

Hemorrhagic and Ischemic Outcomes After Bivalirudin Versus Unfractionated Heparin During Carotid Artery Stenting

A Propensity Score Analysis From the NCDR

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Background—The direct thrombin inhibitor, bivalirudin, is associated with similar efficacy and superior safety in patients undergoing percutaneous coronary intervention. However, the role of direct thrombin inhibitors in carotid artery stenting is not well defined. The objective of this study was to compare the safety and effectiveness of bivalirudin and unfractionated heparin (UFH) for carotid artery stenting. We hypothesized that bivalirudin would be associated with less in-hospital postprocedure bleeding than UFH but similar rates of in-hospital and 30-day ischemic outcomes.

Methods and Results—We compared the incidence of in-hospital hemorrhagic and in-hospital/30-day ischemic outcomes among patients in the CARE Registry who underwent carotid artery stenting between May 2005 and March 2012 using bivalirudin or UFH. Propensity score matching was used to obtain a balanced cohort of 3555 patients in each treatment group. Patients treated with bivalirudin had a significantly lower incidence of bleeding or hematoma requiring red blood cell transfusions (0.9% versus 1.5%; odds ratio, 0.57 [0.36–0.89]; $P=0.01$) when compared with UFH-treated patients. The incidence of in-hospital and 30-day ischemic outcomes, including death, myocardial infarction, stroke, transient ischemic attack, and the composite outcome, death/myocardial infarction/stroke, did not differ significantly between groups.

Conclusions—Bivalirudin was associated with lower rates of hemorrhagic outcomes compared with UFH during the index hospitalization for carotid artery stenting. In-hospital and 30-day ischemic events were similar between the 2 groups. Randomized comparisons of these agents are needed to confirm these findings. (*Circ Cardiovasc Interv.* 2013;6:131-138.)

Key Words: bivalirudin ■ bleeding ■ carotid artery stenting ■ heparin

Carotid artery stenting (CAS) is an alternative to carotid endarterectomy (CEA) for preventing stroke among patients with symptomatic or asymptomatic carotid artery stenosis.^{1,2} Unfractionated heparin (UFH) is the most commonly used agent for intraprocedural anticoagulation during CAS.³ However, UFH directly activates platelets, promotes platelet aggregation, and thereby may aid in propagation of thrombus.⁴ UFH also binds to plasma proteins, resulting in a variable anticoagulant response.⁵ By comparison, the direct thrombin inhibitor, bivalirudin, does not bind to plasma proteins, conferring a more predictable dose–response profile and linear pharmacokinetics^{4,5} and inhibits both circulating and fibrin-bound thrombin. In randomized trials of patients undergoing percutaneous coronary intervention for stable and acute coronary syndromes, bivalirudin results in a lower incidence of bleeding, and, in the setting of ST elevation myocardial

infarction, is associated with lower cardiovascular and overall 30-day mortality when compared with UFH.^{6–9} Although the relative safety of bivalirudin has been extensively studied in percutaneous coronary intervention, limited data are available comparing bivalirudin with UFH in CAS.^{10,11} Although a small, single-center randomized study¹¹ demonstrated lower bleeding rates with bivalirudin compared with UFH among patients undergoing CAS, large-scale, real-world data regarding its comparative safety and effectiveness are currently lacking.

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The objective of our study was to examine the incidence of in-hospital hemorrhagic and in-hospital and 30-day ischemic outcomes among patients in the CARE Registry who underwent CAS and were treated with either bivalirudin or UFH. We hypothesized that the use of bivalirudin for CAS would be associated

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WHAT IS KNOWN

- Compared with unfractionated heparin, bivalirudin use has been associated with a lower incidence of bleeding in patients undergoing percutaneous coronary intervention for stable and acute coronary syndromes, and is associated with lower cardiovascular and overall 30-day mortality in the setting of ST elevation myocardial infarction.
- However, data comparing bivalirudin with unfractionated heparin in carotid artery stenting are limited.

WHAT THE STUDY ADDS

- Our study suggests that for carotid artery stenting, bivalirudin is associated with fewer postprocedural hemorrhagic complications than unfractionated heparin without an attendant increase in the risk of ischemic events.

with less in-hospital postprocedure bleeding than UFH but similar rates of in-hospital and 30-day ischemic outcomes.

Methods

Registry

CARE Registry is an initiative of the American College of Cardiology Foundation, the Society for Cardiovascular Angiography and Interventions, the Society of Interventional Radiology, the American Academy of Neurology, the American Association of Neurological Surgeons/Congress of Neurological Surgeons, the Society for Vascular Medicine, and the Society of Vascular and Interventional Neurology.¹² The CARE Registry is a comprehensive national registry of patients undergoing both CAS and CEA. All adult patients 18 years of age or older who undergo CAS or CEA at participating institutions are included in the Registry. Standard data definitions and collection protocols, a data dictionary, and uniform data collection tools have been developed and are posted at the National Cardiovascular Data Registry (NCDR) website: <http://www.ncdr.com/webncdr/common/>. As of March 2012, the Registry included data from 12924 CAS procedures performed at 171 sites in the United States.

Patients

Men or women aged ≥ 18 years that underwent CAS between May 2005 and March 2012 for symptomatic or asymptomatic carotid stenosis, and who received periprocedural bivalirudin or UFH were included. Exclusion criteria included receipt of anticoagulants other than UFH or bivalirudin, receipts of both UFH and bivalirudin, contraindication to UFH or bivalirudin, previous stroke that might confound the assessment of neurological end points (National Institute of Health Stroke Scale >21), acute evolving stroke, spontaneous intracranial hemorrhage within the previous 180 days, severe dementia, CAS performed under general anesthesia, and CAS performed for nonatherosclerotic extracranial carotid artery disease (fibromuscular dysplasia or spontaneous carotid artery dissection).

Anticoagulation

Preprocedure use of aspirin, clopidogrel, or ticlopidine was recorded at the time of admission. In patients receiving UFH, the dose of UFH was administered per local clinical standards. Patients receiving bivalirudin were administered a bolus of 0.75 mg/kg followed by an

infusion of 1.75 mg/kg per hour for the duration of the procedure. At discharge, prescription of aspirin, clopidogrel, or ticlopidine was at the discretion of the treating physician.

Definitions

All study definitions were derived from the CARE Registry data dictionary—elements and definitions v1.08. In-hospital adverse events (defined individually below) included new events occurring during or after the procedure but before discharge. Hemorrhagic complications included procedure-related bleeding or hematoma requiring red blood cell transfusion (primary outcome), and intracerebral hemorrhage. In-hospital vascular complications (ischemic or hemorrhagic) included (1) injury requiring open surgical repair, (2) peripheral embolization/new ischemia of extremities, and (3) pseudoaneurysm requiring thrombin injection or compression. Transient ischemic attack was defined as a focal neurological abnormality of sudden onset, lasting <24 hours, and presumed to be ischemic in origin. Ischemic stroke was defined as focal neurological abnormality resulting in residual symptoms lasting greater than 24 hours, and leading to impaired functional outcomes.

In-hospital mortality was defined as death occurring during the procedure or before hospital discharge. Acute myocardial infarction (MI) was defined as a rise and fall of cardiac biomarkers with at least 1 of the values above normal for the laboratory of the hospital (above the 99th percentile of the upper reference limit) together with evidence of myocardial ischemia defined as at least 1 of these following: ischemic symptoms, ECG changes indicative of new ischemia (new ST-T changes or new left bundle-branch block), development of pathological Q waves in the ECG, and imaging evidence of new loss of viable myocardium or new regional wall motion abnormality. Lesion characteristics included location of lesion (isolated internal carotid artery/common carotid artery or bifurcation), presence of thrombus, ulceration, calcification grade, lesion length, and preprocedure stenosis. Preprocedure stenosis (%) was calculated as follows. For stenoses in the internal carotid artery or at the carotid bifurcation, NASCET (North American Symptomatic Carotid Endarterectomy Trial) methodology was used (ie, 1-minimal luminal diameter at the lesion site/diameter of nontapering segment of internal carotid artery $\times 100$). However, if the distal lumen was collapsed from a low-flow state, the stenosis was graded as being 99% or near total occlusion. For stenosis localized to the common carotid artery, percent diameter stenosis was calculated as: 1-minimal luminal diameter /diameter of the adjacent normal segment of the common carotid artery $\times 100$.

Outcomes

The primary study outcome was bleeding or hematoma requiring red blood cell transfusion. Secondary outcomes included postprocedure intracerebral hemorrhage, periprocedural vascular complications, in-hospital death, MI, stroke, and transient ischemic attack, composite end points incorporating these outcomes, 30-day composite of death/MI/stroke, and its individual components.

Statistical Analysis

Categorical variables are presented as frequencies and percentages, and unadjusted comparisons were performed using χ^2 or Fisher exact tests where appropriate. Continuous variables are presented as mean \pm SD (median with interquartile range where non-normally distributed), and unadjusted comparisons were made using ANOVA and Mann–Whitney tests where appropriate.

We used propensity score methods to mitigate the influence of treatment selection bias introduced by the nonrandom selection of procedural anticoagulant. The propensity score for an individual is defined as the conditional probability of receiving a particular treatment (in this case bivalirudin) given the individual's covariates. To estimate these scores, we created a logistic regression model to predict the use of bivalirudin (versus UFH) conditioned on the following covariates: (1) demographic variables, such as age, sex, race, insurance; (2) clinical variables, such as hyperlipidemia, New York Heart Association functional class III or IV in past 6 weeks, previous ischemic stroke, chronic

lung disease, ischemic heart disease, Canadian Cardiovascular Society class III or IV angina within 6 weeks, dialysis, permanent pacemaker or intracardiac defibrillator, history of seizure or known seizure disorder, history of atrial fibrillation or atrial flutter, hypertension, smoker, MI within 6 weeks, moderate-to-severe mitral stenosis, peripheral arterial disease, history of heart failure, previous hemorrhage or hemorrhagic stroke, moderate-to-severe aortic stenosis, previous transient ischemic attack, diabetes mellitus, and mechanical aortic or mitral valve; (3) procedure-related variables, such as restenosis in target vessel after previous CEA, target lesion symptomatic within past 6 months, lesions difficult to access surgically, previous neck surgery, previous CEA, contralateral carotid artery occlusion, major surgery planned within next 8 weeks, previous CAS, tracheostomy, restenosis in target vessel after previous CAS, embolic protection device use, and preprocedure medication use; and (4) lesion characteristics, such as location of lesion, presence of thrombus, ulceration, calcification grade, lesion length, and preprocedure stenosis.

We performed a 1:1 nearest neighbor match on the logit of the propensity score within a caliper width of 0.2 times the standard deviation of the logit of the propensity score.¹³ The success of matching was examined by comparing standardized differences in the distribution of the covariates between the 2 treatment strategies; a difference of <10% between the 2 groups was considered acceptable. Conditional logistic regression was used to produce odds ratios and 95% confidence intervals. Statistical significance was defined as $P < 0.05$. This study was sufficiently powered (power >80%) to detect an odds ratio of 2 (or 0.5) in the primary outcome (Table in the online-only Data Supplement), and sufficiently powered for all secondary outcomes except for in-hospital all-cause mortality, MI, and intracerebral

hemorrhage; and 30-day all-cause mortality. All statistical analyses were performed using SAS Version 9.2 (SAS Institute, Cary, NC).

Results

A total of 12 924 eligible CAS procedures were identified between May 2005 and March 2012. A total of 2364 patients had at least 1 exclusion criterion presented in the Figure. After excluding these patients, the total analytic cohort numbered 10560 patients. Of these, 4135 patients (39.2%) received bivalirudin, and 6425 patients (60.8%) received UFH. Propensity score matching was used to obtain a balanced cohort of 3555 patients per group (Figure). Except for an initial phase of low enrollment within the CARE Registry (2005–2006), the proportionate use of UFH and bivalirudin remained comparable during each year of the study in the propensity-matched cohort.

Patient characteristics for the unadjusted and propensity score-matched patients are given in Tables 1, 2, and 3. The 2 groups were well matched on demographic, clinical (Table 1), and procedure-related characteristics (Table 2) after propensity matching. Similarly, preprocedural medication usage and medications at discharge were comparable between the 2 groups, except for higher statin usage in the bivalirudin group (Table 3). Rates of missing data were not statistically different between the 2 groups.

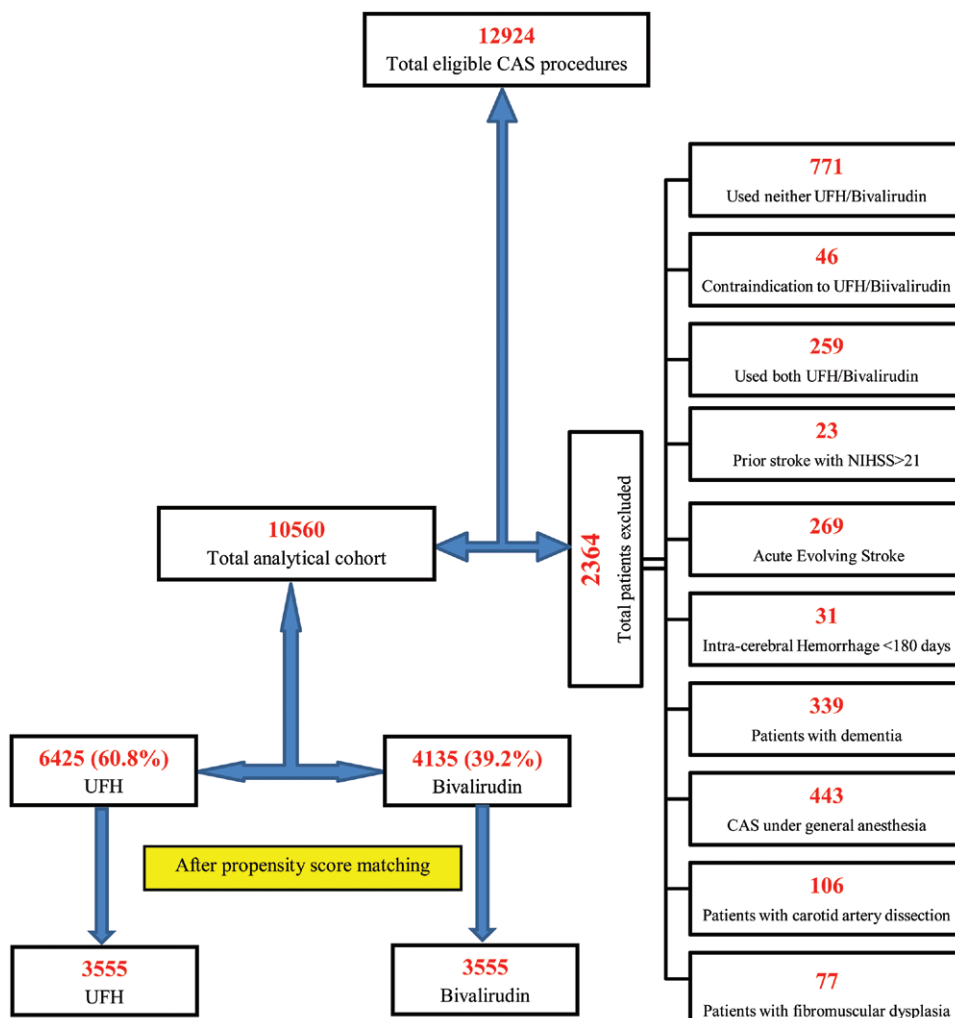


Figure. Flow chart depicting the formation of the balanced cohort. CAS indicates carotid artery stenting; NIHSS, National Institute of Health Stroke Scale; and UFH, unfractionated heparin.

Table 1. Demographic and Clinical Variables by Treatment Group Among Unadjusted and Propensity-Matched Cohort

| Demographic and Clinical Variables | Unadjusted Data | | | Propensity-Matched Data | | |
|---|-----------------|----------------------|-----------------------------|-------------------------|----------------------|-----------------------------|
| | UFH (n=6425) | Bivalirudin (n=4135) | Standardized Difference (%) | UFH (n=3555) | Bivalirudin (n=3555) | Standardized Difference (%) |
| Age | 71±10 | 71±10 | 0.9 | 71±10 | 71±11 | 1.6 |
| Age >80 | 1196 (19%) | 734 (18%) | 2.2 | 648 (18%) | 646 (18%) | 1.4 |
| Men | 3984 (62%) | 2534 (61%) | 1.5 | 2183 (61%) | 2184 (61%) | 0.1 |
| GFR <60 mL/min | 2440 (39%) | 1624 (40%) | 1.6 | 1376 (39%) | 1398 (39%) | 1.3 |
| Currently on dialysis | 185 (3%) | 87 (2%) | 5.0 | 78 (2%) | 79 (2%) | 0.2 |
| Smoker | 4756 (74%) | 3083 (75%) | 1.2 | 2651 (75%) | 2635 (74%) | 1.0 |
| Hypertension | 5819 (91%) | 3790 (92%) | 3.8 | 3260 (92%) | 3255 (92%) | 0.5 |
| Dyslipidemia | 5575 (87%) | 3777 (91%) | 14.7 | 3230 (91%) | 3225 (91%) | 0.5 |
| Peripheral arterial disease | 2842 (44%) | 1748 (42%) | 4.0 | 1532 (43%) | 1523 (43%) | 0.5 |
| Diabetes mellitus | 2439 (38%) | 1588 (38%) | 0.9 | 1394 (39%) | 1389 (39%) | 0.3 |
| Chronic lung disease | 1695 (26%) | 1309 (32%) | 11.7 | 1063 (30%) | 1072 (30%) | 0.6 |
| Previous neck radiation | 448 (7%) | 186 (5%) | 10.7 | 174 (5%) | 167 (5%) | 0.9 |
| Previous neck surgery | 440 (7%) | 176 (4%) | 11.3 | 156 (4%) | 157 (4%) | 0.1 |
| Ischemic heart disease | 3558 (55%) | 2366 (57%) | 3.7 | 2055 (58%) | 2020 (57%) | 2.0 |
| Major surgery planned w/in next 8 wk | 264 (4%) | 112 (3%) | 7.7 | 101 (3%) | 96 (3%) | 0.9 |
| MI w/in 6 wk | 162 (3%) | 87 (2%) | 2.8 | 91 (3%) | 82 (2%) | 1.6 |
| Angina CCS Class III or IV w/in 6 wk | 495 (8%) | 347 (8%) | 2.5 | 317 (9%) | 290 (8%) | 2.7 |
| History of heart failure | 1163 (18%) | 715 (17%) | 2.1 | 643 (18%) | 619 (17%) | 1.8 |
| NYHA Class III or IV w/in 6 wk | 425 (7%) | 406 (10%) | 11.7 | 298 (8%) | 300 (8%) | 0.2 |
| Recent LVEF% ≤30 | 388 (11%) | 268 (12%) | 1.2 | 236 (11%) | 225 (12%) | 1.2 |
| History of atrial fibrillation or flutter | 846 (13%) | 480 (12%) | 4.7 | 413 (12%) | 419 (12%) | 0.5 |
| Moderate-to-severe aortic stenosis | 270 (4%) | 185 (5%) | 1.3 | 155 (4%) | 152 (4%) | 0.4 |
| Moderate-to-severe mitral stenosis | 80 (1%) | 44 (1%) | 1.7 | 42 (1%) | 35 (1%) | 1.9 |
| Mechanical aortic or mitral valve | 140 (2%) | 96 (2%) | 1.0 | 93 (3%) | 79 (2%) | 2.6 |
| Permanent pacemaker or ICD | 556 (9%) | 381 (9%) | 2.0 | 337 (10%) | 323 (9%) | 1.4 |
| History of seizure/known seizure disorder | 180 (3%) | 78 (2%) | 6.1 | 70 (2%) | 71 (2%) | 0.2 |
| Previous carotid intervention | 2118 (33%) | 1135 (27%) | 12.0 | 924 (26%) | 915 (26%) | 2.4 |
| Previous CEA left or right | 1641 (26%) | 755 (18%) | 17.7 | 658 (19%) | 686 (19%) | 2.0 |
| Previous CAS left or right | 636 (10%) | 467 (11%) | 4.5 | 318 (9%) | 299 (8%) | 1.9 |
| Previous TIA | 2053 (32%) | 1275 (31%) | 2.4 | 1037 (29%) | 1092 (31%) | 3.4 |
| Previous ischemic stroke | 1009 (16%) | 473 (11%) | 12.5 | 433 (12%) | 432 (12%) | 0.1 |
| Previous hemorrhage or hemorrhagic stroke | 27 (0.4%) | 12 (0.3%) | 2.2 | 12 (0.3%) | 9 (0.3%) | 1.6 |
| Neurological event(s) prior to procedure | 3079 (48%) | 1786 (43%) | 9.6 | 1522 (43%) | 1554 (44%) | 0.5 |

CAS indicates carotid artery stenting; CCS, Canadian Cardiovascular Society; CEA, carotid endarterectomy; GFR, glomerular filtration rate; ICD, implantable-cardioverter defibrillator; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NYHA, New York Heart Association; TIA, transient ischemic attack; and UFH, unfractionated heparin.

In-Hospital Outcomes

Clinical outcomes in the propensity-matched cohort are given in Table 4. Patients treated with bivalirudin were less likely to have postprocedural (in-hospital) bleeding or hematoma requiring red blood cell transfusion compared with UFH (0.9% versus 1.5%; odds ratio, 0.57 [0.36–0.89]; $P=0.01$). However, the incidence of intracerebral hemorrhage was similar between the 2 groups (Bival, 0.1% versus UFH, 0.2%; odds ratio, 0.62 [0.20–1.91]; $P=0.41$). In-hospital composite of all-cause mortality/MI/stroke and its individual components were not significantly different between the 2 groups. The incidence of vascular complications was similar between the 2 groups (Table 4). No statistically significant interaction

was noted between anticoagulant and symptomatic status with regard to ischemic or hemorrhagic end points.

30-Day Outcomes

Thirty-day follow-up was available in 2802 (78.8%) patients with UFH and 2767 (77.8%) patients with bivalirudin ($P=0.31$). The composite of all-cause death, MI, or stroke as well as its individual components were not significantly different between the 2 groups at 30 days (Table 4).

Discussion

In this large, multicenter, multidisciplinary national Registry of patients who underwent CAS, we observed that

Table 2. Procedure-Related Variables by Treatment Group Among Unadjusted and Propensity-Matched Cohort

| Procedure-Related Variables | Unadjusted Data | | | Propensity-Matched Data | | |
|--|-----------------|----------------------|-----------------------------|-------------------------|----------------------|-----------------------------|
| | UFH (n=6425) | Bivalirudin (n=4135) | Standardized Difference (%) | UFH (n=3555) | Bivalirudin (n=3555) | Standardized Difference (%) |
| Target carotid vessel | | | | | | |
| Right | 3138 (49%) | 1985 (48%) | 1.7 | 1793 (50%) | 1701 (48%) | 5.2 |
| Left | 3287 (51%) | 2150 (52%) | | 1762 (50%) | 1854 (52%) | |
| Target lesion symptomatic w/in past 6 mo | 2666 (42%) | 1479 (36%) | 11.8 | 1255 (35%) | 1301 (37%) | 2.7 |
| Urgent cardiac surgery w/in 30 days | 210 (3%) | 99 (3%) | 5.0 | 94 (3%) | 87 (3%) | 0.9 |
| Restenosis in target vessel after previous CAS | 225 (4%) | 100 (2%) | 6.4 | 92 (3%) | 91 (3%) | 0.2 |
| Restenosis in target vessel after previous CEA | 1193 (19%) | 439 (11%) | 22.7 | 408 (12%) | 418 (12%) | 0.9 |
| Contralateral carotid artery occlusion | 742 (12%) | 331 (8%) | 12.0 | 335 (9%) | 313 (9%) | 2.2 |
| Lesion difficult to access surgically | 1072 (17%) | 550 (13%) | 9.5 | 503 (14%) | 495 (14%) | 0.6 |
| Aortic arch type I | 3312 (54%) | 1893 (48%) | 11.7 | 1922 (54%) | 1862 (52%) | 4.2 |
| Aortic arch type II | 2234 (37%) | 1577 (40%) | | 1304 (37%) | 1325 (37%) | |
| Aortic arch type III | 563 (9%) | 439 (11%) | | 329 (9%) | 368 (10%) | |
| Bovine arch | 807 (13%) | 612 (15%) | 7.1 | 433 (12%) | 528 (15%) | 7.8 |
| Contrast volume, mL | 126.0±70 | 151±75 | 34.8 | 139±66 | 146±68 | 9.9 |
| Fluoroscopy time, min | 18±13 | 16±11 | 16.4 | 16±9 | 16±9 | 3.8 |
| Procedural arterial access site | | | 2.5 | | | 0.8 |
| Femoral | 6304 (99%) | 4037 (98%) | | 3479 (98%) | 3468 (98%) | |
| Brachial/radial/axillary | 80 (1%) | 84 (2%) | | 50 (1%) | 73 (2%) | |
| Direct carotid puncture | 4 (0.1%) | 1 (0.0%) | | 2 (0.1%) | 1 (0.0%) | |
| Carotid cutdown | 6 (0.1%) | 0 (0.0%) | | 4 (0.1%) | 0 (0.0%) | |
| Other | 2 (0.0%) | 1 (0.0%) | | 2 (0.1%) | 1 (0.0%) | |
| Vascular closure device use | 3886 (61%) | 2433 (59%) | 3.3 | 2136 (60%) | 2053 (58%) | 4.7 |
| Lesion characteristics | | | | | | |
| Location of carotid lesion | | | 5.4 | | | 2.8 |
| Isolated CCA | 705 (11%) | 271 (7%) | | 263 (7%) | 252 (7%) | |
| Isolated ICA | 4383 (68%) | 3059 (74%) | | 2626 (74%) | 2598 (73%) | |
| Bifurcation | 1327 (21%) | 787 (19%) | | 666 (19%) | 705 (20%) | |
| Thrombus | 213 (3%) | 99 (2%) | 5.4 | 119 (3%) | 80 (2%) | 6.7 |
| Ulceration | 1542 (24%) | 1438 (35%) | 24.6 | 1070 (30%) | 1106 (31%) | 2.2 |
| Calcification | | | 14.5 | | | 0.6 |
| None | 2430 (38%) | 1249 (31%) | | 1245 (35%) | 1101 (31%) | |
| Mild/moderate | 2989 (47%) | 2424 (60%) | | 1824 (51%) | 2126 (60%) | |
| Dense/concentric | 944 (15%) | 392 (10%) | | 486 (14%) | 328 (9%) | |
| Lesion length (mean in mm ± SD) | 19±10 | 20±9 | 9.4 | 20±10 | 20±9 | 3.3 |
| Preprocedure stenosis (% ± SD) | 84±11 | 85±10 | 12.1 | 85±9 | 85±10 | 1.8 |

CAS indicates carotid artery stenting; CCA, common carotid artery; CEA, carotid endarterectomy; ICA, internal carotid artery; and UFH, unfractionated heparin.

compared with UFH, treatment with bivalirudin was associated with fewer hemorrhagic complications (43% lower odds) requiring red blood cell transfusion. The reduced bleeding rates were not offset by any significant increase in ischemic risk.

Balancing periprocedural ischemic and bleeding complications in patients treated with antithrombotic therapy during invasive cardiovascular procedures remains challenging. Further complicating this balance is the observation that procedure-related bleeding is an independent predictor of adverse ischemic events and mortality.^{14–16} Consequently, bleeding avoidance strategies have gained significant traction. In the

setting of percutaneous coronary intervention, these include the use of anticoagulants with a more favorable bleeding risk profile, like bivalirudin.¹⁷ In contrast, the use of bivalirudin over UFH has not been as well studied as a bleeding avoidance strategy during CAS.

Historically, attempts to compare the bleeding risk associated with various antithrombotic strategies have been undermined by the lack of a uniform definition of postprocedure bleeding. Previous studies have used variable definitions of bleeding (eg, TIMI, GUSTO, ASSENT-3, HERO-2, COMMIT, ACUITY, CURE, OASIS-5, REPLACE-2, and STEEPLE [expanded trial names available in the online-only

Table 3. Periprocedure Medication Usage by Treatment Group Among Unadjusted and Propensity-Matched Cohort

| Medications | Unadjusted Data | | | Propensity-Matched Data | | |
|----------------------------|-----------------|----------------------|-----------------------------|-------------------------|----------------------|-----------------------------|
| | UFH (n=6425) | Bivalirudin (n=4135) | Standardized Difference (%) | UFH (n=3555) | Bivalirudin (n=3555) | Standardized Difference (%) |
| Preprocedure medications | | | | | | |
| Aspirin | 5617 (87%) | 3889 (94%) | 22.5 | 3292 (93%) | 3325 (94%) | 3.6 |
| Clopidogrel | 5420 (84%) | 3751 (91%) | 20.1 | 3162 (89%) | 3198 (90%) | 3.1 |
| Ticlopidine | 78 (1%) | 45 (1%) | 4.4 | 28 (1%) | 40 (1%) | 1.6 |
| Medications at discharge | | | | | | |
| Aspirin | 5871 (92%) | 3908 (95%) | 10.0 | 3331 (94%) | 3349 (95%) | 0.6 |
| Clopidogrel | 6016 (94%) | 3947 (96%) | 10.3 | 3381 (96%) | 3389 (96%) | 2.3 |
| Ticlopidine | 71 (1%) | 44 (1%) | 1.8 | 36 (1%) | 40 (1%) | 0.4 |
| Any statin | 4733 (74%) | 3408 (83%) | 21.5 | 2697 (76%) | 2907 (82%) | 14.5 |
| Other lipid-lowering agent | 1057 (17%) | 855 (21%) | 7.0 | 624 (18%) | 723 (21%) | 3.2 |
| Warfarin | 544 (9%) | 272 (7%) | 11.3 | 271 (8%) | 242 (7%) | 7.2 |

UFH indicates unfractionated heparin.

Data Supplement.]).^{18,19} These definitions have included various single and composite hemorrhagic outcomes (eg, site-specific bleeding, drop in hemoglobin (g/dL), need for red blood cell (RBC) transfusion, hemorrhagic death, cardiac tamponade, requirement for specific interventions to stop bleeding, hypotension, disabling bleeding, hematoma size >5 cm, and need for cardiopulmonary resuscitation). Given information presently captured by the CARE Registry data collection form, we were able to measure bleeding requiring RBC transfusion, which served as our primary outcome of interest.

Few studies have compared the incidence of adverse outcomes after CAS according to anticoagulation strategy. Stabile et al¹¹ randomized 220 patients to bivalirudin or UFH during CAS with proximal embolic protection and found significantly less procedure-related thrombolysis in MI (TIMI) major and minor bleeding (7.3% versus 16.4%; $P<0.05$) in the bivalirudin arm. In an observational study, Lin et al²⁰ noted a significant decrease in hemorrhagic complications as well as 30-day stroke and death after their center switched from UFH to bivalirudin for CAS (6% bleeding rate among the first 54 patients treated with UFH compared with 2% among 146 subsequent patients who received bivalirudin [$P=0.03$]). A recent multi-center observational study (n=365) by Cogar et al²¹ found similar favorable post-procedure and 30 day outcomes with bivalirudin use in CAS. Other cohort studies have also observed significant decreases in periprocedural bleeding and 30-day stroke rates among patients treated with bivalirudin when compared with UFH.^{10,17,22} Although our findings are consistent with the aforementioned studies, our study was much larger, more representative (n=171 centers), incorporated various medical disciplines, used standard outcome definitions, involved prospective ascertainment of outcomes by independent observers, and involved more rigorous statistical techniques to adjust for potential selection bias and confounding. Collectively, the evidence base to date suggests that for CAS, bivalirudin is associated with fewer postprocedural hemorrhagic complications than UFH without an attendant increase in the risk of ischemic events. The lower hemorrhagic complication rate observed with bivalirudin was mainly driven by a significant

reduction in extracranial hemorrhagic complications; rates of intracerebral hemorrhage were similarly low in the 2 groups. This observation is important because hemorrhagic conversion of a cerebral infarction can be an important source of morbidity and mortality in patients with symptomatic carotid disease.

The relatively low-bleeding rates observed in our study may be predominantly because of the restrictive definition of bleeding used in our study. Rates of composite bleeding outcomes (eg, TIMI, GUSTO, etc) used in the aforementioned studies could not be determined given that only data on bleeding requiring RBC transfusion were available in the CARE Registry database. However, the rate of bleeding requiring RBC transfusion observed in our study is comparable with that seen among patients undergoing CAS in the Carotid Revascularization Endarterectomy versus Stenting Trial (CREST) study (1.9%).²

Finally, other attributes beyond bleeding risk may factor into the choice of anticoagulant therapy for CAS. For example, UFH is limited by variable pharmacokinetics, and the potential to cause other complications like heparin induced thrombocytopenia. In contrast, bivalirudin although cost-effective among those at elevated risk of bleeding lacks an antidote, which could be catastrophic in patients who develop intracranial hemorrhage.

Study Limitations

We cannot rule out the potential for residual unmeasured confounding or uncontrolled selection bias despite our using a propensity analysis. Furthermore, although there is standardization and uniformity in CARE Registry data collection, and quality control and participant feedback, any large national database effort is inherently imperfect. Lack of adjudicated outcomes and lack of an angiographic core laboratory are significant limitations. This study was also limited by the definition of bleeding used. The CARE Registry, in its present form, does not allow for bleeds to be characterized by the recently developed Bleeding Academic Research Consortium classification scheme,^{14,18,19} and hence as mentioned above, explains the relatively lower event rates observed in

Table 4. Clinical Outcomes by Treatment Group Among Propensity-Matched Cohort

| Clinical Outcomes | CAS With UFH (n=3555) | CAS With Bival (n=3555) | P Value | OR (95% CI) |
|--|--------------------------|----------------------------|---------|------------------|
| In-Hospital Clinical Outcomes | | | | |
| Bleeding or hematoma requiring red blood cell transfusion. | 54 (1.5%) | 31 (0.9%) | 0.01 | 0.57 (0.36–0.89) |
| Intracerebral hemorrhage | 8 (0.2%) | 5 (0.1%) | 0.41 | 0.62 (0.20–1.91) |
| Composite mortality+stroke+MI | 97 (2.73%) | 76 (2.14%) | 0.11 | 0.78 (0.58–1.06) |
| Composite mortality+MI | 27 (0.76%) | 21 (0.59%) | 0.38 | 0.78 (0.44–1.38) |
| Composite mortality+stroke | 88 (2.5%) | 66 (1.9%) | 0.07 | 0.75 (0.54–1.04) |
| All-Cause Mortality | 15 (0.4%) | 11 (0.3%) | 0.43 | 0.73 (0.34–1.60) |
| MI | 12 (0.34%) | 12 (0.34%) | 0.99 | 1.0 (0.45–2.23) |
| Stroke | 80 (2.3%) | 59 (1.7%) | 0.07 | 0.73 (0.52–1.03) |
| TIA | 40 (1.1%) | 46 (1.3%) | 0.52 | 1.15 (0.75–1.76) |
| Composite stroke+TIA | 120 (3.4%) | 105 (3.0%) | 0.31 | 0.87 (0.67–1.14) |
| Vascular complications | 19 (0.5%) | 23 (0.6%) | 0.54 | 1.21 (0.66–2.23) |
| 30-Day clinical outcomes | | | | |
| Patient follow-up available, n (%) | 2802 (78.8%) | 2767 (77.8%) | 0.31 | |
| Composite mortality/stroke/MI | 139 (4.9%) | 120 (4.3%) | 0.29 | 0.87 (0.68–1.12) |
| Composite mortality/MI | 37 (1.3%) | 37 (1.3%) | 0.94 | 1.02 (0.64–1.61) |
| Composite mortality/stroke | 114 (4.0%) | 95 (3.4%) | 0.23 | 0.84 (0.64–1.11) |
| All-cause mortality | 22 (0.8%) | 20 (0.7%) | 0.80 | 0.93 (0.50–1.70) |
| MI | 25 (0.9%) | 25 (0.9%) | 0.95 | 1.02 (0.58–1.78) |
| Stroke | 102 (3.6%) | 83 (3.0%) | 0.20 | 0.82 (0.61–1.11) |

CAS indicates carotid artery stenting; CI, confidence interval; MI, myocardial infarction; OR, odds ratio; TIA, transient ischemic attack; and UFH, unfractionated heparin.

our study. Although 30-day outcome data were not available for all patients in our study, the rate of incomplete outcome ascertainment was uniform across treatment groups; this loss to follow-up may have led to less precise estimates of 30-day ischemic event rates, but would not have affected our primary outcome, in-hospital bleeding. This study was sufficiently powered (power >80%) to detect an odds ratio of 2 (or 0.5) in the primary outcome (Table in the online-only Data Supplement), and sufficiently powered for all secondary outcomes except for in-hospital all-cause mortality, MI, and intracerebral hemorrhage; and 30-day all-cause mortality. Finally, data on operator experience in CAS, which might influence both ischemic and hemorrhagic procedural risk, are unavailable in the CARE Registry.

Conclusions

Use of bivalirudin for CAS was associated with lower rates of hemorrhagic complications than UFH without an attendant increase in the incidence of in-hospital or 30-day ischemic outcomes. The planned ENDOvascular interventions with angioMAX (ENDOMAX) trial (n≈4000) will randomize patients undergoing endovascular interventions (including carotid stenting) to UFH versus bivalirudin to assess the risk of hemorrhagic complications and net adverse clinical events (NACE) of death, MI, stroke, and major bleeds.

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Disclosures

Dr Aronow is a nonpaid consultant for the Medicines Company and a member of its ENDOMAX trial Steering Committee. The other authors have no conflicts to report.

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