Journal of Medical Economics

ISSN: 1369-6998 (Print) 1941-837X (Online) Journal homepage: informahealthcare.com/journals/ijme20

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To cite this article: C Macaya, N Danchin, A Vinken, WY Tao & T Haider (2005) Economic analysis of the use of contrast media during percutaneous coronary interventions in France and Spain, Journal of Medical Economics, 8:1-4, 111-130, DOI: 10.3111/200508111130

To link to this article: https://doi.org/10.3111/200508111130

Published online: 02 Dec 2008.

Economic analysis of the use of contrast media during percutaneous coronary interventions in France and Spain

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The iso-osmolar contrast medium iodixanol (Visipaqueč; GE Healthcare, UK) has been reported to reduce the risk of major adverse cardiac events and to have a higher success rate when used during percutaneous coronary intervention (PCI) compared with the ionic low-osmolar contrast medium ioxaglate (Hexabrix®; Guerbet, France) for patients at risk of complications. This study assessed to what extent these clinical benefits translate into economic benefits for patients undergoing PCI in France and Spain using a decision tree model. Clinical data were derived from the COURT and VIP trials. Medical resource use data were obtained from panels of French and Spanish interventional cardiologists. Resource use was converted to costs using country-specific tariffs. The study results suggest that using iodixanol rather than ioxaglate confers an economic benefit in addition to the reported clinical benefit in high-risk patients undergoing PCI in both countries. For low-risk patients, iodixanol may be regarded as cost-effective when relating the extra cost to the small reported increase in angiographic success.

Key words: contrast media, costs and cost analysis, cost-effectiveness, angioplasty, percutaneous coronary interventions

Accepted for publication: 11th August 2005

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Introduction

Percutaneous coronary intervention (PCI) has become the most frequently used invasive strategy in the treatment and management of coronary artery disease, and has replaced the previously established strategy of coronary artery bypass grafting (CABG)[1,2]. To improve the long-term effectiveness of PCI, a variety of other technologies and medical treatments have been developed, such as the use of coronary stenting, anticoagulants and platelet-derived growth factor antagonists[2–5].

However, without contrast medium (CM), PCI cannot be undertaken, and the chemical composition of the CM may affect the success of the PCI. There is clinical evidence suggesting that there are differences in the rates of adverse events (AEs) between different types of CMs. This might be due to differences in the osmolarity, chemotoxicity, or composition of ions of the CMs[6,7]. In contrast to low-osmolar contrast medium (LOCM), the iso-osmolar contrast medium (IOCM) iodixanol (Visipaqueč; GE Healthcare, UK) is formulated with sodium and calcium to achieve iso-osmolarity with blood at all available iodine concentrations[8]. There is evidence that the use of iodixanol, compared with LOCMs, is associated with a reduction in the intensity of pain and heat sensation in patients undergoing arterial angiography[9–14]. The nephrotoxicity induced by CM is also commonly recognised, particularly for patients with renal impairment and diabetes[15,16]. Two clinical studies have shown that, compared with ioxaglate iodixanol, reduces the risk of rising serum creatinine in patients at high-risk of contrast-induced nephropathy[17,18].

The COURT trial reported that use of iodixanol reduced the risk of major adverse cardiac events (MACEs), and that the success rate for angioplasty was higher compared with the use of the ionic LOCM ioxaglate (Hexabrix®; Guerbet, France) in patients at high risk of complications19. In this trial, 856 high-risk patients undergoing PCI were enrolled (randomised and double-blind), of whom a total of 815 patients were evaluable; 410 patients receiving ioxaglate and 405 patients receiving iodixanol. High-risk patients were defined as patients having had unstable angina within the last 48 h, myocardial infarction (MI) within the last 72 h, or post-MI ischaemia. MACEs as the primary clinical outcome of the trial included documented abrupt closure of the target vessel, stroke, systemic arterial thromboembolic event, peri-procedural non-fatal MI, emergency recatheterisation, repeat revascularisation, unplanned CABG and cardiac death. The angiographic success rate (defined as a substantial enlargement of the lumen at the target site as assessed immediately after the procedure) in this trial was 85.9% for ioxaglate and 92.2% for iodixanol (p=0.004). Similar rates of occurrence of AEs were reported for patients using each CM (60% for ioxaglate, 59.1% for iodixanol). However, a statistically significant difference was noted for MACEs (9.5% for ioxaglate, 5.4% for iodixanol; p=0.027). Results consistent with those of the COURT trial were reported in the VICC trial at the 2003 American Health Association meeting[20]. Similar to COURT, VICC was a prospective, blinded, multicentre trial.

VICC captured data in 1276 patients undergoing PCI and reported that the use of iodixanol reduced the risk of MACE compared with the non-ionic LOCM iopamidol (4.8% vs. 9.0%; p=0.003).

In the VIP trial, the clinical effects of iodixanol compared with ioxaglate were examined for low-risk patients, with recent MI being an exclusion criterion[21]. A total of 1411 patients undergoing percutaneous transluminal coronary angioplasty (PTCA) were enrolled (randomised and double-blind) in this trial, of whom 714 patients received ioxaglate and 697 patients received iodixanol. In this study, the primary clinical outcome of the trial, namely a MACE, was defined as cardiac death, stroke, Q-wave or non-Q-wave MI, unplanned CABG and emergency re-PTCA at the target lesion or in the target vessel during the hospital stay (2-day follow-up). An angiographic success rate of 83.6% was achieved for patients managed with ioxaglate and 85.5% for

Table 1. The main clinical data used as input for the model[a]

	High-risk (COURT)				Low-risk (VIP)			
	Ioxaglate (n=410)		Iodixanol (n=405)		Ioxaglate (n=714)		Iodixanol (n=697)	
	N	%	N	%	N	%	N	%
Number of patients with:								
Angiographic success	352	85.9%	373	92.1%	597	83.6%	596	85.5%
AEs	246	60.0%	239	59.0%	197	27.6%	192	27.5%
SAEs	57	13.9%	43	10.6%	37	5.2%	48	6.9%
Non-serious AEs	189	46.1%	196	48.4%	160	22.4%	144	20.7%
Number of deaths	1	0.2%	5	1.2%	2	0.3%	0	0.0%
Number of AEs that were[b]:								
SAE and CM-related	46	11.2%	19	4.7%	18	2.5%	11	1.6%
SAE and not CM-related	35	8.5%	38	9.4%	25	3.5%	50	7.2%
Number of AEs that were[b]:								
Non-SAE and CM-related	264	64.4%	234	57.8%	106	14.8%	95	13.6%
Non-SAE and not CM-related	232	56.6%	224	55.3%	155	21.7%	153	22.0%
	CM-related	Not CM-related	CM-related	Not CM-related	CM-related	Not CM-related	CM-related	Not CM-related
SAEs								
Allergy-like	2%	4%	0%	0%	5%	0%	18%	0%
Cardiovascular	95%	96%	100%	97%	95%	100%	82%	100%
Nephrotoxicity	3%	0%	0%	3%	0%	0%	0%	0%
Non-serious AEs								
Allergy-like	31%	16%	34%	16%	26%	20%	8%	22%
Cardiovascular	69%	84%	62%	84%	74%	80%	92%	78%
Nephrotoxicity	0%	0%	4%	0%	0%	0%	0%	0%

AEs, adverse events; SAEs, serious adverse events; CM, contrast medium.

[a]Data for high-risk patients were derived from the COURT trial[19], and for low-risk patients from the VIP trial[21].

[b]Subjects may have both CM-related and not CM-related AEs. Each subject may have more than one AE.

patients managed with iodixanol. No difference in the rate of occurrence of AEs was reported for each patient group (27.6% for ioxaglate, 27.5 % for iodixanol). The patient groups also reported similar rates of MACEs when ioxaglate was used compared with iodixanol (3.9% for ioxaglate, 4.7% for iodixanol; p=0.45). It may therefore be inferred that the reduced rates of MACE and increased rates of angiographic success associated with the use of iodixanol may translate into cost-savings. The objectives of the present study were to undertake a cost-analysis to estimate and compare the direct healthcare costs associated with using ioxaglate and iodixanol in patients undergoing PCI, and to undertake a cost-effectiveness analysis to compare the difference in costs with the difference in health outcomes. This economic evaluation was undertaken for France and Spain, as both CMs are used to some extent in these countries. In addition, a high number of PCI procedures are performed in these countries each year, with approximately 27,000 PCIs in Spain and 80,000 in France in 2000[1,22].

Methods

Model framework

An economic model was developed to compare the healthcare costs of the use of iodixanol with the use of ioxaglate for patients undergoing PCI. The modelling technique used in this study was a decision tree model using the DATA PROč software from TreeAge Software Inc[23]. Decision analysis is an established method for comparing economic and clinical outcomes for different strategies in a single model, and has been used in many published studies calculating the cost-effectiveness of interventional strategies in cardiovascular medicine[24,25,26].

The model used in this analysis was reviewed by one expert from each study country before the model structure was adjusted and finalised. A schematic overview of the model is presented in Figure 1.

In the model, angiographic success is defined as an enlargement of the lumen at the target site as assessed immediately after the procedure. According to the American College of Cardiology/American Heart Association (ACC/AHA) guidelines, angiographic success is defined as a minimum stenosis diameter reduction to <20% of original lumen diameter when stents are used in the procedure, and a minimal reduction to <50% when stents are not used[27]. This definition was identical to the definition of angiographic success used in the COURT and VIP trials. The main groups of AEs studied are: (1) allergy-like events; (2) cardiovascular events; and (3) nephropathic events. Although other AEs (e.g. headache, fever, dyspnoea, etc.) were reported in published studies, these were not included in this economic study. Two reasons determined this choice. First, they do not require any discernible resource use as indicated by the expert panel. Second, as these AEs occur very infrequently, they do not generate additional costs that would affect the outcome of this study.
The three types of AEs mentioned above were divided into serious and non-serious AEs in the model. Serious adverse events (SAEs) are defined as events that: (1) result in death; (2) are life-threatening; (3) require

inpatient hospitalisation or prolongation of existing hospitalisation; or (4) result in persistent or significant disability/incapacity.

Serious and non-serious AEs are further classified as CM-related or not CM-related. It is assumed that CM-related AEs include all AEs classified in the clinical trial reports as certain, likely, uncertain, unlikely and unknown to be related to the CM used, whilst AEs not related to CM refer to those AEs classified in the clinical trial reports as not related to the CM used.

Study population

In the present analysis, two populations were studied. High-risk patients were defined as those undergoing PCI for acute coronary syndrome with at least one of the following conditions: (1) angina at rest (Braunwald's classification IIIb or IIIc)[28] within the previous 48 h; (2) evolving Q-wave or non-Q-wave MI within 72 h, including patients who failed thrombolytics; (3) post-MI ischaemia documented either by angina during the current hospitalisation or within 2 weeks of a MI, or by a positive functional study within 2 weeks of a MI; and (4) not suffering from severe renal

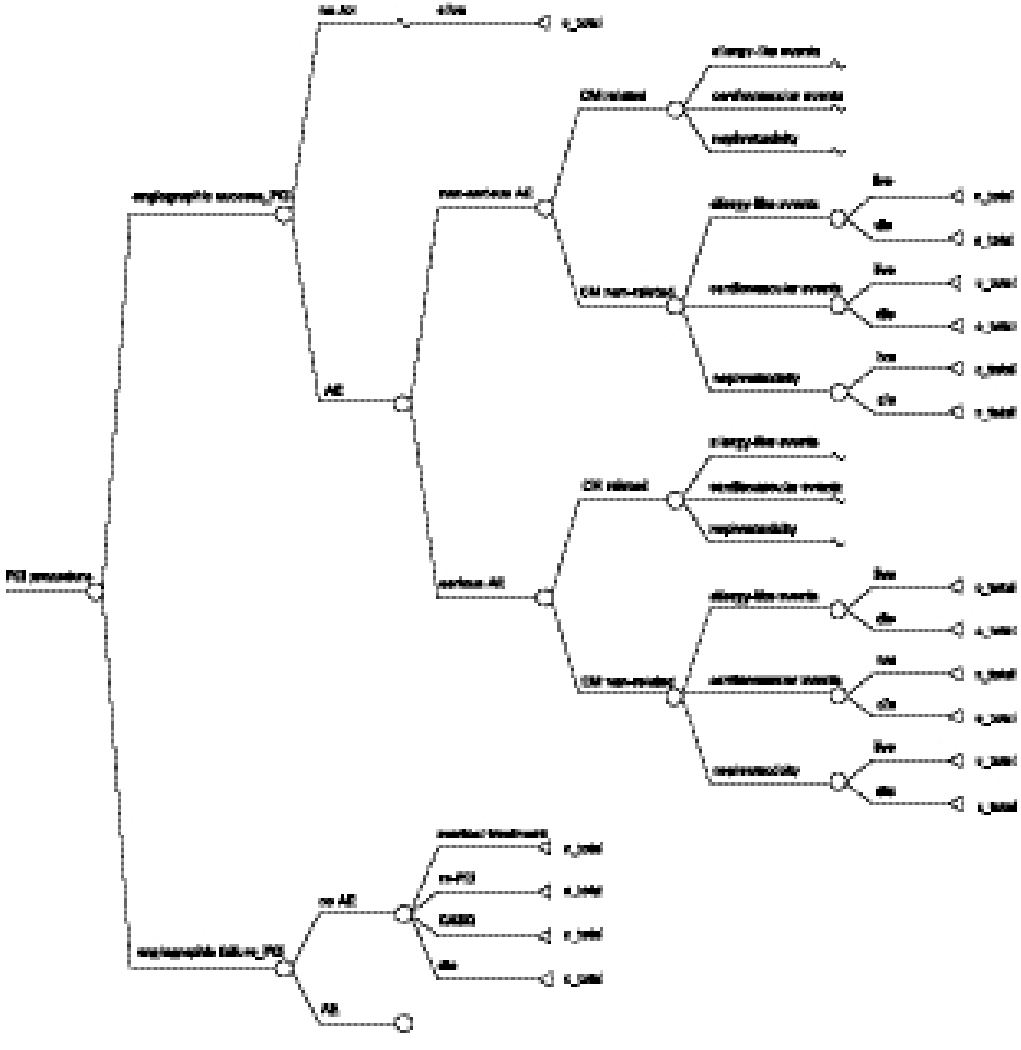
Table 2. Estimated length of stay (days) based on the expert (opinion) panels[a]

	High-risk patients				Low-risk patients			
	France		Spain		France		Spain	
	Mean	Range	Mean	Range	Mean	Range	Mean	Range
Pre treatment	1.4	1–3	1.4	1–3	1.4	1–3	1.0	0–2
Post treatment, no SAE	2.3	1–5	2.6	1–7	1.4	1–2	1.4	1–2
Post treatment when a SAE such as anaphylactic reaction occurs	4.1	3–7	3.6	3–6	3.2	2–6	2.4	1–5
Post treatment when a serious cardiovascular event occurs that was:								
Pulmonary oedema	5.0	3–7	3.6	3–8	4.1	2–6	2.4	1–6
Not life-threatening ECG changes	4.0	3–5	3.6	3–6	3.1	2–4	2.4	1–4
Life-threatening ECG changes	6.0	3–9	4.6	4–6	5.1	2–8	3.4	2–4
Non-fatal MI without the need of re-PCI	6.6	4–9	5.6	4–8	5.7	3–8	4.4	2–7
Non-fatal MI, with the need of re-PCI	7.9	6–9	6.6	5–9	7.0	5–8	5.4	3–7
Cardiogenic shock or cardiac arrest	10.1	7–13	13.6	8–19	9.2	6–12	12.4	6–17
Peripheral thromboembolus event	8.1	6–13	5.6	4–10	7.2	5–12	4.4	3–8
Post treatment when a serious nephrotoxicity occurs								
Doubling of creatinine or increase in creatinine	3.8	3–6	4.4	4–10	2.9	2–5	3.2	2–8
Nephrotoxicity that results in dialysis or hastens death	8.6	4–14	11.7	7–33	7.7	3–13	10.5	6–31

SAE, serious adverse event; ECG, electrocardiogram; MI, myocardial infarction; PCI, percutaneous coronary intervention.

[a]Data were obtained from the expert (opinion) panels consisting of 12 French cardiologists and 12 Spanish cardiologists geographically spread over the different regions.

Figure 1. Schematic overview of the model for percutaneous coronary intervention (PCI)



AE, adverse event; CM, contrast medium; CABG, coronary artery bypass grafting.

impairment, defined as a serum creatinine >2.0 mg/dl. Low-risk patients were defined as those undergoing PCI and having one or more of the following conditions: (1) stable (Canadian Cardiovascular Society functional classification)[29,30] angina; (2) unstable angina (Braunwald's classification); (3) silent ischaemia; and (4) not with a recent (<7 days) acute MI, unprotected left main stenosis or the need for oral anticoagulation with anti-vitamin K.

The definition for high-risk patients was obtained from the COURT trial[19], and for low-risk patients from the VIP trial[21]. They were also similar to those used in the ACC/AHA PCI guidelines[27]. The definitions were also reviewed by the experts who were consulted during this study and were deemed as appropriate.

Time horizon

The time horizon used in the model is the hospitalisation period following the PCI. Based on the input from the interviewed interventional cardiologists, this period was on average 1–2 days for patients without complications. The average length of stay (LOS) for the management of complications varied with type of complication, ranging from 1 additional day for the management of an allergy-like event to around 10 additional days for the management of a cardiovascular event. Long-term complications, including renal failure potentially related to the choice of CM, may occur following a PCI, however these are infrequent and reliable rates are not available from prospective studies. Hence, the costs of long-term complications have not been included in the present study.

Study perspective and countries

The perspective adopted for this model analysis was that of the hospital perspective in the French and Spanish healthcare setting.

Study endpoints

The main health outcome used in this study is the rate of patients undergoing PCI who achieved angiographic success. In addition, the model is used to estimate the cost per treated patient, which takes into account the probabilities of occurrence of different clinical events (AEs, angiographic success, angiographic failure, etc.) and their associated costs, by calculating a probability-weighted average cost.

Key assumptions

Key assumptions used in this study are summarised below.

- The high-risk patient population is assumed to represent both chronic and acute patient types, whereas the low-risk population is assumed to predominantly reflect chronic patients.
- It is assumed that all AEs caused by CM will occur during the initial hospitalisation period.
- It is assumed that all non CM-related AEs will occur equally often for each strategy of the analysis.
- The probabilities of various AEs for patients with an angiographic failure are assumed to be equal to those for patients with an angiographic success, i.e. it is assumed that the probability of an AE is related to the CM and not to the clinical outcome of the PCI procedure.
- Healthcare resource utilisation for the treatment of an AE is assumed to be independent of the choice of CM.
- The treatment of an AE for patients with angiographic success is assumed to be the same as the treatment of the same AE for patients with angiographic failure.

Clinical data

The clinical events, therapeutic choices and the rates of occurrence of specific AEs classified as allergy-like events, cardiovascular events and nephrotoxicity were derived for high-risk patients from the COURT trial[19] and for low-risk patients from the VIP trial[21]. The rates of these events used in the analysis are shown in Table 1.

The clinical data used in this model were compared with other published data to determine whether any evident major differences might cast doubt on the validity of the clinical trial data used within the model. The angiographic success rates and the rates of AEs seen in other publications ranged from 83% to 93% and from 7% to 68%, respectively[2,31–37]. It should be noted that the rate of AEs of 7% seen in one of the publications included only those AEs that occurred within 24 h after the PCI procedure and is therefore likely to be underestimated relative to the time perspective of this study. Comparing these published data with the data derived from the COURT and VIP trials (83.6– 92.2% for angiographic success rates, 27.5– 60% for the rates of AEs), no major differences were found.

Resource use data

Estimates of the healthcare resources used for PCI could not be derived from publications or clinical trials. Hence, an expert opinion panel was used. The use of expert opinion panels is a recognised means of data estimation, as participants are

Table 3. Model-based cost results (€) of patients undergoing percutaneous coronary intervention (PCI) in France and Spain[a]

Cost component	Ioxaglate	Iodixanol	Difference[b]	Ioxaglate	Iodixanol	Difference[b]
	France, high-risk			Spain, high-risk		
Pre treatment	502 (11%)	502 (12%)	0	891 (15%)	891 (16%)	0
PCI (excluding CM cost)	2,400 (54%)	2,400 (57%)	0	2,400 (41%)	2,400 (43%)	0
CM cost	115 (3%)	132 (3%)	+17	75 (1.3%)	130 (2.3%)	+55
Standard post treatment	395 (9%)	395 (9%)	0	1,302 (22%)	1,302 (23%)	0
Non-serious AEs	6 (0.1%)	6 (0.1%)	0	13 (0.2%)	13 (0.2%)	0
SAEs	760 (17%)	613 (15%)	–147	944 (16%)	764 (14%)	–180
Re-PCI or CABG	232 (5%)	131 (3%)	–101	216 (4%)	121 (2%)	–95
Total cost (weighted estimate)	4,410	4,179	–231	5,841	5,621	–220
	France, low-risk			Spain, low-risk		
Pre treatment	144 (4%)	144 (4%)	0	478 (11%)	478 (10%)	0
PCI (excluding CM cost)	2,400 (69%)	2,400 (68%)	0	2,400 (53%)	2,400 (52%)	0
CM cost	108 (3%)	122 (3%)	+14	71 (2%)	120 (3%)	+49
Standard post treatment	133 (4%)	133 (4%)	0	699 (16%)	698 (15%)	–1
Non-serious AEs	3 (0.1%)	3 (0.1%)	0	5 (0.1%)	5 (0.1%)	0
SAEs	284 (8%)	362 (10%)	+78	357 (8%)	457 (10%)	+100
Re-PCI or CABG	417 (12%)	370 (10%)	–47	490 (11%)	434 (9%)	–56
Total cost	**3,489**	**3,534**	**+45**	**4,500**	**4,592**	**+92**

CM, contrast medium; AEs, adverse events; SAEs, serious adverse events; CABG, coronary artery bypass grafting.

[a]The overall costs of treatment were calculated by multiplying each health resource used per patient, as collected via the expert panel, with the unit cost of each healthcare utilisation and taking into account the probabilities of occurrence of a clinical event associated with resource utilisation (see Table 1). Owing to rounding, the percentages may not add up to 100%.

[b]Difference = cost iodixanol – cost ioxaglate; negative result indicates saving with iodixanol.

recruited for their expertise in the field of interest[38–41].

The expert opinion panel used in this study consisted of 12 French interventional cardiologists and 12 Spanish interventional cardiologists, geographically spread over the different regions within each country. Criteria for selecting panel members included a minimum of 5 years of clinical experience in the field of PCI, currently practicing cardiologists, not teaching cardiologists. All cardiologists worked in general or academic hospitals.

Panel members were asked to complete questionnaires containing sample patient profiles (both high-risk and low-risk patients) representing patients following different clinical pathways ('branches' in the model). They were asked to estimate LOS, medications used, diagnostic procedures and laboratory tests performed, and manpower associated with these procedures during the hospital stay before and after the PCI. Resource use was also estimated for each AE that might occur and require management during the hospitalisation period.

The volume of CM administered for high-risk and low-risk patients was derived from the COURT and VIP trials, respectively. The volume was calculated as the mean of each individual volume rounded up to the nearest 100 ml (i.e. a whole vial), as it is assumed that the unused portion of an open vial of CM is discarded. This resulted in similar amounts for both agents (high-risk patients: 312 ml ioxaglate, 296 ml iodixanol; low-risk patients: 293 ml ioxaglate, 273 ml iodixanol).

Unit costs

In this economic study, a 'bottom-up' approach to costing has been used, in which individual items of medical resource utilisation are costed and the overall cost is the aggregate of these costs. This approach will allow differentiating the total costs according to specific events occurring during the hospital stay, to CM used or to at-risk status of the patient.

For this analysis, the unit costs of the following variables were included: CM, medications, tests and procedures, inpatient admissions, and CABG and PCI procedures[42,43]. Other unit costs such as the cost of inpatient admissions were obtained from French PMSI ('*Programme de Médicalisation du Système d'Information*') database[44]. For Spain, the unit costs of medications were obtained from '*Catálogo de Especialidades Farmacéuticas*', whilst the unit costs of procedures and inpatient admissions were obtained from SOIKOS Spanish Health Costs Database 2001[45,46].

The prices of the CMs used in the model were the 2002 official list prices for France and Spain[46,47]. It was assumed that the cost of administration of each CM was part of the overall cost and independent of the CM used.

The cost of the PCI procedure itself was derived from published literature[48]. This cost (approximately €2,400 at 2002 prices) includes the cost of a surgical room, medical personnel, devices and doses of medications used during the procedure, but not the cost of managing AEs. Outpatient costs and indirect costs (i.e. missed working days) were not included in this analysis.

The overall cost of the PCI admission was calculated by summing up the costs of all resource use along each path weighted by the probability of occurrence of different clinical events (AEs, angiographic success, etc.) triggering the resource use.

Cost per unit of health outcome and incremental cost-effectiveness ratio

The cost per unit of health outcome of each CM was determined by dividing the average cost per patient by the proportion of patients for whom the PCI was angiographically successful. One choice of CM will be considered dominant when the cost of that choice is lower and the outcome is better than the cost and outcome of the alternative choice. However, if there is no dominant choice, it is necessary to consider the incremental cost-effectiveness ratio (ICER), which is the extra cost required to obtain one unit of additional angiographic success when using one intervention rather than an alternative.

Sensitivity analysis

The data used to populate the model come from a number of sources, making it difficult to reflect the uncertainty of the input data into the results of the model through traditional statistical methods. Therefore, three one-way sensitivity analyses were performed to study the robustness of the conclusions by specifying a lower and upper value for each individual parameter tested and running the economic analysis using those valued. The robustness of the model-based results is assessed by examining how they change as parameters are varied. The first sensitivity analysis involved changing the amount of iodixanol used during the PCI. The second sensitivity analysis involved changing several occurrence rates of clinical events such as the rate of angiographic success. The third analysis involved changing the rate of SAEs

Table 4. Differences in costs and health outcomes for patients undergoing percutaneous coronary intervention (PCI) in France and Spain[a]

	France			Spain		
	Ioxaglate	Iodixanol	Difference	Ioxaglate	Iodixanol	Difference
High-risk patients						
Cost per patients (€)	4,410	4,179	–231	5,841	5,621	–220
% with angiographic success	85.9%	92.2%	+6.3%	85.9%	92.2%	+6.3%
Low-risk patients						
Cost per patients (€)	3,489	3,534	+45	4,500	4,592	+92
% with angiographic success	83.6%	85.5%	+1.9%	83.6%	85.5%	+1.9%
Cost per angiographic success (€)[b]	4,173	4,133	—	5,383	5,371	—
Extra cost per extra angiographic success (ICER) (€)[c]			2,368			4,842

aThe average cost per patient undergoing PCI was calculated using the model, and the rate of angiographic success for high-risk patients was derived from the COURT[19] and for low-risk patients from the VIP trials[21].

bThe cost per unit of health outcome was determined by dividing the average cost per patient by the proportion of patients experiencing an angiographic success.

cThe incremental cost-effectiveness ratio (ICER) is defined as the difference in costs divided by the difference in angiographic success rate.

when iodixanol is used. These parameters were selected since there is uncertainty associated with their value and they have a potentially large impact on the difference in treatment costs.

Results

Resource use

According to the interviewed French and Spanish interventional cardiologists (the expert panel), management of AEs was similar for patients with high or low risk of complications with regard both to the type of medications used and the procedures performed. In addition, the cardiologists reported that the treatment of AEs does not depend on the type of CM used or whether the patient has an angiographic failure or success. The CMs most often used at the experts' hospitals are ioxaglate, iodixanol, iomeprol and iohexol.

The mean values of the pre- and post-treatment LOS for high- and low-risk patients undergoing PCI obtained from the expert opinion panel are summarised in Table 2. For high-risk patients, the mean pre-treatment LOS is 1.4 days both in France and Spain, whilst for low-risk patients it is 1.4 days in France and 1 day in Spain. The mean post-treatment LOS (standard without any AEs) for high-risk patients is 2.3 days in France and 1.0 days in Spain, and for low-risk patients it is 1.4 days both in France and Spain.

No additional LOS was estimated for the treatment of non-serious AEs such as itching, rashes, vomiting and hypotension in both patient populations and in both study countries. For patients suffering from SAEs, the mean LOS varies, depending on the type of AE (Table 2), e.g. in France the mean LOS for a high-risk patient with the serious allergy-like event (anaphylactic reaction) is 4.1 days, whilst it is 6.6 days for a high-risk patient having the serious cardiovascular event non-fatal MI without the need of re-PCI.

Model-based outcomes

The total estimated direct costs and its components of the PCI (cost of intervention) together with associated treatment during the period of hospitalisation for high- and low-risk patients in France and Spain are shown in Table 3. The cost of intervention with subsequent treatment for high-risk patients undergoing PCI in France is €4,410 for ioxaglate and €4,179 for iodixanol, whilst in Spain it is €5,841 for ioxaglate and €5,621 for iodixanol. The cost of intervention with subsequent treatment for a low-risk patient undergoing PCI in France is €3,489 for ioxaglate and € 3,534 for iodixanol, and in Spain it is €4,500 for ioxaglate and €4,592 for iodixanol. The difference in cost of intervention is due to the difference in the cost of study CM, the cost of treatment of SAEs and the cost of re-PCI or CABG for patients with an intervention resulting in angiographic failure.

Cost-effectiveness

Table 4 summarises the average cost per high- and low-risk patient undergoing PCI calculated by the model as well as the effectiveness of the treatment (angiographic success rate) derived from the COURT and VIP trials. For high-risk patients, the average cost per patient for iodixanol was €231 (France) and €220 (Spain) lower than

that for ioxaglate. The rate of angiographic success for iodixanol was 6.3% higher than for ioxaglate (85.9% for ioxaglate and 92.2% for iodixanol). For low-risk patients, the cost of intervention per patient was €45 (France) and €92 (Spain) higher for iodixanol compared with ioxaglate. A slightly higher rate of angiographic success was also seen when iodixanol is used in this group of patients (83.6% for ioxaglate and 85.5% for iodixanol).
Since both the cost of intervention and the angiographic success rate are higher for iodixanol than for ioxaglate in low-risk patients, the costs per unit of health outcome (i.e. the cost per angiographically successful PCI) for these two CMs were also calculated (Table 4). It was shown that the cost per angiographic success for ioxaglate and iodixanol was €4,173 and €4,133 in France, and €5,383 and €5,371 in Spain, respectively.

Table 4 also shows the incremental cost-effectiveness ratio (ICER) for iodixanol versus ioxaglate per low-risk patient,

Table 5. One-way sensitivity analysis results for patients undergoing percutaneous coronary intervention (PCI) in France and Spain

	France				Spain			
	Base case	Min.	Max.	Break-even point[a]	Base case	Min.	Max.	Break-even point[a]
High-risk patients								
Variable changed: CM volume iodixanol	296 ml	40 ml	630 ml	—	296 ml	40 ml	630 ml	—
Outcome: cost of intervention iodixanol	€4179	€4,065	€4,329	—	€5,621	€5,509	€5,767	—
Variable changed: rate of angiographic success iodixanol	92.2%	87.9%	96.5%	—	92.2%	87.9%	96.5%	—
Outcome: cost of intervention iodixanol	€4,179	€4,251	€4,109	—	€5,621	€5,687	€5,554	—
Variable changed: % of SAEs iodixanol	18.0%	10.8%	25.2%	—	18.0%	10.8%	25.2%	24.3%
Outcome: cost of intervention iodixanol	€4,179	€3,953	€4,402	—	€5,621	€5,339	€5,897	€5,841
Low-risk patients								
Variable changed: CM volume iodixanol	273 ml	55 ml	780 ml	177.8 ml	273 ml	55 ml	780 ml	66.9 ml
Outcome: cost of intervention iodixanol	€3,534	€3,437	€3,760	€3,489	€4,592	€4,496	€4,814	€4,500
Variable changed: rate of angiographic success iodixanol	85.5%	81.8%	89.2%	87.7%	85.5%	81.8%	89.2%	88.9%
Outcome: cost of intervention iodixanol	€3,534	€3,628	€3,440	€3,489	€4,592	€4,703	€4,481	€4,500
Variable changed: % of SAEs iodixanol	25.0%	20.5%	29.5%	20.6%	25.0%	20.5%	29.5%	—
Outcome: cost of intervention iodixanol	€3,534	€3,479	€3,589	€3,489	€4,592	€4,522	€4,662	—

Break-even point indicates the point at which the total cost of intervention when using iodixanol is the same as the cost of intervention when using ioxaglate

indicating that the choice of iodixanol as CM, rather than ioxaglate, costs an additional €2,368 per additional successful PCI procedure in France, and €4,842 in Spain.

Sensitivity analysis results

Table 5 summarises the main results of the sensitivity analyses. The first sensitivity analysis involved changing the amount of iodixanol used during the PCI. The range of this parameter was derived from the corresponding trials, varying from 40 ml to 630 ml for high-risk patients and 55 ml to 780 ml for low-risk patients, which were the per-patient lower and upper limits of volume of CM used. The second sensitivity analysis involved changing the angiographic success rate and the third involved changing the probability of SAEs when iodixanol was used. The ranges of these two parameters were based on the 95% confidence intervals of values derived again from the corresponding trial and are also presented in Table 5. At the point of value where the cost of intervention is the same for both CMs, a break-even point is reached.

Table 5 reveals that for high-risk patients, there were often no break-even points over the range of values of the parameters tested in both study countries, indicating that the results and conclusions of the model analysis are relatively insensitive to changes in the parameter values over the indicated range. However, for the probability of SAEs when iodixanol is used in Spain, it is shown that when the rate increased to 24.3% (compared with base case value 18% of SAEs among all AEs (43 of 239)), the cost of intervention is equal for both CMs (break-even point).

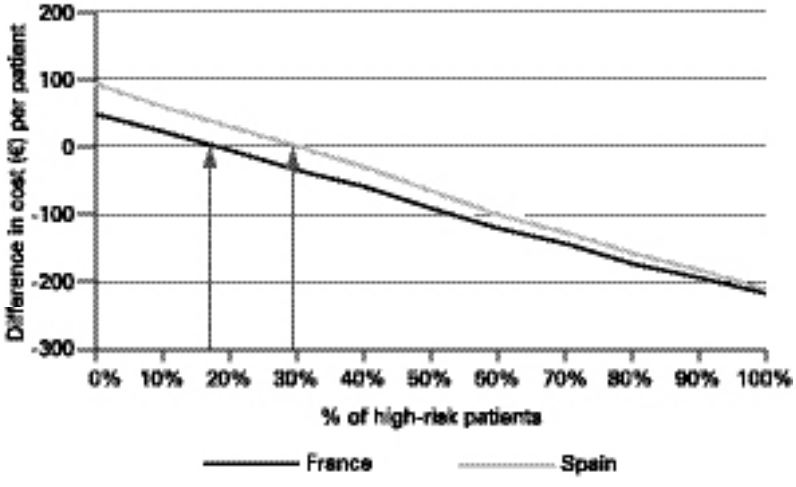
In the low-risk patient group, sensitivity analysis showed that the mean amount of iodixanol used needs to be 177.8 ml (2 vials) in France and 66.9 ml (1 vial) in Spain for the total cost of intervention to be equal for the CMs. For the angiographic success rate, Table 5 shows that the rate needs to be 87.7% in France and 88.9% in Spain (compared with base case value 85.5%) to become cost-neutral. For the probability of SAE when iodixanol is used, a break-even point was reached at the rate of 20.6% (compared with base case value of 25%) in France. In Spain, however, there was no break-even point over the range of values tested.

Discussion

In this study, a decision analysis model for the treatment of patients undergoing PCI was developed for the French and Spanish hospital settings. This model is used to calculate the cost of care of two treatment options: the use of IOCM iodixanol or the use of ionic LOCM ioxaglate. This study showed that for high-risk patients the total direct cost of intervention per patient, including treatment of potential subsequent events, was €231 (France) and €220 (Spain) lower when using iodixanol than when using ioxaglate. For low-risk patients, the total direct cost of intervention per patient was €45 (France) and €92 (Spain) higher when iodixanol was used compared with ioxaglate.

For both study countries and in both patient populations, the cost of pre

Figure 2. Combined analysis on the difference in cost by % of high-risk patients when using iodixanol versus ioxaglate in France and Spain



treatment and the cost of the PCI procedure (excluding the cost of CM) do not depend on the type of CM used. However, post-procedural costs are dependent on the rate at which AEs occur and this is associated with the CM used. More precisely, the extended LOS and the need for additional treatment resulting from an AE are the factors driving the difference in the cost of PCI using iodixanol compared with PCI using ioxaglate. The cost of treatment of non-serious AEs is similar for both CMs used, despite the difference in the rate of non-serious AEs reported for these two CMs. This is because non-serious AEs, such as itching and vomiting, have low treatment costs. For there to be a perceptible difference in costs owing to a difference in the rate of non-serious AEs, there would need to be a much larger difference than seen in this study. Conversely, SAEs have a high associated cost, suggesting that small differences in the rate of occurrence of SAEs can have a substantial impact on the total direct cost of intervention. The rate of SAEs reported in the COURT trial was 13.9% for ioxaglate and 10.6% for iodixanol for high-risk patients (Table 1), hence the cost of treatment of SAEs for iodixanol is found to be lower than that for ioxaglate in both study countries (€147 lower in France and €180 lower in Spain) (Table 3). However, for low-risk patients, the cost of treatment of SAEs for iodixanol is found to be higher than that for ioxaglate (€78 higher in France and €100 higher in Spain) (Table 3). This is owing to a slightly higher rate of occurrence of SAEs for iodixanol than for ioxaglate seen in the VIP trial (5.2% for ioxaglate versus 6.9% for iodixanol) (Table 1).

The cost of angiographic failure leading to re-PCI or CABG is also lower for iodixanol than for ioxaglate both in high- and low-risk patients in both study countries owing to the lower rate of occurrence of angiographic failure for iodixanol (Table 1). It is also worth noting that the analysis performed in this study is conservative, since the potential cost of outpatient

treatment after a patient experiences an angiographic failure is not included. The cost associated with this outpatient treatment would tend to be higher for the group with higher rates of failure and lower rates of angiographic success.

The amount of CM used in terms of the mean volume of individual volumes rounded up to the nearest 100 ml (i.e. a whole vial) was similar for both CMs (312 ml for ioxaglate and 296 ml for iodixanol for high-risk patients, and 293 ml and 273 ml, respectively, for low-risk patients). Since the unit price for iodixanol (100 ml) is higher than for ioxaglate (100 ml) (€44.61 versus €36.78 in France and €43.84 versus €24.16 in Spain), this results in a higher cost of the CM used for iodixanol (Table 3). Although iodixanol has a higher acquisition cost, this is offset by lower post-procedural costs to the hospital for high-risk patients since iodixanol has a more favourable adverse drug reaction profile. For low-risk patients, however, this cost was not offset owing to a similar adverse drug reaction profile for the two CMs. Sensitivity analysis showed that if the number of vials of iodixanol used during the PCI is decreased to 1–2 vials in low-risk patients, the cost of intervention will be equal for both CMs. Nevertheless, the difference in the total cost of intervention per low-risk patient between these two CMs is small (€45 in France and €92 for Spain), and the ICER indicates that iodixanol costs an additional €2,368 per additional successful PCI procedure for France and €4,842 for Spain (Table 4).

Based on the information obtained from the expert opinion panel, it was noted that in many instances only one CM is placed in the hospital formulary list and used for both high- and low-risk patients. It was thus deemed appropriate to perform a combined analysis to estimate the total cost-savings potential by treating all patients with one CM regardless of risk (Figure 2). This was done by calculating the difference in cost when using iodixanol versus ioxaglate while the rate of high-risk patients varied from 0% to 100% in the total population. Figure 2 shows that if the patient population contains a minimum of 17% high-risk patients in France and 30% high-risk patients in Spain, cost-savings can be expected with iodixanol.

When comparing the cost of intervention for patients undergoing PCI in France and in Spain, a higher cost is seen in the Spanish hospital setting than in the French hospital setting both for high- and low-risk patients. This is mainly owing to the more aggressive use of expensive medication such as GPIIb/IIIa inhibitors as indicated by the interviewed Spanish cardiologists, as well as the higher unit cost for a hospital bed day in Spain (€249 in Spain versus €150 in France).

The costs of intervention calculated by our model were compared with those reported in other studies[1,3,49–52]. The cost of intervention reported in other studies for patients undergoing PCI (independent of the risk of the patient) in France and Spain varies from €2,334 to €6,411, therefore the model results (€3,489 to €5,841) fall within the range reported in the literature. It should be noted that the cost of €2,334 mentioned in one of the publications refers to the cost of PCI procedure only[1], and not

the total cost of in-hospital intervention. The cost calculated by this model is also similar to the amount reimbursed to hospitals via the prospective payment system used in each study country, the '*Grupos de Diagnóstico Relacionados*' (GDR) in Spain and the '*Groupes Homogènes de Malades*' (GHM) in France[44,53]. These systems have been modelled on the US Diagnosis Related Group (DRG) system, in which all costs involved in the management of care (including AEs), such as the cost of medications, procedures and consultations, are included in one fee charged to the third-party payer. This is a 'top-down' approach to costing where the cost to the purchaser is a blanket charge that does not take into account the relative cost of individual items. In the present study, a 'bottom-up' method was used, which is considered to be more appropriate since differences in cost in individual items of medical resources used within a DRG code can be examined. The amount reimbursed to the hospital via GHM ranged from €2,906 (standard pathology) to €5,003 (severe cardiac pathology) in France. The cost of intervention calculated by the model is €3,534 using iodixanol for low-risk patients and €4,179 for high-risk patients, which falls within the range calculated by the GHM, which is also the case for ioxaglate. In Spain, the average amount reimbursed to the hospital via GDR is €4,993 independent of the risk of patients, whilst the cost of intervention calculated by our model is €5,621 using iodixanol for high-risk patients and €4,592 for low-risk patients. In the present model, a mixed population with 39% high-risk patients and 61% low-risk patients would yield an average cost of €4,993 when using iodixanol.

All model-based analyses are subject to limitations. Two main general limitations of the modelling approach are also relevant here. First, in an effort to keep the model simple, a number of assumptions were made in this study. These assumptions are conservative, and we have shown that some of these assumptions were confirmed to be real-life practice by the interviewed cardiologists. One such assumption is that treatment of an AE for patients with angiographic success was the same as the treatment of the same AE for patients with angiographic failure. Another is that healthcare resource utilisation for the treatment of an AE was independent of choice of CM.

Second, potential biases may occur from amalgamation of multiple data sources. In this study the clinical data were derived from randomised, double-blind clinical trials, whilst resource use was collected from a panel of clinical experts. The unit costs were based on country-specific tariffs and statistics were derived from national DRG databases. Alternatives to this approach, such as economic evaluation alongside clinical trials, are not always the optimal method, as resource use in the clinical trials may not reflect routine practice, and they may be no more informative than modelling[48]. We therefore considered modelling in this case as the best approach since no single source of all the data needed was available.

Although this model is subject to the limitations mentioned above, sensitivity analysis showed that the results based on

the model are robust for high-risk patients, where none of the changes in parameters led to major changes in the results affecting the conclusions. For low-risk patients, sensitivity analysis revealed that the number of vials of iodixanol used during the PCI needs to be decreased to 1–2 vials for treatment with iodixanol to become cost-neutral, and the rate of angiographic success needed to be slightly higher and the rate of SAEs needed to be slightly lower than those seen in the VIP trial (but still within the confidence intervals of this study) for the cost of intervention when using iodixanol to be equal to cost of intervention when using ioxaglate (Table 5).

Conclusion

This model-based analysis suggests that, based on the results of the COURT trial, the total direct cost of PCI in high-risk patients to hospitals in France and Spain when using the IOCM iodixanol is lower than the cost when using the ionic LOCM ioxaglate. For low-risk patients, based on the results of the VIP trial, the total direct cost of PCI when using iodixanol is higher than the cost of PCI when using ioxaglate, but iodixanol may be regarded as cost-effective when relating the extra cost to the small reported increase in angiographic success. Cost-savings through using iodixanol in patients at all risks (combined) are expected if the proportion of high-risk patients is above 17% in France and 30% in Spain.

Disclaimer

This study was funded by an unrestricted educational grant from GE Healthcare (formerly Amersham Health).

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