Outcomes of coronary artery aneurysms: insights from the Coronary Artery Ectasia and Aneurysm Registry (CAESAR)

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Outcomes of coronary artery aneurysms: insights from the Coronary Artery Ectasia and Aneurysm Registry (CAESAR)

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Summary

BACKGROUND: Coronary artery ectasias and aneurysms (CAE/CAAs) are among the less common forms of coronary artery disease, with undefined long-term outcomes and treatment strategies.

AIMS: To assess the clinical characteristics, angiographic patterns, and long-term outcomes in patients with CAE, CAA, or both.

METHODS: This 15-year (2006–2021) retrospective single-centre registry included 281 patients diagnosed with CAE/CAA via invasive coronary angiography. Major adverse cardiovascular events included all-cause death, non-fatal myocardial infarction, unplanned ischaemia-driven revascularisation, hospitalisation for heart failure, cerebrovascular events, and clinically overt bleeding. Time-dependent event risks for the CAE and CAA groups were assessed using Cox regression models and Kaplan-Meier curves.

RESULTS: CAEs (n = 161, 57.3%) often had a multi-district distribution (45.8%), while CAAs (78, 27.8%) exhibited a single-vessel pattern (80%). The co-existence of CAAs and CAE was observed in 42 cases (14.9%), and multivessel obstructive coronary artery disease was prevalent (55.9% overall). Rates of major adverse cardiovascular events were 14.3% in-hospital and 38.1% at a median follow-up of 18.9 (interquartile range [IQR] 6.0–39.9) months. The presence of CAAs was associated with increased major adverse cardiovascular events risk in comparison to CAE (hazard ratio [HR] = 2.26, 95% confidence interval [CI] 1.38–3.69, p = 0.001), driven by a higher hazard ratio of non-fatal myocardial infarctions (HR = 5.00, 95% CI 1.66–15.0, p = 0.004) and unplanned ischaemia-driven revascularisation in both dilated (HR = 3.23, 95% CI 1.40–7.45, p = 0.006) and non-dilated coronary artery segments (HR 3.83, 95% CI 2.08–7.07, p = 0.001).

CONCLUSIONS: Overlap between obstructive and dilated coronary artery disease is frequent. Among the spectrum of dilated coronary artery disease, the presence of a CAA was associated with worse long-term outcomes.

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Introduction

Expansive (or positive) coronary artery remodelling occurs in the initial phase of atherosclerotic plaque formation [1]. The migration of leukocytes, foam cell formation in the vessel wall, and subsequent extracellular matrix degradation are considered the fundamental mechanisms underpinning this process [1]. This remodelling can maintain the diameter of the vessel lumen, potentially acting as an early compensatory mechanism to prevent luminal narrowing. However, dysregulation of the inflammatory response and proteolysis of extracellular matrix proteins [2] might lead to reverse remodelling with plaque deposition and luminal narrowing or a further increase in the vessel's lumen, locally enlarging the vessel's diameter to the point where it reaches the criteria for coronary ectasia [3]. Degradation or injury to any of the vessel layers, particularly the media, can lead to the formation of an aneurysm [4].

Coronary artery ectasias and aneurysms (CAE/CAAs) have typically been defined as a diffuse or focal coronary dilation that exceeds the diameter of normal adjacent segments or the diameter of the patient's largest coronary vessel by 1.5 times [5]. CAE/CAAs are uncommon forms of coronary artery disease and have been diagnosed with increasing frequency since the introduction of coronary angiography. Their incidence has been reported to vary from 1.5% to 5.0%, with a suggested male predominance [6]. Although several causes have been proposed, atherosclerosis accounts for more than 50% of CAAs in adults [7]. Reported complications include thromboses and distal embolisations, vasospasms, and ruptures that produce ischaemia, heart failure, or arrhythmias [2]. The natural pro-

ABBREVIATIONS

CAA:	coronary artery aneurysm
CAE:	coronary artery ectasia

gression of CAE/CAAs and their long-term outcomes remain uncertain due to the scarcity of definitive data, which are often skewed by varying anatomical definitions and inclusion criteria. Furthermore, a direct comparison between the two forms of dilated coronary artery disease is lacking. Controversies also persist over the use of medical treatment (such as anti-thrombotic therapy) or interventional/surgical procedures.

Therefore, in this study, we aimed to delineate the clinical and angiographic characteristics of patients presenting with CAE, CAA or both, confirmed using invasive coronary angiography. Moreover, clinical outcomes were assessed over an extended period, allowing for a more comprehensive understanding of these conditions.

Methods

Study design

The coronary artery ectasia and aneurysm registry (CAESAR) is a monocentric, retrospective registry that includes all-comer patients with angiographical evidence of CAE or CAA based on invasive coronary catheterisation.

Retrospective patient recruitment consisted of (a) a clinical database query for a CAE/CAA diagnosis dating from January 1, 2006 to December 31, 2021 (see appendix), (b) manual screening of electronic medical records and a review of angiographies, and (c) visual confirmation of the diagnosis and classification of CAE, CAA and CAA-CAE (if combined), performed by catheterisation laboratory personnel. Any ambiguities were resolved through group consensus.

CAA was visually defined as a focal dilation of coronary segments of at least 1.5 times the adjacent normal segment, whereas CAE was associated with a more diffuse dilatation (>20 mm in length). Morphologically, CAAs were defined as "*saccular*" if the transverse diameter exceeded the longitudinal diameter, "*fusiform*" in the opposite case, and "*giant*" if the transverse diameter exceeded 20 mm. CAEs were defined as "*diffuse*" if they involved more than one vessel segment and "*focal*" if confined within one vessel segment. CAE "*types*" were defined according to the combination of diffuse and focal components [2]:

- Type I: diffuse ectasia involving two or three vessels
- Type II: diffuse disease in one vessel accompanied by localized disease in another vessel
- Type III: diffuse ectasia confined to one vessel
- Type IV: localized ectasia

We excluded patients with lesions localised in a bypass graft, those upstream of a chronically occluded vessel (CTO), or patients presenting a stent within the vessel dilation at the time of the index coronary angiography. Patients without coronary angiograms available for visual inspection were also excluded. Coronary artery disease was identified and defined as a visual diameter stenosis above 50%.

Hospital records were screened for baseline clinical characteristics and co-morbidities (including inflammatory and oncologic diseases) as well as for cardiovascular and non-cardiovascular (i.e. the de novo diagnosis of infectious, inflammatory and oncologic diseases) outcomes for each enrolled patient, starting from the index invasive coronary angiography. Major adverse cardiovascular events (MACE) were defined as a composite of any incidental all-cause death, non-fatal myocardial infarctions or acute coronary syndromes (ACSs), unplanned ischaemia-driven percutaneous coronary interventions (PCIs), re-hospitalisation for heart failure (HF), acute cerebrovascular events and clinically overt bleeding (Bleeding Academic Research Consortium [Bleeding Academic Research Consortium] ≥2). Follow-up data collection ended on December 31, 2022.

The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the local ethics committee (BASEC 2021-01119). Retrospective patient inclusion was possible for patients who signed the general consent for research at the University Hospital of Zurich and provided an informed written agreement for clinical data usage for research purposes. Approval by the Data Governance Board of the University Hospital of Zurich was obtained for database queries and extractions.

Statistical analysis

All statistical analyses were performed at a per-patient level to compare the three classification groups (CAE, CAA and CAA-CAE). Continuous variables with normal distributions are presented as mean ± standard deviation (SD), and non-normally distributed variables as medians (interquartile range [IQR]). Categorical variables are presented as percentages. The Chi-squared test was used for comparing categorical variables, while the Kruskal-Wallis test was used for continuous variables. Time-to-event data are presented as Kaplan-Meier estimates. Follow-up calculations were based on the time from the index invasive coronary angiography to the occurrence of a major adverse cardiovascular event or the last follow-up date. Censoring events included patients who were lost to follow-up or had not experienced a major adverse cardiovascular event by the end of the study period. Cox proportional-hazards regression models were used to compare the risk of incident events by CAA or CAE. To avoid ambiguity, the CAA-CAE group was omitted from the time-to-event and event prediction analyses. Anatomical and functional variables presenting a univariate relationship with incident events were included in the Cox proportional-hazards regression models. The proportional hazards assumption was verified as part of the Cox regression analysis and the Schoenfeld residual test. All analyses were performed using SPSS Statistics 29 (IBM Corp. Armonk, NY, USA) and MATLAB (Version R2022, MathWorks, Natick, MA, USA).

Results

Over 15 years (figure 1), a total of 281 patients presented with either a CAA (27.8%), a CAE (57.3%) or both (14.9%).

Clinical characteristics

Patients were predominantly male (87.9%), with a median age of 66 (57.7–74.5) years. The CAA group had a higher percentage of female patients (19.2% vs 10.6%, p = 0.045) and a higher median age (70.9 vs 65.4 years, p = 0.077), see table 1. The CAA group also had a lower prevalence of ST segment elevation myocardial infarctions (STEMIs)

at the index event than the CAA-CAE and the CAE groups (7.7% vs 26.2% vs 14.3%, p = 0.022, respectively). Among the 40 patients presenting with STEMI, the causal lesion could be identified in 11 cases with an ectatic segment and in 3 cases with an aneurysmatic segment. Approximately one-fourth of the patients were admitted with symptoms or signs of acute heart failure (23.1% overall), while more than half had a preserved left ventricular ejection fraction (median = 53% overall). Nearly one-third of the patients presented ectatic or aneurysmatic vessels in other body areas. CAA patients were more likely to have undergone previous cardiac surgery (19.2% vs 0.0% vs 8.1%, p = 0.002). No differences were found regarding previous occurrences of cancer (19.9% overall) or inflammatory diseases among the groups (11.7% overall). High-sensitivity C-reactive protein (hs-CRP) concentration at baseline was comparable between the groups (3.30 mg/l overall), see appendix table S1.

Angiographic characteristics and treatment strategies at the index event

At the angiographical evaluation, CAAs were primarily found in a single vessel (80%), with a relatively low incidence in all three coronary arteries (6.7%), as reported in table 2. Fusiform aneurysms were the most common CAA type (65.8%). The co-occurrence of fusiform and saccular CAAs within the same patient was rare (5.0%). In contrast, CAE demonstrated a multi-district distribution in nearly half of the cases (45.8%), with types 2 and 4 being the most frequently observed (21.0% and 20.6%, respectively).

Over half of the patients (55.9%) exhibited multi-vessel coronary artery disease, with a trend towards reduced prevalence in those with CAE (absence of coronary artery disease: CAA 15.4% vs CAE 23.0%), although the differences between the three groups were not significant (p = 0.061), as shown in table 3.

A percutaneous coronary intervention was conducted in 43.4% of the cases during the initial procedure, with no significant distinctions between groups (p = 0.166), table 4. Interventions targeting dilated coronary segments occurred more frequently in CAA and CAA-CAE patients compared to those with CAE alone (24.4% vs 35.7% vs 14.3%, p = 0.853, respectively) and drug-eluting stents (DES) were generally used (47/57 of cases, p = 0.948). Patients with CAE had the highest prevalence of conservative medical treatment (49.7%, p = 0.138). Illustrated case examples of percutaneous coronary interventions on dilated coronary arteries are presented in appendix figures S1–S6.

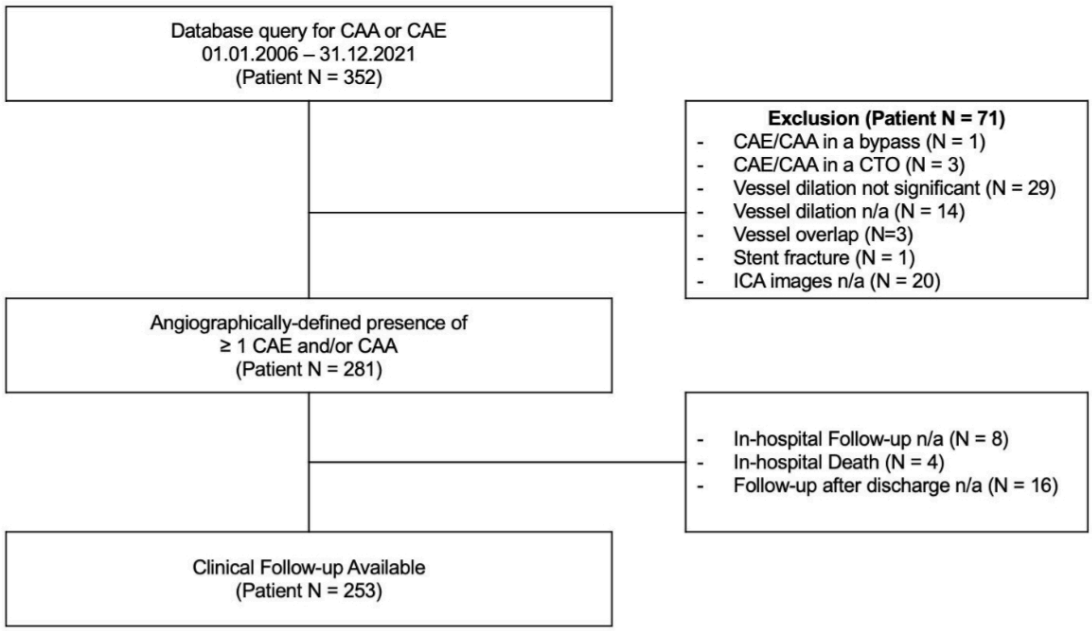
At the vessel level, both saccular and fusiform CAAs were frequently identified in the left anterior descending (LAD) artery (33.0% and 40.5%, p <0.001, respectively), whereas three out of the four giant CAAs (75.0%, p <0.001) were localised in the right coronary artery (RCA). CAEs were often detected in the right coronary artery (46.9%), with type 2 being the most common CAE subtype (33.6%), as illustrated in appendix table S2.

In-hospital and long-term outcomes

Clinical adverse events were documented in 80 cases (28.3%) prior to hospital discharge, with no significant differences between the groups (33.8% vs 21.1% vs 29.1%, p = 0.369, respectively). Rates were primarily driven by periprocedural bleeding (5.49%, p = 0.223) and acute heart failure (6.23%, p = 0.841), as shown in appendix table S3.

Over a median follow-up period of 18.9 months (IQR 6.0–39.9), the incidence of major adverse cardiovascular events was substantial (CAA 44.0%, CAA-CAE 40.5% and CAE 34.5%; p = 0.367). Patients with the mixed dis-

Figure 1: Study flowchart. From the initial 352 patients presenting with a coronary aneurysm or ectasia according to the database query, 71 met the study exclusion criteria, and 281 were included in the study. Clinical follow-up was available in 253 cases. CAA: coronary artery aneurysm; CAE: coronary artery ectasia; CTO: chronic total occlusion; ICA: invasive coronary angiography; n/a: not available.



ease form exhibited a higher rate of percutaneous coronary interventions targeting the dilated coronary segment (10.7%, 27.0% and 9.7%; p = 0.014), which was driven by a higher acute coronary syndrome rate (6.7%, 18.9% and

Table 1:
Baseline clinical characteristics.

		Total	"CAA"	"CAA-CAE"	"CAE"	p-value
		Patient n = 281	Patient n = 78	Patient n = 42	Patient n = 161	2-sided
Age, years		66.1 (57.7–74.5)	70.9 (58.4–76.3)	63.01 (58.5–71.5)	65.4 (57.2–73.2)	0.077
Female, n (%)		34 (12.1)	15 (19.2)	2 (4.76)	17 (10.6)	0.045
BMI, kg/m^2		28.0 (24.9–31.3)	28.31 (24.8–30.5)	27.99 (25.2–32.7)	27.85 (24.9–31.5)	0.710
Chest pain, n (%)		183 (65.1)	49 (62.8)	37 (88.1)	97 (60.3)	0.003
Dyspnoea, n (%)		148 (52.7)	47 (60.3)	17 (40.5)	84 (52.2)	0.115
	NYHA class ≥III, n (%)	62 (22.1)	19 (24.4)	8 (19.1)	35 (21.7)	0.666
Stabile angina, n (%)		65 (23.1)	15 (19.2)	11 (26.2)	39 (24.2)	0.608
Acute coronary syndrome, n (%)		115 (40.9)	30 (38.5)	23 (54.8)	62 (38.5)	0.142
	STEMI, n (%)	40 (14.2)	6 (7.7)	11 (26.2)	23 (14.3)	0.022
	NSTEMI, n (%)	59 (21.0)	20 (25.6)	10 (23.8)	29 (18.0)	0.354
	Unstable angina, n (%)	16 (5.69)	4 (5.13)	2 (4.76)	10 (6.21)	0.907
Acute heart failure, n (%)		65 (23.1)	21 (26.9)	8 (19.1)	36 (22.4)	0.583
LVEF, %		53 (40–59)	55 (42–60)	55 (45–58)	51 (39–58)	0.497
eGFR <30 ml/min, n (%)		14 (4.98)	5 (6.41)	0 (0.00)	9 (5.59)	0.272
Ectasia or aneurysm in other body districts*		84 (29.9)	29 (37.2)	11 (26.1)	44 (27.3)	0.252
	Thorax	47	12	6	29	
	Abdomen	37	15	5	17	
	Other	14	7	1	6	
Hypertension, n (%)		197 (70.1)	55 (70.5)	27 (64.3)	115 (71.4)	0.664
Dyslipidaemia, n (%)		178 (63.4)	50 (64.1)	26 (61.9)	102 (63.4)	0.972
Type 2 diabetes mellitus, n (%)		81 (28.8)	22 (28.2)	8 (19.1)	51 (31.7)	0.271
Smoking, n (%)		186 (66.2)	52 (66.7)	31 (73.8)	103 (64.0)	0.484
Positive family history, n (%)		98 (34.9)	30 (38.5)	13 (31.0)	55 (34.2)	0.697
History of coronary artery disease, n (%)		94 (33.5)	30 (38.5)	11 (26.2)	53 (32.9)	0.388
History of cardiac surgery, n (%)		28 (10.0)	15 (19.2)	0 (0.00)	13 (8.07)	0.002
History of peripheral artery disease, n (%)		23 (8.19)	10 (12.8)	3 (7.14)	10 (6.21)	0.216
History of cerebrovascular insult, n (%)		21 (7.47)	6 (7.69)	2 (4.76)	13 (8.07)	0.759
History of cancer, n (%)		56 (19.9)	14 (18.0)	8 (19.0)	34 (21.1)	0.837
History of inflammatory disease, n (%)		33 (11.7)	9 (11.5)	8 (19.1)	16 (9.9)	0.263

The study population was stratified according to the presence of coronary artery aneurysms (CAAs), coronary artery ectasia (CAE) or a combination of both (CAA-CAE). Continuous variables are presented as medians and interquartile ranges (IQRs). Categorical variables are presented as frequencies and percentages. BMI: body mass index; eGFR: estimated glomerular filtration rate; LVEF: left ventricular ejection fraction; NSTEMI: non-ST-elevation myocardial infarction; NYHA: New York Heart Association; STEMI: ST-elevation myocardial infarction.

* Note: ectasia and aneurysms in multiple districts are possible within the same patient.

Table 2:
Angiographic characteristics at the index coronary angiography.

		Any CAA	"CAA"	"CAA-CAE"	"CAE"	p-value
		Patient n = 120	Patient n = 78	Patient n = 42	Patient n = 161	2-sided
Number of coronary arteries presenting CAA, n (%)						0.621
	One	96 (80.0)	64 (82.1)	32 (76.2)	–	
	Two	16 (13.3)	10 (12.8)	6 (14.3)	–	
	Three	8 (6.67)	4 (5.13)	4 (9.52)	–	
CAA type, n (%)						<0.001
	Saccular	35 (29.2)	25 (32.1)	10 (23.8)	–	
	Fusiform	79 (65.8)	48 (61.5)	31 (73.8)	–	
	Combined	6 (5.0)	5 (6.41)	1 (2.38)	–	
		Any CAE	**"CAA"**	**"CAA-CAE"**	**"CAE"**	**p-value**
		Patient n = 203	**Patient n = 78**	**Patient n = 42**	**Patient n = 161**	**2-sided**
Number of coronary arteries presenting CAE, n (%)						0.291
	One	110 (54.2)	–	27 (64.3)	83 (51.6)	
	Two	62 (30.5)	–	11 (26.2)	51 (31.7)	
	Three	31 (15.3)	–	4 (9.52)	27 (16.8)	
CAE type, n (%)						<0.001
	Type 1	39 (13.9)	–	7 (16.7)	32 (19.9)	
	Type 2	59 (21.0)	–	23 (54.7)	36 (22.4)	
	Type 3	47 (16.7)	–	0 (0.00)	47 (29.2)	
	Type 4	58 (20.6)	–	12 (28.6)	46 (28.6)	

The study population was stratified according to the presence of coronary artery aneurysms (CAAs), coronary artery ectasia (CAE) or a combination of both (CAA-CAE).

7.6%; p = 0.070), as detailed in table 4. Among the twelve reported patients with in-stent restenosis, four occurred in stents deployed in a dilated coronary artery segment (two cases in CAA vessels, one case in a CAE vessel, and one in a vessel presenting a mixed form). Only one stent thrombosis occurred in a dilated coronary artery (an aneurysmatic vessel). The detection of de novo cancers, inflammatory diseases and infectious diseases was reported in 8.2%, 3.1%, and 16.7% of cases for CAA, CAA-CAE, and CAE, respectively, with no significant differences between the groups (p >0.05 in all groups), appendix table S4.

Longitudinally, patients with angiographically identified CAA exhibited worse clinical outcomes than those with CAE, which reflected a higher incidence of acute coronary syndrome at follow-up and higher rates of coronary re-intervention (either at the level of the dilated coronary segment or in any normal coronary artery segment), figure 2 and appendix figure S7.

The Cox proportional hazards regression analysis found that aneurysmatic coronary artery segments exhibited a higher risk of adverse events compared to CAE (hazard ratio [HR] = 2.75, 95% confidence interval [CI] 1.84–4.10), p <0.0001) and major adverse cardiovascular events (HR = 2.26, 95% CI 1.38–3.69, p = 0.001), driven by a higher acute coronary syndrome hazard (HR = 5.00, 95% CI 1.66–15.02, p = 0.004) and percutaneous coronary intervention hazard (in a dilated coronary segment: HR 3.23, 95% CI 1.40–7.45, p = 0.006; in any coronary segment: HR 3.83, 95% CI 2.08–7.07, p = 0.001), figure 3 and figure S8 in the appendix. The presence of obstructive coronary artery disease did not significantly influence the risk of major adverse cardiovascular events at the follow-up in CAA or CAE patients, appendix figure S9.

Discussion

In this study, a total of 281 patients with dilated coronary artery disease were investigated, and clinical characteristics, angiographic patterns and the long-term adverse outcomes of patients presenting with CAE and CAA were described. The main results of the study were: (a) CAE demonstrated a multi-district distribution, while CAAs were primarily isolated to a single coronary segment; (b) multi-vessel obstructive coronary artery disease was prevalent in more than half of the patients; (c) clinical adverse events were common in-hospital and at the long-term follow-up; and (d) aneurysmatic coronary artery segments were associated with a higher risk of adverse events and major adverse cardiovascular events, which was driven by higher hazards of acute coronary syndrome and percutaneous coronary intervention at the follow-up.

The spectrum of coronary artery remodelling

The initial phase of atherosclerotic plaque formation involves leukocyte migration, foam cell formation, and extracellular matrix degradation, leading to expansive coronary remodelling that maintains lumen diameter and prevents narrowing [1]. Dysregulation of these mechanisms by injury or degradation of the vessel layers, especially the media, can cause either reverse remodelling with luminal narrowing or further dilation, resulting in coronary ectasia and aneurysm formation [2–4]. As such, both obstructive and dilative coronary artery disease can co-exist within the same coronary artery tree. In our analysis, only a small percentage of the vessels included in the study failed to exhibit a (significant) obstructive coronary artery disease form (18.2%). Instead, extensive three-vessel disease was the most common coronary artery disease variant associated with either CAA (34.6%) or CAE (28.6%). This, coupled with the high prevalence of traditional cardiovascular risk factors in both dilative coronary artery disease subgroups, supports the theory of a significant overlap in the pathobiology between obstructive and dilative coronary artery disease [8]. Notably, this disease form appears to predominantly affect males (ca. 88% of male patients in our cohort), a trend consistent with the literature [9].

Coronary aneurysms and ectasia as two different biological conditions

While sharing a similar pathophysiology, in our analysis, CAAs and CAEs appeared to be distinct entities with marginally overlapping clinical characteristics. In the study population, coronary aneurysms and ectasia co-existed, however, only 14.9% of patients presented with both conditions. The CAA group had a higher proportion of female

Table 3:
Coronary artery disease prevalence and treatment strategy at the index coronary angiography.

		Total	"CAA"	"CAA-CAE"	"CAE"	
		Patient n = 281	Patient n = 78	Patient n = 42	Patient n = 161	2-sided
Number of coronary arteries presenting coronary artery disease, n (%)						0.061
	One	73 (26.0)	17 (21.8)	10 (23.8)	46 (28.6)	
	Two	68 (24.2)	22 (28.2)	14 (33.3)	32 (19.9)	
	Three	89 (31.7)	27 (34.6)	16 (38.1)	46 (28.6)	
	No coronary artery disease	51 (18.2)	12 (15.4)	2 (4.8)	37 (23.0)	
Any percutaneous coronary intervention, n (%)		122 (43.4)	32 (41.0)	24 (57.2)	66 (41.0)	0.166
Percutaneous coronary intervention of CAE/CAA, n (%)		57 (20.3)	19 (24.4)	15 (35.7)	23 (14.3)	0.853
	With BMS, n (%)	3 (1.1)	1 (1.3)	1 (2.3)	1 (0.6)	0.954
	With drug-eluting stent, n (%)	47 (16.7)	15 (19.2)	12 (28.6)	20 (12.4)	0.948
	With a covered stent, n (%)	3 (1.1)	2 (2.6)	1 (2.3)	0 (0.0)	0.302
	With plain old balloon angioplasty, n (%)	4 (1.4)	1 (1.3)	1 (2.3)	2 (1.2)	0.909
Coronary artery bypass grafting, n (%)		32 (11.4)	13 (16.7)	4 (9.52)	15 (9.30)	0.172
Conservative treatment, n (%)		127 (45.2)	33 (42.3)	14 (33.3)	80 (49.7)	0.138

The study population was stratified according to the presence of coronary artery aneurysms (CAAs), coronary artery ectasia (CAE) or a combination of both (CAA-CAE).

patients, was older, and was more likely to have undergone cardiac surgery than the CAE group. A similar prevalence of inflammatory and oncological conditions was found in both groups. A trend toward higher hs-CRP in the CAA group was also found, suggesting a higher prevalence of residual inflammatory risk [10, 11].

Angiographic characteristics also varied among groups. CAAs were primarily localised in a single vessel, whereas CAE exhibited a multi-district distribution in nearly half of the cases. The distribution of CAA was relatively balanced among the three major coronary arteries, except for the giant form, which was almost invariably located in the right coronary artery. Conversely, CAE was most frequently located in the right coronary artery (46.9% of cases). Furthermore, CAAs had a more extensive representation along the coronary tree, also appearing at the level of diagonal and marginal side branches, a trait not observed in CAE cases. Nevertheless, coronary ectasia had, in 79.0% of cases, a diffuse manifestation (i.e. type 1, type 2 or type 3) with the involvement of more than one segment along the epicardial vessel.

Coronary aneurysms and ectasia present different clinical and risk profiles

The scientific literature regarding clinical outcomes in patients with dilated coronary artery disease is typically sparse, often biased by varying anatomical definitions and inclusion criteria, and marked by controversial conclusions. Luo et al. demonstrated a lower coronary flow (quantified in terms of TIMI frame counts) in patients with CAA compared to those with CAE, suggesting that impaired intravascular haemodynamics could lead to ischaemia [12]. Núñez-Gil et al. reported that morbidity and mortality rates in large European and North American populations with CAA exceeded 30% and 15%, respectively [9]. Several studies have indicated worse post-procedural outcomes in the form of dilated coronaropathy than obstructive coronary artery disease [2]. However, a comprehensive comparison of long-term clinical outcomes in patients presenting with either CAA or CAE has not been adequately addressed.

Our longitudinal analysis of patient outcomes specifically underscored the distinct clinical behaviour of CAAs and CAEs. In our cohort, patients with angiographically iden-

Table 4:
Events at follow-up.

		Total	"CAA"	"CAA-CAE"	"CAE"	p-value
		Patient n = 257	Patient n = 75	Patient n = 37	Patient n = 145	2-sided
Follow-up event, n (%)		149 (58.0)	44 (58.7)	25 (67.6)	80 (55.2)	0.391
Follow-up duration, days		568 (180–1197)	713 (225–1305)	428 (182–1220)	543 (161–1155)	0.378
Re-coronary angiography, n (%)		96 (37.4)	26 (34.7)	17 (45.9)	53 (36.6)	0.487
Major adverse cardiovascular events, n (%)		98 (38.1)	33 (44.0)	15 (40.5)	50 (34.5)	0.367
All-cause death, n (%)		49 (19.1)	20 (26.7)	5 (13.5)	24 (16.6)	0.126
Cardiac death, n (%)		10 (3.9)	3 (4.0)	1 (2.7)	6 (4.1)	0.920
Acute coronary syndrome, n (%)		23 (8.9)	5 (6.7)	7 (18.9)	11 (7.6)	0.070
Percutaneous coronary intervention, n (%)		59 (23.0)	17 (22.7)	12 (32.4)	30 (20.7)	0.316
Percutaneous coronary intervention of CAE/CAA, n (%)		32 (12.5)	8 (10.7)	10 (27.0)*	14 (9.7)	0.014
In-stent restenosis, n (%)		12 (4.7)	4 (5.3)	4 (10.8)	4 (2.8)	0.111
Stent thrombosis, n (%)		3 (1.2)	1 (1.3)	0 (0.0)	2 (1.4)	0.774
Cerebrovascular event, n (%)		7 (2.7)	2 (2.7)	1 (2.7)	4 (2.8)	0.999
Re-hospitalisation for heart failure, n (%)		9 (3.5)	5 (6.7)	1 (2.7)	3 (2.1)	0.205
Bleeding, n (%)		30 (11.7)	7 (9.3)	6 (16.2)	17 (11.7)	0.566
Medication upon admission	Single anti-platelet therapy, n (%)	30 (11.7)	9 (12.0)	3 (8.1)	18 (12.4)	0.763
	Dual anti-platelet therapy, n (%)	26 (10.1)	7 (9.3)	5 (13.5)	14 (9.7)	0.758
	Oral anticoagulant, n (%)	17 (6.6)	4 (5.3)	4 (10.8)	9 (6.2)	0.524
	Dual anti-thrombotic therapy, n (%)	13 (5.1)	3 (4.0)	1 (2.7)	9 (6.2)	0.606
	Triple anti-thrombotic therapy, n (%)	2 (0.8)	1 (1.3)	0 (0.0)	1 (0.7)	0.739
Medication at discharge	Single anti-platelet therapy, n (%)	14 (5.4)	5 (6.7)	1 (2.7)	8 (5.5)	0.684
	Dual anti-platelet therapy, n (%)	43 (16.7)	12 (16.0)	8 (21.6)	23 (15.9)	0.690
	Oral anticoagulant, n (%)	9 (3.5)	1 (1.3)	2 (5.4)	6 (1.4)	0.446
	Dual anti-thrombotic therapy, n (%)	11 (4.3)	3 (4.0)	2 (5.4)	6 (1.4)	0.934
	Triple anti-thrombotic therapy, n (%)	13 (5.1)	4 (5.3)	1 (2.7)	8 (5.5)	0.778
Bleeding classification						0.642
	BARC 1, n (%)	2 (0.8)	1 (1.3)	0 (0.0)	1 (0.7)	
	BARC 2, n (%)	6 (2.3)	2 (2.7)	0 (0.0)	4 (2.8)	
	BARC 3a, n (%)	3 (1.2)	1 (1.3)	0 (0.0)	2 (1.4)	
	BARC 3b, n (%)	5 (1.9)	1 (1.3)	2 (5.4)	2 (1.4)	
	BARC 3c, n (%)	7 (2.7)	2 (2.7)	3 (8.1)	2 (1.4)	
	BARC 4, n (%)	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.7)	
	BARC 5a, n (%)	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.7)	
	BARC 5b, n (%)	5 (1.9)	0 (0.0)	1 (2.7)	4 (2.8)	

The study population was stratified according to the presence of coronary artery aneurysms (CAAs), coronary artery ectasia (CAE) or a combination of both (CAA-CAE). Follow-up durations are expressed as medians and interquartile ranges (IQRs). BARC: Bleeding Academic Research Consortium.

* In the CAA-CAE, 4 percutaneous coronary interventions occurred in an ectatic segment, while 6 percutaneous coronary intervention occurred in an aneurysmatic segment.

tified CAAs demonstrated worse clinical outcomes than those with CAEs. This was not only indicated by a higher incidence of acute coronary syndrome during follow-up but also by an increased rate of coronary re-interventions involving dilated coronary segments and other normal coronary artery segments. The Cox proportional hazards regression analysis further corroborated these findings, revealing that aneurysmal coronary artery segments were associated with a significantly higher risk of adverse events and major adverse cardiovascular events, predominantly driven by a higher incidence of acute coronary syndrome and a subsequent requirement for a percutaneous coronary intervention during follow-up. This was observed in a mixed, real-world study population where patients were equally treated operatively and conservatively at baseline.

Elevated rate of stent failure in dilated coronary disease

The high rates of in-stent restenosis and stent thrombosis in our cohort were noteworthy. Considering only the subgroup of patients who underwent a percutaneous coronary

Figure 2: Event incidence at the long-term follow-up. Patients presenting either coronary artery ectasia (CAE) or coronary artery aneurysm (CAA) showed an elevated incidence of adverse events at the long-term follow-up. ACS: acute coronary syndrome; MACE: major adverse cardiovascular events; PCI: percutaneous coronary intervention.

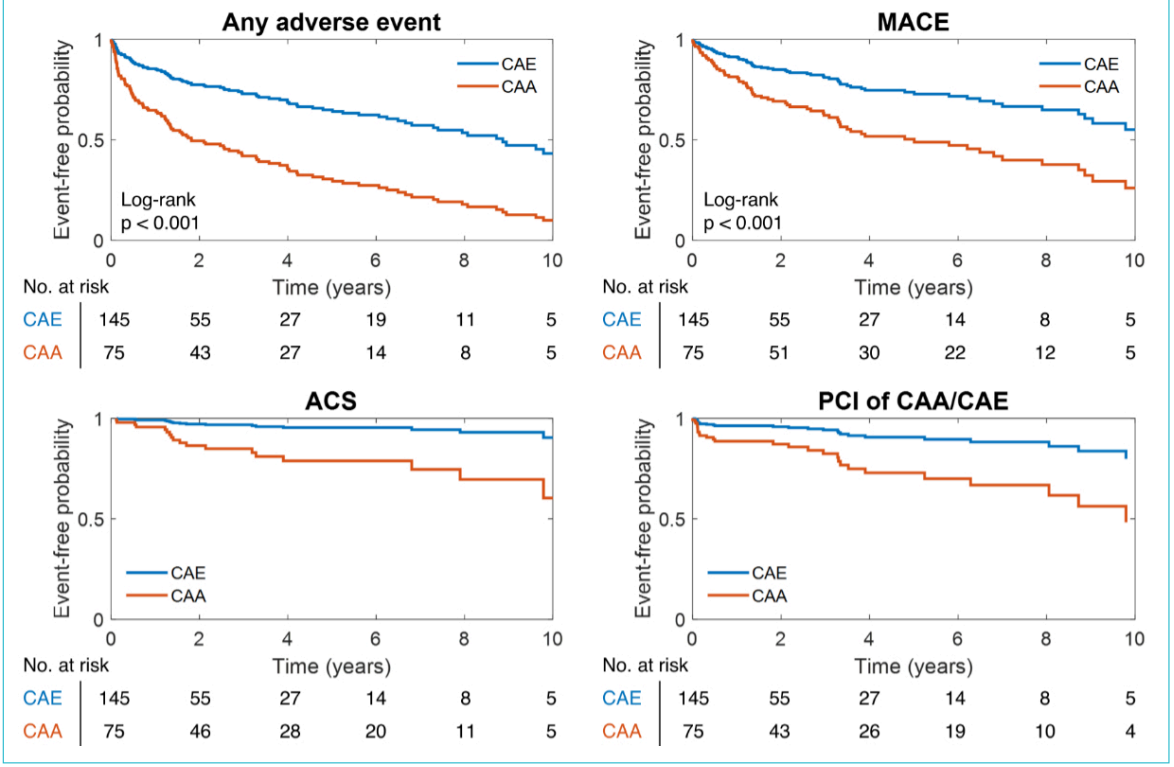
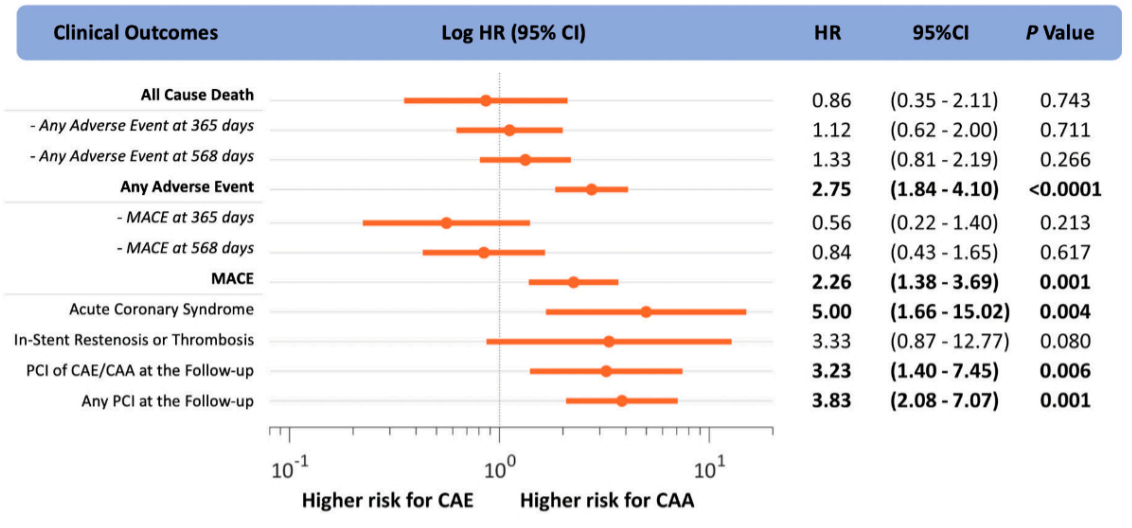


Figure 3: Time-dependent event risk. Results of the Cox models for coronary artery ectasia (CAE) or coronary artery aneurysm (CAA) and the time-dependent hazard ratio (HR) of adverse events. In dash, the shorter-term outcomes with respect to the one reported in bold (maximum follow-up time). MACE: major adverse cardiovascular events; PCI: percutaneous coronary intervention.



intervention at the baseline coronary angiography, the rates of in-stent restenosis and stent thrombosis were recorded at 9.8% and 2.5%, respectively, over a median follow-up period of 18.9 months. In particular, one-third of the recorded stent failures occurred in stents positioned within a dilated coronary artery segment, where in-stent restenosis and stent thrombosis rates reached 22.2% and 1.8%, respectively. The causes of stent failure within an enlarged vessel segment may be secondary to procedural factors, such as sub-optimal stent apposition, stent fracture or edge dissection due to forceful post-dilation or a lack of post-procedural imaging control [13]. Aneurysm ceilings with covered stents were rare, performed in two out of nineteen treated CAAs. However, the reasons for the increased risk in non-dilated coronary artery segments are less clear. Potential factors could be alterations in intra-coronary haemodynamics, such as a decreased flow speed downstream of a coronary aneurysm or secondary flow patterns with blood re-circulation and platelet activation [14–16]. Alongside these factors, the presence of a biologically favourable environment with heightened pro-inflammatory activity – as the registered elevated hs-CRP levels might suggest – could also play a role in affecting the long-term performance of stents in these patients [17]. Larger studies are needed to substantiate the evidence of an elevated stent failure rate in this population and to properly address its aetiology.

Limitations

This study acknowledges several limitations. Firstly, patient selection was executed using a comprehensive system query based on pre-defined keywords rather than a visual examination of each coronary angiography performed at our institution. Nevertheless, considering the extensive timeframe for patient inclusion (15 years) and the numerous operators performing angiography procedures, the risk of selection bias is minimal. Secondly, the classification of CAA or CAE was based on visual assessments of the coronary angiograms rather than intravascular imaging (e.g. intravascular ultrasound or optical coherence tomography). Consequently, the precision of the assessment may be impaired, and the inadvertent inclusion of coronary pseudoaneurysms cannot be ruled out. However, the implemented methodology better represents current routine clinical practice. Third, the study lacks a comparative analysis with a control group with obstructive coronary artery disease without CAA/CAE. However, it should be noted that obstructive coronary artery disease prevalence in the investigated cohort was large. This fact, in conjunction with the high prevalence of traditional risk factors for coronary artery disease, implies a significant overlap between the two types of coronary diseases, making a direct comparison less informative. Finally, the observed increased risk associated with CAA could be partially attributed to the longer follow-up period for this group (a median follow-up duration of 713 days) compared to the CAE group (a median follow-up duration of 543 days), highlighting the importance of considering the follow-up duration when interpreting these results.

Conclusions

Aneurysmatic coronary segments presented a more aggressive clinical course compared to coronary ectasia, emphasising the need for a nuanced approach to patient management that also accounts for the different manifestations of dilative coronary artery disease. Further research is necessary to elucidate the mechanisms behind these divergent outcomes and to develop targeted therapeutic strategies for patients presenting with either form of dilated coronary artery disease.

Potential competing interests

All authors have completed and submitted the International Committee of Medical Journal Editors form for disclosure of potential conflicts of interest. Competing Interests – *AC* has consultancy agreements with Medyria AG and Nanoflex AG. *JS* is supported by a Monash University scholarship and received speaker's fees from Abbott and Edwards Lifesciences and a travel grant from Abbott. *BS* received research grants to the institution from the OPO Foundation, the Iten-Kohaut Foundation, the German Centre for Cardiovascular Research (DZHK), Boston Scientific, and Edwards Lifesciences and has received consulting and speaker fees from Boston Scientific and Abbott Vascular. *CT* received institutional grants from Abbott Vascular, Medtronic, SMT, the Iten-Kohaut Foundation and the Swiss Heart Foundation, as well as consulting grants from Biotronik, Microport, Inova Medical. *CT* and *BS* were supported by the H.H. Sheikh Khalifa bin Hamad Al-Thani Research Programme. No other potential conflict of interest related to the content of this manuscript was disclosed.

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Appendix

Database query

A local database was queried from 01/01/2006 to 31/12/2021 for cardiac catheterisation reports (number of reports screened = 17,896) containing any of the following German keywords: Koronaraneurysma OR Koronaraneurysmen OR Aneurysma OR Aneurysmen OR aneurysmatisch OR Koronarektasie OR Koronarektasien OR Ektasie OR Ektasien OR ektatisch OR Koronarerweiterung OR Koronarerweiterungen OR Koronardilatation OR Koronardilatationen.

Figure S1

A case example of the percutaneous coronary treatment of a patient presenting with a dilated coronary artery disease form. Upper panels: invasive coronary angiography projection at baseline. Lower panel: invasive coronary angiography projection after a PCI. Abbreviations: CAA: coronary artery aneurysm; PCI: percutaneous coronary intervention.

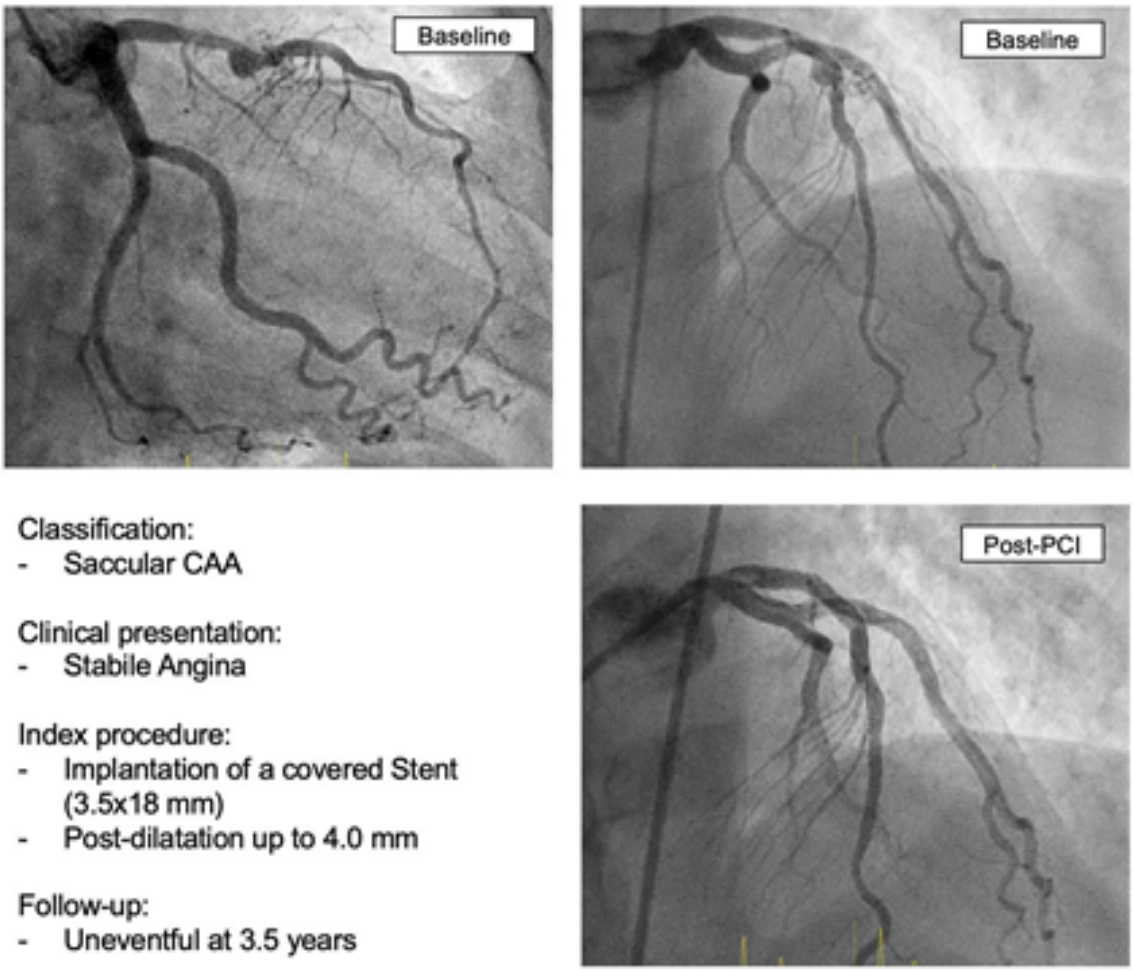


Figure S2

A case example of percutaneous coronary treatment of a patient presenting with a dilated coronary artery disease form. Upper panel: invasive coronary angiography projection at baseline. Lower panel: invasive coronary angiography projection after a PCI. Abbreviations: CAE: coronary artery ectasia; LAD: left anterior descending artery; PCI: percutaneous coronary intervention; RCA: right coronary artery.

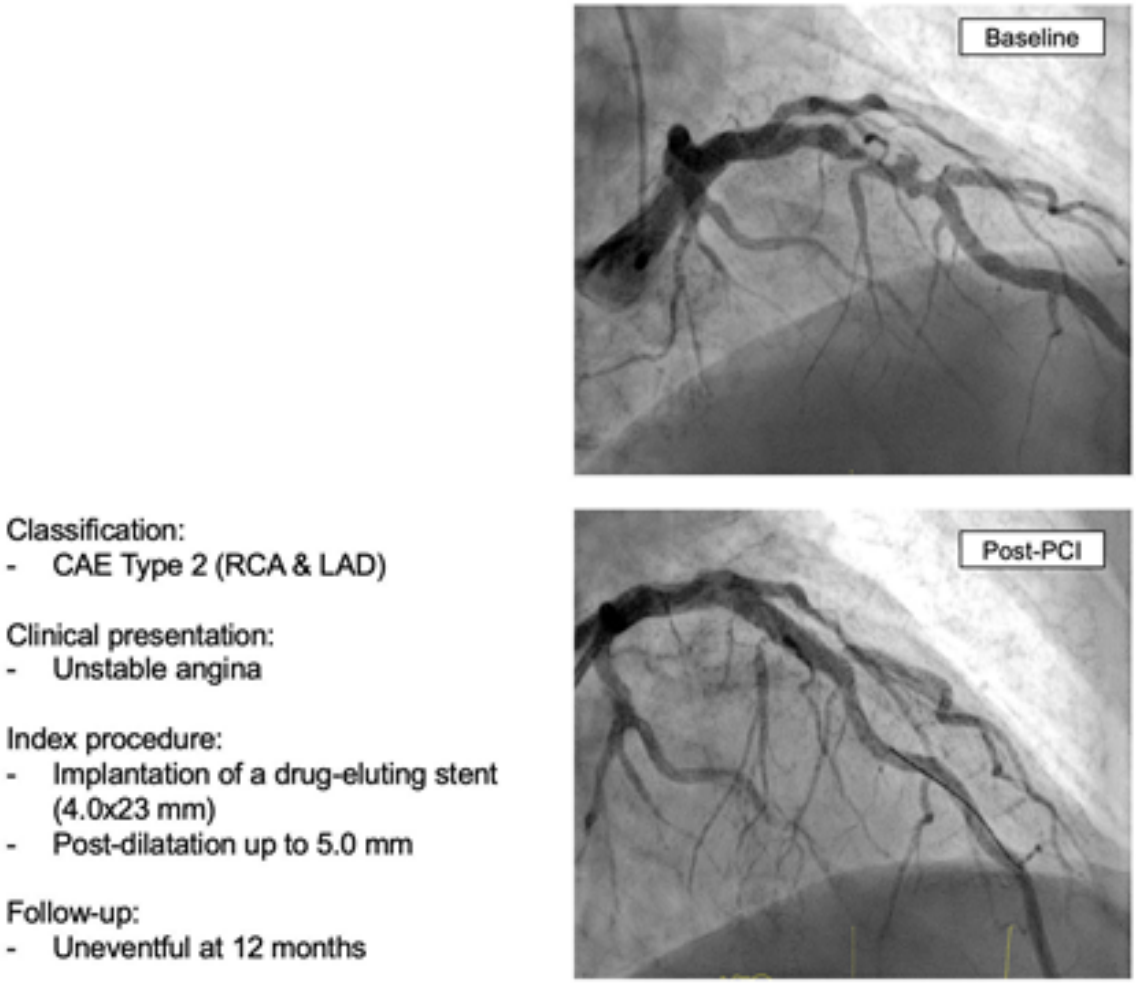
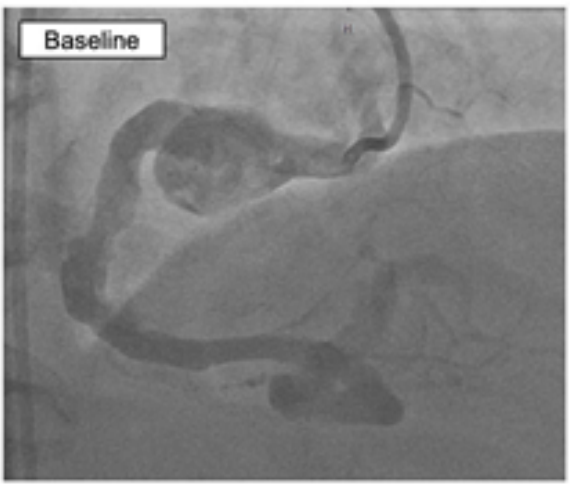


Figure S3

A case example of percutaneous coronary treatment of a patient presenting with a dilated coronary artery disease form. Upper panel: invasive coronary angiography projection at baseline. Lower panel: invasive coronary angiography projection after a PCI. Abbreviations: CAA: coronary artery aneurysm; CT: computed tomography; CTO: chronic total occlusion; PCI: percutaneous coronary intervention.

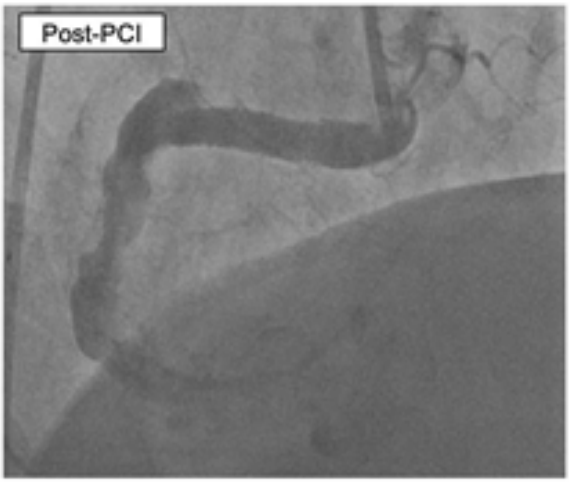


Classification:
- Giant saccular CAA

Clinical presentation:
- Elective evaluation (accidental finding in CT)

Index procedure:
- Implantation of a covered stent (4.8x26 mm)
- Post-dilatation up to 7.0 mm

Follow-up:
- First diagnosis of CTO after 3 years



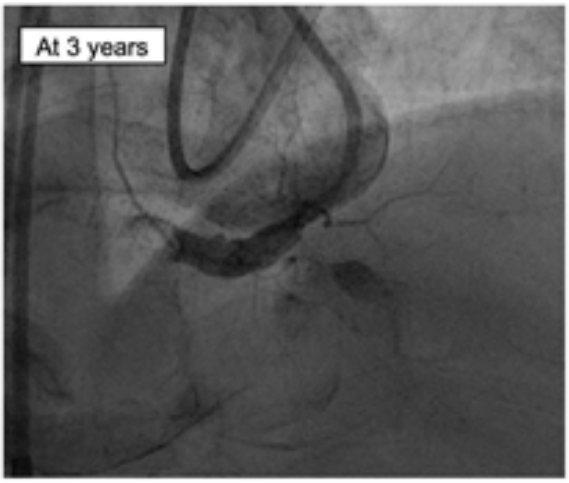


Figure S4

A case example of percutaneous coronary treatment of a patient presenting with a dilated coronary artery disease form. Upper panel: invasive coronary angiography projection at baseline. Lower panel: invasive coronary angiography projection after a PCI. Abbreviations: CAE: coronary artery ectasia; CTO: chronic total occlusion; PCI: percutaneous coronary intervention; PDA: posterior descendent artery.

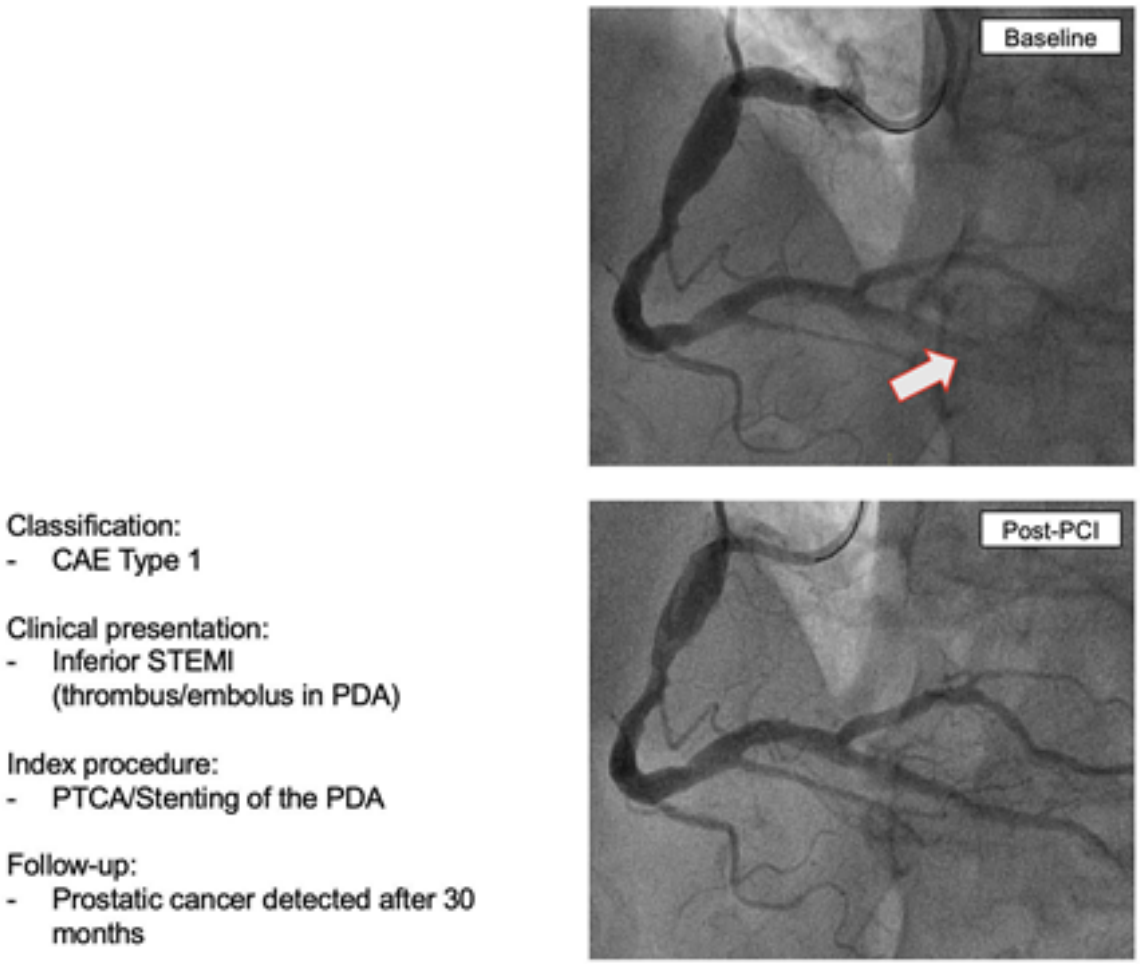


Figure S5

A case example of percutaneous coronary treatment of a patient presenting with a dilated coronary artery disease form. Upper panel: invasive coronary angiography projection at baseline. Lower panel: invasive coronary angiography projection after a PCI. Abbreviations: CAE: coronary artery ectasia; PCI: percutaneous coronary intervention; STEMI: ST segment elevation myocardial infarction.

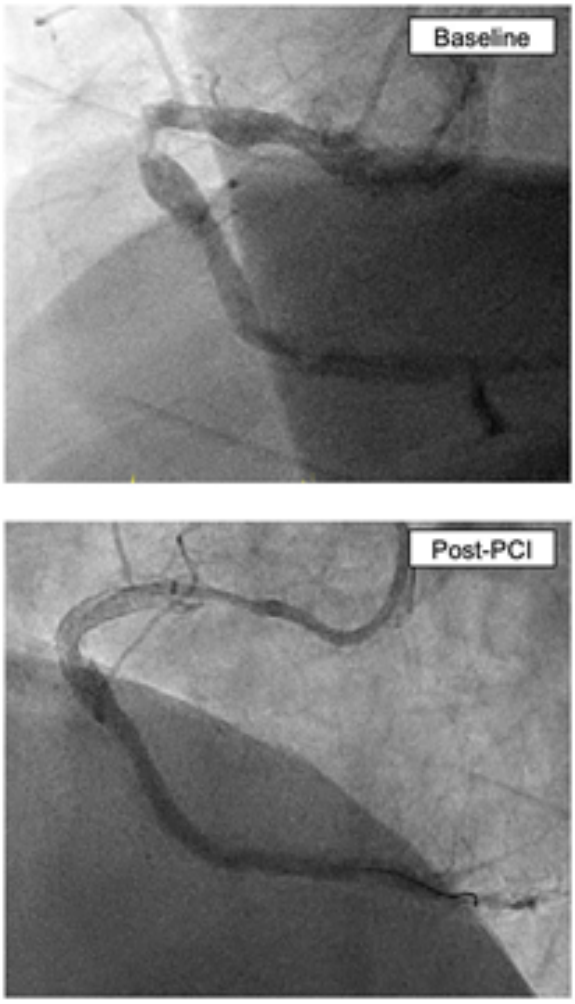


Figure S6

A case example of percutaneous coronary treatment of a patient presenting with a dilated coronary artery disease form. Upper panel: invasive coronary angiography projection at baseline. Lower panel: invasive coronary angiography projection after a PCI. Abbreviations: CAE: coronary artery ectasia; PCI: percutaneous coronary intervention.

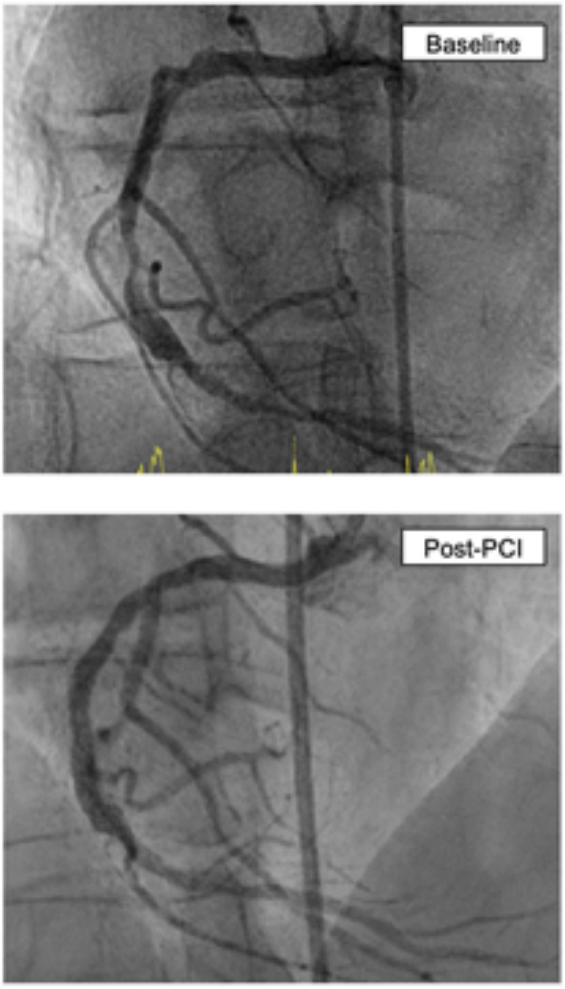
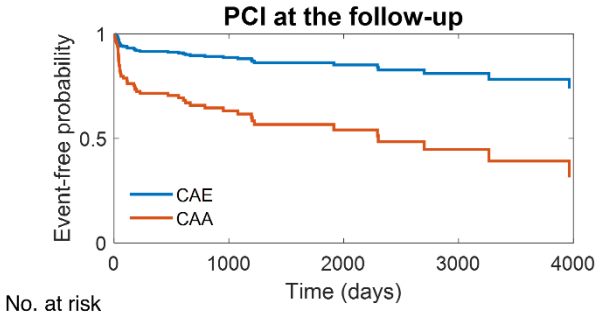
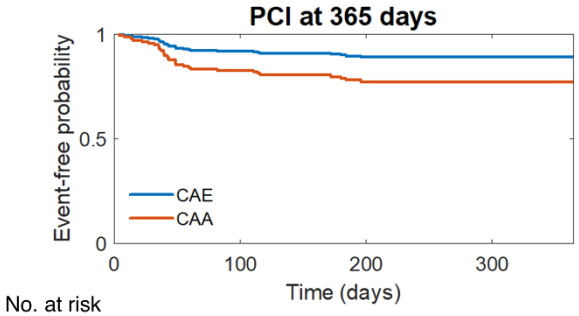


Figure S7

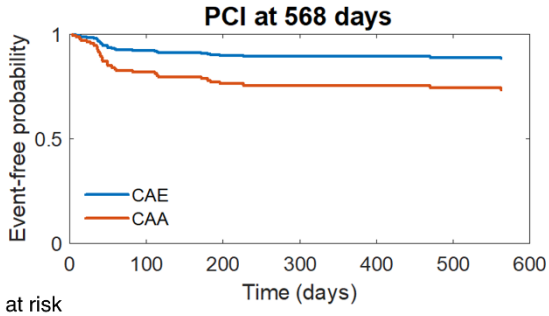
Patients presenting either coronary artery ectasia (CAE) or coronary artery aneurysms (CAAs) showed an elevated incidence of percutaneous coronary interventions (PCIs) in not-dilated coronary artery segments at follow-up.



No. at risk				
CAE	145	43	16	8
CAA	75	32	16	8



No. at risk				
CAE	145	116	108	98
CAA	75	61	49	49



No. at risk						
CAE	145	116	108	98	85	77
CAA	75	61	49	49	49	44

Figure S8

Results of the Cox models for coronary artery ectasia (CAE) or coronary artery aneurysms (CAAs) and time-dependent hazard ratios (HRs) of a single-event component of major adverse cardiovascular events (MACE). Other abbreviations: FUP, follow-up; PCI, percutaneous coronary intervention.

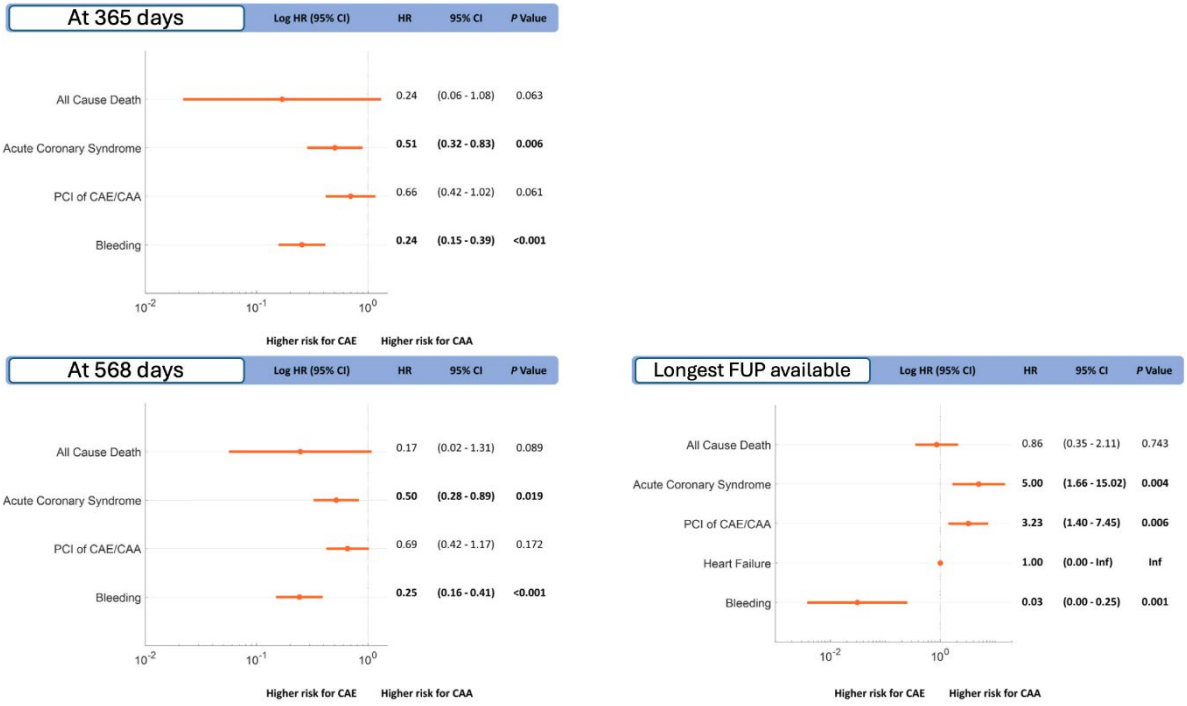


Figure S9

Results of the Cox models for coronary artery ectasia (CAE) or coronary artery aneurysms (CAAs) and the time-dependent hazard ratios (HRs) of major adverse cardiovascular events (MACE) in the presence or absence of coronary artery disease (CAD).

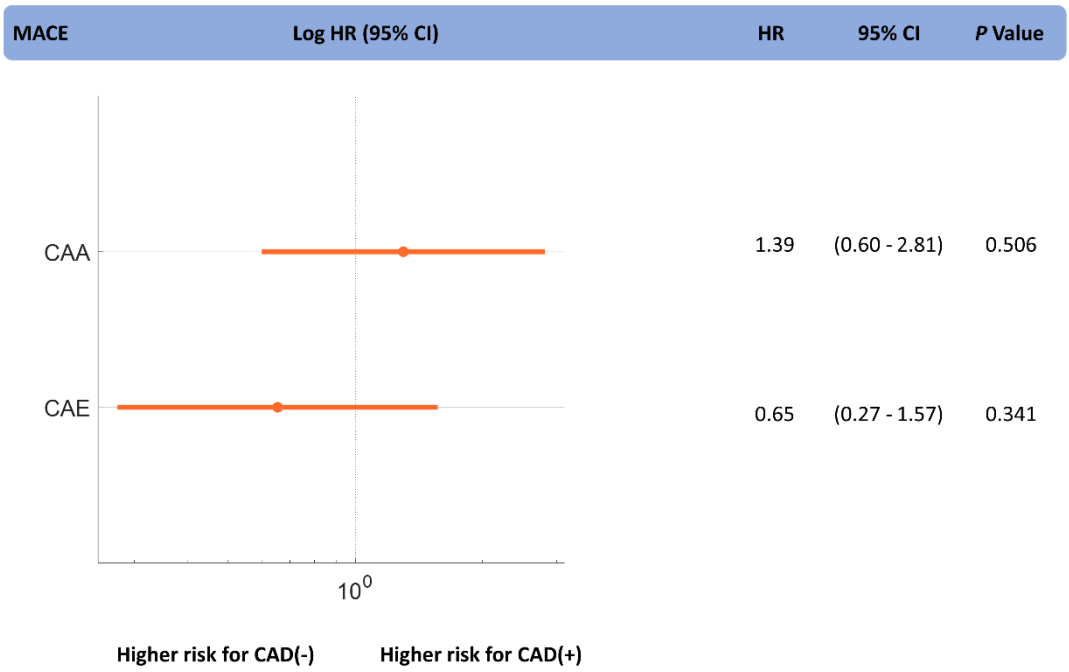


Table S1 – Baseline laboratory values.

	Total (Patient N = 281)	**"CAA"** (Patient N = 78)	**"CAA-CAE"** (Patient N = 42)	**"CAE"** (Patient N = 161)	***p-value*** (2-sided)
Haemoglobin, g/dL	13.6 (11.7–14.8)	13.1 (9.7–14.7)	13.3 (11.0–15.1)	13.8 (12.2–14.9)	0.316
Leukocytes, $\times 10^9$/L	7.59 (6.19–9.49)	7.45 (6.26–9.59)	7.83 (6.32–10.86)	7.43 (6.17–9.32)	0.472
hs-CRP, mg/L	3.30 (1.00–8.40)	4.30 (1.40–9.40)	3.40 (1.40–7.40)	2.70 (0.80–7.80)	0.256
hs-troponin T, ng/L	26.00 (12.00–189.00)	21.00 (11.00–90.00)	47.00 (11.00–1068.00)	27.00 (12.00–141.00)	0.729
Creatinine, µmol/L	86.00 (74.00–106.00)	87.00 (74.00–103.00)	85.00 (73.00–101.00)	86.00 (74.50–109.00)	0.741
HbA1c, %	5.80 (5.50–6.10)	5.70 (5.40–6.00)	5.80 (5.50–6.10)	5.80 (5.50–6.10)	0.146
LDL cholesterol, mmol/L	2.20 (1.60–3.20)	2.30 (1.60–3.00)	2.50 (1.90–3.40)	2.10 (1.50–3.20)	0.484
HDL cholesterol, mmol/L	1.09 (0.92–1.32)	1.15 (0.95–1.39)	1.09 (0.92–1.32)	1.05 (0.92–1.31)	0.431
Triglycerides, mmol/L	1.32 (0.93–1.99)	1.38 (0.99–1.98)	1.07 (0.76–1.78)	1.35 (0.91–2.09)	0.220
TSH, mIU/L	1.74 (1.28–2.47)	1.92 (1.32–3.21)	1.70 (1.21–2.47)	1.62 (1.25–2.20)	0.370

Abbreviations: HbA1c: Haemoglobin A1c; HDL: High-Density Lipoprotein; hs-CRP: High-sensitivity C-reactive protein; LDL: Low-Density Lipoprotein; TSH: Thyroid-Stimulating Hormone.

Table S2 – Vessel-level analysis.

	Coronary artery ectasia (CAE)									
	Total		**Type 1**		**Type 2**		**Type 3**		**Type 4**		***p-value***
	(N = 324)		**(N = 100)**		**(N = 109)**		**(N = 47)**		**(N = 68)**		
LMCA	13	4.0%	7	7.0%	5	4.6%	1	2.1%	0	0.0%	0.018
LAD	71	21.9%	26	26.0%	27	24.8%	3	6.4%	15	22.1%	<0.001
DA	2	0.6%	2	2.0%	0	0.0%	0	0.0%	0	0.0%	0.112
LCX	86	26.5%	32	32.0%	23	21.1%	11	23.4%	20	29.4%	0.015
RCA	152	46.9%	33	33.0%	54	49.5%	32	68.1%	33	48.5%	0.029

	Coronary artery aneurysm (CAA)								
	Total		**Fusiform**		**Giant**		**Saccular**		
	(N = 152)		**(N = 106)**		**(N = 4)**		**(N = 42)**		***p-value***
LMCA	11	7.2%	10	9.4%	0	0.0%	1	2.4%	<0.001
LAD	52	34.2%	35	33.0%	0	0.0%	17	40.5%	<0.001
DA	8	5.3%	4	3.8%	0	0.0%	4	9.5%	0.135
LCX	33	21.7%	25	23.6%	1	25.0%	7	16.7%	<0.001
OM	6	3.9%	4	3.8%	0	0.0%	2	4.8%	0.135
RCA	39	25.7%	25	23.6%	3	75.0%	11	26.2%	<0.001
PDA	1	0.7%	1	0.9%	0	0.0%	0	0.0%	0.368
PLA	2	1.3%	2	1.9%	0	0.0%	0	0.0%	0.135

Abbreviations: LMCA: left main coronary artery; LAD: left anterior descending artery; DA: diagonal artery; LCX: circumflex branch of the left coronary artery; OM: obtuse marginal branch; RCA: right coronary artery; PDA: patent ductus arteriosus; PLA: posterior left ventricular artery.

Table S3 – Clinical events during the index hospitalisation.

	Total (Patient N = 273)	**"CAA"** (Patient N = 77)	**"CAACAE"** (Patient N = 38)	**"CAE"** (Patient N = 158)	***p-value*** (2-sided)
In-hospital Event, n (%)	80 (28.30)	26 (33.77)	8 (21.05)	46 (29.11)	0.369
MACE, n (%)	39 (14.29)	13 (16.88)	4 (10.53)	22 (13.82)	0.644
Death, n (%)	4 (1.47)	2 (2.60)	1 (2.63)	1 (0.63)	0.407
Re-animation, n (%)	2 (0.73)	1 (1.30)	1 (2.63)	0 (0.0)	0.184
Periprocedural MI, n (%)	4 (1.47)	1 (1.30)	0 (0.0)	3 (1.90)	0.675
Bleeding, n (%)	15 (5.49)	6 (7.79)	0 (0.0)	9 (5.70)	0.223
Stroke, n (%)	4 (1.47)	1 (1.30)	0 (0.0)	3 (1.90)	0.675
Acute Heart Failure, n (%)	17 (6.23)	4 (5.19)	2 (5.26)	11 (6.96)	0.841
Acute Kidney Failure, n (%)	12 (4.40)	4 (5.19)	1 (2.63)	7 (4.43)	0.819

The study population was stratified according to the presence of coronary artery aneurysms (CAAs), coronary artery ectasia (CAE) or a combination of both (CAA-CAE). Other Abbreviations: MACE: major adverse cardiovascular events; MI: myocardial infarction.

Table S4 – De novo cancers, inflammatory diseases and infections at follow-up.

	Total (Patient N = 257)	**"CAA"** (Patient N = 75)	**"CAA-CAE"** (Patient N = 37)	**"CAE"** (Patient N = 145)	***p-value*** (2-sided)
Cancer at follow-up, n (%)	21 (8.2)	5 (6.7)	5 (13.5)	11 (7.6)	0.427
Type of cancer:					0.433
• Ethmoidal cell carcinoma, n (%)	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.7)	
• Gastrointestinal stromal tumour, n (%)	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.7)	
• Hepatocellular carcinoma, n (%)	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.7)	
• Kidney, n (%)	1 (0.4)	1 (1.3)	0 (0.0)	0 (0.0)	
• Lung, n (%)	4 (1.6)	2 (2.7)	1 (2.7)	1 (0.7)	
• Lymphoma, n (%)	1 (0.4)	0 (0.0)	1 (2.7)	0 (0.0)	
• Melanoma, n (%)	2 (0.8)	1 (1.3)	1 (2.7)	0 (0.0)	
• Non-melanoma skin cancer, n (%)	6 (2.4)	1 (1.3)	2 (5.4)	3 (2.1)	

• Prostate, n (%)	3 (1.2)	0 (0.0)	0 (0.0)	3 (2.1)	
• Stomach, n (%)	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.7)	
Inflammatory disease at follow-up, n (%)	8 (3.1)	2 (2.7)	2 (5.4)	4 (2.8)	0.686
Type of inflammatory disease:					0.135
• Amyloidosis, n (%)	1 (0.4)	0 (0.0)	1 (2.7)	0 (0.0)	
• Arthritis, n (%)	2 (0.8)	0 (0.0)	1 (2.7)	1 (0.7)	
• CNS inflammatory diseases, n (%)	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.7)	
• Gout, n (%)	3 (1.2)	1 (1.3)	0 (0.0)	2 (1.4)	
• Vasculitis, n (%)	1 (0.4)	1 (1.3)	0 (0.0)	0 (0.0)	
Infection at follow-up, n (%)	43 (16.7)	13 (17.3)	4 (10.8)	26 (17.9)	0.577
Type/site of infection:					0.689
• COVID-19, n (%)	3 (1.2)	1 (1.3)	0 (0.0)	2 (1.4)	
• Dermatological, n (%)	6 (2.3)	3 (4.0)	0 (0.0)	3 (2.1)	

•	FUO, n (%)	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.7)
•	Gastrointestinal, n (%)	8 (3.1)	3 (4.0)	0 (0.0)	5 (3.4)
•	Pneumological, n (%)	15 (5.8)	5 (6.7)	3 (8.1)	7 (4.8)
•	Otorhinolaryngological, n (%)	2 (0.8)	0 (0.0)	1 (2.7)	1 (0.7)
•	Urological, n (%)	8 (3.1	1 (1.3)	0 (0.0)	7 (4.8)

The study population was stratified according to the presence of coronary artery aneurysms (CAAs), coronary artery ectasia (CAE) or a combination of both (CAA-CAE). Other Abbreviations: CNS: central nervous system; FUO: fever of unknown origin.