# The role of voltage mapping and cardiac CT angiography in patients undergoing ablation for atrial fibrillation

PhD thesis

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# 1. Introduction

## 1.1 *Significance of atrial fibrillation (AF)*

AF is the most common cardiac arrhythmia in our population with a continuously rising prevalence. It is associated with ischaemic stroke, a decrease in cognitive function, heart failure, lower quality of life (QoL), extended medical costs, as well as increased mortality. The treatment of AF requires an integrated management. The holistic 'ABC' pathway is suggested by the European Society of Cardiology's new prevention guideline: anticoagulation for avoiding stroke ('A'), better symptom management ('B'), cardiovascular and comorbidity optimization ('C').

## 1.2 *Catheter ablation for AF*

Better symptom control helps to improve AF-related symptoms with rate control and/or rhythm control therapy. Rhythm control strategy refers to attempts to restore and maintain sinus rhythm, which could be used in combination. These treatments include electrical or pharmacological cardioversion, antiarrhythmic drug (AAD) administration, catheter ablation (CA), and surgical cure with Maze procedure.

CA's main benefit is the improvement of QoL with a long-term recurrence-free, asymptomatic period, significant reduction of cardiovascular (CV) hospitalizations, lowering antiarrhythmic drug utilization and prescription drug expenditures as well. CA might be a first-line therapy for symptomatic AF patients. The aim of CA is to eliminate the arrhythmogenic substrate, most commonly found around the ostia of pulmonary veins (PV) in the left atrium (LA). For isolation, radiofrequency or cryo energy-based ablation catheters are used, inserted percutaneously from the femoral vein, guided transseptal to the LA. The ablation catheter creates an

electrically non-conducting, transmural myocardial scar establishing sinus rhythm. The single procedure one-year success rate has varied between 40-94%, the two-year success rate has been 45-85%. The particularly variable success rates highlight the importance of different risk factors associated with AF recurrence. Growing literature confirms the role of atrial fibrosis as well.

*1.3    Atrial fibrosis and its quantification by voltage mapping*
Atrial fibrosis is a significant contributor to the complex pathomechanism of AF, thus, it is associated with AF recurrence after rhythm therapy. In order to quantify atrial fibrosis, various methods have been developed to help the risk stratification of AF patients. Voltage mapping is an invasive method to assess the voltage of the myocardial surface with a high density electroanatomical mapping system (HD-EAMS) during the EP procedure in order to detect low voltage area (LVA) associated with underlying atrial fibrosis. A mapping catheter's location and the simultaneously collected local electrical data (electrogram, activation, timing, unipolar or bipolar voltage values) are stored by EAMS. Bipolar endocardial voltage is calculated as a difference between two adjacent unipolar signals with the use of a differential amplifier or by post-processing. In general, LVA is estimated based on the presence of $\geq 3$ adjacent low-voltage points by rectified contact bipolar endocardial voltage measurement, that are $< 3$ mm apart from each other, and reported as a percentage area of the total mapped atrium. A HD-EAM presenting LVAs is shown in Figure 1.
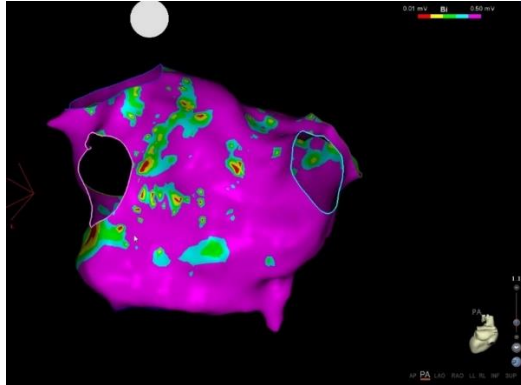
Figure 1. HD-electroanatomic map (CARTO 3® platform with a CONFIDENSE™ module) displaying the low voltage areas of the left atrium (red, yellow, green and blue areas) and normal voltage areas (purple) – postero-anterior view (image of our working group).

There is a significant diversity in the cut-off values determining the burden of LA LVA, ranging from 0.1-1.5mV, and < 0.5mV is the most commonly used term. There is no consensus on the cut-offs for defining the groups of fibrosis severity used in the prediction of outcomes.

Although AF is known to cause biatrial fibrosis, the literature has focused on the LA. As a result, scarce evidence is available on the fibrosis of the right atrium (RA).

### 1.4    The peri-ablation role of cardiac CT angiography (CTA)

In 49%, pre-ablation cardiac CTA is used to tailor ablation, however our Electrophysiology Laboratory applies it on a routine basis nearly for every AF patient, since among other findings, a variant left atrial anatomy may affect the ablation strategy, or even predict the outcome after CA.

Additionally, if cardiac CTA is well-timed, it can be also used for pre-ablation thrombus exclusion replacing the invasive transoesophageal echocardiography. Furthermore, cardiac CTA could be a useful alternative tool for LA fibrosis diagnosis. An additional benefit of pre-ablation cardiac CTA could be the newly diagnosed incidental findings, which would alter the patient's management and may also have a potential lifesaving effect.

During cardiac CTA the coronary artery status could be also revealed. According to several publications, at least 10%, or in some cases even 70% of patients with AF had newly diagnosed coronary artery disease (CAD) (Figure 2.). Since symptoms suggesting ischemic heart disease, such as chest pain could be observed in AF patients also without CAD, predicting CAD in AF patients is often challenging. An incidental CAD may require preventive treatment to decrease potential ischaemic events. It may also cause the reclassification of the most commonly used thromboembolic risk stratification, the $CHA_2DS_2$-VASc score, which could alter the anticoagulant strategy of AF patients. A subclinical CAD may affect the success of AF ablation, however, some publications reported no significant impact.
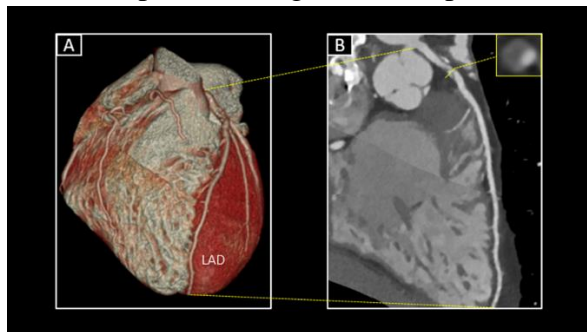


*Figure 2.* Obstructive CAD – significant stenosis on LAD (left anterior descending artery) diagnosed by coronary CTA

## 2. Objectives

### 2.1 *Atrial low voltage area*

We aimed to assess the LA LVA on HD-EAMs by a novel software package which allows its automated quantification in our patients undergoing their first PVI for AF. We studied pre-procedural variables to set up factors associated with atrial fibrosis. Our goal was also to assess the relationship between RA and LA LVA. Next we intended to analyse the predictive value of the Dublin Classification (Diseased LA Tissue Burden) of recurrent AF in patients undergoing their first PVI.

### 2.2 *Coronary artery disease*

We aimed to assess the incidence of obstructive CAD by pre-ablation coronary CTA in consecutive patients prior to AF ablation. Our goal was also to study the relationship between traditional cardiovascular risk factors, the presence of chest pain and newly diagnosed obstructive CAD.

## 3. Methods

### 3.1 *Quantification and risk factors of atrial low voltage area and its relationship with the success rate of AF ablation*

In our observational, prospective, single-centre study one hundred consecutive patients without previous LA ablation, with either paroxysmal or persistent AF were included who underwent pulmonary vein isolation (PVI) in 2017 in the Mater Private Hospital, Dublin. In a subset of the patient population, biatrial HD-EAM, including RA LVA, was obtained, which served as a basis for our second observational study. Patients with prior RA ablation were excluded. In the follow-up study we extended our study population and included the follow-up data to analyse the factors

associated with the recurrence of AF, excluding patients who received any additional non-PVI LA site ablation.

The PVI was performed in line with the up-to-date routine clinical AF ablation protocols. HD-EAM was performed in sinus rhythm by using the CARTO 3® platform with a CONFIDENSE™ module and a circular multipolar catheter with 20 electrodes (Biosense Webster Inc., Irvine, California, USA). After merging the created EAM with the pre-procedural cardiac CTA images, PVI with bilateral wide antral circumferential RF ablation method was performed with the ablation catheter. LVAs were not a target during ablation. In the next study, the mapping strategy was extended to include the RA as well: after LA mapping and PVI the mapping catheter was pulled back to the RA to acquire a HD-EAM.

Analysis of the HD-EAMs was made offline with a novel, automatic voltage histogram analysis (VHA) tool of the CARTO 3® platform. In every case the LA appendage, the pulmonary veins, and the mitral annulus were manually excluded from the voltage map. Areas with voltage ≤ 0.2mV were defined as "Dense LA Scar", while areas with voltage ≤ 0.5mV as "Diseased LA Tissue", and quartiles were calculated to categorize patients by their extent (percentage). The lowest percentage surface area quartile was categorized as "Class I", while the highest as "Class IV". In our third study we named the classification by Diseased LA Tissue, as "Dublin Classification", using the same burden as set in our first study, thus, inventing a novel classification for LVAs. During the offline RA voltage map analysis, inferior and superior vena cava and the tricuspid annulus were excluded from the RA map. In our second study, the quartiles for Diseased LA Tissue (≤ 0.5mV) and RA Tissue (≤ 0.5mV) were created for each atrium: Q1 as the

lowest quartile, while Q4 as the highest quartile of Diseased LA/RA Tissue.

Follow-up data were collected for our third publication. Patients were scheduled for follow-up visits regularly, and in case of any symptoms, an unscheduled visit was organised. At every visit a 12-lead ECG and 24-hour Holter-ECG were obtained. Recurrence was defined as a documented episode of AF, LA tachycardia or LA flutter lasting for more than 30 seconds. Ablation was regarded as successful, if no recurrence has happened after the three months long blanking period. Antiarrhythmic drug (AAD) therapy was terminated after 3 months. At the discretion of the investigator, in some cases, regular AAD was continued or restarted. Therefore, two separate success-analyses defining different primary endpoints (success definitions) were presented. Firstly, in patients without AADs (*OFF AAD*), the documented recurrence or AAD administration after the blanking period (even without any documented arrhythmia) were the primary endpoints. The second analysis (*ON AAD*) determined the primary endpoint only in case of documented recurrence, irrespective of AAD usage.

*3.2      Obstructive coronary artery disease in patients with AF*
This was a retrospective, observational study. Inclusion criteria were: patients with a history of AF and ≥ 18 years old in whom coronary CTA was performed before ablation between 2013 and 2020 at the Heart and Vascular Centre of Semmelweis University, Budapest, Hungary. Patients with previously known CAD, non-diagnostic CTA image and duplications were excluded. Demographics, medical history, and symptoms were collected pre-procedurally from questionnaires and medical documentation. Two groups were identified based on whether the patients had reported

any type of chest pain or had no chest pain. Afterwards, we analysed the relationship between the collected data and novel obstructive CAD diagnosed by coronary CTA.

Coronary CTA examinations were performed on a 256-slice scanner (Brilliance iCT 256, Philips Healthcare, Best, The Netherlands) with a prospective ECG-triggered axial acquisition mode. Coronary artery calcium score (CACS) was also measured. Coronary artery status was analysed with a semi-automated software (HeartBeat-CS, Philips IntelliSpace Portal, Philips Healthcare, Best, The Netherlands). Coronary artery stenosis was classified into groups according to the percentage of the measured most severe luminal stenosis. We defined obstructive CAD as a lesion with ≥ 50% luminal coronary artery stenosis.

## 4. Results

*4.1   Quantification and risk factors of atrial LVA and its relationship with the success rate of AF ablation*

*4.1.1   Quantitative assessment of LA scar*

One hundred patients were involved in our study, 27/100 (27%) were female, the median age was 64 [56-72] years. Persistent AF was present in 39/100 (39%) of the cases. A median of 1,049 [690-1,405] points were taken per voltage map in a median of 10 [8-15] minutes. We created quartiles for Dense LA Scar (≤ 0.2mV) and Diseased LA Tissue (≤ 0.5mV), as shown in Table 1. Figure 3. presents examples of HD-EAMs from each class of Diseased LA Tissue.

*Table 1*. Thresholds for quartiles I-IV for classification of Dense Left Atrial (LA) Scar and Diseased LA Tissue. (LA = left atrium)

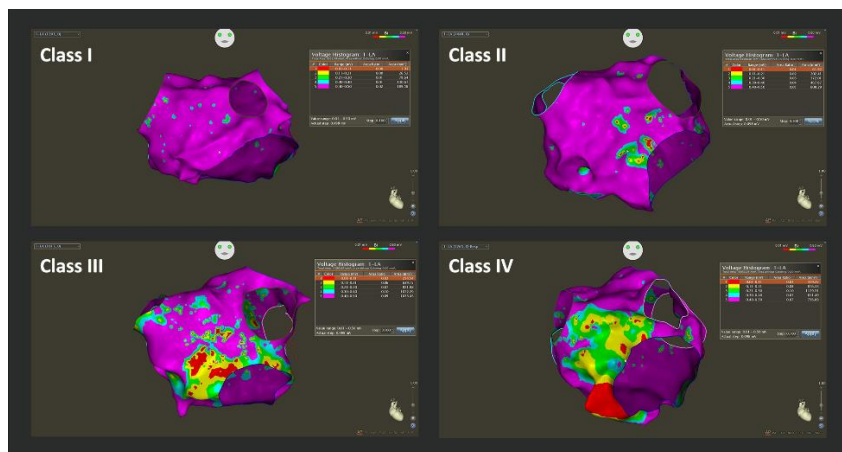| Classification by the extent of Dense LA Scar ($\leq 0.2$mV) | | Classification by the extent of Diseased LA Tissue ($\leq 0.5$mV) (later named Dublin Classification) | |
|---|---|---|---|
| Class I | < 1% | Class I | < 9% |
| Class II | 1-3% | Class II | 9-18% |
| Class III | 3.1-8% | Class III | 18.1-31% |
| Class IV | > 8% | Class IV | > 31% |



*Figure 3.* Voltage Histogram Analysis of LA Voltage Maps: Class I-IV of Diseased LA Tissue burden

Trend analysis showed that the prevalence rate of female sex (p=0.003), age $\geq$ 65 years (p<0.0001), persistent AF (p=0.004), and CHA$_2$DS$_2$-VASc score $\geq$ 2 (p<0.0001) increased with every increment in Diseased LA Tissue from Class I to IV. Multivariate analysis proved that only age $\geq$ 65 years (OR=4.70, CI 95%: 1.50-14.71, p=0.008) and persistent AF (OR=10.50, CI 95%: 2.93-37.63, p<0.0001) were independently associated with the Diseased LA Tissue Class IV.

### 4.1.2  RA scar burden in the prediction of LA scar burden

A total of 36 patients were included in this study with a median age of 69 [58-75] years, who were mainly male (27/36, (75%)), and had persistent AF in 21/36 (58%) of the cases. During the procedure, nearly one thousand homogenous points (987 [680-1,165] for LA; 897 [658-1,153] for RA) were collected in 8 [6-9] and 7 [6-8] minutes of procedure times for the LA and the RA, respectively. The median Diseased Tissue burden ($\leq$ 0.5mV) assessed by the VHA tool was 19% [13-53%] for the LA and 24% [14-34%] for the RA.

Patients with a $CHA_2DS_2$-VASc score $\geq$ 2 (p=0.03), larger LA volume index (LAVI) measured on cardiac CTA (p=0.02) and on EAM (p=0.006), larger RA volume index (RAVI) measured on EAM (p=0.002) had significantly higher RA diseased tissue burden.

We found a statistically significant correlation of LA and RA low voltage area percentages ($\leq$ 0.1mV: p<0.0001, R = 0.576; $\leq$ 0.2mV: p<0.0001 R = 0.625; $\leq$ 0.3mV: p<0.0001 R = 0.612; $\leq$ 0.4mV: p<0.0001, R = 0.666; $\leq$ 0.5mV: p<0.0001, R = 0.646, Spearman's correlation). Patients with higher Diseased LA Tissue quartiles had higher percentage of Diseased RA Tissue (p=0.003), while patients with higher Diseased RA Tissue quartiles had a higher percentage of Diseased LA Tissue area % (p=0.001) according to Kruskal-Wallis test, as presented in Figure 4. Also, patients in RA-Q4 more frequently belonged to LA-Q4 (OR=7.1, CI 95%: 1.3-38.9, p=0.01, Chi-square test).
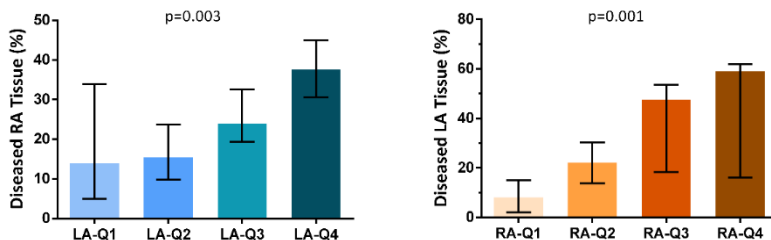
*Figure 4.* Comparison of Diseased Left Atrial (LA) and Right Atrial (RA)
Tissue burden (Kruskal-Wallis test; median with IQR; Q – quartiles).

### 4.1.3 Predictive value of LA diseased tissue burden for the outcome of ablation

In our third study, 109 dominantly male (83/109 (76%)) patients were included with a median age of 62 [55-70] years. Almost one third (34/109 (31%)) of the patients had persistent AF. During the procedure, 958 [658-1,257] points were collected while mapping the LA in the median of 10 [8-14] minutes. All patients were classified: (1) by the extent of Dense LA Scar ($\leq 0.2mV$) and (2) by the extent of Diseased LA Tissue ($\leq 0.5mV$) defined as Dublin Classes I-IV (Table 2.), based on the classification range set in our previous publication (Table 1.)

*Table 2.* Distribution of the study population in the Dense LA Scar and Dublin Classes. (LA – left atrium)

| Classification by the extent of Dense LA Scar ($\leq 0.2mV$) | | No. patients (n=109) | | Classification by the extent of Diseased LA Tissue ($\leq 0.5mV$) (Dublin Classification) | | No. patients (n=109) | |
|---|---|---|---|---|---|---|---|
| Class I | < 1% | 36 | (33%) | Dublin Class I | < 9% | 36 | (33%) |
| Class II | 1-3% | 21 | (19%) | Dublin Class II | 9-18% | 25 | (29%) |
| Class III | 3.1-8% | 29 | (27%) | Dublin Class III | 18.1-31% | 27 | (25%) |
| Class IV | > 8% | 23 | (21%) | Dublin Class IV | > 31% | 21 | (19%) |

The median duration of the follow-up period was 632 [469-760] days. 30/109 (28%) patients had arrhythmias during the blanking

period. We detected 33/109 (30%) recurrences with ON AAD analysis, and 35/109 (32%) with OFF AAD analysis. Altogether 12/109 (11%) patients underwent electrical cardioversion and 24/109 (22%) patients underwent repeated ablation. The overall success rate was 78% and 67% ON AAD, and 74% and 67% OFF AAD at 1- and 2-years follow-up, respectively. Firstly, the success rates of CA in the different Dense LA Scar Classes (I-IV) were compared, but no statistically significant difference was found (p=0.20 for ON AAD; p=0.38 for OFF AAD; log-rank test). In the Diseased LA Tissue burden analysis, there was a statistically significant separation of the four survival curves (p=0.01 for ON AAD; p=0.03 for OFF AAD; log-rank test). Patients with Dublin Class IV had a significantly lower success rate, than patients with Dublin Class I-III, irrespective of AAD use (p=0.004 for ON AAD; p=0.008 for OFF AAD; Figure 5.).



*Figure 5.* Success rates of patients with Dublin Class IV vs Dublin Class I-III, ON AAD (left) and OFF AAD (right) analysis, log-rank test

Among the various clinical and procedural parameters, only two significant predictors of recurrence were found with the univariate Cox-regression analysis: the presence of arrhythmia in the blanking period (OR=3.14, CI 95%: 1.55-6.36, p=0.001 for ON AAD; OR=3.28, CI 95%: 1.65-6.52, p=0.001 for OFF AAD) and Dublin Class IV (OR=2.51, CI 95%: 1.22-5.14, p=0.01 for ON AAD; OR=2.27, CI 95%: 1.12-4.61, p=0.02 for OFF AAD).

## 4.2 Obstructive coronary artery disease in patients with AF

A total of 3,335 pre-ablation coronary CTA examinations have met inclusion criteria. After applying the exclusion criteria, 2,321 patients with paroxysmal and persistent AF were included in our study population (Figure 6.).
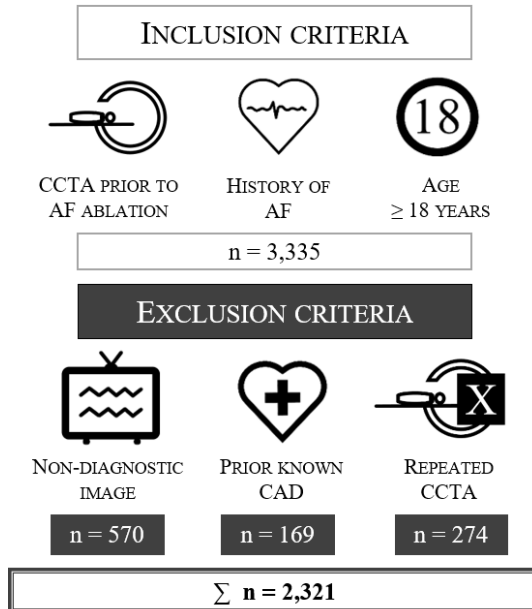


*Figure 6.* Illustration of our study population (CCTA – coronary CT angiography, CAD – coronary artery disease).

The median age of the involved patients was 63 [54-69] years. The population was rather overweight: the median body mass index was 29 [26-32] kg/m$^2$. Hypertension was present in 68% (1,580/2,321) of the patients, 35% (803/2,321) had dyslipidaemia, and 31% (724/2,321) had a history of smoking. 17% (401/2,321) of the patients reported having a positive family history of cardiovascular diseases. There were 404/2,321 (17%) patients who mentioned any chest pain before the coronary CTA without any known CAD.

Multivariable analysis was performed; factors associated with any chest pain were age > 65 years (OR=1.30, 95% CI: 1.03-1.64, p=0.02) female sex (OR=1.84, 95%CI: 1.47-2.30, p<0.001), positive cardiovascular family history (OR=1.70, 95%CI: 1.30-2.22, p<0.001), and peripheral vascular disease (OR=1.74, 95%CI: 1.11-2.75, p=0.01). Obstructive CAD (≥ 50% luminal stenosis revealed by the current coronary CTA) was not associated with symptoms of chest pain (OR=1.06, 95%CI: 0.80-1.39, p=0.69). Obstructive CAD was in equal distribution in both groups (23% (91/404) vs 21% (397/1,917), p=0.41).

In total, 488/2,321 (21%) patients were diagnosed with novel obstructive CAD (≥ 50% luminal stenosis). The total median CACS was 17.8 [0.0-168.6]. In multivariable analysis age > 65 years (OR=2.52, 95% CI: 2.02-3.13, p<0.001), male sex (OR=1.59, 95% CI: 1.28-1.98, p<0.001), hypertension (OR=1.40, 95% CI: 1.08-1.81, p=0.01), diabetes (OR=1.50, 95% CI: 1.13-1.99, p=0.006), dyslipidaemia (OR=1.33, 95% CI: 1.07-1.66, p=0.01), and history of smoking (OR=1.34, 95% CI: 1.07-1.68, p=0.01) were identified as statistically significant associated factors for obstructive CAD. Any chest pain reported was not associated with obstructive CAD statistically significant (OR=1.06, 95% CI: 0.81-1.40, p=0.67).

## 5. Conclusions

We analysed LVA, assessing Diseased LA Tissue burden (≤ 0.5mV) and Dense LA Scar (≤ 0.2mV) in patients undergoing PVI by creating high-density bipolar voltage maps. We found that the highest quartile of Diseased LA Tissue burden (Dublin Class IV) and arrhythmias in the blanking period predicted the two-year outcome of PVI, while Dense LA Scar showed no predictive value. The usage of AAD did not affect the success rates. The application

of the Dublin Classification may be a useful clinical tool in predicting recurrent AF post PVI, and may develop a more personalized management for patients with AF.

We found also that the Diseased RA Tissue burden has a strong correlation with the Diseased LA Tissue burden, suggesting that the RA is a window of the LA, thus, biatrial remodelling and fibrosis are present in patients with AF.

According to pre-ablation coronary CTA images, we observed a high (21%) incidence of obstructive CAD ($\geq$ 50% luminal stenosis) among AF patients. Chest pain was not associated with the incidence of obstructive CAD. Our findings suggest that it is beneficial extending the routine pre-ablation cardiac CTA with characterization for coronary artery stenosis even for patients experiencing no chest pain, since a newly diagnosed obstructive CAD could raise the ischaemic and thromboembolic risk and alter medical treatment strategies.

# 6. Bibliography of the candidate's publication

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*co-first authorship
#expected IF value