Published in final edited form as:

Catheter Cardiovasc Interv. 2016 November ; 88(5): 727–737. doi:10.1002/ccd.26353.

The Assessment of Thrombotic Markers Utilizing Ionic versus Non-Ionic Contrast During Coronary Angiography and Intervention (ATOMIC) Trial

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Abstract

Objective—To determine how two different types of iodinated contrast media (CM), low-smolar ionic dimer ioxaglate (Hexabrix) and iso-osmolar nonionic dimer, iodixanol (Visipaque), affect multiple indices of hemostasis.

Background—*In vitro* models demonstrate differential effects of ionic and non-ionic CM on markers of hemostasis.

Methods—This blinded endpoint trial randomized 100 patients to ioxaglate or iodixanol. The primary endpoint was change in endogenous thrombin potential (ETP) following diagnostic angiography. Secondary endpoints included change in markers of fibrinolysis (tissue plasminogen activator (tPA) and plasminogen activator inhibitor 1 (PAI-1)) and platelet aggregation following diagnostic angiography and percutaneous coronary intervention (PCI) with bivalirudin. Data are presented as median [interquartile range].

Results—ETP significantly decreased after diagnostic angiography in both ioxaglate (baseline 1810 nM*minute [1540-2089] to post-angiography 649 nM*minute [314-1347], $p<0.001$) and iodixanol groups (baseline 1682 nM*minute [1534-2147] to post-angiography 681 nM*minute [229-1237], $p<0.001$), but the decrease was not different between CM ($p=0.70$). There was a significant increase in ETP during PCI ($n=45$), despite the use of bivalirudin, suggesting a prothrombotic effect of PCI (post-angiography 764 nM*minute [286-1283] to post-PCI 1081 nM*minute [668-1552], $p=0.02$). There were no significant differential effects on tPA, PAI-1, and markers of platelet activity.

Conclusion—There were no significant differential effects between ioxaglate and iodixanol. Both CM led to significant reductions in thrombin generation and no significant effects on fibrinolytic activity or platelet activity, thereby contributing to a favorable antithrombotic milieu.

Keywords

Cardiac catheterization; contrast; thrombosis and haemostasis

Introduction

Thrombotic complications are among the most serious major adverse cardiac events following coronary angiography and percutaneous coronary intervention (PCI). The final common pathway in the formation of a mature clot is generation of thrombin, which cleaves fibrinogen to active fibrin strands to stabilize thrombus (1). Thrombin is also a potent endogenous platelet agonist and, via its own production feedback loops, promotes further generation of thrombin (2). Advances in pharmacology have led to classes of agents targeted at one of the three main components of the thrombotic process: thrombin, fibrin, and platelets. Contrast media (CM) has been shown in animal models and *in vitro* experiments to have variable effects on each of these three components (3-4). These data suggest that ionic CM may have greater antithrombotic properties than nonionic CM, at the expense of higher osmolality and fluid retention. However, data from patient-derived samples are lacking.

The Assessment of Thrombotic Markers Utilizing Ionic versus Non-Ionic Contrast During Coronary Angiography and Intervention (AToMIC) Trial was designed to determine how two different types of iodinated CM agents, the low-osmolar ionic dimer, ioxaglate (Hexabrix), and the iso-osmolar nonionic dimer, iodixanol (Visipaque), affect thrombin generation and other measures of thrombotic risk in patients undergoing coronary angiography with possible PCI. A secondary aim was to delineate the differential effects of bivalirudin and PCI on any CM-related changes in these thrombotic parameters.

Materials and Methods

Study design

The AToMIC trial was a prospective blinded endpoint randomized study of patients undergoing coronary angiography and possible PCI, enrolling patients between February and July of 2013 at a single tertiary care center. Patients ≥ 18 years of age, referred for a diagnostic coronary angiogram with possible PCI, and on dual anti-platelet therapy with aspirin (total dose 325 mg ≥ 2 hours prior to procedure) and clopidogrel (total dose 600 mg prior to procedure, timing defined below) were eligible to participate. Patients were excluded if they met one of the following criteria: 1) Use of anti-platelet therapy other than aspirin and clopidogrel (e.g. prasugrel, ticagrelor, cilostazol, persantine); 2) Use of warfarin, low molecular-weight heparin within 12 hours of angiography, or unfractionated heparin with an activated clotting time > 150 seconds at time of angiography; 3) Use of a non-steroidal anti-inflammatory drug within 72 hours of angiography; 4) Known allergy to CM; 5) Exposure to CM within 24 hours of angiography; 6) Glomerular filtrate rate ≤ 30 mL/min/1.73m²; 7) Plan to undergo angiography via a trans radial approach given the varied approaches to intra

procedural use of unfractionated heparin; or 8) Enrolled in a competing research study (Figure 1).

Laboratory technicians evaluating the endpoints were blinded to study group. Patients provided written informed consent, and the New York University School of Medicine Institutional Review Board approved the study. The trial is registered at [ClinicalTrials.gov](https://clinicaltrials.gov) (identifier: NCT01848899) and funded by a grant from Guerbet (Bloomington, IN). Diagnostica STAGO S.A.S. (France) provided reagents for the calibrated automated thrombogram. The sponsor had no role in protocol development, enrollment, data analysis, or presentation of this manuscript.

Stratification and randomization

Eligible patients were stratified into 3 groups based on the time frame during which they received clopidogrel 600 mg: Group 1, within 2 hours; Group 2, between 2 and 6 hours; or Group 3, 6 hours pre-procedure with daily therapy thereafter, or clopidogrel 75 mg daily for 7 days. After stratification, patients were randomly assigned to receive either ioxaglate (Guerbet LLC, Bloomington, IN) or iodixanol (GE Healthcare Inc, Princeton, NJ) during coronary angiography and PCI. The randomization sequence was computer-generated by the biostatistician using random blocks of 2 and 4.

Coronary angiography and blood sample collection

Arterial access was obtained via a 6 French sheath in the femoral artery. The first blood sample was collected from the arterial sheath immediately after insertion. Thereafter, 500 International Units (IU) of diluted unfractionated heparin was administered via the arterial sheath and diagnostic angiography was performed. The second blood sample was collected from the arterial sheath following the diagnostic angiogram. For patients in whom intravascular ultrasound, fractional flow reserve, or PCI was clinically indicated, bivalirudin was administered according to standard protocol, and a third blood sample was collected from the arterial sheath 2 minutes after the administration of the intravenous bivalirudin bolus. In patients undergoing PCI, a fourth blood sample was collected from the arterial sheath at the end of the procedure prior to sheath removal. (Figure 2)

For each blood sample collection, the first 5 cc of blood collected were discarded and the subsequent 14 cc of blood were collected in 3.2% (0.109 mol/L) sodium citrate tubes (BD Vacutainer, 2.7 mL). Citrate-anticoagulated blood designated for plasma collection was centrifuged within 15 minutes of collection at 2500g for 10 minutes and then stored at -80°C until analysis. Good clinical practices were followed to certify proper storage and daily and long-term quality control of reagents, instruments, and technique.

Primary endpoint

The primary endpoint was the percent change in thrombin generation from baseline to following the completion of diagnostic angiography. Thrombin generation indices were measured in triplicate using stored plasma and a calibrated automated thrombogram (Diagnostica STAGO Inc., France). Thrombin Calibrator was added to control plasma to calculate the molar concentration of thrombin during measurement. Reagents containing

diluted thromboplastin were added to plasma, followed by a mixture of fluorogenic substrate and calcium to trigger coagulation (5). The Thrombinoscope Software program was used to calculate all parameters of the thrombogram.

Secondary endpoints

Secondary endpoints included percent change in clotting time; markers of fibrinolysis, including plasma levels of tissue plasminogen activator (tPA) and plasminogen activator inhibitor-1 (PAI-1); and markers of platelet activity, including measured by light transmission aggregometry (LTA), platelet surface expression of PAC-1 and P-selectin, and extent of monocyte- and leukocyte-platelet aggregates following diagnostic angiography and following PCI.

For the evaluation of tPA and PAI-1, stored plasma were analyzed using a multiplex assay (Luminex, Austin, TX). For the evaluation of platelet activity via LTA, citrate-anticoagulated blood was centrifuged within 15 minutes of collection at 200g for 10 minutes to obtain platelet rich plasma. LTA was then performed immediately on the AggGRAM light transmission aggregometer (Helena Biosciences, Beaumont, TX), and platelet aggregation was assessed in response to 10 μ M epinephrine, 1600 μ M arachidonic acid, and 20 μ M of adenosine diphosphate (ADP) following a 10-minute evaluation. The remaining citrate-anticoagulated blood was evaluated within 15 minutes of collection for extent of monocyte- and leukocyte-platelet aggregates and platelet surface expression of PAC-1 and P-selectin via an Accuri C6 flow cytometer (BD Biosciences, Franklin Lakes, NJ) using directly conjugated CD14-PE (monocyte), CD45-PE (leukocyte), PAC-1-FITC, CD62-FITC (P-selectin), and CD42-PE or CD61-FITC (platelet) antibodies.

Covariates

Demographic information was self-reported. Height, weight, and abdominal circumference were measured by trained clinical nurses or study investigators. Pertinent medical history was obtained from patient interview and review of the electronic medical record. Baseline laboratory data was performed in routine clinical laboratories within 30 days of the procedure and collected from review of electronic medical record. Left ventricular ejection fraction was categorized as normal ($\geq 50\%$), mildly or moderately reduced (35% to 49%), or severely reduced ($< 35\%$) and collected from review of noninvasive data or left ventricular angiography. Indication for coronary angiography was determined by a physician investigator based on patient interview and categorized as objective evidence of myocardial ischemia on non-invasive testing with or without symptoms, stable angina with at least 2 out of 3 classic features (substernal, occurs with exertion, relieved with rest or nitroglycerin), or non ST-segment elevation acute coronary syndrome. Procedural data were collected in real-time. Potential reactions to CM, such as hives, rash, nausea or vomiting, were monitored for 24 hours post-procedure or until discharge, whichever was sooner.

Statistical analysis

Continuous variables are presented as median [interquartile range] and categorical variables are presented as proportions. Distribution of continuous variables was assessed for normality using Shapiro-Wilks test. Baseline variables were compared between ioxaglate and

iodixanol groups with two sample t-test for normally distributed continuous variables, Mann-Whitney for skewed continuous variables, and tests of proportions for categorical variables. Changes in endpoints over time within and between groups were compared using a two-way ANOVA test with factors including blood collection time point, type of contrast used, and the interaction term between these two variables. For the PCI sub analysis using the total PCI cohort, endpoints were evaluated between time points using a related-sample Wilcoxon signed rank test. Statistical significance for the primary endpoint was tested using a two-sided alpha level of 0.05. Due to the number of secondary endpoints, a two-sided alpha level of 0.01 was used for secondary analyses. Data were analyzed using Statistical Package for the Social Sciences (IBM, Armonk, NY) and Statistical Software R (a free language and environment for statistical computing and graphics).

Sample size calculation

Since preliminary data comparing thrombin generation between the two different CM studied in the current trial were not available, sample size calculation was based on extent of monocyte-platelet aggregates, a marker that has been shown to correlate with adverse cardiovascular events (6-7). Based on preliminary data (mean 20.6% and standard deviation 13.4% at baseline on arterial access in patients undergoing coronary angiography with or without PCI), a sample size of 50 was required in each group to provide 80% power to detect a 20% difference at a two-sided 0.05 level of significance

Results

Baseline characteristics

Baseline characteristics were not significantly different between patients randomized to the ioxaglate (n=50) and iodixanol (n=50) groups (Table 1). A clopidogrel load was administered <2 hours, 2 to 6 hours, or 6 hours prior to baseline in 48%, 2%, and 50%, respectively, in the ioxaglate group and 52%, 4%, 44%, respectively, in the iodixanol group. There was no significant difference in the volume of CM used during diagnostic angiography between the ioxaglate and iodixanol groups (72 mL [56,85] versus 74 mL [63,91], $p=0.40$). The proportions of patients experiencing hives or a rash (2% versus 2%, $p=1.0$) or nausea/vomiting (2% versus 0%, $p=1.0$) were low in both the ioxaglate and iodixanol groups.

Thrombin generation and clotting time

A valid thrombogram was generated post-diagnostic angiography in 86% (n=43) of the patients in the ioxaglate group and 74% (n=37) of the patients in the iodixanol group ($p=0.21$). In these patients, endogenous thrombin potential significantly decreased after diagnostic angiography in both the ioxaglate and iodixanol groups but the decrease was not different between groups (Figure 3). Results were similar when the missing endogenous thrombin potential data were defined as zero and when the missing data were treated with imputation (data not shown). There was a significant decrease in peak thrombin generation but no significant change in lag time (clotting time) after diagnostic angiography (Figure 3). These changes were not different between groups.

Markers of fibrinolysis

There was no significant change between baseline and following diagnostic angiography in both plasma tPA level (ioxaglate group (n=49): 467 pg/mL [357,575] vs 484 pg/mL [338,717], $p=0.38$; iodixanol group (n=50): 389 pg/mL [248,541] vs 414 pg/mL [256,533], $p=0.78$; $p=0.67$ between groups) and plasma PAI-1 level (ioxaglate group (n=49): 7267 pg/mL [4801,10762] vs 7693 pg/mL [4487,11053], $p=0.31$; iodixanol group (n=50): 7014 pg/mL [4591,10157] vs 8037 pg/mL [4835,10591], $p=0.38$; $p=0.93$ between groups).

Markers of platelet activity

The extent of platelet aggregation did not differ significantly among the time points of 180 seconds, 300 seconds, or maximal aggregation, and, therefore, data from LTA are shown as the percent of maximal platelet aggregation. Percent change in maximal platelet aggregation from baseline to following diagnostic angiography in response to 10 μ M epinephrine, 1600 μ M arachidonic acid, and 20 μ M of ADP are shown in Figure 4 and showed no significant change within or between groups.

There was also no significant change within or between groups in extent of monocyte platelet aggregation, extent of leukocyte platelet aggregation, platelet surface expression of PAC-1, and platelet surface expression of P-selectin from baseline to following diagnostic angiography (Supplemental Figure).

Patients undergoing PCI

Nearly half of the study population underwent PCI following diagnostic angiography (n=25 in the ioxaglate group and n=20 in the iodixanol group). There was no significant difference between the ioxaglate and iodixanol groups in the total volume of CM used during the procedure (176 mL [148,202] versus 195 mL [147,220], $p=0.68$) or the activated clotting time during PCI (364 seconds [353,399] versus 360 seconds [351,374], $p=0.17$).

Change in endogenous thrombin potential after CM administration, bivalirudin bolus, and PCI are shown in Figure 5. There was no significant difference in the percent change in endogenous thrombin potential from baseline to following PCI between the ioxaglate (n=20) and iodixanol (n=18) groups (-32.7% [$-61.0, -19.0$] vs -36.3% [$-56.0, -28.8$], $p=0.39$).

Both plasma tPA and PAI-1 levels did not change significantly from baseline to following PCI in the combined group of patients undergoing PCI (tPA (n=44): 456 pg/mL [248,551] vs 464 pg/mL [276,729]; $p=0.15$; PAI-1 (n=44): 8520 pg/mL [5477,11644] vs 8109 pg/mL [5648,11342]; $p=0.85$). Similarly, the percent change in plasma tPA and PAI-1 levels from baseline to following PCI did not significantly differ between the ioxaglate (n=25) and iodixanol (n=19) groups (tPA: $+5.8\%$ [$-3.0, +31.1$] vs $+4.5\%$ [$-8.1, +10.3$], $p=0.37$; PAI-1: -2.9% [$-13.9, +28.6$] vs -3.1% [$-10.6, +12.1$], $p=0.94$). The percent change in maximal platelet aggregation from baseline to following PCI in response to 10 μ M epinephrine, 1600 μ M arachidonic acid, and 20 μ M of ADP are shown in Figure 6.

Discussion

This is the first study to comprehensively assess indices of thrombin generation, fibrinolysis, and platelet activity in patients undergoing coronary angiography with possible PCI randomized to receive either the low-osmolar ionic dimer CM, ioxaglate, or the iso-osmolar nonionic dimer CM, iodixanol. Both ioxaglate and iodixanol demonstrated an antithrombotic effect and no change in fibrinolytic or platelet activity. However, unlike prior experimental studies, there were no differential effects on parameters of thrombin generation, suggesting that the more favorable profile noted with ionic compared to nonionic CM *in vitro* does not translate *in vivo* during coronary angiography when ioxaglate is compared to iodixanol.

Ionic CM dissociates in solution and is, therefore, higher in osmolality than nonionic CM. A tri-iodinated benzene ring makes up each CM molecule. When a second ring is added, a dimer is created of one ionizing and one nonionizing tri-iodinated benzene ring and the osmolality is decreased by more than half. Ioxaglate, a benzene dimer, is the only ionic CM currently used during coronary angiography in the United States and has an overall low osmolality (600 mOsm) compared to both ionic monomer CM (>1400 mOsm) and commonly used nonionic monomer CM, iopamidol (Isovue, 796 mOsm) and iohexol (Omnipaque, 844 mOsm). Iodixanol, on the other hand, is a nonionic dimer CM, and, therefore, iso-osmolar (290 mOsm). However, given iodixanol's inability to dissociate in solution, this large contrast molecule has the highest viscosity of all the low-osmolar agents, while the viscosity of ioxaglate is significantly lower. These viscous properties are suggested to be partly responsible for the more favorable effect of ioxaglate over iodixanol on coagulation parameters observed in experimental models.

Prior studies evaluated markers of thrombogenesis in *in vitro* and animal models and observed an anticoagulant effect with CM. An *in vitro* model by Corot et al demonstrated increased thrombin time with ioxaglate, iohexol, and iodixanol compared to saline controls (8). Similarly, in a baboon thrombosis model, all three agents were inherently antithrombotic compared to stents infused with saline (9). However, in these studies, ioxaglate was associated with a thrombin time more than five times that with iodixanol. Ioxaglate was also associated with a lower amount of fibrin deposition on stents compared with iohexol, which in turn was associated with a lower amount of fibrin deposition than iodixanol (8-9). In an *in vitro* model conducted by Jones et al, no thrombi were formed when blood was mixed with ioxaglate, while thrombi formed with iohexol weighed less than those formed with iodixanol (4). Together, these data suggested an association between variability in thrombus formation and viscosity of the blood/CM mixture. The current study not only examined samples derived from patients undergoing coronary angiography, but also utilized the thrombin generation assay, a novel and more contemporary method to evaluate thrombin generation. This more direct and comprehensive examination demonstrated that the differential effects observed on parameters of thrombosis in experimental models did not translate *in vivo*.

Evidence examining the effects of CM on clinical outcomes is conflicting and largely from the pre-stent era. The Randomized Trial of Contrast Media Utilization in High-Risk PTCA (COURT trial) was a multicenter prospective double-blind randomized trial of 856 patients

undergoing PCI (10). “High-risk” patients randomized to receive ioxaglate versus iodixanol had a higher rate of in-hospital major adverse clinical events, a composite of 8 event types including a soft endpoint of emergent repeat diagnostic coronary angiography without revascularization. Two subsequent double-blind randomized studies comparing ioxaglate and iodixanol demonstrated no statistically significant difference in rates of adverse clinical outcomes (11-12). A more recent prospective single-center study by Le Feuvre et al examined 498 patients undergoing PCI (13). Patients were assigned to receive ioxaglate or iodixanol on alternating months and all patients received enoxaparin, aspirin, and clopidogrel. Furthermore, glycoprotein IIb/IIIa inhibitor was used in 42% of the study cohort. Patients receiving ioxaglate versus iodixanol had significantly fewer in-hospital major adverse clinical events and significantly less frequent angiographic evidence of large thrombus and abrupt target vessel closure.

Contemporary data, however, support net clinical benefit with the use of dual antiplatelet therapy and either unfractionated heparin alone (without the use of glycoprotein IIb/IIIa inhibitor) or the direct thrombin inhibitor bivalirudin, as examined in the current study (14-15). Only one study examined the effect of CM on thrombogenesis using the thrombin generation assay. This *in vitro* study demonstrated an additive inhibitory effect with ioxaglate in the setting of heparin and glycoprotein IIb/IIIa inhibitor, such that ioxaglate completely abolished thrombin generation, while iodixanol slowed clotting time but had no effect on the amount of thrombin formed (16). Furthermore, only one prior study evaluated the effect of CM and bivalirudin on blood samples derived from patients with severe coronary artery disease on dual anti-platelet therapy (3). Similar to prior experimental studies, *in vitro* addition of ioxaglate demonstrated a more favorable profile on coagulation parameters than iodixanol, but these differential effects did not change with the addition of bivalirudin (3). Although, in the current study there was no differential effect on endogenous thrombin potential between ioxaglate and iodixanol, there was a significant increase in thrombin generation noted from the end of the diagnostic angiogram to the end of PCI, despite the use of bivalirudin, indicating a prothrombotic effect of PCI.

Circulating plasminogen changes configuration upon binding to thrombus, becoming vulnerable to conversion to active plasmin by tPA, which then degrades fibrin found in formed thrombus (17). This fibrinolytic system is inhibited by PAI-1, and in the setting of low fibrinolytic activity, circulating tPA levels increase, such that elevated levels of both enzymes are associated with adverse cardiovascular outcomes (18-20). Prior reports demonstrated a delay in intrinsic and extrinsic fibrinolysis in the presence of CM (3-4,21-22). However, these *in vitro* models also demonstrated less of a delay in fibrinolysis with ioxaglate compared to iohexol and iodixanol. Experimental data suggest that ioxaglate inhibits fibrin polymerization and the binding of anion substrates on thrombin’s exosite I, which thereby inhibits the formation of fibrin from fibrinogen (16,23-24). The higher viscosity of iodixanol, on the other hand, is postulated to adversely modify the physical properties of fibrin (22). The current study demonstrated no significant change in fibrinolytic activity with either CM, possibly in part due to a decrease in CM viscosity when warmed to body temperature *in vivo* (3).

In the current study, there was no significant change in platelet activity in response to epinephrine, arachadonic acid or ADP, and surface markers of platelet adhesion and activation did not significantly change after administration of either ioxaglate or iodixanol. These findings are concordant with data from *in vitro* models that showed no significant effect on platelet activity with ionic CM or iodixanol (3-4). Although one study did demonstrate different degrees of platelet inhibition with a variety of non-ionic CM when compared to normal controls, these changes were only observed at higher CM concentrations and not at lower steady-state concentrations (25).

The coagulation and fibrinolytic systems are complex with multiple mechanisms, and markers of these pathways may not adequately reflect the potentially altered architecture and physical properties of fibrin that may be associated with different types of CM. Second, it remains unclear if other commonly used CM, such as the nonionic monomers iopamidol or iohexol, would have differential effects on markers of hemostasis more consistent with the findings noted in *in vitro* models. Third, the population studied was a relatively low risk cohort predominately presenting with stable syndromes. It is not known if CM would have a differential effect on markers of hemostasis in the presence of heavy thrombus burden or higher platelet activity, as seen in acute coronary syndrome. Fourth, the sample size was calculated based on available data for monocyte-platelet aggregation and an expected relative difference of 20%. In the current study, the mean difference [95% confidence interval] in extent of monocyte-platelet aggregation between the two types of CM was 23% pre-contrast (3.5 [-1.01, 8.06]) and 30% post-contrast (6.8 [-0.41, 14.01]) assuming iodixanol as the reference (pre-contrast: mean 18.54 ioxaglate, 15.01 iodixanol; post-contrast: mean 15.57 ioxaglate, 22.37 iodixanol). However, the difference in the lower bound of the 95% confidence interval was much smaller, and, therefore, smaller than observed differences in monocyte-platelet aggregation cannot be ruled out. Similarly, the study may be underpowered for the other markers studied. Finally, the current study only evaluated PCI in the setting of a steady bivalirudin infusion. It remains uncertain if these findings can be extended to PCI in the setting of intermittent boluses of unfractionated heparin. Nonetheless, this is the largest, most comprehensive prospective randomized blinded end-point study to compare the only ionic CM and the only iso-osmolar nonionic CM currently used during coronary angiography. Unlike prior studies, the current study also examined patient-derived samples to better reflect changes that occur *in vivo* during coronary angiography and PCI. Furthermore, the markers evaluated in the current trial have been well studied, correlate with clinical outcomes, and are feasible to measure in this relatively large cohort.

Conclusions

This study demonstrated that the low-osmolar ionic dimer ioxaglate and the iso-osmolar nonionic dimer iodixanol decreased thrombin generation to a similar degree but had no significant effect on fibrinolytic or platelet activity in patients undergoing coronary angiography with or without PCI. Thus, although both CM produce a favorable antithrombotic milieu, the suggestion of a more favorable anti-thrombotic effect with ioxaglate noted in multiple prior experimental studies does not translate *in vivo* during coronary angiography and PCI in low to moderate risk patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

We acknowledge the contributions of Manjiri Tule, MD; Liza Karotkin, BA; Jeffrey Le, BA; and Mansi Maini of NYU School of Medicine to the data collection. Binita Shah was partially funded by a NIH/NHLBI grant (T32HL098129 in 2012; UL1 TR000038 in 2013). Dr Berger was partially funded by the NIH/NHLBI (RO1HL114978), AHA (13CRP14410042) and Doris Duke Charitable Foundation (2010055). Data analysis was partially supported by the NYU School of Medicine Immune Monitoring Core, which is partially supported by the NIH (UL1TR000038) and the NYU Cancer Institute's Cancer Center Support Grant (P30CA016087).

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Figure 1.
Screening, enrollment, and randomization of study population

Figure 2.

Blood sample collection in the Assessment of Thrombotic Markers Utilizing Ionic versus Non-Ionic Contrast During Coronary Angiography and Intervention (ATOMIC) Trial FFR = fractional flow reserve, IVUS = intravascular ultrasound, PCI = percutaneous coronary intervention

Figure 3.

A) Sample thrombogram, B) endogenous thrombin potential (ETP), C) peak thrombin generation, and D) lag time pre- and post-contrast administration in patients undergoing coronary angiography randomized to ioxaglate versus iodixanol contrast media

Figure 4.

Percent change in maximal platelet aggregation from pre- to post-contrast administration in response to A) 10 µM epinephrine, B) 1600 µM arachidonic acid, and C) 20 µM of ADP in patients undergoing coronary angiography randomized to ioxaglate versus iodixanol contrast media

Figure 5.

A) Sample thrombogram and B) Endogenous thrombin potential (ETP) pre- and post-contrast administration, post-bivalirudin bolus, and post-percutaneous coronary intervention (PCI) in patients randomized to ioxaglate versus iodixanol contrast media undergoing PCI

Figure 6. Percent change in maximal platelet aggregation from baseline- to post- percutaneous coronary intervention (PCI) in response to A) 10 μ M epinephrine, B) 1600 μ M arachidonic acid, and C) 20 μ M of ADP in patients randomized to ioxaglate versus iodixanol contrast media undergoing PCI

Table 1

Baseline characteristics

	Ioxaglate (n=50)	Iodixanol (n=50)	p-value
Age, years	69 [61-76]	68 [60-73]	0.19
Male sex, % (n)	74 (37)	78 (39)	0.82
Race, % (n)			
White	84 (42)	72 (36)	0.14
Black	0	8 (4)	
Hispanic	8 (4)	14 (7)	
Asian	8 (4)	6 (3)	
Body mass index, kg/m ²	28 [25-32]	27 [24-32]	0.80
Abdominal circumference, cm	100 [92-112]	99 [91-109]	0.74
Medical history, % (n)			
Hypertension	74 (37)	68 (34)	0.66
Dyslipidemia	92 (46)	86 (43)	0.53
Diabetes mellitus	26 (13)	28 (14)	1.0
Myocardial infarction	14 (7)	12 (6)	1.0
Percutaneous coronary intervention	52 (26)	48 (24)	0.84
Coronary artery bypass surgery	14 (7)	16 (8)	1.0
Peripheral artery disease	8 (4)	8 (4)	1.0
Stroke or transient ischemic attack	4 (2)	4 (2)	1.0
History of tobacco use, % (n)	58 (29)	68 (34)	0.41
Current tobacco use, % (n)	14 (7)	14 (7)	1.0
Laboratory data			
Serum creatinine, mg/dL	0.9 [0.8-1.1]	0.9 [0.8-1.1]	0.89
Serum glucose, mg/dL	98 [91-115]	98 [91-120]	0.70
White blood cell count, K/uL	6.7 [5.7-7.6]	6.8 [5.4-7.9]	0.91
Hemoglobin level, g/dL	14 [13-15]	14 [13-15]	0.59
Platelet count, K/uL	213 [181-269]	226 [192-259]	0.68
Hemoglobin A1c, %	6.0 [5.7-7.0]	6.2 [5.8-6.9]	0.61
Left ventricular ejection fraction, % (n)			0.51
Normal	82 (41)	86 (43)	
Indication for coronary angiography, % (n)			0.35
Equivocal symptoms with objective evidence of myocardial ischemia	50 (25)	58 (29)	
Stable angina	42 (21)	30 (15)	
Non ST-segment elevation acute coronary syndrome	8 (4)	12 (6)	

-Continuous variables presented as median [interquartile range]

-Normally-distributed and skewed continuous variables compared between groups using independent sample t-test and Mann-Whitney test, respectively

-Categorical variables presented as proportions (n) and compared between groups using Pearson Chi-Square or Fisher's Exact test