

Conditions and Factors Associated With Spontaneous Coronary Artery Dissection (from a National Population-Based Cohort Study)



Chayakrit Krittanawong, MD^a, Anirudh Kumar, MD^b, Kipp W. Johnson, BS^c, Yiming Luo, MD^a, Bing Yue, MD^a, Zhen Wang, PhD^{d,e}, and Deepak L. Bhatt, MD, MPH^{f,*}

The pathophysiology of spontaneous coronary artery dissection (SCAD) is heterogeneous, associated with systemic arteriopathies and inflammatory diseases, and often compounded by environmental precipitants, genetics, or stressors. However, the frequency of these associated conditions with SCAD on a population level remains unknown. Therefore, the objective of this analysis was to evaluate heterogeneous phenotypes of SCAD in the United States using data from the Nationwide Inpatient Sample collected from January 1, 2004, to September 31, 2015. Among 66,360 patients diagnosed with SCAD, the mean age was 63.1 ± 13.2 years and 44.2% were women. A total of 3,415 (5.14%) had depression, 670 (1.0%) had rheumatoid arthritis, 640 (0.96%) had anxiety, 545 (0.82%) had a migraine disorder, 440 (0.66%) used steroids, 385 (0.58%) had malignant hypertension, 280 (0.42%) had systemic lupus erythematosus, 250 (0.38%) had cocaine abuse, 215 (0.32%) had hypertensive heart or renal disease, 130 (0.19%) had coronary spasm, 105 (0.16%) had fibromuscular dysplasia, 85 (0.13%) had Crohn's disease, 75 (0.11%) had celiac disease, 60 (0.09%) had adult autosomal dominant polycystic kidney disease, 60 (0.09%) had hormone replacement therapy, 55 (0.08%) had sarcoidosis, 55 (0.08%) had amphetamine abuse, 15 (0.02%) had granulomatosis polyangiitis, 10 (0.02%) had α 1-antitrypsin deficiency, 10 (0.02%) had Marfan syndrome, 10 (0.02%) had Ehlers-Danlos syndrome, 10 (0.02%) had Kawasaki disease, 10 (0.02%) had polyarteritis nodosa, and 5 (0.01%) had multiparity. In conclusion, most cases of SCAD had no apparent concomitant arteriopathy, inflammatory disorder, or evident risk factor. © 2018 Elsevier Inc. All rights reserved. (Am J Cardiol 2019;123:249–253)

Spontaneous coronary artery dissection (SCAD), associated with systemic arteriopathies, inflammatory diseases, and illicit drug use, is frequently seen in men and women presenting with acute coronary syndrome (ACS).¹ Despite advances in diagnosis using angiography, intravascular ultrasound, and optical coherence tomography, the pathogenesis of SCAD remains unknown. Interestingly, SCAD patients tend not to have typical risk factors for ACS such as diabetes mellitus, smoking, dyslipidemia, or obesity. In fact, the pathophysiology of SCAD appears heterogeneous, including possible inherited or acquired arteriopathies, prothrombotic states, genetic predisposing factors, hormonal influences, or systemic inflammatory diseases.^{2,3} SCAD

has also been described in relation with Crohn's disease,⁴ systemic lupus erythematosus,^{5,6} Marfan syndrome,⁷ Ehlers-Danlos,⁸ fibromuscular dysplasia (FMD),⁹ cocaine abuse,¹⁰ amphetamine abuse,¹¹ steroid use,^{12–14} and migraine disorder.¹⁵ In addition, SCAD has been frequently described with coexisting depression or anxiety.^{16,17} An analysis of a large database such as Nationwide Inpatient Sample (NIS) could potentially shed light on the diagnosis and treatment of heterogeneous clinical syndromes such as SCAD. We hypothesized that using a large population database may identify phenotypes of SCAD and could potentially classify and guide prognosis and treatment.

Methods

We performed the analysis using the NIS database, a component of the Healthcare Cost and Utilization Project sponsored by the Agency for Healthcare Research and Quality. The NIS aggregates yearly data from over 8 million hospital stays involving over 1,000 hospitals and provides nationwide information on hospital utilization, charges, and quality of care (<http://www.hcup-us.ahrq.gov/db/nation/nis/nisrelatedreports.jsp>). Data were extracted from the NIS using ICD-9 codes from January 1, 2004, to September 31, 2015. SCAD diagnosis using ICD-9 codes from the NIS has been previously described.¹ Conditions and factors associated with SCAD including rheumatoid arthritis, migraine disorder, systemic lupus erythematosus, FMD, adult autosomal dominant

^aDepartment of Internal Medicine, Icahn School of Medicine at Mount Sinai St' Luke and Mount Sinai West Hospitals, New York, New York; ^bHeart and Vascular Institute, Cleveland Clinic, Ohio; ^cInstitute for Next Generation Healthcare, Department of Genetics and Genomic Sciences, Icahn School of Medicine at Mount Sinai, New York, New York; ^dRobert D. and Patricia E. Kern Center for the Science of Health Care Delivery, Mayo Clinic, Rochester, Minnesota; ^eDivision of Health Care Policy and Research, Department of Health Sciences Research, Mayo Clinic, Rochester, Minnesota; and ^fBrigham and Women's Hospital Heart & Vascular Center, Harvard Medical School, Boston, Massachusetts. Manuscript received July 31, 2018; revised manuscript received and accepted October 2, 2018.

See page 251 for disclosure information.

*Corresponding author: Tel: 857-307-1992; fax: 1-857-307-1955.

E-mail address: dlbhattmd@post.harvard.edu (D.L. Bhatt).

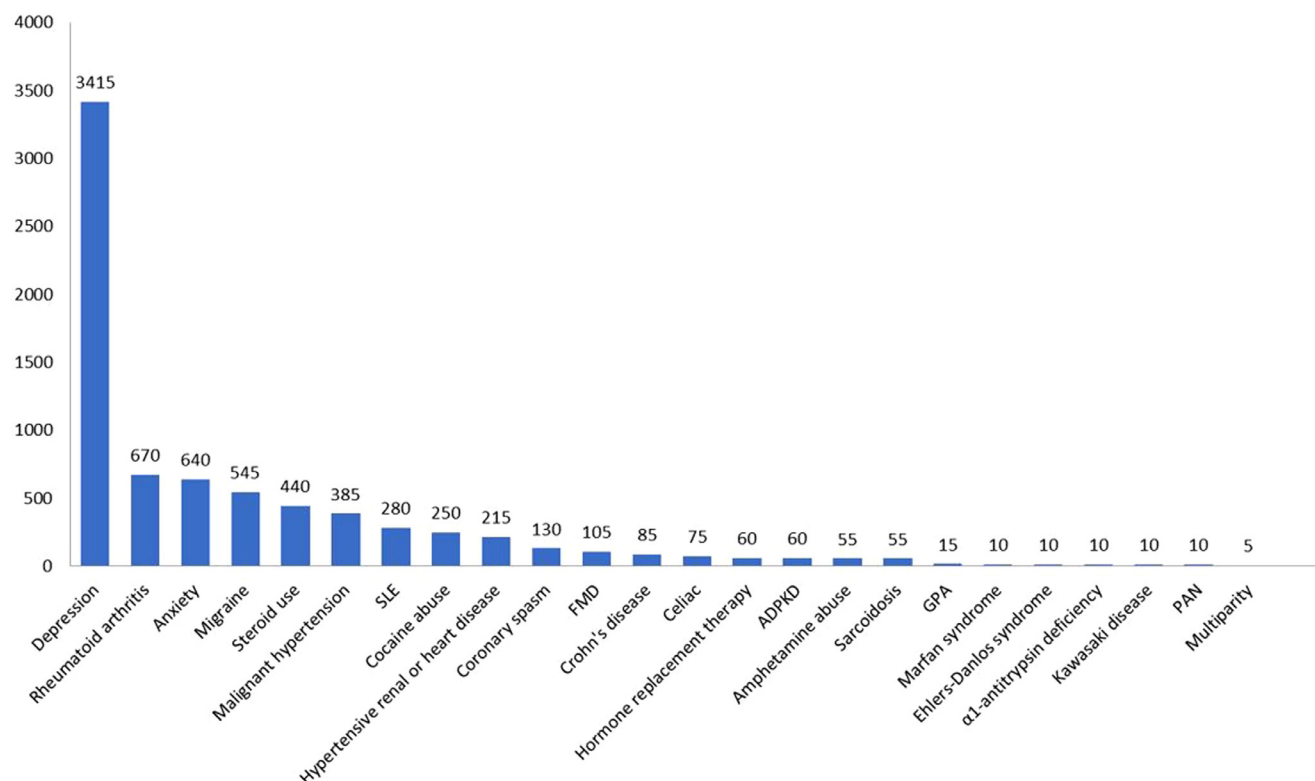


Figure 1. The prevalence in conditions and factors associated with SCAD. ADPKD = adult autosomal dominant polycystic kidney disease; GPA = granulomatosis polyangiitis; FMD = fibromuscular dysplasia; PAN = polyarteritis nodosa; SLE = systemic lupus erythematosus.

polycystic kidney disease, celiac disease, sarcoidosis, granulomatosis polyangiitis (or Wegener's granulomatosis), α 1-antitrypsin deficiency, Marfan syndrome, Ehlers-Danlos syndrome, Kawasaki disease, malignant hypertension, cocaine abuse, amphetamine abuse, steroid use, depression, anxiety, and multiparity were evaluated using their specific ICD-9-CM codes (online Supplementary Table 1). We used methodologic standards that complied with the Agency for Healthcare Research and Quality's recommendations (online Supplementary Table 2).¹⁸ We conducted descriptive analyses using R 3.4.0 and Stata version 14.2. Percentages and means \pm standard deviations were computed for categorical and continuous variables, respectively. Categorical variables were compared using the chi-square test or Fisher's exact tests, when appropriate. All p values were 2-sided, and statistical significance was determined at the level of $p < 0.05$.

Results

A total of 66,360 of patients were diagnosed with SCAD. The mean age was 63.1 ± 13.2 years and 44.2% were women. SCAD and its associated conditions are presented in Figure 1. SCAD was associated with $<1\%$ each of coronary spasm, cocaine abuse, amphetamine abuse, migraine disorder, rheumatoid arthritis, Ehlers-Danlos syndrome, Marfan syndrome, α 1-antitrypsin deficiency, adult polycystic kidney disease, polyarteritis nodosa, Kawasaki disease, celiac disease, granulomatosis polyangiitis, steroid use, and sarcoidosis. Table 1 demonstrated

associated conditions by comparing between SCAD and non-SCAD ACS patients.

Discussion

To the best of our knowledge, this is the first study about conditions related to SCAD using a national database. There were 2 main findings. First, consistent with previously published case reports, we demonstrated that SCAD was associated with a variety of heterogeneous conditions, many of which are not associated with traditional ACS.^{4,5,10,12} Second, our study highlighted the use of a large database potentially to characterize an uncommon disease such as SCAD.

Although SCAD is mainly believed to be associated with nonatherosclerotic dissection, the underlying etiology seems to be multifactorial. Two potential mechanisms for SCAD have been proposed: (1) intimal tear leading to separation of the arterial wall; and (2) spontaneous rupture from increased density of the vasa vasorum, leading to medial hemorrhage.¹⁹ Identifying phenotypes of SCAD is crucial because it can lead to better prognostication and appropriate management. For example, whereas statins have been shown to reduce cardiovascular mortality in ACS,²⁰ some studies have suggested that they can increase risk for recurrent SCAD.²¹ The use of heparin and dual antiplatelet therapy in SCAD remains controversial.²² Although β blockers are recommended in SCAD patients, the role of β blockers in SCAD related to cocaine abuse and the role of ACE-

Table 1

A comparison between SCAD and Non-SCAD ACS patients and associated conditions

	SCAD (%)	Non-SCAD ACS (%)	P values
Cocaine abuse	0.377	0.748	<0.001
Amphetamine abuse	0.083	0.173	<0.001
Migraine	0.821	0.487	<0.001
Crohn's disease	0.128	0.157	<0.001
Rheumatoid arthritis	1.010	1.209	<0.001
Systemic lupus erythematosus	0.422	0.378	<0.001
α 1-antitrypsin deficiency	0.015	0.007	<0.001
Polycystic kidney disease	0.090	0.067	<0.001
Ehlers-Danlos syndrome	0.015	0.004	<0.001
Marfan syndrome	0.015	0.006	<0.001
Coronary spasm	0.196	0.091	<0.001
Hormone replacement therapy	0.090	0.032	<0.001
Steroid use	0.663	0.641	<0.001
Celiac disease	0.113	0.051	<0.001
Kawasaki disease	0.015	0.004	<0.001
Granulomatosis with polyangiitis	0.023	0.029	<0.001
Sarcoidosis	0.083	0.154	<0.001
Polyarteritis nodosa	0.015	0.009	<0.001
Depression	5.146	5.475	<0.001
Anxiety	0.964	1.269	<0.001
Multiparity	0.008	0.0001	0.663
Malignant hypertensive heart/kidney disease	0.324	0.522	<0.001
Malignant hypertension	0.580	0.692	<0.001
Fibromuscular dysplasia	0.163	0.006	<0.001

inhibitors in SCAD have largely remained unexplored.^{23,24} Most studies of SCAD are either case reports or studies from single centers that cannot be generalized. The incidence of SCAD and its associated conditions using a large population database could potentially yield the mechanisms of heterogeneity and allow for future study of more appropriate therapy.

Although, in some case reports and small studies, SCAD has been previously reported with several conditions such as psychological stress, autoimmune and inflammatory conditions,^{2,25} or cocaine and amphetamine use, our results did not show those associated conditions were higher in SCAD than non-SCAD ACS patients. However, our results are consistent with previous reports that SCAD is associated with genetic arteriopathies, FMD, both anabolic steroid and corticosteroid use, migraines, and some autoimmune and inflammatory conditions (Table 1).

We classified potential associations with SCAD into the following. First, SCAD could be associated with genetic arteriopathies such as Marfan and Ehlers-Danlos syndromes. Although these connective tissue conditions are uncommon (1% to 2%),^{2,25} SCAD has been associated with a number of these syndromes, and predisposing connective tissue disorders could potentially be a factor related to SCAD. However, studies of genetic testing in SCAD are rare.

The first genetic study of SCAD by Goel et al²⁶ found that family history of SCAD was relatively uncommon in SCAD patients (1.2%), whereas a study by Kaadan et al²⁷

reported that in 44 patients from a prospective SCAD registry, 6 patients had a pathogenic variant and 3 patients had a deleterious variant in *COL3A1*, the gene believed to cause vascular Ehlers-Danlos syndrome. Additionally, studies have shown minor morphologic alterations of the connective tissue structure from skin biopsies despite no clinical signs of a known connective tissue disorder in patients with cervical artery dissection.^{28,29} Further characterization of SCAD using genetic methods (i.e., SCAD-*COL3A1* or SCAD-SNP related to connective tissue) is needed. In addition, previous studies and case reports demonstrated that SCAD is associated with FMD.^{2,19} Interestingly, our study showed that 0.16% of SCAD cases had FMD.^{2,21} Potentially, genetic screening in FMD patients or FMD screening in SCAD patients may help in risk stratification.

Second, both SCAD and non-SCAD ACS could be associated with psychological stress. A few case reports have demonstrated the association between SCAD and emotional stress.³⁰⁻³³ A previous study demonstrated high rates of depression and anxiety after SCAD.¹⁶ Previous studies found 12.5% to 48.3% of patients reported extreme emotion before or after SCAD.^{23,34} The mechanism between emotional stress and SCAD is unclear. Many case reports have suggested that SCAD can be present with Takotsubo cardiomyopathy.^{35,36} Indeed, both SCAD and non-SCAD ACS might share some of the same mechanisms as Takotsubo cardiomyopathy. For example, increased sympathetic stimulation leading to elevated catecholamines could potentially cause an intimal tear or rupture of the vasa vasorum.³⁷

Third, both anabolic steroid and corticosteroid use could be related to 1 of the SCAD phenotypes. Steroid use could result in weakness of the arterial wall, increased atheroma in the coronary wall, and arterial reactivity.³⁸⁻⁴⁰ Steroids are atherogenic, and atherosclerotic plaques may be ruptured by severe hypertension during weight lifting. There are case reports about SCAD and anabolic steroid use and corticosteroid steroid use.^{12,13} One proposed explanation is steroid-induced vasospasm, perhaps superimposed on a proatherogenic state.⁴¹

Fourth, SCAD may be associated with autoimmune and inflammatory conditions due to the cellular immune response. One of the proposed mechanisms of SCAD is eosinophilic infiltration of the vessel followed by the release of lytic enzymes, causing dissection.⁴²

There are limitations to this study. First, we could not find codes for specific connective tissue diseases such as Loeys-Dietz syndrome. Second, despite a large national cohort, SCAD and its associated conditions are relatively infrequent and we lack statistical power to estimate mortality. Third, the NIS database did not provide discharge medications or some known risk factors for SCAD (e.g., extreme physical activity) which may be important predictors of mortality among SCAD patients.

In conclusion, most cases of SCAD had no apparent concomitant arteriopathy, inflammatory disorder, or evident risk factor.

Disclosures

Dr. Deepak L. Bhatt discloses the following relations—Advisory Board: Cardax, Elsevier Practice Update

Cardiology, Medscape Cardiology, Regado Biosciences; Board of Directors: Boston VA Research Institute, Society of Cardiovascular Patient Care, TobeSoft; Chair: American Heart Association Quality Oversight Committee; Data Monitoring Committees: Baim Institute for Clinical Research (formerly Harvard Clinical Research Institute, for the PORTICO trial, funded by St. Jude Medical, now Abbott), Cleveland Clinic, Duke Clinical Research Institute, Mayo Clinic, Mount Sinai School of Medicine (for the ENVISAGE trial, funded by Daiichi Sankyo), Population Health Research Institute; Honoraria: American College of Cardiology (Senior Associate Editor, Clinical Trials and News, ACC.org; Vice-Chair, ACC Accreditation Committee), Baim Institute for Clinical Research (formerly Harvard Clinical Research Institute; RE-DUAL PCI clinical trial steering committee funded by Boehringer Ingelheim), Belvoir Publications (Editor in Chief, Harvard Heart Letter), Duke Clinical Research Institute (clinical trial steering committees), HMP Global (Editor in Chief, Journal of Invasive Cardiology), Journal of the American College of Cardiology (Guest Editor; Associate Editor), Population Health Research Institute (for the COMPASS operations committee, publications committee, steering committee, and USA national co-leader, funded by Bayer), Slack Publications (Chief Medical Editor, Cardiology Today's Intervention), Society of Cardiovascular Patient Care (Secretary/Treasurer), WebMD (CME steering committees); Other: Clinical Cardiology (Deputy Editor), NCDR-ACTION Registry Steering Committee (Chair), VA CART Research and Publications Committee (Chair); Research Funding: Abbott, Amarin, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Chiesi, Eisai, Ethicon, Forest Laboratories, Idorsia, Ironwood, Ischemix, Lilly, Medtronic, PhaseBio, Pfizer, Regeneron, Roche, Sanofi Aventis, Synaptic, The Medicines Company; Royalties: Elsevier (Editor, Cardiovascular Intervention: A Companion to Braunwald's Heart Disease); Site Co-Investigator: Biotronik, Boston Scientific, St. Jude Medical (now Abbott), Svelte; Trustee: American College of Cardiology; Unfunded Research: FlowCo, Merck, Novo Nordisk, PLx Pharma, Takeda. None of the authors has any disclosures.

Acknowledgment

None.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at <https://doi.org/10.1016/j.amjcard.2018.10.012>.

- arteriopathies and precipitating stressors and cardiovascular outcomes. *Circ Cardiovasc Interv* 2014;7:645–655.
3. Alfonso F, Paulo M, Lennie V, Dutary J, Bernardo E, Jimenez-Quevedo P, Gonzalo N, Escaned J, Banuelos C, Perez-Vizcaino MJ, Hernandez R, Macaya C. Spontaneous coronary artery dissection: long-term follow-up of a large series of patients prospectively managed with a "conservative" therapeutic strategy. *JACC Cardiovasc Interv* 2012;5:1062–1070.
4. Srinivas M, Basumani P, Muthusamy R, Wheeldon N. Active inflammatory bowel disease and coronary artery dissection. *Postgrad Med J* 2005;81:68.
5. Sharma AK, Farb A, Maniar P, Ajani AE, Castagna M, Virmani R, Suddath W, Lindsay J. Spontaneous coronary artery dissection in a patient with systemic lupus erythematosus. *Hawaii Med J* 2003;62:248–253.
6. Reddy S, Vaid T, Ganiga Sanjeeva NC, Shetty RK. Spontaneous coronary artery dissection as the first presentation of systemic lupus erythematosus. *BMJ Case Rep* 2016, bcr-2016-216344. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5015165/>.
7. Judge DP, Dietz HC. Marfan's syndrome. *Lancet* 2005;366:1965–1976.
8. Henkin S, Negrotto SM, Tweet MS, Kirmani S, Deyle DR, Gulati R, Olson TM, Hayes SN. Spontaneous coronary artery dissection and its association with heritable connective tissue disorders. *Heart* 2016;102:876–881.
9. Ahmed Z, Bajwa A, Bhardwaj B, Laster SB, Magalski A. Spontaneous coronary artery dissection: the management dilemma continues. *BMJ Case Rep* 2015, bcr-2015-211061. <http://casereports.bmj.com/content/2015/bcr-2015-211061.long>.
10. Steinhilber JR, Caulfield JB. Spontaneous coronary artery dissection associated with cocaine use: a case report and brief review. *Cardiovasc Pathol* 2001;10:141–145.
11. Afzal AM, Sarmast SA, Weber NA, Schussler JM. Spontaneous coronary artery dissection in a 22-year-old man on lisdexamfetamine. *Proc (Bayl Univ Med Cent)* 2015;28:367–368.
12. Heidari A, Sabzi F, Faraji R. Spontaneous coronary artery dissection in anabolic steroid misuse. *Ann Card Anaesth* 2018;21:103–104.
13. Keir ML, Dehghani P. Corticosteroids and spontaneous coronary artery dissection: a new predisposing factor. *Can J Cardiol* 2016;32:395.e397–395.e398.
14. Chung SE, Yoon TH, Lee KM, Kim HG, Kim BJ. A case report of multiple cervical artery dissection after peripheral type facial palsy and use of steroids. *BMC Neurol* 2018;18:74.
15. Faden MS, Bottega N, Benjamin A, Brown RN. A nationwide evaluation of spontaneous coronary artery dissection in pregnancy and the puerperium. *Heart* 2016;102:1974–1979.
16. Liang JJ, Tweet MS, Hayes SE, Gulati R, Hayes SN. Prevalence and predictors of depression and anxiety among survivors of myocardial infarction due to spontaneous coronary artery dissection. *J Cardiopulm Rehabil Prev* 2014;34:138–142.
17. Krittanawong C, Tweet MS, Hayes SE, Bowman MJ, Gulati R, Squires RW, Hayes SN. Usefulness of cardiac rehabilitation after spontaneous coronary artery dissection. *Am J Cardiol* 2016;117:1604–1609.
18. Khera R, Angraal S, Couch T, et al. Adherence to methodological standards in research using the national inpatient sample. *JAMA* 2017;318:2011–2018.
19. Maehara A, Mintz GS, Castagna MT, Pichard AD, Satler LF, Waksman R, Suddath WO, Kent KM, Weissman NJ. Intravascular ultrasound assessment of spontaneous coronary artery dissection. *Am J Cardiol* 2002;89:466–468.
20. Stone NJ, Robinson JG, Lichtenstein AH, Bairey Merz CN, Blum CB, Eckel RH, Goldberg AC, Gordon D, Levy D, Lloyd-Jones DM, McBride P, Schwartz JS, Shero ST, Smith SC Jr, Watson K, Wilson PW, Eddleman KM, Jarrett NM, LaBresh K, Nevo L, Wnek J, Anderson JL, Halperin JL, Albert NM, Bozkurt B, Brindis RG, Curtis LH, DeMets D, Hochman JS, Kovacs RJ, Ohman EM, Pressler SJ, Sellke FW, Shen WK, Smith SC Jr, Tomaselli GF. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association task force on practice guidelines. *Circulation* 2014;129:S1–S45.
21. Tweet MS, Hayes SN, Pitta SR, Simari RD, Lerman A, Lennon RJ, Gersh BJ, Khambatta S, Best PJ, Rihal CS, Gulati R. Clinical features, management, and prognosis of spontaneous coronary artery dissection. *Circulation* 2012;126:579–588.

1. Krittanawong C, Kumar A, Hassan VH, Yue B, Wang Z, Bhatt DL. Trends in incidence, characteristics, and in-hospital outcomes of patients presenting with spontaneous coronary artery dissection (from a national population-based cohort study between 2004 and 2015). *Am J Cardiol* 2018. S0002-9149(18)31621-7. <https://www.ncbi.nlm.nih.gov/pubmed/30293656>.
2. Saw J, Aymong E, Sedlak T, Buller CE, Starovoytov A, Ricci D, Robinson S, Vuurmans T, Gao M, Humphries K, Mancini GB. Spontaneous coronary artery dissection: association with predisposing

22. Hayes SN, Kim ESH, Saw J, Adlam D, Arslanian-Engoren C, Economy KE, Ganesh SK, Gulati R, Lindsay ME, Mieres JH, Naderi S, Shah S, Thaler DE, Tweet MS, Wood MJ. Spontaneous coronary artery dissection: current state of the science: a scientific statement from the American Heart Association. *Circulation* 2018;137:e523–e557.
23. Saw J, Humphries K, Aymong E, Sedlak T, Prakash R, Starovoytov A, Mancini GBJ. Spontaneous coronary artery dissection: clinical outcomes and risk of recurrence. *J Am Coll Cardiol* 2017;70:1148–1158.
24. Krittanawong C, Rozanski A, Palazzo A. Should we recommend cardiac rehabilitation in patients with spontaneous coronary artery dissection. *J Am Coll Cardiol* 2018;71:472–473.
25. Prasad M, Tweet MS, Hayes SN, Leng S, Liang JJ, Eleid MF, Gulati R, Vrtiska TJ. Prevalence of extracoronary vascular abnormalities and fibromuscular dysplasia in patients with spontaneous coronary artery dissection. *Am J Cardiol* 2015;115:1672–1677.
26. Goel K, Tweet M, Olson TM, Maleszewski JJ, Gulati R, Hayes SN. Familial spontaneous coronary artery dissection: evidence for genetic susceptibility. *JAMA Intern Med* 2015;175:821–826.
27. Kaadan MI, MacDonald C, Ponzini F, Duran J, Newell K, Pitler L, Lin A, Weinberg I, Wood MJ, Lindsay ME. Prospective cardiovascular genetics evaluation in spontaneous coronary artery dissection. *Circ Genom Precis Med* 2018;11:e001933.
28. Debette S, Goeggel Simonetti B, Schilling S, Martin JJ, Kloss M, Sarikaya H, Hausser I, Engelter S, Metso TM, Pezzini A, Thijs V, Touze E, Paolucci S, Costa P, Sessa M, Samson Y, Bejot Y, Altintas A, Metso AJ, Herve D, Lichy C, Jung S, Fischer U, Lamy C, Grau A, Chabriot H, Caso V, Lyrer PA, Stapf C, Tatlisumak T, Brandt T, Tournier-Lasserre E, Germain DP, Frank M, Baumgartner RW, Grond-Ginsbach C, Bousser MG, Leys D, Dallongeville J, Bersano A, Arnold M. Familial occurrence and heritable connective tissue disorders in cervical artery dissection. *Neurology* 2014;83:2023–2031.
29. Hausser I, Muller U, Engelter S, Lyrer P, Pezzini A, Padovani A, Moormann B, Busse O, Weber R, Brandt T, Grond-Ginsbach C. Different types of connective tissue alterations associated with cervical artery dissections. *Acta Neuropathol* 2004;107:509–514.
30. Anisman SD, Joelson JM. Left main coronary artery dissection associated with emotional stress. *Dis Mon* 2006;52:227–253.
31. Mayr A, Klug G, Jaschke W, Pachinger O, Metzler B. Persistent spontaneous dissection of the left anterior descending coronary artery after emotional pressure. *Wien Klin Wochenschr* 2010;122:515–517.
32. Eugène M, Siam-Tsieu V, Pillière R, Deblaise J, Dubourg O, Mansencal N. Recurrent spontaneous coronary artery dissection: unexpected evolution and major role of emotional stress. *Int J Cardiol* 2015;201:316–318.
33. Du Y, Han K, Bai L, Liu P. [a rare case of spontaneous coronary artery dissection after emotional stress in a postmenopausal woman]. *Nan Fang Yi Ke Da Xue Xue Bao* 2017;37:1010–1013.
34. Tweet MS, Hayes SN, Codsì E, Gulati R, Rose CH, Best PJM. Spontaneous coronary artery dissection associated with pregnancy. *J Am Coll Cardiol* 2017;70:426–435.
35. Y-Hassan S, Themudo R, Maret E. Spontaneous coronary artery dissection and takotsubo syndrome: the chicken or the egg causality dilemma. *Catheter Cardiovasc Interv* 2017;89:1215–1218.
36. Buccheri D, Zambelli G. The link between spontaneous coronary artery dissection and takotsubo cardiomyopathy: analysis of the published cases. *J Thorac Dis* 2017;9:5489–5492.
37. Wittstein IS, Thiemann DR, Lima JA, Baughman KL, Schulman SP, Gerstenblith G, Wu KC, Rade JJ, Bivalacqua TJ, Champion HC. Neurohumoral features of myocardial stunning due to sudden emotional stress. *N Engl J Med* 2005;352:539–548.
38. McCredie RJ, McCrohon JA, Turner L, Griffiths KA, Handelsman DJ, Celermajer DS. Vascular reactivity is impaired in genetic females taking high-dose androgens. *J Am Coll Cardiol* 1998;32: 1331–1335.
39. Mortensen KH, Thuesen L, Kristensen IB, Christiansen EH. Spontaneous coronary artery dissection: a Western Denmark Heart Registry Study. *Catheter Cardiovasc Interv* 2009;74:710–717.
40. Sholter DE, Armstrong PW. Adverse effects of corticosteroids on the cardiovascular system. *Can J Cardiol* 2000;16:505–511.
41. McCrohon JA, Jessup W, Handelsman DJ, Celermajer DS. Androgen exposure increases human monocyte adhesion to vascular endothelium and endothelial cell expression of vascular cell adhesion molecule-1. *Circulation* 1999;99:2317–2322.
42. Robinowitz M, Virmani R, McAllister HAJ. Spontaneous coronary artery dissection and eosinophilic inflammation: a cause and effect relationship. *Am J Med* 1982;72:923–928.