That doubting pleases me no less than knowing!
Inferno, Canto XI
Divine Comedy

1. INTRODUCTION
Transcatheater aortic valve implantation (TAVI) has become in recent years a safe and efficient treatment for most patients with symptomatic severe aortic stenosis, regardless of the risk group to which they belong. The transfemoral access (TF) has been largely responsible for this success and has become the “gold standard”, in addition to being the most frequently used.

In multiple analyses, alternative transapical (TA) and transaortic (TAo), or “classic transthoracic” accesses have been associated with a significant increase in adverse events and mortality compared to the TF or extrathoracic accesses (1-4). This has justified guideline recommendations to consider surgical aortic valve replacement (SAVR) in the absence of adequate femoral arteries. Among the latest studies that have shown the superiority and non-inferiority of TAVI with respect to SAVR in patients with low surgical risk, the use of the TF access represented an inclusion criterion in the PARTNER 3 study and 99% of the accesses in the EVOUT Low Risk study. (5, 6)

Technological advances and the growing experience of operators have allowed TF-TAVI to be globally responsible for around 90% of TAVI, in addition to becoming a minimally invasive procedure with the possibility of discharge on the following day. (7) In the remaining 10% of patients, alternative extrathoracic accesses have been used with increasing frequency in recent years, which may be preferable to surgery or even compete with the TF access in high-risk patients. (8, 9)

2. TRANSAXILLARY/TRANS-SUBCLAVIAN ACCESS
Introduction
In contrast with the femoral artery, the axillary/subclavian artery is relatively resistant to atherosclerosis, less tortuous, compressible, and its proximity to the heart allows a shorter and more direct route towards the aortic valve. (10) On the other hand, it is generally smaller in diameter, has a less resistant histological structure, and is located near the brachial plexus and lung. (11) The pre-procedure evaluation is performed through computed tomography (CT), and the standard field of vision -when a transaxillary access (TAX) is planned in advance- is extended with a subsequent specific study or through Doppler ultrasound or angiography. Once the feasibility of the access has been determined (diameter, tortuosity, angulation, calcifications), a direct dissection and puncture is performed either of the left or right artery, trying to avoid the side corresponding to the patient’s skilled hand and eventual bypass, although there is no solid evidence to recommend one over the other. The ideal puncture site is in the first segment, which is usually free of important collaterals (Figure 1). It can be performed percutaneously, preferably by ultrasound-guided puncture, with ProGlide-type closure devices (Abbott Vascular) and ensuring access with a protection guide. (12, 13) (Figure 2). The implantation does not differ with respect to the other accesses (Video 1). Some operators prefer to use a balloon to facilitate access closure after the procedure (“Dry closure”) (Figure 3).

Evidence
In a retrospective study of the UK TAVI registry in the United Kingdom (year 2015) that included 3,962 patients (TF, n=2,828; TAo, n=185; TA, n=761 and TAX, n=188), the survival at one year was similar between TF (84.6 ± 0.7%) and TAX (80.5 ± 3%, p = 0.27) accesses; and significantly lower for TAVI with TA (74.7 ± 1.6%, p <0.001) and TAo (75.2 ± 3.3%, p <0.001) accesses. The Cox regression analysis showed that there were no differences in the 2-year survival between TAX and TF accesses (HR: 1.22; 95% CI: 0.88-1.70; p=0.24), but there were differences (with worse results) for TA (HR: 1.74; 95% CI: 1.43-2.11; p <0.001) and TAo accesses (HR: 1.55; 95% CI: 1.13-2.14 ; p <0.01). (14)
In the case of self-expanding valves, a retrospective study that included patients from the CoreValve United States Pivotal Trial Program performed a propensity score matching of 202 patients treated with TAVI-TAx (out of a total of 2,687 patients) and patients treated by TF access. There were no significant differences in any of the results at 30 days, with a trend towards less need for pacemaker in the TAx group (19.5% vs. 26.4%, p = 0.090). Death or infarction was observed in 12 patients in the TAx group and 14 patients in the TF group (p = 0.685), and there was lower postdilation rate (17.9% vs. 26.7%, p = 0.03) and greater use of general anesthesia (99.0% vs. 89.6%, p < 0.001) in TAx cases. There were no differences in the duration (57.8 ± 45.3 vs. 57.5 ± 32.1 min, p = 0.94) or in the success (VARC-I) (p = 0.89) of the procedure. Survival curves did not show significant differences at one year. (15)

A 2018 meta-analysis including 6 studies and a total of 4,504 patients (3,886 with TF and 618 with TAx) showed that the TAx group exhibited a greater logistic EuroSCORE and higher prevalence of coronary and peripheral disease. No significant differences were observed in 30-day mortality (OR: 1.37; 95% CI: 0.85-2.21; p = 0.20), the success of the procedure, the rate of stroke at 30 days, new pacemaker implantation, major vascular complications or new dialysis. Moreover, there were no differences in 1-year mortality. (16)

In one of the largest studies published to date involving patients from the Society of Thoracic Surgeons/American College of Cardiology TVT (Transcatheter Valve Therapy), the results obtained using TAx access exclusively with the SAPIEN 3 valve (Edwards Lifesciences, Irvine, California) were analyzed. Among a total of 3,628 alternative accesses (5.7% of the total registry), 1,249 were TAx (34.4% of the total alternative accesses). The success of the device was 97.3% and the rate of major cardiovascular complications was 2.5%. After propensity score matching, it was observed that, compared with TA and TAo accesses, the TAx access had lower 30-day mortality (5.3% vs. 8.4%; p < 0.01), shorter intensive care unit and in-hospital stay and increase in the rate of stroke (6.3% vs. 3.1%; p < 0.05). There was also a change in trend over time regarding the choice of alternative access: TAx went from 20% in the third quarter of 2015 to 49% in the fourth quarter of 2017 (p < 0.001 for trend) with a concomitant reduction in TA and T Ao accesses over the same period, from 61.9% to 35.3% (p < 0.001 for trend). The mean number of cases per center was 2 and no differences were observed between percutaneous or surgical accesses. (3)

In a recently published single center study that included 200 consecutive patients undergoing Tax-TAVI, vascular complications associated with access and predictive variables were analyzed. In 18.5% of cases, vascular complications were observed (37 pa-
of which 36 were minor complications, and 1 was a rupture of the subclavian artery ostium, with subsequent death of the patient. Minor complications included dissection (n=32; 16%), stenosis (n=3; 1.5%), and perforation/rupture (n = 2; 1.0%). Fourteen patients required a stent (7%) and 3 patients had to undergo surgery (1.5%). None of the patients reported hand claudication or loss of function during follow-up. Among baseline characteristics, female sex (aOR: 3.88; 95% CI: 1.48-10.14; p=0.006) and age (aOR: 1.08; 95% CI: 1.01-1.16; p=0.034) were associated with vascular complications, as well as the ratio of the introducer area / artery area equal to or greater than 1.63 (OR: 3.95, 95% CI: 1.29-12.12, p = 0.016), although with an area under the curve of 0.67. Introducer or artery diameters were not associated with complications. (17)

Conclusion
Observational studies and meta-analyses suggest that TAx and TF accesses offer similar results, despite the worse baseline characteristics of the population. The increase in the incidence of stroke in the TVT registry is worrying and it is difficult to establish whether it is due to the access, the device, the small volume of procedures or the baseline characteristics of patients. This phenomenon was not observed in the FRANCE TAVI registry (see “Transcarotid access” section). To add variables, the possibility of using Sentinel type embolic protection devices (ideal, since they cover the right subclavian and left carotid arteries, leaving only the necessary access free) and the simplification of the procedure with the arrival of the new Sapien 3 Ultra (valve premounted on the balloon) are included. Another point that calls the attention of the TVT registry is the low rate of vascular complications observed (probably due to underreporting or to the lack of central event adjudication), with the apparent absence of a “learning curve”. The latter contrasts with what many studies report and with guideline recommendations. (18)

Despite the apparent increase in stroke, there seems to be no doubt about the superiority of TAx with respect to classic transthoracic accesses. It still remains to be demonstrated whether the increasing confidence that this access has gained will not increase TAx cases in patients with “non-ideal” femoral arteries, in whom TF access may increase the frequency of vascular complications. Within a TAVI program, TAx access should be incorporated progressively and, preferably, supervised, to minimize complications in the initial stages.

3- TRANSCAROTID ACCESS

Introduction
After the first description in 2010, various studies have shown the feasibility and safety of transcarotid access (TCa), and have even managed to position it as the one preferred by some groups. (19) The procedure consists of the common carotid artery dissection through a small incision (2-3 cm), preferably the left one due to its greater coaxiality, and subsequent direct puncture. The proximity to the aortic valve facilitates the maneuver of the delivery system and the ensuing implantation. To avoid embolic complications and cases of cerebral hypoperfusion during the procedure, a prior tomographic evaluation is essential to establish the compatibility of the aortic arch, the presence of a carotid artery with diameter greater than 6-7 mm, without tortuosities, significant atherosclerosis (>30%), or severe ostial calcifications, which also evaluates the Willis polygon and the eventual col-

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<th>Advantages</th>
<th>Disadvantages</th>
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<td>Compressible axillary artery, proximity to the heart, not usually affected by atherosclerosis.</td>
<td>Technically more demanding: room layout, operators unfamiliar with axillary artery anatomy. Percutaneous closure: cost, echo-guided puncture, protection guide, “dry closure”.</td>
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<tr>
<td>Minimalist approach: local anesthesia/conscious sedation, percutaneous closure, early ambulation, early discharge</td>
<td>Potentially more serious complications: proximity to the brachial plexus.</td>
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<td>Percutaneous resolution of complications.</td>
<td>Delivery and introducer devices developed for TF access (much of the length of the introducer remains outside the artery).</td>
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<td>Anatomical analysis easily incorporated into the pre-TAVI CT protocol</td>
<td>Less space to mount the valve (not for self-expanding and S3 Ultra). Homolateral access to a bypass is not recommended.</td>
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Questions
Why does stroke increase in the TVT registry?
Do self-expanding valves offer better results?
What will be the role of embolic protection devices?
Is it worth to use percutaneous closure (cost and greater technical difficulty vs. 2 cm incision)?
When should anticoagulation be started?
lateral circulation. During the procedure, perfusion can be monitored by non-invasive brain oximetry. For this access, there are currently no percutaneous alternatives, although it can be performed using a minimalist approach with locoregional anesthesia and/or sedation.

Evidence

In 2018, a multicenter observational study was published (3 tertiary centers in Canada and France) in patients using alternative accesses, including 101 TCa-TAVI. All procedures were performed under general anesthesia and 97% through the left internal carotid artery. A similar 30-day mortality (2.1% vs. 4.6%; P = 0.37), stroke (2.1% vs. 3.5%; P = 0.67), frequency of new pacemaker implantation and major vascular complications was observed compared with 228 procedures performed by TA and TAo access. Also, TCa-TAVI was associated with a lower rate of atrial fibrillation (3.2% vs. 19.0%; P = 0.002), major or life-threatening bleeding (4.3% vs. 19.9%; P = 0.002), acute kidney injury (0% vs. 12.1%; P = 0.002), and shorter hospital stay (6 days vs. 8 days; P < 0.001). (20)

A recently published retrospective registry that included 50 TCa-TAVI (out of a total of 317 procedures) performed over a 14-month period in a hospital in France showed that, unlike the previous study, 64% of cases were performed under locoregional anesthesia and 74% of the secondary accesses were via the right radial access, which, together with the relative number of TCa cases, shows the clear preference of the operators for this access. Another difference was the use of balloon expandable valves in 78% of cases. All procedures, except one, was considered successful (in one patient sufficient stability with the support guide was not achieved). In the short-term follow-up, there were no deaths; however, a stroke and transient ischemic accident were observed. With regards to bleeding, one life-threatening incident was observed (hemopericardium that required pericardiocentesis), 2 major and 5 minor bleedings, in addition to 5 minor and no major vascular complications (21)

An observational study that included patients from the FRANCE-TAVI registry analyzed results 30 days after TF access and compared them with those of “non-femoral” TAx and TCa accesses. Among 21,611 procedures, 1,616 were performed through alternative extrathoracic accesses; 43.5% TAx and 56.5% TCa. A propensity score matching was performed including 1,613 patients per group. As we have seen before, patients in the TAx/TCa group presented a higher EuroSCORE (19.95 vs. 16.99; P < 0.001) and more comorbidities. Self-expanding valves were used in two thirds of these patients. Results showed no differences in mortality (3.97% vs. 2.91% in the TF group; p = 0.211) or stroke (3.35% vs. 2.17%, p = 0.156). There were no differences in any of the complications evaluated according to the access route in the groups compared, except for a smaller number of major vascular complications (0.68% vs. 1.36%, p = 0.032) and of unprogrammed vascular repairs (3.10% vs. 6.70%, p < 0.001) in the TAx/TCa group. In the multivariate analysis, TF access was an independent predictor of major vascular complications, even after adjusting for type of prosthesis and period of time. In the direct comparison between TAx and TCa accesses, no differences in stroke rates were observed. Considering the overall duration of the study (5 years), a significant increase in the cases performed by TF access (79.95% in 2013-2015 versus 89.12% in 2016-2017) and a significant reduction in transthoracic accesses (from 11.99% to 3.76%) was observed, with TAx/TCa accesses stable over time (7.66% to 6.62%). (4)

In a recent comparison between TCa (n=374) and TAx (n=128) accesses in 4 centers in France where a 1:2 comparison of TAx / TCa was performed, no significant differences were observed in mortality at one month (TAX 5.5% vs. TCA 4.5%; OR: 1.23; 95% CI: 0.40-3.70) or in stroke/TIA (3.2% vs. 6.8%; OR: 0.52; 95% CI: 0.14-1.84). Minor bleeding (2.7% vs. 9.3%; OR: 0.26; 95% CI: 0.07-0.92) and bruising in the access site were more frequent in the TCa group (3.6% vs. 10.3%; OR: 0.034; 95% CI: 0.09-0.92). No differences in clinical efficacy and safety results were observed between accesses. (21)

Conclusion

Despite the mistrust that may arise in operators when manipulating the carotid artery for its use as access route, the precise pre-procedure evaluation, the operators’ experience, and the joint work with vascular surgeons have achieved results comparable to those of the TF access. Regarding the external validity of these data, it should be noted that the high volume of French operators, as a result of the concentration of cases in a few centers, may not be representative of other systems, and, if we consider the volume/results relationship that exists for TF-TAVI, it is to be expected that in a more complex procedure performed less frequently, this relationship is even more evident. (18, 23)

Finally, it is reassuring that FRANCE TAVI has not shown an increase in strokes as in the case of TVT with TAx. Perhaps future comparisons between these two large registries can establish with greater precision which variables are associated with this outcome.

4- TRANSCAVA ACCESS

Introduction

The newest alternative access is the transcaval (TCv) access. It consists of a primary femoral venous access with subsequent crossover through an assisted puncture from the vena cava into the aorta using a guiding catheter, a microwire, and a guidewire connected to an electrosurgical unit. Subsequently, the guidewire is captured from a secondary arterial access, the exchange is made with a support guidewire and the introducer sheath is positioned in the aorta. From a
theoretical point of view, since the pressure in the retroperitoneal space exceeds that of the inferior vena cava, the blood that eventually leaks towards it from the aorta should return to the venous system. Identifying a healthy puncture site is essential to avoid major complications. Once the procedure is finished, the created communication is closed with an “Amplatzer” type device.

Evidence
The initial human experience with TCv access was published by Greenbaum et al. in 2014 and included a total of 19 patients. Access and closure were effective in all cases and they successfully performed TAVI in 17 patients (one ventricular valve embolization). Mean STS score was 7.8±3.8%. Six patients experienced major vascular complications with surgical resolution in 2 of them, and 79% required transfusions. No deaths associated with access route were observed. At an average follow-up of 111 days, no complications attributable to access were observed. (24)

The following prospective observational study by Greenbaum preceded by exchanges with heart surgeons (25, 26) was published in 2017. This was a multicenter study including 100 patients. Mean STS score was 9.7±6.3%. In one patient it was not possible to cross the aorta with the guidewire (a complicated TF access attempt was subsequently made with iliac rupture) and in one patient the implantation of a coated stent was required in the aorta. There were no deaths associated with the access. In-hospital and 30-day survival was 96% and 92%, respectively. Life-threatening bleeding (VARC-2) was 7% and vascular complications associated with the access were 13%. (27)

In a recently feasibility and safety study published in EuroIntervention, which included 50 patients not candidates for TF/TAx-TAVI from 5 extensively experienced European centers, it was observed that TCv access was feasible in 49 of 50 cases, with 94% success of the device. Median STS score was 6.1%, and 86% of the cases were performed under general anesthesia. One of the patients suffered an aortic rupture during the passage of the introducer, with subsequent hemorrhagic shock and death. Device closure of the puncture site was successful in all cases (complete closure in 46% and minor leaks in 52%). One of the patients had to undergo a subsequent closure of the defect with a covered aortic stent, due to a drop in the hemoglobin level on the first day after TAVI. Life-threatening bleeding (VARC-2) was 4% and vascular complications greater than 10%. (28)

Conclusions
Although initial experiences show acceptable adverse event rates in relation to the risk of the included population, the greater technical difficulty, the higher cost and the potential complications probably limit the use of the TCv access to high-risk patients who do not have other possible accesses. If we consider the significant increase in cases that can be carried out by TF route and the growth of the other alternative accesses, we estimate that this access will become infrequent. It is interesting to mention that in the most recently published work, patients not candidates for TF or TAx access were included, which shows, in some way, the positioning of the latter as an alternative access of choice. Until further evidence is available, it is difficult to establish the role that TCv access will play in the future, and most TAVI centers will likely choose to improve others in the first instance.

5. CONCLUSIONS
Although a randomized study comparing different alternative accesses seems distant, the available evidence is uniform and supports the trend in favor of extrathoracic accesses, which are likely to continue increasing until dominating the “non-femoral” group of TAVI. Consequently, the classic transthoracic accesses will be relegated to a small and selected group of patients. Adding up all the recent evidence, the recommendation in favor of SAVR in non-candidates for TF access may

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<th>Advantages</th>
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<tr>
<td>Superficial and easily dissected artery.</td>
<td>More demanding pre-procedure evaluation.</td>
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<td>Versus TAx: distance from the brachial plexus, does not involve eventual mammary artery bypass</td>
<td>Impossibility of percutaneous closure (need for an experienced vascular surgeon).</td>
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<tr>
<td>Possible minimalist approach: local anesthesia/conscious sedation, early ambulation, early discharge.</td>
<td>Potentially more severe complications (proximity to vagus nerve, jugular vein, respiratory tract)</td>
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<td>The most “coaxial” of accesses</td>
<td>It prevents the use of embolic protection devices.</td>
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<td></td>
<td>Less space to mount the valve (advantage for self-expanding valves and S3 Ultra).</td>
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<td>Increased operator discomfort/more radiation exposure.</td>
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Questions
Could the development and use of specific devices improve results?
be modified in the new guidelines, especially in high-intermediate risk groups. Until then, during this expansion phase and as experience increases at different speeds, we will observe some variability in the adoption of alternative accesses between countries.

One of the challenges of future heart teams will be to individualize patients with high-risk characteristics for TF access and direct them to the alternative access that best suits their anatomy, the experience of the team and the preferences of the center, as well as previous results. The interrelationship between operators, proctoring and training programs will be essential to overcome without complications technical difficulties in the initial stages.

Conflicts of interest
None declared.
(See authors’ conflicts of interest forms on the website/Supplementary material)

Ethical approval
Not applicable.

REFERENCES