In the past decade, carotid artery stenting (CAS) has been carefully studied as a treatment for symptomatic and asymptomatic carotid artery stenosis. In the Carotid Revascularization Endarterectomy vs. Stenting Trial (CREST) trial, it was shown that the composite outcome of death, stroke, or myocardial infarction is similar for CAS versus carotid endarterectomy when performed by experienced operators. During this time period, significant advances have been made with regards to patient selection and procedural techniques. In addition, there have been improvements in embolic protection and stent technology. With these advancements, CAS outcomes have continued to improve with a low rate of peri-procedural adverse events observed in numerous single-center and multicenter studies.

In comparison with recent advances in CAS technology, intraprocedural anticoagulation during CAS has been relatively understudied. The initial randomized studies of CAS, including Stenting and Angioplasty with Protection in Patients at High-Risk for Endarterectomy, Endarterectomy versus Angioplasty in Patients with Symptomatic Severe Carotid Stenosis (EVA-3S), Stent-Supported Percutaneous Angioplasty of the Carotid Artery versus Endarterectomy (SPACE), and the International Carotid Stenting Study (ICSS), all used heparin for adjunctive pharmacotherapy. In the CREST trial, patients randomized to CAS could be treated with either heparin (86%) or bivalirudin (14%). Most of the current evidence for CAS is, therefore, based on using heparin as the intraprocedural anticoagulant. The current societal guidelines for CAS do not make a specific recommendation regarding periprocedural anticoagulation but state that either heparin or bivalirudin may be used.

A direct thrombin inhibitor, such as bivalirudin, could have significant advantages as an anticoagulant during CAS. Bivalirudin can be administered as weight-based infusion with minimal intraprocedural monitoring and predictable pharmacokinetics. In comparison, heparin has variable between-person pharmacokinetics, and the correct dose of heparin for the goal level of anticoagulation (typically an activated clotting time of 250–300 s) is not always predictable. Heparin may also cause platelet activation, may require frequent monitoring of the activated clotting time, and may cause heparin-induced thrombocytopenia. The more uniform and consistent anticoagulation obtained with bivalirudin could, therefore, translate into a lower risk of hemorrhagic events during CAS, thereby further increasing the overall safety of CAS.

**Bivalirudin in Coronary and Peripheral Arterial Interventions**

Bivalirudin has been extensively studied in the setting of percutaneous coronary interventions among a wide spectrum of patients. In patients with stable coronary artery disease or unstable angina, the Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment (HORIZONS-AMI) trial reported both reduced major bleeding and a reduction in long-term mortality among patients with ST-segment-elevation myocardial infarction randomized to bivalirudin versus heparin plus IIb/IIIa inhibitor. More recently, the Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI) trial reported both reduced major bleeding and a reduction in long-term mortality among patients with ST-segment-elevation myocardial infarction randomized to bivalirudin versus heparin plus IIb/IIIa inhibitor. On the basis of these studies, bivalirudin is associated with a ≥40% reduction in major bleeding and a possible reduction in mortality, especially in the highest risk patients.

Bivalirudin has also been studied in peripheral arterial interventions, albeit in less detail. The Angiomax Peripheral Procedure Registry of Vascular Events (APPROVE) trial was a single-arm study of 505 patients treated with bivalirudin during iliac, renal, or femoral interventions. The authors reported a low rate of ischemic events (1.4%) and protocol-defined major hemorrhage rates of 2.2%. Other single-center registries have also confirmed the safety of bivalirudin in peripheral arterial interventions, with a consistent theme of low access-related bleeding rates and no apparent increase in intraprocedural thrombotic events when compared with observational controls.

The only published data on the use of bivalirudin for CAS consist of small observational studies and 1 single-center randomized trial. The largest observational study of bivalirudin for CAS included 536 CAS procedures and reported very low rates of major bleeding (0.7%) and a 30-day stroke or death rate of only 1.7%. The 1 randomized study of CAS included...
220 asymptomatic and symptomatic patients treated with proximal embolic protection and randomized to bivalirudin or heparin. The use of bivalirudin was associated with a lower rate of combined thrombolysis in myocardial infarction major and minor bleeding (7% versus 16%) and no difference in rates of ischemic or hemorrhagic stroke. Because patients in this study were treated solely with proximal embolic protection and attendant larger sheath sizes (8–10 French), these results may not apply directly to the larger population of CAS, whereas smaller sheath sizes are often used in conjunction with distal embolic protection. More data on the relative safety and efficacy of bivalirudin in comparison with heparin are, therefore, needed to guide clinical practice.

Anticoagulation During Carotid Artery Stenting in the Carotid Artery Revascularization and Endarterectomy Registry

In this issue of *Circulation: Cardiovascular Interventions*, Wayangankar et al report the outcomes of bivalirudin versus heparin as an anticoagulant during CAS among patients in the National Cardiovascular Data Registry–Carotid Artery Revascularization and Endarterectomy (NCDR-CARE) Registry. The study cohort included 10,560 patients, with 4,135 patients (39%) treated with bivalirudin as the sole anticoagulant. The overall rates of in-hospital bleeding were lower: 1.5% among the matched cohort treated with heparin and 0.9% among patients treated with bivalirudin. The rate of closure device use (61% and 59%) was similar between groups. After propensity matching to adjust for baseline differences in treatment selection, use of bivalirudin during CAS was associated with a decreased odds (odds ratio, 0.57; 95% confidence interval, 0.36–0.89) of in-hospital bleeding requiring blood transfusion. There was no difference between groups in neurological end points, including stroke, intracerebral hemorrhage, or transient ischemic attack. There was also no association between anticoagulant choice and 30-day major adverse cardiovascular events.

The study by Wayangankar et al has several strengths. These include its large size and use of standardized outcomes measures. The Carotid Artery Revascularization and Endarterectomy Registry currently includes 171 sites in the United States. Although the study is observational in nature, the 2 groups were similar enough in measured baseline characteristics that propensity weighting likely reflects the true effect of bivalirudin in the overall population of patients undergoing CAS, rather than a specific subgroup of patients for whom bivalirudin was preferentially used. The major weakness of the study relates to the imperfect nature of assessing bleeding outcomes among registry data, including the lack of rigorously adjudicated end points. Although in-hospital blood transfusion is an adverse event of clinical importance, it does not meet the more stringent bleeding definitions of other studies, such as thrombolysis in myocardial infarction major bleeding or the recently delineated Bleeding Academic Research Consortium definitions. However, the consistency of these findings with the findings of other studies of bivalirudin lend credence to the conclusion that bivalirudin during CAS is safe and associated with fewer adverse bleeding events than heparin without attendant increases in adverse neurological outcomes.

Do the results of the current study suggest that bivalirudin should be the anticoagulant of choice among all patients undergoing CAS? The 39% use of bivalirudin in the current report suggests that a significant percentage of physicians have already adopted bivalirudin as their anticoagulant of choice during CAS. There are likely many reasons for this adoption despite the lack of previous data specific to CAS. Bivalirudin has consistently been associated with decreased rates of hemorrhagic complications in numerous studies, and the association of major bleeding with subsequent mortality among studies of percutaneous coronary intervention makes a strong argument for increased use of bivalirudin. However, other strategies to reduce bleeding complications may also be efficacious, including dedicated use of ultrasound-guided micropuncture access, closure devices, or radial artery access. Bivalirudin is, therefore, 1 part of an overall procedural strategy for successful CAS with the lowest possible rate of procedural complications.

Bivalirudin on the HORIZON

As endovascular procedures continue to rise in number, specific studies are required to examine the effect of novel anticoagulants and antiplatelet agents on procedural outcomes. The potential for access-related complications (eg, groin hematoma, bleeding requiring transfusion) may even be greater for noncoronary procedures, because of the high prevalence of concomitant peripheral arterial disease. There are also unique, vascular bed–specific end points, such as the risk of intraprocedural stroke during CAS, that need to be rigorously assessed in randomized trials of these agents. The Endovascular Interventions with Angiomax (ENDOMAX) trial, which will randomize patients to heparin versus bivalirudin during peripheral arterial procedures, will assess the incidence of major bleeding rates and net adverse cardiovascular events among patients undergoing peripheral arterial interventions. This study will include CAS as at least 25% of the overall cohort. With this data in hand, new evidence for optimal treatment strategies in peripheral arterial interventions will be on the immediate horizon.

Disclosures

Dr Laird is a consultant/advisory Board Member for Abbott Vascular, Bard Vascular, Boston Scientific, Covidien, and Medtronic. He also receives research support from Atrium Medical and WL Gore. Dr Armstrong has no conflicts to report.

References


**Key Words:** Editorials  ■ anticoagulation ■ bivalirudin ■ carotid stenting ■ heparin