Current state of alternative access for transcatheter aortic valve implantation

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KEYWORDS

- **access site**
- **aortic stenosis**
- **review**
- **transcatheter aortic valve implantation (TAVI)**

Abstract

The transfemoral (TF) route constitutes the undisputed default access for transcatheter aortic valve implantation (TAVI). In patients in whom anatomical constraints preclude a TF approach, several alternative access routes have been used. Transthoracic (transapical and transaortic) access routes show higher mortality and bleeding complication rates than the TF approach, which is attributable to the higher baseline risk of the selected patients and the more invasive nature of these procedures. Alternative transarterial approaches (transaxillary, transcarotid, transinnominate) have demonstrated high technical success rates and a favourable safety profile in selected patients and are particularly valuable in the presence of poor respiratory function or previous cardiothoracic surgery. The transcaval approach is an innovative fully percutaneous approach that allows the introduction of large-bore sheaths and shows promising results in high-risk patients. Diligent procedural planning, appropriate patient selection and the expertise of the Heart Team allow the achievement of an adequate safety and efficacy profile of TAVI performed via alternative access. Future studies incorporating standardised and independent outcome assessment are required to gain further knowledge on the risk/benefit relation pertaining to the specific approaches and improve selection of the appropriate access route for the individual patient.

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Abbreviations

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MSCT	multislice computed tomography
SAVR	surgical aortic valve replacement
STS-PROM	Society of Thoracic Surgeons Predicted Risk of Mortality
TA	transapical
TAo	transaortic
TAVI	transcatheter aortic valve implantation
TAx	transaxillary
TC	transcarotid
TCv	transcaval
TF	transfemoral
TI	transinnominate

Introduction

In 2002 the first transcatheter aortic valve implantation (TAVI) was performed via an anterograde transseptal approach[1]. Since then, TAVI has become an established therapy for patients with severe symptomatic aortic stenosis (AS) deemed at increased risk for surgical aortic valve replacement (SAVR)[2].

Vascular complications and access-site bleeding remain the most frequent complications of TAVI **(Supplementary Table 1, Supplementary Table 2)**[3]. They are associated with increased mortality, longer hospital stay and higher costs of care[4,5]. The frequency of bleeding complications drastically declined following the introduction of low-profile delivery systems and introducer sheaths, widespread adoption of the transfemoral (TF) access route and closure device systems, as well as a shift in the risk profile of the treated population[3,6-8]. Meta-analyses of randomised controlled trials comparing TAVI to SAVR in high- and intermediate-risk patients indicate a survival benefit of TF TAVI compared to SAVR[9]. Due to the familiarity of the interventional cardiologist with the femoral access, improved delivery systems allowing insertion in small-calibre and diseased iliofemoral arteries and the compelling scientific evidence showing favourable, highly reproducible results, the TF route has nowadays become the undisputed default access approach for TAVI[2]. Nevertheless, some patients cannot be subjected to TF access due to small arterial vessel calibres, calcifications, tortuosity, or a combination of these factors. Several alternative access sites have been developed, used, and technically refined in order to enable minimally invasive transcatheter treatment of aortic stenosis when the anatomic properties of the iliofemoral arteries are unfavourable **(Figure 1)**. This review aims to provide an overview on the use and state of evidence on the different alternative access routes used for TAVI.

EVOLUTION OF TAVI SYSTEMS

TAVI systems have undergone constant refinements to address limitations such as paravalvular regurgitation, stroke, vascular complications and pacemaker rates. Notably, a remarkable reduction in introducer sheath size has been achieved **(Supplementary Table 3)**.
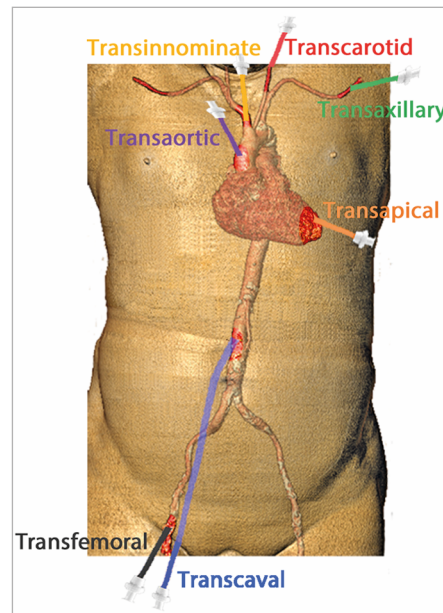
Figure 1. *Access routes for TAVI.*

In less than 10% of patients undergoing TAVI, the iliofemoral arteries do not formally accommodate the latest low-profile delivery systems[10]. The low-profile self-expanding valve systems, notably the CoreValve® series (Medtronic, Minneapolis, MN, USA), are most frequently applied for peripheral arterial alternative access, occasionally in a sheathless fashion. When considering the eSheath for an alternative peripheral arterial access, the maximum local expansion **(Supplementary Table 3)**, as well as the fact that the crimped valve needs to be aligned onto the balloon within the body, has to be taken into account.
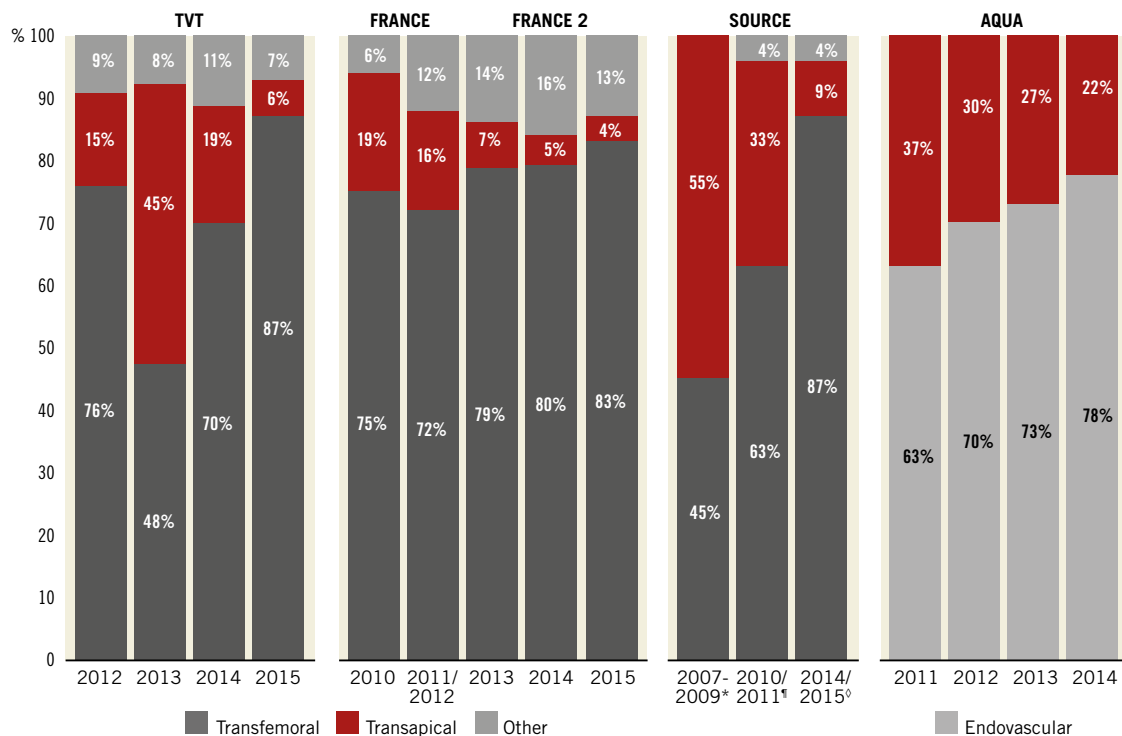
ADOPTION OF ACCESS ROUTES

A clear rise in the proportion of patients treated via the TF access in recent years reflects the favourable outcomes and technical advances of the default TAVI access route. In large registries from Europe and the USA, the proportion of patients treated by the TF approach has consistently increased over the years, reaching more than 85% in 2015 **(Figure 2)**[7,8,11-14]. Nowadays, many individual centres reach TF rates of well above 90%.

In the following paragraphs, the different access routes are presented in anatomical order from central to peripheral **(Figure 1)**.

Transapical (TA)

The first case of TA TAVI without cardiopulmonary bypass was performed in 2005[15]. During the early years of TAVI, the TA approach rapidly emerged as the most frequently used alternative access route as the large introducer sheaths precluded alternative peripheral arterial access routes for patients with unsuitable iliofemoral arteries[16-18]. More recently, its use has clearly declined owing to the high proportion of patients amenable to a TF approach, complications related to the TA access site, and the advent of a variety of alternative access strategies **(Figure 2)**.

Figure 2. *Temporal trends of access site use for transcatheter aortic valve implantation (TAVI). The proportion of transfemoral, transapical and other access routes used for TAVI in the TVT[8], FRANCE[11] and SOURCE (*Source[12], ¶Source XT[13], ◊Source 3[7]) registries as well as endovascular access and transapical use reported in the AQUA registry[14].*

Multislice computed tomography (MSCT) allows assessment of the relationship and distance of the apex to the chest wall and the angle of trajectory from the apex to the aortic annulus. Currently available transapical TAVI systems are limited to the balloon-expandable SAPIEN 3 (Edwards Lifesciences, Irvine, CA, USA) delivered over an 18 or 21 Fr sheath and the self-expanding ACURATE *neo*™ (Boston Scientific, Marlborough, MA, USA) with an outer transapical delivery system diameter equivalent to a 19 Fr sheath **(Supplementary Table 3)**. The steps of the TA access have been published elsewhere[19].

EVIDENCE
Studies reporting independently adjudicated adverse events after TA TAVI are listed in **Table 1**. A meta-analysis, incorporating the landmark PARTNER 1 and PARTNER 2A trials, showed no survival benefit of transthoracic TAVI (TA or transaortic [TAo]) over SAVR at two years (hazard ratio [HR] for all-cause mortality 1.17, 95% CI: 0.88-1.56)[9], nor did the results of the PARTNER 1A trial when comparing five-year mortality rates between TA TAVI and SAVR (HR 1.37, 95% CI: 0.98-1.92)[20].

Observational studies and registries report higher mortality rates in patients treated by TA compared to TF TAVI, but inferences are precluded due to differences in baseline risk profiles[13,18,21]. Propensity score-matched or score-adjusted comparisons between TA and TF TAVI derived from studies using independent event adjudication suggest a higher short- and long-term mortality, similar 30-day stroke rates, higher rates of major bleeding and longer length of hospital stay for patients treated by the TA approach. Blackstone et al compared 501 propensity-matched pairs of high-risk or inoperable patients with severe AS treated with TA or TF TAVI in the PARTNER 1 trial or continued access registry[16]. TA compared to TF TAVI was associated with a significantly higher 30-day mortality rate (9.1% versus 3.7%), a similar 30-day stroke rate (3.4% vs. 3.3%), a longer length of hospital stay (5 versus 8 days; p<0.0001), and a trend towards a lower rate of procedural major vascular injury (3.8% vs. 6%, p=0.10) but a higher rate of major bleeding (7.2% vs. 4.8%, p=0.12)[16]. A propensity score-adjusted study derived from the same PARTNER 1 trial and registry cohort including 2,084 patients confirmed a negative impact of the TA approach on two-year all-cause mortality for both patients with (left ventricular ejection fraction [LVEF] <50%) and those without left ventricular dysfunction and reported a lower degree of LVEF recovery in the TA group (TF-TA difference +4.04%, 95% CI: 2.39% to 5.69%; p<0.0001) compared to TF TAVI[22]. Some risk-adjusted and risk-unadjusted comparisons showed no difference in mortality, stroke or bleeding complications between TA and TF access; however, these studies were smaller and lacked independent event adjudication[23,24]. Adjusted comparisons between TA and other alternative approaches that allow meaningful inferences are not available[25-27].

Table 1. Outcomes of transcatheter aortic valve implantation by alternative access.

Study	Year*	Device	Delivery sheath (ID)	N	Age	STS-PROM (LES)	Endpoints					
							Def.	Major vascular complication (30-day)	Life-threatening bleeding (30-day)	Major bleeding (30-day)	Stroke (30-day)	Mortality (30-day) (1-year)
Non-TF												
Source 3 registry[7]	2014-2015	SAPIEN 3	18 or 21 Fr	252	81	– (21.8%)	VARC-2	3.2%	9.6%	–	2.8%	4% 18.5%[60]
Transapical or transaortic												
PARTNER 2 - intermediate risk[59]	2011-2013	SAPIEN XT	24 Fr	236¶	81¶	6%¶	VARC-2	5.9%¶	22.6%¶	–	9.8%¶	6.8%¶ 19.9%¶
PARTNER 2 SAPIEN 3 - high-risk/inoperable[60]	2013-2014	SAPIEN 3	18 or 21 Fr	92	–	–	VARC-2	4.4%	9.8%	22.9%	1.1%	5.4% 25.3%[61]
PARTNER 2 SAPIEN 3 - intermediate risk[60]	2014	SAPIEN 3	18 or 21 Fr	125	–	–	VARC-2	4%	12.7%	24.6%	4%	1.6% –
Transapical												
TRAVERCE trial[62]	2006-2008	Cribier-Edwards or SAPIEN	26 or 33 Fr	168	82	– 27%	–	–	–	–	2%	15% 37%
Partner IA trial[63]	2007-2009	SAPIEN	26 or 33 Fr	104	83¶	11.8%¶ (29.8%¶)	–	3.9%	–	8.8%	8%	8.7% 29.1%
PARTNER IA trial and continued access registry[64]	2007-2012	SAPIEN	24 or 26 Fr	1,100	85	12% (27.6%[65])	–	3.5%	–	8.8%	2.6%	8.7% (22.1%[65])
SOURCE XT registry[13]	2010-2011	SAPIEN XT	24 or 26 Fr	894	80	7.9% (21.9%)	VARC	3.5%	8.3%	13.9%	4.2%	10% 27.1%
PREVAIL TRANSAPICAL[66]	2009-2010	SAPIEN XT	24 or 26 Fr	150	82	7.5% (24.3%)	–	–	–	–	2.7%	8.7% 22.1%[67]
ACURATE neo TA[68]	2015-2016	ACURATE neo	≈ 19 Fr	60	80	4.3% (20.9%)	VARC-2	3.4%	1.7%	–	1.7%	8.3% –
Transaortic												
CoreValve ADVANCE DA study[32]	2012-2014	CoreValve	18 Fr	92	82	5.9% (20.3%)	VARC-2	6.5%	10.9%	6.6%	1.1%	4.4% 17.9%
CoreValve US Pivotal Trial and continued access registry[31]	2011-2014	CoreValve	18 Fr	394	83	9.7% –	VARC	4.1%	Life–threatening and major combined: 66.7%		5.7%	10.9% 28.1%
Transaxillary												
Italian CoreValve Registry[44]	2007-2011	CoreValve	18 Fr	141	83	– (23.7%)	VARC	(5%§#)	(7.8%§#)	(36.2%§#)	(2.1%§)	5.7%§ –
CoreValve US Pivotal Trial and continued access registry[45]	2011-2014	CoreValve	18 Fr	202	81	9.7% (20.7%)	VARC	11.9%	11.4%	27.8%	6.5%	5.4% 23.3%
CoreValve ADVANCE study◊	2010-2011	CoreValve	18 Fr	96	81	– (22.8%)	VARC	8.5%	4.2%	9.5%	4.3%	7.3% –
Transcaval												
Transcaval access and closure[55]	2014-2016	SAPIEN XT, SAPIEN 3, CoreValve & Evolut R	Mean sheath OD: 8.0 mm	100	80	9.6% –	VARC-2	19.2%§#	12.1%§#	6.1%§#	5%§	8%§ –

Selected studies reporting baseline characteristics and outcomes adjudicated by independent event committees including at least 50 patients are listed. Age, STS-PROM and LES are reported as mean. Reported endpoints correspond to Kaplan-Meier estimates unless stated otherwise; 95% confidence intervals are reported in brackets if available. In case different reports comprise overlapping study populations, the most recent and largest cohort was chosen. *year of recruitment. ¶referring to intention-to-treat cohort. ◊data of transaxillary subcohort as presented at ESC 2012, Munich. §incidence proportion. #in-hospital/periprocedural instead of 30-day outcomes. Fr: French; Def: definition; ID: inner diameter; LES: logistic EuroSCORE; N: number; Non-TF: non-transfemoral; OD: outer diameter; STS-PROM: Society of Thoracic Surgeons Predicted Risk of Mortality; VARC: Valve Academic Research Consortium

Transaortic (TAo)

The first TAo TAVI was reported in 2009[28]. Rates of TAVI performed by TAo access have increased, partially at the expense of the TA approach, as the former entails less respiratory compromise and no direct myocardial injury, while preserving the benefit of a short distance to the landing zone and a good control of valve delivery **(Table 2)** [29]. A suitable calcium-free entry site at the anterolateral ascending aorta with a minimum distance of 5 cm (6 cm

Table 2. Features and limitations of alternative access routes.

Anatomical constraints & limiting conditions	Mode of access & anaesthesia	Advantages	Disadvantages/specific complications
Transapical (TA)			
– Apical aneurysm, thrombus or severe hypertrophy – Intra-thoracic adhesions (previous cardiothoracic surgery) – Severe thoracic deformations – Poor LV function – Poor respiratory function	– Surgical: left-anterior mini-thoracotomy – General anaesthesia	– Anterograde procedure – Direct and short distance to aortic annulus (well-controllable delivery) – Favourable implantation angle, also in horizontal aorta – Accommodates large sheaths – Little interference with aorta – Technically feasible in almost everyone, independent of peripheral vessel site	– Higher invasiveness (access to chest & pleural cavity) – Direct myocardial injury – Respiratory compromise – Recovery time/chest discomfort – Device choice restricted to dedicated anterograde delivery systems – Risk of apical tear/rupture – Risk of pseudoaneurysm formation
Transaortic (TAo)			
– Lack of calcium-free target entry window – Distance aortic entry site to annulus <5 cm – Severe chest deformations – Hx of CABG, prior sternotomy ◊ – Close proximity of innominate vein and/or aorta to upper third of sternum ◊ – Ascending aorta to the right of the midline, horizontally angulated aorta ◊ – Poor respiratory function *	– Surgical: - upper mini-sternotomy OR - right thoracotomy (2. ICS) – General anaesthesia	– Access familiar to cardiac surgeons – Short and direct working distance (well-controllable delivery) – No interaction with aortic arch – Independent of peripheral artery size – Accommodates all sheath sizes – No direct myocardial injury – Rapid installation of CPB possible Mini-sternotomy: – Avoids opening of pleural cavity – Rapid conversion to full sternotomy possible	– Invasiveness – Recovery time/chest discomfort – Respiratory compromise (thoracotomy) – Intercostal bleeding, neuralgia (thoracotomy)
Transinnominate (TI)			
– Deformity of cervical spine restricting neck extension – Thyroid disease/previous surgery – Severe calcifications of innominate artery or its base at aortic arch	– Surgical: cut-down, if located at upper third of sternal manubrium, otherwise mini-sternotomy – General anaesthesia	– No injury to chest wall, pleural cavity or myocardium – Short and direct working distance (well-controllable delivery) – No interaction with aortic arch – Often free of adhesions despite previous cardiac surgery – Rarely atheromatous or calcified – Accommodates all sheath sizes – Faster recovery than transthoracic accesses	– Not accessible for direct compression in case of bleeding complications – Unfavourable trajectory in case of horizontally angulated aortic root – Tracheal, vascular or nerve injuries
Transaxillary (TAx)			
– Min. vessel diameter <6 mm – Calcification and tortuosity – Patent internal mammary artery graft ¶ – Pacemaker ¶ – Anatomical variants of aortic arch and course of brachial plexus	– Surgical OR – Percutaneous – General anaesthesia OR – Local anaesthesia with conscious sedation	– Accessible in obese patients – No interaction with descending & abdominal aorta – No myocardial injury – No chest wall injury, no entry in pleural cavity – No restrictions in presence of prior cardiac surgery – Rapid recovery	– More delicate than femoral artery (vascular dissection, rupture) – Not accessible for effective manual compression – Right-side: unfavourable alignment, particularly if angle between annular plane and horizontal axis >30°
Transcarotid (TC)			
– Min. vessel diameter <6 mm – Calcification and tortuosity – Short neck – Prior ipsilateral carotid artery intervention – Stenosis or occlusion of contralateral carotid artery or vertebral arteries – Anticipated difficult airway	– Surgical – General anaesthesia OR – Local anaesthesia with conscious sedation	– No interaction with descending & abdominal aorta – No myocardial injury – No chest wall injury, no entry in pleural cavity – No restrictions in presence of prior cardiac surgery – Rapid recovery	– Complications of access preparation (nerve injury) – Monitoring of cerebral perfusion required – Right-side: unfavourable alignment if steep angle between annular plane and horizontal axis
Transcaval (TCv)			
– Lack of calcium-free target window – Proximity of renal arteries or aorto-iliac bifurcation to target entry site (15 mm) – Pedunculated abdominal aortic atheroma – Bilateral iliofemoral artery occlusion (precluding bail-out procedures) – Celiac and superior mesenteric artery obstruction (risk of mesenteric ischaemia) – Aortic stent graft and aneurysm ¶	– Percutaneous – General anaesthesia	– True percutaneous procedure – No myocardial injury – No chest wall injury, no entry in pleural cavity – Accommodates all sheath sizes – Standard working position for operator, most distant from radiation source	– Risk of retroperitoneal bleeding – Risk of residual aorto-caval fistula with haemodynamic compromise – Risk of bowel injury

¶ no contraindication. ◊ may complicate TAo access via upper mini-sternotomy. * may complicate TAo access via right thoracotomy. CABG: coronary artery bypass grafting; CPB: cardiopulmonary bypass; Hx: history; ICS: intercostal space; LV: left ventricular; Min: minimum

for the CoreValve series) to the aortic annular plane and a favourable trajectory to the landing zone are preconditions for TAo TAVI. Further assessments derived from MSCT focus on the course and angulation of the aorta and innominate vein as well as the localisation of aorto-coronary bypass grafts if present. A mini-sternotomy is favoured in case of respiratory compromise to avoid entering the pleural cavity[29]. It also allows rapid conversion to full sternotomy if needed. Recovery is faster than after thoracotomy with rib spreading[29]. A right anterior mini-thoracotomy is more suitable if the aorta is located to the right of the midline; it prevents injury to bypass grafts, if present, and provides a more coaxial trajectory to the annular plane in case of a horizontal angulation of the aortic root. Procedural steps of TAo TAVI have been published previously[30].

EVIDENCE

Studies based on independently adjudicated outcomes after TAo TAVI are scarce **(Table 1)**[31,32]. In 92 patients undergoing TAo TAVI in the CoreValve ADVANCE Direct Aortic study, all-cause mortality was 4.4% and the stroke rate was 1.1% at 30 days[32]. Thirty-day rates of major vascular complications, life-threatening or disabling bleeding and major bleeding were 6.5%, 10.9% and 6.6%, respectively. Notably, only 30% of the included patients were not considered candidates for a TF or other alternative approaches[31]. The "Registry of the Utilisation of the TAo-TAVR approach using the Edwards SAPIEN Valve" (ROUTE) reported the outcomes of 301 patients (mean age 81.7 years, mean Society of Thoracic Surgeons Predicted Risk of Mortality [STS-PROM] score 9.0%), but did not include independent event adjudication[33]. Valve success was documented in 96.7%, 30-day mortality amounted to 6.1%, stroke to 1.0%, major vascular complications to 3.4%, and life-threatening bleeding to 3.4%[33].

A comparison between TAo and TF access in 394 propensity score-matched pairs of the CoreValve US Pivotal Trials and continued access registry showed a significantly higher rate of 30-day all-cause mortality (10.9% vs. 4.1%, p<0.001), stroke (5.7% vs. 2.6%, p=0.028) and life-threatening or major bleeding (66.7% vs. 35.4%, p<0.001) for the TAo group, but a lower rate of major vascular complications (4.1% vs. 9.4%, p=0.003)[31]. Observational studies report similar survival rates between TAo and TA TAVI; however, well-adjusted comparisons and independent event adjudication are lacking[25,26].

Transinnominate (TI)

The first TI TAVI reported in the literature was conducted in 2011[34]. The transinnominate (or suprasternal) approach is reported to have few anatomical constraints as the innominate artery usually provides a generous luminal diameter, stays unaffected in patients with previous cardiac surgery, and only rarely shows relevant atheromatous disease **(Table 2)**[35].

Preparatory MSCT assessment focuses on the relationship and angle of the sternum to the spine, the course of the innominate artery in relation to the sternum, the diameter, extent and location of calcium, and the anticipated trajectory to the annular plane[35]. In order to avoid cerebral hypoperfusion after sheath insertion, perfusion can be surveilled by means of a right radial arterial line or cerebral oximetry[36]. Procedural steps have been published elsewhere[35].

EVIDENCE

Only small observational studies without independent event adjudication have reported on outcomes after TI TAVI. The largest one comprised 30 patients (mean age 79.8 years, mean STS-PROM score 6.7%) and reported no relevant adverse events during hospitalisation and a short median hospital duration of four days[37]. In another series encompassing 26 patients, all patients survived to 30 days, one stroke occurred and there were three major vascular access-site related complications[36].

Transaxillary (TAx)

The first reports on TAVI via a TAx approach were published in 2008 and 2009[38,39]. The frequently applied term "transsubclavian access" is misleading as generally the axillary artery is used as entry site. Cardiac surgeons are familiar with this access as it is occasionally used as a cannulation site for cardiopulmonary bypass. The axillary arteries often show little calcification and tortuosity as well as larger lumina, even in the presence of diseased iliofemoral arteries[40]. The short distance to the valve landing zone allows good control of the delivery system. TAx TAVI can be performed as a true percutaneous procedure and under local anaesthesia with conscious sedation[41,42]. Particular care has to be taken as the axillary arteries are more delicate than the iliofemoral ones and effective manual compression is hampered by the anatomical conditions[42].

Information on the origin and course of the subclavian and axillary arteries, their diameter and tortuosity, as well as the presence, localisation and extent of calcification is obtained by MSCT. The left axillary artery is generally preferred over the right one due to a more favourable implantation angle providing better axial alignment of the device with the aortic root. An angle >30° between the annular plane and the horizontal axis is regarded as a significant limitation for right-sided TAx access[42]. The artery's minimum diameter should measure ≥6 mm. Specific conditions such as a patent LIMA graft or a pacemaker are not strict contraindications, but have to be taken into account when evaluating patients for a TAx approach[42]. In the former case, verification of a sufficiently large vessel diameter (at least 7-8 mm) is recommended to ensure perfusion of the graft during the intervention[42]. Procedural steps have been published in detail previously[42,43].

EVIDENCE

The majority of the experience with this access route is based on the use of the self-expanding CoreValve platform. Three studies have reported outcomes based on independent event adjudication **(Table 1)**. A propensity-matched comparison of 141 pairs treated either by TAx or TF access showed similar adverse event rates in the two groups and a lower rate of direct access-related bleeding

complications with the TAx approach[44]. Gleason et al matched 202 patients from the CoreValve US Pivotal Trial and continued access registry treated by TAx approach 1:1 to patients undergoing TF TAVI based on propensity scores[45]. Mortality amounted to 5.4% at 30 days, and 23.3% at one year **(Table 1)**. Rates of major vascular complications and life-threatening bleeding were 11.9% and 11.4%, respectively[45]. Neither the mortality rates nor rates of other adverse events differed significantly between the TAx and TF groups[45]. Ninety-six patients treated by TAx TAVI in the CoreValve ADVANCE study showed a higher incidence of major adverse cardiovascular and cerebrovascular events (13.5% vs. 7.9%, p=0.05) compared to patients treated by TF TAVI, but they also had a higher mean logistic EuroSCORE (data presented at ESC 2012, Munich). For individual endpoints, differences in 30-day rates did not reach statistical significance.

A meta-analysis encompassing 618 patients treated by TAx and 3,886 patients treated by TF TAVI reported no difference in 30-day mortality, stroke, major vascular complications or life-threatening bleeding despite a higher mean logistic EuroSCORE and a higher prevalence of coronary and peripheral artery disease in the TAx group[46]. Compared with transthoracic (TA and TAo) access routes, a trend towards fewer periprocedural events with the TAx approach is suggested by registry data; however, populations differed in baseline characteristics and risk profiles[27,47].

Several studies have proved the feasibility and suggest the safety of a direct percutaneous TAx approach[41,48]. The largest one included 100 patients in whom access vessel closure was performed with two Perclose ProGlide® systems (Abbott Vascular) achieving successful closure in 94.8%; 11% required covered stent implantation, but no major access-site complication occurred. Thirty-day mortality amounted to 6% and life-threatening bleeding to 3%; no strokes were reported[41].

Of note, nerve injury as a consequence of the TAx approach appears to occur rarely[49].

Transcarotid (TC)

The first TC TAVI procedure was performed in 2009[50]. Cardiovascular surgeons are familiar with the TC access. The short distance to the annulus provides good control of the valve delivery system. Coaxial alignment of the system and the aortic root is generally better from the left carotid artery. MSCT allows assessment of vessel properties and identification of congenital variants of the aortic arch. Flow-limiting stenoses can be detected by Doppler ultrasound examination. Magnetic resonance imaging (MRI) with cerebral angiography is used to assess the arterial circle of Willis and collateral blood flow and to detect previous strokes[51]. At the beginning of the procedure, cerebral perfusion is assessed during a cross-clamping test by means of a neurological assessment if performed under local anaesthesia, or by use of cerebral oximetry and distal backflow arterial pressure monitoring if the patient is under general anaesthesia. In case of signs of hypoperfusion, a femoro-carotid shunt is inserted. Procedural steps have been published previously[51,52].

EVIDENCE

Three large prospective observational reports from French TC TAVI cohorts are available; however, none of these reported independently adjudicated events[51-53]. The largest one included 174 patients (mean age 80.5 years, mean STS-PROM score 8.4%)[53]. Vascular access and valve deployment was successful in all cases. All-cause mortality amounted to 7.4% at 30 days and 12.6% at one year[53]. A higher rate of perioperative strokes was observed with general anaesthesia (four strokes [2.2%] and six transient ischaemic attacks [TIA] [3.4%]) than under local anaesthesia with conscious sedation (none)[53]. The majority of the events were localised contralateral to the access site and hence appear to be related to the TAVI procedure rather than the access. No major vascular complication related to the carotid access occurred. Another study with 145 patients (mean age 79.8 years, mean logistic EuroSCORE 20.7%) reported similar 30-day mortality (6.3%), stroke (2%) and TIA (3.5%) rates[52]. One case of late asymptomatic carotid dissection was recorded[52]. Bleeding complications were frequent (25.6%) but mainly driven by a liberal use of blood transfusions[52].

Transcaval (TCv)

The first human case of TCv TAVI was performed in 2013[54]. The transcaval approach relates to obtaining percutaneous femoral venous access and entering the aorta through the inferior vena cava by means of an electrified stiff coronary guidewire. Subsequently, microcatheters in a "mother and child" set-up, a stiff guidewire and, eventually, the delivery sheath are inserted. At the end of the procedure a nitinol occluder device is implanted at the aortic entry site.

Rapid pressurisation of the retroperitoneal space and consecutive drainage of aortic blood via shunting into the vena cava constitutes the concept underlying the feasibility of this approach and explains haemodynamic stability as observed during temporal removal of the cavo-aortic sheath or in case of persistent aorto-caval fistula[55,56].

Neither surgeons nor interventional cardiologists were familiar with this approach prior to its introduction for TAVI. However, it is performed by use of off-the-shelf equipment and procedural steps can be acquired rapidly with the support of proctors. The TCv route constitutes the only non-transthoracic approach that does not rely on an adequately sized peripheral artery for delivery sheath insertion. The distensible venous system allows accommodation of large sheaths with no restriction regarding the choice of valve system.

MSCT is crucial for assessment of eligibility for TCv TAVI. A sufficiently large calcium-free target zone (≥1 cm is favourable) of the right-sided abdominal aortic wall and a trajectory from the vena cava without interposed obstacles (bowel) are preconditions[57]. Projections orthogonal to the anticipated cavo-aortic crossing trajectory, as well as anatomical landmarks used for orientation during fluoroscopy, are identified. At least one peripheral artery should be patent and provide a lumen that allows bail-out aortic balloon occlusion or covered stent implantation. The aortic entry site should be

sufficiently distant from the major arterial branches and the aorto-iliac bifurcation (≥1.5 cm) to avoid occlusion of relevant arteries in case of bail-out stent implantation. The distance between the femoral venous puncture and aortic entry site provides information on the adequacy of the delivery sheath working length[57]. Of note, procedures across abdominal grafts as well as abdominal aortic aneurysms are feasible[57]. Step-by-step instructions have been published previously[56]. **Moving image 1** illustrates TCv access and closure.

EVIDENCE

A prospective observational study including 100 patients and comprising on-site monitoring, independent event adjudication as well as core laboratory assessment of MSCTs was conducted between July 2014 and June 2016[55]. Patients were at extreme risk or considered unsuitable for TF, TA or TAo access and hence showed a high mean STS score of 9.7% and a high burden of comorbidities[55]. Device success, defined as successful transcaval access and deployment of a closure device without death or emergency open abdominal surgery, was achieved in 98% of the patients. No patient died as a direct consequence of TCv access or required surgical bail-out. The observed 30-day mortality rate amounted to 8%, and the stroke rate to 5%[55]. Rates of major vascular complications, life-threatening bleeding and major bleeding were 19.2%, 12.1%, and 6.1%, respectively[55]. Notably, a considerable proportion of major bleeding events could be attributed to retroperitoneal haematoma, not clinically apparent but detected in the routinely performed pre-discharge MSCTs.

In 36% of the patients, the aorto-caval fistula was closed at the end of the procedure[55]. Abdominal aortic covered stent implantation was performed in 8% of the patients. There were no vascular complications after hospital discharge. In 72% of the patients for whom a MSCT was available, no aorto-caval fistula was present at 30 days, and for 64% of the overall study population imaging proof of the occluded aorto-caval tract was available[55].

Discussion

Since the advent of TAVI a variety of alternative access modes has been used and described. However, studies encompassing independent adjudication of events after TAVI performed via alternative access are scarce and completely lacking for the TC and TI approaches. Information and publication bias possibly distort the knowledge gained from observational studies.

Selection of an alternative access route is inherently linked to the presence of extensive peripheral artery disease and a higher burden of comorbidities; unsurprisingly, non-transfemoral TAVI inevitably comes at the price of increased adverse event rates driven by the baseline risk of these patients. Comparisons between different alternative access routes derived from observational studies are hampered by selection bias and residual unmeasured confounding. Randomised head-to-head comparisons between alternative access routes are precluded as patients selected for different approaches are not interchangeable, and adequately powered trials are not realisable due to the low rates of alternative access use.

The transthoracic approaches (TA and TAo) constitute the alternative approaches for TAVI that are best documented with respect to evidence derived from studies comprising independent event adjudication. Propensity-matched comparisons and observational data suggest a higher mortality rate, more bleeding complications and a prolonged recovery compared to the TF approach. Although selection bias and residual confounding probably distort these comparisons, the findings are consistent and plausible in view of the higher invasiveness of the transthoracic procedures comprising myocardial injury (in TA) and respiratory compromise.

The arterial alternative access modes (TAx, TC, TI with cutdown) spare opening of the chest. They are valuable alternative access options, in particular in patients with chest pathologies, poor respiratory function or previous cardiothoracic surgery. Studies reporting independently adjudicated events are scarce and limited to the TAx approach. Available observational reports on TAx TAVI suggest a high technical success rate, a favourable safety profile and reproducible results if conducted in appropriately selected patients.

The transcaval access constitutes an innovative approach performed completely percutaneously and allowing the introduction of large-bore sheaths despite the presence of severe peripheral artery disease. Results of a well-conducted prospective study have dispelled concerns related to access complications and uncontrollable bleeding and showed acceptable adverse event rates considering the high-risk features of the patients included[55]. Dedicated devices for aortic entry site closure will probably render this approach more attractive and increase its adoption in clinical practice.

Due to the unavailability of comparative data, the choice of alternative access should be made by the Heart Team on a case-by-case basis. Each alternative approach is associated with advantages, disadvantages and specific complications **(Table 2)**. Imaging by means of contrast-enhanced MSCT is critical to assess patient eligibility for different access sites, to anticipate complications and to plan bail-out strategies. In general, the least invasive method should be chosen in order to minimise post-procedural pain and allow fast recovery, particularly in elderly and frail patients. However, next to anatomical preconditions and comorbidities, the choice of access is largely driven by the operator and local site experience and preference, as well as the infrastructure and reimbursement. Given the relatively low volume of TAVI patients requiring alternative access, the learning curve leading to technical proficiency can take significant time and smaller centres may concentrate on a specific alternative approach.

Conclusion

We conclude that with appropriate patient selection and an experienced team a favourable safety and efficacy profile can be achieved for most alternative approaches for TAVI. Future studies with thorough and standardised outcome assessment will shed further light on the risk/benefit relation pertaining to different approaches and improve selection of the appropriate access route for the individual patient.

Conflict of interest statement

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Supplementary data

Supplementary Table 1. Valve Academic Research Consortium-2 (VARC-2) definitions of vascular access-site and access-related complications and bleeding complications[69].

Supplementary Table 2. Outcomes of transcatheter aortic valve implantation by transfemoral access.

Supplementary Table 3. Currently available transcatheter aortic valve implantation systems and predecessors with CE (Conformité Européenne) mark.

Moving image 1. Transcaval access and closure.

The supplementary data are published online at:
http://www.pcronline.com/eurointervention/
AB_issue/5

Supplementary data

Supplementary Table 1. Valve Academic Research Consortium-2 (VARC-2) definitions of vascular access-site and access-related complications and bleeding complications [69].

VASCULAR ACCESS-SITE AND ACCESS-RELATED COMPLICATIONS ACCORDING TO VARC-2

Major vascular complications
- Any aortic dissection, aortic rupture, annulus rupture, left ventricle perforation, or new apical aneurysm/pseudo-aneurysm OR
- Access-site or access-related vascular injury (dissection, stenosis, perforation, rupture, arteriovenous fistula, pseudoaneurysm, haematoma, irreversible nerve injury, compartment syndrome, percutaneous closure device failure) leading to death, life-threatening or major bleeding*, visceral ischaemia, or neurological impairment OR
- Distal embolisation (non-cerebral) from a vascular source requiring surgery or resulting in amputation or irreversible end-organ damage OR
- The use of unplanned endovascular or surgical intervention associated with death, major bleeding, visceral ischaemia or neurological impairment OR
- Any new ipsilateral lower extremity ischaemia documented by patient symptoms, physical exam, and/or decreased or absent blood flow on lower extremity angiogram OR
- Surgery for access site-related nerve injury OR
- Permanent access site-related nerve injury

Minor vascular complications
- Access-site or access-related vascular injury (dissection, stenosis, perforation, rupture, arteriovenous fistula, pseudoaneurysms, haematomas, percutaneous closure device failure) not leading to death, life-threatening or major bleeding*, visceral ischaemia, or neurological impairment OR
- Distal embolisation treated with embolectomy and/or thrombectomy and not resulting in amputation or irreversible end-organ damage OR
- Any unplanned endovascular stenting or unplanned surgical intervention not meeting the criteria for a major vascular complication OR
- Vascular repair or the need for vascular repair (via surgery, ultrasound-guided compression, transcatheter embolisation, or stent-graft)

Percutaneous closure device failure

Failure of a closure device to achieve haemostasis at the arteriotomy site leading to alternative treatment (other than manual compression or adjunctive endovascular ballooning)

BLEEDING COMPLICATIONS

Life-threatening or disabling bleeding
- Fatal bleeding (BARC type 5) OR
- Bleeding in a critical organ, such as intracranial, intraspinal, intraocular, or pericardial necessitating pericardiocentesis, or intramuscular with compartment syndrome (BARC type 3b and 3c) OR
- Bleeding causing hypovolaemic shock or severe hypotension requiring vasopressors or surgery (BARC type 3b) OR
- Overt source of bleeding with drop in haemoglobin ≥5 g/dL or whole blood or packed red blood cells (RBCs) transfusion ≥4 units† (BARC type 3b)

Major bleeding (BARC type 3a)
- Overt bleeding either associated with a drop in the haemoglobin level of at least 3.0 g/dL or requiring transfusion of two or three units of whole blood/RBC, or causing hospitalisation or permanent injury, or requiring surgery AND
- Does not meet criteria of life-threatening or disabling bleeding

Minor bleeding (BARC type 2 or 3a, depending on the severity)
- Any bleeding worthy of clinical mention (e.g., access-site haematoma) that does not qualify as life-threatening, disabling, or major

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* Refers to VARC bleeding definitions. † Given that one unit of packed RBC typically will raise the haemoglobin concentration by 1 g/dL, an estimated decrease in haemoglobin will be calculated.
BARC: Bleeding Academic Research Consortium; RBC: red blood cell

	Study	Year*	Device	Delivery sheath (ID)	N	Age	STS (LES)	**Endpoints**					
								Def.	Major vascular complication (30-day)	Life-threatening bleeding (30-day)	Major bleeding (30-day)	Stroke (30-day)	Mortality (30-day) (1-year)
Transfemoral	PARTNER IA trial [63]	2007 - 2009	SAPIEN	22 & 24 Fr	240	84[§]	11.7%[§] (29.1%)[§]	-	14.2%	-	10.9%	≈ 3.3%	3.7% 21.3%
	PARTNER IB trial [70]	2007 - 2009	SAPIEN	22 & 24 Fr	179[§]	83[§]	11.2%[§] (26.4%)[§]	-[§]	16.2%[§]	-[§]	16.8%[§]	6.7%[§]	5.0%[§] 30.7%[§]
	PARTNER IA trial and continued access registry [16]	2007 - 2012	SAPIEN	22 & 24 Fr	1,521	84	- -	-	(intraprocedural: 8.3%)	-	(intraprocedural: 7.5%)	(3.6% (time period not reported)	4.5% -
	SOURCE XT registry [13]	2010 - 2011	SAPIEN XT	18 & 19 Fr	1,685	82	8.0% (19.8%)	VARC	7.9%	3.8%	7.7%	3.4%	4.2% 15.0%
	CoreValve ADVANCE study [†]	2010 - 2011	CoreValve	18 Fr	879	81	- 18.4%	VARC	11.2%	4.0%	9.5%	2.9%	4.3% -
	CoreValve US Pivotal extreme risk [71]	2011 - 2012	CoreValve	18 Fr	489[§]	83	10.3% (22.6%)	VARC	8.2%	12.7%	24.9%	4%	8.4% 24.3%
	PARTNER 2A trial [59]	2011 - 2013	SAPIEN XT	18 or 19 Fr	775[§]	82[§]	5.8%[§]	VARC-2	8.5%[§]	6.7%[§]	-[§]	4.2%[§]	3.0% 10.0%

Study	Year*	Valve	Sheath (ID)	N	Age	STS/LES	Def.					
PARTNER 2 SAPIEN 3-high-risk/inoperable [60]	2013 - 2014	SAPIEN 3	14 & 16 Fr eSheath	491	83 **	8.7% ** (-)	VARC-2	5.5%	5.5%	12.3%	1.4%	1.6% 12.3% [61]
PARTNER 2 SAPIEN 3 - intermediate risk [60]	2014	SAPIEN 3	14 & 16 Fr eSheath	953	82 **	5.3% ** (-)	VARC-2	6.3%	3.6%	8.7%	2.5%	1.1% 6.5% [72]
SOURCE 3 Registry [7]	2014 - 2015	SAPIEN 3	14 & 16 Fr eSheath	1,695	82	- (17.8%)	VARC-2	4.3%	4.3%	-	1.3%	1.9% 11.8% [58]
REPRISE III [73]	2014-2015	CoreValve & Evolut R	18 Fr	297	83§	6.9%§	VARC, VARC-2	4.7%	5.1%	6.4%	4.7%	2.7% 13.1%
REPRISE III [73]	2014-2015	Lotus	Lotus introducer sheath Small & large	576	83§	6.7%§	VARC, VARC-2	6.8%	7.1%	5.7%	5.7%	3.1% 11.5%

Supplementary Table 2. Outcomes of transcatheter aortic valve implantation by transfemoral access.
Selected studies reporting baseline characteristics and outcomes adjudicated by independent event committees including at least 300 patients are listed. Age, STS and LES are reported as mean. Endpoint rates are reported with 95% confidence intervals in brackets if available. Reported rates correspond to Kaplan-Meier estimates unless stated otherwise. In case different reports comprise overlapping study populations, the most recent and largest cohort was chosen.
* year of recruitment.
** referring to total TAVI cohort (including a minority of non-transfemoral cases.)
§ referring to intention-to-treat cohort.
† data of transaxillary subcohort as presented at ESC 2012, Munich

Def.: definition; Fr: French; ID: inner diameter; LES: logistic EuroSCORE; N: number; STS-PROM: Society of Thoracic Surgeons Predicted Risk of Mortality; VARC: Valve Academic Research Consortium

	Device system (manufacturer)	CE mark*	Possible access modes	Valve sizes (mm)	Delivery sheath diameter ID (Fr) / OD (mm)	Min. vessel diameter†
Balloon-expandable	SAPIEN (Edwards Lifesciences)	2007	TF	23	22 / 8.4 (Retroflex)	7 mm
				26	24 / 9.2 (Retroflex)	8 mm
		2008	TA (TAo)	23, 26	26 or 33 / - (Ascendra) later 24 Fr / - (Ascendra II)	
	SAPIEN XT (Edwards Lifesciences)	2010	TF (TAx, TC, TCv)	23	16 / - (eSheath) 18 / 7.2 (NovaFlex)	6 mm
				26	18 / - (eSheath) 19 / 7.5 (NovaFlex)	6.5 mm
		2012		29	20 / - (eSheath)	7 mm
		2010	TA, TAo	23, 26	24 or 22 / - (Ascendra II or +)	
		2011	TA, TAo	29	26 / - (Ascendra)	
	SAPIEN 3 (Edwards Lifesciences)	2014	TF (TAx, TC, TCv)	20	$14 / \approx 7.65$§	5 mm
				23, 26	$14 / \approx 7.64$§	5.5 mm
				29	$16 / \approx 8.18$§	6 mm
		2014	TA, TAo	23, 26	18 / - (Certitude sheath)	
				29	21 / - (Certitude sheath)	
Self-	CoreValve (Medtronic)	2007	TF, TAx, TAo (TC, TCv)	23, 26, 29, 31	$18 / \approx 6.7$ (3rd gen.) (first gen.: 25 / -)	6 mm

CoreValve Evolut R (Medtronic)	2014	TF, TAx, TAo (TC, TCv)	23, 26, 29	18 / - OR sheathless ‡: 6	5 mm
			34	20 / - OR sheathless ‡: 6.7	5.5 mm
CoreValve Evolut PRO (Medtronic)	2017	TF, TAx, TAo (TC, TCv)	23, 26, 29	20 / - OR sheathless ‡: 6.7	5.5 mm
Portico (St. Jude Medical)	2012	TF (TAo, TAx, TC, TCv)	23, 25	18 / 6.8 (Ultimum)	6 mm
	2015		27, 29	19 / 7.3 (Ultimum)	6.5 mm
ACURATE TA (Boston Scientific)	2011	TA	23 (S), 25 (M), 27 (L)	delivery catheter ≅ 28 Fr sheath system	
ACURATE neo (Boston Scientific)	2014	TF (TAo, TAx, TC, TCv)	23 (S), 25 (M), 27 (L)	18 / -	6 mm
	2017	TA	23 (S), 25 (M), 27 (L)	19 / ≈ 7.3	
NVT Allegra (NVT GmbH)	2017	TF (TAo, TAx, TC, TCv)	23, 27, 31	18 / -	6 mm
CENTERA (Edwards Lifesciences)	2018	TF, TAx (TAo, TC, TCv)	23, 26, 29	14 (expandable sheath) / -	5 mm

Supplementary Table 3. Currently available transcatheter aortic valve implantation systems and predecessors with CE (Conformité Européenne) mark.

Access modes in brackets constitute possible access routes used at that time but without CE mark approval.
* only earliest year of approval for any of listed access modes reported.
† as recommended by manufacturer.
§ max. expanded eSheath diameter as published by Koehler T. in BioMed Research International. 2015;2015:572681.

‡ outer diameter (mm) if delivered with in-line sheath only.

Manufacturers: Edwards Lifesciences, Irvine, CA, USA; Medtronic, Minneapolis, MN, USA; Boston Scientific (BSC), Marlborough, MA, USA; St. Jude Medical, St. Paul, MN, USA (part of Abbott Vascular, Abbott Park, IL, USA); NVT GmbH, Hechingen, Germany.

Fr: French; gen.: generation; ID: inner diameter; Min.: minimum; OD: outer diameter; TA: transapical; TAo: transaortic (direct aortic); TAx: transaxillary; TC: transcarotid; TCv: transcaval