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STATE-OF-THE-ART PAPER

Bleeding Avoidance Strategies

Consensus and Controversy

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Bleeding complications after coronary intervention are associated with prolonged hospitalization, increased hospital costs, patient dissatisfaction, morbidity, and 1-year mortality. *Bleeding avoidance strategies* is a term incorporating multiple modalities that aim to reduce bleeding and vascular complications after cardiovascular catheterization. Recent improvements in the rates of bleeding complications after invasive cardiovascular procedures suggest that the clinical community has successfully embraced specific strategies and improved patient care in this area. There remains controversy regarding the efficacy, safety, and/or practicality of 3 key bleeding avoidance strategies for cardiac catheterization and coronary intervention: procedural (radial artery approach, safezone arteriotomy), pharmacological (multiple agents), and technological (vascular closure devices) approaches to improved access. In this paper, we address areas of consensus with respect to selected modalities in order to define the role of each strategy in current practice. Furthermore, we focus on areas of controversy for selected modalities in order to define key areas warranting cautious clinical approaches and the need for future randomized clinical trials in this area. (J Am Coll Cardiol 2011;58:1–10) © 2011 by the American College of Cardiology Foundation

Marso et al. (1) summarized a percutaneous coronary intervention (PCI)-related performance measure by coining the term *bleeding avoidance strategies* (BAS) in their analysis of over 1.5 million patients undergoing PCI in contemporary U.S. practice. This analysis demonstrated that BAS incorporating vascular closure devices (VCDs) and bivalirudin strategies were associated with a significantly reduced bleeding risk across a broad spectrum of patients undergoing PCI. These findings challenge the recent American Heart Association (AHA) scientific statement generating a Class III/contraindication for VCDs as a method of avoiding bleeding complications (2). This controversy is clinically relevant because major bleeding complications are associated with significant cost, transfusions, lengthened hospitalization, and increased 1-year morbidity and mortality (3–7). Furthermore, implementation of best practices may improve quality of care, and guideline recommendations are a component of this process (8). Thus, identification of acceptable practices in preventing bleeding complications is of paramount clinical importance.

In this article, we address this controversy by analyzing BAS in the context of temporal trends in bleeding complications, recognizing that changes in multiple variables may explain these trends. We categorize BAS in 3 broad themes (Fig. 1)—procedural, pharmacological, and technological—to identify areas of consensus for clinical practice as well as areas of controversy that warrant further investigation.

Temporal Trends in Bleeding and Vascular Complications

Temporal trend studies from the CathPCI Registry, Northern New England Cardiovascular Disease Study Group, Mayo Clinic, and Wake Forest University demonstrate that major bleeding complications among patients undergoing PCI have decreased over time (9–13) (Fig. 2). Among >250,000 acute coronary syndrome (ACS) patients undergoing PCI in the CathPCI Registry, access site bleeding complications in 2005 were 1.2% and reduced to 0.78% in 2009 ($p < 0.001$). During this period of time, there were significant increases in the use of at least 2 potential PCI BAS strategies: the radial approach and use of bivalirudin (10). Access site bleeding improvements are not confined to

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Abbreviations and Acronyms

ACS = acute coronary syndrome(s)

AHA = American Heart Association

BAS = bleeding avoidance strategy/strategies

CI = confidence interval

GPI = glycoprotein IIb/IIIa inhibitor(s)

NCDR = National Cardiovascular Data Registry

PCI = percutaneous coronary intervention

VCD = vascular closure device

low-risk groups: women are higher risk than men for bleeding complications, yet temporal trends in women show a similar 50% reduction in bleeding and vascular complications during the past decade (12).

Bleeding complications can occur at a variety of locations. Among patients undergoing PCI, the most common site of bleeding is the vascular access site; however, in the ACS population, in which there is a substantial proportion of patients treated medically or with coronary artery bypass surgery, the majority of bleeding complications are not access site related (14). Studies indicate that gastrointestinal bleeding is the most common non-access site of hemorrhage among ACS patients and those undergoing PCI (15,16), and is associated with significant early mortality risk (17). There are few studies that have examined site-specific trends in bleeding, but ACS registries have come to differing conclusions on trends in overall major bleeding. The GRACE (Global Registry of Acute Coronary Events) investigators have shown a reduced frequency of major bleeding for ACS patients between 2000 and 2007 (2.6% to 1.8%; $p < 0.0001$) (18). In contrast, Roe et al. (10) examined the ACTION Registry–Get With the Guidelines and found that in-hospital bleeding complications remained unchanged between 2007 and 2009 (10). In addition, among ACS patients in the National Cardiovascular Data Registry (NCDR) CathPCI registry, gastrointestinal bleeding increased a small, but significant, amount between 2005 and 2009 (0.54 vs. 0.67%, $p < 0.0001$).

One confounding variable occurring throughout this discussion of bleeding trends and BAS is the variable definition of bleeding. This variability occurs across all registries as well as multiple different trial-based definitions (14,19,20). Not only does this make interstudy comparisons difficult or impossible, the utilization of the clinically most appropriate definition of bleeding may affect conclusions regarding relative efficacy of BAS. An example of this debate is the inclusion of large hematoma (≥5 cm) in the definition of major bleeding in some trials (21,22) or the reliance on Thrombolysis In Myocardial Infarction major bleeding to define clinical significance (14,20). Unlike other areas that have accepted uniform definitions related to important clinical endpoints (23), a unifying definition of bleeding is still being established (24).

Despite this problem with definitions, we have registry evidence that: 1) post-PCI access site bleeding has improved; 2) this improvement is seen across a broad spectrum of risk; and 3) trends in nonaccess site bleeding are unclear, and there may have been a slight increase in gastrointestinal bleeding. These temporal trend findings follow consistent evidence in randomized clinical trials for certain BAS techniques: bivalirudin (as compared with unfractionated

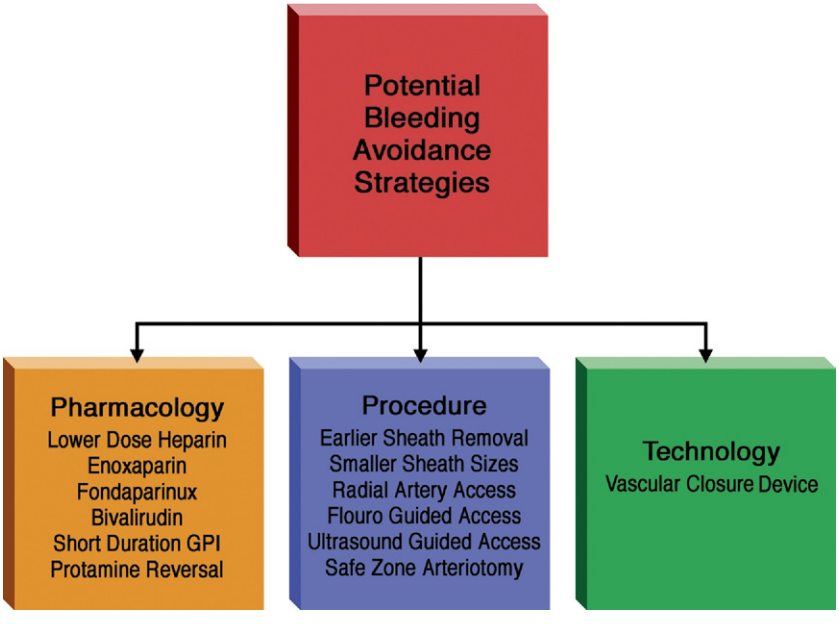

Figure 1 **Bleeding Avoidance Strategies Classified Into 3 Broad Categories**

Potential improvements in bleeding complications may be related to procedural, pharmacological, and technology changes occurring over the past 2 decades. GPI = glycoprotein IIb/IIIa inhibitor(s).

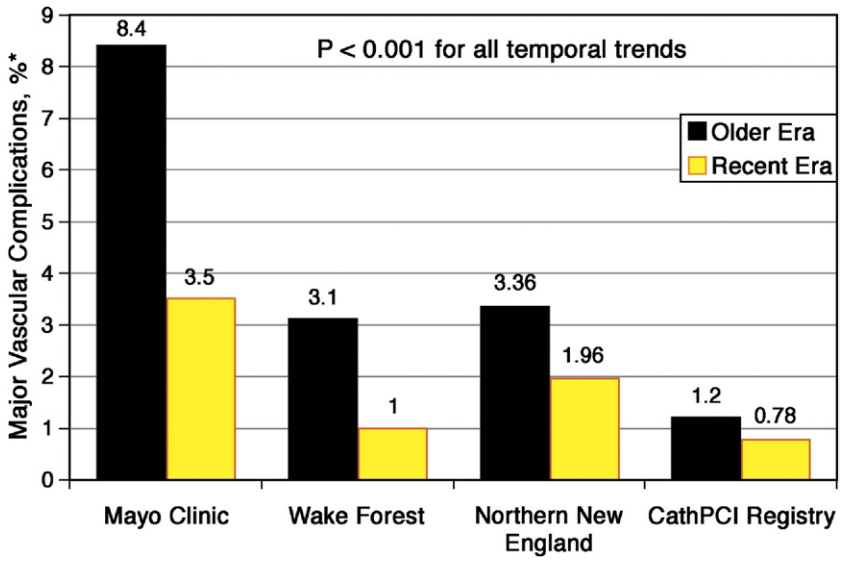

Figure 2 **Temporal Trends in Bleeding Complications After Percutaneous Coronary Intervention**

Each registry study shows a significant reduction in access site bleeding complications over time at each center or region analyzed. Bleeding definitions may vary among the registries, and the time periods of comparison are also different.

heparin/glycoprotein IIb/IIIa inhibitors [GPIs]) (25), fondaparinux (as compared with enoxaparin) (26), and the radial artery approach (as compared with the femoral approach) (27) decrease post-PCI bleeding complications by at least 40% compared with the control strategy. For other BAS techniques, randomized clinical trial evidence is not definitive (13,28,29), and registry data must support or refute the temporal trend findings. For each BAS, knowledge gaps remain, and thus controversy can be identified (Table 1). In order to better understand how each BAS may potentially be contributing to the positive temporal trends in bleeding complications, the ensuing sections will analyze areas of consensus and controversy for each approach.

Procedural Reduction in Bleeding Complications and the Radial Artery Approach

A number of procedural developments have been implemented with a goal of reducing access site–related bleeding complications (Fig. 1). Earlier sheath removal and use of smaller femoral artery sheaths have been associated with reduction in bleeding complications (9,30–32). More recent

Table 1 **Selected Bleeding Avoidance Strategies: Consensus and Controversy**

	Consensus	Controversy
Pharmacology		
Bivalirudin	Reduction in bleeding	Mechanism of mortality benefit
		Benefit compared to UFH alone
		Benefit during radial artery PCI
Fondaparinux	Reduction in bleeding	Utilization in PCI
		Catheter thrombus
Enoxaparin	Predictable anticoagulation	Intravenous, subcutaneous doses
		Monitoring
		Increased, decreased, or neutral bleeding complications
Technology		
Vascular closure devices	Improved ambulation	Increased, decreased, or neutral bleeding complications
	Improved comfort	
Procedural		
Radial artery	Reduction in bleeding	Operator issues and learning curve
		Patient suitability
		Prevention of radial artery occlusion
Optimized femoral access	Reduction in selected bleeding complications	Universal applicability and efficacy (angiography, fluoroscopy, ultrasound)

PCI = percutaneous coronary intervention; UFH = unfractionated heparin.

procedural approaches include optimization of femoral access with the goal of reducing multiple needle punctures and non-safezone arteriotomy (puncture above the inferior epigastric artery or below the common femoral artery) (28,33). Such optimization techniques include fluoroscopic-guided (34) or ultrasound-guided access, with superiority of the ultrasound guidance approach demonstrated in a single multicenter randomized trial (35). Because ultrasound-guided access is not widely used, it is unlikely that this particular modality can explain the recent favorable trends in access site bleeding complications.

A procedural approach that has been consistently associated with reduced bleeding and vascular complications is transradial cardiac catheterization and PCI (27,36,37). Both the randomized (27,37) and observational data (36) show a consistency in directionality of the effect of the radial approach on bleeding. From a pathophysiological standpoint, the underlying mechanisms related to the bleeding reduction with transradial PCI are straightforward: the radial artery is superficial, small in caliber, and easily compressed. The largest observational study involved over 593,000 patients in the NCDR CathPCI Registry undergoing femoral or radial procedures (36). This study demonstrated that the radial approach was associated with a 67% reduction in bleeding and vascular complications as compared with the femoral approach, without an increase in procedural failure. This is consistent with multiple randomized trials that have compared transradial PCI with non-radial access techniques (27,37,38).

As opposed to the CathPCI registry analysis, randomized trials have shown that there may be a higher rate of procedure failure with the radial approach, necessitating crossover to femoral access (27,37). This discrepancy is likely the result of selection bias inherent in observational studies conducted in countries where there is low uptake of the radial approach (such as in the United States) (39). The success of transradial PCI may be dependent on operator experience (40–42). Although a minimum number of procedures necessary to achieve competence has not been identified, the rates of procedure failure may plateau after 100 cases (43). It should be noted that crossover to the femoral approach from the radial approach may be lower at centers where the primary approach is transradial; moreover, crossover from femoral to radial access also occurs but is rarely captured in registry data.

Access site bleeding is associated with significant discomfort and patient dissatisfaction. In this context, patients appear to prefer the radial to the femoral approach (44). In addition, reduction in vascular and bleeding complications is associated with cost savings from the hospital perspective (38,41,44,45). Given these data, wider adoption of the radial approach to improve the safety of PCI is a reasonable objective. Of note, improvement of traditional efficacy measures (such as death and myocardial infarction) with the radial approach could not be demonstrated in a recently published randomized trial (RIVAL [An International Randomized Trial of Trans-radial Versus Trans-femoral Percutaneous Coronary Intervention (PCI) Access Site Approach in Patients With Unstable Angina or Myocardial Infarction Managed With an Invasive Strategy]) (37,38).

Other issues related to the radial approach that require further investigation include radiation exposure and radial artery occlusion (46). The latter appears to occur with a frequency between 0.6% and 12% (47–49). Radial artery occlusion is often asymptomatic due to the presence of collateral flow in the hand in most patients (50); however, it is not known whether transradial PCI impacts the suitability of the radial artery as a conduit for coronary artery bypass grafting. Radial artery occlusion can be minimized by the use of anticoagulation during transradial procedures, smaller catheters, and "patent hemostasis" after sheath removal (47,49).

Despite the relatively large effects of transradial PCI on bleeding complications, large registry studies show that transradial PCI accounts for <5% of U.S. PCI procedures (36); it is much more common outside the United States (39). Therefore, although the data for decreased bleeding complications with the radial approach are consistent, the low adoption rate of the radial approach in the United States makes it unlikely to be a main explanation for the decrease in bleeding complications in the United States. Given this low adoption rate for radial-mediated BAS, it is worthwhile to consider alternative (pharmacological and mechanical) BAS strategies.

Pharmacological Reduction in Bleeding Complications

Similar to the radial artery approach, pharmacological developments have already passed the test of appropriate randomized clinical trials. First, the use of unfractionated heparin with and without GPI agents has changed over the past decade. Between 1991 and 1997, 3 trials of the use of abciximab demonstrated progressive improvements in bleeding rates (30,51). Comparing the control arms of each study, which received heparin without a GPI, the overall bleeding rates decreased by 79% (8.2% in the EPIC [Evaluation of c7E3 for the Prevention of Ischemic Complications] trial vs. 1.7% in the EPISTENT [Evaluation of Platelet IIb/IIIa Inhibitor for Stenting] trial, $p < 0.001$). This improvement was attributed to reductions in the dose of heparin and the lower target activated clotting time levels in the later trials (30). The active treatment arm patients receiving abciximab also experienced a 90% reduction in vascular bleeding rates from 20.2% to 2.1% (30). Similarly, the ISAR (Intracoronary Stenting and Antithrombotic Regimen) group has recently demonstrated an association between lower heparin dosing (100 U/kg) and a reduction in bleeding complications after PCI in a comparison with a historical control group (140 U/kg) (52).

More predictable anticoagulation may be achieved with low molecular weight heparins. Enoxaparin has been exten-

sively studied, and well-designed trials have demonstrated reduction in bleeding complications with enoxaparin versus unfractionated heparin (53,54). Other studies have either shown a neutral effect on bleeding with enoxaparin (55), or an increased risk of bleeding with this agent compared with unfractionated heparin (56,57). These findings may be explained by differences in patient populations, sheath management, drug dosing, and route of administration (i.e., intravenous versus subcutaneous) (32,58). Of note, enoxaparin use has increased outside the United States in recent temporal trends studies (2000 to 2007) of acute coronary syndromes; during that period of time, bleeding has decreased (18). On the other hand, enoxaparin use has decreased in U.S. practice, and bleeding has also decreased (10). These data point to the complexity of understanding the role of any single pharmacological, technological, or procedural approach in accounting for recent favorable trends in bleeding.

Other randomized clinical trial evidence is more consistent: the indirect factor Xa inhibitor fondaparinux significantly reduces bleeding risk as compared with enoxaparin with similar rates of ischemic complications at 9 days (59,60). These benefits may be especially prominent in patients with renal dysfunction (61). Limited adoption of fondaparinux for PCI patients (due to concerns about catheter-related thrombus [59]) make this agent unlikely to be a major component of recent favorable bleeding trends. Whether recent randomized trial data on efficacy of adjunctive low-dose unfractionated heparin to prevent catheter thrombus formation impacts utilization of this agent remains to be determined (62).

Bivalirudin, a direct thrombin inhibitor, is associated with a 40% to 50% reduction in bleeding complications when compared with heparin-based strategies (25,63,64). Of note, bivalirudin does not protect against bleeding complications when used in conjunction with GPI agents (as compared with unfractionated heparin with GPI) (25). The bleeding reduction with bivalirudin compared with unfractionated heparin/GPI regimens remains significant even in the presence of lower doses of heparin: in the PROTECT–TIMI 30 (Randomized Trial to Evaluate the Relative PROTECTion against Post-PCI Microvascular Dysfunction and Post-PCI Ischemia among Anti-Platelet and Anti-Thrombotic Agents–Thrombolysis In Myocardial Infarction 30), a heparin dose of 50 U/kg was tested in conjunction with GPI and bivalirudin still maintained a significant reduction in bleeding complications (65). An even more creative way to limit the impact of unfractionated heparin dosing on GPI-related bleeding effects is to reverse heparin with protamine after PCI completion: comparison of bivalirudin against this ultimate low-dose heparin/GPI strategy, though, still reveals a significant reduction in bleeding complications with bivalirudin (66,67). More recent studies have explored the use of shorter duration or intracoronary-bolus-only administration of GPI agents to limit bleeding side effects: whether these approaches reduce bleeding compared with bivalirudin alone has not been examined (68,69). Lastly, the bleeding reduction seen with bivalirudin is not confined to selected clinical trial populations; large-scale registry studies have similarly demonstrated significant associations between reduced bleeding complications and bivalirudin utilization (1,12).

Many areas of controversy remain regarding implementation of bivalirudin in clinical practice: for example, upstream use of unfractionated heparin (with switching), dosing of clopidogrel, and mortality reduction in STEMI (ST-segment elevation myocardial infarction) trials remain areas of ongoing discussion and subgroup analysis (70–73). Even more controversial is the comparison of bivalirudin to unfractionated heparin alone (i.e., without routine use of GPI). The ISAR-REACT 3 (Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment 3) trial compared bivalirudin against heparin alone (140 U/kg) and found that bivalirudin reduced bleeding complications; unlike the bivalirudin versus heparin/GPI trials (63,64), the net efficacy of a bivalirudin strategy compared with heparin alone in this stable/unstable angina PCI population could not be demonstrated (74–76). However, the reduction in bleeding complications with bivalirudin compared with either heparin alone or heparin/GPI is consistent. Whether or not bivalirudin is superior to a lower-dose heparin strategy (or heparin reversed with protamine) has not been determined. Changes in pharmacology are a plausible component of positive bleeding temporal trends: for example, utilization of bivalirudin for PCI has increased absolutely an approximate 20% in U.S. practice between 2005 and 2009 ($p < 0.001$) with concomitant decreased use of heparin and GPI regimens (10).

Mechanical Reduction in Bleeding Complications: VCDs

A recent AHA Scientific Statement has issued a Class III (Level of Evidence: B) recommendation/contraindication related to VCDs for the purpose of reducing vascular complications (2). Manual compression of the femoral artery access site has been the gold standard in obtaining hemostasis at the access site for the past several decades. After almost 60 years of percutaneous arterial access, hemostasis by manual compression remains unchanged; the exception is the introduction of topical hemostasis patches that have not demonstrated a reduction in major bleeding complications in trials or registries (77,78).

In the early 1990s, VCDs were introduced. Koreny et al. (79) evaluated clinical outcomes from randomized clinical trials of VCDs versus manual compression. They identified 30 studies with almost 4,000 patients and demonstrated less time to ambulation and shorter length of hospitalization with VCDs as compared with manual compression. The safety analysis was neutral: neither improvement nor reduction in the rates of vascular complications with VCDs compared with manual compression could be demonstrated.

This meta-analysis is often cited as evidence of "VCD risk," but this was based upon a sensitivity analysis of only 2 of the 30 trials in which intention to treat could be identified. Nikolsky et al. (80), in a broader meta-analysis that included both randomized trials and registries, identified 30 studies with 37,066 patients comparing clinical outcomes after VCDs versus manual compression. These authors observed an overall higher risk of vascular complication with VCDs compared with manual compression when all studies were combined. But, the adverse risk of VCDs was shown to be a result of a significantly higher rate of vascular complications particularly with the VasoSeal device (Datascope, Montvale, New Jersey) compared with manual compression. Contrary to these two studies, Vaitkus (81) and the U.S. Federal Drug Administration (82) came to a different conclusion: examining 2001 data from the NCDR CathPCI Registry, the Federal Drug Administration observed findings similar to that of Vaitkus: the use of VCDs was associated with a significant reduction in vascular complications as compared with manual compression, and VasoSeal was a notable exception to those positive trends (Table 2).

Several factors are relevant in examining the use of the older data to determine the current safety of VCDs. First, VCDs may have improved over time (83), especially with the removal of the VasoSeal product (82). Second, there is a learning curve with the use of VCDs (84,85); it is possible that better patient selection and knowledge of device use itself has resulted in lower rates of vascular complications. Unfortunately, the potential benefit of these incremental changes has not been absolutely proven: the equivocal and conflicting results did not spur the VCD industry to settle the question finally and definitely with a single, large randomized clinical trial.

However, since the conflicting meta-analyses of 2004, there have been at least 5 large (>10,000 patients), broadly inclusive observational and multicenter registries evaluating the safety of VCDs (Table 2). Arora et al. (86) looked at rates of vascular complications in 12,937 patients from 2002 to 2005. They observed an almost 50% propensity-adjusted reduction in rates of vascular complications associated with VCD utilization. Ahmed et al. (12) examined the rates of vascular complications in patients undergoing PCI from the Northern New England Cardiovascular Disease Study Group from 2002 to 2007. They observed a 28% decrease in the risk-adjusted rates of vascular complications in over 13,563 women with VCDs compared with manual compression. Applegate et al. (11) evaluated rates of vascular complications in 35,016 patients over a 10-year study period, ending in 2007: VCD use was an independent factor associated with lower rates of vascular complications. Sanborn et al. performed a post-hoc analysis of the ACUITY (Acute Catheterization and Urgent Intervention Triage strategY) trial (87): in 11,621 patients, there was a significant 22% risk-adjusted decrease in the rates of vascular complications with the use of VCDs compared with manual compression. Finally, Marso et al. (1) reviewed the data from the American College of Cardiology NCDR from 2004 to 2008. Over 1.5 million patients were included in the study, with a significantly lower rate of vascular complications with VCD use compared with manual compression across a broad spectrum of risk.

An appropriately powered randomized trial is needed prior to definitive conclusions (i.e., Class I or Class III recommendations). The etiologies of favorable temporal trends is complex and not easily attributable to a single device or intervention: in the Mayo Clinic study of 17,901 consecutive patients between 1994 and 2005, major femoral vascular complications were reduced by 58% (from 8.4% to 3.5%, $p < 0.001$); notably, the use of VCDs comprised <5% of patients during the study period (9). Although the Northern New England group also demonstrated a 50% reduction in bleeding complications over time, Northern New England operators utilized VCDs in 43% of patients (12). The potential benefit of VCDs (early ambulation, comfort [13,88]) coupled with the inconsistent data regarding safety of VCDs (80,82) do not meet the burden of proof of harm; clinicians should be left in the appropriate gray area of Class II recommendations for this technology.

Table 2 Studies With 10,000 or More Patients: VCD Versus MC

First Author (Ref. #)	Year Published	N	Study Type	Endpoint	Complication Rates		p Value
					VCD	MC	
Nikolsky et al. (80)	2004	36,066	Trial and registry meta-analysis	Hematoma	OR: 1.34	95% CI: 1.01–1.79	<0.05
Tavris et al. (90)	2004	166,680	National registry (NCDR)	Any VC	1.10%	1.70%	<0.001
Tavris et al. (82)	2005	13,878	National registry (NCDR)	Any VC	OR: 0.99	95% CI: 0.77–1.28	NS
Arora et al. (86)	2007	12,937	Single-center registry	Any VC	2.40%	4.90%	<0.01
Ahmed et al. (12)	2007	13,563	Multicenter registry	Bleeding/VC	OR: 0.72	95% CI: 0.59–0.89	0.02
Applegate et al. (11)	2008	35,016	Single-center registry	Any VC	1.60%	2.10%	0.03
Sanborn et al. (87)	2009	11,621	ACUITY post-hoc	Access site bleeding	2.50%	3.30%	0.01
Marso et al. (1)	2010	1,522,935	National registry (NCDR)	Periprocedural bleeding	OR: 0.77	95% CI: 0.73–0.80	<0.05

ACUITY = Acute Catheterization and Urgent Intervention Triage strategY trial; CI = confidence interval; MC = manual compression; NCDR = National Cardiovascular Data Registry; NS = not significant; OR = odds ratio; VC = vascular closure; VCD = vascular closure device.

Systematic Reduction in Bleeding Complications and Cost Effectiveness

Systematic improvements in bleeding complications may require broad initiatives to address patient selection and BAS implementation. One approach is the application of a Bleeding Risk Score to individualize patient approaches with tailoring of therapies according to patient risk (21,74,89,90). Therapeutic strategies based upon risk stratification for bleeding complications, though, may be limited by the overlap between ischemic risk factors and bleeding risk factors (74,89). As another example, the relative benefit of VCDs as compared with manual compression may depend upon the adequacy of femoral artery access and selection of appropriate patients (28,29,34,91). The consequences of VCD closure failure are not small: Bangalore reported a VCD failure rate of 2.3% in 9,853 consecutive patients, demonstrating that VCD failure was associated with a 4.8-fold increased risk of vascular complication compared with successful VCD deployment in a propensity-matched analysis (92). Thus, systematic attempts to optimize femoral access (including potentially fluoroscopy-guided access, selected ultrasound-guided access, and routine femoral angiography [28,34,35]) in order to determine which VCDs are appropriate in selected situations warrants further study.

Even if appropriately deployed BAS conclusively reduce bleeding, can the incremental costs of bivalirudin/fondaparinux (compared with heparins) and VCDs (as compared with manual compression) be justified? The significant economic costs of bleeding and vascular complications following PCI can provide additional incentive for increased focus on bleeding reduction strategies. A detailed analysis of the incremental costs of complications based on administrative data from 335,477 Medicare beneficiaries who underwent PCI in 2002, demonstrated an incremental cost of $6,377 and an increased length of stay of 2.8 days for patients suffering a vascular complication (93).

Exploring the ACUITY randomized clinical trial data, Pinto et al. (45) determined that the use of bivalirudin was associated with a net cost savings, ostensibly through the reduction of bleeding complications. Specifically, minor bleeding events were associated with an attributable cost of $2,282, whereas major bleeding episodes were associated with an increased attributable cost of $8,658 (45). Similarly, a detailed attributable cost analysis of specific vascular and bleeding complications demonstrated significant incremental additional costs of hematoma ($1,399, 95% confidence interval [CI]: $700 to $6,955), clinically significant bleeding ($5,440, 95% CI: $2,250 to $10,226), and pseudoaneurysm formation ($6,357, 95% CI: $4,900 to $10,408) (5). Given the significant costs associated with bleeding and vascular complications following PCI, BAS may ultimately be cost-effective investments of health care.

As noted previously, the radial access strategy has been found to be associated with a significant reduction of access site bleeding complications as compared with femoral access procedures. Balancing the costs and clinical advantages of VCDs, bivalirudin, and radial access is complex. Although radial access obviates the need for VCD use, many radial access interventionalists recommend the use of specially designed hydrophilic sheaths, wires, and radial access site hemostasis devices to help improve the success and patient comfort associated with the radial artery approach. The incremental costs for these specialized radial access devices range from $55 to $75 per procedure above the costs of traditional femoral access equipment. Although there are potential advantages for bivalirudin to reduce nonaccess site bleeding in radial artery access procedures as compared with a strategy of heparin use, lesser absolute reductions in overall bleeding complications are likely to result in lesser cost effectiveness as compared with the demonstrated cost advantages in femoral access (45,94).

Consensus, Controversy, and Practice Recommendations

BAS have emerged as an evolving and important part of cost-effective, high-quality clinical practice. Consensus points from randomized clinical trials and registries are robust:

- Access site bleeding complication rates are less frequent now than 10 years ago in the setting of multiple pharmacological, technological, and procedural advances.
- Bivalirudin, fondaparinux, and lower-dose unfractionated heparin are associated with a significant reduction in bleeding complications compared with regimens incorporating higher-dose unfractionated heparin and/or GPI.
- The radial approach reduces access site bleeding compared with the femoral approach, but the slow adoption in the United States makes it unlikely to fully explain the falling rates of bleeding complications.
- The radial artery approach and vascular closure devices allow earlier ambulation and improve patient comfort compared with femoral access/manual compression strategy.
- Bleeding complications are associated with increased hospital costs, lengthened hospitalization, and mortality.

On the other hand, controversy remains regarding other aspects of BAS:

- Early meta-analyses and registry studies demonstrate harm, benefit, and neutrality of VCDs compared with manual compression, depending upon analysis of overall results versus sensitivity analyses. In contrast, 5 recent large (>10,000 patients) registries suggest a benefit for VCDs compared with manual compression. Based on these registries, a large randomized trial is warranted to prove the concept that VCDs decrease complications.
- Are BAS-related pharmacological agents necessary in the setting of the radial approach? Can U.S barriers to radial adoption be overcome?

- Finally, although bleeding is clearly associated with 1-year death, the mechanism (i.e., cessation of guideline recommended antiplatelet therapy [95]) remains speculative.

Conclusions

The coining of the term *bleeding avoidance strategies* summarizes a broad multimodality approach to quality improvement for invasive cardiovascular procedures. The trends in this area are positive, indicating that clinicians are moving in the right direction. Randomized clinical trial data are robust in many areas and allow for considerable consensus. On the other hand, controversy is both expected and warranted in areas where adequately sized clinical trials have not yet been performed. In such areas, clinical judgment, patient selection, and cautious utilization are consistent with other gray areas of current practice.

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