Use of Protamine for Anticoagulation During Carotid Endarterectomy
A Meta-analysis

Karina A. Newhall, MD; Elizabeth C. Saunders, BA; Robin J. Larson, MD, MPH; David H. Stone, MD; Philip P. Goodney, MD, MS

**IMPORTANCE** Protamine sulfate can be administered at the conclusion of carotid endarterectomy (CEA) to reverse the anticoagulant effects of heparin and to limit the risk for postoperative bleeding. Protamine use remains controversial owing to concern for increased thrombotic complications with its use.

**OBJECTIVE** To review the evidence for and against protamine use, both in its association with increased thrombotic complications and with decreased bleeding.

**DATA SOURCES** We searched Medline (1946-2014), EMBASE (1966-2014), Cochrane Library (1972-2014), clinical trial registries (World Health Organization International Clinical Trials Registry and clinicaltrials.gov), and abstracts from conferences of the Society of Vascular Surgery (2002-2014) and American Heart Association Scientific Sessions (1980-2014) in November 2014. No language restrictions were applied.

**STUDY SELECTION** We included clinical trials and observational studies comparing reversal of heparin with protamine sulfate vs no reversal in patients undergoing carotid revascularization and reporting stroke during hospitalization. Of 360 records screened, 12 studies (3%) of CEA were eligible for data pooling.

**DATA EXTRACTION AND SYNTHESIS** Two reviewers extracted data and assessed quality. Random-effects models were used to summarize relative risks (RRs).

**MAIN OUTCOME AND MEASURE** Stroke after CEA.

**RESULTS** We included 12 observational studies involving 10,621 patients in the meta-analysis. Event rates did not differ significantly between patients who received protamine vs those who did not for the following outcomes: stroke (RR, 0.84; 95% CI, 0.55-1.29; I² = 15%; 9 studies), myocardial infarction (RR, 0.89; 95% CI, 0.53-1.51; I² = 0%; 3 studies), or mortality (RR, 0.9; 95% CI, 0.62-1.29; I² = 0%; 7 studies). The use of protamine was associated with a significant decrease in major bleeding complications requiring reoperation (RR, 0.57; 95% CI, 0.39-0.84; I² = 32%; 10 studies).

**CONCLUSIONS AND RELEVANCE** Based on available evidence, the use of protamine following CEA is associated with a reduction in bleeding complications, without increasing major thrombotic outcomes, including stroke, myocardial infarction, or death.
While carotid revascularization reduces the long-term risk for stroke when compared with medical treatment alone, the procedure carries with it an increased risk for stroke in the perioperative period, estimated at 3% to 7%. Standardization of processes of care has helped to make carotid surgery safer in recent years. For example, heparin is routinely administered to reduce thrombus formation during artery clamping. However, while heparin use is essentially universal, reversal of heparin with protamine is not. Some surgeons reverse heparin with protamine at the conclusion of the procedure to limit bleeding; other surgeons do not, citing concern that protamine reversal increases the risk for thrombotic events, namely stroke.

Uncertainty about the risks of reversing heparin with protamine is reflected in ongoing variation of practice patterns. Studies have described up to 5-fold variation in the use of protamine, ranging from less than 20% of procedures to nearly 100% by surgeons. Concern for thrombotic complications with protamine use stems from early trials that showed increased risk for stroke with protamine. However, several observational studies have failed to replicate this increase in stroke rates or other thrombotic complications among patients receiving protamine following carotid endarterectomy (CEA). These studies showed a lower risk for bleeding when protamine was used, suggesting that protamine is effective in limiting the risk for bleeding after carotid surgery. Reported risks for bleeding during CEA vary as well, from 1.2% to 12%, owing in part to a lack of standardized definitions. Determining whether protamine is associated with lower rates of bleeding after CEA is an important goal because bleeding carries significant risk for airway compromise or reoperation—both independent risk factors for perioperative mortality.

Therefore, we performed a meta-analysis of evidence relating both stroke and bleeding with protamine use in carotid artery revascularization. A better understanding of the relationships between protamine use, stroke, and bleeding across existing randomized and observational studies will help determine whether protamine use is justified in clinical practice. Because of limited literature regarding protamine in carotid stenting and the different nature of bleeding complications between stenting (at the access site) and surgery (in the neck), our quantitative analysis was limited to CEA.

Methods

Review Protocol
Prior to conducting the review, we outlined our planned approach to the identification and selection of the studies. Meta-Analyses of Observational Studies in Epidemiology guidelines were used to report methods and findings (eAppendix 1 in the Supplement). The original protocol is available on request.

Study Eligibility Criteria
We aimed to include all studies that addressed the use of protamine in carotid revascularization. The following eligibility criteria were specified: (1) the design was a randomized clinical trial, retrospective or prospective cohort, nested case-control, before-and-after study, or secondary analysis of a randomized trial; (2) the population included adult patients undergoing any carotid procedures who were therapeutically anticoagulated with heparin; (3) the intervention/exposure was protamine sulfate to reverse heparin at the end of the procedure; (4) the comparison was no reversal of heparin; and (5) the study reported incidence of stroke during hospitalization. Our analysis focused on CEA, although we included the relevant stenting studies in the Table.

Outcome Measures
Stroke was the primary outcome of interest. Any type or severity of stroke was included in the analysis as long as it was diagnosed using objective criteria. Secondary outcomes included thromboembolic complications (death, myocardial infarction [MI], and transient ischemic attack). To capture the potential benefits of protamine use, postoperative bleeding events were examined as a secondary outcome. Bleeding was defined as reoperation for bleeding.

Search Methods
With consultation from reference librarians, we searched electronic databases including Medline (1946-2014), EMBASE (1966-2014), and the Cochrane Library (1972-2014) during November 2014. By using MeSH terms and key words, we created sets for the various carotid procedures (CEA or carotid artery stenting) and the exposure (protamine). To find studies including both of these components, we used the Boolean term AND to combine the 2 sets. We used no limits or language restrictions (search strategies are in eAppendix 2 in the Supplement).

Several strategies were used to identify unpublished, incomplete, or ongoing clinical trials. Two electronic trial registries were searched in October 2014: clinicaltrials.gov and International Clinical Trials Registry. Additionally, we hand searched the annual proceedings from the annual meetings of the Society for Vascular Surgery (2002-2014) and the American Heart Association Scientific Sessions (1980-2014), as well as references of included articles in November 2014.

Two reviewers independently screened the titles and abstracts of all records. Obviously irrelevant studies were excluded. Two reviewers independently reviewed the remaining full-text articles and selected relevant studies based on our inclusion criteria. At least 2 reviewers independently extracted data from each eligible study. Additional information from principal investigators was sought as needed. All discrepancies were resolved by consensus. Reviewers were health researchers and physicians, in regular consultation with senior vascular surgeons. For articles and abstracts not in English, we relied on translation by native speaker colleagues at The Dartmouth Institute for Health Policy and Clinical Practice (Lebanon, New Hampshire).

Assessment of Risk for Bias
Two reviewers independently assessed the risk for bias using a modified version of the Newcastle-Ottawa Scale, which accommodates both observational studies and randomized trials. This scale consists of 3 categories: selection, comparability, and outcome, with questions in each domain cor-
Table. Characteristics of Included Studies

<table>
<thead>
<tr>
<th>Source</th>
<th>Design</th>
<th>Patients</th>
<th>Mean Age, y</th>
<th>Characteristic, %</th>
<th>Shunt Use</th>
<th>Patch Use</th>
<th>Protamine Dose</th>
<th>Heparin Dose</th>
<th>Aspirin Use, %</th>
<th>Hypertension, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carotid endarterectomy</td>
<td>Nested case-control</td>
<td>145</td>
<td>66</td>
<td>Male</td>
<td>Symptomatic</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>27.5</td>
</tr>
<tr>
<td>Treiman et al.12, 1990</td>
<td>Retrospective cohort</td>
<td>I: 328</td>
<td>C: 369</td>
<td>I: 71</td>
<td>L: 48</td>
<td>C: 55</td>
<td>Routine</td>
<td>I: 53.6</td>
<td>C: 19.5</td>
<td>15-75 mg</td>
</tr>
<tr>
<td>Coyne et al.21, 1994</td>
<td>Prospective cohort</td>
<td>I: 11</td>
<td>C: 31</td>
<td>68</td>
<td>67</td>
<td>NR</td>
<td>35</td>
<td>0.5 mg/100 U</td>
<td>heparin</td>
<td>NR</td>
</tr>
<tr>
<td>Mauney et al.13, 1995</td>
<td>Retrospective cohort</td>
<td>I: 193</td>
<td>C: 155</td>
<td>65.9</td>
<td>I: 59</td>
<td>C: 70</td>
<td>I: 75</td>
<td>C: 85</td>
<td>NR</td>
<td>1 mg/kg</td>
</tr>
<tr>
<td>Fearn et al.11, 1997</td>
<td>Randomized prospective trial</td>
<td>I: 31</td>
<td>C: 33</td>
<td>66</td>
<td>61</td>
<td>NR</td>
<td>6.5</td>
<td>C: 24</td>
<td>20-64 mg</td>
<td>3500-7000 IU</td>
</tr>
<tr>
<td>Salles et al.22, 1997</td>
<td>Retrospective cohort</td>
<td>I: 33</td>
<td>C: 69</td>
<td>40% &gt; 70</td>
<td>66</td>
<td>53.9</td>
<td>10</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Dellagrammaticas et al.16, 2008</td>
<td>Secondary analysis of RCT</td>
<td>I: 594</td>
<td>C: 1513</td>
<td>I: 70</td>
<td>L: 68</td>
<td>C: 70</td>
<td>L: 57</td>
<td>NR</td>
<td>I: 50</td>
<td>25 mg</td>
</tr>
<tr>
<td>Stone et al.14, 2010</td>
<td>Retrospective cohort</td>
<td>I: 2087</td>
<td>C: 2500</td>
<td>I: 69</td>
<td>C: 70</td>
<td>I: 60</td>
<td>L: 34</td>
<td>C: 38</td>
<td>NR</td>
<td>I: 91</td>
</tr>
<tr>
<td>Liu et al.24, 2013</td>
<td>Retrospective cohort</td>
<td>I: 75</td>
<td>C: 20</td>
<td>67</td>
<td>I: 61</td>
<td>C: 39</td>
<td>NR</td>
<td>I: 0</td>
<td>C: 1.6</td>
<td>NR</td>
</tr>
<tr>
<td>Mazzalai et al.15, 2014</td>
<td>Prospective cohort</td>
<td>I: 201</td>
<td>C: 1294</td>
<td>I: 76</td>
<td>C: 75</td>
<td>I: 71</td>
<td>L: 71</td>
<td>C: 65</td>
<td>I: 10.5</td>
<td>C: 15</td>
</tr>
<tr>
<td>Morales-Gisbert et al.17, 2014</td>
<td>Nested case cohort</td>
<td>502</td>
<td>67</td>
<td>82.9</td>
<td>46</td>
<td>21.9</td>
<td>91.6</td>
<td>NR</td>
<td>3000-5000 IU</td>
<td>28.8</td>
</tr>
<tr>
<td>Carotid stent</td>
<td>Secondary analysis of RCT</td>
<td>2014</td>
<td>71</td>
<td>(median)</td>
<td>63.4</td>
<td>24</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>McDonald et al.26, 2013</td>
<td>Nested case cohort</td>
<td>I: 555</td>
<td>C: 555</td>
<td>I: 71</td>
<td>C: 71</td>
<td>I: 55</td>
<td>C: 54</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

Abbreviations: C, control; I, intervention; NR, not reported; RCT, randomized clinical trial.

* Any dose.

responding to study quality. A study received a star in each category when it met the definition for high quality. Discrepancies were resolved by consensus. The results of the risk for bias assessment informed the sensitivity analyses (eAppendix 3 in the Supplement).

Statistical Analysis
Relative risks (RRs) were used to summarize those studies amenable to quantitative pooling. Three otherwise eligible studies were excluded from the meta-analysis of stroke.17,18,21 These studies did not specify whether the patients who experienced stroke had received protamine, and adequate data could not be obtained. As they otherwise met inclusion criteria, these studies were included when possible in the analysis of secondary outcomes.

Data Synthesis
Review Manager version 5.3 (Cochrane Collaboration) was used to calculate summary estimates using both fixed- and random-effects models. Findings were reported based on random-effects models to account for heterogeneity among treatment effects across studies.

Assessment of Heterogeneity
Heterogeneity among the study findings contributing to each summary was estimated based on Review Manager output. Excess heterogeneity was considered present if either the I² (inconsistency) was greater than 50% or the P value was less than .10 and identification of responsible studies was attempted. Both method and clinical characteristics of studies were examined for possible explanations. Summary estimates were recalculated based on the largest group of homogeneous studies that could be combined.

Assessment of Reporting Biases
To assess for evidence of publication bias, funnel plots of stroke and bleeding risk were created in Review Manager. Authors examined plots for an inappropriate correlation between sample size and effect size.

Subgroup Analyses
We had planned subgroup analysis by routine protamine use and use of dual antiplatelet agents prior to starting the analysis. However, we were unable to perform these analyses owing to a lack of usable data. A post hoc analysis of patch
angioplasty and shunt use was performed after it was noted that this characteristic differed significantly among groups receiving and not receiving protamine in most studies.

**Sensitivity Analyses**
Three analyses were prespecified to evaluate the impact of method quality on the overall summary estimates. First, because the studies were published over 2 decades, studies were stratified by year of publication (prior to 2000 and after 2000). Second, because there were several very large studies, studies were stratified by size (<1000 patients and >1000 patients). Last, components of the modified Newcastle-Ottawa Scale and summary estimates were recalculated and restricted to studies considered at low risk for bias. We compared whether the direction, magnitude, or statistical significance of the restricted summary estimates meaningfully differed from the overall estimates.

**Results**

**Results of Search**
As shown in Figure 1, our search yielded 360 potentially relevant records. We excluded 217 based on title and abstract screening, and 129 based on full-text review. This left 14 studies that met all inclusion criteria: 12 related to CEA and 2 related to carotid stenting.11-18,21-26

**Included Studies**
The Table shows the characteristics of the 14 studies that were eligible for the review. Among the 12 studies evaluating patients undergoing endarterectomy, designs included a randomized clinical trial,11 a secondary analysis of a randomized trial,16 8 observational cohorts,12-14,21-24 a nested case-cohort,17 and a nested case-control.18 Sample sizes ranged from 42 to 4587, and baseline characteristics, including age, sex, and race/ethnicity, were similar between the protamine and no protamine groups. When mentioned, goal activated clotting time ranged from 250 to 350 seconds. Between the 2 studies evaluating patients undergoing carotid stenting, one was a pooled analysis of data from 4 randomized trials,25 while the other was a nested case-cohort study.26 Sample sizes were 2104 and 1110, respectively. Baseline characteristics including age, sex, and race/ethnicity were again similar among the protamine and no protamine groups. As a whole, the patients in the carotid stenting studies were older than those in the endarterectomy studies (age range, 70-80 years vs 60-80 years, respectively) and less likely to receive protamine (8%-8.3% vs 10%-60%, respectively).

We applied the modified Newcastle-Ottawa Scale to assess for the risk for bias among both randomized and nonrandomized trials. The most common risk for bias was related to the selection of experimental and control groups. In 5 studies, there was a risk that patients receiving protamine systematically differed from patients not receiving protamine.11,15,18,21,24 Of these, 4 failed to describe the derivation of the protamine
group, while I selectively used protamine in patients with surgical wounds deemed "excessively hemorrhagic," a term that could not be used to categorize the other procedures.

**Primary Outcome: Periprocedural Stroke**
Nine studies involving 9932 patients undergoing CEA provided usable data on stroke during hospitalization. Pooling the study findings, the rate of perioperative stroke was 62 of 3907 (1.59%) among patients who received protamine and 122 of 6025 (2.02%) among those who did not receive protamine (Figure 2A). The weighted summary estimate demonstrated no significant differences between groups (RR, 0.84; 95% CI, 0.55-1.29). Heterogeneity among the trials was low ($P = .31; I^2 = 15\%$), suggesting a consistent lack of difference in stroke risk between patients who received and did not receive protamine. These findings remained unchanged after sensitivity analyses to account for high risk for bias, older studies, or larger sample size.

Stroke definition varied across studies. Five studies defined stroke by clinical presentation (symptoms persisting >24 hours), while 1 by direct thrombus visualization, and 1 by database-defined criteria. No studies used imaging alone to define stroke.

**Secondary Outcome: Bleeding**
Ten studies involving 8553 patients undergoing CEA reported data on major bleeding, defined as bleeding events that...
Significant difference between groups,11,13,16-18,24 and 4 had no
bleeding risk reduction for patients given protamine (RR, 0.57; 95\% CI, 0.39-0.84; test for overall effect: z = 2.96 (P = .003). After sensitivity analysis, heterogeneity:

\[ \text{Heterogeneity: } \chi^2 = 8.86 (P = .018), I^2 = 32\%; \text{ test for overall effect: } z = 2.85 (P = .004). \]

M-H indicates Mantel-Haenszel.

* Heterogeneity: \( \chi^2 = 13.31 (P = .10); I^2 = 40\%; \text{ test for overall effect: } z = 2.56 (P = .01). \)

required reoperation during hospitalization.11-18,21,24 Three
studies significantly favored protamine,12,14,15 6 found no
significant difference between groups,15,16,18,24 and 4 had no
events in 1 or both arms.15,16,21,24 Pooling the findings across
studies, the risk for major bleeding was 66 of 3887 (1.7\%) among
patients who received protamine and 217 of 6225 (3.5\%) among
patients who did not. The weighted pooled estimate demon-
strated a statistically significant difference favoring the use of
protamine among all 10 studies (RR, 0.52; 95\% CI, 0.34-0.80;
\( I^2 = 40\% ; P = .10 \)). Owing to a borderline heterogeneity test,
we performed a sensitivity analysis by study design. Two
excluded studies using a single-surgeon study design11,15 cre-
ated a statistically homogenous group, which showed similar
bleeding risk reduction for patients given protamine (RR, 0.57;
95\% CI, 0.39-0.84; \( I^2 = 32\% \) ) (Figure 3).

Eleven studies provided data on the risk for any bleeding
events, which included wound hematomas and requirement of
transfusion.11,18,21,24,24 Again, the use of protamine was asso-
ciated with a significantly lower rate of bleeding events (RR,
0.46; 95\% CI, 0.38-0.73). As in the outcome of bleeding requir-
ing reoperation, the test of heterogeneity was again borderline
(\( P = .07; I^2 = 42\% \)). Sensitivity analysis was performed by study
design and excluded 2 studies using a single-surgeon study de-
sign to create a statistically homogenous group, with similar effect (RR, 0.52; 95\% CI, 0.38-0.73; \( P = .20; I^2 = 27\% \) ).

Other Outcomes: All-Cause Mortality
and Myocardial Infarction
Seven studies reported data on all-cause mortality among pa-
patients undergoing CEA.11-16 Pooling the findings, there was no
significant difference between patients who received pro-
tamine (40/3458; 1.2\%) and patients who did not (101/5933;
1.7\%) (weighted pooled estimate: RR, 0.9; 95\% CI, 0.62-1.29;
\( I^2 = 0\% \)). Similarly, 3 studies assessed rates of MI following CEA
and demonstrated no difference between study arms (RR, 0.89;
95\% CI, 0.53-1.51; \( I^2 = 0% \) )14-16 (Figure 2B and C).

Subgroup Analyses
We were able to perform a post hoc analysis of stroke risk in
studies using 2 characteristics of surgical processes of care
during CEA: shunt use and patch angioplasty. Three studies had
data stratified by patch and shunt use.11,13,23 Protamine use was
not associated with an increased risk for stroke in the patch
angioplasty or shunt subgroups (Figure 4).

Sensitivity Analyses
We performed sensitivity analyses, using only those studies
with high-quality score/low risk for bias within each domain
of the Newcastle-Ottawa Scale (selection, comparability, and
exposure). This did not meaningfully alter the study findings
for stroke. Within each restricted analysis, the findings be-
tween the protamine and no protamine groups did not differ
significantly. Additional sensitivity analyses based on study age
(published before 2000) or sample size (excluding the largest
studies) did not meaningfully change the risk for stroke (full
analysis shown in eAppendix 4 in the Supplement).

After repeating these restricted analyses for the major
bleeding outcome, all 7 restricted estimates continued to fa-
vor protamine and 5 remained statistically significant. When
findings were restricted to only those studies published after
2000, there was no change in stroke risk with protamine use.
However, the benefit of protamine for decreasing bleeding was
not significant when restricted only to studies published af-
ter 2000 or to larger studies, although these analyses had
heterogeneity (\( I^2 = 60\% \) and \( I^2 = 76\% \), respectively), which
could not be eliminated through further sensitivity analyses.

Publication Bias
We found no evidence of publication bias based on the fun-
el plot for stroke. However, we noted that all published
small studies strongly favored protamine with regard to the
major bleeding outcome (eFigure 1 and eFigure 2 in the
Supplement).
Protamine for Anticoagulation During Carotid Endarterectomy

Original Investigation Research

(Reprinted) JAMA Surgery

jamasurgery.com

Copyright 2016 American Medical Association. All rights reserved.
were differences among studies in perioperative use of aspirin or β-blockers, both routinely recommended. Three studies continued aspirin through the day of surgery,11,13,21 while 2 studies explicitly stopped aspirin within 1 week of surgery for most patients.15,17 Only 1 study provided information regarding use of β-blockers or statins. Finally, most studies were performed in academic centers, so these findings may not be replicable across smaller private hospitals. However, 2 of the studies were single-surgeon trials11,15 and the largest database included all levels of hospitals,14 which allows the findings to be applicable to all surgeon practices.

The risk for bias was considered low overall, based on our assessment tool. The lack of heterogeneity in stroke and bleeding rates across studies, as well as the lack of between-study differences in other outcomes (transient ischemic attack, MI, and death) suggests that our findings reflect a real effect across a range of study designs and settings.

We minimized the possibility of missing trials using multiple methods to search both published and unpublished literature. Furthermore, contact with several study authors did not reveal any additional unpublished data on the topic. We were limited by missing data for the primary outcome, despite attempted contact with the 3 authors whose stroke outcome was not stratified by protamine use.17,18,21 That noted, we performed analysis with all strokes for each study occurring within the protamine arm, and our main finding remained unchanged.

Stroke remains a difficult outcome to standardize owing to differing definitions across studies. Our study was no exception: we were unable to discern thromboembolic from other stroke etiologies, as authors often included all perioperative stroke. However, hemorrhagic stroke during CEA is not thought to be associated with procedural factors, and so the rate should be equally distributed across both groups. Furthermore, hypotension due to protamine reaction has been cited as a possible etiology for stroke: no included study included patients who experienced protamine reaction.30,31

A second difficulty in studying stroke risk is that as it becomes increasingly rare following CEA, differences related to protamine use are more difficult to discern. This trend is unlikely to have biased our findings, as our findings were stable across sensitivity analyses of older and newer studies. Furthermore, our study of protamine use in CEA had similar findings to previously published meta-analyses of the use of protamine in coronary angioplasty, which found no increased risk of stroke.22 Finally, the trials included in our analysis varied widely with regard to operative technique and patient characteristics. Despite this, diversity did not affect heterogeneity on our main outcome measure: stroke. Given the wide variety of clinical practice in CEA, both in operative technique and preoperative medical management, we think this study is more representative of the use of protamine in a real-world environment.

Other potential sources of bias in our meta-analysis might include the broad inclusion criteria, limited randomized clinical trials, lack of studies that included other procedures, inability to explore subgroups that might have explained heterogeneity, and the varied definitions for bleeding complications across studies. We performed analyses with both narrow and broad definitions of bleeding, and the benefit of protamine use remained unchanged.

Conclusions

Our study has important implications. Surgeons should consider routinely using protamine during CEA owing to the decreased risk for bleeding with its use. While the net reduction in bleeding complications is small, reoperation for any reason after CEA has the potential for increased morbidity. Given that there were fewer studies examining protamine use in carotid artery stenting, further research on protamine and carotid stenting is needed to determine whether our findings are consistent across all types of carotid revascularization.

Jamasurgery.com

The Benefit of Heparin Reversal With Protamine During Carotid Endarterectomy

Invited Commentary

Claudio Baracchini, MD; Enzo Balotta, MD

Protamine sulfate is a strong alkaline polypeptide used mainly to reverse the anticoagulant effects of heparin. When injected intravenously, the alkaline protamine combines with the acidic heparin to form a neutral salt, thereby annulling heparin’s anticoagulating properties. The controversy over heparin reversal with protamine during carotid endarterectomy (CEA) is a surgical Rorschach test. Like the inkblots psychiatrists use to probe a patient’s subconscious, reports on clinical adverse responses to protamine tell more about the reader than about the information at hand. Advocates of protamine use believe that most articles gathering disastrous reactions to protamine have been case reports, retrospective studies, or reviews. They claim that heparin reversal with protamine achieves a significant reduction in the perioperative risk for bleeding or onset of cervical hematoma needing surgical reexploration, without increasing the incidence of thrombotic complications.1-3 At the other end of the spectrum, surgeons who prefer not to reverse heparin with protamine tacitly accept a reasonable risk for perioperative bleeding complications for fear of cerebral or cardiac thrombotic complications, which can be devastating.4-6 They interpret even anecdotal reports of anaphylactic reactions, systemic