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Bleeding Avoidance Strategies: Consensus and Controversy

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Abstract

Bleeding complications after coronary intervention are associated with prolonged hospitalization, increased hospital costs, patient dissatisfaction, morbidity and one year mortality. Bleeding Avoidance Strategies represent 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 suggests 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), pharmacologic (multiple agents) and technological (vascular closure devices) approaches to improved access.

In this article, 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.

Keywords

bleeding; radial; pci; vascular closure device

Marso and colleagues 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 (1). This analysis demonstrated that BAS incorporating vascular closure devices (VCD) and bivalirudin strategies was 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 VCD's 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 Bleeding Avoidance Strategies 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 (Figure 1)—procedural, pharmacologic and technological—to identify areas of consensus for clinical practice as well as controversy that warrants 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) (Figure 2). Among > 250,000 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 two potential PCI BAS strategies: the radial approach and bivalirudin (10). Access site bleeding improvements are not confined to low risk groups: women are higher risk than men for bleeding complications yet temporal trends in women similarly 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, where there are 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 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 and colleagues 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 NCDR CathPCI registry, gastrointestinal bleeding increased a small but significant amount between 2005 and 2009: (0.54 vs 0.67%, $P < 0.0001$)(10).

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 inter-study comparisons difficult or impossible, the utilization of the clinically most appropriate definition of bleeding may impact 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 TIMI 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 a) post PCI access site bleeding has improved, b) this improvement is seen across a broad spectrum of risk, and c) trends in non-access 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 UFH/

GPI(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 (Figure 1). Earlier sheath removal and use of smaller femoral artery sheaths has been associated with reduction in bleeding complications (9, 30-32). More recent 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 (34) or ultrasound guided access, with superiority of the ultrasound guidance approach in a single multicenter randomized trial(35). As 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 to 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 (like the United States)(39) The success of transradial PCI may be dependent on operator experience (40-42). While 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 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. Whether this approach will also improve traditional efficacy measures like death or MI is the objective of an ongoing

randomized trial—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 (RIVAL) (37).

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

Pharmacologic Reduction in Bleeding Complications

Similar to the radial artery approach, pharmacologic 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, three 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 glycoprotein 2b3a inhibitor (GPI), the overall bleeding rates decreased by 79% (8.2% in EPIC vs. 1.7% in EPISTENT, $p<0.001$). This improvement was attributed to reductions in the dose of heparin and the lower target ACT 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 group has recently demonstrated an association between lower heparin dosing (100units/kg) and a reduction in bleeding complications after PCI in a comparison to a historical control group (140 units/kg) (52).

More predictable anticoagulation may be achieved with low molecular weight heparins. Enoxaparin has been extensively studied and well designed trials have demonstrated reduction in bleeding complications with enoxaparin vs 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 to unfractionated heparin (56, 57). These findings may be explained by differences in patient populations, sheath management, drug dosing and route of administration (ie, intravenous versus subcutaneous)(32, 58). Of note, enoxaparin use has increased outside the U.S in recent temporal trends studies (2000-2007) 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 pharmacologic, technologic 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 40-50% 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 to 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 trial, a heparin dose of 50u/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 to 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 trials remain areas of ongoing discussion and subgroup analysis(70-72). Even more controversial is the comparison of bivalirudin to unfractionated heparin alone (i.e, without routine use of GPI). The ISAR-REACT 3 trial compared bivalirudin against heparin alone (140 units/kg) and found that bivalirudin reduced bleeding complications (73); unlike the bivalirudin vs heparin/GPI trials (63, 64), the net efficacy of a bivalirudin strategy compared to 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—Vascular Closure Devices

A recent AHA Scientific Statement has issued a class III (level of evidence B) recommendation/contraindication related to VCD 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 which have not demonstrated a reduction in major bleeding complications in trials or registries(77, 78).

In the early 1990's, early generation VCD were introduced. Koreny et al evaluated clinical outcomes from randomized clinical trials of VCD versus manual compression (79). They identified 30 studies with almost 4,000 patients and demonstrated less time to ambulation and length of hospitalization with VCD as compared to manual compression. The safety analysis was neutral: neither improvement nor reduction in the rates of vascular complications with VCD compared to 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 two of the 30 trials in which intention to treat could be identified. Nikolsky et al, in a broader meta-analysis that included both randomized trials and registries, identified 30 studies with 37,066 patients comparing clinical outcomes after VCD versus manual compression (80). These authors observed an overall higher risk of vascular complication with VCD compared to manual compression when all studies were combined. But, the adverse risk of VCD was shown to be a result of a significantly higher rate of vascular complications particularly with the VasoSeal device compared to manual compression. Contrary to these two studies, Vaitkus et al(81) and the FDA(82) came to a different conclusion: examining 2001 data from the NCDR CathPCI Registry, the FDA observed findings similar to that of Vaitkus et al: the use of VCD were associated with a significant reduction in vascular complications as compared to 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 VCD. First, VCD devices 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 VCD (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 VCD (Table 2). Arora et al looked at rates of vascular complications in 12,937 patients from 2002 to 2005 (86). They observed an almost 50% propensity adjusted reduction in rates of vascular complications associated with VCD utilization. Ahmed et al examined the rates of vascular complications in patients undergoing PCI from the Northern New England Cardiovascular Disease Study Group from 2002-2007(12). They observed a 28% decrease in the risk-adjusted rates of vascular complications in over 13,563 women with VCD compared to manual compression. Applegate et al evaluated rates of vascular complications in 35,016 patients over a 10-year study period, ending in 2007(11): VCD was an independent factor associated with lower rates of vascular complications. Sanborn et al performed a post hoc analysis of the ACUTY trial (87): in 11,621 patients, there was a significant 22% risk adjusted decrease in the rates of vascular complications with the use of VCD compared to manual compression. Finally, Marso et al reviewed the data from the ACC NCDR from 2004-2008 (1). Over 1.5 million patients were included in the study with a significantly lower rate of vascular complications with VCD use compared to manual compression across a broad spectrum of risk.

An appropriately powered randomized trial is needed prior to definitive conclusions (ie, 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 VCD comprised less than 5% of patients during the study period (9). While the Northern New

England group also demonstrated a 50% reduction in bleeding complications over time, Northern New England operators utilized VCD in 43% of patients (12). The potential benefit of VCD (early ambulation, comfort (13, 88)) coupled with the inconsistent data regarding safety of VCD (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.

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). 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 VCD as compared to manual compression may depend upon the adequacy of femoral artery access and selection of appropriate patients(28, 29, 34, 90). 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 (91). 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 VCD are appropriate in selected situations warrants further study.

Even if appropriately deployed BAS strategies conclusively reduce bleeding, can the incremental costs of bivalirudin/fondaparinux (compared to heparins) and VCD (as compared to 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 (92)

Exploring the ACUTY randomized clinical trial data, Pinto and colleagues 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 while 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% CI: \$700–\$6,955), clinical significant bleeding (\$5,440 95% CI: \$2,250–\$10,226) and pseudoaneurysm formation (\$6,357 95% CI: \$4,900–\$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 VCD, bivalirudin, and radial access is complex. While radial access obviates the need for VCD use, many radial access interventionalists recommend the use of specially designed hydrophilic sheaths, wires and specially designed 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. While there are potential advantages for bivalirudin to reduce non-access 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 to the demonstrated cost advantages in femoral access(45, 93).

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 pharmacologic, technologic 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 UFH and/or GPI.
- The radial approach reduces access site bleeding compared with the femoral approach, but the slow adoption in the U.S 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 to 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 VCD compared to manual compression depending upon analysis of overall results versus sensitivity analyses. In contrast, 5 recent large (> 10,000 patient) registries suggest a benefit for VCD compared to manual compression. Based on these registries, a large randomized trial is warranted to prove the concept that VCD decreased complications.
- Are BAS related pharmacologies necessary in the setting of radial approach? Can U.S barriers to radial adoption be overcome?
- Finally, while bleeding is clearly associated with 1 year death, the mechanism (ie, cessation of guideline recommended antiplatelet therapy(94)) remains speculative.

In conclusion, the coining of the term “Bleeding Avoidance Strategies” summarizes a broad multi-modality 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 is robust in many areas and allows for considerable consensus. On the other hand, controversy is both expected and warranted in areas where adequate sized clinical trials have not yet been performed. In such areas, clinical judgement, patient selection and cautious utilization is consistent with other gray areas of current practice.

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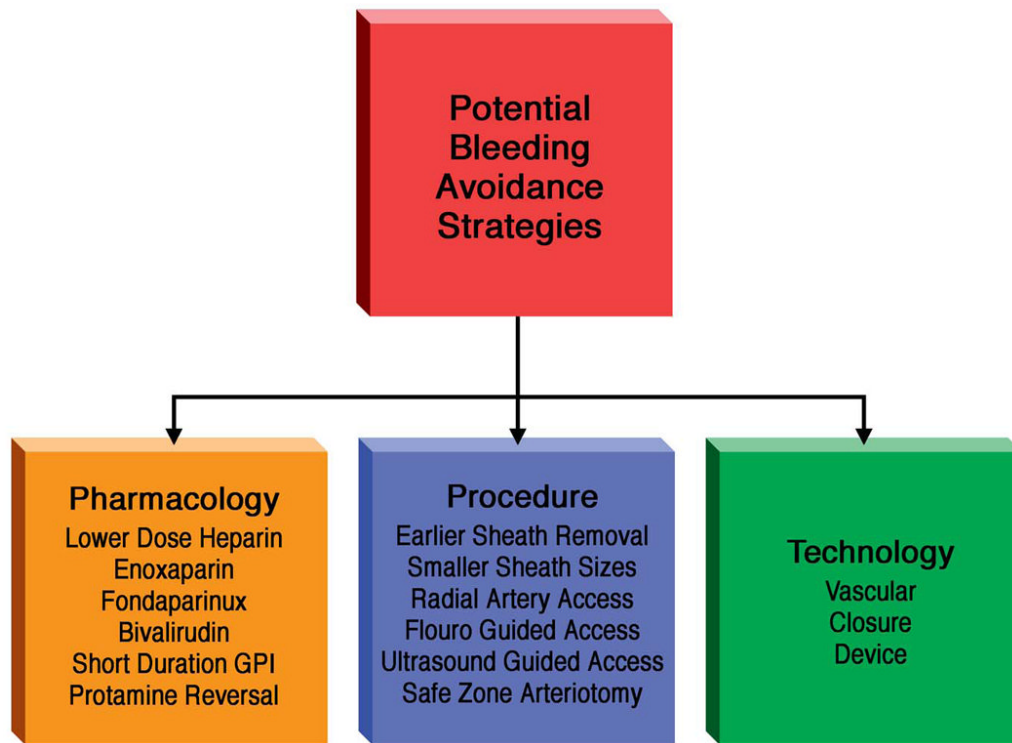


Figure 1. Bleeding Avoidance Strategies classified into 3 broad categories
Potential improvements in bleeding complications may be related to procedural, pharmacologic and technology changes occurring over the past two decades.

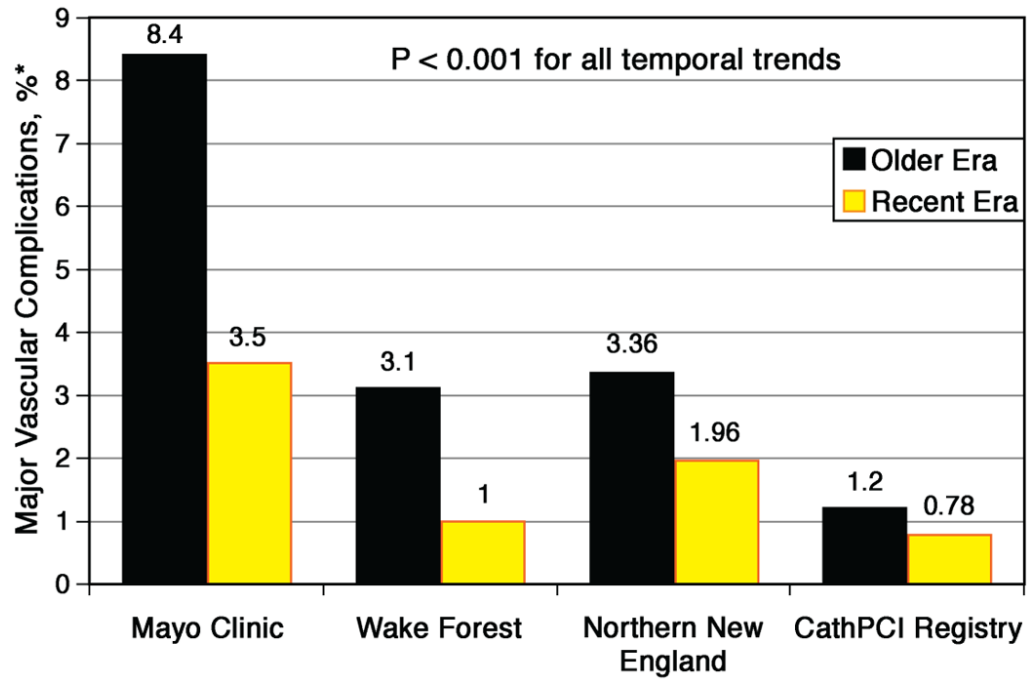


Figure 2. Temporal trends in bleeding complications after PCI

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 time periods of comparison are also different.

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	Improved ambulation Improved comfort	Increased, decreased or neutral Devices bleeding complications
Procedural		
Radial Artery	Reduction in bleeding	Operator issues and learning curve Patient suitability Prevention of radial artery occlusion
Optimized Femoral Access:	Reduction in selected	Universal applicability and efficacy bleeding complications (angiography, fluoro, ultrasound)

Table 2
Studies with 10,000 or more patients: VCD vs manual compression

Study	Year published	# patients	Study type	Endpoint	Complication Rates		
					VCD	MC	P Value
Nikolsky	2004	36,066	Trial and Registry Meta-Analysis	Hematoma	OR 1.34	CI 1.01-1.79	P < .05
Tavris	2004	166,680	National Registry (NCDR)	any VC	1.10%	1.70%	P<0.001
Tavris	2005	13,878	National Registry (NCDR)	any VC	OR 0.99	CI 0.77-1.28	P=ns
Arora	2007	12,937	Single Center Registry	any VC	2.40%	4.90%	P < 0.01
Ahmed	2007	13,563	Multicenter registry	Bleeding/VC	OR: 0.72	CI 0.59-0.89	P=0.02
Applegate	2008	35,016	Single Center Registry	any VC	1.60%	2.10%	P=0.03
Sanborn	2009	11,621	ACUTY post hoc	Access site bleeding	2.50%	3.30%	P=0.01
Marsso	2010	1,522,935	National Registry (NCDR)	Peri-procedural bleeding	OR: 0.77	CI 0.73-0.80	P < 0.05

* OR = odds ratio