Coronary artery aneurysms, insights from the international coronary artery aneurysm registry (CAAR)

INTRODUCTION

Coronary Aneurysms are classically defined as a focal dilatation in the diameter of a coronary artery segment of more than 1.5-fold normal size, considering as such the adjacent non-dilated segments[1-3]. The earliest reports by Morgagni date back to 1761, being one of the first series, with 21 cases, published in 1929[2,4].

Since then, some small series have suggested a variable prevalence of 0.3-12%, with a 4.9% in the largest one ever published in adults[3]. This later included 978 patients from the Coronary Artery Surgery Study (CASS), between 1975-1979[3]. At that time, aneurysmal coronary artery disease (CAD) was considered mainly a variant of coronary atherosclerosis[5]. Thence, CAD management options have evolved rapidly and greatly, with novel interventional procedures and antithrombotic drugs known to improve symptoms and survival in this setting. Despite this, coronary aneurysms are not mentioned in current -European or American- CAD guidelines and several clinical or treatment questions on this matter remain unanswered together with the current natural history of this condition[4].

Moreover, to the best of our knowledge, no prospective studies assessing the contemporary outcomes or addressing the therapeutic management for this condition have been reported[4-14].

The objective of this study was to investigate the clinical profile, prognostic predictors, and the long term-outcome of coronary artery aneurysms.

METHODS

Study population

The coronary artery aneurysm registry (CAAR, Clinical Trial registration-Clinical Trials.gov: NCT02563626) is a multicenter study involving, at the moment, 32 hospitals across 9 countries (Canada, Cuba, Czech Republic, Germany, Italy, The Netherlands, Spain, United States and Uruguay). Protocol data were collected in accordance with regulations set forth by institutional review boards and complied with the declaration of Helsinki, as previously reported[15]. Patients were ambispectively included in the registry on the basis of the angiographic classical coronary aneurysm definition (focal 1.5x dilation compared with a healthy vessel segment). Aneurysm were considered as giant when their size reached about 4x dilation[15].

All patients (≥18 years) after an invasive angiography with one or various established coronary aneurysms fulfilling the previous criteria were eligible, unless they refused.

The review of all coronary angiograms was done in each institution. The period of time was locally chosen on investigator´s criteria, but procedures were strictly consecutive. During the mentioned chosen time frame, all consecutive patients were recruited after review by two experienced interventional cardiologists. When eligibility for inclusion was uncertain, cases were reviewed by a core lab team to reach consensus[15]. Standardized and anonymized forms were used to collect patient data, including baseline characteristics, management and long term outcomes.

Outcomes and follow up.

We recorded the clinical features, all in-hospital medications and complications, including cardiogenic shock, bleeding and death from any cause. After discharge, the following events were recorded: any cause death, readmission because of unstable angina, re-infarction, heart failure, bleeding, stroke, embolic events, and any reason for new coronary angiography. A detailed data gathering on in-hospital and after discharge medical treatment was performed, focusing on antiplatelet and anticoagulation management. Revascularization procedures were assessed and recorded paying attention to the procedure chosen (interventional –PCI- vs surgical –CABG-) and, if PCI was performed, the type of stent and technique used. Follow-up data was prospectively obtained by researchers based on clinical visits, medical records, or telephone interviews.

A total of 83 patients were considered as lost to follow up due to inability to complete a follow more than 30 days, excluding those patients who died during that period. Nevertheless, all were included in the Kaplan Meier estimates.

Statistical analysis

For statistical analysis we used the SPSS v23.0 (IBM-SPSS, USA) and OFFICE 2010 software package (Microsoft, USA) for graphs compiling. The data is presented as mean±standard deviation or median and range, as applicable. Categorical variables are reported with percentages. Comparisons between groups were performed using the appropriate test for qualitative or continuous variables. Long-term event free survival curves for the different exploratory analysis and groups were obtained using the Kaplan-Meier method and comparisons between groups were performed using the log-rank test. The level of statistical significance was set at a two-tailed $p \leq 0.05$.

RESULTS

We reviewed a total of 436,467 consecutive invasive coronary angiograms performed over the period 2004 and 2016. Of those, we found 1,561 consecutive patients fulfilling criteria for at least one coronary aneurysm. Appendix Table A1 displays the numbers of patients recruited by each center, the period of time and the number of coronariographies reviewed by each group. Other 4 nonconsecutive cases were added by researchers because presented inclusion criteria and were considered, outside the prevalence estimation, for the rest of the analysis, figure 1. Finally, 1,565 patients were included in this analysis of the registry.

Prevalence and clinical features

Overall prevalence was calculated in relation to the number of cardiac catheterization procedures. It was estimated as 0.35% (minimum: 0.07-maximum: 3.19%, between centers, Table A1).

With a mean age of 65.5 years, patients were predominantly male (78.5%) and with frequent cardiovascular risk factors, the clinical profile is shown in tables 1 and more detailed in Table A2.

Additional peripheral arterial occlusive disease was seen in 11.1% of the cases; an history of aortopathy was reported in 137 (8.7%) patients, any type of collagenopathy (2.2%) and a confirmed Kawasaki disease was rare (0,3%).

Coronary aneurysms description and anatomy.

The main indication for the coronariography was an acute coronary syndrome in 966 (61.5%) cases, being 318 with ST segment elevation. Stable angina was the reason in 244 (15.6%) and chest pain in 175 (11.2%) cases; table 1.

After angiography, right coronary dominance was shown in 83.8%. Most patients presented a severe coronary stenosis: 1-vessel disease, 434 patients; 2-vessel disease, 394 and 3-vessel disease 517 cases.

Regarding the aneurysm features, most of them were saccular (834 cases). The presence of diffuse disease or ectasia was a common finding in 30.0% of the cases, added to “focal” aneurysms. In 82 cases the aneurysms were considered as giant.

Most patients presented only one (83.0%) or two coronary aneurysms (12.8%). Only three patients had 6 (2 cases) or 7 (1 case) aneurysms. The number of aneurysms was higher and proportional in patients with more severe CAD. Thus, patients with severe stenosis in one vessel displayed >1 aneurysm in the 13%, while two vessel disease-patients depicted >1 aneurysm in 16% and those with three stenotic vessels presented >1 aneurysm in 22.4% (p=0.002).

Overall, the most affected vessel with aneurysms was the left anterior descending artery (762 cases, 48.6%), followed by the right coronary artery (498, 31.8%) and the circumflex (441, 28.1%). We observed the left main involvement in 84 patients, figure 2. One case had an aneurysm in the left internal mammary graft and another case in a saphenous vein graft.

The presence of aortic aneurysms was found to be related with a higher number of coronary aneurysms (mean numbers: 1.42 vs 1.21, p=0.000).

Revascularization strategy, outcomes and discharge antiplatelet therapy.

Most patients received any revascularization procedure (1079, 68.9%) during their index hospitalization. The coronary territory where they had aneurysms was treated in 561 (33.4%) and other coronary segments in 905 cases (57.8%).

Most patients (n=829) underwent PCI, with any type of stent in 776 patients (BMS in 259, DES in 493, covered stents/grafts 17, not specified 7), Figure 1. In patients who received any revascularization procedure, we found less frequently heart failure (7.3% vs. 10.7%; p=0.024) but no differences regarding unstable angina, infarction, MACE, embolism, bleeding, cardiovascular /any cause death, aneurysm growing or complications at this level.

With regard to the aneurysmal segments: 12 patients received a balloon angioplasty, 2 were treated with a drug eluting balloon, 95 patients received a BMS, 221 patients at least a DES and 17 patients a stent graft. Two hundred and fourteen patients received a bypass graft in that segment.

Regarding the other stenotic coronary segments, 221 patients were treated with CABG and 684 were managed percutaneously.

Overally, there were no differences on aneurysm complications, unstable angina, infarction, embolism, stroke, bleeding, MACE (31.6% vs. 31.4%; p=0.963) or death

either (15.6% vs. 15.9%, p=0.925) regarding CABG vs PCI, but we found higher rates of heart failure in the CABG group (10.8% vs. 5.9%; p=0.009), in the univariate assessment.

New aneurysms (3.3% vs. 2.2%, p=0.70) or aneurysm growing (8.8% vs. 4.4%, p=0.72) did not reach a statistical difference between the treatment groups (PCI vs CABG). Since PCI vs. CABG displayed no differences, we compared the use of BMS with DES. No restenosis was found in aneurysms treated with DES, 0 over 161 patients, but those with BMS displayed 4 cases over 70; p=0.002. The comparison favored the use of DES for MACE and death, without differences in bleeding or aneurysm complications (any type, growing or new aneurysms development), Figure 3.

Regarding the antithrombotic treatment, most patients received aspirin at discharge (1412, 90.2%), any type of dual antiplatelet therapy (DAPT) in 1013 (64.8%) and 211 (13.4%) were on anticoagulation. In 89 cases, the initial purpose was to maintain DAPT indefinitely. Considering for these patients a duration equal to their follow-up, the median DAPT length was 12 months (IQR: 6-12).

Long-term Follow up and outcomes.

The median follow-up was 37.2 months (interquartile range, IQR:15.5-72.1). Two hundred forty (15.3%) patients died during the follow-up, 31 (2.0%) of them during the first 30 days. Eighty five patients died of a known cardiovascular cause.

Four hundred eighty five patients (31.0%) displayed the combined variable (MACE), considered as a combination of all cause death or heart failure, unstable angina pectoris and re-infarction. Table A3 depicts the events registered during follow-up stratified by the main cause for the index cardiac catheterization.

A follow-up catheterization was performed in 395 cases (25.2%) after a median of 12.6 months (IQR:3.3-39.1). Out of these, 36 were elective PCIs, 78 for control purposes only and the remaining cases for new symptoms or prior surgery -no cardiac- (3). A significant growing in the aneurysm was found in 25 cases (after a median follow-up of 41.2 months) and a new aneurysm development was depicted in 16 patients (median follow-up: 24.2 months).

Aneurysm complication was seen in 32 cases (8.2%) with 19 thrombosis, 9 progression of existing coronary stenosis or stent restenosis and only 1 rupture.

This unique rupture was documented 30.9 months after the index angiography. The patient was admitted with NSTEMI symptoms and the ruptured aneurysm was successfully treated with a stent graft.

DISCUSSION

The Coronary Artery Aneurysm Registry is the largest multicenter registry designed to study the contemporary prevalence, clinical profile and long-term outcomes of coronary aneurysms. With more than 1,500 adult patients from 32 hospitals over 9 countries, CAAR shows that this condition as infrequent but not rare, accounting for about 0.35% over more than 435,000 cardiac catheterizations. The diagnosis of this disease, with the widespread of non-invasive coronary imaging techniques and the increasing use of invasive cardiac catheterization in the acute setting is likely to increase in the next years, posing the physicians in front of a disease with a lack of evidence based medicine data.

CAAR patients presented a high cardiovascular risk burden, with a high proportion of cases with renal insufficiency and peripheral arterial occlusive disease. This fact, points out an advanced or aggressive atherosclerotic CAD as a common underlying condition. Despite that, the current practice guidelines on ischemic heart disease, do not include any recommendation about patients with coronary aneurysms, neither regarding antithrombotic therapy or when/how/where perform a revascularization procedure.

Other comorbidities, such aortopathies probably mark a pathophysiologic link, with abnormalities of the vessel media and subsequent dilation[4]. This relationship has been recently suggested also by retrospective study including pediatric and adult patients from Taiwan[17]. When we reviewed the patients (n=174) without previous revascularization and no severe stenosis during the index admission, they were younger with less cardiovascular risk factors (less males, hypertension, dyslipemia, diabetes, smoking habit and peripheral vessel disease) than in the remaining cohort with coronary stenosis. In addition, the percentage of any aortopathy in these patients was higher (13.8% vs 7.7%, 0.006) supporting the previously mentioned link.

Despite the typical and well known association of coronary artery aneurysms with some inflammatory (Kawasaki, Takayasu, lupus, Churg Strauss, rheumatoid arthritis…) and connective tissue disorders (Marfan syndrome, Ehlers-Danlos syndrome…) in the CAAR

registry the number of patients with those conditions was low, suggesting those diseases as relatively uncommon in patients with aneurysms diagnosed in the adulthood.

Thus, considering the clinical profile, the cardiovascular risk burden and the most frequent presentation (ischemic) the attending physician should probably manage this condition such an aggressive CAD with high ischemic risk.

Other important point is the antithrombotic therapy. CAAR findings suggest that antiplatelet therapy without additional long-term anticoagulation after revascularization (PCI or CABG) in acute and non-acute patients might be enough. However, the most advanced stages of the disease (aneurysms with multivessel disease) could have a benefit with prolonged antiplatelet strategy. This approach could be more even compelling in the presence of other prothrombotic comorbidities (acute setting, smoking habit, VIH[18], or others..).

Regarding the revascularization procedures, the interventional approach seems to be long-term safe and effective, when compared with CABG. Published studies showed that the use of first generation DES might be associated with aneurysm development compared with BMS (e.g. Taxus-V trial, 1.4 % vs 0.2%; p=0.07)[19,20]. Our data, in contrast to these findings, displayed a clear advantage in terms of decreasing combined events and even mortality with the use of DES. This way, CAAR points out that the default preferred strategy for this patients would be last generation DES, something reasonable if we consider these patients as high ischemic risk. DES would have a low rate of long-term complications, like some series have suggested previously [21]. The use of other devices, such as covered stents performed well for huge aneurysms exclusion, but numbers are low and longer follow-up data is needed. Due to its full coverage with polymer, re-endothelialization within the covered stent is delayed, and reported data indicate that restenosis rates are higher than with conventional stents[22].Gercken et al. implanted 78 PTFE-covered stents in 70 patients and performed invasive follow-up examinations after a mean of 159 days[23].Restenosis occurred in 31.5% of cases and in the majority was located at the stent edges. However, more studies investigating covered stents in the setting of aneurysm sealing are needed in order to know their actual long-term perfomance[24].

Limitations

The prevalence calculation was adjusted to the number of coronary angiographies performed, which probably does not allow direct extrapolations to the general or "healthy" population. Recently, a retrospective population based study from Taiwan's National Health Insurance Research Database, between 2005 and 2011, including adult and pediatric patients reported an incidence rate – of aneurysms/ectasias- of 0.85 per 10^5 person-years[25].

While these observations give us with an overall idea of the prognosis of the disease, they do not provide information as robust as a clinical trial would do. We can only generate hypotheses regarding therapeutics; however, when we consider data from the long-term follow-up, CAAR probably reveals a realistic depiction of the results and the contemporary real life prognosis of patients who are diagnosed with a coronary aneurysm.

CONCLUSION

Aneurysmal coronary artery disease is not uncommon. It is usually associated with severe underlying coronary stenosis and a high cardiovascular risk burden, pointing out an aggressive atherosclerotic status. Antiplatelet therapy, without anticoagulation, seems a reasonable antithrombotic option along with a percutaneous approach was safe and effective.

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TABLES

Table 1. Clinical Features of the study patients.

	Overall aneurysms cohort (n=1565)
Gender /male (%)	1229 (78.5%)
Age (mean±SD)	65.5 ± 12.7
Hypertension (%)	1131 (72.3%)
Dyslipemia (%)	931 (59.3%)
Diabetes Mellitus (%)	400 (25.5%)
Smoking habit (%)	644 (41.2%)
Renal failure /CrCl<30 (%)	128 (8.2%)
Peripheral vascular disease (%)	173 (11.1%)
Working diagnosis (%)	
-Chest pain.	175 (11.2%)
- Stable angina	244 (15.6%)
- NSTEACS	645 (41.2%)
- STEACS	318 (20.3%)
-Ventricular tachycardia/fibrillation/sudden death	13 (0.8%)
- Valvular study	95 (6.1%)
- Presurgery (non cardiac)	14 (0.9%)
- Syncope	3 (0.2%)
Coronary artery disease, number of vessels (%)	1.77±1.05
- **1**	434 (27.7%)
- **2**	394 (25.2%)
- **3**	517 (33.0%)
Left ventricular ejection fraction (mean±SD), %	54.8± 13.2 %

FIGURE LEGENDS

Figure 1: Total population assessed**,** CAAR recruitment, management and follow-up.

Figure 2: Anatomic distribution of coronary aneurysms regarding its morphology. Among the 1565 study patients, the most common type of coronary aneurysm was the saccular form (834; 53.29% patients), panels A and B depict the coronary distribution of this type of aneurysm. C and D refer to the fusiform aneurysms (in 671 patients; 38.01%). E and F show the coronary territory distribution for giant aneurysms (see definition in methods; 48 were saccular, 25 fusiform, 7 mixed morphology and 2 no specified). Overall, sixty cases were considered to be mixed or not specified (17), and thus were not included in this graph. The same aneurysm could be present in two or more coronary territories. A, C and E display the right coronary territory and B, D and F the left coronary.

Figure 3: Kaplan Meier free survival curves for the combined event –MACE- (A, B) and death (C,D), regarding the use of bare metal stents (BMS) or drug eluting stents (DES). A and C depict the whole cohort group treated with those devices. B and D refer only to those patients with specific treatment at the segment with aneurysm.