JACC: CARDIOVASCULAR INTERVENTIONS
VOL. 9, NO. 15, 2016

ISSN 1936-8798/$36.00
PUBLISHED BY ELSEVIER
http://dx.doi.org/10.1016/j.jcin.2016.06.024

EDITORIAL COMMENT

The Fuzzy Math of Anticoagulation and Access Site

When 1 + 1 Does Not Always Equal 2*

Sunil V. Rao, MD,[a] Rahman Shah, MD[b]

Performing percutaneous coronary intervention (PCI) involves choices. The operator must choose the access site, the guide catheter, the guidewire, the antithrombotic therapy, the general approach, the stent type, and the closure method. Some of these decisions can affect the success of the procedure, but it is the combination of the access site and the antithrombotic therapy that ultimately determines safety. The evolution of PCI has resulted in very high rates of procedural success and very low rates of procedural mortality, even in the highest risk patients (1). Bleeding and vascular complications are the most common adverse post-procedural events, and so-called major bleeding, as defined by multiple different scales, is associated with an increased risk for major adverse cardiovascular events, recurrent bleeding, and short- and longer term mortality (2). Given this relationship, strategies that reduce bleeding risk have been the focus of clinical research over the past decade.

Radial access and the use of the direct thrombin inhibitor bivalirudin are 2 of the most commonly studied "bleeding avoidance strategies" in large randomized trials. Combined, trials that have studied 1 or the other (or both) have included more than 40,000 patients (3,4). Given the numbers, it would seem that the best bleeding avoidance strategy should be clear. The data unequivocally support radial access as being safer than femoral access, and bivalirudin is safer than the combination of unfractionated heparin and a glycoprotein IIb/IIIa inhibitor. Where the data are not clear is when bivalirudin is compared with unfractionated heparin alone (4) and when radial access is combined with bivalirudin anticoagulation (5). Because radial access practically eliminates access-site bleeding, and bivalirudin reduces the risk for non-access-site bleeding, using radial access on a background of bivalirudin could result in the lowest bleeding risk. Only 1 trial has specifically studied this strategy (6); the bulk of the data come from post hoc analyses of the bivalirudin trials or observational studies.

SEE PAGE 1523

In this issue of *JACC: Cardiovascular Interventions*, Mina et al. (7) report a meta-analysis of 8 randomized trials including 27,491 patients to examine whether bivalirudin and radial access provide complementary bleeding reduction in patients with acute coronary syndrome undergoing PCI. They find that bivalirudin reduces bleeding in patients undergoing femoral access but not in patients undergoing radial access; similarly, radial access reduces bleeding risk in patients treated with unfractionated heparin but not in those treated with bivalirudin. The investigators should be commended for addressing an area of confusion for interventional cardiologists. Indeed, the intersection of anticoagulation and access site remains an unresolved issue in the setting of randomized controlled trials that seem to provide contradictory results. The message from this meta-analysis seems straightforward: if you are using femoral access, use bivalirudin for anticoagulation; if you are using unfractionated heparin, use radial access. But does the math add up?

Some limitations of their analysis should be noted. First, with the exception of the MATRIX (Minimizing

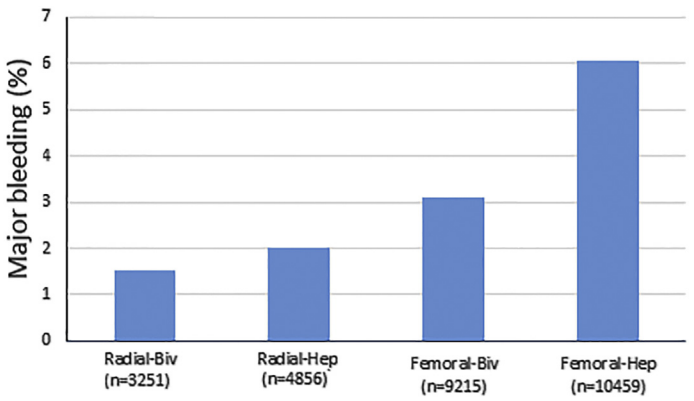
*Editorials published in *JACC: Cardiovascular Interventions* reflect the views of the authors and do not necessarily represent the views of *JACC: Cardiovascular Interventions* or the American College of Cardiology.

From [a]The Duke Clinical Research Institute, Durham, North Carolina; and the [b]University of Tennessee Health Sciences Center, Memphis, Tennessee. Both authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Adverse Haemorrhagic Events by Transradial Access Site and Systemic Implementation of Angiox) trial, the individual treating physician determined the choice of access site in the anticoagulant-based comparison. Thus, there may be unmeasured confounders in what is essentially a post hoc subgroup analysis that should be considered hypothesis generating and not definitive. Second, only trials that compared bivalirudin with unfractionated heparin with or without glycoprotein IIb/IIIa inhibitors were included, and more than a dozen trials comparing radial with femoral access were excluded. If the goal were to compare access site and anticoagulation, then a more comprehensive analysis would include all trials comparing the relevant treatment approaches. In addition, not all trials comparing bivalirudin and heparin were included in the analysis for each endpoint, thus limiting the statistical power to detect differences. The lack of power may be further compounded by the use of a random-effects model when there is a small of studies being analyzed (8). A Bayesian approach may provide more accurate estimates in this setting.

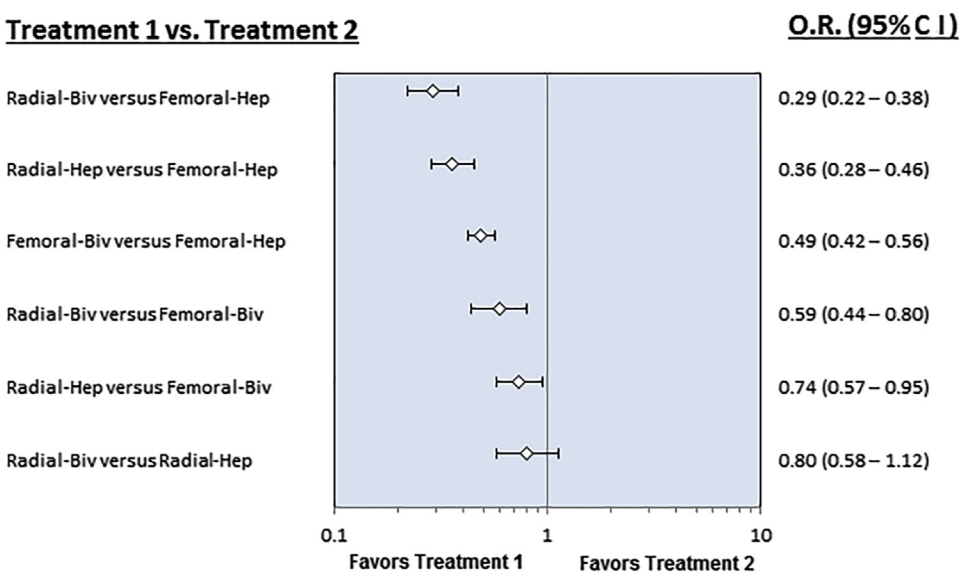
To demonstrate how a more comprehensive analysis could affect the findings, we performed a search for randomized controlled trials comparing bivalirudin with unfractionated heparin with or without glycoprotein IIb/IIIa inhibitors, as well as those comparing access site. We found 19 randomized trials that included 27,781 patients. As shown in Figure 1, the cumulative event rate for major bleeding was lowest with the combination of radial access and bivalirudin anticoagulation. A Bayesian network

FIGURE 1 Cumulative Event Rates for Major Bleeding in Randomized Controlled Trials Based on Access Site and Anticoagulation



The figure shows that the lowest rate of bleeding is seen with the combination of radial access and bivalirudin (Biv). Hep = heparin; n = total number of patients in each group.

FIGURE 2 A Network Meta-Analysis Showing the Effects of Various Combinations of Access Site and Anticoagulation Regime on Major Bleeding



The figure shows that the combination of radial access and bivalirudin (Biv) has the lowest odds of major bleeding compared with other combinations of access site and anticoagulation. The combination of radial access and bivalirudin has similar odds of major bleeding as radial access and unfractionated heparin (Hep) anticoagulation. CI = confidence interval; O.R. = odds ratio.

meta-analysis using a fixed-effects model showed that radial access plus bivalirudin was associated with the lowest odds of bleeding and that the radial approach was safer than the femoral approach irrespective of anticoagulant type (**Figure 2**). Of course, these findings should also be interpreted cautiously, because they were derived from post hoc subgroup analyses.

Aside from access site and anticoagulant choice, other factors should be considered when reducing bleeding risk. For example, the dosing of antithrombotic therapy significantly affects the incidence of major bleeding. Data from large registries indicate that women, older patients, and patients with chronic kidney disease or on dialysis are most likely to either receive doses too high for their level of renal function or be prescribed antithrombotic agents that are contraindicated (9–11). This overdosing is associated with a significantly higher risk for hemorrhagic complications. Similarly, some antiplatelet agents are contraindicated in certain patient groups because of an increased risk for bleeding; for example, patients with prior transient ischemic attack or stroke should not be treated with prasugrel. A lower maintenance dose may be considered in patients older than 75 years and those with body weight <60 kg (12). Algorithms incorporated into the electronic medical record may reduce such dosing errors. In addition to these strategies, safe arterial access is essential to reducing PCI-related vascular complications and bleeding. Although radial access nearly eliminates access-site bleeding, safe femoral arterial access into the common femoral artery is also associated with lower risks for retroperitoneal hematoma or local hematoma and pseudoaneurysm compared with higher or lower arteriotomies, respectively (13). Ultrasound guidance may be especially helpful in facilitating safe femoral arterial access (14). Other factors, such as the size of the introducer sheath and the quality and duration of post-procedural femoral artery manual compression, are also important in determining the risk for post-procedural bleeding.

The study by Mina et al. (7) serves as an important reminder that the patient outcome equation includes several variables, including access site and anticoagulation. However, reducing bleeding requires a systems approach that encompasses all potential factors affecting the patient's risk. Access site and anticoagulation are cornerstones of that approach and have been the most studied in randomized trials. Taken together, the data suggest that the combination of radial access and bivalirudin is associated with the lowest bleeding risk, but this should not distract interventional cardiologists from other aspects that can be addressed to ensure the safest patient experience.

REPRINT REQUESTS AND CORRESPONDENCE: Dr. Sunil V. Rao, The Duke Clinical Research Institute, 508 Fulton Street (111A), Durham, North Carolina 27705. E-mail: sunil.rao@duke.edu.

REFERENCES

1. Singh M, Rihal CS, Gersh BJ, et al. Twenty-five-year trends in in-hospital and long-term outcome after percutaneous coronary intervention: a single-institution experience. Circulation 2007;115:2835–41.

2. Doyle BJ, Rihal CS, Gastineau DA, Holmes DR Jr. Bleeding, blood transfusion, and increased mortality after percutaneous coronary intervention: implications for contemporary practice. J Am Coll Cardiol 2009;53:2019–27.

3. Bertrand OF, Belisle P, Joyal D, et al. Comparison of transradial and femoral approaches for percutaneous coronary interventions: a systematic review and hierarchical Bayesian meta-analysis. Am Heart J 2012;163:632–48.

4. Cavender MA, Sabatine MS. Bivalirudin versus heparin in patients planned for percutaneous coronary intervention: a meta-analysis of randomised controlled trials. Lancet 2014;384:599–606.

5. Bertrand OF, Jolly SS, Rao SV, et al. Meta-analysis comparing bivalirudin versus heparin monotherapy on ischemic and bleeding outcomes after percutaneous coronary intervention. Am J Cardiol 2012;110:599–606.

6. Valgimigli M, for the MATRIX Investigators. Design and rationale for the Minimizing Adverse Haemorrhagic Events by Transradial Access Site and Systemic Implementation of Angiox program. Am Heart J 2014;168:838–45.

7. Mina GS, Gobrial GF, Modi K, Dominic P. Combined use of bivalirudin and radial access in acute coronary syndromes is not superior to the use of either one separately: meta-analysis of randomized controlled trials. J Am Coll Cardiol Intv 2016;9:1523–31.

8. Bornstein M, Hedges LV, Higgins JP, Rothstein HR. A basic introduction to fixed-effect and random-effects models for meta-analysis. Res Synth Methods 2010;1:97–111.

9. Alexander KP, Chen AY, Newby LK, et al. Sex differences in major bleeding with glycoprotein IIb/IIIa inhibitors: results from the CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the ACC/AHA Guidelines) initiative. Circulation 2006;114:1380–7.

10. Alexander KP, Chen AY, Roe MT, et al. Excess dosing of antiplatelet and antithrombin agents in the treatment of non-ST-segment elevation acute coronary syndromes. JAMA 2005;294:3108–16.

11. Tsai TT, Maddox TM, Roe MT, et al. Contraindicated medication use in dialysis patients undergoing percutaneous coronary intervention. JAMA 2009;302:2458–64.

12. Wiviott SD, Braunwald E, McCabe CH, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 2007;357:2001–15.

13. Sherev DA, Shaw RE, Brent BN. Angiographic predictors of femoral access site complications: implication for planned percutaneous coronary intervention. Catheter Cardiovasc Interv 2005;65:196–202.

14. Seto AH, Abu-Fadel MS, Sparling JM, et al. Real-time ultrasound guidance facilitates femoral arterial access and reduces vascular complications: FAUST (Femoral Arterial Access With Ultrasound Trial). J Am Coll Cardiol Intv 2010;3:751–8.

KEY WORDS bivalirudin, radial, unfractionated heparin