Anticoagulants and Thrombolytics

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Introduction

Anticoagulants and thrombolytics are used during several procedures that the interventionalist performs. In this chapter, we will review patient safety issues with the use of these agents.

Heparin

Heparin is used in several access interventions. Two formulations of heparin exist – unfractionated heparin (UFH) and low molecular weight heparin (LMWH). UFH has a molecular weight of 15,000 Da, and LMWH, which is prepared by de-polymerization of UFH, has a molecular weight of approximately 5000 Da. Since LMWH is typically not used in the interventional nephrology setting, discussions in this chapter will be limited to UFH.

Heparin is an indirect thrombin inhibitor (Fig. 5.1). It forms a complex with the heparin binding site of antithrombin, which is a circulating cofactor and at baseline is a slow inactivator of thrombin, factor Xa, and, to a lesser extent, factors XIIa, XIa, and IXa. The binding of heparin accelerates the inactivating function of antithrombin by 1000–4000-fold [1, 2].

With IV dosing, the onset of action is immediate. The half-life of elimination is dose dependent. With the usual doses used in interventional nephrology procedures (3000–5000 units), the half-life is 30 min. The limitations of heparin include a narrow therapeutic window of anticoagulation (without bleeding) and a highly variable dose–response relation. In addition, heparin has a reduced ability to inactivate thrombin bound to fibrin as well as factor Xa bound to activated platelets within a thrombus. As a result, a thrombus may continue to grow during heparin therapy [3].

The most dreaded adverse reaction to heparin is bleeding. Although there is a strong clinical correlation between subtherapeutic activated partial thromboplastin time (aPTT) and recurrent thromboembolism, the relation between supratherapeutic aPTT and bleeding is less clear. Patients who have had recent surgery or trauma, or who have other clinical factors which predispose to bleeding, such as occult malignancy, liver disease, hemostatic defects, age >65 years, female gender, and a reduced baseline hemoglobin concentration, seem to be at a higher risk for bleeding with heparin.

Bleeding Risk During Interventional Procedures

The incidence of bleeding complications during and after thrombectomy (Fig. 5.2) is about 2–3%, with the incidence increasing to 10–15% with the use of pharmacologic thrombolysis. Bleeding, when it occurs, is usually seen at the sites of cannulation. Bleeding from the sites of attempted cannulation by dialysis staff is unfortunately common. Education of dialysis staff to examine the AV access for patency before attempting to cannulate can help reduce the incidence of such bleeding. Manual compression or placement of percutaneous sutures at the sites of cannulation is usually adequate to prevent/treat such bleeding.

Periaccess hematomas are often encountered. Most are small hematomas that do not impede flow in the access. Rarely expanding hematomas may occur, and these may impede flow. Such hematomas can be treated by prolonged angioplasty of the affected site (the angioplasty balloon catheter is held dilated at the affected site for 1–2 min) (Fig. 5.3:

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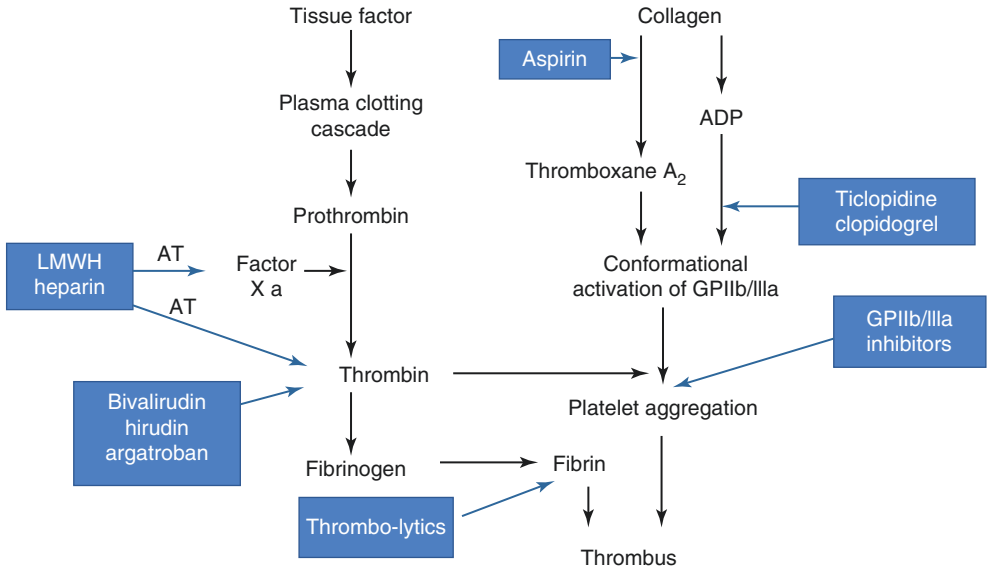

Fig. 5.1 Coagulation cascade

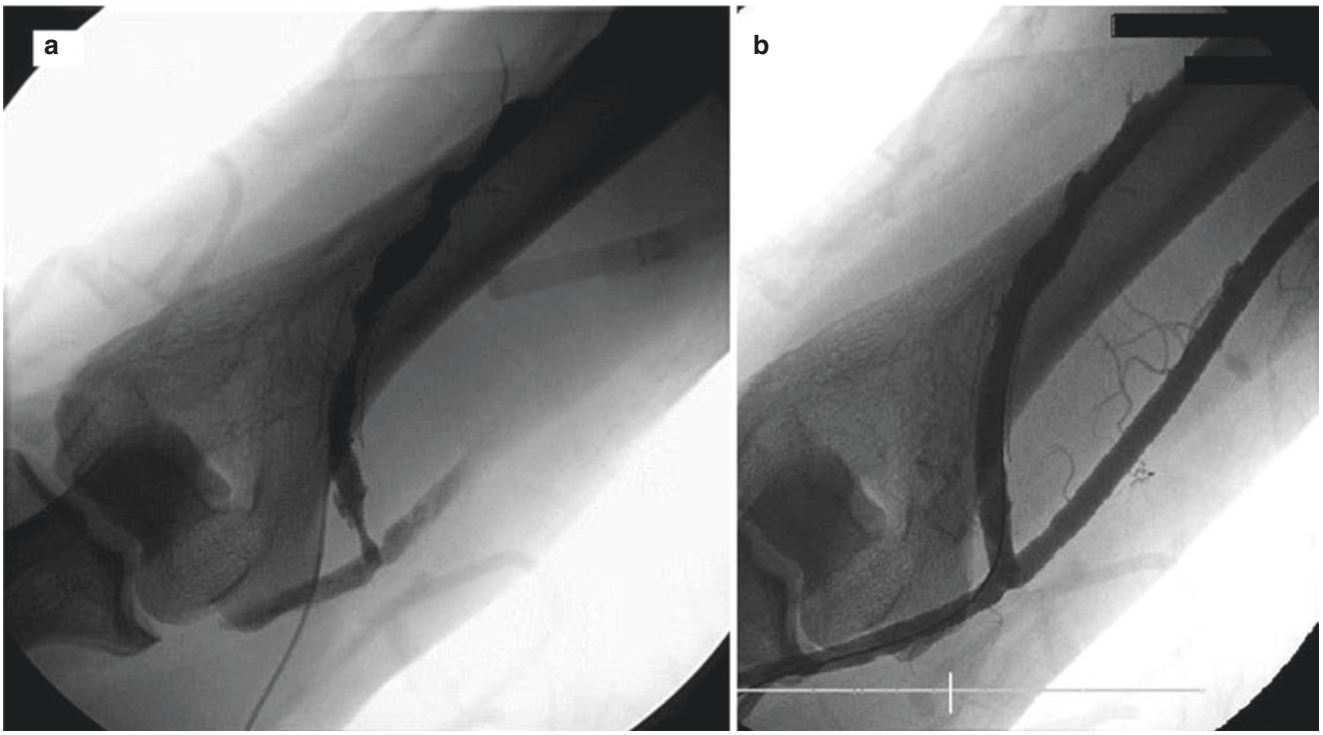

Fig. 5.2 Lesion leading to thrombosis (**a**) and eventual thrombectomy (**b**)

plates d–f) and/or placing a stent across the site of bleeding. In extreme cases the hematoma may not stabilize and may lead to arterial insufficiency of the upper extremity by compression of the brachial artery. In such instances, external compression and occlusion of inflow with an inflated angioplasty balloon catheter while the patient is transported to the hospital can be limb and life-saving.

Hematomas can also occur at the site of angioplasty of juxta-anastomotic stenoses. After angioplasty of the juxta-anastomotic stenoses, the inflow artery is usually selectively catheterized, and an arteriogram is performed to evaluate for complications of the angioplasty and to avoid vein rupture associated with retrograde injection. While withdrawing the catheter, it could inadvertently "flip" and injure the vessel wall and result in a hematoma (Fig. 5.3). To avoid this, it is advisable to introduce a guidewire into the catheter and remove the catheter over the guidewire.

Delayed bleeding is possible, when patients are sent back to their dialysis centers after thrombectomy and they receive

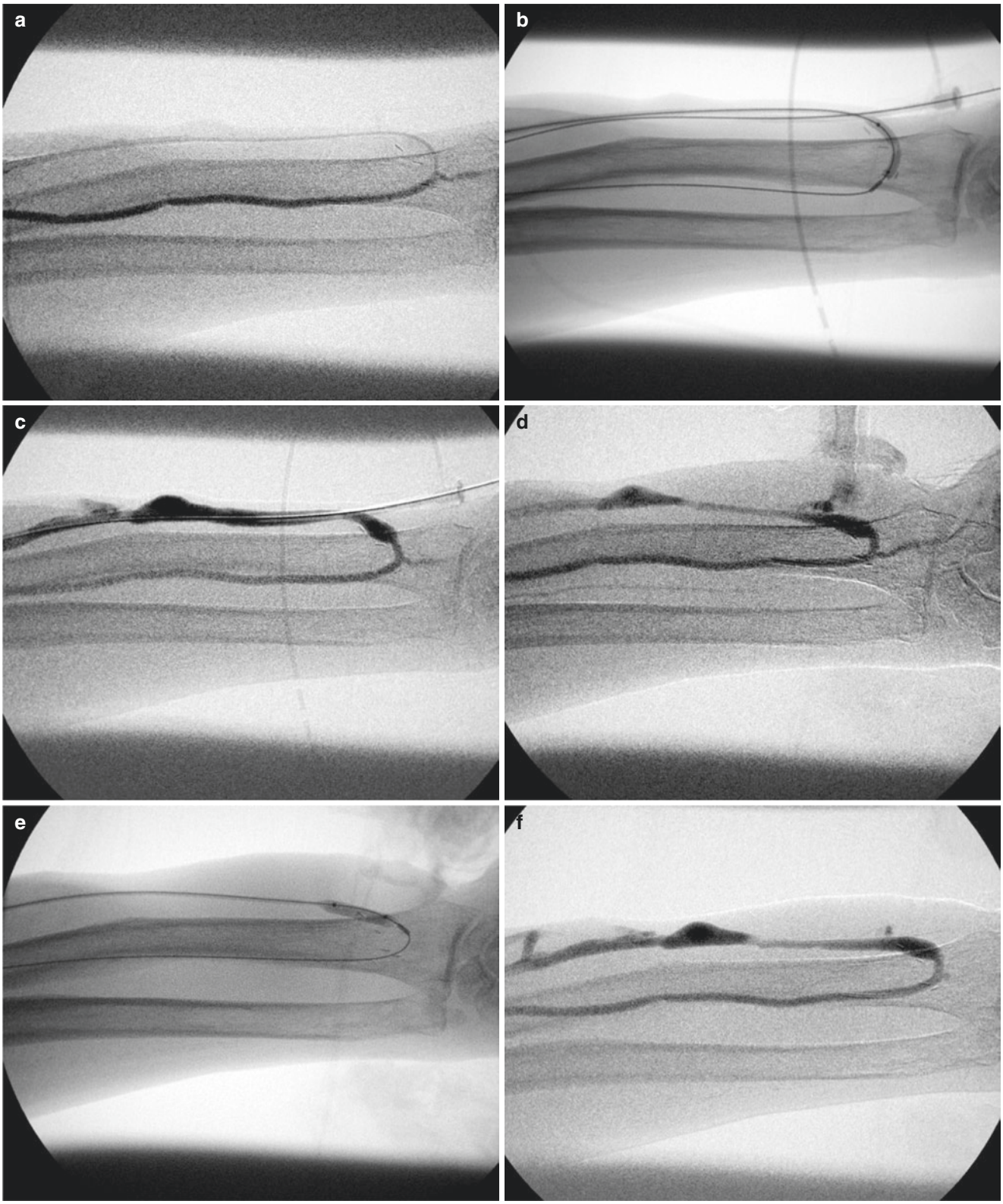

Fig. 5.3 Extravasation at the site of juxta-anastomotic stenosis. (**a**) Severe juxta-anastomotic stenosis with minimal flow into the fistula. (**b**) Angioplasty of the stenosis. (**c**) Post-angioplasty angiogram with improved flow. (**d**) Extravasation/hematoma after withdrawal of the vascular catheter – the catheter "flipped" and injured the vessel wall. There is sluggish flow in the fistula. (**e**) Prolonged angioplasty. (**f**) Resolution of extravasation and improved flow

additional doses of heparin. A common practice employed is to use a reduced bolus dose of heparin if dialysis is provided post-procedure on the same day.

Dialysis Catheter Procedures

After a failed thrombectomy procedure, the patient would likely need a tunneled dialysis catheter placement to continue receiving hemodialysis. The patient would have received heparin during the thrombectomy procedure. As described above, the half-life of heparin in the usual doses used for outpatient interventions is 30 min. It is safe to place a tunneled dialysis catheter after a failed thrombectomy. However, central venous patency should be evaluated with an angiogram prior to insertion of the catheter because central venous stenoses could increase the pressure in the jugular vein and if untreated could lead to bleeding from the venotomy or from the exit site.

Heparin-Induced Thrombocytopenia

Heparin is used routinely as an anticoagulant during hemodialysis and for dialysis access interventions. Heparin-induced thrombocytopenia (HIT) is a well-recognized complication of heparin therapy. As many as 10–20% of patients receiving unfractionated heparin will experience a decrease in platelet count to less than the normal range or a 50% decrease in platelet count from the baseline.

There are two major mechanisms causing thrombocytopenia. In majority of the cases, the thrombocytopenia occurs within the first 48–72 h after heparin initiation. The platelet counts return to normal with continued heparin use. This is Type 1 HIT and is of no clinical consequence. The mechanism is non-immune and appears to be due to a direct effect of heparin on platelet activation.

Type 2 occurs in 0.5–3% of patients receiving heparin. These patients develop an immune thrombocytopenia, mediated by antibodies to a heparin-platelet factor 4 complex [4].

In contrast to other autoimmune thrombocytopenias, the platelet count usually does not drop below 50,000, and spontaneous bleeding is unusual. However, in patients who have been diagnosed with HIT, the subsequent 30-day risk of a thrombotic event (arterial and/or venous) is 53% [5]. Pulmonary embolism was the most common life-threatening thrombotic event.

The patients receiving hemodialysis are continually exposed to heparin and are at risk of developing heparin-platelet factor 4 complex antibodies. Reports have described the prevalence of these antibodies in this population with frequencies ranging from 0% to 12% [6, 7].

It is important to note that the mere presence of heparin-platelet factor 4 complex antibodies does not suggest a diagnosis of HIT in the absence of other clinical events.

In addition, several case reports have reported a dramatic improvement in access patency after discontinuing heparin with hemodialysis and beginning treatment with warfarin. This suggests that heparin antibodies have a role in recurrent vascular access occlusion in some patients [8].

Planning Interventions in Patients Receiving Warfarin

Dialysis patients who present to the interventionalist may be on warfarin therapy for various reasons. For instance, the prevalence of atrial fibrillation is about 10% in US dialysis patients [9]. A large proportion of these patients can be expected to be treated with warfarin. The question arises as to the safety of performing vascular access interventions in these patients. There is a paucity of data regarding this. The placement of tunneled dialysis catheters in patients on warfarin is safe [10].

It should be a standard practice to routinely evaluate patients on warfarin for central venous stenosis and perform angioplasty on any such lesions before placing a tunneled dialysis catheter. As described before in this chapter, this decreases the pressure in the jugular vein and the chances of postoperative bleeding.

During thrombectomy procedures, it is unknown whether the dose of heparin given systemically should be reduced. In the absence of specific data, we reduce the dose of heparin to 3000 units (instead of the 5000 units that is routinely used in thrombectomy procedures) in patients who have a therapeutic INR. In such cases, to avoid embolizing all the thrombus material, we also aspirate as much of the thrombus with the aid of a 6-French vascular catheter. A 6-French vascular catheter is passed over a guidewire, and several passes are made while applying negative pressure and thrombus material aspirated and discarded, reducing the volume of the thrombus embolized centrally.

Warfarin to Prevent Thrombosis of Dialysis Accesses

Warfarin does not prevent thrombosis/failure of an AV graft, and its use is associated with increased incidence of bleeding. In a multicenter randomized control study, 107 patients

with new grafts were randomly assigned to receive warfarin (target INR of 1.4–1.9) or placebo. There was no difference in graft thrombosis between the two groups. The incidence of major hemorrhage was 10% despite close monitoring of the INR [11].

A subset of dialysis patients in whom thrombosis of the AV graft occurs within the first 48 h of surgery, and those who have recurrent graft thrombosis, may have a hypercoagulable state contributing to thrombosis. In such patients evaluation for a hypercoagulable state could be performed, and if such a condition is present, warfarin therapy could be considered [12–14]. However, there is paucity of strong data supporting this recommendation. A case could be made for performing a hypercoagulable state evaluation in select patients as follows:

1. Patients in whom the graft thrombosis occurs is in the first 48 h of surgery
2. Patients in whom the graft thromboses are without an anatomical lesion *AND* in whom the blood pressure is normal
3. Patients who have had more than three episodes of thrombosis in a calendar year

Anti-phospholipid antibodies (aka anti-cardiolipin antibodies), lupus anticoagulant, beta-2 glycoprotein (IgM, IgG), activated protein C resistance, protein C and S levels, and evaluation for antithrombin deficiency could be obtained. If the work-up above is positive, then low-dose warfarin therapy (target INR of 1.5–2.0) could be considered.

Newer Anticoagulant Medications

The new orally active anticoagulants (dabigatran, rivaroxaban, and apixaban) are increasingly being used in the dialysis patients. However, there are no safety data with intervention on the use of these medications in this subset of patients. Lack of effective antidotes and risk of bleeding with interventions in patients who are on these agents cannot be advocated at this time. Most common practice is to discontinue these agents for at least 48–72 h prior to any endovascular intervention, balancing the risk of thrombosis in other vascular beds versus bleeding post-procedure.

Thrombolytics

Thrombolytic therapy is used in the management of thrombosed AV accesses. The most commonly used agent is alteplase (recombinant tissue plasminogen activator – tPA). When given intravenously, the onset is almost instantaneous. The drug binds to fibrin in a thrombus and converts entrapped plasminogen into plasmin, thus initiating local fibrinolysis. It is a short-acting drug with about half the drug present in the plasma cleared in 5 min after termination of the infusion and more than 80% cleared within 10 min.

Reteplase (onset of thrombolysis in 30–90 min and half-life of elimination of 13–15 min) and urokinase have been used as well. Due to the delayed onset of reteplase and the predominantly extravascular activation of fibrinolysis by urokinase (in contrast to tPA which is largely responsible for initiating intravascular fibrinolysis), neither is used commonly during endovascular procedures.

Doses of 0.5–2 mg of tPA are usually used. With such doses the incidence of complications is about 10–15% [15]. Most are minor complications and include bleeding from dialysis cannulation sites and periaccess hematomas. Major complications are uncommon and include vein rupture. These can be treated with prolonged angioplasty and/or stenting. Rarely arterial rupture can be a complication (Fig. 5.4). If this happens, the first and only priority is to save the limb. A stent could be placed across the rupture. More often than not, ligation of the access and arterial bypass may be needed. It is of paramount importance to evaluate the artery with an arteriogram after arterial angioplasty to recognize this complication.

Given the rapid clearance of tPA, it is safe to place tunneled dialysis catheters should a thrombectomy be unsuccessful. In the in-patient setting, continuous tPA infusion has been used to achieve thrombolysis, however increasing the risk of systemic bleeding complications.

Summary and Recommendations

1. The use of anticoagulants and thrombolytics in percutaneous interventions of dialysis accesses is safe.
2. The most common complication of the use of anticoagulants and thrombolytics is bleeding.
3. Bleeding from access cannulation sites can be controlled with percutaneous sutures.
4. Bleeding from sites of angioplasty can be treated with prolonged balloon tamponade and/or stenting.
5. After selective catheterization of an artery, removal of the catheter over a guidewire should be considered.
6. If a tunneled dialysis catheter is needed after the patient has received anticoagulants and/or thrombolytics, central venous patency should be evaluated with an angiogram. If central venous stenoses are noted, then these should be treated before placement of a catheter.

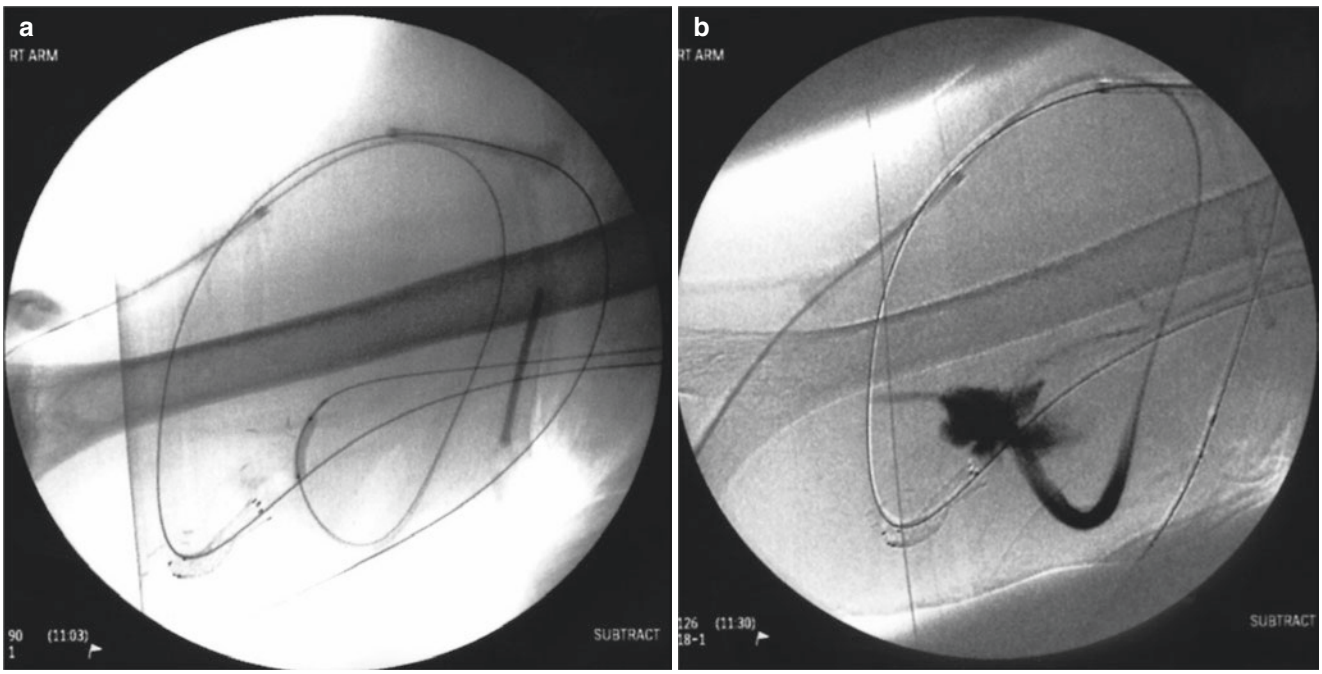

Fig. 5.4 Arterial anastomotic angioplasty complicated by arterial rupture. The patient underwent brachial artery bypass (**a**) Angioplasty balloon across the arterial anastomosis. (**b**) Arterial rupture post angioplasty requiring surgical intervention

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