFVR is negative, conditional on positive SPECT	0.0476	0.00249-0.259

* Using the effectiveness data from the intermediate lesion, a probability of 0.111 was calculated for the probability of an event after PTCA for the patients who actually received a PTCA of the intermediate lesion. Given the few patients in this group (n=9), that probability is a weak estimate and might at best be considered as an absolute minimum estimate. The probability of an event after PTCA of the severe lesion (40/191, 20.9%) is in accordance with previous reports in other research[20-24] and was therefore chosen as the probability of an event after PTCA of the intermediate lesion in the model.

Table 3. Overview of unit costs, used for decision modelling, as derived from the ILIAS study. Prices are expressed in Euros (1999).

Costs (c) of		**€**	**Range (1/2 - 2 times)**
SPECT			
- personnel		134	
- material		123	
- overheads		291	
	Total costs	**548**	**(274-1096)**
CFVR			
- personnel		36	
- material		610	
- overheads		294	
	Total costs	**940**	**(470-1880)**
Additional PTCA of intermediate lesion (ad-hoc, as part of an ongoing PTCA procedure of severe lesion)		1276	(638-2552)
Event (weighted mean)		**7362**	**(3681-14,724)**
- Myocardial infarction		7597	
- PTCA		5884	
- CABG		13,533	
Follow-up*		-	
- Diagnostic cardiac catheterisation		690	
- Repeat SPECT		548	
- Medication		177	
- Consultation cardiologist		57	
- Travel expenses		6	

* calculated per outcome group (see Methods section).

considered over a 12-month follow-up period following diagnosis and eventual PTCA of the intermediate lesion. Effect was defined as the probability of an event-free follow-up period. This probability depends on the functional severity of the intermediate lesion as indicated by the test results and whether or not PTCA of the intermediate lesion has been performed.

Costs

Costs were estimated in an ILIAS substudy. Only the costs related to disease management of the intermediate lesion were taken into account. Essentially, these costs were examined from a societal perspective, focusing on the direct (non)medical costs generated during diagnosis and the follow-up period, irrespective of payer source. The costs reflect the use of inpatient and outpatient diagnostic examinations and therapeutic procedures, inpatient days, medication, outpatient hospital consultations, out-of-hospital consultations by the general practitioner, as well as out-of-pocket expenses of patients for disease-related travel. The costs were expressed in euros in 1999. A detailed description of the recording of the data, attribution of events, use of resources, and unit costing is given in the appendix.

Comparison of management strategies

For acceptance of CFVR in daily clinical decision-making, proof of cost-effectiveness is mandatory. This depends on, among other things, society's so-called 'willingness-to-pay' (WTP, appendix).

CFVR, and extensive and restrictive strategies were evaluated on economic grounds against SPECT as the reference strategy for the intermediate lesion. For each comparison of two strategies the ratio of the extra costs to the additional health benefit – the incremental cost-effectiveness ratio – was determined. If the incremental cost-effectiveness ratio is negative, dominance occurs, i.e. the dominant strategy is associated with both more effect and lower costs. With a positive incremental cost-effectiveness ratio, the ratio closest to and below a given WTP level suggests the most preferable strategy. Thus, the incremental cost-effectiveness ratio reflects the additional costs to be invested for the more effective

Table 4. Mean use of resources per management strategy.

	Management strategy			
	SPECT	**CFVR**	**Extensive**	**Restrictive**
SPECT	1	0	1	1
CFVR measurement	0	1	0.843	0.157
Additional PTCA	0.157	0.241	0.351	0.047
Event-related PTCA, CABG or MI treatment	0.122	0.098	0.115	0.104
Event-related in-patient days	0.781	0.625	0.739	0.667
During follow-up:				
Consultations cardiologist	1.613	1.502	1.577	1.493
Consultations general practitioner	0.742	0.668	0.718	0.662
Additional SPECT	0.097	0.061	0.097	0.087
Additional coronary angiographies	0.129	0.107	0.128	0.103
Duration of triple therapy in years	0.185	0.167	0.179	0.166
Patient-related travel in kilometres	86	79	84	79

strategy. If no strategy was clearly preferable after comparisons with the reference strategy, a comparison of remaining nondominated strategies was performed.

Sensitivity analyses using Monte Carlo simulation

To account for uncertainties in all probability (test outcomes and health effect) and cost parameters simultaneously, probabilistic sensitivity analysis was performed using Monte Carlo simulation.[9] Beta distributions were assumed for the probability parameters,[10] triangular distributions were assumed for the cost parameters with the calculated cost value as the most likeliest one within a range of half and twice this value. For each of the 25,000 runs in the Monte Carlo simulation the diagnostic strategy with the highest net benefit given some willingness-to-pay level was taken as the preferred option.[11] Since the willingness-to-pay level may vary by changing ethics or macroeconomics, the diagnostic strategies under scrutiny were evaluated at different willingness-to-pay levels to account for this potential variability. Therefore, the overall simulation results reflect the acceptability of each diagnostic strategy and are presented for five willingness-to-pay scenarios (0, 10,000, 20,000, 50,000 and 100,000 Euros). Additionally, the results from the Monte Carlo simulation with a WTP value of €20,000 were used in multinomial logistic regression analysis to derive the model parameters for which the treatment decision was most sensitive.

Results

Probabilities and costs

Test outcomes of SPECT and CFVR, and the probabilities of an event during 12-month follow-up period are depicted in table 2. Most cardiac events were revascularisation procedures (16/19, 84%). Table 3 shows the unit costs for different (healthcare) resources associated with the diagnosis and subsequent treatment of the intermediate lesion. Table 4 shows the estimated mean volumes of used resources associated with the diagnostic strategies.

Economic evaluation

Point estimates of the costs and effects per strategy are depicted in table 5. The incremental cost-effectiveness ratio can be calculated from this table. Figure 2 shows the comparisons of the three alternative strategies with the SPECT strategy, using these point estimates. It can be appreciated that a strategy based on SPECT is dominated by the restrictive strategy. The SPECT strategy is less effective than the CFVR or extensive strategy. However, the amount to pay to prevent an event (i.e. target vessel revascularisation) in the follow-up period is €11,061 for CFVR and €150,448 for the extensive strategy, respectively.

The restrictive policy had the lowest cost-effectiveness ratio and dominated the strategy based on SPECT and the extensive strategy. CFVR was the strategy with the highest effect; the restrictive strategy was associated with the lowest costs. The strategy based on CFVR was more effective than the restrictive policy (0.902 vs. 0.896), however also more costly (€2236 vs. €1804, table 5); the incremental cost-effectiveness ratio was €66,041. Hence, if society's WTP exceeds €66,041, the CFVR strategy is most cost-effective; below this amount the restrictive strategy is society's best choice.

Sensitivity analyses using Monte Carlo simulation

The results of the Monte Carlo simulation are summarised in figure 3. For each of the 25,000

Table 5. The costs and effect per management strategy.

	Management strategy			
	SPECT	**CFVR**	**Extensive**	**Restrictive**
Costs				
- SPECT	548	0	548	548
- CFVR measurement	0	940	792	147
- Additional PTCA	201	307	448	60
- Event	898	718	849	766
- Follow-up costs	322	271	316	282
Total costs	1969	2236	2954	1804
Effect				
Probability of an event-free first year after diagnosis (with respect to the intermediate lesion)	0.878	0.902	0.885	0.896

simulations the most cost-effective strategy was calculated at a given WTP value. The willingness-to-pay (WTP) determines the most cost-effective strategy. Overall, the restrictive strategy should be preferred (91% of all simulations if WTP is €0, to 45% if WTP is €100,000). Moreover, a strategy based on CFVR alone is increasingly preferable as the WTP raises (8% if WTP is €0 up to 49% if WTP is €100,000).

The most sensitive parameters that constituted the data in figure 3 were the probability of an event after a negative CFVR, the probability of an event after a negative SPECT, the probability of a positive CFVR, and the costs of a strategy based on CFVR.

Discussion

In this prospective economic evaluation, the restrictive strategy (SPECT and only subsequent CFVR if SPECT is positive) had the lowest cost-effectiveness ratio for diagnosis and treatment of the intermediate lesion in multivessel disease. However, management based on

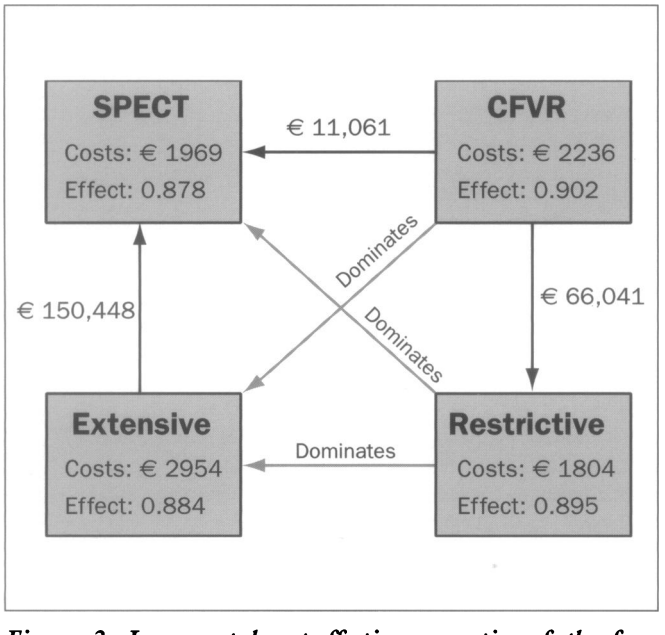

Figure 2. Incremental cost-effectiveness ratios of the four management strategies. The arrows indicate either dominance or the amount of extra money needed to prevent an additional event related to the intermediate lesion.

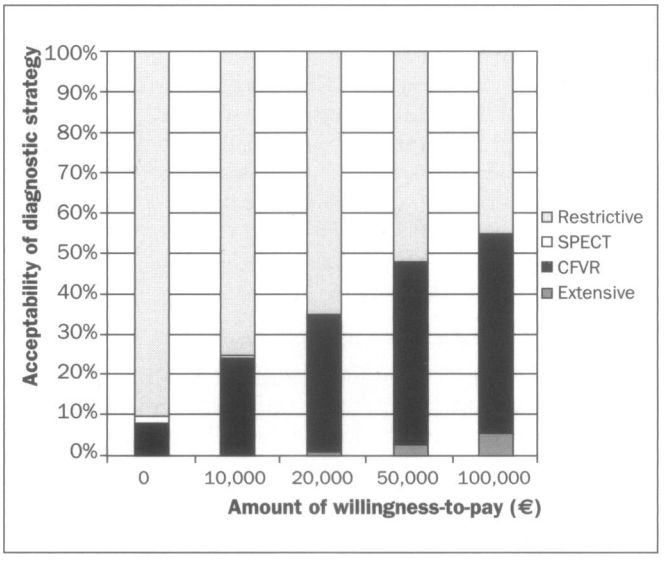

Figure 3. Multivariate sensitivity analysis using 18 variables (6 costs, 12 probabilities). This Monte Carlo simulation model (25,000 samples) was performed for five different willingness-to-pay values (WTP, x-axis); per WTP value, the percentage of samples (y-axis) in which a strategy demonstrating the highest net benefit that is chosen per strategy is depicted.

CFVR alone appeared to be most effective, and this strategy has practical advantages (i.e. one instead of two investigations, and thus more patient comfort) over a combined strategy. Society's willingness-to-pay for an event-free year determines the most cost-effective strategy.

Cost-effectiveness analysis

Cost-effectiveness analysis in the diagnosis of cardiac disease helps to improve patient outcome and limits costs of healthcare. Thus, cost-effectiveness research is increasingly attracting the attention of both policymakers and the medical profession.[12] Recently, the rationale and methods of cost-effectiveness analysis in cardiac disease were described.[13] We followed these recommendations in general, i.e. prospectively acquired data of a multicentre trial were evaluated within a team approach, combining the expertise of cardiologists, nuclear medicine physicians, economists, and clinical epidemiologists. We designed a decision model in order to investigate whether CFVR can serve as a diagnostic tool (either to replace or to supplement SPECT) for diagnosis and treatment of the intermediate lesion (figure 1) and performed multivariate sensitivity analysis using Monte Carlo simulation.

A discrepancy is present in the interpretation of costs and effectiveness, both on patient level and in societal perspective. In the current study, three alternative strategies using CFVR were evaluated against the classical approach (SPECT), as the prognostic value of CFVR is better in this patient cohort.[8] We calculated that additional costs for an event-free-year saved were €11,061 up to €150,448 (figure 2). Eventual replacement depends merely on society's so-called willingness-to-pay. A Bayesian approach was incorporated in the analysis to clarify the issue of 'willingness-to-pay' (figure 3). It can be appreciated that for a WTP value of €20,000 the restrictive strategy is preferred in 65% and CFVR strategy in 35% of all simulations; given this WTP value, SPECT or extensive strategy is preferred in less than 0.5%. These results are important for policymakers to decide whether or not to reimburse the costs of CFVR measurement for the diagnosis of coronary artery disease.

Design of the economic subanalysis

In the current analysis we considered for the combined strategies that all patients underwent SPECT before cardiac catheterisation, in which PTCA of the severe lesion is planned. Thus, we excluded the possibility of starting with CFVR, followed by SPECT and, if necessary, a repeat cardiac catheterisation during which PTCA of the intermediate lesion will be performed. It is obvious that this combined policy of CFVR and SPECT will be very costly, apart from the patient discomfort and increased risk.

In this study, relatively small differences in effectiveness (first year event-free survival: 0.878-0.902, table 5) were observed. However, in terms of risk for an event (predominantly the need for revascularisation) these figures are 9.8% for CFVR vs. 12.2% for SPECT; that is an increase of 24%. Moreover, significant and clinically relevant conclusions can be obtained from this economic assessment of the clinical data. The results demonstrate that cost-effectiveness analysis is very useful for both policymakers and cardiologists for decision-making in daily clinical practice. Based on these relatively small differences in effectiveness between the different strategies and given that the event rate in the whole population was 10.4% (19/182), the possibility to defer angioplasty of the intermediate lesion anyway, without expensive and diagnostic testing using SPECT and/or CFVR measurements might be feasible. It is obvious that such a strategy is associated with low costs (€1233) in comparison with the other strategies (table 4). However, such a strategy is not favoured in clinical practice for two reasons. First, performing CFVR allows the cardiologist to perform a clinically important risk stratification, necessary for adequate patient management. Second, the quality of life of the patients is not incorporated in this analysis. An expectative strategy for the intermediate lesion resulted in 10% event rate during one-year follow-up; these events were predominantly associated with revascularisation procedures and, thus, with a period of stable angina symptoms in the majority of patients.

Comparison with other studies

To the best of our knowledge, this is the first report on cost-effectiveness analysis between SPECT and CFVR for management of patients with multivessel coronary artery disease. Previous studies on cost-effectiveness for SPECT and CFVR have been performed,[14-16] although the patient groups were not comparable with the population investigated in the ILIAS study. Patterson et al.[15] compared exercise ECG, SPECT, positron emission tomography (PET) and angiography for diagnosis of coronary artery disease, based on a mathematical model with data from the literature. PET appeared to be the most cost-effective test. In this model, the fee for SPECT ($1200) was incorporated; this is higher than the value we calculated for SPECT (€548), based on the real costs. Of note, the fee in the Netherlands for performing SPECT is about €500. The EMPIRE study was a retrospective review of patients newly presenting with symptoms suggestive of coronary artery disease.[14] All participating centres supplied information on costs and charges for procedures. For myocardial perfusion imaging, mean costs were calculated at £220, which is somewhat lower than the value we calculated for SPECT (€548).

In the DEBATE II trial (provisional stent placement guided by Doppler flow velocity measurements),[16] direct medical front-office costs were calculated. For measuring CFVR only the costs of a Doppler flow guidewire (€483) were reported; we report a price of €568 for a Doppler flow guidewire

(based on real cost data from the 1999 hospital ledger and purchase department of the Academic Medical Centre, Amsterdam). Moreover, in the present study we additionally calculated direct medical back-office costs (overheads).

In particular, the costs of a Doppler guidewire (€568, as a part of the total costs of CFVR, i.e. €940) contributed considerably to the costs of a strategy based on CFVR. Based on marketing developments, the price of a Doppler guidewire is expected to drop in the near future. Univariate sensitivity analysis revealed that the CFVR strategy will dominate (i.e. more effective, less costs) at least SPECT, if the unit costs of the Doppler guidewire are below €357 (total costs of a strategy based on CFVR are €729).

Limitations

In general, the recommended outcome in cost-effectiveness analyses is the quality adjusted life years (QALY), which allows comparison with other studies. However, the present patient population with multivessel coronary artery disease did not allow such analysis, since QALY will mainly be influenced by the natural course of the severe coronary lesions. Therefore, cost per proportion of patients without a cardiac event related to the intermediate lesion during one year of follow-up was chosen.

During the follow-up period of the ILIAS study, 19 events occurred which were assigned to the intermediate lesion: three myocardial infarctions, three CABG and 13 PTCA procedures. Cost data were based on these events. There were no cardiac deaths. When considering the willingness-to-pay, it is important to realise that the events predicted by SPECT and/or CFVR were only associated with ischaemia-driven target vessel revascularisation procedures.

Cost data were calculated per arm of the decision tree and not per included patient. However, sensitivity analysis on cost data revealed that a reasonable variability in these cost data did not affect the main results (compare figures 2 and 3).

The diagnostic gain in this patient population was relatively low, i.e. the observed numbers of positive test results for the intermediate lesion were low (16% positive SPECT and 24% positive CFVR, respectively). Apparently, this illustrates that an intermediate lesion in the presence of multivessel disease is often not functionally significant. The indication for assessment of functional severity of the intermediate lesion was mediated by the planned intervention for the severe lesion. Therefore, the relatively 'early' diagnosis of the intermediate lesion is inherent to the chosen protocol. We attempted to create a model that simulates an increase in the diagnostic gain, by increasing the number of patients with positive results on both tests, respecting the observed ratio over the other three groups. Furthermore, the observed event rates in these four groups were extrapolated in this new model. Interestingly, the restrictive strategy was dominated by the CFVR strategy by increasing the diagnostic gain (i.e. more positive test results on both SPECT and CFVR), suggesting that the value of CFVR is even greater in more diseased coronary arteries.

Clinical implications

The restrictive strategy is the most cost-effective strategy to decide upon PTCA in patients with intermediate coronary narrowing in the presence of multivessel disease; CFVR is the most effective strategy with respect to cardiac events. Therefore, society's willingness-to-pay (and thus potential reimbursement) determines which strategy is the favourite one.

With increasing WTP values, the decision between the restrictive and CFVR strategy becomes arbitrary. In general, for daily clinical practice in this patient cohort we recommend the following: only measurement of CFVR during cardiac catheterisation if SPECT has been performed and showed reversible perfusion defects in the area of interest; then, only performance of PTCA if CFVR <2.0 (i.e. a restrictive strategy). However, if SPECT has not been performed before a patient is admitted to the cardiac catheterisation laboratory (e.g. unstable angina, ad-hoc setting), we recommend performing CFVR measurements, and subsequent clinical decisions can be based on this CFVR value, with a cut-off value of 2.0. ■

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Appendix

Cost-effectiveness and society's willingness-to-pay

Applying a diagnostic strategy to a patient will result in some health benefit at some cost. Strategies can be evaluated by studying the cost differences in relation to the differences in effects. Obviously, if a new strategy is cheaper and more effective than the reference strategy, it is also more cost-effective. However, if the new treatment is both more expensive and more effective, then one should wonder whether it offers enough value for money. We are only willing to pay the *extra* costs for the additional health benefit if the ratio of these extra costs to the additional health benefit lies below some predefined limit. This willingness-to-pay level depends on the effects to be observed; for example, we are willing to pay more to prevent immediate cardiac death compared with a high cholesterol level.

Recording data, attribution of events and use of resources

Clinical event and resource use data were prospectively recorded during initial assessment and during the 12-month follow-up with specially designed case report forms. Detailed information was available on sources for performing SPECT, coronary angiography, CFVR measurements, and PTCA.

The intracoronary flow velocity assessment of the intermediate lesion and, eventually, the PTCA of the intermediate lesion itself were part of an ongoing catheterisation procedure of the severe lesion. Events occurring during the procedure or in the one-year of follow-up may relate to either the severe or the intermediate lesion. Events were assigned to either of them by an independent and blinded Critical Event Committee.[8] For consistency, attribution rules for the use of resources to the type of lesion were formulated. The use of the following resources was attributed to the severe lesion solely:

- Medication and diagnostic angiography during the screening phase;
- PTCA of the severe lesion;
- All subsequent overnight hospital stays if periprocedural event was attributed to the intermediate lesion.

The use of the following resources was attributed to the intermediate lesion:

- Scintigraphic testing;
- Extra procedure time, guiding catheters (in case of lesions in left and right coronary arteries), and balloons for intracoronary flow velocity assessment and, eventually, PTCA of the intermediate lesion respectively;
- Extra inpatient days, diagnostic examinations and therapeutic procedures above the average for PTCA of the severe lesion, if an event attributable to the intermediate lesion occurred during the initial PTCA procedure;
- All healthcare resources related to the treatment of an event that occurred during follow-up and was attributed to the intermediate lesion.

All other use of resources during follow-up was estimated and, subsequently, attributed to the intermediate lesion by proportion of the intermediate lesion related events to the total number of events. These resources included triple medication (β-blockers, calcium antagonists, nitrates), outpatient hospital monitoring, out-of-hospital consultations by the general practitioner, as well as out-of-pocket expenses of patients for disease-related travel.

Unit costing

Most emphasis was put on estimating the costs of inpatient and outpatient hospital care. In general, the management of patients with multivessel coronary artery disease in the Netherlands is specialist based with only modest involvement of out-of-hospital care providers as the general practitioner and physiotherapist. Indirect nonmedical costs of lost productivity related to the intermediate lesion were not expected to be considerable in the target population (many retired patients, presence of severe lesions).

With the most relevant cost components identified, prior sensitivity analyses were performed with the decision model from figure 1 to assess the required detail in calculating the unit costs.[17] (Farm Economics 2002;20:443-54 and 2003;21:263-71) The parameters reflected 1. reasonable, but preliminary expert opinion estimates of unit costs of CFVR, SPECT, PTCA, follow-up treatment and revascularisation, and 2. the ILIAS probabilities of intermediate lesion-related events after having observed approximately 75% of the total number of person-years. With all parameter values halved or doubled, the decision for the most cost-effective diagnostic strategy was quite insensitive for univariate changes of the cost parameters. Based on these results multiple valuation methods including real cost data, tariffs, guidelines for cost research in Dutch healthcare, prior research data, and other guides were chosen to derive unit costs.

The unit costs of both diagnostic procedures (SPECT and CFVR) were based on real cost data for personnel, materials, and overheads (including housing) from the 1999 hospital ledger and purchase department of the Academic Medical Centre Amsterdam (AMC). This was also done for the PTCA of the intermediate lesion, as a part of the PTCA session for the severe lesion. The overhead costs were calculated from pro rata cost allocation after discriminating production from nonproduction centres. The costs of nonproduction centres were lowered with revenues from the external activities by these centres before the 'back-office' costs were allocated to the production centres. The resulting costs were allocated pro rata to the production centres based on the total costs of these centres (no correction for revenues from external production here) and, consequently, allocated to all production (including external production). During allocation, weights that had been derived from workload data and expert opinion were used for different production units. Tariffs[18] and real cost data from prior research,[17,19] adjusted for the year 1999 using price indices for the healthcare sector, were used for other diagnostic and therapeutic procedures. These procedures included re-PTCA, CABG and the treatment of myocardial infarction during follow-up (cardiac death did not occur in this study). Unit costs for inpatient days, for outpatient hospital and out-of-hospital consultations, and travel expenses per kilometre were based on guidelines for cost accounting in healthcare.[17] The price for triple medication was derived from the Pharmacotherapeutic Guide 2000/2001. Costs in 1999 were expressed in euros.