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Argatroban and Bivalirudin for Perioperative Anticoagulation in Cardiac Surgery

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UNFRACTIONATED heparin (UFH) is the mainstay of anticoagulation for cardiovascular surgery, for patients requiring extracorporeal membrane oxygenation (ECMO), initially for ventricular assist devices (VADs), and for postoperative thrombosis prophylaxis. The elimination half-life of heparin is dose dependent and increases from approximately 30 min after a bolus of 25 U/kg, to 60 min with a bolus of 100 U/kg and 150 min with a bolus of 400 U/kg.[1] UFH has many advantages in this setting, including the ability to monitor using standard coagulation assays or point of care tests, including activated clotting time (ACT), the ability for safe usage in patients with renal failure, and complete and rapid reversal with protamine. Heparin, unlike other anticoagulants, requires a cofactor antithrombin to inhibit thrombin and factor Xa. One of the potential unique aspects of heparin is that alterations in the heparin dose response can occur. In case of "heparin resistance," very high or increasing dosages of heparin are required to achieve the targeted anticoagulant effect.[1] The most important factors contributing to this condition are critically decreased concentrations of antithrombin, high fibrinogen levels and thrombocytosis.[1]

The major adverse effect of heparin is heparin-induced thrombocytopenia (HIT), a paradox in which an anticoagulant causes a severe procoagulant condition due to antibodies directed against the complex of heparin and platelet factor 4, a protein constituent of alpha granules and platelets that is released following platelet activation.[2] This HIT antigen/antibody complex leads to platelet activation and thrombin generation and maybe associated with concomitant thromboembolic complications.[2] In patients with acute HIT or other contraindications to heparin in perioperative settings, the parenteral direct thrombin inhibitors (DTI) argatroban and bivalirudin are currently the first line alternatives. However, the use of these agents requires additional understanding of their pharmacology, monitoring, data supporting their use, and their potential side effects. In this review, we summarize clinical data of argatroban and bivalirudin and evaluate their potential use in the setting of cardiovascular surgery as well as in the intensive care unit (ICU).

Pharmacology of Argatroban and Bivalirudin

In contrast to heparins that require antithrombin to inhibit thrombin, argatroban and bivalirudin are DTIs that bind to thrombin independent of antithrombin, as shown in figure 1. DTIs, unlike UFH, inhibit both plasma and fibrin bound thrombin.[3] Fibrin bound thrombin activates platelets in the forming thrombus for clot stabilization. DTIs inhibit clot bound thrombin, decreasing clot stabilization, and promote thrombolysis.[3] In addition, recent data indicate that argatroban and bivalirudin increase the fibrin network permeability, rendering it less resistant to fibrinolysis.[4] These "thrombolytic" effects may contribute to their clinical efficacy in percutaneous coronary intervention (PCI), thrombolysis for VAD thrombosis, and thrombosis prophylaxis.[5] However, in conjunction with the lack of a reversal agent, these effects may contribute to potentially severe bleeding complications within the context of high-dose administration as used during cardiac surgery. The specific pharmacology of these parenteral DTIs will be discussed.

Argatroban

Argatroban is a synthetic, nonpeptide small molecular weight (~500 Da) L-arginine derivative that reversibly inhibits thrombin by means of univalent binding to the active site (exosite 3; fig. 1A).[6] Argatroban is recommended for use in patients with renal failure as it undergoes hepatic elimination with a half-life of 40 to 50 min, but can be prolonged with moderate to severe hepatic dysfunction.[6] The advantage of

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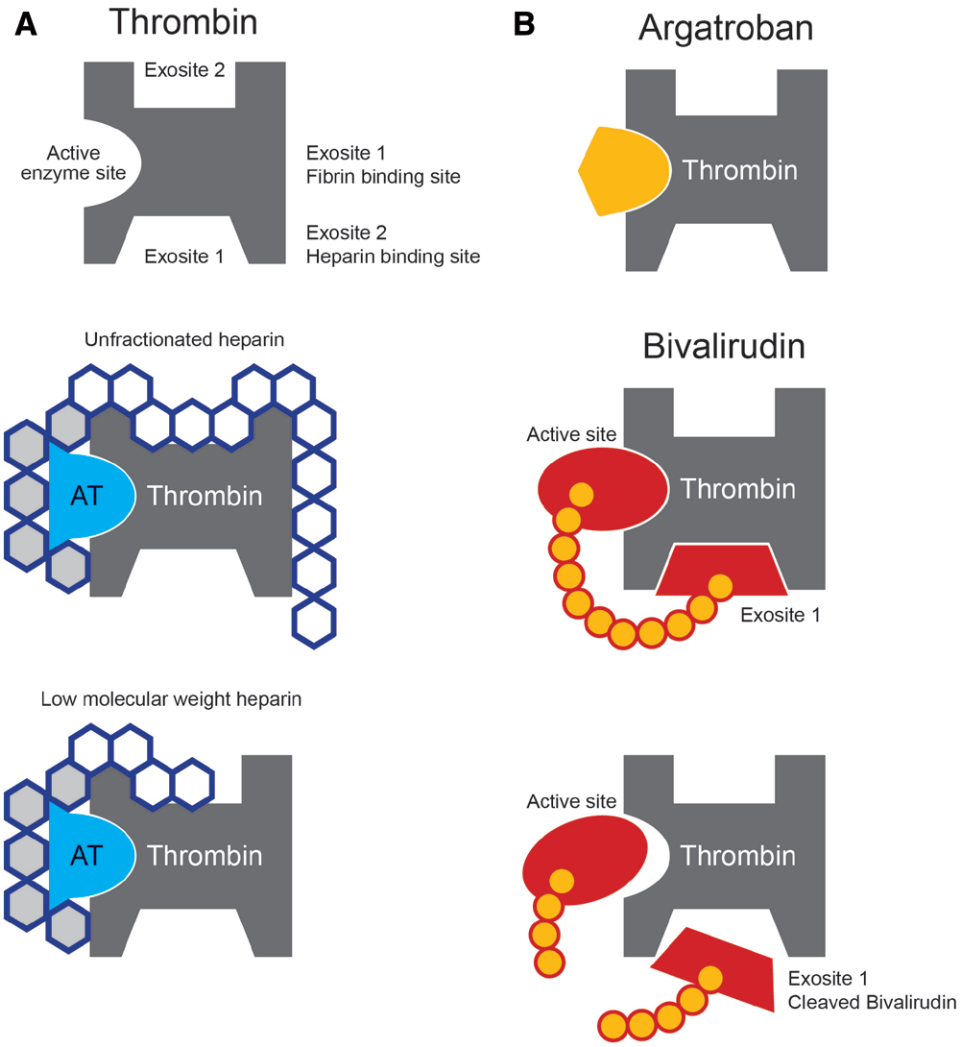

Fig. 1. (*A*) Indirect inhibition of thrombin by antithrombin, which is activated via unfractionated or low molecular weight heparin. (*B*) Direct inhibition of thrombin by argatroban and bivalirudin. Bivalirudin is cleaved by thrombin via proteolysis. This represents the major elimination mechanism of bivalirudin. Modified from Lee CJ, Ansell JE: Direct thrombin inhibitors. Br J Clin Pharmacol 2011; 72:581–92. AT = antithrombin.

this agent is its lack of antigenicity, hepatic elimination, and relatively short half-life independent of renal elimination. Current labeling for argatroban is for prophylaxis or treatment of thrombosis in patients with HIT, and as an anticoagulant in adult patients with or at risk for HIT undergoing PCI (https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/022485lbl.pdf; accessed November 28, 2017).

Bivalirudin

Bivalirudin is a small peptide with a molecular weight (~4,000 Da) that inhibits thrombin by reversibly binding to both the active site and the fibrinogen binding site region (exosite site 1; fig. 1B).[3,7] Bivalirudin is cleaved by proteases including thrombin with ~80% elimination by enzymatic cleavage; approximately 20% will be renally eliminated (fig. 1B). The elimination half-life of bivalirudin is 20 to 30 min in the presence of normal renal function while with renal dysfunction, half-life can be prolonged to 60 min, and up to 240 min in anephric renal failure requiring hemodialysis.[3,8] Therefore, baseline renal function is important when administering bivalirudin for cardiac surgery or in critically ill patients. Bivalirudin is currently approved in the United States and most European countries for patients with unstable angina undergoing percutaneous transluminal coronary angioplasty or PCI with provisional use of glycoprotein IIb/IIIa inhibitor and in patients at risk of HIT undergoing PCI (http://www.angiomax.com/downloads/ANG_USPI.pdf; accessed November 28, 2017).

Despite their relatively short half-lives, no specific reversal agents are available for either of these intravenous agents. While extracorporeal elimination *via* renal replacement therapy (RRT) has only a modest impact on pharmacokinetics of argatroban, it can significantly reduce the plasma concentration of bivalirudin.[9,10] Although not currently approved for cardiac surgery or other perioperative use, bivalirudin is the only "alternative anticoagulant" which has been prospectively

Table 1. Clinical Trials/Studies with Bivalirudin

Study	Design	Control	Bivalirudin (n) / Control (n)	Primary Endpoint	Primary Endpoint/ Incidence (%)	Postoperative Blood Loss (ml)	Re-exploration (%)	Transfused (%)
OPCAB								
Merry AF *et al.*[23]	RCT, single center	Heparin/ Protamine	100	12 h blood loss	NA	793 (532–1214)	4	24
			100		NA	805 (517–1117)	0	18
Smedira N *et al.*[24]	RCT, multicenter, open label	Heparin/ Protamine	101	Freedom of death, MI, stroke, repeat revascularization at day 7	96	717 (475–1190)	7	45.5
			56		94.6	783 (528–1032)	6	58.9
Dyke CM *et al.*[25]	Prospective, multicenter	None	51 (HIT)	Freedom of death, MI, stroke, repeat revascularization at day 7	92	936 ± 525	4	53
Palmer G *et al.*[26]	Prospective, observational, single center	None	243	Stroke MI In-hospital mortality	1.2 2.5 0.4	NA	1.2	48.1
Cardiopulmonary bypass								
Koster A *et al.*[28]	Prospective dual center	None	20	Freedom of death, MI, stroke repeat revascularization	95	800	5	60
Koster A *et al.*[29]	Prospective, single center	None	10	Blood loss, re-exploration	NA	510 ± 280	10	NA
Dyke CM *et al.*[30]	RCT, multicenter, open label	Heparin/ Protamine	98	Freedom of death, MI, stroke repeat revascularization at day 7	94.9	793	6.1	58.2
			52		96.2	668	1.9	59.6
Koster A *et al.*[31]	Prospective, multicenter	None	49 (HIT)	Freedom of death, MI, stroke, repeat revascularization at day 7	94	998 ± 595	4.1	84
LVAD implantation on arterio-venous ECMO support								
Ljajikj E *et al.*[34]	Retrospective, single center	Heparin/ Protamine	21	Re-exploration <7 days postoperatively	19	750 (530–1755)	19	100
			36		16.7	1135 (665–2238)	16.7	100

(*Continued*)

Table 1. (Continued)

Study	Design	Control	Bivalirudin (n) Control (n)	Primary Endpoint	Primary Endpoint/ Incidence (%)	Postoperative Blood Loss (ml)	Re-exploration (%)	Transfused (%)
TAVI								
Lange P *et al.*[36]	Retrospective, single center	Heparin/ Protamine	339	Life-threatening bleeding Major bleeding Minor bleeding 72-h mortality 30-day mortality	2.4 8.3 8.3 3.0 5.3	NA	NA	NA
			122	Life-threatening bleeding Major bleeding Minor bleeding 72-h mortality 30-day mortality	3.3 8.2 7.4 3.3 4.1	NA	NA	NA
Dangas DG *et al.*[37]	Prospective, randomized multicenter	Heparin/ Protamine	404	Major bleeding within 48 h, 30-day major adverse events of mortality, MI, stroke (MAE)	6.9 14.4	NA	NA	NA
			398	Major bleeding within 48 h, 30-day major adverse events of mortality, MI, stroke (MAE)	9 16.1	NA	NA	NA
Pre- and postoperative ECMO support								
Pieri M *et al.*[53]	Retrospective, single center	Heparin	10	Major bleeding Thromboembolic event Procedural success	30 10 60	NA	NA	NA
			10	Major bleeding Thromboembolic event Procedural success	40 30 50	NA	NA	NA
Ranucci M *et al.*[54]	Retrospective, single center	Heparin	13	Major bleeding Thromboembolic event Procedural success	0 7.6 70	NA	NA	NA
			8	Major bleeding Thromboembolic event Procedural success	25 25 37.5	NA	NA	NA
VAD								
Pieri M *et al.*[55]	Retrospective, single center	None	12	Minor bleeding Thromboembolic event Procedural success	16 0 100	NA	NA	NA

B = bivalirudin; CPB = cardiopulmonary bypass; ECMO = extracorporeal membrane oxygenation; H = heparin; HIT = heparin-induced thrombocytopenia; (L)VAD = (left) ventricular assist device; MAE = major adverse events; MI = myocardial infarction; NA = not available; OPCAB = off-pump coronary artery bypass grafting; RCT = randomized controlled trial; TAVI = transcatheter aortic valve implantation.

studied in cardiac surgery in HIT and non-HIT patients (table 1). According to current American College of Clinical Pharmacology guidelines it is the preferred agent for patients with HIT requiring urgent cardiac surgery.[2]

Monitoring of Direct Thrombin Inhibitors and Effect on Viscoelastic Tests

Intraoperative monitoring of DTI anticoagulation is usually performed with the ACT. However, pharmacokinetic studies during cardiac surgery are only available for bivalirudin.[11,12] During surgery with cardiopulmonary bypass (CPB), a 2.5-fold prolongation of the ACT baseline value has been recommended as the target value.[7] Although the different ACT assays revealed a good correlation to plasma bivalirudin concentrations (target concentration of 10 to 15 μg/ml during CPB), the response of different commercially available test systems to bivalirudin anticoagulation varies significantly.[11] During "off-pump coronary artery bypass" (OPCAB) surgery, bivalirudin dosing and monitoring often follows the PCI regimen with a target ACT value greater than 300 s.[7,12] Following this strategy, the mean bivalirudin concentration during the grafting procedure was 11.2 ± 2.32 μg/ml and consistently exceeded the target concentration greater than 6.5 μg/ml, which in large PCI studies had been evaluated as being effective.[3,12]

The partial thromboplastine time (PTT) alone is routinely used to monitor the effect of DTIs when used as prophylactic or therapeutic anticoagulation agents in the ICU. Exceptions in this regard are patients on ECMO support where, similar to the use of UFH, both the PTT and ACT are most often used (table 1). The commercially available PTT reagents show significant variation in response to the different DTIs.[7,13] Additionally, most PTT assays are not linearly related to DTI levels at high plasma levels (exceeding approximately the threefold prolongation of the reference PTT value) where the PTT may plateau and increases in plasma levels may not significantly increase PTT values.[14,15] This is relevant in cases of bleeding, or in patients requiring emergency invasive procedures. More specific assays, such as the diluted thrombin time, ecarin clotting time or a chromogenic anti-IIa assay, better assess DTIs plasmatic concentrations.[15] However, these tests are not routinely available in all hospitals and target values need to be better defined and validated in controlled studies.

Of note, both drugs interfere with the prothrombin time.[14] The effect is more pronounced with the monovalent DTI argatroban than with the bivalent DTI bivalirudin. Differences in the molar concentrations of DTI required for the therapeutic effect appear to be responsible for this observation.[14] This condition should be considered when transitioning patients from argatroban to vitamin K antagonists. For argatroban, recent recommendations provide useful information for this transition period.[16] In the case of bivalirudin, an algorithm has recently been validated.[17] Most patients had undergone cardiac surgery—in particular the implantation of a VAD.

Although viscoelastic testing using different activators and antagonists is used extensively as part of point-of-care testing for bleeding algorithms to guide therapy with procoagulants and hemostatic agents, there is little data describing its use for parenteral direct thrombin inhibitors. Direct thrombin inhibitors, including argatroban and bivalirudin, can increase the clot formation time, but may have only a minor effect on the maximum clot strength.[18] The use of an ecarin clotting time, currently under development, can more accurately measure concentrations of DTIs, and may be helpful to guide therapy.[19]

Intraoperative Use

Argatroban

There are scant data with regard to the use of argatroban during cardiac surgery, particularly when CPB is employed. While several articles described the successful use of argatroban in patients undergoing OPCAB surgery, several publications also report catastrophic bleeding when argatroban was used for anticoagulation during CPB.[20,21] In the largest case series published, argatroban was used in seven HIT patients undergoing left ventricular assist device (LVAD) implantation with arterio-venous ECMO support. Major complications ranged from one intraoperative device thrombosis to uncontrollable bleeding in four patients; in one patient it was lethal.[22]

Bivalirudin

The use of bivalirudin for anticoagulation in adults undergoing cardiac surgery has been studied in multiple prospective and randomized controlled trials (RCTs; table 1). The dosing of bivalirudin during cardiac surgery follows standardized protocols (table 1). Protocols vary, dependent upon if the procedure is performed with or without CPB or ECMO support (table 2).

Bivalirudin was initially compared to UFH in patients undergoing OPCAB surgery.[23] While the authors did not report any significant differences in terms of postoperative blood loss between groups, coronary graft blood flow evaluated 3 months postoperatively *via* angiography was significantly higher in the bivalirudin group. In the subsequent multicenter, open label trial (EVOLUTION OFF trial), patients undergoing OPCAB surgery were randomized to receive either bivalirudin or UFH.[24] The objective was to assess the safety and efficacy of bivalirudin in this indication. The study concluded that bivalirudin was an effective anticoagulant, without excessive bleeding and with a safety profile similar to heparin. In the prospective multicenter "CHOOSE OFF" trial, bivalirudin anticoagulation for OPCAB surgery was performed in patients with HIT antibodies.[25] The safety and efficacy profiles were comparable to the results of the aforementioned studies in non-HIT patients (table 1). In an attempt to avoid HIT and provide a "heparin-free" environment, one group performed OPCAB surgery in a large series of consecutive patients.[26] Results showed excellent clinical outcomes of bivalirudin within this indication.

The unique pharmacology of bivalirudin has implications for the surgical technique, which, however, are minor during

Table 2. Dosing of Bivalirudin

Type of System	Bolus Patient (mg/kg)	Continuous Infusion (mg · kg^{-1} · h^{-1})	Bolus ECC (mg/kg)	ACT (s)	Type of Surgery	Precautions
During Cardiac Surgery: Established Protocols from RCTs						
Off-pump	0.75	1.75		> 300	OPCAB, TAVI	Avoid stasis in grafts, devices Intermittent flushing after 10–15 min
CPB[25]	1.0	2.5	50	> 2.5 x baseline value	Cardiac surgery, Surgery of thoracic aorta	Avoid stasis in reservoirs, devices, etc. Replace cardiotomy suction by cell saving Reconnect CPB system after weaning Add 50 mg and re-circulate CPB No hemofiltration during CPB
During Cardiac Surgery: Protocols for Special Procedures						
ECMO[33]	0.25–0.5	0.25–0.5	none	180–220	LVAD implantation	Reduce duration of blood stasis in the device (LVAD) as much as possible; dose dependent on baseline ACT value
ECMO[34]	0.2*	0.1–0.2	none	160–180	Lung transplantation	
For Pre- and Postoperative ECMO Support in Cardiac Surgery: Single-center Studies						
	Start Dose (µg · kg^{-1} · min^{-1})	Continuous Dose (µg · kg^{-1} · min^{-1})		Anticoagulation Assay Target (s)		
ECMO[53]	0.025	≈ 0.03–0.05		PTT 45–60		Dose dependent on renal function and RRT
ECMO[54]	0.03–0.05	≈ 0.05–0.1		ACT 160–180		

*Suggested based on author experience.

ACT = activated clotting time; CPB = cardiopulmonary bypass; ECCS = extracorporeal circulation circuit; ECMO = extracorporeal membrane oxygenation system; (L)VAD = (left) ventricular assist device; OPCAB = off-pump coronary artery bypass grafting; PTT = partial thromboplastin time; RCT = randomized controlled trial; RRT = renal replacement therapy; TAVI = transcatheter aortic valve implantation.

OPCAB surgery (table 2). In contrast, when using a standard CPB system and performing complex open-heart surgery, surgical and perfusion techniques require specific considerations as listed in table 2.[27] In view of the promising results in patients undergoing OPCAB surgery, bivalirudin was subsequently evaluated in patients undergoing cardiac surgery with CPB[28,29] (table 1). The final dosing and protocols for performance of CPB was extrapolated from *in vitro* studies, former PCI studies, and the results of these pilot studies.[28,29]

Using these standardized protocols for bivalirudin anticoagulation during CPB, in the open label multicenter randomized "EVOLUTION ON" trial, which predominately included lower-risk patients undergoing coronary artery bypass grafting surgery or isolated valve surgery patients, bivalirudin anticoagulation was compared to heparin/protamine management[27,30] (table 2). The safety and efficacy profile was similar between groups (table 1). In the prospective "CHOOSE ON" trial, bivalirudin anticoagulation was used in patients with HIT antibodies.[31] In this trial, patients with a higher perioperative risk, undergoing more complex cardiac surgical procedures, including reoperations and combined procedures, were included.[31] Although the safety and efficacy profiles were comparable to the aforementioned studies, the rate of transfused patients markedly increased in patients treated with bivalirudin (table 1).

Over the last years, bivalirudin anticoagulation has also been used in high-risk patients undergoing complex cardiac surgery procedures such as LVAD implantation or procedures requiring deep hypothermic cardiac arrest.[32,33] Even though the procedures were successful, transfusion requirements and blood loss were increased when compared to the results reported in previous prospective studies performed in lower-risk patients undergoing less complex surgical procedures. The increased bleeding tendency was explained by renal failure with prolongation of the elimination half-life of bivalirudin thus leading to a prolonged anticoagulant effect.[32]

Bivalirudin anticoagulation has also been used for intraoperative procedures that replaced CPB by arterio-venous ECMO support.[34,35] Using a modified implantation technique for a VAD, which reduces the period of blood stasis in the system, and a completely closed biocompatible system, the dose of bivalirudin, when compared to CPB, was reduced considerably (one fifth to one tenth). This strategy, which is comparable to the aforementioned case series performed using argatroban anticoagulation, had been recently assessed in a larger group of patients with HIT antibodies and compared to the standard of heparin/protamine given in patients without HIT antibodies[22,34] (table 1). Outcomes for bleeding complications, such as early re-exploration, delayed chest closure, and postoperative blood loss were comparable between groups.

In one case, bivalirudin was used during double-lung transplantation with ECMO support.[35] The use of a completely closed biocompatible surface system and absence of a period of blood stasis in a device or graft allowed for a further reduction of the bivalirudin dose (table 2). Transfusion requirements and postoperative blood loss were comparable to institutional results achieved with heparin anticoagulation.

In a small single center and the large multicenter prospective Effect of Bivalirudin on Aortic Valve Intervention Outcomes-3 (BRAVO-3) trial, bivalirudin was compared to heparin/protamine during transfemoral transcatheter aortic valve implantation (TAVI).[36,37] The BRAVO-3 trial was powered to assess the superiority of bivalirudin particularly with regard to major bleeding events and noninferiority with regard to 30-day cardiovascular events. However, the control group exhibited only approximately 50% of the expected major bleeding complications, therefore the study was underpowered and the superiority of bivalirudin over UFH could not be demonstrated with respect to major bleeding events (table 1). The same protocol had been successfully used for transapical TAVI of an aortic valve in a patient with antiphospholipid syndrome.[38]

Pre-/Postoperative Anticoagulation, Renal Replacement Therapy, and ECMO Support

Argatroban

Based on the results of first prospective clinical studies, the recommended starting dose of argatroban for treatment of acute HIT was 2 $\mu g \cdot kg^{-1} \cdot min^{-1}$.[39] However, more recent studies showed that patients with heart failure and organ dysfunction required decreased dosing (~0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ or less; table 3).[40] After cardiac surgery, argatroban doses have been further reduced in order to decrease the risk of postoperative bleeding complications.[41–45] However, even the relatively low dosing provided effective inhibition of thrombin activation.[46]

Argatroban has also been investigated in larger series of patients after cardiac surgery for anticoagulation during RRT (table 3).[47,48] Due to the fact that argatroban pharmacokinetics are not impacted by renal function and the filter systems, dosing is predictable and rather stable. In both studies, transfusion requirements were within the normal range for ICU patients needing RRT, and no case of severe bleeding was reported (table 3).

Successful use of argatroban has also been reported in two larger cohorts of patients with HIT after implantation of LVADs (table 3).[49,50] Additionally, argatroban has been effectively used for thrombolysis in patients with thrombosis of a LVAD system.[5]

Outside the indication of HIT and cardiac surgery, argatroban has also been employed in ICU patients showing "heparin resistance."[51] The results of this retrospective study suggest that argatroban may be an option in this condition.

Bivalirudin

Bivalirudin, however, outside the context of cardiac surgery, has been used for anticoagulation during RRT in HIT and non-HIT patients.[52] In contrast to argatroban, pharmacokinetics are influenced by renal function. Furthermore, bivalirudin is cleared through RRT itself. This explains the more volatile dosing protocols which depend on creatinine clearance and the use of different filter systems.

In patients before or after cardiac surgery needing ECMO support, successful use of bivalirudin has been reported in smaller series of HIT and non-HIT patients[53,54] (table 1). Dosing protocols varied depending on patients' renal function, as did the coagulation test systems used, as well as target values. However, blood loss and transfusion rates were comparable to heparin anticoagulation. In both studies, the anticoagulant effect of bivalirudin was more predictable and stable than with heparin and resulted in lesser adjustments of the infusion rate.

One single center study reported excellent results when bivalirudin was used in non-HIT patients after implantation of an LVAD (table 2).[55]

Additional Clinical Considerations

Argatroban and bivalirudin are important anticoagulation alternatives for patients with HIT who require urgent surgery and/or perioperative anticoagulation. Although employed for more than a decade in the complex setting of cardiac surgery, scientific data are limited to a restricted number of smaller prospective and retrospective, mostly single center studies. In the high-risk cardiac surgery patients with HIT, it is often challenging to identify the etiology of adverse outcomes that could either be attributed to the patient's underlying condition or the drugs used. These major limitations must be considered when trying to balance potential risks and benefits of these potent anticoagulants.

The unique pharmacokinetics of bivalirudin render this agent an interesting option, particularly for a short-term, high-dose anticoagulant effect, as needed during interventions such as PCI and cardiac surgery. However, limitations are the lack of a standardized reliable point-of-care monitoring during CPB, as well as a reversal agent. Initial bivalirudin studies were performed in comparably lower-risk patients undergoing noncomplex standard cardiac surgical procedures. In patients with progressively impaired multiorgan and, in particular, severely impaired renal function, the bleeding risk associated with bivalirudin appears to be markedly higher. In such patients, however, modification of the surgical and perfusion strategy, which may enable surgery without CPB and/or a reduction of the bivalirudin dose, might help to improve results. One example is the LVAD implantation during ECMO support using low-dose bivalirudin anticoagulation.[34] In older or high-risk patients with significantly impaired renal function who are scheduled for aortic valve replacement, performing the procedure as TAVI using bivalirudin anticoagulation might be the preferable option.[38] The large BRAVO-3 trial demonstrated successful use of bivalirudin in this indication. In an attempt to avoid CPB and reduce surgical trauma, a hybrid procedure using TAVI and OPCAB might also be an option for high-risk

Table 3. Argatroban Anticoagulation after Cardiac Surgery, with and without Heart Failure, and with Renal Replacement Therapy

Study	Study Design	Patients (n)	Start after Surgery (h)	Starting Dose ($\mu g \cdot kg^{-1} \cdot min^{-1}$)	Continuous Dose ($\mu g \cdot kg^{-1} \cdot min^{-1}$)	Target PTT (s; 1.5–3 times)	Thrombosis (%)	Bleeding (%)
After cardiac surgery								
Koster A *et al.*[41]	Prospective, controlled, open label, dual center	2	0.5	2.0	NA	> 80	NA	50
		14	0.5	0.8–1.0	0.3–0.5	50–70	NA	0
Yoon JH *et al.*[44]	Retrospective, single center	31	within 72	NA	median 0.66	NA	NA	64.6
Hoffmann WD *et al.*[45]	Retrospective, single center	39	NA	median 0.5	median 0.6	45–90	NA	10.2
Demma LJ *et al.*[42]	Retrospective single center	47	NA	1,5 0.5 (hepatic impairment)	NA	< 100	NA	6
With and without heart failure								
Begelmann SM *et al.*[40]	Retrospective, single center	65	NA	1.14 ± 0.62	0.97 ± 0.6 (no HF) 0.58 ± 0.28 (no HF)	42–84	NA NA	13.8
Renal replacement therapy after cardiac surgery								
Koster *et al.*[47]	Retrospective, single center (iHeD/cHeF)	iHeD (9)	NA	1.0	0.06 ± 0.11	50–80	0	0
		cHeF (6)	NA		0.13 ± 0.21		0	0
Klingele *et al*.[48]	Retrospective, single center (cHeF)	A (41)	NA	0.25	NA	60–90	NA	NA
		H+A (26)	NA		NA		NA	NA
VAD								
Samuels LE *et al.*[50]	Retrospective, single center	H (5)	NA	NA	NA	60–90	20	20
		H+A (8)	NA	0.5–1	NA		13	38
		A (20)	NA	0.5–1	NA		15	5
Pappalardo F *et al*.[49]	Retrospective, single center	Pre HIT (11)	NA	0.02 — ±0.42	0.02 ± 015	45–80	18	22
		Post HIT (16)	NA					

A = argatroban; apt = activated partial thromboplastine time; cHeF = continuous hemofiltration; H = heparin; H+A = heparin followed by argatroban; HF = heart failure; HIT = heparin-induced thrombocytopenia; iHeD = intermittent hemodialysis; NA= not available; PTT = activated partial thromboplastin time; VAD = ventricular assist device.

patients who need aortic valve replacement and concomitant coronary artery bypass grafting surgery. However, there are still high-risk patients scheduled for urgent surgery where the perfusion strategy cannot be modified (*e.g.,* heart transplantation). In such patients, a persistent anticoagulant effect may be associated with severe diffuse bleeding. In such a situation, the chest may have to remain open, the patient was transferred to the ICU and RRT was installed to augment bivalirudin elimination. After normalization of coagulation parameters (usually after 4 to 6 h), secondary closure of the chest may be performed.[32]

Both drugs have been successfully used in cardiac surgical and critically ill populations, for prophylactic and therapeutic anticoagulation. The optimal monitoring of these drugs, particularly regarding the preference of functional "clotting tests," such as the PTT or assays which monitor drug concentrations, is the subject of ongoing research.[56] However, target drug levels for the different indications have not yet been defined and validated.[56] In view of the available data for argatroban and bivalirudin, it appears that even for extracorporeal procedures like renal replacement therapy and ECMO, a target value of an approximately twofold prolongation of the PTT ensures effective anticoagulation.[46] As the PTT, in this range, provides a linear correlation to the drug level, the risk of overdosing, excessive anticoagulation and bleeding appears to be low.

All available data indicate that argatroban, when adequately dosed and monitored in this indication, provides effective anticoagulation at complication rates almost comparable to the standard of UFH anticoagulation. However, in ICU patients, particularly when multiorgan failure exists, the starting dose of argatroban has to be reduced to 0.5 to 1.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$, and particularly during the initial 24 h, monitored tightly (every 2 to 4 h).[15] The main limitation for the use of argatroban in the perioperative setting of major cardiac surgery is the fact that no option for extracorporeal elimination is available. Particularly in critical patients with impaired liver function, the elimination half-life of argatroban increases considerably. This may lead to hard to treat bleeding complications in case urgent/emergency surgery must be performed. Viewing this condition, in patients with impaired liver function and a high risk for urgent surgery, indicates that bivalirudin may be considered as an alternative

option, as the elimination half-life *per se* is shorter and elimination can be effectively augmented *via* RRT.

Conclusions

In the setting of cardiac surgery, argatroban and bivalirudin are alternatives to UFH anticoagulation. However, their use appears to be basically limited to the rare indication of HIT. During cardiac surgery, the lack of a reversal agent must be considered as a potential hazard and challenge. One indication in which a more preemptive use of both DTIs is discussed, are patients on ECMO and VAD support. These patients appear to reveal a high risk of HIT, which is often associated with detrimental outcomes.[57,58] A "heparin-free environment" may improve results.[56] All available data indicate that both drugs can be used to achieve results comparable to the standard of care (*e.g.,* UFH). However, particularly in these patients, due to changes in the coagulation system caused by the contact of blood with nonendothelial surfaces and alterations in blood flow, the delicate balance between sufficient anticoagulation and prevention of bleeding complication is hard to achieve.[59]

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Competing Interests

The authors declare no competing interests.

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References

1. Baglin TP, Weitz JI, Samama MM: Parenteral anticoagulants: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012;141(2 Suppl):e24S–e43S
2. Linkins LA, Dans AL, Moores LK Bona R, Davidson BL, Schulman S, Crowther M; American College of Chest Physicians: Treatment and prevention of heparin-induced thrombocytopenia: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012; 141(2 Suppl):e495S–530S
3. Chew DP: Bivalirudin, a bivalent, thrombin specificanticoagulant as an alternative to heparin in interventional procedures. Haemostaseologie 2002; 22:60–6
4. He S, Blombäck M, Bark N, Johnsson H, Wallén NH: The direct thrombin inhibitors (argatroban, bivalirudin and lepirudin) and the indirect Xa-inhibitor (danaparoid) increase fibrin network porosity and thus facilitate fibrinolysis. Thromb Haemost 2010; 103:1076–84
5. Badiye A, Hernandez GA, Chaparro S: Argatroban as novel therapy for suspected thrombosis in patients with continuous-flow left ventricle assist device and hemolysis. ASAIO J 2014; 60:361–5
6. Swan SK, Hursting MJ: The pharmacokinetics and pharmacodynamics of argatroban: Effects of age, gender, and hepatic or renal dysfunction. Pharmacotherapy 2000; 20:318–29
7. Warkentin TE, Greinacher A, Koster A: Bivalirudin. Thromb Haemost 2008; 99:830–9
8. Robson RF: The use of bivalirudin in patients with renal impairment. J Invasive Cardiol 2000; 12 Suppl F:33F–6
9. Keyl C, Zimmer E, Bek MJ, Wiessner M, Trenk D: Argatroban pharmacokinetics and pharmacodynamics in critically ill cardiac surgical patients with suspected heparin-induced thrombocytopenia. Thromb Haemost 2016; 115:1081–9
10. Koster A, Buz S, Krabatsch T, Dehmel F, Kuppe H, Hetzer R, Aronson S, Dyke CM: Effect of modified ultrafiltration on bivalirudin elimination and postoperative blood loss after on-pump coronary artery bypass grafting: Assessment of different filtration strategies. J Card Surg 2008; 23:655–8
11. Zucker ML, Koster A, Prats J, Laduca FM: Sensitivity of a modified ACT test to levels of bivalirudin used during cardiac surgery. J Extra Corpor Technol 2005; 37:364–8
12. Koster A, Spiess B, Jurmann M, Dyke CM, Smedira NG, Aronson S, Lincoff MA: Bivalirudin provides rapid, effective, and reliable anticoagulation during off-pump coronary revascularization: Results of the "EVOLUTION OFF" trial. Anesth Analg 2006; 103:540–4
13. Gosselin RC, King JH, Janatpour KA, Dager WE, Larkin EC, Owings JT: Comparing direct thrombin inhibitors using aPTT, ecarin clotting times, and thrombin inhibitor management testing. Ann Pharmacother 2004; 38:1383–8
14. Warkentin TE, Greinacher A, Craven S, Dewar L, Sheppard JA, Ofosu FA: Differences in the clinically effective molar concentrations of four direct thrombin inhibitors explain their variable prothrombin time prolongation. Thromb Haemost 2005; 94:958–64
15. Van Cott EM, Roberts AJ, Dager WE: Laboratory monitoring of parenteral direct thrombin inhibitors. Semin Thromb Hemost 2017; 43:270–6
16. Alatri A, Armstrong AE, Greinacher A, Koster A, Kozek-Langenecker SA, Lancé MD, Link A, Nielsen JD, Sandset PM, Spanjersberg AJ, Spannagl M: Results of a consensus meeting on the use of argatroban in patients with heparin-induced thrombocytopenia requiring antithrombotic therapy—a European Perspective. Thromb Res 2012; 129:426–33
17. Hohlfelder B, Sylvester KW, Rimsans J, DeiCicchi D, Connors JM: Prospective evaluation of a bivalirudin to warfarin transition nomogram. J Thromb Thrombolysis 2017; 43:498–504
18. Young G, Yonekawa KE, Nakagawa PA, Blain RC, Lovejoy AE, Nugent DJ: Recombinant activated factor VII effectively reverses the anticoagulant effects of heparin, enoxaparin, fondaparinux, argatroban, and bivalirudin *ex vivo* as measured using thromboelastography. Blood Coagul Fibrinolysis 2007; 18:547–53
19. Carroll RC, Chavez JJ, Simmons JW, Snider CC, Wortham DC, Bresee SJ, Cohen E: Measurement of patients' bivalirudin plasma levels by a thrombelastograph ecarin clotting time assay: A comparison to a standard activated clotting time. Anesth Analg 2006; 102:1316–9
20. Martin ME, Kloecker GH, Laber DA: Argatroban for anticoagulation during cardiac surgery. Eur J Haematol 2007; 78:161–6
21. Tanigawa Y, Yamada T, Matsumoto K, Nakagawachi A, Torikai A, Sakaguchi Y: Non-recovery of ACT in a patient with heparin-induced thrombocytopenia type II during mitral valve replacement using argatroban anticoagulation. J Anesth 2013; 27:951–5
22. Hillebrand J, Sindermann J, Schmidt C, Mesters R, Martens S, Scherer M: Implantation of left ventricular assist devices

under extracorporeal life support in patients with heparin-induced thrombocytopenia. J Artif Organs 2015; 18:291–9

23. Merry AF, Raudkivi PJ, Middleton NG, McDougall JM, Nand P, Mills BP, Webber BJ, Frampton CM, White HD: Bivalirudin *versus* heparin and protamine in off-pump coronary artery bypass surgery. Ann Thorac Surg 2004; 77:925–31
24. Smedira NG, Dyke CM, Koster A, Jurmann M, Bhatia DS, Hu T, McCarthy HL 2nd, Lincoff AM, Spiess BD, Aronson S: Anticoagulation with bivalirudin for off-pump coronary artery bypass grafting: The results of the EVOLUTION-OFF study. J Thorac Cardiovasc Surg 2006; 131:686–92
25. Dyke CM, Aldea G, Koster A, Smedira N, Avery E, Aronson S, Spiess BD, Lincoff AM: Off-pump coronary artery bypass with bivalirudin for patients with heparin-induced thrombocytopenia or antiplatelet factor four/heparin antibodies. Ann Thorac Surg 2007; 84:836–9
26. Palmer GJ, Sankaran IS, Sparkman GM, Koster A, Dyke CM, Ebra G: Routine use of the direct thrombin inhibitor bivalirudin for off-pump coronary artery bypass grafting is safe and effective. Heart Surg Forum 2008; 11:E24–9
27. Veale JJ, McCarthy HM, Palmer G, Dyke CM: Use of bivalirudin as an anticoagulant during cardiopulmonary bypass. J Extra Corpor Technol 2005; 37:296–302
28. Koster A, Yeter R, Buz S, Kuppe H, Hetzer R, Lincoff AM, Dyke CM, Smedira NG, Spiess B: Assessment of hemostatic activation during cardiopulmonary bypass for coronary artery bypass grafting with bivalirudin: Results of a pilot study. J Thorac Cardiovasc Surg 2005; 129:1391–4
29. Koster A, Spiess B, Chew DP, Krabatsch T, Tambeur L, DeAnda A, Hetzer R, Kuppe H, Smedira NG, Lincoff AM: Effectiveness of bivalirudin as a replacement for heparin during cardiopulmonary bypass in patients undergoing coronary artery bypass grafting. Am J Cardiol 2004; 93:356–9
30. Dyke CM, Smedira NG, Koster A, Aronson S, McCarthy HL II, Kirshner R, Lincoff AM, Spiess BD: A comparison of bivalirudin to heparin with protamine reversal in patients undergoing cardiac surgery with cardiopulmonary bypass: The EVOLUTION-ON study. J Thorac Cardiovasc Surg 2006; 131:533–9
31. Koster A, Dyke CM, Aldea G, Smedira NG, McCarthy HL 2nd, Aronson S, Hetzer R, Avery E, Spiess B, Lincoff AM: Bivalirudin during cardiopulmonary bypass in patients with previous or acute heparin-induced thrombocytopenia and heparin antibodies: Results of the CHOOSE-ON trial. Ann Thorac Surg 2007; 83:572–7
32. Nhieu S, Nguyen L, Pretorius V, Ovando J, Moore D, Banks D, Koster A, Morshuis M, Faraoni D: CASE 1–2015: Left ventricular assist device insertion in a patient with heparin-induced thrombocytopenia and renal failure. J Cardiothorac Vasc Anesth 2015; 29:210–20
33. Koster A, Amin-Parsa M, Kaufmann M, Meyer-Jark T, Rudloff M, Diekmann J, Georg WM, Liebke M, Schirmer U, Gummert JF: Fulminate heparin-induced thrombocytopenia and surgery with deep hypothermic circulatory arrest using bivalirudin. Ann Thorac Surg 2013; 95:1079–81
34. Ljajikj E, Zitttermann A, Morshuis M, Börgermann J, Ruiz-Cano M, Schoenbrodt M, Gummert J; Koster A: Bivalirudin anticoagulation for left ventricular assist device implantation on an extracorporeal life support system in patients with heparin-induced thrombocytopenia antibodies. Interact Cardiovasc Thorac Surg 2017; 25:898–904
35. Koster A, Niedermeyer J, Gummert J, Renner A: Low dose bivalirudin anticoagulation for lung transplantation with extracorporeal membrane oxygenation in a patient with acute heparin-induced thrombocytopenia. Eur J Cardiothorac Surg 2017; 51:1009–11
36. Lange P, Greif M, Bongiovanni D, Thaumann A, Näbauer M, Bischoff B, Helbig S, Becker C, Schmitz C, D'Anastasi M, Mehilli J, Boekstegers P, Massberg S, Kupatt C: Bivalirudin vs heparin in patients who undergo transcatheter aortic valve implantation. Can J Cardiol 2015; 31:998–1003
37. Dangas GD, Lefèvre T, Kupatt C, Tchetche D, Schäfer U, Dumonteil N, Webb JG, Colombo A, Windecker S, Ten Berg JM, Hildick-Smith D, Mehran R, Boekstegers P, Linke A, Tron C, Van Belle E, Asgar AW, Fach A, Jeger R, Sardella G, Hink HU, Husser O, Grube E, Deliargyris EN, Lechthaler I, Bernstein D, Wijngaard P, Anthopoulos P, Hengstenberg C; BRAVO-3 Investigators: Bivalirudin *versus* heparin anticoagulation in transcatheter aortic valve replacement: The randomized bravo-3 trial. J Am Coll Cardiol 2015; 66:2860–8
38. Koster A, Ensminger S, Vlachojannis M, Birschmann I: Bivalirudin anticoagulation for minimal invasive transapical transcatheter aortic valve replacement in a patient with antiphospholipid antibodies. J Clin Anesth 2016; 33:373–5
39. Lewis BE, Wallis DE, Berkowitz SD, Matthai WH, Fareed J, Walenga JM, Bartholomew J, Sham R, Lerner RG, Zeigler ZR, Rustagi PK, Jang IK, Rifkin SD, Moran J, Hursting MJ, Kelton JG; ARG-911 Study Investigators: Argatroban anticoagulant therapy in patients with heparin-induced thrombocytopenia. Circulation 2001; 103:1838–43
40. Begelman SM, Baghdasarian SB, Singh IM, Militello MA, Hursting MJ, Bartholomew JR: Argatroban anticoagulation in intensive care patients: Effects of heart failure and multiple organ system failure. J Intensive Care Med 2008; 23:313–20
41. Koster A, Buz S, Hetzer R, Kuppe H, Breddin K, Harder S: Anticoagulation with argatroban in patients with heparin-induced thrombocytopenia antibodies after cardiovascular surgery with cardiopulmonary bypass: first results from the ARG-E03 trial. J Thorac Cardiovasc Surg 2006; 132:699–700
42. Demma LJ, Paciullo CA, Levy JH: Recognition of heparin-induced thrombocytopenia and initiation of argatroban therapy after cardiothoracic surgery in the intensive care unit. J Thorac Cardiovasc Surg 2012; 143:1213–8
43. Jeske WP, Fareed J, Hoppensteadt DA, Lewis B, Walenga JM: Pharmacology of argatroban. Expert Rev Hematol 2010; 3:527–39
44. Yoon JH, Yeh RW, Nam KH, Hoffman WD, Agnihotri AK, Jang IK: Safety and efficacy of the argatroban therapy during the early post-cardiac surgery period. J Thromb Thrombolysis 2010; 30:276–80
45. Hoffman WD, Czyz Y, McCollum DA, Hursting MJ: Reduced argatroban doses after coronary artery bypass graft surgery. Ann Pharmacother 2008; 42:309–16
46. Harder S, Merz M, Klinkhardt U, Lorenz H, Koster A: Influence of argatroban on coagulation parameters in heparin-induced thrombocytopenia patients after cardiothoracic surgery. J Thromb Haemost 2007; 5:1982–4
47. Koster A, Hentschel T, Groman T, Kuppe H, Hetzer R, Harder S, Fischer KG: Argatroban anticoagulation for renal replacement therapy in patients with heparin-induced thrombocytopenia after cardiovascular surgery. J Thorac Cardiovasc Surg 2007; 133:1376–7
48. Klingele M, Bomberg H, Lerner-Gräber A, Fliser D, Poppleton A, Schäfers HJ, Groesdonk HV: Use of argatroban: Experiences in continuous renal replacement therapy in critically ill patients after cardiac surgery. J Thorac Cardiovasc Surg 2014; 147:1918–24
49. Pappalardo F, Scandroglio AM, Potapov E, Stepanenko A, Maj G, Krabatsch T, Zangrillo A, Koster A, Hetzer R: Argatroban anticoagulation for heparin induced thrombocytopenia in patients with ventricular assist devices. Minerva Anestesiol 2012; 78:330–5
50. Samuels LE, Kohout J, Casanova-Ghosh E, Hagan K, Garwood P, Ferdinand F, Goldman SM: Argatroban as a primary or secondary postoperative anticoagulant in patients implanted with ventricular assist devices. Ann Thorac Surg 2008; 85:1651–5
51. Treichl B, Bachler M, Lorenz I, Friesenecker B, Oswald E, Schlimp CJ, Pedross F, Fries D: Efficacy of argatroban in critically ill patients with heparin resistance: A retrospective analysis. Semin Thromb Hemost 2015; 41:61–7

52. Kiser TH, Burch JC, Klem PM, Hassell KL: Safety, efficacy, and dosing requirements of bivalirudin in patients with heparin-induced thrombocytopenia. Pharmacotherapy 2008; 28:1115–24
53. Pieri M, Agracheva N, Bonaveglio E, Greco T, De Bonis M, Covello RD, Zangrillo A, Pappalardo F: Bivalirudin *versus* heparin as an anticoagulant during extracorporeal membrane oxygenation: a case-control study. J Cardiothorac Vasc Anesth 2013; 27:30–4
54. Ranucci M, Ballotta A, Kandil H, Isgrò G, Carlucci C, Baryshnikova E, Pistuddi V; Surgical and Clinical Outcome Research Group: Bivalirudin-based *versus* conventional heparin anticoagulation for postcardiotomy extracorporeal membrane oxygenation. Crit Care 2011; 15:R275
55. Pieri M, Agracheva N, Di Prima AL, Nisi T, De Bonis M, Isella F, Zangrillo A, Pappalardo F: Primary anticoagulation with bivalirudin for patients with implantable ventricular assist devices. Artif Organs 2014; 38:342–6
56. Keyl C, Lehane C, Zimmer E, Trenk D: Monitoring anticoagulation with argatroban in critically ill patients: Activated partial thromboplastin time *versus* diluted thrombin time. Thromb Haemost 2016; 116:1180–1
57. Laverdure F, Louvain-Quintard V, Kortchinsky T, Rezaiguïa-Delclaux S, Imbert A, Stéphan F: PF4-heparin antibodies during ECMO: Incidence, course, and outcomes. Intensive Care Med 2016; 42:1082–3
58. Warkentin TE, Greinacher A, Koster A: Heparin-induced thrombocytopenia in patients with ventricular assist devices: Are new prevention strategies required? Ann Thorac Surg 2009; 87:1633–40
59. Shah P, Tantry US, Bliden KP, Gurbel PA: Bleeding and thrombosis associated with ventricular assist device therapy. J Heart Lung Transplant 2017; 36:1164–73

ANESTHESIOLOGY REFLECTIONS FROM THE WOOD LIBRARY-MUSEUM

The Summer of 1884: Nitrous Oxide from Drs. Gross and Basehore

This early color-free image of two well-dressed girls (*left*) is the obverse of a trade card from the Wood Library-Museum's Ben Z. Swanson Collection. "Gross & Basehore, Dentists" advertised dental extraction services in York, Pennsylvania "without pain, using nitrous oxide gas." A shoemaker-turned-dentist, Milton H. Gross (1857 to 1935) earned his D.D.S. in 1880 from the Baltimore College of Dental Surgery. Related to one of Dr. Gross's dental school classmates, Horace E. Basehore (1862 to 1931) abandoned bartending to become Gross's preceptee. Analysis of newspaper advertisements helps date this trade card to the summer of 1884. (Copyright © the American Society of Anesthesiologists' Wood Library-Museum of Anesthesiology.)

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