Myocardial infarction during giant cell arteritis: A cohort study

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Hélène GREIGERT,[1,2,3] Marianne ZELLER,[4] Alain PUTOT,[4,5] Eric STEINMETZ,[6] Béatrice TERRIAT,[2] Maud MAZA,[4] Nicolas FALVO,[1] Géraldine MULLER,[7] Louis ARNOULD,[8] Catherine CREUZOT-GARCHER,[8] André RAMON,[9] Laurent MARTIN,[10] Georges TARRIS,[10] Tibor PONNELLE,[11] Sylvain AUDIA,[1,3] Bernard BONNOTTE, [1,3] Yves COTTIN,[12] Maxime SAMSON[1,3]

1 - Department of Internal Medicine and Clinical Immunology, Dijon University Hospital, Dijon, France
2 - Department of Angiology, Dijon University Hospital, Dijon, France
3 - Université Bourgogne Franche-Comté, INSERM, EFS BFC, UMR1098, RIGHT Interactions Greffon-Hôte-Tumeur/Ingénierie Cellulaire et Génique, F-21000 Dijon, France
4 - PEC2, EA 7460 Dijon, France
5 - Department of Geriatric Internal Medicine, Dijon University Hospital, Dijon, France
6 - Department of Cardiovascular and Thoracic Surgery, Dijon University Hospital, Dijon, France
7 - Department of Internal Medicine and Systemic Diseases, Dijon University Hospital, Dijon, France
8 - Department of Ophthalmology, Dijon University Hospital, Dijon, France
9 - Department of Rheumatology, Dijon University Hospital, Dijon, France
10 - Department of Pathology, Dijon University Hospital, Dijon, France
11 – Cypath pathology center, Dijon, France
12 - Cardiology Department, Dijon University Hospital, Dijon, France

CORRESPONDENCE TO:
Prof. Maxime Samson
Service de Médecine Interne et Immunologie Clinique
Hôpital François Mitterrand,
Centre Hospitalier Universitaire de Dijon
14 boulevard Gaffarel
21000 Dijon, France
Tel: +33 3 80 29 34 32
Fax: +33 3 80 29 38 46
Email: maxime.samson@u-bourgogne.fr; maxime.samson@chu-dijon.fr

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ABTRACT

Background: Cardiovascular risk is increased in giant cell arteritis (GCA). We aimed to characterize myocardial infarction (MI) in a GCA cohort, and to compare the GCA and non-GCA population affected by MI.

Methods: In patients with a biopsy-proven diagnosis of GCA between 1 January 2001 and 31 December 2016 in Côte D'Or (France), we identified patients with MI by crossing data from the territorial myocardial infarction registry (*Observatoire des Infarctus de Côte d'Or*) database. Five controls (non-GCA + MI) were paired with one case (GCA + MI) after matching for age, sex, cardiovascular risk factors and prior cardiovascular disease. MI were characterized as type 1 MI (T1MI), resulting from thrombus formation due to atherothrombotic disease, or type 2 MI (T2MI), due to a myocardial supply/demand mismatch. GCA-related MI was defined as MI occurring within 3 months of a GCA flare (before or after).

Results: Among 251 biopsy-proven GCA patients, 13 MI cases were identified and paired with 65 controls. MI was GCA-related in 6/13 cases, accounting for 2.4% (6/251) of our cohort. T2MI was more frequently GCA-related than GCA-unrelated (80% vs. 16.7%, p=0.080), and GCA diagnosis was the only identified triggering factor in 75% of GCA-related T2MI. GCA-unrelated MI were more frequently T1MI and occurred in patients who had received a higher cumulative dose of prednisone (*p*=0.032). GCA was not associated with poorer one-year survival.

Conclusions: GCA-related MI are mainly T2MI probably caused by systemic inflammation rather than coronaritis. GCA-unrelated MI are predominantly T1MI associated with atherothrombotic coronary artery disease.

INTRODUCTION

Giant cell arteritis (GCA) is the most frequent vasculitis in adults over 50 years. It is a granulomatous large-vessel vasculitis mainly involving the aorta and cranial arteries [1-3]. Clinical signs of GCA include nonspecific symptoms related to systemic inflammation such as asthenia and fever, and ischemic symptoms that are triggered by vascular remodelling of the affected arteries, leading to arterial stenosis [4] and ischemic complications such as headache, anterior ischemic optic neuropathy or stroke [5-7]. A temporal artery biopsy (TAB) showing granulomatous vasculitis with transmural infiltration by mononuclear cells is the gold standard for the diagnosis of GCA [8, 9]. The treatment of GCA relies on glucocorticoids (GC) which are very effective. However, relapses are frequent when the doses are tapered. This leads to GC-related side effects, which are the primary cause of morbidity in GCA patients [10] and sometimes requires to use GC-sparing drugs such as methotrexate or tocilizumab [11-14].

Acute myocardial infarction (MI) is currently defined as the association of a rise and/or a fall in cardiac troponin (cTn) values with at least one value above the 99th percentile of the upper reference limit and clinical evidence of myocardial ischemia (chest pain or electrocardiography) [15]. Type 1 MI (T1MI), the classical MI type, is due to atherothrombotic coronary artery disease (CAD) and is related to an acute atherothrombotic coronary event as plaque rupture, ulceration, or erosion, resulting in intraluminal thrombosis or distal coronary embolization leading to cardiomyocyte necrosis. Type 2 MI (T2MI) was described more recently and is caused by myocardial ischemia resulting from an imbalance between oxygen supply and demand in the myocardium, in the absence of an acute atherothrombotic coronary event, with or without underlying CAD [15]. Multiple heterogeneous situations may lead to a myocardial supply/demand mismatch [15-21], but no specific criteria have been established so far. The most common underlying mechanisms associated with T2MI are anemia, arrhythmia and sepsis [16, 18].

In addition to the classical cranial phenotype of GCA, 29% to 83% of patients have extra-cranial large-vessel involvement such as aneurysm, particularly in the thoracic aorta, occlusion or stenosis [22-28]. Along this line, the risk of cardiovascular events (stroke, peripheral artery disease or MI) is higher in the first months after GCA onset, highlighting the potential role of vasculitis in the occurrence of these events [29-31]. Almost 16% of GCA patients have a stroke in the year after GCA diagnosis [32]. In 2.8 to 7% of cases, the strokes are GCA-related, meaning that the stroke occurred between the onset of GCA symptoms and 4 weeks after the start of treatment [5, 6, 33]. We previously demonstrated that GCA-related strokes were mainly triggered by a vasculitis process involving vertebral arteries [6]. Regarding MI, some cohort studies have reported an increased risk of MI, with

an adjusted hazard ratio (HR) ranging from 1.57 to 2.06 [31, 34, 35] and a higher risk during the first year after GCA diagnosis [31, 34]. Some case reports describing granulomatous vasculitis in coronary arteries after post-mortem examination of patients with MI have been reported [36], but no data are currently available to describe the precise characteristics of MI in GCA patients.

Taking advantage of the French regional myocardial infarction registry *Observatoire des Infarctus de Côte d'Or* (RICO) database, we designed this study to characterize MI in a GCA cohort and compare them to a non-GCA control population suffering from MI.

METHODS

In order to identify cases of MI associated with GCA in a geographically defined area (Côte d'Or, France, 533,819 inhabitants in 2017), this population-based study relied on crossing data from two different databases.

Ascertainment of biopsy-proven GCA cases

Cases of GCA were identified using a database collecting all patients who underwent a TAB between 1 January 2001 and 31 December 2016 at the Dijon University Hospital, France, and at one private pathology center also located in Dijon, France. These two centers are responsible for the management of all TAB performed in patients living in Côte d'Or. Each TAB was performed on the side where symptoms were predominant. When possible, the TAB was guided by Doppler sonography. When clinical symptoms suggested GCA but the first TAB was negative, a second TAB was possible but not mandatory. Biopsies were also considered for patients with isolated polymyalgia rheumatica (PMR), even without specific manifestations of GCA, especially if general symptoms were severe and/or erythrocyte sedimentation rate (ESR) >50 mm/h. The two pathology departments used a similar protocol for microscopic examination of TAB: the artery was divided into several 2 mm segments, embedded in paraffin, and transverse slices 3–5 mm thick were stained with hematoxylin and eosin. TAB were then analyzed by expert pathologists (LM and TP). A positive TAB was defined as a biopsy showing mononuclear cell infiltration of the 3 layers of the artery wall (adventitia, media, intima), with or without the presence of granulomas and/or multinucleated giant cells [37]. A diagnosis of GCA was retained if patients fulfilled ≥3/5 American College of Rheumatology (ACR) criteria together with a positive TAB [2].

Ascertainment of MI cases

Cases of MI were identified using the RICO database. As previously described [38], RICO is a population-based survey that, since 1st January 2001, has prospectively collected data from all consecutive patients hospitalized for MI in the cardiology intensive care units of all public or privately funded hospitals receiving MI emergencies in Côte d'Or, a region in eastern France. Cases were ascertained by the prospective collection of consecutive admissions. MI was identified by an increase in serum troponin I (greater than the upper limit of normal for each hospital) and clinical symptoms of ischemia and/or characteristic electrocardiographic signs, according to current definition [15].

In order to identify cases of MI among our TAB-positive GCA population, we searched the RICO database for MI cases identified among patients diagnosed with GCA between 1 January 2001 and 31 December 2016.

Control population

Controls (MI patients without GCA) were extracted from the RICO database and paired with GCA cases (5:1 ratio) after matching for age, sex, cardiovascular risk factors (hypertension, diabetes, hyperlipidemia, smoking, and coronary disease heredity), and prior cardiovascular disease (stroke, carotid surgery, and peripheral artery disease).

Data collection and definitions

The clinical, biological and therapeutic data of patients with GCA were retrospectively obtained from the patient medical files.

For patients with MI, demographic data, cardiovascular risk factors and history of cardiovascular disease (prior MI, stroke, carotid surgery and peripheral artery disease) were collected prospectively, along with electrocardiogram (ECG) features on admission, and clinical and biological data. ST-segment elevation MI (STEMI) was diagnosed when new ST segment elevation ≥ 1 mm was seen in any location or when new left bundle branch block was found on the qualifying ECG. Blood samples were drawn at admission. Peak cardiac troponin I (cTnI) was also measured during the hospital stay. Left ventricular ejection fraction (LVEF) was measured <48h after admission by echocardiography. The GRACE score, which assesses the risk of in-hospital mortality, was calculated at admission [39, 40]. Data on coronary angiography, reperfusion procedures and medical treatment were also collected. For patients included in 2012 or later, the SYNTAX score was calculated for each coronary angiography.

CAD was defined as obstructive if coronary angiography showed at least one stenosis ≥ 50%, nonobstructive if there was at least one stenosis ≥ 20% but ≤ 50%, and patients were considered to have no CAD if coronary angiography showed no stenosis [41]. When stenoses (≥ 20%) were observed in several coronary arteries, CAD was defined as extensive. Type 1 or type 2 MI were retrospectively reviewed according to the fourth universal definition (2018) [15] and adjudicated by three experts (HG, AP and YC). Type 2 MI was diagnosed if coronary angiography showed no evidence of plaque rupture and at least one of the conditions considered to trigger an imbalance between demand and supply of oxygen in the myocardium at the onset of MI, as defined previously (sup Table 1) [15-21]. GCA was retained as a clinical condition triggering type 2 MI if it occurred at the time of a GCA flare. A GCA flare was defined as the occurrence of at least one clinical symptom of GCA with or without C-reactive protein (CRP) elevation, or a persistent increase CRP greater than 10 mg/L for at least 2 consecutive weeks, without any cause other than GCA and requiring an increase in GC dosage and/or immunosuppressant addition or change.

The diagnosis of GCA-related MI was retained when MI occurred within 3 months before or after a GCA flare.

Statistical analyses

Continuous variables, expressed as medians (interquartile range), were compared with Mann-Whitney tests. Qualitative variables, expressed as numbers (%), were compared with $\chi 2$ or Fisher's exact tests, as appropriate. The Kaplan-Meier method was used to estimate survival. Factors associated with survival were analyzed using log-rank tests. Then, a multivariate Cox regression model with backward selection (exit threshold: $p < 0.2$) was used to identify variables independently associated with death. Candidate variables were all non-redundant variables with $p \leq 0.2$ in the univariate analysis. Thresholds for continuous variables were set using medians, 25^{th} or 75^{th} percentiles. Statistical significance was set at $p < 0.05$ (two-tailed). IBM® SPSS® Statistics 22.0 software was used for statistical analyses.

Ethics

The RICO Survey complies with the Declaration of Helsinki and was approved by the ethics committee of the University Hospital of Dijon. Each patient gave written consent before participation.

RESULTS

Studied population

Between 1 January 2001 and 31 December 2016, a biopsy-proven diagnosis of GCA was made in 251 consecutive patients in Côte d'Or, France. Sixteen of these patients were identified as having MI in the RICO database, and 3 of the 16 were excluded from the analysis because MI occurred more than 3 months before the diagnosis of GCA. Finally, 13 patients were included in the study and paired with 65 non-GCA controls (Figure 1).

Characteristics of MI in GCA patients

Table 1 shows MI and GCA characteristics of the 13 cases (GCA + MI). MI was considered to be related to a GCA flare in 6 patients (46%, patients no. 1-6) with a median time of 25 days between GCA diagnosis and occurrence of MI (range 0.1 to 127 months). The frequency of GCA-related MI in our cohort was 2.4% (6/251). GCA-related MI occurred more frequently at the time of GCA diagnosis (4/6, 67%) than at the time of a relapse (2/6, 33%). The majority of GCA-related MI were type 2 MI (4/5, 80%), and the vasculitis flare was the only identified triggering factor in 3/4 patients of GCA-related type 2 MI (75%). In addition, patient n°1 had healthy coronary arteries at coronary angiography and his left ventricular ejection fraction (LVEF) improved from 35% to 55% after 4 months of GC therapy. Patient n°4 had an obstruction of the left anterior descending coronary artery due to a thrombosed aneurysm without atherosclerotic lesion on coronary arteries, thus suggesting an underlying vasculitis process. This patient had also an inflammatory parietal thickening of the wall of subclavian and axillary arteries together with an aortitis revealed by PET-CT (sup Figure 1). Since there was no evidence of atheromatous plaque rupture, the diagnosis of type 2 MI related to a GCA flare was retained.

Comparison between GCA-related and GCA-unrelated MI

Comparisons between GCA-related MI and GCA-unrelated MI are summarized in Table 2. Patients with GCA-related MI were younger (79 vs. 86 years, p = 0.005). Although the frequency of cardiovascular risk factors was not different between groups, none of the patients with GCA-related MI had a prior cardiovascular event, whereas 57.1% of patients with a GCA-unrelated MI had at least one prior cardiovascular event (p = 0.070). So, while none of the GCA-related MI patients were treated with antiplatelet therapy at the time of MI diagnosis, 57% of the other group was (p = 0.070). The cTnI level was higher in GCA-related MI than GCA-unrelated MI (29.6 vs. 8.6 µg/L, p = 0.035). Type 2 MI tended to be more frequent in GCA-related MI (80 vs. 16.7%, p = 0.080). Coronary artery

disease was always extensive in patients with GCA-unrelated MI whereas it concerned only 33.3% of patients with GCA-related MI (p = 0.034).

Regarding the characteristics relative to GCA, the only difference between groups was the significantly higher cumulative doses of prednisone at 3, 6, and 12 months in patients whose MI was unrelated to GCA (Table 2).

Comparison of MI characteristics between GCA patients and controls

Table 3 depicts the comparison of MI between cases (GCA patients) and matched controls. Biological parameters related to systemic inflammation were more pronounced in the GCA group: lower hemoglobin (11.0 vs. 14.3 g/dL, p = 0.006) and higher CRP (36.9 vs. 5.0 mg/L, p = 0.006). The left main coronary artery was more often responsible for MI in GCA patients (16.7%) than controls (0%) (p = 0.028). Other MI characteristics, including left ventricular function, GRACE score, SYNTAX score and MI treatment, did not differ between groups.

Outcomes

One-year survival after MI tended to be poorer in cases than controls (67 vs. 84%, p = 0.157) (Figure 2A). Subsequent analyses showed that one-year survival was dramatically lower in patients with GCA-unrelated MI than in matched controls among non-GCA patients (50 vs. 91%; p = 0.004), which was not the case for GCA-related MI patients and matched controls among non-GCA patients (83 vs. 74%; p = 0.729) (Figures 2B and 2C). Regardless of the multivariate model used, a GRACE score >173 was the only factor associated with poorer survival one year after the occurrence of MI. Age, GCA diagnosis, and the relation between MI and GCA had no effect (Table 4).

DISCUSSION

Using the RICO database, our study provides an original description of the characteristics of MI occurring in GCA patients, which was not provided in the previous studies reporting an increased risk of MI in GCA [29, 31, 34, 35]. Furthermore, by matching cases and controls on major cardiovascular risk factors and history of cardiovascular disease, we were able to specifically investigate the prognostic value of GCA in MI. Our results confirm that GCA-related MI is a rare event. It occurred in only 2.4% of our GCA cohort, which is 2-3 times lower than GCA-related stroke (7%), as reported in a previous study with the same design and in the same geographical area [6].

When we compared the characteristics of MI in GCA patients and a matched control population, the left main coronary artery was more frequently involved as a culprit artery in GCA patients than in controls. By way of comparison, in the whole RICO population over 50 years included during the

same period, only 2.1% of the patients (338/15,768) presented a MI related to left main coronary artery. This artery arises directly from the aorta, so that we hypothesize it could be preferentially affected in GCA because of its contiguity with vasculitis of the ascending thoracic aorta. Indeed, one of our patients had left main MI and a dilated ascending aorta (45 mm) with aortic insufficiency, which are usual complications of aortitis.

Contrary to strokes, which are generally related to vasculitis involving the vertebral arteries, vasculitis involving the coronary arteries does not seem to be the main reason behind the occurrence of MI in GCA [6]. Specifically, only one patient had morphological abnormalities in the coronary arteries suggestive of coronary vasculitis. Our results indicate that GCA-related MI are mainly type 2 MI, usually triggered by a GCA flare and preferentially occurring at the time of GCA diagnosis, when systemic inflammatory response is the strongest.[47] Systemic inflammation, which is a hallmark of GCA flares, probably triggers type 2 MI in GCA through a mechanism similar to what has been described in sepsis, *i.e.* increasing myocardial oxygen demand because of high heart rate and reducing perfusion pressure due to vasodilation, resulting in decreased preload [16, 18, 19, 42, 43].

MI that were unrelated to GCA occurred several years after the diagnosis of GCA, usually while the disease was in remission. GCA-unrelated MI was also found in older patients who tended to have extensive CAD and at least 1 prior cardiovascular event. Consistently, these MI were more frequently type 1 MI. It is worth noting that these patients had received a higher cumulative dose of prednisone than the patients who had GCA-related MI. This result underlines that GC probably contributes to the development of atherosclerosis and the occurrence of cardiovascular events [44-46]. In addition, GCA-unrelated MI was associated with a poorer prognosis, which was not related to GCA but rather to the severity of MI, as reported by the GRACE score.

Our study has some limitations. First, the small number of GCA + MI patients identified in this work, mainly because MI is a very rare event in the course of GCA. Second, RICO only identifies MI in patients hospitalized in cardiac intensive care units. Therefore, the rate of GCA-related MI may have been underestimated in our study. It is indeed possible that some fragile patients might have not been hospitalized in cardiology units while they had a MI [19]. The number of patients with GCA could also have been underestimated. Even if all TAB performed in patients living in Côte d'Or were retrieved, it cannot be excluded that some GCA patients refused the biopsy or that TAB was not performed because GCA diagnosis was confirmed otherwise. Indeed, GCA can be diagnosed even if TAB is negative since the sensitivity of TAB ranges from ~60% to 80% [2, 47] and because some GCA patients have an extra-cephalic phenotype without cervical artery involvement but evidence of vasculitis in large-vessel vasculitis such as the aorta, subclavian and/or carotid arteries [48]. Along

this line, *Muratore and al.* demonstrated that in this population, accounting for 36% of GCA patients of their cohort, TAB was positive in only 52% of cases [48]. Even if we assume that our study design may have underestimated the number of GCA patients and thus cases of MI, restricting our analysis to biopsy-proven GCA allowed us to analyze a population of GCA patients with a homogenous phenotype and a definite diagnosis.

CONCLUSION

We provide here, for the first time, an in-depth insight of MI characteristics occurring in biopsy-proven GCA patients. Even if the present study is limited by its retrospective design and the limited number of cases, it demonstrates that GCA-related MI is a rare event with specific characteristics and also suggest that these cases of MI are mainly type 2 MI whose mechanism is not clear but that seem to be triggered by systemic inflammation rather than vasculitis involving the coronary arteries. Altogether, our results suggest that GCA could be considered as a cause of type 2 MI. By contrast, in patients whose GCA is under control, GC therapy is associated with preponderance of type 1 MI, further supporting the hypothesis of a pro-atheromatous effect of GC.

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LEGENDS OF THE FIGURES

Figure 1: Flow Chart of the study

Figure 2 A, B, C: Overall survival, calculated from the date of MI diagnosis. A: comparison of overall survival between non-GCA patients and cases (MI + GCA) patients; B: comparison of overall survival between non-GCA patients and GCA-related MI patients; C: comparison of overall survival between non-GCA patients and GCA-unrelated MI. P is the result of log-rank tests

DISCLOSURES

Maxime SAMSON: Roche-Chugaï (invitation to congress, personnel fees for symposium and boards), Abbvie (consulting).

Bernard BONNOTTE: Roche-Chugaï (personnel fees for symposium and boards)

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CONTRIBUTORSHIP STATEMENT

HG and MS were the principal investigators and take primary responsibility for the paper. HG, AP, GM, AR, SA, BB, YC and MS recruited the patients. HG, MZ, AP, BT, MM, NF, GM, LA, CCG, AR, LM, GT, TP, BB, YC and MS collected data. HG, MZ, AP, ES, BT, YC, BB and MS contributed to data interpretation. HG and MS did statistical analyses. HG, BB, YC and MS drafted the manuscript.

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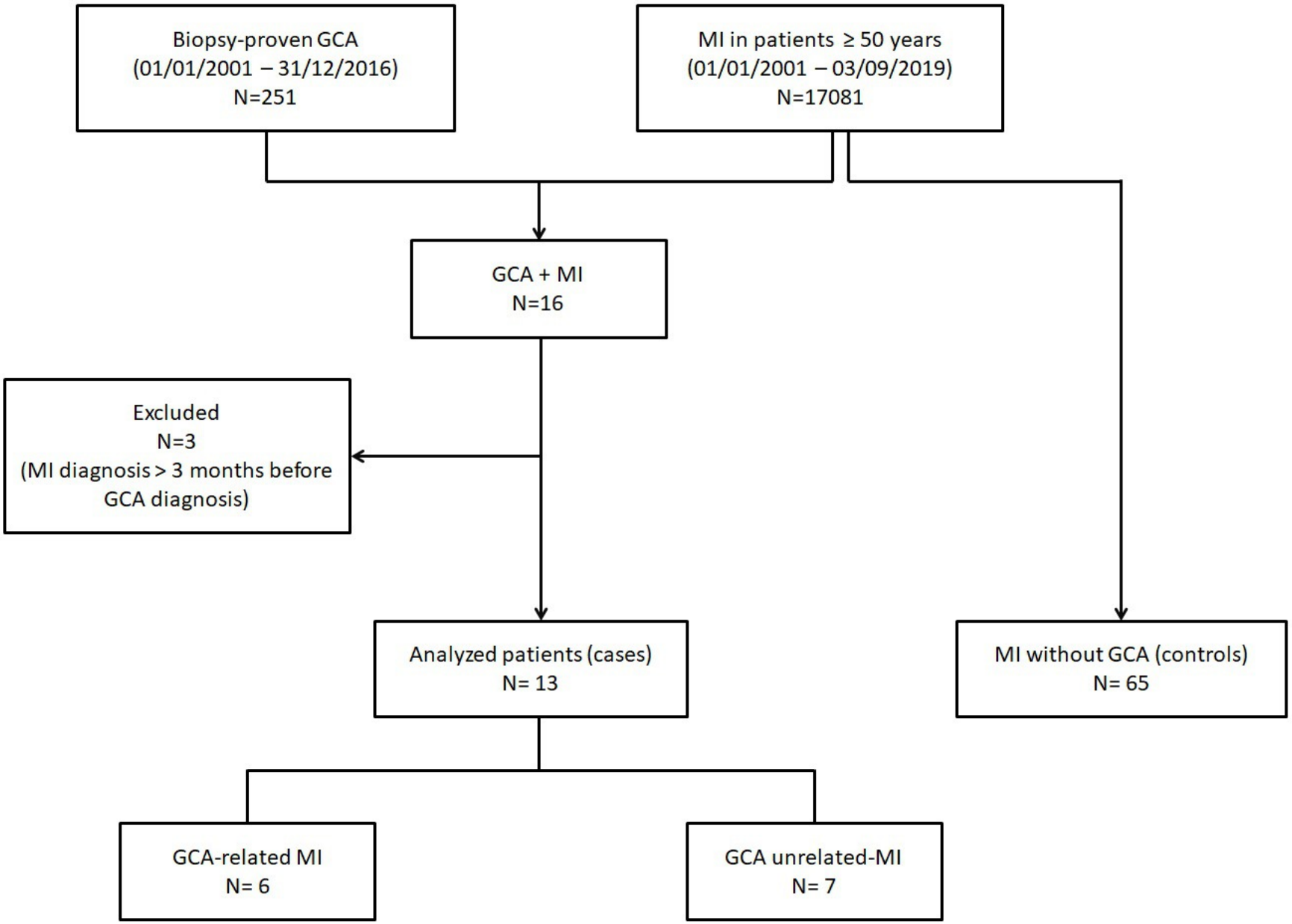
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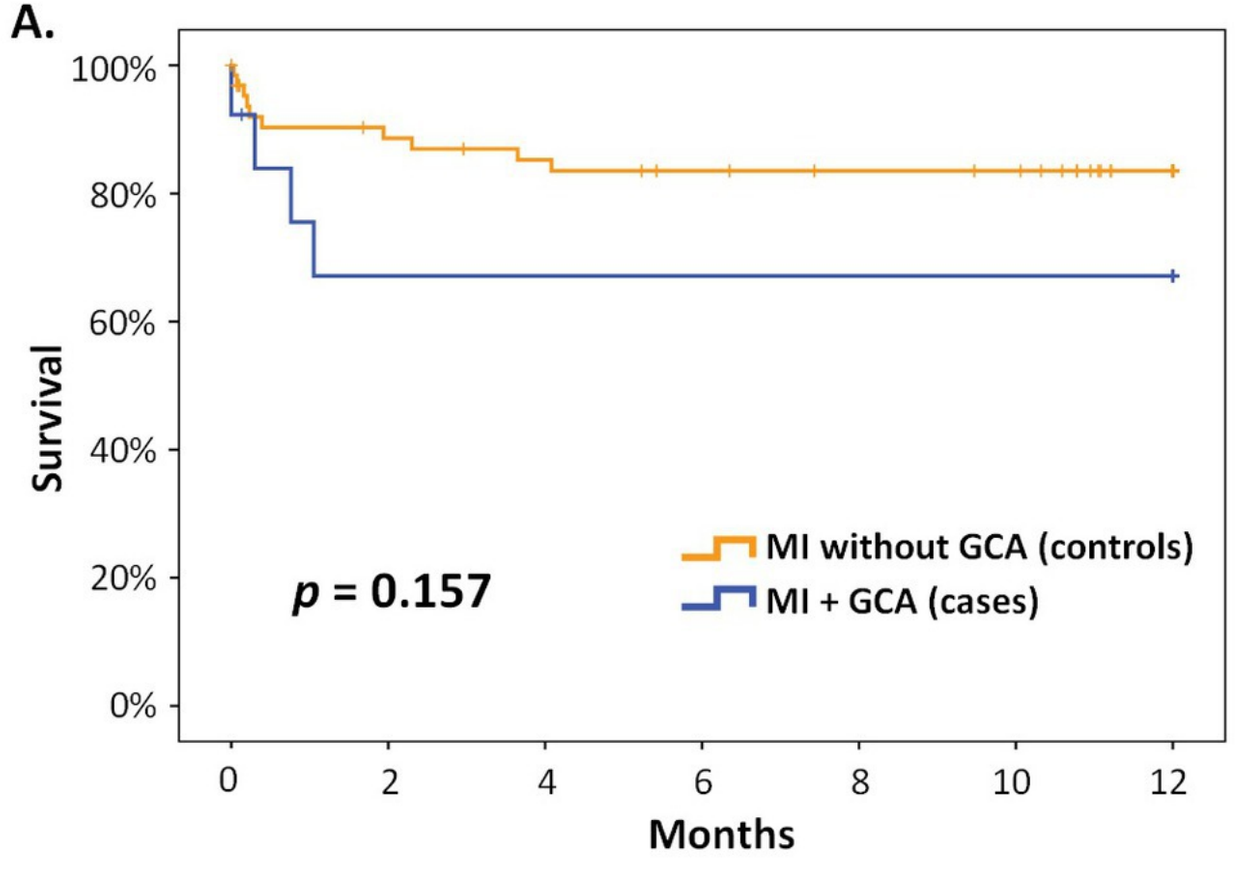
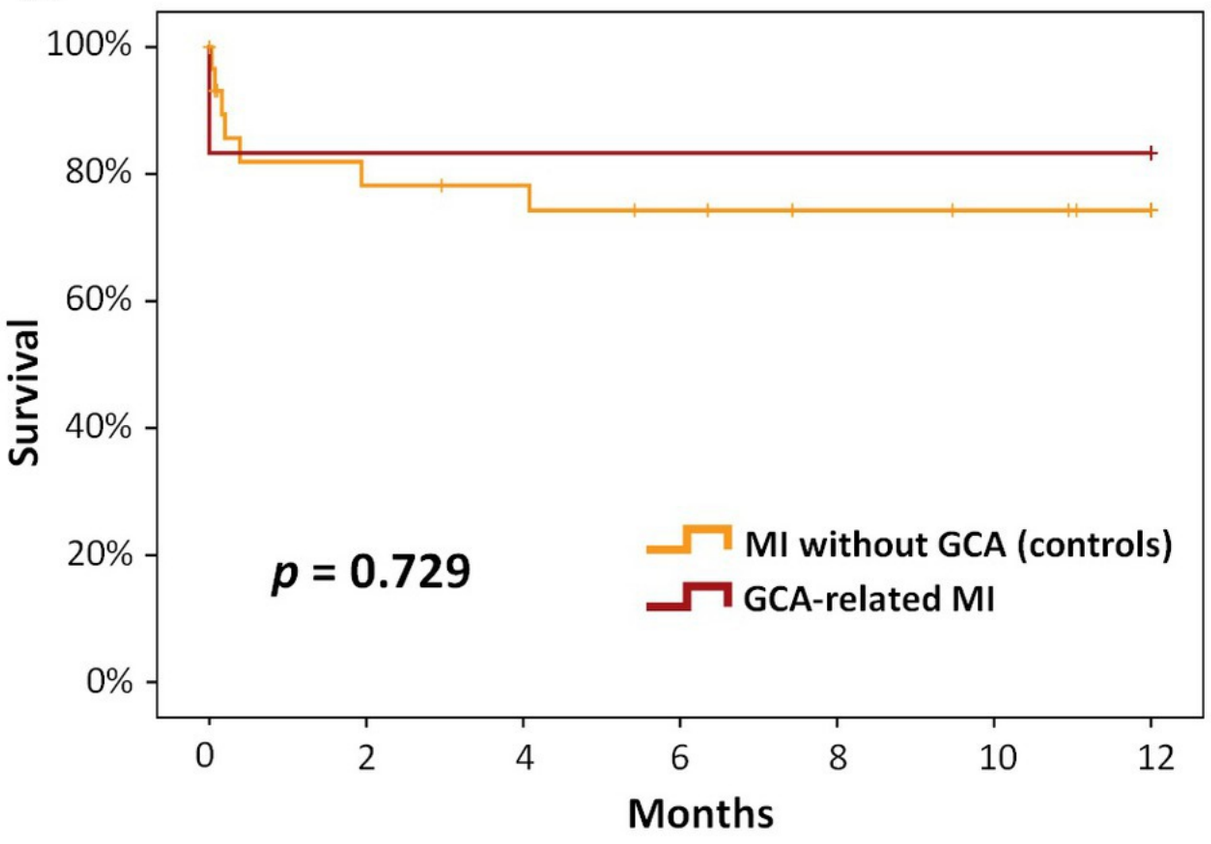
(01/01/2001 – 31/12/2016)
N=251
MI in patients ≥ 50 years
(01/01/2001 – 03/09/2019)
N=17081
GCA + MI
N=16
Excluded
N=3
(MI diagnosis > 3 months before GCA diagnosis)
Analyzed patients (cases)
N= 13
MI without GCA (controls)
N= 65
GCA-related MI
N= 6
GCA unrelated-MI
N= 7

A.


100%
80%
60%
40%
20%
0%
Survival
p = 0.157
MI without GCA (controls)
MI + GCA (cases)
0
2
4
6
8
10
12
Months

B.


100%
80%
60%
40%
20%
0%
Survival
p = 0.729
MI without GCA (controls)
GCA-related MI
0
2
4
6
8
10
12
Months

C.

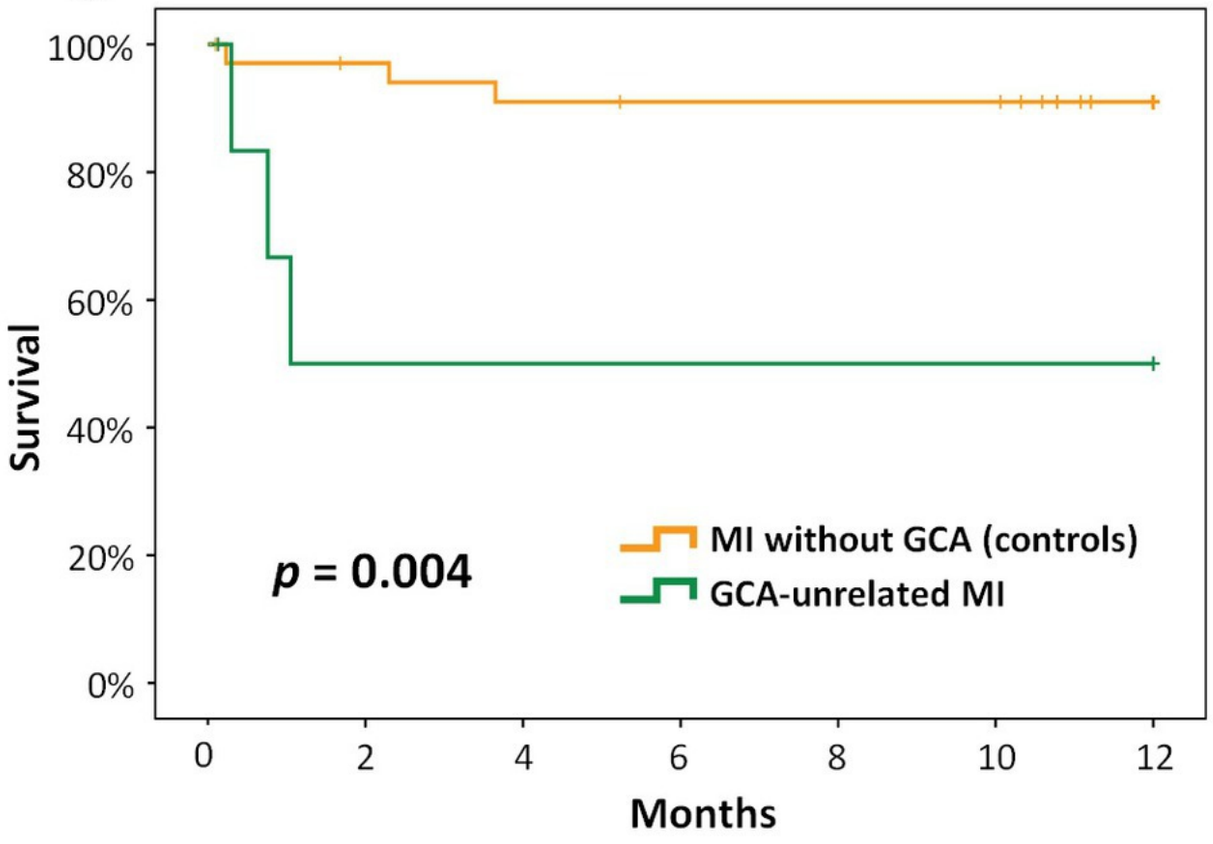

100%
80%
60%
40%
20%
0%
Survival
p = 0.004
MI without GCA (controls)
GCA-unrelated MI
0
2
4
6
8
10
12
Months

Table 1: MI characteristics of the 13 cases

	Age at GCA diagnosis	Sex	GCA characteristics at diagnosis	Vascular complication(s) at GCA diagnosis (apart from MI)	Time between GCA and MI (months)	Age at MI diagnosis	GCA characteristics at MI diagnosis	Type of MI	Triggering factor(s) of T2MI	Type of CAD	Extension of CAD	Culprit coronary artery	CRP at MI diagnosis (mg/L)	GCA-related MI
Patient 1	67	F	fever, headache, temporal pulse abolition	–	0.1	67	Diagnosis	2	Vasculitis	no CAD	–	–	165	yes
Patient 2	79	F	headache, scalp tenderness	Stroke	0.2	79	Diagnosis	1	–	ob-CAD	Not extensive	Left anterior descending artery	130	yes
Patient 3	72	F	*ND*	–	0.3	72	Diagnosis	*NA*	*NA*	ob-CAD	Not extensive	Left main coronary artery	4	yes
Patient 4	80	F	weight loss	Inflammatory parietal thickening of subclavian and axillary arteries (US and scan), aortitis (PET-CT)	1	80	Diagnosis	2	Vasculitis	ob-CAD	Not extensive	Left anterior descending artery	12	yes
Patient 5	83	F	fever, asthenia	–	21	85	Relapse	2	Vasculitis	ob-CAD	Extensive	Right coronary artery	107	yes
Patient 6	71	M	asthenia	–	127	81	Relapse	2	Sepsis and vasculitis	ob-CAD	Extensive	Left anterior descending artery	113	yes
Patient 7	82	F	jaw claudication	–	8	82	MI > 3 months of a GCA flare	*NA*	*NA*	ob-CAD	Extensive	Circumflex coronary artery	25	no
Patient 8	82	M	asthenia, weight loss, scalp tenderness, jaw claudication	Dilatation of the ascending thoracic aorta (45 mm)	48	86	Remission	1	–	ob-CAD	Extensive	Left main coronary artery	49	no
Patient 9	82	F	headache	–	52	86	Remission	1	–	ob-CAD	Extensive	Right coronary artery	10	no
Patient 10	74	F	headache	Bilateral carotid stenoses, right PION	78	81	Remission	2	Sepsis	ob-CAD	Extensive	Right coronary artery	182	no
Patient 11	77	F	asthenia, scalp tenderness	Stroke, stenosis of the left subclavian artery	117	87	Remission	1	–	ob-CAD	Extensive	*NA*	3	no
Patient 12	75	F	asthenia, weight loss, scalp tenderness, jaw claudication, temporal pulse abolition	–	138	87	MI > 3 months of a GCA flare	1	–	ob-CAD	Extensive	Circumflex coronary artery	8	no
Patient 13	76	F	fever, asthenia, weight loss, temporal pulse abolition	–	154	89	Remission	1	–	ob-CAD	Extensive	Right coronary artery	*NA*	no

CAD = coronary artery disease; F = female; GC = glucocorticoids; GCA = giant cell arteritis; M = male; MI = myocardial infarction; NA = not available; ob-CAD = obstructive-CAD; PION = posterior ischemic optic neuropathy; T2MI = type 2 myocardial infarction; US = ultrasonography

Table 2: Characteristics of patients with GCA-related or GCA-unrelated MI

	GCA-related MI (n = 6)	GCA-unrelated MI (n = 7)	*p*
MI characteristics			
Cardiovascular risk factors at MI onset			
Age (years), median (IQR)	79 (70 - 82)	86 (82 - 87)	**0.005**
Sex (M/F)	1/5	1/6	1.000
BMI (kg/m²), median (IDR)	24 (21 - 32)	24 (22 - 27)	1.000
Hypertension, n (%)	3 (50)	6 (85.7)	0.266
Hypercholesterolemia, n (%)	2 (33.3)	1 (14.3)	0.559
Diabetes, n (%)	1 (16.7)	2 (28.6)	1.000
Current smoker, n (%)	1 (16.7)	0 (0)	0.462
Family history of coronary disease, n (%)	0 (0)	3 (42.9)	0.192
History of cardiovascular event at MI onset, n (%)			
≥ 1 prior cardiovascular event	0 (0)	4 (57.1)	0.070
MI	0 (0)	1 (14.3)	1.000
Stroke	0 (0)	2 (28.6)	0.462
Carotid surgery	0 (0)	1 (14.3)	1.000
Peripheral artery disease	0 (0)	1 (14.3)	1.000
Biology, median (IQR)			
CRP (mg/L)	110 (10 - 139)	17 (7 - 82)	0.394
Creatinine clearance (ml/min/1,73m² (CKDEPI))	71 (39 - 86)	39 (30 - 61)	0.234
Peak of cTnI (µg/L)	29.6 (15.8 - 55.8)	8.6 (1.4 - 19.0)	**0.035**
LVEF, %, median (IQR)	55 (33 - 60)	45 (40 - 63)	0.755
GRACE score at admission, median (IQR)	150 (135 - 197)	174 (151 - 205)	0.429
STEMI, n (%)	2 (33.3)	3 (42.9)	1.000
Type of MI, n (%)			0.080
Type 1	1/5 (20)	5/6 (83.3)	
Type 2	4/5 (80)	1/6 (16.7)	
Coronary angiography characteristics			
Coronary artery disease, n (%)			0.462
No CAD	1 (16.7)	0 (0)	
nonobstructive-CAD	0 (0)	0 (0)	
obstructive-CAD	5 (83.3)	7 (100)	
CAD extension, n (%)			**0.034**
Not extensive	3 (50)	0 (0)	
Extensive	2 (33.3)	7 (100)	
Treatment, n (%)			
Reperfusion strategy			
Percutaneous coronary intervention	3 (50)	5 (71.4)	0.592
Coronary bypass surgery	0 (0)	1 (14.3)	1.000
Medical treatment alone	2 (33.3)	1 (14.3)	0.559
Antiplatelet medication (aspirin or clopidogrel) before MI	0 (0)	4 (57.1)	0.070
Statin before MI	3 (50)	2 (28.6)	0.592
Follow-up			
Duration of follow-up (months), median (IQR)	54.7 (27.7 - 111.8)	1.1 (0.3 - 29.6)	0.138
MI relapse in the following year, n (%)	2 (33.3)	1 (14.3)	0.559
GCA characteristics			
Age at GCA diagnosis (years), median (IQR)	75 (69 - 80)	77 (75 - 81)	0.445
Biology at GCA diagnosis, median (IQR)			
Haemoglobin (g/dL)	11.2 (9.8 - 13.3)	11.4 (9.9 - 12.3)	1.000
CRP (mg/L)	130 (54 - 150)	81 (36 - 113)	0.222
Clinical signs at GCA diagnosis, n (%)			
Fever	2/5 (40)	1 (14.3)	0.523
Asthenia	2/5 (40)	4 (57.1)	1.000
Weight loss	1/5 (20)	3 (42.9)	0.576
Headache	3/5 (60)	4 (57.1)	1.000
Stroke	1/5 (20)	1 (14.3)	1.000
Polymyalgia rheumatica	2/5 (40)	2 (28.6)	1.000
Glucocorticoids, median (IQR)			
Starting dose, mg/kg/day	0.7 (0.6 - 1.0)	0.9 (0.7 - 1.1)	0.429
Cumulative dose 3 months after diagnosis, mg	2900 (1600 - 3300)	3800 (2800 - 4000)	0.106
Cumulative dose 6 months after diagnosis, mg	4200 (3100 - 4500)	5100 (4500 - 6100)	**0.048**
Cumulative dose 12 months after diagnosis, mg	5700 (4450 - 6200)	7400 (6400 - 8325)	**0.032**
Cumulative dose 18 months after diagnosis, mg	7000 (5000 - 8150)	9800 (7900 - 11175)	0.063
Immunosuppressants, n (%)	1/5 (20)	2/6 (33.3)	1.000
GCA relapse, n (%)	4/5 (80)	5/6 (83.3)	1.000

CAD = coronary artery disease; BMI = body mass index; CRP = C-reactive protein; cTnI = cardiac troponin I; GCA = giant cell arteritis; IQR = interquartile range; LVEF = left ventricular ejection fraction; MI = myocardial infarction; n= number; STEMI = ST elevation myocardial infarction; TAB = temporal artery biopsy

Table 3*:* Characteristics of MI in GCA patients and controls

	Controls (MI without GCA) (n = 65)	Cases (MI + GCA) (n = 13)	*p*
Cardiovascular risk factors at MI onset			
Age (years), median (IQR)	82 (80 - 86)	82 (79 - 86)	0.962
Sex (M/F)	10/55	2/11	1.000
BMI (kg/m²), median (IDR)	25 (22 - 28)	24 (21 - 27)	0.578
Hypertension, n (%)	45 (69.2)	9 (69.2)	1.000
Hypercholesterolemia, n (%)	15 (23.1)	3 (23.1)	1.000
Diabetes, n (%)	15 (23.1)	3 (23.1)	1.000
Current smoker, n (%)	5 (7.7)	1 (7.7)	1.000
Family history of coronary disease, n (%)	15 (23.1)	3 (23.1)	1.000
History of cardiovascular event at MI onset, n (%)			
≥ 1 prior cardiovascular event	21 (32.3)	4 (30.8)	1.000
MI	6/64 (14.1)	1/12 (8.3)	1.000
Stroke	11/64 (17.2)	2 (15.4)	1.000
Carotid surgery	2 (3.1)	1 (7.7)	0.426
Peripheral artery disease	4 (6.2)	1 (7.7)	1.000
Biology, median (IQR)			
Haemoglobin (g/dL)	14.3 (13.0 - 14.5)	11.0 (9.4 - 13.2)	**0.006**
CRP (mg/L)	5.0 (2.9 - 24.4)	36.9 (8.3 - 125.8)	**0.006**
Creatinine clearance (ml/min/1,73m² (CKDEPI))	46.5 (35.2 - 61.5)	37.9 (24.3 - 69.5)	0.253
NT-pro-BNP (µg/mL)	2688 (1002 - 6161)	6868 (322 - 10231)	0.775
Peak of cTnI peak (µg/L)	9.0 (2.8 - 30.3)	19.0 (3.0 - 30.3)	0.955
LVEF, %, median (IQR)	50 (40 - 60)	48 (36 - 60)	0.933
GRACE score at admission, median (IQR)	174 (150 - 191)	169 (136 - 199)	0.538
STEMI, n (%)	30 (46.2)	5 (38.5)	0.763
Type of MI, n (%)			0.511
Type 1	34/52 (65.4)	6/11 (54.5)	
Type 2	18/52 (34.6)	5/11 (45.5)	
Coronary angiography characteristics			
Coronary artery disease, n (%)			0.615
No CAD	6/62 (9.7)	1 (7.7)	
nonobstructive-CAD	4/62 (6.5)	0 (0)	
obstructive-CAD	52/62 (83.9)	12 (92.3)	
CAD extension, n (%)			0.800
Not extensive	10/62 (16.1)	3 (23.1)	
Extensive	45/62 (72.6)	9 (69.2)	
Culprit coronary artery, n (%)			
Left main coronary artery	0/57 (0)	2/12 (16.7)	**0.028**
Left anterior descending artery	24/57 (42.1)	3/12 (25)	0.342
Left circumflex coronary artery	8/57 (14)	2/12 (16.7)	1.000
Right coronary artery	17/57 (29.8)	4/12 (33.3)	1.000
SYNTAX score, median (IQR)	5 (0 - 19)	7 (2 - 19)	0.950
Treatment, n (%)			
Reperfusion strategy			
Percutaneous coronary intervention	44 (67.7)	8 (61.5)	0.751
Coronary bypass surgery	0 (0)	1 (7.7)	0.167
Medical treatment alone	18 (27.7)	3 (23.1)	1.000
Antiplatelet medication (aspirin or clopidogrel) before MI	23/64 (35.9)	4 (30.8)	1.000
Statin before MI	6 (9.2)	5 (38.5)	**0.016**
Follow-up			
Duration of follow-up (months), median (IQR)	11 (5 - 30)	30 (1 - 78)	0.546
MI relapse in the following year, n (%)	0 (0)	2/54 (3.7)	0.431

CAD = coronary artery disease; BMI = body mass index; CRP = C-reactive protein; cTnI = cardiac troponin I; GCA = giant cell arteritis; IQR = interquartile range; LVEF = left ventricular ejection fraction; MI = myocardial infarction; n= number; STEMI = ST elevation myocardial infarction

Table 4: Factors associated with one-year survival after MI diagnosis

	Univariate analysis	Multivariate analysis (model 1) Hazard ratio (IC 95%)	*p*	Multivariate analysis (model 2) Hazard ratio (IC 95%)	*p*
Groups					
GCA-related MI vs. GCA-unrelated MI vs. controls	0.135	1.604 (0.764-3.37)	0.212		
Cases (MI + GCA) vs. controls	0.157			2.242 (0.6-8.375)	0.230
Age at MI					
> 80 years	0.936				
> 82 years	0.408				
> 86 years	0.256				
Cardiovascular risk factors					
Hypertension	0.583				
Diabetes	0.594				
Hypercholesterolemia	0.792				
Family history of coronary disease	0.779				
Current smoker	0.966				
Biology					
Kidney failure (CKDEPI < 60 mL/min/1,73m²)	0.057	-		-	
CRP					
> 10 mg/L	0.300				
> 35 mg/L	0.764				
cTnI >10 µg/L	0.569				
History of cardiovascular disease	0.339				
LVEF > 50%	0.032	-		-	
STEMI	0.840				
Time in cardiac intensive care unit > 4 days	0.502				
GRACE score					
> 149	0.028				
> 173	0.010	5.967 (1.319-26.997)	0.020	6.422 (1.396-29.540)	0.017
> 191	0.029				
Type of MI (type 1 vs. type 2)	0.446				
Coronary angiography characteristics					
Culprit coronary artery					
Left main	0.843				
Left anterior descending artery	0.234				
Left circumflex coronary artery	0.446				
Right coronary artery	0.964				
CAD (no CAD, non-obstructive or obstructive-CAD)	0.697				
CAD extension (no CAD, only one affected coronary artery or extensive)	0.694				
SYNTAX score > 6	0.345				
Percutaneous coronary intervention	0.122	0.458 (0.153-1.374)	0.164	2.242 (0.6-8.375)	0.230
Platelet aggregation inhibitors before MI	0.622				

CAD = coronary artery disease; CRP = C-reactive protein; cTnI = cardiac troponin I; GCA = giant cell arteritis; LVEF = left ventricular ejection fraction; MI = myocardial infarction; n= number; STEMI = ST elevation myocardial infarction