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Penetrating aortic ulcer

Defining risks and therapeutic strategies

Acute aortic syndrome (AAS), subsuming classic aortic dissection (AD), intramural hematoma (IMH), and penetrating aortic ulcer (PAU), has attracted considerable attention among aortic specialists over the last decade [40]. Advanced imaging modalities such as computed tomography (CT) angiography, magnetic resonance imaging (MRI), and positron emission tomography (PET) have hereby provided greater insight into these aortic wall pathologies, notably PAU [27, 39]. Despite a substantial clinical overlap with AD and IMH, several questions regarding pathophysiology, surveillance, management, and treatment indications remain to be answered—especially in patients with asymptomatic PAU. At present, general consensus for surgical repair includes patients with symptomatic or ruptured PAU [51]. Contemporarily, endovascular stent grafting has emerged as the primary treatment option for these patients. However, the indication for treatment in asymptomatic patients remains controversial [58]. The aim of this article is to review and discuss the current understanding of PAU, its treatment indications, defined risk factors and operative results in the endovascular era.

Disease characteristics

Initially characterized in 1934 by Shennan, PAU is defined as a focal atherosclerotic lesion that ulcerates and disrupts the internal elastic lamina of the aortic wall [55, 66]. Subsequently, development of an intramural hematoma may occur due to erosion of the vasa vasorum by the ulcer. However, the reverse, namely IMH-triggered formation of PAU has recently been postulated [27]. Potential added complications are pseudoaneurysm formation, progression to classic AD, and propensity to rupture. Compared to aortic dissection, the risk of rupture (7% for type A AD and 3.6% for type B AD) is considerably higher (up to 40%) [9, 61].

Albeit clinical differentiation of PAU from IMH and AD may be challenging as all of them present with classic "chest pain", the radiologic presentation of PAU is somewhat unique. Today, PAU is best diagnosed by contrast-enhanced CT scanning [52]. Typical radiologic features of PAU are an out-pouching ulcer crater, intimal calcification, and localized intramural hemorrhage in conjunction with the presence of severe atherosclerotic disease (**Fig. 1**, [17, 42]). PAU is more frequently seen in the descending thoracic aorta (DTA) than in the aortic arch or the abdominal aorta (**Fig. 2**, [9, 22, 25, 32, 57, 63, 65]). Ulcers are often multiple and may range from 4–30 mm in depth and from 2–25 mm in diameter [63].

Data from previous studies suggest an incidence of PAU ranging from 2.3–11% in patients presenting with AAS [4, 65]. In an autopsy series by Hirst and Barbour [29], nearly 5% of dissections originated from PAU. However, as screening for PAU is not performed in asymptomatic patients, the true prevalence of this pathology is unknown. Whereas some authors suspect the incidence of PAU to have risen because of evolving imaging modalities, others assume that it might not be as high as suspected [4, 40]. A recently performed study on incidental findings on cardiac CT scans revealed only 2 PAUs among 966 scans [43]. Another group only found 1 PAU in 395 CT scans obtained for suspected acute coronary syndrome [41].

PAU typically occurs in older men (>70 years) with significant cardiovascular comorbidities, including hypertension, tobacco abuse, coronary artery disease, chronic obstructive lung disease, and renal insufficiency. Usually, their life expectancy does not exceed 10 years postdiagnosis, underlining the severity of disease in these patients [3, 44, 59, 63]. The presence of concurrent abdominal aortic aneurysms has been observed in up to 60% of patients with abdominal PAU [8, 10].

Assessment of natural history and outcome

There is an ongoing debate in the literature on the nature of PAU. It should be of note that differences in outcome, frequency of symptoms, and progression between the series available may be due to selection bias, since several studies are based on the suspicion of aortic dissection. As many series combine lesions of the ascending and descending aorta in their analysis, a thorough understanding of the behavior is further complicated.

Due to the "potentially progressive and serious nature" of PAU, aggressive surgical treatment of symptomatic patients was already recommended in the pioneering report by Stanton et al. [57]. Cooke et al. [11] equally advocated surgical repair in symptomatic cases, as their experience with conservative medical therapy frequently led to recurrence of symptoms. In an early study by the Yale group [9], surgical intervention was encouraged in patients who exhibit early clinical or radiologic signs of deterioration, as 40% of primarily con-

Tab. 1 Indication algorithm for endovascular treatment of penetrating aortic ulcer according to clinical symptoms and radiographic signs

Symptomatic	Asymptomatic	
Emergency treatment	**Accepted indication**	**Relative indication**
Rupture	PAU with pleural effusion	Stable lesions
Type A PAU	PAU with associated IMH	Increasing PAU depth
Urgent treatment	Type A PAU	Large pseudoaneurysm
Recurrent/persistent pain		
Aortobronchial fistula		
Aortoenteric fistula		

PAU penetrating aortic ulcer, IMH intramural hematoma, type A according to the Stanford Classification of aortic dissection.

servatively treated patients with thoracic PAU needed emergency interventions for rupture. The group has recently re-enforced their advocacy due to an observed early rupture rate of 38%, a hospital mortality of 15%, and an intervention rate of 65% among 26 patients with thoracic PAU. Surgical replacement of the diseased aortic portion was recommended "as long as the patient's comorbidities do not preclude surgical intervention" [61]. However, both series are based on patients undergoing diagnostic workup for the suspicion of aortic dissection. Their point of view was shared by the Stanford group, based on their experience of treatment of 65 IMH cases, 33 of them with PAU. If PAU was present, progression occurred in 48%. A strictly conservative regimen led to 10% mortality within a mean of just 9.3 days [21].

On the other hand, a number of authors reported satisfactory results with a conservative approach to PAU. Quint et al. [50] provided retrospective CT data from 33 lesions, in which follow-up scans were available (mean interval, 18.4 months). Twenty-one of the 33 lesions (64%) were stable over time. In 10 lesions (36%), an increase in diameter was detected. In 3 of 8 surgically treated cases, follow-up CT scans were obtained prior to resection or stent-graft placement: 1 lesion was stable, 1 regressed, and 1 progressed on CT. Cho et al. [8] retrospectively reported on 105 cases with PAU of the DTA or aortic arch, of which 75% showed symptoms at admission. The period under review was 25 years; all data were derived from their institution's AAS database. Conservative treatment was successfully applied in 66% of cases. The 30-day mortality for medical and surgical treatment was 4% and 21%, respectively ($p < 0.05$). Therefore, the authors pointed out that many PAU may be managed non-operatively—even in the acute setting. This is in line with Hussain et al. [31], who have also reported on effective application of medical therapy. In their series, 4 of 5 patients with PAU survived without surgery. Kazerooni et al. [33] reported suspension of symptoms in 8 of 9 conservatively treated patients.

Defining treatment indications

In absence of randomized controlled trials, the level of evidence in the treatment of PAU is low (Level C). Recommendations for treatment are mostly based on case-series studies and expert opinion [59]. While it is difficult to support a data-driven approach for the indication of surgical treatment of PAU due to the heterogeneity of data available, there are several clear-cut indications (**Tab. 1**). Recurrent or refractory pain is considered to be one of the most important clinical symptoms in determining the appropriateness of surgical intervention [10, 11, 21, 57]. In addition, Ganaha et al. [21] identified increasing pleural effusion ($p = 0.0003$) and both the maximum PAU diameter and maximum PAU depth (21.1 ± 8.0 mm and 13.7 ± 4.2 mm; $p = 0.004$ and $p = 0.003$, respectively) as risk factors for progression. In their series, presence of PAU in conjunction with IMH was associated with a significantly worse prognosis compared to presence of IMH alone. If a causal PAU is present in patients with IMH, endovascular repair is recommended (**Tab. 1**, [59]). Further interesting data, highlighting the association between PAU and

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Penetrating aortic ulcer. Defining risks and therapeutic strategies

Abstract

In addition to classic aortic dissection and intramural hematoma, acute aortic syndrome also includes penetrating aortic ulcers (PAU). The recent advent of highly detailed axial imaging allows closer assessment of PAU and its pathophysiology. However, there is still ongoing discussion about the natural history of the disease, leading to challenging questions concerning the optimal treatment strategy, particularly in asymptomatic patients. In this review, current indications for treatment, with an emphasis on PAU repair in the endovascular era, are discussed.

Keywords

Penetrating aortic ulcer · Acute aortic syndrome · Aortic diseases · Endovascular procedures · Stent-graft

Das penetrierende Aortenulkus. Definition von Risiken und Therapiestrategien

Zusammenfassung

Das penetrierende Aortenulkus (PAU) zählt mit dem intramuralen Hämatom und der klassischen Aortendissektion zur Entität des akuten Aortensyndroms. Trotz moderner Schnittbildgebung, welche eine hochauflösende Darstellung dieser Aortenpathologie erlaubt, sind die dem PAU zugrunde liegenden pathophysiologischen Zusammenhänge noch nicht vollständig geklärt. Aufgrund der unzureichenden Datenlage bezüglich des natürlichen Verlaufs der Erkrankung bestehen nach wie vor offene Fragen hinsichtlich der optimalen Behandlungsstrategie. Dies trifft insbesondere bei klinisch asymptomatischen Patienten zu. In der vorliegenden Übersichtsarbeit werden aktuelle Behandlungsindikationen und Therapieansätze bei PAU mit dem Schwerpunkt der endovaskulären Versorgung diskutiert.

Schlüsselwörter

Penetrierendes Aortenulkus · Akutes Aortensyndrom · Aortale Wanderkrankungen · Endovaskuläre Verfahren · Stentgraft

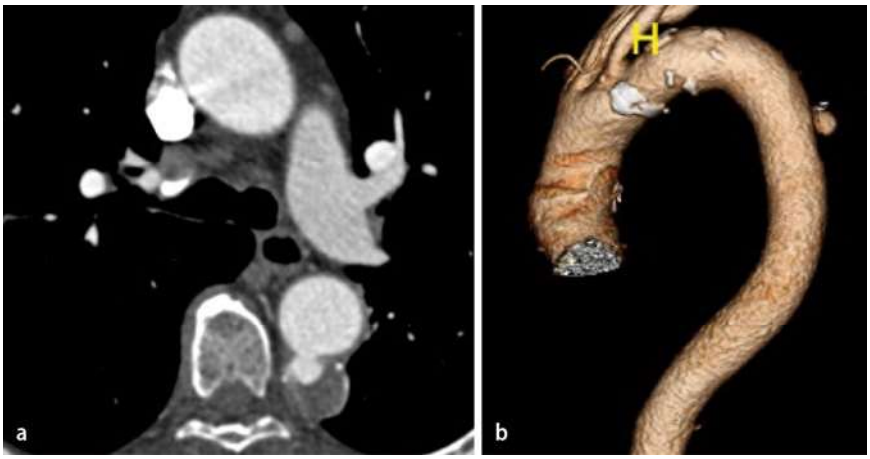

Fig. 1 ▲ **a** Axial contrast-enhanced CT image showing penetrating aortic ulcer on the posterior aspect of the upper descending thoracic aorta. **b** Corresponding 3D reconstruction demonstrating the outpouching character of the lesion

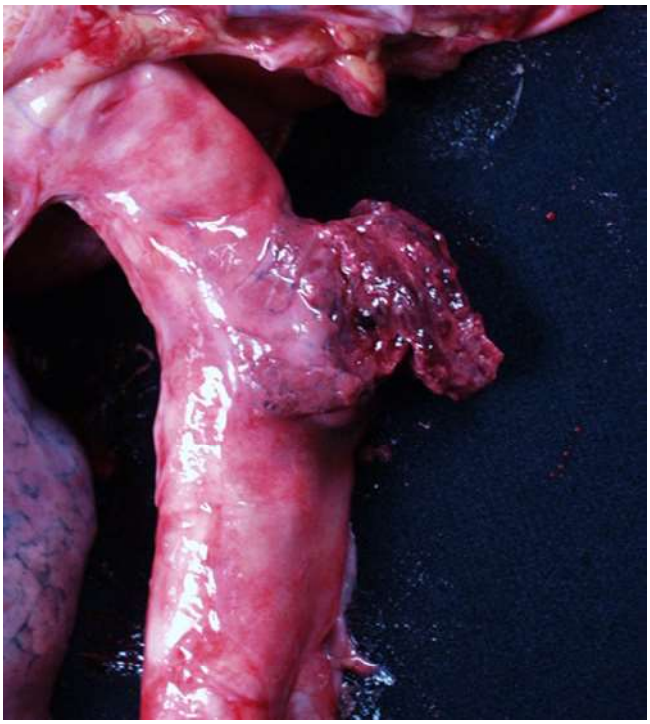

Fig. 2 ◀ Autopsy specimen of the thoracic portion of the aorta including penetrating aortic ulcer

IMH, have been recently provided by the Michigan group [46]. Patel et al. identified the presence of an associated intramural hematoma as a risk factor for TEVAR treatment failure ($p = 0.033$).

Rapid increase of aortic diameter and hemodynamic instability have been equally described as criteria for immediate surgery [9, 25]. Moreover, it has been suggested that the maximum aortic diameter may be a useful indicator for surgical intervention. In our own series, asymptomatic patients had a significantly smaller maximum aortic diameter ($p = 0.002$); others, however, reported that a maximum diameter > 50 mm was an independent risk factor for death ($p = 0.021$) [25]. The difference in behavior according to lesion location has been well described for classic AD [58]. Although data concerning type A vs. type B PAU are rare, anecdotal evidence suggests that distinction between those located within the ascending aorta or arch, and those involving the descending aorta can be adopted for PAU as well [35, 56]. Therefore, urgent surgical repair is recommended for type A lesions (◘ **Tab. 1**, [17]). In infrarenal PAU, distal embolization and aortoenteric or aortobronchial fistulas have to be considered as indication for repair [7, 20, 26]. In the 2008 expert consensus document on the treatment of DTA disease, endovascular stent-grafting of thoracic PAU is recommended in all symptomatic patients not suitable for open repair [59].

Evidence for the best treatment strategy in asymptomatic patients is still lacking. The current recommendation classification is III, level of evidence C [59]. In any case, close follow-up including serial aortic imaging, whether with CT or MRI, is recommended [32]. In addition, PET-CT may be helpful to evaluate the grade of inflammation in order to identify patients at risk for progression [39]. At our institution, patients diagnosed with an asymptomatic PAU are scanned twice within the first year after diagnosis for close evaluation of disease progression. In case of a stable lesion, scans can be obtained once a year, with larger intervals during the further course of follow-up. Because lack of symptoms does not necessarily imply lesion stability, we follow up these patients with CT imaging in the same fashion as we do for those with thoracic aortic aneurysms. Subsequent indications for therapy are based on documented radiologic PAU deterioration, symptoms, or morphologic aspects (e.g., large pseudoaneurysm; ◘ **Tab. 1**). Furthermore, consequent treatment of the present comorbidities is also sought. Undoubtedly, we currently recommend elective endovascular repair due to our favorable experience with this approach in this subset of patients [22, 32]. A conservative approach to symptomatic PAU usually involves close monitoring in the intensive care unit with antihypertensive therapy and repeated CT angiography scans. However, long-term application of such a strategy is not part of our philosophy because of the well-described risks associated with PAU progression.

Endovascular treatment of PAU—current status

The traditional therapeutic approach to PAU in symptomatic patients is open surgical repair and replacement of the diseased aortic segment [9]. As previously highlighted, the majority of patients presenting with PAU may not be suitable for conventional surgery because of their gen-

Tab. 2 Overview of selected publications ($n \geq 10$) on TEVAR in patients with thoracic penetrating aortic ulcer

Author/year of publication	*n*	Symptoms (%)	Technical success (%)	pEndoleak I (%)	In-hospital mortality (%)	Morbidity (%)	Mid-term survival (%)
Kos et al. 2002 [37]	10	60	100	40/30	0	10	N.A.
Demers et al. 2004 [15]	26	23	92	8/8	12	19	76[b]/70[c]
Eggebrecht et al. 2006 [16]	22	64	96	5/5	0	5	83[a]/62[c]
Brinster et al. 2006 [5]	21	76	100	0	0	5	N.A.
Dalanais et al. 2007 [14]	18	100	100	6/0	0	39	N.A.
Piffaretti et al. 2007 [49]	11	45	100	0	0	45	100[b]/89[c]
Gottardi et al. 2008 [25]	27	26	100	0	11	11	78[b]/70[c]
Geisbüsch et al. 2008 [22]	48	65	94	19/4	15	31	74[b]/61[c]
Botta et al. 2008 [3]	19	37	95	6/0		22	72[b]/67[c]
Patel et al. 2010 [46]	37	60	100	8/5		14	84[c]e/46[c]ue

N.A. not applicable, **pEndoleak I** primary endoleak type I, **e** elective, **ue** urgent or emergent, [a]2-year survival, [b]3-year survival, [c]5-year survival.

Tab. 3 Overview of selected publications on EVAR in patients with abdominal penetrating aortic ulcer

Author/year of publication	*n*	Symptoms (%)	Technical success (%)	pEndoleak I (%)	In-hospital mortality (%)	Morbidity (%)	Mid-term survival (%)
Tsuji et al. 2003 [64]	4	75	100	0	0	0	N.A.
Batt et al. 2005 [2]	3	67	100	0	0	0	N.A.
Piffaretti et al. 2007 [48]	13	77	100	0	0	8	N.A.
Hyhlik-Dürr et al. 2010 [32]	20	25	100	20/5	10	25	69[a]/69[b]

N.A. not applicable, **pEndoleak I** primary endoleak type I, [a]3-year survival, [b]5-year survival.

eral condition or significant comorbidities. In high-volume centers, conventional replacement of the DTA is associated with a mortality of 5–20% [12, 18, 19, 67]. Regarding DTA replacement for PAU, a mortality of approximately 15% is reported in the literature [8, 61]. Although open surgery is an effective therapeutic option, endovascular repair has emerged as a treatment modality favorably obliging the patient's increased risk profile. Early reports of low procedural mortality and morbidity rates associated with endografts contributed to their widespread use for the repair of both abdominal and thoracic aortic pathologies, including PAU [59]. Consequently, the use of open surgical approaches for the repair of abdominal and descending thoracic aortic aneurysms has decreased [23]. As PAU is commonly observed as a segmental, localized wall pathology, the entity represents an ideal target for endovascular stent-grafting. Today, endovascular repair of PAU is generally considered as the treatment strategy of choice [40].

TEVAR of PAU

In-hospital mortality in endovascularly treated patients with PAU of the DTA is estimated to be 7% (**Tab. 2**, [17]). In our own series, an in-hospital mortality of 14% (7/48) after TEVAR was observed. At admission, nearly 65% of patients (31/48) presented with symptoms of AAS. Perioperative mortality was significantly higher in symptomatic patients compared to asymptomatic cases (22.5% vs 0%, respectively; p=0.036) [22]. Postoperative complications occurred in 15 patients (31%). In an earlier study by Gottardi et al. [25], in-hospital mortality was 11% (3/27). Demers et al. [15] reviewed their experience in 26 patients with PAU, 6 (23%) of whom had ruptured and 3 (12%) died within 30 days. Botta et al. [3] observed a mortality of 11% (2/19). Among their 19 cases, 37% (7/19) showed symptoms. In 2006, Brinster et al. [5] presented data from 21 patients with PAU of the DTA who underwent endovascular repair. A total of 76% were considered symptomatic; the in-hospital mortality was 0%. No in-hospital death was equally reported by Eggebrecht et al. [16] in a series containing 22 cases of PAU, despite the fact that contained aortic rupture was present in 14% (3/22). Besides one minor stroke, there were no other in-hospital complications. In early 2010, the Michigan group presented their data on 37 patients, who underwent TEVAR for PAU. Reported early mortality and morbidity rates were 5.4% (2/37) and 13.5% (5/37), respectively. A novel localized strategy for endovascular PAU repair has recently been published by Kleisli and Wheatley. In a technical report, the authors describe the successful treatment of a single PAU in the DTA with an Amplatzer occluder [34].

EVAR of PAU

Data on series investigating abdominal PAU are limited due to the less frequent occurrence of the disease in this portion of the aorta (**Tab. 3**). In 2010, we published our experience of 20 patients—5 of them symptomatic—who underwent endovascular repair exclusively for infrarenal PAU at our institution [32]. Postoperatively, complications were observed in 25% of patients (5/20), including 4 myocardial infarctions. In-hospital mortality was 10% (2/20), predominantly related to cardiac complications. In a prospective observational study by Piffaretti et al. [48], no postoperative death was observed among 13 patients with abdominal PAU. However, 1 patient postoperatively suffered a transient ischemic attack. Data on endovascular infrarenal PAU repair

were also published by Batt et al. [2]. The authors reviewed 46 patients with PAU. Yet, only data of 8 patients were derived from their own experience and just 9 patients were treated by endovascular stent-graft repair. Among those, no perioperative death occurred.

Despite the fact that endovascular treatment of thoracic and abdominal PAU has yielded favorable perioperative results, considering the high-risk-profile of the underlying patient population, the available mid-term outcome underlines the significance of comorbidities: 5-year survival is usually around 65% (**Tab. 2** and **Tab. 3**, [3, 16, 22, 32]).

Endovascular treatment of PAU—potential risks

Albeit the technical success rate of endovascular PAU repair approaches 100%, there are considerable caveats in the setting of endovascular treatment of PAU. The majority are linked to the diffuse atherosclerotic setting in which PAU arises. Coronary artery disease, endoleak, access difficulties, and neurologic complications are briefly discussed below.

Coronary artery disease

Severe coronary artery disease is a common finding in patients with PAU, underlining the systemic atherosclerotic burden in these patients [8]. At our institution, cardiac complications were frequently observed after endovascular PAU repair. In the study by Geisbüsch et al. [22], one-third of the postoperative morbidity was cardiac related. In the study by Hylik-Dürr et al. [32], 2 patients died of myocardial infarction, while an additional 4 patients suffered myocardial infarction. A meticulous preoperative cardiologic evaluation is recommended in patients presenting with PAU in order to minimize periprocedural cardiac complications. Successful concomitant coronary artery bypass grafting has been reported in both endovascular and conventional PAU repair [46, 60].

Endoleak

Endoleak represents a frequent complication of endovascular aortic repair [53]. In patients with PAU, jagged wall conditions and laminated thrombus are not ideal for stent graft landing zones. In the series by Botta et al. [3], endoleak was observed in 3 of 16 patients (18%). Two of 3 patients in this series needed further intervention. Hylik-Dürr et al. [32] report on 4 primary endoleaks (20%) and 1 secondary endoleak (5%). Surgical re-intervention was necessary in primary endoleak. Geisbüsch et al. [22] reported on a total of 9 primary and 2 secondary endoleaks in 48 patients (19% and 4%, respectively). Re-intervention was necessary in 4 of the detected 11 endoleaks (36%). The occurrence of secondary endoleaks in these series highlights the need of close life-long follow-up.

Access site complications

In patients with PAU, access complications due to heavily calcified femoral and iliac arteries may represent a significant proportion of periprocedural morbidity [4, 36, 54]. Therefore, preoperative meticulous examination of the target vessels is mandatory to achieve safe access. In patients with unfavorable conditions, alternative access options such as retroperitoneal exposure of the iliac arteries may be considered [6, 47].

Spinal cord injury

Endovascular repair should aim for exclusion of all suspicious lesions neighboring the ulcer as the formation of de novo penetrations at the end of the deployed stent-graft has been described [13, 45, 54]. Sufficient landing zones represent a keystone of successful and durable PAU exclusion. At the authors' institution, a minimum of 15 mm is generally warranted. However, providing adequate landing zones may be attended by coverage of a considerable portion of aorta proximal and distal to the lesion [24]. As the length of aortic coverage represents an independent predictor for spinal cord ischemia, occlusion of an extensive amount of segmental arteries should be prevented whenever possible [1]. In cases where an intentional coverage of the left subclavian artery is necessary to provide a sufficient proximal landing zone, subclavian artery debranching is recommended in selected cases in order to minimize spinal cord ischemia [38].

Stroke

Periprocedural stroke is one of the most dreadful complications in aortic stent-grafting. In recent studies on thoracic PAU, repair resulted in stroke rates which undulate around 4% [3, 16, 22, 46]. Due to evolving device technology—no longer requiring anything except a guide wire—the occurrence of stroke has decreased, as excessive manipulation across a diseased arch can be prevented [30, 62]. Nevertheless, in patients with thoracic PAU and high grade atheroma of the aortic arch, care has to be taken to minimize the risk of embolic stroke events caused by guide wire manipulation during thoracic stent-graft implantation [28].

Conclusions

Given the dynamic character of PAU, a prudent case and stage-adapted treatment strategy is crucial. In symptomatic lesions, intervention is advocated. Endovascular repair has, thereby, emerged as the modality of choice as it favorably obliges both the lesions' segmental nature and the patients' increased risk profile. In asymptomatic patients, general treatment recommendations have yet to be defined due to the lack of reliable data concerning the natural course of PAU. Close follow-up is mandatory in order to detect disease progression. In the absence of randomized trials, elective stent-graft repair represents a valuable and rational option for selected lesions in asymptomatic patients. Ultimately, the patients overall prognosis is highly dependent on the accompanying comorbidities, which highlights the necessity of rigorous multidisciplinary risk factor management in these patients.

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Conflict of interest. The corresponding author states that there are no conflicts of interest.

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