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Comparative Tolerability of Contrast Media Used for Coronary Interventions

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Abstract

Radiographic contrast media (CM) are necessary to provide x-ray absorption of the bloodstream; all other observed effects need to be regarded as adverse. Four types of CM are currently used in diagnostic and interventional cardiology: ionic high-osmolar CM (HOCM), either ionic or non-ionic low-osmolar CM (LOCM), and non-ionic iso-osmolar CM (IOCM). Focusing on the potential cardiovascular effects caused by the CM, there is a clear difference between HOCM and the LOCM or IOCM. HOCM have a poorer profile due to a higher incidence of hypotension and electrophysiological effects. To prevent contrast-induced nephropathy, HOCM should be avoided and patients should receive the minimal dose of LOCM or IOCM with intravenous hydration before and after the procedure. Clinical hyperthyroidism has been detected after CM use, but the condition appears, ultimately, to be self-limited and to occur mainly in elderly patients. When assessing the need for a CM in terms of improved patient safety, preventing serious complications should be the major factor determining the choice. CM should not be selected on the basis of minor adverse effects since these are, ultimately, of low clinical relevance. Thrombotic events, in contrast, carry a high clinical relevance and we consider that these should be the main issue governing current choice. Ionic LOCM appear to have better profile than other CM with

respect to interaction with platelet function and coagulation. In relation to thrombotic events in randomised clinical studies, ionic CM have been associated, mainly, with favourable and some neutral results compared with non-ionic agents. Only one trial indicated a more pronounced antithrombotic effect of the non-ionic IOCM relative to the ionic LOCM. The antithrombotic advantages of ionic over non-ionic LOCM are, in part, balanced by a greater frequency of minor adverse effects such as nausea, vomiting or cutaneous rashes. A matter of concern is the delayed adverse effects observed with non-ionic IOCM. However, severe and life-threatening reactions are exceptional and there are probably no significant differences between IOCM and LOCM whether ionic or non-ionic. However, in patients with known allergies, non-ionic CM are to be recommended. On the basis of the available pre-clinical and clinical data, the ionic LOCM or the non-ionic IOCM are the agents to be recommended in percutaneous coronary interventions because of their antithrombotic advantages over non-ionic LOCM.

Radiographic contrast media (CM) are necessary to provide x-ray absorption of the bloodstream so as to distinguish vascular and cavity structures from cardiac tissue. Iodinated CM is used in several millions of cardiac catheterisations performed each year around the world. Conventional CM employed for cardiovascular imaging consisted of ionic high osmolar agents but, since 1986, agents with lower osmolality have been marketed. Recently, additional agents with low osmolality and different characteristics have become available and considerable differences of opinion have arisen as to their possible safety implications.

When assessing the need for CM the important issue is to improve patient safety, mainly by preventing serious complications. All effects, apart from radiation absorption, need to be regarded as adverse.

The chemistry and pharmacology varies between the different agents and can explain part of their adverse effects. We review, here, the cardiac effects: haemodynamic and electrophysiological, together with the non-cardiac effects: renal, anaphylactoid and thrombogenic. Since our comparisons are focused mainly on percutaneous coronary interventions (PCI), the thrombogenic effects of the CM are reviewed in depth. Finally, we take economic issues into account in defining an optimal CM.

1. Chemical Structures and Osmolality

Contrast toxicity can be considered to have four main components: ionicity, osmolality, viscosity and chemotoxicity.

Four types of CM are currently used in diagnostic and interventional cardiology (figure 1): ionic monomers (diatrizoate sodium [sodium amidotrizoate]), ionic dimers (ioxaglate sodium), non-ionic monomers (iobitridol, iohexol, iomeprol, iopamidol, iopromide, ioversol) and non-ionic dimers

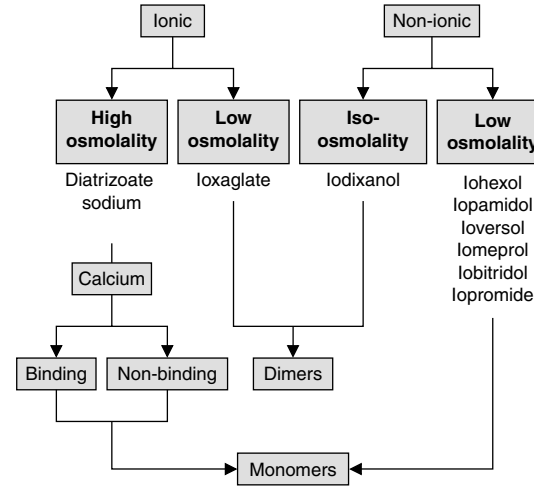
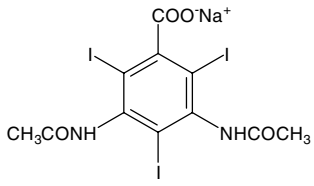


Fig. 1. Types of contrast media.



Diatrizoate sodium
HOCM–ratio 1.5

Fig. 2. High-osmolar contrast media (HOCM).

(iodixanol). The ionic monomers can be divided into calcium-binding and non-calcium-binding subgroups.[1,2]

The chemical structures of the most common CM are derivatives of tri-iodinated benzoic acid as seen in figures 2, 3 and 4.

The primary effect of CM is the attenuation or absorption of radiation by the iodine component of the molecule. The 'imaging effect' is a function of the number of iodine atoms and the 'osmotic effect' of the number of particles in solution. The ratio of iodine atoms to the number of osmotically active particles is an important factor in minimising osmolality-related toxicity. Hyperosmolality is undesirable, partly because of volume overload but also because it determines much of the cardiotoxic effect. High-osmolar CM (HOCM) are ionic monomers with sodium and meglumine ions with three iodine atoms per two particles (1.5 **:** 1) [figure 2]. Low-osmolar CM (LOCM) are either ionic dimers (ionic low-osmolar) with six iodine atoms per two particles (3 **:** 1), or non-ionic monomers (non-ionic low-osmolar) that have had the sodium and meglumine ions eliminated and have three iodine atoms per particle (3 **:** 1) [figure 3]. Iso-osmolar CM (IOCM) are non-ionic dimers that have six iodine atoms per particle (6 **:** 1) [figure 4]. The osmolalities of the different CM, relative to plasma, are shown in figure 5. In practice, the new compounds (IOCM and LOCM) have achieved more than the theoretical reduction in osmolality. The new compounds have a tendency to form molecular aggregates in solution, resulting in a greater overall reduction in osmolality.

The CM used for coronary angiography and PCI need to have a high iodine content (figure 5). No objective differences in relation to image quality have been detected between these CM.

In general, reducing the osmolality of a CM increases its viscosity. The non-ionic CM have, in general, higher viscosities at different temperatures, as summarised in figure 6. Theoretically this can be a limiting factor in achieving high injection rates and could contribute to stasis in the microcirculation. In practice, however, warming the CM to body temperature reduces the viscosity and its disadvantages.

2. Cardiovascular Effects

2.1 Haemodynamic Effects

The haemodynamic responses to bolus injections of CM are influenced by the interaction of three different phenomena: the effects on intravascular volume, the effects on myocardial contractility and the effects on systemic vascular resistance.[2] The arteriolar vasodilation caused by the CM explains the transitory sensation of warmth and the decrease in arterial pressure.[3] The magnitude of the vasodilation activity is directly related to the osmolality of each CM and the volume injected. High osmolality agents cause not only more intense vasodilation than iso-osmolality or low osmolality agents but also greater increase in left ventricular end-diastolic pressure. This is due to the acute expansion of intravascular volume and the depression of myocardial contractile performance.[4,5] High osmolality agents can cause significantly more hypotension than non-ionic LOCM (table I).[6-9] It is interesting to note that there are differences in the incidences of hypotension between the different series of patients studied despite the same agent being used in the investigations. This can be explained on the basis of the non-homogeneous definition of hypotension that had been applied in the different studies.

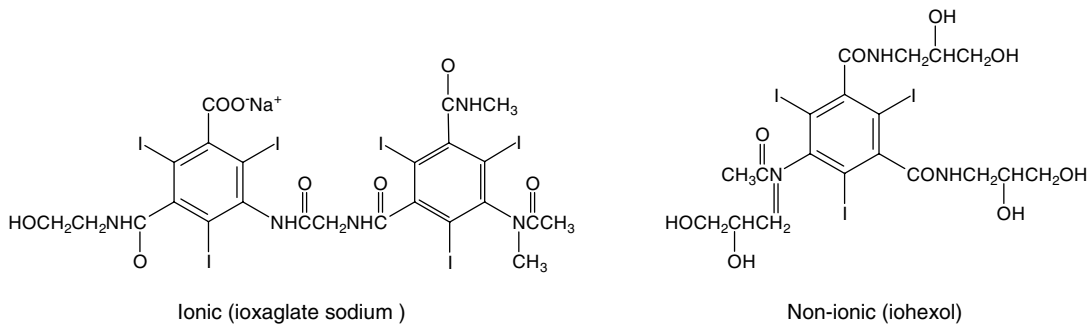


Fig. 3. Low-osmolar contrast media (LOCM) either ionic or non-ionic.

In normal coronary arteries vasodilatation is often seen, mainly in relation to the osmolality of CM. However, coronary artery disease can interfere with the vasomotor reaction of coronary arteries to CM.[10] Non-ionic CM (iopramide and iodixanol) induced dilatation in normal coronary segments and constriction in segments close to coronary stenosis. Ionic CM (ioxaglate sodium injection) did not induce significant luminal diameter changes in any coronary segment. The mechanism responsible for the divergent vasomotor response is unknown, but not linked to osmolality. These findings could have clinical implications as vasoconstriction of coronary arteries can cause angina pectoris.

2.2 Electrophysiological Effects

Several electrophysiological effects can be observed with selective intracoronary injection of CM. Of these, three are particularly important clinically: depression of atrio-ventricular nodal conduction, depression of sinoatrial automaticity and increased vulnerability to ventricular fibrillation or ventricular tachycardia.[11,12] As shown in table II,[6,7,9] the most frequent electrophysiological effect is an asymptomatic change in the ECG, mainly due to T wave inversion which, generally, is a self-limiting effect. Electrophysiologically relevant disturbances expected with a high osmolality ionic agent compared with a non-ionic low osmolality

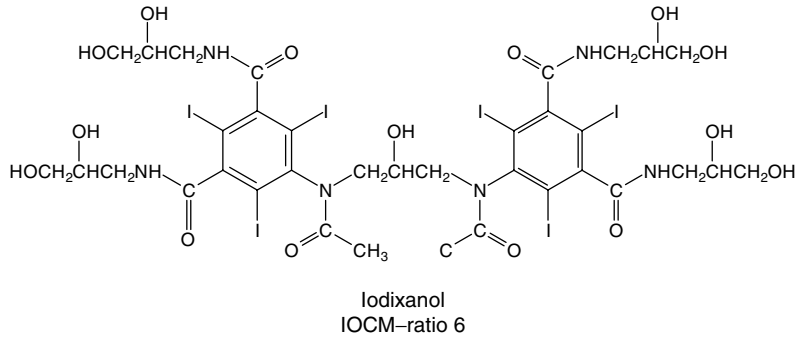


Fig. 4. Iso-osmolar contrast media (IOCM).

agent indicate clear differences favouring the low osmolality agent. If low- and iso-osmolality agents are then compared, there are more clinically relevant effects when using a non-ionic agent. These differences, however, do not reach statistical significance. It is important to note high osmolality agents containing calcium-chelating additives are associated with a higher incidence of ventricular fibrillation compared with similar high-osmolality agents that do not chelate calcium.[5,13]

Focusing on the potential cardiovascular effects caused by CM, there appears to be a clear difference between high osmolar agents and the low or iso-osmolar agents. High osmolality has the poorer profile because of a greater incidence of hypotension and electrophysiological effects, even though the majority of these adverse effects can be treated quite easily.

3. Non-Cardiovascular Effects

3.1 Renal Effects

With the increasing use of contrast agents in diagnostic coronary intervention and PCI, contrast-induced nephropathy (CN) has become an important cause of iatrogenic acute renal impairment. Patients undergoing these clinical examinations often present with multiple pathologies and are more vulnerable to CN, which can lead to substantial morbidity and even mortality.[14,15]

CN is defined as an acute decline in renal function following the administration of contrast agents, in the absence of other causes. A rise in serum creatinine of ≥25–50%,[15-17] or >0.5 mg/dl (44 μmol/L)[18] above the baseline value, has been used as a definition of CN. Serum creatinine shows an acute rise 24–48 hours following the contrast study, generally peaks at 4–5 days and returns to baseline value by 7–10 days.[16,19] CN may also present as a more severe acute renal failure, particularly in high-risk patients. In this situation, oliguria may develop within 24 hours of contrast administration, with a peak increase exceeding 5 mg/dl (440 μmol/L). A minority of patients become dialysis dependent. Patients undergoing coronary angiography often have vascular disease elsewhere and the differential diagnosis includes atheromatous embolisation, which carries an even poorer prognosis.[14]

The induction of CN is low in patients with normal renal function and varies between 0 and 10%.[15] The incidence of CN is likely to be higher following interventional procedures rather than

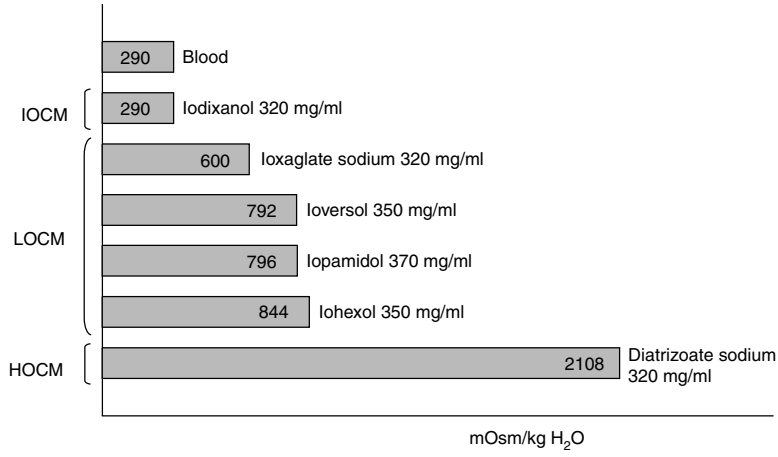


Fig. 5. Osmolality of different contrast media relative to plasma. **HOCM** = high osmolar contrast media; **IOCM** = iso-osmolar contrast media; **LOCM** = low osmolar contrast media.

	20˚C	37˚C
Diatrizoate sodium	18.5	8.9
Iohexol	23.3	10.6
Ioxaglate sodium	15.7	7.5
Iodixanol	25.4	11.4

Fig. 6. Viscosity (in centipoise) of contrast media in relation to temperature.

after diagnostic coronary angiography. McCullough et al.[20] observed an incidence of CN of 14.5% in non-selected patients undergoing PCI. An incidence of CN ranging from 12–27% has been reported in several prospective studies.[21-23] Incidences of up to 40–50% have been described in high-risk patient populations.[14,24,25]

The pathogenesis of CN is complex. It is widely accepted that ischaemic damage to the renal medulla, secondary to renal vasoconstriction, and a direct toxic effect of the contrast agent on the renal tubular cells, are of considerable importance. The nature of the contrast agent, associated ions, concentration, and concomitant hypoxia are all important in the degree of cellular damage, while the osmolality of the solution appears to be of secondary importance.[26] Alterations in the metabolism of prostaglandin, nitric oxide, endothelin, or adenosine may play a role.[18]

Patients most at risk are those with impaired renal function, as judged by an increase in serum creatinine concentration. The risk appears to rise exponentially with the creatinine elevation.[27] Renal impairment prolongs the elimination half-life of the contrast agent, which leads to longer exposure of the damaged kidney to these agents. The presence of diabetes mellitus further amplifies this risk and leads to an approximate doubling of the incidence.[23,26] Patients with diabetes mellitus and pre-existing renal insufficiency represent a group with an extremely high risk of developing CN. Diabetes mellitus *per se*, without renal impairment, is not a risk factor.[23] Other factors (table III) that increase the risk include the volume and the concentration of the CM employed,[28] advanced age of the patient, congestive heart failure, dehydration, nephrosis, cirrhosis or concurrent use of potentially nephrotoxic drugs such as nonsteroidal anti-inflammatory drugs and ACE inhibitors.[15-17] Multiple myeloma has been suggested as a risk factor for CN but recent studies failed to demonstrate an increased risk in these patients.[29]

The most effective measure in preventing CN is oral or intravenous hydration at the time of CM administration. Many protocols[22,23,30] have employed 0.45% saline at 100–150 ml/h with urine volumes 75–125 ml/h. Patients with evidence of renal impairment should receive 1L of saline in the 12 hours before and a further 1L in the 12 hours after CM administration.[17] In urgent cases involving patients with elevated serum creatinine, a regimen of 500ml saline over half an hour followed by 1L in the subsequent 12 hours has been suggested.[29] In all patients with pre-existing renal dysfunction, serum creatinine level should be checked at 1 and 4 days post-procedure.

Barret and Carlisle performed a meta-analysis of all randomised trials available prior to the end

Table I. Haemodynamic effects of contrast media (% of patients with hypotension)

Diatrizoate sodium (HOCM)	Ioxaglate sodium (ionic LOCM)	Iodixanol (IOCM)	Non-ionic LOCM	p-Value	Reference
5.4	N/A	N/A	0.4	<0.0001	6
N/A	1.4	0.32	0.54	NS	7
N/A	10	8.4	N/A	NS	8
N/A	11.3	N/A	12.4	NS	9

HOCM = high-osmolar contrast media; **IOCM** = iso-osmolar contrast media; **LOCM** = low-osmolar contrast media; **N/A** = data not available; **NS** = non-significant.

Table II. Electrophysiological effects of contrast media (% of patients)

	Diatrizoate sodium (HOCM)	Ioxaglate sodium (ionic LOCM)	Iodixanol (IOCM)	Non-ionic LOCM	p-Value	Reference
Bradycardia	N/A	3	N/A	10.5	0.06	9
	8.5	N/A	N/A	0.8	<0.0001	6
Tachyarrhythmia	0.8	N/A	N/A	0.3	NS	6
Cardiac arrest	N/A	0.46	0.16	0.27	NS	7
VT/VF	N/A	0	N/A	2.9	0.08	9
ECG changes	N/A	45	11.3	12.6	<0.001	7
T wave inversion	N/A	39.3	7.9	7.18	<0.001	7

HOCM = high-osmolar contrast media; **IOCM** = iso-osmolar contrast media; **LOCM** = low-osmolar contrast media; **N/A** = data not available; **NS** = non-significant; **VT/VF** = ventricular tachycardia/ventricular fibrillation.

of 1991.[31] Pooled probability values suggested a reduction in nephrotoxicity with low-osmolality media; albeit of borderline statistical significance. The risk of developing CN was about 50% less with LOCM in patients with pre-existing renal insufficiency. In a multicentre study, the incidence of CN in patients with diabetic nephropathy was 27% following the administration of HOCM and 12% following LOCM.[21] The available data suggest that the use of the ionic LOCM agent ioxaglate sodium can reduce the risk of CN, at least to the same extent as that which occurs with non-ionic LOCM.[31] A recent study showed that the IOCM agent iodixanol may be slightly less nephrotoxic than the non-ionic LOCM agent iohexol.[32]

Diuretics, dopamine, theophylline, atrial natriuretic peptide and calcium channel antagonists cannot be routinely recommended to prevent CN since the currently available data regarding their use are equivocal.[29] Preliminary studies suggest that fenoldopam may be beneficial.[18] Considerable speculation has resulted from preliminary studies assessing the use of acetylcysteine in patients with chronic renal failure receiving CM.[33-35] This drug demonstrated a favourable effect on CN, which is thought to be the result of its antioxidant activity. Diabetic patients with renal insufficiency who are receiving the antihyperglycaemic agent metformin, may have an accumulation of this agent in body tissues which may induce lactic acidosis. Current guidelines suggest discontinuation of metformin 48 hours before an angiographic procedure or, if this is not possible, patients should be monitored for evidence of change in renal function or lactic acidosis.[18]

In summary, the most effective strategy for the prevention of CN is a careful procedure selection and patient assessment. Risk factors for CN should be corrected before exposure to contrast agents. Patients with no correctable risk factors should receive the minimal dose of low- or iso-osmolality CM with intravenous hydration before and after the procedure. Serum creatinine levels should be monitored for several days following the procedure.

Table III. Risk factors for contrast nephropathy

Advanced age
Pre-existing renal impairment
Diabetes mellitus
High dose of contrast media
Decrease in effective arterial volume
Congestive heart failure
Dehydration
Nephrosis
Cirrhosis
Concurrent use of nephrotoxic drugs
Nonsteroidal anti-inflammatory drugs
ACE inhibitors

3.2 Hypersensitivity Reactions

Hypersensitivity reactions to CM during cardiac catheterisation are of considerable concern because of their high frequency and the potential morbidity associated. The frequency of immediate reaction is higher with ionic CM of high or low osmolality compared with non-ionic CM.[36-41] However, severe anaphylactic reactions are observed in only 0.04–0.22% of procedures.[42] The recurrence rate of reactions to ionic contrast material is 16–44% in patients who have had a previous reaction.[41] The risk of having a breakthrough reaction, despite LOCM and corticosteroid premedication, is approximately 10%.[43]

Increased levels of plasma histamine and tryptase have been described in patients with immediate reactions to CM, and the increase correlates with the severity of the reaction.[41] Complement activation has been demonstrated by numerous authors,[44] but this could be a consequence of tryptase release and not the initiating mechanism of histamine release.[41]

Factors that could indicate an increased propensity towards an adverse reaction to contrast agents include a history of allergy, asthma, drug allergy, food or seafood allergy, a previous serious adverse reaction to CM, serious cardiac abnormalities, renal insufficiency, diabetes mellitus and pheochromocytoma.[40,41] Individuals with an immunoglobulin E-mediated allergy to drugs, food or environmental antigens have a 2-fold increased risk for an adverse reaction to CM.[39,40,45]

Adverse reactions categorised as being allergy-like include sneezing and nasal congestion, hives, itching, rash, and swelling; laryngeal oedema; bronchospasm; and anaphylaxis. Other reactions include rigors (chills, fever); seizures; numbness; malaise and achiness; and pulmonary oedema, chest pain and hypertension.[37] With respect to breakthrough reactions, patients whose initial reaction was anaphylactic are at a particularly high risk. If the initial reaction was mild, then the breakthrough reaction is, frequently, mild as well. Severe or life threatening reactions, have been observed in 24% of these patients.[43]

Several studies have demonstrated significantly higher incidences of adverse reactions soon after cardiac catheterisation using ionic CM than when non-ionic CM had been used. In the studies of Gertz et al.[46] and Wisnesky et al.[47] early reactions attributable to the contrast agent occurred more frequently in the ionic LOCM (ioxaglate sodium) group than in the non-ionic LOCM (iopamidol) group. Fransson et al.[48] documented similar findings when ioxaglate sodium was compared with the non-ionic agent iodixanol. Significantly fewer early adverse contrast-related reactions occurred in the iodixanol group. In the study of Sutton et al.[7] the incidence of early reactions (nausea, vomiting or cutaneous rashes) to CM in diagnostic cardiac catheterisation was lower with the use of either of the two non-ionic agents (iopamidol, iodixanol) compared with the ionic agent ioxaglate sodium. However, delayed adverse effects (skin reactions) were observed mainly with iodixanol and severe reactions were seen equally with ioxaglate sodium and non-ionic CM.[7]

The combination of LOCM, non-ionic agents and a corticosteroid premedication regimen has been advocated to reduce the likelihood of an adverse reaction.[38,49] Diphenhydramine and ephedrine or cimetidine, or both,[43] have been incorporated in some protocols. CM should be used with caution in patients who have had prior reactions, despite a corticosteroid premedication being prescribed. This is particularly important if the patients have a history of seafood allergy or of hayfever.[43] A previous serious reaction to ionic CM requires corticosteroid premedication and use of a non-ionic CM.[40]

3.3 Effects on Thyroid Function

Iodinated CM can cause thyroid biochemistry changes without clinical manifestations or real thyroid dysfunction; either hyperthyroidism or hypothyroidism.[50] However, measurement of serum thyroxine or thyroid-stimulating hormone is rarely

performed as a routine pre-catheterisation laboratory test. Clinical hyperthyroidism has been detected in up to 3% of cases after non-ionic CM radiography, but the condition appears, ultimately, to be self-limited and occurs mainly in elderly patients.[51,52] Fassbender[53] prospectively studied thyroid function in 102 euthyroid patients undergoing coronary angiography. Thyroid function parameters (thyroxine, thyroid-stimulating hormone) were significantly altered independent of antibody status and the amount of CM administered, but clinical hyperthyroidism was not observed in any patient. In young patients from iodine non-deficient areas, self-limited hypothyroidism can occasionally be detected after CM use.[50] There is need for greater awareness of how different CM compare clinically with respect to thyroid function, especially in the current era of an increasingly ageing population.

4. Thrombogenic Effects

4.1 *In Vitro* Studies

Thrombotic complications occurring during PCI can be influenced by the type of CM used (table IV). Four interactions with CM need to be highlighted in relation to haemostasis: platelet function, coagulation factors, fibrinolytic agents and the endothelium.[54-68]

Platelet activation can be studied *in vitro* by analysing platelet degranulation. In the presence of the ionic LOCM agent ioxaglate sodium or the IOCM agent iodixanol[55,59,63] no platelet degranulation has been detected. Conflicting data have been obtained with the ionic HOCM agent diatrizoate sodium; either no degranulation[54,55] or considerable platelet degranulation.[59] Profound platelet degranulation was detected in all the studies with non-ionic LOCM agents.[54,55,59,63]

When mixed with CM, platelet activators like collagen or adenosine diphosphate (situations that occur in PCI) caused considerable platelet activation (non-ionic CM agents, iodixanol and iohexol) or no activation (ionic CM agent, ioxaglate sodium).[60] *In vitro* platelet secretion of β-thromboglobulin, as an expression of platelet activation, was observed with iohexol but not with iodixanol or ioxaglate sodium.[61]

Platelet activation can also be measured as the *in vitro* bleeding time. When CM was administered following heparin, the bleeding time was higher in those who received the ionic CM agent diatrizoate sodium compared with non-ionic CM agent

Table IV. Thrombogenic effects of contrast media (*in vitro* studies)

Mechanism	Test	Diatrizoate sodium (HOCM)	Ioxaglate sodium (ionic LOCM)	Iodixanol (IOCM)	Non-ionic LOMC	Reference
Platelet	Direct activation	+/0	0	0	+ + +	54,55,59,63
	Effect on platelet activation	N/A	0	+/0	+ +	60-63
	Bleeding time/PFA100™	+	+ +	+	+	56,58
Coagulation	Factor Xa generation	– –	– –	N/A	–	65
	aPTT increase	+ +	+ + +	N/A	+	65
	TT increase	+ + +	+	N/A	+ +	65
Clot lysis	Optimal reperfusion	–	0	N/A	–	66
Endothelium	Secretion prothrombotic agent	+ + +	0	N/A	0	67
	Platelet adhesion	+ + +	0	N/A	0	67

0 = no effect; number of **+** or **–** denotes degree of increase or decrease, respectively; **aPTT** = activated partial thromboplastin time; **HOCM** = high-osmolar contrast media; **IOCM** = iso-osmolar contrast media; **LOCM** = low-osmolar contrast media; **N/A** = data not available; **PFA 100™** = platelet function analyser; **TT** = thrombin time.

iohexol.[56] More recently, the anti-aggregation effect of CM has been measured with the platelet function analyser PFA-100™ that quantifies membrane closure time. When three different CM were compared[58] they caused prolongation of the membrane closure time, but the antiplatelet effect of the ionic CM agent ioxaglate sodium (prolongation: 300 seconds) was significantly ($p < 0.05$) greater than that of the non-ionic CM agents, iodixanol (179 seconds) and iohexol (171 seconds).

Also, as has been demonstrated,[65] ionic CM agents (diatrizoate sodium, ioxaglate sodium) are more potent inhibitors of thrombin formation and function (inhibition of tissue factor-dependent factor Xa generation, of the prothrombinase complex, and of thrombin binding to fibrin) than non-ionic CM agents (ioversol). The final clinical result would be that of a greater prolongation of activated partial thromboplastin time with ionic CM.[65]

In general, ioxaglate sodium appears to have a better profile than other CM when interaction of these agents with platelet function and coagulation are considered.

In an animal model, the administration of diatrizoate sodium or iohexol before thrombolytic therapy delayed reperfusion, compared with ioxaglate sodium.[66] CM inhibition of pharmacological fibrinolysis appears to be related to ionic as well as osmolar properties.

Possible endothelial injury caused by CM has been reported. Fauser et al.[67] analysed the secretion of different prothrombogenic substances by the endothelium in contact with three different CM (diatrizoate sodium, ioxaglate sodium and iopamidol). Diatrizoate sodium had the worst profile with significantly increased secretion of von Willebrand factor. Ioxaglate sodium and iopamidol had lesser and/or a similar degree of effect. Riemann et al.[68] also studied the effect of diatrizoate sodium, ioxaglate sodium and ioversol and they also found that diatrizoate sodium had the worst profile while ioxaglate sodium and ioversol had similar effects. CM alteration of endothelial cells appears to be related to osmolality but not to ionicity.

4.2 Large-Scale Clinical Trials

Several trials (table V)[8,9,69-80] have been conducted to evaluate differences between CM in PCI. The hypothesis has been that CM following arterial injury produced by coronary angioplasty or stenting could result in varying degrees of platelet deposition and coronary thrombosis. Thromboembolism is an inherent risk when catheters and guide wires are introduced into the vascular system and it increases with intervention procedures that require prolonged catheter manipulation with accompanying endothelium disruption.

In 1991, Gasperetti et al.[69] were the first to retrospectively assess the incidence of coronary thrombus (intraluminal filling defect, distal embolisation) in 124 consecutive patients undergoing coronary angioplasty and receiving either diatrizoate sodium (n = 57) or iopamidol (67). New thrombi were seen in 4% of diatrizoate sodium and 18% of iopamidol recipients ($p < 0.02$). Acute myocardial infarction was only observed in iopamidol recipients (6%). In particular, patients with recent myocardial infarction or resting angina pectoris or with an eccentric coronary plaque were more likely to develop a new thrombus. Non-cardiac complications were not different between groups. This was a retrospective non-randomised study involving a small number of patients without control of activated clotting time (ACT) during the procedures (10 000IU initial bolus of heparin).

Lembo et al.,[70] in 1991, evaluated the complications of coronary angioplasty in 1058 procedures in 913 patients who were prospectively randomised to receive either diatrizoate sodium (n = 551) or iopamidol (507). Ventricular tachycardia or fibrillation developed in 2.5% of diatrizoate sodium and 1% of iopamidol recipients ($p = 0.045$), but there were no differences in the frequency of hypotension (9.5 vs 8.5%), bradycardia (5.1 vs 5.7%), myocardial infarction (6.8 vs 6.1%) or death (0.4 vs 0.2%). The purpose of this study was

Table V. Thrombogenic effects (clinical trials)

Reference	Year	No. of patients	Endpoint definition	Contrast media (CM)	Thrombogenic effects (% patients)	p-Value	Increased clinical events
Gasperetti et al.[69]	1991	124	AT	Diatrizoate sodium	4	p < 0.02	NS
				Iopamidol	18		
Lembo et al.[70]	1991	913		Diatrizoate sodium	N/A		VT/VF
				Iopamidol	N/A		
Esplugas et al.[71]	1991	100	AT	Ioxaglate sodium	2	p < 0.005	NS
				Iohexol	22		
Piessens et al.[72]	1993	500	AT	Ioxaglate sodium	3.2	p < 0.05	
				Iohexol	7.2		AMI
Lefèvre et al.[73]	1994	64	Platelets (SEM)	Ioxaglate sodium	N/A	p < 0.004	N/A
				Iopamidol	N/A		
Grines et al.[9]	1996	211 (ACS)	DCF	Ioxaglate sodium	8.1	p = 0.04	
				Iohexol	17.8		IE
Qureshi et al.[74]	1997	30 (ACS)	Thrombus (AG)	Ioxaglate sodium	33.3	p = 0.028	N/A
				Iohexol	73.6		
Malekianpour et al.[75]	1998	205 (ACS)	AT	Ioxaglate sodium	10.6	NS	NS
				Iopamidol	16.3		
Lefèvre et al.[76]	1998	771	ACC	Ioxaglate sodium	2.1	p = 0.03	NS
				Iopamidol	4.9		
Schräder et al.[77]	1999	2000	ACC	Ioxaglate sodium	7.1	NS	NS
				Iomeprol	6.0		
Batchelor et al.[78]	2000	454 (AMI)		Ioxaglate sodium	N/A		
				Non-ionic CM	N/A		IE
Bertrand et al.[79]	2000	1411	ACC	Ioxaglate sodium	3.4	NS	NS
				Iodixanol	2.6		
Davidson et al.[8]	2000	815 (ACS)	ACC	Ioxaglate sodium	2.4	p < 0.05	IE
				Iodixanol	0.7		
Scheller et al.[80]	2001	3990	ACC	Ioxaglate sodium	0.3	p = 0.001	
				Non ionic CM	1.3		IE

ACC = acute coronary closure; **ACS** = acute coronary syndrome ; **AG** =angioscopy; **AMI** = acute myocardial infarction; **AT** = angiographic thrombus; **DCF** = decreased coronary flow; **IE** = ischaemic events; **SEM** = scanning electron microscopy; **N/A** = data not available; **NS** = non-significant**; VT/VF** = ventricular tachycardia/ventricular fibrillation.

to determine the clinical complications. Unfortunately, however, no attempt had been made to quantify the incidence of coronary thrombus related to coronary angioplasty, and ACT was not available (heparin 10 000IU initial bolus and 5000IU after 1 hour).

Also in 1991, Esplugas et al.[71] were the first to compare two different LOCM in relation to the incidence of thrombus formation during coronary angioplasty. The patients (n = 100) were prospectively randomised to ioxaglate sodium (50) or iohexol (50) groups to assess the incidence of coronary thrombus formation (intraluminal filling defect, total occlusion without dissection). New thrombi were observed in 2% of patients receiving ioxaglate sodium and 22% of patients receiving iohexol ($p < 0.005$). The occurrence of acute myocardial infarction was not significantly different between ioxaglate sodium and iohexol treatment groups (2 and 4%, respectively). Non-cardiac

complications were not statistically different between the groups. There were no deaths associated with either treatment. The limitations of this study were the small number of patients involved and the absence of ACT during the procedures (heparin 10 000IU initial bolus and 2500IU after 2 hours). The high incidence (7% overall) of thrombotic residues seen on the guidewire immediately after the procedure was associated with the use of first-generation non-teflon coated guidewires which is a limitation, by today's standard, of all the procedures conducted in the late 1980s.

Piessens et al.,[72] in 1993, prospectively studied 500 consecutive patients randomised to ioxaglate sodium (n = 250) or iohexol (250) groups during coronary angioplasty. The purpose of the study was to evaluate the incidence of thrombotic events during (intraluminal filling defect, total occlusion) or after (ischaemic pain and/or ST-segment changes with angiographic confirmation) the procedure. In-laboratory thrombotic events were seen in 3.2% of ioxaglate sodium and in 7.2% of iohexol recipients ($p < 0.05$). Out-of-laboratory thrombotic events were not significantly different between ioxaglate sodium (7.2%) and iohexol (5.6%) recipients. The lower incidence of in-laboratory thrombotic events in the ioxaglate sodium group, compared with the iohexol group, was clinically reflected in the smaller proportion of acute myocardial infarctions (0 vs 1.6%; $p < 0.05$). As the authors stated, the differences between the in-laboratory and out-of-laboratory events can be explained by the short half-life of CM, i.e. by the time the patient is discharged from the catheterisation laboratory, the pharmacological effects of the CM will have waned considerably. As with previous studies, the angiographic definition of thrombus may have underestimated the real incidence, but this shortcoming applied to both groups. ACT was not used (heparin 10 000 initial bolus, 1000 IU/h infusion and 5000IU after 1 hour). There were no statistically significant differences between groups with respect to other complications. Severe bronchospasm occurred in one asthmatic patient with ioxaglate sodium but this was effectively treated medically.

In 1994, Lefèvre et al.[73], were the first to search, using scanning electron microscopy, for the presence of thrombotic material on the guiding catheter and guide wires. They randomised 64 patients with stable angina pectoris, type A coronary lesions and ACT monitoring (10 000IU initial bolus of heparin) either to ioxaglate sodium (n = 32) or iopamidol (32). Angiographic filling defects were observed in four patients (13%) in the iopamidol group and no patients in the ioxaglate sodium group. This difference was not significant. The numbers of thrombotic elements (erythrocytes, platelets and constituted thrombus) observed on the guiding catheters were negligible in both groups. There were significant differences ($p < 0.004$) in the numbers of platelets observed on the guide wires but not in the number of erythrocytes and constituted thrombi. It has to be emphasised that this study was performed in a small number of low-risk patients under strictly standardised conditions. The short time that the guiding catheter (31 minutes) and the guide wire (17 minutes) had been in the circulation raises the question of the amount of thrombotic material in complex procedures and high-risk patients.

Grines et al.,[9] in 1996, were the first to study patients (n = 211) with a high likelihood of having a hypercoagulable status. Patients were randomised to ioxaglate sodium (106) or iohexol (105) if they had acute coronary syndrome: unstable angina pectoris (24%), acute myocardial infarction (43%) or post-infarct angina pectoris (33%). All the coronary angioplasty procedures were monitored with an ACT time >350 seconds (heparin 10 000IU initial bolus and 2500–5000IU, if required). The primary endpoints were angiographic evidence of intermittent patency (reduction of 1 or more Thrombolysis In Myocardial Infarction [TIMI] grade flow compared with baseline), thrombus formation or distal embolisation during the procedure. Secondary endpoints were recurrent ischaemia and the necessity for repeat

revascularisation. Patients receiving ioxaglate sodium were significantly less likely to have decreased flow compared with patients receiving iohexol (8.1 vs 17.8%; p = 0.04). Obvious thrombus (2 vs 3%), abrupt closure (3 vs 3%) and distal embolisation (1 vs 3%) were similar between ioxaglate sodium and iohexol groups. However, patients receiving ioxaglate sodium had fewer recurrent ischaemic events requiring repeat catheterisation (3 vs 11.4%; p = 0.02) and repeat angioplasty during the initial hospitalisation (1 vs 5.8%; p = 0.06). The lack of correlation between angiographic evidence of thrombus and the clinical outcome findings may be explained by difficulty in diagnosing thrombus. There is also the possibility that the formation of small thrombi and the occurrence of microembolisations may only manifest as transient episodes of decreased coronary flow. Non-cardiac adverse effects were not statistically different between the groups, but patients receiving ioxaglate sodium tended to have a lower incidence of severe bradycardia (3 vs 10.5%; p = 0.06) or ventricular fibrillation or tachycardia (0 vs 2.9%). This study had the limitation of small sample size that required a composite primary endpoint of 'soft' parameters. The intermittent vessel patency (reduction of TIMI flow) may not be easy to appreciate and is of uncertain clinical significance. The in-laboratory ACT was not reported but it was higher in the ioxaglate sodium group, post-procedure.

Qureshi et al.,[74] in 1997, were the first to evaluate the effect of CM on thrombus generation using percutaneous intracoronary angioscopy. Patients (n = 30) with unstable angina were randomised to either ioxaglate sodium (15) or iohexol (15) groups and underwent angioscopy pre- and post-angioplasty. The number of patients with angioscopically visible thrombus, observed pre-angioplasty, was not significantly different in the ioxaglate sodium (n = 10) and iohexol (8) groups. Post-angioplasty, five patients (33.3%) in the ioxaglate sodium and 11 (73.6%) in the iohexol group developed new thrombi (p = 0.028). Although small with respect to the numbers of patients, this study used the most highly specific method for thrombus diagnosis.

In 1998, Malekianpour et al.[75] randomised 205 patients to ioxaglate sodium (n = 103) or iopamidol (102) if they had unstable angina pectoris, but excluded those with acute myocardial infarction and complete occlusion of the culprit vessel. The endpoints considered were angiographic thrombus, myocardial ischaemia, acute myocardial infarction, repeat angioplasty or surgery, and death. To reduce the difficulty in diagnosing thrombus angiographically, films were analysed independently by two interventional cardiologists and two cardiac radiologists. There was a nonsignificant trend towards more thrombi in the iopamidol group (16.3%), compared with the ioxaglate sodium group (10.6%). There were no appreciable differences in other clinical endpoints. The study had the limitations of small sample size and ACT not being routinely measured during the procedure (heparin 10 000IU initial bolus and 5000IU after 1 hour), which could be an important limitation in these high-risk patients.

Lefèvre et al.,[76] in 1998, were the first to study the influence of CM on the results of angioplasty in the era of coronary stenting. They compared 771 consecutive patients dilated using ioxaglate sodium (n = 384) or iopamidol (387). The measured ACT was above 300 seconds (heparin 7500IU initial bolus and 2500IU if needed). Significantly fewer patients in the ioxaglate sodium versus the iopamidol group experienced acute coronary closure (2.1 vs 4.9%; p = 0.03) and bailout stenting (2 vs 4.9%; p = 0.04). There were no significant differences between the ioxaglate sodium and iopamidol groups in terms of acute myocardial infarction (0.5 vs 0.75%) and death (0.8 vs 0.3%). The ACT at the same heparin dosage was significantly higher with ioxaglate sodium. This study was, however, non-randomised.

In 1999, Schräder et al.[77] performed a double-blind study of 2000 patients randomised to ioxaglate sodium (n = 999) or to iomeprol (1001). The

primary endpoint was abrupt vessel closure in-laboratory or out-of-laboratory (ischaemic pain and/or ST-segment changes with angiographic confirmation of vessel closure). Secondary endpoints were myocardial infarction and death. There were no significant differences between ioxaglate and iomeprol in abrupt closure either in-laboratory (3 vs 2.9%) or out-of-laboratory (4.1 vs 3.1%), or in acute myocardial infarction (2 vs 1.8%) and cardiac death (0.2 vs 0.2%). The clinical decision for stenting was at the discretion of the operator (25.7 vs 31.6%; $p < 0.004$). The stents were used, predominantly, for the treatment of dissection or an unsatisfactory angiographic result following balloon angioplasty. There were no significant differences in endpoints between both CM groups, either in patients with or without stents. One case of bronchospasm requiring therapy was seen with ioxaglate sodium. The ACT was not measured, but all patients received a very high initial heparin bolus of 20 000 IU. The true incidence of acute myocardial infarction may have been underestimated since post-angioplasty creatine kinase levels were measured only in symptomatic patients, or when ECG changes occurred.

In 2000, Batchelor et al.[78] studied the patients in the Global Use of Strategies to Open Occluded Coronary Arteries in Acute Coronary Syndromes (GUSTO) IIb trial who had primary angioplasty for acute myocardial infarction. The patients received either ioxaglate sodium (n = 181) or non-ionic LOCM (273), mainly iohexol, ioversol or iopamidol. Selection of CM was left to the discretion of the investigator and recorded on the case report form. The intention-to-examine outcomes with respect to the type of CM were defined *a priori*. The primary endpoint was a triple composite (death, reinfarction and refractory angina pectoris at 30 days), which occurred less frequently in the ioxaglate sodium versus the non-ionic LOCM group (5.5 vs 11%; odds ratio [OR] 0.47; 95% CI 0.23–0.99; $p = 0.044$). Although the differences were no longer statistically significant after adjustment for imbalance in baseline characteristics (OR 0.48 [95% CI 0.22–1.02]; $p = 0.055$), the trend persisted in favour of ioxaglate sodium. The retrospective design of this study with inter-group differences at baseline introduced bias into the comparisons of outcomes and which the authors attempted to reduce with statistical adjustments. No intracoronary stents or glycoprotein IIb/IIIa inhibitors had been used.

Also in 2000, Bertrand et al.[79] published the Visipaque in Percutaneous Transluminal Coronary Angioplasty (VIP) trial, which was a randomised double-blind study of 1411 patients receiving either ioxaglate sodium (n = 714) or iodixanol (697). Measured ACT was above 300 seconds (heparin 10 000IU initial bolus). Intracoronary stents were allowed but pre-treatment with glycoprotein IIb/IIIa antagonists was not. The primary endpoint was a composite of major adverse cardiac events including death, stroke, myocardial infarction, coronary bypass and re-angioplasty after 2 days. No significant differences were observed in patients experiencing major adverse cardiac events between the ioxaglate sodium and iodixanol groups (3.9 vs 4.7%). Neither were there differences in thrombus formation (2.1 vs 2.4%) or in acute coronary closure (3.4 vs 2.6%). Hypersensitivity reactions, mainly nausea, vomiting and rash, occurred less frequently with iodixanol than with ioxaglate sodium (2.5 vs 0.7%; $p = 0.007$). One patient receiving ioxaglate sodium had anaphylactoid shock. Intracoronary stent implantation was similar in both the ioxaglate sodium and iodixanol groups (60.9 vs 59.8%). Patients who underwent stent implantation had a 4.6% chance of developing major adverse cardiac events; the chance was 3.3% when stenting was planned and 5.3% when unplanned. The rate for non-stented patients was 3.9% (p = NS). Glycoprotein IIb/IIIa antagonists were given during or after the angioplasty procedure in patients with abrupt closure, stent occlusion, or coronary dissection; 11 patients had received ioxaglate sodium and 12 patients had received iodixanol. As indicated by the authors, during the planning phase of the study a stenting

rate of 40% of patients had been anticipated. However, as the indications for implantation of intracoronary stents increased during the late 1990s, the actual data showed a rate of 60% stenting. This could have contributed to a lower major adverse cardiac events rate than expected (4.3% instead of the 6% anticipated) and may have affected the ability to detect a difference between the CM groups. As previously stated, the glycoprotein IIb/IIIa inhibitors were not allowed before the procedure which was performed in patients with unstable angina (50%), stable angina (40%) and silent ischaemia (10%).

Davidson et al.[8] in 2000, published the Contrast Media Ulilization in High-Risk PTCA Trial (COURT), which was a randomised double-blind study of 815 high-risk patients receiving either ioxaglate sodium (n = 410) or iodixanol (405). High-risk patients were defined as angina at rest (54%) or evolving Q or non-Q wave myocardial infarction (32%) or post-infarction angina pectoris (14%). Patients undergoing angioplasty for acute coronary syndromes with any FDA-approved device were eligible (492 balloon, 255 stent, 47 rotablator, 11 laser and 4 directional coronary atherectomy). Device selection was at the discretion of the operator. The primary endpoint was a composite of in-hospital major adverse cardiac events including death, stroke, systemic arterial thromboembolic event, myocardial infarction, abrupt coronary closure, re-catheterisation or re-angioplasty, and bypass surgery. ACT had to be above 300 seconds. The use of a glycoprotein IIb/IIIa antagonist (abciximab) was left to the discretion of the operating physician and was 42% in each group. The major adverse cardiac events endpoint was more frequent in those receiving ioxaglate sodium compared with those receiving iodixanol (9.5 vs 5.4%, p = 0.004). In patients receiving abciximab, the number of patients experiencing major adverse cardiac events was not significantly different between of the ioxaglate sodium cohort (20; 11.5%) and the iodixanol cohort (18; 10.5%). However, in patients not receiving abciximab, the occurrence of major adverse cardiac events was significantly greater in the ioxaglate sodium group (19; 8.1%), compared with the iodixanol group (4; 1.7%; p = 0.001). The results of this trial are in discordance with all the others previously reviewed. It is the only study to demonstrate a more pronounced, and clinically relevant, anticoagulant effect with the non-ionic dimer compared with the ionic CM. However, there were several limitations. Although not stated in the report, the trial appears to have been designated as an equivalent study since, based on the event rates observed, between 1 300 and 1 800 patients would have been required to demonstrate a superiority study. The lack of an intention-to-treat design needs to be taken into account, as does the primary endpoint of a rather unusual composite of seven single endpoints. Additionally, more laser and directional coronary atherectomy strategies were performed in the ioxaglate sodium group, which could account for the additional events observed in this group.

In 2001, Scheller et al.[80] published the largest randomised clinical trial to date comparing ioxaglate sodium (n = 2 182) with non-ionic CM (1 808) in patients with coronary stent placement. It was designed prospectively and patients were allocated randomly over an inclusion period of 4.5 years. The non-ionic group consisted of iobitridol (3%), iomeprol (18%), iopamidol (8%), iopromide (27%), ioversol (39%) and iodixanol (5%). Target ACT was 250–350 seconds. Abciximab was used in a similar number of patients in the ioxaglate sodium (5.3%) and non-ionic (4.9%) groups. Different stent types were used and all patients received ticlopidine 500mg daily for 4 weeks following stent placement. The primary endpoint was acute (<72 hours) or subacute (<30 days) stent occlusion. The secondary endpoint was a composite of death, re-angioplasty and coronary bypass surgery within 12 months. Any adverse effect secondary to CM was documented. Compared with ioxaglate sodium, the incidence of acute as well as subacute stent occlusion was significantly higher

in the non-ionic group (acute occlusion: 0.3 vs 1.3% p = 0.001; subacute occlusion: 0.7 vs 2.4% p = 0.001). The incidence of the combined clinical secondary endpoint was also higher in the non-ionic group (16.3 vs 22.9%; p = 0.001). Compared with ioxaglate sodium, the incidence of adverse effects attributable to the CM was significantly lower in the non-ionic group (7.6 vs 4.3%; p = 0.001). The incidence of severe, life-threatening adverse effects did not differ significantly between the groups (0.1 vs 0.1%). However, the study was not double-blind, the randomisation technique was unusual and ioxaglate sodium was compared with six different non-ionic agents. The relatively high incidence of clinical endpoints probably reflects today's 'real world' of stent use and the presence of clinically acute coronary syndrome in about one-third of the patients. Stenting and acute coronary syndrome is associated with much higher platelet activation than balloon angioplasty in stable patients.[81] The authors advocated the use of both types of CM (non-ionic for diagnosis and low-osmolar ionic for interventions). Criticisms of this suggestion have already appeared in the literature.[82]

5. Cost

Controversy continues regarding the reasons for the variation in costs between high, low and iso-osmolar CM. Suppliers of the CM cite high development and manufacturing investments as the primary explanation for the costs. However, critics highlight that the differences in costs that exist between countries can only be a result of marketing strategies.

In the past era of mainly diagnostic cardiac angiography[6,83] in a large group of patients at low risk of adverse effects who derived no clinical benefit from LOCM and in whom almost all adverse reactions of HOCM could be easily managed, the consensus was for selective rather than universal use of the more expensive low-osmolar agents. The implication was that the strategy of reserving these agents for use in patients with a high risk of adverse reactions would be more cost-effective than one recommending their use in all patients. Even if all adverse effects were abolished with the LOCM, only part of the additional costs would be recovered by the hospital.

Although physicians need to be sensitive to economic issues, their primary obligation is to the patient. Hundreds of studies in animals and humans have shown that low/iso-osmolar agents cause less discomfort and have fewer adverse effects than HOCM. It seems appropriate that physicians, in consultation with their patients, should determine the choice of the CM to be used on the basis of clinical judgement and institutional budget. However, in today's era of PCI with increasingly high-risk patients and ad hoc diagnostic-interventional procedures, the strategy of implementing selective use of CM is much more difficult. Currently, the issue is to consider which of the low/iso-osmolar CM is the most cost-effective and has the least severe complications.

6. Is There an Optimal Contrast Medium?

The cardiovascular effects caused by CM appear to be related to the osmolality of the agents. Apart from the issue of cost, the low/iso-osmolar agents are clearly preferable to HOCM since they reduce cardiovascular contrast-related adverse effects. When assessing the need for a CM in terms of improved patient safety, preventing serious complications should be the major factor determining the choice. CM should not be selected on the basis of minor adverse effects since these are, ultimately, of low clinical relevance. Thrombotic events, in contrast, carry a high clinical relevance and we consider that these should be the main issue governing current choice.

The biological profiles of CM depend, at least in part, on their chemical structure; particularly their interaction with platelets and the coagulation cascade. In general, ioxaglate sodium has a better profile than other CM when platelet function and coagulation are considered. However, since most

physicians recognise the potential gap between *in vitro* data and daily clinical practice, the selection of CM for cardiac angiography and PCI has been influenced mostly by clinical data and by cost.

It is difficult to be categorical regarding the true incidence of thrombus formation in PCI since it may be subclinical or unappreciated angiographically. It needs to be emphasised that thrombotic events include not only the macroscopic aspect (thrombus, acute coronary occlusion) but also the less evident microscopic aspects (embolisation, increase in cardiac markers).

Non-ionic CM have weaker antithrombotic effects than ionic compounds. However, there are many other factors, both clinical (coronary anatomy, myocardium at risk, lesion morphology, stable or unstable or acute myocardial infarction) and technical (aspirin, clopidogrel, heparin, glycoprotein IIb/IIIa antagonists, stents) that can affect the incidence of thrombus, abrupt vessel closure and major ischaemic events in coronary angioplasty. These considerations highlight the difficulties in comparing the outcomes of trials that have been designed to investigate the effects of CM on ischaemic complications in PCI when the CM is applied repeatedly at very high local concentrations.

However, when thrombotic events are considered in randomised clinical studies, ionic CM have been associated with either favourable[9,69,71,72,78,80] or neutral results[75-77,79] compared with non-ionic agents. One trial[8] has demonstrated a more pronounced antithrombotic effect of the non-ionic dimer relative to the ionic dimer.

The antithrombotic advantages of ionic over non-ionic LOCM are in part balanced by a greater frequency of minor adverse effects such as nausea, vomiting or cutaneous rashes. However, these reactions are usually of low clinical relevance. A matter of concern is the delayed adverse effects (skin reactions) observed with dimeric non-ionic CM. On the other hand, severe and life-threatening reactions are exceptional and, probably, there are no significant differences between low/iso-osmolar agents, either ionic or non-ionic. However, in patients with known allergies, non-ionic CM should be recommended.

In general, the amount of CM should be as low as possible, avoiding ventriculography when not strictly needed. Low/iso-osmolar CM (either ionic or non-ionic) are better than HOCM for nephrotoxicity reduction and have less haemodynamic effects.

We do not advocate the use of 'consecutive mixing' of CM (non-ionic for diagnostic coronary arteriography and ioxaglate sodium for angioplasty and stenting) as suggested by Scheller,[80] because we consider thrombosis as the main issue compared with other adverse effects in the era of *ad hoc* PCI.

There are experimental data on the interactions between CM and glycoprotein IIb/IIIa antagonists[84] but, at present, there is a paucity of reliable clinical studies. As suggested by the results of Davidson et al.[8] and the meta-analysis of Aguirre et al.,[85] the use of abciximab may neutralise the different platelet effects of the CM used in coronary angioplasty. However, a large clinical trial would be needed to provide definitive data on this aspect.

7. Conclusions

On the basis of the available preclinical and clinical data, the ionic LOCM (ioxaglate sodium) or the non-ionic IOCM (iodixanol) are the agents to be recommended in PCI, because of their antithrombotic advantages over non-ionic LOCM.

In patients with known allergies, non-ionic CM should be used. In patients with risk factors of contrast nephrotoxicity, HOCM should be avoided.

Conversely, there is a considerable need for a greater awareness of how different CM compare clinically with respect to adverse effects, synergism with glycoprotein IIb/IIIa antagonists and new, coated eluting stents.

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References

1. Almen T. Contrast media: the relation of chemical structure, animal toxicity and adverse clinical effects. Am J Cardiol 1990; 66: 2F-8F
2. Hirshfeld JW. Cardiovascular effects of iodinated contrast agents. Am J Cardiol 1990; 66: 9F-17F
3. Hirshfeld JW, Wieland J, Davis CA, et al. Hemodynamic and electrocardiographic effects of ioversol during cardiac angiography: comparison with diatrizoate. Invest Radiol 1989; 24: 138-43
4. Hirshfeld JW, Laskey WK, Martin JL, et al. Hemodynamic changes induced by cardiac angiography with ioxaglate: comparison with diatrizoate. J Am Coll Cardiol 1983; 2: 954-60
5. Murdock CJ, Davis MJ, Ireland MA, et al. Comparison of meglumine sodium diatrizoate, iopamidol and iohexol for coronary angiography and ventriculography. Cathet Cardiovas Diagn 1990; 19: 179-83
6. Barret BJ, Parfrey PS, Vavasour HM, et al. A comparison of non-ionic, low-osmolality radiocontrast agents with ionic, high-osmolality agents during cardiac catheterization. N Engl J Med 1992; 326: 431-6
7. Sutton AG, Finn P, Grech E, et al. Early and late reactions after the use of iopamidol 340, ioxaglate 320, and iodixanol 320 in cardiac catheterization. Am Heart J 2001; 141: 677-83
8. Davidson CJ, Laskey W, Hermiller J, et al. Randomized trial of contrast utilization in High-Risk PTCA: the COURT trial. Circulation 2000; 101: 2172-7
9. Grines C, Schreiber T, Savas V, et al. A randomised trial of low osmolar ionic versus non-ionic contrast media in patients with myocardial infarction or unstable angina undergoing percutaneous transluminal coronary angioplasty. J Am Coll Cardiol 1996; 27: 1381-6
10. Limbruno U, Petronis AS, Amoroso G, et al. The impact of coronary disease on the coronary vasomotor response to nonionic contrast media. Circulation 2000; 101: 491-7
11. Sullivan ID, Wainwright RJ, Freidy JF, et al. Comparative trial of iohexol 350, a non-ionic contrast medium with diatrizoate (Urographin 370) in left ventriculography and coronary arteriography. Br Heart J 1984; 51: 643-9
12. Missri J, Jeresaty RM. Ventricular fibrillation during coronary angiography: reduced incidence with non-ionic contrast media. Cathet Cardiovasc Diagn 1990; 19: 4-7
13. Zukerman LS, Friehling TD, Wolf NM, et al. Effect of calcium-binding additives on ventricular fibrillation and repolarization changes during coronary angiography. J Am Coll Cardiol 1987; 10: 1249-53
14. Manske CL, Sprafka JM, Strony JT, et al. Contrast nephropathy in azotemic patients undergoing coronary angiography. Am J Med 1990; 89: 615-20
15. Morcos SK. Contrast media-induced nephrotoxicity-questions and answers. Br J Radiol 1998; 71: 357-65
16. Murphy SW, Barret BJ, Parfrey PS. Contrast nephropathy. J Am Soc Nephhrol 2000; 11: 177-82
17. Baker CS, Baker LR. Prevention of contrast nephropathy after cardiac catheterisation. Heart 2001; 85: 361-2
18. Waybill MM, Waybill PN. Contrast media-induced nephrotoxicity: identification of patients at risk and algorithms for prevention. J Vasc Interv Radiol 2001; 12: 3-9
19. Solomon R. Nephrology forum: contrast-medium-induced acute renal failure. Kidney Int 1998; 53: 230-42
20. McCullough PA, Wolyn R, Rocher LL, et al. Acute renal failure after coronary intervention: incidence, risk factors, and relationship to mortality. Am J Med 1997; 103: 368-75
21. Rudnick MR, Goldfarb S, Wexler L, et al. Nephrotoxicity of ionic and non-ionic contrast media in 196 patients: a randomized trial. Kidney Int 1995; 47: 254-61
22. Schwab SJ, Hlatky MA, Piper KS, et al. Contrast nephrotoxicity: a randomized controlled trial of a non-ionic and ionic radiographic contrast agent. N Engl J Med 1989; 320: 149-53
23. Parfrey PS, Griffiths SM, Barret BJ, et al. Contrast material-induced renal failure in patients with diabetes mellitus, renal insufficiency, or both: a prospective controlled study. N Engl J Med 1989; 320: 143-9
24. Lautin EM, Freeman NJ, Schoenfeld AH, et al. Radiocontrast-associated renal dysfunction: incidence and risk factors. Am J Roentgenol 1991; 157: 49-58
25. Weisberg LS, Kurnik PB, Kurnik BR. Risk of radiocontrast nephropathy in patients with and without diabetes mellitus. Kidney Int 1994; 45: 259-65
26. Barret BJ. Contrast nephrotoxicity. J Am Soc Nephrol 1994; 5: 125-37
27. Davidson CJ, Hlatky M, Morris KG, et al. Cardiovascular and renal toxicity of a non-ionic radiographic contrast agent after cardiac catheterization: a prospective trial. Ann Intern Med 1989; 110: 119-24
28. Albert SG, Shapiro MJ, Brown WW, et al. Analysis of radiocontrast-induced nephropathy by dual-labeled radionuclide clearance. Invest Radiol 1994; 29: 618-23
29. Rudnick MR, Berns JS, Cohen RM, et al. Nephrotoxic risks of renal angiography: contrast media-associated nephrotoxicity and atheroembolism: a clinical review. Am J Kidney Dis 1994; 24: 713-27
30. Solomon R, Werner C, Mann D, et al. Effects of saline, mannitol, and furosemide on acute decreases in renal function induced by radiocontrast agents. N Engl J Med 1994; 331: 1416-20
31. Barret BJ, Carlisle EJ. Meta-analysis of the relative nephrotoxicity of high-and low-osmolality iodinated contrast media. Radiology 1993; 188: 171-8
32. Chalmers N, Jackson RW. Comparison of iodixanol and iohexol in renal impairment. Br J Radiol 1999; 72: 701-3
33. Tepel M, van der Giet M, Schwarzfeld C, et al. Prevention of radiographic-contrast-agent-induced reductions in renal function by acetylcysteine. N Engl J Med 2000; 343: 180-4
34. Adamian MG, Moussa I, Mehran R, et al. The role of mucomyst administration prior to percutaneous interventions on renal function in patients with chronic renal failure [abstract]. J Am Coll Cardiol 2002; 39 Suppl. A: 1A
35. Mouhayar EN, Tadros G, Akinwande AAO, et al. Prevention of contrast-induced renal dysfunction with acetylcysteine in patients undergoing coronary angiography [abstract]. J Am Coll Cardiol 2002; 39 Suppl. A: 1A
36. Lasser EC, Lyon SG, Berry CC. Reports on contrast media reactions: analysis of data from reports to the US Food and Drug Administration. Radiology 1997; 203: 605-10
37. Cochran ST, Bomyea K, Sayre JW. Trends in adverse events after IV administration of contrast media. AJR Am J Roentgenol 2001; 176: 1385-8

38. Lieberman P. Anaphylactoid reactions to radio-contrast. Ann Allergy 1991; 67: 91-102
39. McClean BL. Ionic and non-ionic iodinated contrast media: evolution and strategies for use. AJR Am J Roentgenol 1990; 155: 225-33
40. Halpern JD, Hopper KD, Arredondo MG, et al. Patient allergies: role in selective use of non-ionic contrast material. Radiology 1996; 199: 359-62
41. Laroche D, Aimone-Gastin I, Dubois F, et al. Mechanisms of severe, immediate reactions to iodinated contrast material. Radiology 1998; 209: 183-90
42. Kayatama H, Yamaguchi K, Kozuka T, et al. Adverse reactions to ionic and nonionic contrast media. Radiology 1990; 175: 621-8
43. Freed KS, Leder RA, Alexander C, et al. Breakthrough adverse reactions to low-osmolar contrast media after steroid premedication. AJR Am J Roentgenol 2001; 176: 1389-92
44. Eloy R, Corot C, Belleville J. Contrast media for angiography: phsiochemical properties, pharmacokinetics and biocompatibility. Clin Mater 1991; 7: 189-97
45. Enright T, Chua-Lim A, Duda E, et al. The role of a documented allergic profile as a risk factor for radiographic contrast media reaction. Ann Allergy 1989; 62: 302-5
46. Gertz EW, Wisneski JA, Miller R, et al. Adverse reactions of low osmolality contrast media during cardiac angiography: a prospective randomized multicenter study. J Am Coll Cardiol 1992; 19: 899-906
47. Wisneski JA, Gertz EW, Dahlgren M, et al. Comparison of low osmolality ionic (ioxaglate) versus non-ionic (iopamidol) contrast media in cardiac angiography. Am J Cardiol 1989; 63: 489-95
48. Fransson SG, Stenport G, Andersson M. Immediate and late adverse reactions in coronary angiography: a comparison between iodixanol and ioxaglate. Acta Radiol 1996; 37: 218-22
49. Anderson JA. Allergic reactions to drugs and biological agents. JAMA 1992; 268: 2845-57
50. Utiger R. The thyroid: physiology, thyrotoxicosis, hypothyroidism and the painful thyroid. In: Felig P, Frohman L, editors. Endocrinology and metabolism. 4th ed. New York: McGraw Hill, 2001: 261-347
51. Martin FI, Tress BW, Colman PE, et al. Iodine-induced hyperthyroidism due to nonionic contrast radiography in the elderly. Am J Med 1993; 95: 78-82
52. Conn JJ, Sebastian MJ, Deam D, et al. A prospective study of the effect of nonionic contrast media on thyroid function. Thyroid 1996; 6: 107-10
53. Fassbender WJ, Schluter S, Stracke H, et al. Thyroid function after iodine-containing contrast agent administration in coronary angiography: a prospective study of euthyroid patients [in German]. Z Kardiol 2001; 90: 751-9
54. Alabanese JR, Veneditto JA, Patel GC, et al. Effects of ionic and nonionic contrast media on *in vitro* and *in vivo* platelet activation. Am J Cardiol 1995; 76: 1059-63
55. Chronos NA, Goodall AH, Wilson DJ, et al. Profound platelet degranulation is an important side effect of some types of contrast media used in interventional cardiology. Circulation 1993; 88: 2035-44
56. Melton LG, Dehmer GJ, Tate DA, et al. Variable influence of heparin and contrast agents on platelet function as assessed by the *in vitro* bleeding time. Thromb Res 1996; 83: 265-77
57. Gabriel DA, Jones MR, Reece NS, et al. Platelet and fibrin modification by radiographic contrast media. Circ Res 1991; 68: 881-7
58. D'Anglemont De Tassigny A, Ide E JM, Carot AC. Comparative effects of ionic and nonionic iodinated low-osmolar contrast media on platelet function with the PFA-100 (platelet function analyzer). Invest Radiol 2001; 36: 276-82
59. Grabowski EF, Jang IK, Gold H, et al. Variability of platelet degranulation by different contrast media. Acad Radiol 1996; 3 Suppl. 3: S485-7
60. Li X, Gabriel DA. Differences between contrast media in the inhibition of platelet activation by specific platelet agonists. Acad Radiol 1997; 4: 108-14
61. Sakariassen KS, Barstad RM, Hamers MJ, et al. Iohexol, platelet activation and thrombosis: I. iohexol-induced platelet secretion does not affect thrombus formation in native blood. Acta Radiol 1998; 39 (4): 349-54
62. Sakariassen KS, Buchmann M, Hamers MJ, et al. Iohexol, platelet activation and thrombosis: I. iohexol-induced platelet secretion does not affect collagen induces or tissue-factor-induced thrombus formation in blood that is anticoagulated with heparin and aspirin. Acta Radiol 1998; 39 (4): 355-61
63. Heptinstall S, White A, Edwards N, et al. Differential effects of three radiographic contrast media on platelet aggregation and degranulation: implications for clinical practice? Br J Haematol 1998; 103 (4): 1023-30
64. Scheller B, Hennen B, Thunkenkotter T, et al. Effect of X-ray contrast media on blood flow properties after coronary angiography. Thromb Res 1999; 96 (4): 253-60
65. Fay WP, Parker AC. Effects of radiographic contrast agents on thrombin formation and activity. Thromb Haemost 1998; 80: 266-72
66. Pislaru S, Pislaru C, Szilard M, et al. *In vitro* effects of contrast media on coronary thrombolysis. J Am Coll Cardiol 1998; 32: 1102-8
67. Fauser C, Ullisch EV, Kubler W, et al. Differential effects of radiocontrast agents on human umbilical vein endothelial cells: cytotoxicity and modulators of thrombogenicity. Eur J Med Res 2001; 6 (11): 465-72
68. Riemann CD, Massey CV, McCarron DL, et al. Ionic contrast agent-mediated endothelial injury causes increased platelet deposition to vascular surfaces. Am Heart J 1993; 125 (1): 71-8
69. Gasperetti CM, Feldman MD, Burwell LR, et al. Influence of contrast media on thrombus formation during coronary angioplasty. J Am Coll Cardiol 1991; 48: 443-50
70. Lembo NJ, King SB, Roubin GS, et al. Effects of non-ionic versus ionic contrast media on complications of percutaneous transluminal coronary angioplasty. Am J Cardiol 1991; 67: 1046-50
71. Esplugas E, Cequier A, Jara F, et al. Risk of thrombosis during coronary angioplasty with low osmolality contrast media. Am J Cardiol 1991; 68: 1020-4
72. Piessens JH, Stammen F, Vrolix MC, et al. Effects of an ionic versus a non-ionic low osmolar contrast agent on the thrombotic complications of coronary angioplasty. Cathet Cardiovasc Diagn 1993; 28: 99-105
73. Lefèvre T, Bernard A, Bertrand M, et al. Comparaison en microscopie électronique du potentiel antithrombogène de deux produits de contraste iodés de basse osmolalité au cours de l'angioplastie coronarie transluminale percutanée. Arch Mal Coeur 1994; 87: 225-33
74. Qureshi NR, den Heijer P, Crijns HJ. Percutaneous coronary angioscopic comparison of thrombus formation during percutaneous coronary angioplasty with ionic and non-ionic low osmolality contrast media in unstable angina. Am J Cardiol 1997; 80 (6): 700-4

75. Malekianpour M, Bonan R, Lespérance J, et al. Comparison of ionic and non-ionic low osmolar contrast media in relation to thrombotic complications of angioplasty in patients with unstable angina. Am Heart J 1998; 135: 1067-75
76. Lefèvre T, Adjeroud N, Royer T, et al. Influence of contrast media on the results of percutaneous transluminal coronary angioplasty with provisional stenting: a comparative study. J Invasive Cardiol 1998; 10 (7): 380-4
77. Schräder R, Esch I, Ensslen R, et al. A randomized trial comparing the impact of a non-ionic (Iomeprol) versus an ionic (Ioxaglate) low osmolar contrast medium on abrupt vessel closure and ischemic complications after coronary angioplasty. J Am Coll Cardiol 1999; 33: 395-402
78. Batchelor WB, Granger ChB, Kleiman NS, et al. A comparison of ionic versus non-ionic contrast medium during primary percutaneous transluminal coronary angioplasty for acute myocardial infarction (GUSTO IIb). Am J Cardiol 2000; 85: 692-7
79. Bertrand ME, Esplugas E, Piessens J, et al. Influence of a non-ionic, iso-osmolar contrast medium (Iodixanol) versus an ionic, low-osmolar contrast medium (Ioxaglate) on major adverse cardiac events in patients undergoing percutaneous transluminal coronary angioplasty: a multicenter, randomized, double-blind study. Circulation 2000; 101: 131-6
80. Scheller B, Hennen B, Pohl A, et al. Acute and subacute stent occlusion: risk-reduction by ionic contrast media. Eur Heart J 2001; 22: 385-91
81. Inoue T, Sohma R, Miyazaki T, et al. Comparison of activation process of platelets and neutrophils after coronary stent implantation versus balloon angioplasty for stable angina pectoris. Am J Cardiol 2000; 86: 1057-62
82. Schrader R. Ionic or non-ionic contrast media in stent placement [letter]. Eur Heart J 2001; 22: 2029
83. Steinberg EP, Moore RD, Powe NR, et al. Safety cost effectiveness of high-osmolality as compared with low-osmolality contrast material in patients undergoing cardiac angiography. N Engl J Med 1992; 326: 425-30
84. Al Dieri R, Béguin S, Hemker HC. Anticoagulant- and antiplatelet-effect of an iodinated contrast medium, but not of a nonionic one [abstract]. Am J Cardiol 2000; 86: 100i
85. Aguirre FV, Simoons ML, Ferguson JJ, et al. Impact of contrast media on clinical outcomes following percutaneous coronary interventions with platelet glycoprotein IIb/IIIainhibition: meta-analysis of clinical trials with Abciximab [abstract]. Circulation 1997; 96 Suppl. 1: 161

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