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Review

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Review

From Fibromuscular Dysplasia to Arterial Dissection and Back

Justine Huart,[1,2] Maria S. Stoenoiu,[3] Marialuisa Zedde,[4] Rosario Pascarella,[5] David Adlam,[6] and Alexandre Persu[7,8,*]

[1]Division of Nephrology, University of Liège Hospital (ULiège CHU), University of Liège, Liège, Belgium;
[2]Groupe Interdisciplinaire de Génoprotéomique Appliquée (GIGA), Division of Cardiovascular Sciences, University of Liège, Liège, Belgium;
[3]Department of Internal Medicine, Rheumatology, Cliniques Universitaires Saint-Luc, Université catholique de Louvain, Brussels, Belgium;
[4]Neurology Unit, Stroke Unit, AUSL-IRCCS di Reggio Emilia, Reggio Emilia, Italy;
[5]Neuroradiology Unit, AUSL-IRCCS di Reggio Emilia, Reggio Emilia, Italy;
[6]Department of Cardiovascular Sciences, University of Leicester and NIHR Leicester Biomedical Research Centre, Leicester, UK;
[7]Division of Cardiology, Cliniques Universitaires Saint-Luc, Université catholique de Louvain, Brussels, Belgium;
[8]Pole of Cardiovascular Research, Institut de Recherche Expérimentale et Clinique, Université catholique de Louvain, Brussels, Belgium

[*]Corresponding author: Alexandre Persu (alexandre.persu@uclouvain.be).

Fibromuscular dysplasia (FMD) is an idiopathic and systemic non-inflammatory and non-atherosclerotic arterial disease. Fifteen to 25% of patients with FMD present with arterial dissection in at least one arterial bed. Conversely, a substantial number of patients with renal, carotid, and visceral dissection have underlying FMD. Also, while few patients with FMD develop coronary artery dissection, lesions suggestive of multifocal FMD have been reported in 30–80% of patients with spontaneous coronary artery dissection (SCAD), and the relation between these two entities remains controversial. The frequent association of FMD with arterial dissection, both in coronary and extra-coronary arteries raises a number of practical and theoretical questions: (i) Are FMD and arterial dissections two different facets of the same disease or distinct though related entities? (ii) Is SCAD just a manifestation of coronary FMD or a different disease? (iii) What is the risk and which are predictive factors of developing arterial dissection in a patient with FMD? (iv) What proportion of patients who experienced an arterial dissection have underlying FMD, and does this finding influence the risk of subsequent arterial complications? In this review we will address these different questions using fragmentary, mostly cross-sectional evidence derived from large registries and studies from Europe and the United States, as well as arguments derived from demographics, clinical presentation, imaging, and when available histology and genetics. From there we will derive practical consequences for nosology, screening and follow-up.

Keywords: arterial dissections; blood pressure; fibromuscular dysplasia; hypertension; spontaneous coronary artery dissection.

Fibromuscular dysplasia (FMD) is a non-inflammatory and non-atherosclerotic arterial disease affecting mainly medium-sized arteries. The most frequent form of FMD is multifocal FMD (80–90% of cases). The characteristic lesion of multifocal FMD is the so-called "string of beads," an alternation of dilatation and stenosis, usually in the mid and distal portions of the artery. In the absence of an alternative diagnosis, patients with a focal stenosis occurring in any segment of the artery are also considered to have a form of FMD named focal FMD. Focal and multifocal FMD roughly correspond to the medial and intimal histological forms of FMD.[1,2]

Once considered primarily a rare cause of renovascular hypertension in young women, FMD is now increasingly recognized as not so rare. It is a truly systemic arterial disease, with a wide spectrum of manifestations and severity, ranging from asymptomatic disease to a condition with life-threatening consequences. Possible clinical presentations include renovascular hypertension, subarachnoid hemorrhage, ischemic and hemorrhagic stroke, mesenteric, renal, and myocardial infarction. While FMD predominantly affects young-to-middle aged women, it may also be diagnosed in children, men and elderly patients.[1,2]

In addition to arterial stenosis, arterial dissections (15–20% of cases), aneurysms (20–25% of cases), and arterial tortuosity may also be found in patients with FMD.[1,3–5] Conversely, many patients first presenting with these manifestations are subsequently found to have underlying FMD.[6,7] Nevertheless, the nature and extent of the overlap between FMD and arterial dissection remains unclear. The recently identified association of spontaneous coronary artery dissection (SCAD) with FMD is particularly intriguing.[8,9] While some consider SCAD as a manifestation of coronary FMD,[10,11] other favor the view that SCAD and FMD are distinct though related entities.[12]

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In this review, we will discuss

- The prevalence of FMD in patients with arterial dissection.
- The prevalence and predictors of dissection in patients with FMD, both as the initial manifestation of FMD and as an imaging finding on baseline head-to-pelvis arterial scan.
- The risk of *de novo* dissection during follow-up of patients with FMD.
- The risk of dissection recurrence in patient with dissection with and without FMD.
- The difference and similarities between SCAD and FMD.

Based on these elements, we will make proposals for practical management and follow-up of patients with FMD and dissection.

FMD AND ARTERIAL DISSECTION: EXTENT OF THE OVERLAP

Prevalence of FMD in patients with arterial dissection

Fibromuscular dysplasia is frequently found in patients with spontaneous cervical (8–20%),[6,13] renal (16–46%),[7] and coronary artery dissection (42.9–77.6% in unblinded and uncontrolled studies including over 100 patients with SCAD[14,15]; 31.8% in a blinded study including 173 patients[12]) (Figure 1).

However, the reported prevalence of FMD lesions in patients with arterial dissection may be underestimated in studies with incomplete or suboptimal exploration and vary according to imaging methods and diagnostic criteria. In particular, in published series of patients with an arterial dissection, the diagnostic work-up often does not include screening for asymptomatic arterial involvement in territories other than that of the dissection. This issue may have a major impact on the reported prevalence of FMD. For example, in a large national series of patients with spontaneous carotid and vertebral dissections where no other vascular site was formally studied, the prevalence of FMD was reported as 8%,[6] while in a small series where a standardized protocol of brain-to-pelvis CT-angiography (CTA) was applied, it was as high as 39.5%.[16] Conversely the prevalence of FMD may be overestimated in unblinded studies where minor irregularities or very subtle beading, may be labeled as multifocal FMD, particularly in some SCAD studies.[12,17] In the absence of biomarkers of FMD or a universally accepted imaging protocol and grading system, the reported prevalence of FMD is difficult to compare across different studies.

Prevalence of dissection in patients with FMD

Alternatively, among 921 patients enrolled in the U.S. Registry for FMD as of October 2014, 25.7% had at least one arterial dissection in any vascular bed, 27.8% of whom having dissection in at least two arterial beds.[3] The prevalence of arterial dissection was 15.1% in the French-Belgian ARCADIA Registry (n = 469),[4] 12.5% in the ARCADIA-POL study (n = 232),[18] and 5.6% in the European-International FEIRI registry (n = 1,022).[5] As cerebrovascular arteries are the most frequently dissected arteries in patients with FMD, these differences may mirror the prevalence of a cerebrovascular presentation in these different cohorts (US registry: not reported but certainly >50%; ARCADIA: 35.2%; ARCADIA-POL: 24.6%; FEIRI: 11.6%).[3–5] Notably, since the initial publication of the FEIRI registry, subsequent inclusion of more Neurology centers has led to a substantial increase of the proportion of patients with dissection, particularly among incident patients (A. Persu, personal communication).

The prevalence of dissections in patients with FMD and the prevalence of FMD in patients with extra-coronary dissection, (both overall and divided into the main arterial beds) are illustrated in Figure 2.[3–7,13,16,18–24] The prevalence of FMD in patients with SCAD is illustrated in Figure 3.[12,15,17,25–34]

Affected arterial beds

In patients with FMD, the most frequently dissected vessels are cerebrovascular arteries (from 9 to 39.5% of patients).[2–4,16,18] Carotid artery dissections are two to four times more frequent than vertebral artery dissections,[2,3,23] a proportion similar to that reported in cohorts of patients with cerebrovascular dissection, irrespective of FMD status.[35] This difference is also in line with the higher prevalence of carotid vs. vertebral FMD.[36] The next most frequently dissected arteries are renal and visceral arteries (Figure 2).

Note, coronary dissections are not included here because whilst patients with SCAD are included in analysis from the US registry of FMD,[3] SCAD is not included in current reports from the ARCADIA[4] and FEIRI[5] registries. Furthermore, as will be discussed below in more detail, the concept of SCAD as a complication of FMD is not universally accepted.

Differential diagnosis

Segmental arterial mediolysis.

Patients with multiple unexplained arterial dissections are also often labeled as having FMD, and the smallest string of beads would be taken in support of this diagnosis. However some of these patients may in fact suffer from Segmental arterial mediolysis (SAM). Considering SAM in the differential diagnosis is particularly relevant in patients with isolated or predominant involvement of visceral arteries.[37] SAM is typically a progressive and often life-threatening disease and the overall outcome is worse than the one of FMD.[38] However, the differential diagnosis with FMD is difficult and relies mostly on histology, which is seldom available,[39] and the very existence of SAM is questioned by some experts.

Hereditary connective tissue disorders.

Some patients with vascular Ehlers-Danlos with arterial dissection may also be misdiagnosed as having FMD, as healing dissections in patients with this condition may display an angiographic appearance similar to a string of beads.[1] Therefore, in cases with extra-arterial manifestations suggestive of Hereditary Connective Tissue Disorders (for example, uterine or colonic rupture), carotido-cavernous fistula or a family history of dissection this diagnosis should be seriously considered.[40] Nevertheless, the frontier between FMD and inherited arteriopathies may be less tight than previously thought, as patients with severe FMD may display mild connective tissue disease features[41] and harbor variants in connective tissue disease genes.[42]

Genetic aspects

Genetic similarities between patients with dissection and FMD.

The prevalence of familial FMD appears higher in FMD patients with arterial dissections and/or aneurysms, and there is increasing evidence that these entities share a partly common genetic architecture.[43] In particular, the intronic *PHACTR1* variant has been associated as well with FMD[44] as with cervical dissection[45]

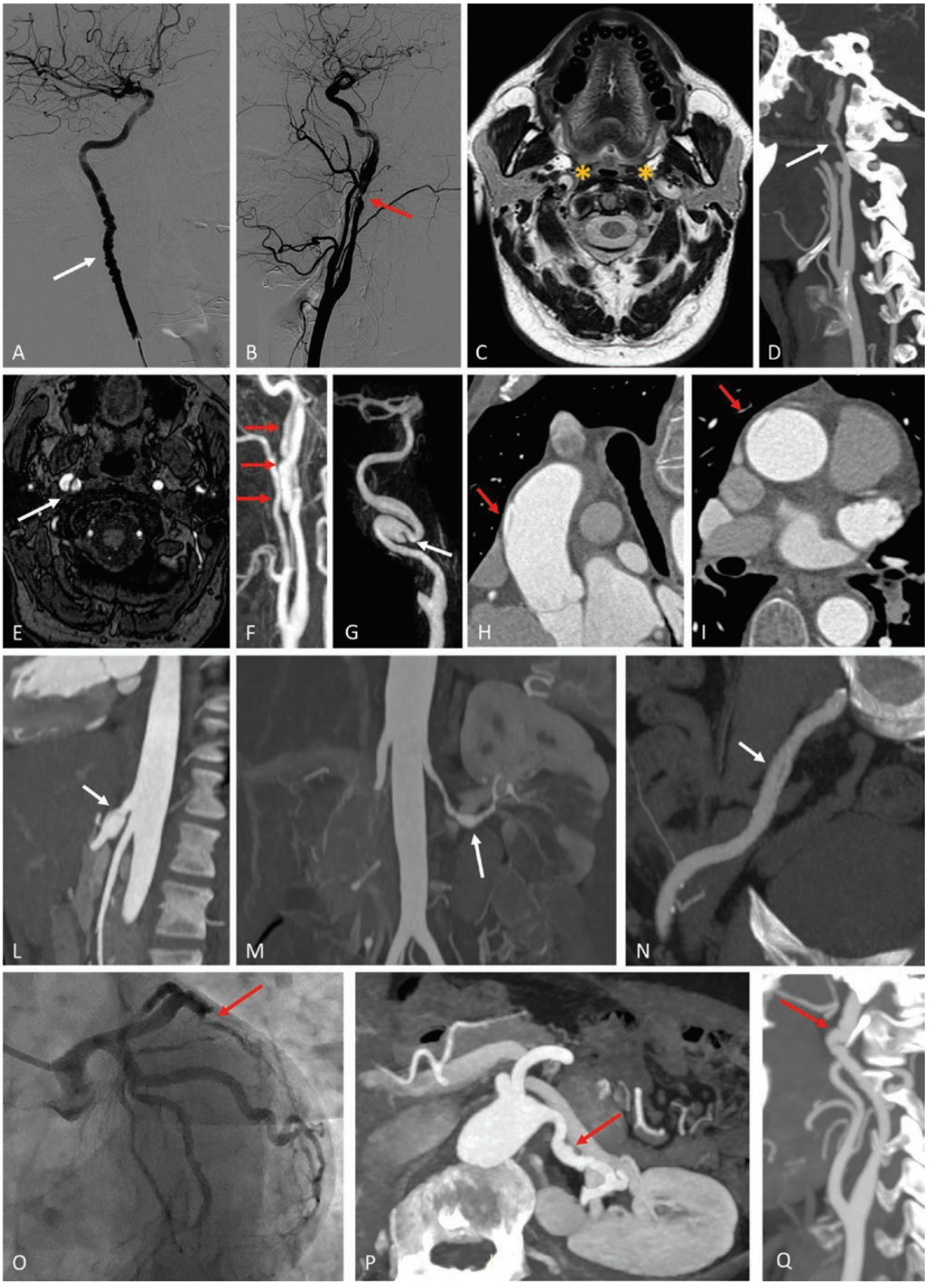

Figure 1. Examples of arterial dissection in patients with FMD. (**a** and **b**) Digital subtraction angiography of the right internal carotid artery (ICA) (white arrow) (**a**) and left carotid axis (**b**) showing the typical string of beads appearance in (**a**) and the angiographic appearance of ICA dissection with a severe, irregular stenosis followed by a dilated segment (red arrow) (same patient in **a** and **b**). (**c** and **d**) Acute bilateral ICA dissection with the mural hematoma as hyperintense crescent sign within the wall of ICA in axial T2W DIXON sequence (yellow asterisk) (**c**) and the corresponding CTA with Maximum Intensity Projections (MIP) reconstructions of the right ICA, showing a long, irregular stenosis in the dissected segment (white arrow) (**d**). (**e** and **f**) MRA with right ICA intimal flap and double lumen (white arrow) (**e**) and the corresponding CE-MRA reconstruction of the dissected segment with a spiroid pattern and enlargement of vessel caliber (red arrows) (**f**). (**g**) Tridimensional reconstruction (CE-MRA) of an ICA dissecting aneurysm with a persistent intimal flap (white arrow). (**h** and **i**) CTA with focal aortic dissection in a patient with FMD (sagittal and axial planes in **h** and **i**, respectively) (red arrows). (**l**) Celiac trunk dissection with aneurysm (MIP reconstructed CTA) (white arrow). (**m**) Left renal artery dissection with irregular severe tubular stenosis, followed by an aneurysm and persistent occlusion of left inferior polar artery with renal infarction (MIP reconstructed CTA) (white arrow). (**n**) Right common iliac artery dissection with an intraluminal flap (MIP reconstructed CTA) as incidental finding in the follow-up of a patient with FMD patient (white arrow). (**o**–**q**) Same patient with a left coronary artery dissection (**o**), a left renal artery multifocal FMD lesion (**p**) and a right ICA string of beads pattern (**q**) (red arrows).

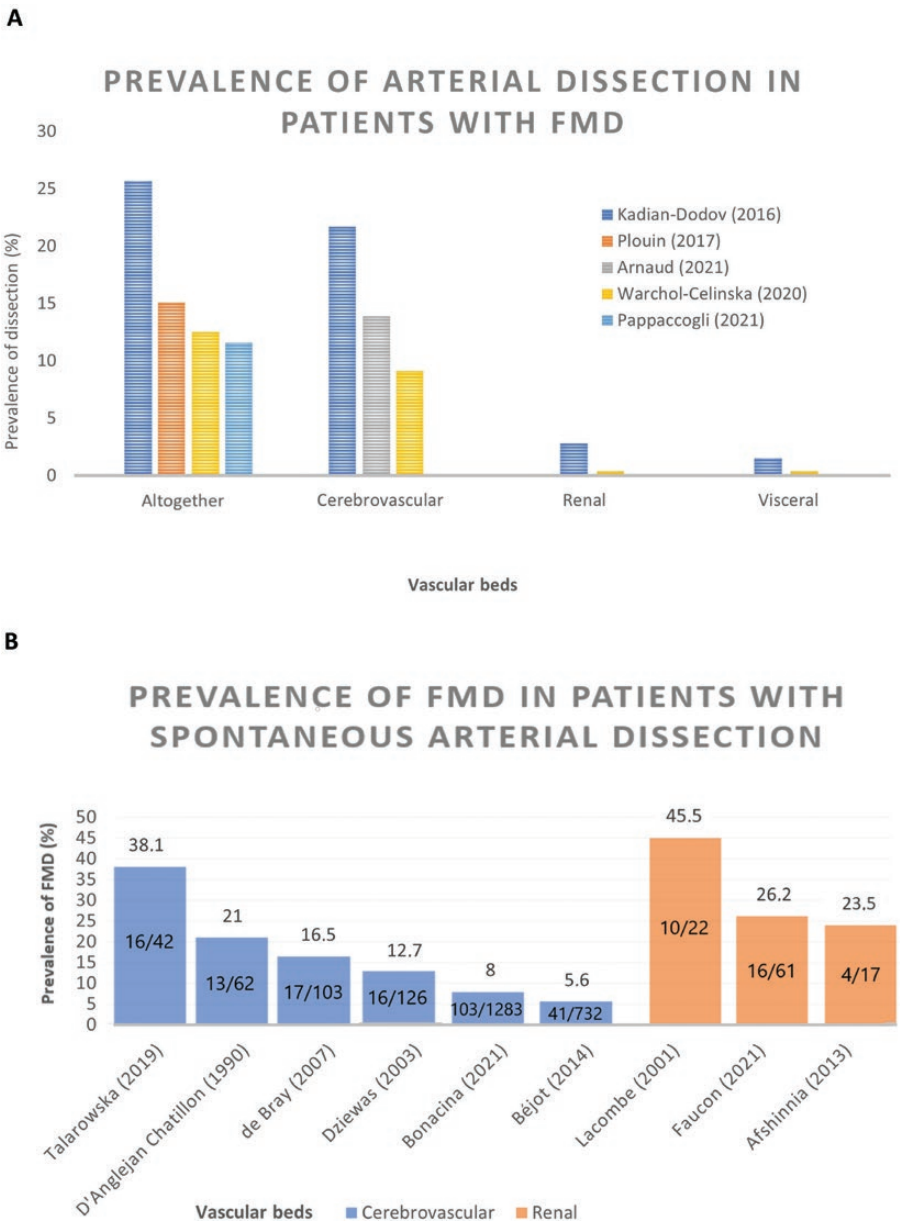

Figure 2. Arterial dissections in patients with FMD and FMD in patients with arterial dissections. (**a**) Prevalence of arterial dissection in patients with FMD. (**b**) Prevalence of FMD in patients with extra-coronary dissection. (Selected studies).

and SCAD.[46] Rare variants in *COL5A1*, a gene involved in classical Ehlers-Danlos syndrome have been identified in a minority of patients with FMD and dissections.[47] The latter has also occasionally been involved in SCAD, along with other collagen genes.[48]

Genetic differences between patients with dissection and FMD.

Nevertheless, overall, common genetic variants identified in Genome wide Association Studies[49,50] and potentially causal rare genetic mutations found in a minority of patients[42] differ significantly between FMD and SCAD. For example, an increased burden of variants in Loeys-Dietz genes has been shown in patients with SCAD but not in a subset of FMD patients enriched for arterial dissections.[51] Finally, a polygenic risk score for SCAD was shown to predict increased risk of SCAD also in patients with FMD,[52] confirming that beyond shared genetic *loci* such as *PHACTR1*, distinct genetic risk factors exist as well.[42]

RISK OF ARTERIAL DISSECTION IN SUBJECTS WITH FMD: A PATIENT-ORIENTED VIEW

The substantial prevalence of arterial dissection in large registries is part of the rationale underlying the recommendation in current consensus recommendations to perform baseline head-to-pelvis CT or MR-angiography in all patients with FMD.[1] However, this reported "prevalence" is somewhat of an artificial construct as it arises from two different clinical scenarios: (i) where a symptomatic carotid, renal, or visceral dissection led to the diagnosis of FMD in a contralateral artery or another arterial bed, and dissection was subsequently "assigned" to FMD; (ii) where a previously unknown dissection was identified during the vascular work-up of patients presenting with, for instance, multifocal renal FMD. Importantly also, the reported prevalence of arterial dissection in patients with FMD is derived from cross-sectional analysis of

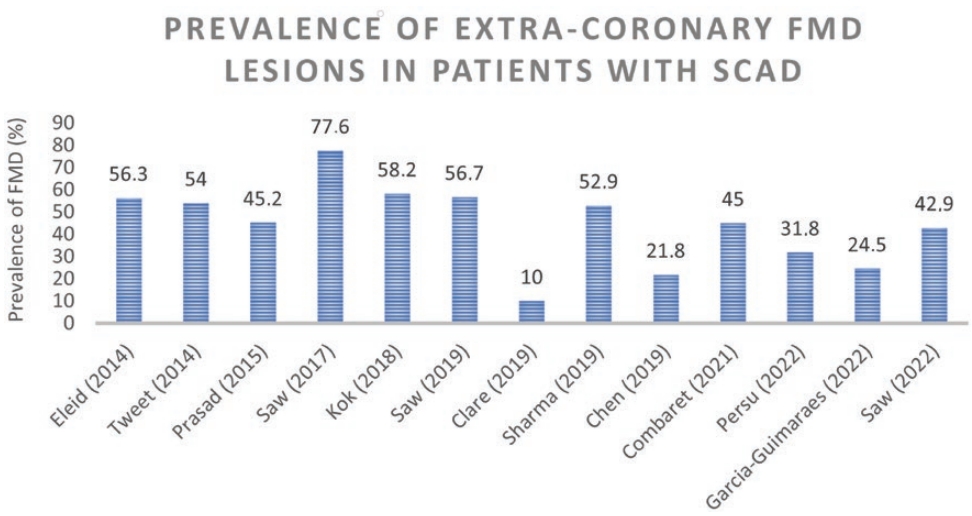

Figure 3. Prevalence of extra-coronary FMD in patients with SCAD. (Selected cohorts including >100 patients). Updated from Table 5 in ref. 14.

registries and therefore does not say anything about the incidence of symptomatic dissections during follow-up of patients already diagnosed with FMD.

Perhaps therefore the true questions one has to address clinically for a patient already diagnosed with FMD with or without arterial dissection at presentation are: (i) What is the likelihood of detecting a previously unknown arterial dissection during vascular work-up? (ii) What is the risk of developing a *de novo* arterial dissection during follow-up?

What is the likelihood of detecting an arterial dissection during vascular work-up?

Some clues about the prevalence of previously unknown arterial dissections identified on baseline head-to-pelvis CTA or MR-angiography (MRA) screening may be derived from the ARCADIA[4,23] and ARCADIA-POL[18] studies. In the ARCADIA study,[4] the authors report the presence of a dissection in 71 out of 469 patients (15.1%). They further report that the initial clinical presentation included a cervical dissection in 45 patients (9.6%) and an acute renal infarction (likely due to renal artery dissection) in 11 additional patients (2.3%). Therefore, the proportion of patients with a symptomatic arterial dissection at diagnosis is in the range of 9.6–11.9% (the higher estimate implying that a renal dissection was identified in all patients with renal infarction and that no patient had both a cervical dissection and a renal dissection). Therefore CTA/MRA led to the identification of 3.2–5.5% new dissections. This relatively low yield is consistent with a more recent report from the same ARCADIA registry focused on cervical dissections stating that 65 patients (14%) had a least one cervical dissection.[23] As we know that 45 were part of the clinical picture at presentation, it means that 20 additional dissections were identified by CTA or MRA screening in patients with renovascular presentation (4.3% of all patients enrolled in ARCADIA; 6.6% of patients with renovascular presentation). Similarly, in a report of the ARCADIA-POL study including 207 patients with confirmed FMD,[18] 29 (14%) patients had at least one arterial dissection, only 3 (1.4%) of which were detected on systematic screening by CTA. This contrasts with aneurysms which were detected in 57 (24.6%) additional patients during systematic screening. This striking difference probably reflects the fact that acute dissection is usually a symptomatic event while aneurysms often remain silent or are only associated with atypical symptoms unless rupture occurs.

What is the risk of developing an arterial dissection during follow-up?

To our knowledge, the incidence of arterial dissection in patients with FMD during prospective follow-up has been evaluated only in a single cohort followed at the Mount Sinai Medical Centre using various imaging modalities (mostly carotid duplex).[53] Among 146 FMD patients (35.6% with at least one dissection at baseline) followed-up for a mean duration of 35.5 months (range: 5–153 months), a *de novo* dissection was identified in only three patients (2%) between 15 and 23 months. All three were carotid dissections, were heralded by suggestive symptoms (neck and facial pain in two cases, Amaurosix fugax in one) and occurred within areas of know multifocal FMD. All three patients made a full neurological recovery. Two out of three had a history of previous arterial dissection, one in the coronary and the other in the contralateral carotid artery. The results of larger prospective studies with systematic CT or MR angiographic follow-up are awaited, including the unpublished PROFILE study (NCT NCT02961868). However, current data suggest that the incidence of *de novo*, clinically relevant dissections in patients with FMD is low, particularly in the absence of arterial dissection at baseline or in vessels unaffected by FMD.

PREVALENCE AND INCIDENCE OF DISSECTION IN PATIENTS WITH SCAD

These results are paralleled by those obtained in a blinded cross-sectional MRA analysis of extra-coronary arteries of 173 patients with SCAD (31.8% with documented multifocal FMD).[12] In the latter, only three extra-coronary arterial dissections were identified at screening, two cerebrovascular and one iliac. In 170 out of 173 evaluable patients, a single extra-coronary arterial event was reported during a median follow-up of five years (IQR, 4–7) and the latter, a stroke secondary to embolism of a left ventricular thrombus following recurrent SCAD was neither related to extra-coronary FMD nor due to an extra-coronary dissection. The remaining three patients with no detailed follow-up were known to be alive at the time of the analysis. Furthermore, in a recent large Canadian prospective cohort of 750 patients with SCAD, only 1.9% of patients experienced a new coronary dissection at three years,[15] that is, much fewer than previously reported, mostly in observational studies.[54]

Overall, it may be concluded that, in patients with SCAD as in patients with primary FMD, the prevalence of dissection in other arterial beds at diagnosis is low. Furthermore, the risk of recurrent dissection is rather small as well, and appears mostly restricted to the initially affected arterial bed, that is, the coronary vasculature.

PREDICTORS OF DISSECTION IN PATIENTS WITH FMD

Even if *de novo* dissections occur rarely during the follow-up of FMD, they may have devastating consequences. Therefore, identification of patients with FMD likely to develop an arterial dissection remains important. No prospective study has yet investigated predictors of dissection and such a study may be challenged by the low expected event rates. Independent factors associated with arterial dissection in patients with FMD have been reported in a cross-sectional analysis of the first 1,022 patients included in the FEIRI registry.[5] These included older age at diagnosis of FMD (OR 1.02 per year), male gender (OR 4.35), stroke/neurovascular presentation (OR 2.19) and multivessel FMD (OR 3.15). In contrast, arterial hypertension/renovascular presentation was negatively correlated with dissections (OR 0.3).[5] Similarly, in the ARCADIA registry,[23] independent factors associated with cervical dissection, the most frequent form of dissection in patients with FMD, included male gender (OR 2.66) and involvement of three or more arterial beds (OR 2.49), while a history of arterial hypertension was protective (OR 0.35). In the same report, the authors confirmed the association of male gender with cervical dissection (OR 2.04, $P < 0.0001$) in a meta-analysis including the ARCADIA and FEIRI registries, the US registry for FMD and two other smaller cohorts from France[55] and Taiwan.[56] The association of male gender with any dissection in patients with FMD is also consistent with previous results from the US FMD registry showing a three-fold higher proportion of men among patients with FMD and dissection compared to those without dissection (13.5 vs. 4.1, $P < 0.0001$).[3]

The association of arterial dissection with a neurovascular rather than renovascular presentation is not surprising, as cervical arteries are the most frequently dissected arteries in patients with FMD, and carotid dissection is one of the main causes of stroke in these patients. The association with multivessel/widespread FMD is of limited relevance, as most cases of dissection were the cause of the index clinical presentation which led to the diagnosis of FMD (A. Persu, personal communication), often in another arterial bed (as diagnosis of FMD in the artery where dissection occurred is questionable). Therefore, by definition, most patients presenting with an arterial dissection in whom FMD was subsequently diagnosed have at least two vessels affected (one with the FMD-related stenosis and one with the dissection) and these patients will be labeled as having multivessel FMD. The positive correlation with age may reflect the time needed to develop a dissection in patients with arterial frailty related to FMD. Alternatively, it may result from an exploration bias, as screening for FMD will not often be performed, for example in older patients with hypertension, but a symptomatic dissection occurring at any age will require at least a minimal etiological work-up.

The association of arterial dissection with male gender in patients with FMD is the most replicated finding and also the most intriguing. It may seem paradoxical that severe, extra-coronary dissection tends to occur more often in men while FMD is predominantly a disease of women.[3,5,23] Nevertheless, it is unlikely to reflect an exploration bias and could even be underestimated because it was consistently found across different studies despite the fact that, based on common knowledge, women with dissection are more likely to be screened for FMD than men.

Also in support of this observation, with the notable exception of SCAD which is diagnosed in an overwhelming majority of women (>90% in most series)[8,9] and irrespective of the presence of underlying FMD, spontaneous arterial dissections are predominantly diagnosed in men: 66.9% of 4,428 patients with aortic dissection[57]; 57.5% of 1,283,[6] and 74.6% of 1,601[45] patients with carotid dissection; 94.9% of 39[58] and 82% of 224[59] patients with visceral dissection; and 70.5% of 61 patients with renal dissection associated with renal infarction.[7] While a possible role of higher tobacco consumption and physical activity, hormonal, and environmental factors may partly account for this association[7,58] for the time being, these potential explanations remain purely speculative.

The proportion of male patients with FMD with or without dissection is shown in Figure 4.[3,5–7,15,19–23,26,27,32,45,57–65]

FMD, A PREDICTOR OF RECURRENCE IN PATIENTS WITH ARTERIAL DISSECTION

FMD and risk of recurrent cervical dissection

The Italian multicentre IPSYS CeAD study[6] included 1,283 patients with cerebrovascular dissection (mean age, 47.8 years; 57.5% of men). Based on acute and post-acute (3–6 months after the index event) vascular imaging, 103 of them (8%) were diagnosed with FMD. However, in the absence of systematic imaging of FMD in other arterial beds than cerebrovascular, this proportion may be an underestimation. Independent factors associated with FMD were coexistence of cerebral aneurysms (OR: 8.71) and migraine (OR: 1.78) while the likelihood of FMD was lower in patients with a history of minor trauma (OR: 0.48). During a 34-month median follow-up, a recurrent cervical dissection was observed in 39 out of 1,194 patients in whom follow-up was available (3.3%).[6] Fourteen were asymptomatic, 12 of which were detected within six months after the first dissection event. However, this high proportion may have been influenced by the fact that systematic MRA imaging was performed only within this time frame (usually, at three and six months). Overall, the median time between the index dissection and dissection recurrence was three months. In multivariable analysis, the single independent direct predictors of recurrence were FMD (OR 3.4) and migraine (OR 2.07). The latter were confirmed when limiting the analysis to the first six months in which all patients were systematically investigated by serial MRA.[6] It should nevertheless be emphasized that a cerebrovascular dissection or dissection recurrence does not mean automatically a dissection-related stroke,[35] and the impact of FMD on the risk of stroke in patients with cervical dissection presenting without stroke is unknown, because the only information available comes from administrative data which lack the needed granularity.[66]

FMD and risk of recurrent SCAD

In the multicentre Canadian cohort of patients with SCAD,[15] the presence of extra-coronary FMD (42.9% of patients, 56.4% of fully explored patients) was an independent predictor of recurrent coronary dissection. However, the odds ratio was relatively low (1.51) and the *P*-value was borderline (0.038). Most importantly, only 58% of patients underwent complete screening for extra-coronary FMD and 23% of patients were not screened at all, with a potential for selection bias.[54]

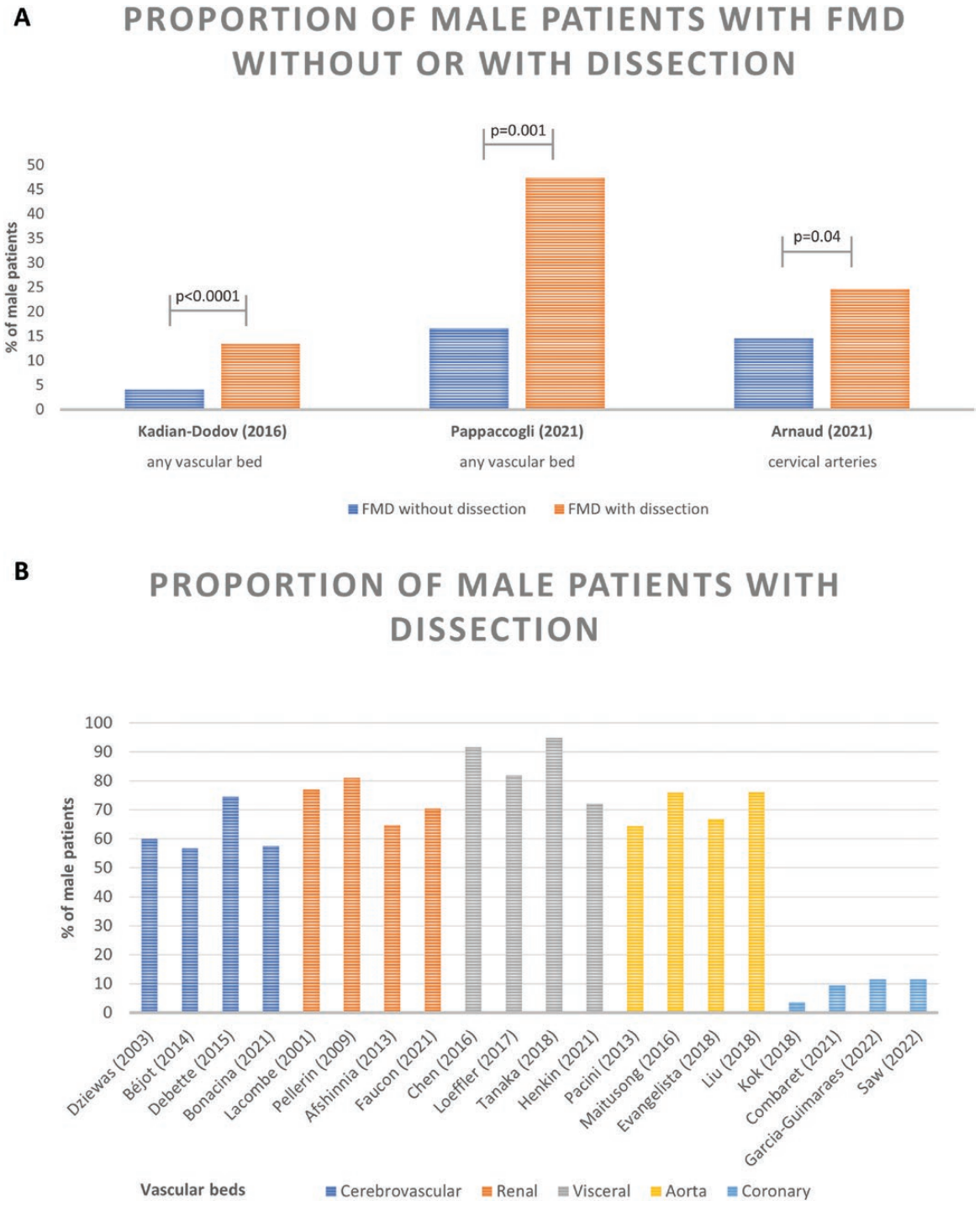

Figure 4. Proportion of men. (**a**) In patients with FMD with or without dissection. (**b**) In patients with dissection irrespective of FMD status. (Selected studies).

FMD and recurrent renal artery dissection

In a French single-center retrospective cohort of patients with unexplained renal artery dissection (n = 61) who underwent a complete arterial exploration at diagnosis,[7] 25% (4/16) of patients with documented FMD had recurrent renal artery dissection and 6.3% (1/16) *de novo* extra-renal dissection during a median follow-up of 51 months, while no new dissection occurred in patients diagnosed with isolated renal artery dissection.[7]

As a whole, although the evidence is fragmentary, it may be concluded that the presence of FMD in patients with arterial dissection is associated with a higher- though still low-risk of dissection recurrence.

FMD AND SCAD

The association between SCAD and FMD is the most studied but also the most controversial. Extra-coronary FMD lesions were

described for the first time in 2012 by Toggweiler *et al.*[67] in 3 out of 12 patients with SCAD. This initial report was followed by the seminal publication by Saw *et al.*[68] suggesting a prevalence of 80% of multifocal FMD in 50 patients with FMD. Since then, the association of SCAD with extra-coronary FMD and other arterial lesions often associated with FMD has been confirmed in hundreds of patients, though with variable prevalence (see above). Extra-coronary FMD in patients with SCAD were reported to be mostly of the multifocal subtype and have been identified most commonly in renal, cerebrovascular, and iliac arteries. Other extra-coronary vascular abnormalities linked with FMD, such as aneurysms and dissections have also been documented.[12,30,68]

Furthermore, tentative criteria for coronary FMD have been proposed.[10,11] This has been used as an argument in favor of a continuum between FMD and SCAD such that SCAD is effectively a manifestation of FMD of the coronary arteries. However, proposed criteria for coronary FMD are strikingly similar to those proposed for SCAD, reports of classical string of beads in coronary arteries are scarce, and most were published several decades ago with suboptimal documentation.[69] Therefore, the jury is still out on whether SCAD and FMD are manifestations of the same disease entity, or overlapping entities, and in the latter case, the nature and extent of this overlap.

The differences and similarities between SCAD and FMD are summarized in Table 1.

On one side, the epidemiology and demographics of FMD and SCAD are quite similar with a mean age at diagnosis around 50–55 years in contemporary registries and a strong female predominance in FMD (80–90%), even stronger in SCAD (>90% in most series).[8,9,42]

Nevertheless, as detailed higher, in patients with primary FMD, dissection of extra-coronary arteries has been strongly and consistently associated with male gender.[6,7,58,62] In this respect, SCAD would appear as the exception as it is primarily a disease of women.[8,9] Furthermore, in a large Canadian series of 1,173 patients with SCAD,[70] the prevalence of FMD was lower in men than in women (27.8% vs. 52.7%; $P = 0.001$), which is again at odds with the association of FMD-related dissections of other arterial beds with male gender. This supposes that the association of gender with dissection is vessel-specific, or alternatively that despite the observed association between both entities, SCAD is not the direct consequence of FMD.

Second, in a blinded analysis of 173 centrally confirmed cases of SCAD and 41 controls,[12] the prevalence of dissections (1.7%), aneurysms (7.5%) and multivessel FMD (29.1%) were lower than in large registries of primary FMD.[3–5,18] Furthermore, in contrast with previous findings in patients with FMD,[71] when compared with controls, neither the presence of an S-curve nor arterial tortuosity at large were associated with SCAD.[12]

Third, as detailed above, despite some degree of overlap, known genetic determinants of FMD and SCAD are markedly different.[42,49–52]

Finally, pathological examination of diseased coronary arteries performed in a series of 36 patients with SCAD and sudden death disclosed limited intimal fibro-elastic thickening but no specific features of FMD. Notably, autopsy reports included renal and/or other extra-coronary arteries in 19 patients, none of which mentioned lesions of FMD in the corresponding vessels.[72] While the latter were performed on a routine basis, it is worth noting that the only reported post-mortem case of SCAD with documented renal string of beads does not describe the histological findings of this artery.[73]

Therefore, available pathological results do not support the view that SCAD is a direct complication of underlying coronary FMD. Furthermore, currently, there is no current demonstration that the histological counterpart of "string of beads" or "irregularities" of extra-coronary arteries documented in patients with SCAD is medial FMD as in primary FMD. It cannot be excluded that different pathophysiological mechanisms may lead to the same or similar "beading" aspects and the "FMD" seen in SCAD patients is effectively a radiological phenocopy.

Ongoing work from our group is in progress to determine whether the tentative urinary proteomic signature identified for FMD[74] also allows identification of patients with SCAD associated or not with extra-coronary FMD. Imaging biomarkers such as ultra-high sensitivity ultrasound may also allow similarities and differences between FMD and SCAD with or without FMD to be investigated.[75]

CONCLUSIONS AND PRACTICAL IMPLICATIONS

A high proportion of patients with arterial dissection have underlying FMD and vice-versa, and both entities partly share common genetic determinants.[42] While patients with FMD are mostly women, dissections in patients with FMD are strongly associated with male gender[3,5,23] (with the notable exception of SCAD). In case of FMD and dissection, a differential diagnosis with vascular Ehlers-Danlos syndrome should be considered, as healing dissections may mimic the typical string of beads of FMD.[1,40] The prevalence of arterial dissections in patients with FMD is usually in the range of 15–25%.[3–5,18] However, in most cases, dissection is the index event leading to the diagnosis of FMD, and a few additional dissections are identified by systematic baseline imaging.[4,18,23] Along the same lines, fragmentary evidence available suggests that the incidence of *de novo*, clinically relevant dissections during follow-up is low, particularly in the absence of arterial dissection at baseline/in vessels unaffected by FMD.[53] A possible exception is renal artery dissection, which tends to recur in the contralateral artery.[7]

Table 1. Similarities and differences between FMD and SCAD

	Similarities	Differences
Demographics	Majority of women in both cases Similar age range at diagnosis	Strong association of dissections with male gender in presence or absence of underlying FMD with the exception of SCAD
Clinical presentation	Both FMD and SCAD associated with extra-coronary dissections and aneurysms	Less frequent multivessel involvement, aneurysms, and dissections in SCAD vs. FMD FMD but not SCAD associated with extra-coronary arterial tortuosity
Histology	–	No specific FMD lesions at post-mortem examination of coronary arteries of SCAD patients
Genetics	Some shared common genetic determinants including *PHACTR1* variant	A polygenic risk score for SCAD allows prediction of an increased risk of SCAD also in patients with FMD, suggesting distinct genetic determinants

In spite of these reassuring elements, the recommendation to perform a head-to-pelvis CTA or MRA at baseline in patients with FMD[1] is reasonable to detect additional FMD lesions, aneurysms (which in the absence of complication are usually asymptomatic and may therefore remain unnoticed)[3–5,18] and a small number of asymptomatic dissections. The same holds true for patients with SCAD,[8,9] though extra-coronary lesions appear to be milder than in patients with primary FMD, and almost never lead to clinically relevant complications.[12]

Despite the absence of formal recommendation, whole body imaging at baseline seems also appropriate in patients with carotid and vertebral,[6] renal,[7] and possibly visceral dissection. It allows detecting signs of inflammatory arteriopathies (thickening of the aortic wall), inherited arteriopathies/connective tissue diseases (vascular Ehlers-Danlos syndrome: multiple arterial dissections, carotid-cavernous fistula; Loeys-Dietz syndrome: marked arterial tortuosity) or FMD (the characteristic string of beads). The prognosis of FMD is clearly better than that of arterial dissections occurring in the context of other systemic arteriopathies. Nevertheless, the risk of dissection recurrence seems to be higher in patients with FMD than in those presenting an isolated arterial dissection.[6,7]

Though only a small minority of patients diagnosed with FMD subsequently develop a SCAD (a single case in over 100 patients followed in our center) (A. Persu, personal communication), lesions radiologically indistinguishable from multifocal FMD are often found in extra-coronary arteries of patients with SCAD.[14] However, these lesions tend to be milder, less widespread and are seldom the cause of clinically relevant events.[12] An autopsy study of SCAD patients failed to show typical lesions of FMD in dissected coronary arteries, and no pathological analysis of arteries with "FMD" lesions in patients with SCAD is yet available.[72] Genetic factors associated with SCAD and FMD are only partly similar.[42,44,46–52] Novel imaging[75] and proteomic[74] biomarkers may shed further light on the similarities and differences between FMD, SCAD and arterial dissections with or without FMD lesions, hopefully allowing to improve classification and to individualize follow-up and management of non-atherosclerotic non-inflammatory arterial diseases as a whole.

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Conflict of interest

The authors declared no conflict of interest.

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