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Multicenter Randomized Evaluation of High Versus Standard Heparin Dose on Incident Radial Arterial Occlusion After Transradial Coronary Angiography

The SPIRIT OF ARTEMIS Study

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ABSTRACT

OBJECTIVES The aim of this study was to test the hypothesis that more intensive over standard anticoagulation administered during coronary angiography would significantly reduce rates of radial artery occlusion (RAO).

BACKGROUND RAO, although silent, remains a frequent and therefore worrisome complication following transradial coronary angiography. Anticoagulation is effective in reducing RAO, but the optimal heparin dose remains ill defined.

METHODS In this multicenter, randomized superiority trial, a high dose (100 IU/kg body weight administered in divided doses) and a standard dose (50 IU/kg body weight) of heparin during 5- or 6-F coronary angiography were compared. A total of 3,102 patients were randomized, of whom 1,836 patients not proceeding to percutaneous coronary intervention and without need for arterial access crossover entered the trial. Post-catheterization hemostasis did not follow a rigid protocol.

RESULTS A total of 102 early RAOs were found on ultrasonography (incidence 5.6%). In the high-dose heparin group, the rate of RAO was significantly lower compared with the standard-dose heparin group (27 [3.0%] vs. 75 [8.1%]; odds ratio: 0.35; 95% confidence interval: 0.22 to 0.55; $p < 0.001$), without compromising safety. The time to achieve hemostasis was similar between groups. To avoid 1 RAO, the number of patients needed to treat in the high-dose heparin group was approximately 20. These results were corroborated by our integrated database, showing an 80% reduction of forearm artery occlusions in high versus low heparin dose patients and our updated meta-analysis of randomized controlled trials demonstrating significant benefit of higher over lower anticoagulation intensity.

CONCLUSIONS High compared with standard heparin dose significantly reduced the rate of RAO in patients undergoing coronary angiography. High-intensity anticoagulation should be considered in transradial diagnostic procedures. (High [100IU/Kg] Versus Standard [50IU/Kg] Heparin Dose for Prevention of Forearm Artery Occlusion; NCT02570243) (J Am Coll Cardiol Intv 2018;11:2241-50) © 2018 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

BARC = Bleeding Academic Research Consortium

CAG = coronary angiography

PCI = percutaneous coronary intervention

RA = radial artery

RAO = radial artery occlusion

RCT = randomized controlled trial

TF = transfemoral

TR = transradial

UFH = unfractionated heparin

Transradial (TR) coronary angiography (CAG) and percutaneous coronary interventions (PCIs) are becoming increasingly popular worldwide because of their inherent very low incidence of major bleeding and other local complications. Although technically challenging in comparison with the transfemoral (TF) approach, the TR access route is associated with more convenience, shorter length of hospitalization, and higher patient acceptance rates (1,2). In the complication spectrum of TR coronary procedures, however, occlusion of the radial artery (RA) is prominent, despite being almost invariably asymptomatic. Once an RA occlusion (RAO) occurs, several issues emerge, including inability of the interventionalist to reuse the vessel, shortage as a graft for possible coronary artery bypass surgery, and teleological, nephrological, and unknown long-term natural history aspects (3).

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One recent meta-analysis revealed that every tenth patient after CAG might be at risk for RAO and that adequate anticoagulation was effective in reducing rates of RAO (4). The relevance of RAO and the impact of anticoagulation appear not to be adequately addressed by the interventional community (5). In a previous report we suggested that a 50% increase in the dose of unfractionated heparin (UFH) could result in a 50% reduction of incident RAO (3). We therefore designed this prospective, randomized, multicenter superiority study to test the hypothesis that more intensive (i.e., 100 IU/kg body weight UFH) compared with standard (i.e., 50 IU/kg body weight UFH) anticoagulation administered during CAG would significantly reduce the rate of RAO.

METHODS

This multicenter, randomized, active-control superiority study of parallel design was performed at 7 Greek centers. Patients were enrolled if they were older than 18 years and were scheduled for 5- or 6-F CAG and the interventional cardiologist was willing to proceed with RA access. Informed consent was obtained from all study patients. Exclusion criteria before randomization included long-term hemodialysis, oral anticoagulation as current therapy, hemodynamic instability, severe dermomyoskeletal forearm deformity, history of coronary artery bypass grafting, bilateral use of either the internal mammary artery or RA, history of bypass surgery and ipsilateral use of both the internal mammary artery and RA, and admission for elective PCI. After randomization, patients were excluded if crossover to another arterial access site was required or ad hoc PCI had to be performed. In our trial patients were eligible irrespective of baseline Allen test results (3).

For randomization, computer-generated random numbers were used stratified by center. Patients were randomized before diagnostic catheterization to receive either intravenously or intraarterially either 100 or 50 IU/kg body weight UFH in a 1:1 ratio.

Patients who were randomized to the high heparin dose received a half dose after sheath insertion, with the second half dose administered after CAG completion and just before sheath removal. In this way, unnecessarily intense anticoagulation during CAG would be avoided should the patient experience TR access failure and subsequent crossover to the TF route.

The primary endpoint of the study was early RAO, as documented by vascular ultrasonography within 10 days after CAG. After sheath removal, hemostasis was obtained with diverse hemostatic devices. The operators did not apply routinely the patent hemostasis technique and, to reflect a "real-world" approach, the hemostasis protocol was left to the discretion of each participating center. The hemostatic device was left in place until access-site bleeding was no longer evident. No measurements of activated clotting time were performed during or after CAG. Patients were scheduled for discharge usually within 3 to 6 h after CAG.

Assessment of entry-site and bleeding complications was performed by physicians who were unaware of the previously administered UFH dose. The patency status of the RA in each patient was evaluated using vascular ultrasonography either in hospital or during a subsequent visit within 10 days after discharge by a single physician who was blinded to the actual anticoagulation treatment. The RA was considered occluded if it exhibited no antegrade flow signal both at baseline and after reevaluation on a second occasion. Initially patent arteries were not reexamined and were thought to remain permanently patent.

Additionally, we monitored bleeding events according to Bleeding Academic Research Consortium (BARC) definition: "actionable" (type 2) and major (type 3) bleeding was defined as a hemoglobin decrease of >3 to <5 g/dl requiring transfusion or decrease of ≥ 5 g/dl or any life-threatening bleeding such as intraocular or intracranial hemorrhage or associated with cardiac tamponade or requiring surgical correction or inotropic support. Possible investigation of severe bleeding events requiring imaging as well as identification of large local

FIGURE 1 Study Flowchart

The present study randomized 3,102 patients and compared high with standard heparin dose during transradial coronary angiography. Among these patients, 1,836 patients not proceeding to percutaneous coronary intervention (PCI) and without need for arterial access crossover in whom follow-up was available entered the trial.

hematomas (i.e., extending beyond the forearm) were also protocol-mandated.

PARTICIPANT DATA POOLED ANALYSIS. We assessed arterial access site occlusion rate by UFH dose in an individual participant data pooled analysis of the present study and 2 other randomized controlled trials (RCTs) that enrolled patients eligible for low versus standard heparin dose during 5-F CAG (3) as well as for ulnar artery versus RA access with or without PCI (6).

META-ANALYSIS UPDATE. We updated our meta-analysis of RCTs to assess the effect of high versus low UFH dose on the rate of RAO (4). We performed electronic searches for relevant studies published from 1989 through August 15, 2017 (4). The update of this meta-analysis by further search for studies published from August 16, 2017, to February 18, 2018, did not yield additional RCTs. Six original studies, including the present trial, were deemed eligible for the meta-analysis. The search for published studies, selection of studies, and extraction of data were initiated independently by 2 investigators (G.H. and K.A.) using a standardized approach (4). Disagreements were resolved by consensus. We adopted the occlusion rates (numeric aggregate data) as mentioned in the original reports (3,4-10).

STATISTICAL ANALYSIS. Continuous data with normal and skewed distributions are presented as mean ± SD and median (interquartile range), respectively. The Kolmogorov-Smirnov test was used for normality assessment of continuous data. Categorical data are expressed as frequencies and group percentages. The Fisher exact test and 2-sample Student's *t*-test were used for comparisons of categorical and normally distributed continuous data, respectively.

TABLE 1 Demographic and Baseline Characteristics of the Study Patients

	Heparin 50 IU/kg (n = 928)	Heparin 100 IU/kg (n = 908)	p Value
Age (yrs)	64.1 ± 11.7	64.7 ± 11.3	0.30
Male	665 (71.7)	646 (71.1)	0.80
BMI (kg/m^2)	29.0 ± 4.7	28.0 ± 4.3	<0.001
History			
Diabetes mellitus	232 (25.0)	222 (24.4)	0.80
Insulin dependent	45 (4.8)	43 (4.7)	0.90
Smoking	348 (37.5)	339 (37.3)	0.90
Hypertension	561 (60.5)	563 (62.0)	0.50
Dyslipidemia	460 (49.6)	470 (51.8)	0.40
PAD	36 (3.9)	38 (4.2)	0.80
Prior PCI	132 (14.2)	114 (12.6)	0.30
Prior CABG	23 (2.5)	18 (2.0)	0.50
Prior stroke	45 (4.8)	28 (3.1)	0.06
Diagnosis at admission			
STEMI	18 (1.9)	15 (1.7)	
NSTE-ACS	222 (23.9)	221 (24.3)	
Stable or suspected CAD	610 (65.7)	583 (64.2)	
Heart valve disease	78 (8.5)	89 (9.8)	
Peri-procedural antiplatelet medication			
Aspirin	590 (63.6)	554 (61.0)	0.30
Clopidogrel	368 (39.7)	347 (38.2)	0.50
Prasugrel	14 (1.5)	17 (1.9)	0.60
Ticagrelor	23 (2.5)	29 (3.2)	0.40
Other medication			
Beta-blocker	437 (47.1)	456 (50.2)	0.20
ACE inhibitor	250 (26.9)	253 (27.9)	0.70
ARB	251 (27.0)	220 (24.2)	0.20
CCB	141 (15.2)	145 (16.0)	0.70
Statin	513 (55.3)	515 (56.7)	0.50
Diuretic agent	210 (22.6)	228 (25.1)	0.20
Nitrate	26 (2.8)	30 (3.3)	0.60
Prior oral anticoagulation	11 (1.2)	12 (1.3)	0.80
Laboratory evaluation			
	(n = 720)	(n = 671)	
Ht (%)	41.5 ± 4.9	41.5 ± 4.4	0.90
	(n = 703)	(n = 647)	
CrCl (ml/min)*	91.5 ± 36.3	89.6 ± 34.6	0.30
CrCl <60 ml/min	127 (18.1)	123 (19.0)	0.70

Values are mean ± SD or n (%). *CrCl was calculated using the Cockroft-Gault formula.

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; BMI = body mass index; CABG = coronary artery bypass grafting; CAD = coronary artery disease; CCB = calcium channel blocker; CrCl = creatinine clearance; Ht = hematocrit; NSTE-ACS = non-ST-segment elevation acute coronary syndrome; PAD = peripheral artery disease; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction.

The Mann-Whitney *U* test was used for comparisons of skewed continuous data. The primary endpoint of the present study was analyzed using the Fisher exact test.

Non-pre-specified exploratory stratified analyses were performed and odds ratios with 95% confidence intervals for interactions were obtained using fixed-effects modeling. The subgroups examined were age (<75 and ≥75 years), sex, Allen test result at the attempted upper arm (normal vs. abnormal), body mass index (<25, ≥25 to ≤35, and >35 kg/m^2), prior stroke, sheath type, sheath size, CAG duration above and below the median time, hemostatic device type, hemostasis duration, and successful patent hemostasis. The significance level for interaction was set at 0.05. No adjustment for multiple comparisons was made.

Statistical analyses were performed using SPSS version 16.0 for Windows (SPSS, Chicago, Illinois), Number Cruncher Statistical System 8 (NCSS, Kaysville, Utah), and GraphPad Prism version 5.00 for Windows (GraphPad Software, San Diego, California).

PARTICIPANT DATA POOLED ANALYSIS. To evaluate arterial access site occlusion in the integrated data, we fitted a logistic regression model, adjusting for sex, age, body mass index, smoking, diabetes, hypertension, Allen test result, number of diagnostic catheters used, dose of heparin, reason for admission, periprocedural antiplatelet agent use, number of attempts, ulnar access site, duration of CAG, and occurrence of moderate to severe spasm.

META-ANALYSIS UPDATE. The rate of RAO of each study is reported as a percentage. We obtained pooled estimate of RAO rates for the whole cohort of studies. The proportion of inconsistency across studies was quantified using the I^2 statistic. Heterogeneity among subgroups was calculated using the Cochran Q test. Because of heterogeneity among studies, a random-effects model was used to obtain the pooled estimate. We performed stratified analysis to evaluate whether the pooled rates of RAO differed between the groups of high and low dose of heparin. Estimates of occlusion rates between subgroups were compared using a test of interaction (4). All tests used were 2 sided. Results were considered statistically significant at $p < 0.05$. All analyses were performed using Comprehensive Meta Analysis version 2 (Biostat, Englewood, New Jersey).

SAMPLE SIZE CALCULATION. We assumed 7.5% and 3.5% rates of RAO with 50 and 100 IU/kg heparin, respectively, corresponding to a relative reduction of 53.3% in occlusion rate with high heparin dose (3–5). For a study power of 85% with a 2-sided p value of 0.05, at least 850 patients would have been required in each treatment group. Assuming a dropout rate of 6%, recruitment was set to at least 904 patients in each treatment group.

All patients gave informed consent, and the study was approved by the hospital's ethics committee.

RESULTS

Between February 2015 and September 2017, 3,102 patients were randomized to receive either 50 or 100 IU/kg heparin. In total 1,251 patients were excluded after randomization, and 15 patients were lost to follow-up, leaving 928 and 908 patients receiving standard and high heparin doses, respectively (**Figure 1**). The demographics and baseline characteristics of the study patients are presented in **Table 1**. Patients who received the standard heparin dose were slightly more obese compared with those who received the high heparin dose. The procedural and angiographic characteristics of the 2 groups are shown in **Table 2**. The rate of abnormal Allen test result and the number of diagnostic catheters used were higher in the high compared with the standard heparin dose group.

At a median time of 2 days (interquartile range: 1 to 8 days) after diagnostic catheterization, we observed 102 RAOs, as assessed using Doppler examination, corresponding to an incidence of 5.6%. The rate of RAO, the primary endpoint of the present study, was lower in the high-dose compared with the standard-dose heparin group: we observed 27 of 908 (3.0%) versus 75 of 928 (8.1%) arterial occlusions with high- versus low-intensity anticoagulation, respectively (odds ratio: 0.35; 95% confidence interval: 0.22 to 0.55; $p < 0.001$) (**Figure 2, Table 3**). To avoid 1 RAO, the number of patients needed to treat with 100 IU/kg heparin was 19.6 (95% confidence interval: 13.9 to 32.9). RAO rates by the time of detection appeared stable up to the sixth week after CAG (Online Figure 1). Incident RAO rates varied between 0.4% and 10% among the participating centers (Online Table 1).

The overall rates of local hematomas was 23.0% and 23.6% with standard and high heparin doses, respectively (p = NS). No study patient experienced BARC type 3 bleeding episodes, and no patient required a blood transfusion. With respect to the rate of RAO, we detected no significant interactions between the studied subgroups, indicating that high-dose heparin was beneficial regardless of baseline features, hemostasis characteristics, and time to ultrasonography (**Figure 3**).

TABLE 2 Procedural and Angiographic Characteristics

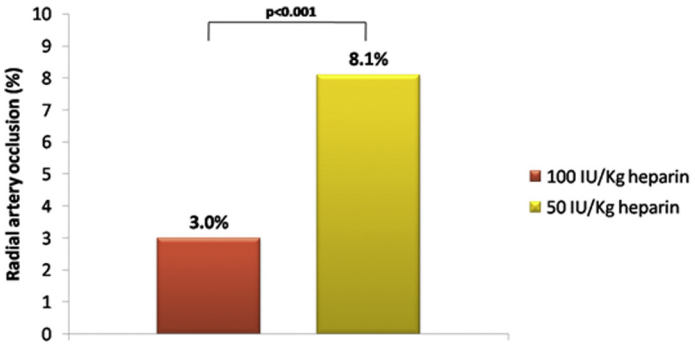
	Heparin 50 IU/kg (n = 928)	Heparin 100 IU/kg (n = 908)	p Value
Right radial access site	827 (89.1)	812 (89.4)	0.90
Allen test result abnormal	16 (1.7)	32 (3.5)	0.02
Radial pulse quality*	8.7 ± 1.1	8.6 ± 1.2	0.60
Ulnar pulse quality*	7.1 ± 2.1	7.1 ± 2.2	0.80
Attempts	1.4 ± 0.9	1.4 ± 0.8	0.90
Arterial access time (min)	2 (1-3)	2 (1-4)	0.30
Radiation time (min)	2.3 (1.4-4.2)	2.3 (1.4-4.1)	0.80
Coronary angiography time (min)	8 (6-11)	8 (6-11)	0.90
Contrast volume (ml)	73.0 ± 39.6	72.8 ± 32.5	0.90
Diagnostic catheters	1.7 ± 0.8	1.8 ± 0.9	0.04
	(n = 884)	(n = 863)	
Sheath type			0.80
Arrow	99 (11.2)	103 (11.9)	
Terumo	0 (0)	2 (0.2)	
Cordis	74 (8.4)	70 (8.1)	
KDL	583 (66.0)	566 (65.6)	
Other	172 (18.5)	167 (18.4)	
Hemostasis device type			0.10
TR band	132 (14.2)	109 (12.0)	
Radifocus	4 (0.4)	4 (0.4)	
KDL	291 (31.4)	328 (36.1)	
Other	501 (54.0)	467 (51.4)	
Patent hemostasis	0.7		
Not performed	446 (48.1)	455 (50.1)	
Unsuccessful	33 (3.6)	34 (3.7)	
Doubtful	28 (3.0)	32 (3.5)	
Successful	421 (45.4)	387 (42.6)	
Doppler follow-up (days from catheterization)	2 (1-7)	2 (1-8)	0.50
	(n = 746)	(n = 737)	
Hemostasis duration (h)	3.5 (3.0-4.3)	3.7 (3.1-4.5)	0.20

Values are n (%), mean ± SD, or median (interquartile range). *Pulse quality from 0 (no pulsation) to 10 (excellent pulsation).
TR = transradial.

POOLED ANALYSIS OF THE INTEGRATED DATABASE. For the individual participant data pooled analysis, we analyzed 731 patients with available follow-up data from our previously published studies (3,6) and 1,836 patients from the present study. The characteristics of the patients in this database by forearm access site patency are depicted in Online Table 2. In total, 186 of 2,567 arterial occlusions (7.2%) were observed. Results of multivariate analysis showed that forearm artery occlusions were independently associated with female sex, RA use, lower UFH dose, arterial spasm, and multiple access artery attempts, whereas CAG indication for non-ST-segment elevation acute coronary syndromes versus stable disease protected from RAO. Furthermore, a heparin dose of >75 IU/kg compared with <50 IU/kg conferred an 80% risk reduction for RAO (**Figure 4**).

META-ANALYSIS UPDATE OF RCTs. After inclusion of the present with the previous 5 RCTs (3,7-10), we found that more intensive compared with less intensive anticoagulation was associated with a significantly lower rate of RAO (3.6% [95% confidence interval: 2.0% to 6.5%] vs. 9.4% [95% confidence

FIGURE 2 Rates of Radial Artery Occlusion: The Study's Primary Endpoint



Incident radial artery occlusions (RAOs) were lower in the high compared with the standard heparin group (odds ratio: 0.35; 95% confidence interval: 0.22 to 0.55; $p < 0.001$). To avoid 1 RAO, the number of patients needed to be treated with 100 IU/kg heparin was about 20.

interval: 5.5% to 15.6%]; $Q = 5.44$, $p = 0.02$ between subgroups with random-effects model) (Online Figure 2).

DISCUSSION

This RCT demonstrated that a heparin dose of 100 IU/kg, compared with the standard dose of 50 IU/kg, strikingly reduced the rate of early RAO from 8.1% to 3.0% ($p < 0.001$). Notably, with the standard dose, the rate of RAO was within the range of our recent meta-analysis (4). To avoid heparin overtreatment in case of TR-to-TF crossover, the high-dose UFH group of patients had to receive heparin in divided doses. The figures correspond to an RAO risk reduction of 65%, avoidance of 48 RAOs among our study patients, and a number needed to treat of about 20 patients to prevent 1 vessel occlusion in favor of the high heparin dose group. Despite homogeneous identification of occlusions by vascular ultrasonography, this study revealed a profound diversity of RAO rates among the participating centers (Online Table 1). This is in line with published findings (4,11). Potential factors were analytically discussed by the corresponding principal investigators, but no clear causes for this diversity beyond the play of chance could be identified. In view of the multifactorial etiology of RAOs, TR operators should become aware of their own RAO figures and strive for the best possible improvement.

These results confirmed our primary hypothesis of halving RAO rates after a heparin dose increase from 50 to 100 IU/kg (3) and are in line with fewer RAOs in fully anticoagulated PCI patients over those undergoing CAG with inherent inadequate anticoagulation (4).

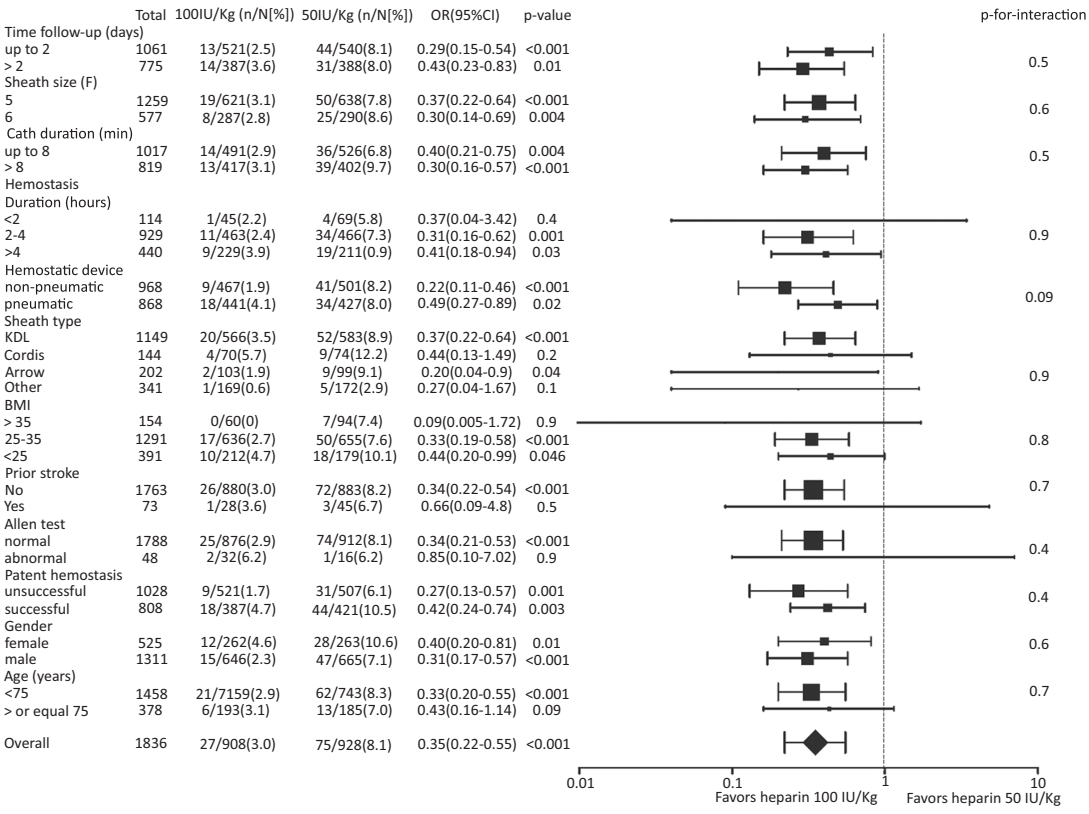
The beneficial effect of 100 IU/kg heparin was evident in all examined subgroups regardless of catheterization parameters, hemostasis techniques, or time of RA ultrasonography below or above the median of 2 days and without increases of major bleedings, other safety issues, or time to hemostasis. Indeed, interventionalists performing TR PCI only infrequently encounter major hemorrhagic or other local complications or excessively long hemostasis times despite full anticoagulation and dual-antiplatelet therapy. Although lower anticoagulation intensity may reasonably shorten time to hemostasis, our findings indicate that even intense anticoagulation in the context of a diagnostic coronary procedure results in an acceptable post-CAG delay, thereby not interfering with the anticipated early discharge of the patients. Furthermore, our integrated database findings revealed the deleterious effects of procedural difficulties and inadequate anticoagulation, indicating that both heparin dose and expertise in performing TR coronary procedures are essential issues to minimize incident RAO. Specifically, among >2,500 patients, we found an 80% risk reduction for RAO with the highest compared with the lowest heparin dose (**Figure 4**). Similarly, the updated meta-analysis strengthened the results of

TABLE 3 Outcomes

	Heparin 50 IU/kg (n = 928)	Heparin 100 IU/kg (n = 908)	p Value
Radial artery occlusion	75 (8.1)	27 (3.0)	<0.001
Local hematoma			0.60
None	715 (77.0)	694 (76.4)	
<5 cm	201 (21.7)	202 (22.2)	
5–10 cm	12 (1.3)	9 (1.0)	
>10 cm	0 (0)	2 (0.2)	
Above the forearm	0 (0)	1 (0.1)	
Perforation	7 (0.8)	4 (0.4)	0.50
Arteriovenous fistula	1 (0.1)	0 (0)	1.00
Pseudoaneurysm	1 (0.1)	3 (0.3)	0.40
Compartment syndrome	0 (0)	1 (0.1)	0.50
BARC type 2 bleeding	16 (1.8)	20 (2.2)	0.30
BARC type 3 bleeding	0 (0)	0 (0)	NA
Blood transfusion	0 (0)	0 (0)	NA
Spasm			0.06
None	849 (91.5)	814 (89.6)	
Mild	51 (5.5)	52 (5.7)	
Moderate	20 (2.2)	38 (4.2)	
Severe	8 (0.9)	4 (0.4)	

Values are n (%).
BARC = Bleeding Academic Research Consortium; NA = not applicable.

FIGURE 3 Stratified Analyses of Radial Artery Occlusion



We found no significant interactions between the studied subgroups, indicating that more intense anticoagulation was beneficial in all examined subgroups.

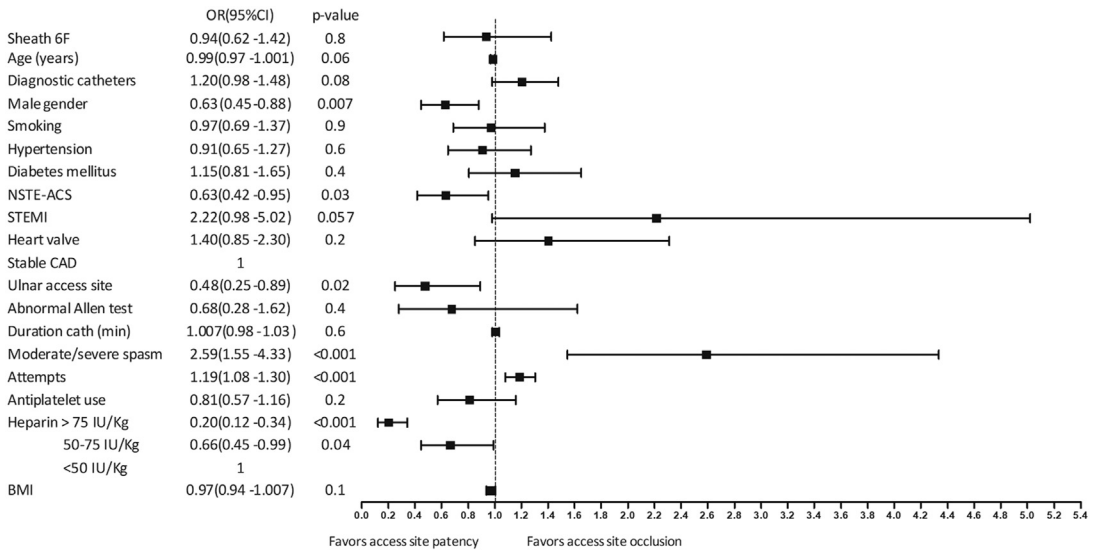
our previous work (4) regarding the benefit of more versus less intensive anticoagulation (Online Figure 2). Therefore, the overall results of the current trial provide several lines of evidence that adequate anticoagulation is a straightforward and simplifying measure to increase RA patency rates.

PRIOR STUDIES. It is of interest that the interventional cardiologists have not fully realized the magnitude of the CAG-associated hazard of RAO or the preventive effect of anticoagulation. In a significant minority of TR procedures, patients do not receive adequate heparin dose or do not have their RA patency status checked (5). Yet an occlusion of the RA is relatively common despite the short-lasting nature of CAG (3,6). Furthermore, some patients once informed may prefer the <1% absolute additional risk for major bleeding with a TF approach (11-13) rather than the more frequent risk for an RAO surrounding the anticoagulation recommendations of current guidelines (1,11,14).

The RA has a much smaller caliber compared with the femoral artery. Imaging observations indicate ubiquitous vessel trauma after TR coronary procedures (15,16). Multiple RA alterations may persist for several weeks and predispose to RAO, with women being more vulnerable in this respect (11,14-16).

Several measures have been proposed to encounter RAO, including smaller sheaths, diverse hemostatic devices (11,17-22), and the patent hemostasis technique (7,23,24). In 2 recent studies, this technique, in combination with ipsilateral ulnar artery compression, resulted in a low RAO frequency (23,24). In both studies, patency of the RAO was not uniformly assessed using vascular ultrasound. Because the feasibility of the patent hemostasis technique may be as low as <80% (23,24) and dedicated personnel are required to ensure an adequate plethysmographic signal for ongoing vessel patency, this approach represents an important limitation in its routine use in busy

FIGURE 4 Predictors of Arterial Access Site Occlusion in the Pooled Data



Arterial occlusions were independently associated with female sex, radial artery use, lower anticoagulation intensity, spasm, and multiple access-site attempts as well as coronary angiography indication for stable disease. Heparin dose of >75 IU/kg versus <50 IU/kg conferred an 80% risk reduction.

laboratories. Moreover, ipsilateral ulnar artery compression either routinely or to ensure recanalization of an RAO (23,24) raises safety issues that could be addressed only in the context of a large-scale clinical experience. Recent reports described disturbing high RAO rates between 9% and 19%, respectively, either after having applied patent hemostasis (19) or among PCI patients (21). Overall, it appears that a truly patent hemostasis technique has been poorly adopted by the interventional community, whereas hemostatic techniques have only little impact on RA patency rates (25,26).

Although CAG was performed even in study patients with abnormal Allen test results, and 3 RAOs occurred in these patients, no clinical sequalae were observed, thereby confirming experience both from our (3) and other (27,28) studies. This is in keeping with prior evidence showing that recruitment of ulnar circulation occurs acutely in these patients during catheterization and prevents possible hand ischemic occurrences (29). In the MATRIX trial, patients were also eligible irrespective of Allen test results, and no hand complications were observed (28). Our findings confirm and extend the feasibility and safety of radial catheterization in patients in whom ulnar circulation is not yet properly developed and further question the usefulness of the Allen test to select patients for TR catheterization.

STUDY LIMITATIONS. The main limitation of the present trial is that almost 50% of the initially randomized patients were excluded after randomization. A confirmatory randomization study comparing an extra heparin dose or not at the time of sheath removal would be desirable.

The operators in this study were not blinded to the allocation arm of each patient. However, the assessment of entry-site and bleeding complications was performed by physicians who were blinded to the previously administered heparin dose. Similarly blinded were the physicians who performed all vascular sonographic studies.

The absence of a shared rigid protocol for post-procedural hemostasis may be a subject of critique. However, this RCT reflects more closely real-world practice of the hemostasis approach after TR catheterization and reveals similar efficacy of intense anticoagulation in all examined subgroups (**Figure 3**).

This study was not powered to assess differences in major bleeding rates between groups. Overall, the 0% rate of BARC type 3 and the very low incidence of BARC type 2 bleedings appear reassuring, but bleeding events remote from the access arterial site, which are identified largely in patients with longer hospital stays, remain a relevant issue requiring further investigation.

We did not assess activated clotting time upon sheath removal. Activated clotting times would probably have enabled us to calibrate more precisely the needs of our study patients in terms of anticoagulation intensity for more robust reduction of incident RAO. Further research on this topic is warranted.

CONCLUSIONS

The administration of a high heparin dose during TR diagnostic procedures resulted in a striking reduction of early RAO rates compared with a standard anticoagulation regimen. This benefit was evident without meaningful hemostasis prolongation. Because as many as every tenth patient may be at RAO risk and in view of existing large practice disparities regarding heparin use and appropriate dose (30), intensive anticoagulation should be considered the standard approach for RAO prevention during CAG.

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PERSPECTIVES

WHAT IS KNOWN? RAO following CAG is frequent. Higher versus lower heparin dose is beneficial, but the optimal anticoagulation intensity is uncertain.

WHAT IS NEW? We found that PCI-equivalent compared with standard heparin dose reduced occlusion rates by 65% without meaningful hemostasis prolongation or bleeding events.

WHAT IS NEXT? A future trial that randomizes patients by adding heparin immediately before sheath removal in the experimental arm as compared with the initially given heparin dose in the standard anticoagulation arm is warranted. This randomization approach would result in avoiding the exclusion of PCI and crossover patients. Such a study could be coupled with information of activated thromboplastin times at sheath removal to allow more precise patient management.

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APPENDIX For supplemental figures and tables, please see the online version of this paper.