Current Rheumatology Reports (2020) 22: 72
https://doi.org/10.1007/s11926-020-00952-1

VASCULITIS (L ESPINOZA, SECTION EDITOR)

Cardiovascular Manifestations of Systemic Vasculitides

Luis H. Silveira[1]

Published online: 27 August 2020

Abstract

Purpose of Review Vasculitis can cause heart disease and are associated with premature atherosclerosis, causing increased morbidity and mortality. Consequently, it is important to know how they can affect the cardiovascular system in order to detect and treat the abnormalities in earlier phases.

Recent Findings A clear increasing trend of inpatient burden of myocardial infarction and thromboembolic events in granulomatosis with polyangiitis has been observed lately. Behçet's disease has been linked to an increased risk of atrial fibrillation. Studies showing increased atherosclerosis and thromboembolic phenomena in vasculitis are continuously published. Improvement in imaging techniques has consistently showed that subclinical cardiovascular involvement is frequent.

Summary Vasculitis may affect seriously the cardiovascular system causing an important increase in morbidity and mortality. Subclinical involvement is frequent. Early treatment with immunosuppression and sometimes surgery, is of paramount importance to improve the prognosis.

Keywords Vasculitis · Heart disease · Cardiovascular disease · Takayasu arteritis · Eosinophilic granulomatosis with polyangiitis · Behcet's disease

Introduction

Systemic vasculitides are rarely associated with cardiac disease; less than 10% of patients are affected overall [1]. However, most of the vasculitic entities can cause heart disease and the frequency of affection varies among them. Takayasu arteritis (TA) and eosinophilic granulomatosis with polyangiitis (EGPA) are the most frequently affected by heart disease. The early detection of these abnormalities is of paramount importance since they are associated with increased morbidity and mortality and treatment should be started as soon as they are detected. Vasculitides are related to cardiovascular risk by means of the severe inflammatory process in the vessel wall [2]. Moreover, they are also associated with premature atherosclerosis [3].

Topical Collection on *Vasculitis*

✉ Luis H. Silveira
luis_hsil@hayoo.com

[1] Department of Rheumatology, Instituto Nacional de Cardiología Ignacio Chávez, Juan Badiano No. 1, colonia Sección XVI, 14080 Ciudad de México, Mexico

I will review the cardiovascular manifestations observed in the different adult primary vasculitides according to the vessel size involved.

Large-Vessel Vasculitis

Takayasu Arteritis Cardiac abnormalities are very frequent in TA, around 40% of patients have them. They are associated with increased morbidity and mortality and are related to poor prognosis [4••]. Cardiovascular manifestations have also been linked to disease activity [5]. The most frequent structures involved are the valves, the coronary arteries, the myocardium, and the pericardium (Table 1).

Valvular abnormalities are the most common cardiac manifestations in TA. Aortic insufficiency (AI) has been present in 15 to 50% of patients [1, 4••, 5, 6•, 7, 8, 9, 10]. Li et al. found in a retrospective study that 164 of 411 (39.9%) Chinese patients with TA had heart involvement [4••]. Valvular affection was described in 134 (32.6%) patients; AI was the most common abnormality (84/134, 62.7%; 20.4% overall), followed by mitral insufficiency (MI) (55/134, 41.0%), tricuspid insufficiency (TI) (19/134, 14.2%), thickening of aortic valve (12/134, 9.0%), anterior mitral valve prolapse (8/134, 6.0%),

pulmonary insufficiency (PI) (7/134, 5.2%), and aortic stenosis (AS) plus MI (1/134, 0.6%). Most of the valvular insufficiency cases were mild (80.6%). Another retrospective study found that 414 of the 1069 (38.7%) Chinese patients had valve abnormalities [6•]; the most frequent were AI (373 patients, 34.9%; 69.7% of the patients affected by valve abnormalities), followed by MI (39.1%), TI (34.6%), PI (11.8%), and AS (2.7%). Almost half of the patients with AI (49.6%) had moderate to severe involvement. In a study performed in our hospital (National Institute of Cardiology in Mexico City) by Soto and colleagues, AI was found in 31 of the 76 TA patients (40.8%) seen in our Aorta Clinic and studied by transthoracic echocardiography (TTE) [7].

TA is a vasculitis that involves the aorta and its main branches; consequently, the aortic is expected to be the most frequently affected valve. AI occurs as a consequence of annular dilatation and valvular leaflet separation produced by ascending aortitis and aneurysm formation, and occasionally as a consequence of an inflammatory retraction of the aortic valve [1]. Symptomatology varies from no symptoms to rapidly progressive congestive heart failure (CHF). AI was found more frequently in patients with active disease in a Korean study [5]. Appropriate treatment will depend on the severity of the AI, the grade of activity of the disease, and the ventricular function. Pharmacological treatment with glucocorticoids and immunosuppresives, mainly methotrexate, is indicated. Surgical treatment is necessary when AI is symptomatic or causes ventricular dysfunction. A retrospective Chinese study that included 46 patients showed that treatment with those agents before the surgery can effectively control the patient's condition, improve the rate of remission, and effectively reduce the incidence of postoperative complications [10]. Ideally, surgery should be performed when the disease is inactive [10-12]. Aortic valve replacement and composite graft replacement (CGR) are the main options available. A recent retrospective Chinese study in 41 patients has found that CGR was associated with fewer adverse events; paravalvular leak was the main postoperative complication [13].

Coronary arteries involvement has varied among reports in TA patients. It is a mortality predictor [7]. Li found that 19 of the 164 TA patients with heart involvement (11.6%) had coronary abnormalities (4.64% of the total 411 patients). All of them, detected by catheter angiography or computed tomography angiography (CTA), were not secondary to the expansion of the aortic root. Clinical manifestations consisted of angina pectoris in 14 (73.7%) of the 19 patients and myocardial infarction (MI) in 3 (15.8%). Patients may also have arrythmia, conduction abnormalities, and congestive heart failure (CHF). A very recent Chinese retrospective study that included 143 patients confirmed that TA patients are more prone to have coronary artery involvement [14]. This abnormality was more frequent in patients with Numano type V TA than patients with non-type V TA (33.8% vs 17.4%, $p = 0.025$). Lesions in the left anterior descending (LAD) and left circumflex (LCx) coronary arteries were more frequent in patients with Numano type V TA patients tan in non-type V TA. A meta-analysis of 35 studies that included 3262 patients found a pooled prevalence of stroke in TA of 8.9% (95% CI: 7.0-10.9%) and of MI of 3.4% (95% CI: 2.1-4.8%), confirming that stroke and MI are frequent in TA [15]. A systematic review of 59 articles, looking for coronary involvement, found 141 patients with 276 coronary lesions [16••]. Patients mean age was 35.7 ± 16.9 (0.58-73) years; most of them were younger than 40 years (63.3%). Right coronary artery was the most commonly affected (31.5%) followed by the left main coronary artery (28.6%); 17 (12.1%) patients had acute MI.

Acute MI has been occasionally found as the first manifestation of TA [17-19]. Cavalli et al. investigated the prevalence of TA in young Italian women (< 40 years old) presenting with ischemic heart disease (IHD) to the Emergency Department in a retrospective study [20]. Overall, 1950 women were studied; 40 had acute IHD and TA was diagnosed in 4 cases (10%). MI is very rare in young women; however, when it occurs, the diagnosis of TA should not be overlooked. An atypical presentation, not previously described, was reported in a 19-year-old Japanese woman who had ischemic cardiomyopathy after an acute MI induced by ostial stenosis of the left main coronary trunk due to localized TA and who was successfully treated with heart transplantation [21].

Stenosis and occlusions usually occur in the coronary ostia and proximal segments [1, 16••]. The mechanisms involved in coronary arteriopathy are vascular inflammation, extension of the adjacent aortic process (intimal proliferation and fibrotic retraction), and atherosclerosis. Patients with TA have accelerated and premature atherosclerosis [22]. This has been confirmed in a recent French prospective study, that included 64 TA patients [23••]. Subclinical atherosclerosis was found in 87% of TA patients versus 76% in RA patients ($p = 0.088$) and 48% of controls ($p < 0.001$). Arterial stiffness measured by brachial-ankle pulse wave velocity (baPWV), a simple and useful indicator for evaluating atherosclerosis, was performed in 240 Chinese patients in a cross-sectional study [24]. Seventy four (30.8%) patients had cardiovascular events (CVE); baPWV was independently associated with CVE and may be a potential marker to predict them in patients with TA.

C-reactive protein (CRP) has been linked to CVE in TA. A retrospective Chinese study that included 60 patients with coronary artery involvement with TA and 60 patients with coronary disease without TA found that high-sensitive CRP was a significant and independent predictor of major adverse cardiovascular events (MACE) in patients with TA coronary arteritis [25]. Furthermore, Li found that CRP levels were higher in patients with heart involvement (10.0 mg/L) than in patients without heart involvement (7.0 mg/L) ($p = 0.017$) [4••].

Treatment of coronary arteries involvement in TA includes pharmacologic and surgical options. Pharmacological treatment involves glucocorticoids and immunosuppressive agents, including methotrexate, mycophenolate mofetil, and cyclophosphamide. In a very recent Chinese retrospective study, involving 22 TA patients with coronary disease, tocilizumab decreased TA activity, improved lumen stenosis caused by coronary artery wall inflammation, and reduced GC dosage [26]. Moreover, pharmacological treatment with prednisone, methotrexate, and tocilizumab, regressed coronary ostial stenosis in an 18-year-old Japanese woman with TA [27].

Surgical treatment is mandatory when there is no response to pharmacological treatment or the coronary artery disease (CAD) is severe. Revascularization can be obtained with coronary artery bypass grafting (CABG), balloon angioplasty followed by stenting, and transaortic endarterectomy [1]. Ideally, surgery must be performed when TA is inactive since activity favors restenosis [10, 12]. Several studies have shown that CABG is superior to percutaneous interventional therapy (PCI), mainly because restenosis is more common in the latter (50-78%) than in the former (9.5-36%) [16••, 28, 29, 30, 31]. Moreover, risk of MACE was 9.9-fold higher in PCI than in CABG in one study [29], although risk of stroke was higher with CABG than with PCI in a meta-analysis (OR 5.18 95% CI: 2.78-9.62) [30]. The use of drug-eluting stents (with sirolimus or paclitaxel) might decrease or delay the occurrence of restenosis according to some reports [32-34]; however, this was not confirmed by recent studies [28, 29]. Some other techniques can be used in selected cases. Recently, a successful case of an arterioplasty of the left main coronary artery using a glutaraldehyde-fixed autologous pericardial patch performed in a 24-year-old Chinese woman has been reported; 10 years of follow-up demonstrated the patency of the ostium of the artery [35].

Myocardial involvement, including myocarditis, can also be present. Li reported myocardial abnormalities in 26 (6.3%) of the 411 patients in his study, including diffusely decreased ventricular wall motion, cardiac chambers enlargement, and decreased contractility [4••]. Myocarditis is rare in TA, and it is only reported as single case reports, including silent disease [36, 37]. Bechman et al. retrospectively reviewed a British database to identify TA and giant cell arteritis (GCA) patients with cardiac involvement at presentation [38]. There were 139 patients with TA; they found myocarditis in 3 (2.15%). Non-invasive techniques, TTE, and cardiac magnetic resonance (CMR), were sufficient for diagnosis of clinically significant myocarditis. Two patients significantly improved with prednisolone plus cyclophosphamide and one with tocilizumab. CMR is very useful to reach the diagnosis since late gadolinium enhancement suggests myocardial damage [1, 2]. Cardiomyopathy may also be secondary to valvulopathy, ischemic heart disease, and hypertension [1].

Pericardium may be rarely affected in TA. Li found pericardial effusion in 30 (6.32%) of the 411 patients in his study [4••]. Pericardial involvement can be occasionally the first manifestation of TA [39].

Pulmonary arteries (PA) involvement has been reported in up to 88% of TA patients [2]. However, recent studies found a frequency of affection of 6.25-25.93% [40, 41•, 42••]. PA involvement is usually silent, but may manifest as pulmonary hypertension (PH) in 10.5-58.8% of cases [7, 40, 41•, 42••, 43]. PH is associated with longer disease duration, more severe symptoms [44], higher mortality [42••, 44], and poor prognosis [40, 41•].

Finally, systemic arterial hypertension (SAH), secondary to aortic or renal artery stenosis, is very frequent in patients with TA. Soto found a frequency of 53% in her study conducted at our center [7]. SAH and its complications are some of the problems that we constantly confront in our clinic.

Giant Cell Arteritis Cardiac involvement is rare in GCA. Coronary arteries, pericardium, and myocardium may be affected (Table 1). GCA-increased risk for IHD has been established. Amiri et al. conducted a matched cohort analysis of 809 Canadian patients and 8577 controls; 83 (10.25%) patients developed MI and 60 (7.41%) developed stroke [45]. They found a threefold increased risk of MI and a twofold increased risk of stroke compared with controls. The risk was highest during the first year of the diagnosis of GCA, although it remained significant after 5 years of follow-up. A cross-sectional study that used the database of the largest healthcare provider in Israel, that included 5659 GCA patients and 28,621 controls, found a higher proportion of IHD in patients (27.5%) than in controls (12.5%) ($p < 0.001$) [46]. Diabetes mellitus, hypertension, hiperlipidemias, and smoking were more prevalent in GCA; however, after stratifying for those comorbidities using logistic regression, GCA kept its independent association with IHD, OR 1.247 ($p < 0.001$).

Table 1 Cardiovascular manifestations in large-vessel vasculitis

Takayasu arteritis
Valvular abnormalities (mainly aortic insufficiency)
Coronary arteritis
Myocarditis
Pericarditis
Pulmonary arteries involvement
Systemic arterial hypertension
Giant cell arteritis
Coronary arteritis
Pericarditis
Myocarditis

The IHD in GCA might be secondary to vasculitis or to atherosclerosis, since traditional cardiovascular risk factors are frequent in this group of age [1]. The presence of clinical manifestations of GCA activity may suggest coronary vasculitis. Treatment with glucocorticoids at high doses and an immunosuppressant (usually methotrexate) should be started in addition to treatment of the IHD.

The association of GCA with vascular diseases has also been reported. Li et al. identified 9778 newly diagnosed GCA patients and compared them with 92,268 non-vasculitis patients, using a British ongoing longitudinal database [47••]. Patients with GCA had more prior vascular diseases and other comorbidities before the diagnosis. They also had increased risk for all types of incident vascular disease compared with non-vasculitis patients after the diagnosis: MI, stroke, peripheral vascular disease, aortic aneurysm, and venous thromboembolism (VTE). They had increased risk for other incident comorbidities (type 2 diabetes, obesity, hypertension, dyslipidemias, and depression) too.

Pericarditis is unfrequent in GCA. A cross-sectional study that also utilized the database of the largest healthcare provider in Israel included 4329 GCA patients and 21,611 controls [48]. Pericarditis was found in 53 GCA patients (1.22%) and 72 controls (0.33%) ($p < 0.001$). There was an independent association between GCA and pericarditis, especially in patients younger than 70 years old.

Myocarditis is very rare in GCA; it is reported as single cases [49]. In the previously mentioned retrospective study by Bechman, there were 24 patients with GCA and cardiac disease at presentation, and only one had myocarditis (4.16%) [38]. This is a very serious complication that can cause CHF. CMR (late gadolimium enhancement) is a very useful diagnostic aid. Treatment with high-dose glucocorticoids and immunosuppressives is indicated.

Medium-Vessel Vasculitis

Polyarteritis Nodosa (PAN) Frequency of heart involvement in PAN has been difficult to establish since populations of patients described in the past were not homogeneous because PAN and microscopic polyangiitis (MPA) had not yet been differentiated. Heart abnormalities consisting of coronary arteritis, pericarditis, and myocarditis, occur in 5 to 22.4% of patients [1, 50].

Coronary arteritis in the main coronary arteries and their proximal branches has been found in old series in 40 to 50% of the patients, and vasculitis limited to the small myocardial arterioles in a smaller percentage, but clinical MI is present in less than 5% of patients [1, 51]. Clinical manifestations are not different from the traditional IHD. Consequently, differential diagnosis with atherosclerotic coronary artery disease may be difficult, and the presence of some manifestations suggestive of vasculitis activity should direct the diagnosis [52]. Coronary angiography may show focal and diffuse areas of narrowing and occlusion or the typical "beads on a string" pattern. Treatment with high-dose glucocorticoids and cyclophosphamide should be used. Sometimes, revascularization with CABG is necessary.

Coronary arteritis and hypertension can cause CHF [1]. The French Vasculitis Study Group published a systematic retrospective study that included 1628 patients with systemic vasculitis, 348 with PAN (21.4%); 78 (22.4%) had cardiac and/or vascular manifestations [50]. Patients with PAN were classified as non-HBV-related PAN and HBV-related PAN; vasculitis-related cardiomyopathy was found in 26 (7.5%) patients, more frequently in HBV-related PAN (12.3% vs 4.4% in non-HBV-related PAN). Severe hypertension was detected in 24 (6.9%) patients, more frequently in HBV-related PAN (10.6% vs 4.9%). MI, sudden death, and hypertension were important causes of mortality. This has been confirmed in other studies; cardiac involvement is associated with increased risk of mortality within the first year and on follow-up in patients with PAN [2, 53]. Hypertension can be caused by renal artery stenosis. Cardiomyopathy should be treated with immunosuppression when the vasculitis is active [1].

Pericarditis is unfrequent in PAN. In the previously mentioned French study, it was found in 19 of the 348 (5.5%) patients with PAN [50]. It was reported in 10 of 36 (27.7%) patients in an autopsy series [51]. Mild interstitial myocarditis was seen in 6 (16.6%) patients.

Small-Vessel Vasculitis

Eosinophilic Granulomatosis with Polyangiitis EGPA is the least frequent small-vessel or ANCA-associated vasculitis (AAV), but it is the most frequently affected by heart abnormalities, which occur in 15 to 62% of cases [1, 54-56]. Cardiomyopathy, pericarditis, and valvular abnormalities are the most common manifestations (Table 2). Cardiomyopathy may cause arrhythmia and CHF, but a good proportion of patients with heart involvement are asymptomatic.

Comarmond and colleagues conducted a systematic retrospective French study of 383 patients with EGPA classified as ANCA-positive and ANCA-negative [54]. Cardiac manifestations were diagnosed with clinical findings, echocardiogram, and electrocardiogram (ECG); 105 (27.4%) patients had cardiovascular manifestations, which were more frequent in ANCA-negative patients (30.4%) than in ANCA-positive patients (18.5%) ($p = 0.02$). Cardiomyopathy was found in 63 (16.4%) patients, and it was also more frequent in ANCA-negative patients (19.2%) than in ANCA-positive patients (8.3%) ($p = 0.01$). Pericarditis was detected in 58 (15.1%) patients; there was no significant difference between patients with positive and negative ANCA. Finally, deep venous

Table 2 Cardiovascular manifestations in small-vessel vasculitis

Eosinophilic granulomatosis with polyangiitis
Cardiomyopathy
Pericarditis
Valvular abnormalities (mainly mitral insufficiency)
Granulomatosis with polyangiitis
Pericarditis
Cardiomyopathy
Coronary arteritis
Valvular abnormalities (mainly aortic insufficiency)
Microscopic polyangiitis
Pericarditis
Cardiomyopathy
Valvular abnormalities (mainly aortic insufficiency)

thrombosis (DVT)/pulmonary embolism (PE) was found in 29 (7.6%) patients. Cardiomyopathy was associated with mortality. A Dutch group published two prospective studies, one with 32 and the other with 50 patients with EGPA in sustained remission, who had detailed cardiac evaluation with ECG, echocardiography, and CMR [55, 56]. They found that 62% of patients in one study and 66% in the other study had cardiac abnormalities in comparison to 3% in one study and 20% in the other study of controls ($p < 0.001$, $p = 0.104$, respectively). They concluded that cardiac involvement in EGPA patients with sustained remission is high, even if symptoms are absent and ECG is normal, and that cardiac involvement is a strong predictor of mortality. Other studies have confirmed the role of CMR in the detection of cardiac involvement in EGPA, mainly in patients with no cardiac symptoms [57, 58]. Late gadolinium enhancement suggests myocarditis or fibrosis and correlates with echocardiographic findings, mainly diastolic dysfunction [57]. A French prospective study with 20 patients found that fluoro-2-deoxyglucose positron-emission tomography (PET) may help in the evaluation of patients with late gadolinium enhancement since PET might help to distinguish between inflammation and fibrosis [59]. Myocarditis and pericarditis may occasionally be the first manifestation of EGPA [60-64].

Valvular lesions are present in 7 to 13% of cases [55, 56]. The most frequent abnormality is MI, followed by AI; they are usually subclinical or asymptomatic. Coronary vasculitis, heart block, intraventricular thrombus, and ventricular masses are rarely seen [1].

The mechanism of cardiac injury, mainly myocardial, is eosinophilic tissue infiltration with the subsequent release of intracelullar enzymes that cause tissue injury; vasculitis is rarely seen as it is seen in some other organs in EGPA [1, 2].

Severe cardiac disease should be treated with high-dose glucocorticoids and an immunosuppressant, usually cyclophosphamide [1]. These patients may very rarely need cardiac transplantation [2, 65]. Groh and colleagues conducted a retrospective international multicenter study [65]. They identified 9 patients that received a heart transplant; 7 of them had active vasculitis despite ongoing immunosuppression. The overall 5-year survival rate was 56%; 4 patients (44%) suffered sudden death after survival lasting 3 to 60 months (mean 32 ± 29 months). The survivors had been followed up for a mean of 6 years.

Granulomatosis with Polyangiitis (GPA) Heart involvement in GPA is rare. Pericarditis and cardiomyopathy are the most common manifestations [1]. Arrhythmias, coronary arteritis, cardiac thrombus, valvular lesions, and intracardiac masses are less frequently observed (Table 2). Arrhythmias consist of atrioventricular block (AVB), usually together with supraventricular tachycardias. McGeoch and colleagues conducted a longitudinal study using data obtained from the Vasculitis Clinical Research Consortium (United States and Canada) [66]. A large cohort of 517 patients was obtained; 17 (3.3%) had cardiac manifestations as follows: pericarditis ($n = 6$, 35%; 1.16% overall), cardiomyopathy ($n = 5$, 30%; 0.96% overall), CAD ($n = 2$, 12%; 0.38% overall), valvular disease ($n = 1$, 6%; 0.19% overall), concomitant CAD and valvular disease ($n = 1$, 6%), concomitant pericarditis and cardiomyopathy ($n = 1$, 6%), and severe conduction disorder ($n = 1$, 6%). Cardiac involvement was not associated neither with poorer outcomes nor with other disease manifestations. In a prospective Polish study, 88 patients with GPA in remission were evaluated by echocardiography [67]. The only abnormality that occurred significantly more often in the GPA group than in controls (28% vs 7.5%; $p = 0.03$) was AI. This study shows that the frequency of abnormalities can vary importantly among series and that the majority of clinical cardiac manifestations are asymptomatic.

CMR has also showed that it is a very important instrument to evaluate GPA patients and detect cardiac abnormalities in early stages. A previously mentioned Dutch prospective study also included 41 GPA patients in sustained remission [54]. They found that 61% of patients had cardiac abnormalities in CMR in comparison to 20% of controls; abnormalities had been found by ECG and echocardiography in only 46% of patients. They concluded that cardiac involvement in GPA patients with sustained remission is also high (as in EGPA), even if symptoms are absent and ECG is normal, and that cardiac involvement is a strong predictor of mortality. In a cross-sectional study, 31 consecutive, unselected, active or in remission patients, followed up at the French Reference Center for Necrotizing Vasculitis, underwent cardiac MRI [68]. At least one abnormality was observed in 19 (61%) patients. The most frequent abnormalities were left ventricle

regional wall motion abnormalities in 11 patients (35%), late gadolinium enhancement in 10 patients (32%), pericarditis in 8 (26%), and impaired left ventricle ejection fraction in 4 (13%) patients.

We can conclude that clinical heart involvement in GPA is low, but there are many subclinical cases [1]. There are also some isolated case reports of low frequency manifestations such as pericardial tamponade as the first manifestation [69] or complete AVB with ocular manifestations (bilateral panuveitis and exudative retinal detachment) as the only manifestations of GPA [70].

Microscopic Polyangiitis (MPA) Cardiac involvement in MPA is rare, although it has been rarely studied [1, 2]. Pericarditis, cardiomyopathy, and valvular disease, are the most frequent abnormalities (Table 2). Shuai and colleagues published a prospective Chinese study with 132 patients with AAV; 128 of them had MPA [71]. Heart involvement was found in 26 (19.7%) patients; 12 (9.1%) patients had pericarditis, 9 (6.8%) patients had chronic heart failure/cardiomyopathy, one patient had AI, and another patient had new onset arrhythmia. They only report the findings in the whole group of patients. A retrospective series of 85 patients from de French Vasculitis Study Group reported cardiac failure in 15 (17.6%) patients, pericarditis in 9 (10.6%) patients, and MI in 2 (2.4%) patients [72]. Both studies reported only clinical manifestations. Heart involvement seems to be more frequent if imaging is used to detect subclinical disease. A Greek study utilized CMR to investigate 39 patients with systemic vasculitides; 16 of them had MPA. They found fusiform coronary aneurysms in 4 (25%) patients, coronary ectasias in 14 (87.5%) patients, and myocardial necrosis in 2 (12.5%) patients [73]. Case reports of unstable angina with a subarachnoid hemorrhage and noninfective endocarditis in the mitral valve have been published [74, 75].

Cardiovascular Risk in AAV The risk for CVE and thromboembolism (TEB) is clearly increased in patients with AAV. Béjot and colleagues conducted a retrospective study in 125 patients with AAV, 99 (79.2%) with GPA, and 26 (20.8%) with MPA, at Touluse University Hospital [76•]. The ischemic stroke incidence and the CAD incidence were 4 times higher in vasculitis patients than in the general population (comparative morbidity/mortality figure [CMR], 4.65 and 4.22, respectively). Mortality in AAV was 1.5 times higher in patients than in the general population (CMF, 1.56). A comprehensive systematic review that included almost 14,000 patients with AAV found that patients had a relative risk of 1.65 for all CVE, 1.60 for IHD, and 1.20 for cerebrovascular accidents (CVA). There was an increased cardiovascular risk in patients with AAV of ~ 65% [77••]. A very recent retrospective cross-sectional study that used the National Inpatient Sample database in the USA explored the trends in the inpatient burden of CAD in GPA and compare it with non-GPA, between 2005 and 2014 [78••]. The proportion of CAD in GPA hospitalizations increased significantly from 16.6 in 2005 to 22.7% in 2014 and CAD with heart failure from 4.3 in 2005 to 9.9% in 2014. The difference in trends for acute MI (1.2 in 2005 to 1.1% in 2014) and for non-GPA hospitalizations were not significant. This observed trend might be explained by the advances in treatment and improved survival en GPA patients.

The increased risk for TEB has also been demonstrated by several studies [79••, 80•, 81•]. Kronbichler and colleagues conducted a study with patients recruited in 4 randomized controlled trials from 70 hospitals in 15 countries of the European Vasculitis Society (EUVAS) between 1995 and 2002 [79••]. VTE occurred in 41 of 417 (9.8%) patients. C-reactive protein, cutaneous involvement, gastrointestinal involvement, and baseline creatinine levels were associated with VTE. A retrospective population-based incident AAV cohort of 58 patients diagnosed between 1996 and 2015 in Olmsted County, Minnesota, was identified by medical record review [80•]. Despite a similar prevalence of cardiovascular risk factors at baseline, the risk of cardiovascular disease was threefold higher, and the risk of CVA was eightfold higher in patients with incident AAV than in matched comparator subjects. Kang et al. identified 204 patients with AAV in a retrospective observational study at the Imperial College Renal and Transplant Centre in London [81•]. Event rates were 15 times higher for coronary events, 11 times higher for incident stroke, and 20 times higher for VTE, in patients with AAV in comparison to reported rates for the UK population.

Finally, a study conducted, with a cohort of 484 patients of the Partners Healthcare System (2012-2017) in Boston, found that cardiovascular disease was the most common cause of death in patients. MPO-ANCA$^+$ patients were at a fivefold higher risk of cardiovascular death than PR3-ANCA$^+$ patients [82••]. The increased risk for CVE and TEB in AAV patients seems to contribute very importantly to the mortality observed in these patients.

Variable-Size Vasculitis

Behçet's Disease (BD) Cardiac involvement has been reported to be between 2.4 and 6.4% of patients with BD in 2 large series [83, 84•]. Geri and colleagues found 52 (6.4%) patients with cardiac lesions out of a large French cohort (Pitié-Salpetrière Hospital) of 807 patients with BD [83]. Pericarditis was seen in 20 (2.5%) patients, valvular insufficiency (mostly AI) in 14 (1.7%) patients, intracardiac thrombosis in 10 (1.2%) patients, MI in 9 (1.1%) patients, endomyocardial fibrosis in 4 (0.5%) patients, and myocardial aneurysm in one (0.1%) patient. Patients with cardiac involvement were more frequently male and had more arterial (42.3% vs 11.1%; $p < 0.01$) and venous lesions (59.6% vs 35.8%;

$p < 0.01$) compared to those without cardiac manifestations. Cardiac disease was the first manifestation of BD in 17 (32.7%) patients. The prognosis of BD was poorer in patients with cardiac involvement and was improved with the use of immunosuppressants, colchicine, and anticoagulants. In a retrospective study of 213 Tunisian patients, vascular involvement was found in 64 (30%) patients; 40 (18.8%) patients had DVT, 15 (7%) patients had superficial venous thrombosis, 6 (2.8%) patients had pulmonary embolism, and one (0.5%) patient had ascending aorta aneurysm [84•]. Cardiac involvement was only seen in 5 (2.4%) patients; 2 (0.9%) of them had cardiac thrombosis, and pericarditis, myocarditis, and MI was seen in one patient (0.5%) each. Predictive factors associated with vascular and cardiac involvement were male gender, erythema nodosum, and neurologic involvement. In summary, vascular manifestations seem to me more frequent than cardiac manifestations; both are more frequent in men, and both are associated with poor prognosis.

Coronary involvement is rare in BD. Chen and colleagues conducted a retrospective, case-control study with 476 Chinese patients with BD; 19 (4%) had coronary involvement (17 males) [85•]. Multiple coronary stenoses, multiple aneurysms, and occlusion were described. Clinical manifestations were angina, acute MI, and arrhythmias. The most frequently affected arteries were the LAD, the right coronary, and the LCx coronary arteries. Pathergy reaction was the independent risk factor. In an Israeli case-control, cross-sectional study that utilized the largest health services database, 817 patients with BD and 4349 controls were compared [86]. IHD was present in 95 patients (10.9%) with BD and in 307 (7.52%) controls ($p = 0.001$). BD was associated with IHD on multivariable analysis. Age younger than 70 and male gender were increased in BD. Coronary involvement might be very serious. A case of a 29-year-old Turkish man with acute MI was reported [87]. He developed an aneurysm in the right coronary artery, that later ruptured and caused tamponade. A 30-year-old Chinese man with BD had aneurysms in the LAD coronary artery that caused recurrent MI was also reported; he was successfully treated with a covered stent, immunosuppressive therapy, and anticoagulation regimen [88].

Intracardiac thrombosis is another rare manifestation of BD, that was found in 1.2% [83] and 0.94% [84•] of patients in previously mentioned series. Two studies look specifically for the prevalence and characteristics of this manifestation. A Chinese retrospective study found intracardiac thrombus in 12 (1.9%) of the 626 patients with BD and a retrospective Tunisian study found thrombus in 8 (1.5%) of the 518 patients with BD [89, 90]. The great majority of patients were male, young, had the thrombus in the right heart, and had frequently associated pulmonary aneurysm and/or thrombosis [89, 90].

Sun and colleagues conducted a prospective Korean study looking for early cardiac manifestations of BD in patients who had no history of heart disease, using speckle-tracking echocardiography [91]. They recruited 85 patients and 145 controls. Patients showed intrinsic left ventricular dysfunction despite no apparent abnormality on routine echocardiography. A meta-analysis that included 22 studies with 1624 subjects found that diastolic dysfunction, detected by echocardiography, was increased in patients in comparison to controls [92]. Other findings found in patients were increased left atrial dimension, lower ejection fraction, and increased aortic diameter.

Arrhythmia can also be present occasionally in patients with BD. Lee et al. used a Korean nationwide population database and compared 6635 newly diagnosed BD patients with 31,040 controls [93••]. After adjustment, BD patients showed a 1.8-fold higher risk of atrial fibrillation than controls. Patients aged ≤ 40 years and men had a higher risk (2.5-fold compared to women). Complete AVB has been described in isolated case reports [94]. Another manifestation that has been rarely reported is interventricular septal dissection, that appears as a cystic-like mass in the TTE [95, 96].

Treatment of cardiac manifestations of BD includes the use of low-dose aspirin, colchicine, as well as glucocorticoids and immunosuppressants for active lesions. Some cases of IHD and valvular lesions might need revascularization and surgical valve replacement [1]. Successful postoperative outcomes will depend on the appropriate perioperative immunosuppressive treatment. A Brazilian study suggests that CABG is a procedure with high mortality, especially in the acute period, and that the on-pump surgery technique is safe in case multiple bypasses are required and in patients older than 40 years [97]. Another study, conducted in Korea, suggests that valve replacement for AI has a better outcome when it is combined with mechanical aortic root replacement and a low postoperative CRP level is maintained [98]. Intracardiac thrombosis treatment requires immunosuppression and surgery [1]. Anticoagulation is controversial and implies extreme caution due to the possibility of pulmonary aneurysms.

Conclusions

Vasculitides are a group of serious diseases that can affect the cardiovascular system. These entities may involve the heart, and by means of the severe inflammatory process they cause in the vessel wall, and its association with premature atherosclerosis, they increase morbidity and mortality and shadow the prognosis. Pathology and imaging studies have shown that subclinical involvement is frequent. Treatment consists of immunosuppression, and sometimes surgery, for coronary and valvular involvement. An increasing trend of inpatient burden of MI and TE phenomena in GPA has been observed lately, and this is probably related to the increased patient survival.

Compliance with Ethical Standards

Conflict of Interest The author declares that he has no conflict of interest.

Human and Animal Rights an Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
• Of importance
•• Of major importance

1. Miloslavsky E, Unizony S. The heart in vasculitis. Rheum Dis Clin N Am. 2014;40:11-26. https://doi.org/10.1016/j.rdc.2013.10.006.
2. Misra DP, Shenoy SN. Cardiac involvement in primary systemic vasculitis and potential drug therapies to reduce cardiovascular risk. Rheumatol Int. 2017;37:151-67. https://doi.org/10.1007/s00296-016-3485-1.
3. Cohen Tervaert JW. Cardiovascular disease due to accelerated atherosclerosis in systemic vasculitides. Best Pract Res Clin Rheumatol. 2013;27:33-44. https://doi.org/10.1016/j.berh.2012.12.004.
4.•• Li J, Li H, Sun F, Chen Z, Yang Y, Zhao J, et al. Clinical characteristics of heart involvement in Chinese patients with Takayasu arteritis. J Rheumatol. 2017;44:1867-74. https://doi.org/10.3899/jrheum.161514 **This retrospective study with a large number of patients describes the type and frequency of cardiac abnormalities in TA**.
5. Lee GY, Jang SY, Ko SM, Kim EK, Lee SH, Han H, et al. Cardiovascular manifestations of Takayasu arteritis and their relantionship to the disease activity; analysis of 204 Korean patients at a single center. Int J Cardiol. 2012;159:14-20. https://doi.org/10.1016/j.ijcard.2011.01.094.
6.• Zhang Y, Yang K, Meng X, Tian T, Fan P, Zhang H, et al. Cardiac valve involvement in Takayasu arteritis is common: a retrospective study of 1,069 patients over 25 years. Am J Med Sci. 2018;356:357-64. https://doi.org/10.1016/j.amjms.2018.06.021 **This retrospective study with a very large number of patients establishes the frequency of valve abnoramlities in TA**.
7. Soto ME, Espinola N, Flores-Suarez LF, Reyes PA. Takayasu arteritis: clinical features in 110 Mexican mestizo patients and cardiovascular impact on survival and prognosis. Clin Exp Rheumatol. 2008;26(3 Suppl 49):S9-15.
8. Hashimoto Y, Oniki T, Aerbajinai W, Numano F. Aortic regurgitation in patients with Takayasu arteritis: assessment by color doppler echocardiography. Heart Vessel. 1992;/:111-115. Doi:https://doi.org/10.1007/BF01744555.
9. Keenan N, Mason JC, Maceira A, Assomull R, O'Hanlon R, Chan C, et al. Integrated cardiac and vascular assessment in Takayasu arteritis by cardiovascular magnetic resonance. Arthritis Rheum. 2009;60:3501-9. https://doi.org/10.1002/art.24911.
10. Zheng T, Zhu S, Ou J-F, Fang W-G, Qiao Z-Y, Qi R-D, et al. Treatment with cosrticosteroid and/or immunosuppressive agents before surgery can effectively improve the surgical ourcome in patients with Takayasu's arteritis. J Investig Surg. 2019;32:220-7. https://doi.org/10.1080/08941939.2017.140718.
11. Matsuura K, Ogino H, Kobayashi J, Ishibashi-Ueda H, Matsuda H, Minatoya K. Surgical treatment of aortic regurgitation due to Takayasu arteritis: long-term morbidity and mortality. Circulation. 2005;112:3707-12. https://doi.org/10.1161/CIRCULATIONAHA.105.535724.
12. Fields CE, Bower TC, Cooper LT, Hoskin T, Noel AA, Panneton JM, et al. Takayasu's arteritis: operative results and influence of disease activity. J Vasc Surg. 2006;43:64-71. https://doi.org/10.1016/j.jvs.2005.10.010.
13. Zhang Y, Fan P, Zhang H, Ma W, Song L, Wu H, et al. Surgical treatment in patients with aortic regurgitation due to Takayasu arteritis. Ann Thorac Surg. 2019;S0003-4975(19):31708-4. https://doi.org/10.1016/j.athoracsur.2019.10.006 Online ahead of print.
14. Li T, Du J, Gao N, Guo X, Pan L. Numano type V Takayasu arteritis patients are more prone to have coronary artery involvement. Clin Rheumatol 2020 May 18. Doi:https://doi.org/10.1007/s10067-020-05123-2. On line ahead of print.
15. Kim H, Barra L. Ischemic complications in Takayasu's arteritis: a meta-analysis. Semin Arthritis Rheum. 2018;47:900-6. https://doi.org/10.1016/j.semarthrit.2017.11.001.
16.•• Yuan SM, Lin HZ. Coronary artery involvements in Takayasu arteritis: systematic review of reports. Gen Thorac Cardiovasc Surg 2020 May 19. Doi:https://doi.org/10.1007/s11748-020-01378-3. Online ahead of print. **Systematic review that describes the characteristics of coronary involvement in TA.**
17. Chen T, Mi J, Zhong M-H, Sun Z-H, Jia Z, Song Y, et al. Acute inferior myocardial infarction as the first manifestation of Takayasu arteritis in a young boy. Chin Med J. 2015;128:2414. https://doi.org/10.4103/0366-6999.163383.
18. Ishiyama Y, Eguchi K, Yokota K, Ikemoto T, Kario K. New-onset Takayasu's arteritis as acute myocardial infarction. Intern Med. 2018;57:1415-20. https://doi.org/10.2169/internalmedicine.9690-17.
19. Isaza N, Posada AM, Diaz ME, Isaza-Restrepo D. Cardiogenic shock as the first manifestation of large vessel vasculitis in a young patient: case report. Eur Heart J Case Rep. 2018;2:yty091. https://doi.org/10.1093/ehjcr/yty091.
20. Cavalli G, Tomelleri A, Di Napoli D, Balchissera E, Dagna L. Prevalence of Takayasu arteritis in young women with acute ischemic heart disease. Int J Cardiol. 2018;252:21-3. https://doi.org/10.1016/j.ijcard.2017.10.067.
21. Tokunaga C, Nakajima H, Kaneyuki D, Takazawa A, Izumida H, Hayashi J. Ischemic cardiomyopathy due to localized Takayasu arteritis treated by heart transplantation following left ventricular assisted device implantation: a case report. Transplant Proc. 2019;51:3174-7. https://doi.org/10.1016/j.transproceed.2019.06.004.
22. Seyahi E, Ugurlu S, Cumali R, Balci H, Seyahi N, Yurdakul S, et al. Atherosclerosis in Takayasu arteritis. Ann Rheum Dis. 2006;65:1202-7. https://doi.org/10.1136/ard.2005.047498.
23.•• Hatri A, Guermaz R, Laroche J-P, Zekri S, Brouri M. Arterité de Takayasu et athéroesclerosé. J Med Vasc. 2019;44:311-7. https://doi.org/10.1016/j.jdmv.2019.07.002 **This propsective study establishes that atherosclerosis is frequent in TA and even more frequent than in rheumatoid arthritis**.
24. He Y, Cheng N, Dang A, Lu N. Association between arterial stiffness measured by brachial-ankle pulse wave velocity and cardiovascular events in patients with Takayasu's arteritis. Clin Exp Rheumatol. 2019;37(Suppl 117):S65-71.
25. Wang X, Dang A, Lv N, Liu Q, Chen B. High-sensitivity C-reactive protein predicts adverse cardiovascular events in patients with Takayasu arteritis with coronary artery involvement. Clin Rheumatol. 2016;35:679-84. https://doi.org/10.1007/s10067-015-2873-6.
26. Pan L, Du J, Liu J, Liao H, Liu X, Guo X, et al. Tocilizumab treatment effectively improves coronary artery involvement in

patients with Takayasu arteritis. Clin Rheumatol 2020 Mar 6. Doi: https://doi.org/10.1007/s10067-020-05005-7. Online ahead of print.
27. Yokokawa KH, Kaneshiro T, Ichimura S, Yoshihisa A, Furuya MY. Regressed coronary ostial stenosis in a young female with Takayasu arteritis: a case report. BMC Cardiovsc Dis. 2019;19: 79. https://doi.org/10.1186/s12872-019-1066-7.
28. Yang Y, Tian T, Yang K, Zhang Y, Meng X, Fan P, et al. Outcomes of percutaneous coronary intervention and coronary artery bypass grafting in patients with Takayasu arteritis. In J Cardiol. 2017;241: 64-9. https://doi.org/10.1016/j.ijcard.2017.02.041.
29. Wang X, Dang A, Lv N, Cheng N, Cheng X, Yang Y, et al. Long-term outcomes of coronary artery bypass grafting versus percutaneous coronary intervention for Takayasu arteritis patients with coronary artery involvement. Semin Arthritis Rheum. 2017;47: 247-52. https://doi.org/10.1016/j.semarthrit.2017.03.009.
30. Jung JH, Song GG, Jeong HS, Kim JH, Sj C. Endovascular versus open surgical intervention in patients with Takayasu's arteritis: a meta-analysis. Eur J Vasc Endovasc Surg. 2018;55:888-99. https://doi.org/10.1016/j.ejvs.2018.02.030.
31. Maksimowicz-McKinnon K, Clark TM, Hoffman GS. Limitations of therapy and a guarded prognosis in an American cohort of Takayasu arteritis patients. Arthritis Rheum. 2007;56(1000):9. https://doi.org/10.1002/art.22404.
32. Furukawa Y, Tamura T, Toma M, Abe M, Saito N, Ehara N, et al. Sirolimus-eluting stent for in-stent restenosis of left main coronary artery in Takayasu arteritis. Circ J. 2005;69:752-5. https://doi.org/10.1253/circj.69.752.
33. Kang WC, Han SH, Ahn TH, Shin EK. Successful management of left main coronary artery stenosis with a paclitaxel-eluting stent in Takayasu's arteritis. Int J Cardiol. 2006;108:120-3. https://doi.org/10.1016/j.ijcard2005.02.024.
34. Lee K, Kang WC, Ahn T, Moon CII, Han SH, Shin EK. Long-term outcome of drug-eluting stent for coronary artery stenosis in Takayasu's arteritis. Int J Cardiol. 2010;145:532.5-535. https://doi.org/10.1016/j.ijcard.2010.04.066.
35. Zhang H, Ma X, Zhang Q, Jiao Q, Zou C. Arterioplasty in Takayasu's arteritis with left main coronary artery involvement. Ann Thorac Surg. 2018;105:e247-8. https://doi.org/10.1016/j.athoracsur.2018.01.022.
36. Kotake T, Sueyoshi E, Sakamoto I, Izumida S. Myocarditis associated with Takayasu arteritis. Eur Heart J. 2015;36:2564. https://doi.org/10.1093/eurheartj/ehv169.
37. Chattopadhyay A, Singhal M, Debi U, Sharma A, Jain S. Silent myocarditis in Takayasu arteritis. J Clin Rheumatol 2018 Nov 29. Doi:https://doi.org/10.1097/RHU0000000000000957. Online ahead of print.
38. Bechman K, Gopalan D, Nihoyannopoulos P, Mason JC. A cohort study reveals myocarditis to be a rare and life-threatening presentation of large vasculitis. Semin Arthritis Rheum. 2017;47:241-6. https://doi.org/10.1016/j.semarthrit.2017.03.023.
39. Pons Dolset J, Lahoza Pérez MC, Ilundain González AI, Sáenz Abad D, Jordán Domingo M, Marquina Barcos A. Takayasu arteritis presenting as acute pericarditis. Rev Esp Cardiol (Eng Ed). 2016;69:980-1. https://doi.org/10.1016/j.rec.2016.04.043.
40. Yang Y, Peng M, Shi J, Zheng W, Yu X. Pulmonary artery involvement in Takayasu's arteritis: diagnosis before pulmonary hypertension. BMC Pulm Med. 2019;19:225. https://doi.org/10.1186/s12890-019-0983-7.
41.• Kong X, Ma L, Lv P, Cui X, Chen R, Ji Z, et al. Involvement of the pulmonary arteries in patients with Takayasu arteritis: a prospective study from a single centre in China. Arthritis Res Ther. 2020;22: 131. https://doi.org/10.1186/s13075-020-02203-1 **This prospective study investigates the frequency of pulmonary arteries affection in 216 patients with TA**.
42.•• He Y, Lv N, Dang A, Cheng N. Pulmonary artery involvement in patients with Takayasu arteritis. J Rheumatol. 2020;47:264-72. https://doi.org/10.3899/jrheum.190045 **This retrospective study analyzes the characteristics of pulmonary artery involvement in patients belonging to a very large series of patients (815)**.
43. Sari A, Sener YZ, Firat E, Armagan B, Erden A, Oksul M, et al. Pulmonary hypertension in Takayasu arteritis. Int J Rheum Dis. 2018;21:1634-9. https://doi.org/10.1111/1756-185X.13354.
44. Gong J, Yang Y, Ma Z, Guo X, Wang J, Kuang T, et al. Clinical and imaging manifestations of Takayasu's arteritis with pulmonary hypertension: a retrospective cohort study in China. Int J Cardiol. 2019;276:224-9. https://doi.org/10.1016/j.ijcard.2018.08.047.
45. Amiri N, De VM, Choi HK, Sayre EC, Avina-Zubieta JA. Increased risk of cardiovascular disease in giant cell arteritis: a general population-based study. Rheumatology (Oxford). 2016;55:33-40. https://doi.org/10.1093/rheumatology/kev262.
46. Dagan A, Mahroum N, Segal G, Tiosano S, Watad A, Comaneshter D, et al. The association between giant cell arteritis and ischemic heart disease: a population-based cross-sectional study. Isr Med Assoc J. 2017;19:411-4.
47.•• Li L, Neogi T, Jick S. Giant cell arteritis and vascular disease-risk factors and outcomes: a cohort study using UK clinical practice research datalink. Rheumatology (Oxford). 2017;56:753-62. https://doi.org/10.1093/rheumatology/kew482 **This big study in a very large series of patients (9,778) with GCA found an increased risk of incident vascular disease**.
48. Tiosano S, Adler Y, Azrielant S, Yaune Y, Gendelman O, Shor DBA, et al. Pericarditis among giant cell arteritis patients: from myth to reality. Clin Cardiol. 2018;41:623-7. https://doi.org/10.1002/clc.22927.
49. Kushnir A, Restaino SW, Yuzefpolskaya M. Giant cell arteritis as a cause of myocarditis and atrial fibrillation. Circ Heart Fail. 2016;9: e002778. https://doi.org/10.1161/CIRCHEARTFAILURE.115.002778.
50. Pagnoux C, Seror R, Henegar C, Mahr A, Cohen P, Le Guern V, et al. Clinical features outcomes in 348 patients with polyarteritis nodosa. A systematic retrospective study of patients diagnosed between 1963 and 2005 and entered into the French Vasculitis Study Group database. Arthritis Rheum. 2010;62:616-26. https://doi.org/10.1002/art.27240.
51. Schrader ML, Hochman JS, Bulkley BH. The heart in polyarteritis nodosa: a clinicopathologic study. Am Heart J. 1985;109:1353-9. https://doi.org/10.1016/0002-8703(85)90365-5.
52. Lewandowski M, Goracy J, Kossuth I, Peregud-Pogorzelska M. Vasculitis or coronary atherosclerosis? Optical coherence tomography images in polyarteritis nodosa Kardiol Pol 2018;76:813. Doi: https://doi.org/10.5603/KP.2018.0087.
53. Bourgarit A, Le Toumelin P, Pagnoux C, Cohen P, Mahr A, Le Guern V, et al. Deaths occurrring during the first year after treatment onset for polyarteritis nodosa, microscopic polyangiitis, and Churg-Strauss syndrome: a retrospective analysis of causes and factors predictive of mortality based on 595 patients. Medicine (Baltimore). 2005;84:323-30. https://doi.org/10.1097/01.md.0000180793.80212.17.
54. Comarmond C, Pagnoux C, Khellaf M, Cordier J-F, Hamidou M, Viallard J-F, et al. Eosinophilic granulomatosis with polyangiitis (Churg-Strauss). Clinical characterisitics and long-term followup of the 383 patients enrolled in the French vasculitis study group cohort. Arthritis Rheum. 2013;65:270-81. https://doi.org/10.1002/art,37721.
55. Dennert RM, van Passen P, Schalla S, Kuztentsova T, Alzand BS, Staessen JA, et al. Cardiac involvement in Churg-Strauss syndrome. Arthritis Rheum. 2010;62:627-34. https://doi.org/10.1002/art.27263.
56. Hazebroek MR, Kemna MJ, Schalla S, Sanders-van Wijk S, Gerretsen SC, Dennert R. Prevalence and prognostic relevance of

cardiac involvement in ANCA-associated vasculitis: Eosinophilic granulomatosis with polyangiitis and granulomatosis with polyangiitis. Int J Cardiol. 2015;199:170-9. https://doi.org/10.1016/j.ijcard.2015.06.087.

57. Yune S, Choi DC, Lee BJ, Lee JY, Jeon ES, Kim SM, et al. Detecting cardiac involvement with magnetic resonance in patients with active eosinophilic granulomatosis with polyangiitis. Int J Card Imaging. 2016;32(Suppl 1):155-62. https://doi.org/10.1007/s10554-016-0843-y.
58. Cereda AF, Pedrotti P, De Capitani L, Giannattasio C, Roghi A. Comprehensive evaluation of cardiac involvement in eosinophilic granulomatosis with polyangiitis (EGPA) with cardiac magnetic resonance. Eur J Intern Med. 2017;39:51-6. https://doi.org/10.1016/j.ejim.2016.09.014.
59. Marmursztejn J, Guillevin L, Trebossen R, Cohen P, Guilpain P, Pagnoux C, et al. Churg-Strauss syndrome cardiac involvement evaluated by cardiac magnetic resonance imaging and positron-emission tomography: a prospective study on 20 patients. Rheumatology (Oxford). 2013;52:642-50. https://doi.org/10.1093/rheumatology/kes155.
60. Bluett R, McDonneell D, O'Dowling C, Vaughan C. Eosinophilic myocarditis as a first presentation of eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome). BMJ Case Rep. 2017;2017:bcr2017221227. https://doi.org/10.1136/bcr-2017-221227.
61. Qiao L, Gao D. A case report and literature review of Churg-Strauss syndrome presenting with myocarditis. Medicine (Baltimore). 2016;95:e5080. https://doi.org/10.1097/MD.0000000000005080.
62. Dey M, Nair J, Sankaranarayanan R, Kanagala P. Myopericarditis as a presentation of eosinophilic granulomatosis with polyangiitis (EGPA). BMG Case Rep. 2019;12:e230593. https://doi.org/10.1136/bcr-2019-230593.
63. Yano T, Ishimura S, Furukawa T, Koyama M, Tanaka M, Shimoshige S, et al. Cardiac tamponade leading to the diagnosis of eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome): a case report and review of the literature. Heart Vessel. 2015;30:841-4. https://doi.org/10.1007/s00380-014-0556-x.
64. Yamamoto Y, Otani Y, Okabe F, Yoneda M, Morimura O, Abe K. Anti-proteinase 3-positive eosinophilic granulomatosis with polyangiitis revealed by cardiac tamponade. Intern Med. 2019;58:3045-50. https://doi.org/10.2169/internalmedicine.2937-19.
65. Groh M, Masciocco G, Kirchner E, Kristen A, Pellegrini C, Varnous S, et al. Heart transplantation in patients with eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome). J Heart Lung Transplant. 2014;33:842-50. https://doi.org/10.1016/j.healun.2014.02.023.
66. McGeoch L, Carette S, Cuthbertson D, Hoffman GS, Khalidi N, Koening CL, et al. Cardiac involvement in granulomatosis with polyangiitis. J Rheumatol. 2015;42:1209-12. https://doi.org/10.3899/jrheum141513.
67. Życińska K, Borowiec A, Zielonka TM, Rusinowicz T, Hadzik-Blaszczyk M, Cieplak M, et al. Echocardiographic assessment in patients with granulomatosis with polyangiitis. Adv Exp Med Biol. 2017;1022:27-33. https://doi.org/10.1007/5584_2017_43.
68. Pugnet G, Gouya H, Puéchal X, Terrier B, Kahan A, Legmann P, et al. Cardiac involvement in granulomatosis with polyangiitis: a magnetic resonance imaging study of 31 consecutive patients. Rheumatology (Oxford). 2017;56:947-56. https://doi.org/10.1093/rheumatology/kew490.
69. Vanga A, Rana AZ, Kowaleska J, Rust H. Pericardial tamponade: an uncommon clinical presentation in cANCA related vasculitis and glomerulonephritis in association with very high titres of ANA. Case Rep Nephrol. 2019;2019:4983139-5. https://doi.org/10.1155/2019/4983139.
70. Rogaczewska M, Puszczewicz M, Stopa M. Exclusively ocular and cardiac manifestations of granulomatosis with polyangiitis - a case report. BMC Ophthalmol. 2019;19:139. https://doi.org/10.1186/s12886-019-1148-4.
71. Shuai ZW, Lv YF, Zhang MM, Hu ZY. Clinical analysis of patients with myeloperoxidase antineutrophil cytoplasmic antibody-associated vasculitis. Genet Mol Res. 2015;14:5296-303. https://doi.org/10.4238/2015.May.18.22.
72. Guillevin L, Durand-Gasselin B, Cevallos R, Gayraud M, Lhote F, Callard P. Microscopic polyangiitis: clinical and laboratory findings in eighty-five patients. Arthritis Rheum. 1999;42:421-30. https://doi.org/10.1002/1529-0131(199904)42:3<421::AID-ANR5>3.0.CO;2-6.
73. Mavrogeni S, Manoussakis MN, Karagiorga TC, Douskou M, Panagiotakos D, Bournia V, et al. Detection of coronary artery lesions and myocardial necrosis by magnetic resonance in systemic necrotizing vasculitides. Arthritis Care Res. 2009;61:1121-9. https://doi.org/10.1002/art.24695.
74. Aratani S, Sakai Y, Tsuruoka S. A case of microscopic polyangiitis with subarachnoid hemorrhage and cardiovascular complications. J Nippon Med Sch. 2017;84:251-5. https://doi.org/10.1272/jnms.84.251.
75. Muñoz-Grajales C, Chavarriaga JC, Márquez JD, Pinto LF. Noninfective endocarditis in microscopic polyangiitis: report of a case with a successful response to immunosuppressive therapy. Reumatol Clin. 2019;15:e21-3. https://doi.org/10.1016/j.reuma.2017.07.005.
76.• Mourget M, Chauveau D, Faguer S, Ruidavets JB, Béjot Y, Ribes D, et al. Increased ischemic stroke, acute coronary artery disease and mortality in patients with granulomatosis with polyangiitis and microscopic polyangiitis. J Autoimmun. 2019;96:134-41. https://doi.org/10.1016/j.jaut.2018.09.004 **This retrospective study establishes a high stroke and coronary artery disease incidence in GPA and MPA**.
77.•• Houben E, Penne EL, Voskuyl AE, van der Heijden JW, Otten RHJ, Boers M, et al. Cardiovascular events in anti-neutrophil cytoplasmic antibody-associated vasculitis: a meta-analysis of observational studies. Rheumatology (Oxford) 2018;57:555-562. Doi: https://doi.org/10.1093/rheumatology/kex338. **Comprehensive systematric review that included almost 14,000 patients with AAV and found an increase risk of cardiovascular events.**
78.•• Luo Y, Xu J, Jiang C, Krittanawong C, Wu L, Yang Y, et al. Trends in the inpatient burden of coronary artery disease in granulomatosis with polyangiitis: a study of large national dataset. J Rheumatol 2020 Jun 15;jrheum.200374. Doi:https://doi.org/10.3899/jrheum.200374. Online ahead of print. **This very important study found an increased trend in inpatient burden of coronary artery disease and heart failure in GPA.**
79.•• Kronbichler A, Leierer J, Leierer G, Mayer G, Casian A, Höglund P, et al. Clinical associations with venous thromboembolism in antineutrophil cytoplasm antibody-associated vasculitides: Rheumatology (Oxford) 2017;56:704-708. Doi:https://doi.org/10.1093/rheumatology/kew465. **Large multinational European study that found an increased incidence of venous thromboembolism in AAV.**
80.• Berti A, Matteson EL, Crowson CS, Specks U, Cornec D. Risk of cardiovascular disease and venous thromboembolism among patients with incident ANCA-associated vasculitis: a 20-year population-based cohort study. Mayo Clin Proc. 2018;93:597-606. https://doi.org/10.1016/j.mayocp.2018.02.010 **This retrospective study reported a higher risk of cardiovascular diseases and cerebrovascular accidents in incident AAV patients than in controls**.
81.• Kang A, Antomelou M, Wong NL, Tanna A, Arulkumaran N, FWK T, et al. High incidence of arterial and venous thrombosis in antineutrophil cytoplasmic antibody-associated vasculitis. J

Rheumatol. 2019;46:285-93. https://doi.org/10.3899/jrheum.170896 **Retrospective study that found a higher event rates of coronary disease, incident stroke, and venous thromboembolism in AAV**.

82.•• Wallace ZS, Fu X, Harkness T, Stone JH, Zhang Y, Choi H. All-cause and cause-specific mortality in ANCA-associated vasculitis: overall and according to ANCA type. Rheumatology (Oxford). 2019;17:kez589. https://doi.org/10.1093/rheumatology/kez589 **This important study found that cardiovascular disease was the most common cause of death in AAV patients**.

83. Geri G, Wedisler B, Thi Huong du L, Isnard R, Piette JC, Amara Z, et al. Spectrum of cardiac lesions in Behçet disease. Medicine (Baltimore). 2012;91:25-34. https://doi.org/10.1097/MD.0b013e.3182428f49.

84.• Kechida M, Salah S, Kahloun R, Klii R, Hammami S, Khochtali I. Cardiac and vascular complications of Behçet disease in the Tunisian context: clinical characteristics and predictive factors. Adv Rheumatol. 2018;58:32. https://doi.org/10.1186/s423-58-018-0032-x **This retrospective study reported a high incidence of vascular events in BD**.

85.• Chen H, Zhang Y, Li C, Wu W, Liu J, Zhang F, et al. Coronary involvement in patients with Behçet's disease. Clin Rheumatol. 2019;38:2835-41. https://doi.org/10.1007/s10067-019-04640-2 **Case-control study that reports the characteristics of coronary artery involvement in BD patients**.

86. Yaume Y, Tiosano S, Watad A, Comaneshter D, Cohen AD, Amital H. Investigating the link between ischemic heart diasease and Behcet's disease: a cross-sectional analysis. Int J Cardiol. 2017;241:41-5. https://doi.org/10.1016/j.ijcard.2017.02.135.

87. Keskin M, Bozbay M, Kayacioğlu I, Koçoğullari C, Bozbay AY, Hayiroğlu MI, et al. Spontaneous right coronary artery rupture and acute cardiac tamponade in Behçet's disease. Heart Lung Circ. 2016;25:e149-51. https://doi.org/10.1016/j.hlc.2016.04.022.

88. Guo Y, Tang L, Tang J, Zhou S. Recurrent myocardial infarction due to coronary artery aneurysm in Behçet's syndrome: a case report. Eur Heart J Case Rep. 2019;3:1-4. https://doi.org/10.1093/ehjcr/ytz204.

89. Wang H, Guo X, Tian Z, Liu Y, Wang Q, Li M, et al. Intracardiac thrombus in patients with Behcet's disease: clinical correlates, imaging features, and outcome: a retrospective, single-center experience. Clin Rheumatol. 2016;35:2501-7. https://doi.org/10.1007/s10067-015-3161-1.

90. Ghorbel IB, Belfeki N, Houman MH. Intracardiac thrombus in Behçet's disease. Reumatismo. 2016;68:148-53. https://doi.org/10.4081/reumatismo.2016.887.

91. Sun BJ, Park J-H, Yoo S-J, Park Y, Kim YJ, Lee IS, et al. Intrinsic changes of left ventricular function in patients with Behçet disease and comparison according to systemic disease activity. Echocardiography. 2018;35:809-16. https://doi.org/10.1111/echo.13844.

92. Aslam F, Bandeali SJ, Crowson C, Alam M. Cardiac function and diastolic dysfunction in Behcet's disease: a systematic review and meta-analysis. Int J Rheumatol. 2016;2016:9837184-11. https://doi.org/10.1155/2016/9837184.

93.•• Lee E, Choi E-K, Jung J-H, Han K-D, Lee S-R, Cha M-J, et al. Increased risk of atrial fibrillation in patients with Behçet's disease: a nationwide population-based study. Int J Cardiol. 2019;292:106-11. https://doi.org/10.1016/j.ijcard.2019.06.045 **This study found an increased risk of atrial fibrillation in a very large series of newly diagnosed BD patients (6,636).**

94. Butt S-U-R, McNeil J. Complete heart block in a Caucasian woman with Behcet's disease: a case report. J Med Case Rep. 2016;10:102. https://doi.org/10.1186/s13256-016-0890-y.

95. Yu S, Han J, Gao S, Ruan Y, Gu X, Sun L, et al. Echocardiographic features of interventricular septal dissection in patients with Behçet's disease. Echocardiography. 2019;36:394-400. https://doi.org/10.1111/echo.14235.

96. Gu X, He Y, Luan S, Zhai Y, Sun L, Zhang H, et al. Dissection of the interventricular septum: echocardiographic features. Medicine (Baltimore). 2017;96:e6191 MD.0000000000006191.

97. Vural U, Kizilay M, Aglar AA. Coronary involvement in Behcet's disease: what are its risks and prognosis? (rare cases and literatura review). Braz J Cardiovasc Surg. 2019;34:749-58. https://doi.org/10.21470/1678-9741-2019-0003.

98. Ghang B, Kim JB, Jung S-H, Chung CH, Lee JW, Song JM, et al. Surgical outcomes in Behcet's disease patients with severe aortic regurgitation. Ann Thorac Surg. 2019;107:1188-94. https://doi.org/10.1016/j.athoracsur.2018.08.040.