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Medicine Master Thesis

Computed tomography angiography for the diagnosis of coronary artery disease among patients undergoing transcatheter aortic valve implantation

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Table of contents

Abstract

Background

Coronary artery disease (CAD) is frequently seen in patients suffering from severe aortic valve stenosis (AS), as both pathologies share the same pathophysiology. In a transcatheter aortic valve implantation (TAVI) work-up, patients beneficiate from both computed tomography angiography (CTA) and invasive coronary angiography (ICA). Some studies evaluated the performance of CTA to diagnose CAD among patients undergoing TAVI and showed interesting results[1-4]. Nevertheless, data remain scarce and this diagnostic method is not validated in this population. In this context, we thought to evaluate the diagnostic performance of CTA to diagnose CAD among patients selected for TAVI.

Methods

A total of 199 patients that had a TAVI in the Lausanne University Hospital between the 1st of June 2013 and the 31st of December 2017 were retrospectively included. Exclusion criteria were coronary artery bypass graft (CABG) prior to CTA and unavailable CTA images. Finally, 127 patients were included. Two independent radiologists – blinded for ICA report – were asked to read the CTA of these patients and to indicate the presence of ≥50% and ≥70% stenosis in the 4 main coronary vessels. Their evaluation was then compared with ICA reports and analyses were performed at vessel and patient levels.

Results

A total of 342 vessels were analyzable. Based on ICA, significant CAD (at least 1 ≥50% stenosis) was present in 49 (38.6%) patients. Severe CAD (≥70% stenosis) was found in 29 (22.8%) patients. Sensitivity, specificity, positive predictive value, negative predictive value and accuracy of CTA to diagnose significant CAD were 81.1%, 87.9%, 44.8%, 97.5% and 87.1% at vessel level using the cut-off of 50% and 42.8%, 97.8%, 56.3%, 96.3% and 94.4% for severe CAD, using the cut-off of 70%. At patient level, sensitivity, specificity, positive and negative predictive values were respectively 84.6%, 64.6%, 56.4% and 88.6% for significant CAD.

Conclusion

Pre-TAVI CTA shows good performance to rule out significant and severe CAD and could be used as a gatekeeper for ICA. Positive findings on CTA should be confirmed with ICA given the low positive predictive value.

Keywords: computed tomography angiography, coronary artery disease, transcatheter aortic valve implantation, aortic valve stenosis.

Background

Aortic valve stenosis and coronary artery disease

Aortic valve stenosis (AS) is currently the most frequent form of valvular heart disease in European countries[5]. In population-based studies, the prevalence of at least moderate AS is estimated at 2.8% among >75 years old people in developed countries and is bound to increase in the next years with the constant aging of the population[6]. The prognosis of a severe AS becomes unfortunately really poor as soon as the patient becomes symptomatic, with a mortality rate of about 25% per year[7]. A valve replacement must therefore quickly be considered. Currently, there are two different ways to change an aortic valve: surgical aortic valve replacement (SAVR) and transcatheter aortic valve replacement (TAVR), also known as transcatheter aortic valve implantation (TAVI). Initially, as it was recommended in the guidelines of the European Society of Cardiology of 2012, TAVI procedure was only performed as an alternative to SAVR in patients who had been assessed as inoperable by a Heart Team or if their surgical risk was considered very high[8]. As of today, TAVI tend to take a more important place in the treatment of severe aortic valve stenosis. As a matter of proof, some recent studies showed that it was not inferior to SAVR for intermediate risk patients in terms of 2 years mortality and stroke[9, 10]. In the most recently published (2017) European guidelines for the management of valvular heart disease, these indications remain present and other criteria such as an age of more than 75 years old are now criteria in favor of a percutaneous replacement[11].

It is not uncommon to find concomitant coronary artery disease (CAD) in patients suffering from severe AS, as both pathologies share the same pathophysiology and risk factors, which are mostly age, male sex, tobacco, arterial hypertension, diabetes mellitus and hyperlipidemia[12, 13]. Indeed, the early lesion of degenerative aortic stenosis is an inflammatory process relatively similar to atherosclerosis[14]. Therefore, it is even more common to find CAD among patients who have been selected for a TAVI procedure, as they are usually older and tend to have more comorbidities than patients undergoing SAVR. The exact prevalence of CAD in patients undergoing TAVI is not known as there are important disparities in the definition of CAD among the different studies and variability in the assessment of coronary stenoses by angiography, but it stands somewhere between 34 and 75%[15]. As a matter of consequence, it is important to search actively for coronary artery disease in patients suffering from severe aortic valve stenosis before any intervention as both pathologies are closely related.

Computed tomography angiography

In a classical TAVI workup, patients benefit from a computed tomography angiography (CTA) to evaluate the dimensions of the aorta, the aortic annulus, and the peripheral vascular accesses and from an invasive coronary angiography (ICA), to search for CAD[16]. The CTA performed in a TAVI workup is different from a coronary CTA, whose main and only goal is to show precise images of the coronary arteries. A coronary CTA requires most of the time a heart rate control with beta-blockers to reach an ideal heart rate of less than 65 bpm, and vessel dilatation with nitroglycerin[17, 18]. None of those specific dispositions figures in the pre-TAVI CTA protocol, as they are usually contra-indicated in patients suffering from severe aortic valve stenosis as they don't tolerate well a diminution in preload.

The comparison between coronary CTA and ICA to diagnose CAD was realized in multiple studies and showed a very good negative predictive value, from 96 to 100%[19]. Coronary CTA is recommended to rule out CAD in patients with low to intermediate pre-test probabilities[19, 20]. On the other hand, stenoses visualized on coronary CTA need to be confirmed with ICA as the positive predictive value of CTA is ranged from 69 to 93%[19]. Patients selected for TAVI tend to have a significantly higher probability of CAD and heavier coronary calcifications than other patients. Even though those calcifications are known to cause artifacts on coronary images, the performance of coronary CTA with newer CT systems was proven to remain high in case of severe coronary calcifications[21, 22]. Nevertheless, the CT-scan realized in a TAVI workup is still not used to diagnose CAD and an ICA is systematically performed. Ruling out CAD with CTA could minimize the global cost of a TAVI procedure and reduce the total contrast product volume injected (which is clearly beneficial in a population with frequently impaired renal function). It could also have a positive effect in term of morbidity and mortality, as ICA is still an invasive procedure with possible catheter-related complications.

Some studies evaluated the performance of CTA to diagnose CAD among patients undergoing TAVI and showed interesting results[1-4]. Nevertheless, it is not yet validated. In this context, we thought to evaluate the diagnostic performance of CTA to diagnose CAD among patients selected for TAVI.

Methods

Study design and population

This is a retrospective study to evaluate the performance of computed tomography angiography in the diagnosis of coronary artery disease in patients undergoing transcatheter aortic valve implantation in the Lausanne University Center Hospital from the 1st of June 2013 to the 31st of December 2017. To meet our inclusion criteria, patients also had to give their written consent to be included in our registry.

CTA protocol and analysis

CT-scans were all performed using at least a 64-row detector CT-scanner. Retrospective ECG-gating was used for coronary CTA. No heart rate control or vasodilatation were used prior to the procedure.

CTA images were retrospectively read by two radiology residents experienced in cardiovascular CT imaging. They were blinded from ICA images and results. 15% of images were randomly selected and read by both of them separately to determine the inter-observer variability using the κ of Cohen test. They evaluated the four main coronary arteries of each patient (right coronary artery, left main artery, left circumflex artery and left anterior descending artery), which makes a total of 508 vessels analyzed. Firstly, the quality of each vessel was qualified as optimal, suboptimal or unanalyzable in term of delineation between lumen and wall of the artery, filling with contrast material and opacification quality. Then, CAD analysis was realized on vessels whose quality was rated as optimal or suboptimal. Therefore, lumen diameter reductions were searched in those four main arteries and the following classification was applied on all of them: no significant CAD (0-49% lumen diameter reduction), moderate CAD (50-69% lumen diameter reduction), severe CAD (70-99% lumen diameter reduction or occlusion). If there was more than one stenosis on a vessel, only the most severe one was taken into account. Arteries were analyzed until a distal limiting diameter of 2.5mm, as stenoses present further wouldn't have any clinical relevance. The Agatston Calcium Score was also calculated in the coronary arteries to give us an idea of the amount of calcium present in the arteries of our patients.

ICA protocol and analysis

Every patient beneficiated from an ICA in accordance with the usual procedure of our institution. All standard views were obtained. The ICA images were retrospectively read by an experienced interventional cardiologist and/or a student in master thesis under supervision. Both were blinded to CTA images and results. A CAD visual analysis was performed in each vessel using the same classification as for the CTA analysis. ICA images were also read until a distal limiting diameter of 2.5mm.

Statistical analysis

Statistical analysis was carried out using SPSS 24.0 software (SPSS Inc., Chicago, Illinois). Clinical characteristics of the patients were gathered from a database created and completed by the cardiology department of the Lausanne University Hospital for the SWISS TAVI registry. The SWISS TAVI Registry is a national, multi-center, prospective cohort study collecting clinical characteristics of patients undergoing transcatheter aortic valve implantation (TAVI) in Switzerland. The study was approved by the ethic committee of the Bern University Center. Continuous variables were expressed as means ± standard deviation or medians (P25; P75) depending on their distribution while categorical variables were expressed as frequencies (percentage). The inter-observer variability was calculated using the κ of Cohen test, for the quality assessment and for the diagnosis of significant CAD at vessel level.

Using ICA as gold standard, the performance of CTA to detect CAD among our patients was evaluated in terms of sensitivity (SN), specificity (SP), positive predictive value (PPV), negative predictive value (NPV) and accuracy (ACC). It was expressed as percentage. We decided to use two different cut-offs to evaluate this performance, as they are the most commonly used in the literature: ≥50% lumen diameter reduction, which corresponds to significant CAD and ≥70% lumen diameter reduction, which corresponds to severe CAD. We conducted an analysis at vessel level. Subgroup analyses based on quality were made at vessel level with a subgroup with vessels presenting an optimal quality on CTA and another one with those presenting a suboptimal quality on CTA images. We also made analyses at patient level, calculating the capacity of CTA to exclude or to diagnose CAD. A patient was considered positive for CAD when at least one vessel showed CAD. We also used two different cut-offs: ≥50% lumen diameter reduction for significant CAD and ≥70% lumen diameter reduction for severe CAD.

Results

Patients characteristics

199 patients met our inclusion criteria. A part of those patients had the whole or part of the TAVI workup in a peripheral hospital and the CTA or/and ICA images of 44 of them were not available for analysis. We also decided to exclude 28 patients that had a coronary artery bypass graft prior to the TAVI workup. The study was therefore realized on a total of 127 patients (**Figure 1**).

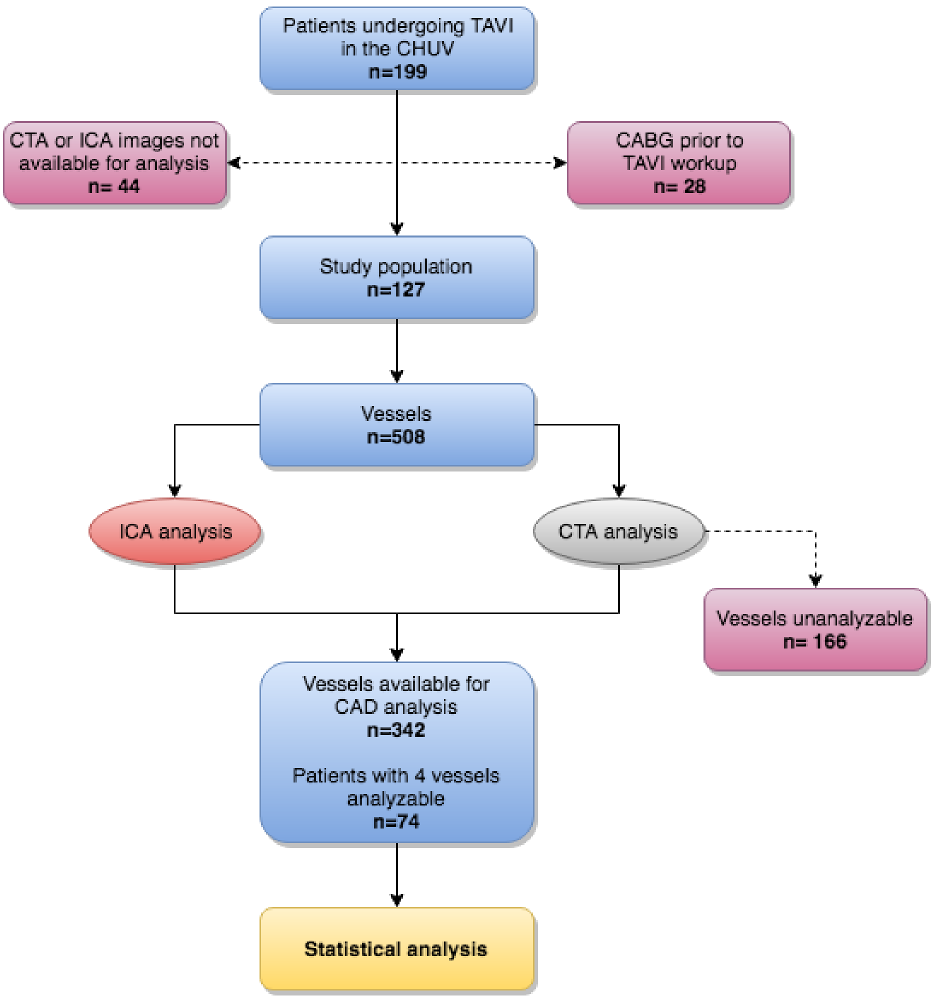

Figure 1. Flowchart of the study design

Characteristics of patients included in this study are summarized in **Table 1**. Mean age was 82.3 years ±7.3. Dyslipidemia and arterial hypertension, which are two important risk factors for AS, were present among the majority of patients included in the study, with prevalence of respectively 69 (54.3%) and 98 (77.2%). The median value of estimated glomerular filtration rate (calculated with the Cockroft and Gault formula) was 43 ml/min/1.73m^2 (36; 58). There were 21 patients with a history of percutaneous coronary intervention and the median mortality risk after a cardiac intervention estimated with the EuroSCORE II was 3.7% (2.3; 5.4). The median Agatston Calcium Score was 703 (195; 1665) but was calculated only among 83 (65.4%) of patients. It could not be calculated in 21 (16.5%) patients because of an important noise, that the software misinterprets as calcium and in 23 (18.1%) patients because the dedicated native sequence was not available. Based on ICA analysis, 49 (38.6%) of patients were suffering from significant CAD and 29 (22.8%) of them had at least one severe stenosis (≥70%). A total of 508 vessels were analyzed and a significant stenosis was found in 67 of them.

Patients characteristics (n=127)	
Variable	*Result*
Age (years)	82.3 ±7.3
Male	49 (38.6%)
BMI (kg/m2)	26.5 ±5.1
Dyslipidemia	69 (54.3%)
Arterial hypertension	98 (77.2%)
Diabetes mellitus	36 (28.3%)
COPD	15 (11.8%)
History of PCI	21 (16.5%)
eGFR (ml/min/1.73m)	43 (36; 58)
EuroSCORE II (%)[1]	3.7 (2.3; 5.4)
Agatston Calcium Score	703 (195; 1665)
Coronary artery disease	49 (38.6%)
1 vessel disease	33 (26%)
2 vessels disease	14 (10.9%)
3 vessels disease	2 (1.6%)

Table 1. BMI body mass index, COPD chronic obstructive pulmonary disease, eGFR estimated glomerular filtration rate, PCI percutaneous coronary intervention.

Age and BMI are expressed in mean ± standard deviation as they are normally distributed according to Kolmogorov-Smirnof. eGFR, EuroSCORE II and Agatston Calcium Score are expressed in median (P25; P75) as they are not normally distributed according to Kolmogorov-Smirnof. Categorical variables are expressed in number (percentage).

[1] Mean Euroscore II was calculated among 101 (79.5%) patients. Missing data could not be completed in the former TAVI database.

[2] Mean Agatston Calcium Score was calculated among 83 (65.4%) patients. The score was sometimes uncalculable because of important noise (that the software misinterpret as calcium) or because the dedicated native sequence was not performed).

CTA performance

A κ of 0.51 was found for the quality assessment, which corresponds to a moderate inter-observer agreement. For the diagnosis of significant CAD at vessel level, κ was calculated at 0.61, which corresponds to a good inter-observer agreement. Both agreements were significant with a p-value <0.05.

First of all, as mentioned in methods, the CTA images quality of each artery was assessed using a 3 items scale: optimal, suboptimal or unanalyzable. 166 vessels (32.7%) were rated as unanalyzable on CTA and were excluded from the CAD analysis, meaning that the analysis for CAD was performed on 342 vessels. The quality of images of the LM were the most optimal, with 63 (49.6%) vessels rated as optimal, which is not surprising, as this vessel is much shorter than the other ones. On 127 patients included in the study, the CTA of 74 patients (58.3%) had 4 coronary vessels analyzable, 9 (7.1%) had 3 vessels analyzable, 8 (6.3%) had 2 vessels analyzable, 3 (2.4%) patients had only one vessel analyzable and for 33 (25.8%) of them, all four arteries were unanalyzable. CTA images quality results are visible in detail on **Table 2** and represented in **Figure 2.**

CTA images quality results

Vessel	*Quality (n (%))*		
	Optimal	*Suboptimal*	*Unanalyzable*
RCA (n=127)	29 (22.8%)	52 (40.9%)	46 (36.2%)
LM (n=127)	63 (49.6%)	29 (22.7%)	35 (27.3%)
LCX (n=127)	24 (18.8%)	59 (22.8%)	44 (34.6%)
LAD (n=127)	25 (19.7%)	61 (48%)	41 (32.3%)
All Vessels (n=508)	141 (27.8%)	201 (39.6%)	166 (32.7%)

Table 2. LAD left anterior descending artery, LCX left circumflex artery, LM left main artery, RCA right coronary artery.

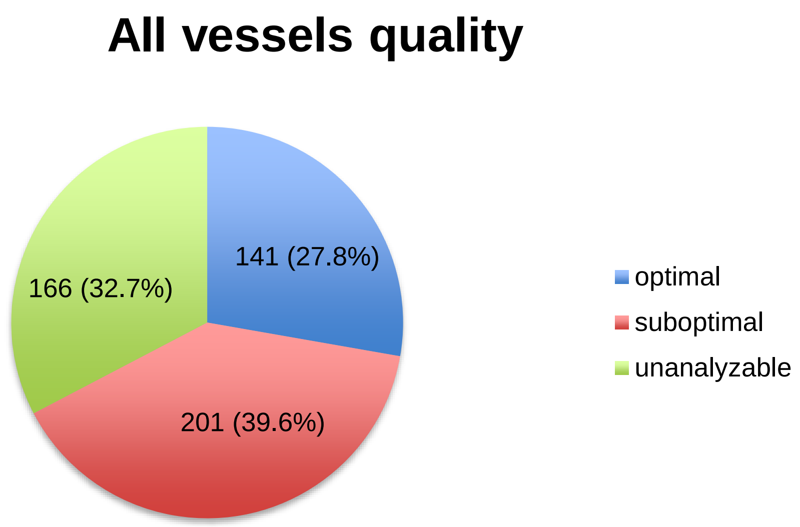

Figure 2. Repartition of the vessels according to the quality of their CTA images

The CTA performance to diagnose CAD was evaluated on 342 vessels on a per vessel analysis. To diagnose significant CAD at all vessels level, SN was 81.1%, SP was 87.9%, PPV was 44.8%, NPV was 97.5% and ACC was 87.1%. Analysis was also done for each vessel separately, with a total of 81 RCA, 92 LM, 83 LCX and 86 LAD analyzed. The results can be seen on **Table 3**. The performance of CTA was also evaluated to diagnose severe CAD (cut-off for diameter reduction ≥70%). Results figure in **Table 4**.

We also conducted a subgroup analysis at vessel level depending on the quality of images on CTA. The performance of CTA was analyzed in a group of vessels whose CTA images quality was rated as optimal and in another group of vessels whose CTA images quality was rated as suboptimal. We found a slightly better performance for images of optimal quality to rule out CAD, with a NPV of 99.2% versus 95.9% in favor of optimal quality vessels for significant stenoses (≥50%) and 98.5% versus 94.7%, also in favor of optimal quality vessels, for severe stenoses (≥70%). A least one significant stenosis was found in 16.4% of suboptimal quality vessels but only in 2.8% of optimal quality vessels. Detailed results can be seen on **Table 5**, **Table 6** and **Figure 3**.

CTA performance to diagnose significant CAD (≥50% diameter reduction) among TAVI patients

	N	*TP (n)*	*TN (n)*	*FP (n)*	*FN (n)*	*Sensitivity (%)*	*Specificity (%)*	*PPV (%)*	*NPV (%)*	*Accuracy (%)*
RCA	81	9	67	5	0	100	93.1	64.3	100	93.8
LM	92	1	86	5	0	100	94.5	16.7	100	94.6
LCX	83	3	67	11	2	60	85.9	26.7	97.1	84.3
LAD	86	17	48	16	5	73.9	75	51.5	90.6	74.7
All vessels	342	30	268	37	7	81.1	87.9	44.8	97.5	87.1

Table 3. FN false negative, FP false positive, LAD left anterior descending artery, LCX left circumflex artery, LM left main artery, number NPV negative predictive value, PPV positive predictive value, RCA right coronary artery, TN true negative, TP true positive.

CTA performance to diagnose severe CAD (≥70% diameter reduction) among TAVI patients

	N	*TP (n)*	*TN (n)*	*FP (n)*	*FN (n)*	*Sensitivity (%)*	*Specificity (%)*	*PPV (%)*	*NPV (%)*	*Accuracy (%)*
RCA	81	4	74	2	1	80	97.4	66.7	98.7	96.3
LM[1]	92	0	91	0	1	-	-	-	-	-
LCX	83	1	77	3	2	33.3	96.3	25	97.5	94
LAD	86	4	72	2	8	33.3	97.3	66.7	90	88.4
All vessels	342	9	314	7	12	42.8	97.8	56.3	96.3	94.4

Table 4. FN false negative, FP false positive, LAD left anterior descending artery, LCX left circumflex artery, LM left main artery, number NPV negative predictive value, PPV positive predictive value, RCA right coronary artery, TN true negative, TP true positive.

[1]Sensitivity, specificity, positive predictive value, negative predictive value and accuracy could not be calculated for the left main artery as there was no severe stenosis on this artery.

Subgroup analysis to diagnose significant CAD (≥50%) according to the quality of the vessels

Quality	*N*	*TP (n)*	*TN (n)*	*FP (n)*	*FN (n)*	*Sensitivity (%)*	*Specificity (%)*	*VPP (%)*	*VPN (%)*	*Accuracy (%)*
Optimal	141	3	126	11	1	75	91.7	21.4	99.2	91.4
Suboptimal	201	27	142	26	6	81.8	84.5	50.9	95.9	84.1

Table 5. FN false negative, FP false positive, LAD left anterior descending artery, LCX left circumflex artery, LM left main artery, number NPV negative predictive value, PPV positive predictive value, RCA right coronary artery, TN true negative, TP true positive.

Subgroup analysis to diagnose severe CAD (≥70%) according to the quality of the vessels

Quality	*N*	*TP (n)*	*TN (n)*	*FP (n)*	*FN (n)*	*Sensitivity (%)*	*Specificity (%)*	*VPP (%)*	*VPN (%)*	*Accuracy (%)*
Optimal	141	1	135	3	2	33.3	97.8	25	98.5	96.4
Suboptimal	201	8	179	4	10	44.4	97.8	66.7	94.7	93

Table 6. FN false negative, FP false positive, LAD left anterior descending artery, LCX left circumflex artery, LM left main artery, number NPV negative predictive value, PPV positive predictive value, RCA right coronary artery, TN true negative, TP true positive.

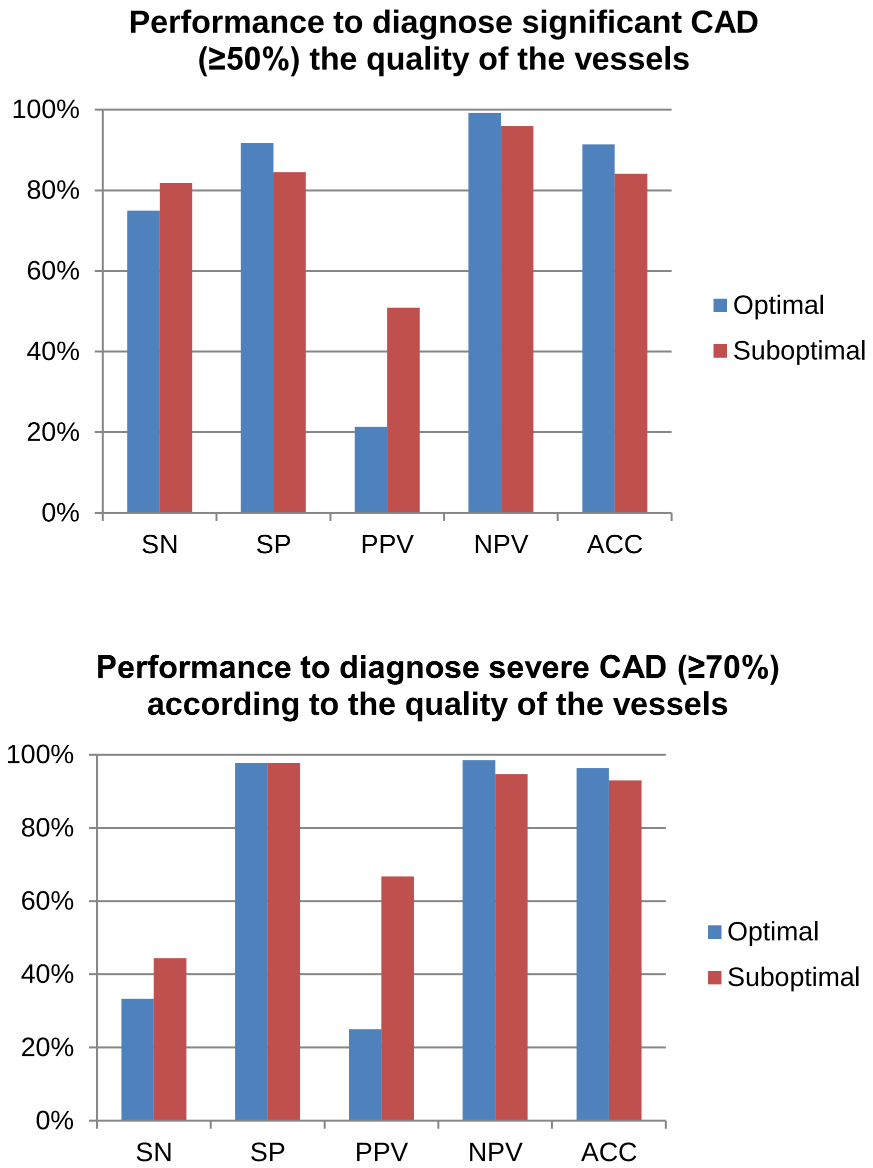

Figure 3. Comparison of the performance of CTA to diagnose CAD between optimal and suboptimal quality vessels

ACC accuracy, NPV negative predictive value, PPV positive predictive value, SN sensitivity, SP specificity.

The analysis at patient level was only performed in the 74 patients whose 4 arteries had an analyzable quality on CTA using the two stenosis cut-offs of 50 and 70%.

CTA compared to ICA to diagnose significant CAD at patient level		**ICA**	
		no ≥50% stenosis	*at least one ≥50% stenosis*
CTA	*no ≥50% stenosis*	31	4
	at least one ≥50% stenosis	17	22

Table 7.

For the 50% cut-off, the capacity of CTA to exclude significant CAD, which corresponds to the specificity, was 64.6%. Its capacity to diagnose significant CAD, which is the sensitivity, was 84.6%. Positive and negative predictive values were respectively 56.4 % and 88.6%. Of note, among the 26 patients with at least one ≥50% stenosis, there was always at least one diseased vessel with concordance between ICA and CTA in 25 patients but in 1 patient, one lesion visualized on ICA was not observed on CTA but this latter showed a stenosis non-existing on ICA, meaning that for this patient, there was an agreement at patient level without any agreement at vessel level.

CTA compared to ICA to diagnose severe CAD at patient level		**ICA**	
		no ≥70% stenosis	*at least one ≥70% stenosis*
CTA	*no ≥70% stenosis*	57	7
	at least one ≥70% stenosis	3	7

Table 8.

For the 70% cut-off (severe CAD,) the sensitivity, specificity, positive and negative predictive values were respectively 50%, 95%, 70% and 89.1%.

Discussion

Our study main findings can be summarized as followed:

1) CTA shows very good accuracy and negative predictive value for the diagnosis of CAD among TAVI patients. Negative findings must therefore be considered as true negatives.
2) CTA positive predictive value to diagnose CAD is low. Positive findings must therefore be confirmed with ICA.
3) CTA tends to overdiagnose CAD among TAVI patients.

The recent meta-analysis from Van Den Boogert and al. gathering 7 single center studies showed interesting results about performance of pre-TAVI CTA to diagnose significant CAD, especially to rule out CAD. At patient level, SN, SP, PPV and NPV were respectively 95, 65, 71 and 94%[23]. However, 6 out of these 7 studies included patients who beneficiated from a CABG prior to the pre-TAVI work-up. The only study that did exclude CABG patients was Rossi and al[24]. This study included 140 patients and showed similar results to ours in term of sensitivity, specificity, positive and negative predictive values.

Our results confirm the fact that the negative predictive value of CTA to detect CAD is really good among patients selected for TAVI, with a NPV of 88.6%. However, CTA tends to overdiagnose CAD, with a capacity to exclude CAD of 64.6%, meaning that 35.4% of positive findings are actually negative. As of today, in our daily practice, CTA is still not used to evaluate coronary arteries in the TAVI work-up. We must obviously wait for a higher level of evidence before we definitely use CTA to rule out CAD. However, we could ask ourselves if it would not be beneficial for patients suffering from severe renal failure to go "off-label" and start using CTA as a gatekeeper for ICA. A needed condition to do so would be that the radiologist reports a good image quality of coronary vessels.

In our subgroup analysis, SN and PPV were higher in the suboptimal quality group than in the optimal one. This is explained by the fact that the prevalence of CAD was much higher in suboptimal quality vessels than in those of optimal quality, which was expected. In optimal quality group, significant stenosis was only found in 4 arteries, when it was found in 33 arteries in suboptimal quality group.

Limitations

The number of unanalyzable vessels was much higher in our study than in those included in the meta-analysis of Van Den Boogert and al[23]. Indeed, 32.7% of vessels were unanalyzable in our study. Also, the inter-observer variability for quality was moderate. This probably comes from the fact that quality classification is really subjective and therefore can differ a lot from one observer to another.

Conclusion

Pre-TAVI CTA showed good performance to rule out significant and severe CAD. However, it tends to overdiagnose it. In a TAVI work-up, coronary arteries should therefore be analyzed on CTA as it could be used as a gatekeeper for ICA if the quality of images is acceptable. This should be even more highly considered in patients with impaired renal function.

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