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Covering/Overstenting of the left subclavian artery in TEVAR intervention to treat various thoracic/thoracoabdominal aortic lesions: Is revascularization of the left arm a must? (A retrospective real-world cohort study with 12 years of experience and literature review)

(Short title: TEVAR in the daily clinical setting **)**

Dissertation

To fulfill the attainment of the academic title of
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Pathologies of the thoracic aorta impose themselves as a therapeutic challenge. On one hand, such pathologies must be well secured with the least possible complication; on the other hand, however, the widely varying pathological pictures and likewise anatomical variations of the thoracic aorta are implicated by therapeutic guidelines and recommendations. Hence, the choice of the best therapy is regarded with daily debates in a vascular surgeon's routine work.

This study aims to consider blockage of the left subclavian artery (LSA) as a mandate for the endovascular treatment of the pathologies of the thoracic and suprarenal abdominal aorta - this is not uncommon but scarcely contemplated in the literature- in a unicentric retrospective real-world cohort study. The patient cohort consists of those who underwent endovascular thoracic aortic reconstruction from 2006 to 2018; it contains patients who underwent either pure endovascular or hybrid endovascular/open operative therapy of different thoracic aorta pathologies. Excluded were the patients who suffered from diseases of ascending aorta and infrarenal aortic pathologies.

The aim is to prove that the revascularization of LSA - in case of other intact supra-aortic arteries, especially the vertebral arteries, and the continuous circle of Willis without any right-to-left circulatory interruptions - is not necessarily required.

The yearly postoperative control of the clinical status and further control-examination of the posterior cerebral/left arm circulation (Doppler-/Duplex-ultrasonography examination, comparative measurement of blood pressure) is sufficient to exclude late postoperative circulatory disturbance of the left arm as well as the cerebral circulation.

Keywords: Thoracic, Aorta, Aneurysm, Dissection, Penetration, Ulcer, Intramural, Hematoma, Morbidity, Mortality, Subclavian, Blockage, Ischemia, Over-stenting, TEVAR

List of contents

Section **page**

Abreviations and acronyms

AA	Abdominal aorta
AAA	Abdominal aortic aneurysm
ABF	Aortobronchial fistula
AEF	Aortoesophageal fistula
AD	Aortic dissection
AAD	Acute aortic dissection
AAS	Acute aortic syndromes
ACS	Acute coronary syndrome
BSA	Body surface area
CCA	Common carotid artery
CFD	Computational fluid dynamics
CG	Chimney graft
CSB	Carotidosubclavian bypass
CST	Carotidosubclavian transposition
CTA	Computed tomography angiography
cTns	Cardiac troponins
CVA	Cerebrovascular accident
CVD	Cardiovascular diseases
CVS	Cardiovascular system
DM	Diabetes mellitus
DSA	Digital substraction angiography
ECM	Extracellular matrix
ESVS	European Society of Vascular Surgery
EVAR	Endovascular aortic reconstruction / repair
IMH	Intramural hematoma
LDS	Leoys-Dietz syndrome
LSA	Left subclavian artery
MFS	Marfan's syndrome
MRA	Magnetic-resonance-(imaging) angiography
NT pro-BNP	N-terminal pro-brain natriuretic peptide
PAD	Peripheral arterial disease
PAU	Penetrating aortic ulcer
PIS	Postimplantation syndrome
RCT	Randomized controlled trials
RSA	Right subclavian artery

SCB	Subclavia-carotid bypass
SCT	Subclavia-carotid transposition
SMAD	Small mother against decapentaplegic (Protein family that transfers signals from cell receptors to the nucleus)
SSEP	Somatosensory evoked potential
SSS	Subclavian steal syndrome
TA	Thoracic aorta
TAA	Thoracic aortic aneurysm
TAAA	Thoracoabdominal aortic aneurysm
TAADs	Thoracic aortic aneurysms and dissections
TEE	Transesophageal echocardiography
TEVAR	Thoracic endovascular aortic reconstruction / repair
TGF	Transforming growth factor
TTE	Transthoracic echocardiography
vs.	*versus*
VSMC	Vascular smooth muscle cell
vEDS	Vascular Ehler–Danlos syndrome
WSS	Wall shear stress

1. Introduction

1.1. General remarks

Pathologies of the descending thoracic aorta inwardly extended toward the aortic arch can shorten the proximal landing zone of aortic prosthesis, thereby worsening the feasibility of the aorta for endovascular therapies. To overcome this difficulty, the literature shows that it is either possible

- To overlap the encroachment area of the varying pathologies into the aortic arch, which forces the therapist to block the supra-aortic vessels. This criterion is mainly met in the left subclavian artery (LSA),

  or otherwise (which is nowadays rare)
- The patient undergoes conventional (open) vascular surgical intervention ("old" traditional way) without any implication of endovascular methods.

In case of lesion encroachment into the aortic arch with a possible blockage of the LSA in order to achieve thoracic endovascular maneuvers, the term "revascularization" needs to be considered. This refers to ensuring the blood supply for the left arm either prophylactic preoperatively or stepwise postoperatively by means of transposition or bypass implantation [(1).]

The literature contains an ongoing debate as to whether it is primarily indicated to revascularize the LSA before performing the endovascular therapy of different pathologies of descending thoracic aorta with short landing zones less than 2 cm long.

This work is specifically designed as a retrospective unicenter observational study in a consecutive patient cohort that considers the coverage of the LSA through the endovascular treatment of pathologies of the descending aorta. This is a main work-question based on the hypothesis that obligatory preventive revascularization of the LSA, prior to the endovascular approach such as TEVAR, is not regularly required and can be avoided, except in rare but well-defined anatomic variants or the vascular pathologies of cerebrovascular blood supply.

1.2. Anatomy, physiology, and hemodynamics of the thoracic aorta and peri-aortic region

1.2.1. Anatomy of the aorta

The aorta mainly has two parts: the thoracic aorta (comprising three segments - the ascending aorta, the aortic arch, and the descending aorta - and then continues downwards to become the abdominal aorta) which begins from the tri-leaflet aortic valve (from the left ventricle at the level of sinuses of Valsalva at the aortic annulus) to the emergence point of the aorta through the diaphragm at the level of thoracic vertebra number 10 and abdominal aorta that runs downward till the iliac bifurcation against lumbar vertebra 4 [(2)]. The thoracic aorta can also be divided into different sealing/landing zones considering the endovascular aortic repair in general. Here Zone 0 begins against the Valsalva sinuses of the aortic root till the origin of the brachiocephalic artery; Zone 1 corresponds to further areas till the origin of the left common carotid artery and goes further on to zone 2, which stands against the origin of the LSA; Zone 3 begins just after the origin of the LSA till about 2 cm distally to

the LSA origin; and Zone 4 (of the descending thoracic aorta) goes approximately till thoracic vertebra 6, which goes downward to Zone 5 till the beginning of the abdominal aorta [3] (**Fig. 1**).

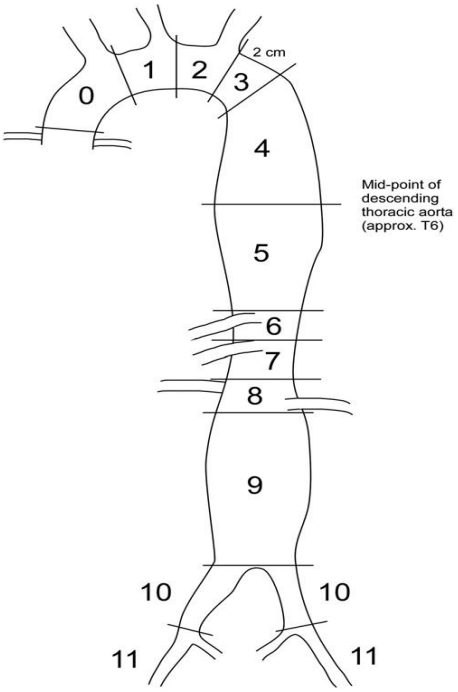

Fig. 1: Landing zones of the aorta, including proximal sealing/landing zones of the thoracic aorta [3]. (Republished under the online issued license number 4882990010786 dated 08/06/2020 from publisher Elsevier Co. through Copyright Clearance Center, Inc.)

The microanatomy of the aorta shows a highly elastic structure, which is created to combat a highly pressurized volume of blood at each heartbeat. Its histology shows a strong yet distensible thick muscular layer with surrounding elastic connective tissue pads as well as a thin intima-layer. The vascular nutrition of the aorta itself is established through the "vasa vasorum" (VV) network. It is confirmed from "vasa vasorum externae" (VVE), which come directly from the major branches of the aorta itself, and then the "vasa vasorum internae" (VVI), which directly originate from the aortic lumen [4]. Anatomically, VV are characterized by the presence of endothelial cells, smooth muscle cells, and by being externally covered with connective tissue. These features are similar to those encountered in small coronary arteries, indicating that VV can regulate their own tone and consequently result in arterial wall perfusion [5].

1.2.2. Anatomy of the left subclavian artery (LSA)

The LSA

- gets off directly from the aortic arch at different individual distances from the origin of the left common carotid artery,
- passes with the roots of the brachial plexus between the scalene muscles anterior and middle (and)
- ends at the outer border of the first rib as the left axillary artery.

The anterior scalene muscle divides the artery into three parts:

- first part between the origin and the medial border of the muscle,
- second part under the muscle (and)
- third part between the lateral border of the muscle and the lateral border of first rib.

The first part of the LSA gives the left vertebral artery, which runs upward through the vertebral artery canal in lateral vertebral processes to continue as the basilar artery that contributes to the posterior cerebral circulation. Otherwise, the first part provides the origin of the internal thoracic artery and further goes on to the thyrocervical trunk; the second part gives rise to the costo-cervical trunk; and the third part provides the origin of the dorsal scapular artery. The subclavian artery, in general, supplies the upper extremity as well as a part of the upper thoracic wall, and its vertebral branch participates in posterior cerebral circulation through its antecedent basilar artery [(6)].

1.2.3. Diameters of the thoracic aorta

Varrying with age, sex, body surface area, and genetic factors, the diameter of the thoracic aorta is presented with a range of values. It depends also on the way the investigation is carried out (either echocardiographic or with CT-/MR-angiography). The indication to treat could be seen in cases of thoracic/thoracoabdominal aortic aneurysms (TAA/TAAA) - accordingly considering sex of the patients (male/female) - for lesions equal/more than (5.5/5) cm. However, it is still debated whether the measurement should be exclusively for the inner diameter of aorta or the external aortic wall should be included [(7)].

1.2.4. Physiology and hemodynamics of the thoracic aorta

The hemodynamics of the thoracic aorta, as described also by Morbiducci *et al.* [(8)], originates partially from complicated geometry including:

1-Non-planar curvatures [(9)]

2-The originating branches at the apex of aortic arch

3-The significant tapering of distensible vessel walls

4-The dynamic movements of ascending aorta

5-The structures projecting into the flowing blood stream or above the level of the aortic valve

6-The ventricular twisting and torsion during contraction

7-The thoracic aorta is the site in the cardiovascular system (CVS) where laminar turbulent flows are present.

These reasons enhance helical patterns in the aortic blood flow, thereby presuming to ease the cardiac effort by ventricular ejection. However, the direct causality of this pattern is still unclear [10].

1.3. Pathophysiology of thoracic aortic lesions

1.3.1. Pathology of thoracic aortic aneurysms (TAA)

1.3.1.1. *Micro- and molecular pathology*

TAA develop as a result of the weakening of the normal structural flexibility of the vessel wall. This imbalances the vessel wall resistence against the expanding powe r of the blood stream and turns the weakening process into a closed circle of positive feedback mechanism according to La-Place's law [11]. This law states that the tension on a vessel wall at certain points is positively related to the radius of this vessel and the pressure at this point, and negatively to the thickness of the vessel wall at the same point. The original La-Place equation is described in the following:

$$Pic = k\ Ws\ h/Req$$

where "Pic" is the "pressure inside the vessel," "k" is a constant and equivalent to external atmospheric pressure, "Ws" is the wall tension, "h" is wall thickness, and finally, "Req" is the vessel radius. With a little modification and procrastination of the low-valued "k constant, we get the final product as the following:

$$Ws= Pic\ Req/\ h$$

According to the definition, aneurysm is a permanent localized arterial dilation to more than 50 % of the normal diameter. Considering the earlier mentioned La-Place equation, it has been confirmed that further aortic dilatation does not relieve the stress on the vessel wall. Rather, the dilation worsens it into a continuous vicious circle till the point where no vessel-wall-withstand is reached and consequently a rupture occurs.

1.3.1.2. *Anatomical classification of thoracic/thoracoabdominal aortic aneurysms*

In the reviewed literature it has been noticed that an explicit anatomical classification of the TAA is not often marked, which is in contrast to the detailed classification of the aortic dissection (AD). However, Crawford anatomically classified the TAAA in 1986 into the following:

Crawford Type 1 - involves most of the descending thoracic aorta from the origin of the LSA to the suprarenal abdominal aorta

Crawford Type 2 - the most extensive, extending from the subclavian to the aortoiliac bifurcation,

Crawford Type 3 - involves the distal thoracic aorta to the aortoiliac bifurcation

Crawford Type 4 - is limited to the abdominal aorta below the diaphragm (and)

Crawford Type 5 - Modification of the original classification by Safi's group, which extends from the distal thoracic aorta, including the celiac and superior mesenteric origins but not the renal arteries [12, 13].

1.3.2. Pathophysiology of acute aortic syndromes of the thoracic aorta

Anatomically, the lesions of AASs can be subclassified either according to DeBakey's classification or Stanford classification. While DeBakey classifies the lesions as

- Type 1, which represents lesions with the entrance in the ascending aorta and could extend into the descending aorta,
- Type 2, which has entrance from the ascending aorta and stays in the area of the ascending aorta (inlet-exit in the ascending aorta), and finally,
- Type 3, which confines the entry and the exit to the descending aorta.

Stanford classification specifies the classification [14, 15] according to the entry point whether from the ascending aorta, which takes Type A (subclassification A1 for exit in the descending aorta or Type A2 for the exit in the ascending aorta) or Type B that encompasses the lesions with entry and exit in the area of the descending aorta.

AD can be clinically classified into:

- acute dissection (14 days from the first dissection), with concomitant aortic rupture, malperfusion syndromes (visceral, renal, lower limb), impending rupture (persistent pain), or refractory hypertension
- subacute dissection (15-92 days) with complicated/symptomatic dissection, aortic expansion of > 5.5 cm, or aortic diameter > 4.0 cm with true and false lumens being both patent;
- chronic dissection (> 92 d) with complicated/symptomatic dissection, aortic diameter > 5.5 cm, or expanding to > 0.5 cm/year.

1.3.3. Pathology of the traumatic thoracic aortic lesions

Traumatic thoracic aortic lesions are either penetrating lesions or blunt aortic injury (BAI), which can be classified into:

- Grade I – intimal tear,
- Grade II – intramural hematoma
- Grade III – pseudoaneurysm
- Grade IV – rupture with extravasation of contrast [16].

Either way, BAI could also be classified according to the CT findings [17] into:

1- Intimal and/or medial damage with or without associated narrowing of the vessel lumen and the creation of a dissection plane
2- Aneurysmatic dilatation and/or pseudoaneurysm formation
3- Complete vascular occlusion
4- Arteriovenous (AV) fistula
5- Complete vascular transection.

1.3.4. Pathology of the aorto-esophageal/-bronchial fistula (AEF/ABF)

Roberto Chiesa et al. [18] decribed in detail the pathogenesis and types of AEF/ABF, as well as the drawbacks of their therapy. AEF/ABF could be primary, which develops prior to any interventional or operative treatment. This accounts for less than 10 % of all AEF/ABFs.

Primary AEFs almost co-occur with the aortic rupture. Its less common causes are:

- Resulting from benign or malignant esophageal lesions
- Associated with lung infection caused by *Aspergillus* spp or tuberculous pneumonia
- Caused by the ingestion of a forign body/longstanding placement of nasogastric tube

Secondary AEF/ABFs occur postoperatively as a consequence of the pressure/erosion effect of the pulsating prosthesis on the neighbouring structures, prothesis infection, or pseudoaneurysmatic malformation with fistula formation.

1.4. Epidemiology of thoracic aortic lesions

1.4.1. Epidemiology of TAAs

TAAs are considered with elevated prevalence along with increased age and with the masculine gender in German literature [19] . In the european guideline for treatment of thoracic aortic lesions, an estimated incidens of 6-10.4 per 100000 person-years was mentioned [21].

1.4.2. Epidemiology of acute aortic syndromes AASs (AD, IMH, PAU)

According to clinical practice guidelines of the ESVS, 2.9–4.0 per 100,000 person years are affected by AD Type B. The exact incidence remains still unknown. In symptomatic patients which are suspected of AAS, the prevalence of PAU is 2.3–7.6 %, and the lesion is localized in the descending TA in 90 % of patients [20]. IMH may be related to PAU. This is accounting for 5–20 % of patients with AAS and is more commonly involving the descending TA (60 %) more than the ascending aorta. In the German literature, it was reported that by 60–70% of the patients with AD, the intimo-medial tear is positioned in the ascending aorta. While in just 20–30 % of those patients, those tears are positioned in the descending aorta. In only 5–10 % of patients with AD, tears were found in the abdominal aorta. It was also reported that the incidence of acute AD stands between 2–4/100,000 person years with 80–90 % of male gender preference. The occurrence of AD is reported as in the

fifth and sixth decade of life for Type A and a decade later for Type B. It has also been reported that 30–40 % of patients with PAU in the descending aorta also showed the occurrence of AAA [19].

1.4.3. Epidemiology of the traumatological injury of the TA

Trauma is the leading cause of death during the first four decades of life; it accounts for more than 250,000 deaths every year in the European Union alone [21]. Blunt aortic injury is the second leading cause of death in these patients: Although it occurs in less than 1 % of all motor vehicle accidents, it accounts for 16 % of all traumatic deaths (Riambau *et al*. 2017) [21].

1.4.4. Risk factors for thoracic aortic lesions

According to the type of thoracic aortic lesions, risk factors widely vary. For example, in syndromic TAAs stand the genetic mutations as the essential role player, wherby other known risk factors play in this special type of thoracic aortic lesions as the second role player. The genetic mutations were described in detail in the section of the pathology of this study. The same applies to the familial non-syndromic genetic-based connective tissue malformation of the descending thoracic aorta. The sporadic etiologies of the TAAs show otherwise direct and indirect relationships with various risk factors. While systemic arterial hypertension plays an important role in the formation of the ADs of the thoracic aorta (Mussa *et al.* 2016) [22], systemic atherosclerosis shows in the same context a strong correlation with the formation of TAAs along with hyperlipoproteinemia [23].

1.5. <u>Diagnostic work of the thoracic aortic lesions</u>

1.5.1. History taking and clinical examination

1.5.1.1. *TAAs*

TAAs are almost silent clinically and discovered accidently through other diagnostics. Either way, TAAs can be symptomatic with

- Accompanied back pain
- Shortness of breath
- Chest pain (or) in worst case with
- Ruptured loss of consciousness and hemorrhagic shock.

Asymptomatic TAAs require no screening test, It could be asserted that the mortality of untreated asymptomatic TAAs is not high and therefore the decision for a screening method is yet to be established. The patients with a well-known family history of familial TAAD or accompanying clinical signs (facial dysmorphology, myopia, ocular lens dislocation, etc.) should undergo regular screenings [24].

1.5.1.2. *AAS including acute AD Type B, PAU, IMH*

Massive annihilating chest pain presents the patients with AASs in the ER as they seek rapid relief of that pain. In such cases, the first hour is the golden hour for the further survival chance of the patient. Various studies state that chest pain is the main symptom of such syndromes. In contrast to the AD, PAUs are represented commonly with less painful symptoms, this could be misinterpreted or under-interpreted [(25)]. The same applies to the IMH, although with IMH, there is a possibility for further extension with less pain till the formation of cardiac tamponade The diagnosis of Type B AD is supported primarily by the difference of blood pressure measurements between the two arms. This difference is mostly higher in the right arm.

1.5.1.3. *Other aortic pathologies*

Symbas *et al.* [(26)] describe a frequently occurring triad of traumatic aortic coarctation as:

- Increased blood pressure in the upper limbs
- Decreased blood pressure in the lower limbs
- Widened mediastinum on radiography.

Considering the AEF/ABF, the clinical presentation varies. Sepsis and hemoptysis are yet to be mentioned as unspecific signs of AEF/ABF [(127)].

1.5.2. Biomarkers of different thoracic lesions

Laboratory work is used mainly in cases of thoracic aortic lesions in seeking for prediction of the pathology of incoming lesion. In turn, by early discovery of these lesions, further complication will be prevented. Such theme has been discussed by few studies. Hence, biomarkers do not play a big role in the acute phase where a rapid response is demanded.

1.5.3. Ultrasound and other imaging diagnostics of TAADs

Although the CTA is still the gold standard as the primary diagnostic of TAADs [(27)], it is still a static presentation of the TAADs. Muhs *et al.*2008 [(28)] focussed on the importance of dynamic diagnostics of the TAADs, and hence, as stated, the static imaging methods can cause undersizing of the proximal landing zone of about 17.2 %, whereas the oversizing of the endograft done routinely for about 10 % of the original measurement of the proximal landing zone. This could lead to the development of endoleak Type 1a.

1.6. <u>Therapy of thoracic aortic lesions</u>

1.6.1. Non-operative therapy of TAADs

Control and restriction of risk factors like smoking, atherosclerosis, hyperlipidemia, and hypertension are applied side-by-side till the indication for surgical therapy of TAADs is given in the right manner. This is done according to the clinical stage of TAADs and in correlation with their radiologic

extension [29]. As long as the time point on which surgical intervention is indicated is not reached, conservative measures, the best medical treatment (BMT) should be provided in order to slow the progression of TAADs.

1.6.2. Operative therapy of TAADs

1.6.2.1. *Indications for operative repair*

Considering the TAA of Type B, the elective therapy can be indicated with the aneurysmatic diameter of more than 5–5.5 cm for men and 4–4.5 cm for women. The growth progrediance of Type-B TAA should not exceed 0.5 cm per year, otherwise the operative treatment should be undertaken. The growth-progress condition is suited only for the fusiform Type-B TAAs, otherwise symptomatic TAAs and saccular TAA are considered an urgent indication for operative repair with minor regard for the size progression. Otherwise, the other elements of acute aortic syndromes, such as PAU and IMH, require urgent interventional/operative therapy (Erbel *et al.* 2014) [30].

1.6.2.2. *Details of surgical techniques*

1.6.2.2.1. The open therapy of TAADs [7, 31]

The use of this method is merely reduced in today's era of endovascular correction of thoracic aortic lesions. Thus, this method is beyond the scope of this study. In brief , this method is done through lateral thoracotomy with the opening of the diaphragm, deflation of the left lung, and approaching the mediastinum to do the corresponding aortic repair. It is either done in the clamp and saw technique, which demands the heart-and-lung machine or the sequential clamping technique. The interposition-grafting uses polyester material/dacron graft. These grafts are either plain dacron or are impregnated, mainly with antibiotics such as Rifampicin or antimicrobial agents such as silver. The occurance of SCI could reach 2–28 % after elective open surgery of the descending aorta [32].

1.6.2.2.2. Endovascular repair of TAADs [33, 34]

Under local or general anesthesia, considering the general condition of the patient and the urgency of the procedure, as well as the access sites, femoral vessels, are either directly punctured under ultrasound guidance or are exposed by an open (classical) vascularsurgical approach called arteriotomy. If the access vessels are altered with high-grade, hemodynamically relevant atherosclerotic stenosis or highly kinked iliac vessels, a vascular iliac conduit is to be prompted in such cases. After the vascular access has been established using Seldinger's technique, a vascular sheath of 7 Fr. is placed and fixed. Next, over a soft guide wire (mostly a Terumo® soft wire), the angio-pig-tail-catheter is introduced till its tip reaches the aortic arch. Primary angiography will be performed to display the whole thoracic aortic tree. After that for specific presentation of the aortic arch branches, including the left subclavian vessels, the brachial artery is to be punctured with the insertion of a 7-Fr.-catheter sheath, the insertion of a Terumo® guide wire, and the insertion of the

angio-catheter till the tip reaches the branching point of the LSA. Next, the aortic arch and aortic branches, as previously mentioned, are to be imaged with the marking of the branching point of the LSA. Following that, the intraoperative measurement of the landing zones, especially the proximal one with special consideration of the distance between the lesion and the LSA, takes place. When the landing zones are within the safe range (>2 cm), the stenting process can begin with the exchange of the Terumo® soft guide wire with stiffer guide wires (commonly available in trade, Amplatz, Backup Meyer, or Linderquest super stiff), the stiffness of those stiffer guide wires is graded accordingly and is applied to the practice according to the nature of the aorta and the presence/absence of kinking positions. Hereafter, a suitable vascular sheath for the stent extractor is inserted through the femoral vessels beginning with the 20-F-sheath size. Over the sheath, the stent extractor is to be introduced and the stent will be placed under the visual control of the contrast material. The placement of the stent in the goaled aortic part - it is either thoracic or thoraco-abdominal - is undertaken with high consideration of the curvature degree of the aortic arch in order to avoid the bird peaking situation postoperatively with possible occurrences of the retrograde type A aortic dissection as a consequent complication of the TEVAR maneuver. According to the length of the thoracic/thoracoabdominal lesion, it will be decided whether one stent graft suffices or more than one graft should be used. After problemless placement and fixation of the stent grafts, a finishing contrast-enhanced imaging of the stented aorta with immediate exclusion of the irritating endoleak Type 1 is indicated . This is the standard course of action without over-stenting or blocking of the supra-aortic, renal, or visceral vessels.

1.6.2.2.3. Hybrid repair of thoracic/thoracoabdominal aortic lesions [35]

When the supra-aortic vessels are altered, the debranching is done either via supra- or infraclavicular approaches. While the supraclavicular pathway is preferred for the transposition of the LSA and the LCA, the infraclavicular access is more preferred for positioning a bypass between the supra-aortic vessels, especially when the TEVAR stent is indicated for covering only Zone 2 with no further approach on Zones 0 and 1 of the aortic arch. In the thoracoabdominal aortic lesions with the involvement of the renal and/or visceral vessels, stenting of the whole aortic length is to be done, under spinal protective measures, with the placement of an octopus bypass graft over the more patent iliac vessels as retrograde revascularization of the kidneys and abdominal organs.

1.7. Complications of variant therapeutic modalities of thoracic/thoracoabdominal lesions and their specific therapies

According to Daye and Walker [36], the complications can be subclassified into device-related and systemic complications.

1.7.1. Device-related complications

1.7.1.1. *Endoleak*

The term endoleak could be defined as a continuous inflow of blood outside the graft lumen, as well as into the aneurysmatic sac with its further growth. Five types of endoleaks have been described in the literature:

- Type 1 Inflow of blood through leaky sites in the proximal (1a) or distal (1b) ends of the stent grafts,
- Type 2 Backflow of blood through the still open side branches of the stented part of the aorta,
- Type 3 Inflow of blood into the aneurysmatic sac through junctional defects between the stent parts (junctional endoleak),
- Type 4 Leaking through stent material pores (and)
- Type 5 Tension endoleak with further unexplained causes.

1.7.1.2. *Endograft migration, fracture, collapse, kinking, and occlusion*

Graft migration has been reported to occur following in 1.0–2.8 % of TEVAR at one-year post-intervention [36] On the other hand, graft collapse is, according to Daye and Walker, related mainly to oversizing of the graft in accordance with the proximal landing zone and it results consequently in endoleak Type 1a after TEVAR with bird peaking formation. Graft collapse occurs more frequently with small proximal aortic curvature. A higher possibility of graft collapse correlates with the indicated TEVAR due to trauma, mainly within the first 30 postoperative days

1.7.1.3. *Endograft infection and subsequent aorto-esophageal fistula/aorto-bronchial fistula,*

The infection of TEVAR-stent grafts is associated with increased postoperative mortality according to data from multiple referneces out of the medical literature [37]. Heyer *et al*. [38] stated that the possibility of graft infection related to TEVAR could reach 8 % [39] . The corresponding genesis varies microbiologically between *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Streptococcus viridans*, *Pseudomonas aeruginosa*, *Ericheria coli*, and *Enterococcus* species [40]. The clinical symptomatology of infection comprises thoracic pain accompanied with fever, which can proceed to manifest sepsis. Beside the clinical signs, the endograft infection is diagnosed with CT-A of the thorax and the upper abdomen, including possible punctures and sample collection for further microbiological assessment. Further on, with the FDG-PET (fluor-desoxy-glucose positron emission

tomography) the actual site of the prosthesis infection can be located. A complete laboratory work, including blood cultures, should be conducted to measure how grave is the infection and how emergent should be the therapy.

The therapy is either conservative in term sof suitable antibiotic therapy under medical supervision mainly with admission to the hospital, or open surgical replacement of the endovascular stent with silver-coated polyester prosthesis or back-table tinkered PTFE prosthesis.

1.7.2. Systemic complications

1.7.2.1. *Post-implantation syndrome*

PIS is characterized by

- Manifest fever (> 38°C),
- Increase in the white blood cell count (> 12,000/µL),
- High level of acute phase reactants (CRP; IL-6), but negative blood cultures, (and) more importantly
- Negative procalcitonin levels.

The PIS after TEVAR-interventions can represent, in some cases, a diagnostic dilemma and problematic situation for vascular surgeons. Additionally, the patients suffer occasionally from diffused chest pain of an unclear nature and progressive dyspnea.

It is debated frequently in the literature [39, 41] as to whether preoperative antibiotics and if the preoperative steroids have the potential to prevent PIS, yet there is no evidence through RCT/SRs to support this hypothesis. The treatment of the PIS is mainly supportive through fluids, anti-inflammatory drugs, and analgesics.

1.7.2.2. *Ischemia of end organs, neurological complications, stroke, and paraplegia*

This study focuses mainly on complications related to thoracic, rather than the less commonly occuring thoracoabdominal, aortic lesions. Thus, the light will be spotted here on central nervous lesions (stroke, paraplegia) as well as upper limb ischemia in cases of overstenting of the LSA [106].

1.7.2.2.1. Stroke and TEVAR

The cerebral stroke following TEVAR has two main causes:

- First, embolic stroke due to manipulations at the origin of the carotid vessels, especially in interventions done in the landing zones 1 & 2, this affects the anterior cerebral circulation supplied from the carotids.
- Either way, the over-stenting of the LSA with subsequent vertebral artery occlusion and posterior cerebral ischemia.

The possibility of stroke in association with TEVAR is presented between 3 % and 7 % in keeping with the study of [42], while it ranges from 4 % to 8 % in keeping with the study of [36].

1.7.2.2.2. Spinal cord ischemia (SCI) and TEVAR

The incidence of this devastating complication is rated by various literature data as ranging from 3 % to 6 % [43] (others, up to 22 % [44]. The genesis of SCI is still unclear, but there are multiple theoretical postulations based on the anatomical and physiological factors affecting the spinal circulation. Anatomically, the spinal cord is supplied through the

- One anterior (and)
- Two posterior spinal arteries

which are nourished through the radicular branches of posterior intercostal arteries. The first is the midthoracic radicular branch, which begins from the T7-posterior intercostal artery and supplies the fourth till the eighth segments of the spinal cord, while the second is the thoracolumbar radicular branch (also known as the artery of Adamkiewitz) that arises from one of the T9–T12 posterior intercostal arteries and supplies the lower thoracic cord [45]. · The intraspinal blood circulation is directly affected by the minimal change of the systemic blood pressure and intrathecal pressure [46,47].

1.8. Special consideration on TEVAR in landing zones 1–2 with over-stenting of LSA

Since the beginning of the endovascular era, blocking of the branching vessels in order to lengthen the landing zones has been imposing a big challenge for vascular surgeons. Subclavian coverage during TEVAR is one of the clear examples and yet without a definite and finally stated solution through the literature.

Beside the aforementioned spinal and cerebral ischemic complications after TEVAR in general, special consideration should be paid to the postoperative ischemic changes of the left arm. This can be manifested either with arm cludications or with left subcalvian steal syndrome (SSS) [106]. The left SSS is mainly aymptomatic und is caused by revese of the blood flow through the left vertebral artery over the circle of Willis in order to overrun the blocked inflow through the overstenting. When being symptomatic, the SSS could be manifested by vertigo and dizziness when putting the left arm in action.

Through this work, we will discuss as primary goal whether the revascularization/preconditioning of the subclavian artery is a *must* by TEVAR operations. The end point is either the occurrence of SCI, ischemic changes of the left arm (manifested bei claudication pain or by symptomatic left subclavian steal syndrome) , or the occurrence of posterior strokes. Anatomically, the subclavian artery represents an important circulatory role player not only for its essential arm blood supply, but also for its contribution to intracranial cerebral circulation through the vertebral artery—the branch from the first part of the subclavian artery—as well as its contribution to the extracranial spinal circulation through tributaries into the anterior spinal artery and the two posterior spinal arteries. Further anatomical explanations considering the subclavian artery have already been discussed in the anatomy section (see above).

Some literature data and guidelines (Society of Vascular Surgery [SVS] [48] show the tendency of the overall revascularization before LSA over-stenting, [48, 49, 50, 51, 52, 53, 54] while other literature data favors the tendency of minimizing the indication for the primary LSA revascularization in TEVAR ([55, 56, 57]
Even highly ranked meta-analyses divaricate between

- The primary tendency for revascularization, as advocated by Chen *et al.* [58] and Cooper *et al.* [42], against
- No tendency for primary revascularization without definite urgent indications, as favored by Hajebandeh *et al.* [59]

This revascularization-conservative hypothesis is also supported by Rehman *et al.* [60] with their systematic review.
The possible ways of LSA revascularization are either through open surgical debranching of supra-aortic vessels (LSA) in terms of subclavia-carotid bypass (SCB) or subclavia-carotid transposition (SCT) [1]. It should be considered that the advantage of open LSA revascularization is to overcome the aforementioned complications of the LSA over-stenting outweighing the possible risks of such operations, such as recurrent laryngeal nerve paralysis, phrenic nerve palsy, injury of the left subclavian vein, and last but not least, the possible stroke risk [61].
The new alternative endovascular techniques include in-situ laser-fenestration of the over-stenting TEVAR endograft, followed by balloon-expandable covered stent deployment in the LSA, as described by Redlinger *et al.* [62], as well as the chimney grafting (CG) of the LSA, as described by Xiang *et al.* [63], or the periscope endografting, as described by Lachat *et al.* [64].

2. Patients und Methods

2.1. Aim of the study

This study aimed mainly to conceal the theoretically recommended obligation for primary revascularization of the LSA in order to manage the thoracic aortic lesions approching the osteum of that artery. In addition, it was aimed at bringing our own clinical experience in this topic supported with a comparative review of literature, so as to spare unnecessary medical efforts for whom, who in need of them.
Secondary goal of this study was to present a mid-term experience of 12 years in the treatment of different thoracic aortic lesions (i.e., thoracic aortic aneurysm [TAA], thoracic aortic dissections [TAD], penetrating aortic ulcers [PAU], traumatic aortic lesion, etc.) in different morphologies, ages, and etiologies. This could help the ongoing clinical research work in the field of aortic surgery in terms of making those surgeries more safe and effective for the patients.

2.2. Patients

This study includes 112 consecutive cases who had suffered from different pathologies of the thoracic/thoracoabdominal aorta and underwent respective therapy (endovascular, hybrid, or open operative treatment) at the Division of Vascular Surgery (Dept. of General, Abdominal, Vascular and Transplant Surgery), University Hospital of the Otto-von-Guericke University in Magdeburg, Germany, over a defined period of time. Further inclusion criteria were:

- Adult age (≥ 18 years old),
- Acquired thoracic aortic pathologies (such as:
    * Thoracic aortic aneurysm [TAA]/thoracoabdominal aortic aneurysm [TAAA]
    * Aortic dissection [AD] Type II
    * Penetrating aortic ulcer [PAU]
    * Intramural hematoma [IMH]
    * Iatrogenic causes
    * Trauma
    * Infiltration by [adherent] tumor lesions nearby
    * Endoleaks as complication / consequence of TEVARs
    * Infections),
- Different corresponding therapies (endovascular-hybrid).

Excluded are subjects with lesions of the ascending aorta and infrarenal aortic lesions, underaged subjects (< 18 years old), and congenital aortic diseases.

The study parameters (as listed below) were collected from the patients' information archive of Magdeburg's University Hospital. Different parameters are put under particular sugroups according to:

-Aspects of vascular surgical interventions

-Diagnoses

-Radiologic characteristics

-Complications and their therapies

-Morbidity, mortality, and follow-up details.

The patients' informed consent for data collection was done as part of each patient's admission to the hospital.

2.3. Methods

By means of a retrospective unicenter observational study on real-world data in a consecutive patient cohort, different parameters were investigated, including:

- Therapeutic procedure (either purely endovascular *vs.* hybrid)
- Year of the therapy
- Symptomatic *vs.* asymptomatic status of patients
- Epidemiological factors (age, sex, risk factors, mortality, and follow up)

- Overstenting/blocking of the LSA
- Complications of applied therapies, further operations/interventions to treat complications
- Radiological aortic measurements (lumen extensions, false-lumen measurements, distance to the supra-aortic and visceral vessels etc.)
- Multiple other pathological/radiological features (such as intrathoracic hematoma, tracheo-/esophagoaortic fistula, endoleak from previous interventions, PAU, intramural hematoma etc).

The aortic measurement was performed using the PACS radiological program (Chili Web, digital Radiology, version 4.18, Nexus/Chili GmbH; Dossenheim/Heidelberg, Germany) in previous (preoperative) CT-angiography images; in particular, the distances of pathognomonic thoracic/thoracoabdominal aorta are measured at its outer border. Commentaries of visual findings of preoperative pathologies were included as part of the measurement parameter.

The varying postoperative complications were subclassified in a standardized manner into two main categories: they are either systemic or device-related. The systemic complications are either general postoperative complications such as:

- Pneumonia
- Urinary tract infections
- Sepsis
- Multiorgan failure
- Postoperative delirium
- Cardiac complicatons including postoperative cardiac arrest
- Hemothorax, chylothorax
- Systemic inflammatory response syndrome
- Esophageal/bronchial injury with/without formation of the aortoesophageal/-broncheal fistula, or
- Specific postoperative ischemic change
- Ischemic complications related to the supraaortic vessels, such as:
  *Cerebrovascular attacks
  *Spinal cord ischemia
  *Ischemia of the left arm including caludication and/or left subclavian steel syndrome.
- Ischemic renal failure with or without urgency for dialysis
- Visceral ischemia with symptomatic ileus
- Peripheral vascular occlusions.

The device-related complications include:

- Stent kinking
- Stent collapse
- Stent fracture
- Stent migration

- Stent infection with/without mandatory stent excision
- Endoleak, whose therapy includes:
  *Conservative wait-and-see strategy with yearly CT-controls
  *Embolization with the Onyx material or coiling
  *Anchoring/proximal stent extension
  *Revision with stent excision and replacement.

The postopertive mortality and follow up was done for part of the patient clientele on the ground of the compliance issue of other patients for yearly visits to CT-controls.
The aforementioned parameters were studied and analyzed for the main patients' group and for the subgroup of the patients who had unergone LSA coverage.

2.4. Statistics

The statistical analysis was provided by the Institute of Biometry and Medical Informatics at the Otto-von-Guericke University of Magdeburg with University Hospital, Magdeburg/Germany, using the SPSS program (version 16.0, SPSS Inc.; Chicago/IL, U.S.A.). For descriptive statistics, the parameters mean, median, range, and standard deviation were used. Survival was studied using the Kaplan–Meier assessment in the whole patients' group and in the over-stented patients. The analysis of variance (as comparative statistics) was done for independent parameters such as:

- Age, sex, length of stay
- Variant risk factors (high blood pressure, diabetes mellitus, renal insufficiency with or without dialysis, concomitant peripheral arterial diseases/coronary heart diseases)
- Postoperative complications (either systemic or device-related complications)
- Perioperatve mortality (and)
- Follow-up period.

Included are the revascularized *vs.* non-revascularized groups of patients who had undergone LSA coverage. The statistical significance is tested by means of *U*-test, with a *p*-value of < 0.05 for statistically significant difference.
The illustrations of different statistical parameters were done using the Excel program (Microsoft Office 365, Microsoft company, Redmond/WA, U.S.A.).

2.5. Literature review

The literature review was achieved by means of a search in PubMed, Google scholar, Research Gate, ScienceDirect, and Cochrane library using the following terms: endovascular, TEVAR, revascularization, stroke, left subclavian artery (LSA)-ischemia, spinal cord ischemia, and left arm ischemia.

Under the previously noted MeSH, 775 different topic-related titles were found. Those titles were refined with exclusion of non-related titles. Finally, 130 abstracts were reviewed. From those 130 abstracts, four categories emerged.

The primarily collected literature material under the aformentioned MeSH terms was further filtered according to the inclusion and exclusion criteria.

Included were the corresponding papers:

- which are published in the last 20 years (2000–2020)
- whose abstracts were written in/translated into English and thus they appear on different search mashines
- which are either cohort studies, case/control studies, or SR/MA studies.

The references and their main results were classified in 2 groups as "pro or con" the pursued hypothesis.

Two other subgroups are compiled as following:

-Papers dealt with innovative endovascular treatment options of the overstented LSA mainly as bail-out by old cases that cannot comply with the open debranchment

-Papers demonstrated the related SR/MA.

2.6. Ethical statement

The study is registered by the German registry for clinical studies ("Deutsches Register für klinische Studie") under registration number DRKS00023743, date 11/26/2020.

Every patient signed an informed consent prior to undertaking the corresponding treatment. The study was done with the approval of the Ethics Committee of Magdeburg's University Hospital (registration No., R18-20, date 12/01/2020). The regulations and instructions of the "Declaration of Helsinki for Biomedical Research" by the "World Medical Association" from 1964 as well as the requirements of "Good Clinical Practice" were considered strictly through the steps of this study.

3. Results

3.1. Overview

The study results are classified in terms of whether they have a general goal or specific for the cases with over-stenting of the LSA. Both categories are subclassified into:

-Epidemiologic parameters including the risk factors

-Operative parameters

-Diagnoses

-Radiologic parameters

-Complications and their therapies.

3.2. Results of the general study population

3.2.1. Epidemiologic parameters

This study encompasses 112 patients (sex ratio, 69 males [61.6 %] and 43 females [38.4 %]) from 2006 to 2018. The mean age was 72.76 (range, 25–98; standard deviation [S_D], ± 14.366) years. The mean hospital stay was 17 days (range,3-51, standard deviation [S_D], ±11,643)days.

The spectrum of risk factors (**Fig. 2**) comprises (decreasing portions):

- Arterial hypertension (*n*=75; 67 %),
- Hyperlipoproteinemia (*n*=32; 28.6 %),
- Chronic renal insufficiency without any need of dialysis (*n*=27; 24.1 %),
- Atrial fibrillation (*n*=26; 23.2 %),
- Coronary arterial disease (*n*=20; 17.9 %),
- Diabetes mellitus (DM) (*n*=19; 17 %),
- Smoking (*n*=18; 16 %).

The presence of concomitant AAA was documented in:

- *n*=1 case (0.9 %) already treated with EVAR (whereas)
- *n*=4 cases (3.6 %) with isolated AAA in the medical history.

The access-site (iliacofemoral) vessels showed a stenosis in one case (0.9 %) and aneurysmatic changes in two cases (1.8 %). TAAs represent the highest portion in the enrolled patients (*n*=42; 37.5 %), and Type-B aortic dissection was found in *n*=26 (23.2 %; TAAA, *n*=21 → 18.8 %).

- Spectrum of thoracic aortic lesions in CT-angiography:

TAAA and TAA showed the highest portion with *n*=23 (20.5 %) and *n*=22 (19.6 %), respectively (AD type B, *n*=21; 18 %). Intrathoracic hematoma (as a related sign of other diseases of the thoracic aorta, such as

- Traumatic aortic tears,
- Open aortic perforations with different etiologies,
- Bleeding associated with

    * Eroding infections [or] * Tumor lesions, etc.) was seen in 20 cases (17.9 %).

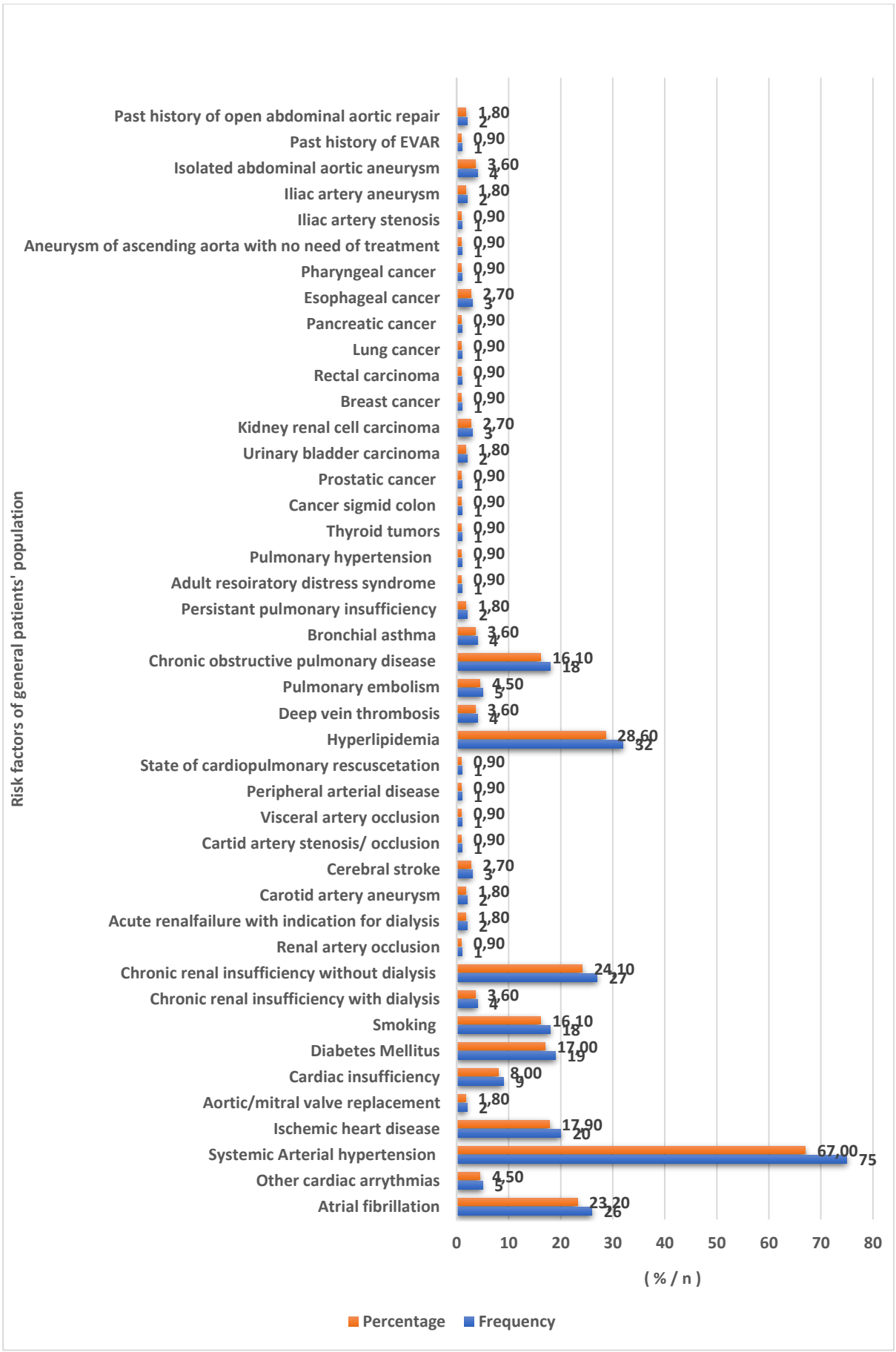

Fig. 2. Risk factors' distribution

3.2.2. Diagnoses and symptomatology of the treated thoracic aortic lesions

The related diagnoses of the treated cases are shown in (**Fig. 3**). TAAs represent the highest patient clientele with the patient toll of 42–37.5 %, and afterwards, the Type-B aortic dissections with 26–23.2 %. The TAAAs occupy the third place with 21–18.8 %. The symptomatic *vs.* asymptomatic case distribution was, respectively, 41 % (*n*=66 cases) *vs.* 59 % (*n*=46 cases).

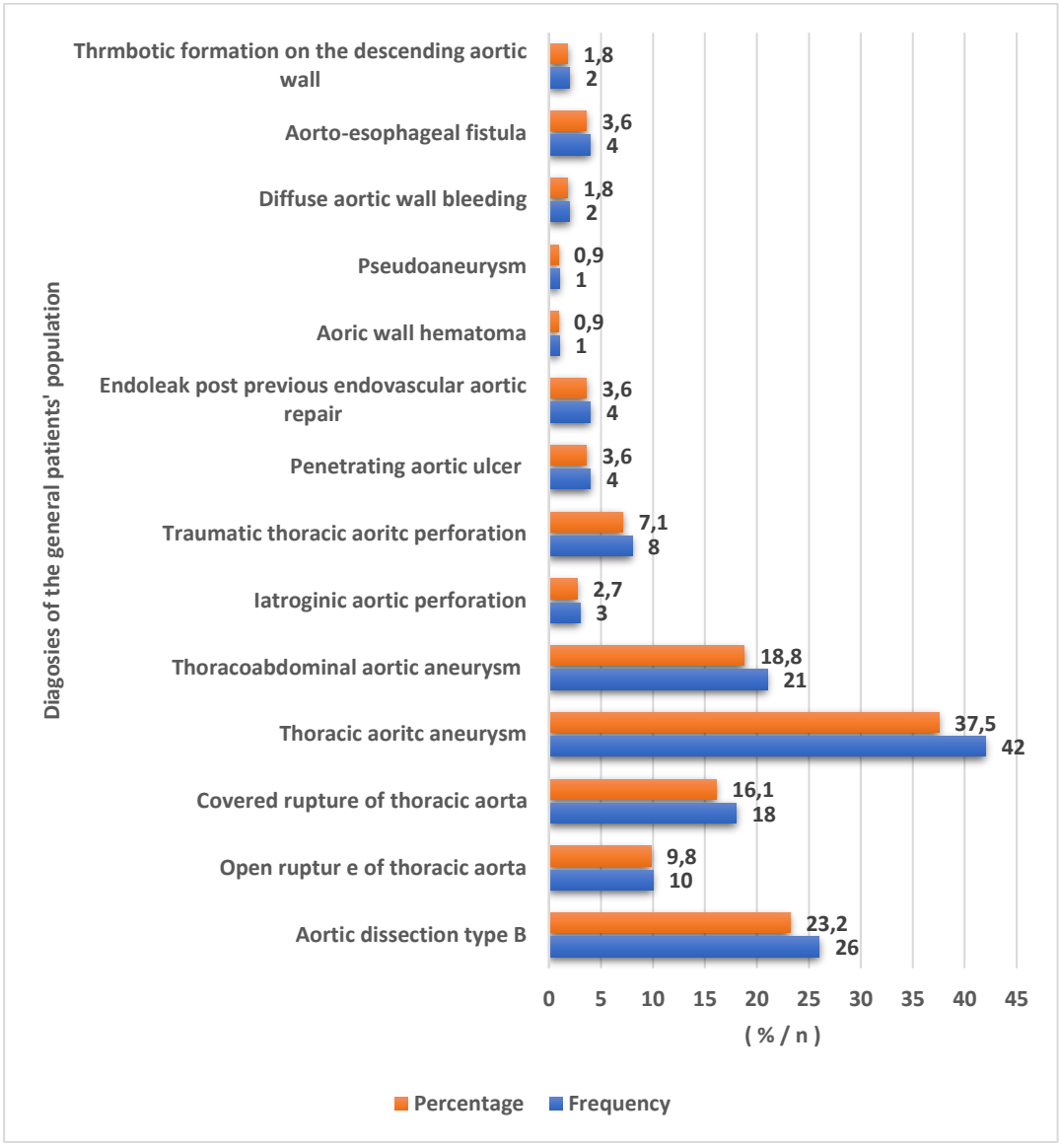

Fig. 3. Spectrum of diagnoses

3.2.3 Statistics of different diagnostic findings

This part illustrates the different measurements and findings of preoperative CT-angiographies, as briefly shown in **Table 1**.

- The mean proximal landing zone length for the lesions not reaching the LSA was 8.26 cm, (range, 1-27; standard deviation [S_D], ± 6,654) cm.
- The mean distal landing zone length for the lesions not reaching the

renal/visceral vessels was 15,7 cm (range, 1-30; standard deviation [S_D], ± 8,292) cm.

Table 1. Preoperative CT-A measurements in general study population

CT measurments	No. of measured cases	Mean value	Standard deviation	Median	Minimum	Maximum
Proximal landing zone length (TEVAR cases outside zones 1–2)	70	8.26	6.654	6.5	1	27
Distal landing zone length (TEVAR cases lesions not reaching the visceral/renal vessels)	63	15.7	8.292	18	1	30
Diameter of the lesions (Aneurysms-dissecting aneurysms-PAU)	93	5.14	5	2	1	14
Length of the lesions	93	14.8	13.004	11	1	53
True lumen diameter (in AD cases)	34	3.03	1.167	3	1	6
False lumen diameter (in AD cases)	28	3.36	4.011	2.5	1	22

The mean distal landing zone length was 15.7 cm with a maximum length of 30 cm and a minimum length of 1 cm.

- The cases with lesions approaching the supra-aortic vessesls proximally or the renal/visceral vessels at the distal site are illustrated comparatively in the following figure (**Fig. 4**). The lesions approaching the LSA proximally countered 27 cases (24.1 %), while the lesions reaching the celiac trunk distally countered the toll of 36 cases (32.1 %).

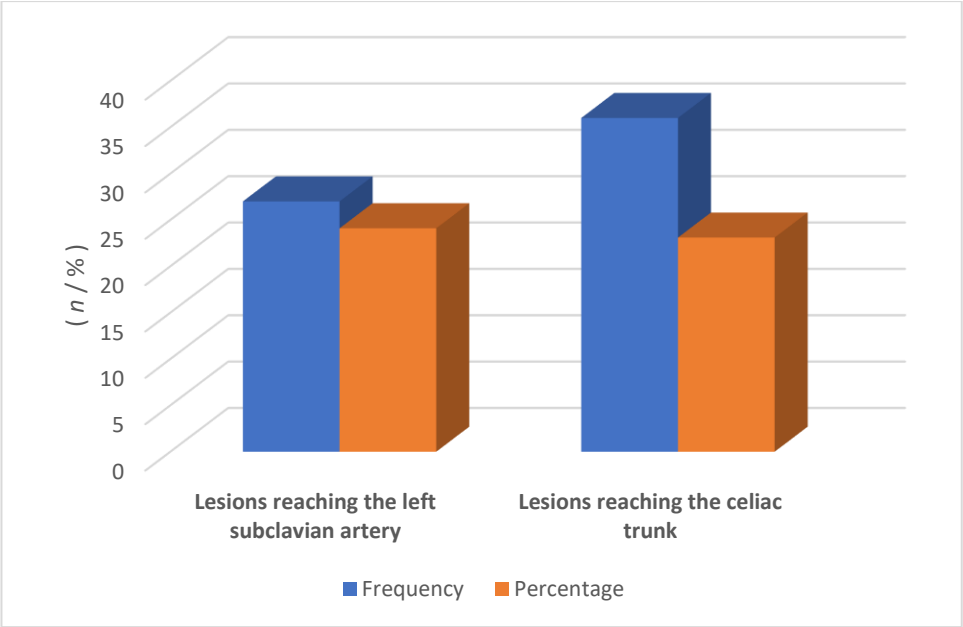

Fig. 4. Lesions reaching the LSA *vs.* lesions reaching the celiac trunk.

Differently discovered thoracic aortic lesions in the CT-A are illustrated in (**Fig. 5**.). Statistically, it showed that the TAA and AD type B represent the highest case volume with 41–36,9 % to 26–23,2 %, and after that, TAAA with 22–19,6 %. The intrathoracic hematoma (as a related sign of other diseases of the thoracic aorta, such as traumatic aortic tears and open aortic perforations with different etiologies, bleeding associated with eroding infections, or tumor lesions etc.) is represented with 20 cases (17.9 %).

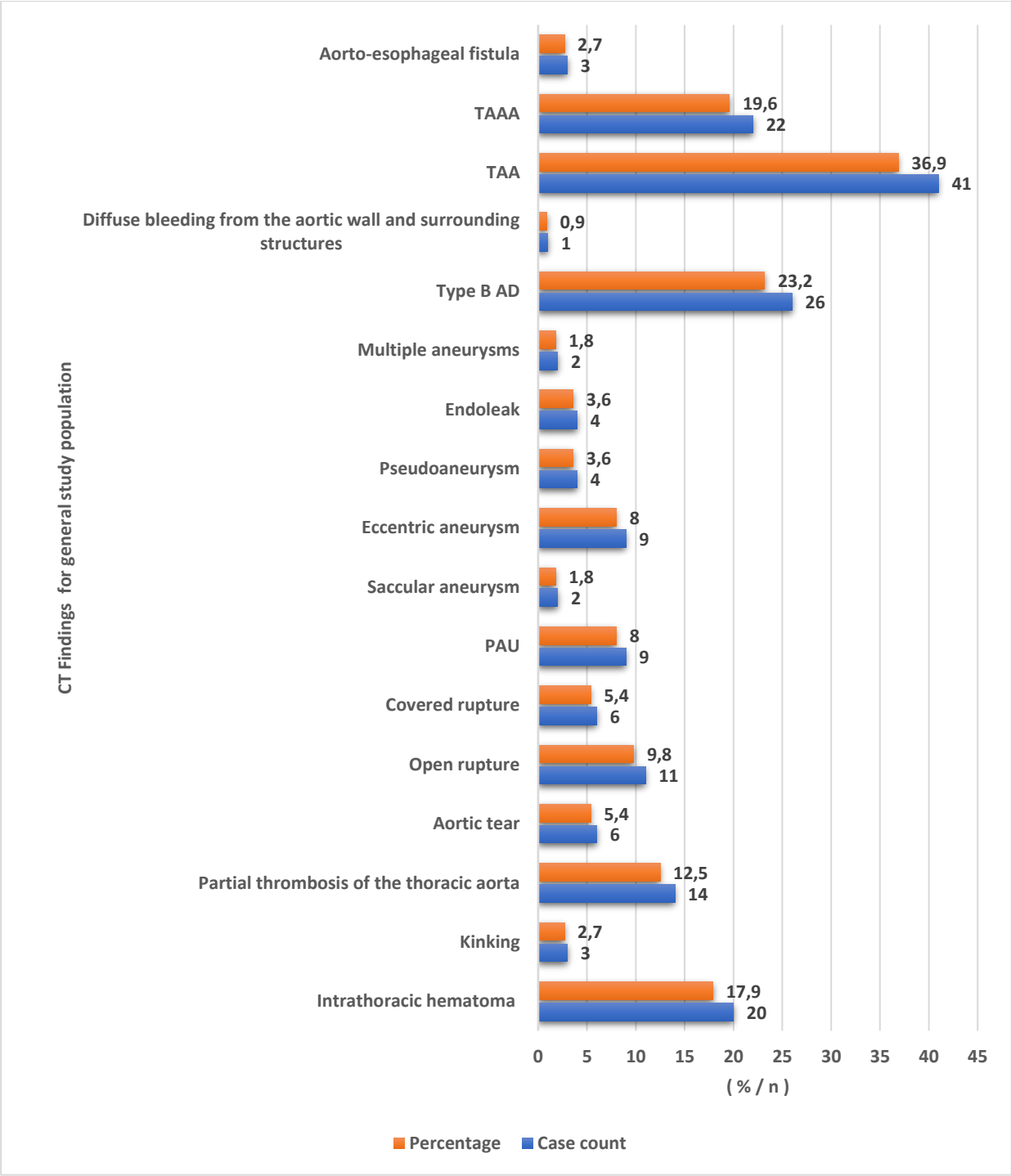

Fig. 5. Different aortic findings in the CT-A examinations of the involved cases

3.2.4. Operative / technical statistics of different therapeutic modalities **(Figs. 6-7)**

The endovascular-only therapy without any accompanying open therapy represents the majority of treatment modalities (82–73.2 %). All the other modalities ranged from 1 to 15 patients (0.9–13.4 % in percentage). The hybrid procedures at the supra-aortic vessels and (in lower percentages) at the renal/visceral vessels, in combination with the endovascular repair of the thoracic/thoracoabdominal aortic lesions, represent only a minor range of the performed operations/interventions. The pure over-

stenting of the LSA/supraaortic vessels counted for 23 (20.5 %) cases, whereas the combined over-stenting and debranching of the supraaoartic vessels counted for 13 cases (11.6 %). In total, there was over-stenting of the supraaortic vessels in 36 cases (32.1 %). Over-stenting of the renal/visceral arteries (either pure or with debranching) was not considered primarily by this study.

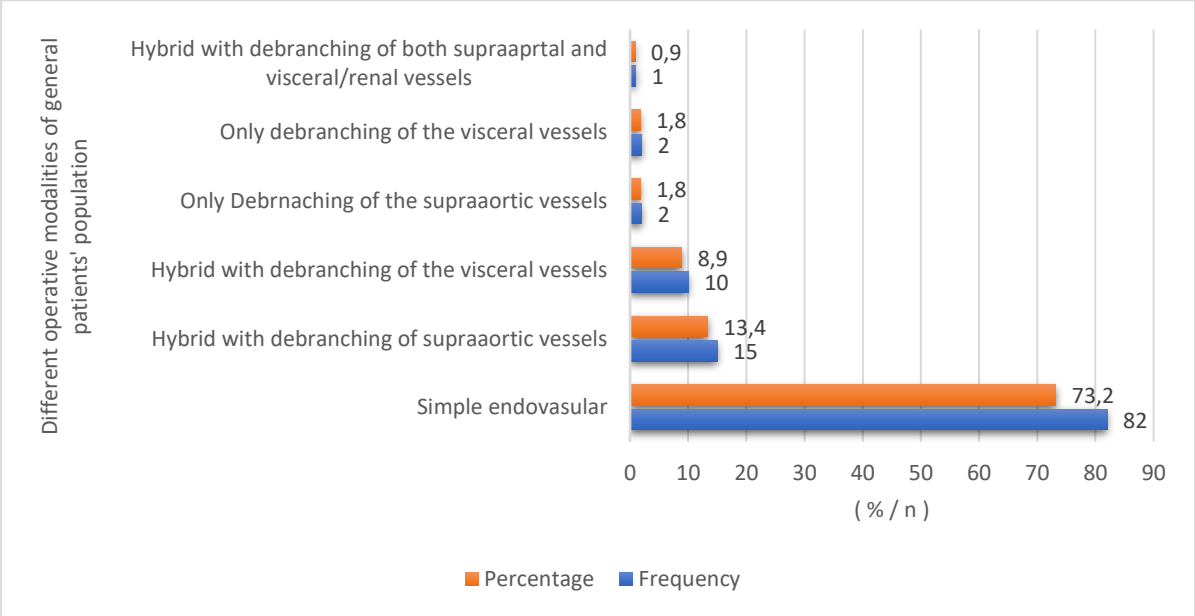

Fig. 6. Different operative modalities to treat the thoracic/thoracoabdominal lesions of this study-corresponding cases.

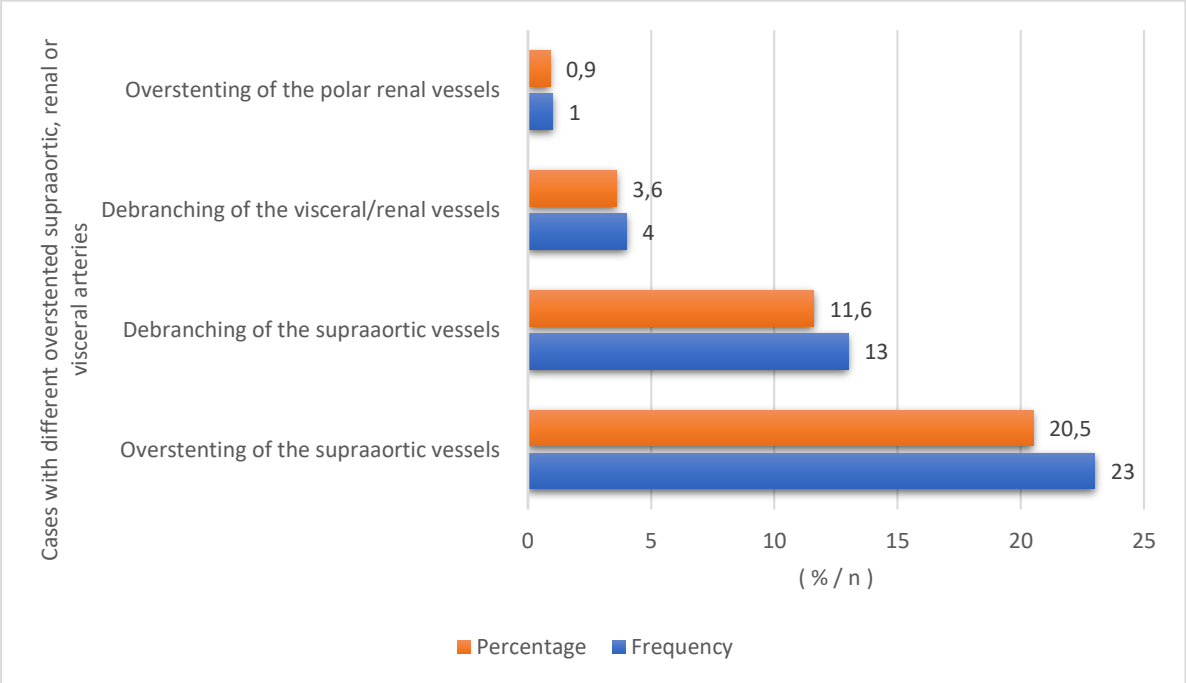

Fig. 7. Over-stenting of the supra-aortic, renal, or visceral arteries

3.2.5. Postoperative complications **(Fig. 8 a-d)**

The main (most frequent) systemic complication was postoperative pneumonia (*n*=7; 6.3 %). The postoperative systemic inflammatory response syndrome (SIRS) accounted for one case (0.9 %). Postoperative ischemic changes of the supplied end organs, including spinal ischemia and postoperative stroke, were observed in 12 cases (10.8 %) that were subclassified into:

- five cases (4.5 %) of spinal ischemia,
- one case (0.9 %) of postoperative stroke,
- three cases of postoperative acute renal failure (2.7 %) and
- three cases of peripheral vascular occlusion (2.7 %).

The device-related postoperative complications comprise endograft infection with four cases (3.6 %) and occlusion of the endograft prosthesis in two subjects (1.8 %). Dissection of the adjacent vessels encountered one case (0.9 %). Esophageal trauma with the aortoesophageal fistula encountered one case (0.9 %) and the distal aortoduodenal fistula encountered also one case (0.9 %). The majority of the endoleak cases represent Type 1 with six cases (5.4 %), then Type 2 with four cases (3.6 %), and finally, Type 3 with two cases (1.8 %). Types 4 and 5 are not noticed to happen within the case-scope of this study.

The therapeutic spectrum of postoperative complications is illustrated in (**Fig. 8-d**), which extends from thrombectomy of the occluded access vessels and the occluded endograft (*n*=4 cases; 3.6 %) to laparotomy/relaparotomy by graft infection/bleeding (*n*=4 cases; 3.6 %).

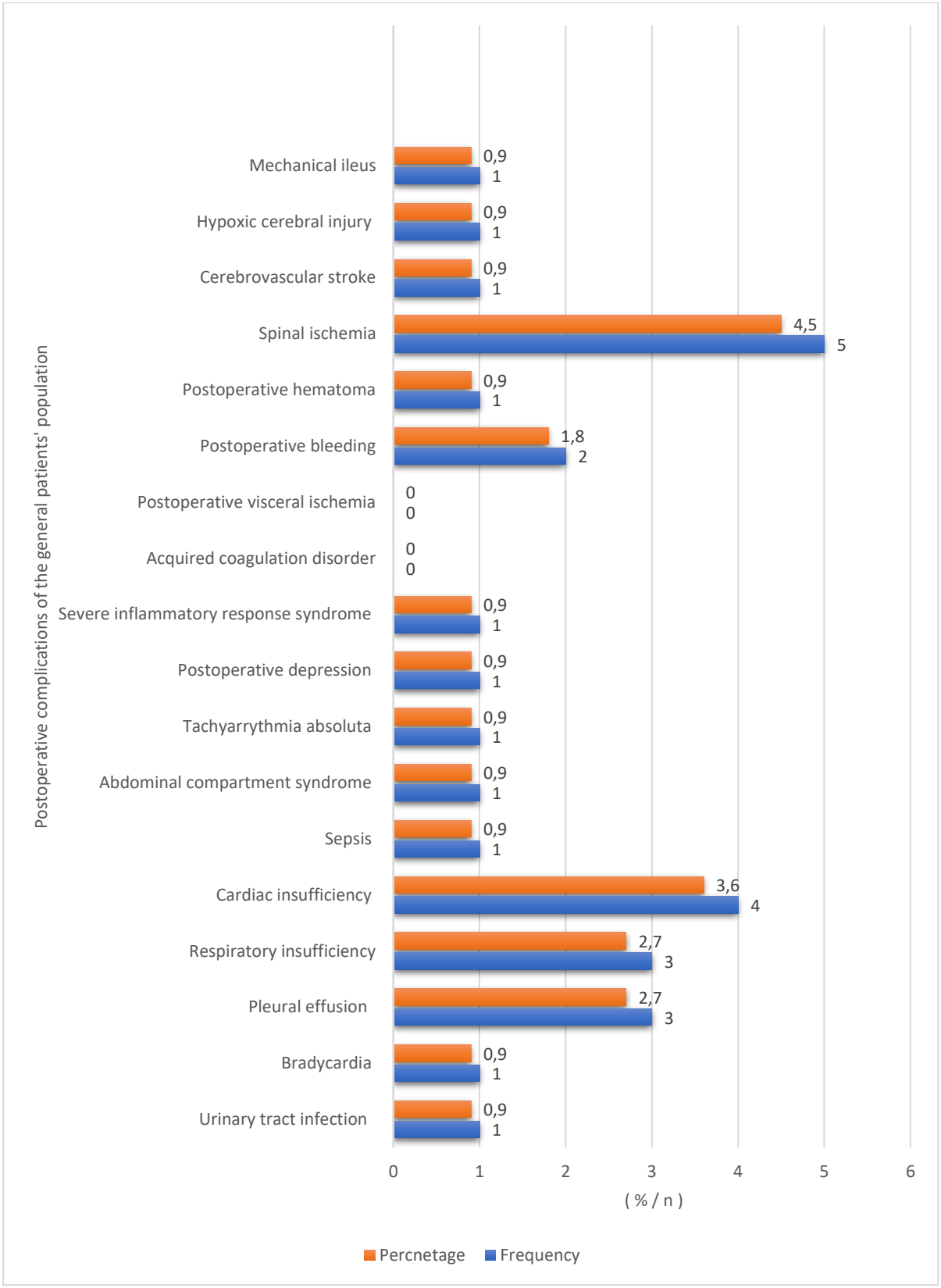

Fig. 8-a) Systemic complications

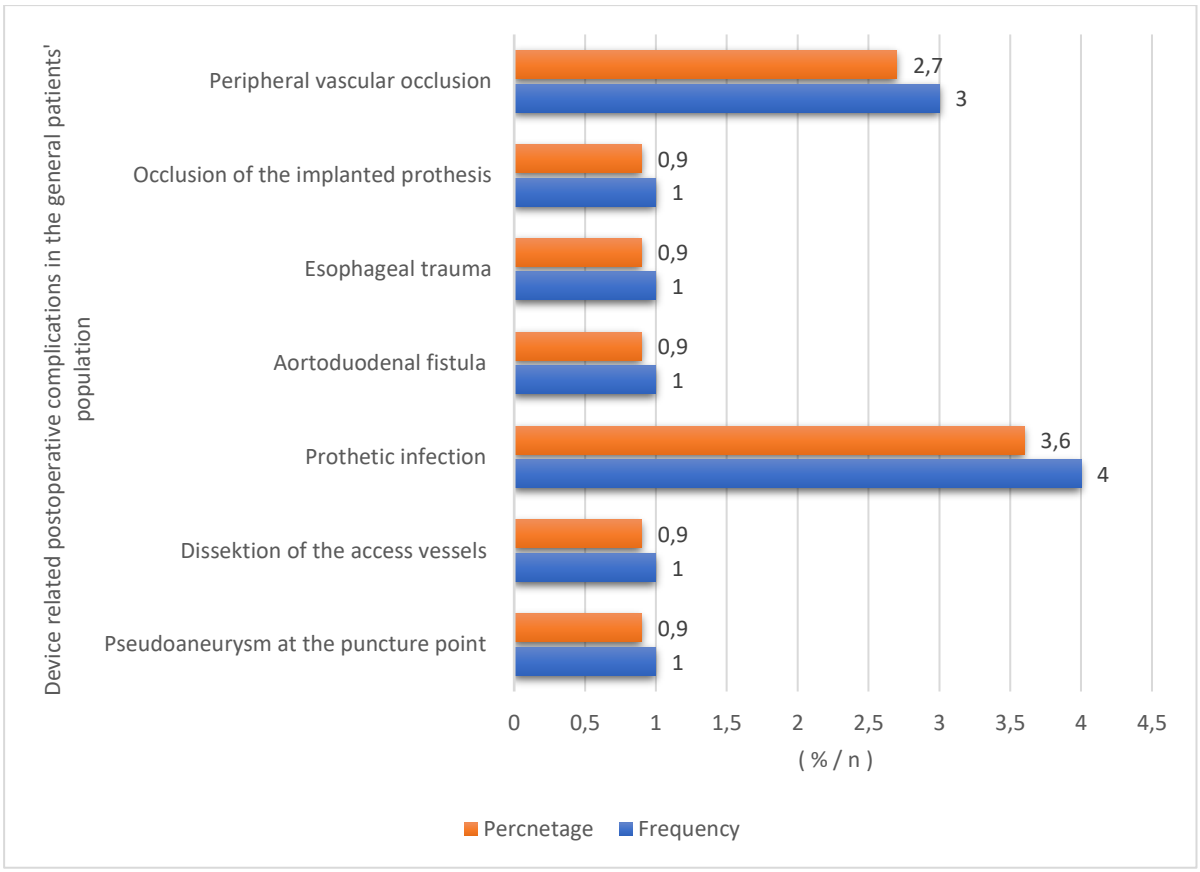

Fig. 8-b) Complications - device-related

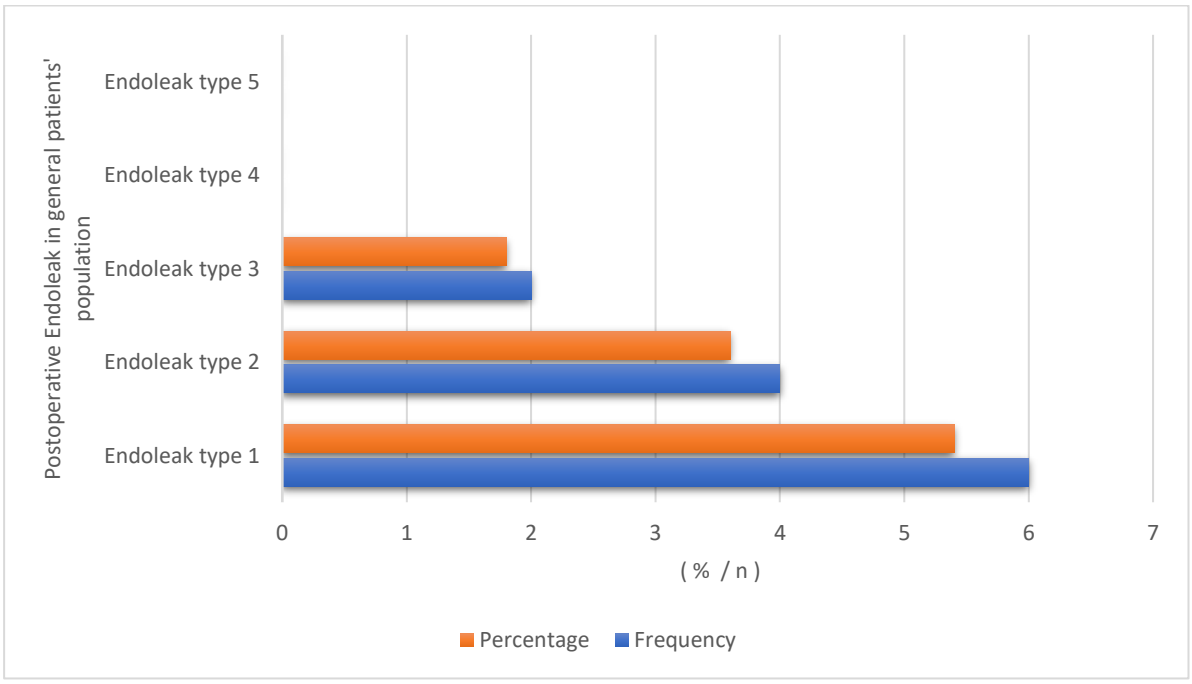

Fig. 8-c) Complications - endoleak

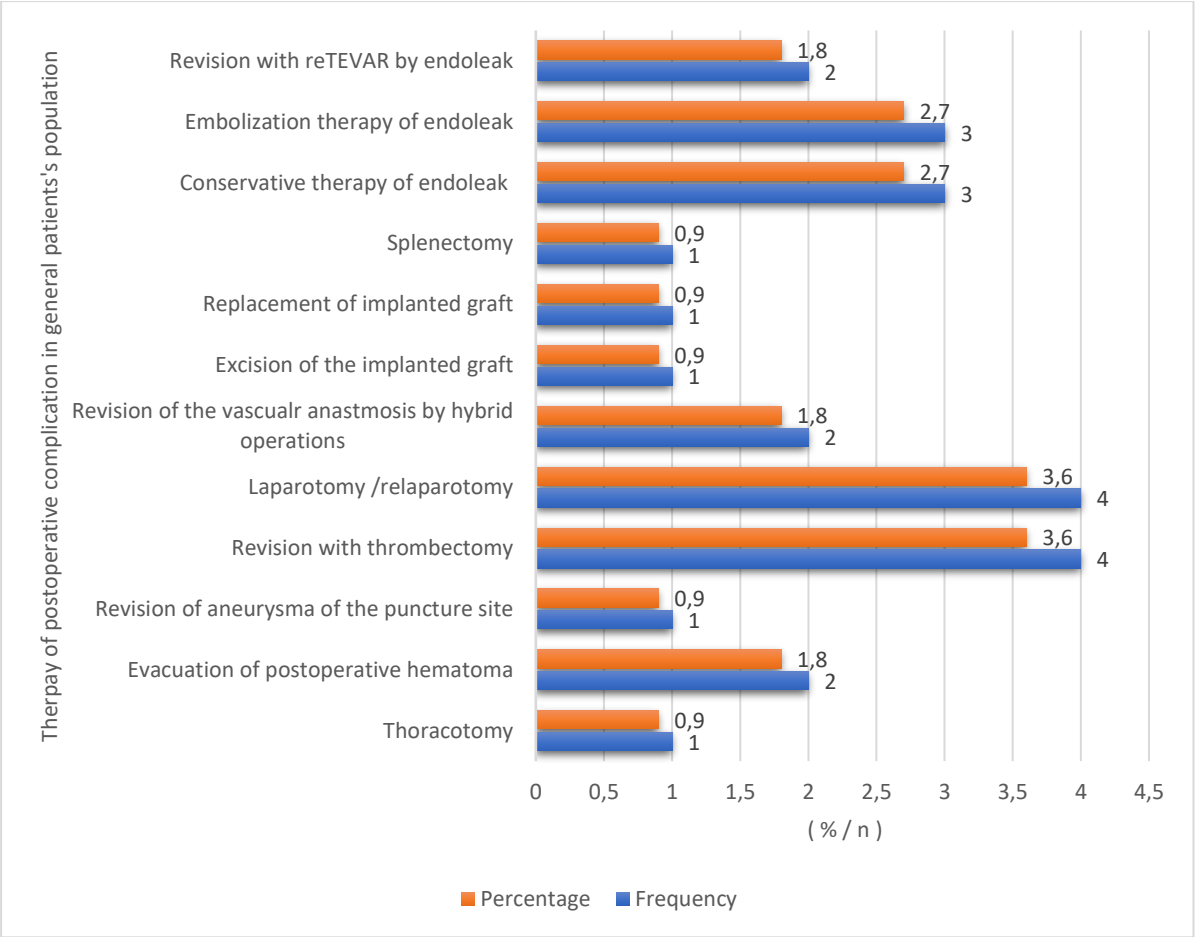

Fig. 8-d) Therapy of postoperative complications

Endoleak therapy includes re-TEVAR (*n*=2 cases; 1.8 %), embolization (*n*=3 cases; 2.7 %), and conservative measures with follow-up controls (*n*=3 cases; 2.7 %). The endograft was excised and replaced in one case (0.9 %). Revision of the puncture site due to aneurysm was diagnosed in a further case (0.9 %), whereas operative revision of the anastomosis in hybrid operation was required in two individuals (1.8 %).

3.2.6. Postoperative mortality **(Figs. 9 a-b**)

Early postoperative mortality within the first three postoperative months encountered 18 cases (16.1 %), while late postoperative mortality encountered two cases (1.8 %). Causally, the most common causes of postoperative mortality through this study are hemorrhagic shock and cardiac arrest with five cases each (4.5 %). The second common causes are multiorgan failure (MOV) and preexisting therapy-resistant aortoesophageal fistula with four cases each (3.6 %). The other causes include postoperative aortic rupture, sepsis, multiorgan failure, and postoperative pancreatitis with one case each (0.9 %).

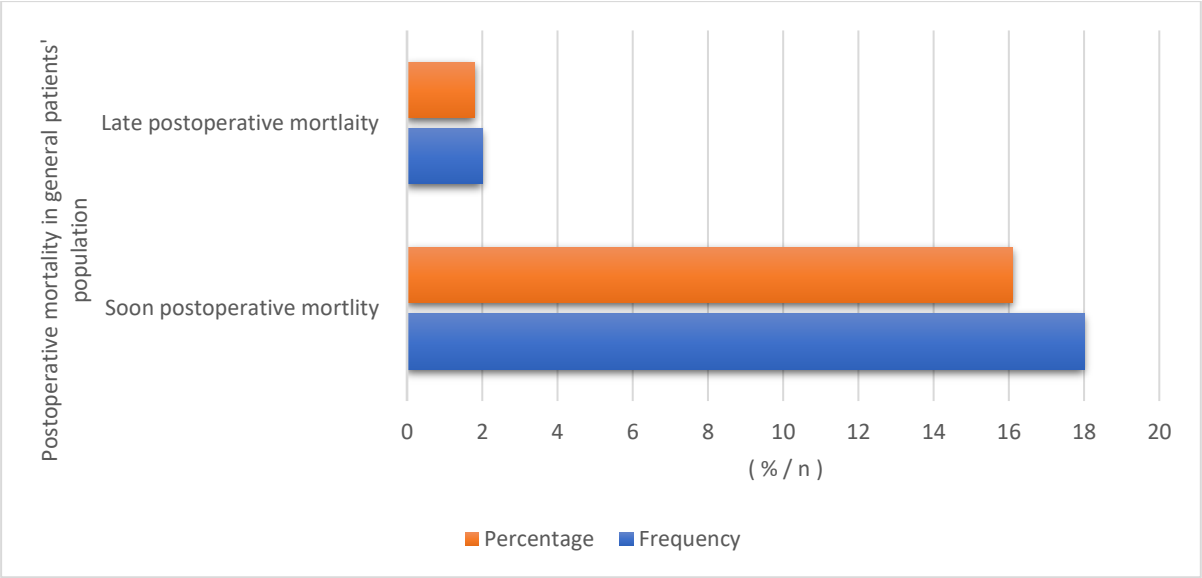

Fig. 9-a Mortality classified chronologically

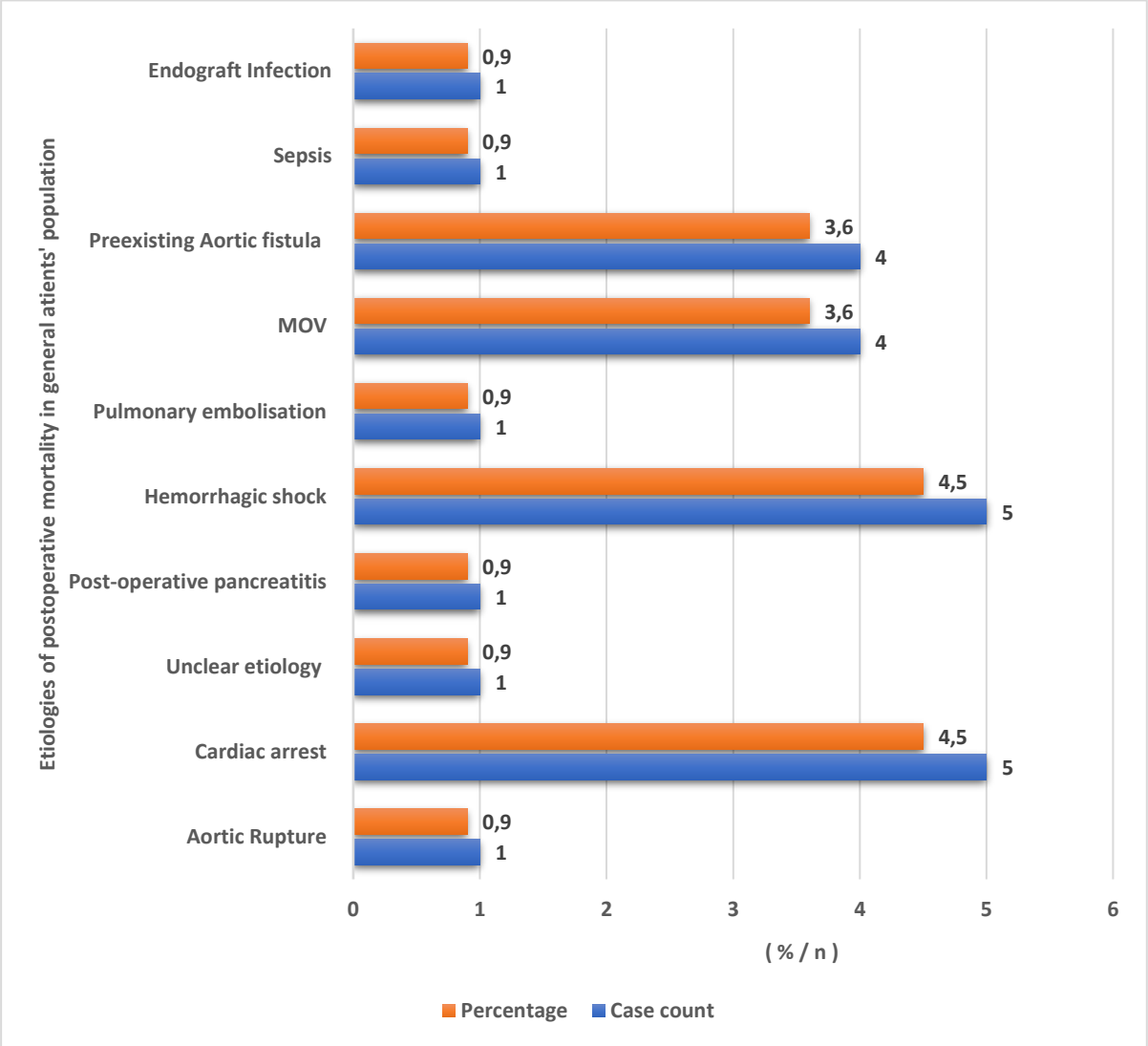

Fig. 9-b Etiologies of postoperative mortalities

3.2.7. Post-operative follow-up (**Fig. 10**)

The extractable information of 38 patients – who were commited for regular follow ups- are illustrated in (**Fig. 10**). Most cases (30 patients) were represented with good and stable controls. While two patients (1.8 %) were represented with an endoleak and two more with thrombotic vascular precipitations (1.8 %). Abdominal aortic aneurysm was discovered in one patient (0.9 %) and infra-renal aortic dissection was found in another patient (0.9 %).

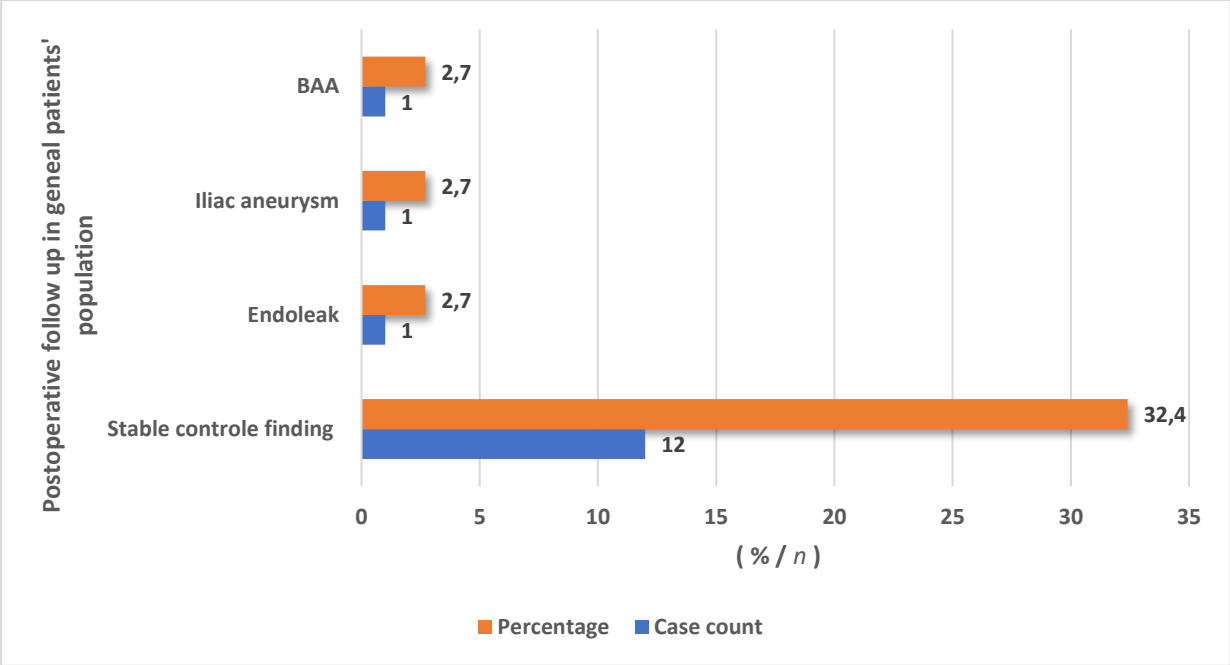

Fig. 10. Postoperative follow-up

3.3. Statistics of the study population concerning the cases with over-stenting of the left subclavian artery as pure endovascular and in combination with debranching of the supra-aortic vessels

3.3.1. Overview

In total, 35 patients underwent over-stenting/covering of supra-aortic vessels, especially the LSA. Those patients either:

- were treated with only EVAR of the thoracic aortic lesion with covering LSA (or)
- underwent the debranching of the supraaortic vessels in order to prepare for the accompanying endovascular therapy.

3.3.2. Epidemiologic parameters

The sex ratio with the over-stenting of LSA/supra-aortic vessels shows a male predominance with 74,3 % (*n*=26 cases) *vs.* nine female cases (25,7 %), respectively. The yearly incidence of the interesting cases and their therapies (i.e., thoracic aortic lesions with the urgency to cover the LSA/ supra-aortic vessels) is characterized by an increase from 2014 to 2015 and a “re-rise” in 2018. The mean hospital stay was 12 (range, 3–51) days (mean age, 70 [range, 25–96] years).

The risk factors of this specific patient group was very similar to those for the general case description (see above). The highest portion of accompanying diseases was found for arterial hypertension, then (with decreasing percentage) hyperlipidemia, and respiratory and cardiac factors. Interestingly, preexisting intracerebral vascular occlusion/stenosis and renal and visceral artery occlusions/stenoses were not detectable (**Fig. 11**).

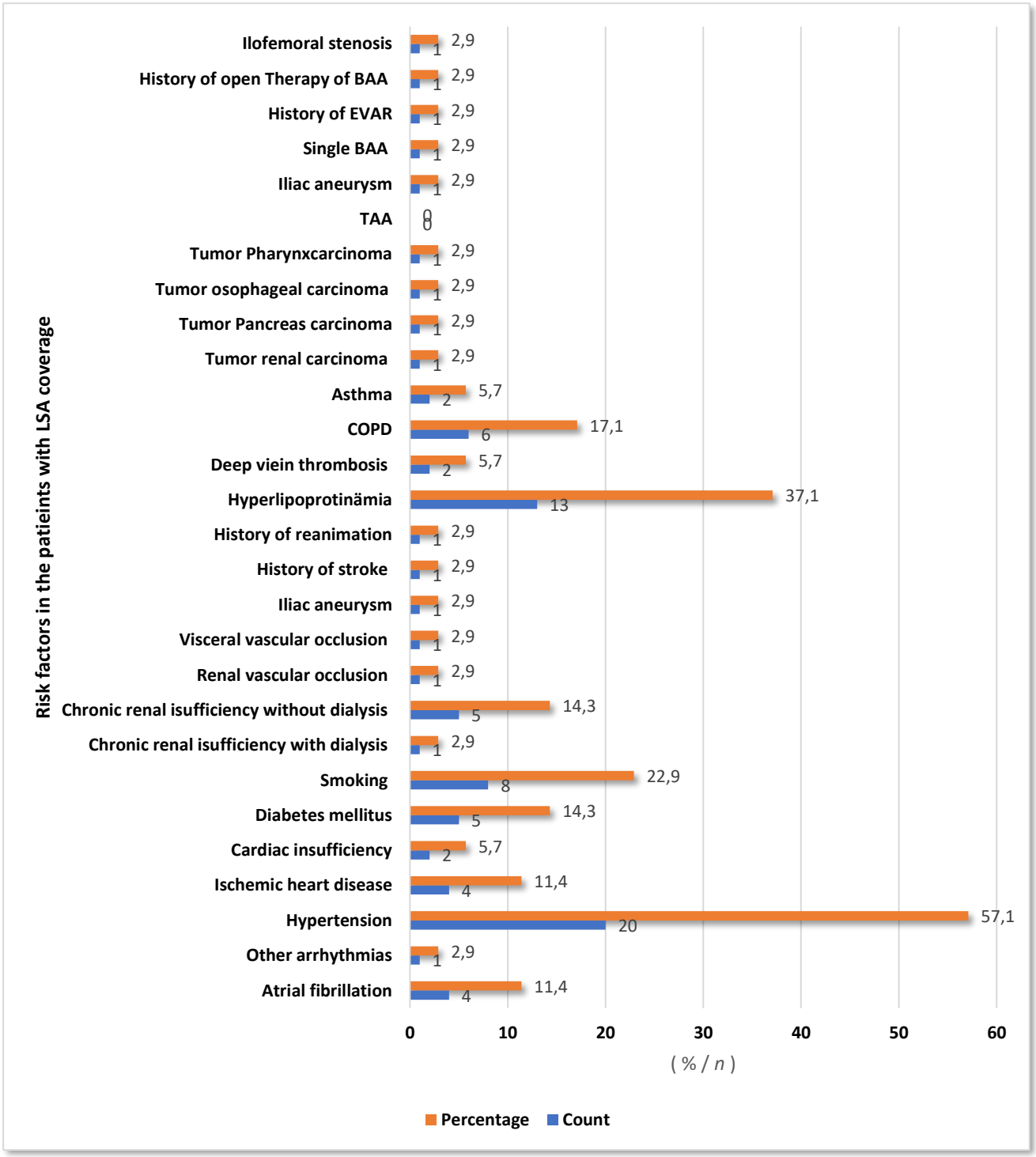

Fig. 11. Risk factors of the TEVAR cases with LSA coverage **(**TAA; tacyharrythmia absoluta, COPD; chronic obstructive pulmonary disease)

3.3.3. Diagnoses and symptoms of the treated thoracic aortic lesions **(Fig. 12)**

As presented in (**Fig. 12**), the illustrated spectrum of diagnoses shows a similar "ranking" as detected in the main patient group (see also above)—for example:

- the first rank is represented by TAA (*n*=14 cases; 40 %) whereas
- the second rank by the aortic dissection Type B (*n*=13 cases; 37.1 %).

Covered and open aortic ruptures were diagnosed in seven patients (20 %) and four patients (10.8 %), respectively. This diagnosis is accompanied by either TAA, Type-B thoracic AD, traumatic rupture, or inflammatory/neoplastic etiologies. The ratio of symptomatic/asymptomatic cases is as follows: 20 symptomatic (57.1 %) *vs.* 15 asymptomatic cases (42.9 %). The symptomatic cases showed a relatively close correlation with the presence of TAA with eight cases (21.6 %).

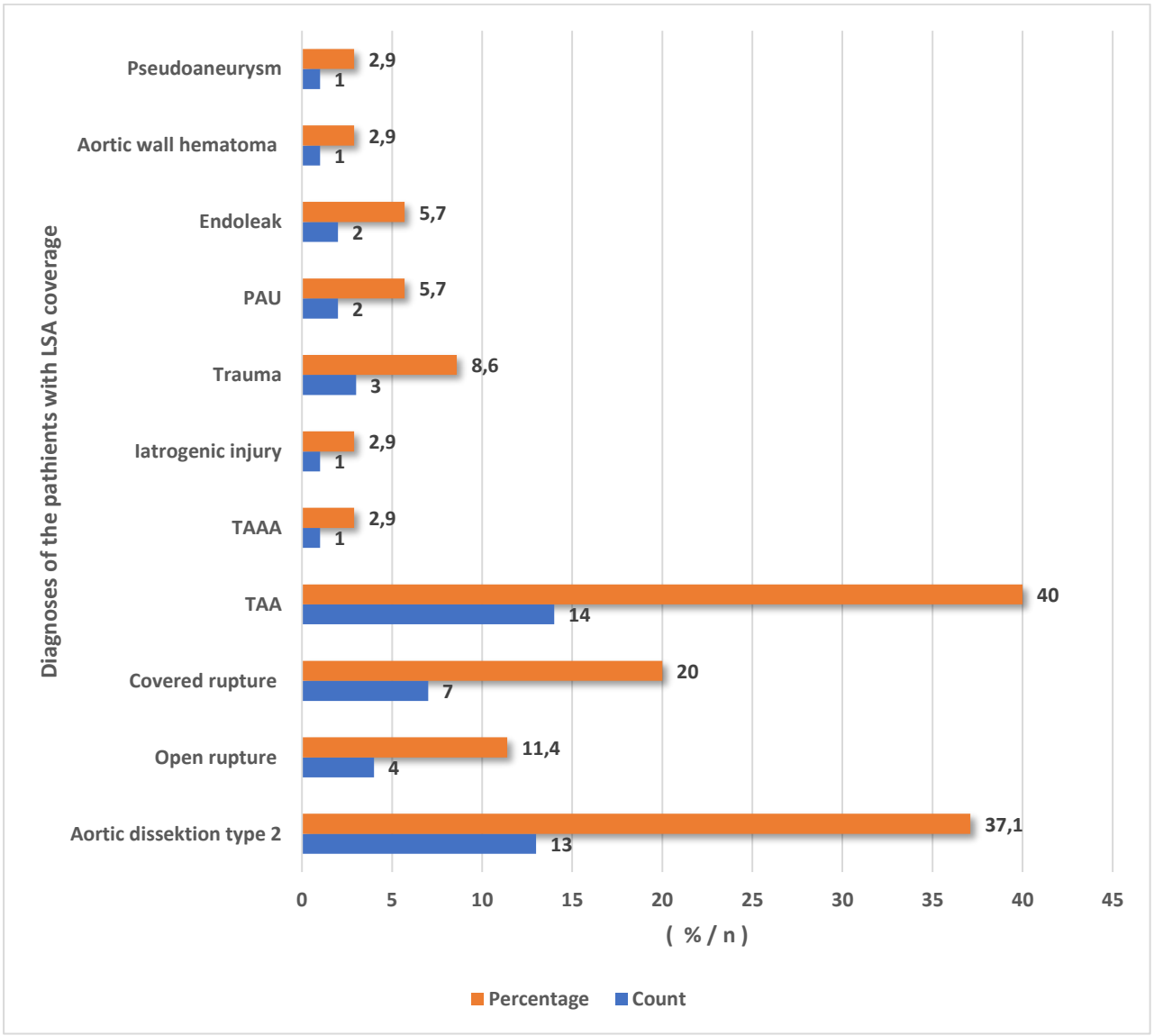

Fig. 12. Diagnoses and indications of the TEVAR cases with LSA coverage

3.3.4 Statistics of different diagnostic findings

Preoperative CT scans demonstrated a mean proximal landing zone of 2 (range, 2–7; S_D, $\pm$ 1.732) cm *vs.* a mean distal landing zone of 22 (range, 23–30; S_D, $\pm$ 5.394) cm **(Table 2).**

Table 2. Preoperative CT measuerments of the cases concerned with LSA covering

CT measurements	**Number of measured cases**	**Medium**	**Standard deviation**	**Median**	**Maximum**
Proximal landing zone length (TEVAR cases outside zones 1-2)	11	2	1.732	2	7
Distal landing zone length (TEVAR cases lesions not reaching the visceral/renal vessels)	23	22	5.394	23	30
Diameter of the lesions (Aneurysms-dissecting aneurysms-PAU)	30	4.86	2.08	5	8.1
Length of the lesions	29	11.72	12.864	5	44
True lumen diameter (in AD cases)	13	2.69	0.947	3	5
False lumen diameter (in AD cases)	13	4.31	5.483	3	22

3.3.5. Operative/technical statistics of the different therapeutic modalities

The profile of the performed therapeutic maneuvers (simple endovascular operations with LSA coverage without revascularization *vs.* hybrid operations) comprises 21 subjects (60 %) and 14 individuals (40 %), respectively.

3.3.6. Postoperative complications

- Systemic complications **(Fig. 13-a)**

The systemic postoperative complications show postoperative pneumonia (3 cases; 8.6 %) and postoperative spinal ischemia (3 cases; 8.6 %) in this patients' sample. (**Fig. 13-a**) shows one case of hypoxic brain injury (2.9 %) and the representation of other cardiopulmonary complications with one case each (2.9 %). The differential and comparative study of the complications between the revascularized and non-revascularized groups will be undertaken as analysis of variance (ANOVA) as part of this work.

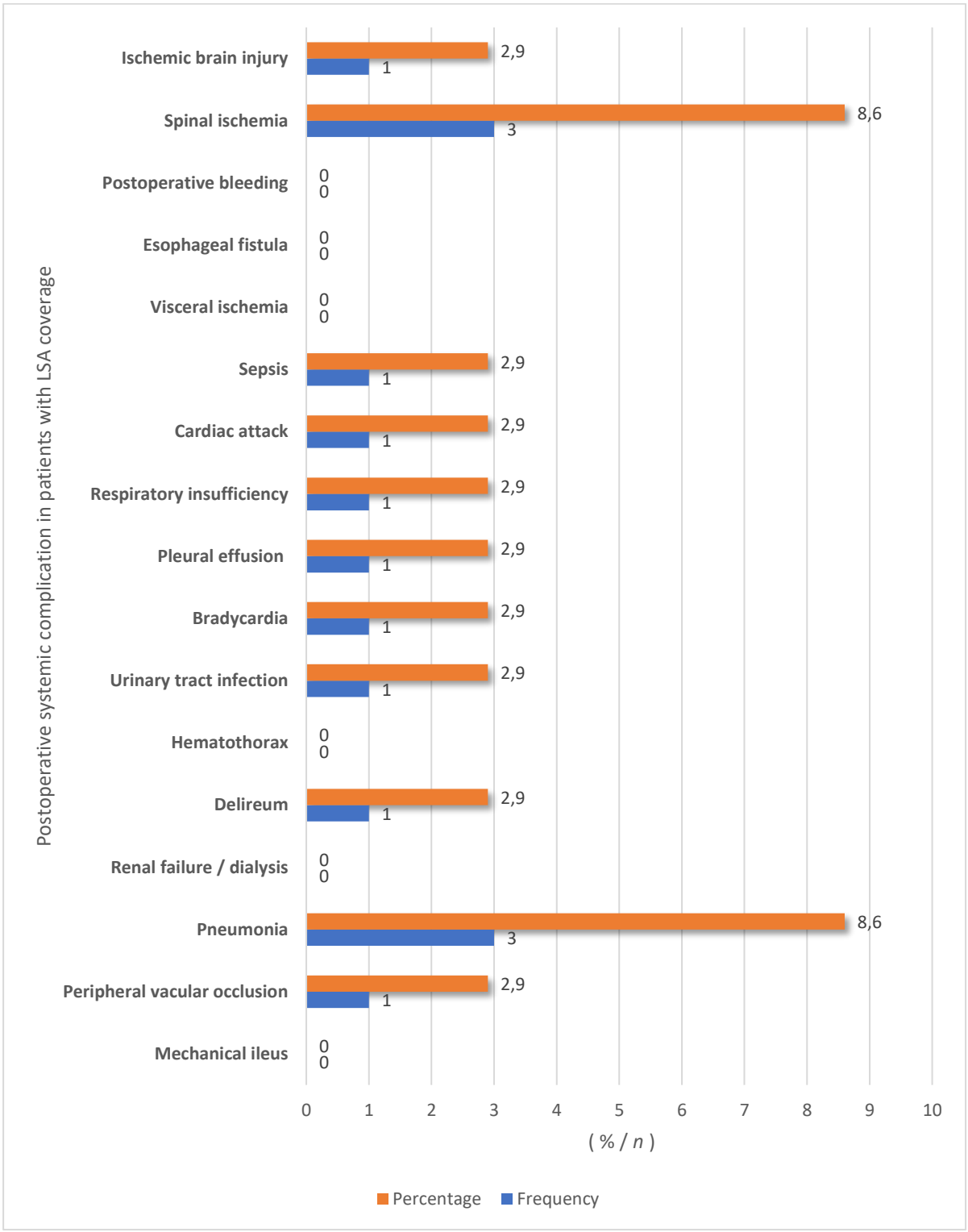

Fig. 13-a Systemic complications of TEVAR with LSA coverage Rand

- Device-related complications (**Fig. 13-b**)

There were only six device-related complications:

- one intraoperative kinking of the proximal end of the prosthesis - 2.9 %

(which required the proximal extension into the Ishimaru landing zone 2 with no further

complications and fully sustained left arm functionality) and

- *n*=4 subjects with perioperative endoleak of Type 1 (11.4 %) as well as
- one case of Type 3 (2.9 %),
- no cases of other types of endoleak were recorded.
- no cases of ischemia of left arm was registered (including claudication of the left arm or symptomatic subclavian steel syndrome).

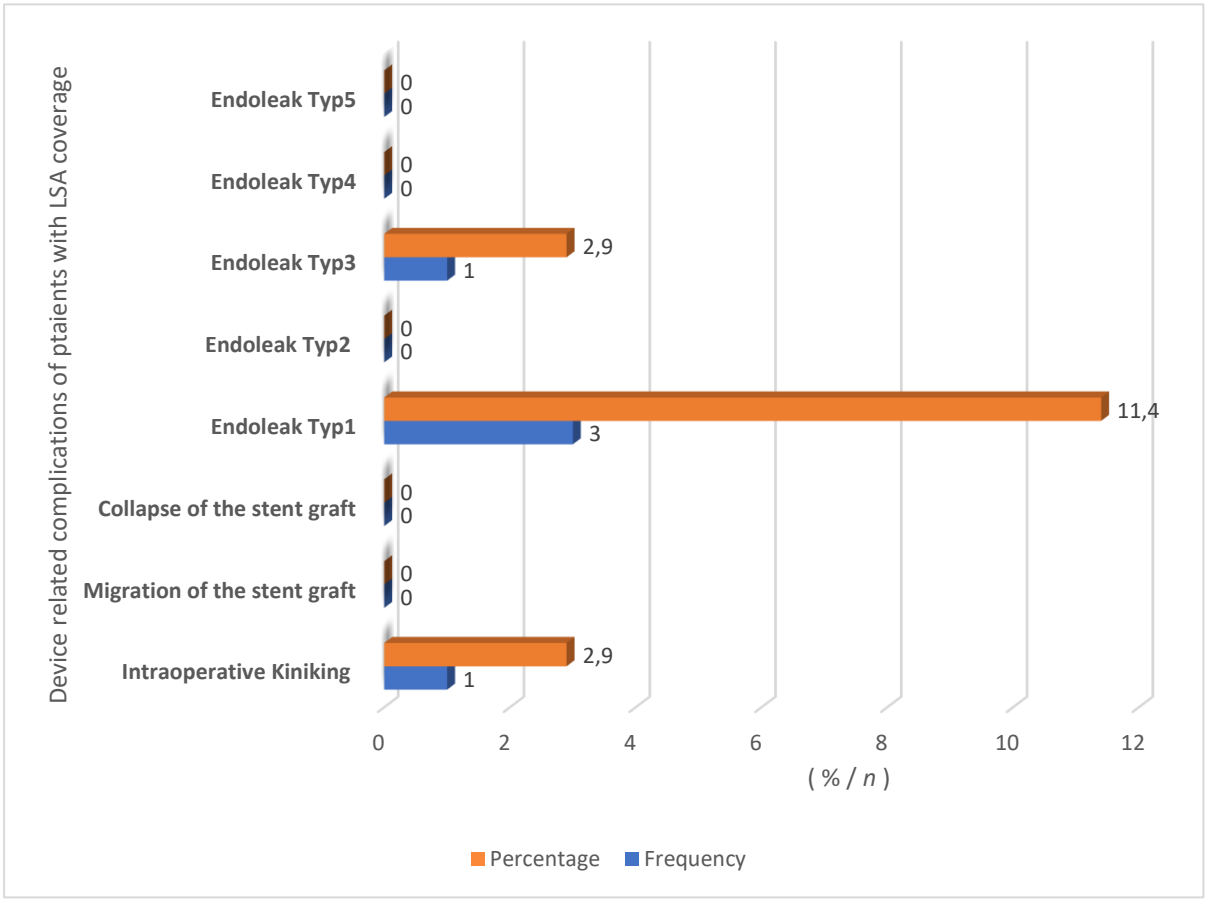

Fig. 13-b Device-related complications of TEVAR with LSA coverage

Therapy of postoperative complications/endoleak

The therapeutic profile contains, in particular, thrombectomy of the access vessels as the only pure postoperative mandated therapy of general complications. In addition, thoracotomy and hematoma excavation were performed in one case (2.9 %), this case showed (before the operation) massive diffuse bleeding from the descending aorta and that was the indication of TEVAR. Finally, as therapeutic measure against the postoperative endoleak, three cases (8.6 %) underwent conservative therapy without further complications, whereas two cases (5.7 %) underwent embolization of the LSA and one case (2.9 %) underwent re-TEVAR.

3.3.7. Postoperative mortality and survival (**Table 3**)

Early postoperative mortalities (within the first 30 days after surgery) encountered (*n*=6 cases; 17.1%), 4 cases showed registered causes for deaths as following:

- cardiac arrest (*n*=2 cases; 5.7 %),
- postoperative bleeding (*n*=1 case; 2.9 %),
- unclear cause (*n*=1 case; 2.9 %), and

In contrast, there was no registered mortality at all in this patients' cliental with causal relation to the undertaken LSA-covering TEVAR with/without LSA revascularization.

The Kaplan–Meier curve of survival probability shows the median of 39.652 (95% CI, 32.138–47.166; SE, 3.834) months. The 6-months survivabilty was 79%. (**Fig. 14**).

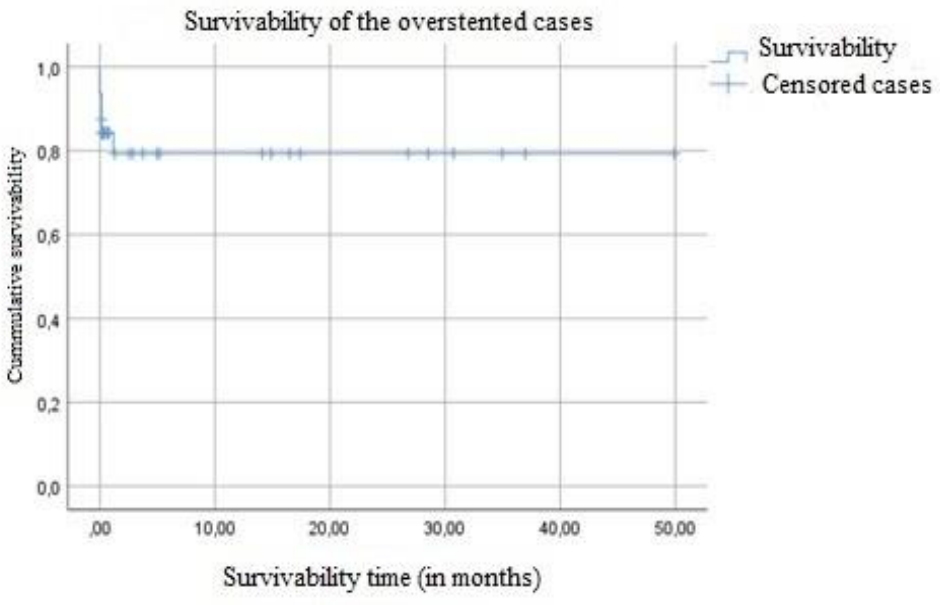

Fig. 14. Kaplan–Meier survival curve for the overstented patient's population, the censored cases are the Patients who got out of the study without reaching the endpoint of death.

3.3.8. Post-operative follow-up

The late follow-up findings of the patients who showed up in their followup-appointments (13patients; 37%) were characterized by stable and uncomplicated clinical and CT findings in 10/13 cases (76.9 %), whereby endoleak was found in one case (7.69 %). Besides those relevant findings, abdominal aortic aneurysm and iliac aneurysm were found in one case (7.69 %) each.

3.4. Analysis of multiple independent variants between the revascularized and non-revascularized groups

It showed, in general (considering sex ratio, risk factors, CT findings and measurements, complications, mortality, and survival probability,) no statistically significant difference comparing the two patient groups-revascularized *vs.* not revascularized patients- with *p*-value > 0.05.

- Individual parameters with significant impact

Renal insufficiency had a significant impact as a risk factor in hybrid operations (*n*=1 case; 7.1 % - *P*=0.028), otherwise postoperative pneumonia provided a tendential impact after hybrid operation with debranching of the supraaortic vessels (*n*=3 cases; 21.4 % - *P*=0.058).

Despite scattered complications, those complications did not create any significant impact (*p*-values > 0.05): spinal ischemia was observed in not-revascularized and revascularized patients in 2 cases (9.5 %) and one case (7.1 %), respectively (hypoxic brain injury in one [4.8 %] *vs.* 0 case [0 %]; *P*=1) - no arm ischemia at all). The survival probability in both patient groups showed+ no statistically significant difference when comparing non-revascularized *vs.* vascularized: 22 (95% CI, 14.154–29.904) months *vs.* 43 (95% CI, 33.655–51.921) months. The comparative 6-months survivabilty of the pure endovascular (no revascularization) *vs.* hybrid (with revascularization) was (71.1 *vs.* 85.7% respevtively). The comparative survivability check was done using Chi-square test in 3 test methods (Log Rank (Mantel-Cox), Breslow (Generalized Wilcoxon) and Tarone-Ware, all results showed *p>0.05* with no significant stastistical difference.

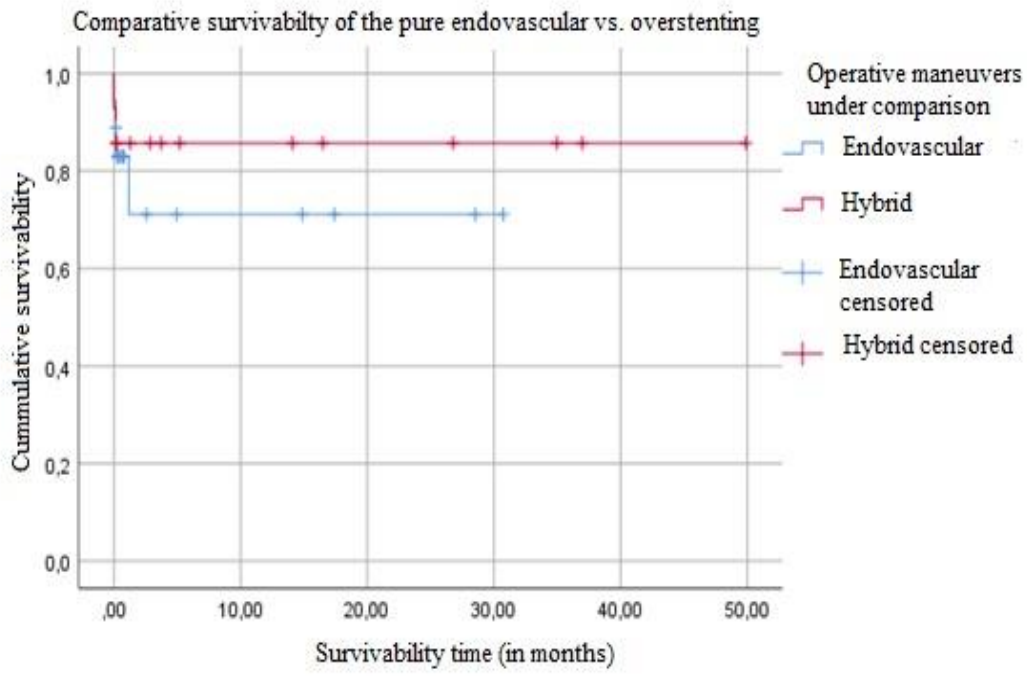

Fig. 15. Comparative Kaplan–Meier survival curve for the overstented patient's population, the censored cases are the Patients who got out of the study without reaching the endpoint of death.

3.5. Literature review (**Table 3**)

Under the previously noted MeSH, 775 different topic-related titles were found. Those titles were refined with the exclusion of not related titles. Finally, 130 abstracts were reviewed. From those 130 abstracts, four categories emerged, as listed in (**Table 3**).

Table 3. Categories and contents of publications with regard to "pro's and con's" of LSA revascularization as well as alternative approaches (TEVAR: thoracic endovascular repair; LSA: left subclavian artery; pats.: patients; w/: with; w/o: without; &: and; CG: chimney graft; OR: odds ratio)

AUTHOR	**Year of publication**	**Study period**	**No. of patients [n]**	**Main content**
I) Data supporting the hypothesis of no necessity for primary standard revascularization of the LSA in TEVAR with LSA coverage				
1. Gombert *et al.* [65]	**2017**	1996–2006	**46**	- As much as 76 % of the patients mandate covering of the LSA, from them 2 % (*n*=1 patient) was revascularized w/ carotido-carotid subclavian bypass graft. The authors used the DASH score for postop. functionality of the arm (mid-term left-arm function, adequate results in comparison with the control group)
2. Youssef *et al.* [57]	**2018**	2010–2014	**40**	- The mean age, 65.4 years [y]; portion of LSA-covered patients, 82.5 %; 2.5 % were revascularized with LCCA–LSA transpositon & 10 % using the LCCA–LSA bypass graft. Only one patient (2.5 %) in the covered group developed critical arm ischemia & another patient (2.5 %) developed anterior spinal cord syndrome
3. McBride *et al.* [66]	**2015**	2005–2012	**82**	- The patients w/ TEVAR & covered LSA (*n*=32/82; 39.5 %) were compared w/ TEVAR patients w/o LSA coverage; postop. questionnaire was used focusiong onto arm pain, numbness, parathesia, or fatigue - conclusion, no significant (signif.) difference when comparing covered *vs.* uncovered group

4. Loh *et al.*[67]	**2011**	2010–2011	**1,189**	- Major adverse events (cerebrovascular events CVA &/or spinal cord ischemia SCI) were subclassified into 3 groups; TEVAR w/ uncovered LSA (Gr. A), TEVAR w/ covered LSA (Gr. B: *n*=349 patients; 33.1 %), & TEVAR w/ covered revascularized LSA (Gr. C: *n*=180/349; 46 %) - subgroup analysis, no signif. dfference comparing Gr. B & C (SCI, 6.3 % *vs.* 6.1 %; CVA, 6.7 % *vs.* 6.1 %) → LSA revascularization, not protective for SCI (7.5 % *vs.* 4.1 %; *P*=0.3) or CVA (6.1 % *vs.* 6.4 %; *P*=0.9)
5. Janczak *et al.*[68]	**2019**	2014–2017	**51**	- Mean age, 66 y; comparison groups, w/ covered LSA (n=18 patients; 35.3 %) *vs.* w/ uncovered LSA (n=33 patients; 64.7 %) by doing TEVAR → no signif. difference considering the cerebrovascular events or spinal ischemia (stroke, *P*=0.37; SCI, *P*=0.58)
6. Kotelis *et al.*[69]	**2009**	1997–2008	**220**	- Patients' groups, w/ covered LSA (n=88; 40 %) out of them 4 patients (1.8 %) were revascularized w/ LCCA-LSA transposition & 1 patient (0.4 %) w/ LCCA-LSA bypass graft - postop. Stroke, & paraplegia were lower in the not-revascularized gr. *vs.* revascularized gr. & not-revascularized *vs.* revascularized, resp., for postop. stroke (3 % *vs.* 3.9 %; Odds ratio [OR], 0.570; 95% CI, 0.118–2.761; *P*=0.7269), whereas for postop. paraplegia (1.5 % *vs.* 1.9 %; OR, 0.774; 95% CI, 0.038–6.173; *P*=1.0) - ischemic changes of the left arm occurred in 2 pats. (3 %) while subclavian steal syndrome in 2 pats. & required secondary revascualrization → conclusion, revascularization of the LSA should be done selectively and not generally in certain indications like long segmental aortic coverage, prior to concomitant infrarenal aortic replacement, a hypoplastic right vertebral artery, the need of a patent left internal mammarian

				artery for CABG operations (Op), & a functioning dialysis fistula
7. Skripochnik *et al.*[70]	**2018**	2006–2017	**30**	- The cohort retrospective study in patients with BTAI; LSA was covered to achieve a good conceal of the proximal landing zone in 7 pats. (23.3 %) - procedural success, 96 / 100 % for the uncovered / covered groups - conclusion, TEVAR for BTAI in pats. w/ short proximal landing zones of 10–20 mm as well as in select pats. w/ landing zones of 5–10 mm appears to be safe & efficacious (revascularization could yet be used for shorter aneurysmatic necks)
8. Woo *et al.*[71]	**2008**	1997–2007	**308**	- In total, 70 pats. w/ covered LSA (22.7 %), among whom 5 (7.14 %) were revascularized w/ LSA-LCCA transposition, 3 (4.5 %) w/ LCCA-LSA bypass graft & ligation of the occluded LSA, while 34 pats. (48.6 %) were revascularized w/ bypass graft after coil embolization of the LSA (no paraplegia; stroke rate, 0.8 % w/o direct relation to LSA blockage; no posterior cerebral infarcts) - Left arm symptoms in 5 pats. (18 %) w/o LSA revascularization (out of them, 2 revascularizations [n=1 for critical leftarm ischemia) - No permanent left upper extremity dysfunction or ischemia registered - Conclusion, zone-2 TEVAR w/ LSA coverage can be safely done w/o revascularization (except for the patent LIMA-LAD bypass) - urgent revascularization may be necessary
9. Dunning *et al.*[72]	**2008**		**1,161 (n=498 w/ TEVAR & LSA**	- Literature review, 45 non-randomized trials & 213 non-controlled papers - Complications, 13 strokes (2.6 %), 8 cases w/ paraplegia/paraparesis (1.6 %), & 6 endoleaks due to the backflow from covered LSA (1.2 %) - n=51 cases w/ left-arm ischemia (out of them, 20 pats. underwent postprocedural revascularization [4 %]) - conclusion, TEVAR w/ LSA

			coverage)	coverage can be done safely w/o urgency for revascularization under certain conditions (good & controlled patency of the carotid & vertebral arteries, as well as the circle of Willis)
10. Wojciechowski *et al.*[73]	**2014**	2004–2012	**125**	- *n*=53 pats. with covered LSA in TEVAR (42 % called as Gr. A *vs.* non-covered LSA as Gr. B) → no signif. difference comparing both groups considering 30-d mortality/morbidity, also for complications, such as SCI (*P*=0.39) & CVA (*P*=0.82)
11. Zhu *et al.*[74]	**2017**	2004–2012	**125**	- In total, 94 & 66 pats. underwent partial & complete LSA coverage in TEVAR, resp. Out of the 66 pats., 10 underwent right-CA to left-CA bypass w/o involvement of the vertebral artery, 4 underwent LCCA-LSA bypass graft (RCCA-LCCA-LSA bypass graft in 3 cases), 6 of the last 7 pats. underwent proximal LSA ligation. In all patients, despite paleness & numbness of the left upper limb, no further critical ischemic reactions, which urged secondary revascularization → conclusion, the decision depends on vertebral arteries & the circle of Willis (if both are intact, LSA can be covered w/o further intentions; if the right vertebral artery is advantagious, then the ballon occlusion test of the LSA osteum is favored to test the patency of the circle of Willis - if negative → LSA can be covered / if positive → need of revascularization). In case of an advantageous left vertebral artery from its origin → revascularization with the bypass graft is preferred.
12. Klocker *et al.* [75]	**2014**		**138**	- Postop. questionnaire to assess left arm functionality in TEVAR with LSA coverage for not-revascularized (n=40 pats.; 29 %) *vs.* revascualrized pats. (n=9; 6.5 %) - 2 components were relevant. M ental & physical score (in addition, DASH score) → no preferential results for any gr.

13. Eisenberg *et al.* [76]	**2016**	1996–2014	**4**	- 75 % procedural success with 1 postop. stroke w/o intervention, otherwise an axillo-axillary bypass graft by in advert coverage of the LSA - no SCI ischemia was registered; conclusion, TEVAR w/ partial LSA coverage in patients with a landing zone less than 2 cm → effectively (for further studies needed)
14. Antonello *et al.*[77]	**2013**	2001–2005	**31** (w/ traumatic aortic injuries & covered LSA in TEVAR)	- No postop. stroke, vertebrobasilar insufficiency, or paraplegia (n=9 pats. [36 %] w/ arm claudication [ischemic pain, **i) is** defined as within 60 s of the beginning of arm exercise & decrease of PSV from 50–60 %; **ii)** risk factors left vertebralartery Ø < 3 mm [p, 0.0001]); significant correlation between the degree of PSV reduction & left arm symptoms (p<0.0001); there was an improvement of ischemic arm symptoms (p<0.0001) during the mean follow-up period of 36 months. Freedom of reintervention (at 48 months), 93.5 %. Conclusion, LSA coverage in TEVAR to extend the landing zone → feasible if a suitable Ø of the left vertebral artery
15. Galili *et al.* [78]	**2007**	2000–2004	**30**	- LSA blockage in 11 pats. (36.7 %) w/ revascularization of 2 subjects (6.7 %) - one (11 %) of the remaining 9 pats. suffered mild claudication & required no reintervention (Duplex scan showed a reverse flow in the left vertebral artery in 8 / 9 not-revascularized pats. & occlusion in 1 pat. (in whom the left vertebral artery originates directly from the aortic arch)
16. Preventza *et al.*[79]	**2006**	2000–2005	**255**	- In total, 71 (27.8 %) & 47 pats. (18.4 %) w/ complete & partial LSA coverage, resp.: 15 pats. (5.9 %) underwent preop. revascularization (transposition-bypass), 1 pat. (1.8 %) required carotido-subcl. bypass secondary to left-arm claudication - conclusion, routine preop. carotido-

				subcl. bypass is not necessary, except for pats. w/ a mandatory patent left internal mammarian artery for the left anterior descending artery byass graft or pats. w/ contralateral vertebral artery disease
17. Riesenmann *et al.*[80]	**2007**	2000–2005	**112**	- In total, 24 pats. w/ zone-2 TEVAR (among them, 10 pats. [42 %] & 19 pats. underwent partial & complete LSA blockage, resp., in particular, of the antegrade flow through the LSA origin): 3 pats. (15.8 %) developed left-arm symptoms w/o need for intervention (1 pat. [5.3 %] developed arm rest pain w/ revascularization by subcl. Stenting.
18. Si *et al.*[81]	**2014**	2009–2010	**171**	- In total, 128 pats. underwent intentional LSA coverage based on systolic RR difference between right & left arms (no postinterventional malperfusion syndrome was reported. Seven patients reported mild symptoms of subclavean steal syndrome w/ no requirement for secondary intervention. The authors concluded that LSA osteal occlusion during TEVAR was tolerated by all pats. w/o functional deficit. In the absence of stenotic carotid/vertebral arteries w/ documented an intact vertebrobasilar system, TEVAR w/ LSA coverage can be done w/o primary revascularization.
19. Görich *et al.*[82	**2002**		**23**	- All the patients underwent intentional LSA coverage. Postoperatively, 20 pats. (78.5 %) w/ no complaints during a mean follow-up period of 12.1 months. Moreover, 3 pats. complainted about exercise-dependant parasthesia, non-exercise-dependent, intermittent, & completely reversible dizziness, as well as the temperature difference between the upper extremities w/ no decrease in strength.

20. Lee *et al.*[55]	**2013**	2006–2011	**126**	- In total, 29 pats. required LSA coverage w/o revascularization. The 30-d mortality was 6.9 % (n=2/29), No occurance of SCI or posterior CVAs was registered. Embolic anterior CVA was recorded in 2 patients (7.4 %). Transient left arm ischemic symptoms occurred in 5 pats. (18.5 %) w/ no need of secondary intervention.
21. Onishi *et al.* [83]	**2017**		**29**	- In total, 18 pats. (62 %) underwent LSA-covering TEVAR w/ no revascularization, whereas 11 pats. (38 %) underwent revascularization w/ the axilla-carotid-axilla bypass graft procedure. Moreover, 26 pats. underwent clinical assessment of left arm functionality afterward.
22. Baba *et al.*[84]	**2015**	2006–2014	**178**	- In total, 121 pats. (68%) underwent TEVAR in Zone 2. Coil embolization was done in 72.2 % of all cases. Cerebral infarction (CI) was, in general, in 6.6 % & paraplegia in 1.7 %. There were significant differences (univariate analysis) of the covering range of the aorta (> 300 mm; P=0.003) & of the shaggy aorta (P=0.044). Left upper extremity symptoms occurred in 7 pats. (5.8 %) & vertebrobasilar insufficiency in 5 pats. (4.1 %). The authors concluded that the mid- & long-term results of TEVAR w/ LSA coverage were acceptable & routine revascularization was not necessary.
23. Si *et al.* [85]	**2009**	2007–2008	**111**	- The pats. were divided into 4 groups (totally covered TC, less than 50 % covering LTC, more than 50 % covering MTC & non-covered NC); their distribution was: 55 (49.6 %), 18 (16.2 %), 7 (6.3 %), & 31 pats. (27.9 %), resp. There was no stroke, paraplegia, or hemiparalysis in the pats. w/ TC. The blood pressure difference between the TC group & the other 3 groups was significant (P<0.01). Five pats. suffered from amaurosis & spotted vision, while 7 pats. suffered from left-upper-arm claudication. The authors concluded that intentional coverage of the LSA

				during TEVAR to obtain an adequate proximal landing zone is, with some exceptions, safe & well tolerated.
II) Reports which oppose the hypothesis that the primary standard revascularization of the LSA in TEVAR with LSA coverage is necesary				
1. Teixeira *et al.*([86])	**2015**	2011–2014	**2,063**	- The study linked between the LSA occlusion/revasculrization w/ SCI as primary outcome & CVAs as secondary outcome. In total, 508 patis. (24.6 %) underwent TEVAR w/ LSA coverage, among whom 58.9 % underwent revascularization. SCI occurred accordingly (not-revascularized group *vs.* the revascularized group): 12.1 % *vs.* 8.5 % (adjusted odds ratio, 2.29 [95%-CI, 1.03–5.14], P=0.043). CVAs likewise were represented with 12.1 % *vs.* 8.5 % (adjusted odds ratio, 1.55 [95%-CI, 0.74–3.26], P=0.244). It was concluded that the revascularization was associated w/ statistically significant lower SCI incidence.
2. Peterson *et al.* ([87])	**2006**	2001–2005	**70**	- In total, 30 (43 %) pats. had aortic lesions adjacent or involving the origin of the LSA. Moreover, 8 pats. underwent LSA coverage w/o revascularization. Among them, 5 pats. (63 %) developed complications. One patient developed symptomatic steal syndrome & received subsequently transposition of the LSA 7 months later. Also, 23 pats. (32.9 %) underwent primary revascularization of the LSA (transposition, n=21; bypass, n=2). One patient developed lower extremity paraparesis secondary to SCI. The authors advocate LSA–LCCA transposition if the aortic lesions is within 15 mm from the osteum of LSA. The goal is to prevent Type-II endoleak or perfusion of a dissecting false lumen. Other conditions are ipsilateral vertebral artery and coronary revascularization w/ patent internal mammarian artery.

3. Nagarsheth *et al.* [88]	**2015**	2005–2011	**392**	- Data acquired from the National Surgical Quality Improvement Program (NSQIP) database: There are 2 groups: TEVAR w/ covered LSA *vs.* uncovered LSA. There were higher incidence of stroke (under other complications) w/ significant difference in the covered group *vs.* the uncovered group, resp. (9 % vs 3 %; P=0.03). Therefore, the authors concluded that LSA coverage during TEVAR increases perioperative morbidity. Based on that, LSA revascularizaton should be cautiously recommended.
4. Botta *et al.* [89]	**2008**	1998–2017	**31**	- The patients' cohort consists of acute traumatic rupture of the discending thoracic aorta: 2 had the LSA totally covered during TEVAR & 2 more had the LSA partially covered (6.4 % each). One patient w/ intentional totally covered LSA experienced a cerebellar stroke, yet the further follow-up period showed no further complications, death, or endoleaks (32.7 +/- 27.5 months).
5. Ferriera *et al.* [90]	**2007**	2001–2008	**81**	- In total, 21 pats. (25.9 %) underwent LSA occlusion to gain more area for a safe seal zone. Moreover, 4 pats. (23.5 %) developed subclavian steal syndrrome (SSS). Among them, 3 were treated w/ subclavian-carotid transposition → the authors recommended primary revascularization of the LSA to avoid SSS.
6. Luehr *et al.* [91]	**2018**	2001–2016	**176**	- Out of the patients' cohort, 55 subjects (31.3%) underwent LSA revascularization and 122 pats. (68.7 %) stayed w/o revascualrization. Isolated left arm ischemia occurred in 12 pats. (9.9 %) out of the not-revascularized group. The left-hemispheric stroke was observed 4 times more frequently in the not-revascularized pats. The authors emphasized the importance of the LSA revascularization to prevent such complications.

7. Bradshaw *et al.* [54]	**2016**	2007–2014	**96**	- Patients' cohort w/ covered LSA comprised 41 pats. (42.7 %), while the revascularized patient group counted 55 cases (57.3 %). The revascularization included laser fenestration with stenting (n=33) & surgical revascularization w/ transposition (n=10) or bypass (n=12). The 30-d stroke risk was higher in pats. w/ no LSA revascularization in comparison with the revascularized pats. (n=6/41 [14.6 %]) *vs.* n=1/55 [1.8 %]), resp.; *P*=0017). There was no significant difference comparing laser fenestration w/ stenting & surgical correction w/ transposition. SCI was over all 2.1 %, there was no significant difference (*P*=0.098), although there was signficant difference in 2-yr SCI w/ higher SCI incidence in the not-revascularized group (*P*=0.04). The authors concluded that complete or partial coverage of the LSA increases the risk of a stroke & possibly SCI, thereby emphasizing the importance of revascularization.
8. Bensley *et al.* [92]	**2011**	2005–2008	**352**	- The patients' data were extracted from the registry of the American College of Surgeons National Surgical Quality Improvement Program database: 120 pats. (34.1 %) underwent LSA coverage, among whom 10 pats. (8.3 %) underwent LSA revascularization procedures.The postoperative stroke rate was significantly higher in the not-revascularized *vs.* revascuarized pats. as follows: 7.5 % *vs.* 2.6 %; odds ratio, 3.6 [95%-CI, 1.1–10.9], *P*=0.03). The authors concluded that TEVAR for the TAA of the discending aorta with LSA involvement indulges a high risk of postoperatve stroke; therefore, they recommended LSA revasculaization to reduce such complications.
9. Reece *et al.* [93]	**2007**	1999–2006	**64**	- In total, 27 pats. required occlusion of the LSA (42 %). Among them, 7 pats. (25.9 %) mandated preoperative revascularization. Four pats. developed late symptoms w/ necessity of LSA revascularization. No patient developed paraplegia. Three pats. suffered from neurological

				symptoms, which were not related to the posterior circulation. The authors concluded that TEVAR coverage w/ selective revascularization was safe for the pats.; nevertheless, 11/27 pats. (40.7 %) either pre- or postoperative revascularization. The authors emphasized the importance of selective LSA revascularization.
10. Maldonado *et al.* [108]	2013	2000-2010	1189	-Retrospective meulticenter study. Major adverse events were spinal cord ischemia SCI and cerebrovascular accendents CVA. The patients were subclassified into non covered LSA (group A), covered LSA (group B) and covered /revascularized LSA (group C). The subgroup analysis showed no significant difference between groups B/C (SCI, 6.3% vs 6.1%: CVA, 6.7% vs 6.1%). LSA revascularization was not protective for SCI (7.5% vs 4.1%; *P*=.3) or CVA (6.1% vs 6.4%; *P*=.9). The authors concluded that the LSA coverage does not appear to result in increase the incidence of the SCI/CVA.
III) Publications on various novel and innovative endovascular methods for LSA revascularization				
1. Murphy *et al.*[94]	**2009**		**1**	- Method: Laser fenestration and iCAST stent of the LSA - the patient suffered blunt chest trauma w/ aortic transection at the distal site of the LSA origin. Aortic arch has "bovine feature" w/ common origin of the innominate artery & the LCCA. The stent graft was successfully fenestrated with the LASER catheter at the origin of the LSA. Next, the fenestration was dilated with an iCast stent. Postoperative controls showed adequate outcome results at 6 weeks & 8 months, resp.
2. Redlinger *et al.* [62]	**2013**		**60**	- Method: laser fenestration & iCAST stent of the LSA (Methodology of applied laser fenestration as described by the authors: Via retrograde brachial access, a 0.018-inch wire, followed by the Spectranetics Turbo Elite 2.0–2.5-

				mm laser catheter is placed in the SCA ostium. W/ gentle laser-endograft contact pressure, 45 mJ/mm^2 at 25 pulses/s is applied to the endograft for 3 to 5 seconds to create a fenestration. The 0.018-inch wire is then advanced through the laser into the endograft lumen and substituted by a 0.035-inch wire. After endograft predilation, an Atrium iCAST 8- to 10-mm stent is deployed approximately one quarter into the lumen and three quarters into the branch vessel. The endograft portion of the covered stent is then flared & a completion of angiogram is performed). The technical success was 83 % in 5 out of the 6 pats. One fenestration attempt was abandoned because of the acute angle of the LSA origin & the Type-III aortic arch. Here, the LSA stent was snorkeled into the aorta proximally to the graft. All LSA stents were patent at the time of discharge & afterward controls. Conclusion, in-situ laser fenestration is safe & feasible in cases in which LSA must be revascularized.
3. Saito *et al.* (95)	**2005**	1999–2004	**17**	- Method: Inoue single-branched stent-graft implantation – pats. w/ either TAA or TAD type B, underwent the aforementioned. In total, 8 older pats. (47 %) were considered not fit for open surgery. SCI developed in one patient (5.9 %). Also, 3 endoleaks were discovered—2 at the proximal end & 1 at the distal end of the deployed stent graft. Further, 2 cases with late fatal outcomes were documented during the follow-up period (causes, cerebral bleeding, & pneumonia). All 3 endoleak patients underwent endovascular correction. The postoperative patency of the single branch was 100 %.
4. Lachat *et al.*(64)	**2013**	2010–2013	**14**	- Method: TEVAR with the periscope endograft (Maneuver: The size of periscope endografts were 1–2 mm larger than the branch

				artery [LSA] at the intended landing zone. The caudal end was extended distally to the intended distal landing site of the thoracic stent-graft, which was usually deployed after the PG. Both the PG & thoracic stent-grafts were generally molded using the kissing balloon technique) There were different etiologies: 10 TAA, 2 ruptured aortic aneurysms, & 2 TAD Type B. The immediate technical success was 100 %. The Kaplan–Meier estimate at 2 yrs was 93 %. Afterward, one periscope was occluded & one patient died (out of the patients' cohort w/ ruptured aortic aneurysms). The authors concluded that the TEVAR w/ periscope graft (PG) can be performed transformally & percutaneously with encouraging early & mid-term results. Long-term results are needed before wide application of this revascularization method.
5. Zhang *et al.* [96]	**2018**	2013–2016	**43**	- Method: Comparison of the chimney graft (CG - group A) & branched stent graft (SBSG - group B). Four complications occurred in Gr. A: two CGs occlusions, one Type-I endoleak, & one death from the dissecting aneurysm rupture compared w/ two in Gr. B (one side-arm graft twist & one death from myocardial infarction). The authors concluded that both techniques showed comparable results and need further evaluation before being applied as revasculaization methods.
6. Hsu *et al.* [97]	**2017**	2014–2015	**13**	- Method: Sandwich technique with the body flossing wire - technical success was 100 %. One sandwiched graft (0.5 %) was occluded but not treated because of the absence of related complications. At a mean follow-up period of 9.7 (range, 4-17) months, all the treated pathologies showed thrombosis of the related lesions. There was no neurological defect, but 2 non-procedure-related coomplications.

7. Huang *et al.* [98]	**2017**	2013–2014	**3**	- Method: Unibody single branch stent - 3 PAU pats. underwent TEVAR w/ single branched stent to avoid LSA coverage & additional reconstruction of the LCCA. Early postoperative mortality was 0 %. One late death due to myocardial infarction occured. No endoleak was reported. One compression of the chimney graft was observed.
8. van der Weijde *et al.* [99]	**2016**		**29**	- Systematic review of the published literature of the custom-made scalloped graft - results showed a high technical success rate with a low rate of complications.
9. Xue *et al.* [100]	**2015**	2010–2012	**59**	- Method: Chimney graft (CG) of the LSA - technical success rate was 98.3 % (n=58/59).In total, 69 thoracic stent grafts were used. As many as 62 chimney stents, including 55 uncovered & 7 covered stents, were implanted in 59 LSAs. Endoleak occured in 9/59 of the pats. (15.3 %). Mortality during the follow-up period was 5.4 % (n=3/56). Complications during the follow-up period included endoleak (overall, 14.3 %, n=8/56), retrograde Type-A aortic dissection (n=1/59), collapse (n=3/59, 5.4 %), or occlusion (n=2/59, 3.6 %) of the chimney → conclusion, CG of the LSA during TEVAR is feasible.
10. Tan *et al.* [101]	**2016**			- Case study of a 68-year-old patient – method: Percutaneous in-situ fenestration of LSA using the reentry catheter. The authors concluded that this technique can be used as alternative method for LS -revascularization for in-situ fenestration w/ the advantage that laser equipment is not required.

IV) Spectrum of systematic reviews and meta-analyses that treated the revascularization of the LSA in TEVAR with LSA coverage				
1. Hajibandeh *et al.* [102]	**2016**		**1,161**	- Systematic review (5 studies): Accumulatively, 444 pats. (38.2 %) underwent LSA covering, while others had TEVAR w/o LSA covering. The primary outcome comprised postoperative stroke, SCI, & mortality. The combined effect sizes were calculated using the fixed effect or random effects model. The results are reported as odds ratio (OR) with 95% confidence interval (CI). LSA revascularization was associated with a similar risk of stroke (OR, 0.70 [95%-CI, 0.43–1.14], *P*=0.15), SCI (OR, 0.56 [95%-CI, 0.28–1.10], *P*=0.09), & mortality (OR, 0.87 [95%-CI, 0.55–1.39], *P*=0.56) compared w/ no LSA revascularization. The authors concluded that LSA revascularization was not found to have a significant effect on reduction of the postoperative stroke, SCI, or mortality in patients undergoing TEVAR with LSA coverage.
2. Huang *et al.* [103]	**2018**		**2,591**	- Systematic review & meta-analysis (16 cohort studies): The perioperative stroke rate was 6.8 % (n=176/2,591). The perioperative stroke rates w/ & w/o LSA revascularization were 5.4 % & 7.8 %, resp. Compared with no LSA revascularization, patients w/ LSA revascularization had a significantly lower peri-operative stroke rate (RR, 0.61 [95%-CI, 0.45–0.82]; I2 = 20%) and a peri-operative spinal cord ischaemia (SCI) rate (RR 0.59; 95% CI 0.39–0.90; I2 = 0). No significant difference was noted considering the postoperative mortality. The authors concluded that according to the results, LSA revascularization was associated with significantly lower perioperative stroke & SCI rates.
3. Cooper *et al.* [42]	**2009**			- Systematic review & meta-analysis: According to the authors, the results occured comparatively as follows: The risk of CVA increased in patients with LSA coverage alone (4.7

				% *vs.* 2.7 %; POR, 2.28 [95%-CI, 1.28–4.09]; *P*=0.005) & in those with LSA coverage after revascularization (4.1 % *vs.* 2.6 %; POR, 3.18 [95%-CI, 1.17–8.65]; *P*=0.02). The risk of SCI also increased in patients requiring LSA coverage (2.8 % *vs.* 2.3 %; POR, 2.39 [95%-CI, 1.30–4.39; *P*=0.005), but not for LSA coverage after revascularization (0.8 % *vs.* 2.7 %; POR, 1.69 [95%-CI, 0.56–5.15]; *P*=0.35). The authors concluded that the risk of neurological complications increased by LSA coverage, yet such revascularization does not offer protection against CVAs. In contrast, revascularization could offer protection against SCI.
4. Sepehripour *et al.*[104]	**2001**		**1,740**	- Systematic review of studies from 1997 to 2010 (94 studies): There were no registered occurance of postoperative stroke, SCI, endoleak, stent migration, or mortality when the LSA was partially covered. In particular, the isolated total LSA coverage w/o revascularization increases the prevalence of left arm ischaemia (prevalence, 4.1 % *vs.* 0 %, P<0.001)]; stroke (prevalence, 1.19 % *vs.* 0.23 %, *P*=0.025) & the need for additional procedure (prevalence, 2.86 % *vs.* 0.86 %, *P*=0.004). The authors concluded that LSA coverge should be avoided. If it is necessary, partial coverage is better than complete coverage. Otherwise, if complete coverage is seen, revascularization might be considered.
5. Rizvi *et al.*[105]	**2009**			- Systematic review & meta-analysis (51 studies): Results showed that LSA coverage was associated with a significant increase in the risk of arm ischemia (OR, 47.7 [95%-CI, 9.9–229.3], I(2)=72 %, 19 studies) & vertebrobasilar ischemia (OR, 10.8 [95%-CI, 3.17–36.7], I(2)=0%; 8 studies), as well as nonsignificant increases in the risk of spinal cord ischemia (OR, 2.69 [95%-CI, 0.75–9.68], I(2)=40 %; 8 studies) & anterior circulation stroke (OR, 2.58 [95%-CI, 0.82–8.09], I(2)=64 %, 13 studies). There were no significant associations of LSA coverage

				w/ death, myocardial infarction, or transient ischemic attacks. The authors concluded that with a very low level of evidence, LSA coverage increases the risk of arm ischemia, vertebrobasilar ischemia, & possibly SCI, as well as anterior circulation stroke.
6. Patterson *et al.* [53]	**2014**		**1,002**	- Systematic review & meta-analysis (6 studies - 5 sponsored trials & 1 series): The stroke rate was 2.2 % in patients with no coverage of the LSA *vs.* 9.1 % with coverage alone, & 5.1 % in patients who underwent LSA revascularization before coverage (P<0.001). Coverage of the LSA w/o revascularization was independently associated with stroke (OR, 3.5 [95%-CI, 1.7–7.1]), specifically in the posterior territory (OR, 11.7 [95%-CI, 2.5–54.6]), as was previous cerebrovascular accident (OR, 7.1 [95%-CI, 2.2-23.1]; *P*=0.001). LSA coverage was not associated with SCI. The authors emphasized the imortance of LSA revascularization as a protective measure against the proven effect of LSA covering as a risk factor of postoperative cerebral stroke.
7. Waterford *et al.* [52]	**2016**		**3,000**	- 63 studies: The authors concluded that the stroke risk by TEVAR increases with LSA coverage, and LSA revascularization reduces that risk.
8. Chen *et al.* [58]	**2019**			- 32 studies: Results showed manifest decrease in SCI, stroke, & arm ischemia after revascularization of LSA by TEVAR as follows: SCI (OR, 0.62 [95%-CI, 0.41–0.92], *P*=0.02; I2=0 %), cerebrovascular accident (OR, 0.63 [95%-CI, 0.42–0.95], *P*=0.03; I2=22 %) & left upper extremity ischemia (OR, 0.18 [95%-CI, 0.09–0.36], P<0.00001; I2=0 %). However, no significant differences were found in the risk of paraplegia (OR, 0.91 [95%-CI, 0.55–1.51], *P*=0.71; I2=0) & 30-d mortality (OR, 0.89 [95%-CI, 0.59-1.36], *P*=0.60; I2=21 %). The

				authors concluded that LSA revascularization was associated with decreased risk of CVAs, SCIs, & left-arm ischemia. Revascularization was associated with possible vocal cord paralysis.
9. Weigang *et al.* [106]	**2011**			- 23 studies: The authors classified the therapeutic concepts of LSA coverage into three categories, (prophylactic, conditionally prophylactic, & no prophylactic LSA revascularisation). The collected evidence supports prophylactic revascularization (LSA–LCCA transposition or bypass graft procedure) if the imaged supraaortic vessels show abnormalities. Any planned LSA coverage should receive LSA revascularization to avoid related neurological complications.

4. Discussion

4.1. Should LSA coverage during TEVAR be revascularized or not

Several aspects (among them, there are a few contradictory) with regard to the necessity of LSA revascularization during aorta Ishimaru-zone-2-approaching TEVAR may make decision-making difficult for vascular surgeons in daily clinical practice. The blocking of LSA osteum harbors not only the danger of left-arm ischemia, but also spinal cord ischemia through the contribution of the LSA in the spinal circulation via the vertebral and first intercostal branches, besides the danger of posterior cerebral ischemia through the vertebral branch(es).

By this study, there was no significant difference between the not-revascularized and revascularized groups considering the cerebrovascular events (n=1 case [4.8 %] *vs.* 0 cases (0 %); P=1) or the spinal cord ischemia (n=2 cases [9.5 %] *vs.* 1 case [7.1 %]; P=1). There was no registered cases of left arm ischemia and mortality/survival probability in both groups (22 [95% CI, 14.154–29.904] months *vs.* 43 [95% CI, 33.655–51.921] months).

The only statistically significant risk factor is the renal insufficiency with a p-value of 0.028 with a tendency toward the urgency of revascularization. Other risk factors show no statistical significance with $p > 0.05$.

Postoperatively, pneumonia showed tendential impact with P=0.058 toward the revascularized cases (n=0 cases of not- revascularized cases *vs.* n=3 cases [21.4 %] of the revascularized cases). Other complications showed no statistically significant impact with $p > 0.05$.

Those results favor the tendency against the primary revascualrization of the covered LSA during aorta-zone-2 TEVAR. However, in the presented study, all cases underwent preoperative CT-angiogram of the TAA and the supraaortic vessels, including the vertebral arteries and the extra-/intracranial cerebral vessels. The patency of the vertebral vessels at both sides was posed as primary condition/prediction under which the endovascular procedure can be proceeded. In case the vertebral and intracranial cerebral circulation was not sufficient, the primary revascularization was done exceptionally to overcome this obstacle.

Our inclusion criteria for preventing unnecessary primary revascularization of the LSA met a match with 23 abstracts (with accumulative patients' count of n=4,575). This literature is composed mainly of retrospective cohort studies of patients who underwent TEVAR with LSA blocking either against a revascularized group or against patients with no LSA coverage. The main analytical parameters of those literature reviews included comparisons of the representation of thecerebrovascular accidents (CVA), spinal cord ischemia (SCI), and left arm ischemic changes (claudication/left subclavian steal syndrome). Other parameters included mortality and endoleak occurrence. Some authors, such as Gombert *et al.* [107] and Klocker *et al.* [75], used the DASH score for post-aortic traumatic TEVARs with LSA coverage. The DASH score represents an evaluation system of left arm functionality after such procedures. Otherwise, McBride *et al.* used a questionnaire with main points of left arm pain, numbness, paraesthesia, or fatigue to assess the possibility of postoperative arm ischemia [66]. On the

other hand, CVA and SCI are evaluated comparatively in the works of Youssef *et al.*, Loh *et al.*, Janczak *et al.*, Kotelis *et al.*, Woo *et al.*, Wojciechowski *et al.*, Zhu *et al.* and others [57, 67, 69, 71, 73, 74,] . Antonello *et al.* [77] focussed on the postoperative left arm symptoms with positive correlation with the degree of reductionof peak systolic velocity (PSV) and left arm symptoms; nevertheless, there was significant improvement of the ischemic-arm symptoms during the mean follow-up of 36 months (p<0.0001). The non-significant correlation between the postoperative arm ischemia and the necessity of LSA revasculation is depicted through the works of Riesemann *et al.*, Preventza *et al.*, and others [79, 80].

The importance of the patency of the vertebral arteries and likewise of the circle of Willis is discussed in more detail in the work of Zhu *et al.* [74]. When both the vertebral arteries and circle of Willis are open, LSA could be covered without further revascularization. Otherwise, when the right vertebral artery is advantagious, the balloon occlusion test of the LSA should be performed, as mentioned in the "Results" section. When the left vertebral artery is advantagious, then the revascularization should be undertaken. Preventza *et al.* [79] emphasize the conditions under which the LSA revascuarization should be done.

In contrast to the aforementioned supporting literature of this work hypothesis, a few papers (accumulatively, n=3,325 patients) emphasized the importance of primary revascularization in order to prevent the possible drawbacks of the LSA blockage during zone-2 TEVAR [86, 88, 89, 90 , 91, 109] Those showed a significant decrease of the CVA-SCI-left arm ischemia in the patients' portion who underwent LSA revascularization. Teixeira *et al.* [86] demonstrated that SCI occurred with significantly fewer rates in the revascularized group (P=0.043). Peterson *et al.* [87] advocated the LSA–LCCA transposition when the aortic lesions lay within 15 mm from the LSA origin—this aimed to avoid endoleak II. This also refers to cases with ipsilateral vertebral artery or the revascularized coronary artery with the internal mammarian artery. Nagarsheth *et al.* [88] stated higher CVA occurence in the not-revascularized group than in the revascularized group (9 % *vs.* 3 %; P=0.03). Bradshaw *et al.* [54] provided evidence that the late SCI occurred more frequently in the not- revascularized group (P=0.04) in two years. So, as emphasized in the other abstracts, the importance of primary LSA revascularization is to prevent postoperative CVA, SCI, or left arm ischemia. Maldonado *et al.* [108] emphasized that, there is no significant difference considering the incidence of SCI/CVA in their multicenteric study between the LSA covered patients *vs.* the LSA covered/revscularized patients. Weigang et al. [106] focussed the light through part of their work on the left arm ischemia an subclavian steel syndrome (SSS) in relation to the overstenting of the left subclavian artery by TEVAR operations. They stated an SSS-incidence of 5-37.5%. This syndrome is almost asymptomatic and when symptomatic it turns transient thanks to the flow inversion in the left vertebral artery. Its symptomatology is caused mainly through abnormal left vertebral artery or inadequate blood supply over the circle of Willis. This is manifested with progressive vertigo and dizziness when the left arm is put in action.

By studying the related papers, two other extra paper groups were classified. These are the papers with or against which the hypothesis of our paper works. These two groups are:

- Papers dealt with innovative endovascular revascularization methods of the LSA;
- Systematic review, meta-analyses, and literature reviews dealt with the subject of our own research.

The first group of papers showed multiple and variant innovative endovascuar methods of the blocked LSA. These are:

- Laser fenestration and iCast Stent of the LSA (Murphy *et al.* and Redlinger *et al.* [94, 62])
- Inoue single-branched stent-graft implantation (Saito *et al.* [95])
- Periscope endograft (Lachat *et al.* [64])
- Sandwich technique with the body flossing wire (Hsu *et al.* [97])
- Custom-made scalloped graft (van der Weijde *et al.* [99])
- Chimney graft of the LSA (Xue *et al.* [100]) - also comparison study of the chimney graft against the branched stent graft (Zhang *et al.* [96]).

Each technique is described in the "Results" section (**Table 3**). The author described favorable success rates of each technique. Nevertheless, the wide implication of those techniques needs more evidence with greater patient groups. The indication of these techniques should, however, be limited to inoperable cases with a high possibility of CVA, SCI or left arm ischemia, such as in case of inadequate cerebral nourishment through the circle of Willis or vertebral artery stenosis. Other indications are in the need of a patent internal mammarian artery as an aorto-coronary bypass candidate or in the presence of a left-arm dialysis shunt.

The other category of papers comprises meta-analyses, systematic reviews, and literature reviews with various points of view. The paper groups include: Hajibandeh *et al.* [59], a systematic review with demonstration of no significance of LSA revascularization considering the occurance of the CVA, SCI, or left arm ischemia(claudication/SSS). Otherwise, more systematic reviews and meta-analyses support the importance of LSA revascularization in order to prevent CVA (Huang *et al.*, Sepehripour *et al.*, Patterson *et al.*, Chen *et al.* [103, 104, 53, 58]), SCI (Cooper *et al.*, Chen *et al.* ([42, 58]), or left arm ischemia (Sepehripour *et al.* [104]). Those results supported the importance of a conditioned revascularization of the blocked LSA rather than the primary unconditioned revascularization. The dissymmetry of the results range among the studies: In some studies, a significant correlation between the neurological complications of LSA coverage appeared, while in others they appeare as non-significant, thereby showing that there could be a selection bias. Last but not least, all the included studies are not blinded, which lowers the extracted level of evidence.

4.2. General aspects of the study

In keeping with 12 years experience of treating different thoracic/thoracoabdominal aortic lesions, different aspects of diagnostic and therapeutic maneuvers were consolidated. To put the right orientation of the pathway till the right therapeutic decision, the pathophysiology of aortic lesions, including aortic hemodynamics, should be closely considered. The correlation between our results, published literature, and theoritical basics will guide through this discussion.

4.2.1. Aetiology/pathophysiology

Aetiologically, the encountered cases with TAAs dominate the case counts, followed by cases with Type-B aortic dissections and then TAAAs. The other elements of acute thoracic syndrome (PAU-IMH) showed minority cases in our study. Hemodynamically, the common sites of dissection is near the origin of the branching blood vessels. For a better understanding of aortic hemodynamics and its relation to the development of different aortic pathologies, wall shear stress (WSS) must be considered. It is defined as the frictional effect of the blood stream on the aortic wall. According to Gardhagen *et al.* [110], it can be calculated as the viscosity mutiplied by the velocity gradient at the vessel wall (wall shear rate, WSR):

$$\mathrm{WSS} = \mu \cdot \mathrm{WSR} = \mu \frac{\partial V}{\partial n}\Big|_{wall}$$

WSS is, however, frequently calculated with "*Eq*" equation [110] .This formula is derived for the fully developed, stationary, laminar flow of a Newtonian fluid with constant viscosity μ in a straight, circular pipe with constant radius r, and accordingly, provides a circumferential average in a cross-section with volume flow rate Q. This particular flow is known as the Hagen–Poiseuille flow.

$$\mathrm{WSS}_{HP} = \frac{4\mu Q}{\pi r^3}$$ (110)

The calculation of the hemodynamics of the thoracic aorta has been humbled for a long time and could be done only *in vitro.* Thanks to the newly developed computational fluid dynamic (CFD) calculation techniques this could be done *in vivo* recently. These techniques are time-dependent 3D-simulations of the blood flow through the thoracic aorta based on pictures gained from 2D-investigations like MR-A or CT-A [114]. Otherwasys, the TAA/TAAA are affected by other common and specific factors. Atherosclerotic changes in the vasa vasorum, hypertensive provocation of those changes, vascular kinkings, and angulations with flow accelerations, among others, accelerate changes in the vascular smooth muscle cell (VSMC) with degeneration and inflammation. This will develop aneurysmatic changes. The study of El-Hamamsy *et* Yacoub [115] spotted the light on the structural microanatomy of the thoracic aorta and further on the applied pathophysiological element of those structural features in the development of different pathologies of the thoracic aorta. This will be stated briefly in the following and consequently also in the pathophysiology section.

The basic functional unit of the thoracic aorta is the elastic - with the elapsed recoil property - and highly contractile muscle layer (first nominated by Wolinsky *et* Glagov [116]), which is built basically from the VSMC. The laminal layer is "sandwiched" between two supportive connective tissue layers. The surrounding extracellular connective tissue matrix (ECM) is formed primarily from intercalating collagen fibers undermined with elastin and fibrillin networks.

The VSMCs are contractile and secretory muscle cells, which are arranged in laminar bundles attached to the extracellular skeleton. The cells produce the elastin fibers, which make the extracellular tissue support of the vessel wall and provide the wall with structural elastic recoil. This imposes the basic flexibility feature of the thoracic aorta. Further on, the ECM contains fibrillin fibers and collagen fibers. The collagen fibers are from Types I and III as well as in the adventitia, where the collagen-Type IV is located. While it was suggested in the literature that the abdominal media is completely avascular, the outer layers of the thoracic media contain vasa vasorum, which actually originate from the adventitia [117, 118].

The pathological changes of the wall of the thoracic aorta encompass the medial degeneration with apoptosis of the VSMC and lysis of the elastin fibers through the increased activity of matrix metalloproteinase (MMP)-2 and -9 [119]. This will cause the microscopic picture of media cystic necrosis. The destruction of the medial elastin fibers will disorganize the intercalating VSMCs and result in dysfunction of those cells [113]. It, therefore, contributes to aneurysmatic formation [120]. The hyperactivity of the metalloproteinases -2 and -9 is mainly caused by overproduction of the transforming growth factor (TGF-β) [111]. The signaling of this factor has two pathways: a well-acknowledged pathway in the literature by transducing the transcription of the modified SMAD4 gene [112]. through activation of the cellular receptors SMAD 2/3 and a yet-to-be well acknowledged pathway through phosphorylation of the extracellular signal-regulated kinase (ERK), Jun N-terminal kinase, and p38 [120] . The hyperoxygenation stress through the angiotensin-II-mediated NADH/NADPH oxidase plays a main role in the development of TAA through activation of the MMPs and starting the above-mentioned chain reaction [122].

For specific pathophysiologies, the aortic dissection can be also classified in keeping with the blockage of the branching vessels into:

- dynamic blockage where the false lumen of the aortic dissection at the origin point of those vessels expands to obstruct those vessels under various circumstances, or
- static blockage, which is a further stage where the false lumen not only expands, but also becomes the dissection itself,

in which the dissection goes through the branching vessels and then blocks them with or without the formation of post-dissection thrombus. This, in turn, worsens the local condition of the artery [123].

Considering the pathogensis of genetic-based familial TAAs, the study of Braverman [24] illustrated the genetic basis of different familial aortic diseases, beginning with Marfan's syndrome with the mutation of fibrillin gene N1 (FBN1), going through other diseases such as Ehler–Danlos with the

mutation of Type-3 procollagen gene (COL3A1), and last but not least, Loeys–Dietz syndrome (LDS) with direct connection with the mutation of transforming growth factor gene 1 and 2 (TGF-β1 and TGF-β2). This study illustrated the role of the mutation of the smooth muscle alpha-actin (ACTA2) as an enhancing factor for smooth muscle weakening. This gene is activated also through the activated mutated TGF-β gene. Alarming clinical signs, which should arouse the suspicion of familial connected aortic diseases (aneurysms, dissections, etc.), are facial dysmorphology, myopia, ocular lens dislocation, premature cataracts, bifid uvula, cleft palate hypertelorism, bluish sclera, abnormal uvula, dental crowding, tall palate, malar hypoplasia, retrognathia, elongated digits, pectus deformities, scoliosis, flat feet, club feet, joint contractures, hyperflexible joints, soft velvety skin, hyperlucent skin, and atrophic scars [24, 124, 125].

4.2.2. Epidimiology/risk factors

Epidemiologically, the presented results correlate with the internationally published data. The age of treated patients ranged from 25 to 98 years with the mean age of 72.76 (S_D, ±14.366) years. The male and female ratio shows a tendency toward the male patients as being reported in other published studies. Furthermore, the control of the related risk factors will slow the progression of various thoracic aortic pathologies. The stratified risk factors through this study coincide with the reported rank for risk factors in the literature. Hypertension is the most common risk factor in our study. In the literature, it is highly associated with the occurance of thoracic aortic dissection.

Considering the epidemiology of the TAAs, an overview of the up-to-date literature shows internationally in the English-written literature [126] that according to the Center of Dieseases Control (CDC), TAAs are the 15th leading cause of death in individuals more than 55 years old and 19th leading cause of death in general. It was also reported that although the prevalence of TAAs is less than that of AAAs, the TAAs are more important due to their higher mortality. Yet, approximately 60 % of TAAs occur in the root or ascending aorta, 10 % in the arch, 40 % in the descending aorta, and 10 % in the thoracoabdominal aorta, and aneurysm may involve multiple aortic segments. TAAs are asymptomatic in 95 % of cases, which means that most TAAs remain undetected unless incidentally discovered [7]. Nevertheless, many fatal TAA-ruptures or dissections are misdiagnosed as myocardial infarction and hence lead to underestimation of the true prevalence of TAAs. The prevalence of asymptomatic TAAs has been measured to be ranging from 0.16 % to 0.34% [126]. The annual incidence of TAAs has been assessed at approximately six to 10 cases/100,000 patient years [128 ,129]. TAA are more and more considered as a familial disease. As reported in the literature, 21 % of patients with TAAs have at least one family member with a known aneurysm (any type) of these familial forms and 77 % inherit an autosomal dominant pattern with variable penetrance [127, 130, 131] Another study showed that about 9 % of TAA patients suffered from concurrent intracranial aneurysms with a higher prevalence than the general population. Meanwhile, patients with familial TAAs generally present at an earlier age (56.8 years) than those with sporadic TAAs (64.3 years) [131].

When it comes to the epidemiology of the growth rates of TAAs, patients with familial TAA have faster growth rates of 0.21 cm/y (combining ascending and descending TAAs) compared to those with sporadic TAAs (0.16 cm/y) and thus those patients present themselves usually with TAAs earlier as other patients. While syndromic TAAs, such as Marfan aortas, grow at 0.1 cm/y, the TAAs of Loeys–Dietz syndrome can grow faster than 1.0 cm/y, resulting in the mean age of death of 26 years [130, 132].
In the most asymptomatic cases of Type-B thoracic aortic dissections, medical treatment slows the progression of the lesion. Suzuki *et al.* [133] gathered essential data from different guidelines for the medical treatment of Type-B aortic dissection (European guidelines [ESC], American guidelines [ACC/AHA] and Asian guidelines [Japanese society]). ESC gave a systolic blood pressure target of 100–120 mmHg, otherwise they emphasized the use of the beta-blockers with no evidence of significant effect of the calcium channel blocker. The Japanese guidelines aimed also at a blood pressure value of 100–120 mmHg. A further chronic (within two weeks) therapeutic recommendation concerned, besides blood pressure, a heart rate less than 50 beats per minute to prevent any expansion of the dissection. Notably, in the Japanese guidelines elevated blood pressure in therapy-resistent patients is not considered a necessary cause of any increased risk of rupture. Guidelines from (AHA/ACC) noted that 71 % of patients with sustaining Type-B aortic dissections had a systolic blood pressure greater than 150 mmHg. The aimed is to put the high blood pressure and heart rate under control so as to reduce the dissection expansion and protect the vital organs from the related ischemic changes with an initial heart rate of 60 beats per minute and systolic blood pressure of 100–120 mmHg with emphasis on the beta-blocker effect.
Other related risk factors, such as hyperlipoproteinemia, renal insufficiency, atherosclerosis/peripheral arterial disease (PAD), concomitant AAA, and coronary artery diseases (CAD), showed only a minor effect in comparison with arterial hypertension. According to the literature, important risk factors leading to aortic pathologies are mainly the male sex, hypertension, and smoking [134].

4.2.3. Diagnostics

All the included patients (*n*=112) underwent preoperative/preinterventional CT-A as a standard—except for certain cases—with demonstration of the thoracoabdominal aorta, supraaortic vessels including the vertebral artery, and the access iliacofemoral vessels. Further, cranial CT-A was performed in certain cases where pathologies in the supraaortic vessels were detected. After admission, each patient underwent complete laboratory assessment including a complete blood picture, acute phase reactants (CRP-fibrin), electrolytes, coagulation profile (PT-PTT-INR), and abdominal profile (bilirubin-gGT-LDH-lipase). In case of any suspicion of possibly familiar/unfamiliar autoimmune genesis, an angiological/hematological consultation was to be done to achieve interdisciplinarily the related genetic/laboratory diagnostics.
Considering the laboratory diagnostics, Pilozzi *et al.* [135] and others [132, 136] have classified the biological markers of different thoracic aortic lesions in five ranks as the following:

- Genetic markers; established and already used biomarkers, which either for syndromic TAA like fibrillin 1 FBN-1 gene in Marfan's syndrome [137], transforming growth factor-β receptors TGF-βR1 and TGF-βR2 for Loeys–Dietz syndrome and Marfan's syndrome [138]. For familial non-syndromic TAAD, TGF-βR1 and TGF-βR2 [139] were applied also as biomarkers with cross-identification. Whereby, the matrix metalloproteinase (MMP) enzyme and mutation of the ACTA2 gene were applied for sporadic TAADs. This is related to the familial non-syndromic TAAs and affects the contractile protein of the vascular SMCs.

On the other hand, there are emerging newly but not widely used, just as the myosin light chain kinase (MYLK) mutation gene [140] - which affects the myosin interaction with the actin fibers and affects the contractility activity of the aortic wall - this is linked with the non-syndromic familial TAAD; thrombospondin 2 (THBS2) is a sporadic TAA mutating gene, which affects the organization and stability of the extracellular matrix. The mutation of the SMAD3 gene [141], which contributes to the activation of TGF-β, besides its primary role of activating cell proliferation, differentiation, and extracellular matrix production.

- Inflammatory, oxidative stress, and hemostatic markers; those markers are mainly used in the acute phase of the TAAD in context with further preparation of the most rapid possible intervention (open/endovascular surgery). According to Pilozzi *et al.* [135], those biomarkers include classicwise; some already have used biomarkers as well as the newly emerging ones. The established parameters include, for example, C-reactive protein (CRP), which is an acute-phase reactant used as a lab-diagnostic tool for TAD and TAA either in acute or chronic phase. The accountability and creditability of the CRP is still being debated, but it is already being used as part of routine lab work in the diagnosis of the already mentioned diseases [142, 143, 144, 145]. This applies also to the white blood cell count [135] and Interleukin-6 [146], yet Pilozzi *et al.* [135] considered IL-6 and other IL-family members as emerging but not yet established parameters of the TAADs. Plasma D-dimer (DD) is a product of plasmin fibrinolysis and an indirect indicator of tissue coagulation. This parameter is used mainly for the diagnosis of deep venous thrombosis and arterial pulmonary embolism [135]. Yet, DD is still considered nonspecific for the diagnosis of TAADs; it is mentioned in the literature as an already used and sensitive indicator for the diagnosis of TAADs [144, 147, 148]. Emerging but not yet established biomarkers include, besides the IL family [145], another cytokine, namely interferon-gamma [149]. A study of Papralla *et al.* [150] describes different haemostatic factors, which appear in the context of coagulative reaction when the blood stream floods into the false lumen, especially in the TAD Type B; these factors include, for example, prothrombin fragment F1.2, plasmin–antiplasmin complex, and platelet factor 4.
- Markers of matrix remodeling factors, which include the tissue matrix metalloproteinases (tMMPs) family and their inhibitors TIMMP-1 tissue inhibitor MMP-1 (interstitial collagenase), that increase during the formation and later the growth of the TAAs. [151] In other words, elastin

degradation products (sELAF) also stand as a marker for the formation of acute aortic dissections (AADs) [152].

- Markers of cell damage represent more the AASs, as they express the acute phase of cell damage of such events. Those markers – which include, for example, cardiac troponins (cTns) - are commonly used in the diagnosis of the ACS, yet some studies show a correlated rise of the cTns with 10–20 % of the AAD patients [153]. Otherwise, the smooth muscle myosin heavy chain (SMMHC), which is an end product of the destruction of the cSMC, can be implemented in the diagnosis of the AAD. More recently, new parameters are added to the biomarker list of the AASs—for example, the calponin, a smooth muscle analogue of troponin and a calcium-binding protein, that inhibits the ATPase activity of myosin in smooth muscles, which controls the actin/myosin interactions. This biomarker is suggested also in some studies to be used for differentiation between Type-A and -B ADs [154].
- Other markers can be used additionally for the diagnosis and monitoring of the TAADs, such as the N-terminal pro-brain natriuretic peptide (NT pro-BNP), which is used mainly to rule out heart failure in combination with the B-type natriuretric peptide. However, it is considered as effective as diagnostic and prognostic factors in assessment of the AADs and TAAs, as well as with an increased level of this marker in both cases [144]. It could come in the context of left-side heart failure by developing TAADs.
- Finally, the biomarker micro-ribonucleic acid (miRNA) stands as a potential predictor of the formation and development of the ADs and TAAs [155]. MiRNAs are short RNA molecules whose function is the regulation of genes either negatively through transcript degradation and sequestration as well as translational suppression, or positively through transcriptional or translational activation. By these gene-manipulation, miRNAs are involved in many biological processes and thus can affect the development of the ADs through down- or upregulation [156].

Until now, screening of the thoracic aortic lesions was not implied as a routine diagnostic work, except for vulnarable cases. Cases with Marfan's syndrome, collagen disorders like Loeys–Dietz syndrome, and vascular Ehlers–Danlos syndrome could undergo such diagnostics. Markers in suspicious cases with family history or phenoypes of collagen diseases could predict the occurance of such changes when the cases could undergo CT-A screening as off-label use. Those markers include genetic markers, markers of oxidative stress, inflammatory markers, etc.

For better demonstration of aortic hemodynamics, the dynamic diagnostics should be implied. These include either the sonographic methods as transthoracic TTE, or transesophageal TEE, or the hemodynamics-demonstrating CT-A/MR-A. One problem with the sonographic examination is the individuality of the findings according to the experience of the examiner—the TTE is limited with the bony cage of the chest, whereby the TTE demonstrates mainly the ascending aorta and part of the aortic arch, but it is tremendously limited considering the descending thoracic aorta [28]. It is stated in the article written by Baliga *et al* [157]. that the dilatation of the descending aorta could be diagnosed

through transthoracic echocardiografy TTE in the long-axis parasternal view posterior to the atrioventricular septum. Also, through transesophageal echocardiografy TEE-when the image is rotated for 90 °- the longitudinal image of the descending aorta can be demonstrated. IRAD stated that the sensitivity of TEE can reach 99 % and specificity of 89 %, positive predicting value of 89 %, and negative predictive value of 99 [158]. Nevertheless, imaging studies such as CT-A/MR-A stay the cornerstone of TAAD diagnosis. Dynamic CT-/MR-A imaging, such as the ECG-gated CT-/MR-A, could be implemented in further diagnosis of TAADs—the main use was for real-time diagnosis of the AD Type A—to avoid the movement artifacts, which can cause the false-cited thickening of the aortic wall, doubling of the aortic wall or even a false-cited aortic flap. The use of the ECG-gated CT-A/MR-A is not yet evidence-based to be as profitable as a precise diagnostic method for the proximal landing zone of AD Type B, especially when this zone approximates the aortic arch beyond the branching point of the LSA, LCA [159]. However, Perry Choi and Hamid Mojibian annotated in their article ("Trends in emergency aortic imaging") [160] the importance of ECG-gated imaging in diagnosis of the pathologies of the thoracic aorta. However, the focus was rather put on the branching vessels, coronaries, and valve lesions more than the whole aortic presentation. The prerequisite for the ECG-gated CT-A/MR-A is a regular paced heart frequency, which is mainly gained through administration of the proper beta-blocker medication [161].

The measurement ways of the thoracic aorta and the related lesions in terms of planning for TEVAR have been comparatively described in the study by Kaladji *et al.* [162], in which two ways of measurements—centerline 3D-technique or measurement of the outer curvature distances—are implemented in planning the endograft size for 74 patients who underwent TEVAR within a certain time period. This study shows the outer curvature measurement method in comparison with the centerline method with a better tortuosity ratio. However, Chiesa *et al*. have emphasized the importance of 3D-interpretation software techniques of The CT-As [163]. Those imagings showed the proximal landing zone (distance from the LSA origin) with an average value of 8.26 (range, 1–27; S_D, 6.654) cm and the distal landing zone (distance from the coeliac trunk origin) with an average value of 15.7 (range, 1–30; S_D, 8.292) cm. Under this cliental of patients, a subgroup of patients with overstenting of the LSA was described and discussed in the previous separate section. Unless the proximal landing zone is less than 2 cm with which there was a clear indication of the LSA blocking, there was no other primary indication for LSA overstenting. The length of the lesions varied with an average value of 14.8 (range, 1–53; S_D, 13.004) cm. The stated correlation in the literature between the length of the covered part of the aorta with the stent-graft and the occurance of SCI could not be evidenced in this study. In correlation with the published literature data, TAAA and TAA formed the majority of the treated cases through this study, followed by the Type-B AD. As stated further on through the literature, the diameter of TAA/TAAA is the main criterion of decision-making for the treatment of such lesions either in a conservative or therapeutic pathway. It is not the lone determinant of the treatment module of the TAA/TAAAs and should be correlated with the body surface area

(BSA) to the measured diameter of the TAA/TAAA. Beside the BSA, the presence of one or more of the risk factors (aHTN- DM- HLP-…. etc.) affects the decision to treat. Innovative diagnostics like real-time CT-A with ECG rhythmic synchronization of heart beats, hemodynamic-representing MR-A demonstrate the most vulnarable and pathologically affected part of the blood vessel. This will help to plan better for the therapy.

In their virtuous work named "Open repair of descending thoracic aneurysms." Chiesa et al. described how Dr. Ratib and his co-workers from the University of Genève had developed the OsiriX software [(163)]. This software is dedicated to "DICOM" images (Digital Imaging and Communications in Medicine) produced by current CT devices and runs on regular Mac OS X computers, the navigation and likewise interpretation of the CT images has been made easier and more 3D-oriented. From only axial transverse images, we can develop nowadays sagittal and coronal images. The newly added curved multiplanar reconstruction of the CT images (C-MPR) through the OsiriX program allows the identification of the main intercostal arteries contributing to spinal cord circulation, the artery of Adamkiewisz, which, in turn, impacts a big role in planning the open/endovascular repair of the TAADs. This applies also for the origins of the hypogastric(iliac) and subclavian vessels.

DSA is used mainly intraoperatively to guide the whole TEVAR process. However, the intravascular ultrasonography has been recently introduced in the TEVAR in order to reduce the contrast-based complications as well as the exposition to the ionizing radiation associated with the DSA [(164, 165).]. Even the IVUS has been further introduced as an upcoming promising way for endograft measuring in terms of planning for TEVAR[(166)]; however, the IVUS stays as an invasive method which pulls IVUS backward.

4.2.4. Therapeutics of different thoracic aortic lesions

Our study focuses on the operative therapies of thoracic aortic lesions, this could be either purely endovascular or as a hybrid intervention with the debranching of supraaortic or infracoelicac vessels. The medical non-operative therapy of thoracic aortic lesions is reviewed in scattered literature. Danyil *et al.* have illustrated in their work ("Medical therapy of thoracic aortic aneurysm, are we there yet") [(29)] in a schematic way the different medical treatment possibilities, in which:

- An angiotensin activation pathway is blocked through the angiotensin-converting enzyme inhibitors (ACEI).
- The effect of the angiotensin is blocked through angiotensin-receptor blockers (ARB).
- The NADP/NADPH system is blocked through statin therapy.
- The MMP system is blocked through tetracyclin/macrolids.
- The shear stress effect is blocked through the beta-blockers.

Blunt traumatic aortic injuries do not indicate surgical operation unless they reach Grades III–IV. Till then, the non-operative therapy aims - similar to the medical treatment of the Type-B thoracic aortic

dissection - to achieve hemodynamic stability and decreasing of the shear stress in order to prevent the danger of aortic perforation [167].

The operative therapy in this study was mainly purely endovascular (73.2 %) with insertion of the stent-graft through a bilateral femoroiliac access and left-side brachial access for further assistance and intraoperatively clear demonstration of the LSA. The rest of cases underwent hybrid operation with debranching of the supra-aortic vessels (13.4 %) or hybrid with debranching the infracoeliac vessels (8.9 %). Meanwhile some other cases underwent only debranching of the supra-aortic and/or infracoeliac vessels and yet did not further proceed into the planned endovascular correction because of variant factors. The overstenting was mainly for the LSA (20.5 %) and infracoelliac vessels (3.6 %), whereas debranching counted for the supraaortic vessels (11.6 %) and the infracoeliac vessels (3.6 %). Only one case (0.9 %) underwent overstenting of the polar renal vessels.

The pure open repair of the descending aortic lesions does not meet the inclusion criteria of the study. Therefore, it will not be considered in this discussion.

In contrast to the planning of the EVAR for abdominal aortic lesions with the essential role of the central line and reconstruction technique in the precise decision-making for the length and calibers of the stent prosthesis, thoracic lesions are of simpler planning conditions with no urgency in the implication of the central line and other planning techniques. The requirements of a successful TEVAR without complications vary according to the type of the used prosthesis and the anatomy of the aortic arch, aortic wall, and the length of the lesion - for example - the TAA/TAAAs require supersizing of about 20–30 % of the healthy aneurysmal neck; the neck width itself generally should not exceed 42 mm; and the length should not exceed 20 mm. In case of TAD /TAAD, oversizing is not acquired and even should be avoided in terms of precaution against the gutter phenomena.

4.2.5. Complications of various therapeutic maneuvers of thoracic aortic lesions and the suitable therapies

Systematically related, pneumonia was the most common complication (*n*=7 patients - 6.3 %). This correlates with the literature-based register for postoperative complications. In the general population of this study, there was minimal occurrence of postoperative neurological complications.

To prevent stroke strikes with TEVAR, it was recommended in the literature that TEVAR should be done under somatosensory evoked potential (SSEP) control. When an extended TEVAR is electively to be done, it should be done under brain-protective measures such as perioperative hypothermia. The most important protective measure against stroke accompanying TEVAR is good planning with a precise assessment of intracranial cerebral circulation and extracranial supra-aortic vessels.

Considering the perioperative SCI in patients who underwent TEVAR, the blockage of the posterior intercostal arteries and their radicular branches through the aortic stenting without any previous collateral formation will end up in devastating paraplegic incidences. Despite the absence of vascular cross-clamping in case of TEVAR (in comparison with the open thoracic aortic repair) with avoidance

of its cardiovascular complications, such as left-side heart overload and failure, ischemic changes of end organs, and the increase in cerebral blood flow with (in turn) an increase in cerebrospinal fluid production and higher intracerebral/intrathecal pressure, TEVAR still presents a risk of SCI, especially in long-distance TEVAR more than 200 mm. According to multiple reviewed literature [46, 168, 169], other highly relevant risk factors include unstable perioperative blood pressure with mean arterial pressure (MAP) less than 60 mmHg, previous occlusion of the lumbar and hypogastric vessels through abdominal EVAR, and concomitant subclavian blockage through overstenting.

In case of SCI, paraplegia can be graded according to the neurological assessment by Tavlor [46]:

4. Normal function,
3. Movement against the gravity,
2. Movement with the gravity,
1. Light movement,
0. Paraplegia with no movement.

The precautions against SCI-associated paraplegia are:

- Good planning and putting in action the measures in advancement to suspicious situations like covering more the 200 mm of the aorta and previous EVAR;
- Stabilizing the blood pressure before, through, and after the operation with MAP more than 80 mmHg ;
- Intraoperative neurological monitoring using SSEP and MEP [170 171];
- Spinal drainage with maintaining the intrathecal pressure lower than 10 mmHg is an essential measure, especially in planned cases with previously mentioned risk factors [172 173];
- Avoiding the blockage of essential vessels like LSA and hypogastric vessels in dangerous and suspicious cases. [174, 175].

Ischemic changes of the left arm (either as arm claudicationor vertig/dizziness in the context of postoperative left subclavian steal syndrome) was not noticed in the patient sample of this study. A few patients suffered from postoperative acute renal failure (2.7 %). No postoperative inflammatory syndrome (PIS) was registered. The PIS was first reported in the work by Velázquez *et al.* (“Perigraft air, fever, and leukocytosis after endovascular repair of abdominal aortic aneurysms”) in 1999 [176]. Etiological theories vary between the inflammatory reaction of the aortic wall against the inserted prosthesis with the production of humoral inflammatory mediators (TNF, IL-1α, IL-1β, IL-6). It is still being debated which stent material causes PIS with high possibility, whether it is polyester or polytetrafluroethylene (PTFE), whether the steel skeleton contributes actively in the PIS genesis or the nitinol frame can cause it more than steel frame. There is still no RCT to estimate the comparative risk-contribution of every stent present now on the TEVAR market.

Each of these ways stands hypothetically for the etiology of the following contributing factors:

- The thrombus in the aneurysmatic sac with production of inflammatory reaction,

- Bacterial translocation from the gastrointestinal tract into the surrounding tissue around the stent prosthesis (and)
- The contributing effect of contrast material use on the activation of the inflammatory reaction associated with PIS.

The application of the Iohexol contrast material could cause neutrophilic degranulation with activation of the inflammatory cascade of PIS [177].

The registered postoperative device-related complications showed a minority patient count, as reported in the "Results" section. The device-related types include, for example, stent migration, stent fracture and collapse, endoleak, graft infection, etc.

Regarding endoleak, according to Nation *et* Wang from Pennsylvania University, the U.S.A., endoleak with TEVAR is uncommon with an incidence of 3.9–15 % , by other means the guidelines from the European Society of Vascular Surgery (ESVS) stated that the incidence of endoleak overall was 5.2 % [173].

The endoleak can occur either primarily in unsuitable anatomic situation (tapering aneurysmatic neck, kinking, and angulations), or secondarily by graft migration, enfolding of the graft, metal instability and graft fracture, as well as due to continuous tissue changes such as in Marfan's syndrome,.

The treatment of endoleak depends on its type and further growth of the aneurysmatic sac. In Type 1 with a high possibility of further rapid growth of the sac, it should be treated either with balloon-remodeling, stent-straightening, for example, with a high radial force, balloon-mounted bare-metal Palmaz® stent (Cordis Endovascular, Warren/ NJ, U.S.A.) or anchoring. Type-2 endoleak could be put accordingly under a follow-up period with growth-rate control, yet it can be treated with embolization (chemical such as liquid embolic agents, e.g., n-butyl cyanoacrylate, thrombin and ethylene vinyl alcohol copolymer [Onyx®, Covidien-Medtronic, Minneapolis/MN, U.S.A.], or coiling), or with stent excision and bypass-graft in case of rapid growth. Just like Type-3, Type 1 should be treated in a rapid way through stent elongation. Type 4 is self-controlling and in most cases does not require further therapy. Type 5 with excessive growth of the sac requires stent excision and bypass replacement, [36, 37, 180].

While the graft migration is one of the common causes of endoleak, graft fracture, kinking, and occlusion of the TEVAR grafts is uncommonly notified in the literature in contrast to the EVAR grafts. The treatment of graft collapse is mainly through alignment by using the straightening stent.

The literature stated that the infection of the endograft was the most common cause of the formation of the aorto-esophageal fistula, which is accompanied with high mortality. The aorto-esophageal fistula (AEF) is manifested clinically with massive hematemesis, dysphagia, and mid-thoracic pain ("Chiari triad"). Once the suspicion is aroused, further investigation should be carried out in a short time as CT-A with CM, CEUS, esophagoscopy, and esophagogram with dye. In general, the AEF/ABF is either primary without prior surgical intervention due to ruptured aortic lesions with a super-infection or penetrating esophageal/bronchial lesions, or it could be secondary after TEVAR/esophageal or less

likely bronchial operations. The post-TEVAR AEF/ABF could be attributed mainly to the oversizing of the endograft with subsequent pressing on the aortic wall against the esophageal/bronchial wall. This could cause pressure necrosis with inflammatory reaction with the formation of AEF/ABF. Once, AEF/ABF is diagnosed, therapeutic measures must be immediately undertaken according to the aforementioned literature in this section subtitle, and the mortality in those cases could reach 100 % when they are left untreated for more than six hours. The treatment comprises either open surgery through thoracotomy with replacement of the inflamed (stented) thoracic aorta with the ventral aorta through the right thoracic cavity and away from the original aortic pathway—it starts from the ascending aorta/aortic arch till the abdominal aorta below the diaphragm. The replacing material is either an autogenic material preserved from other donating cadavers, silver-impregnated Dacron/Teflon, or back-table-made bio-/xenogenic materials. On the same operation's set, the esophageal tear can be directly repaired. Either way, endovascular re-repair for such lesions with corresponding sealing stents for either the aorta or the esophagus is still scarcely discussed and needs more research.

4.2.6. Postoperative mortality and survivability

The registered information showed postoperative mortality of (*n*=6/112 cases - 5.4 %). The first two causes are cardiac arrest and postoperative bleeding.

In comparison with the related literature, Scali *et al.* [178] demonstrate in their work ("Preoperative prediction of mortality within one year after elective thoracic endovascular aortic aneurysm repair") using a univariate Cox proportional hazard model as the risk-model design, a 30-day and one-year mortality of 3 % (*n*=7/224) and 15 % (*n*=33/224), respectively. The univariate predictor of one-year mortality is defined as mortality within one year of the TEVAR which included age > 70 years (*P*= 0.005), CAD (*P*=0.04), congestive heart failure (*P*=0.009), PAD (*P*=0.004), CVOD (*P*=0.07), COPD (*P*=0.07), aneurysm diameter (*P*=0.07), the need for adjunctive procedures (*P*=0.004), and hyperlipidemia (*P*=0.2). By multivariate analysis, factors are independently associated with one-year mortality included: age > 70 years (*P*=0.001; HR, 5.8; 95% CI, 2.1–16.0), adjunctive intra-operative procedures (e.g., brachiocephalic/visceral stents, concomitant arch de-branching procedures) (*P*=0.001; HR, 4.5; 95% CI, 1.9–10.8), PAD (*P*=0.006; HR, 3.0; 95% CI, 1.4–6.7), CAD (*P*=0.02; HR, 2.4; 95% CI, 1.1–4.9), and COPD (*P*=0.06; HR, 1.9; 95% CI, 1.0–3.9). A diagnosis of hyperlipidemia was protective (*P*=0.006; HR, 0.4; 95% CI, 0.2–0.7). In the multivariate model, the prediction of mortality after TEVAR in the mentioned study ranged from 0.9 % with no risk factors up to 54.2 % with four or more risk factors. When the risk factors had been stratified, the following values were extractred: 0–1 (*n* = 78; 35 %), 2 (*n* = 81; 36 %), 3 (*n* = 48; 22 %), or 4+ risk factors (*n* = 16; 7 %) with one-year mortality of 3 %, 10 %, 27 %, and 54 %, respectively. Scali *et al.* mention that the mean diameter with no independent risk factor for mortality within one year was 55 mm, while the mean diameter was 70 mm for patients with four risk factors. It was stated likewise that a linear trend

was found between the number of risk factors and the mean aneurysmatic size at the time of the repair (P=0.03). It was concluded that most deaths within one year after TEVAR does not occur in the perioperative period. Besides, patients with four or more independent predictors of one-year mortality have predicted more than 50 % mortality. Hence, older and sicker patients may be best served by waiting for a larger aneurysmatic size to justify the risk of the procedure. Likewise, Hu *et al.* [179] mention the importance of the data-extracted risk score as a mortality-prognostic tool in the preoperative risk stratification of patients being evaluated for TEVAR.

4.2.7. Postoperative follow-up

Our study showed a successful follow up in 38 patients with stable results in 30/38 patients while considering the postoperative endoleak and dissection as well as the newly discovered abdominal aneurysms in the count of minimal patients.

In his work ("After the procedure, endoleak management and postoperative surveillance following endovascular repair of thoracic aortic aneurysms"), Ricotta [180] has emphasized the importance of the lifetime follow up after TEVAR by demonstrating different surveillance methods and putting a special focus on endoleak as one of the most important complications after TEVAR. Methodologically, either 3-image chest X-ray, CT-A, MR-A, or transesophageal echocardiography are recommended. The gold standard is the CT-A. Canaud *et al.* [181] mention in their work ("Minimum 10-year follow-up of endovascular repair for acute traumatic transection of the thoracic aorta") a surveillance schedule of one week, three months, six months, and annually thereafter. We use the same schedule in our hospital. Technical success was 100 %, with one case of an endoleak (Type 1) being treated with the proximal implantation of a second stent-graft, four patients with covered LSA, and one stent-migration that was intraoperatively treated with the distal traction. During the 10-year CT-based follow-up period, there was no stent-graft migration, endoleak, or collapse. Clinically, there were no strokes or paraplegia. It was noted that the proximal neck diameter increased relatively by 3.3 ± 1.5 mm. In 10 years, in the younger group of patients (younger than 30 years old), the net increase in the neck diameter was significantly greater than that in the older patients (older than 30 years old): P=0.0037; 4 ± 1.2 mm *vs.* 1.5 $\pm$ 1.7 mm. The net increase in the neck diameter relative to the first postoperative scan was 2.7 $\pm$ 1 mm. At 10 years, the net increase in the neck diameter demonstrates a tendency to be greater in the group of patients < 30 years old, but this difference failed to reach statistical significance (P=0.065; 3.3 ± 1.6 mm *vs.* 2.1 ± 1.6 mm). It was concluded that over a 10-year follow-up period, there is a reduction in the operative mortality in TEVAR compared with open repair. However, there were distal and proximal neck changes over time. This change was more pronounced in patients < 30 years old.

5. Conclusion

5.1. Specific conclusion

There is no significant statistical difference considering the occurance of the related postoperative neurovascular complications (CVA-SCI or left-arm ischemia) when the not-revascularized patients' group *vs.* the revascularized patients' group are compared. The revascularization of the blocked LSA in Ishemaru-zone-2-approaching TEVAR should be limited to the following indications:

An inadequate intracerebral circle of Willis

-An advantageous left vertebral artery with a(n) stenosis/inadequate right vertebral artery

-The left vertebral artery originating directly from the aortic arch and must be blocke

-Need of an adequate left internal thoracic artery for CABG

-Need of a patent LSA for dialysis shunt of the left arm.

However, the up-to-date evidence lacks blinded wide-ranged studies, which should be designed as a multicenter study and organized in order to issue a terminal solution of this problem.

On the other side, the above-mentioned endovascular revascularization methods can be undertaken in certain inoperable cases.

5.2. General conclusions

- Real-time hemodynamic diagnostics (real-time ECG triggered CT-A/MR-A, TEE) should be considered for a wider use in order to reach a more precise imaging and representation of the thoracic aortic lesions, as well as for better therapy planning.
- More consideration for the biomarkers as a diagnostic tool for thoracic aortic lesions, especially in cases of the phenotyping demonstration of genetic-based thoracic aortic lesions and different collagen diseases. This will help to make a follow-up line for the natural history of the aortic changes. Special consideration also should be paid for younger patients (< 30 years old) as they are more prone to the occurrence of aortic changes.
- Medical therapy of thoracic aortic lesions, except for acute aortic syndrome, should be considered in order to avoid the postoperative drawbacks in weighing out long-term medical therapy benefits.
- The use of less contrast material during the TEVAR procedure through wider implications of the IVUS. This prevents the disadvantage of the radiation exposure for the patient as well as for the performing vascular surgeon.

6. Summary

Pathologies of the descending thoracic aorta inwardly extended toward the aortic arch can shorten the proximal landing zone for aortic prosthesi. This, in turn, worsens the feasibility of the aorta for endovascular therapeutic options of those pathologies.

Aim: This work considers the blockage of the left subclavian artery (LSA) by endovascular treatment of the pathologies of the descending aorta. This is the main work-question based on the hypothesis that there is no necessity for primary standard revascularization of the LSA in TEVAR with LSA covering. In addition, the review of 12 years of experience in treatment of different thoracic aortic lesions will be discussed.

Patients and methods: All the patients who had undergone endovascular, hybrid, or open operative therapy of variant descending aorta pathologies were included in this retrospective unicenter cohort study in order to describe the real-world situation of daily clinical practice. Various parameters were investigated including: therapeutic procedures, such as **i)** pure endovascular *vs.* hybrid, **ii)** year of therapy, **iii)** symptomatic *vs.* asymptomatic status of the patients, **iv)** variant epidemiological factors (age, sex, risk factors, mortality and follow up), **v)** overstenting/blocking of the LSA, **vi)** complications of applied therapies, **vii)** further operations/interventions to treat complications, **viii)** radiologic aortic measurements (such as lumen extensions, false lumen measurements, distance to the supra-aortic, and visceral vessels), and **ix)** multiple other pathological features. Different statistical parameters were examined. Survival was analyzed by Kaplan–Meier assessment in the whole patients' group *vs.* the over-stented patients' group. Analysis of variance is carried out for the independent parameters when the revascularized and not-revascularized patients who had undergone LSA coverage were compared. For statistical approval, *U*-test was used. Also, p-value < 0.05 was considered to be significantly different. The literature review was achieved by a search in: PubMed, Google scholar, Research Gate, ScienceDirect, and Cochrane library using the following terms—endovascular, TEVAR, revascularization, stroke, and left-subclavian-artery ischemia. The literature is classified accordingly. If specifically related to the main topic, the literature is analyzed further with or against our hypothesis.

Results: Overall, 112 patients were enrolled in the study. There was no significant difference comparing the not- revascularized *vs.* the revascularized groups of patients considering the consequences of cerebrovascular blood circulation (in particular, n=1 case [4.8 %] *vs.* no case [0 %]; P=1) or spinal cord ischemia (n=2 [9.5 %] *vs.* n=1 [7.1 %]; P=1). As a main result, there was no cases of manifest left arm ischemia and deaths (mortality, 0). In both groups, survival was as follows: 22 [95% CI, 14.154–29.904] months *vs.* 43 [95% CI, 33.655–51.921] months **with no significant statistical difference (P>0.05).** The only statistically significant risk factor found was renal insufficiency (P=0.028), but there was a trend of the urgency of revascularization. Postoperatively, pneumonia showed a trend of higher frequency (P=0.058) in the revascularized cases (n=0 in the not-revascularized *vs.* n=3 [21.4 %] in the revascularized cases). There was no significant difference

considering the occurance of postoperative neurovascular complications (such as cerebrovascular accidents, spinal cord ischemia, or left arm ischemia) when the not-revascularized and the revascularized groups of patients were compared.

Conclusion: The revascularization of the overstented LSA due to TEVAR should be limited to certain indications including **i)** an nadequate intracerebral circle of Willis, **ii)** a predominantly perfused left vertebral artery with inadequate blood perfusion via the right vertebral artery (e.g., by stenosis), **iii)** anatomic variance such as the left vertebral artery originating directly from the aortic arch (and must be blocked by TEVAR), **iv)** the need of an adequate left internal thoracic artery for coronary-artery-bypass grafting (CABG), and **v)** the need of a patent LSA for dialysis shunt of the left arm. There is, however, still no appropriate evidence based on sufficient study results achieved in trials with an advanced design (such as [double-]blind, multicenter randomized study).

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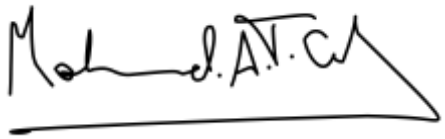


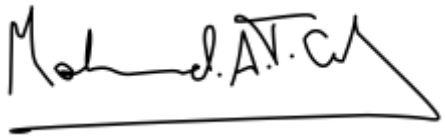
Mohamed Ghanem

9. Declaration

I declare herby that I submit this doctoral thesis under the title (Covering / Overstenting of the left subclavian artery in TEVAR interventions to treat various thoracic/thoracoabdominal aortic lesions: Is revascularization of the left arm a must? (A retrospective real-world cohort study of 12-years of experience and the literature review)) to the Medical Faculty of Otto von Guericke University to fulfill the attainment of the academic title of "Dr. med." (doctor medicinae). The related research work is carried out in the Section for Vascular Surgery, Clinic for General, Visceral, Vascular and Transplant Surgery without any outside help in the preparation of the dissertation. The rights of third parties were not violated when writing the dissertation. I have not yet submitted this dissertation for a doctorate degree at any domestic or foreign university. I give the medical faculty the right to produce and distribute further copies of my dissertation.

I hereby declare too that I have not been convicted of a criminal offence relating to scienctific issues/scientific publication.

Regensburg, 03.10.2021



Mohammad Ghanem

10. Curriculum Vitae

Mohammad Ghanem

Career pathway

03.2021-up to date	**Resident of vascular surgery** *Regensburg university hospitals, Regensburg*
02.2020 –12.2020	**Resident of general, visceral, and vascular surgery** *Klinikum Bremen Nord, Bremen*
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01.2019 – 07.2019	**Resident of intensive medicine** *Klinikum Magdeburg, Magdeburg*
04.2017 – 12.018	**Resident of vascular surgery** *Otto von Guericke University hospital, Magdeburg*
12.2016 – 03.2017	**Resident of vascular surgery** *Elblandklinikum Riesa, Riesa*
10.2016– 12.2016	**Cources; doppler ultrasonography, radiation protection**
10.2014– 10.2016	**Resident of general, visceral, and vascular surgery** *Asklepios Klinik Pasewalk, Pasewalk*
07.2014 – 10.2014 12.2013 – 03.2014	**Hospitant for general-, and visceral surgery** *Evangelisches Krankenhaus Unna, Unna*
04.2014 – 07.2014 09.2012 – 10.2013	**Resident of oncosurgery** *Nasser Institute hospital, Cairo, Egypt*
07.2010 – 09.2011	**Resident of pathology** *Nasser Institute hospital & Elbank Elahly hospital, Cairo, Egypt*
09.2008 – 07.2010	**Physician in state service** *Egyptian ministry of health, Cairo, Egypt*

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Publications

Ghanem M, Meyer F, Jechorek D, Schoeder V, Ignatov A, Fadel M, Halloul Z. Intravascular (post-hysterectomy) leiomyoma (IVL) as late tumor thrombus within the inferior vena cava (IVC)-A rare case primarily imposing as IVC thrombus originating from left renal vein after former left nephrectomy status. Pathol Res Pract. 2019 Jun;215(6):152359. doi: 10.1016/j.prp.2019.02.009 . Epub 2019 Feb 28. PMID: 30853174 .

Ghanem M, Meyer F, Halloul Z. Covering/Overstenting of the left subclavian artery (LSA) in thoracic endovascular repair (TEVAR) to treat various thoracic/thoracoabdominal aortic lesions: Is revascularization of the left arm a must? (A retrospective cohort study with 12 years of experience to describe the real-world situation of daily clinical practice and the literature review) submitted by Polnish journal of surgery.

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Regensburg, 03.10.2021

Mohammad Ghanem

11. Addendum

11.1. List of figure legends

11.2. List of table legends